Evaluate Vantage

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Therapeutic focus – Survival benefit still eludes ovarian cancer trials

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Amgen's announcement last week that trebananib had failed to extend the survival of ovarian cancer patients in a large pivotal study did not, unfortunately, come as a huge surprise. The 1.8-month extension in progression-free survival revealed last year was statistically significant but not particularly impressive clinically, lowering hopes for the overall survival readout – a secondary endpoint but ultimately the yardstick by which ovarian cancer drugs are judged, in the US at least.

The FDA's insistence on the importance of overall survival in this cancer remains controversial, and means that a handful of drugs refused US endorsement are available elsewhere in the world. Avastin is a high-profile example, although the FDA is due to deliver its verdict on the antibody by November 19 in the second setting in which Roche has sought approval. Considering the drug has never managed to show a survival benefit, the decision will be watched with great interest by others with late-stage ovarian projects (see table below).

Roche is seeking US approval for Avastin in patients with recurrent platinum-resistant ovarian cancer. Few options are available to women whose disease has become resistant to the platinum-based chemotherapies that are the cornerstone of treatment for this tumour type, and the drug has priority review in this use.

The Aurelia study was conducted in this setting and found that Avastin plus chemotherapy reduced risk of disease recurrence by 52%, with a median PFS of 6.7 versus 3.4 months for chemo alone. Overall survival was not significantly lengthened. European regulators backed approval in this use earlier this year.

In Europe Avastin has been available since 2011 as a front-line and maintenance therapy for advanced ovarian cancer, based on two studies that showed a significant PFS benefit (*ASCO – Avastin approval chances inch higher in ovarian cancer, June 6, 2011*). However neither trial demonstrated a survival benefit and the FDA indicated that approval was unlikely, so US endorsement was never formally sought by Roche.

This has not stopped Avastin being widely used off-label in the US in these settings; it is even recommended by numerous guideline-setting organisations including the National Comprehensive Cancer Network.

Proving a benefit

The FDA has voiced a number of concerns with PFS in ovarian cancer in the past. These include the difficulties in measuring a tumour's progression in what is an intra-abdominal disease process, both consistently and without bias, and the extent to which the measure translates into an overall survival benefit.

Critics counter that PFS can be measured consistently in ovarian cancer, but that multiple lines of therapy that patients with recurrent disease receive make it difficult to tease out a clear overall survival benefit.

Of course, the FDA takes much more into consideration than these two measures – Avastin, for example, was also shown to contribute to a big deterioration in quality of life in its two front-line pivotal studies (*Avastin in ovarian gets EU backing but US will be harder won, September 26, 2011*).

The FDA has not delivered a verdict on any novel targeted agent in this cancer type since Roche approached it in 2011, so it is not clear if its stance has changed in the interim. This seems unlikely, and any drug that fails to show a survival benefit will have to present a very convincing case on other measures to even hope for a green light.

Hence the pessimism on Amgen's trebananib. As well as the modest PFS benefit and lack of survival benefit, a 20% discontinuation rate was seen against 7% in the placebo arm. Two further studies are due to report, one conducted in combination with a different chemotherapy and another larger study called Trinova-3 in a front-line setting. Data are not due until next year and 2016, but few hopes for success remain.

Moving on

The approaching FDA verdict on Avastin in the Aurelia setting will therefore provide the next insight into the US regulator's thoughts on approvability in this disease. Given the niche use being proposed and limited

options available, a negative decision will take some justification.

Following this, the agency's verdict on AstraZeneca's Parp inhibitor Lynparza, due by January 2, will perhaps be even more interesting for the space. The UK company is seeking accelerated approval based on a subgroup analysis from a failed phase II study; a predefined subgroup identified using a retrospective biomarker found a significant 7.1-month PFS benefit in patients with the BRCA mutation.

Despite growing acceptance for this mechanism of action – two other Parp inhibitors are now in pivotal testing – an FDA advisory committee was not impressed and voted 11-2 against approval (*Olaparib slapdown undermines Astra's hype, June 26, 2014*).

This does not bode well for a green light, and in any case the FDA will also be mindful of the impact approval could have on the two pivotal studies that AstraZeneca has already started in this setting. If a definitive picture of efficacy is what the regulator is really concerned about, risking the progress of trials seeking to provide this seems contradictory.

Ones to watch: commercial phase III studies in ovarian cancer

Project	Company	Status (enrolment)	Trial ID	Primary completion
Trebananib	Amgen	Active, not recruiting (919)	NCT01204749 (Trinova-1)	June 2013
		Active, not recruiting (223)	NCT01281254 (Trinova-2)	October 2014
		Active, not recruiting (1,015)	NCT01493505 (Trinova-3)	May 2016
Lynparza	AstraZeneca	Recruiting (440)	NCT01874353 (Solo-2)	July 2015
		Recruiting (2,500)	NCT01844986 (Solo-1)	July 2016
Perjeta	Roche	Recruiting (184)	NCT01684878	April 2016
Niraparib	Tesaro	Recruiting (360)	NCT01847274 (Nova)	March 2016
Binimetinib	Novartis/Array	Recruiting (300)	NCT01849874 (Milo)	June 2016
Rucaparib	Clovis Oncology	Recruiting (540)	NCT01968213 (Ariel3)	January 2016
Yondelis	J&J/Pharmamar	Recruiting (670)	NCT01846611	October 2018
Yondelis	J&J/Pharmamar	Recruiting (588)	NCT01379989 (Inovatyon)	December 2019
Opaxio	CTI (NCI-sponsored)	Active, not recruiting (1,100)	NCT00108745	January 2022

The two other Parp inhibitors in phase III are niraparib and rucaparib, owned by Tesaro and Clovis Oncology respectively.

Tesaro, which has not restricted enrolment to patients with the BRCA mutation, expects to complete enrolment by the end of the year. Clovis is running a larger programme with rucaparib – a 180-patient phase II is also recruiting – and it is also looking beyond the BRCA mutation cohort, although it is initially focusing on these patients and those with other DNA repair deficiencies.

Outside of the Parp class, few significant phase III trials are under way by commercial companies.

Binimetinib, a MEK inhibitor that is being developed under a licensing deal between Novartis and Array, is being tested in patients with low-grade serious carcinomas. And CTI Biopharma revealed in January that recruitment had been completed in a large maintenance trial of Opaxio, a "biologically enhanced" form of paclitaxel. The trial, which is being run by the NCI, passed the first of four interim analyses in January 2013.

The NCI is also running several large phase III ovarian cancer studies testing various chemotherapies in different settings, several of them including Avastin. Roche itself is not funding any ongoing pivotal studies with Avastin in ovarian, although it is testing Pejeta, its next-generation Her2 antibody, in a small, 184-patient, European phase III.

Finally, Johnson & Johnson is still pushing to get Yondelis on the market in the US, having first sought approval back in 2008.

The chemotherapy received approval in 2009 in Europe for the treatment of relapsed platinum-sensitive ovarian cancer. The story in the US is familiar: a pivotal trial showed a significant improvement in PFS but ultimately failed to establish a survival benefit, and J&J eventually pulled its submission in 2011 after the FDA said it wanted to see another phase III study.

As a cytotoxic agent Yondelis is not without its side effects, though J&J maintains that it represents an important non-platinum based option. Two pivotal studies are recruiting, testing the drug in combination with Doxil; J&J is running a 670-patient study in patients who have already received two lines of platinum-based chemotherapy.

The other is a Europe-based study that is largely funded by a research group; it is perhaps no coincidence that only non-commercially sponsored studies in this analysis use overall survival as a primary endpoint.

Whatever the arguments are in favour of PFS as a reliable endpoint, it also comes down to time – and this readout is much quicker to generate. Companies desperate to generate a return on their investment will be keen to see any shift in the FDA's focus away from overall survival. The impending decisions on Avastin and Lynparza will be scrutinised with interest.

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