CTX-471, a novel agonistic antibody targeting CD137, eradicates very large tumors by selectively reprogramming the tumor microenvironment without causing hepatic toxicity

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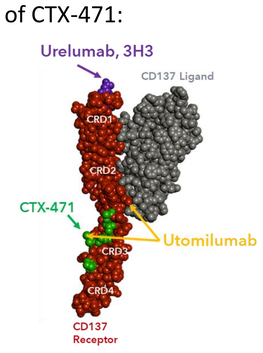
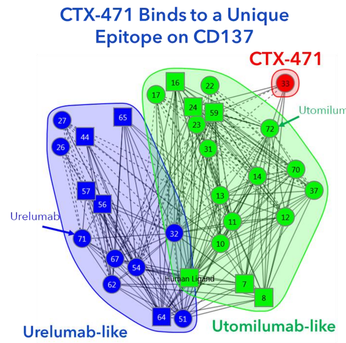
Discovery of CTX-471: Best in Class CD137 Agonist

- CD137 (a.k.a. 4-1BB and TNFSR9) is a member of the TNFR superfamily that provides costimulatory signals to activated cytotoxic lymphocytes.
- Agonistic antibodies against CD137 have shown promising therapeutic activity in mouse tumor models. However, current clinical-stage molecules have shown limited clinical activity for different reasons:
  - A strong agonist (urelumab) leads to hepatic toxicity in humans and in animal models (3H3)
  - A weak agonist (utomilumab) spares toxicity, but likely provides suboptimal activation
- Here we describe the discovery and characterization of CTX-471:
  - A fully human, IgG4 agonist antibody of CD137
  - Optimized signaling via a unique epitope
  - Human/cyno/mouse cross-reactive
  - Curative efficacy in syngeneic models
  - Well-tolerated in mice & cynomolgus monkeys

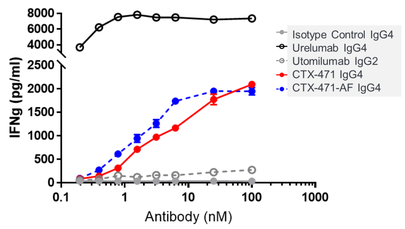
	Affinity (nM) against:	Human	Cyno	Mouse
Clinical lead →	CTX-471	47	52	748
Mouse affinity-matched version →	CTX-471-AF	3.3	5.8	87



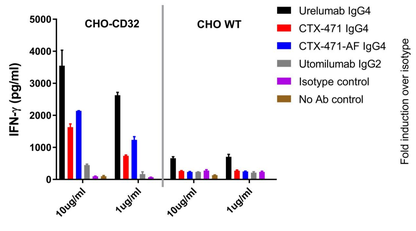


CTX-471 Shows Differentiated Activity in Human Assays

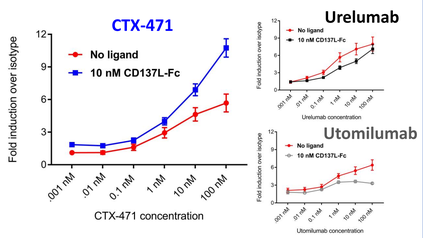
Human T cell Costimulation Assay



FcγR-Dependent Activity



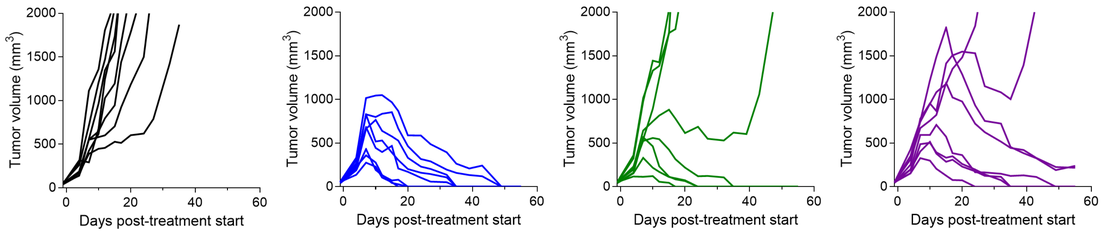
NFκB Signaling in Presence of CD137L



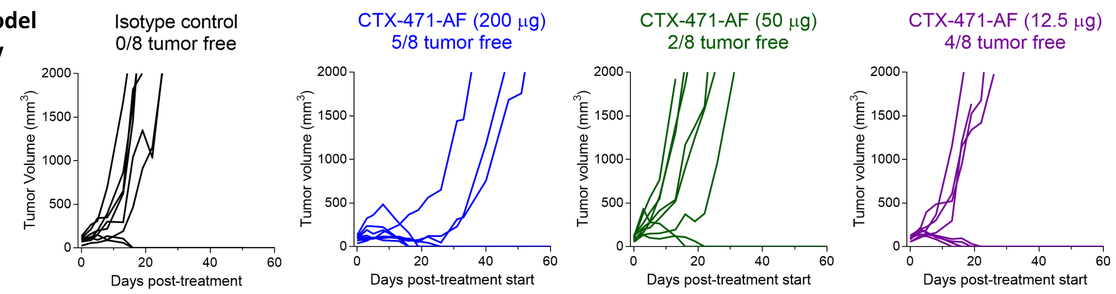
- In a primary human T cell costimulation assay in which CD8+ T cells were stimulated with anti-CD3 in co-culture with CHO cells engineered to express FcγRIIb (CHO-CD32), CTX-471 displayed an intermediate level of activity that fell between urelumab and utomilumab.
- The activity of both urelumab and CTX-471 is driven by FcγR-mediated cross-linking; CTX-471 activity is completely FcγR-dependent.
- In the presence of CD137L, NFκB signaling (measured using an engineered HEK293 line) by CTX-471 is potentiated, whereas urelumab signaling remains unchanged and utomilumab signaling is attenuated.

Curative Monotherapy Activity in Mouse Models

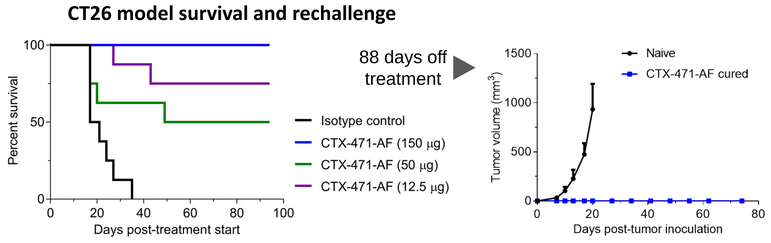
CT26 model efficacy



A20 model efficacy



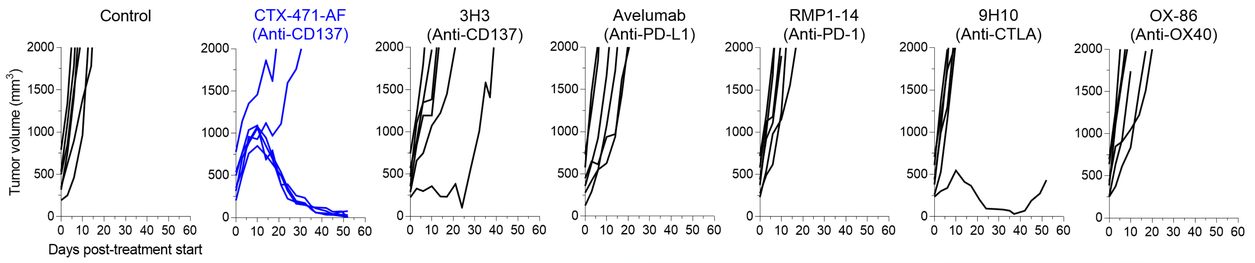
CT26 model survival and rechallenge

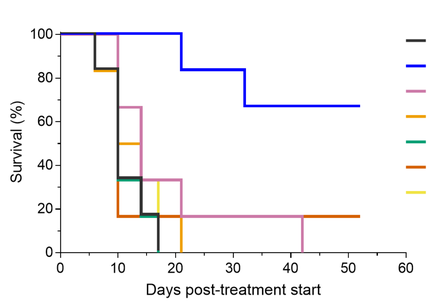


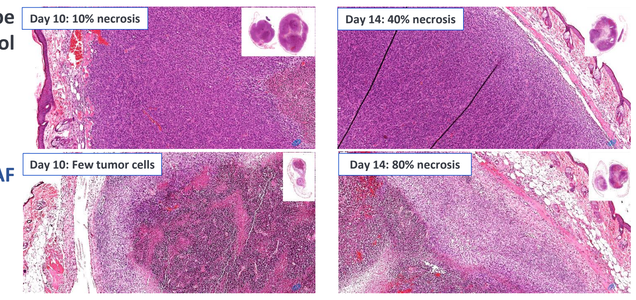
88 days off treatment

- CTX-471 & CTX-471-AF showed highly potent anti-tumor activity over a wide dose range.
- High rate of complete cures in established syngeneic models (CT26, A20, EMT-6 and MC38^{OVA}) observed.
- All cured mice showed long-term protection from tumor growth upon rechallenge, indicating potent induction of immune memory.

Unique Ability to Eradicate Very Large Tumors

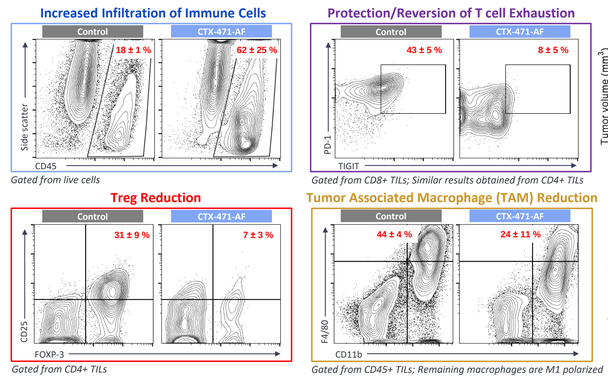


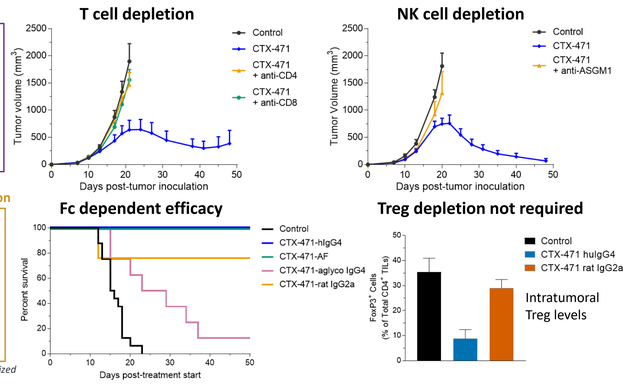




- CT26 s.c. tumors were on average **450 mm^3** at treatment start. Treating extremely large tumors of this size is generally considered futile.
- Mice received either CD137 agonists (CTX-471 or 3H3; 25 μg/ms on days 0, 7, 14), checkpoint inhibitors (Avelumab, RMP-14, or 9H10; 200 μg/ms on days 0, 3, 6) or an OX40 agonist (OX-86; 200 μg/ms on days 0, 3, 6).
- Compared to a panel of well-validated IO antibodies, CTX-471 showed a unique ability to cure mice of large, established tumors.
- Histological analysis revealed the mass destruction of CT26 tumors caused by CTX-471-AF treatment of the mice.

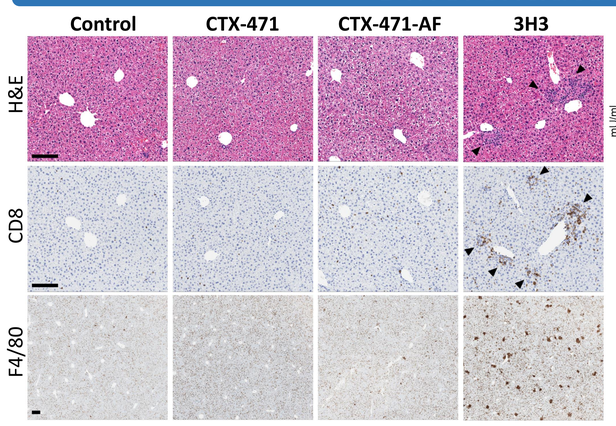
Dramatic Immune Reprogramming within the TME & MoA

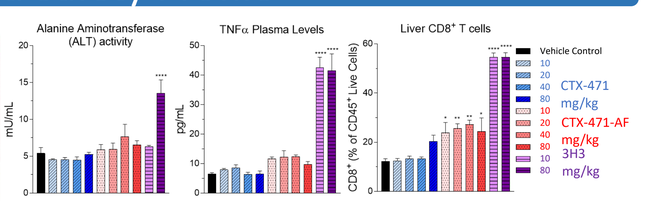




- Immunophenotypic analysis of CT26 tumors by flow cytometry revealed increased infiltration of CD45$^+$ cells, protection/reversal of T cell exhaustion, & depletion of suppressive Tregs and TAMs. These effects are seen across a wide dose range (12.5 to 200 μg) and with various dosing schedules.
- In order to further delineate the mechanisms of action, a series of immune subset depletion and isotype switch experiments were conducted in the CT26 tumor model. The data suggest cooperative involvement of both innate (NK cells) and adaptive immunity (CD4$^+$ and CD8$^+$ T cells) in the anti-tumor activity of CTX-471. Potent anti-tumor efficacy was observed with CTX-471 as hIgG4 (binds FcγRs, induces ADCP) and rat IgG2a (binds FcγRs, cannot induce ADCP) but not with aglycosylated IgG4 (no FcγR binding, cannot induce ADCP).

Differentiated Safety Profile





- Four-week repeated dose (up to 80 mg/kg/week) toxicity studies were conducted in mice.
- Urelumab-like anti-mouse CD137 Ab, clone 3H3, induced hepatic toxicity in mice and formation of inflammatory foci in livers.
- CTX-471 did not induce T cell or macrophage foci, and spared cytokine induction and transaminase elevations.
- In contrast to 3H3, the anti-tumor efficacy of CTX-471 is achieved at dose levels that are completely sparing of hepatic toxicity.

Conclusions

To our knowledge, CTX-471's level of monotherapy efficacy against very large tumors is unprecedented for an IO antibody. CTX-471 displays a favorable and well-differentiated efficacy-safety profile that is attributed to a unique epitope, optimized affinity, and FcγR-dependent activity. IND-enabling toxicology studies are underway, and a Phase 1 trial is planned for the first-half of 2019.