Roche reaches end of Avastin appeal road

Lisa Urquhart

The second day of the appeal hearing into the FDA's decision to withdraw Avastin's approval in breast cancer may have contained persuasive and plausible arguments by Roche in support of its flagship drug, but in the end it made little difference.

The oncology drugs advisory committee (ODAC) overwhelmingly rejected any notion that Avastin has a clinically meaningful benefit in metastatic breast cancer and voted unanimously against Roche's proposal to keep Avastin on the market while the Swiss group conducts another confirmatory trial. The FDA's Commissioner, Dr Margaret Hamburg, is expected to make a final ruling within a couple of months so Roche's last hope appears to hang on its offer to restrict Avastin's use to only the most severe forms of breast cancer. But as with all aspects of the appeal process so far, the odds remain stacked against the company.

Punch and counter-punch

Roche's opportunity to present to the ODAC focused on countering the arguments made by the FDA that the benefit/risk ratio for Avastin in breast cancer has shifted toward risk, in light of efficacy and safety data from two confirmatory studies (Questions remain as emotions run high at opening of Avastin appeal - June 29, 2011).

Throughout Roche’s presentation and subsequent cross-examination by the FDA and ODAC, there was much debate about the robustness of the E2100 trial – which was the basis for Avastin’s accelerated approval in breast cancer in 2008 – the magnitude of the progression free survival (PFS) rates in terms of hazard ratios and median survival times, and the extent to which Avastin causes adverse events and death.

There was also lots of discussion around what constitutes a clinically meaningful PFS, whether the FDA moved the goalposts on what the agency was expecting the confirmatory trials to achieve, and indeed to what extent metastatic breast cancer is an unmet medical need.

However, in the absence of any overall survival (OS) benefit from any of the five key trials of Avastin in 3,500 breast cancer patients, and with the debate going around in circles, it increasingly became an academic and philosophical exercise.

“We have tried to slice this pie in lots of ways, but no matter which way we look at it, all we are left with are crumbs,” said ODAC panellist, Dr Mikkael Sekeres of the Cleveland Clinic Taussig Cancer Institute.

A third way

Perhaps Roche had seen the writing on the wall, as the most intriguing aspect of the company's presentation was the offer to restrict Avastin's label to severe forms of breast cancer.

Dr Joyce O'Shaughnessy, of Baylor Charles Sammons Cancer Center, Texas, and a consultant for Genentech, urged the FDA to keep Avastin available as an approved option even if that meant, “limiting the indication to patients with metastatic triple negative and aggressive ER+ breast cancer, while a confirmatory study can be conducted”.

Hal Barron, Genentech’s executive vice president of global product development and chief medical officer, then confirmed this search for a compromise. “We are willing to work with the FDA in the search for a modified or restrictive label [for Avastin in breast cancer].”

Whether discussions about restricting Avastin's label in such a way have already taken place between Roche and the FDA is unknown and it is hard to judge how much consideration the agency is likely to give this proposal. However, the FDA pointed to multiple subset analyses of the trials which showed no PFS or OS benefit in any subpopulations, including metastatic triple negative breast cancer, indicating the regulator is unlikely to accede to Roche's request.

No more bites at the cherry
Much has been made of Roche’s proposal to conduct a new confirmatory trial of Avastin in breast cancer and the hearing revealed new details on the suggested study.

The study has mainly been designed to try and replicate the PFS survival of 5.5 months seen in the E2100 trial, but it will also assess blood plasma levels of the potential biomarker VEGF-A, given the theory that Avastin is most effective in patients with high levels of VEGF-A.

However, the timing and feasibility of the trial are questionable. The trial will enrol a relatively modest 480 patients, will start in the first quarter of 2012, run for three and a half years to the futility analysis point, after which it will continue for another 12 months. As such, data from the trial is unlikely to be submitted to the FDA until 2016.

Meanwhile, there are concerns that if Avastin remains approved for breast cancer in the US, as it is in Europe, enrolment will prove difficult given the likely reticence of patients to be randomised and potentially not receive an approved drug. Roche appears to largely acknowledge this given that the trial will only have seven sites in the US and the majority of patients will be from outside the US and Europe. Roche estimates that the feasibility analysis of this study will complete in July.

Then there is the question of whether Roche should be attempting a trial to prove OS, not just PFS, a study which the company contends is not really feasible as it will have to enrol 1,500 to 2,200 patients and take many more years to complete. However, Dr Sekeres believes that such a trial would actually be “the right thing to do” given that overall survival remains the gold standard in proving efficacy and safety.

Resounding rejection

Listed below are the results of four votes taken by ODAC, in every case the panel voted unanimously with the FDA, which intends to withdraw the breast cancer approval from Avastin’s label. Indeed, the comments made by ODAC panellists in describing their reasoning behind their votes were forceful and sometimes damning.

Dr Natalie Compagni-Portis, a patient representative on the panel, was surprisingly hawkish on Avastin. “After E2100 there was reason to be hopeful. We all wanted Avastin to succeed, but the reality is that these studies did not bear out this hope. A 0.8 month improvement in progression free survival does not translate into a better quality of life.”

Addressing one of the themes throughout the hearing, that Roche included more anecdotal evidence in its appeal, Dr Sekeres commented that “the plural of anecdote is not data”.

As such, it would be a major surprise if Dr Hamburg does not rule to withdraw Avastin’s approval on the US market to treat metastatic breast cancer. The fall out from such a decision will be significant for patients and insurance companies alike. Meanwhile, Roche’s decision to fight the FDA on this issue always appeared curious and futile – the outcome of the hearing could be another blow to sentiment towards a drug which is generating negative headlines with worrying regularity these past 18 months.

ODAC votes:

- do the Avado and Ribbon-1 trials fail to verify the clinical benefit of Avastin for the breast cancer indication for which it was approved?
  - Yes: 6  No: 0
  - a) does the available evidence demonstrate that Avastin has not been shown to be effective for the breast cancer indication for which it was approved?
    - Yes: 6  No: 0
  - b) does the available evidence on Avastin demonstrate that the drug has not been shown to be safe for the breast cancer indication for which it was approved, in that Avastin has not been shown to present a clinical benefit that justifies the risks associated with use of the product for this indication?
    - Yes: 6  No: 0
  - If the Commissioner agrees with the grounds for withdrawal set out in issue 1, issue 2.a, or issue 2.b, should the FDA nevertheless continue the approval of the breast cancer indication while the sponsor designs and conducts additional studies intended to verify the drug’s clinical benefit?
    - Yes: 0  No: 6