COM701 in combination with BMS-986207 (anti-TIGIT antibody) and nivolumab - preliminary results of safety, tolerability and pharmacokinetics in patients with advanced solid tumors (NCT04570839)

Ecaterina Elena Dumbrava[1], Manish Sharma[2], Gini F Fleming[3], Kyriakos P. Papadopoulos[4], Ryan Sullivan[5], Daniel A. Vaena[6], Amita Patnaik[4], Adam ElNaggar[6], Adeboye H. Adewoye[7], Robina Smith[7], Yan Yan[7], Pierre Ferre[7], Inbal Barbiro[7], Emerson A Lim[7], Drew W. Rasco[4].
[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]START-Midwest, Grand Rapids, MI; [3]University of Chicago Medicine, Chicago, IL; [4]START-San Antonio, San Antonio, TX; START, San Antonio, TX; [5]Massachusetts General Hospital, Boston, MA; [6]West Cancer Center and Research Institute., Memphis, TN; [7]Compugen USA Inc., South San Francisco, CA; [8]Columbia University-Herbert Irving Comprehensive Cancer Center, New York, NY.

Abstract Number 478

BACKGROUND

- COM701 is a novel 1st in-class immune checkpoint inhibitor that binds to poliovirus receptor related immunoglobulin domain containing (PVRIG) leading to enhanced activation of T and NK-cells
- COM701 monotherapy and in combination with nivolumab has a favorable safety profile, is well tolerated and demonstrates preliminary antitumor activity[1]
- There is an urgent medical need to develop treatment options for patients who are refractory to or relapse after treatment with anti-PD-(L)1 based regimens
- We hypothesized that by blocking the DNAM axis; a triplet combination consisting of COM701, nivolumab and BMS-986207 (an inhibitor of TIGIT) will have an acceptable safety/tolerability profile
- We present preliminary results on safety, tolerability, antitumor activity, pharmacokinetics, immunophenotyping and cytokine analyses

METHODS

- Using an accelerated titration and 3+3 study design we enrolled 13 patients (pts) with advanced solid tumors
- Doses of COM701 evaluated were 0.3, 1, 3, 10 or 20 [mg/kg IV Q4W]; in combination with fixed doses of nivolumab and BMS-986207 (both 480 mg IV Q4W)
- Dose-limiting toxicity was evaluated in the 1st 28 days in the 1st cycle of dose escalation
- Antitumor activity (per investigator) was evaluated per RECIST v1.1 with CT imaging every 8 weeks starting from the first dose during the first 6 cycles of the study and every 16 weeks thereafter (or at any time point progressive disease is suspected)
- Study treatment for 2yrs unless PD, toxicity, withdrawal of consent, PI discretion

ELIGIBILITY CRITERIA AND OBJECTIVES

Key Inclusion Criteria:

- Histologically confirmed locally advanced or metastatic solid malignancy
- Has exhausted all available standard treatment or is not a candidate for available standard therapy
- ECOG 0-1
- Measurable disease not required in dose escalation

Key Exclusion Criteria:

- History of inflammatory pneumonitis or interstitial lung disease
- History of immune-related toxicities on prior immunotherapy treatment leading to discontinuation

Key Primary Objectives:

- Safety and tolerability of COM701 with BMS-986207 and nivolumab (Triplet) in pts with advanced solid tumors
- The MTD and/or recommended dose for expansion of the Triplet
- PK profile of the Triplet

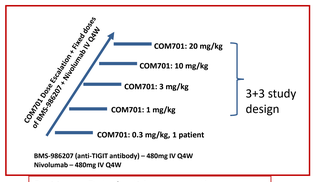
Secondary Objectives:

- Antitumor activity of the Triplet (Expansion cohorts only)

Exploratory Objectives:

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

STUDY DESIGN



- **Cohort Dose Expansion – COM701 at RDFE in combination with fixed doses of nivolumab and BMS-986207**
- **Mandatory biopsy pre and on-treatment**
- **All patients must have measurable disease**
- **Ovarian cancer (platinum resistant/refractory)**
- **Endometrial cancer (Relapsed/refractory)**
- **Basket cohort (high expression of PVRL2 in tumor)**
- **Head and neck squamous cell cancer; 2 cohorts: IO-naïve cohort and cohort with prior IO therapy**

Red box – Data for this presentation.

- CT imaging every 8 weeks starting from the first dose during the first 6 cycles of the study and every 16 weeks thereafter (or at any time point progressive disease is suspected).
- Study treatment for 2yrs unless PD, toxicity, withdrawal of consent, PI discretion –All pts.

RESULTS

- No DLTs were reported in any of the dose levels
- Maximum tolerated dose of COM701 in the combination was not reached
- Three pts (23%) with stable disease
- The most frequent TEAE was fatigue 7 pts (50%) [≤G2, 6 pts (43%), G3 1 pt (7%)]
- Serious adverse events [≥2 pts] were vomiting G3 and abdominal pain G3 with 2 pts each (14%) all assessed by the investigator as unrelated to study drugs
- Median (min, max) 10 (1-19) number of prior therapies
- Study treatment discontinuation reported in 2 pts (14%); at COM701 doses of 1 mg/kg [vomiting G3 and abdominal pain G3, serious, both unrelated to study drugs] and 10 mg/kg [Aspartate Aminotransferase increased G3, deemed possibly related to study drugs]
- Preliminary PK profiles of COM701 were generally dose proportional
- Peripheral pharmacodynamic analysis showed increased level of immune activation with study treatment

DEMOGRAPHICS

DLT evaluable population.

Characteristics	0.3 mg/kg* n (%)	1 mg/kg* n (%)	3 mg/kg* n (%)	10 mg/kg* n (%)	20 mg/kg* n (%)	All patients n (%)
Age, n(%)						
≤65 yrs	1 (100)	2 (67)	1 (33)	2 (67)	-	6 (46)
>65 yrs	-	1 (33)	2 (67)	1 (33)	3 (100)	7 (54)
Sex, n(%)						
F	1 (100)	1 (33)	2 (67)	1 (33)	1 (33)	6 (46)
M	-	2 (67)	1 (33)	2 (67)	2 (67)	7 (54)
ECOG (0, 1), n(%)						
0	-	2 (67)	2 (67)	1 (33)	-	5 (39)
1	1 (100)	1 (33)	1 (33)	2 (67)	3 (100)	8 (61)
Tumor type	Ovarian cancer.	CRC, Prostate cancer, Pancreatic cancer.	NSCLC, Melanoma, CRC.	Gastric cancer, CRC, Esophageal cancer.	Prostate cancer, Fallopian tube cancer, Melanoma.	CRC (3), Prostate cancer (2), Melanoma (2), Ovarian cancer/Fallopian tube cancer (2). One each: NSCLC, Pancreatic cancer, Esophageal cancer, Gastric cancer.

*Dose of COM701 IV Q4W
All pts received BMS-986207 + nivolumab [both 480 mg IV Q4W]

CRC – colorectal cancer, NSCLC – Non small cell lung cancer.

PATIENT DISPOSITION SUMMARY

DLT evaluable population. DATACUT 03SEP2021

	0.3 mg/kg* n (%)	1 mg/kg* n (%)	3 mg/kg* n (%)	10 mg/kg* n (%)	20 mg/kg* n (%)	All patients n (%)
Number of patient enrolled and treated - n(%)	1 (100)	3 (100)	3 (100)	3 (100)	3 (100)	13 (100)
Dose limiting toxicity - n(%)	-	-	-	-	-	-
Median (Min, Max) #Prior Therapies[1]	16 (16,16)	4 (4,13)	6 (1,19)	11 (10,12)	9 (1,12)	10 (1,19)
Prior Immune checkpoint inhibitor	1 (100)	-	2 (67)	-	1 (33)	4 (34)
Discontinued study treatment - n(%)	1 (100)	3 (100)	3 (100)	3 (100)	2 (67)	12 (92)
Reasons for study treatment discontinuation (n)						
• Progressive disease per RECIST v1.1	-	2 (67)	2 (67)	1 (33)	2 (67)	7 (58)
• Clinical PD	1 (100)	-	1 (33)	1 (33)	-	3 (25)
• Adverse event	-	1 (33)*	-	1 (33)**	-	2 (17)

[1]Prior therapies/regimens are systemic therapies and do not include radiation or surgery. *Dose of COM701 IV Q4W.

* A pt with pancreatic cancer and Grade 3 Vomiting and abdominal pain assessed by the investigator as related to disease not related to any of the study drugs.
** A pt with esophageal cancer and G1 AST increased assessed by the investigator as possibly related to study drugs. AST resolving from maximum G3, progressive disease suspected in a CT scan 4 wks earlier.

SUMMARY OF ADVERSE EVENTS

DATACUT 03SEP2021

Parameter	All Adverse Events n = 14 (%)
Any TEAE	13 (93)
No TEAE	1 (7)
≤G2	4 (29)
G3	7 (50)
G4	1 (7)
Grade 5	1 (7)

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

INCIDENCE OF TEAES IN ≥3 PATIENTS

Datacut 03SEP2021

PREFERRED TERM (PT)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)
ANY TEAE	4 (29)	7 (50)	1* (7)	1* (7)	13 (93)
FATIGUE	6 (43)	1 (7)	-	-	7 (50)
DECREASED APPETITE	4 (29)	-	-	-	4 (29)
ABDOMINAL PAIN	1 (7)	2 (14)	-	-	3 (21)
ASCITES	3 (21)	-	-	-	3 (21)
CONSTIPATION	3 (21)	-	-	-	3 (21)
NAUSEA	3 (21)	-	-	-	3 (21)
PYREXIA	3 (21)	-	-	-	3 (21)
VOMITING	2 (14)	1 (7)	-	-	3 (21)

Safety analysis set – patients who received ≥1 dose of any of the study drugs. Safety per CTCAE v5.0.
* A pt with pancreatic cancer and Grade 4 aspartate aminotransferase increased and G5 hepatic failure due to underlying liver metastasis with rapid progression. Assessed by the investigator as not related to any of the study drugs.

INCIDENCE OF SERIOUS ADVERSE EVENTS - ALL PATIENTS

DATACUT 03SEP2021

PREFERRED TERM (PT)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)
ANY SERIOUS	-	3 (21)	-	1 (7)	4 (28)
ABDOMINAL PAIN	-	2 (14)	-	-	2 (14)
VOMITING	1 (7)	1 (7)	-	-	2 (14)
ABDOMINAL DISTENSION	-	1 (7)	-	-	1 (7)
ASCITES	1 (7)	-	-	-	1 (7)
HEPATIC FAILURE*	-	-	-	1* (7)	1 (7)
LARGE INTESTINAL OBSTRUCTION	-	1 (7)	-	-	1 (7)
NAUSEA	1 (7)	-	-	-	1 (7)
PLEURAL EFFUSION		1 (7)			1 (7)

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. All SAEs assessed by PI as not related to any of the study drugs. Safety per CTCAE v5.0.

*A pt with advanced pancreatic cancer. Hepatic failure due to underlying liver metastasis with rapid progression. Assessed by the investigator as not related to any of the study drugs.

A pt with NSCLC [COM701 3 mg/kg IV Q4W] with reported Grade 3 Colitis starting 7 weeks after discontinuing study drugs and 16 days after initiating subsequent therapy with an investigational agent [antibody drug conjugate that targets beta-6.]. This SAE was assessed by the investigator as related to study drugs: COM701, nivolumab and BMS-986207.

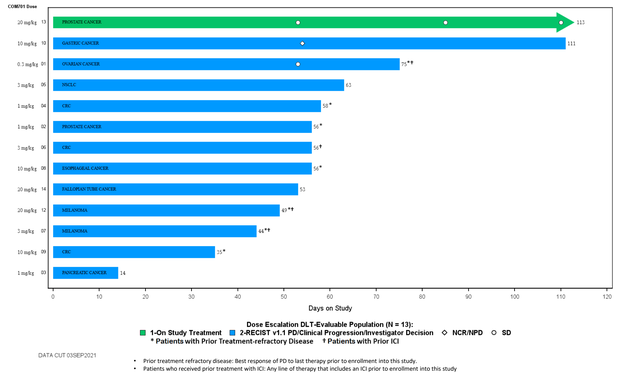
SUMMARY OF INVESTIGATOR ASSESSED RESPONSE (RECIST V1.1)

DATACUT 03SEP2021

Parameter	All patients n = 13 (%)
ORR (CR+PR)	-
Disease control rate (CR+PR+SD*)	3 (23)
Best response	
CR	-
PR	-
SD	2 (15)
Non-CR/Non-PD	1 (8)
PD	10 (77)

DLT evaluable population.
*Includes a patient with Non-Cr/Non-PD

SWIMMER PLOT

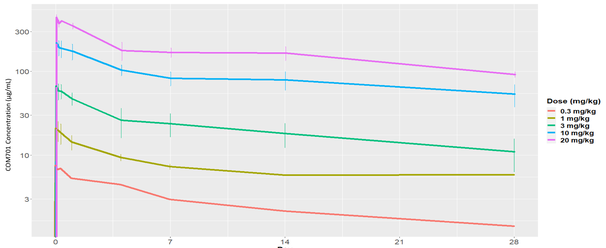


DATA CUT 03SEP2021

- Prior treatment refractory disease: Best response of PD to last therapy prior to enrollment into this study.
- Patients who received prior treatment with ICI: Any line of therapy that includes an ICI prior to enrollment into this study

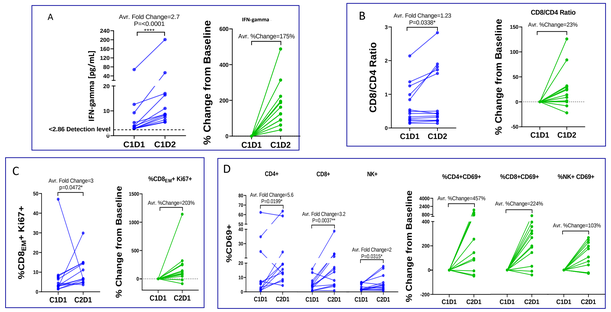
PHARMACOKINETICS

COM701 Pharmacokinetic profile following IV infusion on Cycle 1 Day 1



Dose-related increase of COM701 exposure, supportive of COM701 dosing every 4 weeks.

PHARMACODYNAMIC ACTIVATION OF THE IMMUNE SYSTEM WITH STUDY TREATMENT



Legend
Peripheral blood was collected from 14 patients at baseline (C1D1), one day post treatment (C1D2) and before the start of consecutive drug administration (IV, Q4W; every 4 weeks, i.e C2D1 reflects blood collected 4 weeks post treatment and prior to the second cycle of treatment) of COM701 at escalating doses (0.3-20 mg/kg), and fixed doses of Nivolumab (480 mg) and BMS-986207 (480 mg). Samples were assessed for serum IFNγ levels, measured using a pro-inflammatory human cytokine 10-plex assay kit and Meso Scale Discovery (MSD) **(A)** and by flow cytometry for CD4+ and CD8+ T cell ratio **(B)** proliferation (KI67+) of CD8+ effector memory (EM) CD45RA-CCR7- T cells **(C)** and expression of CD69 on T and NK cells **(D)**. Shown in blue graphs (left in each panel) are the raw values of each parameter, and in green (right in each panel) are the percent of change compared to baseline for the same parameter. Average magnitude of effect compared to baseline and relevant statistical comparison by paired Student's t-test are indicated in each panel.

Results

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, which was apparent through patients from all COM701 doses.

(A) Increase in serum IFNγ
(B) Increased CD8/CD4 ratio
(C) Increased proliferation of CD8+CD45RA-CCR7- effector memory (EM) T cells as reflected by increase in Ki67
(D) Increased activation of immune populations as reflected by increase in CD69+ expression on CD4 and CD8 T cells and NK cells

CONCLUSION

- The combination of COM701 with nivolumab and BMS-986207 is well tolerated and has a favorable safety and toxicity profile
- No dose limiting toxicity reported in any of the dose cohorts evaluated
- In a heavily pretreated and heterogenous pt population with median (min, max) 10 (1-19) prior therapies, stable disease reported in 3 pts (23%) during dose escalation
- COM701 20 mg/kg selected as the RDFE in combination with nivolumab and BMS-986207 (both 480 mg); all study drugs administered IV Q4W
- The PK profile of COM701 permits IV Q4W dosing in combination with nivolumab and BMS-986207 at the doses evaluated
- Pharmacodynamic changes suggest synergistic immune activation following triplet blockade, as compared to COM701 mono and combination results as well as published data
- The expansion cohorts are enrolling pts with platinum resistant ovarian cancer, endometrial cancer, basket cohort and head and neck squamous cell cancer

REFERENCE

1. 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).

ACKNOWLEDGEMENT

- We thank the patients for participating in this clinical trial and their families, the investigators and their staff at the clinical trial sites
- Study Sponsor Compugen Ltd in collaboration with Bristol Myers Squibb