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The rapidly evolving paradigm of neoadjuvant immunotherapy across cancer types

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Gil Awada[1], Tina Cascone[2], Michiel S. van der Heijden[3], Christian U. Blank[3], Marleen Kok[3] & Myriam Chalabi[3,4]

Neoadjuvant immunotherapy is rapidly changing the treatment landscape for many tumor types. The superiority of neoadjuvant compared to adjuvant immunotherapy has now been established in both preclinical studies and clinical trials. Neoadjuvant immunotherapy, either as monotherapy or in combination with other immune checkpoint inhibitors or other agents, has become a standard of care for several cancer types, while many new indications are expected. Future research should focus on determining the benefit of treatment combinations versus monotherapy and the contribution of adjuvant after neoadjuvant (or perioperative) treatment versus neoadjuvant treatment alone as well as on identifying predictive biomarkers of response.

The introduction of immunotherapy, in particular, the monoclonal antibody immune checkpoint inhibitors (ICIs) targeting programmed cell death 1 (PD-1) and its ligand (PD-L1), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or lymphocyte-associated gene 3 (LAG-3), has substantially impacted the management of a multitude of advanced (unresectable or metastatic) solid tumors, either as a monotherapy or in combination with other ICIs, chemotherapy and/or other agents[1–9].

Based on their efficacy and manageable toxicity profile (especially with monotherapy and to a lesser extent with combination therapy), ICIs are now increasingly being investigated in the early setting. An argument for administering ICIs in the early setting is that immune dysfunction is less prominent in early-stage cancer than in late-stage cancer, where a higher metastatic tumor burden is often associated with less immunogenic tumor clones and more pronounced immune evasion, cancer-associated inflammation and cancer cell-intrinsic metabolic changes (for example, the Warburg effect)[10–13]. In this context, PD-(L)1 ICIs have been approved as an adjuvant therapy following complete surgical resection of stage III and high-risk stage II melanoma[14–16], stage IB–III non-small cell lung cancer (NSCLC)[17], esophageal cancer[18], renal cell carcinoma (RCC)[19] and muscle-invasive urothelial carcinoma (UC)[20], with the aim of eliminating any residual microscopic disease.

More recently, promising results on neoadjuvant (before surgical resection of the primary tumor and any locoregional lymph nodes (LNs)) and perioperative (neoadjuvant plus adjuvant) ICI therapy have been reported. This has led to the regulatory approval of several ICIs in the neoadjuvant and perioperative settings for selected cancer types. In this Review, we discuss the rationale for neoadjuvant immunotherapy, elaborate on trial design, endpoint selection and pathological assessment after neoadjuvant immunotherapy, summarize the current data and approved indications and finally discuss novel neoadjuvant immunotherapy-based therapeutic strategies.

Rationale for neoadjuvant versus adjuvant immunotherapy

In general, the administration of oncological therapies in the neoadjuvant setting for local or locoregionally advanced cancer has several advantages. Downsizing the tumor can render initially unresectable tumors resectable and enable surgical de-escalation, thereby decreasing morbidity and facilitating organ preservation[21–23]. The response to

[1]Department of Medical Oncology, Vrije Universiteit Brussel/Universitair Ziekenhuis Brussel, Brussels, Belgium. [2]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [3]Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands. [4]Department of Gastrointestinal Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands. e-mail: m.chalabi@nki.nl

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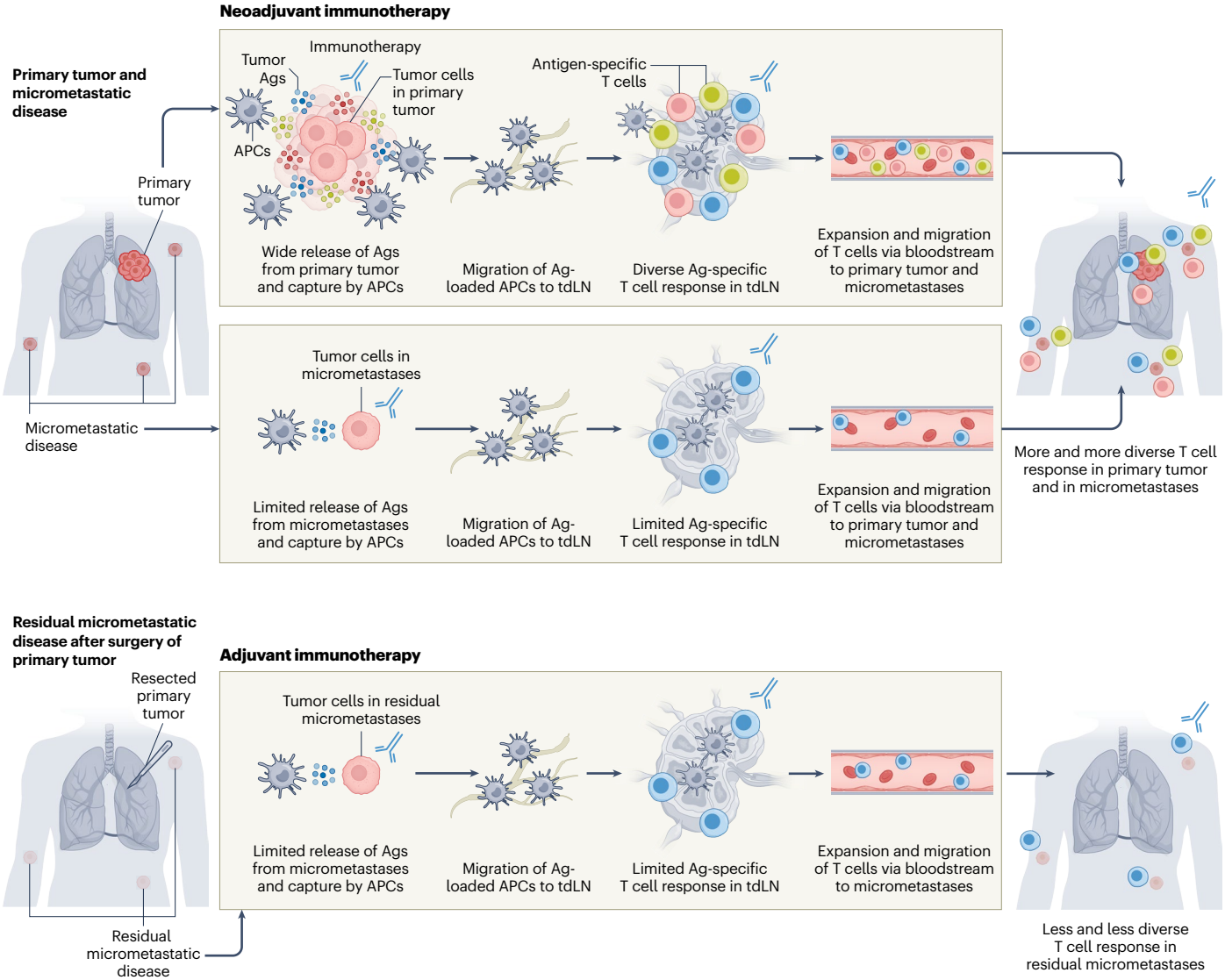

Fig. 1 | Rationale for neoadjuvant versus adjuvant immunotherapy. Cancer cells release tumor antigens (Ags) in the tumor microenvironment, which are ingested by antigen-presenting cells (APCs). These cells present the antigens to the T cell receptor on T cells in the draining LNs. Activated T cells undergo expansion and migrate to the tumor tissue where they will recognize tumor cells through their T cell receptor and induce cancer cell death ('cancer–immunity cycle'). Administration of neoadjuvant immunotherapy, when the tumor and draining regional LNs are still in place, could result in higher levels of antigen presentation, more T cell priming and expansion and eventually a broader, more effective and durable immune response against the primary tumor and micrometastases. By contrast, administering immunotherapy after resection of the macroscopically visible tumor load (in the adjuvant setting) could lead to a less robust immune response against residual micrometastatic disease. tdLN, tumor-draining LNs.

neoadjuvant therapy may provide important prognostic information and instruct on the need for additional adjuvant treatments and the development of more effective neoadjuvant regimens[18,24–30]. It also allows time for surgical planning, implementation of patient rehabilitation programs (for example, smoking cessation) and, if indicated, genetic testing (for example, in patients with a possible pathogenic germline genetic variant). Risks of neoadjuvant therapy include locoregional and/or distant tumor progression before surgery, decline of the patient's performance status and complications due to systemic therapy that could delay or compromise curative surgery[30,31].

The basis for the use of neoadjuvant immunotherapy has been provided by preclinical studies in breast and lung cancer models, showing increased systemic expansion of tumor-specific effector T cells and better long-term outcome with neoadjuvant than with adjuvant immunotherapy[32–34].

ICIs act by reinvigorating the antitumor immune response[35,36] (Fig. 1). While the release of tumor antigens by cancer cells leads to tumor antigen presentation and activation of tumor-specific T cells, the concomitant upregulation of inhibitory immune checkpoints hampers the antitumor immune response. By blocking these checkpoints, ICIs reactivate T cells in the tumor microenvironment and in the LNs, leading to immunogenic cell death[35,36]. Consequently, administration of neoadjuvant ICIs, when the tumor and draining regional LNs are still in place, could result in higher levels of antigen presentation, priming and expansion of multiple T cell clones and eventually in a more effective and durable immune response against the primary tumor and micrometastases[31,32,37] (Fig. 1). Conversely, administering ICIs after resection of the macroscopically visible tumor load (as one would do in the adjuvant setting) could lead to a less robust immune response limited to tumor antigens expressed by the residual micrometastatic disease (Fig. 1). As clinical supporting evidence, in the OpACIN trial, patients with macroscopic stage III melanoma who were treated with neoadjuvant immunotherapy had larger numbers of tumor-specific T cell clones in the peripheral blood than patients who received the

Table 1 | Examples of biomarkers for efficacy to neoadjuvant immunotherapy across tumor types

Tumor cell related	- Tumor mutational burden - Neoantigen/neoepitope burden - Viral antigen burden (in virus-associated malignancies) - Mismatch repair deficiency/microsatellite instability - Driver mutations (for combinations of MTT and ICIs)
Tumor microenvironment related	- MHC expression - Expression of immune checkpoints: PD-L1, CTLA-4, LAG-3, TIGIT, TIM-3 - T cell receptor repertoire - Cellular infiltration: $CD8^+$ tumor-infiltrating lymphocytes, regulatory T lymphocytes, tumor-associated macrophages, ($BATF3^+$) dendritic cells, cancer-associated fibroblasts, B cells - Spatial distribution of immune cells - Stromal cytokines: TGFβ, IFNγ, IL-2, CXCL2 - Gene expression signatures: tumor inflammation signature, IFNγ signature, $BATF3^+$ dendritic cell signature, tertiary lymphoid structure signature - Tertiary lymphoid structures
Host related	- Microbiome - HLA - Comorbidities (immune deficiencies) - Immunosuppressive drugs

$BATF3^+$, basic leucine zipper ATF-like transcription factor 3 positive; CD, cluster of differentiation; CXCL2, chemokine ligand 2; HLA, human leukocyte antigen; IL-2, interleukin-2; MHC, major histocompatibility complex; TGFβ, transforming growth factor-β.

same treatment in the adjuvant setting[38]. In addition, to our knowledge, there is no literature showing a negative effect of surgical removal of the LNs after an immune response has been already initiated following neoadjuvant immunotherapy. The findings of tumor-specific T cells in the peripheral blood, together with the improved outcomes after neoadjuvant therapy, suggest that this is not the case.

Furthermore, the availability of and access to pretreatment and post-treatment blood, tumor and other specimens allows for translational research to elucidate mechanisms and biomarkers of response, resistance and toxicity to neoadjuvant ICIs. In this context, preclinical and translational research can originate in the clinical setting (patient care or clinical trials), a process of so-called reverse translation from bedside to bench[31,39]. An overview of biomarkers for efficacy to neoadjuvant ICI therapy across tumor types is summarized in Table 1.

Neoadjuvant immunotherapy trial designs

In neoadjuvant immunotherapy trials, both radiological and pathological evaluation criteria are being used as clinical endpoints in patients with measurable disease. Radiological responses can be evaluated according to the Response Evaluation Criteria In Solid Tumours and provide endpoints such as the objective response rate (ORR) and event-free survival (EFS)[40]. Assessing radiological responses to neoadjuvant ICI therapy can be challenging due to the generally small and localized tumor load and due to atypical response patterns. The ORR is generally defined as the proportion of patients with a complete or partial response, while the EFS is generally defined as the time between randomization or inclusion and progression of disease that precludes surgery, local or distant recurrence or death.

Guidelines for the pathological response assessment after neoadjuvant immunotherapy have been originally defined for melanoma by the International Neoadjuvant Melanoma Consortium and are also used beyond melanoma trials[41]. A pathological complete response (pCR) is defined as the absence of residual viable tumor (RVT), a near-pCR as >0% to ≤10% RVT, a partial pathological response (pPR) as >10% to ≤50% RVT and no pathological response as >50% RVT and are based on the total tumor bed. A major pathological response (MPR) denotes the sum of pCR and near-pCR (≤10% RVT), and the pathological response rate is defined as the sum of pCR, near-pCR and pPR (≤50% RVT)[42]. As new trial results across tumor types emerge, these data may lead to revision and improvement of these pathological response criteria.

Based on trials with neoadjuvant chemotherapy, especially in the field of breast cancer, pCR was positioned as a surrogate (and regulatory) endpoint for durable efficacy and explains the frequent use of pCR as a primary endpoint in neoadjuvant immunotherapy trials in breast cancer[24,43]. Results from multiple neoadjuvant immunotherapy trials suggest, however, that also MPR is associated with an improved long-term outcome[44–47]. Although these data support the use of MPR as an endpoint in trials with neoadjuvant immunotherapy, MPR has not (yet) been designated as a regulatory endpoint by the Food and Drug Administration (FDA). Both pCR and MPR should also be validated for tumor types beyond breast cancer where pathological response is not an accepted surrogate for survival outcomes (such as colorectal cancer (CRC)). Of note, in melanoma, MPR and pCR to neoadjuvant molecular-targeted therapy (MTT) with BRAF and mitogen-activated protein kinase kinase (MEK) inhibition are associated with significantly higher rates of disease recurrence than the same pathological response to neoadjuvant ICI[44]. These data suggest that not all pathological responses are created equal, and the type of neoadjuvant therapy should be considered here.

In randomized trials involving neoadjuvant immunotherapy, the novel therapeutic approach is compared to the standard of care (SOC), which can be neoadjuvant or adjuvant therapy. In randomized trials in which a neoadjuvant therapy is compared to adjuvant therapy, only survival outcomes should be considered as valid primary endpoints. In randomized trials comparing two (or more) neoadjuvant therapies or in single-arm trials, pathological response endpoints can also be envisaged. Furthermore, when comparing endpoints such as EFS (encompassing both preoperative and postoperative events) between treatment arms, one must be aware of the timing of events (incidence of preoperative versus postoperative events) in the neoadjuvant treatment arm to assess and compare efficacy but also the feasibility of a treatment regimen. Advantages and disadvantages of endpoints used in trials with neoadjuvant immunotherapy are summarized in Table 2.

Landscape of neoadjuvant ICIs targeting PD-(L)1, CTLA-4 and LAG-3

In this section, we will discuss current data and approved indications with neoadjuvant ICIs targeting PD-(L)1, CTLA-4 and LAG-3 across tumor types.

Melanoma

Neoadjuvant immunotherapy has a long tradition in melanoma. High-dose interferon (IFN), ipilimumab (CTLA-4 ICI) or their combination has been tested with promising response rates[48–50]. Neoadjuvant studies, however, were long considered as drug development platforms or phase 0 presurgical trials designed to comprehend immunological mechanisms of action[51,52]. This notion led to extensive investigation of ICIs in the adjuvant setting, and only recently the neoadjuvant setting has become the focus of treatments for early-stage disease[31,42].

OpACIN was the first trial directly comparing neoadjuvant versus adjuvant checkpoint inhibition and showed stronger and broader immune activation in the former[53]. Several subsequent investigator-initiated trials[54] have tested neoadjuvant PD-1 blockade alone (pCR rate, 25%)[55] or in combination with ipilimumab (pCR rate, 25–57%)[55,56], high-dose IFN (pCR rate, 43%)[57] or MTT against BRAF and MEK (pCR rate, 50%)[58]. In general, all these combination therapies induced higher pCR and MPR rates but at the cost of higher grade 3–4 adverse event (AE) rates[54]. Recently, neoadjuvant ICI has become the SOC for macroscopic stage III melanoma (Table 3) following results from the phase 2 SWOG S1801 trial testing a sandwich approach of

Table 2 | Advantages and disadvantages of endpoints in clinical trials with neoadjuvant immunotherapy

Trial endpoint	Advantages	Disadvantages
Translational endpoint (for example, immune activation)	- Indicator of biological activity of therapy - Rapidly available (biopsy pre-surgery and/or at surgery)	- Does not necessarily correlate with clinical outcome - Not routinely available in daily clinical practice - Can be different in 'cold' versus 'hot' tumors
pCR	- Indicator of at least short-term meaningful clinical activity of therapy - Considered as emerging surrogate endpoint for long-term outcome - Rapidly available (at surgery)	- May not be sufficient for regulatory approval - Excludes patients who progress during neoadjuvant therapy or do not undergo surgery - Benefit can extend beyond pCR
MPR	- Indicator of at least short-term meaningful clinical activity of therapy - Considered as emerging surrogate endpoint for long-term outcome (but possibly less robust than pCR for some tumor types) - Rapidly available (at surgery)	- May not be sufficient for regulatory approval - Excludes patients who progress during neoadjuvant therapy or do not undergo surgery - Impact of diagnostic procedures may preclude accurate assessment (for example, in bladder cancer) - Requires training by pathologist
EFS	- Clinically meaningful endpoint directly related to the patient's outcome in the middle-to-long term - Comprises multiple events including disease progression before and relapse after surgery and death from any cause - Easily assessable - Indicator of feasibility and dropout before surgery	- Available after longer follow-up - Not always a surrogate for OS - May not be sufficient for regulatory approval
OS	- Clinically meaningful endpoint directly related to the patient's outcome in the long term - Easily assessable - Regulatory endpoint	- Available after longer follow-up (longer than EFS)
Quality of life	- Patient-centered endpoint - Supports acceptance and/or approval of a drug regimen	- Issues with data collection - Not indicative of biological or clinical activity

neoadjuvant pembrolizumab (PD-1 ICI) followed by adjuvant pembrolizumab[59] and the randomized phase 3 NADINA trial testing neoadjuvant ipilimumab plus nivolumab (PD-1 ICI) followed by adjuvant therapy in patients without an MPR only[47,60]. Both studies showed a highly significant EFS benefit with neoadjuvant treatment compared to SOC adjuvant PD-1 blockade (in the SWOG S1801 trial, the 2-year EFS was 72% versus 49%, and, in the NADINA trial, 18-month EFS was 80.8% versus 53.9%, respectively).

The use of perioperative nivolumab plus the LAG-3 ICI relatlimab for resectable stage III or oligometastatic stage IV melanoma has been investigated in a phase 2 trial, showing a 57% pCR rate and a 70% pathological response rate[61]. Similarly, two cycles of neoadjuvant favezelimab (LAG-3 ICI) plus pembrolizumab have been investigated, showing a pCR and an MPR rate of 38% and 58%, respectively[62]. RELATIVITY-048 investigated the combination of nivolumab–ipilimumab–relatlimab as a first-line treatment for advanced melanoma, showing an ORR of 58.7%, with toxicity consistent with other immunotherapy combinations[63]. This triplet is now being tested in the neoadjuvant setting in patients with locally advanced melanoma (NCT06295159). First attempts for neoadjuvant approaches in patients with stage II melanoma are also underway (NCT04274816, NCT03757689, NCT05418972, NCT06240143).

Several questions persist, however, such as the role of predictive biomarkers, to identify patients who will respond to ICI monotherapy versus those who derive benefit from addition of combinations as well as the value of surgery, adjuvant therapy and follow-up in patients with an MPR. For example, patients harboring a high IFNγ signature at baseline seem to achieve similar MPR rates with PD-1 ICI monotherapy than with dual PD-1–CTLA-4 blockade, suggesting the opportunity for neoadjuvant treatment personalization in the future[64–66].

NSCLC

The advent of ICIs has also led to expanded treatment options for patients with early-stage, resectable NSCLC. The first pilot study that evaluated the feasibility and safety of neoadjuvant nivolumab monotherapy in stage I–IIIA resectable NSCLC showed an MPR rate of 45%[45,67]. Subsequent trials of neoadjuvant PD-(L)1 ICIs in resectable NSCLC reported MPR and pCR rates ranging from 6.7% to 45.0% and 0% to 16.2%, respectively[68–75].

Combinations of ICIs have also been evaluated. In the phase 2 NEOSTAR platform study, nivolumab alone or combined with ipilimumab in resectable stage I–IIIA NSCLC produced MPR rates of 22% and 38% and pCR rates of 9% and 29%, respectively[70]. The nivolumab–ipilimumab arm of the phase 3 CheckMate 816 trial in resectable stage IB–IIIA NSCLC demonstrated a pCR rate of 20.4% and a median EFS of 54.8 months (compared to 4.6% and 20.9 months, respectively, with chemotherapy alone)[76]. The phase 2 NEOpredict trial for resectable NSCLC reported MPR and pCR rates of 27% and 13% in the nivolumab arm and 30% and 17% in the nivolumab–relatlimab arm, respectively[77].

Several phase 2 trials evaluated neoadjuvant chemotherapy plus ICI monotherapy in resectable NSCLC and reported MPR rates between 32.1% and 83% and pCR rates between 18% and 63%[78–83]. The phase 3 randomized CheckMate 816 trial also evaluated neoadjuvant chemotherapy plus nivolumab and demonstrated a significant improvement in EFS and pCR rate with the combination regimen versus chemotherapy alone[84,85] (Table 3). These results led to regulatory approval of nivolumab plus platinum-based chemotherapy for resectable NSCLC in the neoadjuvant setting[86,87]. Volrustomig (or MEDI5752) is a monovalent bispecific antibody targeting PD-1 and CTLA-4. It is currently under investigation in combination with neoadjuvant chemotherapy in the NeoCOAST-2 trial (NCT05061550).

In addition, the efficacy of perioperative immunotherapy added to neoadjuvant chemotherapy in resectable NSCLC has been assessed in several global phase 3 trials[88–91], leading to regulatory approvals of perioperative ICIs for select patients with stage IIA–IIIB resectable NSCLC[92–94] (Table 3).

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Table 3 | Pivotal neoadjuvant immunotherapy trials

Tumor type	Trial name and NCT number	Trial phase	Number of patients	Tumor stage	Treatment regimens	Timing surgical resection	Results of primary endpoint	Key secondary endpoints	Median follow-up	Translational data available	Regulatory approval
Melanoma	SWOG S1801, NCT03698019 (ref. 59)	2	313	Clinically detectable, measurable and resectable stage IIIB–IIID or oligometastatic resectable stage IV	3× neoadjuvant PEMBRO Q3W followed by surgery and 15× adjuvant PEMBRO Q3W versus 18× adjuvant PEMBRO Q3W	Within 5 weeks after last neoadjuvant PEMBRO dose	2-year EFS of 72% (95% CI, 64–80%) for neoadjuvant–adjuvant arm versus 49% (95% CI, 41–59%) for adjuvant arm; HR, 0.58; $P = 0.004$	pCR rate in neoadjuvant–adjuvant arm of 21%	14.7 months	Not reported	No
Melanoma	NADINA, NCT04949113 (refs. 47,60)	3	423	Resectable, macroscopic stage III	2× neoadjuvant IPI, 80 mg plus NIVO, 240 mg Q3W versus 12× adjuvant NIVO, 480 mg Q4W Only patients in the neoadjuvant group with a pPR/pNR received adjuvant treatment.	3 weeks after last neoadjuvant IPI plus NIVO dose	18-month EFS of 80.8% for neoadjuvant group versus 53.9% for adjuvant group; HR, 0.32 (95% CI, 0.22–0.48); $P < 0.001$	MPR rate in neoadjuvant arm of 60.8% 2-year DMFS of 85.7% for neoadjuvant arm versus 62.4% for adjuvant arm; HR, 0.37 (95% CI, 0.24–0.57); $P < 0.0001$	15.4 months	Not available yet	No
NSCLC	CheckMate 816, NCT02998528 (refs. 84,85)	3	358	Resectable stage IB (≥4 cm) to IIIA	3× neoadjuvant NIVO plus platinum-doublet CT Q3W followed by surgery and adjuvant CT/RT if required versus 3× neoadjuvant platinum-doublet CT Q3W followed by surgery and adjuvant CT/RT if required	Within 6 weeks after the completion of neoadjuvant treatment	pCR rate of 24.0% (95% CI, 18.0–31.0%) for NIVO-plus-CT arm versus 2.2% (95% CI, 0.6–5.6%) for CT arm; OR, 13.94 (99% CI, 3.49–55.75); $P < 0.001$ Median EFS of 43.8 months for NIVO-plus-CT arm versus 18.4 months for CT arm; HR, 0.66 (95% CI, 0.49–0.90)	MPR rate of 36.9% for NIVO-plus-CT arm versus 8.9% for CT arm Median OS, NR in both arms	57.6 months	ctDNA clearance higher in those receiving NIVO. EFS longer in patients with ctDNA clearance	FDA, EMA
NSCLC	KEYNOTE-671, NCT03425643 (refs. 88,91,197)	3	797	Resectable stage II, IIIA, or IIIB (N2)	4× neoadjuvant PEMBRO plus cisplatin-doublet CT Q3W followed by surgery and adjuvant PEMBRO Q3W up to 1 year versus 4× neoadjuvant PLB plus cisplatin-doublet CT Q3W followed by surgery and adjuvant PLB Q3W up to 1 year	No later than 20 weeks after the receipt of the first dose of therapy	Median EFS of 47.2 months (95% CI, 32.9–NR) for PEMBRO-plus-CT arm versus 18.3 months (95% CI, 14.8–22.1) for PLB-plus-CT arm; HR, 0.59 (95% CI, 0.48–0.72); $P < 0.001$ Median OS, NR (95% CI, NR–NR) for PEMBRO-plus-CT arm versus 52.4 months (95% CI, 45.7–NR) for PLB-plus-CT arm; HR, 0.72 (95% CI, 0.56–0.93); $P = 0.0052$	pCR rate of 18.1% (95% CI, 14.5–22.3%) for PEMBRO-plus-CT arm versus 4.0% (95% CI, 2.3–6.4%) for PLB-plus-CT arm; $P < 0.0001$ MPR rate of 30.2% (95% CI, 25.7–35.0%) for PEMBRO-plus-CT arm versus 11.0% (95% CI, 8.1–14.5%) for PLB-plus-CT arm; $P < 0.0001$	36.6 months	Benefit for PEMBRO plus CT regardless of PD-L1 expression	FDA, EMA

Table 3 (continued) | Pivotal neoadjuvant immunotherapy trials

Tumor type	Trial name and NCT number	Trial phase	Number of patients	Tumor stage	Treatment regimens	Timing surgical resection	Results of primary endpoint	Key secondary endpoints	Median follow-up	Translational data available	Regulatory approval
NSCLC	AEGEAN, NCT03800134 (refs. 89,95)	3	802	Resectable stage II–IIIB	4× neoadjuvant DURVA plus platinum-based CT Q3W followed by surgery and 12× adjuvant DURVA Q3W versus 4× neoadjuvant PLB plus platinum-based CT Q3W followed by surgery and 12× adjuvant PLB Q3W	Within 40 d after the administration of the last dose of neoadjuvant treatment	Median EFS, NR (95% CI, 42.3–NR) for DURVA-plus-CT arm versus 30.0 months (95% CI, 20.6–NR) for PLB-plus-CT arm; HR, 0.69 (95% CI, 0.55–0.88) pCR rate of 17.2% (95% CI, 13.5–21.5%) for DURVA-plus-CT arm versus 4.3% (95% CI, 2.5–6.9%) for PLB-plus-CT arm; difference, 13.0% (95% CI, 8.7–17.6%); $P<0.001$	MPR rate of 33.3% for DURVA-plus-CT arm versus 12.3% for PLB-plus-CT arm; difference, 21.0% (95% CI, 15.1–26.9%); $P<0.001$ Median DFS, NR (95% CI, NR–NR) for DURVA-plus-CT arm versus NR (95% CI, 41.5–NR) for PLB-plus-CT arm; HR, 0.66 (95% CI, 0.47–0.92) Median OS, NR (95% CI, NR–NR) for DURVA-plus-CT arm versus 53.2 (95% CI, 44.3–NR) for PLB-plus-CT arm; HR, 0.89 (95% CI, 0.70–1.14)	25.9 months	Not reported	FDA
NSCLC	CheckMate 77T, NCT04025879 (refs. 90,96)	3	461	Resectable stage II–IIIB	4× neoadjuvant NIVO plus platinum-doublet CT Q3W followed by surgery and adjuvant NIVO Q4W up to 1 year versus 4× neoadjuvant PLB plus platinum-doublet CT Q3W followed by surgery and adjuvant PLB Q4W up to 1 year	Within 6 weeks after the last neoadjuvant treatment	Median EFS, 40.1 months (95% CI, 33.7–NR) for NIVO-plus-CT arm versus 17.0 months (95% CI, 13.6–28.1) for PLB-plus-CT arm; HR, 0.59 (95% CI, 0.45–0.79)	pCR rate of 25.3% (95% CI, 19.8–31.5%) for NIVO-plus-CT arm versus 4.7% (95% CI, 2.4–8.3%) for PLB-plus-CT arm; odds ratio, 6.64 (95% CI, 3.40–12.97) MPR rate of 35.4% (95% CI, 29.2–41.9%) for NIVO-plus-CT arm versus 12.1% (95% CI, 8.2–17.0%) for PLB-plus-CT arm; odds ratio, 4.01 (95% CI, 2.48–6.49)	33.3	Not reported	FDA
Colon cancer	NICHE-2, NCT03026140 (refs. 98,100)	2	115	Locally advanced, previously untreated dMMR	Neoadjuvant NIVO, 3 mg/kg on day 1 and day 15 plus IPI, 1 mg/kg on day 1	Within 6 weeks after enrollment	98% (97.5% CI, 93–100%) of patients underwent timely surgery 3-year DFS of 100%	MPR rate of 95% (95% CI, 89–98%) pCR rate of 68% (95% CI, 58–76%)	36.5 months	Preoperative ctDNA levels lower in patients who would achieve pCR versus MPR	No
Rectal cancer	NCT04165772 (refs. 108,109)	2	42	Previously untreated dMMR	Neoadjuvant DOS, 500 mg Q3W for 6 months	No surgical resection	100% cCR	No secondary endpoint defined	17.9 months	ctDNA clearance at 3 months	No

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Table 3 (continued) | Pivotal neoadjuvant immunotherapy trials

Tumor type	Trial name and NCT number	Trial phase	Number of patients	Tumor stage	Treatment regimens	Timing surgical resection	Results of primary endpoint	Key secondary endpoints	Median follow-up	Translational data available	Regulatory approval
TNBC	KEYNOTE-522, NCT03036488 (refs. 114–117)	3	1,174	Stage II–III	Neoadjuvant PEMBRO plus CT (carboplatin–paclitaxel and anthracycline–cyclophosphamide) followed by surgery and adjuvant PEMBRO up to 1 year versus neoadjuvant PLB plus CT followed by surgery and adjuvant PLB up to 1 year	3–6 weeks after the last treatment cycle of the neoadjuvant phase	pCR rate of 64.8% (95% CI, 59.9–69.5%) for PEMBRO-plus-CT arm versus 51.2% (95% CI, 44.1–58.3%) for PLB-plus-CT arm; difference, 13.6% (95% CI, 5.4–21.8%); $P<0.001$ 5-year EFS of 81.2% (95% CI, 78.3–83.8%) for PEMBRO-plus-CT arm versus 72.2% (95% CI, 67.4–76.4%) for placebo-plus-CT arm; HR, 0.65 (95% CI, 0.51–0.83); $P<0.001$	5-year OS of 86.6% (95% CI, 84.0–88.8%) for PEMBRO-plus-CT arm versus 81.7% (95% CI, 77.5–85.2%) for placebo-plus-CT arm; HR, 0.66 (95% CI, 0.50–0.87); $P=0.0015$	75.1 months	Benefit for PEMBRO plus CT regardless of PD-L1 expression	FDA, EMA
ER-positive, HER2-negative breast cancer	CheckMate 7FL, NCT04109066 (refs. 131,132)	3	510	T1c–T2 N1–N2 or T3–T4 N0–N2; grade 3 with ER ≥ 1% or grade 2 with ER 1–10%	Neoadjuvant NIVO plus CT (paclitaxel and anthracycline–cyclophosphamide) followed by surgery and adjuvant NIVO up to 1 year versus PLB plus CT followed by surgery and adjuvant placebo up to 1 year	3–6 weeks after the last treatment cycle of the neoadjuvant phase	pCR rate of 24.5% for NIVO-plus-CT arm versus 13.8% for placebo-plus-CT arm; $P=0.0021$	pCR in the PD-L1 IC ≥ 1% of 44.3% for NIVO-plus-CT arm versus 20.2% for placebo-plus-CT arm RCB 0–1 rate of 30.7% for NIVO-plus-CT arm versus 21.3% for placebo-plus-CT arm	Not reported	Greater PD-L1 expression associated with higher pCR and RCB 0–1 rates	No
ER-positive, HER2-negative breast cancer	KEYNOTE-756, NCT03725059 (refs. 133,134)	3	1,278	T1c–T2 N1–N2 or T3–T4 N0–N2	Neoadjuvant PEMBRO plus CT (paclitaxel and anthracycline–cyclophosphamide) followed by surgery and adjuvant PEMBRO up to 1 year versus PLB plus CT followed by surgery and adjuvant placebo up to 1 year	Within 6 weeks after the completion of neoadjuvant treatment	pCR rate of 24.3% for NIVO-plus-CT arm versus 15.6% for placebo-plus-CT arm; $P=0.0005$ Coprimary endpoint of EFS immature	RCB 0–1 rate of 35.0% for PEMBRO-plus-CT arm versus 23.6% for placebo-plus-CT arm	Not reported	Greater PD-L1 expression associated with higher pCR and RCB 0–1 rates	No
MIBC	NIAGARA, NCT03732677 (refs. 147)	3	1,063	Cisplatin-eligible cT2–T4a N0–N1 M0	4× neoadjuvant DURVA plus cisplatin–gemcitabine Q3W followed by surgery and 8× adjuvant DURVA Q3W versus 4× cisplatin–gemcitabine Q3W followed by surgery	2–8 weeks after the last dose of neoadjuvant therapy	pCR rate of 37.3% for DURVA plus CT versus 27.5% for CT; RR, 1.34 (95% CI, 1.13–1.60) 2-year EFS, 67.8% (95% CI, 63.6–71.7%) for DURVA-plus-CT arm versus 59.8% (95% CI, 55.4–64.0%) for CT arm; HR, 0.68 (95% CI, 0.56–0.82); $P<0.001$	2-year OS, 82.2% (95% CI, 78.7–85.2%) for DURVA-plus-CT arm versus 75.2% (95% CI, 71.3–78.8%) for CT arm; HR, 0.75 (95% CI, 0.59–0.93); $P=0.01$	42.3 months	EFS benefit for DURVA plus CT regardless of PD-L1 expression	FDA

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Table 3 (continued) | Pivotal neoadjuvant immunotherapy trials

Tumor type	Trial name and NCT number	Trial phase	Number of patients	Tumor stage	Treatment regimens	Timing surgical resection	Results of primary endpoint	Key secondary endpoints	Median follow-up	Translational data available	Regulatory approval
RCC	PROSPER EA8143, NCT03055013 (refs. 150)	3	819	≥T2 or any T with positive nodes	1× neoadjuvant NIVO followed by surgery and 9× adjuvant NIVO versus surgery alone	1–4 weeks after last neoadjuvant treatment cycle	HR for RFS for NIVO plus surgery versus surgery, 0.94 (95% CI, 0.74–1.21); $P=0.32$	HR for OS for NIVO plus surgery versus surgery, 1.28 (95% CI, 0.84–1.95); $P=0.26$	30.4 months	Not reported	No
Gastric or gastroesophageal adenocarcinoma	KEYNOTE-585, NCT03221426 (refs. 156)	3	804	≥cT3 or any cT with positive nodes	Main cohort: 3× neoadjuvant PEMBRO plus cisplatin-doublet CT Q3W followed by surgery and 3× adjuvant PEMBRO plus cisplatin-doublet CT Q3W followed by 11× adjuvant PEMBRO Q3W versus 3× neoadjuvant PLB plus cisplatin-doublet CT Q3W followed by surgery and 3× adjuvant PLB plus cisplatin-doublet CT Q3W followed by 11× adjuvant PLB Q3W Small cohort: 3× neoadjuvant PEMBRO Q3W plus 4× neoadjuvant FLOT CT Q2W followed by surgery and 3× adjuvant PEMBRO Q3W plus 4× adjuvant FLOT CT Q2W followed by 11× adjuvant PEMBRO Q3W versus 3× neoadjuvant PLB Q3W plus 4× neoadjuvant FLOT CT Q2W followed by surgery and 3× adjuvant PLB Q3W plus 4× adjuvant FLOT CT Q2W followed by 11× adjuvant PLB Q3W	6 weeks after last neoadjuvant treatment cycle	pCR rate of 12.9% (95% CI, 9.8–16.6%) for PEMBRO-plus-cisplatin-doublet CT arm versus 2.0% (95% CI, 0.9–3.9%) for PLB-plus-cisplatin-doublet CT arm; difference, 10.9% (95% CI, 7.5–14.8%); $P<0.00001$ Median EFS, 44.4 months (95% CI, 33.0–NR) for PEMBRO-plus-CT arm versus 25.3 months (95% CI, 20.6–33.9) for PLB-plus-CT arm; HR, 0.81 (95% CI, 0.67–0.99); $P=0.0198$ Median OS, 60.7 months (95% CI, 51.5–NR) for PEMBRO-plus-CT arm versus 58.0 months (95% CI, 41.5–NR) for PLB-plus-CT arm; HR, 0.90 (95% CI, 0.73–1.12); $P=0.174$	Incidence of grade ≥3 AEs of 78% for PEMBRO-plus-CT arm versus 73% for PLB-plus-CT arm	47.7 months	Not reported	No

Table 3 (continued) | Pivotal neoadjuvant immunotherapy trials

Tumor type	Trial name and NCT number	Trial phase	Number of patients	Tumor stage	Treatment regimens	Timing surgical resection	Results of primary endpoint	Key secondary endpoints	Median follow-up	Translational data available	Regulatory approval
Gastric or gastroesophageal adenocarcinoma	MATTERHORN, NCT04592913 (refs. 157)	3	948	Stage II–IVA	2× neoadjuvant DURVA Q4W plus 4× neoadjuvant FLOT CT Q2W followed by surgery and 2× adjuvant DURVA Q4W plus 4× adjuvant FLOT CT Q2W followed by 10× adjuvant DURVA Q4W versus 2× neoadjuvant PLB Q4W plus 4× neoadjuvant FLOT CT Q2W followed by surgery and 2× adjuvant PLB Q4W plus 4× adjuvant FLOT CT Q2W followed by 10× adjuvant PLB Q4W	4–8 weeks after last neoadjuvant treatment cycle	EFS not available	pCR rate of 19% for DURVA-plus-FLOT CT arm versus 7% for PLB-plus-FLOT CT arm; difference, 12%; OR, 3.08 (95% CI, 2.03–4.67); $P<0.00001$ Combined pCR plus near-pCR (defined as single or rare small groups of cancer cells at time of resection) rate of 27% for DURVA-plus-FLOT CT arm versus 14% for PLB-plus-FLOT CT arm; difference, 12%; OR, 2.19 (95% CI, 1.58–3.04); $P<0.00001$	Not reported	Not reported	No
CSCC	NCT04154943 (refs. 166,167)	2	70	Resectable stage II–IV	Up to 4× neoadjuvant CEMI followed by surgery and adjuvant CEMI, RT or observation at physician's discretion	75–100 d after start of neoadjuvant therapy	pCR rate of 51%	MPR rate of 64% 12-month EFS of 89% (95% CI, 79–94%)	18.7 months	Not reported	No

CEMI, cemiplimab; CI, confidence interval; CT, chemotherapy; DMFS, distant metastasis-free survival; DOS, dostarlimab; DURVA, durvalumab; EMA, European Medicines Agency; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IC, immune cell score; IPI, ipilimumab; M, metastatic stage; N, nodal stage; NCT, National Clinical Trial; NIVO, nivolumab; NR, not reached; OR, odds ratio; PEMBRO, pembrolizumab; PLB, placebo; pNR, no pathological response; RCB, residual cancer burden; RFS, recurrence-free survival; RR, risk ratio; RT, radiotherapy; T, tumor stage; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks.

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The phase 3 randomized KEYNOTE-671 trial demonstrated significant improvements in EFS (47.2 versus 18.3 months) and overall survival (OS) as well increased pCR and MPR rates with neoadjuvant chemotherapy plus perioperative pembrolizumab versus neoadjuvant chemotherapy plus perioperative placebo in patients with stage IIA–IIIB NSCLC[88,91]. The phase 3 AEGEAN trial tested neoadjuvant chemotherapy plus perioperative durvalumab versus neoadjuvant chemotherapy plus perioperative placebo in stage II–IIIA NSCLC. EFS outcomes were significantly improved with durvalumab (median EFS not reached versus 30.0 months) and pCR rates of 17.2% and 4.3% in the chemotherapy–durvalumab and chemotherapy–placebo arms, respectively[89,95].

The phase 3 CheckMate 77T trial tested neoadjuvant chemotherapy plus perioperative nivolumab versus neoadjuvant chemotherapy plus perioperative placebo in *EGFR*- and *ALK*-wild-type stage IIA–IIIB resectable NSCLC. At a median follow-up of 25.4 months, the 18-month EFS and the pCR rates were 70.2% and 25.3% in the chemotherapy–nivolumab group and 50.0% and 4.7% in the chemotherapy–placebo arm, respectively[90]. Updated results with a median follow-up of 33.3 months from this study revealed a median EFS of 40.1 months versus 17.0 months, respectively[96].

As the immune-based treatment landscape for resectable NSCLC continues to evolve and results of exploratory analyses regarding the efficacy of perioperative immunotherapy in selected subgroups of patients continue to emerge with longer survival follow-up, it will be critical to identify patient and disease factors that can inform who can potentially be cured with neoadjuvant chemoimmunotherapy only and who will instead benefit from more intensified biomarker-driven treatment strategies.

CRC

Mismatch repair-deficient (dMMR) CRCs are considered among the most immunogenic tumor types, often harboring a high tumor mutational burden and high densities of immune cell infiltration. ICIs have become an SOC in patients with metastatic dMMR disease[5,97]. In NICHE-2, a single-arm phase 2 study, patients with locally advanced dMMR colon cancers were treated with two doses of nivolumab and a single low dose of ipilimumab, followed by surgery within a median of 5.4 weeks[98] (Table 3). MPR and pCR were observed in 95% and 68% of patients, respectively. Conversely, in previous studies with neoadjuvant chemotherapy, pathological responses were observed in only 7% of patients with dMMR tumors. While pathological response is not an accepted surrogate in CRC[99], data from several other tumor types suggest improved long-term survival outcomes for patients with a good pathological response. More recently, NICHE-2 showed an unprecedented 100% 3-year disease-free survival (DFS) rate, in line with the pathological response rate observed in this study[100].

Other studies have provided additional evidence for the efficacy of ICIs in dMMR CRCs, albeit with a variety of treatment regimens and durations[101]. In the NEOPRISM study, a pCR rate of 58% was observed following 9 weeks of neoadjuvant pembrolizumab[102]. In NICHE-3, nivolumab–relatlimab demonstrated efficacy similar to that of nivolumab–ipilimumab with a 68% pCR and a 92% MPR rate[103,104]. Similarly, in IMHOTEP, a pCR rate of 47% after one cycle and of 68% after two cycles of pembrolizumab was reported, with a median time to surgery of 7 weeks[105]. The PICC study tested toripalimab (PD-1 ICI) with or without the cyclooxygenase 2 inhibitor celecoxib with a total of six cycles and found a pCR rate of 65% without and 88% with celecoxib with a median time to surgery of 13 weeks[106]. So far only one study randomized patients to either two cycles of sintilimab (PD-1 ICI) monotherapy versus its combination with one dose of IBI310 (CTLA-4 ICI) and reported pCRs of 47% and 78%, respectively, with a median time to surgery of 6–7 weeks[107].

AZUR2 (NCT05855200) is the only ongoing randomized clinical trial in which patients with locally advanced dMMR colon cancers are randomized to perioperative dostarlimab (PD-1 ICI) or direct surgery followed by adjuvant chemotherapy. While exceptional responses have been observed following 4–12 weeks of neoadjuvant ICI alone, the contribution of adjuvant immunotherapy is unknown and analysis will not be possible in AZUR2 due to the lack of a second randomization.

For patients with rectal cancer, the mainstay of treatment often involves radiotherapy and/or chemotherapy, followed by total mesorectal excisional surgery and, in case of very distal location of the tumors, a permanent stoma. While mismatch repair deficiency is observed in approximately 15% of early-stage colon cancers, only 3% of early-stage rectal cancers are dMMR. Dostarlimab given neoadjuvantly for 6 months was recently shown to be highly efficacious in a small cohort of patients with dMMR rectal cancers, with 100% clinical complete responses (cCRs), without the need for surgery, radiation or chemotherapy to date[108,109] (Table 3). Currently, AZUR1 (NCT05723562), a multicenter, single-arm study, is being conducted to validate these findings.

Although mismatch repair-proficient (pMMR) CRCs are generally considered 'cold' and non-immunogenic and, despite the lack of benefit of first-generation ICIs in patients with metastatic CRC, responses to neoadjuvant ICIs have been observed in early-stage disease. The pMMR cohort of the NICHE study was the first to show responses to neoadjuvant nivolumab–ipilimumab in eight of 31 patients with colon cancer, including six MPRs and one cCR[110]. More recently, in the NEST study, pathological responses to neoadjuvant botensilimab (second-generation F_c-enhanced CTLA-4 ICI) plus balstilimab (PD-1 ICI) were observed in 12 of 20 patients with pMMR tumors, including seven MPRs[111]. The UNICORN study, also testing neoadjuvant botensilimab–balstilimab, showed 71% pathological responses and 36% MPRs[112]. Conversely, in patients who were treated with botensilimab alone, 43% had a pathological response, while no MPRs were observed. Botensilimab–balstilimab is investigated in a pan-cancer study of dMMR and pMMR tumors, including CRC (NEOASIS, NCT06279130).

Pending additional data, no progression and consequent unresectability have been described to date in these pMMR studies. So far, limited data are available on predictive biomarkers of response in pMMR tumors. In four of 15 pMMR responders in the NICHE pMMR cohort, CD8 and PD-1 double-positive T cells were suggested as possible predictors of response[110]. Considering the current landscape and more encouraging data from NICHE and other trials, efforts should be made to validate previous data and provide other potential predictive biomarkers, which in turn can be used to select patients in future studies.

Breast cancer

Triple-negative breast cancer (TNBC) is considered the most immunogenic subtype of breast cancer with relatively high levels of tumor-infiltrating lymphocytes (TILs)[113]. For advanced TNBC, pembrolizumab added to chemotherapy is the SOC for patients with PD-L1-positive disease based on the randomized phase 3 KEYNOTE-355 trial[7]. For early-stage TNBC, the phase 3 KEYNOTE-522 trial has changed the current SOC[114–117] (Table 1). Pembrolizumab added to neoadjuvant chemotherapy (carboplatin–paclitaxel followed by anthracycline–cyclophosphamide) followed by adjuvant pembrolizumab for a total duration of 1 year resulted in an improvements of the pCR rate (64.8% versus 51.2%), the 5-year EFS (81.2% versus 72.2%) and the 5-year OS (86.6% versus 81.7%), compared with chemotherapy alone. In line with the evidence that pCR after neoadjuvant chemotherapy is a good surrogate endpoint for survival in TNBC, patients with a pCR had a good 5-year OS of 95.1% after chemotherapy plus pembrolizumab compared to 94.4% after chemotherapy alone[116,118]. Benefit of perioperative pembrolizumab was seen regardless of PD-L1 expression[116]. For atezolizumab (PD-L1 ICI) added to neoadjuvant chemotherapy, a similar increase in pCR rate has been reported[119].

Given the lack of a second randomization after surgery in the KEYNOTE-522 study, the contribution of adjuvant pembrolizumab

is unknown. Importantly, in the GeparNuevo and the NeoPACT phase 2 trials[120,121], patients with a pCR had excellent survival even without adjuvant immunotherapy, suggesting a modest, if any, role for adjuvant immunotherapy. In addition, trials evaluating whether immunotherapy results in better DFS when added to adjuvant chemotherapy or when used in the post-neoadjuvant setting have shown negative results[122,123]. The phase 3 OptimICE-PCR trial (NCT05812807) is currently investigating whether adjuvant pembrolizumab is beneficial for patients with a pCR after neoadjuvant chemotherapy plus pembrolizumab.

The SCARLET trial (NCT05929768) evaluates the efficacy of anthracycline-free chemotherapy plus pembrolizumab, and the NeoTRACT study (NCT05645380) tests the tailoring of chemoimmunotherapy duration based on TIL levels. The phase 2 BELLINI platform study has shown that, with only 4 weeks of immunotherapy, immune activation can be achieved in 50–60% of patients[124]. In patients with high numbers of TILs, a pCR and an MPR were observed in five and eight of 15 patients treated with two cycles of nivolumab–ipilimumab and in seven and 11 of 15 patients treated with two cycles of nivolumab–relatlimab, respectively[125].

While TIL levels can be relatively high in human epidermal growth factor receptor 2 (HER2)-positive breast cancers, so far results on the value of neoadjuvant PD-(L)1 ICI when added to chemotherapy–anti-HER2 therapy did not meet expectations. Atezolizumab added to neoadjuvant anti-HER2 therapy and doxorubicin–cyclophosphamide–paclitaxel did not increase pCR rates in the randomized phase 3 IMpassion050 study[126]. However, the ABCSG-52 trial showed that atezolizumab added to de-escalated chemotherapy (epirubicin) plus dual HER2 blockade increased the pCR rate by 10%[127]. Despite that it is still largely unknown why HER2-positive breast cancers are in general unresponsive to ICIs, the outcome of this breast cancer subtype has improved spectacularly with anti-HER2 treatments, creating a high bar to improve the outcome of this disease even further.

Estrogen receptor (ER)-positive breast cancer is in general considered a non-inflamed ('cold') tumor type; however, a subgroup of ER-positive breast cancers harbors TILs and is characterized by a disease course and genetic profiles mimicking TNBC[128]. In the I-SPY platform trial, pCR rates increased from 13–14% to 28–30% with the addition of immunotherapy (with or without the poly-ADP ribose polymerase (PARP) inhibitor olaparib) to chemotherapy[129,130]. Recently, two large phase 3 studies for high-risk (grade 3 and stage II–III) ER-positive disease (CheckMate 7FL and KEYNOTE-756) increased pCR rates with approximately 10% upon the addition of nivolumab or pembrolizumab to neoadjuvant chemotherapy (Table 3), with more pronounced increases in pCR in patients with higher TILs or lower ER levels, but the impact on EFS is yet unknown[131–134]. If improvement in EFS is seen with longer follow-up, these results may lead to changes in the SOC for high-risk ER-positive breast cancer and will pose new questions about who benefits from ICI.

UC

ICIs have demonstrated OS benefit as maintenance and as second-line therapy in advanced UC[2] and more recently against platinum-based chemotherapy in previously untreated advanced UC in combination with cisplatin–gemcitabine[135] and with the anti-Nectin-4 antibody–drug conjugate (ADC) enfortumab vedotin[136]. Additionally, the value of adjuvant immunotherapy in high-risk muscle-invasive bladder cancer (MIBC) has been tested in three phase 3 trials, showing a survival improvement with adjuvant nivolumab[20] and pembrolizumab[137] but not with atezolizumab[138].

Given the increase in response rate when testing ICIs in earlier disease settings of advanced UC, several single-arm trials testing preoperative PD-(L)1 ICI monotherapy were initiated[139,140]. In the PURE-01 study, three cycles of preoperative pembrolizumab were tested in patients having clinical T2–3N0 bladder cancer (invading the muscularis or beyond the muscularis, respectively), with a reported pCR rate of 37%[139]. Similarly, the ABACUS trial showed a pCR rate of 31% after two cycles of neoadjuvant atezolizumab in 95 patients having LN-negative MIBC[140].

While these results were encouraging, response was mainly observed in smaller tumors having pre-existing T cell immunity[140,141]. Adding CTLA-4 ICI may broaden and intensify this immune response. With respect to CTLA-4 ICI, the first results with preoperative ipilimumab in MIBC were published as early as 2010, showing feasibility before cystectomy[142]. In cohort 1 of the phase 1b NABUCCO trial in 24 patients with stage III UC treated with preoperative ipilimumab and nivolumab[143], a 46% pCR rate was observed, while the absence of invasive disease was observed in 58% of patients. Given the high rate of grade 3–4 immune-related AEs (55%), a second cohort of NABUCCO tested lower dosing of ipilimumab. However, ipilimumab (3 mg per kg) remained more effective than lower-dose ipilimumab (1 mg per kg) in combination with nivolumab. In addition, this study showed that clearance of circulating tumor DNA (ctDNA) tracked with complete response and clinical outcome as was observed in the ABACUS trial[144]. Combining highly active systemic ICI-based induction therapy with accurate disease monitoring by ctDNA assessment may provide opportunities to enable bladder-sparing alternatives to cystectomy[145,146]. A trial combining neoadjuvant nivolumab–relatlimab in UC is ongoing (NCT06237920).

Other phase 3 trials mainly investigate combinations of checkpoint inhibitors with non-immunotherapy agents. The phase 3 NIAGARA trial reported an improvement in both EFS (2-year EFS of 67.8% versus 59.8%) and OS (2-year OS of 82.2% versus 75.2%) with perioperative durvalumab added to standard neoadjuvant cisplatin–gemcitabine compared to neoadjuvant cisplatin–gemcitabine alone in patients with operable bladder cancer[147] (Table 3). The pCR rate was also improved in the immunotherapy arm (37.3% versus 27.5%). In upper-tract UC, adding durvalumab to neoadjuvant chemotherapy did not improve the pCR rate[148].

RCC

In metastatic RCC, ICIs, as a monotherapy or in combination with other ICIs or MTT, have clearly shown efficacy by improving median progression-free survival (PFS) and OS compared to the prior SOC sunitinib[6]. Furthermore, in patients with RCC who underwent surgery and were at high risk of recurrence, 1 year of adjuvant therapy with pembrolizumab led to a significant improvement in DFS and OS as compared to placebo in the phase 3 KEYNOTE-564 trial[149]. However, treatment with perioperative nivolumab in patients with high-risk RCC undergoing nephrectomy did not improve RFS versus surgery only followed by observation in the open-label randomized phase 3 PROSPER EA8143 trial[150] (Table 3). A phase 1b trial combining neoadjuvant durvalumab and tremelimumab (CTLA-4 ICI) in RCC was suspended due to high toxicity rates[151]. A trial combining neoadjuvant nivolumab–relatlimab is ongoing (NCT05148546).

Head and neck squamous cell carcinoma

Several phase 1–2 trials have investigated the use of ICIs, either as monotherapy or combined with other ICIs, radiotherapy or chemotherapy in the neoadjuvant setting in head and neck squamous cell carcinoma (HNSCC), with varying pathological, clinical and radiological responses[152]. In the phase 1–2 IMCISION trial, 4 weeks of neoadjuvant nivolumab monotherapy or nivolumab–ipilimumab in patients with locoregionally advanced HNSCC led to an MPR rate of 35% with nivolumab–ipilimumab and 17% with nivolumab monotherapy[46].

In a trial with human papillomavirus (HPV)-negative stage T3–T4 HNSCC, patients underwent treatment with one cycle of neoadjuvant pembrolizumab 1–3 weeks before surgery followed by radiotherapy with concurrent pembrolizumab for six cycles if they had high-risk features. Patients with a pathological response had an improved 1-year DFS of 92% compared to 72% in patients without a pathological response[153]. In another trial, patients with surgically

resectable HNSCC were randomized to neoadjuvant treatment of 4 weeks with nivolumab, nivolumab–ipilimumab or nivolumab–relatlimab[154]. Pathological responses (in this trial defined as 0–90% RVT) were more frequent with nivolumab–relatlimab (11 of 13) versus nivolumab–ipilimumab (six of ten) or nivolumab monotherapy (four of ten). In a nonrandomized phase 2 trial, neoadjuvant nivolumab–chemotherapy led to a response in 53% of patients with HPV-negative stage IVa–IVb HNSCC[155]. Phase 3 clinical trials are currently investigating neoadjuvant chemotherapy plus immunotherapy (NCT06102395, NCT05798793).

Gastric and gastroesophageal junction carcinoma

Perioperative chemoimmunotherapy for patients with gastric or gastroesophageal junction (G/GEJ) carcinoma has been tested in several phase 2–3 randomized controlled trials.

In the KEYNOTE-585 study, patients were randomized to chemotherapy with or without pembrolizumab, while only a subgroup of patients received the current SOC FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel) chemotherapy regimen[156] (Table 3). While the pCR rate was significantly higher in the pembrolizumab arm (12.9% versus 2.0%) and, despite a numerical difference of 20 months, the coprimary endpoint of EFS was not met. The MATTERHORN study had a similar design as KEYNOTE-585, yet with the difference that all patients received FLOT chemotherapy and were randomized to durvalumab or placebo[157] (Table 3). The pCR and combined pCR-plus-near-pCR (defined in this study as single or rare small groups of cancer cells at time of resection) rates observed in this study were significantly higher in the durvalumab group (19% versus 7% and 27% versus 14%, respectively). The phase 2 DANTE study, which investigated FLOT plus atezolizumab versus FLOT alone, reported pCR rates of 24% versus 15% and combined pCR and near-pCR (in this study defined as <10% RVT) rates of 48% versus 39%, respectively[158,159]. The study was converted into a phase 3 study and is currently ongoing. Survival data from both MATTERHORN and DANTE have not yet been reported. In the small phase 2 PANDA study, patients with G/GEJ cancers were treated with a single dose of atezolizumab monotherapy, followed by four cycles of atezolizumab plus docetaxel–oxaliplatin–capecitabine chemotherapy and did not receive adjuvant treatment[160]. In this single-arm study, pCR and MPR rates were 45% and 70%, respectively. Analysis of on-treatment biopsies in this study revealed significant immune activation in responders compared to nonresponders after the first atezolizumab administration. These results suggest that immune induction strategies before the introduction of chemotherapy may increase responses in an unselected patient population, yet these data need to be validated in larger studies.

Two small single-arm phase 2 studies investigated neoadjuvant dual ICIs in a selected population of patients with dMMR G/GEJ cancers. In NEONIPIGA, patients were treated with nivolumab–ipilimumab[161], while, in INFINITY, patients received durvalumab–tremelimumab[162]. Both studies reported high pCR (59% and 60%, respectively) and combined pCR and near-pCR (defined as <10% RVT; 73% and 80%, respectively) rates. In a separate cohort of the INFINITY study, which excluded T4 tumors due to low rates of pCR in a prior cohort, the option of nonsurgical management was explored in patients with cCR to durvalumab–tremelimumab. Of 17 evaluable patients, 13 patients with a cCR underwent active surveillance, providing the first data on a nonoperative management following immunotherapy in patients with G/GEJ cancers.

While most of the described studies have shown encouraging pCR rates, the impact on survival is uncertain, and neoadjuvant immunotherapy regimens are currently not an SOC for patients with G/GEJ cancers.

Basal cell carcinoma and cutaneous squamous cell carcinoma

The efficacy of the PD-1 ICI cemiplimab in patients with advanced basal cell carcinoma has led to the investigation of its efficacy in the neoadjuvant setting[163]. In a phase 1b trial in patients with resectable, locally advanced basal cell carcinoma of the head and neck, a pCR was observed in three of 13 patients treated with preoperative pembrolizumab[164]. A phase 2 trial with cemiplimab is ongoing (NCT05929664).

While early-stage disease cutaneous squamous cell carcinoma (CSCC) can be managed by surgery alone, locoregionally advanced disease can involve extensive and disfiguring surgery and may also necessitate radiotherapy and systemic therapy[165]. In a nonrandomized phase 2 trial, patients with resectable stage II–IV (M0) CSCC were treated with up to four doses of cemiplimab before surgery with curative intent. A pCR was observed in 51% of patients, and an MPR was observed in 64% of patients[166] (Table 3). None of the 40 patients with a pCR had a recurrence, and the DFS rate at 12 months was 92%[167]. The NEO-CESQ trial reported an MPR rate of 48% following perioperative cemiplimab (two doses preoperatively followed by 1 year of cemiplimab postoperatively) in patients with surgically resectable high-risk stage III–IV CSCC[168]. Finally, the phase 2 MATISSE trial randomized patients with CSCC with an indication for extensive surgery with or without adjuvant radiotherapy to either 4 weeks of neoadjuvant nivolumab monotherapy or neoadjuvant nivolumab–ipilimumab. Responses (MPR at surgery or a cCR) were observed in 50% and 61% of patients treated with nivolumab monotherapy and nivolumab–ipilimumab, respectively[169]. Trials with neoadjuvant nivolumab–relatlimab (NCT06288191) and pembrolizumab–favezelimab (NCT06036836) are ongoing.

Merkel cell carcinoma

In the phase 1–2 CheckMate 358 study in patients with resectable virus-associated cancers, including Merkel cell carcinoma (MCC), patients received two neoadjuvant administrations of nivolumab followed by surgery. Among 36 patients with MCC who underwent surgery, a pCR was observed in 17 patients (47.2%)[170]. A trial with neoadjuvant nivolumab–relatlimab in stage I–III MCC is ongoing (NCT06151236).

Glioblastoma

Patients with glioblastoma (GB) have a dismal prognosis. In a phase 2 study with 35 patients with surgically resectable recurrent GB, patients who received perioperative pembrolizumab had significantly extended OS compared to patients who received adjuvant immunotherapy alone[171]. A trial investigating perioperative and intratumoral (during surgery) nivolumab-plus-ipilimumab administration in patients with recurrent GB is ongoing (NCT06097975). Recently, a patient was reported on neoadjuvant treatment with a single dose of nivolumab, ipilimumab and relatlimab before primary surgery of a newly diagnosed GB, showing increased TIL numbers in the surgical specimen and prolonged PFS[172]. This observation needs to be confirmed in a clinical trial (NCT06816927).

Alternative immunotherapies in the neoadjuvant setting

In addition to neoadjuvant ICI regimens targeting PD-(L)1, CTLA-4 and LAG-3 as described above, several alternative immunotherapies are being investigated in the neoadjuvant setting, often with a PD-1 or PD-L1 ICI serving as the backbone in combinatorial regimens (Table 4).

ICIs targeting the inhibitory immune checkpoint T cell immunoreceptor with Ig and ITIM domains (TIGIT), such as vibostolimab and tiragolumab, are being studied in the neoadjuvant setting. The combination of pembrolizumab–vibostolimab in stage III melanoma led to a pCR in 38% of patients, a near-pCR in 12% of patients and a pPR in 31% of patients, while median RFS and EFS were not reached[173] (Table 4). Trials with neoadjuvant tiragolumab in combination with atezolizumab are ongoing in melanoma (NCT03554083), operable HNSCC (NCT03708224) and UC (NCT05394337).

T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) is an immune checkpoint expressed on exhausted T cells, and

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Table 4 | Neoadjuvant combinations of immunotherapy and non-immunotherapeutic drugs under investigation

Immunotherapy backbone	Novel drug and mechanism of action	Tumor types and NCT number	Phase	Estimated enrollment	Primary endpoint (result if reported)
Pembrolizumab (PD-1 ICI)	Vibostolimab (TIGIT ICI)	Stage III melanoma (NCT04303169)	1/2	26	Toxicity (8% grade 3–4 AEs) and pCR rate (38%[173])
Atezolizumab (PD-L1 ICI)	Tiragolumab (TIGIT ICI)	HNSCC (NCT03708224)	2	55	Proportion of participants with a ≥40% increase in CD3 counts and R0 resection rate
		Cisplatin-ineligible UC (NCT05394337)	1/2	10	RFS and OS
		High-risk stage III melanoma (NCT03554083)	2	30	pCR rate
Dostarlimab (PD-1 ICI)	Cobolimab (TIM-3 ICI)	Stage III–IV–M1a/M1b melanoma (NCT04139902)	2	56	MPR rate
Durvalumab (PD-L1 ICI)	Monalizumab (NKG2A ICI)	Stage IA3–IIIA NSCLC (NCT03794544)	2	20	MPR rate (30.0%[75])
Durvalumab (PD-L1 ICI)	Platinum-doublet chemotherapy plus monalizumab (NKG2A ICI)	Resectable stage IIA–IIIB NSCLC (NCT05061550)	2	72	pCR rate (26.7%[177])
Durvalumab (PD-L1 ICI)	Oleclumab (anti-CD73)	Stage IA3–IIIA NSCLC (NCT03794544)	2	21	MPR rate (19.0%[75])
		MIBC	1	12	Toxicity
Durvalumab (PD-L1 ICI)	Platinum-doublet chemotherapy plus oleclumab (anti-CD73)	Resectable stage IIA–IIIB NSCLC (NCT05061550)	2	76	pCR rate (20.0%[177])
Pembrolizumab (PD-1 ICI)	mRNA-4157 (individualized mRNA-based neoantigen therapy)	Locally advanced resectable CSCC (NCT06295809)	2/3	1,012	EFS
Nivolumab	Vidutolimod (TLR9 agonist)	Resectable stage III melanoma	2	43	MPR rate (55%[179])
Nivolumab (PD-1 ICI)	T-VEC (oncolytic virus)	Resectable early-stage or metastatic (IIIB–IV-M1a) melanoma (NCT04330430)	2	24	Pathological response rate
Pembrolizumab (PD-1 ICI)	Gebasaxturev (oncolytic virus)	Stage III melanoma (NCT04303169)	2	25	Toxicity (16% grade 3–4 AEs) and pCR rate (28%[173])
Atezolizumab (PD-L1 ICI)	RP1 (oncolytic virus)	Stage I TNBC (NCT06067061)	2	51	Safety and RCB 0–1 rate
Durvalumab (PD-L1 ICI)	Trastuzumab deruxtecan (HER2 ADC)	Stage III HER2-positive and HER2-low breast cancer (NCT05795101)	2	63	pCR rate
Penpulimab (PD-1 ICI)	Disitamab vedotin (HER2 ADC)	Stage II–III HER2-positive breast cancer (NCT05726175)	2	20	pCR rate
Cemiplimab (PD-1 ICI)	ARX788 (HER2 ADC)	HER2-positive early-stage breast cancer (NCT01042379)	2	Not reported	pCR rate
Pembrolizumab (PD-1 ICI)	Sacituzumab govitecan (TROP2 ADC)	T1cN0 and stage II–III TNBC (NCT04230109)	2	260	pCR rate
		T1cN1–N2 and T2–T4 N0–N2 TNBC (NCT05675579)	2	25	Toxicity
		Cisplatin-ineligible MIBC (NCT05535218)	2	48	pCR rate
		Resectable stage II–III NSCLC (NCT06055465)	2	37	pCR rate
Durvalumab (PD-L1 ICI)	Datopotamab deruxecan (TROP2 ADC)	HER2-negative breast cancer amenable to neoadjuvant therapy (NCT01042379)	2	106	pCR rate (54%[191])
Durvalumab (PD-L1 ICI)	Single-agent platinum-based chemotherapy plus datopotoamb deruxtecan (TROP2 ADC)	Resectable stage IIA–IIIB NSCLC (NCT05061550)	2	54	pCR rate (34.1%[177])
Pembrolizumab (PD-1 ICI)	Enfortumab vedotin (Nectin-4 ADC)	Cisplatin-eligible MIBC (NCT04700124)	3	784	EFS
		Cisplatin-ineligible MIBC (NCT04960709)	3	677	EFS
Pembrolizumab (PD-1 ICI)	Dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor)	Anaplastic thyroid carcinoma (NCT04675710)	2	30	R0/R1 resection rate and OS
Pembrolizumab (PD-1 ICI)	Lenvatinib (multitargeted kinase inhibitor)	Stage III melanoma (NCT04207086)	2	20	pCR rate (40%[193])

Table 4 (continued) | Neoadjuvant combinations of immunotherapy and non-immunotherapeutic drugs under investigation

Immunotherapy backbone	Novel drug and mechanism of action	Tumor types and NCT number	Phase	Estimated enrollment	Primary endpoint (result if reported)
Avelumab (PD-L1 ICI)	Axitinib (VEGFR inhibitor)	RCC (NCT03341845)	2	40	Radiological response rate (30%[192])
Adebrelimab (PD-L1 ICI)	Almonertinib (EGFR inhibitor) plus chemotherapy	Stage II–IIIB NSCLC (NCT06300424)	2	32	MPR rate
Durvalumab (PD-L1 ICI)	Olaparib (PARP inhibitor)	Stage II–III HER2-negative breast cancer (NCT01042379)	2	372	MPR rate (47% in TNBC subgroup[130])
Dostarlimab (PD-1 ICI)	Niraparib (PARP inhibitor)	Stage I–III HER2-negative breast cancer (NCT04584255)	2	62	Change in TILs and pCR rate
		Surgically resectable locally advanced HNSCC (NCT04681469)	2	49	MPR rate and toxicity
Volrustomig (bispecific antibody targeting PD-1 and CTLA-4)	Chemotherapy	Resectable stage IIA–IIIB NSCLC (NCT05061550)	2	70	pCR rate

R0, resection with free margins; R1, resection with invaded margins.

targeting this receptor has shown efficacy in preclinical models in combination with PD-1 ICIs[174]. The TIM-3 ICI cobolimab is being investigated in combination with dostarlimab in the neoadjuvant setting in patients with melanoma in a randomized phase 2 trial (NCT04139902).

Monalizumab is an antibody ICI that prevents killer cell lectin-like receptor C1 (NKG2A) from binding to human leukocyte antigen E on natural killer cells and T cells, thereby reactivating these cells to destroy cancer cells[175]. Monalizumab plus durvalumab has been investigated in the phase 2 NeoCOAST platform trial as a neoadjuvant therapy for resectable stage IA3–IIIA NSCLC showing an MPR rate of 30.0% in the intent-to-treat population[75] (Table 4).

Oleclumab is a monoclonal antibody that inhibits CD73, thus reducing extracellular adenosine production, which is considered immunosuppressive, and promoting antitumor immunity[176]. In the same NeoCOAST trial in NSCLC, an MPR was observed in 19.0% of patients[75]. A phase 1 trial in MIBC with durvalumab plus oleclumab is ongoing (NCT03773666). Based on the positive results of the AEGEAN trial with perioperative durvalumab plus neoadjuvant chemotherapy in resectable stage IIA–IIB NSCLC, the NeoCOAST-2 trial investigated the combination of neoadjuvant durvalumab–chemotherapy combined with oleclumab or monalizumab[177]. The pCR and MPR rates were 20.0% and 45.0% for the oleclumab arm and 26.7% and 53.3% for the monalizumab arm, respectively.

In addition, novel vaccine therapies are now widely being investigated. For example, messenger RNA (mRNA)-4157 (V940), an individualized mRNA-based neoantigen therapy derived from patient tumor samples, has been investigated in combination with pembrolizumab as an adjuvant treatment in resected high-risk melanoma in a randomized phase 2 trial (KEYNOTE-942)[178]. The rationale for this combination derives from increasing neoantigen presentation, recognition and immune activation, augmenting the effects of ICIs. This combination prolonged the RFS as compared to pembrolizumab monotherapy. This combination is now investigated in a randomized phase 3 trial in the adjuvant setting for resected high-risk melanoma (NCT05933577) and resected stage II–IIIB NSCLC (NCT06077760) as well as in a randomized phase 2 trial in the adjuvant setting for RCC (NCT06307431). A trial with perioperative pembrolizumab plus mRNA-4157 in locally advanced resectable CSCC is underway (NCT06295809).

For some tumor types such as melanoma or breast cancer, direct intratumoral administration of immunotherapy is an elegant therapeutic approach. Intratumor vidutolimod, a Toll-like receptor 9 (TLR9) agonist, has been investigated in combination with three preoperative doses of nivolumab in a phase 2 trial, showing an MPR rate of 55%[179]. Another example of intratumoral immunotherapy is an oncolytic virus. These are engineered viruses designed to preferentially infect and destroy tumor cells, and administration of these oncolytic viruses in the tumor can provoke direct cytotoxicity (leading to antigen release) while also inducing local and systemic immune responses through viral expression of pro-inflammatory cytokines[180]. Talimogene laherparepvec (T-VEC) is a genetically engineered herpes simplex virus and has shown activity in advanced melanoma[181]. A trial combining T-VEC and nivolumab in the neoadjuvant setting for resectable early-stage or metastatic (IIIB–IV–M1a) melanoma with injectable disease is currently recruiting patients (NCT04330430). A small trial with T-VEC added to neoadjuvant chemotherapy in nonmetastatic TNBC showed promising pCR rates[182], while a pilot study with nivolumab–ipilimumab–T-VEC in HER2-negative breast cancer was terminated due to notable endocrinopathies[183]. Neoadjuvant gebasaxturev (based on a coxsackievirus) in combination with pembrolizumab for stage III melanoma showed a pCR rate of 28% and an MPR rate of 40% in the KEYMAKER-U02 platform trial[173]. In cT1cN0 TNBC, the combination of RP1, an oncolytic herpes virus, and atezolizumab is being investigated in the neoadjuvant setting[184]. Multiple trials combining different oncolytic viruses with ICIs are ongoing[180].

At the time of writing, it is difficult to predict which novel combinations are most promising, having the potential to further change the neoadjuvant treatment landscape. Numerous agents, including bispecific antibodies and immunocytokines, are in development, and, because most investigators and pharmaceutical companies are aware of the advantages of neoadjuvant trials, interesting data from immunomodulatory agents beyond ICIs can be expected in the coming years.

Immunotherapy and non-immunotherapy drug combinations

While much progress has been made in the field of immunotherapy, other non-immunotherapeutic drugs such as ADCs and MTT have also substantially changed the therapeutic landscape of solid tumors (Table 4).

For example, ADCs targeting HER2, such as trastuzumab deruxtecan, have shown impressive efficacy for advanced HER2-positive breast cancer, HER2-positive gastric cancer and HER2-mutant NSCLC[185–187]. The combination of trastuzumab deruxtecan plus durvalumab is currently being investigated in a phase 2 trial as a neoadjuvant therapy for stage III HER2-positive and HER2-low breast cancer (NCT05795101). Other ADCs targeting HER2 (disitamab vedotin, ARX788) are also investigated in combination with PD-1 ICI as neoadjuvant therapy for HER2-low or HER2-positive breast cancer (NCT05726175, NCT01042379).

ADCs targeting trophoblast cell surface antigen 2 (TROP2) (sacituzumab govitecan, datopotamab deruxtecan) now have become

a new treatment option in advanced HER2-negative breast cancer and NSCLC[188–190]. Neoadjuvant sacituzumab govitecan plus pembrolizumab is being investigated in multiple early-phase trials in TNBC (NCT04230109, NCT05675579), MIBC (NCT05535218) and resectable NSCLC (NCT06055465). In the I-SPY platform trial (breast cancer), datopotamab deruxtecan plus durvalumab showed encouraging pCR rates (up to 54%)[191]. In the NeoCOAST-2 trial in resectable stage II–IIIA NSCLC, a pCR rate of 34.1% and an MPR rate of 65.9% were observed with neoadjuvant durvalumab plus single-agent platinum-based chemotherapy combined with datopotamab deruxtecan in the intent-to-treat population[177]. The combination of enfortumab vedotin and pembrolizumab has shown a significant improvement in PFS and OS against chemotherapy in previously untreated advanced UC[136]. Several phase 3 trials including neoadjuvant EV plus PD-1, PD-L1 and CTLA-4 ICIs are ongoing (NCT04700124, NCT04960709).

Similar to melanoma[44], the neoadjuvant combination of the BRAF inhibitor dabrafenib, the MEK inhibitor trametinib and pembrolizumab is under investigation for *BRAF*^{V600}-mutant anaplastic thyroid cancer (NCT04675710).

Combining tyrosine kinase inhibitors and ICIs has shown impressive efficacy in tumors such as RCC[6]. In the single-arm phase 2 NeoAvAx trial, patients with high-risk nonmetastatic RCC were treated in the neoadjuvant setting with avelumab (PD-L1 ICI) and the vascular endothelial growth factor receptor (VEGFR) inhibitor axitinib, showing a radiological partial response (primary endpoint) in 30% of patients[192]. For melanoma, neoadjuvant pembrolizumab plus lenvatinib showed a pCR rate of 43%[193]. Multiple trials involving neoadjuvant ICIs plus lenvatinib and axitinib are ongoing across tumor types.

Epidermal growth factor receptor (EGFR) inhibitors have shown impressive activity in the advanced and adjuvant setting in *EGFR*-mutant NSCLC[194]. A neoadjuvant strategy involving the EGFR tyrosine kinase inhibitor almonertinib followed by chemoimmunotherapy in stage II–IIIB NSCLC is under investigation (NCT06300424).

Combination of neoadjuvant ICI plus the PARP inhibitor olaparib and chemotherapy has been investigated in the I-SPY trial in breast cancer, showing an increase in pCR rates compared to chemotherapy (47% versus 27% in the TNBC subgroup)[130]. A trial combining neoadjuvant treatment with the PARP inhibitor niraparib plus dostarlimab in surgically resectable, HPV-negative (p16-negative status) locally advanced HNSCC is also ongoing (NCT04681469).

Conclusions and future perspectives

The neoadjuvant administration of immunotherapy for early-stage cancer has a clear biological rationale, with the potential to elicit a more robust and effective immune response when the tumor is still in place, as compared to the adjuvant setting when the immune response is directed against residual micrometastatic disease. Encouraging results from multiple clinical trials involving preoperative or perioperative treatment with ICI monotherapy or ICIs combined with other agents have led to a change in the therapeutic approach for several localized or locoregionally advanced tumor types, including melanoma, NSCLC, TNBC, dMMR CRC and UC. Multiple trials are ongoing in other tumor types. Furthermore, novel immunotherapies and breakthrough drugs such as ADCs and MTT are currently being tested in the neoadjuvant setting in combination with ICIs. While many of these trials show promising results, there is large variability in pathological response rates and survival between tumor types. This is partly explained by differences in patient populations, treatment regimens (monotherapy or combination therapy), timing of administration (neoadjuvant only or perioperative) and duration of therapy. Importantly, this is also inherent to the different biology across tumor types. Highly immunogenic tumors, such as dMMR tumors and melanoma, show the highest pathological response rates to neoadjuvant ICI, while, in other tumors, establishing pathological response in a subset of patients is considered successful. In addition, neoadjuvant immunotherapy combinations can increase efficacy but may also increase the risk of AEs and surgical delay. The additive or synergistic effect of combinatorial treatments as well as the toxicity of individual drugs can only be evaluated in a randomized trial. Another open question remains on the value of adjuvant therapy in patients who achieve a pCR or MPR to neoadjuvant immunotherapy[195,196]. In the phase 3 NADINA trial in stage III melanoma, patients who achieved an MPR to neoadjuvant nivolumab–ipilimumab and omitted adjuvant therapy had an excellent EFS[47]. Randomized trials should address this question. Future research should also focus on a better understanding of the tumor and immune microenvironment and more profound biomarker research, including pan-tumor predictors of response to neoadjuvant ICI, which will eventually lead to a personalized treatment approach.

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Additional information

Correspondence and requests for materials should be addressed to Myriam Chalabi.

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