COM701 plus nivolumab demonstrates preliminary antitumor activity and immunemodulation of tumor microenvironment in patients with metastatic MSS-CRC and liver metastases.

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Introduction

- COM701 is a novel, 1st in-class, humanized IgG4 monoclonal antibody that binds with high affinity to PVRIG, blocking its interaction with its natural ligand PVRL2 expressed in tumor cells and antigen-presenting-cells
- We have reported antitumor and pharmacodynamic activity of COM701 monotherapy and in combination in several tumor types[1]
- We present preliminary clinical and translational results of the combination of COM701 + nivolumab in patients with microsatellite stable colorectal cancer [MSS-CRC]

1. Vaena D et al, COM701+nivolumab: Results of an ongoing P1 study of safety, tolerability & preliminaryantitumor activity in pts with advanced solid malig. J Clin Onco 39, 2021 (suppl 15; abst 2504).

MSS-CRC Patients in Urgent Need of New Treatment Options

MSS-CRC represents 95% of metastatic CRC with limited treatment options

SOC limited efficacy in refractory MSS-CRC[1,2]			
Standard of Care [3L+]	ORR	Median PFS	Median OS
Regorafenib/ TAS-102	~1-2%	~2 months	~6-7 months

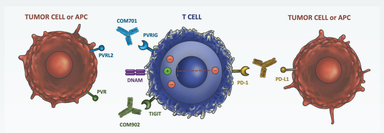
Majority of patients with 3L+ MSS-CRC patients have metastases to the liver

- Presence of liver metastases correlates with lack of response to PD-1/PD-L1 inhibition 0% ORR [n=54][3]
- Nivolumab + regorafenib showed 0% ORR [n=47][4]
- Balstilimab [anti-PD-1] + botensilimab [anti-CTLA-4] showed 0% ORR (n=17)[5]

1. Van Cutsem, 2012, ASCO 2. Mayer et al. N Eng J Med. 2015;372:1909-1919 3. Wang et al, JAMA 2021 4. Fakih et al , 2021, ASCO 5. Bullock AJ et al, 2022 ESMO GI

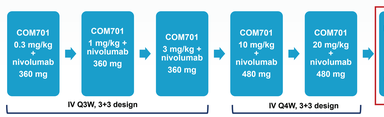
DNAM Axis Pathway

PVRIG may be the missing piece when current checkpoint inhibitors fail



- Two parallel and complementary inhibitory pathways (PVRIG & TIGIT) - discovered by Compugen's computational discovery platform
- Potential intersection between PVRIG/TIGIT and PD-1 pathway

Study Schema – Combination Dose Escalation and Expansion



CT imaging Q2 cycles – All pts
Study treatment for 2yrs unless PD, toxicity, withdrawal of consent, PI discretion – all pts

*Dose expansion Cohort (P1b) (mandatory biopsy pre and on-treatment), 20 patients/tumor type
All patients must have measurable disease

- MSS-CRC
- OVCA
- Breast
- Endometrial

In this study we report on 22 patients:

- Combination dose escalation - 2 pts [COM701 0.3,1mg/kg + nivolumab 360 mg both IV Q3W]
- Combination dose expansion - 20 pts cohort [COM701 20mg/kg + nivolumab 480mg both IV Q4W]

Key Eligibility Criteria and Study Objectives

Key Inclusion Criteria [MSS-CRC]:

- Histologically confirmed adenocarcinoma of the colon/rectum; Stage IV disease
- Prior PD-1/PD-L1 permissible
- Documented MSS status by an FDA approved test e.g. genomic testing, IHC for mismatch repair proficient
- Disease progression with ≥2 prior systemic therapies for metastatic CRC that must have included the following: fluoropyrimidines, irinotecan, and oxaliplatin
- Measurable disease

Key Exclusion Criteria:

- Active autoimmune disease requiring systemic treatment
- History of immune-related toxicities on prior immunotherapy treatment leading to discontinuation

Key Primary Objective:

- Safety and tolerability of profile of COM701 ± nivolumab

Secondary Objectives:

- Immunogenicity of COM701 ± nivolumab
- Antitumor activity of COM701 + nivolumab [combination expansion cohort]

Exploratory Objective:

- COM701-mediated pharmacodynamic effect in blood [COM701 ± nivolumab], immune-related changes [cytokines, immunophenotyping]

Demographics

Parameter	COM701 + Nivolumab n = 22 [%]
Sex, M	16/22 [73]
Age ≤ 65 yrs	17/22 [77]
Median prior therapies (range)	3 [2, 10]
Race [white]	18 [82]
Prior PD1/PD-L1	2 [9]
Liver metastases	17/22 [77]
ECOG (0, 1) 0	10 [45]
Prior regorafenib or TAS-102	7 [32]
KRAS mutation	
Mutated	13 [59]
Wildtype	6 [27]
Missing	3 [14]

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Patient Disposition Summary

Parameter	COM701 + Nivolumab n = 22 [%]
Number of cycles of study drug[s]; Median (Min, Max)	2.0 (1,16)
Discontinued study treatment	22 (100)
Reasons for study treatment discontinuation	
• PD per RECIST v1.1	17 (77)
• Physician decision clinical PD/loss of clin benefit	3 (14)
• Adverse event	2 (9)*

*Grade 3 blood bilirubin increased, assessed by the investigator as related to disease, not related to study drugs

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Incidence of Treatment Emergent Adverse Events in ≥15% of Patients

PREFERRED TERM (PT)	Grade 1/2 n [%]	Grade 3 n [%]	Grade 4 n [%]	Grade 5 n [%]	All Grades n [%]
Any TEAE	11 (50)	10 (46)	-	-	21 [96]
Anaemia	7 [32]	1 [5]	-	-	8 [36]
Hypoalbuminaemia	5 [23]	-	-	-	5 [23]
Fatigue	5 [23]	-	-	-	5 [23]
Ascites	3 [14]	1 [5]	-	-	4 [18]
Vomiting	3 [14]	1 [5]	-	-	4 [18]
Aspartate aminotransferase increased	4 [18]	-	-	-	4 [18]
Oedema peripheral	4 [18]	-	-	-	4 [18]

Safety analysis set – patients who received ≥1 dose of any of the study drugs, includes adverse events deemed related or not related to study drug[s] by the investigator. Safety per CTCAE v4.03.

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Incidence of All Serious Adverse Events*

PREFERRED TERM (PT)	Grade 1/2 n [%]	Grade 3 n [%]	Grade 4 n [%]	Grade 5 n [%]	All Grades n [%]
Any SAE	2 [9]	7 [32]	-	-	9 [41]
Abdominal distension	-	1 [4]	-	-	1 [4]
Abdominal pain	-	1 [4]	-	-	1 [4]
Small intestinal obstruction	-	1 [4]	-	-	1 [4]
Blood bilirubin increased	-	2 [9]	-	-	2 [9]
Troponin increased	1 [4]		-	-	1 [4]
Device related infection	-	1 [4]	-	-	1 [4]
Sepsis	-	1 [4]	-	-	1 [4]
Hyperbilirubinaemia	-	1 [4]	-	-	1 [4]
Hypokalaemia	-	1 [4]	-	-	1 [4]
Back pain	1 [4]	-	-	-	1 [4]
Cancer pain	-	1 [4]	-	-	1 [4]
Device dislocation	-	1 [4]	-	-	1 [4]
Dyspnoea	1 [4]	-	-	-	1 [4]

Safety analysis set – patients who received ≥1 dose of any of the study drugs. Safety per CTCAE v4.03.
*All SAEs were assessed by the investigator as related to disease, not related to study drugs

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Summary of Investigator Assessed Response [RECIST v1.1]

Parameter	COM701 + Nivolumab n = 22 (%)
ORR (CR+PR)	2 (9)
Disease control rate (CR+PR+SD)	6 (27)
Best response of CR, PR or SD (≥ 6 months)	2 (9)
Liver metastases PR SD Disease control rate (CR+PR+SD)	17 [77] 2 [12] 3 [18] 5 [29]
Best response	
CR	-
PR	2 (9)
SD	4 (18)
PD	13 (59)
Clinical PD/lack of clinical benefit	3 (13)

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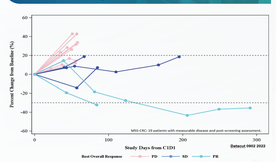
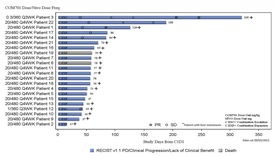
Waterfall Plot

Spider Plot



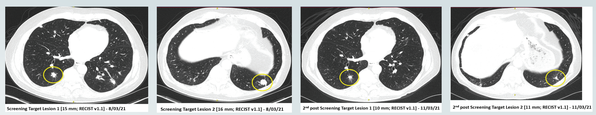
Swimmer Plot



Clinical Vignette – Patient with Partial Response

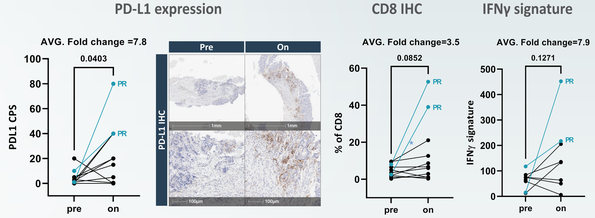
72yr old white male, MSS-CRC stage IV diagnosed 2015; metastases to liver. Had 2 prior lines in the metastatic setting FOLFOX [2016; best response CR]; FOLFIRI [2020; best response SD]. Mutations: positive TP53 AND APC, KRAS mutated. Tumor marker: CEA 36.38 U/mL [screening]; 8.16 U/mL on 11/03/21 [partial response]

At time of PD [12/2021] due to brain metastases – RECIST v1.1 [partial response] target lesion response maintained with 32% reduction in target lesions [below] and non-target lesions, liver metastases present but not measurable



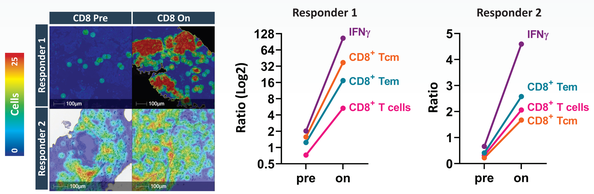
RECIST v1.1: Partial response with 32% reduction in target lesions

COM701+nivolumab combination induces TME immune modulation in patients with MSS-CRC



- 9/13 patients showed an increase in CPS PD-L1
- 7/11 patients showed an increase in % CD8
- 5/8 patients showed an increase in IFNγ signature

Extensive TME modulation in MSS-CRC patients partially responding to COM701+ nivolumab



- Responder 1 had immune desert TME pretreatment with an extensive T cell infiltration following treatment
- Responder 2 had an excluded TME pretreatment, becoming inflamed following treatment

Conclusion

Combination of COM701 + nivolumab is well tolerated with a favorable safety profile. Cumulative ORR 2/22 [9%] COM701+nivolumab; in heavily pretreated subject population [median 3 prior lines]. The ORR [9%] is higher than ORR [1-2%] reported for SOC- regorafenib or TAS-102. Exploratory analysis demonstrated encouraging preliminary antitumor activity in the patients with liver metastases – ORR 2/17 [12%], disease control rate 5/17 [29%]. Historically patients with liver metastases appear to be not responsive to ICI. Translational data demonstrated potent TME immune activation, most notable in responders and consistent with COM701 MOA. Such modulation is not typical of CPIs treatment in "cold" indications. Previous preclinical and clinical translational data have shown most potent immune activation with PVRIG&PD-1&TIGIT triple blockade, suggesting that adding TIGIT blocker could increase response rate. Phase 1 study evaluating COM701 + COM902 [TIGIT inhibitor] and a PD-1 inhibitor is planned. COM701 therapeutic activity in "cold" indications will be further demonstrated at ESMO/IO by data from dual (PVRIG&PD-1) and triple (PVRIG&PD-1&TIGIT) combination blockade in PROC patients