A feasibility analysis to align fit-for-purpose real-world data to emulate the AZUR-1 single-arm clinical trial in patients with mismatch repair deficient/microsatellite instability-high locally advanced rectal cancer

Digital poster

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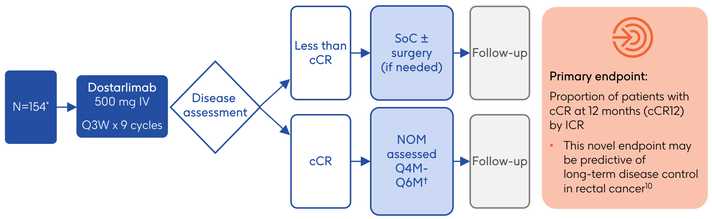
Background

- Colorectal cancer is the third most common cancer globally, with rectal cancer accounting for ~30% of all colorectal cancers[1,2]
- SoC for untreated locally advanced rectal cancer typically involves a multidisciplinary approach including a combination of chemotherapy, radiotherapy, and surgery, which is effective for many patients but can be associated with a wide range of adverse effects and long-term impacts that may reduce quality of life[3–5]
- Tumors with dMMR/MSI-H status represent a distinct subgroup within colorectal cancer and typically respond poorly to chemotherapy[6,7]
- In a phase II single institution trial in the US, dostarlimab, a PD-1 inhibitor, demonstrated a 100% cCR rate in 49 patients with dMMR locally advanced rectal cancer who completed treatment, with all patients proceeding with NOM and 37 patients maintaining cCR at 12 months after treatment[8]
  - Further clinical trials, such as AZUR-1 (NCT05723562), are required to confirm these findings in a larger global cohort of patients
- AZUR-1 is an ongoing global, single-arm, open-label, non-randomized phase II clinical trial evaluating dostarlimab monotherapy for patients with previously untreated locally advanced dMMR/MSI-H rectal cancer (**Figure 1**)[9]
  - AZUR-1 has a single-arm design (N=154 patients enrolled) due to the rarity of dMMR/MSI-H in rectal cancer (2%–3%), the known clinical activity of dostarlimab in locally advanced rectal cancer, and complications of the current multimodal SoC, which includes the heterogeneity of treatment among patients and the potential high withdrawal rates resulting from SoC-related toxicities in a potential control arm[3–5, 8]

Figure 1: **AZUR-1 trial design**



**Patients have histologically confirmed Stage II/III (T3–T4, N0 or T any N+) locally advanced rectal adenocarcinoma without prior radiation therapy, systemic therapy or surgery for management of rectal cancer; †patients are evaluated for salvage therapy and transitioned to SoC in the event of recurrent disease.*

- Considering the single-arm nature of AZUR-1, there is a need to identify robust and regional real-world data sources that can emulate the AZUR-1 population and be used to contextualize AZUR-1 trial results

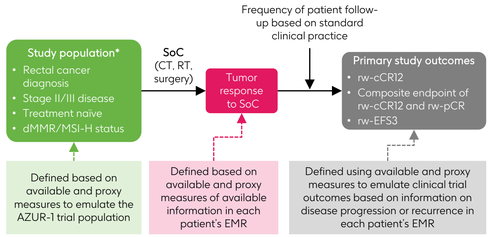
Objective

- To perform feasibility assessments of US real-world data sources to identify fit-for-use data for a natural history study emulating the AZUR-1 trial population that will be used to contextualize the trial results

Methods

- A robust natural history study using real-world data was designed to emulate the AZUR-1 trial in patients with dMMR/MSI-H locally advanced rectal cancer (**Figure 2**)

Figure 2: **Study design for natural history studies**



**Additional AZUR-1 selection criteria were applied where applicable.*

- The US-based Flatiron Health Research Database was selected during data landscaping; an additional in-depth feasibility assessment was required to evaluate data quality, including the availability and completeness of key study variables, based on US/EU regulatory guidance and frameworks
  - The Flatiron Health Research Database is an EHR-derived de-identified database comprising patient-level data originating from over 280 oncology practices at over 800 unique sites of care in the US (~25% from academic medical centers), curated via technology-enabled abstraction[11]
  - The database includes real-world data to define the SoC to be studied in the natural history study, and key study variables needed to emulate the AZUR-1 trial, such as patient baseline clinical characteristics, tumor response assessments, disease progression, and mortality
- A preliminary feasibility assessment was conducted using a cohort of 50 patients with dMMR/MSI-H locally advanced rectal cancer (feasibility cohort) with a data cutoff date of February 28, 2023
  - Patients were randomly selected adults (at the diagnosis date) with Stage II/III rectal cancer and evidence of a dMMR or MSI-H status result on or after the initial diagnosis date until data cutoff or metastatic diagnosis date, and who did not have a normal MMR/MSI-low/MSS result on or after initial diagnosis date
  - Patients were only eligible if they had unstructured documents (e.g., clinical notes/pathology reports/radiology summaries) in the Flatiron Health Research Database that were relevant for review

Results

- Among the 50 patients included, the median age was 56 years (IQR: 48, 65) and 72% of patients were White (**Table 1**)
- The median duration of follow-up was 32.3 months (IQR: 11.2, 63.1); 72.0% of patients had ≥12 months of follow-up from a locally advanced rectal cancer diagnosis

Table 1: **Demographic and clinical characteristics of the feasibility cohort**

Patient characteristic	Feasibility cohort N=50
Age (years), median (IQR)	56 (48, 65)
Sex, n (%)	
Female	27 (54)
Race, n (%)	
White	36 (72)
Deidentified*	10 (20)
Unknown/not documented	4 (8)
Ethnicity, n (%)	
Not Hispanic or Latino	37 (74)
Deidentified*	5 (10)
Unknown/not documented	8 (16)
Year of initial diagnosis, median (IQR)	2018 (2015, 2021)
Follow-up time from initial Stage II/III diagnosis (months), median (IQR)	32.3 (11.2, 63.1)
Follow-up time in months from initial diagnosis, n (%)	
<12	14 (28)
12–23	9 (18)
24–35	4 (8)
36–59	7 (14)
>59	16 (32)
Availability of ECOG PS score before or within 90 days after initial diagnosis, n (%)	33 (66)
Known dMMR/MSI-H status, n (%)	
Before treatment initiation†	27 (56.3)
Before treatment initiation and ≤3 months after treatment initiation†	34 (70.8)
By data cutoff or by metastatic rectal cancer diagnosis	50 (100)
Time from date of specimen collection to date of result of dMMR or MSI-H status (days), median (IQR)‡	11.5 (5.5, 29.2)

**Not all race or ethnicity categories reported, as data were deidentified for demographic variables if there was a cell count n<11 for patient confidentiality; †n=48 due to two patients with no treatment; ‡assessed among biomarker tests of dMMR or MSI-H status with both specimen collection date and result date available.*

- The most common treatments received by patients were systemic therapy (88%), radiotherapy (78%), and surgery (66%) (**Table 2**)
- The most common systemic therapies were FOLFOX (52%), and capecitabine (48%)
- Immunotherapies were received by a small proportion (10%) of patients overall

Table 2: **Treatment patterns in the feasibility cohort**

Treatment received for Stage II/III rectal cancer at any time in treatment journey, n (%)	Feasibility cohort N=50	Academic N=8	Community N=42
Systemic therapy	44 (88)	8 (100)	36 (86)
Radiation therapy	39 (78)	8 (100)	31 (74)
Surgery for primary rectal tumor	33 (66)	8 (100)	25 (60)
Chemotherapy			
FOLFOX*	26 (52)	6 (75)	20 (48)
Capecitabine†	24 (48)	7 (88)	17 (40)
CAPEOX‡	9 (18)	1 (13)	8 (19)
5-FU + or – leucovorin	9 (18)	0 (0)	9 (21)
FOLFIRI	1 (2)	0 (0)	1 (2.4)
Immunotherapy			
Pembrolizumab	3 (6)	0 (0)	3 (7.1)
Nivolumab	2 (4)	0 (0)	2 (4.8)
Other	3 (6)	1 (13)	2 (4.8)

**Modified FOLFOX, mFOLFOX, mFOLFOX6; †capecitabine was most commonly administered as part of a chemoradiotherapy regimen; ‡CAPOX, XELOX.*

Conclusions

- A robust natural history study using real-world data has been designed to help contextualize the AZUR-1 single-arm clinical trial evaluating the efficacy of dostarlimab monotherapy in patients with dMMR/MSI-H locally advanced rectal cancer
- The distribution of the characteristics of patients in the feasibility cohort from the US-based Flatiron Health Research Database align with existing clinical data for this population, indicating that key study variables can be evaluated using this database for dMMR/MSI-H locally advanced rectal cancer
- 10% of patients in the feasibility cohort received immunotherapy; this is reflective of the addition in 2023 of neoadjuvant immunotherapy as a recommendation in NCCN and ESMO guidelines for patients with dMMR/MSI-H locally advanced rectal cancer, despite lacking formal approval in this setting[3,12]
- In this feasibility cohort, only 56% of patients had known dMMR/MSI-H status prior to treatment initiation, highlighting that pre-treatment biomarker testing rates may be suboptimal in locally advanced rectal cancer
- This was an initial feasibility assessment; a common data model will be implemented in the full natural history study to emulate the AZUR-1 trial population and to reflect the current real-world SoC and treatment outcomes to the best extent possible

Abbreviations

5-FU, 5-fluorouracil; CAPEOX/CAPOX, capecitabine and oxaliplatin; cCR, complete clinical response; cCR12, complete clinical response at 12 months; CT, chemotherapy; dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS3, 3-year event-free survival; EMR, electronic medical record; ESMO, European Society for Medical Oncology; EU, European Union; FOLFIRI, folinic acid (leucovorin), fluorouracil, and irinotecan; FOLFOX, folinic acid (leucovorin), fluorouracil, and oxaliplatin; ICR, independent central review; IQR, interquartile range; IV, intravenous; mFOLFOX, modified folinic acid (leucovorin), fluorouracil, and oxaliplatin; mFOLFOX6, modified FOLFOX6 (folinic acid [leucovorin], fluorouracil, and oxaliplatin, regimen 6); MMR, mismatch repair; MSI-H, microsatellite instability-high; MSI-low, microsatellite instability-low; MSS, microsatellite stable; N, node stage/status; NCCN, National Comprehensive Cancer Network; NOM, non-operative management; pCR, pathological complete response; PD-1, programmed death protein 1; Q3W, every 3 weeks; QnM, every n months; RT, radiotherapy; rw, real-world; SoC, standard of care; T, tumor stage/status; US, United States; XELOX, capecitabine and oxaliplatin.

References

1. Cihan YB, Ozturk A. *Support Care Cancer.* 2021;29(12):7411–20.
2. Bray F, et al. *CA Cancer J Clin.* 2024;74(3):229–63.
3. Hofheinz RD, et al. *Ann Oncol.* 2025;36(9):1007–24.
4. Contin P, et al. *Int J Colorectal Dis.* 2014;29:165–75.
5. Hassan I, Cima RR. *J Surg Oncology.* 2007;96:684–92.
6. Cercek A, et al. *Clin Cancer Res.* 2020;26(13):3271–9.
7. Lunenberg RA, et al. *Int J Cancer.* 2025;doi: 10.1002/ijc.70127.
8. Cercek A, et al. *N Engl J Med.* 2025;392:2297–308.
9. Cercek A, et al. *Clin Colorectal Cancer.* 2025;24(2):325–30.
10. Thompson HM. *JAMA Netw Open.* 2024;7(1):e2350903.
11. Flatiron. Database Characterization Guide. https://flatiron.com/database-characterization. (Accessed December 2025).
12. Benson AB, et al. *J Natl Compr Canc Netw.* 2024;22(6):366–75.

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