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Editorial

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A step towards the ambition of precision oncology in recurrent ovarian cancer

Silvana Talisa Wijaya (iD),[1] **David Shao Peng Tan** (iD) [1,2,3]

[1]Department of Haematology-Oncology, National University Cancer Institute Singapore, Singapore
[2]Cancer Science Institute, National University of Singapore, Singapore
[3]Yong Loo Lin School of Medicine, National University of Singapore, Singapore

> ▶ See the article "Biomarker-guided targeted therapy in platinum-resistant ovarian cancer (AMBITION; KGOG 3045): a multicentre, open-label, five-arm, uncontrolled, umbrella trial" in volume 33, e45.

Correspondence to
David Shao Peng Tan
Department of Haematology-Oncology, National University Cancer Institute Singapore, 1E Kent Ridge Road, National University Health System Tower Block Level 7, Singapore 119228.
Email: david_sp_tan@nuhs.edu.sg

ORCID iDs
Silvana Talisa Wijaya (iD)
https://orcid.org/0000-0003-4674-9802
David Shao Peng Tan (iD)
https://orcid.org/0000-0001-9087-5262

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The treatment of recurrent ovarian cancer with a platinum-free interval (PFI) of less than 6 months (ROC-TFIp <6 months) remains a significant clinical challenge. Sequential use of single-agent therapy with a non-platinum drug such as pegylated liposomal doxorubicin, paclitaxel, topotecan, and gemcitabine continues to be the mainstay of treatment [1]. Typical response rates with these agents are less than 20%, and median progression-free survival (PFS) ranges 3 to 4 months. The AURELIA trial showed that the addition of bevacizumab significantly improves response rates and PFS [2]. Aside from this, no significant advances in the treatment of ROC-TFIp <6 months have emerged in clinical practice. Despite the uniform manner in which ROC-TFIp <6 months is treated, it is a highly heterogenous disease. The AMBITION study is one of the first biomarker-driven trials with an umbrella-design for ROC-TFIp <6 months and represents an important step towards precision oncology in this area of unmet need [3].

AMBITION is an open-label, investigator-initiated, phase 2 umbrella trial that enrolled 70 patients with ROC-TFIp <6 months who had received at least 2 prior lines of chemotherapy. The trial schema is summarized in **Fig. 1**. Patients were given combination therapy based on their homologous recombination deficiency (HRD) and programmed death ligand 1 (PD-L1) status. HRD-positive patients were randomized to either olaparib + cediranib or olaparib + durvalumab; both of these combinations have previously shown encouraging and synergistic activity in phase 2 trials with patients with platinum-sensitive recurrence [4-6].

Overall response rate (ORR), the primary endpoint of the trial, was 37.1% in the overall cohort, with a median PFS was 4.76 months. The ORR was 50%, 42.9%, 20%, 33.3%, and 29.4%, and median PFS were 5.62, 5.36, 3.68, 3.98, and 5.13 months for arms 1, 2, 3, 4 and 5 respectively. The ORR in this trial compares favorably with the 30% ORR in the AURELIA trial [2], and is particularly impressive for arms 1 and 2, despite the fact that the cohort participating in the AMBITION trial were more heavily pre-treated and the majority had received bevacizumab previously, thus reflecting what could be considered a post-AURELIA cohort. These encouraging findings show that biomarker-driven trials are viable in ovarian cancer and that biomarker-driven targeted therapy may have greater efficacy than non-stratified treatment strategies for ROC-TFIp <6 months. The combination of olaparib with cediranib or durvalumab for HRD+ ROC-TFIp <6 months and addition of an immune checkpoint inhibitor to standard
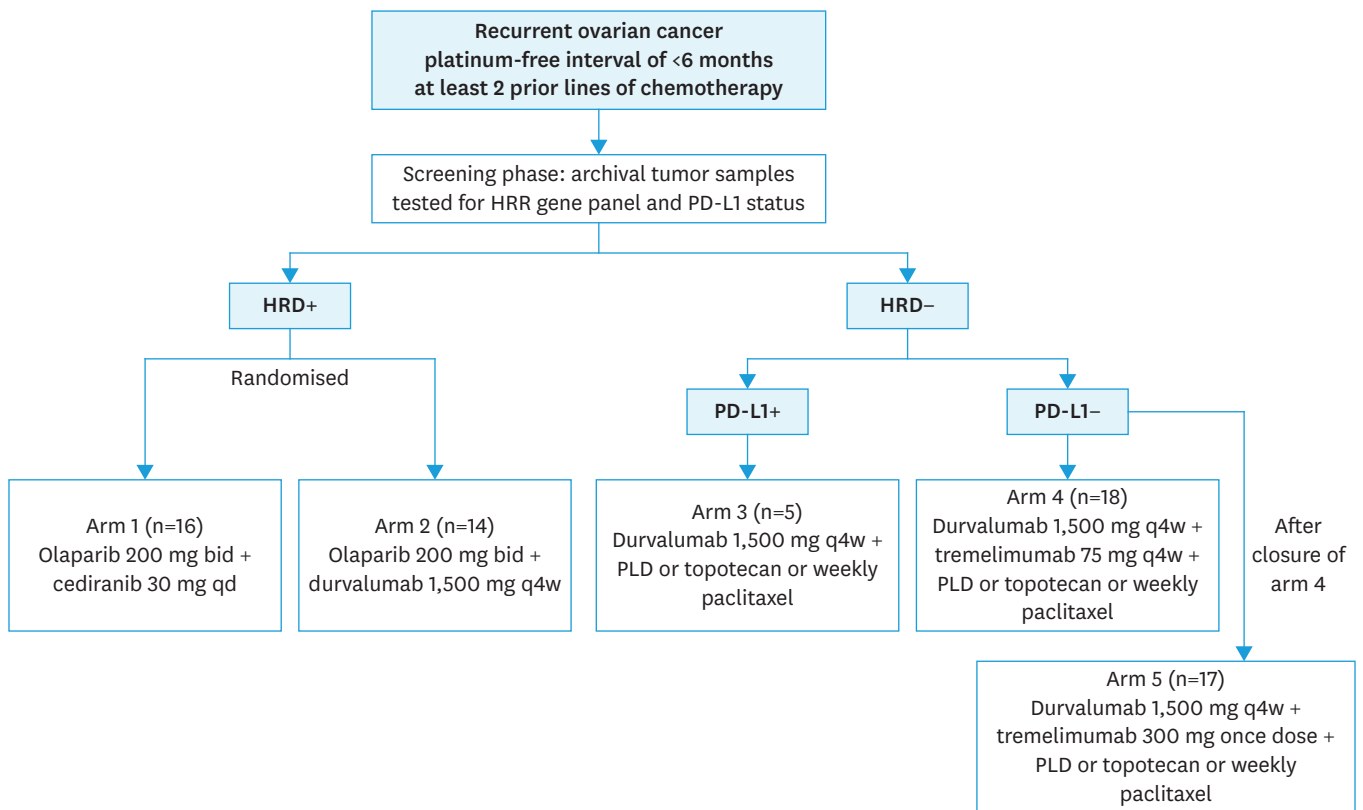
Fig. 1. AMBITION trial schema, adapted from Lee et al. [7].
HRR, homologous recombination repair; PD-L1, program death ligand 1; HRD+, HRD positive (defined as presence of at least one mutation of 15 HRR pathway genes); HRD−, HRD negative; PD-L1+, PD-L1 positive (defined as tumor proportion score of 25% or more); PLD, pegylated liposomal doxorubicin.

chemotherapy for HRD− tumors showed promising efficacy suggestive of synergism and tolerable toxicity profiles, and therefore individually warrant further confirmation in phase 3 trials. It should be noted, however, that patients previously treated with poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) were excluded from this trial. With established evidence for the efficacy of maintenance PARPi and approval for their use in the front-line setting in advanced ovarian cancers, as well as increasing accessibility to its use, the actual proportion of HRD+ patients without prior exposure to PARPi in the recurrent setting may be limited. It remains to be seen whether the combination of olaparib + cediranib/durvalumab has similar efficacy in the context of previous PARPi exposure.

The main point of contention of this study is in the use of a homologous recombination repair (HRR) gene panel for the classification of HRD+ tumors, and studies evaluating the predictive value of HRR gene mutation panels for PARPi therapy efficacy have been conflicting [8]. In a recent subgroup analysis of the PAOLA-trial, HRR gene panels did not have equivalent predictive value for olaparib + bevacizumab benefit compared with the Myriad myChoice genomic instability score (GIS) [9]. In the phase 2 trial by Liu et al. [4], it was the wild-type or unknown BRCA cohort that derived greater benefit from the olaparib + cediranib combination compared with olaparib alone. Conversely, the phase 2 study of olaparib + durvalumab showed more promising activity in germline BRCA-mutated recurrent ovarian cancers than in non-germline BRCA-mutated cancers, though a direct comparison was not made [5,6]. Both of these aforementioned trials, however, focused on ROC-TFIp >6 months, and the predictive value of HRR gene mutation status, or indeed HRD based on the

Foundation CDx loss of heterozygosity (LOH) score or Myriad myChoice GIS score in the setting of ROC-TFIp <6 months remain uncertain. While the results from the AMBITION study seem to suggest that patients with HRR-related gene mutations may benefit from PARPi combinations in this context, it is worth noting that the majority of patients in the HRD+ group had *BRCA1/2* gene mutations.

Some studies, such as KEYNOTE-100 [10], have suggested that recurrent ovarian cancer tumors that express PD-L1 have a better potential of responding favorably to immunotherapy, although findings related to the utility of PD-L1 as a predictive biomarker in this setting were not always consistent. This trial demonstrated a lower-than-anticipated rate of PD-L1 expressing tumors, resulting in the early closure of Arm 3 and a limited ability to evaluate the efficacy of the single agent immunotherapy-chemotherapy combination. Arms 4 and 5 do, however, demonstrate encouraging activity that supports the hypothesis that dual checkpoint inhibition may increase immune activity against tumors that are otherwise considered immunologically 'cold'.

The AMBITION trial investigators should be congratulated for successfully completing one of the first biomarker-driven umbrella studies in recurrent ovarian cancer, an achievement that necessitated careful design and close collaboration among multiple stakeholders. While the trial's small size and lack of a randomized control arm limit conclusions about the efficacy of treatment combinations and the validity of biomarkers, it does show that rational and biomarker-driven targeted therapy has the potential to enhance outcomes. We anticipate that this study will pave the way for the development of further biomarker-driven trials evaluating the role of novel targeted therapies and their combinations, leveraging our growing understanding of the molecular processes underlying the heterogeneity of recurrent ovarian cancer.

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