COM701 in Combination With COM902 and Pembrolizumab Demonstrates Preliminary Antitumor Activity in Patients With MSS-CRC and Liver Metastases. NCT04354246.

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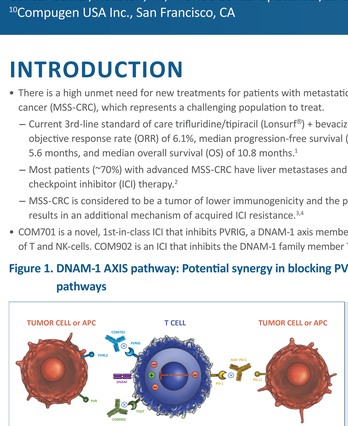
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INTRODUCTION

- There is a high unmet need for new treatments for patients with metastatic microsatellite stable colorectal cancer (MSS-CRC), which represents a challenging population to treat.
  - Current 3rd-line standard of care trifluridine/tipiracil (Lonsurf®)[1] + bevacizumab demonstrated an objective response rate (ORR) of 6.1%, median progression-free survival (mPFS) of 5.6 months, and median overall survival (OS) of 10.8 months.[1]
  - Most patients (~70%) with advanced MSS-CRC have liver metastases and do not respond well to immune checkpoint inhibitor (ICI) therapy.[2]
  - MSS-CRC is considered to be a tumor of lower immunogenicity and the presence of liver metastases results in an additional mechanism of acquired ICI resistance.[3,4]
- COM701 is a novel, 1st-in-class ICI that inhibits PVRIG, a DNAM-1 axis member (**Figure 1**), leading to activation of T and NK-cells. COM902 is an ICI that inhibits the DNAM-1 family member TIGIT.[5]

Figure 1. DNAM-1 AXIS pathway: Potential synergy in blocking PVRIG, TIGIT and PD-1 pathways



- PVRIG and TIGIT discovered by Compugen's discovery platform[6]
- 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 TME[7]
- PVRL2 broadly expressed in PD-L1 high and low tumors

APC, antigen presenting cell; TME, tumor microenvironment

- In a prior phase I clinical trial, the combination of COM701 + nivolumab demonstrated encouraging preliminary antitumor activity in participants with MSS-CRC (N=22), 77% of whom had liver metastases.[8]
  - Among participants with liver metastases, ORR was 12% (n=2/17), 2 participants with PR, and disease control rate (DCR) was 24% (4/17).[8]
- We hypothesized that a triplet combination of COM701 and COM902 plus pembrolizumab (anti-PD1),[9] would demonstrate antitumor activity by inhibiting the DNAM-1 axis in participants with metastatic MSS-CRC, and that this combination would have a favorable safety and tolerability profile.

OBJECTIVE

- We report preliminary results on safety, tolerability, translational pharmacodynamics, and anti-tumor activity of the triplet combination (COM701+COM902+pembrolizumab) in patients with MSS-CRC, including patients with liver metastases.

METHODS

Trial design

- Data are from the MSS-CRC triplet expansion cohort of an ongoing phase I, open-label, multi-center, dose-escalation and expansion trial (NCT04354246) that is being conducted in the US (**Figure 2**).

Figure 2. Trial Schema: Triplet combination expansion cohorts

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

Platinum resistant OVCA [PROC] Triplet Expansion (N ~40 total)*
• COM902 3mg/kg +COM701 15mg/kg +pembrolizumab 200 mg Q3W

OVCA, ovarian carcinoma; PROC, platinum-resistant ovarian cancer; Q3W, every 3 weeks.
*Measurable disease per RECIST v1.1.

- Tumors are assessed (per RECIST v1.1) every 6 weeks for the first 6 cycles and every 12 weeks thereafter, or upon suspicion of progressive disease.
- Trial treatment is administered for up to 35 cycles (~24 months), until disease progression, unacceptable toxicity, initiation of new anticancer therapy, withdrawal of consent, or death.
  - To account for the phenomenon of pseudoprogression or delayed response with ICI, participants may continue to receive trial treatment beyond RECIST-defined progression at the discretion of the investigator and be assessed again within 6–8 weeks from initial progression to confirm disease progression.
  - Participants with confirmed disease progression per RECIST but with clinical benefit as per investigator assessment may continue to receive the investigational products.
- Blood inflammatory markers (i.e., serum cytokines) including IFN-γ, IL-6 and IL-8 levels were tested on C1D1 Pre-infusion, C1D2, C1D8 and C2D1 pre-infusion.
- Participants were required to have a tumor biopsy taken prior to first dose and after the second dose (but prior to third dose).
- The trial is ongoing; we report results up to a data cut-off date of April 5, 2024.

Trial objectives

- **Key primary objective:** evaluate the safety and tolerability of the triplet combination (COM701+COM902+pembrolizumab), based on adverse event (AE) monitoring per NCI CTCAE v5.0.
- **Secondary objective:** characterize immunogenicity of COM902 in combination with COM701 and pembrolizumab.
- Prespecified exploratory objectives included:
  - Preliminary antitumor activity of the triplet combination (COM701+COM902+pembrolizumab).
  - Pharmacodynamic effects of trial drug(s) in the tumor and in blood, including changes in serum cytokine levels.

Participants

Key Inclusion Criteria:

- Age ≥ 18 years
- Stage IV histologically confirmed adenocarcinoma of the colon/rectum
- Measurable disease as defined by RECIST v1.1
- Documented MSS status by an FDA approved test (e.g. genomic testing or immunohistochemistry for mismatch repair proficient)
- Disease progression with ≤3 prior lines of treatment including fluoropyrimidines, irinotecan, and oxaliplatin
- No prior treatment with an anti-PD-1/PD-L1/2 agent, anti-CD96 antibody, anti-OX-40 antibody, anti-CD137 antibody, anti-LAG3 agent, anti-TIM3 agent, or anti-CTLA4 antibody.

Key Exclusion Criteria:

- Prior receipt of ICI, including anti-PVRIG or anti-TIGIT therapy.
- History of immune-related toxicities on prior immunotherapy treatment leading to discontinuation.

RESULTS

Participant baseline characteristics and disposition

- Baseline characteristics for the 20 participants with MSS-CRC are summarized in **Table 1**.
- Most (15/20 [75%]) participants had liver metastases at baseline
  - Demographics were similar between the entire cohort and subset of participants with liver metastases.
- All participants were previously treated with cytotoxic therapy, and none reported prior anti-PD-1/PDL1 therapy (as per eligibility criteria).

Table 1. Baseline demographic and disease characteristics

Characteristic, n (%)	COM701+COM902+pembrolizumab	
	Overall cohort (n=20)	Participants with liver metastases (n=15)[a]
Sex, male	9 (45)	7 (47)
Age		
≤65 years	15 (75)	11 (73)
Median [range]	58 [40–80]	58 [50–80]
Race, white	17 (85)	14/15 (93)
ECOG PS		
0	8 (40)	4 (27)
1	11 (55)	10 (67)
2[b]	1 (5)	1 (7)
Liver metastases	15 (75)	15 (100)
Median [range] months since diagnosis	32 [13–92]	32 [13–92]
Median [range] number of prior lines of therapy	3 [2–3]	3 [2–3]
KRAS mutation		
Positive/present	16 (80)	12 (80)
Negative	4 (20)	3 (20)

ECOG PS, Eastern Cooperative Oncology Group performance status; MSS-CRC, microsatellite stable colorectal cancer.
[a]Post data cut, 2 May 2024, 1 participant was reassessed as having non target liver lesion of uncertain etiology at baseline.
[b]One participant had ECOG score 1 at screening and ECOG score of 2 at C1D1.

- By data cut-off, 17 participants (85%) had discontinued trial treatment, all due to disease progression (**Table 2**).
- The trial is ongoing, and 3 participants remained on treatment at data cut-off.

Table 2. Disposition and exposure summary

	COM701+COM902+pembrolizumab	
	Overall cohort (n=20)	Participants with liver metastases (n=15)[a]
Participants enrolled and treated, n (%)	20 (100)	15 (100)
Cycles of trial drug, median [range] number	3 [1–14]	2 [1–14]
Time on treatment, median [range] weeks	7 [3–39]	6 [3–39]
Discontinued trial treatment, n (%)	17 (85)	13 (87)
Discontinued due to PD per RECIST v1.1	13 (76)	9 (69)
Discontinued due to PD per clinical evaluation	4 (24)	4 (31)

MSS-CRC, microsatellite stable colorectal cancer; PD, progressive disease.
Data cut-off: Apr 5, 2024.
[a]Post data cut, 2 May 2024, 1 participant was reassessed as having non target liver lesion of uncertain etiology at baseline.

Safety

- Treatment-emergent AEs (TEAEs) were reported in 17/20 (85%) participants (**Table 3**).
- The most frequently reported TEAEs overall were fatigue, anemia, myalgia, and nausea, which are commonly reported in cancer patients treated with pembrolizumab and other approved PD-[L]1 inhibitors.
- Most TEAEs were mild to moderate in severity (≤grade 2).
- There were no grade 4 or 5 (life threatening or fatal) TEAEs.
- Eight participants (40%) experienced ≥1 serious event.
- Immune-mediated events were reported in 3 participants; all were considered possibly related to trial drugs:
  - One participant had a serious grade 3 immune mediated encephalitis, which was the only serious possibly related event.
  - One participant had grade 1 hyperthyroidism followed by grade 2 hypothyroidism.
  - One experienced a grade 1 rash.

Table 3. Summary of TEAEs and serious TEAEs by preferred term and maximum grade

Participants, n (%)	COM701+COM902+pembrolizumab (N=20)		
	Any grade	Grade 1/2	Grade 3
Any TEAE	**17 (85)**	**8 (40)**	**9 (45)**
TEAEs reported by ≥3 (15%) participants			
Fatigue	5 (25)	5 (25)	–
Anemia	4 (20)	2 (10)	2 (10)
Myalgia	4 (20)	4 (20)	–
Nausea	4 (20)	3 (15)	1 (5)
Abdominal pain	3 (15)	3 (15)	–
Constipation	3 (15)	3 (15)	–
Cough	3 (15)	3 (15)	–
Decreased appetite	3 (15)	3 (15)	–
Diarrhea	3 (15)	2 (10)	1 (5)
Hematuria	3 (15)	1 (5)	2 (10)
Musculoskeletal pain	3 (15)	3 (15)	–
Peripheral edema	3 (15)	3 (15)	–
Urinary tract infection	3 (15)	2 (10)	1 (5)
Vomiting	3 (15)	2 (10)	1 (5)
Any serious TEAE	**8 (40)**	**2 (10)**	**6 (30)**
Serious TEAEs reported by ≥1 participant			
Pleural effusion	2 (10)	1 (5)	1 (5)
Ascites	1 (5)	1 (5)	–
Aspartate aminotransferase increased	1 (5)	–	1 (5)
Blood creatinine increased	1 (5)	1 (5)	–
Confusional state	1 (5)	–	1 (5)
Coronary artery disease	1 (5)	1 (5)	–
Dehydration	1 (5)	–	1 (5)
Immune-mediated encephalitis	1 (5)	–	1 (5)
Metastases to central nervous system	1 (5)	–	1 (5)
Nausea	1 (5)	–	1 (5)
Sepsis	1 (5)	–	1 (5)
Urinary tract infection	1 (5)	–	1 (5)
Vomiting	1 (5)	–	1 (5)

MSS-CRC, microsatellite stable colorectal cancer; TEAE, treatment-emergent adverse event.
Data cut-off: Apr 5, 2024.
TEAEs include any AEs with a start date on or after the first dose of trial drug.
Severity grading determined by NCI CTCAE v 5.0.

Anti-tumor activity

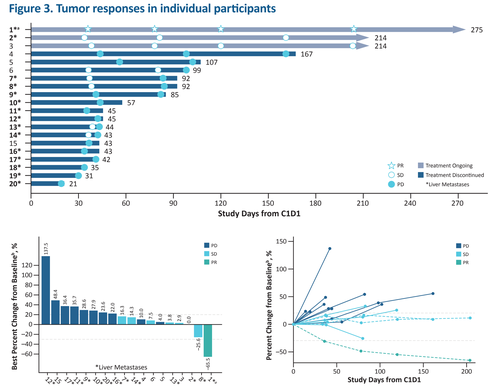
- In both the overall cohort of participants with MSS-CRC and the subset of participants with liver metastases, the DCR was 40% (N=8/20 and 6/15, respectively) (**Table 4; Figure 3**).
- One participant achieved a sustained partial response (see clinical vignette).

Table 4. Summary of investigator-assessed tumor response (per RECIST v1.1)

Parameter, n (%)	COM701+COM902+pembrolizumab	
	Overall cohort (n=20)	Participants with liver metastases (n=15)[f]
ORR (CR + PR)[a]	1 (5)	1 (7)
DCR (CR + PR + SD)[b]	8 (40)	6 (40)
Best overall response		
PR	1 (5)	1 (7)[c]
SD	7 (35)	5 (33)
PD[d]	12 (60)	9 (60)

CR, complete response; DCR, disease control rate; MSS-CRC, microsatellite stable colorectal cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Data cut-off: Apr 5, 2024.
[a]ORR is defined as confirmed CR or PR.
[b]DCR includes best overall response of CR, PR, or SD, with all responses included (including unconfirmed responses).
[c]Post data cut, 2 May 2024, participant with PR was reassessed as having non target liver lesion of uncertain etiology at baseline.
[d]Participants who clinically progressed prior to on trial tumor assessment were classified as having PD.

Figure 3. Tumor responses in individual participants

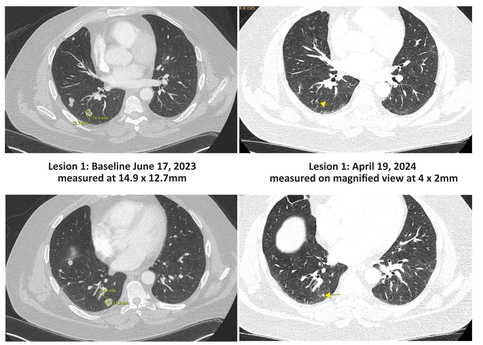


C1D1, trial drug cycle 1, day 1; PD, progressive disease; PR, partial response; SD, stable disease.
Data cut-off: Apr 5, 2024.
[a]Post data cut, 2 May 2024, participant with PR was reassessed as having non target liver lesion of uncertain etiology at baseline.
[b]Change from baseline refers to the sum of diameters of target lesions according to RECIST 1.1.
Two participants are not included as they had clinical PD prior to on-trial tumor assessment.
Dashed line: subject is ongoing.

Clinical vignette: Participant with a partial response

- 52 y/o male, ECOG I with stage IV rectal cancer (histology: adenocarcinoma).
  - Initial diagnosis: 2016
  - Diagnosed stage IV: 2021
  - MSS KRAS negative.
- At study entry the participant had target lesions in the lungs and a non target lesion in the liver which was reported as a hypo-dense lesion (post data cut, 2 May 2024, liver lesion was reassessed to be of uncertain etiology).
- 3 prior lines treatment, including multiple combinations of standard of care chemotherapy, panitumumab and bevacizumab.
  - The last regimen prior to trial entry was FOLFOX + bevacizumab (best response: progressive disease).
- By time of data cutoff participant was on treatment and completed cycle 14.

Figure 4. Imaging assessment for participant with partial response



Lesion 1: Baseline June 17, 2023 measured at 14.9 x 12.7mm

Lesion 1: April 19, 2024 measured on magnified view at 4 x 2mm

Lesion 2: Baseline June 17, 2023 measured at 14.4 x 14.3mm

Lesion 2: April 19, 2024 measured at 5 x 4mm

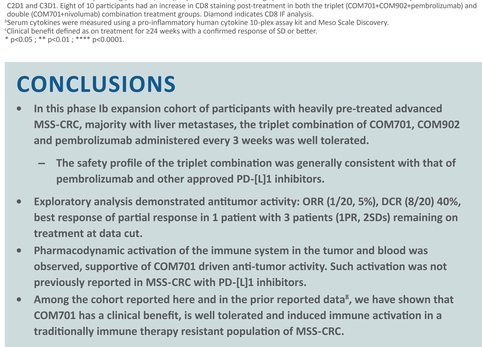
Most recent tumor assessment was performed shortly after data cut-off date and is therefore shown here.

Pharmacodynamic activation of the immune system

- Increased CD8+ T cell infiltration was observed in tumors after treatment (**Figure 5A**):
  - A median 2-fold increase in CD8+ T cell infiltration was observed after COM701+COM902+pembrolizumab, higher than with the doublet combination of COM701+nivolumab as reported from a previous trial.[8]
- Robust IFNγ induction was observed in patients' serum after treatment (**Figure 5B**).
- Significantly lower serum concentrations of immunosuppressive cytokines IL-6 and IL-8 were observed pre- and post-treatment among participants benefiting from treatment for more than 24 weeks (**Figure 5C**).

Figure 5. Pharmacodynamic activation of the immune system observed in tumor and serum after treatment in participants with MSS-CRC

A. CD8+ T cell infiltration is increased post-treatment in tumor biopsies obtained between Cycle 2 day 1 and Cycle 3 Day 1 from individual participants treated with COM701+COM902+pembrolizumab (n=10) or COM701+nivolumab (n=11)[a]



B. Serum IFNγ levels[b] in individual participants treated with COM701+COM902+pembrolizumab (N=20)

C. Mean (SE) serum IL-6 and IL-8 concentrations[b] among participants with (n=3) and without (n=17) clinical benefit[c] following treatment with COM701+COM902+pembrolizumab

C2D1, cycle 2 day 1; C3D1, cycle 3 day 1; CB, clinical benefit; NCB, no clinical benefit; SD, stable disease; SE, standard error.
[a]CD8 immunohistochemistry staining (clone C8/144B), expressed as the percentage positive cells out of total cells on tumor biopsies taken between C2D1 and C3D1. Eight of 10 participants had an increase in CD8 staining post-treatment in both the triplet (COM701+COM902+pembrolizumab) and doublet (COM701+nivolumab) combination treatment groups. Diamond indicates CDB if applicable.
[b]Serum cytokines were measured using a pro-inflammatory human cytokine 10-plex assay kit and Meso Scale Discovery.
[c]Clinical benefit defined as on treatment for ≥24 weeks with a confirmed response of SD or better.
* p<0.05 ; ** p<0.01 ; **** p<0.0001.

CONCLUSIONS

- In this phase Ib expansion cohort of participants with heavily pre-treated advanced MSS-CRC, majority with liver metastases, the triplet combination of COM701, COM902 and pembrolizumab administered every 3 weeks was well tolerated.
  - The safety profile of the triplet combination was generally consistent with that of pembrolizumab and other approved PD-[L]1 inhibitors.
- Exploratory analysis demonstrated antitumor activity: ORR (1/20, 5%), DCR (8/20) 40%, best response of partial response in 1 patient with 3 patients (1PR, 2SDs) remaining on treatment at data cut.
- Pharmacodynamic activation of the immune system in the tumor and blood was observed, supportive of COM701 driven anti-tumor activity. Such activation was not previously reported in MSS-CRC with PD-[L]1 inhibitors.
- Among the cohort reported here and in the prior reported data[8], we have shown that COM701 has a clinical benefit, is well tolerated and induced immune activation in a traditionally immune therapy resistant population of MSS-CRC.
  - This data suggestive of COM701-driven effects in this resistant population may warrant further evaluation of other COM701 drug combinations.

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ACKNOWLEDGMENTS

We are grateful to the trial participants and their families as well as the investigators and trial site personnel. This research was supported by Compugen Ltd. Medical writing support, under the direction of the authors, was provided by Erin Bekes, PhD, of ICON Plc. in accordance with Good Publication Practice guidelines, and funded by Compugen Ltd.

Presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO), May 31 to June 4, 2024, Chicago, IL, USA.