Tumor-activated Fc-engineered Anti-CTLA-4 Monoclonal Antibody, XTX101, Demonstrates Tumor-selective PD and Efficacy in Preclinical Models

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BACKGROUND

- The clinical benefit of CTLA-4 blockade to cancer patients has been well established
- However, efficacy of current therapies is impaired by dose limiting toxicity arising from systemic immune activation

- **XTX101** is a tumor-selective anti-CTLA-4 mAb that is designed to improve upon the therapeutic index of existing anti-CTLA-4 therapies by overcoming potency and tolerability limitations
- **XTX101** has improved potency
  - Higher affinity binding to the target CTLA-4
  - Enhanced Fc effector function
- **XTX101** has reduced peripheral immune activity
  - Inactive while in circulation in the periphery due to masking of the CDR sequences
  - Activated by protease-dependent release of the masks
  - Active selectively in the tumor microenvironment and avoids toxicity associated with systemic immune activation

Ipilimumab data strongly validate potential for improved α-CTLA4 mAb

Ipilimumab Melanoma Randomized Phase 3 Study[1]

	Dose	Median OS	Adverse Events: gr 3/4 irAEs/discont.
Standard Approved Dose	3 mg/kg	11.5 mo	14% / 19%
	10 mg/kg	15.7 mo	30% / 31%

Conclusion: Treatment with higher dose resulted in increased OS but also increased AEs and discontinuations

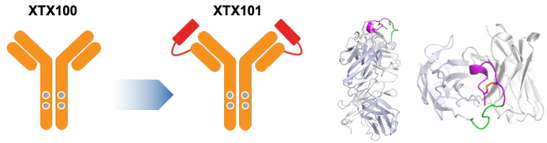
- Ipilimumab shows preliminary evidence of promising antitumor activity in a range of tumor types, outside of the approved indications[2,3,4]
- Patients with high affinity FcγR polymorphisms have shown improved clinical responses to ipilimumab[5,6,7]
- Ipilimumab is more active when combined with nivolumab, including increased rate of irAEs[8,9,10]
- The therapeutic potential of ipilimumab mono-therapy or in combination with anti-PD-1 is curtailed by dose limiting systemic immune toxicities

Xilio's approach is to combine tumor selectivity and enhanced potency of anti-CTLA4 treatment to achieve an improved therapeutic index (TI)

Sources: [1] Ascierto PA, Lancet Oncol. (2017); [2] Beer TM, J. Clin. Oncol. (2017), [3] Hellmann MD, NEJM (2019); [4] Kao HF, Head Neck. (2019); [5] Arce-Vargas F, Cancer Cell (2018); [6] Quezada SA Clin. Cancer Res. (2019); [7] Snyder A, NEJM (2014); [8] Wolchok JD, Lancet Oncol. (2010); [9] Hamid O., J. Trans. Med (2011); [10] Lebbé C, J. Clin. Onc (2019)

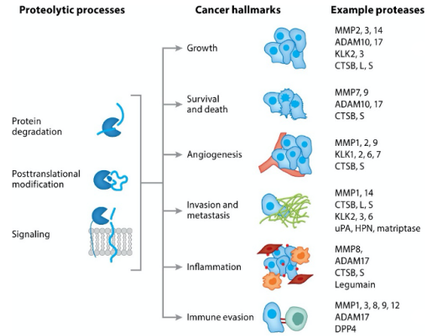
BACKGROUND

XTX101: Affinity and Fc enhancements combined with tumor selectivity for optimized TI



- α-CTLA4 mAb
- Improved affinity over ipilimumab
- Fc mutations for enhanced FcγR binding and ADCC

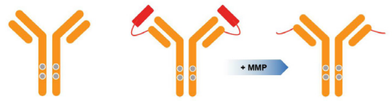
- Tumor-selectivity
  - Increased potency through improved affinity and enhanced ADCC to deplete Tregs
  - Improved tolerability by adding tumor-selectivity
  - Combining increased potency and improved tolerability to maximize opportunity for improved TI

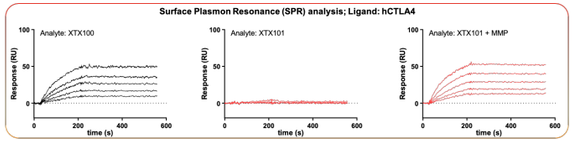


Modified from Dudani JS, et al. Annu Rev Cancer Bio (2018)

RESULTS

After proteolytic activation, full binding is restored to XTX101

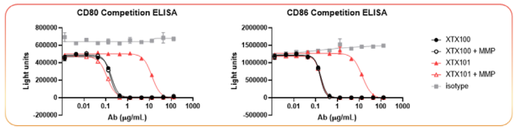




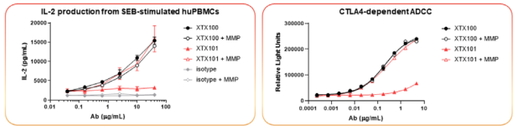
- Protease-dependent activation of XTX101 *in vitro*: biophysical assay

RESULTS

After proteolytic activation, XTX101 inhibits binding of CTLA4 to its cognate ligands CD80 and CD86, and mediates cellular activity in PBMC and ADCC bioreporter assays

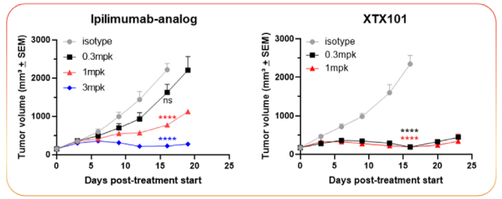


- Protease-dependent activation of XTX101 *in vitro*: biophysical assay



- Protease-dependent activation of XTX101 *in vitro*: biophysical assay

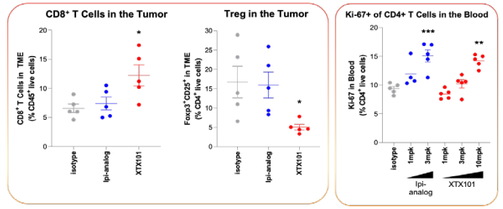
XTX101 is more potent than ipilimumab-analog



- XTX101 drives potent TGI, superior to ipilimumab-analog
- A dose of 3 mg/kg of ipilimumab-analog is required to achieve similar efficacy and CR rate as XTX101 at 0.3 mg/kg, suggesting XTX101 has 10x higher potency

MB49 cells were inoculated subcutaneously into C57BL/6-huCTLA4 mice. Mice were dosed single-dose i.v. A two-way ANOVA with Bonferonni's multiple comparisons post-test was performed to determine the statistical significance of treatment vs. isotype on Day 16 (ns not significant,;*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001).

XTX101 demonstrates potent intratumoral PD, superior to ipilimumab-analog

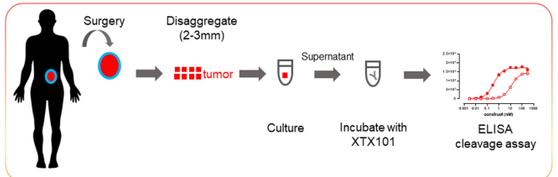


- XTX101 shows Treg depletion in the tumor and no effect on peripheral Treg levels
- A dose of 3 mg/kg of ipilimumab-analog is required to achieve similar peripheral PD as XTX101 at 10 mg/kg, consistent with better tolerability of XTX101 in mice

MB49 cells were inoculated subcutaneously into C57BL/6-huCTLA4 mice. Mice were dosed single-dose i.v. A one-way ANOVA with Bonferroni's multiple comparisons post-test was performed to determine the statistical significance of treatment vs. isotype (*P<0.05; **P<0.01; ***P<0.001).

RESULTS

Broad activation of XTX101 across human tumors in *ex vivo* assay



Cancer type	Melanoma	RCC	Ovary	Bladder	Colon	NSCLC	Breast	Liver	Total
% Tumors that activate XTX101	71%	57%	58%	67%	91%	67%	75%	67%	66%
Sample size	7	30	12	6	11	9	4	6	85

- Broad potential for tumor selective XTX101 activity leads to opportunities in many indications
- Given the broad activation of XTX101 across diverse tumor types, Companion Diagnostic (CDx) biomarker for protease activity or expression likely not required

CONCLUSION

- The clinical benefit of CTLA-4 blockade is well established, but remains limited due to toxicities arising from systemic immune activation
- XTX101 is a potent, tumor-selective anti-CTLA4 mAb with the potential to significantly expand the TI relative to ipilimumab and therefore potentially reduce toxicity while enhancing efficacy

- Functional characterization of XTX101 confirmed protease-dependent activity
  - XTX101 binds to CTLA-4 with high affinity in a protease-dependent manner
  - XTX101 exhibits protease dependent inhibition of CD80/86 binding to CTLA-4
  - Protease-dependent activation of XTX101 overcomes CTLA-4 inhibition of T cell activation
  - Enhanced effector function of XTX101 confers potent protease & CTLA-4 binding dependent ADCC activity
- Tumor-selective activity of XTX101 was demonstrated by in vivo studies
  - XTX101 demonstrates 10x improvement in potency in tumor growth inhibition studies
  - XTX101 exhibited enhanced Treg depletion in tumors
  - XTX101 showed reduced peripheral immune activation by comparison to ipilimumab-analog

- XTX101 is activated broadly across multiple tumor indications based on ex vivo studies in fresh human tumor tissue
- These data support evaluation of XTX101 in clinical studies