Furmonertinib

Furmonertinib, also known as HMPL-504, is a third-generation epidermal growth factor receptor tyrosine kinase inhibitor that is currently under investigation for the treatment of non-small cell lung cancer (NSCLC). It is being developed by HUTCHMED (also known as Hutchison China MediTech) and is currently in clinical trials.

Furmonertinib is designed to selectively target cancer cells with Epidermal growth factor receptor mutation, which is a common driver of NSCLC. It has been shown in preclinical studies to be effective against a range of EGFR mutations, including the T790M mutation that often develops in response to first- and second-generation EGFR TKIs.

Clinical trials have shown that furmonertinib has promising activity against EGFR-mutant NSCLC, including those with the T790M mutation, with high response rates and durable responses. It has also demonstrated a favorable safety profile in early studies.

If furmonertinib proves to be effective in later-stage clinical trials, it may provide a new treatment option for patients with EGFR-mutant NSCLC, particularly those with the T790M mutation who have developed resistance to other EGFR TKIs.

Furmonertinib can reach a higher concentration in the cerebrospinal fluid (CSF) than other tyrosine kinase inhibitors, and exhibit a beneficial effect in NSCLC patients with leptomeningeal metastases (LM) harboring sensitive EGFR mutation. Qian et al. reports that two-stage IV pulmonary adenocarcinoma patients with LM harboring an EGFR L858R mutation benefit from the third-generation EGFR-TKIs rechallenge after immune checkpoint inhibitor (ICI) and anti-angiogenic agent combination therapy. Complete response (CR) to partial response (PR) of the central nervous system (CNS) response was achieved immediately after the administration of furmonertinib and osimertinib. They conducted next-generation sequencing (NGS) and IHC to elucidate the evolution of driver mutations and the immune microenvironment. In conclusion, these two cases might provide a therapeutic strategy for further clinical practice. More research was needed to elucidate the resistance mechanisms and improve current treatment strategies in EGFR-mutated patients with LM [1)].

Hu et al. report the pooled central nervous system (CNS) efficacy data of furmonertinib in patients with EGFR T790M mutated non-small cell lung cancer (NSCLC) from two phase 2 studies.

Methods: This was a pooled, posthoc analysis of two phase 2 studies (NCT03127449 [phase 2a study of furmonertinib], NCT03452592 [phase 2b study of furmonertinib]). In the phase 2a study, patients received furmonertinib 40 mg, 80 mg, 160 mg, or 240 mg orally once daily. In the phase 2b study, all patients received furmonertinib 80 mg orally once daily. CNS efficacy of furmonertinib was analyzed in patients with baseline CNS lesions by an independent review center per Response Evaluation Criteria in Solid Tumors version 1.1.

Results: A total of 132 patients with baseline CNS metastases were included in this analysis. In 52 patients with measurable CNS lesions, CNS objective response rates were zero (0/1), 65% (22/34), 85% (11/13), and 25% (1/4), and CNS disease control rates were zero (0/1), 97% (33/34), 100%

(13/13), and 100% (4/4) in the 40 mg, 80 mg, 160 mg, and 240 mg orally once daily group, respectively. In patients with measurable or non-measurable CNS lesions, median CNS progression-free survival was 2.8 months (95% confidence interval [CI] 1.4-8.3), 11.6 months (95% CI 8.3-13.8), 19.3 months (95% CI 5.5-not available [NA]), and not reached (95% CI 2.8 months-NA) in the 40 mg, 80 mg, 160 mg, and 240 mg orally once daily group, respectively.

Furmonertinib showed promising CNS efficacy in doses of 80 mg orally once daily or higher in patients with EGFR T790M mutated NSCLC.

Trial registration: Both studies were registered on ClinicalTrial.gov. The phase 2a study was registered with NCT03127449 on April 25, 2017; The phase 2b study was registered with NCT03452592 on March 2, 2018 [2)].

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Qian C, Zhang Y, Cheng W, Zhang Q, Li M, Fang S. Case report: Rechallenge with EGFR-TKIs after immunotherapy in EGFR-mutated non-small cell lung cancer with leptomeningeal metastasis. Front Oncol. 2022 Nov 15;12:957661. doi: 10.3389/fonc.2022.957661. PMID: 36457498; PMCID: PMC9705570.
2)
Hu X, Zhang S, Ma Z, Feng J, Wu L, Lv D, Zhou J, Zhang X, Liu L, Yu Q, Liao W, Zhang Y, Wang X, Cheng Y, Niu H, Wang Z, Wang D, Huang C, Liu C, Zhao H, Feng J, Li J, Ying K, Yang N, Qin S, Hu J, Liu F, Jiang Y, Ge N, Shi Y. Central nervous system efficacy of furmonertinib (AST2818) in patients with EGFR T790M mutated non-small cell lung cancer: a pooled analysis from two phase 2 studies. BMC Med. 2023 Apr 28;21(1):164. doi: 10.1186/s12916-023-02865-z. PMID: 37118803.