The Lancet Oncology

Avelumab in combination with and/or following chemotherapy versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100): results from a randomised phase 3 trial terminated at interim analysis

--Manuscript Draft--

Abstract: Background: Although most patients with epithelial ovarian cancer (EOC) respond to frontline platinum-based chemotherapy, the majority will relapse within 3 years. The phase 3 JAVELIN Ovarian 100 trial compared avelumab (anti–PD-L1) in combination with and/or following chemotherapy vs chemotherapy alone in patients with treatment-naive EOC.

Methods: Eligible women aged ≥18 years with stage III–IV epithelial ovarian, fallopian tube, or peritoneal cancer (post-debulking/cytoreductive surgery or candidates for neoadjuvant chemotherapy) and an Eastern Cooperative Oncology Group performance status of 0 or 1 were randomised (1:1:1) via interactive response technology to receive chemotherapy (6 cycles; carboplatin AUC 5 or 6 intravenously [IV] every 3 weeks [Q3W] plus paclitaxel 175 mg/m2 Q3W or 80 mg/m2 weekly [investigators' choice]) followed by avelumab maintenance (10 mg/kg IV every 2 weeks [Q2W]), chemotherapy plus avelumab (10 mg/kg IV Q3W) followed by avelumab maintenance (10 mg/kg IV Q2W), or chemotherapy followed by observation (control).

Randomization was stratified by paclitaxel regimen (weekly vs Q3W) and resection status (residual tumour; complete/microscopic vs incomplete ≤1 cm vs incomplete >1 cm vs neoadjuvant). The primary endpoint was progression-free survival (PFS) by blinded independent central review in all randomised patients (analysed by intention-to-treat). This trial is registered with ClinicalTrials.gov, number NCT02718417. The trial was fully enrolled and terminated at interim analysis for futility and efficacy is no longer being assessed. Results are reported from the interim analysis, which is the only analysis of the primary endpoint.

Findings: Between May 19, 2016 and Jan 23, 2018, 998 patients were randomised. At the planned interim analysis (data cutoff Sept 7, 2018), PFS was not improved in either avelumab arm vs control, prespecified futility boundaries were crossed, and the trial was stopped as recommended by the Independent Data Monitoring Committee. Median duration of follow-up for PFS was 10·8 months (IQR 7·1–14·9) for all patients, 11·1 months (interquartile range [IQR] 7·0–15·3) for chemotherapy followed by avelumab; 11·0 months (IQR 7·4–14·5) for chemotherapy plus avelumab followed by avelumab; and 10·2 months (IQR 6·7–14·0) for the control arm. Hazard ratios (95% CI) for PFS vs control were 1·43 (1·051–1·946) for chemotherapy followed by avelumab and 1·14 (0·832–1·565) for chemotherapy plus avelumab followed by avelumab. Median PFS (95% CI) was 16·8 months (13·5 to not estimable [NE]) with chemotherapy followed by avelumab, 18·1 months (14·8–NE) with chemotherapy plus avelumab followed by avelumab, and NE (18·2 months to NE) with control. No new safety signals were observed. In the chemotherapy followed by avelumab, chemotherapy plus avelumab followed by avelumab, and control arms, grade ≥3 treatment-emergent adverse events occurred in 68%, 72%, and 63%, respectively. The most common grade 3–4 adverse events (≥10% of patients) were anaemia (69 [21%] in the chemotherapy followed by avelumab arm, 63 [19%] in the chemotherapy plus avelumab followed by avelumab arm, 53 [16%] in the control arm), neutropenia (91 [28%], 99 [30%], 88 [26%]), and neutrophil count decreased (49 [15%], 45 [14%], 59 [18%]). In the chemotherapy followed by avelumab, chemotherapy plus avelumab followed by avelumab, and control arms, serious adverse events occurred in 92 (28%), 118 (36%), and 64 patients (19%), respectively. Treatment-related deaths occurred in 1 patient (<1%) in the chemotherapy followed by avelumab arm (atrial fibrillation) and 1 patient (<1%) in the chemotherapy plus avelumab followed by avelumab arm (disease progression).

Interpretation: This trial did not meet its primary objectives of significantly improving PFS with frontline avelumab in combination with and/or following chemotherapy vs chemotherapy alone in advanced EOC. Results do not support the use of avelumab in the frontline treatment setting.

Funding: Pfizer and Merck KGaA, Darmstadt, Germany.

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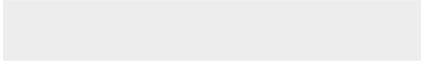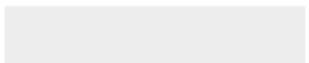
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Figure 2
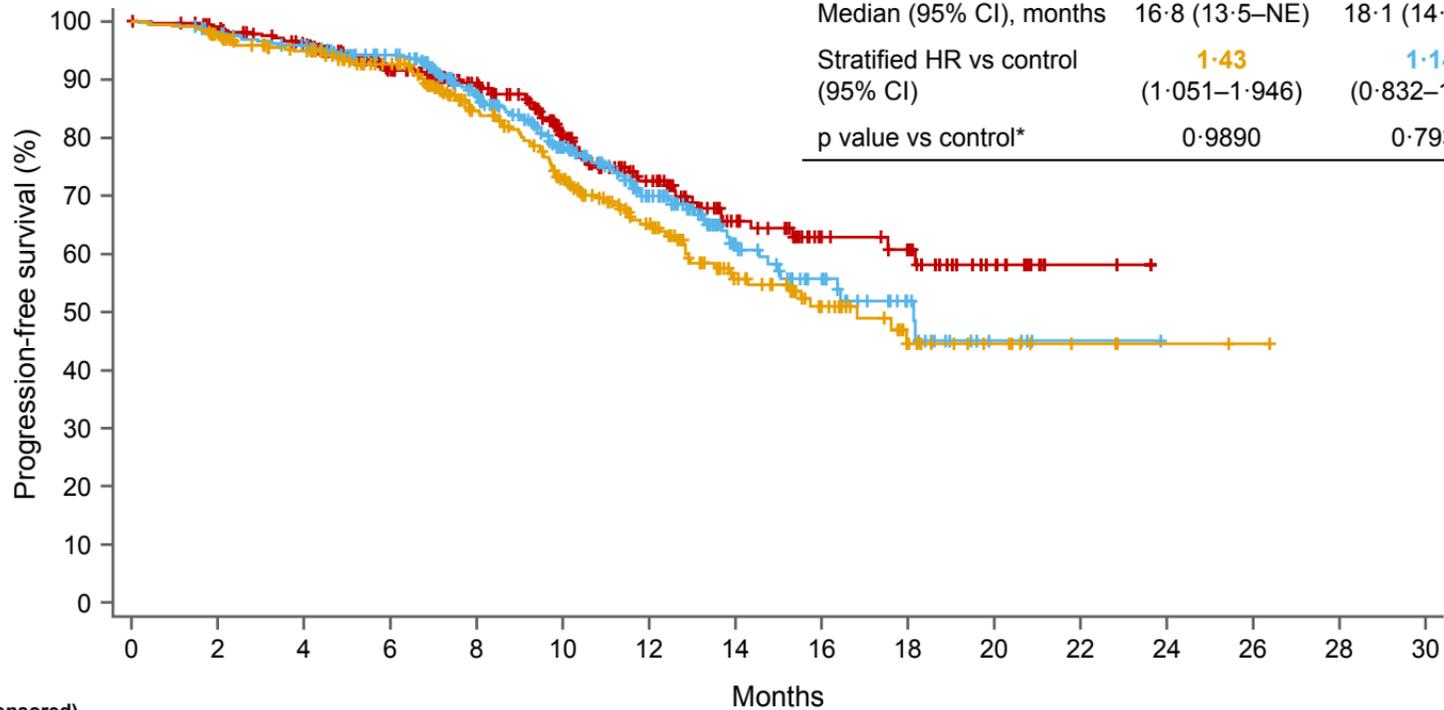
	Chemo → Avel (N=332)	Chemo + Avel → Avel (N=331)	Chemo → Obs (N=335)
Events, n (%)	99 (29·8)	88 (26·6)	70 (20·9)
Median (95% CI), months	16·8 (13·5–NE)	18·1 (14·8–NE)	NE (18·2–NE)
Stratified HR vs control (95% CI)	1·43 (1·051–1·946)	1·14 (0·832–1·565)	–
p value vs control*	0·9890	0·7935	–

No. at risk (No. censored)

Chemo → Avel	332 (0)	303 (22)	280 (36)	252 (58)	186 (104)	143 (122)	100 (152)	58 (182)	36 (200)	18 (215)	10 (223)	4 (229)	2 (231)	1 (232)
Chemo + Avel → Avel	331 (0)	310 (15)	297 (21)	271 (42)	211 (84)	157 (118)	101 (160)	54 (198)	33 (214)	17 (228)	4 (239)	1 (242)		
Chemo → Obs	335 (0)	313 (19)	294 (29)	241 (69)	190 (115)	136 (152)	90 (186)	55 (214)	32 (235)	26 (240)	10 (255)	2 (263)		

Figure 3A

Subgroup		Events/patients Chemo → Avelumab	Chemo → Observation		HR (95% CI)
All patients	Stratified	99/332	70/335		1·43 (1·051–1·946)
	Unstratified	99/332	70/335		1·39 (1·026–1·894)
Paclitaxel regimen	QW	31/100	19/104		1·47 (0·828–2·598)
	Q3W	68/232	51/231		1·37 (0·950–1·966)
Resection	Complete/microscopic	19/105	17/105		1·03 (0·534–1·980)
	Incomplete ≤1 cm	8/34	8/36		0·92 (0·347–2·464)
	Incomplete >1 cm	20/57	11/57		2·08 (0·988–4·362)
	Neoadjuvant	52/136	34/137		1·54 (1·001–2·379)
Geographical region	North America	23/93	17/85		0·83 (0·441–1·575)
	Europe	52/147	31/149		1·75 (1·119–2·729)
	Asia	21/78	21/90		1·24 (0·679–2·279)
	Rest of the world	3/14	1/11		2·43 (0·252–23·369)
Stage	III	59/252	51/247		1·07 (0·738–1·563)
	IV	40/77	17/81		2·78 (1·576–4·915)
ECOG PS	0	40/184	38/190		1·04 (0·666–1·621)
	≥1	56/144	32/140		1·75 (1·132–2·702)
CA-125 at baseline	≤2 x ULN	19/86	14/93		1·45 (0·724–2·888)
	>2 x ULN	79/238	55/236		1·41 (0·997–1·987)

Favors Chemo → Avelumab   Favors Chemo → Observation

Figure 3B

	Subgroup	Events/patients		HR (95% CI)
		Chemo + Avel → Avel	Chemo → Observation	
All patients	Stratified	88/331	70/335	1·14 (0·832–1·565)
	Unstratified	88/331	70/335	1·18 (0·858–1·609)
Paclitaxel regimen	QW	25/102	19/104	1·20 (0·658–2·174)
	Q3W	63/229	51/231	1·17 (0·806–1·690)
Resection	Complete/microscopic	22/105	17/105	1·27 (0·672–2·387)
	Incomplete ≤1 cm	8/35	8/36	1·02 (0·380–2·737)
	Incomplete >1 cm	18/55	11/57	1·55 (0·726–3·303)
	Neoadjuvant	40/136	34/137	1·01 (0·639–1·598)
Geographical region	North America	27/103	17/85	0·86 (0·466–1·593)
	Europe	38/139	31/149	1·14 (0·711–1·840)
	Asia	22/79	21/90	1·35 (0·742–2·470)
	Rest of the world	1/10	1/11	1·05 (0·066–16·869)
Stage	III	65/265	51/247	1·09 (0·754–1·572)
	IV	22/64	17/81	1·58 (0·839–2·979)
ECOG PS	0	39/181	38/190	0·99 (0·634–1·553)
	≥1	47/146	32/140	1·31 (0·832–2·047)
CA-125 at baseline	≤2 x ULN	9/73	14/93	0·87 (0·377–2·020)
	>2 x ULN	79/255	55/236	1·17 (0·827–1·649)

Favors Chemo + Avel → Avel   Favors Chemo → Observation

1   **JAVELIN Ovarian 100 primary manuscript**

2   **Title:** Avelumab in combination with and/or following chemotherapy versus chemotherapy

3   alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100):

4   results from a randomised phase 3 trial terminated at interim analysis.

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15   * These authors were co-international leads for this trial and contributed equally to the

16   manuscript.

17   [†]At the time the study was conducted.

18

19 **Abstract**

20 **Background:** Although most patients with epithelial ovarian cancer (EOC) respond to

21 frontline platinum-based chemotherapy, the majority will relapse within 3 years. The phase 3

22 JAVELIN Ovarian 100 trial compared avelumab (anti–PD-L1) in combination with and/or

23 following chemotherapy vs chemotherapy alone in patients with treatment-naive EOC.

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25 or peritoneal cancer (post-debulking/cytoreductive surgery or candidates for neoadjuvant

26 chemotherapy) and an Eastern Cooperative Oncology Group performance status of 0 or 1

27 were randomised (1:1:1) via interactive response technology to receive chemotherapy (6

28 cycles; carboplatin AUC 5 or 6 intravenously [IV] every 3 weeks [Q3W] plus paclitaxel 175

29 mg/m^2 Q3W or 80 mg/m^2 weekly [investigators' choice]) followed by avelumab maintenance

30 (10 mg/kg IV every 2 weeks [Q2W]), chemotherapy plus avelumab (10 mg/kg IV Q3W)

31 followed by avelumab maintenance (10 mg/kg IV Q2W), or chemotherapy followed by

32 observation (control). Randomization was stratified by paclitaxel regimen (weekly vs Q3W)

33 and resection status (residual tumour; complete/microscopic vs incomplete ≤1 cm vs

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39 the primary endpoint.

40 **Findings:** Between May 19, 2016 and Jan 23, 2018, 998 patients were randomised. At the

41 planned interim analysis (data cutoff Sept 7, 2018), PFS was not improved in either

42 avelumab arm vs control, prespecified futility boundaries were crossed, and the trial was

43 stopped as recommended by the Independent Data Monitoring Committee. Median duration

44 of follow-up for PFS was 10·8 months (IQR 7·1–14·9) for all patients, 11·1 months

45 (interquartile range [IQR] 7·0–15·3) for chemotherapy followed by avelumab; 11·0 months

46   (IQR 7·4–14·5) for chemotherapy plus avelumab followed by avelumab; and 10·2 months

47   (IQR 6·7–14·0) for the control arm. Hazard ratios (95% CI) for PFS vs control were 1·43

48   (1·051–1·946) for chemotherapy followed by avelumab and 1·14 (0·832–1·565) for

49   chemotherapy plus avelumab followed by avelumab. Median PFS (95% CI) was 16·8

50   months (13·5 to not estimable [NE]) with chemotherapy followed by avelumab, 18·1 months

51   (14·8–NE) with chemotherapy plus avelumab followed by avelumab, and NE (18·2 months

52   to NE) with control. No new safety signals were observed. In the chemotherapy followed by

53   avelumab, chemotherapy plus avelumab followed by avelumab, and control arms, grade ≥3

54   treatment-emergent adverse events occurred in 68%, 72%, and 63%, respectively. The most

55   common grade 3–4 adverse events (≥10% of patients) were anaemia (69 [21%] in the

56   chemotherapy followed by avelumab arm, 63 [19%] in the chemotherapy plus avelumab

57   followed by avelumab arm, 53 [16%] in the control arm), neutropenia (91 [28%], 99 [30%], 88

58   [26%]), and neutrophil count decreased (49 [15%], 45 [14%], 59 [18%]). In the chemotherapy

59   followed by avelumab, chemotherapy plus avelumab followed by avelumab, and control

60   arms, serious adverse events occurred in 92 (28%), 118 (36%), and 64 patients (19%),

61   respectively. Treatment-related deaths occurred in 1 patient (<1%) in the chemotherapy

62   followed by avelumab arm (atrial fibrillation) and 1 patient (<1%) in the chemotherapy plus

63   avelumab followed by avelumab arm (disease progression).

64   **Interpretation:** This trial did not meet its primary objectives of significantly improving PFS

65   with frontline avelumab in combination with and/or following chemotherapy vs chemotherapy

66   alone in advanced EOC. Results do not support the use of avelumab in the frontline

67   treatment setting.

68   **Funding:** Pfizer and Merck KGaA, Darmstadt, Germany.

69 **Research in context**

70 *Evidence before this study*

71 Platinum-based chemotherapy administered before or after debulking surgery is the current

72 standard-of-care frontline treatment for patients with advanced epithelial ovarian cancer

73 (EOC). Additionally, the anti-vascular endothelial growth factor antibody, bevacizumab, is

74 administered with chemotherapy and/or used as maintenance in some patients where

75 available. Most patients respond to initial treatment; nonetheless, approximately 70% of

76 patients will relapse within 3 years. Because immunologic activity appears to predict

77 outcomes in patients with EOC, there has been interest in investigating the use of immune

78 checkpoint inhibitors in this disease. Single-agent immune checkpoint inhibitor treatment has

79 shown limited activity in early-phase trials in patients with recurrent EOC. Combining anti–

80 PD-1/PD-L1 agents with chemotherapy has the potential to increase efficacy, as seen in

81 randomised trials in other tumours. Using immune checkpoint inhibitors as either switch or

82 continuation maintenance could therefore increase and/or prolong the benefits of frontline

83 therapy. We conducted a literature search using PubMed on May 4, 2021, using the terms

84 ("ovarian cancer" OR "epithelial ovarian cancer") AND ("PD-1" OR "PD-L1" OR "programmed

85 death" OR "checkpoint inhibitor") AND ("study" OR "trial") for clinical trials of immune

86 checkpoint inhibitors in EOC published in English. We identified 15 manuscripts reporting

87 data from phase 1–3 trials in various EOC populations (5 phase 1, 1 phase 1/2, 6 phase 2,

88 and 1 phase 3 trial). No manuscripts were found that reported a clinical study of an immune

89 checkpoint inhibitor as maintenance treatment in patients with EOC. One manuscript

90 reported a phase 3 clinical study of an immune checkpoint inhibitor combined with

91 chemotherapy in the frontline setting; this study (IMagyn050) investigated the addition of

92 atezolizumab, an anti–PD-L1 antibody, to platinum-based chemotherapy and bevacizumab

93 vs placebo in patients with treatment-naive stage III/IV EOC. In this trial, the addition of

94   atezolizumab did not significantly improve progression-free survival in the overall or PD-L1+

95   populations.

96   *Added value of this study*

97   To our knowledge, JAVELIN Ovarian 100 is one of the first phase 3 trials of an immune

98   checkpoint inhibitor in patients with previously untreated EOC to be reported. The trial failed

99   to meet either of its two primary objectives of significantly improving progression-free

100   survival with chemotherapy followed by avelumab or chemotherapy plus avelumab followed

101   by avelumab vs chemotherapy followed by observation. Subgroup analyses based on

102   baseline characteristics, stratification factors, or PD-L1 status did not identify subsets with

103   clear benefit in either avelumab arm. No new safety signals were observed in either

104   avelumab arm.

105   *Implications of all the available evidence*

106   The findings from this trial suggest that the addition of an immune checkpoint inhibitor to

107   frontline chemotherapy does not improve progression-free survival in the overall population,

108   highlighting that further study is needed to determine whether immune checkpoint inhibitors

109   have a role in frontline treatment of EOC.

Introduction

Ovarian cancer is responsible for approximately 185,000 deaths annually worldwide.[1] More than 70% of women diagnosed with ovarian cancer have advanced disease.[2,3] Ovarian cancer is a heterogenous disease; however, most tumours (approximately 90%) are epithelial ovarian cancers (EOC),[3] a term that also includes cancers originating from cells lining the fallopian tubes and peritoneum, which are managed similarly.[4] Current standard-of-care frontline treatment for patients with advanced EOC consists of combination carboplatin and paclitaxel chemotherapy before or after debulking surgery.[3,4] Frontline treatment with bevacizumab, an anti-vascular endothelial growth factor antibody, in combination with chemotherapy followed by bevacizumab maintenance is approved in various countries worldwide for the treatment of advanced EOC irrespective of biomarker status. The addition of bevacizumab is associated with an improvement in progression-free survival (PFS) but an overall survival (OS) benefit was limited to women at high risk of disease recurrence.[5,6] Currently, most patients (around 70–80%) respond to initial treatment; however, median PFS ranges from 10 to 17 months,[5,7-10] and approximately 70% of patients will relapse within 3 years.[3]

Although not considered a strongly immunogenic cancer, EOC tumours are characterised by immunologic activity. Programmed death ligand 1 (PD-L1), a key suppressor of T cell function, is expressed on ovarian tumour cells and tumour-infiltrating lymphocytes in more than half of patients.[11] The presence of tumour-infiltrating lymphocytes, specifically CD8+ T cells, is associated with longer OS.[12] Trials of immune checkpoint inhibitors as monotherapy in patients with previously treated EOC have shown limited clinical activity,[13-15] prompting interest in the use of immune checkpoint inhibitors in combination with established treatments. Furthermore, accumulating evidence suggests that chemotherapy agents may regulate antitumour immune responses. For example, cytotoxic chemotherapy can stimulate tumour immunosurveillance by increasing antigen release and presentation, modifying the suppressive tumour microenvironment (eg, by suppressing T regulatory cells), and

7

137   promoting infiltration of T cells, potentially making tumours more susceptible to immune

138   attack.[16,17] It has also been hypothesised that DNA-damaging chemotherapies could

139   increase the mutational burden within tumours, thereby increasing the repertoire of

140   neoantigens available for tumour-directed immune responses.[18] Therefore, it was

141   hypothesized that combining chemotherapy with an immune checkpoint inhibitor could

142   provide improved clinical activity by stimulating the activity of CD8+ tumour-infiltrating

143   lymphocytes and overcoming immunosuppressive mechanisms. Increased clinical activity

144   and manageable toxicity have been seen in trials of combined

145   chemotherapy/immunotherapy regimens in other tumour types;[19-21] however, data in EOC

146   with similar treatment regimens are limited.

147   Avelumab, an anti–PD-L1 monoclonal antibody, showed clinical activity as monotherapy in a

148   cohort of a phase 1b study that included 125 heavily treated patients with resistant or

149   refractory EOC, with an objective response rate of 10%.[13] However, in the phase 3 JAVELIN

150   Ovarian 200 trial, avelumab did not show superiority vs pegylated liposomal doxorubicin

151   (PLD), either as monotherapy or in combination with PLD in patients with platinum-resistant

152   or platinum-refractory EOC.[22]

153   Here, we report results from the randomised, open-label, phase 3 JAVELIN Ovarian 100

154   trial, which compared avelumab in combination with and/or following frontline platinum-

155   based chemotherapy vs chemotherapy followed by observation in patients with previously

156   untreated EOC.

157

158   **Methods**

159   *Study design and participants*

160   JAVELIN Ovarian 100 was a global, open-label, three-arm parallel, phase 3 trial at 159

161   hospitals and cancer treatment centres in 25 countries (Bulgaria, Canada, Croatia, Estonia,

162   Germany, Hong Kong, Hungary, Ireland, Italy, Japan, Republic of Korea, Latvia, Mexico,

163 Netherlands, Poland, Romania, Russia, Singapore, Slovakia, Switzerland, Taiwan, Turkey,

164 Ukraine, UK, and USA). Eligible patients were aged ≥18 years (≥20 years in Japan); had

165 previously untreated, histologically confirmed, stage III–IV (per the American Joint

166 Committee on Cancer and Union for International Cancer Control TNM cancer staging

167 system and the International Federation of Gynaecology and Obstetrics Staging System

168 2014 edition) epithelial ovarian, fallopian tube, or primary peritoneal cancer (including

169 malignant mixed Müllerian tumours with a high-grade serous component); and had received

170 debulking surgery or were candidates for neoadjuvant chemotherapy. Patients enrolled prior

171 to initiation of neoadjuvant chemotherapy underwent interval debulking surgery after 3 cycles

172 of chemotherapy (± avelumab) and then completed the remaining 3 cycles post-surgery.

173 Other eligibility criteria included Eastern Cooperative Oncology Group performance status of

174 0 or 1; estimated life expectancy >3 months; adequate haematologic (absolute neutrophil

175 count ≥1·5×10^9 per L, haemoglobin ≥9 g per dL, and platelet count ≥100×10^9 per L), hepatic

176 (aspartate and alanine aminotransferase concentrations ≤2·5×upper limit of normal and total

177 bilirubin concentration ≤1·5×upper limit of normal), and renal (creatinine clearance ≥50

178 mL/min according to the Cockcroft-Gault equation) function; and negative pregnancy test

179 and use of effective contraception (women of childbearing potential). All patients were

180 required to have an archival formalin-fixed, paraffin-embedded tumour tissue block or a

181 minimum of 15 tumour slides. If archived tissue was not available, a de novo (ie, fresh)

182 tumour sample was obtained. Exclusion criteria included nonepithelial tumour or tumour with

183 low malignant potential (ie, borderline tumour); mucinous tumours; cancer for which

184 bevacizumab was identified as a clinically beneficial frontline treatment; planned

185 intraperitoneal chemotherapy; prior treatment with a T-cell–targeting immune checkpoint

186 inhibitor; known brain, leptomeningeal, or spinal cord metastases; other cancer diagnosis

187 within 5 years; known hypersensitivity to monoclonal antibodies, carboplatin, or paclitaxel;

188 and serious cardiovascular disease or other severe medical condition. Full eligibility criteria

189 are listed in the appendix.

190 The trial was conducted in accordance with the ethics principles of the Declaration of

191 Helsinki and the International Council on Harmonisation guidelines on Good Clinical

192 Practice. The protocol was approved by the institutional review board or ethics committee of

193 each centre. All patients (or their legal representatives) provided written informed consent

194 before enrolment.

195 *Randomisation and masking*

196 Patients were enrolled by study investigators and were centrally randomized (1:1:1) via

197 interactive response technology to receive either chemotherapy (6 cycles; carboplatin plus

198 paclitaxel) followed by avelumab maintenance, chemotherapy plus avelumab followed by

199 avelumab maintenance, or chemotherapy followed by observation (stratified permuted block

200 randomisation with a block size of six). Randomisation was stratified by paclitaxel regimen

201 (weekly [QW] vs every 3 weeks [Q3W]) and resection status (residual tumour;

202 complete/microscopic vs incomplete ≤1 cm vs incomplete >1 cm vs neoadjuvant). The trial

203 was open label, although patients and investigators were blinded to assignment to the two

204 chemotherapy arms without avelumab at time of randomisation until completion of the

205 chemotherapy phase. The sponsor and BICR committee (third party) remained blinded to

206 treatment assignments until after study termination.

207 *Procedures*

208 Avelumab was administered at a dose of 10 mg/kg by 1-hour intravenous (IV) infusion Q3W

209 in the chemotherapy phase and 10 mg/kg every 2 weeks in the maintenance phase.

210 Chemotherapy regimens consisted of 6 cycles of either paclitaxel 80 mg/m^2 by 1-hour IV

211 infusion QW or 175 mg/m^2 by 3-hour IV infusion Q3W (investigators choice; once selected,

212 dosage was not changed for the study duration) plus carboplatin area under the serum-

213 concentration-time curve (AUC) 5 or 6 by 1-hour IV infusion Q3W. Carboplatin was

214 administered 1 hour after completing the paclitaxel infusion. Premedication with an

215 antihistamine (eg, oral or IV diphenhydramine 25–50 mg or equivalent) and paracetamol

216 (acetaminophen; eg, oral or IV paracetamol 500–650 mg or equivalent) was mandatory 30–

217 60 minutes prior to each avelumab infusion. Premedications to minimise toxicities related to

218 chemotherapy were administered according to local guidelines. For avelumab, no dose

219 reductions were permitted; carboplatin and/or paclitaxel doses could be reduced following

220 significant toxicity based on investigator judgment.

221 After completing the chemotherapy phase, if the patient had experienced stable disease or a

222 partial or complete response, they entered the maintenance phase. Treatment was given

223 until disease progression (assessed by investigator but confirmed by blinded independent

224 central review [BICR]), unacceptable toxicity, or withdrawal (potential reasons leading to

225 withdrawal included global deterioration of health status, pregnancy, significant protocol

226 deviation, patient refusal, loss to follow up, termination of the study by the sponsor, or death;

227 appendix, p 26); avelumab could be continued while awaiting confirmation of disease

228 progression based on the investigator's clinical judgment. Treatment in the maintenance

229 phase was received for a maximum of 24 months (excluding the chemotherapy phase).

230 Patients who discontinued (or, if receiving observation maintenance, reached the end of

231 treatment or withdrew) were followed every 12 weeks until death or end of study. Crossover

232 between study arms was not permitted.

233 Tumours were assessed by computed tomography or magnetic resonance imaging at

234 baseline, after 3 cycles of chemotherapy, and at completion of chemotherapy to determine

235 eligibility for maintenance. Patients who underwent interval debulking surgery were required

236 to have an additional tumour assessment after surgery. Assessments were performed every

237 12 weeks in the maintenance phase until confirmed disease progression, irrespective of

238 subsequent anticancer therapy. Objective tumour response was evaluated per Response

239 Evaluation Criteria in Solid Tumours (RECIST) version 1.1 based on BICR. Complete and

240 partial responses and progressive disease were confirmed by repeated imaging performed

241 ≥4 weeks after initial documentation. Blood samples were taken at each trial visit (QW for

242 those receiving paclitaxel QW) for haematology and day 1 of each cycle in the

11

243   chemotherapy phase and Q2W in the maintenance phase for other routine laboratory

244   analyses, including core serum chemistry and haemostaseology. Urine samples were taken

245   at screening and on day 1 of each cycle in the maintenance phase for urinalysis.

246   Adrenocorticotropic hormone, free thyroxine, and thyroid-stimulating hormone

247   concentrations were tested at screening, on day 1 of each odd cycle of the chemotherapy

248   phase, day 1 of the third cycle of the maintenance phase, and then every 12 weeks

249   thereafter while on treatment. Adverse events (AEs) and laboratory abnormalities were

250   graded according to the US National Cancer Institute's Common Terminology Criteria for

251   Adverse Events version 4·03. Immune-related AEs and infusion-related reactions were

252   identified using a prespecified list of terms in the Medical Dictionary for Regulatory Activities.

253   PD-L1 expression was assessed in pretreatment tissue samples using an

254   immunohistochemical assay based on the SP263 (Ventana Medical Systems) antibody.

255   Selection of the PD-L1 cutoff was based on post hoc analyses of several scoring algorithms

256   and cutoffs from the JAVELIN Ovarian 200 trial, and the optimal cutoff for predicting

257   improved activity for the combination of avelumab and chemotherapy was selected. A

258   sample was considered PD-L1+ if the percentage of tumour cells expressing membranous

259   PD-L1 was ≥1% and/or the percentage of tumour area populated by PD-L1+ immune cells

260   was ≥5%.

261   An external data monitoring committee was established to review safety and efficacy data

262   from the trial.

263   *Outcomes*

264   The primary endpoint was PFS by BICR (defined as the time from randomisation to the date

265   of the first documented disease progression per RECIST 1·1 or death due to any cause,

266   whichever occurred first). Secondary endpoints included OS (defined as the time from

267   randomisation to the date of death due to any cause); PFS by investigator assessment per

268   RECIST 1·1; objective response, duration of response, and maintenance PFS (defined in

269　patients who did not have disease progression by BICR during the chemotherapy phase and

270　entered maintenance phase as the time from initiating maintenance treatment to the date of

271　first documented disease progression per RECIST 1·1 or death due to any cause, whichever

272　occurred first); pathological complete response; PFS2 (defined as the time from

273　randomisation to start of second subsequent treatment after objective disease progression,

274　or death due to any cause, whichever occurred first); PFS by Gynecological Cancer

275　Intergroup (GCIG) criteria; safety and tolerability; pharmacokinetic parameters;

276　immunogenicity of avelumab; tumour biomarker assessments (including, but not limited to,

277　PD-L1 expression); and patient-reported outcomes. PFS2 and PFS by GCIG criteria are not

278　reported in this manuscript because the required assessments were not completed after the

279　early termination of the trial. Pharmacokinetic parameters, immunogenicity, and patient-

280　reported outcomes are not reported in this manuscript because it focuses on the clinical

281　aspects of the trial and because these analyses had limited relevance given that the trial

282　failed to meet its primary endpoints. Additional biomarker analyses are ongoing and are not

283　presented in this manuscript.

284　*Statistical analysis*

285　The trial aimed to demonstrate superiority of avelumab in combination with and/or following

286　chemotherapy in prolonging PFS compared with the control arm who received

287　chemotherapy followed by observation in all randomised patients (analysed by intention-to-

288　treat). Two independent and adequately powered comparisons were performed:

289　chemotherapy followed by avelumab vs control and avelumab plus chemotherapy followed

290　by avelumab vs control. The study used a two-look group-sequential design with a Lan-

291　DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a

292　gamma family β-spending function to determine the nonbinding futility boundary, with one

293　planned interim and one final analysis based on the primary endpoint. The overall type I

294　error rate was maintained at or below a 1-sided significance level of 0·025 by allocating an α

295　level of 0·0125 to both PFS comparisons; a fraction of alpha (0.0022) for efficacy was

296   planned to be spent at the interim analysis. For each PFS comparison, it was estimated that

297   272 events within each comparison would provide the trial with 90% power to detect a

298   hazard ratio (HR) of 0·65 using a 1-sided log-rank test. An interim analysis was planned after

299   approximately 181 (67%) of 272 events for each PFS comparison had occurred. This

300   manuscript reports efficacy results from the interim analysis (data cutoff date: Sept 7, 2018)

301   and updated safety data and analyses based on baseline PD-L1 status from an additional

302   later cutoff (May 16, 2019).

303   Efficacy was analysed in all patients who were randomised to study treatment, and safety

304   was analysed in all patients who received at least one dose of study treatment. Time-to-

305   event endpoints were estimated using the Kaplan-Meier method, and 95% CIs for the

306   median were calculated using the Brookmeyer-Crowley method. Duration of follow-up was

307   estimated using the reverse Kaplan-Meier method.[23] The Cox proportional hazards model

308   was used to calculate HRs and corresponding 95% CIs for PFS (including prespecified

309   subgroup analyses [randomization stratification factors, age, race, ethnicity, pooled

310   geographic region, *BRCA 1/2* mutation status, disease stage, ECOG PS, CA-125, and PD-

311   L1 status]) and OS analyses. PFS and OS were analysed using a 1-sided stratified log-rank

312   test. Objective response rates and rates of pathological complete response were calculated

313   for each treatment arm, along with 2-sided 95% CIs using the Clopper-Pearson method.

314   Statistical analyses were performed in SAS (version 9·4). This study is registered with

315   ClinicalTrials.gov, number NCT02718417.

316   *Role of the funding source*

317   The trial was sponsored by Pfizer as part of an alliance between Pfizer and Merck KGaA,

318   Darmstadt, Germany. The sponsors provided the study drugs, worked with a study steering

319   committee to design the trial and collect, analyse, and interpret the data, and provided

320   funding for a professional medical writer with access to the data. All authors had access to

321   the data reported and the lead and senior authors (BJM and JAL) and co-authors who were

322   employees of the sponsor (RAS, XZ, JPS, and CL) had access to the raw data. All authors

323 contributed to subsequent drafts and provided final approval to submit the manuscript for

324 publication.

325

326 **Results**

327 Between May 19, 2016 and Jan 23, 2018, 998 patients were enrolled and randomly

328 assigned: 332 to chemotherapy followed by avelumab maintenance (referred to as the

329 avelumab maintenance arm), 331 to avelumab plus chemotherapy followed by avelumab

330 maintenance (referred to as the avelumab combination arm), and 335 to chemotherapy

331 followed by observation (control arm; figure 1). Baseline characteristics were well balanced

332 across the three arms (table 1). At the planned interim analysis (data cutoff date: Sept 7,

333 2018), both avelumab arms had crossed prespecified futility boundaries. The trial was

334 stopped due to futility of efficacy in alignment with the recommendation of both the

335 Independent Data Monitoring Committee and the Protocol Steering Committee. Among

336 treated patients, nearly all received premedication with systemic corticosteroids (328 [100%]

337 of 328 in the avelumab maintenance arm, 327 [99%] of 329 in the avelumab combination

338 arm, and 333 [>99%] of 334 in the control arm).

339 In the analysis of all randomised patients, median duration of follow-up for PFS was 10·8

340 months (IQR 7·1–14·9) for all patients, 11·1 months (interquartile range [IQR] 7·0–15·3) for

341 the avelumab maintenance arm; 11·0 months (IQR 7·4–14·5) for the avelumab combination

342 arm; and 10·2 months (IQR 6·7–14·0) for the control arm. In the chemotherapy phase, as of

343 May 16, 2019, 328 patients had received treatment in the avelumab maintenance arm, 329

344 patients in the avelumab combination arm, and 334 patients in the control arm. Median

345 duration of treatment for all study drugs in the chemotherapy phase was ≥19 weeks. Most

346 patients (>80%) completed the chemotherapy phase. In the avelumab maintenance arm,

347 275 (83%) and 280 (84%) patients completed assigned paclitaxel and carboplatin treatment,

348 respectively; in the avelumab combination arm, 284 (86%), 281 (85%), and 290 (88%)

349   patients completed assigned avelumab, paclitaxel, and carboplatin treatment, respectively;

350   and in the control arm, 279 (83%) and 289 (86%) patients completed assigned paclitaxel and

351   carboplatin treatment, respectively. The most common reasons for treatment discontinuation

352   during the chemotherapy phase were AE, withdrawal by patient, and progressive disease

353   (figure 1). In the maintenance phase, 265 and 279 patients were treated with avelumab in

354   the maintenance and combination arms, respectively. Median duration of avelumab

355   treatment in these arms was 35·7 weeks (IQR 21·9–52·0) and 36·0 weeks (IQR 23·9–52·9),

356   respectively. The most common reason for treatment discontinuation in all three arms in the

357   maintenance phase was study termination (114 patients [34%] in the avelumab maintenance

358   arm, 140 patients [42%] in the avelumab combination arm, and 135 patients [40%] in the

359   control arm), and as of May 16, 2019, no patient remained on study.

360   Analysis of all efficacy endpoints was based on BICR unless otherwise specified. As of Sept

361   7, 2018, a PFS event had occurred in 99 (30%) of 332 patients in the avelumab

362   maintenance arm, 88 (27%) of 331 patients in the avelumab combination arm, and 70 (21%)

363   of 335 patients in the control arm. The stratified HR for PFS vs control was 1·43 (95% CI

364   1·051–1·946; 1-sided p=0·99) with avelumab maintenance and 1·14 (95% CI 0·832–1·565;

365   1-sided p=0·79) with avelumab combination. Median PFS was 16·8 months (95% CI 13·5 to

366   not estimable [NE]; IQR 9·8–NE) in the avelumab maintenance arm, 18·1 months (95% CI

367   14·8–NE; IQR 11·1–NE) in the avelumab combination arm, and NE (95% CI 18·2 months to

368   NE; IQR 10·8 to NE) in the control arm (figure 2). Prespecified exploratory subgroup

369   analyses of PFS based on patient and disease characteristics showed similar results (figure

370   3). The stratified HR for PFS by investigator vs control was 1·21 (95% CI 0·935–1·578; 1-

371   sided p=0·93) with avelumab maintenance and 0·90 (95% CI 0·688–1·189; 1-sided p=0·24)

372   with avelumab combination. Median PFS by investigator assessment was 13·8 months (95%

373   CI 12·1–15·9) in the avelumab maintenance arm, 16·1 months (95% CI 13·9–19·4) in the

374   avelumab combination arm, and 15·0 months (95% CI 13·2–18·7) in the control arm.

375   Maintenance PFS was assessed in patients who had not experienced disease progression

376 in the chemotherapy phase and subsequently entered the maintenance phase; this

377 comprised 248 patients in the avelumab maintenance arm, 267 patients in the avelumab

378 combination arm, and 247 in the control arm; median maintenance PFS was 13·6 months

379 (95% CI 9·3–NE), 13·8 months (95% CI 11·1–NE), and NE (95% CI 13·8 months to NE),

380 respectively. The stratified HR for maintenance PFS vs control was 1·56 (95% CI 1·078–

381 2·267; 1-sided p=0·99) with avelumab maintenance and 1·26 (95% CI 0·862–1·847; 1-sided

382 p=0·89) with avelumab combination.

383 OS data were not mature at the time of the interim analysis, with a total of only 54 deaths

384 across the three arms (20 [6%] in the avelumab maintenance arm, 21 [6%] in the avelumab

385 combination arm, and 13 [4%] in the control arm). Median follow-up for OS was 12·4 months

386 (IQR 9·0–15·9) for all patients, 12·6 months (IQR 9·1–16·0) in the avelumab maintenance

387 arm, 12·6 months (IQR 9·5–16·1) in the avelumab combination arm, and 11·8 months (IQR

388 8·5–15·6) in the control arm. OS results are shown in appendix p 21. Response data are

389 summarised in appendix, p 9. Interval debulking surgery after neoadjuvant treatment was

390 received by 108 patients in the avelumab maintenance arm, 115 patients in the avelumab

391 combination arm, and 116 patients in the control arm. Pathological complete response

392 occurred in 17 (16% [95% CI 12–29]), 20 (17% [95% CI 13–30]), and 30 patients (26% [95%

393 CI 21–40]), respectively.

394 In prespecified analyses (data cutoff, May 16, 2019), the predictive role of tumour PD-L1

395 status was assessed in 813 evaluable patients (appendix p 22). Tumours were PD-L1+ in

396 487 patients (60%), with a mixture of staining patterns observed, including PD-L1+ immune

397 cells only in 218 (27%), PD-L1+ tumour cells only in 73 (9%), and PD-L1+ tumour and

398 immune cells in 196 (24%). For the PD-L1 subgroups, PFS by BICR and by investigator

399 assessment are shown in the appendix, p 22 and 24.

400 No new safety signals were observed for avelumab administered as maintenance or in

401 combination with chemotherapy. As of May 16, 2019, treatment-emergent AEs of any grade

402 or causality occurred in 323 (98%) of 328 patients in the avelumab maintenance arm, 328

403   (>99%) of 329 patients in the avelumab combination arm, and 321 (96%) of 334 patients in

404   the control arm (table 2 and appendix, p 12). The most common any grade AEs (≥30% in all

405   arms) were alopecia, anaemia, nausea, neutropenia, and fatigue. AEs that differed by >5%

406   between arms (avelumab maintenance, avelumab combination, and control arms,

407   respectively) were constipation (35%, 31%, and 29%), vomiting (27%, 24%, and 20%),

408   diarrhoea (26%, 31%, and 19%), arthralgia (23%, 26%, and 17%), myalgia (20%, 16%, and

409   13%), neutrophil count decreased (18%, 16%, and 22%), and rash (18%, 20%, and 7%).

410   Grade 3–5 AEs occurred in 223 (68%), 238 (72%), and 210 patients (63%), respectively.

411   The most common grade ≥3 AEs (≥10% of patients in all arms) were anaemia, neutropenia,

412   and neutrophil count decreased. No grade ≥3 AEs differed by >5% between arms. Serious

413   AEs of any grade occurred in 92 patients (28%) in the avelumab maintenance arm, 118

414   patients (36%) in the avelumab combination arm, and 64 patients (19%) in the control arm.

415   Grade 3–5 serious AEs occurred in 72 (22%), 93 (28%), and 48 patients (14%), respectively.

416   In the avelumab maintenance, avelumab combination, and control arms, AEs led to

417   discontinuation of any study drug in 42 (13%), 63 (19%), and 24 patients (7%), and resulted

418   in death in 5 (2%; pulmonary embolism [n=2], disease progression [n=1], atrial fibrillation

419   [n=1], and embolism [n=1]), 6 (2%; disease progression [n=3], multiple organ dysfunction

420   syndrome [n=1], perforation [n=1], cardiopulmonary failure [n=1], small intestinal obstruction

421   [n=1], and abdominal abscess [n=1]), and 3 (1%; death from unspecified cause [n=1],

422   malignant neoplasm progression [n=1], and pulmonary embolism [n=1]), respectively. Dose

423   reductions are detailed in the appendix p 11. Treatment-related AEs (TRAEs) of any grade

424   occurred in 315 patients (96%) in the avelumab maintenance arm, 324 patients (98%) in the

425   avelumab combination arm, and 318 patients (95%) in the control arm. Grade 3–5 TRAEs

426   occurred in 175 (53%), 205 (62%), and 186 patients (56%), respectively. In the avelumab

427   maintenance, avelumab combination, and control arms, serious TRAEs occurred in 43

428   (13%), 62 (19%), and 29 patients (9%), respectively; the most common (≥2% patients) were

429   febrile neutropenia (10 [3%]), anaemia (5 [2%]), and vomiting (5 [2%]) in the avelumab

430   maintenance arm, febrile neutropenia (7 [2%]), anaemia (7 [2%]), vomiting (7 [2%]),

thrombocytopenia (5 [2%]), and nausea (5 [2%]) in the avelumab combination arm, and febrile neutropenia (7 [2%]) in the control arm. TRAEs led to discontinuation of any study drug in 35 patients (11%) in the avelumab maintenance arm, 53 patients (16%) in the avelumab combination arm, and 21 patients (6%) in the control arm; the most common reasons (≥3 patients) were diarrhoea (4 [1%]), peripheral neuropathy (3 [1%]), and anaemia (3 [1%]) in the avelumab maintenance arm, infusion-related reaction (5 [2%]), alanine aminotransferase increased (4 [1%]), thrombocytopenia (4 [1%]), neutrophil count decreased (3 [1%]), platelet count decreased (3 [1%]), peripheral neuropathy (3 [1%]), and peripheral sensory neuropathy (3 [1%]) in the avelumab combination arm, and peripheral sensory neuropathy (5 [1%]) and peripheral neuropathy (3 [1%]) in the control arm. Treatment-related deaths occurred in 1 patient (<1%) in the avelumab maintenance arm (atrial fibrillation) and 1 patient (<1%) in the avelumab combination arm (disease progression). In the safety analyses, the total number of deaths in treated patients irrespective of relationship to study treatment was 34 (10%) of 328 patients in the avelumab maintenance arm, 31 (9%) of 329 in the avelumab combination arm, and 20 (6%) of 334 in the control arm; reasons included disease progression (29 [9%], 26 [8%], and 17 [5%], respectively), AE not related to study treatment (5 [2%], 8 [2%], 2 [1%]), study treatment toxicity (1 [<1%], 0, 0), other (2 [1%], 3 [1%], 1 [<1%]), and unknown reasons (1 [<1%], 2 [1%], 3 [1%]).

As of Sept 7, 2018, in the avelumab maintenance, avelumab combination, and control arms, immune-related AEs of any grade occurred in 53 (16%), 92 (28%), and 0 patients, respectively (appendix p 20). In the avelumab maintenance and avelumab combination arms, grade 3–5 immune-related AEs occurred in 10 (3%) and 24 patients (7%), respectively, and led to discontinuation of any study drug in 8 (2%) and 19 patients (6%). No deaths were attributed to immune-related AEs. Infusion-related reactions of any grade occurred in 58 patients (18%) in the avelumab maintenance arm, 65 patients (20%) in the avelumab combination arm, and 44 patients (13%) in the control arm (appendix p 20). Grade 3–5 infusion-related reactions occurred in 2 (1%), 6 (2%), and 6 (2%) patients, respectively.

458   Discontinuation of any study drug due to infusion-related reactions occurred in 3 (1%), 7

459   (2%), and 4 (1%) patients, respectively.

460

461   **Discussion**

462   The JAVELIN Ovarian 100 trial did not meet either of its two primary objectives of improving

463   PFS with avelumab in combination with and/or following chemotherapy vs chemotherapy

464   followed by observation. At interim analysis, both avelumab arms had crossed prespecified

465   futility boundaries and the trial was stopped. HRs for PFS favoured the control arm,

466   indicating an observed detrimental effect in both avelumab arms. OS data were immature.

467   No benefit was observed in either experimental arm compared with the control arm in terms

468   of objective response rate, maintenance PFS, or pathological complete response. The safety

469   profile of avelumab administered in combination with chemotherapy and/or as maintenance

470   therapy was broadly similar to chemotherapy alone, with slight increases in a small number

471   of AEs and occurrence of low rates of immune-related AEs, consistent with the known safety

472   profile of avelumab monotherapy.[24] No new safety signals were identified.

473   Exploratory subgroup analyses based on baseline characteristics and stratification factors

474   did not identify subsets of patients with clear PFS benefit in either avelumab arm.

475   Additionally, PD-L1 status also did not predict benefit with avelumab treatment, either as

476   maintenance therapy or in combination with chemotherapy, which is in contrast with findings

477   from the phase 3 JAVELIN Ovarian 200 trial of avelumab as monotherapy or in combination

478   with PLD vs PLD alone in patients with platinum-resistant or platinum-refractory EOC.[22]

479   Although the JAVELIN Ovarian 200 trial failed to meet its primary objectives of significantly

480   improving PFS or OS in the overall population, biomarker analyses indicated that PD-L1

481   status may predict benefit with avelumab plus PLD vs PLD alone. The absence of a potential

482   predictive effect for PD-L1 status in the current trial may be due to the differences in tumour

483   biology or microenvironment or different immunological effects of chemotherapies[25,26]

484   administered in patients with previously untreated EOC vs platinum-resistant/refractory EOC,

485   and as result, tumours that have recurred after frontline chemotherapy and are PD-L1+ may

486   be more sensitive to subsequent combination treatment with chemotherapy and immune

487   checkpoint inhibitors than PD-L1+ treatment-naive tumours.

488   No pharmacokinetic interactions were expected between paclitaxel and carboplatin and

489   avelumab because these agents have distinct clearance pathways. In patient assessments,

490   exposure to carboplatin and paclitaxel was similar irrespective of administration of avelumab;

491   however, because of study design limitations and observed high variability, no conclusions

492   about the effect of carboplatin and paclitaxel on exposure to avelumab could be drawn (data

493   not shown).

494   It has been reported recently that a phase 3, randomised trial of a different anti–PD-L1

495   antibody, atezolizumab, administered with bevacizumab, paclitaxel, and carboplatin in

496   patients with newly diagnosed advanced EOC (IMagyn050) also failed to meet one of its

497   primary endpoints of improved PFS vs bevacizumab, paclitaxel, and carboplatin.[27] Data for

498   the other primary endpoint of OS are immature, and follow-up is ongoing. Results from our

499   trial and IMagyn050 suggest that the addition of an immune checkpoint inhibitor to frontline

500   chemotherapy does not improve efficacy in an unselected population. The negative outcome

501   of our trial was unexpected and there is no obvious explanation for these results. Several

502   other phase 3 studies investigating the activity of immune checkpoint inhibitors in

503   combination with chemotherapy, bevacizumab, and/or poly-ADP ribose polymerase (PARP)

504   inhibitors in the frontline advanced EOC setting are in progress, including durvalumab (anti–

505   PD-L1) plus chemotherapy and bevacizumab followed by durvalumab plus bevacizumab and

506   olaparib (PARP inhibitor) maintenance (DUO-O; NCT03737643); dostarlimab (anti–PD-1)

507   plus chemotherapy and niraparib (PARP inhibitor; FIRST/ENGOT-0V44; NCT03602859),

508   and pembrolizumab plus chemotherapy followed by olaparib (KEYLYNK-001/ENGOT-OV43;

509   NCT03740165). It is hoped these ongoing trials will provide further clarity on whether

510   immune checkpoint inhibitors have any role in the frontline treatment of patients with EOC.

511   This trial had several limitations. Firstly, no predictive biomarkers were available to aid

512   patient selection for the trial. Secondly, baseline data on *BRCA* status were not

513   systematically collected during the trial, therefore, the association between *BRCA* status and

514   outcomes could not be evaluated. Patients were not assessed for homologous

515   recombination deficiency, which has recently become a biomarker of interest for the

516   treatment of patients with EOC using other agents. Additionally, data on second-line

517   therapies were not collected in most patients because the trial was terminated at the interim

518   analysis. Lastly, longer-term efficacy data was not obtained because, when the trial was

519   stopped after the interim analysis, maintenance treatment was discontinued and long-term

520   follow-up was not performed, consistent with the recommendations of the Independent Data

521   Monitoring Committee.

522   In conclusion, the JAVELIN Ovarian 100 trial showed that avelumab as maintenance or in

523   combination with chemotherapy did not improve PFS in patients with previously untreated

524   EOC compared with chemotherapy alone.

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.

Contributions

BJM, MJB, RAS, JAL contributed to study design. BJM, NC, AMO, KF, MJB, LR, EVP, GS, YVS, MCL, SMB, JS, KY, RAS, CL, JAL contributed to data collection. BJM, RAS, XZ, CL contributed to data analysis. BJM, AMO, LR, RAS, XZ, JPS, CL, JAL contributed to data interpretation. BJM, XZ, and JAL accessed and verified the data. All authors contributed to manuscript writing.

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584   RAS reports employment at Pfizer at the time when the study was conducted and owns

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586   XZ reports employment at and owns stock in Pfizer.

587   JPS reports employment at and owns stock in Pfizer.

588   CL reports employment at Pfizer and owns stock in Eli Lilly and Pfizer.

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590   President of The European Society of Gynaecological Oncology and an Editor of the

591   Gynaecological Clinical Practice Guidelines for the European Society for Medical Oncology.

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670

FIGURE LEGENDS

672 **Figure 1. Trial profile at the updated safety data cutoff date (May 16, 2019).** Because

673 both avelumab arms had crossed prespecified futility boundaries, the trial was stopped due

674 to futility of efficacy in alignment with the recommendation of both the Independent Data

675 Monitoring Committee and the Protocol Steering Committee.

676 **Figure 2. Progression-free survival.** HR=hazard ratio. NE=not evaluable. * 1-sided log-

677 rank test. Data cutoff: Sept 7, 2018.

678 **Figure 3. Forest plots: progression-free survival in baseline subgroups for (A)**

679 **chemotherapy followed by avelumab and (B) chemotherapy plus avelumab followed**

680 **by avelumab, each vs chemotherapy followed by observation.** ECOG PS=Eastern

681 Cooperative Oncology Group performance score. HR=hazard ratio. QW=every week.

682 Q3W=every 3 weeks. ULN=upper limit of normal. Except for the primary analysis (all

683 patients), which was stratified according to randomisation stratification factors, all other

684 analyses presented were unstratified. Data for subgroups defined by ethnicity are not

685 reported because >95% of the patient population were non-Hispanic/Latino. Data cutoff:

686 Sept 7, 2018.

687

688

1   **JAVELIN Ovarian 100 primary manuscript**

2   **Title:** Avelumab in combination with and/or following chemotherapy versus chemotherapy

3   alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100):

4   results from a randomised phase 3 trial terminated at interim analysis.

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17   [†]At the time the study was conducted.

18

Abstract

Background: Although most patients with epithelial ovarian cancer (EOC) respond to frontline platinum-based chemotherapy, the majority will relapse within 3 years. The phase 3 JAVELIN Ovarian 100 trial compared avelumab (anti–PD-L1) in combination with and/or following chemotherapy vs chemotherapy alone in patients with treatment-naive EOC.

Methods: Eligible women aged ≥18 years with stage III–IV epithelial ovarian, fallopian tube, or peritoneal cancer (post-debulking/cytoreductive surgery or candidates for neoadjuvant chemotherapy) and an Eastern Cooperative Oncology Group performance status of 0 or 1 were randomised (1:1:1) via interactive response technology to receive chemotherapy (6 cycles; carboplatin AUC 5 or 6 intravenously [IV] every 3 weeks [Q3W] plus paclitaxel 175 mg/m^2 Q3W or 80 mg/m^2 weekly [investigators' choice]) followed by avelumab maintenance (10 mg/kg IV every 2 weeks [Q2W]), chemotherapy plus avelumab (10 mg/kg IV Q3W) followed by avelumab maintenance (10 mg/kg IV Q2W), or chemotherapy followed by observation (control). Randomization was stratified by paclitaxel regimen (weekly vs Q3W) and resection status (residual tumour; complete/microscopic vs incomplete ≤1 cm vs incomplete >1 cm vs neoadjuvant). The primary endpoint was progression-free survival (PFS) by blinded independent central review in all randomised patients (analysed by intention-to-treat). This trial is registered with ClinicalTrials.gov, number NCT02718417. The trial was fully enrolled and terminated at interim analysis for futility and efficacy is no longer being assessed. Results are reported from the interim analysis, which is the only analysis of the primary endpoint.

Findings: Between May 19, 2016 and Jan 23, 2018, 998 patients were randomised. At the planned interim analysis (data cutoff Sept 7, 2018), PFS was not improved in either avelumab arm vs control, prespecified futility boundaries were crossed, and the trial was stopped as recommended by the Independent Data Monitoring Committee. Median duration of follow-up for PFS was 10·8 months (IQR 7·1–14·9) for all patients, 11·1 months (interquartile range [IQR] 7·0–15·3) for chemotherapy followed by avelumab; 11·0 months

46   (IQR 7·4–14·5) for chemotherapy plus avelumab followed by avelumab; and 10·2 months

47   (IQR 6·7–14·0) for the control arm. Hazard ratios (95% CI) for PFS vs control were 1·43

48   (1·051–1·946) for chemotherapy followed by avelumab and 1·14 (0·832–1·565) for

49   chemotherapy plus avelumab followed by avelumab. Median PFS (95% CI) was 16·8

50   months (13·5 to not estimable [NE]) with chemotherapy followed by avelumab, 18·1 months

51   (14·8–NE) with chemotherapy plus avelumab followed by avelumab, and NE (18·2 months

52   to NE) with control. No new safety signals were observed. In the chemotherapy followed by

53   avelumab, chemotherapy plus avelumab followed by avelumab, and control arms, grade ≥3

54   treatment-emergent adverse events occurred in 68%, 72%, and 63%, respectively. The most

55   common grade 3–4 adverse events (≥10% of patients) were anaemia (69 [21%] in the

56   chemotherapy followed by avelumab arm, 63 [19%] in the chemotherapy plus avelumab

57   followed by avelumab arm, 53 [16%] in the control arm), neutropenia (91 [28%], 99 [30%], 88

58   [26%]), and neutrophil count decreased (49 [15%], 45 [14%], 59 [18%]). In the chemotherapy

59   followed by avelumab, chemotherapy plus avelumab followed by avelumab, and control

60   arms, serious adverse events occurred in 92 (28%), 118 (36%), and 64 patients (19%),

61   respectively. Treatment-related deaths occurred in 1 patient (<1%) in the chemotherapy

62   followed by avelumab arm (atrial fibrillation) and 1 patient (<1%) in the chemotherapy plus

63   avelumab followed by avelumab arm (disease progression).

64   **Interpretation:** This trial did not meet its primary objectives of significantly improving PFS

65   with frontline avelumab in combination with and/or following chemotherapy vs chemotherapy

66   alone in advanced EOC. Results do not support the use of avelumab in the frontline

67   treatment setting.

Research in context

Evidence before this study

Platinum-based chemotherapy administered before or after debulking surgery is the current

standard-of-care frontline treatment for patients with advanced epithelial ovarian cancer

(EOC). Additionally, the anti-vascular endothelial growth factor antibody, bevacizumab, is

administered with chemotherapy and/or used as maintenance in some patients where

available. Most patients respond to initial treatment; nonetheless, approximately 70% of

patients will relapse within 3 years. Because immunologic activity appears to predict

outcomes in patients with EOC, there has been interest in investigating the use of immune

checkpoint inhibitors in this disease. Single-agent immune checkpoint inhibitor treatment has

shown limited activity in early-phase trials in patients with recurrent EOC. Combining anti–

PD-1/PD-L1 agents with chemotherapy has the potential to increase efficacy, as seen in

randomised trials in other tumours. Using immune checkpoint inhibitors as either switch or

continuation maintenance could therefore increase and/or prolong the benefits of frontline

therapy. We conducted a literature search using PubMed on May 4, 2021, using the terms

("ovarian cancer" OR "epithelial 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 EOC published in English. We identified 15 manuscripts reporting

data from phase 1–3 trials in various EOC populations (5 phase 1, 1 phase 1/2, 6 phase 2,

and 1 phase 3 trial). No manuscripts were found that reported a clinical study of an immune

checkpoint inhibitor as maintenance treatment in patients with EOC. One manuscript

reported a phase 3 clinical study of an immune checkpoint inhibitor combined with

chemotherapy in the frontline setting; this study (IMagyn050) investigated the addition of

atezolizumab, an anti–PD-L1 antibody, to platinum-based chemotherapy and bevacizumab

vs placebo in patients with treatment-naive stage III/IV EOC. In this trial, the addition of

94   atezolizumab did not significantly improve progression-free survival in the overall or PD-L1+

95   populations.

96   *Added value of this study*

97   To our knowledge, JAVELIN Ovarian 100 is one of the first phase 3 trials of an immune

98   checkpoint inhibitor in patients with previously untreated EOC to be reported. The trial failed

99   to meet either of its two primary objectives of significantly improving progression-free

100   survival with chemotherapy followed by avelumab or chemotherapy plus avelumab followed

101   by avelumab vs chemotherapy followed by observation. Subgroup analyses based on

102   baseline characteristics, stratification factors, or PD-L1 status did not identify subsets with

103   clear benefit in either avelumab arm. No new safety signals were observed in either

104   avelumab arm.

105   *Implications of all the available evidence*

106   The findings from this trial suggest that the addition of an immune checkpoint inhibitor to

107   frontline chemotherapy does not improve progression-free survival in the overall population,

108   highlighting that further study is needed to determine whether immune checkpoint inhibitors

109   have a role in frontline treatment of EOC.

Introduction

Ovarian cancer is responsible for approximately 185,000 deaths annually worldwide.[1] More than 70% of women diagnosed with ovarian cancer have advanced disease.[2,3] Ovarian cancer is a heterogenous disease; however, most tumours (approximately 90%) are epithelial ovarian cancers (EOC),[3] a term that also includes cancers originating from cells lining the fallopian tubes and peritoneum, which are managed similarly.[4] Current standard-of-care frontline treatment for patients with advanced EOC consists of combination carboplatin and paclitaxel chemotherapy before or after debulking surgery.[3,4] Frontline treatment with bevacizumab, an anti-vascular endothelial growth factor antibody, in combination with chemotherapy followed by bevacizumab maintenance is approved in various countries worldwide for the treatment of advanced EOC irrespective of biomarker status. The addition of bevacizumab is associated with an improvement in progression-free survival (PFS) but an overall survival (OS) benefit was limited to women at high risk of disease recurrence.[5,6] Currently, most patients (around 70–80%) respond to initial treatment; however, median PFS ranges from 10 to 17 months,[5,7-10] and approximately 70% of patients will relapse within 3 years.[3]

Although not considered a strongly immunogenic cancer, EOC tumours are characterised by immunologic activity. Programmed death ligand 1 (PD-L1), a key suppressor of T cell function, is expressed on ovarian tumour cells and tumour-infiltrating lymphocytes in more than half of patients.[11] The presence of tumour-infiltrating lymphocytes, specifically CD8+ T cells, is associated with longer OS.[12] Trials of immune checkpoint inhibitors as monotherapy in patients with previously treated EOC have shown limited clinical activity,[13-15] prompting interest in the use of immune checkpoint inhibitors in combination with established treatments. Furthermore, accumulating evidence suggests that chemotherapy agents may regulate antitumour immune responses. For example, cytotoxic chemotherapy can stimulate tumour immunosurveillance by increasing antigen release and presentation, modifying the suppressive tumour microenvironment (eg, by suppressing T regulatory cells), and

7

137 promoting infiltration of T cells, potentially making tumours more susceptible to immune

138 attack.[16,17] It has also been hypothesised that DNA-damaging chemotherapies could

139 increase the mutational burden within tumours, thereby increasing the repertoire of

140 neoantigens available for tumour-directed immune responses.[18] Therefore, it was

141 hypothesized that combining chemotherapy with an immune checkpoint inhibitor could

142 provide improved clinical activity by stimulating the activity of CD8+ tumour-infiltrating

143 lymphocytes and overcoming immunosuppressive mechanisms. Increased clinical activity

144 and manageable toxicity have been seen in trials of combined

145 chemotherapy/immunotherapy regimens in other tumour types;[19-21] however, data in EOC

146 with similar treatment regimens are limited.

147 Avelumab, an anti–PD-L1 monoclonal antibody, showed clinical activity as monotherapy in a

148 cohort of a phase 1b study that included 125 heavily treated patients with resistant or

149 refractory EOC, with an objective response rate of 10%.[13] However, in the phase 3 JAVELIN

150 Ovarian 200 trial, avelumab did not show superiority vs pegylated liposomal doxorubicin

151 (PLD), either as monotherapy or in combination with PLD in patients with platinum-resistant

152 or platinum-refractory EOC.[22]

153 Here, we report results from the randomised, open-label, phase 3 JAVELIN Ovarian 100

154 trial, which compared avelumab in combination with and/or following frontline platinum-

155 based chemotherapy vs chemotherapy followed by observation in patients with previously

156 untreated EOC.

157

158 **Methods**

159 *Study design and participants*

160 JAVELIN Ovarian 100 was a global, open-label, three-arm parallel, phase 3 trial at 159

161 hospitals and cancer treatment centres in 25 countries (Bulgaria, Canada, Croatia, Estonia,

162 Germany, Hong Kong, Hungary, Ireland, Italy, Japan, Republic of Korea, Latvia, Mexico,

8

163 Netherlands, Poland, Romania, Russia, Singapore, Slovakia, Switzerland, Taiwan, Turkey,

164 Ukraine, UK, and USA). Eligible patients were aged ≥18 years (≥20 years in Japan); had

165 previously untreated, histologically confirmed, stage III–IV (per the American Joint

166 Committee on Cancer and Union for International Cancer Control TNM cancer staging

167 system and the International Federation of Gynaecology and Obstetrics Staging System

168 2014 edition) epithelial ovarian, fallopian tube, or primary peritoneal cancer (including

169 malignant mixed Müllerian tumours with a high-grade serous component); and had received

170 debulking surgery or were candidates for neoadjuvant chemotherapy. Patients enrolled prior

171 to initiation of neoadjuvant chemotherapy underwent interval debulking surgery after 3 cycles

172 of chemotherapy (± avelumab) and then completed the remaining 3 cycles post-surgery.

173 Other eligibility criteria included Eastern Cooperative Oncology Group performance status of

174 0 or 1; estimated life expectancy >3 months; adequate haematologic (absolute neutrophil

175 count ≥1·5×10^9 per L, haemoglobin ≥9 g per dL, and platelet count ≥100×10^9 per L), hepatic

176 (aspartate and alanine aminotransferase concentrations ≤2·5×upper limit of normal and total

177 bilirubin concentration ≤1·5×upper limit of normal), and renal (creatinine clearance ≥50

178 mL/min according to the Cockcroft-Gault equation) function; and negative pregnancy test

179 and use of effective contraception (women of childbearing potential). All patients were

180 required to have an archival formalin-fixed, paraffin-embedded tumour tissue block or a

181 minimum of 15 tumour slides. If archived tissue was not available, a de novo (ie, fresh)

182 tumour sample was obtained. Exclusion criteria included nonepithelial tumour or tumour with

183 low malignant potential (ie, borderline tumour); mucinous tumours; cancer for which

184 bevacizumab was identified as a clinically beneficial frontline treatment; planned

185 intraperitoneal chemotherapy; prior treatment with a T-cell–targeting immune checkpoint

186 inhibitor; known brain, leptomeningeal, or spinal cord metastases; other cancer diagnosis

187 within 5 years; known hypersensitivity to monoclonal antibodies, carboplatin, or paclitaxel;

188 and serious cardiovascular disease or other severe medical condition. Full eligibility criteria

189 are listed in the appendix (p 18).

190 The trial was conducted in accordance with the ethics principles of the Declaration of

191 Helsinki and the International Council on Harmonisation guidelines on Good Clinical

192 Practice. The protocol was approved by the institutional review board or ethics committee of

193 each centre. All patients (or their legal representatives) provided written informed consent

194 before enrolment.

195 *Randomisation and masking*

196 Patients were enrolled by study investigators and were centrally randomized (1:1:1) via

197 interactive response technology to receive either chemotherapy (6 cycles; carboplatin plus

198 paclitaxel) followed by avelumab maintenance, chemotherapy plus avelumab followed by

199 avelumab maintenance, or chemotherapy followed by observation (stratified permuted block

200 randomisation with a block size of six). Randomisation was stratified by paclitaxel regimen

201 (weekly [QW] vs every 3 weeks [Q3W]) and resection status (residual tumour;

202 complete/microscopic vs incomplete ≤1 cm vs incomplete >1 cm vs neoadjuvant). The trial

203 was open label, although patients and investigators were blinded to assignment to the two

204 chemotherapy arms without avelumab at time of randomisation until completion of the

205 chemotherapy phase. The sponsor and BICR committee (third party) remained blinded to

206 treatment assignments until after study termination.

207 *Procedures*

208 Avelumab was administered at a dose of 10 mg/kg by 1-hour intravenous (IV) infusion Q3W

209 in the chemotherapy phase and 10 mg/kg every 2 weeks in the maintenance phase.

210 Chemotherapy regimens consisted of 6 cycles of either paclitaxel 80 mg/m^2 by 1-hour IV

211 infusion QW or 175 mg/m^2 by 3-hour IV infusion Q3W (investigators choice; once selected,

212 dosage was not changed for the study duration) plus carboplatin area under the serum-

213 concentration-time curve (AUC) 5 or 6 by 1-hour IV infusion Q3W. Carboplatin was

214 administered 1 hour after completing the paclitaxel infusion. Premedication with an

215 antihistamine (eg, oral or IV diphenhydramine 25–50 mg or equivalent) and paracetamol

216 (acetaminophen; eg, oral or IV paracetamol 500–650 mg or equivalent) was mandatory 30–

217 60 minutes prior to each avelumab infusion. Premedications to minimise toxicities related to

218 chemotherapy were administered according to local guidelines. For avelumab, no dose

219 reductions were permitted; carboplatin and/or paclitaxel doses could be reduced following

220 significant toxicity based on investigator judgment.

221 After completing the chemotherapy phase, if the patient had experienced stable disease or a

222 partial or complete response, they entered the maintenance phase. Treatment was given

223 until disease progression (assessed by investigator but confirmed by blinded independent

224 central review [BICR]), unacceptable toxicity, or withdrawal (potential reasons leading to

225 withdrawal included global deterioration of health status, pregnancy, significant protocol

226 deviation, patient refusal, loss to follow up, termination of the study by the sponsor, or death;

227 appendix, p ~~18~~26); avelumab could be continued while awaiting confirmation of disease

228 progression based on the investigator's clinical judgment. Treatment in the maintenance

229 phase was received for a maximum of 24 months (excluding the chemotherapy phase).

230 Patients who discontinued (or, if receiving observation maintenance, reached the end of

231 treatment or withdrew) were followed every 12 weeks until death or end of study. Crossover

232 between study arms was not permitted.

233 Tumours were assessed by computed tomography or magnetic resonance imaging at

234 baseline, after 3 cycles of chemotherapy, and at completion of chemotherapy to determine

235 eligibility for maintenance. Patients who underwent interval debulking surgery were required

236 to have an additional tumour assessment after surgery. Assessments were performed every

237 12 weeks in the maintenance phase until confirmed disease progression, irrespective of

238 subsequent anticancer therapy. Objective tumour response was evaluated per Response

239 Evaluation Criteria in Solid Tumours (RECIST) version 1.1 based on BICR. Complete and

240 partial responses and progressive disease were confirmed by repeated imaging performed

241 ≥4 weeks after initial documentation. Blood samples were taken at each trial visit (QW for

242 those receiving paclitaxel QW) for haematology and day 1 of each cycle in the

243   chemotherapy phase and Q2W in the maintenance phase for other routine laboratory

244   analyses, including core serum chemistry and haemostaseology. Urine samples were taken

245   at screening and on day 1 of each cycle in the maintenance phase for urinalysis.

246   Adrenocorticotropic hormone, free thyroxine, and thyroid-stimulating hormone

247   concentrations were tested at screening, on day 1 of each odd cycle of the chemotherapy

248   phase, day 1 of the third cycle of the maintenance phase, and then every 12 weeks

249   thereafter while on treatment. Adverse events (AEs) and laboratory abnormalities were

250   graded according to the US National Cancer Institute's Common Terminology Criteria for

251   Adverse Events version 4·03. Immune-related AEs and infusion-related reactions were

252   identified using a prespecified list of terms in the Medical Dictionary for Regulatory Activities.

253   PD-L1 expression was assessed in pretreatment tissue samples using an

254   immunohistochemical assay based on the SP263 (Ventana Medical Systems) antibody.

255   Selection of the PD-L1 cutoff was based on post hoc analyses of several scoring algorithms

256   and cutoffs from the JAVELIN Ovarian 200 trial, and the optimal cutoff for predicting

257   improved activity for the combination of avelumab and chemotherapy was selected. A

258   sample was considered PD-L1+ if the percentage of tumour cells expressing membranous

259   PD-L1 was ≥1% and/or the percentage of tumour area populated by PD-L1+ immune cells

260   was ≥5%.

261   An external data monitoring committee was established to review safety and efficacy data

262   from the trial.

263   *Outcomes*

264   The primary endpoint was PFS by BICR (defined as the time from randomisation to the date

265   of the first documented disease progression per RECIST 1·1 or death due to any cause,

266   whichever occurred first). Secondary endpoints included OS (defined as the time from

267   randomisation to the date of death due to any cause); PFS by investigator assessment per

268   RECIST 1·1; objective response, duration of response, and maintenance PFS (defined in

269   patients who did not have disease progression by BICR during the chemotherapy phase and

270   entered maintenance phase as the time from initiating maintenance treatment to the date of

271   first documented disease progression per RECIST 1·1 or death due to any cause, whichever

272   occurred first); pathological complete response; PFS2 (defined as the time from

273   randomisation to start of second subsequent treatment after objective disease progression,

274   or death due to any cause, whichever occurred first); PFS by Gynecological Cancer

275   Intergroup (GCIG) criteria; safety and tolerability; pharmacokinetic parameters;

276   immunogenicity of avelumab; tumour biomarker assessments (including, but not limited to,

277   PD-L1 expression); and patient-reported outcomes. PFS2 and PFS by GCIG criteria are not

278   reported in this manuscript because the required assessments were not completed after the

279   early termination of the trial. Pharmacokinetic parameters, immunogenicity, and patient-

280   reported outcomes are not reported in this manuscript because it focuses on the clinical

281   aspects of the trial and because these analyses had limited relevance given that the trial

282   failed to meet its primary endpoints. Additional biomarker analyses are ongoing and are not

283   presented in this manuscript.

284   *Statistical analysis*

285   The trial aimed to demonstrate superiority of avelumab in combination with and/or following

286   chemotherapy in prolonging PFS compared with the control arm who received

287   chemotherapy followed by observation in all randomised patients (analysed by intention-to-

288   treat). Two independent and adequately powered comparisons were performed:

289   chemotherapy followed by avelumab vs control and avelumab plus chemotherapy followed

290   by avelumab vs control. The study used a two-look group-sequential design with a Lan-

291   DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a

292   gamma family β-spending function to determine the nonbinding futility boundary, with one

293   planned interim and one final analysis based on the primary endpoint. The overall type I

294   error rate was maintained at or below a 1-sided significance level of 0·025 by allocating an α

295   level of 0·0125 to both PFS comparisons; a fraction of alpha (0.0022) for efficacy was

296   planned to be spent at the interim analysis. For each PFS comparison, it was estimated that

297   272 events within each comparison would provide the trial with 90% power to detect a

298   hazard ratio (HR) of 0·65 using a 1-sided log-rank test. An interim analysis was planned after

299   approximately 181 (67%) of 272 events for each PFS comparison had occurred. This

300   manuscript reports efficacy results from the interim analysis (data cutoff date: Sept 7, 2018)

301   and updated safety data and analyses based on baseline PD-L1 status from an additional

302   later cutoff (May 16, 2019).

303   Efficacy was analysed in all patients who were randomised to study treatment, and safety

304   was analysed in all patients who received at least one dose of study treatment. Time-to-

305   event endpoints were estimated using the Kaplan-Meier method, and 95% CIs for the

306   median were calculated using the Brookmeyer-Crowley method. Duration of follow-up was

307   estimated using the reverse Kaplan-Meier method.[23] The Cox proportional hazards model

308   was used to calculate HRs and corresponding 95% CIs for PFS (including prespecified

309   subgroup analyses [randomization stratification factors, age, race, ethnicity, pooled

310   geographic region, *BRCA 1/2* mutation status, disease stage, ECOG PS, CA-125, and PD-

311   L1 status]) and OS analyses. PFS and OS were analysed using a 1-sided stratified log-rank

312   test. Objective response rates and rates of pathological complete response were calculated

313   for each treatment arm, along with 2-sided 95% CIs using the Clopper-Pearson method.

314   Statistical analyses were performed in SAS (version 9·4). This study is registered with

315   ClinicalTrials.gov, number NCT02718417.

316   *Role of the funding source*

317   The trial was sponsored by Pfizer as part of an alliance between Pfizer and Merck KGaA,

318   Darmstadt, Germany. The sponsors provided the study drugs, worked with a study steering

319   committee to design the trial and collect, analyse, and interpret the data, and provided

320   funding for a professional medical writer with access to the data. All authors had access to

321   the data reported and the lead and senior authors (BJM and JAL) and co-authors who were

322   employees of the sponsor (RAS, XZ, JPS, and CL) had access to the raw data. All authors

323 contributed to subsequent drafts and provided final approval to submit the manuscript for

324 publication.

325

326 **Results**

327 Between May 19, 2016 and Jan 23, 2018, 998 patients were enrolled and randomly

328 assigned: 332 to chemotherapy followed by avelumab maintenance (referred to as the

329 avelumab maintenance arm), 331 to avelumab plus chemotherapy followed by avelumab

330 maintenance (referred to as the avelumab combination arm), and 335 to chemotherapy

331 followed by observation (control arm; figure 1). Baseline characteristics were well balanced

332 across the three arms (table 1). At the planned interim analysis (data cutoff date: Sept 7,

333 2018), both avelumab arms had crossed prespecified futility boundaries. The trial was

334 stopped due to futility of efficacy in alignment with the recommendation of both the

335 Independent Data Monitoring Committee and the Protocol Steering Committee. Among

336 treated patients, nearly all received premedication with systemic corticosteroids (328 [100%]

337 of 328 in the avelumab maintenance arm, 327 [99%] of 329 in the avelumab combination

338 arm, and 333 [>99%] of 334 in the control arm).

339 ~~Median~~ In the analysis of all randomised patients, median duration of follow-up for PFS was

340 10·8 months (IQR 7·1–14·9) for all patients, 11·1 months (interquartile range [IQR] 7·0–

341 15·3) for the avelumab maintenance arm; 11·0 months (IQR 7·4–14·5) for the avelumab

342 combination arm; and 10·2 months (IQR 6·7–14·0) for the control arm. In the chemotherapy

343 phase, as of May 16, 2019, 328 patients had received treatment in the avelumab

344 maintenance arm, 329 patients in the avelumab combination arm, and 334 patients in the

345 control arm. Median duration of treatment for all study drugs in the chemotherapy phase was

346 ≥19 weeks. Most patients (>80%) completed the chemotherapy phase. In the avelumab

347 maintenance arm, 275 (83%) and 280 (84%) patients completed assigned paclitaxel and

348 carboplatin treatment, respectively; in the avelumab combination arm, 284 (86%), 281

15

349 (85%), and 290 (88%) patients completed assigned avelumab, paclitaxel, and carboplatin

350 treatment, respectively; and in the control arm, 279 (83%) and 289 (86%) patients completed

351 assigned paclitaxel and carboplatin treatment, respectively. The most common reasons for

352 treatment discontinuation during the chemotherapy phase were AE, withdrawal by patient,

353 and progressive disease (figure 1). In the maintenance phase, 265 and 279 patients were

354 treated with avelumab in the maintenance and combination arms, respectively. Median

355 duration of avelumab treatment in these arms was 35·7 weeks (IQR 21·9–52·0) and 36·0

356 weeks (IQR 23·9–52·9), respectively. The most common reason for treatment

357 discontinuation in all three arms in the maintenance phase was study termination (114

358 patients [34%] in the avelumab maintenance arm, 140 patients [42%] in the avelumab

359 combination arm, and 135 patients [40%] in the control arm), and as of May 16, 2019, no

360 patient remained on study.

361 Analysis of all efficacy endpoints was based on BICR unless otherwise specified. As of Sept

362 7, 2018, a PFS event had occurred in 99 (30%) of 332 patients in the avelumab

363 maintenance arm, 88 (27%) of 331 patients in the avelumab combination arm, and 70 (21%)

364 of 335 patients in the control arm. The stratified HR for PFS vs control was 1·43 (95% CI

365 1·051–1·946; 1-sided p=0·99) with avelumab maintenance and 1·14 (95% CI 0·832–1·565;

366 1-sided p=0·79) with avelumab combination. Median PFS was 16·8 months (95% CI 13·5 to

367 not estimable [NE]; IQR 9·8–NE) in the avelumab maintenance arm, 18·1 months (95% CI

368 14·8–NE; IQR 11·1–NE) in the avelumab combination arm, and NE (95% CI 18·2 months to

369 NE; IQR 10·8 to NE) in the control arm (figure 2). Prespecified exploratory subgroup

370 analyses of PFS based on patient and disease characteristics showed similar results (figure

371 3). The stratified HR for PFS by investigator vs control was 1·21 (95% CI 0·935–1·578; 1-

372 sided p=0·93) with avelumab maintenance and 0·90 (95% CI 0·688–1·189; 1-sided p=0·24)

373 with avelumab combination. Median PFS by investigator assessment was 13·8 months (95%

374 CI 12·1–15·9) in the avelumab maintenance arm, 16·1 months (95% CI 13·9–19·4) in the

375 avelumab combination arm, and 15·0 months (95% CI 13·2–18·7) in the control arm.

376 Maintenance PFS was assessed in patients who had not experienced disease progression

377 in the chemotherapy phase and subsequently entered the maintenance phase; this

378 comprised 248 patients in the avelumab maintenance arm, 267 patients in the avelumab

379 combination arm, and 247 in the control arm; median maintenance PFS was 13·6 months

380 (95% CI 9·3–NE), 13·8 months (95% CI 11·1–NE), and NE (95% CI 13·8 months to NE),

381 respectively. The stratified HR for maintenance PFS vs control was 1·56 (95% CI 1·078–

382 2·267; 1-sided p=0·99) with avelumab maintenance and 1·26 (95% CI 0·862–1·847; 1-sided

383 p=0·89) with avelumab combination.

384 OS data were not mature at the time of the interim analysis, with a total of only 54 deaths

385 across the three arms (20 [6%] in the avelumab maintenance arm, 21 [6%] in the avelumab

386 combination arm, and 13 [4%] in the control arm). Median follow-up for OS was 12·4 months

387 (IQR 9·0–15·9) for all patients, 12·6 months (IQR 9·1–16·0) in the avelumab maintenance

388 arm, 12·6 months (IQR 9·5–16·1) in the avelumab combination arm, and 11·8 months (IQR

389 8·5–15·6) in the control arm. OS results are shown in appendix p ~~13~~21. Response data are

390 summarised in appendix, p 9. Interval debulking surgery after neoadjuvant treatment was

391 received by 108 patients in the avelumab maintenance arm, 115 patients in the avelumab

392 combination arm, and 116 patients in the control arm. Pathological complete response

393 occurred in 17 (16% [95% CI 12–29]), 20 (17% [95% CI 13–30]), and 30 patients (26% [95%

394 CI 21–40]), respectively.

395 In prespecified analyses (data cutoff, May 16, 2019), the predictive role of tumour PD-L1

396 status was assessed in 813 evaluable patients (appendix p ~~14~~22). Tumours were PD-L1+ in

397 487 patients (60%), with a mixture of staining patterns observed, including PD-L1+ immune

398 cells only in 218 (27%), PD-L1+ tumour cells only in 73 (9%), and PD-L1+ tumour and

399 immune cells in 196 (24%). For the PD-L1 subgroups, PFS by BICR and by investigator

400 assessment are shown in the appendix, p ~~14~~22 and ~~16~~24.

401 No new safety signals were observed for avelumab administered as maintenance or in

402 combination with chemotherapy. As of May 16, 2019, treatment-emergent AEs of any grade

403   or causality occurred in 323 (98%) of 328 patients in the avelumab maintenance arm, 328

404   (>99%) of 329 patients in the avelumab combination arm, and 321 (96%) of 334 patients in

405   the control arm (table 2 and appendix, p 12). The most common any grade AEs (≥30% in all

406   arms) were alopecia, anaemia, nausea, neutropenia, and fatigue. AEs that differed by >5%

407   between arms (avelumab maintenance, avelumab combination, and control arms,

408   respectively) were constipation (35%, 31%, and 29%), vomiting (27%, 24%, and 20%),

409   diarrhoea (26%, 31%, and 19%), arthralgia (23%, 26%, and 17%), myalgia (20%, 16%, and

410   13%), neutrophil count decreased (18%, 16%, and 22%), and rash (18%, 20%, and 7%).

411   Grade 3–5 AEs occurred in 223 (68%), 238 (72%), and 210 patients (63%), respectively.

412   The most common grade ≥3 AEs (≥10% of patients in all arms) were anaemia, neutropenia,

413   and neutrophil count decreased. No grade ≥3 AEs differed by >5% between arms. Serious

414   AEs of any grade occurred in 92 patients (28%) in the avelumab maintenance arm, 118

415   patients (36%) in the avelumab combination arm, and 64 patients (19%) in the control arm.

416   Grade 3–5 serious AEs occurred in 72 (22%), 93 (28%), and 48 patients (14%), respectively.

417   In the avelumab maintenance, avelumab combination, and control arms, AEs led to

418   discontinuation of any study drug in 42 (13%), 63 (19%), and 24 patients (7%), and resulted

419   in death in 5 (2%; pulmonary embolism [n=2], disease progression [n=1], atrial fibrillation

420   [n=1], and embolism [n=1]), 6 (2%; disease progression [n=3], multiple organ dysfunction

421   syndrome [n=1], perforation [n=1], cardiopulmonary failure [n=1], small intestinal obstruction

422   [n=1], and abdominal abscess [n=1]), and 3 (1%; death from unspecified cause [n=1],

423   malignant neoplasm progression [n=1], and pulmonary embolism [n=1]), respectively. Dose

424   reductions are detailed in the appendix p 11. Treatment-related AEs (TRAEs) of any grade

425   occurred in 315 patients (96%) in the avelumab maintenance arm, 324 patients (98%) in the

426   avelumab combination arm, and 318 patients (95%) in the control arm. Grade 3–5 TRAEs

427   occurred in 175 (53%), 205 (62%), and 186 patients (56%), respectively. In the avelumab

428   maintenance, avelumab combination, and control arms, serious TRAEs occurred in 43

429   (13%), 62 (19%), and 29 patients (9%), respectively; the most common (≥2% patients) were

430   febrile neutropenia (10 [3%]), anaemia (5 [2%]), and vomiting (5 [2%]) in the avelumab

431   maintenance arm, febrile neutropenia (7 [2%]), anaemia (7 [2%]), vomiting (7 [2%]),

432   thrombocytopenia (5 [2%]), and nausea (5 [2%]) in the avelumab combination arm, and

433   febrile neutropenia (7 [2%]) in the control arm. TRAEs led to discontinuation of any study

434   drug in 35 patients (11%) in the avelumab maintenance arm, 53 patients (16%) in the

435   avelumab combination arm, and 21 patients (6%) in the control arm; the most common

436   reasons (≥3 patients) were diarrhoea (4 [1%]), peripheral neuropathy (3 [1%]), and anaemia

437   (3 [1%]) in the avelumab maintenance arm, infusion-related reaction (5 [2%]), alanine

438   aminotransferase increased (4 [1%]), thrombocytopenia (4 [1%]), neutrophil count decreased

439   (3 [1%]), platelet count decreased (3 [1%]), peripheral neuropathy (3 [1%]), and peripheral

440   sensory neuropathy (3 [1%]) in the avelumab combination arm, and peripheral sensory

441   neuropathy (5 [1%]) and peripheral neuropathy (3 [1%]) in the control arm. Treatment-related

442   deaths occurred in 1 patient (<1%) in the avelumab maintenance arm (atrial fibrillation) and

443   1 patient (<1%) in the avelumab combination arm (disease progression). In the safety

444   analyses, the total number of deaths in treated patients irrespective of relationship to study

445   treatment was 34 (10%) of 328 patients in the avelumab maintenance arm, 31 (9%) of 329 in

446   the avelumab combination arm, and 20 (6%) of 334 in the control arm; reasons included

447   disease progression (29 [9%], 26 [8%], and 17 [5%], respectively), AE not related to study

448   treatment (5 [2%], 8 [2%], 2 [1%]), study treatment toxicity (1 [<1%], 0, 0), other (2 [1%], 3

449   [1%], 1 [<1%]), and unknown reasons (1 [<1%], 2 [1%], 3 [1%]).

450   As of Sept 7, 2018, in the avelumab maintenance, avelumab combination, and control arms,

451   immune-related AEs of any grade occurred in 53 (16%), 92 (28%), and 0 patients,

452   respectively (appendix p ~~12~~20). In the avelumab maintenance and avelumab combination

453   arms, grade 3–5 immune-related AEs occurred in 10 (3%) and 24 patients (7%),

454   respectively, and led to discontinuation of any study drug in 8 (2%) and 19 patients (6%). No

455   deaths were attributed to immune-related AEs. Infusion-related reactions of any grade

456   occurred in 58 patients (18%) in the avelumab maintenance arm, 65 patients (20%) in the

457   avelumab combination arm, and 44 patients (13%) in the control arm (appendix p ~~12~~20).

458   Grade 3–5 infusion-related reactions occurred in 2 (1%), 6 (2%), and 6 (2%) patients,

459   respectively. Discontinuation of any study drug due to infusion-related reactions occurred in

460   3 (1%), 7 (2%), and 4 (1%) patients, respectively.

461

462   **Discussion**

463   The JAVELIN Ovarian 100 trial did not meet either of its two primary objectives of improving

464   PFS with avelumab in combination with and/or following chemotherapy vs chemotherapy

465   followed by observation. At interim analysis, both avelumab arms had crossed prespecified

466   futility boundaries and the trial was stopped. HRs for PFS favoured the control arm,

467   indicating an observed detrimental effect in both avelumab arms. OS data were immature.

468   No benefit was observed in either experimental arm compared with the control arm in terms

469   of objective response rate, maintenance PFS, or pathological complete response. The safety

470   profile of avelumab administered in combination with chemotherapy and/or as maintenance

471   therapy was broadly similar to chemotherapy alone, with slight increases in a small number

472   of AEs and occurrence of low rates of immune-related AEs, consistent with the known safety

473   profile of avelumab monotherapy.[24] No new safety signals were identified.

474   Exploratory subgroup analyses based on baseline characteristics and stratification factors

475   did not identify subsets of patients with clear PFS benefit in either avelumab arm.

476   Additionally, PD-L1 status also did not predict benefit with avelumab treatment, either as

477   maintenance therapy or in combination with chemotherapy, which is in contrast with findings

478   from the phase 3 JAVELIN Ovarian 200 trial of avelumab as monotherapy or in combination

479   with PLD vs PLD alone in patients with platinum-resistant or platinum-refractory EOC.[22]

480   Although the JAVELIN Ovarian 200 trial failed to meet its primary objectives of significantly

481   improving PFS or OS in the overall population, biomarker analyses indicated that PD-L1

482   status may predict benefit with avelumab plus PLD vs PLD alone. The absence of a potential

483   predictive effect for PD-L1 status in the current trial may be due to the differences in tumour

484   biology or microenvironment or different immunological effects of chemotherapies[25,26]

485   administered in patients with previously untreated EOC vs platinum-resistant/refractory EOC,

486   and as result, tumours that have recurred after frontline chemotherapy and are PD-L1+ may

487   be more sensitive to subsequent combination treatment with chemotherapy and immune

488   checkpoint inhibitors than PD-L1+ treatment-naive tumours.

489   No pharmacokinetic interactions were expected between paclitaxel and carboplatin and

490   avelumab because these agents have distinct clearance pathways. In patient assessments,

491   exposure to carboplatin and paclitaxel was similar irrespective of administration of avelumab;

492   however, because of study design limitations and observed high variability, no conclusions

493   about the effect of carboplatin and paclitaxel on exposure to avelumab could be drawn (data

494   not shown).

495   It has been reported recently that a phase 3, randomised trial of a different anti–PD-L1

496   antibody, atezolizumab, administered with bevacizumab, paclitaxel, and carboplatin in

497   patients with newly diagnosed advanced EOC (IMagyn050) also failed to meet one of its

498   primary endpoints of improved PFS vs bevacizumab, paclitaxel, and carboplatin.[27] Data for

499   the other primary endpoint of OS are immature, and follow-up is ongoing. Results from our

500   trial and IMagyn050 suggest that the addition of an immune checkpoint inhibitor to frontline

501   chemotherapy does not improve efficacy in an unselected population. The negative outcome

502   of our trial was unexpected and there is no obvious explanation for these results. Several

503   other phase 3 studies investigating the activity of immune checkpoint inhibitors in

504   combination with chemotherapy, bevacizumab, and/or poly-ADP ribose polymerase (PARP)

505   inhibitors in the frontline advanced EOC setting are in progress, including durvalumab (anti–

506   PD-L1) plus chemotherapy and bevacizumab followed by durvalumab plus bevacizumab and

507   olaparib (PARP inhibitor) maintenance (DUO-O; NCT03737643); dostarlimab (anti–PD-1)

508   plus chemotherapy and niraparib (PARP inhibitor; FIRST/ENGOT-0V44; NCT03602859),

509   and pembrolizumab plus chemotherapy followed by olaparib (KEYLYNK-001/ENGOT-OV43;

510   NCT03740165). It is hoped these ongoing trials will provide further clarity on whether

511   immune checkpoint inhibitors have any role in the frontline treatment of patients with EOC.

512   This trial had several limitations. Firstly, no predictive biomarkers were available to aid

513   patient selection for the trial. Secondly, baseline data on *BRCA* status were not

514   systematically collected during the trial, therefore, the association between *BRCA* status and

515   outcomes could not be evaluated. ~~Additionally, p~~Patients were not assessed for homologous

516   recombination deficiency, which has recently become a biomarker of interest for the

517   treatment of patients with EOC using other agents. <u>Additionally, data on second-line</u>

518   <u>therapies were not collected in most patients because the trial was terminated at the interim</u>

519   <u>analysis.</u> Lastly, longer-term efficacy data was not obtained because, when the trial was

520   stopped after the interim analysis, maintenance treatment was discontinued and long-term

521   follow-up was not performed, consistent with the recommendations of the Independent Data

522   Monitoring Committee.

523   In conclusion, the JAVELIN Ovarian 100 trial showed that avelumab as maintenance or in

524   combination with chemotherapy did not improve PFS in patients with previously untreated

525   EOC compared with chemotherapy alone.

Data sharing statement

533 Upon request, and subject to certain criteria, conditions and exceptions (see

534 https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information),

535 Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored

536 global interventional clinical studies conducted for medicines, vaccines and medical devices

537 (1) for indications that have been approved in the US and/or EU or (2) in programs that have

538 been terminated (i.e., development for all indications has been discontinued). Pfizer will also

539 consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be

540 requested from Pfizer trials 24 months after study completion. The de-identified participant

541 data will be made available to researchers whose proposals meet the research criteria and

542 other conditions, and for which an exception does not apply, via a secure portal. To gain

543 access, data requestors must enter into a data access agreement with Pfizer.

Contributions

545 BJM, MJB, RAS, JAL contributed to study design. BJM, NC, AMO, KF, MJB, LR, EVP, GS,

546 YVS, MCL, SMB, JS, KY, RAS, CL, JAL contributed to data collection. BJM, RAS, XZ, CL

547 contributed to data analysis. BJM, AMO, LR, RAS, XZ, JPS, CL, JAL contributed to data

548 interpretation. BJM, XZ, and JAL accessed and verified the data. All authors contributed to

549 manuscript writing.

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671

FIGURE LEGENDS

673 **Figure 1. Trial profile at the updated safety data cutoff date (May 16, 2019).** Because

674 both avelumab arms had crossed prespecified futility boundaries, the trial was stopped due

675 to futility of efficacy in alignment with the recommendation of both the Independent Data

676 Monitoring Committee and the Protocol Steering Committee.

677 **Figure 2. Progression-free survival.** HR=hazard ratio. NE=not evaluable. * 1-sided log-

678 rank test. Data cutoff: Sept 7, 2018.

679 **Figure 3. Forest plots: progression-free survival in baseline subgroups for (A)**

680 **chemotherapy followed by avelumab and (B) chemotherapy plus avelumab followed**

681 **by avelumab, each vs chemotherapy followed by observation.** ECOG PS=Eastern

682 Cooperative Oncology Group performance score. HR=hazard ratio. QW=every week.

683 Q3W=every 3 weeks. ULN=upper limit of normal. Except for the primary analysis (all

684 patients), which was stratified according to randomisation stratification factors, all other

685 analyses presented were unstratified. Data for subgroups defined by ethnicity are not

686 reported because >95% of the patient population were non-Hispanic/Latino. Data cutoff:

687 Sept 7, 2018.

688

689

Figure 1

1167 patients assessed for eligibility

169 discontinued prior to randomization
130 screening failures
25 withdrawal by patient
10 no longer met eligibility
4 other reasons

998 enrolled and randomised

---

332 assigned to chemotherapy
328 received at least one dose of carboplatin and paclitaxel

331 assigned to chemotherapy + avelumab
327 received at least one dose of carboplatin
329 received at least one dose of paclitaxel
327 received at least one dose of avelumab

335 assigned to chemotherapy
331 received at least one dose of carboplatin
333 received at least one dose of paclitaxel

---

52 discontinued carboplatin
5 died
11 disease progression
8 adverse events
6 physicians decision
4 no longer met eligibility
3 global deterioration of
health status
13 withdrawal by patient
2 other reasons
280 completed carboplatin in the
chemotherapy phase

57 discontinued paclitaxel
5 died
11 disease progression
14 adverse events
5 physicians decision
4 no longer met eligibility
4 global deterioration of
health status
12 withdrawal by patient
2 other reasons
275 completed paclitaxel in the
chemotherapy phase

41 discontinued carboplatin
4 died
7 disease progression
17 adverse events
1 physicians decision
2 no longer met eligibility
2 global deterioration of
health status
8 withdrawal by patient
290 completed carboplatin in the
chemotherapy phase

50 discontinued paclitaxel
4 died
7 disease progression
26 adverse events
1 physicians decision
2 no longer met eligibility
2 global deterioration of
health status
8 withdrawal by patient
281 completed paclitaxel in the
chemotherapy phase

47 discontinued avelumab
4 died
7 disease progression
23 adverse events
3 physicians decision
2 no longer met eligibility
2 global deterioration of
health status
6 withdrawal by patient
284 completed avelumab in the
chemotherapy phase

46 discontinued carboplatin
1 died
10 disease progression
13 adverse events
4 physicians decision
1 no longer met eligibility
1 global deterioration of
health status
15 withdrawal by patient
1 other reasons
289 completed carboplatin in the
chemotherapy phase

56 discontinued paclitaxel
1 died
10 disease progression
23 adverse events
4 physicians decision
1 no longer met eligibility
1 global deterioration of
health status
15 withdrawal by patient
1 other reasons
279 completed paclitaxel in the
chemotherapy phase

---

267 continued to avelumab maintenance
265 received at least one dose

288 continued to avelumab maintenance
279 received at least one dose

284 continued to observation in the
maintenance phase

---

266 discontinued avelumab
1 died
100 disease progression
21 adverse events
114 study terminated by sponsor
6 physicians decision
5 global deterioration of
health status
17 withdrawal by patient
2 other reasons

287 discontinued avelumab
1 died
88 disease progression
26 adverse events
140 study terminated by sponsor
7 physicians decision
1 no longer met eligibility
3 global deterioration of
health status
20 withdrawal by patient

282 discontinued observation
2 died
92 disease progression
1 adverse events
135 study terminated by sponsor
9 physicians decision
1 global deterioration of
health status
34 withdrawal by patient
1 loss to follow-up

Manuscript reference number: THELANCETONCOLOGY-D-21-00367R2

Avelumab in combination with and/or following chemotherapy versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100): results from a randomised phase 3 trial terminated at interim analysis

Monk BJ, et al.

Reviewer comments	Author response and changes made	Page number in revised paper
Editor comments		
1. Please add a sentence to the Discussion explaining that data on second-line therapies were not collected because the trial was terminated at the interim analysis.	We have added the following sentence to the limitations section of the Discussion: • *Additionally, data on second-line therapies were not collected in most patients because the trial was terminated at the interim analysis.*	22
2. In the summary Methods, you state that "The primary endpoint was progression-free survival (PFS) by blinded independent central review in all randomised patients". By saying "in all randomised patients", do you mean that it was analysed by intention-to treat? If so, please add wording to clarify this.	We have added wording to clarify that "all randomised patients" refers to the intention-to-treat population. • *The primary endpoint was progression-free survival (PFS) by blinded independent central review in all randomised patients (analysed by intention-to-treat).*	3
3. In the Summary Findings, thank you for providing the median (IQR) follow-up for PFS in each treatment group. Do you have the overall median (IQR) follow-up for the trial as a whole please?	We have added median (IQR) follow-up for PFS for the trial as a whole to the Summary. • *Median duration of follow-up for PFS was 10·8 months (IQR 7·1–14·9) for all patients,…*	4
4. In the main Methods, statistical analysis section, please add text to clarify that the primary endpoint was analysed by intention-to-treat.	We have added this text to the statistical analysis section of the Methods. • *The trial aimed to demonstrate superiority of avelumab in combination with and/or following chemotherapy in prolonging PFS compared with the control arm who received chemotherapy followed by observation in all randomised patients (analysed by intention-to-treat).*	13
5. In the main Results, thank you for providing the median (IQR) follow-up for PFS and OS in each treatment group. Do you have the overall median (IQR) follow-up for PFS and OS in the trial as a whole please?	We have added median (IQR) follow-up for PFS and OS for the trial as a whole to the Results. • *…median duration of follow-up for PFS was 10·8 months (IQR 7·1–14·9) for all patients,…* • *Median follow-up for OS was 12·4 months (IQR 9·0–15·9) for all patients,…*	15 17
6. Please add a sentence to the main Results clarifying that all randomised patients were included in the analyses (if this is the case; or add suitable alternative text if not).	We have added the following text to the main Results section to clarify that all randomised patients were included in the primary endpoint/efficacy analyses: • *In the analysis of all randomised patients, median duration of follow-up for PFS was…*	15
7. Thank you for clarifying that the analysis by PD-1 expression status was prespecified. Where are the results for your other biomarker analyses (as in the Outcomes section of the Methods, you state that you planned to do biomarker assessments "including, but not limited to, PD-L1 expression"). If the other biomarker analyses are not presented in this paper, please add a sentence to the Outcomes section of the Methods stating this and explaining why. Alternatively, if you have these analyses, perhaps they could be added to the web appendix and cited in the Results?	Other biomarker analyses for this trial are ongoing and are therefore not included in the current paper. We have added this information to the Methods. • *Additional biomarker analyses are ongoing and are not presented in this manuscript.*	13

8.	Thank you for providing the full table of treatment-emergent adverse events stratified by grade (table 3). However, the table is now rather large. Please could you amend the table so that it shows grade 1-2 events that occurred in 10% or more patients in any group and grade 3, 4, and 5 events that occurred in 2% or more patients in any group. The full table can be placed in the web appendix and a footnote could then be added to table 3 to indicate where the full table can be found.	We have amended Table 3 so that it shows grade 1-2 adverse events occurring in ≥10% and grade 3–5 occurring ≥2% of patients in any group. We have also moved the full table to the appendix and added a footnote to table 3, as suggested. • *A table showing AEs of grade 1–2 occurring in ≥10% of patients and all AEs of grade 3, 4 or 5 is included in the appendix, p 12.*	Tables, pg 5 Tables, pg 12
9.	Please resupply figure 1 (the trial profile) as an editable Word file (.doc or .docx) or powerpoint file (.ppt or .pptx) and made of boxes with editable text.	Figure 1 has been supplied as an editable powerpoint file.	–

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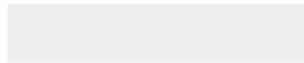
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1 **TABLES**

2 **Table 1.** Baseline characteristics

	Chemotherapy → avelumab (N=332)	Chemotherapy + avelumab → avelumab (N=331)	Chemotherapy → observation (N=335)
Median age (IQR), years	59·0 (52·0–67·0)	60·0 (50·0–66·0)	57·0 (49·0–66·0)
ECOG PS, n (%)*			
0	186 (56)	179 (54)	196 (59)
1	145 (44)	150 (45)	136 (41)
2	0	2 (1)	2 (1)
Pooled geographic region, n (%)			
North America	93 (28)	103 (31)	85 (25)
Europe	147 (44)	139 (42)	149 (44)
Asia	78 (23)	79 (24)	90 (27)
Rest of the world	14 (4)	10 (3)	11 (3)
Race, n (%)			
White	236 (71)	238 (72)	236 (70)
Asian	86 (26)	82 (25)	95 (28)
Black or African American	2 (1)	4 (1)	1 (<1)
Other[†]	8 (2)	7 (2)	3 (1)

Site of primary tumour, n (%)[‡]			
Ovary	261 (79)	259 (78)	270 (81)
Peritoneum	38 (11)	41 (12)	32 (10)
Fallopian tube	33 (10)	31 (9)	32 (10)
Not reported	0	1 (<1)	1 (<1)
Histology, n (%)			
High-grade serous	258 (78)	257 (78)	247 (74)
Low-grade serous	18 (5)	23 (7)	21 (6)
Clear cell	19 (6)	15 (5)	21 (6)
Endometrioid	12 (4)	10 (3)	10 (3)
Other epithelial ovarian cancer[§]	25 (8)	26 (8)	36 (11)
Histopathological grade, n (%)			
Grade 1	16 (5)	16 (5)	22 (7)
Grade 2	34 (10)	36 (11)	31 (9)
Grade 3	278 (84)	265 (80)	272 (81)
Not reported	4 (1)	14 (4)	10 (3)
Measurable disease at baseline by BICR, n (%)			
Yes	232 (70)	228 (69)	226 (67)
No	100 (30)	102 (31)	109 (33)
No disease	0	1 (<1)	0

Paclitaxel regimen, n (%)[‖]			
QW	100 (30)	102 (31)	104 (31)
Q3W	232 (70)	229 (69)	231 (69)
Resection (residual tumour), n (%)[‖]			
Complete resection/microscopic disease	105 (32)	105 (32)	105 (31)
Incomplete resection ≤1 cm	34 (10)	35 (11)	36 (11)
Incomplete resection >1 cm	57 (17)	55 (17)	57 (17)
Neoadjuvant	136 (41)	136 (41)	137 (41)
PD-L1 status, n (%)[¶]			
Positive	158 (48)	160 (48)	169 (50)
Negative	112 (34)	103 (31)	111 (33)
Not evaluable	62 (19)	68 (21)	55 (16)

3   BICR=blinded independent central review. ECOG PS=Eastern Cooperative Oncology Group performance status. IQR=interquartile range.

4   QW=every week. Q3W=every 3 weeks.

5   * Not reported for 2 patients (1 in the chemotherapy → avelumab arm, 1 in the chemotherapy → observation arm).

6   [†] Includes American Indian or Alaska Native and other.

7   [‡] One patient in the chemotherapy + avelumab → avelumab arm had a primary tumour recorded in two sites (ovary and peritoneum).

8   [§] Includes adenocarcinoma, undifferentiated carcinoma, and not reported.

9   [‖] Recorded at randomisation.

10   ¶ PD-L1+ status was defined as expression in ≥1% of tumour cells and/or ≥5% of immune cells (Ventana PD-L1 SP263 immunohistochemistry

11   assay).

Table 2. Treatment-emergent adverse events

	Chemotherapy → avelumab (N=328)				Chemotherapy + avelumab → avelumab (N=329)				Chemotherapy → observation (N=334)			
	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 AE, n (%)	100 (30)	151 (46)	67 (20)	5 (2)	90 (27)	148 (45)	84 (26)	6 (2)	111 (33)	131 (39)	76 (23)	3 (1)
Alopecia	165 (50)	0	2 (1)	0	169 (51)	0	0	0	174 (52)	2 (1)	1 (<1)	0
Nausea	147 (45)	6 (2)	0	0	145 (44)	7 (2)	0	0	147 (44)	5 (1)	0	0
Fatigue	117 (36)	6 (2)	0	0	102 (31)	12 (4)	1 (<1)	0	98 (29)	12 (4)	0	0
Constipation	111 (34)	3 (1)	0	0	101 (31)	0	1 (<1)	0	93 (28)	3 (1)	0	0
Peripheral sensory neuropathy	91 (28)	0	0	0	76 (23)	0	0	0	82 (25)	0	0	0
Anaemia	82 (25)	69 (21)	0	0	92 (28)	61 (19)	2 (1)	0	90 (27)	53 (16)	0	0
Vomiting	78 (24)	9 (3)	0	0	72 (22)	8 (2)	0	0	61 (18)	7 (2)	0	0
Diarrhoea	78 (24)	8 (2)	0	0	97 (29)	6 (2)	0	0	57 (17)	7 (2)	0	0
Arthralgia	75 (23)	1 (<1)	0	0	81 (25)	5 (2)	0	0	56 (17)	1 (<1)	0	0
Myalgia	66 (20)	1 (<1)	0	0	51 (16)	2 (1)	0	0	40 (12)	3 (1)	0	0
Abdominal pain	65 (20)	5 (2)	0	0	64 (19)	6 (2)	0	0	52 (16)	8 (2)	0	0
Decreased appetite	63 (19)	1 (<1)	0	0	54 (16)	1 (<1)	0	0	36 (11)	1 (<1)	0	0
Neuropathy peripheral	62 (19)	1 (<1)	0	0	74 (22)	3 (1)	0	0	64 (19)	1 (<1)	0	0
Rash	57 (17)	2 (1)	0	0	60 (18)	6 (2)	0	0	24 (7)	0	1 (<1)	0
Headache	55 (17)	1 (<1)	0	0	50 (15)	1 (<1)	0	0	30 (9)	0	0	0
Insomnia	50 (15)	2 (1)	0	0	39 (12)	0	0	0	30 (9)	2 (1)	0	0
Dizziness	44 (13)	0	1 (<1)	0	37 (11)	1 (<1)	0	0	28 (8)	0	0	0
Pruritus	37 (11)	1 (<1)	0	0	36 (11)	1 (<1)	0	0	19 (6)	0	0	0
Pyrexia	37 (11)	0	0	0	48 (15)	1 (<1)	0	0	23 (7)	1 (<1)	0	0
Dyspnoea	36 (11)	3 (1)	1 (<1)	0	45 (14)	4 (1)	0	0	29 (9)	1 (<1)	0	0
Cough	36 (11)	1 (<1)	0	0	55 (17)	0	0	0	22 (7)	0	0	0
Thrombocytopenia	33 (10)	13 (4)	1 (<1)	0	37 (11)	16 (5)	10 (3)	0	41 (12)	15 (4)	3 (1)	0
Urinary tract infection	33 (10)	4 (1)	0	0	42 (13)	8 (2)	0	0	27 (8)	2 (1)	0	0
Hypothyroidism	33 (10)	1 (<1)	0	0	33 (10)	0	0	0	5 (1)	0	0	0
Hypomagnesaemia	31 (9)	1 (<1)	0	0	38 (12)	3 (1)	1 (<1)	0	27 (8)	0	0	0
Abdominal pain upper	31 (9)	1 (<1)	0	0	38 (12)	2 (1)	0	0	24 (7)	0	0	0
Asthenia	30 (9)	5 (2)	0	0	44 (13)	2 (1)	0	0	21 (6)	1 (<1)	0	0
Back pain	29 (9)	2 (1)	0	0	34 (10)	2 (1)	0	0	28 (8)	3 (1)	0	0
Pain in extremity	29 (9)	1 (<1)	0	0	32 (10)	0	0	0	37 (11)	0	0	0
Alanine aminotransferase increased	27 (8)	1 (<1)	0	0	28 (9)	5 (2)	0	0	17 (5)	3 (1)	0	0
Neutropenia	23 (7)	54 (16)	37 (11)	0	26 (8)	54 (16)	45 (14)	0	25 (7)	48 (14)	40 (12)	0
Platelet count decreased	18 (5)	6 (2)	1 (<1)	0	28 (9)	8 (2)	3 (1)	0	29 (9)	14 (4)	1 (<1)	0

	Chemotherapy → avelumab (N=328)				Chemotherapy + avelumab → avelumab (N=329)				Chemotherapy → observation (N=334)			
	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
Hypokalaemia	16 (5)	7 (2)	0	0	15 (5)	9 (3)	3 (1)	0	15 (4)	4 (1)	1 (<1)	0
Leukopenia	15 (5)	12 (4)	1 (<1)	0	17 (5)	10 (3)	1 (<1)	0	15 (4)	5 (1)	0	0
Hypertension	12 (4)	4 (1)	0	0	12 (4)	7 (2)	0	0	10 (3)	3 (1)	0	0
Rash maculo-papular	12 (4)	1 (<1)	0	0	16 (5)	5 (2)	0	0	5 (1)	0	0	0
Hypertriglyceridaemia	12 (4)	0	0	0	10 (3)	5 (2)	0	0	8 (2)	1 (<1)	0	0
Neutrophil count decreased	11 (3)	31 (9)	18 (5)	0	9 (3)	29 (9)	16 (5)	0	16 (5)	32 (10)	27 (8)	0
Hyperglycaemia	10 (3)	4 (1)	1 (<1)	0	2 (1)	3 (1)	1 (<1)	0	4 (1)	2 (1)	1 (<1)	0
White blood cell count decreased	9 (3)	22 (7)	1 (<1)	0	13 (4)	15 (5)	3 (1)	0	17 (5)	15 (4)	2 (1)	0
Blood creatine phosphokinase increased	7 (2)	2 (1)	1 (<1)	0	4 (1)	4 (1)	1 (<1)	0	2 (1)	1 (<1)	0	0
Ascites	6 (2)	6 (2)	0	0	4 (1)	4 (1)	0	0	4 (1)	2 (1)	0	0
Lymphocyte count decreased	4 (1)	4 (1)	1 (<1)	0	4 (1)	6 (2)	0	0	2 (1)	3 (1)	1 (<1)	0
Hyponatraemia	4 (1)	4 (1)	0	0	3 (1)	5 (2)	0	0	0	3 (1)	0	0
Gamma-glutamyltransferase increased	4 (1)	3 (1)	0	0	9 (3)	5 (2)	2 (1)	0	9 (3)	4 (1)	0	0
Intestinal obstruction	3 (1)	1 (<1)	2 (1)	0	1 (<1)	6 (2)	1 (<1)	0	0	7 (2)	0	0
Small intestinal obstruction	3 (1)	1 (<1)	0	0	1 (<1)	7 (2)	0	0	1 (<1)	0	0	0
Febrile neutropenia	2 (1)	11 (3)	0	0	0	11 (3)	2 (1)	0	1 (<1)	9 (3)	1 (<1)	0
Haemoglobin decreased	2 (1)	4 (1)	1 (<1)	0	1 (<1)	2 (1)	0	0	1 (<1)	2 (1)	0	0
Lipase increased	1 (<1)	4 (1)	2 (1)	0	4 (1)	6 (2)	1 (<1)	0	1 (<1)	2 (1)	0	0
Pulmonary embolism	0	7 (2)	2 (1)	2 (1)	2 (1)	5 (2)	1 (<1)	0	3 (1)	3 (1)	1 (<1)	1 (<1)

13

14   AE=adverse event.

15   AEs of grade 1–2 occurring in ≥10% or grade 3–5 in ≥2% of patients in any arm are shown. A table showing AEs of grade 1–2 occurring in
16   ≥10% of patients and all AEs of grade 3, 4 or 5 is included in the appendix, p 12.

1 **TABLES**

2 **Table 1.** Baseline characteristics

	Chemotherapy → avelumab (N=332)	Chemotherapy + avelumab → avelumab (N=331)	Chemotherapy → observation (N=335)
Median age (IQR), years	59·0 (52·0–67·0)	60·0 (50·0–66·0)	57·0 (49·0–66·0)
ECOG PS, n (%)*			
0	186 (56)	179 (54)	196 (59)
1	145 (44)	150 (45)	136 (41)
2	0	2 (1)	2 (1)
Pooled geographic region, n (%)			
North America	93 (28)	103 (31)	85 (25)
Europe	147 (44)	139 (42)	149 (44)
Asia	78 (23)	79 (24)	90 (27)
Rest of the world	14 (4)	10 (3)	11 (3)
Race, n (%)			
White	236 (71)	238 (72)	236 (70)
Asian	86 (26)	82 (25)	95 (28)
Black or African American	2 (1)	4 (1)	1 (<1)
Other[†]	8 (2)	7 (2)	3 (1)

Site of primary tumour, n (%)[‡]			
Ovary	261 (79)	259 (78)	270 (81)
Peritoneum	38 (11)	41 (12)	32 (10)
Fallopian tube	33 (10)	31 (9)	32 (10)
Not reported	0	1 (<1)	1 (<1)
Histology, n (%)			
High-grade serous	258 (78)	257 (78)	247 (74)
Low-grade serous	18 (5)	23 (7)	21 (6)
Clear cell	19 (6)	15 (5)	21 (6)
Endometrioid	12 (4)	10 (3)	10 (3)
Other epithelial ovarian cancer[§]	25 (8)	26 (8)	36 (11)
Histopathological grade, n (%)			
Grade 1	16 (5)	16 (5)	22 (7)
Grade 2	34 (10)	36 (11)	31 (9)
Grade 3	278 (84)	265 (80)	272 (81)
Not reported	4 (1)	14 (4)	10 (3)
Measurable disease at baseline by BICR, n (%)			
Yes	232 (70)	228 (69)	226 (67)
No	100 (30)	102 (31)	109 (33)
No disease	0	1 (<1)	0

Paclitaxel regimen, n (%)[‖]			
QW	100 (30)	102 (31)	104 (31)
Q3W	232 (70)	229 (69)	231 (69)
Resection (residual tumour), n (%)[‖]			
Complete resection/microscopic disease	105 (32)	105 (32)	105 (31)
Incomplete resection ≤1 cm	34 (10)	35 (11)	36 (11)
Incomplete resection >1 cm	57 (17)	55 (17)	57 (17)
Neoadjuvant	136 (41)	136 (41)	137 (41)
PD-L1 status, n (%)[¶]			
Positive	158 (48)	160 (48)	169 (50)
Negative	112 (34)	103 (31)	111 (33)
Not evaluable	62 (19)	68 (21)	55 (16)

3   BICR=blinded independent central review. ECOG PS=Eastern Cooperative Oncology Group performance status. IQR=interquartile range.

4   QW=every week. Q3W=every 3 weeks.

5   * Not reported for 2 patients (1 in the chemotherapy → avelumab arm, 1 in the chemotherapy → observation arm).

6   [†] Includes American Indian or Alaska Native and other.

7   [‡] One patient in the chemotherapy + avelumab → avelumab arm had a primary tumour recorded in two sites (ovary and peritoneum).

8   [§] Includes adenocarcinoma, undifferentiated carcinoma, and not reported.

9   [‖] Recorded at randomisation.

3

10 ¶ PD-L1+ status was defined as expression in ≥1% of tumour cells and/or ≥5% of immune cells (Ventana PD-L1 SP263 immunohistochemistry

11 assay).

12 **Table 2.** Treatment-emergent adverse events

	Chemotherapy → avelumab (N=328)				Chemotherapy + avelumab → avelumab (N=329)				Chemotherapy → observation (N=334)			
	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 AE, n (%)	100 (30)	151 (46)	67 (20)	5 (2)	90 (27)	148 (45)	84 (26)	6 (2)	111 (33)	131 (39)	76 (23)	3 (1)
Alopecia	165 (50)	0	2 (1)	0	169 (51)	0	0	0	174 (52)	2 (1)	1 (<1)	0
Nausea	147 (45)	6 (2)	0	0	145 (44)	7 (2)	0	0	147 (44)	5 (1)	0	0
Fatigue	117 (36)	6 (2)	0	0	102 (31)	12 (4)	1 (<1)	0	98 (29)	12 (4)	0	0
Constipation	111 (34)	3 (1)	0	0	101 (31)	0	1 (<1)	0	93 (28)	3 (1)	0	0
Peripheral sensory neuropathy	91 (28)	0	0	0	76 (23)	0	0	0	82 (25)	0	0	0
Anaemia	82 (25)	69 (21)	0	0	92 (28)	61 (19)	2 (1)	0	90 (27)	53 (16)	0	0
Vomiting	78 (24)	9 (3)	0	0	72 (22)	8 (2)	0	0	61 (18)	7 (2)	0	0
Diarrhoea	78 (24)	8 (2)	0	0	97 (29)	6 (2)	0	0	57 (17)	7 (2)	0	0
Arthralgia	75 (23)	1 (<1)	0	0	81 (25)	5 (2)	0	0	56 (17)	1 (<1)	0	0
Myalgia	66 (20)	1 (<1)	0	0	51 (16)	2 (1)	0	0	40 (12)	3 (1)	0	0
Abdominal pain	65 (20)	5 (2)	0	0	64 (19)	6 (2)	0	0	52 (16)	8 (2)	0	0
Decreased appetite	63 (19)	1 (<1)	0	0	54 (16)	1 (<1)	0	0	36 (11)	1 (<1)	0	0
Neuropathy peripheral	62 (19)	1 (<1)	0	0	74 (22)	3 (1)	0	0	64 (19)	1 (<1)	0	0
Rash	57 (17)	2 (1)	0	0	60 (18)	6 (2)	0	0	24 (7)	0	1 (<1)	0
Headache	55 (17)	1 (<1)	0	0	50 (15)	1 (<1)	0	0	30 (9)	0	0	0
Insomnia	50 (15)	2 (1)	0	0	39 (12)	0	0	0	30 (9)	2 (1)	0	0
Dizziness	44 (13)	0	1 (<1)	0	37 (11)	1 (<1)	0	0	28 (8)	0	0	0
Pruritus	37 (11)	1 (<1)	0	0	36 (11)	1 (<1)	0	0	19 (6)	0	0	0
Pyrexia	37 (11)	0	0	0	48 (15)	1 (<1)	0	0	23 (7)	1 (<1)	0	0
Dyspnoea	36 (11)	3 (1)	1 (<1)	0	45 (14)	4 (1)	0	0	29 (9)	1 (<1)	0	0
Cough	36 (11)	1 (<1)	0	0	55 (17)	0	0	0	22 (7)	0	0	0
Thrombocytopenia	33 (10)	13 (4)	1 (<1)	0	37 (11)	16 (5)	10 (3)	0	41 (12)	15 (4)	3 (1)	0
Urinary tract infection	33 (10)	4 (1)	0	0	42 (13)	8 (2)	0	0	27 (8)	2 (1)	0	0
Hypothyroidism	33 (10)	1 (<1)	0	0	33 (10)	0	0	0	5 (1)	0	0	0
Hypomagnesaemia	31 (9)	1 (<1)	0	0	38 (12)	3 (1)	1 (<1)	0	27 (8)	0	0	0
Abdominal pain upper	31 (9)	1 (<1)	0	0	38 (12)	2 (1)	0	0	24 (7)	0	0	0
Asthenia	30 (9)	5 (2)	0	0	44 (13)	2 (1)	0	0	21 (6)	1 (<1)	0	0
Back pain	29 (9)	2 (1)	0	0	34 (10)	2 (1)	0	0	28 (8)	3 (1)	0	0
Pain in extremity	29 (9)	1 (<1)	0	0	32 (10)	0	0	0	37 (11)	0	0	0
~~Stomatitis~~	~~28 (9)~~	~~0~~	~~0~~	~~0~~	~~24 (7)~~	~~0~~	~~0~~	~~0~~	~~19 (6)~~	~~1 (<1)~~	~~0~~	~~0~~
Alanine aminotransferase increased	27 (8)	1 (<1)	0	0	28 (9)	5 (2)	0	0	17 (5)	3 (1)	0	0
~~Infusion related reaction~~	~~25 (8)~~	~~1 (<1)~~	~~0~~	~~0~~	~~30 (9)~~	~~3 (1)~~	~~1 (<1)~~	~~0~~	~~19 (6)~~	~~0~~	~~0~~	~~0~~

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	Chemotherapy → avelumab (N=328)				Chemotherapy + avelumab → avelumab (N=329)				Chemotherapy → observation (N=334)			
	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
Procedural pain	24 (7)	3 (1)	0	0	21 (6)	1 (<1)	0	0	11 (3)	1 (<1)	0	0
Neutropenia	23 (7)	54 (16)	37 (11)	0	26 (8)	54 (16)	45 (14)	0	25 (7)	48 (14)	40 (12)	0
Abdominal distension	23 (7)	0	0	0	17 (5)	0	0	0	17 (5)	2 (1)	0	0
Pain	20 (6)	1 (<1)	0	0	21 (6)	2 (1)	0	0	13 (4)	1 (<1)	0	0
Platelet count decreased	18 (5)	6 (2)	1 (<1)	0	28 (9)	8 (2)	3 (1)	0	29 (9)	14 (4)	1 (<1)	0
Aspartate aminotransferase increased	17 (5)	1 (<1)	0	0	25 (8)	4 (1)	0	0	20 (6)	1 (<1)	0	0
Hypokalaemia	16 (5)	7 (2)	0	0	15 (5)	9 (3)	3 (1)	0	15 (4)	4 (1)	1 (<1)	0
Leukopenia	15 (5)	12 (4)	1 (<1)	0	17 (5)	10 (3)	1 (<1)	0	15 (4)	5 (1)	0	0
Weight decreased	14 (4)	1 (<1)	0	0	17 (5)	0	0	0	11 (3)	2 (1)	0	0
Hyperthyroidism	13 (4)	1 (<1)	0	0	11 (3)	0	0	0	0	0	0	0
Bone pain	13 (4)	0	1 (<1)	0	13 (4)	0	0	0	14 (4)	0	0	0
Hypertension	12 (4)	4 (1)	0	0	12 (4)	7 (2)	0	0	10 (3)	3 (1)	0	0
Anxiety	12 (4)	1 (<1)	0	0	17 (5)	1 (<1)	0	0	15 (4)	0	0	0
Rash maculo-papular	12 (4)	1 (<1)	0	0	16 (5)	5 (2)	0	0	5 (1)	0	0	0
Blood creatinine increased	12 (4)	1 (<1)	0	0	11 (3)	2 (1)	0	0	6 (2)	0	0	0
Muscle spasms	12 (4)	1 (<1)	0	0	10 (3)	0	0	0	9 (3)	0	0	0
Palpitations	12 (4)	0	1 (<1)	0	6 (2)	0	0	0	6 (2)	0	0	0
Hypoaesthesia	12 (4)	0	0	0	21 (6)	0	0	0	12 (4)	1 (<1)	0	0
Hypertriglyceridaemia	12 (4)	0	0	0	10 (3)	5 (2)	0	0	8 (2)	1 (<1)	0	0
Neutrophil count decreased	11 (3)	31 (9)	18 (5)	0	9 (3)	29 (9)	16 (5)	0	16 (5)	32 (10)	27 (8)	0
Neck pain	11 (3)	2 (1)	0	0	6 (2)	0	0	0	3 (1)	0	0	0
Oedema	11 (3)	1 (<1)	0	0	6 (2)	0	0	0	6 (2)	0	0	0
Hyperglycaemia	10 (3)	4 (1)	1 (<1)	0	2 (1)	3 (1)	1 (<1)	0	4 (1)	2 (1)	1 (<1)	0
Hypersensitivity	10 (3)	1 (<1)	0	0	13 (4)	0	0	0	9 (3)	2 (1)	1 (<1)	0
Weight increased	10 (3)	1 (<1)	0	0	5 (2)	3 (1)	0	0	5 (1)	1 (<1)	0	0
White blood cell count decreased	9 (3)	22 (7)	1 (<1)	0	13 (4)	15 (5)	3 (1)	0	17 (5)	15 (4)	2 (1)	0
Abdominal pain lower	9 (3)	1 (<1)	0	0	15 (5)	0	0	0	7 (2)	0	0	0
Dermatitis	9 (3)	1 (<1)	0	0	7 (2)	0	0	0	2 (1)	0	0	0
Mucosal inflammation	8 (2)	1 (<1)	0	0	7 (2)	2 (1)	0	0	8 (2)	0	0	0
Influenza	8 (2)	0	0	0	10 (3)	2 (1)	0	0	5 (1)	0	0	0
Blood creatine phosphokinase increased	7 (2)	2 (1)	1 (<1)	0	4 (1)	4 (1)	1 (<1)	0	2 (1)	1 (<1)	0	0
Dehydration	7 (2)	2 (1)	0	0	10 (3)	4 (1)	0	0	6 (2)	1 (<1)	0	0
Hypotension	7 (2)	2 (1)	0	0	9 (3)	2 (1)	0	0	6 (2)	0	0	0

	Chemotherapy → avelumab (N=328)				Chemotherapy + avelumab → avelumab (N=329)				Chemotherapy → observation (N=334)			
	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
~~Chest pain~~	~~7 (2)~~	~~2 (1)~~	~~0~~	~~0~~	~~9 (3)~~	~~2 (1)~~	~~0~~	~~0~~	~~3 (1)~~	~~1 (<1)~~	~~0~~	~~0~~
~~Drug hypersensitivity~~	~~7 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~10 (3)~~	~~0~~	~~0~~	~~0~~	~~3 (1)~~	~~1 (<1)~~	~~0~~	~~0~~
~~Erythema~~	~~7 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~7 (2)~~	~~0~~	~~0~~	~~0~~	~~3 (1)~~	~~0~~	~~0~~	~~0~~
~~Hypoalbuminaemia~~	~~7 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~5 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~5 (1)~~	~~3 (1)~~	~~0~~	~~0~~
~~Chest discomfort~~	~~7 (2)~~	~~0~~	~~0~~	~~0~~	~~5 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~3 (1)~~	~~0~~	~~0~~	~~0~~
Ascites	6 (2)	6 (2)	0	0	4 (1)	4 (1)	0	0	4 (1)	2 (1)	0	0
~~Amylase increased~~	~~6 (2)~~	~~4 (1)~~	~~0~~	~~0~~	~~3 (1)~~	~~0~~	~~0~~	~~0~~	~~3 (1)~~	~~1 (<1)~~	~~0~~	~~0~~
~~Pneumonia~~	~~6 (2)~~	~~2 (1)~~	~~0~~	~~0~~	~~5 (2)~~	~~1 (<1)~~	~~1 (<1)~~	~~0~~	~~1 (<1)~~	~~1 (<1)~~	~~0~~	~~0~~
~~Haemorrhoids~~	~~6 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~6 (2)~~	~~0~~	~~0~~	~~0~~	~~6 (2)~~	~~0~~	~~0~~	~~0~~
~~Hyperuricaemia~~	~~6 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~4 (1)~~	~~1 (<1)~~	~~0~~	~~0~~	~~1 (<1)~~	~~0~~	~~0~~	~~0~~
~~Blood alkaline phosphatase increased~~	~~6 (2)~~	~~0~~	~~0~~	~~0~~	~~6 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~10 (3)~~	~~0~~	~~0~~	~~0~~
Lymphocyte count decreased	4 (1)	4 (1)	1 (<1)	0	4 (1)	6 (2)	0	0	2 (1)	3 (1)	1 (<1)	0
Hyponatraemia	4 (1)	4 (1)	0	0	3 (1)	5 (2)	0	0	0	3 (1)	0	0
Gamma-glutamyltransferase increased	4 (1)	3 (1)	0	0	9 (3)	5 (2)	2 (1)	0	9 (3)	4 (1)	0	0
~~Herpes zoster~~	~~4 (1)~~	~~2 (1)~~	~~0~~	~~0~~	~~7 (2)~~	~~0~~	~~0~~	~~0~~	~~4 (1)~~	~~0~~	~~0~~	~~0~~
~~Bronchitis~~	~~4 (1)~~	~~0~~	~~0~~	~~0~~	~~5 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~2 (1)~~	~~1 (<1)~~	~~0~~	~~0~~
~~Fall~~	~~4 (1)~~	~~0~~	~~0~~	~~0~~	~~5 (2)~~	~~0~~	~~0~~	~~0~~	~~1 (<1)~~	~~1 (<1)~~	~~0~~	~~0~~
~~Flank pain~~	~~4 (1)~~	~~0~~	~~0~~	~~0~~	~~4 (1)~~	~~1 (<1)~~	~~0~~	~~0~~	~~5 (1)~~	~~1 (<1)~~	~~0~~	~~0~~
~~Hyperkalaemia~~	~~4 (1)~~	~~0~~	~~0~~	~~0~~	~~4 (1)~~	~~1 (<1)~~	~~0~~	~~0~~	~~1 (<1)~~	~~0~~	~~0~~	~~0~~
~~Deep vein thrombosis~~	~~4 (1)~~	~~0~~	~~0~~	~~0~~	~~3 (1)~~	~~0~~	~~0~~	~~0~~	~~4 (1)~~	~~0~~	~~1 (<1)~~	~~0~~
~~Electrocardiogram QT prolonged~~	~~4 (1)~~	~~0~~	~~0~~	~~0~~	~~2 (1)~~	~~1 (<1)~~	~~0~~	~~0~~	~~3 (1)~~	~~0~~	~~1 (<1)~~	~~0~~
~~Abdominal hernia~~	~~4 (1)~~	~~0~~	~~0~~	~~0~~	~~2 (1)~~	~~1 (<1)~~	~~0~~	~~0~~	~~1 (<1)~~	~~0~~	~~0~~	~~0~~
~~Ileus~~	~~3 (1)~~	~~2 (1)~~	~~0~~	~~0~~	~~2 (1)~~	~~3 (1)~~	~~1 (<1)~~	~~0~~	~~6 (2)~~	~~4 (1)~~	~~1 (<1)~~	~~0~~
~~Dental caries~~	~~3 (1)~~	~~2 (1)~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~
Intestinal obstruction	3 (1)	1 (<1)	2 (1)	0	1 (<1)	6 (2)	1 (<1)	0	0	7 (2)	0	0
~~Muscular weakness~~	~~3 (1)~~	~~1 (<1)~~	~~0~~	~~0~~	~~10 (3)~~	~~0~~	~~0~~	~~0~~	~~5 (1)~~	~~1 (<1)~~	~~0~~	~~0~~
~~Hypophosphataemia~~	~~3 (1)~~	~~1 (<1)~~	~~0~~	~~0~~	~~3 (1)~~	~~0~~	~~0~~	~~0~~	~~2 (1)~~	~~0~~	~~0~~	~~0~~
Small intestinal obstruction	3 (1)	1 (<1)	0	0	1 (<1)	7 (2)	0	0	1 (<1)	0	0	0
~~Cellulitis~~	~~3 (1)~~	~~0~~	~~0~~	~~0~~	~~6 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~
~~Rash pruritic~~	~~3 (1)~~	~~0~~	~~0~~	~~0~~	~~5 (2)~~	~~1 (<1)~~	~~0~~	~~0~~	~~1 (<1)~~	~~1 (<1)~~	~~0~~	~~0~~
~~Phlebitis~~	~~3 (1)~~	~~0~~	~~0~~	~~0~~	~~1 (<1)~~	~~0~~	~~1 (<1)~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~
~~Drug eruption~~	~~3 (1)~~	~~0~~	~~0~~	~~0~~	~~0~~	~~1 (<1)~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~
~~Diabetes mellitus~~	~~3 (1)~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~1 (<1)~~	~~0~~	~~0~~

	Chemotherapy → avelumab (N=328)				Chemotherapy + avelumab → avelumab (N=329)				Chemotherapy → observation (N=334)			
	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
Febrile neutropenia	2 (1)	11 (3)	0	0	0	11 (3)	2 (1)	0	1 (<1)	9 (3)	1 (<1)	0
Haemoglobin decreased	2 (1)	4 (1)	1 (<1)	0	1 (<1)	2 (1)	0	0	1 (<1)	2 (1)	0	0
C-reactive protein increased	2 (1)	2 (1)	1 (<1)	0	2 (1)	0	0	0	1 (<1)	0	0	0
Embolism	2 (1)	2 (1)	0	1 (<1)	3 (1)	2 (1)	0	0	4 (1)	1 (<1)	0	0
Haematuria	2 (1)	1 (<1)	0	0	4 (1)	1 (<1)	0	0	5 (1)	0	0	0
Viral infection	2 (1)	1 (<1)	0	0	4 (1)	0	0	0	2 (1)	0	0	0
Presyncope	2 (1)	1 (<1)	0	0	2 (1)	0	0	0	1 (<1)	0	0	0
Psoriasis	2 (1)	1 (<1)	0	0	2 (1)	0	0	0	1 (<1)	0	0	0
Somnolence	2 (1)	1 (<1)	0	0	2 (1)	0	0	0	1 (<1)	0	0	0
Proteinuria	2 (1)	1 (<1)	0	0	2 (1)	0	0	0	0	0	0	0
Lymphocele	2 (1)	1 (<1)	0	0	0	0	0	0	1 (<1)	0	0	0
Escherichia urinary tract infection	2 (1)	1 (<1)	0	0	0	0	0	0	0	0	0	0
Atrial fibrillation	2 (1)	0	0	1 (<1)	1 (<1)	0	1 (<1)	0	1 (<1)	0	0	0
Pneumonitis	2 (1)	0	0	0	7 (2)	1 (<1)	0	0	0	0	0	0
Colitis	2 (1)	0	0	0	4 (1)	2 (1)	0	0	2 (1)	1 (<1)	0	0
Restless legs syndrome	2 (1)	0	0	0	4 (1)	1 (<1)	0	0	1 (<1)	0	0	0
Neurotoxicity	2 (1)	0	0	0	3 (1)	0	0	0	1 (<1)	2 (1)	0	0
Cancer pain	2 (1)	0	0	0	2 (1)	1 (<1)	0	0	1 (<1)	0	0	0
Autoimmune thyroiditis	2 (1)	0	0	0	2 (1)	1 (<1)	0	0	0	0	0	0
Hypoacusis	2 (1)	0	0	0	1 (<1)	1 (<1)	0	0	2 (1)	0	0	0
Urine output decreased	2 (1)	0	0	0	0	0	0	0	0	1 (<1)	0	0
Lipase increased	1 (<1)	4 (1)	2 (1)	0	4 (1)	6 (2)	1 (<1)	0	1 (<1)	2 (1)	0	0
Syncope	1 (<1)	3 (1)	0	0	2 (1)	3 (1)	0	0	2 (1)	1 (<1)	0	0
Gastroenteritis	1 (<1)	2 (1)	0	0	2 (1)	0	0	0	2 (1)	0	0	0
Hypocalcaemia	1 (<1)	1 (<1)	0	0	3 (1)	0	1 (<1)	0	0	0	0	0
Epigastric discomfort	1 (<1)	1 (<1)	0	0	3 (1)	0	0	0	2 (1)	0	0	0
Respiratory tract infection	1 (<1)	1 (<1)	0	0	2 (1)	0	0	0	3 (1)	0	0	0
Transaminases increased	1 (<1)	1 (<1)	0	0	2 (1)	0	0	0	0	0	0	0
Hypertransaminasaemia	1 (<1)	1 (<1)	0	0	1 (<1)	0	0	0	2 (1)	0	0	0
Carpal tunnel syndrome	1 (<1)	1 (<1)	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Tooth abscess	1 (<1)	1 (<1)	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Incisional hernia	1 (<1)	1 (<1)	0	0	1 (<1)	0	0	0	0	0	0	0
Sarcoidosis	1 (<1)	1 (<1)	0	0	1 (<1)	0	0	0	0	0	0	0
Device-related infection	1 (<1)	1 (<1)	0	0	0	2 (1)	0	0	0	1 (<1)	0	0
Cholelithiasis	1 (<1)	1 (<1)	0	0	0	1 (<1)	0	0	2 (1)	0	0	0
Dermatitis bullous	1 (<1)	1 (<1)	0	0	0	0	0	0	0	0	0	0

	Chemotherapy → avelumab (N=328)				Chemotherapy + avelumab → avelumab (N=329)				Chemotherapy → observation (N=334)			
	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
Pleural effusion	1 (<1)	0	1 (<1)	0	8 (2)	1 (<1)	0	0	2 (1)	0	0	0
Sciatica	1 (<1)	0	0	0	2 (1)	1 (<1)	0	0	0	0	0	0
Hernia	1 (<1)	0	0	0	2 (1)	0	0	0	0	1 (<1)	0	0
Wound infection	1 (<1)	0	0	0	1 (<1)	1 (<1)	0	0	4 (1)	2 (1)	0	0
Wound dehiscence	1 (<1)	0	0	0	1 (<1)	1 (<1)	0	0	2 (1)	0	0	0
Impaired healing	1 (<1)	0	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	0	0	0
Tooth infection	1 (<1)	0	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	0	0	0
Enteritis	1 (<1)	0	0	0	1 (<1)	1 (<1)	0	0	0	0	0	0
Hyperlipidaemia	1 (<1)	0	0	0	1 (<1)	0	0	0	3 (1)	1 (<1)	0	0
Nephrolithiasis	1 (<1)	0	0	0	1 (<1)	0	0	0	0	1 (<1)	0	0
Cystitis noninfective	1 (<1)	0	0	0	0	1 (<1)	0	0	2 (1)	0	0	0
Contrast media allergy	1 (<1)	0	0	0	0	1 (<1)	0	0	1 (<1)	0	0	0
Leukocytosis	1 (<1)	0	0	0	0	1 (<1)	0	0	1 (<1)	0	0	0
Pneumothorax	1 (<1)	0	0	0	0	1 (<1)	0	0	1 (<1)	0	0	0
Femoral neck fracture	1 (<1)	0	0	0	0	1 (<1)	0	0	0	0	0	0
Lymphopenia	1 (<1)	0	0	0	0	1 (<1)	0	0	0	0	0	0
Cerebrovascular accident	1 (<1)	0	0	0	0	0	1 (<1)	0	0	0	0	0
Pulmonary oedema	1 (<1)	0	0	0	0	0	1 (<1)	0	0	0	0	0
Post procedural haemorrhage	1 (<1)	0	0	0	0	0	0	0	0	1 (<1)	0	0
Haematoma	1 (<1)	0	0	0	0	0	0	0	0	0	1 (<1)	0
Pulmonary embolism	0	7 (2)	2 (1)	2 (1)	2 (1)	5 (2)	1 (<1)	0	3 (1)	3 (1)	1 (<1)	1 (<1)
Acute kidney injury	0	2 (1)	0	0	2 (1)	1 (<1)	0	0	0	0	0	0
Peritonitis	0	2 (1)	0	0	0	0	0	0	1 (<1)	0	0	0
Sepsis	0	1 (<1)	1 (<1)	0	0	0	1 (<1)	0	0	0	0	0
Type 1 diabetes mellitus	0	1 (<1)	1 (<1)	0	0	0	0	0	0	0	0	0
Infection	0	1 (<1)	0	0	3 (1)	0	0	0	1 (<1)	1 (<1)	0	0
Blood pressure increased	0	1 (<1)	0	0	1 (<1)	1 (<1)	0	0	0	1 (<1)	0	0
Confusional state	0	1 (<1)	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Vaginal cuff dehiscence	0	1 (<1)	0	0	1 (<1)	0	0	0	0	1 (<1)	0	0
Lymphadenopathy	0	1 (<1)	0	0	1 (<1)	0	0	0	0	0	0	0
Seroma	0	1 (<1)	0	0	1 (<1)	0	0	0	0	0	0	0
Urogenital fistula	0	1 (<1)	0	0	1 (<1)	0	0	0	0	0	0	0
Pyelonephritis	0	1 (<1)	0	0	0	2 (1)	0	0	1 (<1)	0	0	0
Hydronephrosis	0	1 (<1)	0	0	0	1 (<1)	0	0	0	0	0	0
Urosepsis	0	1 (<1)	0	0	0	1 (<1)	0	0	0	0	0	0
Glucose tolerance impaired	0	1 (<1)	0	0	0	0	0	0	1 (<1)	0	0	0

	Chemotherapy → avelumab (N=328)				Chemotherapy + avelumab → avelumab (N=329)				Chemotherapy → observation (N=334)			
	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
White blood cell count	0	1 (<1)	0	0	0	0	0	0	1 (<1)	0	0	0
Essential hypertension	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Fistula	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Guttate psoriasis	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Hypernatraemia	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Intestinal dilatation	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Intestinal haemorrhage	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Lymph gland infection	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Malignant pleural effusion	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Metabolic acidosis	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Peripheral sensorimotor neuropathy	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Respiratory acidosis	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Tachypnoea	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Toxicity to various agents	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Tuberculosis	0	1 (<1)	0	0	0	0	0	0	0	0	0	0
Gastrointestinal obstruction	0	0	2 (1)	0	0	1 (<1)	0	0	0	0	0	0
Blood triglycerides increased	0	0	1 (<1)	0	0	0	0	0	4 (1)	0	0	0
Hypercalcaemia of malignancy	0	0	1 (<1)	0	0	0	0	0	0	0	0	0
Oliguria	0	0	1 (<1)	0	0	0	0	0	0	0	0	0
Pancreatitis	0	0	1 (<1)	0	0	0	0	0	0	0	0	0
Procedural intestinal perforation	0	0	1 (<1)	0	0	0	0	0	0	0	0	0
Disease progression	0	0	0	1 (<1)	0	0	0	3 (1)	0	0	0	0
Adrenal insufficiency	0	0	0	0	3 (1)	2 (1)	0	0	0	0	0	0
Postoperative wound infection	0	0	0	0	3 (1)	1 (<1)	0	0	1 (<1)	0	0	0
Hypoxia	0	0	0	0	2 (1)	0	0	0	1 (<1)	1 (<1)	1 (<1)	0
Bacteriuria	0	0	0	0	2 (1)	0	0	0	0	1 (<1)	0	0
Ankle fracture	0	0	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	0	0	0
Cholecystitis acute	0	0	0	0	1 (<1)	1 (<1)	0	0	0	0	0	0
Facial nerve disorder	0	0	0	0	1 (<1)	1 (<1)	0	0	0	0	0	0
Hypovolaemia	0	0	0	0	1 (<1)	1 (<1)	0	0	0	0	0	0
Respiratory distress	0	0	0	0	1 (<1)	1 (<1)	0	0	0	0	0	0
Subileus	0	0	0	0	1 (<1)	0	0	0	1 (<1)	1 (<1)	1 (<1)	0

	Chemotherapy → avelumab (N=328)				Chemotherapy + avelumab → avelumab (N=329)				Chemotherapy → observation (N=334)			
	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
Erythema multiforme	0	0	0	0	0	2 (1)	0	0	0	0	0	0
Hypopituitarism	0	0	0	0	0	2 (1)	0	0	0	0	0	0
Large intestinal obstruction	0	0	0	0	0	2 (1)	0	0	0	0	0	0
Malignant melanoma	0	0	0	0	0	2 (1)	0	0	0	0	0	0
Pancytopenia	0	0	0	0	0	1 (<1)	1 (<1)	0	0	0	0	0
Abdominal abscess	0	0	0	0	0	1 (<1)	0	1 (<1)	0	0	0	0
Anaphylactic reaction	0	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Infected lymphocele	0	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Bacteraemia	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Blood calcium decreased	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Breast cancer	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Depression suicidal	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Diaphragmatic hernia	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Disseminated intravascular coagulation	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Drooling	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Erythropenia	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Escherichia sepsis	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Hypoglycaemia	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Immune-mediated enterocolitis	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Immune-mediated hepatitis	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Malnutrition	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Melanocytic naevus	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Normocytic anaemia	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Pelvic inflammatory disease	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Pelvic venous thrombosis	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Pseudomembranous colitis	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Pulmonary infarction	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Renal colic	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Retinal vein occlusion	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
Skin neoplasm excision	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Systemic lupus erythematosus	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Urogenital disorder	0	0	0	0	0	1 (<1)	0	0	0	0	0	0

	Chemotherapy → avelumab (N=328)				Chemotherapy + avelumab → avelumab (N=329)				Chemotherapy → observation (N=334)			
	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
Large intestine perforation	0	0	0	0	0	0	1 (<1)	0	1 (<1)	0	0	0
Anaphylactic shock	0	0	0	0	0	0	1 (<1)	0	0	0	0	0
Anastomotic leak	0	0	0	0	0	0	1 (<1)	0	0	0	0	0
Meningitis bacterial	0	0	0	0	0	0	1 (<1)	0	0	0	0	0
Subdural haematoma	0	0	0	0	0	0	1 (<1)	0	0	0	0	0
Cardiopulmonary failure	0	0	0	0	0	0	0	1 (<1)	0	0	0	0
Multiple organ dysfunction syndrome	0	0	0	0	0	0	0	1 (<1)	0	0	0	0
Perforation	0	0	0	0	0	0	0	1 (<1)	0	0	0	0
Faecaloma	0	0	0	0	0	0	0	0	1 (<1)	1 (<1)	0	0
Pelvic infection	0	0	0	0	0	0	0	0	1 (<1)	1 (<1)	0	0
Blood sodium decreased	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Cardiac function disturbance postoperative	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Empyema	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Escherichia infection	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Glomerular filtration rate decreased	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Haematocrit decreased	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Incarcerated hernia	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Menorrhagia	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Myocardial infarction	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Peripheral nerve paresis	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Peritoneal adhesions	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Persistent depressive disorder	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Red blood cell count decreased	0	0	0	0	0	0	0	0	0	1 (<1)	0	0
Death	0	0	0	0	0	0	0	0	0	0	0	1 (<1)
Malignant neoplasm progression	0	0	0	0	0	0	0	0	0	0	0	1 (<1)

AE=adverse event.

AEs of grade 1–2 occurring in ≥10% orof patients and all grade 3–5 in ≥2% of patients in any arm are shown. A table showing AEs of grade 1–2 occurring in ≥10% of patients and all AEs of grade 3, 4 or 5 is included in the appendix, p 12.