UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Celltrion, Inc. and Pfizer, Inc.
Petitioners,

v.

Genentech, Inc.
Patent Owner.

Case IPR2017-01122
Patent 7,892,549

**DECLARATION OF ROBERT EARHART, M.D., Ph.D.
IN SUPPORT OF CELLTRION'S SUR-REPLY IN OPPOSITION TO
PATENT OWNER'S MOTION TO AMEND**

1. I, Robert Earhart, M.D., Ph.D., declare as follows:

I. Introduction

2. I am the same Robert Earhart who submitted a declaration in support of Celltrion's Petition for *Inter Partes* Review of U.S. Patent 7,892,549 (the '549 patent) in March 2017, and a declaration in support of Celltrion's Reply to Patent Owner's Response in March 2018. A detailed description of my background and qualifications may be found in the first declaration that I submitted in March 2107, which I refer to as my "first declaration."

3. I am being compensated at my standard rate for my time spent preparing this declaration, and my compensation is not contingent on the outcome of any matter or on any of the opinions provided below. I have no financial interest in the outcome of this proceeding.

4. I provided my understanding of legal concepts as they relate to this proceeding in my first declaration. My understanding of those concepts has not changed since I submitted my first declaration.

5. I understand that the parties have proposed different definitions for a person of ordinary skill in the art. (Petition at 43; POR at 35.) In the institution decision, the Board adopted Patent Owner's definition, but noted that it does not discern an appreciable difference in the parties' respective definitions. (Paper 9 at 9-10.) It further noted that "both parties contend that a person of ordinary skill in

the art would have had experience with breast-cancer research and treatment." I have such experience, including experience in the evaluation of data which either support or reject the decision to conduct a clinical trial to administer anticancer treatments in adult patients with solid tumors. My own professional experience of 40 years in strategic clinical program design, protocol development, clinical study monitoring and conduct under Good Clinical Practice principles, clinical data analysis, manuscript and report generation, analysis of published clinical trial reports, and teaching of principles in the field of oncology drug development have provided me with an intimate understanding of the processes and standards by which such a person of ordinary skill in the art decides that a given course of clinical trial development is obvious. I have reviewed both definitions and to the extent there are difference, those differences do not affect the opinions set forth in any of my declarations.

II. Standard Statistical Methods Should Be Used in Determining Whether There Was an Increase in Severe Adverse Events

6. A person of ordinary skill in the art would have noted that the specification reports a difference of 2% in the incidence of serious adverse events observed with the combination of trastuzumab and paclitaxel versus paclitaxel alone, and thus there was an increase in adverse events with the combination.

7. The '549 patent does not provide enough information for a person of ordinary skill in the art to determine, however, whether the increase in severe

adverse events observed with the combination of trastuzumab and paclitaxel over paclitaxel alone was statistically significant.

8. A person of ordinary skill in the art thus would not have been able to determine whether the disclosed treatment with trastuzumab and paclitaxel was "without increase in overall serious adverse events" as required by the claims.

III. Dr. Kerbel's Criticisms of Baselga's Data and Methods Are Misplaced

9. Dr. Kerbel, Patent Owner's expert, argues in his Supplemental Declaration that the data set forth in Baselga Abstract 53 was unreliable as it only measured response rate one point in time. In a prominent group like Baselga's from Sloan-Kettering, it would have been highly unusual to measure response rate at a single point in time. As is confirmed by the later publication of Baselga 1998, Baselga collected the data daily and plotted it on a curve, using standard methods employed in the analysis of xenograft data. Ex. 1047 at 2828. A person of ordinary skill in the art would have understand that xenograft data would have been collected over a series of time points, which would have been plotted to develop a curve of tumor size. Baselga Abstract 53 simply reports a data point, at 35 days, where the curve for the paclitaxel/trastuzumab combination showed greater tumor inhibition than the other curves. Ex. 1019. That does not mean, or even suggest, that that was the only time point at which data was collected or analyzed.

10. Dr. Kerbel also argues that xenograft studies could not predict all of the toxicity issues associated with treatment. Ex. 2143 at ¶¶ 16-18. Once again, Dr. Kerbel misunderstand that purpose of xenograft studies. These studies are designed to show acute toxicity and immediate reactions, and not to show every potential long-term complication. See Ex. 1053 at 111, 121. For example, a five - week xenograft study would not be expected to reveal potential long-term cardiotoxicity in humans; the animals are only observed for a small part of their overall lifespan, and in any case their cardiac status is not specifically investigated in such studies. Yet, that does not preclude a person of ordinary skill in the art from having a reasonable expectation that there would be no increase in overall severe adverse events based on the available clinical data for each individual agent.

11. Dr. Tannenbaum, another of Patent Owner's experts, criticized Baselaga 1996 for its "small" sample size. Baselga 1996 was a Phase II clinical trial, and as such, would have been designed to be appropriately powered for its desired endpoint. This means that the study would have been designed to enroll enough patients to establish whether a new therapeutic agent shows statistically significant efficacy in the target patient population. In my experience, 46 participants is not unusual for a phase II study. The fact that there were only 46 participants does not affect the quality of the data collected, nor would it suggest that a person of ordinary skill in the art would not have relied upon it.

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