Chinese Medical Journal®

Immunotherapy in non-small cell lung cancer: advancements and challenges

Fei Zhou, Cai-Cun Zhou

Department of Medical Oncology, Shanghai Pulmonary Hospital, Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai 200433, China.

In the past 10 years, immune-checkpoint inhibitors (ICIs), targeting programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis, have altered the therapeutic landscape of non-small cell lung cancer (NSCLC) and have resulted in long-term survival benefits in a subset of patients. In this editorial, we focused on recent advancements and challenges of ICIs in patients with NSCLC.

ICIs for First-line Treatment of Advanced NSCLC

The landmark KEYNOTE-024 study demonstrated that pembrolizumab significantly improved progression-free survival (PFS, 10.3 *vs.* 6.0 months, $P < 0.001$) and overall survival (OS, 30.0 *vs.* 14.2 months, $P = 0.002$) compared with standard chemotherapy in patients with treatment-naïve advanced NSCLC with PD-L1 tumor proportion score (TPS) ≥50% and without *EGFR/ALK* genetic aberrations.[1] The KEYNOTE-042 study further demonstrated OS benefits for pembrolizumab monotherapy over chemotherapy in an expanding patient population (OS in PD-L1 TPS ≥1%: 16.7 *vs.* 12.1 months, $P = 0.0018$).[2] However, further exploratory subgroup analysis of KEYNOTE-042 study found no significant benefit in OS in PD-L1 TPS 1–49% population,[2] suggesting that the survival benefits of pembrolizumab monotherapy may mostly come from higher PD-L1 expression population (≥50%).

ICI in combination with chemotherapy represents another promising treatment paradigm [Supplementary Table 1, http://links.lww.com/CM9/A444].[3-9] Pembrolizumab combined with chemotherapy has been approved by the National Medical Products Administration (NMPA) for the first-line treatment of advanced squamous and nonsquamous NSCLC without *EGFR/ALK* genetic aberrations, regardless of PD-L1 expression.[3,8] Camrelizumab plus pemetrexed/carboplatin also demonstrated significant improvements in terms of objective response rate (ORR; 60.0% *vs.* 39.1%, $P < 0.0001$), PFS (11.3 *vs.* 8.3 months, $P = 0.0002$) and OS (not reached *vs.* 20.9 months, $P = 0.0272$) compared with first-line pemetrexed/carboplatin for Chinese patients with nonsquamous NSCLC without *EGFR/ALK* genetic aberrations.[7] Atezolizumab in combination with carboplatin/nab-paclitaxel (IMpower130) or bevacizumab and carboplatin/nab-paclitaxel (IMpower150) also provided PFS and OS superiority over chemotherapy alone in patients with advanced nonsquamous NSCLC.[4,6]

ICIs in Early-stage Resectable or Locally Advanced, Unresectable NSCLC

Concurrent chemoradiotherapy plays a pivotal role in patients with locally advanced, unresectable NSCLC. How to prevent metastases and improve the survival is essential for these patients after definitive treatment. Recently, the PACIFIC study demonstrated consolidation immunotherapy with durvalumab was effective in patients with locally advanced NSCLC after completed definitive chemoradiotherapy.[10] In PACIFIC study, durvalumab yielded significant improvements in median PFS compared with placebo (17.2 *vs.* 5.6 months). The updated OS analyses also demonstrated a clinically meaningful OS benefits with consolidation durvalumab *vs.* placebo (not reached *vs.* 29.1 months).[11] The findings from PACIFIC study established consolidation durvalumab as the standard of care for patients with locally advanced NSCLC after completed definitive chemoradiotherapy.

A previous study has revealed that immune suppression may occur at pre-invasive stages of cancer development,[12] suggesting a possible role of ICIs in early-stage NSCLC. A pilot study investigated the safety and efficacy of nivolumab as neoadjuvant therapy in resectable early-stage NSCLC.[13] In 21 patients, 20 achieved complete resection with acceptable side-effect profile. Notably, despite only two patients had partial response, 9 of 20 (45%) patients had a major pathologic response (MPR, defined as 10% residual tumor present). Several studies also demonstrated the promising role of neoadjuvant PD-1/PD-L1 inhibitors either as monotherapy or in combination with ipilimumab or chemotherapy. Although the role of MPR as the primary

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001338

Correspondence to: Prof. Cai-Cun Zhou, Department of Medical Oncology, Shanghai Pulmonary Hospital, Thoracic Cancer Institute, Tongji University School of Medicine, No. 507 Zhengmin Road, Yangpu District, Shanghai 200433, China
E-Mail: caicunzhoudr@163.com

Chinese Medical Journal 2021;134(10)

Received: 30-06-2020 **Edited by:** Pei-Fang Wei

endpoint is questionable, multiple phase III studies are ongoing to evaluate the long-term benefits of neoadjuvant ICI treatment in patients with early-stage, resectable NSCLC. Furthermore, ongoing studies are also evaluating the role of ICI as adjuvant therapy in stage I-IIIA NSCLC after definitive surgical resection.

Predictive Biomarkers

Despite rapid advances of ICIs in NSCLC, only a minority of patients respond to single-agent ICI treatment. Even in a highly selected patient population (PD-L1 TPS ≥50%), only 44.8% of patients achieved an objective response when treated with pembrolizumab monotherapy.[1] Due to the complex immune response process, any single biomarker may not be effective and reproducible enough to predict the benefits of ICIs. For instance, although PD-L1 expression has been widely used for patient selection, several limitations make it an imperfect biomarker, including spatial-temporal heterogeneity of PD-L1 expression, high discordance in PD-L1 expression read on immune cells, and different cutoffs used in each assay. Tumor mutation burden (TMB) is another potential biomarker. In CheckMate-227 study, for patients with high TMB (≥10 mutations per megabase), nivolumab plus ipilimumab resulted in longer PFS (7.2 *vs.* 5.5 months, $P < 0.001$) and higher ORR (45.3% *vs.* 26.9%) compared with chemotherapy alone.[14] However, the OS benefits were independent of TMB level.[15] Recently, a combined biomarker analysis revealed that T-cell-inflamed gene-expression profile, PD-L1 expression, and TMB may help identify patients who are more likely to derive benefits from ICI treatment.[16] These findings indicate a direction to pursue predictive biomarkers in further studies. We should integrate multiple biomarkers to better reflect the complex cancer-immune interactions between the tumor, tumor microenvironment and host immunity.

Immune-related Adverse Events (irAEs)

With the growing use of ICIs in oncology, awareness and management of irAEs become more important. Unlike the toxicity profiles of classical chemotherapy, irAEs may occur in wide ranges of organs, as consequences of nonspecific and excessive activation of immune system. In a recent meta-analysis involving 16 trials and 6208 patients with advanced NSCLC, the overall incidence of irAEs was 22% for all grades and 4% for grade ≥3 irAEs.[17] In addition, fatal irAEs were observed in 0.34% of patients and most deaths (79%) were attributed to pneumonitis.[17] Therefore, ICIs were generally well-tolerated and the majority of irAEs can be successfully managed with corticosteroids or other immunosuppressive agents based on the guidelines on the management of irAEs.

Corticosteroids Use

As mentioned above, corticosteroids are the mainstay for the management of irAEs and commonly used in patients with NSCLC in a variety of conditions. Given the immunosuppressive effects of corticosteroids and pleiotropic impact on T-cell function, concerns regarding the adverse effect of corticosteroids use on the outcomes of ICIs arose. In a recent retrospective study, baseline corticosteroid use of ≥10 mg of prednisone was associated with inferior clinical outcomes in patients with NSCLC when receiving ICIs.[18] Ricciuti *et al*[19] further investigated the effect of different reasons for corticosteroids uses (cancer-related palliative reasons *vs.* cancer-unrelated indications) on outcomes of patients with advanced NSCLC who were administrated with ICIs. Interestingly, patients who received ≥10 mg of prednisone for cancer-related palliative reasons had poorer outcomes than those who received ≥10 mg of prednisone for cancer-unrelated indications or 0 to 10 mg of prednisone. In light of current evidence, necessary corticosteroid uses therefore should not be decreased or discontinued before the start of ICI treatment.

Hyperprogression and Pseudoprogression

Hyperprogressive disease (HPD) is an atypical response pattern of ICI treatment, characterized by an acceleration of tumor growth kinetics. The incidence of HPD in patients with advanced NSCLC after ICI treatment varied from 9% to 20%.[20] In a large-sample cohort including 406 advanced NSCLC patients treated with ICIs, 13.8% (56/406) of patients experienced HPD, with a dismal OS of only 3.4 months.[21] Several clinical or genetic factors have been identified to be associated with HPD, including increased age (>65 years), more than two metastatic sites before ICI treatment, a lower frequency of effector/memory subsets of T cells or *EGFR* alterations, *STK11* mutations, *MDM2/4* amplifications.[22] However, the molecular and immunological bases of HPD remain unclear. A better understanding of the biology of HPD is essential to avoid this detrimental effect of ICI-based therapy on outcomes.

Pseudoprogression represents another atypical response pattern of ICI treatment, which was characterized by initial disease progression but followed by radiologic tumor remission with continued use of ICIs. Pseudoprogression is considered as a result of infiltration of inflammatory cells, hemorrhage, edema or necrosis upon ICI treatment, which lead to accumulated tumor lesions temporarily. This phenomenon was uncommon and found in only 5% of patients with advanced NSCLC treated with ICIs.[21] In clinical practice, the unidimensional immune-related response criteria or the immune Response Evaluation Criteria in Solid Tumors (RECIST) criteria were helpful in distinguishing radiologic pseudoprogression from true progression. Furthermore, circulating tumor DNA (ctDNA) levels may be useful for early recognition of pseudoprogression in patients during ICI treatment.

Overcoming Primary and Acquired resistance to ICIs

As mentioned above, although predictive biomarker could help identify patients who may benefit from ICI treatment, a substantial number of patients still do not respond to ICIs, namely primary resistance. A characterization of hot, altered (immunosuppressed/excluded) and cold tumor phenotypes on the basis of the level and spatial distribution of CD3+ and CD8+ T cell infiltration may help understand the mechanisms of primary resistance.[23] Hot tumors, characterized by a high degree of T cell infiltration, represent a tumor phenotype that is suitable for ICI monotherapy or immune-oncology combinations.[23] For altered-immunosuppressed immune tumors or altered-excluded immune tumors, varied combination therapies

are needed to eliminate the immunosuppressed tumor microenvironment (inhibitory molecules, including transforming growth factor-β, interleukin-10 and vascular endothelial growth factor or inhibitory immune cells, including myeloid-derived suppressor cells and Treg cells) and facilitate T cells into the center of tumor (combined with T cell trafficking modulators or physical barrier breakers). For cold tumors, the principle of treatment is to turn cold tumors into hot tumors. ICI in combination with chemotherapy or radiotherapy has been proved effective in patients with NSCLC. Furthermore, how to manage acquired resistance to ICI treatment continues to be a challenge. Varied combinations of PD-1/PD-L1 inhibitors and other checkpoint molecules (cytotoxic T lymphocyte antigen 4 [CTLA-4], T cell immunoglobulin domain and mucin domain-3 [TIM-3], lymphocyte activation gene-3 [LAG-3]), immune-stimulatory agents, metabolic modulators and other immune modulators are being investigated to overcome resistance to ICI treatment.

In the future, a considerable amount of work still needs to be done to maximize the efficacy of ICI treatment and bring about long-term survival in patients with lung cancer.

Funding

This study was partially supported by a grant from the National Natural Science Foundation of China (No. 81703020).

Conflicts of interest

None.

References

1. Reck M, Rodriguez-Abreu D, Robinson AG, Hui RN, Csoszi T, Fulop A, *et al*. Updated Analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol 2019;37:537–546. doi: 10.1200/Jco.18.00149.
2. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, *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;393:1819–1830. doi: 10.1016/S0140-6736(18)32409-7.
3. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, *et al*. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078–2092. doi: 10.1056/NEJMoa1801005.
4. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, *et al*. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018;378:2288–2301. doi: 10.1056/NEJMoa1716948.
5. Nishio M, Barlesi F , West H, Ball S, Bordoni R, Cobo M, et al. Atezolizumab plus chemotherapy for first-line treatment of non-squamous non-small cell lung cancer: results from the randomized phase III IMpower132 trial. J Thorac Oncol 2020. doi: 10.1016/j.jtho.2020.11.025.
6. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, *et al*. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:924–937. doi: 10.1016/S1470-2045(19)30167-6.
7. Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, *et al*. OA04.03 A randomized phase 3 study of camrelizumab plus chemotherapy as 1st line therapy for advanced/metastatic non-squamous non-small cell lung cancer. J Thorac Oncol 2019;14:S215–S216. doi: 10.1016/j.jtho.2019.08.425.
8. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, *et al*. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018;379:2040–2051. doi: 10.1056/NEJMoa1810865.
9. Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodriguez-Abreu D, Hussein M, *et al*. Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous NSCLC (IMpower131): results from a randomized phase III trial. J Thorac Oncol 2020;15:1351–1360. doi: 10.1016/j.jtho.2020.03.028.
10. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, *et al*. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379:2342–2350. doi: 10.1056/NEJMoa1809697.
11. Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, *et al*. Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC-update from PACIFIC. J Thorac Oncol 2020;15:288–293. doi: 10.1016/j.jtho.2019.10.002.
12. Mascaux C, Angelova M, Vasaturo A, Beane J, Hijazi K, Anthoine G, *et al*. Immune evasion before tumour invasion in early lung squamous carcinogenesis. Nature 2019;571:570–575. doi: 10.1038/s41586-019-1330-0.
13. Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, *et al*. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 2018;378:1976–1986. doi: 10.1056/NEJMoa1716078.
14. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, *et al*. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018;378:2093–2104. doi: 10.1056/NEJMoa1801946.
15. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, *et al*. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med 2019;381:2020–2031. doi: 10.1056/NEJMoa1910231.
16. Ott PA, Bang YJ, Piha-Paul SA, Razak ARA, Bennouna J, Soria JC, *et al*. T-Cell-inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. J Clin Oncol 2019;37:318–327. doi: 10.1200/JCO.2018.78.2276.
17. Sun X, Roudi R, Dai T, Chen S, Fan B, Li H, *et al*. Immune-related adverse events associated with programmed cell death protein-1 and programmed cell death ligand 1 inhibitors for non-small cell lung cancer: a PRISMA systematic review and meta-analysis. BMC Cancer 2019;19:558. doi: 10.1186/s12885-019-5701-6.
18. Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, *et al*. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. J Clin Oncol 2018;36:2872–2878. doi: 10.1200/JCO.2018.79.0006.
19. Ricciuti B, Dahlberg SE, Adeni A, Sholl LM, Nishino M, Awad MM. Immune checkpoint inhibitor outcomes for patients with non-small-cell lung cancer receiving baseline corticosteroids for palliative versus nonpalliative indications. J Clin Oncol 2019;37:1927–1934. doi: 10.1200/JCO.19.00189.
20. Champiat S, Dercle L, Ammari S, Massard C, Hollebecque A, Postel-Vinay S, *et al*. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. Clin Cancer Res 2017;23:1920–1928. doi: 10.1158/1078-0432.CCR-16-1741.
21. Ferrara R, Mezquita L, Texier M, Lahmar J, Audigier-Valette C, Tessonnier L, *et al*. Hyperprogressive disease in patients with advanced non-small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. JAMA Oncol 2018;4:1543–1552. doi: 10.1001/jamaoncol.2018.3676.
22. Kocikowski M, Dziubek K, Parys M. Hyperprogression under immune checkpoint-based immunotherapy-current understanding, the Role of PD-1/PD-L1 tumour-intrinsic signalling, future directions and a potential large animal model. Cancers (Basel) 2020;12:804. doi: 10.3390/cancers12040804.
23. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov 2019;18:197–218. doi: 10.1038/s41573-018-0007-y.

How to cite this article: Zhou F, Zhou CC. Immunotherapy in non-small cell lung cancer: advancements and challenges. Chin Med J 2021;134:1135–1137. doi: 10.1097/CM9.0000000000001338