

Leronlimab in combination with trifluridine/tipiracil plus bevacizumab for patients with metastatic colorectal cancer (mCRC): the phase 2 CLOVER study

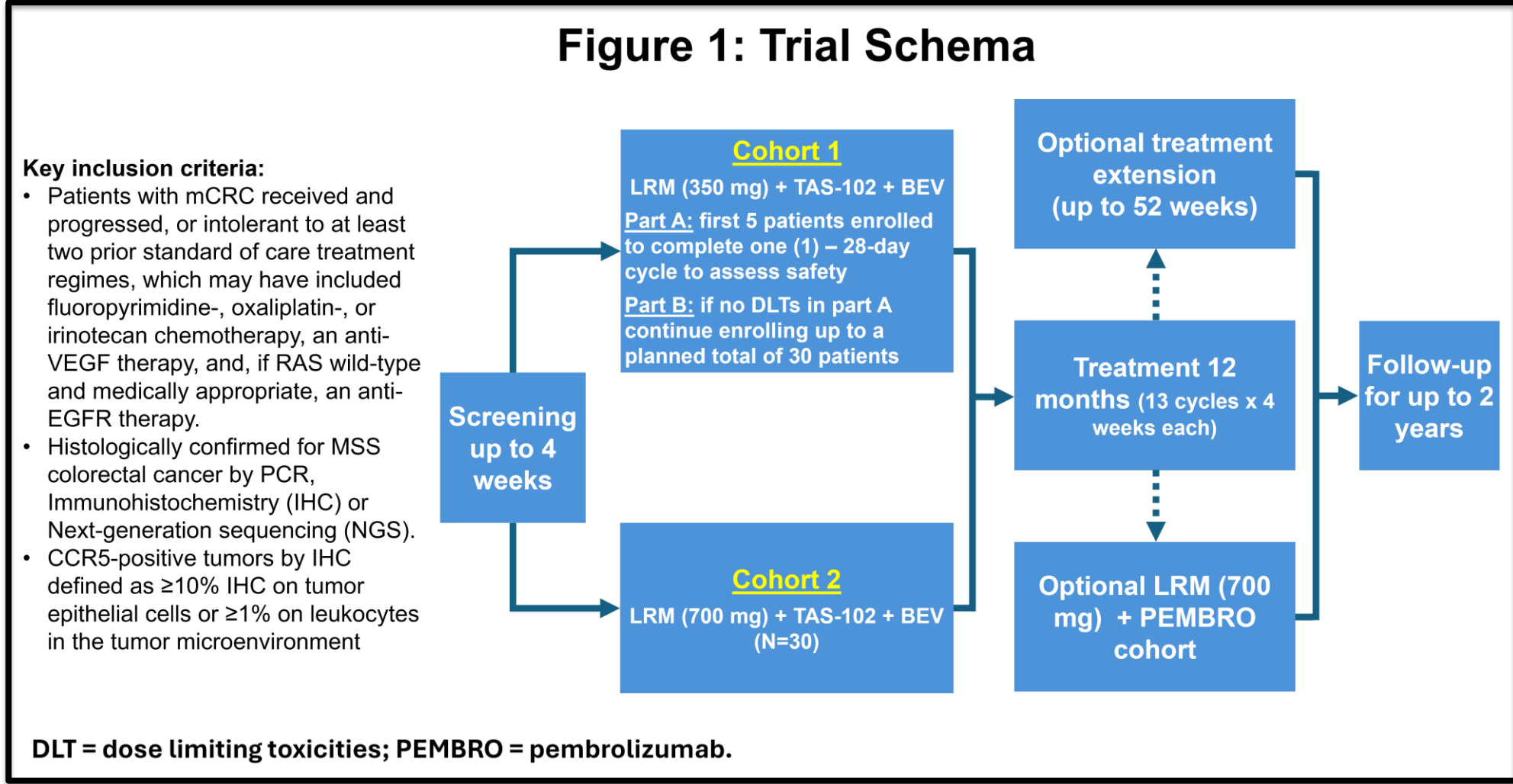
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INTRODUCTION

- The open-label phase-2 CLOVER (CCR5-targeting Antibody with Oral chemotherapy and VEGF-inhibitor Enriched Regimen) study evaluates the efficacy and safety of leronlimab (LRM) in combination with trifluridine/tipiracil (TAS-102) + bevacizumab (BEV) in patients with mismatch repair-proficient (pMMR) / microsatellite stable (MSS) metastatic colorectal cancer (mCRC) (NCT06699836).
- Leronlimab, is a humanized IgG4k monoclonal antibody (mAb) to C-C Chemokine Receptor type 5 (CCR5) that is in development to treat indications including mCRC, mTNBC, and various other oncological conditions.
- CCR5 is overexpressed in CRC primary tumors and in liver and lung metastases^{1,2} with pre-clinical models demonstrating that inhibition of CCR5 delays tumor growth and metastasis.^{3,4} In a systematic review and meta-analysis including 56 studies involving 3735 evaluable patients with mCRC, increasing circulating tumor DNA (ctDNA) levels during systemic therapy were strongly associated with decreased PFS and OS.⁵ In a further study in first-line patients with mCRC undergoing systemic anti-cancer therapy, clearance of ctDNA was shown to be an early indicator of benefit.⁶
- The phase 3 SUNLIGHT study in patients with refractory mCRC randomized patients to either TAS-102+BEV (n=246) or TAS-102 alone (n=246). The majority of patients in the SUNLIGHT study (97.4%; 479/492) had previously received ≤2 prior lines of therapy in the metastatic setting.⁷ For patients receiving TAS-102+BEV the objective response rate (ORR) was reported to be 6.1% (95% CI, 3.5 to 9.9).⁷
- A real-world study of TAS-102+BEV in 92 patients undergoing late-line treatment of mCRC reported an ORR of 3.2% among patients who received TAS-102+BEV treatment either bi-weekly or every 4 weeks.⁸

MATERIALS AND METHODS

- The CLOVER study (target enrollment n=60) enrolled adult patients with CCR5-positive metastatic colorectal cancer (Figure 1).



- Leronlimab is administered weekly at 350 mg (Cohort 1) or 700 mg (Cohort 2) subcutaneously, with TAS-102+BEV at standard doses, with Cohort 2 initiated after no leronlimab dose-limiting toxicities (DLTs) observed in the first 5 patients allocated to Cohort 1.
- The primary endpoint of the study is the objective response rate (ORR) per RECIST v1.1 criteria in the modified ITT population (mITT) defined as all patients with measurable disease at baseline who have received at least one dose of leronlimab. ORR is reported by blinded independent central review (BICR).
- ORR as reported by the study investigators is included as a secondary study endpoint.
- Other evaluations includes safety, ctDNA kinetics, and PD-L1 expression on circulating tumor cells (CTCs) and cancer associated macrophage-like cells (CAMLs).
- ctDNA was analysed using a clinically validated, personalized, tumor-informed 16-plex PCR-NGS assay (Signatera™, Natera, Inc.).

RESULTS

- Overall, 65 patients were enrolled and received at least one dose of leronlimab (ITT population) across 7 US sites between June 2025 and May 2026. The mITT population includes 64 patients.
- Baseline patient disease characteristics are summarized in Table 1.
 - Overall, the median age of the enrolled patients enrolled was 57 years (range 31–79 years).
 - The majority of patients were female (44/65, 67.7%).
 - Among all enrolled patients, 55.4% (36/65) had a primary diagnosis of colon cancer.
 - The majority of patients 70.8% (46/65) were diagnosed with liver metastasis.
 - Most patients (52.3%, 34/65) had received ≥3 lines of therapy in the metastatic setting.

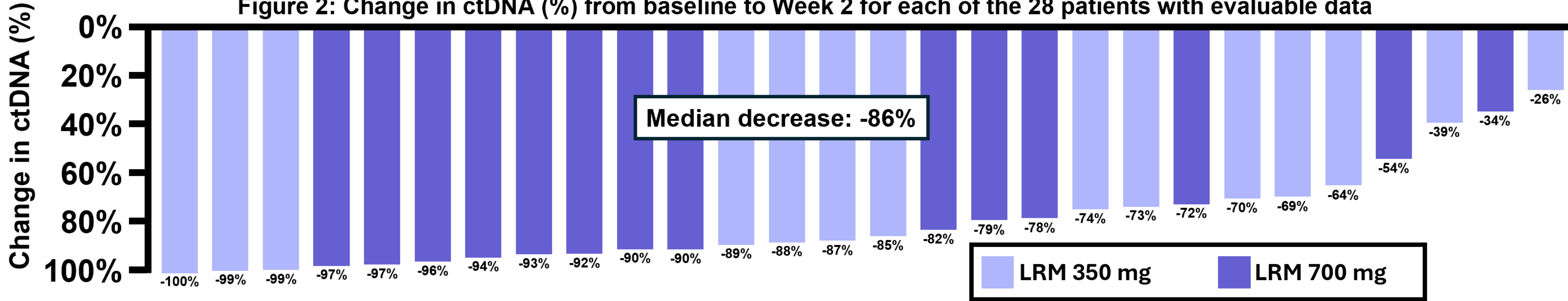
Table 1: Baseline characteristics

Parameter	Leronlimab 350 mg (N=33)	Leronlimab 700 mg (N=32)	Total (N=65)
Primary diagnosis, n (%)			
Colon	19 (57.6)	17 (53.1)	36 (55.4)
Rectal	11 (33.3)	14 (43.8)	25 (38.5)
Colon/rectal	3 (9.1)	1 (3.1)	4 (6.2)
Presence of liver metastasis, n (%)	24 (72.7)	22 (68.8)	46 (70.8)
Tumor tissue CCR5 positive, n (%)*	33 (100%)	32 (100%)	65 (100%)
Prior lines of therapy in the metastatic setting, n (%)			
≤2	16 (48.5)	15 (46.9)	31 (47.7)
≥3	17 (51.5)	17 (53.1)	34 (52.3)
Prior BEV experience, n (%)	31 (93.9)	25 (78.1)	56 (86.2)
Median (range) duration of disease – weeks	121.1 (42.4–354.9)	135.8 (56.4–594.9)	124.9 (42.4–594.9)

*CCR5 tumor positivity was a requirement for enrollment

- No DLTs were observed in the first 5 patients allocated 350 mg of leronlimab in Cohort 1, Part A, allowing the study to enroll further patients into Cohort 1, Part B (leronlimab 350 mg) and Cohort 2 (leronlimab 700 mg).
- To date 4/64 (6.3%; mITT population) ORR was reported by the BICR. An additional 7 investigator-reported partial responses are currently being assessed.
- Three patients discontinued study treatment for curative-intent surgery (1 with PR and 2 with SD) all included in the denominator to assess ORR.
- No leronlimab-related SAEs have been reported, and no patient has discontinued treatment or had dosing adjusted due to ≥ Grade 2 leronlimab-related adverse events.
- Figure 2 presents data for the decline in ctDNA at Week 2 for patients with evaluable data (both 350 mg and 700 mg doses combined), showing a median -86% decline in ctDNA by Week 2 (range -100% to -26%).
- Figure 3 presents data for the decline in ctDNA the best molecular response (defined as the largest ctDNA decline within 4 weeks) for patients with evaluable data at Week 4 from the CLOVER study (n=12) compared to patients receiving TAS-102 alone (n=30) or TAS-102+BEV (n=75) historical control data from a proprietary real-world multi-modal data platform (Natera, Inc.).

Figure 2: Change in ctDNA (%) from baseline to Week 2 for each of the 28 patients with evaluable data



DISCUSSION

- All evaluable patients treated with leronlimab in combination with TAS-102+BEV demonstrated a decrease in ctDNA by Week 2, with the majority experiencing substantial declines (Figure 2).
- For the patients with evaluable data at Week 4, decreases in ctDNA in the CLOVER study were significantly greater than historical data among patients treated with TAS-102+BEV (Figure 3; p=0.0005).
- Currently the ORR by the BICR is 6.3% (4/64) in the protocol defined mITT population. This rate is encouraging considering that most patients previously received ≥3 prior lines of therapy in the metastatic setting with the majority of patients having baseline liver metastases. In the SUNLIGHT study patients randomized to TAS-102+BEV achieved an ORR of 6.1% in a population of patients with mCRC, 97.4% of whom had previously received ≤2 prior lines of therapy in the metastatic setting.
- Mechanistically, CCR5 inhibition by leronlimab may reduce tumor cell migration, invasion, and metastatic dissemination, potentially contributing to reductions in circulating tumor DNA.
- The combination of leronlimab (CCR5 blockade), TAS-102 (cytotoxic chemotherapy), and BEV (anti-angiogenic therapy) may provide complementary mechanisms of antitumor activity enabling a rapid biologic response seen in the observed early decline in ctDNA.
- Patients are now starting to be consented to rolling over to the optional leronlimab plus pembrolizumab cohort (see Figure 1).

CONCLUSIONS

- Leronlimab plus TAS-102+BEV has been well tolerated with no leronlimab-related DLTs. Despite the CLOVER study enrolling a heavily pre-treated population, rapid declines in ctDNA were observed suggesting potential molecular activity of leronlimab-based therapy.
- Early results are encouraging and support further evaluation of this combination in patients with MSS mCRC.

Figure 3: change in ctDNA levels (measured in MTM/mL) from baseline to Week 4, observed in CLOVER study compared to control data from real world database*

