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Patient-reported outcomes and final overall survival results from the randomized phase 3 PENELOPE trial evaluating pertuzumab in low tumor human epidermal growth factor receptor 3 (HER3) mRNA-expressing platinum-resistant ovarian cancer

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HIGHLIGHTS

- PENELOPE evaluated chemotherapy ± pertuzumab for biomarker-selected platinum-resistant ovarian cancer.
- Adding pertuzumab to chemotherapy did not improve overall survival.
- Except for increased diarrhea symptoms, pertuzumab had no impact on patient-reported outcomes.

ABSTRACT

Introduction The PENELOPE trial evaluated pertuzumab added to chemotherapy for biomarker-selected platinum-resistant ovarian cancer. As previously reported, pertuzumab did not statistically significantly improve progression-free survival (primary end point: HR 0.74, 95% CI 0.50 to 1.11), although results in the paclitaxel and gemcitabine cohorts suggested activity. Here, we report final overall survival and patient-reported outcomes.

Patients and methods Eligible patients had ovarian carcinoma that progressed during/within 6 months of completing ≥4 platinum cycles, low tumor human epidermal growth factor receptor 3 (HER3) mRNA expression, and ≤2 prior chemotherapy lines. Investigators selected single-agent topotecan, gemcitabine or weekly paclitaxel before patients were randomized to either placebo or pertuzumab (840→420 mg every 3 weeks), stratified by selected chemotherapy, prior anti-angiogenic therapy, and platinum-free interval. Final overall survival analysis (key secondary end point) was pre-specified after 129 deaths. Patient-reported outcomes (secondary end point) were assessed at baseline and every 9 weeks until disease progression.

Results At database lock (June 9, 2016), 130 (83%) of 156 randomized patients had died. Median follow-up was 27 months in the pertuzumab arm versus 26 months in the control arm. In the intent-to-treat population there was no overall survival difference between treatment arms (stratified HR 0.90, 95% CI 0.61 to 1.32; p=0.60). Results in subgroups defined by stratification factors indicated heterogeneity similar to previous progression-free survival results. Updated safety was similar to previously published results. Compliance with patient-reported outcomes questionnaire completion was >75% for all validated patient-reported outcomes measures. Pertuzumab demonstrated neither beneficial nor detrimental effects on patient-reported outcomes compared with placebo, except for increased diarrhea symptoms.

Discussion Consistent with the primary results, adding pertuzumab to chemotherapy for low tumor HER3 mRNA-expressing platinum-resistant ovarian cancer did not improve overall survival, but showed trends in some cohorts. Except for increased diarrhea symptoms, pertuzumab had no impact on patient-reported outcomes.

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INTRODUCTION

Patients progressing after a short platinum-free interval of <6 months, formerly described as platinum-resistant ovarian cancer, have a poor prognosis, limited treatment options, and typically a considerable symptom burden.[1] The double-blind placebo-controlled randomized phase 3 PENELOPE trial evaluated chemotherapy with or without pertuzumab in a patient population with platinum-resistant ovarian cancer selected for low tumor human epidermal growth factor receptor 3 (HER3) mRNA expression.[2] These patients were considered to have a particularly poor prognosis and were anticipated to benefit from pertuzumab based on exploratory subset analyses of a randomized phase 2 trial.[3] Previously we reported results from the primary analysis of the PENELOPE

trial.[2] Adding pertuzumab to chemotherapy (investigator's choice of single-agent gemcitabine, topotecan, or weekly paclitaxel) for platinum-resistant ovarian cancer did not significantly improve independent review committee-assessed progression-free survival (primary end point). The hazard ratio (HR) for progression-free survival was 0.74 (95% confidence interval (CI) 0.50 to 1.11) in the intent-to-treat population. However, results in the paclitaxel and gemcitabine cohorts suggested activity, with HRs of 0.56 (95% CI 0.29 to 1.09) and 0.63 (95% CI 0.34 to 1.14), respectively.

The most recent Gynecologic Cancer InterGroup consensus recommended that in recurrent ovarian cancer clinical trials, progression-free survival alone is not adequate as a primary end point and should be supported by additional evidence of clinical benefit.[4] In populations with a life expectancy ≤12 months, overall survival is generally the preferred end point. However, when considering the effect of treatment, it is important to consider not only the impact on overall survival, but also the effect on quality of life and the burden of treatment (including the time and effort spent on therapy with respect to treatment administration and management of side effects). Here we report the final clinical results from the PENELOPE trial, including final overall survival and pre-specified analyses of patient-reported outcomes.

PATIENTS AND METHODS

Patients

Eligible patients had so-called platinum-resistant or platinum-refractory epithelial ovarian, primary peritoneal, or fallopian tube carcinoma (progression during platinum therapy or within 6 months of completing ≥4 cycles of platinum-containing therapy), and low tumor HER3 mRNA expression. HER3 mRNA expression was assessed using quantitative reverse transcriptase polymerase chain reaction on cobas z480 (Roche Molecular Diagnostics, Pleasanton, CA, USA). Low HER3 mRNA expression was defined as a concentration ratio ≤2.81. Patients previously treated with >2 prior lines of chemotherapy were ineligible. All patients provided written informed consent before undergoing any study-specific procedures. The trial conformed to the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the ethics committee of each participating site. There was no patient or public involvement in the trial design.

Study Design

PENELOPE comprised two parts: part 1 was a safety run-in and part 2 was a double-blind, placebo-controlled, randomized phase 3 trial. The design and primary results of both parts have been described in detail previously.[2 5] Here we present results of part 2 only. In brief, part 2 of the trial evaluated the addition of pertuzumab to the investigator's chosen chemotherapy. Before random assignment, investigators selected the backbone chemotherapy regimen for each patient (topotecan 1.25 mg/m^2, days 1–5 every 3 weeks; paclitaxel 80 mg/m^2, days 1, 8, and 15 every 3 weeks; or gemcitabine 1000 mg/m^2, days 1 and 8 every 3 weeks). Patients were stratified by selected chemotherapy (topotecan vs paclitaxel vs gemcitabine), prior anti-angiogenic therapy (yes vs no) and platinum-free interval (<3 vs 3–6 months) and randomly assigned by dynamic hierarchical randomization allocation using an interactive web- and voice-response system to receive either placebo or pertuzumab (840 mg loading dose on day 1, followed by 420 mg on day 1 of each subsequent cycle) with the selected chemotherapy. Pertuzumab/placebo and chemotherapy were continued until disease progression, unacceptable toxicity, consent withdrawal, or death, whichever occurred first. Patients, all study site personnel, and the sponsor (but not the interactive web- and voice-response system service provider, pharmacokinetic/pharmacodynamic laboratory personnel, and members of the independent data monitoring committee) were blinded to treatment assignment throughout the controlled period.

End Points

The primary end point was independent review committee-assessed progression-free survival. Overall survival was a key secondary end point. Additional secondary end points included investigator-assessed progression-free survival, objective response rate, clinical benefit rate, safety, tolerability (all of which were reported at the time of the primary analysis[2]), and patient-reported outcomes. Based on patient-reported outcome assessments in the AURELIA trial,[6 7] four validated patient-reported outcome measures—the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core module, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire ovarian cancer-specific module, the Hospital Anxiety Depression Scale, and the Functional Assessment of Cancer Therapy/National Comprehensive Cancer Network Ovarian Symptom Index—were used. Questionnaires were completed before tumor assessment and treatment administration during the patient's visit at baseline and every 9 weeks thereafter until investigator-assessed disease progression. Post-baseline assessments were linked to on-study tumor assessments rather than treatment cycles to avoid biased data collection. A fifth (unvalidated) instrument, initially designed for use in the AURELIA trial,[7] assessed the three worst symptoms at baseline.

Statistical Analysis

The planned part 2 sample size comprised 154 randomly assigned patients to ensure 140 evaluable patients (70 per treatment arm), assuming a 10% dropout rate. The trial had 80% power for overall survival (key secondary end point) using a closed-test procedure to adjust the significance level for multiple statistical testing. The final overall survival analysis was planned after 129 deaths.

Overall survival was estimated using the Kaplan-Meier method. P values for the stratified log-rank test (using randomization stratification factors) were calculated. The Lan-DeMets α-spending function was used with the O'Brien-Fleming stopping boundary to control for the α level. In addition, HRs and associated 95% CIs were calculated using the Cox regression model. Efficacy analyses were performed on the intent-to-treat population (all randomly assigned patients). Safety analyses were performed on the safety population (all patients who received at least one dose of study therapy).

Compliance with patient-reported outcome measures completion was calculated using the number of randomized patients in each arm as the denominator at baseline and the number of patients known to be alive, progression-free and on study treatment at the start of the relevant time period in each arm for all other time points. The predefined primary patient-reported outcome end point was a mixed-model repeated measures analysis of the Quality of Life Questionnaire ovarian cancer-specific module abdominal/gastrointestinal symptoms scale. Secondary patient-reported outcome end points focused on

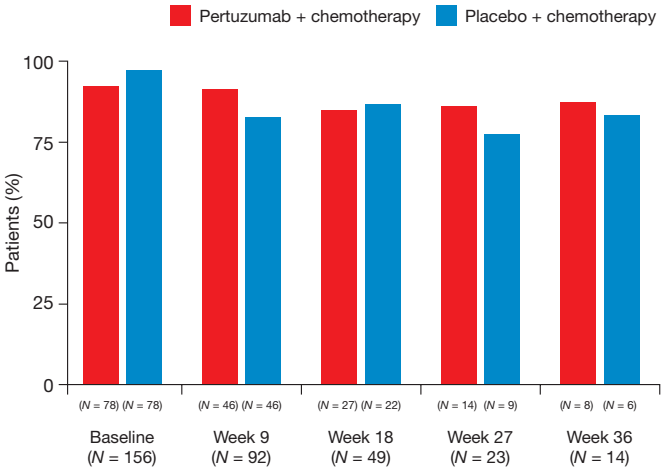

Figure 1 Compliance rates for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire ovarian cancer-specific module (primary patient-reported outcome instrument). The denominator used to calculate the percentage at baseline is the number of randomized patients in each treatment arm. For all other time points, the denominator is the number of patients in each arm known to be alive, progression-free and on study treatment at the start of the time period.

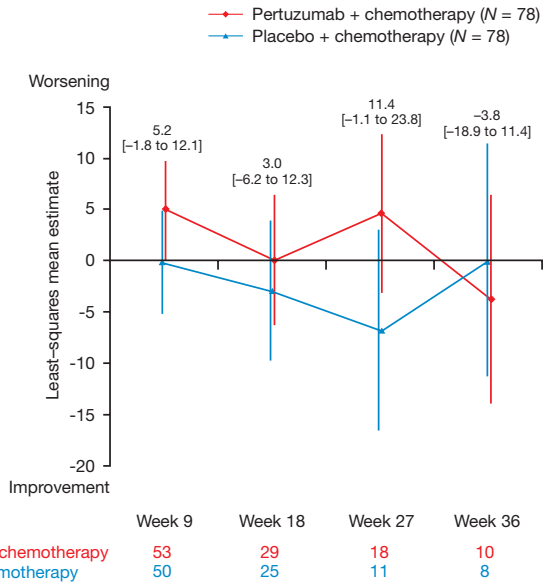

Figure 2 Mixed-model repeated measures analysis of change from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire ovarian cancer-specific module abdominal/gastrointestinal symptom scale (primary patient-reported outcome end point). Vertical bars represent 95% CIs. Numbers above vertical bars represent the difference between treatment arms (pertuzumab – placebo) at each time point.

the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core module functional and symptom scales most relevant to pertuzumab and platinum-resistant ovarian cancer: physical functioning, emotional functioning, fatigue, nausea and vomiting, and diarrhea. There were no specific patient-reported outcome hypotheses for the Hospital Anxiety Depression Scale and Functional Assessment of Cancer Therapy/National Comprehensive Cancer Network Ovarian Symptom Index patient-reported outcomes, which were analyzed descriptively, as was the unvalidated worst symptoms questionnaire.

Analyses of patient-reported outcomes (secondary end point) were not powered. No multiplicity adjustment was applied.

RESULTS

Patient Population

Between October 2, 2013 and September 18, 2014, 156 patients from 52 European centers were randomly assigned. Baseline characteristics were generally well balanced between treatment arms and have been reported previously (online supplementary table 1).

Patient-Reported Outcomes

The Quality of Life Questionnaire ovarian cancer-specific module patient-reported outcome measure was completed at baseline by 148 (95%) of the 156 randomized patients. There was similarly high compliance with questionnaire completion at all post-baseline time points in both treatment arms (figure 1). However, sample sizes beyond week 9 were small, as expected given the short progression-free survival in this population. The most common reason for missing questionnaires was missed site administration (online supplementary table 2). Compliance was similar for Quality of Life Questionnaire core module, Hospital Anxiety Depression Scale, and Functional Assessment of Cancer Therapy/National Comprehensive Cancer Network Ovarian Symptom Index questionnaire completion, whereas only 54% of patients completed the worst symptoms questionnaire at baseline.

There were no notable differences between treatment arms in the baseline scores for any Quality of Life Questionnaire ovarian cancer-specific module items or any of the five scales of Quality of Life Questionnaire core module predefined for secondary patient-reported outcome analyses (online supplementary table 3). The mean baseline score for Quality of Life Questionnaire ovarian cancer-specific module abdominal/gastrointestinal symptoms was 33.5 in the pertuzumab arm and 29.6 in the placebo arm.

For the primary patient-reported outcome end point (abdominal/gastrointestinal symptoms) there was no significant difference over time between treatments (figure 2). The treatment difference averaged over the entire assessment period was 3.9 (95% CI –3.3 to 11.2; p=0.28). Treatment-by-time interaction was not significant (p=0.35).

Of the five predefined Quality of Life Questionnaire core module scales analyzed for the secondary patient-reported outcome objective, the only scale with a significant difference between treatment arms was the diarrhea scale (table 1). Diarrhea symptoms worsened significantly more with pertuzumab plus chemotherapy than with placebo plus chemotherapy (profile difference 21.2, 95% CI 10.1 to 32.3; p=0.0003; treatment-by-time interaction p=0.51).

The secondary patient-reported outcome end points of Hospital Anxiety Depression Scale and Functional Assessment of Cancer Therapy/National Comprehensive Cancer Network Ovarian Symptom Index showed no difference between treatment arms (online supplementary table 4). Among the 84 patients who completed the 'three worst symptoms' questionnaire, the symptom

Table 1 Secondary patient-reported outcome end points: mixed-model repeated measures analysis of change from baseline in five pre-specified scales of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core module

	Least-squares mean estimate (95% CI), overall profile				
Scale	Pertuzumab + chemotherapy	Placebo + chemotherapy	Difference: pertuzumab – placebo	P value*	Treatment-by-time interaction P value
Physical functioning	–8.1 (–12.6 to –3.5)	–5.5 (–10.5 to –0.5)	–2.6 (–9.4 to 4.2)	0.4558	0.98
Emotional functioning	4.8 (–1.0 to 10.5)	0.1 (–6.2 to 6.4)	4.6 (–4.0 to 13.2)	0.2881	0.22
Fatigue	9.4 (3.7 to 15.1)	6.9 (0.5 to 13.3)	2.5 (–6.2 to 11.1)	0.5705	0.50
Nausea and vomiting	8.6 (1.7 to 15.6)	4.4 (–3.4 to 12.2)	4.2 (–6.2 to 14.6)	0.4251	0.74
Diarrhea	23.9 (16.6 to 31.2)	2.7 (–5.7 to 11.0)	21.2 (10.1 to 32.3)	0.0003	0.51

*Not adjusted for multiplicity.

most commonly ranked as worst was abdominal pain (14 patients; 17%), followed by fatigue (13 patients; 15%). The symptom most commonly ranked within the three worst symptoms was fatigue (n=33; 39%), followed by trouble sleeping (n=28; 33%), bloated feeling in the abdomen/stomach (n=27; 32%), and pain (n=26; 31%).

Overall Survival

The data cut-off for the pre-specified final overall survival analysis was June 9, 2016. By this date, all patients had discontinued all study treatments and 130 (83%) of the 156 randomized patients had died. Median follow-up was 27 vs 26 months in the pertuzumab and placebo arms, respectively. In the intent-to-treat population there was no difference in overall survival between treatment arms (stratified HR 0.90, 95% CI 0.61 to 1.32, p=0.60; unstratified HR 0.76, 95% CI 0.54 to 1.08) (figure 3). Median overall survival was 10.2 months with pertuzumab versus 8.4 months with placebo. Overall survival in subgroups defined by the randomization stratification factors indicated considerable heterogeneity (table 2). There was a numerical improvement in overall survival versus placebo as assessed by HR in the paclitaxel cohort (HR 0.74, 95% CI 0.41 to 1.36) and the gemcitabine cohort (HR 0.58, 95% CI 0.32 to 1.06).

Safety

Updated safety results with longer follow-up (median 26–27 months) were almost identical to previously published safety results at the time of the primary progression-free survival analysis (10 months' median follow-up).[2] Grade ≥3 adverse events were reported in 69% of pertuzumab-treated patients versus 75% in the control arm. The only grade ≥3 adverse events occurring in >10% of patients in either arm were neutropenia/decreased neutrophil count (31% vs 21% for pertuzumab vs control, respectively), diarrhea (14% vs 1%), and fatigue/asthenia (8% vs 12%).

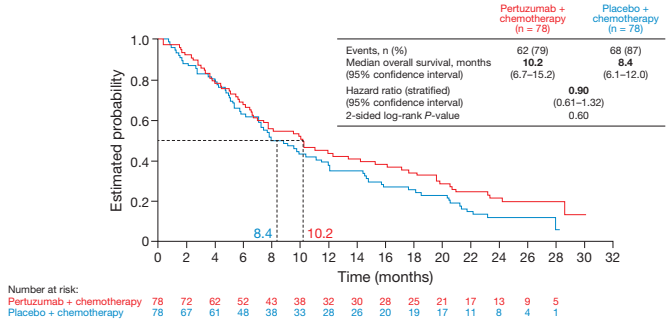

Figure 3 Overall survival in the intent-to-treat population.

DISCUSSION

The efficacy objectives of the PENELOPE trial were not met; adding pertuzumab to chemotherapy in patients with platinum-resistant ovarian cancer and low tumor HER3 mRNA expression improved neither progression-free survival nor overall survival. The short median overall survival in the control arm (8.4 months vs 13.3 months with chemotherapy alone in the AURELIA trial in platinum-resistant ovarian cancer[6]) is consistent with a particularly poor prognosis in the low HER3 mRNA-selected population enrolled in PENELOPE.

In subgroup analyses, median overall survival in the control arm was similar in the three chemotherapy cohorts (7.4, 9.5, and 8.8 months with gemcitabine, paclitaxel, and topotecan, respectively). In the gemcitabine and paclitaxel cohorts (but not the topotecan cohort), an overall survival signal for pertuzumab as assessed by the HR was observed, consistent with patterns seen for progression-free survival in the primary analysis.[2]

For the other stratification factors, the effect of pertuzumab on overall survival appeared to be more pronounced in patients not previously exposed to anti-angiogenic therapy and in those with a platinum-free interval of 3–6 (vs <3) months. One might speculate that pertuzumab may be of more interest in patients with a longer platinum-free interval. However, results were also negative from a previous prospective randomized phase 2 trial of pertuzumab in the platinum-sensitive ovarian cancer setting.[8] Furthermore, owing to the small patient numbers and imbalances in baseline characteristics, valid interpretation of these post hoc subgroup results is limited. The main conclusion should be based on the intent-to-treat population, which showed no significant overall survival benefit from pertuzumab.

Compliance with questionnaire completion was high. However, pertuzumab plus chemotherapy demonstrated neither beneficial nor detrimental effects on patient-reported outcomes compared with placebo plus chemotherapy for platinum-resistant ovarian cancer, except for increased diarrhea symptoms. The effect of diarrhea on patient-reported outcomes is consistent with the

Table 2 Summary of overall survival results

Patient subgroup		Unstratified overall survival HR (95% CI)	No. of overall survival events/ patients (%)		Median overall survival (months)	
			Pertuzumab + chemotherapy	Placebo + chemotherapy	Pertuzumab + chemotherapy	Placebo chemotherapy
All patients (n=156)		0.76 (0.54 to 1.08)	62/78 (79)	68/78 (87)	10.2 (95% CI 6.7 to 15.2)	8.4 (95% CI 6.1 to 12.0)
Selected chemotherapy	Gemcitabine (n=53)	0.58 (0.32 to 1.06)	21/27 (78)	24/26 (92)	7.8	7.4
	Paclitaxel (n=54)	0.74 (0.41 to 1.36)	20/26 (77)	23/28 (82)	15.2	9.5
	Topotecan (n=49)	1.05 (0.57 to 1.93)	21/25 (84)	21/24 (88)	6.2	8.8
Prior anti-angiogenic therapy	Yes (n=57)	1.22 (0.69 to 2.14)	25/27 (93)	26/30 (87)	6.2	9.6
	No (n=99)	0.61 (0.39 to 0.95)	37/51 (73)	42/48 (88)	14.2	7.8
Platinum-free interval, months	<3 (n=40)	1.12 (0.57 to 2.20)	16/19 (84)	18/21 (86)	7.0	8.5
	3–6 (n=116)	0.69 (0.46 to 1.04)	46/59 (78)	50/57 (88)	12.0	8.4

physician-reported higher incidence of diarrhea adverse events (grade ≥3 in 14% of pertuzumab-treated patients vs 1% of the placebo group).

The symptoms most frequently considered to be worst in the PENELOPE population were abdominal pain, fatigue, trouble sleeping, abdominal bloating, and pain, consistent with findings from stage I of the Gynecologic Cancer InterGroup Symptom Benefit Study.[1] In platinum-resistant ovarian cancer, patients typically have substantial symptoms, theoretically making it easier to demonstrate or detect an improvement in patient-reported outcomes. Nevertheless, few trials in platinum-resistant ovarian cancer have shown an impact of treatment on symptoms. The main exception is the AURELIA trial in an unselected population of patients with platinum-resistant ovarian cancer. In AURELIA, the addition of bevacizumab to chemotherapy was associated with a significant improvement in abdominal/gastrointestinal symptoms, the predefined primary patient-reported outcome end point.[7] This amelioration of abdominal/gastrointestinal symptoms may reflect the efficacy of bevacizumab-containing regimens and their effect on tumor shrinkage and ascites control: adding bevacizumab to single-agent chemotherapy more than doubled the response rate (31% vs 13% with chemotherapy alone by Response Evaluation Criteria in Solid Tumors and/or Gynecologic Cancer InterGroup cancer antigen-125 criteria; 27% vs 11% by Response Evaluation Criteria in Solid Tumors),[6] indicating a substantial effect on tumor burden and symptoms. In contrast, PENELOPE showed no difference in response rate with the addition of pertuzumab to chemotherapy (13% vs 9% by Response Evaluation Criteria in Solid Tumors by independent review committee).[2] This lack of effect on response (and the lack of significant progression-free survival improvement) seems the most likely explanation for the absence of impact on patient-reported outcomes in PENELOPE.

Recent exploratory analyses of the AURELIA dataset suggested that baseline symptoms are independent prognostic factors for outcome. Both physical function and abdominal/gastrointestinal symptoms appeared to be independent prognostic factors for overall survival.[9] Interestingly, the mean abdominal/gastrointestinal symptom scores in PENELOPE were very similar to those in the AURELIA trial (investigational arm: 33.5 vs 32.3, respectively; control arm: 29.6 in both trials). However, overall survival was shorter in PENELOPE than in AURELIA, as mentioned above.

In conclusion, despite hints of activity in some cohorts, the addition of pertuzumab to chemotherapy did not significantly improve overall survival (key secondary end point) in the PENELOPE trial. Likewise, the patient-reported outcome analyses described here show no benefit from the addition of pertuzumab to chemotherapy in this biomarker-selected platinum-resistant ovarian cancer population. However, they do provide insight into the disease symptoms considered most troublesome to patients. There is widespread agreement on the importance of evaluating patient-reported outcomes in clinical trials.[10] Use of the Measure of Ovarian Symptoms and Treatment (version 2), which includes a multi-item scale focusing on abdominal symptoms, should be considered for the assessment of patient-reported outcomes in future trials in platinum-resistant ovarian cancer.[11] Additional insight into this difficult-to-treat population may be gained from evaluation of the extensive tumor sample collection amassed in PENELOPE. Gene mutational analyses may provide important insight into the biology of this subset of platinum-resistant ovarian cancer, which could help in identifying new candidate targeted therapies for these patients with such a poor prognosis.[12] Although the primary objective was not met, results from PENELOPE nevertheless provide important new information in platinum-resistant ovarian cancer.

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Competing interests DL has participated in advisory boards for Roche, AstraZeneca, Clovis, Merck and Tesaro; her institution has received research support from Clovis, PharmaMar and Merck. FH has a consultant and advisory relationship with Roche, AstraZeneca and MSD. AGM has consulting and advisory relationships with Roche, Tesaro, AstraZeneca, Pfizer, Clovis, PharmaMar and ImmunoGen. PO has a consulting or advisory role with Novartis, GSK, MSD, Clovis and Tesaro. FS has served as a consultant for Roche and Tesaro. NC has received personal fees from AstraZeneca, Clovis, Tesaro, Roche, PharmaMar, Takeda and Pfizer. BP has participated in advisory boards for Clovis and Tesaro. IV has participated in advisory boards for Advaxis Inc, Eisai Inc, MSD Belgium, Roche NV, Genmab A/S, F. Hoffmann-La Roche Ltd, PharmaMar, Millennium Pharmaceuticals, Clovis Oncology Inc, AstraZeneca NV, Novocure GMBH, Morphotek Inc, Mateon Therapeutics Inc, Immunogen Inc, Eli Lilly Benelux NV, Amgen Inc, Pfizer Inc, Vifor Pharma België NV, Novartis Pharma AG, Oxigene Inc, Nektar Therapeutics and Bayer Pharma AG, has contract research (via K U Leuven) with Oncoinvent AS and Genmab A/S – Genmab B.V., has received grants for corporate-sponsored research from Amgen and Roche, and has received accommodation/travel expenses from Takeda Oncology, PharmaMar, Genmab, Roche and AstraZeneca. AR has consultant and advisory roles with Roche, Tesaro, AstraZeneca, Clovis, PharmaMar, Amgen, Lilly and Novartis, and research funding from Roche, PharmaMar and Eisai. AC and LB-T are employees of and shareholders in Roche. AdB has a consulting and advisory relationship with AstraZeneca, Roche, Tesaro, Pfizer, Clovis, PharMar and Genmab. CK has a consultant and advisory relationships with Roche, AstraZeneca, Tesaro and Genomic Health. All remaining authors have declared no conflicts of interest.

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