Avelumab alone or in combination with chemotherapy vs chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): a randomised, open-label, phase 3 study

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Abstract

Background: Most patients with ovarian cancer will relapse after receiving frontline platinum-based chemotherapy and eventually develop platinum-resistant or platinum-refractory disease. We report results of avelumab alone or avelumab plus pegylated liposomal doxorubicin (PLD) compared with PLD alone in patients with platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200 trial).

Methods: In this open-label, phase 3 trial, eligible women aged ≥18 years with epithelial ovarian, fallopian tube, or peritoneal cancer (maximum of 3 prior lines for platinum-sensitive disease, none for platinum-resistant disease) and an Eastern Cooperative Oncology Group performance status of 0 or 1 were randomised (1:1:1) via interactive response technology to avelumab (10 mg/kg intravenously every 2 weeks), avelumab plus PLD (40 mg/m^2 intravenously every 4 weeks), or PLD and stratified by disease platinum status (refractory vs resistant), number of prior anticancer regimens (1 vs 2 or 3), and bulky disease (tumour size ≥5 vs <5 cm). Primary endpoints were progression-free survival by blinded independent central review and overall survival in all randomised patients, with the objective to demonstrate that avelumab alone or avelumab plus PLD would be superior to PLD. This trial is registered with ClinicalTrials.gov, number NCT02580058. The trial is no longer enrolling patients and this is the final analysis of both primary endpoints.

Findings: Between January 5, 2016 and May 16, 2017, 566 patients were randomised. At data cutoff (September 19, 2018), median duration of follow-up for overall survival was 18·4 months (interquartile range [IQR] 15·6–21·9) for the combination arm, 17·4 months (IQR 15·2–21·3) for the PLD arm, and 18·2 months (IQR 15·8–21·2) for the avelumab arm. Improvement in progression-free survival by blinded independent central review or overall survival with avelumab plus PLD vs PLD alone did not reach statistical significance (hazard ratios, 0·78 [repeated CI 0·59–1·24; one-sided P=0·030] and 0·89 [repeated CI 0·74–1·24; one-sided P=0·21]). Avelumab alone did not improve progression-free survival by blinded

independent central review or overall survival vs PLD (hazard ratios, 1·68 [repeated CI 1·32–2·60; one-sided P>0·99] and 1·14 [repeated CI 0·95–1·58; one-sided P=0·83]). Progression-free survival rates at 12 months were 18% (95% CI 12–25) in the combination arm, 9% (95% CI 5–16) in the PLD arm, and 6% (95% CI 3–11) in the avelumab arm; 12-month overall survival rates were 60% (95% CI 52–67), 57% (95% CI 49–64), and 49% (95% CI 42–57), respectively. In the combination, PLD, and avelumab arms, grade ≥3 treatment-related adverse events occurred in 78 (43%) of 182 patients, 56 (32%) of 177 patients, and 30 (16%) of 187 patients, respectively. The most common grade 3–4 treatment-related adverse events (≥5% of patients) were palmar-plantar erythrodysaesthesia syndrome (18 [10%] in the combination arm, 9 [5%] in the PLD arm, 0 [0%] in the avelumab arm), rash (11 [6%], 3 [2%], 0 [0%]), fatigue (10 [5%], 3 [2%], 0 [0%]), stomatitis (10 [5%], 5 [3%], 0 [0%]), anaemia (6 [3%], 9 [5%], 3 [2%]), and neutropenia (9 [5%], 9 [5%], 0 [0%]). Serious treatment-related adverse events occurred in 32 patients (18%) in the combination arm, 19 (11%) in the PLD arm, and 14 (7%) in the avelumab arm. Treatment-related adverse events resulted in death in 2 patients (sepsis [PLD arm] and intestinal obstruction [avelumab arm]).

Interpretation: The trial did not meet its primary objectives of significantly improving progression-free survival or overall survival with avelumab plus PLD or avelumab alone vs PLD. These results provide insights for patient selection in future studies of immune checkpoint inhibitors in platinum-resistant or platinum-refractory ovarian cancer.

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Research in context

Evidence before this study

Although most patients with ovarian cancer respond to frontline treatment, approximately 70% relapse within 3 years. Immunologic activity appears to be an important determinant of patient outcomes in ovarian cancer. Additionally, randomised trials in other tumours (eg, NSCLC and triple-negative breast cancer) demonstrate the potential for increased efficacy by combining anti–PD-1/PD-L1 agents with chemotherapy. We conducted a literature search using PubMed on February 3, 2021, using the terms (“ovarian cancer”) AND (“PD-1” OR “PD-L1” OR “programmed death” OR “checkpoint inhibitor”) AND (“study” OR “trial”) for clinical trials of immune checkpoint inhibitors in ovarian cancer published in English. We identified 13 manuscripts reporting data from phase 1–2 trials in various ovarian cancer populations (5 phase 1 and 7 phase 2 trials). These trials investigated immune checkpoint inhibitors as monotherapy and in combination with other agents. Results from these trials suggest that immune checkpoint inhibitor monotherapy has modest but encouraging antitumour activity, with preliminary data suggesting improved activity with combinations. One phase 2 study reported a numerically higher response rate in tumours with higher vs lower tumour PD-L1 expression (KEYNOTE-100).

Added value of this study

To our knowledge, this is the first phase 3 trial of an immune checkpoint inhibitor in patients with ovarian cancer to be reported. JAVELIN Ovarian 200 failed to meet its primary objectives of significantly improving progression-free survival or overall survival with avelumab or avelumab plus PLD vs PLD in patients with platinum-resistant or platinum-refractory ovarian cancer. No new safety signals were observed with avelumab as monotherapy or in combination with PLD.

Implications of all the available evidence

Although the JAVELIN Ovarian 200 trial failed to show a significant progression-free survival or overall survival benefit in the overall population, results from this trial provide insights for patient selection in future studies of immune checkpoint inhibitors in the treatment of platinum-resistant or platinum-refractory ovarian cancer.

Introduction

Patients with platinum-resistant or platinum-refractory ovarian cancer have a poor prognosis and limited treatment options. Standard treatment involves sequential nonplatinum chemotherapy, which is associated with low objective response rates (≤15%), short progression-free survival (median, 3–4 months), and limited life expectancy (≤12 months).[1]

The immune system has a critical role in the evolution of ovarian cancer.[2,3] Tumour-infiltrating lymphocytes, specifically CD8+ T cells, are associated with a better prognosis.[4] However, immunosuppressive cells (eg, regulatory T and myeloid-derived suppressor cells) are often present in the ovarian cancer tumour microenvironment,[5,6] and programmed death ligand 1 (PD-L1), a key suppressor of T-cell function, is expressed on ovarian tumour cells and tumour-infiltrating lymphocytes in ≥50% of patients.[7] Avelumab, a human anti–PD-L1 antibody, showed antitumour activity as monotherapy in a phase 1b study of 125 patients with heavily pretreated recurrent or refractory ovarian cancer, demonstrating an objective response rate of 10% and median overall survival of 11·2 months.[8] Chemotherapy, including doxorubicin, can promote immune priming by enhancing antigen presentation[9,10] and modifying the suppressive microenvironment, increasing infiltration of active T cells.[2] Therefore, chemotherapy could enhance the activity of PD-L1 blockade, as seen in preclinical studies[11] and several trials in other tumours.[12–15]

Here, we report results from the final analysis of the randomised, open-label, phase 3 JAVELIN Ovarian 200 trial, which compared avelumab monotherapy or avelumab plus pegylated liposomal doxorubicin (PLD) with PLD alone in patients with platinum-resistant or platinum-refractory ovarian cancer, including prespecified biomarker analyses. To our knowledge, this is the first phase 3 trial of an immune checkpoint inhibitor in ovarian cancer to be reported.

Methods

Study design and participants

JAVELIN Ovarian 200 was a global, open-label, parallel three-arm, phase 3 trial performed at 149 hospitals and cancer treatment centres in 24 countries (Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Greece, Hong Kong, Hungary, Ireland, Israel, Japan, Netherlands, Norway, Poland, Russia, Singapore, South Korea, Spain, Switzerland, Taiwan, UK, and USA). Eligible patients were aged ≥18 years and had histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer (including malignant mixed Müllerian tumours with a high-grade serous component); either platinum-resistant disease (defined as progression within 180 days following last platinum dose) or platinum-refractory disease (defined as progression or no response during last platinum-based therapy); a maximum of 3 prior lines for platinum-sensitive disease (most recent line containing platinum) with no prior systemic therapy for platinum-resistant disease; ≥1 nonirradiated lesion measurable by Response Evaluation Criteria in Solid Tumors (RECIST), version 1·1; Eastern Cooperative Oncology Group performance status of 0 or 1; life expectancy of ≥3 months; negative pregnancy test and use of effective contraception (women of childbearing potential); and adequate haematologic (absolute neutrophil count ≥1·5×10^9 per L, platelet count ≥100×10^9 per L, and haemoglobin ≥9 g per dL), hepatic (total bilirubin concentration ≤1·5×upper limit of normal and aspartate and alanine aminotransferase concentrations ≤2·5×upper limit of normal), and renal (creatinine clearance ≥50 mL/min according to the Cockcroft-Gault equation) function. A tumour biopsy, taken before study treatment or ≤3 months before enrolment with no intervening treatment, was required. Exclusion criteria included nonepithelial tumour or tumour with low malignant potential (ie, borderline tumour), prior immune checkpoint inhibitor treatment, and PLD-resistant disease (defined as lack of response or progression within 6 months of the last dose of PLD). Full eligibility criteria are provided in the protocol (appendix p 37).

The trial was conducted in accordance with the ethics principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines on Good Clinical Practice. The protocol was approved by the institutional review board or independent ethics committee of each centre or country. All patients provided written informed consent before enrolment.

Randomisation and masking

Patients were enrolled by study investigators and were randomly assigned (1:1:1) via interactive response technology to receive either avelumab, avelumab plus PLD, or PLD (stratified permuted block randomisation with a block size of six). Randomisation was stratified by disease platinum status (refractory vs resistant), number of prior anticancer regimens (1 vs 2 or 3), and bulky disease (tumour size ≥5 vs <5 cm). The trial was open-label, so neither patients nor investigators were masked to treatment allocation.

Procedures

Avelumab 10 mg/kg was administered by 1-hour intravenous infusion every 2 weeks. PLD 40 mg/m^2 was administered by 1-hour intravenous infusion every 4 weeks. Antihistamine and acetaminophen premedication was mandatory 30 to 60 minutes before avelumab infusions but optional before PLD infusions. For the combination arm, PLD was infused before avelumab, and premedication could be repeated at the investigator's discretion. Avelumab dose adjustment was not permitted; the PLD dose could be reduced following significant toxicity based on investigator judgment. Treatment was given until disease progression (confirmed by blinded independent central review [BICR]), unacceptable toxicity, global deterioration of health status, pregnancy, significant protocol deviation, patient refusal, loss to follow up, termination of the study by the sponsor, or death (appendix, p 37). Because of the potential for pseudoprogression (ie, increase in tumor burden observed in a radiologic assessment that is not confirmed as disease progression in the subsequent assessment), avelumab monotherapy could be continued beyond disease progression if the

investigator judged that the patient was experiencing clinical benefit. Crossover between study arms was not permitted.

Tumours were assessed by computed tomography or magnetic resonance imaging at baseline and every 8 weeks until disease progression, irrespective of subsequent anticancer therapy. Objective tumour response was evaluated per RECIST 1·1 based on BICR. Complete and partial responses and progressive disease were confirmed by repeated imaging performed ≥4 weeks after initial documentation. Safety assessments occurred at each treatment visit, end of treatment, and at safety follow-up visits (day 30, 60, and 90). Blood samples were taken at each trial visit (every 2 weeks) for routine laboratory analyses, including core serum chemistry, haematology, and haemostaseology. Urine samples were taken at screening and on day 1 of cycle 1 for urinalysis. Adrenocorticotropic hormone, free thyroxine, and thyroid-stimulating hormone concentrations were tested prior to treatment, every 8 weeks for 2 additional measurements, and then every 12 weeks thereafter while on treatment. Adverse events (AEs) and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Immune-related AEs and infusion-related reactions were identified using a prespecified list of terms in the Medical Dictionary for Regulatory Activities. PD-L1 and CD8 expression was assessed in pretreatment tissue samples (archival or de novo) at a central laboratory via immunohistochemistry using assays based on the SP263 (Ventana Medical Systems) and C8/144B antibodies, respectively. Selection of the PD-L1 cutoff was based on post hoc analyses of several cutoffs and scoring algorithms, including the combined positive score algorithm, and the optimal cutoff for predicting improved activity for the combination vs PLD was selected. A sample was considered PD-L1+ if ≥1% of assessed tumour cells expressed membranous PD-L1 and/or ≥5% of immune cells within the tumour area expressed PD-L1. Several cutoffs for CD8 expression were assessed. A sample was considered CD8+ if ≥1% of cells within the tumour area expressed CD8; this cutoff was found to be close to the median CD8 expression in this study and was the most predictive cutoff identified.

Patient-reported outcome questionnaires European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30), and its corresponding module for ovarian cancer, EORTC QLQ–Ovarian Cancer 28 (EORTC QLQ-OV28) were administered on day 1 of every cycle, and at the end of treatment visit and safety follow-up visits (days 30, 60, and 90) prior to any other study participation or medical procedures. The questionnaires were scored in accordance with EORTC guidelines[16] and were considered completed if ≥1 item was completed.

An external data monitoring committee was established to review safety and efficacy data from the trial. Protocol deviations are summarized in the appendix (p 26); however, none were determined to have had a meaningful impact on safety or efficacy results.

Outcomes

This trial had two primary endpoints: progression-free survival by BICR (defined as the time from randomisation to the date of the first documented disease progression per RECIST 1·1 or death due to any cause, whichever occurred first) and overall survival (defined as the time from randomisation to the date of death due to any cause). Progression-free survival by BICR was added as a primary endpoint via a protocol amendment (December 15, 2016) because an improvement of overall survival may have been difficult to observe in a population with long duration of survival post progression due to post-study treatments. Secondary endpoints included objective response (defined as complete or partial response per RECIST 1·1), duration of response (defined for patients with an objective response as the time from first documentation of complete or partial response to the first documentation of disease progression per RECIST 1·1 or death due to any cause, whichever occurred first), and disease control (defined as complete or partial response or stable disease per RECIST 1·1) by BICR and investigator; progression-free survival by investigator per RECIST 1·1; safety and tolerability; pharmacokinetic parameters; immunogenicity of avelumab; tumour biomarker assessments; and patient-reported outcomes. Pharmacokinetic parameters and

immunogenicity of avelumab have not yet been fully analysed and are not reported in this manuscript.

Statistical Analysis

The trial aimed to demonstrate superiority of avelumab alone or avelumab plus PLD in prolonging progression-free survival by BICR or overall survival compared with PLD in all randomised patients. There were two independent comparisons (avelumab vs PLD and avelumab plus PLD vs PLD) for each of the two primary endpoints (progression-free survival by BICR and overall survival). The study used a two-look group-sequential design with a Lan-DeMets (O'Brien-Fleming) alpha-spending function to determine the efficacy boundary and a gamma-family beta-spending function to determine the nonbinding futility boundary, with one interim analysis and one final analysis. The overall type I error rate was maintained at or below a one-sided significance level of 0·025 by allocating an alpha level of 0·0115 to each overall survival comparison and 0·001 to each progression-free survival comparison. We planned to enrol around 550 patients. For each overall survival comparison, an estimated 196 events (deaths) provided ≥90% power to detect a hazard ratio (HR) of 0.6 using a one-sided stratified log-rank test (assumed median overall survival: ≥20 months for experimental arms, 12 months for PLD). For each progression-free survival comparison, an estimated 325 events provided ≥93% power to detect a HR of 0·6 using a one-sided stratified log-rank test (assumed median progression-free survival: ≥5·8 months for experimental arms, 3·5 months for PLD). An interim analysis was planned after approximately 131 (67%) of the 196 overall survival events and 267 (82%) of the 325 progression-free survival events had occurred within each comparison. The final analysis was planned after all patients had been followed for ≥12 months and ≥196 overall survival events and ≥325 progression-free survival events had occurred within each comparison.

Efficacy analyses were performed in all patients who were randomised to study treatment (intention-to-treat population) and safety analyses were performed in all patients who

received at least one dose of study treatment. Progression-free survival, overall survival, and duration of response were summarised using the Kaplan-Meier method. The Cox proportional hazards model was used to estimate HRs and corresponding CIs. Primary analyses of progression-free survival by BICR and overall survival were stratified per randomisation strata. To account for the group-sequential design (ie, multiple sequential analyses of the primary endpoints), two-sided repeated CIs (RCIs) were constructed for HRs in primary endpoints. The proportional hazards assumption was checked visually for the primary endpoints by plotting log(−log[overall survival or progression-free survival]) vs log(time) within each randomisation stratum. Additionally, Schoenfeld residuals, including a locally weighted smoothing (LOESS) curve, were plotted to investigate graphically violations of the proportional hazards assumption. Objective response rates were estimated for each treatment arm, along with two-sided 95% CIs using the Clopper-Pearson method. Association between treatment and objective response was assessed by the general association statistic of the Cochran-Mantel-Haenszel test. Prespecified subgroup analyses of progression-free survival by BICR and overall survival were performed using a 2-sided unstratified log-rank test. Statistical analyses were performed in SAS (version 9·4). This study is registered with ClinicalTrials.gov, number NCT02580058.

Role of the funding source

The trial was sponsored by Pfizer as part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany. The sponsors provided the study drugs, worked with a study steering committee to design the trial and collect, analyse, and interpret the data, and provided funding for a professional medical writer with access to the data. All authors had access to the data reported and the lead and senior authors (EPL and BJM) and co-authors who were employees of the sponsor (FZ, RAS, CW, and SSD) had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication. All authors contributed to subsequent drafts and provided final approval to submit the manuscript for publication.

Results

Between January 5, 2016 and May 16, 2017, 566 patients were enrolled and randomly assigned to the avelumab plus PLD (n=188), PLD (n=190), or avelumab (n=188) arms (figure 1). Baseline characteristics were well balanced between arms (table 1). Most patients (393 [69%]) had high-grade serous histology and 73 (13%) had clear cell histology. Around half of patients (273 [48%]) had primary resistant disease (ie, only one prior line of therapy), 210 (37%) had bulky disease, and 142 (25%) had platinum-refractory disease. A prespecified interim analysis was conducted after ≥73% of the target number of events had occurred in all four primary endpoint comparisons (data cutoff, January 23, 2018). Comparing avelumab with PLD, the futility boundary was crossed for both progression-free survival by BICR and overall survival (appendix p 27). Comparing the combination with PLD, the futility boundary was crossed for progression-free survival by BICR but not for overall survival. Because three of four primary endpoint comparisons had crossed the futility boundary, the final analysis of these three endpoints was rendered exploratory in nature, and P values are reported for descriptive purposes only.

At the final analysis (data cutoff, September 19, 2018), median duration of follow-up for overall survival was 18·4 months (interquartile range [IQR] 15·6–21·9) for the combination, 17·4 months (IQR 15·2–21·3) for PLD, and 18·2 months (IQR 15·8–21·2) for avelumab. Median duration of treatment in the combination arm was 16·9 weeks (IQR 9·1–35·9) for avelumab and 16·3 weeks (IQR 8·1–32·0) for PLD; in the PLD arm, it was 16·0 weeks (IQR 8·0–25·0), and in the avelumab arm, it was 10·1 weeks (IQR 7·0–19·4). At data cutoff, trial treatment was ongoing for 10 patients (5%) in the combination arm (5 receiving both drugs; 5 receiving avelumab only), no patients in the PLD arm, and 6 patients (3%) in the avelumab arm. The most frequent primary reason for treatment discontinuation in all arms was progressive disease (figure 1).

Disease progression by BICR or death had occurred in 134 (71%) of 188 patients in the combination arm, 125 (66%) of 190 patients in the PLD arm, and 154 (82%) of 188 patients in the avelumab arm. The stratified HR for progression-free survival by BICR for the combination vs PLD was 0·78 (RCI 0·59–1·24; one-sided P=0·030) and for avelumab vs PLD was 1·68 (RCI 1·32–2·60; one-sided P>0·99). Median progression-free survival by BICR with the combination, PLD, and avelumab was 3·7 months (95% CI 3·3–5·1), 3·5 months (95% CI 2·1–4·0), and 1·9 months (95% CI 1·8–1·9), respectively (figure 2A); 12-month progression-free survival rates were 18% (95% CI 12–25), 9% (95% CI 5–16), and 6% (95% CI 3–11), respectively. The number of patients who had died was 102 (54%) of 188 patients in the combination arm, 104 (55%) of 190 patients in the PLD arm, and 109 (58%) of 188 patients in the avelumab arm. The stratified HR for overall survival for the combination vs PLD was 0·89 (RCI 0·74–1·24; one-sided P=0·21) and for avelumab vs PLD was 1·14 (RCI 0·95–1·58; one-sided P=0·83). Median overall survival with the combination, PLD, and avelumab was 15·7 months (95% CI 12·7–18·7), 13·1 months (95% CI 11·8–15·5), and 11·8 months (95% CI 8·9–14·1), respectively (figure 2B); 12-month overall survival rates were 60% (95% CI 52–67), 57% (95% CI 49–64), and 49% (95% CI 42–57), respectively. Tests for the proportional hazard assumption for each treatment arm comparison for both progression-free survival by BICR and overall survival indicated that hazards were nonproportional in the comparisons of avelumab vs PLD (P=0·011 and P=0·006, respectively), but not in the comparisons of avelumab plus PLD vs PLD (P=0·36 for both comparisons); however, because no significant differences were observed in these endpoints, interpretation of data was not affected. Prespecified subgroup analyses based on patient and disease characteristics are shown in figure 3 and appendix p 9-13. The number of patients with a confirmed objective response by BICR was 25 (13% [95% CI 9–19]) with the combination, 8 (4% [95% CI 2–8]) with PLD, and 7 (4% [95% CI 2–8]) with avelumab (table 2). Disease control by BICR was achieved in 108 patients (57% [95% CI 50–65]) in the combination arm, 93 (49% [95% CI 42–56]) in the PLD arm, and 62 (33% [95% CI 26–40]) in the avelumab arm. Antitumour activity based on investigator assessment is shown in

the appendix (p 28).The median progression-free survival per investigator assessment was 4·7 months (95% CI 3·7–6·0) for the combination, 3·7 months (95% CI 3·5–5·4) for PLD, and 1·9 months (95% CI 1·8–1·9) for avelumab; 12-month progression-free survival rates by investigator were 17% (95% CI 12–24), 12% (95% CI 7–19), and 5% (95% CI 2–9), respectively.

Prespecified biomarker analyses included assessment of efficacy in subgroups defined by expression of PD-L1 and CD8 in tumours. Of 508 patients evaluable for PD-L1 expression, 288 (57%) had PD-L1+ tumours and 220 (43%) had PD-L1− tumours. Unstratified HRs for progression-free survival by BICR vs PLD in the PD-L1+ subgroup were 0·65 (95% CI 0·46–0·92) for the combination and 1·45 (95% CI 1·03–2·04) for avelumab (appendix p 14). Unstratified HRs for overall survival vs PLD in the PD-L1+ subgroup were 0·72 (95% CI 0·49–1·05) for the combination and 0·83 (95% CI 0·57–1·23) for avelumab (appendix p 14). All comparisons of progression-free survival by BICR and overall survival vs PLD in the PD-L1− subgroup had observed HRs >1 (appendix p 15).

Of 500 patients evaluable for CD8 expression, 228 (46%) had CD8+ tumours and 272 (54%) had CD8− tumours. Unstratified HRs for progression-free survival by BICR vs PLD within the CD8+ subgroup were 0·64 (95% CI 0·44–0·95) for the combination and 1·58 (95% CI 1·09–2·29) for avelumab (appendix p 17). Unstratified HRs for overall survival vs PLD within the CD8+ subgroup were 0·66 (95% CI 0·43–1·02) for the combination and 1·03 (95% CI 0·67–1·57) for avelumab (appendix p 17). All comparisons of progression-free survival by BICR and overall survival vs PLD within the CD8− subgroup had observed HRs >0.9 (appendix p 18).

CD8+ and PD-L1+ populations demonstrated incomplete overlap. Of 495 patients evaluable for both PD-L1 and CD8 status, 174 (35%) were PD-L1+/CD8+, 53 (11%) were PD-L1−/CD8+, 107 (22%) were PD-L1+/CD8−, and 161 (33%) were PD-L1−/CD8−. Unstratified HRs for the combination arm vs PLD in the PD-L1+/CD8+ subgroup were 0·53 (95% CI

0·34–0·83) for progression-free survival by BICR and 0·53 (95% CI 0·32–0·89) for overall survival (appendix p 20 and 23). Unstratified HRs for the combination arm vs PLD in the other PD-L1/CD8 subgroups ranged from 0·89 to 1·43 for progression-free survival by BICR and from 0·92 to 1·31 for overall survival (appendix p 21-22 and 24-25).

No new safety signals were observed for avelumab administered alone or in combination with PLD. AEs of any grade occurred in 180 of 182 patients (99%) in the combination arm, 173 of 177 patients (98%) in the PLD arm, and 180 of 187 patients (96%) in the avelumab arm, including grade 3–5 AEs in 125 (69%), 105 (59%), and 93 (50%), respectively. Treatment-related AEs (TRAEs) of any grade occurred in the combination, PLD, and avelumab arms in 168 (92%), 151 (85%), and 135 (72%), including grade 3–5 TRAEs in 78 (43%), 56 (32%), and 30 (16%), respectively (Table 3 and appendix p 30). Grade 3–5 TRAEs that occurred in ≥5% of patients in the combination arm were palmar-plantar erythrodysesthesia syndrome (PPE; 18 [10%]), rash (11 [6%]), fatigue (10 [5%]), stomatitis (10 [5%]), and neutropenia (9 [5%]) and in the PLD arm were anaemia (9 [5%]), neutropenia (9 [5%]), and PPE (9 [5%]); no grade 3–5 TRAE occurred in >5% of patients in the avelumab arm. Serious TRAEs occurred in 32 patients (18%) in the combination arm, 19 (11%) in the PLD arm, and 14 (7%) in the avelumab arm; those occurring in more than one patient in each arm were pyrexia (5 [3%]), infusion-related reaction (single preferred term; 3 [2%]), fatigue (2 [1%]), nausea (2 [1%]), stomatitis (2 [1%]), dyspnoea (2 [1%]), hypopituitarism (2 [1%]), and PPE (2 [1%]) in the combination arm, vomiting (3 [2%]) and febrile neutropenia (3 [2%]) in the PLD arm, and pyrexia (4 [2%]) and diarrhoea (2 [1%]) in the avelumab arm. Dose reductions, defined as an incomplete infusion with <90% of planned dose given, of avelumab occurred in no patients in the combination arm and in 5 patients (3%) in the avelumab arm; PLD dose was reduced in 47 patients (26%) in the combination arm and 24 patients (14%) in the PLD arm. In the combination, PLD, and avelumab arms, TRAEs led to treatment discontinuation in 8 (4%; both drugs), 13 (7%), and 12 (6%), respectively, and resulted in death in 1 patient (1%) in the PLD arm (sepsis) and 1 patient (1%) in the

avelumab arm (intestinal obstruction). The total number of deaths in treated patients irrespective of relationship to study treatment was 98 (54%) in the combination arm, 103 (58%) in the PLD arm, and 108 (58%) in the avelumab arm; the most common cause of death in all arms was disease progression (51%, 51%, and 49%, respectively).

In the combination, PLD, and avelumab arms, immune-related AEs of any grade occurred in 51 (28%), 8 (5%), and 25 (13%) and led to treatment discontinuation in 10 (5%; either drug), 1 (1%), and 4 (2%), respectively (appendix p 34). No deaths were attributed to immune-related AEs. In the combination, PLD, and avelumab arms, infusion-related reactions (composite term, including several prespecified preferred terms in addition to signs and symptoms of infusion-related reaction) occurred in 30 (16%), 17 (10%), and 38 (20%) and led to discontinuation in 1 (1%), 2 (1%), and 2 (1%), respectively.

Baseline completion rates for the EORTC QLQ-C30 and QLQ-OV28 questionnaires were 98% for the combination arm, 97% for the PLD arm, and 96% for the avelumab arm; completion rates at end of treatment visit were 73%, 69%, and 72%, respectively. The proportions of patients whose scores improved, deteriorated, or remained stable (defined using a 10-point minimally important difference) for both questionnaires are summarised in the appendix p 35. Distributions were generally similar across the three arms.

Discussion

In JAVELIN Ovarian 200, avelumab plus PLD showed clinical activity, but the trial did not meet its primary objectives of significantly prolonging progression-free survival by BICR or overall survival vs PLD in the overall population. Consistent with the poor prognosis in this patient population, approximately 50% of patients in all arms died, experienced disease progression, or withdrew from the study within 2 months of randomisation, although a small subgroup of patients appeared to have more prolonged benefit from treatment; however, this benefit was observed in underpowered subgroup analyses. Efficacy findings for the combination were consistent with early-phase studies of other immune checkpoint inhibitors

combined with PLD in ovarian cancer,[17,18] and results in the avelumab arm were similar to findings in a phase 1b study of avelumab monotherapy.[8]

In subgroup analyses, which included known prognostic characteristics, overall survival analyses for avelumab plus PLD (n=188) vs PLD (n=190) in patients who had received two to three prior treatment regimens (52% of patients) had a HR and corresponding 95% CI below 1, whereas in those with only one prior regimen (48% of patients; ie, those with primary resistant/refractory disease) the HR was above 1. Similarly, in an exploratory analysis of the AURELIA trial of bevacizumab plus chemotherapy vs chemotherapy alone in patients with platinum-resistant ovarian cancer, progression-free survival and overall survival benefits with the addition of bevacizumab were longer in patients with secondary platinum resistance than in those with primary platinum resistance.[19] These findings suggest that different biological mechanisms may drive primary and secondary platinum resistance, which warrants further study. No differences were seen based on tumour histology.

Prespecified biomarker analysis indicated that PD-L1 and/or CD8 expression may predict benefit with avelumab plus PLD treatment in ovarian cancer. In a previous study of pembrolizumab monotherapy in patients with advanced recurrent ovarian cancer, higher PD-L1 expression correlated with higher response;[20] however, a different PD-L1 assay was employed (SP263 here vs 22C3 in the pembrolizumab study) and a slightly different definition of PD-L1 positivity was used (expression in ≥1% of tumour cells and/or ≥5% of immune cells vs combined positive score ≥10, respectively). Additionally, CD8 expression has been shown to predict benefit with immune checkpoint inhibitor treatment in various cancers,[21,22] though to our knowledge, our study is the first to assess its predictive value in ovarian cancer and in a randomised setting where prognostic impact can be accounted for. Furthermore, PD-L1 and CD8 status did not overlap in approximately one-third of patients, and the HRs for combination treatment vs PLD were lower in the subgroup with PD-L1+ and CD8+ tumours than in subgroups defined by only one of these biomarkers, suggesting that the dual positive subgroup may be of particular interest for future studies.

Avelumab administered alone and in combination with PLD showed acceptable safety from a clinical perspective, with no new safety signals seen compared with previous studies.[23,24] Some TRAEs were more frequent in the combination arm, including fatigue, rash, stomatitis, and PPE. In addition, combination treatment vs PLD alone resulted in higher rates of grade ≥3 TRAEs (43% vs 32%, respectively) and serious TRAEs (18% vs 11%, respectively). However, rates of discontinuation due to TRAEs were similar between the combination and PLD arms (4% vs 7%, respectively). Additionally, patient-reported outcomes of quality of life and treatment-related symptom burden were generally similar across all arms.

This trial had several limitations. Firstly, combination treatment involving bevacizumab was not assessed as control treatment; however, because bevacizumab is widely used in the frontline setting, and bevacizumab use is not indicated in patients with prior bevacizumab treatment in various locations, selection of PLD alone as control treatment was considered a reasonable option and enabled wider patient eligibility. Additionally, the study was not designed or powered to show statistical differences in biomarker-defined subgroups, which had small numbers of patients, and P values presented were not adjusted for multiplicity of analyses. Baseline data on BRCA status were not systematically collected during the trial, meaning that the association between BRCA status and outcomes could not be evaluated. Lastly, longer-term efficacy and safety data are not available because the trial was stopped after the final analysis.

In conclusion, the JAVELIN Ovarian 200 trial failed to meet its primary objectives. However, key aspects of the immunobiology of ovarian cancer were explored and, for the first time in a randomised setting, to our knowledge, subpopulations were identified in whom future studies of immune checkpoint inhibitors in combination with PLD should be directed, specifically patients without primary platinum resistance or with PD-L1+ and/or CD8+ tumours.

Contributors

EPL, RK, FZ, RAS, CW, SSD, and BJM contributed to data analysis. EPL, JAL, AMO, RK, I-LR-C, CS, KY, SB, AL, KHJ, RM, FZ, RAS, CW, SSD, and BJM contributed to data interpretation. EPL, KF, JAL, AMO, RK, I-LR-C, GER, CS, KY, SB, AL, AVT, KHJ, RM, S-YP, RAS, CKA, CW, and BJM contributed to data collection. EPL, JAL, AMO, CS, CW, and BJM contributed to study design. EPL, CW, and BJM accessed and verified the data. SSD contributed to study supervision. All authors contributed to writing of the manuscript.

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Data sharing statement

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Declaration of interest

EPL reports personal fees from AstraZeneca, Clovis Oncology, Incyte, Pfizer, Roche, and Tesaro; non-financial support from AstraZeneca, Roche, and Tesaro; and is the chair of ARCAGY-Research. KF reports grants and personal fees from Pfizer during the conduct of the study; and grants and personal fees from AstraZeneca, Chugai Pharma, Eisai, Genmab, Merck & Co., Taiho Pharmaceutical, and Zeria Pharmaceutical; grants from GSK, Immunogen, Lilly, OncoTherapy, and Regeneron; and personal fees from Daiichi Sankyo, Janssen, Kyowa Hakko Kirin, Mochida, Nippon Kayaku, and Novartis outside the submitted work. JAL reports serving as a consultant or advisor for Artios Pharma, AstraZeneca, Clovis Oncology, Eisai, GSK, Merck & Co., Pfizer; has received research funding from AstraZeneca and Merck & Co.; has received honoraria from AstraZeneca, Clovis Oncology, Eisai, and GSK; and has other relationships with Regeneron. AMO has no competing interests. RK reports personal fees from Clovis Oncology, Eisai, GSK, Incyte, and Roche; has received non-financial support from GSK; and grants from Merck & Co. I-LR-C reports personal fees from AstraZeneca, Clovis Oncology, GSK, Merck KGaA, Mersana Therapeutics, and Roche; received grants from Bristol Myers Squibb and GSK; and has received reimbursement for travel and accommodation expenses from AstraZeneca and GSK. GER has no competing interests. CS has no competing interests. KY reports serving as a consultant or advisor for AstraZeneca, Chugai Pharma, Eisai, Novartis, and Takeda; and received honoraria from AstraZeneca, Eisai, Pfizer, Takeda, and Taiho Pharmaceutical. SB reports personal fees from AstraZeneca, Clovis Oncology, Genmab, Immunogen, Merck KGaA, Mersana Therapeutics, Pfizer, Roche, and Tesaro; and has received grants from AstraZeneca, GSK, Merck & Co., and Tesaro. AL reports grants from Pfizer during the conduct of the study; serving as a consultant or advisor for AstraZeneca, BIOCAD, Clovis Oncology, GSK/Tesaro, Merck KGaA, Merck & Co., and Zentalis Pharmaceuticals; and has received reimbursement for travel and accommodation expenses from AstraZeneca, Clovis Oncology, and GSK/Tesaro. AVT has received honoraria and grants from AstraZeneca. KHJ reports

personal fees from AstraZeneca, Celgene, Novartis, Roche, and Takeda Pharmaceuticals. RM has no competing interests. S-YP has no competing interests. CKA has no competing interests. FZ reports employment at and holds stock in Pfizer. RAS reports employment at Pfizer at the time when the study was conducted. CW reports employment at and holds stock in Pfizer. SSD reports employment at Pfizer. BJM reports serving as a consultant or advisor for and has received honoraria from Agenus, Akeso Bio, Aravive, AstraZeneca, Clovis Oncology, Eisai, Elevar Therapeutics, Genmab/Seattle Genetics, GOG Foundation, Gradalis, ImmunoGen, Iovance, Karyopharm, Merck & Co., Mersana Therapeutics, Myriad Pharma, Novocure, Pfizer, Puma Biotechnology, Roche/Genentech, Tesaro/GSK, and VBL Therapeutics; is a member of a speakers' bureau for AstraZeneca, Clovis Oncology, Eisai, Merck & Co., Roche/Genentech, and Tesaro/GSK; and reports employment at McKesson/US Oncology.

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FIGURE LEGENDS

Figure 1. Trial profile.

PLD=pegylated liposomal doxorubicin.

Figure 2. Progression-free survival by BICR and overall survival.

Progression-free survival (Panel A) and overall survival (Panel B) in the overall population. * One-sided log-rank test; † Did not meet significance threshold (<0.0002); ‡ Did not meet significance threshold (<0.0103). BICR=blinded independent central review. PLD=pegylated liposomal doxorubicin.

Figure 3. Forest plots for progression-free survival by BICR (Panel A) and overall survival (Panel B) with avelumab plus PLD vs PLD in baseline subgroups.

Except for the primary analysis (all patients), which was stratified according to randomisation stratification factors, all other analyses presented were unstratified. BICR=blinded independent central review. ECOG PS=Eastern Cooperative Oncology Group performance status. PLD=pegylated liposomal doxorubicin.

TABLES

Table 1. Baseline characteristics.

	Avelumab + PLD (N=188)	PLD (N=190)	Avelumab (N=188)
Median age (IQR), years	60·0 (53·0–67·0)	60·0 (53·0–69·0)	61·0 (53·0–69·5)
ECOG PS, n (%)*			
0	89 (47)	99 (52)	98 (52)
1	98 (52)	91 (48)	88 (47)
≥2	0	0	2 (1)
Region, n (%)			
North America	45 (24)	50 (26)	49 (26)
Western Europe	68 (36)	63 (33)	78 (41)
Eastern Europe	20 (11)	26 (14)	21 (11)
Asia	49 (26)	38 (20)	30 (16)
Australasia	6 (3)	12 (6)	10 (5)
Middle East	0	1 (1)	0
Race, n (%)			
White	133 (71)	135 (71)	148 (79)
Asian	53 (28)	46 (24)	34 (18)
Black or African American	2 (1)	6 (3)	2 (1)
Other†	0	3 (2)	4 (2)
Site of primary tumour, n (%)			
Ovary	167 (89)	157 (83)	162 (86)
Peritoneum	12 (6)	23 (12)	14 (7)
Fallopian tube	9 (5)	10 (5)	12 (6)

Histology, n (%)			
High-grade serous	122 (65)	135 (71)	136 (72)
Low-grade serous	9 (5)	7 (4)	7 (4)
Clear cell	29 (15)	24 (13)	20 (11)
Endometrioid	7 (4)	6 (3)	5 (3)
Mucinous carcinoma	10 (5)	5 (3)	6 (3)
Other epithelial ovarian cancer‡	11 (6)	13 (7)	14 (7)
No. of prior lines of anticancer therapy, n (%)§			
1	91 (48)	91 (48)	91 (48)
2 or 3	97 (52)	99 (52)	97 (52)
Prior bevacizumab, n (%)	49 (26)	53 (28)	63 (34)
Prior PLD, n (%)	3 (2)	2 (1)	1 (1)
Bulky disease (tumour ≥5 cm), n (%)§			
Yes	69 (37)	71 (37)	70 (37)
No	119 (63)	119 (63)	118 (63)
Platinum status, n (%)§			
Resistant	141 (75)	142 (75)	141 (75)
Refractory	47 (25)	48 (25)	47 (25)
Platinum-free interval, n (%)			
0–3 months	79 (42)	84 (44)	88 (47)
>3–6 months	90 (48)	79 (42)	79 (42)
>6 months	3 (2)	2 (1)	3 (2)
Not reported	16 (9)	25 (13)	18 (10)
PD-L1 status, n (%)¶			

Positive	100 (53)	88 (46)	100 (53)
Negative	73 (39)	77 (41)	70 (37)
Not evaluable	15 (8)	25 (13)	18 (10)
CD8 status, n (%)[‖]			
Positive	80 (43)	72 (38)	76 (40)
Negative	91 (48)	92 (48)	89 (47)
Not evaluable	17 (9)	26 (14)	23 (12)

ECOG PS=Eastern Cooperative Oncology Group performance status. IQR=interquartile range. PD-L1=programmed death ligand 1. PLD=pegylated liposomal doxorubicin.

* Not reported for 1 patient in the avelumab plus PLD arm.

† Includes Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, unknown, and other races.

‡ Includes mixed or unspecified histology (adenocarcinoma [n=4]; carcinosarcoma [n=6]; clear cell/endometrioid carcinoma [n=1]; endometrioid carcinoma/clear cell [n=1]; sero/mucinous carcinoma [n=2]; serous carcinoma [grade not specified; n=12]; undifferentiated carcinoma [n=10]; undifferentiated/endometrioid carcinoma [n=1]), or not reported (n=1).

§ Recorded at randomisation.

¶ Based on PD-L1 expression on ≥1% of tumour cells and/or ≥5% of immune cells.

‖ Based on CD8 expression on ≥1% of immune cells.

Table 2. Antitumour activity based on BICR.

	Avelumab + PLD (N=188)	**PLD (N=190)**	**Avelumab (N=188)**
Confirmed best overall response by BICR, n (%)			
Complete response	2 (1)	0	0
Partial response	23 (12)	8 (4)	7 (4)
Stable disease	78 (41)	70 (37)	45 (24)
Non-complete response/non-progressive disease	5 (3)	15 (8)	10 (5)
Progressive disease	60 (32)	61 (32)	101 (54)
Not evaluable	20 (11)*	36 (19)†	25 (13)‡
Objective response rate (95% CI), %	13 (9–19)	4 (2–8)	4 (2–8)
Odds ratio (95% CI)	3·46 (1·46–9·10)	–	0·89 (0·27–2·90)
P value§	0·0018	–	0·8280
Disease control rate (95% CI), %	57 (50–65)	49 (42–56)	33 (26–40)
Median duration of confirmed response (range), months	8.5 (6.1–NE)	13.1 (5.5–NE)	9.2 (6.4–NE)

BICR=blinded independent central review. NE=not estimable. PLD=pegylated liposomal doxorubicin.

* Reasons for response not evaluable: no adequate baseline assessment (in 2 patients), no postbaseline assessments due to early death (in 5 patients) or other reasons (in 9 patients), all postbaseline assessments had overall response of not evaluable (in 2 patients), patient

started new anticancer therapy before first postbaseline assessment (in 1 patient), or patient had stable disease <6 weeks after randomisation (in 1 patient).

† Reasons for response not evaluable: no adequate baseline assessment (in 5 patients), no postbaseline assessments due to early death (in 6 patients) or other reasons (in 18 patients), patient started new anticancer therapy before first postbaseline assessment (in 1 patient), patient had stable disease <6 weeks after randomisation (in 5 patients), or patient had progressive disease >12 weeks after randomisation (in 1 patient).

‡ Reasons for response not evaluable: no adequate baseline assessment (in 5 patients), no postbaseline assessments due to early death (in 8 patients) or other reasons (in 6 patients), patient started new anticancer therapy before first postbaseline assessment (in 1 patient), or patient had stable disease <6 weeks after randomisation (in 5 patients).

§ Test not prespecified in the overall testing strategy; two-sided Cochran-Mantel-Haenszel test.

Table 3. Treatment-related adverse events.

	Avelumab + PLD (n=182)				PLD (n=177)				Avelumab (n=187)			
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Any TRAE, n (%)	90 (49)	70 (38)	8 (4)	0	95 (54)	47 (27)	8 (5)	1 (1)	105 (56)	25 (13)	4 (2)	1 (1)
Nausea	62 (34)	3 (2)	0	0	63 (36)	1 (1)	0	0	25 (13)	0	0	0
Fatigue	50 (27)	10 (5)	0	0	39 (22)	3 (2)	0	0	42 (22)	0	0	0
PPE syndrome	42 (23)	18 (10)	0	0	31 (18)	9 (5)	0	0	1 (1)	0	0	0
Stomatitis	41 (23)	10 (5)	0	0	31 (18)	4 (2)	1 (1)	0	4 (2)	0	0	0
Rash	34 (19)	11 (6)	0	0	13 (7)	3 (2)	0	0	9 (5)	0	0	0
Anaemia	33 (18)	6 (3)	0	0	25 (14)	9 (5)	0	0	16 (9)	3 (2)	0	0
Decreased appetite	32 (18)	1 (1)	0	0	26 (15)	0	0	0	11 (6)	0	0	0
Pyrexia	22 (12)	0	0	0	5 (3)	0	0	0	21 (11)	0	0	0
Mucosal inflammation	21 (12)	3 (2)	0	0	14 (8)	3 (2)	0	0	3 (2)	1 (1)	0	0
Vomiting	20 (11)	1 (1)	0	0	25 (14)	3 (2)	0	0	15 (8)	1 (1)	0	0
Pruritus	19 (10)	0	0	0	6 (3)	0	0	0	7 (4)	0	0	0
Diarrhoea	18 (10)	1 (1)	0	0	20 (11)	0	0	0	19 (10)	5 (3)	0	0
Infusion-related reaction*	18 (10)	1 (1)	0	0	13 (7)	0	1 (1)	0	13 (7)	0	0	0
Asthenia	17 (9)	4 (2)	0	0	8 (5)	1 (1)	0	0	8 (4)	0	0	0
Neutropenia	15 (8)	7 (4)	2 (1)	0	17 (10)	7 (4)	2 (1)	0	0	0	0	0
Constipation	14 (8)	0	0	0	17 (10)	0	0	0	6 (3)	0	0	0
WBC count decreased	10 (5)	5 (3)	0	0	10 (6)	4 (2)	1 (1)	0	3 (2)	0	0	0
Neutrophil count decreased	9 (5)	7 (4)	1 (1)	0	3 (2)	6 (3)	1 (1)	0	3 (2)	0	0	0
Rash maculopapular	9 (5)	5 (3)	0	0	8 (5)	1 (1)	0	0	3 (2)	0	0	0
Lymphocyte count decreased	6 (3)	5 (3)	0	0	3 (2)	1 (1)	0	0	0	0	0	0
Hyponatraemia	4 (2)	1 (1)	0	0	1 (1)	0	1 (1)	0	1 (1)	3 (2)	0	0
Leukopenia	3 (2)	1 (1)	0	0	4 (2)	3 (2)	0	0	1 (1)	0	0	0
Febrile neutropenia	0	0	1 (1)	0	0	1 (1)	2 (1)	0	0	0	0	0

* Single preferred term

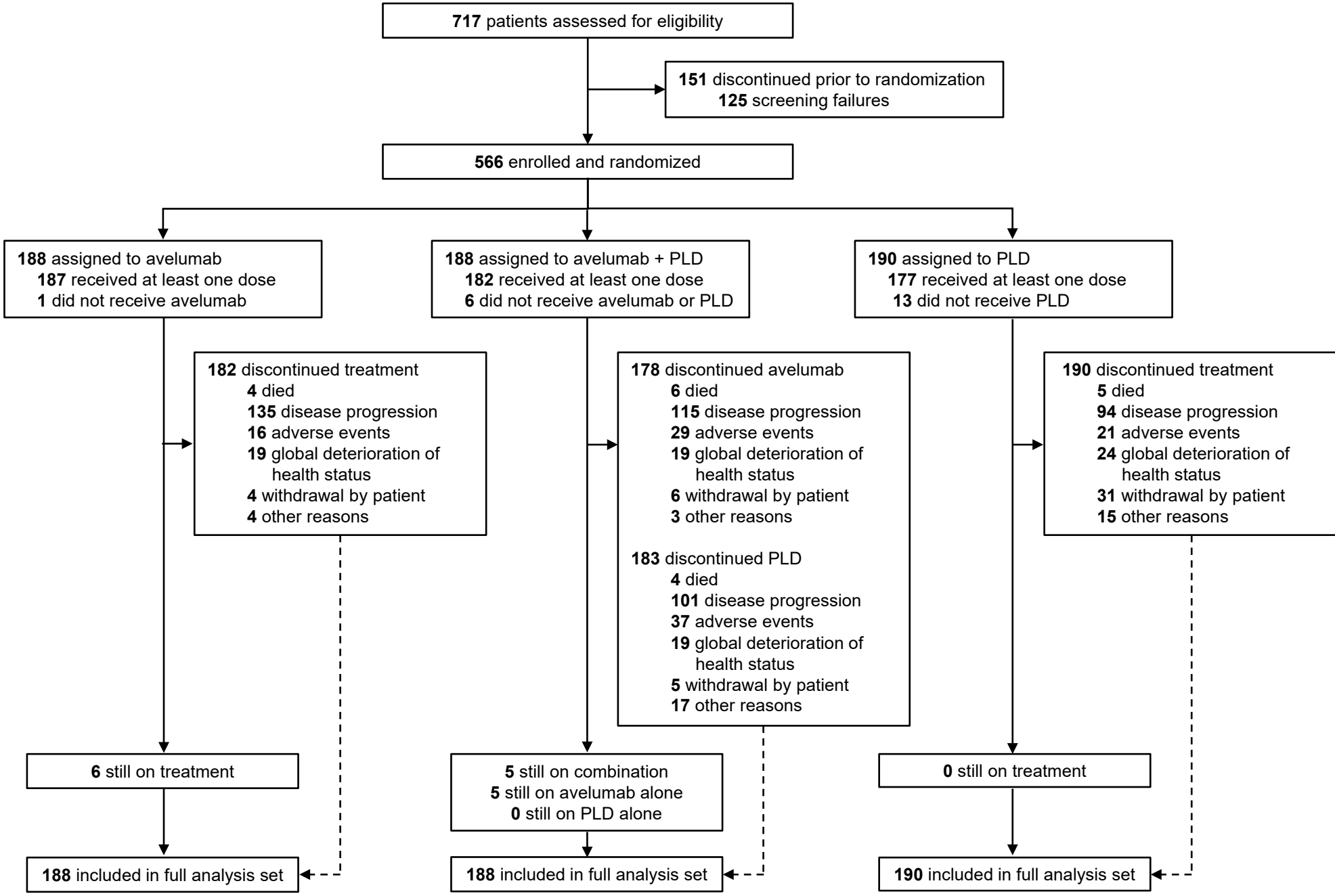
41 PLD=pegylated liposomal doxorubicin. PPE=palmar-plantar erythrodysaesthesia syndrome. TRAE=treatment-related adverse event.

42 WBC=white blood cell.

43 TRAEs of grade 1–2 occurring in ≥10% of patients and grade 3–5 occurring in ≥2% of patients are shown.

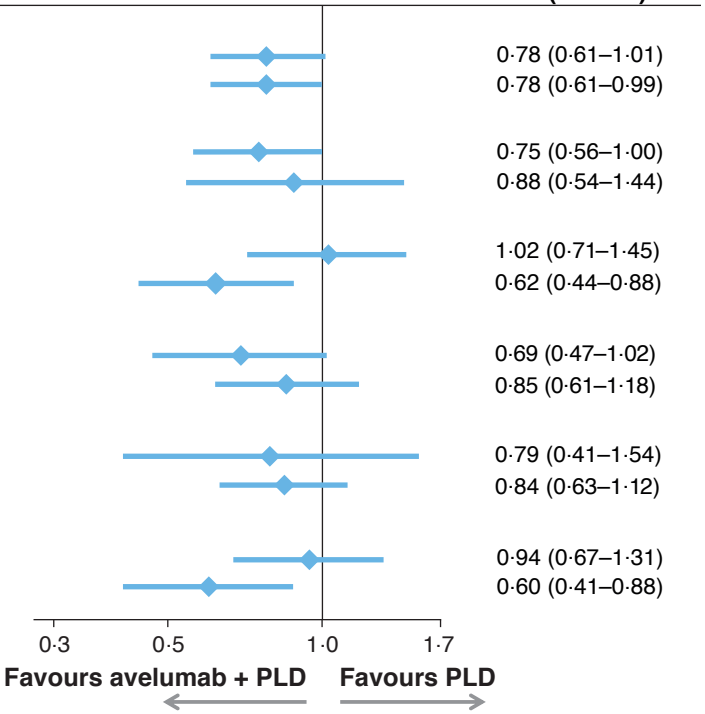
44

45


717 patients assessed for eligibility
151 discontinued prior to randomization
125 screening failures
566 enrolled and randomized
188 assigned to avelumab
187 received at least one dose
1 did not receive avelumab
188 assigned to avelumab + PLD
182 received at least one dose
6 did not receive avelumab or PLD
190 assigned to PLD
177 received at least one dose
13 did not receive PLD
182 discontinued treatment
4 died
135 disease progression
16 adverse events
19 global deterioration of health status
4 withdrawal by patient
4 other reasons
178 discontinued avelumab
6 died
115 disease progression
29 adverse events
19 global deterioration of health status
6 withdrawal by patient
3 other reasons
183 discontinued PLD
4 died
101 disease progression
37 adverse events
19 global deterioration of health status
5 withdrawal by patient
17 other reasons
190 discontinued treatment
5 died
94 disease progression
21 adverse events
24 global deterioration of health status
31 withdrawal by patient
15 other reasons
6 still on treatment
5 still on combination
5 still on avelumab alone
0 still on PLD alone
0 still on treatment
188 included in full analysis set
188 included in full analysis set
190 included in full analysis set

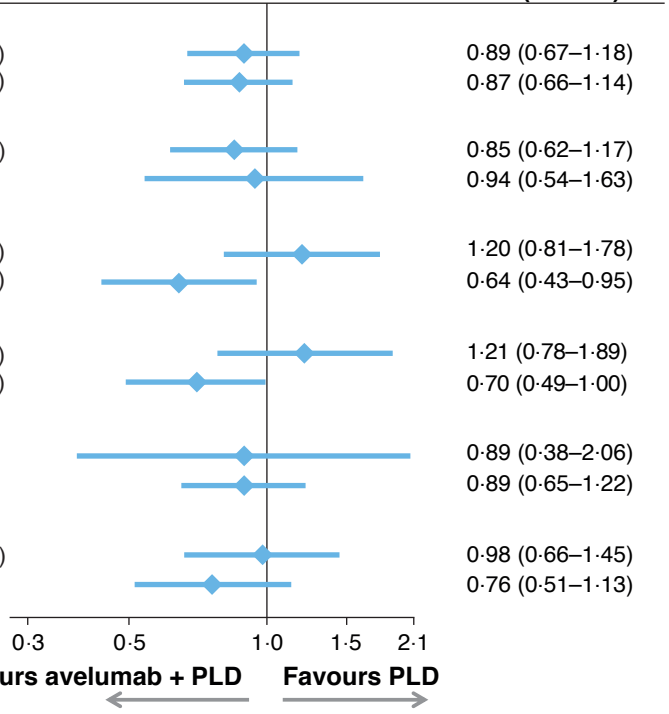
Forest_PFS

	No. of PFS events/No. of patients		Median PFS (95% CI), months		
	Avelumab + PLD	PLD	Avelumab + PLD	PLD	HR (95% CI)
All patients					
Stratified	134/188	125/190	3·7 (3·3–5·1)	3·5 (2·1–4·0)	0·78 (0·61–1·01)
Unstratified	134/188	125/190	3·7 (3·3–5·1)	3·5 (2·1–4·0)	0·78 (0·61–0·99)
Platinum status					
Platinum-resistant	100/141	92/142	3·8 (3·5–5·4)	3·6 (2·1–4·1)	0·75 (0·56–1·00)
Platinum-refractory	34/47	33/48	2·4 (1·9–5·6)	3·2 (1·8–5·5)	0·88 (0·54–1·44)
Prior regimens					
1	69/91	57/91	2·2 (1·9–3·7)	3·6 (1·9–5·5)	1·02 (0·71–1·45)
2 or 3	65/97	68/99	4·9 (3·7–7·4)	3·3 (1·9–4·7)	0·62 (0·44–0·88)
Bulky disease					
Yes	50/69	56/71	3·7 (1·9–6·4)	1·9 (1·8–3·6)	0·69 (0·47–1·02)
No	84/119	69/119	3·7 (3·3–5·6)	3·8 (3·3–5·6)	0·85 (0·61–1·18)
Histology					
Clear cell	24/29	15/24	2·8 (1·8–4·9)	2·1 (1·8–4·1)	0·79 (0·41–1·54)
Serous	97/137	95/147	3·9 (3·5–5·6)	3·6 (3·1–5·4)	0·84 (0·63–1·12)
ECOG PS					
0	74/98	66/101	3·7 (2·2–5·1)	3·6 (2·0–5·4)	0·94 (0·67–1·31)
≥1	57/87	59/89	4·9 (2·7–7·5)	3·5 (1·9–4·1)	0·60 (0·41–0·88)

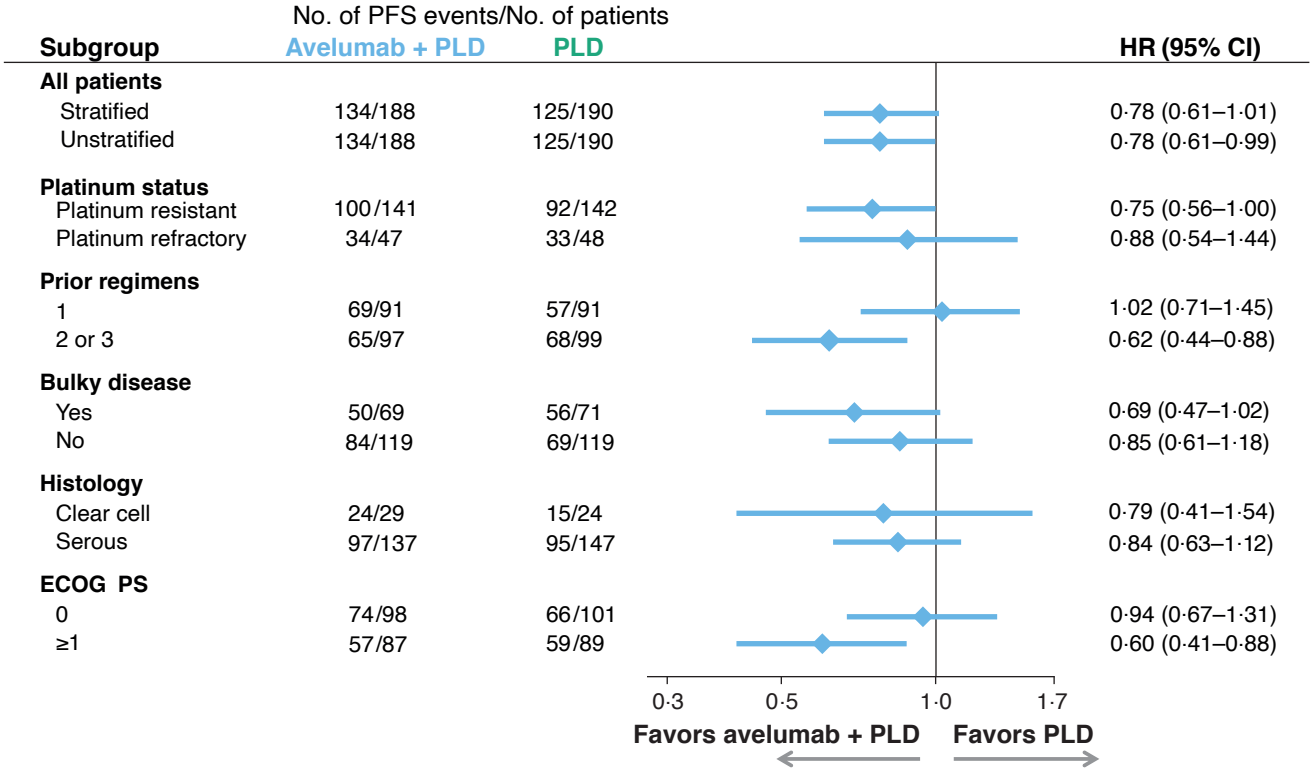


Forest_OS

	No. of OS events/No. of patients		Median OS (95% CI), months		HR (95% CI)
	Avelumab + PLD	PLD	Avelumab + PLD	PLD	
All patients					
Stratified	102/188	104/190	15·7 (12·7–18·7)	13·1 (11·8–15·5)	0·89 (0·67–1·18)
Unstratified	102/188	104/190	15·7 (12·7–18·7)	13·1 (11·8–15·5)	0·87 (0·66–1·14)
Platinum status					
Platinum-resistant	77/141	77/142	15·7 (12·7–19·9)	14·1 (11·8–15·6)	0·85 (0·62–1·17)
Platinum-refractory	25/47	27/48	13·8 (8·6–20·4)	12·6 (8·8–18·4)	0·94 (0·54–1·63)
Prior regimens					
1	54/91	47/91	13·6 (8·5–18·7)	14·6 (12·1–18·8)	1·20 (0·81–1·78)
2 or 3	48/97	57/99	18·4 (13·7–25·0)	12·6 (11·4–15·0)	0·64 (0·43–0·95)
Bulky disease					
Yes	42/69	39/71	9·2 (7·4–12·7)	14·5 (10·5–16·9)	1·21 (0·78–1·89)
No	60/119	65/119	18·4 (15·6–21·4)	13·1 (11·4–15·6)	0·70 (0·49–1·00)
Histology					
Clear cell	15/29	9/24	17·7 (8·0–22·8)	15·5 (5·6–NE)	0·89 (0·38–2·06)
Serous	75/137	82/147	15·7 (12·7–18·7)	13·1 (11·8-15·6)	0·89 (0·65–1·22)
ECOG PS					
0	51/98	51/101	17·7 (12·7–20·7)	14·9 (12·4–18·8)	0·98 (0·66–1·45)
≥1	48/87	53/89	15·7 (8·4–20·4)	11·8 (9·2–15·6)	0·76 (0·51–1·13)



Forest_PFS


No. of PFS events/No. of patients
Subgroup
Avelumab + PLD
PLD
HR (95% CI)
All patients
Stratified 134/188 125/190 0·78 (0·61–1·01)
Unstratified 134/188 125/190 0·78 (0·61–0·99)
Platinum status
Platinum resistant 100/141 92/142 0·75 (0·56–1·00)
Platinum refractory 34/47 33/48 0·88 (0·54–1·44)
Prior regimens
1 69/91 57/91 1·02 (0·71–1·45)
2 or 3 65/97 68/99 0·62 (0·44–0·88)
Bulky disease
Yes 50/69 56/71 0·69 (0·47–1·02)
No 84/119 69/119 0·85 (0·61–1·18)
Histology
Clear cell 24/29 15/24 0·79 (0·41–1·54)
Serous 97/137 95/147 0·84 (0·63–1·12)
ECOG PS
0 74/98 66/101 0·94 (0·67–1·31)
≥1 57/87 59/89 0·60 (0·41–0·88)
0·3
0·5
1·0
1·7
Favors avelumab + PLD
Favors PLD

Forest_OS

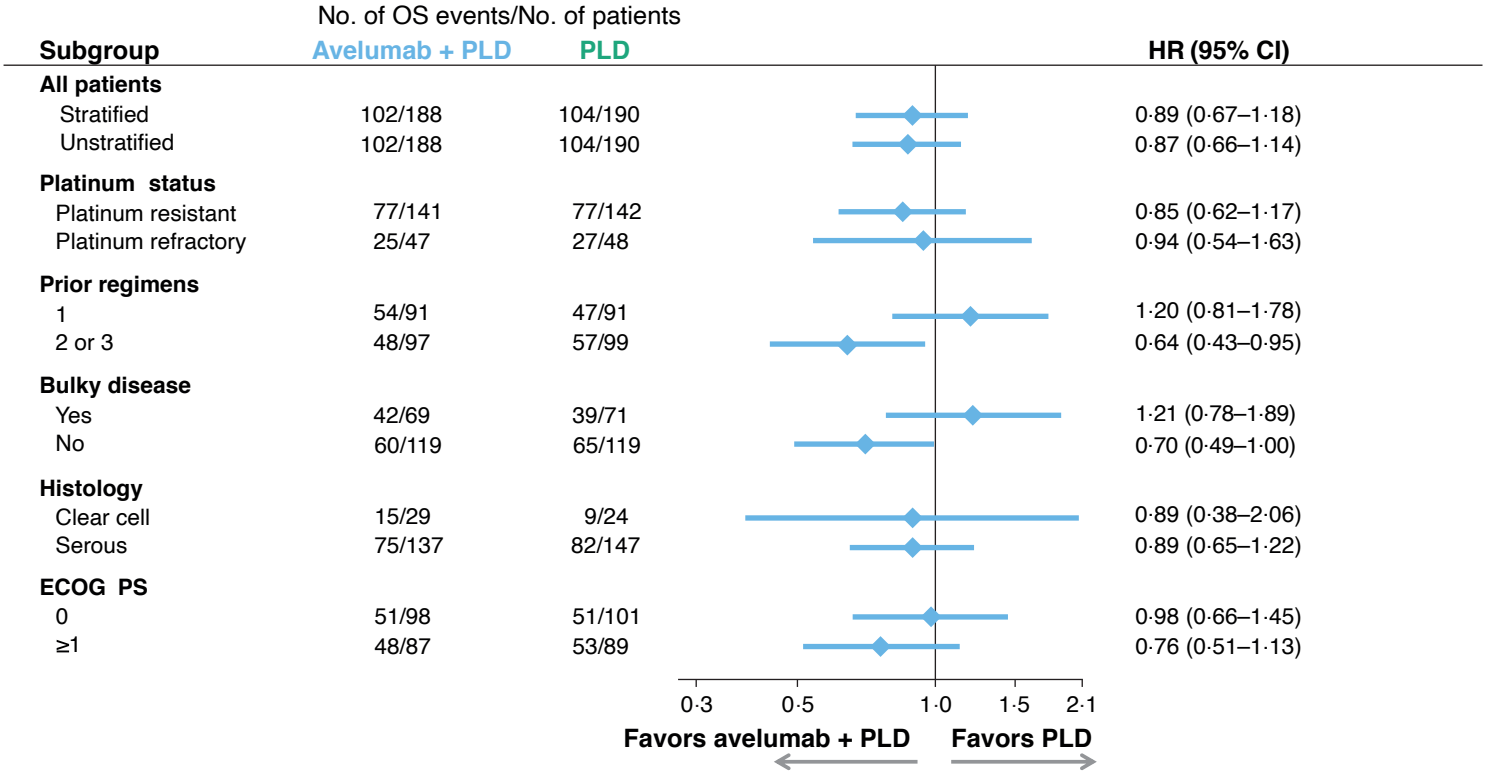
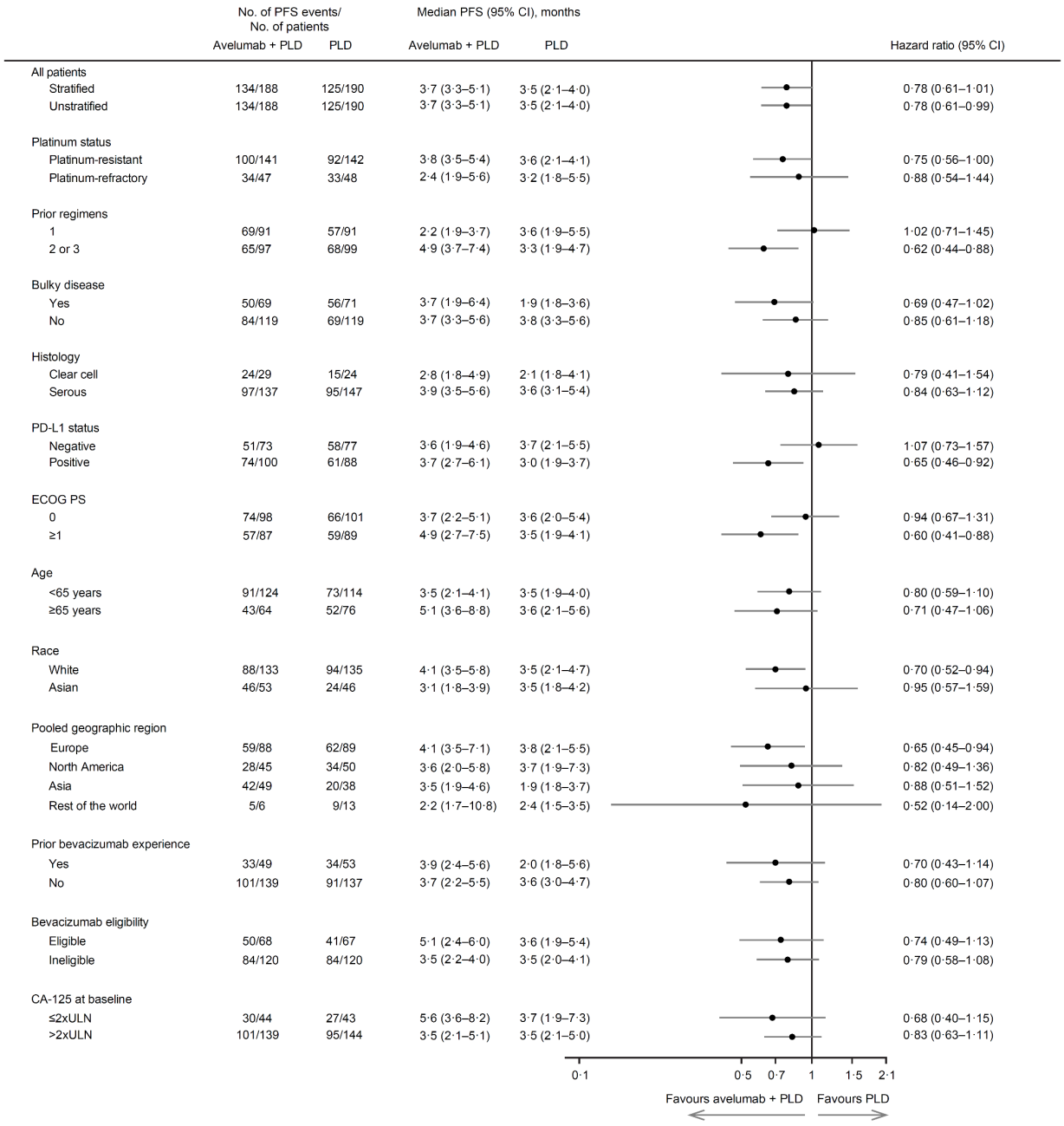
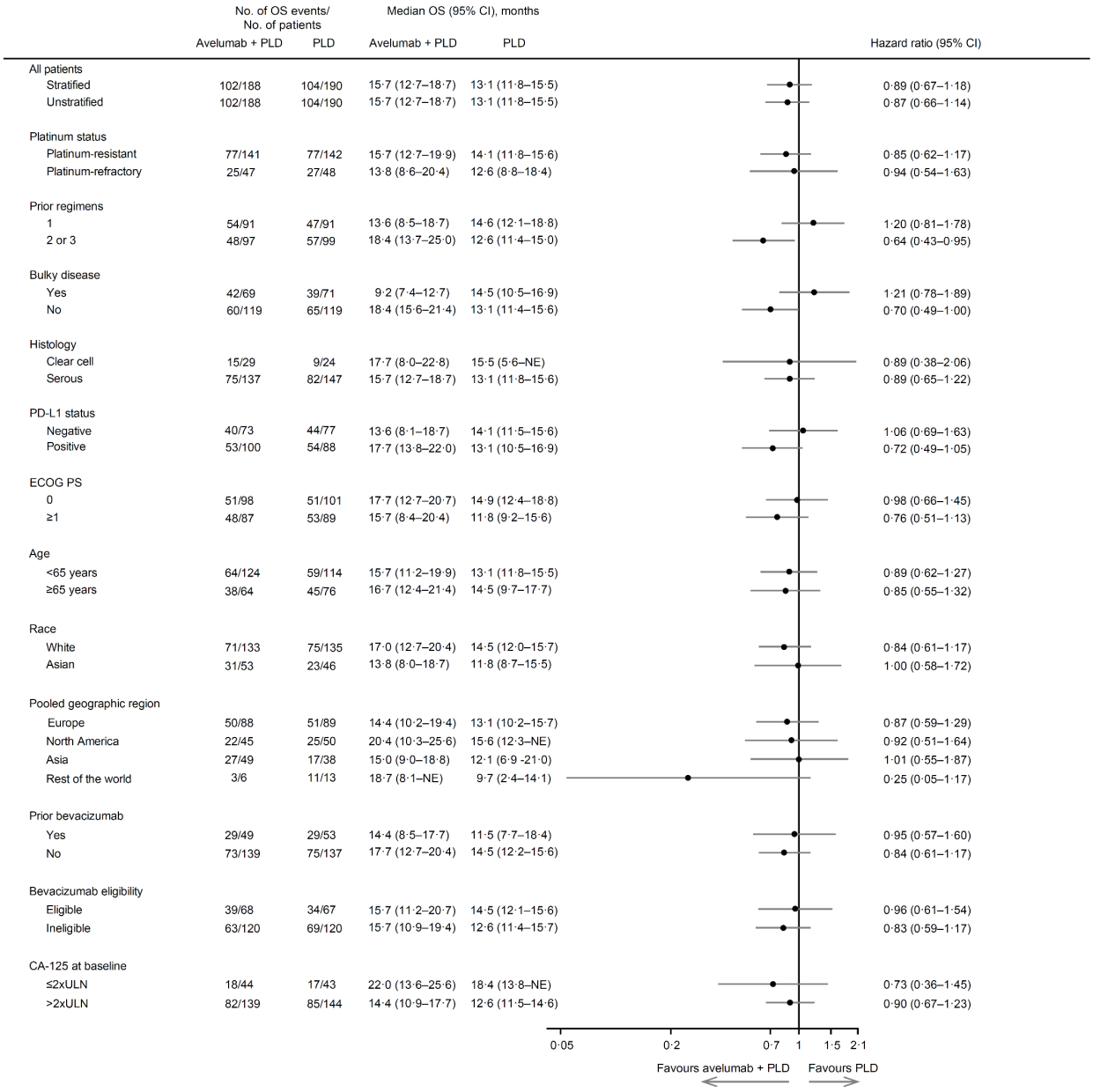

No. of OS events/No. of patients
Subgroup
Avelumab + PLD
PLD
HR (95% CI)
All patients
Stratified 102/188 104/190 0·89 (0·67–1·18)
Unstratified 102/188 104/190 0·87 (0·66–1·14)
Platinum status
Platinum resistant 77/141 77/142 0·85 (0·62–1·17)
Platinum refractory 25/47 27/48 0·94 (0·54–1·63)
Prior regimens
1 54/91 47/91 1·20 (0·81–1·78)
2 or 3 48/97 57/99 0·64 (0·43–0·95)
Bulky disease
Yes 42/69 39/71 1·21 (0·78–1·89)
No 60/119 65/119 0·70 (0·49–1·00)
Histology
Clear cell 15/29 9/24 0·89 (0·38–2·06)
Serous 75/137 82/147 0·89 (0·65–1·22)
ECOG PS
0 51/98 51/101 0·98 (0·66–1·45)
≥1 48/87 53/89 0·76 (0·51–1·13)
0·3
0·5
1·0
1·5
2·1
Favors avelumab + PLD
Favors PLD

Figure S1. Forest plots for progression-free survival by BICR (Panel A) and overall survival (Panel B) with avelumab plus PLD vs PLD in prespecified subgroups defined by patient and disease characteristics.

A



B

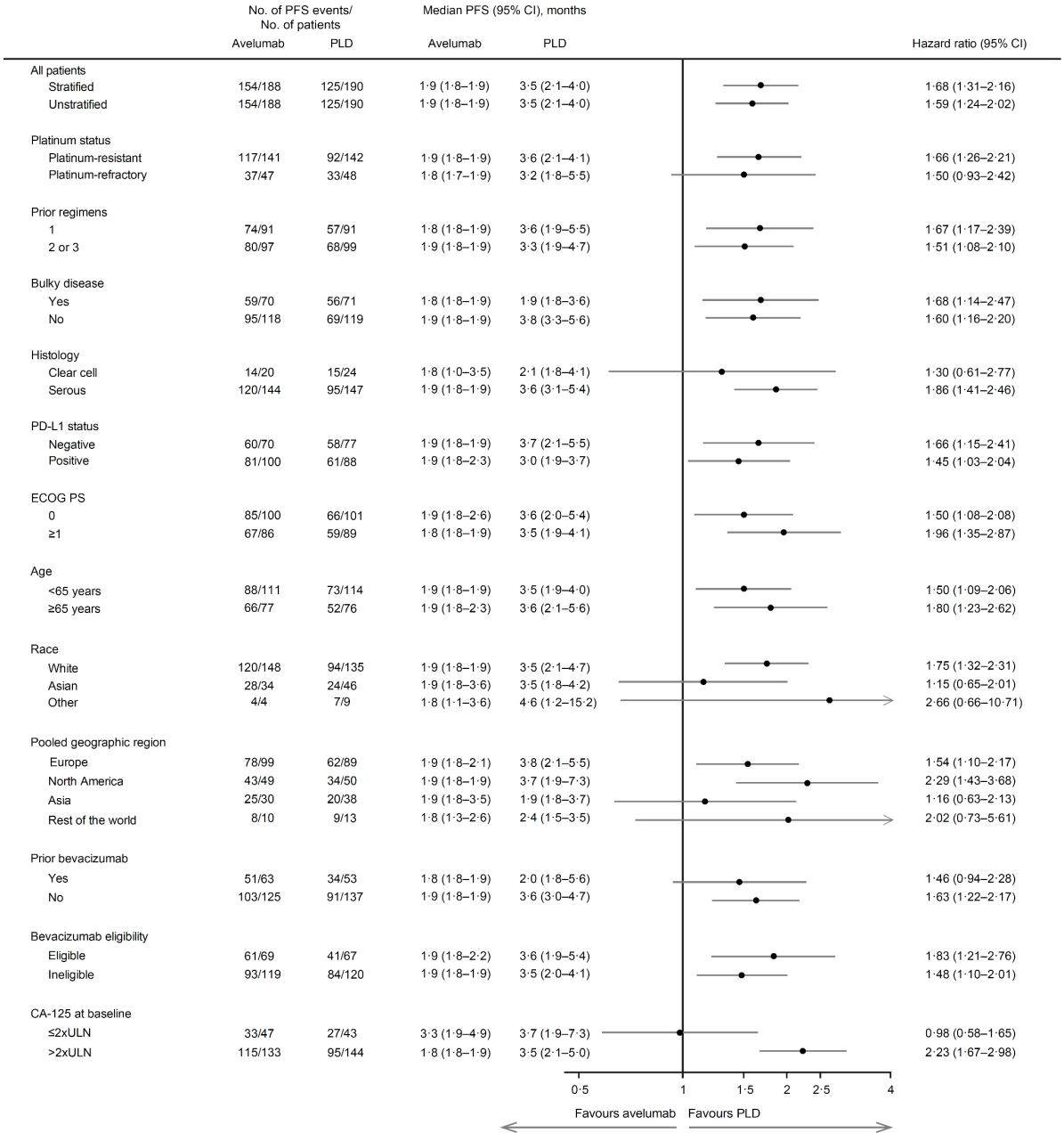


Except for the primary analysis (all patients), which was stratified according to randomisation stratification factors, all other analyses presented were unstratified. In subgroups defined by "Race", data for patients categorized as "Other" are not shown because only 2 patients were categorized in this subgroup in the avelumab + PLD arm and no PFS or OS events occurred, therefore median PFS and OS were NE. BICR=blinded independent central review. ECOG PS=Eastern Cooperative Oncology Group performance status. NE=not

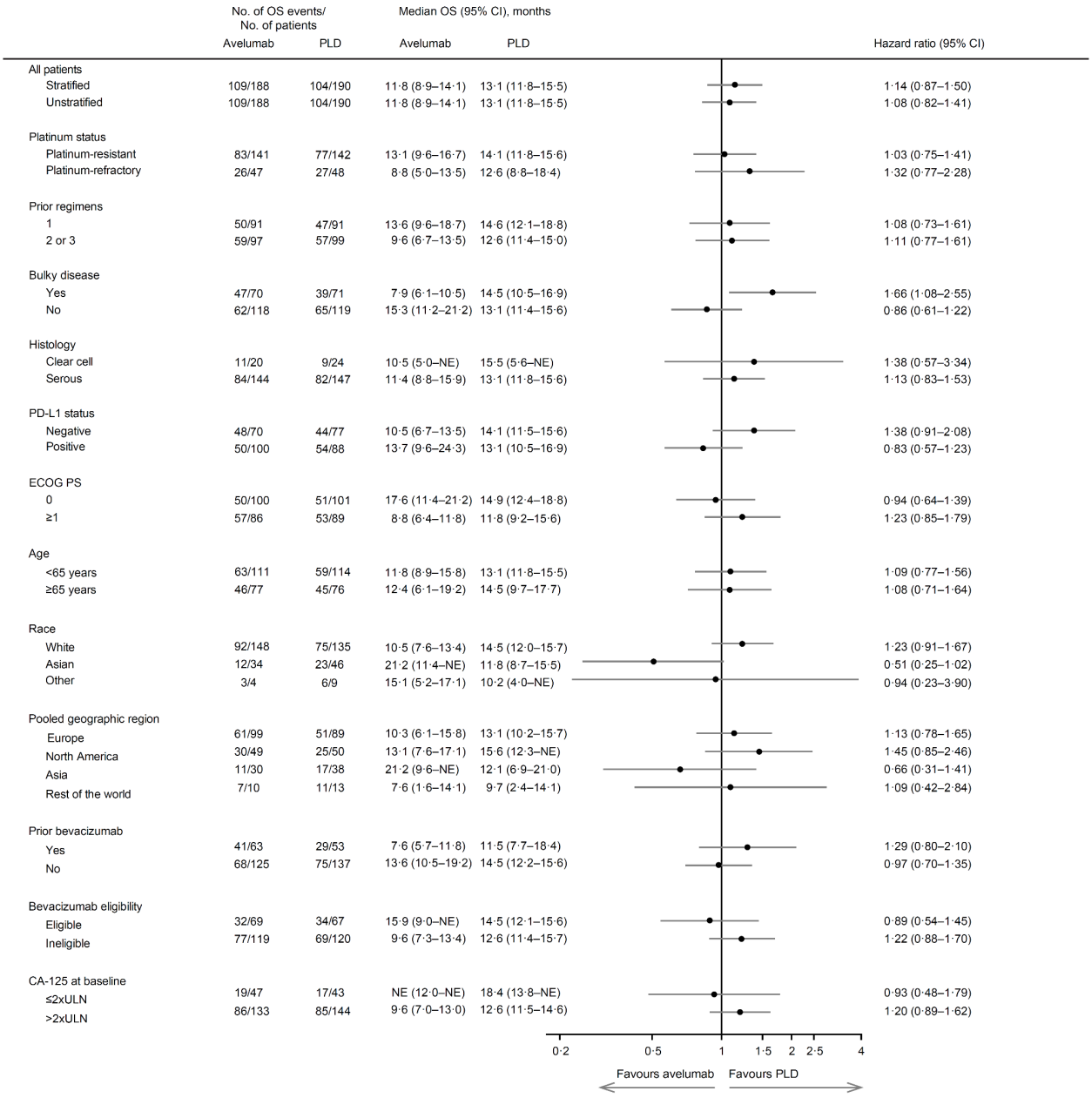
estimable. PFS=progression-free survival. PLD=pegylated liposomal doxorubicin. ULN=upper limit of normal.

Figure S2. Forest plots for progression-free survival by BICR (Panel A) and overall survival (Panel B) with avelumab vs PLD in prespecified subgroups defined by patient and disease characteristics.

A



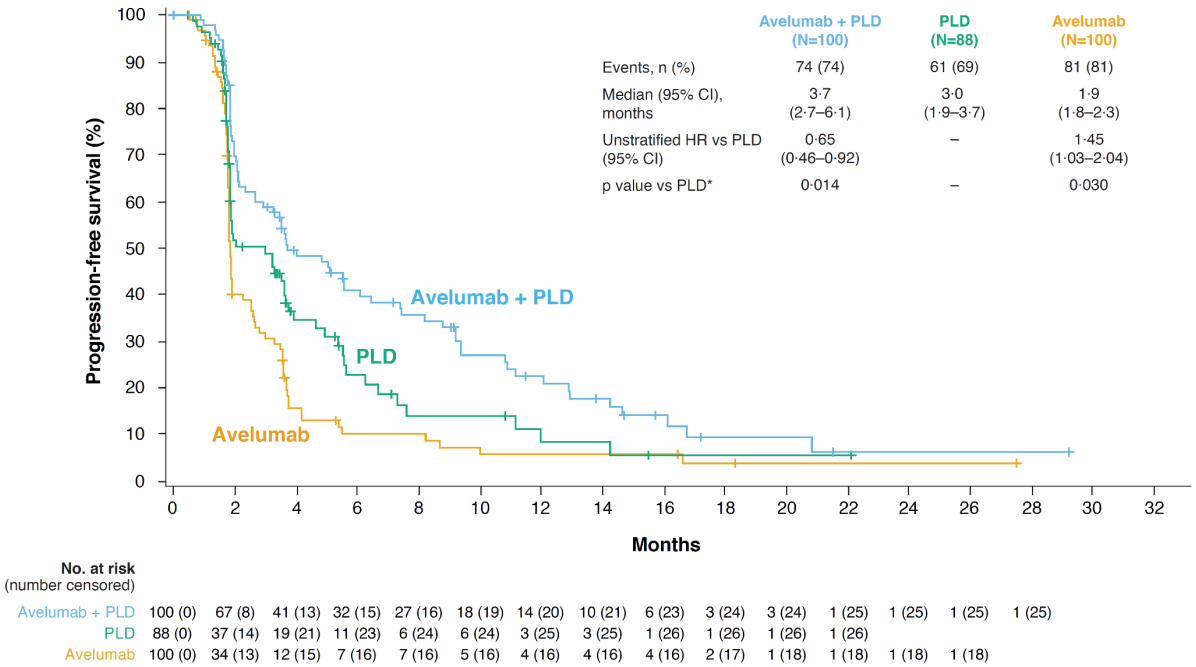
B



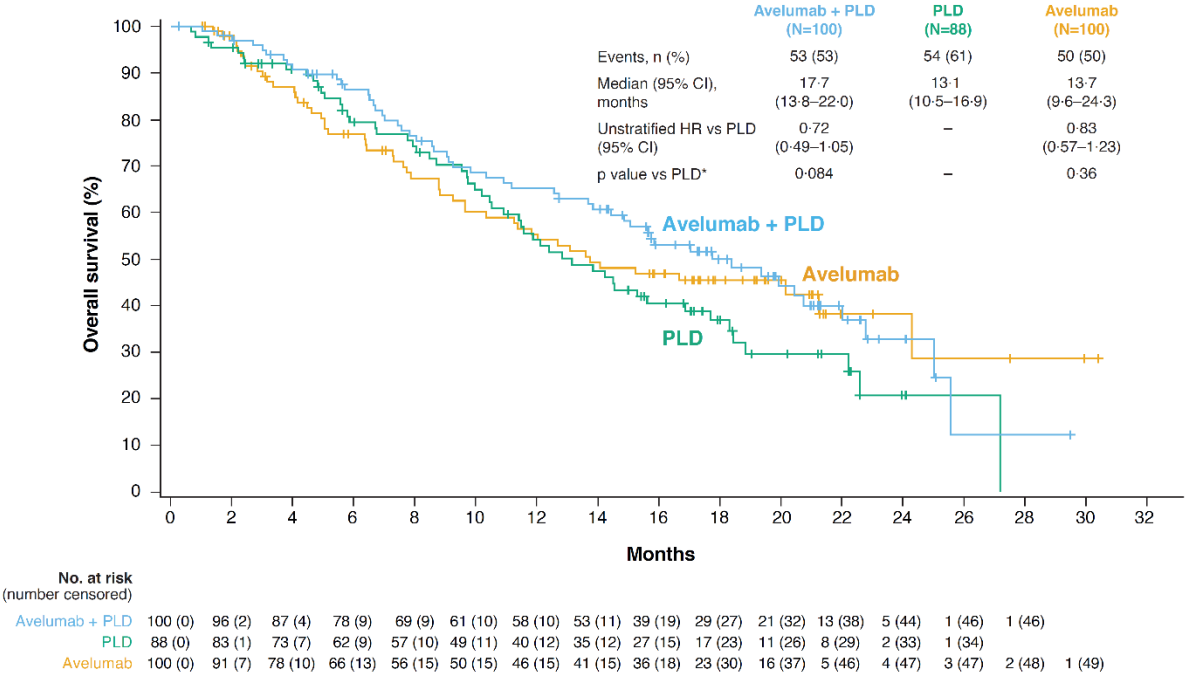
Except for the primary analysis (all patients), which was stratified according to randomisation stratification factors, all other analyses presented were unstratified. BICR=blinded independent central review. ECOG PS=Eastern Cooperative Oncology Group performance status. NE=not estimable. PFS=progression-free survival. PLD=pegylated liposomal doxorubicin. ULN=upper limit of normal.

Figure S3. Progression-free survival per BICR (Panel A) and overall survival (Panel B) in the PD-L1+ subgroup

A



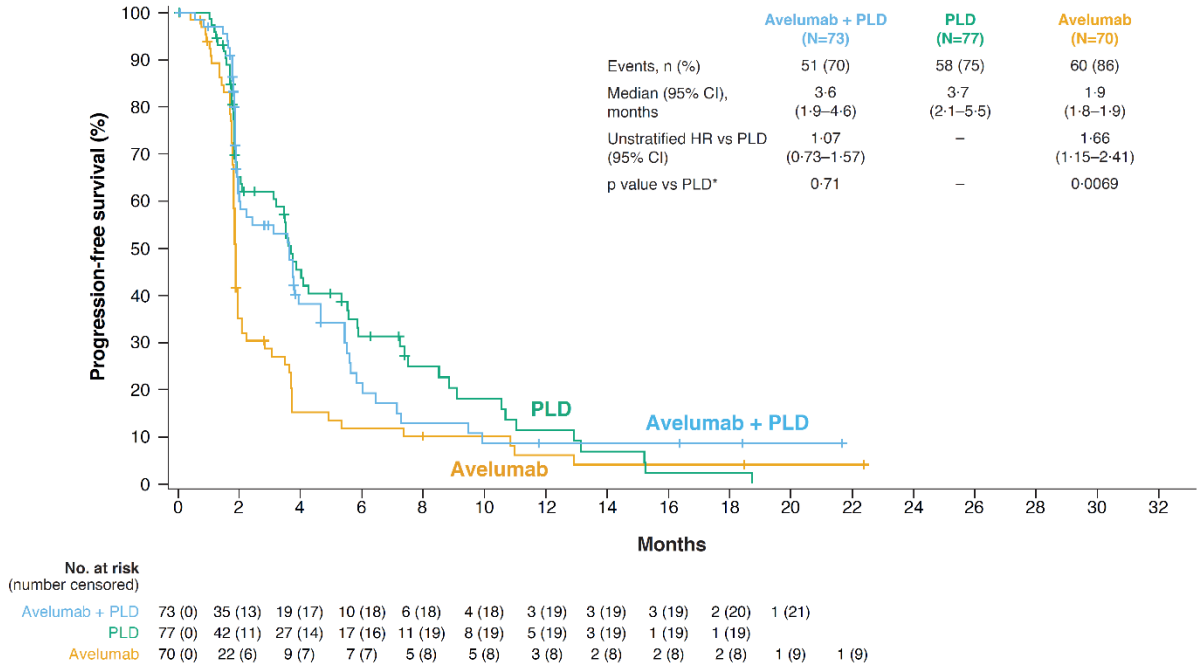
B



* P values for descriptive purposes only; two-sided unstratified log-rank test. BICR=blinded independent central review. PLD=pegylated liposomal doxorubicin. PD-L1=programmed death ligand 1.

Figure S4. Progression-free survival per BICR (Panel A) and overall survival (Panel B) in the PD-L1− subgroup

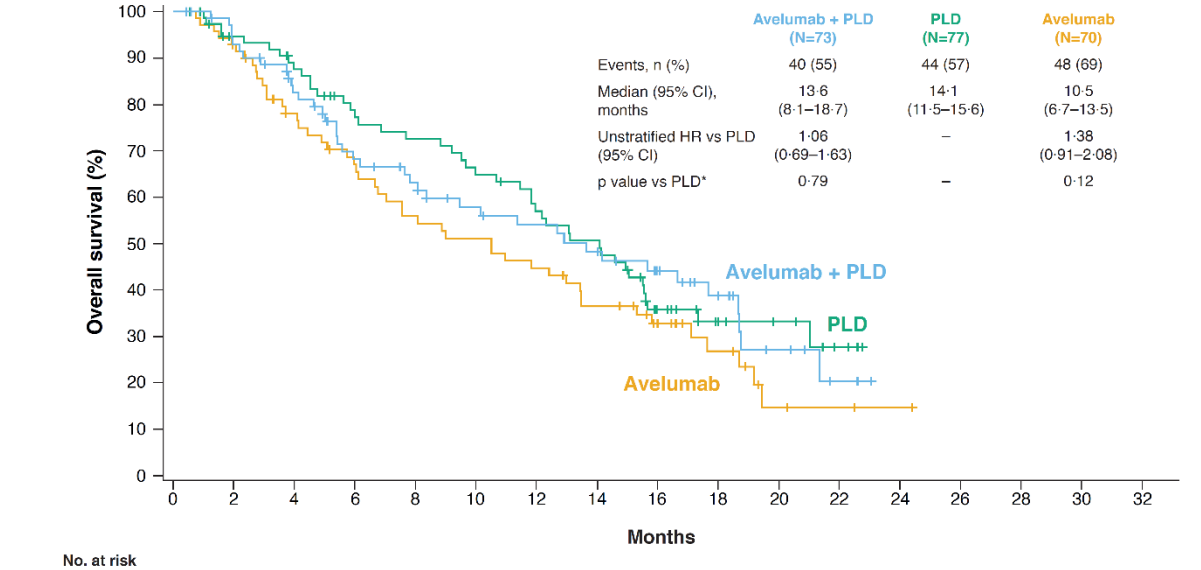
A



No. at risk (number censored)

Avelumab + PLD	73 (0)	35 (13)	19 (17)	10 (18)	6 (18)	4 (18)	3 (19)	3 (19)	3 (19)	2 (20)	1 (21)
PLD	77 (0)	42 (11)	27 (14)	17 (16)	11 (19)	8 (19)	5 (19)	3 (19)	1 (19)	1 (19)	
Avelumab	70 (0)	22 (6)	9 (7)	7 (7)	5 (8)	5 (8)	3 (8)	2 (8)	2 (8)	2 (8)	1 (9)	1 (9)

B



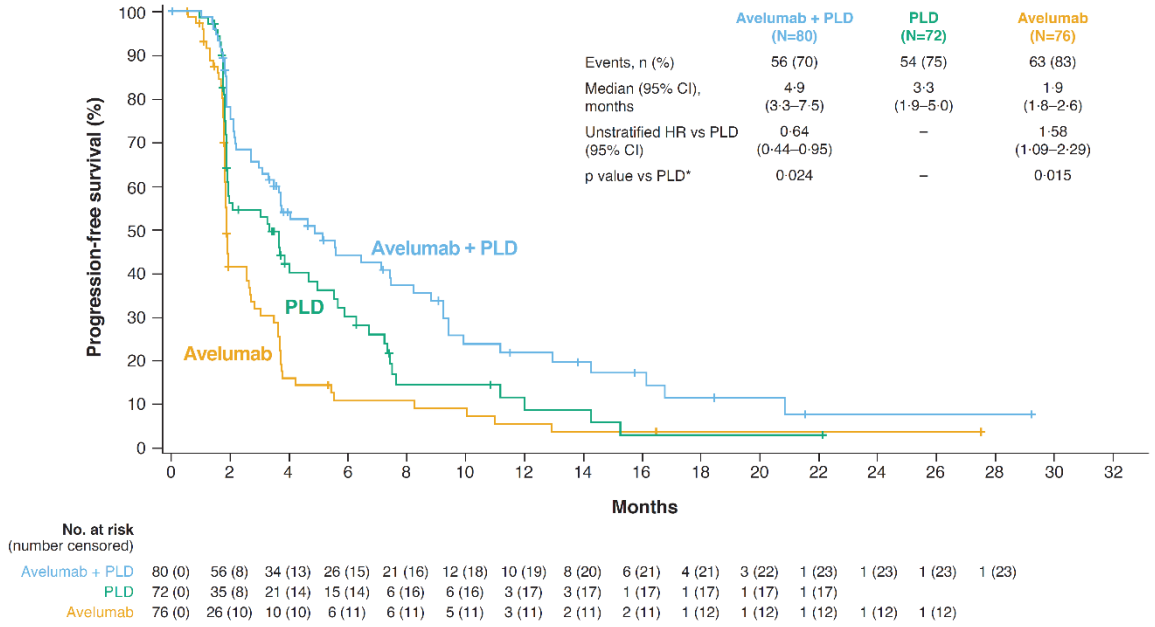
No. at risk (number censored)

Avelumab + PLD	73 (0)	65 (3)	54 (7)	42 (10)	37 (12)	31 (15)	28 (16)	25 (16)	19 (20)	13 (24)	6 (28)	2 (31)
PLD	77 (0)	68 (5)	61 (7)	51 (11)	47 (11)	42 (11)	36 (12)	32 (12)	18 (17)	11 (23)	7 (27)	3 (30)
Avelumab	70 (0)	64 (1)	50 (5)	42 (6)	35 (6)	32 (6)	28 (6)	22 (7)	16 (11)	9 (16)	3 (19)	2 (20)	1 (21)

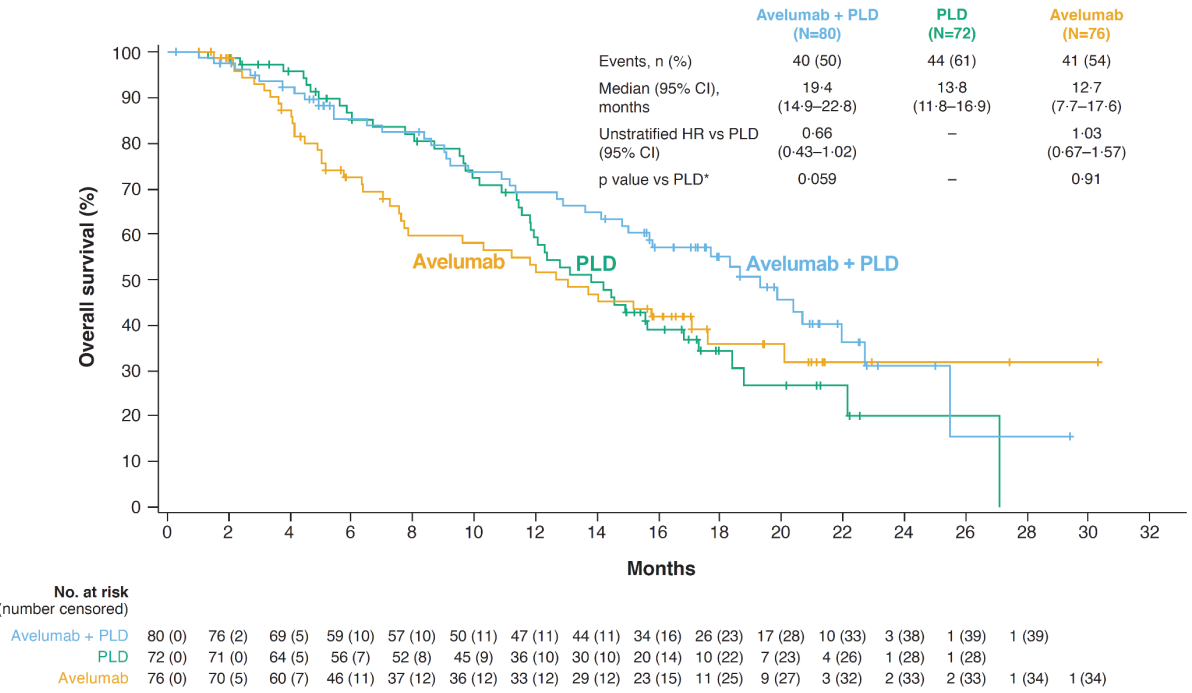
* P values for descriptive purposes only; two-sided unstratified log-rank test. Unstratified HRs for progression-free survival by BICR between the PD-L1+ and PD-L1− subgroups were 0·71 (95% CI 0·49–1·02) in the combination arm, 1·16 (95% CI 0·80–1·67) in the PLD arm, and 0·95 (95% CI 0·67–1·34) in the avelumab arm. Unstratified HRs for overall survival between the PD-L1+ and PD-L1− subgroups were 0·65 (95% CI 0·43–0·99) in the combination arm, 0·99 (95% CI 0·66–1·48) in the PLD arm, and 0·62 (95% CI 0·42–0·92) in the avelumab arm. PD-L1=programmed death ligand 1. PLD=pegylated liposomal doxorubicin.

Figure S5. Progression-free survival per BICR (Panel A) and overall survival (Panel B) in the CD8+ subgroup

A



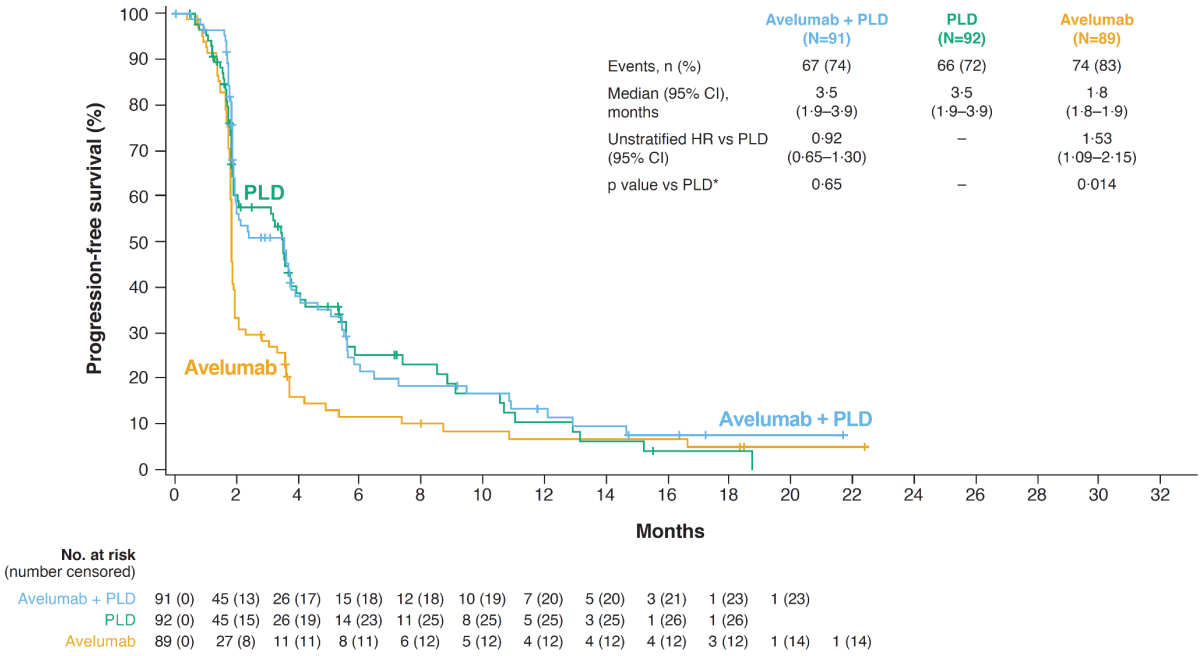
B



* P values for descriptive purposes only; two-sided unstratified log-rank test. BICR=blinded independent central review. PLD=pegylated liposomal doxorubicin. PD-L1=programmed death ligand 1.

Figure S6. Progression-free survival per BICR (Panel A) and overall survival (Panel B) in the CD8− subgroup

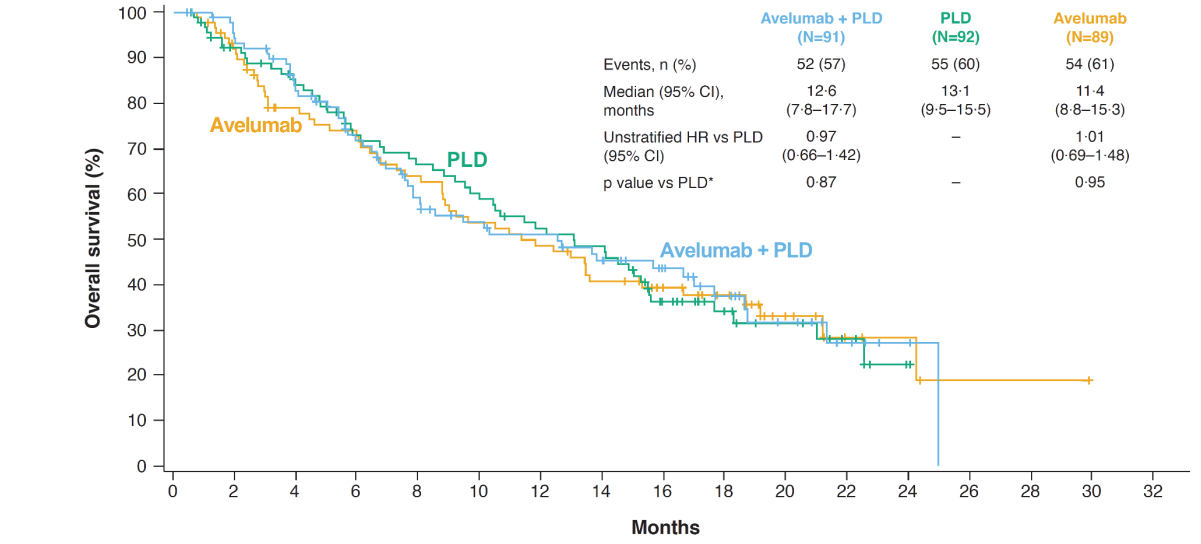
A



No. at risk (number censored)

Avelumab + PLD	91 (0)	45 (13)	26 (17)	15 (18)	12 (18)	10 (19)	7 (20)	5 (20)	3 (21)	1 (23)	1 (23)	
PLD	92 (0)	45 (15)	26 (19)	14 (23)	11 (25)	8 (25)	5 (25)	3 (25)	1 (26)	1 (26)		
Avelumab	89 (0)	27 (8)	11 (11)	8 (11)	6 (12)	5 (12)	4 (12)	4 (12)	4 (12)	3 (12)	1 (14)	1 (14)

B



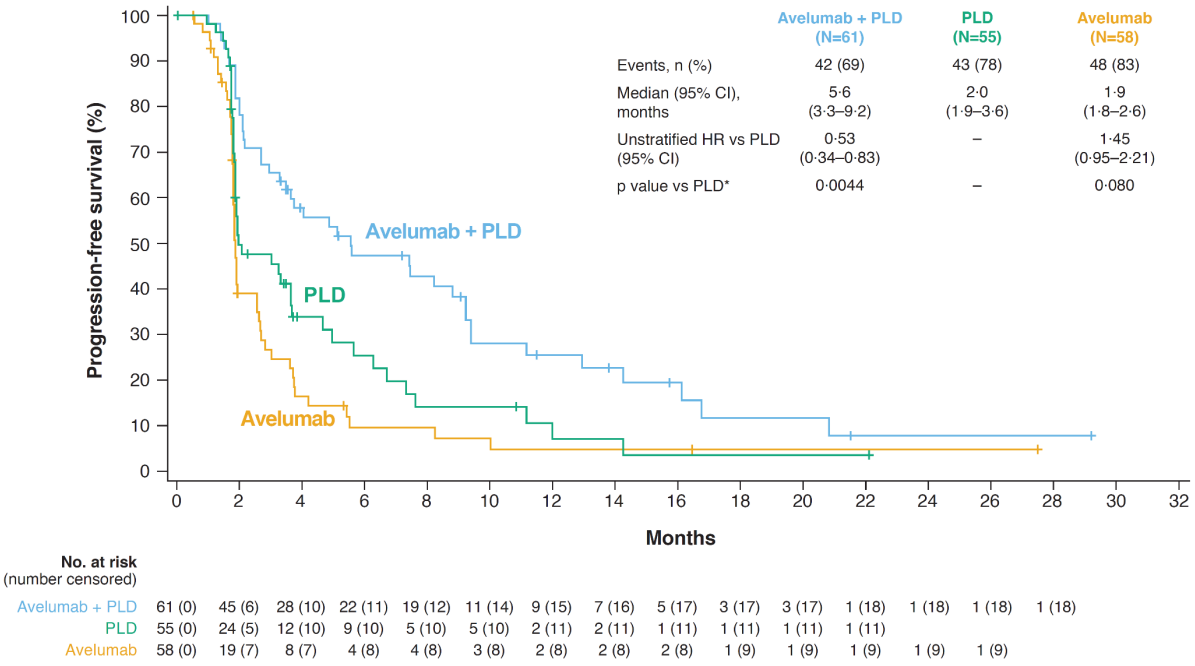
No. at risk (number censored)

Avelumab + PLD	91 (0)	83 (3)	70 (6)	58 (9)	46 (11)	39 (14)	36 (15)	31 (16)	24 (22)	16 (27)	10 (31)	5 (35)	2 (38)	
PLD	92 (0)	80 (5)	70 (8)	57 (12)	52 (12)	46 (12)	40 (13)	37 (13)	23 (18)	16 (24)	10 (29)	6 (32)	1 (36)	
Avelumab	89 (0)	79 (3)	63 (8)	58 (8)	50 (9)	42 (9)	38 (9)	31 (10)	26 (14)	20 (19)	10 (27)	4 (32)	3 (33)	1 (34)	1 (34)

* P values for descriptive purposes only; two-sided unstratified log-rank test. Unstratified HRs for progression-free survival by BICR between the CD8+ and CD8− subgroups were 0·69 (95% CI 0·48–0·98) in the combination arm, 0·95 (95% CI 0·66–1·36) in the PLD arm, and 0·93 (95% CI 0·66–1·32) in the avelumab arm. Unstratified HRs for overall survival between the CD8+ and CD8− subgroups were 0·62 (95% CI 0·41–0·94) for the combination arm, 0·88 (95% CI 0·59–1·31) for the PLD arm, and 0·89 (95% CI 0·59–1·33) for the avelumab arm. PLD=pegylated liposomal doxorubicin.

Figure S7. Progression-free survival per BICR by PD-L1 and CD8 status. PD-L1+/CD8+ (Panel A), PD-L1+/CD8− (Panel B), PD-L1−/CD8+ (Panel C), and PD-L1−/CD8− (Panel D)

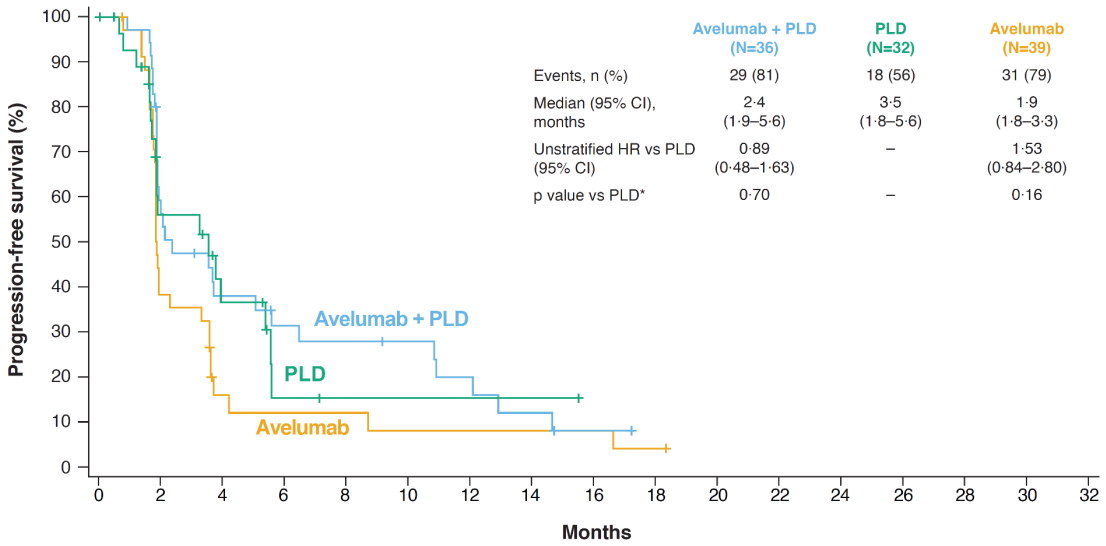
A



No. at risk (number censored)

Avelumab + PLD	61 (0)	45 (6)	28 (10)	22 (11)	19 (12)	11 (14)	9 (15)	7 (16)	5 (17)	3 (17)	3 (17)	1 (18)	1 (18)	1 (18)	1 (18)
PLD	55 (0)	24 (5)	12 (10)	9 (10)	5 (10)	5 (10)	2 (11)	2 (11)	1 (11)	1 (11)	1 (11)	1 (11)			
Avelumab	58 (0)	19 (7)	8 (7)	4 (8)	4 (8)	3 (8)	2 (8)	2 (8)	2 (8)	1 (9)	1 (9)	1 (9)	1 (9)	1 (9)	

B

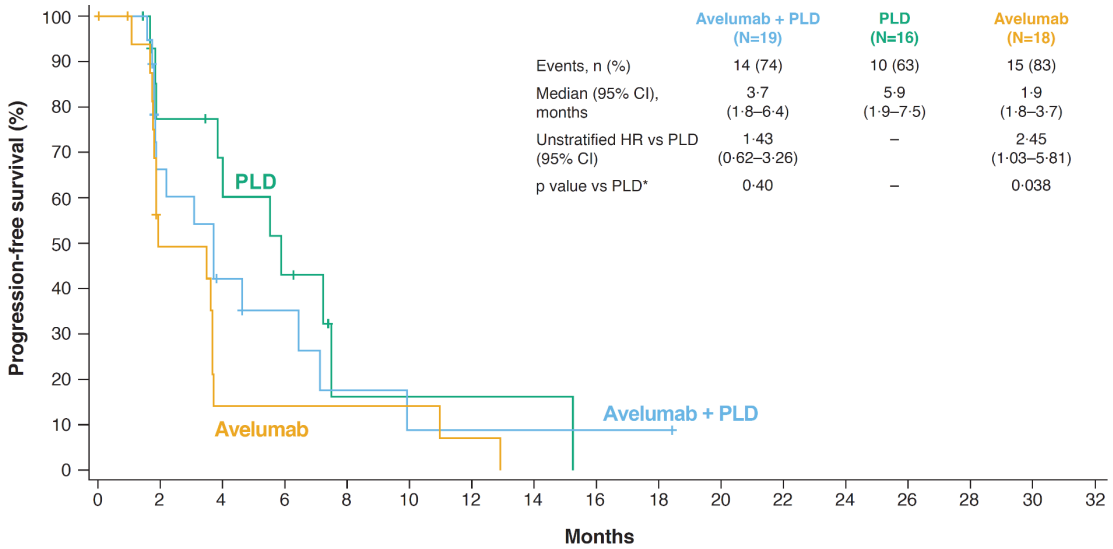


	Avelumab + PLD (N=36)	PLD (N=32)	Avelumab (N=39)
Events, n (%)	29 (81)	18 (56)	31 (79)
Median (95% CI), months	2·4 (1·9–5·6)	3·5 (1·8–5·6)	1·9 (1·8–3·3)
Unstratified HR vs PLD (95% CI)	0·89 (0·48–1·63)	–	1·53 (0·84–2·80)
p value vs PLD*	0·70	–	0·16

No. at risk (number censored)

Avelumab + PLD	36 (0)	20 (2)	12 (3)	9 (4)	8 (4)	7 (5)	5 (5)	3 (5)	1 (6)	
PLD	32 (0)	13 (8)	7 (10)	2 (12)	1 (13)	1 (13)	1 (13)	1 (13)		
Avelumab	39 (0)	13 (5)	4 (7)	3 (7)	3 (7)	2 (7)	2 (7)	2 (7)	2 (7)	1 (7)

C

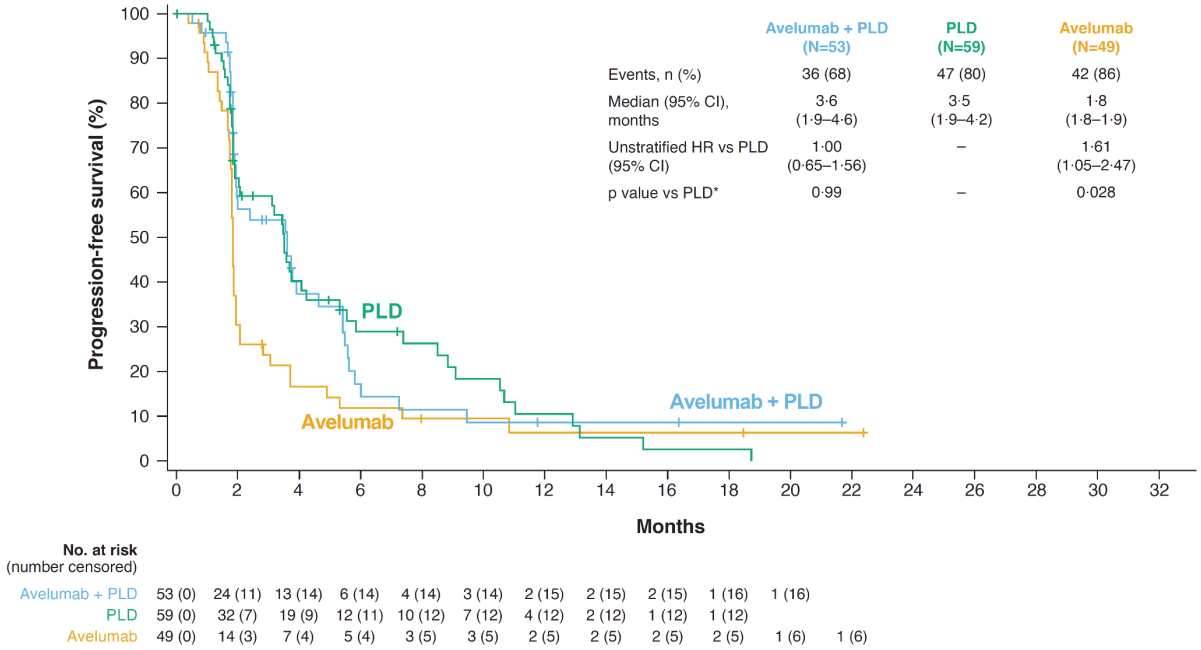


	Avelumab + PLD (N=19)	PLD (N=16)	Avelumab (N=18)
Events, n (%)	14 (74)	10 (63)	15 (83)
Median (95% CI), months	3·7 (1·8–6·4)	5·9 (1·9–7·5)	1·9 (1·8–3·7)
Unstratified HR vs PLD (95% CI)	1·43 (0·62–3·26)	–	2·45 (1·03–5·81)
p value vs PLD*	0·40	–	0·038

No. at risk (number censored)

Avelumab + PLD	19 (0)	11 (2)	6 (3)	4 (4)	2 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)
PLD	16 (0)	10 (3)	8 (4)	5 (4)	1 (6)	1 (6)	1 (6)	1 (6)		
Avelumab	18 (0)	7 (3)	2 (3)	2 (3)	2 (3)	2 (3)	1 (3)			

D



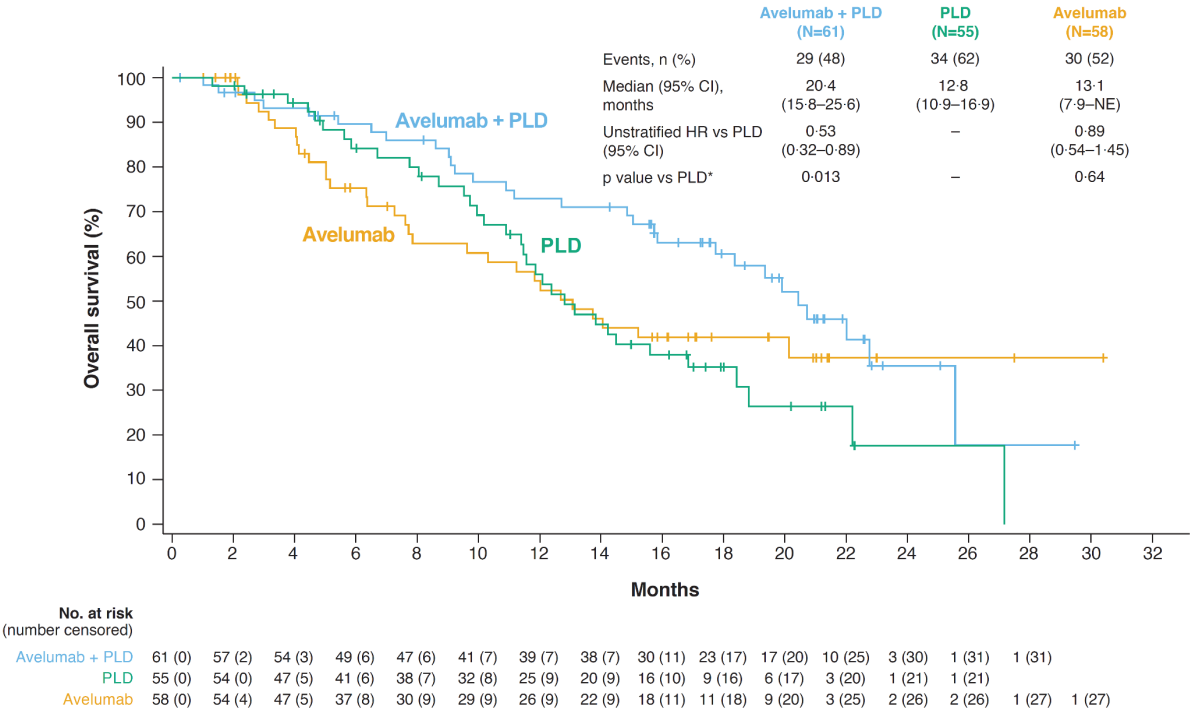
No. at risk (number censored)

Avelumab + PLD	53 (0)	24 (11)	13 (14)	6 (14)	4 (14)	3 (14)	2 (15)	2 (15)	2 (15)	1 (16)	1 (16)
PLD	59 (0)	32 (7)	19 (9)	12 (11)	10 (12)	7 (12)	4 (12)	2 (12)	1 (12)	1 (12)	
Avelumab	49 (0)	14 (3)	7 (4)	5 (4)	3 (5)	3 (5)	2 (5)	2 (5)	2 (5)	2 (5)	1 (6)	1 (6)

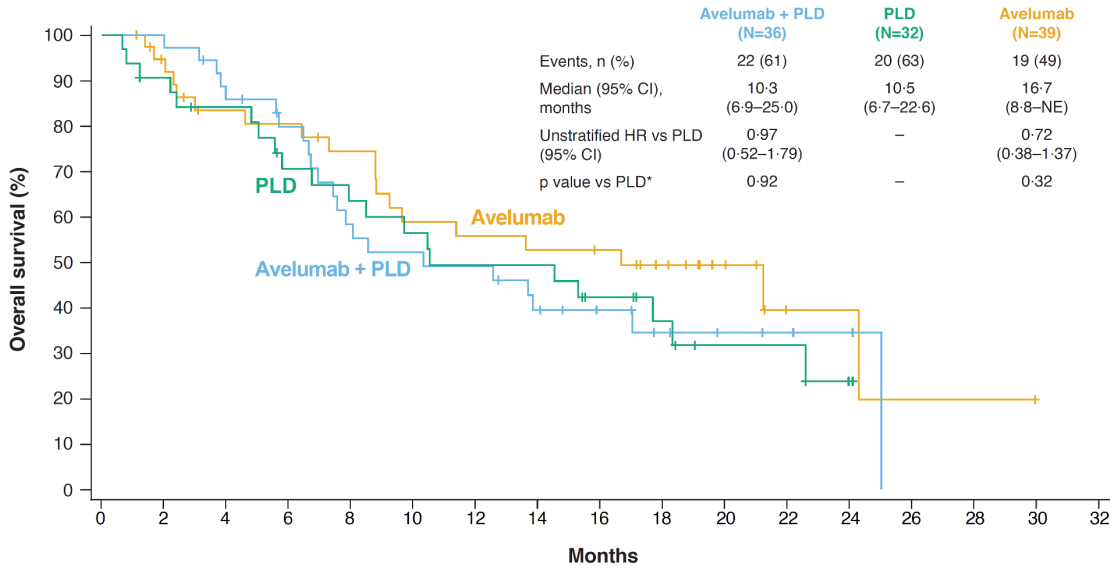
* P values for descriptive purposes only; two-sided unstratified log-rank test. PLD=pegylated liposomal doxorubicin.

Figure S8. Overall survival by PD-L1 and CD8 status. PD-L1+/CD8+ (Panel A), PD-L1+/CD8− (Panel B), PD-L1−/CD8+ (Panel C), and PD-L1−/CD8− (Panel D)

A

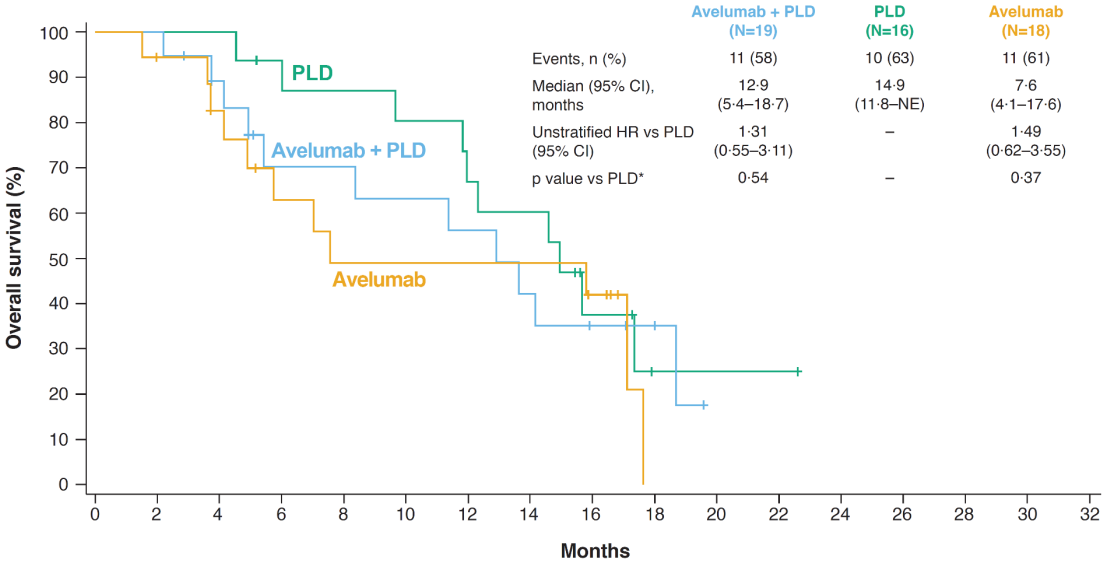


B



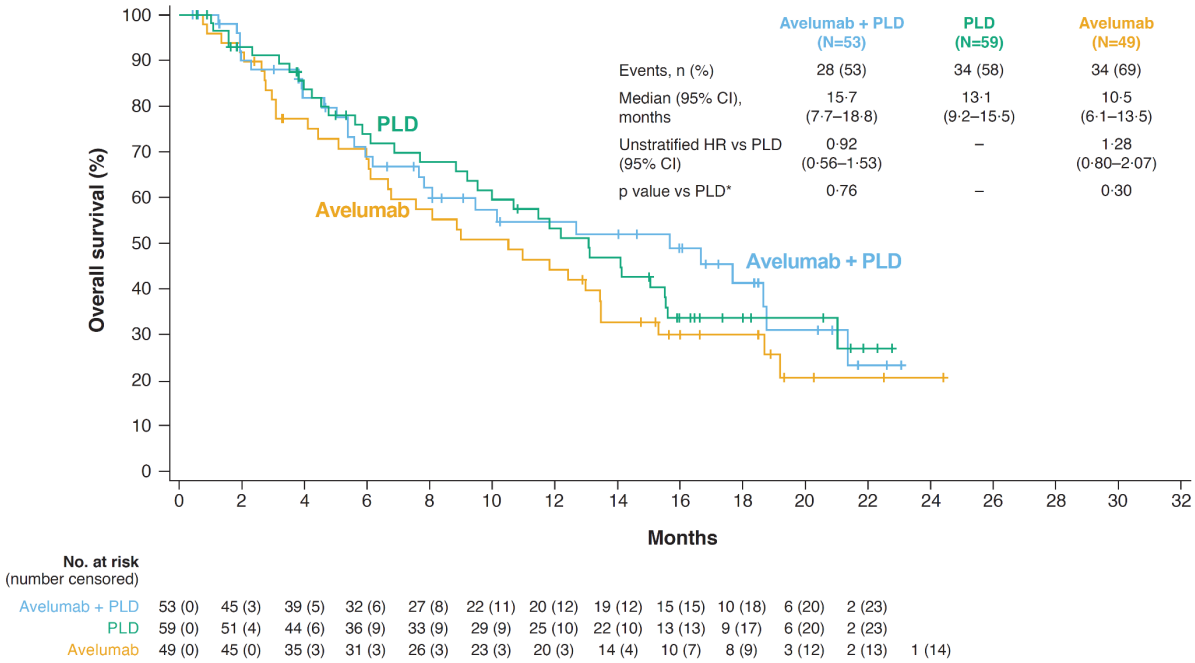
No. at risk (number censored)															
Avelumab + PLD	36 (0)	36 (0)	30 (1)	26 (3)	19 (3)	17 (3)	16 (3)	12 (4)	9 (7)	6 (9)	4 (11)	3 (12)	2 (13)		
PLD	32 (0)	28 (1)	25 (2)	20 (3)	18 (3)	16 (3)	14 (3)	14 (3)	10 (5)	7 (7)	4 (9)	4 (9)	1 (11)		
Avelumab	39 (0)	34 (3)	28 (5)	27 (5)	24 (6)	19 (6)	18 (6)	17 (6)	16 (7)	12 (10)	7 (15)	2 (19)	2 (19)	1 (19)	1 (19)

C



No. at risk (number censored)												
Avelumab + PLD	19 (0)	19 (0)	15 (2)	10 (4)	10 (4)	9 (4)	8 (4)	6 (4)	4 (5)	3 (6)		
PLD	16 (0)	16 (0)	16 (0)	14 (1)	13 (1)	12 (1)	10 (1)	9 (1)	4 (3)	1 (5)	1 (5)	1 (5)
Avelumab	18 (0)	16 (1)	13 (2)	9 (3)	7 (3)	7 (3)	7 (3)	7 (3)	5 (4)			

D



* P values for descriptive purposes only; two-sided unstratified log-rank test. NE=not estimable. PLD=pegylated liposomal doxorubicin.

Table S1. Protocol deviations

	Avelumab + PLD (N=188)	**PLD (N=190)**	**Avelumab (N=188)**
Any deviation, n (%)	95 (51)	75 (39)	74 (39)
Type of deviation, n (%)			
Concomitant medication	26 (14)	13 (7)	13 (7)
Eligibility criteria	21 (11)	18 (9)	23 (12)
Informed consent procedures	14 (7)	13 (7)	8 (4)
Investigational product use	25 (13)	11 (6)	12 (6)
Laboratory tests	3 (2)	3 (2)	2 (1)
Other procedures/tests	5 (3)	4 (2)	4 (2)
Discontinuation criteria	23 (12)	14 (7)	4 (2)
Stratification	9 (5)	8 (4)	9 (5)
Safety reporting	28 (15)	12 (6)	24 (13)

Table S2. Summary of overall survival and progression-free survival by BICR at interim and final analysis

	Interim analysis	**Final analysis**
Progression-free survival		
Avelumab + PLD vs PLD	HR 0·84 (RCI 0·60–1·39) 1-sided P=0·10	HR 0·78 (RCI 0·59–1·24) 1-sided P=0·030*
Avelumab vs PLD	HR 1·85 (RCI 1·41–2·93) 1-sided P>0·99	HR 1·68 (RCI 1·32–2·60) 1-sided P>0·99*
Overall survival		
Avelumab + PLD vs PLD	HR 0·89 (RCI 0·59–1·40) 1-sided P=0·24	HR 0·89 (RCI 0·74–1·24) 1-sided P=0·21
Avelumab vs PLD	HR 1·34 (RCI 0·96–2·05) 1-sided P=0·97	HR 1·14 (RCI 0·95–1·58) 1-sided P=0·83*

All comparisons shown are based on stratified analysis; P values were calculated using a log rank test.

BICR=blinded independent central review; HR=hazard ratio; RCI=repeated confidence interval.

* P values provided for descriptive purposes only.

Table S3. Antitumour activity based on investigator assessment.

	Avelumab + PLD (N=188)	**PLD (N=190)**	**Avelumab (N=188)**
Confirmed best overall response by investigator, n (%)			
Complete response	3 (2)	2 (1)	0
Partial response	32 (17)	16 (8)	10 (5)
Stable disease	80 (43)	86 (45)	54 (29)
Non-complete response/non-progressive disease	1 (<1)	0	0
Progressive disease	54 (29)	52 (27)	101 (54)
Not evaluable	18 (10)*	34 (18)†	23 (12)‡
Objective response rate (95% CI), %	19 (13–25)	9 (6–15)	5 (3–10)
Disease control rate (95% CI), %	62 (54–69)	55 (47–62)	34 (27–41)

PLD=pegylated liposomal doxorubicin.

* Reasons for response not evaluable: no adequate baseline assessment (in 2 patients), no postbaseline assessments due to early death (in 5 patients) or other reasons (in 9 patients), patient started new anticancer therapy before first postbaseline assessment (in 1 patient), or patient had stable disease <6 weeks after randomisation (in 1 patient).

† Reasons for response not evaluable: no adequate baseline assessment (in 5 patients), no postbaseline assessments due to early death (in 6 patients) or other reasons (in 18 patients), all postbaseline assessments had overall response of not evaluable (in 1 patient), patient started new anticancer therapy before first postbaseline assessment (in 1 patient), patient had stable disease <6 weeks after randomisation (in 2 patients), or patient had progressive disease >12 weeks after randomisation (in 1 patient).

‡ Reasons for response not evaluable: no adequate baseline assessment (in 5 patients), no postbaseline assessments due to early death (in 6 patients) or other reasons (in 8 patients), all postbaseline assessments had overall response of not evaluable (in 3 patients), or patient started new anticancer therapy before first postbaseline assessment (in 1 patient).

Table S4. Treatment-related adverse events.

	Avelumab + PLD (n=182)				PLD (n=177)				Avelumab (n=187)			
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Any TRAE, n (%)	90 (49)	70 (38)	8 (4)	0	95 (54)	47 (27)	8 (5)	1 (1)	105 (56)	25 (13)	4 (2)	1 (1)
Nausea	62 (34)	3 (2)	0	0	63 (36)	1 (1)	0	0	25 (13)	0	0	0
Fatigue	50 (27)	10 (5)	0	0	39 (22)	3 (2)	0	0	42 (22)	0	0	0
PPE syndrome	42 (23)	18 (10)	0	0	31 (18)	9 (5)	0	0	1 (1)	0	0	0
Stomatitis	41 (23)	10 (5)	0	0	31 (18)	4 (2)	1 (1)	0	4 (2)	0	0	0
Rash	34 (19)	11 (6)	0	0	13 (7)	3 (2)	0	0	9 (5)	0	0	0
Anaemia	33 (18)	6 (3)	0	0	25 (14)	9 (5)	0	0	16 (9)	3 (2)	0	0
Decreased appetite	32 (18)	1 (1)	0	0	26 (15)	0	0	0	11 (6)	0	0	0
Pyrexia	22 (12)	0	0	0	5 (3)	0	0	0	21 (11)	0	0	0
Mucosal inflammation	21 (12)	3 (2)	0	0	14 (8)	3 (2)	0	0	3 (2)	1 (1)	0	0
Vomiting	20 (11)	1 (1)	0	0	25 (14)	3 (2)	0	0	15 (8)	1 (1)	0	0
Pruritus	19 (10)	0	0	0	6 (3)	0	0	0	7 (4)	0	0	0
Diarrhoea	18 (10)	1 (1)	0	0	20 (11)	0	0	0	19 (10)	5 (3)	0	0
Infusion-related reaction*	18 (10)	1 (1)	0	0	13 (7)	0	1 (1)	0	13 (7)	0	0	0
Asthenia	17 (9)	4 (2)	0	0	8 (5)	1 (1)	0	0	8 (4)	0	0	0
Neutropenia	15 (8)	7 (4)	2 (1)	0	17 (10)	7 (4)	2 (1)	0	0	0	0	0
Constipation	14 (8)	0	0	0	17 (10)	0	0	0	6 (3)	0	0	0
Dry skin	13 (7)	0	0	0	6 (3)	1 (1)	0	0	5 (3)	0	0	0
WBC count decreased	10 (5)	5 (3)	0	0	10 (6)	4 (2)	1 (1)	0	3 (2)	0	0	0
Platelet count decreased	10 (5)	0	0	0	6 (3)	1 (1)	0	0	3 (2)	0	1 (1)	0
Neutrophil count decreased	9 (5)	7 (4)	1 (1)	0	3 (2)	6 (3)	1 (1)	0	3 (2)	0	0	0
Rash maculopapular	9 (5)	5 (3)	0	0	8 (5)	1 (1)	0	0	3 (2)	0	0	0
Dyspnoea	9 (5)	0	0	0	9 (5)	0	0	0	7 (4)	1 (1)	0	0
Oedema peripheral	7 (4)	1 (1)	0	0	3 (2)	0	0	0	1 (1)	0	0	0
Lymphocyte count decreased	6 (3)	5 (3)	0	0	3 (2)	1 (1)	0	0	0	0	0	0
Oropharyngeal pain	6 (3)	1 (1)	0	0	5 (3)	0	0	0	0	0	0	0
Neuropathy peripheral	6 (3)	1 (1)	0	0	4 (2)	0	0	0	1 (1)	0	0	0
Abdominal pain	5 (3)	1 (1)	0	0	8 (5)	1 (1)	0	0	10 (5)	0	0	0

Thrombocytopenia	5 (3)	0	0	0	4 (2)	1 (1)	0	0	0	0	0	0
AST increased	5 (3)	0	0	0	2 (1)	0	0	0	0	2 (1)	0	0
ALT increased	4 (2)	2 (1)	0	0	2 (1)	0	0	0	2 (1)	0	0	0
Oral candidiasis	4 (2)	1 (1)	0	0	5 (3)	0	0	0	0	0	0	0
Skin toxicity	4 (2)	1 (1)	0	0	1 (1)	1 (1)	0	0	0	0	0	0
Hyponatraemia	4 (2)	1 (1)	0	0	1 (1)	0	1 (1)	0	1 (1)	3 (2)	0	0
Oesophagitis	4 (2)	1 (1)	0	0	1 (1)	0	0	0	0	0	0	0
Influenza like illness	4 (2)	1 (1)	0	0	0	0	0	0	6 (3)	0	0	0
Blood creatine phosphokinase increased	4 (2)	1 (1)	0	0	0	0	0	0	1 (1)	0	0	0
Amylase increased	4 (2)	0	1 (1)	0	0	1 (1)	0	0	3 (2)	0	0	0
Ejection fraction decreased	4 (2)	0	0	0	2 (1)	1 (1)	0	0	0	1 (1)	0	0
GGT increased	3 (2)	1 (1)	1 (1)	0	1 (1)	0	0	0	3 (2)	2 (1)	0	0
Leukopenia	3 (2)	1 (1)	0	0	4 (2)	3 (2)	0	0	1 (1)	0	0	0
Skin exfoliation	3 (2)	1 (1)	0	0	1 (1)	0	0	0	0	0	0	0
Pneumonitis	3 (2)	0	0	0	0	1 (1)	0	0	3 (2)	1 (1)	0	0
Hyperthyroidism	3 (2)	0	0	0	0	0	0	0	4 (2)	1 (1)	0	0
Hypomagnesaemia	2 (1)	2 (1)	0	0	3 (2)	0	0	0	2 (1)	0	0	0
Rash erythematous	2 (1)	0	0	0	0	0	0	0	1 (1)	1 (1)	0	0
Lipase increased	1 (1)	1 (1)	1 (1)	0	0	0	0	0	0	1 (1)	0	0
Rash pruritic	1 (1)	1 (1)	0	0	3 (2)	0	0	0	0	0	0	0
Hypersensitivity	1 (1)	1 (1)	0	0	1 (1)	0	0	0	1 (1)	0	0	0
Adrenal insufficiency	1 (1)	1 (1)	0	0	0	0	0	0	0	0	0	0
Hepatocellular injury	1 (1)	1 (1)	0	0	0	0	0	0	0	0	0	0
Hypopituitarism	1 (1)	1 (1)	0	0	0	0	0	0	0	0	0	0
Abdominal pain lower	1 (1)	0	0	0	1 (1)	1 (1)	0	0	0	0	0	0
Skin ulcer	1 (1)	0	0	0	1 (1)	1 (1)	0	0	0	0	0	0
Lymphopenia	1 (1)	0	0	0	0	1 (1)	0	0	1 (1)	0	0	0
Dehydration	1 (1)	0	0	0	0	1 (1)	0	0	0	2 (1)	0	0
Urinary tract infection	1 (1)	0	0	0	0	1 (1)	0	0	0	0	0	0
Hypokalaemia	0	2 (1)	0	0	2 (1)	1 (1)	0	0	0	0	0	0
Hypertension	0	1 (1)	0	0	1 (1)	0	0	0	1 (1)	2 (1)	0	0
Pneumonia	0	1 (1)	0	0	0	0	0	0	0	1 (1)	0	0

Activated partial thromboplastin time prolonged	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Cholestasis	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Colitis	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Dermatitis diaper	0	1 (1)	0	0	0	0	0	0	0	0	0	0
GGT	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Hypercholesterolaemia	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Localised oedema	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Oral fungal infection	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Pulmonary embolism	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Staphylococcal infection	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Vasculitic ulcer	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Febrile neutropenia	0	0	1 (1)	0	0	1 (1)	2 (1)	0	0	0	0	0
Hypercalcaemia	0	0	1 (1)	0	0	0	0	0	1 (1)	0	0	0
Hyperuricaemia	0	0	1 (1)	0	0	0	0	0	0	0	0	0
Blood creatinine increased	0	0	0	0	2 (1)	0	0	0	2 (1)	1 (1)	0	0
Hypophosphataemia	0	0	0	0	2 (1)	0	0	0	0	1 (1)	0	0
Pancytopenia	0	0	0	0	0	2 (1)	0	0	0	0	0	0
Administration site extravasation	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Anaphylactic reaction	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Device related infection	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Haematemesis	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Hepatic failure	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Influenza	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Septic shock	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Staphylococcal sepsis	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Vaginal infection	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Dermatitis exfoliative generalised	0	0	0	0	0	0	1 (1)	0	0	0	0	0
Sepsis	0	0	0	0	0	0	0	1 (1)	0	0	0	0
Ascites	0	0	0	0	0	0	0	0	2 (1)	2 (1)	0	0
Hyperkalaemia	0	0	0	0	0	0	0	0	1 (1)	1 (1)	0	0

Lichen planus	0	0	0	0	0	0	0	0	1 (1)	1 (1)	0	0
Acute kidney injury	0	0	0	0	0	0	0	0	0	1 (1)	0	0
Atrial fibrillation	0	0	0	0	0	0	0	0	0	1 (1)	0	0
Blood sodium decreased	0	0	0	0	0	0	0	0	0	1 (1)	0	0
CA125 increased	0	0	0	0	0	0	0	0	0	1 (1)	0	0
Haematuria	0	0	0	0	0	0	0	0	0	1 (1)	0	0
Immune-mediated adverse reaction	0	0	0	0	0	0	0	0	0	1 (1)	0	0
Lymphocyte count increased	0	0	0	0	0	0	0	0	0	1 (1)	0	0
Autoimmune hepatitis	0	0	0	0	0	0	0	0	0	0	1 (1)	0
General physical health deterioration	0	0	0	0	0	0	0	0	0	0	1 (1)	0
Renal failure	0	0	0	0	0	0	0	0	0	0	1 (1)	0
Respiratory failure	0	0	0	0	0	0	0	0	0	0	1 (1)	0
Intestinal obstruction	0	0	0	0	0	0	0	0	0	0	0	1 (1)

* Single preferred term

ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT= gamma-glutamyltransferase. PLD=pegylated liposomal doxorubicin.

PPE=palmar-plantar erythrodysaesthesia syndrome. TRAE=treatment-related adverse event. WBC=white blood cell.

TRAEs of grade 1-2 occurring in ≥10% of patients and all grade 3, 4, or 5 are shown.

Table S5. Adverse events of special interest

	Avelumab + PLD (n=182)		**PLD (n=177)**		**Avelumab (n=187)**	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
irAE, n (%)*	**51 (28)**	**15 (8)**	**8 (5)**	**1 (1)**	**25 (13)**	**7 (4)**
Immune-related rash	33 (18)	12 (7)	6 (3)	1 (1)	6 (3)	1 (1)
Hypothyroidism	17 (9)	0	2 (1)	0	7 (4)	0
Hyperthyroidism	3 (2)	0	0	0	5 (3)	1 (1)
Pneumonitis	3 (2)	0	0	0	4 (2)	1 (1)
ALT increase	1 (1)	1 (1)	0	0	2 (1)	1 (1)
AST increased	0	0	0	0	2 (1)	2 (1)
Adrenal insufficiency	2 (1)	1 (1)	0	0	0	0
Hypopituitarism	2 (1)	1 (1)	0	0	0	0
Infusion-related reaction, n (%)	**30 (16)**	**1 (1)**	**17 (10)**	**2 (1)**	**38 (20)**	**0**

ALT=alanine aminotransferase. AST=aspartate aminotransferase. irAE=immune-related adverse event. PLD=pegylated liposomal doxorubicin.

* Immune-related adverse events of any grade in ≥2 patients are shown.

Table S6. Summary of patient-reported outcomes based on the EORTC QLQ-C30 and QLQ-OV28 questionnaires

	Avelumab + PLD (N=188)				PLD (N=190)				Avelumab (N=188)			
	N*	Deterior-ation, n (%)	Improve-ment, n (%)	Stable, n (%)	N*	Deterior-ation, n (%)	Improve-ment, n (%)	Stable, n (%)	N*	Deterior-ation, n (%)	Improve-ment, n (%)	Stable, n (%)
EORTC QLQ-C30												
Global quality of life	166	65 (39)	20 (12)	81 (49)	148	46 (31)	26 (18)	76 (51)	152	46 (30)	23 (15)	83 (55)
Functional scales												
Physical	165	50 (30)	19 (12)	96 (58)	148	44 (30)	12 (8)	92 (62)	152	45 (30)	21 (14)	86 (57)
Role	165	73 (44)	21 (13)	71 (43)	148	51 (34)	27 (18)	70 (47)	152	58 (38)	22 (14)	72 (47)
Emotional	166	22 (13)	40 (24)	104 (63)	148	18 (12)	41 (28)	89 (60)	152	37 (24)	31 (20)	84 (55)
Cognitive	166	46 (28)	38 (23)	82 (49)	148	39 (26)	25 (17)	84 (57)	152	35 (23)	24 (16)	93 (61)
Social	166	49 (30)	38 (23)	79 (48)	148	45 (30)	26 (18)	77 (52)	152	48 (32)	35 (23)	69 (45)
Symptom scales/items												
Fatigue	166	72 (43)	30 (18)	64 (39)	147	54 (37)	22 (15)	71 (48)	152	69 (45)	24 (16)	59 (39)
Nausea and vomiting	166	41 (25)	16 (10)	109 (66)	148	26 (18)	12 (8)	110 (74)	151	42 (28)	17 (11)	92 (61)
Pain	166	57 (34)	41 (25)	68 (41)	148	50 (34)	38 (26)	60 (41)	152	52 (34)	31 (20)	69 (45)
Dyspnoea	164	54 (33)	25 (15)	85 (52)	146	44 (30)	31 (21)	71 (49)	152	43 (28)	22 (14)	87 (57)
Insomnia	166	45 (27)	46 (28)	75 (45)	146	37 (25)	39 (27)	70 (48)	150	41 (27)	43 (29)	66 (44)
Appetite loss	166	63 (38)	31 (19)	72 (43)	148	57 (39)	19 (13)	72 (49)	149	50 (34)	17 (11)	82 (55)
Constipation	166	59 (36)	38 (23)	69 (42)	147	42 (29)	28 (19)	77 (52)	152	39 (26)	27 (18)	86 (57)

Diarrhoea	164	32 (20)	30 (18)	102 (62)	146	30 (21)	27 (18)	89 (61)	151	31 (21)	19 (13)	101 (67)
Financial difficulties	166	27 (16)	28 (17)	111 (67)	148	23 (16)	24 (16)	101 (68)	152	15 (10)	24 (16)	113 (74)
EORTC QLQ-OV28												
Symptom scale												
Abdominal/GI symptoms	165	38 (23)	30 (18)	97 (59)	147	26 (18)	34 (23)	87 (59)	153	37 (24)	17 (11)	99 (65)
Peripheral neuropathy	165	49 (30)	32 (19)	84 (51)	146	46 (32)	24 (16)	76 (52)	153	49 (32)	38 (25)	66 (43)
Other chemotherapy side-effects	165	43 (26)	33 (20)	89 (54)	146	30 (21)	25 (17)	91 (62)	153	26 (17)	21 (14)	106 (69)
Hormonal/menopausal symptoms	165	37 (22)	43 (26)	85 (52)	146	32 (22)	31 (21)	83 (57)	153	30 (20)	24 (16)	99 (65)
Body image	165	42 (25)	44 (27)	79 (48)	144	39 (27)	35 (24)	70 (49)	151	40 (26)	38 (25)	73 (48)
Attitude to disease/treatment	165	44 (27)	61 (37)	60 (36)	142	34 (24)	54 (38)	54 (38)	151	40 (26)	65 (43)	46 (30)
Sexuality	160	17 (11)	14 (9)	129 (81)	138	17 (12)	13 (9)	108 (78)	140	21 (15)	8 (6)	111 (79)

Higher scores represent higher (better) levels of functioning and/or a higher (worse) level of symptoms. A ≥10-point worsening or improvement in the average of mean changes was classed as deterioration or improvement, respectively; patients with neither deterioration nor improvement were classed as stable.

EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30.

EORTC QLQ-OV28=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Ovarian Cancer 28.

GI=gastrointestinal.

* Number of patients with a baseline and postbaseline score for the specific subscale.