Amivantamab

2022

https://www.sciencedirect.com/science/article/abs/pii/S1098301522006039

EE153 Budget Impact Analysis of Introducing Mobocertinib for Locally Advanced or Metastatic Epidermal Growth Factor Receptor Exon 20 Insertion-Positive Non-Small-Cell Lung Cancer in the United States from the Payer Perspective.

Citation

Value in Health. 2022;25(7, Supplement):S364.

Authors

Hernandez LG, Young M.

Abstract

Objectives

Amivantamab and mobocertinib received accelerated approval by the US FDA in May and September 2021, respectively, for the treatment of locally advanced or metastatic non-small-cell lung cancer (mNSCLC) harboring epidermal growth factor receptor (EGFR) exon 20 insertion (ex20ins) mutations previously treated with platinum-based chemotherapy (PBC). Before May 2021, there were no approved targeted treatments for this underserved population. This study quantifies the budget impact (BI) of...

Methods

A dynamic budget impact model based on a partitioned survival structure was developed to compare a reference scenario reflecting available options before the approval of mobocertinib including amivantamab and physician's choice [PC] each with 50% market share vs. an alternative scenario with mobocertinib replacing PC. Treatment patterns and efficacy of PC were obtained from the US Flatiron database. The efficacy and safety of amivantamab were from the literature and for mobocertinib from the...

Results

Over five years, an estimated 55 people in a health plan of 10 million members will suffer from mNSCLC harboring EGFR ex20ins mutations and would have been previously treated with PBC. Given the projected uptake of mobocertinib, the BI per member of the health plan per month (PMPM) was $0.05, at $0.01 each year. Across extensive scenario analyses the BI PMPM ranged from $0.01 to $0.06...

Conclusions

Mobocertinib treats a rare subset of patients with NSCLC and is associated with a minimal budget impact for US payers....

https://www.sciencedirect.com/science/article/abs/pii/S1098301522007215

EE274 Estimated Costs of Adverse Event Management in NSCLC Patients with Epidermal Growth Factor Receptor Exon 20 Insertion Mutations Treated with Amivantamab or Mobocertinib after Progression on Platinum-Based Chemotherapy.

Citation

Value in Health. 2022;25(7, Supplement):S387.

Authors

Vadagam P, Vanderpoel J, Khan A, Malek M, Musci R, Zou D.

Abstract

Objectives

To estimate the costs of grade 3/4 adverse events (AEs) related to amivantamab or mobocertinib among patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor exon 20 insertion mutation with disease progression despite prior platinum-based chemotherapy, from a Commercial or Medicare payer perspective...

Methods

Grade 3/4 AEs including laboratory abnormalities (anemia, lymphopenia, thrombocytopenia, hypoalbuminemia, hypophosphatemia and hypokalemia) and clinical symptoms (diarrhea, fatigue, infusion-related reaction and nausea) occurring with either treatment were identified from prescribing information. A specialist visit cost was applied to nausea, fatigue, hypoalbuminemia, hypophosphatemia or hypokalemia; inpatient management costs were applied to other AEs. Specialist costs were identified from...

Results

Incidence of anemia (3.5%), lymphopenia (15%), thrombocytopenia (0.9%), diarrhea (22%), fatigue (3.5%) and nausea (4.4%) were more common with mobocertinib treatment, whereas hypoalbuminemia (8%), hypophosphatemia (8%), hypokalemia (6%), and infusion-related reactions (3.1%) were more common with amivantamab treatment. The estimated total AE management cost per patient treatment course was $1,712 for amivantamab and $4,158 for mobocertinib from the Commercial perspective, and $1,717 for...

Conclusions

Costs of Grade 3/4 AE management were estimated to be lower for amivantamab than for mobocertinib. Higher costs associated with mobocertinib were due to higher inpatient management cost per each event of anemia, diarrhea, lymphopenia, and thrombocytopenia...

https://aacrjournals.org/cancerres/article/82/12_Supplement/4113/704323

Response to amivantamab, a bispecific EGF and MET receptor directed antibody, in a patient with an atypical EGFR mutated (G719X) non-small cell lung cancer (NSCLC) with leptomeningeal disease who progressed on osimertinib [abstract].

Citation

In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; Cancer Res 2022;82(12_Suppl):Abstract nr 4113.

Authors

Jinah Kim, Horyun Choi, Yeun Ho Lee, Leeseul Kim, Young Kwang Chae.

Abstract

Amivantamab is a bispecific antibody against EGF and MET receptors, approved for patients with locally advanced or metastatic NSCLC harboring EGFR exon 20 insertion after disease has progressed on or after platinum-based chemotherapy. Existing data is insufficient in establishing its efficacy on other rare EGFR mutated subtypes, central nervous system (CNS), or its resistance to 3rd generation tyrosine kinase inhibitor (TKI), osimertinib. Here, we report a case showing a good response on single agent amivantamab in an atypical EGFR mutation (G719A, exon18 substitution) NSCLC that progressed to CNS involvement on osimertinib. A 67-year-old male presented with stage IVB squamous cell carcinoma of lung with osseous metastases. CT chest, abdomen, and pelvis revealed a speculated 7.7 cm right upper lung lesion with hilar and subcarinal lymphadenopathies. MRI brain and spine showed multiple bone metastases without CNS involvement. Tissue biopsy confirmed poorly differentiated squamous cell carcinoma with PD-L1 IHC 75%. Tissue next generation sequencing (NGS) showed EGFR G719A. He was started on osimertinib. Two months later, he was hospitalized for drug-induced pneumonitis which prompted off osimertnib. CT angiogram chest showed new diffuse pericardial thickening and nodularity, suggestive of progressive disease. Two cycles of chemotherapy were delivered followed by immunotherapy with ipilimumab and nivolumab. In 10 weeks, progression of

disease was revealed in MRI brain demonstrating new parenchymal and leptomeningeal metastases. Amivantamab monotherapy was initiated with discontinuation of immunotherapy. The patient tolerated amivantamab without major complications. His performance status remained the same before and after amivantamab. He denied fatigue, anorexia, nausea or vomiting, however, endorsed rash, which was managed with hydrocortisone cream. Repeat scans in 6 weeks showed decreased leptomeningeal enhancement, and reduction in the size of parenchymal lesions, lung mass, and lymphadenopathies. The highest variant allele fraction from circulating tumor DNA NGS assay from Guardant360 was significantly improved on amivantamab from 25.6% (EGFR G719A), at time of diagnosis, to non-detectable. Amivantamab monotherapy has shown an encouraging outcome in a patient with an atypical EGFR mutated (G719X) NSCLC with leptomeningeal disease who progressed on osimertinib. Our case has shown significant response on CNS involvements, which is contrary to known poor blood-brain barrier penetration of amivantamab. This supports current trial evaluating the efficacy of amivantamab for NSCLC with rare EGFR mutations such as G719X, and ones progressed on 3rd Gen TKI treatment. Additional studies evaluating the efficacy of amivantamab on CNS metastasis are warranted.

https://www.sciencedirect.com/science/article/pii/S0169500222003749

Amivantamab compared with real-world therapies in patients with advanced non-small cell lung cancer harboring EGFR exon 20 insertion mutations who progressed after platinum-based chemotherapy.

Citation

Lung Cancer. 2022;168:74–82.

Authors

Minchom A, Viteri S, Bazhenova L, Gadgeel SM, Ou S-HI, Trigo J, Bauml JM, Backenroth D, Bhattacharya A, Li T, Mahadevia P, Girard N.

Abstract

Background

In the single-arm CHRYSALIS study, amivantamab showed durable responses and manageable safety in patients with advanced non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) exon 20 insertion mutations (ex20ins) who progressed on prior platinum-based chemotherapy. External controls can provide context for interpreting amivantamab efficacy.

Methods

External controls were selected from three US-based databases (ConcertAI, COTA, and Flatiron). Key inclusion criteria were diagnosis of EGFR ex20ins advanced NSCLC, prior platinum-based chemotherapy, and performance status score ≤ 1. Duplicate external controls were identified using a tokenization procedure and removed, and adjustment for differences in baseline characteristics between amivantamab-treated and external control cohorts was achieved using propensity score weighting.

Results

Amivantamab-treated and pooled external control cohorts included 81 and 125 patients, respectively. Baseline characteristics were generally similar across cohorts, except more amivantamab-treated patients were Asian (56% vs 13%). Most common therapies received by external controls were non-platinum-based chemotherapy (25.1%), immuno-oncology therapies (24.2%), EGFR tyrosine kinase inhibitors (16.3%), and platinum-based chemotherapy (16.3%). Overall response rate was 40% among amivantamab-treated patients and 16% among external controls. Amivantamab-treated patients had longer progression-free survival (median 8.3 vs 2.9 months; hazard ratio [HR; 95% CI]: 0.47 [0.34–0.65]), time to next therapy (median 14.8 vs 4.8 months; HR [95% CI]: 0.40 [0.28–0.57]), and overall survival (median 22.8 vs 12.8 months; HR [95% CI]: 0.49 [0.31–0.77]) than external controls. Results were consistent in sensitivity analyses comparing each external control dataset against the amivantamab-treated group separately.

Conclusion

Among post-platinum patients with EGFR ex20ins advanced NSCLC, those treated with amivantamab had improved outcomes, including 10-month longer overall survival, versus external controls.

Keywords

AmivantamabReal world; Non-small cell lung cancer; Epidermal growth factor receptor; Exon 20 insertion

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https://aacrjournals.org/cancerres/article/82/12_Supplement/CT198/704449

Subcutaneous delivery of amivantamab in patients with advanced solid malignancies: Initial safety and pharmacokinetic results from the PALOMA study [abstract].

Citation

In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; Cancer Res 2022;82(12_Suppl):Abstract nr CT198.

Authors

Krebs MG, Johnson ML, Cho BC, Lee S-H, Kudgus-Lokken R, Zemlickis D, Mitselos A, Berkay E, Bauml JM, Knoblauch RE, Hellemans P, Minchom A.

Abstract

Background: Amivantamab, an epidermal growth factor receptor (EGFR)-MET bispecific antibody, is approved for patients with advanced EGFR exon 20 insertion non-small cell lung cancer after progression on platinum-based chemotherapy. First-dose intravenous (IV) delivery leads to infusion-related reactions (IRR) among 66% of patients, resulting in dose interruptions and slower infusion restart rates (infusion duration ranges 2-4 hours) and necessitates splitting of the dose over 2 days (Park Ann Oncol 32[suppl_5]:S981). Subcutaneous (SC) administration of amivantamab, which could simplify and accelerate administration, is being investigated in an ongoing phase 1 study (PALOMA; NCT04606381). Preliminary safety (including IRR) and pharmacokinetics (PK) of SC formulations of amivantamab ± recombinant human hyaluronidase (rHuPH20) for enhanced absorption were evaluated.

Methods: PALOMA is an ongoing phase 1 dose escalation study of amivantamab SC in patients with advanced solid tumors who may derive benefit from EGFR or MET-directed therapy. Eligible patients must have progressed after standard-of-care therapy for metastatic disease, be ineligible for, or have declined current standard therapies. The study objectives were to evaluate the feasibility of administration, safety, and PK of a low concentration formulation, 50 mg/mL of amivantamab ± rHuPH20 (Part 1) and a high concentration formulation, 160 mg/mL of amivantamab ± rHuPH20 (Part 2). Patients in Part 1 and Part 2 received the currently approved dosage of amivantamab, 1050 mg (1400 mg for bodyweight ≥80 kg) SC (weekly for the first 4 weeks and every other week thereafter). This study also evaluated administering the full dose of amivantamab on the first day.

Results: The full safety, PK, bioavailability, and receptor occupancy data of patients enrolled in Part 1 (n=16) and Part 2 (n=17) will be presented. Compared to IV administration, initial SC experience demonstrates the co-formulation of high concentration amivantamab with rHuPH20 shortened the needed infusion time to less than 5 minutes, with initial bioavailability of approximately 65% of IV administration. Saturation of soluble free EGFR and MET was achieved after the first SC dose. The incidence of IRRs was 18.2%, with all events of grade 1-2 severity. The full amivantamab SC dose was safely given at first administration to 14 patients, potentially obviating the need for split dosing.

Conclusions: Initial SC amivantamab ± rHuPH20 was well tolerated with improvements in time and ease of administration and associated with a meaningful reduction in IRRs, eliminating the need for split dosing compared with IV administration. Higher SC dose levels and alternative dosing schedules are being explored.

https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.9008

Amivantamab in patients with NSCLC with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study.

Citation

Journal of Clinical Oncology. 2022;40(16_suppl):9008–9008.

Authors

Krebs M, Spira AI, Cho BC, Besse B, Goldman JW, Janne PA, Ma Z, Mansfield AS, Minchom AR, Ou S-HI, Salgia R, Wang Z, Perez CL, Gao G, Curtin JC, Roshak A, Schnepp RW, Thayu M, Knoblauch R, Lee CK.

Abstract

Background: Amivantamab, a fully human bispecific antibody targeting epidermal growth factor receptor (EGFR) and MET, is approved for the treatment of non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion after prior platinum-based chemotherapy. Given its bispecific nature, amivantamab is being explored in patients (pts) with primary MET exon 14 skipping mutation (METex14) in the MET-2 cohort of the CHRYSALIS study. Methods: CHRYSALIS (NCT02609776) is an ongoing phase 1 dose escalation/dose expansion study of amivantamab in pts with advanced NSCLC. Pts with primary METex14 whose disease progressed on or who declined current standard of care therapy were treated with amivantamab 1050 mg (pts <80 kg) or 1400 mg (pts ≥80 kg) weekly in cycle 1 and biweekly thereafter. Response was assessed by investigators using RECIST v1.1. Results: As of 2 Dec 2021, 43 pts with METex14 had received amivantamab. Median age was 70 y (range, 43-88), 58% were women, median prior lines of therapy was 2 (range, 0-10) [eg, crizotinib (n=13), capmatinib (n=11), tepotinib (n=5), anti-MET antibody (n=1)], and 23% had history of brain metastases at baseline. In 36 pts with ≥1 postbaseline disease assessment, median duration of follow-up was 5.8 months (range, 0.3-15.8); 6 pts had no prior treatment, 11 had no prior MET inhibitor, and 19 had a prior MET inhibitor. Overall response rate was 33% (50% [3/6] in treatment-naïve pts, 46% [5/11] in pts with no prior MET inhibitor, and 21% [4/19] in pts with prior MET inhibitor therapy). Clinical benefit rate was >54% regardless of prior treatment (Table). Median duration of response (DOR) was not reached

(range, 2.1-12.2 months); 67% (8/13) had DOR ≥6 months. Ten of the 12 responders remain on treatment (6.0-14.4 months) with ongoing responses; 2 discontinued after 2 and 12 months, respectively. Safety profile was consistent with previously reported experience of amivantamab (Sabari 2021 JTO 16(3):S108-109). Treatment-related adverse events leading to dose reduction or discontinuation occurred in 3 pts, each. Conclusions: Amivantamab demonstrates anti-tumor activity in primary METex14 NSCLC including after prior MET inhibitor treatment. Enrollment is ongoing and updated data will be shown. Clinical trial information: NCT02609776.

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https://europepmc.org/article/med/35616682

Amivantamab: A new hope in targeting non-small cell lung cancer. Anti-cancer agents in medicinal chemistry.

Citation

Anti-cancer Agents in Medicinal Chemistry. Published online May 2022.

Authors

Billowria K, Das Gupta G, A Chawla P.

Abstract

Background

Amivantamab was approved on 21 May 2021 by United states food and drug administration with the brand name Rybervant, used particularly for the adult patients with exon20 insertion of epithelial growth factor receptor with locally advanced metastatic non-small cell lung cancer.

Objective

In this review, we explain the non-small cell lung cancer and molecular distinctions between non-small cell lung cancer and small cell lung cancer. We also conclude numerous components of non-small cell lung cancer which include signs and symptoms of Amivantamab on inhibiting the cancer cell growth, various clinical trials on Amivantamab, adverse effects, and the contraindications of the Amivantamab.

Methods

A comprehensive literature search was conducted in the relevant databases like ScienceDirect, PubMed, ResearchGate, and Google Scholar to identify studies.

Conclusion

Amivantamab is a new bispecific antibody that targets non-small cell lung cancer by two different pathways, by bindings to epithelial growth factor receptor and mesenchymal epithelial transition factor. Amivantamab gets tightly bound to Fcγ3R and thus mediates the macrophage and NK-cell for the killing of cancer cells. Biological treatment of Amivantamab shows effectiveness against the epithelial growth factor receptor Exon20 insertions according to the preclinical data of the animal model.

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https://www.annalsofoncology.org/article/S0923-7534(22)00160-0/fulltext

35P Real-world treatment outcomes of amivantamab in pre-approval access (PAA) participants with advanced non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations (ex20ins).

Citation

Annals of Oncology. 2022;33:S48.

Authors

Kim TM, Lee S-H, Chang G-C, Shih J-Y, Hochmair MJ, Sabari JK, Spira AI, Schioppa CA, Rose JB, Chioda M, Panaccione A, Mahadevia P, Cho BC.

Abstract

Background

Amivantamab, an epidermal growth factor receptor (EGFR)-MET bispecific antibody, is approved for the treatment of patients with advanced EGFR ex20ins NSCLC that progressed on or after platinum-based chemotherapy. We present initial real-world experience with amivantamab acquired through the global PAA program.

Methods

Patients who were eligible for PAA (NCT04599712) had EGFR ex20ins NSCLC that progressed after platinum-based chemotherapy. Amivantamab (1050 mg; 1400 mg for bodyweight ≥80 kg) was administered intravenously once weekly for the first 4-week cycle, then every 2 weeks thereafter. Investigator assessment of response, based on radiologic and clinical judgement, was provided at the time of drug re-supply and was optional.

Results

As of 29 Oct 2021, 218 patients had received treatment with amivantamab across 120 sites in 19 countries; 66% from Asia, 22% from Europe, 8% from North America, and 5% from South America. The median age was 62 years

(range, 24–84), and the median number of prior lines was 2 (range, 1–9), with 63% of patients heavily-pretreated with ≥2 prior lines. At the time of data cutoff (median follow-up of 4 months), 139 patients (64%) remain on treatment. The safety profile was consistent with previously-reported safety at the recommended dose (Park K, JCO 2021;39:3391); no new safety signals were identified. Among 82 patients with response information available, 25 (30%) reported partial responses. Frequency and response by site of exon 20 insertion will be reported at the time of the meeting. Median time to treatment discontinuation (events include patients who did not request drug within 45 days from last supply; patients who transitioned to commercial amivantamab were treated as censored) was 5.2 months (95% CI, 4.2–not evaluable).

Conclusions

The real-world experience of amivantamab from the PAA program was consistent with that observed from the registrational clinical trial (NCT02609776). At the time of data cutoff, 64% of patients remain on treatment. Patients who entered the amivantamab PAA program were heavily-pretreated, underscoring the high unmet need for patients with EGFR ex20ins NSCLC.

Clinical trial identification

NCT04599712.

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https://www.annalsofoncology.org/article/S0923-7534(22)00144-2/fulltext

19P Stable disease (SD) on amivantamab in post-platinum epidermal growth factor receptor (EGFR) exon 20 insertion (Exon20ins) mutated non-small cell lung cancer (NSCLC): A response-based analysis.

Citation

Annals of Oncology. 2022;33:S38.

Authors

Girard N, Park K, Viteri S, Schioppa CA, Diels J, Oguz M, Rodrigues BH, Rahhali N, Sermon J, Ghilotti F, Li T, Knoblauch RE, Mahadevia P, Cho BC.

Abstract

Background

EGFR exon20ins NSCLC has been associated with poor prognosis, especially after progression on standard of care platinum-based chemotherapy. Amivantamab, an EGFR-MET bispecific antibody, was recently approved for this population. As anti-tumor activity in single-arm studies typically focuses on complete response and partial response (PR), it is of clinical interest to evaluate outcomes in patients (pts) with SD. A landmark analysis was performed to assess outcomes in pts who achieved SD as best response and did not progress on amivantamab at 12 weeks.

Methods

This analysis included 114 pts with post-platinum EGFR exon20ins NSCLC in the CHRYSALIS study (NCT02609776; 30 Mar 2021 data cutoff). Response was assessed by blinded independent central review using RECIST v1.1. Pts alive at landmark of 12 weeks were grouped by response observed at 12 weeks (PR or better [PR+], SD, or progressive disease [PD]). Progression-free survival (PFS) and overall survival (OS) by responder cohort were estimated using the Kaplan–Meier method, and hazard ratios (HR) and 95% confidence intervals (CI) between response cohorts were estimated using Cox proportional hazards regression.

Results

Among pts alive at week 12 (n=107), 42 (39%) had PR+, 52 (49%) had SD, and 13 (12%) had PD. Among pts with PR+ and SD, the median PFS was 12.2 mo and 7.0 mo, respectively. A corresponding improvement in OS was observed in pts who achieved PR+ (median not reached; HR vs PD=0.21 [95% CI: 0.08–0.54]) and SD (median 23.0 mo; HR vs PD=0.33 [95% CI: 0.14–0.77]), relative to those with PD (median 14.0 mo).

Conclusions

Treatment benefit with amivantamab was observed in pts who achieved SD, in addition to those achieving PR+ as best response, with a 67% and 79% reduction in risk rate of death, respectively, compared to those with PD. These data demonstrate the value of disease control, regardless of depth of response, with amivantamab.

Clinical trial identification

NCT02609776.

Free Full Text of Entire Article

https://www.annalsofoncology.org/article/S0923-7534(22)00145-4/fulltext

20P Risk and management of intracranial progression on amivantamab in epidermal growth factor receptor (EGFR) exon 20 insertion (ex20ins)-mutated non-small cell lung cancer (NSCLC).

Citation

Annals of Oncology. 2022;33:S38–S39.

Authors

Trigo J, Cho BC, Park K, Girard N, Viteri S, Garrido P, Krebs MG, Thayu M, Knoblauch RE, Xie J, Baumi JM, Schnepp RW, Londhe A, Mahadevia P, Leighl N.

Abstract

Background

Amivantamab, an EGFR-MET bispecific antibody, is approved for the treatment of advanced EGFR ex20ins NSCLC patients (pts) that have progressed on platinum-based chemotherapy. In this exploratory analysis, we investigated the patterns of progression on amivantamab therapy among pts in this population.

Methods

The CHRYSALIS study (NCT02609776) enrolled pts with advanced NSCLC and allowed the inclusion of pts with treated brain metastases. Baseline brain MRI was required at screening in the dose expansion phase; however, postbaseline surveillance MRIs were performed according to local practice and not required per protocol. Sites of target, non-target, and new lesion progression were reported. This analysis includes 114 post-platinum pts with EGFR ex20ins NSCLC who received amivantamab on or before Jun 4, 2020 (110 from dose expansion).

Results

At the Mar 30, 2021 data cutoff (median follow-up of 12.5 months [range, 0.2–30.5]), RECIST-defined PD was described in 72 of 114 pts (63%), 25 of whom continued amivantamab post progression for a median of 4.2 additional months (range, 1.0–12.5). Baseline brain metastases were reported in 38 of 114 pts. 13 pts (11.4%) had intracranial disease as sole site of progression, 4 had intra- and extracranial progression, and 55 had extracranial progression (most common in lung, bone, lymph node, and liver). 8 of 13 pts with intracranial-only progression had a history of brain metastases at baseline. The median time to progression for pts with intracranial-only progression was 4.5 months (range, 1.4–16.6), as compared with 5.5 months (range, 0.6–24.1) for those pts with systemic progression. 6 of 13 pts with intracranial-only progression underwent stereotactic radiosurgery (SRS) while continuing amivantamab. Adverse events temporally associated with SRS were nausea (10 days after SRS) and fatigue, reported in 1

pt each. For these 6 pts, the median duration of amivantamab treatment after progression was 4.0 months (range, 2.3–6.0).

Conclusions

Intracranial-only progression on amivantamab therapy occurred in 11.4% of pts. Treatment of brain progression with SRS while continuing amivantamab appears feasible and tolerable.

Clinical trial identification

NCT02609776.

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://ons.confex.com/ons/2022/meetingapp.cgi/Paper/11817

Practical guide for infusion-related reaction (IRR) management with amivantamab for Exon 20 insertion mutation (Ex20ins) non-small cell lung cancer (NSCLC): A nurse's view.

Citation

In: ONS 47th Annual Congress. ONS; 2022.

Authors

Dougherty L, Bhaumik A, D'Andrea D, Johnson A.

Abstract

Amivantamab, an EGFR-MET bispecific antibody, was recently FDA-approved for the treatment of patients with Ex20ins NSCLC. IRRs, a common toxicity of monoclonal antibodies observed within minutes to hours post-infusion, were reported in 67% of patients receiving amivantamab in the phase 1 CHRYSALIS study. Symptoms associated with amivantamab IRRs include pyrexia, nausea, vomiting, chest pain, chills, and shortness of breath. This post-hoc analysis evaluated infusion duration, time to onset, and resolution of IRRs with descriptive summary statistics (mean, median, interquartile range [IQR], range). 97% of amivantamab IRRs were grade 1-2, and 98% occurred during the first dose infusion, with median onset of 60 minutes from infusion initiation. Notably, grade 3-4 IRRs occurred in only 2% of patients and included dyspnea, hypoxia, hypotension, hypertension, and vomiting. Median infusion times at Cycle 1 Day 1 (C1D1) were 4.70 hours for the 1050-mg dose and 5.08 hours for the 1400-mg dose, decreasing to 2.20 and 2.25 hours, respectively, by C1D22. Most IRRs were manageable with intervention strategies or treatment modifications (dose interruptions in 56%; dose reductions in 53%; only 1% led to discontinuation) and resolved in a median of 60 minutes (IQR: 30-118). Additionally, dose interruptions ≥ 28 days were not associated with IRRs upon reinfusion, and only 7 IRRs occurred post-infusion (median: 28 minutes).

Nurses play a critical role in the prevention, identification, and timely management of IRRs, along with educating patients/caregivers on what to expect with amivantamab infusions. The multiple strategies nurses can use to prevent and mitigate IRRs include: administration of premedications (antihistamines, antipyretics, and glucocorticoids) prior to amivantamab infusion on C1D1/D2 and as necessary for subsequent infusions; infusion rate reductions; and infusion interruptions/dose reductions. Nurses can also help set patient expectations on the anticipated frequency and length of clinic visits, especially during the first 4 weeks of treatment, and provide

overarching support to patients and caregivers throughout the treatment journey. Here we present the latest data from CHRYSALIS on the incidence, timing, and management of IRRs, as well as nursing recommendations to optimize prevention and management of IRRs with amivantamab infusion. In summary, amivantamab IRRs are representative of those reported with other antibody infusions and can be effectively managed by nurses with appropriate guidance.

Free Full Text of Entire Article

https://www.crstonline.com/article.asp?issn=2590-3233;year=2022;volume=5;issue=1;spage=122;epage=130;aulast=Panda

EGFR exon 20 insertion in non-small cell lung cancer.

Citation

Cancer Res Stat Treat 2022;5:122-30.

Authors

Panda GS, Noronha V, Shetty O, Yadav S, Kumar R, Patil V, Chandrani P, Janu A, Mahajan A, Chougule A, Prabhash K.

Abstract

CASE SUMMARY

History and Examination

A 50-year-old lady with no history of smoking and no comorbidities presented in December 2020 with a 6-month history of dry cough and weight loss. At presentation, she had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 and there was no palpable lymphadenopathy. Investigations and Diagnosis Computed tomography (CT) thorax revealed an area of consolidation measuring 8.5 x 4 x 4.5 cm in the anterior basal and medial basal segments of the lower lobe of the right lung, mediastinal lymphadenopathy, and bilateral lung nodules, suspicious for metastatic malignancy [Figure 1]. CT-guided biopsy from the lung mass revealed adenocarcinoma. Thus, the patient was diagnosed with lung adenocarcinoma, cT4cN3cM1a, staged according to the American Joint Committee on Cancer (AJCC) staging system, 8th edition.[1] Immunohistochemistry for anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), and programmed death-ligand 1 (PD-L1) was negative. Fluorescence in situ hybridization (FISH) for ALK1 was also negative.

Treatment

The patient refused intravenous chemotherapy; therefore, she was empirically started on erlotinib in January 2021. The in-house epidermal growth factor receptor (EGFR) reverse transcription-polymerase chain reaction (RT-PCR) report, which was available in March 2021, showed an EGFR exon 20 insertion mutation (Ex20ins). The patient

continued to refuse chemotherapy, and she was, therefore, continued on erlotinib after a thorough discussion of the possible treatment options, effects, and side effects. In April 2021, she had disease progression with multiple new-onset lung nodules. At progression, she had an ECOG PS of 1, there was no deterioration of her general condition, and there were no fresh complaints. Erlotinib was stopped and the patient was again advised chemotherapy. Repeat biopsy from the lung mass revealed adenocarcinoma. Next-generation sequencing (NGS) was performed on this specimen. The patient consented to receive chemotherapy. She was started on pemetrexed–carboplatin doublet, and radiologic imaging revealed stable disease after four cycles. Maintenance pemetrexed was administered. The disease progressed in the lungs in Sept 2021 after four cycles of maintenance pemetrexed. The patient's general condition was well preserved with an ECOG PS of 1 and she had not developed any new symptoms.

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https://www.sciencedirect.com/science/article/pii/S2666621922000096

Response to Mobocertinib in a patient with advanced Non-Small Cell Lung Cancer harboring EGFR exon 20 insertion after several therapies including Amivantamab.

Citation

Current Problems in Cancer: Case Reports. 2022;5:100145.

Authors

Corral de la Fuente E, Olmedo García ME, Orejana Martín I, Orejana Martín I, Benito Berlinches A, Gómez Rueda A, Lage Alfranca Y, Garrido P.

Abstract

Abstract

Patients harboring EGFR exon 20 insertion (EGFRex20ins) advanced Non-Small Cell Lung Cancer (NSCLC) represent a poor prognosis population of oncogene-addicted cancers in need of targeted therapy, since they are

resistant to available EGFR tyrosine kinase inhibitor (TKIs) and there is limited efficacy data of immunotherapy.

New drugs targeting EGFRex20ins are under development, such as mobocertinib, an antiEGFR TKI or amivantamab, a bispecific antibody targeting EGFR and MET, which have shown promising results in pre-treated patients. The activity of mobocertinib after treatment with amivantamab and vice versa is currently unknown.

We present a 49-year-old, non-smoking woman with advanced EGFRex20ins NSCLC who had a significant response to mobocertinib after several treatments, including amivantamab. We discuss new treatments in development for patients with EGFRex20ins NSCLC.

Keywords

EGFR; Exon20 insertions; Non-Small Cell lung cancer; Mobocertinib; targeted therapy

https://www.sciencedirect.com/science/article/pii/S0169500221006620

Amivantamab (JNJ-61186372) induces clinical, biochemical, molecular, and radiographic response in a treatment-refractory NSCLC patient harboring amplified triple EGFR mutations (L858R/ T790M/G796S) in cis.

Citation

Lung Cancer. 2022;164:52–55.

Authors

Nagasaka M, Balmanoukian AS, Madison R, Zhang SS, Klempner SJ, Ou SHI.

Abstract

The sequential use of 1st-/2nd-generation to 3rd-generation epidermal growth factor (EGFR) tyrosine kinase inhibitors (TKIs) has led to the emergence of triple EGFR mutations generally consisting of the founder mutation (del 19 or L858R), gatekeeper mutation (T790M) and mutation (C797S) that abolishes the covalent binding of osimertinib to the EGFR protein (i.e., del 19 or L858R/T790M/C797S). Besides C797S, other tertiary mutations confer structural steric hindrance to osimertinib rather than preventing its covalent binding to the EGFR kinase domain such as solvent front mutation (G796S) or others such as L792F/H mutation. “Fourth-generation” EGFR TKIs are being developed to inhibit these triple mutations, in particular, in the background of compound T790M/C797S mutations but they are still in early clinical stages of

development. Amivantamab, a bi-specific EGFR/MET monoclonal antibody that can affect Fc mediated trogocytosis of the EGFR protein has been approved for the treatment of EGFR exon20 insertion mutations and has demonstrated activity against a myriad of compound EGFR mutations. Here we report amivantamab monotherapy induced symptomatic, biochemical, molecular, and radiographic responses in a NSCLC patient with triple EGFR mutations in cis in the background of EGFR amplification.

Keywords

Amivantamab; EGFR triple mutation; L858R/T790M/G796SEGFR amplification; bi-specific antibody; EGFR/MET dual inhibition; Osimertinib resistance

2021

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8648093/

Spotlight on Amivantamab (JNJ-61186372) for EGFR Exon 20 Insertions Positive Non-Small Cell Lung Cancer.

Citation

Lung Cancer (Auckl). 2021 Dec 2;12:133-138.

Authors

Brazel D, Nagasaka M.

Abstract

Non-small cell lung cancer (NSCLC) patients demonstrating sensitizing oncogenic driver mutations have derived clinical benefit from targeted therapy. EGFR mutations constitutively activate the signaling pathway, leading to prosurvival and antiapoptotic signals. Classic sensitizing EGFR mutations, such as exon 19 deletions and exon 21 L858R point mutations, respond well to tyrosine kinase inhibitors (TKIs). On the other hand, EGFR exon 20 in-frame insertions are observed in 4–12% of EGFR-mutated NSCLC and are resistant to targeted therapy with TKIs. In May 2021, the Federal Drug Administration (FDA) provided accelerated approval to amivantamab (Rybrevant) in adults with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations after treatment with platinum-based chemotherapy. Here, we discuss properties of amivantamab, clinical trial results, and management of patients with EGFR exon 20 insertion mutated NSCLC.

Keywords: amivantamab, epidermal growth factor receptor, mesenchymal-epithelial transition factor, MET, non-small cell lung cancer, tyrosine kinase inhibitors

https://www.tandfonline.com/doi/full/10.1080/14737140.2022.2016397

Amivantamab for the treatment of EGFR exon 20 insertion mutant non-small cell lung cancer.

Citation

Expert Review of Anticancer Therapy. 2022;22(1):3–16.

Authors

Vyse S, Huang PH.

Abstract

Introduction: Amivantamab is a monoclonal bispecific anti-EGFR-MET antibody that is the first targeted therapy to be approved for non-small cell lung cancer (NSCLC) patients harboring EGFR exon 20 insertion mutations following progression on chemotherapy, marking a watershed moment for a class of mutations which is generally associated with poor outcomes.

Areas covered: In this article, we outline the drug profile of amivantamab compared with EGFR kinase inhibitors under evaluation in EGFR exon 20 insertion mutant NSCLC. We also review the efficacy and safety data reported from the CHRYSALIS phase I trial, which forms the basis of the recent approval of amivantamab.

Expert opinion: Unlike small molecule EGFR kinase inhibitors, amivantamab has an extracellular mode of action and dual activity against EGFR and MET. It remains to be determined what role MET inhibition plays in toxicity and efficacy and whether dual target inhibition can delay the onset of drug resistance in these cancers. Due to its large molecular size, amivantamab is expected to have poor activity to treat brain metastases. Building on the clinical data so far, future trials that will evaluate combination treatments with brain-penetrant EGFR kinase inhibitors will be critical to move the drug toward a first line treatment.

Keywords

Amivantamab, EGFR, exon 20 insertions, lung cancer, monoclonal antibody

https://www.jto.org/article/S1556-0864(21)02802-1/fulltext

P24.14 Validation of Companion Diagnostics for the Identification of Patients with EGFR Exon20ins NSCLC for Amivantamab Therapy.

Citation

Journal of Thoracic Oncology. 2021;16(10, Supplement):S1036.

Authors

Jatkoe T, Wang S, Odegaard J, Velasco Roth AM, Osgood D, Martinez G, Lucas P, Curtin J, Karkera J.

Abstract

Introduction

Amivantamab, an epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell-directing activity, targets activating/resistance EGFR mutations and MET mutations/amplifications. In the ongoing CHRYSALIS study (NCT02609776), amivantamab demonstrated antitumor activity in patients with EGFR exon 20 insertion (Exon20ins) disease. To identify patients likely to benefit from amivantamab therapy, we clinically validated 2 novel candidate companion diagnostics (CDx) for detecting Exon20ins variants in tumor tissue and plasma, with combined coverage of >100 variants.

Methods

Banked plasma and tumor samples from the CHRYSALIS efficacy population (first 81 patients enrolled with EGFR Exon20ins NSCLC who had progressed on platinum chemotherapy) were tested using Guardant360® CDx and Oncomine™ Dx Target Test (ODxT). Overall response rate (ORR) of patients identified by Guardant360 CDx and ODxT was compared with that observed in the CHRYSALIS efficacy population. Agreement analysis was performed using samples with a valid CDx result from the CHRYSALIS study and samples from supplementary populations.

Results

Of the 81 CHRYSALIS efficacy population patients, 78 plasma and 51 tissue samples were tested. Guardant360CDx identified 62 positive (16 negative) and ODxT identified 39 positive (3 negative) for EGFR Exon20ins mutation (Figure). Demographic and baseline characteristics were similar between

CHRYSALIS, Guardant360 CDx, and ODxT populations. Agreement with local tests used for enrollment demonstrated high adjusted negative predictive value (99.6% and 99.9%) and positive predictive value (100% for both) for Guardant360CDx and ODxT, respectively. Comparable ORRs were observed in CHRYSALIS, Guardant360CDx, and ODxT populations (Table). ORR in Exon20ins patients identified by either Guardant360CDx or ODxT (39%) resembles that observed in the CHRYSALIS study (40%; Table).

Conclusion

EGFR Exon20ins mutations identified by either plasma-based Guardant360CDx or tissue-based ODxT demonstrate the robust antitumor activity of amivantamab. Both tests provide accurate, comprehensive, and complementary approaches to identifying patients who could benefit from this targeted therapy.

Keywords

EGFR Exon 20 Insertion, Companion Diagnostics, Amivantamab

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https://www.jto.org/article/S1556-0864(21)02955-5/fulltext

P50.04 Amivantamab in Combination With Chemotherapy in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC).

Citation

Journal of Thoracic Oncology. 2021;16(10, Supplement):S1116.

Authors

Nagasaka M, Goto K, Gomez J, Hida T, Shu C, Lee CK, Park K, Cho BC, Lee J, Ou S, Bestvina C, Natale R, Haddish-Berhane N, Bhattacharya A, Verheijen R, Agrawal T, Knoblauch R, Govindan R.

Abstract

Introduction

No targeted therapies are available for metastatic epidermal growth factor receptor mutant (EGFRm) NSCLC after progression on osimertinib or for tyrosine kinase inhibitor (TKI)-resistant mutations such as EGFR exon 20 insertions (Exon20ins); for these patients, chemotherapy remains the standard of care (SOC). Amivantamab, an EGFR-MET bispecific antibody with immune cell-directing activity, has demonstrated monotherapy activity in patients with diverse EGFRm NSCLC, including Exon20ins and osimertinib-relapsed disease. Combining amivantamab with chemotherapy in

metastatic EGFRm NSCLC may improve outcomes due to the antibody's dual-targeting nature and immune cell-directing activity. We present the preliminary experience with amivantamab in combination with chemotherapy from the ongoing CHRYSALIS study (NCT02609776).

Methods

Patients had advanced NSCLC and were eligible for platinum-based chemotherapy in accordance with SOC. Amivantamab was dosed weekly at 1400 mg (1750 mg ≥80 kg) for the first 4 doses, then at 1750 mg (2100 mg ≥80 kg) every 3 weeks (Q3W) + pemetrexed (500 mg/m2) and carboplatin (AUC 5; up to cycle 4) in a 21-day cycle. Response was assessed by investigator per RECIST v1.1. Tolerability was assessed using a 3+3 dose de-escalation design.

Results

Of the 5 patients who were initially dosed, 3 were evaluable for dose-limiting toxicity (DLT); no DLTs were observed, and dose expansion up to 20 patients has been initiated. As of 20 Oct 2020, 16 patients (3 with bodyweight ≥80 kg) had received the combination; 13 were treated beyond cycle 1 and 5 beyond cycle 3. Median age was 63 years, 15 had EGFR mutation, 2 had baseline brain metastases, and 13 had ≥1 prior lines of therapy (LOT), with 8 heavily-pretreated (2–7 prior LOT). Most common treatment-emergent adverse events (TEAEs) were infusion-related reaction (69%) and rash (44% dermatitis acneiform + 31% rash). Seven patients (44%) had grade ≥3 TEAEs; most frequent events collectively reflected anticipated cytopenias (19% neutropenia, 6% anemia, 6% thrombocytopenia) – one patient discontinued carboplatin due to anemia. Preliminary cycle 1 pharmacokinetic (PK) data (n=9) suggest no impact of chemotherapy on amivantamab exposure. Preliminary trough concentration comparisons suggest that higher doses of amivantamab given Q3W (21-day cycle), are similar to the recommended dose for monotherapy given every 2 weeks (28-day cycle). Six patients had disease assessments by the 20 Oct 2020 data cut: 2 partial responses (PRs, including 1 patient with treatment-naïve EGFR Exon20ins), 3 stable disease, and 1 progressive disease. Since the clinical cut off, 2 other patients with treatment-naïve EGFR Exon20ins reported PRs, for a total of 3/3 responses in this subpopulation.

Conclusion

Amivantamab combined with chemotherapy was tolerable, with toxicity profiles consistent with that observed with each therapy alone. Amivantamab exposure was not impacted by chemotherapy, and preliminary PK results support Q3W dosing. This regimen is being evaluated in the frontline treatment of EGFR Exon20ins NSCLC in the phase 3 PAPILLON study (NCT04538664).

Keywords

Amivantamab, EGFR Exon 20 Insertion, Chemotherapy

Editorial: Global Regulatory Initiatives Deliver Accelerated Approval of the First Bispecific Therapeutic Monoclonal Antibody for Advanced Non-Small Cell Lung Cancer (NSCLC).

Citation

Med Sci Monit. 2021 Sep 27;27:e934854.

Authors

Parums DV.

Abstract

The coronavirus disease 2019 (COVID-19) pandemic has affected the number of completed clinical trials, particularly in oncology. Between 80–85% of all lung cancers are non-small cell lung cancer (NSCLC), and of these, between 2–3% have an EGFR exon 20 insertion, which is associated with increased cell proliferation, metastasis, and a lack of response to chemotherapy and epidermal growth factor receptor (EGFR) inhibitors. Until this year, there were no available targeted therapies for advanced NSCLC with this genetic subtype. However, in May 2021, the US Food and Drug Administration (FDA) granted accelerated approval for amivantamab-vmjw (Rybrevant®), a bispecific monoclonal antibody, targeting activating and resistant EGFR and MET mutations and amplifications. This FDA approval was for adult patients with locally advanced metastatic NSCLC, with disease progression on or following platinum-based chemotherapy. The FDA also approved the Guardant360® companion diagnostic, a next-generation sequencing platform for circulating tumor DNA (ctDNA), which is a liquid biopsy assay. In 2019, Project Orbis was launched by the FDA Oncology Center of Excellence as a global collaborative review program to facilitate rapid global access for patients to innovative cancer therapies. This Editorial aims to highlight how global regulatory initiatives from the FDA have delivered accelerated approval of the first bispecific therapeutic monoclonal antibody, amivantamab-vmjw (Rybrevant®), and a companion diagnostic for patients with advanced NSCLC with an EGFR exon 20 insertion.

Keywords: Editorial, Non-Small Cell Lung Cancer, NSCLC, Targeted Therapy, Monoclonal Antibody, EGFR, MET

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https://ascopubs.org/doi/abs/10.1200/jco.21.01494

Amivantamab: Treating EGFR Exon 20–Mutant Cancers With Bispecific Antibody-Mediated Receptor Degradation.

Citation

Journal of Clinical Oncology. 2021;39(30):3403–3406.

Authors

Köhler J, Jänne PA.

Abstract

Insertions in exon 20 of the epidermal growth factor (EGF) receptor (EGFR Ex20ins) represent the third most common type of activating EGFR mutations in non-small-cell lung cancer (NSCLC). With some geographical variation, they are detected in up to 4% of all advanced NSCLC and in 4%-12% of EGFR mutation-positive NSCLC. EGFR Ex20ins are more common in tumors among never smokers, but unlike common Exon19 deletions or Exon21 L858R point mutations, most of the Ex20ins mutations (except for EGFR A763_Y764FQEA) exhibit de novo resistance to the currently approved first-line EGFR tyrosine kinase inhibitors (TKIs): erlotinib, gefitinib, afatinib and osimertinib. Therefore, chemotherapy represents the mainstay treatment option. Mechanisms of TKI resistance are multifactorial including steric hindrance, similar TKI affinities to Exon20ins-mutant EGFR, and unchanged ATP binding of mutant compared with wild-type EGFR.

Recent early phase clinical trials have reported efficacy of poziotinib and mobocertinib (TAK-788), a new generation of Ex20ins-selective TKIs, which has led to a US Food and Drug Administration break-through therapy designation for mobocertinib. Other mutation-selective EGFR inhibitors are currently under clinical investigation (eg, BDTX-189, CLN-081/TAS-6417, and DZD9008) and are demonstrating early signs of clinical efficacy. However, treatment responses with mobocertinib and poziotinib occur in <50% of patients, are restricted by dose-limiting toxicities and progression-free survivals for these agents (poziotinib, 4.2 months; 6.5 months in the expanded access program; and mobocertinib, 7.3 months) are shorter than those for osimertinib for patients with EGFR exon 19 deletion and L858R mutations (10.1 months in the second-line setting). Therefore, innovative treatment approaches are urgently required to improve the poor prognosis of patients with Ex20ins-mutant cancers.

In this issue of Journal of Clinical Oncology, Park et al report intriguing findings from CHRYSALIS, a single-arm dose-escalation and dose-expansion

phase I trial (NCT02609776) with high conceptual importance and potentially far-reaching implications for other Ex20ins-driven cancers. CHRYSALIS investigated amivantamab-vmjw (Rybrevant, previously JNJ-61186372), a fully humanized first-in-class antibody simultaneously targeting two tumor antigens, EGFR (both wild-type and mutant protein) and mesenchymal-epithelial transition factor (MET), via their extracellular protein domains. Despite being not specifically designed for this mutational subtype, patients whose lung tumors harbored EGFR Ex20ins mutations gained therapeutic benefit from amivantamab and the US Food and Drug Administration granted accelerated approval for this NSCLC subtype in May 2021. Exon 20 insertions can also be found in the EGFR of 18% of urothelial cancers and 68% of sinonasal squamous cell carcinomas, a rare form of head and neck cancer.

https://ascopubs.org/doi/10.1200/JCO.21.00662

Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study.

Citation

Journal of Clinical Oncology. 2021;39(30):3391–3402.

Authors

Park K, Haura EB, Leighl NB, Mitchell P, Shu CA, Girard N, Viteri S, Han J-Y, Kim S-W, Lee CK, Sabari JK, Spira AI, Yang T-Y, Kim D-W, Lee KH, Sanborn RE, Trigo J, Goto K, Lee S-K, Yang JC-H, Govindan R, Bauml JM, Garrido P, Krebs MG, Reckamp KL, Xie J, Curtin JC, Haddish-Berhane N, Roshak A, Millington D, Lorenzini P, Thayu M, Knoblauch RE, Cho BC.

Abstract

PURPOSE

Non–small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion (Exon20ins) mutations exhibits inherent resistance to approved tyrosine kinase inhibitors. Amivantamab, an EGFR-MET bispecific antibody with immune cell–directing activity, binds to each receptor's extracellular domain, bypassing resistance at the tyrosine kinase inhibitor binding site.

METHODS

CHRYSALIS is a phase I, open-label, dose-escalation, and dose-expansion study, which included a population with EGFR Exon20ins NSCLC. The primary end points were dose-limiting toxicity and overall response rate. We

report findings from the postplatinum EGFR Exon20ins NSCLC population treated at the recommended phase II dose of 1,050 mg amivantamab (1,400 mg, ≥ 80 kg) given once weekly for the first 4 weeks and then once every 2 weeks starting at week 5.

RESULTS

In the efficacy population (n = 81), the median age was 62 years (range, 42-84 years); 40 patients (49%) were Asian, and the median number of previous lines of therapy was two (range, 1-7). The overall response rate was 40% (95% CI, 29 to 51), including three complete responses, with a median duration of response of 11.1 months (95% CI, 6.9 to not reached). The median progression-free survival was 8.3 months (95% CI, 6.5 to 10.9). In the safety population (n = 114), the most common adverse events were rash in 98 patients (86%), infusion-related reactions in 75 (66%), and paronychia in 51 (45%). The most common grade 3-4 adverse events were hypokalemia in six patients (5%) and rash, pulmonary embolism, diarrhea, and neutropenia in four (4%) each. Treatment-related dose reductions and discontinuations were reported in 13% and 4% of patients, respectively.

CONCLUSION

Amivantamab, via its novel mechanism of action, yielded robust and durable responses with tolerable safety in patients with EGFR Exon20ins mutations after progression on platinum-based chemotherapy.

Free Full Text of Entire Article

https://link.springer.com/article/10.1007/s40265-021-01561-7

Amivantamab: First Approval.

Citation

Drugs. 2021;81(11):1349–1353.

Authors

Syed YY.

Abstract

Amivantamab (amivantamab-vmjw; Rybrevant™), a bispecific monoclonal antibody targeting epidermal growth factor receptor (EGFR) and mesenchymal epithelial transition factor (MET), is being developed by Janssen Biotech for the treatment of non-small cell lung cancer (NSCLC). On 21 May 2021, amivantamab received its first approval in the USA for the treatment of adult patients with locally advanced or metastatic NSCLC

harbouring EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. Amivantamab is in preregistration for NSCLC in the EU, Australia, Japan, Canada, Switzerland and China. This article summarizes the milestones in the development of amivantamab leading to this first approval for NSCLC.

https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.9052

Amivantamab compared with real-world therapies in patients with NSCLC with EGFR Exon 20 insertion mutations who have progressed after platinum doublet chemotherapy.

Citation

Journal of Clinical Oncology. 2021;39(15_suppl):9052–9052.

Authors

Minchom AR, Girard N, Bazhenova L, Ou S-HI, Gadgeel SM, Trigo J, Viteri S, Backenroth D, Bhattacharya A, Li T, Mahadevia P, Bauml J.

Abstract

Background: Amivantamab is an epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell-directing activity. Amivantamab has demonstrated efficacy and safety in patients (pts) with EGFR exon 20 insertion (Exon20ins) in the ongoing CHRYSALIS phase 1 study in advanced non-small cell lung cancer (aNSCLC). Because CHRYSALIS is a non-randomized, single arm study, external controls (EC) can add valuable context in interpreting amivantamab's efficacy and appreciating the unmet needs given real-world therapies. A protocol-driven treatment comparison was conducted of amivantamab vs real-world therapies in pts with Exon20ins aNSCLC who progressed after platinum chemotherapy. Methods: Custom curated, real-world data abstracting clinically relevant measures that are not typically available from off-the-shelf datasets were obtained from 3 US-based companies: Flatiron, COTA, and ConcertAI. Datasets were de-duplicated via a tokenization procedure, analyzed separately and as a single pooled database. Key eligibility for the EC included: Exon20ins aNSCLC, prior platinum chemotherapy, ≥1 line after platinum therapy, and ECOG PS 0 or 1. Propensity score weighting (average treatment effects on the treated) was used to adjust for differences in age, brain metastases, ECOG PS, and number of prior lines of therapy (LOT). Results: The amivantamab-treated population (N = 81) included post-platinum pts with EGFR Exon20ins aNSCLC treated at the recommended phase 2 dose (Sabari WCLC 2020 Abs #3031). After de-duplication of the custom real-world datasets, 126 unique pts formed the EC. Most frequent treatments after platinum doublet chemotherapy in the EC

group were checkpoint inhibitors (CPI; 25%), single-agent, non-platinum chemotherapies (25%), and EGFR tyrosine-kinase inhibitors (TKIs; 16%). Baseline demographics were generally similar between amivantamab and the EC pts; notable differences included a higher percentage of Asian pts (56% vs 9%) and more prior LOT (median 2 vs 1) among the amivantamab compared to the EC pts. Median overall survival (OS) among amivantamab pts was 22.8 months and EC pts was 13.1 months (HR = 0.53 [95% CI, 0.33, 0.86]). Similarly, amivantamab pts had longer progression-free survival (8.3 vs 2.9 months; HR = 0.46 [95% CI, 0.33, 0.63]) and time to next treatment (14.8 vs 4.8 months; HR = 0.42 [95% CI, 0.29, 0.6]) compared to the EC pts. Confirmed overall response rate was 40% among amivantamab pts and 10% for the EC pts (odds ratio = 4.44 [95% CI 2.42, 8.14]). Conclusions: Amivantamab demonstrated a 10-month higher OS than real-world therapies in the post-platinum setting. The poor performance of the EC, frequently treated with CPI, single chemotherapies, and EGFR TKI, highlights the ineffectiveness of these agents and the urgent need to find more alteration-specific treatments in aNSCLC.

https://www.jto.org/article/S1556-0864(21)00326-9/fulltext

OA04.04 Amivantamab in Post-platinum EGFR Exon 20 Insertion Mutant Non-small Cell Lung Cancer.

Citation

Journal of Thoracic Oncology. 2021;16(3, Supplement):S108–S109.

Authors

Sabari JK, Shu CA, Park K, Leighl N, Mitchell P, Kim S, Lee J, Kim D, Viteri S, Spira A, Han J, Trigo J, Lee CK, Lee KH, Girard N, Yang T, Goto K, Sanborn RE, Yang JC, Xie J, Roshak A, Thayu M, Knoblauch RE, Cho BC.

Abstract

Introduction

Despite sharing similar tumor biology to other epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) tumors, no targeted therapies have been approved for NSCLC harboring EGFR Exon 20 insertion mutations (Exon20ins). The standard of care remains platinum-based chemotherapy for the front-line, with no clear subsequent options available. Amivantamab (JNJ-61186372) is a novel, fully human EGFR-MET bispecific antibody with immune cell-directing activity that targets activating and resistance EGFR mutations, as well as MET mutations and amplifications, and has received FDA Breakthrough Therapy Designation for the treatment of

patients with EGFR Exon20ins NSCLC after platinum-based chemotherapy. Here we present updated results on the Exon20ins cohort from the CHRYSALIS study (NCT02609776).

Methods

The dose escalation phase enrolled patients with advanced NSCLC to determine the recommended phase 2 dose (RP2D) of 1050 mg (1400 mg for ≥80 kg) amivantamab. The dose expansion phase assessed the safety and efficacy of amivantamab in patients with EGFR- and MET-mutant NSCLC treated at the RP2D. Disease response was assessed by the investigator per RECIST v1.1 and is presented for those patients with Exon20ins NSCLC who had progressed on prior platinum-based chemotherapy, were treated at the RP2D, and had at least 3 post-baseline disease assessments (18 weeks) or discontinued, progressed, or died prior to the 3rd assessment (the Post-Platinum Cohort). The data cutoff date was 8 Jun 2020.

Results

In the Post-Platinum Cohort (n=81), median age was 62 (42 – 84), 59% were women, 49% were Asian, median prior lines of therapy was 2 (1 – 7), and 53% were never-smokers. At a median follow-up of 6.5 months (1.1 – 29.3), investigator-assessed overall response rate (ORR) was 36% (29/81; 95% CI, 25 – 47), with all responders achieving partial response (PR). The clinical benefit rate (≥PR or stable disease ≥11 weeks) was 73% (59/81; 95% CI, 62 – 82). Responses were durable at a median of 6.8 months (95% CI, 5.0 – not reached) with ongoing responses in 18/29 (longest at 16+ months). Median progression-free survival was 8.3 months (95% CI, 5.5 – 12.7) and median overall survival was 22.8 months (95% CI, 14.0 – not reached). Among all phase 1 patients, across a variety of EGFR genomic alterations and lines of therapy, treated with amivantamab monotherapy at the RP2D (n=258), the most common adverse events (AEs) were rash (78%), infusion related reaction (IRR; 65%), and paronychia (40%). Additional EGFR-related AEs were stomatitis (19%), pruritus (19%), and diarrhea (11%). Grade ≥3 AEs were reported in 39% of patients; 14% were considered treatment-related, with rash (3%) and IRR (2%) being most frequent. No treatment-related deaths were reported. The incidence of treatment-related AEs leading to dose reduction and discontinuation was 10% and 3%, respectively.

Conclusion

Amivantamab treatment led to promising efficacy with durable responses in patients with EGFR Exon20ins NSCLC post-platinum doublet and continues to demonstrate a manageable safety profile in over 250 patients treated at the RP2D. A phase 3 study, PAPILLON, evaluating amivantamab in combination with chemotherapy in the front-line setting is in planning stages.

Keywords

amivantamab, Exon20ins, Bispecific antibody

Antitumor activity of amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in diverse models of EGFR Exon 20 insertion-driven NSCLC.

Citation

Cancer Discov. 2020;10(8):1194-1209.

Authors

Yun J, Lee S-H, Kim S-Y, Jeong S-Y, Kim J-H, Pyo K-H, Park C-W, Heo SG, Yun MR, Lim S, Lim SM, Hong MH, Kim HR, Thayu M, Curtin JC, Knoblauch RE, Lorenzi MV, Roshak A, Cho BC.

Abstract

EGFR exon 20 insertion driver mutations (Exon20ins) in non–small cell lung cancer (NSCLC) are insensitive to EGFR tyrosine kinase inhibitors (TKI). Amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR–MET, has shown preclinical activity in TKI-sensitive EGFR-mutated NSCLC models and in an ongoing first-in-human study in patients with advanced NSCLC. However, the activity of amivantamab in Exon20ins-driven tumors has not yet been described. Ba/F3 cells and patient-derived cells/organoids/xenograft models harboring diverse Exon20ins were used to characterize the antitumor mechanism of amivantamab. Amivantamab inhibited proliferation by effectively downmodulating EGFR–MET levels and inducing immune-directed antitumor activity with increased IFNγ secretion in various models. Importantly, in vivo efficacy of amivantamab was superior to cetuximab or poziotinib, an experimental Exon20ins-targeted TKI. Amivantamab produced robust tumor responses in two Exon20ins patients, highlighting the important translational nature of this preclinical work. These findings provide mechanistic insight into the activity of amivantamab and support its continued clinical development in Exon20ins patients, an area of high unmet medical need.

Significance:

Currently, there are no approved targeted therapies for EGFR Exon20ins–driven NSCLC. Preclinical data shown here, together with promising clinical activity in an ongoing phase I study, strongly support further clinical investigation of amivantamab in EGFR Exon20ins–driven NSCLC.

This article is highlighted in the In This Issue feature, p. 1079

Development of [89Zr]ZrDFO-amivantamab bispecific to EGFR and c-MET for PET imaging of triple-negative breast cancer.

Citation

Eur J Nucl Med Mol Imaging. 2021 Feb;48(2):383-394.

Authors

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Abstract

Background: Amivantamab is a novel bispecific antibody that simultaneously targets the epidermal growth factor receptor (EGFR) and the hepatocyte growth factor receptor (HGFR/c-MET) that are overexpressed in several types of cancer including triple-negative breast cancer (TNBC). Targeting both receptors simultaneously can overcome resistance to mono-targeted therapy. The purpose of this study is to develop 89Zr-labeled amivantamab as a potential companion diagnostic imaging agent to amivantamab therapy using various preclinical models of TNBC for evaluation.

Methods: Amivantamab was conjugated to desferrioxamine (DFO) and radiolabeled with 89Zr to obtain [89Zr]ZrDFO-amivantamab. Binding of the bispecific [89Zr]ZrDFO-amivantamab as well as its mono-specific "single-arm" antibody controls were determined in vitro and in vivo. Biodistribution studies of [89Zr]ZrDFO-amivantamab were performed in MDA-MB-468 xenografts to determine the optimal imaging time point. PET/CT imaging with [89Zr]ZrDFO-amivantamab or its isotype control was performed in a panel of TNBC xenografts with varying levels of EGFR and c-MET expression.

Results: [89Zr]ZrDFO-amivantamab was synthesized with a specific activity of 148 MBq/mg and radiochemical yield of ≥ 95%. Radioligand binding studies and western blot confirmed the order of EGFR and c-MET expression levels: HCC827 lung cancer cell (positive control) > MDA-MB-468 > MDA-MB-231 > MDA-MB-453. [89Zr]ZrDFO-amivantamab demonstrated bispecific binding in cell lines co-expressed with EGFR and c-MET. PET/CT imaging with [89Zr]ZrDFO-amivantamab in TNBC xenografted mice showed standard uptake value (SUVmean) of 6.0 ± 1.1 in MDA-MB-468, 4.2 ± 1.4 in MDA-MB-231, and 1.5 ± 1.4 in MDA-MB-453 tumors, which are consistent with their receptors' expression levels on the cell surface.

Conclusion: We have successfully prepared a radiolabeled bispecific antibody, [89Zr]ZrDFO-amivantamab, and evaluated its pharmacologic and imaging properties in comparison with its single-arm antibodies and non-specific isotype controls. [89Zr]ZrDFO-amivantamab demonstrated the greatest uptake in tumors co-expressing EGFR and c-MET.

Keywords: 89Zr; Bispecific antibody; C-MET; EGFR; Triple-negative breast cancer.

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Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, in patients with EGFR exon 20 insertion (exon20ins)-mutated non-small cell lung cancer (NSCLC).

Citation

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Authors

Park K, John T, Kim S-W, Lee JS, Shu CA, Kim D-W, Ramirez SV, Spira AI, Sabari JK, Han J-Y, Trigo JM, Lee CK, Lee KH, Girard N, Lorenzini PA, Xie J, Roshak A, Thayu M, Knoblauch RE, Cho BC.

Abstract

Background: EGFR exon20ins-mutated NSCLC is generally refractory to EGFR tyrosine kinase inhibitors (TKIs) and is associated with poor prognosis. Amivantamab (JNJ-61186372) is a novel, fully human anti-EGFR-MET bispecific antibody whose mechanism of action can target both EGFR- and MET-driven disease and has shown monotherapy activity in patients (pts) with diverse EGFR mutant disease characterized by EGFR C797S, T790M, exon20ins, and MET amplification. We present preliminary results of pts with advanced NSCLC harboring exon20ins mutations from CHRYSALIS, an ongoing phase 1 study of amivantamab (NCT02609776). Methods: This study comprises a dose escalation phase in pts with advanced NSCLC and a dose expansion phase in pts with EGFR- and MET-mutated disease. This analysis includes all enrolled pts with exon20ins disease who received the recommended phase 2 dose (RP2D) of 1050 mg (1400 mg, pts ≥80 kg) amivantamab. Response was assessed by investigator per RECIST v1.1. Results: As of 30 Oct 2019, 50 pts with exon20ins mutations had received amivantamab at the RP2D. 39/50 pts were response-evaluable and had ≥2 disease assessments or had discontinued therapy prior to the assessment period; among these pts, 29 had prior platinum-based chemotherapy (PBCT). Median age for response-evaluable pts was 61 y (40–78), 51% were female,

and median prior lines was 1 (0–7). In the 50 pts harboring exon20ins mutations treated at the RP2D, the most common adverse events (AEs) reported were rash (72%), infusion related reaction (60%), and paronychia (34%). Additional EGFR-related AEs included stomatitis (16%), pruritus (14%), and diarrhea (6%). Grade ≥3 AEs were reported in 36% of pts; 6% were treatment-related. One grade 3 diarrhea and no grade ≥3 rash was reported. Among the 39 response-evaluable pts, with a median follow-up of 4 months (1–26), the overall response rate (≥partial response [PR]) was 36% (95% CI, 21–53), and 41% (95% CI, 24–61) for the 29 pts who had prior PBCT. The clinical benefit rate (≥PR or stable disease ≥11 weeks) was 67% for response-evaluable pts and 72% for pts who had prior PBCT. Among all 14 responders, median duration of response was 10 months (1–16), with ongoing responses in 9 pts at data cutoff. Median progression-free survival was 8.3 months (95% CI, 3.0–14.8) for response-evaluable pts and 8.6 months (95% CI, 3.7–14.8) for pts who had prior PBCT. Conclusions: Amivantamab demonstrates robust and durable antitumor activity in pts with exon20ins disease, with a manageable safety profile. Clinical trial information: NCT02609776.

"Amivantamab 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."