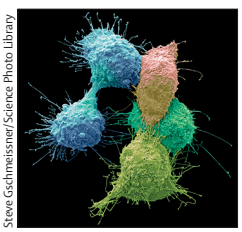
Ovarian cancer: time to move beyond one size fits all



Steve Gschmeissner/Science Photo Library

Published Online
May 7, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30285-2

See Articles page 862

Paclitaxel and carboplatin therapy has been the cornerstone of chemotherapy for epithelial ovarian, tubal, and peritoneal cancer for more than two decades. Unfortunately, despite tremendous research commitment and engagement, 5-year overall survival in ovarian cancer has improved only slightly since 1995.[1]

In *The Lancet Oncology*, Ignace Vergote and colleagues[2] report the results of TRINOVA-3/ENGOT-ov2/GOG-3001, a randomised, double-blind, phase 3 trial comparing trebananib plus carboplatin and paclitaxel with placebo plus carboplatin and paclitaxel followed by maintenance trebananib or placebo as first-line treatment in advanced ovarian cancer. Trebananib is a peptibody that targets the ANG–TIE–TEK pathway by binding angiopoietin (Ang)1 and Ang2 and neutralising their interaction with the Tie2 receptor. The addition of trebananib to paclitaxel and carboplatin did not show improved survival outcomes in an unselected patient population.

There are encouraging and cautionary key points to learn from the present study, including the importance of international collaboration, evaluation of novel therapeutics in unselected patient populations, and prioritisation of experimental therapies. First, the authors are congratulated for their efforts and completion of TRINOVA-3, which represents an important change in clinical trial conduct. The present trial is the first international collaborative effort between European Network of Gynaecological Oncological Trial (ENGOT) groups and Gynecological Oncology Group (GOG) Partners. GOG Partners was developed in an effort to adapt to changes announced by the National Cancer Institute in 2010 requiring restructuring the cooperative oncology group system. The future was uncertain and continued robust gynecological cancer research in the USA would require innovation, resilience, and agile adaptability. ENGOT and GOG Partners leadership overcame obstacles to navigate a new collaborative relationship, culminating in the successful completion of TRINOVA-3. This study broke through previous geographical barriers, representing a global strategy for recruitment across 14 countries spanning three continents. The collaboration has remained strong with more than ten trials either completed or underway in less than 7 years.

TRINOVA-3, like many current trials, continued to use a one-size-fits-all approach, despite data showing that ovarian cancer subtypes are molecularly distinct and, even within subtypes, have substantially different genomic profiles.[3,4] 13 active or recruiting all-comer, randomised, phase 3 clinical trials evaluating biological therapies in women with newly diagnosed advanced ovarian cancer are ongoing.[5] Enrolment for these studies includes more than 11 000 women. Similar to TRINOVA-3, two other phase 3 trials, JAVELIN Ovarian 100 (NCT02718417) and FORWARD 1 (NCT02631876), reported negative interim results in unselected patient populations.

Several completed and ongoing trials include translational components with biomarker evaluation that could inform differential clinical benefit in select subgroups and lead to patient-centric approaches. However, biomarker assessments have typically been exploratory, as is the case in TRINOVA-3, despite adequate evidence for more robust integral and integrated biomarker evaluation. Biomarker analysis in TRINOVA-3 did not include predictive interactive assessment for trebananib activity, optimisation of biomarker cut-points, or enrichment for a biomarker-positive cohort. More efficient and meaningful therapeutic advancements depend upon adaptive clinical trials based on critical molecular or immunological characteristics and selecting therapeutic agents in tandem with biomarkers. The unprecedented results of SOLO1,[6] showing that maintenance olaparib yielded impressive progression-free survival benefit in women with newly diagnosed advanced ovarian cancers characterised by *BRCA* mutations, is a testament to this type of approach and the promise of precision medicine in ovarian cancer.[6]

Another key issue is optimal prioritisation of experimental therapies, given the cadre of potential targets and biological therapies. The rationale behind TRINOVA-3 development was based on traditional metrics, including promising preclinical and early phase trial data. Trebananib targets the ANG–TIE–TEK angiogenic pathway, which is complex because Ang1 and 2 have conflicting roles. Ang1 (a Tie2 agonist) increases vascular maturity, microvessel density, vessel enlargement, and protects against vascular leak induced by vascular endothelial growth factor and various

inflammatory stimuli. By contrast, Ang2, which is primarily a Tie2 antagonist, binds Tie2 with the same high affinity as Ang1, thereby inhibiting Ang1-induced vascular stability.[7] The complex interplay between the two includes complementary yet counter-regulatory roles in angiogenesis regulation. That trebananib targets and binds both Ang1 and Ang2 ligands might be a limitation of the drug. Given the considerable cost of bringing drugs to market and restricted resources, a focus on newer methods to enhance success is needed. Deep learning and computational chemistry could represent novel approaches to pharmaceutical research for drug discovery, prioritisation, and toxicity prediction.[8,9]

It is an exciting time for ovarian cancer, with results anticipated from several potentially practice changing phase 3 randomised trials in the near future. Whether the promise of precision and personalised medicine in ovarian cancer will be realised or the one-size-fits-all approach will yield another negative result remains to be seen.

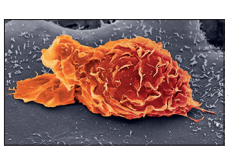
Angeles Alvarez Secord
Division of Gynecology Oncology, Department of Obstetrics and Gynecology, Duke Cancer Institute, Duke University Medical Center, Durham, NC 27710, USA
angeles.secord@duke.edu

I report research funding from Amgen during the conduct of the study; research funding from AbbVie, Astex Pharmaceuticals, AstraZeneca, Clovis, Astellas Pharma Boehringer Ingelheim, Bristol Myers Squibb, Eisai, Endocyte, Exelixis, Incyte, Merck, PharmaMar, Immutep Ltd, Roche/Genentech, Seattle Genetics, TapImmune, and Tesaro outside the submitted work; a grant from the National Cancer Trial Network outside the submitted work; and honoraria and advisory board fees from Alexion, Aravive, Astex Pharmaceuticals, AstraZeneca, Clovis, Janssen–Johnson & Johnson, Merck, Mersana, Myriad, Oncoquest, Roche–Genentech, and Tesaro outside of the submitted work.

1 National Cancer Institute. SEER cancer statistics review 1975–2015. https://seer.cancer.gov/csr/1975_2015/results_merged/topic_survival.pdf (accessed April 13, 2019).
2 Vergote I, Scambia G, O'Malley DM, et al. Trebananib or placebo plus carboplatin and paclitaxel as first-line treatment for advanced ovarian cancer (TRINOVA-3/ENGOT-ov2/GOG-3001): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2019; published online May 7. http://dx.doi.org/10.1016/S1470-2045(19)30178-0.
3 The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011; **474:** 609–15.
4 Tothill RW, Tinker AV, George J, et al. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. *Clin Cancer Res* 2008; **14:** 5198–208.
5 US National Library of Medicine. ClincalTrials.gov. https://clinicaltrials.gov (accessed April 13, 2019).
6 Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018; **379:** 2495–505.
7 Augustin HG, Koh GY, Thurston G, et al. Control of vascular morphogenesis and homeostasis through the angiopoietin-Tie system. *Nat Rev Mol Cell Biol* 2009; **10:** 165–77.
8 Chen H, Engkvist O, Wang Y, et al. The rise of deep learning in drug discovery. *Drug Discov Today* 2018; **23:** 1241–50.
9 Zhang L, Zhang H, Ai H, et al. Applications of machine learning methods in drug toxicity prediction. *Curr Top Med Chem* 2018; **18:** 987–97.

Multidisciplinary care in tenosynovial giant cell tumours

Tenosynovial giant cell tumour is a rare neoplastic condition of the joint that generally affects patients younger than 40 years.[1] It is not a malignancy per se, but for many, it is far from a benign disease and often causes substantial morbidity and disability due to pain, joint destruction, the need for repeated surgical intervention, and the use of analgesics and narcotics. Although not life-threatening, tenosynovial giant cell tumours can disrupt daily living and adversely alter an individual's life trajectory. Tenosynovial giant cell tumour is a complex disease with a wide breadth of clinical sequalae. Understanding of this disease has changed substantially in the past 10 years after causative genomic events were described.[2] The discovery of these genomic events has allowed for the development and application of promising therapeutics targeting *CSF1* signalling, which are further driving our knowledge base and greatly informing clinical practice.[1,3] The introduction of *CSF1* receptor inhibitors came with the realisation that much needed to be learned about what patients with tenosynovial giant cell tumours go through and how the medical community could best serve them. This realisation prompted the medical and pharmaceutical community to partner with patients, patient advocacy, and patient support groups to learn more about the disease, to develop novel patient-reported outcome measures[4] and potentially new imaging techniques,[1] and to review and scrutinise historical experiences.[5] This effort is paramount because the correct application of targeted therapies in tenosynovial giant cell tumours is not straightforward. Although active, many drugs have serious side-effects and associated financial costs. Much still needs to be learned about appropriate application, patient selection, timing of therapy, and length of use; decisions that need to be


Steve Gschmeissner/SPL

Published **Online**
April 24, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30173-1

See **Articles** page 877