Introduction

Gastrointestinal (GI) cancers are the most common human tumors encountered worldwide. Surgical resection continues to be the primary curative treatment for the majority of GI cancers, although a large proportion of patients are unresectable at the time of diagnosis. For patients who undergo resection alone, the overall 5-year survival rate remains poor. The addition of neoadjuvant or adjuvant chemotherapy and radiation therapy only modestly improves the overall long-term survival. With the exception of colon cancer, no efficacious screening methods currently are available for most GI malignancies, resulting in diagnosis at an advanced stage. Therefore, it is imperative to develop not only effective screening modalities but also effective treatments for patients who have advanced unre-
fectable disease in order to downstage it to resectable disease or improve disease control.

Although immunotherapeutic approaches have been extensively promoted in other cancers such as melanoma and renal cell carcinoma, the potential use of immune-based therapy to treat advanced GI malignancies is just being realized. It is known that tumor-specific T cells can be isolated from patients with GI cancers.40 Infiltration of T cells into GI tumors correlates with improved prognosis in several types of GI cancers.45-50 The presence of negative regulatory factors, such as regulatory T cells and myeloid-derived suppressor cells, which can inhibit antitumor T-cell responses, correlates with a poor prognosis in several GI cancers.21-23 With the identification of tumor-associated antigens on GI tumors, as shown in Table 1,24-37 strategies to target these antigens are currently being developed. Although multiple approaches to induce immunity against GI malignancies have been tested, this article focuses on the use of monoclonal antibodies, adoptive cell transfer, and vaccine-based immunotherapy for GI cancers (Figure).

**Immunotherapeutic Strategies for GI Malignancies**

**Monoclonal Antibody Therapy**

Monoclonal antibodies (mAbs) are used to target specific antigens expressed on tumor cells. Some of the mechanisms of action of mAb therapy include blocking growth factor/receptor interactions, down-regulating proteins required for tumor growth, and activating effector mechanisms of the immune system (including complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity [ADCC]). Unlike conventional chemotherapy, which affects mitotically active normal cells in addition to neoplastic cells, mAb therapy has the distinct potential advantage of tumor antigen-specific recognition and therefore fewer and less severe adverse effects compared with cytotoxic therapy. Antibodies can be readily produced in large quantities for easy implementation and can be used in all patients who express the specific antigen on their tumor. Currently, mAb therapy is the most utilized immunotherapy for GI cancers; to date, the US Food and Drug Administration (FDA) has approved four mAb therapies targeting GI malignancies: bevacizumab, cetuximab, panitumumab, and trastuzumab (Table 2).

Immunomodulatory mAb therapies directly target immune cells, as opposed to tumor antigens. Ipilimumab is a mAb that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) on the surface of T cells, leading to increased numbers of activated T cells.58 Ipilimumab has shown efficacy in inducing clinical responses and has been approved by the FDA for patients with metastatic melanoma.39 Blocking the programmed death-1 (PD-1) receptor on activated T cells with mAbs has been shown to overcome immune resistance and induce clinical responses in patients with solid tumors.40 These and other novel immunomodulatory mAb therapies are currently being explored for GI malignancies.

**Cancer Vaccines**

The goals of cancer vaccination are to activate and expand tumor-specific T cells as effective means of augmenting immunity. To induce a robust antitumor immune response, peptides derived from tumor-associated antigens must be presented to T cells. Effective vaccination requires these peptides to be presented by a professional antigen-presenting cell, such as a dendritic cell (DC). Immature DCs reside in peripheral tissues, where they take up and process antigens. Within the DCs, antigens are targeted to the proteasomal or endocytic pathway, degraded to peptides, and bound to major histocompatibility complex (MHC) class I molecules for presentation to CD8+ cytotoxic T cells or to MHC class II molecules for presentation to CD4+ helper T cells. As immature DCs acquire antigen at the site of vaccination, they may come into contact with immune-stimulating adjuvants or activated T cells, which induce full maturation of DCs and migration to draining lymph nodes. Mature DCs demonstrate diminished antigen uptake but upregulate costimulatory molecules for enhanced interaction with T cells. Within the lymph nodes, DCs educate naive T cells for the stimulation of primary antitumor responses and induction of immunologic memory. Activated T cells migrate to the site of antigen expression, the tumor, to exert effector functions such as cell cytotoxicity and inflammatory cytokine production. Such activity results in tumor regression.

Therapeutic vaccinations are designed to enhance preexisting immunity or induce novel, robust

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>GI Tumor Involved</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overexpressed self-antigen</td>
<td>HER2 MUC1 Mesothelin</td>
<td>Gastric Pancreatic</td>
<td>Ross, McKenna28 Ross29 Lepisto et al29 Pecher et al30 Li et al30 Johnston et al31</td>
</tr>
</tbody>
</table>

AFP = alpha-fetoprotein, CEA = carcinoembryonic antigen, HER2 = human epidermal growth factor receptor 2, MUC1 = mucin-1.
antitumor immune responses in patients with cancer. Vaccine strategies have included the use of peptides derived from tumor-associated antigens, whole tumor cells, tumor-associated antigen-encoding DNA, or viral vectors alone or with in vitro generated DCs. DCs are the most potent antigen-presenting cells, capable of activating naive and memory T cells.\textsuperscript{41}

Tumor antigen-pulsed DC-based vaccines have been shown to induce both CD8\textsuperscript{+} and CD4\textsuperscript{+} T-cell responses in patients with advanced cancers.\textsuperscript{42} Although

![Image](image_url)

**Figure.** — Immunotherapeutic strategies. (A) Vaccine-based immunotherapy. Vaccination leads to the presentation of peptides on major histocompatibility complex (MHC) classes I and II molecules of antigen-presenting cells, such as dendritic cells (DCs), to stimulate antitumor CD8\textsuperscript{+} and CD4\textsuperscript{+} T cells, respectively. Activated CD4\textsuperscript{+} T cells send costimulatory signals to induce full maturation of DCs and activation of CD8\textsuperscript{+} T cells. Activated CD8\textsuperscript{+} T cells migrate to the site of tumor and mediate tumor killing. (B) Monoclonal antibody therapy. Injection of monoclonal antibodies leads to antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cytotoxicity (CDC), or apoptosis by blockade of required growth factors and signals. Alternatively, monoclonal antibodies bind to immune cells to enhance immune responses. (C) Adoptive cell therapy. Immune cells isolated from the peripheral blood, tumor, and/or lymph nodes are activated in vitro with high-dose interleukin-2 (IL-2). High numbers of activated immune cells are injected back into the patient to mediate tumor cell cytotoxicity.

**Table 2.** — FDA-Approved Monoclonal Antibodies for Use in Gastroesophageal Cancers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Year of FDA Approval</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>2004</td>
<td>First-line therapy for EGFR-expressing metastatic colorectal cancer in combination with irinotecan in patients whose disease is refractory to irinotecan-based chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2007</td>
<td>Monotherapy for patients with EGFR-expressing metastatic colorectal cancer after failure of both irinotecan and oxaliplatin-based chemotherapy regimens</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>2004</td>
<td>First-line therapy for metastatic colorectal cancer in combination with FOLFIRI therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2006</td>
<td>Second-line therapy for metastatic colorectal cancer in combination with FOLFOX therapy</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>EGFR</td>
<td>2006</td>
<td>First-line therapy for EGFR-expressing metastatic colorectal carcinoma in combination with FOLFIRI therapy</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2</td>
<td>2010</td>
<td>First- or second-line therapy for HER2-positive metastatic gastric or gastroesophageal adenocarcinoma in combination with cisplatin and a fluoropyrimidine</td>
</tr>
</tbody>
</table>

EGFR = epidermal growth factor receptor. FOLFIRI = 5-fluorouracil, leucovorin, irinotecan. FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin. HER2 = human epidermal growth factor receptor 2. VEGF = vascular endothelial growth factor.
clinical trials using DC-based vaccines in patients with advanced cancers have led to positive immunologic endpoints, few clinical responses have been seen.43-45 One exception is the use of sipuleucel-T.

Sipuleucel-T is a DC-containing cellular vaccine loaded with a fusion protein of prostatic acid phosphatase and granulocyte macrophage-colony stimulating factor (PAP-GM-CSF) and has been shown to increase overall survival (OS) in patients with metastatic prostate cancer.46 Sipuleucel-T is the first therapeutic cancer vaccine to receive FDA approval and has raised the potential for the use of DC-based vaccines in other cancers, including GI tumors.

**Adoptive Cell Therapy**

Adoptive cell therapy is the passive transfer of tumor-specific T cells into a tumor-bearing host for the direct destruction of tumors. Unlike mAb therapy, adoptive cell therapies are “personalized” for each patient. The discovery of interleukin-2 (IL-2) as a critical T-cell growth factor allowed for the expansion of large numbers of T cells ex vivo.

The first clinical trial of adoptive cell therapy in patients with advanced cancers was the transfer of lymphokine-activated killer (LAK) cells.47 LAK cells were generated by culturing peripheral lymphocytes in high concentrations of IL-2 that resulted in the generation of cytotoxic cells, which could directly lyse tumor cells. Since then, strategies to isolate and expand tumor antigen-specific T cells have been developed. Adoptive cell therapy with autologous tumor-infiltrating lymphocytes (TILs) takes advantage of lymphocytes that have demonstrated the ability to home to the tumor. Adoptive cell therapy with TILs isolated from resected tumors, expanded ex vivo, and administered to patients in combination with IL-2 has demonstrated a 50% response in patients with metastatic melanoma.48-51 This approach is currently under investigation for the treatment of nonmelanoma tumors. TILs have been isolated from a variety of GI tumors and may be a promising new approach for patients with metastatic GI cancers.52

**Immunotherapeutic Approaches to GI Malignancies**

**Colorectal Cancer**

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer deaths worldwide.53,54 Colon cancer mortality is decreasing in the United States, with colon cancer screening being the most important contributing factor.54 Despite these successes, half of patients with CRC will develop metastases.55 Historically, the median survival of patients with metastatic CRC not amenable to surgery is 6 to 12 months.55 Survival significantly improves if the patient has resectable metastatic disease, with a 5-year survival rate of 26% to 40%.55

Colon cancer is one of the few GI cancers with existing FDA-approved immunotherapy. Cetuximab is a mAb that directly inhibits the epidermal growth factor receptor (EGFR).56 There is evidence that cetuximab also mediates ADCC.57 Cetuximab was first approved by the FDA in early 2004 for patients with metastatic CRC in combination with irinotecan. Rates of response and time to tumor progression for the combination were superior with cetuximab to irinotecan alone.58 In 2007, cetuximab as monotherapy was approved for patients with EGFR-expressing metastatic CRC after both irinotecan- and oxaliplatin-based chemotherapy regimens failed.

In mid-2004, bevacizumab was approved as first-line therapy for metastatic CRC in combination with 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI).59 Bevacizumab is a mAb that inhibits angiogenesis by directly targeting the vascular endothelial growth factor (VEGF) protein.60 In 2006, bevacizumab was approved by the FDA as second-line therapy for metastatic CRC in combination with 5-FU, leucovorin, and oxaliplatin (FOLFOX). The combination resulted in a significantly improved survival when bevacizumab was added to the regimen.61

Panitumumab, another EGFR inhibitor, was approved by the FDA in 2006 for patients with EGFR-expressing metastatic CRC. Panitumumab has been shown to mediate ADCC through myeloid-derived granulocytes.62 Patients with EGFR-expressing tumor cells were found to have significant benefit in progression-free survival (PFS) when panitumumab was added to a FOLFIRI regimen.63,64 A subsequent randomized phase III trial also showed a significant improvement of PFS with panitumumab and FOLFOX therapy.65

An initial clinical trial has raised the potential for immunomodulatory mAb therapy for CRC. In a phase I study, treatment with anti–PD-1 antibody led to a complete response in a patient with metastatic CRC.66 Further studies are warranted to determine whether targeting immune cells will improve the treatment of CRC.

Autologous tumor-based vaccination has led to successes in the treatment of CRC. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-01 phase III trial demonstrated that postoperative therapy with the immunostimulating adjuvant bacillus Calmette Guérin (BCG) led to a significantly improved OS in patients with resected Dukes’ stage B or C colon adenocarcinoma.67 After a 10-year follow-up, the authors concluded that there was no difference in disease-free survival but a statistically significant increase in OS for patients who received BCG, whereas chemotherapy did not portend a survival benefit.67 Combining BCG with an autologous tumor cell vaccine, currently in phase III trials, has been shown to increase disease-free survival and OS in patients with resected stage II/III colorectal adenocarcinoma.68-70 Another cell-based vaccine for the treatment of CRC involves Newcastle disease virus (NDV) infected autologous tumor cells; in a phase III clinical trial, patients with colon cancer demonstrated increased metastasis-free survival and OS with this vaccine.71,72
Carcinoembryonic antigen (CEA) is a tumor-associated antigen expressed by most CRCs and has been one of the most popular targets for vaccine-based immunotherapeutic strategies. DNA vaccination with plasmid coexpressing the CEA antigen and hepatitis B surface antigen (HbsAg) genes demonstrated positive immunologic responses to both CEA and HbsAg in patients with metastatic CRC. Unfortunately, no objective tumor responses were observed in this study.

Viral-based vaccinations using fowlpox and vaccinia viruses encoding the CEA antigen and TRICOM (B7.1, ICAM-1, and LFA-3) demonstrated induction of anti-CEA–specific T-cell responses and stable disease in 40% of patients with metastatic cancer, including CRC. A phase II clinical trial in patients with metastatic CRC examined combination chemotherapy and vaccination with a canary pox virus encoding CEA and the T-cell costimulatory molecule CD80 (ALVAC-CEA/B7.1). The trial demonstrated that anti-CEA–specific T-cell responses could be successfully generated in patients undergoing chemotherapy. Objective clinical responses were observed in 40% of the patients.

Early-phase clinical trials have been undertaken to determine the efficacy of DC-based therapy. Patients with advanced CRC were vaccinated with DCs pulsed with CEA peptides or CEA mRNA. The majority of patients demonstrated positive CEA-specific T-cell responses after vaccination, and induction of stable disease was determined in several patients. Together, these trials have demonstrated the safety of vaccine-based strategies and have shown positive immunologic and clinical endpoints.

Although infiltrating T cells are correlated with an improved prognosis, relatively few adoptive cell therapy trials for the treatment of CRC have been performed. In a phase I clinical trial, 14 patients with resected metastatic CRC received adoptive cell therapy with TILs in combination with high-dose IL-2. Although persistence of adoptively transferred T cells correlated with disease-free survival, there was no statistical difference between patients treated with TILs and those treated with traditional chemotherapy regarding disease-free survival. In another pilot study, T cells were expanded from the tumor-draining sentinel lymph nodes and reinfused back into patients with disseminated or locally advanced CRC. Four of 9 patients experienced a complete response. Although data supporting immunotherapy for CRC are the most mature for all GI malignancies, there is ample opportunity for further clinical investigation.

**Esophageal Cancer**

Esophageal cancer is the eighth most common cancer worldwide. The two most common types are squamous cell carcinoma (SCC), with a higher incidence worldwide, and adenocarcinoma, which has a higher incidence in the United States. Five-year OS rates after resection are 20% to 30% and 20% to 25%, respectively. The incidence of esophageal cancer is rising in the Western world secondary to an increase in esophageal adenocarcinoma.

As overexpression of EGFR in esophageal cancer has been correlated with a poor prognosis, mAb therapy to target the EGFR signaling pathway is currently being tested in esophageal cancer. The efficacy of cetuximab for the treatment of patients with esophageal adenocarcinoma or SCC has yet to be established in prior and ongoing clinical trials. Additional trials to examine mAb therapy with cetuximab and trastuzumab alone or in combination with radiation or chemotherapy have been performed (Table 385-88 and Table 489-95).

Data involving the use of vaccine-based or adoptive cell transfer immunotherapy for esophageal carcinoma are scarce. A phase I trial was reported with a peptide vaccine administered to 10 patients with stage III or IV esophageal SCC whose disease had progressed on conventional treatment, with 1 complete response and stable disease in 3 patients. The peptides were derived from three novel HLA-A24–restricted cancer-testis antigen peptides, and peptide-specific T-cell responses were detected in 9 of 10 patients after vaccination.

To date, only one phase I/II trial has been conducted for esophageal SCC with adoptive cell therapy. Peripheral blood mononuclear cells were stimulated in vitro with autologous tumor cells. T cells were directly injected into primary tumors, metastatic lymph nodes, pleural spaces, or ascites in combination with intravenous IL-2. The authors reported objective tumor responses in half of the patients. Four of 11 patients (36%) had confirmed complete or partial responses. The same group published a case report of another patient with recurrent esophageal SCC who had a partial response to the same therapy. Additional trials are required to determine the efficacy of vaccine and T-cell–based therapies for esophageal carcinoma.

**Gastroesophageal Junction Adenocarcinoma**

**Gastric Adenocarcinoma**

Over the past few decades, gastric cancer mortality has dropped significantly, but it remains a disease with a poor prognosis and high mortality. Gastric cancer is the fourth most common cancer and the second leading cause of cancer deaths worldwide. Gastric cancer portends a 5-year survival rate of less than 20%. As overexpression of EGFR in esophageal cancer has been correlated with a poor prognosis, mAb therapy to target the EGFR signaling pathway is currently being tested in esophageal cancer. The efficacy of cetuximab for the treatment of patients with esophageal adenocarcinoma or SCC has yet to be established in prior and ongoing clinical trials. Additional trials to examine mAb therapy with cetuximab and trastuzumab alone or in combination with radiation or chemotherapy have been performed (Table 385-88 and Table 489-95).

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was recently used in phase III trials for patients with HER2/neu-positive, locally advanced and/or metastatic gastric or gastroesophageal adenocarcinoma. Patients with HER2/neu-positive gastroesophageal or gastric adenocarcinoma had significantly improved OS with trastuzumab in combination with chemotherapy compared with patients who underwent chemotherapy alone. With these promising results, trastuzumab gained FDA approval in 2010 for the treatment of HER2-positive gastric or gastroesophageal junction adenocarcinoma.

HER2/neu overexpression in gastric cancer has also been explored for DC therapy. Patients with advanced gastric cancer were treated with DCs pulsed with HER2/neu-derived peptides in a phase I trial. The vaccine was found to be safe and efficacious at inducing tumor-specific T-cell responses, with 2 of 9 patients exhibiting an objective clinical response. Adoptive cell therapy has also had some success in patients with gastric cancer. In a nonrandomized trial, patients treated with oxaliplatin combined with adoptive cell therapy with cytokine-induced killer cells produced from peripheral blood mononuclear cells had increased survival compared with those who received oxaliplatin alone.

In a randomized trial, patients with gastric cancer treated with cisplatin/5-FU in combination therapy with tumor-associated lymphocytes purified from ascites, pleural fluid, and/or lymph nodes demonstrated an increased survival compared with those treated with chemotherapy alone. Similar to esophageal cancer, targeted immunotherapy for gastric cancer is the most established modality, with alternative immunotherapies currently being explored.

**Hepatocellular Cancer**

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide. The incidence is particularly high in Asia and sub-Saharan Africa, but the incidence of HCC is climbing in North America and Europe. The incidence in the United States has been increasing for the past two decades. Over 70% of patients are not candidates for surgical resection and/or liver transplantation. These limitations

### Table 3. — Phase II Clinical Trials for Patients Undergoing Neoadjuvant Monoclonal Antibody Therapy With Chemotherapy ± Radiation Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Pathology</th>
<th>No. of Patients</th>
<th>No. of Partial Responses</th>
<th>No. of Complete Responses</th>
<th>Median Survival (mos)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + FOLFOX/RT + surgery</td>
<td>E, ESCC</td>
<td>41</td>
<td>12</td>
<td>8</td>
<td>17</td>
<td>De Vita et al[85]</td>
</tr>
<tr>
<td>Cetuximab + cisplatin/docetaxel/RT + surgery</td>
<td>E, ESCC</td>
<td>28</td>
<td>10</td>
<td>9</td>
<td>NA</td>
<td>Ruhstaller et al[86]</td>
</tr>
<tr>
<td>Cetuximab + carboplatin/paclitaxel/RT ± surgery</td>
<td>E, G, ESCC</td>
<td>60</td>
<td>NA</td>
<td>13</td>
<td>NA</td>
<td>Safran et al[87]</td>
</tr>
<tr>
<td>Trastuzumab + paclitaxel/cisplatin/RT + surgery</td>
<td>E (HER2+)</td>
<td>19</td>
<td>1</td>
<td>3</td>
<td>24</td>
<td>Safran et al[88]</td>
</tr>
</tbody>
</table>

E = esophageal adenocarcinoma, ESCC = esophageal squamous cell carcinoma, FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin, G = gastric adenocarcinoma, HER2 = human epidermal growth factor receptor 2, NA = not available, RT = radiation therapy.

### Table 4. — Phase I or II Clinical Trials of Monoclonal Antibody Therapy for Patients With Metastatic Esophageal, Gastroesophageal, and Gastric Cancers

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Pathology</th>
<th>No. of Patients</th>
<th>No. of Partial Responses</th>
<th>No. of Complete Responses</th>
<th>Median Survival (mos)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>E, GEJ, G</td>
<td>35</td>
<td>1</td>
<td>0</td>
<td>3.1</td>
<td>Chan et al[89]</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>E, GEJ</td>
<td>55</td>
<td>3</td>
<td>0</td>
<td>4.0</td>
<td>Gold et al[90]</td>
</tr>
<tr>
<td>Cetuximab + FOLFOX</td>
<td>GEJ, G</td>
<td>52</td>
<td>26</td>
<td>4</td>
<td>9.5</td>
<td>Lordick et al[91]</td>
</tr>
<tr>
<td>Cetuximab + cisplatin/docetaxel</td>
<td>GEJ, G</td>
<td>72</td>
<td>27</td>
<td>1</td>
<td>9.0</td>
<td>Pinto et al[92]</td>
</tr>
<tr>
<td>Cetuximab + FOLFOX</td>
<td>G</td>
<td>40</td>
<td>21</td>
<td>0</td>
<td>9.9</td>
<td>Han et al[93]</td>
</tr>
<tr>
<td>Cetuximab + 5-FU/cisplatin vs 5-FU/cisplatin</td>
<td>ESCC</td>
<td>32 vs 30</td>
<td>11 vs 8</td>
<td>0 vs 1</td>
<td>9.5 vs 5.5</td>
<td>Lorenzen et al[94]</td>
</tr>
<tr>
<td>Cetuximab + FOLFIRI</td>
<td>GEJ, G</td>
<td>38</td>
<td>11</td>
<td>4</td>
<td>16</td>
<td>Pinto et al[95]</td>
</tr>
</tbody>
</table>

E = esophageal adenocarcinoma, ESCC = esophageal squamous cell carcinoma, FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin, FOLFIRI = 5-fluorouracil, leucovorin, irinotecan, 5-FU = 5-fluorouracil, G = gastric adenocarcinoma, GEJ = gastroesophageal junction adenocarcinoma, NA = not available.
are typically due to impaired liver function secondary to cirrhosis or a prohibitively high tumor burden.109

Some success has been reported with mAb therapy in HCC. In phase II studies, bevacizumab has been used in combination with targeted therapy, yielding a significant increase in PFS compared with historic controls.110 Levels of alpha-fetoprotein (AFP) are elevated in the serum of the majority (50% to 80%) of patients with HCC.32 This marker has been exploited for DC-based vaccination therapy.

A phase I/II trial examined vaccination of patients with HCC with DCs pulsed with four AFP-derived peptides.111 Six of 10 patients demonstrated positive T-cell responses to AFP after vaccinations. In another trial, DCs pulsed with autologous tumor cells resulted in 68% of patients achieving stable disease or partial response and an increase in OS. The subset of patients who received monthly booster DC vaccines had a robust response, with 1-year survival rates increased over 50 months compared with those who received DC-pulsed therapy alone.112

In a phase II study of patients with advanced HCC, patients received intravenous vaccination with DCs pulsed with lysate derived from the HepG2 liver tumor cell line.113 A partial response or stable disease was measured in 28% of patients. In a phase I trial, autologous immature DCs were injected intratumorally after radiation therapy and were able to induce tumor-specific and innate immunity, with only 5 of 14 patients (38%) having progressive disease.114 Adjuvant tumor lysate vaccines after partial hepatectomy have been shown to decrease recurrence and increase overall and recurrence-free survival rates in phase II studies.115,116

A few adoptive cell therapy trials have been performed in patients with resected HCC. Early studies examined the efficacy of adoptive transfer of IL-2–activated LAK cells in combination with doxorubicin, which decreased recurrence in patients with resected HCC.117 Another adoptive cell therapy trial utilizing TILs in combination with high-dose IL-2 demonstrated a decrease in disease recurrence in patients with resected HCC compared with historic controls.118 Multiple infusions of intravenous peripheral blood lymphocytes stimulated ex vivo with IL-2 and anti-CD3 decreased recurrence and increased recurrence-free survival but did not significantly increase OS in patients with resected HCC.10 Immunotherapeutic approaches have been most extensively investigated for HCC, with adoptive transfer and vaccine-based therapies limited to investigational reports and early-phase clinical trials.

**Pancreatic Cancer**

Pancreatic cancer is the fourth leading cause of cancer death in the United States and has the highest fatality rate worldwide.51 The overwhelming majority of patients with pancreatic adenocarcinoma have locally advanced and/or metastatic disease at the time of presentation, thereby precluding any prospect of complete tumor extirpation.119-121 Complete tumor resection for pancreatic adenocarcinoma is the only chance for long-term survival.122-126 Patients who undergo pancreatic resection for pancreatic adenocarcinoma portend a 5-year survival rate of up to 20%.127,128 Treatment with chemotherapy, including gemcitabine and FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin), results in a median OS of 6.8 months and 11.1 months, respectively, for patients with unresectable pancreatic cancer.129

Unlike with other GI malignancies, mAb therapy has shown little efficacy for the treatment of pancreatic cancer. In separate phase III trials, cetuximab or bevacizumab in combination with gemcitabine did not significantly improve the response rate, PFS, or OS when compared with gemcitabine alone.130,131 Ipilimumab is currently being investigated for patients with pancreatic adenocarcinoma. In a study of 27 patients, delayed tumor regression was observed in 1 patient treated with ipilimumab.132 Treatment with the agonist CD40 mAb, a novel therapy that activates antigen-presenting cells, in combination with gemcitabine therapy led to partial responses in 4 of 21 patients.135

Whole-cell vaccine-based therapies have been explored for the treatment of pancreatic cancer in resected patients. Antimesothelin immunity has been measured in patients with pancreatic cancer.31 Vaccination with GM-CSF–secreting tumor cells led to the induction of mesothelin-specific T-cell responses, which correlated with disease-free survival.134,135 Algenpantucel-L is an irradiated allogeneic human pancreatic cancer cell line that expresses the murine enzyme α-1,3 galactosyl transferase to induce a hyperacute immunologic response. This study was based on impressive phase II data in which survival at 12 and 24 months was improved to 91% and 54%, respectively, when compared with expected survival of 63% and 32%, respectively.136 A phase III trial examining combination therapy with gemcitabine, 5-FU–radiation, and algenpantucel-L after resection of pancreatic adenocarcinoma is currently ongoing.

Several DC-based vaccine trials for pancreatic cancer have been performed. In patients with locally advanced and metastatic melanoma, intratumoral injection of DCs in combination with an adenovector containing the gene for tumor necrosis factor-α and radiation has led to tumor regression in 2 patients, which correlated with immune reactivity and enhanced T-cell infiltration into tumors.137 In patients with resected pancreatic cancer, a phase I clinical trial examining mucin-1 (MUC1) peptide-pulsed DCs led to long-term survival in 4 of 12 patients.28,29

Little has been done with adoptive cell therapy for the treatment of pancreatic cancer.138 Peripheral blood mononuclear cells from patients with pancreatic cancer were stimulated in vitro with MUC1-expressing tumor cell lines to generate cytotoxic T lymphocytes. Transfer of these T cells led to enhanced survival in resected patients compared with historic controls re-
The potential for the use of immunotherapy for pancreatic cancer. Vaccine-based immunotherapies using whole tumor cells or dendritic cells have been shown to enhance antitumor cell responses and improve responses in patients with advanced pancreatic cancer. This is an exciting time for immunotherapy in GI cancers. Additional novel and exciting immuno-stimulatory mAb therapies are under investigation for GI malignancies. We believe that early successes will lead to the optimization of vaccination approaches and the determination of the most effective vaccination strategy and most beneficial tumor-associated antigens for the treatment of resected or advanced GI cancers. Development of adoptive cell therapies for GI cancers is underway and may provide a promising new therapeutic modality in the future. As our understanding of suppressive factors in patients with GI cancers increases, new strategies to decrease immune suppression and enhance endogenous immunity in patients with GI cancers are being developed. Together, we believe that advances in immunology, increased knowledge of the tumor microenvironment, and prior successes will drive clinicians and researchers alike to achieve practical and effective immunotherapeutic strategies.

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complete tumor extirpation improves survival benefit despite larger tumors


