FLORIDA CANCER SPECIALISTS & Research Institute

TOP ARTICLES OF THE MONTH

MARCH 2021 | Lucio N. Gordan, MD

1. Mutations in *BRCA1/2* and Other Panel Genes in Patients With Metastatic Breast Cancer —Association With Patient and Disease Characteristics and Effect on Prognosis

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PURPOSE

Among patients with metastatic breast cancer (mBC), the frequency of germline mutations in cancer susceptibility genes and the clinical relevance of these mutations are unclear. In this study, a prospective cohort of patients with mBC was used to determine mutation rates for breast cancer (BC) predisposition genes, to evaluate the clinical characteristics of patients with mutations, and to assess the influence of mutations on patient outcome.

PATIENTS AND METHODS

Germline DNA from 2,595 patients with mBC enrolled in the prospective PRAEGNANT registry was evaluated for mutations in cancer predisposition genes. The frequencies of mutations in known BC predisposition genes were compared with results from a prospective registry of patients with nonmetastatic BC sequenced using the same QIAseq method and with public reference controls. Associations between mutation status and tumor characteristics, progression-free survival, and overall survival were assessed.

RESULTS

Germline mutations in 12 established BC predisposition genes (including BRCA1 and BRCA2) were detected in 271 (10.4%) patients. A mutation in BRCA1 or BRCA2 was seen in 129 patients (5.0%). BRCA1 mutation carriers had a higher proportion of brain metastasis (27.1%) compared with nonmutation carriers (12.8%). Mutations were significantly enriched in PRAEGNANT patients with mBC compared with patients with nonmetastatic BC (10.4% v 6.6%, $P < .01$). Mutations did not significantly modify progression-free survival or overall survival for patients with mBC.

CONCLUSION

Multigene panel testing may be considered in all patients with mBC because of the high frequency of germline mutations in BRCA1/2 and other BC predisposition genes. Although the prognosis of mutation carriers and nonmutation carriers with mBC was similar, differences observed in tumor characteristics have implications for treatment and for future studies of targeted therapies.

2. Primary Tumor Resection Plus Chemotherapy Versus Chemotherapy Alone for Colorectal Cancer Patients With Asymptomatic, Synchronous Unresectable Metastases (JCOG1007; iPACS): A Randomized Clinical Trial

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PURPOSE

It remains controversial whether primary tumor resection (PTR) before chemotherapy improves survival in patients with colorectal cancer (CRC) with asymptomatic primary tumor and synchronous unresectable metastases.

PATIENTS AND METHODS

This randomized phase III study investigated the superiority of PTR followed by chemotherapy versus chemotherapy alone in relation to overall survival (OS) in patients with unresectable stage IV asymptomatic CRC and three or fewer unresectable metastatic diseases confined to the liver, lungs, distant lymph nodes, or peritoneum. Chemotherapy regimens of either mFOLFOX6 plus bevacizumab or CapeOX plus bevacizumab were decided before study entry. The primary end point was OS, which was analyzed by intention-to-treat.

RESULTS

Between June 2012 and September 2019, a total of 165 patients were randomly assigned to either chemotherapy alone (84 patients) or PTR plus chemotherapy (81 patients). When the first interim analysis was performed in September 2019 with 50% (114/227) of the expected events observed among 160 patients at the data cutoff date of June 5, 2019, the Data and Safety Monitoring Committee recommended early termination of the trial because of futility. With a median follow-up of 22.0 months, median OS was 25.9 months (95% CI, 19.9 to 31.5) in the PTR plus chemotherapy arm and 26.7 (95% CI, 21.9 to 32.5) in the chemotherapy-alone arm (hazard ratio, 1.10; 95% CI, 0.76 to 1.59; one-sided P = .69). Three postoperative deaths occurred in the PTR plus chemotherapy arm.

CONCLUSION

Given that PTR followed by chemotherapy showed no survival benefit over chemotherapy alone, PTR should no longer be considered a standard of care for patients with CRC with asymptomatic primary tumors and synchronous unresectable metastases.

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3. Phase III Trial of Avelumab Maintenance After First-Line Induction Chemotherapy Versus Continuation of Chemotherapy in Patients With Gastric Cancers: Results From JAVELIN Gastric 100

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PURPOSE

The role of maintenance therapy for gastric (GC) or gastroesophageal junction cancer (GEJC) is unclear. We investigated avelumab (anti–programmed death ligand-1 [PD-L1]) maintenance after first-line induction chemotherapy for GC/GEJC.

PATIENTS AND METHODS

JAVELIN Gastric 100 was a global, open-label, phase III trial. Eligible patients had untreated, unresectable, human epidermal growth factor receptor 2–negative, locally advanced or metastatic GC or GEJC. Patients without progressive disease after 12 weeks of first-line chemotherapy with oxaliplatin plus a fluoropyrimidine were randomly assigned 1:1 to avelumab 10 mg/kg every 2 weeks or continued chemotherapy, stratified by region (Asia v non-Asia). The primary end point was overall survival (OS) after induction chemotherapy in all randomly assigned patients or the PD-L1–positive randomly assigned population (≥ 1% of tumor cells; 73-10 assay).

RESULTS

A total of 805 patients received induction; 499 were randomly assigned to avelumab (n = 249) or continued chemotherapy (n = 250). Median OS was 10.4 months (95% CI, 9.1 to 12.0 months) versus 10.9 months (95% CI, 9.6 to 12.4 months) and 24-month OS rate was 22.1% versus 15.5% with avelumab versus chemotherapy, respectively (hazard ratio [HR], 0.91; 95% CI, 0.74 to 1.11; P = .1779). In the PD-L1–positive population (n = 54), the HR for OS was 1.13 (95% CI, 0.57 to 2.23; P = .6352). In an exploratory analysis of the PD-L1–positive population, defined as combined positive score ≥ 1 (22C3 assay; n = 137), median OS was 14.9 months (95% CI, 8.7 to 17.3 months) with avelumab versus 11.6 months (95% CI, 8.4 to 12.6 months) with chemotherapy (unstratified HR, 0.72; 95% CI, 0.49 to 1.05). With avelumab and chemotherapy, treatment-related adverse events (TRAEs) occurred in 149 (61.3%) and 184 (77.3%) patients, including grade ≥ 3 TRAEs in 31 (12.8%) and 78 (32.8%) patients, respectively.

CONCLUSION

JAVELIN Gastric 100 did not demonstrate superior OS with avelumab maintenance versus continued chemotherapy in patients with advanced GC or GEJC overall or in a prespecified PD-L1–positive population.

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4. Lenalidomide-Epoetin Alfa Versus Lenalidomide Monotherapy in Myelodysplastic Syndromes Refractory to Recombinant Erythropoietin

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PURPOSE

Impaired response to erythropoietin underlies ineffective erythropoiesis and anemia in myelodysplastic syndromes (MDS). We investigated whether treatment with lenalidomide (LEN), which augments erythropoietin receptor signaling in vitro, can restore and improve hemoglobin response to epoetin (EPO) alfa in patients with lower-risk, non-del(5q) MDS who have anemia that is refractory to or have low probability of benefit from treatment with recombinant erythropoietin.

METHODS

In a phase III, US intergroup trial, we randomly assigned patients to receive either LEN and EPO alfa or LEN alone following stratification by serum erythropoietin concentration and prior erythropoietin treatment.

RESULTS

A total of 195 evaluable patients were randomly assigned: 99 patients to the LEN-EPO alfa cohort and 96 to LEN alone. After four cycles of treatment, the primary end point of major erythroid response (MER) was significantly higher (28.3%) with the combination compared with LEN alone (11.5%) (P = .004). Among 136 patients who completed 16 weeks of study treatment, 38.9% and 15.6% achieved MER, respectively (P = .004). Additionally, minor erythroid response was achieved in 18.2% and 20.8% of patients, for an overall erythroid response rate of 46.5% versus 32.3%. Among LEN nonresponders, 38 crossed over to the addition of EPO alfa with 10 patients (26.3%) achieving a MER. Responses to the combined treatment were highly durable with a median MER duration of 23.8 months compared with 13 months with LEN alone.

CONCLUSION

LEN restores sensitivity to recombinant erythropoietin in growth factor–insensitive, lower-risk, non-del(5q) MDS, to yield a significantly higher rate and duration of MER compared with LEN alone (funded by the National Cancer Institute; E2905 ClinicalTrials.gov identifier: NCT02048813).

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5. Open-Label, Single-Arm, Phase II Study of Pembrolizumab Monotherapy as First-Line Therapy in Patients With Advanced Non–Clear Cell Renal Cell Carcinoma

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PURPOSE

Programmed death 1 (PD-1) pathway inhibitors have not been prospectively evaluated in patients with non-clear cell renal cell carcinoma (nccRCC). The phase II KEYNOTE-427 study (cohort B) was conducted to assess the efficacy and safety of single-agent pembrolizumab, a PD-1 inhibitor, in advanced nccRCC.

METHODS

Patients with histologically confirmed, measurable (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) nccRCC and no prior systemic therapy received pembrolizumab 200 mg intravenously once every 3 weeks for ≤ 24 months. The primary end point was objective response rate (ORR) per RECIST v1.1.

RESULTS

Among enrolled patients (N = 165), 71.5% had confirmed papillary, 12.7% had chromophobe, and 15.8% had unclassified RCC histology. Most patients (67.9%) had intermediate or poor International Metastatic RCC Database Consortium risk status and tumors with programmed death ligand 1 (PD-L1) combined positive score (CPS) ≥ 1 (61.8%). The median time from enrollment to database cutoff was 31.5 months (range, 22.7-38.8). In all patients, the ORR was 26.7%. The median duration of response was 29.0 months; 59.7% of responses lasted ≥ 12 months. The ORR by CPS ≥ 1 and CPS < 1 status was 35.3% and 12.1%, respectively. The ORR by histology was 28.8% for papillary, 9.5% for chromophobe, and 30.8% for unclassified. Overall, the median progression-free survival was 4.2 months (95% CI, 2.9 to 5.6); the 24-month rate was 18.6%. The median overall survival was 28.9 months (95% CI, 24.3 months to not reached); the 24-month rate was 58.4%. Overall, 69.7% of patients reported treatment-related adverse events, most commonly pruritus (20.0%) and hypothyroidism (14.5%). Two deaths were treatment related (pneumonitis and cardiac arrest).

CONCLUSION

First-line pembrolizumab monotherapy showed promising antitumor activity in nccRCC. The safety profile was similar to that observed in other tumor types.

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6. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

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BACKGROUND

Patients with advanced urothelial carcinoma have poor overall survival after platinum-containing chemotherapy and programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor treatment.

METHODS

We conducted a global, open-label, phase 3 trial of enfortumab vedotin for the treatment of patients with locally advanced or metastatic urothelial carcinoma who had previously received platinum-containing chemotherapy and had had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor. Patients were randomly assigned in a 1:1 ratio to receive enfortumab vedotin (at a dose of 1.25 mg per kilogram of body weight on days 1, 8, and 15 of a 28-day cycle) or investigator-chosen chemotherapy (standard docetaxel, paclitaxel, or vinflunine), administered on day 1 of a 21-day cycle. The primary end point was overall survival.

RESULTS

A total of 608 patients underwent randomization; 301 were assigned to receive enfortumab vedotin and 307 to receive chemotherapy. As of July 15, 2020, a total of 301 deaths had occurred (134 in the enfortumab vedotin group and 167 in the chemotherapy group). At the prespecified interim analysis, the median follow-up was 11.1 months. Overall survival was longer in the enfortumab vedotin group than in the chemotherapy group (median overall survival, 12.88 vs. 8.97 months; hazard ratio for death, 0.70; 95% confidence interval [CI], 0.56 to 0.89; P=0.001). Progression-free survival was also longer in the enfortumab vedotin group than in the chemotherapy group (median progression-free survival, 5.55 vs. 3.71 months; hazard ratio for progression or death, 0.62; 95% CI, 0.51 to 0.75; P<0.001). The incidence of treatment-related adverse events was similar in the two groups (93.9% in the enfortumab vedotin group and 91.8% in the chemotherapy group); the incidence of events of grade 3 or higher was also similar in the two groups (51.4% and 49.8%, respectively).

CONCLUSION

Enfortumab vedotin significantly prolonged survival as compared with standard chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who had previously received platinum-based treatment and a PD-1 or PD-L1 inhibitor. (Funded by Astellas Pharma US and Seagen; EV-301 ClinicalTrials.gov number, NCT03474107.)

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7. Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

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BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired disease characterized by chronic complement-mediated hemolysis. C5 inhibition controls intravascular hemolysis in untreated PNH but cannot address extravascular hemolysis. Pegcetacoplan, a pegylated peptide targeting proximal complement protein C3, potentially inhibits both intravascular and extravascular hemolysis.

METHODS

We conducted a phase 3 open-label, controlled trial to assess the efficacy and safety of pegcetacoplan as compared with eculizumab in adults with PNH and hemoglobin levels lower than 10.5 g per deciliter despite eculizumab therapy. After a 4-week run-in phase in which all patients received pegcetacoplan plus eculizumab, we randomly assigned patients to subcutaneous pegcetacoplan monotherapy (41 patients) or intravenous eculizumab (39 patients). The primary end point was the mean change in hemoglobin level from baseline to week 16. Additional clinical and hematologic markers of hemolysis and safety were assessed.

RESULTS

Pegcetacoplan was superior to eculizumab with respect to the change in hemoglobin level from baseline to week 16, with an adjusted (least squares) mean difference of 3.84 g per deciliter ($P<0.001$). A total of 35 patients (85%) receiving pegcetacoplan as compared with 6 patients (15%) receiving eculizumab no longer required transfusions. Noninferiority of pegcetacoplan to eculizumab was shown for the change in absolute reticulocyte count but not for the change in lactate dehydrogenase level. Functional Assessment of Chronic Illness Therapy–Fatigue scores improved from baseline in the pegcetacoplan group. The most common adverse events that occurred during treatment in the pegcetacoplan and eculizumab groups were injection site reactions (37% vs. 3%), diarrhea (22% vs. 3%), breakthrough hemolysis (10% vs. 23%), headache (7% vs. 23%), and fatigue (5% vs. 15%). There were no cases of meningitis in either group.

CONCLUSION

Pegcetacoplan was superior to eculizumab in improving hemoglobin and clinical and hematologic outcomes in patients with PNH by providing broad hemolysis control, including control of intravascular and extravascular hemolysis. (Funded by Apellis Pharmaceuticals; PEGASUS ClinicalTrials.gov, NCT03500549.)

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8. Oral Ixazomib, Lenalidomide, And Dexamethasone For Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma

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KEY POINTS

- Addition of Ixazomib to Rd for non-transplant NDMM patients causes a nonstatistically significant increase in PFS (HR 0.830, p = 0.073).
- Ixazomib-Rd is a feasible and tolerable all-oral triplet regimen in this setting, with a well-characterized and manageable safety profile.

Continuous lenalidomide-dexamethasone (Rd)-based regimens are among the standards of care in transplant-ineligible newly diagnosed multiple myeloma (NDMM) patients. The oral proteasome inhibitor ixazomib is suitable for continuous dosing, with predictable, manageable toxicities. In the double-blind, placebo-controlled

TOURMALINE-MM2 trial, transplant-ineligible NDMM patients were randomized to ixazomib 4 mg (n = 351) or placebo (n = 354) plus Rd. After 18 cycles, dexamethasone was discontinued and treatment was continued using reduced-dose ixazomib (3 mg) and lenalidomide (10 mg) until progression/toxicity. The primary endpoint was progression-free survival (PFS). Median PFS was 35.3 vs 21.8 months with ixazomib-Rd vs placebo-Rd, respectively (hazard ratio [HR], 0.830; 95% confidence interval, 0.676-1.018; P = .073; median follow-up, 53.3 and 55.8 months). Complete (26% vs 14%; odds ratio [OR], 2.10; P < .001) and ≥ very good partial response (63% vs 48%; OR, 1.87; P < .001) rates were higher with ixazomib-Rd vs placebo-Rd. In a prespecified high-risk cytogenetics subgroup, median PFS was 23.8 vs 18.0 months (HR, 0.690; P = .019). Overall, treatment-emergent adverse events (TEAEs) were mostly grade 1/2. With ixazomib-Rd vs placebo-Rd, 88% vs 81% of patients experienced grade ≥3 TEAEs, 66% vs 62% serious TEAEs, and 35% vs 27% TEAEs resulting in regimen discontinuation; 8% vs 6% died on study. Addition of ixazomib to Rd was tolerable with no new safety signals and led to a clinically meaningful PFS benefit of 13.5 months. Ixazomib-Rd is a feasible option for certain patients who can benefit from an all-oral triplet combination. This trial was registered at www.clinicaltrials.gov as #NCT01850524.

9. Anticoagulant Therapy For Splanchnic Vein Thrombosis: A Systematic Review And Meta-Analysis

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KEY POINTS

- Anticoagulant therapy was associated with a high rate of splanchnic vein recanalization and a low rate of thrombosis progression.
- Major bleeding risk and overall mortality of patients with splanchnic vein thrombosis were reduced by anticoagulant therapy.

Treatment of splanchnic vein thrombosis (SVT) is challenging, and evidence to guide therapeutic decisions remains scarce. The objective of this systematic review and meta-analysis was to determine the efficacy and safety of anticoagulant therapy for SVT. MEDLINE, EMBASE, and clinicaltrials.gov were searched from inception through December 2019, without language restrictions, to include observational studies and randomized controlled trials reporting radiological or clinical outcomes in patients with SVT. Pooled proportions and risk ratios (RRs) with 95% confidence intervals (CIs) were calculated in a random-effects model. Of 4312 records identified by the search, 97 studies including 7969 patients were analyzed. In patients receiving anticoagulation, the rates of SVT recanalization, SVT progression, recurrent venous thromboembolism (VTE), major bleeding, and overall mortality were 58% (95% CI, 51-64), 5% (95% CI, 3-7), 11% (95% CI, 8-15), 9% (95% CI, 7-12), and 11% (95% CI, 9-14), respectively. The corresponding values in patients without anticoagulation were 22% (95% CI, 15-31), 15% (95% CI, 8-27), 14% (95% CI, 9-21), 16% (95% CI, 13-20), and 25% (95% CI, 20-31). Compared with no treatment, anticoagulant therapy obtained higher recanalization (RR, 2.39; 95% CI, 1.66-3.44) and lower thrombosis progression (RR, 0.24; 95% CI, 0.13-0.42), major bleeding (RR, 0.73; 95% CI, 0.58-0.92), and overall mortality (RR, 0.45; 95% CI, 0.33-0.60). These results demonstrate that anticoagulant therapy improves SVT recanalization and reduces the risk of thrombosis progression without increasing major bleeding. The incidence of recurrent VTE remained substantial in patients receiving anticoagulation, as well. Effects were consistent across the different subgroups of patients. This trial was registered on the PROPERO database at (https://www.crd.york.ac.uk/prospero//display_record.php?ID=CRD42019127870) as #CRD42019127870.

10. Secondary Cytoreduction Followed By Chemotherapy Versus Chemotherapy Alone In Platinum-Sensitive Relapsed Ovarian Cancer (Soc-1): A Multicentre, Open-Label, Randomised, Phase 3 Trial

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BACKGROUND

The benefits of secondary cytoreduction for platinum-sensitive relapsed ovarian cancer are still widely debated. We aimed to assess the efficacy of secondary cytoreduction plus chemotherapy versus chemotherapy alone in this patient population.

METHODS

This multicentre, open-label, randomised, controlled, phase 3 trial (SOC-1), was done in four primarily academic centres in China (two in Shanghai, one in Hangzhou, and one in Guangzhou). Eligible patients were women aged 18 years and older with platinum-sensitive relapsed epithelial ovarian cancer with a platinum-free interval of at least 6 months after the end of first-line platinum-based chemotherapy and were predicted to have potentially resectable disease according to the international model (iMODEL) score and PET-CT imaging. iMODEL score was calculated using six variables: International Federation of Gynecology and Obstetrics stage, residual disease after primary surgery, platinum-free interval, Eastern Cooperative Oncology Group performance status, serum level of cancer antigen 125 at recurrence, and presence of ascites at recurrence. An iMODEL score of 4·7 or lower predicted a potentially complete resection. As per a protocol amendment, patients with an iMODEL score of more than 4·7 could only be included if the serum level of cancer antigen 125 was more than 105 U/mL, but the principal investigators assessed the disease to be resectable by PET-CT. Eligible participants were randomly assigned (1:1) via a permuted block design (block size of six) and stratified by study centre, iMODEL score, residual disease at primary surgery, and enrolment in the Shanghai Gynecologic Oncology Group SUNNY trial, to undergo secondary cytoreductive surgery followed by intravenous chemotherapy (six 3-weekly cycles of intravenous paclitaxel [175 mg/m2] or docetaxel [75 mg/m2] combined with intravenous carboplatin [area under the curve of 5 mg/mL per min]; surgery group) or intravenous chemotherapy alone (no surgery group). Primary endpoints were progression-free survival and overall survival, analysed in all participants randomly assigned to treatment, regardless of treatment received (intention-to-treat [ITT] population). Here, we report the final analysis of progression-free survival and the prespecified interim analysis of overall survival. Safety was assessed in all participants who received their assigned treatment and had available adverse event data. This study is registered with ClinicalTrials.gov, NCT01611766, and is ongoing but closed to accrual.

FINDINGS

Between July 19, 2012, and June 3, 2019, 357 patients were recruited and randomly assigned to the surgery group (182) or the no surgery group (175; ITT population). Median follow-up was 36·0 months (IQR 18·1–58·3). In the no surgery group, 11 (6%) of 175 participants had secondary cytoreduction during second-line therapy while 48 (37%) of 130 participants who had disease progression crossed-over and had surgery at a subsequent recurrence. Median progression-free survival was 17·4 months (95% CI 15·0–19·8) in the surgery group and 11·9 months (10·0–13·8) in the no surgery group (hazard ratio [HR] 0·58; 95% CI 0·45–0·74; p<0·0001). At the interim overall survival analysis, median overall survival was 58·1 months (95% CI not estimable to not estimable) in the surgery group and 53·9 months (42·2–65·5) in the no surgery group (HR 0·82, 95% CI 0·57–1·19). In the safety population, nine (5%) of 172 patients in the surgery group had grade 3–4 surgical morbidity at 30 days, and no patients in either group had died at 60 days after receiving assigned treatment. The most common grade 3–4 adverse events during chemotherapy were neutropenia (29 [17%] of 166 patients in the surgery group vs 19 [12%] of 156 patients in the no surgery group), leucopenia (14 [8%] vs eight [5%]), and anaemia (ten [6%] vs nine [6%]).

Four serious adverse events occurred, all in the surgery group. No treatment-related deaths occurred in either group.

INTERPRETATION

Secondary cytoreduction followed by chemotherapy was associated with significantly longer progression-free survival than was chemotherapy alone in patients with platinum-sensitive relapsed ovarian cancer, and patients should be counselled about the option of secondary cytoreduction in specialised centres. Long-term survival outcomes will be assessed using mature data on overall survival.