Consensus

Expert consensus on neoadjuvant immunotherapy for non-small cell lung cancer

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide and in China (1). According to the statistics of the National Cancer Center of China, there were 733,300 new cases of non-small cell lung cancer (NSCLC) and approximately 610,200 related deaths in 2015 (2). For patients with early staged disease, surgery is the mainstay of treatment, and it is commonly followed by adjuvant chemotherapy for patients with locally advanced resectable NSCLC. Although complete surgical resection may be curative for NSCLC, 25–70% of patients (with different proportion according to stage) eventually relapse despite complete resection (3). Platinum-based adjuvant chemotherapy has been shown to marginally increase the 5-year survival rate of patients by 4–8% (4-6). Even after treatment with surgery and indicated adjuvant therapies in eligible cases, approximately 20–30% of stage I, 50% of stage II, and 60% of stage IIIA patients still die within 5 years (7). In the past decade, experts have conducted a number of investigations on the perioperative management of resectable NSCLC; however, progress remains slow, and patients still have a high risk of recurrence and death.

Neoadjuvant therapy is defined as any therapy delivered prior to definitive local therapy intended to increase the cure rate. It provides several theoretical benefits in managing such patients with NSCLC. In the setting of, neoadjuvant therapy given prior to radical surgery this approach can also have the goals of downstaging, improving the resection rate, and more promptly treating subclinical micro-metastases than adjuvant approaches, delivered after the definitive local therapy. In addition, the compliance with neoadjuvant therapy has been shown to be better than in the adjuvant setting, and the biological effect of the neoadjuvant therapy can be analyzed directly in the resected tumor specimens (8). A meta-analysis on patients with stage IB–IIIA NSCLC that compared chemotherapy plus subsequent surgery *vs.* surgery alone showed that the 5-year survival rate was 5% higher after receiving neoadjuvant chemotherapy (NCT) (9). Therefore, the comprehensive NSCLC data suggest that, for resectable NSCLC, NCT improves survival compared with surgery alone but appear to show no significant survival benefit compared with adjuvant chemotherapy (10).

In the last 5 years, immune checkpoint inhibitors (ICIs) have profoundly changed the treatment paradigm for patients with advanced NSCLC (11-15). Immunotherapy has provided hope for long-term survival benefits to a minority of patients with metastatic lung cancer. For treatment-naive patients with driver mutation-negative NSCLC, the 5-year survival rate of single agent pembrolizumab was 23.2%; for the previously treated patients with driver mutation-negative NSCLC, the 5-year survival rates of single agent pembrolizumab and nivolumab were 15.5% and 16%, respectively (16,17). Given the profound impact made by immunotherapy drugs for patients with advanced disease, significant attention has been directed in recent years toward investigating the potential role for early-stage NSCLC patients, and whether they, too, can achieve long-term benefits from the inclusion of immunotherapy into their treatment algorithms.

Many phase Ib/II clinical trials have reported promising results, and a series of large-scale phase III clinical trials are underway. However, these various investigations have employed different strategies of neoadjuvant immunotherapy, in terms of the specific regimens as well as number of treatment cycles (18). To better guide Chinese thoracic surgeons in the neoadjuvant immunotherapy of NSCLC, well-known thoracic surgeons in China participated in an in-depth discussion on the hot topics and controversial issues of neoadjuvant immunotherapy and formed the *Expert consensus on neoadjuvant immunotherapy for non-small-cell lung cancer* by incorporating the latest evidence on neoadjuvant immunotherapy.

Consensus 1: preoperative use of neoadjuvant immunotherapy with or without platinum-based chemotherapy for patients with resectable stage IB–IIIA NSCLC may be considered

In 1994, Rosell and Roth published two classic prospective randomized controlled trials of NCT for stage IIIA NSCLC, and since then a number of studies since have demonstrated that, for early-stage NSCLC, the efficacy of preoperative NCT plus surgery is similar to that of surgery plus postoperative adjuvant chemotherapy, and both strategies including systemic treatment are better than surgery alone in terms of overall survival (OS) (9,19-21). Due to the relevant toxicity of neoadjuvant/adjuvant chemotherapy, patient tolerance can, at times, be poor. Compared with surgery alone, the addition of neoadjuvant or adjuvant chemotherapy only modestly improves the 5-year OS rate by about 5% (9,21). Thus, there is a clear need for well-tolerated and effective neoadjuvant and adjuvant therapies for resectable NSCLC. Compared with conventional chemotherapy, immunotherapy is better

tolerated in most patients, and treatment-related toxicities may have minimal influence on ability to complete surgical resection. Immunotherapy is being actively explored for the perioperative management of NSCLC.

When programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors kill tumors, antigen-presenting cells (APC) are needed so that the tumor cells can be recognized by host T cells. By blocking the PD-1/PD-L1 interaction with inhibitory antibodies, immunotherapy allows the activated T cells to release cytokines, perforines, granzymes and others to kill tumor cells. In terms of mechanisms involved, when the tumor volume is relatively large, APC bears a relatively large antigen load, which elicits a stronger antitumor T cell response. Therefore, neoadjuvant immunotherapy could theoretically be better than adjuvant immunotherapy and may yield an even greater survival long-term benefit (22). Preclinical studies support these hypotheses. In animal models, compared with adjuvant immunotherapy, neoadjuvant immunotherapy resulted in greater prolongation of median survival time and a higher survival rate (23-25).

No data from large-scale phase III clinical trials of neoadjuvant immunotherapy are yet available, but the results of several phase II clinical trials showed that neoadjuvant immunotherapy may play an important role in the multi-disciplinary management of early-stage NSCLC (26-31). The results of trials of neoadjuvant immunotherapy were summarized in *Table 1*.

CheckMate-159 is a phase II clinical trial which evaluated the safety and feasibility of a preoperative neoadjuvant immunotherapy with two-cycle nivolumab monotherapy, in resectable stage I–IIIA NSCLC. This single-arm study enrolled 22 patients, of which 20 patients received two cycles of the experimental treatment and 20 underwent complete surgical resection. This study showed that neoadjuvant nivolumab monotherapy was safe, tolerable and effective. The major pathologic response (MPR, defined as residual viable tumor cells less than 10%) rate was 45% (26). The phase II clinical trial, TOP1501, was designed to evaluate the safety and feasibility of another preoperative neoadjuvant immunotherapy, two cycles of pembrolizumab monotherapy, in patients with stage IB–IIIA NSCLC. This monotherapy was also found to be safe and efficacious. The MPR rate was 28%, and up to 80% of patients had pathological remission ≥50% (28). The LCMC3 phase II clinical study of PD-L1 inhibitors showed that in patients with stage IB–IIIA NSCLC (plus selected stage IIIB patients), two-cycle atezolizumab monotherapy was found to be well-tolerated and have promising outcomes. The MPR rate was 19%, the pathologic complete remission (pCR, defined as no residual viable tumor) was 5%, and the MPR was unrelated to PD-L1 expression (27). In addition to the above immunomonotherapies, neoadjuvant immunotherapy combined with chemotherapy is associated with higher MPRs in cross-trial comparisons and a suggestion of longer OS utilizing the same cross-trial comparators. A phase II study by Shu *et al.* (32) aimed to investigate the safety and efficacy of preoperative neoadjuvant immunotherapy in the form of four cycles of atezolizumab monotherapy plus carboplatin plus albumin-bound paclitaxel in patients with stage IB–IIIA NSCLC, and the results revealed that this treatment algorithm was feasible, tolerable, and beneficial. The MPR was 50%, and the pCR reached 21.4%. The NADIM study presented at ASCO in 2019 aimed to assess the safety and efficacy of preoperative neoadjuvant immunotherapy in the form of three-cycle nivolumab monotherapy plus carboplatin plus paclitaxel in patients with stage IIIA (N2 or T4N0) NSCLC, and results were promising. The MPR was 83%, the pCR was 71%, and tumor was down-staged in 90% of the patients (33). Currently, the experimental groups of all phase III clinical trials are including neoadjuvant immunotherapy with PD-1/PD-L1 inhibitors plus platinum-based doublet chemotherapy, such as CheckMate-816 (NCT02998528), KEYNOTE-671 (NCT03425643), IMpower-030 (NCT03456063), AEGEAN (NCT03800134), CheckMate-77T (NCT04025879). The ongoing trials were summarized in Table S1.

In summary, this consensus suggests that preoperative use of neoadjuvant immunotherapy with or without platinum-based chemotherapy might be considered for patients with resectable stage IB–IIIA NSCLC.

Consensus 2: there is no evidence that molecular markers uniformly predict the efficacy of neoadjuvant immunotherapy so that biomarker-based selection is not essential. However, it should be cautious to use neoadjuvant single agent immunotherapy in patients with potentially negative factors, such as epidermal growth factor receptor (EGFR)—sensitive mutation/ALK fusion

PD-1/PD-L1 inhibitors have changed the treatment strategies of advanced NSCLC, but we know that not all

Table 1 The results of trials of neoadjuvant immunotherapy

Study title	NCT.no	Key inclusion and exclusion criteria	Drug	Major result
A Randomized, Double-Blind, Phase III Study of Platinum + Pemetrexed Chemotherapy With or Without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-189)	NCT02578680	Patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations	Cisplatin; carboplatin; pemetrexed; dexamethasone; pembrolizumab	(I) OS at 12 months was 69.2% in the pembrolizumab-combination group versus 49.4% in the placebo-combination group. (II) PFS was 8.8 months in the pembrolizumab-combination group and 4.9 months in the placebo-combination group. (III) Adverse events of grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group
A Randomized, Double-Blind, Phase III Study of Carboplatin-Paclitaxel/ Nab-Paclitaxel Chemotherapy With or Without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-407)	NCT02775435	Untreated metastatic squamous NSCLC	Paclitaxel; nab-paclitaxel; carboplatin; pembrolizumab	(I) OS was 15.9 months in the pembrolizumab-combination group and 11.3 months in the placebo-combination group. (II) PFS was 6.4 months in the pembrolizumab-combination group and 4.8 months in the placebo-combination group. (III) Adverse events of grade 3 or higher occurred in 69.8% of the patients in the pembrolizumab-combination group and in 68.2% of the patients in the placebo-combination group
A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) Versus Platinum Based Chemotherapy in Treatment Naïve Subjects With PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (Keynote 042)	NCT02220894	Patients with previously untreated metastatic NSCLC without EGFR or ALK mutations and with an ECOG performance status score of 0 or 1, life expectancy 3 months or longer, and a PD-L1 TPS of 1% or greater.	Carboplatin; paclitaxel; pemetrexed; pembrolizumab	(I) The median survival values by TPS population (≥50%, ≥20%, ≥1%) were 20.0 months for pembrolizumab versus 12.2 months for chemotherapy, 17.7 months versus 13.0 months, and 16.7 months versus 12.1 months, respectively. (II) Treatment-related adverse events of grade 3 or worse occurred in 18% of the patients in the pembrolizumab group and in 41% of those in the chemotherapy group and led to death in 2% and 2% patients, respectively
Phase I Study of Single Agent Pembrolizumab (MK-3475) in Patients With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma (KEYNOTE 001)	NCT01295827	Patients had confirmed locally advanced/ metastatic NSCLC and provided a contemporaneous tumor sample for PD-L1 evaluation by immunohistochemistry using the 22C3 antibody.	Pembrolizumab	(I) Median OS was 22.3 months in treatment-naive patients and 10.5 months in previously treated patients. (II) Estimated 5-year OS was 23.2% for treatment-naive patients and 15.5% for previously treated patients. (III) In patients with a PD-L1 tumor proportion score of 50% or greater, 5-year OS was 29.6% and 25.0% in treatment-naive and previously treated patients, respectively. (IV) Compared with analysis at 3 years, only three new-onset treatment-related grade 3 adverse events occurred
A Phase 1, Open-Label, Multicenter, Multidose, Dose Escalation Study of BMS-936558 (Nivolumab) in Subjects With Selected Advanced or Recurrent Malignancies	NCT00730639	Advanced melanoma, RCC, or NSCLC who received nivolumab and were enrolled between October 30, 2008, and December 28, 2011	Nivolumab	OS was significantly longer among patients with treatment-related AEs of any grade (median, 19.8 months) or grade 3 or more (median, 20.3 months) compared with those without treatment-related AEs (median, 5.8 months)

Table 1 (*continued*)

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Study title	NCT.no	Key inclusion and exclusion criteria	Drug	Major result
Neoadjuvant Nivolumab, or Nivolumab in Combination With Ipilimumab, in Resectable Non-Small-Cell Lung Cancer.	NCT02259621	Adults with untreated, surgically resectable early (stage I, II, or IIIA) NSCLC	Nivolumab	Neoadjuvant nivolumab was associated with few side effects, did not delay surgery, and induced a major pathological response in 45% of resected tumors
A Randomized Open-Label Phase III Trial of MK-3475 Versus Platinum Based Chemotherapy in 1L Subjects With PD-L1 Strong Metastatic Non-Small Cell Lung Cancer	NCT02142738	Previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and without EGFR or ALK mutations	Paclitaxel; carboplatin; pemetrexed; cisplatin; gemcitabine; pembrolizumab	(I) PFS was 10.3 months in the pembrolizumab group versus 6.0 months in the chemotherapy group. (II) OS at 6 months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group. (III) The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% *vs.* 27.8%). (IV) Treatment-related adverse events of any grade were less frequent (occurring in 73.4% *vs.* 90.0% of patients), as were grade 3, 4, or 5 treatment-related adverse events (26.6% *vs.* 53.3%)
An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum Doublet Chemotherapy Versus Platinum Doublet Chemotherapy in Subjects With Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)	NCT02477826	Patients with stage IV or recurrent NSCLC that was not previously treated	Nivolumab; ipilimumab; carboplatin; cisplatin; gemcitabine; pemetrexed; paclitaxel	(I) The 1-year PFS rate was 42.6% with nivolumab plus ipilimumab versus 13.2% with chemotherapy, and the median PFS was 7.2 months versus 5.5 months. (II) The objective response rate was 45.3% with nivolumab plus ipilimumab and 26.9% with chemotherapy. (III) The rate of grade 3 or 4 treatment-related adverse events was 31.2% with nivolumab plus ipilimumab and 36.1% with chemotherapy
An Open-Label Randomized Phase III Trial of BMS-936558 (Nivolumab) Versus Docetaxel in Previously Treated Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC)	NCT01673867	Patients with nonsquamous NSCLC that had progressed during or after platinum-based doublet chemotherapy	Nivolumab; docetaxel	(I) The OS was 12.2 months in the nivolumab group and 9.4 months in the docetaxel group. At 1 year, the OS rate was 51% with nivolumab versus 39% with docetaxel. OS rate at 18 months was 39% with nivolumab versus 23% with docetaxel. (II) The response rate was 19% with nivolumab versus 12% with docetaxel. (III) The rate of PFS at 1 year was higher with nivolumab than with docetaxel (19% and 8%, respectively). (IV) Treatment-related adverse events of grade 3 or 4 were reported in 10% of the patients in the nivolumab group, as compared with 54% of those in the docetaxel group.

Table 1 (*continued*)

Table 1 (*continued*)

Study title	NCT.no	Key inclusion and exclusion criteria	Drug	Major result
A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) Versus Docetaxel in Previously Treated Subjects With Non-Small Cell Lung Cancer	NCT01905657	Patients with previously treated non-small-cell lung cancer with PD-L1 expression on at least 1% of tumour cells	Pembrolizumab; docetaxel	(I) OS was 10.4 months with pembrolizumab 2 mg/kg, 12.7 months with pembrolizumab 10 mg/kg, and 8.5 months with docetaxel. (II) PFS was 3.9 months with pembrolizumab 2 mg/kg, 4.0 months with pembrolizumab 10 mg/kg, and 4.0 months with docetaxel (III) Among patients with at least 50% of tumour cells expressing PD-L1, OS was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (14.9 *vs.* 8.2 months) and with pembrolizumab 10 mg/kg than with docetaxel (17.3 *vs.* 8.2 months).PFS was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (5.0 *vs.* 4.1 months) and with pembrolizumab 10 mg/kg than with docetaxel (5.2 *vs.* 4.1 months) (IV) Grade 3-5 treatment-related adverse events were less common with pembrolizumab than with docetaxel (13% of the patients given 2 mg/kg, 16% of given 10 mg/kg, and 35% of 309 given docetaxel)
A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) Versus Platinum Based Chemotherapy in Treatment Naïve Subjects With PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (Keynote 042)-China Extension Study	NCT03850444	Chinese participants with PD-L1-positive NSCLC	Pembrolizumab; carboplatin; paclitaxel; pemetrexed	(I) OS (TPS of ≥50%)was 20.0 months in the pembrolizumab group and 14.0 months in the Chemotherapy group. OS (TPS of ≥20%) was 20.0 months in the pembrolizumab group and 13.7 months in the Chemotherapy group. OS (TPS of ≥1%) was 20.0 months in the pembrolizumab group and 13.7 months in the Chemotherapy group. (II) PFS (TPS of ≥50%) was 8.3 months in the pembrolizumab group and 6.5 months in the Chemotherapy group. PFS (TPS of ≥20%) was 6.3 months in the pembrolizumab group and 6.5 months in the Chemotherapy group. PFS (TPS of ≥1%) was 6.3 months in the pembrolizumab group and 6.4 months in the Chemotherapy group
A Randomized, Double-Blind, Phase III Study of Platinum + Pemetrexed Chemotherapy With or Without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-189)	NCT03950674	Adult Japanese participants with advanced or metastatic nonsquamous NSCLC who have not previously received systemic therapy for advanced disease	Dexamethasone; cisplatin; carboplatin; pemetrexed	(I) PFS was 16.5 months in the pembrolizumab group and 7.1 months in the Chemotherapy group. (II) ORR was 56% in the pembrolizumab group and 33.3% in the Chemotherapy group

Table 1 (*continued*)

Table 1 (*continued*)

Study title	NCT.no	Key inclusion and exclusion criteria	Drug	Major result
An Open-label Randomized Multinational Phase 3 Trial of Nivolumab Versus Docetaxel in Previously Treated Subjects With Advanced or Metastatic Non-small Cell Lung Cancer (CheckMate 078: CHECK point Pathway and nivoluMAb Clinical Trial Evaluation 078)	NCT02613507	Advanced or Metastatic NSCLC who have failed prior platinum-based doublet chemotherapy	Nivolumab; docetaxel	(I) OS was 11.99 months in the Nivolumab group and 9.63 months in the Docetaxel group. (II) ORR was 16.6% in the Nivolumab group and 4.2% in the Docetaxel group
A Phase 3, Randomized Study of Nivolumab Plus Ipilimumab in Combination With Chemotherapy *vs.* Chemotherapy Alone as First Line Therapy in Stage IV Non-Small Cell Lung Cancer	NCT03215706	Stage IV NSCLC have not previously received systemic therapy	Ipilimumab; Nivolumab; Carboplatin; Paclitaxel; Pemetrexed; Cisplatin	(I) OS was 14.13 months in the Nivolumab + Ipilimumab + Chemotherapy group and 10.74 months in the Chemotherapy group. (II) PFS was 6.83 months in the Nivolumab + Ipilimumab + Chemotherapy group and 4.96 months in the Chemotherapy group. (III) ORR was 37.7% in the Nivolumab + Ipilimumab + Chemotherapy group and 25.1% in the Chemotherapy group
An Open-Label, Randomized, Phase 3 Trial of Nivolumab Versus Investigator's Choice Chemotherapy as First-Line Therapy for Stage IV or Recurrent PD-L1+ Non-Small Cell Lung Cancer	NCT02041533	Stage IV or Recurrent PD-L1^{+} NSCLC	Nivolumab; Gemcitabine; Cisplatin; Carboplatin; Paclitaxel; Pemetrexed	(I) PFS was 4.21 months in the Nivolumab group and 5.82 months in the Chemotherapy group. PFS (TPS of ≥5%) was 4.21 months in the Nivolumab group and 5.88 months in the Chemotherapy group. (II) OS was 13.73 months in the pembrolizumab group and 13.80 months in the Chemotherapy group. OS (TPS of ≥5%) was 14.36 months in the pembrolizumab group and 13.21 months in the Chemotherapy group
A Dose Frequency Optimization, Phase IIIB/IV Trial of Nivolumab 240 mg Every 2 Weeks *vs.* Nivolumab 480 mg Every 4 Weeks in Subjects With Advanced or Metastatic Non-small Cell Lung Cancer Who Received up to 12 Months of Nivolumab at 3 mg/kg or 240 mg Every 2 Weeks	NCT02713867	Advanced/metastatic (Stage IIIb/IV) NSCLC	Nivolumab	(I) PFSR at 6 months was 0.76 in the Nivolumab 480mg Q4W group and 0.79 in the Nivolumab 240 mg Q2W group. (II) OS was at 6 months 0.966 of 180 patients in the Nivolumab 480 mg Q4W group and 0.956 183 patients in the Nivolumab 240 mg Q2W group

patients can benefit from them. For patients with driver mutation–negative NSCLC, the response rate of PD-1/PD-L1 inhibitor monotherapy has been approximately 14–20%, and that of first-line monotherapy in advanced NSCLC patients with PD-L1 expression ≥50% is approximately 50% (34). Therefore, it is critical to identify predictive biomarkers to select patients who can benefit from PD-1/PD-L1 inhibitors, avoiding the treatment to those patients who will not benefit. The most promising marker as such is PD-L1 so far. Supported by well-founded evidence. KEYNOTE-024 and KEYNOTE-042 studies indicated that among patients with high or positive PD-L1 expression, pembrolizumab monotherapy was superior to the standard chemotherapy. The higher the PD-L1 expression, the more benefit the patients received from single agent immunotherapy. Therefore, all guidelines consistently recommend PD-L1 as the companion diagnostic for patients with driver mutation–negative NSCLC receiving immunotherapy (13,35). The IMpower110 study also showed that among the patients with driver mutation–negative NSCLC and high PD-L1 expression in tumor cells and/or interstitial cells (TC3/IC3), atezolizumab monotherapy was superior to the standard chemotherapy (36). Some results of KEYNOTE-016, KEYNOTE-164, KEYNOTE-1022, KEYNOTE-028, KEYNOTE-177 and KEYNOTE-158 indicated that the objective remission rate of pembrolizumab monotherapy reached 39.6% in solid-tumor patients with microsatellite instability high (MSI-H) or mismatch repair deficiency. Based on this finding, the United States Food and Drug Administration (FDA) approved pembrolizumab monotherapy for patients with disease progression after previous treatment or metastatic solid tumor patients with MSI-H or mismatch repair deficiency, which is the first indication for cancer treatment based on biomarkers (37). However, these features are very rare in NSCLC.

The use of PD-L1 as a biomarker, however, remains to be complicated by a number of factors including the variability in tissue collection timing, the antibody and methodology used for staining (including the definition of positivity and the non-standardised test design), the heterogeneity and dynamic of PD-L1 expression within different tumors, and the role of PD-L1 expression on tumor-infiltrating lymphocytes and other immune cells versus the malignant cell population. In addition, PD-L1 is regarded to be a biological continuum and therefore might be of limited value as a biomarker in this subset of patients. Pembrolizumab (anti-PD-1) is approved (EMA, FDA) for first-line treatment of NSCLC patients with advanced or metastatic cancers (with PD-L1 expression ≥50% using the Dako 22C3 IHC assay), whereas for second-line treatment a PD-L1 expression of ≥1% is required. Both, nivolumab (anti-PD-1) and atezolizumab (anti-PD-L1) are also approved (EMA, FDA) in the first- and second-line setting, but PD-L1 screening is only mandatory for atezolizumab, however, complementary PD-L1 diagnostics are approved for NSCLC. Durvalumab (anti-PD-L1) is currently for stage non-resectable IIIA/IIIB NSCLC, PD-L1 testing is recommended. To date, many groups of oncologists are attempting to establish better predictive biomarkers in NSCLC for monoclonal antibodies targeting the PD-1/PD-L1 axis to select patients who might have a greater benefit from immune checkpoint therapies.

In addition to PD-L1 and MSI-H, tumor mutation burden (TMB) is also considered a potential biomarker for immunotherapy. Noteworthy, TMB can be assessed in different ways and, as a continuous variable, 'high' can also be variably defined. Although the retrospective analyses of KEYNOTE-042 and KEYNOTE-189 trials, and the prospective study CheckMate-227 all showed that TMB could not effectively predict the efficacy of immunotherapy alone or immunotherapy combined with chemotherapy as first-line treatment of advanced NSCLC (38), the KEYNOTE-158 results showed that, among patients with disease progression or metastases after previous treatment, the outcomes of single-agent pembrolizumab in those with high TMB were significantly better than in those with low TMB. Based on this, the FDA approved the pembrolizumab monotherapy for patients with high TMB as defined by ≥10 mutations/Mb and disease progression after previous treatment and for metastatic solid tumor patients (39).

The IMpower150 trial is the first phase III study to demonstrate a clinically meaningful and significant PFS benefit with atezolizumab plus bevacizumab and chemotherapy (paclitaxel and carboplatin) versus bevacizumab plus chemotherapy in the first-line stetting of advanced or metastatic NSCLC (8.3 versus 6.8 months, HR =0.62, P<0.0001) and the PFS benefit was seen regardless of the PD-L1 status in all patients. The PFS benefit, however, was even more pronounced in patients expressing a T effector gene signature (11.3 versus 6.8 months, HR =0.51, P<0.0001) indicating that the expression of gene signatures may be more robust to predict clinical response following treatment with PD-L1 inhibitors (40).

Of note, in experimental systems with NSCLC-bearing xenografts, the tumor microenvironment (TME) has also

been found to significantly contribute to the response to CPIs. Several lines of evidence have suggested that tumor-associated macrophages (TAMs: positivity for PD-L1, CD133, and CD163) within the TME can reduced responses to immunotherapies by suppressing CD8-positive cytotoxic T cells (CTLs) They are also regarded to be responsible for the hyperprogression following immunotherapy (41). In addition, cancer-associated fibroblasts (CAFs) have also been shown to suppress responses to CPIs by decreasing CD8-positive CTLs. Ford *et al.* (42) have provided the first evidence that TGF-β can stimulate NADPH-Oxidase 4 (NOX-4) which in turns produces reactive oxygen species that can activate CAFs and thereby confer resistance to IO treatments. Although so far these are experimental approaches, it is likely that the CAF and TAM status will guide immunotherapy treatment strategies in the neoadjuvant setting in the future as well.

Differently from advanced NSCLC, immunotherapy for early-stage NSCLC is still under investigation. Clinical studies have yet to find biomarkers that can predict the efficacy of neoadjuvant immunotherapy (27,43). The NEOSTAR study showed that, when using neoadjuvant nivolumab monotherapy or nivolumab combined with ipilimumab monotherapy to treat stage I–IIIA NSCLC, the baseline PD-L1 expression in patients obtaining complete/partial response (CR/PR) was higher than that in patients obtaining stable/progressive disease (SD/PD), and the baseline PD-L1 expression in patients obtaining MPR was higher than those who did not (43). In the LCMC3 study, neoadjuvant atezolizumab monotherapy was given to patients with stage IB-IIIB NSCLC. Pathological remission and MPR were observed regardless of the expression level of PD-L1, and TMB had no correlation with pathological remission and MPR (27). Immunotherapy for early-stage NSCLC is still under investigation, and biomarkers in this setting are also being explored. All currently completed studies are small-scale phase I/II clinical trials, and the role of biomarkers, including PD-L1, MSI-H, T_{eff} cell signatures, and TMB, remains unclear, warranting further exploration.

Over the past 20 years, with the discovery of driver genes such as *EGFR*, *ROS*, *RET*, and *ALK* and the development of targeted agents, the treatment of NSCLC has entered the era of precision drug therapy, greatly improving the prognosis of molecularly selected subgroups of patients with advanced NSCLC (44). As described above, ICIs can bring long-term benefits to patients with driver mutation–negative NSCLC (11-13). Therefore, many researchers have explored whether ICIs can also bring long-term benefits to NSCLC patients with driver mutations.

CheckMate-057 is a phase III clinical study aiming to explore the efficacy of nivolumab monotherapy as the second-line treatment of advanced nonsquamous NSCLC, and its efficacy was compared to that of docetaxel. In this study, 82 *EGFR*-mutated NSCLC patients and 21 patients with *ALK* translocation were included, and they all had previously received the first-line platinum-based doublet chemotherapy. Subgroup analysis of *EGFR*-mutated NSCLC patients showed that OS and progression-free survival (PFS) were not improved in patients receiving nivolumab monotherapy compared to those receiving docetaxel (45). Another III randomized clinical trial, KEYNOTE-010, comparing pembrolizumab *vs.* docetaxel, performed subgroup analysis on EGFR-mutated NSCLC patients and showed that pembrolizumab did not improve OS compared to docetaxel (46). A recent, real-world, retrospective analysis showed that *EGFR*-mutated and *ALK*-rearranged NSCLC patients did not benefit from PD-1/PD-L1 monotherapy. A number of clinical trials and retrospective studies have shown that for advanced *EGFR*-mutated or *ALK*-rearranged patients, the chance of benefit with immunotherapy is modest, and the addition of ICIs on the corresponding targeted therapies does not bring an additional benefit but increases the occurrence of toxic and side effects. Further support for this proposal came from the observation that *EGFR* mutations may decrease PD-L1 expression (47).

In addition to the poor efficacy of immunotherapy in NSCLC patients with driver mutations (positive *EGFR* and *ALK*), genes such as *STK11* that are tumor suppressor genes are frequently mutated in NSCLC and may reduce cluster of differentiation (CD) 8^+ T cell density or function, thus affecting the tumor-related immune response through multiple pathways (48). The MYSTIC study showed that the prognosis of patients with *STK11*-mutated NSCLC receiving single-agent durvalumab was poor (49). The exploratory analysis of KEYNOTE-042 showed that regardless of the *STK11* mutation status, the patients who received pembrolizumab monotherapy showed better PFS and OS than the patients who received standard chemotherapy (50). However, complete responses to nivolumab in patients with STK11 mutation have been also reported (51). At present, it is not clear whether *STK11* mutation is a prognostic factor or a predictive factor in patients with NSCLC receiving for PD-1/PD-L1 inhibitor therapy.

Although the roles of driver genes, such as *EGFR* and *ALK*, and inhibitory genes, such as *STK11*, in immunotherapy for early-stage NSCLC are still not clear. Based on the above data, patients with potentially unfavorable factors such as EGFR-sensitive mutation or ALK fusion should be cautious to receive neoadjuvant single agent immunotherapy.

Consensus 3: for neoadjuvant immunotherapy, two to four cycles are recommended, and after every two cycles, review and evaluation should be performed to update the treatment plan

The purpose of neoadjuvant immunotherapy is to enhance downstaging, improve the R0 resection rate, and subsequently treat subclinical micrometastases. A short course of neoadjuvant immunotherapy may not be adequate for immunotherapy to have an effect, but if the duration of immunotherapy is too long, tumor progression may lead to the loss of surgical window of opportunity, so the length of neoadjuvant immunotherapy is very important (52). A preclinical study showed that the presence of a primary tumor appeared to be key to the efficacy of neoadjuvant immunotherapy, and the efficacy was closely correlated with the timing of tumor resection after neoadjuvant immunotherapy (53). To prevent progression in patients with drug resistance, the International Neoadjuvant Melanoma Consortium (INMC) recommends six to eight weeks of neoadjuvant therapy for melanoma, depending on the cycle length of the clinical trial (54). At present, the effects of neoadjuvant immunotherapy on early-stage NSCLC are known only from phase I/II clinical trials, without large-scale phase III trials. The neoadjuvant single agent immunotherapy in CheckMate159, LCMC3, and TOP1501, was performed for two cycles, and surgery was performed 28–56 days after the first cycle (26-28). Neoadjuvant immunotherapy combined with chemotherapy (NADIM: phase II with N=51) or combination of two checkpoint inhibitors (PD-1 and CTLA-4) (NEOSTAR: phase II with N=44) was performed for three to four cycles, and surgery was performed 3–7 weeks after the end of the neoadjuvant therapy (43). Currently, the role of neoadjuvant immunotherapy in early-stage NSCLC is still not fully elucidated, and review after every two cycles is recommended to assess tumor remission and update the treatment plan. However, as there is a low predictive value of CT scans or of RECIST criteria, in case no distant metastases are found, patients should proceed to surgical resection if still feasible.

In summary, two to four cycles are recommended for neoadjuvant immunotherapy, and re-evaluate after every two cycles is recommended to refine the treatment plan.

Consensus 4: the benefit from neoadjuvant immunotherapy should be preferably assessed by positron-emission tomography (PET)-computed tomography (CT), in conjunction with serum tumor markers and/or circulating tumor DNA (ctDNA) load

Tumor shrinkage after the treatment is clear evidence for the antitumor activity of neoadjuvant therapy, and the objective remission rate is an important indicator to evaluate tumor shrinkage and antitumor activity. CT is often used to assess the response of NSCLC patients to neoadjuvant therapy. The Response Evaluation Criteria in Solid Tumors (RECIST) by CT is an important predictor of OS in NSCLC patients after NCT (55). However, the histopathological response of 41–45% patients may be inconsistent with the CT evaluation (26,56). Changes in inflammation and interstitial or fibrotic components of tumors may affect the CT results, leading to the inability of CT imaging to accurately predict histopathological responses after neoadjuvant therapy. When using imaging examinations, the efficacy is determined by continuously measuring changes in tumor size in these patients, which has inherent limitations. Therefore, conventional imaging combined with metabolic imaging may be required to determine efficacy (56). Some investigators have suggested that PET-CT may be more advantageous in the evaluation of neoadjuvant therapy because the uptake of ^{18}F-fluorodeoxyglucose by the tumor is closely related to the proliferative activity and the number of remaining vital tumor cells. Multiple PET-CT studies have shown that PET-CT can effectively evaluate the efficacy of neoadjuvant therapy. Although the response to neoadjuvant therapy as seen on PET-CT may be related to an improved prognosis, the role of PET-CT in neoadjuvant therapy at early stage still requires further exploration (31,55,57). In addition, incorporating serum tumor markers or ctDNA may increase the accuracy of tumor load assessment (58,59). This is particularly important for assessment of neoadjuvant immunotherapy, given that discrepancy between radiologic and pathologic response, as well as pseudo progression, have been extensively reported (24,28).

In summary, the benefit of neoadjuvant immunotherapy is preferred to be assessed by PET-CT, in conjunction with tumor markers and/or ctDNA load. However, more research on the accuracy and the need for standardization, especially for ctDNA measurements, of these modalities is needed before they can be introduced in standard of care.

Consensus 5: surgery can be performed 4–6 weeks after the last cycle of neoadjuvant immunotherapy

It is very difficult to determine the timing of surgery after neoadjuvant immunotherapy. For neoadjuvant chemotherapy, early surgery may lead to serious surgical complications, while delayed surgery may lead to tumor progression (52). However, neoadjuvant immunotherapy is distinct from neoadjuvant chemotherapy in terms of adverse events. Before determining the optimal time for neoadjuvant immunotherapy and surgery, it is important to understand the T cell amplification cycle, determine the best time for effector cells to exert their effects, and time the tumor resection for when the impact on antitumor immunity will be the least. Experimentally, this may be very challenging, though recent studies have shown that it is possible to measure the human antigen-specific T cell response over time through systematic deuterium labeling, but further basic and clinical trials are still needed to determine the optimal timing of surgery (60). Although the results of neoadjuvant immunotherapy on early-stage NSCLC are all from phase I/II clinical trials, they still have reference value. CheckMate 159, LCMC3, and TOP1501 included two cycles of neoadjuvant single agent immunotherapy, and surgery was performed 28 to 56 days after the first cycle, i.e., 1–5 weeks after the end of immunotherapy (26-28). Neoadjuvant immunotherapy combined with chemotherapy (NADIM, NCT02716038) or the combination of two immunotherapies (NEOSTAR) was performed for three to four cycles, and surgery was performed 3–7 weeks after the end of the neoadjuvant immunotherapy (43). In summary, surgery is recommended at 4–6 weeks after the last neoadjuvant immunotherapy cycle.

Consensus 6: There is no definitive evidence that neoadjuvant immunotherapy affects the conduct or safety of surgery

The morbidity and safety of surgery after neoadjuvant immunotherapy is still not definitively known. Some clinical trials have demonstrated that after neoadjuvant radiotherapy (NRT) or NCT, surgery is safe and feasible, but that neoadjuvant immunotherapy may lead to tissue adhesion, thus increasing the operative difficulty. Thus, appropriate concerns have been raised as to whether neoadjuvant immunotherapy may increase the surgery complexity (61,62). Currently, the phase I/II studies of neoadjuvant immunotherapy showed that the incidence of any adverse events caused by neoadjuvant single agent immunotherapy was approximately 57%, the incidence of adverse events ≥ grade 3 was approximately 4.5–8%, and the completion rate of planned surgery was 78–100%, which are all similar to those of NCT and NRT (26-28). The NEOSTAR study assessed surgical difficulty and pulmonary function after neoadjuvant immunotherapy, and the results showed that ICIs had less impact on the surgical resection rate and surgical complexity and had no adverse effect on perioperative outcomes (43). A retrospective analysis of 19 patients in the United States showed that, for metastatic or unresectable patients, pneumonectomy after neoadjuvant immunotherapy was feasible, with a high R0 rate, while surgery may be challenging, serious complications were rare (63). There are still no clear conclusions about the impact and safety of neoadjuvant immunotherapy on surgical procedures, and more data are needed.

In summary, based on the available data, there is no conclusive evidence that neoadjuvant immunotherapy adversely affects surgical procedures or their safety.

Consensus 7: pathological remission (MPR, pCR) needs to be assessed, recorded, and reported by specialized pathologist after neoadjuvant immunotherapy

In a prospective multicenter phase II study of stage IIIA and IIIB NSCLC in 1997, Junker *et al.* (64) developed a tumor regression grading system based on resection specimens (62 cases) from 28 patients with lung squamous-cell carcinoma and 12 patients with lung adenocarcinoma after combined NCT and NRT. The results were compared to spontaneous regressive changes in a control group of 50 untreated NSCLC patients. The proposed three-level grading system of pathological response included grade I (no or only slight tumor regression), grade IIA (significant but incomplete tumor regression, more than 10% vital tumor

tissue), grade IIB (less than 10% vital tumor tissue), and grade III (complete tumor regression without vital tumor tissue). Patients with grade IIB or III tumor regression had a much longer survival time than those with grade II or IIA tumor regression (64). Later, Junker *et al.* improved the grading criteria for tumor regression and defined grade I as no tumor regression or only spontaneous tumor regression, grade II as treatment-induced tumor regression, grade IIa as more than 10% vital tumor tissue, grade IIb as less than 10% vital tumor tissue, and grade III as complete tumor regression. The authors also found that along with the complete resection of the tumor, treatment-induced tumor regression and less than 10% vital tumor tissue were essential for improving long-term outcomes (65). However, many later trials questioned whether the percentage of vital tumor tissue remaining after NCT in NSCLC patients was associated with prognosis. The response of lung squamous-cell carcinoma to NCT was significantly better than that of lung adenocarcinoma, the median percentages of vital tumor tissue were 40% and 60%, respectively, and the critical MPR values were 26% and 12%, respectively (66). In 2017, the College of American Pathologists still recommended MPR as the study endpoint of clinical trials on neoadjuvant immunotherapy for lung cancer. Currently, MPR is defined as neoadjuvant therapy-induced tumor regression with less than 10% vital tumor tissue, and pCR is defined as neoadjuvant therapy-induced complete tumor regression without vital tumor tissue (67).

Because ICIs have only been used in neoadjuvant therapy for NSCLC in recent years, most of the current results come from phase I/II clinical trials. The MPR of neoadjuvant single agent immunotherapy is in the range of 19–45%, and that of immunotherapy combined with neoadjuvant therapy fluctuates within 33–83% (26-28,43). These studies are small, the results have not been verified in phase III clinical trials, and the relationships of MPR with PFS and OS need further confirmation. However, immunotherapy has brought higher MPR and surgical resection rates. The current clinical trials of neoadjuvant immunotherapy can collect more specimens for further exploration.

In summary, pathological remission (MPR, pCR) needs to be assessed, recorded and reported by specialized pathologist after neoadjuvant immunotherapy.

Consensus 8: for neoadjuvant immunotherapy in nonprogressive patients, immunotherapy can be resumed after surgery, and it can be maintained for 1 year

PD-1/PD-L1 inhibitors have greatly altered the treatment strategies of advanced NSCLC. The Chinese Society of Clinical Oncology (CSCO) guidelines recommend that advanced NSCLC patients with positive PD-L1 expression and negative driver mutations can be treated with pembrolizumab monotherapy, and the immunotherapy can be withdrawn at disease progression or 35 cycles (2 years). Advanced NSCLC patients whose tumors do not harbor driver mutations, regardless of PD-L1 expression, can be treated with pembrolizumab monotherapy combined with chemotherapy for 4 cycles, followed by maintenance pembrolizumab monotherapy for a total of 2 years. The CSCO guidelines also recommend 1-year maintenance therapy of durvalumab after concurrent chemoradiotherapy for stage III unresectable NSCLC patients. Currently, there is no definitive recommendation on immune maintenance therapy after neoadjuvant immunotherapy, and it varies from no postoperative immune maintenance therapy to 1-year immune maintenance therapy (26-28,43).

Recently, Antonia *et al.* reported the results of the phase III PACIFIC study (NCT02125461) (68). In this study the role of immune checkpoint blockade with durvalumab in locally advanced, unresectable, stage III NSCLC was evaluated. Eligible patients had NSCLCs without progression after they had been treated with at least two cycles of platinum-based chemotherapy concurrent with radiotherapy (chemo-radiotherapy) at a dose of 54 to 66 Gy. A total of 713 patients were randomly assigned in a 2:1 ratio to receive either durvalumab (10 mg/kg) or placebo every 2 weeks for up to 12 months. Results showed that the co-primary end point of median PFS was 16.8 months in the durvalumab group versus 5.6 months in the placebo group (HR =0.52; 95% CI, 0.42–0.65). In addition, the ORR (assessed by blinded independent central review) was found to be higher in the durvalumab group than in the placebo group (28.4% *vs.* 16.0%, P<0.001). Interestingly, clinical benefit was observed irrespectively of NSCLC tumor stage (IIIA or IIIB), histologic type, or geographic distribution. Most notably, however, brain metastases developed far more frequently in the placebo group as in the durvalumab group

(11.0% *vs.* 5.5%) (16,17). The OS was also significantly increased with not reached versus 29.1 months (HR =0.68).

Given the experience with immunotherapy in advanced NSCLC and stage III unresectable NSCLC, the neoadjuvant immunotherapy of nonprogressive patients can be resumed after surgery, and can be maintained for 1 year.

Consensus 9: immunotherapy or induction chemotherapy can be offered in borderline resectable locally advanced NSCLC, and consideration for surgery should be reevaluated upon restaging

The standard treatment for stage IIIA/B unresectable NSCLC is maintenance therapy with durvalumab monotherapy after concurrent chemoradiotherapy (based on the results of the PACIFIC Trial). Debate exists as to whether these patients are best served by surgery after induction therapy. The ESPATUE study (N =246 of 500 planned, trial had been stopped due to slow recruitment) showed that some patients with stage III unresectable disease may benefit from induction chemotherapy or chemoradiotherapy: their T and N stages were significantly downgraded, and tumors became surgically resectable with a downgrade rate of 44%. Patient characteristics were balanced between the two arms, in which 81 were assigned to surgery (arm A), and 80 were assigned to a chemoradiotherapy boost. In arm B, 81% underwent R0 resection. With a median follow-up after random assignment of 78 months, 5-year OS and PFS did not differ between arms. OS rates of 44% for arm B and 40% for arm A (log-rank P=0.34) and PFS rates of 32% for arm B and 35% for arm A (log-rank P=0.75). OS at 5 years was 34.1% (95% CI, 27.6–40.8%) in all 246 patients, and 216 patients (87.8%) received definitive local treatment (69).

Most recently Reck *et al.* (70)provided the first evidence that the combination of immunotherapy followed by chemotherapy and subsequently maintenance therapy resulted in a significantly improved mOS (CheckMate-9LA). In this phase III trial patients (N=719) were randomized between immunotherapy with ipilimumab and nivolumab (plus two cycles of platinum-based chemotherapy) followed by ipilimumab plus nivolumab as maintenance until progression versus four cycles of platinum-based chemotherapy followed by maintenance therapy (until progression). The ORR rate for the immunotherapy arm was 38% (2% complete remission), mOS rates after one year were 63% versus 47% (HR =0.66) (approved by FDA and EMA). The results were seen regardless of the PD-L1 status. From this trial the authors concluded that the IO-chemotherapy combination should be considered m effective and well-tolerated novel treatment opportunity for advanced and/or metastatic NSCLC. Although this trial was conducted in stage IV NSCLC patients, the ORR of 38% (including 2% CR rate) is remarkable and further studies are currently planned to evaluate this regimen in earlier stages of NSCLC in the neoadjuvant setting.

Although surgical resection did not increase the postoperative PFS and OS compared to radical chemoradiotherapy, selected patients (T3N2, T4N0/T4N1) had a significant long-term survival benefit in the subgroup analysis, and the benefit in the cohort of patients with stage III B (T4N0-1) patients was the most significant (69). Although many immunotherapy neoadjuvant clinical trials are still underway, the NADIM study indicated that after stage III (N2 or T4N0/N1) patients received four cycles of nivolumab monotherapy combined with chemotherapy, mPFS was found to be 77.1% after 24 months. 30% of patients had treatment-related adverse events of grade 3 or worse; however, none of the adverse events were associated with surgery delays or deaths. The downstage rate was 90.2%, the completion rate of planned surgery was 89.1%, and the MPR rate was 83%, indicating a promising long-term survival benefit in this group of patients (71).

In summary, induction immunotherapy with or without chemotherapy can be considered for unresectable locally advanced NSCLC (particularly in selected N2 and T4 patients), and after the tumor stage is downgraded, the possibility of surgery could be reevaluated. The results of randomized phase III trials with OS as the primary endpoint should be awaited before this strategy is introduced into standard of care.

Key questions and perspectives

Do you use neoadjuvant PD-1/PD-L1 blockade in routine practice? Why or why not?

Rafael Rosell: Neoadjuvant PD-L1 approach is still not standardized, therefore I prefer to include patients in available clinical trials on immune checkpoint inhibitors in combination with chemotherapy. However, understanding that there are patients who may not have access to clinical trials, the use of preoperative neoadjuvant immunotherapy could be adequate for stage IIIA NSCLC patients.

Mariano Provencio: I believe that the results of chemo-immunotherapy could support its use in clinical practice, it makes all the same sense as in advanced stages and the results are much better than just chemotherapy. Perhaps we should wait for the ongoing trials, but their adoption should be quick and perhaps accept surrogates of pathological response… but it is not approved in my country.

Erminia Massarelli: Yes, I use it within clinical trials of neoadjuvant immunotherapy.

I truly believe that checkpoint inhibitors alone or plus chemotherapy can significantly downstage tumors and I believe the advantage especially in stage II–III NSCLC is significant. However, so far we are only using it within clinical trials.

Mara B. Antonoff: We try to enroll as many patients as possible onto trials evaluating neoadjuvant PD-L1 blockade; however, outside of a clinical trial, we do not routinely use it in the neoadjuvant setting as it is not yet approved for use outside of a trial.

Toyoaki Hida: We don't use neoadjuvant PD-1/PD-L1 blockade in routine practice, because immune checkpoint inhibitors (ICIs) are not yet approved for the use of preoperative treatment in lung cancer in Japan. We use ICIs for preoperative treatment in clinical trials only.

Marc de Perrot: I do not use neoadjuvant PD-L1 blockade in routine practice due to the lack of access. Neoadjuvant IO is part of clinical trials in our institution.

Steven H. Lin: No, all our patients with this approach are treated on clinical trial, since it is currently not a standard approach for the use of neoadjuvant immunotherapy although early studies have shown promising major pathologic response. All neoadjuvant approaches should be done on the ongoing numerous single arm or randomized trials. Neoadjuvant chemotherapy is still a good option as the control arm in those randomized trials.

Massimo Di Maio: We do not currently use neoadjuvant PD-1/PD-L1 blockade in routine practice, because this is not a standard approach according to our national guidelines by AIOM (Italian Association of Medical Oncology). In general, neoadjuvant treatment is not commonly used for patients who are judged eligible for surgery, with the exception of a known positivity of mediastinal lymph nodes, when a neoadjuvant chemotherapy is commonly considered before re-evaluation with the surgeon.

As a general rule, Italy has a publicly funded health system, and only treatments approved and reimbursed can be considered in clinical practice. Furthermore, AIOM has chosen to produce recommendations only for drugs/ treatments that are reimbursed by the national health system, considering that it would make no sense to recommend something that cannot be used in clinical practice.

At the moment, use of neoadjuvant PD-1/PD-L1 blockade is limited to participation in clinical trials.

Antonio Rossi: I do not use neoadjuvant PD-1/PD-L1 blockade in routine practice because, despite the very interesting results coming from phase I/II trials, it is still an experimental approach. The Site in which I worked had no possibility to be involved in trials addressing this issue in order to participate to the investigation of this strategic approach. Randomized trials are ongoing and if the results will be positive this approach should be evaluated by regulatory agencies and then considered for clinical practice.

Dirk de Ruysscher: No, only in the context of a clinical trial. There are no phase III data showing an increase of OS.

Robert A. Ramirez: No. The data looks promising for combination chemo/IO in the neoadjuvant setting, however, outside of a clinical trial we don't have large scale studies to guide us. Plus, in the US we run into reimbursement issues and cannot get this in the neoadjuvant setting.

Wolfram C. M. Dempke: In our institution neoadjuvant therapies are currently not used routinely as they are not FDA/EMA approved so far (with very few exceptions). However, we participate in clinical studies.

D. Ross Camidge: NO—It is not licensed and its OS benefit is not clear. It needs to be compared with adjuvant therapy as it will cause delay in surgery.

Nicolas Guibert: I do, but only within clinical trials because no ICIs as neoadjuvant therapies are approved in France yet.

Raffaele Califano: It's not in routine practice as not approved/funded.

Do you think biomarker is necessary in choosing neoadjuvant PD-1/PD-L1 blockade therapy? If yes, which ones?

Rafael Rosell: Needless to say, immune biomarkers are desirable and a PD-L1 tumor proportion score (TPS) of more than 50% could serve and encourage patients. However, patients with a TPS of lower than 50%, but more than 1%, are also suitable for the neoadjuvant immunotherapy approach. Furthermore, if liquid biopsy is accessible, a high blood TMB is also orientative to predict

response to immune checkpoint inhibitors. NSCLC with driver mutations or gene fusions cannot be considered for neoadjuvant immunotherapy approaches.

Mariano Provencio: No, I don't think so.

Erminia Massarelli: No, I do not think current biomarkers are needed considering that PD-L1 negative patient have good benefit as well. I believe we still need to discover reliable markers of response in PD-L1< or=50%.

Mara B. Antonoff: We know that PD-L1 status can help determine patients who are likely to do well, and we also know that patients with EGFR and ALK mutations are not likely to derive benefit, and would not include such patients on these trials when they can receive targeted therapy instead.

Toyoaki Hida: Yes: We think biomarker may be necessary in choosing neoadjuvant PD-1/PD-L1 blockade therapy in the case of single ICI use.

Candidate for biomarker: PD-1 CD8 T cells, PD-1 regulatory T (Treg) cells, frequency of PD-1 CD8 T cells relative to that of PD-1 Treg cells.

It may be not necessary in the cases of ICI use in combination with platinum-doublet chemotherapy, although it would be better to have biomarkers that can predict the effect.

Marc de Perrot: PD-L1 expression on tumor cell is a good biomarker when PD-1/PD-L1 is used as single therapy. However, biomarker may not be necessary when PD-1/PD-L1 blockade is combined with chemotherapy.

Steven H. Lin: We select for patients who shouldn't get immunotherapy, which are patients who have an oncogene driven mutation such as EGFR, ALK, ROS, RET. We don't select for other markers like PD-L1 status.

Massimo Di Maio: Very good question. It probably depends if we are talking about single agent PD-1/PD-L1 blockade or combination with chemotherapy. If combined with chemotherapy, based on the results obtained in the advanced setting, we could avoid a pre-treatment selection according to PD-L1 expression. In fact, we know that chemotherapy is an acceptable and effective strategy as neoadjuvant treatment, so the risk of undertreatment would be limited. On the other hand, in the case of single-agents, we know that a not negligible proportion of patients would be at risk of not obtaining a response, so a selection should be probably considered (with the only exception of a very short planned duration of treatment, which would not delay the timing of surgery), probably based on the PD-L1 expression. Unfortunately, evidence about biomarkers' role in this setting (including PD-L1 expression but also TMB) is not robust.

Antonio Rossi: Biomarkers should drive the treatment for any stage of NSCLC disease. Unfortunately, we do not have biomarkers for every subgroup of NSCLC patients. However, with the available data, in the neoadjuvant setting, no specific biomarker can help in defining the subgroup of patients which could much benefit by neoadjuvant immunotherapy. The potential role of PD-L1 expression and other potential biomarkers such as MSI or TMB, in this setting should be evaluated more extensively in the ongoing randomized trials, in order to have the possibility to select NSCLC patients who could much benefit from neoadjuvant immunotherapy.

Dirk de Ruysscher: At present, we do not have a good marker for concurrent chemo-PD-1/PD-L1 blockage, while for anti-PD-1/PD-L1 alone, tumor PD-L1 expression is still the best. There are many new developments such as the T-cell (CD8 and Treg) density on the initial tumor biopsy, which are promising.

Robert A. Ramirez: No. I suppose if someone were PD-L1 >50%, MSI high or high TMB that may sway me to use single agent IO, however, we run into lack of data as above. We also know the RR in the combination chemo/IO is higher in the metastatic setting regardless of biomarkers.

Wolfram C. M. Dempke: This is a controversial discussion. We follow the label of the IOs (have added this in the manuscript as well), but truly believe that additional biomarkers are urgently warranted (for new examples see my paragraph within the manuscript).

D. Ross Camidge: I suspect it may influence outcomes – the obvious cases would be ALK and EGFR.

Nicolas Guibert: No clear biomarker of response (including TMB and PD-L1) has been identified yet in the neoadjuvant setting like it has been well stated in the manuscript.

I would thus not recommend the use of biomarker to guide neoadjuvant ICI yet.

I would, however, like proposed in the manuscript, suggest to avoid neoadjuvant ICI monotherapy in patients with EGFR, ALK or STK11 alterations, given the low response rates observed in these populations in advanced stages.

This extrapolation may however need to be validated in clinical trials.

More endeavors are however needed to better select patients.

Raffaele Califano: PD-L1 using single agent PD-1/PD-L1 blockade. No need for biomarker if using neoadjuvant

Chemo + IO.

How do/will you determine the cycles of neoadjuvant PD-1/PD-L1 blockade therapy?

Rafael Rosell: At present, there is no pre-specified number of cycles. Two to four cycles are the recommendation.
Mariano Provencio: We use 3 cycles.
Erminia Massarelli: Usually Two to three cycles as per clinical trials guidelines.
Mara B. Antonoff: We believe anywhere from 2–4 cycles is beneficial, and the data don't yet define an optimal number. We don't use it outside of a clinical trial, so at this time, we use it for the designated amount of time based on the clinical trial. We need further data from these studies to decide the exact number of cycles.
Toyoaki Hida: 2-3 cycles depending on the degree of bone marrow suppression (degree of irAE).
Marc de Perrot: Two to four cycles are sufficient in the neoadjuvant setting.
Steven H. Lin: Standardly it has been as little as one cycle to 2 cycles, +/– chemotherapy. Neoadjuvant chemoradiation with IO is being explored as well.
Massimo Di Maio: I would determine the cycles of neoadjuvant PD-1/PD-L1 blockade according to the evidence produced by clinical trials.

In the case of combination with chemotherapy, I would have no problem to plan 3 or 4 cycles of treatment, considering that the risk of undertreatment should be negligible. In the case of immunotherapy alone, it would be necessary to avoid a long treatment that could increase the risk of disease progression. In this latter case, as a rule of thumb, I would limit the treatment to 1 month/1.5 months.
Antonio Rossi: Based on the available data and the design of the ongoing randomized trials, 2–4 cycles of neoadjuvant single-agent immunotherapy or combined with platinum-based chemotherapy should be appropriate.
Dirk de Ruysscher: The best for the future may be ctDNA, but this needs more development and especially standardization. Advanced quantitative imaging methods based on e.g., deep learning algorithms show great promise.
Robert A. Ramirez: I agree that 2 cycles of neoadjuvant treatment be followed by imaging and a multidisciplinary review to see when the right time for surgery should be. If responding following 2 cycles but still borderline resectable, then an additional 2 cycles could be beneficial.
Wolfram C. M. Dempke: It depends on the early responses seen—if there is a response, we normally go for 4 cycles with a re-evaluation after two cycles.
D. Ross Camidge: To date 2–4 cycles are given but the stress of delaying surgery has to be weighed against data.
Nicolas Guibert: The number of cycles will depend on the approvals obtained in France. It will follow the regimen studied in the RCT that will lead to this approval. The most appealing data have however been observed with ICI and chemo combinations, with 3 to 4 cycles.
Raffaele Califano: We will consider a cycle 3 or 4 weeks of treatment.

What adjuvant treatment regimen do/will you choose among those respond to neoadjuvant PD-1/PD-L1 blockade therapy?

Rafael Rosell: For responding patients with complete or major pathological response, adjuvant immunotherapy for 1 year could be recommended.
Mariano Provencio: We use carbo-taxol-nivolumab.
Erminia Massarelli: I continue same immunotherapy plus or minus chemotherapy. However if MPR is significant I only continue immunotherapy if patients were treated with IO alone as induction.
Mara B. Antonoff: This depends on the stage of disease. For those with early-stage disease, no need for adjuvant therapy. However, for recurrent disease, node positive disease, or large tumors that would otherwise get adjuvant systemic therapy, immunotherapy should be given to those with elevated PD-L1 expression.
Toyoaki Hida: We choose ICI used in the preoperative treatment.
Marc de Perrot: PD-1/PD-L1 blockade will be maintained in the adjuvant setting.
Steven H. Lin: Although chemotherapy is not used adjuvant even if it is given concurrently with immunotherapy, only the immunotherapy as a single agent is used in the adjuvant setting for most trials. Radiotherapy is used per the discretion of the trial, with some global trials excluding the use of postoperative radiotherapy for IIIA-N2 disease resected to negative margins.
Massimo Di Maio: We have no data to produce evidence-based recommendations. For patients who have not received chemotherapy, I would consider adjuvant chemotherapy according to current guidelines. For patients who have received chemotherapy as neoadjuvant treatment (i.e., combo of chemo + immuno), probably they could receive no further systemic treatment after surgery. I prefer waiting for clinical trials.

Antonio Rossi: Platinum-based doublets, if not received in neoadjuvant setting, should be considered the standard-of-care with or without PD-1/PD-L1 inhibitors as adjuvant treatment. At the moment, this combination approach is reserved for patients enrolled in clinical trials.
Dirk de Ruysscher: In case of an MPR or a pCR: the same anti-PD-1/PD-L1 as pre-operatively. In case no MPR or pCR was achieved: (I) if only neoadjuvant immunotherapy: 4 cycles of a platinum doublet depending on the histology of the tumor; (II) if concurrent chemotherapy and immunotherapy: no further adjuvant therapy or no systemic therapy has shown a benefit.
Robert A. Ramirez: If the patient has not received neoadjuvant chemo and only received IO then if adjuvant therapy is indicated then I would use a cisplatin-based regimen based on histology.
Wolfram C. M. Dempke: We believe that the adjuvant treatment regimen should be the same as used for the neoadjuvant setting, however without chemotherapy if already used in the neoadjuvant part.
D. Ross Camidge: Trial specific at present.
Nicolas Guibert: Again, the adjuvant regimen will depend on the approvals obtained in France that will follow the main RCTs' outcomes. Most trials were however designed with ana approximately 1-year adjuvant immunotherapy (13 additional pembrolizumab adjuvant cycles in the KEYNOTE 617, 16 cycles of atezolizumab in the IMPOWER 030) and it is very likely that this approach may be the most suited. It will also certainly depend on the pathological response (CR, MPR) and definitive pathological stage (pTNM) after surgery.
Raffaele Califano: We will give platinum/vinorelbine ×4 cycle.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-2020-63). The authors have no conflicts of interest to declare. The authors have no conflicts of interest to declare.

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