Review Article

The beginning of a new era in induction treatment for operable non-small cell lung cancer: a narrative review

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Background and Objective: The survival benefit of induction therapy for non-small cell lung cancer (NSCLC) remains controversial. Recently, the outcomes of systemic therapy for NSCLC have dramatically changed with the advent of molecular target drugs and immune checkpoint inhibitors (ICIs). The present review was conducted to investigate the outcomes of induction therapy with reference to randomized control trials (RCTs).

Methods: We reviewed RCTs and ongoing clinical trials between 1990 and 2022 using relevant databases: PubMed, Web of Science, and EMBASE database. We investigated the outcomes of induction therapy.

Key Content and Findings: Induction therapy was associated with longer overall survival in comparison to surgery alone in several RCTs for stage III disease. However, its benefit in early-stage (I–II) disease was unclear. Regarding induction chemotherapy and chemoradiotherapy, the safety and survival outcomes did not differ between the two arms. Epidermoid growth factor receptor (EGFR) tyrosine kinase inhibitors as induction therapy in patients with proven EGFR mutations may be a sufficient choice for the improvement of overall survival. In ongoing single arm clinical trials and a randomized control study, the administration of ICIs as induction therapy was associated with a good pathological response and satisfactory safety, which will lead to a better survival outcome. Long-term observation is needed to evaluate the toxicity and survival impact of induction therapy with ICIs.

Conclusions: Induction chemotherapy and EGFR-TKIs for stage IIIA NSCLC may contribute to the improvement of survival outcomes although the effect of systemic therapy on stage I-II remains controversial. ICIs may be considered as a valuable treatment option because of their feasibility and safety for induction therapy.

Keywords: Non-small cell lung cancer (NSCLC); induction; neoadjuvant; immune checkpoint inhibitor (ICI); randomized control study

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Introduction

Lung cancer is the leading cause of cancer death worldwide and the most common type of cancer (1). Surgery is one of the curative treatment choices for non-small cell carcinoma (NSCLC), although NSCLC remains associated with poor overall survival (OS) with the exception of stage I disease. This is likely to be explained by the fact that approximately 30% of cases are diagnosed at an advanced stage (2), and a high incidence of local and distant recurrence (21–55%) after surgery (3-5). To prevent local and distant recurrence, it is essential to eliminate

Table 1 The search strategy summary

Items	Specification
Date of search	From 1st February 2022 to 15 March 2022
Databases and other sources searched	PubMed, Web of Science, Embase, ClinicalTrials.gov, and Chinese clinical trial registry
Search terms used	Please see Table S1
Timeframe	From 1st January 1990 to 1st January 2022
Inclusion and exclusion criteria	Inclusion criteria: randomized trials, induction chemotherapy, induction chemoradiotherapy
	Exclusion criteria: the manuscript with the same trial
Selection process	The two reviewers (S Shinohara, H Kuroda) independently screened the manuscripts according to the eligible criteria for the research. The articles satisfied with the inclusion criteria were obtained by H Matsushita and K Masago. When the decision of the two reviewers is not agreed with a discussion, a third reviewer (Y Takahashi) makes a final decision
Additional considerations	Duplicated articles are excluded by the review authors

circulating tumor cells (6,7) and reduce the cancer volume at the local site before surgery, which helps to facilitate curative resection. Therefore, surgeons and oncologists assume that the combination of surgery and chemo- or chemoradiotherapy are optimal choices for the curative treatment of advanced NSCLC. Induction systemic therapy has therefore been regarded as a key therapeutic strategy for stage IIIA NSCLC. Consequently, several randomized control trials (RCTs) were conducted to elucidate whether induction chemotherapy contributes to the improvement of survival (8-11). Certainly, induction systemic therapy would be a choice for advanced NSCLC with IIIA disease; however, the best regimen for induction therapy remains unclear. We believe that efficacy and tumor volume reduction are the most important to accomplish complete resection for the choices of induction systemic therapy. Molecular target drugs, including epidermoid growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), have dramatically improved survival in advanced NSCLC (12-14). It is necessary to elucidate the possible application of EGFR-TKIs in induction therapy because EGFR-TKIs have relevant effects on the EGFR mutation harboring NSCLC. In addition, the advent of immune checkpoint inhibitors (ICIs) has dramatically changed drug therapy for NSCLC due to its remarkable efficacy in the treatment of tumors with the high expression of programmed death-ligand 1 (PD-L1) (15). A network meta-analysis showed that combination therapy with ICI and platinum doublet is better than monotherapy for inoperable NSCLC (16). Patients with high PD-L1 expression are greatly expected to N2 down staging and tumor shrinking, which leads to resect cancer completely. We would like to elucidate whether ICI therapy for operable NSCLC as induction therapy improves the poor OS. However, the efficacy and safety of ICI therapy before surgery remain unknown.

We consider these new drugs may control the long-term progression and restrain distant metastasis due to the cytotoxicity reaction for the circulating tumor cells and residual lymph node cancer cells. In this manuscript, we review the efficacy of induction systemic therapy for operable NSCLC referring RCTs and investigate the possible application of EGFR-TKI and ICI treatment in NSCLC induction therapy. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-957/rc).

Methods

We reviewed the articles using terms via PubMed, Web of Science, and EMBASE (Table S1). Regarding ICI ongoing studies, we investigated using ClinicalTrials.gov, and Chinese clinical trial registry. The eligible studies were searched from 1 January 1990 to 1 January 2022. The two reviewers independently screened the manuscripts according to the eligible criteria for the research. When the decision of the two reviewers is not coincided with a discussion, a third reviewer made a final decision (*Table 1*).

Results

The included and excluded process is demonstrated in

Figure S1 with regard of the narrative review of RCTs.

Comparison of induction chemotherapy (chemotherapy vs. surgery alone) with platinum doublet

The survival benefit of induction chemotherapy followed by surgery was summarized by several RCTs (9,17-21) (*Table 2*). Rosell *et al.* showed that the induction chemotherapy arm, who received mitomycin/ifosfamide/cisplatin, had better OS in comparison to the surgery alone arm among patients with stage IIIA disease (26 *vs.* 8 months, P<0.001) (20). Similarly, Roth *et al.* reported that patients treated with perioperative chemotherapy (cisplatin/cyclophosphamide/etoposide) showed better OS in comparison to those who received surgery alone (21 *vs.* 14 months, P=0.048) (21). However, several reports demonstrated no survival benefit of induction chemotherapy on OS in stage IIIA patients (26,27,29,31). Pass *et al.* demonstrated no significant difference for OS between their induction chemotherapy group and their surgery alone group. In particular, it should be noted that the studies included patients with multiple positive N2 disease (multiple positive N2: 13/23), which are considered to be inoperable according to the present criteria (31). Nagai *et al.* reported that induction chemotherapy showed no significant impact (27). Although the study was well designed, the recruitment for the eligible patients was too slow and the number of patients enrolled in the study did not meet the initial expectation (27). In addition, there were no patients with a complete response and the response rate was low (28%) (27).

For patients with stage I-IIIA disease, the benefit of induction chemotherapy is unclear. Eight RCTs for stage I-IIIA NSCLC have been conducted (9,17,22-25,28,30). The Chemotherapy in Early stages NSCLC Trial (ChEST) reported that the induction chemotherapy arm (cisplatin plus gemcitabine) showed better OS in comparison to surgery alone (7.8 *vs.* 4.8 years, P=0.04) (9). The reason for the positive outcome in the induction chemotherapy arm was explained by the high response rate (35.4%) of this trial, and the statistically significant impact of preoperative chemotherapy on the outcomes in the stage IIB/IIIA subgroup (3-year PFS rate: 36.1% *vs.* 55.4%; P=0.002) (9). Unfortunately, the study was terminated early as the superiority of adjuvant chemotherapy was proven by other clinical trials in that time. Of note, in a subgroup analysis of patients with stage IB/IIA disease, there was no significant difference in OS between the induction chemotherapy arm and the surgery alone arm (HR, 1.02; 95% CI, 0.58–1.19; P=0.94) (9). On the other hand, among patients with stage IIB/IIIA disease, OS was longer in the induction chemotherapy arm than in the surgery alone arm (HR, 0.42; 95% CI, 0.25–0.71; P=0.001) (9). Similarly, the three arms clinical trial [Neoadjuvant/Adjuvant Taxol/Carboplatin Hope (NATCH)], which enrolled patients with IA-IIIA disease (T3N1) and excluded patients with N2 disease, demonstrated that the disease-free survival (DFS) of the induction chemotherapy and surgery alone group did not differ to a statistically significant extent (HR, 0.92; 95% CI, 0.81–1.04; P=0.17) (29). Moreover, a subgroup analysis of patients with stage II-IIIA disease showed that DFS tended to be better in the induction chemotherapy arm than in the surgery alone arm (HR, 0.81; 95% CI, 0.64–1.02; P=0.07) (29). Thus, induction chemotherapy improves the OS of patients with stage II/IIIA disease but not patients with stage I disease. The benefit of induction chemotherapy for I-IIIA disease was also proven by a meta-analysis (32,33). Song *et al.* reported that induction chemotherapy significantly improves OS in comparison to surgery alone in stage I-III NSCLS (HR, 0.84; 95% CI, 0.77–0.92; P<0.001) (33). The results in patients with stage IIIA disease were similar (HR, 0.84; 95% CI, 0.75–0.95; P=0.005). Thus, induction chemotherapy would significantly improve OS in patients with stage IIIA disease, but the outcome in early-stage disease, particularly stage I disease, is controversial. The best regimen is also unclear; thus, it should be investigated in a large RCT.

Lastly, the safety and feasibility are sufficient for induction therapy, even in the cases in which surgery is postponed. However, the complete resection rate of the induction therapy arm was also the same as that of the surgery alone arm (*Table 1*). Of note, this did not correspond with the favorable OS of patients who received induction therapy in comparison to those who received surgery alone. This may imply that, systemic intervention (e.g., chemotherapy, which regulates circulating tumor cells) leads to better OS by preventing distant metastasis rather than by providing local disease control.

However, these results should be interpreted carefully because the clinical trials were performed more than 10 years ago. The TNM classification and mediastinal lymph node staging are different in each era.

Comparison of the outcomes of chemotherapy vs. chemoradiotherapy

For stage IIIA (N2) disease, it remains unclear whether chemotherapy or chemoradiotherapy is better for induction

Table 2 Characteristics of randomized control trial comparing induction therapy *vs.* non-induction therapy

Author	Year	Number	Excluded	Male	Female	Stage	Treatment modality	Treatment regimen	Control mortality	Results	Outcome	Study	Complete resection
Chen *et al.* (17)	2013	356	19	259	78	I-IIIA	CSCRiii	MVP	SCRiii	57.6 *vs.* 45.4 months (HR 1.67, P=0.016)	Median survival (OS)	Positive	NR
Scagliotti *et al.* (9)	2012	270	0	225	45	IB-IIIA	CS	CDDP + GEM	S	7.8 *vs.* 4.8 years, P=0.04	Median survival (OS)	Positive	88% *vs.* 84%
Felip *et al.* (22)	2010	413	4	359	50	IA-IIIA	CSRiii	CBDCA + PTX	SRiii	38.3% *vs.* 34.1% (HR 0.92, P=0.176)	5-year DFS rate	Negative	NR
Pisters *et al.* (23)	2010	354	17	222	115	IB-IIIA	CS	CBDCA + PTX	S	62 *vs.* 40 months (HR 0.79, P=0.11)	Median survival (OS)	Negative	88% *vs.* 87%
Gilligan *et al.* (24)	2007	519	0	374	143	IA-IIIB	CS	CDDP + GEM or CBDCA + DOC or PTX etc.	S	54 *vs.* 55 months (HR 1.02, P=0.86)	Median survival (OS)	Negative	81% *vs.* 79%
Sorensen *et al.* (25)	2005	90	0	NR	NR	IB-IIIA	CS	CDDP + PTX	S	34.4 *vs.* 22.5 months[*1]	Median survival (OS)	Negative	79% *vs.* 70%
Yao *et al.* (19)	2004	456	NR	333	123	III	CS	CDDP + GEM, CDDP + NVB, MVP, EP	S	34.2% *vs.* 23.0% (P<0.001)	5-year OS rate	Positive	87.0% *vs.* 83.7%
Yang *et al.* (26)	2005	40	0	NR	NR	IIIA	CS	CBDCA + GEM	S	11/19 *vs.* 9/21	Total survival number	Negative	89.5% *vs.* 90.5%
Nagai *et al.* (27)	2003	62	0	41	21	IIIA	CS	CDDP + VDS	S	17 *vs.* 16 months (P=0.53)	Median survival (OS)	Negative	65% *vs.* 77%
Yi *et al.* (18)	2003	84	0	52	32	I-III	CS	MVP	S	no detail, but P=0.047	Total survival rate	Positive	NR
Depierre *et al.* (28)	2002	373	18	332	23	I-IIIA	CSCRiii	MIP	SRiii	37 *vs.* 26 months (P=0.15)	Median survival (OS)	Negative	42.1% *vs.* 40.7%
Wu *et al.* (29)	2002	55	0	NR	NR	IIIA	CS	CBDCA + DOC	S	36.4% *vs.* 19.2%[*2]	Total survival rate	Nr	77.3% *vs.* 80.8%
Splinter *et al.* (30)	2000	79	0	NR	NR	IB-II	CS	CBDCA + PTX or CDDP + teniposide	S	NR[*3]	NR	Nr	NR

Table 2 (*continued*)

Table 2 (*continued*)

Author	Year	Number	Excluded	Male	Female	Stage	Treatment modality	Treatment regimen	Control mortality	Results	Outcome	Study	Complete resection
Rosell *et al.* (20)	1994	60	0	59	1	IIIA	CSRiii	MIP	SRiii	26 *vs.* 8 months (P<0.001)	Median survival (OS)	Positive	85.1% *vs.* 90%
Roth *et al.* (21)	1998	60	0	44	16	IIIA	CSC	CDDP + CPA + etoposide	S	21 *vs.* 14 months (P=0.048)	Median survival (OS)	Positive	60.7% *vs.* 65.6%
Pass *et al.* (31)	1992	27	0	12	15	IIIA	CSC	EP	SRiii	28.7 *vs.* 15.6 months (P=0.095)	Median survival (OS)	Negative	84.6% *vs.* 85.7%
Dautzenberg *et al.* (11)	1990	26	0	24	2	II-III	CSC	CDDP + CPA + VDS	S	21 *vs.* 23 months (P=0.85)	Median survival (OS)	Negative	NR

*[1], the difference was not significant although P value was not declared; *[2], the present study was available on the conference abstract. *[3], the median survival has not yet been reached. NR, not recorded; CSCRiii, induction chemotherapy followed by surgery, and adjuvant chemoradiotherapy for stage III; CS, induction chemotherapy followed by surgery; CSRiii, induction chemotherapy followed by surgery, and adjuvant radiotherapy for stage III; CSC, induction chemotherapy followed by surgery, and adjuvant chemotherapy; MVP, mitomycin + vinblastine + cisplatin; CDDP, cisplatin; GEM, gemcitabine; CBDCA, carboplatin; PTX, paclitaxel; DOC, docetaxel; NVB, vinorelbine; EP, etoposide + cisplatin; VDS, vindesine; MIP, mitomycin + ifosfamide + cisplatin; CPA, cyclophosphamide; SCRiii, surgery and adjuvant chemoradiotherapy for stage III; S, surgery alone; SRiii, surgery followed by adjuvant radiotherapy for stage III; HR, hazard ratio; OS, overall survival.

therapy. Four RCTs showed no survival difference between induction chemotherapy and chemoradiotherapy arms (8,10,34,35) (*Table 3*). Thomas *et al.* conducted the largest RCT comparing induction chemoradiotherapy to chemotherapy followed by surgery among patients with pathologically proven N2 using mediastinoscopy (34). No significant difference in progression-free survival (PFS) was observed between the two groups (5-year PFS 16% *vs.* 14%; HR, 0.99, 95% CI, 0.81–1.19; P=0.87). The problem of the trial was the high rate of N3 disease (11.4%) and pneumonectomy (35.1%), which resulted in the poor prognosis. In addition, induction chemoradiotherapy followed by pneumonectomy was associated with high mortality in comparison to lobectomy (26% *vs.* 1%) in the INT0139 trial (36). Therefore, special attention is required when performing induction chemotherapy followed by pneumonectomy. As the same result, Pless *et al.* showed no survival difference between chemotherapy and chemoradiotherapy while the adverse events in chemotherapy were not increased in chemoradiotherapy (8). Katakami *et al.* reported that induction chemoradiotherapy did not improve PFS or OS did in comparison to induction chemotherapy (HR, 0.68; 95% CI, 0.38–1.21; P=0.187, HR, 0.77; 95% CI, 0.42–1.41; P=0.397, respectively) (10). While the study was terminated because of a low accrual rate, we the result should be interpreted with care.

Tong *et al.* carried out a systematic review and meta-analysis to elucidate the efficacy and toxicity of induction chemoradiotherapy in comparison to chemotherapy (37). The manuscript indicated that the rates of grade 3–4 adverse events of leukopenia and nausea did not differ between the two groups (RR, 0.84; 95% CI, 0.40–1.77; P=0.65, RR, 1.50; 95% CI, 0.84–2.67; P=0.17, respectively). Unexpectedly, the incidence of grade 3–4 infection in the chemoradiotherapy group was significantly lower than that in the chemotherapy group (RR, 0.38; 95% CI, 0.16–0.94; P=0.04). Thus, chemoradiotherapy would be acceptable with regard to safety and tolerability. Interestingly, chemoradiotherapy has benefits in terms of R0 resection, although there is no survival contribution by a meta-analysis Chen *et al.* reported (38). The curative resection and pathological response may be surrogate marker, but special attention is needed to consider the results of clinical trials with advanced NSCLC.

Although several RCTs were conducted, whether chemotherapy or chemoradiotherapy is better has been controversial.

Table 3 Characteristics of RCT comparing induction chemotherapy *vs.* chemoradiotherapy

Characteristics	Pless *et al.* (8)	Katakami *et al.* (10)	Thomas *et al.* (34)	Girard *et al.* (35)
Year	2015	2012	2008	2010
Number	232	60	558	62
Excluded	0	2	34	2
Male	155	40	431	46
Female	77	20	93	14
Stage	IIIA	IIIA	III	IIIA
Treatment modality	CRiiiS	CRiiiS	CRiiiS	CRiiiS
Treatment regimen	CDDP + DOC	CBDCA + DOC	CDDP + etoposide	CDDP + VNR or CBDNA + PTX
Control mortality	CS	CS	CSRiii	CS
Control arm	CDDP + DOC	CBDCA + DOC	CDDP + etoposide	CDDP + VNR
Outcome	12.8 *vs.* 11.6 months (P=0.67)	39.6 *vs.* 29.9 months (HR 0.77, P=0.397)	32.4 *vs.* 33.0 months (P=0.54)	13 *vs.* 24 months (P=0.268)[*2]
Outcome	Median event-free survival	Median survival (OS)	Median survival (OS)	Median survival (OS)
Study	Negative	Negative	Negative	Negative
Complete resection	91% *vs.* 81% (P=0.06)	69.0% *vs.* 54.5%[*1]	84% *vs.* 77%	71.4% *vs.* 78.1%

[*1], complete resection rate was re-calculated in the review as follows: the number of complete resections/that of patients undergone surgery. [*2], the study is the three arm RCT. In the review, we declared the result of two arms. RCT, randomized control trial; CRiiiS, induction chemoradiotherapy for stage III followed by surgery; CSRiii, induction chemotherapy followed by surgery, and adjuvant radiotherapy for stage III; CS, induction chemotherapy followed by surgery; CDDP, cisplatin; DOC, docetaxel; CBDCA, carboplatin; VNR, vinorelbine; PTX, paclitaxel; HR, hazard ratio; OS, overall survival.

Comparison of the outcomes of EGRF TKI vs. platinum-based chemotherapy

Variations in induction therapy regimens have a large influence on OS. Since induction systemic therapy was started, cisplatin-based regimens have been the gold standard. Whereas, the appearance of EGFR-TKIs has dramatically changed the therapeutic strategy for advanced NSCLC. EGFR-TKIs significantly prolong OS and PFS in advanced NSCLC harboring EGFR mutations. Because of the large benefit of EGFR-TKIs in advanced NSCLC, many oncologists and surgeons consider that EGFR-TKIs would be beneficial in neoadjuvant settings. Recently, two RCTs showed that EGFR-TKI induction therapy for patients with adenocarcinoma harboring EGFR mutations tended to improve OS and PFS in comparison to platinum-based regimens (39,40) (*Table 4*).

EMERGING-CTONG 1103 is a randomized phase 2 study for stage IIIA-N2 adenocarcinoma harboring EGFR mutations in exons 19 or 21, which was designed to compare the benefit of induction erlotinib *vs.* gemcitabine plus cisplatin. The median PFS of the erlotinib arm was significantly better than that of the gemcitabine plus cisplatin arm (21.5 *vs.* 11.4 months; HR, 0.39; 95% CI, 0.23–0.67; P<0.001) (39), although OS was not different between the two arms (45.8 *vs.* 39.2 months; HR, 0.77; 95% CI, 0.41–1.45; P=0.417). The incidence of adverse events did not differ between the two arms (75.7% and 88.2%, respectively). It should be noted that the contribution of induction therapy in that study is unclear because the study design called for both arms to receive adjuvant treatment after induction treatment.

Chen *et al.* (40) conducted an RCT for stage IIIA adenocarcinoma harboring EGFR mutations to evaluate the induction of erlotinib versus pemetrexed plus cisplatin followed by surgery. The study showed that the OS of the erlotinib arm tended to be longer in comparison to the pemetrexed plus cisplatin arm, although the difference was not statistically significant (56 *vs.* 40 months, P=0.053). Currently, the

Table 4 Characteristics of randomized control trial comparing EGFR-TKI *vs.* platinum doublet

Characteristics	Zhong *et al.* (39)	Chen *et al.* (40)
Year	2019	2018
Number	72	86
Excluded	0	0
Male	19	26
Female	53	60
Stage	IIIA	IIIA
Treatment modality	CSC	CS
Treatment regimen	Erlotinib	Erlotinib
Control mortality	CSC	CS
Control arm	CDDP + GEM	CDDP + PEM
Adjuvant chemotherapy	Yes	No
Results	21.5 *vs.* 11.4 months (HR, 0.39, P<0.001)	56 *vs.* 40 months (P=0.053)
Outcome	Median survival (PFS)	Median survival (OS)
Study	Positive	Negative
Complete resection	73.0% *vs.* 62.9% (P=0.358)	90.7% *vs.* 83.7%

EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; CSC, induction chemotherapy followed by surgery, and adjuvant chemotherapy; CS, induction chemotherapy followed by surgery; CDDP, cisplatin; GEM, gemcitabine; PEM, pemetrexed; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

clinical trial of induction Osimertinib for EGFR harboring adenocarcinoma is ongoing (NeoADAURA) (39). The clinical trial is important because Osimertinib is the most effective and harmless EGFR-TKI. We should focus on the result of NeoADAURA in the future (41).

Thus, EGFR-TKIs would be a valuable choice to improve the survival of patients with stage IIIA-N2 lung adenocarcinoma harboring EGFR mutations. However, these results should be interpreted with care due to the very small size of these RCTs. In addition, the timing to use EGFR-TKIs is a crucial matter because early administration of EGFR-TKIs may lead drug-resistant clones. We should investigate the optimal timing to use EGFR-TKIs, whether adjuvant, induction or recurrence is best for NSCLC treatment.

Possible application of ICI as induction systemic therapy

Following the introduction of ICI therapy, there has been a great focus on the tumor immune microenvironment related to the elimination of cancer cells. Certainly, the benefit of adjuvant ICI therapy has been proven in Impower010 (42); however, it is unclear whether ICI induction therapy can contribute to the prognosis of NSCLC. Recently, ICI induction therapy has been applied to stage I-III NSCLC in clinical trials. The efficacy and safety of induction therapy consisting of ICI with PD-1 and PD-L1 drugs is being assessed. There are six RCTs, including ongoing studies (43-48) and six non-randomized trials with available data (49-54) (*Table 5*). In these reports, the efficacy of induction ICI treatment was relatively satisfied with a high pathological complete response (pCR) rate (range, 5–57.1%) and a high objective response rate (range, 7–86%) (*Table 4*).

NEOSTAR is a phase 2 randomized trial that enrolled 44 patients with operable stage I-IIIA disease to compare nivolumab *vs.* nivolumab plus ipilimumab combination therapy (43). Overall, the major pathologic response (MPR) rate (defined as <10% residual viable malignant cells) was 25% (4/23 in nivolumab *vs.* 11/21 in nivolumab plus ipilimumab). The pCR rate reached 15% (2/23 *vs.* 6/21).

Checkmate 816 is the first phase 3 RCT comparing the efficacy of the combination of ICI and platinum doublet (45). Patients with stage IB-IIIA disease were recruited. The primary endpoint was event-free survival

Table 5 Characteristics of clinical studies related to induction immune checkpoint inhibitor

Name/trial number	Clinical trial	Regimen	Cycles	Stage	Sample size	MPR	pCR	ORR
Checkmate159 (49)/ NCT02259621	Open-label phase 2	Nivolumab *vs.* carboplatin + paclitaxel	2	I-IIIA	22	45.0%	10.0%	10.0%
LCMC3 (50)/ NCT02927301	Open-label single arm phase 2	Atezolizumab	2	IB-IIIB	101	18.0%	5.0%	7.0%
NEOSTAR (43)/ NCT03158129	Open-label randomized phase 2	Nivolumab *vs.* nivolumab + ipilimumab	3	IA-IIIA	44*[1]	25.0%	18.0%	22.0%
ChiCTR-OIC-17013726 (51)	Open-label single arm phase 1b	Sintilimab	2	IB-IIIA	40	40.5%	8.1%	20.0%
NADIM (54)/ NCT03081689	Open-label single arm phase 2	Nivolumab + carboplatin + paclitaxel	3	IIIA	46	83.0%	59.0%	74.0%
NCT02716038 (52)	Open-label single arm phase 2	Atezolizumab + carboplatin + nab-paclitaxel	2	IB-IIIA	14	60.0%	27.3%	57.0%
SAKK16/14 (53)/ NCT02572843	Open-label single arm phase 2	Cisplatin + docetaxel + durvalumab	2	IIIA	55	60.0%	18.0%	58.0%
Checkmate816 (45)/ NCT02998528	Open-label phase 3 randomized control trial	Nivolumab + platinum doublet *vs.* platinum doublet	3	IB-IIIA	358	36% (ITT)	24% (ITT)	54% (ITT)
KEYNOTE-671 (46)/ NCT03425643	Open-label phase 3 randomized control trial	Pembrolizumab + platinum doublet *vs.* platinum doublet	4	III	786	Unknown	Unknown	Unknown
IMpower030 (47)/ NCT03456063	Double blind phase 3 randomized control trial	Atezolizumab + platinum doublet *vs.* placebo + platinum doublet	4	II-III	453	Unknown	Unknown	Unknown
AEGEAN (48)/ NCT03800134	Double blind phase 3 randomized control trial	Durvalumab + platinum doublet *vs.* placebo + platinum doublet	4	II-III	800	Unknown	Unknown	Unknown
NCT04338620 (44)	Open-label phase 3 randomized control trial	Camrelizumab + nab-paclitaxel *vs.* platinum doublet	3	III	43*[2]	65.1%	25.9%	72.1%

*[1], MPR, pCR and ORR were calculated by all cases. *[2], sample size was calculated based on the intention to treat. MPR, major pathological response; pCR, pathological complete response; ORR, overall response rate; ITT, intention to treat.

(EFS) and pCR rate. The median EFS was longer in the nivolumab plus platinum doublet arm than in chemotherapy alone (30.2 *vs.* 20.8 months; HR 0.63: 97.38% CI, 0.43–0.91; P=0.005). The pCR rate of the nivolumab plus platinum doublet arm was significantly higher than that of the platinum doublet arm (24% *vs.* 2.2%; OR, 13.94; 99% CI, 3.49–55.75; P<0.0001). No significant difference was observed between the two arms with respect to the number of patients who received delayed surgery (21% *vs.* 24%). Interestingly, the subgroup analysis showed that the pCR rate was not influenced by the stage, histological subtype (squamous cell carcinoma or non-squamous cell carcinoma), or PD-L1 expression rate in either of the arms. Adverse events were equally observed in both arms. Chemotherapy-related deaths were not observed in the nivolumab plus platinum doublet arm, while treatment-related death was observed in the platinum doublet arm. Moreover, grade 3–4 immune-mediated adverse events were observed in only 4 patients (2.3%). However, the grade 5 surgery-related adverse events were only reported in the nivolumab

plus platinum doublet arm but not in the platinum doublet arm. Of note, inflammatory response following ICI therapy greatly influenced on the surgical procedure. It makes dissection of the pulmonary artery branches difficult. The influence of ICI on surgical procedures should be taken carefully. Overall, the safety of induction therapy with ICIs may be feasible; however, long-term observation is needed to evaluate its toxicity and impact on survival.

NADIM is a single-arm phase II trial among patients with stage IIIA NSCLC who were administrated with neoadjuvant nivolumab plus paclitaxel and carboplatin (54). The 3-year OS reached 81.9% (95% CI, 66.8–90.6) and showed the possibility of ctDNA clearance as the favorable predictive biomarker for OS in induction ICI therapy. Interestingly, the OS predictivity of pCR was inferior to ctDNA clearance (C-index for OS: 0.72 *vs.* 0.82). The result implies that ctDNA may be a better predictive biomarker for the response of ICI treatment. Thereby, it is essential to elucidate the most favorable biomarker for the prediction of the benefit of induction ICI therapy.

Thus, ICIs addressed the great effect of cancer cell elimination in several clinical trials, we expect the downstaging of previously unresectable NSCLS and the control of lymph node metastasis when we use ICIs as induction setting. In the future, ICIs may be a standard induction therapy instead of chemotherapy and chemoradiotherapy.

Conclusions

Induction therapy for stage IIIA NSCLC has sufficient value to improve OS and PFS. However, current evidence does not support the application of induction therapy in the treatment of early-stage NSCLC (stage I and II). EGFR-TKIs may be a choice for induction therapy for stage IIIA NSCLC. ICIs may be considered as a valuable treatment option due to their feasibility and safety for induction therapy; however, long-term evaluation is needed.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-957/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-957/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 The detailed search strategy

#1	Carcinoma, Non-Small-Cell Lung[Mesh term]
#2	nonsmall cell*[Title/Abstract]
#3	non-small cell*[Title/Abstract]
#4	lung tumour*[Title/Abstract]
#5	lung tumor*[Title/Abstract]
#6	lung neoplasm*[Title/Abstract]
#7	lung carcinoma*[Title/Abstract]
#8	lung cancer*[Title/Abstract]
#9	nsclc[Title/Abstract]
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	thoracotomy[Mesh term]
#12	Pneumonectomy[Mesh term]
#13	pneumonectom*[Title/Abstract]
#14	lobectom*[Title/Abstract]
#15	segmentectom*[Title/Abstract]
#16	sublobar[Title/Abstract]
#17	lung resection*[Title/Abstract]
#18	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	perioperative[Title/Abstract]
#20	neoadjuvant[Title/Abstract]
#21	preoperative[Title/Abstract]
#22	induction[Title/Abstract]
#23	#19 OR #20 OR #21 OR #22
#24	#10 AND #18 AND #23

https://dx.doi.org/10.21037/jtd-22-957

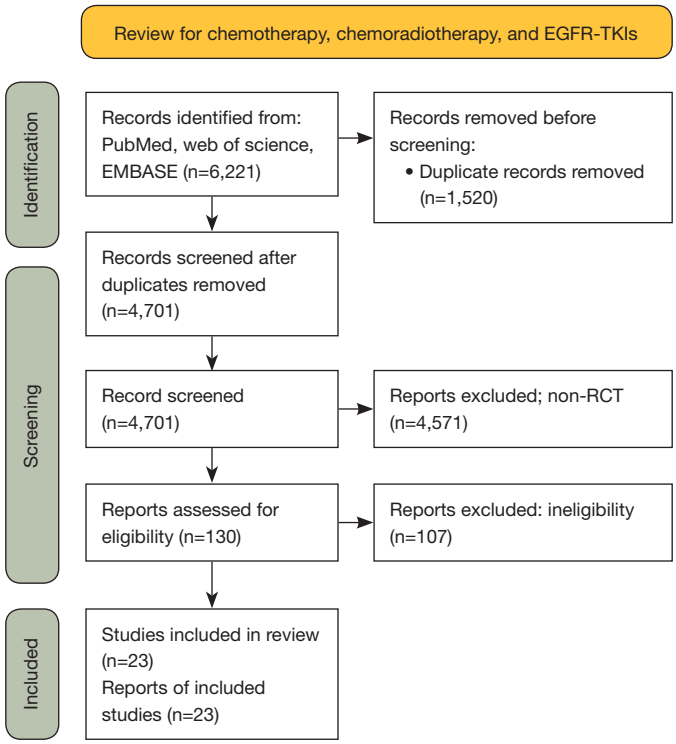

Figure S1 PRISMA flowchart of study selection process.

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