American Association for Cancer Research (AACR) Annual Meeting, April 17–22, 2026. Poster number 6466

Contact email: kasi@coh.org

Leronlimab in combination with trifluridine/tipiracil (TAS-102) plus bevacizumab for patients with refractory metastatic colorectal cancer (mCRC): The phase 2 CLOVER study

Pashtoon M. Kasi[1], Ari D. Baron[2], Arvind Chaudhry[3], Laura Tenner[4], Namrata Vijayvergia[5], Michael F. Driscoll[6], Daniel L. Adams[7], Alexis B. Duffy[7], Hallgeir Rui[8], Richard G. Pestell[9,10], Patrick Vittner[11], Joseph Meidling[11], and Jacob P. Lalezari[11]

[1]Department of Medical Oncology & Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, [2]Division of Hematology Oncology, Sutter/California Pacific Medical Center, San Francisco, CA, [3]Summit Cancer Centers, Spokane, WA, [4]University of Nebraska Medical Center, Fred and Pamela Buffett Cancer Center, Omaha, NE, [5]Fox Chase Cancer Center, Philadelphia, PA, [6]Norton Healthcare, Louisville, KY, [7]Creatv MicroTech, Inc., Monmouth Junction, NJ, [8]Thomas Jefferson University, Philadelphia, PA, [9]Pennsylvania Cancer and Regenerative Medicine Research Center, Wynnewood, PA, [10]The Wistar Cancer Center, Philadelphia, PA,[11]CytoDyn, Inc., Vancouver, WA.

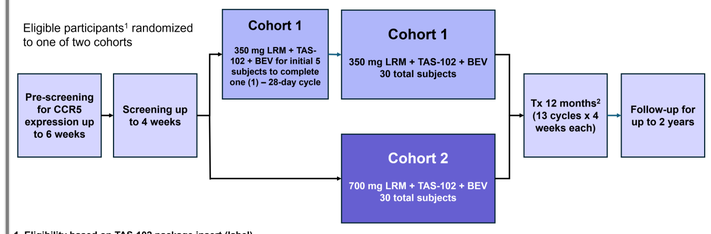
INTRODUCTION

- The phase 3 SUNLIGHT trial in patients with refractory mCRC showed that median overall survival (mOS) was 10.8 months among patients receiving TAS-102 plus BEV versus 7.5 months among patients receiving TAS-102 alone (hazard ratio for death, 0.61; 95% confidence interval [CI], 0.49 to 0.77; P<0.001). In the same study the median progression-free survival (mPFS) was 5.6 months (TAS-102 plus BEV) versus 2.4 months (TAS-102 alone).[1] It was also reported that the objective response rate (ORR) was 6.3% (TAS-102 plus BEV) versus 0.9% (TAS-102 alone).[2]
- A recent US analysis of real-world data showed that mOS, after propensity score matching, among 472 patients receiving TAS-102 plus BEV was 8.9 months compared to 5.8 months among 472 patients receiving TAS-102 alone TPI (P<0.001).[3]
- C-C motif chemokine receptor 5 (CCR5) is overexpressed in CRC primary tumors and in liver and lung metastases[4,5] with pre-clinical models demonstrating that inhibition of CCR5 delays tumor growth, and metastasis.[6,7] Higher CCR5 expression is associated with higher tumor mutational burden; higher in mismatch repair deficient/microsatellite instability-high (dMMR/MSI-high tumors) than mismatch repair proficient/microsatellite stable (pMMR/MSS); higher PD-L1 levels; and higher immune cell infiltration in the tumor microenvironment of pMMR/MSS tumors.[5] In human clinical specimens CCR5 expression is associated with prognosis. Compared to CRC patients classified as CCR5-low, patients classified as CCR5-high were shown to have a significantly poorer prognosis.[8]
- In a systematic review and meta-analysis including 56 studies involving 3735 evaluable patients with mCRC, increases from baseline in circulating tumor DNA (ctDNA) during systemic therapy was strongly associated with decreased PFS and OS.[9] In a further study in first-line mCRC patients undergoing systemic anti-cancer therapy, clearance of ctDNA was shown to be an early indicator of benefit.[10]
- The open-label phase-2 CLOVER (CCR5-targeting Antibody with Oral chemotherapy and VEGF-inhibitor Enriched Regimen) trial evaluates the efficacy and safety of leronlimab (LRM) in combination with TAS-102 plus BEV (NCT06699836) in patients with pMMR/MSS metastatic colorectal cancer.

MATERIALS AND METHODS

- The CLOVER study will enroll up to 60 patients with refractory mCRC eligible for TAS-102 plus BEV and with CCR5-positive tumors by IHC (Figure 1).

Figure 1: CLOVER Trial – Study Design



1. Eligibility based on TAS-102 package insert (label).
2. Participants still on study treatment at the time of completion may continue to receive study treatment if they are experiencing clinical benefit.

- LRM will be administered weekly at 350 mg (cohort 1) or 700 mg (cohort 2) subcutaneously, with TAS-102 plus BEV at standard doses.
- Cohort 2 will be initiated if no LRM dose-limiting toxicities (DLTs) are seen in cohort 1.
- Primary objectives include safety and objective response rate per RECIST v1.1 criteria.
- Other evaluations include ctDNA kinetics, and PD-L1 expression on circulating tumor cells (CTCs) and cancer associated macrophage-like cells (CAMLs).

RESULTS

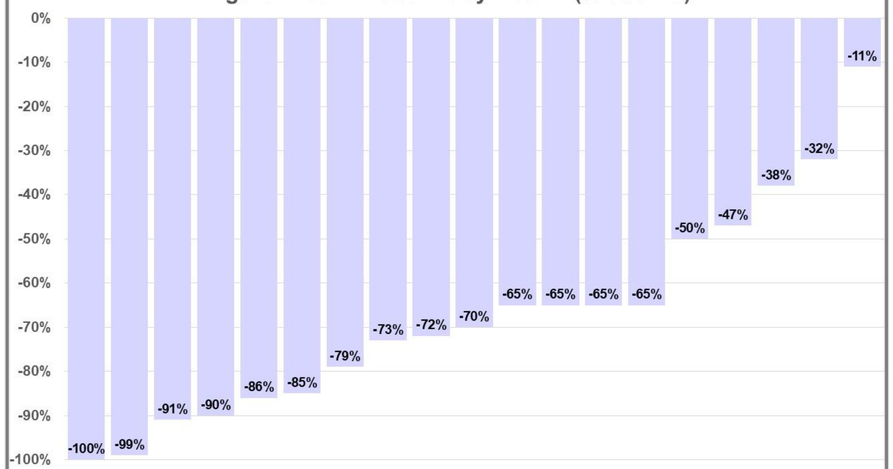
- As of drafting the poster 32 patients have been enrolled and started treatment out of approximately 60 patients identified in screening, with baseline demographics being reasonably well balanced across arms (Table 1).
- Overall, the median age of the patients enrolled is 58 years (range 31–76 years), 23 patients were scored as ECOG of 0 and 5 patients were scored as ECOG ≥1. Most patients (62.5%; 15/24) with available data had a KRAS and/or NRAS mutation at baseline.
- No LRM-related DLTs have been observed at 350 mg and 700 mg dosing has commenced.
- Figure 2 presents preliminary data for the median decline in ctDNA for 18 patients at City of Hope, Orange County, showing median -70% decline by week 2 (range -100% to -11%) with 9 out of the 13 patients with available RECIST data showing shrinkage or stable disease.
- Figure 3 presents pre- and post-scans from a patient at City of Hope, Orange County, showing the multi-focal liver metastases (top) and lung metastases (bottom). Patient had KRAS-G12V mutant/MSS; prior FOLFOX, FOLFIRI and BEV, as well as FUDR hepatic artery infusion therapy (initial diagnosis 2023). This patient is still active on study (Cycle 7, as of April 2026).

Table 1: Baseline characteristics

Parameter	LRM 350 mg (N=23)	LRM 700 mg (N=9)	Total (N=32)
Median age, years (range)	57 (38–76)	59 (31–71)	58 (31–76)
Gender, n (%)			
Female	9 (39.1%)	2 (22.2%)	11 (34.4%)
Male	14 (60.9%)	7 (77.8%)	21 (65.6%)
Race, n (%)			
Asian	3 (13.0%)	3 (33.3)	6 (18.8%)
Black of African American	1 (4.4%)	0	1 (3.1%)
White	19 (82.6%)	6 (66.6%)	25 (78.1%)
Median weight, kg (range)	168 (71–193)	168 (73–180)	168 (71–193)
RAS mutations n/N (%)†			
With KRAS mutation	7/16 (43.8%)	6/8 (75.0%)	13/24 (54.2%)
With NRAS mutation	2/16 (12.5%)	0/8 (0)	2/24 (8.3%)
With KRAS or NRAS mutation	9/16 (56.3%)	6/8 (75.0%)	15/24 (62.5%)
ECOG, N (%)			
0	20	7	23
≥1	3	2	9
Tumor tissue CCR5 positive, n (%)*	23 (100%)	9 (100%)	32 (100%)

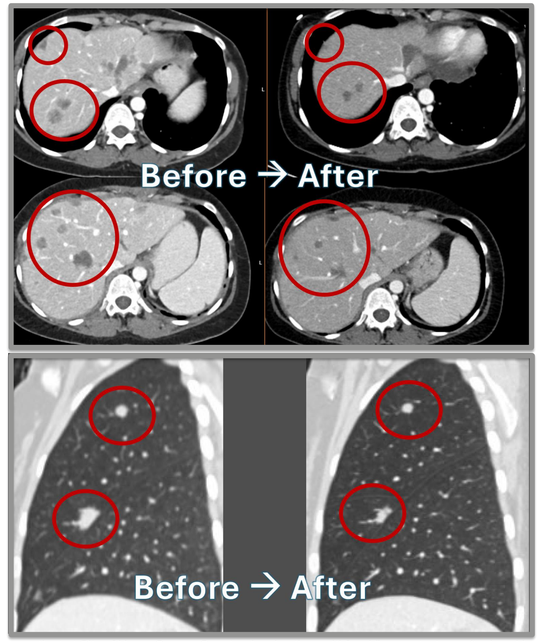
*CCR5 tumor positivity was a requirement for enrollment. All 81 out of 81 evaluable tissue samples from pre-screening were shown to be CCR5+
†Data from subset of 24 patients enrolled at City of Hope, Orange County.

Figure 2: ctDNA decline by week 2 (% decline)



Preliminary data observed in 19 patients from City of Hope, Orange County, exploratory dataset requiring validation.

Figure 3: Scans from a patient showing a response to treatment.



Pre- and post-scans from a patient at City of Hope, Orange County, showing the multi-focal liver metastases (top) and lung metastases (bottom)

DISCUSSION

- All evaluable patients treated with LRM in combination with TAS-102 and BEV demonstrated a decrease in ctDNA by week 2, with the majority experiencing substantial declines (Figure 2).
- ctDNA reductions occurred prior to radiographic assessment and were frequently associated with tumor shrinkage or disease stabilization.
- Mechanistically, CCR5 inhibition by LRM may reduce tumor cell migration, invasion, and metastatic dissemination, potentially contributing to reductions in circulating tumor DNA.
- The combination with TAS-102 (cytotoxic chemotherapy), BEV (anti-angiogenic therapy), and LRM (CCR5 blockade) may provide complementary mechanisms of antitumor activity enabling a rapid biologic response, as early as week 2, as reflected in the observed early decline in ctDNA.
- The amended protocol prospectively collects ctDNA at baseline and post-baseline to evaluate the relationship between early ctDNA kinetics, radiographic response, longer-term outcomes.
- Increases in CPS/PD-L1 on paired tissue and CTC/CAMLs has been observed and will be reported in a larger dataset at an upcoming conference.

CONCLUSIONS

- LRM in combination with TAS-102 plus BEV has been well tolerated with no LRM-related DLTs.
- Despite the CLOVER trial enrolling an advanced patient population rapid declines in ctDNA were observed suggesting potential molecular activity of LRM-based therapy.
- As of end of March 2026 the CLOVER trial is approaching full enrollment.
- Early results are encouraging and support further evaluation of this combination in patients with MSS, refractory, mCRC.

FUNDING / MEDICAL WRITING SUPPORT / REFERENCES

Study funded by CytoDyn Inc. Medical writing support was provided by Neil Buss, Nucleus Global, Switzerland, funded by CytoDyn Inc., Vancouver, WA, USA.

[1] Prager GW, et al. N Engl J Med 2023; 388(18): 1657-67; **[2]** Tabernero J. et al. J Clin Oncol 41, 2023 (suppl 4; abstr 4; slide 9). Accessed 3 February 2026; **[3]** Nusrat M, et al. NEJM Evidence 2026; 5(3): EVIDoa2500120; **[4]** Cambien B, et al. PLoS One 2011; 6(12): e28842; **[5]** Battaglin F, et al. J Immunother Cancer 2024; 12(1); **[6]** Tanabe Y, et al. Oncotarget 2016; 7(30): 48335-45; **[7]** Ward ST, et al. Br J Cancer 2015; 112(2): 319-28; **[8]** Nishikawa G, et al. Cell Death Dis 2019; 10(4): 264; **[9]** Holz A, et al. Cancer Treat Rev 2025; 139: 102999; **[10]** Ghidini M, et al. Clin Cancer Res 2025; 31(4): 707-18.