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Neoadjuvant immunotherapy of locoregionally advanced solid tumors

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ABSTRACT

Definitive management of locoregionally advanced solid tumors presents a major challenge and often consists of a combination of surgical, radiotherapeutic and systemic therapy approaches. Upfront surgical treatment with or without adjuvant radiotherapy carries the risks of significant morbidities and potential complications that could be lasting. In addition, these patients continue to have a high risk of local or distant disease relapse despite the use of standard adjuvant therapy. Preoperative neoadjuvant systemic therapy has the potential to significantly improve clinical outcomes, particularly in this era of expanding immunotherapeutic agents that have transformed the care of patients with metastatic/unresectable malignancies. Tremendous progress has been made with neoadjuvant immunotherapy in the treatment of several locoregionally advanced resectable solid tumors leading to ongoing phase 3 trials and change in clinical practice. The promise of neoadjuvant immunotherapy has been supported by the high pathologic tumor response rates in early trials as well as the durability of these responses making cure a more achievable potential outcome compared with other forms of systemic therapy. Furthermore, neoadjuvant studies allow the assessment of radiologic and pathological responses and the access to biospecimens before and during systemic therapy. Pathological responses may guide future treatment decisions, and biospecimens allow the conduct of mechanistic and biomarker studies that may guide future drug development. On behalf of the National Cancer Institute Early Drug Development Neoadjuvant Immunotherapy Working Group, this article summarizes the current state of neoadjuvant immunotherapy of solid tumors focusing primarily on locoregionally advanced melanoma, gynecologic malignancies, gastrointestinal malignancies, non-small cell lung cancer and head and neck cancer including recent advances and our expert recommendations related to future neoadjuvant trial designs and associated clinical and translational research questions.

INTRODUCTION

Neoadjuvant therapy refers to the systemic induction therapy of cancer prior to definitive treatment, which is usually surgery (ie, preoperative therapy), but may also include any curative intent treatment such as radiation or chemoradiation therapy. Locally and regionally advanced solid tumors where neoadjuvant therapy may apply are often managed with definitive surgical resections with or without subsequent adjuvant radiotherapy and systemic therapy. These complex surgical resections are often associated with significant morbidities and risks, and in the absence of systemic adjuvant therapy the risk of distant disease relapse continues to be high. Neoadjuvant systemic therapy of these advanced cancers has been shown to improve the clinical outcomes of patients with different types of operable solid tumors, including neoadjuvant chemotherapy in head and neck cancer, lung cancer, breast cancer, bladder cancer, esophageal cancer and colorectal cancer.[1–4] Indeed, these neoadjuvant studies have reported improvements in survival, tumor resectability, organ preservation and/or local disease control. Experimentally, neoadjuvant systemic therapy trials make possible the evaluation of clinical/radiological and pathological tumor responses. Moreover, access to tumor and blood before and after systemic therapy provides opportunities for a thorough investigation of the molecular mechanisms involved in response and resistance to treatment. It also allows the development of biomarkers that may estimate the risks of treatment-related toxicities. Ultimately, it may improve the therapeutic index and cost-effectiveness of systemic therapies in the neoadjuvant setting and other disease states.

Exciting advances in immunotherapy in the treatment of advanced inoperable cancers have triggered significant interest in investigating immunotherapeutic agents and combinations in the neoadjuvant setting. The promise of neoadjuvant immunotherapy has been supported by high tumor response rates and the durability of these responses making cure a more achievable potential outcome as compared with other forms of systemic therapy. Tremendous progress has been made with neoadjuvant immunotherapy in the treatment of several advanced solid tumors

leading to multiple ongoing trials including phase 3 trials and change in clinical practice. However, there are still many key questions that need to be addressed for the optimal development of neoadjuvant immunotherapy. Open questions include defining the optimal neoadjuvant immunotherapy regimen(s) for a specific disease, duration of the neoadjuvant phase prior to the planned surgical resection, ideal outcome measures the durability of tumor in both radiologic and pathologic responses, predictive biomarkers of therapeutic benefits, biomarkers that may estimate the risks of treatment-related toxicities, and implications for future study designs. In a recent National Cancer Institute (NCI) Early Drug Development (EDD) neoadjuvant immunotherapy meeting we discussed these questions focusing primarily on locoregionally advanced melanoma, gynecologic malignancies, gastrointestinal malignancies, non-small cell lung cancer (NSCLC) and head and neck cancer. On behalf of the NCI EDD Neoadjuvant Immunotherapy Working Group, this article summarizes the outcomes of this discussion of the state of neoadjuvant immunotherapy including recent advances and our expert recommendations related to future neoadjuvant trial designs and associated clinical and translational research questions.

MELANOMA

Rationale for neoadjuvant immunotherapy in melanoma

Patients with melanoma and clinically detectable regional lymphadenopathy with or without in-transit metastases belong to American Joint Committee on Cancer (AJCC V.8) stages IIIB–D and carry a high risk of relapse that approaches 90% for IIID with surgical management alone.[5 6] These patients are candidates for systemic neoadjuvant therapy that has the potential of improving disease operability and clinical outcomes. Previous neoadjuvant studies tested chemotherapy with temozolomide where the clinical activity was significantly limited.[7] Biochemotherapy (BCT) was tested in two neoadjuvant studies and showed high tumor response rates including a small percentage of pathological complete response (pCR); however, BCT was ultimately abandoned following its failure to demonstrate survival benefits in randomized trials of metastatic disease.[8] More recently, success of immunotherapy and targeted therapy (TT) in managing metastatic inoperable melanoma generated considerable interest to investigate these novel strategies in the neoadjuvant setting. A number of neoadjuvant targeted and immunotherapy studies have been completed in melanoma to date and have yielded promising clinical activity.[9]

Immunity to melanoma is essential for disease control. Spontaneous regression of melanoma has been reported, suggesting a role for host immunity, that is also indirectly supported histologically by findings of tumor infiltrating lymphocytes (TILs) in primary melanoma associated with tumor regression.[10] Furthermore, lymphoid immune infiltrates within the tumor have been shown to be prognostic in primary melanoma and melanoma metastatic to regional lymph nodes.[11 12] T cell infiltrates within regional nodal metastasis were associated with response following neoadjuvant interferon-α (IFNα) and ipilimumab.[11 13 14] These immune features of melanoma are consistent with the role of systemic immunotherapy in its management, including cytokine therapy, immune checkpoint inhibitors (ICI), adoptive cell therapy, oncolytic viral therapy and tumor vaccination strategies.

Investigations of neoadjuvant immunotherapy in locally–regionally advanced operable melanoma have accelerated over the past decade following the successes in treating metastatic disease. The leading studies reported to date tested high dose interferon-α (HDI), ipilimumab, pembrolizumab, the combination of HDI with ipilimumab or pembrolizumab, talimogene laherparepvec (T-VEC) as well as combinations of ipilimumab and nivolumab, and nivolumab and relatlimab among others. These studies have provided a model for later neoadjuvant immunotherapy studies in this disease and are summarized in online supplemental table 1.

Clinical experience in neoadjuvant trials in melanoma and laboratory correlates

High dose interferon-α

The first neoadjuvant immunotherapy study in melanoma investigated the effect of HDI in patients with stage IIIB–C (AJCC V.7) melanoma.[13] Patients received HDI intravenously for 4 weeks before undergoing complete lymphadenectomy. A pCR was observed in 15% of the patients. There was evidence of upregulation of pSTAT1 following IFNα with downregulation of pSTAT3 and total STAT3 levels in tumor cells and lymphocytes.[15] Furthermore, there were significantly increased endotumoral infiltrates of CD11c+ and CD3+ cells following IFNα in responders as compared with non-responders.

Ipilimumab as monotherapy and in combination with IFNα

Tarhini *et al* conducted two trials with neoadjuvant ipilimumab first as monotherapy and later in combination with HDI.[14 16] The first trial investigated neoadjuvant ipilimumab at the high dose of 10 mg/kg intravenously for two doses given 3 weeks apart prior to definitive surgery.[14] No pCR was observed but about 10% of the patients had a major pathological response (MPR) with only microscopic residual disease. Neoadjuvant evaluation revealed a significant immunomodulating role for ipilimumab on regulatory T cells, myeloid-derived suppressor cells (MDSC), and effector T cells in the circulation and tumor microenvironment. A greater decrease in the monocyte gate MDSC (Lin1-/HLA-DR-/CD33+/CD11b+) was associated with improved recurrence-free survival (RFS) (p=0.03). Lower baseline levels of circulating regulatory T cells (Tregs, CD4 +CD25hi+CD39+) was associated with improved RFS (p=0.04).[17] High interleukin (IL)-17 serum levels at baseline were associated with the risk of developing high grade diarrhea and colitis. Within the tumor microenvironment (TME), ipilimumab treatment resulted in a massive infiltration by CD8 +T cells (p=0.02)

that were fully activated (CD69+) as well as TME infiltration by CD69+/CD3+/CD4 +T cells and evidence of induction/potentiation of memory T-cells (CD45RO+). Gene expression profiling utilizing the tumor biopsies of treated patients identified immune-related pathways enriched with immune-related genes that were significantly predictive of clinical outcome.[18]

The second study tested neoadjuvant ipilimumab (3 mg/kg or 10 mg/kg) given in combination with HDI.[16] The neoadjuvant phase consisted of 6 weeks of preoperative systemic therapy followed by definitive surgery. A pCR was found in 32% of the patients. Immunosequencing of T-cell receptor (TCR) β chains revealed a significant increase in tumor and peripheral blood mononuclear cells clonality following treatment that was associated with improved clinical outcomes.[19] In examining the temporal changes in TILs and peripheral TCR repertoire, responders were found to have significantly higher clonal expansion of TILs in the circulation than non-responders.

Pembrolizumab as monotherapy and in combination with IFNα

A single dose of pembrolizumab (200 mg intravenously) in the neoadjuvant setting led to a pCR of 19%, and all patients who experienced a pCR remained disease-free at the time of publication.[20] Additionally, patients with pCR showed an accumulation of exhausted CD8 T cells in the tumor while patients with later recurrent disease after surgery exhibited evidence of immune resistance including low percentage of CD8 +T cells, low Ki67 and prominent increase in CD163 +myeloid cells. In another study, pembrolizumab was given concomitantly with HDI for 6 weeks followed by definitive surgery and adjuvant combination immunotherapy.[21] The radiographic overall response rate (ORR) was 73.3%, with a 43% pCR rate. Additionally, overall survival (OS) and RFS were not reached at data cut-off (29.7 months). In this study, intratumoral programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1) interaction and HLA-DR expression were associated with pCR.

Talimogene laherparepvec

Neoadjuvant oncolytic viral immunotherapy with T-VEC was investigated in resectable stage IIIB–IVM1a melanoma. This randomized phase 2 clinical trial reported a pCR of 17.1% and no unexpected toxicities.[22] It estimated a 25% reduction in the risk of disease recurrence for neoadjuvant T-VEC plus surgery versus upfront surgery which was the study's primary endpoint, further supporting the role of neoadjuvant immunotherapy.

Ipilimumab plus nivolumab

Three neoadjuvant studies combined nivolumab 1 or 3 mg/kg and ipilimumab 1 or 3 mg/kg with variable numbers of cycles and durations of treatments as summarized in online supplemental table 1. Overall, these studies demonstrated improved pathological responses with the combination with pCR rates approaching 50% and varying toxicity rates that increased with increasing the dose of ipilimumab.[23–25] Most recently, the OpACIN-Neo phase 2 trial investigated three neoadjuvant dosing regimens: two cycles of ipilimumab 3 mg/kg plus nivolumab 1 mg/kg one time every 3 weeks (arm 1), two cycles of ipilimumab 1 mg/kg plus nivolumab 3 mg/kg one time every 3 weeks (arm 2), and two cycles of ipilimumab 3 mg/kg one time every 3 weeks directly followed by two cycles of nivolumab 3 mg/kg one time every 2 weeks (arm 3). Within the first 3 months, grade 3–4 immune-related adverse events were observed in 40% of patients in arm 1, 20% in arm 2, and 50% in arm 3. The pCRs occurred in 57% of patients in arm 1, 47% in arm 2, and 23% in arm 3. Based on the results of these studies it can be concluded that two cycles of ipilimumab 1 mg/kg plus nivolumab 3 mg/kg is the most optimal neoadjuvant dosing regimen taking into account efficacy and toxicity profiles.

Nivolumab plus relatlimab

Neoadjuvant nivolumab in combination with anti-LAG3 antibody relatlimab was recently examined in patients with resectable clinical stage III melanoma.[26] In this study, high pCR and MPR rates with a favorable toxicity profile were achieved (ORR=57%, pCR rate=59% and MPR=66%; no grade 3/4 treatment-related adverse events (AEs) during neoadjuvant therapy; 26% of patients had a grade 3/4 AE that arose during ongoing adjuvant treatment). In parallel, this combination demonstrated significant improvement in progression-free survival (PFS) in treating metastatic inoperable melanoma.[27]

Neoadjuvant targeted therapy with dabrafenib and trametinib

Amaria *et al* led a study in which patients were randomly assigned to upfront surgery and consideration for standard of care (SOC) adjuvant therapy or neoadjuvant plus adjuvant dabrafenib and trametinib.[28] After a median follow-up of 18.6 months, 58% of the patients in the neoadjuvant plus adjuvant therapy group who underwent surgery achieved pCR and 17% pathological partial response (pPR). These results were confirmed by another trial of neoadjuvant dabrafenib plus trametinib for the treatment of resectable, stage IIIB-C, BRAF (V600) mutation-positive melanoma.[29] In this phase 2, single-arm study, all patients achieved a partial response (PR), including 49% with pCR. In addition to these two studies, the recently published results of the REDUCTOR trial demonstrated that short-term neoadjuvant cytoreductive therapy with dabrafenib plus trametinib allowed radical resection of metastases in 81% of patients with prior unresectable locally advanced melanoma.[30]

Optimization of neoadjuvant immunotherapy in melanoma: suggestions for future progress

Altogether the above-mentioned studies show that neoadjuvant systemic therapy may play a significant role in locoregionally advanced melanoma that carries a high risk of relapse and death with surgery alone (table 1). Indeed, the results reported in these trials demonstrate that

Table 1 Optimization of neoadjuvant immunotherapy in early phase trials

	Melanoma	Gastrointestinal malignancies*	Gynecologic malignancies	Non-small cell lung cancer	Head and neck malignancies
Outcome measures	► pCR (preferred)† ► EFS ► ORR ► RFS ► OS	► pCR ► DFS ► EFS	► pCR (not well defined) ► ORR ► EFS	► pCR (preferred) ► MPR ► EFS ► OS	► pCR/MPR/LPR ► ORR ► RFS ► EFS
Duration of neoadjuvant phase	6–12 weeks‡	6–17 weeks	9–12 weeks	4–12 weeks	3–6 weeks
Comparators in randomized trials	► Anti-PD-1§ ► Ipi1–Nivo3 ► Rela–Nivo	► Chemotherapy ► Chemoradiation ► Anti-PD-L1 ► Observation	► Chemotherapy (EOC, EC, Cx) ► Chemoradiation (Cx)	Platinum doublet chemotherapy	► Anti-PD-1 ► Anti-PD-1/ CTLA-4
Adjuvant therapy	► Preferred¶	► Preferred	► Preferred	Adjuvant therapy given in all but one (CheckMate 816) of the phase 3 trials	Pathologic risk-adapted adjuvant therapy
Biospecimens for biomarker studies	► Baseline ► At surgery ► Follow-up	► Baseline ► At surgery ► Follow-up	► Baseline ► At surgery ► Follow-up	► Serial circulating tumor DNA ► Baseline ► At surgery ► Follow-up	► Baseline ► At surgery ► Follow-up

*Dependent on primary tumor type.
†pCR is the preferred endpoint in early phase trials in melanoma. EFS, RFS and OS become more important for large, randomized trials.
‡Duration may be tailored based on the expected clinical activity of the agent(s) being tested. An interim clinical assessment may be planned if there are concerns about disease progression.
§Anti-PD-1 monotherapy, ipilimumab 1 mg/kg+nivolumab 3 mg/kg, relatlimab–nivolumab.
¶Studies may consider randomizing patients who achieve a pCR to observation versus continued systemic adjuvant therapy.
.CTLA-4, cytotoxic T-lymphocytes-associated protein 4; Cx, cervix; DFS, disease-free survival; EC, endometrial cancer; EFS, event-free survival; EOC, epithelial ovarian cancer; LPR, laryngopharyngeal reflux; MPR, major pathologic response; ORR, overall response rate; OS, overall survival; pCR, pathologic complete response; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival.

neoadjuvant immunotherapy and TT are active and associated with high pCR rates and improved RFS. Menzies *et al* reported a pooled analysis of six of the neoadjuvant clinical trials described above: four with neoadjuvant anti-PD1 as monotherapy and in combination with ipilimumab and two with neoadjuvant dabrafenib plus trametinib.[31] The 2-year RFS was higher with immunotherapy than with TT (76% vs 44%), and pCRs were significantly more durable with immunotherapy and correlated with improved RFS and OS.

Optimal outcome measures

RFS and OS are major outcomes measure for neoadjuvant therapy. However, the study by Menzies *et al* also suggests that pathological response should be considered as an important endpoint.[31] Indeed, the authors found that pCR correlated with improved RFS (pCR 2-year 89% vs no pCR 50%, p<0.001) and OS (pCR 2-year 95% vs no pCR 83%, p=0.027). Pathological near-complete response should also be considered. Finally, radiologic response should be interpreted with caution. During the 2021 American Society of Clinical Oncology (ASCO) meeting Dr. Amaria presented the trial that tested neoadjuvant and adjuvant nivolumab with anti-LAG3 antibody relatlimab looking at pathological response versus radiologic response and showed that radiologic response often underestimates pathological response.[26] This was like the observations by Blank *et al* who also reported that radiologic responses underestimated the pathologic responses in their neoadjuvant trials testing ipilimumab plus nivolumab.[24] In order to achieve accurate and reproducible pathologic response assessment in neoadjuvant treated specimens, specific guidelines have been developed and proposed to estimate the residual viable tumor (RVT).[32 33] In this regard, RVT (or %RVT) is defined as the total surface cross-sectional area of RVT divided by the total tumor bed area (comprizing RVT area +areas of necrosis). Using these criteria, the following definitions of pathologic response have been recommended: (1) Pathologic complete response (pCR; 0% RVT, absence of viable tumor cells in the surgically resected post-treatment specimen); (2) Pathologic near-complete or major response (MPR; 0 to ≤10% RVT; that is, near-complete absence

of viable tumor cells in the surgically resected post-treatment specimen); (3) Pathologic partial response (pPR; >10% RVT but ≤50% RVT); (4) Pathologic non-response (pNR; >50% RVT; that is, >50% viable tumor in the surgically resected post-treatment specimen). Furthermore, event-free survival (EFS) should be considered as an endpoint to account for cases where disease progression may occur prior to surgery. In addition, surgical delay beyond the target surgical time point should also be monitored as an endpoint including the impact on the overall clinical outcome.

Treatment regimens and optimal study design

Based on the neoadjuvant immunotherapy trials so far, the optimal neoadjuvant immunotherapy regimens seem to be anti-PD-1 monotherapy, ipilimumab 1 mg/kg plus nivolumab 3 mg/kg and nivolumab with anti-LAG3 antibody relatlimab. However, activity with anti-PD-1 monotherapy is modest and combination regimens are an area of need in this setting. In addition, the immune-related toxicity associated with the combination regimens should be monitored closely. Intratumorally injected agents (eg, TLR agonists, plasmid IL-12, oncolytic viral therapy, proinflammatory cytokines) in combination with anti-PD-1 may provide an option that maximizes regional neoadjuvant treatment efficacy while minimizing systemic toxicity and are worth investigating. Also, while in most studies the duration of the neoadjuvant phase ranges from 6 to 12 weeks, there is a rationale to investigate in the setting of a clinical trial the possibility of having an interim analysis (eg, at 6 weeks). If patients demonstrate an objective radiologic response, neoadjuvant therapy may be continued and surgery delayed in order to maximize the pathological response, while monitoring patients. While prior studies reported a lack of correlation between radiologic and pathologic responses at the fixed surgical dates of the clinical trials, it may be of interest to investigate whether prolonging systemic neoadjuvant immunotherapy in objectively responding patients as assessed clinically and radiologically may further improve the pathologic responses. Therefore, in terms of optimal neoadjuvant study designs, we suggest considering adding endpoints that investigate the time to surgery and whether this can be tailored to patients' needs while conducting interim regular tumor and toxicity assessments. Additionally, 2-year RFS with neoadjuvant immunotherapy is a candidate primary endpoint for randomized trials evaluating patients with pathological complete or near-complete responses that may be randomized between continued systemic adjuvant therapy or observation.

Potential role for the 'index' lymph node in de-escalating surgical care

In a published series of 82 patients with locoregionally advanced melanoma treated with neoadjuvant ipilimumab and nivolumab followed by lymph node dissection (LND), the 'index' lymph node (ILN, the largest lymph node metastasis at baseline) was marked and histologically analyzed in comparison to all remaining nodes in order to assess what the outcome would have been with ILN removal alone. The pathologic response in the ILN was concordant with the entire LND specimen response in 81 of 82 patients (99%). In the single patient with a discordant response, the ILN response (20% viable tumor, partial pathologic response) somewhat underestimated the entire LND specimen response (5% viable, near-complete pathologic response). It did not appear that there were any cases of a pCR in the ILN with residual disease in the other nodes in this series.[34] A subsequent study (The PRADO extension cohort of the OpACIN-neo trial), incorporated the ILN into the study design where patients achieving MPR (≤10% viable tumor) in their ILN, therapeutic LND and adjuvant therapy were omitted. The 24-month RFS and distant metastasis-free survival rates were 93% and 98%, respectively, in this cohort of patients with MPR.[35] In both reported cohorts, patients received only two doses of ipilimumab and nivolumab, and it is possible that additional systemic therapy may have further deepened the histologic response. Overall, the results strongly support continued exploration of the concept of using the ILN status to support omission of lymphadenectomy in carefully selected patients undergoing neoadjuvant immunotherapy.

Predictive and prognostic biomarkers in the neoadjuvant setting

A major advantage of neoadjuvant therapy is the possibility to study the tumor molecular response to treatment by performing sequential specimen collections before, during and after treatment. The molecular changes can then be correlated with the patients' outcomes. This allows the identification of predictive and prognostic biomarkers that can be used in later trials to select patients that are more likely to benefit from each therapeutic regimen. Furthermore, mechanistic studies can be conducted that may identify mechanisms of resistance and optimal combinations. Therefore, it is essential that neoadjuvant trials integrate biomarker studies into their design.

In conclusion, locoregionally advanced melanoma carries a high risk of relapse and death where neoadjuvant systemic therapy may play a significant role. Indeed, neoadjuvant immunotherapy and TT are active and are associated with high pCR rates. Additionally, the ability to achieve pCR correlates with improved RFS and OS. In terms of drug development, biomarker and mechanistic studies can be accelerated through neoadjuvant trials given the access to biospecimens before and during therapy to select the best drugs and combinations.[36] Importantly, newer targeted and immunotherapeutic agents and combinations are currently being translated into the neoadjuvant setting at an accelerated pace and carry significant promise.

GASTROINTESTINAL MALIGNANCIES

Gastrointestinal (GI) cancers are composed of multiple malignancies with variable molecular alterations, resulting in multiple treatment approaches across the diseases (online supplemental table 1). Because GI cancers do not have many inherent features rendering them susceptible

to immunotherapy, the role of such treatment has been relatively focused on ICI in advanced stage and treatment refractory cancers. There has been limited success in the use of immunotherapy to treat pancreatic,[37] biliary,[38 39] and neuroendocrine tumors.[40] However, there has been success in colorectal, gastroesophageal, and anal cancer.

Colorectal cancer

Rationale for neoadjuvant immunotherapy in colorectal cancer

Colorectal tumors are typically characterized by the status of the DNA mismatch repair pathway and level of microsatellite instability (MSI). Tumors with deficient mismatch repair (dMMR) have high levels of DNA MSI (MSI-H) compared with tumors with proficient MMR (pMMR). This leads to an increased mutational burden, making them attractive targets for immunotherapy.[41]

A study comparing pembrolizumab response in dMMR and pMMR progressive metastatic colorectal carcinoma demonstrated improved immune-related ORR (40% vs 0%, respectively) and immune-related PFS (78% vs 11%).[42] Additionally, the KEYNOTE-177 trial demonstrated improved PFS in patients with MSI-H-dMMR metastatic colorectal cancer treated with pembrolizumab as single-agent first-line therapy compared with chemotherapy (16.5 vs 8.2 months, HR 0.60, p=0.0002).[43]

Clinical experience in neoadjuvant trials for colorectal cancer and laboratory correlates

In an effort to move it into the curative treatment setting, ICI is being assessed particularly for dMMR colorectal cancer in the neoadjuvant and adjuvant settings. An ongoing phase 3 study (A021502) will help determine whether the addition of adjuvant atezolizumab to chemotherapy (oxaliplatin, leucovorin calcium, and fluorouracil; FOLFOX) will improve disease-free survival (DFS) compared with FOLFOX chemotherapy alone in patients with stage III dMMR colon cancer. In the neoadjuvant setting, EA2201 explores pCR rates in stage II or III dMMR rectal cancers treated with nivolumab and ipilimumab in combination with radiation therapy.

Gastroesophageal cancer

Rationale for neoadjuvant immunotherapy in gastroesophageal cancer

Treatment for gastroesophageal cancer standardly involves a combination of neoadjuvant chemoradiotherapy (carboplatin, paclitaxel, and radiation therapy)[44 45] followed by surgical resection, or perioperative chemotherapy (docetaxel, oxaliplatin, leucovorin, and fluorouracil; FLOT).[4] Unfortunately, pCR rates to neoadjuvant therapy are generally below 30%.[46–48]

Gastroesophageal cancer may be susceptible to immunotherapy based on genomic subtype, specifically those characterized as Epstein-Barr virus positive, MSI-H, or chromosomally unstable.[49] Nivolumab has shown promise both in refractory and previously untreated unresectable gastric or gastroesophageal junction cancers. Patients with metastatic disease and progression after two previous lines of therapy showed an increased OS compared with placebo (5.26 months vs 4.14 months, respectively, HR 0.63, p<0.0001).[50] In the CheckMate 649 study, the addition of nivolumab to chemotherapy (FOLFOX or capecitabine and oxaliplatin; XELOX) in the metastatic setting improved OS (13.8 months vs 11.6 months, HR 0.80, p=0.0002) and PFS (7.7 months vs 6.9 months, HR 0.77) compared with FOLFOX or XELOX alone.[51]

Clinical experience in neoadjuvant trials for gastroesophageal cancer and laboratory correlates

Esophageal adenocarcinoma is the one area in GI malignancies where there is a SOC indication for the use of ICI therapy in the curative setting. In the adjuvant setting, the CheckMate 577 trial demonstrated improved DFS in patients treated with adjuvant nivolumab compared with placebo (22.4 months vs 11.0 months, HR 0.69, p<0.001).[52]

Because chemoradiotherapy induces upregulation of PD-L1 and increases T cell dysfunction, there is expected to be complementary activity between chemoradiotherapy and ICI. In an effort to supersede the elusive 30% pCR rate, an ongoing clinical trial is exploring the use of immunotherapy in a perioperative setting. The EA2174 trial tests neoadjuvant carboplatin and paclitaxel with concurrent radiation therapy with or without nivolumab followed by surgery and adjuvant immunotherapy consisting of nivolumab with or without ipilimumab. Trials using perioperative FLOT plus placebo or durvalumab (MATTERHORN)[53] and a similar trial using pembrolizumab (KEYNOTE-585)[54] will help determine whether immunotherapy will be part of the next SOC.

Anal cancer

Rationale for neoadjuvant immunotherapy in anal cancer

Anal cancer is a malignancy associated with high rates of human papillomavirus (HPV) infection, which in turn can result in the upregulation of immune checkpoint proteins. Additionally, there is expected to be complementary activity between chemoradiotherapy and ICI, as mentioned above. In the metastatic setting, both nivolumab[55] and pembrolizumab[56] have shown promise in refractory metastatic anal cancer (24% and 17% response rates, respectively). In response to these studies, the National Comprehensive Cancer Network now recommends immunotherapy as a preferred regimen in the metastatic setting following front-line therapy.

Clinical experience in neoadjuvant trials for anal cancer and laboratory correlates

Efforts are now underway to include ICI in the curative setting given successes in the metastatic setting. The EA2165 trial explores the difference in DFS of patients with high risk, localized anal cancer who receive nivolumab after chemotherapy and radiation as compared with those who do not. The German Anal Cancer Group is currently conducting the RADIANCE trial to evaluate the

addition of immunotherapy (durvalumab) concurrent with chemoradiation for patients with localized disease.

Optimization of neoadjuvant immunotherapy in gastrointestinal malignancies: suggestions for future progress

Overall, ICI are a promising treatment modality for some GI malignancies. Response may be dependent on an inherent characteristic of the tumor, such as high clonality of immunogenic mutations or incorporation with an additional treatment modality that enhances immunogenicity (table 1).[57] Correlative science conducted as part of these ongoing studies will aid in guiding which patients may benefit the most from immunotherapy. Given the multiple tumor types within the GI malignancies, all of which are approached with different treatment paradigms, there is no singular optimal approach to treatment that spans the diseases. At the same time, the commonality is that these tumors are not inherently immunogenic and as a result, any inclusion of immunotherapeutic agents is likely to be additive to SOC treatments and not in place of them. As such, optimal study designs for assessing the role of immunotherapy should include either adding immunotherapy to an existing chemotherapeutic or chemoradiation regimen or utilizing immunotherapy as an additional treatment where observation might have otherwise been appropriate. The exception to this may be the tumors that are dMMR as single-agent immunotherapy has been shown, at least in colorectal cancers, to be superior to cytotoxic chemotherapy. As far as best assessment of efficacy from the stance of clinical trial design, as is the case with melanoma above, the use of pCR rate as a neoadjuvant primary endpoint has been a long-standing metric for long-term success (improved survival outcomes) in the GI malignancies and remains the most utilized neoadjuvant primary endpoint. DFS has generally been the most favored adjuvant primary endpoint given the longer time frame needed to achieve OS data.

GYNECOLOGIC MALIGNANCIES

Neoadjuvant immunotherapy is in the early stages of evaluation in gynecologic malignancies when compared with other cancers such as melanoma (online supplemental table 1). Moreover, the responses to immunotherapy so far have been variable depending on the type of gynecologic cancers, that is, endometrial, cervical, and ovarian cancer, and heavily dependent on biomarkers. Therefore, we will address the question about whether gynecologic malignancies are good candidates for neoadjuvant immunotherapy by gynecologic cancer subtype.

Endometrial cancers

Rationale for neoadjuvant immunotherapy in endometrial cancer

Endometrial cancers (EC) are classified in four different molecular subtypes based on The Cancer Genome Atlas Research Network distribution: DNA-polymerase-ε (POLE) (ultramutated), MSI (hypermutated), copy number low (endometrioid) and copy number high (serous like).[58] POLE mutated tumors represent about 6% of EC and are associated with high grade tumors,[59 60] and MSI tumors comprise approximately 30% of all EC.[61] Both of these EC cancer subtypes have high levels of PD-1/PD-L1 expression, neoantigen load and cytotoxic T cell infiltration[62] so they should be good candidates for immunotherapy, especially ICI. The concept of neoadjuvant chemotherapy does not exist to date for endometrial cancers. Patients with disease metastatic to lymph nodes (stage IIIC1, IIIC2) or metastatic to the ovaries (stage IIIA) are currently treated with surgery followed by platinum and taxane-based chemotherapy with or without radiation. Similarly, patients with lower stage but high-risk histology may receive postoperative chemotherapy. These would be examples of adjuvant therapy where ICI is currently in clinical trials. Patients with stage IVB or recurrent disease are largely dispositioned to platinum and taxane-based chemotherapy. For stage IVB disease, in the setting of excellent clinical response, a patient may undergo a neoadjuvant approach and have an interval surgery followed by more chemotherapy, but this has never been prospectively studied in endometrial cancer and would not be considered SOC. Rationale for moving ICI into the adjuvant setting or the first-line metastatic setting is justified based on data from studies done in the recurrent/second-line setting. In the dMMR/MSI population, Oaknin *et al* recently reported preliminary data from the GARNET study from patients with recurrent or advanced EC.[63] In this trial patients with disease progression after treatment with a platinum-containing chemotherapy regimen received dostarlimab anti-PD-1 immunotherapy. The ORR was 42.3%. By comparison, second-line paclitaxel or doxorubicin in this patient population leads to only 15% of response rate. The GARNET study led to accelerated approval of dostarlimab in dMMR EC. This adds to the data already generated by the KEYNOTE-158 trial which identified an ORR of 57%.[64]

Among patients with EC whose tumors are not POLE or MSI/dMMR, the KEYNOTE-775 study established lenvatinib plus pembrolizumab as SOC for second-line therapy in the recurrent/metastatic setting.[65]

Altogether, the aforementioned data support moving immunotherapy to the front-line metastatic setting for these subcategories (POLE, MSI, dMMR) of EC where immunotherapy has been successful. For a benchmark, patients with de novo stage IV and recurrent EC treated in front-line with paclitaxel plus carboplatin or paclitaxel-doxorubicin-cisplatin have a median OS of 18–20 months[66] with no difference in response based on MMR status with chemotherapy. KEYNOTE-C93 trial (NCT05173987) is enrolling patients with de novo stage IV, measurable stage III and recurrent dMMR EC in the front-line setting with pembrolizumab versus chemotherapy with crossover allowed to pembrolizumab at time of recurrence on the chemotherapy arm. This is the first randomized phase 3 trial focused on eliminating chemotherapy for dMMR EC; however, it is not fully neoadjuvant

as there is not a requirement or even an expectation that surgery will be performed at time of response to assigned therapy with further adjuvant therapy to follow resection. This could be the next iteration of trials in this space.

For patients with EC characterized as pMMR/MSS the LEAP-001 (NCT03884101) phase 3 trial compares paclitaxel plus carboplatin to lenvatinib plus pembrolizumab in stage III/IV or recurrent MSS EC. If this trial is positive, it moves an ICI containing regimen into front-line therapy *instead* of chemotherapy. Similar to KEYNOTE-C93, if positive this opens the door to normalizing a potential neoadjuvant strategy where patients are treated with agents that have expected high efficacy in order to facilitate local therapy and then subsequent adjuvant therapy. Currently both KEYNOTE-C93 and LEAP-001 would be considered treatment for metastatic disease rather than neoadjuvant or adjuvant.

Cervical cancers

Rationale for neoadjuvant immunotherapy in cervical cancer

Cervical cancers (CC) have a high mutational burden close to head and neck or even melanoma malignancies[67] for which strides have already been made regarding the development of immunotherapy. Additionally, genetic analysis support the expression of PD-L1 at least in a subset of cervical and vulvar squamous cell carcinomas providing a rationale for treating these patients with anti-PD-1 therapies.[68] KEYNOTE-158 explored a cohort of patients who had recurrent or metastatic CC previously treated with SOC platinum/taxane±bevacizumab combination therapy. This study reported an ORR of 12.2% of all patients and in 14.3% of the patients with PD-L1 +tumors.[69] The EMPOWER trial provided phase 3 data confirming the efficacy for monotherapy ICI in the recurrent/metastatic second-line or beyond setting. This study compared second-line cemiplimab to monotherapy cytotoxic treatment of physician's choice (TPC) in patients with recurrent and metastatic CC resistant to platinum-based chemotherapy. Cemiplimab was superior to TPC in the primary endpoint of OS (median OS 12 vs 8.5 months) with an associated HR of 0.69 (95% CI 0.56 to 0.84; p=0.00011).[70] These results are very encouraging and confirm the utility of monotherapy ICI in the second-line setting and justified moving ICI up in terms of lines of therapy. Similar to EC, however, is the fact that there is no established 'neoadjuvant' strategy for cervical cancer as a SOC expectation. The closest approximation would be treatment of front-line metastatic and adjuvant treatment in the front-line, local regionally advanced tumors.

KEYNOTE-826 is a phase 3 study which randomized women with metastatic/recurrent CC to paclitaxel, platinum, bevacizumab (if appropriate)±pembrolizumab. Addition of pembrolizumab improved both median PFS and median OS. Notably, the median OS for the intention-to-treat population is now 24.4 months. The HR for improvement is 0.67 (95% CI 0.54 to 0.84; p<0.001).[71] Based on these results, the KEYNOTE-826 regimen has already received Food and Drug Administration (FDA) approval as of October 13, 2021, in PD-L1 positive tumors only (90% of the study population). However, an important question remains whether chemotherapy is even needed for CC. Naumann *et al* led a study of ipilimumab plus nivolumab in patients with CC who either had recurrent disease or refused chemotherapy.[72] Approximately 50% of the patients were chemotherapy naïve (no systemic therapy for metastatic disease) and had an ORR of 44.8%, which is close to what is observed with chemotherapy, and an OS at 12 months of 84.7%. While these results were from a small number of patients, they are still very encouraging. This incorporation of ICI into front-line metastatic setting is exciting, although not precisely neoadjuvant therapy.

Clinical experience in neoadjuvant trials for cervical cancer and laboratory correlates

There are opportunities and studies evaluating incorporation and use of true neoadjuvant ICI in the local regionally advanced setting where patients are treated with cisplatin and radiotherapy (CRT). In a recent trial, Mayadev *et al* investigated ipilimumab systemic immunotherapy following the completion of CRT in patients with very high risk of recurrence.[73] This small single-arm study reported an increase in T cells expressing PD-1 after CRT that was sustained after ipilimumab. In the neoadjuvant setting, Mayadev *et al* conducted a phase 2 study with or without atezolizumab priming followed by atezolizumab plus CRT in locally advanced CC tumors with lymph node-positive disease.[74] While outcome data are pending there was a difference in pCR based on the on-treatment biopsies. For patients who received neoadjuvant atezolizumab the pCR (on biopsy, not resection) was 43% and pCR +pPR was 82%. For the patients who received atezolizumab with CRT the pCR was 27% and pCR +PR was 36%. There was no difference between T cell clonal expansion either in the tumor or peripheral blood between the two arms and what expansion was noted was related to CRT. However, patients with higher pretreatment TCR diversity had increased likelihood of pCR in on-treatment biopsy (p=0.049).[75]

Finally, two major phase 3 randomized studies are ongoing. The CALLA trial (NCT03830866) is evaluating the efficacy and safety of concurrent and adjuvant durvalumab with CRT versus CRT alone in women with locally advanced CC.[76] This trial has not yet been presented but in press release was noted to have not reached its primary endpoint of PFS (https://www.astrazeneca.com/media-centre/press-releases/2022/update-on-calla-phase-iii-trial-for-imfinzi.html). The KEYNOTE-A18 (NCT04221945) study is still accruing at the time of this manuscript and investigates pembrolizumab with CRT in patients with high-risk locally advanced CC.[77] Whether ICI will be incorporated into CRT for local regionally advanced CC is dependent on the findings of the KEYNOTE-A18 trial, but the role of neoadjuvant ICI remains to be further elucidated.

Ovarian cancer

Rationale for neoadjuvant immunotherapy in ovarian cancer

The SOC for ovarian cancer (OC) is platinum-based chemotherapy followed by maintenance therapy which includes poly (ADP) ribose polymerase inhibitors (PARPi) with or without bevacizumab in tumors with BRCA mutations or homologous recombination deficiency (HRD) and 'may' include PARPi, bevacizumab or close monitoring for tumors without BRCA or HRD. Unlike EC and CC, there is a paradigm of neoadjuvant treatment for front-line OC to improve resectability, and it is followed by additional cycles of adjuvant therapy. Both neoadjuvant and adjuvant are platinum and taxane-based therapies. Based on the strong efficacy of PARPi in the recurrent and front-line settings, especially among tumors harboring BRCA mutations, there is one ongoing trial attempting to replace platinum and taxane therapy with a PARPi in the neoadjuvant setting among BRCA mutated tumors (NCT03943173).[78–80] Unfortunately, in the recurrent setting, responses to monotherapy ICI has been consistently disappointing across a number of studies in OC.[81–83] Attempts to incorporate ICI into front-line SOC carboplatin and paclitaxel±bevacizumab (inclusive of patients dispositioned to neoadjuvant chemotherapy) has been evaluated in the JAVELIN 100 study (avelumab) and IMagyn050 (atezolizumab), neither of which demonstrated a benefit to the addition of ICI to front-line therapy even when adjusted for PD-L1 status.[84 85]

Clinical experience in neoadjuvant trials for cervical cancer and laboratory correlates

There are three completed front-line studies which include the triplet of PARPi, ICI and bevacizumab (NCT03602859; NCT03737643, NCT05116189) which should start reporting results in 2023. A strong signal in the hard-to-treat homologous recombination proficient group would pave a path for inclusion of ICI in front-line therapy inclusive of the neoadjuvant setting but use of ICI as a pure (replacement) neoadjuvant strategy has not yet been studied. A recent GINECO trial evaluated the addition of pembrolizumab to paclitaxel and carboplatin only in a neoadjuvant setting to assess whether pembrolizumab increased resectability at the time of interval surgery. This study did not show any difference with the addition of pembrolizumab.[86] In conclusion, while endometrial and CCs are ready for prime-time immunotherapy clinical trials in the neoadjuvant setting, OC still has a long way to go where the value of current neoadjuvant immunotherapy-based regimens appears to be limited.

Optimization of neoadjuvant immunotherapy in gynecologic malignancies: suggestions for future progress

Given the current and emerging data, the most likely space for ICI neoadjuvant therapy to be successful is in the setting of advanced/metastatic EC with dMMR (table 1). Whether this is converted from just a metastatic/recurrent strategy to a neoadjuvant strategy where responses can lead to local therapy followed by adjuvant treatment has not yet been studied. This is an area of great interest. If replacement of chemotherapy with ICI (either as monotherapy or in combination with lenvatinib) leads to higher and more robust responses, the opportunity to treat metastatic EC more akin to an OC paradigm may result in significantly improved PFS. This would require trials to confirm but is an exciting possibility. In addition, the small study of combination ipilimumab and nivolumab in the advanced/recurrent setting suggests a role for maybe doing the same here. Optimize responses as part of a neoadjuvant strategy followed by local therapy such as surgery or radiation makes sense and then continue with adjuvant therapy. Enthusiasm for incorporation of ICI with and to follow CRT in local regionally advanced CC has waned somewhat given the negative CALLA trial. However, work by Dr Mayadev with translational characterization may demonstrate a more effective sequencing of these interventions and bring neoadjuvant ICI back into focus for this disease type as well. The efficacy of ICI in OC, while of great interest, has not yet materialized for treatment in any setting. Ongoing combination studies in front-line OC, which include patients dispositioned to neoadjuvant chemotherapy, may change this status; however, replacing chemotherapy with ICI in a neoadjuvant therapy has yet to be studied.

HEAD AND NECK MALIGNANCIES

Rationale for neoadjuvant immunotherapy in head and neck cancer

Head and neck cancers are often described by their cause; (1) tobacco/carcinogen associated cancer, typically driven by alterations to the p53 pathway, or (2) HPV associated, driven by alterations in E6 and E7 (online supplemental table 1). These differing etiologies offer an interesting opportunity to study and compare response to immunotherapy in a neoadjuvant setting.

Clinical experience in neoadjuvant trials for head and neck cancer and laboratory correlates

Although EGFR is expressed in over 90% of head and neck squamous cell carcinomas (HNSCC), treatment with cetuximab is only effective in 10%–15% of patients. To explore possible predictive biomarkers response to cetuximab, researchers conducted analysis on samples derived from clinical trial participants treated with cetuximab. They found that an increased number of EGFR-specific T cells correlated with a decrease in tumor size.[87] Patients who responded to cetuximab treatment had higher TCR genotypic richness than non-responders, both before and after cetuximab treatment.[88] Non-responders, however, had an increase of MDSCs[89] and cytotoxic T-lymphocytes-associated protein 4 (CTLA-4)$^{+}$ Treg cells[90] post-treatment compared with baseline.

These biomarker results directed the next neoadjuvant clinical trial involving cetuximab and radiotherapy plus ipilimumab. Two-year PFS and OS reached 72% and 78%, respectively, which is improved over the expected

50% survival in high-risk head and neck cancers (UPCI 12–084).

Additional biomarker studies suggested PD-L1 as a potential target for treatment.[91] As such, Ferris *et al* began looking for TT to use in combination with cetuximab to induce inflammation. Indeed, addition of motolimod (TLR8 agonist) to neoadjuvant cetuximab showed enhanced inflammatory stimulation in the TME.[92] CheckMate 141 demonstrated an increased OS in patients treated with nivolumab over chemotherapy[93]; however, it was unclear why not all of the participants responded to nivolumab. Preclinical studies found that inhibition of the EGFR pathway with cetuximab prevented IFNγ-mediated upregulation of PD-L1.[91] More detailed analysis of the CheckMate 141 responders showed an enhanced response to nivolumab in patients who had not previously been treated with cetuximab,[94] suggesting an importance in timing of such combination therapy. Ongoing studies suggest that concurrent treatment with cetuximab and nivolumab is more successful than treating cetuximab-refractory patients with nivolumab. Although neoadjuvant treatment with nivolumab alone does reduce tumors in 15%–24% of head and neck cancer,[95] the combination of neoadjuvant nivolumab and ipilimumab seems even more promising.[96]

Optimization of neoadjuvant immunotherapy in head and neck malignancies: suggestions for future progress

Table 1 summarizes our recommendations for optimal neoadjuvant trial designs where the intent of neoadjuvant immunotherapy is both therapeutic and translational. Furthermore, window of opportunity trials may have a significant value in moving the field of neoadjuvant immunotherapy forward. A window trial where an experimental therapy is introduced prior to the planned curative surgical resection is a careful balance of benefits and risks in maximizing information gained while ensuring patient safety. This balance is especially critical as window trials are most often conducted in a curative intent patient population. Potential risks include unexpected toxicity delaying or preventing curative surgical resection or causing postoperative complications precluding or affecting the tolerance of SOC adjuvant therapy. Additionally, there is risk of progression during trial treatment which could hamper the ability to provide curative intervention. To reduce these risks there are several important considerations in designing and conducting a window trial. First, patient safety is paramount. As such a drug or combination therapy should have an established tolerated dosage from a phase 1 trial prior to inclusion in a window trial. Additionally, adequate toxicity stopping rules should be included and/or frequent discussions about toxicity during trial should be conducted by the research team. Timing and the length of the intervention must be considered, including the additional lag time for screening and enrollment to the trial. Most window trials in HNSCC have had a systemic intervention of 3–4 weeks (range 1–6 weeks) and there were no delays in the planned surgical resection in most reported trials. Still, window trials should be conducted at centers experienced in multidisciplinary care and clinical trial monitoring, to reduce these risks as much as possible. While these potential risks, without likelihood of direct benefit, can deter patients from enrolling, trials discussed in this review highlight the feasibility of single arm or randomized trials with modest sample sizes (median 31 patients). The primary endpoints in most window trials are biomarker or safety based. These endpoints are typically most feasible and in line with the goals of a window trial. If appropriate, pre and post imaging for response correlation and peripheral blood samples should also be collected. Given the limitations of in vitro and in vivo experiments in mouse models, a major advantage of a window trial is the ability to examine the effect of the therapeutic intervention, with pre-therapy and post-therapy tissue samples, directly in patients. Towards the goal of being able to decipher the effect of a therapeutic intervention, having a control or comparator arm is important. If no drug is appropriate for comparison, then placebo can be used. Alternatively, a randomized design can be used whereby a portion of the patients go right to surgery, so this pathologic specimen can be used as a control without risking progression on placebo. We favor the latter design rather than having a placebo arm. The window trial is especially important in the era of immunotherapy. Currently both pembrolizumab and nivolumab are approved in recurrent/metastatic HNSCC after failure of platinum-based chemotherapy. Nivolumab, for example, significantly improved OS compared with TPC in a randomized phase 3 trial.[93] While this is the first drug in a randomized trial to ever prolong OS in recurrent/metastatic disease after platinum failure, response rate was only 13% with an additional 20% achieving stable disease. Therefore, most patients will progress and not benefit from single agent anti-PD-1 monoclonal antibody therapy. With a seemingly infinite number of possible immuno-oncology (IO) combinations, validation of proposed mechanisms of action and synergy, and biomarker selection of patients will be critical to determining which combinations to move forward into a phase 3 trial, and ultimately to be able to select a combination most likely to benefit each individual patient. There are several immunotherapy-based window of opportunity trials in HNSCC currently enrolling (NCT02919683, NCT02002182, NCT03618654). As the oncology field continues to work towards a more personalized approach to treatment, both with immunotherapy and TT, window of opportunity trials will continue to become even more important for guiding appropriate combinations and biomarker driven clinical trial design.

NON-SMALL CELL LUNG CANCER

Rationale for neoadjuvant immunotherapy in non-small cell lung cancer

For the last two decades perioperative chemotherapy, either as neoadjuvant or adjuvant therapy,[97–101] has been the SOC for resectable stage II–IIIA NSCLC (online supplemental table 1).[102] However, with an absolute survival benefit of 5.4% at 5 years compared with no chemotherapy,[103] much more need to be done for

patients with NSCLC. Also, while some patients with molecularly-defined NSCLC do benefit from TT, notably adjuvant osimertinib for EGFR-mutated lung cancer, most patients have NSCLC tumors that lack targetable alterations. Therefore, within the past 5 years thoracic oncologists have tried to determine whether immunotherapy, which has shown positive outcomes in other cancers such as melanoma, could also benefit patients with resectable NSCLC.

Clinical experience in neoadjuvant trials for cervical cancer and laboratory correlates

Results from the KEYNOTE-024[104] studies led to the US FDA approval of first-line pembrolizumab treatment of patients with metastatic NSCLC tumor expressing PD-L1.[105] Similarly, the CheckMate 017 and 057 trials led to the US FDA approval of nivolumab for treatment of squamous and non-squamous NSCLC that has progressed during or after platinum-based chemotherapy.[106] These studies encouraged Forde *et al* to lead a phase 2 neoadjuvant trial testing nivolumab in adults with untreated, surgically resectable early-stage NSCLC.[107] They showed that nivolumab-induced MPR in 45% of resected tumors (compared with an average of 20% usually observed with chemotherapy[99]) without delaying surgery and with few side effects. It is important to note here that for NSCLC, MPR is being studied as a possible surrogate endpoint for OS and has been shown in retrospective analyses to correlate with long-term survival.[99 108] In the meantime, several other phase 2 trials with neoadjuvant immunotherapy (anti-PD-1, anti-PD-L1 or anti-CTLA-4) showed MPR and pCR rates of 20%–45% and 8%–29%, respectively.[107 109–112] Since then, phase 3 trials of neoadjuvant chemotherapy plus PD-1/PDL-1 inhibitors (pembrolizumab, atezolizumab, nivolumab, or durvalumab) have been launched. Four trials, NCT04025879/CheckMate77T,[113] KEYNOTE-671,[114] AEGEAN,[115] and IMpower030[116] are ongoing and one more has reported results for both primary endpoints, CheckMate 816.[117] The CheckMate 816 trial evaluated, in the neoadjuvant setting, nivolumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone in newly diagnosed patients with resectable stage IB to IIIA NSCLC. In the intent-to-treat population, adding nivolumab to chemotherapy significantly increased the pCR from 2.2% to 24% (2.8% to 25.7% in primary tumor only). Additionally, in patients who completed resection, the addition of nivolumab to chemotherapy increased the pCR from 3.2% to 30.5%. Of note, 17% of patients who received nivolumab plus chemotherapy underwent pneumonectomy compared with 25% with chemotherapy alone. The MPR rate in patients who went on to surgery was also improved with nivolumab plus chemotherapy (46.8%) versus chemotherapy alone (12.7%). No significant difference in the magnitude of pCR benefit with the addition of nivolumab was observed based on PD-L1 status and tumor mutational burden, cancer stage, or squamous versus non-squamous cancers. Finally, the addition of nivolumab did not appear to increase all-cause AEs. In March 2022, the FDA approved the combination of nivolumab plus chemotherapy as neoadjuvant therapy for resectable NSCLC that measures 4 cm or greater and/or is node positive.

The neoadjuvant setting provides investigators with the opportunity to conduct correlative studies comparing tissues before and after treatment. In their phase 2 nivolumab neoadjuvant study Forde *et al* observed that following treatment tumor tissues were heavily infiltrated with CD8 +cytotoxic T cells.[107] Additionally, analyzing tumor tissues before and after treatment demonstrated a correlation between the depth of pathological response overall and the number of non-synonymous mutations. Finally, they showed that early circulating tumor DNA (ctDNA) dynamics predicted pathological response to neoadjuvant nivolumab.[118] Interestingly, the same authors in their phase 3 study CheckMate 816 showed that ctDNA was more likely to clear when nivolumab was given with chemotherapy (56%) versus chemotherapy alone (34%). Additionally, pCR was more likely to be achieved with clearance of ctDNA (pCR=46% in patients with ctDNA clearance vs 13% in those without it). Furthermore, patients with pCR and clearance of ctDNA were more likely to have surgical resection. Finally, it has recently been shown that analyzing the transcriptional programs of mutation-associated neoantigens-specific TILs in NSCLC could provide important insights for overcoming resistance to PD-1 blockade.[119]

Optimization of neoadjuvant immunotherapy in NSCLC: suggestions for future progress

PD-1 pathway blockade has rapidly become a mainstay of management of advanced NSCLC with multiple agents and regimens approved in the first-line setting (table 1). In contrast development of novel therapies in earlier stage resectable NSCLC has evolved much more slowly despite historically poorer outcomes after surgical resection than other common cancers. This is partly due to the long follow-up needed to demonstrate benefit in adjuvant therapy clinical trials. Neoadjuvant immunotherapy has shown safety, feasibly and preliminary efficacy in multiple phase 1 and 2 NSCLC trials. The relatively high rates of MPR and pCR reported in those studies compared with historical data with chemotherapy have led to the adoption of pCR as a co-primary endpoint for several ongoing neoadjuvant chemotherapy±PD-L1 blockade phase 3 trials. One of these studies (CheckMate 816) has reported a significant increase in pCR and EFS with the addition of neoadjuvant nivolumab to chemotherapy. Other studies are ongoing, however, notably CheckMate 816 is the only phase 3 trial where no adjuvant IO is administered.

Neoadjuvant chemoimmunotherapy has the potential to offer an early read out in terms of pCR as well as providing benefit for more locally advanced stage II and IIIA tumors. At present neoadjuvant combination immune checkpoint blockade (eg, anti-PD-1 plus anti-CTLA-4) is not being explored in the phase 3 setting

in NSCLC; however, phase 2 studies of novel IO combinations with chemotherapy are underway. Given the high pCR rates reported with chemotherapy plus PD-1 blockade, it is likely that chemotherapy will continue to have a role to play in the neoadjuvant setting.

CONCLUSION

Neoadjuvant systemic therapy has transformed the care of patients with locally and regionally advanced solid malignancies including disease control, organ preservation and improved outcome. However, derived benefits continue to be limited and there is a need to take advantage of emerging immunotherapeutic agents that have transformed the care of many advanced malignant tumors. Immunotherapy involving ICI as monotherapy and combinations has conferred promising results in early neoadjuvant trials of several malignancies and has become part of the SOC for some tumors including melanoma. Ongoing neoadjuvant trial efforts are accelerating at a rapid pace taking advantage of an ever-expanding armamentarium of novel immunotherapeutic agents that are bound to make significant improvements in the care of our patients.

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