CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc.

Investigational Product: Avelumab, Compound Number: PF-06834635

Clinical Study Report Synopsis: Protocol JAVELIN OVARIAN 100 (B9991010)

Protocol Title: A Randomized, Open-Label, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Avelumab (MSB0010718C) in Combination With and/or Following Chemotherapy in Patients With Previously Untreated Epithelial Ovarian Cancer

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Center(s): Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None.

Study Initiation Date: 19 May 2016.

Report Date: 05 September 2019

Previous Report Date(s): Not applicable.

Phase of Development: Phase 3

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Primary and Secondary Study Objectives and Endpoints:

Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
Efficacy	To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance is superior to platinum-based chemotherapy alone followed by observation in prolonging progression-free survival (PFS) in patients with previously untreated epithelial ovarian cancer (EOC).	PFS as determined by blinded independent central review (BICR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
	To demonstrate that platinum-based chemotherapy alone followed by avelumab maintenance is superior to platinum-based chemotherapy alone followed by observation in prolonging PFS in patients with previously untreated EOC.	PFS as determined by BICR by RECIST v1.1
Secondary		
Efficacy	To compare avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance and platinum-based chemotherapy alone followed by avelumab maintenance to platinum-based chemotherapy alone followed by observation in patients with previously untreated EOC, with respect to overall survival (OS).	OS
	To evaluate the anti-tumor activity in each treatment arm.	PFS by Investigator assessment Objective response (OR); Duration of response (DR); Maintenance PFS (mPFS) by BICR assessment and Investigator assessment; pathologic complete response (pCR); PFS2; and PFS by Gynecological Cancer Intergroup (GCIG) criteria.
Safety	To evaluate the overall safety profile in each treatment arm.	Adverse events (AEs) (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.03); laboratory abnormalities (as graded by NCI CTCAE v4.03); vital signs (blood pressure, pulse rate); electrocardiograms (ECGs)
PK (None Reported)	To evaluate the pharmacokinetics (PK) of paclitaxel and carboplatin alone and in combination with avelumab.	PK Parameters, including Minimum (trough) observed drug concentration (C_{trough}), maximum concentration (C_{max}), volume of distribution, (Vd), clearance (CL), area under the concentration time curve (AUC) for avelumab, paclitaxel, and carboplatin, as data permit.
	To evaluate the PK of avelumab alone and in combination with	PK Parameters, including C_{trough}, C_{max}, Vd, CL, AUC for avelumab,

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Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint
	carboplatin-paclitaxel.	paclitaxel, and carboplatin, as data permit.
Immunogenicity (None Reported)	To evaluate the immunogenicity of avelumab alone and in combination with carboplatin-paclitaxel.	Anti-drug antibodies (ADA) and neutralizing antibody (nAb) against avelumab.
[redacted]		
PRO (None Reported)	To evaluate patient-reported outcome (PRO) in the experimental arms versus the control arm in patients with previously untreated EOC including the assessment of treatment side effects and disease-related symptoms.	Functional Assessment of Cancer Therapy Ovarian Symptom Index 18 (FOSI-18) and EuroQoL5 Dimension (EQ-5D-5L)
[redacted]		

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METHODS

Study Design: This was a Phase 3, open-label, international, multi-center, efficacy, and safety study of avelumab in combination with and/or following platinum-based chemotherapy.

In this Phase 3 trial, approximately 951 patients who were candidates for frontline platinum-based chemotherapy were to be randomized in a 1:1:1 ratio stratified by paclitaxel regimen (once every 3 weeks [Q3W] versus once weekly [QW]) and by adjuvant (complete resection/microscopic disease) versus adjuvant (incomplete resection ≤1 cm) versus adjuvant (incomplete resection >1 cm) versus neoadjuvant to one of the following treatment arms.

Treatment Arms:

- Arm A: platinum-based chemotherapy alone followed by observation (control arm)
- Arm B: platinum-based chemotherapy alone followed by avelumab maintenance (experimental arm)
- Arm C: platinum-based chemotherapy in combination with avelumab followed by avelumab maintenance (experimental arm)

Diagnosis and Main Criteria for Inclusion: Patients with previously untreated, Stage III-IV epithelial ovarian cancer (EOC), Fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) who were candidates for platinum-based chemotherapy.

Study Treatment: All patients received chemotherapy consisting of carboplatin administered Q3W in combination with paclitaxel either QW or Q3W. Patients in one of the experimental arms also received avelumab Q3W in combination with the carboplatin/paclitaxel regimen. Patients in both experimental arms received avelumab every 2 weeks (Q2W) during the maintenance phase (after completion of the chemotherapy regimen). Patients received carboplatin, paclitaxel, and avelumab as intravenous (IV) infusions. Avelumab investigational product description is presented in Table S2 (see Appendix 16.1.6 for complete list of investigational product descriptions).

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Table S2. Avelumab Investigational Product Description

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1F004	15-006068	200 mg	SOLUTION
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1F013	16-000916	200 mg	SOLUTION
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1G003	16-003176	200 mg	SOLUTION
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1E002	15-002315	200 mg	SOLUTION

Source: Appendix 16.1.6.

Efficacy Endpoints:

Primary Efficacy Endpoint: Progression-free survival (PFS) as determined by blinded independent central review (BICR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. PFS is defined as the time from the date of randomization to the date of the first documentation of progressive disease (PD) based on BICR assessment or death due to any cause, whichever occurs first.

Secondary Efficacy Endpoints:

Overall survival (OS) is defined as the time from the date of randomization to the date of death due to any cause. PFS is defined as the time from the date of randomization to the date of the first documentation of PD based on investigator assessment or death due to any cause, whichever occurs first. Other secondary efficacy endpoints included objective response (OR), duration of response (DR), maintenance PFS by BICR assessment, and pathologic complete response (pCR).

Safety Evaluations: Safety assessments included collection of adverse events (AEs), Serious Adverse Events (SAEs), vital signs, physical examination, electrocardiogram (ECG) (12-lead), and laboratory assessments.

Statistical Methods:

The study was designed to test, in parallel, 2 hypotheses:

- The true PFS hazard ratio (HR) for chemotherapy in combination with avelumab followed by avelumab maintenance over chemotherapy alone followed by observation was ≥1; versus the alternative hypothesis that the true HR was <1.
- The true PFS HR for chemotherapy alone followed by avelumab maintenance over chemotherapy alone followed by observation was ≥1; versus the alternative hypothesis that the true HR was <1.

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RESULTS

Patient Disposition and Demography:

A summary of patient disposition at the end of treatment chemotherapy phase is presented in Table S3. Within each treatment arm the majority of patients completed the chemotherapy phase. Patients discontinued from the study during the chemotherapy phase most often due to AEs, withdrawal by subject, and PD.

A summary of patient disposition at the end of treatment maintenance phase is presented in Table S4. Within each treatment arm approximately half of the patients were ongoing at the time of data cut off. Patients discontinued from the study during the maintenance phase most often due to withdrawal by subject and PD.

Overall, demographic characteristics were balanced across treatment arms. All enrolled patients were female, most were <65 years old, and the majority were white.

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Table S3. Subject Disposition for Study Drugs at End of Treatment Chemotherapy Phase - Full Analysis Set

	Chemotherapy -> Avelumab (N=332)		Chemotherapy + Avelumab -> Avelumab (N=331)			Chemotherapy -> Observation (N=335)	
	Paclitaxel n (%)	Carboplatin n (%)	Avelumab n (%)	Paclitaxel n (%)	Carboplatin n (%)	Paclitaxel n (%)	Carboplatin n (%)
Disposition phase: end of chemotherapy							
Discontinued	57 (17.2)	52 (15.7)	47 (14.2)	50 (15.1)	41 (12.4)	56 (16.7)	45 (13.4)
Reason for discontinuation							
Death	5 (1.5)	5 (1.5)	4 (1.2)	4 (1.2)	4 (1.2)	1 (0.3)	1 (0.3)
Progressive disease	11 (3.3)	11 (3.3)	7 (2.1)	7 (2.1)	7 (2.1)	10 (3.0)	10 (3.0)
Adverse event	14 (4.2)	8 (2.4)	23 (6.9)	26 (7.9)	17 (5.1)	24 (7.2)	13 (3.9)
Physician's decision	5 (1.5)	6 (1.8)	3 (0.9)	1 (0.3)	1 (0.3)	4 (1.2)	4 (1.2)
No longer meets eligibility criteria	4 (1.2)	4 (1.2)	2 (0.6)	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)
Global deterioration of health status	4 (1.2)	3 (0.9)	2 (0.6)	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)
Withdrawal by subject	12 (3.6)	13 (3.9)	6 (1.8)	8 (2.4)	8 (2.4)	15 (4.5)	15 (4.5)
Other	2 (0.6)	2 (0.6)	0	0	0	0	0
Completed	275 (82.8)	280 (84.3)	284 (85.8)	281 (84.9)	290 (87.6)	279 (83.3)	290 (86.6)
Ongoing	0	0	0	0	0	0	0

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 14MAY2019 (23:39) Source Data: ADDS Output File: ./B9991010_restricted/B9991010_CSR/adds_s001g Date of Generation: 06JUN2019 (15:54)
Table 14.1.1.2.7 is for Pfizer internal use.

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Table S4. Subject Disposition for Study Drugs at End of Treatment Maintenance Phase - Full Analysis Set

	Chemotherapy -> Avelumab (N=332) Avelumab n (%)	Chemotherapy + Avelumab -> Avelumab (N=331) Avelumab n (%)	Chemotherapy -> Observation (N=335) Observation n (%)
Disposition phase: end of maintenance			
Discontinued	112 (33.7)	107 (32.3)	114 (34.0)
Reason for discontinuation			
Death	0	1 (0.3)	2 (0.6)
Progressive disease	72 (21.7)	64 (19.3)	66 (19.7)
Adverse event	16 (4.8)	23 (6.9)	1 (0.3)
Physician's decision	4 (1.2)	5 (1.5)	9 (2.7)
Protocol deviation	0	0	0
Study terminated by sponsor	0	0	1 (0.3)
No longer meets eligibility criteria	0	1 (0.3)	0
Global deterioration of health status	5 (1.5)	2 (0.6)	1 (0.3)
Withdrawal by subject	13 (3.9)	10 (3.0)	27 (8.1)
Lost to follow-up	0	0	2 (0.6)
Other	2 (0.6)	1 (0.3)	5 (1.5)
Completed	0	0	1 (0.3)
Ongoing	155 (46.7)	180 (54.4)	172 (51.3)

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 14MAY2019 (23:39) Source Data: ADDS Output File: ./B9991010_restricted/B9991010_CSR/adds_s001h Date of Generation: 06JUN2019 (16:00)
Table 14.1.1.2.8 is for Pfizer internal use.

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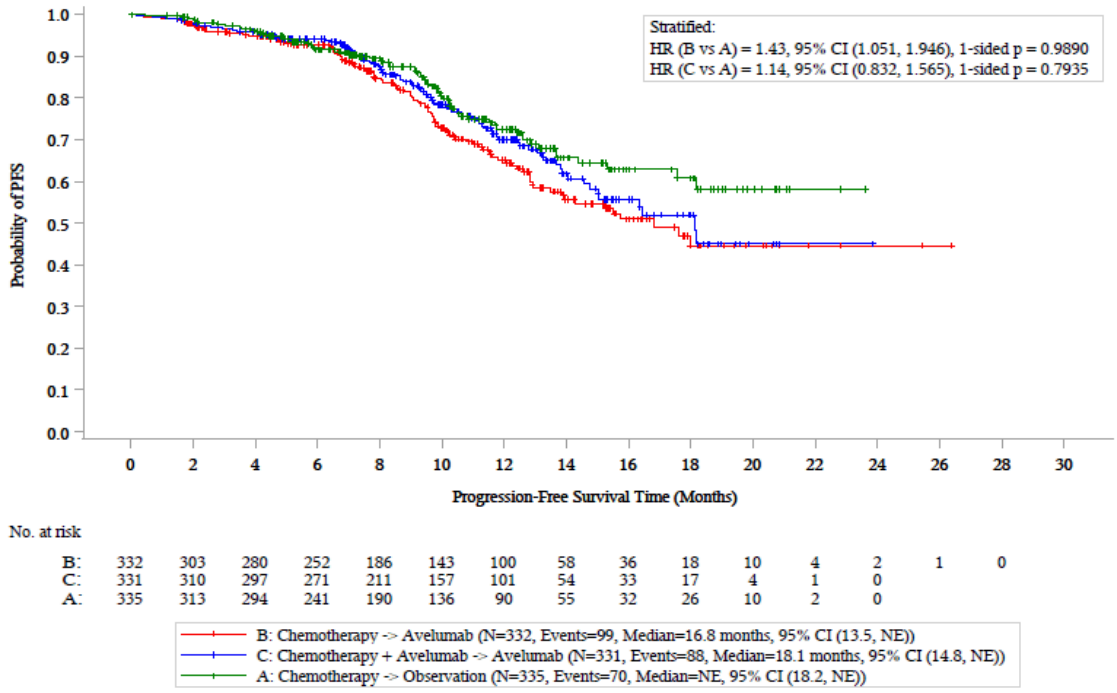
Primary Efficacy Results:

The study did not meet its primary endpoint of PFS as assessed by BICR in either experimental arm. The stratified HRs comparing each of the experimental arms against the control arm were >1 favoring the control arm: 1.43, 95% confidence interval (CI) (1.051, 1.946) for chemotherapy alone followed by avelumab maintenance and 1.14, 95% CI (0.832, 1.565) for chemotherapy in combination with avelumab followed by avelumab maintenance (Figure S1).

Figure S1. Kaplan-Meier Plot of Progression-Free Survival (Primary Analysis) Based on BICR Assessment (RECIST v1.1) - Full Analysis Set

Figure 14.2.5.1.1 Page 1 of 1
MSB0010718C Protocol B9991010 (Cut-Off Date : 07SEP2018, Snapshot Date: 14MAY2019)
Kaplan-Meier Plot of Progression-Free Survival (Primary Analysis) Based on BICR Assessment (RECIST v1.1) - Full Analysis Set



PFIZER CONFIDENTIAL SDTM Creation: 14MAY2019 (23:39) Source Data: ADTTEB Output File: ./B9991010_restricted/B9991010_CSR/adtteb_pfs_f001 Date of Generation: 09JUL2019 (17:10)

Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; NE = not evaluable; RECIST = Response Evaluation Criteria in Solid Tumors.

Secondary Efficacy Results:

The OS data were still immature at the time of the analysis. The stratified HRs in both experimental arms compared to the control arm were >1, favoring the control arm.

Despite a higher early discrepancy rate (reflecting a higher frequency with which investigator declared PFS events earlier than BICR), the results for PFS based on investigator assessment were similar to those observed based on BICR assessment.

The Objective Response Rate was similar across the treatment arms based on both BICR (30.4% for patients who received chemotherapy alone followed by observation, 30.4% for patients who received chemotherapy alone followed by avelumab maintenance, 36.0% for patients who received chemotherapy in combination with avelumab followed by avelumab maintenance) and investigator assessment (27.8% for patients who received chemotherapy alone followed by observation, 25.9% for patients who received chemotherapy alone followed by avelumab maintenance, 31.1% for patients who received chemotherapy in combination with avelumab followed by avelumab maintenance).

The median DR was not reached in any of the treatment arms.

Maintenance PFS time (based on BICR and based on investigator assessment) appeared to be similar across treatment arms; median maintenance PFS was not reached in any of the treatment arms.

The observed pCR rates for patients in the experimental arms (15.7% for patients who received chemotherapy alone followed by avelumab maintenance, 17.4% for patients who received chemotherapy in combination with avelumab followed by avelumab maintenance) were lower than that observed for patients in the control arm (25.9%).

Safety Results:

The overall proportions of patients who reported treatment-emergent adverse events (TEAEs) were similar across treatment arms. In general, the control arm had the lowest and the treatment arm of chemotherapy in combination with avelumab followed by avelumab maintenance had the highest proportions of patients with TEAEs of all causality, treatment-related TEAEs of Grade ≥3, serious TEAEs, TEAEs leading to interruption or discontinuation of any study drug, and infusion-related adverse events (irAEs). Higher proportions of patients in the experimental arms experienced serious TEAEs or serious treatment-related TEAEs compared to patients in the control arm. Deaths occurred more frequently in the experimental arms than in the control arm, and were most often due to disease progression.

Deaths occurred in 19 patients (5.8%) who received chemotherapy alone followed by avelumab maintenance and 21 patients (6.4%) who received chemotherapy with avelumab followed by avelumab maintenance compared with 13 patients (3.9%) who received chemotherapy alone followed by observation. These deaths were most often due to disease progression (15 patients [4.6%] who received chemotherapy alone followed by avelumab

maintenance, 17 patients [5.2%] who received chemotherapy with avelumab followed by avelumab maintenance, and 11 patients [3.3%] who received chemotherapy alone followed by observation).

TEAEs during the on-treatment period leading to death occurred in <2% of patients in all treatment arms. Treatment-related TEAEs during the on-treatment period leading to death only occurred in 1 patient who received chemotherapy alone followed by avelumab maintenance (preferred term [PT] of atrial fibrillation; of note, this AE had an onset during the chemotherapy phase prior to initiating avelumab) and 1 patient who received chemotherapy with avelumab followed by avelumab maintenance (PT of disease progression). No patient had an irAE or immune-related reaction (IRR) leading to death.

TEAEs leading to permanent discontinuation of any study drug was reported for 11.3% of patients who received chemotherapy alone followed by avelumab maintenance, 19.1% of patients who received chemotherapy with avelumab followed by avelumab maintenance, and 7.5% of patients who received chemotherapy alone followed by observation. Treatment-related TEAEs leading to permanent discontinuation of any study drug was reported for 9.8% of patients who received chemotherapy alone followed by avelumab maintenance, 15.5% of patients who received chemotherapy with avelumab followed by avelumab maintenance, and 6.6% of patients who received chemotherapy alone followed by observation.

Discontinuations of any study drug due to irAEs occurred in 8 patients (2.4%) who received chemotherapy alone followed by avelumab maintenance and 19 patients (5.8%) who received chemotherapy with avelumab followed by avelumab maintenance. Discontinuations of any study drug due to IRRs occurred in 3 patients (0.9%) who received chemotherapy alone followed by avelumab maintenance and 7 patients (2.1%) who received chemotherapy with avelumab followed by avelumab maintenance compared with 4 patients (1.2%) who received chemotherapy alone followed by observation.

The proportions of patients who reported TEAEs were similar across treatment arms (Table S5). The most frequent all-causality TEAEs (all grades) experienced by ≥30% of patients in all 3 treatment arms were alopecia, anemia, nausea, neutropenia, and fatigue. Constipation was also reported by ≥30% of patients who received chemotherapy alone followed by avelumab maintenance. Serious treatment-related TEAEs were experienced by 42 patients (12.8%) who received chemotherapy alone followed by avelumab maintenance, 63 patients (19.1%) who received chemotherapy with avelumab followed by avelumab maintenance, and 29 patients (8.7%) who received chemotherapy alone followed by observation. Patients who received chemotherapy with avelumab followed by avelumab maintenance had the highest proportions of patients with serious treatment-related TEAEs.

The most common serious TEAEs (any grade in ≥2% of patients or Grade ≥3 in ≥2% of patients) were pyrexia, anaemia, febrile neutropenia, urinary tract infection and ileus in all 3 treatment arms and in general were experienced by higher proportions of patients who received chemotherapy with avelumab followed by avelumab maintenance followed by patients who received chemotherapy alone followed by avelumab maintenance compared to patients who received chemotherapy alone followed by observation (Table S6).

Table S5. Summary of Most Common TEAEs (Any Grade in ≥10% Subjects or Grade ≥3 in ≥5% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period - Safety Analysis Set

Preferred Term	Chemotherapy -> Avelumab (N=328)		Chemotherapy + Avelumab -> Avelumab (N=329)		Chemotherapy -> Observation (N=334)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Subjects with events	322 (98.2)	218 (66.5)	327 (99.4)	233 (70.8)	321 (96.1)	209 (62.6)
Alopecia	166 (50.6)	2 (0.6)	169 (51.4)	0	177 (53.0)	3 (0.9)
Anaemia	150 (45.7)	68 (20.7)	155 (47.1)	63 (19.1)	143 (42.8)	52 (15.6)
Nausea	151 (46.0)	6 (1.8)	150 (45.6)	6 (1.8)	152 (45.5)	5 (1.5)
Neutropenia	114 (34.8)	91 (27.7)	124 (37.7)	99 (30.1)	113 (33.8)	88 (26.3)
Fatigue	121 (36.9)	6 (1.8)	114 (34.7)	12 (3.6)	109 (32.6)	12 (3.6)
Constipation	114 (34.8)	2 (0.6)	98 (29.8)	1 (0.3)	94 (28.1)	3 (0.9)
Diarrhoea	83 (25.3)	8 (2.4)	97 (29.5)	5 (1.5)	63 (18.9)	7 (2.1)
Arthralgia	72 (22.0)	1 (0.3)	77 (23.4)	5 (1.5)	54 (16.2)	1 (0.3)
Neuropathy peripheral	63 (19.2)	1 (0.3)	77 (23.4)	3 (0.9)	64 (19.2)	1 (0.3)
Vomiting	87 (26.5)	9 (2.7)	77 (23.4)	7 (2.1)	68 (20.4)	7 (2.1)
Peripheral sensory neuropathy	91 (27.7)	0	75 (22.8)	0	82 (24.6)	0
Abdominal pain	64 (19.5)	5 (1.5)	64 (19.5)	6 (1.8)	58 (17.4)	8 (2.4)
Rash	55 (16.8)	2 (0.6)	63 (19.1)	7 (2.1)	25 (7.5)	1 (0.3)
Thrombocytopenia	47 (14.3)	14 (4.3)	62 (18.8)	25 (7.6)	59 (17.7)	18 (5.4)
Neutrophil count decreased	60 (18.3)	49 (14.9)	54 (16.4)	45 (13.7)	75 (22.5)	59 (17.7)
Decreased appetite	63 (19.2)	1 (0.3)	53 (16.1)	1 (0.3)	38 (11.4)	1 (0.3)
Myalgia	67 (20.4)	1 (0.3)	53 (16.1)	2 (0.6)	43 (12.9)	3 (0.9)
Cough	35 (10.7)	1 (0.3)	51 (15.5)	0	20 (6.0)	0
Dyspnoea	39 (11.9)	3 (0.9)	48 (14.6)	4 (1.2)	30 (9.0)	1 (0.3)
Headache	51 (15.5)	1 (0.3)	48 (14.6)	0	28 (8.4)	0
Urinary tract infection	36 (11.0)	4 (1.2)	47 (14.3)	8 (2.4)	29 (8.7)	2 (0.6)
Asthenia	34 (10.4)	5 (1.5)	46 (14.0)	2 (0.6)	22 (6.6)	1 (0.3)
Pyrexia	37 (11.3)	0	43 (13.1)	1 (0.3)	23 (6.9)	1 (0.3)
Hypomagnesaemia	32 (9.8)	1 (0.3)	42 (12.8)	4 (1.2)	27 (8.1)	0
Insomnia	50 (15.2)	2 (0.6)	39 (11.9)	0	32 (9.6)	2 (0.6)
Platelet count decreased	25 (7.6)	7 (2.1)	39 (11.9)	11 (3.3)	44 (13.2)	15 (4.5)
Dizziness	43 (13.1)	1 (0.3)	37 (11.2)	1 (0.3)	28 (8.4)	0
Abdominal pain upper	28 (8.5)	1 (0.3)	35 (10.6)	2 (0.6)	21 (6.3)	0
Infusion related reaction	26 (7.9)	1 (0.3)	34 (10.3)	4 (1.2)	19 (5.7)	0
Pruritus	36 (11.0)	0	34 (10.3)	1 (0.3)	19 (5.7)	0
Hypothyroidism	28 (8.5)	0	33 (10.0)	0	4 (1.2)	0
White blood cell count decreased	32 (9.8)	23 (7.0)	31 (9.4)	18 (5.5)	34 (10.2)	17 (5.1)

Table S5. Summary of Most Common TEAEs (Any Grade in ≥10% Subjects or Grade ≥3 in ≥5% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period - Safety Analysis Set

Preferred Term	Chemotherapy -> Avelumab (N=328)		Chemotherapy + Avelumab -> Avelumab (N=329)		Chemotherapy -> Observation (N=334)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Pain in extremity	27 (8.2)	1 (0.3)	30 (9.1)	0	37 (11.1)	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For subjects reporting more than one AE within a preferred term, the AE with maximum grade is included in the table.
Adverse events are sorted by descending frequency of PT in 'Chemotherapy + Avelumab -> Avelumab' treatment group.
MedDRA (v21.1) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 14MAY2019 (23:39) Source Data: ADAE Output File: ./B9991010_restricted/B9991010_CSR/adae_s999a Date of Generation: 07JUN2019 (02:43)
Table 14.3.1.2.4 is for Pfizer internal use.

Table S6. Summary of Most Common Serious TEAEs (Any Grade in ≥2% Subjects or Grade ≥3 in ≥2% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period - Safety Analysis Set

Preferred Term	Chemotherapy -> Avelumab (N=328)		Chemotherapy + Avelumab -> Avelumab (N=329)		Chemotherapy -> Observation (N=334)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Subjects with events	89 (27.1)	69 (21.0)	115 (35.0)	92 (28.0)	63 (18.9)	48 (14.4)
Pyrexia	6 (1.8)	0	10 (3.0)	1 (0.3)	2 (0.6)	1 (0.3)
Anaemia	6 (1.8)	4 (1.2)	8 (2.4)	5 (1.5)	6 (1.8)	3 (0.9)
Febrile neutropenia	10 (3.0)	9 (2.7)	8 (2.4)	8 (2.4)	7 (2.1)	6 (1.8)
Urinary tract infection	7 (2.1)	4 (1.2)	7 (2.1)	6 (1.8)	2 (0.6)	2 (0.6)
Ileus	3 (0.9)	1 (0.3)	3 (0.9)	2 (0.6)	9 (2.7)	5 (1.5)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For subjects reporting more than one AE within a preferred term, the AE with maximum grade is included in the table.
Adverse events are sorted by descending frequency of PT in 'Chemotherapy + Avelumab -> Avelumab' treatment group.
MedDRA (v21.1) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 14MAY2019 (23:39) Source Data: ADAE Output File: ./B9991010_restricted/B9991010_CSR/adae_s999c Date of Generation: 07JUN2019 (03:24)
Table 14.3.2.2.1.1 is for Pfizer internal use.

Based on the irAE case definition and subsequent medical review, patients who received chemotherapy with avelumab followed by avelumab maintenance most frequently experienced irAEs, irAEs considered Grade ≥3, and serious irAEs. Only 1 Grade 4 irAE occurred (PT of type 1 diabetes mellitus); no Grade 5 irAEs occurred. Immune-related AEs were experienced by 53 patients (16.2%) who received chemotherapy alone followed by avelumab maintenance and 92 patients (28.0%) who received chemotherapy with avelumab followed by avelumab maintenance. These irAEs were considered to be Grade ≥3 in 10 patients (3.0%) who received chemotherapy alone followed by avelumab maintenance and 24 patients (7.3%) who received chemotherapy with avelumab followed by avelumab maintenance. Serious irAEs were experienced by 7 patients (2.1%) who received chemotherapy alone followed by avelumab maintenance and 15 patients (4.6%) who received chemotherapy with avelumab followed by avelumab maintenance.

The most frequently reported irAEs (any grade) were from the clusters of immune-related rash and immune-related endocrinopathies: thyroid disorders (17 patients [5.2%] and 27 patients [8.2%] who received chemotherapy alone followed by avelumab maintenance, and 38 patients [11.6%] and 37 patients [11.2%] who received chemotherapy with avelumab followed by avelumab maintenance).

Based on case definition, IRRs were experienced by 58 patients (17.7%) who received chemotherapy alone followed by avelumab maintenance and 65 patients (19.8%) who received chemotherapy with avelumab followed by avelumab maintenance compared with 44 patients (13.2%) who received chemotherapy alone followed by observation. These IRRs were considered to be Grade ≥3 in 2 patients (0.6%) who received chemotherapy alone followed by avelumab maintenance and 6 patients (1.8%) who received chemotherapy with avelumab followed by avelumab maintenance compared with 6 patients (1.8%) who received chemotherapy alone followed by observation. Serious IRRs occurred infrequently and were experienced by 2 patients (0.6%) who received chemotherapy alone followed by avelumab maintenance and 6 patients (1.8%) who received chemotherapy with avelumab followed by avelumab maintenance. No patients who received chemotherapy alone followed by observation experienced a serious IRR.

The proportions of patients who had any grade and Grade ≥3 hematology abnormalities was similar across all 3 treatment arms for anemia (all grades: 93.3% to 95.1%; Grade ≥3: 19.2% to 22.4%), platelet count decreased (all grades: 61.0% to 66.9%; Grade ≥3: 6.1% to 11.6%), and neutrophil count decreased (all grades: 76.7% to 81.0%; Grade ≥3: 44.2% to 48.8%). For lymphocyte count decreased, Grade ≥3 events were reported by 19.3% of patients who received chemotherapy with avelumab followed by avelumab maintenance, 10.7% of patients who received chemotherapy alone followed by avelumab maintenance, and 8.8% of patients who received chemotherapy alone followed by observation where as the proportion reporting all grades for this hematological abnormality was similar between all treatment arms (55.5% to 63.5%).

There were no clinically relevant differences in the proportions of patients who had all grades and Grade ≥3 chemistry abnormalities across all 3 treatment arms for creatinine increased (all grades: 82.6% to 88.6%; Grade ≥3: 0.0% to 2.1%), serum amylase increased (all grades: 16.3% to 28.3%; Grade ≥3: 1.6% to 3.1%) and lipase increased (all grades: 26.5% to 31.0%; Grade ≥3: 3.4% to 7.4%). Overall, the proportions of patients who had liver function test abnormalities was similar across all 3 treatment arms. Of these patients, none met the criteria for a potential Hy's Law case (ie, concurrent alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥3 × upper limit of normal [ULN] and total bilirubin ≥2 × ULN and alkaline phosphatase ≤2 × ULN or missing).

Conclusions:

- The study did not meet its primary objective and failed to demonstrate that either platinum-based chemotherapy alone followed by avelumab maintenance or avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance was superior to platinum-based chemotherapy alone followed by observation in prolonging PFS in patients with previously untreated EOC.

- The OS data were immature at the time of the analysis and no definitive conclusions can be drawn.

- No apparent benefit on OR, DR, maintenance PFS time, or pCR was observed in either experimental arm compared to the control arm.

- The safety profile of avelumab administered either at maintenance following chemotherapy (carboplatin and paclitaxel) alone or in combination with chemotherapy and at maintenance as treatment for patients with EOC was generally tolerable, manageable, and consistent with the known safety profiles of avelumab and chemotherapy when administered as monotherapies.