Abstracts

568  XTX201, A PROTEIN-ENGINEERED IL-2, EXHIBITS TUMOR-SELECTIVE ACTIVITY IN MICE WITHOUT PERIPHERAL TOXICITIES IN NON-HUMAN PRIMATES


Background High-dose recombinant human interleukin-2 (aldesleukin) elicits durable anti-tumor immunity and gained FDA approval two decades prior to checkpoint blockers. However, use of aldesleukin is limited due to treatment-related life-threatening toxicities. Second generation efforts to alleviate these toxicities and improve the therapeutic index of IL-2 as an anti-tumor immunotherapy, we employed protein engineering to generate XTX201, a highly potent 3rd generation IL-2 that is designed to be selectively active in tumors, stimulating cytolytic responses against tumor cells while sparing systemic immune activation.

Methods XTX201 binding interactions were measured with SPR, and bioactivity was measured using STAT-5 phosphorylation in human PBMCs and reporter cell lines. Anti-tumor efficacy and immune activation was evaluated in tumors compared to peripheral organs in syngeneic tumor mouse models. This approach may enhance tumor localization of therapeutic antibodies inhibiting PD-1/PD-L1

Results The parental anti-PD-L1 IgM antibody bound recombinant and cellular PD-L1 more potently than an IgG antibody with the same binding domain. In functional PD-L1 and PD-1 blocking studies the anti-PD-L1 IgM was as efficacious as the IgG. PD-L1-ISA provided a potent proliferation signal to primary human NK and CD8 T cells in vitro with little/no impact on regulatory or CD4 T cells. Limited cytokines were detected following 3–4 days culture with human PBMCs. PD-L1-ISA had similar potencies for both human and cynomolgus CD8 T cells, and a 2–3-fold lower potency for mouse cells. Pharmacodynamic studies in humanized and BALB/c mice showed transient and dose-dependent increases in circulating NK and CD8 T cells. PD-L1-ISA enhanced in vitro killing of PD-L1 positive MDA-MB-231-Luc cells by human PBMCs, CD8 T and NK cells compared to the anti-PD-L1 IgM (no IL-15). PD-L1-ISA also demonstrated efficacy in a hPD-L1-CT26 HuCELL mouse model, with most treated animals having complete tumor regressions. Durable anti-tumor immune memory responses were observed upon tumor rechallenge.

Conclusions We have engineered an IL-15 immunostimulatory anti-PD-L1 IgM antibody that binds PD-L1 more potently than an IgG, stimulates NK and CD8 expansion in vitro and in vivo and induces complete tumor regressions in mouse models. This approach may enhance tumor localization of 2Rβ/γ biased cytokine that inhibits tumor growth in syngeneic models, and exhibits tumor-specific pharmacodynamic effects without peripheral toxicities. XTX201 has the potential to be a best-in-class IL-2 immunotherapy by expanding the curative anti-tumor activity of aldesleukin while minimizing dose-limiting toxicities.

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569  TARGETING IL-15 DELIVERY TO PD-L1 EXPRESSING TUMORS WITH AN ANTI-PD-L1-IL-15 CYTOKINE FUSION IGM TO ENHANCE T CELL AND NK CELL MEDIATED TUMOR CYTOTOXICITY

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Background Therapeutic antibodies inhibiting PD-1/PD-L1 have demonstrated clinical efficacy though only a fraction of patients respond. Combinations are being explored to enhance responses including anti-PD-1/PD-L1 IgG antibodies with IL-15-pathway stimulating agents to remove PD-1 immunosuppressive signaling and enhance anti-tumor NK and memory CD8 T cell expansion and survival. We have engineered an anti-PD-L1 pentameric high affinity, high avidity IgM, to target low PD-L1 expressing tumors, with an IL-15 superagonist fused to the joining (J) chain.

Methods An anti-PD-L1 IgM was generated by grafting heavy chain variable regions of a high affinity IgG onto the IgM heavy chain framework and co-expressed with the light chains. The IL-15 superagonist fused to the J chain generated PDL1-ISA. Anti-PD-L1 binding was performed using recombinant antigen ELISAs and on cells by FACS. Reporter assays and PBMCs were used for potency testing. Cytokines were evaluated by CBA assays. In vitro cytotoxicity assays used luciferase tagged MDA-MB-231 cells with PBMCs, NK or CD8 T cells. Pharmacodynamic and efficacy studies were conducted in syngeneic and humanized mouse models.

Results The parental anti-PD-L1 IgM antibody bound recombinant and cellular PD-L1 more potently than an IgG antibody with the same binding domain. In functional PD-L1 and PD-1 blocking studies the anti-PD-L1 IgM was as efficacious as the IgG. PDL1-ISA provided a potent proliferation signal to primary human NK and CD8 T cells in vitro with little/no impact on regulatory or CD4 T cells. Limited cytokines were detected following 3–4 days culture with human PBMCs. PDL1-ISA had similar potencies for both human and cynomolgus CD8 T cells, and a 2–3-fold lower potency for mouse cells. Pharmacodynamic studies in humanized and BALB/c mice showed transient and dose-dependent increases in circulating NK and CD8 T cells. PDL1-ISA enhanced in vitro killing of PD-L1 positive MDA-MB-231-Luc cells by human PBMCs, CD8 T and NK cells compared to the anti-PD-L1 IgM (no IL-15). PDL1-ISA also demonstrated efficacy in a hPD-L1-CT26 HuCELL mouse model, with most treated animals having complete tumor regressions. Durable anti-tumor immune memory responses were observed upon tumor rechallenge.

Conclusions We have engineered an IL-15 immunostimulatory anti-PD-L1 IgM antibody that binds PD-L1 more potently than an IgG, stimulates NK and CD8 expansion in vitro and in vivo and induces complete tumor regressions in mouse models. This approach may enhance tumor localization of