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Abstracts

ANGI-12. EFFICACY OF THE PENTRA® BODY DLX1008, A MONOVALENT ANTIBODY FRAGMENT WITH LOW PICOMOLAR AFFINITY TO VEGF-A, IN HUMAN GLIOMA MODELS *IN VITRO* AND *IN VIVO*

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Angiogenesis mediated by vascular endothelial growth factor (VEGF) is a hallmark of glioblastoma. Moreover, VEGF may exert tumor-intrinsic survival properties mediated both by VEGF receptors 1 and 2. Although various VEGF inhibitors have shown limited clinical activity in glioblastoma, notably determined by responses on neuroimaging and prolongation of progression-free survival (PFS), no VEGF antagonist has so far been demonstrated to unequivocally improve overall survival in any clinical setting in glioblastoma. Based on response rates and improved PFS, although not overall survival (OS), the 149 kDa anti-VEGF-A IgG antibody bevacizumab (Avastin®) is approved in the US and Japan for recurrent glioblastoma and in Japan for newly diagnosed glioblastoma. However, it is not approved in the EU. Here we characterize DLX1008, a 26 kDa anti-VEGF-A single chain antibody fragment which binds with 22 pM and 27 pM affinity to mouse and human VEGF-A, respectively. *In vitro*, in a tube formation assay with human cerebral microvascular endothelial cells (HCMEC), it was demonstrated that DLX1008 is at least as active as Avastin®. In addition, DLX1008 showed superiority to Avastin® in the inhibition of VEGF-A binding to VEGF-R1 in ELISA by a factor of around 10. *In vivo*, DLX1008 significantly improved survival in a mouse orthotopic U87 xenograft model compared to vehicle control ($p = 0.00026$) and significantly inhibited tumor growth in a mouse subcutaneous U87 xenograft model compared to vehicle control ($p = 0.0021$). In summary, these data warrant further clinical development of DLX1008 in a biomarker-driven approach to glioblastoma. DLX1008 may provide improved clinical benefit in glioblastoma, especially in overall survival, due to higher affinity and smaller size leading to improved tumor penetration.