Evaluation of safety, tolerability, pharmacokinetics (PK) and efficacy of dabrafenib and trametinib combination (Dab + Tra) therapy in Japanese patients (pts) with BRAF V600 mutation-positive advanced cutaneous melanoma: a phase (Ph) I/II study

A. Tsutsumida, N. Yamazaki, A. Takahashi, K. Namikawa, Y. Fujinara, S. Kondo, S. Yoshikawa, Y. Yoshino, A. Suzuki, A. Mukayama, Y. Nishimura, Y. Kiyohara

1Department of Dermatologic Oncology, National Cancer Center Hospital, Tokyo, Japan
2Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan
3Dermatology Division, Shizuoka Cancer Center, Shizuoka, Japan
4Oncology Development, Medical Affairs Department, Novartis Pharma K.K., Tokyo, Japan

Aim/Background: Combination of dabrafenib (Dab, 150 mg twice daily [BID]), a BRAF inhibitor, and trametinib (Tra, 2 mg once daily [QD]), a MEK inhibitor, is clinically active in BRAF V600 mutation-positive metastatic melanoma, and approved in the US and elsewhere. The tolerability, safety, PK and efficacy of the combination in Asians have not been evaluated. We investigated this combination in Japanese pts.

Methods: In Ph I, pts with BRAF V600E/K mutation-positive advanced solid tumors, refractory to standard therapies, received Dab 150 mg BID + Tra 2 mg QD, dose-limiting toxicity, safety and PK were assessed. In Ph II, pts with BRAF V600E/K mutation-positive unresectable (stage IIIc) or metastatic (stage IV) cutaneous melanoma were enrolled and the confirmed overall response rate (ORR) was evaluated (NCT01928940).

Results: Japanese pts with BRAF V600E mutation-positive advanced cutaneous melanoma (n = 12) received Dab + Tra (6 in Ph I and 6 in Ph II), and comprised 7 men and 5 women. Mean age was 55.6 years (range 21–77). No DLT was seen in Ph I. AEs (≥ 50%) reported in Ph I were pyrexia, nasopharyngitis, rash maculo-papular, erythema, aspartate aminotransferase (AST) increased, decreased appetite, headache, alopecia, dermatitis acniform, and blood alkaline phosphatase increased. AEs (≥ 50%) reported in Ph II were pyrexia, oedema peripheral, AST increased, and stomatitis. No squamous cell carcinoma was seen. PK results in repeat dosing in Ph I showed absorption of both drugs was rapid with a median plasma Tmax of ≈ 2 h for Dab and 1 h for Tra. Steady-state was achieved within ≈ 21 days after the first dose of Tra. Best confirmed responses per investigator in Ph II (n = 6) were 2 (33%) complete responses (CR), 3 (50%) partial responses (PR) and 1 (17%) stable disease. The confirmed ORR (CR + PR) was 83% (95% CI 35.9–99.6).

Conclusions: Dab + Tra was well tolerated with a manageable safety profile in Japanese pts, and clinically meaningful antitumor activity was seen. Japanese clinical and PK outcomes were comparable to those of Caucasian pts. Dab + Tra should be further investigated in Japanese pts.

Clinical trial identification: NCT01928940

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