A phase 1b/2 study of toripalimab and nadunolimab for the treatment of chemotherapy-refractory metastatic microsatellite stable (MSS) colorectal cancer (CRC)

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Abstract

Background: MSS CRC accounts for more than 90% of all metastatic CRC cases. Conventional immunotherapy with PD-1blockade and CTLA-4 blockade has shown minimal activity against MSS CRC with liver metastases. Single-cell profiling has revealed a profoundly immunosuppressive tumor microenvironment (TME) in MSS CRC, dominated by suppressive myeloid cells. Our group demonstrated the stromal-myeloid axis as the key driver of immunosuppression in liver metastases in preclinical mouse models. Targeting IL1RAP, the shared subunit of IL-1 and IL-33 receptor, disrupts the stromal-myeloid axis and restores sensitivity to immunotherapy.

Methods: This is an investigator-initiated phase 1b/2 trial to assess the safety and efficacy of nadunolimab (anti-IL1RAP, Cantargia AB) plus toripalimab (anti-PD1, Coherus) in patients with metastatic MSS CRC. Eligible patients must have biopsy-proven MSS CRC (non-MSI-H or MMRp), whose disease has progressed after chemotherapy including 5-FU, oxaliplatin and irinotecan. Patients will receive nadunolimab 5mg/kg and toripalimab 240mg every 3 weeks for up to 1 year or until disease progression. The primary endpoints are the occurrence of DLT (phase 1b lead-in of 3+3 patients) and the ORR (phase 2). Other endpoints include DCR, PFS, OS and duration of responses. The operating characteristics for 21 patients will test a null hypothesis of poor ORR of 5% or less versus an alternative hypothesis of a promising ORR of 20% or more at a 10% one-sided significance level and 80% power. Patients will undergo core needle biopsy and serial blood collection before and during treatment. For exploratory analyses, we will conduct comprehensive genomic, transcriptomic, proteomic, and digital pathology analyses of biopsies and blood samples to characterize the dynamic immune responses to IL1RAP blockade, identify biomarkers of responses, and define the mechanisms of resistance.

As of January 12th, 2026, two patients (10%) have been enrolled as of January 12th, 2026.

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Background & Scientific Rationale

Anti-PD(L)-1 agents have shown no significant monotherapy activity against MSS CRC [1]. Patients with MSS CRC have few therapeutic options beyond chemotherapy, and all salvage regimens yield less than 10% response rates and significant toxicities [2,3]. Despite resistance to PD-(L)-1 blockade, T cell infiltration in MSS CRC is strongly correlated with improved disease outcomes, underscoring the anti-tumor potential of T cells [4]. Analyses of immune and stromal cells from MSS CRC liver metastases revealed marked enrichment of suppressive myeloid cells and cancer-associated fibroblasts (CAF) in the tumors (Fig 1A). Further analyses of the single-cell libraries of CRC liver metastases revealed gene expression and downstream signaling of IL-1 and IL-33 in these cells (data not shown). Both IL-1 and IL-33 signaling are mediated by receptor complexes containing IL1RAP. In the AKPS (loss of Apc, Tp53 and Smad4 and Kras G12D mutation) mouse model, IL1RAP blockade in combination with anti-PD-1 demonstrated robust anti-tumor effects in liver metastases (Fig. 1B). IL1RAP blockade reduces tumor-infiltrating eosinophils and reprograms immunosuppressive macrophages and enhances CD8+ T cell expansion and cytotoxicity (Fig. 1C).

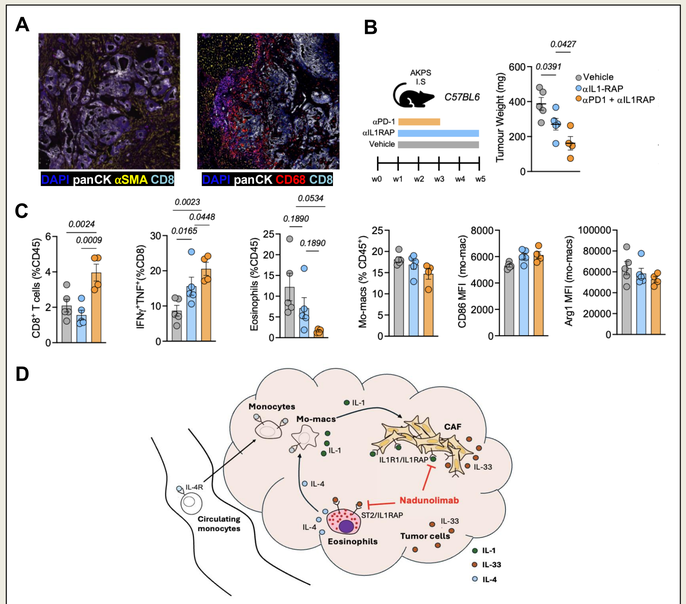
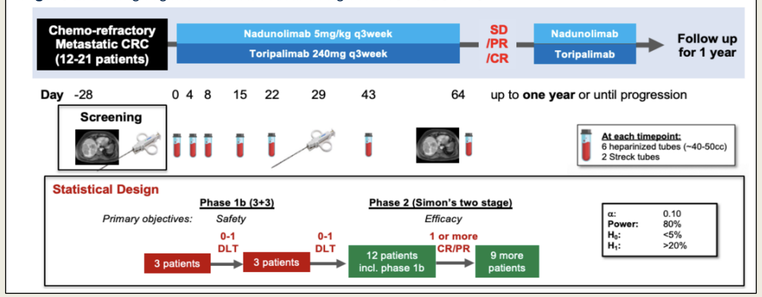


Figure 1. A. Fibroblasts and macrophages in human MSS CRC liver metastases (IF: panCK – tumor, aSMA – fibroblasts, CD68 – macrophages).B. IL1RAP and PD-1 blockade reduce tumor burden in liver metastases. C. Changes in tumor-infiltrating CD8+ T cells and myeloid cells in response to combination anti-PD1 and anti-IL1RAP. D. Mechanisms of action by IL1RAP blockade (schematic illustration, data on IL1-RAP not published).

Methods & Trial Design

Patients with chemotherapy-refractory metastatic MSS CRC will be enrolled. Subjects will receive toripalimab (240 mg) and nadunolimab (5 mg/kg) every 3 weeks for up to 1 year or until progression (Figure 2). Subjects enrolled will undergo core needle biopsy during screening, and 4 weeks after receipt of first treatment and repeat imaging on Day 64 ± 9 days. There will be a Phase 1b trial with 3+3 run-in subjects, in which first 3 subjects will be enrolled, and the first cycle (21 days) constitutes the DLT window. If there are 2 or more subjects experiencing a DLT, the trial will be halted and discussed with the Data and Safety Monitoring Committee (DSMC). The 21-subject cohort will follow a two-stage minimax design, with 12 subjects in Stage 1 and 9 subjects in Stage 2. Based on the clinical signal in the current cohort and new pre-clinical findings, we intend to add additional cohorts testing different immunotherapy combinations in the same patient population with the same endpoints and statistic method in the future.

Figure 2. Dosing regimen and statistical design for NCT07281716



Trial Objectives

Primary Objective

Phase 1b: Safety and tolerability of nadunolimab and toripalimab
Phase 2: Efficacy of nadunolimab and toripalimab in MSS CRC, by objective response rate (ORR) achieved.

Secondary Objectives

Assess toxicity of combined treatment of nadunolimab/toripalimab.
Assess efficacy of the combination immunotherapy with the following endpoints: Progression-free survival (PFS); Overall survival (OS); Disease control rate (DCR); Duration of response (DoR).

Exploratory Objectives

Analyze tumor biopsies and peripheral blood samples using histologic, immunologic, genetic, and transcriptomic characterization in bulk and single cell level as well as spectral flow analysis of PBMCs, seromic analysis (ELISA and/or O-link technologies).

Key Inclusion & Exclusion Criteria

Inclusion Criteria

- Biopsy-proven MSS CRC (non-MSI-H or MMRp) with progression after standard chemotherapy, and/or anti-VEGF or anti-EGFR antibodies.
- At least 1 measurable target lesion at baseline ≥ 10mm.
- Age ≥ 18 years.
- ECOG Performance Status 0-1
- Adequate organ and marrow function.

Exclusion Criteria:

- Received chemo or other investigational agent 14 days prior to trial.
- Active infection, symptomatic congestive heart failure, unstable angina.
- Major surgery within 4 weeks prior to 1st treatment dose.
- Patients who discontinued prior ICIs due to irAE
- Diagnosis of immunodeficiency; receiving systemic steroid or immunosuppressive therapy within 7 days prior to the first trial treatment.
- Active autoimmune disease requiring systemic treatment in past year.
- HIV+ with detectable viral load, or with <200 CD4+ T cells/microliter.
- Known active Hepatitis B or active Hepatitis C
- History of allogeneic hematopoietic cell transplantation or solid organ transplantation.
- Receipt of live vaccine or TNF-alpha inhibitors within 28 days of trial
- Documented allergic or hypersensitivity response to protein therapeutics
- History of ILD or pneumonitis due to prior immunotherapy.

Conclusions

Our preclinical studies and analysis of human CRC tumors suggests that IL1RAP blockade can work synergistically with anti-PD-1 therapy to disrupt the immunosuppressive stromal-myeloid access and induce potent anti-tumor immunity. We have initiated a phase 1b/2 study of toripalimab and nadunolimab to study the efficacy and effects of IL1RAP blockade in combination with anti-PD1 therapy in humans with progressing, metastatic, chemotherapy refractory MSS CRC.

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