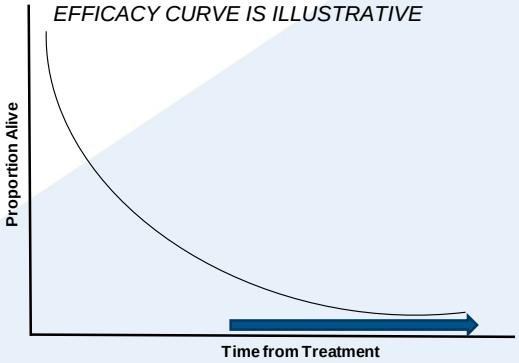
XOMA

XOMA NON-CONFIDENTIAL PRESENTATION: APRIL 2018

Augmenting Anti-tumor Immunity with a Novel IL-2 Antibody Immunotherapy

Interleukin-2 Has Durable Clinical Activity

- **Aldesleukin (Proleukin®), recombinant human IL-2, was the first cancer immunotherapy approved by the FDA in 1992 for metastatic renal cell carcinoma (mRCC)**



- **IL-2 has demonstrated durable long-term responses in ~10% of patients for metastatic melanoma and renal cancer[1]**
- **Approximately 70% of patients with complete responses have been cured, maintaining complete regression for more than 25 years[1]**

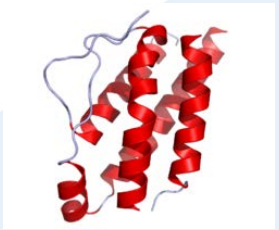
- **Commercial use limited due to cytokine release syndrome/vascular toxicity/ICU care**
- **Anti-tumor efficacy is limited by expansion of the immunosuppressive Treg pool**

1 - Rosenberg SA. Raising the bar: the curative potential of human cancer immunotherapy. Sci Transl Med 2012;4:127ps8;

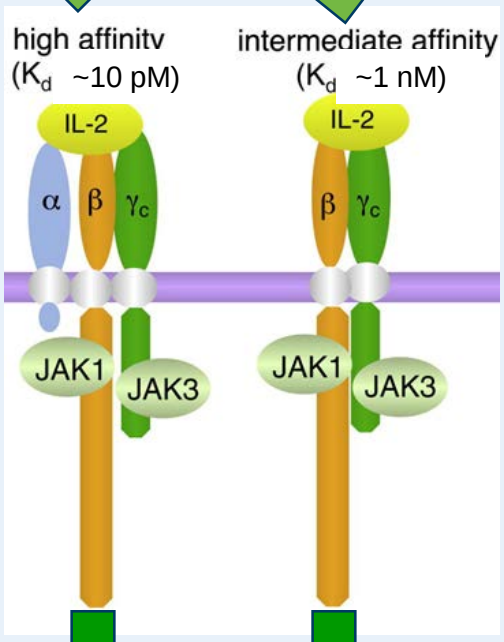
SUMMARY: XOMA's mAb19 Next Generation IL-2 Approach

	Attribute	Outcome
✓	NK & CD8 T cell expansion without cytokine release and vascular leak	Increased therapeutic window
✓	Limited expansion of Tregs (i.e. limit IL-2Rα)	Allows full cytotoxic activity
✓	Long half-life - estimated ~ q2wk dosing	Ease meets current strategies
✓	Potential for stand-alone activity Able to combine with current immunotherapies	Augments anti-tumor efficacy
✓	No issues with immunogenicity	Fully human molecules
✓	Ease of manufacturing	Established mAb CMC

IL-2 Normally Acts at Both the High-Affinity IL-2Rαβγ on Treg Cells AND the Intermediate Affinity IL-2Rβγ on Effector T and NK Cells



IL-2

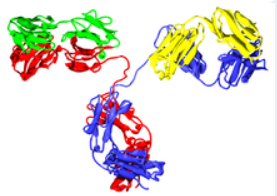


T_{reg}
Immunosuppression
Vascular Leak

T_{eff} & NK anti-tumor immunity enhanced

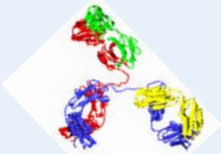
XOMA's mAb19 Disrupts IL-2 Interaction with IL-2Rαβγ but Not IL-2Rβγ, Thereby Promoting T_{eff} and NK Anti-tumor Immunity without Treg Immunosuppression

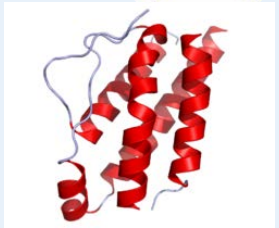
mAb19



mAb19 administered with very low dose Proleukin

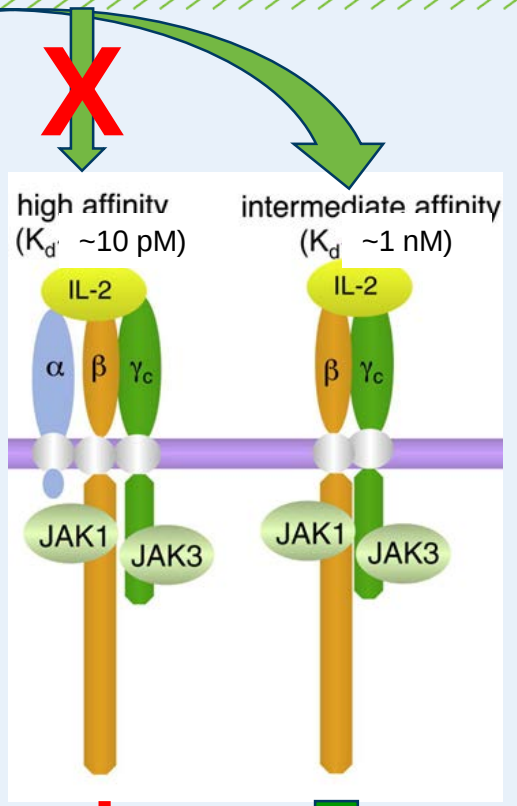
mAb19





IL-2

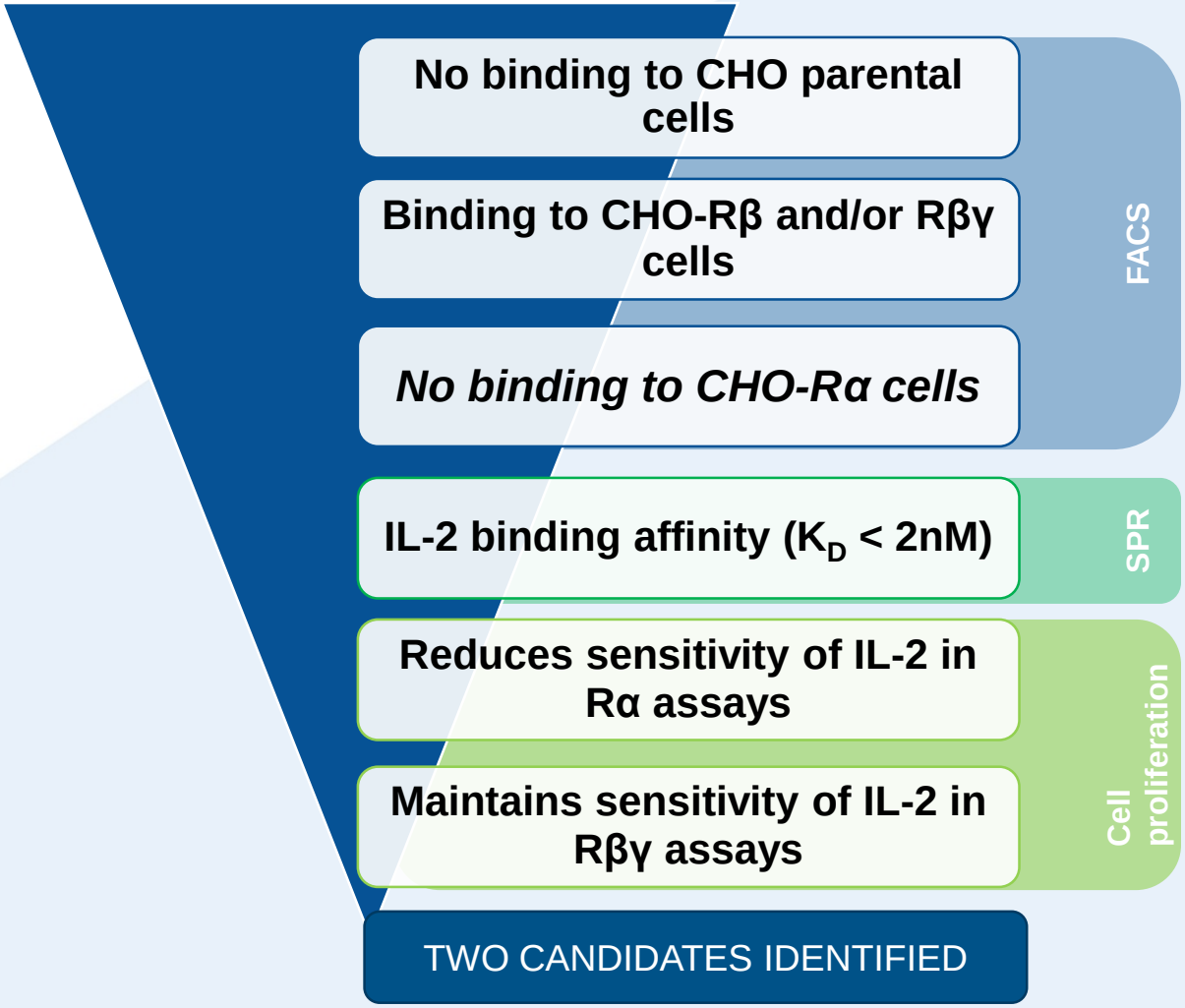
- *mAb19 binds to the IL-2Rα-binding domain of IL-2*
- *IL-2 activity directed to IL-2Rβγ-bearing anti-tumor effector cells and not T_{regs}*



T_{reg} Immunosuppression Vascular Leak

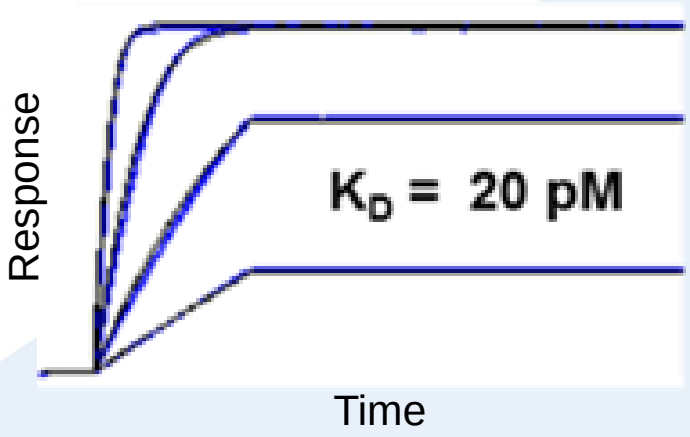
T_{eff} & NK anti-tumor immunity enhanced

Screening Strategy Flowchart for XOMA's Fully Human anti-human IL-2 mAbs

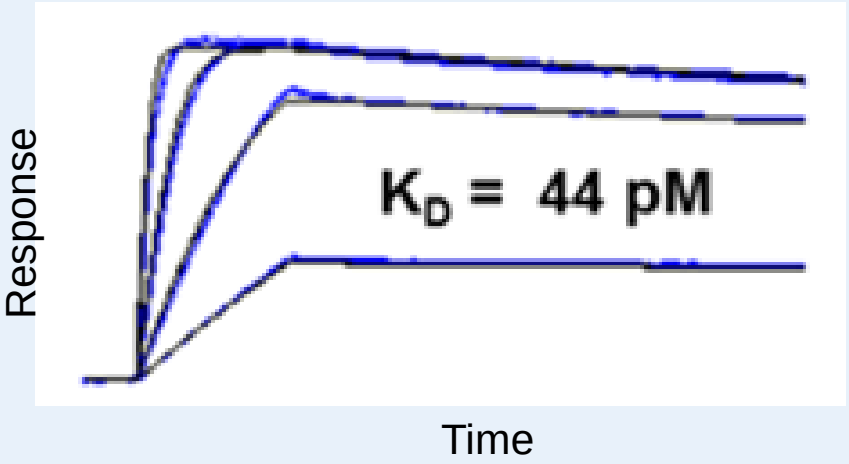


Lead Anti-IL-2 Modulating mAbs are Potent Binders to Human IL-2

mAb19



mAb99



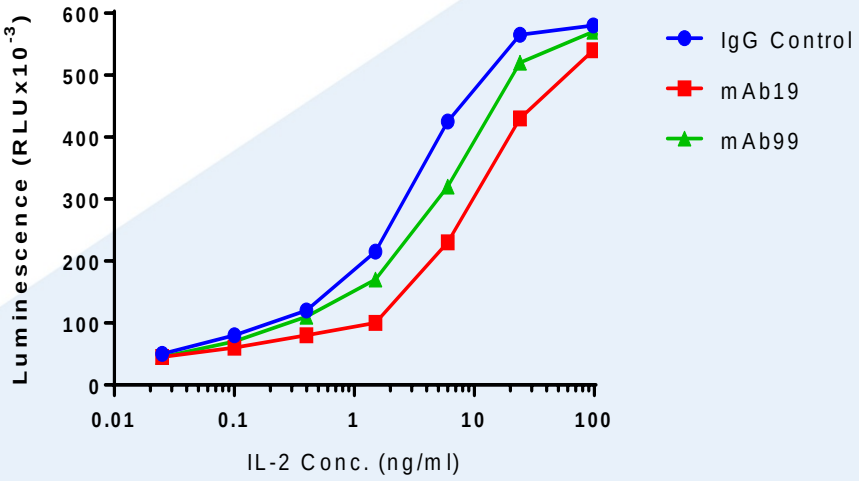
- **mAb19 is the most potent binder to human IL-2**

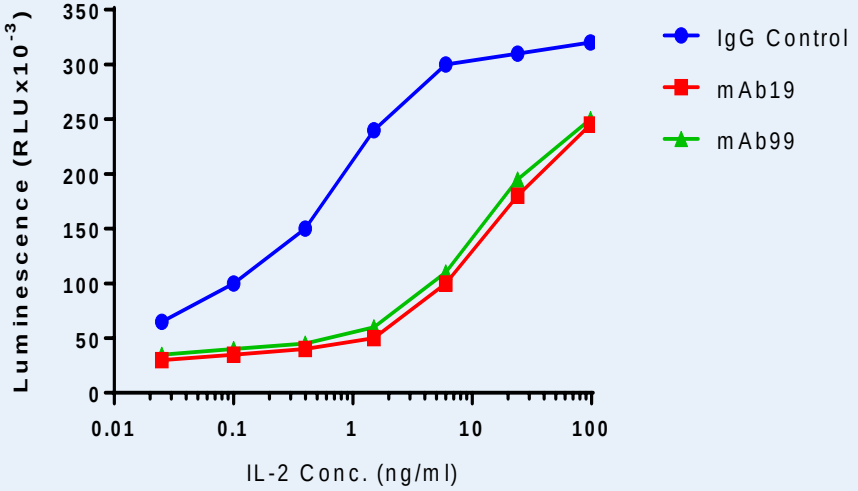
Analysis by surface plasmon resonance

XOMA Lead mAbs Especially Disrupt IL-2 Activity at the IL-2Rαβγ Complex (i.e. T_{reg}) vs βγ (desired effector cells)

BaF3/IL-2 Rβγ cell line is a surrogate for CD8+ T cells and NKs

NK92 cell line is a surrogate for T regs





EC_{50} fold-shift from control Ig:

Test Antibody	BaF3 cells (IL-2R βγ)	NK-92 cells (IL-2R αβγ)
mAb19 anti-IL-2	4.5	**31**
mAb99 anti-IL-2	2.5	23

EC_{50} IL2Rβγ mAb19/IL2=0.65nM

Study Design: FACS Analysis for Immune Cell Subpopulation Immune Cell Subpopulation Shifts in Naïve B6 Mice

- **Mice treated i.p. with XOMA mAb + low-dose human IL-2 or standard high-dose IL-2**
  - *mAb's are not cross-reactive with mouse IL-2*

- **N =** 4 animals per group

- **Doses:**

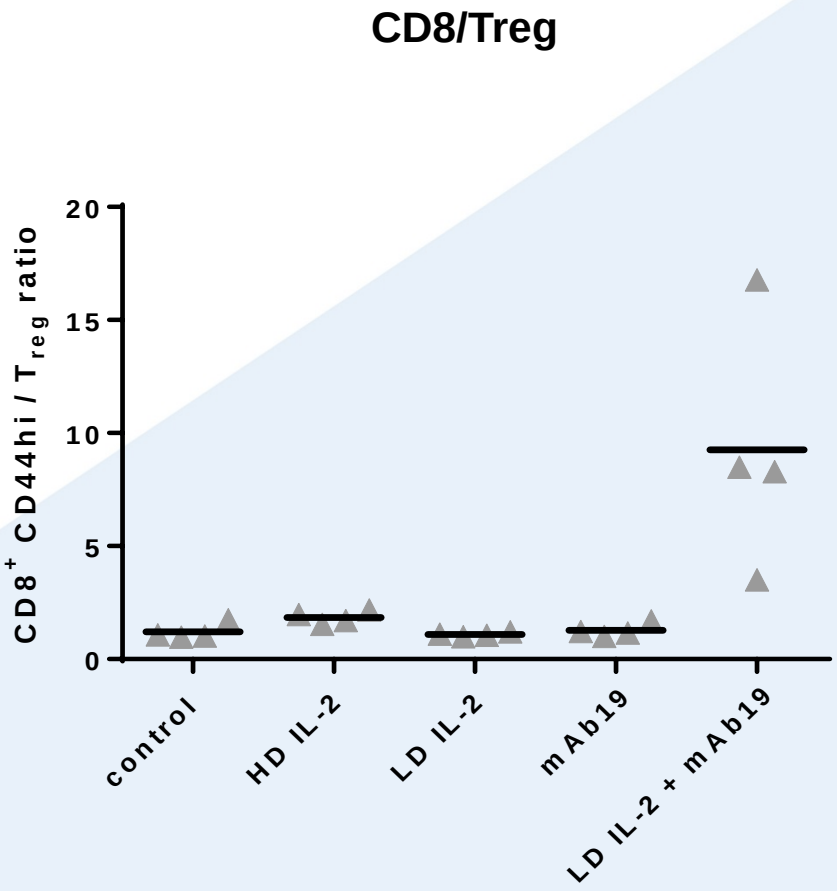
  HD IL-2 = 100 µg/mouse *(standard requirement for mouse anti-tumor efficacy)*
  LD IL-2 = 1.5 µg/mouse
  mAb19 = 7.5 µg/mouse *(<1 mg/kg as precomplexed with IL-2)*

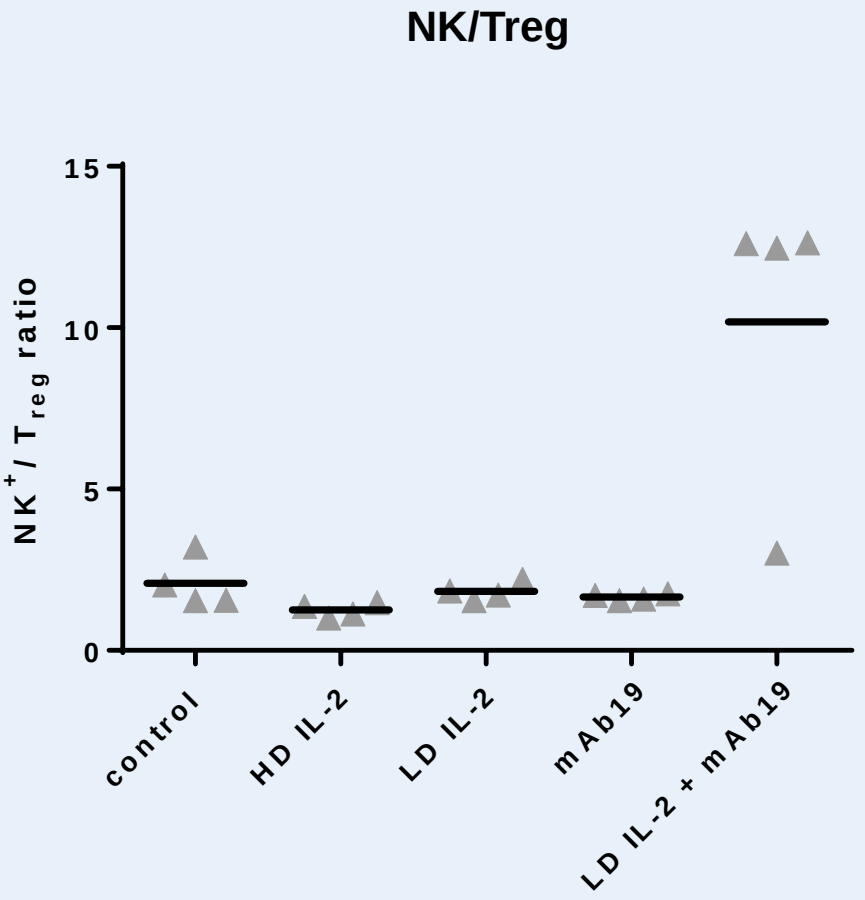
- **Dosing interval:**
- LD IL-2 & mAb 19: M, W, F *(less frequent dosing given longer duration of action)*
- HD IL-2: M, T, W, T, F

- **SPLC isolation and FACS analysis on Day 7**

And Low Dose IL-2 + mAb19 Induces Stronger Ratios of CD8 & NK to Treg Ratios vs Standard IL-2 in B6 Mice

Splenocyte Subpopulation Ratios

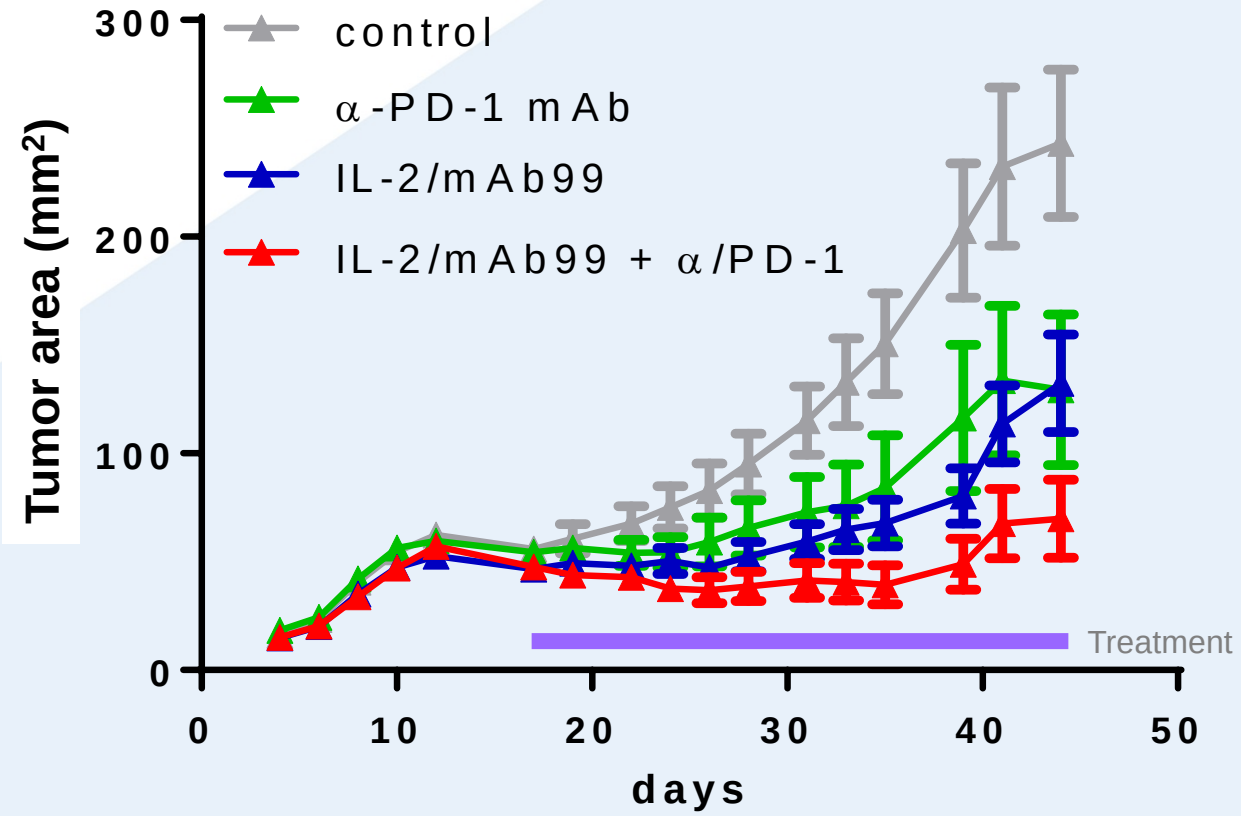




Study Design for Focus Study of Lewis Lung Carcinoma Tumor Response by IL-2 + mAb and/or anti-PD-1 mAb

- **Timeline**
  - $1x10^6$ LLC (LLC-A9F1) injected s.c.
  - Treatment begins (day 17, median tumor size ~$50mm^2$)
  - Treatment continued x 3 weeks
- **Conditions (n=15/group; all injections i.p.):**
  - control (vehicle)
  - Human LD IL-2 + mAb99 only
  - anti-PD-1 mAb only
  - Human LD IL-2 + mAb99 + anti-PD-1 mAb
- **Dosing**
  - IL-2 + mAb99
    - *2ug IL-2 + 10ug antibody, pre-complexed, i.p. 3x/week*
  - anti-PD-1 mAb (clone RMP1-14)
    - *200ug/injection, i.p. 2x/week*

Low-Dose IL-2 + mAb99 is Effective Alone and Efficacy is Increased Upon Combination with anti-PD-1



Long-term Anti-tumor Memory With Combination LD IL-2 / mAb99 + Anti-PD-1

LLC Tumor Rechallenge Study

- Objective: test induction of memory by rechallenging complete responders from initial experiment with LLC tumor, injected subcutaneously
- Rechallenge conducted approximately five months after start of initial experiment and approximately four months after final treatment (1E6 cells initially, 1.5E6 in rechallenge)
- **Day 22 Post-Rechallenge Results**
  - Synergy demonstrated between mAb / IL-2 complex and checkpoint blockade
    - In mAb / LD IL-2 complex + αPD-1 mAb group, 100% (6/6) of rechallenged mice remained tumor free

Previous Treatment	CRs	# mice challenged	# tumor free	Comment
None (control naïve mice)	0/15	10	0	
mAb99 / LD IL2 complex	1/15	1	(1)	markedly delayed tumor growth
αPD-1 mAb	2/15	2	2	
mAb99 / LD IL-2 complex + αPD-1 mAb	6/15	6	6	

Mouse Colon Carcinoma CT26 Tumor Model Study Design

- **Balb/c mice**

- **N:** 6-12 animals per group

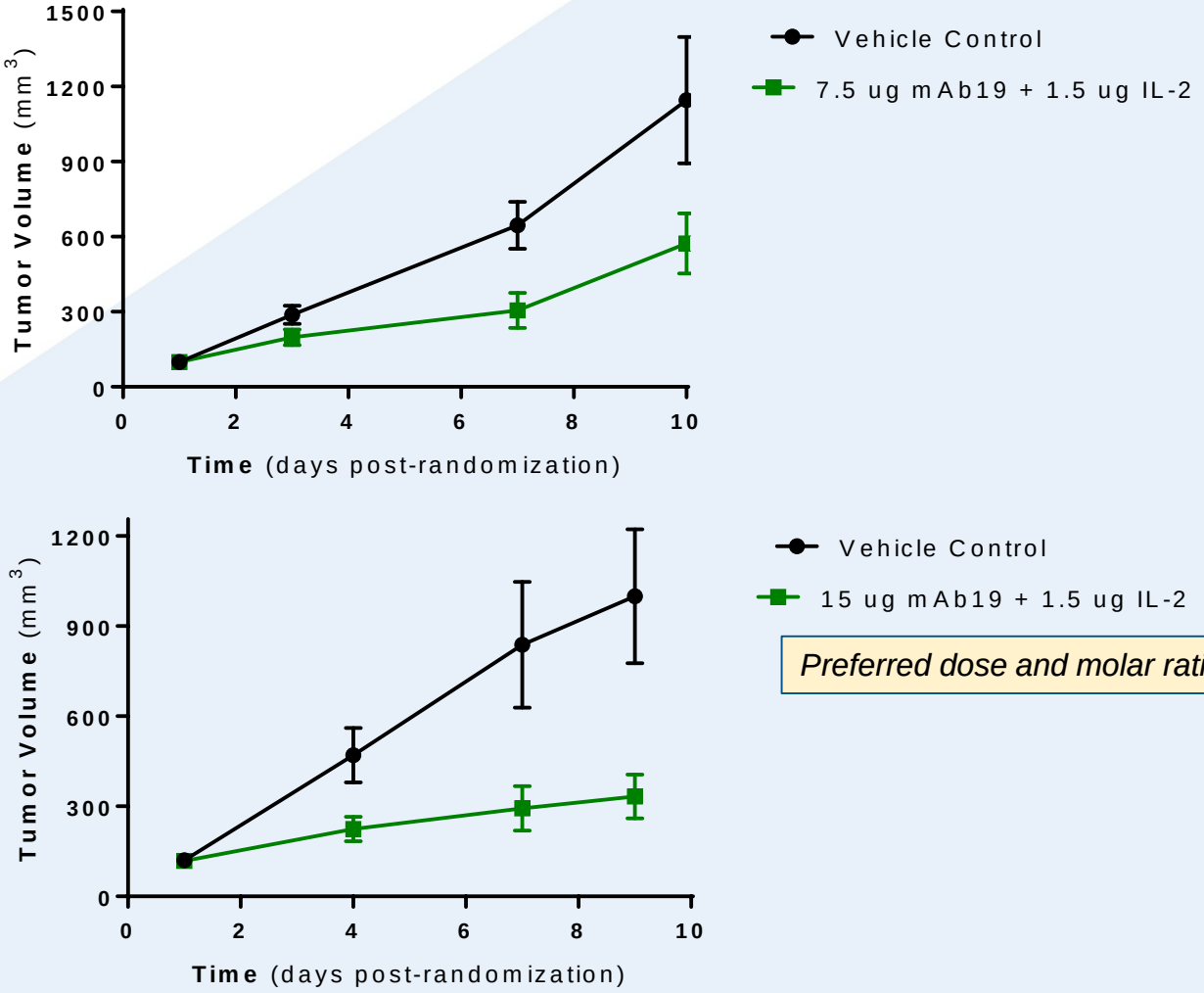
- **Doses:** HD IL-2 = 50 µg, 100 µg per mouse (2.5, 5 mg/kg)

LD IL-2 = 1.5 ug/mouse (0.075 mg/kg)
mAb19 =15 µg/mouse (0.75 mg/kg)

- **Dosing interval:**

i.p.
HD IL-2 = once daily for five days with two days off followed by another five day regimen;
mAb 19 15 µg + IL-2 1.5 µg: i.p. q3-4d

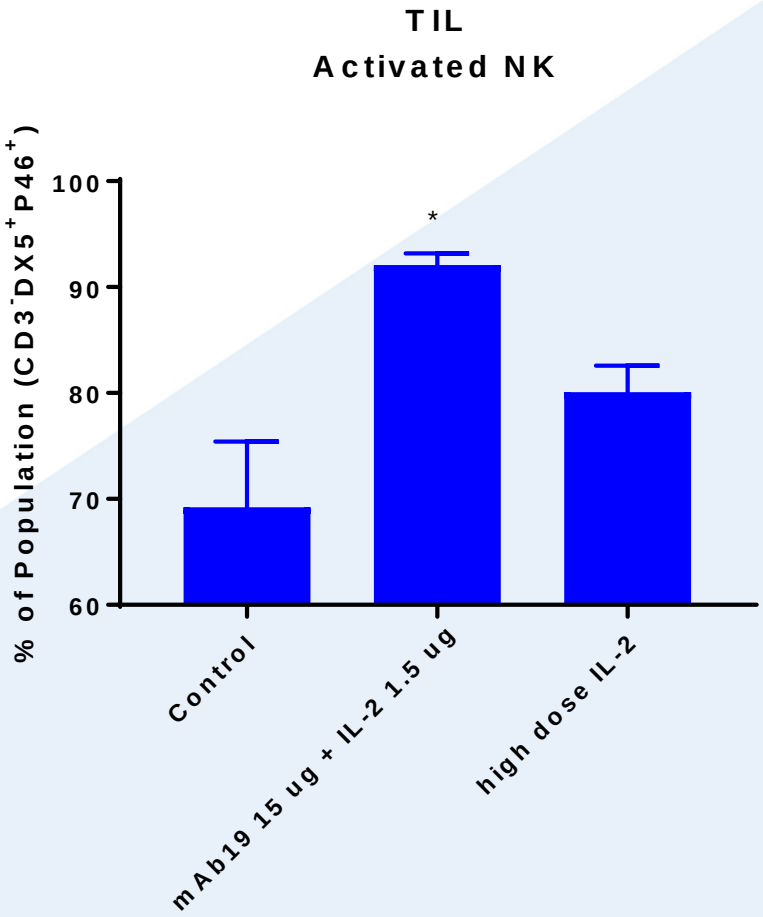
Proof-of-Concept and Initial Dose-Ranging of mAb19 + low-dose IL-2 in the CT26 Colon Carcinoma Model

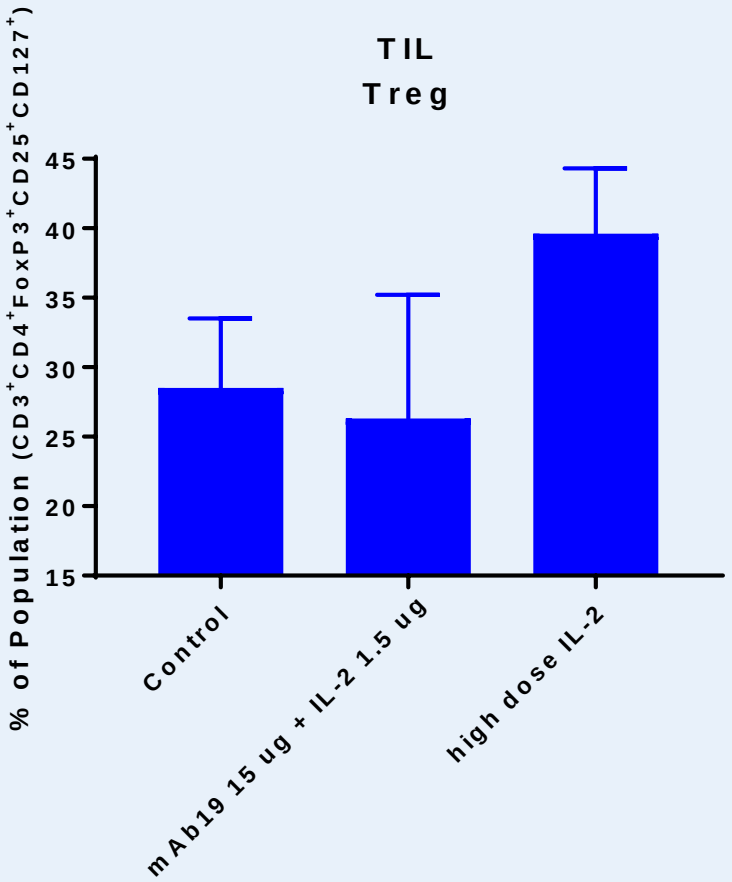


Preferred dose and molar ratio

Q3d dosing i.p. BALB/c mice

mAb19+IL2 Dosing Favors CT26 Tumor Infiltrating NK Expansion without Tregs





The mAb19 Immunotherapy Approach Engages Multiple Anti-tumor Mechanisms

- Enhanced $T_{effectors}$ (including CD8 memory)
- Enhanced innate immunity (e.g. NKs)
- Potentially increases PD-1, PD-L1, MHC cI, cold to hot tumor
- Suitability for combination therapy – e.g. checkpoint inhibitors, tumor-targeted ADCC agents, others