EVALUATION OF SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF DABRAFENIB, A BRAF INHIBITOR, IN JAPANESE PATIENTS WITH BRAF V600 MUTATION-POSITIVE ADVANCED SOLID TUMORS: A PHASE I STUDY

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Aim: Dabrafenib, a potent and selective BRAF inhibitor, has demonstrated clinical significance for BRAF V600 mutation-positive metastatic melanoma and has been approved in the US and EU. However, there is less clinical experience of treatment with dabrafenib in the Japanese population. Therefore, this study has been designed and conducted to evaluate safety, tolerability, pharmacokinetics (PK) and efficacy of dabrafenib in Japanese patients with BRAF V600 mutation-positive advanced solid tumors as the first clinical trial.

Methods: Patients with BRAF V600 mutation-positive advanced solid tumors refractory to standard therapies were enrolled. Dose escalation was performed according to a standard 3 + 3 design. Dabrafenib was given twice a day (BID), which started 7 days after a single dose administration for a single-dose PK analysis. Antitumor activity was evaluated based on RECIST version 1.1. This study was registered at www.clinicaltrials.gov as NCT01582997.

Results: Twelve patients (11 melanoma and 1 papillary thyroid cancer) with BRAF V600E mutation received dabrafenib at doses of 75 mg (n = 3), 100 mg (n = 3), or 150 mg (n = 6). The median duration of treatment was approximately 39 weeks. No dose-limiting toxicities were observed in these three dose cohorts. The most common adverse events (AEs) included alopecia, leucopenia, pyrexia and arthralgia. Most AEs were reported as grade 1 or 2. Squamous-cell carcinoma or keratoacanthoma, which is a well-documented BRAF inhibitor class toxicity, was not observed in this study. Preliminary PK results showed no obvious ethnic difference. Partial responses were confirmed in 7 patients (58.3%), 6 melanoma patients and 1 papillary thyroid cancer patient. The data also suggested dabrafenib had an antitumor activity in Japanese patients with BRAF V600 mutation-positive melanoma as well as papillary thyroid cancer.

Conclusions: Compared with the data published for the caucasian population, dabrafenib exhibited comparable tolerability, safety and PK profiles in Japanese patients at the dose of 150 mg BID. This dose also gave a suggestive outcome for the potential efficacy to the Japanese population.

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