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Case series

Predictors of response to immune checkpoint inhibition in a real world gynecologic cancer population☆

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ABSTRACT

Prognostic factors for immune checkpoint inhibitor (CPI) response in gynecologic cancer are limited. This retrospective study aimed to identify prognostic factors associated with improved overall response rate (ORR) and progression free survival (PFS) in gynecologic cancer patients receiving at least two cycles of CPI. PFS was compared by univariate cox regressions. Univariate and multivariable analyses were used for prognostic factors of PFS and ORR. 72 patients were identified (20 ovarian, 36 endometrial, 13 cervix, 1 vaginal, 2 others). Immune related adverse events (IRAE) occurred in 40.3% of patients (29/72). IRAE was associated with higher ORR (44.8% IRAE vs 20.9% no IRAE, OR 3.1, p = 0.024), improved PFS (12.9 m IRAE vs 4.7 m no IRAE, HR 0.43, p = 0.004) and improved OS (22.9 m IRAE vs 12.2 m no IRAE, HR 0.47, p = 0.021). Additionally, Clear cell histology had superior ORR compared to MSI stable endometrial and ovarian cancers (ORR 57.1% vs 11.8%, OR 10.0, p = 0.032). Responders more often had ARIDIA mutation, PI3K/PTEN alteration and less often had a P53 mutation. In a subset of six MSI-H, recurrent, chemo-naive endometrial cancer ORR was 83.3%. Overall, we found favorable outcomes after CPI for clear cell tumors and patients who developed IRAE. Additionally, first-line systemic therapy with CPI in recurrent MSI-H endometrial cancer had encouraging ORR with durable responses.

1. Background

Checkpoint inhibitors (CPIs) are monoclonal antibodies targeted at the ligands and receptors involved in immune checkpoint activation. CPI therapy leads to the release of T cells inhibition within the tumor microenvironment allowing for cancer directed attack (Grywalska et al., 2019).

CPI use in gynecologic cancer has resulted in a wide range of responses (Matanes and Gotlieb, 2019). Although response rates are low in most gynecologic tumor types, durable responses in previously treatment-resistant tumors have been reported highlighting the value of this treatment in a subset of gynecologic cancer patients (Hamanishi et al., 2015). Methods to identify patients who may derive the most benefit from CPI are currently limited, with the exception of microsatellite instability (MSI-H) (Le et al., 2017).

The present retrospective study aims to identify clinical, pathologic, and genomic factors associated with overall response rate (ORR) and progression free survival (PFS) in a diverse group of gynecologic cancer patients.

2. Methods

2.1. Patient population

After institutional review board approval, a retrospective review of gynecologic oncology patients receiving CPI was completed. Patients were identified through electronic medical records at an academic institution. Inclusion required completion of at least two cycles of CPI therapy and a diagnosis of gynecologic cancer. There were no additional exclusion criteria.

☆ Data reported in this manuscript have been presented at the ASCO 2020 as a virtual abstract, WAGO 2020 as a virtual poster and Cleveland Society of Obstetricians & Gynecologists 2020 as a virtual plenary.

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2.2. Outcomes

The primary objective of this study was to identify variables associated with primary outcomes of ORR and PFS. PFS and OS were measured as date of initiation of CPI to date of progression or last follow up, respectively. Type of response (partial response = PR, complete response = CR, stable disease = SD), was determined by clinical judgment of the treating physician, abstracted from clinic notes.

2.3. Data

Demographic, clinical, pathologic, and genomic data were retrospectively abstracted from the medical record. Germline and somatic genomic mutation data were abstracted from reports of routinely used third party testing companies. MSI-H status was assigned based on the presence of mismatch repair protein deficiency (MMRd) on tumor immunohistochemistry (MSH2, MSH6, PMS2 and MLH1), or microsatellite instability on somatic next generation sequencing. Immune related adverse events (IRAE) were abstracted from clinical documentation and lab results. Immune related toxicities were graded as per the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer et al., 2018).

2.4. Statistics

Approximately normally distributed continuous measures were summarized using means and standard deviations. Continuous measures that show departure from normality and ordinal measures were summarized using medians and quartiles. Categorical factors were summarized using frequencies and percentages. Univariate logistic regressions were fit to explore associations with overall response. For survival analysis, starting dates were set to be the date of checkpoint inhibitor initiation. Month was defined as 30 days. Cox proportional hazards regression right-censored univariate models were performed for PFS and OS, log-rank tests and Cox univariate Wald tests were performed. One multivariable PFS Cox model was fit for analysis groups and development of toxicity. All analyses were done using SAS (version 9.4, The SAS Institute, Cary, NC) and a $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient and treatment data

72 patients were included (ovarian cancer N = 20, endometrial cancer N = 36, cervical cancer N = 13, vaginal cancer N = 1). Two patients had immunostaining consistent with gynecologic primary however could not be further specified (site unknown). Patients initiated CPI from June 2015 to August at the study institution.

Patient and treatment characteristics are summarized in Table 1. Most tumors were of endometrioid (27.8%) or serous (31.9%) histology with high tumor grade (19% grade 2, 71.4% grade 3). 93.1% received CPI for recurrent disease with a median of 2 prior lines of systemic therapy. Pembrolizumab (58.3%) was the most common CPI followed by nivolumab (38.9%). 5.6% received combination CPI (ipilimumab + nivolumab) and only 6.9% of patients were on CPI clinical trial.

3.2. Clinical outcomes

Clinical outcomes are outlined in Table 2. ORR was 41.7% for endometrial cancer, 20% for ovarian cancer, and 15.4% for cervical cancer. A median of 2.7 months of CPI therapy lapsed until initial response was identified. Time to initial response appeared consistent across disease sites. There was a notable delay from initial response until identification of CR with a median time to CR of 11.5 months after CPI initiation.

3.3. Prognostic features in full cohort

On univariate logistic regressions in the full cohort MSI-H status was associated with ORR (ORR: MSI-H 54.2% vs microsatellite stable (MSS) 25%, OR 3.5, p = 0.034). There was no significant association of ORR or PFS with age (ORR: OR 1.01, p = 0.57; PFS: HR 0.99, p = 0.14), performance status (PS 0 vs > 0, ORR: 1.2, p = 0.79; PFS: HR 0.89, p = 0.67), tumor grade (grade 1 or 2 vs 3, ORR: OR 0.71, p = 0.55; PFS: HR 1.11, p = 0.77), or number of prior chemotherapy lines (0–2 vs 3 + prior lines, ORR: OR 0.52, p = 0.24; PFS: HR 1.39, p = 0.24).

IRAE was prevalent, occurring in 40.3% of patients. The most common IRAE was thyroid dysfunction (N = 10), including hyperthyroidism (N = 4, 5.6%) and hypothyroidism (N = 9, 12.5%), with three patients experiencing both hypo- and hyperthyroidism. All immune mediated thyroid dysfunction occurred in only grade 1 and 2 severities. Grade 3 toxicities included pneumonitis (N = 3), dermatitis (N = 2), nephritis (N = 1), hepatitis (N = 1) and colitis (N = 1). Mean time to toxicity onset was 5.2 months (0.4 m – 21.5 m) (supplemental table e2). Development of IRAE was associated with higher ORR (44.8% IRAE vs 20.9% no IRAE, OR 3.1, p = 0.024), improved PFS (12.9 m IRAE vs 4.7 m no IRAE, HR 0.43, p = 0.004) and improved OS (22.9 m IRAE vs 12.2 m no IRAE, HR 0.47, p = 0.021) (Fig. 1**a).** IRAE remained independently associated with improved PFS on multivariable analysis (HR 0.43, 95%CI 0.24–0.77, p = 0.005).

3.4. Genomic and immunohistochemical data

17 patients underwent PDL-1 testing and tumor mutational burden (TMB) was available for 27 patients (Table 1). Neither PDL-1 positivity or TMB was associated with ORR (ORR 11.1% PDL1 + vs 25% PDL1-, p = 0.58) (low vs intermediate or high, OR 0.92, p = 0.92), Fig. 1**b**.

Somatic testing was performed on 31 tumors (14 ovarian, 14 endometrial, 2 cervix, 1 unspecified) with 54 mutation types identified. The five most common mutations were TP53 (N = 15), ARID1A (N = 8), PIK3CA (N = 8), KRAS (N = 6) and PTEN (N = 5). The 3 most frequent mutations in responders were ARID1A, PIK3CA and PTEN. All three were more prevalent in responders vs. non-responders, ARID1A (55.6% vs.13.6%), PIK3CA (44.4% vs. 18.2%) and PTEN (33.3% vs. 9.0%). TP53 was the most frequent mutation in non-responders (54.5% non-responders vs. 33.3% responders) (Fig. 1**c**). Genomic mutation summary is presented in *Supplemental table e1*.

3.5. Ovarian and endometrial subgroup

Given the more closely aligned characteristics for endometrial and ovarian cancer in this study, these were combined for subgroup analysis. Three mutually exclusive prognostic variables groups were created for analysis– MSI-H, MSS and clear cell histology.

Univariate analysis of these prognostic groups showed MSI H (ORR 52.2% v 11.8%, OR 8.2, p = 0.015) and clear cell (ORR 57.1% vs 11.8%, OR 10.0, p = 0.032) were both associated with higher ORR compared to MSS. Of the 7 clear cell patients, 3 achieved PR, 1 CR and 2 SD. SDs had durable disease stability for 17 and 19 CPI cycles, respectively.

On PFS analysis, MSI-H was associated with improved PFS compared to MSS (10 m vs 4.7 m, HR 0.42, p = 0.018). Clear cell trended towards improved PFS compared to MSS (12.5 m vs 4.7 m) however small numbers limited formal analysis **(**Fig. 1**d).**

In a binary multivariable analysis for the full cohort, clear cell histology and MSI-H remained associated with improved PFS compared to MSS (HR 0.5, 95% CI 0.8–0.89, p = 0.0019).

3.6. First line systemic therapy MSI-H endometrial cancer

Six chemo- naïve patients with recurrent, MSI-H, endometrioid endometrial cancer received pembrolizumab, Table 3. All patients refused or were not medically eligible for chemotherapy at recurrence

Table 1
Patient and Treatment Characteristics.

Variable	All (N = 72)	Ovarian (N = 20)	Endometrial (N = 36)	Cervix (N = 13)	Site Unknown (N = 2)	Vaginal (N = 1)
Age	64.2 ± 13.8	62.7 ± 11.3	69.1 ± 11.3	54.4 ± 18.0	50.0 ± 5.7	73.0
BMI	29.0 ± 7.9	27.1 ± 6.5	31.0 ± 8.6	27.7 ± 7.0	23.3 ± 11.7	21.8
Comorbidities						
Hypertension	37 (51.4)	7 (35.0)	24 (66.7)	6 (46.2)	0 (0.00)	0 (0.00)
CAD	7 (9.7)	2 (10.0)	4 (11.1)	1 (7.7)	0 (0.00)	0 (0.00)
CVD	2 (2.8)	0 (0.00)	1 (2.8)	1 (7.7)	0 (0.00)	0 (0.00)
DVT/PE	20 (27.8)	6 (30.0)	12 (33.3)	1 (7.7)	1 (50.0)	0 (0.00)
Diabetes	15 (20.8)	5 (25.0)	8 (22.2)	1 (7.7)	1 (50.0)	0 (0.00)
CKD	2 (2.8)	1 (5.0)	1 (2.8)	0 (0.00)	0 (0.00)	0 (0.00)
CHF	5 (6.9)	2 (10.0)	3 (8.3)	0 (0.00)	0 (0.00)	0 (0.00)
A Fib	6 (8.3)	0 (0.00)	5 (13.9)	1 (7.7)	0 (0.00)	0 (0.00)
COPD	5 (6.9)	1 (5.0)	3 (8.3)	0 (0.00)	1 (50.0)	0 (0.00)
OSA	2 (2.8)	0 (0.00)	2 (5.6)	0 (0.00)	0 (0.00)	0 (0.00)
ECOG PS						
0	41 (56.9)	15 (75.0)	17 (47.2)	7 (53.8)	1 (50.0)	1 (100.0)
1	18 (25.0)	1 (5.0)	14 (38.9)	3 (23.1)	0 (0.00)	0 (0.00)
2	8 (11.1)	2 (10.0)	3 (8.3)	2 (15.4)	1 (50.0)	0 (0.00)
3	5 (6.9)	2 (10.0)	2 (5.6)	1 (7.7)	0 (0.00)	0 (0.00)
Histology						
Clear cell	8 (11.1)	5 (25.0)	3 (8.3)	0 (0.00)	0 (0.00)	0 (0.00)
Endometrioid	20 (27.8)	0 (0.00)	20 (55.6)	0 (0.00)	0 (0.00)	0 (0.00)
Serous	23 (31.9)	13 (65.0)	10 (27.8)	0 (0.00)	0 (0.00)	0 (0.00)
Carcinosarcoma	1 (1.4)	1 (5.0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Mucinous	1 (1.4)	0 (0.00)	1 (2.8)	0 (0.00)	0 (0.00)	0 (0.00)
Small cell	2 (2.8)	0 (0.00)	0 (0.00)	2 (15.4)	0 (0.00)	0 (0.00)
Squamous	11 (15.3)	0 (0.00)	0 (0.00)	10 (76.9)	0 (0.00)	1 (100.0)
Other	5 (6.9)	1 (5.0)	1 (2.8)	1 (7.7)	2 (100.0)	0 (0.00)
Unknown	1 (1.4)	0 (0.00)	1 (2.8)	0 (0.00)	0 (0.00)	0 (0.00)
Grade*						
1	6 (9.5)	0 (0.00)	5 (14.7)	0 (0.00)	0 (0.00)	1 (100.0)
2	12 (19.0)	1 (5.0)	10 (29.4)	1 (16.7)	0 (0.00)	0 (0.00)
3	45 (71.4)	19 (95.0)	19 (55.9)	5 (83.3)	2 (100.0)	0 (0.00)
Primary	5 (6.9)	2 (10.0)	0 (0.00)	2 (15.4)	1 (50.0)	0 (0.00)
Recurrent	67 (93.1)	18 (90.0)	36 (100.0)	11 (84.6)	1 (50.0)	1 (100.0)
Number of Prior Lines	2.0 (0, 11)	3.0 (0,11)	1.5 (0, 5)	2.0 (0, 8)	1.00 (0, 2)	2.0 (2, 2)
Prior VEGFi	26 (36.1)	7 (35.0)	14 (38.9)	4 (30.8)	1 (50.0)	0 (0.00)
Prior PARPi	7 (9.7)	6 (30.0)	1 (2.8)	0 (0.00)	0 (0.00)	0 (0.00)
Prior Pelvic RT	27 (37.5)	0 (0.00)	17 (47.2)	9 (69.2)	0 (0.00)	1 (100.0)
Prior VBT	20 (27.8)	0 (0.00)	17 (47.2)	3 (23.1)	0 (0.00)	0 (0.00)
MSI status*						
Stable	28 (38.9)	12 (60.0)	11 (30.6)	4 (30.8)	1 (50.0)	0 (0.00)
High/Unstable	24 (33.3)	0 (0.00)	23 (63.9)	0 (0.00)	1 (50.0)	0 (0.00)
TMB						
low	15 (20.8)	8 (40.0)	4 (11.1)	2 (15.4)	1 (50.0)	0 (0.00)
intermediate	9 (12.5)	4 (20.0)	5 (13.9)	0 (0.00)	0 (0.00)	0 (0.00)
high	3 (4.2)	0 (0.00)	3 (8.3)	0 (0.00)	0 (0.00)	0 (0.00)
PDL1 status						
Positive	9 (12.5)	0 (0.00)	3 (8.3)	5 (38.5)	0 (0.00)	1 (100.0)
Negative	8 (11.1)	3 (15.0)	4 (11.1)	1 (7.7)	0 (0.00)	0 (0.00)
not tested	55 (76.4)	17 (85.0)	29 (80.6)	7 (53.8)	2 (100.0)	0 (0.00)
CPI						
Pembrolizumab	42 (58.3)	2 (10.0)	30 (83.3)	8 (61.5)	1 (50.0)	1 (100.0)
Nivolumab	28 (38.9)	16 (80.0)	6 (16.7)	5 (38.5)	1 (50.0)	0 (0.00)
Ipilimumab	4 (5.6)	2 (10.0)	0 (0.00)	2 (15.4)	0 (0.00)	0 (0.00)
Avelumab	2 (2.8)	2 (10.0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
CPI Combination	4 (5.6)	2 (10.0)	0 (0.00)	2 (15.4)	0 (0.00)	0 (0.00)
Clinical Trial	5 (6.9)	5 (25.0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Concurrent Agent						
PARPi	5 (6.9)	4 (20.0)	1 (2.8)	0 (0.00)	0 (0.00)	0 (0.00)
Chemotherapy	4 (5.6)	2 (10.0)	0 (0.00)	1 (7.7)	1 (50.0)	0 (0.00)
Radiation	8 (11.1)	1 (5.0)	4 (11.1)	3 (23.1)	0 (0.00)	0 (0.00)
VEGFi	1 (1.4)	1 (5.0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Surgery	3 (4.2)	1 (5.0)	2 (5.6)	0 (0.00)	0 (0.00)	0 (0.00)

Statistics presented as Mean ± SD, Median (min, max), Median [P25, P75], N (column %).
*Denotes missing values: Grade:9 missing, MSI status: 20 missing, TMB: 45 not evaluated.
Abbreviations: BMI: body mass index, CAD: coronary artery disease, CVD: cerebro-vascular disease, DVT: deep vein thrombosis, PE: pulmonary embolism, CKD: chronic kidney disease, CHF: congestive heart failure, A fib: atrial fibrillation, COPD: chronic obstructive pulmonary disease, OSA: obstructive sleep apnea, ECOG PS: Eastern Cooperative Oncology Group performance status, No.: number, VEGFi: vascular endothelial growth factor inhibitor, PARPi: poly ADP ribose polymerase inhibitor, RT: radiation therapy, VBT: vaginal brachytherapy, TMB: tumor mutational burden, PDL1: programmed death ligand-1, CPI: checkpoint inhibitor.*Denotes missing values: Grade:9 missing, MSI status: 20 missing, TMB: 45 not evaluated.

Table 2
Clinical Outcomes with Checkpoint Inhibitor Therapy.

	All (N = 72)	Ovarian (N = 20)	Endometrial (N = 36)	Cervix (N = 13)	Site Unknown (N = 2)	vaginal (N = 1)
Number of CPI Cycles	7.5 (2, 32)	7.0 (2, 20)	8.0 (2, 27)	5.0 (3, 32)	7.0 (3, 11)	12.0 (12)
Follow-up Period	13.4 [6.5, 20.5]	15.6 [6.0, 26.2]	13.4 [6.7, 20.4]	10.2 [4.0, 17.4]	16.9 [7.6, 26.3]	7.9 [7.9]
Response Type						
Partial response	16 (22.2)	3 (15.0)	12 (33.3)	1 (7.7)	0 (0.00)	0 (0.00)
Complete response	6 (8.3)	1 (5.0)	3 (8.3)	1 (7.7)	1 (50.0)	0 (0.00)
Stable disease	26 (36.1)	10 (50.0)	12 (33.3)	3 (23.1)	0 (0.00)	1 (100.0)
Progressive disease	24 (33.3)	6 (30.0)	9 (25.0)	8 (61.5)	1 (50.0)	0 (0.00)
Time to initial response	2.7 [2.6, 3.4]	2.8 [2.4, 3.2]	2.7 [2.5, 3.4]	3.7 [2.6, 4.8]	2.7 [2.7, 2.7]	—
Time to CR	11.5 [10.0, 13.4]	20.6 [20.6, 20.6]	10.5 [10.0, 13.4]	12.5 [12.5, 12.5]	7.4 [7.4, 7.4]	—
Duration of Response	6.6 [4.4, 12.5]	7.8 [5.4, 11.1]	5.6 [2.8, 10.4]	11.6 [5.9, 17.3]	18.9 [18.9, 18.9]	—
Duration of SD	6.2 [4.7, 11.6]	5.8 [5.3, 11.6]	6.8 [4.5, 12.3]	3.0 [3.0, 15.7]	—	6.3 [6.3]
Pseudoprogression						
Followed by Response	6 (8.3)	1 (5.0)	4 (11.1)	1 (7.7)	0 (0.00)	0 (0.00)
Followed by Stable Disease	5 (6.9)	2 (10.0)	2 (5.6)	1 (7.7)	0 (0.00)	0 (0.00)
Time to Subsequent Response	3.8 [2.7, 4.8]	2.9 [2.9, 2.9]	3.7 [2.4, 7.6]	4.8 [4.8, 4.8]	—	—
PFS	6.4 (4.1–10.0)	6.4 (2.7–11.6	8.9 (4.7–11.6)	2.8 (2.1-.)	—	—
1 year PFS (%)	31.6 (19.8,43.3)	26.5 (4.9,48.1)	32.7 (16.0,49.5)	28.8 (3.2,54.5)	50.0 (0.0,100.0)	0.0 (0.0)
OS	15.2 (10.3–21.2)	15.9 (5.5-.)	16.3 (9.6–26.9)	10.2 (3.1-.)	—	—
1 year OS (%)	69.6 (49.3,90.0)	69.6 (49.3,90.0)	60.0 (43.8,76.3)	38.5 (12.0,64.9)	50.0 (0.0,100.0)	—

Disease response data presented as Median [P25, P75], N (column %) where appropriate. Survival statistics presented as median survival month (P25, P75 survival month); 1 year PFS/OS percentage (95% CI).
Abbreviations: CPI: checkpoint inhibitor, CR: complete response, SD: stable disease, PFS: progression free survival, OS: overall survival.

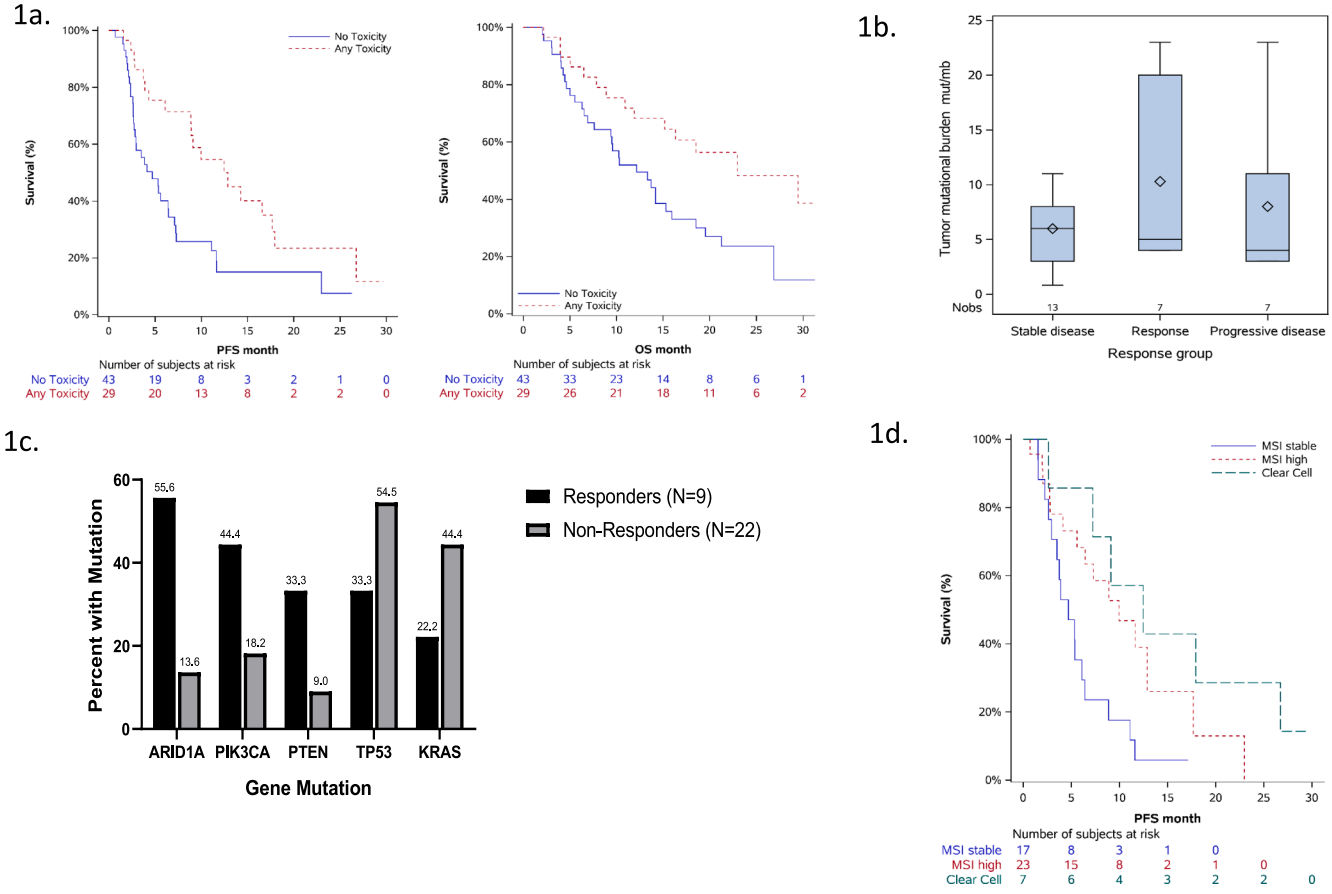

Fig. 1. *Features of Gynecologic Oncology Patients receiving Checkpoint Inhibitor Therapy.* (1a) *Left:* progression free survival Kaplan Meier curves for the full cohort in those who developed an immune related adverse event (any toxicity) versus those who did not (no toxicity). *Right*: Kaplan Meier curves for overall survival of the full cohort in those who developed an immune related adverse event (any toxicity) versus those who did not (no toxicity). (1b) Boxplot demonstrating relationship of tumor mutational burden reported in mutations per megabase (mut/mb) and tumor response to checkpoint inhibition. (1c) Bar graph demonstrating the five most common gene mutations identified on somatic testing displayed by frequency of mutation in responders (N = 9) and non-responders (N = 22). (1d) Kaplan Meier curves for progression free survival in the endometrial and ovarian cancer subgroup comparing analysis groups of microsatellite stable tumors (MSI stable), microsatellite unstable tumors (MSI high), and clear cell tumors.

Table 3
Summary of Patients Receiving Checkpoint inhibition as Primary Systemic Therapy.

	N = 6
Age	79.5 [59.0, 86.0]
BMI	31.1 [30.3, 31.9]
ECOG PS	
0	2 (33.3)
1	4 (66.7)
Comorbidities	
Hypertension	3 (50.0)
Coronary Artery Disease	1 (16.7)
History of Cerebral Vascular Accident	1 (16.7)
Deep Venous Thrombosis or Pulmonary Embolism	3 (50.0)
Diabetes	1 (16.7)
Chronic Kidney Disease	1 (16.7)
Congestive Heart Failure	2 (33.3)
Atrial Fibrillation	1 (16.7)
Endometrioid Histology	6 (100.0)
Grade	
1	1 (16.7)
2	4 (66.7)
3	1 (16.7)
Prior Pelvic Radiation	4 (66.7)
Prior Hysterectomy	5 (83.3)
Recurrent Disease	6 (100.0)
CPI Agent: Pembrolizumab	6 (100.0)
Total Number of CPI Cycles	14.0 [10.0, 18.0]
Response Type	
Stable disease	1 (16.7)
Partial response	5 (83.3)
Time to initial response	2.7 [2.5, 2.7]
Duration of Response	9.0 [5.6, 9.9]
Length of follow-up	11.3 [9.5, 13.2]
Progression Free Survival	7.3 [7.3, 7.3]
Progression free at last follow up	5 (83.3)
Overall Survival	9.5 [8.9, 9.6]
Alive at Last Follow up	3 (50.0)

Statistics presented as Median [P25, P75], N (column %). Duration of response, time to response, progression free survival, overall survival all presented as months.
Abbreviations: BMI: body mass index, ECOG PS: Eastern Cooperative Oncology Group performance status, CPI: checkpoint inhibition.

and therefore were offered CPI therapy. Median age for this group was higher than the full cohort (79.5 vs 64.2). Five patients achieved PR, and one SD with an ORR 83.3%. Median duration of response was 9.0 months. At a median follow up of 11.3 months, 3 patients remained alive with ongoing responses, 2 were dead of intercurrent disease, and 1 was dead of disease.

4. Discussion

Outcomes with CPI therapy in gynecologic cancer have varied per disease site with response rates ranging from < 10% to > 60% and limited factors to guide patient selection for therapy (Grywalska et al., 2019). There remains vast room for improvement regarding our knowledge on expected therapeutic outcomes and toxicity risks with CPI in gynecologic cancer. In this retrospective study we aimed to further investigate predictors of response to CPI in a diverse, real-world gynecologic cancer cohort with most patients receiving non-clinical trial treatment. Our findings show clear cell histology and immune related toxicity were both significant predictors of response.

Previous ovarian cancer data has shown low response rates to CPI therapy (7.4–15%) (Matanes and Gotlieb, 2019; Disis et al., 2019; Matulonis et al., 2019; Rubinstein and Makker, 2020). The relative resistance of ovarian cancer to CPI is thought to be multifactorial relating to a low intrinsic tumor immunogenicity and mutational burden along with redundant immunosuppressive mechanisms within the tumor microenvironment (Odunsi, 2017). Surprisingly, there have been durable responses to CPI in platinum resistant ovarian cancer which offers hope where there is otherwise a poor prognosis (Hamanishi et al., 2015). Identifying favorable CPI responders prior to therapy initiation could potentially alter the traditional treatment algorithm and limit unnecessary toxicity for those who are less likely to benefit.

In the phase II study of nivolumab in platinum resistant ovarian cancer, both complete responses were clear cell histology or had clear cell- like gene expression profile (Hamanishi et al., 2015; Oda et al., 2018). Due to the low incidence of clear cell ovarian cancer, there is relatively little representation of these tumors in clinical trials, and therefore it is difficult to determine the extent of benefit from CPI. Advanced or recurrent clear cell tumors have demonstrated chemoresistance and are associated with a poor prognosis (Tan and Kaye, 2007; McMeekin et al., 2007). Therefore, albeit small numbers, the demonstration of high CPI response rates for clear cell tumors with prolonged clinical benefit in our study despite the microsatellite stable status (ORR: 60% ovarian, 50% endometrial) offers a promising treatment option. Additionally, we found that ARID1A and PIK3CA mutations, both common findings in clear cell carcinomas, were more prevalent in responders (ARID1A 55.6%, PIK3CA 44.4%) compared to non-responders (ARID1A 13.6%, PIK3CA 18.2%). Whether these genomic mutations correlate with response independent of histology is not able to be determined by this study due to small numbers and confounding effect. Further study into these genomic mutations as it relates to CPI response may elucidate the etiology of such favorable responses (Oda et al., 2018).

Although MMRd/MSI-H is well-known to be predictive of CPI response, little data exists CPI response rates in chemo-naïve MMRd endometrial carcinoma. In the present study, a respectable ORR of 83% (5 PR, 1 SD) was achieved with ongoing responses at 1-year in three patients and one PR converting to CR after data analysis. Compared to historical ORR of 57% from GOG177 with paclitaxel, doxorubicin, and cisplatin (TAP), our ORR of 83% to CPI suggests reasonable efficacy in chemotherapy naïve endometrial cancer. When there are limited treatment options due to patient factors, CPI seems reasonable in MSI-H endometrial cancer. Larger studies will hopefully provide more robust data for CPI as an early treatment strategy for these patients.

Lastly, IRAE was significantly associated with improved ORR, PFS and OS in this study. Improved outcomes with CPI use in association with immune toxicity has been previously reported in other non-gynecologic cancers however, to the best of our knowledge, this association in gynecologic cancer has not been previously reported (Palmieri and Carlino, 2018). Further investigation into the biologic basis of this finding would likely offer valuable insight into patient selection for therapy and treatment optimization.

The current report presents significant and clinically relevant findings of clear cell histology and IRAE as new prognostic factors for CPI use in gynecologic cancer. However, this study remains a retrospective review and therefore is subject to implicit bias. This study was limited by a fixed number of patients precluding formal power calculation. Despite these limitations, our findings overall support prioritizing CPI therapy for gynecologic clear cell cancers as these tumors demonstrate high response rates with favorable PFS. Gynecologic cancer patients should be counseled on the high rate of immune toxicity with CPI, however, when found may be associated with improved oncologic outcomes.

5. Author contribution statement**a

MK (conceived and designed work that led to submission, acquired data, interpreted results, drafted and revised manuscript, approved final version, agreed to be accountable for all aspects of the work), CB (designed the work, acquired data, revised manuscript, approved final version, agreed to be accountable for all aspects of the work), YM (designed work that led to submission, acquired data, interpreted results, revised manuscript, approved final version, agreed to be accountable for all aspects of the work), AJP (designed work that led to submission, acquired data, revised manuscript, approved final version,

agreed to be accountable for all aspects of the work), PR (conceived work that led to submission, acquired data, revised manuscript, approved final version, agreed to be accountable for all aspects of the work), HM (conceived and designed work that led to submission, acquired data, interpreted results, drafted and revised manuscript, approved final version, agreed to be accountable for all aspects of the work).

6. Ethics approval and consent to participate**a

This project was Cleveland Clinic IRB approved (Study # 13–498) and a waiver of written consent was granted with assurance of protections for privacy and confidentiality due to the minimal risk nature of this retrospective study.

7. Data availability**a

De-identified Data used for analysis in this manuscript is available upon request from the corresponding author Dr. Haider Mahdi.

8. Funding information**a

This research did not receive any funding.

Declaration of Competing Interest

The Authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2020.100671.

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