Evaluate Vantage

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Events overtake Bavencio in ovarian cancer

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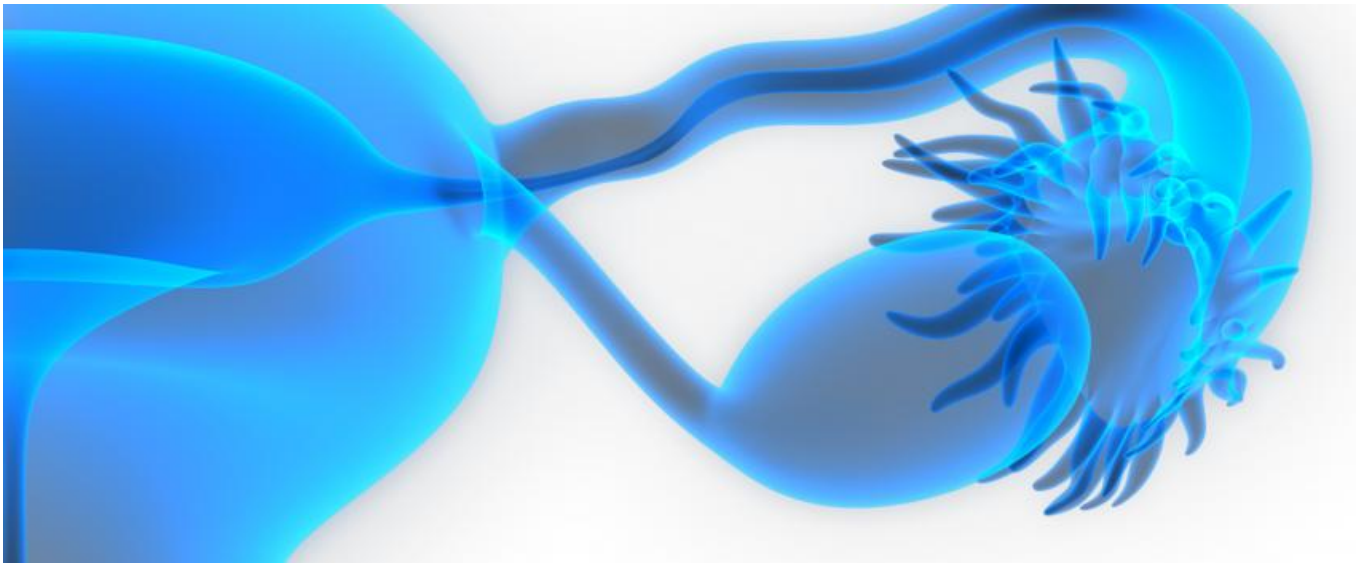

Pfizer/Merck KGaA scrap a pivotal trial, partly because it tested Bavencio against what is no longer the relevant standard of care.

It looks like Pfizer and Merck KGaA have become the latest companies to demonstrate the peril of studying a drug in a disease whose treatment is changing fast. After revolutions in prostate and lung cancers that meant newcomers effectively had to beat a new standard of care, a similar thing is happening in ovarian cancer.

This is the key reason behind the discontinuation of Pfizer/Merck's Javelin Ovarian Parp 100 trial of Bavencio followed by the Parp inhibitor Talzenna. True, doubt has been cast on Bavencio's relevance, but above all it is the approval of Astrazeneca's Parp inhibitor Lynparza in first-line maintenance that scuppered the study's design.

Javelin Ovarian Parp 100 was a first-line study in which subjects in the comparator arm got Avastin maintenance while still responding to chemo plus Avastin. That was the standard of care when the study started last year, but in December Lynparza got the nod for maintenance use in first-line patients with the BRCA mutation.

Not only did this suddenly mean that Bavencio and Talzenna were being compared against an out-of-date therapy, it could be argued that it was becoming unethical to deny control arm subjects Lynparza and put them on Avastin instead.

To their credit, Pfizer/Merck explained they were the first to test an immunotherapy in first-line ovarian cancer, and their study clearly followed the rules in place at the time. An earlier change of standard of care scuppered Bavencio's second-line NSCLC Javelin Lung 200 trial – along with those of several competitors.

Not good enough?

Sceptics will, of course, want another question answered, namely whether Bavencio, as a relative latecomer to the PD-(L)1 game, is simply not good enough to compete.

Today's announcement from Pfizer and Merck noted that the decision to can Javelin Ovarian Parp 100 was also due to analysis of a separate study, Javelin Ovarian 100, which compared Bavencio maintenance, after first-line chemo with or without Bavencio, against chemo alone. Javelin Ovarian 100 failed an interim analysis and was scrapped in December.

Investors will also cast an eye at the design of competing studies that, like Javelin Ovarian Parp 100, test a PD-(L)1 MAb combined with a Parp inhibitor in first-line ovarian cancer. The same problem that tripped up

Talzenna/Bavencio could hit Clovis's Rubraca/Opdivo and Glaxosmithkline's Zejula/dostarlimab, neither of whose studies has a Lynparza comparator.

Parp/PD-(L)1 combinations in front-line ovarian cancer				
Parp inhibitor	**Combination PD-(L)1 asset**	**Setting**	**Comparator arm**	**Trial**
Zejula (niraparib)	TSR-042 (dostarlimab)	1st-line treatment	Pt +/- Avastin	First (NCT03602859)
Rubraca (rucaparib)	Opdivo	1st-line maintenance	Placebo	Athena (NCT03522246)
Talzenna (talazoparib)	Bavencio	1st-line treatment & maintenance	Pt + Avastin	Javelin Ovarian Parp 100 (NCT03642132)
Pt=platinum chemo. Note: Zejula and Rubraca are approved for second-line ovarian cancer maintenance; Talzenna is not approved in ovarian cancer.				

Fortunately for Glaxo, a separate opportunity has presented itself for dostarlimab, the PD-1 inhibitor previously known as TSR-042 and, like Zejula, acquired through the takeover of Tesaro.

This is in the related setting of endometrial cancer, in which Glaxo yesterday presented results of the Garnet study at the Society of Gynecologic Oncology meeting. Among the 125 relapsed subjects who were evaluable, dostarlimab resulted in 37 remissions, six of these complete.

A particularly interesting fact was that patients' microsatellite instability (MSI) status was tested, revealing that the benefit was driven by the 41 who were MSI-high, where the remission rate was an impressive 49%. Opdivo and Keytruda are both approved in MSI-high tumours irrespective of cancer type.

Glaxo said it would use the data to file dostarlimab in endometrial cancer by the end of the year. This would at best make dostarlimab the seventh anti-PD-(L)1 drug to be approved, so it is just as well that none of the others has endometrial cancer on its label.

A niche use is the easiest way to get one of these drugs to the market, as Sanofi/Regeneron found with Libtayo. Taking on a game-changing drug on its own turf has become virtually impossible in terms of study design – a lesson the Parp players are now learning in ovarian cancer.