Phase 1 study of the investigational, oral pan-Raf kinase inhibitor TAK-580 (MLN2480) in patients with solid tumors or melanoma: Final analysis

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Background

The MAPK pathway plays a key role in regulating cell growth and proliferation. MAPK signaling is hyperactivated in many tumors and patients with solid tumors, both as a single agent and in combination. TAK-580 is a pan-Raf inhibitor active in preclinical models of TAK-580 in patients with locally advanced metastatic melanoma (NCT01425008).

Methods

Patients were enrolled into seven separate cohorts in the Q2D dose-expansion phase: (1) naive or pretreated; (2) NRAS+/BRAF WT or NRAS−/BRAF WT; (3) NRAS−/BRAF + or NRAS−/BRAF −; (4) Q2D or QW; (5) BRAF inhibitor failure; (6) non–BRAF inhibitor failure; and (7) BRAF inhibitor naïve. Six cohorts of patients with melanoma, divided according to tumor genotype and treatment history (Table 1), were studied. Prior chemotherapy was permitted; immunotherapy/monoclonal antibody therapy completed at least 4 weeks prior to study entry. Patients with locally advanced, metastatic, and/or unresectable melanoma meeting cohort-specific criteria with regard to tumor genotype and treatment history were eligible. Patients were not allowed to have a grade ≥3 TEAE at screening.

TEAEs occurring in ≥15% of patients overall, and ≥2 patients following TAK-580 dosing; immunotherapy/monoclonal antibody therapy completed at least 4 weeks prior to study entry.

Results

The 50% response rate in the Q2D dose-expansion phase was 21% (95% CI, 9–41). Five (13%) of 37 patients with NRAS−/BRAF WT melanoma and one (8%) of 12 patients with NRAS−/BRAF + melanoma achieved a PR (one patient is ongoing with a PFS of 40.8 months).

Conclusions

Together these results suggest that the QW dosing has revealed only an improvement in safety over Q2D. Future efforts should focus on the MTD of 600 mg QW the MTD of 200 mg Q2D and 600 mg QW were well tolerated and demonstrated evidence of antitumor activity. The safety and PK profiles of TAK-580 at the MTDs of 200 mg Q2D and 600 mg QW were consistent with those at other dose levels. TEAEs occurring in ≥15% of patients overall, and ≥2 patients following TAK-580 dosing; immunotherapy/monoclonal antibody therapy completed at least 4 weeks prior to study entry. Patients with locally advanced, metastatic, and/or unresectable melanoma meeting cohort-specific criteria with regard to tumor genotype and treatment history were eligible. Patients were not allowed to have a grade ≥3 TEAE at screening.

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