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

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Background: COM701 a novel, 1st in-class, humanized IgG4 monoclonal antibody 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 [1]. Anti-PD1/L1 therapies have limited to no activity in MSS-CRC. Therefore, novel ICI are urgently needed for the treatment of pts with MSS-CRC particularly pts with liver metastasis. We present preliminary clinical and translational results of the combination in pts with MSS-CRC.

Methods: This is a phase I clinical trial of COM701 and nivolumab (NCT03667716). Key objectives were safety/tolerability [primary], preliminary antitumor activity, immune-related changes [secondary/exploratory]. Key inclusion criteria: Age ≥18 yrs, histologically/cytologically confirmed advanced malignancy who have exhausted all available standard therapy or not a candidate for standard therapy, MSS-CRC determination per local testing. Pre- and on-treatment biopsies were obtained and analyzed by IHC for PDL1, CD8 expression and omics profiling.

Results: A total of 22 pts were enrolled: 2 pts combination dose-escalation [COM701 0.3,1mg/kg + nivolumab 360 mg] both IV Q3W and 20 pts dose-expansion cohort [COM701 20mg/kg + nivolumab 480mg IV Q4W]. Age ≤65 17/22, [77%], male 16/22 [73%], median [Min, Max] of 3 (2, 10) prior lines of therapy, 17/22 [77%] had liver metastases. Overall, ORR 9% (2/22 pts, PRs]; ORR 12% [2/17] in pts with liver metastases [1 PR, PFS 44 weeks; 1 PR, PFS 16 weeks due to brain metastasis, however, response of target and non-target lesions still maintained]; DCR (CR+PR+SD) 27% (6/22). No new safety findings are reported. In 13 paired biopsy samples, 9 demonstrated induction in PD-L1 expression (mean 16.3+/-7% PD-L1 CPS-score increase, $p<0.05$), suggesting TME immune-modulation following treatment. In pts with PR or SD >6months greater induction in PD-L1 expression was seen (49.7+/-14.9%). CD8 T-cell quantification was available in 12 paired biopsies with increase >1% in 8 pts (mean %CD8 increase of 9.1+/-4.4% , $p=0.08$), with substantial increases in responders (36.5% and 44.7% %CD8 increase). In responding pts IFNɣ signature up-regulation, increased T-cell clonality and specific clonal expansion, were demonstrated between baseline and on-treatment biopsies.

Conclusion: COM701 + nivolumab demonstrates preliminary antitumor activity in pts with heavily pretreated metastatic MSS-CRC with 12% ORR in pts with liver metastases [typically unresponsive to ICI]. TME immune modulation observed in the majority of pts, substantial in responders, suggests

unique potential of COM701 in less inflamed tumors such as MSS-CRC. The combination warrants further development. Data cut June 17, 2022.

Reference: Vaena, DA, Fleming, GF, Chmielowski B *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). Journal of Clinical Oncology 2021 39:15_suppl, 2504-2504.