Triple blockade of the DNAM-axis with COM701 + BMS-986207 + nivolumab demonstrates preliminary antitumor activity in patients with platinum resistant OVCA. (NCT04570839).

JW. Moroney[1], O. Yeku[2], G. Fleming[3], L. Emens[4], D. Vaena[5], E. Dumbrava[6], D. Rasco[7], M. Sharma[8], K. Papadopoulos[7], A. Patanaik[7], R. Sullivan[9], A. Adewoye[10], E. Ophir[11], G. Cojocaru[12], P.Ferre[13], I. Barbiro[13], B. Izar[14], S. Gaillard[15].

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Abstract Number 158P

BACKGROUND

- COM701 is a novel,1st-in-class ICI-blocker that binds to PVRIG, a DNAM-1 axis member, leading to activation of T-and NK-cells; BMS-986207 [anti-TIGIT inhibitor], nivolumab [PD-1 inhibitor]
- We have reported that PVRIG pathway is highly expressed in ovarian cancer tumors[1]
  - We have reported preliminary anti tumor activity with COM701 ± nivolumab including a confirmed PR with COM701 monotherapy in a patient with OVCA [primary peritoneal cancer][1]
- There is a high unmet medical need for the treatment of patients with platinum resistant epithelial ovarian cancer [PROC], defined as disease recurrence <6 months after completion of platinum-based therapy
- Immune checkpoint inhibitors have limited activity in patients with platinum resistant OVCA
  - Pembrolizumab monotherapy, pembrolizumab + vibostolimab [anti-TIGIT inhibitor] ORR ~8%[3,4]
- We hypothesized that in patients with PROC, triple blockade of PVRIG, TIGIT and PD-1 would demonstrate antitumor activity with a favorable safety and tolerability profile
- We present encouraging preliminary results on safety and preliminary anti tumor activity

METHODS

- We enrolled 20 patients with platinum resistant epithelial OVCA, fallopian tube or primary peritoneal cancer; ECOG 0-1
- All patients received COM701 20 mg/kg + BMS-986207 + nivolumab both 480 mg; all IV Q4W
- Antitumor activity (per investigator) was evaluated per RECIST v1.1 with CT imaging every 8 weeks or at any time point progressive disease is suspected
- Study treatment for 2yrs unless PD, toxicity, withdrawal of consent, PI discretion
- Safety assessment evaluated per CTCAE v5.0

ELIGIBILITY CRITERIA AND OBJECTIVES

Key Inclusion Criteria:

- Histologically confirmed locally advanced or metastatic solid malignancy and has exhausted all available standard treatment or is not a candidate for available standard therapy
- Measurable disease
- Mandatory biopsy: pre and on-treatment
- No limitation on the number of prior lines of therapy

Key Exclusion Criteria:

- Active autoimmune disease requiring systemic treatment
- Anti-TIGIT or PD-(L)1 inhibitor, anti-CTLA-4 antibody, anti-OX-40 antibody, anti- CD137 antibody.
- History of immune-related toxicities on prior immunotherapy treatment leading todiscontinuation

Key Primary Objective:

- Safety and tolerability of the combination

Key Secondary Objective:

- Preliminary antitumor activity of the combination

Key Exploratory Objectives:

- Immunogenicity of COM701
- COM701-mediated pharmacodynamic effect in blood, immune-related changes (cytokines, immunophenotyping)

DEMOGRAPHICS

Characteristics	
Age, n(%) ≥65 years	10 (50)
ECOG (0, 1), n(%) 1	14 (70)
Histology	
High grade serous	11 (55%)
Clear cell	3 (15%)
Not available	6 (30%)
Prior bevacizumab-containing regimen	16 (80%)
Prior Parp inhibitor	6 (30%)

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PATIENT DISPOSITION SUMMARY

	n = 20 (%)
Number of patient enrolled and treated - n(%)	20 (100)
Median (Min, Max) #Prior Lines	4 (1,10)
Discontinued study treatment - n(%)	16 (80)
Reasons for study treatment discontinuation (n)	
• Progressive disease per RECIST v1.1/clinical PD	15(75)
• Adverse event*	1 (5)

*G3 AST elevation, G2 ALT elevation

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SUMMARY OF TREATMENT RELATED ADVERSE EVENTS

Parameter	All Adverse Events n = 20 (%)
Any TRAE	11 (55%)
No TRAE	9 (45%)
≤G2	4 (20%)
G3	7 (35%)
≥G4	-
TRAE leading to study treatment discontinuation	1 (5%)*

Safety analysis set – patients who received ≥1 dose of any of the study drugs. Safety per CTCAE v5.0.

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INCIDENCE OF TRAEs (15% OF PATIENTS)

PREFERRED TERM (PT)	Grade 1/2 n [%]	Grade 3* n [%]	Grade 4 n [%]	Grade 5 n [%]	All Grades n [%]
ANY TRAE	4 (20)	7 (35)	-	-	11 (55)
Nausea	6 (30)	-	-	-	6 (30)
Diarrhoea	3 (15)	1 (5)			4 (20)
Fatigue	4 (20)	-	-	-	4 (20)
Alanine amino transferase increased	2 (10)	1 (5)	-	-	3 (15)
Anaemia	2 (10)	1 (5)	-	-	3 (15)
Hyponatraemia	3 (15)	-	-	-	3 (15)
Pruritus	3 (15)	-	-	-	3 (15)

Safety analysis set – patients who received ≥1 dose of any of the study drugs. AEs reported within 30 days of last dose of study treatment. Safety per CTCAE v5.0.
*Grade 3 TRAE, 1 patient each with: [Diarrhoea, Colitis], [ALT increased], [Anaemia], [Hypercalcaemia], [AST increased], [Dyspnoea], [Lymphocyte count decreased].

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INCIDENCE OF RELATED SERIOUS ADVERSE EVENTS - ALL PATIENTS

PREFERRED TERM (PT)	Grade 1/2 n [%]	Grade 3 n [%]	Grade 4 n [%]	Grade 5 n [%]	All Grades n [%]
Any serious	1 (5)	2 (10)	-	-	3 (15)
Dyspnoea	-	1 (5)	-	-	1 (5)
Hypercalcaemia	-	1 (5)	-	-	1 (5)
Proctalgia	1 (5)	-	-	-	1 (5)
Pulmonary embolism	1 (5)	-	-	-	1 (5)
Pyrexia	1 (5)	-	-	-	1 (5)

Safety analysis set – patients who received ≥1 dose of any of the study drugs. AEs reported within 30 days of last dose of study treatment. Safety per CTCAE v5.0.

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SUMMARY OF INVESTIGATOR ASSESSED RESPONSE (RECIST v1.1)

Parameter	All patients n = 20 (%)
ORR (CR+PR)	4 (20); (95% CI: 6-44%)
Disease control rate (CR+PR+SD*)	9 (45); (95% CI: 23-68%)
Best response	
CR	-
PR	4 (20)
SD	5 (25)
PD	11 (55)

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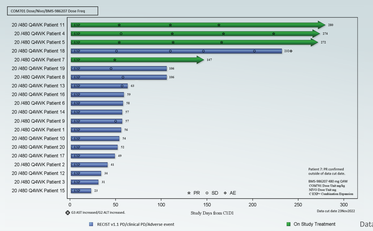
SWIMMER PLOT



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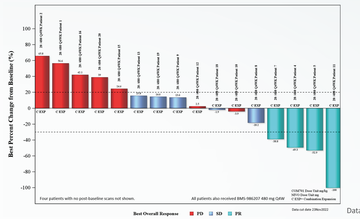
WATERFALL PLOT



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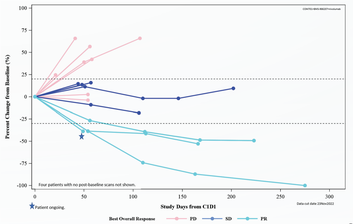
SPIDER PLOT



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CHARACTERISTICS OF RESPONDERS

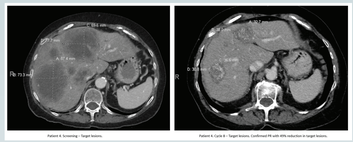
Patient ID	Histology	Ongoing study treatment Y/N	PR confirmed Y/N	Number of prior lines of therapy	PD-L1 assessment (Combined Positive Score)
Patient 4	Serous adenocarcinoma	Y	Y	3	pending
Patient 5	Serous adenocarcinoma	Y	Y	7	3*
Patient 7	Serous adenocarcinoma	Y	Y	6	pending
Patient 11	Clear cell	Y	Y	2	<1

*Sponsor assessment
Translational and biomarker work on pre and on treatment biopsies is ongoing/pending

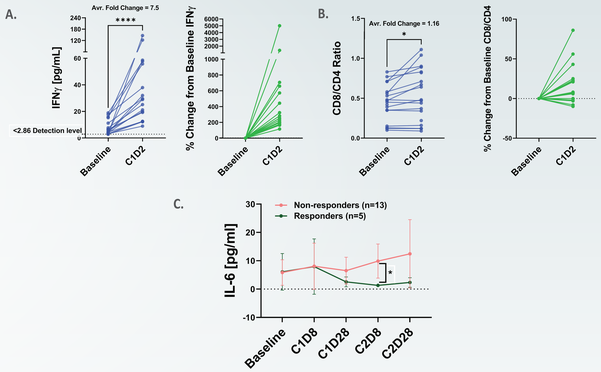
CLINICAL VIGNETTE [patient 4]

68yr old female with high grade serous ovarian carcinoma with a history of 3 prior lines of non-maintenance therapy: carboplatin/paclitaxel, Y90 hepatic radioembolization, carboplatin/pegylated liposomal doxorubicin/bevacizumab [best response for all: PD at 1st re-staging]

On study treatment with confirmed partial response.



PHARMACODYNAMIC ACTIVATION OF THE IMMUNE SYSTEM WITH STUDY TREATMENT



Translational assessment of peripheral blood, including profiling of cytokines and circulating immune cells, clearly showed a positive pharmacodynamic activation of the immune system following PD1/TIGIT/PVRIG blockade. Peripheral IL-6 reduction was detected from D28 post first treatment (C1D28), among patients responding to treatment (partial response or SD>180 days per RECIST) compared to nonresponding patients.

(A) Increase in serum IFN in C1D2 compared to baseline
(B) Increased CD8/CD4 ratio in C1D2 compared to baseline
(C) Post treatment decrease in serum IL-6 with correlation to response

REFERENCE:

1. Whelan S, Ophir E, et al. PVRIG and PVRL2 Are Induced in Cancer and Inhibit CD8+ T-cell Function. Cancer Immunol Res. 2019 Feb;7(2):257-268. **2.** Vaena, DA, Fleming GF et al. COM701 with or without nivolumab: Results of an ongoing phase 1 study of safety, tolerability and preliminary antitumor activity in patients with advanced solid malignancies (NCT03667716). J Clin Oncol 39, 2021 (suppl 15; abstr 2504). **3.** Ursula M, Shapira-Frommer R et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent OVCA: Final results from the P2 KEYNOTE-100 study. ASCO Annual Meeting 2020. **4.** Ruth, P, Gutierrez, M et al. Safety and efficacy of vibostolimab plus pembrolizumab and coformulation of vibo/pembro in ovarian cancer naive to PD-1/PD-L1 inhibitors. In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; Cancer Res 2022;82(12_Suppl):Abstract nr CT180

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DISCLOSURES

JW, Moroney, MD reports: Institutional clinical trial support - Mersana, Laekna, Genentech, Merck, Immunogen, Aravive, Verastem; Eli Lilly Compensated: None; Uncompensated - Laekna Safety Review Committee.

Conclusion

The combination of COM701 with BMS-986207 and nivolumab is well tolerated and has a favorable safety and toxicity profile. Encouraging preliminary antitumor activity in a heavily pretreated and heterogenous patient population with: Confirmed ORR of 20%, DCR 45%. Low pre-treatment PD-L1 expression in 2 of the responders [CPS <1 and 3]. Median duration of response not reached responders ongoing study treatment. Antitumor activity in diverse histology – high-grade serous (a histological type that is typically not responsive to checkpoint inhibitors), clear cell. Pharmacodynamic changes suggest synergistic immune activation following triplet blockade, as compared to COM701 mono and combination results as well as published data. Further translational work is ongoing. The data are encouraging and merits further investigation.