

Genetic signature of prostate cancer resistant to optimized hK2 targeted alpha-particle therapy

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Abstract

Hu11B6 is a monoclonal antibody that internalizes in cells expressing androgen receptor (AR)-regulated prostate specific enzyme human kallikrein 2 (hK2; *KLK2*). In multiple rodent models, Actinium-225 labeled hu11B6-IgG₁ (²²⁵Ac]hu11B6-IgG₁) has shown promising treatment efficacy. In the current study we investigated options to enhance and optimize [²²⁵Ac]hu11B6 treatment. Firstly, we evaluated the possibility of exploiting IgG₃, the immunoglobulin G (IgG) subclass with superior activation of complement and ability to mediate FC-gamma-receptor binding, for immunotherapeutically enhanced hK2 targeted alpha-radioimmunotherapy. Secondly, we compared the therapeutic efficacy of a single high activity vs. fractionated activity. Finally, we used RNA sequencing to analyze the genomic signatures of prostate cancer that progressed after targeted alpha therapy. [²²⁵Ac]hu11B6-IgG₃ was a functionally enhanced alternative to [²²⁵Ac]hu11B6-IgG₁ but offered no improvement of therapeutic efficacy. Progression free survival was slightly increased with a single high activity compared to fractionated activity. Tumor free animals succumbing after treatment revealed no evidence of treatment associated toxicity. In addition to upregulation of canonical aggressive prostate cancer genes, such as *MMP7*, *ETV1*, *NTS* and *SCHLAP1*, we also noted a significant decrease in both *KLK3* (PSA) and *FOLH1* (PSMA) but not in *AR* and *KLK2*, demonstrating efficacy of sequential [²²⁵Ac]hu11B6 in a mouse model.

Conflict of interests: HL and DU are consultant/advisory board members for and hold ownership interest in Diaprost AB. DU is listed as co-inventors on several patents regarding the humanized form of 11B6, which is owned by Diaprost.

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