SO-29 Efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase fusion-positive gastrointestinal cancer: An expanded dataset

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Background: Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are oncogenic drivers in a range of adult and pediatric malignancies but are generally rare in patients with gastrointestinal (GI) cancer, with a prevalence of around 0.3% in colorectal cancer (CRC; Forsythe et al, Ther Adv Med Oncol 2021). Larotrectinib is a first-in-class, central nervous system (CNS)-active, highly selective tyrosine receptor kinase (TRK) inhibitor approved for the treatment of adult and pediatric patients with TRK fusion-positive cancer, demonstrating an objective response rate (ORR) of 78% across 175 adult and pediatric patients with various non-CNS cancers (McDermott et al, ESMO 2020). We report data on an expanded dataset of patients with TRK fusion-positive GI tumors.

Methods: Patients with TRK fusion-positive GI cancer treated with larotrectinib in the phase II clinical trial NAVIGATE (NCT02576431) were included in this analysis. Response was investigator-assessed using RECIST v1.1.

Results: As of July 20, 2020, 18 patients with metastatic TRK fusion-positive GI cancer were enrolled. Median age was 67.0 years (range 32.0 to 84.0 years). Of the 10 patients with CRC, 7 were microsatellite instability-high (MSI-H), 2 were microsatellite stable (MSS) and phenotype was unknown in 1 patient. The other tumor types were cholangiocarcinoma (n=3), pancreatic (n=2), appendiceal (n=1), esophageal (n=1), and hepatocellular carcinoma (n=1). Overall, 13 patients (72%) had received $\geq$2 prior lines of therapy, 3 (17%) of whom had received immunotherapy. The best response to last prior therapy was 2 partial responses (PR), 6 stable disease (SD), 3 progressive disease (PD), and 7 unknown, unevaluable or not applicable. ORR in the 17 evaluable patients was 41% (95% CI 18–67): 1 complete response (CR), 6 PR (1 pending confirmation), 7 SD, 2 PD and 1 not determined. Median time to response in the 6 confirmed responders was 1.9 months (range 1.7 to 5.0 months). Median duration of

response (DoR) was 5.5 months (95% CI 3.5—27.3). Median progression-free survival (PFS) was 5.4 months (95% CI 2.2—11.6) at a median follow-up of 20.3 months. Median overall survival (OS) was 14.1 months (95% CI 2.8—33.4) at a median follow-up of 7.8 months. In the 10 patients with CRC, ORR was 50% (95% CI 19—81): 1 CR, 4 PR (1 pending confirmation), and 5 SD. For these patients, median DoR was 15.5 months (95% CI 3.7—27.3), median PFS was 5.5 months (95%CI 2.2—29.4) and median OS was 29.4 months (95% CI 2.8—36.5). Duration of treatment for all GI patients ranged from 0.26+ to 29.3 months. At data cut-off, 10 patients had progressed, with 3 continuing treatment post-progression. Adverse events were mostly Grade 1—2. Treatment-related adverse events (TRAEs) occurred in 11 patients. Grade 3/4 TRAEs occurred in 2 patients (increased alanine aminotransferase, increased aspartate aminotransferase, and nausea). There were no treatment discontinuations due to TRAEs.

Conclusions: In patients with TRK fusion-positive GI cancer, larotrectinib demonstrated rapid responses with high survival rates and a favorable safety profile. These results support testing for NTRK gene fusions in patients with GI cancer, particularly in patients with MSI-H CRC.

Clinical trial identification: NCT02576431.

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