Furmonertinib

2022

https://www.mdpi.com/1420-3049/27/14/4474

Determination of Osimertinib, Aumolertinib, and Furmonertinib in Human Plasma for Therapeutic Drug Monitoring by UPLC-MS/MS.

Citation

Molecules. 2022;27(14).

Authors

Li Y, Meng L, Ma Y, Li Y, Xing X, Guo C, Dong Z.

Abstract

The third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), osimertinib, aumolertinib, and furmonertinib represent a new treatment option for patients with EGFR p.Thr790 Met (T790 M)-mutated non-small cell lung cancer (NSCLC). Currently, there are no studies reporting the simultaneous quantification of these three drugs. A simple ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS) method was developed and validated for the simultaneous quantitative determination of osimertinib, aumolertinib, and furmonertinib concentrations in human plasma, and it was applied for therapeutic drug monitoring (TDM). Plasma samples were processed using the protein precipitation method (acetonitrile). A positive ion monitoring mode was used for detecting analytes. D3-Sorafenib was utilized as the internal standard (IS), and the mobile phases were acetonitrile (containing 0.1% formic acid) and water with gradient elution on an XSelect HSS XP column (2.1 mm × 100.0 mm, 2.5 µm, Waters, Milford, MA, USA) at a flow rate of 0.5 mL·min−1. The method's selectivity, precision (coefficient of variation of intra-day and inter-day ≤ 6.1%), accuracy (95.8–105.2%), matrix effect (92.3–106.0%), extraction recovery, and stability results were acceptable according to the guidelines. The linear ranges were 5–500 ng·mL−1, 2–500 ng·mL−1, and 0.5–200 ng·mL−1 for osimertinib, aumolertinib, and furmonertinib, respectively. The results show that the method was sensitive, reliable, and simple and that it could be successfully applied to simultaneously determine the osimertinib, aumolertinib, and furmonertinib blood concentrations in patients. These findings support using the method for TDM, potentially reducing the incidence of dosing blindness and adverse effects due to empirical dosing and inter-patient differences.

Keywords: UPLC-MS/MS; osimertinib; aumolertinib; furmonertinib; therapeutic drug monitoring

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https://pubmed.ncbi.nlm.nih.gov/34789919/

Effect of autoinduction and food on the pharmacokinetics of furmonertinib and its active metabolite characterized by a population pharmacokinetic model.

Citation

Acta Pharmacol Sin. 2022 Jul;43(7):1865-1874.

Authors

Zou HX, Zhang YF, Zhong DF, Jiang Y, Liu F, Zhao QY, Zuo Z, Zhang YF, Yan XY.

Abstract

Furmonertinib (AST2818) is a novel third-generation irreversible EGFR TKI and recently has been approved in China for the treatment of non-small cell lung cancer (NSCLC) with EGFR-sensitizing and T790M resistance mutations. In the current study, we developed a semi-mechanistic population pharmacokinetic model to characterize the nonstationary pharmacokinetics (PK) of the furmonertinib and its active metabolite AST5902 simultaneously. The PK data of furmonertinib and AST5902 were obtained from 38 NSCLC patients and 16 healthy volunteers receiving 20-240 mg furmonertinib in three clinical trials. A nonlinear mixed-effects modeling approach was used to describe the PK data. The absorption process of furmonertinib was described by a transit compartment model. The disposition of both furmonertinib and AST5902 was described by a two-compartment model. An indirect response model accounted for the autoinduction of furmonertinib metabolism mediated by CYP3A4. The model-based simulation suggested that furmonertinib clearance was increased in one cycle of treatment (orally once daily for 21 days) compared to baseline, ranging from 1.1 to 1.8 fold corresponding to the dose range of 20-240 mg. The concentration of furmonertinib was decreased over time whereas that of AST5902 was increased. Interestingly, the concentration of the total active compounds (furmonertinib and AST5902) appeared to be stable. The food intake, serum alkaline phosphatase and body weight were identified as statistically significant covariates. The mechanism of food effect on PK was investigated, where the food intake might increase the bioavailability of furmonertinib via increasing the splanchnic blood flow. Overall, a population PK model was successfully developed to characterize the nonstationary PK of furmonertinib and AST5902 simultaneously. The concentrations of total active compounds were less affected by the autoinduction of furmonertinib metabolism.

Keywords: NSCLC; alkaline phosphatase; autoinduction; body weight; food effect; furmonertinib; modeling and simulation; pharmacokinetics.

https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.e21029

Preliminary clinical investigations of high-dose furmonertinib in NSCLC with EGFR Exon 20 insertions (20ins).

Citation

Journal of Clinical Oncology. 2022;40(16_suppl):e21029–e21029.

Authors

Lin Y, Hu Z, Zhang Y, Sun S, Yu H, Zhao X, Wu X, Wang H, Wang J.

Abstract

Background: Currently neither chemotherapy nor approved EGFR TKIs have satisfactory efficacy in most EGFR 20ins mutations. Activity of high-dose furmonertinib, a novel 3rd generation EGFR TKI, against EGFR 20ins was assessed in preclinical models and a phase lb study. This study aimed to retrospectively investigate the efficacy of high-dose furmonertinib against EGFR 20ins in the real world. Methods: Retrospective search identified 14 metastatic NSCLC patients (pts) with EGFR 20ins treated with high-dose furmonertinib (160mg qd) in Fudan University Shanghai Cancer Center. The clinical efficacy and safety were investigated. Results: Median age was 60 years old (range 40-75) in this cohort with 28% female. At data cutoff date of January, 2022, 9 pts had ≥1 disease assessment. 5 out of 9 pts achieved PR, and 3 patients achieved SD. No CR was observed and 1 patient PD at first assessment. The most common adverse events (AE, ≥20%) were diarrhea, paronychia, skin fissures, anorexia, pain in extremity, rash and stomatitis. No grade ≥3 AE was observed. Conclusions: High-dose furmonertinib has shown encouraging anti-tumor activity in NSCLC with EGFR 20ins.

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https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.e21063

Short-term efficacy of furmonertinib in treatment of NSCLC patients with EGFR exon20 insertion.

Citation

Journal of Clinical Oncology. 2022;40(16_suppl):e21063–e21063.

Authors

Zhou X, Dong H, Li P, Wu C, Lu H, Xiao M, Zhou T.

Abstract

Background: EGFR is a key driver gene of lung cancer, in which exon 20 insertion (Ex20ins) mutation accounts for about 1-5%. However, the first- and second-generation EGFR-TKI had poor efficacy on patients with Ex20ins mutation (ORR = 6.9%, mPFS = 1.9 months, mOS = 12.9 months, DCR = 44.8%). Our study retrospectively observed the short-term efficacy and safety of furmonertinib in Chinese NSCLC patients with EGFR Ex20ins mutation. Methods: The study retrospectively collected 15 NSCLC patients with EGFR Ex20ins mutant who were treated in two medical institutions in Changzhou City, Jiangsu Province from April 2021 to December 2021. All patients received targeted therapy with furmonertinib. The last follow-up time was December 30, 2021. All patients received 160 mg furmonertinib orally until disease progression, drug intolerance, patient refusal or death. EGFR Ex20ins mutation was confirmed by ARMS or next generation sequencing (NGS). The patient's gender, age, score of Eastern Cooperative Oncology Group (ECOG), smoking history, pathological type, tumor stage, gene status and other basic clinical characteristics and adverse events (AES) were collected. The clinical efficacy was evaluated according to RECIST version 1.1, and the adverse events were evaluated according to the NCI-CTCAE version 5.0. SPSS 25.0 software was used to record and analyze the data. Results: All 15 patients had received ≥2 lines of therapy. The median age was 62 (25-80) years old, and there were 8 male patients (53.3%). Most patients had no smoking history (13 cases, 86.7%). ECOG score was mostly 1 (13 cases, 86.7%). In 15 patients, we found 10 different EGFR Ex20ins variants, among which p.A767_V769dup (n = 3) and p.A767_V769dup (n = 4) were more common. By the end of follow-up, 15 patients had completed at least one efficacy evaluation, and all had different degrees of tumor regression. No patient reached CR, 8 patients had PR and 7 patients had SD. This preliminary efficacy data showed that the overall ORR was 53.5% and DCR was 100%. No grade 3 or above adverse events were observed. The 3-months PFS rate was 100%. Conclusions: The results of this study in ≥2 lines patients treated with twice the conventional dose had a good curative effect (compared with 3 times of conventional dosage in FAVOUR study), which provided more treatment options for NSCLC patients in multiple lines of treatment and could alleviate part of their economic pressure, but the PFS and OS data still need further follow-up and verification of a larger sample size. The overall findings suggested that furmonertinib is a third generation EGFR-TKI with good efficacy and acceptable safety. Given the heterogeneity of EGFR Ex20ins mutation, the efficacy of targeted therapy may vary in different mutation types and requires further investigation.

https://www.sciencedirect.com/science/article/abs/pii/S2213260022001680

Furmonertinib (AST2818) versus gefitinib as first-line therapy for Chinese patients with locally advanced or metastatic EGFR mutation-positive non-small-cell lung cancer (FURLONG): a multicentre, double-blind, randomised phase 3 study.

Citation

The Lancet Respiratory Medicine. Published online 2022.

Authors

Shi Y, Chen G, Wang X, Liu Y, Wu L, Hao Y, Liu C, Zhu S, Zhang X, Li Y, Liu J, Cao L, Cheng Y, Zhao H, Zhang S, Zang A, Cui J, Feng J, Yang N, Liu F, Jiang Y, Gu C.

Abstract

Background

Furmonertinib (AST2818) is an irreversible, selective, third-generation EGFR tyrosine-kinase inhibitor. We aimed to investigate the efficacy and safety of furmonertinib versus the first-generation EGFR tyrosine-kinase inhibitor gefitinib as first-line treatment in patients with EGFR mutation-positive locally advanced or metastatic non-small-cell lung cancer (NSCLC).

Methods

The FURLONG study is a multicentre, double-blind, randomised, phase 3 study done in 55 hospitals across mainland China. We enrolled patients who were aged 18 years or older and had histologically confirmed, locally advanced or metastatic, stage IIIB, IIIC, or IV unresectable NSCLC with EGFR exon 19 deletions or exon 21 Leu858Arg mutation on tissue biopsy confirmed by a central laboratory. Eligible patients were stratified according to EGFR mutation (exon 19 deletions or exon 21 Leu858Arg) and CNS metastases (with or without) and randomly assigned (1:1) to receive either oral furmonertinib (80 mg/day) or oral gefitinib (250 mg/day) in 21-day cycles until disease progression, the occurrence of intolerable toxicities, withdrawal of consent, or other discontinuation reasons judged by the investigators. Investigators, clinicians, participants, independent review centre (IRC) members, the sponsor, and those analysing the data were all masked to treatment allocation. The primary endpoint was IRC-assessed progression-free survival and, along with safety, was analysed in the full analysis set, which comprised all randomly assigned patients who had received at least one dose of study drug. This study is registered with ClinicalTrials.gov, NCT03787992, and is ongoing for survival follow-up.

Findings

Between May 30, 2019, and Dec 5, 2019, 750 patients were screened, of whom 358 were randomly assigned to receive either furmonertinib and gefitinib-matching placebo (n=178) or gefitinib and furmonertinib-matching placebo (n=180). 178 patients randomly assigned to furmonertinib and 179 patients randomly assigned to gefitinib were treated and were included in the full analysis set. Median follow-up was 21·0 months (IQR 18·0–23·5) in the furmonertinib group and 21·0 months (18·0–23·5) in the gefitinib group. Median IRC-assessed progression-free survival was 20·8 months (95% CI 17·8–23·5) in the furmonertinib group and 11·1 months (9·7–12·5) in the gefitinib group (hazard ratio 0·44, 95% CI 0·34–0·58; p<0·0001). Treatment-related adverse events of a grade 3 or more occurred in 20 (11%) of 178 patients in the furmonertinib group and in 32 (18%) of 179 patients in the gefitinib group. Treatment-related serious adverse events were reported in ten (6%) patients in the furmonertinib group and in 11 (6%) patients in the gefitinib group. Ten (6%) patients in the furmonertinib group and three (2%) patients in the gefitinib group died due to adverse events, which were all judged to be possibly unrelated to study treatment by the investigators.

Interpretation

Furmonertinib showed superior efficacy compared with gefitinib as first-line therapy in Chinese patients with EGFR mutation-positive NSCLC, along with an acceptable safety profile without new signals. Furmonertinib is a new potential treatment option for this population.

Funding

Shanghai Allist Pharmaceuticals and the China National Major Project for New Drug Innovation.

Translation

For the Chinese translation of the abstract see Supplementary Materials section.

https://web.p.ebscohost.com/abstract?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=10093419&AN=156995012&h=Z2j%2fOZ6tKOeV1zK2UMKjux92igoKJTERs6TXimjz%2fORNoSL1P5jpTVAj2esuZtSz3GSrPTwDpPuZcKJA%2fim%2b6g%3d%3d&crl=c&resultNs=AdminWebAuth&resultLocal=ErrCrlNotAuth&crlhashurl=login.aspx%3fdirect%3dtrue%26profile%3dehost%26scope%3dsite%26authtype%3dcrawler%26jrnl%3d10093419%26AN%3d156995012

Advances in Treatment of Non-small Cell Lung Cancer Harboring EGFR Exon 20 Insertion Mutations.

Citation

Chinese Journal of Lung Cancer . May2022, Vol. 25 Issue 5, p337-350. 14p.

Authors

Yang X, Zhao J

Abstract

Epidermal growth factor receptor (EGFR) exon 20 insertion mutations are the third most prevalent activating EGFR mutation in non-small cell lung cancer (NSCLC), accounting for 5%-12% of all EGFR mutations in NSCLC cases. Patients harboring EGFR exon 20 insertion mutations exhibit similar clinical characteristics except for worse prognosis as compared to those with 'classic' EGFR mutations. EGFR exon 20 insertion mutations are considered as a heterogeneous class of alterations that cause different conformational changes in EGFR. The majority of mutations (almost 90% of cases) is positioned in the loop that immediately follows the C-terminal of the C-helix, and the most widely reported subtype of insertion mutations is D770_N771>ASVDN(A767_V769dupASV) with frequency of 21%-28%. NSCLC patients with EGFR exon 20 insertion mutations show primary drug resistance to previously approved EGFR tyrosine kinase inhibitors and are generally insensitive to conventional chemotherapy and immunotherapy. The recently approved targeted drugs Amivantamab and Mobocertinib shift the treatment paradigm for NSCLC patients harboring EGFR exon 20 insertion mutations. There are also several new compounds targeting NSCLC EGFR exon 20 insertion mutations are in development. In this article, we provide a through overview on the treatment development in EGFR exon 20 insertion mutant NSCLC.

https://www.tandfonline.com/doi/abs/10.1080/07357907.2022.2077566

Management of Non-Small Cell Lung Cancer: Updates from the European Lung Cancer Congress 2022.

Citation

Cancer Investigation. 2022;0(0):1–13.

Authors

Arora S, Asawa P, Kataria N, Hendriks LEL, Desai AP.

Abstract

The recently concluded European Lung Cancer Congress 2022 (ELCC22) showcased some very exciting data, with more than 200 abstracts presented

during the meeting. Through this review, we focus on selected clinically relevant abstracts that in our opinion represent significant updates in the current management of non-small cell lung cancer (NSCLC). Here, we summarize the updates in surgical management, adjuvant therapy and therapy for advanced stage NSCLC and put these advances in the context of the current clinical standard of care.

https://journals.lww.com/americantherapeutics/Fulltext/9900/Successful_Salvage_Therapy_With_a_High_Dose_of.30.aspx?casa_token=_Ho0f3dMOYsAAAAA:98zLfNFI23V1vWyH1S78E9RtCd_2EVHd905nloIS9Z1hCQFhGTbcDO_j1NjhWJKJGMTBZkDGZgTp1nEpgmH9uH8V1TQUzNKchek

Successful salvage therapy with a high dose of furmonertinib in a case of lung adenocarcinoma harboring EGFR Exon 20 insertion.

Citation

Am J Ther. Published online 2022:10.1097/MJT.0000000000001504.

Authors

Jiang W, Sha M, Chen C.

Abstract

INTRODUCTION

Exon 20 insertions (ex20ins) are the third most common epidermal growth factor (EGFR) mutation, after exon 19 deletions and exon 21 point mutations. Patients with non–small-cell cancer (NSCLC) with EGFR ex20ins acquire fewer benefits from EGFR tyrosine kinase inhibitors (TKIs)1 and have lower overall survival2 than patients with other mutations.

To date, no effective targeted therapy has been developed for patients with NSCLC with EGFR ex20ins. Moreover, the use of furmonertinib to treat EGFR ex20ins NSCLC is uncommon. We report a patient with lung adenocarcinoma harboring EGFR ex20ins who achieved disease control after receiving high-dose furmonertinib.

Free Full Text of Entire Article

https://link.springer.com/article/10.1186/s40364-022-00372-6

EGFR exon 20 insertion mutations in advanced non-small-cell lung cancer: current status and perspectives.

Citation

Biomarker Research. 2022;10(1):21.

Authors

Hou J, Li H, Ma S, He Z, Yang S, Hao L, Zhou H, Zhang Z, Han J, Wang L, Wang Q.

Abstract

Platinum-based chemotherapy was previously the first-choice treatment for lung cancer. The discovery of epidermal growth factor receptor (EGFR) gene mutations and the development of EGFR tyrosine kinase inhibitors (TKIs) marked the beginning of the targeted therapy era for non-small-cell lung cancer (NSCLC). Thirty percent of NSCLC patients carry EGFR gene mutations. For these advanced NSCLC patients, EGFR-TKIs are currently preferred for their superior activity and survival benefits over platinum-based chemotherapy. However, therapeutic efficacy is quite different in patients with EGFR exon 20 insertion (ex20ins) mutations versus common mutations. Patients with ex20ins mutations are insensitive to EGFR-TKIs and have poor prognosis. Some drugs targeting EGFR ex20ins mutations have been approved. Here, we systematically reviewed the recent clinical research of and treatments used for EGFR ex20ins mutations, summarized the latest data on emerging therapies, and discussed future prospects and treatments.

Free Full Text of Entire Article

https://www.tandfonline.com/doi/abs/10.1080/07357907.2022.2069254

Three third-generation epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer: Similarities and differences.

Citation

Cancer Invest. Published online 2022:1-14.

Authors

Chen L, Zhou Y, Gan C, Wang X, Liu Y, Dong C, He R, Yang J.

Abstract

Osimertinib, almonertinib and furmonertinib are third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) approved for non-small cell lung cancer (NSCLC) patients with EGFR T790M mutation.

This article reviews research advances in pharmacokinetics, pharmacodynamics, treatment-related adverse events, and other aspects related to the three EGFR-TKIs were systematically reviewed in order to provide references for clinical drug selection. There are differences in dosing schedule and incidence of adverse events among three drugs. Optimization of third-generation EGFR-TKIs options for individuals may produce the maximal benefits to NSCLC patients with EGFR T790M mutation.

Keywords: Osimertinib, almonertinib, furmonertinib

https://www.jto.org/article/S1556-0864(22)00052-1/fulltext

The challenges of third-generation EGFR tyrosine kinase inhibitors in the therapy of advanced NSCLC.

Citation

J Thorac Oncol. 2022;17(4):481-486.

Authors

Wang F, Zhou Q.

Abstract

The EGFR tyrosine kinase inhibitors (TKIs) have initiated the era of precision medicine in lung cancer. In the past two decades, EGFR TKIs have dramatically extended the overall survival (OS) of patients with advanced NSCLC with EGFR-activating mutations from less than 12 months in the chemotherapy era1 to 3 years or more in the targeted therapy era.2 From quinazoline-based reversible inhibitors to irreversible pan-HER inhibitors then to pyrimidine-based irreversible inhibitor, the third-generation (3G) EGFR TKIs target Thr790Met (T790M) “gatekeeper” mutation, a first-generation (1G)/second-generation (2G) TKI-resistance mutation, by a strong covalent binding to cysteine 797 residue in the adenosine triphosphate binding site of the EGFR kinase domain.3 So far, more than four 3G TKIs have striking clinical efficacy.

Osimertinib is the first and the only 3G TKI approved by the Food and Drug Administration, European Medicines Agency, and Chinese National Medical Products Administration based on its impressive survival benefit found both in the later-line setting in patients harboring the T790M mutation4, 5, 6, 7, 8, 9, 10, 11 and in treatment-naive patients.2 Other 3G TKIs including almonertinib (HS-10296)12 and furmonertinib (alflutinib/AST2818)13 have been approved by the Chinese National Medical Products Administration recently for previously treated, metastatic EGFR T790M-positive NSCLC. Nevertheless, not all 3G TKIs have been successfully developed. For example,

the development of rociletinib (CO-1686), olmutinib (HM61713/BI 1482694), maverlertinib (PF06747775), and naquotinib (ASP8273) has been discontinued owing to off-target toxicity and modest efficacy. Against this backdrop, Cho et al.14 report a phase 1/2 study of another 3G EGFR TKI lazertinib 240 mg in T790M-mutant advanced NSCLC after previous 1/2G TKI therapy in this issue of Journal of Thoracic Oncology.

Lazertinib (YH25448) is a novel irreversible inhibitor selectively targeting EGFR single (exon 19 deletion [ex19del], L858R, T790M) and double (ex19del/T790M and L858R/T790M) mutations.15 Preclinical data support the ability of lazertinib to penetrate the blood–brain barrier. In this study, lazertinib 240 mg maintained its promising clinical performance after 2 years of follow-up, exhibiting comparable efficacy with the other 3G TKIs, osimertinib, almonertinib, and alflutinib, in a similar population (Fig. 1 and Supplementary Table 1). In terms of intracranial control, lazertinib had excellent results as well with the objective response rate of 86% (6 of 7) and intracranial progression-free survival (PFS) of 26 months, which is superior to the data currently released by the other 3G TKIs. If these observations can be repeated in larger studies or in the real world in the future, lazertinib may be the drug of choice for patients with brain metastasis. The adverse event spectrum of lazertinib was comparable with that of osimertinib, with the exception that the incidence of cardiac toxicity and interstitial lung disease seemed to be less. Nevertheless, the proportions of treatment adjustments owing to adverse event were higher than that reported for the other 3G TKIs (Table 1).

Advanced lung adenocarcinoma patient with EGFR exon 20 insertion benefits from high-dose furmonertinib for nine months after progression from mobocertinib: a case report.

Citation

Ann Transl Med. 2022 Mar;10(6):386.

Authors

Jia K, Yang S, Chen B, Yu J, Wu Y, Li W, Zhou F, Wu F, Feng G, Ren S.

Abstract

Background

The treatment landscape of non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutation has significantly changed in the past decade. However, EGFR exon 20 insertion (20ins), which accounts for at least 9% of all EGFR mutated cases, has been generally associated with resistance to common EGFR tyrosine kinase inhibitors (TKIs). In recent years, major progress has been made in the precision treatment of NSCLC harboring EGFR exon 20ins, thanks to the development of TKIs and mAb-based agents specifically targeting EGFR 20ins. However, the efficacy of these novel agents, such as mobocertinib and amivantamab, is not quite satisfactory. Therefore, there is an urgent need to identify other effective targeted drugs.

Case Description

Herein, we describe a case with EGFR 20ins diagnosed by amplification refractory mutation system polymerase chain reaction (ARMS-PCR) who benefited from high-dose (160 mg/d comparing with Phase II recommended dose 80 mg/d) furmonertinib, a novel third-generation EGFR TKI, after progression from mobocertinib. A 58-year-old male was referred to our clinic with multiple lung lesions detected in computed tomography (CT) scanning. The patient participated in a phase I/II trial (NCT02716116) receiving TAK-788 and was confirmed with partial response at follow-up. Intriguingly, after progression from 9 months of TAK-788 treatment, the patient still showed response to furmonertinib. The progression free survival was 10 months with no complications or adverse events observed. The overall survival was 34 months till last follow-up in March, 2022. The patient is still in follow-up.

Conclusions

Supported by this case and data from other studies, the potency of furmonertinib warrants further evaluation in patients with EGFR 20ins, especially those pretreated with TKIs.

Keywords: Lung adenocarcinoma, EGFR exon 20 deletion, mobocertinib, furmonertinib, case report

Furmonertinib (AST2818) versus gefitinib as first-line therapy for locally advanced or metastatic EGFR mutation-positive non-small cell lung cancer: A multi-center, double-blind, randomized phase 3 study (FURLONG).

Citation

SSRN Electron J. Published online 2022.

Authors

Shi Y, Chen G, Wang X, Liu Y, Wu L, Hao Y, Liu C, Zhu S, Zhang X, Li Y, Liu J, Cao L, Cheng Y, Zhao H, Zhang S, Zang A, Cui J, Feng J, Liu F, Jiang Y, Gu C.

Abstract

Background: Furmonertinib (AST2818) is an irreversible, selective third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). We compared the efficacy and safety of furmonertinib with the first-generation EGFR-TKI gefitinib as first-line treatment in EGFR mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

Methods: A randomized, double-blind, phase 3 study was conducted in 55 hospitals across mainland China. We enrolled patients who were aged ≥18 years, histologically diagnosed with NSCLC, stage IIIB/IIIC/IV, with centrally confirmed EGFR exon 19 deletion (Ex19del) or exon 21 Leu858Arg mutation using tissue biopsy. Eligible patients were randomly assigned to receive furmonertinib 80 mg/d or gefitinib 250 mg/d until disease progression or other cessation criteria were met. The primary endpoint was progression-free survival assessed by a blinded independent review center (IRC). This study is registered with ClinicalTrials. gov (NCT03787992) and is ongoing for survival follow-up.

Findings: Between May 30 2019 and Dec 5 2019, 358 eligible patients were randomized to furmonertinib (n=178) or gefitinib (n=180)group. Median follow-up was 21·0 months in both groups. Median progression-free survival assessed by IRC was 20·8 months (95% CI 17·5-23·5) in the furmonertinib group and 11·1 months (95% CI 9·7-12·5) in the gefitinib group (hazard ratio 0·44 [95% CI 0·34-0·58]; p<0·0001). Grade ≥3 treatment-related adverse events occurred in 11% (20/178) patients in the furmonertinib group versus 18% (32/179) in the gefitinib group. Treatment-related serious adverse events occurred in 6% of both the furmonertinib (10/178) and gefitinib (11/179) groups. No treatment-related deaths were recorded in either group. Interpretation Furmonertinib showed superior efficacy to gefitinib as first-line therapy in EGFR mutation-positive NSCLC, along with lower rates of grade ≥3 treatment-related adverse events. Furmonertinib is a new potential treatment option for this population.

Trial Registration: This study is registered with ClinicalTrials. gov (NCT03787992) and is ongoing for survival follow-up.

Funding: Shanghai Allist Pharmaceutical Technology, China National Major Project for New Drug Innovation (2017ZX09304015).

Declaration of Interest: FL, YJ and CG are employees and shareholders of Shanghai Allist

Pharmaceutical Technology. All other authors declare no competing interests.

Ethical Approval: The protocol was approved by the institutional review

board or ethics committee of each participating center.

Keywords: Furmonertinib, AST2818, NSCLC, EGFR, TKI

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2021

https://link.springer.com/article/10.1007/s11864-021-00911-7

Systemic Therapy for Lung Cancer Brain Metastases.

Citation

Current Treatment Options in Oncology. 2021;22(12):110.

Authors

Pellerino A, Bruno F, Rudà R, Soffietti R.

Abstract

Systemic therapy for brain metastases (BM) is quickly moving from conventional cytotoxic chemotherapy toward targeted therapies, that allow a disruption of driver molecular pathways. The discovery of actionable driver mutations has led to the development of an impressive number of tyrosine kinase inhibitors (TKIs), that target the epidermal growth factor receptor (EGFR) mutations, anaplastic-lymphoma-kinase (ALK) rearrangements, and other rare molecular alterations in patients bearing metastatic non-small cell lung cancer (NSCLC) in the brain, with remarkable results in terms of intracranial disease control and overall survival. Moreover, these drugs may delay the use of local therapies, such as stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT). New drugs with higher molecular specificity and ability to cross the CNS barriers (BBB, BTB and blood-CSF) are being developed. Two major issues are related to targeted therapies. First, the emergence of a resistance is a common event, and a deeper understanding of molecular pathways that are involved is critical for the successful development of effective new targeted agents. Second, an early detection of tumor progression is of utmost importance to avoid the prolongation of an ineffective therapy while changing to another drug. In order to monitor over time the treatment to targeted therapies, liquid biopsy, that allows the detection in biofluids of either circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) or exosomes, is increasingly employed in clinical trials: with respect to BM the monitoring of both blood and CSF is necessary. Also, radiomics is being developed to predict the mutational status of the BM on MRI.

For patients without druggable mutations or who do not respond to targeted agents, immunotherapy with checkpoint inhibitors is increasingly employed, alone or in combination with radiotherapy. Pseudoprogression after immunotherapy alone maybe a challenge for several months after the start of treatment, and the same is true for radionecrosis after the combination of

immunotherapy and SRS. In this regard, the value of advanced MRI techniques and PET imaging for a better distinction of pseudoprogression/radionecrosis and true tumor progression is promising, but needs validation in large prospective datasets. Last, a new frontier in the near future will be chemoprevention (primary and secondary), but we need to identify among solid tumors those subgroups of patients with a higher risk of relapsing into the brain and novel drugs, active on either neoplastic or normal cells of the microenvironment, that are cooperating in the invasion of brain tissue.

Keywords

ALK inhibitors; Brain metastases; EGFR tyrosine kinase inhibitors; Immunotherapy; Radiotherapy; Rare druggable mutations

1210P Preclinical and preliminary clinical investigations of furmonertinib in NSCLC with EGFR exon 20 insertions (20ins).

Citation

Annals of Oncology. 2021;32:S964.

Authors

Han B, Zhou C, Wu L, Yu X, Li Q, Liu F, Shen C.

Abstract

Background

Currently neither chemotherapy nor approved EGFR TKIs have satisfactory efficacy in most EGFR 20ins mutations. Activity of furmonertinib, a novel 3rd generation EGFR TKI, against EGFR 20ins was assessed in preclinical models and a phase Ib study.

Methods

The preclinical activity of furmonertinib were evaluated in vitro and in vivo. Then the clinical efficacy and safety were investigated in a phase Ib study (FAVOUR 1, NCT04858958) in which 30 advanced NSCLC patients (pts) with EGFR 20ins were planned to be enrolled: Cohort 1 (10 pts): treatment-naïve, furmonertinib 240mg qd; cohort 2 and 3: previously treated, 240mg qd and 160mg qd respectively. Previously treated pts would be randomized into cohort 2 or 3. The primary endpoint was ORR.

Results

In preclinical studies, furmonertinib effectively inhibited BaF3 cells expressing EGFR 20ins with mean IC50 of 11~20 nM. Good efficacy and well tolerance were also observed in patient-derived xenograft models harboring EGFR 20ins (LU0387) with furmonertinib at 45mg/kg/day. As of 30 Apr 2021, 10 EGFR 20ins advanced NSCLC pts were enrolled in cohort 1 and received furmonertinib 240mg qd. In these pts: median age, 67.5y (range 47–69); women, 70%; ECOG 0/1, 30%/70%. Median time on treatment was 3.5 months and all pts remain on treatment. At data cutoff, all pts had ≥1 disease assessment. The best response was PR in 7 pts and SD in 3 pts. 5/7 objective responses (all PR) were confirmed, with 2 awaiting confirmation. All pts showed tumor shrinkage in target lesions (median best percent change, -43.0% [-72.3%, -3.0%]). The most common treatment emergent adverse events (TEAE, ≥20%) were diarrhea, paronychia, skin fissures (each 30%), anorexia, upper respiratory tract infection, creatinine renal clearance decreased, pain in extremity, rash, face oedema and stomatitis (each 20%). No grade ≥3 TEAE was observed. Dose interruption was reported once due to diarrhea. No dose reduction or discontinuation were observed.

Conclusions

Furmonertinib has shown encouraging anti-tumor activity in EGFR 20ins NSCLC based on the preclinical data and the preliminary results of the phase Ib study without new safety signals. Further exploration of this phase Ib study is ongoing.

Clinical trial identification

NCT04858958.

Free Full Text of Entire Article

https://link.springer.com/article/10.1007/s40265-021-01588-w

Furmonertinib: First Approval.

Citation

Drugs. 2021;81(15):1775–1780.

Authors

Deeks ED.

Abstract

Furmonertinib mesylate (hereafter furmonertinib) [Ivesa®] is a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) being developed by Allist Pharmaceuticals for the treatment of patients with EGFR mutation-positive non-small cell lung cancer (NSCLC). In March 2021, furmonertinib received its first approval in China for the treatment of patients with locally advanced or metastatic NSCLC with confirmed EGFR T790M mutation whose disease has progressed during or after EGFR TKI therapy. Furmonertinib (as monotherapy and/or combination therapy) continues to be assessed in phase I/II and phase III trials for NSCLC with EGFR mutation in China, and its clinical development is also underway/planned in China and elsewhere for NSCLC with various EGFR mutations. This article summarizes the milestones in the development of furmonertinib leading to this first approval for EGFR T790M-positive NSCLC.

https://www.ingentaconnect.com/content/ben/cdm/2021/00000022/00000011/art00004

Metabolite identification in the preclinical and clinical phase of drug development.

Citation

Curr Drug Metab. 2021;22(11):838-857.

Authors

Wu Y, Pan L, Chen Z, Zheng Y, Diao X, Zhong D.

Abstract

Metabolite identification plays a critical role in the phases during drug development. Drug metabolites can contribute to efficacy, toxicity, and drug-drug interaction. Thus, the correct identification of metabolites is essential to understand the behavior of drugs in humans. Drug administration authorities (e.g., FDA, EMA, and NMPA) emphasize evaluating the safety of human metabolites with exposure higher than 10% of the total drugrelated components. Many previous reviews have summarized the various methods, tools, and strategies for the appropriate and comprehensive identification of metabolites. In this review, we focus on summarizing the importance of identifying metabolites in the preclinical and clinical phases of drug development. Summarized scenarios include the role of metabolites in pharmacokinetics/pharmacodynamics (PK/PD) analysis, disproportional exposure of metabolites that contribute to drug toxicity, changes in metabolite exposure in renal-impaired patients, covalent tyrosine kinase inhibitors (anticancer drugs), and metabolite identification of drug candidates from

natural medicines. This review is aimed to provide meaningful insight into the significant role of metabolite identification in drug development.

https://www.spandidos-publications.com/10.3892/ijo.2021.5270

Mechanisms and management of 3rd-generation EGFR-TKI resistance in advanced non-small cell lung cancer (Review).

Citation

Int J Oncol. 2021;59(5).

Authors

He J, Huang Z, Han L, Gong Y, Xie C.

Abstract

Targeted therapy with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) is a standard modality of the 1st-line treatments for patients with advanced EGFR-mutated non-small cell lung cancer (NSCLC), and substantially improves their prognosis. However, EGFR T790M mutation is the primary mechanism of 1st- and 2nd-generation EGFR-TKI resistance. Osimertinib is a representative of the 3rd-generation EGFR-TKIs that target T790M mutation, and has satisfactory efficacy in the treatment of T790M-positive NSCLC with disease progression following use of 1st- or 2nd-generation EGFR-TKIs. Other 3rd-generation EGFR-TKIs, such as abivertinib, rociletinib, nazartinib, olmutinib and alflutinib, are also at various stages of development. However, the occurrence of acquired resistance is inevitable, and the mechanisms of 3rd-generation EGFR-TKI resistance are complex and incompletely understood. Genomic studies in tissue and liquid biopsies of resistant patients reveal multiple candidate pathways. The present review summarizes the recent findings in mechanisms of resistance to 3rd-generation EGFR-TKIs in advanced NSCLC, and provides possible strategies to overcome this resistance. The mechanisms of acquired resistance mainly include an altered EGFR signaling pathway (EGFR tertiary mutations and amplification), activation of aberrant bypassing pathways (hepatocyte growth factor receptor amplification, human epidermal growth factor receptor 2 amplification and aberrant insulin-like growth factor 1 receptor activation), downstream pathway activation (RAS/RAF/MEK/ERK and PI3K/AKT/mTOR) and histological/phenotypic transformations (SCLC transformation and epithelial-mesenchymal transition). The combination of targeted therapies is a promising strategy to treat osimertinib-resistant patients, and multiple clinical studies on novel combined therapies are ongoing.

Free Full Text of Entire Article

https://www.sciencedirect.com/science/article/abs/pii/S2213260020304550

Efficacy, safety, and genetic analysis of furmonertinib (AST2818) in patients with EGFR T790M mutated non-small-cell lung cancer: a phase 2b, multicentre, single-arm, open-label study.

Citation

The Lancet Respiratory Medicine. 2021;9(8):829–839.

Authors

Shi Y, Hu X, Zhang S, Lv D, Wu L, Yu Q, Zhang Y, Liu L, Wang X, Cheng Y, Ma Z, Niu H, Wang D, Feng J, Huang C, Liu C, Zhao H, Li J, Zhang X, Jiang Y, Gu C.

Abstract

Background

Furmonertinib (AST2818) is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) targeting both sensitising EGFR and EGFR Thr790Met (T790M) mutations. This study aimed to assess the efficacy and safety of furmonertinib in patients with EGFR T790M mutated advanced non-small-cell lung cancer (NSCLC).

Methods

This study was a single-arm, open-label, phase 2b study at 46 hospitals across mainland China. Patients with locally advanced or metastatic NSCLC with centrally confirmed EGFR T790M mutations in tumour tissue who progressed after first or second generation EGFR TKIs or with primary EGFR T790M mutations received furmonertinib 80 mg orally once daily. The primary endpoint was objective response rate. Efficacy was assessed by blinded independent central review as per the Response Evaluation Criteria in Solid Tumors (version 1.1) in all patients who had measurable disease at baseline and received at least one dose of furmonertinib. Safety was assessed as per the Common Terminology Criteria for Adverse Events (version 4.03) in all patients who received at least one dose of furmonertinib with at least one safety assessment during follow-up. This study is registered with ClinicalTrials.gov (NCT03452592) and is ongoing for survival follow-up.

Findings

From Jun 4, 2018, to Dec 8, 2018, 220 patients received furmonertinib treatment. All 220 patients were included in the efficacy and safety analyses. At the data cutoff point of Jan 29, 2020, 71 (32%) patients remained on

treatment. The median duration of follow-up was 9·6 months (range 0·7–19·4). The objective response rate was 74% (163 of 220 [95% CI 68–80]). Grade 3 or higher adverse events occurred in 58 (26%) patients and treatment-related grade 3 or higher adverse events occurred in 25 (11%) patients. The most common all-cause grade 3 or higher adverse events were increased γ-glutamyltransferase (five; 2%), increased aspartate aminotransferase, increased alanine aminotransferase, hyponatraemia, hypertension, pulmonary infection, hypermagnesaemia, and pericardial effusion (three each; 1%). Treatment-related diarrhoea was reported in ten (5%) patients and rashes were reported in 16 (7%) patients, all grade 1–2. Serious adverse events were reported in 52 (24%) patients, of which 12 (5%) were possibly treatment-related as evaluated by the investigator.

Interpretation

Furmonertinib has promising efficacy and an acceptable safety profile for the treatment of patients with EGFR T790M mutated NSCLC. Furmonertinib is expected to become a new treatment option after first or second generation EGFR TKIs in the Chinese population.

Funding

Shanghai Allist Pharmaceutical Technology, Ministry of Science and Technology of the People's Republic of China, and Chinese Academy of Medical Sciences.

Translation

For the Chinese translation of the abstract see Supplementary Materials section.

https://www.jto.org/article/S1556-0864(20)31105-9/fulltext

Beyond Osimertinib: The Development of Third-Generation EGFR Tyrosine Kinase Inhibitors For Advanced EGFR+ NSCLC.

Citation

J Thorac Oncol. 2021 May;16(5):740-763.

Authors

Nagasaka M, Zhu VW, Lim SM, Greco M, Wu F, Ou SI.

Abstract

Single-agent osimertinib is the standard of care for the first-line treatment of advanced EGFR+ NSCLC and remained the only marketed third-generation EGFR tyrosine kinase inhibitor (TKI) until March 2020 when almonertinib

(HS-10296) was approved in the People's Republic of China for the treatment of advanced EGFR T790M+ NSCLC based on a phase 2 expansion study of a phase 1/2 trial. In this review, we profiled many of the third-generation EGFR TKIs in late-stage clinical development (e.g., almonertinib, lazertinib, alflutinib1, rezivertinib, ASK120069, SH-1028, D-0316, and abivertinib) based on their interim results from phase 1 and phase 2 trials, and included the designs of the phase 3 trials and their chemical structures when publicly available. We also listed other third-generation EGFR TKIs in pipeline development based on the search of clinical trial registration websites. In addition, we summarized the results of clinical trials that previously reported third-generation EGFR TKIs (rociletinib, olmutinib, nazartinib, mavelertinib), including phase 3 results of rociletinib and naquotinib. We further profiled combination clinical trial design of the third-generation EGFR TKIs including FLAURA2 (NCT04035486), MARIPOSA (NCT04487080), ACROSS1 (NCT04500704), and ACROSS2 (NCT04500717) that if positive can potentially usher in the next standard of care for advanced EGFR+ NSCLC.

Keywords: Alflutinib; Almonertinib; Furmonertinib; Lazertinib; Osimertinib; Rezivertinib; T790M.

https://www.sciencedirect.com/science/article/abs/pii/S1043661821001675

EGFR mutation mediates resistance to EGFR tyrosine kinase inhibitors in NSCLC: From molecular mechanisms to clinical research.

Citation

Pharmacological Research. 2021;167:105583.

Authors

Dong R-F, Zhu M-L, Liu M-M, Xu Y-T, Yuan L-L, Bian J, Xia Y-Z, Kong L-Y.

Abstract

With the development of precision medicine, molecular targeted therapy has been widely used in the field of cancer, especially in non-small-cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) is a well-recognized and effective target for NSCLC therapies, targeted EGFR therapy with EGFR-tyrosine kinase inhibitors (EGFR-TKIs) has achieved ideal clinical efficacy in recent years. Unfortunately, resistance to EGFR-TKIs inevitably occurs due to various mechanisms after a period of therapy. EGFR mutations, such as T790M and C797S, are the most common mechanism of EGFR-TKI resistance. Here, we discuss the mechanisms of EGFR-TKIs resistance induced by secondary EGFR mutations, highlight the development of targeted

drugs to overcome EGFR mutation-mediated resistance, and predict the promising directions for development of novel candidates.

https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.e21071

Progression pattern and post-progression treatment of furmonertinib (AST2818) in EGFR T790M mutation positive NSCLC patients: A post-hoc analysis from a multicenter, single-arm study.

Citation

Journal of Clinical Oncology. 2021;39(15_suppl):e21071–e21071.

Authors

Hu X, Zhang S, Lv D, Wu L, Yu Q, Zhang Y, Liu L, Wang X, Cheng Y, Ma Z, Niu H, Wang D, Feng J, Huang C, Liu C, Zhao H, Li J, Zhang X, Jiang Y, Shi Y.

Abstract

Background: Furmonertinib (AST2818) is a selective third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), which can irreversibly inhibit both EGFR sensitizing and T790M resistant mutations. However, like other EGFR-TKIs, progression is still unavoidable when treated with furmonertinib. Methods: In a multi-center, single-arm phase IIb study (NCT03452592), non-small cell lung cancer (NSCLC) patients with EGFR T790M mutation received furmonertinib 80mg/d treatment until disease progression, death or treatment cessations for other reasons. This is a post-hoc analysis of the progression pattern and post-progression treatment. Results: A total of 220 patients were enrolled in this study. At baseline, 105 (48%) patients had central nervous system (CNS) metastases, 84 (38%) were EGFR L858R mutated and 9 (4%) were ECOG performance status 2. At data cut-off (December 31, 2020), 179 out of 220 (81%) patients had progressed assessed by investigators (patients who died before assessed as progression were excluded). The most frequent progression site was lung (n = 106, 48%), followed by CNS (n = 33, 15%), lymph node (n = 22, 10%), liver (n = 20, 9%) and bone (n = 16, 7%). CNS progression rate were 3%, 8%, 13% and 15% at 3, 6, 12 and 18 months, respectively. After progression, 52% (93/179) patients continued furmonertinib monotherapy based on the judgement of continuous benefit by investigators which was permitted in the protocol. The median post-progression treatment time of furmonertinib was 3.02 months (range 0.03-18.27). Overall, 48% (86/179) patients discontinued furmonertinib and later-line treatments were decided by investigators. The post-progression survival (PPS) was 17.3 months in the furmonertinib-continued group and 12.4 months in the furmonertinib-not-continued group (HR 0.57 [95%CI 0.40-0.80], p = 0.0048). Conclusions: Although about half patients had CNS

metastases at baseline, CNS progression rate was relatively low in this study. Post-progression continuous treatment of furmonertinib monotherapy might still bring survival benefit to certain NSCLC patients with EGFR T790M mutation which need further exploration. Clinical trial information: NCT03452592.

https://chemistry-europe.onlinelibrary.wiley.com/doi/epdf/10.1002/cmdc.202100166

Next-Generation Kinase Inhibitors Targeting Specific Biomarkers in Non-Small Cell Lung Cancer (NSCLC): A Recent Overview.

Citation

ChemMedChem. 2021;16(16):2459–2479.

Authors

Das D, Wang J, Hong J.

Abstract

Lung cancer causes many deaths globally. Mutations in regulatory genes, irregularities in specific signal transduction events, or alterations of signalling pathways are observed in cases of non-small cell lung cancer (NSCLC). Over the past two decades, a few kinases have been identified, validated, and studied as biomarkers for NSCLC. Among them, EGFR, ALK, ROS1, MET, RET, NTRK, and BRAF are regarded as targetable biomarkers to cure and/or control the disease. In recent years, the US Food and Drug Administration (FDA) approved more than 15 kinase inhibitors targeting these NSCLC biomarkers. The kinase inhibitors significantly improved the progression-free survival (PFS) of NSCLC patients. Challenges still remain for metastatic diseases and advanced NSCLC cases. New discoveries of potent kinase inhibitors and rapid development of modern medical technologies will help to control NSCLC cases. This article provides an overview of the discoveries of various types of kinase inhibitors against NSCLC, along with medicinal chemistry aspects and related developments in next-generation kinase inhibitors that have been reported in recent years.

Free Full Text of Entire Article

https://www.nature.com/articles/s41401-021-00667-8

Metabolic disposition of the EGFR covalent inhibitor furmonertinib in humans.

Citation

Acta Pharmacol Sin. 2022;43(2):494-503.

Authors

Meng J, Zhang H, Bao JJ, Chen Z-D, Liu X-Y, Zhang Y-F, Jiang Y, Miao L-Y, Zhong D.

Abstract

Furmonertinib was designed for the treatment of non-small cell lung cancer (NSCLC) patients with EGFR T790M mutation. In this study, we investigated the metabolic disposition and mass balance in humans and tissue distribution in rats. After a single oral administration of 97.9 μCi/81.5 mg [14C]-furmonertinib mesylate to six healthy male volunteers, the absorption process of furmonertinib was fast with a tmax of total plasma radioactivity at 0.75 h. Afterward, furmonertinib was extensively metabolized, with the parent drug and active metabolite AST5902 accounting for 1.68% and 0.97% of total radioactivity in plasma. The terminal t1/2 of total radioactivity in plasma was as long as 333 h, suggesting that the covalent binding of drug-related substances to plasma proteins was irreversible to a great extent. The most abundant metabolites identified in feces were desmethyl metabolite (AST5902), cysteine conjugate (M19), and parent drug (M0), which accounted for 6.28%, 5.52%, and 1.38% of the dose, respectively. After intragastric administration of 124 μCi/9.93 mg/kg [14C]-furmonertinib to rats, drug-related substances were widely and rapidly distributed in tissues within 4 h. The concentration of total radioactivity in the lung was 100-fold higher than that in rat plasma, which could be beneficial to the treatment of lung cancer. Mass balance in humans was achieved with 77.8% of the administered dose recovered in excretions within 35 days after administration, including 6.63% and 71.2% in urine and feces, respectively. In conclusion, [14C]-furmonertinib is completely absorbed and rapidly distributed into lung tissue, extensively metabolized in humans, presented mostly as covalent conjugates in plasma, and slowly eliminated mostly via fecal route.

https://www.jto.org/article/S1556-0864(21)01164-3/fulltext

P76.65 CNS Efficacy of AST2818 in Patients with T790M-Positive Advanced NSCLC: Data from a Phase I-II Dose-Expansion Study.

Citation
Journal of Thoracic Oncology. 2021;16(3, Supplement):S616.

Authors

Shi Y, Hu X, Liao W, Zhang S, Wang Z, Yang N, Wu L, Zhou J, Ying K, Ma Z, Feng J, Liu L, Qin S, Fang J, Zhang X, Jiang Y, Ge N.

Abstract

Introduction

Furmonertinib (AST2818, former name: alflutinib) is a new third-generation EGFR-tyrosine kinase inhibitor that selectively inhibits EGFR-sensitizing and EGFR T790M mutation. We have reported promising clinical activity and well-characterized tolerability of AST2818 in EGFR T790M-positive locally advanced or metastatic non-small-cell lung cancer (NSCLC) patients including its preliminary efficacy in patients with central nervous system (CNS) metastases (Shi Y et al JTO 2020;15(6):1015-1026). Herein, we report the result of recent subgroup analysis from phase I-II dose-expansion study (NCT03127449) where the CNS efficacy of different AST2818 doses was evaluated.

Methods

Patients aged ≥18 years with centrally confirmed EGFR T790M-positive locally advanced or metastatic NSCLC received AST2818 ranging from 40-240 mg doses once daily until disease progression. Patients with asymptomatic, stable CNS metastases not requiring steroids for at least 4 weeks before the first dose of AST2818 were enrolled. A subgroup analysis was conducted in patients with ≥1 measurable CNS lesion (per RECIST 1.1) at baseline brain imaging (CNS evaluable-for-response set, cEFR) and patients with ≥1 measurable and/or non-measurable CNS lesion at baseline brain imaging (CNS full analysis set, cFAS) by blinded independent central review (BICR). CNS efficacy was evaluated in terms of CNS objective response rate (ORR), CNS disease control rate (DCR), CNS progression-free survival (PFS), and CNS duration of response (DoR) (assessed by BICR).

Results

At data cutoff (29 January 2020), 116 patients were enrolled, of which 45 patients (38.8%) were included in cFAS and 23 patients (19.8%) were included in cEFR. Confirmed CNS ORR was 65.2% (15/23) while CNS DCR was 91.3% (21/23) in cEFR. The CNS ORR in the 40-, 80-, 160-, and 240-mg groups was 0 (no response of 1), 60% (3/5 partial response [PR]), 84.6% (1/13 complete response [CR] and 10/13 PR), and 25% (1/4 PR), respectively. In the cFAS, median CNS PFS was not reached (95% confidence interval [CI], 8.3 months to not reached), while median CNS PFS in 40-, 80-, 160-, and 240-mg groups were 2.8, 9.7, 19.3 months, and not reached, respectively. Median CNS DoR (19% maturity) in cFAS was not reached (range, 2.8 months to not reached). At 12 months, 50%, 81.8%, and 100% of patients were estimated to remain in response in 80-, 160-, and 240-mg groups, respectively.

Conclusion

AST2818 demonstrated clinically meaningful efficacy against CNS metastases. 160 mg provided relevant benefit with a high CNS ORR and PFS. Further studies are required to confirm these findings.

Keywords

Brain metastases, tyrosine kinase inhibitors, advanced NSCLC

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https://journals.lww.com/co-oncology/Fulltext/2021/01000/EGFR_mutant_NSCLC__emerging_novel_drugs.15.aspx?casa_token=YBZ8Wm6eRKIAAAAA:26j61dZdVYtJMonU01VEuauFCPC2ryiz4IBiV5eJgd6UT0tJtEDnhtmOodi0SYIqOsj5zIU-IOpQFRkh8yDvnVrEY4iaSz6OHys

EGFR-mutant NSCLC: Emerging novel drugs.

Citation

Curr Opin Oncol. 2021;33(1):87-94.

Authors

Ye L, Chen X, Zhou F.

Abstract

Purpose of review

Despite the significant advances in EGFR-mutant nonsmall cell lung cancer (NSCLC), some challenges remain. One of the permanent and inevitable issues is the emergence of acquired resistance. Therefore, blocking the activation of EGFR pathway and overcoming drug resistance with novel agents are still in high demand. Here, we review the development of novel drugs in EGFR-mutant, advanced NSCLC, including targeting EGFR exon 20 insertion (EGFR20ins), and novel role of epidermal growth factor receptor, tyrosine kinase inhibitor (EGFR-TKIs) in early-stage NSCLC.

Recent findings

EGFR-TKIs as adjuvant therapy or neoadjuvant therapy in patients with early-stage NSCLC with EGFR-sensitizing mutations have shown promising efficacy. The resistance mechanisms of third-generation EGFR-TKIs can be divided into two types: EGFR dependent and EGFR independent. Several clinical trials have demonstrated that the addition of MET inhibitors to EGFR-TKIs was an effective option for patients who had acquired resistance to EGFR-TKIs caused by hepatocyte growth factor receptor gene (MET)

amplification or overexpression. Novel compounds that selectively and potently inhibit EGFR20ins are being investigated in phase III studies.

Summary

A better characterization and understanding of resistance mechanisms to first-line osimertinib and adjuvant osimertinib is helpful to guide further treatment.

Free Full Text of Entire Article

2020

https://www.sciencedirect.com/science/article/pii/S1556086420300319

Safety, Clinical Activity, and Pharmacokinetics of Alflutinib (AST2818) in Patients With Advanced NSCLC With EGFR T790M Mutation.

Citation

Journal of Thoracic Oncology. 2020;15(6):1015–1026.

Authors

Shi Y, Zhang S, Hu X, Feng J, Ma Z, Zhou J, Yang N, Wu L, Liao W, Zhong D, Han X, Wang Z, Zhang X, Qin S, Ying K, Feng J, Fang J, Liu L, Jiang Y.

Abstract

Introduction

Alflutinib (AST2818) is a newly developed third-generation EGFR tyrosine kinase inhibitor selective for EGFR-sensitizing and T790M-resistant mutations. We assessed the safety, efficacy, and pharmacokinetics of alflutinib in patients with advanced NSCLC with confirmed EGFR T790M mutation, whose status progressed after the first- or second-generation EGFR tyrosine kinase inhibitor therapy.

Methods

In the dose-escalation (NCT02973763) and dose-expansion (NCT03127449) studies, patients received alflutinib orally until disease progression, unacceptable toxicity, or subject withdrawal. The primary end points were safety, tolerability, and pharmacokinetics for the dose-escalation study and the objective response rate (assessed by an independent radiological review committee) for the dose-expansion study.

Results

Between November 30, 2016, and July 24, 2018, a total of 130 patients (14 in dose escalation, 116 in dose expansion) received alflutinib treatment (20 mg, 40 mg, 80 mg, 160 mg, or 240 mg once daily). On October 30, 2018, 79

patients (61%) remained on the treatment. No dose-limiting toxicities were observed in the dose-escalation study. In the dose-expansion study (40–240 mg), the overall objective response rate was 76.7% (89 of 116), and it was 70.6% in patients with central nervous system metastases (12 of 17). A total of 79% of all patients had possibly treatment-related adverse events (AEs) (103 of 130); 8% had treatment-related grade 3 or higher AEs (11 of 130). Serious AEs were reported in 15% of patients (20 of 130), and two serious AEs were related to treatment. No clear dose-response (antitumor activity and AEs) relationships were observed. Exposures to alflutinib and its active metabolite (AST5902) were comparable at steady state.

Conclusions

Alflutinib was clinically effective with an acceptable toxicity profile in patients with advanced NSCLC (including those with central nervous system metastases) with EGFR T790M mutation. Further investigation is ongoing.

Keywords

Alflutinib; NSCLC; EGFR T790M mutation; Efficacy; Safety

A randomized, open, single-centre, crossed study of the effect of food on the pharmacokinetics of one oral dose of alflutinib mesylate tablets (AST2818) in healthy male subjects.

Citation

Iran J Pharm Res. 2020;19(3):24-33.

Authors

Zhu S, Deng J, Tang Q, Heng J, Qu J, Chen Y, Chen X, Yang N, Liu X, Li K.

Abstract

The aim of the study was to study the PK of AST2818 tablets after one oral dose in healthy male subjects on an empty stomach and in a postprandial state and to evaluate the effect of food on AST2818 bioavailability. Sixteen healthy Chinese male subjects were randomly divided into two groups: a fasting-postprandial group and a postprandial-fasting group. The drug was administered once per evaluation at a dose of 80 mg, with an interval of 22 days between the two treatments. The LC-MS/MS method was used to determine the concentrations of AST2818 and its metabolite AST5902.

Plasma pharmacokinetic parameters were calculated by noncompartmental analysis (NCA). WinNonlin® version 7.0 was used to analyse PK parameters, and SAS version 9.4 was used for statistical analyses. After a meal, the peak concentration of alflutinib increased by approximately 53%, and the AUC increased by approximately 32%; The peak concentration of its metabolite AST5902 decreased by approximately 20%, and the AUC decreased by approximately 8%. There was no significant change in peak time. The peak AST5902 concentration and AUC0-∞ were 27.4% and 71.4%, respectively, of that of alflutinib. None of the subjects experienced serious AEs, and both fasting and high-fat meal administration were safe. There was no statistically significant difference between groups in AEs (P = 0.102, RR = 1.40) or adverse reactions (P = 0.180, RR = 1.30). The effects of food may not need to be considered for the clinical use of alflutinib. No serious AEs occurred, and drug administration was safe and tolerable after fasting or a high-fat meal.

Key Words: Alflutinib mesylate tablets, Pharmacokinetics, Healthy volunteers, Bioavailability, High-fat meal

https://www.jto.org/article/S1556-0864(20)30173-8/fulltext

Does the Lung Cancer Field Need Another Third-Generation EGFR Tyrosine Kinase Inhibitor?

Citation

Journal of Thoracic Oncology. 2020;15(6):881–883.

Authors

Wang F, Adjei AA.

Abstract

The discovery of EGFR mutations as oncogenic drivers in NSCLC and identification of EGFR tyrosine kinase inhibitors (TKIs) as effective drugs against mutant tumors have revolutionized the treatment of NSCLC. Similar to other oncogene-driven tumors, development of resistance to EGFR TKIs is an ongoing problem. Initially, the irreversible pan-HER inhibitors, afatinib and dacomitinib (second-generation inhibitors), were designed as an approach to overcome resistance to the first-generation inhibitors, erlotinib, and gefitinib. Nevertheless, the most common mechanism of acquired resistance to EGFR TKIs is development of a second mutation in exon 20 of the EGFR gene. This mutation, Thr790Met (T790M), substitutes threonine for methionine at position 790 of exon 20, altering the adenosine triphosphate-

binding pocket of the EGFR kinase domain, thus shifting affinity for binding to adenosine triphosphate and less so for the first-generation inhibitors. In response to these findings, third-generation EGFR inhibitors have been developed with specific affinity for T790M and affinity for other sensitizing mutations. One of these agents, osimertinib, is approved in more than 75 countries, including the United States, Japan, People's Republic of China, and the European Union, for first-line treatment of EGFR-mutant tumors on the basis of results from the FLAURA study. In some other countries, osimertinib is approved for T790M-mutant NSCLC in the second line of treatment only.

A second third-generation EGFR TKI, lazertinib, is in phase III trial in comparison with gefitinib for the first-line therapy of NSCLC (NCT04248829). Other third-generation inhibitors under active investigation include maverlertinib (PF-06747775), nazartinib (EGF816), avitinib (abivertinib/AC0010), CK-101, D-0316, BPI-7711, SH-1028, HS-10296, ASK120067, ZN-e4 (KP-673), and TQB33456. The development of other third-generation inhibitors, such as rociletinib (CO-1686), olmutinib (HM61713/BI 1482694), and naquotinib (ASP8273), has been discontinued on the basis of a combination of toxicity in the setting of modest efficacy. Against this backdrop, Shi et al.3 reported a phase I study of third-generation EGFR TKI, alflutinib, in EGFR-mutant tumors in this issue of the Journal of Thoracic Oncology.

https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.9602

Efficacy and safety of alflutinib (AST2818) in patients with T790M mutation-positive NSCLC: A phase IIb multicenter single-arm study.

Citation

Journal of Clinical Oncology. 2020;38(15_suppl):9602–9602.

Authors

Shi Y, Hu X, Zhang S, Lv D, Zhang Y, Yu Q, Wu L, Liu L, Wang X, Ma Z, Cheng Y, Niu H, Wang D, Feng JF, Huang C, Liu C, Zhao H, Li J, Zhang X, Jiang Y.

Abstract

Background: Alflutinib (AST2818) is a third generation EGFR-TKI. This phase IIb, multicenter, single arm study (ALSC003, NCT03452592) aimed to assess the efficacyand safety of Alflutinib in patients with EGFR T790M mutated non-small cell lung cancer (NSCLC). Methods: Patients with locally advanced or metastatic EGFR T790M mutated NSCLC who progressed after

first/second-generation EGFR-TKIs therapy or primary EGFR T790M mutation positive received 80 mg Alflutinib orally once daily. Tumor tissue samples underwent central laboratory testing for EGFR T790M mutation. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety. Efficacy was assessed by independent radiological review committee per RECIST 1.1. Safety was assessed by NCI CTCAE version 4.03. Results: From Jun 4, 2018 to Dec 8, 2018, 220 patients were enrolled with a median age of 61.0 (range 29 to 80) years. According to the AJCC version 8 staging system, 212 (96.4%) cases were in stage IV, and 8 (3.6%) cases in stage III. All patients had EGFR T790M mutation. By April 12, 2019, the ORR was 73.6% (95% CI 67.3–79.3). The DCR estimated at 6 and 12 weeks were 87.3% (95%CI 82.1-91.4) and 82.3% (95%CI 76.6-87.1), respectively. The median PFS was 7.6 months (95% CI 7.0–NA). Median OS and DoR have not been reached. 209 (95.0%) patients had at least one adverse events (AEs), which were mostly grade 1 or 2 and well tolerable. The most common AEs were increased aspartate aminotransferase (33 [15.0%]), upper respiratory tract infection (33 [15.0%]), and cough (33 [15.0%]). Grade 3 to 5 AEs occurred in 42 (19.1%) patients. The most common one was elevated γ-glutamyltransferase (n = 4). There were 3 deaths patients, 2 of which possibly not be related to the study drug, and 1 could not be determined. No interstitial pneumonia was reported. Conclusions: Alflutinib has promising efficacy and acceptable safety profile for the treatment of EGFR T790M mutated NSCLC patients. Clinical trial information: NCT 03452592.

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Alflutinib (AST2818), primarily metabolized by CYP3A4, is a potent CYP3A4 inducer.

Citation

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Abstract

Alflutinib (AST2818) is a third-generation epidermal growth factor receptor (EGFR) inhibitor that inhibits both EGFR-sensitive mutations and T790M mutations. Previous study has shown that after multiple dosages, alflutinib exhibits nonlinear pharmacokinetics and displays a time- and dose-dependent increase in the apparent clearance, probably due to its self-induction of

cytochrome P450 (CYP) enzyme. In this study, we investigated the CYP isozymes involved in the metabolism of alflutinib and evaluated the enzyme inhibition and induction potential of alflutinib and its metabolites. The data showed that alflutinib in human liver microsomes (HLMs) was metabolized mainly by CYP3A4, which could catalyze the formation of AST5902. Alflutinib did not inhibit CYP isozymes in HLMs but could induce CYP3A4 in human hepatocytes. Rifampin is a known strong CYP3A4 inducer and is recommended by the FDA as a positive control in the CYP3A4 induction assay. We found that the induction potential of alflutinib was comparable to that of rifampin. The Emax of CYP3A4 induction by alflutinib in three lots of human hepatocytes were 9.24-, 11.2-, and 10.4-fold, while the fold-induction of rifampin (10 μM) were 7.22-, 19.4- and 9.46-fold, respectively. The EC50 of alflutinib-induced CYP3A4 mRNA expression was 0.25 μM, which was similar to that of rifampin. In addition, AST5902 exhibited much weak CYP3A4 induction potential compared to alflutinib. Given the plasma exposure of alflutinib and AST5902, both are likely to affect the pharmacokinetics of CYP3A4 substrates. Considering that alflutinib is a CYP3A4 substrate and a potent CYP3A4 inducer, drug–drug interactions are expected during alflutinib treatment.

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