Editorial Commentary

Dual immuno-oncology agents as neoadjuvant therapy for patients with resectable non-small cell lung cancer

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Comment on: Cascone T, Kar G, Spicer JD, *et al.* Neoadjuvant Durvalumab Alone or Combined with Novel Immuno-Oncology Agents in Resectable Lung Cancer: The Phase II NeoCOAST Platform Trial. Cancer Discov 2023;13:2394-411.

Keywords: Immuno-oncology (IO); neoadjuvant therapy; non-small cell lung cancer (NSCLC); surgery

Submitted Nov 13, 2023. Accepted for publication Jan 10, 2024. Published online Feb 20, 2024.
doi: 10.21037/tlcr-23-738
View this article at: https://dx.doi.org/10.21037/tlcr-23-738

Although lung cancer is the most frequent cause of cancer-related deaths globally (1), post-therapeutic prognosis has steadily improved, especially after the introduction of molecular-targeted therapy. Both tyrosine kinase inhibitors for tumors harboring oncogene mutations and immuno-oncology (IO) agents, especially anti-programmed death-1/programmed death ligand-1 (PD-1/PD-L1) agents, are important for improving lung cancer treatment. IO agents were introduced in the 2010s for the treatment of patients with advanced non-small cell lung cancer (NSCLC). Nivolumab, an anti-PD-1 agent, was introduced as a second-line treatment for patients with advanced NSCLC in 2015 (2,3). Thereafter, pembrolizumab (another anti-PD-1 agent) and atezolizmab (an anti-PD-L1 agent) were introduced as second-line treatments for patients with advanced NSCLC in 2016 (4) and 2017 (5), and these agents have resulted in marked improvements in post-therapeutic prognosis, especially in patients with tumors showing PD-L1 expression. Currently, IO agents are used in first-line therapy as monotherapy or in combination with cytotoxic chemotherapy and have become the most important, principal drug for the treatment of patients with advanced NSCLC. An IO agent is then administered to patients with locally advanced but unresectable disease. Durvalumab, an anti-PD-L1 agent, was introduced as consolidation therapy following chemoradiation therapy for patients with locally-advanced, unresectable NSCLC in 2018 and showed tremendous results compared to a placebo (6). Recently, these trends have shifted toward a perioperative setting for the treatment of resectable NSCLC. First, these agents were introduced as adjuvant treatments and they resulted in tremendous improvement in postoperative disease-free survival if patients had tumors with PD-1/PD-L1 expression (7). Currently, the trend is to use these agents in a neoadjuvant setting. Several clinical trials evaluating the efficacy of IO agents have shown favorable results (*Table 1*) (8-19); however, all of these studies (except one) evaluated the efficacy of PD-1/PD-L1 inhibitors as monotherapy or combined with cytotoxic chemotherapy.

Cascone *et al.* reported the results of the NeoCOAST trial, a phase 2, open-label, randomized, multicenter, multi-drug platform window-of-opportunity study (22). This study evaluated the efficacy and safety of neoadjuvant dual-IO therapy in patients with previously untreated, resectable stage IA3–IIIA NSCLC. The patients were randomized into four arms that consisted of the administration of (I) durvalumab alone, (II) durvalumab + oleclumab, (III) durvalumab + monalizumab, or (IV) durvalumab + danvatirsen. Oleclumab is an anti-CD73 human immunoglobulin G1 (IgG1) monoclonal antibody. It selectively binds to CD73 on the cell surface, inhibits it, and reduces its cell surface expression, consequently

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Table 1 Trials evaluating the efficacy of IO agents as neoadjuvant or perioperative therapy

Study	Reported year	Phase	N	Patients' cohort	Agent used for neoadjuvant therapy	Classification	Cycle	MPR (%)	pCR (%)	TRAE (G >3; %)	Resection rate† (%)
CheckMate159 (8)	2018	II	22	I–IIIA	Nivo	Mono	2 (q14d)	45.0‡	15.0‡	4.5	95.0
PRINCEPS (9)	2020	II	30	IA (2 cm)–IIIA (non-N2)	Atezo	Mono	1 (q14d)	0	0	3.3	100
Gao *et al.* (10)	2020	Ib	40	IA–IIIB	Sinti	Mono	2 (q21d)	40.5‡	16.2‡	10.0	92.5
NADIM (11)	2020	II	46	IIIA	Nivo + CT	Mono + CT	3 (q21d)	74.0	57.0	30.0	89.0
Shu *et al.* (12)	2020	II	30	IB–IIIA	Atezo + CT	Mono + CT	4 (q21d)	57.0	33.0	50.0	97.0
NEOSTAR (13)	2021	II	23	IA–IIIA	Nivo	Mono	3 (q14d)	22.0	9.0	4.3	95.7
			21		Nivo + Ipi	Dual		38.0	29.0	4.8	81.0
SAKK16/14 (14)	2021	II	67	IIIA (N2)	CT → Durva	CT → Mono	2 (q14d)	62.0‡	18.0‡	88.0	88.1
Eichhorn *et al.* (15)	2021	II	15	II–IIIA	Pembro	Mono	2 (q21d)	27.0	13.0	33.3	100
LCMC3 (16)	2022	II	181	IB–IIIB	Atezo	Mono	2 (q14d)	20.0§	6.0§	11.0	88.0
Tong *et al.* (17)	2022	II	30	IB–IIIA	Pembro	Mono	2 (q14d)	28.0‡	12.0‡	3.3	83.3
IONESCO (18)	2022	II	46	IB–IIIA (non-N2)	Durva	Mono	3 (q14d)	19.0‡	7.0‡	0	93.5
CheckMate816 (19)	2022	III	179	IB–IIIA	Nivo + CT	Mono + CT	3 (q21d)	36.9	24.0	33.5	83.2
					CT	CT only		8.9	2.2	36.9	75.4
KEYNOTE-671 (20)	2023	III	397	II–IIIB (N2)	Pembro + CT	Mono + CT	4 (q21d)	30.2	18.1	44.9	81.9
			400		CT	CT only		11.0	4.0	37.3	79.3
AEGEAN (21)	2023	III	366	II–IIIB (N2)	Durva + CT	Mono + CT	4 (q21d)	33.3	17.2	42.4	80.6
			374		CT	CT only		12.3	4.3	43.2	80.7
NeoCOAST (22)	2023	II	27	IA3–IIIA	Durva	Mono	1 (q28d)	11.1	3.7	3.8	84.6
			21		Durva + Ole	Dual		19.0	9.5	4.8	81
			20		Durva + Mona	Dual		30.0	10	0	90
			16		Durva + Dan	Dual		31.3	12.5	6.3	93.8

†, including incomplete resection; ‡, among resected patients; §, among resected patients without an *EGFR/ALK* mutation. IO, immuno-oncology; MPR, major pathological response; pCR, pathological complete response; TRAE, treatment-related adverse event; G, grade; Nivo, nivolumab; q14d, every 14 days; Atezo, atezolizumab; Sinti, sintilimab; q21d, every 21 days; CT, chemotherapy; Ipi, ipilimumab; Durva, durvalumab; Pembro, pembrolizumab; q28d, every 28 days; Ole, oleclumab; Mona, monalizumab; Dan, danvatirsen.

reducing extracellular adenosine production and promoting antitumor immunity. Monalizumab is an anti-NKG2A humanized IgG4 monoclonal antibody. The mechanism by which monalizumab enhances antitumor immunity involves binding to the inhibitory receptor NKG2A on natural killer (NK) cells and $CD8^+$ T cells, which blocks the binding of NKG2A to HLA-E on tumor cells, thereby reducing the inhibitory effect of NK cells and $CD8^+$ cells. Danvatirsen, a unique IO agent, is an anti-STAT3 antisense oligonucleotide. STAT3 signaling is associated with an immunosuppressive tumor microenvironment. Danvatirsen administration downregulates *STAT3* messenger RNA (mRNA) expression, reverses the suppressive tumor microenvironment, and promotes changes in proinflammatory gene expression. The mechanisms by which these agents enhance antitumor immunity are different from and complementary to those of durvalumab.

For efficacy evaluation, the NeoCOAST trial (22)

Table 2 Trials stratified according to the classification of administered agents for neoadjuvant therapy

Study	Classification	Phase	N	Patients' cohort	Agent used for neoadjuvant therapy	Cycle	MPR (%)	pCR (%)	TRAE (G >3; %)	Resection rate[†] (%)
CheckMate816 (19)	CT only	III	179	IB–IIIA	CT	3 (q21d)	8.9	2.2	36.9	75.4
KEYNOTE-671 (20)	CT only	III	400	II–IIIB (N2)	CT	4 (q21d)	11.0	4.0	37.3	79.3
AEGEAN (21)	CT only	III	374	II–IIIB (N2)	CT	4 (q21d)	12.3	4.3	43.2	80.7
CheckMate159 (8)	Mono	II	22	I–IIIA	Nivo	2 (q14d)	45.0[‡]	15.0[‡]	4.5	95.0
PRINCEPS (9)	Mono	II	30	IA (2 cm)–IIIA (non-N2)	Atezo	1 (q14d)	0	0	3.3	100
Gao *et al.* (10)	Mono	Ib	40	IA–IIIB	Sinti	2 (q21d)	40.5[‡]	16.2[‡]	10.0	92.5
NEOSTAR (13)	Mono	II	23	IA–IIIA	Nivo	3 (q14d)	22.0	9.0	4.3	95.7
Eichhorn *et al.* (15)	Mono	II	15	II–IIIA	Pembro	2 (q21d)	27.0	13.0	33.3	100
LCMC3 (16)	Mono	II	181	IB–IIIB	Atezo	2 (q14d)	20.0[§]	6.0[§]	11.0	88.0
Tong *et al.* (17)	Mono	II	30	IB–IIIA	Pembro	2 (q14d)	28.0[‡]	12.0[‡]	3.3	83.3
IONESCO (18)	Mono	II	46	IB–IIIA (non-N2)	Durva	3 (q14d)	19.0[‡]	7.0[‡]	0	93.5
NeoCOAST (22)	Mono	II	27	IA3–IIIA	Durva	1 (q28d)	11.1	3.7	3.8	84.6
NEOSTAR (13)	Dual	II	21	IA–IIIA	Nivo + Ipi	3 (q14d)	38.0	29.0	4.8	81.0
NeoCOAST (22)	Dual	II	21	IA3–IIIA	Durva + Ole	1 (q28d)	19.0	9.5	4.8	81
NeoCOAST (22)	Dual	II	20	IA3–IIIA	Durva + Mona	1 (q28d)	30.0	10	0	90
NeoCOAST (22)	Dual	II	16	IA3–IIIA	Durva + Dan	1 (q28d)	31.3	12.5	6.3	93.8
SAKK16/14 (14)	CT → Mono	II	67	IIIA (N2)	CT → Durva	2 (q14d)	62.0[‡]	18.0[‡]	88.0	88.1
NADIM (11)	Mono + CT	II	46	IIIA	Nivo + CT	3 (q21d)	74.0	57.0	30.0	89.0
Shu *et al.* (12)	Mono + CT	II	30	IB–IIIA	Atezo + CT	4 (q21d)	57.0	33.0	50.0	97.0
CheckMate816 (19)	Mono + CT	III	179	IB–IIIA	Nivo + CT	3 (q21d)	36.9	24.0	33.5	83.2
KEYNOTE-671 (20)	Mono + CT	III	397	II–IIIB (N2)	Pembro + CT	4 (q21d)	30.2	18.1	44.9	81.9
AEGEAN (21)	Mono + CT	III	366	II–IIIB (N2)	Durva + CT	4 (q21d)	33.3	17.2	42.4	80.6

[†], including incomplete resection; [‡], among resected patients; [§], among resected patients without an *EGFR*/*ALK* mutation. MPR, major pathological response; pCR, pathological complete response; TRAE, treatment-related adverse event; G, grade; CT, chemotherapy; q21d, every 21 days; Nivo, nivolumab; q14d, every 14 days; Atezo, atezolizumab; Sinti, sintilimab; Pembro, pembrolizumab; Durva, durvalumab; q28d, every 28 days; Ipi, ipilimumab; Ole, oleclumab; Mona, monalizumab; Dan, danvatirsen.

showed that the major pathological response (MPR) rates, the primary endpoint of this study, were higher in each dual IO arm than in the durvalumab alone arm (19.0% in the oleclumab arm, 30.0% in the monalizumab arm, 31.3% in the danvatirsen arm, and 11.1% in the durvalumab-alone arm). In addition, the pathological complete response (pCR) rates were higher in each dual IO arm than in the durvalumab alone arm (9.5% in the oleclumab arm, 10.0% in the monalizumab arm, 12.5% in the danvatirsen arm, and 3.7% in the durvalumab alone arm). According to previous studies (8-10,13,15-18), the MPR rates and pCR rates of mono-IO therapies as neoadjuvants are 0–45.0% (median, 22.0%) and 0–16.2% (median, 9.0%), respectively (*Tables 1*,*2*). It seems that the

data from the NeoCOAST trial are inferior to the data from previous studies; however, this may be due to the short period of the neoadjuvant course, as the authors described in their article. The trial introduced only one course of neoadjuvant IO per 28 days, and approximately 90% of patients received surgery within 42 days (mean, 38.2 days) of IO agent administration. However, considering the onset time of immune-related adverse events (irAEs) (23), the peak time for immunity promotion by IO agents may have been at least 5–6 weeks after the first administration of IO agents. Thus, patients in the NeoCOAST trial may have undergone surgical resection before reaching the peak time of promoting immunity, and consequently, showed slightly unsatisfactory results in pathological responses in all arms compared to previous studies. The issue concerning the appropriate administration cycle and timing for surgical resection may remain; however, the superior efficacy of dual IO over durvalumab alone can be expected considering the differences in the MPR rate and pCR rate between the dual IO arms and the durvalumab alone arm, which were approximately 20.0 and 7.0 points, respectively.

Regarding the safety of dual IO neoadjuvant therapy, the NeoCOAST trial showed no statistically significant differences in treatment-related adverse events (TRAEs) between the durvalumab alone arm and each dual IO arm. This was especially for TRAEs > grade 3, and the addition of each novel IO to durvalumab as a neoadjuvant therapy showed no additional safety risk in the trial. Moreover, the resection rate after neoadjuvant therapy was similar between the patients in each arm. According to the NEOSTAR trial, which is the only study to evaluate the efficacy of a neoadjuvant dual IO agent, nivolumab + ipilimumab (an anti-cytotoxic T-lymphocyte antigen-4 monoclonal antibody), for resectable NSCLC (13), the addition of ipilimumab also showed no additional risk of TRAEs. Although patients in the nivolumab + ipilimumab arm showed a slightly lower resection rate than patients in the nivolumab alone arm in the NEOSTAR trial (13), no patients were unable to undergo surgery due to TRAEs. Thus, dual IO agents can be administered safely as neoadjuvant therapy, similar to neoadjuvant mono-IO therapy. Rather, the addition of cytotoxic chemotherapy to the mono-IO agents may result in a high risk of TRAEs at a grade ≥3 (*Table 2*) (11,12,19-21).

The NeoCOAST trial (22) investigated the correlation between several biomarkers (in particular, immune-related biomarkers) and the efficacy of IO agents. The authors reported that the trial revealed an association between pre-therapeutic tumor PD-L1 expression levels and efficacy in the oleclumab and monalizumab arms, similar to the results of several previous trials. However, I consider this an overestimation. Certainly, more than 40% of patients with MPR showed PD-L1 expression in both the oleclumab and the monalizumab arms; however, further patients had a "PD-L1 unknown" status, including 44.4% (8/18) of the patients in the oleclumab arm and 55.5% (10/18) of patients in the monalizumab arm. Under such conditions, the relationship between PD-L1 expression and the efficacy of dual IO agents is not conclusive, and further evaluation is needed.

A similar issue exists in the relationship between *EGFR* driver mutations and the efficacy of dual IO agents. The authors noted that two patients with tumors harboring *EGFR* driver mutations achieved MPR by administering durvalumab + oleclumab. However, only approximately 56% of the patients (10/18) in the oleclumab arm were tested for *EGFR* driver mutations. The efficacy of durvalumab + oleclumab, even for patients harboring *EGFR* driver mutations, may also be overestimated and further evaluation is warranted.

In contrast, CD73 expression levels measured by immunohistochemistry may be a good biomarker for durvalumab + oleclumab therapy. The NeoCOAST study demonstrated that high CD73 expression levels in pre-therapeutic tumors were statistically correlated with the number of remaining viable tumors in surgical specimens from patients in the durvalumab alone arm, despite being strongly correlated with fewer viable tumors in surgical specimens from patients in the durvalumab + oleclumab arm. These results are reasonable, considering the role of CD73 in the therapeutic mechanism of oleclumab. CD73 on the surface of tumor cells promotes the conversion of adenosine triphosphate (which activates anti-tumor immunity) to adenosine in the tumor microenvironment. Adenosine suppresses the immune activity of regulatory T cells (Tregs). Thus, high CD73 expression levels in pre-therapeutic tumors are recognized as a suppressive antitumor immune environment. In such an environment, the administration of oleclumab, an anti-CD73 monoclonal antibody, eliminates the suppression of Treg activity, activates antitumor cells (e.g., NK cells), and promotes the effect of durvalumab. In addition, a previous study (24) reported that patients with MPR in the durvalumab + oleclumab arm demonstrated a decrease in the number of $CD73^+$ tumor cells and an increase in the number of $NKG2A^+$ cells and $CD8^+$ T cells in resected tumor

specimens. If so, "tri IO therapy", which consists of durvalumab + oleclumab followed by monalizumab (anti-NKG2A monoclonal antibody) as neoadjuvant therapy, or monalizumab administration for tumors with resistance to durvalumab + oleclumab therapy, may be effective.

The NeoCOAST trial also reported a correlation between changes in the detection status of circulating tumor DNA (ctDNA) and therapeutic efficacy; however, none of the patients showed complete clearance of ctDNA in pre-surgery status. As described in the article, the CheckMate816 trial (19) demonstrated that ctDNA clearance before surgery may be closely associated with pCR after neoadjuvant therapy; however, the treatment strategy may not be drastically changed due to the ctDNA status. Thus, ctDNA is valuable, not for the evaluation of therapeutic efficacy, but for the early detection of post-therapeutic recurrence, and the evaluation of prognostic endpoints may be needed in future trials.

To summarize, the NeoCOAST trial investigated the ideal combination of dual IO therapy as neoadjuvant therapy for patients with NSCLC and by analyzing several immune-related factors showed that: (I) oleclumab and monalizumab have the potential to be next-generation agents for dual IO neoadjuvant therapy for NSCLC, because these agents showed sufficient efficacy and no additional safety risk compared to durvalumab alone; and (II) CD73 has potential to become a biomarker for predicting the therapeutic efficacy of oleclumab. According to the researchers of the NeoCOAST trial, the next phase 2, randomized "NeoCOAST-2" trial, which aims to evaluate the efficacy and safety of neoadjuvant + adjuvant therapy using dual IO (including oleclumab and monalizumab) + cytotoxic chemotherapy is underway based on the results of the NeoCOAST trial. Considering the results of the KEYNOTE-671 (20) and AEGEAN trials (21), the results of the NeoCOAST-2 trial may be promising in terms of pathological response. However, TRAEs tended to be more frequent and the resection rate tended to decrease with the addition of cytotoxic chemotherapy to mono-IO therapy in a neoadjuvant setting (*Table 2*). In addition, the NIPPON study (25), which was a randomized phase 3 trial comparing a cytotoxic chemotherapy + pembrolizumab arm with a cytotoxic chemotherapy + nivolumab + ipilimumab arm as perioperative therapy for patients with resectable NSCLC, was terminated early owing to the high number of treatment-related deaths. Of the 131 patients who received perioperative therapy with cytotoxic chemotherapy + nivolumab + ipilimumab in the NIPPON study, 9 (6.9%) died as a result of grade 5 irAEs. As such, dual IO + cytotoxic chemotherapy as perioperative therapy can be expected to have better efficacy from the aspect of therapeutic response, but may induce severe TRAEs, and consequently, patients will be incapable of undergoing surgery. Different to the dual IO + cytotoxic chemotherapy for advanced disease, perioperative therapy targets patients with 'resectable' disease. Of the perioperative therapeutic courses, the crucial and most effective modality is surgical resection; thus, we need to prevent patients from becoming inoperable due to the administration of neoadjuvant therapy as much as possible. It should be noted that administering dual IO + cytotoxic chemotherapy as neoadjuvant or perioperative therapy to increase therapeutic efficacy may be harmful for patients, if surgical resection is then impossible owing to the TRAEs induced by dual IO + cytotoxic chemotherapy.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-738/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-738/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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Cite this article as: Adachi H, Ito H, Nagashima T, Isaka T, Saito A. Dual immuno-oncology agents as neoadjuvant therapy for patients with resectable non-small cell lung cancer. Transl Lung Cancer Res 2024;13(2):229-235. doi: 10.21037/tlcr-23-738