nature reviews clinical oncology

https://doi.org/10.1038/s41571-025-01054-6

Supplementary information

Therapeutic targeting of mismatch repair-deficient cancers

In the format provided by the authors and unedited

Supplementary Table 1. Representative clinical trials of immune checkpoint blockade in advanced or metastatic MMRd colorectal and endometrial cancer

Trial Name	Type of Treatment	Prior Treatments for Metastatic Disease	Number of Patients	ORR (%)	CR (%)	PD (%)	Median PFS (Months)	Median DOR (Months)	Median OS (Months)
Colorectal Cancer									
KEYNOTE 016 (expansion analysis)[1]	aPD-1	≥1	40	52.5	12.5	10.0	NR	Not reported	NR
KEYNOTE 164 (Cohort A)[2]	aPD-1	≥2	61	32.8	3.3	45.9	2.3	NR	31.4
KEYNOTE 164 (Cohort B)[2]	aPD-1	≥1	63	33.3	7.9	39.7	4.1	NR	NR
CheckMate 142[3]	aPD-1	≥1	74	31.1	0.0	25.7	14.3	NR	NR
GARNET[4]	aPD-1	≥1	115	43.5	12.2	Not reported	8.4	NR	NR
KEYNOTE 177[5]	aPD-1	0	153	45.1	13.1	29.4	16.5	NR	NR
CheckMate 142[6]	aPD-1 + aCTLA-4	0	45	68.9	13.3	13.3	NR	NR	NR
CheckMate 142[7]	aPD-1 + aCTLA-4	≥1	119	64.7	12.6	11.8	NR	NR	NR
CheckMate 8HW[8]	aPD-1 + aCTLA-4	0	171	Not reported	Not reported	Not reported	NR	Not reported	Not reported
CheckMate 8HW[8]	aPD-1 + aCTLA-4	≥0	296	70.6	30.4	10.1	NR	NR	Not reported
CheckMate 8HW[8]	aPD-1	≥0	286	57.7	28.0	18.9	39.3	NR	Not reported
Endometrial Cancer									
KEYNOTE 016 (expansion analysis)[9]	aPD-1	≥1	15	53.3	20.0	20.0	Not reported	Not reported	Not reported
KEYNOTE 158[10]	aPD-1	≥1	79	48.1	13.9	29.1	13.1	NR	NR
GARNET[4]	aPD-1	≥1	143	45.5	16.1	Not reported	6.0	NR	NR
NRG-GY018[11]	Carboplatin + Paclitaxel + aPD-1	0	112	Not reported	Not reported	Not reported	NR	Not reported	Not reported
RUBY[12]	Carboplatin + Paclitaxel + aPD-1	0	53	77.6	30.6	4.1	NR	NR	NR
DUO-E[13]	Carboplatin + Paclitaxel + aPD-L1	0	46	Not reported	Not reported	Not reported	NR	Not reported	Not reported

Legend: ORR = objective response rate; CR = complete response; PD = progressive disease; PFS = progression-free survival; DOR = duration of response; OS = overall survival; aPD-1 = anti-programmed cell death protein 1; aCTLA-4 = anti-cytotoxic T-lymphocyte associated protein 4; aPD-L1 = anti-programmed death ligand 1; NR = not reached

Supplementary Table 2. Representative clinical trials of immune checkpoint blockade in advanced or metastatic MMRd non-CRC/EC tumors

Trial Name and Treatment Type	Tumor Type	Number of Patients	ORR (%)	CR (%)	PFS (Months)	DOR (Months)	OS (Months)
KEYNOTE 158 (aPD-1)[14]	Gastric	24	45.8	16.7	11.0	NR	NR
	Cholangiocarcinoma	22	40.9	9.1	4.2	NR	24.3
	Pancreatic	22	18.2	4.5	2.1	13.4	4.0
	Small intestine	19	42.1	15.8	9.2	NR	NR
	Ovarian	15	33.3	20.0	2.3	NR	NR
	Brain	13	0.0	0.0	1.1	Not applicable	5.6
KEYNOTE 016 (aPD-1)[1]	Pancreatic	8	62.5	25.0	Not reported	Not reported	Not reported
	Gastroesophageal	5	60.0	60.0	Not reported	Not reported	Not reported
	Small intestine	5	80.0	40.0	Not reported	Not reported	Not reported
	Cholangiocarcinoma	4	25.0	25.0	Not reported	Not reported	Not reported
	Ampullary	4	25.0	25.0	Not reported	Not reported	Not reported

GARNET (aPD-1)[4]	Small intestine	23	39.1	21.7	8.1	NR	31.6
	Gastric	22	45.5	4.5	5.5	NR	20.1
	Pancreatic	12	41.7	0.0	3.3	NR	12.7
	Ovarian	7	42.9	0.0	Not reported	Not reported	Not reported

Legend: ORR = objective response rate; CR = complete response; PFS = progression-free survival; DOR = duration of response; OS = overall survival; aPD-1 = anti-programmed cell death protein 1; aPD-L1 = anti-programmed death ligand 1; NR = not reached

Supplementary Table 3. Representative clinical trials of neoadjuvant immune checkpoint blockade in MMRd solid tumors

Study Author, Year, and Name (if applicable)	Type of Treatment	Cancer Type	Neoadjuvant Treatment Regimen	Median Duration of Treatment (Months)	Organ Sparing Strategy	Number of patients for pCR or cCR analysis	Complete Response Rate (pCR or cCR)
Anti PD-1/PD-L1 monotherapy							
Avallone et al. 2020 (NICOLE)[15]	aPD-1	Colorectal	Nivolumab	1.00	No	3	0%
Xu et al. 2024[16]	aPD-1	Colorectal	Sintilimab	1.50	No	44	48%
Eerkens et al. 2024[17]	aPD-1	Endometrial	Pembrolizumab	1.50	No	10	0%
de la Fourchardiere et al. 2023 (IMHOTEP)[18]	aPD-1	Colorectal	Pembrolizumab	2.00	Possible	76	54%
Shiu et al. 2024 (NEOPRISM)[19]	aPD-1	Colorectal	Pembrolizumab	2.25	No	32	53%
de la Fourchardiere et al. 2023 (IMHOTEP)[20]	aPD-1	Non-CRC	Pembrolizumab	2.40	Possible	41	32%
Hu et al. 2024 (PICC)[21]	aPD-1	Colorectal	Toripalimab	3.00	No	22	73%
Xie et al. 2023[22]	aPD-1	Rectal	Pembrolizumab, Sintilimab, or Toripalimab	3.00	No	8	88%
Li et al. 2024[23]	aPD-L1	Colon	Envafolimab	3.00	Possible	15	67%
Pei et al. 2023[24]	aPD-1	Colorectal	Sintilimab	4.20	No	11	91%
Zhang et al. 2022[25]	aPD-1	Colorectal	Pembrolizumab, Sintilimab, or Toripalimab	4.50	Possible	24	79%
Cercek et al. 2025[26]	aPD-1	Rectal	Dostarlimab	6.00	Possible	49	100%
Cercek et al. 2025[26]	aPD-1	Colon	Dostarlimab	6.00	Possible	22	82%
Cercek et al. 2025[26]	aPD-1	Non-CRC	Dostarlimab	6.00	Possible	32	53%
Ludford et al. 2023[27]	aPD-1	Agnostic	Pembrolizumab	6.00	Possible	17	65%
Chen et al. 2023[28]	aPD-1	Rectal	Sintilimab	6.00	Possible	16	75%
Kothari et al. 2022[29]	aPD-1	Colorectal	Pembrolizumab or Nivolumab	7.00	No	4	100%
Anti-PD-1 + anti-CTLA-4							
Chalabi et al. 2020 (NICHE-1)[30]	aPD-1 + aCTLA-4	Colon	Nivolumab and ipilimumab	1.00	No	32	69%
Chalabi et al. 2024 (NICHE-2)[31]	aPD-1 + aCTLA-4	Colon	Nivolumab and ipilimumab	1.00	No	111	68%
Pan et al. 2024[32]	aPD-1 + aCTLA-4	Colorectal	Nivolumab and ipilimumab	1.00	No	10	80%
Xu et al. 2024[33]	aPD-1 + aCTLA-4	Colorectal	Sintilimab and IBI310	1.50	No	50	80%
Andre et al. 2022 (NEONIPIGA)[34]	aPD-1 + aCTLA-4	Gastric	Nivolumab and ipilimumab	3.00	No	29	59%
Raimondi et al. 2024 (INFINITY – Cohort 1)[35]	aPD-1 + aCTLA-4	Gastric or GEJ	Durvalumab and tremelimumab	3.00	No	15	60%
Raimondi et al. 2024 (INFINITY – Cohort 2)[35]	aPD-1 + aCTLA-4	Gastric or GEJ	Durvalumab and tremelimumab	3.00	Possible	17	76%
Other combinations that include anti-PD-1 therapy							
de Gooyer et al. 2024 (NICHE-3)[36]	aPD-1 + aLAG-3	Colon	Nivolumab and relatlimab	2.00	No	59	68%
Hu et al. 2024 (PICC)[21]	aPD-1 + COX2i	Colorectal	Toripalimab and celecoxib	3.00	No	20	90%
Yu et al. 2024 (NEOCAP – Surgical Cohort)[37]	aPD-1 + VEGFRi	Colorectal	Camrelizumab and apatinib	3.00	Possible	23	61%
Yu et al. 2024 (NEOCAP – Non-surgical Cohort)[37]	aPD-1 + VEGFRi	Colorectal	Camrelizumab and apatinib	6.00	Possible	29	83%

Legend: pCR = pathologic complete response; cCR = clinical complete response; aPD-1 = anti-programmed cell death protein 1; aPD-L1 = anti-programmed death ligand 1; CRC = colorectal cancer; aCTLA-4 = anti-cytotoxic T-lymphocyte associated protein 4; aLAG-3 = anti-lymphocyte activation gene 3; COX2i = cyclooxygenase 2 inhibitor; VEGFRi = vascular endothelial growth factor receptor inhibitor; GEJ = gastroesophageal junction.

1. Le D.T. *et al*. PD-1 blockade in tumors with mismatch-repair deficiency. *N. Engl. J. Med.* **372**, 2509-2520 (2015).
2. Le D.T. *et al*. Pembrolizumab for previously treated, microsatellite instability-high/mismatch repair-deficient advanced colorectal cancer: final analysis of KEYNOTE-164. *Eur. J. Cancer* **186**, 185–195 (2023).
3. Overman M.J. *et al*. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol.* **18**, 1182–1191 (2017).
4. André T. *et al*. Antitumor activity and safety of dostarlimab monotherapy in patients with mismatch repair deficient solid tumors: a nonrandomized controlled trial. *JAMA Netw Open.* **6**, e2341165 (2023).
5. Diaz L.A. *et al*. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *Lancet Oncol*. **23**, 659–670 (2022).
6. Lenz H.J. *et al*. First-line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the phase II CheckMate 142 Study. *J. Clin. Oncol.* **40**, 161-170 (2022).
7. André T. *et al*. Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. *Ann Oncol*. 33, 1052–1060 (2022).
8. André T. *et al*. Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial. *Lancet* **405**, 383–395 (2025).
9. Bellone S. *et al*. A phase 2 evaluation of pembrolizumab for recurrent Lynch-like versus sporadic endometrial cancers with microsatellite instability. *Cancer*. **128**, 1206–1218 (2022)
10. O'Malley D.M. *et al*. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: results from the KEYNOTE-158 study. *J. Clin. Oncol.* **40**, 752–761 (2022).
11. Eskander R.N. et al. Pembrolizumab plus chemotherapy in advanced or recurrent endometrial cancer: overall survival and exploratory analyses of the NRG GY018 phase 3 randomized trial. *Nat Med.* 31, 1539–1546 (2025).
12. Powell M.A. *et al*. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. *Ann Oncol* **35**, 728–738 (2024).
13. Westin S.N. *et al*. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: the phase III DUO-E trial. *J. Clin. Oncol.* **42**, 283–299 (2024).
14. Marabelle A. *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*. **38**, 1–10 (2020).
15. Avallone A. *et al*. Neoadjuvant nivolumab in early stage colorectal cancer. *Ann Oncol*. **31** suppl 4, S449 (2020).

16. Xu R.H. *et al*. Neoadjuvant treatment of IBI310 (anti-CTLA-4 antibody) plus sintilimab (anti-PD-1 antibody) in patients with microsatellite instability-high/mismatch repair-deficient colorectal cancer: Results from a randomized, open-labeled, phase Ib study. *J Clin Oncol.* **42**, suppl_16, 3505 (2024).
17. Eerkens A.L. *et al*. Neoadjuvant immune checkpoint blockade in women with mismatch repair deficient endometrial cancer: a phase I study. *Nat Commun*. **15**, 7695 (2024)
18. de La Fouchardiere C *et al*. IMHOTEP Phase II trial of neoadjuvant pembrolizumab in dMMR/MSI tumors: Results of the colorectal cancer cohort. *Ann Oncol*. **35**, suppl_2 S429 (2024).
19. Shiu, K.K. *et al*. NEOPRISM-CRC: neoadjuvant pembrolizumab stratified to tumour mutation burden for high risk stage 2 or stage 3 deficient-MMR/MSI-high colorectal cancer. *J. Clin. Oncol.* **42**, suppl 17:LBA3504 (2024).
20. de la Fouchardiere, C. *et al*. IMHOTEP phase II trial of neoadjuvant pembrolizumab in dMMR/MSI localized cancers: results of the digestive non-colorectal cancer cohorts. *Ann Oncol*. **35**, suppl 2, S899–S900 (2024).
21. Hu, H. *et al*. Long-term outcomes of neoadjuvant toripalimab with or without celecoxib in patients with dMMR/MSI-H locally advanced colorectal cancer: 3-month treatment cohort of the randomized phase II PICC trial. *Ann Oncol*. **35**, suppl 2, S452–S453 (2024).
22. Xie Y. *et al*. Prevalent Pseudoprogression and Pseudoresidue in Patients With Rectal Cancer Treated With Neoadjuvant Immune Checkpoint Inhibitors. *J Natl Compr Cancer Netw JNCCN*. **21**, 133–142 (2023)
23. Li Y. *et al*. Efficacy and safety of neoadjuvant subcutaneous envafolimab in dMMR/MSI-H locally advanced colon cancer. *Target Oncol.* **19**, 601–610 (2024).
24. Pei F. *et al*. Single-agent neoadjuvant immunotherapy with a PD-1 antibody in locally advanced mismatch repair-deficient or microsatellite instability-high colorectal cancer. *Clin Colorectal Cancer.* **22**, 85–91 (2023).
25. Zhang X. *et al*. Efficacy and safety of neoadjuvant monoimmunotherapy with PD-1 inhibitor for dMMR/MSI**-**H locally advanced colorectal cancer: a single-center real-world study. *Front Immunol.* **13**, 913483 (2022).
26. Cercek A. *et al*. Nonoperative management of mismatch repair-deficient tumors. *N. Engl. J. Med.* doi:10.1056/NEJMoa2404512 (2025).
27. Ludford K. *et al*. Neoadjuvant pembrolizumab in localized microsatellite instability high/deficient mismatch repair solid tumors. *J. Clin. Oncol*. **41**, 2181–2190 (2025).
28. Chen, G. *et al*. Neoadjuvant PD-1 blockade with sintilimab in mismatch-repair deficient, locally advanced rectal cancer: an open-label, single-centre phase 2 study. *Lancet Gastroenterol Hepatol.* **8**, 422–431 (2023).
29. Kothari A. *et al*. Pathological response following neoadjuvant immunotherapy in mismatch repair-deficient/microsatellite instability-high locally advanced, non-metastatic colorectal cancer. *Br. J. Surg.* **109**, 489-492 (2022).
30. Chalabi M. *et al*. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med.* **26**, 566–576 (2020).
31. Chalabi M. *et al*. Neoadjuvant immunotherapy in locally advanced mismatch repair-deficient colon cancer. *N. Engl. J. Med.* 390, 1949–1958 (2024).
32. Pan T. *et al*. Neoadjuvant immunotherapy with ipilimumab plus nivolumab in mismatch repair deficient/microsatellite instability-high colorectal cancer: a preliminary report of case series. *Clin Colorectal Cancer.* **23**,104–110 (2024).

33. Xu R.H. *et al*. Neoadjuvant treatment of IBI310 (anti-CTLA-4 antibody) plus sintilimab (anti-PD-1 antibody) in patients with microsatellite instability-high/mismatch repair-deficient colorectal cancer: Results from a randomized, open-labeled, phase Ib study. *J Clin Oncol.* **42**, suppl 16, 3505 (2024).
34. André T. *et al*. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: The GERCOR NEONIPIGA phase II study. *J Clin. Oncol.* **41**, 255-265 (2023).
35. Raimondi A. *et al*. Multicentre, multi-cohort, single-arm phase II trial of tremelimumab and durvalumab as neoadjuvant or definitive treatment of patients (pts) with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC): The INFINITY study. *Ann Oncol*. 35, suppl_1, S172 (2024).
36. de Gooyer P.G.M. et al. Neoadjuvant nivolumab and relatlimab in locally advanced MMR-deficient colon cancer: a phase 2 trial. *Nat Med*. 30, 3284-3290 (2024).
37. Yu J.H. *et al*. Neoadjuvant camrelizumab plus apatinib for locally advanced microsatellite instability-high or mismatch repair-deficient colorectal cancer (NEOCAP): a single-arm, open-label, phase 2 study. *Lancet Oncol.* **25**, 843-852 (2024).