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The Rationale and Emerging Use of Neoadjuvant Immune Checkpoint Blockade in Solid Malignancies

Emily Z. Keung, Esosa U. Ukpomwan, Alex Cogdill, and Jennifer A. Wargo*

Departments of Surgical Oncology and Genomic Medicine, The University of Texas MD Anderson Cancer, Center Houston, Texas

Abstract

There have been unprecedented advances in the treatment of cancer through the use of immunotherapy, with several agents now FDA-approved for use in widespread metastatic disease across cancer types. Immune checkpoint blockade represents a particularly promising class of agents that block inhibitory molecules on the surface of T cells - resulting in their activation and propagation of an immune response. Treatment with these agents may reinvigorate anti-tumor immunity resulting in therapeutic responses, and use of these agents is now being studied in the adjuvant setting. Additionally, there is a strong rationale for their use in the neoadjuvant setting for high-risk resectable disease (such as in the setting of regional nodal disease in the case of melanoma). This is based on the relatively high risk of relapse in these patients, as well as scientific evidence suggesting that long-term immunologic memory and tumor control may be superior in the setting of treatment with an intact tumor (i.e. neoadjuvant therapy) as opposed to treatment in the setting of micrometastatic disease (as in the setting of adjuvant treatment). Potential advantages of this approach as well as the current landscape for neoadjuvant immune checkpoint blockade will be discussed herein, as will caveats that should be considered in contemplating this strategy.

The Current Landscape of Immune Checkpoint Blockade for Cancer

Cancer care has been revolutionized through the use of immunotherapy. The generation of an effective immune response against cancer is dependent on recognition of tumor antigens on a cancer cell by a cytotoxic T cell. This interaction occurs via the T cell receptor and tumor antigen presented in the context of the major histocompatibility complex (MHC), and is also dependent on a secondary immune-stimulatory signal provided by an antigen presenting cell (Figure 1).^{1–14} However, immune “checkpoints” exist that normally serve to down-regulate an effective immune response may also be upregulated in pathogenic conditions such as cancer. Therapeutic targeting of these immune checkpoints in patients with cancer has demonstrated significant success over the past decade.

*Corresponding author: T. Boone Pickens Academic Tower (FCT17.6054), 1515 Holcombe Blvd, Unit 1484, Houston, TX 77030, Telephone: 713-745-1553.

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Immune Checkpoint Blockade in the Setting of Advanced/Metastatic Disease

The first of the immune checkpoint inhibitors to be studied in clinical trials involved monoclonal blocking antibodies targeting the cytotoxic T lymphocyte-associated antigen 4 (CTLA4) on the surface of T cells (Figure 1).^{1–14} CTLA-4 is expressed on activated T lymphocytes and functions physiologically to down-regulate an effective immune response by competing with the immunostimulatory molecule CD28 for their ligand (CD80/86) on antigen-presenting cells (APCs)—typically in lymphoid tissues. Thus, by blocking the interaction of this inhibitory molecule, T lymphocytes in the peripheral compartment may be stimulated to help mediate an anti-tumor immune response. This was first studied in patients with metastatic melanoma with data reported by Hodi et al in 2010¹⁵ demonstrating that treatment with ipilimumab, an anti-CTLA-4 antibody, was associated with durable responses in 15–20% of treated patients – substantiating the FDA approval of this agent in 2011. However the clinical efficacy of these agents as monotherapy was limited in other cancer types such as non-small cell lung carcinoma (NSCLC), renal cell carcinoma (RCC), and small cell lung carcinoma in multiple phase I/II studies.¹⁶ Nonetheless, additional agents targeting this axis, such as tremelimumab, are being tested alone or in combination with other strategies across multiple cancer types.¹⁶

Another immune checkpoint that has been successfully targeted in the treatment of cancer is the programmed death receptor-1, or PD-1.^{17–32} PD-1 is another checkpoint receptor which is induced by pro-inflammatory cytokines and binds PD-L1, its ligand that is expressed by a large variety of lymphoid and non-lymphoid cells and organs. Although CTLA-4 and PD-1 prevent excessive T-cell responses with CTLA-4 restricting the priming of CD4+ T cells in lymphatic tissues and PD-1 restricting the action of CD8+ cytotoxic T-cells in the periphery in their normal functions, tumors have developed various mechanisms to evade anti-tumor immune responses of T-cells including exploiting the inhibitory PD-1/PD-L1 axis through PD-L1 expression to inactivate effector T-cells and induce immune tolerance.

Since the elucidation of how T cell immune responses are controlled through these “on and off switches,” unprecedented strides have been made in the treatment of advanced and metastatic solid malignancies with immune checkpoint inhibitors with numerous FDA approvals (Figure 2).^{33–35}

Immune Checkpoint Blockade in the Adjuvant Setting (Melanoma)

With the successful use of these agents in the setting of treatment with stage IV cancer, these treatment modalities are now being studied in the adjuvant setting. The first of the immune checkpoint inhibitors to be tested in the adjuvant setting was ipilimumab – which was investigated in a double-blind, phase 3 trial (EORTC 18071) in which 951 patients with stage III cutaneous melanoma (excluding lymph node metastasis <1 mm or in-transit metastasis) following adequate resection of lymph nodes and who had not received previous systemic therapy for melanoma were assigned to ipilimumab versus placebo.³⁶ Patients with completely resected high-risk stage III melanoma who received adjuvant ipilimumab experienced significantly improved recurrence-free survival (RFS, median 26.1 vs 17.1 months, $p=0.0013$) at a median follow-up of 2.74 years. Based on these data, ipilimumab was approved for use in the adjuvant setting for treatment of melanoma involving regional

lymph nodes (>1 mm involvement) following complete resection including lymphadenectomy (at 10 mg/kg every 3 weeks for 4 doses followed by 10 mg/kg every 12 weeks for up to 3 years).

The role of anti-PD-1 therapy in the adjuvant setting is also being investigated. Single agent nivolumab was compared to ipilimumab in the adjuvant setting among patients who underwent complete resection of stage IIIB/C or IV melanoma in CheckMate-238 (NCT02388906).³⁷ Patient who received nivolumab had improved RFS (70.5% vs 60.8%, HR 0.65, 97.56% CI 0.51–0.83, $P<0.001$), lower rates of grade 3/4 adverse events (14.4% vs 45.9%), and higher rates of completing 1 year of adjuvant therapy (60.8% vs 26.9%). KEYNOTE-054 (NCT02362594) and U.S. Intergroup Trial S1404 are two trials compare adjuvant pembrolizumab to placebo in the former or to either standard adjuvant therapy with high dose IFN or high dose ipilimumab in the latter.

Rationale for Neoadjuvant Immune Checkpoint Blockade

With the rapid progress made in cancer immunotherapy in the metastatic and high-risk adjuvant setting, there has also been increasing interest in applying immune checkpoint blockade in the neoadjuvant setting for earlier stage malignancies. With conventional chemo(radio)therapy, the neoadjuvant approach has been considered for patients with locally advanced disease for whom upfront surgery may not be feasible, with the goal of down-staging disease to allow definite resection and improving local disease control. The neoadjuvant approach towards conventional chemo(radio)therapy has also been shown to improve survival and/or improve surgical outcomes in patients with bladder,³⁸ breast,^{39–43} laryngeal,⁴⁴ esophageal cancers^{45–49} and rectal cancers.^{50,51} Additionally, efficacy of treatment can be evaluated preoperatively by monitoring tumor response and postoperatively by pathologic evaluation of the resected tumor tissue. This allows a more tailored treatment as therapy can be modified or changed in patients who did not respond to the neoadjuvant therapy.

The success of immune checkpoint therapy in advanced, unresectable malignancies and in the adjuvant setting in patients with advanced high-risk stage III resected melanoma, as well as the precedent of neoadjuvant approach towards conventional chemotherapy, have led to significant interest in exploring the potential role of neoadjuvant immune checkpoint blockade in a variety of malignancies (Table 1). Although there is currently limited clinical data to support the use of immune checkpoint blockade in the neoadjuvant setting, there are well over 60 ongoing studies exploring this strategy in several tumor types, including melanoma, NSCLC, bladder cancer, RCC, ovarian cancer, prostate cancer, gastroesophageal cancer, colorectal cancer, mesothelioma, pancreatic cancer, breast cancer, and glioblastoma (Clinicaltrials.gov).

In the preclinical space, there are studies to suggest that neoadjuvant immune checkpoint blockade may not only facilitate surgical resectability of high-risk or borderline resectable lesions but also improve recurrence and survival outcomes compared to immune checkpoint blockade administered in the adjuvant setting.^{52–54} In a recent study, Liu and colleagues asked the highly relevant question using preclinical models of breast cancer: Should

immunotherapy be instituted before or after surgery?⁵⁴ Using two transplantable models of breast cancer that spontaneously metastasize to the lungs, the authors tested three immunomodulatory monoclonal antibodies (mAbs) (anti-CD25 mAbs or other experimental strategies to deplete regulatory T cells, anti-PD-1 mAbs to block checkpoint activity, anti-CD137 to costimulate T cells) for their effect on overall survival when administered in the neoadjuvant versus adjuvant settings. Although anti-PD-1 plus anti-CD137 mAbs combination was the most effective treatment, survival benefit was better with all treatments when administered prior to surgery. The authors demonstrate that neoadjuvant regimens engender more robust anti-tumor CD8+ T-cell responses compared to adjuvant regimens, which are required for therapeutic efficacy in these models.

Mechanistically, a neoadjuvant approach towards immune checkpoint blockade would seem to be favorable.⁵² Prior to surgery, tumor-infiltrating lymphocytes, the majority of cells expressing targets for immune checkpoint inhibitors, are present in the presence of abundant tumor antigen available for cross-priming at the time of immunotherapy. Additionally, recirculation of T lymphocytes from the primary tumor infiltrate may address microscopic metastatic disease. These provocative preclinical studies clearly support the currently ongoing and future planned clinical trials to investigate and compare adjuvant, neoadjuvant, and combined neoadjuvant plus adjuvant immunotherapy regimens.

Current Approaches Using Neoadjuvant Immune Checkpoint Blockade

Clinical Trials of Neoadjuvant Immune Checkpoint Blockade in Melanoma⁵⁵

There is significant interest in examining the role of immune checkpoint blockade in the neoadjuvant setting in patients with resectable stage III and oligometastatic stage IV melanoma. Investigators hypothesize that neoadjuvant immune checkpoint blockade may facilitate ease of surgical resection and possibly convert patients with borderline resectable stage III/IV disease to resectable disease by the time of surgery. Additionally, there is interest in evaluating the impact of neoadjuvant checkpoint blockade on RFS and overall survival (OS) in these patients.

There are presently three phase 2 clinical trials currently accruing which evaluate either anti-PD-1 antibody alone or in combination with anti-CTLA-4 antibody in the neoadjuvant setting for patients with stage III/IV melanoma (Table 1). OpACIN-neo (NCT02977052) is an open-label, three-arm phase 2 trial which evaluates 90 stage III melanoma patients randomized 1:1:1 to receive either 1) 2 courses of ipilimumab 3 mg/kg + nivolumab 1 mg/kg every 3 weeks, 2) 2 courses of ipilimumab 1 mg/kg + nivolumab 3 mg/kg every 3 weeks, or 3) 2 courses of ipilimumab 3 mg/kg, directly followed by 2 courses of nivolumab 3 mg/kg every 2 weeks. All three treatment arms then undergo surgery. Primary outcomes measures include response rate by RECIST1.1, safety, and pathologic response. Secondary outcomes measures include RFS, late adverse events, and correlatives.

NCT02519322 is a phase 2 study accruing patients with high-risk resectable stage III and oligometastatic stage IV melanoma to receive either nivolumab alone (3 mg/kg every 2 weeks) or in combination with ipilimumab (nivolumab 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks) prior to surgery. Adjuvant nivolumab (3 mg/kg every 2 months) will be

administered postoperatively for 6 months. Primary outcome measure is pathologic response by evaluation of resected melanoma specimen. Secondary outcome measure is immunologic response to therapy as determined by change in T cell infiltrate from baseline to on-treatment and surgical specimens.

NeoPembroMel (NCT02306850) is a phase 2 study that differs from the former two trials in that it is enrolling patients with unresectable stage III/IV melanoma to determine if treatment with pembrolizumab can convert/shrink unresectable disease to resectable tumors. Primary outcome is resectability rate, defined as the proportion of patients in the trial that were unresectable at baseline who become eligible for curative resection with complete metastectomy after treatment with pembrolizumab (200 mg every 3 weeks for at least 24 weeks and up to 2 years).

There are 2 additional trials of neoadjuvant combination therapy with pembrolizumab and high dose IFN- α 2b (NCT02339324) and with ipilimumab and high dose IFN- α 2b (NCT01608594) which are not recruiting participants but are ongoing. Patients will receive adjuvant IFN- α 2b after recovery from surgery every other day three times weekly for 46 additional weeks. Primary outcome measure of these two phase 1 trials is safety of these combination with secondary outcome of pathologic and radiologic response rate, progression-free survival, and OS.

Clinical Trials of Neoadjuvant Immune Checkpoint Blockade in Other Solid Malignancies

As in melanoma, there is much excitement regarding the potential use of immune checkpoint blockade in the neoadjuvant setting across solid tumor types, including NSCLC, head/neck squamous cell carcinoma (HNSCC), urothelial carcinoma and RCC, breast cancer, gastroesophageal cancer, colorectal cancer, pancreatic adenocarcinoma, and soft tissue sarcoma, with over 60 ongoing clinical trials (Table 1). These are predominantly phase 1 or 2 studies investigating the safety and feasibility of preoperative administration of anti-CTLA-4 and/or anti-PD-1 antibody therapies either as single agents or in combination, with patients receiving additional adjuvant immune checkpoint therapy postoperatively in some studies. Additionally, some phase 2 studies of certain disease sites (NSCLC, breast, gastroesophageal, and pancreatic) aim to evaluate the safety and feasibility of combining neoadjuvant immune checkpoint blockade with conventional chemo(radio)therapies and endocrine therapies. NCT02812524 is a phase 1 study testing the feasibility of intratumor ipilimumab injections prior to surgical resection in patients with HNSCC. Outcome measures of interest in these studies include clinical objective response rate, pathologic response, efficacy of neoadjuvant immune checkpoint blockade with respect to facilitating surgical resection as well as impact on RFS, distant RFS, and OS.

There is currently one phase 3 study recruiting 766 patients with non-metastatic stage II or greater RCC, randomized either to surgical resection followed by observation or neoadjuvant nivolumab (q2wks x 2 doses) followed by resection and adjuvant nivolumab (q2wks for 6 doses followed by qmonth x 6 doses) (PROSPER RCC, NCT03055013). Primary outcome measure is RFS and secondary outcomes measures include OS and incidence of adverse events.

Caveats and Future Directions

Despite the tremendous success of immune checkpoint blockade in advanced malignancies and the marked excitement in the expanding role of these novel therapies in earlier stage disease and in the neoadjuvant setting, a number of questions remains where data are currently lacking. First, there is concern that pursuing a neoadjuvant approach to immune checkpoint therapy may result in patients losing the opportunity for surgical resection (becoming unresectable with disease progression in nonresponders). Thus, current and future research investigating predictors of response and resistance to immune checkpoint blockade is of utmost importance and relevance.⁵⁶ This is also of importance as immunotherapies are not benign and are associated with immune related adverse drug reactions, including colitis, hepatitis, pneumonitis, and endocrinopathies.⁵⁷ Second, although the main outcomes of many studies of neoadjuvant immune checkpoint blockade are response rate and pathologic response rate, it remains to be seen whether response rate will truly predict long-term survival benefit conferred by immune check-point inhibitors when administered in the neoadjuvant setting.

This is an exciting time in clinical oncology as we are embarking upon an era of novel immunotherapies, including immune checkpoint blockade. While the PD-1/PD-L1 axis and CTLA-4 govern the most prominent immune pathways targeted at present, antibodies targeting other inhibitor receptors (such as LAG-3) and activating immune receptors (such as CD27 and OX40) are being developed and investigated in preclinical and clinical studies. The potential of these new therapies in the neoadjuvant setting are unknown. As we begin to elucidate the role of immune checkpoint blockade in earlier stage malignancies and in the neoadjuvant setting, another set of as yet unanswered questions is the interplay between immunotherapy and current standard treatment regimens (radiation, conventional chemotherapy) and whether neoadjuvant immunotherapy in combination with these may provide synergistic benefit.

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Synopsis

Immunotherapy has led to unprecedented improvement in the treatment and prognosis of high-risk resectable and metastatic disease across cancer types. There is great interest in applying immune checkpoint blockade in the neoadjuvant setting for earlier stage malignancies.

Figure 1. Currently approved immune checkpoint inhibitors target immunoinhibitory interactions between T cells, antigen-presenting cells, and tumor cells

Immune activation is opposed by upregulation of immunoinhibitory molecules (such as CTLA-4 and PD-1) on T cells or their ligands (such as PD-L1) which may be subverted by tumor cells to facilitate immune escape. Currently approved immune checkpoint inhibitors target CTLA-4, PD-1, and PD-L1.

Figure 2a

Figure 2b

Figure 2c

Figure 2.

Timeline of FDA approvals of immune checkpoint blockade in (a) melanoma, (b) non-small cell lung cancer, and (c) other tumor types

Figure 3a

Pretreatment

On treatment

Figure 3b

Pretreatment

On treatment

Figure 3.

Representative radiographic images of (a) a patient who achieved complete response to combination ipilimumab/nivolumab and (b) a patient who progressed on pembrolizumab

Figure 4.
Study schema of phase 2 clinical trial of neoadjuvant immune checkpoint blockade for patients with high-risk resectable metastatic melanoma (NCT02519322)

Table 1

Representative ongoing neoadjuvant trials using immune checkpoint inhibitors in solid tumor types

ClinicalTrials.gov Identifier	Study Name	Phase of Clinical Trial	Trial Status (estimated accrual)	Stated Trial Purpose
Melanoma				
NCT02977052	Optimal neo-adjuvant combination scheme of ipilimumab and nivolumab (OpACIN-neo)	2	Recruiting (90)	Open-label 3-arm trial of stage III melanoma patients randomized 1:1:1 to receive either 2 courses 3 mg/kg ipilimumab + 1 mg/kg nivolumab Q3W (Arm A), 2 courses 1 mg/kg ipilimumab + 3 g/kg nivolumab Q3W (Arm B), or 2 courses ipilimumab 3 mg/kg, directly followed by 2 courses nivolumab 3 mg/kg Q2W (Arm C). All treatment arms are applied prior to surgery at week 6.
NCT02519322	Neoadjuvant and adjuvant checkpoint blockade in patients with clinical stage III or oligometastatic stage IV melanoma	2	Recruiting (40)	The goal of this clinical research study is to learn if giving nivolumab alone or in combination with ipilimumab before and after surgery can help to control metastatic melanoma.
NCT02306850	Neoadjuvant pembrolizumab for unresectable stage III and unresectable stage IV melanoma (NeoPembroMel)	2	Recruiting (15)	This study is being done to see if using the study drug, pembrolizumab, can shrink down melanoma tumors enough so that they will be small enough to cut out, so that there will be no cancer left in the body. Eligible participants include those who have not received any systemic melanoma therapies and those who have failed all available systemic options.
NSCLC				
NCT02259621	Neoadjuvant nivolumab, or nivolumab in combination with ipilimumab, in resectable NSCLC (NA_00092076)	2	Recruiting (30)	The proposed study will evaluate the safety and feasibility of preoperative administration nivolumab +/- ipilimumab in patients with high-risk resectable NSCLC, and will facilitate a comprehensive exploratory characterization of the tumor immune milieu and circulating immune cells and soluble factors in these patients.
NCT02818920	Neoadjuvant pembrolizumab (TOP1501)	2	Recruiting (32)	This multi-institutional clinical trial is studying two doses of pembrolizumab administered prior to surgery and 4 doses administered after surgery for stage IB, II or IIIA NSCLC.
NCT02572843	Anti-PD-L1 in stage IIIa(N2) NSCLC	2	Recruiting (68)	The objective of the trial is to demonstrate that the addition

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				of neoadjuvant and adjuvant immunotherapy (with the anti-PD-L1 antibody MEDI4736) to standard neoadjuvant chemotherapy (with cisplatin/docetaxel) in primary resectable stage IIIA(N2) NSCLC is efficacious and feasible.
NCT03081689	Neoadjuvant immunotherapy with nivolumab for NSCLC patients	2	Recruiting (46)	Single-arm, open-label multicenter study that assesses feasibility, safety and efficacy of combined neoadjuvant chemotherapy and immunotherapy with nivolumab 360 mg IV Q3W + paclitaxel 200 mg/m ² + carboplatin AUC 6 IV Q3W in resectable stage IIIA N2-NSCLC adult patients followed by adjuvant treatment for 1 year with nivolumab 240 mg IV Q2W for 4 months and nivolumab 480 mg Q4W for 8 months.
NCT02716038	Neoadjuvant MPDL3280A, Nab-paclitaxel and carboplatin in NSCLC	2	Recruiting (30)	This is a research study to test the effectiveness of nab-paclitaxel + carboplatin + MPDL3280A for treatment of NSCLC. The study aims to determine if chemotherapy combined with immune-based therapy can lead to improvement in tumor response rates over historical response rates with chemotherapy alone.
NCT02994576	Atezolizumab as induction therapy in non-small cell lung cancer (PRINCEPS)	2	Recruiting (60)	The role of immunotherapeutic approaches for NSCLC in the neoadjuvant setting is currently unknown. Based on the survival efficacy of immunotherapeutic strategies in advanced NSCLC where the tumor has not been removed which could produce higher immunogenicity and based on the efficacy of neoadjuvant treatments in NSCLC, we propose to test the safety and efficacy of atezolizumab as neoadjuvant therapy in subjects diagnosed with stage IB, II, or IIIA (non N2) NSCLC and who are deemed suitable for surgical resection.
NCT03158129	Study of induction checkpoint blockade for untreated stage I-IIIa non-small cell lung cancers amenable for surgical resection	2	Not yet recruiting (66)	The goal of this clinical research study is to compare nivolumab alone to nivolumab plus ipilimumab when given to patients with non-small cell lung cancer (NSCLC) that can be surgically treated. Researchers want to learn how effective both study treatments

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				may be in helping to control NSCLC after surgery.
HNSCC				
NCT02296684	Immunotherapy with MK-3475 in surgically resectable HNSCC	2	Recruiting (46)	The goal of this trial is to test the ability of pembrolizumab to improve locoregional recurrence and distant metastatic rates in high-risk patients with locally advanced HNSCC that are treated with current standard of care surgical approaches.
NCT03129061	Study to evaluate immunological response to PD-1 inhibition in HNSCC	1	Recruiting (24)	This is a single-center cross-sectional imaging and correlative biomarker study in patients with HNSCC. Cohort 1 will be patients with unresectable or metastatic HNSCC receiving standard of care anti-PD-1 treatment and Cohort 2 will be neoadjuvant study participants who will receive one dose of anti-PD-1 treatment prior to tumor resection or radiation.
NCT03003637	ImmunoModulation by the combination of ipilimumab and nivolumab neoadjuvant to surgery in advanced or recurrent HNSCC (IMCISION)	1/2	Not yet recruiting (32)	This trial aims to examine feasibility and safety of neoadjuvant checkpoint blockade to standard of care surgery in advanced stage HNSCC.
NCT02812524	Ipilimumab for head and neck cancer patients	1	Recruiting (18)	This study is for patients with squamous cell carcinoma of the head and neck to test the feasibility of the administration of intratumoral injections of ipilimumab prior to surgical resection, and the immune system response to treatment.
NCT03021993	Trial of nivolumab as a novel neoadjuvant pre-surgical therapy for locally advanced oral cavity cancer	2	Not yet open (19)	The purpose of this study is to look at the effectiveness of nivolumab in patients with oral cavity cancer who are about to undergo surgery.
Urologic malignancies				
NCT03055013	Nivolumab in treating patients with localized kidney cancer undergoing nephrectomy (PROSPER)	3	Recruiting (766)	This randomized trial compares nephrectomy with or without nivolumab in treating patients with localized kidney cancer. It is not yet known whether nivolumab and nephrectomy is more effective than nephrectomy alone in treating patients with kidney cancer.
NCT02736266	Neoadjuvant pembrolizumab for muscle invasive urothelial bladder cancer	2	Recruiting (90)	Patients with T2–T4a N0 urothelial bladder carcinoma with residual disease following transurethral resection will be given pembrolizumab in 3 weekly cycles before cystectomy.

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				Primary end point is pathological clinical response.
NCT02762006	Neoadjuvant MEDI4736 +/- tremelimumab in locally advanced RCC	2	Recruiting (54)	The purpose of this study is to investigate the safety and feasibility of administering investigational drugs (meaning not Food and Drug Administration (FDA)-approved for kidney cancer) prior to surgical treatment for kidney cancer.
NCT02575222	Study of neoadjuvant nivolumab in patients with non-metastatic stage II–IV clear cell renal cell carcinoma	1	Recruiting (30)	This study will evaluate the use of nivolumab before surgery in patients with high-risk clear cell renal cell carcinoma who are eligible for nephrectomy.
NCT02595918	Nivolumab in treating patients with high-risk non-metastatic kidney cancer	1	Recruiting (29)	This is a pilot study of the side effects of nivolumab and how well it works in treating patients with high-risk kidney cancer that has not spread to other places in the body.
NCT02812420	Pre-surgical study evaluating anti-PD-L1 antibody (durvalumab) plus anti-CTLA-4 (tremelimumab) in patients with muscle-invasive, high-risk urothelial carcinoma who are ineligible for cisplatin-based neoadjuvant chemotherapy	1	Recruiting (15)	The goal of this clinical research study is to learn if the combination of durvalumab and tremelimumab is safe and tolerable when given to patients with bladder cancer before surgery to remove the bladder.
NCT02845323	Neoadjuvant nivolumab with and without urelumab in patients with cisplatin-ineligible muscle-invasive urothelial carcinoma of the bladder	2	Not yet open (44)	This study evaluates the post cystectomy CD8+ tumor response of patients receiving nivolumab plus urelumab versus nivolumab alone.
Breast carcinoma				
NCT02957968	Neoadjuvant pembrolizumab + decitabine followed by standard neoadjuvant chemotherapy for locally advanced HER2 negative breast cancer	2	Recruiting (50)	This study is a 2-cohort, open-label, multicenter study of a short course of immunotherapy consisting of sequential decitabine followed by pembrolizumab administered prior to a standard neoadjuvant chemotherapy regimen for patients with locally advanced HER2-negative breast cancer.
NCT02489448	Neoadjuvant MEDI4736 concomitant with weekly Nab-paclitaxel and dose-dense AC for stage I–III triple negative breast cancer	1/2	Recruiting (64)	The purpose of the study is to address the following hypotheses: (i) Anti-PD-L1 therapy with MEDI4736 administered concomitantly with weekly nab-paclitaxel followed by MEDI4736 concomitant with ddAC neoadjuvant chemotherapy will induce higher pathologic complete response (pCR) rate (>55%) in triple negative breast cancer than historical pCR rates (30–40%) observed with chemotherapy alone. (ii) MEDI4736 can be safely co-

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				administered at full dose with sequential with nab-paclitaxel (100 mg/m ²) and ddAC (60 mg/m ² and 600 mg/m ² respectively).
NCT02999477	A study of changes in PD-L1 expression during preoperative treatment with Nab-Paclitaxel and pembrolizumab in hormone receptor-positive breast cancer	2	Recruiting (50)	This research study is exploring chemotherapy in combination with immunotherapy (pembrolizumab and Nab-paclitaxel) as a possible treatment for hormone receptor positive breast cancer.
NCT02997995	Durvalumab and endocrine therapy in ER+/Her2-breast cancer after CD8+ infiltration effective immune-attractant exposure (ULTIMATE)	2	Recruiting (240)	This is an open-label, multicentric, international trial testing aromatase inhibitors in combination with durvalumab in patients with CD8+ T cell infiltration (>10% CD8+ T cells in the tumor). The trial includes two sequences: The first part of the treatment will consist in 4–6 weeks treatment with immune-attractants; in the second part, CD8+ patients will receive 6 months of durvalumab combined with exemestane.
NCT02833233	A study of preoperative treatment with cryoablation and immune therapy in early stage breast cancer	1	Recruiting (6)	This study is being done to evaluate the safety of combining two strategies called "cryoablation" and "immune therapy" in women with curable early stage breast cancer.
Gastro-esophageal cancers				
NCT02735239	Study of anti-PD-L1 in combination with chemo(radio)therapy for esophageal cancer	1/2	Recruiting (75)	This is an open-label study to evaluate the safety of durvalumab (MED14736) in combination with oxaliplatin/capecitabine chemotherapy in metastatic/locally advanced oesophageal cancer (OC) and with neoadjuvant chemo(radio)therapy before surgery in operable OC. Immunotherapy will be given for a 4-week period before starting the standard chemo(radio)therapy, continuing durvalumab treatment once the chemotherapy starts.
NCT02918162	Perioperative chemo and pembrolizumab in gastric cancer	2	Recruiting (40)	To determine and evaluate the efficacy of combination therapy with immune checkpoint blockade and chemotherapy used in the perioperative period in eradicating micrometastatic disease. To compare paired tissue and serum samples (pre-treatment and post-treatment) from individually

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				treated patients to explore the immune effects of combination therapy and predictors of response.
NCT03044613	Nivolumab or nivolumab/ipilimumab prior to chemoradiation plus nivolumab with II/III gastro/esophageal cancer	1	Not yet open (32)	Anti-PD-1 (nivolumab) or anti-PD-1/CTLA-4 (ipilimumab) administration in the pre-operative setting and nivolumab combined with chemoradiation will be safe and feasible in patients with resectable distal esophageal/gastroesophageal junction cancer and will change cellular and molecular characteristics of the tumor microenvironment that will improve survival.
Pancreatic cancer				
NCT02305186	Safety and immunological effect of pembrolizumab in resectable or borderline resectable pancreatic cancer (UVA-PC-PD101)	1/2	Recruiting (56)	The purpose of this clinical trial is to study pembrolizumab for use in combination with chemotherapy and radiation therapy for patients with resectable or borderline resectable pancreatic cancer.
NCT02930902	Preoperative pilot study to assess safety and immunological effect of pembrolizumab in combination with paricalcitol with or without chemotherapy in patients with resectable pancreatic cancer	1	Recruiting (30)	The goal of this clinical research is to learn about the safety and tolerability of pembrolizumab in combination with paricalcitol, with or without standard chemotherapy in patients who have resectable pancreatic cancer.
NCT03153410	Pilot study with CY, pembrolizumab, GVAX and IMC-CS4 (LY3022855) in patients with borderline resectable adenocarcinoma of the pancreas	1	Not yet recruiting (12)	This study will be looking at whether combining cyclophosphamide, pembrolizumab, GVAX (pancreatic cancer vaccine), and IMC-CS4 (LY3022855) (an antibody that blocks a molecule called CSF1-R which prevents the body's ability to fight cancer) is effective and safe in patients with borderline resectable pancreatic cancer.
Colorectal cancer				
NCT02754856	Tremelimumab (anti-CTLA-4) plus MEDI4736 (anti-PD-L1) in resectable colorectal liver metastases	1	Recruiting (35)	The goal of this clinical research study is to learn if tremelimumab in combination with MEDI4736 can help to control colorectal cancer that has spread to the liver. The safety of these drugs will also be studied.
NCT03026140	Nivolumab, ipilimumab and Cox2-inhibition in early stage colon cancer: an uniaised approach for signals of sensitivity (NICHE)	2	Recruiting (60)	Patients with stage 1–3 adenocarcinoma of the colon with no signs of distant metastases will be treated with short-term immunotherapy + COX2-inhibitors. This

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				treatment will be given during the window period (~6 weeks) until surgical resection of the tumor.
NCT02948348	Study to nivolumab following preoperative chemoradiotherapy	1/2	Recruiting (50)	This is an open-label, single-arm, multicenter study to investigate the safety, efficacy, and proof of concept of monotherapy with nivolumab as a sequential therapy following chemoradiotherapy with capecitabine and subsequent surgical therapy in patients with locally advanced resectable rectal cancer.
NCT03127007	Safety and efficacy of atezolizumab combined to preoperative radio-chemotherapy in localized rectal cancer (R-IMMUNE)	1/2	Not yet recruiting (54)	This study aims to determine the safety and tolerance of administration at a fixed dosing of 1200 mg/3 weeks, concomitantly to the standard preoperative radio-chemotherapy and to explore efficacy of atezolizumab in combination with the standard preoperative chemo/radiotherapy in stage II and III rectal cancers.
Sarcoma				
NCT03116529	Neoadjuvant durvalumab and tremelimumab plus radiation for high risk soft-tissue sarcoma (NEXIS)	1/2	Not yet recruiting (35)	Chemotherapy is controversial for soft tissue sarcoma that has not yet metastasized. Surgery and radiation are effective for local control, but there are no highly effective interventions to prevent metastatic spread of soft tissue sarcoma. Immunotherapy has shown promise in other types of cancer. Combining two types of immunotherapy agents with preoperative radiation may help the immune system recognize the sarcoma and stimulate an anti-tumor immune response.

HNSCC: head and neck squamous cell carcinoma

NSCLC: non-small cell lung cancer

RCC: renal cell carcinoma