The effect of BI836880 in PDX Xeno-2117

In vivo evaluation of VEGF/Ang-2 bispecific nanobody BI836880 in nasopharyngeal carcinoma (NPC)

Chi-Hang Wong 1, Gigi Lam 2, Connie Hui 1, Rachel C.T. Lam 2, K.W. Lo 3, Edwin P. Hui 1, Anthony T.C. Chan 1, Brigette B.Y. Ma 1*

1State Key Laboratory of Translational Oncology, Sir YK Pao Centre for Cancer, Dept of Clinical Oncology, Cancer Drug Testing Unit, Hong Kong Cancer Institute and Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong (CUHK)
2Faculty of Medicine – Medical School, The Chinese University of Hong Kong
3Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong

Abstract

BI836880 is a humanized bispecific nanobody directed against angiopoietin-2 (Ang2) and vascular endothelial growth factor (VEGF)-derived peptides, with selective and potent antiangiogenic and antineoplastic activities. It comprises of blocking domains that bind to Ang2 and VEGF and prevents Ang2- and VEGF-mediated signaling; thus, inhibits both angiogenesis and tumor cell proliferation. Tumor angiogenesis contributes to NPC progression and VEGF/ receptor inhibitors agents have activity in NPC patients. In this study, we examined the preclinical activity of a novel VEGF/Ang-2 bispecific nanobody, BI836880, in two NPC-PDX models - Xeno-2117 and Xeno-666. The effect of BI836880 on tumor growth was compared with the control, bevacizumab – an anti-VEGF antibody which has been evaluated in NPC patients. Tumor-bearing mice were randomized into three groups: vehicle control, 15mg/kg bevacizumab (b.i.w) and 15mg/kg BI836880 (b.i.w). Drug was administered by intraperitoneal injection and the treatment duration was four weeks. Tumor sizes and body weights were monitored by caliper and balance, respectively. The results showed that BI836880 was very well tolerated in mice, with no signs of stress and loss of weight observed during the treatment. At day 14, the mean tumor volumes of BI836880, bevacizumab vs vehicle control was 264.5±36.0, 290.0±32.4 vs 697.38±88.4 mm3 in Xeno-666 (p<0.001, BI836880 vs control), and 293.5±39.3, 319.6±37.6 vs 1016.8±107.6 mm3 in Xeno-2117 (p=0.0001, BI836880 vs control), respectively. Angiogenesis marker CD34 was analyzed by IHC staining and the microvessel densities were calculated by Image J. The results showed that BI836880 could significantly reduce the number of microvessels to a comparable extent as bevacizumab in NPC model. In addition, BI836880 had increased the tumor internal necrotic area by 118.7% compared to vehicle control in Xeno-2117 (p=0.0148), but the effect was insignificant in Xeno-666 (p=0.5467).

Conclusion

In conclusion, BI836880 can inhibit NPC growth to an extent that is comparable to bevacizumab but with a stronger intratumoral necrotic effect, further investigation in combination with cytotoxic or immunotherapeutic agents are warranted.