Evaluate Vantage

June 03, 2017

Asco – Zytiga moves back to centre stage in prostate cancer

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Prostate cancer looks set to see another seismic shift in its treatment landscape, once again courtesy of the UK consortium-run Stampede study. Two years after this multi-agent, multi-arm trial brought the ageing chemotherapy docetaxel back from use in late-stage castration-resistant patients to earlier-stage hormone-sensitive ones, it has done the same for Johnson & Johnson's Zytiga.

Data from Stampede reported at Asco showed a 37% relative improvement in survival and a 71% improvement in failure-free survival from the addition of Zytiga to androgen deprivation therapy (ADT) in hormone-sensitive prostate cancer (HSPC), in both cases to very high levels of statistical confidence. This could see Zytiga make up ground on Pfizer's Xtandi, and could threaten the design of many competing prostate cancer trials (see table below).

Zytiga's p value for failure-free survival, measured by worsening scans or symptoms or elevated PSA level, was a remarkable 10 to the minus 63, a figure that must please even the most sceptical statistician. And this benefit was confirmed in the Latitude phase III study, which showed a 38% improvement in survival and 53% improvement in radiographic PFS, equivalent to an 18.2-month median gain.

Practice-changing

Stampede's principal investigator, Dr Nicholas James, said the results were clearly practice-changing, though they posed several new questions. The first one is whether Zytiga should be used in preference to docetaxel, whose use in HSPC was itself established based the earlier Stampede result.

Zytiga has shown a larger magnitude of benefit than docetaxel, which conferred a 25% improvement in survival, but this is still an across-trial comparison given the different Stampede data cuts. However, this question will be answered more satisfactorily when Stampede renders a direct head-to-head comparison, which Dr James believes should be available in time for Esmo in September.

Another question is whether the two agents should be used in combination in newly diagnosed prostate cancer. Dr James postulates that this strategy would likely produce an additive benefit, given the differing mechanisms, although this has yet to be proved.

Advantage J&J

J&J is the obvious commercial beneficiary, since a move to earlier use of Zytiga would give it major advantage over its key rival, Pfizer/Astellas's Xtandi.

The duration of this advantage is debatable, as composition-of-matter patents on Zytiga start to expire in November, and thus it is possible that generics will become available soon. *EvaluatePharma* sellside data suggest Zytiga sales tapering down and declining sharply from 2019, presumably on the introduction of generics, although this in part would assume some degree of substitution by J&J's follow-up agent, apalutamide.

However, J&J has been running its own phase III study designed to support a registration application for Zytiga in HSPC, which suggests that it has an internal expectation of retaining commercial exclusivity for a longer period. This study renders results in 2018, although the Stampede data might allow it to obtain a compendia listing for HSPC before this.

Xtandi is also being studied in HSPC, but the data are not due until 2020, and by then the control arm (ADT alone) is likely to be have been supplanted. Indeed, this is a problem that is likely to face most if not all of the ongoing studies in this space.

Phase III studies in newly diagnosed hormone-sensitive prostate cancer						
Product	**Company**	**Study**	**Enrolment**	**Design**	**Trial ID**	**Data**
Prostatak	Advantagene	-	711	vs placebo	NCT01436968	Sep 2017
Jevtana + ADT	Sanofi	Peace II*	1,048	vs placebo	NCT01952223	Sep 2019
Xtandi	Astellas/Pfizer	Enzarad*	800	vs ADT	NCT02446444	Sep 2021
Apalutamide	J&J	Atlas	1,500	vs bicalutamide	NCT02531516	Dec 2022
Xtandi	Astellas/Pfizer	Embark	1,860	ADT +/-	NCT02319837	Dec 2020
Zytiga	J&J	-	1,209	ADT +/-	NCT01715285	Jul 2018
Zytiga	J&J	Peace I*	916	ADT +/- RT +/-	NCT01957436	May 2017
Darolutamide	Bayer/Orion	Arasens	1,300	ADT + docetaxel +/-	NCT02799602	Jan 2022
Xtandi	Astellas/Pfizer	Arches	1,100	ADT+/-	NCT02677896	Apr 2020
Apalutamide	J&J	Titan	1,000	ADT +/-	NCT02489318	Nov 2020
*RT = radiotherapy. *Investigator or co-operative group-sponsored study.*						

Once again, it seems that Stampede has rendered a result that will change the treatment of prostate cancer. Given the similarity of Zytiga to Xtandi and the second-generation agents apalutamide and darolutamide, it seems possible that all the agents confer a benefit in HSPC. The question might become which will be shown to be the most effective in this setting.