Society for Immunotherapy of Cancer

Phase I trial of IL-15 “superagonist” ALT-803 (IL-15N72D:IL-15RαSu/IgG1 Fc complex) in advanced solid tumors: tolerability and correlates of activity

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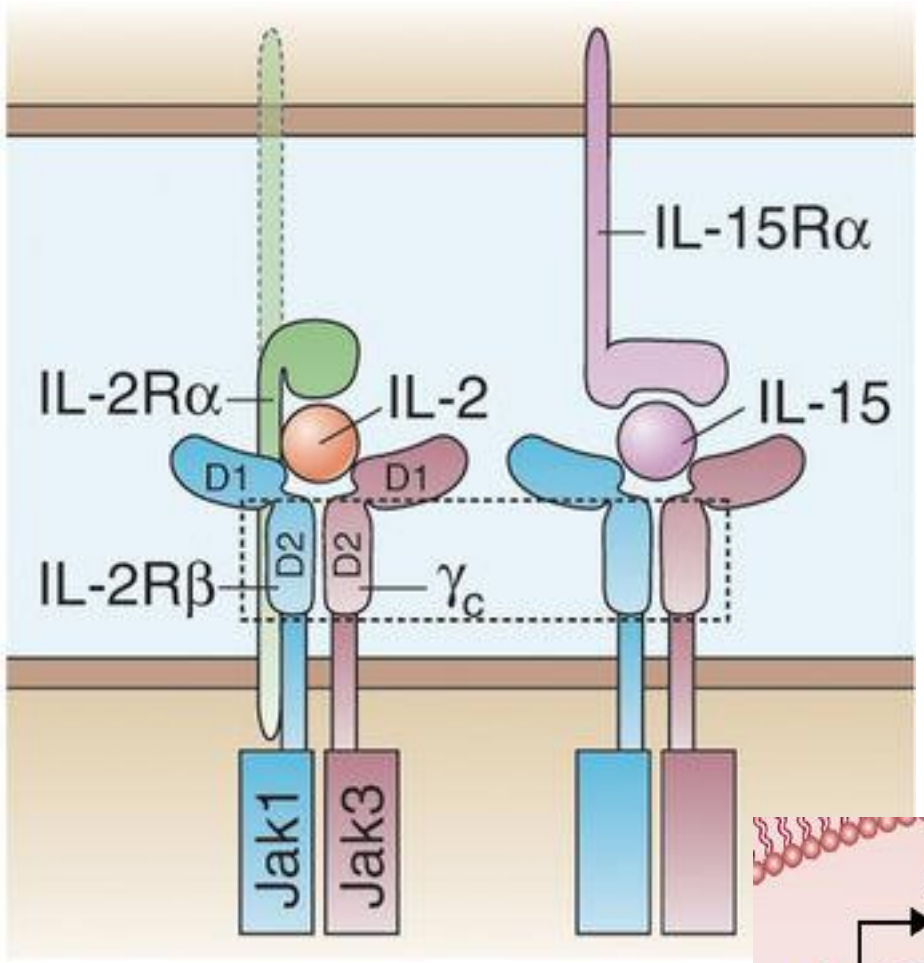
cancer immunotherapy trials network

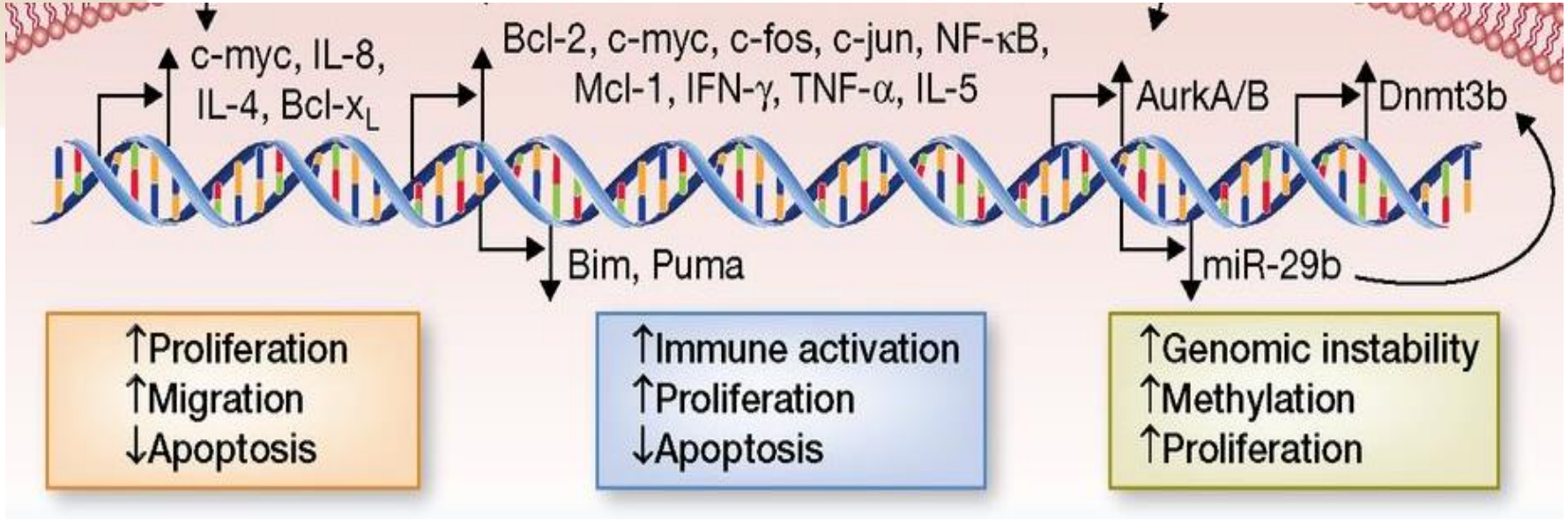
Background—IL-15 and ALT-803

- IL-15 is a common gamma chain receptor (***γ***c) cytokine
  - IL-15 receptor shares a ***β*** chain with IL-2 receptor but ***α*** chain is distinct
- Predominant actions
  - NK cells: activates, expands, promotes survival
  - CD8+ T cells: activates, expands, promotes memory development
- Main source of IL-15: DCs
  - Coordinately expresses IL-15 alpha (***α***) receptor
  - Presents IL-15 in trans via its ***α*** receptor chain, targeting cells expressing ***βγ*** receptors
- Important differences from IL-2
  - Less Treg expansion
  - No activation-induced cell death of CD8+ T cells

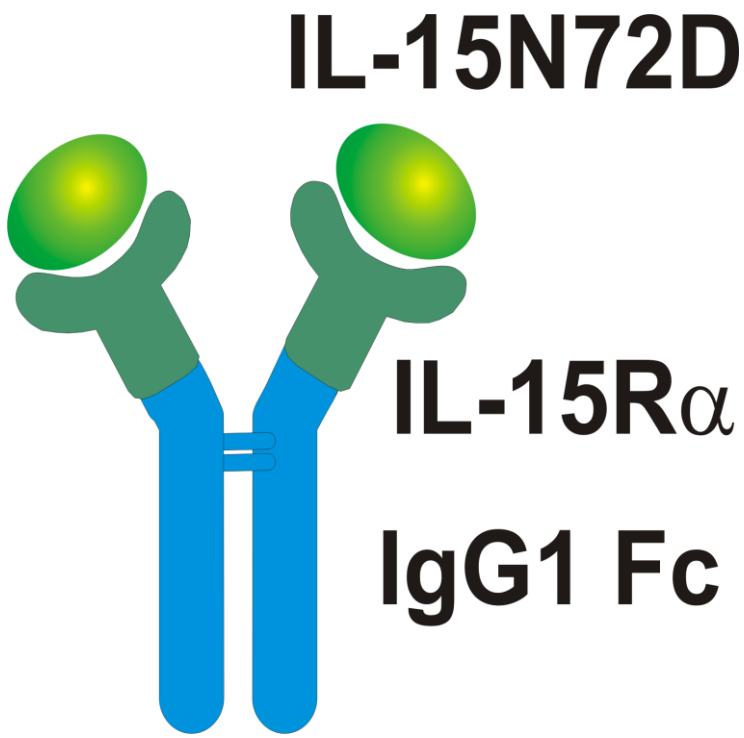


IL-15 signaling

- Signaling through JAK1/STAT3
- Increased expression of anti-apoptotic, proliferation and inflammatory genes



ALT-803: An IL-15 Superagonist Fusion Complex



Improved IL15Rβγ binding activity through N72D mutation and IL15-Rα

30x more active vs IL-15 *in vivo*

Induces IFNγ- and NK and CD8+ T cell proliferation

Increased serum half-life

25 h in vivo vs <40 min for IL-15

Longer residence time in lymphoid tissue for lymphocyte stimulation

Zhu X, et al. *J Immunol.* 2009;183(6):3598-3607; Han KP, et al. *Cytokine.* 2011;56(3):804-810; Xu W, et al. *Cancer Res.* 2013;73(10):3075-3086; Rhode PR, et al. *Cancer Immunol Res*. 2016 Jan;4(1):49-60.

Trial rationale and design

- Eligibilities
  - Advanced solid tumors: melanoma, head and neck, lung, sarcoma, renal cancer (others eligible but not treated)
  - Unlimited prior standard therapy
  - Adequate organ function, no active brain metastases

- Therapy
  - Initial route i.v. weekly, 4 consecutive weeks of every 6-week cycle
  - Subsequent route s.c. on the same schedule
  - Protocol amended to allow intratumoral injection but only 2 patients treated

Patient demographics

- 26 patients enrolled between 5/2014 and 7/2017
  - 11 received i.v. ALT-803 (0.3, 0.5, 1, 3, and 6 mcg/kg)
  - 13 treated with s.c. ALT-803 (6, 10, 15 and 20 mcg/kg)
  - 2 received intratumoral ALT-803 at 10 mcg/kg followed by 15 mcg/kg s.c.
- Histologies
  - 9 melanoma
  - 6 renal cancer
  - 3 head and neck squamous cancer
  - 7 NSCLC
  - 1 soft-tissue sarcoma

Highest AE grade/dose cohort for SC dosing

Adverse event	Total pts (N=13)	Pts at 15 or 20 mcg/kg (N=7)	Highest AE Grade (s.c. dosing)			
			6 mcg/kg	10 mcg/kg	15 mcg/kg	20 mcg/kg
Injection site reaction	11	7	2	2	2	1
Fatigue	7	4		2	2	2
Hypoalbuminemia	6	4	2	2	2	2
Anemia	5	4		2	3	2
Fever	5	2	1	2	2	2
Lymphopenia	4	3		3	4	2
Arthralgia	3	2		2	1	
Nausea/emesis	3	2		2	1	

Toxicities of i.v. dosing at highest dose of 6 mcg/kg: grade 1-2 fatigue, nausea, chills and fever.
One pt with lung CA at 20 mcg/kg s.c. developed reversible cardiomyopathy unlikely related to ALT-803

Skin reactions with s.c. ALT-803

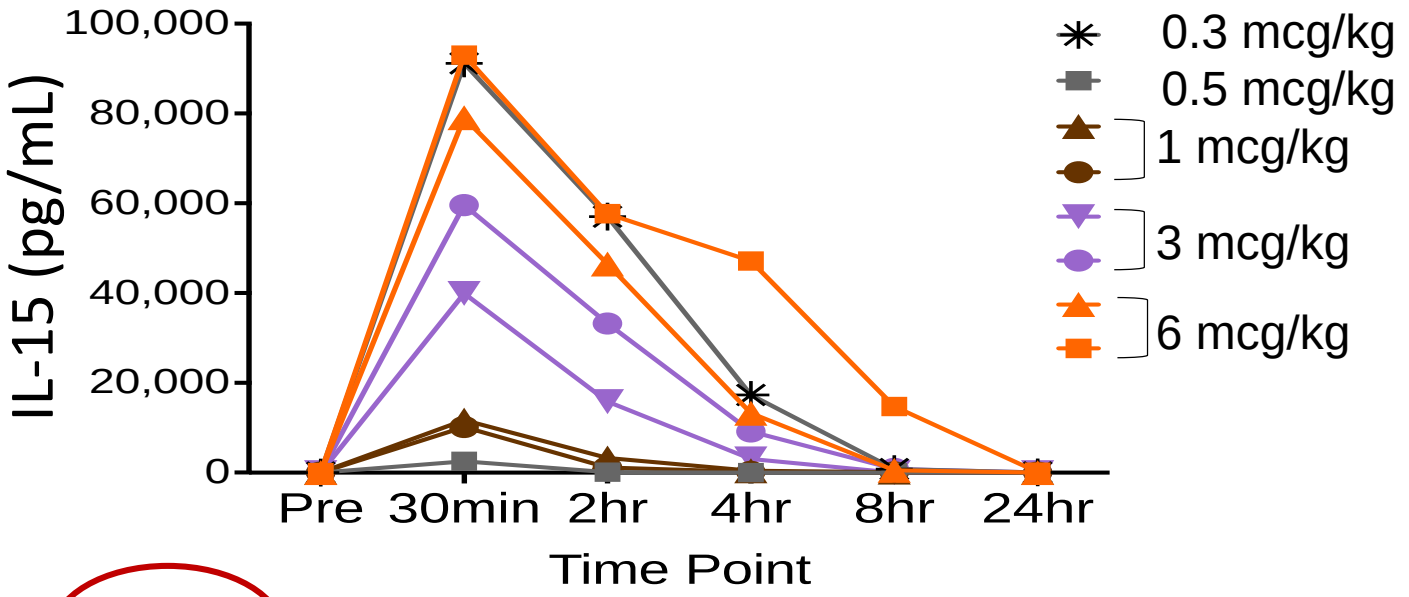
Common in patients receiving ≥6 mcg/kg doses; no recall at previously resolved site w/ H1 and H2 blocker premeds

Onset ~3 days post-injection, peak at ~5 days and resolving by 7 days.

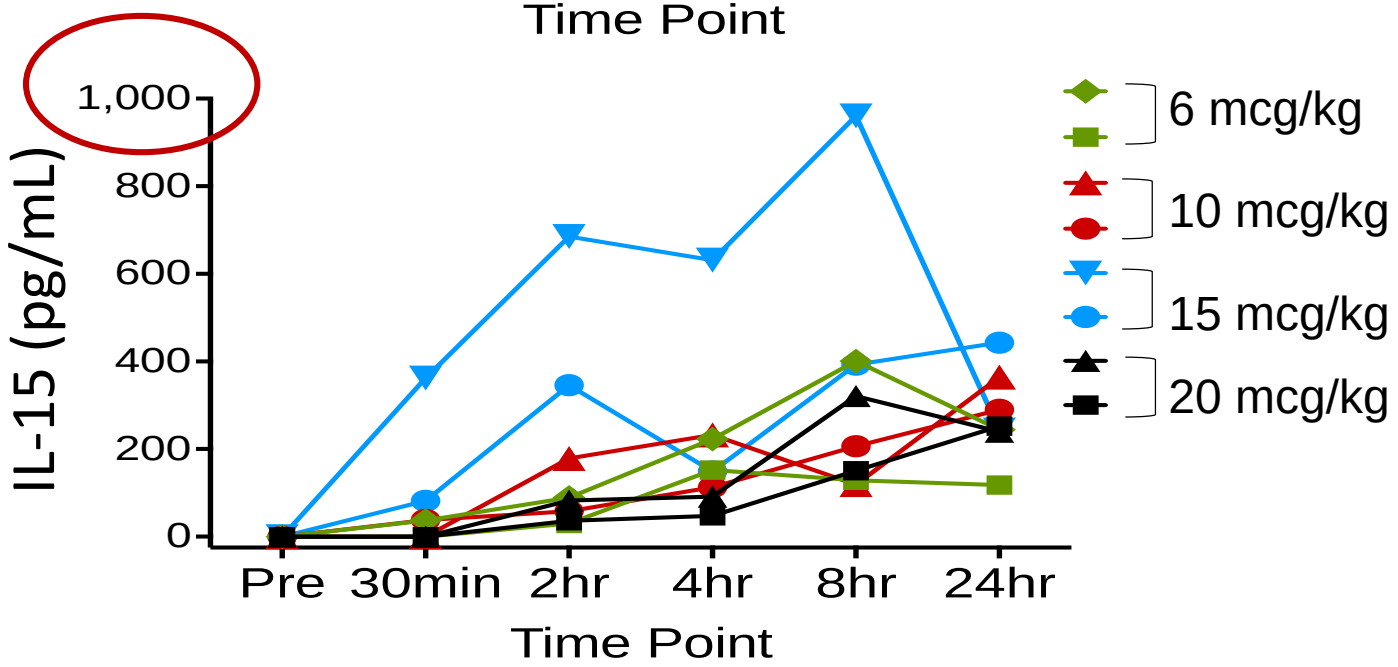
Histology: intense perivascular lymphomononuclear infiltrate (CD3+ [~50% CD4+ and 50% CD8+] and CD68+) with rare CD20+ B and CD56+ NK/NKT cells

ALT-803 Pharmacokinetics

IV

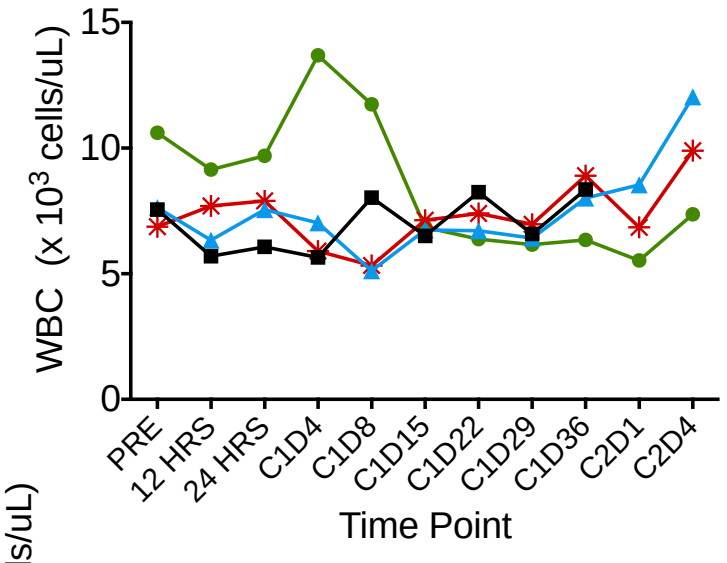


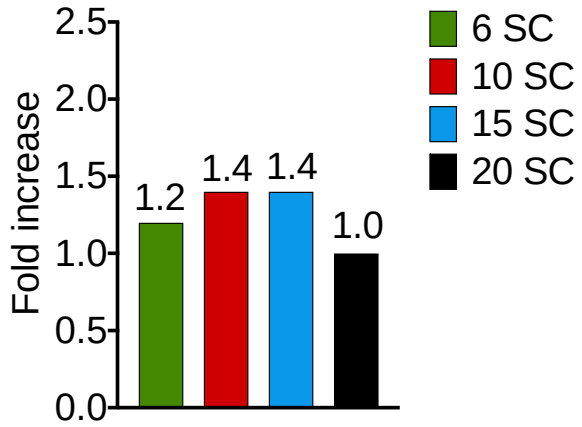
SC



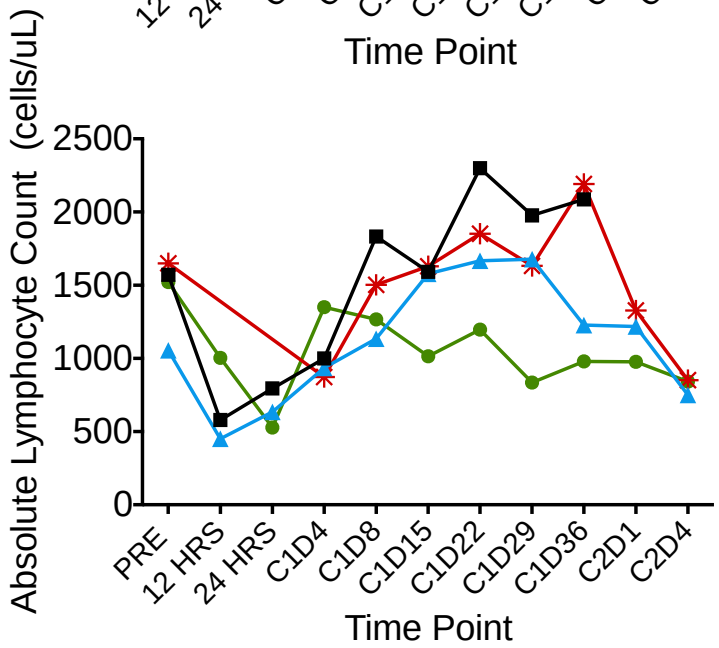
Effect of SC ALT-803 on total WBC and absolute lymphocyte counts

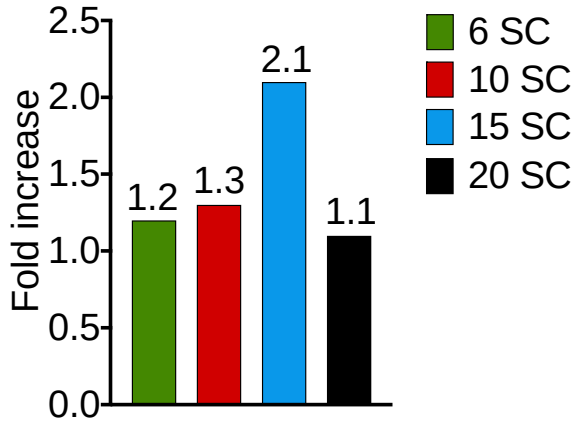
WBC





ALC





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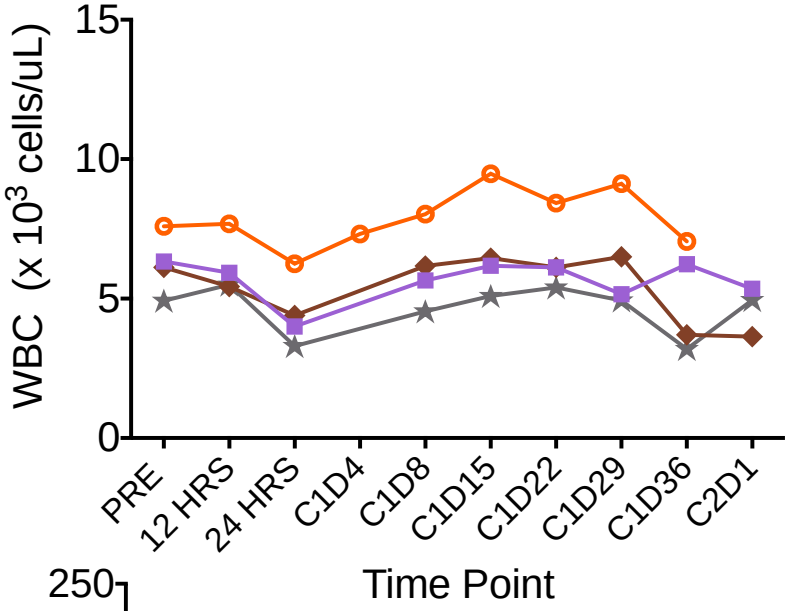
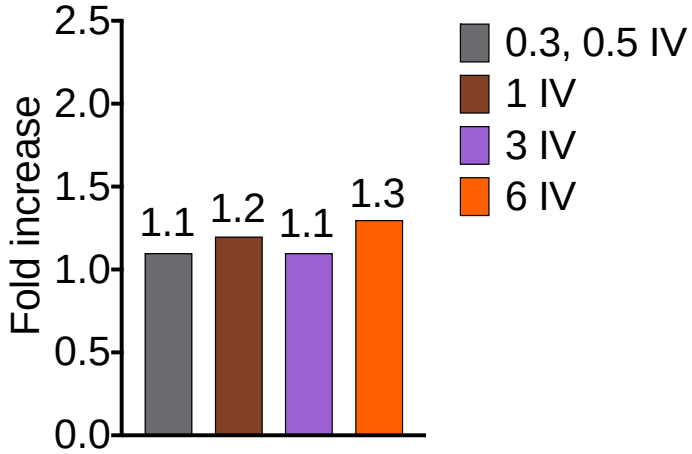
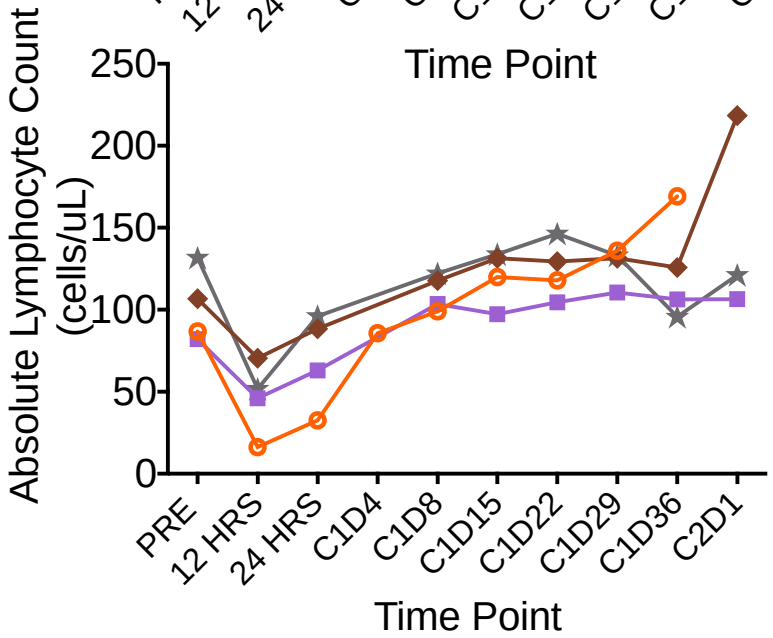
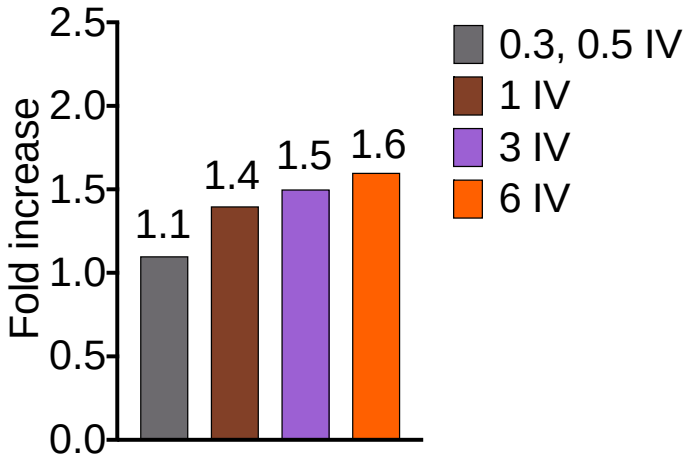




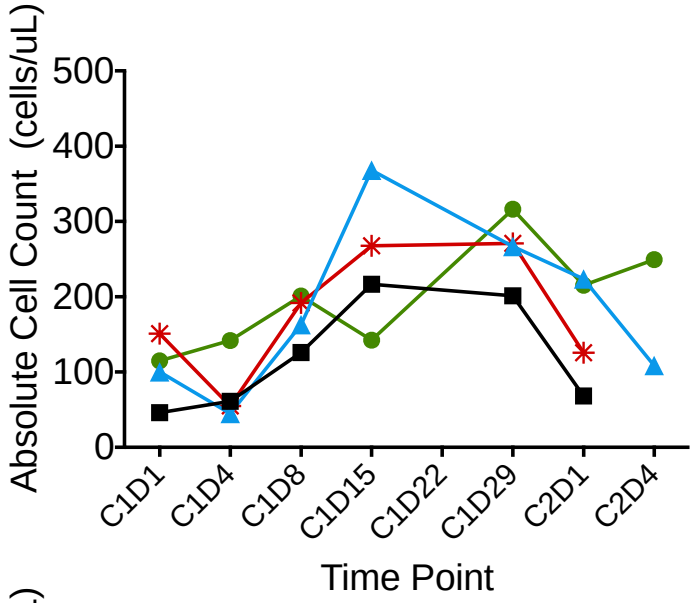
ALC

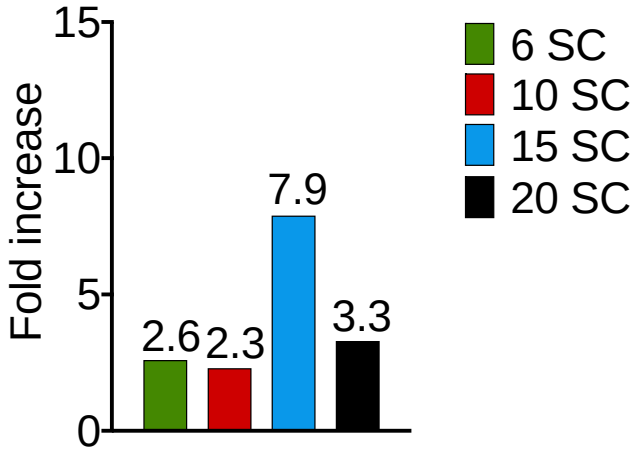




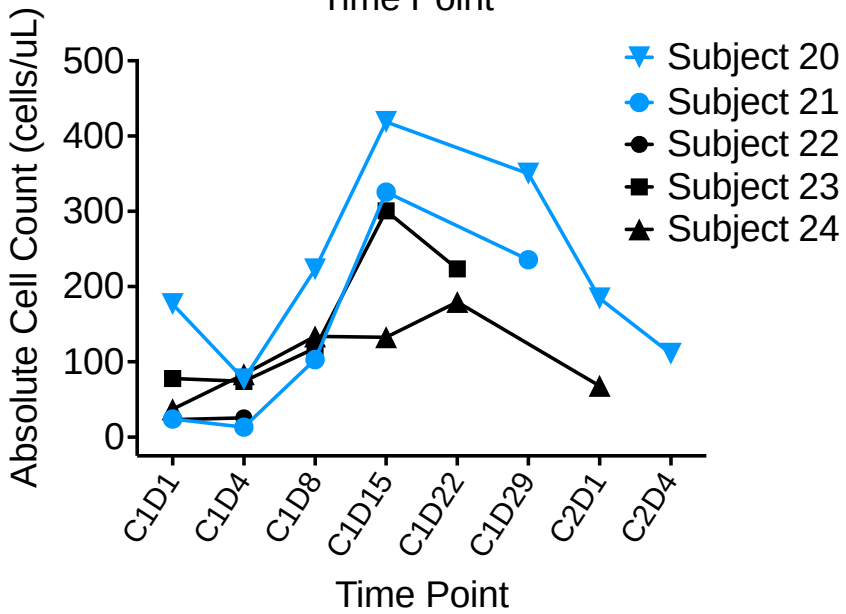
Effect of SC ALT-803 on Circulating Total CD3-CD56+ NK cells

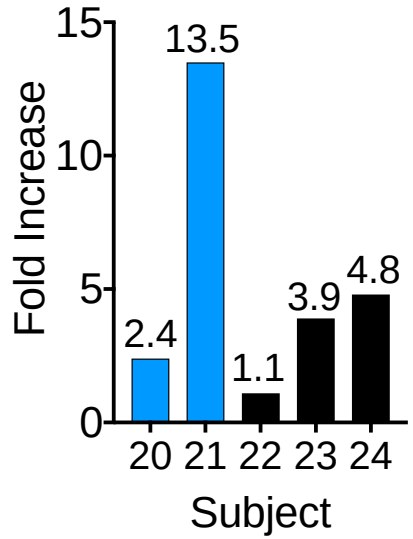
By Dose Cohort





By Subject
(15 & 20ug/kg)

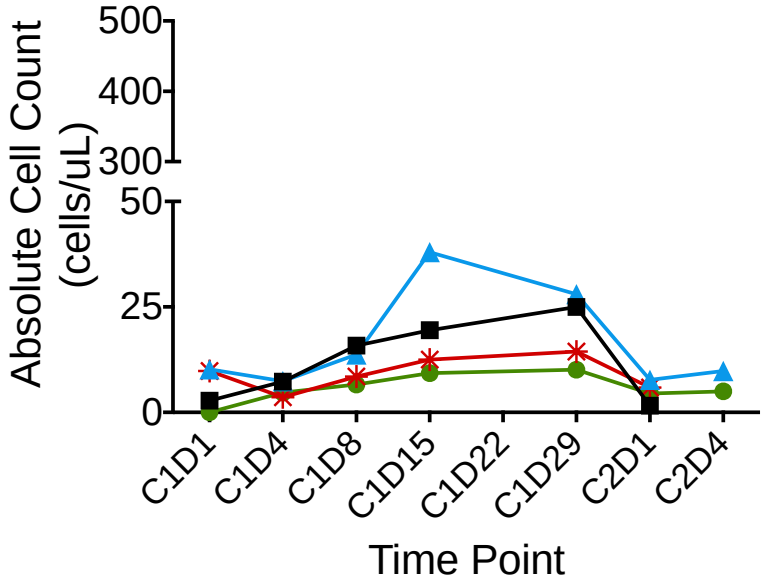


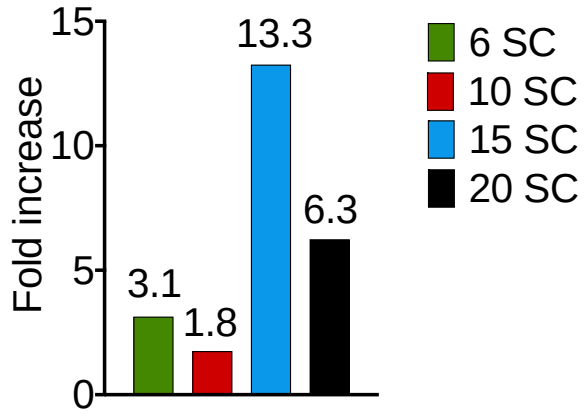


Effect of i.v. ALT-803 on total CD3-CD56+ cells not shown as not significant; CD8+ cells also not shown for similar reason

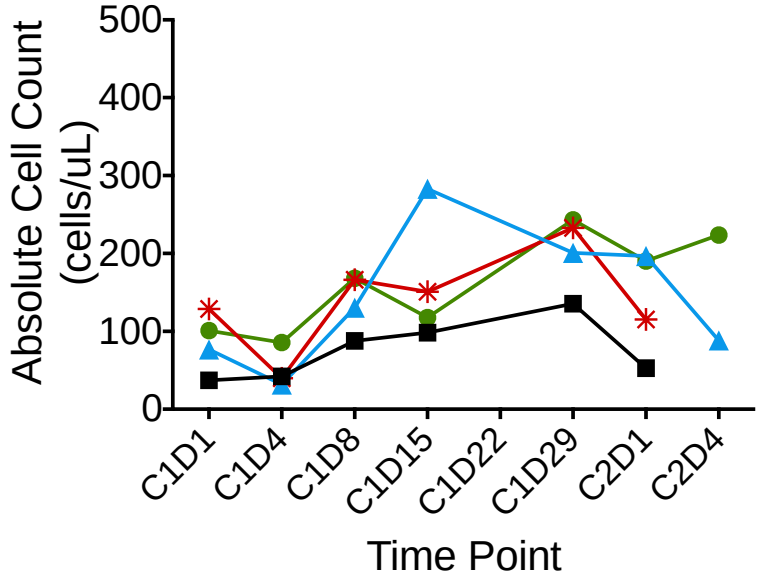
Effect of SC ALT-803 on Circulating NK cell Subsets

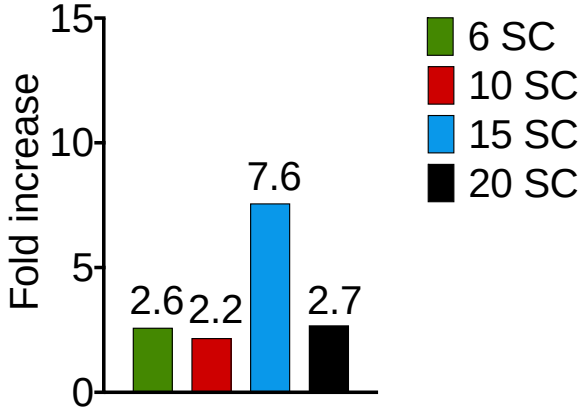
CD56^{bright} NK





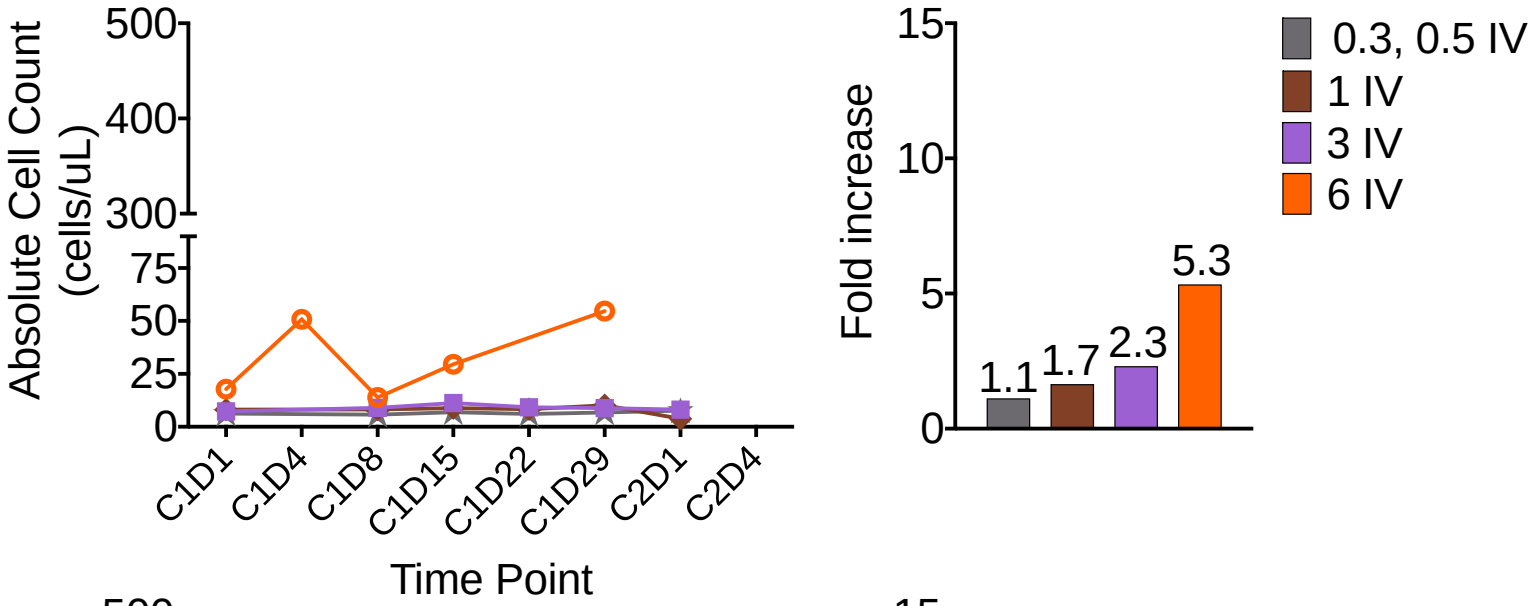
CD56^{dim} NK



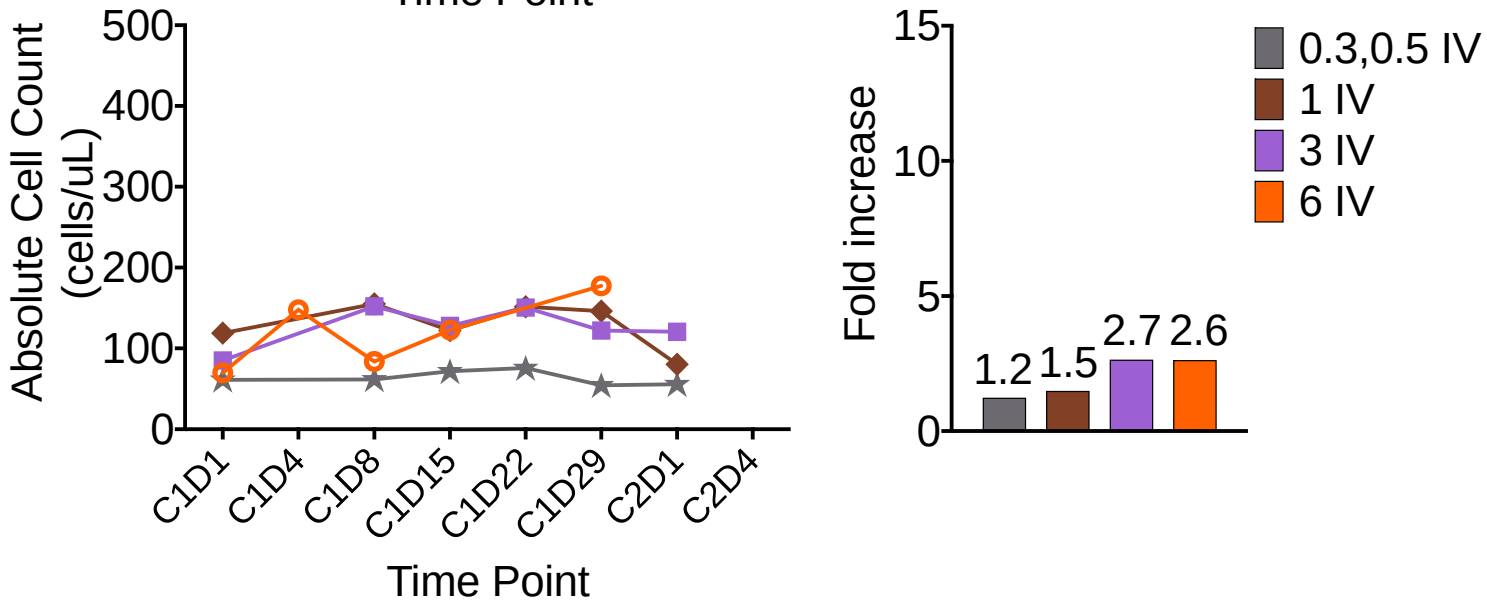


Effect of IV ALT-803 on Circulating NK cell Subsets

CD56^{bright} NK

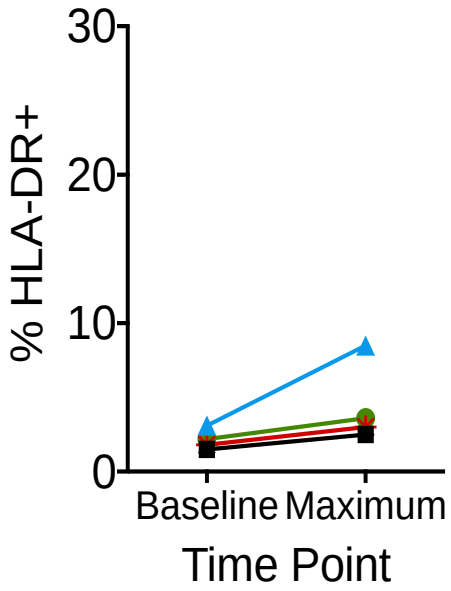


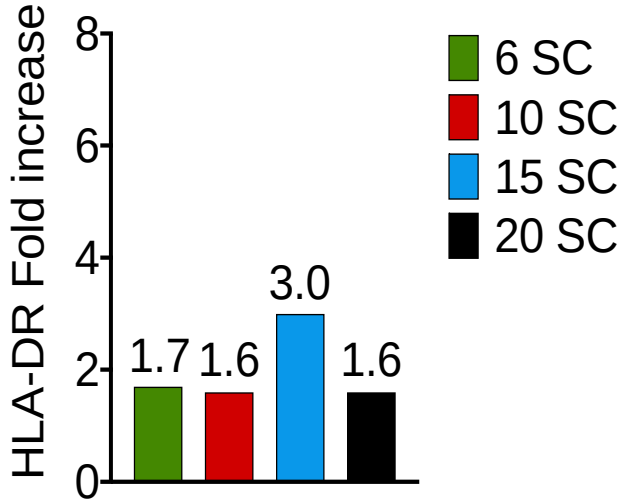
CD56^{dim} NK



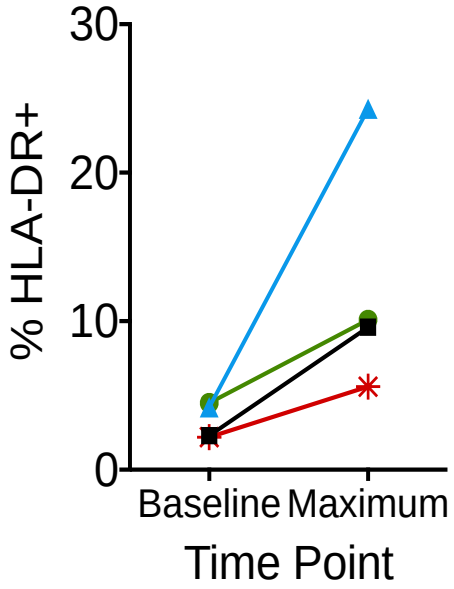
Effect of SC ALT-803 on T cell HLA-DR Expression

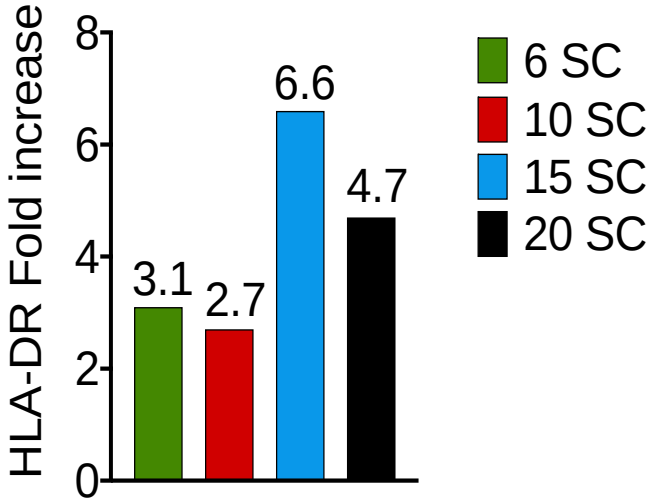
CD4+





CD8+





Effect of IV ALT-803 on T cell HLA-DR Expression

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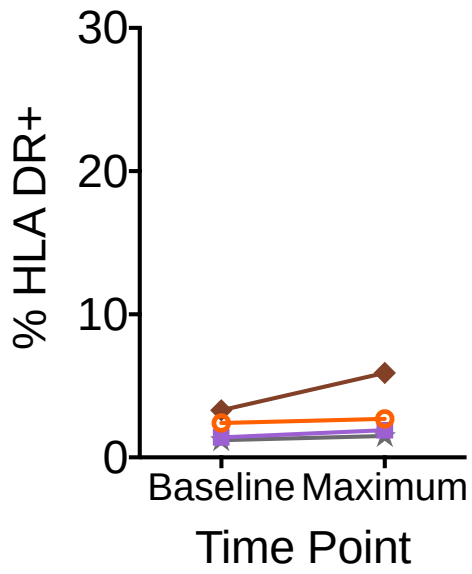
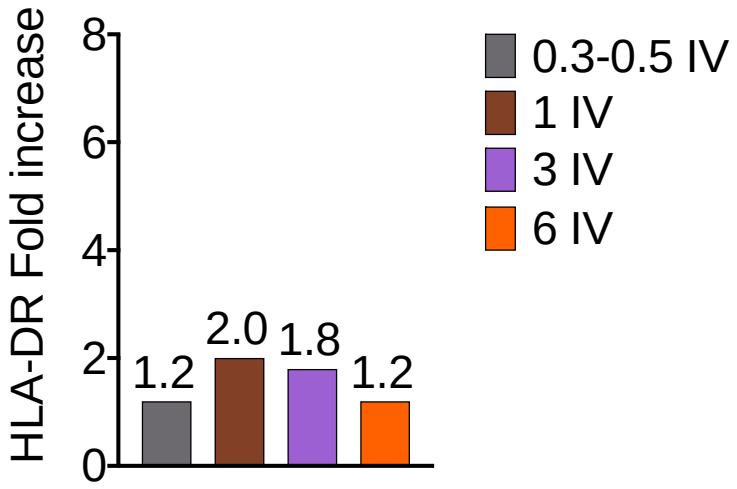
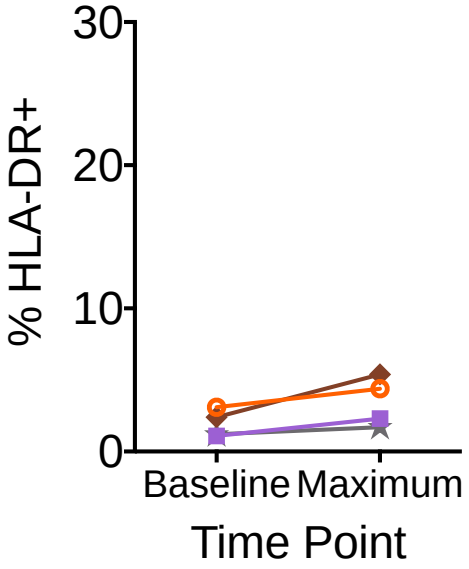
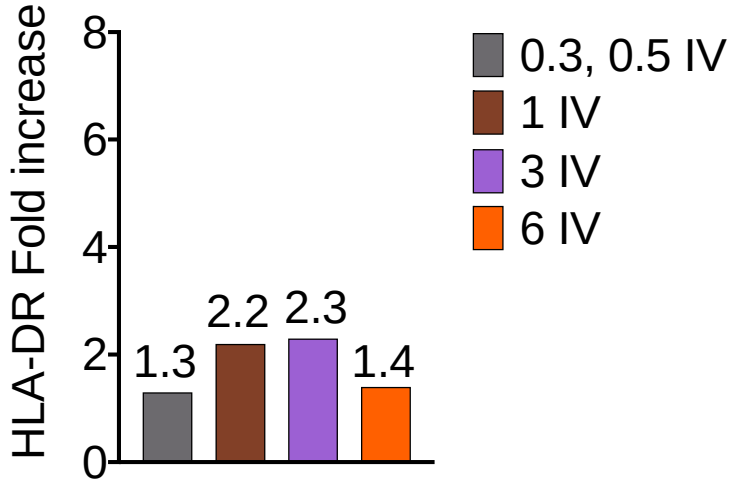


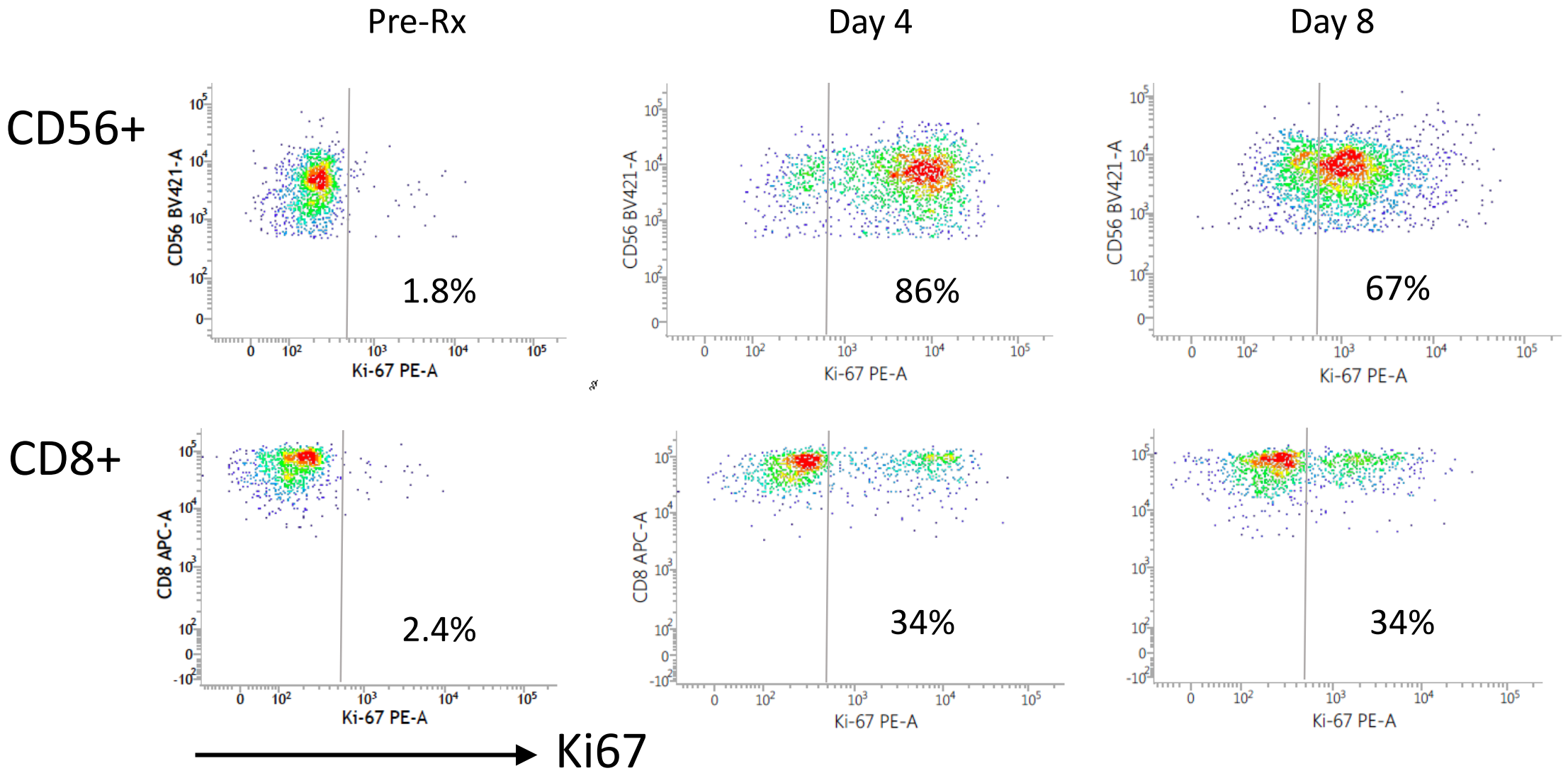


CD8+





Ki67+ cells – representative patient



Conclusions and future plans

- Peak ALT-803 level at 8+ hours post-s.c. dosing
- Excellent tolerance of s.c. ALT-803 up to 20 mcg/kg weekly
  - Skin reactions at injection site likely depot effect
  - Systemic toxicity mild, reversible
- Next step: testing ALT-803 in combination
  - With antitumor Abs for B-cell malignancies—human trials ongoing (NHL with rituximab) or planned (myeloma with daratumumab)
  - With immune checkpoint Abs—substantial animal data/some human (lung cancer) to overcome resistance to PD-1 block→upfront testing
    - Ongoing for lung cancer
    - In development for SCC of head and neck
    - In development for melanoma

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