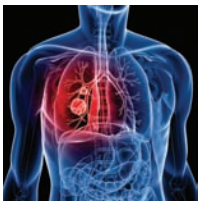
Clinical Trials

Major finding: Osimertinib achieved objective responses in 77% of patients with treatment-naïve NSCLC.

Mechanism: Putative resistance mutations and amplifications, but not *EGFR* T790M, were detectable in ctDNA.

Impact: Osimertinib warrants further investigation for the treatment of treatment-naïve patients with NSCLC.

OSIMERTINIB MAY BE AN EFFECTIVE FIRST-LINE THERAPY IN EGFR-MUTANT NSCLC



The selective EGFR tyrosine kinase inhibitor (TKI) osimertinib is active against EGFR-TKI–sensitizing mutations (*EGFR*m) and the *EGFR* T790M mutation, which promotes resistance to other EGFR-TKIs. Thus, osimertinib is indicated for patients with metastatic non–small cell lung cancer (NSCLC) who have progressed on other EGFR-TKI therapies. Osimertinib has been shown to delay the development of resistance in *EGFR*m tumors in preclinical studies, but has not been investigated as a first-line treatment in patients with NSCLC. Ramalingam and colleagues evaluated the safety and activity of osimertinib in 60 treatment-naïve patients with locally advanced or metastatic *EGFR*m NSCLC as part of the open-label, phase I AURA trial. The patients were enrolled in two cohorts receiving either 80 mg or 160 mg of osimertinib daily. End points included objective response rate, duration of response, progression-free survival, and safety evaluation. The overall objective response rate was 77% (67% in the 80 mg group and 87% in the 160 mg group) and the disease control rate was 97% across doses. The median progression-free survival was 20.5 months across doses, and the median duration of response was 18 months across doses. Post-progression plasma samples were obtained from 38 patients, 19 (50%) of whom had no detectable circulating tumor DNA (ctDNA). Genetic alterations potentially involved in resistance were detected in ctDNA from 9 of 19 patients, including amplifications of *MET*, *EGFR*, and *KRAS*; mutations in *MEK1*, *KRAS*, *PIK3CA*, and *JAK2*; an insertion in *HER2*; and *EGFR* C797S mutations. The *EGFR* T790M mutation was not detected. The safety profile of osimertinib was consistent with previous reports, and 62% of patients experienced grade 3 or greater adverse events. The 80 mg dose was better tolerated. Collectively, these findings support further investigation of osimertinib as first-line therapy in patients with *EGFR*m NSCLC and suggest potential mechanisms of resistance independent of *EGFR* T790M mutations. ■

Ramalingam SS, Yang JC, Lee CK, Kurata T, Kim DW, John T, et al. Osimertinib as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer. J Clin Oncol 2017 Aug 25 [Epub ahead of print].

Immunotherapy

Major finding: CMTM6 binds to PD-L1 on the plasma membrane to promote its stability and inhibitory activity.

Concept: CMTM6 depletion reduces constitutive and IFNγ-induced PD-L1 expression in a variety of cancer cells.

Impact: CMTM6 is a potential therapeutic target to indirectly inhibit PD-L1 and overcome tumor immune evasion.

CMTM6 REGULATES PD-L1 EXPRESSION AND ANTITUMOR IMMUNITY

Immune checkpoint therapies targeting the PD-1–PD-L1 interaction promote the antitumor activity of tumor-specific T cells and have been approved for the treatment of multiple tumor types. However, the mechanisms by which PD-L1 expression is regulated on tumor cells remain poorly understood. In two related studies, Burr and colleagues and Mezzadra and colleagues identified the type-3 transmembrane protein CMTM6 as a critical regulator of PD-L1 using a genome-wide CRISPR/Cas9 screen in pancreatic cancer cells and a haploid genetic modifier screen, respectively. CMTM6 depletion resulted in reduced expression of PD-L1, reducing both basal expression and IFNγ-induced expression of PD-L1, in a variety of cancer cell lines, including breast, lung, pancreas, thyroid, and colorectal cancers, melanoma, and chronic myeloid leukemia, as well as in primary dendritic cells. Moreover, CMTM4 was also able to positively regulate PD-L1 expression in the absence of CMTM6, although other CMTM family proteins did not. CMTM6 does not function as a transcriptional regulator of PD-L1; instead, CMTM6 loss resulted in a rapid decay of PD-L1 protein. CMTM6 bound directly to PD-L1 on the plasma membrane and in recycling endosomes, where it was required for endocytic recycling of PD-L1. Thus, CMTM6 prevented lysosomal degradation of PD-L1 to enhance PD-L1 stability. Further, in coculture experiments, CMTM6 depletion in tumor cells enhanced T-cell activity as measured by increased cytotoxic activity and augmented secretion of proinflammatory cytokines. Collectively, these studies identify CMTM6 as a positive regulator of PD-L1 expression on tumor cells that increases its inhibitory function and suggest the potential for therapeutic targeting of CMTM6 to enhance antitumor immunity. ■

Burr ML, Sparbier CE, Chan YC, Williamson JC, Woods K, Beavis PA, et al. CMTM6 maintains the expression of PD-L1 and regulates anti-tumour immunity. Nature 2017;549:101–5.

Mezzadra R, Sun C, Jae LT, Gomez-Eerland R, de Vries E, Wu W, et al. Identification of CMTM6 and CMTM4 as PD-L1 protein regulators. Nature 2017;549:106–10.

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