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Regeneron & Bayer caught in Genentech's VEGF trap

In the UK leg of the litigation relating to the potential blockbuster drug Eylea (aflibercept, also known as VEGF Trap Eye), marketed by Regeneron Pharmaceuticals, Inc. and Bayer Healthcare, the High Court has handed down a judgement ruling that Eylea infringes a patent held by Genentech, Inc.

Background

Eylea is a treatment for wet AMD, a disease which typically affects older adults and results in blindness in the centre of the field of vision. Regeneron, which has exclusive rights in the U.S., has recently forecast 2012 U.S. Eylea net product sales of $250 million to $300 million. Bayer holds the exclusive marketing rights for the rest of the world, and is currently awaiting approval from the European Medicines Agency to place the product on the market in Europe.

In separate actions, Regeneron and Bayer applied for the revocation of European Patent (UK) No 1 238 986 and also sought a declaration of non-infringement of the patent in respect of Eylea.

Claim 1 of the patent is a "swiss type" medical use claim directed to the use of a VEGF antagonist in the preparation of a medicament for the treatment of a non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation, wherein the antagonist is: (a) an anti-VEGF antibody or antibody fragment; (b) an anti-VEGF receptor antibody or antibody fragment; or (c) an isolated hVEGF receptor. The patent is thus concerned with biological medicines for the treatment of diseases in which there is increased growth of new blood vessels ("excessive neovascularisation") but wherein the condition is not cancerous ("non-neoplastic").

Validity

Regeneron and Bayer asserted that the patent was invalid for lacking novelty and inventive step over a journal publication which described an anti-VEGF antibody and suggested its use in therapy. The judge opined that the general suggestion in the prior art that the anti-VEGF antibody should be useful in therapy in diseases involving the growth of new blood vessels did not provide the specific feature that the antibody would be effective in the treatment of a non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation. Thus he ruled that the claim was novel.

The arguments on inventive step turned on whether it was obvious to try to target VEGF in order to treat non-neoplastic diseases with excessive neovascularisation. The judge concluded that it was not, because there was no teaching that would cause the skilled person to select VEGF as a target over any of the other proteins that were being discussed at the relevant time as being mediators of neovascularisation. In particular, he noted that the indication that the prior art antibody would be useful in therapy must "be viewed against the background that the vast majority of research in this area on all relevant factors would have had therapy as an end objective", and that this indication "is not the same as a claim to utility in the treatment of disease". Interestingly, the judge considered that secondary evidence, in the form of the scientific community's reaction to the invention, could play a role in the assessment of obviousness in this case, noting, however, that such evidence should be kept in its place. Thus the fact that one of the inventors had received the Lasker-DeBakey Medical Award in 2010 for, amongst other things, "the discovery of VEGF as a major mediator of angiogenesis" was deemed to represent secondary evidence that the work described in the patent "established VEGF as the critical target, and opened the door to a range of therapies". On this basis the judge thought that it was "appropriate to describe that contribution as an inventive step".

The patent was also unsuccessfully attacked for insufficiency of disclosure on a number of grounds, one of which was that it would not be possible for the skilled person to identify which portions of the full length VEGF receptors were the therapeutically relevant portions (i.e. to identify the portions used in Eylea).

This particular attack was dismissed by the judge who affirmed that "the fact that one can continue to refine one's receptor beyond the point at which one has a viable construct does not, as it seems to me, matter. A patent is not insufficient because it may take much work to develop the most refined or elegant embodiment of the invention".

The patent as granted was thus deemed to be valid.

Infringement

The sole issue to be decided here was whether or not the product, which is a hybrid protein comprising portions of two of the naturally occurring receptors for VEGF found in humans and the Fc region of an antibody, fell within the term "an isolated VEGF receptor". The judge considered that the patent spoke in general terms about variants and truncated forms of the full length VEGF receptors and that this was sufficient for a finding of infringement. He dismissed the arguments of Regeneron and Bayer based on the fact that Eylea was only developed after a major research project, and restated that for infringement, "it is no part of that exercise to embark on a consideration of whether the specific construct alleged to infringe was contemplated by the patentee, or on an analysis of the route or amount of effort involved in arriving at the construct".

Comment

The judgement is clearly unwelcome for Regeneron and Bayer as they attempt to clear the way for the release of Eylea. Bayer is reported to have set out its intention to appeal, noting that the decision is limited only to the UK on a patent that expires in October 2012 and thus that the decision is not considered to represent a major obstacle to the marketing of Eylea in Europe.

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