1293P | FINAL RESULTS OF A JAPANESE PHASE 1 TRIAL EVALUATING A C-MET INHIBITOR TIVANTINIB IN COMBINATION WITH AN EGFR INHIBITOR ERLOTINIB IN ADVANCED/METASTATIC NON-SMALL CELL LUNG CANCER (ARQ 197-003/005 STUDY)

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Background

Tivantinib (formerly ARQ 197) is a selective, oral, non-ATP-competitive, small-molecule inhibitor of c-MET, and is metabolized by CYP2C19 and moderately by CYP3A4. A Japanese phase 1 study testing tivantinib as a single agent demonstrated that the major dose-limiting toxicity was neutropenia, and that the recommended doses were 360 mg bid for CYP2C19 extensive metabolizers (EMs) and 240 mg bid for poor metabolizers (PMs). A Western phase 2 study showed a prolonged progression free survival in metastatic NSCLC patients treated with tivantinib in combination with an EGFR inhibitor erlotinib, which is mainly metabolized by CYP3A4. Here we evaluate the safety and tolerability of tivantinib in combination with erlotinib, in Japanese EMs and PMs (ARQ 197-003 /005), respectively.

Methods

Heavily pretreated patients with advanced or metastatic NSCLC received tivantinib as a single agent for single dose analysis on day 1, and thereafter, started a repeating dose of tivantinib and erlotinib combination until progression or unacceptable toxicity. Tivantinib was separately escalated in EMs and PMs, up to the dose respective doses recommended by the previous single agent phase 1. Erlotinib was administered at 150 mg/day for all patients.

Results

A total of 25 patients (16 EMs, 9 PMs) were treated. Tivantinib, when combined with erlotinib, was well tolerated up to 360 mg bid for EMs and 240 mg bid for PMs. Rash, dry skin, diarrhea, and nausea were the treatment emergent adverse events (TEAEs) observed in >25% of all patients. Grade ≥3 neutropenia was observed in 2 PMs (8% in all patients) throughout the studies, and the rate was not largely different from the previous phase 1 study. Drug-drug interaction was not observed in tivantinib metabolism in combination with erlotinib. All patients were evaluable for response; 3 PRs and 10 SD.

Conclusion

Tivantinib at the recommended dose in single agent phase 1 could be combined with erlotinib without accelerating tivantinib-related AE, or significantly changing the pharmacokinetics. A pivotal phase 3 trial is currently underway in Asian non-squamous NSCLC with wild-type EGFR, to evaluate the OS-prolongation by the combination over erlotinib alone.

Disclosure

All authors have declared no conflicts of interest.

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