BERLIN 2025 ESMO congress

1847MO

Activity of zipalertinib against active central nervous system (CNS) metastases in patients with non-small cell lung cancer (NSCLC) harboring EGFR exon 20 insertion (ex20ins)/other uncommon mutations

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Background

CNS metastasis in patients with *EGFR*-mutant (*EGFR*mt) NSCLC is associated with poor prognosis. Zipalertinib, a highly selective, irreversible EGFR TKI, has demonstrated clinical activity against ex20ins *EGFR*mt NSCLC in a phase I/II trial, including patients with CNS metastases.

Methods

We report preliminary results from the ongoing multicohort phase IIb REZILIENT2 trial (NCT05967689) of zipalertinib (100 mg orally, twice daily), including patients with NSCLC harboring ex20ins/other uncommon *EGFR*mt and ≥1 active CNS metastases and/or leptomeningeal disease (LMD). In addition to objective response rate (ORR) and duration of response (DOR) by RECIST v1.1, this cohort was assessed for intracranial ORR (iORR), DOR (iDOR), and disease control rate (iDCR) by RANO-BM, and safety.

Results

At data cutoff (February 17, 2025), 32 patients were enrolled. Median age was 62.5 (range, 23–83) years; patients received a median of 2 (1–4) prior lines of therapy. Ex20ins and other uncommon (including G719X, S768I, L861Q, and compound) mutations were reported in 21 and 13 patients, respectively. In 16 evaluable patients by RANO-BM–measurable CNS disease (including 3 with LMD), iORR was 31.3% (95% CI: 11.0, 58.7; complete response, n=1; partial response, n=4); this included patients with ex20ins (n=4) and other uncommon *EGFR*mt (n=1). iDCR was 68.8% (95% CI: 41.3, 89.0) and median iDOR was 8.1 months (95% CI: 3.1, non-estimable). Preliminary ORR by RECIST 1.1 (n=29) was 27.6% (95% CI: 12.7, 47) and median DOR was 7.62 months (95% CI: 2.07, 9.07). Zipalertinib 100 mg twice daily was well tolerated, with Grade ≥3 treatment-related adverse events occurring in 8 (25.0%) patients (including anemia [n=3] and interstitial lung disease [ILD; n=2]); 1 death due to ILD was reported.

Conclusions

In summary, zipalertinib demonstrated clinically meaningful intracranial antitumor activity in patients with NSCLC harboring ex20ins/other uncommon *EGFR*mt, similar to the overall systemic anticancer activity in this population, with no new safety signals observed. Cohort enrollment is ongoing to better characterize clinical activity of zipalertinib against CNS lesions.

Clinical trial identification

NCT05967689.

Editorial acknowledgement

Medical writing assistance was provided by Harlene Ghuman, of Envision Pharma Group.

Legal entity responsible for the study

Taiho Oncology, Inc.

Funding

Taiho Oncology, Inc.

Disclosure

K. Ohashi: Financial Interests, Other, Honoraria: Eli Lilly, Novartis Pharma, Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., Amgen; Financial Interests, Research Grant: Nippon Boehringer Ingelheim Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan, Daiichi Sankyo Co., Ltd. H.A. Yu: Financial Interests, Advisory Role: AbbVie, Amgen, AstraZeneca, Black 30 Diamond, Blueprint Medicines, Cullinan Therapeutics, Daiichi Sankyo, Janssen, Takeda, Taiho Oncology, Inc. R. Ariyasu: Financial Interests, Personal, Invited Speaker: AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceuticals, Bristol Myers Squibb International; Financial Interests, Institutional, Local PI: AstraZeneca, Chugai Pharmaceutical, Amgen, Taiho, Lilly, Nuvalent. J. Zugazagoitia: Financial Interests, Other, Grant/Contract/Travel: AstraZeneca, F. Hoffmann-La Roche; Financial Interests, Other, Advisory Board/Speaker Fees/Travel: Boehringer Ingelheim, Pfizer; Financial Interests, Other, Speaker Fees: Bristol Myers Squibb, Merck Sharp and Dohme, Pierre Fabre Pharmaceuticals; Financial Interests, Other, Travel: Johnson & Johnson, Sanofi; Financial Interests, Other, Speaker Fees/Travel: Takeda Oncology. S. Miura: Financial Interests, Personal, Invited Speaker: Chugai Pharmaceutical, Taiho Pharmaceutical, Ono Pharmaceutical, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Boehringer Ingelheim Japan, Pfizer, Novartis, MSD, Kyowa Hakko Kirin, Daiichi Sankyo, Amgen, Merck, Takeda Pharmaceutical, Novocure, GSK, Janssen. A.L.O. Ortega Granados: Financial Interests, Full or part-time Employment: Servicio Andaluz de Salud; Financial Interests, Advisory Role: Roche, Bristol Myers Squibb, Merck Sharp Dohme. R. Califano: Financial Interests, Personal, Advisory Board: AstraZeneca, Bayer, Lilly, Roche, Pfizer, MSD, Takeda, Amgen, Bayer, Janssen and Novartis, Sanofi, GSK, BioNTech ArriVent and PharmaMar; Financial Interests, Personal, Invited Speaker: AstraZeneca, Lilly Oncology, Roche, Pfizer, MSD, Takeda, Amgen, GSK and Janssen; Financial Interests, Personal, Other, speaker in educational activities: Medscape, TOUCHIME and PEERVOICE; Financial Interests, Personal, Ownership Interest, partnership: The Christie Private Care - LOC; Financial Interests, Personal, Stocks/Shares: Supportive care UK; Financial Interests, Institutional, Local PI, principal investigator for clinical trial: Roche, AstraZeneca, Pfizer, Clovis, Lilly Oncology, MSD, BMS, AbbVie, Takeda, Janssen, and Novartis; Financial Interests, Institutional, Local PI: PharmaMar, ArriVent, Taiho and GSK; Non-Financial Interests, Member, member of Lung Cancer Group: EORTC. A.I. Spira: Financial Interests, Leadership Role: NEXT Oncology Virginia; Financial Interests, Stocks/Shares: Eli Lilly; Financial Interests, Other, Honoraria: CytomX Therapeutics, AstraZeneca/MedImmune, Merck, Takeda, Amgen, Janssen, Novartis, Bristol Myers Squibb, Bayer; Financial Interests, Speaker, Consultant, Advisor: Incyte, Amgen, Novartis, Mirati Therapeutics, Gritstone Oncology, Jazz Pharmaceuticals, Takeda, Janssen Research & Development, Mersana, Gritstone Bio, Daiichi Sankyo/AstraZeneca, Regeneron, Array BioPharma, AstraZeneca/MedImmune, Merk, Bristol Myers Squibb, Blueprint Medicines; Financial Interests, Research Funding: LAM Therapeutics, Regeneron, Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, NewLink Genetics, Incyte, AbbVie, Ignyta, Takeda, Macrogenics, CytomX Therapeutics, Astex Pharmaceuticals, Bristol Myers Squibb, Loxo, Arch Therapeutics, Gritstone Bio, Plexxikon, Amgen, Daiichi Sankyo, ADCT, Janssen, Mirati Therapeutics, Rubius, Synthekine, Mersana, Blueprint Medicines, Alkermes, Revolution Medicines, Trovagene. Y.Y. Elamin: Financial Interests, Advisory Role: AstraZeneca, Eli Lilly, Novartis, Spectrum, Sanofi, Takeda, Turning Point Therapeutics, BMS, Nuvation, Mirati, Merus, Taiho Oncology, Inc.; Financial Interests, Research Funding: AstraZeneca, Spectrum, Takeda. M. Granier, L. Wei: Financial Interests, Full or part-time Employment: Taiho Oncology, Inc. M. Gil: Financial Interests, Institutional, Other, Consultant Medical Monitor: Taiho Oncology, Inc.; Financial Interests, Personal, Stocks/Shares: Eli Lilly, Viatris. J. De Castro: Financial Interests, Advisory Board: AstraZeneca, BeiGene, Boehringer Ingelheim, Gilead, GSK, Hoffman La Roche, Janssen-Cilag, Lilly, Merck Sharp and Dohme, Pfizer, Sanofi Aventis, Takeda; Financial Interests, Invited Speaker: Pfizer.