Background: Tivantinib is a small molecule inhibitor of c-Met. A previous phase 2 study suggested a clinical benefit of tivantinib as a second-line therapy for hepatocellular carcinoma (HCC) with high expression of c-Met. This Japanese study aimed to confirm the efficacy and safety of tivantinib in this population (NCT02029157).

Methods: Main inclusion criteria were HCC patients refractory or intolerant to a prior sorafenib therapy, Child Pugh A, ECOG PS ≤ 1, at least one measurable lesion according to RECIST 1.1, and diagnosed as c-Met high (regarded as ≥ 2 + in ≥ 50% of tumor cells, by IHC). Enrolled patients were blindly randomized to either tivantinib or placebo group in 2:1 ratio. Stratification factors were vascular invasion (Y/N) and ECOG PS (0/1). Tivantinib (120 mg bid) or placebo was orally administered until discontinuation criteria was met. Primary endpoint was PFS by the independent review committee, based on CT/MRI every 6 weeks. Secondary endpoints included OS and safety. A sample size of 160 patients and 136 PFS events were calculated to detect a HR of 0.6 (improvement in median PFS from 8.3 to 13.3 weeks), with 10% dropout, 80% power, and log-rank test with 5% two-sided alpha.

Results: From 60 sites in Japan, 386 patients were consented, and 195 patients were randomized (tivantinib; n = 134, placebo; n = 61). As results, median PFS was 2.8 months in the tivantinib group, whereas 2.3 months in the placebo group (HR = 0.72 [95% CI 0.51-1.02], p = 0.083). Median OS at the time of analysis was 9.9 months in the tivantinib group, whereas 8.5 months in the placebo group (HR = 0.85 [95% CI 0.59-1.22]), but additional follow up may be needed to confirm long-term outcome. Grade ≥ 3 AE occurring ≥ 5% were neutropenia (31.6%), leukopenia (24.8%), lymphopenia (7.5%), anemia (14.3%) and febrile neutropenia (6.0%) in the tivantinib group, whereas none in the placebo group. New toxic profile was not identified except for known AE in the previous study.

Conclusions: Although favorable survival were observed in the tivantinib group, this study in Japan could not show the significant clinical benefit of tivantinib as a second-line therapy for c-Met high HCC.

Clinical trial identification: NCT02029157

Legal entity responsible for the study: Kyowa Hakko Kirin

Funding by: Kyowa Hakko Kirin