Chinese Medical Journal®

Combination therapies with mitogen-activated protein kinase kinase inhibitors and immune checkpoint inhibitors in non-small cell lung cancer

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In the past few decades, tremendous advances have been made in terms of advanced non-small cell lung cancer (NSCLC). The identification of oncogenic drivers and the development of targeted therapies led to the development of "precision" medicine. On the other hand, more attention has been paid to cancer immune escape and a new class of immunomodulatory agents has been developed. It is very attractive to explore the combination strategies of the two approaches, which may also be meaningful from the perspective of immunology.

The mitogen-activated protein kinase (MAPK) pathway is essential for normal cellular functions [Supplementary Figure 1, http://links.lww.com/CM9/A376]. It is implicated in the tumorigenesis of many cancers including NSCLC. The Ras-Raf-mitogen-activated protein kinase kinase (MEK)-extracellular regulated protein kinase (ERK) signaling pathway is the classical pathway among the four MAPK pathways. As a gatekeeper of downstream ERK, MEK is a key component of this pathway and is easily inhibited. MEK inhibitors (MEKi) may have pleiotropic effects on the microenvironment,[1,2] thus facilitating better tumor recognition and killing by the immune system. Researches have shown promising results by combining MEKi and immunotherapies in melanoma.[1,3] In addition, NSCLC exhibits *KRAS* and *BRAF* mutations in the MAPK pathways, but *KRAS*-mutant NSCLC remains challenging. Here, we review the current status of the combination strategies of targeting the MAPK pathway and immunotherapies, mainly focusing on MEKi and anti-programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) antibodies.

MEKi alone or combined with *BRAF* inhibitors can regulate the immune microenvironment through the following mechanisms: (1) generation of an immune stimulating microenvironment by up-regulating the immune-stimulatory molecules and downregulating the immunosuppressive molecules[4,5]; (2) increased T cell infiltration[6]; (3) enhanced recognition by T cells[7,8]; and (4) enhanced T cell cytotoxicity and activity.[7] Latest studies have shown that MEKi regulate the tumor immune microenvironment also via pyroptosis, which is an inflammatory form of cell death.[9] Therapeutic efficacy of MEKi treatment *in vivo* depends on an intact immune system. Immunodeficient mice administered with MEKi showed significantly shorter term of tumor regrowth suppression compared to immunocompetent mice.[9]

Considering the immunomodulatory effects of MEKi, the combination of MEKi with anti-PD1/PD-L1 antibodies may generate an enhanced anti-tumor effect and improve tumor control. In a *KRAS*-mutant CT26 mouse colorectal tumor model, trametinib with immune checkpoint inhibitors demonstrated much more effective anti-tumor activity than any single agent.[4] A similar effect was observed in a mouse model with $HRAS^{G12D}$ mutation for head and neck squamous cell carcinoma.[10] In a *KRAS* mutation and p53 deficiency-driven lung cancer mouse model, the combinatorial administration of trametinib with anti-PD-1/PD-L1 antibodies synergistically increased anti-tumor response and prolonged survival. The combinational treatments not only increased tumor infiltrating CD4+ and CD8+ T cells, but also attenuated myeloid-derived suppressor cells.[11] Moreover, a synergism of selumetinib with either atezolizumab or avelumab was found in NSCLC patient derived three-dimensional *ex vivo* spheroids. Selumetinib exerted both direct cancer cell toxicity and immune-stimulatory effect.[2] A phase I/II study of BRAF and MEKi with pembrolizumab in $BRAF^{V600}$-mutant melanoma (KEYNOTE-022) showed an objective response of 73%

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001070

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Chinese Medical Journal 2020;133(20)

Received: 06-05-2020 **Edited by:** Pei-Fang Wei

(11/15) with tolerable adverse effects.[3] Many clinical trials focusing on combination therapy in melanoma, lung cancer, pancreatic cancer, and colorectal cancer are ongoing.

Except for trametinib and cobimetinib approved for melanoma, phase I–III clinical trials for other MEKi including selumetinib, binimetinib, pimasertib, refametinib, and PD-0325901 are ongoing. For NSCLC, trametinib is the only MEKi approved for advanced patients with $BRAF^{V600E}$ mutation when administered together with dabrafenib. In recent years, clinical trials on NSCLC combining MEKi and checkpoint inhibitors have been very active [Supplementary Table 1, http://links.lww.com/CM9/A308].

NCT03225664 is a phase Ib/II trial studying the side effects and best dose of trametinib when given together with pembrolizumab and seeing how well they work in treating patients with metastatic, recurrent, unresectable or locally advanced NSCLC. NCT03581487 investigates the best dose of selumetinib in combination with durvalumab and tremelimumab in stage IV NSCLC. Experimental Cohort E of NCT03178552 was designed to evaluate the safety and efficacy of targeted therapies in combination with atezolizumab in advanced NSCLC patients with $BRAF^{V600}$ mutation. Experimental Cohort 1 and Cohort 2 of NCT03337698 evaluated the efficacy, safety, and pharmacokinetics of cobimetinib combined with atezolizumab in metastatic NSCLC. Then, another phase II study of this combination (NCT03600701) was launched. How well the couple works will be evaluated. In addition, another five clinical trials on solid tumors, including lung cancer, are also underway to study the combination of MEKi and anti-PD-1/PD-L1 antibodies. Although most trials are "active" or "recruiting" and no results have been posted, we believe that the results of these studies will be promising.

KRAS mutation occurs in approximately 25% lung adenocarcinomas. Targeting *KRAS* signaling aims at its downstream targets. However, monotherapy of MEKi for *KRAS*-mutant NSCLC results in disappointing clinical outcome. An ongoing clinical trial NCT03299088 is aiming to evaluate the combination of trametinib and pembrolizumab especially for *KRAS*-mutant NSCLC [Supplementary Table 1, http://links.lww.com/CM9/A308].

However, many confounding factors may affect the treatment effects. Different sub-types of *KRAS* mutations have been identified in lung cancer, which may be functionally distinct. For example, $KRAS^{G12C}$ tumors are more sensitive to selumetinib either alone or combined with chemotherapy, compared to $KRAS^{G12D}$ tumors.[12] Moreover, *TP53* co-mutation rendered the sensitivity of $KRAS^{G12C}$ tumors to MEKi. Indeed, concurrent mutation has gained increasing attention. According to the most common co-mutations including serine/threonine kinase 11/liver kinase B1, *TP53* and cyclin-dependent kinase inhibitor 2A/B inactivation, *KRAS*-mutant NSCLC has been classified into three subsets: KL, KP, and KC.[13] Many studies have found significantly different clinical responses of KL and KP tumors to immune checkpoint blockade.[14] Furthermore, KRAS dimerization could not only impact the oncogenic activity of *KRAS* mutation but also the sensitivity to MEKi.[15] Response to MEKi may also be different due to downstream activation of AKT or signal transducer and activator of transcription 3. Therefore, a proper signature predicting the response to combination therapies with MEKi and checkpoint inhibitors is required in *KRAS*-mutant NSCLC.

Mono-immunotherapy is less effective in NSCLC patients harboring epidermal growth factor receptor (*EGFR*) mutation because of the notably low immune infiltrating levels. However, when disease progresses after EGFR-tyrosine kinase inhibitor (TKI) treatment, T790M-negative patients have a higher PD-L1 expression level compared to T790M-positive patients.[16,17] A recent study suggested that T790M-negative patients are more likely to benefit from nivolumab after EGFR-TKI treatment.[17] Pre-clinical studies demonstrated that acquired resistance of EGFR-TKI could occur through the MEK/ERK pathway by major histocompatibility complex class I molecules down-regulation, which may be reversed by MEKi.[18] Taken together, when EGFR-TKI failure occurs in EGFR-driven NSCLC patients, we propose that combination of MEKi and immunotherapies can be considered. Further clinical trials are needed.

Although immune-stimulatory effects of MEKi have been confirmed, the tumor microenvironment may change during MEKi treatment. The treatment sequence needs to be discussed further. Evidence suggests that pulsatile administration of MEKi may be superior to continuous administration. The latter could induce feedback regulation and thus re-activate MEK signaling.[19] Long-term inhibition of T-cell receptor signaling by MEKi could damage the function and proliferation of T cells. In a CT26 mouse model, transient pre-treatment or lead-in treatment of MEKi combined with checkpoint inhibitors showed better tumor control.[20] Finding the most effective therapy sequence of combination therapy is particularly important. In addition, signaling pathways or key proteins may be activated in a compensatory manner during the treatment of MEKi. Inhibition of these pathways or proteins may prevent the adaptive resistance to MEKi. This is also a challenge for combination therapy with MEKi and immunotherapy. Therefore, optimization strategies of combination therapies in NSCLC need further evaluation.

Considerable evidence provides a strong rationale for combination strategies with MEKi and checkpoint inhibitors in NSCLC. However, many hurdles and challenges still remain. Toxicities of monotherapy of MEKi or immunotherapy are usually manageable. But the adverse effects of the combination must be considered. Questions about optimal timing or sequencing, drug resistance, and biomarkers are also unanswered. Current and future clinical trials are needed to address these questions. We are hopeful that the combination strategies with MEKi and immune checkpoint inhibitors will provide greater survival benefits for NSCLC patients.

Funding

This study was supported by the grants from the National Natural Science Foundation of China (No. 81672896), the National Key Research and Development Program: The key technology of palliative care and nursing for cancer patients (No. ZDZX2017ZL-01), and High Level Innovation Team of Nanjing Medical University (No. JX102GSP201727).

Conflicts of interest

None.

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How to cite this article: Xu JL, Wang XZ, Jiang HN, Chen Y, Wang R, Shu YQ. Combination therapies with mitogen-activated protein kinase kinase inhibitors and immune checkpoint inhibitors in non-small cell lung cancer. Chin Med J 2020;133:2495–2497. doi: 10.1097/CM9.0000000000001070