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Invited Review

Immune checkpoint inhibition in early-stage non-small cell lung cancer

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ABSTRACT

The introduction of immune checkpoint inhibitors significantly advanced outcomes in both metastatic and locally advanced non-small cell lung cancer. Despite these advancements, the 5-year survival rate remains suboptimal. Even in early-stage disease a significant portion of patients relapse and die from metastatic progression. The integration of immunotherapy in the management of early-stage NSCLC demonstrated promising results, supported by a plethora of positive clinical trials conducted in recent years. Nonetheless, numerous questions persist. In this manuscript we comprehensively review the currently available data on adjuvant, neoadjuvant, and perioperative treatment strategies. We also address the challenges inherent to these approaches from different stakeholders' perspective.

1. Introduction

Lung cancer is the leading cause of cancer mortality worldwide [1]. Immune checkpoint inhibition (ICI) alone or in combination with chemotherapy significantly improved outcomes in both metastatic and locally advanced non-small cell lung cancer (NSCLC) [2–8]. Nevertheless, the prognosis remains poor, and only a minority of patients exhibit long-lasting responses. Combining PD-L1 and CTLA-4-inhibitors improved outcomes compared to chemotherapy and might benefit long-term-outcomes for selected subgroups, but the toxicity-profile is challenging [9,10].

In early-stage disease prognosis is better, but still 5-year survival rates drop from 60 % for stage IIA to 36 % for stage IIIA disease [11,12]. Adjuvant chemotherapy led to an absolute 5-year overall survival (OS) improvement of 5.4 % but at significant toxicity cost [13]. This benefit was mainly obtained in higher disease stages in contrast to patients with stage IA who did not benefit of adjuvant chemotherapy. Only 59 % of patients receive full cisplatin dose, with toxicity (34 %) being the main reason for early treatment termination. Newer chemotherapy-doublets (e.g. pemetrexed-based) reduced toxicity however did not improve survival [14]. Neoadjuvant chemotherapy is less extensively studied but showed a similar absolute benefit and ameliorated treatment-disposition [15–17].

The consistent improvement of clinical endpoints in advanced NSCLC has evidently led to introduction of ICI in earlier stages of the disease as well. PD-L1-inhibitors became the focus-point of multiple studies in operable NSCLC (Table 1 and 2). In this manuscript we will review current available relevant data on adjuvant, neoadjuvant and *peri*-operative treatment strategies and discuss challenges from different stakeholders' perspective.

1.1. Adjuvant, neoadjuvant or perioperative?

Several strategies can be implemented in patients with resectable NSCLC (r-NSCLC): neoadjuvant, adjuvant and perioperative (Fig. 1). Selection of a particular strategy depends on various factors including patient and tumor characteristics, patient preferences, institutional experience, local drug reimbursement policies, and availability of

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Table 1
Table 1: Overview of neoadjuvant ICI monotherapy or ICI combination therapy trials in resectable NSCLC.

Name	N	Stage	Regimen	Primary Endpoint	Proportion of patients undergoing resection (%)	Proportion of patient with MPR (%)	Proportion of patients with pCR (%)	Proportion of patients undergoing R0 resection (%)	Post-operative 30-day mortality (%)
Forde et al. 2018* [28] NCT02259621	21	I-IIIA	nivolumab	safety	100	45.0	15.0	95	0
NEOSTAR 2021 * [34] NCT03158129	44	I-IIIA	nivolumab +/- ipilimumab	MPR	91.0 77.0	24 50	10 38	100 100	4.3 0
Gao et al. 2020 [30] ChiCTR-OIC-17013726	40	I-IIIB	sintilimab	MPR	92.5	40.5	16.2	97.3	5.4
PRINCEPS* 2020 [31] NCT02994576	30	I-IIIA (no N2)	atezolizumab	toxicity	100	14.0	0	96.7	10
LCMC3 2022 [32] NCT02927301	181	IB-IIIB	atezolizumab	MPR	89.1	20.4	6.8	92.0	1.3
IONESCO 2022 [33] NCT03030131	46	IIB-IIIA	durvalumab	R0 resection	93.5	18.6	0	90.0	NA#
NEOPREDICT 2022 [37] NCT04205552	60	IB-IIIA	Nivolumab +/-relatlimab	safety	100	27 30	14 17	100 97	0 0
NEOCOAST 2023 [40] NCT03794544	83	I-IIIA (single level N2)	Durvalumab +/- oleclumab or monalizumab or danvatirsen	MPR	91.6	11.1 19.0 30.0 31.3	3.7 9.5 10.0 12.5	NA	NA

*: TNM 7th edition, all others 8th edition;
MPR = major pathological response; pCR = pathological complete response.
# IONESCO trial was discontinued due to high 90-day post-operative mortality (8.7%).

approved ICI-based regimens. The multidisciplinary tumor board plays a pivotal role in this decision process.

Several hypothetical advantages favor neoadjuvant treatment. Reduction of tumor-size can lead to less morbid resections and higher rates of R0-resection [18]. The major potential advantage is the induction of a sustained antitumor immune response. In early disease, fitness of host immunity and less tumor heterogeneity can lead to enhanced antitumor effects with expansion and activation of tumor-specific T-cells [19]. In breast and lung cancer mouse models, preoperative ICI increased tumor-specific CD8+ T-cells, reduced disease recurrence and improved survival compared to post-operative ICI [20,21]. These findings emphasize the significance of the primary tumor's presence as antigenic leverage.

Pathological tumor regression after neoadjuvant chemo- or chemoradiotherapy has already shown to correlate with long-term outcomes in patients with r-NSCLC [22,23]. Retrospective data-analysis (n = 339) demonstrated a strong correlation between pathological response and survival after neoadjuvant ICI [24]. Pathological response is often used as clinical endpoint in several neoadjuvant studies and is even considered by many as a surrogate endpoint for survival, even though this still has to be prospectively validated. Uniform reporting of these findings is essential and recently recommendations how to evaluate and score pathological responses were formulated [25,26]. Major pathological response (MPR) is defined as <10 % viable tumor cells and complete pathological response (pCR) indicates no more viable tumor cells in both primary tumor bed and lymph nodes.

Tissue trauma and other perioperative stressors induce protective physiological processes. This stress response disrupts several immunological pathways, dysregulating innate and adaptive immunity [27]. By administering immunotherapy preoperatively, we can avoid an immunosuppressive state. On the other hand, post-operatively administered ICI could potentially revert this situation allowing for elimination of residual disease and enhance immune surveillance. In a perioperative treatment strategy, ICI is administered neoadjuvant and continued post-operatively, aiming to offer patients the potential benefit of both strategies.

Despite the obvious advantages, there are potential risks attached to these strategies. The major risk of delivering an ICI-based therapy pre-operatively, is precluding patients from surgery due to reasons such as disease progression or toxicity. Inversely, post-operative treatment disposition is usually lower, and patients might not be exposed to an adjuvant therapy that potentially can improve their prognosis. Evidently treatment escalation by drug combinations or increased therapy duration, augment the risk for clinically important toxicity with potentially long-lasting impact on patients' quality of life. Therefore case-by-case evaluation of potential advantages or disadvantages of either or neither strategy should be made by a multidisciplinary team of clinicians in close communication with the patient.

Table 2
Table 2: Overview of ICI and chemotherapy combination trials in resectable NSCLC.

Name Year of first outcome publication	Phase	N	Stage	Primary Endpoint	Regimen	Proportion of patients undergoing resection (%)	Proportion of patient with MPR (%)	Proportion of patients with pCR (%)	Proportion of patients undergoing R0 resection (%)	Post-operative 30-day mortality (%)
Shu et al. 2020* [41] NCT02716038	2	30	IB-IIIA	MPR	Atezolizumab + chemotherapy	97.0	57.0	33.0	87.0	3.0
NADIM #* 2020 [50] NCT03081689	2	46	IIIA	PFS	Nivolumab + chemotherapy	89.0	83.0	63.0	100	0
SAKK 16/14 #* 2021 [52] NCT02572843	2	68	IIIA (N2)	EFS	Durvalumab + chemotherapy	81.0	62.0	10.0	93.0	2.0
NEOSTAR* 2023 [46] NCT03158129	2	44	IB-IIIA	MPR	Nivolumab + chemotherapy +/- ipilimumab	100 91.0	32.1 50.0	18.2 18.2	90.0 95.0	0 0
NADIM-II # 2023 [53] NCT03838159	2	86	IIIA – IIIB (N2)	pCR	Nivolumab +/- chemotherapy	93.0 69.0	52.6 13.8	36.8 6.9	NA	NA
Checkmate 816* 2021 [42] NCT02998528	3	358	IB-IIIA	EFS pCR	Nivolumab or placebo + chemotherapy	83.2 75.4	36.9 8.9	24.0 2.2	83.2 77.8	NA
Keynote-671 # 2023 [54] NCT03425643	3	797	II-IIIB (N2)	EFS MPR	Pembrolizumab or placebo + chemotherapy	82.1 79.4	30.2 11.0	18.1 4.0	92.0 84.2	1.8 0.6
AEGEAN # 2023 [56] NCT03800134	3	802	IIA-IIB (N2)	EFS pCR	Durvalumab or placebo + chemotherapy	80.6 80.7	33.3 12.3	17.2 4.3	94.7 91.3	NA
Checkmate 77T # 2023 [58] NCT04025879	3	461	IIA-IIB (N2)	EFS	Nivolumab or placebo + chemotherapy	78.0 77.0	35.4 12.1	25.3 4.7	89.0 90.0	NA
NEOTORCH # 2024 [57] NCT04158440	3	404	II-III	EFS MPR	Toropalimab or placebo + chemotherapy	82.2 73.3	48.5 8.4	8.4 1.0	95.8 92.6	NA
RATIONALE-315 # 2024 [59] NCT04379635	3	453	II-IIIA	EFS MPR	Tislelizumab or placebo + chemotherapy	84.1 76.2	56.2 15	40.7 5.7	95.3 93.1	1.3 1.8

#: Perioperative chemo-immunotherapy.
*: TNM 7th edition, all others 8th edition
MPR = major pathological response; pCR = pathological complete response; EFS = event free survival; PFS = progression free survival; NSCLC = non-small cell lung cancer.

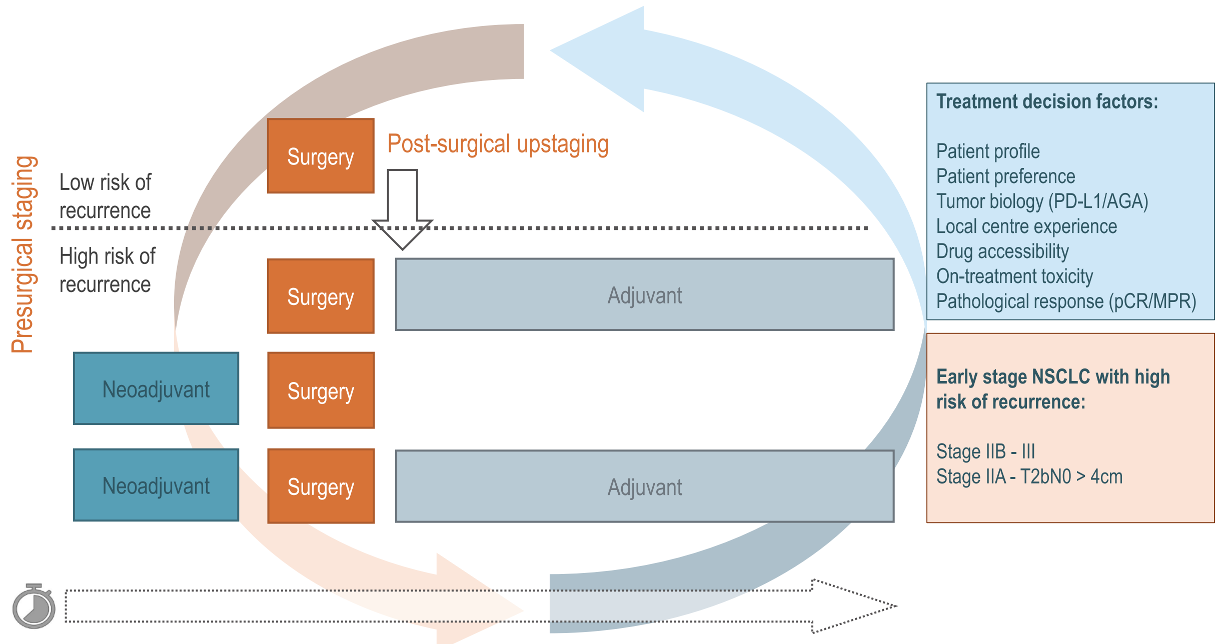

Fig. 1. Treatment strategies and decision factors.

2. Neoadjuvant single-agent ICI in early-stage NSCLC

The pivotal study by Forde et al., published in 2018, reported on preoperative nivolumab in 21 NSCLC patients stages I to IIIA (Union for International Cancer Control – UICC 7th TNM edition) [28]. The primary endpoint of safety and feasibility was met: all patients underwent resection without significant delay. Radiologic partial responses were noted in 10 % of patients. In contrast, 45 % of patients achieved MPR (15 % pCR). Recurrence-free survival (RFS) was 80 % at 12 months. 5-year survival update showed an RFS of 60 % and OS of 80 % [29]. Of patients achieving MPR, 89 % were alive and disease-free at 5 years.

A neoadjuvant study with sintilimab (n = 40) showed comparable results: 40.5 % of patients achieved MPR (16.2 % pCR) [30]. In contrast to the nivolumab study, not all patients underwent surgery (37 of 40). In 10 % of patients, grade 3 or worse treatment-related adverse events (TRAEs) were noted.

Response rates of both trials are higher than expected in an unselected population and could not be confirmed. Neoadjuvant atezolizumab showed an MPR-rate of 14 % in the PRINCEPS (n = 30) and 20.4 % in the LCMC3 (n = 181) trial [31,32]. A comparable result (18.6 % MPR) was seen with durvalumab in the IONESCO trial (n = 46) [33]. IONESCO, however, was discontinued after unexpected high 90-day postoperative mortality with 4 deaths (8.7 %).

3. Neoadjuvant combination ICI in early-stage NSCLC

The single-center phase II randomized NEOSTAR trial (n = 44) compared nivolumab with or without ipilimumab [34]. MPR (50 % versus 24 %) and pCR (38 % versus 10 %) increased in the combination arm. Somewhat worrisome, was the number of patients not undergoing resection (5/44; 4 treated with nivolumab and ipilimumab), which could not be attributed solely to toxicity but was mainly due to disease-progression or irresectability at reevaluation. The NCT02259621 study was amended to add a nivolumab-ipilimumab arm but was stopped at investigator consensus after a concerningly high rate of TRAEs in the first 9 patients enrolled [35].

In the multicentric phase II NEOpredict-Lung study (n = 60), patients with r-NSCLC (IB-IIIA) were treated with combined PD-L1 and LAG-3 inhibition preoperatively [36,37]. The primary endpoint was feasibility and the number of patients that made it to surgery within 43 days after initiation of therapy by continuous assessment (Pocock boundaries). The study met its primary endpoint: all patients underwent surgery within the predefined time window. These findings are reassuring as they confirm that closely monitored preoperative ICI-combinations are feasible. Patients were randomized to short course nivolumab-relatlimab or nivolumab alone. The addition of relatlimab was associated with an increase in objective response rate (27 % versus 11 %) and MPR-rate (32 % versus 28 %). Given the favorable survival rates achieved with nivolumab-relatlimab in melanoma, these results in NSCLC patients are promising and long-term data are awaited [38,39].

The NeoCOAST (n = 83) (n = 83), a multicentric phase II trial, explored neoadjuvant durvalumab combinations in patients with r-NSCLC stages IA3-IIIA [40]. Durvalumab was examined in four arms: as single-agent or combined with oleclumab (anti-CD73), monalizumab (anti-NKG2A) or danvatirsen (anti-STAT3 antisense oligonucleotide). MPR was achieved in respectively 11.1 %, 19.0 %, 30.0 % and 31.3 % of patients. A total of 7 out of 83 patients who received neoadjuvant treatment, did not undergo surgery due to various reasons. Disease progression after which the investigators no longer deemed the tumor resectable occurred in 5 patients and was the most common reason for surgical preclusion.

4. Neoadjuvant ICI and chemotherapy combinations

Combining chemotherapy with ICI significantly improves response rate and survival in advanced disease [6,8,10]. Seeing the encouraging results and feasibility of neoadjuvant ICI in r-NSCLC, neoadjuvant ICI-chemotherapy combinations became of great interest and are already being implemented in daily clinical practice.

Shu et al. were among the first to report on neoadjuvant ICI-chemotherapy combination in r-NSCLC [41]. In this phase II trial (n = 30) atezolizumab-chemotherapy was evaluated in stage IB-IIIA NSCLC patients. Nearly all patients underwent surgery (97 %). A total of 17 patients had an MPR (57 %) of which 10 had a pCR (33 %).

The phase III Checkmate 816 (CM816) study (n = 358) randomized patients to neoadjuvant chemotherapy combined with nivolumab or placebo [42]. The primary endpoints were event-free survival (EFS) and pCR-rate. The pCR-rate significantly increased from 2.2 % to 24 % in the combination arm (p < 0.0001). Median EFS was 31.6 months (95 % CI, 30.2 months to not reached (NR)) in the experimental arm compared to 20.8 months (95 %CI, 14.0–26.7) in the control arm. A follow-up analysis demonstrated a sustained EFS-benefit for the combination with 3-year EFS-rates of 57 % versus 43 % [43]. There was a trend in OS benefit: HR 0.62 (99.34 %CI, 0.36–1.05) and 3-year OS-rates of 78 % in the combination versus 64 % in the chemotherapy arm. The clinical benefit is more pronounced in tumors with PD-L1 ≥ 1 % [44]. In PD-L1 positive patients 3-year EFS-rates of 72 % versus 44 % (HR 0.46; 95 %CI, 0.28–0.77) and 3-year OS-rates of 85 % versus 66 % (HR 0.37; 95 %CI, 0.20–0.71) were noted in favor of the nivolumab group. Despite a significantly higher pCR-rate with nivolumab-chemotherapy in PD-L1 negative patients [16.7 % (95 %CI, 9.2–16.8) versus 2.6 % (95 %CI, 0.3–9.1)], this did not translate into enhanced outcome. No improvement could be demonstrated in EFS nor OS, with 3-year EFS-rates of 42 % versus 39 % and OS-rates of 71 % versus 60 %. Patients were more likely to undergo minimally invasive surgery (30 % versus 22 %), had higher rates of R0-resection (83 % versus 78 %) and were less likely to need a pneumonectomy (17 % versus 25 %) when treated with the combination [45]. Approximately 17 % of patients randomized to nivolumab-chemotherapy versus 25 % of the chemotherapy group did not undergo definitive surgery. This is due to reasons such as adverse events (<1% in both groups) and disease-progression (6.7 % versus 9.5 %).

The previously discussed modular designed NEOSTAR study was amended to compare platinum-based chemotherapy with nivolumab or nivolumab-ipilimumab [46]. MPR-rates were higher in the dual ICI arm (50 % versus 32,1%). Median EFS and OS were not reached in both arms. EFS-rate in the nivolumab-chemotherapy arm was 96 % (95 %CI, 87–100 %) at 12 months and 73 % (95 %CI, 56–94 %) at 24 months. EFS-rate in the ipilimumab arm was 82 % (95 %CI, 67–100) at 12 months and 77 % (95 %CI, 61–97) at 24 months.

5. Adjuvant ICI

Two large adjuvant trials have results to date: IMpower010 (atezolizumab) and Keynote-091 (pembrolizumab) [47,48].

IMpower010 randomized patients with stage IB to IIIA NSCLC after R0-resection and adjuvant chemotherapy, to atezolizumab or best supportive care (n = 495 in each group) [47]. The primary endpoint of DFS was met in patients with stage II-IIIA and PD-L1 ≥ 1 %, (HR 0.66; 95 % CI, 0.50–0.88; p = 0.0039) and in all patients with stage II–IIIA (HR 0.79; 95 %CI, 0.64–0.96; p = 0.020). Adjuvant chemotherapy was mandatory, and majority of patients in the ITT population (94 % in atezolizumab arm and 92 % in the control arm) were able to receive at least 3 cycles platinum-based chemotherapy. In the ITT population, HR for DFS was 0.81 (95 %CI, 0.67–0.99; p = 0.040). A prespecified exploratory OS-analysis took place after 251 deaths occurred in the ITT population [49]. In the stage II-IIIA population, death occurred in 26.0 % of patients receiving atezolizumab and in 26.4 % receiving BSC (HR 0.95; 95 %, CI 0.74–1.24). In the stage II-IIIA group, the survival advantage appeared mainly driven by patients with PD-L1 ≥ 50 %, HR 0.42 (95 %CI, 0.23–0.78).

Keynote-091 enrolled a comparable patient population [48]. Patients with stage IB to IIIA NSCLC were randomized to pembrolizumab (n = 590) or placebo (n = 587) after resection. Adjuvant chemotherapy was to be considered in stage IB and strongly recommended in stage II-IIIA. Approximately 14 % of patients in both arms did not receive any adjuvant chemotherapy at all. The coprimary endpoints were DFS in the overall population and in patients with PD-L1 ≥ 50 %. Further formal statistical testing of secondary endpoints, such as OS, would only occur if both primary endpoints were met. The primary endpoint of DFS improvement was met; HR 0.76 (95 %CI, 0.63–0.91; P = 0.0014). The DFS benefit was however, surprisingly, not statistically significant in the PD-L1 ≥ 50 % population: HR 0.82 (95 %CI, 0.57–1.18; p = 0.14) and further formal testing was not pursued.

6. Perioperative ICI and chemotherapy combinations

The majority of clinical trials evaluating ICI in r-NSCLC adopted a perioperative strategy with preoperative ICI-chemotherapy and postoperative ICI-continuation.

The multicentric single-arm phase II NADIM study (n = 46) enrolled patients with stage IIIA NSCLC [50]. Over 50 % of patients enrolled had multilevel N2-disease. Patients preoperatively received nivolumab-chemotherapy, followed by 1 year of adjuvant nivolumab. The primary endpoint was progression-free survival (PFS) at 24 months. Of 46 patients treated with nivolumab-chemotherapy, 41 (89 %) had surgery. All patients achieved R0-resection. NADIM was a clearly positive study with 24-month PFS of 77.1 % (95 %CI, 60–88). MPR occurred in 83 % (95 %CI, 68–93) and 63 % had pCR (95 %CI, 62–91). Most patients with pCR/MPR were progression-free at 24 months: 97.1 % (95 %CI, 80.9–99.6). In contrast, of patients not achieving MPR, only 57.1 % (95 %CI, 17.2–83.7) were progression-free at 24 months. Longer follow-up showed an imposing 36-month OS of 81.9 % (95 %CI, 66.8–90.6) [51].

The single-arm phase II SAKK16/14-study (n = 68) evaluated neoadjuvant cisplatin-docetaxel followed by durvalumab in stage IIIA NSCLC patients (single or multilevel N2) [52]. Durvalumab was continued 12 months post-surgery. 1-year EFS-rate was 73 % (90 % CI, 63–82). OS-rates at 1 and 2 years were 91 % (95 %CI, 81–96) and 83 % (95 %CI, 71–90). Of surgically treated patients, 62 % achieved MPR and 18 % pCR. Surgical omission occurred in 20 %.

NADIM-II (n = 86) was a randomized phase II study. Patients with stage IIIA or IIIB (N3 excluded) NSCLC received neoadjuvant nivolumab-chemotherapy or chemotherapy alone [53]. Patients treated with ICI-combination would receive 6 months of adjuvant nivolumab. The primary endpoint of pCR was met: 37 % in the nivolumab-chemotherapy arm versus 7 % in the control arm (95 %CI, 1.34–21.23; P = 0.02). Of nivolumab-chemotherapy treated patients 93 % underwent surgery, compared to 69 % of chemotherapy-treated patients. In the control arm 4 patients (13.8 %) did not undergo surgery due to disease-progression. In the combination arm not a single patient experienced disease-progression preoperatively. PFS and OS at 24 months were 67.2 % and 85 % in the experimental and 40.9 % (HR 0.47; 95 %CI, 0.25–0.88) and 63.6 % (HR 0.43; 95 %CI, 0.19–0.98) in the control group. All patients attaining pCR were free from progression and alive at data cutoff.

The first large double-blind randomized phase III trial to report on perioperative ICI was Keynote-671 (KN671) (n = 797) [54]. Patients with stage II to IIIB (N3 excluded) r-NSCLC were randomized to receive neoadjuvant chemotherapy with pembrolizumab or placebo followed by surgery and adjuvant pembrolizumab or placebo for 1 year. Dual primary endpoints were EFS and OS. In the pembrolizumab group 82.1 % underwent surgery and 79.4 % in the placebo group. Disease-progression during neoadjuvant treatment occurred in 3,8% of patients treated with pembrolizumab and in 6.5 % of placebo-treated patients. A superior 2-year EFS of 62.4 % (95 %CI, 56.8–67.5) was demonstrated in the pembrolizumab group compared to 40.6 % (95 % CI, 34.8–46.3) in the placebo group. The median EFS was not reached (95 %CI, 34.1 months to NR) versus 17.0 months (95 %CI, 14.3–22.0) in the placebo arm (HR 0.58; 95 %CI, 0.46–0.72 %; P < 0.001). The primary endpoint of OS was met at a second prespecified interim analysis [55]. OS was significantly improved in the pembrolizumab arm (HR 0.72; 95 %CI, 0.56–0.93; P = 0.00517). 3-year OS-rates were 71.3 % versus 64.0 %.

In the phase III randomized-controlled AEGEAN study (n = 802) patients received neoadjuvant chemotherapy and durvalumab or placebo followed by surgery and 1 year of adjuvant durvalumab or placebo (n = 806) [56]. Patients with stage II to IIIB (N3 excluded) r-NSCLC were enrolled. The primary endpoints were EFS and pCR. In the durvalumab and placebo group 77.6 % and 76.7 % of patients completed surgery. Patients treated with durvalumab had a significantly longer EFS compared to placebo treated patients HR 0.68 [(95 %CI, 0.53–0.88; P =

0.004)]. The 1-year EFS was 73.4 % (95 %CI, 67.9–78.1) in the durvalumab group, compared to 64.5 % (95 %CI, 58.8–69.6). The pCR-rate was significantly higher with durvalumab [(17.2 % versus 4.3 % (95 %CI, 8.7–17.6; P < 0.001)]. No mature OS-data are available yet.

The phase III NEOTORCH (n = 404) evaluated preoperative chemotherapy with toripalimab or placebo [57]. Postoperative one additional combination cycle was foreseen, followed by one year adjuvant toripalimab or placebo. Patients with stage II to III (N3 excluded) r-NSCLC were enrolled. Approximately 70 % of patients had N2-disease in both arms. The primary endpoints were EFS and MPR. In total 17.8 % of patients did not undergo surgery in the experimental arm of which 2.5 % due to disease-progression. In the placebo group 26.7 % did not undergo surgery and 15.3 % experienced progression during neoadjuvant chemotherapy. Median EFS was not estimable (NE) (95 %CI, 24.4 months-NE) in the toripalimab-treated patient group compared with 15.1 months (95 %CI, 10.6–21.9) in placebo-treated patients. The 2-year EFS was 64.7 % versus 38.7 % (HR 0.40; 95 %CI, 0.28–0.57; P < 0.001). A more pronounced EFS-benefit was seen in patients with PD-L1 ≥ 1 % (HR 0.31) compared to PD-L1 < 1 % (HR 0.59). MPR in the ICI-combination group was 48.5 % (95 %CI, 41.4–55.6) compared with 8.4 % (95 %CI, 5.0–13.1). To date, no mature OS-data are available.

In Checkmate 77T (n = 461) patients with stage II to IIIB (N2) r-NSCLC were randomized to receive nivolumab-chemotherapy or chemotherapy-placebo followed by surgery and adjuvant nivolumab or placebo for 1 year. Perioperative nivolumab significantly improved the primary endpoint of EFS. Median EFS was not reached in the nivolumab group (95 %CI, 28.9 months-NR) compared to 18.4 months (95 %CI, 13.6–28.1) in the placebo group (HR 0.58; 97.36 %CI, 0.42–0.81; P = 0.00025) [58].

RATIONALE-315 (n = 453) evaluated perioperative tislelizumab. Stage II to IIIA patients, were randomized to receive preoperative chemotherapy and tislelizumab or placebo, surgery and 1 year of adjuvant ICI or placebo. Dual primary endpoints were EFS and MPR. The median EFS was not reached for either arm. However, a statistically significant difference was noted in EFS (HR 0.56; 95 %CI, 0.40–0.79; P = 0.0003) [59].

7. Open questions and concerns – different perspectives

It is beyond any doubt, that ICI has become an indispensable element of surgical multimodality-treatment of NSCLC. This strategy can induce potent anti-tumoral immunity, impede disease recurrence and enhance cure rate. Yet still many open questions remain. We will look at these from different perspectives:

7.1. The surgeon's perspective

The **first** and most pertinent question is on resectability. What do we define as truly resectable disease and what is considered irresectable? The EORTC-Lung Cancer Group conducted a 13-item survey to establish a consensual definition of resectability in stage III NSCLC [60]. Subdivisions were created for single-level, multilevel, bulky, and invasive N2-disease. Respondents (n = 558) were surgeons (38 %), radiation (27 %) and medical oncologists (16 %) and pulmonologists (13 %). Agreement among ≥ 75 % of respondents was considered consensus. Consensus was found in 65 % of stage III TNM-combinations (8th UICC edition). Only 1 combination was considered as upfront resectable: T3N1. There was broad consensus on unresectability: N3-combinations, T4-tumors with cardiac invasion and invasive or bulky N2-disease were considered as unresectable by majority of respondents. Limited mediastinal nodal involvement (single-level N2) was considered by most as potentially resectable as well as T3 tumors invading chest wall, phrenic nerve, or pericardium. In 35 % of cases, mainly non-bulky non-invasive multilevel N-disease, consensus was not reached. Overall surgeons considered more TNM-combinations resectable. This survey illustrates that resectability is a topic of discussion between different actors of the multidisciplinary tumor board. We must acknowledge that no clear consensus exists on the optimal approach of 'borderline resectable' disease. Moreover, interpreting the current data in anticipation of the forthcoming 9th UICC TNM edition, will complicate discussions even more [61]. In these discussions, it is vital to consider all factors: surgical team's experience, patients' functional status, comorbidities and preferences, tumor biology, and the availability of effective systemic treatment regimens.

Secondly, perioperative safety and the number of patients not making it to surgery, is a concern of neoadjuvant ICI. A large *meta*-analysis confirming the benefit of ICI-chemotherapy preoperatively, also provided more insights on this subject [62]. The proportion of patients treated with chemo-and immunotherapy not undergoing surgery varies from 7.0 to 22.3 %. In 1.0 to 8.9 %, patient refusal precludes surgery. Disease progression led to cancellation of surgery in up to 7.4 % and toxicity in up to 3.1 % of cases. Proponents of primary surgery argue that upfront resection could be a better option for these patients. However, one can assume that patients with primary resistance to chemotherapy and ICI, are likely to relapse as well after primary surgery, even if followed by adjuvant chemotherapy and ICI. We should stress that patients receiving combination therapy preoperatively had a reduced risk of not undergoing surgery (risk ratio: RR 0.81; 95 %CI, 0.70–0.94) or developing disease-progression excluding surgery (RR 0.51; 95 %CI, 0.33–0.79) compared to patients receiving only chemotherapy. Moreover, no significant differences were noted in severe treatment or surgery related adverse events. Surgical outcome analysis of the CM816, indicated a trend towards less invasive surgery and less morbid resections in patients treated with the combination [45]. Patients treated with chemoimmunotherapy preoperatively were more likely to undergo R0-resection (RR 1.05; 95 %CI, 1.02–1.08) [62].

7.2. The pathologist's perspective

The outcome of r-NSCLC improved with ICI, but many patients do not benefit and relapse despite (potentially toxic) treatments. Surgery alone can cure early-stage patients, so additional therapy decisions require careful risk–benefit balance. We currently lack reliable biomarkers for patient selection, crucial for informed treatment choices.

The role of PD-L1 expression in advanced NSCLC is well established. Patients with PD-L1 expression exhibit greater benefit of ICI-treatment [5,8,6]. Patients with high PD-L1 expression (≥50 %) may not even require the addition of chemotherapy [63]. In contrast to typical biomarker dynamics seen in oncogene-driven NSCLC, absence of PD-L1 expression does not exclude patients from exhibiting response [64,65]. In r-NSCLC, a comparable signal is seen with more pronounced benefit for patients exhibiting PD-L1 expression. In both the neoadjuvant and adjuvant setting, (event/disease-free) survival is mainly driven by patients with (high) PD-L1 expression [42,43,49]. Conversely, adjuvant pembrolizumab did not instigate DFS improvement in PD-L1 high patients [48]. Perioperative pembrolizumab showed benefit across PD-L1 strata, but a more pronounced in patients expressing PD-L1 [54]. The aforementioned *meta*-analysis showed EFS-improvement in all PD-L1 subgroups, including PD-L1 negative patients [62]. PD-L1 expression can enrich for clinical outcome but does not preclude patients from therapy-benefit.

The presence of an actionable genomic alteration (AGA), such as activating EGFR mutations or ALK rearrangements, should be considered as a negative biomarker for response. Patients with AGAs are very unlikely to benefit from ICI treatment [66]. Targeted approaches are more appropriate for this specific patient population. Osimertinib has shown to significantly improve DFS and OS in EGFR-mutated patients after surgery [67,68]. More recently adjuvant alectinib also showed a dramatic DFS improvement in ALK-rearranged resected patients [69]. Despite the successes in the postoperative setting, in the neoadjuvant setting so far, targeted regimens have not yet showed major benefit. Neoadjuvant Osimertinib for r-NSCLC with a common EGFR-mutation, even showed a disappointing major pathological response rate of 10.7 % in the multicentric phase II NEOS study (n = 40) [70].

Great effort has been put into a uniform pathological response assessment after neoadjuvant ICI-therapy [25,26,71]. This standardized approach and implementation of well-established definitions of pathological response led to using these parameters as trial endpoints. In contrast to the variable correlations between PD-L1 and different endpoints, pathological response has a consistent effect on outcome [44,50,53,72]. Patients achieving pCR have superior clinical outcomes than those who did not. This led to the adoption of pathological regression as a potential surrogate endpoint for survival outcome after induction therapy [73,74]. The CM816 study showed a strong correlation between pCR and outcome [44]. Patients with pCR had a dramatically improved EFS (HR 0.15; 95 %CI, 0.06–0.37) and OS (HR 0.12; 95 %CI, 0.03–0.50;) compared to non-pCR patients. Exploratory analysis of KN671 showed that pCR-patients had an impressive EFS-benefit, in both the ICI-chemotherapy and placebo-chemotherapy groups (HR 0.33; 95 %CI, 0.09–1.22) [54]. Interestingly, patients not achieving pCR also appeared to show an improved EFS compared to the placebo group (HR 0.69; 95 %CI, 0.55–0.85). While these analyses are exploratory and not formally part of the trial-design, they hint on potential benefit of continued adjuvant ICI for non-pCR patients. pCR could serve as a biomarker to determine which patients should continue adjuvant ICI. A post-hoc analysis of CM77T showed a comparable result, potentially hinting on the importance of continuing adjuvant nivolumab in patients not achieving pCR [58]. However, to definitively address this question, a follow-up randomized, placebo-controlled study assessing the additional benefit of continuing adjuvant treatment in both pCR and non-pCR patients is necessary.

If pCR/MPR were to be validated to tailor further postoperative therapy, there remains a discussion on the optimal cut-off. A single-center retrospective analysis (n = 272) of patients undergoing resection after neoadjuvant chemotherapy demonstrated that the optimal cut-off differs between squamous cell carcinoma and adenocarcinoma [75]. Using maximally selected rank statistics, optimal cut-offs best able to predict lung cancer–specific survival were identified. A residual viable tumor (RVT) of ≤10 % was an independent predictor for better lung cancer–specific survival (p = 0.035) for squamous NSCLC. In patients with adenocarcinoma, RVT of ≤65 % was associated with improved OS (p = 0.050). Different pathological parameters in primary tumor and lymph nodes were prospectively evaluated in a prespecified exploratory analysis of the CM816 study [72]. Regardless of nodal involvement, EFS improved in case of 0 % RVT in the primary tumor, compared to > 0 % RVT (HR = 0.18). The proportion of RVT in the primary tumor was also predictive for EFS: 2-year EFS-rates were 90 %, 60 %, 57 % and 39 % for patients with 0–5 %, >5–30 %, >30–80 % and >80 % RVT respectively.

These reports indicate that pathological response is not a dichotomous but continuous variable. Future trials should prospectively evaluate several cut-offs per histology to determine the optimal threshold for future treatment decisions.

7.3. The radiation oncologist's perspective

For several years, the standard-of-care treatment for many stage III patients has been chemoradiotherapy (CRT) followed by adjuvant durvalumab [7,69,70,76]. The landmark PACIFIC study showed a dramatical improvement in PFS (HR 0.55; 95 %CI, 0.45–0.68; median 16.9 versus 5.6 months) and OS (HR 0.72; 95 %CI, 0.59–0.89; median 47.5 versus 29.1 months) by introducing 1 year of durvalumab after CRT. When we critically appraise the currently available data on neoadjuvant and perioperative ICI in early-stage NSCLC, we must address the glaring issue of the control arm. Is neoadjuvant chemotherapy followed by surgery a fair comparator for a disease considered by many as unresectable as illustrated above? In NADIM and NADIM-II 54 % and 39 % of patients had multilevel N2-disease, [50,53]. Larger RCT's such as CM816, KN671, CM77T and AEGEAN also included multilevel N2 [42,54,56]. Details on the presence of single-or multilevel N2-disease and correlative outcome data, are missing in the former 3 RCT's. Importantly, we should emphasize that currently data on how the diagnosis of N2-disease was obtained, is lacking. Did investigators obtain histological or cytopathological confirmation of nodal involvement or was radiographic diagnosis of N2-disease sufficient and thus were all N2-diseases, truly N2-diseases?

In AEGEAN, 9.4 % of patients in the durvalumab arm, had multilevel N2-disease. Subgroup analysis showed a median EFS of 31.9 months (HR 0.69; 95 %CI, 0.33–1.38). This outcome is fairly comparable to the progression-free survival in the PACIFC study. Long-term survival outcomes however, of patients with multilevel N2-disease treated surgically with neoadjuvant or perioperative ICI remain unclear, and further data are eagerly anticipated. Ideally, a randomized trial should take place comparing patients with a potentially resectable N2-disease to a surgical or radiotherapeutical multimodality treatment. There are many practical and organizational hurdles to such an endeavor, and it is doubtful that this will ever take place in the context of a strict interventional study. A study with a pragmatic trial design or a trials-within-cohorts design could help us solve this question [78].

Radiotherapy and surgery do not necessarily need to be opposing treatment choices. There might also be a future for a combined approach. Promising results were seen in the single-center open-label randomized phase II NCT02904954 trial (n = 60) [79]. Patients with r-NSCLC were randomized to receive neoadjuvant durvalumab alone or preceded by stereotactic body radiotherapy (SBRT). Patients randomized to the radiotherapy arm received three consecutive fractions of 8 Gy delivered to the primary tumor shortly before the first durvalumab cycle. The primary end point of MPR was met. In the durvalumab arm, 6.7 % (95 %CI, 0.8–22.1) of patients achieved MPR. In the durvalumab after SBRT arm, 53.3 % (95 %CI, 34.3–71.7) of patients achieved MPR. The 3-year DFS-rate was 63 % (95 %CI, 46.0–80.4) in the patient group treated with durvalumab monotherapy compared to 67 % (95 %CI, 49.6–83.4) in the dual therapy arm [80].

A potential concern of ICI and lung-directed radiotherapy is the higher incidence of pneumonitis which may lead to interruption or discontinuation of ICI treatment. In the PACIFIC study, pneumonitis of any grade occurred in nearly 33 % of patients who received adjuvant durvalumab, with grade 3 or 4 pneumonitis occurring in 3.4 % [77]. A report on patients from an early access program showed that 9.5 % of patients treated with durvalumab stopped treatment due to pneumonitis [81]. Several others have reported on durvalumab treatment withdrawal in this setting [82,83]. A recent *meta*-analysis concluded that compared with CRT alone, durvalumab consolidation after CRT was associated with a higher incidence of moderate pneumonitis and CRT plus PD-1 inhibitors with an increased risk of severe pneumonitis [84]. Clinicians should be aware of these possible complications when combining radiotherapy and ICI treatment. All these considerations should be taken into account when determining the optimal strategy for a patient with stage III NSCLC.

7.4. The oncologist's perspective

Next to patient-tailored treatment strategy selection, clinicians are confronted with a number of challenges when evaluating a patient during and after the therapy course in daily clinical practice. Pathological response has shown to correlate with outcomes, as previously illustrated, but cannot reliably be assessed non-invasively. A significant discordance (>40 %) arises between RECIST (Response Evaluation Criteria in Solid Tumors) and pathological response when computed tomography (CT) is utilized to evaluate the efficacy of neoadjuvant chemotherapy [85]. Additional prospective analysis within the CM816 study confirmed a poor concordance between imaging and pathological regression [72]. While patients exhibiting complete or partial response per RECIST tend to have less RVT, it is noteworthy that only 6 % of patients achieving pCR demonstrated a complete response on imaging. Moreover, 19 % of patients with MPR did not exhibit any radiographic response. Interestingly, imaging indicated nodal involvement in 36 % of patients, but no nodal metastases were found upon pathological examination. Another difficulty in assessing radiographic response is nodal immune flare, which can mimic disease-progression [86]. PET-CT (Positron Emission Tomography-Computed Tomography) can more adequately evaluate responses to neoadjuvant chemotherapy or chemoradiotherapy [87]. Change in maximum standardized uptake values exhibit a near-linear correlation with MPR, rendering it a likely superior predictor compared to RECIST. In the neoadjuvant sintilimab monotherapy study, tumors were evaluated for partial metabolic response (PMR) using the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) [30]. Out of 36 treated patients, all those showing PMR (36.1 %) achieved MPR. PERCIST shows potential advantages over RECIST in the neoadjuvant context, yet its usefulness requires prospective validation.

Given the limitations of conventional radiographic response assessment, innovative methods, such as circulating tumor DNA (ctDNA) analysis, gained interest. In a retrospective analysis of 85 patients who underwent surgical resection, ctDNA was assessed using a tissue-agnostic assay [88]. Patients with detectable ctDNA at baseline or after treatment, and those who did not clear ctDNA after treatment experienced worse outcomes. The presence of ctDNA before surgery was associated with a statistically significant decrease in OS (HR 3.29; 95 % CI, 0.95–11.45; P = 0.047). After surgery, whether accompanied by neoadjuvant or adjuvant chemotherapy or radiotherapy, persistence of ctDNA was associated with a significantly worse OS (HR 3.99; 95 %CI, 1.40–11.40; P = 0.0053) compared to patients without detectable ctDNA. Patients with ctDNA-clearance after completion of SOC treatment showed outcomes comparable to patients with undetectable ctDNA throughout the study. ctDNA-clearance is linked with pathological response to ICI and indicates improved PFS and OS in r-NSCLC [28,89]. The neoadjuvant nivolumab study already provided evidence that tumors demonstrating MPR, displayed a molecular response characterized by elimination of tumor-specific mutations. Notably, early ctDNA-clearance predicts both PFS and OS. A reduction in ctDNA to undetectable levels correlates with longer PFS and OS compared to those without ctDNA elimination (log-rank P = 0.001 and 0.008, respectively). The CM816 study involved the prospective analysis of ctDNA from 89 evaluable patients [42,72]. Patients exhibit ctDNA-clearance more frequently with nivolumab-chemotherapy (56 %; 95 %CI, 40–71) compared to chemotherapy alone (35 %; 95 %CI, 21–51). Patients with ctDNA-clearance had a higher pCR-rate than those without. EFS appeared longer in patients with ctDNA-clearance in both the nivolumab-chemotherapy (HR 0.60; 95 %CI, 0.20–1.82) and the chemotherapy-alone group (HR 0.63; 95 %CI, 0.20–2.01). Similarly, the AEGEAN study collected ctDNA-samples at protocol-predefined time points [56,90]. Patient-specific panels were used for prospective analysis (186 evaluable patients). In both treatment arms decreases in median variant allele frequencies (VAFs) were observed early (cycle 2). By cycle 3 VAFs were significantly lower in patients achieving pCR/MRP compared to those without pCR/MPR ($P \leq 0.003$). Patients achieving ctDNA-clearance had higher rates of pCR (durvalumab-arm: 50.0 % versus. 15.1 %; placebo-arm: 14.3 % versus. 3.1 %). All patients who were ctDNA-positive at baseline and achieved pCR had ctDNA-clearance by cycle 4. These early molecular responses raise important questions about the current treatment duration and intensity in the preoperative setting and warrant studies looking at shorter or ctDNA-tailored treatment courses. Despite the promise that ctDNA beholds, clinicians should be aware of the limitations of the (current) technology [91]. Besides ctDNA analysis platforms not being broadly available yet and have a significant associated cost, the main limitation is sensitivity. With decreasing disease stage, the probability of detecting ctDNA decreases as well [92]. The estimated clonal VAFs are only 0.008 % (95 % CI 0.002–0.03 %) for cT1b, 0.1 % (95 % CI 0.06–0.18 %) for cT1c and 1.4 % (95 % CI 0.62–3.1 %) for cT3 NSCLC, whereas currently the most sensitive technology typically has a detection limit of 0.01 % [93].

8. Conclusion

In summary, preoperative combination of ICI and a platinum doublet is preferred over chemotherapy alone as this strategy has a lower risk of surgical omission and improved surgical and long-term clinical outcomes. Lack of direct comparative studies between different treatment strategies (neoadjuvant versus adjuvant versus perioperative) make it challenging to evaluate the added benefit of each strategy compared to the other. Shorter course neoadjuvant ICI-combination strategies have biological rationale and show promising results however it is unclear how they will compare to ICI combined with chemotherapy and whether these strategies can reduce the number of patients precluded from surgery. pCR can be potentially used to tailor further adjuvant treatment course but needs prospective validation.

Immune checkpoint inhibition represents a practice-changing approach in the resectable lung cancer treatment landscape. ICI-based treatment strategies have demonstrated remarkable efficacy in improving outcomes for patients undergoing surgery. The ability of ICI to enhance antitumor immune responses and reduce the risk of disease recurrence offers new hope for patients facing a challenging diagnosis. While further research is necessary to optimize patient selection, combination strategies, and long-term outcomes, the burgeoning success of ICI heralds a new era in the management of resectable lung cancer. As we unravel its complexities and refine the integration into multimodal treatment approaches, ICI stands poised to transform the standard of care.

9. AI-declaration

No generative AI or AI-assisted technologies were used in the writing process.

CRediT authorship contribution statement

Kristof Cuppens: Writing – review & editing, Writing – original draft, Conceptualization. **Bert Du Pont:** Writing – review & editing, Writing – original draft. **Joost Knegjens:** Writing – review & editing. **Brigitte Maes:** Writing – review & editing, Writing – original draft. **Paul Baas:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kristof Cuppens: Consultancy for BMS, MSD and AstraZeneca. Bert Du Pont: none. Joost Knegjens: none. Brigitte Maes: none. Paul Baas: Research funding and consultancy for BMS, Consultancy for MSD.

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