Evaluate Vantage

March 14, 2016

Therapy focus – Ovarian cancer field readies for phase III readouts

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Ovarian cancer specialists are in for a lively few months, with a run of pivotal trial readouts, two or more filings and the outcome of an EU submission for a long-forgotten project – events that could collectively move the field forward.

Any such development will be welcome as ovarian cancer remains a difficult-to-treat disease that has seen little progress in recent years (see table below). Moreover, it has so far not been much of a target for immuno-oncology, which has taken great strides in other indications.

Some progress was made with the late 2014 conditional approval of a targeted agent, AstraZeneca's Lynparza, but the mainstay of treatment remains surgery followed by platinum and taxane chemotherapy. Nevertheless, a review of the field reveals a full phase III pipeline, with 11 different agents being examined in a total of 15 studies, and a further six agents in or entering registration-directed phase II or II/III trials.

Moving towards approval

Four of the phase III agents are PARP inhibitors, namely Lynparza, Tesaro's niraparib, Clovis's rucaparib and AbbVie's veliparib. The first three are being studied as maintenance therapies in BRCA-mutant patients, an approach thought to take best advantage of PARP inhibition's role in DNA repair. AbbVie, though, is conducting a larger study of veliparib in combination with first-line chemo, enrolling both wild-type and BRCA-mutant patients.

AstraZeneca's Solo-2 trial should read out this quarter, but some analysts believe that data are more likely later in the year. If this is the case, Tesaro's Nova trial will probably be the first of the PARP studies to report. This evaluates three different subpopulations based on patients' mutation status, and effectively has three opportunities to achieve a positive result (*Therapy Focus – PARP inhibitor class set to come of age in 2016, March 1, 2016*).

Tesaro also expects data from its Quadra phase II trial in fourth-line ovarian cancer around the same time as Nova reports, and believes the combined data sets would support an NDA submission planned for the second half.

Lynparza somewhat controversially gained early US approval – despite a negative advisory committee vote – for third/fourth-line use based on a subgroup analysis of gBRCA mutant patients. This highlighted the fact that regulators, perhaps mindful of the relative lack of new agents in ovarian cancer, were keen to give physicians new therapies.

Back from the dead

One surprise is that AstraZeneca's almost forgotten anti-VEGF tyrosine kinase inhibitor cediranib – which was pretty much consigned to history with a phase III failure in colorectal cancer in 2012 – is in fact under EMA review for ovarian cancer. The project was quietly filed in July 2015 based on phase II data and thus must now be approaching a decision.

AstraZeneca is seeking approval as a monotherapy in Europe, although cediranib is being developed in combination with Lynparza in the third-line setting in an NCI-sponsored phase II/III study, Cocos.

In the shorter term, AstraZeneca could face competition to Lynparza in 2017 from Clovis, which is expected to start a rolling NDA for its PARP inhibitor rucaparib in the second quarter. This will be for platinum-sensitive, relapsed, BRCA-mutant disease, based on the phase II Ariel-2 study in the fourth-line setting.

Clovis is also conducting Ariel-3 in third-line treatment, which is expected to complete enrolment in the next few months and render results around a year later.

Project	Company	Setting/subtype	Trial ID	Data
Phase III				
Lynparza	AstraZeneca	>2L maintenance, gBRCA mutant	NCT01874353	Feb 2016
Niraparib	Tesaro	3L maintenance, pt-sensitive, gBRCA mutant	NCT01847274	Q2 2016
Perjeta	Roche	<3L recurrent pt-resistant, low HER3 mRNA expression	NCT01684878	Apr 2016
Lynparza	AstraZeneca	1L maintenance, gBRCA mutant	NCT01844986	Jul 2016
Rucaparib	Clovis	>3L maintenance, pt-sensitive	NCT01968213	Q2 2017
binimetinib	Array	2-4L, low grade serous	NCT01849874	H2 2017
Lynparza	AstraZeneca	3L relapsed gBRCA mut	NCT02282020	Dec 2017
Vigil Ovarian	Gradalis	1L maintennance	NCT02346747	Dec 2017
Niraparib	Tesaro	1L maintenance, pt-sensitive, HRD-positive	NCT02655016	Mar 2018
Avelumab	Pfizer	<3L, pt-resistant /refractory	NCT02580058	Mar 2018
Yondelis	J&J/Pharmamar	3L, BRCA mutant	NCT01846611	Sep 2018
Lurbinectedin	Pharmamar	<4L, pt resistant	NCT02421588	Oct 2018
Veliparib	Abbvie	1L maintenance	NCT02470585	Jan 2019
Lynparza	AstraZeneca	>3L maintennance pt-sensitive, relapsed, sBRCA or HRR mutant	NCT02392676	Jun 2019
Yondelis	Pharmamar/J&J	<3L, partial pt sensitive	NCT01379989	Dec 2019
Phase II/III				
Cediranib/Lynparza	AstraZeneca	<3L, recurrent pt-resistant or refractory	NCT02502266	N/A
Fosbretabulin	Oxigene	Pt-resistant	NCT02641639	N/A
Phase II				
Farletuzumab	Eisai	Low CA125, pt sensitive	NCT02289950	Nov 2017
AZD1775	AstraZeneca	Pt-resistant TP53-mutated	NCT02272790	Jul 2017
Mirvetuximab soravtansine	Immunogen	Folate receptor alpha positive	NCT02631876	Mar 2018
Vargatef	Boehringer Ingelheim	>3L	NCT01610869	Oct 2017

Regulators have been prepared to accept PFS as a primary endpoint in ovarian cancer, and indeed most of the

pivotal phase III studies use this. An exception is Pfizer/Merck KGaA's Javelin Ovarian 200 study of the PD-L1 inhibitor avelumab. This is one of only two immuno-oncology approaches in the disease, the other being Gradalis's personalised cancer vaccine Vigil.

Ovarian is the fifth-most common cancer affecting women and has a 46% five-year survival rate. Other than achieving earlier diagnosis, there has been relatively little improvement in chemo in recent years, so it will be welcome indeed if some positive data emerge in 2016.

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