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# Non-operative management of mismatch repair deficient tumors

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## Abstract

**Background:** Neoadjuvant checkpoint blockade of locally advanced mismatch repair deficient (MMRd) rectal cancers results in a high rate of clinical complete responses that eliminate the need for surgery. MMRd occurs broadly across solid tumors, but whether these findings could be extended in a tumor agnostic manner is unknown.



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**Methods:** Early stage MMRd solid tumors (stages I-III) eligible for curative intent surgery were enrolled to a study of six months of neoadjuvant dostarlimab, a PD-1 blocking agent. The study was comprised of two cohorts. Cohort 1 enrolled MMRd locally advanced rectal cancers and Cohort 2 enrolled MMRd non-rectal solid tumors. Patients who achieved a clinical complete response (cCR) could elect non-operative management. Patients with an incomplete response or progression were to undergo resection.

**Results:** 117 patients were enrolled and eligible for analysis. In Cohort 1 (MMRd rectal cancers), all 49 patients who completed treatment achieved a cCR and none underwent resection of the primary tumor. In Cohort 2 (MMRd non-rectal solid tumors), 35 of 54 patients achieved a cCR and 33 of 35 elected non-operative management. Across both cohorts, 84 of 103 patients achieved a cCR, 82 of 103 patients did not undergo surgery. The two-year recurrence free survival was 92% (86–99), the median follow-up for recurrence was 20 months (Range 0–60.8 months, n=117). Dostarlimab had mainly low-grade side effects in about 20% of patients and the opportunity for curative resection was never compromised during or after treatment.

**Conclusion:** In the curative setting, neoadjuvant PD-1 blockade offers the option of organ preservation for many patients with MMRd tumors.

## INTRODUCTION

Complete surgical resection is the predominant curative option for early-stage solid tumors.[1] Non-operative management has been successfully implemented for several cancer types, including anal, bladder, rectal, and head and neck cancers, when radiation is combined with chemotherapy.[2–7] Additionally, for small lung tumors, stereotactic radiation therapy can achieve outcomes comparable to surgery.[8]

MMRd tumors are highly sensitive to immune checkpoint blockade, and in the metastatic setting the substantial clinical benefit across tumor types resulted in the first tumor agnostic approval by the FDA.[9–12] In the neoadjuvant setting, elimination of the primary tumor has been reported in colorectal cancers and in rectal cancer specifically, early studies suggest that surgery can be averted when a clinical complete response (cCR) is achieved.[13–16]

The complete elimination of MMRd primary tumors with PD-1 blockade alone in rectal cancer raised the question of whether this approach could be extended beyond rectal cancer to a broader, tumor-agnostic setting—mirroring the benefit of checkpoint blockade across MMRd cancers in the metastatic setting. The potential impact is substantial since 2–10% of all early-stage solid tumors are mismatch repair deficient.[9] Despite data supporting efficacy in metastatic disease, concern exists for the risk of potentially missing the ‘window of opportunity’ if tumors were to progress and become unresectable during the course of treatment with an immune checkpoint inhibitor.

To test the premise of non-operative management for MMRd early-stage tumors, we expanded on our experience in rectal cancer and enrolled patients with early stage MMRd tumors eligible for curative intent therapy from any site. Patients were treated with 6-months of PD-1 blockade with dostarlimab and monitored closely for response, progression, or recurrence.

# METHODS

## Patient eligibility

Patients from Memorial Sloan Kettering, Hartford Heath Care and Miami Cancer institute were screened and referred to the study if found to be MMRd. Patients with newly diagnosed stage I, II and III solid tumors amenable to curative intent therapy with loss of expression of MLH1, MSH2, MSH6, or PMS2 by immunohistochemistry (IHC) were eligible. Additional eligibility criteria are included in the accompanying protocol, available at nejm.org.

## Study design

This study was designed to evaluate neoadjuvant dostarlimab (500mg intravenously every 3 weeks for 9 cycles) in two cohorts, (i) locally advanced MMRd rectal cancers and (ii) non-rectal MMRd solid tumors. Following assessment of response, patients with residual tumor would be treated with standard of care neoadjuvant therapy, and applicable surgery. Patients achieving a clinical complete response following neoadjuvant dostarlimab were offered non-operative management.

## Study Oversight

The institutional review board at Memorial Sloan Kettering approved the protocol and subsequent amendments. All patients provided informed consent. The manuscript was written solely by the authors, who collected the data and attest to its integrity, accuracy, and adherence to the protocol.

## Tumor Genomic Analyses

Patients underwent genomic sequencing of tumor and matched normal blood samples for somatic and germline genomic alterations[17]. All samples were collected under an IRB approved protocol (NCT01775072) and written consent. Relatedness between baseline and post-treatment tumors was evaluated using a mutational profile similarity (MPS) score[18] (Supplemental Appendix).

A tumor-informed approach was used to measure circulating tumor DNA (ctDNA). Somatic mutations were identified with exome sequencing of each patient's tumor tissue and matched normal DNA to assess up to 50 tumor-specific mutations in cell-free DNA isolated from plasma (Supplemental Appendix).

## Statistical analyses

**Cohort 1 (rectal cancer):** The first co-primary endpoint of overall response rate greater that 25% was met when 12 consecutive patients achieved complete clinical responses[15].

In this manuscript, we present the second co-primary endpoint based on data from December 2019 through April 2025, which required a cCR of at least 12 months after completion of dostarlimab with or without chemoradiation in patients who did not undergo surgery or who proceeded to surgery and achieved a pCR. We implemented a Simon's 2-stage minimax design to show an improvement in the sustained clinical complete response

rate from the unacceptable rate of 27.5% to an acceptable rate of 50% with type I error of 0.05 and 80% power. In the first stage, we planned to enroll 15 patients. If 4 or fewer patients achieved a sustained cCR of 12 months or greater after completion of dostarlimab, the study will stop for futility. If 13 or more patients with a sustained cCR of at least 12 months after completion of dostarlimab, the study will stop for efficacy. As previously established[19], a cCR was defined as no residual disease on a digital and endoscopic rectal exam and absence of residual tumor on MRI (Supplemental Appendix, Protocol section 14.0).

**Cohort 2 (all non-rectal solid tumors):** The primary objective for this cohort was exploratory and estimated the complete response rate. (Supplemental Appendix, Protocol section 14.0).

All statistical analyses were performed using R, version 4.3.2. (Supplemental Appendix)

## RESULTS

### Patient and tumor characteristics

124 patients were enrolled. Seven patients were excluded from our analysis for the following reasons: three participants were found to have metastases or second malignancies before treatment and withdrew from the study; two participants opted to discontinue therapy after one dose of dostarlimab; one participant was lost to follow up; and one participant stopped treatment after 4 doses. (Figure 1A, Supplemental Appendix).

Cohort 1 was comprised of only MMRd rectal cancers. Cohort 2 included MMRd non-rectal solid tumors, including esophagogastric, colon, hepatobiliary, genitourinary, and gynecologic tumors (Table 1; Table S1, Figure S1).

On the date of data lock, 103 patients had completed therapy, 49 in cohort 1 and 54 in cohort 2, and 14 remain on therapy. (Figure 1A, Table 1, Table S1)

Across both cohorts most patients had radiographically evident lymph nodes (64%). All tumors had loss of expression of mismatch repair proteins with loss of both MLH1 and PMS2 being the most common. Germline pathogenic variants in a mismatch repair gene were noted in 44% of cases. (Table 1, Table S1)

### Clinical complete responses and non-surgical management

No patients progressed or became unresectable while on therapy.

In Cohort 1 (rectal cancer), 49 patients completed treatment. All 49 achieved a cCR, and all 49 opted for non-operative management. (Figure 1B)

In Cohort 2 (non-rectal solid tumors), 54 patients completed treatment. Thirty-five (65%) of these 54 achieved a clinical complete response, and 33 (61%) also elected nonoperative management. (Figure 1B)

Two patients (one with gastric cancer and one with urothelial cancer) who achieved a cCR, elected to undergo surgical resection. In both cases, no cancer was found in the resection specimen. (Figure 1A, Figure 1B, Table S1-2)

Combining cohorts, among 103 patients who completed treatment, 84 (82%, 95% CI: 72% −88%) achieved a clinical complete response and 82 (80%, 70%−87%) also proceeded with non-operative management. (Figure 1B)

## Incomplete clinical responses

In Cohort 1 (rectal cancer) no incomplete responses were observed. (Figure 1B, Figure 2A)

In Cohort 2 (non-rectal solid tumors), 19 of 54 patients (35%) had incomplete clinical response. Sixteen of these patients underwent surgical resection of their primary tumors and 3 patients deferred surgery. At baseline, all tumors were found to be MMRd and MSI-high, except for one tumor that had subclonal MLH1/PMS2 loss and was found to be microsatellite stable (MSS). (Table S2)

In the 16 patients who underwent surgery, evidence of tumor regression was noted in 14 (87%) of the resected tumors; 1 did not have evaluable tissue; 1 had achieved a pathologic complete response and three had complete pathologic response in the primary tumor but residual tumor present in the lymph nodes. (Supp Table 2).

We were able to compare the sequences of the pre and the remnant post-treatment tumors in the incomplete responders with genomic data and found a high likelihood of genomic relatedness (99.6%: 95% CI 97.43–99.97, n=17)[18] in all but two patients (51 and 90). In these two cases the remnant tumor was likely a new primary as there was a low likelihood of genomic relatedness (mutational profile similarity score < 0.4%[18]). Furthermore, the remnant tumors in these two cases were also not MMRd or MSI-high. (Table S2; Figure S2).

Other than the two unrelated tumors, no meaningful differences were noted between pre and remnant post-treatment tumors in median TMB (43 vs. 34 mutations per MB, Wilcoxon signed rank p=0.43, n=14), mismatch repair protein loss or median microsatellite instability (MSI) sensor score (15 versus 16, Wilcoxon signed rank p=0.47, n=12) (Table S2).

## Durability of response and disease recurrence

Across both cohorts, (n=117) and the two year recurrence free survival was 92% (86–99), (Figure 2A and Figure S3).

In Cohort 1, the two year recurrence-free survival was 96% (90–100) (n=50) and median follow-up for recurrence was 30.2 months (Range 5.8–60.8 months). To date, 37 patients have sustained a cCR for at least 12-months from completion of treatment, which satisfies the second co-primary endpoint.

In Cohort 2, the two year recurrence-free survival was 85% (70–100) (n=67), and the median follow-up for recurrence was 14.9 months (Range 0–32.7 months).

Only 5 patients across both cohorts developed disease recurrence. One patient had tumor regrowth at the rectal primary site and 4 recured solely in lymph nodes. (Table S1) None of these cases required resection of the primary tumor. One patient had resection of a lymph node and currently has no evidence of disease. Four patients restarted PD-1 blockade and 3 are currently disease-free. Original and recurrent tumors were consistently MMRd with high genomic relatedness and no meaningful differences in TMB or MSI between evaluable pre and recurrent tumors. (Table S1; Figure S4). Among this group the median disease-free interval from second recurrence was 6.6 months (3.1 – 14.9 months, n=4). (Supplemental appendix).

No deaths have occurred in either cohort. Across both cohorts, the median follow-up for survival from the start of treatment was 21.5 months (Range 0–60.8 months, 95%CI 19.4–23.6, n=117).

## Treatment Adherence and Adverse Events

In Cohort 1, all but one patient completed all 9 cycles (6 months). One patient chose to stop therapy after 8 cycles because of an unrelated asthma exacerbation. (Table S1)

In Cohort 2 (non-rectal solid tumors), 49 of the 54 patients completed all planned cycles. Three stopped before achieving a complete response due to concerns for lack of response. Two stopped after achieving a cCR due to treatment-related adverse events, per their preference. (Table S1)

The most common grade 1 or 2 adverse events included fatigue (23%), pruritis (20%), and rash/dermatitis (20%). Four patients developed grade 3 events, which included diabetes (1%), lung infection (1%), encephalitis (1%) and one (1%) neutropenia, and one patient developed a grade 4 neutropenia (1%). (Table 2)

## Exploratory response assessments

Various assessment modalities were compared to measure response kinetics in patients who achieved a cCR without subsequent surgery. In combined cohorts, the median time to composite complete response was 6.2 months (95% CI 6.2–6.3 months). (Figure S5) Median time to complete response with imaging was 6.1 months (95% CI 6.1–6.2 months). (Figure S5).

Endoscopies when available showed a median time to complete response of 6.1 months (95% CI 6.0–6.2 months). (Figure S5)

Tumor biopsies were evaluated in both cohorts and the median time to a negative biopsy was 1.5 months (95% CI 1.4–2.7 months). (Figure S5)

Circulating tumor DNA was evaluated in both cohorts. 95% (70/74) patients tested were positive at baseline. For evaluable patients also with cCR (n=52), the median time to ctDNA clearance was 1.4 months (95% CI 1.4–1.5 months). (Figure S5)

A total of 343 biopsies were obtained during the study. Comparison of detectable ctDNA levels, a surrogate for the presence of tumor, and biopsy showed substantial concordance

(Kappa coefficient of 0.76, 95% CI 0.68 to 0.83) with the 307 (89.50%) observed agreements.

Kinetics of ctDNA varied based on response to therapy. Patients whose ctDNA became undetectable during therapy and remained negative at the end of treatment achieved a cCR, whereas those patients whose ctDNA remained detectable during treatment and at the end of therapy had evidence of incomplete responses. In patients who developed recurrence, ctDNA remained detectable during treatment and was slower to clear. (Figure 3)

## DISCUSSION

These data from a small cohort of patients demonstrate that PD-1 blockade enables non-operative management for many Stage I, II and III MMRd tumors. As seen in the metastatic setting, the efficacy of checkpoint blockade appears to be relatively tumor-agnostic, driven primarily by the MMRd phenotype rather than the tumor's site of origin.

In the curative setting, six-months of neoadjuvant PD-1 blockade was associated with few adverse events. Of equal importance, the option for curative intent surgery was never compromised despite a prolonged course of treatment relative to other neoadjuvant studies. A major concern during neoadjuvant treatment is that the 'window of opportunity' for resection may lapse and tumors may grow and spread to the point of no longer being curative by surgery, which often limits the duration of treatment to a few cycles of therapy. To maximize clinical response, we treated with six-months of checkpoint blockade, which in prior studies appears to result in a higher complete clinical response rate than treatment for a shorter duration.[20–22]

All of the patients who achieved a clinical complete response have preserved their organs without additional therapy, In three cases of rectal cancer, patients were able to conceive and deliver healthy children which would not have been possible with standard treatment of rectal cancer[23].

The most common tumor types not to achieve a complete clinical response were prostate and gastroesophageal cancers. In the remaining cases, it is unclear why different sites of primary disease have varying frequency of complete clinical responses, but the contribution of the microbiome and other cellular components of tumor microenvironment, like myeloid cells, and underlying tumor heterogeneity likely contribute to these outcomes. It is also possible that a longer duration of therapy or combination immune checkpoint blockade would have led to complete responses in these tumors.[22]

Of note, only 5 patients developed disease recurrence. In 4 of these cases, recurrence was restricted to lymph nodes that were treated with either resumption of PD-1 blockade (4 patients) or by resection the solitary recurrent lymph node. Anti-PD-1 rechallenge resulted in complete disease regression in every patient, suggesting that resistance had not developed to the pre-existing neoantigens or that new neoantigens emerged sufficient to trigger a de novo immunotherapeutic response.[24–26]

A significant challenge moving forward is to determine the best approach to monitor tumor responses. We employed tumor specific imaging, clinical exam and visualization by endoscopy, and biopsy. While GI tumors were amenable to most of these approaches, tumors in sites not accessible endoscopy relied completely on imaging. Monitoring response with imaging was successful in most cases. However, imaging is not as definitive as obtaining tissue.

Analysis with ctDNA provided a unique window into the dynamic response to PD-1 blockade. This tumor informed approach, where mutations in the tumor are used to design probes to analyze circulating cell-free DNA was first described in mice and later in humans for the purposes of tracking tumor burden and to measure minimal residual disease.[27,28] It is important to note that ctDNA detects active disease in real time, in part, because ctDNA has a short plasma half-life of less than 2 hours.[28] In our study, we employed a novel assay, that achieves very high sensitivity and specificity by simultaneously measuring up to 50 tumor-defined mutations in cfDNA and by discarding sequencing-induced artifactual mutations by requiring detected genomic alterations to be present on the forward and reverse strands of a cfDNA fragment.[29–31] Using this approach, more than 90% of our early-stage tumors were detected at baseline, and we were able to reliably view the therapeutic response in real time. All patients with a complete clinical response cleared ctDNA by the end of treatment, while those with incomplete responses or eventual recurrences were slow to clear ctDNA and levels remained elevated throughout treatment in many cases.

Furthermore, when we compared ctDNA levels with matched biopsy results the concordance was high, suggesting ctDNA was in fact a reliable ‘liquid biopsy’. In the future, this approach will be an important addition to response assessment, as novel therapies enter the neoadjuvant arena and will require methods to measure response, especially when tumors are in locations where direct visualization and biopsies are not feasible.

While encouraging, these data will require a larger study to confirm the long-term benefit of this approach especially for non-rectal cohort with a median follow-up for recurrence of 14 months. Whether these studies are tumor agnostic or restricted to a single tumor type will be an important consideration as well as whether a randomized study is necessary to confirm these findings. In tumors where surgical resection is less morbid and has less impact on quality of life (e.g., colon cancer), a randomized study designed to measure overall survival is prudent. However, in tumors where the surgery itself is significantly life altering (e.g. esophagus, stomach, pancreas, bladder or rectum), randomizing to surgery may be less feasible and here a single arm experience especially in tumors with a high complete response rate should be sufficient to modify clinical practice.

This study provides a foundation to alter the traditional therapeutic paradigm for early stage MMRd tumors and eliminate the need for surgery and other therapy for most patients.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Funding

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## REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Rectal cancer version 5.2024. 2024.
2. Department of Veterans Affairs Laryngeal Cancer Study Group, Wolf GT, Fisher SG, et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991;324(24):1685–90. [PubMed: 2034244]
3. Nigro ND, Seydel HG, Considine B, Vaitkevicius VK, Leichman L, Kinzie JJ. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. Cancer 1983;51(10):1826–9. [PubMed: 6831348]
4. Kang J, Ning MS, Feng H, et al. Predicting 5-Year Progression and Survival Outcomes for Early Stage Non-small Cell Lung Cancer Treated with Stereotactic Ablative Radiation Therapy: Development and Validation of Robust Prognostic Nomograms. Int J Radiat Oncol Biol Phys 2020;106(1):90–9. [PubMed: 31586665]
5. Giacalone NJ, Shipley WU, Clayman RH, et al. Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience. Eur Urol 2017;71(6):952–60. [PubMed: 28081860]
6. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy. J Clin Oncol 2022;40(23):2546–56. [PubMed: 35483010]
7. Verheij FS, Omer DM, Williams H, et al. Long-Term Results of Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy: The Randomized Phase II OPRA Trial. J Clin Oncol 2024;42(5):500–6. [PubMed: 37883738]
8. Stahl JM, Ross R, Harder EM, et al. The Effect of Biologically Effective Dose and Radiation Treatment Schedule on Overall Survival in Stage I Non-Small Cell Lung Cancer Patients Treated With Stereotactic Body Radiation Therapy. Int J Radiat Oncol Biol Phys 2016;96(5):1011–20. [PubMed: 27869080]
9. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357(6349):409–13. [PubMed: 28596308]
10. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372(26):2509–20. [PubMed: 26028255]
11. Lemery S, Keegan P, Pazdur R. First FDA Approval Agnostic of Cancer Site - When a Biomarker Defines the Indication. N Engl J Med 2017;377(15):1409–12. [PubMed: 29020592]
12. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol 2020;38(1):1–10. [PubMed: 31682550]
13. Chalabi M, Verschoor YL, Tan PB, et al. Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair-Deficient Colon Cancer. N Engl J Med 2024;390(21):1949–58. [PubMed: 38838311]
14. Hu H, Kang L, Zhang J, et al. Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomised, phase 2 trial. Lancet Gastroenterol Hepatol 2022;7(1):38–48. [PubMed: 34688374]
15. Cercek A, Lumish M, Sinopoli J, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N Engl J Med 2022;386(25):2363–76. [PubMed: 35660797]

16. Ludford K, Ho WJ, Thomas JV, et al. Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors. J Clin Oncol 2023;41(12):2181–90. [PubMed: 36623241]
17. Cheng DT, Mitchell TN, Zehir A, et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A Hybridization Capture-Based Next-Generation Sequencing Clinical Assay for Solid Tumor Molecular Oncology. J Mol Diagn 2015;17(3):251–64.
18. Foote MB, White JR, Chatila WK, et al. Analysis of Shared Variants between Cancer Biospecimens. Clin Cancer Res 2025;31(2):376–86. [PubMed: 39561276]
19. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy. J Clin Oncol 2022;40(23):2546–56. [PubMed: 35483010]
20. Habr-Gama A, Lynn PB, Jorge JMN, et al. Impact of Organ-Preserving Strategies on Anorectal Function in Patients with Distal Rectal Cancer Following Neoadjuvant Chemoradiation. Dis Colon Rectum 2016;59(4):264–9. [PubMed: 26953984]
21. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372(26):2509–20. [PubMed: 26028255]
22. Rousseau B, White JR, Cercek A, Diaz LA. The Duration of Immunotherapy for Mismatch Repair-Deficient Cancers. N Engl J Med 2025;392(8):824–6. [PubMed: 39970404]
23. Harrold EC, Ogle M, O'Brien E, et al. Fertility outcomes post immune checkpoint inhibitor exposure. Cancer Cell 2024;42(11):1808–10. [PubMed: 39486412]
24. Long GV, Carlino MS, McNeil C, et al. Pembrolizumab versus ipilimumab for advanced melanoma: 10-year follow-up of the phase III KEYNOTE-006 study. Ann Oncol 2024;35(12):1191–9. [PubMed: 39306585]
25. Nardin C, Hennemann A, Diallo K, et al. Efficacy of Immune Checkpoint Inhibitor (ICI) Rechallenge in Advanced Melanoma Patients' Responders to a First Course of ICI: A Multicenter National Retrospective Study of the French Group of Skin Cancers (Groupe de Cancérologie Cutanée, GCC). Cancers (Basel) 2023;15(14):3564. [PubMed: 37509227]
26. Sheth S, Gao C, Mueller N, et al. Durvalumab activity in previously treated patients who stopped durvalumab without disease progression. J Immunother Cancer 2020;8(2):e000650.
27. Rago C, Huso DL, Diehl F, et al. Serial assessment of human tumor burdens in mice by the analysis of circulating DNA. Cancer Res 2007;67(19):9364–70. [PubMed: 17909045]
28. Diehl F, Schmidt K, Choti MA, et al. Circulating mutant DNA to assess tumor dynamics. Nat Med 2008;14(9):985–90. [PubMed: 18670422]
29. Kinde I, Wu J, Papadopoulos N, Kinzler KW, Vogelstein B. Detection and quantification of rare mutations with massively parallel sequencing. Proc Natl Acad Sci U S A 2011;108(23):9530–5. [PubMed: 21586637]
30. Tie J, Cohen JD, Lahouel K, et al. Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer. N Engl J Med 2022;386(24):2261–72. [PubMed: 35657320]
31. Cohen JD, Douville C, Dudley JC, et al. Detection of low-frequency DNA variants by targeted sequencing of the Watson and Crick strands. Nat Biotechnol 2021;39(10):1220–7. [PubMed: 33941929]

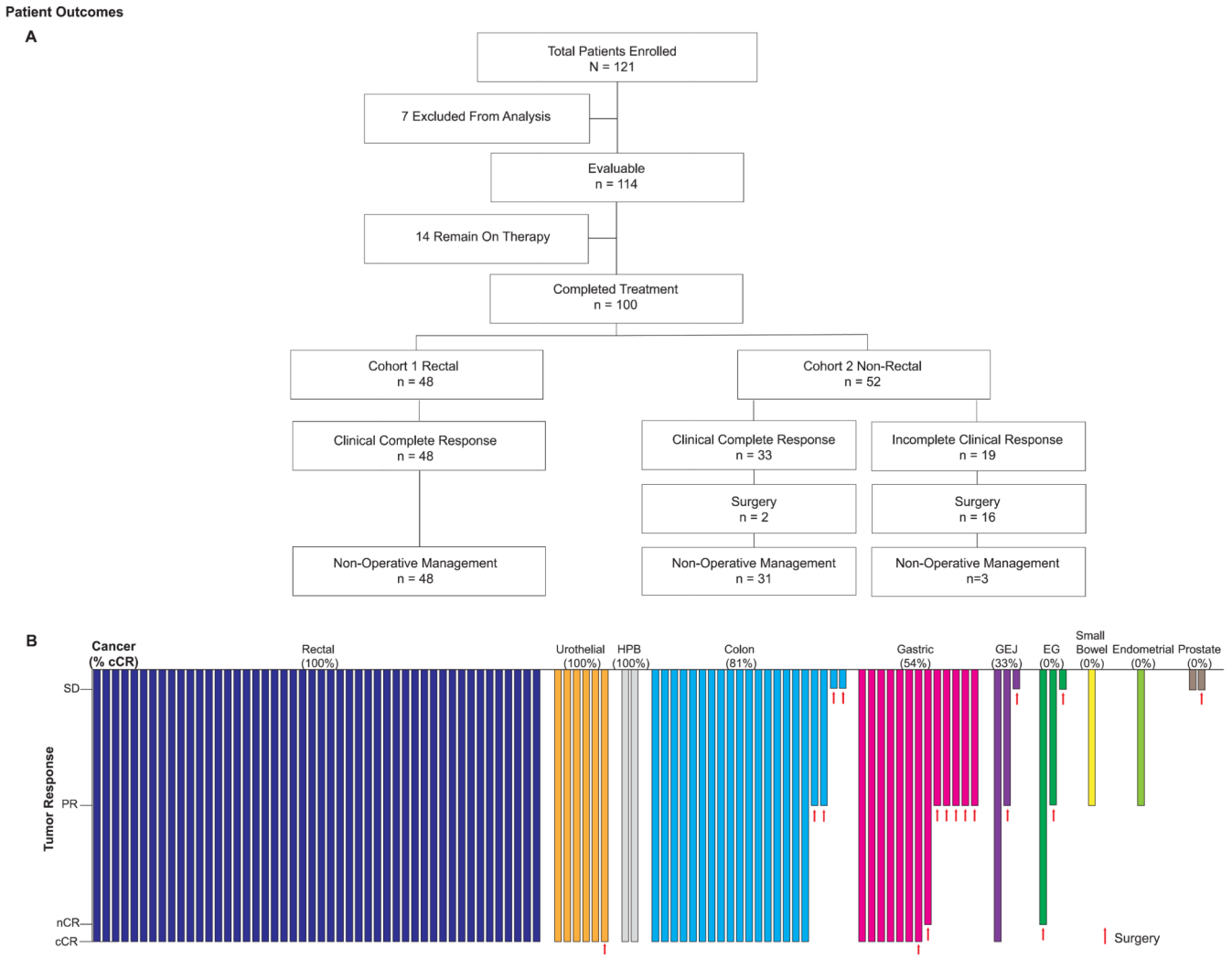


**Figure 1.**

**A. Patient outcome flowchart.** 124 patients were enrolled. Seven patients were excluded from the study: two were found to have metastatic disease before treatment; one was diagnosed with a second brain primary tumor and withdrew from the study; four elected to withdraw from the study. At the time of data cut 103 patients completed dostarlimab therapy and 14 remained on treatment. Cohort 1 included 49 patients with rectal cancer and Cohort 2 included 54 patients with non-rectal solid tumors including gastroesophageal, colon, hepatobiliary, genitourinary and gynecologic cancers.

**B. Clinical responses by tumor type.** Tumor responses are defined as clinical complete response (cCR), near complete response (nCR), partial response (PR) and stable disease (SD).

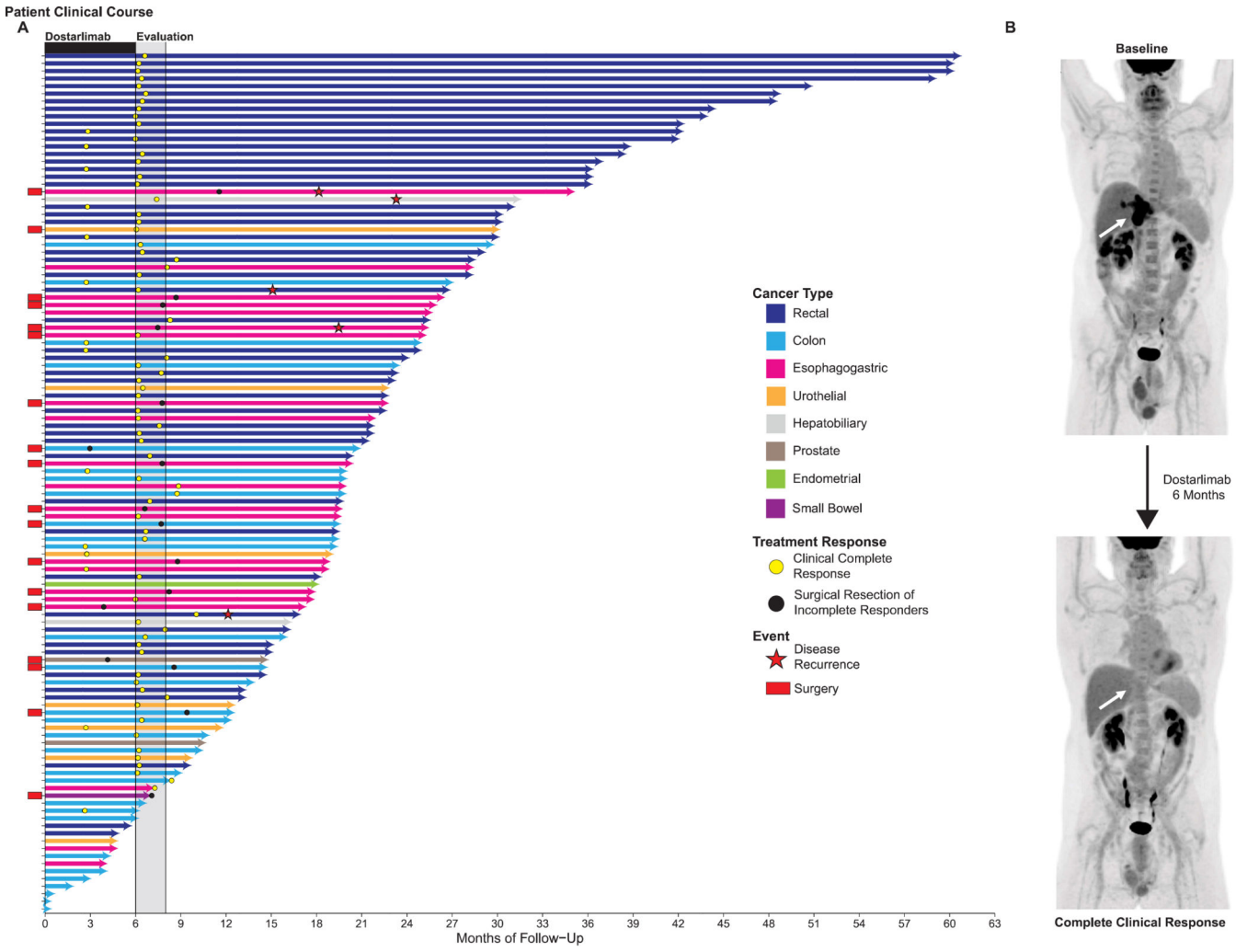


**Figure 2.**

A. Swimmer plot of clinical outcomes in cohort 1 and 2.

**B. Clinical Vignette.** A 55-year-old male with a localized MMRd intrahepatic cholangiocarcinoma. The top panel represents the axial PET images of the tumor at baseline and the bottom panel shows a complete response by PET after completion of 6-months of treatment with dostarlimab.

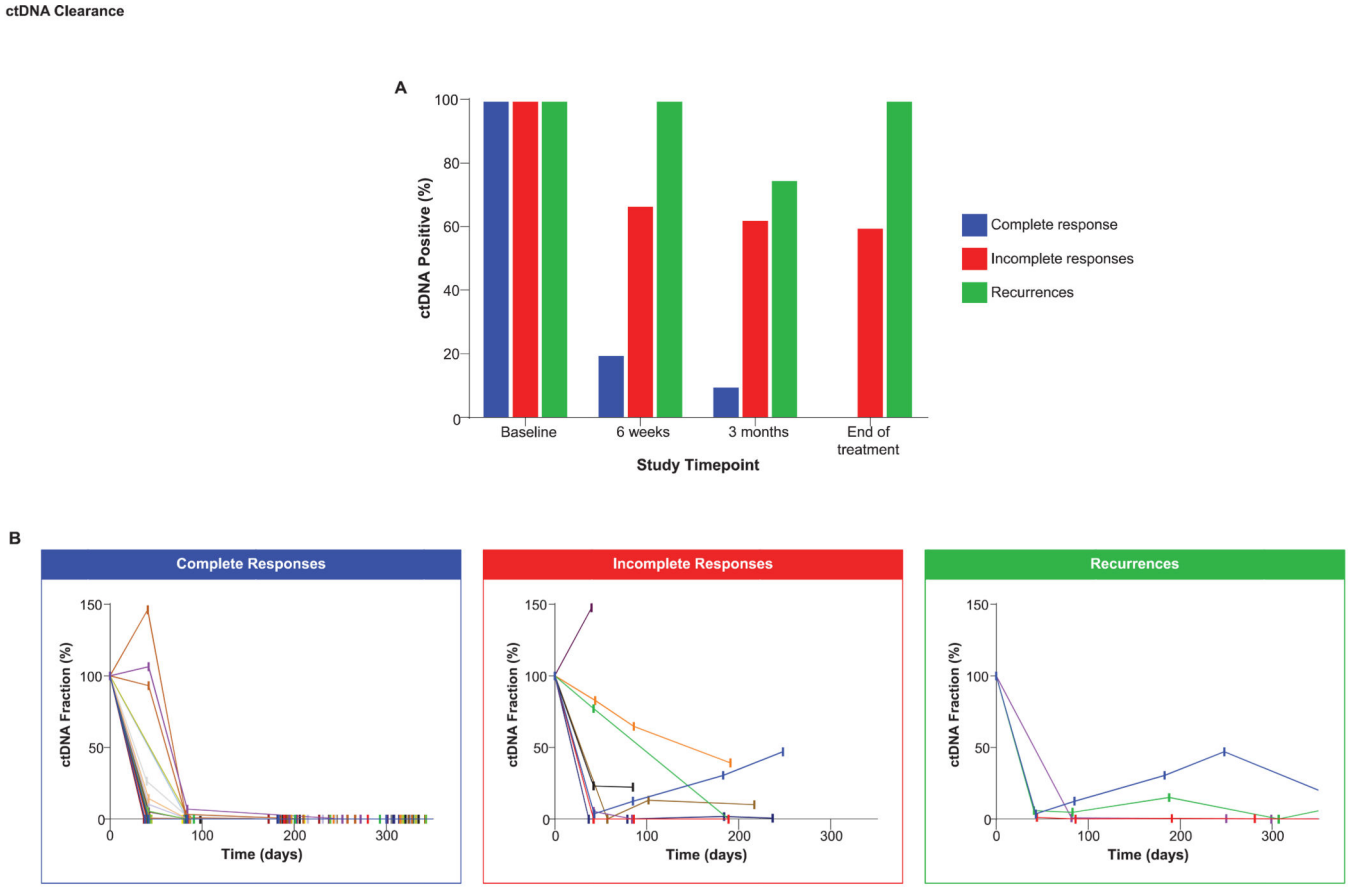


**Figure 3. Circulating tumor DNA dynamics.**

(A) fraction of patients achieving ctDNA clearance over time by type of response, (B) individual patient ctDNA levels normalized to baseline during treatment by type of response. ctDNA fraction is represented as the percent at each timepoint of the original baseline value.

**Table 1.**

Patient and tumor baseline characteristics

| Characteristic | Overall Cohort N = 117 | Cohort 1 N = 50 | Cohort 2 N = 67 |
|---|---|---|---|
| **Gender – no. (%)** | | | |
| Female | 57 (49%) | 28 (56%) | 29 (43%) |
| Male | 60 (51%) | 22 (44%) | 38 (57%) |
| **Age – median (Range)** | 57.0 (26, 87) | 51.0 (26, 78) | 67.0 (28,87) |
| **ECOG – no. (%)** | | | |
| 0 | 88 (75) | 40 (80) | 48 (72) |
| 1 | 29 (25%) | 10 (20%) | 19 (28%) |
| **Tumor Type – no. (%)** | | | |
| Rectal | 50 (43%) | 50 (100%) | 0 (0%) |
| Colon | 33 (28%) | 0 (0%) | 33 (49%) |
| Esophageal | 3 (2.6%) | 0 (0%) | 3 (4.5%) |
| GE Junction | 3 (2.6%) | 0 (0%) | 3 (4.5%) |
| Gastric | 15 (13%) | 0 (0%) | 15 (22%) |
| Urothelial | 7 (6.0%) | 0 (0%) | 7 (10%) |
| Prostate | 2 (1.7%) | 0 (0%) | 2 (3.0%) |
| Periampullary | 1 (0.9%) | 0 (0%) | 1 (1.5%) |
| Cholangiocarcinoma | 1 (0.9%) | 0 (0%) | 1 (1.5%) |
| Small Bowel | 1 (0.9%) | 0 (0%) | 1 (1.5%) |
| Endometrial | 1 (0.9%) | 0 (0%) | 1 (1.5%) |
| **Clinical Tumor Stage – no. (%)** | | | |
| T0 | 1 (0.9%) | 1 (2.0%) | 0 (0%) |
| T1/2 | 27 (23%) | 10 (20%) | 17 (25%) |
| T3 | 65 (56%) | 23 (46%) | 42 (63%) |
| T4 | 24 (21%) | 16 (32%) | 8 (12%) |
| **Clinical Nodal Stage – no. (%)** | | | |
| Node-positive | 75 (64%) | 42 (84%) | 33 (49%) |
| Node-negative | 42 (36%) | 8 (16%) | 34 (51%) |
| **Pathogenic LS-associated germline variants – no. (%)** | | | |
| MLH1 | 16 (14%) | 7 (14%) | 9 (13%) |
| MSH2 | 23 (20%) | 9 (18%) | 14 (21%) |
| MSH6 | 12 (10%) | 8 (16%) | 4 (6.0%) |
| None | 60 (51%) | 23 (46%) | 37 (55%) |
| Unknown | 6 (5.1%) | 3 (6.0%) | 3 (4.5%) |
| **Mismatch repair deficiency by IHC – no. (%)** | | | |
| MLH1 and PMS2 | 61 (52%) | 21 (42%) | 40 (60%) |
| MSH2 and MSH6 | 37 (32%) | 16 (32%) | 21 (31%) |
| MLH1 and MSH6 | 1 (0.9%) | 0 (0%) | 1 (1.5%) |

| Characteristic | Overall Cohort N = 117 | Cohort 1 N = 50 | Cohort 2 N = 67 |
|---|---|---|---|
| MSH2 alone | 3 (2.6%) | 3 (6.0%) | 0 (0%) |
| MSH6 alone | 9 (7.7%) | 5 (10%) | 4 (6.0%) |
| PMS2 alone | 6 (5.1%) | 5 (10%) | 1 (1.5%) |
| **MSI Score - median (Range)** | 18.8 (0.2, 39.4) | 19.3 (2.2, 37.6) | 18.7 (0.2, 39.4) |
| **Unknown** | 12 | 3 | 9 |
| **Tumor Mutational Burden - median (Range)** | 53.2 (4.9,145) | 62.3 (27.2, 106.3) | 50.3 (4.9, 145) |
| **Unknown** | 9 | 3 | 6 |

* The 7 excluded patients are not in this table

**TABLE 2.**

Adverse events

| | Combined Cohort 1 and 2 N=124 | |
|---|---|---|
| | **All Grades no. patients (%)** | **Grade 3 or 4 no. patients (%)** |
| **Dermatologic** | | |
| Rash/dermatitis * | 26 (21) | 0 (0) |
| Flushing | 2 (1.6) | 0 (0) |
| Pruritus | 24 (19) | 0 (0) |
| Dry skin | 5 (4) | 0 (0) |
| **Gastrointestinal** | | |
| Colitis | 2 (1.6) | 0 (0) |
| Constipation | 4 (3) | 0 (0) |
| Diarrhea | 11(9) | 0 (0) |
| Nausea | 8 (6) | 0 (0) |
| Dry mouth | 8 (6.5) | 0 (0) |
| **Constitutional** | | |
| Fatigue | 28 (23) | 0 (0) |
| Chills | 4 (3) | 0 (0) |
| Fever | 3 (2.4) | 0 (0) |
| Myalgia | 3 (2.4) | 0 (0) |
| Hot Flashes | 2(1.6) | 0(0) |
| Arthralgia | 9 (7) | 0(0) |
| Arthritis | 2 (1.6) | 0 (0) |
| **Neurologic** | | |
| Headache | 4 (3) | 0 (0) |
| Encephalitis | 0(0) | 1(1) |
| **Endocrine** | | |
| Diabetes | 0 (0) | 1(1) |
| Hyperthyroidism | 4 (3) | 0 (0) |
| Hypothyroidism | 16 (13) | 1 (1) |
| **Respiratory** | | |
| Cough | 2 (1.6) | 0 (0) |
| Lung Infection | 0 (0) | 1 (1) |
| **Renal/ Hydration/ Nutrition** | | |
| Creatinine increased | 2 (1.6) | 0 (0) |
| **Ophthalmologic** | | |
| Dry eye | 3 (2.5) | 0 (0) |
| **Blood and Lymphatic System** | | |
| **Infections, Other** | | |
| Neutrophil count decreased | 0(0) | 1 (1) |

| | Combined Cohort 1 and 2 N=124 | |
|---|---|---|
| | **All Grades no. patients (%)** | **Grade 3 or 4 no. patients (%)** |
| Febrile Neutropenia | 0 (0) | 1 (1) |
| Infusion Related Reaction | 3 (2.5) | 0 (0) |

*Includes all patients who received one or more doses of dostarlimab

**Only grade 1–2 toxicity in more than 2 subjects are shown