Antitumor activity of belvarafenib in melanoma brain metastasis and NRAS mutation melanoma models

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Abstract

Over the past decade, BRAF inhibitors, either alone or in combination with MEK inhibitors, have set a new milestone in patients with BRAF V600 mutation melanoma, which accounts for about 50% of melanomas. More recently, anti-PD-L1 therapies such as nivolumab or pembrolizumab and atezolizumab have been approved as a very useful treatment for patients with melanoma. Nevertheless, metastasis to the brain in melanoma patients, which are highly aggressive and associated with poor outcomes, still requires better treatment. Also, to date, no targeted therapy has been developed for patients with NRAS mutations, which account for about 20% of melanomas.

Here, we present the results of preclinical model studies suggesting that belvarafenib could be effective in treating melanoma patients with metastases to the brain as well as NRAS mutation melanoma patients. First, the exposure of belvarafenib in the brain was similar to that in the plasma (approximately 100% brain to plasma ratio) in mice and rats after oral administration. This level of brain penetration of belvarafenib suggests the potential for treating BRAF inhibitors that have low brain penetration. Belvarafenib showed excellent antitumor activity in a brain metastasis model using melanoma cells. Belvarafenib significantly prolonged the overall survival in mice that underwent stereotaxic injection of melanoma cells into the brain. Moreover, in the syngeneic mice model with NRAS Q61D/K735 melanoma cells, the combination of belvarafenib with azacitidine (a pan-PD-L1) significantly inhibited tumor growth and greatly enhanced the survival time in an animal model which transplanted melanoma cells into the brain. Overall, our data demonstrated that belvarafenib has therapeutic potential to treat patients with NRAS and BRAF mutation melanoma and its brain metastasis.

Conclusion

Belvarafenib, a pan-RAF inhibitor partially inhibited the growth of BRAF and NRAS mutation melanoma, and also showed strong antitumor activity in both of BRAF mutation (e.g. A375) and NRAS mutation (e.g. SK-MEL-30) cell xenograft mouse models. It appeared that belvarafenib highly distributes into the brain in rodents, suggesting a therapeutic effect against brain metastases. In fact, belvarafenib excellently inhibited the tumor growth and greatly enhanced the survival time in an animal model which transplanted melanoma cells into the brain.

It turned out that Belvarafenib, a pan-RAF inhibitor, can inhibit the signaling of BRAF-BRAF/ CRAF-CRAF dimerization due to RAS mutations as well as oncogenic BRAF mutation monomer.

References