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REVIEW ARTICLE

Cautious optimism—the current role of immunotherapy in gastrointestinal cancers

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ABSTRACT

Immunotherapy has been described as the "fourth pillar" of oncology treatment, in conjunction with surgery, chemotherapy, and radiotherapy. However, the role of immunotherapy in gastrointestinal tumours is still evolving. Data for checkpoint inhibition in esophagogastric, hepatocellular, colorectal, and anal squamous cell carcinomas are expanding. In phase III trials in the second-line setting, PD-1 inhibitors have demonstrated positive results for the subset of esophageal cancers that are positive for PD-L1 at a combined positive score of 10 or more. Based on results of phase II trials, PD-1 inhibitors were approved in North America for use in PD-L1–positive chemorefractory gastric cancers, in hepatocellular carcinoma after sorafenib exposure, and in treatment-refractory deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H) tumours, regardless of tissue site. Combination use of PD-1 and CTLA-4 inhibitors has been approved by the U.S. Food and Drug Administration for chemorefractory dMMR or MSI-H colorectal cancer. Responses to checkpoint inhibition are durable, particularly in the dMMR or MSI-H colorectal cancer cohort. As trials of combination immunotherapy, immunotherapy in combination with other systemic therapies, and immunotherapy in combination with other treatment modalities move forward in multiple tumour sites, cautious optimism is called for. The treatment landscape is continually changing, and expanded indications are likely to be just around the corner.

Key Words Gastrointestinal neoplasms, esophageal neoplasms, stomach neoplasms, hepatocellular cancer, colorectal neoplasms, monoclonal antibodies, immunologic antineoplastic agents, microsatellite instability

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INTRODUCTION

Recognition of the role that immunotherapy can play in cancer treatment dates back to the first reports of tumour regression with interferon published in the 1970s[1]. Some have described immunotherapy as the "fourth pillar" of oncology treatment (in conjunction with surgery, chemotherapy, and radiotherapy) since novel immunotherapy with checkpoint inhibitors revolutionized the treatment landscape in melanoma[2,3], but the application of immunotherapy to gastrointestinal tumours has not been as straightforward.

Key concepts in immunotherapy are that neoantigen formation, because of the presence of genetic and epigenetic mutations in cancer cells, can lead to recognition and therefore destruction of cancer cells by the immune system, and that immune checkpoints can be manipulated to evade such destruction[4,5]. That interplay between the cancer and the immune system is critical to the efficacy of checkpoint inhibition[6,7].

Immune checkpoints facilitate T cell recognition of antigens as either "self" or "non-self," leading to immune tolerance or immune activation respectively[8,9]. Binding of CTLA-4 on a T cell with its corresponding ligand on an antigen-presenting cell prevents T cell activation during presentation of a foreign antigen[10]. Within the tumour microenvironment, binding of PD-1 on a T cell with its corresponding ligand, either PD-L1 or PD-L2, on the tumour cell itself similarly promotes T cell anergy[11]. Using checkpoint inhibitors such as the CTLA-4, PD-1, and PD-L1 inhibitors to block the interactions with T cells that facilitate T cell quiescence removes the inhibitory effect, allowing T cells to become or remain activated and to facilitate immune-mediated destruction of cancer cells. An excellent overview, with illustrative figures, of the pathways involved can be found in the article by Topalian *et al.*[12] in *Cancer Cell.*

Unselected tumours outside of melanoma and renal clear-cell carcinoma have a limited response to checkpoint blockade, in part because of a lower burden of somatic mutations[13]. Gastrointestinal tumours typically have fewer than 10 somatic mutations per megabase[14,15]. A number of early immunotherapy studies enrolled only participants with PD-L1–positive tumours, defined as PD-L1 expression in 1% or more of tumour cells[16,17], or a combined positive score from an assessment of PD-L1 expression in tumour

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and immune cells, finding enriched response rates[18]. Putative predictors of response to immunotherapy are now recognized to include tumour mutational burden (TMB)[19,20]; neoantigen load[21]; deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H), which are surrogates for high TMB[22,23]; T cell infiltrate[19,24]; and PD-L1 expression, quantified by various means[19].

Phase II and III clinical trial data for checkpoint inhibition in esophagogastric, hepatocellular, colorectal, and anal squamous cell carcinomas are expanding, and in the present review, we focus primarily on the data available in those tumour types at 30 June 2019. Response assessment uses RECIST (the Response Evaluation Criteria in Solid Tumors), version 1.1, unless otherwise stated. Biliary cancers, neuroendocrine tumours, and gastrointestinal stromal tumours are not discussed because of a current paucity of data for those sites. Our review also does not focus on the toxicities specific to immunotherapy, apart from highlighting the importance of a high index of suspicion for immune-related adverse events in patients who have received immunotherapy.

To appreciate the rapidity with which the treatment landscape is changing, it is illustrative to compare timelines for the approval of immunotherapeutic drugs for use in gastrointestinal tumours in the United States and Canada up to 30 June 2019 (Figure 1). However, it should be noted that, in Canada, approval by Health Canada does not necessarily imply access to a drug on any provincial formulary[25].

REVIEW

Upper Gastrointestinal Tract Cancers

Esophagogastric Cancer

The phase IB KEYNOTE-028 trial enrolled 475 patients with PD-L1–positive (≥ 1%) cancer at 20 tumour sites; Table I summarizes the data pertinent to gastrointestinal tumours. Table II summarizes phase II data for esophagogastric cancers. Japanese patients with squamous cell carcinoma (SCC) of the esophagus who were chemorefractory or chemointolerant received nivolumab in the ATTRACTION-1 trial[34]. Global phase II data for the PD-1 inhibitor pembrolizumab in tumours of the esophagus and gastroesophageal junction (GEJ) come from KEYNOTE-180, which demonstrated an improved response rate in SCC and PD-L1–positive tumours as defined by a combined positive score (CPS) of 10 or greater[18]. The CPS is calculated by dividing the number of tumour cells, macrophages, and lymphocytes that express PD-L1 by the total number of tumour cells within the microscopic field and then multiplying by 100.

For metastatic gastric or GEJ tumours, the single-arm multi-cohort phase II KEYNOTE-059 study assessed the use of pembrolizumab in patients who had progressed after 2 or more lines of therapy (cohort 1) or who were treatment-naïve (cohorts 2 and 3). Cohort 1 enrolled 259 patients who received pembrolizumab and who experienced a response rate of 12%, with 4 of the 30 responders having MSI-H status[33]. The median duration of response (mDOR) was 8.4 months; the median progression free survival, 2 months; median overall survival (mOS), 5.6 months; and the 12-month overall survival (OS), 23%. In the trial, PD-L1–positivity was defined as a CPS of 1% or greater. The response rate was 16% in PD-L1–positive patients and 6% in PD-L1–negative patients. The mDOR was longer for PD-L1–positive patients than for PD-L1–negative patients (16 months vs. 7 months). Table II summarizes the results for cohorts 2 and 3[31,32]. Based on the KEYNOTE-059 results, the U.S. Food and Drug Administration (FDA) granted approval to pembrolizumab for patients with chemorefractory locally advanced or metastatic gastric or GEJ adenocarcinoma when the tumour expresses PD-L1 as determined by a U.S. FDA–approved test[36].

Moving to phase III studies (Table III), KEYNOTE-181 evaluated pembrolizumab against investigator's choice of paclitaxel, docetaxel, or irinotecan in a global population of patients progressing after first-line therapy for advanced

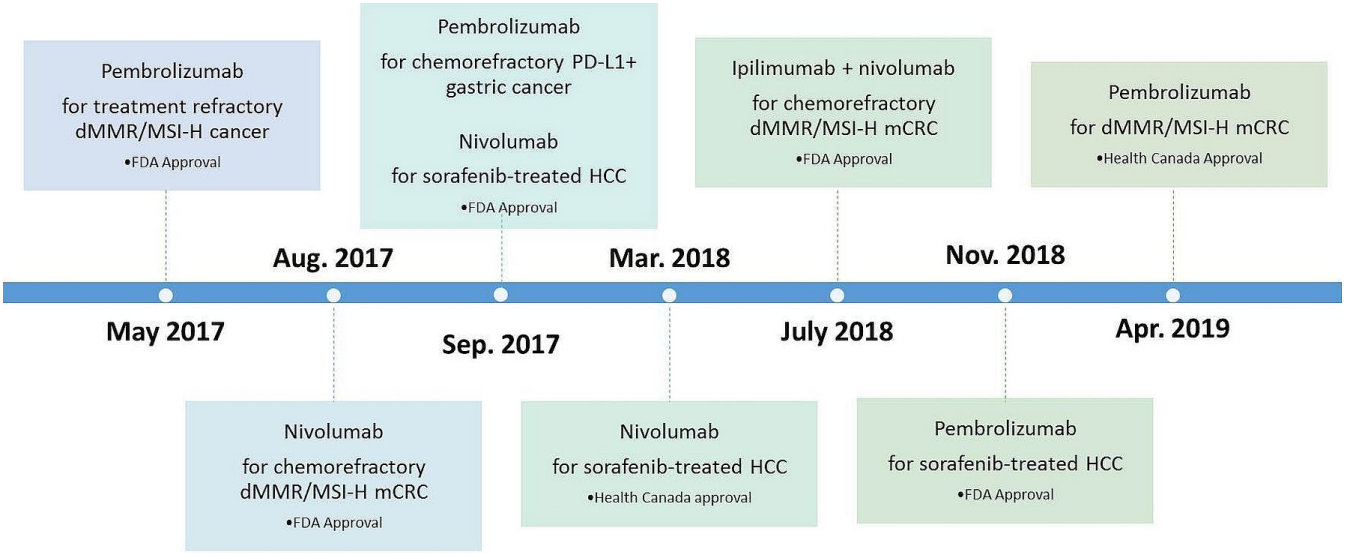

FIGURE 1 U.S. Food and Drug Administration (FDA) and Health Canada approvals for checkpoint inhibitors in gastrointestinal cancers up to 30 June 2019. It should be noted that, in Canada, Health Canada approval does not necessarily imply drug access on a provincial formulary. dMMR/MSI-H = deficient mismatch repair/high microsatellite instability; mCRC = metastatic colorectal cancer; HCC = hepatocellular carcinoma.

or metastatic adenocarcinoma or SCC of the esophagus or Siewert type 1 GEJ adenocarcinoma. Results were presented at the American Society of Clinical Oncology's 2019 Gastrointestinal Cancers Symposium[40]. The KEYNOTE-181 trial met one of its 3 co-primary endpoints of superior OS with pembrolizumab in the subset of patients whose tumours had a PD-L1 CPS of 10 or greater (approximately one third of the patients enrolled). It did not meet its 2 other co-primary endpoints of improved OS with pembrolizumab in the entire intention-to-treat population or in the population with

TABLE I Key phase I data for immunotherapy in gastrointestinal cancers[a]

Reference (study name)	Cancer type	Pts *(n)*	RR [*n* (%)]	mDOR (months)	mPFS (months)	mOS (months)	12-Month OS (%)
Muro *et al.,* 2016[26] (KEYNOTE-012)	Gastric or GEJ carcinoma	39	13 (33)	9.2	1.9	11.4	42
El-Khoueiry *et al.,* 2017[27] (CheckMate 040)	Hepatocellular carcinoma	48	7 (15)	17	3.4	15	Not reported
O'Neil *et al.,* 2017[28]; Ott *et al.,* 2019[19] (KEYNOTE-028)	Colorectal cancer	23	1 (4)	Not reached	1.8	5.3	Not reported
Ott *et al.,* 2017[29]; Ott *et al.,* 2019[19] (KEYNOTE-028)	Anal squamous cell carcinoma	25	4 (17)	Not reached	3	8.3	48
Doi *et al.,* 2018[30]; Ott *et al.,* 2019[19] (KEYNOTE-028)	Esophageal or GEJ carcinoma	23	7 (30)	15	1.8	7	40

[a] Investigational agents: KEYNOTE trials, pembrolizumab; CheckMate trial, nivolumab. Both agents are PD-1 inhibitors. Response rate, mDOR, and mPFS are determined per the Response Evaluation Criteria in Solid Tumors, version 1.1.

Pts = patients; RR = response rate; mDOR = median duration of response; mPFS = median progression free survival; mOS = median overall survival; OS = overall survival; GEJ = gastroesophageal junction.

TABLE II Current phase II data for immunotherapy in esophagogastric cancers[a]

Reference (study name)	Histology	Line of therapy	Treatment	RR (%)	mPFS (months)	mOS (months)	12-Month OS (%)
Bang *et al.,* 2017[31]; Catenacci *et al.,* 2017[32]; Fuchs *et al.,* 2018[33] (KEYNOTE-059)	Gastric or GEJ adenocarcinoma	3+	Cohort 1 (Fuchs): Pembrolizumab 200 mg every 3 weeks	12	2	5.6	23
		1	Cohort 2 (Bang): Pembrolizumab 200 mg every 3 weeks, plus cisplatin, plus fluoropyrimidine	60	6.6	13.8	52
			Cohort 3 (Catenacci): Pembrolizumab 200 mg every 3 weeks	26	3.3	20.7	63
Kudo *et al.,* 2017[34] (ATTRACTION-1)	Esophageal squamous cell carcinoma	2+	Nivolumab 3 mg/kg every 2 weeks	17	1.5	10.8	45
Janjigian *et al.,* 2018[35] (CheckMate 032)	Esophageal, GEJ, or gastric adenocarcinoma	2+	Nivolumab 3 mg/kg every 2 weeks	12	1.4	6.2	39
		2+	Nivolumab 1, ipilimumab 3, every 3 weeks for 4 cycles, then nivolumab 3 mg/kg every 2 weeks	24	1.4	6.9	35
		2+	Nivolumab 3, ipilimumab 1, every 3 weeks for 4 cycles, then nivolumab 3 mg/kg every 2 weeks	8	1.6	4.8	24
Shah *et al.,* 2019[18] (KEYNOTE-180)	Esophageal squamous cell carcinoma or adenocarcinoma; Siewert type 1 GEJ adenocarcinoma	3+	Pembrolizumab 200 mg every 3 weeks	10	2	5.8	28

[a] Pembrolizumab and nivolumab are PD-1 inhibitors. Ipilimumab is a CTLA-4 inhibitor. Response rate and mPFS are determined per the Response Evaluation Criteria in Solid Tumors, version 1.1.

RR = response rate; mPFS = median progression-free survival; mOS = median overall survival; OS = overall survival; GEJ = gastroesophageal junction; nivolumab 1 = nivolumab 1 mg/kg; ipilimumab 3 = ipilimumab 3 mg/kg; nivolumab 3 = nivolumab 3 mg/kg; ipilimumab 1 = ipilimumab 1 mg/kg.

TABLE III Current phase III data for immunotherapy in esophagogastric cancers[a]

Reference (study name)	Histology	Line of therapy	Study arms	RR (%)	mPFS (months)	mOS (months)	12-Month OS (%)
Kang *et al.,* 2017[37] (ATTRACTION-2)	Gastric or GEJ adenocarcinoma	3+	*Investigational:* Nivolumab 3 mg/kg every 2 weeks *Comparator:* Placebo	11 vs. 0	1.6 vs. 1.5	5.3 vs. 4.1 HR: 0.63 95% CI: 0.51 to 0.78	26 vs. 11
Bang *et al.,* 2018[38] (JAVELIN Gastric 300)	Gastric or GEJ adenocarcinoma	3	*Investigational:* Avelumab 10 mg/kg every 2 weeks *Comparator:* Paclitaxel or irinotecan	2 vs. 4	1.4 vs. 2.7	4.6 vs. 5 HR: 1.1 95% CI: 0.9 to 1.4	Not reported
Shitara *et al.,* 2018[39] (KEYNOTE-061)	Gastric or GEJ adenocarcinoma	2	*Investigational:* Pembrolizumab 200 mg every 3 weeks *Comparator:* Paclitaxel	16 vs. 14	1.5. vs. 4.1	9.1 vs. 8.3 HR: 0.82 95% CI: 0.66 to 1.03	40 vs. 27
Kojima *et al.,* 2019[40] (KEYNOTE-181)	Esophageal squamous cell carcinoma or adenocarcinoma, Siewert type 1 GEJ adenocarcinoma	2+	Cohort with PD-L1 CPS ≥ 10 *Investigational:* Pembrolizumab 200 mg every 3 weeks *Comparator:* Paclitaxel, docetaxel, or irinotecan	22 vs. 6	2.6 vs. 3	9.3 vs. 6.7 HR: 0.69 95% CI: 0.52 to 0.93	43 vs. 20
Tabernero *et al.,* 2019[41] (KEYNOTE-062)	Gastric or GEJ adenocarcinoma	1	*Investigational 1:* Pembrolizumab 200 mg every 3 weeks	15 vs. 37	2.0 vs. 6.4	10.6 vs. 11.1 HR: 0.91 99.2% CI: 0.69 to 1.18	47 vs. 46
		1	*Investigational 2:* Pembrolizumab 200 mg every 3 weeks plus cisplatin plus fluoropyrimidine *Comparator 1 and 2:* Cisplatin plus fluoropyrimidine	49 vs. 37	6.9 vs. 6.4	12.5 vs. 11.1 HR: 0.85 95% CI: 0.70 to 1.03	26 vs. 19

[a] Pembrolizumab and nivolumab are PD-1 inhibitors; avelumab is a PD-L1 inhibitor. Response rate and mPFS are determined per the Response Evaluation Criteria in Solid Tumors, version 1.1.

RR = response rate; mPFS = median progression-free survival; mOS = median overall survival; OS = overall survival; GEJ = gastroesophageal junction; HR = hazard ratio; CI = confidence interval; CPS = combined positive score.

squamous histology. For patients with a PD-L1 CPS of 10 or greater, the mOS with pembrolizumab was greater than that with chemotherapy [9.3 months vs. 6.7 months; hazard ratio (HR): 0.69; 95% confidence interval (CI): 0.52 to 0.93; $p = 0.0074$], and the 12-month OS was 43% compared with 20%.

For gastric or GEJ adenocarcinomas, the international KEYNOTE-062 trial compared pembrolizumab with pembrolizumab plus chemotherapy, and with placebo plus chemotherapy, in the first line for unresectable or metastatic disease that was PD-L1–positive (CPS ≥ 1). Combining immunotherapy and chemotherapy might be of benefit, based on the iatrogenic effect on TMB brought about by platinum agents[42]. The mOS with pembrolizumab monotherapy was noninferior to that with chemotherapy (10.6 months vs. 11.1 months; HR: 0.91; 99.2% CI: 0.69 to 1.18), meeting its primary endpoint[41]. However, the response rate and progression-free survival (PFS) were worse with pembrolizumab than with chemotherapy in the overall population with a CPS of 1 or greater—a case that did not hold in the population with a CPS of 10 or greater. Chemotherapy plus pembrolizumab in KEYNOTE-062 was not superior to chemotherapy alone for OS (HR: 0.85; 95% CI: 0.70 to 1.03; $p = 0.046$) or PFS.

The international phase III KEYNOTE-061 trial of pembrolizumab compared with paclitaxel in the second-line setting involved 592 patients in a cohort predominantly made up of those with a PD-L1 CPS of 1 or greater[39]. An OS benefit for pembrolizumab compared with chemotherapy could not be shown. The OS curves crossed, violating the proportional hazards assumption. Although the landmark 12-month OS rate, at 40%, was better for pembrolizumab-treated patients than for chemotherapy-treated patients (27%), second-line treatment with ramucirumab–paclitaxel in the RAINBOW trial was superior to treatment with paclitaxel alone, yielding 12-month OS rates of 40% and 30% respectively[43].

The phase III ATTRACTION-2 trial, conducted in Japan, South Korea, and Taiwan, compared nivolumab with placebo in 493 patients who had gastric or GEJ cancer progressing after, or intolerant to, 2 or more lines of therapy[37]. The mOS

was greater with nivolumab than with placebo (5.3 months vs. 4.1 months; HR: 0.63; 95% CI: 0.51 to 0.78; $p < 0.0001$). The response rate and 12-month OS were 11% and 26% respectively with nivolumab; they were 0% and 11% with placebo. The population was unselected for PD-L1 staining, and a retrospective review of 39% of the cases for PD-L1 expression showed no correlation with treatment outcome. Notably, the phase III TAGS trial comparing trifluridine/tipiracil with placebo in the third- and later-line settings also demonstrated improvement in mOS to 5.7 months from 3.6 months with placebo (HR: 0.69; 95% CI: 0.56 to 0.85; one-sided $p = 0.00029$)[44].

Another phase III trial in the third-line setting, JAVELIN Gastric 300, evaluated the PD-L1 inhibitor avelumab compared with chemotherapy for locally advanced or metastatic gastric or GEJ cancer in a worldwide population of 371 patients[38]. With a response rate of 2% for avelumab and 4% for chemotherapy, and a mOS of 4.6 months for avelumab and 5 months for chemotherapy (HR: 1.1; 95% CI: 0.9 to 1.4; $p = 0.81$), JAVELIN Gastric 300 was a negative trial. A subgroup analysis for OS stratified by PD-L1 expression did not favour either treatment arm.

Combination immunotherapy with nivolumab and the CTLA-4 inhibitor ipilimumab in the chemorefractory setting for advanced or metastatic esophagogastric cancers was investigated in the phase I/II CheckMate 032 trial[35] in a Western population consisting of 160 patients. The response rate was 12% for nivolumab monotherapy, 24% for nivolumab 1 mg/kg and ipilimumab 3 mg/kg, and 8% for nivolumab 3 mg/kg and ipilimumab 1 mg/kg. Response was independent of PD-L1 status. The 12-month OS rates were 39%, 35%, and 24% respectively. The phase III CheckMate 648 trial (NCT03143153 at https://ClinicalTrials.gov/), currently recruiting, is evaluating nivolumab–ipilimumab compared with nivolumab–cisplatin–5-fluorouracil (5FU) and with cisplatin–5FU in the first-line setting for advanced or metastatic SCC or adenocarcinoma of the esophagus.

To summarize the currently available trial data, PD-1 blockade has not been shown in phase III trials to be superior to chemotherapy in the first- or later-line settings for patients with esophagogastric disease, with the exception of patients having esophageal or GEJ cancer with a PD-L1 CPS of 10 or greater receiving pembrolizumab in the second-line setting. For gastric cancers, PD-L1 positivity might enrich the population responding to checkpoint blockade, but has not consistently been shown to be a reliable biomarker. Non-immunotherapy strategies for gastric cancer appear to have clearer efficacy (paclitaxel–ramucirumab in the second-line setting[43] and trifluridine/tipiracil in the third and later lines[44]), within the limits of cross-trial comparison. Compared with their non-Asian counterparts, Asian populations experience more favourable outcomes[45–48] and better responses to immunotherapy[40,41].

Results of the phase III KEYNOTE-590 trial (NCT03189719 at https://ClinicalTrials.gov/), looking at first-line cisplatin –5FU with or without pembrolizumab for advanced or metastatic SCC or adenocarcinoma of the esophagus or Siewert type 1 GEJ adenocarcinoma, are awaited (Figure 2). A phase III study of nivolumab compared with docetaxel or paclitaxel in advanced or recurrent esophageal cancer is ongoing (ONO-4538-24, NCT02569242). CheckMate 577, a phase III trial of adjuvant nivolumab in patients who have residual pathologic disease at surgical resection after chemoradiotherapy for early-stage esophageal or GEJ cancer, will assess whether checkpoint inhibition has a role in the adjuvant setting.

With respect to gastric cancer, ongoing first-line trials include JAVELIN Gastric 100 (NCT02625610), which is looking at the use of avelumab as maintenance after 12 weeks of first-line 5FU–oxaliplatin, and ONO-4538–37(NCT02746796), which is looking at the addition of nivolumab to first-line fluoropyrimidine and oxaliplatin therapy. Currently, neither the U.S. FDA nor Health Canada has approved immunotherapy in esophageal cancer, although that situation might change, given results from KEYNOTE-181 in tumours with a PD-L1 CPS of 10 or greater; the current FDA indication is only for PD-L1–expressing chemorefractory gastric or GEJ adenocarcinomas.

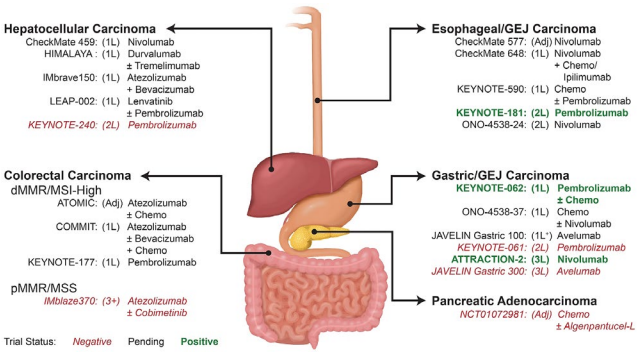

FIGURE 2 Investigational immunotherapy arms of completed and ongoing phase III trials in gastrointestinal cancers. 1L = first line; 2L = second line; GEJ = gastroesophageal junction; Adj = adjuvant; Chemo = chemotherapy; dMMR = deficient mismatch repair; MSI-High = high microsatellite instability; 1L+ = first-line maintenance; 3L = third line; pMMR = proficient mismatch repair; MSS = microsatellite stable; 3+ = third or later lines.

Pancreatic Cancer

Pancreatic adenocarcinoma has a notoriously poor prognosis; patients with metastatic cancer have a 2% 5-year survival rate[49]. Single-agent immunotherapy has had little success in that cohort, and multiple combination strategies are being trialled[50–52]. The results of the Canadian Cancer Trials Group PA.7 trial (NCT02879318 at https://ClinicalTrials.gov/), a phase II trial investigating the addition of the PD-L1 inhibitor durvalumab and the CTLA-4 inhibitor tremelimumab to gemcitabine–nab-paclitaxel in untreated metastatic pancreatic ductal adenocarcinoma, are awaited to assess whether combination immunotherapy in addition to chemotherapy can improve OS[53].

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is an immunogenic tumour with an intratumoural accumulation of CD8+ T cells, but the concomitant presence of PD-1 is associated with impaired effector T cell function[54–56]. Moreover, increased PD-L1 expression in HCC tumours has been correlated with poorer disease-free survival and OS[55,57], creating the perfect conditions for checkpoint inhibition to succeed. Nivolum-

ab and pembrolizumab both have U.S. FDA approval for use in patients with HCC previously treated with sorafenib. The first Health Canada approval for checkpoint inhibitors in gastrointestinal cancers has also been for nivolumab in patients with HCC who are intolerant to or progressing on sorafenib (Figure 1).

Approval for nivolumab was based on the results of the CheckMate 040 phase I/II trial, which enrolled sorafenib-naïve or pretreated patients and included those with hepatitis B or C[27,58]. In the dose-escalation phase for nivolumab (48 patients), the overall response rate by RECIST was 15%, with 43% of patients having stable disease. The mDOR was 17 months; the mOS, 15 months; and the 9-month OS rate, 66%. In the dose-expansion phase using nivolumab 3 mg/kg (214 patients), the response rate was 20%, with 45% of patients having stable disease. The mDOR was 9.9 months, and the 9-month OS was 74%. Retrospective PD-L1 staining in 81% of the dose-expansion cohort revealed that 20% of tested patients had PD-L1 membrane expression on 1% or more of tumour cells. Responses were seen in 9 of 34 patients with PD-L1 expression of 1% or more (26%) and in 26 of 140 patients with PD-L1 expression of less than 1% (19%).

Results from KEYNOTE-224 formed the basis for pembrolizumab approval in the second line[59,60]. That phase II trial enrolled 104 patients Child–Pugh class A liver function to receive pembrolizumab after progression on or intolerance to sorafenib (21% with hepatitis B, 25% with hepatitis C). The response rate by RECIST was 17%, with 44% of patients having stable disease. Immune-mediated hepatitis occurred in 3% of patients; no cases of viral flares were reported. The response rate by modified RECIST represented exploratory endpoints in the CheckMate 040 and KEYNOTE-224 trials: the reported rates were 19% and 16% respectively[27,59]. By comparison, the response rates with first-line sorafenib or lenvatinib in the REFLECT trial were 9% and 24% respectively by modified RECIST[61]; the response rate to second-line regorafenib in the RESORCE trial was 11%[62].

With respect to phase III trials, a preliminary press release reported that, in CheckMate 459 (NCT02576509 at https://ClinicalTrials.gov/), a first-line study of sorafenib compared with nivolumab, statistical significance for the superiority of OS with nivolumab was not reached[63]. The phase III KEYNOTE-240 trial in the second-line setting, though showing a response rate by RECIST (version 1.1) of 17% for pembrolizumab and 2% for placebo, and a HR of 0.78 (95% CI not reported; $p = 0.024$), did not reach statistical significance[64].

Results are awaited from HIMALAYA (NCT03298451), another phase III first-line study comparing sorafenib with durvalumab alone or in combination with tremelimumab; from IMBrave150 (NCT03434379), comparing atezolizumab (PD-L1 inhibitor) plus bevacizumab with sorafenib; and from LEAP-002 (NCT03713593), comparing the addition of pembrolizumab to lenvatinib monotherapy in the first line to see if a changing of the guard is on the horizon. Currently, no phase III trials comparing immunotherapy with targeted agents in the second line are planned.

For patients receiving liver transplantation, only case reports are available as guidance with respect to the use of checkpoint inhibition and the risk of graft failure. Of 14 reported cases in which liver-transplant recipients underwent immunotherapy with a checkpoint inhibitor, liver graft rejection occurred in 4. In 3 cases, rejection was fatal; 4 patients demonstrated a treatment response[65]. The decision to use immunotherapy in this population must be taken on a case-by-case basis.

Lower Gastrointestinal Tract Cancers

Colorectal Cancer

The narrative for immunotherapy in colorectal cancer (CRC) is the story of five trials, with the major breakthrough occurring in the 4% of metastatic CRC tumours that are dMMR or MSI-H[66]. In the phase IB KEYNOTE-028 trial, 23 patients with metastatic CRC were enrolled, and the only response was seen in a patient with MSI-H status[28]. Notably, that patient experienced a pathologic complete response[67].

The phase II KEYNOTE-016 trial was the one that then enrolled patients with dMMR and proficient MMR (pMMR) CRC, as well as dMMR non-CRC. Of 10 patients with dMMR CRC, 4 responded, and of 18 with pMMR CRC, none responded[68]. Median PFS and OS were not reached in the dMMR CRC cohort, which, compared with the pMMR CRC cohort, showed impressive HRs of 0.10 ($p < 0.001$) and 0.22 ($p = 0.05$) for PFS and OS respectively. Objective responses were seen in 14 of the 29 patients with non-CRC dMMR tumours (48%)[69]. That trial was the one that firmly established dMMR status as the biomarker for checkpoint blockade in CRC and, indeed, demonstrated the relevance of that biomarker for multiple tumour sites.

Another phase II study of pembrolizumab in pretreated MSI-H CRC was KEYNOTE-164. In cohort A, whose patients had received a minimum of 2 prior therapies, the response rate was 28% (17 of 61), and the 6-month PFS and OS rates were 43% and 87% respectively[70]. Cohort B enrolled patients who had received at least 1 prior line of therapy. The response rate in that cohort was 32%. The 12-month PFS and OS rates were 41% and 76% respectively[71].

Based on the results of those five single-arm clinical trials (149 patients)—KEYNOTE-028[16], KEYNOTE-016[22], KEYNOTE-164[72], KEYNOTE-158[73] (which enrolled patients with MSI-H non-CRC), and KEYNOTE-012[26] (which enrolled patients with gastric, urothelial, head-and-neck, and triple-negative breast cancers), the U.S. FDA issued its first tissue-agnostic approval of a drug on 23 May 2017[74]. Pembrolizumab was approved for advanced or metastatic dMMR or MSI-H tumours that progress after prior treatment and for which no satisfactory alternative treatment options are available. Patients with dMMR CRC have to have received previous treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. As of April 2019, Health Canada had also approved that indication.

Data for nivolumab comes from CheckMate 142 (Table IV), a phase II parallel-cohort trial involving pretreated and treatment-naïve patients with dMMR MSI-H metastatic CRC. Of 74 pretreated patients in the nivolumab monotherapy arm, 23 (31%) experienced an objective response—again with durability. After a median follow-up of 12 months, the mDOR was not reached. For the 119 pretreated patients allocated to combination nivolumab–ipilimumab, the response rate was 55%, with impressive 12-month PFS and OS rates of 71% and 85% respectively[76]. In the 45 treatment-naïve patients who received combination nivolumab–ipilimumab, the response rate was 60%, and the 12-month PFS and OS

TABLE IV Results from CheckMate 142[75,a]

Study cohort	Treatment	Pts (*n*)	RR (%)	mPFS (months)	mOS (months)	12-Month OS (%)
Treatment-naïve	Nivolumab 3 mg/kg every 2 weeks, plus ipilimumab 1 mg/kg every 6 weeks	45	60	Not reached	Not reached	83
Pretreated	Nivolumab 3 mg/kg every 2 weeks	74	31	14	Not reached	73
Pretreated	Nivolumab 3 mg/kg every 3 weeks for 4 cycles, then every 2 weeks thereafter, plus ipilimumab 1 mg/kg every 3 weeks for 4 cycles	119	55	Not reached	Not reached	85

[a] Phase II trial in patients with deficient mismatch repair or high microsatellite instability metastatic colorectal cancer. Nivolumab is a PD-1 inhibitor. Ipilimumab is a CTLA-4 inhibitor. Response rate and mPFS are determined per the Response Evaluation Criteria in Solid Tumors, version 1.1.

Pts = patients; RR = response rate; mPFS = median progression free survival; mOS = median overall survival; OS = overall survival.

rates were 77% and 83% respectively[77]. In the neoadjuvant setting, combination nivolumab–ipilimumab for up to 6 weeks in the phase II NICHE study was associated with major pathologic responses in all 7 patients with dMMR colon cancers, 4 of whom experienced complete responses[78].

Given the extremely promising phase II data for dMMR or MSI-H CRC treated with immunotherapy, the results of KEYNOTE-177 (NCT02563002 at https://ClinicalTrials.gov/) and COMMIT (NCT02997228), which are comparing pembrolizumab (KEYNOTE-177) or atezolizumab (COMMIT) with standard chemotherapy in the first-line setting for metastatic dMMR or MSI-H CRC, are eagerly anticipated.

Importantly, single-agent PD-1 blockade is not an effective treatment strategy for pMMR or microsatellite-stable (MSS) CRC, which accounts for almost all stage IV CRC. In KEYNOTE-028, treatment with pembrolizumab led to 0 responses in the MSS cohort. The Canadian Cancer Trials Group's phase II CO.26 trial (NCT02870920), comparing combination checkpoint inhibition using durvalumab–tremelimumab with best supportive care in a treatment-refractory CRC cohort with predominantly MSS tumours met its endpoint of superior OS in the immunotherapy arm, per a p value of less than 0.1. Exploratory bioanalyses suggest that high TMB might select for a MSS population that most benefits from that strategy[20,41].

Other combination strategies have also been trialled. On the back of promising phase IB data[79], the phase III IMblaze370 (NCT02788279) trial was developed to randomize patients with chemotherapy-refractory MSS CRC to either atezolizumab, atezolizumab–cobimetinib, or regorafenib. Unfortunately, compared with regorafenib, neither immunotherapy arm showed an OS benefit[80]. In a similar vein, the phase II MODUL trial (NCT02291289) investigated maintenance therapy with fluoropyrimidine, bevacizumab, and atezolizumab or with cobimetinib–atezolizumab after induction chemotherapy. The addition of maintenance atezolizumab showed no OS difference, and the trial was halted[81].

Other strategies to harness the immune system against MSS tumours are being trialled, including CEA CD3 TCB (a novel bispecific T cell antibody that targets carcinoembryonic antigen on tumour cells and CD3 on T cells) alone or in combination with atezolizumab in the phase I space[82].

To summarize, for dMMR or MSI-H CRC, phase III evidence for upfront PD-1 blockade with checkpoint inhibitors is pending. Phase II data support the use of pembrolizumab or nivolumab in pretreated patients with metastatic disease and, from CheckMate 142, combination nivolumab–ipilimumab upfront and in pretreated patients. The role of immunotherapy as an adjunct to chemotherapy or locoregional strategies in the advanced setting—and its role in the adjuvant and neoadjuvant spaces—is still being explored. For MSS CRC, immunotherapy does not have an established role; assessments of combination strategies are in progress.

Anal SCC

The KEYNOTE-028 trial included an anal SCC cohort, and 4 of the 25 patients in that cohort experienced a partial response with pembrolizumab[29]. In the 37 patients enrolled to receive nivolumab monotherapy in the phase II NCI9673 trial, which involved treatment-refractory patients, the response rate was 24%, the 6-month PFS was 38%, and the median OS was 11.5 months[83]. The Canadian Cancer Trials Group–endorsed phase II EA2165 trial, which is studying nivolumab after chemoradiotherapy for high-risk stages II–IIIB anal cancer, is currently recruiting (NCT03233711 at https://ClinicalTrials.gov/).

Looking forward, phase II trials of cancer vaccines and trials of PD-1 inhibitors alone or in combination with CTLA-4 inhibitors, LAG-3 inhibitors, CD38 inhibitors, or engineered T cell therapy are ongoing[84]. In terms of finding biomarkers for this subset of patients, NCI9673 demonstrated that responders had more CD8+ T cells at baseline, greater PD-L1 tumour expression, and greater PD-1 expression on CD8+ T cells.

SUMMARY

Overall, immunotherapy, predominantly with checkpoint inhibitors, is starting to make its mark on gastrointestinal tumours. Inhibitors of PD-1 have an established role in treatment-refractory dMMR tumours, a second-line indication in HCC, and approval for use in PD-L1–positive chemorefractory gastric tumours. Furthermore, combination PD-1 and CTLA-4 inhibition has been approved by the U.S. FDA for chemorefractory dMMR CRC. Responses, when they do occur, are durable. Checkpoint inhibitors are certainly no panacea at this stage, though. Phase II results require validation in phase III trials, be it in the metastatic, adjuvant, or neoadjuvant setting (Figure 2).

The biomarker story for checkpoint blockade continues to evolve. Although patients selected for dMMR or MSI-H status consistently respond to checkpoint blockade in multiple

tumour sites because of their high TMB, PD-L1 testing has not, itself, proven to be a consistently reliable biomarker across all gastrointestinal tumour sites—and that lack of reliability is complicated by the myriad ways in which PD-L1 can be tested and classified. Exploratory analysis of potential biomarkers within KEYNOTE-028 has revealed that patients with a high TMB and high inflammatory markers characterized by a T cell–inflamed gene expression profile or PD-L1 expression identify the population with the greatest likelihood of response[19].

Overall, cautious optimism is called for as trials of combination immunotherapy, immunotherapy in combination with chemotherapy or targeted therapies, and immunotherapy in combination with other modalities move forward, paired with improved biomarker assessment. This is a burgeoning field, and additional indications for checkpoint inhibitor use could be just over the horizon.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SG has received consulting fees from Pfizer, Bristol–Myers Squibb, and Roche. SM has no conflicts to disclose.

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