A Phase II Trial of Guadecitabine Priming and Pembrolizumab in Platinum Resistant Recurrent Ovarian Cancer

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ABSTRACT

Background: Platinum resistant ovarian cancer (PROC) remains a disease of high need. Immune checkpoint inhibitors (ICI) have modest activity in PROC. We hypothesized that treatment with a hypomethylating agent (HMA) guadecitabine (G) will improve the anti-tumor activity of ICI in PROC by enhancing tumor cell recognition by CD8+ T cells.

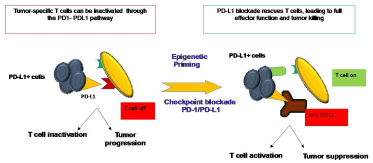
Methods: This open-label phase II study used a Simon's two-stage design. Eligible patients (pts) had recurrent PROC; ECOG PS of 0-1; normal end organ function; and measurable disease. Up to 5 prior cytotoxic regimens were allowed. Treatment consisted of G 30mg/m2 sq D1-4 and Pembrolizumab (P) 200mg iv D5. Each cycle was 21 days. The primary endpoint was response rate (RR). Secondary endpoints were progression-free survival (PFS), clinical benefit rate (CBR), and toxicity assessment. Translational endpoints were LINE1 methylation in PBMCs, global tumor methylation, and immune endpoints. Tumor biopsies were obtained at baseline and after 2 cycles. If 2 patients experienced clinical benefit in stage I [n = 16], enrollment proceeded to stage II. The null hypothesis was rejected for ≥ 6 responses in 35 evaluable patients.

Results: 48 pts were enrolled, 43 were treated, and 33 were evaluable for response. 34 had OC [79%], 6 FTC [14%] and 3 PPC [7%]. Histology was serous (35), endometrioid (2), clear cell (3) and other (3). The median age was 63 (range 40-88), and median number of prior regimens was 4 [range 1-8]. Two PRs were recorded in the first stage, allowing second stage of enrollment. Overall, there were 3 PRs (RR=9.9%) and 16 pts had stable disease (SD) [48%]. The clinical benefit rate (PR + SD > 3 months) was 27%. One patient continued treatment for > 2 yrs. Grade 3-4 related toxicities were neutropenia [20], lymphopenia, (9), anemia (2), neutropenic fever (1), rash (1), and others (8). There were 13 grade 3-4 SAEs and 4 grade 5 SAEs, but no treatment-related deaths. LINE1 was hypomethylated in PBMCs D5 vs. D1 (n=21, p=0.001). Global tumor hypomethylation was measured with Epic arrays (n=11). PDL1 staining in archival tissue included 16 specimens with tumor PDL1 staining > 0 and 20 specimens with tumor/stroma interface staining > 0 (n=35). Antigen-specific cytotoxic T cell activity was increased by treatment in CD8 cells recovered from ascites.

Conclusions: G+P has modest anti-tumor activity in patients with PROC, but some patients experienced prolonged disease stabilization. Biomarkers of response are being investigated.

BACKGROUND

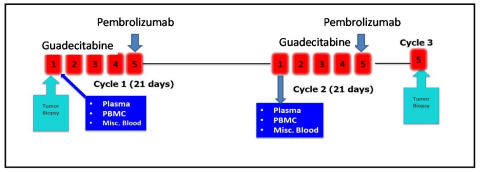
Rationale:



Hypothesis:

Epigenetic priming by using a hypomethylating agent (guadecitabine) will increase anti-tumor immune response elicited by the immune check point inhibitor pembrolizumab.

Study Design:



METHODS

Study Overview

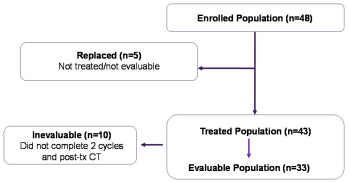
- **Design:**

  Open- label, phase II trial, using Simon's two-stage design.
- **Key Eligibility:**

  - Recurrent or persistent, platinum-resistant OC, FTC, or PPC
  - ECOG PS 0-1
  - Normal end organ function
  - RECIST 1.1 measurable disease
- **Treatment Regimen:** Guadecitabine 30mg/m2 SQ D1-4 and Pembrolizumab 200mg iv D5 (1 cycle = 3 weeks) until progressive disease, unacceptable toxicity, withdrawal, or death.
- **Enrollment:**

  48 patients with platinum-resistant OC, FTC, or PPC were enrolled at Northwestern University/Medical Group and University of Chicago
- **Interim Analysis:**

  Stage I interim analysis (n=12 subjects) was conducted in June 2017, and efficacy parameters were met with ≥ 2 partial or complete response (PR or CR).
- **Statistics and Toxicity Analysis**:
  - Objective response rate (ORR) was calculated as the number of complete responses (CRs) and partial responses (PRs) according to RECIST 1.1 criteria.
  - The Kaplan-Meier method was utilized to estimate the median and overall distribution of progression free survival (PFS) and overall survival (OS).
  - Toxicity was evaluated per NCI-CTCAE v4.03 and was summarized by counts and frequencies.



OBJECTIVES

- **Primary Endpoint:**
  - **Objective response rate (ORR)**

    ORR is defined as the number of CRs and PRs per RECIST 1.1.
- **Secondary Endpoints:**
  - **Progression free survival (PFS)**

    Progression is defined as RECIST 1.1 progression, clinical progression, and/or CA-125 biomarker progression.
  - **Clinical Benefit Rate** = ORR+ Stable disease for at least 3 months
  - **Toxicity assessment** according to NCI-CTCAE v4.03
  - **Treatment induced hypomethylation** in PBMCs (D1 vs. D5 vs. end of treatment)
  - **Treatment induced hypomethylation** in tumor biopsies (C2D5 vs. C1D1)
  - **Immune markers** of response

Patients Characteristics

Variable	No.	Percent
Site of origin		
Ovarian cancer	34	79.07
Peritoneal carcinomatosis	3	6.98
Fallopian tube cancer	6	13.95
Age	**Mean (SD)**	**Median (Range)**
	63.07 (11.68)	63.58 (40.75, 88.33)
Number of prior regimens	**Mean (SD)**	**Median (Range)**
	4.23 (1.82)	4.00 (1.00, 8.00)
Histology		
Serous	35	81.40
Endometrioid	2	4.65
Clear cell	3	6.98
Other	3	6.98

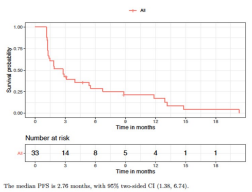
RESULTS

Efficacy

Stage I efficacy parameters were met, and the study proceeded to stage II.

Efficacy parameters	Frequency/Median (Range)
Response Rate	9.09% (3 of 33 patients)
PR	3 of 33
CR	0 of 33
SD	15 of 33
Clinical Benefit Rate = CR+PR+SD > 3months	42% (14 of 33)
PFS	2.76 mos (CI: 1.38-6.74 months)

Median PFS = 2.76 months



The median PFS is 2.76 months, with 95% two-sided CI (1.38, 6.74).

Toxicity

Summary of AEs

Event	All Subjects (n = 43)
	No. (%)
Any AE	43 (100.00)
SAE	16 (37.21)
SAE related to either treatment	7 (16.28)
Grade 3 or 4 SAE	13 (30.23)
Grade 5 SAE	4 (9.30)

AE = Adverse Event
SAE = Serious Adverse Event

Most common gr. 3-4 toxicities

AE Term	Grade 3-4 (%)
Neutrophil count decreased	17 (39.53)
White blood cell decreased	15 (34.88)
Lymphocyte count decreased	9 (20.93)
Hyponatremia	5 (11.63)
Anemia	4 (9.30)
Hypertension	4 (9.30)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	3 (6.98)
Abdominal pain	2 (4.65)
Ascites	2 (4.65)
Dehydration	2 (4.65)
Nausea	2 (4.65)
Pleural effusion	2 (4.65)
Thromboembolic event	2 (4.65)

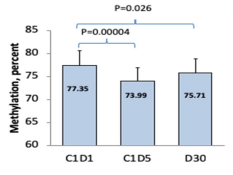
Most common gr. 1-2 toxicities

AE Term	Grade 1-2 (%
Anemia	26 (60.47)
Lymphocyte count decreased	22 (51.16)
Fatigue	21 (48.84)
Hypertension	19 (44.19)
White blood cell decreased	14 (32.56)
Abdominal pain	13 (30.23)
Constipation	13 (30.23)
Hypoalbuminemia	13 (30.23)
Nausea	13 (30.23)
Injection site reaction	12 (27.91)
Alkaline phosphatase increased	11 (25.58)
Anorexia	11 (25.58)
Diarrhea	11 (25.58)
Investigations - Other, specify	9 (20.93)
Vomiting	9 (20.93)
Cough	8 (18.60)
Dry skin	8 (18.60)
Aspartate aminotransferase increased	7 (16.28)
Chills	7 (16.28)
Dyspnea	7 (16.28)
Fever	7 (16.28)
Hypokalemia	7 (16.28)
Weight loss	7 (16.28)
Arthralgia	6 (13.95)
Back pain	6 (13.95)
Bloating	6 (13.95)
Neutrophil count decreased	6 (13.95)
Platelet count decreased	6 (13.95)
Urinary tract infection	6 (13.95)
Alanine aminotransferase increased	5 (11.63)
Headache	5 (11.63)
Hyperuricemia	5 (11.63)
Hypomagnesemia	5 (11.63)
Myalgia	5 (11.63)
Upper respiratory infection	5 (11.63)

RESULTS

Translational Analyses

Line 1 methylation was measured in PBMCs by pyrosequencing

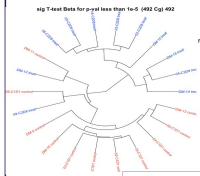


n=34 pairs C1D1 and C1D5

n=16 pairs D30 vs C1D1 or vs C1D5

Global tumor methylation was measured by Epic Arrays (n=11 pairs pre and post-treatment)

Clustering analysis: methylation of control (pre) and treatment (post) tumor biopsies



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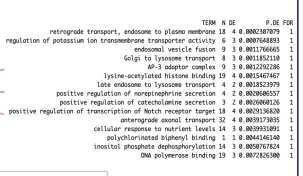
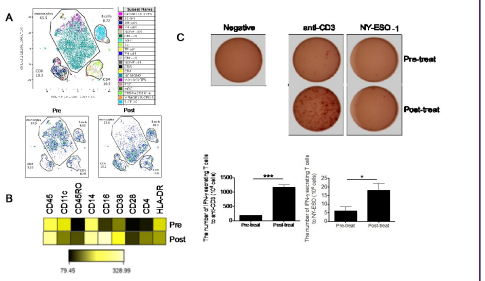


	TERM	N DE	P.DE FOR
retrograde transport, endosome to plasma membrane	18	4	0.0002387079
regulation of potassium ion transmembrane transporter activity	6	3	0.0007648893
endosomal vesicle fusion	9	3	0.0011766665
Golgi to lysosome transport	8	3	0.0011852110
AP-3 adaptor complex	9	3	0.0012292286
lysine-acetylated histone binding	19	4	0.0015467467
late endosome to lysosome transport	4	2	0.0018523979
positive regulation of norepinephrine secretion	4	2	0.0020680557
positive regulation of catecholamine secretion	3	2	0.0026060126
positive regulation of transcription of Notch receptor target	18	4	0.0029136820
anterograde axonal transport	32	4	0.0039173835
cellular response to nutrient levels	14	3	0.0039391091
polychlorinated biphenyl binding	1	1	0.0044146140
inositol phosphate dephosphorylation	14	3	0.0050707824
DNA polymerase binding	19	3	0.0072826300

In Vivo Activity of G+P



Identification of differences in ascites from responder before and after treatment with guadecitabine and pembrolizumab. (A). Exemplified tSNE visualization of overlaid events from responder before and after treatment. (B). The heat map represents the median indicated marker expression within CD45+ cells from responder ascites. (C). ELISPOT analysis of IFN-γ secreting T cells from tumor cell depleted ascites treated as indicated in the absence (negative) and presence of anti-CD3 or NY-ESO-1 peptides. The total number of spots were counted. *p < 0.05, ***p < 0.001.

CONCLUSIONS

- G+P has modest anti-tumor activity in patients with PROC, but some patients experienced prolonged disease stabilization.
- Global hypomethylation was achieved in PBMCs and tumor biopsies.
- Biomarkers of response are being developed.

AKNOWLEDGEMENTS

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