Randomized phase III study of first-line selpercatinib versus chemotherapy and pembrolizumab in RET fusion-positive NSCLC


**Background**

Selpercatinib is a highly selective and potent, brain penetrant RET inhibitor, approved for treatment of advanced RET fusion-positive (RET+) NSCLC. Selpercatinib had not previously been evaluated in a randomized trial.

**Methods**

LIBRETTO-431 (NCT04194944) is a randomized, open-label, phase 3 trial comparing first-line selpercatinib vs chemotherapy (cisplatin/carboplatin + pemetrexed) +/- pembrolizumab. The primary endpoint of blinded independent central review (BICR)-assessed PFS was tested first in patients stratified by investigator’s intent to treat with pembrolizumab, if assigned to the control arm, (ITT-pembro) and then in the ITT population. The pre-planned interim efficacy analysis by BICR occurred after 98 PFS events in the ITT-pembro population. Crossover to selpercatinib was allowed following BICR progression on the control arm.

**Results**

A total of 261 patients were enrolled from 23 countries. Baseline characteristics were balanced across study arms. At a median follow up of approximately 19 months, selpercatinib demonstrated superior PFS vs control in the ITT-pembro (HR: 0.465, 95% CI: 0.309, 0.699; p-value: 0.0002) and ITT populations (HR: 0.482, 95% CI: 0.331, 0.700; p-value: 0.0001). In the ITT-pembro population, median PFS was 24.8 months (95% CI: 16.9, NE) with selpercatinib vs 11.2 months (95% CI: 8.8, 16.8) with control. Clinically meaningful improvements in ORR, DOR, and intracranial response were also observed with selpercatinib vs control. Time to CNS progression was longer with selpercatinib than control (cause-specific HR 0.26; 95% CI: 0.11, 0.59; p=0.0006). Adverse events observed with selpercatinib and the control arm were generally consistent with those previously reported.

**Conclusions**

Selpercatinib achieved a statistically significant and clinically meaningful improvement in PFS compared to chemotherapy + pembrolizumab in advanced RET+ NSCLC. LIBRETTO-431 is the first randomized study to demonstrate superior PFS with a targeted therapy vs chemotherapy + a checkpoint inhibitor in a biomarker selected patient population. These data support comprehensive genomic testing at diagnosis and treatment with first-line selpercatinib in patients with advanced RET+ NSCLC.

**Clinical trial identification**

NCT04194944.

**Editorial acknowledgement**
Disclosure