Background: Neurotrophic tropomyosin receptor kinase (NTRK) gene fusions lead to the transcription of chimeric TRK proteins with overexpressed kinase function; this confers oncogenic potential across several tumor types. Entrectinib is a central nervous system (CNS)-active, potent inhibitor of TRKA/B/C and ROS1. We show integrated efficacy and safety analyses from entrectinib clinical trials.

Methods: Patients (pts) with locally advanced/metastatic NTRK-fusion positive (fp) tumors confirmed by nucleic acid-based methods and enrolled in global (>150 sites, 15 countries) phase 1/2 entrectinib trials (ALKA, STARTTRK-1, STARTTRK-2; EudraCT: 2012-000148-88; NCT02097810; NCT02568267) were included. Tumors were assessed after cycle 1 (4 wk) then every 8 wk. Scans underwent blinded independent central review (BICR) using RECISTv1.1. Primary endpoints: overall response rate (ORR); duration of response (DOR) by BICR. Secondary endpoints: progression-free survival (PFS); overall survival (OS) in pts with and without baseline CNS disease.

Results: The efficacy-evaluable population comprises 54 adult pts with advanced/metastatic NTRK-fp solid tumors (10 tumor types, >19 histopathologies), including pts with baseline CNS metastases. After 15.5 mo follow-up, BICR ORR was 57.4% (95% CI 42.3–70.8), complete responses n = 4 (7.4%); responses seen in all tumor types. Median BICR DOR: 10.4 mo (95% CI 7.1–NR); median BICR PFS: 11.2 mo (95% CI 8.0–14.9); median OS: 20.9 mo (95% CI 14.9–NR). Per baseline CNS status (investigator assessed), median BICR PFS was 12.0 mo (95% CI 8.7–15.7) and 7.7 mo (95% CI 4.7–NR) for patients without (n = 42) and with CNS disease (n = 12), respectively. In the safety population (355 pts who received entrectinib across clinical trials), most treatment-related AEs were grade 1–2 and managed with dose reduction (27.3%); few pts discontinued (3.9%) due to treatment-related AEs.

Conclusions: In this multicenter, pooled analysis of global clinical trials, entrectinib treatment-related AEs were grade 1–2 and managed with dose reduction (27.3%); few the safety population (355 pts who received entrectinib across clinical trials), most