Triple blockade of DNAM-1 axis with COM701 (anti-PVRIG) + COM902 (anti-TIGIT) + pembrolizumab shows preliminary antitumor activity in patients with platinum resistant ovarian cancer, interim results of a Phase I trial

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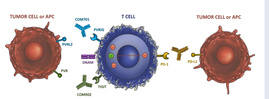
INTRODUCTION

- Ovarian cancer is the 5th leading cause of cancer-related death among women and a leading cause of death among all gynecological cancers.[1]
- Platinum-resistant ovarian cancer (PROC) represents a challenging population to treat with a high unmet need for new treatments.
- The overall response rate (ORR) in patients with PROC treated with anti-PD-(L)1+/ - anti-TIGIT is ~10%.[2-4]
- COM701 is a potential 1st-in-class immune checkpoint inhibitor (ICI) that inhibits the DNAM-1 axis member PVRIG, leading to the activation of T and natural killer (NK) -cells (**Figure 1**). COM902 is a potential best-in-class ICI that inhibits the DNAM-1 family member TIGIT.[5]
- In a prior Phase I clinical trial, the combination of COM701 + BMS-986207 (anti-TIGIT) + nivolumab (anti-PD1) demonstrated an ORR of 4/20 (20%) in PROC patients.[6]
- We hypothesized that a triplet combination immunotherapy of COM701+COM902+pembrolizumab (anti-PD1) would demonstrate antitumor activity by inhibiting the DNAM-1 axis in PROC which would have a favorable safety and tolerability profile.

Figure 1. DNAM-1 AXIS Pathway: Potential Synergy in Blocking PVRIG, TIGIT, and PD-1 Pathways



Support combination approach to overcome immunotherapy resistance

- PVRIG and TIGIT were discovered by Compugen's discovery platform.[7]
- DNAM axis – two parallel and complementary inhibitory pathways (PVRIG & TIGIT).
- Potential synergy in blocking PVRIG, TIGIT and PD-1 pathways.
- Blocking PVRIG is potentially unique in generating new waves of T cells to infiltrate the tumor microenvironment.[8]
- The PVRIG ligand, PVRL2, is broadly expressed in PD-L1 high and low tumors.

APC: antigen-presenting cell; DNAM: DNAX accessory molecule; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; PVRIG: anti-poliovirus receptor-related immunoglobulin; PVRL2: poliovirus receptor-related 2; TIGIT: T cell Ig and immunoreceptor tyrosine-based inhibitory motif domain

OBJECTIVES

- We present preliminary results of a cohort of PROC patients treated with the triplet combination of COM701+COM902+pembrolizumab in **Trial CPG-02-101** demonstrating encouraging safety and antitumor activity, consistent with a prior PROC cohort.[6]

Key Primary Objective

- To evaluate the safety profile of COM701+COM902+pembrolizumab.

Prespecified Exploratory Objectives

- Preliminary antitumor activity of COM701+COM902+pembrolizumab.
- Pharmacodynamic effects of trial drug(s) in the tumor and blood, including changes in serum cytokine levels.

METHODS

Trial Design

- Data reported are from the PROC expansion cohort of **Trial CPG-02-101** (NCT04354246), an ongoing Phase I, open-label, multicenter, dose-escalation, and expansion trial that is being conducted in the US (**Figure 2**).
- The trial is ongoing; we report results up to a **data cut-off date of 29 August 2024**.

Figure 2. CPG-02-01 Trial Schema: Triplet Combination Expansion Cohorts

MSS-CRC Triplet Expansion (N=20 total)*
• COM701 15mg/kg + COM902 3mg/kg + pembrolizumab 200mg Q3W

Platinum-resistant OVCA [PROC] Triplet Expansion (N=25 total)*
• COM701 15mg/kg + COM902 3mg/kg + pembrolizumab 200mg Q3W

N: number of participants; OVCA: ovarian carcinoma; PROC: platinum-resistant ovarian cancer; Q3W: every 3 weeks; RECIST: response evaluation criteria in solid tumors.
*Measurable disease per RECIST v1.1.

Participants

Key Inclusion Criteria:

- Advanced epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.
- PROC defined as disease recurrence <6 months after completion of a platinum-containing regimen.
  - Patients with primary platinum-refractory disease (defined as progression of disease prior to completion of 1st line platinum therapy or immediately following [≤ 3 months following last date of chemotherapy]) were ineligible.
- Patients will have received ≤3 prior lines for PROC.
- Baseline organ function: creatinine clearance ≥40mL/min (Cockcroft and Gault equation), albumin ≥3.0g/dL, hemoglobin ≥8g/dL, and platelet count ≥50,000/mm^3.

Key Exclusion Criteria:

- Prior treatment with a TIGIT inhibitor, PVRIG inhibitor, anti-PD-1/PD-L1/2, anti-CD96 antibody, anti-OX-40 antibody, anti-CD137 antibody, anti-LAG3, anti-TIM3, anti-CTLA4 antibody.
- History of another malignancy within 2 years prior to first study drug administration.

Treatment

- Study treatment up to 35 cycles (~24 months) until progressive disease, unacceptable toxicity, initiation of new anticancer therapy, withdrawal of consent, or death.

Safety and Response Evaluation

- Antitumor activity is evaluated per RECIST v1.1 with tumor assessments performed every 6 weeks for the first 6 cycles and every 12 weeks thereafter or at any time point where PD is suspected.
- Blood inflammatory markers (i.e., serum cytokines) including IFN-γ, IL-6 and IL-8 levels are tested on C1D1 pre-infusion, C1D2, C1D8, and C1D21 (i.e., C2D1 pre-dose).
- Safety is assessed throughout the study until 90 days post last dose of study treatment.

RESULTS

Participant Baseline Demographics and Disease Characteristics

- As of April 2024, **25 participants** were enrolled and treated. Baseline characteristics are summarized in **Table 1**.
- The majority of the participants had high-grade adenocarcinoma / serous adenocarcinoma. Papillary and clear cell carcinoma were present in 2 participants (each) and endometrioid and carcinosarcoma each in 1 participant.
- The patient population was heavily pretreated (median: 4 prior lines of therapy).
  - Majority of participants were treated with bevacizumab and PARP inhibitors prior to enrollment into the study.
  - More than a third of participants (n=9), were previously treated with antibody-drug conjugates (ADC) (n=6) and/or other investigational products (n=5). Two participants were treated with both.

Table 1. Baseline Demographic and Disease Characteristics

	COM701+COM902+pembro (N=25)
Age	
≤65 years, n (%)	15 (60)
Median (range)	63 (40, 77)
Race, n (%)	
White	23 (92)
ECOG at baseline, n (%)	
0 / 1 / 2	3 (12)/ 21 (84)/ 1 (4)
Time since diagnosis (months), median (range)	59 (13, 149)
Prior lines of therapy, median (range)	4 (1, 10)
Prior therapies, n (%)	
Chemotherapy	25 (100)
Bevacizumab	20 (80)
PARP inhibitors	17 (68)
Antibody-drug-conjugates / Investigational product*	9 (36)
Grade at study entry, n (%)	
Grade III / Grade IV / Missing	18 (72)/ 5 (20) / 2 (8)
Histology, n (%)	
Adenocarcinoma/ Serous adenocarcinoma/ Clear cell/ Papillary/ Endometrioid/ Carcinosarcoma	7 (28)/ 12 (48)/ 2 (8)/ 2 (8)/ 1 (4)/ 1 (4)
Primary tumor type, n (%)	
Ovarian/ Fallopian/ Peritoneum	21 (84)/ 3 (12)/ 1 (4)
Stage at study entry, n (%)	
IIA / IIIC / IV	1 (4)/ 5 (20)/ 19 (76)
BRCA Germline / Somatic, n (%)	
Negative, Indeterminate	19 (76)
Not done / Not done	6 (24)

*Mirvetuximab (n=4), NaPi2b (n=1), CDH6 (n=1), CDK2 inhibitor (n=1), CD47 inhibitor (n=2), Smac mimetic (n=1), LILRB2 MAB (n=1).
BRCA: breast cancer gene; ECOG: Eastern Cooperative Oncology Group; n: number of participants; PARP: poly-ADP ribose polymerase; pembro: pembrolizumab.

Participant Disposition and Exposure

- At data cut-off, 21 of the 25 enrolled participants (84%) had discontinued trial treatment: 1 participant due to an AE, 1 due to death, and 19 participants due to disease progression (**Table 2**).
- The trial is ongoing; 4 (16%) participants remain under treatment.

Table 2. Participant Disposition and Exposure Summary

Disposition	COM701+COM902+pembro N=25
Number of participants treated, n (%)	**25 (100)**
Ongoing in study treatment, n (%)	**4 (16)**
Discontinued study treatment, n (%)	**21 (84)**
Adverse event*	1 (5)
Death	1 (5)
Progressive disease per RECIST v1.1	16 (76)
Progressive disease based on clinical evaluation	3 (14)
Exposure	**COM701+COM902+pembro N=24#**
Time on treatment, median (range) weeks	10 (2, 37)
Number of cycles of trial drug, median (range)	4 (1, 13)

Note: The denominator for each reason is the number of participants who discontinued the study treatment.
*Adverse event: immune-related encephalopathy.
#Exposure characteristics are presented in the efficacy evaluable set (EES). N=24.
One participant was excluded from the EES as a pre-treatment biopsy completed prior to C1D1 (results coming back post-dosing) showed another primary malignancy. The participant remained on study and is included in the safety analysis.
EES: efficacy evaluable set; n: number of participants; pembro: pembrolizumab.

Safety

- Treatment-emergent adverse events (TEAEs) were reported in all 25 participants (100%) (**Table 3A**).
- Most TEAEs were mild to moderate in severity (≤ Grade 2).
- Grade ≥3 TEAEs were reported in 7 participants (28%) (**Table 3A**).
- One Grade 5 SAE of cardiac arrest was reported, assessed as not related to study treatment (**Table 3C**).
- One Grade 3 serious immune-related encephalopathy was reported (**Table 3C**):
  - The participant improved following treatment with steroids.
  - Treatment with all 3 study drugs was discontinued.

Table 3A. Safety Summary

Participants, n (%)	COM701+COM902+pembro (N=25) Any grade	Grade ≥3
Any TEAE	**25 (100)**	**7 (28)**
Any TRAE	19 (76)	3 (12)
Any Serious	**4 (16)**	**4 (16)**
Any Serious TRAE*	1 (4)	1 (4)
Leading to discontinuation*	**1 (4)**	**1 (4)**
Immune-related TEAEs	**12 (48)**	**2 (8)**

Note: Each participant is counted once but may have more than one TEAE.
*Participant developed a Grade 3 serious immune-related encephalopathy following 2 cycles of treatment and study treatment was discontinued. The event was assessed as probably related to pembrolizumab and possibly related to both COM701 and COM902.
AE: adverse event; n: number of participants; pembro: pembrolizumab; TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event.

Table 3B. TEAEs Reported in ≥3 Participants by Frequency and Severity

Participants, n (%) MedDRA Preferred Term	COM701+COM902+pembro (N=25) Any grade	Grade ≥3
TEAEs reported by ≥3 participants		
Fatigue	11 (44)	2 (8)
Diarrhoea	8 (32)	
Abdominal pain	6 (24)	1 (4)
Nausea	6 (24)	
Vomiting	5 (20)	
Decreased appetite	4 (16)	1 (4)
Depression	4 (16)	
Dyspnoea	4 (16)	
Pruritus	4 (16)	
Anaemia	3 (12)	1 (4)
COVID-19	3 (12)	
AST increased	3 (12)	
Arthralgia	3 (12)	
Headache	3 (12)	
Rash	3 (12)	
Rash maculo-papular	3 (12)	

Table 3C. Incidence of Grade ≥3 TEAEs

Participants, n (%) MedDRA Preferred Term	COM701+COM902+pembro (N=25) Grade ≥3	Serious
Any Grade ≥3 TEAE	**7 (28)**	**4 (16)**
Fatigue	2 (8)	
Pneumonia	2 (8)	1 (4)
Abdominal pain	1 (4)	
Decreased appetite	1 (4)	
Anaemia	1 (4)	
Urinary tract infection	1 (4)	
Hyperglycaemia	1 (4)	
Hypokalaemia	1 (4)	
Cardiac arrest*	1 (4)	1 (4)
INR increased	1 (4)	1 (4)
Hyponatraemia	1 (4)	
Immune related encephalopathy	1 (4)	1 (4)

*Fatal cardiac arrest, assessed as not related to study treatment.
Each participant is counted once per MedDRA Preferred term but may have more than one event occurrence.
AST: aspartate aminotransferase; n: number of participants; INR: international normalized ratio; pembro: pembrolizumab; TEAE: treatment-emergent adverse event.

Antitumor activity

- 24 of the 25 treated participants were evaluable for response.
- ORR (CR+PR) was 4/24 (17%) and DCR (BOR: CR+PR+SD) was 11/24 (46%) (**Table 4**).
- The clinical benefit rate (CBR: confirmed CR/PR or SD for >180 days) was 7/24 (29%) (**Table 4**).
- Among the 7 participants with CBR, 2 received prior treatment with ADC and 1 with Smac mimetic.
- Four participants (BOR of 1 CR, 1 PR, 2 SDs) continue treatment for >200 days (**Figure 3A**).
  - One of the 2 SDs (**Figure 3B**, Participant #3) presented with a best target lesion response reduction of 29.6% in the last tumor assessment.
- Reductions in CA-125 were observed in 3 of the SD participants, supporting the observed benefit in these participants (**Figure 3D**).

Table 4. Investigator-assessed Tumor Response (RECIST v1.1) (EES)

Parameter, n (%)	COM701+COM902+pembro (N=24)
ORR*	4 (17)
DCR	11 (46)
CBR	7 (29)
Best Overall Response	
CR	1 (4)
PR	3 (13)
SD	7 (29)
PD	13 (54)

*All CR and PR were confirmed
CR: complete response; CBR: clinical benefit rate; DCR: disease control rate; EES: efficacy evaluable set; n: number of participants; ORR: overall response rate; PD: progressive disease; pembro: pembrolizumab; PR: partial response; RECIST: response evaluation criteria in solid tumors; SD: stable disease.

Figure 3. Tumor Responses in Individual Participants (EES)

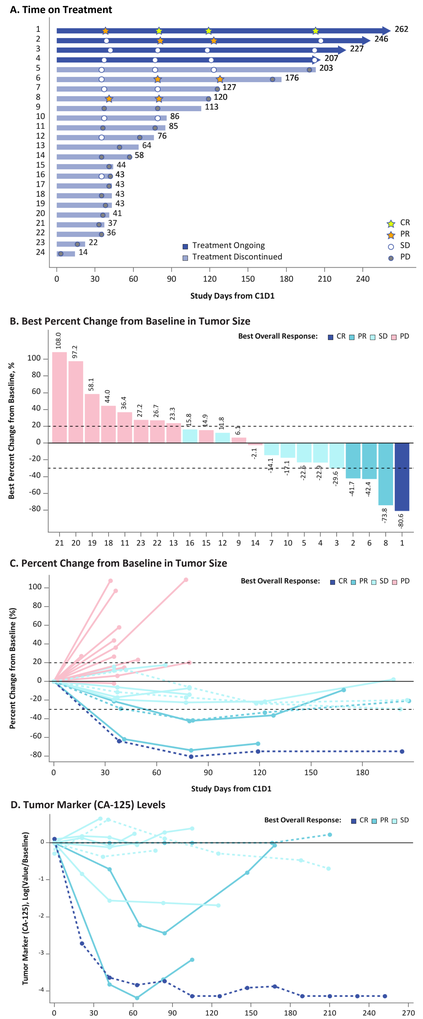
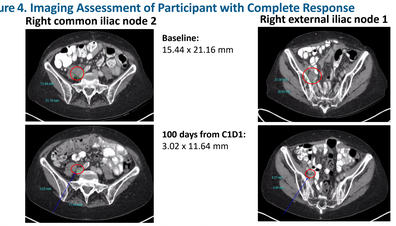


Fig 3A: To account for the phenomenon of pseudoprogression or delayed response with ICI, continuation of trial treatment beyond RECIST-defined progression could continue at the discretion of the investigator. Participants were to be assessed again within 6–8 weeks from initial progression to confirm PD.
Participants with confirmed PD but with clinical benefit as per investigator assessment could continue to receive trial treatment.
Fig 3B and Fig 3C: Change from baseline refers to the sum of diameters of target lesions according to RECIST 1.1. Two participants (#17 and #24) were not included, as target lesion response was assessed as inevaluable.
Fig 3C: A dashed line means the participant is ongoing.
Fig 3D: assessments on or after the end of treatment (EOT) were excluded. A dashed line means the participant is ongoing.
BOR: Best overall response; C1D1: cycle 1 day 1; CR: complete response; EES: efficacy evaluable set; PD: progressive disease; PR: partial response; SD: stable disease.

Clinical Vignette: Participant with a Complete Response (Figure 4)

- 69 y/o with baseline ECOG 1 and stage IV PROC (histology: grade III Serous adenocarcinoma).
- Initial Diagnosis: 2018; Stage IV diagnosed: 2022.
- Prior lines of treatment included combinations of carboplatin and Taxol / Nab-paclitaxel and bevacizumab maintenance.
- The last treatment line in a clinical trial with an investigational product (Smac mimetic) with the best response of SD.
- As of the data cut-off date, the participant was still on treatment (C13).

Figure 4. Imaging Assessment of Participant with Complete Response

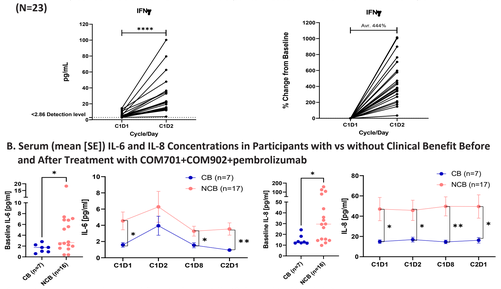


Images were provided by Dr Subha Raman, Florida Cancer Specialists.

Pharmacodynamic Activation of the Immune System

- Statistically significant peripheral IFN-γ induction was observed at C1D2, one day after treatment with COM701+COM902+pembrolizumab, compared with C1D1 (pre-treatment) (**Figure 5A**).
- Significantly lower serum concentrations of immunosuppressive cytokines IL-6 and IL-8 were observed among participants benefiting from treatment, both pre-treatment and during treatment (**Figure 5B**).

Figure 5. Pharmacodynamic Activation of the Immune System



Serum cytokines were measured using a pro-inflammatory human cytokine 10-plex assay kit and Meso Scale Discovery.
Clinical benefit is defined as a confirmed response of CR, PR or SD on treatment for ≥180 days or better.
C1D1: cycle 1 day 1; C1D2: cycle 1 day 2; C1D8: cycle 1 day 8; C2D1: cycle 2 day 1; CB: clinical benefit; NCB: no clinical benefit; SD: stable disease; SE: standard error.
* p<0.05 ; ** p<0.01 ; **** p<0.0001.

CONCLUSIONS

- This ongoing Phase I expansion cohort confirms previous findings showing encouraging efficacy and safety of triple blockade of the DNAM-1 axis in advanced heavily pre-treated PROC patients, where 36% of the population had been on other investigational agents prior to study entry.
- The safety and tolerability profile was generally consistent with approved anti-PD-(L)1s.
- Clinical benefit, with deep and durable responses was observed in patients with high-grade adenocarcinoma, in a patient with carcinosarcoma - historically nonresponsive to ICIs, and in patients previously exposed to ADCs and other investigational drugs.
  - ORR 17%, DCR 46%, CBR 29%, with 4 patients still on treatment at data cut.
- Robust pharmacodynamic activation of the immune system was observed on treatment.
- Lower concentrations of immunosuppressive cytokines prior to and on treatment were associated with a clinical benefit.
- The totality of the data from both cohorts supports the use of the triplet blockade of PVRIG, TIGIT, and PD-1 in ovarian cancer, with the potential to expand beyond PROC into earlier settings.

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