UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PHIGENIX, INC.
Petitioner

v.

IMMNUNOGEN, INC.
Patent Owner

Case IPR2014-00676
Patent 8,337,856 B2

IMMUNOGEN, INC.'S RESPONSE UNDER 37 C.F.R. § 42.120

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In instituting trial, the Board preliminarily determined that it would have been obvious "to substitute the mouse monoclonal TA.1 antibody in the immunoconjugate of Chari 1992 with the humanized mAb huMAB4D5-8 [Herceptin®] to produce the recited immunoconjugates…." Paper 11 at 12. But Phigenix's simple substitution argument cannot withstand scrutiny when it is viewed in light of the state of the art in March 2000– including art suggesting that such immunoconjugates would exhibit unacceptable levels of antigen-dependent toxicity in normal human liver tissue. Phigenix's arguments regarding claims 6 and 8, which are limited to Herceptin-maytansinoid immunoconjugates linked with the non-cleavable linker SMCC, also cannot withstand scrutiny. Phigenix's expert admits that the maytansinoids in maytansinoid-based immunoconjugates must be *released* to have biological activity. But, Phigenix fails to establish why one would have nonetheless selected a *non-cleavable* linker—rather than a cleavable linker—to conjugate a maytansinoid to Herceptin. A skilled artisan would have expected a maytansinoid-based immunoconjugate containing a non-cleavable linker to be ineffective, and thus would have been dissuaded from making the immunoconjugates of claims 6 and 8.

The invention's commercial embodiment, the ground-breaking cancer drug Kadcyla® (also known asTDM-1), exhibits results that were completely unexpected compared to the closest prior art. After several decades of research in an

unpredictable field, Kadcyla succeeded where others have repeatedly failed. Kadcyla was the first, and is the only, FDA-approved antibody-drug conjugate for treating solid tumors. And Kadcyla's data presented to the American Society of Clinical Oncology (ASCO) "wowed the audience." For example, leading oncologist Hal Burnstein hailed Kadcyla as "incredible" and as providing "surprisingly positive" results in patients. By satisfying therapeutic needs that had long gone unmet, Kadcyla dramatically improves the lives of patients. Appropriately, given its safety and efficacy profile, Kadcyla enjoys tremendous commercial success. Consideration of all of the evidence reveals that Phigenix has failed to meet its burden to show obviousness by a preponderance of the evidence.

I. Claims 1-8 would not have been *prima facie* obvious

Immunoconjugates are comprised of an antibody conjugated to a toxic agent. EX1028 Abstract; EX2134 ¶14. While superficially a simple combination of elements—an antibody, a linker, and a cytotoxic agent—designing an efficacious immunoconjugate that exhibited an acceptable level of toxicity was fraught with obstacles and uncertainty in March 2000. EX2134 ¶15. In instituting trial, the Board cited Dr. Rosenblum's declaration, which alleged a person of skill in the art (POSA) would have been motivated to substitute the murine TA.1 antibody of the immunoconjugate of Chari 1992 with Herceptin. But Dr. Rosenblum posits motivations and expectations that the prior art has contradicted. Here, there would

not have been a reason to combine the claimed elements, and a person of ordinary skill would not have had a reasonable expectation of success. Obviousness can be found only by ignoring highly-pertinent evidence in the prior art and resorting to hindsight.

A. Herceptin, HER2 immunoconjugates, and maytansinoids each raised toxicity concerns

An obviousness inquiry must consider the scope and content of the prior art and the differences between the invention and the prior art. *Graham v. John Deere Co* 383 U.S. 1, 17 (1966). Here, one must consider the *scope and content of the art in March of 2000* when considering whether the art provided a reason to select Herceptin (from all the candidate anti-HER2 antibodies) and a maytansinoid (from all the candidate small molecule toxic agents and protein toxins) for conjugation with a reasonable expectation of success. Attempts to show obviousness may fail when there is a "broad selection of choices for further investigation available" or when "the challenges of [the] inventive process would have prevented one of ordinary skill in this art from traversing … multiple obstacles to easily produce the invention in light of the evidence available at the time of invention." *Rolls-Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364-65 (Fed. Cir. 2008). As explained below, a POSA would not had a reason to combine the claimed elements and would not have arrived at claims 1-8 with a reasonable expectation of success

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