Evaluate Vantage

August 07, 2019

Clovis investors feel more Lynparza pressure

Jacob Plieth

As Lynparza threatens Rubraca in prostate cancer, investors should now focus on whether Astra will show a benefit in the ATM-mutant patient population.

After its disappointing second quarter Clovis really could have done without Astrazeneca/Merck & Co's Profound trial of Lynparza reading out positively. But this is exactly what happened today, threatening Clovis's Parp rival Rubraca in prostate cancer, a setting the US biotech had hoped to have to itself at least for a while.

The knockout blow will come if Lynparza is shown to work in ATM-mutants, a subpopulation in which Rubraca has disappointed, and a dataset that Astra is for now keeping under wraps. The threat is considerable, given that analysts expect prostate cancer to overtake Rubraca's sales in its currently approved use of ovarian cancer.

This is a live issue: Rubraca's second-quarter numbers underwhelmed – the drug was approved in ovarian cancer over a year ago – leading to downgrades and a 16% share price fall as the odds of Clovis being bought out lengthened. *EvaluatePharma* consensus sees 2024 sales in ovarian cancer reaching $329m, versus $393m in the prostate setting.

Today, earlier than had been expected, Astra revealed that Lynparza had met the primary endpoint of its Profound study in prostate cancer subjects who had failed either Zytiga or Xtandi. No numbers were disclosed, but Lynparza's efficacy, on radiographic progression-free survival, was statistically significant and clinically meaningful, Astra stated.

The precise population is important. Profound's primary rPFS endpoint concerned only subjects with Brca1/2 or ATM mutations, and Astra is not revealing each subgroup's individual contribution to the overall result. Parp inhibitors are known to work in Brca mutants, but the ATM population could be just as big again, though there is some overlap.

Parp inhibitors in metastatic, castration-resistant prostate cancer			
Study	**Drug**	**Note**	**Trial ID**
Triton 2	Rubraca	3rd-line, single-cohort; 44% ORR in Brca mutant patients	NCT02952534
Triton 3	Rubraca	2nd-line, post-next-gen hormonal anticancer; Zytiga/Xtandi/docetaxel combo; data 2022	NCT02975934
Profound	Lynparza	2nd-line, post-next-gen hormonal anticancer; Zytiga/Xtandi combo; rPFS +ve in Brca or ATM mutant patients	NCT02987543
Propel	Lynparza	1st-line, Zytiga combo; primary completion Apr 2021	NCT03732820
rPFS=radiographic progression-free survival.			

Last year Clovis presented the results of Triton 2, an uncontrolled mid-stage trial in a later setting than Profound, in which Rubraca yielded a 44% remission rate in Brca mutants (*Esmo 2018 – Encouraging early prostate data fail to lift Clovis, October 19, 2018*).

But all Clovis was able to say about the ATM population was that Rubraca was associated with reductions in target lesion diameters and PSA measurements. This was taken as a disappointing lack of activity, though the relevance of ATM in prostate cancer is not really understood.

Clovis is due to provide an update on Triton 2 at next month's Esmo meeting, and Stifel analysts expect the study to lead to an accelerated US filing in the fourth quarter. A direct rPFS comparison between Lynparza and Rubraca will only be possible once the Triton 3 study reads out in 2022.

Triton 3 tests a very similar population to Profound, and also measures rPFS as primary endpoint, but it additionally allows docetaxel as active comparator.

Until more is revealed about Profound, Lynparza's relevance in ATM-mutant patients cannot be gauged. With the possibility of this happening at an Esmo late-breaker Clovis now faces the prospect of having its Esmo thunder stolen. Its investors have to hope that the Astra/Merck drug's activity in prostate cancer is largely driven by Brca mutants.