

Supplementary Table S1. Distribution by tumor type and clinical efficacy of pembrolizumab in dMMR/MSI-H GI cancers.

Tumor type	Patients enrolled (n)	Clinical trials (phase)	Objective response rate, n (%)	Duration of response, range (mo)
Colorectal cancer	90	KEYNOTE-016 (2, multicohort) KEYNOTE-164 (2) KEYNOTE-028 (1b, multicohort)	32 (36%, 95% CI 26% - 46%)	1.6+ - 22.7+ mo
Gastrointestinal non-CRC	24	KEYNOTE-016 (2, multicohort) KEYNOTE-012 (1b, multicohort) KEYNOTE-028 (1b, multicohort) KEYNOTE-158 (2)	14 (58%)	1.9+ - 22.1+ mo
Gastric cancer/GEJ cancer	9		5 (56%, 95% CI 21% - 86%)	5.8+ - 22.1+ mo
Pancreatic cancer	6		5 (83%, 95% CI 36% - 100%)	2.6+ - 9.2+ mo
Small intestinal cancer	8		3 (38%, 95% CI 9% - 76%)	1.9+ - 9.1+ mo
Esophageal cancer	1		1 PR	18.2+ mo

Adapted from pembrolizumab FDA Highlights of Prescribing Information document. 

Abbreviations: CRC, colorectal cancer; GEJ, gastro-esophageal junction; CI, confidence interval; PR, partial response; mo, months.

Supplementary Table S2. Ongoing clinical trials testing different ICI-based strategies in GI cancers.

NCT Number	Phase	IC Ab	Interventions	Setting	Title
Colorectal cancer					
NCT03555149	1/2	Anti-PD-L1 Anti-CD38	Atezolizumab (anti-PD-L1) Isatuximab (anti-CD38) Regorafenib Imprime PGG (PAMP) Bevacizumab	Advanced	A Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients With Metastatic Colorectal Cancer (Morpheus-CRC)
NCT03507699	1	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) CMP-001 (TLR9 agonist) Radiotherapy	Advanced	Combined Immunotherapy and Radiosurgery for Metastatic Colorectal Cancer
NCT03414983	2/3	Anti-PD-1	Nivolumab (anti-PD-1) Oxaliplatin Leucovorin Fluorouracil Bevacizumab	Advanced	An Investigational Immunotherapy Study of Nivolumab With Standard of Care Therapy vs Standard of Care Therapy for First-Line Treatment of Colorectal Cancer That Has Spread
NCT03377361	1/2	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) Trametinib	Advanced	An Investigational Immunotherapy Study of Nivolumab In Combination With Trametinib With or Without Ipilimumab In Patients With Previously Treated Cancer of the Colon or Rectum That Has Spread
NCT03202758	1/2	Anti-PD-L1 Anti-CTLA-4	Durvalumab (anti-PD-L1) Tremelimumab (anti-CTLA-4) FOLFOX	Advanced	Evaluation of the Safety and the Tolerability of Durvalumab Plus Tremelimumab Combined With FOLFOX in mCRC
NCT03186326	2	Anti-PD-L1	Avelumab (anti-PD-L1) Panitumumab/Cetuximab Bevacizumab/Aflibercept FOLFOX/FOLFIRI	Advanced	Standard Chemotherapy vs Immunotherapy in Second-Line Treatment of MSI Colorectal Metastatic Cancer

NCT03169777	1/2	Anti-PD-1 Anti-PD-L1	Nivolumab (anti-PD-1) Avelumab (anti-PD-L1) Bevacizumab Capecitabine Cetuximab Cyclophosphamide Fluorouracil Fulvestrant Leucovorin Nab-paclitaxel Omega-3-acid ethyl esters Oxaliplatin SBRT ALT-803 ETBX-011 ETBX-021 ETBX-051 ETBX-061 GI-4000 GI-6207 GI-6301 haNK	Advanced	QUILT-3.050: NANT Colorectal Cancer (CRC) Vaccine: Combination Immunotherapy in Subjects With Recurrent or Metastatic CRC
NCT03127007	1/2	Anti-PD-L1	Atezolizumab (anti-PD-L1) Chemoradiotherapy	Localized	Safety and Efficacy of Atezolizumab Combined to Preoperative Radio-chemotherapy in Localized Rectal Cancer
NCT03101475	2	Anti-PD-L1 Anti-CTLA-4	Durvalumab (anti-PD-L1) Tremelimumab (anti-CTLA-4) SBRT Radiofrequency ablation	Advanced	Synergism of Immunomodulation and Tumor Ablation
NCT03026140	2	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) Celecoxib	Localized	Nivolumab, Ipilimumab and COX2-inhibition in Early Stage Colon Cancer: an Unbiased Approach for Signals of Sensitivity

NCT02997228	3	Anti-PD-L1	Atezolizumab (anti-PD-L1) Bevacizumab Fluorouracil Leucovorin Oxaliplatin	Advanced	Combination Chemotherapy, Bevacizumab, and/or Atezolizumab in Treating Patients With Deficient DNA Mismatch Repair Metastatic Colorectal Cancer
NCT02876224	1	Anti-PD-L1	Atezolizumab (anti-PD-L1) Bevacizumab Cobimetinib	Advanced	Study of Cobimetinib in Combination With Atezolizumab and Bevacizumab in Participants With Gastrointestinal and Other Tumors
NCT02060188	2	Anti-PD-1 Anti-CTLA-4 Anti-LAG-3	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) Anti-LAG-3 Cobimetinib Daratumumab	Advanced	An Investigational Immunotherapy Study of Nivolumab, and Nivolumab in Combination With Other Anticancer Drugs, in Colon Cancer That Has Come Back or Has Spread
Gastric cancer & Gastroesophageal cancer					
NCT03448835	2	Anti-PD-L1	Atezolizumab (anti-PD-L1) Capecitabine Oxaliplatin Docetaxel	Localized	Neoadjuvant Capecitabine, Oxaliplatin, Docetaxel and Atezolizumab in Resectable Gastric and GE-junction Cancer (PANDA)
NCT03443856	2	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) Chemotherapy	Localized	Postoperative Immunotherapy vs Standard Chemotherapy for Gastric Cancer With High Risk for Recurrence
NCT03281369	1/2	Anti-PD-L1	Atezolizumab (anti-PD-L1) BL-8040 (anti-CXCR4) Fluorouracil Leucovorin Oxaliplatin Cobimetinib Ramucirumab Paclitaxel PEGylated recombinant human hyaluronidase	Advanced	A Study of Multiple Immunotherapy-Based Treatment Combinations in Patients With Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Cancer (G/GEJ) (Morpheus-Gastric Cancer)

			Linagliptin		
NCT02340975	1/2	Anti-PD-L1 Anti-CTLA-4	Durvalumab (anti-PD-L1) Tremelimumab (anti-CTLA-4)	Advanced	A Phase 1b/2 Study of MEDI4736 With Tremelimumab, MEDI4736 or Tremelimumab Monotherapy in Gastric or GEJ Adenocarcinoma
NCT02689284	1/2	Anti-PD-1	Pembrolizumab (anti-PD-1) Margetuximab	Advanced	Combination Margetuximab and Pembrolizumab for Advanced, Metastatic HER2(+) Gastric or Gastroesophageal Junction Cancer
NCT03382600	2	Anti-PD-1	Pembrolizumab (anti-PD-1) Oxaliplatin TS-1 Cisplatin	Advanced	Safety and Efficacy of Pembrolizumab (MK-3475) in Combination With TS-1 + Cisplatin or TS-1 + Oxaliplatin as First-Line Chemotherapy in Gastric Cancer (MK-3475-659/KEYNOTE-659)
NCT03409848	2	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4)	Advanced	Ipilimumab or FOLFOX in Combination With Nivolumab and Trastuzumab in HER2 Positive Esophago-Gastric Adenocarcinoma
Esophageal cancer					
NCT03416244	2	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4)	Advanced	A Multicenter Open-label Phase II Trial to Evaluate Nivolumab and Ipilimumab for Second-Line Therapy in Elderly Patients With Advanced Esophageal Squamous Cell Cancer
NCT03544736	1/2	Anti-PD-1	Nivolumab (anti-PD-1) Radiotherapy Chemotherapy Surgery	Advanced/ Localized	Safety and Feasibility of Irradiation and Nivolumab in Esophageal Cancer (INEC)
NCT03437200	2	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) Chemoradiotherapy	Advanced	Combination of Chemoradiation With Immunotherapy in Inoperable Esophageal Cancer
NCT03377400	2	Anti-PD-L1	Durvalumab (anti-PD-L1)	Advanced	Definitive CCRT Combined With Durvalumab and Tremelimumab for Inoperable Esophageal Cancer
NCT02735239	1/2	Anti-PD-L1 Anti-CTLA-4	Durvalumab (anti-PD-L1) Tremelimumab (anti-CTLA-4) Oxaliplatin Capecitabine Paclitaxel Carboplatin Radiotherapy	Advanced/ Localized	Study of Anti-PD-L1 in Combination With Chemo(Radio) Therapy for Esophageal Cancer

Pancreatic cancer

NCT03336216	2	Anti-PD-1	Nivolumab (anti-PD-1) Cabiralizumab Nab-paclitaxel Liposomal irinotecan Fluorouracil Gemcitabine Oxaliplatin Leucovorin Irinotecan	Advanced	A Study of Cabiralizumab Given With Nivolumab With and Without Chemotherapy in Patients With Advanced Pancreatic Cancer
NCT03193190	1/2	Anti-PD-L1	Atezolizumab (anti-PD-L1) BL-8040 (anti-CXCR4) Nab-Paclitaxel Gemcitabine Oxaliplatin Leucovorin Fluorouracil Cobimetinib PEGPH20	Advanced	A Study of Multiple Immunotherapy-Based Treatment Combinations in Participants With Metastatic Pancreatic Ductal Adenocarcinoma (Morpheus-Pancreatic Cancer)
NCT03168139	1/2	Anti-PD-1	Pembrolizumab (anti-PD-1) Olaptesed pegol	Advanced	Olaptesed (NOX-A12) Alone and in Combination With Pembrolizumab in Colorectal and Pancreatic Cancer
NCT03161379	2	Anti-PD-1	Nivolumab (anti-PD-1) Cyclophosphamide GVAX SBRT	Localized	Phase 2 GVAX Pancreas Vaccine (With CY) in Combination With Nivolumab and SBRT for Patients With Borderline Resectable Pancreatic Cancer
NCT03153410	1	Anti-PD-1	Pembrolizumab (anti-PD-1) IMC-CS4 (anti-CSF1R) Cyclophosphamide GVAX	Localized	Pilot Study With CY, Pembrolizumab, GVAX, and IMC-CS4 (LY3022855) in Patients With Borderline Resectable Adenocarcinoma of the Pancreas
NCT03098160	1	anti-CTLA-4	Ipilimumab (anti-CTLA-4) Evofosfamide	Advanced	Immunotherapy Study of Evofosfamide in Combination With Ipilimumab

NCT02734160	1	Anti-PD-L1	Durvalumab (anti-PD-L1) Galunisertib (TGFβ-Rli)	Advanced	A Study of Galunisertib (LY2157299) and Durvalumab (MEDI4736) in Participants With Metastatic Pancreatic Cancer
NCT02648282	2	Anti-PD-1	Pembrolizumab (anti-PD-1) Cyclophosphamide GVAX SBRT	Advanced	Study With CY, Pembrolizumab, GVAX, and SBRT in Patients With Locally Advanced Pancreatic Cancer
NCT02305186	1/2	Anti-PD-1	Pembrolizumab (anti-PD-1) Chemoradiotherapy	Localized	Safety and Immunological Effect of Pembrolizumab in Resectable or Borderline Resectable Pancreatic Cancer
Hepatocellular carcinoma					
NCT03510871	2	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4)	Localized	Nivolumab Plus Ipilimumab as Neoadjuvant Therapy for Hepatocellular Carcinoma (HCC)
NCT03299946	1	Anti-PD-1	Nivolumab (anti-PD-1) Cabozantinib	Localized	Feasibility and Efficacy of Neoadjuvant Cabozantinib Plus Nivolumab (CaboNivo) Followed by Definitive Resection for Patients With Locally Advanced Hepatocellular Carcinoma (HCC)
NCT03203304	1	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) SBRT	Advanced	Stereotactic Body Radiotherapy (SBRT) Followed by Immunotherapy in Liver Cancer
NCT03071094	1/2	Anti-PD-1	Nivolumab (anti-PD-1) Pexastimogene Devacirepvec	Advanced	A Trial to Evaluate the Safety and Efficacy of the Combination of the Oncolytic Immunotherapy Pexa-Vec With the PD-1 Receptor Blocking Antibody Nivolumab in the First-Line Treatment of Advanced Hepatocellular Carcinoma (HCC)
NCT02988440	1	Anti-PD-1	PDR001 (anti-PD-1) Sorafenib	Advanced	Study of Safety and Tolerability of PDR001 in Combination With Sorafenib and to Identify the Maximum Tolerated Dose and/or Phase 2 Dose for This Combination in Advanced Hepatocellular Patients
NCT02886897	1/2	Anti-PD-1	Anti-PD-1 Dendritic cell activated cytokine-induced killer cell	Advanced	A Study of Combinations of D-CIK Immunotherapy And Anti-PD-1 In Refractory Solid Tumors
NCT02576509	3	Anti-PD-1	Nivolumab (anti-PD-1) Sorafenib	Advanced	An Investigational Immuno-therapy Study of Nivolumab Compared to Sorafenib as a First Treatment in Patients With Advanced Hepatocellular Carcinoma

NCT02519348	2	Anti-PD-L1 Anti-CTLA-4	Durvalumab (anti-PD-L1) Tremelimumab (anti-CTLA-4)	Advanced	A Study of MEDI4736 With Tremelimumab, MEDI4736 or Tremelimumab Monotherapy in Unresectable Hepatocellular Carcinoma
NCT01658878	1/2	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) Sorafenib Cabozantinib	Advanced	An Immunotherapy Study to Evaluate the Effectiveness, Safety and Tolerability of Nivolumab or Nivolumab in Combination With Other Agents in Patients With Advanced Liver Cancer
Biliary tract cancers					
NCT03110328	2	Anti-PD-1	Pembrolizumab (anti-PD-1)	Advanced	Study of Pembrolizumab in Metastatic Biliary Tract Cancer as Second-Line Treatment After Failing to at Least One Cytotoxic Chemotherapy Regimen: Integration of Genomic Analysis to Identify Predictive Molecular Subtypes
NCT03101566	2	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) Gemcitabine Cisplatin	Advanced	Study of Nivolumab in Combination With Gemcitabine/Cisplatin or Ipilimumab for Patients With Advanced Unresectable Biliary Tract Cancer
NCT02829918	2	Anti-PD-1	Nivolumab (anti-PD-1)	Advanced	Study of Nivolumab in Patients With Advanced Refractory Biliary Tract Cancers
NCT02982720	2	Anti-PD-1	Pembrolizumab (anti-PD-1) Sylatron (Peg-IFN α -2b)	Advanced	Evaluating Combination Immunotherapy for Advanced Cholangiocarcinoma With Pembrolizumab and PEG-Intron
Miscellany					
Colorectal cancer & Pancreatic cancer					
NCT03373188	1	Anti-PD-1 Anti-CTLA-4	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) VX15/2503 (anti-SEMA4D) Surgery	Localized/ Advanced	VX15/2503 and Immunotherapy in Resectable Pancreatic and Colorectal Cancer
Cholangiocarcinoma & Pancreatic cancer					
NCT03250273	2	Anti-PD-1	Nivolumab (anti-PD-1) Entinostat (HDACi)	Advanced	A Clinical Trial of Entinostat in Combination With Nivolumab for Patients With Previously Treated Unresectable or Metastatic Cholangiocarcinoma and Pancreatic Adenocarcinoma
Colorectal cancer, Pancreatic cancer & Other Non-GI tumors					

NCT03549000	1	Anti-PD-1 Anti-CD73	PDR001 (anti-PD-1) NZV930 (anti-CD73) NIR178 (anti-A2AR)	Advanced	A Phase I/Ib Study of NZV930 Alone and in Combination With PDR001 and /or NIR178 in Patients With Advanced Malignancies.
NCT03058289	1/2	Anti-PD-1	Anti-PD-1 INT230-6	Advanced	A Phase 1/2 Safety Study of Intratumorally Dosed INT230-6
Colorectal cancer, Pancreatic cancer, Esophageal cancer & Other Non-GI tumors					
NCT01351103	1	Anti-PD-1	PDR001 (anti-PD-1) LGK974 (PORCNI) ^a	Advanced	A Study of LGK974 in Patients With Malignancies Dependent on Wnt Ligands
Colorectal cancer, Pancreatic cancer, Gastric cancer, Hepatocellular carcinoma & Other Non-GI tumors					
NCT01174121	2	Anti-PD-1	Pembrolizumab (anti-PD-1) Young TIL Aldesleukin Cyclophosphamide Fludarabine	Advanced	Immunotherapy Using Tumor Infiltrating Lymphocytes for Patients With Metastatic Cancer
Solid tumors					
NCT03511222	1	Anti-PD-1	Nivolumab (anti-PD-1) Pembrolizumab (anti-PD-1) Vorolanib	Advanced	Vorolanib (X-82) Combined With Checkpoint Inhibitors in Patients With Solid Tumors ^b
NCT03474640	1	Anti-PD-1	TAB001 (anti-PD-1)	Advanced	Safety, Tolerability and Pharmacokinetics of an Anti-PD-1 Monoclonal Antibody in Subjects With Advanced Malignancies
NCT03289962	1	Anti-PD-L1	Atezolizumab (anti-PD-L1) RO7198457	Advanced	A Study of RO7198457 (Personalized Cancer Vaccine [PCV]) as a Single Agent and in Combination With Atezolizumab in Participants With Locally Advanced or Metastatic Tumors
NCT02817633	1	Anti-PD-1 Anti-TIM-3	Anti-PD-1 TSR-022 (anti-TIM-3)	Advanced	A Phase 1 Study of TSR-022, an Anti-TIM-3 Monoclonal Antibody, in Patients With Advanced Solid Tumors
NCT02743494	3	Anti-PD-1	Nivolumab (anti-PD-1)	Localized	An Investigational Immuno-therapy Study of Nivolumab or Placebo in Patients With Resected Esophageal or Gastroesophageal Junction Cancer

NCT02554812	2	Anti-PD-L1 anti-CD137	Avelumab (anti-PD-L1) Utomilumab (anti-CD137) PF-04518600 PD 0360324	Advanced	A Study Of Avelumab In Combination With Other Cancer Immunotherapies In Advanced Malignancies (JAVELIN Medley)
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^a Wnt signaling inhibitor.

^b Dose escalation cohort: histologically or cytologically confirmed diagnosis of a solid tumor that can be treated with either pembrolizumab or nivolumab as part of standard of care.

Abbreviations: ICI, immune checkpoint inhibitors; GI, gastrointestinal; IC Ab, immune checkpoint antibody; PAMP, pathogen-associated molecular pattern; SBRT, stereotactic body radiotherapy; TGFβ-Rli, TGFβ-Receptor I inhibitor; HDACi, histone deacetylase inhibitor; A2AR, adenosine A2A receptor; PORCNI, porcupine inhibitor; TIL, tumor-infiltrating lymphocytes.