Sunvozertinib

2022

https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.9015

Antitumor activity of sunvozertinib in NSCLC patients with EGFR Exon20 insertion mutations after platinum and anti-PD(L)1 treatment failures.

Citation

J Clin Oncol. 2022;40(16_suppl):9015-9015.

Authors

Janne PA, Wang M, Camidge DR, Mitchell P, Fang J, Nian W, Chiu C-H, Zhou J, Zhao Y, Su W-C, Yang T-Y, Zhu VW, Millward M, Fan Y, Huang W-T, Cheng Y, Jiang L, Brungs D, Zheng L, Yang JC-H.

Abstract

Background: Platinum-based chemotherapy is the 1st line standard of care for NSCLC patients with EGFR exon 20 insertion mutations (Exon20ins), with anti-PD(L)1 frequently used as well. Here we present anti-tumor activity of sunvozertinib in these patients whose disease had progressed on these therapies from two ongoing phase 1/2 studies (WK-KONG1, NCT03974022 and WU-KONG2, CTR20192097). Based on these data, sunvozertinib was granted the Breakthrough Therapy Designation by both US FDA and China NMPA. Methods: The objective of this study is to characterize the safety and efficacy of sunvozertinib in platinum-pretreated advanced NSCLC patients harboring EGFR Exon20ins, with or without anti-PD(L1) treatment. In addition, the effect of prior treatment on sunvozertinib's safety and efficacy were explored. Results: As of July 30, 2021, a total of 52 locally advanced or metastatic NSCLC patients harboring EGFR Exon20ins post platinum treatment were enrolled into WU-KONG1 and WU-KONG2 studies, and included in the efficacy analysis set (dose range: 50 mg to 400 mg, once daily). Male/Female: 21/31; Median age 59; Asian/White: 44/8; Prior therapies: median 2.5 (range 1-10); 31% received prior anti-PD(L)1 treatment (all in £ 300 mg cohorts); 40% of the subjects with baseline brain metastasis. Partial response was observed at ≥ 100 mg. At the dose level of 100 mg, 200 mg, 300 mg and 400 mg, confirmed ORR was 50% (1/2), 55.6 % (5/9), 44.8% (13/29) and 22.2% (2/9), respectively. With a median follow-up time of 10.5 months, median DoR was not reached for 200 mg cohort; with a median follow-up of 7 months, median DoR of 300 mg group was 5.6 months. Progression free survival (PFS) rate at 6 months for 100 mg, 200 mg, 300 mg and 400 mg cohorts was 50%, 53.3%, 44.6% and 44.4%, respectively. In patients with/without prior anti-PD(L)1 treatment, comparable efficacy and safety profiles were observed. Conclusions: The data suggest sunvozertinib is active in platinum-pretreated patients with EGFR Exon20ins, irrespective of prior or after anti-PD(L)1 treatment. The updated data will be presented at the

meeting. Sunvozertinib is currently in phase 2 pivotal clinical development (NCT03974022 and China CTR20211009). Clinical trial information: NCT03974022.

https://pubmed.ncbi.nlm.nih.gov/35404393/

Sunvozertinib, a selective EGFR inhibitor for previously treated non-small cell lung cancer with EGFR exon 20 insertion mutations.

Citation

Cancer Discov. 2022 Apr 11:candisc.1615.2021.

Authors

Wang M, Yang JC, Mitchell PL, Fang J, Camidge DR, Nian W, Chiu CH, Zhou J, Zhao Y, Su WC, Yang TY, Zhu VW, Millward M, Fan Y, Huang WT, Cheng Y, Jiang L, Brungs D, Bazhenova L, Lee CK, Gao B, Xu Y, Hsu WH, Zheng L, Janne PA.

Abstract

Epidermal growth factor receptor exon 20 insertion mutations (EGFR exon20ins) are detected in approximately 2% of patients with non-small cell lung cancer (NSCLC). Due to lack of effective therapy, the prognosis of these patients was poor. Sunvozertinib (DZD9008) was designed as an oral, potent, irreversible and selective EGFR tyrosine kinase inhibitor, showing activity against EGFR exon20ins and other mutations. In both cell lines and xenograft models, sunvozertinib shows potent antitumor activity. In the two ongoing phase 1 clinical studies, sunvozertinib was tolerated up to 400 mg once daily. The most common drug-related adverse events included diarrhea and skin rash. Antitumor efficacy was observed at the doses of 100 mg and above in patients with EGFR exon20ins NSCLC across different subtypes, with prior amivantamab treatment as well as with baseline brain metastasis. The median duration of response (DoR) has not been reached.

Significance: We report the discovery and early clinical development of sunvozertinib, a potential treatment option for the unmet medical need of EGFRexon20ins NSCLC. This article is highlighted in the In This Issue feature, p. 1599.

2021

https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.9008

Preliminary safety and efficacy results from phase 1 studies of DZD9008 in NSCLC patients with EGFR Exon20 insertion mutations.

Citation

J Clin Oncol. 2021;39(15_suppl):9008-9008.

Authors

Yang JCH, Wang M, Mitchell P, Fang J, Nian W, Chiu C-H, Zhou J, Zhao Y, Su W-C, Camidge DR, Yang T-Y, Zhu VW, Millward M, Fan Y, Huang WT, Cheng Y, Jiang L, Zheng Li, Ye X, Janne PA.

Abstract

Background: There are no approved targeted therapies for EGFR exon20 insertion (exon20ins) mutant NSCLC. DZD9008 is a rationally designed selective, irreversible EGFR exon20ins inhibitor being studied in two ongoing phase 1/2 studies (NCT03974022 and CTR20192097). Methods: The objectives of the studies are to assess the safety, tolerability, pharmacokinetics, and preliminary anti-tumor efficacy of DZD9008 in NSCLC with EGFR or HER2 mutations. Both studies include dose escalation and expansion cohorts. Pooled analysis is applied to define recommended phase 2 dose (RP2D). Results: Between July 9, 2019 and February 5, 2021, 97 NSCLC patients with EGFR or HER2 mutations were dosed with DZD9008 (dose range: 50 mg to 400 mg, once daily). M/F: 44/53; 59 with EGFR exon 20. DZD9008 was well tolerated up to 400 mg (MTD) once daily. The DLTs were diarrhea and cardiac arrhythmia. The most common TEAEs were diarrhea (grade 3, 5.2%) and skin rash (grade 3, 1%). DZD9008 showed approximately dose-proportional PK, with a half-life of around 50 hours. Fifty-six patients with > 16 different EGFR exon20ins mutations had > 1 post-treatment efficacy assessment. Prior therapies: median 2 (range 1 - 10), prior chemotherapy 92.9% (52/); prior TKI 44.6% (25/56) including 1 patient had poziotinib treatment; 42.9% (24/56) with brain metastasis. Partial response was observed at ≥ 100 mg dose levels. At the RP2D dose of 300 mg once daily, the objective response rate was 48.4% (15/31), and disease control rate (DCR) was 90.3% (28/31). Responses were observed in 2 patients with prior JNJ-61186372 treatment. Anti-tumor activity was observed across different EGFR exon20ins mutation subtypes. By data cut-off, the median treatment duration was 100 days (range 1 – 422). The longest duration of response was over 6 months, and 18 out of 22 responders are still responding. Conclusions: DZD9008 showed a favorable safety profile and promising anti-tumor efficacy in pre-treated NSCLC with EGFR exon20ins mutations. The updated data will

be presented at the meeting. DZD9008 is currently in phase II clinical development (NCT03974022). Clinical trial information: NCT03974022.

2019

https://www.jto.org/article/S1556-0864(21)02506-5/fulltext

OA15.02 phase 1 studies of DZD9008, an oral selective EGFR/HER2 inhibitor in advanced NSCLC with EGFR Exon20 insertion mutations.

Citation

J Thorac Oncol. 2021;16(10):S874.

Authors

Janne P, Wang M, Mitchell P, Fang J, Nian W, Chiu C, Zhao Y, Su W, Camidge DR, Yang T, Zhu V, Millward M, Fan Y, Huang W, Cheng Y, Jiang L, Brungs D, Bazhenova L, Lee CK, Gao B, Qi S, Yu X, Deng C, Chen K, Ye X, Zheng L, Yang Z, Yang JC.

Abstract

Introduction

Approximately 2% of Non-Small Cell Lung Cancer (NSCLC) harbors EGFR Exon20 insertion (Exon20ins) mutations. There are no approved targeted therapies for this patient population, and current available therapy only provides limited clinical benefit. DZD9008 is a rationally designed selective, irreversible EGFR/HER2 inhibitor being studied in two ongoing phase 1/2 studies (NCT03974022 and CTR20192097).

Methods

The objectives of the phase 1/2 studies are to assess the safety, tolerability, pharmacokinetics, and preliminary anti-tumor efficacy of DZD9008 in NSCLC with EGFR or HER2 mutations. Both studies include dose escalation and expansion cohorts.

Results

Between July 9, 2019 and February 5, 2021, 97 NSCLC patients with EGFR or HER2 mutations were dosed with DZD9008 (dose range: 50 mg to 400 mg, once daily). Male/Female: 44/53; Median age 59 (32-85). Patients carry EGFR sensitizing mutation, T790M double mutation, uncommon mutation, Exon20ins or HER2 Exon20ins. DZD9008 showed approximately dose-proportional PK, with a half-life of around 50 hours. DZD9008 was well tolerated up to 400 mg (MTD) once daily. The dose limiting toxicities (DLTs) were diarrhea and cardiac arrhythmia. The most common TEAEs were diarrhea (grade 3, 5.2%) and skin rash (grade 3, 1%). Fifty-six patients

carrying more than 16 different subtypes of EGFR exon20ins had > 1 post-treatment efficacy assessment. These patients received median 2 (range 1 - 10) lines of prior therapies, including prior chemotherapy 92.9% (52/56), prior EGFR TKI 44.6% (25/56) (1 patient had poziotinib treatment), onco-immunotherapy 30.4% (17/56), VEGFR antibody 41.1% (23/56), JNJ-61186372 7.1% (4/56) and others 17.9% (10/56). Twenty-four patients (42.9%, 24/56) had baseline brain metastasis. Partial response was observed at ≥ 100 mg dose levels. The objective response rate (ORR) was 39.3% (22/56) across all dose levels. At the dose level of 300 mg once daily, the ORR was 48.4% (15/31), and disease control rate (DCR) was 90.3% (28/31). Responses were observed in 2 patients with prior JNJ-61186372 treatment. Anti-tumor activity was observed across different EGFR exon20ins mutation subtypes. By data cut-off, the median treatment duration was 100 days (range 1 – 422). The longest duration of response was over 6 months, and 18 out of 22 responders are still responding. In addition, PR was also observed in patients with EGFR sensitizing mutation, double mutation or HER2 Exon20ins. The updated data will be presented in the meeting.

Conclusion

DZD9008 showed a favourable safety profile and promising anti-tumor efficacy in pre-treated NSCLC with EGFR exon20ins and other EGFR or HER2 mutations. DZD9008 is currently in phase 2 clinical development in EGFR Exon20ins NSCLC.

Keywords

DZD9008, NSCLC, Exon20 insertion

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https://aacrjournals.org/cancerres/article/79/13_Supplement/3081/635194/Abstract-3081-DZD9008-an-oral-wild-type-selective

DZD9008, an oral, wild type selective EGFR inhibitor for the treatment of non-small-cell lung cancer with Exon20 insertion and other activating mutations [abstract].

Citation

In: Proceedings of the American Association for Cancer Research Annual Meeting 2019; 2019 Mar 29-Apr 3; Atlanta, GA. Philadelphia (PA): AACR; Cancer Res 2019;79(13 Suppl):Abstract nr 3081.

Authors

Xu Y, Zhang L, Zhu L, Wang Y, Wang M, Yang Z.

Abstract

Background: Several EGFR TKIs have been approved for the treatment of non-small cell lung cancer (NSCLC) with L858R mutation, Exon 19 deletion, and T790M mutations. However, for patients with uncommon mutations, such as EGFR or HER2 Exon20ins, there lacks safe and effective therapy. All Exon20ins inhibitors under clinical development have a negative selectivity profile, inhibiting wild type EGFR more potently than mutant ones. Consequently, severe wild type EGFR-driven toxicities have been observed in patients. DZD9008 is an oral, potent, irreversible, wild type-selective EGFR TKI against EGFR or HER2 Exon20ins and other mutations. The present study shows anti-tumor activity of DZD9008 in tumor cell lines and xenograft models.

Materials and Methods: The enzyme assay was performed by incubating DZD9008 with recombinant enzymes at 2 mM ATP concentrations. The cellular activity of DZD9008, including phosphorylation of EGFR or HER2 and cell proliferation, was evaluated in a panel of cell lines expressing wild type EGFR, mutant EGFR or HER2, using MSD assay and CellTiter-Glo assays. DZD9008 in vivo anti-tumor activity was evaluated in both cell line-derived (CDX) and patient-derived xenograft (PDX) models, carrying EGFR single or double mutations, Exon20ins mutations, and wild type EGFR.

Results: The enzymatic IC50 of DZD9008 in mutant EGFR ranges from 0.4 to 2.1 nM. DZD9008 downregulated pEGFR with IC50 ranging from 1 to 22 nM in a panel of tumor cell lines expressing EGFR L858R, Exon19del, L858R/T790M, various Exon20ins or uncommon mutations. Similar activity against pHER2 was observed in tumor cells with HER2 Exon20ins mutation, with IC50 at 7 nM. In contrast, DZD9008 was less potent in modulating pEGFR in tumor cells expressing wild type EGFR, with IC50 greater than 80 nM. In cell proliferation assays, DZD9008 suppressed cell proliferation with GI50 of 1 to 60 nM in tumor cells carrying EGFR L858R, Exon19del, L858R/T790M, various Exon20ins or uncommon mutations. In CDX and PDX models carrying EGFR Exon19del single mutation, L858R/T790M double mutations, and PDX models harboring G719S/L861Q or Exon20ins, DZD9008 induced dose dependent tumor growth inhibition and regression. Good PK/PD relationship was established across these tumor models.

Conclusion: DZD9008 is a potential EGFR TKI for NSCLC patients with EGFR or HER2 Exon20ins and other activating mutations.

*Sunvozertinib journal articles collated and curated by Exon 20 Group at ICAN Research Team Leader Maria Vasileiou, Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Athens, Greece.