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Cyramza (ramucirumab) Injection
Clinical Update

Clinical Update: Lilly's Cyramza (ramucirumab) Receives FDA Approval as First-Line Treatment for Metastatic EGFR-Mutated Non-Small Cell Lung Cancer.
FDA approval date: May 29, 2020

Cyramza is an antiangiogenic therapy. It is a vascular endothelial growth factor (VEGF) Receptor 2 antagonist that binds specifically to VEGFR-2, thereby blocking the binding of the receptor ligands (VEGF-A, VEGF-C, and VEGF-D) – which may slow tumor growth. It is indicated for following indication.

- as a single agent or in combination with paclitaxel, for treatment of advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
- in combination with erlotinib, for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.
- in combination with docetaxel, for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy.
- in combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- as a single agent, for the treatment of hepatocellular carcinoma in patients who have an alpha fetoprotein of ≥400 ng/mL and have been treated with sorafenib

Cyramza plus erlotinib is the first and only FDA-approved anti-VEGFR/EGFR TKI combination therapy for metastatic EGFR-mutated NSCLC. This approval is based on the efficacy and safety from the global, randomized, placebo-controlled Phase 3 RELAY trial. In the RELAY study, Cyramza, a VEGF receptor 2 antagonist, in combination with erlotinib, a globally approved EGFR-targeting tyrosine kinase inhibitor (TKI), demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) – the time patients lived without their cancer growing or spreading after starting treatment – compared to placebo in combination with erlotinib [19.4 months in the Cyramza-containing arm compared to 12.4 months in the placebo-containing arm (HR=0.59; 95% CI, 0.46, 0.76; p<0.0001)]. The PFS treatment effect was consistent across exon 19 and exon 21 subgroups. The overall safety profile observed in the RELAY study was consistent with that of its individual components. RELAY is the second positive Phase 3 trial of Cyramza in metastatic NSCLC. The first was REVEL, which supported the approval of Cyramza plus docetaxel as a treatment for people with metastatic NSCLC whose cancer has progressed after prior platinum-based chemotherapy.
RELAY is a global randomized, double-blind, placebo-controlled Phase 3 study of Cyramza in combination with erlotinib, compared to placebo in combination with erlotinib, as a first-line treatment in previously untreated patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. EGFR-targeting TKIs are the current standard treatment options for EGFR-mutated NSCLC. Erlotinib, the TKI included in the RELAY trial regimen, is a globally approved treatment option for this type of lung cancer.

Initiated in 2015, the study randomized 449 patients across North America, Europe and Asia. The primary endpoint of the RELAY trial is PFS; key secondary endpoints include safety, overall response rate (ORR), duration of response (DoR), and overall survival (OS). On the primary endpoint of investigator-assessed PFS, Cyramza plus erlotinib (N=224) demonstrated statistically significant and clinically meaningful improvement in median PFS – the time patients lived without their cancer growing or spreading after starting treatment – by seven months compared to placebo plus erlotinib (N=225) [19.4 months in the Cyramza-containing arm compared to 12.4 months in the placebo-containing arm (HR=0.59; 95% CI, 0.46, 0.76; p<0.0001)]. The PFS treatment effect was consistent across exon 19 and exon 21 subgroups. At the time of the final analysis of PFS, OS data were not mature as only 26 percent of planned events for the final analysis had occurred (HR=0.83, 95% CI: 0.53, 1.30).

The most common adverse reactions (all grades) observed in Cyramza with erlotinib-treated patients at a rate of ⩾ 30% of patients and ⩾ 2% higher than placebo with erlotinib-treated patients were infections, hypertension, stomatitis, proteinuria, alopecia, and epistaxis. The most common laboratory abnormalities ⩾30% and ⩾2% higher than the placebo were increased alanine aminotransferase, increased aspartate aminotransferase, anemia, thrombocytopenia, and neutropenia