EXHIBIT 1

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(54) **DOSAGES FOR TREATMENT WITH ANTI-ERBB2 ANTIBODIES**

(75) Inventors: **Sharon A. Baughman**, Ventura, CA (US); **Steven Shak**, Burlingame, CA (US)

(73) Assignee: **Genentech, Inc.**, South San Francisco, CA (US)

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(56) **References Cited**

U.S. PATENT DOCUMENTS

4,676,980	A	6/1987	Segal et al.
4,753,894	A	6/1988	Frankel et al.
4,816,567	A	3/1989	Cabilly et al.
4,935,341	A	6/1990	Bargmann et al.
4,943,533	A	7/1990	Mendelsohn et al.
4,968,603	A	11/1990	Slamon et al.
4,975,278	A	12/1990	Senter et al.
5,169,774	A	12/1992	Frankel et al.
5,183,884	A	2/1993	Kraus et al.
5,288,477	A	2/1994	Bacus
5,359,046	A	10/1994	Capon et al.
5,367,060	A	11/1994	Vandlen et al.
5,401,638	A	3/1995	Carney et al.
5,464,751	A	11/1995	Greene et al.
5,480,968	A	1/1996	Kraus et al.
5,578,482	A	11/1996	Lippman et al.
5,604,107	A	2/1997	Carney et al.
5,641,869	A	6/1997	Vandlen et al.
5,663,144	A	9/1997	Greene et al.
5,677,171	A	10/1997	Hudziak et al.
5,705,157	A	1/1998	Greene
5,720,937	A	2/1998	Hudziak et al.
5,720,954	A	2/1998	Hudziak et al.
5,725,856	A	3/1998	Hudziak et al.
5,726,023	A	3/1998	Cheever et al.
5,728,687	A	3/1998	Bissery
5,747,261	A	5/1998	King et al.
5,770,195	A	6/1998	Hudziak et al.
5,772,997	A	6/1998	Hudziak et al.
5,776,427	A	7/1998	Thorpe et al.
5,783,186	A	7/1998	Arakawa et al.
5,801,005	A	9/1998	Cheever et al.
5,821,337	A	10/1998	Carter et al.
5,824,311	A	10/1998	Greene et al.
5,834,229	A	11/1998	Vandlen et al.
5,837,243	A	11/1998	Deo et al.
5,837,523	A	11/1998	Greene et al.
5,840,525	A	11/1998	Vandlen et al.
5,846,538	A	12/1998	Cheever et al.
5,856,110	A	1/1999	Vandlen et al.
5,859,206	A	1/1999	Vandlen et al.
5,869,445	A	2/1999	Cheever et al.
5,876,712	A	3/1999	Cheever et al.
5,877,305	A	3/1999	Huston et al.
5,908,835	A	6/1999	Bissery
5,910,486	A	6/1999	Curiel et al.
5,922,845	A	7/1999	Deo et al.
5,939,531	A	8/1999	Wels et al.
5,968,511	A	10/1999	Akita et al.
5,977,322	A	11/1999	Marks et al.
5,985,553	A	11/1999	King et al.
6,015,567	A	1/2000	Hudziak et al.
6,028,059	A	2/2000	Curiel et al.
6,054,297	A	4/2000	Carter et al.
6,054,561	A	4/2000	Ring
6,096,873	A	8/2000	Schaefer et al.
6,123,939	A	9/2000	Shawver et al.
6,165,464	A	12/2000	Hudziak et al.
6,333,348	B1 *	12/2001	Vogel et al. 514/449

FOREIGN PATENT DOCUMENTS

EP	0003089	A1	7/1979
EP	0599274	A1	6/1994
EP	616812	A1	9/1994
EP	0711565	B1	8/1998
JP	3-240498		10/1991
JP	5-117165		5/1993
JP	5-170667		7/1993
JP	5-213775		8/1993
JP	5-317084		12/1993
JP	95006982	B2	1/1995
JP	7-59588		3/1995
JP	2761543	B2	6/1998
JP	2895105	B2	5/1999

(List continued on next page.)

OTHER PUBLICATIONS

Wantanabe et al., ASCO, Vol. 17, abstract 702, May 15–18, 1998 Annual Meeting.*

(List continued on next page.)

Primary Examiner—Anthony C. Caputa
Assistant Examiner—Anne L. Holleran
(74) *Attorney, Agent, or Firm*—Wendy M. Lee

(57) **ABSTRACT**

The present invention concerns the treatment of disorders characterized by the overexpression of ErbB2. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 with anti-ErbB2 antibody.

33 Claims, 5 Drawing Sheets

DOSAGES FOR TREATMENT WITH ANTI-ERBB2 ANTIBODIES

RELATED APPLICATIONS

This application is a non-provisional application filed under 37 CFR 1.53(b)(1), claiming priority under 35 USC 119(e) to provisional application No. 60/151,018, filed Aug. 27, 1999 and No. 60/213,822, filed Jun. 23, 2000, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention concerns the treatment of disorders characterized by the overexpression of ErbB2 or disorders expressing epidermal growth factor receptor (EGFR), comprising administering to a human or animal presenting the disorders a therapeutically effective amount of an antibody that binds ErbB2. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 or expressing EGFR, where the treatment is with an anti-ErbB2 antibody administered by front loading the dose of antibody during treatment by intravenous and/or subcutaneous administration. The invention optionally includes treatment of cancer in a human patient with a combination of an anti-ErbB2 antibody and a chemotherapeutic agent, such as, but not limited to, a taxoid. The taxoid may be, but is not limited to paclitaxel or docetaxel. The invention further includes treatment of cancer in a human patient with a combination of anti-ErbB2 antibody and a chemotherapeutic agent, such as, but not limited to, an anthracycline derivative. Optionally, treatment with a combination of anti-ErbB2 and an anthracycline derivative includes treatment with an effective amount of a cardioprotectant. The present invention further concerns infrequent dosing of anti-ErbB2 antibodies.

BACKGROUND OF THE INVENTION

Proto-oncogenes that encode growth factors and growth factor receptors have been identified to play important roles in the pathogenesis of various human malignancies, including breast cancer. It has been found that the human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer (Slamon et al., *Science* 235:177–182 [1987]; Slamon et al., *Science* 244:707–712 [1989]).

Several lines of evidence support a direct role for ErbB2 in the pathogenesis and clinical aggressiveness of ErbB2-overexpressing tumors. The introduction of ErbB2 into non-neoplastic cells has been shown to cause their malignant transformation (Hudziak et al., *Proc. Natl. Acad. Sci. USA* 84:7159–7163 [1987]; DiFiore et al., *Science* 237:78–182 [1987]). Transgenic mice that express HER2 were found to develop mammary tumors (Guy et al., *Proc. Natl. Acad. Sci. USA* 89:10578–10582 [1992]).

Antibodies directed against human erbB2 protein products and proteins encoded by the rat equivalent of the erbB2 gene (neu) have been described. Drebin et al., *Cell* 41:695–706 (1985) refer to an IgG2a monoclonal antibody which is directed against the rat neu gene product. This antibody called 7.16.4 causes down-modulation of cell surface p185 expression on B104-1-1 cells (NIH-3T3 cells transfected with the neu proto-oncogene) a inhibits colony formation of these cells. In Drebin et al. *PNAS* (*USA*) 83:9129–9133 (1986), the 7.16.4 antibody was shown to

inhibit the tumorigenic growth of neu-transformed NIH-3T3 cells as well as rat neuroblastoma cells (from which the neu oncogene was initially isolated) implanted into nude mice. Drebin et al. in *Oncogene* 2:387–394 (1988) discuss the production of a panel of antibodies against the rat neu gene product. All of the antibodies were found to exert a cytostatic effect on the growth of neu-transformed cells suspended in soft agar. Antibodies of the IgM, IgG2a and IgG2b isotypes were able to mediate significant in vitro lysis of neu-transformed cells in the presence of complement, whereas none of the antibodies were able to mediate high levels of antibody-dependent cellular cytotoxicity (ADCC) of the neu-transformed cells. Drebin et al. *Oncogene* 2:273–277 (1988) report that mixtures of antibodies reactive with two distinct regions on the p185 molecule result in synergistic anti-tumor effects on neu-transformed NIH-3T3 cells implanted into nude mice. Biological effects of anti-neu antibodies are reviewed in Myers et al., *Meth. Enzym.* 198:277–290 (1991). See also WO94/22478 published Oct. 13, 1994.

Hudziak et al., *Mol. Cell. Biol.* 9(3):1165–1172 (1989) describe the generation of a panel of anti-ErbB2 antibodies which were characterized using the human breast tumor cell line SKBR3. Relative cell proliferation of the SKBR3 cells following exposure to the antibodies was determined by crystal violet staining of the monolayers after 72 hours. Using this assay, maximum inhibition was obtained with the antibody called 4D5 which inhibited cellular proliferation by 56%. Other antibodies in the panel,including 7C2 and 7F3, reduced cellular proliferation to a lesser extent in this assay. Hudziak et al. conclude that the effect of the 4D5 antibody on SKBR3 cells was cytostatic rather than cytotoxic, since SKBR3 cells resumed growth at a nearly normal rate following removal of the antibody from the medium. The antibody 4D5 was further found to sensitize p 185 -overexpressing breast tumor cell lines to the cytotoxic effects of TNF-α. See also WO89/06692 published Jul. 27, 1989. The anti-ErbB2 antibodies discussed in Hudziak et al. are further characterized in Fendly et al. *Cancer Research* 50:1550–1558 (1990); Kotts et al. *In Vitro* 26(3):59A (1990); Sarup et al. *Growth Regulation* 1:72–82 (1991); Shepard et al. *J. Clin. Immunol.* 11(3):117–127 (1991); Kumar et al. *Mol. Cell. Biol.* 11(2):979–986 (1991); Lewis et al. *Cancer Immunol. Immunother.* 37:255–263 (1993); Pietras et al. *Oncogene* 9:1829–1838 (1994); Vitetta et al. *Cancer Research* 54:5301–5309 (1994); Sliwkowski et al. *J. Biol. Chem.* 269(20): 14661–14665 (1994); Scott et al. *J. Biol. Chem.* 266:14300–5 (1991); and D'souza et al. *Proc. Natl. Acad. Sci.*91:7202–7206 (1994).

Tagliabue et al. *Int. J. Cancer* 47:933–937 (1991) describe two antibodies which were selected for their reactivity on the lung adenocarcinoma cell line (Calu-3) which overexpresses ErbB2. One of the antibodies, called MGR3, was found to internalize, induce phosphorylation of ErbB2, and inhibit tumor cell growth in vitro.

McKenzie et al. *Oncogene* 4:543–548 (1989) generated a panel of anti-ErbB2 antibodies with varying epitope specificities, including the antibody designated TA1. This TA1 antibody was found to induce accelerated endocytosis of ErbB2 (see Maier et al. *Cancer Res.* 51:5361–5369 [1991]). Bacus et al. *Molecular Carcinogenesis* 3:350–362 (1990) reported that the TA1 antibody induced maturation of the breast cancer cell lines AU-565 (which overexpresses the erbB2 gene) and MCF-7 (which does not). Inhibition of growth and acquisition of a mature phenotype in these cells was found to be associated with reduced levels of ErbB2 receptor at the cell surface and transient increased levels in the cytoplasm.

administered is sufficient to maintain the target trough serum concentration such that the interval between administration cycles is at least one week. Preferably the trough serum concentration does not exceed 2500 μg/ml and does not fall below 0.01 μg/ml during treatment. The front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment. The subcutaneous delivery of maintenance doses according to the invention has the advantage of being convenient for the patient and health care professionals, reducing time and costs for drug treatment. Preferably, the initial dose (or the last dose within an initial dose series) is separated in time from the first subsequent dose by 4 weeks or less, preferably 3 weeks or less, more preferably 3 weeks or less, most preferably 1 week or less.

In an embodiment of the invention, the initial dose of anti-ErbB2 is 6 mg/kg, 8 mg/kg, or 12 mg/kg delivered by intravenous or subcutaneous administration, such as intravenous infusion or subcutaneous bolus injection. The subsequent maintenance doses are 2 mg/kg delivered once per week by intravenous infusion, intravenous bolus injection, subcutaneous infusion, or subcutaneous bolus injection. The choice of delivery method for the initial and maintenance doses is made according to the ability of the animal or human patient to tolerate introduction of the antibody into the body. Where the antibody is well-tolerated, the time of infusion may be reduced. The choice of delivery method as disclosed for this embodiment applies to all drug delivery regimens contemplated according to the invention.

In another embodiment, the invention includes an initial dose of 12 mg/kg anti-ErbB2 antibody, followed by subsequent maintenance doses of 6 mg/kg once per 3 weeks.

In still another embodiment, the invention includes an initial dose of 8 mg/kg anti-ErbB2 antibody, followed by 6 mg/kg once per 3 weeks.

In yet another embodiment, the invention includes an initial dose of 8 mg/kg anti-ErbB2 antibody, followed by subsequent maintenance doses of8 mg/kg once per week or 8 mg/kg once every 2 to 3 weeks.

In another embodiment, the invention includes initial doses of at least 1 mg/kg, preferably 4 mg/kg, anti-ErbB2 antibody on each of days 1, 2 and 3, followed by subsequent maintenance doses of 6 mg/kg once per 3 weeks.

In another embodiment, the invention includes an initial dose of 4 mg/kg anti-ErbB2 antibody, followed by subsequent maintenance doses of 2 mg/kg twice per week, wherein the maintenance doses are separated by 3 days.

In still another embodiment, the invention includes a cycle of dosing in which delivery of anti-ErbB2 antibody is 2–3 times per week for 3 weeks. In one embodiment of the invention, each dose is approximately 25 mg/kg or less for a human patient, preferably approximately 10 mg/kg or less. This 3 week cycle is preferably repeated as necessary to achieve suppression of disease symptoms.

In another embodiment, the invention includes a cycle of dosing in which delivery of anti-ErbB2 antibody is daily for 5 days. According to the invention, the cycle is preferably repeated as necessary to achieve suppression of disease symptoms.

The disorder preferably is a benign or malignant tumor characterized by the overexpression of the ErbB2 receptor, e.g. a cancer, such as, breast cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer. The method of the invention may further comprise administration of a chemotherapeutic agent other than an anthracycline, e.g. doxorubicin or epirubicin. The chemotherapeutic agent preferably is a taxoid, such as TAXOL® (paclitaxel) or a TAXOL® derivative.

Preferred anti-ErbB2 antibodies bind the extracellular domain of the ErbB2 receptor, and preferably bind o the epitope 4D5 or 3H4 within the ErbB2 extracellular domain sequence. More preferably, the antibody is the antibody 4D5, most preferably in a humanized form. Other preferred ErbB2-binding antibodies include, but are not limited to, antibodies 7C2, 7F3, and 2C4, preferably in a humanized form.

The method of the present invention is particularly suitable for the treatment of breast or ovarian cancer, characterized by the overexpression of the ErbB2 receptor.

The present application also provides a method of therapy involving infrequent dosing of an anti-ErbB2 antibody. In particular, the invention provides a method for the treatment of cancer (e.g. cancer characterized by overexpression of the ErbB2 receptor) in a human patient comprising administering to the patient a first dose of an anti-ErbB2 antibody followed by at least one subsequent dose of the antibody, wherein the first dose and subsequent dose are separated from each other in time by at least about two weeks (e.g. from about two weeks to about two months), and optionally at least about three weeks (e.g. from about three weeks to about six weeks). For instance, the antibody may be administered about every three weeks, about two to about 20 times, e.g. about six times. The first dose and subsequent dose may each be from about 2 mg/kg to about 16 mg/kg; e.g. from about 4 mg/kg to about 12 mg/kg; and optionally from about 6 mg/kg to about 12 mg/kg. Generally, two or more subsequent doses (e.g. from about two to about ten subsequent doses) of the antibody are administered to the patient, and those subsequent doses are preferably separated from each other in time by at least about two weeks (e.g. from about two weeks to about two months), and optionally at least about three weeks (e.g. from about three weeks to about six weeks). The two or more subsequent doses may each be from about 2 mg/kg to about 16 mg/kg; or from about 4 mg/kg to about 12 mg/kg; or from about 6 mg/kg to about 12 mg/kg. The invention additionally provides an article of manufacture, comprising a container, a composition within the container comprising an anti-ErbB2 antibody, and a package insert containing instructions to administer the antibody according to such methods.

The presently described dosing protocols may be applied to other anti-ErbB antibodies such as anti-epidermal growth factor receptor (EGFR), anti-ErbB3 and anti-ErbB4 antibodies. Thus, the invention provides a method for the treatment of cancer in a human patient, comprising administering an effective amount of an anti-ErbB antibody to the human patient, the method comprising administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB antibody; and administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose. Alternatively, or additionally, the invention pertains to a method for the treatment of cancer in a human patient comprising administering to the patient a first dose of an anti-ErbB antibody followed by at least one subsequent dose of the antibody, wherein the first dose and subsequent dose are separated from each other in time by at least about two

weeks. The invention additionally provides an article of manufacture, comprising a container, a composition within the container comprising an anti-ErbB antibody, and a package insert containing instructions to administer the antibody according to such methods.

In another aspect, the invention concerns an article of manufacture, comprising a container, a composition within the container comprising an anti-ErbB2 antibody, optionally a label on or associated with the container that indicates that the composition can be used for treating a condition characterized by overexpression of ErbB2 receptor, and a package insert containing instructions to avoid the use of anthracycline-type chemotherapeutics in combination with the composition. According to the invention, the package insert further includes instructions to administer the anti-ErbB2 antibody at an initial dose of 5 mg/kg followed by the same or smaller subsequent dose or doses. In another embodiment of the invention, the package insert further includes instructions to administer the anti-ErbB2 antibody subcutaneously for at least one of the doses, preferably for all of the subsequent doses following the initial dose, most preferably for all doses.

In a further aspect, the invention provides a method of treating ErbB2 expressing cancer in a human patient comprising administering to the patient effective amounts of an anti-ErbB2 antibody and a chemotherapeutic agent. In one embodiment of the invention, the chemotherapeutic agent is a taxoid including, but not limited to, paclitaxel and docetaxel. In another embodiment, the chemotherapeutic agent is an anthracyline derivative including, but not limited to, doxorubicin or epirubicin. In still another embodiment of the invention, treatment with an anti-ErbB2 antibody and an anthracycline derivative further includes administration of a cardioprotectant to the patient. In still another embodiment, an anthracycline derivative is not administered to the patient with the anti-ErbB2 antibody. One or more additional chemotherapeutic agents may also be administered to the patient. The cancer is preferably characterized by overexpression of ErbB2.

The invention further provides an article of manufacture comprising a container, a composition within the container comprising an anti-ErbB2 antibody and a package insert instructing the user of the composition to administer the anti-ErbB2 antibody composition and a chemotherapeutic agent to a patient. In another embodiment, the chemotherapeutic agent is other than an anthracycline, and is preferably a taxoid, such as TAXOL®. In still another embodiment, the chemotherapeutic agent is an anthracycline, including but not limited to, doxorubicin or epirubicin. In yet another embodiment, the chemotherapeutic agent is an anthracycline and the package insert further instructs the user to administer a cardioprotectant.

The methods and compositions of the invention comprise an anti-ErbB2 antibody and include a humanized anti-ErbB2 antibody. Thus, the invention further pertains to a composition comprising an antibody that binds ErbB2 and the use of the antibody for treating ErbB2 expressing cancer, e.g., ErbB2 overexpressing cancer, in a human. The invention also pertains to the use of the antibody for treating EGFR expressing cancer. Preferably the antibody is a monoclonal antibody 4D5, e.g., humanized 4D5 (and preferably huMAb4D5–8 (HERCEPTIN® anti-ErbB2 antibody); or monoclonal antibody 2C4, e.g., humanized 2C4. The antibody may be an intact antibody (e.g., an intact IgG, antibody) or an antibody fragment (e.g., a Fab, $F(ab')_2$, diabody, and the like). The variable light chain and variable heavy chain regions of humanized anti-ErbB2 antibody 2C4 are shown in FIGS. **5**A and **5**B.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows epitope-mapping of the extracellular domain of ErbB2 as determined by truncation mutant analysis and site-directed mutagenesis (Nakamura et al. *J. of Virology* 67 (10):6179–6191 [October 1993]; Renz et *J. Cell Biol.* 125(6):1395–1406 [June 1994]). The anti-proliferative MAbs 4D5 and 3H4 b bind adjacent to the transmembrane domain. The various ErbB2-ECD truncations or point mutations were prepared from cDNA using polymerase chain reaction technology. The ErbB2 mutants were expressed as gD fusion proteins in a mammalian expression plasmid. This expression plasmid uses the cytomegalovirus promoter/enhancer with SV40 termination and polyadenylation signals located downstream of the inserted cDNA. Plasmid DNA was transfected into 293S cells. One day following transfection, the cells were metabolically labeled overnight in methionine and cysteine-free, low glucose DMEM containing 1% dialyzed fetal bovine serum and 25 μCi each of ^{35}S methionine and ^{35}S cysteine. Supernatants were harvested either the ErbB2 MAbs or control antibodies were added to the supernatant and incubated 2–4 hours at 4° C. The complexes were precipitated, applied to a 10–20% Tricine SDS gradient gel and electrophoresed at 100 V. The gel was electroblotted onto a membrane and analyzed by autoradiography. SEQ ID NOs:8 and 9 depict the 3H4 and 4D5 epitopes, respectively.

FIG. **2** depicts with underlining the amino acid sequence of Domain 1 of ErbB2 (SEQ ID NO: 1). Bold amino acids indicate the location of the epitope recognized by MAbs 7C2 and 7F3 as determined by deletion mapping, i.e. the "7C2/7F3 epitope" (SEQ ID NO:2).

FIG. **3** is a graph of anti-ErbB2 antibody (HERCEPTIN®) trough serum concentration (μg/ml, mean ±SE, dark circles) by week from week 2 through week 36 for ErbB2 overexpressing patients treated with HERCEPTIN® anti-ErbB2 antibody at 4 mg/kg initial dose, followed by 2 mg/kg weekly. The number of patients at each time point is represented by "n" (white squares).

FIG. **4**A is a linear plot of tumor volume changes over time in mice treated with HERCEPTIN® anti-ErbB2 antibody. FIG. **4**B is a semi-logarithmic plot of the same data as in FIG. **4**A such that the variation in tumor volume for the treated animals is observed more readily.

FIGS. **5**A and **5**B depict alignments of the amino acid sequences of the variable light (V_L)(FIG. **5**A) and variable heavy (V_H) (FIG. **5**B) domains of murine monoclonal antibody 2C4 (SEQ ID Nos. 10 and 11, respectively); V_L and V_H domains of humanized Fab version 574 (SEQ ID Nos. 12 and 13, respectively), and human V_L and V_H consensus frameworks (hum κl, light kappa subgroup I; humIII, heavy subgroup III) (SEQ ID Nos. 14 and 15, respectively). Asterisks identify differences between humanized Fab version 574 and murine monoclonal antibody 2C4 or between humanized Fab version 574 and the human framework. Complementarity Determining Regions (CDRs) are in brackets. Humanized Fab version 574, with the changes ArgH71Val, AspH73Arg and IleH69Leu, appears to have binding restored to that of the original chimeric 2C4 Fab fragment. Additional FR and/or CDR residues, such as L2, L54, L55, L56, H35 and/or H48, may be modified (e.g. substituted as follows-IleL2Thr; ArgL54Leu; TyrL55Glu; ThrL56Ser; AspH35Ser; and ValH48Ile) in order to further refine or enhance binding of the humanized antibody. Alternatively, or additionally, the humanized antibody may be affinity matured in order to further improve or refine its affinity and/or other biological activities.

the subsequent doses are separated in time from each other by at least two weeks.

2. The method of claim **1**, wherein the initial dose is at least approximately 6 mg/kg.

3. The method of claim **2**, wherein the initial dose is at least approximately 8 mg/kg.

4. The method of claim **3**, wherein the initial dose is at least approximately 12 mg/kg.

5. The method of claim **1**, wherein the subsequent doses are separated in time from each other by at least three weeks.

6. The method of claim **1**, wherein the initial dose is administered by intravenous injection, and wherein at least one subsequent dose is administered by subcutaneous injection.

7. The method of claim **1**, wherein the initial dose is administered by intravenous injection, wherein at least two subsequent doses are administered, and wherein each subsequent dose is administered by a method selected from the group consisting of intravenous injection and subcutaneous injection.

8. The method of claim **1**, wherein the initial dose and at least one subsequent dose are administered by subcutaneous injection.

9. The method of claim **1**, wherein the initial dose is selected from the group consisting of approximately 6 mg/kg, 8 mg/kg, or 12 mg/kg, wherein the plurality of subsequent doses are at least approximately 2 mg/kg.

10. The method of claim **9**, wherein the plurality of subsequent doses are separated in time from each other by at least three weeks.

11. The method of claim **10**, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 6 mg/kg.

12. The method of claim **10**, wherein the initial dose is approximately 12 mg/kg, and wherein at least one subsequent dose is approximately 6 mg/kg.

13. The method of claim **9**, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 8 mg/kg.

14. The method of claim **9**, wherein the initial dose is approximately 8 mg/kg, wherein at least one subsequent dose is 8 mg/kg, and wherein administration of the initial dose and subsequent doses are separated in time by at least 2 weeks.

15. The method of claim **14**, wherein the initial dose and subsequent doses are separated in time by at least 3 weeks.

16. A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:

administering to the patient an initial dose of the antibody, wherein the initial dose is a plurality of doses, wherein each of the plurality of initial doses is at least approximately 1 mg/kg and is administered on at least 3 consecutive days, and administering to the patient at least 1 subsequent dose of the antibody, wherein at least one subsequent dose is at least approximately 6 mg/kg, and wherein administration of the last initial dose and the first subsequent and additional subsequent doses are separated in time by at least 3 weeks.

17. The method of claim **1**, wherein said cancer is selected from the group consisting of breast cancer, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer.

18. The method of claim **17**, wherein said cancer is breast cancer.

19. The method of claim **18**, wherein said cancer is metastatic breast carcinoma.

20. The method of claim **1**, wherein said antibody binds to the extracellular domain of the ErbB2 receptor.

21. The method of claim **20**, wherein said antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence.

22. The method of claim **21**, wherein said antibody is a humanized 4D5 anti-ErbB2 antibody.

23. The method of claim **1**, wherein efficacy is measured by determining the time to disease progression or the response rate.

24. A method for the treatment of cancer in a human patient comprising administering to the patient a first dose of an anti-ErbB2 antibody followed by two or more subsequent doses of the antibody, wherein the subsequent doses are separated in time from each other by at least two weeks.

25. The method of claim **24**, wherein the first dose and a first subsequent dose are separated from each other in time by at least about three weeks.

26. The method of claim **24**, wherein the first dose and subsequent doses are each from about 2 mg/kg to about 16 mg/kg.

27. The method of claim **26**, wherein the first dose and subsequent doses are each from about 4 mg/kg to about 12 mg/kg.

28. The method of claim **27**, wherein the first dose and subsequent doses are each from about 6 mg/kg to about 12 mg/kg.

29. The method of claim **24**, wherein from about two to about ten subsequent doses of the antibody are administered to the patient.

30. The method of claim **24**, wherein the subsequent doses are separated in time from each other by at least about three weeks.

31. The method of claim **24**, wherein the two or more subsequent doses are each from about 2 mg/kg to about 16 mg/kg.

32. The method of claim **24**, wherein the two or more subsequent doses are each from about 4 mg/kg to about 12 mg/kg.

33. The method of claim **24**, wherein the two or more subsequent doses are each from about 6 mg/kg to about 12 mg/kg.

* * * * *

EXHIBIT 2

US007371379B2

(12) **United States Patent**
Baughman et al.

(10) **Patent No.: US 7,371,379 B2**
(45) **Date of Patent: May 13, 2008**

(54) **DOSAGES FOR TREATMENT WITH ANTI-ERBB2 ANTIBODIES**

(75) Inventors: **Sharon A. Baughman**, Ventura, CA (US); **Steven Shak**, Burlingame, CA (US)

(73) Assignee: **Genentech, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 540 days.

(21) Appl. No.: **10/600,152**

(22) Filed: **Jun. 20, 2003**

(65) **Prior Publication Data**

US 2004/0037824 A1 Feb. 26, 2004

Related U.S. Application Data

(62) Division of application No. 09/648,067, filed on Aug. 25, 2000, now Pat. No. 6,627,196.

(60) Provisional application No. 60/213,822, filed on Jun. 23, 2000, provisional application No. 60/151,018, filed on Aug. 27, 1999.

(51) **Int. Cl.**
A61K 39/395 (2006.01)

(52) **U.S. Cl.** **424/138.1**; 424/130.1; 424/133.1; 424/141.1; 424/142.1; 424/143.1; 424/155.1; 424/156.1; 424/174.1

(58) **Field of Classification Search** 424/130.1, 424/133.1, 138.1, 141.1, 142.1, 143.1, 155.1, 424/156.1, 174.1
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,676,980	A	6/1987	Segal et al.
4,753,894	A	6/1988	Frankel et al.
4,816,567	A	3/1989	Cabilly et al.
4,935,341	A	6/1990	Bargmann et al.
4,943,533	A	7/1990	Mendelsohn et al.
4,968,603	A	11/1990	Slamon et al.
4,975,278	A	12/1990	Senter et al.
5,169,774	A	12/1992	Frankel et al.
5,183,884	A	2/1993	Kraus et al.
5,288,477	A	2/1994	Bacus
5,359,046	A	10/1994	Capon et al.
5,367,060	A	11/1994	Vandlen et al.
5,401,638	A	3/1995	Carney et al.
5,464,751	A	11/1995	Greene et al.
5,480,968	A	1/1996	Kraus et al.
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5,604,107	A	2/1997	Carney et al.
5,641,869	A	6/1997	Vandlen et al.
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5,677,171	A	10/1997	Hudziak et al.
5,705,157	A	1/1998	Greene
5,720,937	A	2/1998	Hudziak et al.
5,720,954	A	2/1998	Hudziak et al.
5,725,856	A	3/1998	Hudziak et al.
5,726,023	A	3/1998	Cheever et al.
5,728,687	A	3/1998	Bissery
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5,776,427	A	7/1998	Thorpe et al.
5,783,186	A	7/1998	Arakawa et al.
5,801,005	A	9/1998	Cheever et al.
5,821,337	A	10/1998	Carter et al.
5,824,311	A	10/1998	Greene et al.
5,834,229	A	11/1998	Vandlen et al.
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5,840,525	A	11/1998	Vandlen et al.
5,846,538	A	12/1998	Cheever et al.
5,856,110	A	1/1999	Vandlen et al.
5,859,206	A	1/1999	Vandlen et al.
5,869,445	A	2/1999	Cheever et al.
5,876,712	A	3/1999	Cheever et al.
5,877,305	A	3/1999	Huston et al.
5,908,835	A	6/1999	Bissery
5,910,486	A	6/1999	Curiel et al.
5,922,845	A	7/1999	Deo et al.
5,939,531	A	8/1999	Wels et al.
5,968,511	A	10/1999	Akita et al.
5,977,322	A	11/1999	Marks et al.
5,985,553	A	11/1999	King et al.
6,015,567	A	1/2000	Hudziak et al.
6,028,059	A	2/2000	Curiel et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0003089	A1	7/1979
EP	0599274	A1	6/1994
EP	616812	A1	9/1994
EP	711565		8/1998
JP	3-240498		10/1991
JP	5-117165		5/1993
JP	5-170667		7/1993
JP	5-213775		8/1993
JP	5-317084		12/1993
JP	95006982	B2	1/1995

(Continued)

OTHER PUBLICATIONS

Seidman, A.D. et al., Seminars in Oncology, 22(5): 108-116, 1995.*
Baselga, J. et al., Proceedings of the American Association for Cancer Research, 35: 380, Abstract #2262, 1994.*
Baselga, J. et al, Breast Cancer Research and Treatment, 32(suppl): p. 30, Abstract #5, 1994.*

(Continued)

Primary Examiner—Alana M. Harris
Assistant Examiner—Anne L. Holleran
(74) *Attorney, Agent, or Firm*—Wendy M. Lee

(57) **ABSTRACT**

The present invention concerns the treatment of disorders characterized by the overexpression of ErbB2. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 with anti-ErbB2 antibody.

40 Claims, 5 Drawing Sheets

-continued

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Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
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Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Val Gly Tyr Ser Leu
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Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
               110                 115
```

The invention claimed is:

1. A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:

administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody; and

administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose, wherein the subsequent doses are separated in time from each other by at least two weeks; and

further comprising administering an effective amount of a chemotherapeutic agent to the patient.

2. The method of claim **1**, wherein the initial dose is at least approximately 6 mg/kg.

3. The method of claim **2**, wherein the initial dose is at least approximately 8 mg/kg.

4. The method of claim **3**, wherein the initial dose is at least approximately 12 mg/kg.

5. The method of claim **1**, wherein the subsequent doses are separated in time from each other by at least three weeks.

6. The method of claim **1**, wherein the initial dose is administered by intravenous injection, and wherein at least one subsequent dose is administered by subcutaneous injection.

7. The method of claim **1**, wherein the initial dose is administered by intravenous injection, wherein at least two subsequent doses are administered, and wherein each subsequent dose is administered by a method selected from the group consisting of intravenous injection and subcutaneous injection.

8. The method of claim **1**, wherein the initial dose and at least one subsequent dose are administered by subcutaneous injection.

9. The method of claim **1**, wherein the initial dose is selected from the group consisting of approximately 6 mg/kg, 8 mg/kg, or 12 mg/kg, wherein the plurality of subsequent doses are at least approximately 2 mg/kg.

10. The method of claim **9**, wherein the plurality of subsequent doses are separated in time from each other by at least three weeks.

11. The method of claim **10**, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 6 mg/kg.

12. The method of claim **10**, wherein the initial dose is approximately 12 mg/kg, and wherein at least one subsequent dose is approximately 6 mg/kg.

13. The method of claim **9**, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 8 mg/kg.

14. The method of claim **9**, wherein the initial dose is approximately 8 mg/kg, wherein at least one subsequent dose is 8 mg/kg, and wherein administration of the initial dose and subsequent doses are separated in time by at least 2 weeks.

15. The method of claim **14**, wherein the initial dose and subsequent doses are separated in time by at least 3 weeks.

16. The method of claim **1**, wherein said cancer is selected from the group consisting of breast cancer, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer.

17. The method of claim **16**, wherein said cancer is breast cancer.

EXHIBIT 3

US010160811B2

(12) **United States Patent**
Baughman et al.

(10) **Patent No.: US 10,160,811 B2**
(45) **Date of Patent: *Dec. 25, 2018**

(54) **TREATMENT WITH ANTI-ERBB2 ANTIBODIES**

(71) Applicant: **GENENTECH, INC.**, South San Francisco, CA (US)

(72) Inventors: **Sharon A. Baughman**, Ventura, CA (US); **Steven Shak**, Burlingame, CA (US)

(73) Assignee: **Genentech, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 843 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/073,659**

(22) Filed: **Nov. 6, 2013**

(65) **Prior Publication Data**

US 2014/0079692 A1 Mar. 20, 2014

Related U.S. Application Data

(60) Continuation of application No. 13/415,271, filed on Mar. 8, 2012, now abandoned, which is a continuation of application No. 13/167,599, filed on Jun. 23, 2011, now abandoned, which is a continuation of application No. 11/443,943, filed on May 31, 2006, now abandoned, which is a division of application No. 10/600,152, filed on Jun. 20, 2003, now Pat. No. 7,371,379, which is a division of application No. 09/648,067, filed on Aug. 25, 2000, now Pat. No. 6,627,196.

(60) Provisional application No. 60/213,822, filed on Jun. 23, 2000, provisional application No. 60/151,018, filed on Aug. 27, 1999.

(51) **Int. Cl.**

C07K 16/30	(2006.01)
A61K 39/395	(2006.01)
C07K 16/32	(2006.01)
A61K 45/06	(2006.01)
A61K 31/337	(2006.01)
A61K 39/00	(2006.01)
A61K 38/00	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 16/30*** (2013.01); ***A61K 31/337*** (2013.01); ***A61K 39/395*** (2013.01); ***A61K 39/39558*** (2013.01); ***A61K 45/06*** (2013.01); ***C07K 16/32*** (2013.01); *A61K 38/00* (2013.01); *A61K 2039/505* (2013.01); *A61K 2039/54* (2013.01); *A61K 2039/545* (2013.01)

(58) **Field of Classification Search**

CPC A61K 47/48384

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,676,980	A	6/1987	Segal et al.
4,753,894	A	6/1988	Frankel et al.
4,816,567	A	3/1989	Cabilly et al.
4,935,341	A	6/1990	Bargmann et al.
4,943,533	A	7/1990	Mendelsohn et al.
4,968,603	A	11/1990	Slamon et al.
4,975,278	A	12/1990	Senter et al.
5,169,774	A	12/1992	Frankel et al.
5,183,884	A	2/1993	Kraus et al.
5,288,477	A	2/1994	Bacus
5,359,046	A	10/1994	Capon et al.
5,367,060	A	11/1994	Vandlen et al.
5,401,638	A	3/1995	Carney et al.
5,464,751	A	11/1995	Greene et al.
5,480,968	A	1/1996	Kraus et al.
5,578,482	A	11/1996	Lippman et al.
5,604,107	A	2/1997	Carney et al.
5,641,869	A	6/1997	Vandlen et al.
5,663,144	A	9/1997	Greene et al.
5,677,171	A	10/1997	Hudziak et al.
5,705,157	A	1/1998	Greene
5,720,937	A	2/1998	Hudziak et al.
5,720,954	A	2/1998	Hudziak et al.
5,725,856	A	3/1998	Hudziak et al.
5,726,023	A	3/1998	Cheever et al.
5,728,687	A	3/1998	Bissery
5,747,261	A	5/1998	King et al.
5,770,195	A	6/1998	Hudziak et al.
5,772,997	A	6/1998	Hudziak et al.
5,776,427	A	7/1998	Thorpe et al.
5,783,186	A	7/1998	Arakawa et al.
5,801,005	A	9/1998	Cheever et al.
5,821,337	A	10/1998	Carter et al.
5,824,311	A	10/1998	Greene et al.
5,834,229	A	11/1998	Vandlen et al.
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5,837,523	A	11/1998	Greene et al.
5,840,525	A	11/1998	Vandlen et al.
5,846,538	A	12/1998	Cheever et al.
5,856,110	A	1/1999	Vandlen et al.
5,859,206	A	1/1999	Vandlen et al.
5,869,445	A	2/1999	Cheever et al.
5,876,712	A	3/1999	Cheever et al.
5,877,305	A	3/1999	Huston et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0003089	A1	7/1979
EP	0 599 274	A1	6/1994

(Continued)

OTHER PUBLICATIONS

Krop, I.E., et al. J. Clin. Oncol., 28: 2698-2704, 2010.*

(Continued)

Primary Examiner — Ilia I Ouspenski

(74) *Attorney, Agent, or Firm* — Diane L. Marschang; Ginger R. Dreger

(57) **ABSTRACT**

The present invention concerns dosages for treatment of human cancer patients with an anti-Epidermal Growth Factor Receptor (EGFR) antibody.

12 Claims, 5 Drawing Sheets

Specification includes a Sequence Listing.

needle). At least one active agent in the composition is an anti-ErbB2 antibody. The label on, or associated with, the container indicates that the composition is used for treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes. In addition, the article of manufacture may comprise a package inserts with instructions for use, including, e.g., a warning that the composition is not to be used in combination with anthacycline-type chemotherapeutic agent, e.g. doxorubicin or epirubicin.

Deposit of Materials

The following hybridoma cell lines have been deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Md., USA (ATCC):

Antibody Designation	ATCC No.	Deposit Date
7C2	ATCC HB-12215	Oct. 17, 1996
7F3	ATCC HB-12216	Oct. 17, 1996
4D5	ATCC CRL 10463	May 24, 1990
2C4	ATCC HB-12697	Apr. 8, 1999

Further details of the invention are illustrated by the following non-limiting Examples.

EXAMPLES

Example 1: Preparation and Efficacy of HERCEPTIN® Anti-ErbB2 Antibody

Materials and Methods

Anti-ErbB2 Monoclonal Antibody

The anti-ErbB2 $IgG_1\kappa$ murine monoclonal antibody 4D5, specific for the extracellular domain of ErbB2, was produced as described in Fendly et al., *Cancer Research* 5o:1550-1558 (1990) and WO89/06692. Briefly, NIH 3T3/HER2-3_{400} cells (expressing approximately 1×10^5 ErbB2 molecules/cell) produced as described in Hudziak, et al., *Proc. Natl. Acad. Sci.* (*USA*) 84:7159 (1987) were harvested with phosphate buffered saline (PBS) containing 25 mM EDTA and used to immunize BALB/c mice. The mice were given injections i.p. of 10^7 cells in 0.5 ml PBS on weeks, 0, 2, 5 and 7. The mice with antisera that immunoprecipitated ^{32}P-labeled ErbB2 were given i.p. injections of a wheat germ agglutinin-Sepharose (WGA) purified ErbB2 membrane extract on weeks 9 and 13. This was followed by an i.v. injection of 0.1 ml of the ErbB2 preparation and the splenocytes were fused with mouse myeloma line X63-Ag8.653. Hybridoma supernatants were screened for ErbB2-binding by ELISA and radioimmunoprecipitation. MOPC-21 (IgG1), (Cappell, Durham, N.C.), was used as an isotype-matched control.

The treatment was performed with a humanized version of the murine 4D5 antibody (HERCEPTIN® anti-ErbB2 antibody). The humanized antibody was engineered by inserting the complementarity determining regions of the murine 4D5 antibody into the framework of a consensus human immunoglobulin IgG_1 (IgG_1) (Carter et al., *Proc. Natl. Acad. Sci. USA* 89:4285-4289 [1992]). The resulting humanized anti-ErbB2 monoclonal antibody has high affinity for $p185^{HER2}$ (Dillohiation constant [K_d]=0.1 nmol/L), markedly inhibits, in vitro and in human xenografts, the growth of breast cancer cells that contain high levels of $p185^{HER2}$, induces antibody-dependent cellular cytotoxicity (ADCC), and has been found clinically active, as a single agent, in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior therapy. HERCEPTIN® anti-ErbB2 antibody is produced by a genetically engineered Chinese Hamster Ovary (CHO) cell line, grown in large scale, that secretes the antibody into the culture medium. The antibody is purified from the CHO culture media using standard chromatographic and filtration methods. Each lot of antibody used in this study was assayed to verify identity, purity, and potency, as well as to meet Food and Drug Administration requirements for sterility and safety.

Eligibility Criteria

Patients had to fulfill all of the following criteria to be eligible for study admission:

- Metastatic breast cancer
- Overexpression of the ErbB2 (HER2) oncogene (2+ to 3+ as determined by immunohistochemistry or fluorescence in situ hybridization (FISH). [Tumor expression of ErbB2 can be determined by immunohistochemical analysis, as previously described (Slamon et al., [1987] and [1989], supra), of a set of thin sections prepared from the patient's paraffin-archived tumor blocks. The primary detecting antibody used is murine 4D5 MAb, which has the same CDRs as the humanized antibody used for the treatment. Tumors are considered to overexpress ErbB2 if at least 25% of tumor cells exhibit characteristic membrane staining for $p185^{HER2}$].
- Bidimensionally measurable disease (including lytic bone lesions) by radiographic means, physical examination, or photographs

Measurable disease was defined as any mass reproducibly measurable in two perpendicular diameters by physical examination, X-ray (plain films), computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound, or photographs.

Osteoblastic metastases, pleural effusions, or ascites were not considered to be measurable. Measurable lesions must be at least 1 cm in greatest dimension. Enumeration of evaluable sites of metastatic disease and number of lesions in an evaluable site (e.g. lung) had to be recorded on the appropriate Case Report Form (CRF). If a large number of pulmonary or hepatic lesions were present, the six largest lesions per site were followed.

- The ability to understand and willingness to sign a written informed consent form
- Women ≤18 years
- Suitable candidates for receiving concomitant cytotoxic chemotherapy as evidenced by screening laboratory assessments of hematologic, renal, hepatic, and metabolic functions.

Exclusion Criteria

Patients with any of the following were excluded from study entry:

- Prior cytotoxic chemotherapy for metastatic breast cancer
- Patients may have received prior hormonal therapy (e.g. tamoxifen) for metastatic disease or cytotoxic therapy in the adjuvant setting.
- Concomitant malignancy that has not been curatively treated
- A performance status of <60% on the Karnofsky scale
- Pregnant or nursing women; women of childbearing potential, unless using effective contraception as determined by the investigator

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The invention claimed is:

1. A method for the treatment of a human patient diagnosed with breast cancer characterized by 2+ or 3+ overexpression of ErbB2 receptor as determined by immunohistochemistry or fluorescence in situ hybridization (FISH), comprising the steps of administering to the patient an initial dose of 8 mg/kg of anti-ErbB2 huMAb 4D5-8 antibody; and administering to the patient a plurality of subsequent doses of 6 mg/kg of the antibody, wherein all doses are separated in time from each other by three weeks.

2. The method of claim **1**, further comprising administering an effective amount of a chemotherapeutic agent.

3. The method of claim **2**, wherein said chemotherapeutic agent is a taxoid.

4. The method of claim **3**, wherein said taxoid is paclitaxel or docetaxel.

5. The method of claim **4** wherein said taxoid is paclitaxel.

6. The method of claim **1**, wherein said antibody is administered by intravenous injection.

7. A method for the treatment of a human patient diagnosed with breast cancer characterized by 2+ or 3+ overexpression of ErbB2 receptor as determined by immunohistochemistry or fluorescence in situ hybridization (FISH), the method comprising: administering intravenously to the patient an initial dose of 8 mg/kg of anti-ErbB2 huMAb 4D5-8 antibody; and administering intravenously to the patient a plurality of subsequent 6 mg/kg doses of the antibody, wherein the initial dose is separated in time from the first subsequent dose by three weeks, and the subsequent doses are separated from each other in time by three weeks.

8. The method of claim **7**, wherein the intravenous administration is an intravenous infusion.

9. The method of claim **8**, wherein the subsequent doses maintain a trough serum concentration of the anti-ErbB2 huMAb 4D5-8 antibody at or above 10 μg/mL.

10. The method of claim **8**, wherein the subsequent doses maintain a trough serum concentration of the anti-ErbB2 huMAb 4D5-8 antibody at or above 20 μg/mL.

11. The method of claim **7**, wherein the subsequent doses maintain a trough serum concentration of the anti-ErbB2 huMAb 4D5-8 antibody at or above 10 μg/mL.

12. The method of claim **7**, wherein the subsequent doses maintain a trough serum concentration of the anti-ErbB2 huMAb 4D5-8 antibody at or above 20 μg/mL.

* * * * *

EXHIBIT 4

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EXHIBIT 5

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 6

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 7

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Herceptin safely and effectively. See full prescribing information for Herceptin.

HERCEPTIN® (trastuzumab) for injection, for intravenous use
Initial U.S. Approval: 1998

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

See full prescribing information for complete boxed warning

Cardiomyopathy: Herceptin can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy. (2.3, 5.1)

Infusion Reactions, Pulmonary Toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

Embryo-Fetal Toxicity: Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.3)

----------INDICATIONS AND USAGE----------

Herceptin is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer. (1.1, 1.2)
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. (1.3)

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin (1, 2.1).

----------DOSAGE AND ADMINISTRATION----------

For intravenous (IV) infusion only. Do not administer as an IV push or bolus. (2.2)

Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine. (2.2)

Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1, 2.1)

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.2)

Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Herceptin, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy, or
- Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks.

Metastatic HER2-Overexpressing Breast Cancer (2.2)

- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.

Metastatic HER2-Overexpressing Gastric Cancer (2.2)

- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

----------DOSAGE FORMS AND STRENGTHS----------

- For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution
- For Injection: 420 mg lyophilized powder in a multiple-dose vial for reconstitution

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Exacerbation of Chemotherapy-Induced Neutropenia. (5.5, 6.1)

----------ADVERSE REACTIONS----------

Adjuvant Breast Cancer

- Most common adverse reactions (≥5%) are headache, diarrhea, nausea, and chills. (6.1)

Metastatic Breast Cancer

- Most common adverse reactions (≥ 10%) are fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash. (6.1)

Metastatic Gastric Cancer

- Most common adverse reactions (≥10%) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of Herceptin (8.3).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING – CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

1 INDICATIONS AND USAGE
- 1.1 Adjuvant Breast Cancer
- 1.2 Metastatic Breast Cancer
- 1.3 Metastatic Gastric Cancer

2 DOSAGE AND ADMINISTRATION
- 2.1 Patient Selection
- 2.2 Recommended Doses and Schedules
- 2.3 Important Dosing Considerations
- 2.4 Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Cardiomyopathy
- 5.2 Infusion Reactions
- 5.3 Embryo-Fetal Toxicity
- 5.4 Pulmonary Toxicity
- 5.5 Exacerbation of Chemotherapy-Induced Neutropenia

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity
- 6.3 Post-Marketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Adjuvant Breast Cancer
- 14.2 Metastatic Breast Cancer
- 14.3 Metastatic Gastric Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING
- 16.1 How Supplied
- 16.2 Stability and Storage

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

Cardiomyopathy

Herceptin administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving Herceptin with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and withhold Herceptin in patients with metastatic disease for clinically significant decrease in left ventricular function *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

Infusion Reactions; Pulmonary Toxicity

Herceptin administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of Herceptin administration. Interrupt Herceptin infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome *[see Warnings and Precautions (5.2, 5.4)]*.

Embryo-Fetal Toxicity

Exposure to Herceptin during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*.

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature *[see Clinical Studies (14.1)]*) breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

1.2 Metastatic Breast Cancer

Herceptin is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

1.3 Metastatic Gastric Cancer

Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens *[see Indications and Usage (1) and Clinical Studies (14)]*. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

2.2 Recommended Doses and Schedules

- **Do not administer as an intravenous push or bolus. Do not mix Herceptin with other drugs.**
- **Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine.**

Adjuvant Treatment, Breast Cancer

Administer according to one of the following doses and schedules for a total of 52 weeks of Herceptin therapy:

During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

- Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens:

- Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
- Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks *[see Dosage and Administration (2.3)]*.
- Extending adjuvant treatment beyond one year is not recommended *[see Adverse Reactions (6.1)]*.

Metastatic Treatment, Breast Cancer

- Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as a 90-minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30-minute intravenous infusions until disease progression.

Metastatic Gastric Cancer

- Administer Herceptin at an initial dose of 8 mg/kg as a 90-minute intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks until disease progression *[see Dosage and Administration (2.3)]*.

2.3 Important Dosing Considerations

If the patient has missed a dose of Herceptin by one week or less, then the usual maintenance dose (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent Herceptin maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of Herceptin by more than one week, a re-loading dose of Herceptin should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) as soon as possible. Subsequent Herceptin maintenance doses (weekly schedule: 2 mg/kg; three-weekly schedule 6 mg/kg) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

Infusion Reactions

[See Boxed Warning, Warnings and Precautions (5.2)]

- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Discontinue Herceptin for severe or life-threatening infusion reactions.

Cardiomyopathy

[See Boxed Warning, Warnings and Precautions (5.1)]

Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin and at regular intervals during treatment. Withhold Herceptin dosing for at least 4 weeks for either of the following:

- ≥ 16% absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.

Herceptin may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤ 15%.

Permanently discontinue Herceptin for a persistent (> 8 weeks) LVEF decline or for suspension of Herceptin dosing on more than 3 occasions for cardiomyopathy.

2.4 Preparation for Administration

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not ado-trastuzumab emtansine.

<u>420 mg Multiple-dose vial</u>

Reconstitution

Reconstitute each 420 mg vial of Herceptin with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multiple-dose solution containing 21 mg/mL trastuzumab that delivers 20 mL (420 mg trastuzumab). In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized powder of Herceptin, which has a cake-like appearance. The stream of diluent should be directed into the cake. The reconstituted vial yields a solution for multiple-dose use, containing 21 mg/mL trastuzumab.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE**.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.

Table 4 (cont'd)

Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent[a] n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC[b] n = 143	AC[b] Alone n = 135
Digestive					
Nausea	33%	51%	9%	76%	77%
Diarrhea	25%	45%	29%	45%	26%
Vomiting	23%	37%	28%	53%	49%
Nausea and vomiting	8%	14%	11%	18%	9%
Anorexia	14%	24%	16%	31%	26%
Heme & Lymphatic					
Anemia	4%	14%	9%	36%	26%
Leukopenia	3%	24%	17%	52%	34%
Metabolic					
Peripheral edema	10%	22%	20%	20%	17%
Edema	8%	10%	8%	11%	5%
Musculoskeletal					
Bone pain	7%	24%	18%	7%	7%
Arthralgia	6%	37%	21%	8%	9%
Nervous					
Insomnia	14%	25%	13%	29%	15%
Dizziness	13%	22%	24%	24%	18%
Paresthesia	9%	48%	39%	17%	11%
Depression	6%	12%	13%	20%	12%
Peripheral neuritis	2%	23%	16%	2%	2%
Neuropathy	1%	13%	5%	4%	4%
Respiratory					
Cough increased	26%	41%	22%	43%	29%
Dyspnea	22%	27%	26%	42%	25%
Rhinitis	14%	22%	5%	22%	16%
Pharyngitis	12%	22%	14%	30%	18%
Sinusitis	9%	21%	7%	13%	6%
Skin					
Rash	18%	38%	18%	27%	17%
Herpes simplex	2%	12%	3%	7%	9%
Acne	2%	11%	3%	3%	< 1%
Urogenital					
Urinary tract infection	5%	18%	14%	13%	7%

[a] Data for Herceptin single agent were from 4 studies, including 213 patients from Study 6.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

Metastatic Gastric Cancer

The data below are based on the exposure of 294 patients to Herceptin in combination with a fluoropyrimidine (capecitabine or 5-FU) and cisplatin (Study 7). In the Herceptin plus chemotherapy arm, the initial dose of Herceptin 8 mg/kg was administered on Day 1 (prior to

chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was administered at 80 mg/m^2 on Day 1 and the fluoropyrimidine was administered as either capecitabine 1000 mg/m^2 orally twice a day on Days 1–14 or 5-fluorouracil 800 mg/m^2/day as a continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin infusions administered was eight.

Table 5

Study 7: Per Patient Incidence of Adverse Reactions of All Grades (Incidence ≥ 5% between Arms) or Grade 3/4 (Incidence > 1% between Arms) and Higher Incidence in Herceptin Arm

	Herceptin + FC (N = 294) N (%)		FC (N = 290) N (%)	
Body System/Adverse Event	All Grades	Grades 3/4	All Grades	Grades 3/4
Investigations				
Neutropenia	230 (78)	101 (34)	212 (73)	83 (29)
Hypokalemia	83 (28)	28 (10)	69 (24)	16 (6)
Anemia	81 (28)	36 (12)	61 (21)	30 (10)
Thrombocytopenia	47 (16)	14 (5)	33 (11)	8 (3)
Blood and Lymphatic System Disorders				
Febrile Neutropenia	—	15 (5)	—	8 (3)
Gastrointestinal Disorders				
Diarrhea	109 (37)	27 (9)	80 (28)	11 (4)
Stomatitis	72 (24)	2 (1)	43 (15)	6 (2)
Dysphagia	19 (6)	7 (2)	10 (3)	1 (≤ 1)
Body as a Whole				
Fatigue	102 (35)	12 (4)	82 (28)	7 (2)
Fever	54 (18)	3 (1)	36 (12)	0 (0)
Mucosal Inflammation	37 (13)	6 (2)	18 (6)	2 (1)
Chills	23 (8)	1 (≤1)	0 (0)	0 (0)
Metabolism and Nutrition Disorders				
Weight Decrease	69 (23)	6 (2)	40 (14)	7 (2)
Infections and Infestations				
Upper Respiratory Tract Infections	56 (19)	0 (0)	29 (10)	0 (0)
Nasopharyngitis	37 (13)	0 (0)	17 (6)	0 (0)
Renal and Urinary Disorders				
Renal Failure and Impairment	53 (18)	8 (3)	42 (15)	5 (2)
Nervous System Disorders				
Dysgeusia	28 (10)	0 (0)	14 (5)	0 (0)

EXHIBIT 8

FDA Approves Amgen And Allergan's KANJINTI™ (trastuzumab-anns), A Biosimilar To Herceptin® (trastuzumab)

Approval Based on Totality of Evidence Demonstrating KANJINTI is Biosimilar to Herceptin

Third FDA Approval From Amgen's Biosimilars Portfolio

THOUSAND OAKS, Calif., June 13, 2019 /PRNewswire/ -- Amgen (NASDAQ:AMGN) and Allergan plc (NYSE:AGN) today announced that the U.S. Food and Drug Administration (FDA) has approved KANJINTI™ (trastuzumab-anns) for all approved indications of the reference product, Herceptin® (trastuzumab): for the treatment of HER2-overexpressing adjuvant and metastatic breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

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"The FDA approval of KANJINTI is an important milestone for our biosimilars portfolio, providing an additional treatment option for patients across three types of cancer," said David M. Reese, M.D., executive vice president of Research and Development at Amgen. "KANJINTI is the third biosimilar from our portfolio to receive FDA approval, highlighting our long-term commitment to providing patients with serious illnesses access to high-quality biological therapies."

KANJINTI was proven to be highly similar to, and to have no clinically meaningful differences from, Herceptin based on a comprehensive totality of evidence which included extensive comparative analytical, pharmacokinetic and clinical data. At the time of approval, KANJINTI is the only trastuzumab biosimilar to incorporate the evaluation of a single transition in the clinical study, demonstrating similar safety and immunogenicity in patients who were previously on Herceptin.

"KANJINTI is the second of four biosimilars from Amgen and Allergan's collaboration to be approved by the FDA," said David Nicholson, chief research and development officer at Allergan. "We are proud of the progress being made as we continuously strive to develop and deliver high-quality cancer therapies in collaboration with Amgen."

Amgen has a total of 10 biosimilars in its portfolio, three of which have been approved in the U.S. and three that are approved in the European Union (EU).

About KANJINTI™ (trastuzumab-anns) in the U.S.
KANJINTI is a biosimilar to trastuzumab, a recombinant DNA-derived humanized monoclonal immunoglobulin G1 kappa antibody. The active ingredient of KANJINTI is a humanized monoclonal antibody that has the same amino acid sequence, structure and function as trastuzumab. KANJINTI has the same pharmaceutical dosage form and same strength after reconstitution as trastuzumab.

KANJINTI is currently not available commercially. This is not an

EXHIBIT 9

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 10

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EXHIBIT 11

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EXHIBIT 14

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EXHIBIT 15A

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EXHIBIT 15B

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EXHIBIT 20

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 21

Trials@uspto.gov
Tel: 571-272-7822

Paper No. 68
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01139
Patent 6,627,196 B1

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

YANG, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

ORDERS
Granting Petitioner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying-in-Part and Dismissing-in-Part Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Reasonable Expectation of Success

Claims 24, 25, 29, and 30 do not recite either the first or any subsequent dosage amount of trastuzumab. In addition, claims 26 and 31 recite the first dose and subsequent doses "are each from about 2 mg/kg to about 16 mg/kg." As explained above, we find an ordinary artisan would have been motivated to modify the dosing frequency of trastuzumab as claimed. In addition, both Slamon and Herceptin Product Label teach the loading dose of 4 mg/kg and the maintenance doses of 2 mg/kg. Ex. 1005, 5; Ex. 1008, 2. Even so, we find Petitioner has not established by a preponderance of the evidence that claims 24–26 and 29–31 of the '196 patent are unpatentable. This is because Petitioner's analysis of these claims hinges on the same argument of 8 mg/kg loading dose and 6 mg/kg maintenance doses Petitioner asserts in the other claims. For example, the substantive analysis of claim 24, in its entirety, appears in a single paragraph:

> As discussed above with respect to claim 1, it would have been obvious to administer trastuzumab on an every-three-week regimen as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses. *See also* Ex. 1003 at ¶¶ 89–112. This regimen would have satisfied each and every element of claim 24 of the '196 patent, and therefore claim 24 is obvious for the same reasons as set forth with respect to claim 1. Ex. 1003 at ¶¶ 89–112, 115–118.

Pet. 43.

For claim 1, Petitioner analyzes the reasonable expectation of success with respect to efficacy based on an 8 mg/kg loading dose and 6 mg/kg maintenance doses. Pet. 32–38, 42. Because Petitioner has not met its burden to show that an ordinary artisan would have been motivated to modify the dosage amount in the first instance, its reasonable-expectation-

of-success arguments, premised upon efficacy associated with administering those modified dosage amounts over the every-three-week dosing frequency, also fail.

As a result, we conclude that Petitioner has not established by a preponderance of the evidence that claims 24–26 and 29–31 of the '196 patent are unpatentable.

Motions to Exclude

Petitioner's Motion to Exclude

Petitioner filed a Motion to Exclude Exhibits 2004, 2039, 2041, 2061, 2062, and 2067. Paper 51. Patent Owner does not oppose. Paper 55.

Petitioner's Motion to Exclude is granted.

Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1100, 1102, 1105, 1107, 1111, 1121, 1124, 1125, 1126, 1128, and 1130, as well as paragraphs 22, 29, 35–37, 44, 53–58, and 60–73 of Exhibit 1123, i.e., the Reply Declaration of Dr. Ratain. Paper 53. Patent Owner filed an Identification of Improper New Reply Materials, challenging the same exhibits. Paper 52.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[8] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization to file a

[8] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

EXHIBIT 22

Trials@uspto.gov
571-272-7822

Paper No. 83
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00804[1]
Patent 6,627,196 B1

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

PAULRAJ, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

[1] Case IPR2017-01958 has been joined with IPR2017-00804

below the linearity assumed in Dr. Jusko's model. Moreover, unlike Dr. Jusko's "one-compartment" analysis in this proceeding, Koizumi specifically describes a "multicompartmental" analysis conducted using a computer simulation. Ex. 1054, 1247. In this regard, Koizumi notes that "[i]nitial model solutions assumed that the model was linear," but "[u]sing this information it was not possible to fit the data observed for the patients with the model simulations." *Id.* at 1245–46. Furthermore, according to Koizumi:

> [C]ompartmental analysis also raises several problems. If the compartmental model is based upon unlikely assumptions, or inadequately validated, then misleading information follows. While this is self-evident, the complexity of a model addressing the pharmacokinetics of a MAb requires simplifications based upon assumptions in order to permit realistic mathematical handling. These simplifications and assumptions are particularly vulnerable to error in a system such as MAb, wherein many processes remain to be clarified.

Id. at 1252. As such, Koizumi underscores the inherent uncertainty associated with using mathematical models to predict the pharmacokinetic behavior of antibodies.

In sum, for the foregoing reasons, we determine Petitioners have not established the reasonable expectation of success required for obviousness. In reaching this conclusion, we are cognizant that "[c]onclusive proof of efficacy is not required to show obviousness." *Hoffman-La Roche*, 748 F.3d at 1331. Nonetheless, the Federal Circuit has also indicated that reasonable expectation cannot come from a mere "hypothesis" that might form the basis for further testing. *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 647–49 (Fed. Cir. 2017) (finding prior art reference that stated the "expected" benefit of a

clinical trial did not establish a reasonable expectation of success); *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

III. ALLEGED IMPROPER REPLY MATERIALS/PATENT OWNER'S MOTION TO EXCLUDE

Pursuant to our authorization, Patent Owner filed a paper identifying allegedly improper arguments and evidence included with Petitioners' Reply. Paper 67. Specifically, Patent Owner identifies the following materials as improper: Exhibits 1043–1048, 1050, 1052, 1054, and 1055, and portions of Dr. Lipton's reply declaration (Ex. 1056) and Dr. Jusko's reply declaration (Ex. 1057) referencing those exhibits. *Id.* Patent Owner also separately filed a motion to exclude the same evidence it identifies as improper reply materials. Paper 68.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[10] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization

[10] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

EXHIBIT 23

Trials@uspto.gov
571-272-7822

Paper No. 83
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00805[1]
Patent 7,371,379 B2

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

PAULRAJ, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

[1] Case IPR2017-01959 has been joined with IPR2017-00805.

I. INTRODUCTION

Hospira, Inc. ("Hospira") filed a Petition (Paper 1, "Pet."), requesting institution of an *inter partes* review of claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of U.S. Patent No. 7,371,379 B2 (Ex. 1001, "the '379 patent"). Genentech, Inc. timely filed a Patent Owner Preliminary Response (Paper 6, "Prelim. Resp."). We determined, based on the information presented in the Petition and Preliminary Response, that there was a reasonable likelihood that Hospira would prevail in challenging claims 1–3, 5, 7, 9–11, 16–28, and 30–40 as unpatentable under 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, the Board instituted trial on July 27, 2017, as to those claims of the '379 patent. Paper 13 ("Institution Decision" or "Inst. Dec."). Following our institution based on Hospira's Petition, Samsung Bioepis Co., Ltd. ("Samsung") filed a substantially identical Petition challenging the same claims of the '379 patent and requested joinder in this proceeding, which we granted. Paper 40. Thus, Hospira and Samsung together are the "Petitioners" in this proceeding.

Patent Owner filed its Response to the Petition (Paper 42, "PO Resp.") and Petitioners filed a Reply to Patent Owner's Response (Paper 56, "Reply"). Patent Owner filed a Motion to Exclude certain evidence (Paper 64), to which Petitioners filed an Opposition (Paper 69) and Patent Owner filed a Reply in support thereof (Paper 73). Patent Owner also filed a Motion for Observations on Cross-Examination of Petitioners' Reply Declarants (Drs. Allan Lipton and William Jusko) (Paper 65) to which Petitioners filed a Response (Paper 70). Additionally, pursuant to our authorization, Patent Owner filed an Identification of Improper New Reply Materials (Paper 68), to which Petitioners filed a Response (Paper 72) and

Patent Owner filed a Reply (Paper 74). An oral hearing was held on May 8, 2018. The transcript of the hearing has been entered into the record. Paper 80 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Based on the record before us, we conclude that Petitioners have *not* demonstrated by a preponderance of the evidence that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 patent are unpatentable.

A. Related Proceedings

As a related matter, Petitioners and Patent Owner identify a concurrently-filed petition for *inter partes* review (IPR2017-00804) for a related patent, U.S. Patent 6,627,196 ("the '196 patent"). *See* Pet. 2. We issue our Final Written Decision in IPR2017-00804 concurrently with this decision. Additionally, also concurrently with this Decision, we issue Final Written Decisions in two other *inter partes* review proceedings concerning the '196 and '379 patents brought by another petitioner. IPR2017-01139; IPR2017-001140.

The parties also identify litigation matters pending in the U.S. District Courts for the Northern District of California and the District of Delaware and on appeal before the Federal Circuit Court of Appeals concerning the '379 and '196 patents, as well as foreign proceedings concerning counterparts to these patents, as related matters. Paper 81; Paper 82.

B. The '379 Patent (Ex. 1001)

The '379 patent issued on May 13, 2008, with Sharon A. Baughman and Steven Shak as the listed co-inventors. Ex. 1001, (45), (75). The '379 patent claims priority as the divisional of an application filed August 25,

2000, as well as to provisional applications filed June 23, 2000, and August 27, 1999. *Id.* at (22), (60). The parties have not disputed the claimed priority date for the '379 patent.

The '379 patent relates generally to dosages for the treatment of disorders characterized by the overexpression of ErbB2 (also known as HER2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR). *Id.* at 1:15–25, 44–50. The overexpression of ErbB2 has been associated with breast cancer. *Id.* As noted in the '379 patent, a recombinant humanized anti-ErbB2 monoclonal antibody (alternatively referred to as "rhuMab HER2," "trastuzumab," or by its tradename "Herceptin")[2] had been clinically tested and approved for patients with ErbB2-overexpressing metastatic breast cancers who received prior anti-cancer therapy. *Id.* at 3:59–65. The recommended initial "loading dose" for trastuzumab was 4 mg/kg administered as a 90-minute infusion, and the recommended weekly "maintenance dose" was 2 mg/kg, which could be administered as a 30-minute infusion if the initial loading dose was well-tolerated. *Id.* at 3:66–4:3.

The invention described in the '379 patent "concerns the discovery that an early attainment of an efficacious target trough serum concentration by providing an initial dose or doses of anti-ErbB2 antibodies, followed by subsequent doses of equal or smaller amounts of antibody (greater front loading) is more efficacious than conventional treatments." *Id.* at 4:26–31.

[2] For consistency's sake, we will refer to the antibody at issue in this proceeding as trastuzumab unless we are directly quoting one of its alternative names from another document.

The method of treatment, according to the invention described in the patent, "involves administration of an initial dose of anti-ErbB2 antibody of more than approximately 4 mg/kg, preferably more than approximately 5 mg/kg," with the maximum dose not to exceed 50 mg/kg. *Id.* at 4:51–55. "[T]he initial dose or doses is/are followed by subsequent doses of equal or smaller amounts of antibody at intervals sufficiently close to maintain the trough serum concentration of antibody at or above an efficacious target level." *Id.* at 4:65–5:2. Preferably, "the amount of drug administered is sufficient to maintain the target trough serum concentration such that the interval between administration cycles is at least one week," and "the trough serum concentration does not exceed 2500 μg/ml and does not fall below 0.01 μg/ml during treatment." *Id.* at 5:4–9. The patent explains that "[t]he front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment." *Id.* at 5:9–12. As a result, "[t]he efficacious target trough serum concentration is reached in 4 weeks or less . . . and most preferably 1 week or less, including 1 day or less." *Id.* at 4:31–34. Additionally, the patent states that the method of therapy may involve "infrequent dosing" of the anti-ErbB2 antibody, wherein the first and second dose are separated by at least two weeks, and optionally at least about three weeks. *Id.* at 6:23–36.

The '379 patent describes embodiments in which the initial dose of trastuzumab is 6 mg/kg, 8 mg/kg, or 12 mg/kg, followed by subsequent maintenance doses of 6 mg/kg or 8 mg/kg administered once every 2 or 3 weeks, in a manner such that the trough serum concentration is maintained at approximately 10–20 μg/ml during the treatment period. *Id.* at 5:19–43, 45:19–45. The treatment regimen according to the invention may further

comprise administration of chemotherapy along with trastuzumab. *Id.* at 6:6–10, 7:26–32, 46:28–58. Of particular relevance, the '379 patent includes a prophetic example describing the administration of trastuzumab intravenously every three weeks in combination with the chemotherapeutic agent paclitaxel. *Id.* at 46:60–48:32. According to this example, "[s]imulation of the proposed treatment regimen suggests that the trough serum concentrations will be 17 [μ]g/ml, in the range (10–20 [μ]g/ml) of the targeted trough serum concentrations from previous HERCEPTIN® IV clinical trials." *Id.* at 47:1–5. The example sets forth inclusion criteria for a study in which patients will be administered trastuzumab every three weeks. *Id.* at 47:9–48:12. The '379 patent concludes that "[i]t is believed that the above treatment regimen will be effective in treating metastatic breast cancer, despite the infrequency with which HERCEPTIN® is administered to the patient." *Id.* at 48:28–31.

C. Illustrative Claim

Petitioners challenge claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 Patent. Independent claim 1 is illustrative, and is reproduced below:

> 1. A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:
> administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody; and
> administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose, wherein the subsequent doses are separated in time from each other by at least two weeks; and
> further comprising administering an effective amount of a chemotherapeutic agent to the patient.

Ex. 1001, 57:33–46.

D. The Asserted Ground of Unpatentability

Petitioners challenge the patentability of the claims of the '379 Patent based on the following ground:

References	Basis	Claims challenged
Herceptin label,[3] Baselga '96,[4] Pegram '98,[5] and the knowledge of a person of ordinary skill in the art	§ 103(a)	1–3, 5, 7, 9–11, 16–28, and 30–40

Petitioners further rely upon the declarations of Allan Lipton, M.D. (Ex. 1002; Ex. 1056) and William Jusko, Ph.D. (Ex. 1003; Ex. 1057). Patent Owner relies upon the declarations of George Grass, Ph.D. (Ex. 2039) and Karen Gelmon, M.D. (Ex. 2040).

II. ANALYSIS

A. Claim Construction

We interpret claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable construction standard, claim

[3] Genentech, Inc, Herceptin® Trastuzumab, Sept. 1998 (hereinafter "Herceptin Label" (Ex. 1008).
[4] Jose Baselga, *Phase ll Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients With HER2/neu-Overexpressing Metastatic Breast Cancer*, 14 JOURNAL OF CLINICAL ONCOLOGY 737–744 (1996) (hereinafter "Baselga '96") (Ex. 1013).
[5] Mark D. Pegram, *Phase ll Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185^{HER21neu} Monoclonal Antibody Plus Cisplatin in Patients With HER2/neu-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment*, 16 JOURNAL OF CLINICAL ONCOLOGY 2659–71 (1998) (hereinafter "Pegram '98") (Ex. 1014).

terms are generally given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). "Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). "Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioners propose a construction for "ErbB2 receptor." *See* Pet. 24. Patent Owner does not propose any terms to be construed in its post-institution Response. We find that no explicit construction of any claim term is necessary to decide the issues presented in this case. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999))).

B. Level of Skill in the Art

Petitioners contend that a person of ordinary skill in the art for the '379 patent would be a "team" that includes both (1) a clinical or medical oncologist specializing in breast cancer with several years of experience in breast cancer research or clinical trials, and (2) a person with a Ph.D. in pharmaceutical sciences or a closely related field with an emphasis in pharmacokinetics with three years of relevant experience in protein based

drug kinetics. Pet. 23–24 (citing Exs. 1002 ¶ 14; 1003 ¶ 15; 1006 ¶ 32). Patent Owner does not address the requisite level of skill in its Response.

Because it is otherwise undisputed and consistent with the evidence of record, we adopt Petitioners' proposed definition of a person of ordinary skill in the art ("POSITA" or "skilled artisan") for purposes of our analysis. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Patentability Analysis

1. Content of the Prior Art

Petitioners rely upon, *inter alia*, the following prior art teachings to support their challenge.

a. Herceptin Label (Ex. 1008)

As recognized in the '379 patent, trastuzumab was already FDA-approved and commercially sold in the U.S. by 1998 under the tradename Herceptin. Ex. 1001, 3:59–4:3. The Herceptin label teaches:

> The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively. Trastuzumab's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly

> dose studied (500 mg), mean peak serum concentrations were 377 microgram/mL.

Ex. 1008, 1.

The Herceptin label also teaches that "[i]n studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days . . . was observed," and "[b]etween week 16 and 32, Trastuzumab serum concentration reached a steady state with a mean trough and peak concentrations of approximately 79 [mg]/mL and 123 [mg]/mL, respectively. *Id.* The label further describes clinical studies in which metastatic breast cancer patients with certain levels of HER2 overexpression were administered chemotherapy either alone or in combination with trastuzumab given intravenously as a 4 mg/kg loading dose followed by weekly doses at 2 mg/kg. *Id.* The chemotherapy in these clinical studies (e.g., paclitaxel) was administered every 3 weeks (21 days). *Id.*

b. Baselga '96 (Ex. 1013)

Baselga '96 reports the results of a phase II clinical trial in which patients with ErbB2-overexpressing metastatic breast cancer were treated with trastuzumab. Ex. 1013, 737. The pharmacokinetic goal of the trial "was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell grown in the preclinical model." *Id.* at 738. Further, the "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." *Id.*

According to the results reported in Baselga '96, "[m]ore than 90% of the examined population (41 patients) had rhuMAb HER2 trough levels above the targeted 10 μg/mL level. *Id.* at 739. Moreover, the treatment "was remarkably well tolerated." *Id.* "Toxicity [from rhuMAb HER2] was

minimal," and no immune response against the antibody was detected. *Id.* at 737. Out of the 768 times trastuzumab was administered, "only 11 events occurred that were considered to be related to the use of the antibody." *Id.* at 739. Baselga '96 also teaches that in preclinical studies (both *in vitro* and in xenografts), trastuzumab "markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." *Id.* at 743.

c. Pegram '98 (Ex. 1014)

Pegram '98 reports the results of a phase II clinical trial using a combination of trastuzumab plus cisplatin. Ex. 1014, 2659. Pegram '98 states that "[t]hese studies showed that the pharmacokinetics of rhuMAb HER2 were predictable, and that the doses delivered achieved a target trough serum concentration of 10 to 20 μg/mL, which is associated with antitumor activity in preclinical models." *Id.* at 2660. Pegram '98 also reports a toxicity profile of the combination that paralleled the toxicity of cisplatin alone, thereby leading to the conclusion that trastuzumab did not increase toxicity. *Id.* at 2668.

2. Obviousness Based on the Herceptin Label, Baselga '96, Pegram '98, and the Knowledge of a Person of Ordinary Skill in the Art of the Prior Art

Petitioners have provided a claim-by-claim explanation for the basis of their contention that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 are obvious over the Herceptin label in view of Baselga '96, Pegram '98, and the Knowledge of a Person of Ordinary Skill in the Art. Pet. 29–54.

In general terms, the challenged claims are directed to a dosing regimen for the treatment of cancer in which trastuzumab is administered at an initial dose, followed by administration of the antibody at subsequent

doses that are the same or less than the initial dose and separated in time by at least about two weeks. Independent claim 1 specifies an initial dose of approximately 5 mg/kg, while certain dependent claims specify higher initial doses of 6 mg/kg, 8 mg/kg, or 12 mg/kg (e.g., cls. 2, 3, 9), whereas other dependent claims specify that the subsequent doses are separated in time by at least three weeks (e.g., cls. 5, 10). Our obviousness analysis assumes a treatment method in which trastuzumab is administered once every three weeks, as that dosing interval is encompassed by all the challenged claims and is the focus of the parties' arguments and evidence in this proceeding.

Petitioners rely upon the teaching in the Herceptin label that trastuzumab doses of up to 500 mg had been successfully administered to patients. Pet. 31 (citing Ex. 1008, 1). Based on a patient weight range of 55–85 kg, Petitioners calculate that the weight-based dose for the 500 mg absolute dose taught by the Herceptin label ranges from 5.88–9.09 mg/kg. *Id.* at 31–32 (citing Ex. 1002 ¶¶ 55–57; Ex. 1003 ¶ 45; Ex. 1026, 3; Ex. 1027, 334 (Table 7-2)). Petitioners further rely upon the Herceptin label's teaching that trastuzumab doses should be "front-loaded" with a higher initial dose of 4 mg/kg followed by a lower weekly maintenance dose of 2 mg/kg. *Id.* at 33. Additionally, Petitioners rely upon the teaching in the Herceptin label describing the administration of trastuzumab in combination with chemotherapeutic agents, and that these chemotherapeutic agents are administered once every three weeks to patients. *Id.* at 35–36, 43–44. Petitioners further rely upon Baselga '96 and Pegram '98 insofar as they confirm that the weekly dosing regimen encompassed by the Herceptin label was successfully administered to patients in phase II clinical trials, and that

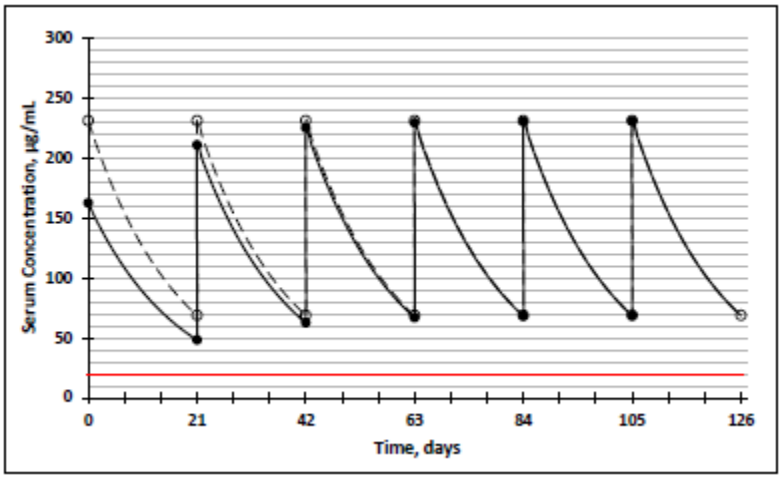
the skilled artisan would have been aware of a target trough serum concentration of 10–20 μg/mL for trastuzumab. Pet. 33, 37.

Petitioners acknowledge that the Herceptin label, along with Baselga '96 and Pegram '98, teach only a *weekly* dosing regimen, but assert that the skilled artisan would nonetheless have been motivated to decrease the frequency of trastuzumab administration to once every three weeks for several reasons. *Id.* at 34–42. First, Petitioners contend that "a skilled artisan would decrease the frequency of injections to improve efficiency, to provide a more convenient dosing regimen—particularly for terminally ill patients—, and to improve patient compliance and quality of life." *Id.* at 34. Second, Petitioners contend that the skilled artisan would have been motivated to apply a tri-weekly (i.e., once every three weeks) regimen for the antibody in order to align with the dosing schedules of the chemotherapy so that a patient would only have to make one trip to the clinic to receive both doses. *Id.* at 36. In support, Petitioners rely upon their oncology expert, Dr. Lipton, who attests that each trip to the clinic to receive even a single infusion of antibody treatment often takes between a half and a full day, which can result in additional time and costs for the patient. Ex. 1002 ¶¶ 42–43.

Petitioners further contend that the skilled artisan would confidently decrease the frequency of injections and use a tri-weekly dosing regimen in view of trastuzumab's known pharmacokinetic properties. *Id.* at 36. Petitioners contend that arriving at the tri-weekly dosing schedule was merely a matter of "routine calculation and optimization" of the therapy outlined in the Herceptin label. *Id.* at 37. In this regard, Petitioners rely upon data from the Herceptin label and Dr. Jusko's opinions to assert that it

would have been a matter of routine calculation for a skilled artisan to determine that a tri-weekly 500 mg trastuzumab dosing regimen would have resulted in a serum concentration well above the target minimum trough concentration of 10–20 µg/mL reported in the prior art. *Id.* at 37–39 (citing Ex. 1003 ¶¶ 46–47, 49–51, 56–58, 62).

Specifically, Dr. Jusko, assuming a "one-compartment" model to approximate drug concentration over time, calculated the initial minimum drug concentration three weeks after first administering a 500 mg antibody dose to a 70 kg patient to be 48.3 µg/mL and the steady-state trough concentration after multiple doses to be 68.7 µg/mL. Ex. 1003 ¶¶ 46–58. Additionally, assuming linear (first-order) kinetics, Dr. Jusko calculated that a 712 mg loading dose followed by 500 mg tri-weekly maintenance doses could be administered to patients while keeping serum drug concentrations within acceptable levels. *Id.* ¶¶ 59–66. Dr. Jusko provides the following graph depicting expected trastuzumab concentrations over time for a 70 kg patient administered 500 mg of trastuzumab every three weeks, with or without an initial 712 mg loading dose (broken and solid lines, respectively):



Ex. 1003 ¶ 62 (Fig. 2). As shown in the figure above, when administering either calculated dosing regimen, Dr. Jusko concludes that the trastuzumab serum concentration would have been expected to stay well above the target minimum trough concentration of 10–20 μg/ml (with 20 μg/ml shown in red). *Id.* ¶ 63.

As noted by Petitioners, Dr. Jusko made three assumptions in performing his calculations: (1) that trastuzumab exhibits non-exponential kinetics; (2) that the initial concentration (C_0) can be estimated by multiplying the dose by the volume of distribution and average mass of a patient; and (3) that the kinetics of trastuzumab remain constant with multiple-dosing. Pet. 42 (citing Ex. 1003 ¶¶ 69–71; Ex. 1028, 91; Ex. 1029, 77).

The two main issues argued in this proceeding are: (a) whether there would have been a motivation to extend the weekly dosing interval taught in the prior art to a tri-weekly dosing interval based on concerns about patient convenience and quality of life, and (b) whether there would have been a reasonable expectation of success in implementing such a dosing regimen based on Dr. Jusko's pharmacokinetic analysis. It is Petitioners' burden to demonstrate both "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (internal citations omitted). As they are distinct legal requirements for obviousness, we address motivation and reasonable expectation of success separately in our analysis. For the reasons explained below, while skilled artisans may have

been motivated to extend the dosing interval, we find that they would not have had a reasonable expectation of success in doing so based on the prior art. Thus, we determine that Petitioners have not shown that the challenged claims are unpatentable for obviousness.

a. Motivation

As discussed above, Petitioners' primary arguments on motivation for extending the dosing interval of trastuzumab from the weekly administration taught in the prior art to tri-weekly is based on a desire to improve patient "convenience," "compliance," "efficiency," and "quality of life." Pet. 34. In its Response, Patent Owner contends these "patient-related" factors would not have served as a reason to extend the dosing interval because the primary focus for skilled artisans in developing a treatment regimen for HER2-positive breast cancer would have been on efficacy. PO Resp. 28–36. Moreover, instead of extending trastuzumab's dosing interval to a tri-weekly schedule, Patent Owner asserts that skilled artisans were actually increasing the frequency of the chemotherapy (paclitaxel) administration in numerous clinical trials so that both drugs could be administered on a weekly schedule. *Id.* at 31–32. Patent Owner also argues that this is not simply a case of selecting an optimal doses from known range of doses in the prior art since the only dosing interval disclosed was weekly. *Id.* at 26. Patent Owner notes that "at the time of the invention, developing an antibody dosing regimen for clinical use was described as a "complicated task" and such drugs "defy easy quantitative description and prediction." *Id.* at 26 (citing Ex. 2004, 11; Ex. 1022, 3:109).

We find that the skilled artisan would have been motivated to extend the dosing interval for the simple (yet compelling) reasons that doing so

would have been more cost-effective and less burdensome for the patient undergoing such treatment, which required in-person visits to the clinic for each antibody infusion. As previously recognized by the Federal Circuit, "[a] relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance." *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014). Patent Owner seeks to limit this statement in *Hoffman-La Roche* to the specific issue addressed in that case, which was whether once-monthly administration of bisphosphonate ibandronate to treat osteoporosis would have been obvious. PO Resp. 38–39. Patent Owner contends that, unlike the facts of *Hoffman-La Roche*, the claimed treatment regimen at issue in this proceeding involves a "first-in-class" therapeutic (i.e., trastuzumab was the only antibody approved at the time for the treatment of "solid" tumors), a fatal disease condition (breast cancer), and a completely different set of prior art. *Id.* at 39. Patent Owner argues that "[c]onvenience considerations that may be applicable in the context of treatments to prevent osteoporosis have little relevance in the context of treating HER2-positive breast cancer." *Id.* at 39. We do not read *Hoffman-La Roche* to stand for a *per se* rule that it would always have been obvious to extend the dosing interval in order to address patient compliance concerns regardless of the particular medical condition or drug at issue. Nonetheless, based on the specific facts of this case, we find that skilled artisans would have been similarly motivated to administer trastuzumab less frequently to treat breast cancer patients.

In support of this finding, we take into account the real-world experiences of the parties' oncology experts, Dr. Lipton (Petitioner's expert) and Dr. Gelmon (Patent Owner's expert), who are both physicians with

extensive experience treating breast cancer patients in clinical settings. Ex. 1002 ¶¶ 4–10; Ex. 2040 ¶¶ 2–5. Dr. Lipton attests that each trip to his clinic to receive even a relatively short infusion of antibody treatment often takes between a half and a full day, which can result in additional time and costs for the patient. Ex. 1002 ¶¶ 42–43. Indeed, some of his patients have had to travel up to one hundred miles each direction to receive treatment at the clinic. *Id.* ¶ 39. As such, we are not persuaded by Dr. Gelmon's contention that efficacy would have taken precedence over convenience as the focus of cancer treatment in the 1990s. Ex. 2040 ¶¶ 30–34. Of course, maintaining efficacy and safety would have been a paramount concern for the skilled artisan seeking to improve upon the weekly dosing regimen that was previously FDA-approved, but that does not mean improving convenience and quality of life for the patient would not have also been motivating concerns. By 1999, efficacy and safety had already been demonstrated for weekly trastuzumab administration as set forth in the Herceptin label. Ex. 1008. Notably, Dr. Gelmon admitted during her deposition that "before 1999 it was known that providing a drug less frequently might provide benefits to certain patients in terms of convenience, cost and quality of life as long as efficacy and safety were shown." Ex. 1058, 328:24-329:7. Indeed, these same concerns factored into Dr. Gelmon's own clinical study involving tri-weekly trastuzumab administration, which took place within months of the '379 patent priority date. *Id.* at 73:19–75:16.[6]

[6] While the publication of Dr. Gelmon's tri-weekly study does not qualify as prior art, we find the fact that she initiated the study so close to the priority date undermines the credibility of her testimony that skilled artisans

Contrary to Patent Owner's arguments, the prior art need not have expressly articulated or suggested patient convenience or quality of life concerns as the motivation to extend the dosing interval. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[T]he [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ."). Nonetheless, the motivation set forth by Dr. Lipton is supported by his citation to prior art articles indicating that quality of life issues for cancer patients have long been a concern to physicians. Ex. 1002 ¶ 44 (citing Coates, et al., *Quality of Life in Oncology Practice: Prognostic Value of EORTC QLQ-C30 Scores in Patients with Advanced Malignanc*y, 33(7) EUROPEAN JOURNAL OF CANCER 1025–30 (1997) (Ex. 1019); Aaronson, et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology*, 85(5) J. NAT'L CANCER INSTITUTE 365–76 (1993) (Ex. 1020); Ferrell, *Quality of Life in Breast Cancer*, 4(6) CANCER PRACTICE 331–40 (1996) (Ex. 1021)).

Additionally, we find that the skilled artisan would have been motivated to match trastuzumab and chemotherapy dosing. As indicated in

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would not have considered extending the dosing interval at the time. In their Reply, however, Petitioners identify additional post-filing evidence supporting their contention that skilled artisans were motivated by "patient-related factors" to investigate tri-weekly dosing of trastuzumab. Reply 14–15. Insofar as these additional references do not qualify as prior art themselves, nor do they purport to recount what was publicly known in the prior art, we decline to give them any weight in our analysis.

the Herceptin label, patients were often prescribed chemotherapy, such as paclitaxel or anthracycline, in combination with trastuzumab. Ex. 1008, 1. The Herceptin label indicates that both paclitaxel and anthracycline were administered once every three weeks (21 days). *Id.* In addition to convenience for the patient, Dr. Lipton notes that "it is also beneficial for the clinic to administer the combined therapies on the same schedule because they only have to prep the patient once." Ex. 1002 ¶ 66. Patent Owner acknowledges that researchers at the time had explored the possibility of administering paclitaxel to match weekly trastuzumab administration. PO Resp. 9; Ex. 2040 ¶¶ 38, 57; *see, e.g.*, M Fornier, *Weekly (W) Herceptin (H) + 1 Hour Taxol (T): Phase II Study in HER2 Overexpressing (H2+) and Non-Overexpressing (H2-) Metastatic Breast Cancer (MBC)*, 18 PROC. AM. SOC'Y CLINICAL ONCOLOGY 126a (Abstract 482) (1999) (Ex. 2029). But, at the time, paclitaxel was FDA-approved for only tri-weekly treatment. Ex. 1058, 180:22–181:1. Regardless, the fact that skilled artisans were considering matching the antibody and chemotherapy treatments on a weekly basis does not mean that they would also not have considered matching the treatments on a tri-weekly basis. Obviousness does not require the claimed regimen to be the only or best choice, nor may a patentee defeat obviousness simply by identifying another alternative. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention.").

Patent Owner also contends that skilled artisans would not have had a reason to select a 500 mg maintenance dose or 712 mg loading dose, as

calculated by Dr. Jusko. PO Resp. 24–27. We are unpersuaded by these arguments because the Herceptin label expressly teaches that a 500 mg dose was considered safe and tolerable, at least when administered on a weekly basis. Dr. Jusko explained that the 500 mg dose level, and associated 12-day half-life, would have been the obvious starting point "because that was the highest reported tolerable weekly dose level with the longest half-life that would give the POSITA the best chance of achieving the minimum serum trough concentrations to establish efficacy at three weeks." Ex. 1057 ¶ 34. Dr. Jusko further notes that "[i]t would have made no sense to choose a lower dose level, as the result of any such simulation would not have been indicative of the feasibility of three-week dosing—a negative result would merely necessitate simulating at the higher dose level, i.e., 500 mg." *Id.* Furthermore, while the 712 mg loading dose is not expressly disclosed in the prior art (Ex. 1003 ¶¶ 59–63), Patent Owner's experts Dr. Grass and Dr. Gelmon do not dispute Dr. Jusko's calculation of this amount, which is based on equations set forth in a basic pharmacokinetics textbook. Ex. 1002 ¶ 72; *see* Rowland, *et al.*, CLINICAL PHARMACOKINETICS: CONCEPTS AND APPLICATIONS (3rd ed. 1995) (vol. 1), at 88 (Ex. 1022) ("Rowland").[7]

[7] Patent Owner also argues that the pharmacokinetic data in the prior art would not have motivated a skilled artisan to extend the dosing interval of trastuzumab. PO Resp. 40–43. We find that the skilled artisan would have been motivated to extend the dosing interval regardless of the pharmacokinetic data set forth in the prior art. But, as discussed below, we find that trastuzumab's non-linear kinetics would not have provided the skilled artisan with a reasonable expectation of success with such an extended dosing interval.

Accordingly, we find that skilled artisans would have been motivated to extend the dosing interval of trastuzumab to once every three weeks, with a 712 mg loading dose followed by 500 mg maintenance doses.

b. Reasonable Expectation of Success

Having found the requisite motivation to arrive at the claimed dosing regimen, we next turn to whether there would have had a reasonable expectation of success with such a treatment regimen. Based on our consideration of the record evidence, we find that Petitioners have not met their burden of establishing a reasonable expectation of success.

In evaluating reasonable expectation of success, we must "consider the appropriate scope of the patent's claimed invention." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965–66 (Fed. Cir. 2014). Here, the claims of the '379 patent are directed to a "method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an *effective* amount of an anti-ErbB2 antibody to the human patient." Ex. 1001, 57:33–36 (emphasis added). Petitioners and Patent Owner both focus their arguments and evidence on whether the skilled artisan would have reasonably expected that trastuzumab plasma concentrations would be maintained above 10–20 μg/mL, which the prior art identifies as the minimum serum trough concentration required for efficacy. In view of the claim scope, we agree that this is an appropriate definition of "success" for purposes of our analysis.

Petitioners contend that the skilled artisan would have extended the dosing interval based on Dr. Jusko's pharmacokinetic analysis as set forth above. Patent Owner disagrees that this type of mathematical analysis would have provided the requisite reasonable expectation of success for the

claimed dosing regimen. In particular, Patent Owner criticizes Dr. Jusko's application of linear pharmacokinetics to predict serum trough concentration insofar as the prior art taught that trastuzumab had demonstrated non-linear (dose-dependent) kinetics. PO Resp. 45–48. As noted by Patent Owner, "[f]or drugs with non-linear kinetics, pharmacokinetic parameters such as half-life do not remain constant but change as a function of the concentration of the drug in the plasma." *Id.* at 46 (citing Ex. 1022, 3:109; Ex. 2008, 123; Ex. 2038 ¶¶ 22–25, 27, 34–36). According to Patent Owner, there is insufficient data in the prior art to accurately predict whether a three-week dosing regimen would be clinically effective, and thus a clinical oncologist would not have confidently used three-week dosing based on Dr. Jusko's pharmacokinetic analysis. *Id.* at 55–57.

As part of our evaluation, we take into account the relative novelty of using antibodies for the treatment of cancer as of the August 27, 1999 priority date. Herceptin had been approved by the FDA for weekly administration in September 1998, less than a year before, was the first antibody approved to target "solid tumors," and the first approved to treat any form of breast cancer. Ex. 1008; Ex. 2003, 388; Ex. 2038, 33:8–17; Ex. 2040 ¶ 23.[8] Petitioners have not pointed to any prior art reference discussing the feasibility or viability of a tri-weekly antibody dosing regimen.

[8] Prior to August 1999, the FDA had approved only one other antibody for treating cancer—Patent Owner's rituximab product, which was approved for non-Hodgkin's lymphoma treatment in 1997. Ex. 2003, 388. We find no evidence of record indicating that rituximab had been approved or successfully tested for anything longer than weekly dosing.

While Dr. Jusko's calculations are based on "textbook" equations that were known in the prior art, the actual pharmacokinetic analysis set forth in his declaration for determining the serum trough concentration associated with a tri-weekly dosing regimen of trastuzumab was not found in any prior art reference. Thus, we find Dr. Jusko's analysis to be largely based on impermissible hindsight. *KSR*, 550 U.S. at 421 ("A factfinder should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.").

Petitioners contend that Dr. Jusko applied the same model that Patent Owner and its collaborators did in the prior art. Reply 17. In particular, Petitioners rely upon Baselga '96's statement that "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." Ex. 1013, 738. However, Baselga '96 did not mention a tri-weekly schedule, and instead determined that a regimen in which patients received an initial dose of 250 mg trastuzumab followed by 100 mg weekly doses was the "optimal dose and schedule." *Id.* Petitioners also speculate that the Herceptin label's reporting of only a single half-life for each dosage level "suggest[s] use of a one-compartment model." Reply 17; Ex. 1003 ¶ 34. But the Herceptin label does not explicitly indicate that a one-compartment model was used to model the weekly dosing regimen discussed therein. In any event, the pharmacokinetics discussed in the Herceptin label were based on actual clinical trials rather than just mathematical predictions. Ex. 1008, 1 ("The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease."). Baselga '96 and the Herceptin label both specifically recognize that trastuzumab has "dose dependent pharmacokinetics." Ex. 1008, 1;

Ex. 1013, 738. The very pharmacokinetics textbook relied upon by Dr. Jusko notes that "dose-dependent and time-dependent kinetic behaviors defy easy quantitative description and prediction." Ex. 1022, vol. 3, 395.

We recognize that Pegram'98 states that Phase I clinical "studies showed that the pharmacokinetics of rhuMAb HER2 were predictable." Ex. 1014, 2660. But as explained by Patent Owner's pharmacokinetic expert Dr. Grass, "[a] skilled artisan would understand 'predictable' in this context to mean that administration of the same dose with the same dosing schedule would likely yield the same serum concentrations if given to a similar patient population." Ex. 2039 ¶ 54. It does not suggest predictability across different dosing intervals. Insofar as the pharmacokinetics discussed in the prior art were only based on studies of weekly administration of lower trastuzumab doses, we do not find that the references support Petitioners' conclusion that the same "one-compartment" model could also be used to reasonably predict the expected serum concentrations for tri-weekly administration using higher doses of the antibody.

The evidence shows that the prior art did not contain sufficient data from which the skilled artisan could reliably predict the plasma concentration for trastuzumab over a three-week dosing interval using a one-compartment model. In this regard, we credit the testimony of Dr. Grass. Dr. Grass explains that one potential source of non-linear kinetics for trastuzumab was the presence of "shed antigens" in the patient's serum, which are extra-cellular domain HER2 receptors (ECD^{HER2}) "shed" from the tumor source that circulate in the patient's blood stream. Ex. 2039 ¶¶ 56, 71, 72. We are unpersuaded by Dr. Jusko's opinion that the effect of shed antigens on half-life and serum trough levels would not have been of

concern to the skilled artisan because it was "only shown to be significant in the small percentage of patients for which shed antigen reached 'high levels,' *i.e.*, greater than about 0.5 μg/mL." Ex. 1057 ¶ 46 (citing Ex. 1013 and Ex. 1014).

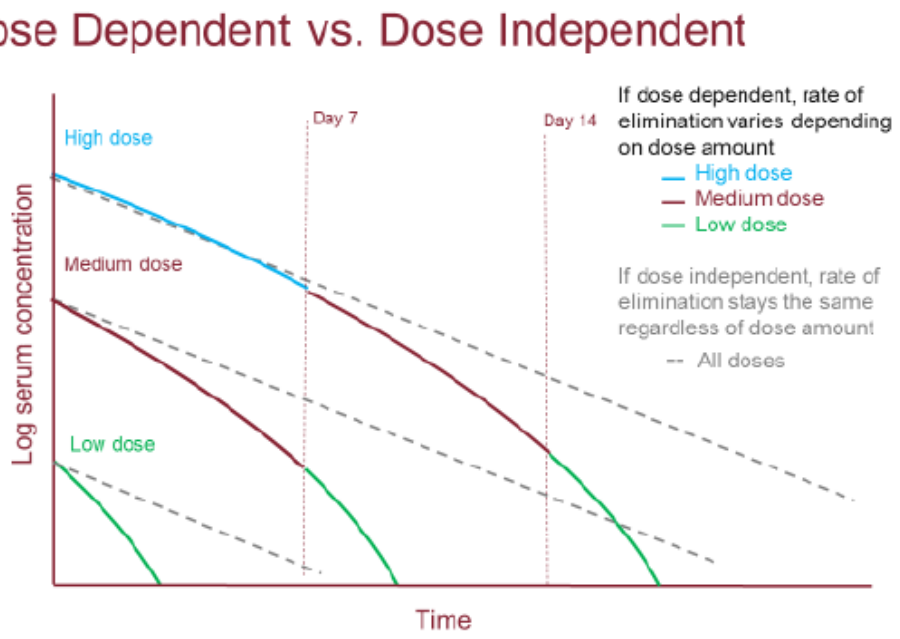
Petitioners' own prior art references highlight the uncertainty caused by the presence of shed antigens on the pharmacokinetics of trastuzumab. For instance, the Herceptin label notes that "64% of patients (287/447) had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL)," and that "[p]atients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations." Ex. 1008, 1. Baselga '96 likewise teaches that "[t]he rhuMAb HER2 serum $t_{1/2}$ was found to be dependent on the presence of circulating ECD^{HER2} released from the tumor into the serum." Ex. 1013, 739. In fact, for those patients with high levels of shed antigen, Baselga '96 teaches that serum levels of the antibody were "suboptimal," and that "the trough levels of rhuMAb HER2 were consistently below detectable levels throughout the treatment course and until disease progression." *Id.* at 739–740 (Fig. 1B). Pegram '98 notes "there was an inverse relationship between rhuMAb HER2 serum half-life and serum shed HER2 ECD of 0.5 μg/mL or greater." Ex. 1014, 2665. Pegram '98 further indicates that "patients with any measurable shed [antigen] serum level, compared with patients without measurable circulating ECD, had lower mean trough rhuMAb HER2 concentrations (18.7 v. 43.6 μg/mL; $P = .0001$) across all time points (n = 443 observations; Fig. 1)." Notably, this prior art data appears to show that patients with *any* detectable shed antigen levels (i.e., 64% of patients as set forth in the Herceptin label) had a mean antibody trough level that was close to the 10–

20 μg/mL threshold for efficacy.[9] As such, we find that skilled artisan would have been concerned that the effect of shed antigens— not taken into account by Dr. Jusko's analysis—could indeed significantly affect serum trough concentrations for tri-weekly administration of trastuzumab.

Contrary to Dr. Jusko's assumptions, Dr. Grass attests that "applying a constant value for half-life over a three-week period, based on the one-week data reported in the prior art, to a dose-dependent drug like trastuzumab could overestimate trough serum concentration levels" because it "fail[s] to account for the nonlinear increase in elimination and corresponding decrease in the half-life that would be expected to occur as serum concentration declines." Ex. 2039 ¶ 25. Dr. Grass also contends that the actual rates of elimination for such a drug would be unpredictable without collecting sufficient data, such as by conducting a "washout study" where serum concentration is collected over several half-lives following a single administration of the drug, but notes that there is no prior art reference for trastuzumab that describes such data. *Id.* ¶ 24.

To illustrate this point, Dr. Grass provides the following graph showing differences that can potentially exist between dose-independent drugs (which exhibit linear kinetics) and dose-dependent drugs (which exhibit non-linear kinetics):

[9] Although Dr. Gelmon testified that later (post-filing) studies showed that shed antigens were not in fact a concern for efficacy of Herceptin, and that dosage is not adjusted based on shed antigen levels today, our analysis is based on what was known in the prior art. Ex. 1058, 62:20–65:6.



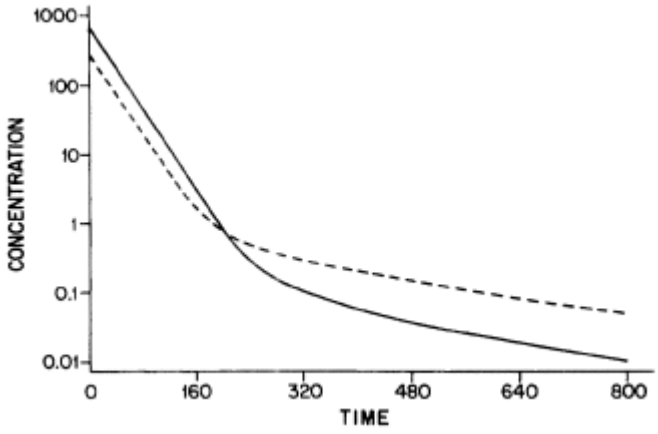
Id. ¶ 23. As shown by the solid lines in the graph above, which correspond to different dosage amounts of a dose-dependent drug, elimination increases (i.e., half-life decreases) as the drug concentration changes over time. Petitioners criticize this graph as being "made up" by Dr. Grass, as it was not derived from any particular data set forth in the prior art. Reply 20 (citing Ex. 1059, 116:16–21). Patent Owner, however, points to post-filing data concerning the anti-cancer agent indisulam as a "real-world example" of a dose-dependent drug that can behave this way, showing how assuming a constant half-life could greatly overestimate the predicted serum concentration over a longer interval. PO Resp. 49–50; Ex. 2039 ¶ 26; Anthe S. Zandvliet et al., *Saturable Binding of Indisulam to Plasma Proteins and Distribution to Human Erythrocytes*, 34 DRUG METABOLISM & DISPOSITION 1041 (2006) (Ex. 2052) ("Zandvliet"). While we recognize that Zandvliet does not qualify as prior art, and concerns a "small molecule" rather than an antibody, we find that it demonstrates at least one example in which assuming linear kinetics could result in an overestimation of trough serum

concentrations for a dose-dependent drug. From the perspective of a skilled artisan as of the August 27, 1999 priority date, we find nothing in the record to suggest that a similar overestimation would not have been a concern for tri-weekly trastuzumab administration.

With its Reply, Petitioners present additional evidence and arguments as to why Dr. Jusko's initial assumptions and analysis were reasonable. In particular, Petitioners contend that Dr. Jusko's analysis would, at worst, have underestimated, not overestimated, serum trough concentrations. Reply 18–23. In support of this contention, Petitioners cite King, APPLICATIONS AND ENGINEERING OF MONOCLONAL ANTIBODIES (1998) (Ex. 1029) ("King '98") as teaching that antibodies follow a common profile associated with "receptor-mediated" (or "target-mediated") drug disposition, with a quick initial clearance and short half-life ($t_{1/2}\alpha$), followed by slower clearance and a longer half-life ($t_{1/2}\beta$). While King '98 includes a table that identifies several antibodies known at the time to have a shorter $t_{1/2}\alpha$ followed by a longer $t_{1/2}\beta$, it *only* reports a $t_{1/2}\beta$ of 199 ± 120 hours for trastuzumab (citing Baselga '96), and Petitioners do not point to any other evidence suggesting a $t_{1/2}\alpha$ for trastuzumab. *See* Ex. 1029, 70 (Table 2.7). Furthermore, King '98 recognizes that the presence of circulating shed antigens could reduce antibody half-life in some cases, and that "[t]he pharmacokinetics of human IgG are unusual in that the half-life varies with concentration." *Id.* at 68, 70. As such, we find that King '98 does not show that Dr. Jusko's linear assumptions would have underestimated serum trough concentrations for trastuzumab.

In further support, Petitioners point to the following graph from Levy, *Pharmacologic target-mediated drug disposition*, 56(3) Clinical

Pharmacology & Therapeutics 248–52 (1994) ("Levy") as demonstrating this type of profile:

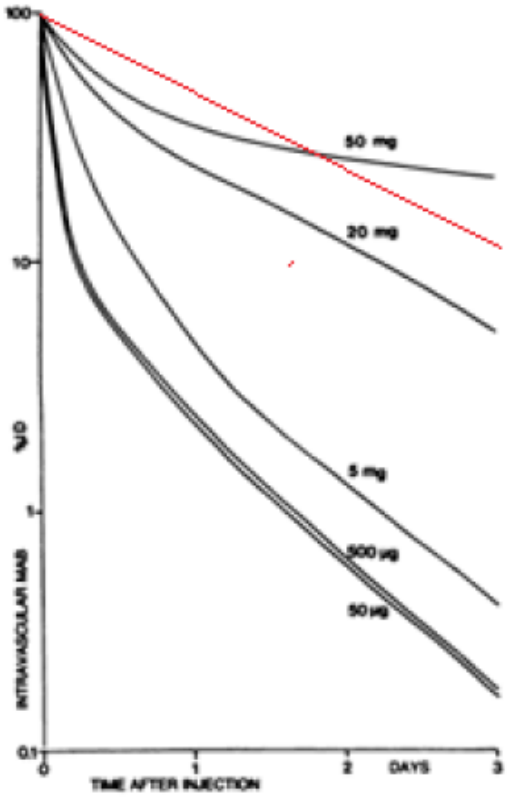


Ex. 1052, 249 (Fig. 1). The figure above shows "[t]ypical concentration-time profile in plasma *(continuous line)* and tissues *(broken line)* for a drug that is subject to high-affinity low-capacity binding in tissues." *Id.*

We do not find that the expected profile for receptor-mediated drug disposition, as shown in Levy, supports the reasonableness of Dr. Jusko's pharmacokinetic analysis for trastuzumab. Levy does not describe the kinetics of antibodies at all, but instead only identifies certain small molecules that might exhibit this "hypothetical behavior." Ex. 2084, 22:10–16, 59:8–16. Specifically, with reference to Figure 1 shown above, Levy notes that "the effect on pharmacokinetics can be quite striking in that the plasma concentration profile exhibits a terminal decay phase with a very long half-life ($t_{1/2}$), as is the case for certain angiotensin-converting enzyme (ACE) and aldose reductase inhibitors." Ex. 1052, 248. In criticizing Dr. Grass's reliance on the indisulam data discussed above, Dr. Jusko notes that skilled artisans would not "rely[] on pharmacokinetic behavior of ***small molecules***, which was known to be fundamentally different to that of antibodies." Ex. 1057 ¶ 5; *see also id.* ¶ 20 n.1 (noting "in addition to the

[differences in] molecular weight, the different mechanisms of disposition of small molecules and antibodies impacts their pharmacokinetic profiles"). Accordingly, we are not persuaded by Dr. Jusko's inconsistent opinion relying upon Levy's teachings with respect to target-mediated disposition of small molecules. Ex. 1057 ¶ 15. Moreover, even with respect to the ACE inhibitors discussed therein, Levy does not make any definitive conclusions as to their pharmacokinetic behavior, noting instead that "[m]ore definitive information can be obtained only in animal studies that permit opening of the 'black box' to explore what goes on in individual tissues." Ex. 1052, 248–49.

Petitioners also point to the following graph from Koizumi, *et al.*, *Multicompartmental Analysis of the Kinetics of Radioiodinated Monoclonal Antibody in Patients with Cancer*, 27(8) J. NUCLEAR MED. 1243–54 (1986) (Ex. 1054) ("Koizumi"):



Reply, 22; Ex. 1054, 1252 (Fig. 8) (annotation in red added by Petitioners). The annotated figure above shows "[m]odel simulated curves" for intravascular monoclonal antibodies (MAb) reflecting the "effect of different amount of injected MAb on blood clearance." *Id.* According to Petitioners, "for a given antibody dose (here 50mg), a linear model (shown in red) would underestimate the actual serum concentration (shown in black) soon after dosing." Reply 21.

We do not find that Koizumi supports the reasonableness of Dr. Jusko's application of a linear model. Indeed, Petitioners' own annotation in the figure above shows that a linear model could overestimate actual serum concentrations for certain doses (e.g., 20 mg) or at certain times after injection (e.g., less than 2 days). For tri-weekly trastuzumab administration, it was unknown whether the actual serum concentration would fall above or

below the linearity assumed in Dr. Jusko's model. Moreover, unlike Dr. Jusko's "one-compartment" analysis in this proceeding, Koizumi specifically describes a "multicompartmental" analysis conducted using a computer simulation. Ex. 1054, 1247. In this regard, Koizumi notes that "[i]nitial model solutions assumed that the model was linear," but "[u]sing this information it was not possible to fit the data observed for the patients with the model simulations." *Id.* at 1245–46. Furthermore, according to Koizumi:

> [C]ompartmental analysis also raises several problems. If the compartmental model is based upon unlikely assumptions, or inadequately validated, then misleading information follows. While this is self-evident, the complexity of a model addressing the pharmacokinetics of a MAb requires simplifications based upon assumptions in order to permit realistic mathematical handling. These simplifications and assumptions are particularly vulnerable to error in a system such as MAb, wherein many processes remain to be clarified.

Id. at 1252. As such, Koizumi underscores the inherent uncertainty associated with using mathematical models to predict the pharmacokinetic behavior of antibodies.

In sum, for the foregoing reasons, we determine Petitioners have not established the reasonable expectation of success required for obviousness. In reaching this conclusion, we are cognizant that "[c]onclusive proof of efficacy is not required to show obviousness." *Hoffman-La Roche*, 748 F.3d at 1331. Nonetheless, the Federal Circuit has also indicated that reasonable expectation cannot come from a mere "hypothesis" that might form the basis for further testing. *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 647–49 (Fed. Cir. 2017) (finding prior art reference that stated the "expected" benefit of a

clinical trial did not establish a reasonable expectation of success); *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

III. ALLEGED IMPROPER REPLY MATERIALS/PATENT OWNER'S MOTION TO EXCLUDE

Pursuant to our authorization, Patent Owner filed a paper identifying allegedly improper arguments and evidence included with Petitioners' Reply. Paper 68. Specifically, Patent Owner identifies the following materials as improper: Exhibits 1043–1048, 1050, 1052, 1054, and 1055, and portions of Dr. Lipton's reply declaration (Ex. 1056) and Dr. Jusko's reply declaration (Ex. 1057) referencing those exhibits. *Id.* Patent Owner also separately filed a motion to exclude the same evidence it identifies as improper reply materials. Paper 64.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[10] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization

[10] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

to file a motion to strike." *Id.* at 17. "In most cases, the Board is capable of identifying new issues or belatedly presented evidence when weighing the evidence at the close of trial, and disregarding any new issues or belatedly presented evidence that exceeds the proper scope of reply or sur-reply." *Id.*

Nevertheless, to the extent necessary, we treat Patent Owner's Motion to Exclude and Identification of Improper New Reply Materials as a motion to strike. We have not relied upon Exhibits 1043–1048, 1050, and 1055 in rendering this decision. We have not given any weight to this evidence to support Petitioners' obviousness arguments because they have publication dates after August 27, 1999, and thus do not qualify as prior art to the '379 patent. *See* Paper 64, 7–10 (explaining why post-priority date references relied upon by Petitioners are irrelevant to obviousness determination in this proceeding). Furthermore, Exhibit 1055 has not been cited or relied upon by Petitioners in their Reply, and we decline to incorporate by reference the opinion in Dr. Jusko's reply declaration concerning that exhibit. *See* 37 C.F.R. § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document."). Accordingly, we dismiss as moot Patent Owner's motion to strike this evidence.

We have taken into consideration Exhibits 1052 and 1054 in our analysis, as discussed above. We determine that these exhibits and Petitioners' arguments in relation to these exhibits are proper reply evidence as they seek to respond to Patent Owner's arguments concerning the reasonableness of Dr. Jusko's pharmacokinetic analysis. Specifically, in relying upon Exhibits 1052 and 1054, and the portions of Dr. Jusko's reply declaration citing those exhibits, Petitioners seek to respond to Patent Owner's criticism that Dr. Jusko's assumptions would have overestimated

serum concentration for dose-dependent drugs such as trastuzumab. With such evidence, Petitioners seek to further support, not modify, their basis for reasonable expectation of success set forth in the Petition. We do not find that Petitioners have presented an "entirely new rationale" worthy of being excluded in their Reply. *Ericsson Inc. v. Intellectual Ventures I LLC*, No. 2017-1521, 2018 WL 4055815, *6 (Fed. Cir. Aug. 27, 2018). Although we find the new exhibits unpersuasive, that does not render them improper reply evidence. We, therefore, deny Patent Owner's motion to strike this evidence.

IV. CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that although Petitioners have shown that a skilled artisan would have been motivated to extend the dosing frequency of trastuzumab from weekly to tri-weekly, Petitioners have not met their burden to show a reasonable expectation of success with respect to such a dosing regimen. As a result, Petitioners have not shown, by a preponderance of the evidence, that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 patent would have been obvious over the combination of the Herceptin Label, Baselga '96, Pegram '98, and the knowledge of the skilled artisan.

V. ORDER

Accordingly, it is:

ORDERED that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 patent have not been shown to be unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2017-00805
Patent 7,371,379 B2

PETITIONERS:

For Hospira, Inc.:
Amanda Hollis
Stefan M. Miller
Benjamin A. Lasky
Sarah K. Tsou
Mark C. McLennan
Christopher J. Citro
KIRKLAND & ELLIS LLP
amanda.hollis@kirkland.com
stefan.miller@kirkland.com
karen.younkins@kirkland.com
benjamin.lasky@kirkland.com
sarah.tsou@kirkland.com
mark.mclennan@kirkland.com
christopher.citro@kirkland.com

For Samsung Bioepis Co., Ltd.:
Dimitrios T. Drivas
Scott T. Weingaertner
Amit H. Thakore
Eric Majchrzak
WHITE & CASE LLP
ddrivas@whitecase.com
scott.weingaertner@whitecase.com
athakore@whitecase.com
eric.majchrzak@whitecase.com

PATENT OWNER:

David L. Cavanaugh
Lauren V. Blakely
Robert J. Gunther, Jr.
Lisa J. Pirozzolo
Kevin S. Prussia

Andrew J. Danford
Robert Galvin
WILMER CUTLER PICKERING HALE AND DORR LLP
david.cavanaugh@wilmerhale.com
lauren.blakely@wilmerhale.com
robert.gunther@wilmerhale.com
lisa.pirozzolo@wilmerhale.com
kevin.prussia@wilmerhale.com
andrew.danford@wilmerhale.com
robert.galvin@wilmerhale.com

Adam R. Brausa
Daralyn J. Durie
DURIE TANGRI LLP
abrausa@durietangri.com
ddurie@durietangri.com

EXHIBIT 24

Trials@uspto.gov
Tel: 571-272-7822

Paper No. 69
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01140
Patent 7,371,379 B2

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

YANG, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

ORDERS
Granting Petitioner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying-in-Part and Dismissing-in-Part Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

INTRODUCTION

Celltrion, Inc. ("Petitioner") filed a Petition (Paper 1 ("Pet.")), requesting an *inter partes* review of claims 1–3, 5, 7, 9–11, 13–28, and 30–40 of U.S. Patent No. 7,371,379 B2 (Ex. 1001, "the '379 patent"). We instituted trial to review patentability of the challenged claims.[1] Paper 31 ("Dec.").

Genentech, Inc. ("Patent Owner") filed a Response to the Petition (Paper 27, "PO Resp."), and Petitioner filed a Reply (Paper 40). The parties also briefed whether certain exhibits should be excluded from the record. Papers 52, 54, 56, 57, 59, 61. In addition, the parties briefed whether certain evidence and argument presented by Petitioner exceeded the proper scope of the Reply. Papers 53, 58, 62. Furthermore, Patent Owner filed a motion for observation on the cross-examination of Petitioner's declarant (Paper 55), and Petitioner filed an opposition thereto (Paper 60).

An oral hearing for this proceeding was held on May 8, 2018. *See* Paper 66.

The Board has jurisdiction under 35 U.S.C. § 6 and issues this final written decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons provided below, we conclude Petitioner has not established by a preponderance of the evidence that claims 1–3, 5, 7, 9–11, 13–28, and 30–40 of the '379 patent are unpatentable.

[1] We inadvertently omitted claims 13–15 in the original Decision to Institute dated October 4, 2017. On January 25, 2018, we reissued the Decision to correct that mistake.

Related Proceedings

The '379 patent is also the subject of IPR2017-00805. Concurrently with this Decision, we issue a final written decision in that case.

We also issue, concurrently with this Decision, final written decisions in IPR2017-00804 and IPR2017-01139 to address the patentability of certain claims of U.S. Patent No. 6,627,196, a patent in the same family of the '379 patent at issue here.

The '379 Patent

The '379 patent claims priority to a provisional application filed August 27, 1999. Ex. 1001, (60).

The '379 patent relates to the treatment of disorders characterized by the overexpression of ErbB2. Ex. 1001, Abstract, 1:15–16. According to the Specification, "human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer." *Id.* at 1:44–49. Before the '379 patent, a recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, also referred to as rhuMAb HER2, trastuzumab, or HERCEPTIN®) had been approved to treat patients with ErbB2-overexpressing metastatic breast cancers. *Id.* at 3:59–65. The recommended initial "loading dose" for Herceptin® was 4 mg/kg administered as a 90-minute infusion, and the recommended weekly "maintenance dose" was 2 mg/kg, which could be administered as a 30-minute infusion if the initial loading dose was well-tolerated. *Id.* at 3:66–4:3.

The invention described in the '379 patent "concerns the discovery that an early attainment of an efficacious target trough serum concentration by providing an initial dose or doses of anti-ErbB2 antibodies followed by subsequent doses of equal or smaller amounts of antibody (greater front loading) is more efficacious than conventional treatments." *Id.* at 4:26–31. According to the '379 patent, "the method of treatment involves administration of an initial dose of anti-ErbB2 antibody of more than approximately 4 mg/kg, preferably more than approximately 5 mg/kg," with the maximum dose not to exceed 50 mg/kg. *Id.* at 4:51–55. "[T]he initial dose or doses is/are followed by subsequent doses of equal or smaller amounts of antibody at intervals sufficiently close to maintain the trough serum concentration of antibody at or above an efficacious target level." *Id.* at 4:66–5:2. Preferably, "the amount of drug administered is sufficient to maintain the target trough serum concentration such that the interval between administration cycles is at least one week," and "the trough serum concentration does not exceed 2500 μg/ml and does not fall below 0.01 μg/ml during treatment." *Id.* at 5:4–9.

The '379 patent explains that "[t]he front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment." *Id.* at 5:9–12. As a result, "[t]he efficacious target trough serum concentration is reached in 4 weeks or less . . . and most preferably 1 week or less, including 1 day or less." *Id.* at 4:31–34. Additionally, it states that the method of therapy may involve "infrequent dosing" of the anti-ErbB2 antibody, wherein the first and subsequent doses are separated from each other by at least about two weeks, and optionally at least about three weeks. *Id.* at 6:23–34.

The '379 patent describes embodiments in which the initial dose of anti-ErbB2 is 6 mg/kg, 8 mg/kg, or 12 mg/kg, followed by subsequent maintenance doses of 6 mg/kg or 8 mg/kg administered once every 2 or 3 weeks, in a manner such that the trough serum concentration is maintained at approximately 10–20 μg/ml during the treatment period. *Id.* at 5:19–43, 45:19–45. The treatment regimen according to the invention may further comprise administration of a chemotherapeutic agent, such as a taxoid, along with the anti-ErbB2 antibody. *Id.* at 6:6–10, 7:26–32, 46:28–58.

Of particular relevance, the '379 patent includes a prophetic example describing the administration of trastuzumab intravenously every three weeks in combination with the chemotherapeutic agent paclitaxel. *Id.* at 46:60–48:32. According to this example, "[s]imulation of the proposed treatment regimen suggests that the trough serum concentrations will be 17 [μ]g/ml, in the range (10–20 [μ]g/ml) of the targeted trough serum concentrations from previous HERCEPTIN® IV clinical trials." *Id.* at 47:1–5. The example sets forth inclusion criteria for a study in which patients will be administered trastuzumab every three weeks. *Id.* at 47:9–48:12. The '379 patent concludes that "[i]t is believed that the above treatment regimen will be effective in treating metastatic breast cancer, despite the infrequency with which HERCEPTIN® is administered to the patient." *Id.* at 48:28–31.

Illustrative Claims

Among the challenged claims, claims 1 and 30 are independent, and are reproduced below:

> 1. A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:

> administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody; and
>
> administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose, wherein the subsequent doses are separated in time from each other by at least two weeks; and
>
> further comprising administering an effective amount of a chemotherapeutic agent to the patient.
>
> 30. A method for the treatment of cancer in a human patient comprising administering to the patient a first dose of an anti-ErbB2 antibody followed by two or more subsequent doses of the antibody, wherein the subsequent doses are separated from each other in time by at least about two weeks, and further comprising administering an effective amount of a chemotherapeutic agent to the patient.

Reviewed Ground of Unpatentability

We instituted *inter partes* review to determine whether the challenged claims would have been obvious over the combination of Slamon,[2] Watanabe,[3] Baselga,[4] and Pegram.[5]

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[2] D. Slamon et al., *Addition of Herceptin(™) (Humanized Anti-HER2 Antibody) to First Line Chemotherapy for HER2 Overexpressing Metastatic Breast Cancer (HER2 +/MBC) Markedly Increases Anticancer Activity: A Randomized Multinational Controlled Phase III Trial*, 17 J. CLIN. ONCOL. 98a, Abstract *377 (1998) (Ex. 1005).

[3] T. Watanabe et al., *Pharmacokinetically Guided Dose Escalation Study of Anti-HER2 Monoclonal Antibody in Patients with HER2/NEU-Overexpressing Metastatic Breast Cancer*, 17 JOURNAL OF CLINICAL ONCOLOGY 182a, Abstract *702 (1998) (Ex. 1006).

[4] Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14 J. CLIN. ONCOL. 737–44 (1996) (Ex. 1007).

[5] Pegram, et al., *Phase II Study of Receptor-Enhanced Chemosensitivity*

In support of their respective arguments, Petitioner relies on the Declarations of Dr. Mark J. Ratain (Exs. 1003, 1123), and Patent Owner relies on the Declarations of Dr. George M. Grass and Dr. Karen A. Gelmon (Exs. 2027, 2028).

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

In the Decision to Institute, we stated that we see no need to expressly construe any claim terms. Dec. 6–7 (citing *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (stating claim terms need only be construed to the extent necessary to resolve the controversy)). During trial, the parties do not argue otherwise, and we see no reason to change our

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Using Recombinant Humanized Anti-p185$^{HER2/neu}$ Monoclonal Antibody Plus Cisplatin in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment, 16 J. CLIN. ONCOL. 2659–71 (1998) (Ex. 1009).

position. Thus, on this record and for purposes of this Decision, we do not expressly construe any claim terms.

Prior Art Disclosures

Slamon

Slamon summarizes the results of a Phase III clinical trial in which patients received Herceptin (H) along with chemotherapy (CRx). Ex. 1005, 5. The chemotherapy (doxorubicin-cyclophosphamide or paclitaxel) was administered once every three weeks. *Id.* The Herceptin was administered intravenously at a 4 mg/kg loading dose, followed by 2 mg/kg weekly doses. *Id.* Slamon indicates that "[a]t a median follow-up of 10.5 months, investigator assessments of time to disease progression (TTP) and response rates (RR) show a significant augmentation of CRx effect by H, without increase in overall severe adverse events (AE)." *Id.* As such, Slamon concludes that the data from the clinical trial "indicate that addition of Herceptin to CRx markedly increases clinical benefit, as assessed by RR and TTP." *Id.*

Watanabe

Watanabe summarizes a phase I dose escalation study of an anti-HER2 monoclonal antibody (MAb 4D5 (MKC-454)) in patients with chemotherapy-resistant metastatic breast cancer. Ex. 1006, 5. In the study, the first dose of antibody was followed in 3 weeks by 9 weekly doses. *Id.* Doses of 1, 2, 4, and 8 mg/kg were administered as 90-minute intravenous infusions. *Id.* Watanabe provides data regarding patients receiving the different dosages of anti-HER2:

MKC454 dose	# of Pts	trough level (μg/ml)	toxicity		tumor response
			grade 2	grade 3≤	
1 mg/kg	6	9		1 fever, 1 n/v	
2 mg/kg	3	19	1 fever, 1 pain		1 MR
4 mg/kg	3	102	1 fever		1 PR
8 mg/kg	6	248		1 pain	1 MR, 2 PR

Id. The chart above reports the trough level, toxicity, and tumor response. According to Watanabe, "[t]arget trough plasma concentration was achieved with 2 mg/kg weekly intravenous infusions." *Id.* Thus, Watanabe concludes that "[f]urther clinical trials examining the efficacy of MAb 4D5 (MKC-454) with 2–4 mg/kg weekly intravenous infusions is warranted." *Id.*

Baselga

Baselga reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer who had received extensive prior therapy. Ex. 1007, 3. Each patient received a loading dose of 250 mg of intravenous rhuMAb HER2, followed by 10 weekly doses of 100 mg. *Id.* The pharmacokinetic goal of the trial "was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell grown in the preclinical model." *Id.* at 4. Further, the "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." *Id.*

According to Baselga, "[a]dequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients. Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients." *Id.* at 3. Out of the 768 times rhuMAb HER2 was administered, "only 11 events occurred that were considered to be related to the use of the antibody." *Id.* at 5. Baselga also teaches that "[i]n preclinical studies, both in vitro and in xenografts, rhuMAb HER2 markedly potentiated the antitumor effects of

several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." *Id.* at 9.

Pegram

Pegram reports the results of a phase II clinical trial using a combination of rhuMAb HER2 plus cisplatin. Ex. 1009, 2. It states that "[t]hese studies showed that the pharmacokinetics of rhuMAb HER2 were predictable, and that the doses delivered achieved a target trough serum concentration of 10 to 20 μg/mL, which is associated with antitumor activity in preclinical models." *Id.* at 3. It also reports a toxicity profile of the combination that paralleled the toxicity of cisplatin alone, thereby leading to the conclusion that rhuMAb HER2 did not increase toxicity. *Id.* at 11.

Level of Ordinary Skill in the Art

According to Petitioner,

> A POSA to whom the '379 patent is directed would have had either an M.D. with subspecialty training in oncology and/or a Ph.D. with substantial experience in oncology drug development. Such an individual would also have had familiarity with the treatment of breast cancer and substantial experience in the design and/or implementation of oncology clinical trials, as well as expertise in clinical pharmacology, including pharmacokinetics.

Pet. 15 (citations omitted). "Patent Owner does not dispute the areas of substantive expertise," but adds that "[a] skilled artisan would have had access to and worked on a team with a number of other individuals involved in drug development with expertise in clinical pharmacology, including pharmacokinetics." PO Resp. 23–24 (citation omitted).

We do not discern an appreciable difference in the parties' respective definitions of the level of ordinary skill in the art, and any perceived distinction does not impact our Decision. We further note that, in this case,

the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown").

Obviousness Analysis

Petitioner contends that claims 1–3, 5, 7, 9–11, 13–28, and 30–40 of the '379 patent would have been obvious over the combination of Slamon, Watanabe, Baselga, and Pegram. Pet. 28–60. After reviewing the entire record, we determine that Petitioner has not established by a preponderance of the evidence that the challenged claims are unpatentable.

For claim 1, Petitioner refers to Slamon for teaching an effective treatment regimen that combined Herceptin with chemotherapy, wherein Herceptin was administered at a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg. Pet. 28 (citing Ex. 1005, 5). Petitioner argues that an ordinary artisan "would have been motivated to administer trastuzumab as disclosed by Slamon, but would have recognized that weekly administration would be inconvenient for patients, who otherwise would need infusions only once every three weeks."[6] *Id.* at 28–29 (citing Ex. 1003 ¶ 89; Ex. 1017, 1–4). Petitioner contends that an ordinary artisan "would have sought to reduce the frequency of trastuzumab administration to align it with the less arduous chemotherapy regimen in

[6] Even though some claims only require administering trastuzumab once every two weeks, our obviousness analysis assumes a treatment method in which trastuzumab is administered once every three weeks, as that dosing interval is encompassed by all the challenged claims and is the focus of the parties' arguments and evidence in this proceeding.

order to improve patient convenience." *Id.* at 29 (citing Ex. 1003 ¶ 90). When modifying the dosing schedule, according to Petitioner, an ordinary artisan "would have recognized the importance of maintaining dose intensity" and would have administered an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses, each administered three weeks apart. *Id.* at 29–30 (citing Ex. 1003 ¶ 91).

With regard to safety concerns, Petitioner contends that based on Watanabe's disclosure that weekly doses as high as 8 mg/kg were safe and well-tolerated, an ordinary artisan "would not have expected an increase in toxicity, or any other safety concerns, for the higher doses required by the every three week regimen." *Id.* at 31 (citing Ex. 1006, 5; Ex. 1003 ¶¶ 72, 92–93). Petitioner emphasizes that "the overall number of severe adverse events was in fact ***lower*** for the six patients treated at the 8 mg/kg dose than Watanabe disclosed for the 1 mg/kg dose." *Id.* Petitioner also cites other prior art references as teaching that trastuzumab was safe at doses as high as 8 mg/kg. *Id.* at 31 (citing Ex. 1008, 1; Ex. 1013, 4; Ex. 1014, 4; Ex. 1012, 11:54–56; Ex. 1015, 2:60–61; Ex. 1018, 48:19–52).

With regard to efficacy, Petitioner relies upon the prior art's disclosure of a target serum concentration (trough concentration) of 10 µg/ml. *Id.* at 33 (citing Ex. 1003 ¶ 96; Ex. 1006, 5; Ex. 1007, 4; Ex. 1009, 3). In determining whether the every-three-week regimen would satisfy this trough concentration, Petitioner relies upon the disclosures in Baselga and Pegram that trastuzumab has a mean half-life of at least one week. *Id.* at 34 (citing Ex. 1003 ¶ 103; Ex. 1007, 5; Ex. 1009, 8). Petitioner argues that because "Baselga further discloses that trastuzumab has dose-dependent pharmacokinetics," an ordinary artisan "would have understood

that its half-life would actually be longer at higher doses." *Id.* at 34–35 (citing Ex. 1003 ¶ 102; Ex. 1007, 3). Thus, Petitioner contends that "the serum concentration would decrease by half no more than three times" before the next 6 mg/kg maintenance dose is administered. *Id.* at 35 (citing Ex. 1003 ¶¶ 104–105). Based on an initial serum concentration of 169 μg/ml (calculated based on Pegram's disclosure), Petitioner estimates that approximately 21.1 μg/ml would remain after three weeks, which is above the 10 μg/ml trough concentration required for efficacy. *Id.* at 35–36 (citing Ex. 1003 ¶¶ 100, 104). Petitioner comes to a similar conclusion based on the pharmacokinetic data disclosed in the 1998 Herceptin label. *Id.* at 38–39.

Patent Owner counters that an ordinary artisan would not have been motivated to administer trastuzumab in accordance with the claimed regimen. PO Resp. 26–42. Patent Owner also contends that Petitioner has not established "a reasonable expectation of success that extending the trastuzumab dosing regimen to three weeks with the claimed loading and maintenance doses would be safe and effective." *Id.* at 42–58.

Motivation to Modify

Dosing Frequency

Patent Owner asserts that an ordinary artisan would not have been motivated to administer trastuzumab on the every-three-week dosing schedule. PO Resp. 26–42. We are not persuaded.

Patent Owner asserts that an ordinary artisan "would not have been motivated to extend the dosing interval for the sake of convenience." *Id.* at 26. According to Patent Owner, in August 1999, the priority date of the

'379 patent, an ordinary artisan would have been focused on improving efficacy of trastuzumab, and not convenience. *Id.* at 24, 26–28. We are not persuaded.

As a preliminary matter, we agree with Patent Owner that none of the asserted prior art references individually teaches the claimed dosing schedule explicitly. *See id.* at 17–23. Non-obviousness, however, cannot be established by attacking references individually where the patentability challenge is based upon the teachings of a combination of references. *See In re Keller*, 642 F.2d 413, 425 (CCPA 1981). Here, as explained below, the prior-art teachings as a whole, together with the knowledge of one of ordinary skill in the art, would have motivated an ordinary artisan to modify the dosing schedule of trastuzumab in order to improve patient convenience.

Patent Owner contends that Petitioner bases the obviousness challenge on a "generalized concern for 'convenience' untethered to the specific patient population of the claims." PO Resp. 29. According to Patent Owner, HER2-positive breast cancer is a serious, life-threatening disease, and "[p]atients thus need little additional convincing in the form of convenience to take trastuzumab." *Id.* at 36–37 (citing Ex. 2028 ¶¶ 42–47), *see also id.* (citing Ex. 2028 ¶¶ 50, 57) (arguing "compliance was not likely to be an issue for breast-cancer patients"). We are not persuaded.

First, except claims 17 and 18, the other challenged claims are not limited to breast cancer. *See* Ex. 1001, 58:56–65 (dependent claim 16 reciting the cancer is selected from at least 24 different types of cancer, including small-cell lung cancer and colorectal cancer), *see also id.* at 15:33–35 ("Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia."). Second, the record reflects

that some patients, despite having metastatic breast cancer, and even in the context of a tightly controlled clinical study, in fact missed treatment due to reasons such as "social obligations" and other "commitments." Ex. 2016, 3355. Thus, prior art suggests convenience and compliance are important, even among patients with metastatic breast cancer.

Patent Owner argues that "[n]othing in the prior art suggests that skilled artisans treating patients with HER2-positive cancer were concerned with convenience in August 1999." PO Resp. 24. But the prior art relied upon by Petitioner need not expressly articulate or suggest patient convenience as a motivation to extend the dosing interval. Indeed,

> The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself. As [the Federal Circuit] explained . . . "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art."

DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1361 (Fed. Cir. 2006) (internal citations omitted).

Patent Owner is correct that one of ordinary skill in the art would have considered efficacy critical in treating cancer. PO Resp. 26–27. Efficacy, however, is not the sole consideration. *See, e.g.*, Ex. 1103, 1 (stating that a new regimen for treating small-cell lung cancer was designed with the objectives to "maintain efficacy, diminish toxicity, enhance compliance, and improve chemotherapy administration convenience at an acceptable cost").

Indeed, in 1998, the FDA issued the Guidance for Industry regarding "New Cancer Treatment Uses for Marketed Drug and Biological Products." Ex. 1118. According to the guideline, "[n]ew dosing regimens (including

changes in the range of doses administered for approved indications and changes in the schedule of administration) can lead to improved effectiveness, tolerance, or convenience." *Id.* at 8.

Dr. Gelmon, an expert for Patent Owner, does not disagree. *See, e.g.*, Ex. 1104, 81:10–15 (testifying that when exploring an alternative dosing schedule, a clinician treating a cancer patient would look at efficacy, safety, and quality of life, "[a]nd one of the factors that comes in after those things is always [the] effect on the patient including convenience"). This approach had been borne out by data from clinical trials. For example, in an article Dr. Gelmon co-authored, the researchers studied bi-weekly paclitaxel as first-line treatment for metastatic breast cancer in a phase I-II trial. Ex. 1101, 1. Based on the results, they concluded that "[t]he good drug tolerance, response rates, and convenience over weekly treatment suggest this may be a worthwhile regimen." *Id.*, *see also id.* at 3 ("The tolerance is similar to the weekly schedule but bi-weekly paclitaxel may be more convenient.").

Other prior art of record confirms that convenience was a motivating factor in exploiting new dosing regimens. Often, after a drug is introduced into clinical trials, an ordinary artisan would pursue different clinical strategies "in an attempt to identify the schedule with the optimal balance between clinical activity, safety, and convenience." Ex. 1017, 2 (discussing alternative dosing schedules for an anti-cancer drug in clinical trials for colorectal cancer, including a weekly schedule and an every-three-week schedule). When developing new dosing strategies for an anti-cancer drug, an ordinary artisan would take into account biology, pharmacology, and toxicity of the drug, as well as pragmatic factors, "including the regimen's

cost, convenience, and ease of compliance. An additional pragmatic consideration is how well the schedule accommodates other drugs . . . that will be given with [the drug-at-issue]." *Id.* at 1–2.

Here, Slamon teaches the results of a combination therapy in which Herceptin "markedly increases anticancer activity" of chemotherapy in HER2 overexpressing metastatic breast cancer. Ex. 1005, 5. In that phase III clinical trial, chemotherapy was administered every three weeks, whereas Herceptin was administered weekly. *Id.* Herceptin Product Label teaches the same. Ex. 1008. In late 1998, the FDA approved Herceptin for treating patients with metastatic breast cancer whose tumors overexpress the HER2 protein. *Id.* at 1. As a first-line treatment, Herceptin is to be used in combination with paclitaxel. *Id.* Paclitaxel is administered once every three weeks, and Herceptin is administered weekly. *Id.* Citing the Declaration of Dr. Ratain, Petitioner argues that an ordinary artisan would have recognized that weekly administration of trastuzumab would be inconvenient for patients, and would have sought to reduce the frequency of trastuzumab administration to that of paclitaxel in order to improve patient convenience. Pet. 28–29 (citing Ex. 1003 ¶¶ 89, 90; Ex. 1017, 1–4).

Patent Owner contends that "Dr. Ratain did not cite any evidence to support these assertions." PO Resp. 29. That, however, is not fatal to Petitioner's position, because an obviousness analysis "not only permits, but *requires*, consideration of common knowledge and common sense." *DyStar*, 464 F.3d at 1367. Furthermore, as discussed above, Petitioners have supported Dr. Ratain's opinions with citations to the prior art. Relying on this prior art, Petitioner argues that "a once every three week regimen 'has the added advantage of greater patient convenience, as it entails less frequent

dosing than is required on a weekly schedule.'" Pet. 29 (citing Ex. 1017, 1–4). Having established that this knowledge was in the art, Dr. Ratain and Petitioner "could then properly rely . . . on a conclusion of obviousness from common knowledge and common sense of the person of ordinary skill in the art without any specific hint or suggestion in a particular reference." *DyStar*, 464 F.3d at 1368 (internal quotation marks omitted).

Patent Owner argues that at the time of the '379 patent, "treatment with weekly trastuzumab could ***improve*** patient quality of life in comparison to treatment with chemotherapy regimens alone, despite the weekly regimen." PO Resp. 27. Patent Owner misses the point. It is undisputed that weekly trastuzumab was known to be efficacious and thus, could improve quality of life for patients in comparison to chemotherapy treatment alone. The proper comparison here though, is not weekly trastuzumab versus chemotherapy regimens, but every-three-week versus weekly trastuzumab.

Patent Owner also asserts that "[s]killed artisans at the time of the invention were motivated by trastuzumab's Phase III results to explore the weekly co-administration of trastuzumab and paclitaxel—not extending trastuzumab to match paclitaxel." PO Resp. 32. Even if this were true, it would not have dissuaded an ordinary artisan from pursuing a regimen to administer trastuzumab every three weeks. That is because, in an obviousness analysis, "the question is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination," not whether the prior art suggests the combination as the most desirable combination available. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (quotation marks and alteration omitted).

Moreover, the only paclitaxel dosing regimen approved by the FDA for treating breast cancer was, and still is, one administered every three weeks. Ex. 1117, 6. Even in the references Patent Owner points to, the ordinary artisan recognized that paclitaxel is effective on either an every-three-week or weekly schedule. Ex. 2036, 385. In addition, "a dose of 175 mg/m^2 by 3-h infusion every three weeks appears to be very reasonable in the treatment of advanced breast cancer. In combination therapy, this dose is often easily combined with other agents, producing manageable toxicity and not usually requiring hematopoietic growth factor support." *Id.* In the challenged '379 patent, paclitaxel is indeed combined with another agent, trastuzumab. Thus, even if an ordinary artisan had tried, or would have preferred, to decrease the dosing interval of paclitaxel to weekly to match that of trastuzumab, we are persuaded that the artisan would also have been motivated to extend the dosing interval of trastuzumab to every three weeks to match that of paclitaxel.

Dosage Amount

Each of claims 1–3, 5, 7, 9–11, and 13–28 requires, either explicitly or through dependency, "an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody," and "a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose." Ex. 1001, 56:63–67. In addition, each of claims 33 and 38 requires at least two or more subsequent doses that "are each from about 4 mg/kg to about 12 mg/kg," and each of claims 34 and 39 requires at least two or more subsequent doses that "are each from about 6 mg/kg to about 12 mg/kg." Patent Owner argues the prior art does not suggest the claimed loading and

maintenance doses. PO Resp. 37–42. After reviewing the entire record, we agree that Petitioner has not met its burden in this regard.

As an initial matter, we are not persuaded by Patent Owner's contention that "the prior art's statements that weekly dosing of trastuzumab was 'optimal' (Ex. 1007 at 4) and 'warranted' (Ex. 1006 at 5) would have pointed a skilled artisan away from three-week dosing." PO Resp. 37. Prior art may not teach away even if a particular solution is not the preferred solution or is inferior to another solution. *In re Fulton*, 391 F.3d at 1200. Instead, a reference teaches away if it criticizes, discredits, or otherwise discourages the solution claimed. *Id.* at 1201.

Here, Dr. Gelmon, an expert for Patent Owner, testified that even after a drug is approved, an ordinary artisan would keep on optimizing the dosing regimen by "changing schedule or changing dosing." Ex. 1104, 64:16–65:4. As explained above, an ordinary artisan would have been motivated to modify the dosing frequency in order to improve patient convenience. And an ordinary artisan would have adjusted the dosage amount accordingly. Thus, just because Watanabe and Baselga described the dosage amount of trastuzumab for a **weekly** dosing regimen as "optimal" or "warranted" would not have dissuaded an ordinary artisan from adjusting the dosage amount for an every-three-week dosing regimen.

We, however, find Petitioner has not met its burden in addressing the motivation for an ordinary artisan to modify the loading and the maintenance dosage as the challenged claims require. Petitioner asserts that "[w]hen modifying the dosing schedule, a POSA would have recognized the

importance of maintaining dose intensity, *i.e.*, the amount of drug administered over a period of time." Pet. 29 (citing Ex. 1003 ¶ 91; Ex. 1024, 1–5; Ex. 1029). According to Petitioner,

> As shown in the table below, when accounting for dose intensity, Slamon's trastuzumab regimen calls for administration of a total of 8 mg/kg over the first three week period, followed by 6 mg/kg every three weeks thereafter:

week	1	2	3	4	5	6	7	8	9	10	11	12
weekly dose (mg/kg)	4	2	2	2	2	2	2	2	2	2	2	2
q 3 week dose (mg/kg)	8			6			6			6		

Id. at 29–30 (citing Ex. 1005, 5; Ex. 1003 ¶ 91).

Patent Owner argues that this approach is flawed because "Petitioner has failed to articulate ***why*** a skilled artisan would apply a chemotherapy dosing strategy to trastuzumab, a targeted antibody treatment." PO Resp. 40 (citing Ex. 2028 ¶ 58). We find Patent Owner's argument persuasive.

When resorting to the principle of "dose intensity," Petitioner and Dr. Ratain initially relied on Exhibits 1024 and 1029. Pet. 29 (citing Exs. 1024, 1029); Ex. 1003 ¶ 91 (citing Ex. 1024, 1; Ex. 1029, 9–10). Both of those two references, however, describe the dosing of doxorubicin, a chemotherapy agent. *See* Exs. 1024, 1029. In response to Patent Owner's challenge that dose intensity is a chemotherapy dosing strategy, Petitioner contends that "POSAs understood that the concept of dose intensity was applicable to a variety of oncology drugs, including targeted antibodies." Reply 15–16 (citing Ex. 1123 ¶ 36; Exs. 1111, 1121, 1126); Ex. 1123 ¶ 36 (citing Exs. 1111, 1121, 1124, 1125, 1126, 1130).

Among the references submitted with the Reply to support the applicability of the concept of dose intensity in this case, only Cheson[7] is directed to an antibody. Cheson teaches Mabthera, an anti-CD20 antibody, "demonstrated activity in intermediate-grade NHL, mantle cell lymphoma, lymphoplasmacytic NHL, and post-transplant lymphoproliferative disorder." Ex. 1126, 4. According to Cheson, "[l]ower response rates in small lymphocytic NHL and CLL, reflecting the low density of CD20 on the malignant cells, may be overcome by **increasing the dose intensity** of Mabthera." *Id.* (emphasis added). Read in this context, the phrase "dose intensity," as used in Cheson, appears to refer to the amount of a single dose, rather than "the amount of drug administered **over a period of time**," as that phrase defined by Petitioner. *See* Pet. 29 (emphasis added). Thus, we agree with Patent Owner that Petitioner has not "cite[d] any evidence that skilled artisans would have applied the concept of 'dose intensity' to antibody treatment." *See* PO Resp. 40.

Petitioner contends that "[t]here was nothing in the prior art about trastuzumab that would have dissuaded a POSA from using the approach of keeping the same dosage amount over time," and "Patent Owner has failed to identify any alternative approach to dose selection that would have been appropriate." Reply 16–17. But it is not Patent Owner's burden to identify an "alternative approach." Rather, Petitioner must prove unpatentability by a preponderance of the evidence (*see* 35 U.S.C. § 316(e); 37 C.F.R.

[7] B. Cheson, *Future Perspective: Mabthera® in the Next Millennium*, Abstracts of Satellite Symposia, Mabthera Future Applications In CD20+ Malignancies (June 1, 1999) (Ex. 1126).

§ 42.1(d)), and that burden never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

Patent Owner asserts that because the goal of antibody dosing is different from that of chemotherapy dosing, an approach that would be desired for chemotherapy may not be necessarily a desired one when administering an antibody. PO Resp. 5–7, 40–41; *see also* Ex. 2028 ¶ 58 ("In 1999, oncologists did not know enough about trastuzumab's mechanism of action to feel comfortable automatically applying principles from chemotherapy dosing to trastuzumab dosing.").

According to Patent Owner, at the time of the '379 patent invention, "the goal of most chemotherapy dosing was to kill the greatest number of tumor cells without causing life-threatening toxicity." *Id.* at 5 (citing Ex. 2028 ¶¶ 30–31). This was achieved, Patent Owner continues, by administering "the highest tolerable dose (typically resulting in a high peak concentration) followed by sufficient time for recovery (and very low troughs)." *Id.* at 41 (citing Ex. 2028 ¶ 31). Dr. Ratain does not appear to disagree. Ex. 2026, 54:12–59:6.

In contrast, Patent Owner argues, "at the time of the invention, skilled artisans believed that trastuzumab should be dosed to maintain a minimum trough concentration over the entire dose interval." *Id.* at 41 (citing Ex. 2028 ¶ 36); *see also* Ex. 2027 ¶¶ 45–47 (Dr. Grass testifying that an ordinary artisan would "want to ensure that any alternative dosing regimen maintained therapeutic trough concentrations throughout the course of treatment"). The prior art confirms this. *See, e.g.*, Ex. 1006, 5 (setting 10 μg/ml as the target trough plasma concentration); Ex. 1007, 4 ("The

pharmacokinetic goal was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell growth in the preclinical model.").

As Petitioner's expert, Dr. Ratain, explains, for a drug at a given total cumulative dose, "as the intervals between doses increase, the fluctuation increases, with higher peaks and lower trough concentrations." Ex. 1003 ¶ 57. In view of the prior-art teaching that trastuzumab should be dosed to maintain a minimum trough concentration over the entire dose interval, this testimony by Dr. Ratain casts doubt as to whether an ordinary artisan would have applied the concept of dose intensity to an antibody treatment, such as trastuzumab.

Further compounding the complexity of the issue is the presence of shed antigen. At the relevant time, it was known that

> Detectable concentrations of the circulating extracellular domain ["ECD"] of the HER2 receptor (shed antigen) are found in the serum of some patients with HER2 overexpressing tumors. Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations.

Ex. 1008, 1. *See also* Ex. 1009, 8 ("[P]atients with any measurable shed HER2/*neu* ECD serum level, compared with patients without measurable circulating ECD, had lower mean trough rhuMAb HER2 concentrations . . . across all time points.").

Accordingly, considering (1) the lack of sufficient evidence from Petitioner to show that an ordinary artisan would have applied the concept of dose intensity to an antibody treatment; (2) the presence of shed antigen, which shows an inverse relationship to serum trough concentration; (3) the

acknowledgment by Dr. Ratain that "there were not enough publications about trastuzumab . . . for those [dose-intensity] analyses to be presented" (Ex. 2026, 64:8–10); and (4) the testimony of Dr. Ratain that "the rationale that would lead [an ordinary artisan] to dose chemotherapy every three weeks would not apply to dosing trastuzumab every three weeks" (*id.* at 59:13–18), we conclude that Petitioner has not met its burden to demonstrate that an ordinary artisan would have had a reason to modify the loading and maintenance doses as claimed.

As a result, we conclude that Petitioner has not established by a preponderance of the evidence that claims 1–3, 5, 7, 9–11, 13–28, 33, 34, 38, and 39 of the '379 patent are unpatentable. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.").

Reasonable Expectation of Success

Claims 30, 31, 35, 36, and 40 do not recite either the first or any subsequent dosage amount of trastuzumab. In addition, claims 32 and 37 require at least two or more subsequent doses "are each from about 2 mg/kg to about 16 mg/kg." As explained above, we find an ordinary artisan would have been motivated to modify the dosing frequency of trastuzumab as claimed. In addition, both Slamon and Herceptin Product Label teach the loading dose of 4 mg/kg and the maintenance doses of 2 mg/kg. Ex. 1005, 5; Ex. 1008, 2. Even so, we find Petitioner has not established by a preponderance of the evidence that claims 30–32, 35–37, and 40 of the '379 patent are unpatentable. This is because Petitioner's analysis of these claims hinges on the same argument of 8 mg/kg loading dose and 6 mg/kg

maintenance doses Petitioner asserts in the other claims. For example, the substantive analysis of claim 30, in its entirety, appears in a single paragraph:

> As discussed above with respect to claim 1, it would have been obvious to administer trastuzumab on an every-three-week regimen as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses. *See also* Ex. 1003 at ¶¶ 89–112. This regimen would have satisfied each and every element of claim 30 of the '379 patent, and therefore claim 30 is obvious for the same reasons as set forth with respect to claim 1. Ex. 1003 at ¶¶ 89–112, 115–118.

Pet. 45.

For claim 1, Petitioner analyzes the reasonable expectation of success with respect to efficacy based on an 8 mg/kg loading dose and 6 mg/kg maintenance doses. Pet. 33–39, 43–44. Because Petitioner has not met its burden to show that an ordinary artisan would have been motivated to modify the dosage amount in the first instance, its reasonable-expectation-of-success arguments, premised upon efficacy associated with administering those modified dosage amounts over the every-three-week dosing frequency, also fail.

As a result, we conclude that Petitioner has not established by a preponderance of the evidence that claims 30–32, 35–37, and 40 of the '379 patent are unpatentable.

Motions to Exclude

Petitioner's Motion to Exclude

Petitioner filed a Motion to Exclude Exhibits 2004, 2039, 2041, 2061, 2062, and 2067. Paper 52. Patent Owner does not oppose. Paper 56.

Petitioner's Motion to Exclude is granted.

Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1100, 1102, 1105, 1107, 1111, 1121, 1124, 1125, 1126, 1128, and 1130, as well as paragraphs 22, 29, 35–37, 44, 53–58, and 60–73 of Exhibit 1123, i.e., the Reply Declaration of Dr. Ratain. Paper 54. Patent Owner filed an Identification of Improper New Reply Materials, challenging the same exhibits. Paper 53.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[8] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization to file a motion to strike." *Id.* at 17. "In most cases, the Board is capable of identifying new issues or belatedly presented evidence when weighing the evidence at the close of trial, and disregarding any new issues or belatedly presented evidence that exceeds the proper scope of reply or sur-reply." *Id.*

Nevertheless, to the extent necessary, we treat Patent Owner's Motion to Exclude and Identification of Improper New Reply Materials as a motion to strike. Patent Owner argues that in paragraphs 35–37 of Ratain Reply Declaration (Ex. 1123), Dr. Ratain relies on Exhibits 1111, 1121, 1124, 1125, 1126, and 1130, and introduces new arguments related to the alleged use of the concept of dose intensity in the development of new dosing regimens. Paper 54, 1, 8–11. According to Patent Owner, these six new

[8] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

exhibits, as well as paragraphs 35–37 of Exhibit 1123 "should be excluded as improper reply evidence used to fill a gap in Petitioner's *prima facie* case." *Id.* at 1. We disagree.

"Evidence admitted in rebuttal to respond to the patent owner's criticisms will commonly confirm the prima facie case. That does not make it necessary to the prima facie case." *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1078 (Fed. Cir. 2015). Such is the case here.

In the Petition, citing the Declaration of Dr. Ratain, Petitioner argues that "[w]hen modifying the dosing schedule, a POSA would have recognized the importance of maintaining dose intensity, *i.e.*, the amount of drug administered over a period of time." Pet. 29 (citing Ex. 1003 ¶ 91; Ex. 1024, 1–5; Ex. 1029). In its Response, citing the Declaration of Dr. Gelmon, Patent Owner counters that an ordinary artisan would not have relied on the concept of dose intensity because it is a chemotherapy concept, whereas trastuzumab, an antibody, works differently from a chemotherapy agent. PO Resp. 40–41 (citing Ex. 2028 ¶¶ 31, 36, 58).

In his Reply Declaration, Dr. Ratain relies on the challenged exhibits to support his opinion that the concept of dose intensity "is applicable to other therapeutic areas and contexts," including antibodies. Ex. 1123 ¶¶ 35–37 (citing Ex. 1111, 1121, 1124, 1125, 1126, 1130). Thus, paragraphs 35–37 in the Ratain Reply Declaration, as well as the exhibits relied on therein, respond directly to Patent Owner's criticism of the dose-intensity principle. With such evidence, Petitioner intends to confirm, not to modify, its prima facie case. Although we find the new exhibits unpersuasive, that

does not render them improper reply evidence. We, therefore, deny Patent Owner's Motion to Exclude regarding paragraphs 35–37 of Exhibit 1123, and Exhibits 1111, 1121, 1124, 1125, 1126, and 1130.

Patent Owner also seeks to exclude Exhibits 1100, 1102, 1105, 1107, and 1128, as well as paragraphs 22, 29, 44, 53–58, and 60–73 of Ratain Reply Declaration (Ex. 1123). Paper 53, 1–2, 5–8, 11–14. We do not rely on any of these exhibits in rendering this Decision. Thus, we dismiss this aspect of Patent Owner's Motion to Exclude as moot.

CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that although Petitioner has shown that an ordinary artisan would have modified the dosing frequency of trastuzumab from weekly to every-three-week, Petitioner has not met its burden to show that an ordinary artisan would have modified the dosage amounts as proposed. In addition, Petitioner has not met its burden to show a reasonable expectation of success because those arguments are solely based on its proposed loading and maintenance dosage amounts. As a result, Petitioner has not shown, by a preponderance of the evidence, that claims 1–3, 5, 7, 9–11, 13–28, and 30–40 of the '379 patent would have been obvious over the combination of Slamon, Watanabe, Baselga, and Pegram.

ORDER

Accordingly, it is

ORDERED that claims 1–3, 5, 7, 9–11, 13–28, and 30–40 of the '379 patent have not been shown to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is granted;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

PETITIONER:

Cynthia Hardman
Robert Cerwinski
GOODWIN PROCTER LLP
chardman@goodwinlaw.com
rcerwinski@goodwinlaw.com

PATENT OWNER:

David L. Cavanaugh
Lauren V. Blakely
Vera Shmidt
Robert J. Gunther, Jr.
Lisa J. Pirozzolo
Kevin S. Prussia
Andrew J. Danford
WILMER CUTLER PICKERING HALE AND DORR LLP
david.cavanaugh@wilmerhale.com
lauren.blakely@wilmerhale.com
vera.shmidt@wilmerhale.com
robert.gunther@wilmerhale.com
lisa.pirozzolo@wilmerhale.com
kevin.prussia@wilmerhale.com
andrew.danford@wilmerhale.com

Adam R. Brausa
Daralyn J. Durie
DURIE TANGRI LLP
abrausa@durietangri.com
ddurie@durietangri.com

EXHIBIT 26

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC.; AMGEN MANUFACTURING, LIMITED; and AMGEN USA INC. Plaintiffs, v. SANOFI; SANOFI-AVENTIS U.S. LLC; AVENTISUB LLC, f/d/b/a AVENTIS PHARMACEUTICALS INC., and REGENERON PHARMACEUTICALS, INC., Defendants.	C.A. No.: 14-1317-SLR (CONSOLIDATED) [redacted] PUBLIC VERSION

PLAINTIFFS' OPENING BRIEF IN SUPPORT OF
MOTION FOR PERMANENT INJUNCTIVE RELIEF

[redacted]

in-suit are invalid. Defendants' infringement has continued unabated since judgment was entered against Defendants. Amgen now seeks a permanent injunction.

V. ARGUMENT

Analyzing the facts of this case under the well-known, four-factor test for an injunction as described by the Court in *eBay*, 547 U.S. at 394, leads to one conclusion: that entry of a permanent injunction is the only appropriate remedy.

A. AN INJUNCTION SHOULD ISSUE BECAUSE DEFENDANTS' CONTINUED INFRINGEMENT IS CAUSING AMGEN IRREPARABLE HARM

Defendants' infringement and direct competition in this two-supplier market is causing Amgen to suffer price erosion, reputational harm, lost sales, and lost market share. It also threatens to disrupt the very business model on which Amgen depends for the long-term, autonomous operation of its business. A permanent injunction is the only remedy to prevent such harm.

1. Defendants' Continued Infringement Is Causing Amgen to Suffer Price Erosion

Price erosion alone is sufficient to establish irreparable harm. *See Edwards Lifesciences AG v. CoreValve, Inc.*, No. CV 08-91, 2014 WL 1493187, at *6 (D. Del. Apr. 15, 2014) (citing *Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 930 (Fed. Cir. 2012)). Amgen has experienced and will continue to experience significant price erosion. By launching Praluent® at-risk, Defendants have enabled insurers to pit the parties against each other to extract larger and larger rebates and other concessions as a condition to being included (even in a parity position) on national formularies, thereby eroding Amgen's net price for Repatha®.[3] *See* Ex. A (summary

[3] Defendants' economics expert Dr. Oster agrees that there is price erosion in this case, and she expects price erosion to continue into the future. Hr'g Tr. 492:4-10 (Oster cross).

[redacted]

Inc. v. Synthes (U.S.A.), 466 F. Supp. 2d 978, 984 (W.D. Tenn. 2006) (noting that dynamic market forces rendered damages award "speculative at best").

3. The Loss of Innovator Status and Reputational Harm that Defendants Have Caused Amgen Are Incalculable

Courts routinely recognize that certain types of harm, such as reputational harm and loss of innovator status, are unquantifiable and thus cannot be compensated with monetary damages. *See, e.g.*, *Douglas Dynamics*, 717 F.3d at 1344 ("Irreparable injury encompasses different types of losses that are often difficult to quantify, including lost sales and erosion in reputation and brand distinction."); *TruePosition*, 568 F. Supp. 2d at 531 (finding inadequate remedy at law where "[d]efendant has taken from plaintiff not only this important business, but the recognition of being a technology innovator and the first global supplier of the patented technology, and an unquantifiable amount of business opportunities flowing therefrom"); *Smith & Nephew*, 466 F. Supp. 2d at 983-85 (same).

Here, Amgen is suffering harm to its reputation, including loss of innovator and first-in-class status. Hr'g Tr. 69:12-70:1 (Bradway direct); Hr'g Tr. 235:6-15 (Berndt direct); Hr'g Tr. 150:23-151:13 (Ryan direct). Defendants' expert Dr. Oster, though she suggests that reputational harm can be quantified, never provides a way to calculate such harm. Hr'g Tr. 479:18-25 (Oster direct).[9] As Amgen's expert Dr. Berndt testified: "How do you quantify the foregone R&D opportunities, the lost reputation, the imposition on Amgen of a forced change in business model to rely instead [of] on patent protected products, on bringing products to market that will suddenly have fast followers[?] I don't know how you can quantify those damages with

[9] Indeed, the sum total of Dr. Oster's conclusory testimony on the subject is: "Q: Ok. And to the extent there even was reputational harm, could that be quantified? A: Yes." Hr'g Tr. 479:18-20 (Oster direct).

[redacted]

responsible for 100% of development costs up to the first successful Phase 3 clinical trial, after which Sanofi is responsible for 80%); *see also* Hr'g Tr. 489:23-490:6 (Oster cross). In the face of an injunction, Regeneron will not earn potential future revenue from the sale of Praluent® in the United States, but—because it will not earn revenue—it will not have to pay back the expense of development. Hr'g Tr. 238:6-22 (Berndt direct). By contrast, Sanofi, a large, diversified, global company (indeed, much larger than Amgen), really has no risk. Hr'g Tr. 238:23-239:6 (Berndt direct); Trial Tr. 359:13-360:6 (Edelberg direct). A permanent injunction would not force Sanofi to change its business model. Hr'g Tr. 238:23-239:6 (Berndt direct). There was no evidence to the contrary.

D. A PERMANENT INJUNCTION WILL SERVE THE PUBLIC INTEREST

The compelling public interest here is manifest: the assurance that there will be a continuous cycle of invention of new medicines to treat the diseases of today and tomorrow. Injunctive relief here will foster the incentives of the patent system to achieve this goal.

1. The Public Has a Strong Interest in a Robust Patent System that Maintains the Incentives for Pharmaceutical Innovation

Since Amgen was founded more than 35 years ago, it has been in the business of inventing, developing, manufacturing, and selling biopharmaceutical medicines to treat serious human illness, with 16 medicines currently on the market today. Trial Tr. 227:12-15 (Bradway direct). Amgen's ability to sustain this engine of innovation is built upon the right to exclude infringers from practicing their inventions for the period of time afforded by their patents. Hr'g Tr. 58:16-59:2 (Bradway direct); Hr'g Tr. 229:7-22 (Berndt direct). Without this patent right, Amgen would not have been able to protect its investment, generate adequate capital to re-invest in innovation-based R&D, or maintain the confidence of its investors. Hr'g Tr. 59:3-10, 61:14-

62:5 (Bradway direct). The same can be said of nearly every other innovation-based biotech and pharmaceutical company. Judge Young made this very point almost a decade ago:

> If the Court allowed [the defendant] to introduce [its infringing product] into the market, perhaps a few patients would benefit, and maybe Medicare would save a few dollars. These arguments, however, could be made for almost any infringing drug. Were courts to refuse injunctions on the basis of such speculation, then pharmaceutical patents would be worth far less than they are today because they would no longer include a right to exclude infringers from the market. The diminishing returns would disincentivize research and development for pathbreaking drugs by lowering the expected value of discovery. By contrast, granting injunctions encourages companies to devote their energies toward developing drugs that will satisfy unmet medical needs. *Were it possible to obtain market entry by making incremental improvements to existing drugs, it is doubtful that companies designed to generate discoveries could exist.*

Amgen, 581 F. Supp. 2d at 226-27 (emphasis added).

The patent laws are designed to reward inventors based on the profits the invention can command in the marketplace over the life of the patent "by offering a right of exclusion for a limited period as an incentive to inventors to risk the often enormous costs in terms of time, research, and development." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1363 (Fed. Cir. 2008) (quoting *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 480 (1974)); Hr'g Tr. 239:10-240:13 (Berndt direct). It is of no consequence that others may have independently arrived at the invention later. *See Radio Corp. of Am. v. Radio Eng'g Labs., Inc.*, 293 U.S. 1, 3 (1934) (J. Cardozo reinstating injunction where four different entities independently arrived at same or nearly the same discovery, stating, "The prize of an exclusive patent falls to the one who had the good fortune to be first."). Indeed, there is a "significant public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents." *Sanofi-Synthelabo*, 470 F.3d at 1384 (internal quotation marks omitted).

EXHIBIT 27

Source, History, and Generation of the Cell Substrate

Table of Contents

1. Development Genetics 2
1.1 Sequence Verification of Reference Product 2
1.2 Cloning and Construction of the ABP 980 Expression Plasmids 2
1.2.1 Dual Selection Plasmids 3
1.2.2 Construction of ABP 980 DHFR Expression Plasmid 3
1.2.3 Construction of ABP 980 Neomycin Expression Plasmid 4
1.2.4 ABP 980 Plasmid Sequence Confirmation 6
2. Cell Line Development 8
2.1 History of the Parental Chinese Hamster Ovary DHFR- Cell Line 8
2.2 Preparation of the ABP 980 Producing Cell Line by Transfection 9

List of Tables

Table 1. Components of the ABP 980 DHFR Expression Plasmid 4
Table 2. Components of ABP 980 Neomycin Expression Plasmid 5

List of Figures

Figure 1. Construction of Plasmids for Expression of ABP 980 3
Figure 2. Plasmid Map of ABP 980 DHFR Expression Plasmid 4
Figure 3. Plasmid Map of ABP 980 Neomycin Expression Plasmid 5
Figure 4. Nucleotide and Amino Acid Sequences of the DNA for ABP 980 HC 7
Figure 5. Nucleotide and Amino Acid Sequences of the DNA for ABP 980 LC 8
Figure 6. Summary of Cell Line Development 10

Source, History, and Generation of the Cell Substrate

The ABP 980 clonal production cell line was generated at Cellca GmbH, Germany, using the following steps:

- The amino acid sequence of ABP 980 is based on that of Herceptin® (trastuzumab), with the exception that ABP 980 sequence was designed without the heavy chain (HC) C-terminal lysine. The deduced DNA sequence was synthesized for the HC and light chain (LC), and the DNA sequences were used to construct the ABP 980 dihydrofolate reductase (DHFR) and ABP 980 Neomycin expression plasmids in a stepwise manner. Each plasmid contains both the ABP 980 HC and LC (Section 1).
- The expression plasmids were co-transfected into Chinese hamster ovary (CHO) DG44 cells. Following a clone screening and selection process, final clone CC-1001 was selected as the ABP 980 production cell line (Section 2).

1. Development Genetics

1.1 Sequence Verification of Reference Product

Verification of the trastuzumab amino acid sequence was performed using mass spectrometry (Regional, Primary Structure). The analysis provided complete amino acid sequence coverage for both the HC and LC. The derived amino acid sequences were used as the templates for synthesis of the HC and LC DNA sequences and cloned into intermediate plasmids. The amino acid sequence of ABP 980 is the same as that of Herceptin® (trastuzumab), with the exception that the C-terminal lysine is absent in the ABP 980 HC, as this codon was not included in the DNA sequence.

1.2 Cloning and Construction of the ABP 980 Expression Plasmids

The ABP 980 expression plasmids were constructed in the following stepwise manner:

1. The synthetic DNA sequences coding for the HC and LC were cloned into intermediate plasmids.
2. Both the HC and LC sequences were cloned into two unique plasmids; one contained a DHFR gene and the other contained a neomycin resistance gene.
3. The final ABP 980 DHFR and neomycin expression plasmids, each containing both the ABP 980 HC and LC sequences, were used to co-transfect the host cell line.

Figure 1 provides a high level summary of the ABP 980 expression plasmid construction steps and the subsequent co-transfection that resulted in the ABP 980 production cell line. The expression plasmids are designed to express functional DHFR and neomycin resistance enzymes upon co-expression in the cell. Details regarding the construction of the ABP 980 expression plasmids are provided in Section 1.2.1, Section 1.2.2, and Section 1.2.3.

EXHIBIT 28

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, v. HOSPIRA, INC., Defendant.	Civil No. 1:15-cv-839-RGA REDACTED PUBLIC VERSION

AMGEN'S OPENING BRIEF IN SUPPORT OF ITS MOTION FOR A PRELIMINARY INJUNCTION

Hospira may argue that it can disregard the notice requirement because the patents-in-suit (U.S. Patent Nos. 5,756,349 and 5,856,298) have expired. But that argument disregards a central purpose of paragraph (8)(A): to allow Amgen "time to make a decision about seeking relief based on *yet-to-be litigated* patents." *Apotex*, 827 F.3d at 1062 (emphasis added). By refusing to provide the manufacturing information required under § 262(*l*)(2)(A), and again refusing Amgen discovery of its manufacturing information in this case, Hospira has successfully limited Amgen's ability to detect process-patent infringement. Amgen continues to seek this information from Hospira, and the Federal Circuit will soon rule on whether Amgen can obtain this information in discovery in the present lawsuit, or otherwise assert its cell-culture patents without such information. If Hospira unlawfully launches its product without having provided to Amgen the manufacturing information required by the BPCIA, Amgen will be irreparably harmed by losing the statutory right to assess and enforce its patents for injunctive relief prior to commercial entry. "[T]he essence of a patent grant is the right to exclude others from profiting by the patented invention." *Dawson Chem. Co. v. Rohm & Haas Co.*, 448 U.S. 176, 215 (1980) (citing multiple Supreme Court cases).

3. Hospira's premature launch will cause Amgen to suffer irreparable harm in the ESA market

Amgen markets two erythropoiesis-stimulating agents ("ESAs"): EPOGEN® and ARANESP®. ESAs are used primarily to treat patients suffering from anemia in connection with chronic kidney disease (including patients on dialysis) or chemotherapy. (Billen Decl. ¶ 5; Gaier Decl. ¶¶ 20-23.) [redacted]

[redacted] Amgen also licenses a third ESA, PROCRIT®, which Johnson & Johnson ("J&J") markets to oncology clinics and other market segments other than dialysis clinics. (Billen Decl. ¶ 6; Gaier Decl. ¶ 21.) PROCRIT® contains the same active ingredient (epoetin alfa) as EPOGEN®, which Amgen manufactures for J&J, and for which Amgen receives royalties from J&J. (Billen Decl. ¶¶ 6, 21.)

Hospira's biosimilar epoetin product will compete with EPOGEN®, ARANESP®, and PROCRIT®, the three ESAs that Amgen either markets or licenses. (Billen Decl. ¶ 11; Gaier Decl. ¶ 39.) The irreparable harm that Amgen will face if Hospira prematurely launches its epoetin biosimilar product are described below and more fully detailed in the accompanying expert declaration of Eric Gaier, Ph.D.

a. Hospira's premature launch would cause Amgen to suffer irreparable price erosion

[redacted] Courts have repeatedly held that the steep loss of market share and revenue, as well as lasting price erosion, caused by the introduction of a generic drug constitute irreparable harm justifying the entry of injunctive relief. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382 (Fed. Cir. 2006) (upholding finding of irreparable harm supporting preliminary injunction, in the form of "irreversible price erosion" due to competitor's marketing of a lower-priced generic version of patentee's drug); *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (likelihood of price erosion and loss of market position are evidence of irreparable harm).

Medicare pays for most dialysis treatments in the United States, regardless of the age of the patient. (Billen Decl. ¶ 22; Gaier Decl. ¶ 30.) Medicare reimburses health-care providers for

dialysis services on a "capitated" or bundled basis. (Billen Decl. ¶ 22; Gaier Decl. ¶ 30.) This means that Medicare pays a single fee for each dialysis treatment, which must cover the cost of any ESA administered to patients. For this reason, healthcare providers administering ESAs in the dialysis setting have an incentive to move to lower-priced ESAs, which will enable Hospira to gain market share by aggressively pricing its epoetin product, resulting in price erosion. (Billen Decl. ¶ 22; Gaier Decl. ¶ 30.)

[redacted]

If Hospira chooses to compete with Amgen in the oncology segment, Hospira will likely offer customers discounts or rebates, which will irreparably harm Amgen. Medicare (and most private payors) reimburse doctors for oncology medication at Average Selling Price ("ASP") plus 6%. (Billen Decl. ¶ 24; Gaier Decl. ¶¶ 45-46.) The higher the ASP, the higher the physicians' profit margin. However, Hospira's newly introduced medications won't have an ASP for 6 to 9 months after launch, so Medicare will use the Wholesale Acquisition Cost, or "WAC" price, to set reimbursement in the interim. (Billen Decl. ¶ 24; Gaier Decl. ¶ 34.) If Hospira's WAC price for its newly-introduced product is greater that the ASP price of the incumbent product, Medicare reimbursement payments will be higher for the newly-introduced product. Thus, the government pays a higher price to reimburse physicians, physicians realize a higher profit margin on Hospira's reimbursements, and Amgen will be forced to lower its price to

compete. (Billen Decl. ¶ 24; Gaier Decl. ¶¶ 34-35, 45-46.)

[redacted] The law recognizes price erosion as irreparable harm due to its "irreversible effects." *Sanofi-Synthelabo v. Apotex Inc.*, 488 F. Supp. 2d 317, 342-43 (S.D.N.Y. 2006), *aff'd*, 470 F.3d 1368 (Fed. Cir. 2006).

b. Hospira's premature launch would cause Amgen to suffer irreparable damage to consumer relationships and goodwill

Hospira's premature entry into the market may irreparably damage Amgen's relationship with its customers and goodwill. (Gaier Decl. ¶¶ 52-54.) If Hospira launches its biosimilar epoetin product and the Court later enjoins it based on Amgen's patent rights, Amgen's enforcing of its patent rights will be portrayed as taking a medicine off the market. If Amgen tries to raise its prices to their level before Hospira's wrongful entry, Amgen's goodwill in the market will be further harmed, particularly where reimbursement rules would likely provide doctors less than full reimbursement for the new cost after the price has been restored. In the context of patent litigation, "[t]here is no effective way to measure the loss of sales or potential growth—to ascertain the people who do not knock on the door or to identify the specific persons who do not reorder because of the existence of the infringer." *Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 930 (Fed. Cir. 2012). Here too, there is no effective way to quantify the effect of Hospira's entry into the market on Amgen's reputation.

biosimilar product that will directly compete with Amgen's EPOGEN® product, but Amgen will be denied the time and information to evaluate and secure, if appropriate, the exclusionary right that a patent uniquely grants to the inventor. The balance of the equities favor Amgen.

D. The public interest favors the entry of an injunction

There is an overriding public interest in prohibiting Hospira from disregarding the notice period in a statute enacted to encourage a predictable set of timelines to govern commercial behavior. When Congress enacted the BPCIA, it sought to strike a balance between the public interest in lower-priced biologics and the public interest in incentives for innovation. Pub. L. No. 111-148, 124 Stat. 119, 804, § 7001(b). Congress created an abbreviated FDA approval pathway for "biosimilars," effectively reducing the time and cost of bringing a competing biological product to market by allowing the applicant to rely on the clinical data and license of the innovator. Coincident with FDA review and licensure of a biosimilar product, Congress also created in the BPCIA a process for the orderly identification and enforcement of the innovator's patent rights *before* commercial marketing of the newly licensed product begins, thereby maintaining the value of patents and the incentives they provide. The public interest is best served by requiring Hospira to following the law, honoring the balance struck by Congress.

There is a strong public interest in encouraging investment in the research and development to create novel biological therapeutics that treat human disease. The fact that a copyist may sell at a lower price does not override this important public interest. *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383-84 (Fed. Cir. 2006). Patents have long been recognized by the courts as an incentive to encourage just such investment: "by offering a right of exclusion for a limited period as an incentive to inventors to risk the often enormous costs in terms of time, research and development." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1363 (Fed. Cir. 2008) (quoting *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 480 (1974)).

EXHIBIT 29

THE INVESTOR
July 06, 2019

Bio & Medicine

Celltrion CEO aims to sell Truxima in US this year

PUBLISHED :March 26, 2019 - 16:14 UPDATED :March 26, 2019 - 17:38

Celltrion's founder and Chairman Seo Jung-jin announced on March 26 that the company aims to begin selling its biosimilar Truxima in the US within the second half of this year.

Seo -- who is in Tokyo on business -- made the announcement over the phone during Celltrion's 28th shareholders meeting held on March 26 in Songdo, Incheon.

Celltrion's founder and Chairman Seo Jung-jin

"Since Celltrion is directly shaping the sales strategy for the US market, instead of through our onsite partner, we will make sure to focus on gaining market share," Seo said.

In November last year, Celltrion obtained marketing authorization from the US Food and Drug Administration for Truxima, a copy version to Roche's blockbuster cancer drug Rituxan, which currently has around 5 trillion won ($4.41 billion) in market share in the US.

Seo also added that Herzuma, a biosimilar of Roche's Herceptin, for which the company also obtained marketing authorization from the US FDA in December last year, will be launched at the beginning of next year, after the introduction of Truxima.

Moreover, Seo also laid out plans to establish a joint venture in China during the first half of this year to expand its presence globally. Celltrion and **Celltrion Healthcare** will fund 60 percent in the joint venture, which will be around 100 billion won, with the Chinese partner funding the remaining 40 percent.

The chairman once again emphasized that Celltrion aims to reach 5 trillion won in sales by 2020 and

EDITOR'S PICKS


KRX unveils timeline to discuss Kolon TissueGene delisting

Startups & Inv

Japanese startup Euglena aims to produc biofuel for Tokyo Olympics

NHN Payco receives W75b investment to upgrade fintech platforms

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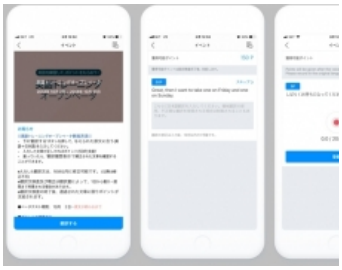
Flitto's kosdaq listing fetches W38b

Startups & Inv

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 16-853 (MSG)
	)	CONSOLIDATED
AMNEAL PHARMACEUTICALS LLC, et al.,	)	REDACTED - PUBLIC VERSION
	)	
Defendants.	)	

AMGEN'S OPENING BRIEF IN SUPPORT OF ITS MOTION FOR AN EMERGENCY INJUNCTION PENDING APPEAL

MORRIS, NICHOLS, ARSHT & TUNNELL LLP
Jack B. Blumenfeld (#1014)
Derek J. Fahnestock (#4705)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@mnat.com
dfahnestock@mnat.com

Attorneys for Amgen Inc.

OF COUNSEL:

John D. Murnane
Joshua I. Rothman
Alicia A. Russo
VENABLE LLP
1290 Avenue of the Americas
New York, NY 10104-3800
(212) 218-2100

Wendy A. Whiteford
Lois M. Kwasigroch
Eric Agovino
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, CA 91320-1789
(805) 447-1000

Originally Filed: March 19, 2019
Redacted Version Filed: March 26, 2019

In short, there is a likelihood that the Federal Circuit will hold on *de novo* review that this Court's approach to prosecution history estoppel was contrary to settled precedent and undermines the familiar maxim that "all aspects of the prosecution must be viewed as they would be viewed by persons of skill in the field of the invention." *Hebert*, 99 F.3d at 1118.

II. Amgen Will Suffer Irreparable Harm.

It is well-known that generic entry[3] can lead to irreparable injuries like price erosion, loss of goodwill, reputational harm, and loss of business opportunities. *See, e.g.*, *Celsis*, 664 F.3d at 930. All of that is bound to happen here, as demonstrated through the attached declarations of Dr. Jerry A. Hausman and Christos Georghiou, as well as case law regarding these issues. While Piramal would be liable for damages in the event of reversal on appeal, such money damages cannot fully compensate Amgen for the well-recognized irreparable harms it will face.

A. Absent An Injunction, Generic Entry Will Destroy The SENSIPAR® Market.

"Where two companies are in competition against one another, the patentee suffers the harm—often irreparable—of being forced to compete against products that incorporate and infringe its own patented inventions." *Douglas Dynamics, LLC v. Buyers Prods. Co.*, 717 F.3d 1336, 1345 (Fed. Cir. 2013). That is particularly true when a patent holder has been "unwilling[] to license," which also "favor[s] finding irreparable injury." *Presidio Components, Inc. v. Am. Tech. Ceramics Corp.*, 702 F.3d 1351, 1363 (Fed. Cir. 2012). The loss of market share and preferred status for a patented pharmaceutical product are both accepted forms of irreparable harm. *See, e.g.*, *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1368

[3] Defendants Watson Laboratories, Inc. and Actavis Pharma, Inc. (collectively, "Watson") undertook a brief at-risk launch of its generic product in late December 2018. However, as explained in a joint motion to the Court (D.I. 412), on January 2, 2019, Amgen and Watson executed a Litigation Settlement Agreement ("the Agreement") fully resolving their respective infringement claims and invalidity counterclaims as to the '405 patent and promptly addressing Watson's launch before it caused market erosion or any other irreparable injuries to Amgen that would have occurred absent such an agreement.

(Fed. Cir. 2001); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382 (Fed. Cir. 2006); *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008).

Piramal's launch will cause Amgen to incur each of these harms. Piramal will have every incentive to sell a flood of products into the distribution channels. Hausman, ¶¶ 27-28; Georghiou, ¶¶ 9-11, 25. The impact to Amgen is likely to be immediate. Typically, entry of a generic product results in immediate loss of 40% of a brand's market share, with additional losses of more than 90% over the long run. Hausman, ¶¶ 14-16. Amgen can expect a loss of up to 70% market share in the first month, and up to a 95% loss of market share within the first six months. Hausman, ¶ 22; Georghiou, ¶¶ 14, 26.

These losses are also likely to persist, because market changes to insurance coverage, reimbursement, and formulary status, as well as price erosion, are deeply engrained and almost impossible to undo. Georghiou, ¶ 21. After a launch, health insurance providers will be unlikely to cover prescriptions for SENSIPAR® without significant bargaining and permanent concessions from Amgen. Hausman, ¶¶ 9-13, 24, 32. These third-party payers have significant influence over the pricing and reimbursement of prescription drugs, Hausman, ¶ 13, and SENSIPAR® is currently a preferred "Tier 1" drug for most insurers. Georghiou, ¶ 20. Now that Piramal has launched, however, SENSIPAR® could plummet to "Tier 3" status, resulting in larger patient copays and leading prescribing physicians to try less expensive treatments first. Georghiou, ¶¶ 20, 24. Moreover, many states *require* generic drug substitution absent explicit instructions from the physician—something physicians are unlikely to do. Georghiou, ¶¶ 18-20.

The Medicare reimbursement policy that presently governs the administration of SENSIPAR®, the "Transitional Drug Add-on Payment Adjustment" policy (TDAPA), could further accelerate Amgen's market share losses. Under TDAPA, until at least January 2020,

EXHIBIT 31

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EXHIBIT 32

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EXHIBIT 33

THE HER2 JOURNEY

INTRODUCTION

01 UNMASKING THE ENEMY

02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK

PERSEVERANCE

THE INSIDE STORY OF A BREAST CANCER BREAKTHROUGH, 30 YEARS IN THE MAKING

By Erin Biba

Erin Biba is a New York-based freelance science writer whose work regularly appears in publications such as Scientific American and Newsweek.

"This part's tough. It always gets me," says Lisa, fighting back tears. She pauses for a moment as she retells the story of her second breast cancer diagnosis. After years in remission, it was back. And this time it had spread to her liver, lungs and bones. "In my mind I'm like: 'You're screwed. It's everywhere. You can't compete with this.'"

But after her terminal diagnosis, Lisa is alive. Small tumors remain throughout her body, and she still has stage IV breast cancer, but thankfully she's been given more time to spend with her three sons. "I'm so glad," she says. "Their hearts were broken when I got sick again."

The information in this story represents a specific point in time when this article was published. The story is not being updated and no representation should be made concerning Lisa's current condition. The story should not be used as a substitute for professional medical advice.

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

Lisa discusses her second breast cancer diagnosis

Lisa's Story

Lisa was just 32 when she reached to pick up her young son's book bag one morning and felt a pain in her breast. She didn't think it could possibly be cancer. "I thought I was way too young," she says.

SEE LISA'S STORY

For the last 30 years, scientists, doctors and patients have been engaged in a war against Lisa's particular type of breast cancer – an especially aggressive form of the disease known as HER2-positive. Developing medicines to treat it has been an exceedingly difficult task and over the course of those decades, there were many moments when it seemed they could not succeed. Though the battle is far from over, the progress they have made not only gave hope to Lisa and others, but also helped to fundamentally change the way we fight cancer.

Chapter 1

UNMASKING THE ENEMY

Cancer has been an all-too-common, formidable enemy for centuries.[1] Often caused by genetic alterations within our own DNA, it's highly complex and extremely difficult to treat.

The discovery in 1976 that cancer-causing genes – or oncogenes – are present in our own cells signified a huge leap forward in our understanding of the disease.[2] But despite that breakthrough, in the years that followed, many unanswered questions remained. For example, scientists and oncologists still didn't know why some people with cancer fared better than others on the available treatments.

"It was frustrating," says Dennis Slamon, M.D., Ph.D., director of clinical and translational research at the University of California, Los Angeles, Jonsson Comprehensive Cancer Center. "We had to pretty much look at the disease with a one-size-fits-all approach. We had one or two different regimens that we used for these patients and they had good outcomes or bad outcomes."

Dennis Slamon M.D., Ph.D., director of clinical and translational research, University of California, Los Angeles, Jonsson Comprehensive Cancer Center

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

He was determined to understand why. The oncogene discovery had opened the door to an exciting period in cancer research and by the early 1980s, scientists had already begun to build a clearer picture of the role that certain genes might play in cancer growth.[3]

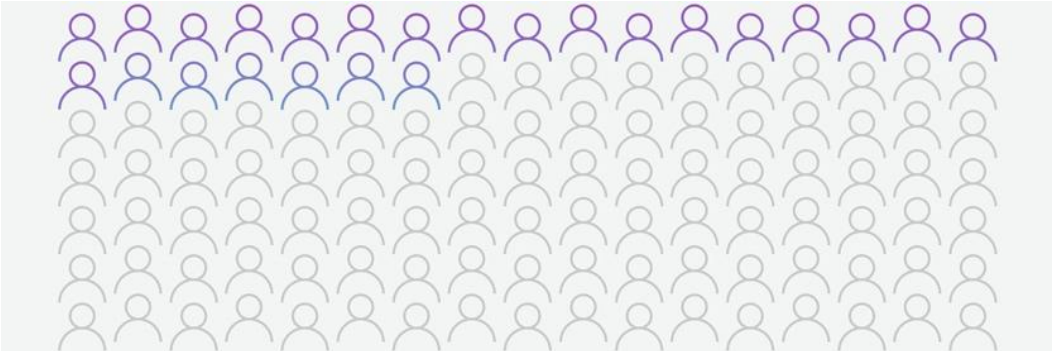
A few hundred miles away in South San Francisco scientists at Genentech, including Art Levinson and Axel Ullrich, had been successful in cloning a number of cell growth-regulating genes as the company worked to develop medicines for a variety of different diseases.[4,5] Slamon was aware of their work and, along with oncologist Dr. Bill McGuire at the University of Texas at San Antonio, they teamed up to understand whether any of these genes might play a role in cancer.

Using DNA probes that the Genentech team had created to identify the genes, they performed a series of experiments to see if any of them might be over-expressed in cancer tumors. One, in particular, stood out.

The gene, called HER2[6-10] instructs cells in the body to form receptors on their surface that send signals telling them to grow and divide.[11] It's part of the normal mechanism that regulates the growth, division and repair of healthy cells. But in some of the breast cancer tumors, there seemed to be higher than normal levels of the gene.

In fact, they saw that about a quarter of the breast cancer tumors had an excess of HER2.[12,13] This meant each cell didn't just have the standard of about 20,000 HER2 receptors but up to 2 million of them, triggering the cancer cells to replicate out of control and the tumors to grow.[11] People with this over-expression had what would eventually become known as "HER2-positive" breast cancer.

15 *to* 20%



of people with breast cancer are HER2-positive[41,47]

INTRODUCTION

01 UNMASKING THE ENEMY

02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

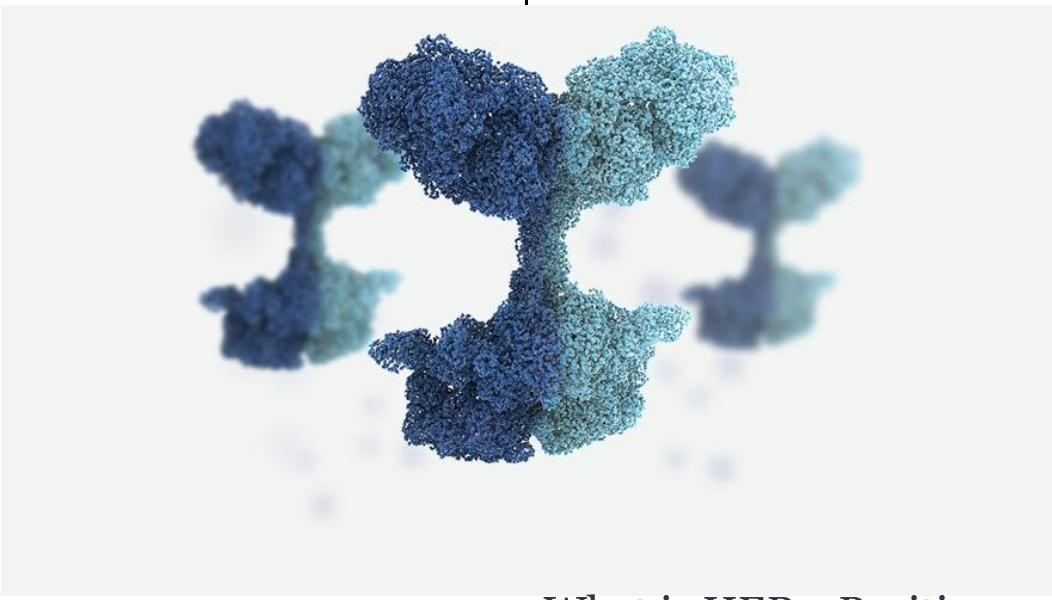
04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK

And thanks to the detailed medical histories that McGuire had collected on each sample in his tumor bank[14] the team could see that, on average, women with these tumors had not responded as well to treatment. Their cancer had recurred more quickly and they also died more quickly. It appeared that having too many HER2 receptors didn't just contribute to breast cancer; it was potentially the driver behind one of the most aggressive and deadly forms.[12]

The scientists had identified an enemy: HER2 was a new target in the war against breast cancer.



What is HER2-Positive Breast Cancer?

WATCH THE VIDEO

Chapter 2

INTO THE UNKNOWN

But how do you attack a target you've only just begun to understand? Determining a mechanism that could drive a specific type of cancer was a huge step forward for research, but it was only the first step. Creating a medicine to slow or stop it wasn't going to be easy.

The scientists at Genentech believed that monoclonal antibodies – man-made copies of proteins that the body's immune system creates to fight off bacteria and viruses – could be an answer. They were able to build mouse versions of these antibodies that would bind to the HER2 receptors on breast cancer cells and help block them from transmitting growth signals.[15,16] If these antibodies worked in people, they might not only stop tumors from growing, but possibly even shrink them.

Mark Sliwkowski, distinguished staff scientist, Genentech

It was an idea that scientists had been considering since the 1970s[17] when "there was great hope that this would be the future of medicine," says Paul Carter, now a senior director and staff scientist at Genentech. Unfortunately, no one was able to make it work in clinical trials. The trouble was, the human immune system saw mouse antibodies as foreign objects and rejected them. As a result, tests with these antibodies had been disappointing and showed little promise.[18,19]

To get around that problem, Carter, together with colleagues Michael Shepard, Len Presta and their teams, took the sections of the mouse antibody that would bind to HER2 and grafted them onto a human antibody, cleverly disguising it so it wouldn't be rejected – a so-called "humanized antibody."[20]

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

Paul Carter, senior director and staff scientist, Genentech

"I think people were actually astonished," Carter says about revealing their research to management. "At the time there were very few examples of this having been done anywhere. There was real surprise."

Success in the lab is one thing, but there were reservations about moving forward with developing a medicine based on Carter's creation. All of the logic and evidence at the time suggested that it was too risky. The technology behind monoclonal antibodies was questionable. HER2 had only recently been identified as a potential target in cancer. And Genentech had never successfully developed a cancer medicine before. In fact, one of its first experimental cancer therapies had just failed in clinical trials.[21] It seemed completely irrational that a small biotech startup would invest in a development program in such an uncharted area.

To get the body of evidence they'd need for Food and Drug Administration (FDA) approval of the medicine, the company would have to engage in large-scale clinical trials. Even if those were successful, could they manufacture enough of these antibodies to meet the need? Not only was there a huge difference in size between these and more common small-molecule medicines like aspirin, they were also far more complex than any of the large-molecule medicines Genentech had already developed.

Monoclonal Antibody: 20,000 atoms[48,49]

Man-made antibodies are more complex and can be up to 800 times larger than small molecules such as aspirin.

Aspirin Molecule: 21 atoms

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

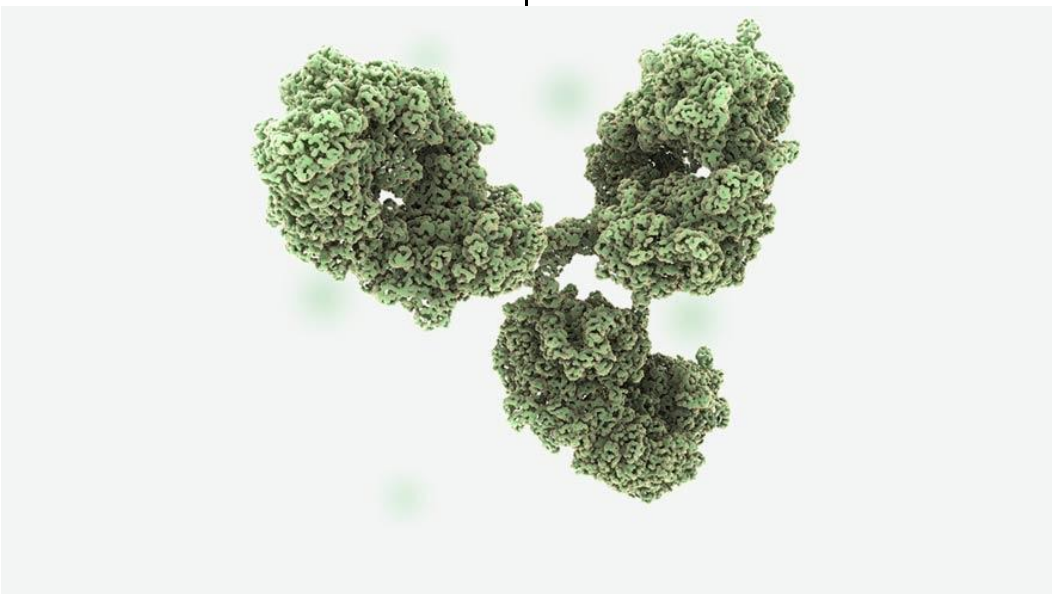
For a period of time, the answer to the question of whether or not to develop the medicine was: No. Genentech decided the project wasn't going forward.

"We were kind of stunned," said Gail Lewis Phillips, a senior research associate at the time. "It's not the kind of thing we expected and not what we wanted to hear."

That decision, however, was later reversed. There were a variety of reasons why. Scientists like Levinson and Shepard, who had worked so hard on the research, were determined not to give up; Dennis Slamon came by the offices regularly, stopping folks in the halls to talk about how impressive the data were; and Bill Young, a vice president who had recently learned his mother had breast cancer, became an advocate for the HER2 program. He knew that patients desperately needed more treatment options.

Gail Lewis Phillips, senior scientist, Genentech

The development program for the antibody that would eventually become Herceptin® (trastuzumab) [Important Safety Information] was now official: It had funding and was moving forward. But no one on the team could have imagined the challenges that lay ahead. It would be years before they could build enough evidence to demonstrate the veracity of their breakthrough to the outside world.



Proposed Mechanism of Action

How Does Herceptin Work?

WATCH THE VIDEO

INTRODUCTION

01
UNMASKING THE ENEMY

Chapter 3

TRIBULATIONS AND TRIALS

In 1991 Barbara's breast cancer was in remission. At the time she was mourning the loss of her daughter to a car accident. Cancer was the least of her worries. And then she discovered a lump in her throat near the collarbone. "I knew what that meant. I wasn't surprised it came back," she says.

Instead of seeking additional treatment, Barbara was going to Mexico, off for a vacation to get ready to say goodbye. Her doctor said he was sending her information to an oncologist in California working on understanding cancer genes. "I said, 'I don't care, do whatever you want.'" She had stage IV cancer; it had spread to her lungs. She says, "I already thought I was dying."

Not long after, Barbara received a call from Dennis Slamon. Would she be interested in participating in a clinical trial for a potential new medicine? He explained to her what HER2 was and its role in her type of breast cancer, as well as the risks of participating in a clinical trial. “He sounded so logical,” Barbara recalls. “And then my husband made me go. ‘You have nothing to lose,’ he said.”

And so Barbara became one of the first women in the world to take the medicine that would become Herceptin. In the six years following the first trial, more than 900 others would volunteer to participate in clinical studies designed to better understand whether it was safe and whether it could help patients.[22]

INTRODUCTION

01 UNMASKING THE ENEMY

02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK

A Serious Problem

Halfway through the Phase III trial for Herceptin, the final step before a potential FDA approval, researchers received very worrying news.

READ THE STORY

Today, Barbara is the only surviving member of the initial group of 15 women who participated in the first trial. Her outcome is far from typical. One of her fellow participants died from kidney failure within the first weeks of starting treatment. Another found the process too emotionally overwhelming, couldn’t handle the side effects anymore, and withdrew from the trial. “Being the only survivor is very emotional. We girls all pretty much bonded with the treatment. The whole attitude of everybody was we wanted to be part of something that would find a way to help,” she says.

Slamon refers to all of those women as his colleagues. "That whole group left an amazing impression on me," he says. "They'd played a critical role in this major part of history, this grand experiment about whether this targeted therapy would work. Everybody talks about targeted therapy today. Back then, there was no such thing."

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

Dennis Slamon M.D., Ph.D., director of clinical and translational research, University of California, Los Angeles, Jonsson Comprehensive Cancer Center

As the trials were being conducted, Genentech was inundated with requests from other breast cancer patients for Herceptin, hoping it could potentially help them. But the medicine hadn't yet been proven safe and effective with enough data for FDA approval. Not to mention the simple fact that supply at the time was extremely limited; they were only able to produce enough for the clinical trials. The challenge of large-scale manufacturing for a medicine so complex had become a problem even before it was approved.

Nonetheless, Herceptin was a beacon of hope for metastatic breast cancer patients who had exhausted all other options. They weren't going to give up, and they were outspoken about their need. Some even came down to Genentech with picket signs to campaign for access.[5,23] The company decided it would have to find a solution.

So in 1995 Genentech worked with patient advocates to set up one of the first FDA-approved expanded access programs for a cancer medicine. It would allow certain people who weren't eligible for the trial to receive Herceptin before its approval.[5,23] According to patient advocate Bob Erwin, who worked with the company on the design and whose wife had succumbed to breast cancer, "Genentech pioneered the program at great cost to itself – not so much financial but stress, time and having to withstand a lot of negative critiques" as they worked out a way to fairly allocate their very limited supplies. However, looking back, "their overall positive experience caused other companies to look at programs like this more favorably."

In 1998 results of the large Phase III trial needed for FDA approval were finally revealed and questions about the safety and efficacy of the medicine were answered. The data showed that in some cases treatment with Herceptin could result in a risk of serious heart problems. Doctors would need to monitor their patients' heart function closely throughout and after treatment. [Important Safety Information]

But there was also some very positive news that finally justified the years of hard work. Adding Herceptin to chemotherapy had been shown to slow the progression of HER2-positive metastatic breast cancer.[24,25] [Important Safety Information]

Upon receiving the news, distinguished staff scientist Mark Sliwkowski walked into Lewis Phillips' office. All he said to her was, "It worked." She knew immediately what he was talking about. "It was a big deal," she says. "We were jumping up and down and hugging each other."

Gail Lewis Phillips, senior scientist, Genentech

INTRODUCTION

01 UNMASKING THE ENEMY

02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK

Portrait of a Scientist

Gail Lewis Phillips in her own words. As told to graphic journalist and illustrator, Wendy MacNaughton

SEE GAIL'S STORY

The first personalized treatment for cancer had arrived.[26] In 1998 Herceptin was approved in combination with paclitaxel chemotherapy by the FDA for HER2-positive metastatic breast cancer. [Important Safety Information] But in reality, scientists at Genentech were just beginning to understand the role of HER2 in cancer. And there were a lot of unanswered questions. For example, could they help some people live longer by treating them earlier – before their cancer had spread to other parts of the body? There was still so much more to be done to help people with the disease.

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

And so they pushed forward with new trials for Herceptin in early stage HER2-positive breast cancer, hoping that treating people earlier might help stop their cancer from returning or reaching a more advanced stage. The results, revealed during the American Society of Clinical Oncology (ASCO) annual meeting in 2005, were hailed as a huge success.

The data showed that, in combination with a type of chemotherapy, Herceptin cut the risk of people's cancer coming back by half, compared to the chemo alone.[27] [Important Safety Information] Oncologists, scientists and researchers remember vividly the moment when the trial results were presented. From the podium, George Sledge, M.D., now chief of medical oncology at Stanford University Medical Center, summed up the data in one brief, but powerful statement: "Ladies and gentlemen, biology has spoken and we should listen."[28]

> "Biology has spoken and we should listen."
>
> GEORGE SLEDGE, M.D., *ASCO 2005*

But for a small group of scientists at Genentech, that ASCO meeting was bittersweet. Despite the overwhelming joy of knowing Herceptin could help people with early breast cancer, there was also a disappointment.

As they had continued to study the role of HER2 they learned that it is not the only receptor on the surface of a cell that triggers growth and division: There are actually four different HER receptors, and in order to efficiently move those growth messages along, the receptors have to pair up.[29] They discovered that one of the

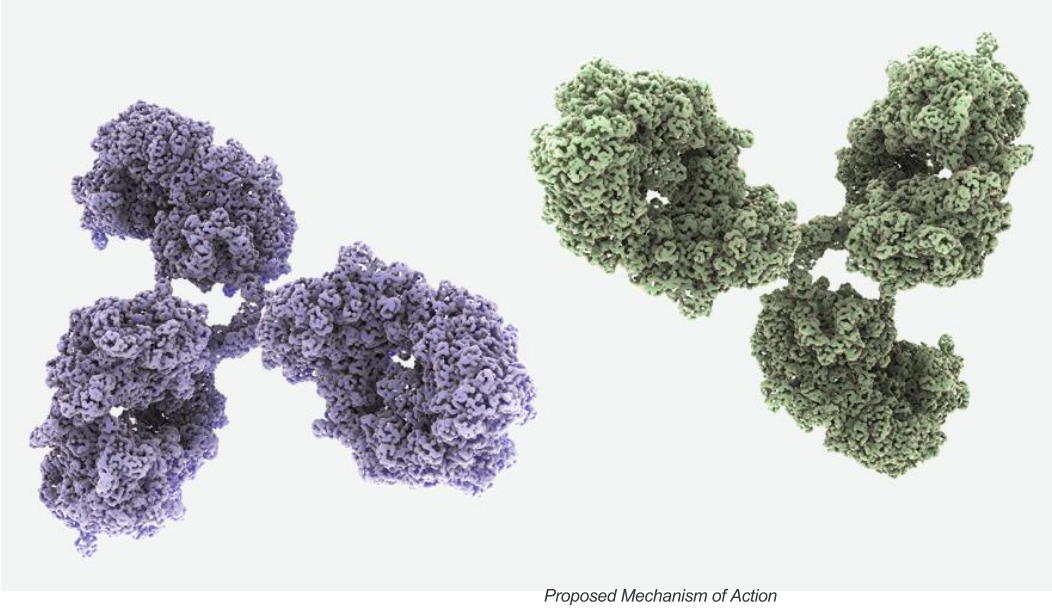
original mouse antibodies they had created at the same time as Herceptin showed promise in stopping this pairing and blocking the growth messages in a different way.[30] Perhaps, they thought, a medicine derived from this antibody might help slow the growth of other types of cancer where HER2 was not over-expressed. [Important Safety Information]

Early studies in the lab suggested that idea might prove to be true. And so the Genentech team collaborated with colleagues at long-term partner Roche to carry out clinical trials for this potential medicine and begin the long, hard work of understanding how it behaved in the human body.

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

Unfortunately, results from Phase II trials, presented at that very same ASCO meeting, showed the drug did little to slow the growth of other types of cancers.[31] Sliwkowski, who had worked on both projects, says the dichotomy was emotionally confusing. Herceptin was at its highest point, but their hopes for this new medicine had been dashed.

Little did they know at that moment that it wasn't completely over for the drug that would eventually become known as Perjeta® (pertuzumab). [Important Safety Information] Despite mounting evidence against it, the Roche development team decided to push forward with additional research and explore one final possibility: What if they tried combining Perjeta with Herceptin in HER2-positive breast cancer? What if the two medicines could work together, in complementary ways, to slow these cancers more effectively than either medicine alone?



Proposed Mechanism of Action

Herceptin & Perjeta Working Together

WATCH THE VIDEO

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

According to Max Hasmann, a Roche scientist who was working on the project in Penzberg, Germany: "It wasn't easy because in the beginning everyone would ask: 'Why do you need two antibodies targeting the same target?' After all, they had already developed Herceptin for HER2-positive breast cancer. Did they really need another medicine for the same thing?"

"It was scientifically plausible. Not standard, but still plausible," says Sliwkowski. The approach was in stark contrast to how second-generation medicines are normally designed – with the objective of the second outperforming the first. But if the success of Herceptin had proved anything, it was that they didn't always have to follow the standard way of doing things, they just had to follow their science.

And sticking with it turned out to be the right decision. The combination was a success, proven by results from a Phase III trial, dubbed CLEOPATRA. Adding Perjeta and Herceptin to docetaxel chemotherapy prolonged the time people with previously untreated HER2-positive metastatic breast cancer lived without their disease getting worse and helped them live longer overall.[32,33] [Important Safety Information]

On average, the Perjeta combination extended the lives of those who received it by almost 16 months compared to Herceptin and chemotherapy alone.[33,34] They lived a median of almost five years – the longest ever observed in people with this aggressive type of advanced breast cancer (56.5 months vs. 40.8 months).[33,34] It's a significant result for a combination of medicines that almost never came to be.

Like Herceptin, Perjeta is associated with serious side effects and may cause heart problems. It carries a boxed warning because of these serious cardiac risks, and doctors must monitor patients' heart function closely. Perjeta also has a boxed warning for the potential to harm an unborn baby.

In June 2012, the FDA approved Perjeta in combination with Herceptin and docetaxel chemotherapy for the first-line treatment of people with HER2-positive metastatic breast cancer. [Important Safety Information]

Lisa is just one of the patients who has benefited since then, although not everyone has or will have the same experience as her. Looking back on her diagnosis, when she was so sure that her life had come to an end, Lisa says she didn't have high hopes but was determined to try it for her boys. She's so happy that she did and is grateful for the time with them. "My children are everything to me," she says.

Lisa discusses her decision to pursue treatment

Chapter 5

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK

Though the advent of new cancer medicines has helped some people live longer, balancing the benefits with the potential side effects remains a challenge to this day. While their sole objective is to kill the cancer, the fact that they are delivered all throughout the body means that they can also affect healthy cells. Chemotherapy, for example, is designed to help kill rapidly dividing cancer cells but they're not the only cells in the body that behave that way – healthy cells in places including the bone marrow, stomach, bowel and hair follicles replicate quickly too. It's part of the reason why patients undergoing these treatments often experience side effects like infections, nausea, diarrhea and hair loss. But chemotherapy continues to play a fundamental role in treating many cancers.[35,36]

Soon after the first approval of Herceptin, the team at Genentech wondered if they could harness the benefits of targeted medicine to somehow help reduce this collateral damage on healthy cells. The concept, called an "antibody-drug conjugate," was another one of these ideas that scientists had been considering for decades but very few had been able to pull off.[37,38]

The thinking was this: You can build an antibody to target a specific receptor on a cell. What if you could attach a chemotherapy drug to that antibody and deliver it directly inside the cancer cell?

"It was a research idea that had been around for at least 20 years by the time we started working on it. There were a number of companies that had been trying to take the idea and turn it into medicines. Very few of them had been successful," says Fred Jacobson, a staff scientist at Genentech.

Fred Jacobson, staff scientist, Genentech

One of the main challenges was how to connect the chemotherapy to the Herceptin antibody. The molecular attachment, also referred to as the linker, turned out to be an important part of this new concept because it had a major impact on whether the medicine would be safe and effective. [39,40,41] If the linkage holding the chemo molecule to the antibody wasn't stable enough and was broken on the way to its target, then the powerful and highly toxic chemotherapy drug would be generally released into the body.[39,40]

INTRODUCTION

01 UNMASKING THE ENEMY

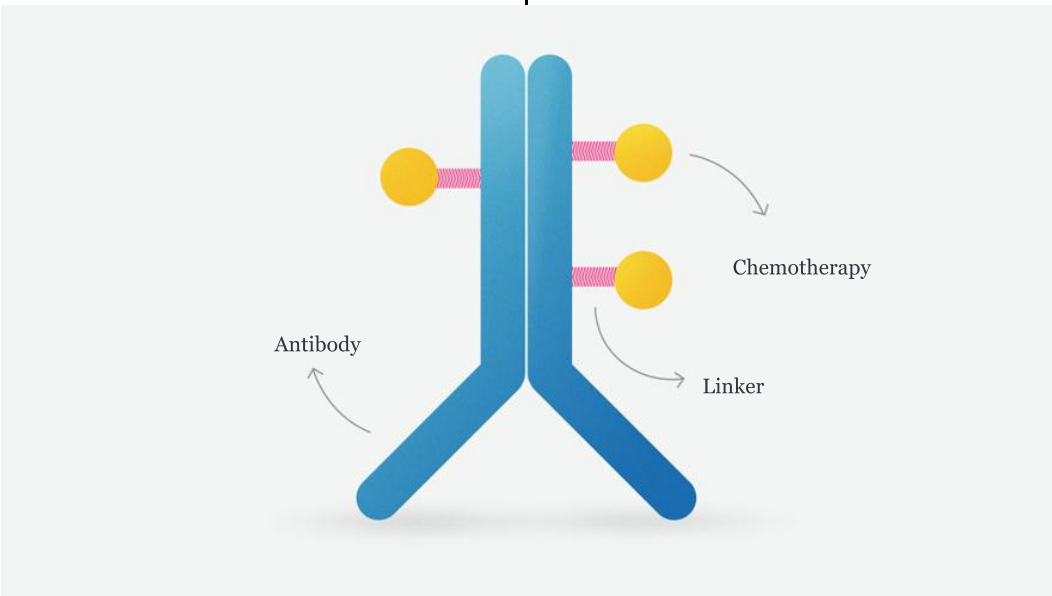
02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK



Genentech scientists spent several years working to find a linker and chemo combination that would remain intact and then break apart only once it entered the cell.[41] To everyone's surprise, the most successful version ended up being very different from what the team had originally envisioned: It was an unbreakable linker that worked best.

"It was sort of an 'Ah Ha!' moment," says Jacobson. It turned out that, in some forms of cancer, even if the linker didn't break, the antibody itself was broken down enough so that the chemotherapy was still capable of killing the cell.[41]

Proposed Mechanism of Action

How Does Kadcyla Work?

WATCH THE VIDEO

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

Following that discovery, in collaboration with Massachusetts-based ImmunoGen, the medicine that would become Kadcyla® (ado-trastuzumab emtansine) was born. [Important Safety Information] Results of the Phase III EMILIA trial that led to its FDA approval in 2013 showed that it helped give certain people with HER2-positive metastatic breast cancer more time before their cancer got worse and extended their lives by almost six months compared to a standard treatment, at the time of the trial.[42-44]

People receiving Kadcyla in the trial still experienced severe side effects, including nerve problems, low levels of red blood cells, tiredness, liver problems, pain, bleeding and constipation. Kadcyla also has boxed warnings for potential heart and liver damage, can also harm an unborn baby and must not be substituted for Herceptin. [Important Safety Information]

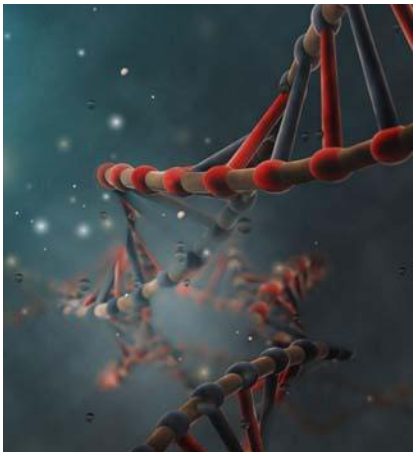
Much like Herceptin and Perjeta before, even after its FDA approval, scientists continued to study other ways Kadcyla might be able to help patients. As part of this effort, they conducted a large trial looking at a different combination involving Kadcyla, hoping it could help people with HER2-positive advanced breast cancer live even longer. But despite their belief in the science, they were disappointed to see that the combination didn't work as they had hoped.

After many successes in the HER2 journey, it reminded the team that medicine development is rife with challenges and often you don't get the result you want. "However," says Ellie Guardino, M.D., Ph.D., oncologist and senior group medical director at Genentech, "You learn. This is science. If you get one answer, it leads to 10 more questions. And 10 more questions are what we're after. All the incremental benefits that you get, in the end if you look from start to finish, are tremendous."

30 Years in the Making

A snapshot of just some of the milestones from the past 30 years in our HER2 medicine development journey

SEE THE TIMELINE



INTRODUCTION

01 UNMASKING THE ENEMY

02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

Chapter 6

BACK TO WORK

When you ask the researchers, scientists and physicians what their takeaway is from these past 30 years, they'll all agree that relentlessly pursuing the

science wherever it leads is what has ultimately helped patients. Even when you have something that is proven to work, you don't just pack up and move on. If you have failures in the development process, you learn from them, answer the new questions they create, believe in your data, and keep moving forward.

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

"Let's understand the biology, let's understand the target," says Dietmar Berger, global head of oncology at Genentech. "If the target is important, work as long as you need in order to find a mechanism to effectively address it." The approach, he says, was entirely new with the advent of medicines like Herceptin. After a time, it "turned the entire industry upside down."

Mark Sliwkowski, distinguished staff scientist, Genentech

Before Herceptin, there were no targeted treatments for solid cancer tumors. In fact, there were also no "personalized" medicines tailored to individual patients paired with companion diagnostic tests.[45] When Herceptin was introduced, there also had to be a sea-change in the way cancer itself was diagnosed. To determine if the medicine would be appropriate, doctors would first have to test their patient's tumor to see if it was HER2-positive. It's a common practice now that was unheard of two decades ago.[26] Today, the field of personalized medicine is widely regarded as one of the most important areas of drug development.

HER2-positive breast cancer is a particularly aggressive disease that once had a very poor prognosis. But today, on average, people who are diagnosed with it have better survival rates than those with HER2-negative cancer.[46] It's a landmark shift in patient care.

And, in the end, helping people is what this is all about. The reason the scientists kept jumping into new and untested areas of research and the reason they persisted in saving projects that looked doomed to fail is because they believed in their data. And when the data give you hope that someday someone's life might be saved, you don't ever stop.

VISIT OUR ONCOLOGY PAGE FOR MORE STORIES

The information in this story represents a specific point in time when this article was published. The story is not being updated and no representation should be made concerning Lisa's current condition. The story should not be used as a substitute for professional medical advice.

INTRODUCTION

01 UNMASKING THE ENEMY

02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK

Adjuvant Breast Cancer

Herceptin is approved for the treatment of early stage breast cancer that is **H**uman **E**pidermal growth factor **R**eceptor **2**-positive (HER2-positive) and has spread into the lymph nodes, or is HER2-positive and has not spread into the lymph nodes. If it has not spread into the lymph nodes, the cancer needs to be estrogen receptor/progesterone receptor (ER/PR)-negative or have one high risk feature.* Herceptin can be used in several different ways:

- As part of a treatment course including the chemotherapy drugs doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel. This treatment course is known as "**AC** → **TH**."
- With the chemotherapy drugs docetaxel and carboplatin. This treatment course is known as "**TCH**."
- Alone after treatment with multiple other therapies, including an anthracycline (doxorubicin)-based therapy (a type of chemotherapy).

Patients are selected for therapy based on an FDA-approved test for Herceptin.

*High risk is defined as ER/PR-positive with one of the following features: tumor size greater than 2 cm, age less than 35 years, or tumor grade 2 or 3.

Metastatic Breast Cancer

Herceptin has two approved uses in metastatic breast cancer:

- Herceptin in combination with the chemotherapy drug paclitaxel is approved for the first-line treatment of **H**uman **E**pidermal growth factor **R**eceptor **2**-positive (HER2-positive) metastatic breast cancer.
- Herceptin alone is approved for the treatment of HER2-positive breast cancer in patients who have received one or more chemotherapy courses for metastatic disease.

Patients are selected for therapy based on an FDA-approved test for Herceptin.

Important Safety Information

Possible serious side effects with Herceptin

Not all people have serious side effects, but side effects with Herceptin therapy are common.

Although some people may have a life-threatening side effect, most do not.

A patient's doctor will stop treatment if any serious side effects occur.

Herceptin is not for everyone. A patient should be sure to contact their doctor if they are experiencing any of the following:

HEART PROBLEMS

These include heart problems—such as congestive heart failure or reduced heart function—with or without symptoms. The risk for and seriousness of these heart problems were highest in people who received both Herceptin and a certain type of chemotherapy (anthracycline). In a study of adjuvant (early) breast cancer, one patient died of significantly weakened heart muscle. A patient's doctor will check for signs of heart problems before, during, and after treatment with Herceptin.

INFUSION REACTIONS, including:

- Fever and chills
- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Pain (in some cases at tumor sites)
- Headache
- Dizziness
- Shortness of breath

These signs usually happen within 24 hours after receiving Herceptin.

A patient should be sure to contact their doctor if they:

Are a woman who could become pregnant, or may be pregnant

Herceptin may result in the death of an unborn baby or birth defects. Contraception should be used while receiving Herceptin and for seven months after a patient's last dose of Herceptin. If a patient is or becomes pregnant while receiving Herceptin or within seven months after their last dose of Herceptin, the patient should immediately report Herceptin exposure to Genentech at (888) 835-2555.

Have any signs of **SEVERE LUNG PROBLEMS**, including:

- Severe shortness of breath
- Fluid in or around the lungs
- Weakening of the valve between the heart and the lungs
- Not enough oxygen in the body
- Swelling of the lungs

- Scarring of the lungs

A patient's doctor may check for signs of severe lung problems when he or she examines the patient.

Have LOW WHITE BLOOD CELL COUNTS

Low white blood cell counts can be life threatening. Low white blood cell counts were seen more often in patients receiving Herceptin plus chemotherapy than in patients receiving chemotherapy alone.

A patient's doctor may check for signs of low white blood cell counts when he or she examines the patient.

Side effects seen most often with Herceptin

Some patients receiving Herceptin for breast cancer had the following side effects:

- Fever
- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Infusion reactions
- Diarrhea
- Infections
- Increased cough
- Headache
- Feeling tired
- Shortness of breath
- Rash
- Low white and red blood cell counts
- Muscle pain

A patient should contact their doctor immediately if they have any of the side effects listed above.

Patients are encouraged to report side effects to Genentech and the FDA. Report side effects to the FDA at (800) FDA-1088 or http://www.fda.gov/medwatch. Report side effects to Genentech at (888) 835-2555.

Please see the Herceptin full Prescribing Information for additional Important Safety Information, including most serious side effects, at http://www.herceptin.com.

INTRODUCTION
01 UNMASKING THE ENEMY
02 INTO THE UNKNOWN
03 TRIBULATIONS AND TRIALS
04 JOINING FORCES
05 INTO THE CELL
06 BACK TO WORK

ABOUT PERJETA

Perjeta Indication Statement

Perjeta (pertuzumab) is approved for use in combination with Herceptin (trastuzumab) and docetaxel in people who have HER2-positive breast cancer that has spread to different parts of the body (metastatic) and who have not received anti-HER2 therapy or chemotherapy for metastatic breast cancer.

Important Safety Information

Side effects with Perjeta

- Not all people have serious side effects; however, side effects with Perjeta therapy are common. It is important for patients to know what side effects may happen and what symptoms patients should watch for.
- A patient's doctor may stop treatment if serious side effects happen. Patients should be sure to contact their healthcare team right away if they have questions or are worried about any side effects.

Most serious side effects of Perjeta

Perjeta may cause heart problems, including those without symptoms (such as reduced heart function) and those with symptoms (such as congestive heart failure).

- A patient's doctor may run tests to monitor the patient's heart function before and during treatment with Perjeta.
- Based on test results, a patient's doctor may hold or discontinue treatment with Perjeta.
- Patients should contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than five pounds in 24 hours, dizziness or loss of consciousness.

Receiving Perjeta during pregnancy can result in the death of an unborn baby and birth defects.

- Birth control should be used while receiving Perjeta and for seven months after a patient's last dose of Perjeta. If a patient is a mother who is breastfeeding, she should talk with her doctor about either stopping breastfeeding or stopping Perjeta.
- If a patient thinks she may be pregnant, she should contact her healthcare provider immediately.

- If a patient is exposed to Perjeta during pregnancy, or becomes pregnant while receiving Perjeta or within seven months following her last dose of Perjeta in combination with Herceptin, she is encouraged to report Perjeta exposure to Genentech at (888) 835-2555.

Other possible serious side effects

- Perjeta should not be used in patients who are allergic to pertuzumab or to any of the ingredients in Perjeta.
- **Infusion-related reactions:** Perjeta is a medicine that is delivered into a vein through a needle. Perjeta has been associated with infusion-related reactions, some fatal. The most common infusion-related reactions when receiving Perjeta, Herceptin and docetaxel were feeling tired, abnormal or altered taste, allergic reactions, muscle pain and vomiting. The most common infusion-related reactions when receiving Perjeta alone were fever, chills, feeling tired, headache, weakness, allergic reactions and vomiting.
- **Severe allergic reactions:** Some people receiving Perjeta may have severe allergic reactions, called *hypersensitivity reactions* or *anaphylaxis*, which may happen quickly and may affect many areas of the body. Severe allergic reactions, some fatal, have been observed in patients treated with Perjeta.

INTRODUCTION

01 UNMASKING THE ENEMY

02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK

Most common side effects

The most common side effects of Perjeta when given with Herceptin and docetaxel for treatment of breast cancer that has spread to other parts of the body (metastatic) are:

- Diarrhea
- Hair loss
- Low levels of white blood cells with or without fever
- Nausea
- Feeling tired
- Rash
- Damage to the nerves (numbness, tingling, pain in hands/feet)

Patients are encouraged to report side effects to Genentech and the FDA. Report side effects to the FDA at (800) FDA-1088 or http://www.fda.gov/medwatch. Report side effects to Genentech at (888) 835-2555.

Please see the Perjeta full Prescribing Information for additional Important Safety Information, including most serious side effects, at http://www.perjeta.com.

ABOUT KADCYLA

Kadcyla Indication Statement

Kadcyla is approved to treat HER2-positive breast cancer that has spread to other parts of the body (metastatic breast cancer) after prior treatment with trastuzumab (Herceptin) and a taxane. Prior treatment could have been for the initial treatment of breast cancer or for the treatment of cancer that had spread to other parts of the body.

Important Safety Information

Kadcyla is not the same medicine as trastuzumab (Herceptin).

Most important safety information about Kadcyla.

Liver problems

- Kadcyla may cause severe liver problems that can be life-threatening. Symptoms of liver problems may include vomiting, nausea, eating disorder (anorexia), yellowing of the skin (jaundice), stomach pain, dark urine or itching.

Heart problems

- Kadcyla may cause heart problems, including those without symptoms (such as reduced heart function) and those with symptoms (such as congestive heart failure). Symptoms may include swelling of the ankles or legs, shortness of breath, cough, rapid weight gain of more than five pounds in 24 hours, dizziness or loss of consciousness, or irregular heartbeat.

Pregnancy

- Receiving Kadcyla during pregnancy can result in the death of an unborn baby and birth defects. Birth control should be used while receiving Kadcyla and for seven months after a patient's last dose of Kadcyla.
- If a patient thinks she may be pregnant, she should contact her healthcare provider immediately.
- If a patient is exposed to Kadcyla during pregnancy, or becomes pregnant within seven months following her last dose of Kadcyla, she is encouraged to report Kadcyla exposure to Genentech at (888) 835-2555.
- If a male patient has a female partner that could become pregnant, birth control should be used during treatment and for four months following his last dose of Kadcyla.
- A patient should not breastfeed during treatment and for seven months after the last dose of Kadcyla.

Patients should contact their doctor right away if they experience symptoms associated with these side effects.

INTRODUCTION

01 UNMASKING THE ENEMY

02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK

Additional possible serious side effects of Kadcyla

Lung problems

- Kadcyla may cause lung problems, including inflammation of the lung tissue, which can be life-threatening. Signs of lung problems may include trouble breathing, cough, tiredness and fluid in the lungs.

Infusion-related reactions

- Symptoms of an infusion-related reaction may include one or more of the following: the skin getting hot or red (flushing), chills, fever, trouble breathing, low blood pressure, wheezing, tightening of the muscles in the chest around the airways or a fast heartbeat. A patient's doctor will monitor the patient for infusion-related reactions.

Serious bleeding

- Kadcyla can cause life-threatening bleeding. Taking Kadcyla with other medications used to thin the blood (antiplatelet) or prevent blood clots (anticoagulation) can increase the risk of bleeding. A patient's doctor should provide additional monitoring if the patient is taking one of these other drugs while on Kadcyla. Life-threatening bleeding may also happen with Kadcyla even when blood thinners are not also being taken.

Low platelet count

- Low platelet count may happen during treatment with Kadcyla. Platelets help the blood to clot. Signs of low platelets may include easy bruising, bleeding, and prolonged bleeding from cuts. In mild cases there may not be any symptoms.

Nerve damage

- Symptoms may include numbness and tingling, burning or sharp pain, sensitivity to touch, lack of coordination, muscle weakness, or loss of muscle function.

Skin reactions around the infusion site

- Kadcyla may leak from the vein or needle and cause reactions such as redness, tenderness, skin irritation, or pain or swelling at the infusion site. If this happens, it is more likely to happen within 24 hours of the infusion.

HER2 testing and Kadcyla

Patients must have a HER2 test to determine if their cancer is HER2-positive before taking Kadcyla, because benefit has been shown only in patients whose tumors are HER2-positive.

Most common side effects of Kadcyla

The most common side effects seen in people taking Kadcyla were:

- Tiredness
- Nausea
- Pain that affects the bones, muscles, ligaments and tendons
- Bleeding
- Low platelet count
- Headache
- Liver problems
- Constipation
- Nosebleeds

Patients are encouraged to report side effects to Genentech and the FDA. Report side effects to the FDA at (800) FDA-1088 or http://www.fda.gov/medwatch. Report side effects to Genentech at (888) 835-2555.

Please see the Kadcyla full Prescribing Information for additional Important Safety Information, including most serious side effects, at http://www.kadcyla.com.

REFERENCES

1 American Cancer Society. History of Cancer. Retrieved June 19, 2017 from https://www.cancer.org/cancer/cancer-basics/history-of-cancer.html

2 Stehelin D, Varmus HE, Bishop JM, Vogt PK. DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. *Nature* 1976;260:170-173.

3 Weinberg RA. The action of oncogenes in the cytoplasm and nucleus. *Science* 1985;230:770-776.

4 Ullrich A, Coussens L, Hayflick JS, et al. Human epidermal growth factor receptor cDNA sequence and aberrant expression of the amplified gene in A431 epidermoid carcinoma cells. *Nature* 1984;309:418-425.

5 Bazell, Robert. *Her-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer*. New York: Random House, 1998.

6 Coussens L, Yang-Feng TL, Liao YC, et al. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science* 1985;230:1132-1139.

7 Schechter AL, Stern DF, Vaidyanathan L, et al. The neu oncogene:an erb-B-related gene encoding a 185,000-Mr tumour antigen. *Nature* 1984;312:513-516.

8 Schechter AL, Hung MC, Vaidyanathan L, et al. The neu gene: an erbB-homologous gene distinct from and unlinked to the gene encoding the EGF receptor. *Science* 1985;229(4717):976-978.

9 King CR, Kraus MH, Aaronson SA. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science* 1985;229:974-976.

10 Yamamoto T, Ikawa S, Akiyama T, et al. Similarity of protein encoded by the human c-erb-B-2 gene to epidermal growth factor receptor. *Nature* 1986;319(6050):230-234.

INTRODUCTION

01 UNMASKING THE ENEMY

02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK

11 Moasser MM. The oncogene HER2; its signaling and transforming functions and its role in human cancer pathogenesis. *Oncogene* 2007;26(45):6469-6487.

12 Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235(4785):177-182.

13 Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989;244:707-712.

14 Osborne CK. In Memoriam. *Journal of Clinical Oncology* 1992;10(9):1377-1378.

15 Fendly BM, Winget M, Hudziak RM, et al. Characterization of murine monoclonal antibodies reactive to either the human epidermal growth factor receptor or HER2/neu gene product. *Cancer Res* 1990;50:1550-1558.

16 Hudziak RM, Lewis GD, Winget M, et al. p185HER2 monoclonal antibody has antiproliferative effects in vitro and sensitizes human breast tumor cells to tumor necrosis factor. *Mol Cell Biol* 1989;9(3):1165-1172.

17 Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 1975;256,495-497.

18 Divgi CR, Welt S, Kris M, et al. Phase I and imaging trial of indium 111-labeled anti-epidermal growth factor receptor monoclonal antibody 225 in patients with squamous cell lung carcinoma. *Journal of the National Cancer Institute* 1991;83(2):97-104.

19 Goldenberg DM. Challenges to the therapy of cancer with monoclonal antibodies. *Journal of the National Cancer Institute* 1991;83(2):78-79.

20 Carter P, Presta L, Gorman CM, et al. Humanization of an anti-p185HER2 Antibody for Human Cancer Therapy. *Proc Natl Acad Sci USA* 1992;89(10):4285-4289.

21 Hughes, Sally Smith. *Genentech: The Beginnings of Biotech*. Chicago: University of Chicago, 2011.

22 Genentech. Biotechnology Breakthrough In Breast Cancer Wins FDA Approval. September 25, 1998. Retrieved June 19, 2017 from http://www.gene.com/media/press-releases/4763/1998-09-25/biotechnology-breakthrough-in-breast-can

23 Baldwin J. Demand Grows for Early Access to Promising Cancer Drugs. *J Natl Cancer Inst* 2002;94(22):1668-1670.

24 Herceptin [package insert]. South San Francisco, Calif.: Genentech, Inc. 2017.

25 Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783-792.

26 U.S. Food and Drug Administration. Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development. October 2013. Retrieved June 19, 2017 from http://www.fda.gov/scienceresearch/specialtopics/personalizedmedicine/default.htm

27 Genentech. Herceptin Plus Chemotherapy Improved Disease-Free Survival and Overall Survival in Adjuvant Setting for Early-Stage Her2-Positive Breast Cancer Patients. May 13, 2005. Retrieved June 19, 2017 from http://www.gene.com/media/press-releases/8429/2005-05-13/herceptin-plus-chemotherapy-improved-dis

28 Tuma RS. Trastuzumab trials steal show at ASCO meeting. *J Natl Cancer Inst* 2005;97(12):870-871.

29 Yarden Y, Sliwkowski M. Untangling the ErbB signalling network. *Nature Reviews Molecular Cell Biology* 2001;2:127-137.

30 Agus DB, Akita RW, Fox WD, et al. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer Cell* 2002;2(2):127-137.

31 Genentech. Data From Omnitarg Clinical Program Presented at American Society of Clinical Oncology Meeting. May 15, 2005. Retrieved June 19, 2017 from http://www.gene.com/media/press-releases/8431/2005-05-15/data-from-omnitarg-clinical-program-pres

32 Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;366:109-119.

33 Perjeta [package insert]. South San Francisco, Calif.: Genentech, Inc. 2017.

34 Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015;372:724-734.

35 American Cancer Society. Chemotherapy Side Effects. Last revised February 15, 2016. Retrieved June 19, 2017 from https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/chemotherapy-side-effects.html

36 American Cancer Society. How Chemotherapy Drugs Work. Last revised February 15, 2016. Retrieved June 19, 2017 from https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/how-chemotherapy-drugs-work.html

37 Carter PJ, Senter PD. Antibody-drug conjugates for cancer therapy. *Cancer Journal* 2008;14(3):154-169.

38 Zolot RS, Basu S, Million RP. Antibody-drug conjugates. *Nature Reviews Drug Discovery* 2013;12:259-260.

39 Chari RVJ. Targeted cancer therapy: conferring specificity to cytotoxic drugs. *Accounts of Chemical Research* 2008;41(1):98-107.

40 Ducry L, Stump B. Antibody-drug conjugates: linking cytotoxic payloads to monoclonal antibodies. *Bioconjugate Chem* 2010;21(1):5-13.

41 Wolff AC, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol 2013;31(31):3997-4014.

42 Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012;367:1783-1791.

43 Genentech. FDA Approves Genentech's Kadcyla (Ado-Trastuzumab Emtansine), the First Antibody-Drug Conjugate for Treating Her2-Positive Metastatic Breast Cancer. February 22, 2013. Retrieved June 19, 2017 from http://www.gene.com/media/press-releases/14347/2013-02-22/fda-approves-genentechs-kadcyla-ado-tras

44 Kadcyla [package insert]. South San Francisco, Calif.: Genentech, Inc. 2016.

45 U.S. Food and Drug Administration. Personalized Medicine and Companion Diagnostics Go Hand-in-Hand. July 31, 2014. Retrieved June 19, 2017 from http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm407328.htm

46 Dawood S, Broglio K, Buzdar AU, et al. Prognosis of Women With Metastatic Breast Cancer by HER2 Status and Trastuzumab Treatment: An Institutional-Based Review. J Clin Onc 2010;28(1):92-98.

47 Pegram M, Slamon D. Biological rationale for HER2/neu (c-erbB2) as a target for monoclonal antibody therapy. *Semin Oncology* 2000;(5 Suppl 9):13-19.

48 Kozlowski S, Woodcock J, Midthun K, Sherman RB. *N Engl J Med* 2011;365:385-388.

49 National Center for Biotechnology Information. PubChem Compound Database; CID=2244. Last revised May 28, 2016. Retrieved June 19, 2017 from https://pubchem.ncbi.nlm.nih.gov/compound/2244

INTRODUCTION

01 UNMASKING THE ENEMY

02 INTO THE UNKNOWN

03 TRIBULATIONS AND TRIALS

04 JOINING FORCES

05 INTO THE CELL

06 BACK TO WORK

EXHIBIT 34

Media Inquiries
(650) 467-6800

EMAIL US

Friday, May 13, 2005

Herceptin Plus Chemotherapy Improved Disease-Free Survival and Overall Survival in Adjuvant Setting for Early-Stage Her2-Positive Breast Cancer Patients

Results from Two Phase III Adjuvant Trials Showed that Adding Herception to Chemotherapy Reduced the Risk of Breast Cancer Recurrence by 52 Percent

South San Francisco, Calif. -- May 13, 2005 --

Genentech, Inc. (NYSE: DNA) today announced that data from a joint interim analysis of two Phase III studies of Herceptin® (Trastuzumab) in early-stage breast cancer showed that human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients receiving Herceptin plus chemotherapy had a 52 percent reduction in the risk of disease recurrence compared to those patients who received chemotherapy alone (or a hazard ratio of 0.48). After four years in the study, 15 percent of women treated with Herceptin plus chemotherapy experienced disease recurrence, compared to 33 percent of women treated with chemotherapy alone. Preliminary survival data showed a 49 percent improvement in overall survival (or a hazard ratio of 0.67, which is equivalent to a 33 percent reduction in the risk of death). Survival data continue to mature.

"The reduction in disease recurrence observed in these trials was the largest improvement I've seen in breast cancer clinical research. Herceptin plus chemotherapy can potentially stop or delay early-stage HER2-positive breast cancer from relapsing," said Edith Perez, M.D., professor of medicine at the Mayo Clinic in Jacksonville, Fla., and the lead investigator in one of the two Herceptin trials. "These trials also underscore the importance for every woman diagnosed with breast cancer to receive a HER2 test."

A preliminary safety analysis showed that adverse events in these studies were consistent with those seen in previous Herceptin clinical trials. Each study had an independent external Data Monitoring Committee (DMC) that reviewed data from the studies, including cardiac safety data on a regular basis. According to the investigators, serious or life-threatening (and in rare cases, fatal) cardiac events, most commonly congestive heart failure (weakening of the heart muscle) occurred approximately 3 to 4 percent more often in the Herceptin plus chemotherapy arms than in the chemotherapy alone arms. Patients in these studies will continue to be followed for any additional side effects.

In these studies, women with early-stage (or cancer that has not spread beyond the breast and the associated lymph nodes) HER2-positive breast cancer received Herceptin plus chemotherapy or chemotherapy alone following initial treatment with surgery and anthracycline and cyclophosphamide (AC). HER2-positive breast cancer is an especially aggressive form of the disease that affects approximately 25 percent of women with breast cancer.

These data were featured in a press briefing at the 41st Annual Meeting of the American Society of Clinical Oncology (ASCO). More detailed data from the study will be presented to meeting attendees by Edward Romond, M.D., of the University of Kentucky during a scientific symposium ("Advances in Monoclonal Antibodies for Breast Cancer" - Monday, May 16, 1:15 p.m. EDT).

"These trials are significant because we may be able to treat HER2-positive patients in the earlier stages of their breast cancer, and prevent or delay development of metastatic disease. We're also excited about the improvements seen in the adjuvant setting, since patient outcomes are measured in years rather than months," said Susan Desmond-Hellmann, M.D., M.P.H., Genentech's president, product development. "We would like to thank our collaborators at NCI, NSABP and NCCTG for their work on this study, as well as the many patients and their families who participated in the trial, for their important role in identifying a potential new treatment option for women with HER2-positive breast cancer."

Based on the strength of this interim joint analysis, Genentech will work with the cooperative groups to prepare these data for discussion with the U.S. Food and Drug Administration (FDA) about filing a supplemental Biologics License Application (sBLA) for Herceptin in the adjuvant setting.

About the Study Designs

The National Surgical Adjuvant Breast and Bowel Project (NSABP) study began enrollment in March 2000 and 2,085 patients have participated in the trial to date. The

North Central Cancer Treatment Group (NCCTG) study enrolled its first patient in June 2000 and 3,406 patients have participated to date. Both studies are supported by the National Cancer Institute. The joint interim analysis was based on data from 3,351 patients. Each of the studies was a randomized, controlled trial that evaluated the combination of anthracycline and cyclophosphamide (AC) followed by paclitaxel chemotherapy, with or without Herceptin, using different treatment schedules of paclitaxel in women with HER2-positive breast cancer.

About the Herceptin Adjuvant Clinical Trial Program

In addition to the NSABP and NCCTG adjuvant studies, Roche and Breast International Group (BIG) announced in April 2005 that the interim analysis of HERA (HERceptin Adjuvant), a large-scale, 39-country, Phase III study with a wide range of chemotherapy regimens, showed that the addition of Herceptin increased disease-free survival for women with early-stage HER2-positive breast cancer.

Enrollment in the HERA trial began in December 2001, and nearly 5,100 patients have been enrolled at 480 sites in 39 countries worldwide. The interim analysis compared 12 months of Herceptin versus observation and did not include a comparison of 24 months of Herceptin versus observation. These data will become available as the study matures.

The HERA study has an external Independent Data Monitoring Committee (IDMC) that regularly reviews safety data. No safety concerns have been raised by the IDMC to date. Patients in this study will continue to be followed for any side effects.

About Herceptin

Herceptin is a targeted therapeutic antibody treatment for women with HER2-positive metastatic breast cancer, an especially aggressive form of the disease that affects approximately 25 percent of women with breast cancer. Special testing is required to identify women who are HER2-positive and who may be candidates for treatment with Herceptin.

Herceptin received FDA approval in September 1998 for use in women with metastatic breast cancer who have tumors that overexpress the HER2 protein. It is indicated for weekly treatment of patients both as first-line therapy in combination with paclitaxel and as a single agent in second- and third-line therapy. Herceptin is marketed in the United States by Genentech, in Japan by Chugai, and outside of the United States and Japan by Roche.

In clinical trials, Herceptin has shown a survival benefit when used in combination with paclitaxel chemotherapy. In December 2001, Genentech received FDA approval to include data that showed a 24 percent increase in median overall survival for women with HER2-positive metastatic breast cancer treated initially with Herceptin and chemotherapy compared to chemotherapy alone (median 25.1 months compared to 20.3 months).

Herceptin Safety Profile

Herceptin therapy does involve risks. Serious side effects have occurred in patients treated with Herceptin in metastatic breast cancer. Herceptin administration can result in the development of ventricular dysfunction and cardiac failure. Severe hypersensitivity reactions (including anaphylaxis), infusion reactions and

pulmonary events have been infrequently reported. Rarely, these were fatal.

Serious reactions were treated by discontinuing Herceptin and administering supportive therapy. In clinical trials, the incidence and severity of cardiac dysfunction was highest in patients receiving Herceptin with anthracycline and cyclophosphamide (AC). Most patients responded to medical therapy, including discontinuation of Herceptin. However, some patients were successfully managed while continuing Herceptin therapy. Patients receiving Herceptin should be monitored for deteriorating cardiac function.

In clinical trials, approximately 40 percent of patients experienced symptoms such as chills and fever during the first infusion. These and other symptoms, including nausea, vomiting and pain, occurred infrequently with subsequent infusions. In clinical trials, the incidence of moderate-to-severe neutropenia and febrile neutropenia was higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those receiving chemotherapy alone. There was an increased incidence of anemia leukopenia, diarrhea and infection when Herceptin was used in combination with chemotherapy.

About Breast Cancer

According to the American Cancer Society, an estimated 211,000 women will be diagnosed with breast cancer and approximately 40,000 women will die of the disease in the United States in 2005. In the United States, breast cancer is the most prevalent form of cancer among women and a woman is diagnosed with breast cancer every three minutes.

About Genentech BioOncology

Genentech is committed to changing the way cancer is treated by establishing a broad oncology portfolio of innovative, targeted therapies with the goal of improving patients' lives. The company is the leading provider of anti-tumor therapeutics in the United States. Genentech is leading clinical development programs for Rituxan® (Rituximab), Herceptin® (Trastuzumab), Avastin™ (bevacizumab) and Tarceva™ (erlotinib), and markets all four products in the United States alone (Avastin and Herceptin), with Biogen Idec Inc. (Rituxan) or with OSI Pharmaceuticals (Tarceva). Genentech has licensed Rituxan, Herceptin, and Avastin, and OSI Pharmaceuticals has licensed Tarceva to Roche for sale by the Roche Group outside of the United States.

The company has a robust pipeline of potential oncology therapies with a focus on four key areas: angiogenesis, apoptosis (i.e. programmed cell death), the HER pathway and B-cell biology. Potential oncology therapies directed at the HER pathway include a therapeutic antibody currently in Phase II trials. Also in early development are a small molecule directed at the hedgehog pathway, a soluble human protein targeting apoptosis and a humanized anti-CD20 antibody for hematology/oncology indications.

Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes biotherapeutics for significant unmet medical needs. A considerable number of the currently approved biotechnology products originated from, or are based on, Genentech science. Genentech manufactures and commercializes multiple biotechnology products directly

in the United States and licenses several additional products to other companies. The company has headquarters in South San Francisco, Calif., and is traded on the New York Stock Exchange under the symbol DNA. For additional information about the company, please visit http://ww.gene.com.

# # #

For full prescribing information, including Boxed Warnings for Avastin, Rituxan and Herceptin, or for Tarceva full prescribing information, please call 800-821-8590 or visit http://ww.gene.com.

OUR PIPELINE

Our pipeline includes new molecular entities that address serious unmet medical needs.

APPROVALS TIMELINE

A look at our approvals past and present.

EXHIBIT 35

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EXHIBIT 36

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 37

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 38

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 39

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 40

Media Inquiries

(650) 467-6800

EMAIL US

Thursday, Feb 28, 2019

FDA Approves Herceptin Hylecta for Subcutaneous Injection in Certain HER2-Positive Breast Cancers

South San Francisco, CA -- February 28, 2019 --

Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY), today announced the U.S. Food and Drug Administration (FDA) has approved Herceptin Hylecta™ (trastuzumab and hyaluronidase-oysk) for subcutaneous (under the skin) injection for the treatment of certain people with HER2-positive early breast cancer (node-positive, or node-negative and ER/PR-negative or with one high-risk feature) in combination with chemotherapy and HER2-positive metastatic breast cancer in combination with paclitaxel or alone in people who have received one or more chemotherapy regimens for metastatic disease. This new treatment includes the same monoclonal antibody as intravenous Herceptin® (trastuzumab) in combination with recombinant human hyaluronidase PH20, an enzyme that helps to deliver trastuzumab under the skin. Herceptin Hylecta is a ready-to-use formulation that can be administered in two to five minutes, compared to 30 to 90 minutes for intravenous Herceptin.

"Over the past 20 years, Herceptin has significantly advanced treatment of HER2-positive breast cancer," said Sandra Horning, M.D., chief medical officer and head of Global Product Development. "The approval of Herceptin Hylecta gives physicians and patients in the United States a new option to select treatment based on individual needs and preferences."

The FDA approval is based on results from three clinical studies in HER2-positive early breast cancer:

- The Phase III HannaH study compared neoadjuvant (before surgery) and adjuvant (after surgery) Herceptin Hylecta to intravenous Herceptin, both in combination with chemotherapy. Subcutaneous administration of Herceptin Hylecta resulted in non-inferior levels of trastuzumab in the blood (pharmacokinetics) and non-inferior clinical efficacy (pathological complete response rate; pCR) compared to intravenous Herceptin.
- The Phase III SafeHER study of adjuvant Herceptin Hylecta identified no new safety signals, with safety and tolerability consistent with the known safety profiles of intravenous Herceptin and Herceptin Hylecta.
- The PrefHER patient preference study of adjuvant Herceptin Hylecta followed by intravenous Herceptin, or the reverse sequence, found the majority (86 percent) of people preferred Herceptin Hylecta over intravenous Herceptin.

The most common side effects in people receiving Herceptin Hylecta for early breast cancer were feeling tired, joint pain, diarrhea, injection site reaction, upper respiratory tract infection, rash, muscle pain, nausea, headache, swelling, flushing, fever, cough and pain in extremity.

For those who qualify, Genentech offers patient assistance programs for people prescribed Herceptin Hylecta by their doctor through Genentech Access Solutions. Please contact Genentech Access Solutions at (866) 422-2377 or visit http://www.Genentech-Access.com for more information.

HannaH, SafeHER and PrefHER study results

HannaH		
	Herceptin Hylecta	**Intravenous Herceptin**
pCR (absence of invasive cancer cells in the breast)	45.4% (118/260) 95% CI 39.2%-51.7%	40.7% (107/263) 95% CI 34.7%-46.9%
Mean level of trastuzumab in the blood (C_{trough}) before dosing eighth cycle	78.7 mcg/mL	57.8 mcg/mL
	Geometric mean ratio 1.3 (90% CI 1.2-1.4)	
Most common adverse events (AEs; ≥10%)	Hair loss, nausea, administration-related reactions, feeling tired, decreased neutrophil count, diarrhea, rash, upper respiratory tract infection, vomiting, mouth blisters or sores, muscle pain, decreased appetite, constipation, radiation skin injury, damage to the nerves (numbness, tingling, pain in the hands/feet), joint pain, headache, flushing, fever, cough, low levels of red blood cells, difficulty breathing, incision site pain, low levels of white blood cells	

	and mucosal inflammation
SafeHER	
	Herceptin Hylecta n=1,864
Safety	No new safety signals for Herceptin Hylecta were identified. Safety and tolerability were consistent with the known safety profiles of intravenous Herceptin and Herceptin Hylecta.
Most common AEs (≥10%)	Administration-related reactions, feeling tired, diarrhea, injection site reaction, weakness, joint pain, rash, muscle pain, nausea, damage to the nerves (numbness, tingling, pain in the hands/feet), headache, swelling, flushing, fever, cough and pain in extremity
PrefHER	
	Herceptin Hylecta followed by intravenous Herceptin (n=121) or intravenous Herceptin followed by Herceptin Hylecta (n=119)
Patient preference	86% of people preferred Herceptin Hylecta, 13% preferred intravenous Herceptin, 1% had no preference
Reasons for preference	The most common reason for preferring Herceptin Hylecta was time savings (179/231). The most common reason for preferring intravenous Herceptin was fewer local injection reactions.

About HER2-positive breast cancer

Breast cancer is the most common cancer among women worldwide. According to the American Cancer Society, approximately 271,000 people in the United States will be diagnosed with breast cancer, and more than 42,000 will die from the disease in 2019. Breast cancer is not one, but many diseases based on the biology of each tumor. In HER2-positive breast cancer, there is excess HER2 protein on the surface of tumor cells. Approximately 15-20 percent of breast cancers are HER2-positive based on the result of a diagnostic test.

About Herceptin Hylecta

Herceptin Hylecta (subcutaneous Herceptin) is a combination of trastuzumab and Halozyme Therapeutics' Enhanze® drug delivery technology. Trastuzumab is the same monoclonal antibody in intravenous Herceptin that targets the HER2 receptor, a protein found on the outside of many normal cells and in high quantities on the outside of cancer cells in HER2-positive cancers. Herceptin is designed to block HER2 signaling that is believed to play a role in tumor growth and survival. Binding of Herceptin to HER2 may also signal the body's immune system to destroy the cancer cells. Halozyme's Enhanze technology is based on a proprietary recombinant human hyaluronidase PH20 (rHuPH20), an enzyme that temporarily degrades hyaluronan, a glycosaminoglycan or chain of natural sugars in the body, to aid in the dispersion and absorption of other injected therapeutic drugs.

Herceptin Hylecta Indication Statements

Adjuvant Breast Cancer

Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) is approved for the treatment of adults with early stage breast cancer that is**H**uman **E**pidermal growth factor **R**eceptor **2**-positive (HER2-positive) and has spread into the lymph nodes, or is HER2-positive and has not spread into the lymph nodes. If it has not spread into the lymph nodes, the cancer needs to be estrogen receptor/progesterone receptor (ER/PR)-negative or have one high-risk feature.* Herceptin Hylecta can be used in several different ways:

- As part of a treatment course including the chemotherapy drugs doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel. This treatment course is known as "**AC® TH**."
- With the chemotherapy drugs docetaxel and carboplatin. This treatment course is known as "**TCH**."
- Alone after treatment with multiple other therapies, including an anthracycline (doxorubicin)-based therapy (a type of chemotherapy).

Patients are selected for therapy based on an FDA-approved test for trastuzumab.

*High risk is defined as ER/PR-positive with one of the following features: tumor size greater than 2 cm, age less than 35 years, or tumor grade 2 or 3.

Metastatic Breast Cancer

Herceptin Hylecta has two approved uses in adults with metastatic breast cancer:

- Herceptin Hylecta in combination with the chemotherapy drug paclitaxel is approved for the

first-line treatment of**H**uman **E**pidermal growth factor **R**eceptor **2**-positive (HER2-positive) metastatic breast cancer.

- Herceptin Hylecta alone is approved for the treatment of HER2-positive breast cancer in patients who have received one or more chemotherapy courses for metastatic disease.

Patients are selected for therapy based on an FDA-approved test for trastuzumab.

Important Safety Information

Possible serious side effects with Herceptin Hylecta

Not all people have serious side effects, but side effects with Herceptin Hylecta therapy are common.

Although some people may have a life-threatening side effect, most do not.

A patient's doctor will stop treatment if any serious side effects occur.

Herceptin Hylecta is not for everyone. A patient should be sure to contact their doctor if they are experiencing any of the following:

HEART PROBLEMS

These include heart problems—such as congestive heart failure or reduced heart function—with or without symptoms. The risk for and seriousness of these heart problems were highest in people who received both Herceptin Hylecta and a certain type of chemotherapy (anthracycline). In a study of adjuvant (early) breast cancer, one patient died of significantly weakened heart

muscle. A patient's doctor will check for signs of heart problems before, during, and after treatment with Herceptin Hylecta.

Patients should contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than five pounds in 24 hours, dizziness or loss of consciousness.

SEVERE LUNG PROBLEMS , including:

- Severe shortness of breath
- Scarring of the lungs
- Fluid in or around the lungs
- Weakening of the valve between the heart and the lungs
- Not enough oxygen in the body
- Swelling of the lungs

A patient's doctor may check for signs of severe lung problems when he or she examines the patient.

These signs usually happen within 24 hours after receiving Herceptin Hylecta.

A PATIENT SHOULD BE SURE TO CONTACT THEIR DOCTOR IF THEY:

ARE A WOMAN WHO COULD BECOME PREGNANT, OR MAY BE PREGNANT

Herceptin Hylecta may result in the death of an unborn baby or birth defects. Contraception should be used while

receiving Herceptin Hylecta and for seven months after a patient's last dose of Herceptin Hylecta. If a patient is or becomes pregnant while receiving Herceptin Hylecta or within seven months after their last dose of Herceptin Hylecta, the patient is encouraged to report Herceptin Hylecta exposure to Genentech at (888) 835-2555.

Have **LOW WHITE BLOOD CELL COUNTS**

Low white blood cell counts can be life threatening. Low white blood cell counts were seen more often in patients receiving intravenous trastuzumab plus chemotherapy than in patients receiving chemotherapy alone.

A patient's doctor may check for signs of low white blood cell counts when he or she examines the patient.

Experience **HYPERSENSITIVITY AND ADMINISTRATION-RELATED REACTIONS**, which have been reported with Herceptin Hylecta. Serious and fatal reactions have been reported after treatment with intravenous trastuzumab products. A patient's doctor will monitor them for signs of these reactions. Patients should contact their healthcare provider immediately if they experience any symptoms of hypersensitivity and administration-related reactions, including dizziness, nausea, chills, fever, vomiting, diarrhea, hives, swelling under the skin, breathing problems or chest pain.

SIDE EFFECTS SEEN MOST OFTEN

The most common side effects seen in treatment of adjuvant breast cancer with Herceptin Hylecta were tiredness, joint pain, diarrhea, injection site reaction, upper respiratory tract infection, rash, muscle pain,

nausea, headache, swelling, flushing, fever, cough and pain in extremity.

The most common side effects seen in treatment of metastatic breast cancer (based on intravenous trastuzumab) are fever, chills, headache, infection, congestive heart failure, insomnia, cough and rash.

A patient should contact their doctor immediately if they have any of the side effects listed above.

Patients are encouraged to report side effects to Genentech and the FDA. Report side effects to the FDA at (800) FDA-1088 or http://www.fda.gov/medwatch. Report side effects to Genentech at (888) 835-2555.

Please see the Herceptin Hylecta full Prescribing Information for additional Important Safety Information, including most serious side effects.

Herceptin Indication Statements

Adjuvant Breast Cancer

Herceptin is approved for the treatment of early stage breast cancer that is **H**uman **E**pidermal growth factor**R**eceptor **2**-positive (**HER2**-positive) and has spread into the lymph nodes, or is HER2-positive and has not spread into the lymph nodes. If it has not spread into the lymph nodes, the cancer needs to be estrogen receptor/progesterone receptor (ER/PR)-negative or have one high-risk feature.* Herceptin can be used in several different ways:

- As part of a treatment course including the chemotherapy drugs doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel. This treatment course is known as "**AC**

®TH."

- With the chemotherapy drugs docetaxel and carboplatin. This treatment course is known as "**TCH**."
- Alone after treatment with multiple other therapies, including an anthracycline (doxorubicin) based therapy (a type of chemotherapy).

Patients are selected for therapy based on an FDA-approved test for Herceptin.

*High risk is defined as ER/PR-positive with one of the following features: tumor size greater than 2 cm, age less than 35 years, or tumor grade 2 or 3.

Metastatic Breast Cancer

Herceptin has two approved uses in metastatic breast cancer:

- Herceptin in combination with the chemotherapy drug paclitaxel is approved for the first-line treatment of **H**uman**E**pidermal growth factor **R**eceptor **2**-positive (HER2-positive) metastatic breast cancer.
- Herceptin alone is approved for the treatment of HER2-positive breast cancer in patients who have received one or more chemotherapy courses for metastatic disease.

Patients are selected for therapy based on an FDA-approved test for Herceptin.

Important Safety Information

Possible serious side effects with Herceptin

Not all people have serious side effects, but side effects

with Herceptin therapy are common.

Although some people may have a life-threatening side effect, most do not.

A patient's doctor will stop treatment if any serious side effects occur.

Herceptin is not for everyone. A patient should be sure to contact their doctor if they are experiencing any of the following:

HEART PROBLEMS

These include heart problems—such as congestive heart failure or reduced heart function—with or without symptoms. The risk for and seriousness of these heart problems were highest in people who received both Herceptin and a certain type of chemotherapy (anthracycline). In a study of adjuvant (early) breast cancer, one patient died of significantly weakened heart muscle. A patient's doctor will check for signs of heart problems before, during and after treatment with Herceptin.

INFUSION REACTIONS, including:

- Fever and chills
- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Pain (in some cases at tumor sites)
- Headache
- Dizziness
- Shortness of breath

These signs usually happen within 24 hours after receiving Herceptin.

A patient should be sure to contact their doctor if they:

Are a woman who could become pregnant, or may be pregnant

Herceptin may result in the death of an unborn baby or birth defects. Contraception should be used while receiving Herceptin and for seven months after a patient's last dose of Herceptin. If a patient is or becomes pregnant while receiving Herceptin or within seven months after their last dose of Herceptin, the patient should immediately report Herceptin exposure to Genentech at (888) 835-2555.

Have any signs of **SEVERE LUNG PROBLEMS**, including:

- Severe shortness of breath
- Fluid in or around the lungs
- Weakening of the valve between the heart and the lungs
- Not enough oxygen in the body
- Swelling of the lungs
- Scarring of the lungs

A patient's doctor may check for signs of severe lung problems when he or she examines the patient.

Have **LOW WHITE BLOOD CELL COUNTS**

Low white blood cell counts can be life threatening. Low white blood cell counts were seen more often in patients

receiving Herceptin plus chemotherapy than in patients receiving chemotherapy alone.

A patient's doctor may check for signs of low white blood cell counts when he or she examines the patient.

Side effects seen most often with Herceptin

Some patients receiving Herceptin for breast cancer had the following side effects:

- Fever
- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Infusion reactions
- Diarrhea
- Infections
- Increased cough
- Headache
- Feeling tired
- Shortness of breath
- Rash
- Low white and red blood cell counts
- Muscle pain

A patient should contact their doctor immediately if they have any of the side effects listed above.

Patients are encouraged to report side effects to Genentech and the FDA. Report side effects to the FDA at (800) FDA-1088 or http://www.fda.gov/medwatch. Report side effects to Genentech at (888) 835-2555.

Please see the Herceptin full Prescribing Information for additional Important Safety Information, including most serious side effects, at http://www.herceptin.com.

About Genentech in breast cancer

Genentech has been advancing breast cancer research for more than 30 years with the goal of helping as many people with the disease as possible. Our medicines, along with companion diagnostic tests, have substantially improved outcomes for HER2-positive breast cancer. As our understanding of breast cancer biology rapidly improves, we are working to identify new biomarkers and approaches to treatment for other subtypes of the disease, including triple-negative and hormone receptor-positive.

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Founded more than 40 years ago, Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes medicines to treat patients with serious and life-threatening medical conditions. The company, a member of the Roche Group, has headquarters in South San Francisco, California. For additional information about the company, please visit http://www.gene.com.

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OUR PIPELINE

Our pipeline includes new molecular entities that address serious unmet medical needs.

APPROVALS TIMELINE

A look at our approvals past and present.

EXHIBIT 41

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 42

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 43

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EXHIBIT 44

Media Inquiries
(650) 467-6800

EMAIL US

Friday, May 3, 2019

FDA Approves Genentech's Kadcyla for Adjuvant Treatment of People With HER2-Positive Early Breast Cancer With Residual Invasive Disease After Neoadjuvant Treatment

Approval based on data showing Kadcyla cut the risk of disease recurring by half compared to Herceptin in the adjuvant setting for specific patients with HER2-positive early breast cancer

Application approved under FDA's Real-Time Oncology Review pilot program

South San Francisco, CA -- May 3, 2019 --

Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY), today announced that the U.S. Food and Drug Administration (FDA) has approved Kadcyla® (ado-trastuzumab emtansine) for adjuvant (after surgery) treatment of people with HER2-positive early breast cancer (EBC) who have residual invasive disease after neoadjuvant (before surgery) taxane and Herceptin® (trastuzumab)-based treatment.

"This approval is a significant treatment advance for HER2-positive early breast cancer. By working closely with the FDA and participating in the Real-Time

Oncology Review pilot program, we are able to make Kadcyla available for people with residual invasive disease after neoadjuvant therapy much sooner than anticipated," said Sandra Horning, M.D., chief medical officer and head of Global Product Development. "With every step forward in reducing the risk of disease recurrence, we come closer to the goal of helping each person with early breast cancer have the greatest opportunity for cure."

The goal in treating EBC is to provide people with the best chance for a cure, which may involve treatment before and after surgery as part of a comprehensive treatment approach. While we come closer to this goal with each advance, many people still have a disease recurrence in the long term. Neoadjuvant treatment is given before surgery with the goal of shrinking tumors and helping to improve surgical outcomes. Adjuvant treatment is given after surgery and aims to eliminate any remaining cancer cells in the body to help reduce the risk of the cancer returning.

The FDA rapidly reviewed and approved the application under the FDA's Real-Time Oncology Review (RTOR) and Assessment Aid pilot programs, leading to an approval 12 weeks after completing the submission. Kadcyla is the first Genentech medicine approved under the RTOR pilot program, which is exploring a more efficient review process to ensure safe and effective treatments are available to patients as early as possible. For this indication, Kadcyla was also granted Breakthrough Therapy Designation, which is designed to expedite the development and review of medicines intended to treat serious or life-threatening diseases.

This approval is based on results of the Phase III KATHERINE study showing Kadcyla significantly reduced the risk of invasive breast cancer recurrence or death from any cause (invasive disease-free survival; iDFS) by 50% (HR=0.50, 95% CI 0.39-0.64, p<0.0001) compared to Herceptin as an adjuvant treatment in people with HER2-positive EBC who have residual invasive disease after neoadjuvant taxane and Herceptin-based treatment. At three years, 88.3% of people treated with Kadcyla did not have their breast cancer return compared to 77.0% treated with Herceptin, an absolute improvement of 11.3%. People who have residual disease after neoadjuvant treatment have a worse prognosis than those with no detectable disease.

The most common Grade 3 or higher side effects (>2%) with Kadcyla in the KATHERINE study were decreased platelet count and high blood pressure. The most common side effects (>25%) with Kadcyla were fatigue; nausea; increased blood levels of liver enzymes; musculoskeletal pain; bleeding; decreased platelet count; headache; numbness, tingling or pain in the hands or feet; and joint pain.

For those who qualify, Genentech offers patient assistance programs for people prescribed Kadcyla by their doctor. Please contact Genentech Access Solutions at (866) 422-2377 or visit http://www.Genentech-Access.com/Kadcyla for more information.

About the KATHERINE study

KATHERINE is an international, multi-center, two-arm, randomized, open-label, Phase III study evaluating the efficacy and safety of Kadcyla versus Herceptin as an

adjuvant therapy in people with HER2-positive EBC who have pathological invasive residual disease in the breast and/or axillary lymph nodes following neoadjuvant therapy that included Herceptin and taxane-based chemotherapy. The primary endpoint of the study is iDFS, which in this study is defined as the time from randomization free from invasive breast cancer recurrence or death from any cause. Secondary endpoints include iDFS including second primary non-breast cancer, disease-free survival and overall survival.

KATHERINE Study Results		
	Kadcyla n=743	**Herceptin n=743**
Median follow-up	40 months	
Invasive disease-free survival (iDFS)		
Risk reduction	HR=0.50, 95% CI 0.39-0.64, p<0.0001	
3-year iDFS	88.3%	77.0%
	11.3% absolute improvement	
Adverse reactions (ARs)		
Grade ≥3 AR	26%	15%
Most common Grade ≥ 3 ARs (>2%)		
Thrombocytopenia	6%	0.3%

(decreased platelet count)		
Hypertension (high blood pressure)	2.0%	1.2%

About HER2-positive breast cancer

Breast cancer is one of the most common cancers among women worldwide. According to the American Cancer Society, approximately 271,000 people in the United States will be diagnosed with breast cancer, and more than 42,000 will die from the disease in 2019. Breast cancer is not one, but many diseases based on the biology of each tumor. In HER2-positive breast cancer, there is excess HER2 protein on the surface of tumor cells. Approximately 15-20% of breast cancers are HER2-positive based on the result of a diagnostic test.

About Kadcyla

Kadcyla is an antibody-drug conjugate (ADC) engineered to deliver potent chemotherapy directly to HER2-positive cancer cells. It is designed to limit damage to healthy tissues, although it can still affect them. Kadcyla can cause serious side effects. It combines two anti-cancer agents using a stable linker: the HER2-targeting trastuzumab (the active ingredient in Herceptin) and the chemotherapy agent DM1. Kadcyla is the only ADC approved for the treatment of HER2-positive early and metastatic breast cancer. In the U.S., Genentech licenses technology for Kadcyla under an agreement with ImmunoGen, Inc.

Kadcyla Indication Statements

Kadcyla is approved as an adjuvant (after surgery) treatment for HER2-positive early breast cancer when the

patient has taken neoadjuvant (before surgery) treatment including a taxane and trastuzumab (Herceptin) and there is cancer remaining in the tissue removed during surgery. Patients are selected for therapy based on an FDA-approved test for Kadcyla.

Kadcyla is approved to treat HER2-positive breast cancer that has spread to other parts of the body (metastatic breast cancer) after prior treatment with trastuzumab (Herceptin) and a taxane. Prior treatment could have been for the initial treatment of breast cancer or for the treatment of cancer that had spread to other parts of the body. Patients are selected for therapy based on an FDA-approved test for Kadcyla.

Important Safety Information

Most important safety information about Kadcyla

Liver problems

- Kadcyla may cause severe liver problems that can be life-threatening. Symptoms of liver problems may include vomiting, nausea, eating disorder (anorexia), yellowing of the skin (jaundice), stomach pain, dark urine, or itching.

Heart problems

- Kadcyla may cause heart problems, including those without symptoms (such as reduced heart function) and those with symptoms (such as congestive heart failure). Symptoms may include swelling of the ankles or legs, shortness of breath, cough, rapid weight gain of more than five pounds in 24 hours, dizziness or loss of consciousness, or irregular heartbeat.

Pregnancy

- Receiving Kadcyla during pregnancy can result in the death of an unborn baby and birth defects. Birth control should be used while receiving Kadcyla and for seven months after a patient's last dose of Kadcyla.

- If a patient thinks she may be pregnant, she should contact her healthcare provider immediately.

- If a patient is exposed to Kadcyla during pregnancy or becomes pregnant within seven months following her last dose of Kadcyla, she is encouraged to report Kadcyla exposure to Genentech by calling (888) 835-2555.

- If a male patient has a female partner that could become pregnant, birth control should be used during treatment and for four months following his last dose of Kadcyla.

- A patient should not breastfeed during treatment and for seven months after the last dose of Kadcyla.

A patient should contact their doctor right away if they experience symptoms associated with these side effects.

Additional possible serious side effects of Kadcyla

Lung problems

- Kadcyla may cause lung problems, including inflammation of the lung tissue, which can be life-threatening. Signs of lung problems may include trouble breathing, cough, tiredness, and fluid in the lungs.

Infusion-related reactions

- Symptoms of an infusion-related reaction may include one or more of the following: the skin

getting hot or red (flushing), chills, fever, trouble breathing, low blood pressure, wheezing, tightening of the muscles in the chest around the airways, or a fast heartbeat. A patient's doctor will monitor the patient for infusion-related reactions.

Serious bleeding

- Kadcyla can cause life-threatening bleeding. Taking Kadcyla with other medications used to thin the blood (antiplatelet) or prevent blood clots (anticoagulation) can increase the risk of bleeding. A patient's doctor should provide additional monitoring if the patient is taking one of these other drugs while on Kadcyla. Even when blood thinners are not also being taken, life-threatening bleeding may occur with Kadcyla.

Low platelet count

- Low platelet count may happen during treatment with Kadcyla. Platelets help the blood to clot. Signs of low platelets may include easy bruising, bleeding, and prolonged bleeding from cuts. In mild cases there may not be any symptoms.

Nerve damage

- Symptoms may include numbness and tingling, burning or sharp pain, sensitivity to touch, lack of coordination, muscle weakness, or loss of muscle function.

Skin reactions around the infusion site

- Kadcyla may leak from the vein or needle and cause reactions such as redness, tenderness, skin irritation, or pain or swelling at the infusion site. If this happens, it is more likely to happen within 24 hours of the infusion.

Most common side effects of Kadcyla

The most common side effects in people taking Kadcyla for early breast cancer are:

- Tiredness
- Nausea
- Liver problems
- Pain that affects the bones, muscles, ligaments and tendons
- Bleeding
- Low platelet count
- Headache
- Weakness, numbness, and pain in the hands and feet
- Joint pain

The most common side effects seen in people taking Kadcyla for metastatic breast cancer are:

- Tiredness
- Nausea
- Pain that affects the bones, muscles, ligaments and tendons
- Bleeding
- Low platelet count
- Headache
- Liver problems
- Constipation
- Nosebleeds

Patients are encouraged to report side effects to

Genentech and the FDA. Patients may contact Genentech by calling (888) 835-2555. Patients may contact the FDA by visiting http://www.fda.gov/medwatch or calling (800) FDA-1088.

Please click here for Kadcyla full Prescribing Information, including Most Important Safety Information, for additional Important Safety Information.

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EXHIBIT 45

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EXHIBIT 46

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 47

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 48

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RITUXAN HYCELA safely and effectively. See full prescribing information for RITUXAN HYCELA.

RITUXAN HYCELA™ (rituximab and hyaluronidase human) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning.
- **Severe mucocutaneous reactions, some with fatal outcomes (5.1).**
- **Hepatitis B virus reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death (5.2).**
- **Progressive multifocal leukoencephalopathy resulting in death (5.3).**

INDICATIONS AND USAGE

RITUXAN HYCELA is a combination of rituximab, a CD20-directed cytolytic antibody, and hyaluronidase human, an endoglycosidase, indicated for the treatment of adult patients with:
- Follicular Lymphoma (FL) (1.1)
  - Relapsed or refractory, follicular lymphoma as a single agent
  - Previously untreated follicular lymphoma in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
  - Non-progressing (including stable disease), follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
- Diffuse Large B-cell Lymphoma (DLBCL) (1.2)
  - Previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia (CLL) (1.3)
  - Previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide (FC)

Limitations of Use:
- Initiate treatment with RITUXAN HYCELA only after patients have received at least one full dose of a rituximab product by intravenous infusion. (1.4, 2.1, 5.4).
- RITUXAN HYCELA is not indicated for the treatment of non-malignant conditions. (1.4)

DOSAGE AND ADMINISTRATION

- **For subcutaneous use only** (2.1)
- All patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving RITUXAN HYCELA by subcutaneous injection (2.1).
- FL/DLBCL: Administer 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously according to recommended schedule (2.2, 2.3).
- CLL: Administer 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human) subcutaneously according to recommended schedule (2.4).
- Premedicate with acetaminophen and antihistamine before each dose; In addition, consider premedication with glucocorticoids (2.5, 5.4)
- Administer specified volume into subcutaneous tissue of abdomen: (2.6)
  - 11.7 mL from 1,400 mg/23,400 Units vial over approximately 5 minutes.
  - 13.4 mL from 1,600 mg/26,800 Units vial over approximately 7 minutes.
  - Observe 15 minutes following administration

DOSAGE FORMS AND STRENGTHS

Injection: (3)
- 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120 mg/2,000 Units per mL) solution in a single-dose vial
- 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL (120 mg/2,000 Units per mL) solution in a single-dose vial

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity and other administration reactions: Local cutaneous reactions may occur more than 24 hours after administration. Interrupt injection if severe reaction develops. Premedicate before injection. (5.4)
- Tumor lysis syndrome: Administer aggressive intravenous hydration, anti hyperuricemic agents, monitor renal function. (5.5)
- Infections: Withhold and institute appropriate anti-infective therapy. (5.6)
- Cardiac adverse reactions: Discontinue in case of serious or life-threatening events. (5.7)
- Renal toxicity: Discontinue in patients with rising serum creatinine or oliguria. (5.8)
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms. (5.9)
- Immunizations: Live virus vaccinations prior to or during treatment not recommended. (5.10)
- Embryo-Fetal toxicity: Can cause neonatal harm. Advise of potential risk to neonates and use of effective contraception. (5.11)

ADVERSE REACTIONS

Most common adverse reactions (incidence of ≥ 20%) are: (6.1)
- FL: infections, neutropenia, nausea, constipation, cough, and fatigue
- DLBCL: infections, neutropenia, alopecia, nausea, and anemia
- CLL: infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Renal toxicity when used in combination with cisplatin. (5.8)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
1 INDICATIONS AND USAGE
1.1 Follicular Lymphoma (FL)
1.2 Diffuse Large B-Cell Lymphoma (DLBCL)
1.3 Chronic Lymphocytic Leukemia (CLL)
1.4 Limitations of Use
2 DOSAGE AND ADMINISTRATION
2.1 Important Dosing Information
2.2 Recommended Dose for Follicular Lymphoma (FL)
2.3 Recommended Dose for Diffuse Large B-Cell Lymphoma (DLBCL)
2.4 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)
2.5 Recommended Premedication and Prophylactic Medications
2.6 Administration and Storage
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Severe Mucocutaneous Reactions
5.2 Hepatitis B Virus Reactivation
5.3 Progressive Multifocal Leukoencephalopathy (PML)
5.4 Hypersensitivity and other Administration Reactions
5.5 Tumor Lysis Syndrome (TLS)
5.6 Infections
5.7 Cardiovascular Adverse Reactions
5.8 Renal Toxicity
5.9 Bowel Obstruction and Perforation
5.10 Immunization
5.11 Embryo-Fetal Toxicity
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.3 Postmarketing Experience
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Follicular Lymphoma
14.2 Diffuse Large B-Cell Lymphoma (DLBCL)
14.3 Chronic Lymphocytic Leukemia (CLL)
14.4 Patient Experience
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Severe Mucocutaneous Reactions

Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA *[see Warnings and Precautions (5.1)]*.

Hepatitis B Virus (HBV) Reactivation

HBV reactivation can occur in patients treated with rituximab-containing products, including RITUXAN HYCELA, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with RITUXAN HYCELA. Discontinue RITUXAN HYCELA and concomitant medications in the event of HBV reactivation *[see Warnings and Precautions (5.2)]*.

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Follicular Lymphoma (FL)

RITUXAN HYCELA is indicated for the treatment of adult patients with:

- Relapsed or refractory, follicular lymphoma as a single agent.
- Previously untreated follicular lymphoma in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.

1.2 Diffuse Large B-Cell Lymphoma (DLBCL)

RITUXAN HYCELA is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

1.3 Chronic Lymphocytic Leukemia (CLL)

RITUXAN HYCELA is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CLL.

1.4 Limitations of Use

- Initiate treatment with RITUXAN HYCELA only after patients have received at least one full dose of a rituximab product by intravenous infusion *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*.
- RITUXAN HYCELA is not indicated for the treatment of non-malignant conditions.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

RITUXAN HYCELA is for subcutaneous use only. RITUXAN HYCELA should only be administered by a healthcare professional with appropriate medical support to manage severe reactions that can be fatal if they occur.

All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before starting treatment with RITUXAN HYCELA. If patients are not able to receive one full dose by intravenous infusion, they should continue subsequent cycles with a rituximab product by intravenous infusion and not switch to RITUXAN HYCELA until a full intravenous dose is successfully administered *[see Warnings and Precautions (5.4)]*.

Refer to the prescribing information for a rituximab product for intravenous infusion for additional information.

Premedicate before each dose of RITUXAN HYCELA *[see Dosage and Administration (2.5)]*.

Dose reductions of RITUXAN HYCELA are not recommended. When RITUXAN HYCELA is given in combination with chemotherapy dose, reduce the chemotherapeutic drugs to manage adverse reactions.

2.2 Recommended Dose for Follicular Lymphoma (FL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion before starting treatment with RITUXAN HYCELA *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*. Premedicate before each dose *[see Dosage and Administration (2.5)]*.

The recommended dose is RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously at a fixed dose irrespective of patient's body surface area according to the following schedules:

- **Relapsed or Refractory, Follicular Lymphoma**
  Administer once weekly for 3 or 7 weeks following a full dose of a rituximab product by intravenous infusion at week 1 (i.e., 4 or 8 weeks in total).
- **Retreatment for Relapsed or Refractory, Follicular Lymphoma**
  Administer once weekly for 3 weeks following a full dose of a rituximab product by intravenous infusion at week 1 (i.e., 4 weeks in total).
- **Previously Untreated, Follicular Lymphoma**
  Administer on Day 1 of Cycles 2–8 of chemotherapy (every 21 days), for up to 7 cycles following a full dose of a rituximab product by intravenous infusion on Day 1 of Cycle 1 of chemotherapy (i.e., up to 8 cycles in total). In patients with complete or partial response, initiate RITUXAN HYCELA maintenance treatment 8 weeks following completion of RITUXAN HYCELA in combination with chemotherapy. Administer RITUXAN HYCELA as a single-agent every 8 weeks for 12 doses.
- **Non-progressing, Follicular Lymphoma after first line CVP chemotherapy**
  Following completion of 6–8 cycles of CVP chemotherapy and a full dose of a rituximab product by intravenous infusion at week 1, administer once weekly for 3 weeks (i.e., 4 weeks in total) at 6 month intervals to a maximum of 16 doses.

2.3 Recommended Dose for Diffuse Large B-Cell Lymphoma (DLBCL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion in combination with CHOP chemotherapy before starting treatment with RITUXAN HYCELA *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*. Premedicate before each dose *[see Dosage and Administration (2.5)]*.

The recommended dose for DLBCL is RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) at a fixed dose irrespective of patient's body surface area in combination with CHOP chemotherapy. Administer RITUXAN HYCELA 1,400 mg/23,400 Units on Day 1 of Cycles 2–8 of CHOP chemotherapy for up to 7 cycles

following a full dose of a rituximab product by intravenous infusion at Day 1, Cycle 1 of CHOP chemotherapy (i.e., up to 6–8 cycles in total).

2.4 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion in combination with FC chemotherapy before starting treatment with RITUXAN HYCELA *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*. Premedicate before each dose *[see Dosage and Administration (2.5)]*.

The recommended dose for CLL is RITUXAN HYCELA 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human) in combination with FC chemotherapy, at a fixed dose, irrespective of patient's body surface area. Administer RITUXAN HYCELA 1,600 mg/26,800 Units on Day 1 of Cycles 2–6 (every 28 days) for a total of 5 cycles following a full intravenous dose at Day 1, Cycle 1 (i.e., 6 cycles in total).

2.5 Recommended Premedication and Prophylactic Medications

Premedicate with acetaminophen and an antihistamine before each dose of RITUXAN HYCELA. Premedication with a glucocorticoid should also be considered *[see Dosage and Administration (2.2, 2.3, 2.4)]*.

Provide prophylaxis for Pneumocystis jiroveci pneumonia (PCP) and herpes virus infections for patients with CLL during treatment and for up to 12 months following treatment as appropriate *[see Warnings and Precautions (5.6)]*.

2.6 Administration and Storage

RITUXAN HYCELA is ready to use. To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration. RITUXAN HYCELA is compatible with polypropylene and polycarbonate syringe material and stainless steel transfer and injection needles. Use the product immediately.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. RITUXAN HYCELA should be a clear to opalescent and colorless to yellowish liquid. Do not use vial if particulates or discoloration is present.

Administration

- Inject RITUXAN HYCELA into the subcutaneous tissue of the abdomen over approximately 5–7 minutes and never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars. No data are available on performing the injection at other sites of the body.
- Inject 11.7 mL of RITUXAN HYCELA 1,400 mg/23,400 Units vial (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously into the abdomen over approximately 5 minutes.
- Inject 13.4 mL of RITUXAN HYCELA 1,600 mg/26,800 Units vial (1,600 mg rituximab and 26,800 Units hyaluronidase human) subcutaneously into the abdomen over approximately 7 minutes.

If administration of RITUXAN HYCELA is interrupted, continue administering at the same site, or at a different site, but restricted to the abdomen.

Observe patients for at least 15 minutes following RITUXAN HYCELA administration *[see Warnings and Precautions (5.4)]*.

During treatment with RITUXAN HYCELA, do not administer other medications for subcutaneous use at the same sites as RITUXAN HYCELA.

Storage

After the solution of RITUXAN HYCELA is withdrawn from the vial, it should be labeled with the peel-off sticker and used immediately. If not used immediately, prepare in controlled and validated aseptic conditions. Once transferred from the vial into the syringe, store the solution of RITUXAN HYCELA in the refrigerator at 2°C–8°C (36°F–46°F) up to 48 hours and subsequently for 8 hours at room temperature up to 30°C (86°F) in diffuse light.

3 DOSAGE FORMS AND STRENGTHS

RITUXAN HYCELA is a colorless to yellowish, clear to opalescent solution for subcutaneous injection:

- Injection: 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120 mg/2,000 Units per mL) in a single-dose vial.
- Injection: 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL (120 mg/2,000 Units per mL) in a single-dose vial.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab-containing products, including RITUXAN HYCELA. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. Discontinue RITUXAN HYCELA in patients who experience a severe mucocutaneous reaction. The safety of re-administration of a rituximab-containing product, including RITUXAN HYCELA, to patients with severe mucocutaneous reactions has not been determined.

5.2 Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab-containing products. HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with a rituximab-containing product. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during treatment with a rituximab-containing product. Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following RITUXAN HYCELA. HBV reactivation has been reported up to 24 months following completion of therapy containing rituximab.

In patients who develop reactivation of HBV while on RITUXAN HYCELA, immediately discontinue treatment and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming RITUXAN HYCELA treatment in patients who develop HBV reactivation. Resumption of RITUXAN HYCELA treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

5.3 Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death has been observed in patients receiving rituximab-containing products, including RITUXAN HYCELA. Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Discontinue RITUXAN HYCELA and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML *[see Adverse Reactions (6.1)]*.

5.4 Hypersensitivity and other Administration Reactions

Systemic Reactions

Patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving RITUXAN HYCELA due to the higher risk of hypersensitivity and other acute reactions during the first infusion *[see Dosage and Administration (2.1)]*. Beginning therapy with a rituximab product by intravenous infusion allows management of hypersensitivity and other administration reactions by slowing or stopping the intravenous infusion.

Rituximab-containing products, including RITUXAN HYCELA, are associated with hypersensitivity and other administration reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.

This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of a rituximab-containing product.

Severe infusion-related reactions with fatal outcome have been reported with the use of intravenous formulations of rituximab products, with an onset ranging within 30 minutes to 2 hours after starting the first intravenous infusion. They were characterized by pulmonary events in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms.

Anaphylactic and other hypersensitivity reactions can also occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion.

Severe cytokine release syndrome is characterized by severe dyspnea, often associated by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with acute respiratory failure and death *[see Warnings and Precautions (5.5)]*. Cytokine release syndrome may occur within 1–2 hours of initiating the infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at a greater risk of poor outcome. Rituximab product administration should be interrupted immediately and aggressive symptomatic treatment initiated.

During RITUXAN HYCELA administration, the injection should be interrupted immediately when observing signs of a severe reaction and aggressive symptomatic treatment should be initiated.

Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq 25{,}000/mm^3$) *[see Warnings and Precautions (5.5, 5.7)]*.

Premedicate patients with an antihistamine and acetaminophen prior to each administration of RITUXAN HYCELA *[see Dosage and Administration (2.5)]*. Premedication with glucocorticoids should also be considered. Observe patients for at least 15 minutes following RITUXAN HYCELA. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

Local Cutaneous Reactions

Local cutaneous reactions, including injection site reactions, have been reported in patients receiving RITUXAN HYCELA. Symptoms included pain, swelling, induration, hemorrhage, erythema, pruritus, and rash *[see Adverse Reactions (6.1)]*. Some local cutaneous reactions occurred more than 24 hours after RITUXAN HYCELA administration. The incidence of local cutaneous reactions following administration of RITUXAN HYCELA was 16%. Reactions were mild or moderate and resolved without any specific treatment. Local cutaneous reactions of any Grade were most common during the first RITUXAN HYCELA cycle (Cycle 2; 5%) with the incidence decreasing with subsequent injections.

5.5 Tumor Lysis Syndrome (TLS)

TLS can occur within 12–24 hours after administration of a rituximab-containing product, including RITUXAN HYCELA. A high number of circulating malignant cells ($\geq 25{,}000/mm^3$) or high tumor burden confers a greater risk of TLS. Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated *[see Warnings and Precautions (5.8)]*.

5.6 Infections

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of therapy with rituximab-containing products, including RITUXAN HYCELA. The incidence of infections with RITUXAN HYCELA vs rituximab was 56% and 49% respectively in patients with CLL, and 46% and 41% respectively in patients with FL/DLBCL in combination with chemotherapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia > 11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue RITUXAN HYCELA for serious infections and institute appropriate anti-infective therapy *[see Adverse Reactions (6.1)]*.

5.7 Cardiovascular Adverse Reactions

Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur with rituximab-containing products, including RITUXAN HYCELA.

Discontinue RITUXAN HYCELA for serious or life threatening cardiac arrhythmias. Perform cardiac monitoring during and after all administrations of RITUXAN HYCELA for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina *[see Adverse Reactions (6.1)]*.

5.8 Renal Toxicity

Severe, including fatal, renal toxicity can occur after administration of rituximab-containing products, including RITUXAN HYCELA. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN HYCELA is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue RITUXAN HYCELA in patients with a rising serum creatinine or oliguria *[see Warnings and Precautions (5.5)]*.

5.9 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA, in combination with chemotherapy. In postmarketing reports, the mean time to documented

gastrointestinal perforation was 6 (range 1–77) days. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

5.10 Immunization

The safety of immunization with live viral vaccines following rituximab-containing products, including RITUXAN HYCELA, therapy has not been studied and vaccination with live virus vaccines is not recommended before or during treatment.

5.11 Embryo-Fetal Toxicity

Based on human data, rituximab-containing products can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero. Advise pregnant women of the risk to a fetus. Females of childbearing potential should use effective contraception while receiving RITUXAN HYCELA and for 12 months following the last dose of rituximab-containing products, including RITUXAN HYCELA.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Mucocutaneous reactions *[see Warnings and Precautions (5.1)]*
- Hepatitis B reactivation including fulminant hepatitis *[see Warnings and Precautions (5.2)]*
- Progressive multifocal leukoencephalopathy *[see Warnings and Precautions (5.3)]*
- Hypersensitivity and other administration reactions *[see Warnings and Precautions (5.4)]*
- Tumor lysis syndrome *[see Warnings and Precautions (5.5)]*
- Infections *[see Warnings and Precautions (5.6)]*
- Cardiac arrhythmias *[see Warnings and Precautions (5.7)]*
- Renal toxicity *[see Warnings and Precautions (5.8)]*
- Bowel obstruction and perforation *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to RITUXAN HYCELA in 892 patients in four controlled trials with exposures ranging from a single injection up to 27 months of treatment.

The population included 382 patients with follicular lymphoma (FL), 369 patients with diffuse large B-cell lymphoma (DLBCL), and 141 patients with chronic lymphocytic leukemia (CLL). The population was aged 18–85 years (with a median age of 60 years), 53% male and 47% female. Most of the patients were Caucasians (84%). In the SABRINA study patients with FL received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human), in combination with chemotherapy for up to 7 doses (i.e., total of 8 doses in combination with chemotherapy), or as monotherapy for up to 12 doses (maintenance treatment). In the MabEase study patients with DLBCL received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human), given in combination with chemotherapy for up to 7 doses (i.e., up to a total of 8 doses). In the SAWYER study patients with CLL on part 2 received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,600 mg rituximab/26,800 Units hyaluronidase human) for up to 5 doses, in combination with fludarabine and cyclophosphamide (i.e., total of 6 doses).

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with FL on the SABRINA study were: infections, neutropenia, nausea, constipation, cough, and fatigue.

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with DLBCL on the MabEase study were: infections, neutropenia, alopecia, nausea, and anemia.

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with CLL on part 2 of the SAWYER study were: infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema.

Administration-related reactions (ARRs)

Administration-related reactions (ARRs) with RITUXAN HYCELA were defined as all the adverse reactions related to the administration of RITUXAN HYCELA within the 24 hours post injection.

The incidence of ARRs with RITUXAN HYCELA was 34% in FL/DLBCL in combination with chemotherapy with injection site erythema (5%), chills (3%), dyspnea, erythema, flushing, injection site pain, nausea, pruritus, pyrexia, rash, and throat irritation (2% each) being the most common ARRs. The incidence of ARRs in FL maintenance setting was 20%. The most common ARRs were injection site erythema (7%), erythema (4%), injection site pain/edema, myalgia, and rash (2% each).

The incidence of ARRs with RITUXAN HYCELA in CLL was 44%.

With the exception of Local Cutaneous Reactions, the incidence and profile of adverse reactions reported for RITUXAN HYCELA were comparable with those for rituximab. The overall incidence of adverse reactions for intravenous rituximab versus RITUXAN HYCELA in combination with chemotherapy for FL/DLBCL was 93% versus 95% (BSA ≤ 1.73 m^2), 89% versus 93% (1.73 < BSA ≤ 1.92 m^2), and 94% versus 94% (BSA > 1.92 m^2). The overall incidence of adverse reactions for rituximab versus RITUXAN HYCELA in CLL was 89% versus 100% (BSA ≤ 1.81 m^2), 97% versus 88% (1.82 < BSA ≤ 1.99 m^2), and 88% versus 93% (BSA > 2.00 m^2).

Summary of Clinical Trial Experience in Follicular Lymphoma (FL)

The data in Table 1 were obtained in the SABRINA study, a two-stage randomized, controlled study in patients with previously untreated FL. The study compared patients receiving RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human; n=197) with patients receiving a rituximab product by intravenous infusion (375 mg/m^2; n=210), both in combination with CHOP or CVP followed by maintenance treatment with RITUXAN HYCELA or a rituximab product by intravenous infusion.

The majority of patients completed all 8 cycles of combination treatment with chemotherapy (91% RITUXAN HYCELA vs. 90% rituximab). In addition, 69% of patients in each of the treatment groups completed all 20 cycles of combination plus maintenance treatment. In both RITUXAN HYCELA and rituximab groups, patients experienced similar median duration of exposure (27.1 months for each arm).

Across the two stages, the overall demographics and baseline characteristics were balanced between the treatment groups. However, there were more female patients (53%) randomized in the study than male patients (47%) and a higher proportion of females were randomized to receive RITUXAN HYCELA (59% female) compared with the rituximab group (48%). The treatment groups in the combined Stage 1 and 2 population were otherwise balanced in regard to baseline demographics, characterized by a median age of 57 years (56.0 years [range 28–85 years] for RITUXAN HYCELA and 57 years [range 28–86 years] for rituximab) and median BSA of 1.83 m^2 (1.80 and 1.84 m^2 for RITUXAN HYCELA and rituximab, respectively).

The incidence of all adverse reactions was 96% for RITUXAN HYCELA vs. 95% for rituximab (Table 1). Grade 3–4 adverse reactions were reported in 55% of patients receiving RITUXAN HYCELA vs. 53% in patients receiving rituximab. Serious adverse reactions were reported in 37% of patients receiving RITUXAN HYCELA vs. 34% of patients receiving rituximab. The most common adverse reactions (occurring in ≥ 20% of patients in any arm) were infections, neutropenia, nausea, constipation, cough, and fatigue.

A total of 36 patients died, including 14/197 patients (7%) who received RITUXAN HYCELA and 22/210 patients (10%) who received rituximab. Of these 36 patients, 19 patients (7 patients RITUXAN HYCELA [4%] vs. 12 patients rituximab [6%]) died due to adverse reactions and 13 patients (6 patients RITUXAN HYCELA [3%] vs. 7 patients rituximab [3%]) died due to disease progression.

The incidence of administration-related reactions (ARRs) due to the subcutaneous route of administration associated with RITUXAN HYCELA was assessed in combination with chemotherapy and during maintenance. Thirty patients (15%) experienced an ARR during the first administration of RITUXAN HYCELA (Cycle 2). Incidence of ARRs generally decreased at subsequent cycles with 18 patients (9%) reporting ARR at Cycle 3, 13 patients (7%) at Cycle 4, 11 patients (6%) at Cycles 5 and 6, 12 patients (7%) at Cycle 7, and 8 patients (4%) at Cycle 8. During RITUXAN HYCELA monotherapy in the maintenance setting the incidence of ARRs at each cycle was ≤ 7% and was observed in 24 patients (14%) overall. Grade 1–2 ARRs constituted 96% of the overall ARRs. Grade 3 ARRs were reported during the first administration of RITUXAN HYCELA at Cycle 2 by 2 patients. Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 32 patients. These events resolved within a median of 2 days from the onset (range 1 to 37 days). Majority of these reactions were Grade 1 and 2 and were observed in 31 patients (16%).

Table 1: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated Follicular Lymphoma Receiving RITUXAN HYCELA or Rituximab in Combination with CHOP or CVP and as Monotherapy for Maintenance Treatment

Body System/Adverse Reactions	RITUXAN HYCELA (n=197)		Rituximab (n=210)	
	All AEs %	Grade 3–4 %	All AEs %	Grade 3–4 %
Gastrointestinal Disorders				
Nausea	31	0	22	0
Constipation	25	0	26	< 1
Diarrhea	18	2	16	< 1
Abdominal Pain	14	0	12	< 1
Vomiting	14	0	12	< 1
Dyspepsia	8	0	7	0
Stomatitis	6	0	5	0
Abdominal Pain Upper	5	0	5	0
General Disorders and Administration Site Conditions				
Fatigue	20	0	18	< 1
Asthenia	17	1	13	0
Pyrexia	15	< 1	16	< 1
Injection Site Erythema	13	0	0	0
Injection Site Pain	8	0	0	0
Chills	8	0	9	0
Chest Pain	6	1	3	0
Edema Peripheral	5	< 1	6	0
Mucosal Inflammation	5	1	6	< 1
Influenza Like Illness	3	0	6	0
Infections				
Upper Respiratory Tract Infection	15	< 1	10	0
Pneumonia	11	5	4	2
Nasopharyngitis	10	0	10	0
Bronchitis	8	< 1	8	< 1
Urinary Tract Infection	8	1	14	< 1
Sinusitis	7	< 1	4	0
Conjunctivitis	5	0	5	0
Influenza	4	0	6	< 1
Blood and Lymphatic System Disorders				
Neutropenia	32	26	27	21
Anemia	15	5	13	0
Febrile Neutropenia	8	7	6	6
Leukopenia	6	4	11	2
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	13	< 1	10	0
Bone Pain	10	< 1	8	0
Pain In Extremity	10	0	5	0
Back Pain	9	< 1	12	< 1
Muscle Spasms	8	0	3	0
Myalgia	8	0	5	0
Nervous System Disorders				
Paresthesia	16	0	12	0
Headache	13	0	9	0
Neuropathy Peripheral	12	2	14	< 1
Dizziness	7	0	7	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	14	< 1	10	< 1
Pruritus	10	0	12	< 1
Rash	10	0	7	0

Body System/Adverse Reactions	RITUXAN HYCELA (n=197)		Rituximab (n=210)	
	All AEs %	Grade 3–4 %	All AEs %	Grade 3–4 %
Erythema	9	0	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	23	0	13	< 1
Dyspnea	11	1	8	2
Oropharyngeal Pain	9	0	8	0
Psychiatric Disorders				
Insomnia	9	0	9	0
Vascular Disorders				
Hypertension	6	1	6	0

Summary of Clinical Trial Experience in Diffuse Large B-Cell Lymphoma (DLBCL)

The data in Table 2 were obtained in the MabEASE study, a comparative, randomized, parallel-group, multicenter study to investigate the efficacy of RITUXAN HYCELA (1,400 mg rituximab and 23,400 Units hyaluronidase human; n=369) versus 375 mg/m^2 a rituximab product by intravenous infusion (n=203) both in combination with CHOP (R-CHOP) in previously untreated patients with CD20-positive DLBCL.

Eighty two percent of patients receiving RITUXAN HYCELA or rituximab completed all 8 cycles of study treatment. In both RITUXAN HYCELA and rituximab treatment groups, patients experienced 4.9 months median duration of rituximab exposure in each arm.

The demographic characteristics were balanced between the two treatment groups. Most patients were Caucasian (79%) and more than half (54%) were male. The study population had a median age of 64 years (61% of patients aged ≥ 60 years) with median BSA of 1.83 m^2 (1.83 and 1.84 m^2 for RITUXAN HYCELA and rituximab groups, respectively).

The incidences of adverse reactions of any grade (RITUXAN HYCELA [94%] vs. rituximab [92%]) (Table 2), Grade 3–4 adverse reactions (RITUXAN HYCELA [63%] vs. rituximab [57%]), and serious adverse reactions (RITUXAN HYCELA [42%] vs. rituximab [37%]) were generally comparable between the two treatment groups. The common adverse reactions (occurring in ≥ 20% of patients in any treatment group) were neutropenia, alopecia, nausea, and anemia.

A total of 91 patients (16%) died, including 58/369 patients (16%) in RITUXAN HYCELA and 33/203 patients (16%) in rituximab. Of these patients, 44 patients (29 patients RITUXAN HYCELA [8%] vs. 15 patients rituximab [7%]) died due to adverse reactions and 35 patients (22 patients RITUXAN HYCELA [6%] vs. 13 patients rituximab [6%]) died due to disease progression. Pneumonia (4 patients RITUXAN HYCELA vs. 1 patient rituximab), septic shock (2 patients RITUXAN HYCELA vs. 3 patients rituximab), and cardiac arrest (1 patient RITUXAN HYCELA vs. 3 patients rituximab) were the most common adverse reactions leading to death.

The incidence of administration-related reactions was balanced between the RITUXAN HYCELA and rituximab groups (28% vs. 29%). Grade 1–2 ARRs constituted 97% of the overall ARRs for the RITUXAN HYCELA arm and 80% for the rituximab arm. Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 17 patients. These events resolved within a median of 2 days from the onset (range 1 to 32 days). Majority of these reactions were Grade 1 and 2 and were observed in 16 patients (4%).

Table 2: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated DLBCL Receiving RITUXAN HYCELA or Rituximab in Combination with CHOP

Body System/Adverse Reactions	RITUXAN HYCELA + CHOP (n=369)		Rituximab + CHOP (n=203)	
	All AEs %	Grade 3–4 %	All AEs %	Grade 3–4 %
Gastrointestinal Disorders				
Nausea	22	< 1	24	< 1
Constipation	15	< 1	17	< 1
Diarrhea	14	1	10	1
Vomiting	11	< 1	8	< 1
Abdominal Pain	7	< 1	7	< 1
Stomatitis	6	< 1	5	0
Dyspepsia	5	0	7	0
General Disorders and Administration Site Conditions				
Fatigue	19	1	15	1
Pyrexia	13	< 1	13	0
Asthenia	11	< 1	12	< 1
Mucosal Inflammation	8	< 1	8	1
Edema Peripheral	8	< 1	4	0
Infections				
Pneumonia	7	3	4	2
Blood and Lymphatic System Disorders				
Neutropenia	31	25	29	19
Anemia	23	5	21	4
Febrile Neutropenia	14	14	12	11
Leukopenia	7	3	7	3
Lymphopenia	5	1	6	3
Investigations				
Neutrophil Count Decreased	14	11	14	11
White Blood Cell Count Decreased	7	4	7	5
Weight Decreased	8	< 1	4	< 1
Lymphocyte Count Decreased	5	2	3	2
Metabolism and Nutrition Disorders				
Decreased Appetite	8	< 1	9	< 1
Nervous System Disorders				
Neuropathy Peripheral	12	< 1	12	0
Paresthesia	9	< 1	6	0
Headache	6	0	7	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	24	0	24	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	11	< 1	9	0
Dyspnea	6	0	4	< 1
Psychiatric Disorders				
Insomnia	7	< 1	6	< 1

Summary of Clinical Trial Experience in Chronic Lymphocytic Leukemia

The data in Table 3 were obtained in part 2 of the SAWYER study, a two-part, comparative, randomized, parallel-group, multicenter study of RITUXAN HYCELA versus a rituximab product by intravenous infusion both in combination with fludarabine and cyclophosphamide (FC) chemotherapy in patients with previously untreated CLL.

The safety analysis population in part 2 of the study included 85 patients receiving RITUXAN HYCELA (1,600 mg rituximab/26,800 Units hyaluronidase human) and 89 patients receiving

500 mg/m^2 rituximab. In both RITUXAN HYCELA and rituximab groups, patients had similar median duration of rituximab exposure (4.9 vs. 4.7 months). The majority of patients received all 6 cycles of study treatment (86% RITUXAN HYCELA vs. 81% rituximab).

The patient population was predominantly Caucasian (96%), male (65%), with a median age of 60 years and median BSA of 1.9 m^2 (1.97 and 1.86 m^2 for the RITUXAN HYCELA and intravenous rituximab groups, respectively). Overall, the treatment groups were balanced with respect to demographic characteristics, with the exception of more males in the RITUXAN HYCELA arm (71% RITUXAN HYCELA vs. 60% rituximab). Baseline disease characteristics were similar between the two groups. Over half of the patients (62%) had Binet Stage B disease and the majority had typical CLL characterizations (93%), with median time from first CLL diagnosis to randomization being 18.5 months.

The incidences of adverse reactions were balanced between the two treatment groups (96% RITUXAN HYCELA vs. 91% rituximab), and the common adverse reactions (occurring in $\geq$ 20% of patients in any arm) were infections, neutropenia, nausea, thrombocytopenia, pyrexia, anemia, vomiting, and injection site erythema. The incidences of Grade 3–4 adverse reactions were also balanced between the two treatment groups (69% RITUXAN HYCELA vs. 71% rituximab). The incidence of serious adverse reactions was 29% for RITUXAN HYCELA and 33% for rituximab. The incidence of administration-related reactions was 44% for RITUXAN HYCELA and 45% for rituximab). Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 15 patients. These events resolved within a median of 6 days from the onset (range 3 to 29 days). Majority of these reactions were Grade 1 and 2 and were observed in 14 patients (16%).

A total of 9 patients (5%) died, including 5 patients in the RITUXAN HYCELA group and 4 patients in the rituximab group. In the RITUXAN HYCELA group, 1 patient died due to herpes zoster infection, 1 patient died as a result of progressive multifocal leukoencephalopathy (PML) (considered by the investigator as related to rituximab), and 3 patients died due to disease progression. In the rituximab group, 2 patients died due to diarrhea and listeriosis and 2 patients died due to disease progression.

Table 3: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated CLL Receiving RITUXAN HYCELA or Rituximab in Combination with FC

Body System/Adverse Reactions	RITUXAN HYCELA + FC (n=85)		Rituximab + FC (n=89)	
	All AEs %	Grade 3–4 %	All AEs %	Grade 3–4 %
Gastrointestinal Disorders				
Nausea	38	1	35	0
Vomiting	21	2	22	1
Diarrhea	12	0	11	3
Abdominal Pain	9	0	6	0
Constipation	8	0	8	0
General Disorders and Administration Site Conditions				
Pyrexia	32	5	25	1
Injection Site Erythema	26	2	0	0
Injection Site Pain	16	1	0	0
Chills	13	0	10	1
Fatigue	11	0	10	0
Asthenia	8	1	17	2
Infections				
Upper Respiratory Tract Infection	13	0	12	1
Respiratory Tract Infection	8	1	4	1
Bronchitis	7	0	6	0
Urinary Tract Infection	2	0	8	1
Pneumonia	2	2	6	2
Blood and Lymphatic System Disorders				
Neutropenia	65	56	58	52
Thrombocytopenia	24	6	26	9
Leukopenia	19	14	16	12
Anemia	13	5	24	9
Febrile Neutropenia	11	8	8	8
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	9	0	1	0
Pain In Extremity	7	1	2	0
Bone Pain	6	0	2	0
Nervous System Disorders				
Headache	7	0	9	0
Skin and Subcutaneous Tissue Disorders				
Erythema	15	0	7	0
Rash	12	0	10	1
Pruritus	8	0	4	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	13	0	11	0
Oropharyngeal Pain	6	0	3	0
Dyspnea	4	0	8	1
Psychiatric Disorders				
Insomnia	1	0	7	0
Vascular Disorders				
Hypotension	1	0	7	1
Hypertension	0	0	6	1

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RITUXAN HYCELA and rituximab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the SABRINA study, where previously untreated patients with follicular lymphoma were treated with RITUXAN HYCELA or rituximab in combination with CVP or CHOP, the incidence of treatment-induced/enhanced anti-rituximab antibodies in the RITUXAN HYCELA group was similar to that observed in the rituximab group (2.0% RITUXAN HYCELA vs. 1.5% rituximab). The incidence of treatment-induced/enhanced anti-recombinant human hyaluronidase antibodies was 13% in the RITUXAN HYCELA group compared with 8% in the rituximab group, and the overall proportion of patients found to have anti-recombinant human hyaluronidase antibodies remained generally constant over the follow-up period in both cohorts. All patients who tested positive for anti-recombinant human hyaluronidase antibodies at any point during the study were negative for neutralizing antibodies.

In the SAWYER study, where previously untreated patients with CLL were treated with RITUXAN HYCELA or rituximab in combination with FC, the incidence of treatment-induced/enhanced anti-rituximab antibodies was 2.4% in the RITUXAN HYCELA group vs. 6.7% in rituximab group. The incidence of treatment-induced/enhanced anti- recombinant human hyaluronidase antibodies was 10.6% in the RITUXAN HYCELA treatment arm. None of the patients who tested positive for anti-recombinant human hyaluronidase antibodies tested positive for neutralizing antibodies.

The clinical relevance of the development of anti-rituximab or anti-recombinant human hyaluronidase antibodies after treatment with RITUXAN HYCELA is not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rituximab-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hematologic: prolonged pancytopenia, marrow hypoplasia, Grade 3–4 prolonged or late-onset neutropenia, hyperviscosity syndrome in Waldenstrom’s macroglobulinemia, prolonged hypogammaglobulinemia
- Cardiac: fatal cardiac failure
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections
- Neoplasia: disease progression of Kaposi’s sarcoma.
- Skin: severe mucocutaneous reactions.
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on human data, rituximab-containing products can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed to rituximab in-utero *(see Clinical Considerations)*. There are no available data on RITUXAN HYCELA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, intravenous administration of a rituximab product to pregnant cynomolgus monkeys during the period of organogenesis caused lymphoid B cell depletion in the newborn offspring at doses resulting in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Reduced fetal weight and increased fetal lethality were observed following subcutaneous administration of hyaluronidase human in mice at a dose > 2700 times higher than the human dose. Comparable systemic exposure levels could occur in a pregnant patient following accidental intravenous administration of an entire vial of RITUXAN HYCELA *(see Data)*. Advise pregnant women of the risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2%–4% and of miscarriage is 15%–20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Observe newborns and infants for signs of infection and manage accordingly.

Data

Human Data

Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Animal Data

RITUXAN HYCELA for subcutaneous injection contains rituximab and hyaluronidase human *[see Description (11)]*.

Rituximab Product:

- An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis period; post coitum days 20 through 50). Rituximab was administered as loading doses on post coitum (PC) Days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.
- A subsequent pre-and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through

postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

Hyaluronidase Human:

- In an embryo-fetal study, mice have been dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase human at dose levels up to 2,200,000 U/kg, which is > 2700 times higher than the human dose. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is > 450 times higher than the human dose.
- In a peri-and post-natal reproduction study, mice have been dosed daily by subcutaneous injection, with hyaluronidase human from implantation through lactation and weaning at dose levels up to 1,100,000 U/kg, which is > 1,300 times higher than the human dose. The study found no adverse effects on sexual maturation, learning and memory or fertility of the offspring.

8.2 Lactation

There are no data on the presence of rituximab or hyaluronidase human in human milk, the effect on the breastfed infant, or the effect on milk production. However, rituximab is detected in the milk of lactating cynomolgus monkeys, and IgG is present in human milk. Since many drugs including antibodies are present in human milk, advise a lactating woman not to breastfeed during treatment and for at least 6 months after the last dose of RITUXAN HYCELA due to the potential for serious adverse reactions in breastfed infants.

8.3 Females and Males of Reproductive Potential

Rituximab-containing products can cause fetal harm *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Females of childbearing potential should use effective contraception while receiving RITUXAN HYCELA and for 12 months following treatment.

8.4 Pediatric Use

The safety and effectiveness of RITUXAN HYCELA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in the SABRINA, MabEase, and SAWYER studies, 37% were 65 and over, while 10% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

RITUXAN HYCELA is a combination of rituximab and hyaluronidase human. Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

RITUXAN HYCELA (rituximab and hyaluronidase human) Injection is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, single-dose vials for subcutaneous administration.

RITUXAN HYCELA is supplied as 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL in single-dose vials or 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL in single-dose vials. Each mL of solution contains rituximab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.53 mg), L-histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate 80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase human increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. In the doses administered, hyaluronidase human in RITUXAN HYCELA acts locally.

The effects of hyaluronidase human are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

Hyaluronidase human has been shown to increase the absorption rate of a rituximab product into the systemic circulation when given in the subcutis of Göttingen Minipigs.

12.2 Pharmacodynamics

Peripheral B-cell counts declined to levels below normal following a dose of rituximab by intravenous infusion. In patients treated with rituximab for hematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer.

Follicular Lymphoma (FL)

Peripheral B-cell counts decline to levels below normal following the first cycle of rituximab and are maintained during treatment with RITUXAN HYCELA. After stopping RITUXAN HYCELA treatment, B-cell repletion followed similar kinetics to that of rituximab with B-cell repletion beginning after 6 months of stopping treatment, although in some patients this may take longer.

Chronic Lymphocytic Leukemia (CLL)

Following the first cycle of treatment of rituximab, B-cells begin to deplete, with 28% of patients B-cell depleted at pre-dose Cycle 2 in the SAWYER study. An increase in the proportion of B-cell depleted patients was observed with subsequent cycles of RITUXAN HYCELA and by Cycle 6, 96% of patients were depleted. Patients remained B-cell depleted until the month 9 follow-up visit, where signs of repletion were seen.

12.3 Pharmacokinetics

The geometric mean rituximab exposures are provided in Table 4. The pharmacokinetic properties of rituximab following the administration of RITUXAN HYCELA in the approved indications are provided in Table 5. The elimination of rituximab was characterized by a time-dependent process that occurred early in therapy and a time-independent process.

Table 4: Rituximab Exposure Values following Subcutaneous Administration of RITUXAN HYCELA[a]

		Study[b]	Cycle	Rituximab
FL[c]	C_{max}, mcg/mL (CV%)	SABRINA	7	237 (29.4)
			18	156 (24.7)[e]
	C_{trough}, mcg/mL (CV%)		7	122.2 (55.3)
			18	45.5 (53.6)[e]
	AUC_{TAU}, mcg•day/mL (CV%)		7	3779 (33.7)
			18	5000 (34.3)[e]
CLL[d]	C_{max}, mcg/mL (CV%)	SAWYER	6	202 (36.1)
	C_{trough}, mcg/mL (CV%)		5	97.5 (42.6)
	AUC_{TAU}, mcg•day/mL (CV%)		5	4088 (34.2)

[a] Pharmacokinetic parameters are presented as geometric mean unless otherwise specified.
[b] For study design information, see *Clinical Studies (14).*
[c] RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human)
[d] RITUXAN HYCELA 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human)
[e] Based on predicted values

In the SABRINA study, the geometric mean C_{trough} in the RITUXAN HYCELA arm was higher than in the rituximab arm with a geometric mean ratio (C_{trough}, RITUXAN HYCELA/C_{trough}, rituximab) of 1.52 (90% CI: 1.36, 1.70) at Cycle 7 *[see Clinical Studies (14.1)]*. In the SAWYER study, the geometric mean C_{trough} in the RITUXAN HYCELA arm was higher than in the rituximab arm with an adjusted geometric mean ratio of 1.53 (90% CI: 1.27–1.85) at Cycle 5 *[see Clinical Studies (14.3)]*.

Table 5: Pharmacokinetic Parameters of Rituximab following Subcutaneous Administration of RITUXAN HYCELA[a]

	FL	CLL
Absorption		
Absolute Bioavailability[b]	0.646 (0.634–0.659[d])	0.634 (0.602–0.665[d])
Distribution		
Volume of Central compartment (L)	4.06 (26)	4.80 (18)
Apparent Volume of Distribution at steady state[c] (L)	8.09 (19)	8.52 (13)
Elimination		
Terminal Half-life (days)	34.1 (27)	32 (24)
Clearance (L/day)	0.18 (34)	0.204 (31)

[a] Parameters represented as geometric mean (%CV) unless otherwise specified
[b] Compared to a rituximab product administered intravenously
[c] Volume of central compartment and peripheral compartment
[d] 95% CI

Specific Populations

The pharmacokinetics of rituximab and hyaluronidase human in children and adolescents is unknown. The effect of either renal or hepatic impairment on the pharmacokinetics of rituximab and hyaluronidase human is unknown.

Drug Interaction Studies

The drug interaction potential of rituximab and hyaluronidase human is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN HYCELA or rituximab, or to determine potential effects on fertility in males or females.

RITUXAN HYCELA contains hyaluronidase human. Hyaluronidase is found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase human. In addition, when hyaluronidase human was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, which is > 90 times higher than the human dose, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

14 CLINICAL STUDIES

14.1 Follicular Lymphoma

The SABRINA study [NCT01200758] was a randomized, two-stage, open-label, multicenter study that enrolled a total of 410 patients with previously untreated, CD20-positive follicular lymphoma of Grade 1, 2 or 3a requiring therapy. The study design is identical in stage 1 and 2. Patients were randomized (1:1) to receive either a rituximab product by intravenous infusion 375 mg/m^2 for 8 cycles or 1 cycle of a rituximab product by intravenous infusion 375 mg/m^2 followed by 7 cycles of RITUXAN HYCELA 1,400mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) both every 3 weeks in combination with a total of 6–8 cycles of CHOP or 8 cycles of CVP chemotherapy. Patients underwent interim staging after 4 cycles. Patients who received R-CHOP and achieved a CR, CRu, PR or SD at the interim assessment could receive either 4 more cycles of R-CHOP or 2 cycles of R-CHOP followed by 2 cycles of

monotherapy with rituximab product or RITUXAN HYCELA depending on randomization arm (i.e., a total of 8 cycles of rituximab product or RITUXAN HYCELA). Patients with at least a PR after combination treatment with chemotherapy continued with single agent maintenance treatment administered every 8 weeks for 24 months with rituximab product or RITUXAN HYCELA as per their randomization (i.e., total of 12 cycles of maintenance treatment).

Randomization was stratified by: underlying chemotherapy backbone (CHOP vs CVP), Follicular Lymphoma International Prognostic Index (FLIPI) (low-risk vs. intermediate-risk vs. high-risk), and region (Europe and North America vs. South and Central America vs Asia). The main outcome measure for Stage 1 was the estimated ratio of observed rituximab serum $C_{trough\ SC}/C_{trough\ IV}$ at Cycle 7 of combination treatment with chemotherapy every 3 weeks. The main outcome measure for Stage 2 was the investigator-assessed ORR consisting of CR, CRu, and PR at the completion of combination treatment with chemotherapy. Additional outcome measures were CRR (CR and CRu) at the end of completion of combination treatment with chemotherapy, ORR and CRR at the end of completion of maintenance treatment, and time-to-event endpoints (progression-free survival (PFS), and overall survival (OS)).

Of all randomized patients, the median age was 57 years, median BSA was 1.83 m^2, 53% were females, and 86% were Caucasian, 45% had high risk or 34% had intermediate risk FLIPI score, and 54% had Ann Arbor Stage IV disease at study entry. Ninety percent of patients completed all 8 cycles of combination treatment with chemotherapy, and 70% of patients completed 20 cycles of both combination and maintenance treatment. Median treatment duration was 27.1 months in both groups. The median number of cycles received was 20 in both groups.

The PK results for the primary endpoint in Stage 1, rituximab C_{trough} at Cycle 7 (i.e., 21 days after Cycle 7 rituximab administration), demonstrated that RITUXAN HYCELA 1,400 mg/23,400 Units was non-inferior compared with rituximab at 375 mg/m^2 in patients receiving combination treatment with chemotherapy*[see Clinical Pharmacology (12.3)]*. The efficacy results for RITUXAN HYCELA were comparable with rituximab and are presented in Table 6.

Table 6: Efficacy Results for SABRINA Study

	RITUXAN HYCELA n=205	Rituximab n=205
Overall Response Rate at End of combination treatment with chemotherapy[a]		
Number of responders (CR/CRu, PR)	173	174
Overall response (CR/CRu, PR) rate (%, [95% CI])	84% [79;89]	85% [79;90]
Difference in overall response rates[b] [95% CI]	-0.5% [-7.7;6.8]	
Number of complete responders (CR/CRu)	66	66
Complete response (CR/CRu) rate (%, [95% CI])	32% [26;39]	32% [26;39]
Difference in complete response rates[b] [95% CI]	0.0% [-9.3;9.3]	
Overall Response Rate at End of Maintenance		
Number of patients treated in maintenance (n)	172	178
Number of responders (CR/CRu, PR)	134	139
Overall response (CR/CRu, PR) rate (%, [95% CI])	78% [71;84]	78% [71;84]
Difference in overall response rates[b] [95% CI]	-0.2 [-9.2;8.8]	
Number of complete responders (CR/CRu)	87	100
Complete response (CR/CRu) rate (%, [95% CI])	51% [43;58]	56% [49;64]
Difference in complete response rates[b] [95% CI]	-5.6 [-16.4;5.2]	
Progression-free survival		
Number of patients with event	50 (24%)	57 (28%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.84 [0.57;1.23]	
Overall survival		
Number of patients with event	16 (7.8%)	20 (9.8%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.81 [0.42;1.57]	

[a] Stage 2 main outcome measure was ORR at the end of combination treatment with chemotherapy; however pooled results which were preplanned are presented in this Table.
Response rates based on investigator assessment.
Response rates at end of maintenance based on patients who received at least one cycle of maintenance treatment (n).
[b] Difference in response rates (RITUXAN HYCELA minus rituximab).

14.2 Diffuse Large B-Cell Lymphoma (DLBCL)

The MabEase study [NCT01649856] enrolled a total of 576 patients with previously untreated CD20-positive DLBCL. Patients were randomized (2:1) to receive either a rituximab product by intravenous infusion, 375 mg/m^2 for 8 cycles or 1 cycle of an rituximab product by intravenous infusion 375 mg/m^2 followed by 7 cycles of RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human), both in combination with up to 6–8 cycles of CHOP chemotherapy, every 14 (CHOP-14) or 21 days (CHOP-21). Randomization was stratified by: age (< 60 years, ≥ 60 years), International Prognostic Index (IPI) risk category (low, low-intermediate, high-intermediate, high), and chemotherapy regimen (CHOP-21 or CHOP-14). The main outcome measure was investigator-assessed complete response rate (CR/CRu) at the end of combination treatment with chemotherapy. Additional outcome measures were time-to-event endpoints (PFS and OS).

Of all randomized patients, 54% of patients were male, the median age was 64 years, 79% Caucasians, median BSA was 1.83 m^2, 31% low risk or 30% low intermediate risk IPI score, 24% high intermediate risk, or 15% high risk IPI score and 42% of patients had Ann Arbor Stage IV disease. A total of 470 patients (82%) received 8 cycles of treatment. Median duration of

exposure to treatment was 4.9 months in both treatment groups. The median number of administrations/cycles (RITUXAN HYCELA or rituximab) was 8 in both groups.

The efficacy results for RITUXAN HYCELA were comparable with rituximab and are presented in Table 7. The median observation time was approximately 28 months.

Table 7: Efficacy Results for MabEase Study

	RITUXAN HYCELA n=381	**Rituximab n=195**
Complete Response Rate (CR/CRu)		
Number of responders (CR/CRu achieved)[a]	179	82
Response rate (%, [95% CI])	47% [42;52]	42% [35;49]
Difference in response rates [95% CI][b]	4.9% [-3.6;13.5]	
Progression-free survival[c]		
Number of patients with event	104 (27%)	44 (23%)
Hazard Ratio [95% CI] (unstratified Cox model)	1.22 [0.85;1.73]	
Overall survival[d]		
Number of patients with event	63 (17%)	29 (15%)
Hazard Ratio [95% CI] (unstratified Cox model)	1.08 [0.70;1.68]	

[a] Four patients in the RITUXAN HYCELA group and 1 patient in the rituximab group had their response downgraded due to their bone marrow data.
[b] Difference in response rates (RITUXAN HYCELA minus rituximab).
[c] Progression-free survival is defined as the time from randomization to the first occurrence of disease progression or relapse, or death from any cause.
[d] Overall survival is defined as the time from randomization until death from any cause.

14.3 Chronic Lymphocytic Leukemia (CLL)

The SAWYER study [NCT01292603] was a randomized, two-part, open-label, multicenter study that enrolled a total of 176 patients with previously untreated CLL. Patients were randomized (1:1) to receive either a rituximab product by intravenous infusion, 375 mg/m^2, in Cycle 1 followed by up to 5 cycles of rituximab, 500 mg/m^2, or rituximab, 375 mg/m^2, in Cycle 1 followed by subsequent cycles (2–6) of RITUXAN HYCELA 1,600 mg /26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human), both in combination with fludarabine and cyclophosphamide (FC) chemotherapy. The main outcome measure was the non-inferiority of the pharmacokinetic profile of RITUXAN HYCELA compared to rituximab.

The patient population comprised 96% Caucasians, 65% males, a median age of 60 years (range 25–78 years), median BSA of 1.9 m^2, 62% had Binet Stage B disease and 93% had typical CLL characterization.

The PK results demonstrated that RITUXAN HYCELA 1,600mg/26,800 Units serum rituximab C_{trough} level was non-inferior compared with rituximab at 500 mg/m^2 in patients receiving combination treatment with chemotherapy *[see Clinical Pharmacology (12.3)]*.

An additional outcome measure in Part 2 was investigator-assessed response rates. Overall response rate was 85% (95% CI: 76; 92) in RITUXAN HYCELA and 81% (95% CI: 71; 88) in the rituximab groups. Overall the response rates were comparable between RITUXAN HYCELA and rituximab with a difference in response rate of 4.6% (95% CI:-7.2; 16.3). Complete response

rate point estimates were 26% (95% CI: 17; 37) and 33% (95% CI: 23; 44) in the RITUXAN HYCELA and rituximab groups, respectively.

14.4 Patient Experience

Previously untreated adult patients outside of the United States with CD20+ diffuse large B-cell lymphoma (DLBCL) or CD20+ follicular non-Hodgkin's lymphoma (FL) Grades 1, 2, or 3a were randomized to receive a standard chemotherapy regimen (CHOP, CVP, or bendamustine) and either RITUXAN HYCELA 1,400mg/23,400 Units at Cycles 2–4 (after the first cycle with intravenous rituximab) or a rituximab product by intravenous infusion at Cycles 1–4. After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining 4 cycles. After Cycle 8, 477 of 620 patients (77%) reported preferring subcutaneous administration of RITUXAN HYCELA over intravenous rituximab and the most common reason was that administration required less time in the clinic. After Cycle 8, 66 of 620 patients (11%) preferred rituximab intravenous administration and the most common reason was that it felt more comfortable during administration. Forty eight of 620 patients (7.7%) had no preference for the route of administration. Twenty nine subjects of 620 (4.7%) received Cycle 8 but did not complete the preference questionnaire.

16 HOW SUPPLIED/STORAGE AND HANDLING

RITUXAN HYCELA (rituximab and hyaluronidase human) Injection formulated for subcutaneous injection is supplied as a sterile preservative-free liquid solution in a single-dose vial. The following configurations are available:

Individually packaged single-dose vials:

- RITUXAN HYCELA 1,400 mg/23,400 Units (NDC 50242-108-01) providing 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL
- RITUXAN HYCELA 1,600 mg/26,800 Units (NDC 50242-109-01) providing 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL

Storage and Stability

Store RITUXAN HYCELA vials in the refrigerator at 2ºC–8ºC (36ºF–46ºF) in the original carton to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Severe Mucocutaneous Reactions

Advise patients to contact their healthcare provider immediately for symptoms of severe mucocutaneous reactions, including painful sores or ulcers on the lips or mouth, blisters, peeling skin, rash, and pustules *[see Warnings and Precautions (5.1)]*.

Hepatitis B Virus Reactivation

Advise patients to contact their healthcare provider immediately for symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes *[see Warnings and Precautions (5.2)]*.

Progressive Multifocal Leukoencephalopathy (PML)

Advise patients to contact their healthcare provider immediately for signs and symptoms of PML, including new or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, decreased strength or weakness on one side of the body, or vision problems *[see Warnings and Precautions (5.3)]*.

Hypersensitivity and Other Administration Reactions

Inform patients about the signs and symptoms of hypersensitivity and administration-related reactions. Advise patients to contact their healthcare provider immediately to report symptoms of

administration-related reactions including dizziness, nausea, chills, fever, vomiting, diarrhea, urticaria, angioedema, breathing problems, or chest pain *[see Warnings and Precautions (5.4)]*.

Tumor Lysis Syndrome (TLS)

Advise patients to contact their healthcare provider immediately for signs and symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy *[see Warnings and Precautions (5.5)]*.

Infections

Advise patients to contact their healthcare provider immediately for signs and symptoms of infections including fever, cold symptoms (e.g., rhinorrhea or laryngitis), flu symptoms (e.g., cough, fatigue, body aches), earache or headache, dysuria, cold sores, and painful wounds with erythema *[see Warnings and Precautions (5.6)]*

Cardiovascular Adverse Reactions

Advise patients of the risk of cardiovascular adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock. Advise patients to contact their healthcare provider immediately to report chest pain and irregular heartbeats. *[see Warnings and Precautions (5.7)]*

Renal Toxicity

Advise patients of the risk of renal toxicity. Inform patients of the need for healthcare providers to monitor kidney function *[see Warnings and Precautions (5.8)]*.

Bowel Obstruction and Perforation

Advise patients to contact their healthcare provider immediately for sign and symptoms of bowel obstruction and perforation, including severe abdominal pain or repeated vomiting *[see Warnings and Precautions (5.9)]*.

Embryo-Fetal Toxicity

Advise a pregnant woman of the potential risk to a fetus. Advise female patients that rituximab containing products can cause fetal harm if taken during pregnancy and to use effective contraception during treatment with RITUXAN HYCELA and for at least 12 months after the last dose of RITUXAN HYCELA. Advise patients to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with RITUXAN HYCELA and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

RITUXAN HYCELA™ [rituximab and hyaluronidase human]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License No.: 1048

MEDICATION GUIDE

RITUXAN HYCELA™ [rih-TUKS-an hye-SELL-uh]
(rituximab and hyaluronidase human)
injection

What is the most important information I should know about RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects that can lead to death, including:

- **Severe skin and mouth reactions.** Tell your healthcare provider or get medical help right away if you get any of these symptoms at any time during your treatment with RITUXAN HYCELA:
  - o painful sores or ulcers on your skin, lips or in your mouth
  - o blisters
  - o peeling skin
  - o rash
  - o pustules
- **Hepatitis B virus (HBV) reactivation.** Before you receive RITUXAN HYCELA, your doctor will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving RITUXAN HYCELA could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure, and death. Your healthcare provider will monitor you for hepatitis B infection during and for several months after you stop receiving RITUXAN HYCELA.

  Tell your healthcare provider right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes during treatment with RITUXAN HYCELA.
- **Progressive Multifocal Leukoencephalopathy (PML)**. PML is a rare, serious brain infection caused by a virus that can happen in people who receive RITUXAN HYCELA. People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML.

  Tell your healthcare provider right away if you have any new or worsening symptoms or if anyone close to you notices these symptoms:
  - o confusion
  - o dizziness or loss of balance
  - o difficulty walking or talking
  - o decreased strength or weakness on one side of your body
  - o vision problems, such as blurred vision or loss of vision
- **Serious allergic reactions and other severe reactions.**

  Serious allergic reactions, and reactions due to release of certain substances by your body that can lead to death, can happen with rituximab products, including RITUXAN HYCELA.

  Skin reactions at or near the injection site (local), including injection site reactions, can happen with RITUXAN HYCELA. Symptoms at or near the injection site may include: pain, swelling, hardness, redness, bleeding, itching, and rash. These reactions sometimes happen more than 24 hours after an injection of RITUXAN HYCELA.

  Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an injection of RITUXAN HYCELA:
  - o hives (red itchy welts) or rash
  - o itching
  - o swelling of your lips, tongue, throat or face
  - o sudden cough
  - o shortness of breath, difficulty breathing, or wheezing
  - o weakness
  - o dizziness or feel faint
  - o palpitations (feel like your heart is racing or fluttering)
  - o chest pain
  - o fever
  - o chills or shaking chills

See **"What are the possible side effects of RITUXAN HYCELA?"** for more information about side effects.

What is RITUXAN HYCELA?

RITUXAN HYCELA is a prescription medicine used to treat adults with:

- **Follicular Lymphoma (FL): alone or with certain chemotherapy medicines.**
- **Diffuse Large B-Cell Lymphoma (DLBCL):** with certain other chemotherapy medicines in people who have not had previous treatment for their DLBCL.
- **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and cyclophosphamide.

You can only receive RITUXAN HYCELA after you receive at least 1 full dose of a rituximab product by IV infusion. Read the rituximab by IV infusion Medication Guide for more information about severe infusion reactions, which usually happen during the first dose with a rituximab product given by IV infusion.

RITUXAN HYCELA is not for use to treat medical conditions other than cancers.

It is not known if RITUXAN HYCELA is safe and effective in children.

Before you receive RITUXAN HYCELA, tell your healthcare provider about all of your medical conditions, including if you:

- have had a severe reaction to a rituximab product or RITUXAN HYCELA
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system
- have or have had any severe infections including:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Parvovirus B19
  - Varicella zoster virus (chickenpox or shingles)
  - West Nile Virus
- have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or during treatment with RITUXAN HYCELA.
- are pregnant or plan to become pregnant. Talk to your healthcare provider about the risks to your unborn baby if you receive RITUXAN HYCELA during pregnancy.

  Females who are able to become pregnant should use effective birth control (contraception) during treatment with RITUXAN HYCELA and for **12 months** after the last dose of RITUXAN HYCELA. Talk to your healthcare provider about effective birth control.
- are breastfeeding or plan to breastfeed. It is not known if RITUXAN HYCELA passes into your breast milk. Do not breastfeed during treatment and for **at least 6 months** after your last dose of RITUXAN HYCELA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RITUXAN HYCELA?

- RITUXAN HYCELA is given as an injection under the skin, in the stomach-area (abdomen).
- RITUXAN HYCELA is injected over 5 or 7 minutes.
- Your healthcare provider will prescribe medicines before the injection of RITUXAN HYCELA to help reduce side effects such as fever and chills.
- Your healthcare provider should monitor you for side effects for at least 15 minutes after you receive an injection of RITUXAN HYCELA.
- If you have CLL, your healthcare provider should prescribe medicines to help prevent certain infections during treatment and for up to 12 months following treatment with RITUXAN HYCELA.

Before each injection of RITUXAN HYCELA treatment, your healthcare provider or nurse will ask you questions about your general health. Tell your healthcare provider or nurse about any new symptoms.

What are possible side effects of RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects, including:

- See "What is the most important information I should know about RITUXAN HYCELA?"
- **Tumor Lysis Syndrome (TLS)**. TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have:
  - kidney failure and the need for dialysis treatment
  - abnormal heart rhythm

  TLS can happen within 12 to 24 hours after an injection of RITUXAN HYCELA. Your healthcare provider may do blood tests to check you for TLS. Your healthcare provider may give you medicine to help prevent TLS.

  Tell your healthcare provider right away if you have any of the following signs or symptoms of TLS:
  - nausea
  - vomiting
  - diarrhea
  - lack of energy
- **Serious infections.** Serious infections can happen during and after treatment with RITUXAN HYCELA, and can lead to death. Rituximab products can increase your risk of getting infections **and** can lower the ability of your immune system to fight infections. Types of serious infections that can happen with RITUXAN HYCELA include bacterial, fungal, and viral infections. After receiving RITUXAN HYCELA, some people have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these people with low antibody levels developed infections. Tell your healthcare provider right away if you have any symptoms of infection:
  - fever
  - cold symptoms, such as runny nose or sore throat that do not go away
  - flu symptoms, such as cough, tiredness, and body aches
  - earache or headache
  - pain during urination
  - white patches in the mouth or throat
  - cuts, scrapes or incisions that are red, warm, swollen or painful
- **Heart problems.** RITUXAN HYCELA may cause chest pain, irregular heartbeats, and heart attack. Your healthcare provider may monitor your heart during and after treatment with RITUXAN HYCELA if you have symptoms of heart problems or have a history of heart problems. Tell your healthcare provider right away if you have chest pain or irregular heartbeats during treatment with RITUXAN HYCELA.
- **Kidney problems** RITUXAN HYCELA can cause severe kidney problems that can lead to death. Your healthcare provider should do blood tests to check how well your kidneys are working.
- **Stomach and serious bowel problems that can sometimes lead to death.** Bowel problems, including blockage or tears in the bowel, can happen if you receive RITUXAN HYCELA with chemotherapy medicines. Tell your healthcare provider right away if you have severe stomach-area (abdomen) pain or repeated vomiting during treatment with RITUXAN HYCELA.

Your healthcare provider will stop treatment with RITUXAN HYCELA if you have severe, serious or life-threatening side effects.

The most common side effects of RITUXAN HYCELA in people with Follicular Lymphoma (FL) include: infections, low white blood cell count, nausea, constipation, cough, and tiredness.

The most common side effects of RITUXAN HYCELA in people with Diffuse Large B-cell Lymphoma (DLBCL) include: infections, low white blood cell count, loss of hair, nausea, and low red blood cell count.

The most common side effects of RITUXAN HYCELA in people with Chronic Lymphocytic Leukemia (CLL) include: infections, low white blood cell count, nausea, low platelet count, fever, vomiting, and injection site redness.

These are not all of the possible side effects with RITUXAN HYCELA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of RITUXAN HYCELA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about RITUXAN HYCELA that is written for health professionals.

What are the ingredients in RITUXAN HYCELA?

Active ingredient: rituximab and hyaluronidase human.

Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, α,α-trehalose dihydrate, and Water for Injection.

Manufactured by: Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990
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Jointly marketed by: Biogen and Genentech USA, Inc.

For more information, go to www.RITUXANHYCELA.com or call 1-877-436-3683.

CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on July 10, 2019 on the following counsel in the manner indicated:

VIA EMAIL:

Neal C. Belgam
Eve H. Ormerod
Jennifer M. Rutter
SMITH, KATZENSTEIN & JENKINS, LLP
1000 West Street, Suite 1501
Wilmington, DE 19801
(302) 652-8400
nbelgam@skjlaw.com
eormerod@skjlaw.com
jrutter@skjlaw.com

Orion Armon
COOLEY, LLP
380 Interlocken Crescent, Suite 900
Broomfield, CO 80021-8023
(720) 566-4119
oarmon@cooley.com

Eamonn Gardner
COOLEY, LLP
4401 Eastgate Mall
San Diego, CA 92121-1909
(858) 550-6086
egardner@cooley.com

Michelle Rhyu
Susan Krumplitsch
Daniel Knauss
Philip H. Mao
Alexandra Leeper
Lauren Krickl
Benjamin S. Lin
Alissa M. Wood
COOLEY, LLP
3175 Hanover Street
Palo Alto, CA 94304-1130
(650) 843-5287
rhyums@cooley.com
skrumplitsch@cooley.com
dknauss@cooley.com
pmao@cooley.com
aleeper@cooley.com
lkrickl@cooley.com
blin@cooley.com
amwood@cooley.com

Nancy Gettel
AMGEN, INC.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
(805) 447-1000
ngettel@amgen.com

Xiaoxiao Xue
1299 Pennsylvania Avenue, NW, Suite 700
Washington, DC 20004-2400
(202) 842-7809
xxue@cooley.com

Attorneys for Defendant Amgen Inc.

Dated: July 10, 2019

/s/ Michael P. Kelly
Michael P. Kelly (#2295)