Consensus

International expert consensus on immunotherapy for early-stage non-small cell lung cancer

Wenhua Liang[1], Kaican Cai[2], Qingdong Cao[3], Chun Chen[4], Haiquan Chen[5], Jun Chen[6], Ke-Neng Chen[7], Qixun Chen[8,9], Tianqing Chu[10], Yuchao Dong[11], Jiang Fan[12,13], Wentao Fang[14], Junke Fu[15], Xiangning Fu[16], Shugeng Gao[17], Di Ge[18], Guojun Geng[19], Qing Geng[20], Jie He[17], Jian Hu[21], Jie Hu[22], Wei-Dong Hu[23], Feng Jiang[24], Tao Jiang[25], Wenjie Jiao[26], He-Cheng Li[27], Qiang Li[28], Shanqing Li[29], Shuben Li[1], Xiangnan Li[30], Yong-De Liao[31], Changhong Liu[32], Hongxu Liu[33], Yang Liu[34], Zhuming Lu[35], Qingquan Luo[36], Haitao Ma[37], Xiaojie Pan[38], Guibin Qiao[39], Shengxiang Ren[40], Weiyu Shen[41], Yong Song[42], Daqiang Sun[43], Guangsuo Wang[44], Jie Wang[45], Mengzhao Wang[46], Qiwen Wang[47], Wen-Xiang Wang[48], Li Wei[49], Ming Wu[50], Nan Wu[51], Hui Xia[52], Shi-Dong Xu[53], Fan Yang[54], Kang Yang[55], Yue Yang[56], Fenglei Yu[57], Zhen-Tao Yu[58], Dong-Sheng Yue[59], Lanjun Zhang[60], Weidong Zhang[61], Zhenfa Zhang[62], Guofang Zhao[63], Jian Zhao[64], Xiaojing Zhao[65], Chengzhi Zhou[66], Qinghua Zhou[67], Kunshou Zhu[68], Yuming Zhu[69], Toyoaki Hida[70], Wolfram C. M. Dempke[71], Antonio Rossi[72], Marc de Perrot[73], Robert A. Ramirez[74], Mariano Provencio[75], Jay M. Lee[76], Antonio Passaro[77], Lorenzo Spaggiari[78,79], Jonathan Spicer[80], Nicolas Girard[81], Patrick M. Forde[82], Tony S. K. Mok[83], Tina Cascone[84], Jianxing He[1]; on behalf of CATO consensus group

[1]Department of Thoracic Surgery and Oncology, The First Affiliated Hospital of Guangzhou Medical University, National Center for Respiratory Medicine, State Key Laboratory of Respiratory Disease and National Clinical Research Center for Respiratory Disease, Guangzhou, China; [2]Department of Thoracic Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, China; [3]Department of Thoracic Surgery, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China; [4]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou, China; [5]Department of Thoracic Surgery and State Key Laboratory of Genetic Engineering, Fudan University Shanghai Cancer Center, Shanghai, China; [6]Department of Lung Cancer Surgery, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, Tianjin, China; [7]Department of Thoracic Surgery, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China; [8]Department of Thoracic Surgery, Cancer Hospital of University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China; [9]Institute of Cancer and Basic Medicine (IBMC), Chinese Academy of Science, Hangzhou, China; [10]Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [11]Department of Respiratory and Critical Care Medicine, Shanghai Changhai Hospital, The First Affiliated Hospital of Second Military Medical University, Shanghai, China; [12]Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; [13]Department of Thoracic Surgery, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai, China; [14]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [15]Department of Thoracic Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [16]Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [17]Thoracic Surgery Department, National Cancer Center–National Clinical Research Center for Cancer–Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [18]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China; [19]Department of Thoracic Surgery, Xiamen Key Laboratory of Thoracic Tumor Diagnosis and Treatment, Institute of Lung Cancer, The First Affiliated Hospital of Xiamen University, School of Clinical Medicine, Fujian Medical University, Xiamen, China; [20]Department of Thoracic Surgery, Renmin Hospital of Wuhan University, Wuhan, China; [21]Department of Thoracic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [22]Department of Pulmonary Medicine, Zhongshan Hospital, Fudan University, Shanghai, China; [23]Department of Thoracic Surgery, Zhongnan Hospital of Wuhan University, Wuhan, China; [24]Department of Thoracic Surgery, Nanjing Medical University Affiliated Cancer Hospital & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China; [25]Department of Thoracic Surgery, Tangdu Hospital, Air Force Medical University, Xi'an, China; [26]Department of Thoracic Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China; [27]Department of Thoracic Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [28]Department of Thoracic Surgery, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China; [29]Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [30]Department of Thoracic Surgery, First Affiliated Hospital of Zhengzhou University, Zhengzhou,

© Translational Lung Cancer Research. All rights reserved.

China; [31]Department of Thoracic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [32]Department of Thoracic Surgery, The Second Hospital of Dalian Medical University, Dalian, China; [33]Department of Thoracic Surgery, Cancer Hospital of China Medical University, Cancer Hospital of Dalian University of Technology, Liaoning Cancer Hospital & Institute, Shenyang, China; [34]Department of Thoracic Surgery, Chinese People's Liberation Army General Hospital, Beijing, China; [35]Department of Cardiothoracic Surgery, Jiangmen Central Hospital, Jiangmen, China; [36]Department of Thoracic Surgery, Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiaotong University, School of Medicine, Shanghai, China; [37]Department of Thoracic Surgery, The First Affiliated Hospital of Soochow University, Suzhou, China; [38]Department of Thoracic Surgery, Shengli Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou China; [39]Division of Thoracic Surgery, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, The Second School of Clinical Medicine, Southern Medical University, Shantou University Medical College, Guangzhou, China; [40]Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; [41]Department of Thoracic Surgery, Ningbo Medical Center Lihuili Hospital, Ningbo University, Ningbo, China; [42]Department of Respiratory Medicine, Jinling Hospital, Nanjing Medical University, Nanjing, China; [43]Department of Thoracic Surgery, Tianjin Chest Hospital, Tianjin, China; [44]Department of Thoracic Surgery, The First Affiliated Hospital of Southern, University of Sciences and Technology, Shenzhen People's Hospital, Shenzhen, China; [45]Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [46]Department of Respiratory and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China; [47]Department of Thoracic Oncosurgery, Jilin Province Tumor Hospital, Changchun, China; [48]Department of Thoracic Surgery II, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University/Hunan Cancer Hospital, Changsha, China; [49]Department of Thoracic Surgery, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, People's Hospital of Henan University, Zhengzhou, China; [50]Department of Thoracic Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [51]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Thoracic Surgery II, Peking University Cancer Hospital & Institute, Beijing, China; [52]Department of Cardiothoracic Surgery, The Fourth Medical Center of PLA General Hospital, Beijing, China; [53]Department of Thoracic Surgery, Harbin Medical University Cancer Hospital, Harbin, China; [54]Department of Thoracic Surgery, Peking University People's Hospital, Beijing, China; [55]Department of Thoracic Surgery, GuiQian International General Hospital, Guiyang, China; [56]Department of Thoracic Surgery II, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; [57]Department of Thoracic Surgery, The Second Xiangya Hospital of Central South University, Changsha, China; [58]Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China; [59]Department of Lung Cancer, Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China; [60]Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China; [61]Department of Thoracic Surgery, Tianjin First Central Hospital, School of Medicine, Nankai University, Tianjin, China; [62]Department of Lung Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China; [63]Department of Thoracic Surgery, Hwa Mei Hospital, University of Chinese Academy of Sciences, Ningbo, China; [64]Department of Thoracic Surgery, Affiliated Cancer Hospital and Institute of Guangzhou Medical University, Guangzhou, China; [65]Department of Thoracic Surgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [66]State Key Laboratory of Respiratory Disease, National Clinical Research Centre for Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China; [67]Lung Cancer Center/Lung Cancer Institute, West China Hospital, Sichuan University, Chengdu, China; [68]Department of Thoracic Surgery, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, China; [69]Department of Thoracic Surgery, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China; [70]Lung Cancer Center, Central Japan International Medical Center, Minokamo, Japan; [71]Department of Hematology and Oncology, University Medical School, Munich, Germany; [72]Oncology Center of Excellence, Therapeutic Science & Strategy Unit, IQVIA, Milan, Italy; [73]Division of Thoracic Surgery, Toronto General Hospital and Princess Margaret Cancer Centre, Toronto, ON, Canada; [74]Department of Internal Medicine, Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN, USA; [75]Service of Medical Oncology, Puerta del Hierro University Hospital of Madrid, Madrid, Spain; [76]Division of Thoracic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [77]Division of Medical Oncology, European Institute of Oncology IRCCS, Milan, Italy; [78]Department of Thoracic Surgery, IEO, European Institute of Oncology IRCCS, Milan, Italy; [79]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; [80]Division of Thoracic Surgery, Department of Surgery, McGill University Health Centre, Montreal, QC, Canada; [81]Thoracic Oncology Service, Thorax Institute Curie Montsouris, Institut Curie, Paris, France; [82]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [83]Department of Clinical Oncology, State Key Laboratory

© Translational Lung Cancer Research. All rights reserved.

of South China, Chinese University of Hong Kong, Shatin, Hong Kong, China; [84]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Correspondence to: Jianxing He. National Center for Respiratory Medicine, China State Key Laboratory of Respiratory Disease and National Clinical Research Center for Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China. Email: drjianxing.he@gmail.com.

Submitted Jun 07, 2022. Accepted for publication Sep 26, 2022.
doi: 10.21037/tlcr-22-617
View this article at: https://dx.doi.org/10.21037/tlcr-22-617

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide and in China (1). According to the National Cancer Center of China, there were more than 815,000 new cases of lung cancer and 714,000 lung cancer-related deaths in 2020 (2), making lung cancer the most prevalent and lethal malignancy in China (3). Non-small cell lung cancer (NSCLC) is the main pathological type of lung cancer, accounting for about 80–85% of all lung cancer cases (4). Although surgery is the mainstay of treatment for early-stage NSCLC, 30–55% of patients experience recurrence despite curative resection (5,6). Over 20% of NSCLC patients with stage I, 50% with stage II, and a staggering 60% with stage IIIA die from disease progression within 5 years despite receiving curative-intent surgery (7). In surgically resected patients, the risk of distant metastases may even be greater than the risk of local and regional recurrence suggesting that there is an urgent need for an earlier and better systemic control. Perioperative chemotherapy has been used in patients with resectable locally advanced NSCLC. However, studies have shown that neoadjuvant or adjuvant chemotherapy can only increase the 5-year overall survival rate by about 5% (8,9). The modest benefit relative to high toxicities often results in poor patient compliance (10).

The development of immune checkpoint inhibitors (ICIs) is a revolutionary milestone in the field of immuno-oncology. ICIs reinvigorate antitumor immune responses by interrupting co-inhibitory signaling pathways and promote immune-mediated elimination of tumor cells. Multiple studies have shown that ICIs provide long-term survival benefits for patients with oncogenic driver negative advanced and unresectable locally advanced NSCLC (11-18). Preliminary studies have suggested that immunotherapy may play a promising role in treating patients with resectable NSCLC. Neoadjuvant immunotherapy can utilize higher levels of endogenous tumor antigens in the intact tumor to enhance T-cell priming, leading to more tumor-specific T-cell activation in the circulation and thereby exerting stronger anti-tumor effects and reducing postoperative relapse (19,20). On the other hand, adjuvant immunotherapy can further activate effector T cells and modulate the post-operative immunosuppressive status (21). In recent years, immunotherapy has been extensively explored in the treatment of early-stage NSCLC.

In the past, several phase II studies (22-26) examining the roles of neoadjuvant immune-based therapy have generally confirmed the short-term pathological response benefits of immunotherapy alone or in combination with chemotherapy. However, many clinical controversies remain to be clarified when adopting immunotherapy for early NSCLC, including patient population, timing of immunotherapy in relation to surgery, predictive biomarkers, treatment duration, etc. With the recent results of phase III clinical studies (27-29), immunotherapy has begun to revolutionize the treatment landscape for patients with resectable early-stage NSCLC. To better guide Chinese thoracic surgeons in the immunotherapy of early-stage NSCLC, well-known thoracic surgeons in China and abroad, as well as international thoracic medical oncologists, were invited to participate in an in-depth discussion on the hot topics and controversial issues of immunotherapy for early-stage NSCLC, and accordingly, this international expert consensus was developed by incorporating the latest evidence.

Consensus 1: Neoadjuvant immunotherapy combined with chemotherapy, or adjuvant immunotherapy (after adjuvant chemotherapy) can be used for patients with resectable stage II–IIIA NSCLC

CheckMate 816 (27) is a phase III randomized controlled trial designed to evaluate the efficacy and safety of 3 cycles

© Translational Lung Cancer Research. All rights reserved.

of nivolumab plus platinum-doublet chemotherapy as neoadjuvant therapy in treating adult patients with epidermal growth factor receptor (*EGFR*)/anaplastic lymphoma kinase (*ALK*)-negative resectable NSCLC (tumor ≥4 cm or lymph node positive). Nivolumab plus chemotherapy significantly improved the co-primary endpoint (pathological complete response, pCR) compared with chemotherapy alone [24% *vs.* 2.2%; odds ratio (OR) = 13.94; 99% confidence interval (CI): 3.49–55.75; P<0.0001], and the combination was safe and tolerable. The event-free survival (EFS), which was another primary endpoint, was also significantly improved. The median EFS was 31.6 months [95% CI: 30.2 months–not reached (NR)] in the nivolumab plus chemotherapy group and 20.8 months (95% CI: 14.0–26.7 months) in the chemotherapy alone group [hazard ratio (HR): 0.63; 95% CI: 0.43–0.91; P<0.005] (30). Based on this study, the United States (USA) Food and Drug Administration (FDA) approved nivolumab in combination with platinum-based doublet chemotherapy as neoadjuvant therapy for the treatment of adult patients with resectable NSCLC (tumor ≥4 cm or node-positive).

Several phase III studies are currently underway in the adjuvant setting, two of which recently announced positive results. IMpower010 (28) is a randomized, multi-center, open-label, phase III study. The eligible patients were diagnosed with stage IB (tumors ≥4 cm) to IIIA NSCLC in accordance with 7th edition of the Union Internationale Contre le Cancer and American Joint Committee on Cancer (UICC/AJCC) staging system. Efficacy and safety were evaluated in patients who were randomly assigned to receive adjuvant atezolizumab (up to 16 cycles) or best supportive care (BSC) after complete resection and adjuvant chemotherapy. Data showed that atezolizumab significantly improved disease-free survival (DFS) compared with BSC in stage II–IIIA patients with programmed death-ligand 1 (PD-L1) was expressed on 1% or more of tumor cells (HR: 0.66; 95% CI: 0.50–0.88; P=0·0039) with 3-year DFS rate of 60% in the treatment arm compared with 48.2% in the BSC arm, meeting one of its endpoints of this study. Notably, for patients with tumor expression of PD-L1 1–49% atezolizumab did not lead to a statistically significant DFS improvement, suggesting that much of the benefit was driven by the population of NSLCs with high PD-L1 expression (≥50%). Accordingly, the US FDA has approved atezolizumab for use as an adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥1% of tumor cells. The European Medicines Agency was even more restrictive with an approval of atezolizumab for the use only in patients with stage II to IIIA NSCLC whose tumors have PD-L1 ≥50% expression.

In addition, the randomized, controlled, triple-blind phase III study KEYNOTE-091 (29) also announced its interim results, confirming the benefit of immunotherapy in adjuvant setting. KEYNOTE-091 was designed to evaluate the efficacy of adjuvant pembrolizumab (18 cycles) versus placebo after R0 resection (adjuvant chemotherapy was not mandatory) in treating stage IB (tumor ≥4 cm) to IIIA NSCLC (as per the UICC/AJCC staging system version 7). The dual primary endpoints were DFS in overall population (regardless of PD-L1 expression status) and that of patients with high PD-L1 expression [tumor proportion score (TPS) ≥50%]. Pembrolizumab was found to significantly improve DFS in the overall population, with a median DFS of 53.6 months, which was significantly superior to that in the placebo group (median DFS, 42.0 months; HR 0.76; 95% CI: 0.63–0.91; P=0.0014). For patients with high PD-L1 expression, pembrolizumab showed a favorable trend, but the pre-specified statistical difference was not reached. Key subgroup analyses showed consistent beneficial trends. Safety profiles are as expected with no new safety signals identified in the pembrolizumab group. The OS data is not yet mature. Thus, pembrolizumab reduces the risk of recurrence or death in patients with resectable NSCLC, regardless of PD-L1 expression level, and could be a new option for postoperative adjuvant therapy in patients with operable stage IB–IIIA (per UICC/AJCC version 7) NSCLC.

As shown in the currently available data, either neoadjuvant or adjuvant immunotherapy can provide benefits to patients with early-stage NSCLC. In terms of prioritization of neoadjuvant immune checkpoint blockade [anti-PD-(L)1 therapy] as monotherapy versus combined with chemotherapy, evidence clearly reveals an increased rate of pCR with the addition of chemotherapy to PD-(L)1 blockade and highly encouraging survival outcomes (DFS or EFS or PFS) (22,23,25-27,31-35). It is conceivable, therefore, that this improved pCR will translate into long-term OS benefits. Most of the studies evaluating neoadjuvant single-agent ICI revealed it to be safe and feasible before curative-intent surgery. The NEOSTAR randomized study tested neoadjuvant nivolumab alone or combined with ipilimumab (36). The treatments were feasible with an overall manageable toxicity profile and the combination demonstrated promising major pathologic response (MPR) and pCR rates. However, a study reported by Reuss *et al.* (37) showed that neoadjuvant ipilimumab

© Translational Lung Cancer Research. All rights reserved.

plus nivolumab underwent early termination of the study arm. Although the combination was feasible, 67% of patients experienced AEs with 33% being grade 3 or higher. These conflicting safety signals may be related to specific clinicopathological and tumor molecular characteristics of the patient populations. Additional trials testing combination of multiple immune pathway inhibition (38,39) will inform us on the efficacy of immunotherapy combinations and on the patient populations who are most likely to derive clinical benefit.

The ultimate goal in early-stage NSCLC should be improving OS. Several on-going phase III studies are evaluating perioperative immunotherapy (neoadjuvant + adjuvant immunotherapy), including KEYNOTE-671 (NCT03425643), IMpower-030 (NCT03456063), AEGEAN (NCT03800134), and CheckMate-77T (NCT04025879). None of these trials, except KEYNOTE-671, include OS as a co-primary endpoint.

We recommend the use of neoadjuvant immunotherapy combined with chemotherapy or adjuvant immunotherapy (monotherapy) after platinum-based chemotherapy in patients with resectable stage II–IIIA NSCLC.

Consensus 2: There are no confirmatory biomarkers that uniformly predict the efficacy of neoadjuvant chemo-immunotherapy. Neoadjuvant/adjuvant immunotherapy should not be used routinely in patients with *EGFR* mutations/*ALK* fusions

For advanced NSCLC, PD-L1 is currently the most widely used predictive biomarker. The results of KEYNOTE-024 and KEYNOTE-042 showed that pembrolizumab monotherapy was superior to standard chemotherapy in patients with PD-L1 ≥50% and PD-L1 ≥1%, respectively (40,41). The IMpower110 study showed that atezolizumab monotherapy was superior to standard chemotherapy in patients with driver-mutation negative NSCLC patients with high PD-L1 expression (TC3/IC3) (42). Accordingly, most guidelines recommend PD-L1 as a companion diagnostic marker for immunotherapy in patients with driver-mutation negative advanced NSCLC. A variety of biomarkers have been explored in previous phase I/II trials on immunotherapy for early-stage NSCLC, but with inconsistent findings. With the release of more data from phase III trials, some new evidence on the biomarkers of immunotherapy for early-stage NSCLC has become available.

Subgroup analysis in the CheckMate 816 showed that nivolumab plus chemotherapy was beneficial in terms of pCR and EFS in patients with different PD-L1 expression levels, especially in the subgroup with PD-L1 ≥50% (30). IMpower010 study confirmed that atezolizumab provided a significant DFS benefit in patients with PD-L1 tumor cell (TC) ≥1%, and subgroup analysis also demonstrated that patients with PD-L1 ≥50% had the most prominent benefit (28), while patients with negative PD-L1 expression experienced no benefit (HR: 0.97; 95% CI: 0.72–1.31). However, KEYNOTE-091 demonstrated that adjuvant pembrolizumab provided DFS benefits regardless of PD-L1 expression levels (29). Therefore, the predictive value of PD-L1 expression level for the efficacy of immunotherapy for early-stage NSCLC remains to be confirmed.

In recent years, with the rapid development of gene sequencing technology, circulating tumor DNA (ctDNA) has become a hot research topic. In an exploratory subgroup analysis of ctDNA clearance rate in the CheckMate 816 study, patients who achieved ctDNA clearance on the first day of the third cycle had a higher pCR rate than patients whose ctDNA was not cleared (27), suggesting that ctDNA may be predictive of the tumor response. In contrast, Zhou *et al.* (43) reported in the IMpower010 study that, regardless of whether ctDNA-minimal residual disease (MRD) was positive or negative, adjuvant atezolizumab could provide DFS benefit. Thus, the predictive value of ctDNA remains controversial.

For advanced NSCLC with positive driver aberrations such as *EGFR* mutation and *ALK* rearrangements, targeted therapy have provided remarkable efficacy and are the current standard treatment of choice. Based on the findings of the ADAURA study and EVIDENCE study, osimertinib and icotinib are approved for adjuvant treatment of *EGFR* mutation-positive resectable early-stage NSCLC after radical surgery, and this has also been recommended by the Chinese Society of Clinical Oncology (CSCO) guidelines (44). In the IMpower010 study (28), 117 patients with *EGFR* mutations and 33 patients with *ALK* rearrangements were included. For patients with stage II–IIIA NSCLC, subgroup analysis showed that patients with *EGFR/ALK* aberrations were less likely to benefit from adjuvant atezolizumab compared to those without mutations. KEYNOTE-091 also included patients with *EGFR/ALK* aberrations. Subgroup analysis revealed that patients with *EGFR* mutations (n=73) showed a trend favoring pembrolizumab (HR: 0.44; 95% CI: 0.23–0.84), which was more prominent than that in patients without *EGFR* mutations (n=434) (HR: 0.78; 95% CI: 0.59–

© Translational Lung Cancer Research. All rights reserved.

1.05) (29). At present, there are no phase III trial data on neoadjuvant immunotherapy for patients with *EGFR/ALK* aberrations. Whether patients with *EGFR/ALK*-positive early-stage NSCLC will benefit from immunotherapy warrants further investigations.

Currently, there is no consistent evidence that molecular markers uniformly predict the efficacy of neoadjuvant/adjuvant immunotherapy. The role of driver genes such as *EGFR* and *ALK* in perioperative immunotherapy for early-stage NSCLC is not yet clear. Based on the currently available data and approved indications, it is recommended that neoadjuvant/adjuvant immunotherapy should not be used routinely in patients with *EGFR* mutations/*ALK* fusions.

Consensus 3: Three cycles of neoadjuvant chemo-immunotherapy are recommended, and the treatment course may be refined when taking account of therapy response, tolerance and surgery difficulties

The purpose of neoadjuvant therapy is to downstage tumors, increase R0 rate, and treat sub-clinical micro-metastases at the earliest time point in the therapeutic course. A short course of neoadjuvant immune-based therapy may not be adequate to take effect. If the duration of therapy is prolonged, however, the disease may unfortunately progress which leads to the loss of surgical window of opportunity, making the duration of neoadjuvant treatment a critical issue. A pre-clinical study (45) 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 treatment. 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 different clinical trials. At present, the effects of neoadjuvant immune-based therapy on early-stage NSCLC have been demonstrated in multiple phase I/II clinical trials, with one phase III trial recently releasing its findings. The neoadjuvant single-agent immunotherapy in the CheckMate 159, LCMC3, and TOP1501 trial was administered for 2 cycles, and surgery was performed 28–56 days after the first cycle (23,33,34). Neoadjuvant therapy with immunotherapy plus chemotherapy (CheckMate 816, NADIM, NCT02716038 and SAKK 16/14) or dual immunotherapy (NEOSTAR) was administered for 2 to 4 cycles, and surgery was performed 3–7 weeks after the end of the neoadjuvant therapy (22,25-27,36,46). Retrospective studies (47,48) also showed that most patients with early-stage NSCLC received neoadjuvant immunotherapy 1–4 weeks before surgery. In another real-world study (49), larger tumor diameter, higher ypN stage, and no MPR after neoadjuvant therapy were associated with worse prognosis. Therefore, under the premise of balancing the difficulty of surgery, an appropriate extension of the treatment course may further reduce the tumor diameter, lower the stage, and provide survival benefits. At present, the duration of neoadjuvant immune-based therapy has not been fully elucidated. Given the phase III data from CheckMate 816, three cycles are recommended for neoadjuvant chemo-immunotherapy. Treatment course may be refined when balancing treatment efficacy and surgery timing in clinical practice.

Consensus 4: The benefit from neoadjuvant immunotherapy can be assessed by positron-emission tomography (PET)-computed tomography (CT), in conjunction with circulating tumor DNA (ctDNA) level and/or serum tumor markers, if available

CT is a routine radiographic modality for assessing response in patients with NSCLC exposed to conventional anti-cancer therapy. The Response Evaluation Criteria in Solid Tumors (RECIST) by CT has been widely adopted and the standard for defining response to treatment (50). However, in 41–45% of patients, the pathological response was found to be inconsistent with the CT findings (23,36,51,52). Changes in inflammation and interstitial or fibrotic components of tumors may affect the CT results, compromising the ability of CT imaging to accurately predict histopathological responses after neoadjuvant therapy. It was suggested that PET-CT provided more useful information on assessing response of advanced NSCLC to immunotherapy than that of CT (53). A recent study suggested that ^{18}F-FDG PET-CT can predict MPR to neoadjuvant anti-PD-1 agent in resectable NSCLC (51). Therefore, PET-CT in assessing immunotherapy response to NSCLC seems to be a valuable in clinical application. However, patients treated with neoadjuvant ICIs may demonstrate radiologically abnormal nodes post-therapy (e.g., nodal immune flare, NIF) that are devoid of cancer upon pathological evaluation. This apparent radiological progression in lymph nodes may occur due to an inflammatory response after neoadjuvant immunotherapy, and such cases should be evaluated by

© Translational Lung Cancer Research. All rights reserved.

pathological examination to distinguish NIF from true nodal progression and to ensure appropriate clinical treatment planning (52).

In addition, incorporating ctDNA or serum tumor markers with imaging may be associated with improved prognosis in NSCLC patients. The CheckMate 816 study (27) evaluated the potential role of ctDNA as a predictive biomarker for neoadjuvant immunotherapy. The results showed that the ctDNA clearance rate in the nivolumab plus chemotherapy group was higher than that in the chemotherapy alone group and might be related to pCR. In addition, an exploratory analysis of the NADIM study (54) showed that pre-treatment ctDNA analysis could identify patients at high risk of progression and was superior to imaging in predicting survival (RECIST v1.1 criteria). On the other hand, postoperative detection of molecular residual disease (MRD) based on ctDNA has demonstrated potential for monitoring lung cancer recurrence and predict prognosis (55). The Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq) study (56) analyzed CAPP-seq ctDNA in 255 blood samples from 40 patients with stage IB–III locally advanced lung cancer, and ctDNA was shown to detect MRD effectively in patients with locally advanced lung cancer after surgery and was earlier than standard imaging in identifying residual/recurrent diseases. The TRACERx study (57) included 24 patients with early-stage lung cancer who received surgical resection and underwent ctDNA monitoring before and after surgery. ctDNA was detected in 92.9% (13/14) of the patients with recurrence before or at the time of recurrence, but was detected in only 1 of 10 patients who did not experience recurrence. Similar results were observed in the MRDetect (58) and DYNAMIC studies (59). In addition, a retrospective study showed that in locally advanced NSCLC, ctDNA-MRD may serve as a predictor to guide treatment plan as it can predict ICI benefit after chemoradiation therapy (60). Therefore, in patients who received neoadjuvant immunotherapy, positive ctDNA-MRD after radical resection of early-stage NSCLC may indicate a high risk of recurrence and such patients require close follow-up, and the escalation of treatment may be considered (61).

In summary, the benefit from neoadjuvant immunotherapy can be assessed by PET-CT, in conjunction with ctDNA and/or serum tumor markers if available.

Consensus 5: Surgery can be performed 4–6 weeks after the last cycle of neoadjuvant immunotherapy, whereas adjuvant immunotherapy can be administered 3–8 weeks after surgery or adjuvant chemotherapy

Determining the timing of surgery after neoadjuvant immunotherapy is critical. Early surgery may lead to serious surgical complications, while delayed surgery may lead to tumor progression. Before determining the timing for neoadjuvant immunotherapy and surgery, it is important to understand the T cell proliferation cycle, the best time for effector cells to function, and when tumor resection has minimal impact on antitumor immunity, which are very challenging experimentally. However, studies (62) have shown that it is possible to measure human antigen-specific T cell responses over time by systematic deuterium labeling, although further basic and clinical trials are still needed to determine the optimal timing of surgery. Although the results of neoadjuvant immune-based therapy for early-stage NSCLC are mostly from phase II trials, they are still informative. In CheckMate159, LCMC3, and TOP1501, surgery was performed 1–5 weeks after the completion of neoadjuvant single-agent immunotherapy (23,33,34). In CheckMate 816, NADIM, SAKK16/14, NCT02716038 and NEOSTAR, surgery was performed 3–7 weeks after the completion of the neoadjuvant treatment (22,25-27,36,46). A recent meta-analysis (63) included 18 publications from 16 studies, in which a total of 548 NSCLC patients received neoadjuvant immunotherapy, 507 of whom underwent surgery. The interval from the final dose of immunotherapy to the surgery was 27–32 days, and 2.0% of patients had their surgery delayed.

For postoperative adjuvant immunotherapy, IMpower010 required 1–4 cycles of platinum-based adjuvant chemotherapy for the enrolled patients before randomization. Up to 16 cycles (or one year) of adjuvant atezolizumab was administered 3–8 weeks after the last chemotherapy. In KEYNOTE-091 study, postoperative adjuvant chemotherapy was considered for stage IB NSCLC (T ≥4 cm, AJCC 7th) and strongly recommended for stage II and IIIA tumors (for up to 4 cycles). Subsequently, adjuvant pembrolizumab was used for no more than 18 cycles.

In summary, surgery can be performed 4–6 weeks

© Translational Lung Cancer Research. All rights reserved.

after the last cycle of neoadjuvant immunotherapy, while adjuvant immunotherapy can be administered 3–8 weeks after surgery or adjuvant chemotherapy.

Consensus 6: Although neoadjuvant immunotherapy has no prominent impact on surgical operation and its safety, attention should be drawn to some rare risks

Several clinical trials have shown that surgery after neoadjuvant radiotherapy or chemotherapy is safe and feasible, however, may cause tissue adhesions and thus increase the difficulty of surgery. Recent phase II studies on neoadjuvant immunotherapy (23,32,34,36,64,65) showed that the incidence of adverse events of any grade caused by neoadjuvant single-agent immunotherapy was 23–62%, the incidence of grade 3 or higher adverse events was 4.5–13%, and the completion rate of scheduled surgeries was 88–100%, which were similar to the data of previous neoadjuvant chemotherapy and radiotherapy studies (23,46,66,67). The phase III CheckMate 816 study (27) showed that the completion rate of scheduled surgeries in patients received neoadjuvant immunotherapy was 83%. The incidence of adverse events of any grade was 82%, and the incidence of grade 3 or higher adverse events was 34%, which was similar to patients with chemotherapy alone, suggesting that neoadjuvant immunotherapy combined with chemotherapy has a tolerable safety profile without undermining the feasibility of surgery. The NEOSTAR (46) study evaluated the surgical difficulty and lung function after neoadjuvant immunotherapy and found that ICIs had little impact on surgical resection rate and surgical complexity, and had no adverse impact on perioperative prognosis. A retrospective analysis (68) of 19 patients from the United States showed that lung resection after neoadjuvant immunotherapy is feasible in patients with metastatic or unresectable NSCLC, with high R0 rate and rare complication. The current evidence shows that neoadjuvant immunotherapy has less impact on surgical operation and its safety. In summary, although neoadjuvant immunotherapy has no prominent impact on surgical operation and its safety, it must be cautioned that there may be some rare risks.

Consensus 7: For non-progressive patients after receiving neoadjuvant chemo-immunotherapy, adjuvant immunotherapy can be considered for up to one year after surgery

At present, there is no clear conclusion on what the best treatment modality for immunotherapy is for early-stage NSCLC (whether it should be used in neoadjuvant or adjuvant setting, or both). In the IMpower010 study, the adjuvant immunotherapy arm received atezolizumab 1200 mg q3w for 16 cycles (or 1 year) after 1–4 cycles of adjuvant chemotherapy. In the KEYNOTE-091 study, subjects received 18 cycles (or 1 year) of adjuvant pembrolizumab 200 mg q3w after surgery. These two phase III studies clearly demonstrated that 1-year adjuvant immunotherapy could provide benefits. In addition, NADIM trial recently released results of the planned secondary endpoint of 3-year OS rate, showing that for IIIA patients treated with neoadjuvant chemotherapy plus nivolumab, followed by adjuvant nivolumab monotherapy (78.4% of patients completed 14–17 cycles of adjuvant treatment), OS at 36 and 42 months was as 91.0% and 87.3%, respectively (69), which is higher than prior studies evaluating neoadjuvant approaches. Although it remains to be determined how much adjuvant nivolumab contributes to the OS, NADIM trial suggested that neoadjuvant immunotherapy followed by adjuvant immunotherapy was feasible and can provide favorable survival benefit. several phase III clinical trials evaluating perioperative immunotherapy are still ongoing.

Based on the data concerning adjuvant immunotherapy for resectable NSCLC for non-progressive patients after receiving neoadjuvant immunotherapy, adjuvant immunotherapy can be considered for up to one year after surgery, especially for those who presented with high risks of recurrence upon pathological evaluation on resected specimens.

Consensus 8: Pathological response (MPR, pCR) should be assessed, recorded, and reported by specialized pathologists after neoadjuvant immunotherapy

It has been recognized that pathological response after neoadjuvant chemotherapy associates with overall survival

© Translational Lung Cancer Research. All rights reserved.

in patients with NSCLC (70). Using pathological response to neoadjuvant therapy as a surrogate for survival may improve the efficiency of trials and expedite advances. MPR (10% or less residue viable tumor) has been proposed as a surrogate endpoint in neoadjuvant trials for resectable NSCLC (71). In a retrospective study of 192 patients treated with neoadjuvant chemotherapy and 166 patients treated with surgery upfront, data showed a 19% MPR rate to neoadjuvant chemotherapy and improved survival in patients who achieved MPR at surgery compared to those who did not. Similar findings have since been reproduced in other studies (72-74).

When it comes to neoadjuvant immune-based therapy, some intertrial variability in MPR is present. Several studies have reported MPR rates to neoadjuvant PD-1/PD-L1 inhibitors either as monotherapy or in combination with CTLA-4 blockade or platinum-based chemotherapy. Two doses of neoadjuvant nivolumab resulted in a 45 % MPR rate in 20 resected NSCLC patients with no major delays in surgery (23). In the LCMC3 study two cycles of neoadjuvant atezolizumab induced a 20% MPR rate in patients with resected NSCLC and 6% of evaluable patients had a pCR (34). Two cycles of neoadjuvant durvalumab monotherapy induced a MPR rate of 6.7% in 30 early-stage NSCLC (75).

Results of NEOSTAR trial showed that, in the intention to treat population nivolumab monotherapy produced a 22% MPR rate, including two patients with pCR, and the dual ICIs regimen produced a 38% rate of MPR including six patients with pCR (36). As for neoadjuvant chemoimmunotherapy, Atezolizumab combined with chemotherapy has induced MPR rates of 57% including 10% patients with pCR (26). In the NADIM study the combination of nivolumab plus chemotherapy resulted in a MPR rate of 83% and a pCR rate of 63% in the resected population of patient (25). The phase III CheckMate 816 study showed that compared with chemotherapy alone, nivolumab plus chemotherapy significantly improved rate of MPR (36.9% *vs.* 8.9%) and pCR (24% *vs.* 2.2%) (27).

As shown above, studies of neoadjuvant immune-base immunotherapy are promising but some intertrial variability in MPR and pCR is present. Whether this variability is due to differing sample sizes, tumor burden, tumor histologies, timing and types of neoadjuvant therapies remains unknown. It was suggested that assessing pathological features of immune-mediated regression may be beneficial for improving interobserver consistency when evaluating tumor response following neoadjuvant ICIs (76). The International Association for the Study of Lung Cancer (IASLC) has outlined detailed recommendations on how to process lung cancer resection specimens and to define pathologic response including MPR and pCR following neoadjuvant therapy including immunotherapy (77).

In summary, pathological response (MPR, pCR) should be assessed, recorded, and reported by specialized pathologists after neoadjuvant immunotherapy.

Consensus 9: Immunotherapy with chemotherapy as induction therapy may be considered for selected cases of unresectable locally advanced NSCLC, and the feasibility of surgery should be reevaluated after the treatment

The standard treatment for stage III unresectable NSCLC is maintenance therapy with durvalumab after concurrent chemoradiotherapy. Debate exists as to whether these patients are best served by surgery after induction therapy, which is further compounded by the fact that definition of resectable *vs.* unresectable stage III NSCLC is challenging, especially for patients with N2 disease (78). The ESPATUE study showed that some patients with stage III unresectable disease benefited from induction chemotherapy or chemoradiotherapy, with their T and N stages significantly downstaged, and the tumors became surgically resectable with a downstaging rate of 44%. Although the postoperative PFS and OS did not increase, subgroup analysis showed that selected patients (T_3N_2 and $T_4N_{0\text{-}1}$) had significant long-term survival benefits, especially in stage IIIB ($T_4N_{0\text{-}1}$). Several studies have shown that most patients with early-stage NSCLC experienced radiological downstaging after receiving neoadjuvant immunotherapy, and the clinical benefits were obvious. The LCMC3 study revealed that atezolizumab single-agent neoadjuvant therapy downstaged the tumors in 43% of patients with operable stage IB–IIIB NSCLC, with a surgery rate of 88% and an MPR rate of 20% (34). The NADIM study (25) showed that, in stage III (N_2 or T_4N_0/N_1) patients who had received 4 cycles of neoadjuvant nivolumab combined with chemotherapy before surgery, the downstaging rate was 90.2%, the planned resection rate was 89.1%, and the MPR rate was 83%. CheckMate 816 (27) showed that neoadjuvant nivolumab combined with chemotherapy in the treatment of operable stage IB-IIIA NSCLC achieved a radiological downstaging rate of 31%, which was better than that in the chemotherapy

© Translational Lung Cancer Research. All rights reserved.

alone group (24%). The planned resection rate was 83% and the primary endpoint pCR was significantly improved. In addition, a recent retrospective study (79) examined 51 patients with initially unresectable stage IIIB NSCLC who received ant-PD-1 monoclonal antibody combined with platinum-based chemotherapy. The results showed that the resection rate was 60.8% and the median surgery time and average blood loss were similar to those in previous studies (25,26,80), although some patients had adhesions or fibrosis that may increase surgical difficulty. However, no surgery-related mortality was recorded, and only 5 patients (16.1%) experienced postoperative complications (no grade 3 or worse complications). Pathological evaluation showed a mediastinal lymph node downstaging rate of 71.0%. The MPR was 67.7%, and the DFS/PFS was longer compared with patients without surgery. Therefore, induction therapy with immunotherapy with chemotherapy in these patients offered surgical opportunity, which may contribute to long-term survival benefit.

In conclusion, immunotherapy with chemotherapy as induction therapy may be considered for selected cases of unresectable locally advanced NSCLC, and the feasibility of surgery should be reevaluated after the treatment.

Consensus 10: Although the incidence of immune-related adverse events (irAEs) seems lower in patients with early-stage NSCLC as compared to that of advance stage, timely monitoring and intervention are still required

In recent years, immunotherapy has changed the landscape of advanced NSCLC treatment. However, the survival benefit of immunotherapy is also accompanied by the occurrence of adverse events (AEs), especially irAEs. Although the overall incidence of irAEs is low, serious consequences may occur. Surgery is required for early-stage resectable NSCLC after neoadjuvant immunotherapy, and for downstaged initially unresectable locally advanced NSCLC after immunotherapy. However, the occurrence of AEs may delay surgery or increase surgical difficulty and/or postoperative complications. As shown in most phase III clinical trials, multiple treatment strategies (e.g., single-agent immunotherapy, or combined with chemotherapy, anti-angiogenic drugs, and other immunotherapy) have brought significant survival benefits to patients with advanced NSCLC. These regimens showed good safety profiles, of which most AEs are presented as grade 1/2 (*Table 1*). Compared with those with advanced NSCLC, neoadjuvant immunotherapy plus chemotherapy for early-stage resectable NSCLC seems to have lower incidences of irAEs, especially AEs ≥grade 3 and AEs leading to drug discontinuation (*Table 2*), which may be attributed to the shorter treatment duration and better physical performance in patients with early-stage disease. Nevertheless, irAEs can occur in multiple systems during the whole course of treatments. The key to its management is timely monitoring and intervention. Most irAEs are reversible and can be controlled by suspending dosing and/or use of corticosteroids, which does not affect the efficacy of immunotherapy.

Therefore, although the incidence of irAE seems lower in patients with early-stage NSCLC than in those with advanced NSCLC, timely monitoring and intervention are still required. Long-term follow-up is also recommended.

Key questions and perspectives

Please describe your clinical experience, if any, related to using immune-oncology (IO) + chemotherapy in the neoadjuvant setting? What are the clinical characteristics that influence your decision to use neoadjuvant IO therapy?

Toyoaki Hida: As for neoadjuvant chemoimmunotherapy, it is only used within clinical trials, because neoadjuvant chemoimmunotherapy is still not available in Japan. Waiting for Ministry of Health, Labour and Welfare approval, in the near future, I would use ICI plus chemotherapy combination in the neoadjuvant setting to increase the rate of R0 resection, and to gain long-term recurrence-free survival and OS.

NSCLC patients for neoadjuvant immunotherapy in real-world clinical practice may have high T stage, multiple N2 metastasis.

Wolfram C. M. Dempke: In our institution, we are using neoadjuvant immune-chemotherapy concepts for all NSCLC patients who are eligible for this approach (no driver-mutations). As atezolizumab is part of this strategy, PD-L1 status is routinely measured and should be ≥50%. For the other patients (PD-L1 <50%) nivolumab plus chemotherapy is used.

Antonio Rossi: Neoadjuvant IO plus platinum-based chemotherapy is not yet a standard approach in routine practice worldwide due to the lack of access as it is not approved and reimbursed by every local regulatory agency, except FDA that granted the approval of neoadjuvant nivolumab plus chemotherapy in this setting. The

© Translational Lung Cancer Research. All rights reserved.

Table 1 Summary of the safety data from phase III studies on single-agent immunotherapy and immunotherapy plus chemotherapy in patients with advanced NSCLC

Treatment strategies	Study	Medications	irAEs (and infusion reactions)	AEs leading to drug discontinuation
Single-agent immunotherapy	KEYNOTE-024	Pembrolizumab (n=154)	34.4%	13.6%
		Chemotherapy (n=150)	5.3%	10.7%
	KEYNOTE-042	Pembrolizumab (n=636)	27.5%	9.1%
		Platinum-based doublet chemotherapy (n=615)	7.3%	9.6%
	EMPOWER-Lung 1	Cemiplimab (n=283)	17%	6%
		Chemotherapy (n=280)	2%	4%
	IMpower 110	Atezolizumab (n=285)	40.2%	–
		Chemotherapy (n=287)	16.7%	–
Immunotherapy plus chemotherapy for squamous NSCLC	KEYNOTE-407	Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel (n=278)	28.8%	35.6%
		Placebo + carboplatin + paclitaxel/nab-paclitaxel (n=280)	13.2%	9.3%
	RATIONALE-307	Tislelizumab + paclitaxel + carboplatin (n=120)	12.5%	–
		Tislelizumab + nab-paclitaxel + carboplatin (n=118)	29.7%	–
		Paclitaxel + carboplatin (n=117)	15.4%	–
Immunotherapy plus chemotherapy for non-squamous NSCLC	KEYNOTE-189	Pembrolizumab + pemetrexed + platinum (n=405)	27.7%	9.1%
		Pemetrexed + platinum (n=202)	13.4%	–
	RATIONALE-304	Tislelizumab + pemetrexed + platinum (n=222)	25.7%	25.7%
		Pemetrexed + platinum (n=110)	–	9.1%
	IMpower130	Atezolizumab + nab-paclitaxel + carboplatin (n=473)	45%	26%
		Nab-paclitaxel + carboplatin (n=232)	–	22%

NSCLC, non-small cell lung cancer; AE, adverse event; irAE, immune-related adverse event.

neoadjuvant IO trials have enrolled resectable NSCLC patients, with tumors ≥4 cm or node positive, who are those who could better benefit from neoadjuvant IO plus platinum-based regimen. The upcoming results from the trials addressing this approach, including the overall survival data, might further define the most appropriate therapy, in terms of the type of regimen and the number of cycles to administer, and the clinical characteristics of patients to treat in this setting.

Marc de Perrot: My experience with neoadjuvant immune-chemotherapy or immune-radiotherapy has been excellent. MPR or pCR was very frequently achieved. The surgical difficulties were not different than neoadjuvant chemoradiation.

Robert A. Ramirez: Since the CM816 regimen was only recently FDA approved I have not had the opportunity to use yet. Each patient is discussed in thoracic tumor board and now the surgeons at our institution are aware of the change and are now sent to medical oncology if they have not already been seen. For patients to be offered neoadjuvant chemo/immunotherapy they need to be a candidate for immunotherapy and agreeable to proceed.

Mariano Provencio: In my hospital we have great experience in the treatment of patients with neoadjuvant chemo-immunotherapy. We do not find a patient who, being in intermediate stages, not N3, is not a candidate for this treatment.

Jay M. Lee: In the United States, the only neoadjuvant chemo-immunotherapy regimen approved to date is based on the CheckMate 816 (chemotherapy plus nivolumab

© Translational Lung Cancer Research. All rights reserved.

Table 2 Summary of the safety data from studies on immunotherapy in patients with early-stage or locally advanced NSCLC

irAE	Study	Medications	IrAEs (and infusion reactions)	AEs leading to drug discontinuation
Neoadjuvant single-agent immunotherapy for early-stage NSCLC	MK3475-223 (65)	Pembrolizumab (n=26)	–	8%
Neoadjuvant immunotherapy plus chemotherapy for early-stage NSCLC	CheckMate 816 (30)	Nivolumab + chemotherapy (n=179)	–	10%
		Chemotherapy (n=179)	–	10%
	NADIM	Nivolumab + paclitaxel + carboplatin (n=46)	–	0%
Adjuvant single-agent immunotherapy for early-stage NSCLC	IMpower 010 (28,81)	Atezolizumab (n=507)	52%	18.2%
		Best supportive care (n=498)	9%	–
	KEYNOTE-091 (29)	Pembrolizumab (n=590)	–	19.8%
		Placebo (n=587)	–	5.9%
Locally advanced NSCLC	PACIFIC	Durvalumab (n=475)	–	15.4%
		Placebo (n=234)	–	9.8%

NSCLC, non-small cell lung cancer; AE, adverse event; irAE, immune-related adverse event.

×3 cycles) regimen for resectable stages IB–III NSCLC (based on 7th edition TNM), regardless of PD-L1 status. In contrast, the 8th edition TNM staging system is currently utilized in clinical management. It is important to point out that stage IB patients in the CheckMate 816 trial had tumors ≥4 cm. On this basis, I have utilized neoadjuvant chemo-immunotherapy in all stage II and III patients who meet this criterion, particularly in preoperatively diagnosed N1 or N2 nodal metastasis or node negative large tumors (≥4 cm). However, the current technology with endobronchial ultrasound and transbronchial needle biopsies of N1 and mediastinal (N2 and N3) lymph nodes or mediastinoscopy with surgical mediastinal lymph node biopsies or dissection is limited in preoperatively staging N1 lymph nodes. As such, a significant number of stage II patients with lymph node metastasis will be diagnosed postoperatively following resection and lymphadenectomy. These patients will receive adjuvant chemotherapy followed by atezolizumab for PD-L1 ≥1% expression in tumor cells based on Impower 010 trial.

Traditional surgical teaching has been to resect based on the original extent of disease for carcinomas. However, in the current era of chemo-immunotherapy, we as a surgical community should be open to a lesser operation given the clinical significance of significant pathologic responses resulting in a potential lung sparing surgery. The CheckMate 816 trial demonstrated a lower incidence of pneumonectomy surgeries in the chemotherapy plus nivolumab arm compared to chemotherapy alone arm. On this basis, I have preferred to use preoperative chemoimmunotherapy in central, hilar, or interlobar tumors regardless of nodal status where there is a high likelihood of a pneumonectomy or bilobectomy for resection. In these patients, neoadjuvant therapy may reduce the tumor burden resulting in sparing amount of lung resection, such as pneumonectomy or bilobectomy.

The limitations of the CheckMate 816 trial are that it is a relatively small phase III trial and there was no adjuvant immunotherapy given by trial design. As such, the subset analysis is difficult to interpret and draw firm conclusions simply because the numbers of patients in the subset analysis are quite small. Nevertheless, the subset analysis showed that PD-L1 negative tumors, squamous cell carcinoma histology, and stage IB/II patients had less impressive hazard ratios for event free survival following chemotherapy plus nivolumab compared to chemotherapy alone. Until

© Translational Lung Cancer Research. All rights reserved.

there is a readout of the other phase III neoadjuvant chemo-immunotherapy trials, I have not used any of these subset analysis factors to impact my decision making of whether to recommend neoadjuvant chemo-immunotherapy.

Antonio Passaro & Lorenzo Spaggiari: To date, the use of PD-1/PD-L1 checkpoint inhibitors is still not globally approved and standardized; our experience regarding the these class of agents, alone or in combination with chemotherapy, is limited to different clinical trials, waiting for EMA and AIFA (Italian Medicines Agency) approval. ECOG Performance status, node involvement and comorbidities should be considered.

Jonathan Spicer: My experience with neoadjuvant immunotherapy or chemo-immunotherapy extends over a 5-year period and has largely been confined to clinical trial patients of whom I've treated approximately 50. We have also treated some patients who were young and fit with extensive tumors in whom radiation fields were considered too large to be safe. In such patients, we were able to access chemo-immunotherapy as if the patient were metastatic and upon completion of 4 cycles of treatment restaging was performed to assess for resectability. We have had success with this approach in well selected patients. Overall, our experience with neoadjuvant immunotherapy has been positive with some very encouraging results. It is clear that predicting pathological response prior to surgery remains elusive and that the difficulty of the operation is also hard to predict.

With respect to factors that influence my use of neoadjuvant chemoIO, I assess patients for their surgical fitness first as well as the extent of disease and whether it is amenable to surgical resection. When the cTNM is consistent with disease that would meet indications for conventional adjuvant chemotherapy (T>4 and/or ipsilateral resectable nodal disease) and EGFR and ALK alterations have been excluded by next-generation sequencing, I favour the use of neoadjuvant chemoIO. Currently in Canada, this can still only be done in the context of a clinical trial as payers have yet to approve the CM816 regimen in our country.

Nicolas Girard: I use neoadjuvant chemotherapy plus immunotherapy for patients with stage II to IIIA resectable NSCLC as a preferred strategy, whatever is the PD-L1 status and in the absence of EGFR or ALK gene alterations. This is my preferred option given the OS benefit and the limited number of cycles then decreasing the duration of perioperative treatment. I do not use adjuvant so far, except for patients with unforeseen pN2 disease (stage IIIA) who would not have received neoadjuvant immunotherapy, and with PD-L1 of 50% or above.

Patrick M. Forde: Please note, I would only use chemo-immunotherapy as neoadjuvant therapy (since those are the phase 3 data). I favor neoadjuvant chemo-immunotherapy for pts who would consider perioperative chemo, who don't have EGFR/ALK and have surgically resectable lung cancer

Tina Cascone: When possible and feasible, in our center we favor enrolling patients with resectable NSCLC, as determined by the consensus of a multidisciplinary group of experts, and without *EGFR* mutations or *ALK* translocations, in neoadjuvant or perioperative immunotherapy-based clinical trials. If a trial is not an option, we favor administering neoadjuvant anti-PD-1 therapy plus platinum-based chemotherapy for a total of three cycles in patients with upfront resectable NSCLC, after resectability has been discussed and confirmed in a multidisciplinary setting, without *EGFR* mutations or *ALK* translocations and regardless of tumor PD-L1 expression, based on the currently available phase 3 data.

Please describe your current experience using adjuvant IO in patients with resectable NSCLC. What patient characteristics do you evaluate for use in this setting? Please explain

Toyoaki Hida: As for adjuvant chemotherapy followed by ICI, it is only used within clinical trials. The selection for subsequent adjuvant treatment will be considered on pathologic results of pCR or MPR, and biomarkers analyses including PD-L1, molecular profile, and ctDNA clearance.

Wolfram C. M. Dempke: Patients who are eligible for adjuvant therapy are treated with adjuvant atezolizumab after definitive resection and subsequent adjuvant chemotherapy (IMPower010 concept). Patients with PD-L1 <50% are enrolled in clinical trials if possible. Patients must not harbour druggable driver-mutations.

Antonio Rossi: Adjuvant IO is not available in clinical practice worldwide yet as it is not approved and reimbursed by every local regulatory agency, with most of experiences coming from clinical trials. According to trials addressing adjuvant IO, patients with resected stage II–IIIA NSCLC with PD-L1 ≥1%, after adjuvant platinum-based chemotherapy, are those showing a marked benefit from this therapy, and FDA granted the approval in this setting. EMA places PD-L1 cutoff ≥50% for the selection of patients to treat with adjuvant atezolizumab. Further updates from this study and results coming from other ongoing trials, paying

© Translational Lung Cancer Research. All rights reserved.

attention to the overall survival data, might better clarify the characteristics of patients who could benefit the most from this approach.

Marc de Perrot: Currently, the access to IO in the adjuvant setting and patient willingness to have another line of therapy have been the limitations.

Robert A. Ramirez: I will primarily use the IMpower 010 regimen and follow the patient characteristics approved by the FDA. PD-L1 <1% will be excluded.

Mariano Provencio: For neoadjuvant treatment, we preferably use it in patients with large tumor size, more than 7 cm and with N2 involvement.

Jay M. Lee: In the United States, the only adjuvant immunotherapy regimen approved to date by the FDA is atezolizumab. Based on the IMpower 010 study, adjuvant atezolizumab following complete (R0) resection and adjuvant chemotherapy for stage II or III NSCLC (based on 7th edition) with PD-L1 ≥1% expression in tumor cells is recommended. In the absence of contraindications to immunotherapy, I have recommended adjuvant atezolizumab for all patients meeting these criteria.

It is important to recognize that the hazard ratios for recurrence (disease free survival) is driven heavily by PD-L1 status and was most impressive for the PD-L1 ≥50% expression in tumor cells. On this basis, the European Union approved adjuvant atezolizumab for only the PD-L1 ≥50% expression in tumor cells subgroup. As such, there is an unmet need to improve survival in the PD-L1 0% and 1-49% subgroups with improved systemic therapies.

At the current time, I have recommended adjuvant atezolizumab for all patients following resection for stage II or III NSCLC with PD-L1 ≥1%. Additionally, the IMpower 010 trial also demonstrated no safety concerns in patients that underwent bilobectomy or pneumonectomy compared to the lobectomy cohorts. As such, the extent of lung resection also does not influence my decision in recommending adjuvant atezolizumab.

At the current time, it is unclear whether neoadjuvant chemo-immunotherapy (with only 3 cycles of nivolumab) or adjuvant chemotherapy followed by 1 year of adjuvant atezolizumab (16 cycles) is superior. The highly anticipated readout of the ongoing phase III neoadjuvant chemo-immunotherapy trials may help to determine this issue. As a result, both regimens are considered acceptable standards of care.

Antonio Passaro & Lorenzo Spaggiari: In Italy, we are waiting for the approval by AIFA (Italian Medicines Agency) for the use of atezolizumab in adjuvant setting, for resected NSCLC. Patients with ECOG PS 0/1, without major comorbidities should be evaluated for adjuvant treatment with immune-checkpoint blockade, without considering biomarkers discussed below.

Jonathan Spicer: Currently in Canada we do not have access of adjuvant IO in patients who have undergone resection and meet IM010 criteria, though Health Canada has approved the regimen, payers have yet to approve its use. Our use of adjuvant IO has been limited to the context of the BR31 trial. However, given our preference for neoadjuvant therapy, we have not enrolled many patients into this trial unless patients have incidental discovery of N1 or N2 positive lymph nodes at resection. I continue to believe that the use of adjuvant IO is specifically for patients who have incidental findings that upstage their disease to stage II or III at resection and for patients who have clinically evident stage II or III disease but cannot undergo pre-operative therapy due to complicating factors such as intractable pain, hemoptysis, post-obstructive pneumonia or co-morbidities that preclude systemic therapy or patient preference. I also believe that adjuvant IO is should largely be reserved for the PD-L1 >50% population.

Nicolas Girard: I do not use adjuvant so far, except for patients with unforeseen pN2 disease (stage IIIA) who would not have received neoadjuvant immunotherapy, and with PD-L1 of 50% or above.

Another exception would be patients with PD-L1 positive tumors and positive postoperative ctDNA without pCR.

Patrick M. Forde: We tend to use adjuvant in patients who have been upstaged pathologically and have PD-L1 positive disease i.e. who were felt to be clinical stage 1 but found to be stage 2 or 3 pathologically

Tina Cascone: We favor administering adjuvant immunotherapy, preferably after standard platinum-based chemotherapy, in patients with pathological stage II/IIIA, disease, without tumor molecular drivers for which adjuvant targeted therapy is the standard of care, and with tumor PD-L1 expression of 1% or greater, if they were not candidates for a neoadjuvant approach (e.g., clinical trial, chemo-immunotherapy, etc.)—which is routinely preferred in our center for patients with resectable NSCLC—or when they present to us after upfront surgical resection of their disease performed elsewhere.

What neoadjuvant IO treatment regimen do/will you choose?

Toyoaki Hida: I will choose nivolumab plus platinum-

© Translational Lung Cancer Research. All rights reserved.

based doublet chemotherapy according to the results from CheckMate 816, because neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival and a higher percentage of patients with a pathological complete response. The addition of nivolumab to chemotherapy did not increase the incidence of AEs or prevent the feasibility of surgery.

Wolfram C. M. Dempke: We use atezolizumab plus chemotherapy (PD-L1 >50%) or nivolumab plus chemotherapy (PD-L1 <50%).

Antonio Rossi: Nivolumab, and pembrolizumab when given in combination with platinum-based regimens, in the neo-adjuvant setting, have shown to improve pathological complete response and event-free survival, primary endpoints, respect to chemotherapy alone. Recently, preliminary data coming from the use of the neoadjuvant combination of durvalumab plus chemotherapy have shown to improve pathological complete response, too. The choice of neoadjuvant IO, when available in clinical practice worldwide, should be based on the updated evidence produced by clinical trials.

Marc de Perrot: We are planning to continue accruing patients in clinical trials and therefore the regimen will vary accordingly.

Robert A. Ramirez: For now, the CM816 regimen is what is indicated and would be approved by insurances. Other regimens would be offered on trial only and there will be more and more trials in this space forthcoming.

Mariano Provencio: Carbo-taxol and Nivolumab

Jay M. Lee: In the United States, the only neoadjuvant chemo-immunotherapy regimen approved to date is based on the CheckMate 816 (chemotherapy plus nivolumab x 3 cycles) regimen for resectable stages IB–III NSCLC (based on 7th edition TNM), regardless of PD-L1 status. On this basis, unless the patient is enrolled in a clinical trial, the CheckMate 816 regimen is the only neoadjuvant chemo-immunotherapy that I choose.

Antonio Passaro & Lorenzo Spaggiari: Based on the last results recently published, a combination of platinum-based chemotherapy, histology driven (squamous *vs.* non-squamous) in combination with PD-1/PD-L1 checkpoint inhibitors should be considered.

Jonathan Spicer: Currently, we choose the regimens that are available within active and recruiting trials given the lack of access to chemoIO as a standard of care treatment in Canada. When the regimen will be approved, we will use 3 doses of platinum-based doublet with nivolumab and may favour the use of carboplatinum. For patients with unresectable disease in whom we are attempting to downstage, our approved metastatic regimen is platinum-doublet with pembrolizumab and we usually will use 4 cycles in the patients can tolerate the treatment. Occasionally, we will get a CT after 2 cycles to ensure that there is adequate response in case we need to change the therapeutic strategy to concurrent chemoradiation.

Nicolas Girard: Based on CheckMate 816, I use cisplatin-based combination preferably cisplatin and pemetrexed for non-squamous, and cisplatin gemcitabine for squamous. Another combination I use is carboplatin paclitaxel is patients not eligible to cisplatin. The IO compound is nivolumab for all patients.

Patrick M. Forde: CheckMate 816.

Tina Cascone: If a clinical trial testing neoadjuvant or perioperative chemo-immunotherapy/immune-based therapies is not an option for a patient with resectable NSCLC without *EGFR* mutations or *ALK* translocations, we favor the regimens used in the Checkmae-816 trial with the chemotherapy doublet tailored to each patient based on clinical characteristics (age, performance status, comorbidities) and tumor histology (squamous versus non-squamous).

How/will you be using PD-L1 expression to guide treatment decision in early-stage NSCLC? Are there any other biomarkers of interest to monitor response to therapy?

Toyoaki Hida: In the adjuvant setting, a benefit of ICI seems to be driven by high (50% or greater) PD-L1 expression, whereas no clear role of PD-L1 in the neoadjuvant setting, although a signal of greater magnitude of benefit with nivolumab plus chemotherapy was observed between the PD-L1-positive group (PD-L1 >1%) compared with negative tumors in the CheckMate 816 trial.

Wolfram C. M. Dempke: As outlined below PD-L1 status is mandatory (PD-L1 >50%: atezolizumab; PD-L1 <50%: nivolumab). In clinical trials we also determine TMB (tumor mutational burden).

Antonio Rossi: The characteristics of patients who could much benefit from adjuvant/neoadjuvant use of IO comes from registrative clinical trials, and the regulatory agencies will give a guidance in the selection of patients to treat in the clinical practice. To date, PD-L1 expression is mandatory to select patients for adjuvant atezolizumab, as by FDA and EMA requirements. Further analyses coming from the current trials will better define the role of PD-L1

© Translational Lung Cancer Research. All rights reserved.

expression and of other biomarkers, such as ctDNA, that might help in selecting patients to treat and/or monitoring the response to therapy.

Marc de Perrot: Currently we do not use PD-L1 expression to guide neoadjuvant therapy. PD-L1 does guide us for the adjuvant IO. We are studying ctDNA as part of a clinical trials, but no other biomarkers is currently tested.

Robert A. Ramirez: In the neoadjuvant space, PD-L1 TPS would not influence my decision to proceed with treatment. In the adjuvant space, PD-L1 would dictate if atezolizumab is indicated. cfDNA in interesting but not ready for widespread clinical use.

Mariano Provencio: PD-L1 expression serves as a predictor of response, more expression, more possibility of complete response, but does not exclude patients with negative PDL expression who have a complete pathologic response, which occurs in 16% of cases with negative DL1.

Jay M. Lee: In the United States, the relevance of PD-L1 tumor cell expression is mainly in the adjuvant setting given the differential approval by the FDA of immune checkpoint inhibitors in the neoadjuvant *vs.* adjuvant settings. The only neoadjuvant chemo-immunotherapy regimen approved to date is based on the CheckMate 816 (chemotherapy plus nivolumab ×3 cycles) regimen for resectable stages IB–III NSCLC (based on 7th edition TNM), regardless of PD-L1 status. In contrast, based on the IMpower 010 study, adjuvant atezolizumab received approval by the FDA following complete (R0) resection and adjuvant chemotherapy only for stage II or III NSCLC (based on 7th edition) with PD-L1 ≥1% expression in tumor cells. As such, PD-L1 negative patients, outside of a clinical trial, are not approved to received adjuvant immunotherapy. Thus, although PD-L1 status is highly relevant in expected response to immune checkpoint inhibitors, PD-L1 expression in tumor cells guide treatment decisions only in the adjuvant setting.

At the current time, there are no standard of care biomarkers to monitor response to immunotherapy. However, the detection of ct-DNA is a promising prognostic factor following resection in early stage NSCLC in predicting recurrence (molecular residual disease). It is important to recognize that the current technology is not sensitive enough to guide determination of need for systemic therapy. In IMpower 010, the ct-DNA detectable and non-detectable subgroups both benefitted from adjuvant chemotherapy followed by atezolizumab. As such, we should not withhold immunotherapy based on ct-DNA levels or detectability.

The use of ct-DNA levels during immunotherapy as a measure of immune checkpoint inhibitor response may be a promising application, but at the current time this concept in early stage NSCLC needs to be studied and validated before declaring as standard of care.

Antonio Passaro & Lorenzo Spaggiari: The role of PD-L1 expression in the perioperative setting of NSCLC is debated and deserves attention for a deep evaluation. Although data are immature and controversial on this topic, only atezolizumab received the EMA approval for patients with PD-L1 expression on ≥50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC. PD-L1 cutoff should be considered to prioritize patients as a candidate for adjuvant atezolizumab; in addition, the use of adjuvant atezolizumab should be limited only to patients without actionable driver mutations and without a history of smoking. Conversely, no clear role of PD-L1 emerged in the neoadjuvant setting, mainly when chemotherapy is part of the neoadjuvant strategy.

Jonathan Spicer: As mentioned earlier, I do not use PD-L1 expression to guide decision when giving chemo-IO in the neoadjuvant setting. It provides useful information about prognosis, but does not help with the decision of whether to give neoadjuvant or not since pathological response is superior across all PD-L1 subgroups. However, in the adjuvant setting, I believe that adjuvant IO should be reserved for patients who can tolerate adjuvant chemo and have PD-L1 >50%.

Nicolas Girard: PD-L1 is a complex biomarker in this setting, as patients with PD-L1 negative tumors seems not to benefit from adjuvant atezolizumab in Impower010, and those with PD-L1 of 50% or more do not seem to benefit from adjuvant pembrolizumab in Keynote-091. The efficacy of the neoadjuvant approach seems less influenced by the PD-L1 status.

After neoadjuvant IO, ctDNA is a key biomarker, as well as pCR for the adjuvant decision making and studies should explore what should be the strategy in those subgroups of patients.

Immunomonitoring of T cell population in the blood after neoadjuvant and during adjuvant IO is probably very interesting although difficult to implement in clinical practice.

Patrick M. Forde: In general favor neoadjuvant chemo-IO irrespective of PD-L1. Would not use IO for tumors with EGFR or ALK.

Tina Cascone: If neoadjuvant/perioperative chemo-immunotherapy is administered in the context of a clinical

© Translational Lung Cancer Research. All rights reserved.

trial, biomarker-driven patient selection and disease monitoring is performed based on protocol criteria. If neoadjuvant platinum-based chemotherapy plus nivolumab (Checkmate-816 regimen) is considered for patients with resectable NSCLC without *EGFR* mutations or *ALK* translocations as a standard of care approach, the regimen is administered regardless of tumor PD-L1 expression (based on Checkmate-816 phase 3 trial data). If adjuvant immunotherapy is considered in resected NSCLC patients preferably following adjuvant platinum-based chemotherapy, the regimen is administered in tumor PD-L1 positive disease.

Acknowledgments

The authors appreciate the academic support from AME Lung Cancer Collaborative Group. The authors appreciate the great support from Dr. Edward B. Garon (David Geffen School of Medicine at UCLA, USA) in improving the quality of this paper. The authors also appreciate the scientific support from Huifeng Peng from MSD China for this paper.
Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-617/coif). TH serves as an unpaid editorial board member of *Translational Lung Cancer Research* from January 2022 to December 2023. AR serves as an unpaid editorial board member of *Translational Lung Cancer Research* from November 2020 to October 2022. RAR serves as an unpaid editorial board member of *Translational Lung Cancer Research* from January 2022 to December 2023. MP serves as an unpaid editorial board member of *Translational Lung Cancer Research* from October 2021 to September 2023. RAR has been a consultant for Amgen, Ipsen Biopharmaceuticals, Novartis, Advanced Accelerator Applications, Curium Pharma, EMD Serono, Astra-Zeneca. He has also received research funding (to institution) from Merck & Co and Aadi Biosciences. He is also on the speaker bureaus for Ipsen Biopharmaceuticals and Astra-Zeneca. Mariano Provencio received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events and consulting fees from BMS, Astra Zéneca, MSD, Roche, Takeda and Pfizer. Jay M. Lee reports advisory board/consultant of Astrazeneca, Bristol Myers Squibb, Genentech, Novartis, Roche; research support from Genentech, Novartis; steering committee of Genentech, Novartis; speaker's bureau of AstraZeneca, Genentech, Roche; stock from Moderna; patents of UCLA. Antonio Passaro received honoraria for consulting, advisory role or lectures from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Jansenn, Merck Sharp & Dohme, Roche Genentech, Novartis, MundiPharma, Daiichi Sankyo, eCancer and Medscape. TC reports speaker fees/honoraria from The Society for Immunotherapy of Cancer, Bristol Myers Squibb, Roche, Medscape, and PeerView; travel, food and beverage expenses from Dava Oncology; advisory role/consulting fees from AstraZeneca, Bristol Myers Squibb, EMD Serono, Merck & Co., Genentech, and Arrowhead Pharmaceuticals; and institutional research funding from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim and EMD Serono. The other authors have no conflicts of interest to declare.

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

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Cao W, Chen HD, Yu YW, et al. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. Chin Med J (Engl) 2021;134:783-91.
3. Zheng RS, Sun KX, Zhang SW, et al. Report of cancer epidemiology in China, 2015. Zhonghua Zhong Liu Za Zhi 2019;41:19-28.

© Translational Lung Cancer Research. All rights reserved.

4. Reck M, Rabe KF. Precision Diagnosis and Treatment for Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2017;377:849-61.
5. Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. Transl Lung Cancer Res 2014;3:242-9.
6. Passaro A, Attili I, de Marinis F. Neoadjuvant Chemotherapy Plus Immunotherapy in Early-Stage Resectable Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:2871-7.
7. Rosner S, Forde PM. Chemotherapy + PD-1/PD-L1 Blockade Should Be the Preferred Option in the Neoadjuvant Therapy of NSCLC. J Thorac Oncol 2022;17:503-9.
8. 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.
9. Burdett S, Pignon JP, Tierney J, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. Cochrane Database Syst Rev 2015;(3):CD011430.
10. Desage AL, Bouleftour W, Tiffet O, et al. Use of adjuvant chemotherapy in resected non-small cell lung cancer in real-life practice: a systematic review of literature. Transl Lung Cancer Res 2021;10:4643-65.
11. Garon EB, Hellmann MD, Rizvi NA, et al. Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol 2019;37:2518-27.
12. Brahmer JR, Rodriguez-Abreu D, Robinson AG, et al. LBA51 - KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50%. Ann Oncol 2020;31:S1142-215.
13. Wu YL, Fan Y, Zhou JY, et al. Pembrolizumab vs chemotherapy in Chinese patients with PD-L1-positive NSCLC: 4-year update from KEYNOTE-042 China study. Presented at: 2022 AACR Annual Meeting; April 8-13, 2022; New Orleans, Louisiana. Accessed April 8, 2022. Poster CT555.
14. Awad MM, Gadgeel SM, Borghaei H, et al. Long-Term Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC. J Thorac Oncol 2021;16:162-8.
15. Gray JE. Pembrolizumab + Pemetrexed-Platinum vs Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189. Abstract FP13.02. Presented at World Conference on Lung Cancer Virtual Conference, 2020 on 28 January 2021.
16. Robinson A, Vicente Baz D, Tafreshi A, et al. 97O - First-Line Pembrolizumab Plus Chemotherapy for Patients With Advanced Squamous NSCLC: 3-Year Follow-up From KEYNOTE-407. J Thorac Oncol 2021;16:S748-802.
17. Cheng Y, Zhang L, Hu J, et al. Pembrolizumab Plus Chemotherapy for Chinese Patients With Metastatic Squamous NSCLC in KEYNOTE-407. JTO Clin Res Rep 2021;2:100225.
18. 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. Erratum in: J Clin Oncol;40:1965.
19. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. Science 2020;367:eaax0182.
20. Gueguen P, Metoikidou C, Dupic T, et al. Contribution of resident and circulating precursors to tumor-infiltrating CD8+ T cell populations in lung cancer. Sci Immunol 2021;6:eabd5778.
21. Bakos O, Lawson C, Rouleau S, et al. Combining surgery and immunotherapy: turning an immunosuppressive effect into a therapeutic opportunity. J Immunother Cancer 2018;6:86.
22. Rothschild SI, Zippelius A, Eboulet EI, et al. SAKK 16/14: Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients With Stage IIIA(N2) Non-Small-Cell Lung Cancer-A Multicenter Single-Arm Phase II Trial. J Clin Oncol 2021;39:2872-80.
23. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Engl J Med 2018;378:1976-86.
24. Lee J, Chaft A, Nicholas A, et al. PS01.05 Surgical and Clinical Outcomes With Neoadjuvant Atezolizumab in Resectable Stage IB–IIIB NSCLC: LCMC3 Trial Primary Analysis. J Thorac Oncol 2021;16:S59-61.
25. Provencio M, Nadal E, Insa A, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21:1413-22.
26. Shu CA, Gainor JF, Awad MM, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21:786-95.
27. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J

© Translational Lung Cancer Research. All rights reserved.

Med 2022;386:1973-85.
28. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021;398:1344-57.
29. Paz-Ares L, O'Brien MER, Mauer M, et al. Pembrolizumab (pembro) versus placebo for early-stage non-small cell lung cancer (NSCLC) following complete resection and adjuvant chemotherapy (chemo) when indicated: Randomized, triple-blind, phase III EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 study. Presented at 2022 ESMO Virtual Plenary Series; March 17, 2022. Abstract VP3-2022.
30. Girard N, Spicer J, Provencio M, et al. Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment for resectable (IB-IIIA) non-small cell lung cancer (NSCLC): Event-free survival (EFS) results from the phase 3 CheckMate 816 trial. Presented at AACR 2022; April 8-13, 2022. Abstract CT012.
31. Ulas EB, Dickhoff C, Schneiders FL, et al. Neoadjuvant immune checkpoint inhibitors in resectable non-small-cell lung cancer: a systematic review. ESMO Open 2021;6:100244.
32. Gao S, Li N, Gao S, et al. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. J Thorac Oncol 2020;15:816-26.
33. Tong BC, Gu L, Wang X, et al. Perioperative outcomes of pulmonary resection after neoadjuvant pembrolizumab in patients with non-small cell lung cancer. J Thorac Cardiovasc Surg 2022;163:427-36.
34. Chaft JE, Oezkan F, Kris MG, et al. Neoadjuvant atezolizumab for resectable non-small cell lung cancer: an open-label, single-arm phase II trial. Nat Med. 2022 Sep 12. doi: 10.1038/s41591-022-01962-5. [Epub ahead of print].
35. Mariano Provencio-Pulla M, Ernest Nadal E, Gonzalez Larriba JL, et al. Nivolumab + chemotherapy versus chemotherapy as neoadjuvant treatment for resectable stage IIIA NSCLC: Primary endpoint results of pathological complete response (pCR) from phase II NADIM II trial. J Clin Oncol 2022;40:abstr 8501.
36. Cascone T, William WN Jr, Weissferdt A, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. Nat Med 2021;27:504-14.
37. Reuss JE, Anagnostou V, Cottrell TR, et al. Neoadjuvant nivolumab plus ipilimumab in resectable non-small cell lung cancer. J Immunother Cancer 2020;8:e001282.
38. Cascone T, García-Campelo R, Spicer J, et al. CT011 - NeoCOAST: open-label, randomized, phase 2, multidrug platform study of neoadjuvant durvalumab alone or combined with novel agents in patients (pts) with resectable, early-stage non-small-cell lung cancer (NSCLC). In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; Cancer Res 2022;82:Abstract nr CT011.
39. Spicer J, Cascone T, Kar G, et al. 929MO - Platform study of neoadjuvant durvalumab (D) alone or combined with novel agents in patients (pts) with resectable, early-stage non-small cell lung cancer (NSCLC): Pharmacodynamic correlates and circulating tumor DNA (ctDNA) dynamics in the NeoCOAST study. Ann Oncol 2022;33:S427-37.
40. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819-30.
41. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol 2021;39:2339-49.
42. Herbst RS, de Marinis F, Giaccone G, et al. IMpower110: updated OS analysis of atezolizumab vs platinum-based hemotherapy as first-line treatment in PD-L1–selected NSCLC. Presented at: 2020 World Conference on Lung Cancer Singapore. January 28-31, 2021. Abstract FP13.03.
43. Zhou C, Das Thakur M, Srivastava MK, et al. Ann Oncol 2021;32:S1373-91.
44. Chinese Society of Clinical Oncology (CSCO) Guideline Working Committee. Guidelines of Chinese Society of Clinical Oncology (CSCO) Non-small cell lung cancer. Beijing: People's Health Publishing House, 2021.
45. Liu J, O'Donnell JS, Yan J, et al. Timing of neoadjuvant immunotherapy in relation to surgery is crucial for outcome. Oncoimmunology 2019;8:e1581530.
46. Sepesi B, Zhou N, William WN Jr, et al. Surgical outcomes after nivolumab or nivolumab with ipilimumab treatment in patients with non-small cell lung cancer. J Thorac Cardiovasc Surg 2022. [Epub ahead of print]. doi: 10.1016/j.jtcvs.2022.01.019.
47. Jiang L, Huang J, Jiang S, et al. The surgical perspective in neoadjuvant immunotherapy for resectable non-small cell lung cancer. Cancer Immunol Immunother 2021;70:2313-21.
48. Shi L, Liu Z, Meng Q, et al. P03.01 Pathologic Response

© Translational Lung Cancer Research. All rights reserved.

to Neoadjuvant PD-1 Inhibitors and Chemotherapy in Squamous Non-Small-Cell Lung Cancer. Presented at: 2021 World Conference on Lung Cancer. P13.03.
49. Liu Z, Gao Z, Zhang M, et al. Real-World Effectiveness and Prognostic Factors Analysis of Stages I-III Non-Small Cell Lung Cancer Following Neoadjuvant Chemo-Immunotherapy or Neoadjuvant Chemotherapy. Ann Thorac Cardiovasc Surg 2022;28:111-20.
50. Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer 2016;62:132-7.
51. Tao X, Li N, Wu N, et al. The efficiency of 18F-FDG PET-CT for predicting the major pathologic response to the neoadjuvant PD-1 blockade in resectable non-small cell lung cancer. Eur J Nucl Med Mol Imaging 2020;47:1209-19.
52. Cascone T, Weissferdt A, Godoy MCB, et al. Nodal immune flare mimics nodal disease progression following neoadjuvant immune checkpoint inhibitors in non-small cell lung cancer. Nat Commun 2021;12:5045.
53. Lopci E, Toschi L, Grizzi F, et al. Correlation of metabolic information on FDG-PET with tissue expression of immune markers in patients with non-small cell lung cancer (NSCLC) who are candidates for upfront surgery. Eur J Nucl Med Mol Imaging 2016;43:1954-61.
54. Provencio M, Nadal E, Insa A, et al. Long Term Survival in Operable Stage Iiia Nsclc Patients Treated With Neoadjuvant Nivolumab Plus Chemotherapy - Nadim Study. J Thorac Oncol 2021;16:S883.
55. Abbosh C, Birkbak NJ, Swanton C. Early stage NSCLC — challenges to implementing ctDNA-based screening and MRD detection. Nat Rev Clin Oncol 2018;15:577-86.
56. Chaudhuri AA, Chabon JJ, Lovejoy AF, et al. Early Detection of Molecular Residual Disease in Localized Lung Cancer by Circulating Tumor DNA Profiling. Cancer Discov 2017;7:1394-403.
57. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature 2017;545:446-51.
58. Zviran A, Schulman RC, Shah M, et al. Genome-wide cell-free DNA mutational integration enables ultra-sensitive cancer monitoring. Nat Med 2020;26:1114-24.
59. Chen K, Zhao H, Shi Y, et al. Perioperative Dynamic Changes in Circulating Tumor DNA in Patients with Lung Cancer (DYNAMIC). Clin Cancer Res 2019;25:7058-67.
60. Moding EJ, Liu Y, Nabet BY, et al. Circulating Tumor DNA Dynamics Predict Benefit from Consolidation Immunotherapy in Locally Advanced Non-Small Cell Lung Cancer. Nat Cancer 2020;1:176-83.
61. Wu Y, Lu S, Cheng Y, et al. Expert Consensus of Molecular Residual Disease for Non-Small Cell Lung Cancer. Journal of Evidence-Based Medicine 2021;21:129-35.
62. Akondy RS, Fitch M, Edupuganti S, et al. Origin and differentiation of human memory CD8 T cells after vaccination. Nature 2017;552:362-7.
63. Cao C, Le A, Bott M, et al. Meta-Analysis of Neoadjuvant Immunotherapy for Patients with Resectable Non-Small Cell Lung Cancer. Curr Oncol 2021;28:4686-701.
64. David J. Kwiatkowski. Non–Small Cell Lung Cancer: Neoadjuvant Immunotherapy for Resectable Disease. ASCO 2019. abstract 8053. Available online: https://ascopost.com/videos/2019-asco-annual-meeting/david-kwiatkowski-on-neoadjuvant-immunotherapy-for-resectable-nsclc/
65. Bar J, Urban D, Redinsky I, et al. OA11.01 Neoadjuvant Pembrolizumab for Early Stage Non-Small Cell Lung Cancer. J Thorac Oncol 2021;16:S865-6.
66. Kwiatkowski DJ, Rusch VW, Chaft JE, et al. Neoadjuvant atezolizumab in resectable nonsmall cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3). J Clin Oncol 2019;37:abstr 8503.
67. Ready N, Tong B, Clarke J, et al. Neoadjuvant Pembrolizumab in Early Stage Non-Small Cell Lung Cancer (NSCLCL): Toxicity, Efficacy, and Surgical Outcomes. J Thorac Oncol 2019;14:S745.
68. Bott MJ, Cools-Lartigue J, Tan KS, et al. Safety and Feasibility of Lung Resection After Immunotherapy for Metastatic or Unresectable Tumors. Ann Thorac Surg 2018;106:178-83.
69. Provencio M, Serna-Blasco R, Nadal E, et al. Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial). J Clin Oncol 2022;40:2924-33.
70. Hellmann MD, Chaft JE, William WN Jr, et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol 2014;15:e42-50.
71. Pataer A, Kalhor N, Correa AM, et al. Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. J Thorac Oncol 2012;7:825-32.
72. William WN Jr, Pataer A, Kalhor N, et al. Computed tomography RECIST assessment of histopathologic

© Translational Lung Cancer Research. All rights reserved.

response and prediction of survival in patients with resectable non-small-cell lung cancer after neoadjuvant chemotherapy. J Thorac Oncol 2013;8:222-8.
73. Cascone T, Gold KA, Swisher SG, et al. Induction Cisplatin Docetaxel Followed by Surgery and Erlotinib in Non-Small Cell Lung Cancer. Ann Thorac Surg 2018;105:418-24.
74. Masip JR, Martinez-Marti A, Costa EC, et al. Major pathological response after preoperative chemotherapy as a surrogate marker of survival in early-stage non-small cell lung cancer. Ann Oncol 2017;28:v453-56.
75. Altorki NK, McGraw TE, Borczuk AC, et al. Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial. Lancet Oncol 2021;22:824-35.
76. Cottrell TR, Thompson ED, Forde PM, et al. Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). Ann Oncol 2018;29:1853-60.
77. Travis WD, Dacic S, Wistuba I, et al. IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy. J Thorac Oncol 2020;15:709-40.
78. Mainguene J, Basse C, Girard P, et al. Surgical or medical strategy for locally-advanced, stage IIIA/B-N2 non-small cell lung cancer: Reproducibility of decision-making at a multidisciplinary tumor board. Lung Cancer 2022;163:51-8.
79. Deng H, Liu J, Cai X, et al. Radical Minimally invasive surgery following immuno-chemotherapy in Initially-unresectable stage IIIB Non-small cell lung cancer. Ann Surg 2022;275:e600-2.
80. Bott MJ, Yang SC, Park BJ, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg 2019;158:269-76.
81. 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:S71.

Cite this article as: Liang W, Cai K, Cao Q, Chen C, Chen H, Chen J, Chen KN, Chen Q, Chu T, Dong Y, Fan J, Fang W, Fu J, Fu X, Gao S, Ge D, Geng G, Geng Q, He J, Hu J, Hu J, Hu WD, Jiang F, Jiang T, Jiao W, Li HC, Li Q, Li S, Li S, Li X, Liao YD, Liu C, Liu H, Liu Y, Lu Z, Luo Q, Ma H, Pan X, Qiao G, Ren S, Shen W, Song Y, Sun D, Wang G, Wang J, Wang M, Wang Q, Wang WX, Wei L, Wu M, Wu N, Xia H, Xu SD, Yang F, Yang K, Yang Y, Yu F, Yu ZT, Yue DS, Zhang L, Zhang W, Zhang Z, Zhao G, Zhao J, Zhao X, Zhou C, Zhou Q, Zhu K, Zhu Y, Hida T, Dempke WCM, Rossi A, de Perrot M, Ramirez RA, Provencio M, Lee JM, Passaro A, Spaggiari L, Spicer J, Girard N, Forde PM, Mok TSK, Cascone T, He J; on behalf of CATO consensus group. International expert consensus on immunotherapy for early-stage non-small cell lung cancer. Transl Lung Cancer Res 2022;11(9):1742-1762. doi: 10.21037/tlcr-22-617

© Translational Lung Cancer Research. All rights reserved.