

# Immune Checkpoint Inhibitors in the Treatment of Gastrointestinal Malignancies: A Review of Current and Future Therapies

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## ABSTRACT

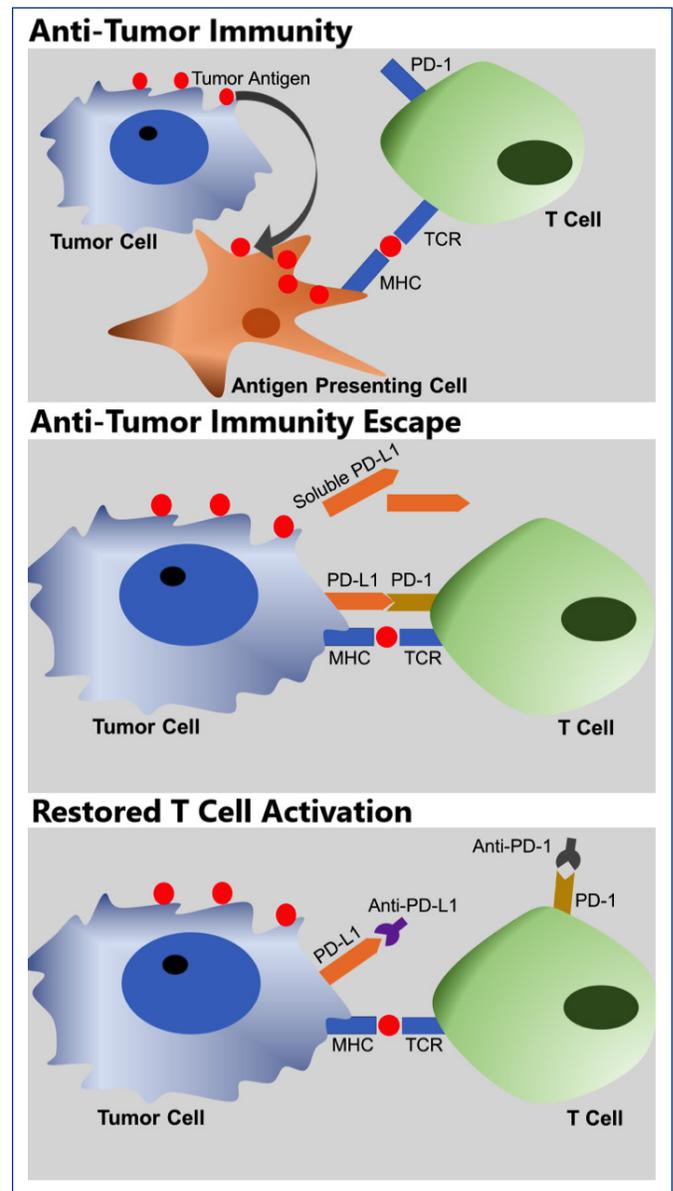
Gastrointestinal cancers are some of the most common malignancies worldwide. Traditional chemotherapy has been disappointing in improving overall survival in patients with unresectable or metastatic disease. The dawn of immunotherapy has led to emerging strategies in incorporating immune checkpoint inhibition either as single agents or in combination when treating gastrointestinal cancers. In this review, a general overview of the state of immunotherapy in the treatment gastrointestinal cancers is first provided. Subsequently, a review of the FDA-approved uses of immunotherapy in gastric, gastroesophageal, hepatobiliary, pancreatic and colorectal cancers will be provided followed by a glimpse into future treatment directions.

**KEYWORDS:** immunotherapy, checkpoint inhibitors, gastrointestinal malignancies, PD-1, PD-L1

## INTRODUCTION

Escape from the immune system is a well-recognized feature of cancer. Despite numerous genetic and epigenetic changes, cancers are able to escape immune destruction by inducing T-cell tolerance through the expression of inhibitory signals. This leads to dysfunctional T-cell signaling by terminating an immune response after antigen activation. Programmed cell death protein-1 (PD-1) is a key immune checkpoint on activated T-cells that can be exploited by tumor cells through the expression of PD-1 ligand (PD-L1) leading to the evasion of immune destruction. Inhibition of PD-1/PD-L1 is thought to restore anti-tumor immunity (Figure 1). The incorporation of immunotherapy in the treatment of cancer has been considered a major scientific and medical breakthrough since the first immune checkpoint inhibitor (ICI) was approved in the United States for the treatment of metastatic melanoma in 2011.<sup>1</sup> Since then, multiple antibodies targeting PD-1, PD-L1, and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) have gained FDA approval in numerous malignancies, thereby reshaping the treatment landscape of cancer. (Please see the accompanying article within this issue of the RIMJ, “Non-Small Cell Lung Cancer in the Era of Personalized Medicine: Molecular Tests that Matter”)

Figure 1. (Top) Activation of cytotoxic T-cell through presentation of tumor antigen; (Middle) Immune evasion by tumor cell through secretion of PD-L1; (Bottom) Restored T cell activation. See text for details



Gastrointestinal (GI) malignancies account for approximately 35% of all cancer-related mortality, making them one of the most common groups of malignancy worldwide.<sup>2</sup>

Due to the insidious nature of these malignancies, a large portion of patients have unresectable or metastatic disease at time of diagnosis, and the opportunity for cure through surgical resection is lost. Furthermore, traditional chemotherapy treatment has been disappointing with a dismal 5-year survival in stage IV disease. Immunotherapy has been evaluated in GI malignancies as single agents and in combination leading to limited approval in the second-line setting (after failure of initial therapy) for gastric, gastroesophageal, hepatic, and colorectal cancers. The role of these agents in the neoadjuvant or adjuvant setting is currently being investigated. Unlike in lung cancer or melanoma, the response rates to immunotherapy in GI malignancies are relatively low. Response rates for ICI monotherapy is approximately 5%–30% in gastroesophageal cancers, 10%–20% in hepatobiliary cancers, 30%–50% in mismatch repair-deficient (dMMR) colorectal cancer, and no clinical benefit in pancreatic cancer.<sup>3-9</sup> Furthermore, PD-1/PD-L1 status and tumor mutation burden (TMB) have not aided in predicting response to ICIs.

One explanation as to why GI malignancies are thought to have such relatively low response rate to ICI monotherapy is the tumor microenvironments that hinder the infiltration of immune cells.<sup>10</sup> Tumor microenvironments create what is termed as “cold tumors,” leading to ineffective T-cell activation and/or penetration of the stroma/parenchyma to reach the tumor.<sup>11</sup> There has been increasing interest in combining ICIs with immunotherapeutic small molecules, targeted therapy, chemotherapy, radiation, or other immunotherapies to convert “cold tumors” into “hot tumors” by altering the tumor microenvironment and enhancing immune efficacy and T-cell penetration.<sup>11</sup>

The combination of different modalities with immunotherapy is thought to lead to enhanced efficacy through the promotion of apoptosis causing increased antigen presentation or direct disruption of the tumor matrix increased antigen exposure and T-cell infiltration.<sup>12</sup> In particular, the combination of ICIs with other immunotherapies is thought to enhance antigen presentation and processing, decrease the secretion of immunosuppressive cytokines and suppressor cells, and enhance T-cell infiltration by targeting different immune checkpoints.<sup>11,13</sup> However, one predictable limitation in combining immunotherapies is the increased incidence of immune-related adverse effects.

Since the first ICI was FDA-approved for the treatment of metastatic melanoma in 2011, hundreds of new drugs have entered the market for the treatment of various conditions. In 2018 alone, 59 new drugs gained FDA approval.<sup>14</sup> The aim of this review article is to focus on the currently studied, FDA-approved uses of ICIs in the treatment of GI malignancies and review ongoing studies examining the combination of ICIs with traditional chemotherapy, immunotherapeutic small molecules, targeted therapy, and/or other immunotherapies.

### IMMUNOTHERAPY IN THE TREATMENT OF GASTRIC AND GASTROESOPHAGEAL CANCER

Currently, first-line treatment of metastatic gastric and

gastroesophageal cancers consists of chemotherapy alone or in combination with trastuzumab in patients with HER-2 positive disease. Second-line treatment includes taxanes and/or irinotecan with ramucicromab in patients who are eligible for vascular endothelial growth factor (VEGF) targeted therapy. The overall outcomes are still poor with survival of less than a year. Of note, ICIs first gained approval in metastatic gastric and esophageal cancers with microsatellite instability (MSI). In general, patients whose tumors demonstrate high microsatellite instability (MSI-H) have a better prognosis.

Pembrolizumab was FDA approved in 2017 for the treatment of chemotherapy-refractory (defined as progression after two lines of therapy), PD-L1-positive gastroesophageal cancers. The approval was based upon the findings in KEYNOTE-059, a phase II, global, open-label, single-arm, multicohort study that enrolled 259 patients. Patients received pembrolizumab 200mg intravenously every three weeks until disease progression. Objective response rate (ORR) was 11.6% with a complete response rate of 2.3%. The ORR was 15.5% and 6.4% in patients with PD-L1 positive and PD-L1 negative tumors, respectively.<sup>4</sup> More recently, the FDA approved pembrolizumab for patients with recurrent, locally advanced or metastatic, squamous cell carcinoma of the esophagus (ESCC) whose tumors expressed PD-L1 (Combined Positive Score [CPS]  $\geq$  10) based upon KEYNOTE-181. KEYNOTE-181 was a randomized, open-label trial that enrolled 628 patients with recurrent, locally advanced or metastatic esophageal cancer who progressed on or after one line of systemic treatment for advanced or metastatic disease. Patients were randomized to receive either pembrolizumab every three weeks or the investigator’s choice of traditional chemotherapy. The hazard ratio for overall survival (OS) in ESCC whose tumors expressed a PD-L1 CPS  $\geq$  10 was 0.64. Median OS was 10.3 months and 6.7 months in the pembrolizumab and control arms, respectively.<sup>15</sup> Another trial that supported these findings with pembrolizumab was KEYNOTE-180, a single-arm, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer who progressed on or after at least two prior systems treatments for advanced disease. In this trial, and in the 35 patients with ESCC expressing PD-L1 CPS  $\geq$  10, ORR was 20% and response durations ranged from 4.2 to 25.1 months.

On the other hand, nivolumab, another PD-1 inhibitor, was evaluated in the treatment of esophageal cancer in CheckMate-032. This phase I/II compared the combination of two immunotherapies (nivolumab and ipilimumab, a CTLA-4 inhibitor), nivolumab monotherapy, and placebo in patients with esophageal cancers who had failed second-line therapy. This trial showed improved ORR and progression free survival (PFS) in the combination group versus the monotherapy group. However, as expected, the combination group experienced more treatment-related toxicities.<sup>16</sup> In another trial, ATTRACTION-02 examined nivolumab monotherapy in the second-line setting and resulted in an 11% ORR, 27.3% 12-month OS, and 10.6% 24-month OS.<sup>17</sup> The results of this trial led to the approval of nivolumab monotherapy in Asia only.

The use of immunotherapy in the front-line treatment has not been successful – in the phase III trial, KEYNOTE-062, the combination of pembrolizumab with chemotherapy versus chemotherapy alone was examined in PD-L1-positive gastroesophageal cancers. The results only trended towards improvement in outcomes, particularly in patients with higher PD-L1 expression, but did not achieve statistical significance.<sup>18</sup> Currently, several trials are examining immunotherapy in combination with chemotherapy in the adjuvant and neoadjuvant setting and its role in maintenance therapy.

### IMMUNOTHERAPY IN THE TREATMENT OF HEPATOBILIARY CANCER

For the purposes of this review, we will address the use of ICIs in hepatocellular carcinoma (HCC) and cholangiocarcinoma/gallbladder cancer only. Currently, first-line treatment for unresectable or metastatic HCC includes sorafenib and more recently, lenvatinib. Until recently, there was not an established second-line treatment following sorafenib failure.

The efficacy of nivolumab in HCC was examined in CheckMate-040, a phase I/II study that enrolled patients with advanced HCC and Child-Pugh A or B cirrhosis who progressed or were intolerant to sorafenib. Forty-nine of the 255 patients assessable for response had an objective anti-tumor response to nivolumab, corresponding to an 18.2% ORR. The benefits of nivolumab were observed in sorafenib-naïve and sorafenib-experienced patients.<sup>19</sup> Based upon this data, nivolumab was FDA-approved for the treatment of HCC in patients who had previously failed sorafenib.

In another similar phase II trial, KEYNOTE-224 evaluated pembrolizumab in patients previously treated with sorafenib resulting in a 17% ORR.<sup>20</sup> A confirmatory study was recently presented at the 2019 American Society of Clinical Oncology (ASCO) meeting: KEYNOTE-240. This trial enrolled 413 patients with advanced HCC with Child-Turcotte-Pugh A cirrhosis after progression or intolerance to sorafenib. Patients were randomized to pembrolizumab versus placebo. Although this study showed improvements in median OS (13.9 versus 10.6 months) and PFS (3 versus 2.8 months), the findings were not statistically significant because pre-specified efficacy boundaries were not reached. Response rates were higher for pembrolizumab compared to placebo (18.3% versus 4.4%).<sup>21</sup>

A phase Ib study examined atezolizumab, a PD-L1 inhibitor, in combination with bevacizumab, a VEGF inhibitor, in the first-line setting for advanced HCC with up to Child-Pugh B7 cirrhosis. Preliminary data revealed a 34% ORR with one complete response and a median PFS of 14.9 months.<sup>22</sup> Given these promising results, the phase III IMbrave150 trial is currently underway and examining the combination of atezolizumab with bevacizumab versus sorafenib.<sup>23</sup> Currently, there are several other ongoing trials that are examining multiple immunotherapy combinations in the front-line treatment of HCC. CheckMate-459 is examining the combination of nivolumab with sorafenib in the front-line setting. Unfortunately, preliminary data suggests

that there is no statistically significant improvement in OS when compared to sorafenib alone.<sup>24</sup> LEAP-002 is a phase III trial currently underway and that is examining the use of pembrolizumab with lenvatinib in the front-line setting.<sup>25</sup>

In unresectable or metastatic biliary tract cancers, first-line treatment includes gemcitabine with a platinum agent (e.g. cisplatin, oxaliplatin). Of note, patients who are dMMR or MSI-H (microsatellite instability – high) have been found to have higher response rates to PD-1/PD-L1 inhibition. Unfortunately, only a minority of patients with biliary tract cancers are MSI-H or dMMR – 5% of gallbladder cancers; 5–13% of extrahepatic cholangiocarcinoma; and 10% of intrahepatic cholangiocarcinoma.<sup>26</sup> Based upon the results of a study by Le, et al. in 2017, pembrolizumab gained approval for use in unresectable or metastatic solid tumors that were dMMR or MSI-H. This trial evaluated patients with dMMR malignancies and resulted in a 53% ORR across twelve different tumor types including HCC and biliary tract cancers.<sup>27</sup> Currently, there are several trials examining the combination of ICIs with standard chemotherapy in the second-line setting.

### IMMUNOTHERAPY IN THE TREATMENT OF PANCREATIC CANCER

First-line treatment for unresectable or metastatic pancreatic cancer consists of one to four drug regimens built upon a backbone of either a fluoropyrimidine or gemcitabine – dependent upon the patient’s age and performance status. Prognosis of advanced pancreatic cancer is very dismal, and survival is less than a year. Pancreatic cancer is traditionally considered non-immunogenic – the majority of patients derive little clinical benefit from ICIs.<sup>28-30</sup> The exception to this rule is pancreatic cancers that are found to be MSI-H or dMMR, which only accounts for 1.2% of pancreatic cancers.<sup>31</sup> One theory to explain the disappointing response rates to ICIs is due to the immunosuppressive tumor micro-environment of pancreatic cancer along with the poorly vascularized and dense surrounding connective tissue that hinders immune cell infiltration.<sup>32</sup> Currently, pembrolizumab is approved in the second-line setting only in pancreatic cancers that are MSI-H or dMMR.

Given the disappointing responses to ICI monotherapy, there has been significant interest in combining immunotherapy with different treatment modalities in the hopes of increasing tumor immunogenicity. Thus far, the majority of trials that have examined the use of ICIs in combination with standard cytotoxic regimens have not resulted in significantly improved response rates when compared to the standard cytotoxic regimens alone.<sup>33-35</sup> Another potential strategy to increase tumor immunogenicity is to use a pancreatic cancer vaccine (GVAX) – created from irradiated, allogeneic pancreatic cancer cells which are then modified to induce a tumor antigen response by a host’s immune system. Currently, there are ongoing trials examining the use of GVAX with and without ICIs; however, to date, the results have been mixed.<sup>36, 37</sup>

## IMMUNOTHERAPY IN THE TREATMENT OF COLORECTAL CANCER

The treatment of metastatic colorectal cancer (mCRC) has been evolving through the last decade. Currently, first-line treatments for unresectable or mCRC include cytotoxic regimens built upon a fluoropyrimidine backbone in combination with targeted therapy. Immunotherapy has been approved for the treatment of mCRC patients whose tumors are MSI or dMMR, which accounts for 15% of CRCs and plays a significant role in predicting a response to ICI therapy.<sup>38, 39</sup>

Pembrolizumab was examined in the second-line setting for mCRC patients who were MMR-deficient (dMMR) and MMR-proficient. In MMR-proficient patients, there was a 0% ORR with an 11% disease control rate (DCR); however, dMMR patients exhibited a 40% ORR with a 78% DCR to pembrolizumab monotherapy. These findings led to the FDA-approval of pembrolizumab in the second-line setting for MSI-H or dMMR mCRC.<sup>26</sup> Nivolumab combined with ipilimumab and nivolumab monotherapy have also been approved for second-line use for MSI-H or dMMR mCRC based on CheckMate-142 which showed a 55% ORR in the dual ICI cohort and a 31% ORR in the monotherapy cohort.<sup>3,40</sup> Of note, those that received dual ICI had received two or more lines of therapy and showed response regardless of PD-1/PD-L1 status, KRAS wild-type, BRAF mutation, or history of Lynch syndrome.<sup>40</sup> Given these promising results from CheckMate-142 regarding dual ICI therapy, there has been much interest in combining ICIs with other treatment modalities in the hopes of improved response rates.

An ongoing phase II trial is combining standard cytotoxic chemotherapy with pembrolizumab in the front-line setting for patients with mCRC irrespective of MMR status. Preliminary data demonstrates a 53% ORR.<sup>40</sup> Other studies have looked into combining ICIs with a VEGF inhibitor (i.e. bevacizumab) with standard chemotherapy in patients who had not received a platinum (i.e., oxaliplatin) containing regimen or without standard chemotherapy in patients who were oxaliplatin-refractory. This has resulted in an 8% ORR without standard chemotherapy and a 36% ORR with standard chemotherapy.<sup>42</sup> Based upon the promising results from a phase I trial, IMblaze370 examined the use of an ICI with a MAP kinase enzyme (MEK) inhibitor in hopes of upregulating antigen presentation leading to increased T-cell tumor accumulation in microsatellite stable (MSS) or MSI-low (MSI-L) mCRC patients who had progressed after two or more lines of therapy. Unfortunately, no statistically significant difference was found in survival when compared to standard therapy.

## CONCLUSION

The introduction of immunotherapy has led to major changes to the treatment paradigms of many cancers. ICIs have made their way into front-line treatment regimens in melanoma and lung cancer. In GI malignancies, the changes to the treatment paradigms have been more modest

– treatment with ICIs are mostly reserved for use in the second-line or beyond, and usually in the setting of PD-1/PD-L1 positivity, MSI-H, or dMMR tumors. However modest, these second-line ICIs give patients reasonable options following progression of their disease that were not available a few years ago.

Why the responses to ICI monotherapy are relatively low in GI malignancies include the immunosuppressive tumor microenvironments and the complex stroma/parenchyma of tumors preventing immune cell infiltration that is necessary for a robust immune response. As a result, the logical next step has been combining ICIs with other treatment modalities such as: standard cytotoxic chemotherapy to help break down the tumor stroma/parenchyma to help expose tumor antigens, increase antigen presentation, and enhance immune cell infiltration: or combine one ICI with another ICI to help enhance the immune response through different mechanisms and/or dampen the immunosuppressive tumor microenvironment.

With an increased understanding of the underlying mechanism of the immune system and how it interacts with the tumor microenvironment, new studies are being devised to assess the safety and efficacy of these combinations on a smaller scale prior to pursuing larger phase III trials.

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