Gynecologic Oncology 154 (2019) 314–322

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Safety, clinical activity and biomarker assessments of atezolizumab from a Phase I study in advanced/recurrent ovarian and uterine cancers☆

Joyce F. Liu [a,*], Michael Gordon [b], Jennifer Veneris [c], Fadi Braiteh [d], Ani Balmanoukian [e], Joseph Paul Eder [f], Ana Oaknin [g], Erika Hamilton [h], Yulei Wang [i], Indrani Sarkar [i], Luciana Molinero [i], Marcella Fassò [i], Carol O'Hear [i], Yvonne G. Lin [i], Leisha A. Emens [j]

[a] Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215-5450, United States
[b] HonorHealth Research Institute, 10510 N 92nd St, Suite 200, Scottsdale, AZ 85258, United States
[c] University of Chicago Medicine, 5841 S Maryland Ave, Chicago, IL 60637, United States
[d] Comprehensive Cancer Centers of Nevada, 3730 S Eastern Avenue, Las Vegas, NV 89169, United States
[e] The Angeles Clinic and Research Institute, 11818 Wilshire Blvd #200, Los Angeles, CA 90025, United States
[f] Yale Cancer Center, Medical Oncology, PO Box 208028, New Haven, CT 06520-8028, United States
[g] Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Centro Cellex, Calle Natzaret, 115-117, 08035 Barcelona, Spain
[h] Tennessee Oncology/Sarah Cannon Research Institute, 250 25th Ave N, Nashville, TN 37203, United States
[i] Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, United States
[j] UPMC Hillman Cancer Center, 300 Halket St, Suite 4628, Pittsburgh, PA 15213, United States

HIGHLIGHTS

- Atezolizumab monotherapy was well tolerated in pre-treated patients with epithelial ovarian or uterine cancer.
- No new safety signals were seen; safety profile in both cohorts was consistent with that known for atezolizumab monotherapy.
- Preliminary evidence of anti-tumor activity with long durability of response was observed in patients from both cohorts.

ARTICLE INFO

Article history:
Received 22 March 2019
Received in revised form 21 May 2019
Accepted 27 May 2019
Available online 14 June 2019

Keywords:
Atezolizumab
Immune checkpoint inhibitor
PD-L1
Epithelial ovarian cancer
Uterine cancer
Molecular markers

ABSTRACT

Objective. Patients with advanced/recurrent epithelial ovarian and uterine cancers have limited treatment options beyond platinum chemotherapy. Both tumor types can express programmed death-ligand 1 (PD-L1), providing a potential therapeutic target for these patients. Here we present data from the ovarian and uterine cancer cohorts of the Phase I atezolizumab monotherapy study (PCD4989g).

Methods. This Phase I, multi-center, first-in-human, open-label, dose-escalation/expansion clinical trial investigated single-agent atezolizumab in cohorts of patients with recurrent epithelial ovarian or uterine cancer. The primary objective was to evaluate the safety and tolerability of single-agent atezolizumab. Anti-tumor activity and preliminary assessment of potential biomarkers were evaluated as secondary and exploratory objectives, respectively.

Results. The ovarian and uterine cancer cohorts enrolled 12 and 15 patients, respectively (10 [83%] and 5 [33%], respectively, had PD-L1 ≥ 5% on tumor-infiltrating immune cells). Atezolizumab was generally well tolerated with no new safety signals identified. The safety profiles in both cohorts were consistent with the known profile of atezolizumab monotherapy. Treatment-related adverse events (AEs) were mostly Grade ≤ 2, with no treatment-related Grade ≥ 4 AEs reported. Preliminary anti-tumor activity, with long durations of response, was observed in 2 patients from each cohort (ovarian cancer, 8.1 and 30.6+ months; uterine cancer, 7.3 and 16.6+ months). High microsatellite instability and tumor mutational burden were noted in the responders from the uterine cancer cohort.

☆ Preliminary data from this study were previously presented at ESMO 2016 (epithelial ovarian cancer cohort) and ASCO 2017 (uterine cancer cohort).

* Corresponding author at: Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, United States.
E-mail addresses: Joyce_Liu@dfci.harvard.edu (J.F. Liu), Michael.Gordon@HonorHealth.com (M. Gordon), Jennifer_Veneris@dfci.harvard.edu (J. Veneris), fadi.braiteh@usoncology.com (F. Braiteh), abalmanoukian@theangelesclinic.org (A. Balmanoukian), joseph.eder@yale.edu (J.P. Eder), aoaknin@vhio.net (A. Oaknin), ehamilton@tnonc.com (E. Hamilton), wang.yulei@gene.com (Y. Wang), sarkar.indrani@gene.com (I. Sarkar), molinero.luciana@gene.com (L. Molinero), fasso.marcella@gene.com (M. Fassò), ohearc@gene.com (C. O'Hear), lin-liu.yvonne@gene.com (Y.G. Lin), emensla@upmc.edu (L.A. Emens).

https://doi.org/10.1016/j.ygyno.2019.05.021

Conclusions. Atezolizumab monotherapy was well tolerated in patients with epithelial ovarian or uterine cancer and may have clinical activity warranting further investigation.
Trial registration. ClinicalTrials.gov identifier: NCT01375842

1. Introduction

Tumors of the female reproductive system are a leading cause of morbidity and mortality worldwide. Epithelial ovarian and uterine cancers comprise the most common gynecologic cancers in the United States [1]. In particular, incidence rates of uterine cancer are anticipated to rise over the next several years, mirroring increasing trends in obesity [2]. Together, these 2 malignancies also comprise the leading causes of death due to gynecologic cancer in the United States [1] and other industrialized nations worldwide.

Platinum-based chemotherapy, with or without other agents (e.g., taxanes, biologics, etc.), forms a cornerstone systemic therapy for epithelial ovarian and uterine cancers. However, recurrent disease remains difficult to treat, with remote, if any, chance for cure [3–5]. Anti-angiogenic agents (e.g., bevacizumab) have clear anti-tumor activity in epithelial ovarian [6] and uterine cancers [7], but they are not broadly curative for either disease. More recently, poly(ADP-ribose) polymerase (PARP) inhibitors (e.g., niraparib, olaparib, rucaparib) have emerged as potent therapeutic options for many ovarian tumors, particularly those with *BRCA* mutations or homologous recombination pathway defects; however, the role of these drugs in uterine cancers is undefined [8].

Distinct histologic subtypes of epithelial ovarian and uterine cancers have been defined, with varying natural histories and susceptibilities to treatment [4,5]. Gene expression patterns and immunologic and genetic markers can also inform treatment. Programmed death-ligand 1 (PD-L1) expression in the tumor microenvironment can inhibit anti-cancer T-cell activity [9]. PD-L1 expression has been detected in the epithelial ovarian cancer tumor microenvironment on tumor cells (TC) and tumor-infiltrating immune cells (IC) [10] and may have prognostic or predictive potential, although the precise relationship requires further elucidation [11]. PD-L1 expression has also been detected in uterine cancer [12–14], suggesting PD-L1 as a therapeutic target in both patient populations. Molecular interrogation efforts have identified an immunoreactive molecular subtype of high-grade serous epithelial ovarian cancers (the most common histologic variant) [15,16], as characterized by genes encoding programmed death-1 (PD-1) and PD-L1 [15,16]; these findings further suggest potential implications for tailoring treatment [15–17].

Genomic alterations (e.g., homologous recombination defects or mismatch repair [MMR] defects, including microsatellite instability [MSI]) may also be important in certain epithelial ovarian or uterine cancers. Depending on the case series, ≤30% of patients with uterine cancer have MSI-high (MSI-H) disease [18]. Furthermore, responses to immune checkpoint inhibitors, like pembrolizumab, have been observed in patients with MSI-H/MMR–deficient endometrial cancer [19,20]. The presence of DNA polymerase ε mutations and high tumor mutational burden have also been associated with neoantigen loads and response to checkpoint inhibitors [21,22].

Atezolizumab is an engineered, humanized immunoglobulin G1 monoclonal antibody that selectively targets PD-L1 on TC and IC to prevent binding to its receptors, PD-1 and B7.1, reinvigorating suppressed T cells to kill cancer cells [23,24]. Atezolizumab is approved for certain types of urothelial, breast and lung cancers [25,26] and is also active in other tumor types [23,27]. Herein, we present data on safety, as well as clinical activity and potential biomarkers of activity, in patients in the uterine and epithelial ovarian cancer cohorts of the Phase I, open-label study of atezolizumab monotherapy (PCD4989g; ClinicalTrials.gov ID: NCT01375842).

2. Methods

2.1. Study oversight

This study was conducted in accordance with the International Conference on Harmonization E6 guidelines for Good Clinical Practice and the US Food and Drug Administration regulations. Approval for the protocol, informed consent forms and any information provided to patients was obtained from each site prior to study initiation. All participating patients provided written informed consent.

2.2. Study design

This was a Phase I, multi-center, first-in-human, open-label, dose-escalation study (PCD4989g; NCT01375842) of single-agent atezolizumab in cohorts of patients with locally advanced or metastatic solid malignancies or hematologic malignancies [23]. The full study design has been reported previously [23]. Dose escalation was performed in the ovarian cancer cohort using single-patient dose escalation for the 0.01, 0.03 and 0.1 mg/kg cohorts, and a traditional 3 + 3 design was used for doses starting from 0.3 mg/kg [see Fig. S1]). The dose-limiting toxicity window was 21 days following atezolizumab administration. In the dose-expansion phase, atezolizumab was administered intravenously at 15 mg/kg or 1200 mg every 3 weeks for 16 cycles or 1 year of treatment (whichever occurred first) unless the patient experienced loss of clinical benefit or unacceptable toxicity. Treatment beyond 16 cycles/1 year and retreatment of patients who had discontinued therapy, regardless of disease status, was later allowed following a protocol amendment.

2.3. Patients

In the cohorts presented here, patients were eligible if they were ≥ 18 years old with documented incurable or metastatic epithelial ovarian cancer or advanced/recurrent uterine cancer. Patients were also required to have adequate hematologic and end organ function, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status ≤1 and availability of archival or freshly collected tumor tissue samples. Patients who had received treatment with any approved anti-cancer therapy within 3 weeks prior to study treatment initiation or who had received prior treatment with anti–PD-L1 or anti–PD-1 targeting agents were excluded. Exclusion criteria also included known primary central nervous system (CNS) malignancy or symptomatic CNS metastases and history of human immunodeficiency virus, hepatitis B or C virus or autoimmune disease.

For the epithelial ovarian cancer cohort, patients were enrolled into the dose-escalation phase of the study regardless of PD-L1 status; however, only patients with PD-L1–positive tumors (defined as PD-L1 expression on IC comprising ≥ 5% of the tumor [IC2/3]) were included in the dose-expansion phase. Patients in the uterine cancer expansion cohort were initially selected based on PD-L1 status (IC2/3); however, a subsequent protocol amendment then allowed enrollment of patients regardless of PD-L1 status.

2.4. Objectives

The primary objective of the study was to evaluate the safety and tolerability of single-agent atezolizumab. The anti-tumor activity of

atezolizumab (objective response rate [ORR], duration of response [DOR] and progression-free survival [PFS]) was evaluated as a secondary objective. Exploratory objectives included preliminary assessment of potential biomarkers of atezolizumab anti-tumor activity and evaluation of overall survival (OS).

2.5. Assessments and procedures

Safety assessments were performed at screening, throughout the study and at the treatment discontinuation visit (≤30 days after last administration of study treatment). Safety follow-up was performed at 60 and 90 days after last administration of study treatment. Adverse events (AEs) were graded according to National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Tumor response was assessed per RECIST 1.1 and immune-related response criteria (irRC) [28,29] every 6 to 12 weeks until disease progression, death or initiation of further systemic cancer therapy. In patients who continued study treatment beyond disease progression (per RECIST 1.1), tumor assessments were also carried out at least every 6 weeks until treatment discontinuation. PD-L1 status at baseline was determined using the Ventana PD-L1 SP142 IHC assay on archival or fresh tumor biopsy samples (VENTANA Medical Systems, Inc., Tucson, Arizona) [30] and was assessed on IC (IC3, ≥10% of PD-L1–expressing IC in the tumor area; IC2, ≥5% and <10%; IC1, ≥1% and <5%; and IC0, <1%) and on TC (TC3, ≥50% of PD-L1–expressing TC; TC2, ≥5% and <50%; TC1, ≥1% and <5%; and TC0, <1%). MSI and tumor mutational burden (TMB) analyses were evaluated using the FoundationOne CDx™ next-generation sequencing panel (Foundation Medicine Inc., Cambridge, MA). DNA damage response (DDR) gene-alteration analyses were evaluated per Foundation Medicine as previously described [31]. A customized NanoString 800GXCodeSet (NanoString Technologies Inc., Seattle, WA) was used to evaluate RNA levels of 800 genes associated with ovarian disease biology [32], including a previously developed transcriptomic subtyping method [33].

2.6. Statistical analysis

The safety-evaluable population was defined as all patients who received ≥1 dose of atezolizumab treatment. Patients were efficacy evaluable if they had received ≥1 mg/kg of atezolizumab in either the dose-escalation or dose-expansion phase. Patients evaluable for ORR were required to have measurable disease at baseline. The Clopper-Pearson method was used to calculate ORR and the corresponding 95% CIs. DOR, PFS and OS were assessed by the Kaplan-Meier method, and the 95% CIs for median PFS and OS were estimated using the Brookmeyer-Crowley method.

3. Results

3.1. Patients and treatment

The epithelial ovarian cancer cohort enrolled 12 patients who received atezolizumab (Fig. S1). Three patients were treated in the dose-escalation phase of the study (0.3 mg/kg atezolizumab, n = 2; 10 mg/kg atezolizumab, n = 1), and 9 patients were treated in the dose-expansion phase (all 15 mg/kg atezolizumab). All patients were evaluated for safety, and the 10 patients who received ≥1 mg/kg atezolizumab were evaluated for efficacy. In total, 15 patients with uterine cancer were treated with atezolizumab, all in the dose-expansion phase of the study (15 mg/kg atezolizumab, n = 1; 1200 mg atezolizumab, n = 14), and all were evaluated for efficacy and safety (Fig. S1). The date of clinical cutoff for analysis of the epithelial ovarian and uterine cancer cohorts was December 31, 2016.

The baseline demographics and disease characteristics of the patients included in the 2 cohorts are shown in Table 1. The median ages of patients in the epithelial ovarian and uterine cancer cohorts were 60.5 years (range, 39–72 years) and 61.0 years (range, 20–74 years), respectively. Approximately half of the patients in each cohort had an ECOG performance status of 1. No patients in either cohort were chemotherapy naive. All 12 patients in the epithelial ovarian cancer cohort had received ≥1 prior platinum and 1 prior taxane agent, while 14 patients (93.3%) in the uterine cancer cohort had received prior therapy with ≥1 platinum and 1 taxane agent. One patient (8.3%) with epithelial ovarian cancer and 10 patients (66.7%) with uterine cancer had received prior radiotherapy.

Table 1
Baseline demographics and disease characteristics.[a]

Characteristics	Epithelial ovarian cancer cohort (n = 12)	Uterine cancer cohort (n = 15)
Age		
Median (range), years	60.5 (39–72)	61.0 (20–74)
≥65 years, n (%)	4 (33.3)	5 (33.3)
ECOG PS, n (%)		
0	6 (50.0)	7 (46.7)
1	6 (50.0)	8 (53.3)
PD-L1 IC score, n (%)		
IC0/1	1 (8.3)	10 (66.7)
IC2/3	10 (83.3)	5 (33.3)
Unknown	1 (8.3)	0
Prior lines of therapy in recurrent setting, n (%)		
0	1 (8.3)	1 (6.7)
1	0	6 (40.0)
≥2	11 (91.7)	8 (53.3)
Prior radiotherapy, n (%)	1 (8.3)	10 (66.7)
Most common prior systemic treatments in any setting, n (%)		
Cytotoxic chemotherapy	12 (100.0)	15 (100.0)
Platinum chemotherapy	12 (100.0)	14 (93.3)
Taxane	12 (100.0)	14 (93.3)
Anthracycline	10 (83.3)	5 (33.3)
Hormonal therapy	1 (8.3)	5 (33.3)
Anti-angiogenic therapy	9 (75.0)	4 (26.7)
Bevacizumab	8 (66.7)	3 (20.0)
≤3 months from last systemic therapy, n (%)	9 (75.0)	7 (46.7)
Median CA 125 (range), U/mL[b]	727.8 (13.3–7726.0)	–
Tumor MSI status, n (%)		
MSI-H	0	1 (6.7)
MSS	6 (60)	12 (80.0)
Unknown	4 (40)	2 (13.3)

CA 125, cancer antigen 125; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, tumor-infiltrating immune cell; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PD-L1, programmed death-ligand 1.
[a] Data based on the safety-evaluable populations for both cohorts.
[b] CA 125 levels at baseline were assessed in 9 patients in the epithelial ovarian cancer cohort.

At the clinical cutoff date, the median duration of treatment was 2.8 months (range, 0–33.4 months) in the epithelial ovarian cancer cohort and 4.1 months (range, 0–20.7 months) in the uterine cancer cohort. The median number of doses in the epithelial ovarian and uterine cancer cohorts was 4.5 (range, 1–49) and 7 (range, 1–30), respectively. Remaining on treatment at the date of clinical cutoff were 1 of 12 patients in the epithelial ovarian cancer cohort, who received 1 prior line of therapy and was treated with 15 mg/kg atezolizumab, and 2 of 15 patients in the uterine cancer cohort, one who received 1 prior line of therapy and the other who received adjuvant therapy but no prior treatment for metastatic disease; both were given 1200 mg atezolizumab (Fig. S1).

3.2. Safety

All patients in the epithelial ovarian and uterine cancer cohorts experienced ≥1 AE regardless of attribution (Table 2). Treatment-related AEs occurred in 11 patients (91.7%) in the epithelial ovarian cancer cohort and 7 patients (46.7%) in the uterine cancer cohort. Table 3 provides a summary of treatment-related AEs in the epithelial ovarian

and uterine cancer cohorts. The majority of treatment-related AEs in either cohort were Grade 1–2. The most common any-grade treatment-related AE in the epithelial ovarian cancer cohort was fatigue in 5 patients (41.7%), followed by chills, pain and pyrexia, which occurred in 4 patients (33.3%) each. The most common any-grade treatment-related AEs in the uterine cancer cohort were diarrhea and fatigue, which occurred in 3 (20.0%) and 2 patients (13.3%), respectively. No Grade 4 or 5 treatment-related AEs were reported in either cohort. Grade 3 treatment-related AEs were maculopapular rash and autoimmune hepatitis in the epithelial ovarian cancer cohort (n = 1 each); and diarrhea, colitis and rash in the uterine cancer cohort (n = 1 each), with diarrhea and colitis both occurring in the same patient. All Grade 3 treatment-related AEs resolved.

Three patients (25.0%) with epithelial ovarian cancer experienced serious AEs (1 of which, Grade 2 pyrexia, was treatment related), as did 8 patients (53.3%) with uterine cancer (including 2 treatment-related AEs: Grade 3 colitis and Grade 3 rash, n = 1 each). One grade 5 AE occurred on study (Table 2): a patient from the uterine cancer cohort experienced a grade 5 acute myocardial infarction, which was considered unrelated to the study drug.

Key AEs of special interest for this study were rash, maculopapular rash, ulcerative keratitis and autoimmune hepatitis (n = 1 each; 8.3%) in the epithelial ovarian cancer cohort, and rash (n = 2; 13.3%), colitis and increased aspartate aminotransferase and bilirubin (n = 1 each; 6.7%) in the uterine cancer cohort. Maculopapular rash and autoimmune hepatitis in the epithelial ovarian cancer cohort were Grade 3, as were increased blood bilirubin, colitis and 1 event of rash in the uterine cancer cohort; all other AEs of special interest were Grade 1–2.

No AEs leading to treatment discontinuation occurred in the epithelial ovarian cancer cohort. One patient (6.7%) with uterine cancer experienced an AE leading to treatment discontinuation (Grade 4 septic shock, assessed by the investigator as related to her underlying disease) (Table 2). AEs leading to treatment interruption were reported in 3 patients (25.0%) with epithelial ovarian cancer (all treatment related) and in 8 patients (53.3%) with uterine cancer (2 treatment related) (Table 2).

3.3. Clinical activity

Table 4 demonstrates the clinical activity of atezolizumab for all patients in the epithelial ovarian and uterine cancer cohorts and by PD-L1 status. In the epithelial ovarian cancer cohort, the confirmed ORR per RECIST 1.1 was 22.2% (95% CI: 2.8, 60.0) for the 9 patients in the cohort who were evaluable for ORR (Table 4). Complete response and partial response were achieved in 1 patient each (Table 4 and Fig. S2A). The DOR in the 2 responding patients was 8.1 months and 30.6+ months.

Table 3
Treatment-related AEs. Any-grade AEs occurring in ≥2 patients and Grade 3 AEs occurring in ≥1 patient.

AE, n (%)	Any grade	Grade 3
Epithelial ovarian cancer cohort (n = 12)		
Fatigue	5 (41.7)	0
Chills	4 (33.3)	0
Pain	4 (33.3)	0
Pyrexia	4 (33.3)	0
Pruritus	3 (25.0)	0
Nausea	3 (25.0)	0
Vomiting	3 (25.0)	0
Decreased appetite	3 (25.0)	0
Asthenia	2 (16.7)	0
Dry skin	2 (16.7)	0
Hyperhidrosis	2 (16.7)	0
Abdominal pain	2 (16.7)	0
Dry mouth	2 (16.7)	0
Arthralgia	2 (16.7)	0
Pain in extremity	2 (16.7)	0
Dyspnea	2 (16.7)	0
Anemia	2 (16.7)	0
Maculopapular rash	1 (8.3)	1 (8.3)
Autoimmune hepatitis	1 (8.3)	1 (8.3)
Uterine cancer cohort (n = 15)		
Diarrhea	3 (20.0)	1 (6.7)
Fatigue	2 (13.3)	0
Colitis	1 (6.7)	1 (6.7)
Rash	1 (6.7)	1 (6.7)

AE, adverse event.
No treatment-related Grade 4–5 AEs occurred.

The former patient is deceased. The median duration of survival follow-up was 7.6 months (range, 1.9–33.4 months) in the epithelial ovarian cancer cohort. Median PFS was 2.9 months (95% CI: 1.3, 5.5), and the 1-year PFS rate was 20.0% (95% CI: 0, 44.8) per RECIST 1.1 (Table 4). Median OS was 11.3 months (95% CI: 5.5, 27.7), and the 1-year OS rate was 41.7% (95% CI: 7.8, 75.6) (Table 4).

In the uterine cancer cohort, the confirmed ORR per RECIST 1.1 was 13.3% (95% CI: 1.7, 40.5) for all 15 evaluable patients in the cohort (Table 4). Two patients achieved partial response, and none experienced complete response (Table 4 and Fig. S2B). The DOR in the 2 responding patients was 7.3 and 16.6+ months. Of these responding patients, 1 subsequently discontinued study treatment due to progressive disease. The uterine cancer cohort also included 2 patients who had a best overall response of stable disease per RECIST 1.1 (Table 4 and Fig. S2B); however, neither of these patients maintained their stable disease status past 24 weeks. The duration of stable disease in these patients was 18.4 and 17.6 weeks. Notably, the latter patient had

Table 2
Safety summary.

Patients with indicated event, n (%)	All safety-evaluable patients	
	Epithelial ovarian cancer cohort (n = 12)	Uterine cancer cohort (n = 15)
≥ 1 AE (any grade)	12 (100.0)	15 (100.0)
Treatment-related AE	11 (91.7)	7 (46.7)
Grade 3–4 AE	6 (50.0)	7 (46.7)
Treatment-related Grade 3–4 AE	2 (16.7)	2 (13.3)
Grade 5 AE	0	1 (6.7)[a]
Treatment-related Grade 5 AE	0	0
Serious AE	3 (25.0)	8 (53.3)
Serious treatment-related AE	1 (8.3)	2 (13.3)
Serious AE leading to treatment withdrawal	0	1 (6.7)
Serious AE leading to dose interruption	0	6 (40.0)
AE leading to treatment withdrawal	0	1 (6.7)
AE leading to dose interruption	3 (25.0)	8 (53.3)
Treatment-related AE leading to dose interruption	3 (25.0)	2 (13.3)

AE, adverse event.
[a] One patient had a Grade 5 acute myocardial infarction that was deemed unrelated to the study drug.

Table 4
Clinical activity by PD-L1 status on IC.

	Epithelial ovarian cancer cohort			Uterine cancer cohort		
	IC0/1	IC2/3	All patients	IC0/1	IC2/3	All patients
	n = 1	**n = 8**	**n = 9**	**n = 10**	**n = 5**	**n = 15**
ORR per RECIST 1.1, n (%)	0	2 (25.0)	2 (22.2)	0	2 (40.0)	2 (13.3)
95% CI for ORR	(0, 97.5)	(3.2, 65.1)	(2.8, 60.0)	(0, 30.9)	(5.3, 85.3)	(1.7, 40.5)
Best confirmed response, n (%)						
CR	0	1 (12.5)	1 (11.1)	0	0	0
PR	0	1 (12.5)	1 (11.1)	0	2 (40.0)[a]	2 (13.3)
SD	0	0	0	1 (10.0)	1 (20.0)	2 (13.3)
PD	0	5 (62.5)	5 (55.6)	7 (70.0)	2 (40.0)	9 (60.0)
NE	1 (100.0)	1 (12.5)	2 (22.2)	2 (20.0)	0	2 (13.3)
Disease control rate[b]	0	2 (25.0)	2 (22.2)	0	2 (40.0)	2 (13.3)
	n = 1	**n = 9**	**n = 10**	**n = 10**	**n = 5**	**n = 15**
Median PFS (95% CI), months	5.2 (NE)	2.6 (1.3, 5.5)	2.9 (1.3, 5.5)	1.4 (1.3, 1.7)	4.2 (1.2, NE)	1.4 (1.3, 4.0)
1-year PFS rate (95% CI), %	NE	22.2 (0, 49.4)	20.0 (0, 44.8)	NE	20.0 (0, 55.1)	6.7 (0, 19.3)
Median OS (95% CI), months	5.2 (NE)	11.3 (5.5, 27.7)	11.3 (5.5, 27.7)	7.2 (4.4, 13.5)	38.2 (5.5, 38.2)	9.6 (6.8, 13.8)
1-year OS rate (95% CI), %	NE	46.9 (10.3, 83.4)	41.7 (7.8, 75.6)	30.0 (1.6, 58.4)	60.0 (17.1, 100.0)	40.0 (15.2, 64.8)

CR, complete response; IC, tumor-infiltrating immune cell; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a] One patient achieved an unconfirmed CR.
[b] Disease control rate is defined as the percentage of patients with a best response of CR, PR or SD for ≥24 weeks.

leiomyosarcoma. The median duration of survival follow-up was 20.4 months (range, 0.6–38.2 months) in the uterine cancer cohort. Median PFS was 1.4 months (95% CI: 1.3, 4.0), and the 1-year PFS rate was 6.7% (95% CI: 0, 19.3) per RECIST 1.1 (Table 4). Median OS was 9.6 months (95% CI: 6.8, 13.8), and the 1-year OS rate was 40.0% (95% CI: 15.2, 64.8) (Table 4). Responses to atezolizumab per RECIST 1.1 and irRC were concordant; however, 1 patient with uterine cancer who had progressive disease per RECIST 1.1 had stable disease by irRC and had received atezolizumab treatment for over 20 months (treatment was still ongoing at the clinical cutoff).

Table 5
Tumor biomarker classification and response status.

Best overall response per RECIST 1.1	Histology subtype	Molecular subtype	PD-L1 IC status	PD-L1 TC status	MSI status	TMB[a]	HRD[b]	DDR gene alterations[c]	*PIK3CA* mutant
Epithelial ovarian cancer cohort (n=10)									
PR	Serous	Immunoreactive	IC2	TC0	MSS	Low	No	No	No
PR	Mixed (endometrioid 95%/clear cell < 5%)	Immunoreactive	IC3	TC0	–	–	–	–	–
PD	Endometrioid	Immunoreactive	IC3	TC0	–		–	–	–
PD	Serous	Immunoreactive	IC2	TC0	–	–	–	–	–
PD	Serous	Immunoreactive	IC3	TC0	–	–	–	No	No
PD	Serous	Immunoreactive	IC2	TC0	MSS	Intermediate	Yes	*BRCA1*	No
PD	Serous	Immunoreactive	IC3	TC0	MSS	Low	Yes	No	No
NA	Serous	–	IC2	TC0	MSS	Intermediate	Yes	No	No
NE	Serous	Differentiated	IC0	TC0	MSS	Low	No	No	No
NE	Serous	Immunoreactive	IC2	TC1	MSS	Low	Yes	No	No
Uterine cancer cohort (n=15)									
PR	Endometrioid	–	IC3	TC2	–	–	–	No	Yes
PR	Endometrioid	–	IC2	TC0	MSI-H	High[d]	–	*ATM*	Yes
SD	Endometrioid	–	IC2	TC0	MSS	Intermediate	–	No	Yes
SD	Leiomyosarcoma	–	IC0	TC0	MSS	Low	No	No	No
PD	Serous	–	IC0	TC0	MSS	Low	–	No	Yes
PD	High-grade endometrial stroma sarcoma	–	IC0	TC0	MSS	Low	No	No	No
PD[e]	Endometrioid	–	IC1	TC0	–	–	–	No	No
PD	Endometrioid	–	IC1	TC0	MSS	Low	–	No	Yes
PD	Endometrioid	–	IC1	TC0	MSS	Intermediate	Yes	No	No
PD	Serous	–	IC0	TC0	MSS	Intermediate	Yes	*BRCA1*	No
PD	Serous	–	IC0	TC0	MSS	Low	Yes	No	No
PD	Serous	–	IC2	TC0	MSS	Low	–	No	Yes
PD	Serous	–	IC3	TC0	MSS	–	–	*BRIP1*	No
NA	Endometrioid	–	IC1	TC1	MSS	Low	–	No	No
NE	Endometrioid	–	IC0	TC0	MSS	–	–	No	Yes

DDR, DNA damage response; IC, tumor-infiltrating immune cell; LOH, loss of heterozygosity; HRD, homologous recombination deficiency; Mb, megabase; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSS, microsatellite stable; Mut, mutations; NA, not applicable; NE, not evaluable; PD, progressive disease; PD-L1, programmed death-ligand 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; PR, partial response; SD, stable disease; TC, tumor cell; TMB, tumor mutational burden.
[a] TMB low, ≥0 to < 6Mut/Mb; TMB intermediate, ≥6 to <16Mut/Mb; TMB high, ≥16 Mut/Mb.
[b] HRD, ≥14% genomic LOH.
[c] DDR genes analyzed included the following: *ATM, ATR, BLM, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, ERCC4, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL, FANCM, MLH1, MSH2, MSH6, MUTYH, NUDT1, PALB2, PARP1, PARP2, PARP3, PMS2, POLD1, POLE, PRKDC, RAD51C, RPA1, TP53.* All gene mutations described had a known or expected loss of function.
[d] TMB=221 Mut/Mb.
[e] This patient was classified as having PD per RECIST 1.1 but had stable disease by irRC. The patient received atezolizumab treatment for >19 months, and treatment was ongoing at the time of clinical data cutoff.

3.4. Biomarkers of atezolizumab clinical activity

Baseline tumor biomarkers were evaluated for patients in both cohorts. Baseline levels of PD-L1 expression on IC in patients with uterine cancer are shown in Fig. S3 and were higher in responders compared with patients with stable or progressive disease. All responses to atezolizumab across the 2 cohorts occurred in patients with IC2/3 tumor status (Table 5). Patients with an IC2/3 status also had

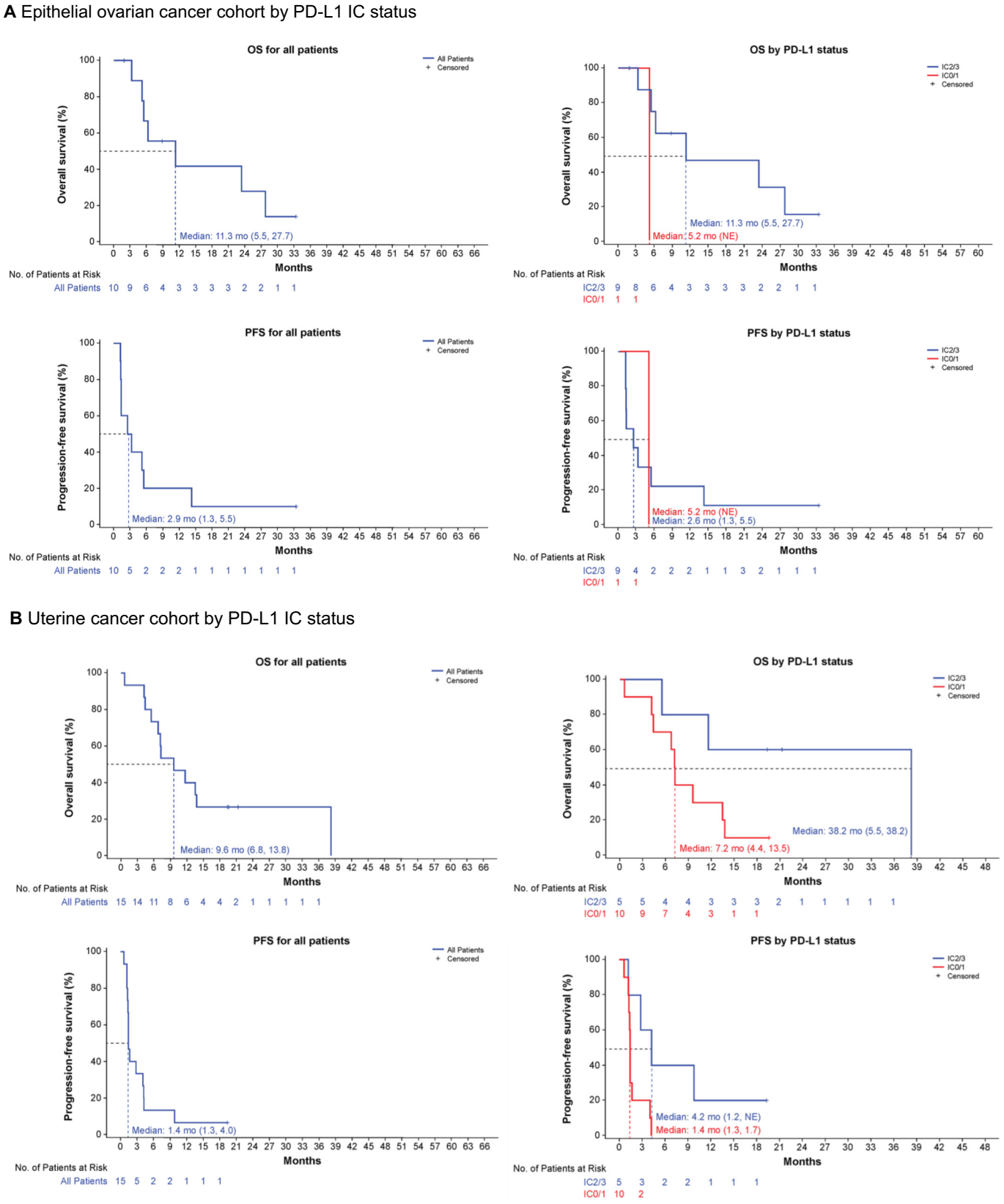

Fig. 1. Kaplan-Meier plots of PFS per investigator-assessed RECIST 1.1 and OS by PD-L1 IC status in (A) the epithelial ovarian cancer cohort and (B) the uterine cancer cohort.

numerically longer PFS (uterine cancer cohort only) and OS compared with patients with IC0/1 status (Fig. 1), although patient numbers are small in several subgroups. The single patient with epithelial ovarian cancer whose tumor was not IC2/3 (IC0) experienced rapid progression, although this observation was not evaluable per RECIST 1.1.

Most patients in the epithelial ovarian cancer cohort had serous tumors and an RNA-based immunoreactive molecular subtype [32,33], while most patients in the uterine cancer cohort had endometrioid tumors (Table 5). One RECIST 1.1 responder with epithelial ovarian cancer had serous histology, and the other had mixed histology (both had the immunoreactive molecular subtype). Both RECIST 1.1 responders with uterine cancer had endometrioid histology. Identified DDR gene alterations are summarized in Table 5. Neither of the patients with germline *BRCA1* mutations (1 per cohort) achieved a response. Both responders in the uterine cancer cohort had tumors with *PIK3CA* mutations, 1 of whom was also the only patient evaluated with an *ATM* mutation, MSI-H status and TMB high status (Table 5). Although 2 *POLE* mutations were detected in this patient, neither was deemed likely to impact the DNA proofreading activity of the enzyme.

In addition to baseline tumor biomarkers, circulating cancer antigen (CA) 125 levels were assessed at baseline (n = 9) in patients in the epithelial ovarian cancer cohort. The median CA 125 level was 727.8 U/mL (range, 13.3–7726.0 U/mL) (Table 1), and responders had lower CA 125 levels at baseline compared with the non-responders (data not shown).

4. Discussion

The Phase I, multi-center, first-in-human, open-label, dose-escalation PCD4989g study reported here investigated the safety and preliminary anti-tumor activity of atezolizumab and characterized potential biomarkers of response in patients with metastatic/recurrent epithelial ovarian or uterine cancer. Atezolizumab was generally well tolerated in heavily pre-treated patients with epithelial ovarian and uterine cancer. No new safety signals were identified, and the safety profile was similar to the known safety profile of atezolizumab monotherapy. Treatment-related AEs were mostly Grade 1 or 2, with no treatment-related Grade 4 or 5 AEs reported.

Preliminary evidence of anti-tumor activity, with long durability of response, was observed in 2 patients from each cohort. All 4 responding patients had at least PD-L1 IC2 status. One patient in the epithelial ovarian cancer cohort had a microsatellite stable (MSS) tumor with low TMB; 1 patient in the uterine cancer cohort had a tumor with high MSI and high TMB, while the remaining 2 patients did not have enough tissue for evaluation. The tumors from both responders in the epithelial ovarian cancer cohort were of the immunoreactive molecular subtypes, as determined by RNA-based NanoString classifiers [32,33]; both these patients had received 5 prior systemic therapies and no prior radiation therapy, while the 2 responders in the uterine cancer cohort each had 3 prior systemic therapies, with 1 patient also having prior radiation therapy. DOR in the 2 patients in the epithelial ovarian cancer cohort was 8.1 and 30.6+ months, and DOR in the 2 patients in the uterine cancer cohort was 7.3 and 16.6+ months. In the uterine cancer cohort, 1 patient who was classified as having progressive disease per RECIST 1.1 had stable disease by irRC. This patient received atezolizumab treatment for >19 months, and treatment was ongoing at the time of clinical data cutoff. Another patient in the uterine cancer cohort, the only one whose tumor was MSI-H, reportedly had a complete response clinically but was classified as having a partial response per RECIST 1.1, likely due to the inherent limitation of assessing tumor responses using RECIST when non-target nodal lesions are present.

The tumor biology of epithelial ovarian and uterine cancers provide rationale for treatment with targeted agents, including cancer immunotherapies. In both cohorts in our study, responses were observed only in patients with PD-L1 IC2/3 tumors, and PD-L1 expression on TC was uncommon. We also present the first report demonstrating responsiveness to an anti–PD-L1/PD-1 agent in epithelial ovarian cancer of the immunoreactive subtype; however, the patient with epithelial ovarian cancer whose tumor was of the differentiated molecular subtype, typically associated with a good prognosis, progressed quickly. Our findings from the uterine cancer cohort were largely consistent with other reports of immune checkpoint inhibition [34]. While MSI-H has been accepted as a tumor-agnostic biomarker for response to immune checkpoint inhibition, we observed a patient from the epithelial ovarian cancer cohort who achieved a partial response to atezolizumab despite being MSS. This finding suggests that multiple factors may predict response to immune checkpoint inhibition (e.g., presence of immunoreactive molecular subtype, high levels of PD-L1 expression [IC2]).

Patients with DDR mutations (e.g., *BRCA*) appeared to have higher TMB levels (intermediate) than those without DDR mutations, and the patient from the uterine cancer cohort with the MSI-H tumor also had high TMB. No patients with *BRCA* mutations in either cohort responded to atezolizumab, nor did they have high TMB. Homologous recombination deficiency (HRD), measured as genomic loss of heterozygosity ≥ 14%, was also not associated with response or high TMB (Table 5), consistent with other recent data in epithelial ovarian cancer [35]. One of the 2 responding patients with uterine cancer was MSI-H with high TMB. This observation is in line with data demonstrating responsiveness to checkpoint inhibitors in MMR-deficient tumors of other cancers [20]. Both responders with uterine cancer had activating *PIK3CA* mutations, suggesting that the PI3K pathway, which has previously been proposed as a possible mechanism of resistance to checkpoint inhibitors [36], may not be as relevant for uterine cancer immune evasion.

Our study is the first trial to report the use of atezolizumab monotherapy in gynecologic cancers. The limitations of this study include small cohort sizes, the single-arm study design (lacking comparison with standard treatment regimens), PD-L1–selected enrollment periods (limiting comparison with the overall patient populations) and multiple lines of previous therapy (giving rise to heterogenous patient populations in each cohort).

Similar to other studies with checkpoint inhibitors [34,37–40], these limited data suggest that this class of agents is safe in gynecologic cancers and may have clinical activity warranting further investigation as potential treatment options. As several potential biomarkers like HRD and TMB (if intermediate) do not appear to correlate with response, and response rates are modest even in patients with PD-L1 IC2/3 tumors, these data highlight the challenges in identifying appropriate biomarker-selected patients for immune checkpoint inhibitor monotherapy. The anti-tumor activity of atezolizumab may be further enhanced through combination with chemotherapies as well as other targeted anti-cancer agents (e.g., with vascular endothelial growth factor–targeting agents or PARP inhibitors). Several Phase III studies of combination treatment regimens with atezolizumab and other immune checkpoint inhibitors are currently ongoing in patients with epithelial ovarian and uterine cancers (e.g., ClinicalTrials.gov IDs NCT03038100, NCT03353831, NCT02891824, NCT03598270, NCT03522246, NCT03642132, NCT02839707, NCT03603184, NCT03517449). These trials reflect the promise of cancer immunotherapy in transforming the treatment landscape for women with ovarian and uterine cancers; however, there remains room for improvement. Biomarker analyses in this study highlight several correlates of atezolizumab anti-tumor activity that supplement existing data in the field and warrant further investigation.

Author contributions

All authors contributed to writing, review and/or revision of the manuscript.

Joyce Liu, Fadi Braiteh, Erika Hamilton and Leisha Emens contributed to data collection, analysis and interpretation.

Michael Gordon contributed to the design of the study, data collection, analysis and interpretation.

Jennifer Veneris contributed to data collection and interpretation.

Joseph Paul Eder, Ani Balmanoukian and Ana Oaknin contributed to data collection.

Yulei Wang contributed to the development of methodology and to data collection, analysis and interpretation.

Indrani Sakar contributed to data analysis and interpretation.

Marcella Fassò, Yvonne Lin and Luciana Molinero contributed to the conception and design of the study, development of methodology and data collection, analysis and interpretation.

Carol O'Hear contributed to the conception and design of the study and data analysis and interpretation.

Data sharing statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform: www.clinicalstudydatarequest.com. Further details on Roche's criteria for eligible studies are available here: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Declaration of Competing Interest

All authors report support of the parent study and funding of editorial support from F. Hoffmann-La Roche, Ltd.

Joyce Liu reports advisory board participation for AstraZeneca, Tesaro, Clovis and Mersana Therapeutics and is the institutional principal investigator on industry-sponsored trials from Acetylon, Agenus, AstraZeneca, Atara Biotherapeutics, Boston Biomedical, Bristol-Myers Squibb, Clovis Oncology, CytomX Therapeutics, Genentech/Roche, Regeneron and Tesaro.

Michael Gordon reports personal fees (advisory board participation) from Agenus, research funding to his institution from Amgen, AstraZeneca/MedImmune, BeiGene, Bristol-Myers Squibb, Celgene, Clovis, Eli Lilly, Gilead, Incyte, Merck, Pfizer, Roche and Tracon and is the Chair of the Data Safety Monitoring Committee for Tracon.

Jennifer Veneris reports employment of spouse at Takeda and Abbott Laboratories.

Fadi Braiteh reports, outside the submitted work, personal fees (advisory board/honorarium and/or speakers bureau) from Amgen, AstraZeneca/MedImmune, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Clovis, Eisai, Eli Lilly, Exelixis, Gilead, Incyte, Ipsen, Lexicon, Loxo Oncology, Merck, Pfizer, Puma Biotechnology, Roche/Genentech, Taiho and Takeda and other support (travel expenses) from Amgen, AstraZeneca/MedImmune, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Exelixis, Incyte, Ipsen, Loxo Oncology, Merck and Roche/Genentech.

Ani Balmanoukian reports other fees (speakers bureau) from Merck, AstraZeneca and Genentech outside the submitted work.

Joseph Paul Eder reports personal fees (advisory board) from F. Hoffmann-La Roche, Ltd., during the conduct of the study.

Ana Oaknin reports grants, during the conduct of the study, from AbbVie Deutschland, Ability Pharmaceuticals, Advaxis Inc., Aeterna Zentaris, Amgen SA, Aprea Therapeutics AB, Clovis Oncology Inc., Eisai Ltd., Regeneron Pharmaceuticals, Immunogen Inc., Merck, Sharp & Dohme de España SA, Millennium Pharmaceuticals Inc., Pharma Mar SA and Tesaro Inc., as well as personal fees and other support (travel or accommodation) from Roche, AstraZeneca and PharmaMar outside the submitted work and personal fees from Clovis Oncology, Tesaro, Immunogen and Genmab outside the submitted work.

Erika Hamilton reports, outside the submitted work, grants (payments to institution for principal investigator role in clinical trial conduct) and other support (payment to institution for consulting services) from Pfizer, Puma Biotechnology, Mersana, Boehringer Ingelheim and Cascadian Therapeutics, grants (payments to institution for principal investigator role in clinical trial conduct), non-financial support (payments or reimbursements of expenses) and other support (payment to institution for consulting services) from Genentech/Roche, Eli Lilly, Daiichi Sankyo and Eisai, personal fees (consulting) from Flatiron, grants (payments to institution for principal investigator role in clinical trial conduct) from Hutchinson MediPharma, OncoMed, MedImmune, Stem CentRx, Curis, Verastem, Zymeworks, Syndax, Lycera, Rgenix, Millennium, TapImmune, Eli Lilly, BerGenBio, Medivation, Kadmon, H3 Biomedicine, Radius Health, Acerta Pharma, Takeda, Macrogenics, AbbVie, Immunomedics, Fujifilm, eFFECTOR Therapeutics, Mallinckrodt, Merus, Nucana, TetraLogic Pharmaceuticals, PharmaMar, Regeneron, Leap Therapeutics, Taiho Pharmaceutical, Syros, CytomX, InventisBio and Oncothyreon, grants (payments to institution for principal investigator role in clinical trial conduct) and non-financial support (payments or reimbursements of expenses) from AstraZeneca, Tesaro, EMD Serono, Clovis and Novartis and non-financial support (payments or reimbursements of expenses) from Amgen, Bayer, Bristol-Myers Squibb, Genzyme, Helsinn Therapeutics, HERON, Lexicon, Medivation, Merck, Roche, Sysmex, Guardant Health and Foundation Medicine.

Yulei Wang reports personal fees (as an employee) from Genentech/F. Hoffman-La Roche, Ltd.

Indrani Sarkar reports personal fees (as an employee) from Genentech/F. Hoffman-La Roche, Ltd.

Luciana Molinero reports personal fees and other support (employment and stock ownership) from Genentech/F. Hoffman-La Roche, Ltd., and has a patent pending outside the submitted work.

Marcella Fassò reports personal fees (as an employee) from Genentech/F. Hoffman-La Roche, Ltd.

Carol O'Hear reports personal fees and other support (employment and stock ownership) from Genentech/F. Hoffman-La Roche, Ltd.

Yvonne Lin reports personal fees and other support (employment and stock ownership) from Genentech/F. Hoffman-La Roche, Ltd.

Leisha Emens reports grants and non-financial support (research support and travel) and other support (steering committee chairmanship for IMpassion130 and KATE2 and advisory board membership) from Roche/Genentech, outside the submitted work, as well as grants (research support) from EMD Serono, Maxcyte, Merck, BCRF and HeritX, grants and non-financial support (research and travel support) from Corvus, grants and personal fees from AstraZeneca (research support and advisory board), personal fees and non-financial support from Syndax (consultancy fees and advisory board) and from Macrogenics, Bayer, Replimune, Novartis, Peregrine and Vaccinex (advisory board and travel support), grants, personal fees and non-financial support (research support, material support and licensing royalties) from Aduro Biotech, personal fees and other support (advisory board and stock options) from Molecuvax, personal fees (advisory board) from AbbVie, Amgen, MedImmune, Gritstone Oncology, Celgene and eTHeRNA and non-financial support from Bristol-Myers Squibb (advisory board and travel). She is also a member of the FDA Advisory Committee on Cell Tissue and Gene Therapies (receiving hourly compensation as special government employee) and a member of the Board of Directors for Society of Immunotherapy of Cancer (receiving honoraria and travel).

Acknowledgements

The authors thank all the patients and their families and the investigators who participated in this study. They also thank Hina Patel for critical review of the manuscript. The study was sponsored by F. Hoffmann-La Roche, Ltd. Medical writing assistance for this manuscript was provided by Katie Wilson, PhD, and Jonathan Lee, PhD, of Health Interactions and funded by F. Hoffmann-La Roche, Ltd.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.05.021.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 68 (2018) 7–30.
[2] M.A. Onstad, R.E. Schmandt, K.H. Lu, Addressing the role of obesity in endometrial cancer risk, prevention, and treatment, J. Clin. Oncol. 34 (2016) 4225–4230.
[3] Y.C. Lee, S. Lheureux, A.M. Oza, Treatment strategies for endometrial cancer: current practice and perspective, Curr. Opin. Obstet. Gynecol. 29 (2017) 47–58.
[4] NCCN, Clinical Practice Guidelines in Oncology. Ovarian Cancer. V1, https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf 2019, Accessed date: 24 April 2019.
[5] NCCN, Clinical Practice Guidelines in Oncology. Uterine Neoplasms. V3, https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf 2019, Accessed date: 24 April 2019.
[6] E. Pujade-Lauraine, F. Hilpert, B. Weber, A. Reuss, A. Poveda, G. Kristensen, et al., Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial, J. Clin. Oncol. 32 (2014) 1302–1308.
[7] C. Aghajanian, V. Filiaci, D.S. Dizon, J.W. Carlson, M.A. Powell, A.A. Secord, et al., A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer, Gynecol. Oncol. 150 (2018) 274–281.
[8] P.A. Konstantinopoulos, U.A. Matulonis, Targeting DNA damage response and repair as a therapeutic strategy for ovarian cancer, Hematol. Oncol. Clin. North Am. 32 (2018) 997–1010.
[9] D.S. Chen, I. Mellman, Elements of cancer immunity and the cancer-immune set point, Nature 541 (2017) 321–330.
[10] J. Hamanishi, M. Mandai, M. Iwasaki, T. Okazaki, Y. Tanaka, K. Yamaguchi, et al., Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer, Proc. Natl. Acad. Sci. U.S.A. 104 (2007) 3360–3365.
[11] Q. Wang, W. Lou, W. Di, X. Wu, Prognostic value of tumor PD-L1 expression combined with CD8(+) tumor infiltrating lymphocytes in high grade serous ovarian cancer, Int. Immunopharmacol. 52 (2017) 7–14.
[12] A. Vanderstraeten, C. Luyten, G. Verbist, S. Tuyaerts, F. Amant, Mapping the immunosuppressive environment in uterine tumors: implications for immunotherapy, Cancer Immunol. Immunother. 63 (2014) 545–557.
[13] T. Herzog, D. Arguello, S. Reddy, Z. Gatalica, PD-1 and PD-L1 expression in 1599 gynecological malignancies-implications for immunotherapy, Gynecol. Oncol. 137 (2015) 204–205.
[14] T.C. Longoria, R.N. Eskander, Immunotherapy in endometrial cancer-an evolving therapeutic paradigm, Gynecol. Oncol. Res. Pract. 2 (2015) 11.
[15] Cancer Genome Atlas Research Network, Integrated genomic analyses of ovarian carcinoma, Nature 474 (2011) 609–615.
[16] G.E. Konecny, C. Wang, H. Hamidi, B. Winterhoff, K.R. Kalli, J. Dering, et al., Prognostic and therapeutic relevance of molecular subtypes in high-grade serous ovarian cancer, J. Natl. Cancer Inst. 106 (2014).
[17] B. Winterhoff, H. Hamidi, C. Wang, K.R. Kalli, B.L. Fridley, J. Dering, et al., Molecular classification of high grade endometrioid and clear cell ovarian cancer using TCGA gene expression signatures, Gynecol. Oncol. 141 (2016) 95–100.
[18] R. Bonneville, M.A. Krook, E.A. Kautto, J. Miya, M.R. Wing, H. Chen, et al., Landscape of microsatellite instability across 39 cancer types, J. Clin. Oncol. Precis. Oncol. 1 (2017) 1–15.
[19] D.T. Le, J.N. Durham, K.N. Smith, H. Wang, B.R. Bartlett, L.K. Aulakh, et al., Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade, Science 357 (2017) 409–413.
[20] A. Oaknin, S.L. Ellard, C. Leath III, V. Moreno, R. Kristeleit, W. Guo, et al., Preliminary safety, efficacy, and PK/PD characterization from GARNET, a phase I clinical trial of the anti–PD-1 monoclonal antibody, TSR-042, in patients with recurrent or advanced MSI-H endometrial cancer, Ann. Oncol. 29 (2018) viii332–viii358.
[21] B.E. Howitt, S.A. Shukla, L.M. Sholl, L.L. Ritterhouse, J.C. Watkins, S. Rodig, et al., Association of polymerase e-mutated and microsatellite-instable endometrial cancers with neoantigen load, number of tumor-infiltrating lymphocytes, and expression of PD-1 and PD-L1, JAMA Oncol. 1 (2015) 1319–1323.
[22] Y.K. Chae, A.A. Davis, K. Raparia, S. Agte, A. Pan, N. Mohindra, et al., Association of tumor mutational burden with DNA repair mutations and response to anti-PD-1/PD-L1 therapy in non-small-cell lung cancer, Clin. Lung Cancer 20 (2019) 88–96.
[23] R.S. Herbst, J.C. Soria, M. Kowanetz, G.D. Fine, O. Hamid, M.S. Gordon, et al., Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients, Nature 515 (2014) 563–567.
[24] D.S. Chen, I. Mellman, Oncology meets immunology: the cancer-immunity cycle, Immunity 39 (2013) 1–10.
[25] TECENTRIQ, (Atezolizumab) [Summary of Product Characteristics], Genentech, Inc., South San Francisco, CA, 2018.
[26] TECENTRIQ, (Atezolizumab) [Package Insert], Genentech, Inc., South San Francisco, CA, 2018.
[27] L.A. Emens, C. Cruz, J.P. Eder, F. Braiteh, C. Chung, S.M. Tolaney, et al., Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study, JAMA Oncol. 5 (2019) 74–82.
[28] J.D. Wolchok, A. Hoos, S. O'Day, J.S. Weber, O. Hamid, C. Lebbe, et al., Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria, Clin. Cancer Res. 15 (2009) 7412–7420.
[29] F.S. Hodi, W.J. Hwu, R. Kefford, J.S. Weber, A. Daud, O. Hamid, et al., Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab, J. Clin. Oncol. 34 (2016) 1510–1517.
[30] VENTANA, PD-L1 (SP142) Assay [Package Insert], Roche Diagnostics, Inc., Indianapolis, IN, 2018.
[31] S. Mariathasan, S.J. Turley, D. Nickles, A. Castiglioni, K. Yuen, Y. Wang, et al., TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells, Nature 554 (2018) 544–548.
[32] L. Ryner, Y. Guan, R. Firestein, Y. Xiao, Y. Choi, C. Rabe, et al., Upregulation of periostin and reactive stroma is associated with primary chemoresistance and predicts clinical outcomes in epithelial ovarian cancer, Clin. Cancer Res. 21 (2015) 2941–2951.
[33] R.W. Tothill, A.V. Tinker, J. George, R. Brown, S.B. Fox, S. Lade, et al., Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome, Clin. Cancer Res. 14 (2008) 5198–5208.
[34] P.A. Ott, Y. Bang, D. Berton-Rigaud, E. Elez, M.J. Pishvaian, H.S. Rugo, et al., Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1–positive endometrial cancer: results from the KEYNOTE-028 study, J. Clin. Oncol. 35 (2017) 2535–2541.
[35] J.A. Ledermann, R. Shapira-Frommer, A. Santin, A.S. Lisyanskaya, S. Pignata, I. Vergote, et al., Association of PD-L1 expression and gene expression profiling with clinical response to pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study, Ann. Oncol. 29 (2018) viii728.
[36] S. George, D. Miao, G.D. Demetri, D. Adeegbe, S.J. Rodig, S. Shukla, et al., Loss of PTEN is associated with resistance to anti-PD-1 checkpoint blockade therapy in metastatic uterine leiomyosarcoma, Immunity 46 (2017) 197–204.
[37] A.D. Santin, S. Bellone, N. Buza, J. Choi, P.E. Schwartz, J. Schlessinger, et al., Regression of chemotherapy-resistant polymerase epsilon (POLE) ultra-mutated and MSH6 hyper-mutated endometrial tumors with nivolumab, Clin. Cancer Res. 22 (2016) 5682–5687.
[38] U.A. Matulonis, R. Shapira-Frommer, A. Santin, A.S. Lisyanskaya, S. Pignata, I. Vergote, et al., Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: interim results from the phase 2 KEYNOTE-100 study, J. Clin. Oncol. 36 (2018) 5511.
[39] J. Hamanishi, M. Mandai, T. Ikeda, M. Minami, A. Kawaguchi, T. Murayama, M. Kanai, et al., Safety and antitumor activity of anti–PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer, J. Clin. Oncol. 33 (2015) 4015–4022.
[40] M.L. Disis, M.H. Taylor, K. Kelly, J.T. Beck, M. Gordon, K.M. Moore, et al., Efficacy and safety of avelumab for patients with recurrent or refractory ovarian cancer: phase 1b results from the JAVELIN Solid Tumor Trial, JAMA Oncol. (2019)https://doi.org/10.1001/jamaoncol.2018.6258 [Epub ahead of print].