Evaluate Vantage

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Lynparza's surprise stumble could finally bury cediranib

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Another trial seems to suggest that adding VEGF blockade to Parp inhibition does little for patients without tumour mutations.

In trial after trial Parp inhibitors have proven themselves highly effective cancer drugs, with Astrazeneca and Merck & Co's Lynparza leading the pack. As such, this drug's failure in a late-stage ovarian cancer study comes as a surprise, as the Parps are well established in this setting.

The academic-led GY004 trial,tested Lynparza plus cediranib, a VEGFr inhibitor. Researchers have for some time been trying to show that combining these mechanisms can open up Parp inhibition to patients without homologous recombinant deficiency (HRD). This theory could well have just taken another knock.

HRD, or defective DNA repair, can be driven by mutations such BRCA; any form of HRD seems to increase a patient's susceptibility to Parp inhibition. It is the patients deemed HRD-negative that researchers are trying to reach – for example by combining mechanisms.

Adding VEGF blockade was tested in the front-line maintenance study, Paola-1, which Astra and Merck presented at Esmo last year. The investigator-sponsored study tested the anti-VEGF antibody Avastin plus Lynparza, and recruited patients regardless of mutation status. Progression-free survival was significantly extended although the result was clearly driven by patients with HRD – in the subgroup of those without evidence of HRD the hazard ratio dropped to an unimpressive 0.92 (*Esmo 2019 – Lynparza pushes Parps forward again, September 28, 2019*).

What happened?

With nothing other than the top-line read out known for GY004, conclusions are hard to draw; however, a high proportion of patients with no HRD could be one explanation for the lack of activity. The study recruited all-comers, regardless of a patient's mutation status.

This NCI-sponsored trial tested Lynparza plus cediranib in patients with relapsed platinum-sensitive disease; subjects could have received more than one prior line of therapy. For the primary endpoint the combination was pitted against platinum chemotherapy, however the trial also contained a Lynparza-only arm.

All that has been disclosed is that the trial did not meet the primary endpoint in the intent-to-treat (ITT) population. The size of the miss remains crucial information, as does the performance of the Lynparza arm, and of course whether there was any imbalance in the arms.

Given Parp inhibitors' proven effectiveness in HRD-positive ovarian cancer, a good reason for Lynparza's apparent impotence needs to be found here. However the conclusion that cediranib is adding nothing seems inescapable – at the very worst it could actually be doing harm.

The kinase inhibitor has been kicking around in Astra's pipeline for years. It was filed for ovarian cancer, then withdrawn, back in 2016, and more notoriously had already crashed out in pivotal colorectal cancer studies. A small academic trial combining it with Lynparza in ovarian cancer raised hopes again, and Astra itself is running the Concerto study, which should read out later this year.

The GY004 result does not prompt optimism for Concerto, though of course the caveats of cross-trial comparison should never been forgotten. Still, a look at ongoing studies of cediranib reveals little beyond academic work, and it looks like this asset is finally approaching the end of the road.

Astra and Merck, meanwhile, will hear in the second quarter on FDA approval for Lynparza plus Avastin as a maintenance treatment for advanced ovarian cancer, regardless of biomarker status. A green light is highly likely, though questions look set to linger around whether all patients will really benefit from this combination of mechanisms.

Trials of cediranib and Lynparza

Name	ID	Sponsor(s)	Setting	PCD
Phase III				
Icon9	NCT03278717	University College, London	Relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer	Dec 2023
GY004	NCT02446600	NCI/Astrazeneca/NRG Oncology	Recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer	Failed Mar 2020
GY005	NCT02502266	National Cancer Institute/ NRG Oncology	Recurrent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer	Jun 2023
Phase II				
Concerto	NCT02889900	AstraZeneca/Myriad/ Merck & Co	Recurrent platinum-resistant ovarian cancer	Aug 2019
-	NCT02498613	NCI/Astrazeneca	Metastatic or unresectable solid tumours	Dec 2020
Octova	NCT03117933	University of Oxford/Astrazeneca	Platinum-resistant ovarian cancer	Mar 2021
Hudson	NCT03334617	Astrazeneca	NSCLC patients, post anti-PD-(L)1 therapy	Sep 2022
Copelia	NCT03570437	University of Manchester/Cardiff University/Astrazeneca	Advanced endometrial cancer, post-chemo	Jan 2021
Ambition	NCT03699449	Yonsei University/Seoul National University Hospital/Korean Gynaecologic Oncology Group/Samsung Genomic Institute/Samsung Medical Cente/Astrazeneca	Platinum-resistant recurrent endometrioid ovarian, primary peritoneal, or fallopian tube cancers	Sep 2022
Dapper	NCT03851614	University Health Network, Toronto/ Astrazeneca	Locally-advanced or metastatic mismatch repair proficient colorectal cancer, pancreatic adenocarcinoma or leiomyosarcoma	Mar 2022

PCD = primary completion date. Source: EvaluatePharma, clinicaltrials.gov.

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