Editorial Commentary

Bringing immune-checkpoint inhibitors earlier in the management of non-small cell lung cancer

Maxime Borgeaud[1]^, Alex Friedlaender[1,2], Alfredo Addeo[1]

[1]Department of Oncology, the University Hospital of Geneva (HUG), Geneva, Switzerland; [2]Department of Oncology, Clinique Générale Beaulieu, Geneva, Switzerland

Correspondence to: Alfredo Addeo, MD. Department of Oncology, the University Hospital of Geneva (HUG), Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland. Email: alfredo.addeo@hcuge.ch.

Comment on: Wakelee H, Liberman M, Kato T, *et al.* Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med 2023;389:491-503.

Keywords: Neoadjuvant immune checkpoint inhibitor; non-small-cell lung cancer (NSCLC); perioperative immune checkpoint inhibitors

Submitted Jul 21, 2023. Accepted for publication Oct 19, 2023. Published online Nov 17, 2023.
doi: 10.21037/tlcr-23-466
View this article at: https://dx.doi.org/10.21037/tlcr-23-466

Surgical resection followed by adjuvant cisplatin-based chemotherapy has long been the standard of care for resectable non-small-cell lung cancer (NSCLC), based on the results of phase III trials (1,2) and a meta-analysis showing an absolute benefit of 5.7% in overall survival (OS) at 5 years for tumors of more than 4 cm or with positive lymph nodes (3). On the contrary, the adoption of neoadjuvant chemotherapy in NSCLC was probably hampered by the earlier adoption of adjuvant therapy, based on high quality data (4). Several trials have however evaluated neoadjuvant chemotherapy in NSCLC, alone and in adjunction to radiotherapy, with a comparable benefit to that observed with the adjuvant approach (5,6), although only one directly compared neoadjuvant *vs.* adjuvant chemotherapy (5). The theorical advantage of a neoadjuvant approach is the possibility to treat more patients, as some individuals will not be able to receive post-operative treatment due to surgical complications or altered performance status after surgery. Other advantages stand in the earlier treatment of micro-metastatic disease, and the opportunity to facilitate surgery through tumor shrinkage. On the other hand, the major theoretical drawback of neoadjuvant therapy is that serious adverse events could preclude a patient from reaching surgery. The 2017 European Society of Medical Oncology (ESMO) guidelines recommended adjuvant cisplatin-based chemotherapy after surgical resection and to consider a neoadjuvant strategy in locally advanced or borderline resectable situations, such as stage III disease. It is important to mention that there is no universal definition of resectability and that practice for stage III disease varies in different centers and different countries (7). In this debate, the results of the PACIFIC trial (8), that established chemoradiotherapy followed by adjuvant durvalumab as the standard of care for unresectable stage III NSCLC, probably led to a shift in practice from surgery and (neo)adjuvant therapy to radio-chemotherapy, especially for borderline cases. Of note, the PACIFIC trial was the first study to demonstrate the efficacy of immune-checkpoint inhibitors (ICIs) in non-metastatic NSCLC.

Since the results of the PACIFIC trial and the subsequent shifts in clinical practices it introduced, the role of ICI in early-stage NSCLC has continued to evolve. Adjuvant pembrolizumab demonstrated a benefit in disease-free survival (DFS) *vs.* placebo in stage IB–III resected NSCLC in the Keynote-091/PEARLS trial. Interestingly, programmed death-ligand 1 (PD-L1) expression did not correlate with outcome. Atezolizumab was also investigated as an adjuvant treatment in the IMpower010 trial, in which, contrarily to Keynote-091, all patients also received adjuvant chemotherapy before ICI. DFS was improved

^ ORCID: 0000-0003-1262-5641.

with atezolizumab in PD-L1 positive patients. The benefit was driven by high PD-L1 expressors (9), leading to the approval of atezolizumab only for patient with PD-L1 ≥50%, by the European Medicines Agency (EMA), United Kingdom and Canada. Similarly, the updated results show an OS benefit only in this exploratory subgroup, without any trends towards a benefit in other PD-L1 expression subsets (10).

As mentioned earlier, as a neoadjuvant approach can carry some advantages, the role of ICI therein was of great interest. The administration of ICI when the tumor antigens and the lymph nodes are still in place, can theoretically enhance the antitumor immune response (11).

In their paper, Wakelee *et al.* tested the efficacy of perioperative pembrolizumab in resectable NSCLC (12). Patients with stage II–IIIB NSCLC according to the tumor-node-metastasis (TNM) American Joint Committee on Cancer (AJCC) 8th edition, with upfront resectable disease after case discussion at multi-disciplinary tumorboard, were included. Molecular testing for epithelial growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangement or other oncogene-addiction was not mandatory. Indeed, the presence of EGFR mutation or ALK rearrangement was not even an exclusion criterion, and 7% of the patients had an EGFR mutation or ALK alteration. Patients were randomized between perioperative pembrolizumab and a placebo arm, with stratification by disease stage (stage II *vs.* III), histology (squamous *vs.* non-squamous), PD-L1 status (≥ or <50%), region of the world (East Asian *vs.* not-East Asian). In the intervention arm, patients received pembrolizumab 200 mg intravenous (IV) every 3 weeks in combination with cisplatin-based chemotherapy, for four cycles, followed by surgery, and adjuvant pembrolizumab for thirteen cycles. The choice of chemotherapy was restricted to cisplatin, and pemetrexed and gemcitabine for non-squamous and squamous histology respectively. In the control arm, patients received neo-adjuvant chemotherapy with placebo, and one year of adjuvant placebo. The co-primary endpoints were OS and event-free survival (EFS), defined as the time from randomization to the first occurrence of local progression precluding the planned surgery, an unresectable tumor, distant progression or recurrence, or death. After a median follow-up of 25 months, EFS was improved in the intervention arm with a hazard ratio (HR) of 0.58 [95% confidence interval (CI): 0.46–0.71, P<0.00001]. OS data were immature at the time of this primary analysis. The rate of major pathological response (MPR), defined as 10% or less of viable tumor cells, was significantly higher with pembrolizumab-chemotherapy compared to chemotherapy alone, 30.2% *vs.* 11.1%, as was pathological complete response (pCR): 18.1% and 4%. Adverse events were slightly more frequent in the intervention arm; however, there were no significant differences between adverse events precluding surgery in both groups, and 82.1% and 79.4% of patient underwent surgery in the pembrolizumab and placebo group respectively.

Three other phase III trials and one randomized phase II trial have recently compared neoadjuvant ICI in combination with chemotherapy in early NSCLC. The different characteristics of these trials are summarized in *Table 1*, for better comparison. Checkmate-816 compared nivolumab and chemotherapy with chemotherapy alone, for three preoperative cycles (13). Interestingly, this is the only phase III trial which did not include an adjuvant phase. The coprimary outcome of EFS was improved with nivolumab with an HR of 0.68 (95% CI: 0.49–0.93). The other coprimary endpoint, pCR, was also improved with nivolumab, at 24.0% (95% CI: 18.0–31.0%) *vs.* 2.2% (95% CI: 0.6–5.6%). With a similar design to the Keynote-671 trial, the phase III AEGEAN trial evaluated the combination of durvalumab-chemotherapy *vs.* placebo-chemotherapy for four cycles in the preoperative setting, followed by adjuvant durvalumab or placebo for one year (14). EFS and pCR were superior with durvalumab compared to placebo with an EFS HR of 0.68 (95% CI: 0.53–0.88, P=0.003902). The NEOTORCH trial, conducted in Asia, tested the combination of toripalimab with chemotherapy to placebo-chemotherapy for three pre-operative cycles, followed by one post-operative cycle of toripalimab-chemotherapy or placebo-chemotherapy, and one year of toripalimab or placebo (15). The primary outcome of MPR and EFS in stage III disease were met, HR of 0.40 (95% CI: 0.277–0.565, P<0.0001). Finally, in the phase II randomized trial, NADIM-2, patients were randomized between nivolumab-chemotherapy and chemotherapy alone (16). Only patients with resectable stage III disease were included. Patient with R0 resection in the intervention group received 6 months of adjuvant nivolumab. The primary outcome of pCR was improved with nivolumab, at 37% *vs.* 7% in the control group. The secondary endpoints of PFS and OS were also improved with nivolumab. Despite its modest size, NADIM-2 was the first study to show a survival benefit for a neoadjuvant ICI-chemotherapy combination in NSCLC.

In terms of safety, as in Keynote-671, the addition of ICI to chemotherapy did not lead to a major increase in

Table 1 Phase III trials on peri-operative ICI-chemotherapy in NSCLC

Characteristics	Phase III trials			
	Keynote-671	AEGEAN	NEOTORCH	Checkmate-816
Location	Global	Global	China	Global
Sex	70.3% male	68.9% male	89.6% male	71.5% male
Squamous	43.1%	46.2%	77.7%	48.6%
Biomarker	PD-L1 ≥50%: 33.2%; PD-L1 <1%: 34.8%	PD-L1 ≥50%: 29.8%; PD-L1 <1%: 33.3%	PD-L1 <1%: 34.2%	PD-L1 ≥50%: 21.2%; PD-L1 <1%: 46.6%
EGFR/ALK	Allowed, included	Allowed, not included in mITT analysis	Not allowed (tested at screening)	Not allowed, but testing up to physician choice (EGFR mandatory only for Asian patients)
ICI treatment details	Pembrolizumab 200 mg IV q3w (or placebo) with chemotherapy for 4 neoadjuvant cycles	Durvalumab 1,500 mg IV q3w (or placebo) with chemotherapy for 4 neoadjuvant cycles	Toripalimab 240 mg IV q3w (or placebo) with chemotherapy for 3 neoadjuvant cycles	Nivolumab 360 mg IV q3w (or placebo) with chemotherapy for 3 neoadjuvant cycles
	Pembrolizumab 200 mg IV q3w (or placebo) for 13 adjuvant cycles	Durvalumab 1,500 mg IV q4w (or placebo) for 12 adjuvant cycles	Toripalimab 240 mg IV (or placebo) with chemotherapy for 1 adjuvant cycle	
			Toripalimab 240 mg IV q3w (or placebo) for 12 adjuvant cycles	
Chemotherapy regimen	Cisplatin-gemcitabine, cisplatin-pemetrexed	Carboplatin-paclitaxel, cisplatin-gemcitabine, cisplatin-pemetrexed, carboplatin-pemetrexed	Cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel (unspecified combinations)	Cisplatin-vinorelbine, cisplatin-docetaxel, cisplatin-gemcitabine, cisplatin-pemetrexed, carboplatin-paclitaxel
Primary outcome	EFS at 24 months: 62.4% *vs.* 40.6%. HR: 0.58 (95% CI: 0.46–0.71, P<0.00001)	mEFS in mITT: NR *vs.* 25.9 months. HR: 0.68 (95% CI: 0.53–0.88, P=0.003902)	mEFS: NR *vs.* 15.1 months. HR: 0.40 (95% CI: 0.277–0.565, P<0.0001)	mEFS: 31.6 *vs.* 20.8 months. HR: 0.63 (97.38% CI: 0.43–0.91, P=0.005)
	OS (immature)	pCR: 17.2% *vs.* 4.3%. Difference in pCR 13.0% (95% CI: 8.7–17.6%, P=0.000036)	MPR: 48.5% *vs.* 8.4%	pCR: 24.0% (95% CI: 18.0–31.0%) *vs.* 2.2% (95% CI: 0.6–5.6%)

ICI, immune-checkpoint inhibitors; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; EGFR, epithelial growth factor receptor; ALK, anaplastic lymphoma kinase; mITT, modified intention to treat analysis; IV, intravenous; q3w, every three weeks; EFS, event-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; mEFS, median event-free survival; NR, not reached; pCR, pathological complete response rate; MPR, major pathological response.

toxicity in these phase III studies. Grade 3 or 4 treatment-related adverse events did not differ between the two groups in Checkmate-816: 33.5% *vs.* 36.9%. In AEGEAN study the all-cause grade 3 or 4 adverse events were similar with durvalumab or placebo: 42.3% *vs.* 43.4%, during the whole treatment-period. In the NEOTORCH trial, the incidence of grade 3 or more all causes adverse events was slightly increased with toripalimab compared to placebo: 63.4% *vs.* 54.0%, as was the rate of immune-related adverse event: 42.1% *vs.* 22.8%. It is also worth mentioning that in all these trials, the addition of ICI did not negatively affect the feasibility of surgery, with around 80% of patient undergoing surgery in the AEGEAN trial, and even a slight increase in the surgery rate in patients treated with ICI and chemotherapy in the NEOTORCH (83% *vs.* 73.3%) and Checkmate-816 trials (83.2% *vs.* 75.4%).

While there is no doubt that preoperative ICI and chemotherapy combination has improved anti-tumor

activity in operable NSCLC, several questions remain.

First, there is the question of the impact and efficacy of the choice of the chemotherapy partners for ICI. The Keynote-671 trial restricted chemotherapy to cisplatin-pemetrexed for non-squamous and cisplatin-gemcitabine for squamous tumors, and did not include taxanes, which are an active drug in NSCLC. The NADIM-2 trial, on the other hand, restricted the choice to carboplatin and paclitaxel, while the other phase III trials mentioned above offered a more diverse choice, with the possibility to use cisplatin or carboplatin, and pemetrexed, paclitaxel, gemcitabine or vinorelbine, depending on the histology. At the moment, it is difficult to determine whether the chemotherapy regimen used in combination with ICI affects the effectiveness of ICI.

Second, the role of PD-L1 expression as a predictive biomarker in the neoadjuvant setting remains a matter of debate. PD-L1 expression is a well-known predictive factor of ICI efficacy in metastatic NSCLC, where patients with PD-L1 negative tumors derive less benefit from ICI (17-19). The subgroup analysis of Keynote-671 stays in line with this observation, with a benefit that seemed higher in PD-L1 positive subgroup. The subgroup analysis of Checkmate 816 goes in the same direction: patients with PD-L1 negative disease seemed to derive less benefit from the addition of nivolumab to chemotherapy, with an HR for EFS of 0.85 (95% CI: 0.54–1.32). While the Food and Drug Administration (FDA) has approved the use of nivolumab with neoadjuvant chemotherapy regardless of PD-L1, strictly following the inclusion criteria of the originator study, the EMA has decided to restrict its use to patients with PD-L1-positive disease, based on this subgroup analysis. Whether this distinction will also be made for pembrolizumab remains to be seen. On the question of biomarkers, the presence of an oncogenic mutation should probably discourage the use of an ICI-based perioperative strategy, as it is well described that these patients respond poorly to immunotherapy (20). For these patients, several perioperative strategies using targeted therapies are being developed (21,22).

Third, the relative contribution of the adjuvant component of the treatment remains unknown. A post-hoc and unplanned analysis compared the outcome of patients with and without MPR and pCR in the Keynote-671 trial and showed that pembrolizumab appears to offer an EFS benefit even without a deep neoadjuvant response, suggesting a potential benefit of the adjuvant component of therapy. Of note, with this post-hoc unplanned analysis, it is still unclear whether these patients derive a benefit from the adjuvant component, or only from the preoperative treatment. A discrepancy between image-based response assessment and progression-free survival or OS has also been described for immunotherapy in other settings (23), possibly due to the delayed impact of immunotherapy, highlighting the fact that neoadjuvant ICI may have a prolonged or delayed impact. Even though cross trial comparisons should be avoided, in terms of absolute numbers, the EFS rate at 2 years appears comparable in the Keynote-671 and Checkmate-816 trials. New prospective data will be needed to determine if some patients could undergo less than a full year of adjuvant treatment or even totally avoid adjuvant treatment. These future studies should, as far as possible, focus on identifying those patients at higher risk, most likely to benefit from additional adjuvant therapy, with biomarkers that go beyond simple pathological response, such as circulating tumor DNA or minimal residual disease (16).

Fourth, in Keynote-671 as in the other trials, the benefit of neoadjuvant ICI and chemotherapy seem to be higher for stage III disease. The NADIM-2 trial shows a significant EFS and OS benefit in stage III disease, confirming the hypothesis that ICI and chemotherapy are effective in this setting. On the other hand, the benefit in stage II disease seems more nuanced, even though this observation should be interpreted with caution, as it is based on a subgroup analysis. In patients presenting with stage II disease with easily resectable tumors, especially those without lymph node involvement, the risk of precluding surgery must be considered. In this respect, it is worth mentioning that about 20% of patient did not undergo surgery in the Keynote-671 trial, the main reasons being adverse events, progressive disease and physician's choice. These numbers are consistent with other neoadjuvant chemo-immunotherapy trials.

Finally, the question of which treatment to give at relapse for these patients is still open to debate (24). Current treatment choices will probably depend on the time between ICI exposure and relapse. Data collected from the efficacy of ICI rechallenge after progression in the experimental arms of the trials discussed herein could be valuable for guiding clinical practice. Regarding treatment at progression, one major limitation of the Keynote-671 trial is that only 57% of patients in the control arm received ICI as further systemic therapy at relapse. This is probably substandard, as ICI represent a standard of care in metastatic NSCLC, except for patients with oncogene

addicted tumors. This limitation could influence the validity of OS results in the future, as the control arm is likely inadequate.

In conclusion, ICI are now part of the treatment algorithm for early-stage NSCLC. Their role in certain situations, such as locally advanced stage III disease is now indisputable. As discussed, several questions remain, such as strategies to better identify patients who are likely to benefit from ICI, particularly regarding the adjuvant therapy in a perioperative approach. Finally, this progress underlies the paramount importance of a good collaboration between all medical specialties involved in the management of NSCLC patients.

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-23-466/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-466/coif). A.F. received payments from Amgen, AstraZeneca, Roche, Astellas, Takeda, Bristol-Myers Squibb, Merck Sharpe Dohme, Pfizer, Merck, Novartis and Janssen, outside the scope of this manuscript. A.A. reports advisory board fees from Amgen, AstraZeneca, Roche, Astellas, Takeda, Merck Sharpe Dohme, Pfizer, Bristol-Myers Squibb, Merck and Novartis; and speaker's bureau fees from Eli-Lilly, AstraZeneca, Amgen and Novartis. The other author has 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.

References

1. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-60.
2. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589-97.
3. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
4. Saw SPL, Ong BH, Chua KLM, et al. Revisiting neoadjuvant therapy in non-small-cell lung cancer. Lancet Oncol 2021;22:e501-16.
5. Felip E, Rosell R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 2010;28:3138-45.
6. Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. J Clin Oncol 2012;30:172-8.
7. Putora PM, Leskow P, McDonald F, et al. International guidelines on stage III N2 nonsmall cell lung cancer: surgery or radiotherapy? ERJ Open Res 2020;6:00159-2019.
8. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:1301-11.
9. Felip E, Altorki NK, Zhou C, et al. 80O Atezolizumab (atezo) vs best supportive care (BSC) in stage II-IIIA NSCLC with high PD-L1 expression: Sub-analysis from the pivotal phase III Impower010 study. Ann Oncol 2022;33:abstr S71.
10. Felip E, Altorki N, Zhou C, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (Impower010): a andomized, multicentre, open-label, phase III trial. Ann

Oncol 2023;34:907-19.
11. Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med 2018;24:1655-61.
12. Wakelee H, Liberman M, Kato T, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med 2023;389:491-503.
13. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.
14. Heymach JV, Harpole D, Mitsudomi T, et al. Abstract CT005: AEGEAN: A phase 3 trial of neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in patients with resectable NSCLC. Cancer Res 2023;83:abstr CT005.
15. Lu S, Wu L, Zhang W, et al. Perioperative toripalimab + platinum-doublet chemotherapy vs chemotherapy in resectable stage II/III non-small cell lung cancer (NSCLC): Interim event-free survival (EFS) analysis of the phase III Neotorch study. J Clin Oncol 2023;41:abstr 425126.
16. Provencio M, Nadal E, González-Larriba JL, et al. Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 2023;389:504-13.
17. Novello S, Kowalski DM, Luft A, et al. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. J Clin Oncol 2023;41:1999-2006.
18. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol 2023;41:1992-8.
19. de Castro G Jr, Kudaba I, Wu YL, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy as First-Line Therapy in Patients With Non-Small-Cell Lung Cancer and Programmed Death Ligand-1 Tumor Proportion Score ≥ 1% in the KEYNOTE-042 Study. J Clin Oncol 2023;41:1986-91.
20. Addeo A, Passaro A, Malapelle U, et al. Immunotherapy in non-small cell lung cancer harbouring driver mutations. Cancer Treat Rev 2021;96:102179.
21. Godoy LA, Chen J, Ma W, et al. Emerging precision neoadjuvant systemic therapy for patients with resectable non-small cell lung cancer: current status and perspectives. Biomark Res 2023;11:7.
22. Lee JM, McNamee CJ, Toloza E, et al. Neoadjuvant Targeted Therapy in Resectable NSCLC: Current and Future Perspectives. J Thorac Oncol 2023;18:1458-77.
23. Nathan P, Hassel JC, Rutkowski P, et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med 2021;385:1196-206.
24. Delasos L, Wei W, Hassan KA, et al. Clinical Outcomes With Pembrolizumab-Based Therapies in Recurrent/Refractory NSCLC After Chemoradiation and Consolidative Durvalumab. Clin Lung Cancer 2023;24:e205-13.

Cite this article as: Borgeaud M, Friedlaender A, Addeo A. Bringing immune-checkpoint inhibitors earlier in the management of non-small cell lung cancer. Transl Lung Cancer Res 2023;12(11):2353-2358. doi: 10.21037/tlcr-23-466