Review Article

Immune checkpoint inhibitors in gastrointestinal malignancies: what can we learn from experience with other tumors?

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Abstract: Gastrointestinal (GI) malignancies are some of the most common cancers worldwide with high rates of morbidity and mortality. Immune checkpoint inhibitors have afforded additional treatment options for patients, but their success has been limited. Conversely, in other tumor types such as lung cancer, melanoma and renal cell carcinoma, treatment strategies with immune checkpoint inhibitors have propelled those agents into the front lines of treatment. Strategies utilized include combining immune checkpoint inhibitors with chemotherapy, other checkpoint inhibitors, and targeted therapy. In this review, we analyze combination strategies employed in other tumor types to help identify current and future approaches toward improving outcomes with immunotherapy in GI malignancies.

Keywords: Immunotherapy; checkpoint inhibitor; gastrointestinal cancer (GI cancer); combination

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Introduction

Gastrointestinal (GI) malignancies include cancers of the esophagus, gallbladder, liver, pancreas, stomach, small intestine, large intestine and the anus. Together, GI malignancies comprise some of the most prevalent cancer types worldwide and also account for a large number of global deaths (1). Treatment of GI tumors consists of a multidisciplinary approach, including surgery, radiation and chemotherapy (2,3). These approaches have improved outcomes in some patients, but the management of patients with metastatic disease remains challenging. New strategies are desperately needed.

It has been long suspected that the immune system plays an important role in the development and progression of cancers (4). Suppression of the tumor microenvironment (TME) and evasion from the immunosurveillance system allow malignant cells to develop into tumors (5). Current research is targeted at reversing immune suppression in the TME as well as uncloaking cancer cells to enable the immune system to recognize them as foreign and destroy them. Immune checkpoints are cell surface receptors expressed by immune cells that regulate the activation of T lymphocytes (6). These co-stimulatory and co-inhibitory checkpoint molecules act as gatekeepers of the immune response. Checkpoints that have been a major focus in research include the cytotoxic T lymphocyte antigen-4 (CTLA-4) interaction with B7 and the programmed death-1 (PD-1) interaction with programmed death-ligand 1 (PD-L1).

In 2011, the first checkpoint inhibitor approved by the FDA was ipilimumab, a CTLA-4 antibody (7). Since then, immunotherapies have been successfully used to treat various solid tumor malignancies. For example, long lasting responses are now possible for patients with metastatic melanoma (8). Similar successes have been noted in renal

cell carcinoma and lung cancer (9,10). Several immune-checkpoint inhibitors have been approved by the FDA. These include ipilimumab (anti-CTLA4); nivolumab, pembrolizumab and cemiplimab (anti-PD-1); and avelumab, durvalumab and atezolizumab (anti-PD-L1).

Immunotherapy, especially checkpoint inhibitors, has been used in GI malignancies. Currently, FDA-approved indications include: nivolumab and pembrolizumab for second-line treatment of advanced hepatocellular carcinoma (HCC) (11,12); nivolumab and pembrolizumab for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors after failure of prior treatment (11,12); nivolumab in combination with ipilimumab for MSI-H or dMMR metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (11); pembrolizumab for metastatic or advanced gastric and esophageal cancers with PD-L1 positive tumors (12). In addition to FDA-approved indications, checkpoint inhibitors have also been recommended by the National Comprehensive Cancer Network® for second-line treatment of metastatic or advanced anal carcinoma (13).

Despite these successes, only a small percentage of patients with GI malignancies respond to immunotherapy. Effective predictive biomarkers are also lacking. Various strategies for improving response rates and survival with these agents have been evaluated in other solid tumor malignancies. For example, in patients with metastatic melanoma, the combination of checkpoint inhibitors (ipilimumab and nivolumab) was shown to improve overall survival and response rate (14). In other tumor types, the combination of chemotherapy or small molecule tyrosine kinase receptor inhibitors with checkpoint inhibitors was found to improve survival outcomes. Can some of these combination strategies be applied to GI malignancies? This article will review combination treatments employed in other tumor types to help identify current and future approaches toward improving outcomes with immunotherapy in GI malignancies.

Checkpoint inhibitor combination with chemotherapy

It is well established that traditional chemotherapy agents mediate their activity via direct cytotoxic actions. By targeting rapidly proliferating cells, cancer cells are particularly vulnerable to cell death. These agents are broadly categorized as alkylating agents (e.g., cisplatin), antimetabolites [e.g., 5-fluorouracil (5-FU), gemcitabine], topoisomerase inhibitors (e.g., irinotecan), microtubule inhibitors (e.g., paclitaxel), and cytotoxic antibiotics (e.g., doxorubicin).

In recent years, it has become increasingly clear that the effectiveness of these agents also relies upon the ability to modulate the host and tumor immune response (15). For example, 5-FU and oxaliplatin can reduce the frequency of circulating T regulatory (Treg) cells (16). Other agents such as gemcitabine, cisplatin, oxaliplatin and paclitaxel can increase the expression of major histocompatibility complex (MHC) class I molecules and increase the antigenicity of cancer cells (17,18). Through lymphodepletion, cytotoxic chemotherapy may also force an immune system "reset" and rebound immune stimulation (19). These preclinical and clinical findings have formed the basis for combining immunotherapy and chemotherapy.

Early clinical trials with combination of chemotherapy and immunotherapy were performed in patients with small cell and non-small cell lung cancers (NSCLCs) (20,21). Both studies found an acceptable rate of adverse effects and promising clinical activity with the combination. These studies laid the foundation for use of chemotherapy in combination with immunotherapy in the first-line treatment of metastatic NSCLC and extensive-stage small cell lung cancer (22,23). Similar effects were observed in patients with metastatic head and neck squamous cell cancers (HNSCC) (24). Pembrolizumab, in combination with platinum-based chemotherapy is now considered a first-line treatment option for HNSCC.

Taken together, these studies form a strong rationale for further evaluation of the combination of immunotherapy with chemotherapy in GI malignancies. Traditional chemotherapy used in GI malignancies (5-FU, oxaliplatin, cisplatin, etc.) have been shown to modulate the immune system and may be synergistic with immunotherapy. An example of a checkpoint inhibitor combination with chemotherapy in GI malignancies comes from the MODUL study. This study reported outcomes from a cohort of 445 mCRC patients that were randomized to receive maintenance therapy with either 5-FU and bevacizumab or atezolizumab with 5-FU and bevacizumab after induction therapy with FOLFOX (5-FU, leucovorin oxaliplatin) and bevacizumab. Unfortunately, adding atezolizumab to first-line maintenance therapy did not improve efficacy outcomes (25). Conversely, a phase II study in patients with metastatic human epidermal growth factor receptor 2 (HER2)-positive, gastric or gastroesophageal junction

(G/GEJ) tumors found promising results. Pembrolizumab when added to first-line therapy consisting of oxaliplatin, capecitabine, and trastuzumab produced an overall response rate of 83% amongst the 24 evaluable patients (26). Grade 3–4 adverse events were uncommon. Based upon these results, a phase III study to evaluate this combination has been initiated (NCT03615326). The phase III KEYNOTE-062 trial assessed HER2-negative, PD-L1 positive, metastatic G/GEJ patients and found that the combination of pembrolizumab plus chemotherapy was not superior over pembrolizumab alone (27). Grade 3–5 drug-related adverse events were seen in 73% patients in the combination arm. Pembrolizumab was also combined with 5-FU and cisplatin in patients with untreated metastatic gastric cancer in a cohort of the KEYNOTE-059 trial (28). The overall response rate observed was 60% in all patients compared historically to ~45% with cisplatin and 5-FU alone (29). Grade 3–4 adverse events were seen in 76% of patients. A similar study combining nivolumab + chemotherapy (CheckMate 649) is currently ongoing with an anticipated completion in March 2021 (NCT02872116) (*Table 1*).

A phase II study of 28 patients combined pembrolizumab with chemoradiotherapy for stage I–III esophageal cancers (30). Chemoradiotherapy consisted of weekly paclitaxel and carboplatin with 44.1 Gy radiotherapy. Pathologic complete response (CR) rates were seen in 46.1% patients with most common adverse events being neutropenia (50%) and liver enzyme elevations (31%).

Combinations of chemotherapy and immunotherapy hold promise in GI malignancies. There are several front-line combination studies ongoing (*Table 1*) with eagerly anticipated results.

Multiple immune checkpoint combinations

In recent years, focus has been placed on combining inhibitors of different immune checkpoint pathways (i.e., CTLA-4 with PD-1 inhibition), especially in malignancies that have been established of having treatment responses to single-agent immunotherapy previously (31). In GI malignancies, the combination of ipilimumab and nivolumab is currently in the early stages of being evaluated in hepatocellular, esophagogastric, and colorectal cancers.

In patients with HCC previously treated with sorafenib, the combination of ipilimumab and nivolumab was evaluated in the CheckMate 040 trial. The objective response rate observed with the combination was twice of that previously seen with nivolumab monotherapy (32). In patients with previously-treated metastatic esophagogastric cancer, the combination of ipilimumab with nivolumab was evaluated in the phase I/II portion of the CheckMate 032 trial. This study included patients irrespective of PD-1/PD-L1 status and demonstrated clinical benefit, thus warranting further phase III evaluation which is currently underway (33).

Initial trials evaluating the combination of ipilimumab with nivolumab utilized a dosing regimen of ipilimumab 3 mg/kg and nivolumab 1 mg/kg every 3 weeks for 4 doses, followed by maintenance nivolumab 3 mg/kg every 2 weeks (34). A major concern with targeting multiple immune checkpoints is the added potential for immune-related adverse events. CTLA-4 targets T cells in the initial stages of naïve T-cell activation, whereas the PD-1 pathway targets previously activated T cells at later stages of the immune response (35). This earlier and expansive activity potentially accounts for the increased toxicity associated with the CTLA-4 inhibitor ipilimumab over PD-1/PD-L1 inhibitors. As such, trials experimenting with doses and schedules of these agents in combination are frequently done.

In the previously treated MSI-H/dMMR mCRC patient population, an analysis of the CheckMate 142 trial using nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by maintenance nivolumab 3 mg/kg every 2 weeks thereafter was presented. At a median 13.4 months in 119 patients, response rates of 55% were reported with 32% of patients experiencing grade 3–4 adverse effects (36). More recently, phase II data from the same CheckMate 142 trial were presented evaluating the combination of nivolumab and ipilimumab in the first-line setting. In this analysis of 45 patients, the dosing of nivolumab 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks continuously until progression or discontinuation was utilized. Preliminary results at a median 13.8 months indicate a comparable response rate (60%) with only 16% of patients experiencing a grade 3–4 adverse event, potentially representing an efficacious dosing schedule that is more tolerable for patients (37).

Checkpoint inhibitor combination with anti-vascular endothelial growth factor (anti-VEGF) therapy

VEGF pathways play an integral role in angiogenesis and repair of healthy tissues (38). This pathway is found to

Table 1 Selected ongoing studies evaluating various combination strategies with immune checkpoint inhibitors

Disease state	Intervention	Combination	Phase	NCT number
Anal cancer—metastatic	Nivolumab ± ipilimumab	Dual ICI	2	NCT02314169
	Avelumab ± cetuximab	EGFR	2	NCT03944252
	mDCF ± atezolizumab	Chemo	2	NCT03519295
BTC—advanced	Durva + treme + gem or gem/cis *vs.* gem/cis	Chemo	2	NCT03473574
	Pembrolizumab + CapeOx	Chemo	2	NCT03111732
	Gem/cis ± pembrolizumab	Chemo	3	NCT04003636
Esophageal cancer—metastatic	Nivolumab + ipilimumab	Dual ICI	2	NCT03416244
GE cancer—resectable	Neoadjuvant CapeOx + docetaxel + atezolizumab	Chemo	2	NCT03448835
	Perioperative atezolizumab + FLOT *vs.* FLOT	Chemo	2	NCT03421288
	Neoadjuvant & adjuvant FOLFOX + pembrolizumab	Chemo	2	NCT03488667
	Neoadjuvant & adjuvant chemo ± pembrolizumab	Chemo	3	NCT03221426
	Neoadjuvant & adjuvant chemo + avelumab	Chemo	2	NCT03979131
GE cancer—metastatic	Cabozantinib + durva	VEGF	1	NCT03539822
	Ramucirumab + durva	VEGF	1	NCT02572687
	FOLFOX ± nivolumab & ipilimumab	Chemo	2	NCT03647969
	Nivolumab + ipilimumab *vs.* nivolumab + chemo	Chemo/Dual ICI	3	NCT02872116
	Ramucirumab + nivolumab	VEGF	1/2	NCT02999295
	Lenvatinib + pembrolizumab	VEGF	2	NCT03321630
	Pembrolizumab + oxaliplatin + capecitabine	Chemo	2	NCT03342937
	Chemotherapy ± pembrolizumab	Chemo	3	NCT03675737
	Avelumab + paclitaxel + ramucirumab	Chemo/VEGF	2	NCT03966118
GE cancer—metastatic HER2+	Nivolumab + trastuzumab + FOLFOX or ipilimumab	Chemo/Dual ICI/ EGFR	2	NCT03409848
	Trastuzumab + chemotherapy ± pembrolizumab	Chemo/EGFR	3	NCT03615326
HCC—resectable	Adjuvant durva + bev *vs.* durva alone	VEGF	3	NCT03847428
HCC—advanced	Durva + treme	Dual ICI	3	NCT03298451
	Durva or treme monotherapy *vs.* durva + treme *vs.* Durva + bev	Dual ICI/VEGF	2	NCT02519348
	Cabozantinib + atezolizumab *vs.* sorafenib	VEGF	3	NCT03755791
	Atezolizumab + bev *vs.* sorafenib	VEGF	3	NCT03434379
	Lenvatinib + nivolumab *vs.* lenvatinib	VEGF	2/3	NCT04044651
	Nivolumab + bev	VEGF	1	NCT03382886
	Nivolumab + ipilimumab	Dual ICI	3	NCT04039607
	Lenvatinib + nivolumab	VEGF	2	NCT03841201
	Sorafenib + nivolumab	VEGF	2	NCT03439891
	Lenvatinib + pembrolizumab *vs.* lenvatinib	VEGF	3	NCT03713593
	Regorafenib + pembrolizumab	VEGF	1	NCT03347292
	Sorafenib + pembrolizumab	VEGF	1/2	NCT03211416
	Axitinib + avelumab	VEGF	1	NCT03289533

Table 1 (*continued*)

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Disease state	Intervention	Combination	Phase	NCT number
mCRC	Durva + treme + FOLFOX	Chemo/Dual ICI	1	NCT03202758
	Durva + treme	Dual ICI	2	NCT02870920
	Azacitidine + durva	Chemo	2	NCT02811497
	FOLFOXIRI + bev + atezolizumab *vs.* FOLFOXIRI + bev	Chemo/VEGF	2	NCT03721653
	Atezolizumab + bev	VEGF	2	NCT02982694
	Capecitabine + bev ± atezolizumab	Chemo/VEGF	2	NCT02873195
	Panitumumab + nivolumab + ipilimumab	EGFR/Dual ICI	2	NCT03442569
	TAS-102 + nivolumab	Chemo	2	NCT02860546
	Pembrolizumab + chemotherapy	Chemo	2	NCT02375672
	Regorafenib + pembrolizumab	VEGF	1/2	NCT03657641
	Pembrolizumab + binimetinib + bev	MEK/VEGF	2	NCT03475004
	Pembrolizumab + capecitabine + bev	Chemo/VEGF	2	NCT03396926
	Cetuximab + pembrolizumab	EGFR	1/2	NCT02713373
	Pembrolizumab + pemetrexed + oxaliplatin	Chemo	1	NCT03626922
	Pembrolizumab + azacitidine	Chemo	2	NCT02260440
	Avelumab + cetuximab	EGFR	2	NCT03608046
	FOLFOX + cetuximab + avelumab	Chemo/EGFR	2	NCT03174405
mCRC BRAF V600E	Encorafenib + binimetinib + nivolumab	BRAF/MEK	1/2	NCT04044430
	Encorafenib + cetuximab + nivolumab	BRAF/EGFR	1/2	NCT04017650
mCRC Ras mutant	Binimetinib + nivolumab ± ipilimumab	BRAF/Dual ICI	1/2	NCT03271047
Pancreas cancer—advanced	Azacitidine + pembrolizumab	Chemo	2	NCT03264404
	Gemcitabine + nab-paclitaxel ± durva + treme	Chemo/Dual ICI	2	NCT02879318
Pancreas cancer—resectable	Neoadjuvant & adjuvant gemcitabine + durva	Chemo	2	NCT03572400

ICI, immune checkpoint inhibitor; EGFR, epidermal growth factor receptor; mDCF, modified docetaxel + cisplatin + 5-fluorouracil; BTC, biliary tree cancer; durva, durvalumab; treme, tremelimumab; gem, gemcitabine; cis, cisplatin; GE, gastroesophageal; CapeOx, capecitabine + oxaliplatin; FLOT, 5-fluorouracil + leucovorin + oxaliplatin + docetaxel; FOLFOX, 5-fluorouracil + oxaliplatin + leucovorin; VEGF, vascular endothelial growth factor; HCC, hepatocellular carcinoma; bev, bevacizumab; mCRC, metastatic colorectal cancer; FOLFOXIRI, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan.

be upregulated in numerous malignancies (39). Targeted inhibition of VEGF signaling pathways has yielded beneficial effects in various malignancies. There are currently several FDA-approved indications for anti-VEGF therapies in GI malignancies. Bevacizumab, an anti-VEGF antibody, has shown to improve overall survival in mCRC patients (40). Ramucirumab, a VEGF receptor (VEGFR) 2 antibody, has also been approved in second-line mCRC, gastric cancer, and esophageal cancer based upon improved overall survival demonstrated in randomized clinical trials (41). Similarly, the VEGFR-targeting tyrosine kinase inhibitors (TKI) sorafenib and lenvatinib are FDA-approved, first-line options in HCC (42,43).

The VEGF pathway is also involved in regulating immune functions in the TME via several mechanisms. *In vitro* and animal model studies suggest that VEGF increases expression of Tregs and myeloid derived suppressor cells (MDSC) (44,45). Tregs and MDSC have shown to inhibit tumor directed T-cell responses and are generally associated with reduced inflammation and an immunosuppressive state (46). VEGFR1 also appears to interfere with dendritic cell (DC) maturation (47). Finally, animal model studies suggest a downregulation of immune stimulatory effector T cells in the presence of high levels of

VEGF, similar to those observed in advanced cancer (48). The overall effect of VEGF pathway overexpression on the TME is immunosuppressive. Upregulation of VEGF compromises the endothelial vasculature and impedes the transit of T-cells to infiltrate a tumor, creating yet another barrier for immune-mediated cytotoxicity (49). Thus, combining immunotherapy with VEGF inhibitor appears to be an attractive strategy in GI malignancies.

The combination of VEGFR TKI and checkpoint inhibitors was first successfully evaluated in metastatic renal cell carcinoma. Initial studies combined checkpoint inhibitors with pazopanib or sorafenib and found grade 3–4 toxicities, especially liver function test abnormalities, to be much higher than anticipated (50,51). Grade 3 elevations in alanine aminotransferase (ALT) were seen in 18% of patients treated with nivolumab plus sunitinib, 20% of patients treated with nivolumab plus pazopanib, and 60–70% of patients treated with pembrolizumab plus pazopanib. On the contrary, grade 3 ALT elevations were seen in only 8% of patients receiving axitinib and pembrolizumab (52). This could be because axitinib is a more selective inhibitor of VEGFR compared to pazopanib and sunitinib. Based upon this experience from renal cell carcinoma, it appears that combining checkpoint inhibitors with more selective VEGFR TKI therapy may be a preferred strategy from a safety standpoint. Similarly, the combination of pembrolizumab with the anti-VEGF antibody bevacizumab was found to be safe and tolerable for patients with metastatic renal cell carcinoma as well as glioblastoma (53,54). In a large randomized study in patients with treatment-naïve metastatic NSCLC, the PD-L1 checkpoint inhibitor atezolizumab was combined with bevacizumab and chemotherapy. This combination showed an improved response rate and a similar adverse event profile compared to the combination without atezolizumab (55). This study ultimately led to the FDA approval for the combination of atezolizumab with bevacizumab and chemotherapy as a first-line option in metastatic, non-squamous NSCLC.

A combination of durvalumab and ramucirumab was evaluated in a multi-cohort phase Ia/Ib study in solid tumors (56). Among the cohort of G/GEJ adenocarcinoma patients, an objective response rate of 36% (n=14) was noted in those with high PD-L1 positive (PD-L1 ≥25% of tumor cells) tumors. In contrast, an objective response rate of 0% (n=12) was noted in G/GEJ patients with low PD-L1 expression. A similar multi-cohort phase Ia/Ib was also conducted to evaluate the combination of pembrolizumab with ramucirumab in solid tumors. Among the cohort of G/GEJ adenocarcinoma patients, an objective response rate of 7% (n=41) was noted (57). Survival was longer in the subgroup of patients with PD-L1 positive tumors (n=22) compared to PD-L1 negative (n=17). Both of these studies indicate that, at least in G/GEJ adenocarcinomas, encouraging response rates are seen only in PD-L1 positive tumors and a different strategy might be needed in non-PD-L1 positive tumors.

Anti-VEGF therapies are utilized across various GI malignancies and the combination of these agents with checkpoint inhibitors remains an attractive approach (*Table 1*).

Checkpoint inhibitor combination with ErbB inhibitors

ErbB receptor tyrosine kinases have been widely studied since the initial discovery of the epidermal growth factor receptor (EGFR) (58). The ErbB family is comprised of the HER members: EGFR/HER1/ErbB1, HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4. EGFR is widely expressed in colon, rectal, and anal cancer and may be considered for patients who test negative for mutations in KRAS/NRAS/BRAF (59). HER2, on the other hand, is overexpressed in a smaller percentage amounts of patients with gastric or esophageal cancers when compared to breast cancer. Agents including cetuximab and trastuzumab have been studied and established as efficacious in these GI malignancies.

Activation of ErbB receptors results in stimulation of downstream signaling pathways, such as MAPK, AKT, and STAT. Dimerization of ErbB receptors is known to be required for activation, which has led to investigation of drugs targeting this process (60). In addition to downstream pathway inhibition, the ErbB receptor inhibitors cetuximab and trastuzumab are known to activate immune cells, such as natural killer (NK) cells (61). It increases production of interferon gamma and stimulates antibody dependent cellular cytotoxicity. The presence of interferon gamma in the TME induces production of PD-L1, a co-inhibitory immune checkpoint. Because of the known immune-mediated effects, it has been suggested that these ErbB receptor blockers in combination with PD-1/PD-L1 blockade may have synergistic antineoplastic effects and improve response rates to treatment.

Cetuximab is currently under investigation with a variety of PD-1 and PD-L1 inhibitors in head and neck, lung, colorectal, anal, and cutaneous malignancies. Safety data has

been presented on the combination of immunotherapy with cetuximab and chemotherapy in colorectal cancer thus far. The AVETUX trial is evaluating avelumab and cetuximab in combination with FOLFOX in previously untreated mCRC (62). At this time, the safety data imply that adverse effects did not impact the feasibility of treating with the combination. The CAVE trial is currently evaluating avelumab in combination with cetuximab in patients with mCRC who have progressed after being previously treated with chemotherapy plus cetuximab (63).

Trastuzumab is currently under investigation with a variety of PD-1 and PD-L1 inhibitors in the breast and esophagogastric cancers. A phase Ib–II study adding pembrolizumab to trastuzumab was completed in patients with trastuzumab-resistant, advanced HER2-positive breast cancer (64). The phase II portion of the study included 52 patients, n=40 with PD-L1-positive tumors and n=12 with PD-L1-negative tumors. An objective response was observed in 6 (15%) of the 40 patients with PD-L1 positive tumors. No patients with PD-L1-negative tumors achieved an objective response. Adding pembrolizumab to the ErbB2 inhibitor trastuzumab demonstrated clinical benefit in patients who previously had progressed on trastuzumab therapy, warranting further expanded evaluation.

As mentioned previously in this review, the PD-1 inhibitor pembrolizumab in combination with the ErbB2 inhibitor trastuzumab and chemotherapy is initially showing efficacy in metastatic esophagogastric adenocarcinoma (26). Future studies will continue to unfold the treatment response potential of this proposed synergistic effect in GI malignancies.

Checkpoint inhibitor combination with BRAF/MEK inhibitors

The BRAF proto-oncogene encodes for the BRAF protein which plays an important role in the EGFR-mediated MAP kinase pathway. This pathway profoundly affects cell growth, proliferation and differentiation (65). Additionally, it affects cell migration and apoptosis. Activating mutations in BRAF account for approximately 15% of mutations across various malignancies (66). The most common type of BRAF mutation is a single nucleotide mutation resulting in substitution of glutamic acid for valine (BRAF V600E) (44). Amongst GI malignancies, mutations in the BRAF gene are most commonly seen in patients with CRC (67). Approximately 10% of CRC patients carry a BRAF mutation (68). These mutations are associated with shorter progression-free survival, shorter overall survival, and overall poor outcomes. Treatment with BRAF inhibitors alone has not proven to be beneficial with a response rate of 5% (69).

BRAF mutations may give rise to an immunosuppressive state in the tumor cells. In addition, treatment with BRAF and MEK inhibitors show an increase in CD4+ and CD8+ T-cell infiltration into the TME. Based upon this rationale, pembrolizumab was combined with the MEK inhibitor trametinib and the BRAF inhibitor dabrafenib in metastatic melanoma (70). An objective response was observed in 11 patients (73%). However, treatment demonstrated a high toxicity rate. Grade 3–4 adverse events were seen in 11 patients (73%). Similarly, another phase I study showed high rates of hepatotoxicity (80%) when combining ipilimumab and vemurafenib (71).

Combination therapy with atezolizumab (PD-L1 inhibitor) and cobimetinib (MEK inhibitor) was compared to regorafenib in the IMblaze370 study (50). This phase III study randomized 363 previously treated patients with mCRC to atezolizumab plus cobimetinib, atezolizumab alone, or single-agent regorafenib. After a median follow up of 7.3 months, overall survival data showed no improvement with atezolizumab or atezolizumab plus cobimetinib over regorafenib. Thus, the study failed to meet its primary endpoint. Approximately 60% of patients in the combination arm had grade 3–4 adverse effects (72). One of the criticisms of this study was the lack of biomarker driven recruitment strategy as 92% of the patients had microsatellite stable tumors (73).

These results indicate that administering BRAF/MEK inhibitors concurrently with immunotherapy may result in high rates of toxicity and novel combination strategies are needed. The disappointing results of the phase III IMblaze370 study also bring into question the one-size fits all approach with immune checkpoint combinations. Unfortunately, preclinical findings of synergy between BRAF/MEK inhibition and immunotherapy did not translate into improved clinical outcomes with this study and hence, this strategy needs revision. Some options include sequencing immunotherapy and targeted therapy and/or reducing the doses to reduce the side-effects. More biomarker-driven approaches may also be beneficial. Ongoing studies evaluating combinations of BRAF inhibitors and immunotherapy in GI malignancies are listed (*Table 1*).

Conclusions

Checkpoint inhibitors first made their mark in oncology

with ipilimumab's approval in 2011 for metastatic melanoma. Since then, the applications for checkpoint inhibitors have evolved immensely and they are now approved in almost all solid tumor subtypes. More recently, novel combination strategies with a strong pre-clinical rationale have propelled forward the outcomes with immune checkpoint blockers. In GI malignancies, immune therapy has made inroads, but so far, it has only been approved as single-agent therapy in the second- or third-line setting. Approaches from other cancer types can help pave the way for future therapy in GI. Using combinations of immune checkpoint inhibitors with various other agents may potentially help unlock the resistance to immunotherapy in GI malignancies.

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Footnote

Conflicts of Interest: Anand B. Shah declares receiving fees for serving on advisory boards from Eisai Inc., Ipsen Biopharmaceuticals, Inc. and Coherus Biosciences Inc.; Katelyn R. Sommerer has no conflicts of interest to declare; Khaldoun Almhanna declares receiving fees for serving on advisory boards from Merck.

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