Review

Combination Strategies on the Basis of Immune Checkpoint Inhibitors in Non–Small-Cell Lung Cancer: Where Do We Stand?

Meng Qiao, Tao Jiang, Shengxiang Ren, Caicun Zhou

Abstract

The era of immune checkpoint inhibitors, especially programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) antibodies in the treatment of advanced non–small-cell lung cancer (NSCLC) is coming. Because of the lack of the definite biomarkers to select the optimal responders, only approximately 20% of patients with advanced NSCLC would respond to single checkpoint inhibitors-based immunotherapy. Moreover, primary or acquired resistance to conventional therapies is inevitable in most cases. Thus, combinations are pushed to move forward to be an alternative strategy and surely, it would be a future direction. Combination approaches on the basis of PD-1/PD-L1 inhibitors are currently designed to re-energize the immune system with complementary/synergetic mechanisms and could achieve durable antineoplastic effects in NSCLC. Herein, we highlight the potential combinations on the basis of PD-1/PD-L1 inhibitors in NSCLC, with other immunotherapies, chemotherapy, radiotherapy, and targeted therapy in this current review.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide.[1] Non–small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases. Although the emergence of targeted therapy benefits the NSCLC patients who harbor specific genomic mutations, resistance is inevitably developed at some certain time point.[2,3] In this state, immunotherapy has come upon the stage in the treatment of NSCLC with the purpose of producing a durable response. Meanwhile, the conventional paradigm has been shifted from eradication of the tumor cell itself to unleash the surrounding suppressive environment. Immune checkpoints such as cytotoxic T–lymphocyte-associated antigen 4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1) have been considered as the main brakes on T cell response, and generate the comfortable environment for tumor growth and escape. Indeed, immune checkpoint inhibitors exhibit unprecedented efficacy in antitumor effect by releasing the brakes, in particular PD-1/PD-L1 inhibitors.[4] Several clinical trials, such as Checkmate-017, Checkmate-057, Keynote-010, Poplar, and OAK verified the efficacy of nivolumab, pembrolizumab, and atezolizumab in the second- or subsequent-line treatment of advanced NSCLC.[5-9] Furthermore, the encouraging results from Keynote-024 prompted immune checkpoint inhibitors as first-line treatment in advanced NSCLC patients with a PD-L1 tumor proportion score (TPS) of at least 50%.[10] However, challenges have arisen. Only a small proportion of patients (approximately 20%) can respond to single-agent treatment on account of no defined biomarkers to select the proper population.[5,6,11] Moreover, primary resistance to PD-1/PD-L1 blockade was also commonly observed.[12] In this circumstance, single-agent treatment is difficult to mount a long-lasting response, and covers only a small population of patients. Throughout Checkmate-012 and Keynote-021, 2 noteworthy clinical trials, combining the anti–PD-1 antibody and ipilimumab and chemotherapy respectively, to conquer cancer with distinct and complementary mechanisms might provide a new insight in solving the single-agent problems mentioned previously.[13,14] Therefore, in this review we focus on the rationale and clinical support of various combinations concerning PD-1/PD-L1 inhibitors and conventional therapies, including other immunotherapies, chemotherapy, radiotherapy, and targeted therapy in NSCLC.

M.Q. and T.J. contributed equally to this work.

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

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Addresses for correspondence: Shengxiang Ren, MD, PhD, or Caicun Zhou, MD, PhD, Department of Medical Oncology, Shanghai Pulmonary Hospital and Thoracic Cancer Institute, Tongji University School of Medicine, No 507, Zheng Min Road, Shanghai 200433, PR China
Fax: +86-21-65111298; e-mail contact: harry_ren@126.com; caicunzhou_dr@163.com

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Combination Strategies

Combined With Other Immunotherapies

Inhibitory Molecules. Cytotoxic T−lymphocyte-associated antigen 4, also named CD152, is a critical coinhibitory molecule exclusively expressed on activated T cells. As a homologue of CD28, CTLA-4 has a higher affinity with B7 complex (CD80/CD86) and subsequently mediates suppression of T cell activity by blocking the second signal transduction for T cell activation. Although CTLA-4 and PD-1 are widely accepted as immune checkpoints to downregulate the activation of T cells, they modulate immune response via complementary mechanisms.[15-17] CTLA-4 exerts its functions dominantly in the priming stage of T cell activation to induce peripheral tolerance, whereas PD-1 inhibits the activity of the effector T cells (termed "exhausted" T cells) to maintain peripheral T-cell tolerance.[18] Therefore, dual inhibition of the CTLA-4 and PD-1/PD-L1 pathways are supposed to synergistically amplify antitumor response by releasing the "brake" of T cells in all phases.

The outcome from Checkmate-012 is of great significance to testify to the efficacy of combination nivolumab and ipilimumab as first-line treatment for patients with advanced NSCLC. However, the promising outcome from Checkmate-012 was partly because of timely dose rectification. At the 2014 American Society of Clinical Oncology (ASCO), Antonia et al reported the interim phase I results from Checkmate-012.[19] Two different dose combinations have been explored: 4 cycles of nivolumab 3 or 1 mg/kg as well as ipilimumab (every 3 weeks [q3w]) 1 or 3 mg/kg followed by nivolumab 3 mg/kg (every 2 weeks [q2w]). Although 16 of 48 patients discontinued the trial because of adverse effects (AEs) and 4 fatalities occurred, treatment with nivolumab 3 mg/kg with ipilimumab 1 mg/kg achieved a higher objective response rate (ORR) regardless of histology type (29%). At 2016 ASCO,[14,20] 77 patients randomly assigned into 2 cohorts either received nivolumab 3 mg/kg q2w with ipilimumab 1 mg/kg every 12 weeks or 6 weeks (38 and 39 patients, respectively). The results showed that patients in the ipilimumab every 12 weeks cohort seemed to have better response to treatment with prolonged median progression-free survival (PFS: 8.1 vs. 3.9 months). The pooled subgroup analysis data indicated that higher levels of tumor PD-L1 expression was associated with better clinical response. When PD-L1 expression was 50% or higher, combined cohorts showed a superior effect in longer PFS (median PFS: not reached, 8.3 months, respectively) and significantly higher 1-year overall survival (OS) rate (100% vs. 83%) than nivolumab monotherapy. Moreover, a phase III clinical trial, Checkmate-227 was designed to validate the effect of nivolumab with ipilimumab on the first-line therapy of advanced NSCLC among all patients including a proportion of patients with negative or low expression PD-L1.

In terms of pembrolizumab and ipilimumab, Patnaik et al[21] reported that 17 patients in cohort D regularly received pembrolizumab with ipilimumab q3w for 4 cycles and followed by pembrolizumab with the same dose as maintenance regimen in 2015 ASCO. Grade 3 AEs only occurred in 2 of 17 patients and no dose-limited toxicity was noted. With a robust antitumor effect (ORR, 54%), pembrolizumab 2 mg/kg and ipilimumab 1 mg/kg as an ideal combination was eagerly applied in cohort H for expanded verification. However, at 2016 ASCO, aggregated analysis up to December 2015 in cohort D and H showed the notable toxicity with 1 treatment-related death and 24% Grade 3/4 AEs. Moreover, no obvious ORR benefit was observed compared with pembrolizumab alone reported in Keynote-001 (24% vs. 19.4%),[11] even in the subgroup analysis on the basis of PD-L1 expression.[22]

The data from a phase Ib trial combining durvalumab with tremelimumab brought hope to the late stage of NSCLC patients even with PD-L1 negative expression.[23] One hundred two patients were given dose-escalated medication of durvalumab from 3 mg/kg to approximately 20 mg/kg and tremelimumab 1, 3, and 10 mg/kg to determine the safe dose strategy. Treatment-related Grade 3/4 AEs occurred least frequently (17%) in the durvalumab 20 mg/kg with tremelimumab 1 mg/kg and all combinations with 1 mg/kg of tremelimumab achieved comparatively optimal antitumor activity despite PD-L1 status. On the basis of safety concerns, administration of durvalumab 20 mg/kg (every 4 weeks [q4w]) for 13 doses and tremelimumab 1 mg/kg (q4w) for 6 doses followed by (every 12 weeks) for 3 doses will be verified in larger population of patients in several phase III studies (ARCTIC: NCT02352948; MYSTIC: NCT02453282; NEPTUNE: NCT02542293; Table 1). It is important to note that in ARCTIC, combination strategy or single agent was designed to apply in patients with PD-L1 negative tumors to see whether they can trump traditional chemotherapy.[24]

Combining 2 immune checkpoint antagonists has emerged to be a promising future in the treatment of advanced NSCLC. However, incidence of concomitant AEs appears to be higher than for any single agent without a doubt. Toxicity and treatment-related AEs should be dealt with carefully and discreetly for the immune cascades because of the completely activated adaptive immune system.[25] Moreover, to avoid unnecessary financial toxicity, oncologists are suggested to weigh the pros and cons before the application of a therapeutic strategy.

Indoleamine-2,3-dioxygenase (IDO) is a catabolizing enzyme that mediates cleavage of tryptocan to kynurenine. High expression of IDO results in an immunosuppressive tumor microenvironment with impaired activity of effector T cells, increased differentiation of regulatory T (T_{reg}) cells and decreased dendritic cell (DC) functions.[26] Treatment with IDO inhibitor reversed suppression by decreasing numbers of myeloid-derived suppressor cells (MDSCs) and T_{reg}s.[27] Expression of IDO is a critical resistance mechanism to CTLA-4 blockade and dual inhibition with CTLA-4 and PD-1 or PD-L1 blockade leads to synergistic antitumor effects in melanoma models.[28,29] Therefore, preclinical data provides a strong theoretical basis for exploration of clinical combinations of IDO inhibitors and immune checkpoint inhibitors.

Interim data demonstrated the robust antitumor response with indoximod, an IDO pathway inhibitor in combination with pembrolizumab at the American Association for Cancer Research Plenary in patients with metastatic melanoma. With 52% and 59% ORR in patients with or without ocular melanoma, this impressive combination delineated a reliable safety profile with low incidence of Grade 3 AEs. On the basis of the encouraging clinical outcome in melanoma, this combination attempts to extend its therapeutic tumor types to all solid tumors, including NSCLC. In a 2017 ASCO abstract, presentation of a phase I/II study reported the efficacy and safety of epacadostat, a selective inhibitor of IDO, with pembrolizumab in the treatment of NSCLC regardless of mutation status.