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ASCO 2023 – A Role For Immuno-Oncology In Ovarian Cancer At Last?

by

AstraZeneca's Duo-O trial suggests that excluding Brca-positive patients could be the key to Imfinzi's apparent success in ovarian cancer.

AstraZeneca PLC appears to have teased out a positive result for Imfinzi in ovarian cancer – a setting that so far has proved intractable for anti-PD-(L)1 drugs. The data, toplined positive in April, concern the Duo-O study of an Avastin/Imfinzi/Lynparza triplet, and have been presented 3 June as an American Society of Clinical Oncology (ASCO) late-breaker.

The result is notable for having apparently succeeded where other PD-(L)1/Parp inhibitor combinations have failed, and one reason for this might be Astra's exclusion of Brca-positive patients, who would normally be expected to do well on Avastin/Lynparza alone. Still, questions will remain about Imfinzi's contribution, the breadth of the effect, and the robustness of a progression-free survival endpoint.

Debate continues about the validity of PFS in ovarian cancer, and there have been cases where a clinical benefit on PFS has been followed by a clearly negative result in terms of overall survival. This has, for instance, seen use of *GSK's Parp inhibitor, Zejula, narrowed in ovarian cancer maintenance*.

Complexities

Duo-O had a complex three-arm design, and included two settings. Active cohorts comprised chemo/Avastin/Imfinzi first line followed by Avastin/Imfinzi with or without Lynparza in the maintenance setting; this was compared against a control cohort of chemo/Avastin followed by Avastin maintenance.

A further crucial twist is that the trial enrolled Brca-negative patients only, and its PFS endpoint was split between two co-primaries: an effect in all-comers, and in Brca-negatives who were nevertheless positive for *some other type of HRD mutation*.

The good news is that the Avastin/Imfinzi/Lynparza maintenance triplet met both co-primaries, with p<0.0001. The bad that Avastin/Imfinzi had no advantage over control at all.

The survival curves reveal another nuance. It might have been assumed that HRD-positive patients are driving the all-comers benefit, but in fact in HRD-negatives, some 60% of the Duo-O Brca-negative population, the triplet also beat control.

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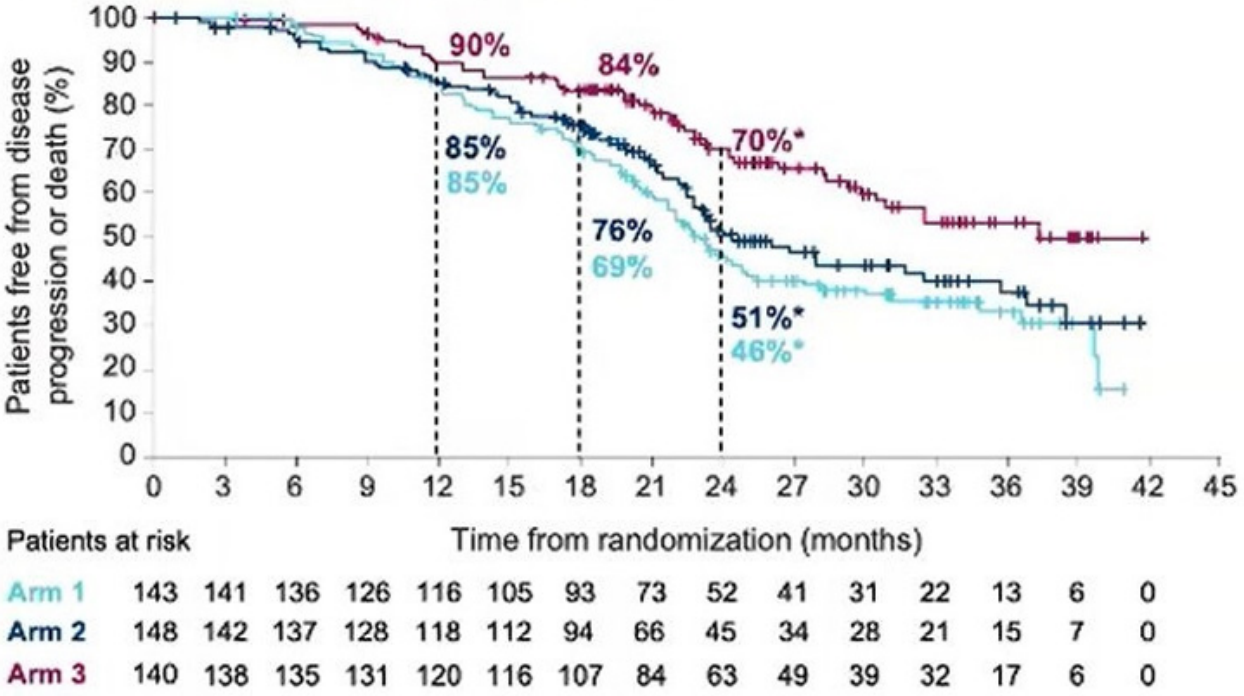
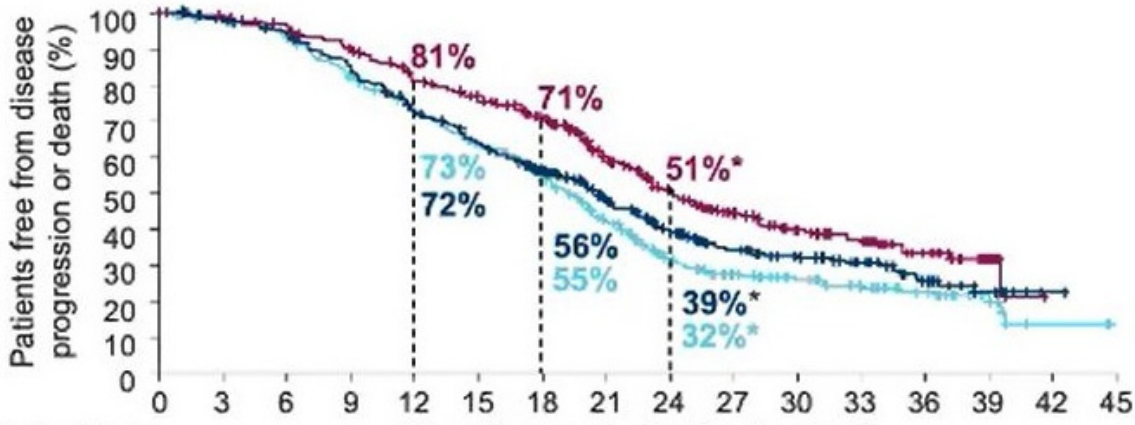
Non-tBRCAm HRD-positive



	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

Non-tBRCAm ITT



PD-(L)1 + Parp inhibition in ovarian cancer					
Roche					
*WO39409**	⩾2L	Tecentriq + Rubraca	Uncontrolled	Ended 2020 after Covid-related protocol amendment, no data reported	None in ovarian cancer cohort
Merck KGaA/Pfizer					
Javelin Ovarian Parp 100	1L & maintenance	Chemo + Bavencio, then Bavencio + Talzenna	Chemo +/- Avastin, then Talzenna or Avastin	*Discontinued after failure of Javelin Ovarian 100 trial*	None evident
Merck & Co and/or Astrazeneca					
Duo-O	1L & maintenance	Chemo + Avastin + Imfinzi, then Avastin + Imfinzi +/- Lynparza	Chemo + Avastin, then Avastin	Maintenance triplet positive for PFS in HRD+ves, all-comers & HRD-ves	Must be Brca-ve (including other HRD+ves)
Keylynk-001	1L & maintenance	Chemo + Keytruda, then Lynparza	Chemo +/- Keytruda, then placebo	PFS in PD-L1+ves & all-comers are co-primaries**; ends Oct 2023	Must be Brca-ve
Bristol Myers Squibb/Pharma& (ex Clovis)					

PD-(L)1 + Parp inhibition in ovarian cancer					
Athena-Combo	1L maintenance	Opdivo + Rubraca	Opdivo or Rubraca or placebo	PFS primary, data were due Q1 2023***	None evident

*Note: *not phase 3; **earlier PFS & OS were co-primaries; ***forecast made by Clovis, which later entered bankruptcy and sold Rubraca to Pharma& for $70m. Source: company statements & clinicaltrials.gov.*

– Jacob Plieth (JacobP@vantageanalysis.com)

This article originally appeared in Evaluate Vantage. Evaluate Vantage and Scrip are part of the same parent company, Norstella.