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Review

Clinical Cancer Research

The Promise of Neoadjuvant Immunotherapy and Surgery for Cancer Treatment

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Abstract

Cancer immunotherapies utilizing immune checkpoint inhibitors (ICI) have demonstrated durable efficacy in a proportion of patients with advanced/metastatic cancers. More recently, the use of ICIs for the adjuvant treatment of patients with surgically resectable melanoma has also demonstrated efficacy by improving relapse-free survival and in the case of ipilimumab (anti–CTLA-4) also improving overall survival. Although promising, the effective scheduling of surgery and immunotherapy and its duration is not well elucidated. Recent preclinical studies suggest that surgery followed by adjuvant therapy might be suboptimal as compared with an approach in which immunotherapy is applied before surgery (neoadjuvant immunotherapy). Encouraging findings from early-phase clinical trials in melanoma, non–small cell lung carcinoma, and glioblastoma support the idea that neoadjuvant immunotherapy might have improved clinical efficacy over an adjuvant application. In this review, we discuss the existing rationale for the use of neoadjuvant immunotherapy, its apparent strengths and weaknesses, and implications for the design of future clinical trials.

Introduction

Cancer immunotherapies using antibodies targeting CTLA-4 and PD-1/PD-L1 relieve tumor-induced immune suppression and induce durable tumor regression (1). When used alone or in combination, these immune checkpoint inhibitors (ICI) have demonstrated remarkable therapeutic efficacy in a proportion of patients with advanced/metastatic cancers such as melanoma, Hodgkin lymphoma, Merkel cell carcinoma, renal cell carcinoma, bladder cancer, microsatellite instability–high tumors, and non–small cell lung carcinoma (NSCLC) among others (1). In an effort to increase the proportion of patients who durably respond to these therapies, focus is now being placed on how immunotherapies can be optimally incorporated with mainstay oncological/medical practices such as cancer surgery, radiotherapy, and chemotherapy. Despite the successes of systemic therapies so far, cancer surgery remains the most effective therapeutic strategy for resectable disease (2). Among patients who undergo complete primary tumor resection at high risk of relapse, adjuvant therapies are often administered with the aim of eliminating microscopic or minimal residual disease and thus preventing relapse (Fig. 1A). Recent studies have demonstrated that the use of adjuvant anti–CTLA-4 or anti–PD-1 after surgery improved recurrence-free survival (RFS) and overall survival (OS) in melanoma patients that were at high risk of relapse (3–5).

In contrast to adjuvant therapy, neoadjuvant (preoperative) therapy (Fig. 1B) using chemotherapy and radiotherapy has demonstrated specific advantages, particularly in breast (6, 7), bladder (8), laryngeal (9), esophageal (10), and rectal cancers (11). This includes allowing one to: (i) determine on-treatment therapeutic response of an individual patient; (ii) to reduce tumor burden prior to surgery; and (iii) to use pathologic response data as a surrogate biomarker for RFS and OS (12, 13). Neoadjuvant approaches using ICI are rare so far. However, in the context of cancer immunotherapy, neoadjuvant treatment may offer an additional advantage; immunotherapies enhance T-cell activation the moment antigen is encountered (14). Exposure to antigen during the period in which the major tumor mass is present may increase the breadth and durability of tumor-specific T-cell responses. Throughout this review, we will discuss the existing preclinical data and emerging clinical findings related to the use of cancer immunotherapy in the neoadjuvant setting and its potential mechanism of action. We will also highlight the potential caveats of neoadjuvant immunotherapy and the questions that remain to be answered using this approach.

Evidence for Why Neoadjuvant May Be More Effective than Adjuvant Immunotherapies

Supporting preclinical studies

Recent preclinical mouse studies have demonstrated that neoadjuvant immunotherapy improved long-term survival and enhanced antitumor immune responses compared with the same therapy administered in the adjuvant setting (15). This was first

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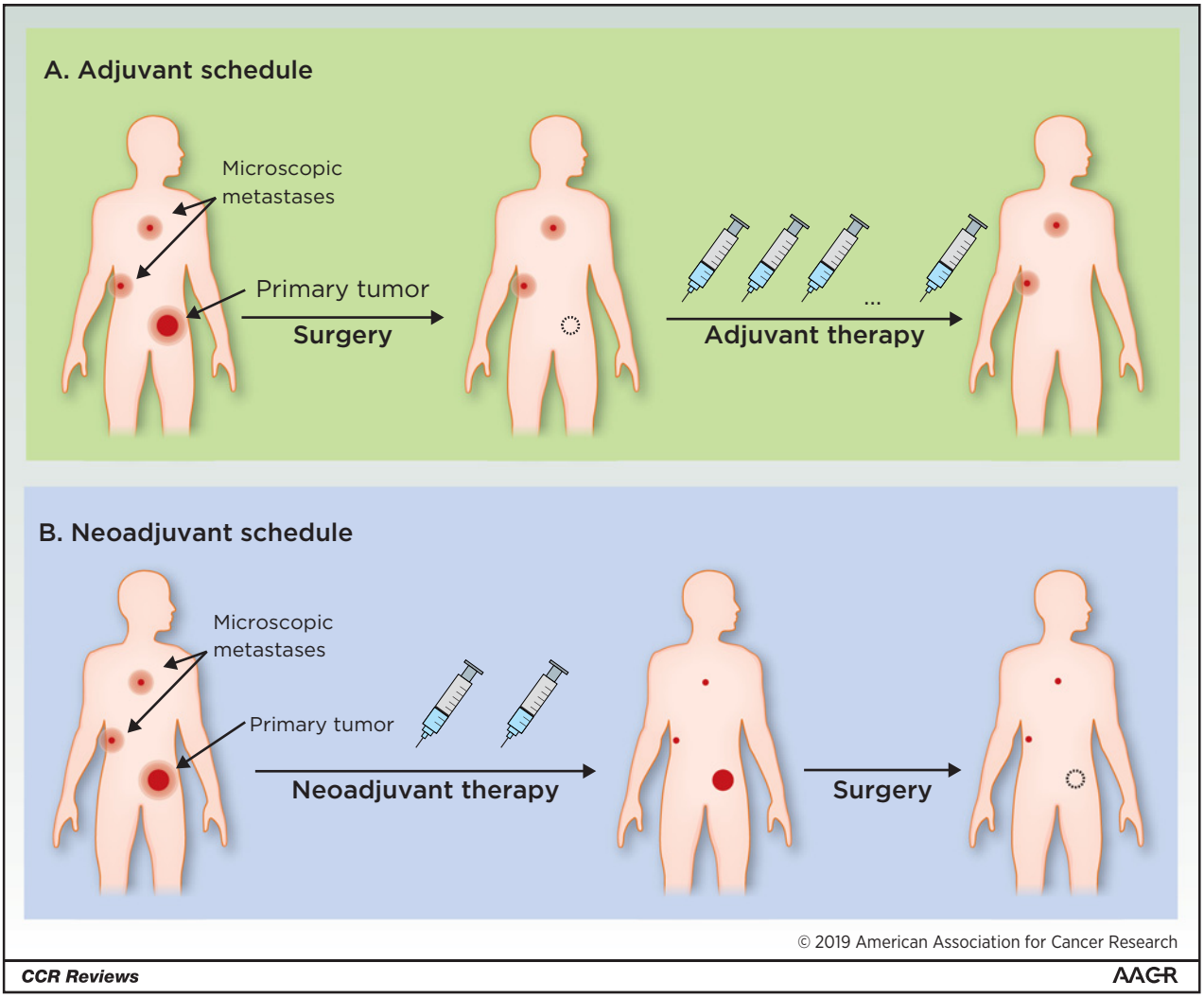

Figure 1.

Neoadjuvant versus adjuvant immunotherapy treatment schedule. **A,** An adjuvant treatment schedule involves identification of a primary tumor, its resection, followed by administration of cancer immunotherapies. This option allows for rapid surgical intervention, and adjuvant therapies are administered with the aim of combatting microscopic metastatic disease. Treatment is often continuous, lasting for years at a time if immune-related adverse events (irAE) are absent or manageable. Dynamic biomarkers are limited in this setting to pretreatment tumor and analysis of blood. **B,** A neoadjuvant treatment schedule involves identification of a primary tumor, followed by administration of cancer immunotherapies. To date, two to three doses have been provided prior to surgery with a time to surgery from treatment of 4 to 9 weeks. Continuous administration of immunotherapy following surgery is an option; however, immune-related toxicities are common. This treatment schedule enables comparisons to be drawn between pre- and on-treatment primary tumor specimens including pathologic response, immune cell infiltration, and T-cell profiling, which can be used to identify tumor-specific T cells within the periphery following treatment.

shown using two mouse models of spontaneously metastatic triple-negative breast cancer (TNBC) in which various combination immunotherapies were administered in either a neoadjuvant or adjuvant setting before or after primary tumor resection, respectively (15). Regardless of the types of immunotherapy used, including anti-CD25 to deplete regulatory T cells, or anti–PD-1 alone or in combination with agonistic anti-CD137 to activate effector T and natural killer (NK) cells, neoadjuvant treatment was superior to adjuvant treatment in the eradication of lethal micrometastases, resulting in cures in a significant proportion of treated mice (15). Subsequently, other groups have tested the efficacy of other neoadjuvant immunotherapy combinations in different preclinical mouse models. In mouse models of TNBC, one study demonstrated that the combination of neoadjuvant poly(I:C) (to stimulate type I IFN) and anti–PD-1 prolonged survival (16), whereas in another study, neoadjuvant oncolytic virotherapy before surgery sensitized TNBC to immune checkpoint therapy resulting in cures in a proportion of treated mice (17). In a transgenic mouse model of resectable pancreatic ductal adenocarcinoma, a treatment regime of neoadjuvant combination of anti–PD-1 and gemcitabine followed by adjuvant anti-CD96 and gemcitabine impressively cured a proportion of mice (18). Interestingly, the addition of adjuvant anti-CD96 (an NK- and T-cell checkpoint regulated by interactions with CD155 on tumor and myeloid cells) to the treatment was critical for the generation of long-term survivors as treatment with anti–PD-1 and gemcitabine

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alone only prolonged survival. Although some of the immunotherapies used in these preclinical studies are currently still in the early stage of clinical development, overall these studies illustrate the concept that therapies that target the immune system to relieve tumor-induced immune suppression and/or to activate antitumor immunity may be more effective when given in a neoadjuvant context. In contrast, chemotherapies such as paclitaxel which does not depend on host immunity for its efficacy did not confer improved benefit when given as a neoadjuvant (15). As such, these encouraging preclinical findings provided strong impetus for the clinical assessment of neoadjuvant immunotherapy.

Supporting clinical studies

To date, two small clinical trials have directly compared neoadjuvant and adjuvant ICIs either alone or in combination of melanoma and glioblastoma. In the first clinical trial that performed a head-to-head comparison of adjuvant and neoadjuvant ICIs for the treatment of stage III resectable melanoma, two doses of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) were administered concurrently at 3-week intervals followed by surgery at 6 weeks (NCT02437279). Additional treatments were administered following surgery in both groups; however, treatment-related toxicities were dose-limiting resulting in a median of two doses given (range, 1–4 courses; ref. 13). In these patients, RFS and OS were 80% and 90% respectively for patients treated with neoadjuvant ICI therapy and 60% and 67% respectively for patients treated with adjuvant ICI therapy at a median follow-up time of 32 months (19). Although the melanoma study by Blank and colleagues was not powered to compare clinical outcome parameters after neoadjuvant versus adjuvant therapy, its findings were supported by a similarly high response rates of neoadjuvant ipilimumab plus nivolumab in another melanoma study by Amaria and colleagues where ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) were given every 3 weeks with surgery at week 9 (NCT02519322). The progression-free survival (PFS) and OS for treatment with ipilimumab plus nivolumab were 82% (at 17.2 months) and 100% (at 24.4 months) respectively versus 58% and 76% (both at 22.6 months) respectively for treatment with nivolumab (20). In the second study comparing neoadjuvant and adjuvant immunotherapy, patients with glioblastoma were randomized to receive either neoadjuvant (including follow-up adjuvant) or adjuvant pembrolizumab (21). Patients in the neoadjuvant arm were treated once with pembrolizumab (200 mg) 14±5 days before surgical resection; patients in the adjuvant only arm did not. Both groups received pembrolizumab (200 mg) every 3 weeks following surgery. The neoadjuvant treatment schedule was found to significantly increase median PFS (3.3 months vs. 2.4 months) and median OS (13.7 months vs. 7.5 months). In a second study of glioblastoma, nivolumab (3 mg/kg) 14±3 days before surgery, and continued every 2 weeks following surgery, was found to result in unexpectedly high PFS (4.1 months) and OS (7.3 months; ref. 22).

Clinically, the efficacy of single-arm neoadjuvant immunotherapy in melanoma, NSCLC, and glioblastoma has also been reported. In the Amaria and colleagues' study, anti–PD-1 neoadjuvant monotherapy was also evaluated (20). Melanoma patients were treated with neoadjuvant nivolumab (3 mg/kg) every 2 weeks with surgery at week 8, followed by further adjuvant treatment for 6 months (20). In another neoadjuvant study in melanoma, one course of neoadjuvant pembrolizumab (200 mg) followed by surgery at week 3, followed by adjuvant treatment for a year was reported (63% RFS and 93% at 2 years; ref. 23). Although treatment-related toxicities were clearly reduced by administering only anti–PD-1, this was at a cost of significantly lower response rates [pathologic complete response (pCR) 25% (20) and 30% (23)]. In contrast, pCR differed in two small studies of early-stage NSCLC. In the first, two doses of nivolumab (3 mg/kg) were administered every 2 weeks, with surgery at week 4 resulted in pCR of 45% (73% RFS at 18 months; ref. 24), and in the second study, two doses of atezolizumab (1,200 mg) every 3 weeks, with surgery at week 6, had pCR of 21% (25). Going forward, new trials with larger cohorts of patients will inform on the true response rate. In a study of glioblastoma patients, neoadjuvant nivolumab was given to patients who required salvage surgery to treat relapsed disease or newly diagnosed patients who required surgery (22). Although no obvious clinical benefit was reported for salvage surgery patients, two of the three newly diagnosed patients remain alive 34 and 28 months later. Overall, these studies suggest that neoadjuvant ICI might be more effective than the more traditional adjuvant schedule.

Immune determinants of effective neoadjuvant immunotherapy

The mechanistic basis underpinning the improved efficacy of neoadjuvant over adjuvant immunotherapy in preclinical mouse models, and in the limited published clinical trials, is not fully understood. A widely accepted hypothesis is that the presence of the full tumor mass at the start of immunotherapy allows the induction of a broader and stronger T-cell response (13). Another idea might be that the presence of activated tumor-specific T cells before surgery might prevent metastatic spreading. Preclinical and translational data support the first idea: effective neoadjuvant immunotherapy was associated with rapid expansion of tumor-specific $CD8^+$ T cells in the peripheral blood (Fig. 2; ref. 15). This was first shown in mice, in which the greatest increase in the proportion of peripheral blood tumor-specific $CD8^+$ T cells was associated with long-term survival (15). Recently, this has also been found in humans; $CD8^+$ T-cell clones identified in the primary tumor on treatment expanded in the blood relative to pretreatment levels, associated with improved RFS (13, 20, 24). In addition, in some cases following neoadjuvant immunotherapy, peripheral expansion of T-cell clones not detected in the primary tumor on treatment was also observed (13, 20, 24). This has two possible explanations: (i) that the expanded T-cell clones were already present in the primary tumor, but baseline readouts fell below the limit of detection (13); or (ii) that the proliferative burst observed for immunodominant T-cell clones immediately following treatment promoted epitope spreading by enabling iterative revolutions of the cancer immunity cycle and the generation of new tumor-specific $CD8^+$ T cells (Fig. 2; ref. 26). These explanations are not mutually exclusive. The expansion of subdominant clones appears to be important for the efficacy of cancer immunotherapy. Indeed, these cells are potentially less susceptible to the development of a dysfunctional phenotype than the immunodominant T-cell population, and thus may play an important role in the ongoing antitumor immune response (27). This hypothesis has been born out to some extent with the finding that all melanoma patients who relapsed following neoadjuvant ICI demonstrated inferior expansion of subdominant T-cell clones on therapy (13).

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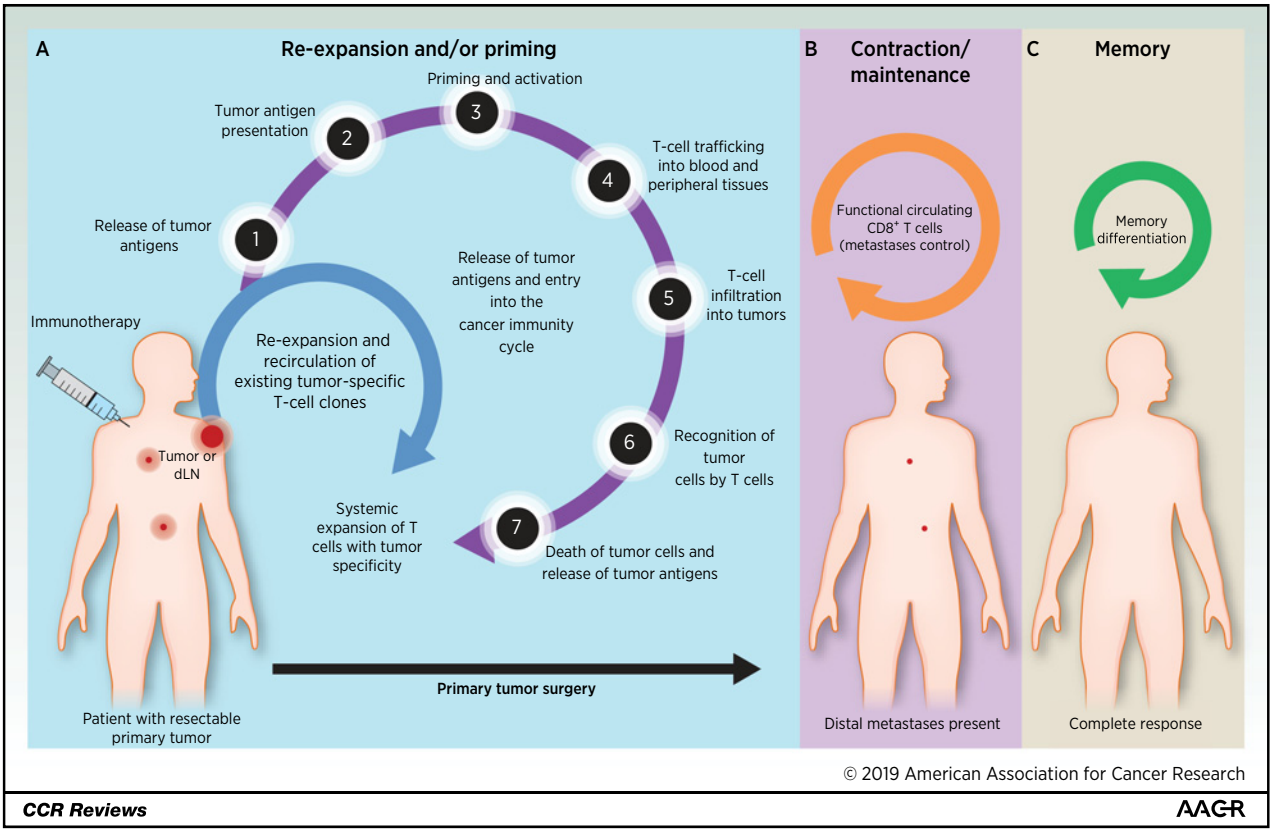

Figure 2.

Neoadjuvant immunotherapy and the tumor-specific T-cell response. **A,** Following administration of cancer immunotherapy, reinvigorated tumor-specific $CD8^+$ T cells can undergo re-expansion. These T cells can kill existing tumor and recirculate into the blood. In addition to this, the existing tumor-specific T-cell response can result in the release of new tumor antigens that are presented by antigen-presenting cells (APC) to prime naïve T cells with tumor specificity against distinct tumor where they circulate in the blood to the tumor/metastatic sites. **B,** Following primary tumor resection, the remaining circulating tumor-specific $CD8^+$ T cells and those present at metastatic sites have an increased T-cell:tumor ratio, which is likely to provide an advantage in the destruction of remaining tumor tissue. **C,** Following clearance of tumor, a stable pool of tumor-specific $CD8^+$ T cells can remain. It is not clear whether these are essential for the maintenance of a complete response; however, they have been observed to remain for life in long-term surviving mice following neoadjuvant immunotherapy.

In mice, we recently found that cross-presenting $Batf3^+$ dendritic cells (DC) in the primary tumor and draining lymph node (dLN) as well as type I IFNs were essential for the systemic expansion of tumor-specific $CD8^+$ T cells following neoadjuvant immunotherapy (28). This was corroborated by the demonstration in human melanomas that a BATF3 gene signature, T-cell inflammatory signature, and a T-cell signature were associated with an improved outcome after neoadjuvant immunotherapy (13, 28). Cross-presenting DCs are essential for the priming and activation of naïve T cells (29) and shown both in preclinical models and clinically to play an important role in the reinvigoration of dysfunctional $CD8^+$ T-cell clones in the tumor following PD-1/PD-L1 blockade (30–32). The efficacy of anti–PD-1 therapy has also been shown to be dependent on CD28 signaling in T cells, initiated by interactions with CD80 and CD86 expressed by antigen-presenting cells (APC; ref. 33). Although speculative, the presentation of antigen to dysfunctional $CD8^+$ T cells by APCs in the tumor and/or dLN might be necessary for their functional reinvigoration, and may enable *de novo* T-cell priming against novel epitopes (33) released by tumor cells killed by preexisting tumor-specific T cells.

It is important to note that preclinically, some peripheral $CD8^+$ T-cell expansion was observed following adjuvant immunotherapy; however, the magnitude of this expansion was considerably smaller than that which occurred following neoadjuvant treatment (15). One explanation is that the primary tumor itself plays a critical role in facilitating tumor-specific T-cell expansion/priming to occur at the time of treatment. The presence or absence of the primary tumor at the time of treatment was the only salient difference between the neoadjuvant and adjuvant schedules, respectively. Also, the primary tumor is likely to be the main source of tumor antigen and to be enriched for T cells with tumor specificity (34). Presumably, the expansion that occurs following treatment might take place at sites of metastases; however, the lack of response observed to this treatment protocol might be due to an inadequate T-cell to tumor antigen ratio (35), the absence of a T-cell response against antigen expressed by tumor cells in metastases, or that metastasis-infiltrating T cells are unable to be reinvigorated by therapy (36). In the two trials that compared neoadjuvant and adjuvant immunotherapies in melanoma (13) and glioma (21), both studies reported an increased expansion of T-cell receptor (TCR) clones in the blood of these patients treated with neoadjuvant compared with adjuvant

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immunotherapy. These two studies provide preliminary evidence that neoadjuvant compared with adjuvant immunotherapy may better expand T cells, although this will need to be confirmed in larger clinical trials.

Timing of surgery and neoadjuvant immunotherapy

Preclinically, the presence of the primary tumor at the time of treatment appears to be important for the efficacy of neoadjuvant immunotherapy (15). However, this effect depends on the timing of tumor resection relative to treatment (37). Preclinical assessment of neoadjuvant immunotherapy in mice involved administration of two doses of antibody therapy followed by surgery, each event separated by 2 days. It has recently been shown that varying this schedule by either delaying or shortening the time to surgery following neoadjuvant treatment dramatically affected OS (37). Specific comparisons drawn between tumor-specific $CD8^+$ T cells from mice receiving a short neoadjuvant treatment schedule (treatments completed 2 days before surgery) and those in which surgery was delayed (treatments completed 8 days before surgery) showed reduced cytokine production and abundance within metastatic sites. This suggests that increasing the duration of exposure to bulk tumor antigen following neoadjuvant treatment may result in reinvigorated T cells to reenter into a dysfunctional state. To date, neoadjuvant ICIs trials have used different schedules (Table 1). Although the studies by Amaria and Huang of neoadjuvant anti–PD-1 in early-stage melanoma gave similar pCR of 25% and 30% respectively, interestingly, the trial in the Amaria and colleagues' study was stopped early on the basis of an early observation of disease progression, preventing surgical resection (20). In contrast, all patients successfully underwent complete resection in the Huang study. The main difference between these studies was the longer duration between treatment courses and surgery.

Translationally, determining the optimal treatment and surgery schedule for neoadjuvant treatment of humans is likely to be challenging. Before determining the optimal duration of treatment and surgery, it will be important to understand at what point T-cell re-expansion and effector function are optimal, and at what point retention of the macroscopic tumor negatively affects these parameters. Experimentally, this is likely to be extremely challenging; however, it was recently shown that measuring antigen-specific T-cell responses in humans over time was possible with systemic deuterium labeling (38). Currently, the International Neoadjuvant Melanoma Consortium (INMC) advises for practical reasons a neoadjuvant timeframe of 6 to 8 weeks (39). This is based on the comparability between individual trials and to prevent deterioration of nonresponders.

T-cell memory

An interesting observation made in mouse models following neoadjuvant immunotherapy has been the persistence of tumor-specific $CD8^+$ T cells in the blood of tumor-free mice at detectable frequency throughout life (Fig. 2; ref. 15). Whether this maintenance of a tumor-specific T-cell population contributes to the efficacy of the antitumor immune response itself or is simply a consequence of an effective response is not clear. However, this is likely to be a positive outcome of effective neoadjuvant immunotherapy, providing life-long protection against tumor reemergence (40). Clinically, a case study reported the ability to identify and track the long-term persistence of mutant oncogene-specific T cells in 2 patients with advanced NSCLC and colorectal carcinoma who derived long-term clinical benefit from PD-1 blockade (41). It will be of interest to see whether this effect is observed among human patients who demonstrate a complete response to neoadjuvant immunotherapy.

Evaluation of neoadjuvant immunotherapies across different cancer types

The recent success of neoadjuvant ICIs in the treatment of early-stage resectable cancers in melanoma, NSCLC, and glioblastoma has led to enthusiasm to evaluate different neoadjuvant ICI treatment strategies across different solid cancer types. An overview on neoadjuvant ICI trials prior to surgery across different tumor types that are active or recruiting is shown in Table 1 (compiled from ClinicalTrials.gov). Most clinical studies (phase I, II, or III) are ongoing in NSCLC, head and neck, and urologic cancers, using different schemes and drug combinations of PD-1, PD-L1, or CTLA-4–blocking antibodies. In addition, various clinical trials are underway in melanoma, breast cancer, ovarian cancer, gastroesophageal cancers, colorectal cancer, hepatocellular carcinoma, pancreatic cancer, and sarcoma, combining different ICIs, and in some cases combining ICI with conventional therapies such as chemotherapy, endocrine therapy, targeted therapy, or radiotherapy. Whether these clinical trials result in long-term, durable prevention of relapse and early readouts like pCR rate, needs to be confirmed to speed up testing different combinations. Moreover, it needs to be established which patients benefit from ICI monotherapies, and under which circumstances combination ICIs are preferable. This is important given the variety of immune-related druggable targets currently being tested (e.g., LAG-3, VISTA, BTLA, TIM-3, OX-40, CD28, CD137, GITR, and TIGIT). The design of neoadjuvant trials (including a streamlined material collection) should be structured to enable comparability across trials. To date, only one such initiative in melanoma, the INMC, exists with this aim.

Although neoadjuvant immunotherapy emerges to be promising, ICI-induced immune-related adverse events (irAE), particularly those used in combinations, might interfere with potentially curative surgery. These irAEs are managed with immune-modulating drugs, such as corticosteroids, and in some cases infliximab or other immunosuppressive therapies (42). In the trials published to date, irAEs induced by neoadjuvant ICIs did not delay the preplanned surgery time point, demonstrating that neoadjuvant therapy is feasible. In the follow-up trial to OpACIN, adjusting the combination scheme (ipilimumab 1 mg/kg plus nivolumab 3 mg/kg) and applying a maximum of two treatment courses reduced the rate of grade 3/4 toxicities to 20% while preserving therapeutic efficacy [77% pathologic response rate (pRR) with 57% pCR rate; ref. 43]. Whether the use of immunosuppressive therapies for the management of irAEs hampers long-term RFS is not known yet. Our own restricted experience argues against this concern (19).

Monitoring Response to Neoadjuvant Immunotherapy

A comprehensive understanding of the efficacy and safety of neoadjuvant therapy is essential to guide treatment. In this regard, having standardized strategies to determine response in patients is of high importance. Clinical evaluation of therapy effectiveness as

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Table 1. Ongoing neoadjuvant ICI trials prior to surgery across different tumor types

ClinicalTrials.gov identifier	Study name	Phase of the clinical trial	Trial status	Estimated enrollment
NSCLC				
NCT03237377	Neoadjuvant Immunoradiation for Resectable Non-Small Cell Lung Cancer	Phase II	Recruiting	32
NCT03197467	Neoadjuvant Anti PD-1 Immunotherapy in Resectable Non-small Cell Lung Cancer (NEOMUN)	Phase II	Recruiting	30
NCT03081689	Neo-Adjuvant Immunotherapy With Nivolumab for Non Small Cell Lung Cancer Patients	Phase II	Active, not recruiting	46
NCT02994576	Atezolizumab as Induction Therapy in Non-small Cell Lung Cancer (PRINCEPS)	Phase II	Recruiting	60
NCT02818920	Neoadjuvant Pembrolizumab (TOP 1501)	Phase II	Recruiting	32
NCT02259621	Neoadjuvant Nivolumab, or Nivolumab in Combination With Ipilimumab, in Resectable NSCLC (NA_00092076)	Phase II	Recruiting	30
NCT02927301	A Study of Atezolizumab as Neoadjuvant and Adjuvant Therapy in Resectable Non-Small Cell Lung Cancer (NSCLC) - Lung Cancer Mutation Consortium (LCMC3)	Phase II	Recruiting	180
NCT02572843	Anti-PD-L1 in Stage IIIA(N2) Non-small Cell Lung Cancer (NSCLC)	Phase II	Recruiting	68
NCT02716038	Neoadjuvant MPDL3280A, Nab-paclitaxel and Carboplatin (MAC) in NSCLC	Phase II	Recruiting	30
NCT03158129	Study Of Induction Checkpoint Blockade For Untreated Stage I-IIIA Non-Small Cell Lung Cancers Amenable For Surgical Resection	Phase II	Recruiting	66
NCT03732664	Neoadjuvant Nivolumab in Resectable Non-Small-Cell Lung Cancer	Phase I	Recruiting	40
Head and neck cancer				
NCT03700905	Study of Nivolumab Alone or in Combination With Ipilimumab as Immunotherapy vs Standard Follow-up in Surgical Resectable HNSCC After Adjuvant Therapy (IMSTAR-HN)	Phase III	Recruiting	276
NCT02296684	Immunotherapy With MK-3475 in Surgically Resectable Head and Neck Squamous Cell Carcinoma	Phase II	Recruiting	66
NCT03021993	Trial of Nivolumab as a Novel Neoadjuvant Pre-Surgical Therapy for Locally Advanced Oral Cavity Cancer	Phase II	Recruiting	19
NCT03247712	Neoadjuvant Immunoradiotherapy in Head & Neck Cancer	Phase I/II	Recruiting	18
NCT03003637	ImmunoModulation by the Combination of Ipilimumab and Nivolumab Neoadjuvant to Surgery In Advanced or Recurrent Head and Neck Carcinoma (IMCISION)	Phase I/II	Recruiting	32
NCT03129061	Study to Evaluate Immunological Response to PD-1 Inhibition in Squamous Cell Carcinoma of the Head and Neck (SCCHN)	Phase I	Recruiting	24
NCT02812524	Ipilimumab for Head and Neck Cancer Patients	Phase I	Recruiting	18
Melanoma				
NCT03639948	Neoadjuvant Combination Targeted and Immunotherapy for Patients With High-Risk Stage III Melanoma (NeoACTIVATE)	Phase II	Recruiting	30
NCT02519322	Nivolumab With or Without Ipilimumab or Relatlimab Before Surgery in Treating Patients With Stage IIIB-IV Melanoma That Can Be Removed by Surgery	Phase II	Recruiting	53
NCT02977052	Optimal Neo-adjuvant Combination Scheme of Ipilimumab and Nivolumab (OpACIN-neo), PRADO extension cohort	Phase II	Recruiting	110
NCT02858921	Neoadjuvant Dabrafenib, Trametinib and/or Pembrolizumab in BRAF Mutant Resectable Stage III Melanoma (NeoTrio)	Phase II	Recruiting	60
NCT02306850	Neoadjuvant Pembrolizumab for Unresectable Stage III and Unresectable Stage IV Melanoma (NeoPembroMel)	Phase II	Recruiting	15
Urologic malignancies				
NCT03055013	Nivolumab in Treating Patients With Localized Kidney Cancer Undergoing Nephrectomy	Phase III	Recruiting	766
NCT03406650	Neoadjuvant and Adjuvant Durvalumab in Combination With Neoadjuvant Chemotherapy in Patients With Operable Urothelial Cancer. (SAKK 06/17)	Phase II	Recruiting	61
NCT02845323	Neoadjuvant Nivolumab With and Without Urelumab in Patients With Cisplatin-Ineligible Muscle-Invasive Urothelial Carcinoma of the Bladder	Phase II	Recruiting	22
NCT03234153	Neoadjuvant Immunotherapy With Durvalumab and Tremelimumab for Bladder Cancer Patients Ineligible for Cisplatin (NITIMIB)	Phase II	Recruiting	68
NCT02736266	Neoadjuvant Pembrolizumab for Muscle-invasive Urothelial Bladder Carcinoma	Phase II	Recruiting	90
NCT03387761	Neo-Adjuvant Bladder Urothelial Carcinoma COmbination-immunotherapy (NABUCCO)	Phase I	Recruiting	24
NCT02812420	Durvalumab and Tremelimumab in Treating Patients With Muscle-Invasive, High-Risk Urothelial Cancer That Cannot Be Treated With Cisplatin-Based Therapy Before Surgery	Phase I	Recruiting	35
NCT02762006	Neoadjuvant MEDI 4736 ± Tremelimumab in Locally Advanced Renal Cell Carcinoma	Phase I	Recruiting	45
NCT02575222	Study of Neoadjuvant Nivolumab in Patients With Non-metastatic Stage II-IV Clear Cell Renal Cell Carcinoma	Phase I	Active, not recruiting	30
NCT02595918	Nivolumab in Treating Patients With High-Risk Non-Metastatic Kidney Cancer	Phase I	Recruiting	29
Breast cancer				
NCT03639948	Neoadjuvant Phase II Study of Pembrolizumab And Carboplatin Plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)	Phase II	Recruiting	100
NCT02957968	Neoadjuvant Pembrolizumab + Decitabine Followed by Std Neoadj Chemo for Locally Advanced HER2- Breast Ca	Phase II	Recruiting	50
NCT02997995	Durvalumab and Endocrine Therapy in ER+/Her2- Breast Cancer After CD8+ Infiltration Effective Immune-Attractant Exposure (ULTIMATE)	Phase II	Recruiting	240
NCT02489448	Neoadjuvant MEDI4736 Concomitant With Weekly Nab-paclitaxel and Dose-dense AC for Stage I-III Triple Negative Breast Cancer	Phase I/II	Recruiting	61
NCT02999477	A Study Of Changes In PD-L1 Expression During Preoperative Treatment With Nab-Paclitaxel And Pembrolizumab In Hormone Receptor-Positive Breast Cancer	Phase I	Recruiting	50
NCT02833233	A Study of Pre-Operative Treatment With Cryoablation and Immune Therapy in Early Stage Breast Cancer	Phase I	Active, not recruiting	5

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Table 1. Ongoing neoadjuvant ICI trials prior to surgery across different tumor types (Cont'd)

ClinicalTrials.gov identifier	Study name	Phase of the clinical trial	Trial status	Estimated enrollment
Ovarian cancer				
NCT03249142	Immunotherapy With Neo-adjuvant Chemotherapy for OVarian Cancer (INeOV)	Phase I/II	Recruiting	66
Gastroesophageal cancers				
NCT03448835	Neoadjuvant Capecitabine, Oxaliplatin, Docetaxel and Atezolizumab in Resectable Gastric and GE-junction Cancer (PANDA)	Phase II	Recruiting	20
NCT02918162	Perioperative Chemo and Pembrolizumab in Gastric Cancer	Phase II	Recruiting	40
NCT02735239	Study of Anti-PD-L1 in Combination With Chemo(Radio)Therapy for Oesophageal Cancer	Phase I/II	Recruiting	75
NCT03044613	Nivolumab ± Relatlimab Prior to Chemoradiation Plus Nivolumab ± Relatlimab With II/III Gastro/Esophageal Cancer	Phase I	Recruiting	32
Colorectal cancer				
NCT03026140	Nivolumab, Ipilimumab and COX2-inhibition in Early Stage Colon Cancer: an Unbiased Approach for Signals of Sensitivity (NICHE)	Phase II	Recruiting	60
NCT02948348	Study to Nivolumab Following Preoperative Chemoradiotherapy	Phase I/II	Recruiting	50
NCT03127007	Safety and Efficacy of Atezolizumab Combined to Preoperative Radio-chemotherapy in Localized Rectal Cancer (R-IMMUNE)	Phase I/II	Recruiting	54
NCT02754856	Tremelimumab (Anti-CTLA-4) Plus Durvalumab (MEDI4736) (Anti-PD-L1) in the Treatment of Resectable Colorectal Cancer Liver Metastases	Phase I	Recruiting	35
Hepatocellular carcinoma				
NCT03299946	Feasibility and Efficacy of Neoadjuvant Cabozantinib Plus Nivolumab (CaboNivo) Followed by Definitive Resection for Patients With Locally Advanced Hepatocellular Carcinoma (HCC)	Phase I	Recruiting	15
Pancreatic cancer				
NCT02305186	Safety and Immunological Effect of Pembrolizumab in Resectable or Borderline Resectable Pancreatic Cancer (UVA-PC-PD101)	Phase I/II	Recruiting	56
NCT02930902	Preoperative Pilot Study to Assess Safety and Immunological Effect of Pembrolizumab (Keytruda) in Combination With Paricalcitol With or Without Chemotherapy in Patients With Resectable Pancreatic Cancer	Phase I	Recruiting	30
NCT03153410	Pilot Study With CY, Pembrolizumab, GVAX, and IMC-CS4 (LY3022855) in Patients With Borderline Resectable Adenocarcinoma of the Pancreas	Phase I	Recruiting	12
Sarcoma				
NCT03116529	Neoadjuvant Durvalumab and Tremelimumab Plus Radiation for High Risk Soft-Tissue Sarcoma (NEXIS)	Phase I/II	Recruiting	35

change in tumor burden is assessed by either radiology following the World Health Organization criteria (44) or RECIST (45, 46). However, in neoadjuvant immunotherapy, assessing tumor response according to conventional response criteria may underestimate the pathologic response, which is to date the best predictor of RFS (13, 20). Therefore, standardized guidelines for pathologic assessment of resection specimens after neoadjuvant therapy to grade pathologic responses are crucial. Rationally, these might include criteria such as immune-related pathologic features including immune infiltrate (lymphocytes, plasma cells, lymphoid aggregates, and macrophages) together with wound-healing characteristics (immature, proliferative fibrosis, and neovascularization; ref. 47). To further advance assessment and prediction of responses in patients receiving neoadjuvant immunotherapy, robust biomarkers are required. Results from the first clinical trials employing neoadjuvant ICIs in patients with melanoma identified markers that associated with response. A study with patients with macroscopic stage III melanoma receiving neoadjuvant ipilimumab plus nivolumab identified that the expansion of tumor-resident T-cell clones and a favorable IFNγ gene signature were associated with RFS (13). Another study in patients with resectable stage III or oligometastatic melanoma receiving neoadjuvant combined ipilimumab plus nivolumab or nivolumab alone showed that patients whose tumors displayed greater $CD8^+$ T-cell infiltration, of which TCR clonality was higher, were more likely to demonstrate a positive response to therapy (20). In a prospective study of 27 patients with either resectable stage III or oligometastatic melanoma treated with neoadjuvant pembrolizumab showed patients with brisk lymphocyte infiltration into the tumor had a higher RFS (89%) compared with patients with lower lymphocyte infiltration (27%; ref. 23). Early results in colon cancer, combining ipilimumab and nivolumab treatment before surgery, showed major pathologic responses (<5% viable tumor cells) in mismatch repair–deficient tumors, with a significant increase in T-cell infiltration after treatment (48). Treatment with anti–PD-1 in resectable NSCLC increased the number of neoantigen-specific T-cell clones both in the tumor and peripheral blood, for which tumor mutational burden (TMB) seemed to be predictive for response (24). In contrast, TMB did not correlate with response in melanoma (13). Potentially, these biomarkers may also serve as predictive markers of outcome in other neoadjuvant immunotherapy trials as they have been used in the advanced/metastatic setting. In addition, it will be interesting to assess whether an RNA signature–driven therapy approach can be also applied for patients relapsing at a later time point. One might envisage that a patient who initially responded well to neoadjuvant immunotherapy but relapsed later (e.g., several years later) could be retreated with the same ICI(s) if their tumor displayed the same RNA signature as their early-stage disease. In contrast, an early-relapse patient (<6 months) that did not respond well to neoadjuvant immunotherapy should be treated with an alternative combination informed by their RNA-driven signature. In addition to monitoring immune response, the presence of circulating tumor DNA (ctDNA) can also be measured. A study in patients with stage III melanoma reported that preoperative ctDNA predicted melanoma-specific survival independent of the American Joint Committee on Cancer stage (49). Potentially, changes in ctDNA before and after neoadjuvant immunotherapy may be another biomarker of response.

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Therapy efficacy and treatment-induced irAEs are strongly independent in neoadjuvant immunotherapy (50); therefore, it would be advantageous to identify patients upfront that are most likely to respond to treatment and/or have a high chance to develop severe irAEs. This is especially important for neoadjuvant approaches in stage III disease, because in melanoma up to 50% of these patients can be cured by surgery only, and thus do not need any adjuvant therapies (51). Given the high incidence of irAEs induced upon ICI, particularly in combination approaches (52), it is crucial to identify biomarkers that can predict response and development of treatment-induced (irreversible) severe irAEs. Going forward, identification of biomarkers that reflect the complex tumor–immune system interaction and immune system–host interaction will aid clinicians decide the patients that will benefit most from neoadjuvant immunotherapy.

Unanswered Questions

There are currently many questions that remain unanswered with regard to the use of neoadjuvant cancer immunotherapy. A key question is to demonstrate the improved efficacy of neoadjuvant over adjuvant immunotherapy in randomized phase III clinical trials. Other questions include: (i) will neoadjuvant immunotherapy be effective for all tumor types? The existing literature suggests that in order for an effective response to occur following neoadjuvant treatment, an ongoing, albeit dysfunctional, immune response must be present within the primary tumor before treatment. Therefore, it is unlikely that a tumor in which a T-cell response has not been generated, or one in which tumor-specific T cells are excluded from tumor tissue would respond any better to neoadjuvant immunotherapy than adjuvant immunotherapy. However, this is yet to be directly tested. (ii) What role does surgery play, and will other tumor ablation therapies work as effectively? For example, if radiotherapy or chemotherapy is capable of destroying the macroscopic tumor, would the neoadjuvant immunotherapy effect hold? Some chemotherapies and radiotherapies have been shown to promote immunogenic cell death and be capable of kick-starting an antitumor immune response (53). It is possible that nonsurgical intervention could be beneficial, given the finding that the immune suppression associated with surgical wound repair can enable the revival and dissemination of occult metastases (54). In addition, it is not known whether chemotherapy and radiotherapy might be more effective in combination with neoadjuvant as opposed to adjuvant immunotherapy. (iii) Are particular immunotherapies more effective than others in a neoadjuvant context? To date, it seems that combination of anti–PD-1 and anti–CTLA-4 is superior to monotherapy anti–PD-1 in terms of pCR; however, this does appear to come at the cost of increased irAEs. (iv) Finally, what are the determinants of response for neoadjuvant immunotherapy? Understanding why neoadjuvant immunotherapy is effective for some patients but not others may allow the identification of biomarkers of response and mechanisms of resistance as recently reported by Huang and colleagues (23). Should future clinical trials validate the promising data from current neoadjuvant immunotherapy clinical trials, this approach may become standard of care for the treatment of patients with early-stage cancer that are at high risk of relapse.

Disclosure of Potential Conflicts of Interest

M.J. Smyth reports receiving commercial research grants from Bristol-Myers Squibb and Tizona Therapeutics, and is a consultant/advisory board member for Tizona Therapeutics and Compass Therapeutics. C.U. Blank reports receiving commercial research grants from Novartis, Bristol-Myers Squibb, and NanoString, and is a consultant/advisory board member for Bristol-Myers Squibb, MSD, Roche, Novartis, Lilly, Pfizer, GenMab, GlaxoSmithKline, and Pierre Fabre. No potential conflicts of interest were disclosed by the other authors.

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