PD-1/PD-L1 immune checkpoint inhibitors in neoadjuvant therapy for solid tumors (Review)

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Abstract. A comprehensive search regarding programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitor monotherapy or combination therapy in neoadjuvant settings of 11 types of solid cancer was performed using the PubMed, Cochrane and Embase databases, and the abstracts of various conferences were screened. Data presented in 99 clinical trials indicated that preoperative treatment with PD-1/PD-L1 combined therapy, particularly immunotherapy plus chemotherapy, could achieve a higher objective response rate, a higher major pathologic response rate and a higher pathologic complete response rate, as well as a lower number of immune-related adverse events compared with PD-1/PD-L1 monotherapy or dual immunotherapy. Although PD-1/PD-L1 inhibitor combination caused more treatment-related adverse events (TRAEs) in patients, most of the TRAEs were acceptable and did not cause marked delays in operation. The data suggest that patients with pathological remission after neoadjuvant immunotherapy exhibit improved postoperative disease-free survival compared with those without pathological remission. Further studies are still required to evaluate the long-term survival benefit of neoadjuvant immunotherapy.

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Abbreviations: ORR, objective response rate; MPR, major pathologic response; pCR, pathologic complete response; TRAE, treatment-related adverse event; irAE, immune-related adverse event; DFS, disease-free survival; OS, overall survival; PFS, progression-free survival; NACT, neoadjuvant chemotherapy; ITT, intention-to-treat; dMMR, mismatch repair-deficient; pMMR, mismatch repair-proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stability; TMB, tumor mutation burden; HR, hormone receptor; SOC, standard-of-care treatment; DLT, dose-limiting toxicities; NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; OCSCC, oral cavity squamous cell carcinoma; TNBC, triple-negative breast cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; CC, colorectal cancer; MIBC, muscle-invasive bladder carcinoma; UC, urothelial cancer MCC, Merkel cell carcinoma

Key words: neoadjuvant therapy, clinical trials, programmed cell death protein 1/programmed death-ligand 1, ORR, MPR, pCR, solid tumor

Contents

1. Introduction

Although breakthroughs have been made in pharmaceutical research and development, cancer is still a global problem and a leading cause of death at present (1,2). The emergence of immunotherapy, particularly anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy, which acts by blocking the immune escape mechanism of cancer cells, has improved the survival of patients with

advanced cancer, especially when specific molecular targets are lacking (3). For example, the OAK study (4) demonstrated that the median overall survival (OS) increased from 9.6 in patients receiving chemotherapy to 13.8 months in patients with advanced non-small cell lung cancer (NSCLC) receiving immunotherapy. Furthermore, if those patients had been treated previously, the median duration of response was notably longer in the atezolizumab group than in the docetaxel group (16.3 and 6.2 months, respectively). In breast cancer, KEYNOTE-355 (5) revealed a median progression-free survival (PFS) of 7.5 months when pembrolizumab plus chemotherapy was applied compared with 5.6 months when the placebo plus chemotherapy was used.

Neoadjuvant therapy (NAT) involves the administration of therapeutic agents prior to surgery. Neoadjuvant chemotherapy (NACT) is typically applied as a preoperative treatment for solid tumors, such as head and neck, lung, and breast cancer (6,7). Evidence has demonstrated that NACT could improve the prognosis of patients with locally advanced and borderline resectable solid cancer by reducing tumor burden, improving the tumor resection rate and controlling micrometastases (7-9). However, most patients may not markedly benefit from NACT and may, on the other hand, suffer strong side effects (10). Given that immunotherapy is a successful treatment for advanced cancer (3), a number of studies (11-13) have explored the feasibility and efficacy of immunotherapy for perioperative applications in early-stage cancer. In addition to the advantages of traditional NACT, immunotherapy uniquely activates tumor-specific T cell function and prolongs postoperative antitumor immunity, which may be associated with improved survival in a neoadjuvant setting (14). In a preclinical study, Liu *et al* (15) demonstrated that neoadjuvant immunotherapy was superior to adjuvant immunotherapy in terms of therapeutic power. Furthermore, immunotherapy is considered an effective approach to re-activate the function of exhausted $CD8^+$ T cells and control cancer progression (14). In addition, >100 clinical trials were searched for in PubMed, Cochrane and Embase (Fig. 1). The present review summarizes the clinical trial data of neoadjuvant immunotherapy for 11 solid tumor types [head and neck cancer, breast cancer, lung cancer, esophageal cancer, gastroesophageal junction and gastric cancer, hepatocellular carcinoma, renal cancer, colorectal cancer (CC), bladder cancer, melanoma and Merkel cell carcinoma]. The selection process is shown in Fig. 1.

2. Neoadjuvant anti-PD-1/PD-L1 therapy according to cancer types

Overview. The PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane (https://www.cochrane.org/) and Embase (https://www.embase.com/) databases were searched to obtain comprehensive and reliable literature. Furthermore, the abstracts of various conferences were screened using Embase. Two reviewers selected studies for inclusion and extracted data, and any disagreement was resolved by a third reviewer. The last search date was March 2022. The reviewers searched for the following combinations of key words: 'Neoadjuvant therapy'; 'Immunotherapy'; 'PD-1/PD-L1'; 'Immune checkpoint inhibitors'; 'pathologic complete response'; 'pCR'; 'objective response rate'; 'ORR'; 'major pathologic response'; 'MPR'. In order to reduce the heterogeneity of different studies, the intention-to-treat (ITT) population of individual studies was considered as the overall size of the study. The objective response rate (ORR) in tumor volume was determined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (16). The major pathologic response (MPR) was defined as the presence of 10% or fewer viable tumor cells in the primary tumor, including pathologic complete response (pCR), which was defined as tumors without any viable tumor cells in the resected cancer specimen and all sampled regional lymph nodes (17-19). The extracted metrics included: ORR, MPR, pCR, treatment-related adverse events (TRAEs), immune-related adverse events (irAEs), treatment-related surgical delay, postoperative complications, not radical resection (the condition in which surgery is completed but the tumor is not completely removed) and no surgery (the number of individuals who had not completed the operation). All data were taken from the text of each reference, and the data were aggregated and displayed in box plots based on different cancer types and different treatment modalities, and effects were compared using the midline. All graphics were generated using GraphPad Prism 8 (GraphPad Software; Dotmatics) and Adobe Illustrator 2021 (Adobe Systems, Inc.).

Head and neck cancer

NCT03342911 trial. The phase 2, single-arm study NCT03342911 assessed the ability of nivolumab in combination with chemotherapy in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) that was suitable for surgical removal. A total of 32 patients had treatment on the study regimen followed by surgery, and 26 patients were either human papillomavirus (HPV)-negative (24 patients) or HPV unknown but had oral cancer (2 patients). Of these 26 patients, MPR was observed in 17 out of 26 patients (65%) and 35% of patients had a pCR. All had negative margins at the surgery (11).

NCT02919683 trial. The phase 2, randomized study NCT02919683 investigated the effect of nivolumab combined with ipilimumab as a neoadjuvant treatment for oral cavity squamous cell carcinoma (OCSCC). A total of 29 patients were enrolled, of which 14 were randomly assigned to the nivolumab group (group 1) and 15 to the dual drugs group (group 2). The ORR was 13% (nivolumab) and 38% (nivolumab combined with ipilimumab). A total of 4 patients had exhibited MPR (nivolumab, n=1; nivolumab combined with ipilimumab, n=3), including 1 patient with a pCR in cohort nivolumab combined with ipilimumab. No surgical delays occurred. irAEs occurred in 21 (72%) patients, including grade ≥3 events in 2 (nivolumab) and 5 (nivolumab combined with ipilimumab) patients. The median follow-up time was 14.2 months, and the 1-year PFS rate was 85% (20).

CIAO (NCT03144778) trial. The phase 1, randomized study *CIAO (NCT03144778)* indicated the security and effectivity of durvalumab with or without tremelimumab in patients with stage II-IVA oropharyngeal squamous cell cancer. Of the 29 patients enrolled, one patient allocated to durvalumab was found to be ineligible, and 28 patients were randomly assigned to the durvalumab (group 1) or durvalumab plus tremelimumab (group 2) for two cycles prior to surgery groups. A total of 2 (7%) of 28 patients achieved an overall MPR, including

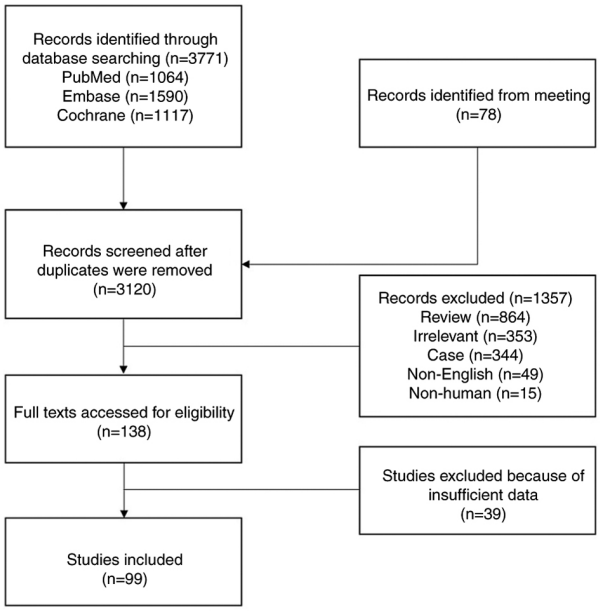

Figure 1. Flow chart of studies identified and selection criteria.

1 patient with a pCR (7%) in group 1 and 1 patient with a MPR (7%) in group 2. A total of 12 patients (43%) had an ORR, including 6 patients (40%) in group 1 and 6 patients (43%) in group 2. A total of 26 patients (90%) experienced a TRAE, including 4 patients (14%) who experienced grade 3 TRAEs. The incidence and severity of TRAEs were similar in the two treatment cohorts (21).

NCT02296684 trial. The phase 2, non-randomized two-group study NCT02296684 examined the feasibility of pembrolizumab in HPV-unrelated head and neck cancer that was resectable. In group 1, 36 patients received one dose of neoadjuvant pembrolizumab before surgery. Grade ≥3 irAEs did not occur in the neoadjuvant stage. The MPR rate was 6%. In group 2, 29 patients enrolled and 25 patients received two doses of neoadjuvant pembrolizumab before surgery. MPR was achieved in 4 patients (14%), including 1 case with a pCR (3%) (22,23).

NIRT-HNC (NCT03247714) trial. The phase 1b, single-arm study *NIRT-HNC (NCT03247714)* investigated the effectiveness of neoadjuvant nivolumab plus stereotactic body radiation therapy (SBRT) in locally advanced HPV-positive and HPV-negative HNSCC. To the best of our knowledge, this was the first report of neoadjuvant immune-radiotherapy in patients with HNSCC. Patients with resected HNSCC received nivolumab and SBRT before surgery, followed by adjuvant nivolumab. A total of 21 of the 24 enrolled patients completed neoadjuvant treatment. There were no therapy-related surgical delays and TRAEs of any grade occurred in all patients. Among the 10 HPV-positive patients treated with nivolumab and SBRT, the ORR was 50%, the MPR rate was 100% and the pCR rate was 90%. Among the 5 HPV-negative patients, the ORR was 60%, the MPR rate was 60% and the pCR rate was 20% (24).

IMCISION (NCT03003637) trial. The phase 1b/2a, non-randomized study *IMCISION (NCT03003637)* demonstrated that nivolumab with or without ipilimumab followed by surgery was an effective and feasible option for patients with resectable HNSCC. A total of 32 patients with HNSCC were treated with nivolumab (MONO; n=6) or nivolumab plus ipilimumab (COMBO; n=26) before surgery. Grade ≥3 irAEs were observed in 33% of MONO and 38% of COMBO patients. The MPR rate was 31% for patients in the COMBO group and the pCR rate of these patients was 4%. The MPR rate of patients in the MONO group was 17%. The patients who achieved MPR did not develop recurrent HSNCC within 24.0 months (25).

NCT03021993 trial. The phase 2, single-arm study NCT03021993 assessed the effectiveness of nivolumab in patients with OCSCC who were about to undergo surgery. A total of 12 patients with stage II-IVA OCSCC were treated with nivolumab followed by definitive surgical resection. Of the patients eligible for efficacy analysis, 4 had >30% response, 4 had stable disease and 4 exhibited progression of disease, resulting in an ORR of 33%. There were no pCR. Any-grade irAEs were observed in 67% of patients, and no grade ≥3 irAEs were observed. There were no delays in surgery. All patients obtained negative margins. This work suggested the feasibility and efficacy of the incorporation of nivolumab for OCSCC in the neoadjuvant stage (26).

NCT02641093 trial. The phase 2, single-arm study NCT02641093 investigated the ability of neoadjuvant pembrolizumab with adjuvant radiotherapy with or without cisplatin in patients with HNSCC. Of the 80 evaluable patients, 6 (8%) had an MPR (27).

CheckMate358 (NCT02488759) trial. The phase 1/2, randomized study *CheckMate358 (NCT02488759)* investigated the effect of nivolumab or nivolumab combination therapy in patients who had virus-associated tumors. A total of 52 patients with stage III-IV resectable HNSCC underwent neoadjuvant nivolumab treatment (26 HPV-positive; 26 HPV-negative). In group 1, the ORR and MPR rates were 12 and 6%, respectively. For group 2, the ORR was 8%, and there was no pCR. Any-grade TRAEs occurred in 73 and 54% of the HPV-positive and HPV-negative cohorts, respectively. A total of 5 (19%) and 3 patients (12%) developed grade ≥3 TRAEs, respectively. The patients had no treatment-related surgical delays (28).

Breast cancer

NCT02685059 (GeparNuevo) trial. The phase 2, randomized, double-blind, placebo-controlled study *NCT02685059 (GeparNuevo)* investigated the effect of NACT with durvalumab compared with placebo in patients with non-metastatic triple-negative breast cancer (TNBC). A total of 88 patients were randomly assigned to the durvalumab group and 86 patients were assigned to the placebo group. In the durvalumab arm, 64% of patients completed all therapies, and durvalumab was discontinued in 23%. A total of 47 out of the 88 patients (53%) treated with durvalumab achieved a pCR. Overall, 30 patients in the durvalumab arm and 29 patients in the placebo arm experienced at least one serious irAEs (12).

NCT02622074 (KEYNOTE-173) trial. The phase 1b, randomized study *NCT02622074 (KEYNOTE-173)* evaluated the efficacy and feasibility of pembrolizumab in combination with six therapeutic schedules as preoperative treatment for patients with TNBC. A total of 60 patients were enrolled and dose-limiting toxicities (DLTs) occurred in 22 patients. The pCR rate across all cohorts was 57% and the ORR was 88%.

irAEs were observed in 18 patients (30%), including grade 3 irAEs in 6 patients (10%) (29).

NCT02489448 trial. The phase 2, single-arm study NCT02489448 assessed the safety and feasibility of using durvalumab concurrently with weekly nab-paclitaxel and dose-dense doxorubicin/cyclophosphamide as neoadjuvant treatment for stage I-III TNBC. A total of 59 patients were enrolled. The ITT population was 55 patients. The pCR rate was 44% in 55 patients treated with 10 mg/kg durvalumab recommended in Phase II. The 17 patients who underwent all therapies had a pCR. In cases that exhibited pCR, there has been no recurrence over a 20-month median follow-up. Grade ≥3 TRAEs were observed in 18 patients (31%). There were no perioperative complications (30).

IMpassion031 (NCT03197935) trial. The phase 3, randomized, double-blind, placebo-controlled study *IMpassion031 (NCT03197935)* evaluated the safety and effect of neoadjuvant treatment with atezolizumab and nab-paclitaxel followed by doxorubicin and cyclophosphamide (nab-pac-AC), or placebo with nab-pac-AC in patients with TNBC who were eligible for surgery. Atezolizumab plus chemotherapy was randomly assigned to 165 patients, while placebo plus chemotherapy was administered to 168 patients. The pCR rate was 58% in the atezolizumab group. TRAEs of all grades occurred in 162 patients (98%) in the atezolizumab group, including grade ≥3 TRAEs in 57%. The number of patients who discontinued atezolizumab or placebo due to TRAEs was 21 (13%). Atezolizumab plus chemotherapy was associated with pCR in 53 (69%) of 77 patients with PD-L1-positive status compared with 37 (49%) of 75 patients in the placebo plus chemotherapy group (31).

KEYNOTE-522 (NCT03036488) trial. The phase 3, randomized, double-blind, placebo-controlled study *KEYNOTE-522 (NCT03036488)* investigated the efficacy and feasibility of pembrolizumab plus chemotherapy vs. placebo plus chemotherapy as NAT in patients with TNBC. Patients were randomly assigned to receive either pembrolizumab or a placebo, with a 2:1 ratio. A total of 240 of 401 patients (60%) in the pembrolizumab plus chemotherapy group had a pCR. irAEs occurred in 39% of patients, including grade 3 irAEs in 13% (32).

I-SPY-2 (NCT01042379) trial. The phase 2, multi-arm study *I-SPY-2 (NCT01042379)* is an adaptively randomized trial. For various breast cancer biomarker subsets, it aimed to identify novel drug combinations with higher pCR rates than standard chemotherapy. There were two results. In early-stage breast cancer, one treatment option was pembrolizumab plus NACT. A total of 69 women were randomly selected to receive four cycles of pembrolizumab in conjunction with weekly paclitaxel, followed by AC. A total of 49 of the women had hormone receptor (HR)-positive tumors, while 29 had triple-negative tumors. The final estimated pCR rates were 44, 30 and 60% for pembrolizumab in the HER2-negative, HR-positive/HER2-negative and triple-negative cohorts, respectively. Patients who achieved pCR had a higher event-free survival rate (33). Another cohort received durvalumab plus the poly (ADP-ribose) polymerase inhibitor Olaparib, combined with the standard chemotherapy [durvalumab/Olaparib/paclitaxel (DOP)] as NAT, which was evaluated in the phase II I-SPY2 trial. A total of 73 patients were randomly selected to receive DOP, including 21 patients with TNBC and 52 patients with HR-positive/HER2-negative breast cancer. On average, durvalumab plus olaparib increased the estimated pCR rates from 27 to 47% in TNBC, from 20 to 37% in HER2-negative cancer, and from 14 to 28% in HR-positive/HER2-negative cancer. In total, 20 patients (27%) in the experimental group experienced irAEs, including 9 patients (12%) in the DOP arm who had grade ≥3 irAEs (34).

NCT02530489 trial. The phase 2, single-arm study NCT02530489 assessed the feasibility and efficiency of atezolizumab plus nab-paclitaxel for the treatment of patients with TNBC. Patients with stage I-III TNBC showing suboptimal response to 4 cycles of doxorubicin and cyclophosphamide (AC) received atezolizumab plus nab-paclitaxel as the second phase of NAT before undergoing surgery followed by adjuvant atezolizumab. A total of 34 patients were enrolled and 33 patients completed NAT plus atezolizumab plus nab-paclitaxel. The pCR rate was 30%. Discontinuation of atezolizumab due to irAEs occurred in 4 patients (12%; nephritis, n=2; adrenal insufficiency, n=1; hepatitis, n=1) (35).

NCT03366844 trial. The phase 2, single-arm study NCT03366844 assessed the safety and feasibility of using pembrolizumab with standard radiation treatment prior to standard treatment for patients with breast cancer. In 20 patients, preoperative pembrolizumab was followed by radiotherapy (24 Gy/3 fractions) followed by standard-of-care treatment (SOC) 3-5 weeks later. The pCR rate was 60%. During the SOC treatment, none of the patients experienced a significant delay. During pembrolizumab with or without radiotherapy treatment, there were no toxicities of grade ≥3. Grade 4 colitis that was attributed to pembrolizumab was reported (36).

NeoTRIPaPDL1 (NCT02620280) trial. The phase 3, randomized study *NeoTRIPaPDL1 (NCT02620280)* tested the safety and effect of the addition of atezolizumab to carboplatin and nab-paclitaxel in patients with TNBC. The study included 280 patients who were randomly divided into carboplatin and nab-paclitaxel with (n=138) or without atezolizumab (n=142) groups. The pCR and ORR rates after treatment with atezolizumab were 49 and 80%, respectively. Notably, 23 patients did not complete the planned therapy. Disease progression while on treatment was documented in 8 patients (6%) treated with the atezolizumab regimen. Overall, during treatment, 98% of patients treated with atezolizumab had at least one TRAE, including grade ≥3 TRAEs in 78% (37).

GIADA (NCT04659551) trial. The phase 2, single-arm study *GIADA (NCT04659551)* evaluated the feasibility and efficacy of nivolumab combined with epirubicin/cyclophosphamide for luminal B-like breast cancer treatment in the neoadjuvant setting. pCR was achieved in 7 out of 43 patients (16%). The ORR was 71%. A total of 9 patients permanently discontinued nivolumab for safety reasons and 3 patients discontinued nivolumab for other reasons (38).

Lung cancer

checkmate-159 (NCT02259621) trial. The phase 2, single-arm study *checkmate-159 (NCT02259621)* examined the safety and efficacy of neoadjuvant nivolumab therapy in patients with high-risk resectable NSCLC. Of 22 patients enrolled, 20 were completely resected. Treatment-related surgical delays did not occur. The ORR, MPR rate and pCR rate were 10, 43 and 10%,

respectively. A total of 5 patients (23%) experienced TRAEs, and only 1 patient (5%) had a grade ≥3 TRAE. Postoperative complications occurred in 10 out of 20 patients (50%) and the most common was atrial arrhythmia (6/20; 30%) (39,40). Another article reported the results of nivolumab + ipilimumab for patients with NSCLC. For the 9 patients enrolled, the ORR was 11%. TRAEs were identified in 6 patients (67%), with 3 patients (33%) experiencing grade ≥3 TRAEs. A total of 2 patients had a pCR. The study was terminated early due to toxic side effects (41).

MK3475-223 (NCT02938624) trial. The phase 1, non-randomized study *MK3475-223 (NCT02938624)* investigated the effectiveness and safety of neoadjuvant pembrolizumab treatment for early-stage resectable NSCLC. Of 10 patients who received 2 cycles (21 days apart) of neoadjuvant pembrolizumab, 4 patients achieved an MPR. DLTs did not occur in the dose-schedule escalation cohorts (42).

NCT02716038 trial. The phase 2, single-arm study NCT02716038 tested the effectiveness of nab-paclitaxel + carboplatin + atezolizumab for the treatment of NSCLC. Of 30 patients enrolled, 29 patients were taken into the operating theatre, and 26 underwent successful R0 resection. The ORR was 63%. A total of 17 (57%) out of 30 patients had an MPR, including 33% of patients who had a pCR. To the best of our knowledge, this was the first published trial of chemotherapy combined with an anti-PD-L1 antibody in patients with resectable NSCLC (43).

NADIM (NCT03081689) trial. The phase 2, single-arm study *NADIM (NCT03081689)* assessed the feasibility, safety and efficacy of combined nivolumab with paclitaxel + carboplatin as NAT in resectable stage IIIA N2-NSCLC. In the postoperative phase, the patients were treated with nivolumab for adjuvant therapy for 1 year. Of the 46 patients enrolled, 41 patients had surgery. Of the 41 patients who underwent surgery, 12 (29%) exhibited postoperative complications. The ORR was 76%. TRAEs occurred during the period of NAT in 43 patients (93%), of which 14 (30%) had grade ≥3 TRAEs. For the ITT population, 34 (74%) patients achieved an MPR, of whom 26 (57%) had a pCR. The study had a PFS rate of 77% and an OS rate of 90% when follow-up reached 24 months (44).

ChiCTR-OIC-17013726 trial. The phase 1b, single-arm study ChiCTR-OIC-17013726 evaluated the safety and outcome of sintilimab for resectable NSCLC. Among the 40 patients enrolled, radical resection was completed in 37 patients. Neoadjuvant TRAEs occurred in 21 patients (53%), of which 4 patients (10.0%) experienced grade ≥3 neoadjuvant TRAEs. The ORR was 20%. Among the 40 patients, 15 (38%) achieved MPR, including 3 patients (8%) with pCR. A total of 2 patients had treatment-related surgical delays, and 1 patient underwent R2 resection (45).

PRINCEPS (NCT02994576) trial. The phase 2, single-arm study *PRINCEPS (NCT02994576)* assessed the feasibility and efficacy of atezolizumab as NAT in patients with resectable NSCLC. A total of 30 patients with clinical stage IA-IIIA non-N2 NSCLC received one injection of atezolizumab followed by surgery. The ORR was 7%, and an MPR was observed in 4 patients (13%). No pCR was observed. A total of 29 patients underwent R0 resection, and 1 underwent R1 resection (46).

LCMC3 (NCT02927301) trial. The phase 2, single-arm study *LCMC3 (NCT02927301)* evaluated the efficacy and toxicity of neoadjuvant and adjuvant atezolizumab in patients with NSCLC that was suitable for surgical resection. Of 181 patients enrolled, 30 patients (17%) achieved an MPR, including 10 patients with pCR. A total of 145 out of 159 patients (91%) had complete (R0) resection. A total of 44 patients (24%) experienced irAEs during neoadjuvant treatment, including 4 patients (2%) who had irAEs of grade ≥3 (47).

SAKK 16/14 (NCT02572843) trial. The phase 2, single-arm study *SAKK 16/14 (NCT02572843)* evaluated the efficacy and feasibility of the addition of durvalumab to standard NACT (with cisplatin/docetaxel) in primary resectable stage IIIA(N2) NSCLC. In 55 patients, the surgical resection rate of R0 was 93%, R1 resection was achieved in 3 patients (5%), and R2 resection was achieved in 1 patient (2%). After neoadjuvant durvalumab, the ORR was 58%. A total of 34 patients (55%) achieved an MPR, including 10 patients (16%) who achieved pCR. A total of 50 patients (81%) had TRAEs during the neoadjuvant phase and 8 patients (13%) experienced TRAEs of grade ≥3 (13).

NeoTAP01 (NCT04304248) trial. The phase 2, single-arm study *NeoTAP01 (NCT04304248)* assessed the safety and efficacy of toripalimab plus standard chemotherapy (carboplatin + pemetrexed/nab-paclitaxel) for stage IIIA or T3-4N2 IIIB NSCLC deemed surgically resectable in the neoadjuvant setting. A total of 33 patients were enrolled, and R0 was achieved in 29 patients who underwent resection. The ORR was 88%. A total of 20 patients (61%) of the population intended for treatment achieved MPR, of which 15 patients (46%) achieved pCR. Furthermore, 18% of patients developed grade ≥3 TRAEs (48).

NEOMUN (NCT03197467) trial. The phase 2, single-arm study *NEOMUN (NCT03197467)* investigated the feasibility and safety of neoadjuvant pembrolizumab therapy for resectable NSCLC. Among the 15 patients enrolled, the ORR was 27%. A total of 4 patients (27%) achieved an MPR, including 2 patients (13%) with pCR. A total of 5 patients (33%) had TRAEs during neoadjuvant treatment and 3 (20%) patients had TRAEs of grade 3. The surgery was lobectomy for all patients and complete tumor resection (R0) was achieved in all 15 patients. The incidence of postoperative complications was 7% (1 patient) due to postoperative common pneumonia (non-treatment related) (49).

NEOSTAR (NCT03158129) trial. The phase 2, randomized study *NEOSTAR (NCT03158129)* investigated the safety and feasibility of nivolumab or nivolumab plus ipilimumab as preoperative therapy for NSCLC. Of the 44 patients enrolled, 23 were randomly assigned to nivolumab monotherapy and 21 to nivolumab + ipilimumab. The ORR in the ITT population was 22% after nivolumab monotherapy, and 19% after nivolumab + ipilimumab. For the monotherapy group, the MPR was 22%, including 2 patients (9%) who achieved pCR. For the dual-drug group, the MPR and pCR rates were 38 and 29%, respectively. The complete (R0) resection rate was 100%. Grade ≥3 TRAEs were observed in 13% of patients treated with monotherapy and 10% of patients treated with combined therapy (50).

NCT02904954 trial. The phase 2, randomized study NCT02904954 evaluated the feasibility and efficacy of SBRT combined with neoadjuvant durvalumab in patients with early-stage NSCLC. The 60 patients enrolled were randomly

divided into a monotherapy group (n=30) and a combined group (n=30). It was observed that 1 patient (3%) in the monotherapy group and 14 patients (47%) in the combined group achieved ORR. No patient had a radiographic complete response. A total of 26 patients in each group completed the surgery and the R0 resection rate was 77% (23 of 30) in the monotherapy group and 83% (25 of 30) in the combined group. MPR was observed in 2 patients (7%) in the monotherapy group, and no pCR was observed. In the combined group, 16 patients (53%) had an MPR, including 8 patients (27%) who had a pCR. Overall, 5 patients (17%) in the monotherapy group and 6 patients (20%) in the combined group were observed to have grade 3-4 TRAEs (51).

TOP 1501 (NCT02818920) trial. The phase 2, single-arm study *TOP 1501 (NCT02818920)* evaluated the safety and efficacy of neoadjuvant pembrolizumab for resectable NSCLC. Of 35 patients enrolled, neoadjuvant pembrolizumab was used in 30 patients, and 25 underwent lung radical resection. A total of 22 patients achieved R0 resection, and MPR was observed in 7 of 30 patients (23%), including 3 patients (10%) with pCR. Only 1 patient had a delay attributed to treatment, and 1 patient had a grade of 3 or more irAE. The most common complication was atrial fibrillation, which affected 6 patients (24%) (52).

CheckMate 816 (NCT02998528) trial. The phase 3, randomized study *CheckMate 816 (NCT02998528)* investigated the safety and effectiveness of nivolumab plus chemotherapy vs. chemotherapy alone and described nivolumab plus ipilimumab's safety and effectiveness in treating resectable NSCLC. Of the 179 patients enrolled in the combined group, 176 patients received treatment. The radiological ORR was 55%. A total of 66 (38%) of the 176 patients achieved an MPR, including 24% of patients with a pCR. Any-grade TRAEs were observed in 145 patients (82%). Grade ≥3 TRAEs were observed in 34% of patients (53).

Esophageal cancer

KEEP-G 03 (NCT03946969) trial. The phase 2, single-arm study *KEEP-G 03 (NCT03946969)* investigated the safety and feasibility of sintilimab plus chemotherapy as a neoadjuvant treatment in esophageal cancer. In the 15 patients enrolled, sintilimab combined with lipo-paclitaxel, cisplatin and S-1 was injected for two cycles every 21 days, followed by esophagectomy. All patients completed neoadjuvant treatment as planned and achieved 100% R0 resection. A total of 8 patients (53%) achieved an MPR, including 4 patients (27%) with pCR. Grade ≥3 TRAEs occurred in 35% of patients (54).

NCT03604991 trial. The phase 2, single-arm study NCT03604991 assessed the feasibility and efficacy of neoadjuvant pembrolizumab plus chemoradiotherapy in resectable esophageal squamous cell carcinoma (ESCC). Of the 20 patients enrolled, 3 patients were still waiting for surgery, 15 patients underwent esophagectomy, and 9 patients (53%) achieved pCR (55).

PALACE-1 (NCT03792347) trial. The phase 1, single-arm study *PALACE-1 (NCT03792347)* investigated the efficacy and safety of neoadjuvant immunotherapy combined with chemoradiotherapy in patients with resectable ESCC. Of the 20 patients enrolled, 18 underwent surgery and no treatment-related surgical delay was observed. The ORR was 90%. A total of 16 patients (80%) achieved an MPR, including 10 patients (50%) with pCR. All patients had TRAEs of any grade, including 13 patients (65%) who had grade ≥3 TRAEs. To the best of our knowledge, this was the first article on the preoperative administration of two doses of pembrolizumab in combination with chemoradiotherapy in patients with resectable ESCC (56).

PERFECT (NCT03087864) trial. The phase 2, single-arm study *PERFECT (NCT03087864)* assessed the safety and efficacy of preoperative therapy with atezolizumab plus chemoradiation (carboplatin, paclitaxel and radiation) in resectable esophageal adenocarcinoma (EAC). Of the 40 patients enrolled, 10 patients (25%) achieved pCR. irAEs were observed in 6 patients (15%), including 2 patients (5%) with grade ≥3 irAEs. A total of 33 patients proceeded to surgery and all patients completed R0 resection (57).

ESONICT-1 (ChiCTR2100045659) trial. The phase 2, single-arm study *ESONICT-1 (ChiCTR2100045659)* investigated the safety and feasibility of sintilimab with cisplatin plus albumin-bound paclitaxel for locally advanced ESCC in a neoadjuvant setting. Among the 30 patients enrolled, the ORR was 67% and the MPR rate of the primary tumor was 40%, with 4 patients (13%) achieving pCR. A total of 28 patients (93%) developed TRAEs of any grade, including 1 patient (3%) who suffered a grade 3 TRAE. For 23 patients who underwent surgery, no surgery was delayed and R0 resection was achieved in all (58).

NCT03985670 trial. The phase 2, randomized study NCT03985670 investigated the efficacy and safety of neoadjuvant toripalimab in combination with chemotherapy in treating locally advanced ESCC. A total of 30 patients were randomized into two groups at a 1:1 ratio, and received chemotherapy plus sequence toripalimab (group 1) or chemotherapy in combination with toripalimab (group 2) at the same time. In the 30 patients, the ORR was 60%. The ORR of group 1 was 53% (8 of 15), and that of group 2 was 67% (10 of 15). A total of 11 patients in group 1 and 13 patients in group 2 underwent radical resection. R0 resection was observed in 24 patients. The pCR rate was 27 and 7% for groups 1 and 2, respectively. All patients had TRAEs (59).

ChiCTR1900023880 trial. The phase 2, single-arm study ChiCTR1900023880 assessed the feasibility and efficacy of camrelizumab in combination with chemotherapy and apatinib as preoperative therapy for ESCC. Of the 30 patients enrolled, 15 patients (50%) attained MPR, including 7 patients with pCR (23%). Grade 3 TRAEs were observed in 11 patients. No grade 4 and grade 5 TRAEs were mentioned. The most frequent grade 3 TRAE was neutropenia (7/30; 23.3%). No surgery-related mortality was observed (60).

NCT04506138 trial. The phase 2, single-arm study NCT04506138 evaluated the safety and efficacy of camrelizumab with chemotherapy as neoadjuvant treatment for resectable ESCC. Of the 46 patients enrolled, 18 (39%) achieved MPR, including 8 patients (17%) with pCR. All 46 patients presented with TRAEs of any grade, including 7 patients (7/46; 15%) who experienced grade ≥3 TRAEs. A total of 9 patients were deemed unsuitable for surgery. All patients who received surgery achieved R0 resection (61).

NIC-ESCC2019 trial. The phase 2, single-arm study NCT04225364 evaluated the efficacy of camrelizumab plus

concurrent chemotherapy as a neoadjuvant approach for patients with operable ESCC. Of the 56 patients enrolled, 51 patients received surgery and all achieved R0 resection. A total of 34 patients (61%) achieved an ORR. A total of 30 patients (54%) had an MPR, including 16 (29%) with pCR. irAEs of any grade occurred in 23 patients (41%), including 2 patients (4%) with grade ≥3 irAEs. Postoperative complications were observed in 14 patients (62).

NCT04177797 trial. The phase 2, single-arm study NCT04177797 assessed the feasibility and efficacy of toripalimab with carboplatin and paclitaxel as a preoperative regiment for ESCC. A total of 20 patients were enrolled and underwent toripalimab plus paclitaxel and carboplatin treatment for 2 cycles (21 days apart), followed by planned esophagectomy. A total of 16 patients did not experience treatment-related surgical delay, and among these, 2 patients did not receive radical resection. In the 20 patients, the ORR was 55%. The MPR rate was 35%, including 3 patients (15%) with pCR. TRAEs were observed in all patients (100%), including 4 patients (20%) with grade ≥3 TRAEs (63).

ChiCTR1900026240 trial. The phase 2, single-arm study ChiCTR1900026240 assessed the safety and efficacy of camrelizumab plus NACT in patients with resectable ESCC. A total of 60 patients received intravenous camrelizumab plus nab-paclitaxel and carboplatin. Of the 60 patients enrolled, 51 patients completed surgery and R0 resection was reached in 50 patients. A total of 24 patients (40%) achieved ORR. A total of 35 patients (58%) had an MPR, including 20 patients with pCR. irAEs occurred in 27 patients (45%), including 2 patients who had grade 3 irAEs. Overall, postoperative complications occurred in 24 of 51 (47%) patients (64).

Gastroesophageal junction (GEJ) and gastric cancer

NCT03044613 trial. The phase 1, single-arm study NCT03044613 assessed the safety and feasibility of neoadjuvant nivolumab combined with chemoradiation in patients with local advanced esophageal/GEJ cancer. Of the 16 patients enrolled, 10 patients underwent surgery at the cut-off time. pCR was achieved in 4 patients (25%). This regimen had an acceptable toxicity profile and did not cause delays in surgery (65).

NCT03939962 trial. The phase 2, single-arm study NCT03939962 evaluated the feasibility and efficacy of camrelizumab plus 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) as preoperative therapy for patients with gastric and GEJ cancer (GC/GEJC). Of the 16 patients enrolled, 15 patients underwent an operation and 13 patients had R0 resection. A total of 3 patients (19%) achieved an MPR, including 1 patient (6%) with pCR. The most common grade ≥3 TRAE was neutropenia (n=3; 19%). No serious TRAEs were observed (66).

NCT02998268 trial. The phase 2, single-arm study NCT02998268 investigated the safety and efficacy of neoadjuvant pembrolizumab in combination with chemoradiotherapy in locally advanced EAC or GEJ adenocarcinoma. Of the 31 patients enrolled, an MPR was achieved in 50% of patients. irAEs of grade ≥3 was not observed. The 1-year disease-free survival (DFS) rate was 100% for patients who achieved MPR (67).

NCT03488667 trial. The phase 2, single-arm study NCT03488667 evaluated the efficacy and tolerability of oxaliplatin + leucovorin + 5-FU (mFOLFOX6) plus pembrolizumab in patients with resectable adenocarcinoma of the GEJ and stomach. Of the 35 patients enrolled, only 32 patients were evaluated for surgery, and 26 had curative intended operations with R0 resection for all. pCR was observed in 5 patients (16%). Grade ≥3 TRAEs were observed in 19 of all 35 patients (54%) and there were no unexpected toxicities (68).

NCT04890392 trial. The phase 2, single-arm study NCT04890392 investigated the safety and efficacy of neoadjuvant tislelizumab combined with s-1 plus oxaliplatin in patients with local advanced GC/GEJC. Of 21 patients enrolled, 13 (62%) achieved an MPR. A total of 5 patients had a complete tumor response (24%) and 2 patients were assessed as disease progression (10%). TRAEs occurred in 11 out of 21 patients (52%). Grade ≥3 TRAEs occurred in only 1 of 21 patients (5%) (69).

NCT04065282 trial. The phase 2, single-arm study NCT04065282 evaluated sintilimab plus CapeOx (oxaliplatin and capecitabine) as preoperative therapy in patients with resectable G/GEJC. For the 36 patients enrolled, the ORR was 11%. RECIST V.1.1 was not considered the best measure of efficacy to assess NAT for GC (70). A total of 17 patients (47%) achieved an MPR, including 7 patients with pCR. All patients completed planned surgery and 1 patient had R1 resection. A total of 33 (92%) and 1 (3%) patient experienced TRAEs and irAEs, respectively. A total of 10 patients (28%) experienced grade 3 TRAEs. The 1-year DFS and OS rates were 90 and 94%, respectively (70).

Hepatocellular carcinoma (HCC)

NCT03299946 trial. The phase 1b, single-arm study NCT03299946 evaluated the safety and efficacy of cabozantinib combined with nivolumab in patients with local advanced HCC. Of 15 patients enrolled, 12 achieved R0 resection, and 5 patients (33%) had an MPR, including 1 patient (7%) with a pCR. The ORR was 7%. TRAEs of any grade were observed in 14 patients (93%), including 2 patients (13%) with grade ≥3 TRAEs (71).

NCT03510871 trial. The phase 2, single-arm study NCT03510871 investigated the tolerability and efficacy of preoperative nivolumab + ipilimumab in patients with resectable HCC. Of 29 patients enrolled, 5 patients (17%) achieved an MPR. The ORR was 24%. The most common all-grade TRAE was hepatitis (48%). Grade ≥3 TRAEs occurred in 12 patients (41%), including 7 patients (24%) with irAEs (72).

NCT03222076 trial. The phase 2, randomized study NCT03222076 assessed the safety and feasibility of neoadjuvant nivolumab monotherapy or nivolumab plus ipilimumab in patients with resectable HCC. The 27 patients enrolled were randomly divided into monotherapy (13 patients) and combination therapy (14 patients) groups. The ORR was 23% for nivolumab monotherapy and 0% for combination therapy. A total of 3 patients (23%) with monotherapy and 3 patients (21%) with nivolumab plus ipilimumab therapy had an MPR, including 2 patients (15%) who achieved a pCR with nivolumab treatment, as did 3 patients (21%) in the combined group. No patients experienced surgery delay. To the best of our knowledge, this was the first study to investigate nivolumab plus ipilimumab as a neoadjuvant treatment in patients with local advanced HCC (73).

NCT03916627 trial. The phase 2, single-arm study NCT03916627 evaluated the clinical activity of neoadjuvant cemiplimab in patients with resectable HCC. A total of 21 patients were injected two cycles of cemiplimab every 21 days followed by radical removal. All patients received planned treatment and 20 patients completed surgery. Of 21 patients enrolled, 3 (14%) had an overall response. A total of 4 patients had marked tumor necrosis, including 3 (14%) who had a pCR. TRAEs of any grade occurred in 6 patients (29%), including 2 patients (10%) with grade 3 TRAEs. No grade 4 or 5 TRAEs were reported (74).

Renal cancer

NCT02210117 trial. The phase 1, randomized study NCT02210117 assessed the safety and clinical activity of nivolumab alone, nivolumab with bevacizumab or nivolumab combined with ipilimumab in patients with metastatic renal cell carcinoma (RCC). A total of 105 patients were randomly assigned (at a ratio of 2:3:2) to receive nivolumab alone, nivolumab in combination with bevacizumab or nivolumab combined with ipilimumab, followed by cytoreductive surgery. The ORR was 55, 44 and 43%, respectively. Grade ≥3 TRAEs were observed in 38% of patients in the nivolumab group, 42% of patients in the nivolumab + bevacizumab group and 47% of patients in the nivolumab + ipilimumab group (75).

NCT03680521 trial. The phase 2, single-arm study NCT03680521 evaluated the safety and efficacy of sitravatinib combined with nivolumab in patients with resectable clear cell RCC. DLTs led to a dose de-escalation, resulting in 7 patients treated at 120 mg 1 day apart (QD) sitravatinib and 13 treated at 80 mg QD. Of 20 patients enrolled, 2 patients (10%) achieved a partial response. There was 1 delayed surgery due to immune-related thyroiditis. TRAEs of any grade occurred in 100% of patients, including grade 3 TRAEs in 45% of patients. No grade 4/5 TRAEs were observed (76).

NCT02575222 trial. The phase 1, single-arm study NCT02575222 evaluated the feasibility and safety of neoadjuvant nivolumab in patients with nonmetastatic RCC. Of 17 patients enrolled, all patients completed three doses of neoadjuvant nivolumab and underwent surgery without delay. Although none met the radiographic criteria for an object response, 1 patient was found to have a pathological partial response. Any-grade irAEs occurred in 10 patients (59%). No grade ≥3 irAEs occurred. No patient experienced a Clavien grade ≥III postoperative complication (77).

*NeoAvAx(*NCT03341845*) trial*. The phase 2, single-arm study *NeoAvAx*(NCT03341845) investigated the safety and efficacy of neoadjuvant avelumab plus axitinib in patients with localized RCC. Of 40 patients enrolled, 12 patients (30%) achieved a partial response. There were no treatment-related surgery delays and no progression. At a median follow-up of 23.5 months, recurrence occurred in 13 patients (78).

NCT02595918 trial. The phase 1, single-arm study NCT02595918 evaluated the feasibility and safety of preoperative nivolumab in patients with localized RCC. All 18 patients completed surgery without delay, and 17 received at least three nivolumab doses, resulting in a feasibility rate of 94%. All patients did not develop progressive disease during the nivolumab administration period. No MPR was observed. irAEs of any grade were observed in 3 patients (17%), including 2 patients (11%) with grade 3 irAEs. No grade 4/5 irAEs were observed (79).

Colorectal cancer (CC)

NICHE (NCT03026140) trial. The phase 2, randomized study *NICHE (NCT03026140)* investigated the efficacy, feasibility and antitumor activity of ipilimumab plus nivolumab with or without celecoxib in patients with mismatch repair (MMR)-proficient (pMMR) and MMR-deficient (dMMR) early-stage colon cancer. Of 40 patients enrolled, 35 patients underwent radical resections within the predefined 6 weeks and 100% of the resections were radical. A total of 20 patients (dMMR) and 8 patients (pMMR) received ipilimumab plus nivolumab, and 7 patients (pMMR) received ipilimumab plus nivolumab with celecoxib. A total of 19 patients (95%) with dMMR tumors had an MPR, including 12 (60%) with pCR. A total of 3 patients with pMMR tumors that received ipilimumab plus nivolumab had an MPR, including 2 patients with pCR. Of the 7 patients with a pMMR tumor who received celecoxib in addition to ipilimumab + nivolumab, only 1 patient (14%) achieved an MPR. TRAEs of any grade occurred in 70% of patients (28 of 40), including 5 patients (13%) who had grade ≥3 TRAEs. Postoperative complications were observed in 9 patients (80).

EPOC1504 (NCT02948348) trial. The phase 1b/2, single-arm study *EPOC1504 (NCT02948348)* assessed the feasibility and efficacy of preoperative nivolumab plus chemoradiotherapy in patients with microsatellite stability (MSS) and microsatellite instability-high (MSI-H) locally advanced rectal cancer (RC). Sequential use of nivolumab combined with chemoradiotherapy and radical surgery was well tolerated. In MSS RC, an MPR was observed in 14 patients (38%), including 11 patients (30%) with a pCR. Among the 5 patients with MSI-H RC enrolled, pCR was observed in 3 patients (60%). irAEs of any grade were observed in 3 patients (7%), including 2 patients (5%) with grade ≥3 irAEs. No treatment-related deaths were observed (81).

NICOLE (NCT04123925) trial. The phase 2, single-arm study *NICOLE (NCT04123925)* evaluated the feasibility and safety of neoadjuvant nivolumab in patients with unselected MMR early-stage CC. Of 22 patients enrolled, including 19 pMMR and 3 dMMR cases, all patients received radical resection without delays. An MPR was observed in 3 patients (14%) with pMMR, including 1 patient (5%) with a pCR. No MPR was observed in patients with dMMR. To the best of our knowledge, this was the first study to assess nivolumab as preoperative treatment in dMMR and pMMR resectable CC (82).

NRG-GI002 (NCT02921256) trial. The phase 2, randomized study *NRG-GI002 (NCT02921256)* assessed the feasibility, safety and efficacy of the addition of pembrolizumab after neoadjuvant chemoradiotherapy combined with FOLFOX in patients with locally advanced RC. A total of 185 patients were randomly assigned to the control arm (n=95) or the pembrolizumab arm (PA; n=90). In the PA group, 69 patients received radical surgery and the R0 resection was observed in 94% of patients. A pCR was observed in 22 patients (24%). irAEs were observed in 35 patients (39%), including 3 patients (3%) with grade 3 irAEs (83).

AVANA (NCT03854799). The phase 2, single-arm study *AVANA (NCT03854799)* investigated the role of avelumab in

combination with neoadjuvant chemoradiotherapy in patients with locally advanced RC. Of 101 patients enrolled, 59 patients (58%) achieved an MPR, including 22 (22%) with a pCR. The rate of grade ≥3 irAEs was 4% (84).

PANDORA (NCT04083365) trial. The phase 2, single-arm study *PANDORA (NCT04083365)* investigated the feasibility and safety of durvalumab in combination with neoadjuvant chemoradiotherapy in patients with locally advanced RC. Of 19 patients enrolled, 18 patients underwent surgery. A pCR was observed in 5 patients (26%). A total of 8 patients (42%) had any-grade irAEs related to durvalumab, and no grade ≥3 irAEs related to durvalumab treatment were observed. The study demonstrated that radiotherapy plus capecitabine followed by durvalumab as a preoperative option had an acceptable toxicity profile and promising antitumor activity (85).

Averectal (NCT03503630) trial. The phase 2, single-arm study *Averectal (NCT03503630)* evaluated the safety and efficacy of short-course radiation followed by mFOLFOX6 with avelumab in patients with locally advanced RC. Of 44 patients enrolled, 40 patients completed at least 1 treatment cycle and total mesorectal excision. An MPR was observed in 27 patients (61%), and 15 patients (34%) achieved a pCR. No grade ≥3 irAEs were reported (86).

R-IMMUNE (NCT03127007) trial. The phase 1b/2, single-arm study *R-IMMUNE (NCT03127007)* evaluated the feasibility and safety of neoadjuvant atezolizumab combined with radio-chemotherapy in patients with locally advanced RC. Of 26 patients enrolled, six patients (23%) achieved a pCR. Overall, 151 TRAEs were reported and 20 (13%) were grade ≥3 in 9 patients (35%), including 2 (10%) anastomotic leakage/infections, 4 (20%) urinary infections, 1 (5%) renal function impairment and 1 (5%) immune thrombocytopenia (87).

PICC (NCT03926338) trial. The phase 2, randomized study *PICC (NCT03926338)* evaluated the feasibility and efficacy of neoadjuvant toripalimab with or without celecoxib in patients with dMMR or MSI-H CC. A total of 34 patients were randomly divided into either the combination group (n=17) or the monotherapy group (n=17) at a 1:1 ratio. All patients in both groups received radical resection within the normal period and 34 (100%) were R0 resections. A total of 16 patients (94%) in the dual drug group and 17 (100%) in the monotherapy group had an MPR, and pCR occurred in 15 patients (88%) in the dual group and 11 patients (65%) in the monotherapy group. TRAEs of any grade were observed in 11 patients (65%) in the combination group and 10 patients (59%) in the monotherapy group, including 1 patient (6%) with grade ≥3 TRAEs in the combination group (88).

Bladder cancer

PURE-01 (NCT02736266) trial. The phase 2, single-arm study *PURE-01 (NCT02736266)* investigated the safety and activity of preoperative pembrolizumab in patients with muscle-invasive bladder carcinoma (MIBC). The study allowed the presence of predominant variant histology (VH), defined as involving >50% of the tumor specimens. Of 114 patients enrolled, VHs were found in 34 patients, with predominant VHs in 19 patients. In total, 42 patients (37%) achieved a pCR, including 3 patients (16%) with predominant VH and 39 patients (41%) with other histological categories. A total of 63 patients (55%) achieved tumor downstaging to pT≤1 (89).

ABACUS (NCT02662309) trial. The phase 2, single-arm study *ABACUS (NCT02662309)* assessed the feasibility and efficacy of preoperative atezolizumab in patients with MIBC. Of 95 patients enrolled, 8 patients did not undergo cystectomy. A total of 58 patients underwent sequential imaging at the preoperative stage. Radiological progression occurred in 16% of patients, and the ORR was 22%. An MPR was observed in 34 patients (36%), including 27 patients (28%) with pCR. Among all patients, 42 patients (44%) had irAEs of any grade, and grade ≥3 irAEs occurred in 10 patients (11%). No surgery was delayed due to treatment-related toxicities. Postoperative complications occurred in 53 patients (90,91).

NCT02812420 trial. The phase 1, single-arm study NCT02812420 investigated the safety and efficacy of neoadjuvant durvalumab plus tremelimumab in cisplatin-ineligible patients with muscle-invasive bladder cancer (MIBC) identified as having high-risk features. Of 28 patients enrolled, 24 patients completed cystectomy and 2 patients had delays related to toxicities. A pCR (pT0N0) was observed in 8 patients (29%). irAEs of any grade occurred in 26 patients (93%), including grade ≥3 irAEs in 21% of patients. No deaths related to therapy occurred (92).

BLASST-2 (NCT03773666) trial. The phase 1, single-arm study *BLASST-2 (NCT03773666)* evaluated the feasibility and safety of neoadjuvant durvalumab in patients with MIBC. Of 10 patients enrolled, 8 patients underwent radical cystectomy. A pCR was observed in 1 patient (10%). A grade 3 TRAE was reported in 1 patient (10%), with no grade ≥4 TRAE. No DLT was observed (93).

DUTRENEO (NCT03472274) trial. The phase 2, randomized study *DUTRENEO (NCT03472274)* prospectively explored the feasibility of preoperative anti-PD-L1 + anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4) vs. chemotherapy in patients with MIBC selected according to a tumor pro-inflammatory IFN-γ signature [tumor immune score (TIS)]. Patients with MIBC who receive cisplatin are classified as 'hot' or 'cold' according to the tumor TIS. A total of 23 patients randomly assigned to the 'hot' arms received durvalumab plus tremelimumab. A pCR was achieved in 8 patients (35%). Grade ≥3 irAEs were reported in 5 patients (22%) (94).

NEODURVARIB (NCT03534492) trial. The phase 2, single-arm study *NEODURVARIB (NCT03534492)* investigated the feasibility and safety of neoadjuvant durvalumab plus olaparib in patients with MIBC. Of 29 patients enrolled, 26 underwent radical cystectomy. Partial response of radiology was observed in 24% of patients. A pCR was observed in 13 patients (45%). No dose reductions were indicated (95).

GU14-188 (NCT02365766) trial. The phase 1b/2, non-randomized study *GU14-188 (NCT02365766)* investigated the safety and efficacy of neoadjuvant pembrolizumab combined with gemcitabine with or without cisplatin in patients with cisplatin-eligible/ineligible muscle-invasive bladder cancer (MIBC). In the cisplatin-eligible group, 43 patients were enrolled. The pCR rate was 44%. A total of 4 patients did not have radical cystectomy (96). In the cisplatin-ineligible group, 37 patients were enrolled. The pCR rate was 45%. There were 4 patients (11%) with grade 3 irAEs. A total of 3 patients did not undergo radical cystectomy (97).

NABUCCO (NCT03387761) trial. The phase 1, randomized study *NABUCCO (NCT03387761)* evaluated the feasibility and safety of neoadjuvant nivolumab plus ipilimumab in patients with locoregionally advanced urothelial cancer (UC). In cohort 1 of the study, 24 patients were injected two doses of ipilimumab and two doses of nivolumab, followed by radical surgery. An MPR was attained in 20 patients (83%), including 11 (46%) with pCR. irAEs of any grade were reported in all patients (100%), and grade ≥ 3 irAEs occurred in 55% of patients (98). In cohort 2, 30 patients were randomly divided into arms A and B, 26 underwent radical surgery, and 24 patients received surgery within 12 weeks. In arm A, 6 patients (40%) had a pCR. In arm B, 1 patient (7%) had a pCR. This trial suggests that a higher dose of ipilimumab is a more efficacious neoadjuvant treatment than a low dose of ipilimumab in UC (99).

NCT02451423 trial. The phase 2, non-randomized study NCT02451423 assessed the best dose of neoadjuvant atezolizumab in treating patients with bladder cancer that has not spread to other places in the body. A total of 20 patients were enrolled and sequentially treated with one (n=6), two (n=5) and three (n=9) cycles of atezolizumab prior to radical cystectomy. pCR was observed in 1 patient (17%) in the one-dose group and 1 patient (20%) in the two-dose group. No pCR was observed in the three-dose group. TRAEs of any grade were observed in 75% of patients, including 10% who had grade 3 TRAEs. There were no grade 4/5 events (100).

PrE0807 (NCT03532451) trial. The phase 1, non-randomized study *PrE0807 (NCT03532451)* evaluated the feasibility and safety of nivolumab with or without lirilumab as a preoperative regimen in patients with resectable MIBC. Among 43 patients enrolled, 13 patients were in the group of nivolumab alone (cohort 1) and 30 were in the group of nivolumab plus lirilumab (cohort 2). The pCR rates for cohorts 1 and 2 were 8 and 18%, respectively. Grade 3 TRAEs occurred in 0% of patients in cohort 1 and 7% of patients in cohort 2. No grade 4/5 traces occurred (101).

SAKK 06/17 (NCT03406650) trial. The phase 2, single-arm study *SAKK 06/17 (NCT03406650)* investigated the safety and efficacy of neoadjuvant durvalumab combined with standard NACT (with cisplatin/gemcitabine) in patients with MIBC. Of 58 patients enrolled, 53 underwent resection and R0 resection was completed in 52 patients. A total of 18 patients (31%) achieved a pCR. TRAEs of grade ≥3 were observed in 75% of patients, and irAEs of grade ≥3 were observed in 8 patients (14%) (102).

LCCC 1520 (NCT02690558) trial. The phase 2, single-arm study *LCCC 1520 (NCT02690558)* evaluated the safety and efficacy of gemcitabine and cisplatin in combination with pembrolizumab as a NAT before radical cystectomy in MIBC. Of 39 patients enrolled, 38 patients underwent radical cystectomy, and 4 patients did not have R0 resection. No patients had clinical or radiographic progression before radical cystectomy. pCR was achieved in 14 patients (36%). All patients experienced at least one TRAE of any grade, and 74% of patients experienced grade ≥3 TRAEs. Only 1 patient (3%) had a grade 3 irAE (103).

NCT02989584 trial. The phase 2, single-arm study NCT02989584 investigated the feasibility and safety of atezolizumab followed by four cycles of gemcitabine and cisplatin (GC) in patients before radical cystectomy and pelvic lymph node dissection (RC-PLND). Of 44 patients enrolled, 36 patients underwent RC-PLND and no patient had TRAE-related surgical delays. A total of 27 patients (61%) achieved non-muscle-invasive downstaging to less than pT2N0, including 16 patients (36%) with a pCR. Among the 44 patients, 98% experienced TRAEs, including 26 patients (59%) with a grade ≥3 TRAE. The most common grade ≥3 TRAE was neutropenia (36%). irAEs of grade 3 occurred in 5 patients (11%). No grade 4 irAEs were observed (104).

Melanoma

OpACIN (NCT02437279) trial. The phase 1b, randomized study *OpACIN (NCT02437279)* examined the safety and efficacy of neoadjuvant vs. adjuvant nivolumab plus ipilimumab in patients with operable stage III melanoma. In the neoadjuvant group, 10 patients were enrolled. All patients in the neoadjuvant treatment arm achieved planned surgery. The ORR was 40%. An MPR was achieved in 6 patients (60%), including 3 patients (30%) with a pCR. TRAEs of any grade were observed in all patients and grade ≥3 TRAEs were observed in 9 patients (90%) in the neoadjuvant arm (105).

NCT02519322 trial. The phase 2, randomized study NCT02519322 assessed the feasibility and efficacy of preoperative nivolumab with or without ipilimumab in patients with high-risk resectable melanoma and evaluated the feasibility of nivolumab in combination with relatlimab. For the nivolumab vs. combined ipilimumab with nivolumab group, 23 patients were randomly assigned to monotherapy (n=12) and combined therapy (n=11). The ORR was 25% with nivolumab monotherapy and 73% with combined ipilimumab and nivolumab therapy. A pCR was observed in 3 patients (25%) and 5 patients (45%), respectively. TRAEs of any grade occurred in 11 patients (92%) with nivolumab monotherapy and 10 (91%) with combined ipilimumab and nivolumab therapy, including grade-3 TRAEs occurring in 1 patient (8%) and 8 patients (73%), respectively. No grade 4 or 5 TRAEs were observed (106). For the nivolumab combined with relatlimab group, 30 patients were enrolled and 29 underwent surgery. The ORR was 57% and the MPR rate was 66%, including a pCR rate of 59%. The 1-year recurrence-free survival (RFS) for patients with an MPR was 100% compared with 80% for patients without an MPR. There were no grade ≥3 TRAEs (107).

OpACIN-neo (NCT02977052) trial. The phase 2, randomized controlled study *OpACIN-neo (NCT02977052)* identified a promising dosing schedule of ipilimumab plus nivolumab. ORR was achieved in 45 patients (52%) overall: 19 patients (63%) in group A, 17 (57%) in group B and 9 patients (35%) in group C. An MPR was observed in 21 patients (70%) in group A [14 (47%) with a pCR], 19 patients (64%) in group B [17 (57%) with a pCR] and 12 patients (46%) in group C [6 (23%) with a pCR]. irAEs of any grade occurred in 29 patients (97%) in group A, 29 patients (97%) in group B and 26 patients (100%) in group C. Grade ≥3 irAEs were reported in 12 patients (40%) in group A, 6 patients (20%) in group B and 13 patients (50%) in group C. None of the 64 patients who achieved a pathological response had relapsed after a median follow-up of 32 months, whereas 9 patients (43%) without pathological response had relapsed or progressed before surgery (108).

NCT02434354 trial. The phase 1, single-arm study NCT02434354 evaluated the safety, tolerability and irAE profile of pembrolizumab in patients with high-risk melanoma, and tumor tissues were collected from patients before and after receipt of pembrolizumab to examine how the experimental drug interacted with tumor tissue. Of 27 patients evaluable at the time of cut-off, 8 patients (30%) achieved an MPR, including 5 patients (19%) with a pCR. All patients who achieved a complete or MPR did not relapse. Grade 3 irAEs were observed in 6 patients (22%), with no grade 4 events and no delays in surgical management (109,110).

OrienX010-II-12 (NCT04197882) trial. The phase 1b, single-arm study *OrienX010-II-12 (NCT04197882)* evaluated the efficacy and tolerability of recombinant human granulocyte-macrophage colony-stimulating factor herpes simplex virus intratumoral injection (OrienX010) combined with toripalimab as a preoperative regimen in patients with local advanced melanoma. In the 30 patients enrolled, the ORR was 33% (10 patients). A total of 21 patients exhibited pathologic responses, including 3 (10%) showing a pCR. All patients had TRAEs and 3 patients (10%) had grade ≥3 TRAEs (111).

*HCI102346(*NCT03259425*) trial*. The phase 2, single-arm study *HCI102346(*NCT03259425*)* evaluated the safety and efficacy of neoadjuvant nivolumab and canerpaturev in resectable stage IIIB, IIIC and IVM1a melanoma. Of 7 patients enrolled, 6 underwent surgery after nivolumab and canerpaturev and were evaluable. A pCR was observed in 5 patients (83%), and R0 resection was achieved in 5 patients. Radiographic complete or partial responses were observed in 4 patients (67%). At a median follow-up of 27.3 months, RFS was achieved in 50% of patients (112).

EudraCT 2018-002172-40 trial. The phase 2, single-arm study EudraCT 2018-002172-40 assessed the safety and efficacy of the ipilimumab/nivolumab combination as primary treatment for patients with locally advanced or oligometastatic melanoma. Of 35 patients enrolled, 3 patients are still in NAT and 3 patients were discontinued before surgery. A total of 6 patients (17%) developed treatment-related grade ≥3 TRAEs. An MPR was achieved in 18 patients (51%), including 16 (46%) with a pCR. Furthermore, 1 patient died 5 months after the end of therapy due to an ischemic stroke (113).

NCT02339324 trial. The pilot phase 1b/2, single-arm study NCT02339324 evaluated the safety and efficacy of neoadjuvant pembrolizumab combined with high-dose IFNa-2b in patients with high-risk surgically resectable stage III or IV melanoma. Of 30 patients enrolled, all patients were evaluated for efficacy and underwent surgery as planned. The ORR was 73% (22 patients). An MPR was achieved in 17 patients (57%), including 13 (43%) with a pCR. All patients experienced at least one TRAE of any grade. The most common grade 3 TRAE was hypophosphatemia, which was observed in 13 patients (43%). At the time of cut-off, the patients with a pCR had not experienced recurrence (114).

Merkel cell carcinoma (MCC)

CheckMate358 (NCT02488759) trial. The phase 1/2, randomized study *CheckMate358 (NCT02488759)* investigated the safety and efficacy of nivolumab monotherapy or nivolumab combination therapy in patients with virus-associated tumors. In the neoadjuvant MCC cohort, 39 patients were enrolled and 36 of these patients received the planned doses of nivolumab. The ORR was 46%. An MPR was achieved in 21 patients (54%), including 17 patients (44%) with a pCR. Any-grade TRAEs were reported in 18 patients (46%), including 3 patients (7%) with grade ≥3 TRAEs (115).

3. Benefits and efficacy of neoadjuvant immunotherapy

A number of studies (7-9) have demonstrated that NACT is an attractive strategy to improve postoperative outcomes. Its primary clinical benefits stem from its ability to reduce the volume of the primary tumor, control micrometastases and decrease growth factor release caused by surgery or subsequent wound healing (8,9,116,117). With immunotherapy being hailed as a potentially practice-changing therapy for advanced cancer, ongoing studies (20,29,48) seek to determine the efficacy of neoadjuvant immunotherapy in the early stages of cancer. The present review demonstrated that immunotherapy is promising in the neoadjuvant setting. In addition to the advantages offered by NACT, a unique feature is that it stimulates tumor-specific T cells against all tumor neoantigens and attacks the minimally residual tumor cells throughout the body (14). Therefore, neoadjuvant immunotherapy may decrease the risk of disease recurrence and benefit the OS of patients with cancer (15).

Details of the clinical trials investigated in this review are listed in Table I. A total of 11 cancer types were included in the analysis, and more than half of the studies were phase 1/2 single-arm trials. Therefore, the sample size of most trials was small. The present review describes seven distinct forms of NAT, including immune checkpoint inhibitor monotherapy (IO), IO in combination with another IO, IO in combination with chemotherapy, IO plus radiotherapy, IO plus chemoradiotherapy, IO in combination with anti-VEGFR drugs and IO plus other regiments (PARP, COX, Virus and IFN). As shown in Fig. 2A-C, patients with breast cancer, esophageal cancer and melanoma had a higher ORR and pCR rate after the neoadjuvant immunotherapy than patients with head and neck cancer, HCC and lung cancer, which may be due to the treatment strategy. Regarding the 11 cancer types, when patients with cancer received immunotherapy combination therapy, they achieved a higher ORR, MPR and pCR compared with those with IO (Fig. 3A-C). Previous studies have reported that chemotherapy enhanced the efficacy of immunotherapy by directly killing tumor cells or activating the immune function of the body (118,119). Among all treatment regimens studied here, regardless of whether radiotherapy was applied, IO plus chemotherapy achieved a higher ORR, MPR and pCR than IO or IO + IO.

The association between radiological and pathological responses is shown in Fig. 4A and B. Patients with a higher ORR were more likely to achieve both a higher MPR and pCR after surgery. This link was more pronounced when the therapies were combined, most notably when IO was combined with chemotherapy. MPR and pCR are partially associated with long-term survival in various cancer types (NSCLC, breast cancer and melanoma) (120-122). This aforementioned finding indicates that patients with a higher ORR after neoadjuvant immunotherapy may also have

Table I. Summary of the studies included in the present review.

First author/s, year	Study name	Tumor	Type	ORR, %	MPR, %	pCR, %	TRAE, %	TRAE ≥3, %	irAE, %	irAEs ≥3, %	(Refs.)
Uppaluri *et al*, 2020	NCT02296684-1	HNSCC	IO	NA	6	0	NA	0	NA	0	(22)
Uppaluri *et al*, 2021	NCT02296684-2	HNSCC	IO	NA	14	3	NA	3	NA	3	(23)
Knochelmann *et al*, 2021	NCT03021993	OCSCC	IO	33	NA	0	67	0	67	0	(26)
Wise-Draper *et al*, 2021	NCT02641093	HNSCC	IO	NA	8	NA	NA	NA	NA	NA	(27)
Ferris *et al*, 2021	CheckMate358-1	HNSCC (HPV+)	IO	12	6	0	73	19	73	19	(28)
Ferris *et al*, 2021	CheckMate358-2	HNSCC (HPV-)	IO	8	0	0	54	12	54	12	
Vos, 2021	IMCISION-1	HNSCC	IO	0	17	0	67	33	67	33	(25)
Ferrarotto *et al*, 2020	CIAO-1	OPSCC	IO	40	7	7	93	20	93	20	(21)
Bar *et al*, 2019	MK3475-223	NSCLC	IO	NA	40	NA	NA	NA	NA	NA	(42)
Gao *et al*, 2020	ChiCTR-OIC-17013726	NSCLC	IO	20	38	8	53	10	53	10	(45)
Besse *et al*, 2020	PRINCEPS	NSCLC	IO	7	13	0	3	0	3	0	(46)
Lee *et al*, 2021	LCMC3	NSCLC	IO	NA	17	6	24	2	24	2	(47)
Eichhorn *et al*, 2021	NEOMUN	NSCLC	IO	27	27	13	33	20	33	20	(49)
Tong *et al*, 2022	TOP 1501	NSCLC	IO	NA	23	10	NA	3	NA	3	(52)
Cascone *et al*, 2021	NEOSTAR-1	NSCLC	IO	22	22	9	NA	13	NA	13	(50)
Altorki *et al*, 2021	NCT02904954-1	NSCLC	IO	3	7	0	NA	NA	NA	NA	(51)
Forde *et al*, 2018 and Bott *et al*, 2019	checkmate-159-1	NSCLC	IO	10	43	10	23	5	23	5	(39,40)
Kaseb *et al*, 2022	NCT03222076-1	HCC	IO	23	23	15	77	23	77	23	(73)
Marron *et al*, 2022	NCT03916627	HCC	IO	14	NA	14	29	10	29	10	(74)
Gao *et al*, 2019	NCT02210117-1	RCC	IO	55	NA	NA	NA	38	NA	38	(75)
Gorin *et al*, 2022	NCT02575222	RCC	IO	0	0	0	59	0	59	0	(77)
Carlo *et al*, 2022	NCT02595918	RCC	IO	0	0	0	17	11	17	11	(79)
Avallone *et al*, 2020	NICOLE	CC	IO	NA	14	5	NA	NA	NA	NA	(82)
Hu *et al*, 2022	PICC-1	CC (dMMR/MSI-H)	IO	NA	100	65	59	0	59	0	(88)
Necchi *et al*, 2020	PURE-01-1	MIBC (VH)	IO	NA	NA	16	NA	NA	NA	NA	(89)
Necchi *et al*, 2020	PURE-01-2	MIBC	IO	NA	NA	41	NA	NA	NA	NA	
Powles *et al*, 2019 and Szabados *et al*, 2021	ABACUS	MIBC	IO	22	36	28	44	11	44	11	(90,91)

Table I. Continued.

First author/s, year	Study name	Tumor	Type	ORR, %	MPR, %	pCR, %	TRAE, %	TRAE ≥3, %	irAE, %	irAEs ≥3, %	(Refs.)
Wei *et al*, 2020	BLASST-2	MIBC	IO	NA	NA	10	NA	10	NA	10	(93)
Grivas *et al*, 2021	PrE0807-1	MIBC (Cis-)	IO	NA	NA	8	NA	0	NA	0	(101)
Natesan *et al*, 2021	NCT02451423-1	MIBC (Cis-)	IO	NA	NA	17	75	10	75	10	(100)
Natesan *et al*, 2021	NCT02451423-2	MIBC (Cis-)	IO			20					
Natesan *et al*, 2021	NCT02451423-3	MIBC (Cis-)	IO			0					
Huang *et al*, 2018 and Huang *et al*, 2019	NCT02434354	Melanoma	IO	NA	30	19	NA	22	NA	22	(109,110)
Amaria *et al*, 2018	NCT02519322-1	Melanoma	IO	25	NA	25	92	8	92	8	(106)
Topalian *et al*, 2020	CheckMate358	MCC	IO	46	54	44	46	8	46	8	(115)
Schoenfeld *et al*, 2020	NCT02919683-1	OCSCC	IO	13	7	0	NA	14	NA	14	(20)
Ferrarotto *et al*, 2020	CIAO-2	OPSCC	IO+IO	43	7	0	86	7	86	7	(21)
Vos *et al*, 2021	IMCISION-2	HNSCC	IO+IO	10	31	4	69	38	69	38	(25)
Reuss *et al*, 2020	checkmate-159-2	NSCLC	IO+IO	11	22	22	67	33	67	33	(41)
Cascone *et al*, 2021	NEOSTAR-2	NSCLC	IO+IO	19	38	29	NA	10	NA	10	(50)
Kaseb *et al*, 2022	NCT03222076-2	HCC	IO+IO	0	21	21	86	43	86	43	(73)
Su *et al*, 2021	NCT03510871	HCC	IO+IO	24	17	NA	NA	41	NA	24	(72)
Gao *et al*, 2019	NCT02210117-3	RCC	IO+IO	43	NA	NA	NA	47	NA	47	(75)
Grivas *et al*, 2021	PrE0807-2	MIBC (Cis-)	IO+IO	NA	NA	18	NA	7	NA	7	(101)
Gao *et al*, 2020	NCT02812420	MIBC (Cis-)	IO+IO	NA	NA	29	93	21	93	21	(92)
Grande *et al*, 2020	DUTRENEO	MIBC (Cis+)	IO+IO	NA	NA	35	NA	22	NA	22	(94)
Van Dorp *et al*, 2021	NABUCCO-1	MIBC	IO+IO	NA	83	46	100	55	100	55	(99)
Van Dorp *et al*, 2021	NABUCCO-2	MIBC	IO+IO	NA	NA	40	NA	NA	NA	NA	
Van Dorp *et al*, 2021	NABUCCO-3	MIBC	IO+IO	NA	NA	7	NA	NA	NA	NA	
Amaria *et al*, 2018	NCT02519322-2	Melanoma	IO+IO	73	NA	45	91	73	91	73	(106)
Amaria *et al*, 2021	NCT02519322-3	Melanoma	IO+IO	57	66	59	NA	0	NA	0	(107)
Blank *et al*, 2018	OpACIN	Melanoma	IO+IO	40	60	30	100	90	100	90	(105)
Rozeman *et al*, 2019	OpACIN-neo-1	Melanoma	IO+IO	63	70	47	97	40	97	40	(108)
Rozeman *et al*, 2019	OpACIN-neo-2	Melanoma	IO+IO	57	64	57	97	20	97	20	
Rozeman *et al*, 2019	OpACIN-neo-3	Melanoma	IO+IO	35	46	23	100	50	100	50	
Cocorocchio *et al*, 2021	EudraCT 2018-002172-40	Melanoma	IO+IO	NA	51	46	NA	17	NA	17	(113)

Table I. Continued.

First author/s, year	Study name	Tumor	Type	ORR, %	MPR, %	pCR, %	TRAE, %	TRAE ≥3, %	irAE, %	irAEs ≥3, %	(Refs.)
Schoenfeld *et al*, 2020	NCT02919683-2	OCSCC	IO+IO	38	20	7	NA	33	NA	33	(20)
Chalabi *et al*, 2020	NICHE-1	CC (dMMR)	IO+IO	NA	95	60	NA	NA	NA	NA	(80)
Chalabi *et al*, 2020	NICHE-2	CC (pMMR)	IO+IO	NA	25	25	NA	NA	NA	NA	
Zinner *et al*, 2020	NCT03342911	HNSCC	IO+Chemotherapy	NA	65	35	NA	35	NA	NA	(11)
Loibl *et al*, 2019	GeparNuevo	TNBC	IO+Chemotherapy	NA	NA	53	NA	NA	NA	NA	(12)
Schmid *et al*, 2020	KEYNOTE-173	TNBC	IO+Chemotherapy	88	NA	57	100	90	30	10	(29)
Foldi *et al*, 2021	NCT02489448	TNBC	IO+Chemotherapy	NA	NA	44	NA	31	NA	9	(30)
Mittendorf *et al*, 2020	IMpassion031	TNBC	IO+Chemotherapy	NA	NA	58	98	57	70	15	(31)
Schmid *et al*, 2020	KEYNOTE-522	TNBC	IO+Chemotherapy	NA	NA	60	99	77	39	13	(32)
Yam *et al*, 2021	NCT02530489	TNBC	IO+Chemotherapy	NA	NA	30	NA	NA	NA	NA	(35)
Gianni *et al*, 2022	NeoTRIPaPDL1	TNBC	IO+Chemotherapy	80	NA	49	98	78	NA	NA	(37)
Dieci *et al*, 2022	GIADA	BC	IO+Chemotherapy	71	NA	16	NA	NA	NA	NA	(38)
Nanda *et al*, 2020	I-SPY-2-1	BC (HER2-)	IO+Chemotherapy	NA	NA	44	NA	NA	NA	NA	(33)
Rothschild *et al*, 2021	SAKK 16/14	NSCLC	IO+Chemotherapy	58	55	16	81	13	NA	NA	(13)
Zhao *et al*, 2021	NeoTAP01	NSCLC	IO+Chemotherapy	88	61	46	NA	18	NA	NA	(48)
Shu *et al*, 2020	NCT02716038	NSCLC	IO+Chemotherapy	63	57	33	NA	NA	NA	NA	(43)
Provencio *et al*, 2020	NADIM	NSCLC	IO+Chemotherapy	76	74	57	93	30	NA	NA	(44)
Forde *et al*, 2022	CheckMate 816	NSCLC	IO+Chemotherapy	55	38	24	82	34	NA	NA	(53)
Gu *et al*, 2020	KEEP-G 03	ESCC	IO+Chemotherapy	NA	53	27	NA	35	NA	NA	(54)
Zhang *et al*, 2021	ESONICT-1	ESCC	IO+Chemotherapy	67	40	13	93	3	NA	NA	(58)
Xing *et al*, 2021	NCT03985670-1	ESCC	IO+Chemotherapy	53	NA	27	100	NA	NA	NA	(59)
Xing *et al*, 2021	NCT03985670-2	ESCC	IO+Chemotherapy	67	NA	7	100	NA	NA	NA	
Xu *et al*, 2022	NCT04506138	ESCC	IO+Chemotherapy	NA	39	17	100	15	NA	NA	(61)
Liu *et al*, 2022	NIC-ESCC2019	ESCC	IO+Chemotherapy	61	54	29	86	11	41	4	(62)
He *et al*, 2022	NCT04177797	ESCC	IO+Chemotherapy	55	35	15	100	20	NA	NA	(63)
Liu *et al*, 2022	ChiCTR1900026240	ESCC	IO+Chemotherapy	40	58	33	97	57	45	3	(64)
Liu *et al*, 2020	NCT03939962	G/GEJC	IO+Chemotherapy	NA	19	6	NA	NA	NA	NA	(66)
Sun *et al*, 2022	NCT03488667	G/GEJC	IO+Chemotherapy	NA	NA	16	NA	54	NA	NA	(68)
Tao *et al*, 2022	NCT04890392	G/GEJC	IO+Chemotherapy	NA	62	NA	52	5	NA	NA	(69)
Jiang *et al*, 2022	NCT04065282	G/GEJC	IO+Chemotherapy	11	47	19	92	28	3	0	(70)

Table I. Continued.

First author/s, year	Study name	Tumor	Type	ORR, %	MPR, %	pCR, %	TRAE, %	TRAE ≥3, %	irAE, %	irAEs ≥3, %	(Refs.)
Hoimes *et al*, 2020	GU14-188-1	MIBC (Cis+)	IO+Chemotherapy	NA	NA	44	NA	NA	NA	NA	(96)
Kaimakliotis *et al*, 2020	GU14-188-2	MIBC (Cis-)	IO+Chemotherapy	NA	NA	45	NA	36	NA	11	(97)
Cathomas *et al*, 2021	SAKK 06/17	MIBC	IO+Chemotherapy	NA	NA	31	NA	75	NA	14	(102)
Rose *et al*, 2021	LCCC 1520	MIBC	IO+Chemotherapy	NA	NA	36	100	74	NA	3	(103)
Funt *et al*, 2022	NCT02989584	MIBC	IO+Chemotherapy	NA	NA	36	98	59	NA	11	(104)
Altorki *et al*, 2021	NCT02904954-2	NSCLC	IO+Radio	47	53	27	NA	NA	NA	NA	(51)
Leidner *et al*, 2021	NIRT-HNC-1	HNSCC (HPV+)	IO+Radio	50	100	90	100	10	NA	NA	(24)
Leidner *et al*, 2021	NIRT-HNC-2	HNSCC (HPV-)	IO+Radio	60	60	20	100	NA	NA	NA	
McArthur *et al*, 2021	NCT03366844	TNBC	IO+CRT	NA	NA	60	NA	NA	NA	10	(36)
Kelly *et al*, 2019	NCT03044613	E/GEJC	IO+CRT	NA	NA	25	NA	NA	NA	NA	(65)
Shah *et al*, 2021	NCT02998268	E/GEJC	IO+CRT	NA	50	NA	NA	NA	NA	0	(67)
Li *et al*, 2020	NCT03604991	ESCC	IO+CRT	NA	NA	53	NA	NA	NA	NA	(55)
Li *et al*, 2021	PALACE-1	ESCC	IO+CRT	90	80	50	100	65	NA	NA	(56)
van den Ende *et al*, 2021	PERFECT	EA	IO+CRT	NA	NA	25	NA	40	15	5	(57)
Rahma *et al*, 2021	NRG-GI002	RC	IO+ CRT	NA	NA	24	NA	NA	39	3	(83)
Salvatore *et al*, 2021	AVANA	RC	IO+CRT	NA	58	22	NA	NA	NA	4	(84)
Tamberi *et al*, 2021	PANDORA	RC	IO+CRT	NA	NA	26	NA	21	42	0	(85)
Shamseddine *et al*, 2021	Averectal	RC	IO+CRT	NA	61	34	NA	NA	NA	0	(86)
Carrasco *et al*, 2021	R-IMMUNE	RC	IO+CRT	NA	NA	23	NA	35	NA	NA	(87)
Yuki *et al*, 2020	EPOC1504-1	RC (MSS)	IO+CRT	NA	38	30	NA	NA	7	5	(81)
Yuki *et al*, 2020	EPOC1504-2	RC (MSI-H)	IO+CRT	NA	NA	60					
Ho *et al*, 2021	NCT03299946	HCC	IO+VEGFR	7	33	7	93	13	NA	NA	(71)
Gao *et al*, 2019	NCT02210117-2	RCC	IO+VEGFR	44	NA	NA	NA	42	NA	NA	(75)
Karam *et al*, 2021	NCT03680521	RCC	IO+VEGFR	10	NA	NA	100	45	NA	NA	(76)
Bex *et al*, 2022	NeoAvAx	RCC	IO+VEGFR	30	NA	NA	NA	NA	NA	NA	(78)
Wang *et al*, 2021	ChiCTR1900023880	ESCC	IO+Chemotherapy+ VEGFR	NA	50	23	NA	37	NA	NA	(60)
Pusztai *et al*, 2021	I-SPY-2-2	BC (HER2-)	IO+Chemotherapy+ PARP	NA	NA	37	NA	NA	27	12	(34)
Hu *et al*, 2022	PICC-2	CC	IO+COX	NA	94	88	65	6	65	6	(88)

Table I. Continued.

First author/s, year	Study name	Tumor	Type	ORR, %	MPR, %	pCR, %	TRAE, %	TRAE ≥3, %	irAE, %	irAEs ≥3, %	(Refs.)
		(dMMR/MSI-H)									
Rodriguez-Moreno *et al*, 2020	NEODURVARIB	MIBC	IO+PARP	24	NA	45	NA	NA	NA	NA	(95)
Wang *et al*, 2021	OrienX010-II-12	Melanoma	IO+Virus	33	NA	10	100	10	NA	NA	(111)
Hyngstrom *et al*, 2022	HCI102346	Melanoma	IO+Virus	67	NA	83	NA	NA	NA	NA	(112)
Najjar *et al*, 2021	NCT02339324	Melanoma	IO+IFN	73	57	43	100	NA	NA	NA	(114)
Chalabi *et al*, 2020	NICHE-3	CC(pMMR)	IO+IO+COX	NA	14	0	NA	NA	NA	NA	(80)

BC, breast cancer; CC, colorectal cancer; Cis, cisplatin; dMMR, mismatch repair-deficient; E/GEJC, esophageal/gastroesophageal junction cancer; EA, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; G/GEJC, gastric and gastroesophageal junction cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IO, immune checkpoint inhibitor alone (PD-1 inhibitor or PD-L1 inhibitor alone); IO+IO, combination of PD-1/PD-L1 inhibitor and cytotoxic T-lymphocyte associated protein 4 inhibitor or lymphocyte activation gene-3 inhibitor; IO+Chemotherapy, combination of PD-1/PD-L1 inhibitor and chemotherapy; IO+Radio, combination of PD-1/PD-L1 inhibitor and radiotherapy; IO+CRT, combination of PD-1/PD-L1 inhibitor and chemotherapy plus radiotherapy; IO+VEGFR, combination of PD-1/PD-L1 inhibitor and angiogenesis inhibitor; IO+Chemotherapy+VEGFR, combination of PD-1/PD-L1 inhibitor + chemotherapy + angiogenesis inhibitor; IO+Chemotherapy+PARP, combination of PD-1/PD-L1 inhibitor + chemotherapy + PARP inhibitor; IO+COX, combination of PD-1/PD-L1 inhibitor and COX inhibitor; IO+PARP, combination of PD-1/PD-L1 inhibitor and PARP inhibitor; IO+Virus, combination of PD-1/PD-L1 inhibitor and Virus; IO+IFN, combination of PD-1/PD-L1 inhibitor and IFN; IO+IO+COX, combination of PD-1/PD-L1 inhibitor and cytotoxic T-lymphocyte associated protein 4 inhibitor or lymphocyte activation gene-3 inhibitor + COX inhibitor; irAE, immune-related adverse event; MCC, Merkel cell carcinoma; MIBC, muscle-invasive bladder carcinoma; MPR, major pathologic response; MSI-H, microsatellite instability-high; MSS, microsatellite stability; NA, not mentioned in the article or the data do not fit into the inclusion criteria; NSCLC, non-small cell lung cancer; OCSCC, oral cavity squamous cell carcinoma; OPSCC, oropharyngeal squamous cell cancer; ORR, objective response rate; pCR, pathologic complete response; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; pMMR, mismatch repair-proficient; RC, rectal cancer; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer; TRAE, treatment-related adverse event; VH, variant histology.

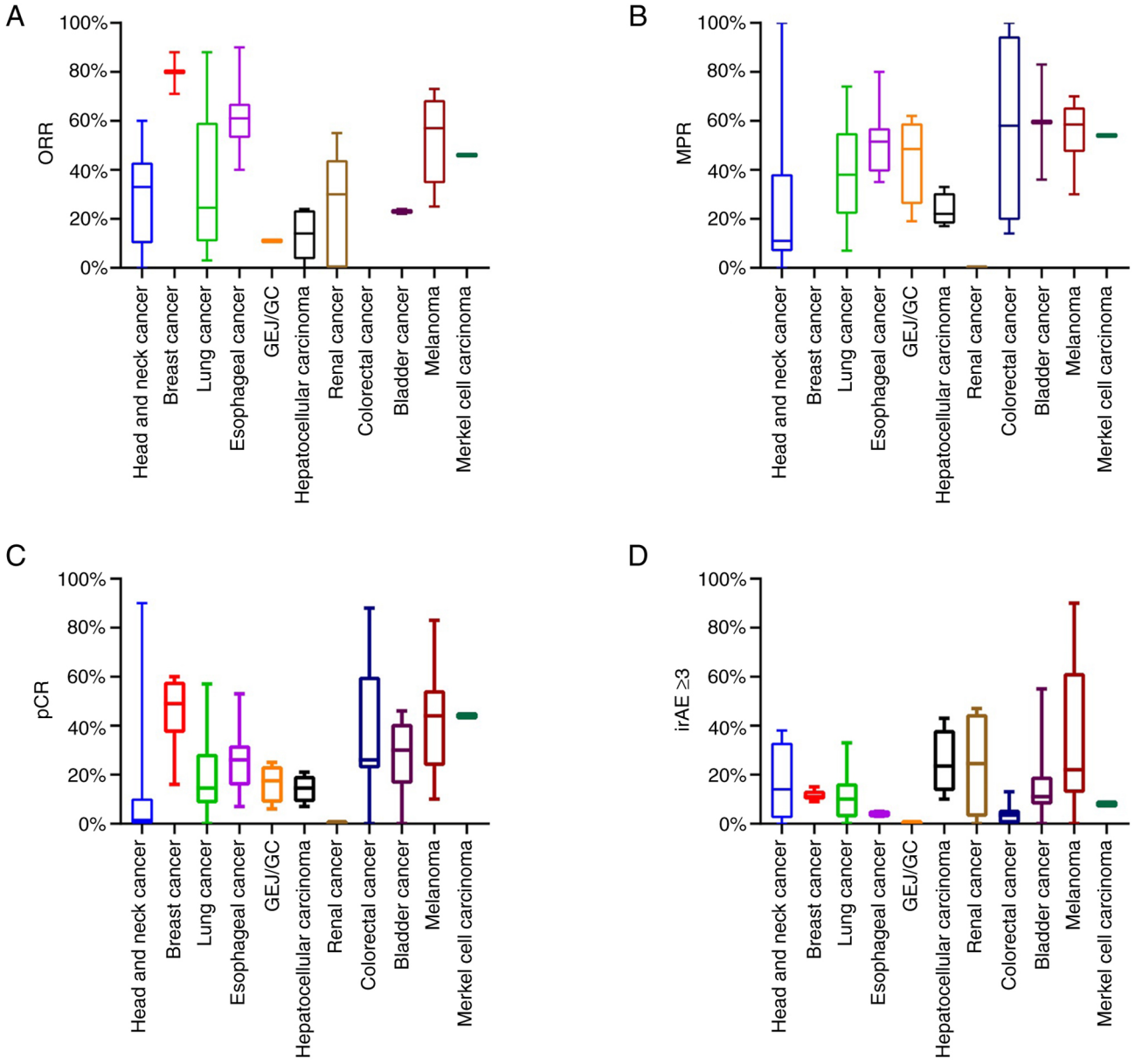

Figure 2. Efficacy and irAEs of neoadjuvant therapy for different types of cancer. (A) ORR. (B) MPR. (C) pCR. (D) Grade ≥3 irAEs. GEJ/GC, gastroesophageal junction and gastric cancer; irAE, immune-related adverse event; MPR, major pathologic response; ORR, objective response rate; pCR, pathologic complete response.

improved survival. Three clinical trials [NCT02641093 (27), NCT03081689 (44) and NCT02437279 (105)], demonstrated that patients with a higher MPR after surgery had an improved DFS time compared with those who had no MPR, implying that MPR (or pCR) may replace DFS as a primary study objective in the future. However, a caveat of these studies (27,44,105) was its small sample size. Therefore, further research is required, and the association between pathological response and survival benefits requires further evaluation in ongoing clinical trials.

As can be seen in Fig. 4C and D, in the neoadjuvant immune dual-drug regimen, NCT02519322 (107) demonstrated that when relatlimab [anti-lymphocyte activating 3 (LAG3)] was combined with nivolumab, it resulted in more substantial antitumor effects than the traditional dual-immunity regimen (nivolumab + ipilimumab). Furthermore, no serious irAEs were observed in melanoma. Since anti-LAG3 drugs produced higher efficacy with lower side effects, they may be an improved PD-1 combination compared with anti-CTLA4 drugs (107). More prospective clinical trials are required to validate this regimen. Additionally, it is hoped that the program will be extended to other cancer types in the future. The PICC clinical trial, which used toripalimab for CC with dMMR/MSI-H status in the neoadjuvant setting, indicated strong antitumor efficacy and no serious irAEs. The dMMR/MSI-H may be a useful immunotherapy biomarker since cancer types with dMMR/MSI-H exhibit high efficacy and low irAEs during immune monotherapy. Therefore, more beneficial biomarkers should be investigated. By contrast, IO did not produce antitumor effects for HPV-infected HNSCC (28), but when combined with chemotherapy or radiotherapy, it produced a strong antitumor effect with mild side

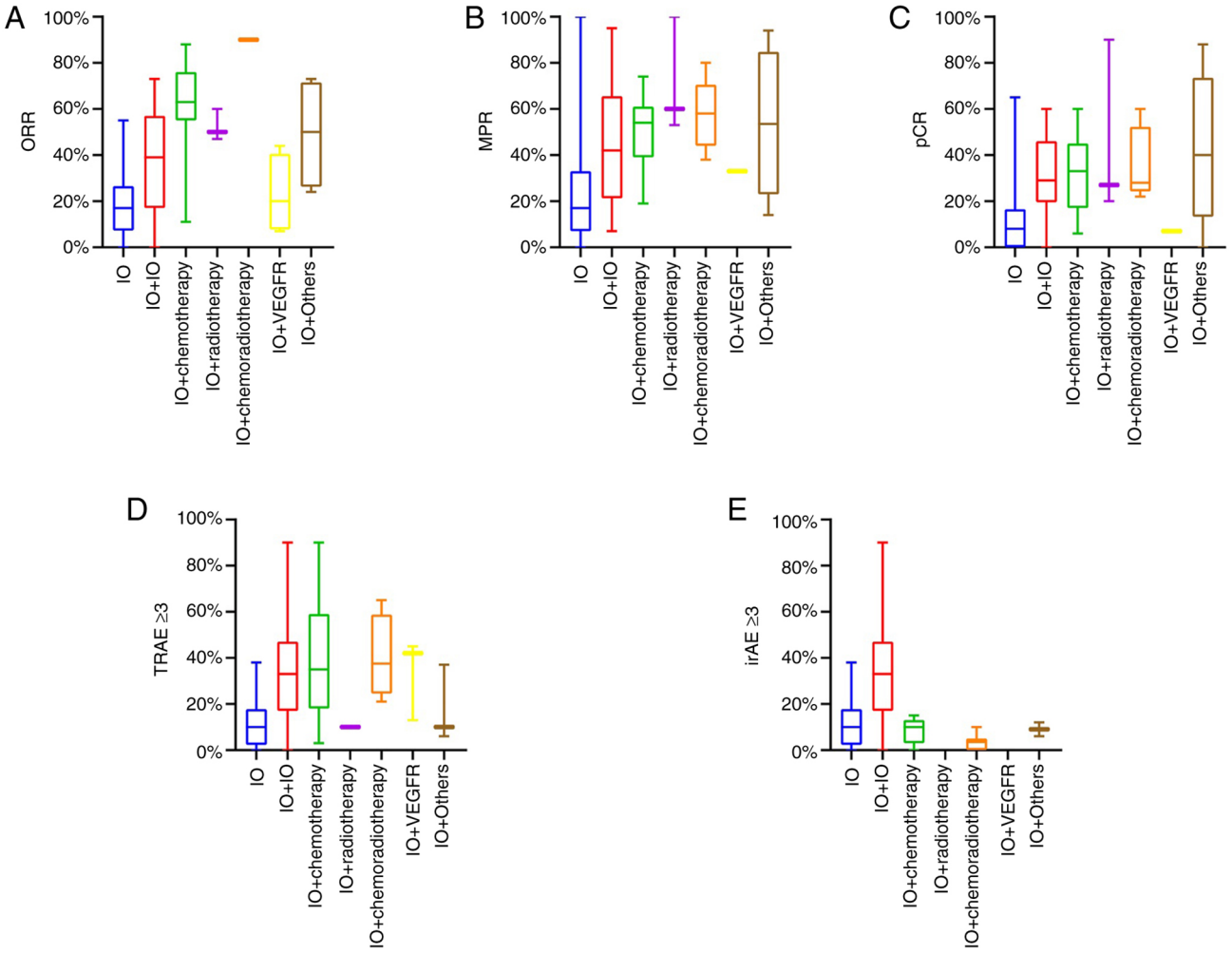

Figure 3. Efficacy and safety (including TRAEs and irAEs) of different neoadjuvant therapy regimens. (A) ORR. (B) MPR. (C) pCR. (D) Grade ≥3 TRAEs. (E) Grade ≥3 irAEs. IO, immune checkpoint inhibitor alone (PD-1 inhibitor or PD-L1 inhibitor alone); IO+IO, combination of PD-1/PD-L1 inhibitor and cytotoxic T-lymphocyte associated protein 4 inhibitor or lymphocyte activation gene-3 inhibitor; IO + chemotherapy, combination of PD-1/PD-L1 inhibitor and chemotherapy; IO + radiotherapy, combination of PD-1/PD-L1 inhibitor and radiotherapy; IO + chemoradiotherapy, combination of PD-1/PD-L1 inhibitor and chemotherapy plus radiotherapy; IO+VEGFR, combination of PD-1/PD-L1 inhibitor and angiogenesis inhibitor; IO + Others, combination of PD-1/PD-L1 inhibitor and special drugs; irAE, immune-related adverse event; MPR, major pathologic response; ORR, objective response rate; pCR, pathologic complete response; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TRAE, treatment-related adverse event.

effects (11,24), suggesting that, for some tumors with specific biomarkers, combination immunotherapy is more appropriate.

4. Adverse effects of neoadjuvant immunotherapy

Although neoadjuvant immunotherapy leads to improved tumor regression rates, its side effects should not be ignored (Fig. S1). Patients with bladder cancer and melanoma showed a higher rate of irAEs than those with other cancer types; however, most irAEs were classified as grade 1-2 irAEs. In addition, irAEs were more frequent for IO or IO + IO than for IO + chemotherapy (Fig. S2). As far as the cancer type is concerned, as shown in Fig. 2D, patients with HCC, renal cancer and melanoma exhibited a higher rate of grade ≥3 irAEs than those with breast cancer, esophageal cancer and GEJ/GC. The reason for this discrepancy is that a combined therapy (IO and a method that can directly kill tumor cells) could lessen the severity of irAEs more than IO or IO + IO (Fig. 3E). Patients with breast and digestive tract cancer are typically treated with IO combined therapy (5,54,68), while patients with HCC, renal cancer and melanoma receive IO or IO + IO (72,105). We hypothesized that chemotherapy not only kills tumor cells but also kills immune cells, resulting in a reduction in irAEs. The NCT03985670 trial showed that a delayed administration of toripalimab after NACT might generate a higher pCR rate than a simultaneous injection (59). Although there was no significant difference in TRAEs between the two groups, there may have been some differences in irAEs. The question of whether the higher efficacy of immunotherapy is directly related to higher incidence of irAEs deserves further exploration. Chemotherapy plus immunotherapy was associated with fewer irAEs than immunologic monotherapy and binary immunotherapy for the same efficacy (Fig. 4C). Treatment with IO plus chemotherapy did not result in a higher incidence of TRAEs than when chemotherapy was used alone (31,53). Therefore, IO + chemotherapy improved the effect index (ORR, MPR and pCR) and reduced the incidence of irAEs. Furthermore, the overall TRAEs and serious TRAEs of IO + chemotherapy were not significantly different from chemotherapy alone (6). This regimen's specific dose, sequence and cycle should be explored further.

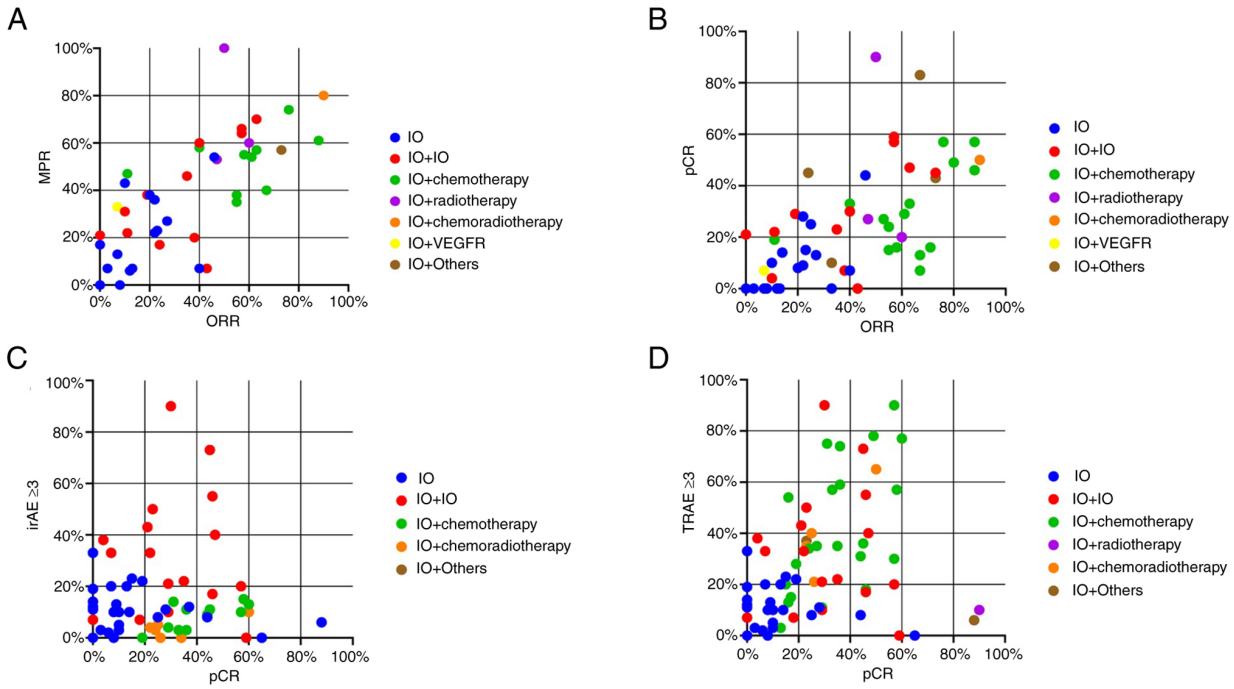

Figure 4. ORR, MPR, pCR and AEs (including TRAEs and irAEs) of neoadjuvant immunotherapy. (A) ORR and MPR. (B) ORR and pCR. (C) pCR and grade ≥3 irAEs. (D) pCR and grade ≥3 TRAEs. IO, immune checkpoint inhibitor alone (PD-1 inhibitor or PD-L1 inhibitor alone); IO+IO, combination of PD-1/PD-L1 inhibitor and cytotoxic T-lymphocyte associated protein 4 inhibitor or lymphocyte activation gene-3 inhibitor; IO + chemotherapy, combination of PD-1/PD-L1 inhibitor and chemotherapy; IO + radiotherapy, combination of PD-1/PD-L1 inhibitor and radiotherapy; IO + chemoradiotherapy, combination of PD-1/PD-L1 inhibitor and chemotherapy plus radiotherapy; IO+VEGFR, combination of PD-1/PD-L1 inhibitor and angiogenesis inhibitor; IO + Others, combination of PD-1/PD-L1 inhibitor and special drugs; irAE, immune-related adverse event; MPR, major pathologic response; ORR, objective response rate; pCR, pathologic complete response; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TRAE, treatment-related adverse event.

5. Comparison between anti-PD-1 and anti-PD-L1 inhibitors in the neoadjuvant settings

It was attempted to discern whether PD-1 inhibitors or PD-L1 inhibitors are more suitable for neoadjuvant immunotherapy. In most solid cancer types, the efficacy of PD-1 and PD-L1 monotherapy was not significantly different in terms of drug efficacy; however, the incidence of irAEs caused by PD-L1 was considerably lower than that of PD-1 (Fig. S3F). Notably, PD-L1 combination chemotherapy achieved a higher pCR than PD-1 combination chemotherapy and caused more TRAEs (Fig. S3). In lung cancer, PD-1 monotherapy had improved efficacy compared with PD-L1 monotherapy, while there was no marked difference in the incidence of irAEs between the two groups. This indicates that PD-1 immune monotherapy was more beneficial in NAT for lung cancer. Similarly, PD-1 inhibitors combined with chemotherapy has a higher efficacy than PD-L1 plus chemotherapy and resulted in fewer grade ≥3 TRAEs than PD-L1 plus chemotherapy (Fig. S4). Further prospective clinical trials are required to provide corresponding evidence.

6. Perioperative complications of neoadjuvant immunotherapy

In addition to the efficacy and side effects of neoadjuvant immunotherapy, the present review also analyzed surgical operations and perioperative complications, an aspect critical for surgeons. As shown in Table II, treatment-related surgery delays were not reported in most trials. Furthermore, some patients did not undergo surgery after neoadjuvant immunotherapy due to disease progression, severe TRAEs or high surgical risks, or declined surgery (23,45). In terms of perioperative complications, it is not easy to evaluate whether they are due to immunotherapy or surgery. Taking lung cancer as an example, an air leak, which is the most common perioperative complication after neoadjuvant immunotherapy, is also a major postoperative complication after lung surgery (50). Additionally, PD-1/PD-L1 inhibitor in combination with a CTLA4 inhibitor as NAT may increase the rate of postoperative complications compared with IO, as shown in the NEOSTAR study (50). However, because the difficulty of intraoperative resection is subjective and there is a lack of quantitative indicators, it was not possible to obtain this indicator in the literature. Previous studies on lung cancer have demonstrated that immunotherapy may induce severe tissue reactions, which can lead to dense fibrosis, thus becoming a technical challenge for surgeons (123,124). However, this phenomenon was not observed in two recent trials on esophageal cancer (58,64). This discrepancy suggests that the immunotherapy may produce different responses depending on which tissue the tumor is located in.

7. Other concerns regarding neoadjuvant immunotherapy

Other concerns remain regarding the concept of neoadjuvant immunotherapy. First, because draining lymph nodes are critical for T cell priming and antigen presentation (125), there is a discussion about whether to use lymph node resection as the standard criteria (126). Second, the dose/regiment of

Table II. Perioperative outcomes of the clinical trials.

First author/s, year	Study name	Tumor	Type	Treatment-related surgical delay, n	Postoperative complications, n	Not radical resection, n	No surgery, n	(Refs.)
Schoenfeld *et al*, 2020	NCT02919683-1	OCSCC	IO	0	5	NA	0	(20)
Ferrarotto *et al*, 2020	CIAO-1	OPSCC	IO	NA	NA	NA	0	(21)
Uppaluri *et al*, 2020	NCT02296684-1	HNSCC	IO	0	NA	NA	0	(22)
Uppaluri *et al*, 2021	NCT02296684-2	HNSCC	IO	NA	NA	NA	1	(23)
Vos *et al*, 2021	IMCISION-1	HNSCC	IO	0	6	0	0	(25)
Knochelmann *et al*, 2021	NCT03021993	OCSCC	IO	0	NA	0	0	(26)
Wise-Draper *et al*, 2021	NCT02641093	HNSCC	IO	NA	NA	NA	NA	(27)
Ferris *et al*, 2021	CheckMate358	HNSCC (HPV+)	IO	0	NA	NA	8	(28)
Ferris *et al*, 2021		HNSCC (HPV-)		0	NA	NA	7	
Reuss *et al*, 2020	checkmate-159-1	NSCLC	IO	0	10	1	0	(40)
Bar *et al*, 2019	MK3475-223	NSCLC	IO	NA	NA	NA	NA	(42)
Gao *et al*, 2020	ChiCTR-OIC-17013726	NSCLC	IO	2	NA	1	3	(45)
Besse *et al*, 2020	PRINCEPS	NSCLC	IO	0	3	1	0	(46)
Lee *et al*, 2021	LCMC3	NSCLC	IO	NA	NA	14	22	(47)
Eichhorn *et al*, 2021	NEOMUN	NSCLC	IO	1	1	0	0	(49)
Cascone *et al*, 2021	NEOSTAR-1	NSCLC	IO	NA	NA	0	2	(50)
Altorki *et al*, 2021	NCT02904954-1	NSCLC	IO	1	NA	3	4	(51)
Tong *et al*, 2022	TOP 1501	NSCLC	IO	1	12	3	5	(52)
Kaseb *et al*, 2022	NCT03222076-1	HCC	IO	0	NA	NA	4	(73)
Marron *et al*, 2022	NCT03916627	HCC	IO	1	NA	NA	1	(74)
Gao *et al*, 2019	NCT02210117-1	RCC	IO	NA	NA	NA	NA	(75)
Gorin *et al*, 2022	NCT02575222	RCC	IO	0	NA	NA	0	(77)
Carlo *et al*, 2022	NCT02595918	RCC	IO	0	4	NA	0	(79)
Avallone *et al*, 2020	NICOLE	CC	IO	0	0	NA	0	(82)
Hu *et al*, 2022	PICC-1	CC (dMMR/MSI-H)	IO	0	3	0	0	(88)
Necchi *et al*, 2020	PURE-01	MIBC (VH)	IO	NA	NA	NA	2	(89)
Necchi *et al*, 2020		MIBC		NA	NA	NA		
Powles *et al*, 2019 and Szabados *et al*, 2021	ABACUS	MIBC	IO	0	53	NA	8	(90,91)

Table II. Continued.

First author/s, year	Study name	Tumor	Type	Treatment-related surgical delay, n	Postoperative complications, n	Not radical resection, n	No surgery, n	(Refs.)
Wei *et al*, 2020	BLASST-2	MIBC	IO	NA	NA	NA	2	(93)
Natesan *et al*, 2021	NCT02451423	MIBC (Cis-)	IO	0	NA	NA	0	(100)
Natesan *et al*, 2021								
Natesan *et al*, 2021								
Grivas *et al*, 2021	PrE0807	MIBC (Cis-)	IO	0	NA	NA	1	(101)
Amaria *et al*, 2018	NCT02519322-1	Melanoma	IO	NA	NA	NA	NA	(106)
Huang *et al*, 2018; Huang *et al*, 2019	NCT02434354	Melanoma	IO	0	NA	NA	0	(109,110)
Topalian *et al*, 2020	CheckMate358	MCC	IO	1	NA	NA	3	(115)
Schoenfeld *et al*, 2020	NCT02919683-2	OCSCC	IO+IO	0	9	NA	0	(20)
Ferrarotto *et al*, 2020	CIAO-2	OPSCC	IO+IO	NA	NA	NA	0	(21)
Vos *et al*, 2021	IMCISION-2	HNSCC	IO+IO	0	24	1	3	(25)
Reuss *et al*, 2020	checkmate-159-2	NSCLC	IO+IO	0	NA	NA	3	(41)
Cascone *et al*, 2021	NEOSTAR-2	NSCLC	IO+IO	NA	NA	0	5	(50)
Su *et al*, 2021	NCT03510871	HCC	IO+IO	NA	NA	NA	14	(72)
Kaseb *et al*, 2022	NCT03222076-2	HCC	IO+IO	0	NA	NA	3	(73)
Gao *et al*, 2019	NCT02210117-3	RCC	IO+IO	NA	NA	NA	NA	(75)
Chalabi *et al*, 2020	NICHE-1	CC (dMMR)	IO+IO	0	NA	0	0	(80)
Chalabi *et al*, 2020	NICHE-2	CC (pMMR)	IO+IO	0	NA	0	0	
Gao *et al*, 2020	NCT02812420	MIBC (Cis-)	IO+IO	2	NA	NA	4	(92)
Grande *et al*, 2020	DUTRENEO	MIBC (Cis+)	IO+IO	NA	NA	NA	3	(94)
van Dijk *et al*, 2020	NABUCCO	MIBC	IO+IO	1	NA	NA	0	(98)
Van Dorp *et al*, 2021				2	NA	NA	1	(99)
Grivas *et al*, 2021	PrE0807	MIBC (Cis-)	IO+IO	0	NA	NA	0	(101)
Blank *et al*, 2018	OpACIN	Melanoma	IO+IO	0	NA	NA	0	(105)
Amaria *et al*, 2018	NCT02519322-2	Melanoma	IO+IO	NA	NA	NA	NA	(106)
Amaria *et al*, 2021	NCT02519322-3	Melanoma	IO+IO	NA	NA	NA	1	(107)
Rozeman *et al*, 2019	OpACIN-neo	Melanoma	IO+IO	1	21	NA	0	(108)
Rozeman *et al*, 2019				0	19		0	
Rozeman *et al*, 2019				2	18		1	

Table II. Continued.

First author/s, year	Study name	Tumor	Type	Treatment-related surgical delay, n	Postoperative complications, n	Not radical resection, n	No surgery, n	(Refs.)
Cocorocchio *et al*, 2021	EudraCT 2018-002172-40	Melanoma	IO+IO	NA	NA	NA	3	(113)
Zinner *et al*, 2020	NCT03342911	HNSCC	IO+Chemotherapy	NA	NA	0	0	(11)
Loibl *et al*, 2019	GeparNuevo	TNBC	IO+Chemotherapy	NA	NA	NA	NA	(12)
Schmid *et al*, 2020	KEYNOTE-173	TNBC	IO+Chemotherapy	NA	NA	NA	NA	(29)
Foldi *et al*, 2021	NCT02489448	TNBC	IO+Chemotherapy	NA	0	NA	NA	(30)
Mittendorf *et al*, 2020	IMpassion031	TNBC	IO+Chemotherapy	1	NA	NA	11	(31)
Schmid *et al*, 2020	KEYNOTE-522	TNBC	IO+Chemotherapy	NA	NA	NA	NA	(32)
Nanda *et al*, 2020	I-SPY-2 -1	BC (HER2-)	IO+Chemotherapy	NA	NA	NA	2	(33)
Yam *et al*, 2021	NCT02530489	TNBC	IO+Chemotherapy	NA	NA	NA	NA	(35)
Gianni *et al*, 2022	NeoTRIPaPDL1	TNBC	IO+Chemotherapy	NA	NA	NA	5	(37)
Dieci *et al*, 2022	GIADA	BC	IO+Chemotherapy	NA	NA	NA	0	(38)
Shu *et al*, 2020	NCT02716038	NSCLC	IO+Chemotherapy	0	0	3	1	(43)
Provencio *et al*, 2020	NADIM	NSCLC	IO+Chemotherapy	0	12	0	5	(44)
Rothschild *et al*, 2021	SAKK 16/14	NSCLC	IO+Chemotherapy	NA	NA	4	7	(13)
Zhao *et al*, 2021	NeoTAP01	NSCLC	IO+Chemotherapy	0	NA	1	3	(48)
Forde *et al*, 2022	CheckMate 816	NSCLC	IO+Chemotherapy	6	62	25	30	(53)
Gu *et al*, 2020	KEEP-G 03	ESCC	IO+Chemotherapy	0	NA	0	0	(54)
Zhang *et al*, 2021	ESONICT-1	ESCC	IO+Chemotherapy	0	NA	0	7	(58)
Xing *et al*, 2021	NCT03985670	ESCC	IO+Chemotherapy	NA	NA	0	4	(59)
Xing *et al*, 2021				NA	NA	0	2	
Xu *et al*, 2022	NCT04506138	ESCC	IO+Chemotherapy	NA	NA	0	9	(61)
Liu *et al*, 2022	NIC-ESCC2019	ESCC	IO+Chemotherapy	NA	14	0	5	(62)
He *et al*, 2022	NCT04177797	ESCC	IO+Chemotherapy	4	NA	2	0	(63)
Liu *et al*, 2022	ChiCTR1900026240	ESCC	IO+Chemotherapy	8	24	1	9	(60)
Liu *et al*, 2020	NCT03939962	G/GEJC	IO+Chemotherapy	0	NA	2	1	(66)
Sun *et al*, 2022	NCT03488667	G/GEJC	IO+Chemotherapy	NA	NA	0	1	(68)
Tao *et al*, 2022	NCT04890392	G/GEJC	IO+Chemotherapy	NA	NA	NA	NA	(69)
Jiang *et al*, 2022	NCT04065282	G/GEJC	IO+Chemotherapy	4	NA	1	0	(70)
Cathomas *et al*, 2021	SAKK 06/17	MIBC	IO+Chemotherapy	NA	NA	1	5	(102)
Rose *et al*, 2021	LCCC 1520	MIBC	IO+Chemotherapy	1	NA	4	1	(103)

Table II. Continued.

First author/s, year	Study name	Tumor	Type	Treatment-related surgical delay, n	Postoperative complications, n	Not radical resection, n	No surgery, n	(Refs.)
Funt et al, 2022	NCT02989584	MIBC	IO+Chemotherapy	0	32	NA	8	(104)
Hoimes *et al*, 2020	GU14-188	MIBC (Cis-)	IO+Chemotherapy	NA	NA	NA	4	(96)
Kaimakliotis *et al*, 2020		MIBC (Cis-)	IO+Chemotherapy	NA	NA	NA	3	(97)
Leidner *et al*, 2021	NIRT-HNC	HNSCC (HPV+)	IO+Radio	0	NA	NA	0	(24)
Leidner *et al*, 2021		HNSCC (HPV-)		0			0	
Altorki *et al*, 2021	NCT02904954-2	NSCLC	IO+Radio	1	NA	1	4	(51)
McArthur *et al*, 2021	NCT03366844	TNBC	IO+CRT	0	NA	NA	0	(36)
Li *et al*, 2020	NCT03604991	ESCC	IO+CRT	0	NA	NA	2	(55)
Li *et al*, 2021	PALACE-1	ESCC	IO+CRT	0	NA	1	2	(56)
van den Ende *et al*, 2021	PERFECT	EA	IO+CRT	0	NA	0	7	(57)
Kelly *et al*, 2019	NCT03044613	E/GEJC	IO+CRT	0	NA	NA	0	(65)
Shah *et al*, 2021	NCT02998268	E/GEJC	IO+CRT	NA	NA	NA	NA	(67)
Yuki *et al*, 2020	EPOC1504	RC (MSS)	IO+CRT	NA	NA	NA	NA	(81)
Yuki *et al*, 2020		RC (MSI-H)						
Rahma *et al*, 2021	NRG-GI002	RC	IO+CRT	NA	NA	4	21	(83)
Salvatore *et al*, 2021	AVANA	RC	IO+CRT	NA	NA	NA	NA	(84)
Tamberi *et al*, 2021	PANDORA	RC	IO+CRT	NA	NA	NA	1	(85)
Shamseddine *et al*, 2021	Averectal	RC	IO+CRT	NA	NA	NA	4	(86)
Carrasco *et al*, 2021	R-IMMUNE	RC	IO+CRT	NA	NA	NA	NA	(87)
Gao *et al*, 2019	NCT02210117-2	RCC	IO+VEGFR	NA	NA	NA	NA	(75)
Karam *et al*, 2021	NCT03680521	RCC	IO+VEGFR	1	NA	NA	NA	(76)
Bex *et al*, 2022	NeoAvAx	RCC	IO+VEGFR	0	NA	NA	NA	(78)
Ho *et al*, 2021	NCT03299946	HCC	IO+VEGFR	0	NA	0	3	(71)
Hu *et al*, 2022	PICC-2	CC (dMMR/MSI-H)	IO+COX	0	2	0	0	(88)
Rodriguez-Moreno *et al*, 2020	NEODURVARIB	MIBC	IO+PARP	NA	NA	NA	3	(95)
Wang *et al*, 2021	OrienX010-II-12	Melanoma	IO+virus	NA	NA	NA	3	(111)
Hyngstrom *et al*, 2022	HCI102346	Melanoma	IO+virus	NA	NA	1	0	(112)
Najjar *et al*, 2021	NCT02339324	Melanoma	IO+IFN	0	NA	NA	0	(114)

Table II. Continued.

First author/s, year	Study name	Tumor	Type	Treatment-related surgical delay, n	Postoperative complications, n	Not radical resection, n	No surgery, n	(Refs.)
Pusztai *et al*, 2021	I-SPY-2 -2	BC (HER2-)	IO+PARP+Chemo	NA	NA	NA	1	(34)
Chalabi *et al*, 2020	NICHE-3	CC (pMMR)	IO+IO+COX	0	NA	0	0	(80)
Wang *et al*, 2021	ChiCTR1900023880	ESCC	IO+Chemotherapy+ VEGFR	5	NA	NA	1	(60)

Not radical resection refers to the number of patients who underwent surgery but did not have a complete resection. BC, breast cancer; CC, colorectal cancer; Cis, cisplatin; dMMR, mismatch repair-deficient; E/GEJC, esophageal/gastroesophageal junction cancer; EA, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; G/GEJC, gastric and gastroesophageal junction cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IO, immune checkpoint inhibitor alone (PD-1 inhibitor or PD-L1 inhibitor alone); IO+IO, combination of PD-1/PD-L1 inhibitor and cytotoxic T-lymphocyte associated protein 4 inhibitor or lymphocyte activation gene-3 inhibitor; IO+Chemotherapy, combination of PD-1/PD-L1 inhibitor and chemotherapy; IO+Radio, combination of PD-1/PD-L1 inhibitor and radiotherapy; IO+CRT, combination of PD-1/PD-L1 inhibitor and chemotherapy plus radiotherapy; IO+VEGFR, combination of PD-1/PD-L1 inhibitor and angiogenesis inhibitor; IO+Chemotherapy+VEGFR, combination of PD-1/PD-L1 inhibitor + chemotherapy + angiogenesis inhibitor; IO+PARP+Chemo, combination of PD-1/PD-L1 inhibitor + chemotherapy + PARP inhibitor; IO+COX, combination of PD-1/PD-L1 inhibitor and COX inhibitor; IO+PARP, combination of PD-1/PD-L1 inhibitor and PARP inhibitor; IO+Virus, combination of PD-1/PD-L1 inhibitor and Virus; IO+IFN, combination of PD-1/PD-L1 inhibitor and IFN; IO+IO+COX, combination of PD-1/PD-L1 inhibitor and cytotoxic T-lymphocyte associated protein 4 inhibitor or lymphocyte activation gene-3 inhibitor + COX inhibitor; MCC, Merkel cell carcinoma; MIBC, muscle-invasive bladder carcinoma; MSI-H, microsatellite instability-high; MSS, microsatellite stability; NA; NSCLC, non-small cell lung cancer; OCSCC, oral cavity squamous cell carcinoma; OPSCC, oropharyngeal squamous cell cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; pMMR, mismatch repair-proficient; RC, rectal cancer; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer; VH, variant histology.

immunotherapy should be recommended before surgery, and it should consider antitumor efficacy and tolerability (22,23,127). The OpACIN-neo study can explain this problem to some extent. In this study, in group B, a tolerable neoadjuvant dosing regimen (two cycles of 1 mg/kg ipilimumab plus 3 mg/kg nivolumab) that might be suitable for broader clinical use was identified (108). However, the NABUCCO study suggested that ipilimumab (3 mg/kg) + nivolumab (1 mg/kg) is more effective than ipilimumab (1 mg/kg) + nivolumab (3 mg/kg) as a neoadjuvant treatment for stage III UC (99). Another clinical trial (NCT02296684) demonstrated that two cycles of pembrolizumab caused a stronger pathological response than one cycle (23). Thirdly, an important question remaining is if adjuvant immunotherapy is still necessary if neoadjuvant immunotherapy has been applied.

Although immunotherapy has a limited efficacy in advanced NSCLC with driver gene mutation (128,129), the clinical value of neoadjuvant immunotherapy in these patients warrants further discussion. Most clinical trials of neoadjuvant immunotherapy exclude driver gene-positive patients (45,68), since immunotherapy is less effective than corresponding targeted therapy in advanced driver gene-positive NSCLC (130). Therefore, it was not possible to obtain large-scale clinical data to explore the link between neoadjuvant immunotherapy and driver gene-positivity. However, two exploratory studies (43,44) demonstrated that neoadjuvant immunotherapy plus chemotherapy could obtain a good pathological response rate for patients with EGFR mutations, although the sample size was small, providing evidence for the use of neoadjuvant immunotherapy plus chemotherapy in patients with driver gene-positive NSCLC. Furthermore, a retrospective multi-center study (131) suggested that 39 of 40 patients with NSCLC with driver gene mutation achieved a R0 resection rate of 97.4% after neoadjuvant immunotherapy. The MPR and pCR rates were 37.5 and 12.5%, respectively, which was superior to those of patients with EGFR-mutant NSCLC receiving the EGFR tyrosine kinase inhibitor erlotinib in the CTONG1103 study. This study (131) indicated the potential clinical feasibility of neoadjuvant immunotherapy for resectable oncogene-mutant NSCLC, especially for EGFR-mutant NSCLC.

Furthermore, a few of the neoadjuvant immunotherapy studies selected patients based on biomarkers. The CM-159 study showed that patients with NSCLC with a higher tumor mutation burden (TMB) exhibited a higher rate of MPR (39), indicating that TMB might be a potential predictor of a higher pathological response. The PICC study demonstrated that patients with CC with dMMR or MSI-H had a 100% rate of MPR in the toripalimab monotherapy group. Therefore, it is critical to investigate further biomarkers related to neoadjuvant immunotherapy in selected patient cohorts (e.g., TMB, MSI-H, PD-L1 or CD8). Considering the long follow-up time for clinical trials of NAT and since MPR indicates an improved DFS time and OS time in some retrospective analyses (17,18), it should be clarified whether MPR could replace DFS or OS as the primary study endpoint. Although current preclinical studies do not fully reflect the situation in humans (15), they may help explore the optimal treatment regimens and strategies for neoadjuvant immunotherapy. Furthermore, in a mouse model of mammary cancer, four additional adjuvant doses of immunotherapy did not significantly improve the overall tumor-free survival if neoadjuvant immunotherapy was administered prior to surgery (132). The NCT03985670 study showed that the efficiency of chemotherapy and toripalimab varied depending on the sequence of drug use that was applied during NAT (59). These studies demonstrated that neoadjuvant immunotherapy was of value and emphasized that the timing of neoadjuvant immunotherapy for surgery is crucial to the outcome.

8. Conclusions

In conclusion, neoadjuvant immunotherapy is effective, safe and feasible for patients harboring resectable tumors (28,41,100). Compared with the traditional neoadjuvant chemo- and radiotherapy, neoadjuvant immunotherapy appears to lead to a higher pathological remission rate, especially for IO combination regimens, and is well tolerated with an acceptable rate of perioperative complications. However, increased vigilance is still necessary concerning the severe TRAEs, as well as increased surgical risk and difficulty after neoadjuvant immunotherapy. Neoadjuvant immunotherapy alone or in combination prolonged PFS compared with NACT alone, and although not significant in some studies (27,105), we hypothesized that this is a good trend and that the benefit of PFS will eventually translate into OS benefits. Neoadjuvant immunotherapy not only prolongs the duration of tumor recurrence, but also reduces tumor burden, and reduces the extent of surgical resection. Thus, neoadjuvant immunotherapy can transform inoperable patients into operable patients. Based on the current data, the neoadjuvant immunotherapy regimen is not yet mature; however, CheckMate816 (53) has been used as the only approved neoadjuvant immunotherapy regimen for NSCLC, and more updated research results to support this result and expand this to other cancer types are anticipated. In the novel era of immunotherapy, exploring the best NAT strategies to balance toxicity and efficacy is necessary. Further studies are required to evaluate the long-term survival benefit of neoadjuvant immunotherapy.

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Availability of data and materials

Not applicable.

Authors' contributions

LP and SX were responsible for the study conception and design. Administrative support and study design were provided

by ZS and JC. QT, SZ and NZ collected and assembled the data, and QT, SZ and NZ were responsible for data analysis and interpretation. JH, LZ and TL contributed to the revision of the review. All authors helped to write the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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