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Facts and Hopes in Neoadjuvant Immunotherapy: Current Approvals and Emerging Evidence

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Abstract

In 2021 and 2022, two immune checkpoint inhibitors received FDA approval in the neoadjuvant setting for the treatment of early-stage triple negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC). Several more studies have since indicated the benefits, and challenges, of administering neoadjuvant immunotherapy prior to definitive surgery in the gastrointestinal, head and neck, and cutaneous realms. Additionally, numerous ongoing phase 2 and phase 3 trials are investigating outcomes of neoadjuvant immune treatment in early-stage disease. As such, it is anticipated that more immune checkpoint inhibitors will receive approval for various neoadjuvant indications in the next several years. Medical oncologists, surgeons and other providers in a multi-disciplinary cancer care team will be presented with alternate treatment paradigms and clinical decisions regarding upfront surgery versus neoadjuvant treatment. Here, we describe the current evidence supporting use of immune checkpoint inhibitors for neoadjuvant treatment, ongoing studies, and clinical considerations of this treatment approach.

Introduction

Monoclonal antibody immune checkpoint inhibitors targeting CTLA-4, PD-1 and PD-L1 have transformed treatment paradigms for metastatic disease. A multitude of clinical trials aim to refine the use of immunotherapy beyond the metastatic setting—including as neoadjuvant treatment for earlier stage disease. In 2021, pembrolizumab, in combination with chemotherapy, was approved for neoadjuvant treatment of triple negative breast cancer (TNBC)(1). In 2022 nivolumab was approved in the neoadjuvant space for non-small cell lung cancer (NSCLC) (2). Concurrently, several studies have demonstrated the benefits, and potential complications, of neoadjuvant immunotherapy across other tumor types. Over 180 clinical trials worldwide investigating neoadjuvant immunotherapy are currently recruiting patients. In the near future, we anticipate the application of immunotherapy to evolve even further in the neoadjuvant space and redefine curative approach treatment. Here, we review the current evidence surrounding neoadjuvant immunotherapy.

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Conflicts of Interest

E.E.W.C. is an employee of Tempus Labs; consultant for Adagene, Astellas,Cidara, Eisai, Genmab, Gilboa, iTeos, EliLiily, MSD, Merck, NectinTx, Novartis, Nykode, Pangea Therapeutics, PCI Biotech,Replimune, Roche, Soteria, Viracta; and stockholder in KinnateBiopharma and PrimmuneTherapeutics. P.V. has no disclosures to report.

Pathophysiology

The Programmed Death 1 checkpoint (PD-1) is transcriptionally activated and expressed on the surface of activated T-cells. The Programmed Death 1 checkpoint ligand (PD-L1) is upregulated on tumor cells via oncogenic signaling and cytokine release in the tumor microenvironment (TME). This interaction between PD-1 and PD-L1 enables tumor cells to evade immune elimination. Although mechanistically distinct, the immune checkpoint receptor cytotoxic T lymphocyte antigen 4 (CTLA-4) similarly downregulates immune responses against tumor cells. The blockade of these two pathways is the premise underlying cancer immunotherapy (3).

Importantly, blockade efficacy relies on facilitating T-cell to tumor cell interactions that generate tumor-specific cytotoxic T-cells. In contrast to neoadjuvant chemotherapy, in which the intent is to debulk tumors for improved surgical feasibility, neoadjuvant immunotherapy is hypothesized to take advantage of the active TME while the bulk of the tumor is in place rather than solely targeting micrometastatic disease after surgical debulking (4). This enables more robust T-cell priming which then exerts a systemically sustained effect post-operatively. Pre-clinically, this phenomenon was observed in TNBC mice models: neoadjuvant anti-PD-1 therapy yielded better long-term survival, even when surgery was performed the same day (5).

Overview by cancer type

Triple Negative Breast Cancer (TNBC)

The KEYNOTE-522 trial which established the efficacy of neoadjuvant pembrolizumab in combination with chemotherapy in early stage TNBC enrolled 1174 patients with previously untreated Stage II-III disease (6). Patients were randomized to either receive neoadjuvant anti-PD1 immunotherapy with pembrolizumab and chemotherapy or four cycles of placebo with the same cytotoxic treatment. Patients then underwent definitive surgery and received either pembrolizumab or placebo adjuvantly. Primary endpoints were pathological complete response (pCR) rate and event free survival (EFS). The rate of pCR at time of surgery in patients receiving neoadjuvant immunotherapy with chemotherapy was 64.8% compared to 51.2% in those receiving placebo with chemotherapy (95% CI, 5.4–21.8; $p < 0.001$). Follow up analysis showed EFS at 36 months to be 84.5% (95% CI, 81.7–86.9) in the immunotherapy with chemotherapy arm and 76.8% (95% CI, 72.2–80.7) in the placebo with chemotherapy arm (7). Treatment related adverse events occurred mostly in the neoadjuvant phase, with 76.8% of patients experiencing Grade 3 events. This led to a discontinuation of the drug in 23.3% of patients; however, it was not specified how many patients had delay in surgery or surgical complications. Of note, the KEYNOTE-522 trial showed benefit of pembrolizumab in patients with varying PD-L1 expression status.

The phase 3 IMpassion031 trial, in contrast, studied the impact of the anti-PDL1 agent atezolizumab: in 333 patients with early-stage TNBC, the addition of atezolizumab to standard of care chemotherapy in the neoadjuvant setting regardless of PD-L1 status yielded a pCR rate of 58% (95% CI 50–65) compared to 48% (95% CI 34–49) with the addition of placebo to chemotherapy (8). This trial was a follow up to the IMpassion130 trial which

showed progression free survival (PFS) and overall survival (OS) benefit of atezolizumab; however the IMpassion130 study did show a distinction between patients rendered positive for PD-L1 (9). Approximately 63% in the immunotherapy arm had grade 3–4 adverse events. As with KEYNOTE-522, this study did not specify whether there were surgical delays or complications.

Smaller studies have investigated various combinations of cytotoxic chemotherapy with immunotherapy. The NeoTRIP Michelangelo, which enrolled 280 patients with TNBC and combined atezolizumab with a non-anthracycline backbone of nab-paclitaxel and carboplatin, did not show a statistically significant difference in the secondary endpoint of pCR in the intention to treat population, although the rate of pCR was noted to be higher in patients with PD-L1 positive disease (10). Data regarding the primary endpoint of EFS is forthcoming. A smaller, open label phase 2 study consisting of 67 patients with early stage TNBC again investigated the pCR rate when adding atezolizumab neoadjuvantly to a non-anthracycline backbone and did indeed find statistically significant difference in pCR rate of 55% in the immunotherapy arm versus 18% in the chemotherapy alone arm (11). Results from the GeparNuevo study, a phase 2 study which enrolled 174 including some with Stage 0 and Stage I disease, suggested that the addition of the immune checkpoint inhibitor durvalumab only yielded a benefit when given two weeks prior to neoadjuvant chemotherapy (12). Early results from the phase 2 BELLINI trial compared immune responses in CD8+ T-cell populations and IFN-gamma signatures with radiologic response in patients with early-stage TNBC receiving anti-PD1 alone or in combination with anti-CTLA, suggesting the potential of de-escalating chemotherapy (13). These studies and additional ongoing studies provide hope regarding our ability to refine the combinations and timing of how immunotherapy is administered in the neoadjuvant setting in early stage TNBC (14). However, we caution against cross-trial comparisons, particularly between anti-PD-1 and anti-PDL1 agents as well as timing of immunotherapy, especially when much of the available data regarding biomarkers and antitumor immune response is in progress.

Non-Small Cell Lung Cancer (NSCLC)

The role of immunotherapy in NSCLC in the adjuvant setting has been clearly established (15–17). Recent approvals for neoadjuvant nivolumab with platinum-doublet chemotherapy were based on the phase 3 CheckMate 816 trial which enrolled 358 patients randomized to receive either neoadjuvant nivolumab with chemotherapy or chemotherapy alone prior to resection (18). Median EFS with neoadjuvant nivolumab in conjunction with chemotherapy was 31 months, while that with chemotherapy alone was 20.8 months (HR for progression of 0.63, 97% CI 0.43–0.91). The 179 patients in the combination arm had a pCR rate of 24.0% versus 2.2% in the chemotherapy alone arm (OR 13.94, 99% CI 3.49–55.75, $p<0.001$). Adverse events delayed surgery in 3.4% of the combination arm and 5.1% of patients receiving chemotherapy alone. Surgical complications were similar between the two. Subgroup analysis did not reveal a difference was noted between squamous and non-squamous histology.

The phase 3 NADIM trial demonstrated similar efficacy with neoadjuvant nivolumab in resectable disease (19). Forty-six patients with Stage IIIA NSCLC received three cycles of

nivolumab with carboplatin/paclitaxel prior to resection, followed by one year of adjuvant nivolumab. PFS at 24 months was 77.1% Neoadjuvant treatment did not result in surgical delays or complications. In the 41 patients who did undergo surgery, 34 had MPR, of whom 26 had a pCR.

Dual checkpoint blockade with neoadjuvant nivolumab plus ipilimumab versus nivolumab alone was the focus of the 2021 phase 2, which enrolled 44 patients, and measured MPR as the primary endpoint. (20). Patients received neoadjuvant nivolumab or nivolumab with ipilimumab followed by surgery. The dual checkpoint blockade group had an MPR rate of 38% and pCR of 38%, while those with nivolumab alone had an MPR rate of 22% and pCR of 10%.

In June 2023, the randomized, double-blind phase 3 KEYNOTE-671 was published (21). 379 patients with resectable NSCLC were randomized to receive four cycles of either neoadjuvant pembrolizumab or placebo with cisplatin-based chemotherapy followed by surgery and then adjuvant pembrolizumab or placebo for 13 cycles. Primary endpoints included EFS and OS and secondary endpoints included pathological response and safety. At 24 months, EFS was 62.4% in the pembrolizumab group and 40.6% in the placebo group (HR for progression 0.58, 95% CI 0.46–0.72, $p<0.0001$). The 24 month OS was 80.9% in the pembrolizumab group and 77.6% in the placebo group, but this did not meet statistical significance. In patients receiving pembrolizumab, pCR was seen in 18.1% and MPR in 30.2%, while 4% of those receiving placebo had pCR and 11% had MPR. Of note, as in Checkmate-816, subgroup analysis did not reveal a distinction between squamous and non-squamous histology. These results are also supported by preliminary findings of the perioperative AEGEAN and NEOTORCH trials (22,23).

Head and Neck Squamous Cell Carcinoma (HNSCC)

Standard of care treatment for early head and neck squamous cell carcinoma (HNSCC) entails a multimodal approach with surgery and radiation. Induction chemotherapy is offered to patients for debulking and symptoms, but does not confer a significant PFS or OS benefit (24,25). Trials have investigated whether neoadjuvant immunotherapy will yield different outcomes. In a nonrandomized, phase 2 trial of 36 patients with human papilloma virus (HPV)-negative Stage III-IVb HNSCC, one dose of neoadjuvant pembrolizumab was administered prior to surgery. Patients received subsequent postoperative chemoradiation per standard of care. Forty-four percent of patients had a pathological response, but 0% of patients had pCR. Eighteen patients with high-risk pathology had a one-year relapse rate of 16.7%. There was a positive correlation between PD-L1 protein expression and pathologic response. There were no adverse events that resulted in surgical delays or complications (26). A phase 2 trial assessed the primary endpoints of safety and volumetric response with secondary endpoints of pathological response, objective response, PFS and OS. Twenty-nine patients with locally advanced HNSCC (not stratified by HPV status) were randomized to receive either two cycles of nivolumab alone or two cycles of nivolumab in combination with ipilimumab as neoadjuvant treatment, followed by surgery with initially planned resection margins regardless of clinical response. Adjuvant treatment was offered per standard of care if patients had positive margins or extranodal extension. Restaging scans

after cycle 1 of treatment showed a volumetric response rate of 50% with nivolumab alone and 80% with combination treatment. Eleven patients did not have response, 3 of whom had growth in tumor. Adjuvant treatment was administered to 19 patients (65%) with one year PFS and OS rates of 85% and 89% (27). The IMCISION, non-randomized phase Ib/IIa trial enrolled 32 patients with HNSCC who were then treated with two cycles of either nivolumab monotherapy or two cycles of nivolumab with a single dose of ipilimumab. The study met the primary end point of feasibility to resect no later than week 6. MPR was assessed in 29 of 32 trial patients, showing a 35% response rate in the combination arm and 17% in the nivolumab alone arm. At 24 month follow up, none of the patients with MPR had recurrence (28). In the largest trial thus far, 92 patients with HPV-negative Stage T3-T4 HNSCC received one cycle of neoadjuvant pembrolizumab 1–3 weeks prior to surgery followed by radiotherapy with concurrent pembrolizumab for six cycles if they had high risk features. Patients with a pathologic response had improved one year disease free survival (DFS) of 92% versus 72% (HR 0.29, 95% CI 11–79%). Surgical wound complications were reported in 36% of patients, although it was not specified if this was thought to be secondary to immunotherapy (29).

Colon and Rectal Cancer

Locally advanced rectal cancer is currently treated with neoadjuvant chemotherapy with fluoropyrimidine and oxaliplatin, followed by definitive chemoradiation or surgery (30,31). Radiation and surgery leave patients with lasting bowel dysfunction and other side effects that impact quality of life (32). Additionally, tumors that are mismatch-repair deficient sometimes respond poorly to this treatment approach (33). Thus, efforts have been made to identify treatment approaches that more effectively treat mismatch-repair deficient (dMMR) tumors, which are known to respond to immune checkpoint blockade in the metastatic setting, and limit intervention with lasting toxicity (34). The NICHE study first investigated a neoadjuvant approach in both dMMR and proficient MMR (pMMR) colorectal tumors and demonstrated that four weeks of ipilimumab and nivolumab treatment prior to surgery resulted in a 100% pathological response rate in dMMR tumors and 27% in pMMR tumors (35). Biomarker analysis revealed that CD8+PD-1+ T cell infiltration predicted response in pMMR tumors, and even tumors that did not respond to neoadjuvant therapy showed evidence of immune activation. Findings of the NICHE study were a gateway to further optimization of neoadjuvant treatment in colorectal cancer. In 2022, a phase 2 study showed six months of treatment with the PD-1 inhibitor dostarlimab yielded a 100% complete response rate in 12 patients with mismatch-repair deficient locally advanced rectal cancer, with response exceeding 6 months (36). No patient underwent chemoradiotherapy or surgery. Of all neoadjuvant immunotherapy studies published thus far, this was the first to forgo definitive treatment after complete response.

Cutaneous Squamous Cell Carcinoma (CSCC)

Cutaneous squamous cell carcinoma (CSCC) can be particularly disfiguring with standard of care treatment of resection and radiation. In 2018, cemiplimab was approved for treatment of unresectable CSCC(37). Since, a pilot phase II trial consisting of 20 patients with newly diagnosed or recurrent Stage II-IVA CSCC of the head and neck received two cycles of neoadjuvant PD-1 inhibition. Fifteen patients (75%, 95% CI 50.9–91.3) had pCR and 6

patients had partial response (30%, 95% CI 11.9–54.3). The 12 month DFS was 89.5% (95% CI, 76.7–100) (38). Patients with pCR did not undergo adjuvant radiation and at a median follow up of 34.5 months, none of these patients had developed recurrence (39). In 2022, Gross et all published a multicenter, nonrandomized confirmatory phase 2 trial which enrolled 79 patients with Stage II-IV CSCC (40). pCR was observed in 51% of patients (95% CI 39–62) and a MPR was seen in 13% of patients (95% CI 6–22). Nine of the 79 patients did not undergo surgery as three declined treatment after having a partial response, one was lost to follow up and one died from a non-treatment related cause. Of note, two patients did progress on cemiplimab and their disease was deemed inoperable. Biomarker analysis was not available for all patients enrolled in the study, but in 56 patients who could be assessed for PD-L1 tumor proportion score (TPS), the percentage of patients with pCR was higher in those who were PD-L1 positive. In 50 patients with available data, tumor mutational burden (TMB) was higher in those who had pCR.

Melanoma

Since adjuvant immunotherapy has changed treatment paradigms in resectable melanoma, multiple studies have since investigated the role of immunotherapy in the neoadjuvant space (41–43). Amaria and colleagues in 2018 published a study of 23 patients with Stage III disease in which patients received either neoadjuvant nivolumab alone or in combination with ipilimumab; however, although the combination group had 73% ORR, accrual was stopped early due to early observation of surgery-precluding disease progression in the monotherapy arm (44). Additionally, patients in the combination arm had a 73% rate of grade 3 adverse events. The phase 1B OpACIN study was a 20 patient study in which patients were randomized to receive ipilimumab and nivolumab in either the adjuvant only or in both the neoadjuvant and adjuvant settings. All patients undergoing neoadjuvant immunotherapy underwent surgery, but with 90% of patients having grade 3–4 adverse events. pCR was 78% in patients treated in the neoadjuvant arm with no relapse at median follow up of 25.6 months (45). Subsequently, the phase 2 OpACIN-neo trial aimed to identify the optimal combination of ipilimumab and nivolumab combination with the conclusion that the most tolerable neoadjuvant dosing schedule to be ipilimumab 1 mg/kg with nivolumab 3 mg/kg—distinct from the initial study with ipilimumab 3 mg/kg and nivolumab 1 mg/kg(46). After four years, none of the patients with pCR had relapsed (47). Another study investigated the effect of a solitary dose of pembrolizumab 3 weeks prior to surgery(48). In 8 of 27 patients treated with pembrolizumab, pCR or MPR was seen with no adverse effects that precluded surgery. Long-term follow up of this trial revealed all 8 patients with pCR or MPR were alive at a median follow up of 61.9 months, with 2 of the eight having a recurrence at a median time of 3.9 years. In those without MPR or pCR, 5 year OS was 72.8%(49).

SWOG S1801 is the largest study to date to test the neoadjuvant hypothesis in melanoma(50). The phase 2 multicenter trial randomized 313 patients to receive either neoadjuvant-adjuvant pembrolizumab or adjuvant only pembrolizumab for a total of 18 cycles. EFS, the primary endpoint, at 2 years was 72% (95% CI 64–80) in the neoadjuvant-adjuvant group and 49% (95% CI 41–59) in the adjuvant only group. Approximately 21% of patients had pCR and 47% had radiographic response. Of the 17 patients in the neoadjuvant-

adjuvant arm who did not undergo surgery, 12 had disease progression, 1 had toxic effects, and one declined after clinical response. The remainder either withdrew consent or had a coexisting condition that precluded surgery. The results of this trial are promising; however, we do not have yet have long term outcomes. Additionally, across all melanoma trials described here, further data on both biomarker analysis and BRAF mutation is needed. The ongoing NeoPele study is investigating combination neoadjuvant pembrolizumab with lenvatinib in advanced melanoma and the ongoing phase 3 NADINA trial is investigating neoadjuvant ipilimumab with nivolumab with adjuvant nivolumab (51,52).

Muscle Invasive Bladder Cancer (MIBC)

The 2019 phase 2 ABACUS trial, performed to investigate alternate treatments in patients with muscle invasive bladder cancer (MIBC) not eligible for standard of care neoadjuvant chemotherapy, found that administration of neoadjuvant atezolizumab yielded a 31% pCR(53). Of note, over 60% had surgical complications, but there were no delays in surgery. The PURE-01 study aimed to assess the efficacy of neoadjuvant pembrolizumab prior to radical cystectomy(54). Conducted in Europe, the rationale for this study was also to identify an alternative systemic treatment in patients who were ineligible for cisplatin (55). Fifty patients enrolled in the in the PURE-01 with cT<3bN0 MIBC underwent three cycles of neoadjuvant pembrolizumab. The study met the primary endpoint of pathologic complete response, with 21 patients categorized as pT0 post-cystectomy (42%, 95% CI 28.2%−56.8%). No patients had a delay in surgery due to systemic treatment toxicity. Biomarker analysis was a secondary endpoint and it was found that patients with PD-L1 CPS > 10% were more likely to have pCR than those with PD-L1 CPS < 10%. In the single arm NABUCCO trial published two years after PURE-01, 24 patients with Stage III urothelial cancer received two dose of combination ipilimumab and nivolumab prior to resection (56). One patient had a delay in surgery due to immune-mediated hemolysis; however 23 of the 24 underwent resection and the primary endpoint of feasibility to resection was met. Of the 24 patients, 11 (46%) had pCR. This trial demonstrated the potential efficacy of combination checkpoint blockade.

Insights

Although the trials discussed here are primarily phase 1 and phase 2 trials (Table 1) and only two drugs have FDA approval for this indication, we have gained key insights from emerging evidence. First, many of the discussed trials use pCR as an endpoint and long-term data is not yet available in any one tumor type to comment on overall survival. Data remains mixed on the correlation between pathologic complete response and overall survival. In breast cancer, a large retrospective analysis of 1,731 patients with breast cancer showed that pCR was associated with 0.36 time the risk of death regardless of hormone receptor status (57). Other studies have demonstrated mixed outcomes across non-immunotherapy neoadjuvant treatment in various tumor types (58–60). However, given the long period of time needed to acquire survival data, pathologic response may be our best short-term indicator of survival outcomes which will lead to faster drug approvals. In light of some promising data in NSCLC, proposals have been made to accept pCR and MPR as surrogate endpoints for overall survival (61). Whether this principle can be applied across every tumor

type, stage of disease, and treatment category remains unknown. Future, phase 3 trials will need to identify appropriate endpoints, including overall survival, which will be the ultimate determinant of the adoption of a neoadjuvant immunotherapy approach as standard of care.

Furthermore, data regarding biomarkers will inform patient selection and further treatment pathways. Some of the later trials reviewed here published data regarding biomarker analysis, while other larger ones such as SWOG S1801 have collected data regarding PD-L1 status and TMB to be published at a later date(50). One systemic review and meta-analysis including 10 studies and 461 NSCLC patients found that patients receiving neoadjuvant treatment with PD-L1 expression >1% were more likely to have pCR and MPR(62). In squamous NSCLC, PD-L1 and TMB have not correlated with overall survival(63). The most robust evidence regarding biomarkers lies in IFN-γ signatures. In melanoma mice models, blockade of type I interferon reduces long term survival after neoadjuvant anti-PD-1+anti-CD137 immunotherapy(64). In clinical studies, it has been demonstrated that patients categorized to have a higher IFN-γ score as defined by a preset 10 gene algorithm, were more likely to respond to neoadjuvant therapy(47). The DOMINI study, a phase 1b study, demonstrated that adding domatinostat, a class 1 histone deacetylase inhibitor previously shown to increase IFN-γ response in preclinical models, to combination of neoadjuvant PD-L1 and CTLA-4 blockade in Stage III melanoma is feasible, albeit dose escalation was limited by skin toxicity (65,66). The trial further showed that IFN-gamma signatures scores were associated with response to neoadjuvant treatment (67).

Overall, it appears that the most robust responses would be expected in those patients whose tumors are positive for defined predictive biomarkers. Larger, randomized control trials with more robust biomarker analysis on IFN-γ, as well as PD-L1, TMB and, on patients who progress during immunotherapy would also be informative in determining which patients do not benefit from neoadjuvant treatment and should proceed directly to surgery.

Lastly, current evidence suggests the potential of treatment de-escalation. The purpose of neoadjuvant chemotherapy was to debulk the tumor for improved surgical outcomes, as in cases of TNBC where breast-preserving surgery was made possible by early systemic treatment (68,69). However, with the responses seen across the neoadjuvant trials discussed here and the potential of immunotherapy to have a lasting effect, it seems feasible to de-escalate treatment by forgoing definitive intervention. In rectal cancer, it has already been demonstrated that a watch and wait approach after neoadjuvant chemotherapy may be appropriate (70). This approach was already illustrated in CSCC trials in which adjuvant radiation was not given to patients with pCR after neoadjuvant immunotherapy(40). Although not currently standard of care at this time, long term data will inform if this treatment approach is judicious.

Conclusions

Emerging evidence in the neoadjuvant immunotherapy space strongly suggests a forthcoming paradigm shift in treatment of early-stage solid tumors. Data presented here demonstrate high rates of response with largely tolerable toxicities. Limitations of many of the trials reviewed here include use of surrogate endpoints, inconsistency in identifying

patients with surgical delays or complications, and sparse biomarker analysis. Even with current data, a neoadjuvant approach gives hope that effective cures can be conferred across many early-stage tumor types without surgical intervention or radiation. With over 180 neoadjuvant immunotherapy clinical trials in progress worldwide, many of these questions regarding survival benefit, optimal dosing, biomarker analysis and de-escalation of therapy will be answered.

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Table 1.

Select Neoadjuvant Immunotherapy Trials

Trial/Year	Tumor Type	Phase	No.	1° Endpoint	Intervention	Results	Surgical Delay/ Complication Data	Biomarker Analysis
KEYNOTE 522 2020(6)	TNBC	3	1174	pCR EFS	Pembrolizumab + chemotherapy v placebo + chemotherapy	pCR 64.8% in IO arm v 51.2% in placebo arm 18 mo EFS HR 0.63	No	Yes; 20% difference in PDL1 +/− subgroups, but benefit seen in both groups
IMpassion031 2020(8)	TNBC	3	333	pCR in all-randomized and PDL1+ subgroup	Atezolizumab + chemotherapy v placebo + chemotherapy	pCR all randomized: 17% rate difference (95% CI 6–27; p=0.0044) pCR in PDL1+: 20% rate difference (95% CI 4–35; p=0.02)	No	Yes; pCR in PDL1+ is co-primary endpoint; PDL1+ pCR 53/77 (69%, 9% CI 57–79) in experimental arm; 37/75 (49%, 38–61) in placebo + chemo arm
NeoTRIP Michelangelo 2022 (10)	TNBC	3	280	EFS Secondary endpoint: pCR	Non-anthracycline chemotherapy +/− atezolizumab	EFS follow up ongoing pCR: OR 1.18 (95% CI 0.74–1.89, p 0.48); did not reach statistical significance	Disease progression in 8 patients	Yes; 7.6% increase in pCR in PDL1+ disease (OR 2.68, 1.64–2.65, p<0.0001)
Ademuyiwa et al 2022 (11)	TNBC	2	67	pCR TIL percentage	Chemotherapy +/− atezolizumab	pCR: 36.8% treatment difference in IO + chemo arm (95% CI 8.5–56.6%, p=0.018)	No data	Yes; pCR increase in both PDL1 + and – patients TIL percentages higher in IO arm
GeparNuevo 2022 (12)	TNBC	2	174	pCR	Durvalumab v placebo 2 weeks prior to chemo, then durvalumab v placebo x 12 weeks, with nab-paclitaxel followed by durvalumab v placebo alone	pCR: effect seen in window group. OR 2.22, 95% Ci (1.06–4.64, p=0.035)	99% of patients underwent surgery, no data on surgical complications	Yes; Higher pCR rate with higher sTILs in both arms; trend toward higher pCR in PDL1 +
CheckMate 816 2022 (18)	NSCLC	3	358	EFS pCR	Nivolumab + platinum-based chemotherapy v. chemotherapy alone	Median EFS 31.6 mo in neoadjuvant IO arm v 20.8 in chemo arm (HR 0.63; 97.38% CI 0.43–0.91, p=0.0005) pCR 24% in NA-IO arm, 2.2% in chemo arm (OR 13.94, 99% CI 3.49–55.75, p<0.001)	Surgery delayed in 3.4% of patients receiving nivo and 5.1% of patients receiving chemo alone	Yes; ctDNA clearance higher in those receiving IO. EFS longer in patients with ctDNA clearance
NADIM 2022 (19)	NSCLC	2	46	PFS at 24 months	Nivolumab + carboplatin/paclitaxel	24 month PFS 77.1%	No surgery delays	Yes; no significant associations with PDL1 and TMB. Reduced PFS with *STK11, KEAP1, RB1, EGFR*

Trial/Year	Tumor Type	Phase	No.	1° Endpoint	Intervention	Results	Surgical Delay/ Complication Data	Biomarker Analysis
NEOSTAR 2021 (20)	NSCLC	2	44	MPR	Nivolumab alone v Nivolumab + ipilimumab	MPR in combo group: 38% MPR in nivo arm: 22%		
KEYNOTE 671 2023 (21)	NSCLC	3	797	EFS OS	Perioperative treatment. Chemo + pembrolizumab v placebo x 4 cycles, surgery, adjuvant pembrolizumab v placebo	24 mo EFS: 62.4% in pembro group, 40.% in placebo group (HR 0.58, CI 0.46–0.72, p<0.001) 24 mo OS: 80.9% in the pembro arm, 77.6% in the placebo group (p=0.02)	3.8% of patients in pembro arm and 6.5% of patients in the placebo group did not undergo surgery due to progression of disease	Yes; higher PD-L1 expression with lower HR for progression, recurrence cand death; but all subgroups benefitted
Uppaluri et al 2020 (26)	HNSCC	2	36	AEs Pathologic tumor response	Pembrolizumab	AEs: no Grade 3–4 AEs prior to surgery pTR-2 in 22% and pTR01 in 22%	No surgical delays/ complications	Yes; positive correlation between pTR and PDL1 expression
Schoenfeld et al 2020 (27)	HNSCC	2	29	Safety Volumetric response	Nivolumab monotherapy v nivolumab + ipilimumab	Safety: Gr 3–4 irAEs in 2 nivo patients and 5 nivo+ipi patients Volumetric response nivo: 50% Volumetric response nivo + ipi: 53%	No surgical delays	Yes; PDL1 did not correlate with volumetric or pathologic response
IMCISION 2021 (28)	HNSCC	1b/2a	32	Feasibility to resect no later than week 6 (phase 1b) Primary tumor pathological response (phase 2a)	Nivolumab monotherapy; nivolumab + ipilimumab	No surgical delay in any patient MPR 35% in combo arm MPR 17% in nivo monotherapy arm	Included as primary endpoint, no delays	Yes; AID/APOBEC-associated mutation profile
Wise-Draper et al 2022 (29)	HNSCC	2	92	One year DFS	Pembrolizumab, 1 cycle, 3	DFS 97% in intermediate-risk group; 66% in high-risk group	33 (36%) patients with surgical complications: dehiscence, fistulas and/or infections	Yes: PD-L1 expression not associated with DFS
NICHE 2020 (35)	Colorectal	2	40	Safety and feasibility	Ipilimumab x 1, nivolumab x 2	Treatment tolerated by all patients; no surgical delays	No surgical delays (primary endpoint)	Yes; CD8+ PD-L1+ T cell infiltration
Cercek et al 2022 (36)	Rectal	2	12	Sustained clinical response 12 months after completion of treatment pCR after dostarlimab therapy w/ or w/o surgery or chemoradiotherapy	Single agent dostarlimab	12/12 patients (100%; 95% CI 74–100) with CR	No patients underwent surgery or chemoradiotherapy	Yes; PD-L1 protein and CD8+ T lymphocytes found in higher levels in tumor-free rectal mucosa after 6 months compared to mid-treatment
Ferrarotto et al 2021(38)	CSCC	2	20	ORR	cemiplimab	ORR: 30%, all partial responses	All patients underwent surgery as planned	Yes; responders had higher levels of IFN-g and TILs

Trial/Year	Tumor Type	Phase	No.	1° Endpoint	Intervention	Results	Surgical Delay/ Complication Data	Biomarker Analysis
Gross et al 2022 (40)	CSCC	2	79%	pCR	cemiplimab	pCR: 51% of patients, MPR 13%	2 patients progressed to inoperable disease; 1 patient progressed and lost to follow up	Yes; PDL1 and TMB data acquired, but no clear association
Amaria et al 2018 (44)	Melanoma	2	23	ORR pCR TRAE	Nivolumab monotherapy v Ipilimumab + nivolumab	ORR combo group: 73% pCR combo group: 45% Grade 3 irAEs combo group: 73%	Trial stopped early due to early observation of progression in nivolumab alone group with high rates of trAEs in combination group	Yes; responders trended toward higher TMB and T-cell clonality
OpACIN 2018 (45)	Melanoma	1b	20	Safety Feasibility Immune activating capacity	Ipilimumab/nivolumab neoadjuvant-adjuvant v adjuvant only	Safety: 90% of patients in each arm with Gr 3–4 AEs Feasibility: surgery performed	Feasibility included as a co-primary endpoint	Yes; sTILs expansion included as co-primary endpoint
OpACIN-neo 2019 (47)	Melanoma	2	86	Grade 3–4 Toxicity pCR and radiologic objective response	A.Ipilimumab 3 mg/kg + nivolumab 1 mg/kg; B.Ipilimumab 1 mg/kg + nivolumab 3 mg/kg; 3. ipilimumab 3 mg//kg followed by nivolumab 3 mg/kg	Grade 3–4 irAEs observed in 40% Group A, 20% Group B 50% group C Radiologic objective response: 63% Group A, 57% Group B, 35% in Group C pCR: 80% Group A, 77% group B, 65% Group C	No cases attributed to neoadjuvant therapy	Yes; IFN-g signature associated with relapse, but not pCR
Huang et al 2019 (48,49)	Melanoma	1b	27	Pathologic response; Immunologic response DFS	Pembrolizumab, single dose	29% pCR or MPR Increase in circulating TILs, associated with path response DFS: 63% at 2 years 100% 5 year OS in responders	No delays or unexpected complications	Yes; included as primary endpoint
SWOG S1801 2023 (50)	Melanoma	2	313	EFS in ITT population	Neoadjuvant-adjuvant or adjuvant only pembrolizumab	2 yr. EFS 72% in NA-A group, 49% in adjuvant-only group	1 patient with toxic effects, 12 patients with disease progression evidence of disease.	No; Data collected but to be published in separate analysis
ABACUS 2019 (53)	MIBC	2	95	Pathologic compete response	Atezolizumab, 2 cycles	pCR 31%	62% surgical complications; 1 post-op death	Yes; tumor CD8+ immune phenotypes, PD-L1, TMB
PURE-01 2018 (54)	MIBC	2	50	Pathologic compete response	Pembrolizumab, 3 cycles	pCR 42%	50% surgical complications	Yes; PD-L1, immune expression assay
NABUCCO 2020 (56)	MIBC	2	24	Feasibility to resect	Ipilimumab x 2, nivolumab x 2	23/24 (95%) patients underwent surgery at pre-defined time 46% with pCR	1 patient with surgical delay due to immune-related hemolysis	Yes; PD-L1, immune expression assay