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Intracranial efficacy of olomorasib, a second-generation KRAS G12C inhibitor, in patients with KRAS G12C-mutant NSCLC who have active, untreated brain metastases

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Background

Olomorasib, a potent and highly selective second-generation inhibitor of GDP-bound KRAS G12C has demonstrated preliminary intracranial (IC) activity in patients (pts) with brain metastases (mets). Brain mets are associated with poor prognosis and occur in 25-42% of pts with KRAS G12C-mutant NSCLC. Here we present updated results on the IC efficacy of olomorasib in pts with KRAS G12C-mutant NSCLC with active, untreated brain mets from the phase I/II LOXO-RAS-20001 (NCT04956640) study.

Methods

ECOG 0-1 and KRAS G12C inhibitor-naïve pts with advanced NSCLC positive for KRAS G12C (tissue or plasma) with active, untreated brain mets received single agent olomorasib (150 mg BID). Safety was assessed in all treated pts. IC response by modified RECIST v1.1 in ≥ 1 measurable (≥ 5 mm) IC lesion was evaluated in pts with at least one post-baseline response assessment or who discontinued treatment before the first assessment.

Results

As of 15 January 2025, 19 pts (median age 65 yrs, range 42-80) were treated. 15 pts had prior systemic therapy - 13 pts in the metastatic setting; 8 pts had ≥ 2 lines of therapy. Median number of IC target lesions was 1 (range, 1-3). Safety was consistent with previous reports of olomorasib. The most common TRAEs ($>15\%$) were low-grade diarrhea, fatigue and nausea; no grade ≥ 3 TRAEs were observed. Among the 18 efficacy-evaluable pts, IC objective response rate was 44.4% (8/18 pts; 95% CI: 21.5-69.2; 1 CR, 5 PR, 2 uPR pending/ongoing) and disease control rate was 83.3% (15/18 pts; 95% CI, 58.6-96.4; 7 SD). Median time to IC response was 2.0 months (range 1.3-3.9) and median duration of response and progression-free survival were not yet reached (5.4 months median follow-up for IC response; 95% CI, 2.79-NE).

Conclusions

Olomorasib continues to demonstrate promising IC activity and disease control in pts with KRAS G12C-mutant NSCLC and active, untreated brain mets. These results support continued clinical development of olomorasib in pts with KRAS G12C-mutant NSCLC including in pts with brain mets. Two global registrational studies investigating olomorasib in combination with immunotherapy in first-line metastatic and early-stage NSCLC are ongoing (NCT06119581, NCT06890598).

Clinical trial identification

NCT04956640.

Editorial acknowledgement

Writing assistance provided by Wambui Mwangi, PhD, Eli Lilly and Company.

Legal entity responsible for the study

Eli Lilly and Company.

Funding

Eli Lilly and Company.

Disclosure

P. Cassier: Financial Interests, Personal, Invited Speaker: Amgen, Merck, Servier, AstraZeneca; Financial Interests, Personal, Other, Advisor: OSE immunotherapeutics; Financial Interests, Personal, Advisory Board: Boehringer Ingelheim, Brenus, Eli Lilly, MabQuest; Financial Interests, Personal, Other, Adviser: START; Financial Interests, Institutional, Local PI: AbbVie, Blueprint, Boehringer Ingelheim, Bristol Myers Squibb, Exelixis, GSK, Incyte, Janssen, Novartis, Roche, Taiho, Toray Industries, Arcus Biosciences, TangoTx, Alligator, Astellas, C4 Therapeutics, Daiichi Sankyo, Ellipse Pharma, Ipsen, iTeos, MabQuest, Regeneron Pharmaceuticals, Relay Therapeutics; Financial Interests, Institutional, Coordinating PI: Amgen, LOXO/Eli Lilly, Transgene; Non-Financial Interests, Institutional, Product Samples: Plexxikon, Novartis, MSD, AstraZeneca, GSK. A. Italiano: Financial Interests, Personal, Advisory Board: Bayer, Roche, Philips, Chugai, GSK; Financial Interests, Institutional, Coordinating PI: Bayer, AstraZeneca, Roche, MSD, Ipsen, Merck. A. 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