Mobocertinib

2022

https://pubmed.ncbi.nlm.nih.gov/35621011/

Non-small cell lung cancer with EGFR exon 20 insertion mutation: a systematic literature review and meta-analysis of patient outcomes.

Citation

Curr Med Res Opin. 2022 Jun 20:1-10.

Authors

Kwon CS, Lin HM, Crossland V, Churchill EN, Curran E, Forsythe A, Tomaras D, Ou SI.

Abstract

Introduction: EGFR exon 20 insertion mutation-positive non-small cell lung cancer (NSCLC) is rare, has a poor prognosis, and outcomes are not fully established. We describe and evaluate outcomes from real-world and clinical evidence in these patients.

Methods: A systematic literature review (SLR) identified interventional and real-world evidence (RWE) studies reporting clinical outcomes for EGFR exon 20 insertion mutation-positive NSCLC. Meta-analyses were conducted by line of therapy to synthesize pooled survival and response outcomes across RWE. Published evidence from interventional studies was summarized individually.

Results: The SLR identified 23 RWE and 19 original interventional studies. In the meta-analysis of RWE, pooled response and survival outcomes were low for first-line EGFR-tyrosine kinase inhibitors (TKIs) and immuno-oncology (IO) agents. First-line chemotherapy resulted in a pooled ORR 25.7%, pooled PFS 5.6 months, and pooled OS 18.3 months. Pooled outcomes were further reduced in second or later lines (≥2 L): pooled ORR was 5.0%, 3.3%, and 13.9%; pooled PFS was 2.1 months, 2.3 months, and 4.4 months; and pooled OS was 14.1 months, 8.8 months, and 17.1 months (not a pooled result) for EGFR-TKIs, IO agents, and chemotherapy, respectively. Interventional studies reported outcomes for TKIs (mobocertinib, poziotinib, osimertinib, afatinib, CLN-081, DZD9008), a monoclonal antibody (amivantamab), and a heat shock protein 90 inhibitor (luminespib). While there is limited RWE for the recently approved agents mobocertinib and amivantamab, which specifically target exon 20 insertion mutations, interventional evidence supports their potential as effective treatment options.

Conclusions: Conventional treatments used in patients with EGFR exon 20 insertion mutation-positive NSCLC have limited efficacy, though chemotherapy appeared to be associated with better response and survival outcomes than non-exon 20 targeting EGFR-TKIs and IO agents. This

supports the need to identify EGFR exon 20 insertion mutations as the availability of new targeted treatments may offer additional therapeutic options to these patients.

Keywords: Non-small cell lung cancer; epidermal growth factor receptor mutation; exon 20 insertion; meta-analysis; systematic literature review.

https://journals.sagepub.com/doi/abs/10.1177/10600280221098398

Targeting EGFR Exon 20 insertion mutation in non-small cell lung cancer: Amivantamab and mobocertinib.

Citation

Ann Pharmacother. Published online 2022:10600280221098398.

Authors

Russell MC, Garelli AM, Reeves DJ.

Abstract

Objective

To evaluate clinical data regarding the use of amivantamab and mobocertinib for epidermal growth factor receptor (EGFR) exon 20 insertion mutation non–small cell lung cancer (NSCLC) and assess their potential impact on the care of patients.

Data Sources

A comprehensive literature search of PubMed and Clinicaltrials.gov was conducted using the terms amivantamab, Rybrevant, JNJ-61186372, mobocertinib, Exkivity, TAK-788.

Study Selection and Data Extraction

Relevant English-language clinical trials were evaluated.

Data Synthesis

Amivantamab and mobocertinib were Food and Drug Administration (FDA) approved based on phases 1 and 2 studies. Amivantamab demonstrated an overall response rate (ORR) of 40% and median progression-free survival (PFS) of 8.3 months. Patients commonly experienced rash (86%), paronychia (45%), and stomatitis (21%). Mobocertinib demonstrated an ORR of 28% and median PFS of 7.3 months in phase 1/2 study. Patients frequently experienced diarrhea (91%), rash (45%), and paronychia (38%). Cardiac monitoring is recommended with mobocertinib due to risk of QTc prolongation and cardiac failure.

Relevance to Patient Care

For NSCLC patients who possess an EGFR exon 20 insertion mutation, amivantamab and mobocertinib are indicated as second-line therapy. Ongoing studies are evaluating these therapies as first-line monotherapy and as part of combination regimens in multiple cancer types. Dosage forms, drug interactions, and patient comorbidities should be considered when deciding which of the 2 agents may be most appropriate.

Conclusion

Amivantamab and mobocertinib target an uncommon NSCLC mutation that has historically marked a poor prognosis because of innate resistance to previously approved EGFR tyrosine kinase inhibitors. Promising results from early phase trials supported accelerated FDA approval.

Keywords: amivantamab, mobocertinib, exon 20 insertion, NSCLC

https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.9099

Mobocertinib (TAK-788) in EGFR exon 20 insertion (ex20ins)+ metastatic non–small cell lung cancer (mNSCLC): Treatment (tx) beyond progressive disease (PD) in platinum-pretreated patients (pts) with and without intracranial PD.

Citation

J Clin Oncol. 2022;40(16_suppl):9099-9099.

Authors

Janne PA, Ramalingam SS, Yang JC-H, Riely GJ, Bunn V, Jin S, Zhou C, Camidge DR.

Abstract

Background: Mobocertinib is a potent, irreversible, oral tyrosine kinase inhibitor selectively targeting EGFR ex20ins in NSCLC. Mobocertinib demonstrated clinical efficacy in 114 platinum-pretreated pts (PPP) with EGFR ex20ins+ mNSCLC in a phase 1/2 study. Methods: In this study (NCT02716116), pts with ECOG status 0–1 and ≥1 prior therapy line for locally advanced/metastatic EGFR ex20ins+ NSCLC received mobocertinib 160 mg QD. Pts were allowed to continue tx beyond PD at the discretion of the investigator (INV) if evidence of clinical benefit existed. We present data on continuation of mobocertinib tx beyond PD in the PPP cohort by site of first PD (brain vs extracranial). Results: At the November 1, 2020, data cutoff, among PPP (n=114; median age 60 y, 66% female, 60% Asian), 59% had ≥2 prior systemic anticancer lines; 35% had baseline brain metastases (Zhou C, et al. JAMA Oncol. 2021;7(12):e214761. doi:10.1001/jamaoncol.2021).

Confirmed objective response rate (cORR) per independent review committee (IRC) was 28%; median duration of response was 17.5 mo. IRC-assessed cORR was 34% among PPP with no baseline brain metastases versus 18% among PPP with baseline brain metastases (Zhou C, et al. JAMA Oncol. 2021;7(12):e214761. doi:10.1001/jamaoncol.2021); median progression-free survival was 9.2 and 3.7 mo, respectively. Per INV assessment, 64 pts had PD. Duration of mobocertinib tx beyond PD is summarized in the Table. Among pts with first site of PD in brain per INV (n=21), 17 (81%) pts remained on mobocertinib tx beyond PD; 7 (33%) received radiotherapy to brain and remained on mobocertinib tx, of whom 3 pts remained on mobocertinib tx for ≥6 mo and 1 pt for ≥12 mo. Among pts with first site of PD outside the brain per INV (n=43), 28 (65%) pts continued tx beyond PD and 4 (9%) pts remained on mobocertinib tx for ≥6 mo. Conclusions: These results suggest that mobocertinib may have limited intracranial activity given the high frequency of first PD in brain (25%) and numerically lower IRC-assessed cORR in pts with baseline brain metastases. Per INV assessment, pts may derive ongoing systemic benefit from mobocertinib. Duration of time to next progression based on local therapy continues to be investigated. Clinical trial information: NCT02716116.

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https://ascopubs.org/doi/pdf/10.1200/JCO.2022.40.16_suppl.9115

Matching-adjusted indirect comparison (MAIC) of mobocertinib versus amivantamab in patients with non–small cell lung cancer (NSCLC) with EGFR exon 20 insertions (ex20ins).

Citation
J Clin Oncol. 2022;40(16_suppl):9115-9115.

Authors
Ou SHI, Prawitz T, Lin HM, Hong J-L, Tan M, Proskorovsky I, Hernandez L, Jin S, Zhang P, Lin J, Patel JD, Nguyen D, Neal JW.

Abstract

Background: Mobocertinib (mobo) and amivantamab (ami) are FDA-approved treatments for patients (pts) with locally advanced or metastatic NSCLC with EGFR ex20ins whose disease progressed on or after platinum-based chemotherapy. An unanchored MAIC was used to compare confirmed overall response rate (cORR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS) between mobo and ami. Methods: Clinical outcomes were compared in platinum-pretreated pts with EGFR ex20ins+ NSCLC treated with mobo 160 mg QD in a phase I/II single-arm study (NCT02716116, cut-off 1 Nov 2020, n=114) or with ami 1,050 mg (1,400 mg, ≥80 kg) in a phase I single-arm study (NCT02609776, cut-off 8 June 2020, n=81). Differences in baseline characteristics reported in both studies,

including age, race, sex, smoking status, Eastern Cooperative Oncology Group, histology, sites of metastasis (brain, bone and liver), time from advanced diagnosis, number of prior lines of therapy, prior immuno-oncology therapy, prior EGFR tyrosine kinase inhibitor treatment and prior EGFR ex20ins targeted therapy, were adjusted with MAIC. Results: After MAIC weighting all reported baseline characteristics were balanced between mobo and ami. OS and cORR per investigator assessment (INV) were similar between mobo and ami (Table). cORR per independent review committee (IRC) was numerically higher for ami (odds ratio [OR]=0.64, p value=0.230). For PFS per IRC, the adjusted hazard ratio (HR) was numerically favorable for mobo (HR=0.82, p value=0.417). Among the responders, DoR was longer for mobo (DoR per INV: HR=0.44, p value=0.049; DoR per IRC: HR=0.56, p value=0.149). Conclusions: Mobo and ami appear to have overall similar efficacy. As each has a different mechanism of action and route of administration, they provide multiple options in the treatment of EGFR ex20ins+ NSCLC. Clinical trial information: NCT02716116.

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https://biomarkerres.biomedcentral.com/articles/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.

Keywords: Lung cancer, EGFR exon 20 insertion mutations, Tyrosine kinase inhibitor, Immune checkpoint inhibitor

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https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2622

Mobocertinib dose rationale in patients with metastatic NSCLC with EGFR Exon 20 insertions: Exposure-response analyses of a pivotal phase I/II study.

Citation

Clin Pharmacol Ther. Published online 2022.

Authors

Gupta N, Largajolli A, Witjes H, Diderichsen PM, Zhang S, Hanley MJ, Lin J, Mehta M.

Abstract

Mobocertinib is an oral tyrosine kinase inhibitor approved for treatment of patients with locally advanced or metastatic non-small cell lung cancer (mNSCLC) with epidermal growth factor receptor gene (EGFR) exon 20 insertion (ex20ins) mutations previously treated with platinum-based chemotherapy. These exposure–response analyses assessed potential relationships between exposure and efficacy or safety outcomes in platinum-pretreated patients with EGFRex20ins-positive mNSCLC who received mobocertinib 160 mg once daily (q.d.) in a pivotal phase I/II study. A statistically significant relationship between the independent review committee-assessed objective response rate and molar sum exposure to mobocertinib and its active metabolites (AP32960 and AP32914) was not discernable using a longitudinal model of clinical response driven by normalized dynamic molar sum exposure or a static model of best clinical response based on time-averaged molar sum exposure. However, the longitudinal model suggested a trend for decreased probability of response with the change in mobocertinib molar sum exposure between the 160- and 120-mg doses (odds ratio: 0.78; 95% confidence interval: 0.55–1.10; P = 0.156). Time-averaged molar sum exposure was a significant predictor of the rate of grade ≥ 3 treatment-emergent adverse events (AEs). Taken together, these exposure–efficacy and exposure–safety results support a favorable

benefit-risk profile for the approved mobocertinib 160-mg q.d. dose and dose modification guidelines for patients experiencing AEs.

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https://pubmed.ncbi.nlm.nih.gov/35316867/

Population pharmacokinetics of mobocertinib in healthy volunteers and patients with non-small cell lung cancer.

Citation

CPT Pharmacometrics Syst Pharmacol. 2022, 11(6):731-744.

Authors

Gupta N, Pierrillas PB, Hanley MJ, Zhang S, Diderichsen PM.

Abstract

Mobocertinib is an oral tyrosine kinase inhibitor approved for treatment of patients with locally advanced or metastatic non-small cell lung cancer (mNSCLC) with epidermal growth factor receptor gene (EGFR) exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. This population pharmacokinetic (PK) analysis describes the PK of mobocertinib and its active metabolites, AP32960, and AP32914, using data from two phase I studies in healthy volunteers (n = 110) and two phase I/II studies in patients with mNSCLC (n = 317), including the pivotal phase I/II study. The plasma PK of mobocertinib, AP32960, and AP32914 were well-characterized by a joint semimechanistic model that included two compartments for mobocertinib with absorption via three transit compartments, two compartments for AP32960, and one compartment for AP32914. The observed time-dependency in PK was described by an enzyme compartment with drug and metabolite concentration-dependent stimulation of enzyme production, resulting in the enzyme increasing the apparent clearance of mobocertinib, AP32960, and AP32914. Effects of healthy volunteer status (vs. patients with mNSCLC) on apparent oral clearance of all three moieties and on apparent central volume of distribution for mobocertinib were included as structural covariates in the final model. No clinically meaningful differences in mobocertinib PK were observed based on age (18-86 years), race, sex, body weight (37.3-132 kg), mild-to-moderate renal impairment (estimated glomerular filtration rate 30-89 ml/min/1.73 m2 by modification of diet in renal disease equation), or mild-to-moderate hepatic impairment, suggesting that no dose adjustment is required based on these covariates in patients with mNSCLC.

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2021

https://www.mdpi.com/2227-9059/9/12/1938

Discovery, development, inventions, and patent trends on mobocertinib succinate: The first-in-class oral treatment for NSCLC with EGFR Exon 20 insertions.

Citation

Biomedicines. 2021;9(12):1938.

Authors

Imran M, Khan SA, Alshammari MK, Alreshidi MA, Alreshidi AA, Alghonaim RS, Alanazi FA, Alshehri S, Ghoneim MM, Shakeel F.

Abstract

The majority of lung cancers are non-small-cell lung cancer (NSCLC) having a low survival rate. Recent studies have indicated the involvement of epidermal growth factor receptor (EGFR) oncogene mutations like EGFR exon 20 insertions (EGFRex20ins) mutation among NSCLC patients. The response of patients of NSCLC with the EGFRex20ins mutation to the currently available EGFR inhibitor is negligible. Mobocertinib is the first oral treatment that has been approved by the USFDA, on 15 September 2021, to treat NSCLC with the EGFRex20ins mutation. This patent review discusses the inventions and patent literature of mobocertinib that will help the scientific community to develop additional and improved inventions related to mobocertinib. The structure of mobocertinib was first reported in 2015. Therefore, this article covered the patents/patent applications related to mobocertinib from 2015 to 25 October 2021. The patent search revealed 27 patents/patent applications related to compound, method of treatment, salt, polymorph, process, composition, and drug combinations of mobocertinib. The authors foresee an exciting prospect for developing a treatment for NSCLC with EGFRex20ins mutation, and other cancers employing a combination of mobocertinib with other approved anticancer agents. The inventions related to novel dosage forms, processes, and intermediates used in the synthesis of mobocertinib are also anticipated.

Keywords: mobocertinib; TAK-788; EGFR mutation; NSCLC; inventions; patent

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https://www.sciencedirect.com/science/article/pii/S2666364321001004

Severe psychiatric symptoms in a patient with EGFR Exon-20 insertion mutation receiving mobocertinib: A case report.

Citation

JTO Clin Res Rep. 2021;2(11):100241.

Authors

Kamel J, Meeder N, Cuellar S, Chan D, Huber M, Pasquinelli M, Hulbert A, Khaddour K, Feldman L.

Abstract

Tyrosine kinase inhibitor therapy is an established standard of care for patients with NSCLC with EGFR mutations, but a worse prognosis has been observed in patients with specific EGFR exon-20 insertion mutations. Mobocertinib (TAK-788) is a novel tyrosine kinase inhibitor developed to target EGFR exon-20 insertion and has exhibited promising response rates and acceptable safety in phase 1 and 2 trials. We report a case of a 59-year-old woman with metastatic NSCLC and EGFR exon-20 mutation responsive to mobocertinib therapy, who developed severe depression and catatonia approximately 4 months after mobocertinib initiation, ultimately necessitating its permanent discontinuation. Given the observed severe depression in this case report, we recommend that, for patients on mobocertinib who develop neuropsychiatric adverse effects, strong consideration should be given for dose interruption or discontinuation.

Keywords

Tyrosine kinase inhibitors; Non–small cell lung cancer; Exon-20 insertion; Mobocertinib; CNS neurotoxicity; Case report

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https://link.springer.com/article/10.1007/s40265-021-01632-9

Mobocertinib: First approval.

Citation

Drugs. 2021;81(17):2069-2074.

Authors

Markham A.

Abstract

Mobocertinib (EXKIVITY™) is a first-in-class EGFR tyrosine kinase inhibitor being developed for the treatment of EGFR exon 20 insertion (EGFRex20ins) -positive non-small cell lung cancer (NSCLC). Based on efficacy in patients whose disease had progressed on or after platinum-based therapy in a phase I/II trial, mobocertinib was recently granted accelerated approval in the USA in this indication. The drug is also being assessed for marketing approval in various other countries and territories including the EU and China. This article summarizes the milestones in the development of mobocertinib leading to this first approval in the USA for locally advanced or metastatic EGFRex20ins-positive NSCLC that has progressed on or after platinum-based chemotherapy.

https://jamanetwork.com/journals/jamaoncology/article-abstract/2784882

Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With EGFR Exon 20 Insertion–Positive Metastatic Non–Small Cell Lung Cancer: A Phase 1/2 Open-label Nonrandomized Clinical Trial.

Citation

JAMA Oncology. 12 2021;7(12):e214761–e214761.

Authors

Zhou C, Ramalingam SS, Kim TM, Kim S-W, Yang JC-H, Riely GJ, Mekhail T, Nguyen D, Garcia Campelo MR, Felip E, Vincent S, Jin S, Griffin C, Bunn V, Lin J, Lin HM, Mehta M, Jänne PA.

Abstract

Importance Metastatic non–small cell lung cancer (mNSCLC) with EGFR exon 20 insertion (EGFRex20ins) mutations is associated with a poor prognosis. Mobocertinib is an oral tyrosine kinase inhibitor designed to selectively target EGFRex20ins mutations.

Objective To evaluate treatment outcomes and safety of mobocertinib in patients with previously treated EGFRex20ins-positive mNSCLC.

Design, Setting, and Participants This 3-part, open-label, phase 1/2 nonrandomized clinical trial with dose-escalation/dose-expansion cohorts (28 sites in the US) and a single-arm extension cohort (EXCLAIM; 39 sites in Asia, Europe, and North America) was conducted between June 2016 and November 2020 (data cutoff date). The primary analysis populations were the platinum-pretreated patients (PPP) cohort and the EXCLAIM cohort. The PPP cohort included 114 patients with platinum-pretreated EGFRex20ins-positive mNSCLC who received mobocertinib 160 mg once daily from the dose-escalation (n = 6), dose-expansion (n = 22), and EXCLAIM (n = 86) cohorts. The EXCLAIM cohort included 96 patients with previously treated EGFRex20ins-positive mNSCLC (10 were not platinum pretreated and thus were excluded from the PPP cohort).

Interventions Mobocertinib 160 mg once daily.

Main Outcomes and Measures The primary end point of the PPP and EXCLAIM cohorts was confirmed objective response rate (ORR) assessed by independent review committee (IRC). Secondary end points included confirmed ORR by investigator, duration of response, progression-free survival, overall survival, and safety.

Results Among the PPP (n = 114) and EXCLAIM (n = 96) cohorts, the median (range) age was 60 (27-84) and 59 (27-80) years, respectively; most patients were women (75 [66%] and 62 [65%], respectively) and of Asian race (68 [60%] and 66 [69%], respectively). At data cutoff, median follow-up was 14.2 months in the PPP cohort (median 2 prior anticancer regimens; 40 [35%] had baseline brain metastases), with confirmed ORR of 28% (95% CI, 20%-37%) by IRC assessment and 35% (95% CI, 26%-45%) by investigator assessment; median duration of response by IRC assessment was 17.5 months (95% CI, 7.4-20.3). Median progression-free survival by IRC assessment was 7.3 months (95% CI, 5.5-9.2). Median overall survival was 24.0 months (95% CI, 14.6-28.8). In the EXCLAIM cohort, median follow-up was 13.0 months, with confirmed ORR by IRC assessment of 25% (95% CI, 17%-35%) and by investigator assessment of 32% (95% CI, 23%-43%). The most common treatment-related adverse events were diarrhea and rash.

Conclusions and Relevance In this open-label, phase 1/2 nonrandomized clinical trial, mobocertinib was associated with clinically meaningful benefit in patients with previously treated EGFRex20ins-positive mNSCLC, with a manageable safety profile.

Trial Registration ClinicalTrials.gov Identifier: NCT02716116

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https://aacrjournals.org/cancerdiscovery/article/11/7/1617/666582/Mobocertinib-A-Potential-Treatment-for-NSCLC-with

Mobocertinib: A potential treatment for NSCLC with EGFR Exon 20 insertions.

Citation

Cancer Discov. 2021;11(7):1617-1619.

Authors

Pacheco JM.

Abstract

Summary:

Amivantamab is the only FDA-approved therapy for non–small cell lung cancer (NSCLC) with EGFR exon 20 insertions. Unfortunately, patients eventually develop progression of disease on this therapy, and most do not respond to this treatment. In this issue of Cancer Discovery, Gonzalvez and colleagues and Riely and colleagues highlight preclinical and early clinical data supporting mobocertinib as a potentially efficacious agent for NSCLC with EGFR exon 20 insertions.

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https://www.annalsofoncology.org/article/S0923-7534(21)04053-9/fulltext

1218P Characterization of GI toxicities and their impact on efficacy in patients (pts) with EGFR exon 20 insertion+ (ex20ins+) non-small cell lung cancer (NSCLC) treated with mobocertinib (TAK-788) who previously received platinum chemotherapy.

Citation

Ann Oncol. 2021;32:S968-S969.

Authors

Nguyen D, Ramalingam SS, Spira A, Riely GJ, Kim TM, Yang JC-H, Piotrowska Z, Garcia Campelo MR, Felip E, Bazhenova L, Jin S, Griffin C, Diderichsen PM, Gupta N, Bunn V, Lin J, Churchill EN, Mehta M, Zhou C, Janne PA.

Abstract

Background

The phase I/II study (NCT02716116) of mobocertinib 160 mg QD in platinum-pretreated pts (PPP) with EGFRex20ins+ NSCLC, demonstrated a confirmed

objective response rate (ORR) of 28% per independent review committee (IRC); GI toxicities were the most common adverse events (AEs).

Methods

We report ORR, duration of response (DoR), and progression-free survival (PFS) per IRC in pts with and without AEs leading to dose reductions, most of which were due to GI toxicity. We report all-grade (gr) and gr 3/4 diarrhea, vomiting, and nausea; further characterize diarrhea in an exposure-safety analysis; and explore the relationship between diarrhea and various covariates, including age.

Results

In PPP (N=114), ORR was 21% (95% CI: 8.0, 39.7) in pts with AEs leading to dose reductions and 31% (21.1, 41.5) in those without; DoR was 5.7 mo (3.7, not reached [NR]) and 17.5 mo (7.4, NR); PFS was 5.9 mo (3.7, 11.0) and 7.3 mo (5.5, 10.8), respectively. Among pts with AEs leading to dose reductions, 21/29 pts had dose reduction due to GI toxicity. 96% of pts in PPP had at least 1 GI toxicity: all-gr and gr 3/4 diarrhea, 93% and 22%; nausea, 40% and 4%; vomiting, 41% and 3%. For all-gr diarrhea, onset was within first 7 days in 62% of pts, mostly low grade at onset, with median time to resolution of 0.29 weeks, and was managed with antidiarrheal medication in 74% of pts (Table). Statistically significant predictors of gr ≥2 diarrhea were mobocertinib plasma exposure (40-mg dose increase; hazard ratio [HR] 1.11 [95% CI: 1.04, 1.19]) and age (≥75 vs <75 y; HR 2.13 [95% CI, 1.38, 3.30]).

Conclusions

Efficacy outcomes were impacted by dose reductions, which were primarily due to GI toxicity. Most GI toxicity was low grade. Diarrhea, the most frequent GI toxicity, occurred most often in the first week, and was influenced by mobocertinib exposure and age ≥75 y.

Clinical trial identification

NCT02716116; Release date: March 23, 2006.

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https://aacrjournals.org/cancerdiscovery/article/11/7/1672/666626/Mobocertinib-TAK-788-A-Targeted-Inhibitor-of-EGFR

Mobocertinib (TAK-788): A targeted inhibitor of EGFR Exon 20 insertion mutants in non-small cell lung cancer.

Citation

Cancer Discov. 2021;11(7):1672-1687.

Authors

Gonzalvez F, Vincent S, Baker TE, Gould AE, Li S, Wardwell SD, Nadworny S, Ning Y, Zhang S, Huang WS, Hu Y, Li F, Greenfield MT, Zech SG, Das B, Narasimhan NI, Clackson T, Dalgarno D, Shakespeare WC, Fitzgerald M, Chouitar J, Griffin RJ, Liu S, Wong KK, Zhu X, Rivera VM.

Abstract

Most EGFR exon 20 insertion (EGFRex20ins) driver mutations in non–small cell lung cancer (NSCLC) are insensitive to approved EGFR tyrosine kinase inhibitors (TKI). To address the limitations of existing therapies targeting EGFR-mutated NSCLC, mobocertinib (TAK-788), a novel irreversible EGFR TKI, was specifically designed to potently inhibit oncogenic variants containing activating EGFRex20ins mutations with selectivity over wild-type EGFR. The in vitro and in vivo activity of mobocertinib was evaluated in engineered and patient-derived models harboring diverse EGFRex20ins mutations. Mobocertinib inhibited viability of various EGFRex20ins-driven cell lines more potently than approved EGFR TKIs and demonstrated in vivo antitumor efficacy in patient-derived xenografts and murine orthotopic models. These findings support the ongoing clinical development of mobocertinib for the treatment of EGFRex20ins-mutated NSCLC.

Significance:

No oral EGFR-targeted therapies are approved for EGFR exon 20 insertion (EGFRex20ins) mutation-driven NSCLC. Mobocertinib is a novel small-molecule EGFR inhibitor specifically designed to target EGFRex20ins mutants. Preclinical data reported here support the clinical development of mobocertinib in patients with NSCLC with EGFR exon 20 insertion mutations.

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https://www.sciencedirect.com/science/article/pii/S266636432030151X

Preclinical characterization of mobocertinib highlights the putative therapeutic window of this novel EGFR inhibitor to EGFR exon 20 insertion mutations.

Citation

JTO Clin Res Rep. 2021;2(3):100105.

Authors

Vasconcelos PENS, Kobayashi IS, Kobayashi SS, Costa DB.

Abstract

Introduction

EGFR exon 20 insertion mutations account for 10% of all EGFR mutations and are mostly insensitive to approved EGFR tyrosine kinase inhibitors (EGFR TKIs). Novel EGFR TKIs have been developed or repurposed for these mutants. A limited number of preclinical studies have detailed these EGFR TKIs. We sought to use commercially available mobocertinib (TAK-788) to characterize the preclinical therapeutic window of this EGFR TKI against EGFR mutations and to probe possible on-target mechanisms of resistance (EGFR-C797S).

Methods

We used models of EGFR mutations to probe representative first, second, third generation, and in-development EGFR exon 20-active (poziotinib, mobocertinib) TKIs. We also introduced EGFR-C797S to these models to identify mechanisms of resistance.

Results

Cells driven by the most common EGFR exon 20 insertion mutations (A767_V769dupASV, D770_N771insSVD, H773_V774insH, and others) were inhibited by in-development EGFR TKIs at doses below those affecting EGFR-wildtype; albeit more common EGFR mutations (exon 19 deletions and L858R) were inhibited more readily by mobocertinib and poziotinib. Mobocertinib was able to inhibit the phosphorylation of EGFR in multiple preclinical models. The presence of EGFR-C797S led to greater than 200-fold resistance in proliferation assays probing mobocertinib and osimertinib. A review of clinical studies of mobocertinib disclosed responses that could be lasting.

Conclusions

This is one of the initial reports to characterize the novel EGFR TKI mobocertinib and highlights its broad activity against EGFR mutants plus the therapeutic window to EGFR exon 20 insertion mutations; and EGFR-C797S as a possible mechanism of resistance. Further clinical development of mobocertinib merits continuation.

Keywords

Lung cancer; EGFR exon 20 insertion; Mobocertinib; C797S; ERBB2

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8286072/

Spotlight on Mobocertinib (TAK-788) in NSCLC with EGFR Exon 20 Insertion Mutations.

Citation

Lung Cancer (Auckl). 2021 Jul 12;12:61-65.

Authors

Zhang SS, Zhu VW.

Abstract

The EGFR exon 20 insertion (EGFRex20ins) mutations are the third most common EGFR mutations seen in non-small cell lung cancer (NSCLC). More than 50 variants of EGFRex20ins mutations have been identified with A767_V769dupASV being the most common variant across multiple surveys. Treatment with currently available EGFR tyrosine kinase inhibitors (TKIs) including osimertinib is generally ineffective. Amivantamab (JNJ-372), a bispecific monoclonal antibody against EGFR and MET, has recently been approved by the US FDA for patients with advanced or metastatic NSCLC harboring EGFRex20ins mutations after disease progression on platinum-based chemotherapy. Among all the TKIs in clinical development, mobocertinib (TAK-788) has been granted priority review by the FDA for the same indication as amivantamab. Here, we provide a concise review on mobocertinib, with a focus on its chemical structure, preclinical data, and phase 1/2 trial results. Future directions will likely focus on combination approach such as TKI plus chemotherapy in the first-line setting, designing drugs with CNS activity, and exploring disease characteristics of various EGFRex20ins mutation variants and how they may affect treatment response.

Keywords: mobocertinib, TAK-788, NSCLC, EGFR exon 20 insertion, TKI, amivantamab

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https://accp1.onlinelibrary.wiley.com/doi/full/10.1002/cpdd.951

Single-dose pharmacokinetics and tolerability of the oral epidermal growth factor receptor inhibitor mobocertinib (TAK-788) in healthy volunteers: Low-fat meal effect and relative bioavailability of 2 capsule products.

Citation

Clin Pharmacol Drug Dev. 2021;10(9):1028-1043.

Authors

Zhang S, Jin S, Griffin C, Feng Z, Lin J, Baratta M, Brake R, Venkatakrishnan K, Gupta N.

Abstract

Mobocertinib (TAK-788) is a tyrosine kinase inhibitor under investigation for treatment of non–small cell lung cancer with activating EGFR exon 20 insertions. This study examined the safety; tolerability; pharmacokinetics (PK), including food effects; and bioavailability of mobocertinib in healthy volunteers. In part 1, fasted volunteers were randomized to placebo or mobocertinib in single-ascending-dose cohorts (20-160 mg). In part 2, mobocertinib (120/160 mg) was administered on day 1 of periods 1 and 2 under fasted or low-fat meal conditions (2-period, 2-sequence crossover design). In part 3, fasted volunteers received mobocertinib 160 mg in 1 of 2 capsule products on day 1 of periods 1 and 2 with 7-day washout. Safety and PK parameters were assessed. Sixty-nine volunteers were enrolled (mean age, 29 years; 75% male). The most common adverse events (AEs; ≥10% of volunteers) were gastrointestinal AEs (25%-50%) and headache (8%-31%). No serious AEs were reported. A low-fat meal did not affect the PK of mobocertinib or its active metabolites. The geometric mean terminal disposition phase half-life (20 hours) supported once-daily dosing. The 2 capsule products were bioequivalent. These data guided dosing and supported administration of mobocertinib without regard to low-fat meal intake in ongoing and planned clinical studies.

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https://aacrjournals.org/cancerdiscovery/article/11/7/1688/666555/Activity-and-Safety-of-Mobocertinib-TAK-788-in

Activity and safety of mobocertinib (TAK-788) in previously treated non-small cell lung cancer with EGFR Exon 20 insertion mutations from a phase I/II trial.

Citation

Cancer Discov. 2021;11(7):1688-1699.

Authors

Riely GJ, Neal JW, Camidge DR, Spira AI, Piotrowska Z, Costa DB, Tsao AS, Patel JD, Gadgeel SM, Bazhenova L, Zhu VW, West HL, Mekhail T, Gentzler RD, Nguyen D, Vincent S, Zhang S, Lin J, Bunn V, Jin S, Li S, Jänne PA.

Abstract

Mobocertinib, an oral epidermal growth factor receptor (EGFR) inhibitor targeting EGFR gene mutations, including exon 20 insertions (EGFRex20ins), in non–small cell lung cancer, was evaluated in a phase I/II dose-escalation/expansion trial (ClinicalTrials.gov NCT02716116). Dose escalation identified 160 mg/d as the recommended phase 2 dose and maximum tolerated dose. Among 136 patients treated with 160 mg/d, the most common any-grade treatment-related adverse events (TRAE; >25%) were diarrhea (83%), nausea (43%), rash (33%), and vomiting (26%), with diarrhea (21%) the only grade ≥3 TRAE >5%. Among 28 EGFRex20ins patients treated at 160 mg/d, the investigator-assessed confirmed response rate was 43% (12/28; 95% confidence interval, 24%–63%) with median duration of response of 14 months (5.0–not reached) and median progression-free survival of 7.3 months (4.4–15.6). Mobocertinib demonstrated antitumor activity in patients with diverse EGFRex20ins variants with a safety profile consistent with other EGFR inhibitors.

Significance:

No oral EGFR-targeted therapies are currently approved for patients with EGFRex20ins NSCLC. Mobocertinib demonstrated antitumor activity with manageable toxicity in patients with advanced EGFRex20ins NSCLC in this study, supporting additional development of mobocertinib in this patient population.

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https://www.jto.org/article/S1556-0864(21)02659-9/fulltext

FP09.02 mobocertinib (TAK-788) in EGFR Exon 20 insertion+ metastatic NSCLC: Patient-reported outcomes from EXCLAIM extension cohort.

Citation

J Thorac Oncol. 2021;16(10):S960-S961.

Authors

García Campelo MR, Zhou C, Ramalingam S, Lin H, Kim T, Riely G, Mekhail T, Nguyen D, Goodman E, Le K, Mehta M, Popat S, Janne P.

Abstract

Introduction

Maintaining health-related quality of life (HRQoL) and independence in daily activities are important factors to cancer patients. Mobocertinib is an oral,

first-in-class EGFR tyrosine kinase inhibitor that selectively targets EGFR exon 20 insertions (ex20ins). We previously reported that mobocertinib resulted in confirmed objective response rates (ORRs) assessed by an independent review committee (IRC) of 25% and a median progression-free survival (PFS) of 7.3 months in patients from the EXCLAIM extension cohort of the phase 1/2 study in EGFR ex20ins+ non–small cell lung cancer (NSCLC). Treatment with mobocertinib in the platinum-pretreated patients from the same study resulted in a confirmed ORR by IRC of 28% and median PFS of 7.3 months in this patient population. Here we present patient-reported outcome (PRO) data from the EXCLAIM extension cohort.

Methods

The EXCLAIM extension cohort of the phase 1/2 multicenter study (NCT02716116) evaluated mobocertinib 160 mg orally once daily in previously treated metastatic NSCLC patients with EGFR ex20ins. PROs were assessed with European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire (EORTC QLQ-C30) v3.0, the lung cancer module (QLQ-LC13) v3.0, the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L), and select items (decreased appetite, difficulty swallowing, nausea, vomiting, diarrhea, rash, fatigue, and dry skin) from the PRO Common Terminology Criteria for Adverse Events (PRO-CTCAE). Questionnaires were administered at baseline and selected visits before any clinical measurements, assessments, or procedures were performed.

Results

Global health status/quality-of-life via the EORTC QLC-C30 was maintained during time on mobocertinib therapy, with most patients maintaining or improving from baseline scores (least-squares mean change -1.8 [P=0.235]). Clinically meaningful improvements from baseline in QLQ-LC13 symptom scores (defined as ≥10-point decrease in symptom scores) were observed for core lung cancer symptoms of dyspnea in 54.4% of patients, coughing in 46.7%, and pain in chest in 38.9%. Improvements were evident at cycle 2 and maintained throughout treatment (least-squares mean changes from baseline: dyspnea -3.2 [P=0.019]; cough -9.3 [P<0.001]; and pain in chest -8.2 [P<0.001]; Figure). Patient health status via the EQ-5D-5L was maintained throughout the study. HRQoL was maintained despite the reporting of common adverse events collected via the PRO-CTCAE, including diarrhea, dry skin, and rash.

Conclusion

PROs for mobocertinib were favorable in previously treated patients with EGFR ex20ins+ metastatic NSCLC. Improvements in core NSCLC symptoms were observed and overall HRQoL was maintained during therapy, despite adverse events such as rash and gastrointestinal-related symptoms, including diarrhea.

Keywords

exon20 insertion, health-related quality of life, non-small cell lung cancer

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https://www.annalsofoncology.org/article/S0923-7534(21)04066-7/fulltext

1231P Characterization and management of mobocertinib (TAK-788) induced skin toxicity in patients with EGFR exon 20 insertion+ (ex20ins+) non-small cell lung cancer (NSCLC) who previously received platinum chemotherapy.

Citation

Ann Oncol. 2021;32:S975.

Authors

Yang JCH, Ramalingam SS, Kim TM, Kim S-W, Riely GJ, Mekhail T, Nguyen D, Garcia Campelo MR, Felip E, Bazhenova L, Jin S, Griffin C, Bunn V, Lin J, Churchill EN, Mehta M, Janne PA, Zhou C.

Abstract

Background

Mobocertinib, an oral EGFR tyrosine kinase inhibitor (TKI) designed to target EGFRex20ins mutations, demonstrated clinical efficacy in 114 platinum-pretreated EGFRex20ins+ NSCLC patients (PPP) in a phase I/II study (NCT02716116). Confirmed objective responses by independent assessment were reported in 28% of patients with median duration of response of 17.5 months. Skin toxicities are commonly reported with irreversible EGFR TKIs, including skin rash, dry skin, and paronychia.

Methods

All patients received 160 mg QD mobocertinib. We report type and incidence of any-grade (gr) and gr ≥3 skin toxicity treatment-emergent adverse events (TEAEs), frequency of dose modifications (reduction, discontinuation), and management of these events.

Results

Among 114 patients in the PPP cohort, skin toxicity events were observed in 105 (92%), with gr ≥3 events in 5 patients (4%). No patients had serious events, 5 (4%) dose reduced, and 1 patient (<1%) required dose discontinuation. Median time to onset was 9 days and median time to resolution of gr 2 and gr 3 events were 9 and 5 weeks, respectively. Rash, paronychia, dry skin, and pruritus were the most commonly reported skin toxicities (>20% of patients) (Table). Proactive management included skin

care and use of topical corticosteroids (43%) including hydrocortisone (12%) and antibiotics (28%), such as clindamycin (21%) and mupirocin (18%).

Conclusions

The majority of skin toxicity events were low grade, started within the first 2 weeks of treatment, and were largely managed with skin care and proactive use of topical steroids and/or antibiotics. Types of skin toxicities observed with mobocertinib are consistent with those reported with the class of EGFR TKIs, with low frequency of high-grade toxicity.

Clinical trial identification

NCT02716116; Release date: 23 March 2006.

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https://www.annalsofoncology.org/article/S0923-7534(21)04081-3/fulltext

1246P A phase I dose-escalation study of mobocertinib (TAK-788), an oral tyrosine kinase inhibitor (TKI), in Japanese NSCLC patients.

Citation

Ann Oncol. 2021;32:S981.

Authors

Hida T, Nishino M, Yoh K, Asato T, Kitagawa T, Zhang S, Mehta M, Ohe Y.

Abstract

Background

Mobocertinib is an orally administered TKI that potently inhibits activating epidermal growth factor receptor (EGFR) mutations, including in-frame insertions in exon 20, which are associated with poor survival. We present results from the phase I open-label, dose-escalation of a phase I/II study (NCT03807778), aimed to confirm the recommended phase II dose (RP2D)/maximum tolerated dose (MTD) identified in global studies (160 mg once daily [QD]) in Japanese patients with NSCLC.

Methods

Patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC refractory to standard available therapies were included. Dose-escalation cohorts started with 40 mg QD followed by higher doses according to a Bayesian logistic regression model [MC1] until an MTD was found or 160 mg QD was shown to be safe and tolerable. MTD was reached

when ≥9 patients at all doses were dose-limiting toxicity (DLT)-evaluable, ≥6 patients at the current dose level were DLT-evaluable, and the next recommended dose was equal to the current dose.

Results

In total, 20 patients (40 mg QD, n=4; 120 mg QD, n=4; 160 mg QD, n=12) were enrolled at 4 sites: 18 (90%) had tumors harboring EGFR exon 20 insertion mutation; all patients had ≥1 prior anticancer therapy, and 55% had received ≥3 regimens. No DLT was observed at 40 mg QD. One patient receiving 120 mg QD reported a DLT of diarrhea (Grade 3), and 2 patients receiving 160 mg QD reported DLT: one had interstitial lung disease (Grade 3), the other had aspartate aminotransferase increased (Grade 2), alanine aminotransferase increased (Grade 3) and diarrhea (Grade 2). All patients in the 160 mg QD cohort reported a treatment-emergent adverse event (TEAE). The most common TEAEs were diarrhea (reported in all but 1 patient receiving 40 mg QD) and nausea (50% of each dose cohort). MTD/RP2D of mobocertinib was confirmed as 160 mg QD. Pharmacokinetic parameters were also assessed and will be presented.

Conclusions

Mobocertinib showed a manageable safety profile in Japanese NSCLC patients. Based on the totality of pharmacokinetics and safety data from various mobocertinib doses, 160 mg QD was selected as the RP2D for further clinical studies in Japanese patients.

Clinical trial identification

TAK-788-1003.

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https://www.jto.org/article/S1556-0864(20)30906-0/fulltext

OFP01.08 tolerability, low-fat meal effect, and relative bioavailability (BA) of oral EGFR inhibitor TAK-788 in healthy volunteers.

Citation

J Thorac Oncol. 2021;16(1):S11.

Authors

Zhang S, Jin S, Griffin C, et al.

Abstract

TAK-788 is an investigational oral tyrosine kinase inhibitor (TKI) targeting EGFR. The TAK-788 clinical development program to treat non-small cell lung cancer (NSCLC) with EGFR exon 20 insertions is ongoing. We report the results of a phase 1, open-label, single rising dose (SRD) study, followed by a study evaluating the effects of a low-fat meal on the pharmacokinetics (PK) of TAK-788, and an evaluation of relative BA between 2 drug-in-capsule formulations in healthy adult volunteers. The study (NCT03482453) was composed of 3 parts: (1) Randomized, doubleblind, placebo-controlled, SRD study of TAK-788 with Capsule-B; (2) The effects of a low-fat meal (≤350 calories and ≤15% calories from fat) on TAK-788 PK with Capsule-A; (3) Relative BA of 4×40 mg size 1 Capsule-B (test) versus 8×20 mg size 2 Capsule-A (reference). In Part 1, 5 cohorts of 8 healthy volunteers each were randomized: 6 volunteers received a single oral dose ranging from 20 to 160 mg (recommended phase 2 dose) of TAK-788 and 2 volunteers received placebo under fasting conditions in each cohort. Parts 2 and 3 were evaluated in a 2-way crossover design with a 7-day washout period. The initial dose in Part 2 was selected as 120 mg (n=6) and subsequently the 160 mg (n=10) dose was tested. In Part 3, 12 volunteers were randomly assigned to 2 crossover sequences and administered a single dose of 160 mg TAK-788 in Capsule-A or Capsule-B on Days 1 and 8 under fasting conditions. In Part 1, no grade >2 TEAE was observed. In Parts 2 and 3, all TEAEs were grade ≤2 except for one grade 3 event of lipase increased. The most common TEAEs by preferred term (≥2 subjects overall) were nausea (12.5%), diarrhea (10.0%), headache (7.5%), and abdominal pain upper (5.0%) in Part 1 and headache (31.3%), nausea (31.3%), abdominal pain upper (18.8%), soft feces (12.5%), and flatulence (12.5%) in Part 2. No TEAE occurred in ≥2 volunteers in Part 3. In Part 2 at the 120 mg dose, the least square geometric mean ratios (90% CI) of TAK-788 Cmax and AUC∞ comparing TAK-788 oral administration with a low-fat meal to those under fasting conditions were 0.881 (0.711, 1.09) and 1.02 (0.898, 1.15), respectively. At 160 mg, these ratios (90% CI) were 0.964 (0.836, 1.11) and 0.951 (0.874, 1.03), respectively. In Part 3, the geometric mean ratios of TAK-788 Cmax and AUC∞ comparing Capsule-B to Capsule-A were 0.932 and 0.960, respectively. The 90% CIs of geometric mean ratios for both TAK-788 Cmax and AUC∞ were 0.846, 1.03 and 0.886, 1.04, falling within the bioequivalence range of 0.80 to 1.25. TAK-788 was well tolerated at single oral doses from 20 to 160 mg in healthy volunteers. A low-fat meal did not affect TAK-788 systemic exposure. Therefore, TAK-788 can be administered with or without a low-fat meal for patients' convenience with TAK-788 daily dosing. Capsules A and B used during the clinical development program have been demonstrated to be bioequivalent.

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2020

https://www.annalsofoncology.org/article/S0923-7534(20)41571-6/fulltext

1261MO Updated results from a phase I/II study of mobocertinib (TAK-788) in NSCLC with EGFR exon 20 insertions (exon20ins).

Citation

Ann Oncol. 2020;31:S815-S816.

Authors

Riely GJ, Neal JW, Camidge DR, Spira A, Piotrowska Z, Horn L, Costa DB, Tsao A, Patel J, Gadgeel S, Bazhenova L, Zhu VW, West H, Mekhail T, Gentzler R, Nguyen D, Bunn V, Jin S, Feng Z, Jänne PA.

Abstract

Background

EGFR exon20ins occur in ~1%–2% of patients (pts) with NSCLC. Currently approved EGFR TKIs have not shown efficacy in most of these mutations. Mobocertinib is an investigational oral EGFR/HER2 inhibitor under evaluation in pts with metastatic NSCLC with EGFR exon20ins. We previously reported dose escalation and establishment of 160 mg qd as RP2D. We report updated antitumor activity and safety results from an open-label, multicenter study of mobocertinib (NCT02716116).

Methods

Antitumor activity by investigator-assessed radiographic response (RECIST 1.1) and toxicity (NCI CTCAE) were determined for pts with advanced, previously treated NSCLC with EGFR exon20ins who received mobocertinib 160 mg qd. Safety data were collected for all pts treated at 160 mg qd.

Results

As of 27 Jan 2020, 28 pts with previously treated NSCLC and EGFR exon20ins were treated in dose escalation/expansion at 160 mg qd. In these pts: median age, 62 y (range 28– 84); women, 75%; ECOG 0/1, 21%/79%; ≥2 prior anticancer therapies, 86%; brain metastases, 43%. Median time on treatment was 12 mo (13 treatment cycles) and 7 pts remain on treatment. Confirmed ORR (PR) was 43% (12/28; 95% CI 24–63). The disease control rate was 86% (24/28; 95% CI 67–96). Two pts had best response of PD; 2 pts were not evaluable. Median duration of response in the 12 pts with confirmed PR was 14 mo (95% CI 5–not reached). The median PFS was 7.3 mo (95% CI 4.4–15.6); 12-mo PFS was 33% (15–52). Response to mobocertinib was observed in diverse EGFR exon20ins variants. Among these 28 pts, most common any grade treatment-related AEs (TRAEs; >25%) as assessed by investigator: diarrhea (82%), rash (46%), nausea (39%), decreased appetite (39%), vomiting (36%), paronychia (29%); grade ≥3 TRAEs (≥5%): diarrhea (32%), nausea (11%), increased lipase (7%), increased amylase (7%), stomatitis (7%), vomiting (7%). In all 136 pts treated with ≥1 dose of 160 mg, most

common TRAEs: diarrhea (83%), nausea (43%), rash (33%), vomiting (27%); grade ≥3 TRAEs: diarrhea (21%) and increased lipase (5%).

Conclusions

Mobocertinib demonstrated antitumor activity in pts with advanced NSCLC with EGFR exon20ins. The safety profile for mobocertinib was consistent with other EGFR TKIs.

Clinical trial identification

NCT02716116 Release date: March 23, 2016.

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https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.9580

Indirect comparison of TAK-788 vs real-world data outcomes in refractory non-small cell lung cancer (NSCLC) with EGFR exon 20 insertions.

Citation

J Clin Oncol. 2020;38(15_suppl):9580-9580.

Authors

Horn L, Lin HM, Padda SK, Aggarwal C, McCoach CE, Zhu Y, Yin Y, Lin J, Li S, Feng Z, Neal JW.

Abstract

Background: Currently approved epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are ineffective in patients (pts) with EGFR exon 20 insertion NSCLC. TAK-788 is an EGFR TKI with potent and selective preclinical inhibitory activity against EGFR exon 20 insertions, and has demonstrated preliminary efficacy in a single-arm phase 1/2 clinical trial (NCT02716116). We performed an indirect comparison of real-world outcomes with clinical trial data for this subset of pts to determine whether TAK-788 provides superior efficacy over standard treatment options. Methods: We compared efficacy in pts with refractory NSCLC with EGFR exon 20 insertions treated with TAK-788 160 mg qd (1–7 prior lines) from the ongoing clinical trial (data cut Mar 1, 2019) vs real-world data (RWD) in the second-line setting from the US Flatiron Health electronic health record–derived database (Jan 2011–Jun 2018). This analysis was conducted using an unadjusted data set, as well as by applying propensity score modeling with inverse probability of treatment weighting (IPTW) to adjust for group differences in key baseline characteristics. Progression-free survival (PFS) and objective response rate (ORR) were compared between groups. Results: A

total of 99 pts were included, n=28 TAK-788 and n=71 RWD; mean age 62/65 y; male 25%/46%; Asian 18%/10%; former smoker 39%/45%; brain metastases 43%/34%. In the RWD, there was no consistent regimen for second-line treatment (including 29.6% immuno-oncologic agents, 25.4% EGFR TKI, 10% docetaxel). Baseline characteristics were comparable after weighting. PFS and ORR showed statistically significant improvements with TAK-788 vs RWD (Table). Specifically, after weighting, median PFS for TAK-788 vs RWD is 7.3 vs 3.5 mo, and ORR is 43% vs 13%. Conclusions: Despite a more heavily pretreated pt population, the efficacy of TAK-788 in pts with refractory NSCLC with EGFR exon 20 insertions appears better than other second-line treatment options used in the real-world setting. Clinical trial information: NCT02716116.

2019

https://www.jto.org/article/S1556-0864(19)31525-4/fulltext

P1.01-127 antitumor activity of the oral EGFR/HER2 inhibitor TAK-788 in NSCLC with EGFR Exon 20 insertions.

Citation

J Thorac Oncol. 2019;14(10):S412-S413.

Authors

Riely G, Neal J, Camidge DR, et al.

Abstract

Background

We report results of a phase 1/2 open-label, multicenter study of TAK-788 (NCT02716116), an oral investigational EGFR/HER2 inhibitor.

Method

Patients with advanced, previously treated NSCLC received daily TAK-788 in dose escalation and expansion cohorts based on tumor genotype. Antitumor activity was determined for patients with EGFR exon 20 insertions who received TAK-788 160 mg QD. Safety is reported for all patients across all doses and at 160 mg. To improve gastrointestinal tolerability, food intake instructions in this ongoing study were amended to allow for administration with or without a low-fat meal based on emerging clinical pharmacokinetic data in a healthy volunteer study (data on file).

Result

As of 14 Sep 2018, 101 patients (median age, 61 y; female, 70%; ≥2 prior anticancer therapies, 76%; brain metastases, 53%) were treated with TAK-788 at 5–180 mg QD. RP2D was determined to be 160 mg QD. 28 patients with EGFR exon 20 insertions were treated with 160 mg QD during dose escalation

or in expansion cohort 1 (3.6 months on treatment; 3.8 treatment cycles [medians]); 24 patients remain on treatment. At data cutoff, best response (RECIST v1.1) among 26 patients with ≥1 disease assessment was PR, n=14; SD, n=9; and PD, n=1 (objective response rate, 54%; 95% CI: 33.4%–73.4%); 2 patients were unevaluable. 7/14 objective responses (all PR) were confirmed (6 awaiting confirmation; 1 unconfirmed PR at 160 mg QD); median time to response in these 14 patients was 56 days. 23/26 patients (89%; 95% CI: 69.9%–97.6%) achieved disease control. 23/24 evaluable patients with EGFR exon 20 insertions treated at 160 mg QD had decreased target lesion measurements (median best percent change, -32.6% [-79.1%–3.8%]). Most common TEAEs (≥20%) in patients treated with 160 mg QD: diarrhea (85%), rash (43%), nausea (41%), vomiting (30%), decreased appetite (28%), stomatitis (22%); grade ≥3 TEAEs (≥5%): diarrhea (26%); hypokalemia, nausea, stomatitis (7% each). Among patients treated with 160 mg QD, median dose intensity was 93%, rate of dose reduction due to AEs was 21.7%, and rate of treatment discontinuation due to AEs was 10.9%. There was no clear trend that response to TAK-788 was enriched in any single EGFR exon 20 insertion variant.

Conclusion

In NSCLC patients with EGFR exon 20 insertions, TAK-788 demonstrated antitumor activity and a safety profile consistent with other EGFR TKIs.

Keywords

EGFR tyrosine kinase inhibitor, EGFR exon 20 mutation

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https://www.sciencedirect.com/science/article/pii/S0923753419621721

Antitumor activity of TAK-788 in NSCLC With EGFR exon 20 insertions.

Citation

Ann Oncol. 2019;30(Supplement_6):vi108.

Authors

Jänne PA, Neal JW, Camidge DR, Spira A, Piotrowska Z, Horn L, Costa DB, Tsao A, Patel J, Gadgeel S, Bazhenova L, Zhu VW, West H, Vincent S, Zhu J, Li S, Riely GJ.

Abstract

Background

We report results of a phase 1/2 open-label, multicenter study of TAK-788 (NCT02716116), an oral investigational EGFR/HER2 inhibitor.

Methods

Pts with advanced, previously treated NSCLC received daily TAK-788 in dose escalation and expansion cohorts based on tumor genotype. Antitumor activity was determined for pts with EGFR exon 20 insertions who received TAK-788 at the RP2D. Safety is reported for all pts across all doses and at 160 mg.

Results

As of 14 Sep 2018, 101 pts (median age, 61 y; female, 70%; ≥2 prior anticancer therapies, 76%; brain metastases, 53%) were treated with TAK-788 at 5-180 mg qd. RP2D was determined to be 160 mg. 28 pts with EGFR exon 20 insertions were treated with 160 mg qd during dose escalation or in expansion cohort 1 (3.6 mo on treatment; 3.8 treatment cycles [medians]); 24 pts remain on treatment. At data cutoff, best response (by RECIST v1.1) among 26 pts with ≥1 disease assessment was PR, n = 14; SD, n = 9; and PD, n = 1; 2 pts were not evaluable. 7/14 objective responses (all PR) were confirmed, with 6 awaiting confirmation and 1 unconfirmed PR at 160 mg qd; median time to response in these 14 pts was 56 days. 23/26 pts achieved disease control. 23/24 evaluable pts with EGFR exon 20 insertions treated at 160 mg qd had decreased target lesion measurements (median best percent change, -32.6% [-79.1%, 3.8%]). Most common TEAEs (≥20%) in pts treated with 160 mg qd: diarrhea (85%), rash (43%), nausea (41%), vomiting (30%), decreased appetite (28%), and stomatitis (22%); gr ≥ 3 TEAEs (≥5%): diarrhea (26%); hypokalemia, nausea, and stomatitis (7% each). Among pts treated with 160 mg qd, median dose intensity was 93%, and the rate of treatment discontinuation due to AEs was 10.7%. There is no clear trend that response to TAK-788 is enriched in any single EGFR exon 20 insertion variant.

Conclusions

In NSCLC pts with EGFR exon 20 insertions, TAK-788 demonstrated antitumor activity and an AE profile consistent with other EGFR TKIs.

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2018

https://www.sciencedirect.com/science/article/pii/S1556086418318598

P1.13-44 safety, PK, and preliminary antitumor activity of the oral EGFR/HER2 Exon 20 inhibitor TAK-788 in NSCLC.

Citation

J Thorac Oncol. 2018;13(10):S599.

Authors

Neal J, Doebele R, Riely G, Spira A, Horn L, Piotrowska Z, Costa D, Zhang S, Bottino D, Zhu J, Kerstein D, Li S, Jänne P.

Abstract

Background

TAK-788 (AP32788) is an investigational tyrosine kinase inhibitor (TKI) with potent, selective preclinical activity against activating EGFR and HER2 mutations, including exon 20 insertions. We report early results of a phase 1/2 first-in-human, open-label, multicenter study of TAK-788 (NCT02716116).

Method

Patients with advanced non-small cell lung cancer (NSCLC) refractory to standard therapy received daily oral doses (5–120 mg) of TAK-788 in the ongoing dose-escalation phase (3+3 design). Preliminary antitumor activity (by RECIST v1.1), safety, and PK are reported for patients who received ≥1 dose.

Result

As of 8-Sep-2017, 34 patients (median age, 60 y; female, 65%; ≥2 prior anticancer therapies, 88%; Table) were treated with TAK-788; 10 remain on treatment at data cutoff. AUC0-24,ss increased in a dose-proportional manner over the dose range evaluated; the effective t1/2 was ~16 (range 6–28) h. The most common treatment-emergent AEs (TEAEs; ≥20%) were diarrhea (47%), nausea (26%), and fatigue (21%). Grade ≥3 TEAEs in ≥2 patients (excluding disease progression) were dyspnea (n=3, 9%) and anemia, asthenia, dehydration, lung infection, pleural effusion, pneumonia, and pneumonitis (n=2 each, 6%). Two DLTs, both pneumonitis, were reported (80 mg, grade 3; 120 mg, grade 5). Of 14 evaluable patients, 3 had PR (80 mg, n=2, both confirmed; 120 mg, single PR awaiting confirmation), 6 had SD (40 mg, n=3; 80 mg, n=2; 120 mg, n=1), and 5 had PD as best response (40 mg, n=3; 80 mg, n=1; 120 mg, n=1). All patients with PR had EGFR exon 20 insertions.

Conclusion

TAK-788 exhibits antitumor activity in patients with EGFR exon 20 insertions with an AE profile consistent with other EGFR TKIs. Phase 2 will begin after determination of the RP2D, with 4 molecularly defined cohorts in NSCLC. Updated data will be presented, including the recommended phase 2 dose (RP2D).

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https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.9015

First report of safety, PK, and preliminary antitumor activity of the oral EGFR/HER2 exon 20 inhibitor TAK-788 (AP32788) in non–small cell lung cancer (NSCLC).

Citation

J Clin Oncol. 2018;36(15_suppl):9015-9015.

Authors

Doebele RC, Riely GJ, Spira AI, Horn L, Piotrowska Z, Costa DB, Neal JW, Zhang S, Reichmann W, Kerstein D, Li S, Janne PA.

Abstract

Background: TAK-788 is an investigational TKI with potent, selective preclinical activity against activating EGFR and HER2 mutations, including exon 20 insertions. We report the first results of a phase 1/2 first-in-human, open-label, multicenter study of TAK-788 (NCT02716116). Methods: Pts with advanced NSCLC refractory to standard therapy received daily oral doses (5–120 mg) of TAK-788 in the ongoing dose-escalation phase (3+3 design). Preliminary antitumor activity (by RECIST v1.1), safety, and PK are reported for pts receiving ≥1 dose. Results: As of 8 September 2017, 34 pts (median age, 60 y; female, 65%; ≥2 prior anticancer therapies, 88%; Table) were treated and 10 remain on TAK-788 at data cutoff. AUC0-24,ss increased in a dose-proportional manner over the dose range with effective t1/2 of ~16 (range 6–28) h. Most common treatment-emergent AEs (TEAEs; ≥20% of pts): diarrhea (47%), nausea (26%), fatigue (21%). Grade ≥3 TEAEs in ≥2 pts (excluding disease progression): dyspnea (n = 3, 9%); anemia, asthenia, dehydration, lung infection, pleural effusion, pneumonia, pneumonitis (n = 2 each, 6%). Two DLTs, both pneumonitis, were reported (80 mg, grade 3; 120 mg, grade 5). Of 14 evaluable pts, 3 had PR (80 mg, n = 2, both confirmed; 120 mg, single PR awaiting confirmation), 6 had SD (40 mg, n = 3; 80 mg, n = 2; 120 mg, n = 1), and 5 had PD as best response (40 mg, n = 3; 80 mg, n = 1; 120 mg, n = 1); all pts with PR or SD had EGFR exon 20 insertions. Conclusions: TAK-788 exhibits antitumor activity in pts with EGFR exon 20 insertions with an AE profile consistent with other EGFR TKIs. Phase 2 will begin after determination of the RP2D, with 4 molecularly defined cohorts in NSCLC. Clinical trial information: NCT02716116.

https://www.jto.org/article/S1556-0864(18)32385-2/fulltext

P2.13-32 TAK-788 is a novel and potent tyrosine kinase inhibitor with selective activity against EGFR/HER2.

Citation

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Authors

Chouitar J, Vincent S, Brake R, Li S.

Abstract

Background

Dysregulation of the EGFR family member HER2 (human epidermal growth factor receptor 2) plays an important role in many cancers. HER2 exon 20 in-frame insertion mutations occur in 2–4% of non-small cell lung carcinomas (NSCLC). Despite current HER2-directed treatments, no approved therapies exist for patients with cancers harboring HER2 mutations. Unlike other activating mutations, exon 20 insertions induce a conformational change leading to significant homology to the ATP-binding pocket of WT proteins. As such, clinical development of tyrosine kinase inhibitors (TKIs) against these insertions has been challenging, as inhibition of WT-EGFR is associated with clinical dose-limiting toxicities, such as diarrhea and skin rash. TAK-788 was designed to potently inhibit oncogenic variants with desirable selectivity over WT-EGFR. TAK-788 inhibits mutant EGFR and HER2 via covalent modification of EGFR-Cys797 and HER2-Cys805. Here, we characterized the non-clinical activity of TAK-788 in HER2 exon 20 insertion and substitution mutants and contrasted it with other TKIs.

Method

In vitro activity was assessed by measuring viability in engineered Ba/F3 lines expressing different HER2 mutation variants (substitutions and insertions). Inhibition of WT-EGFR was assessed by measuring EGFR phosphorylation in A431 cells that overexpress WT-EGFR. In vivo activity was assessed by monitoring tumor volume.

Result

TAK-788 inhibited all HER2 mutations tested, including exon 20 insertions and point mutations, more potently than it inhibits WT-EGFR (Figure), suggesting an acceptable therapeutic window compared with other TKIs. TAK-788 in vitro potency in these mutations has also been confirmed in vivo with tumor xenograft models and in a phase 1 clinical trial.

Conclusion

The favorable selectivity and potency observed in these in vitro experiments for HER2 exon 20 insertions/point mutations supports the ongoing exploration of TAK-788 in NSCLC patients with HER2 mutations (NCT02716116) as well as in other HER2 mutant–driven cancer patients.

Keywords

tyrosine kinase inhibitor, HER2, exon 20

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