Rapid and Robust B Cell Depletion in Preliminary Results of a Phase 2 Study of Ublituximab, Novel Glycoengineered Anti-CD20 Mab, RMS Patients

Amy Lovett-Racke, PhD

May 26, 2017

Slide 1

2 Go to slide master view and add unique titles to all slides. They will not be visible, but will be used by screen reader

tOSU uCOM, 12/28/2015

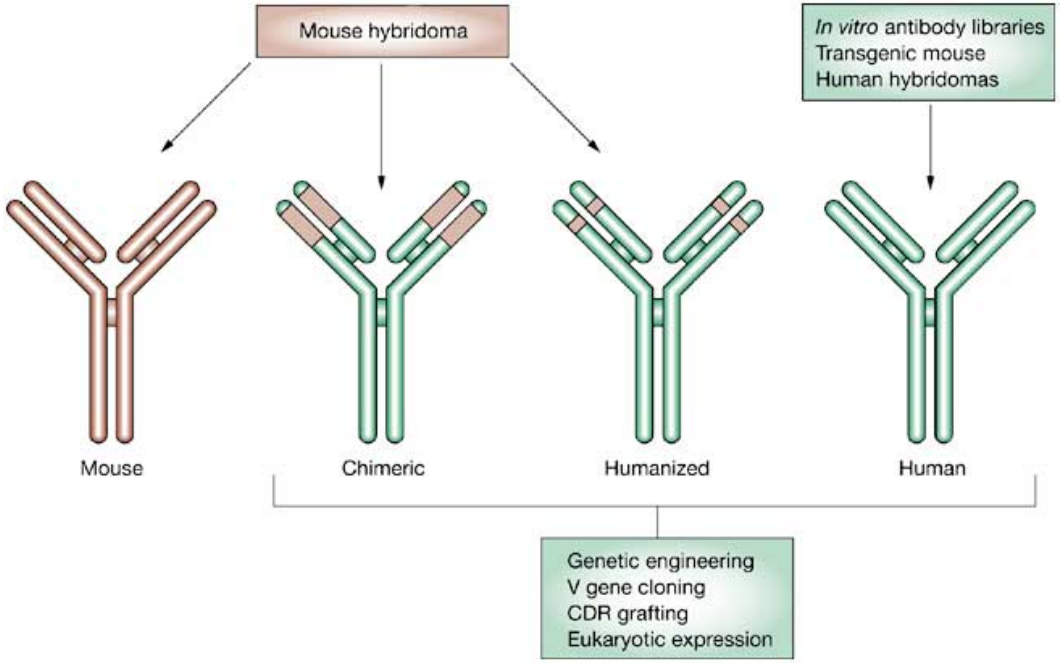
Disclosures

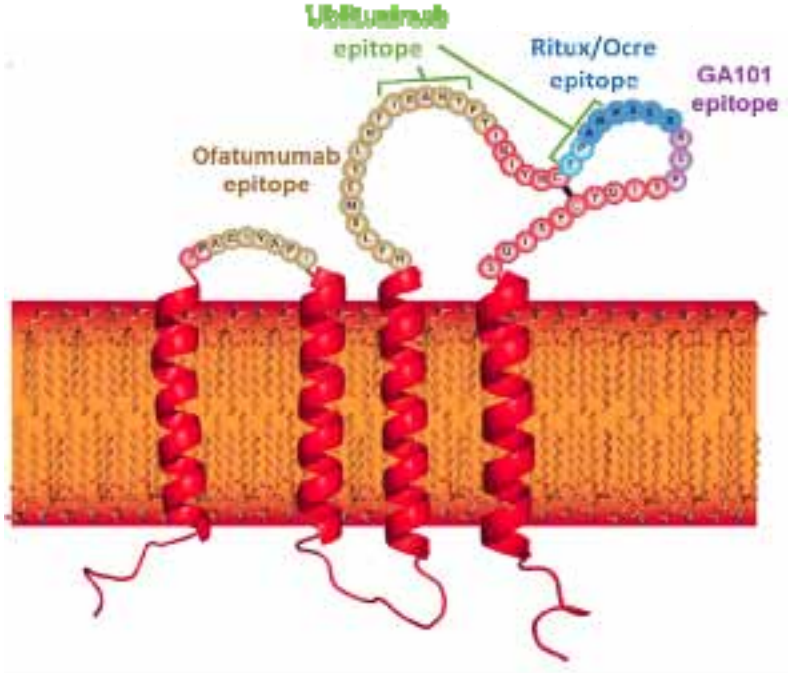
- This clinical trial and immune profile study was funded by TG Therapeutics, New York.

- Grants from these agencies support additional research in my lab.
  - National Institutes of Health
  - National Multiple Sclerosis Society
  - Strategic Pharmaceutical Academic Research Consortium

Background

- Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab





CD20 Antibody Epitopes

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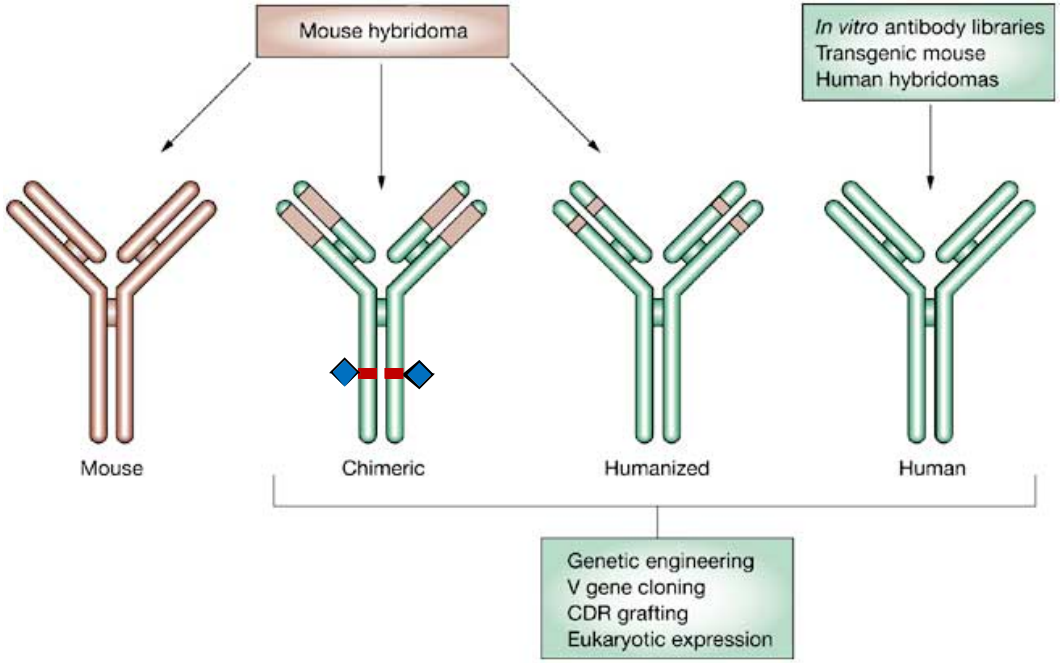

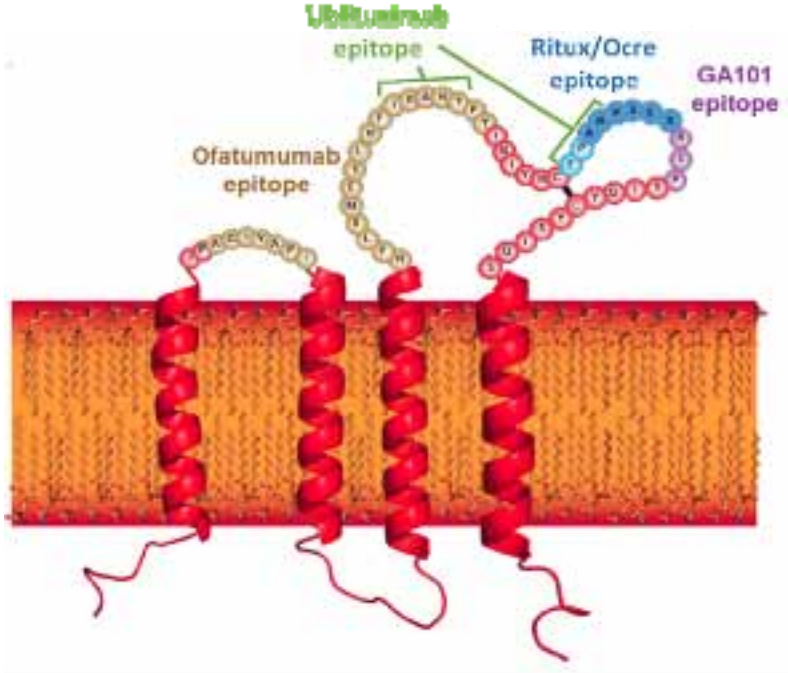

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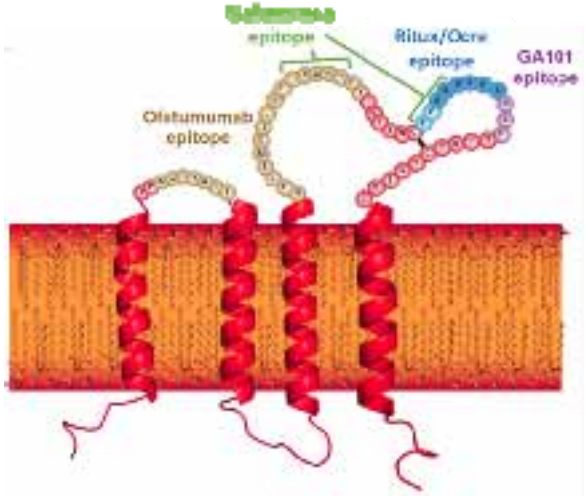

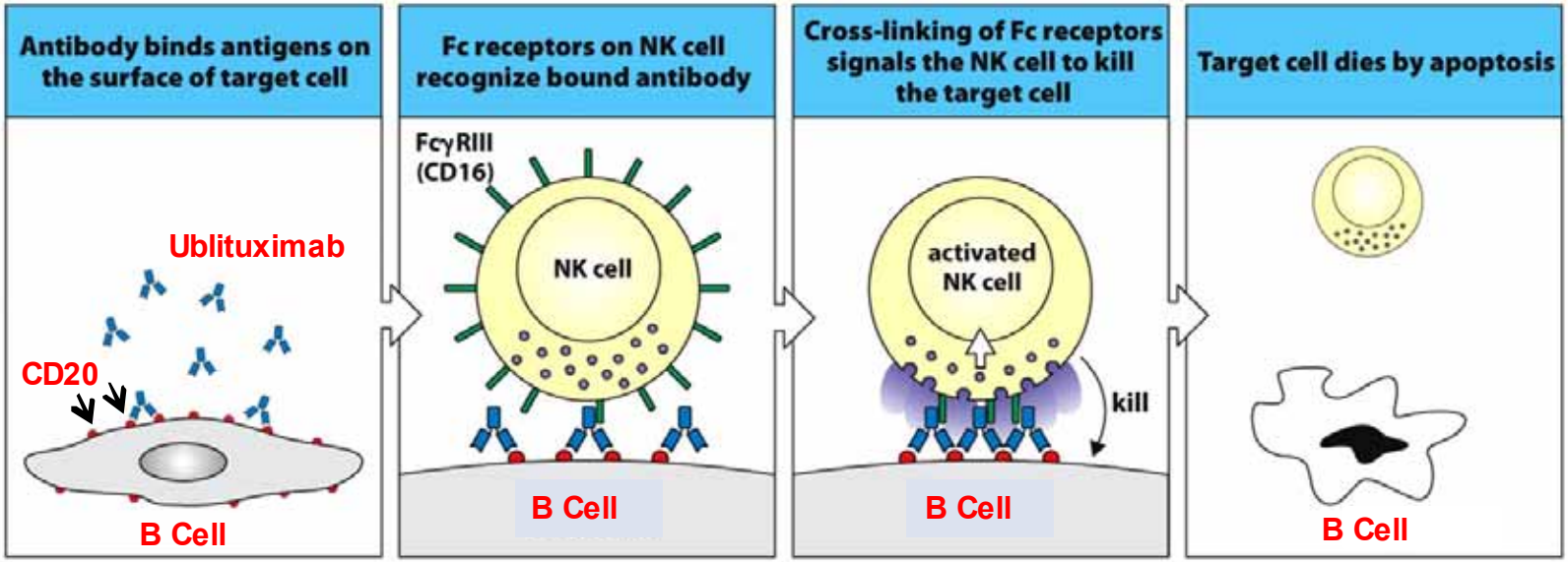

Figure 9.43 The Immune System, 3ed. (© Garland Science 2009)

Background

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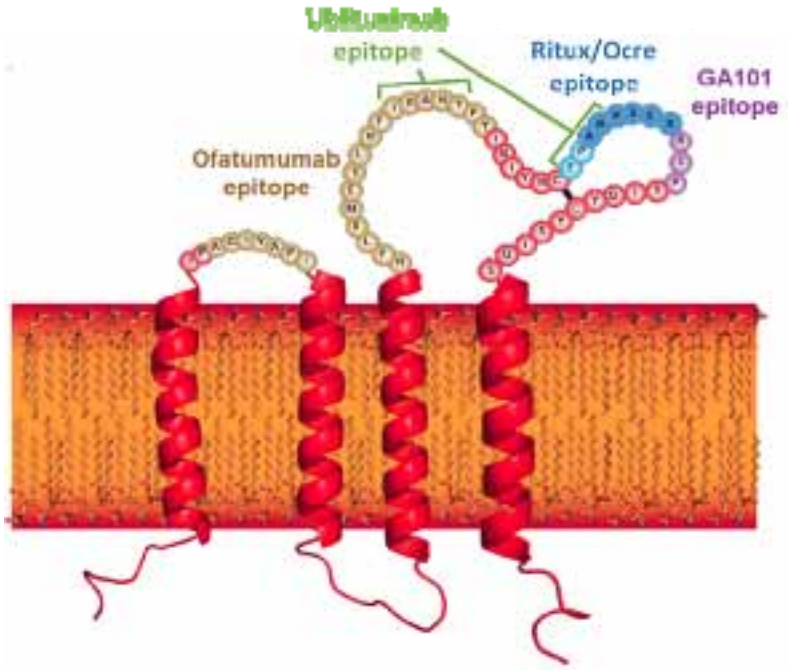
- Ublituximab was originally developed for B cell lymphomas, in response to the need for enhanced potency to deplete malignant B-cells with reduced expression of CD20, that are able to evade depletion via standard anti-CD20 therapies
- To date, over 500 oncology patients have been treated with ublituximab, alone and in combination with other agents, and two large Phase III trials (UNITY and GENUINE) for B cell lymphomas are currently underway. Completed studies have demonstrated robust effects on all endpoints and excellent safety and tolerability
- Evidence for the role of B cells in the pathogenesis of Multiple Sclerosis and the marked efficacy of anti-CD20s tested thus far prompted us to conduct TG1101 RMS201, a Phase IIa proof of concept study in relapsing MS



CD20 Antibody Epitopes

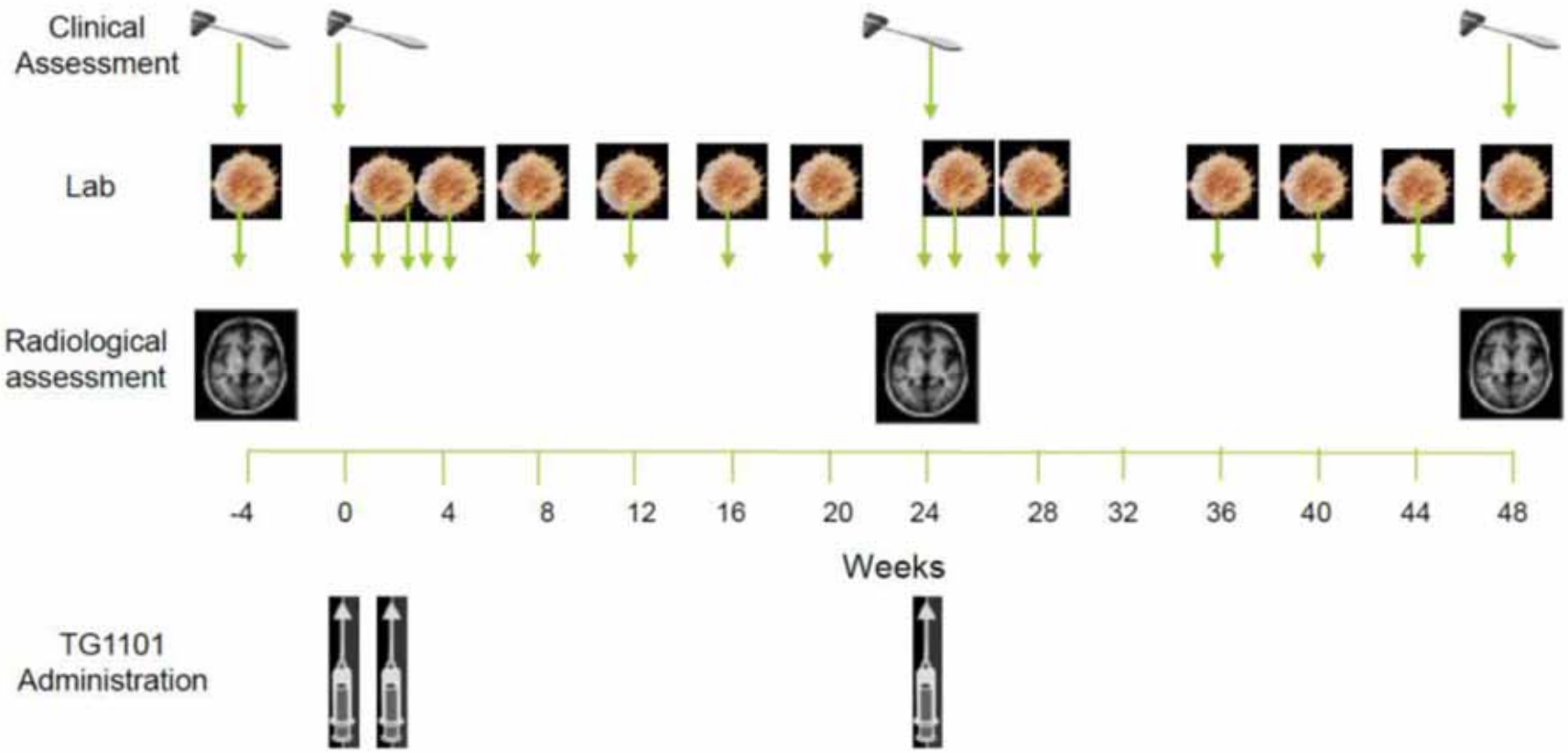
Objective

- TG1101 RMS201 (clinicaltrials.gov NCT02738775) is a randomized, placebo controlled, multi-center study to test the safety and efficacy of ublituximab, at doses markedly less than used in ongoing Phase 3 oncology studies, and at a range of infusion times, with a goal of rapid infusions

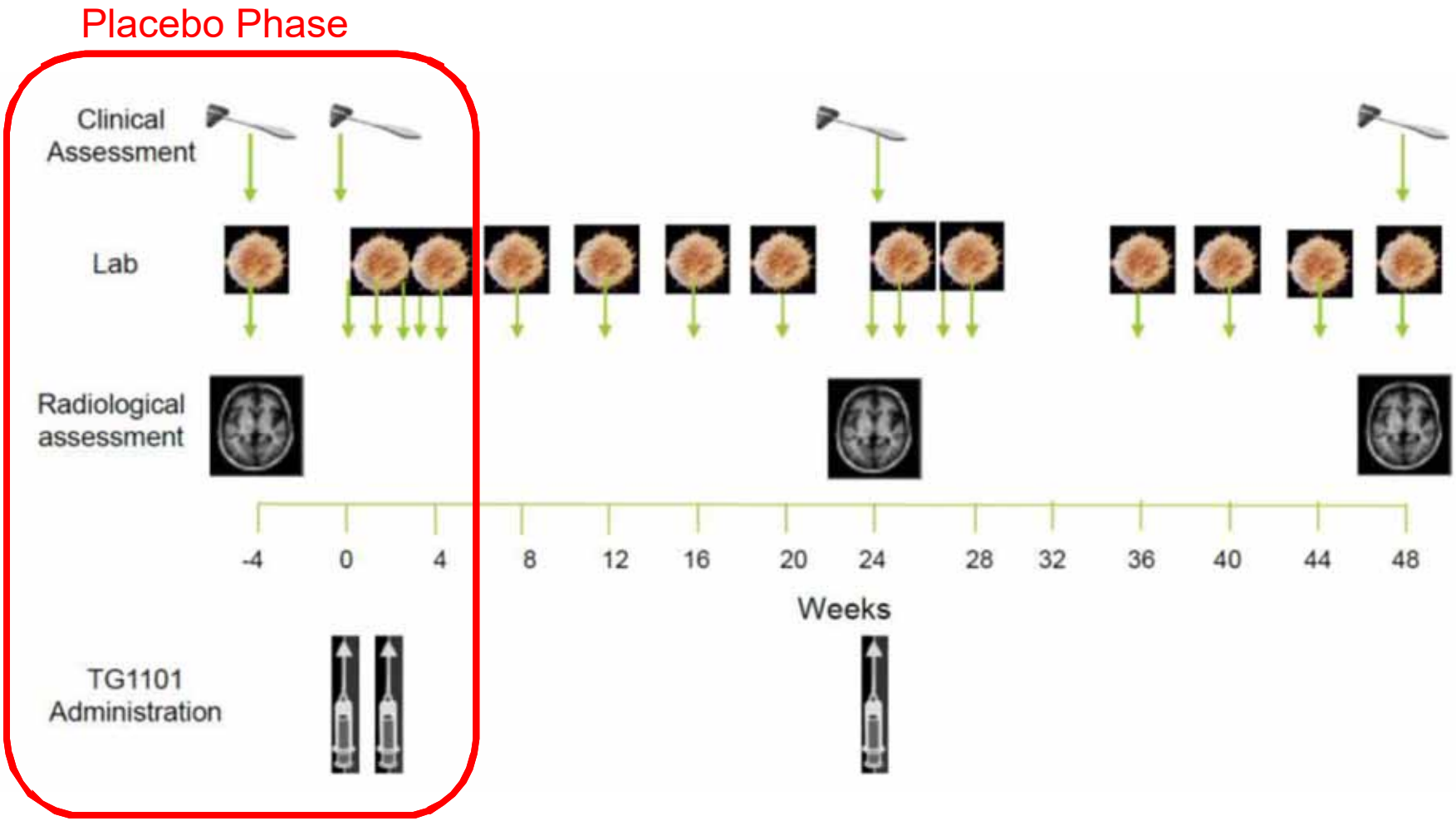
- Primary endpoint is the Responders Rate, defined as percent of subjects with ≥95% reduction in peripheral CD19+ B-cells within 2 weeks after the second infusion (day 15)

- The TG1101 RMS201 study in ongoing and will incorporate additional clinical and MRI measures (see Study Design). We report preliminary results of B cell depletion after the second infusion

Study Design



Study Design



Study Design

	Randomization	Treatment Period		
Cohort	Subjects and treatment	Day 1/ infusion time	Day 15/ infusion time	Week 24/ infusion time
1	**Placebo (n=2)**	**Placebo / 4h**	**Placebo / 3h**	-
	UTX (n=6)	150 mg / 4h	450 mg / 3h	450 mg / 1.5h
2	**Placebo (n=2)**	**Placebo / 4h**	**Placebo / 1.5h**	-
	UTX (n=6)	150 mg / 4h	450 mg / 1.5h	450 mg / 1h
3	**Placebo (n=2)**	**Placebo / 4h**	**Placebo / 1h**	-
	UTX (n=6)	150 mg / 4h	450 mg / 1h	600 mg / 1h

Study Design

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3	**Placebo (n=2)**	**Placebo / 4h**	**Placebo / 1h**	-
	UTX (n=6)	150 mg / 4h	450 mg / 1h	600 mg / 1h

Three additional cohorts have been added to further reduce infusion times to 1 hr.

Patient Demographics

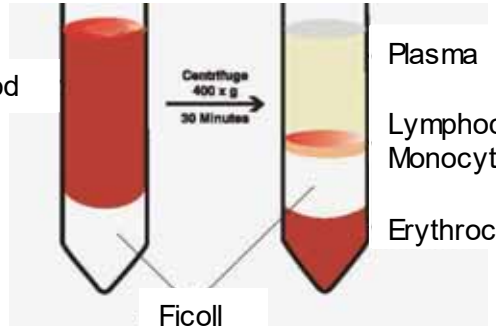
Baseline Demographics				
Cohort	**Subjects and Treatment**	**Age (Years)[1]**	**Gender (% Female)**	**Disease Duration (Years)[1,2]**
1	Placebo (n=2)	39±14	50%	15.5±20.4
	UTX (n=6)	43±12	67%	7.1±7.3
2	Placebo (n=2)	44±1	0%	0.9±1.2
	UTX (n=6)	33±10	100%	5.3±6.4
3	Placebo (n=2)	38±7	50%	11.5±7.5
	UTX (n=6)	40±11	67%	13.4±10.0
Total	**n=24**	**40±11**	**67%**	**8.8±9.0**

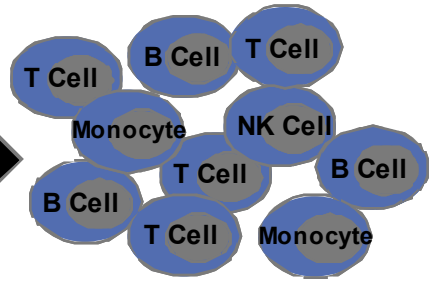
[1] Mean ± Standard Deviation

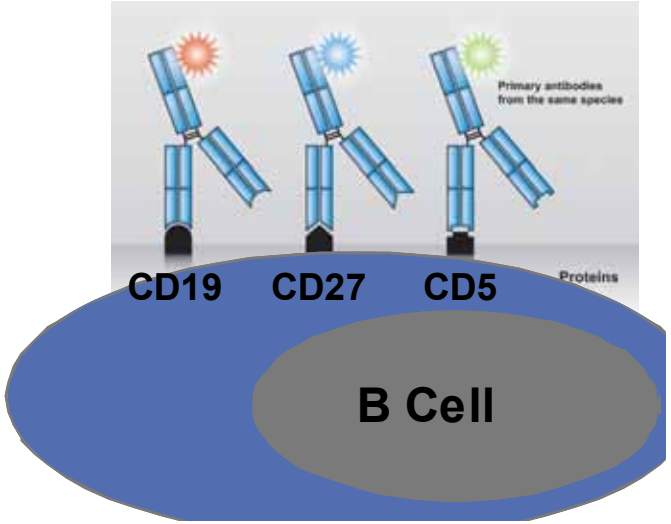
[2] Distribution of times from diagnosis: 11 subjects (45.8%) were less than 5 years, 7 (29.2%) were 5-10 years, and 6 (25%) were greater than 10 years.

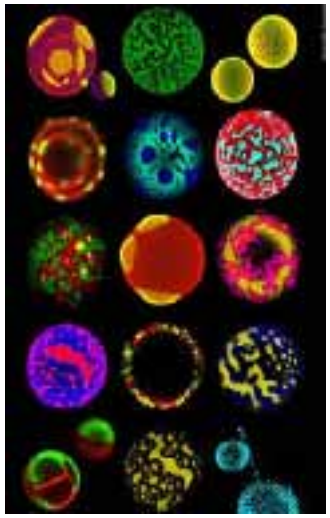
Immune Profiling

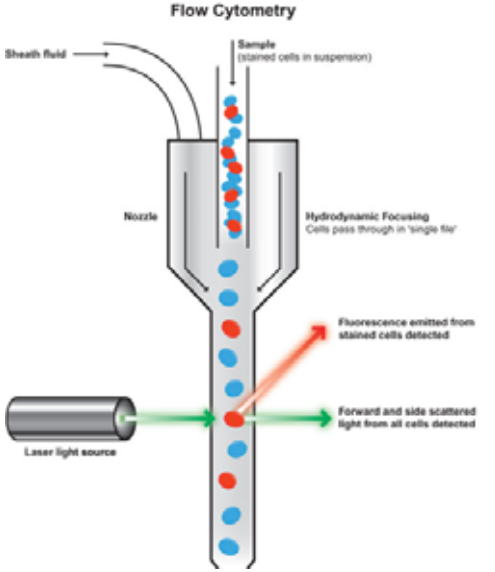
Blood is collected in heparinized tubes and shipped to OSU.











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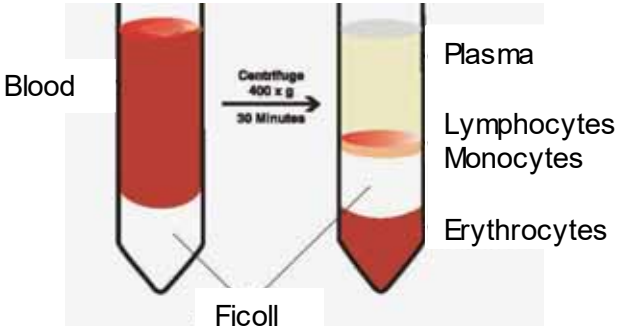
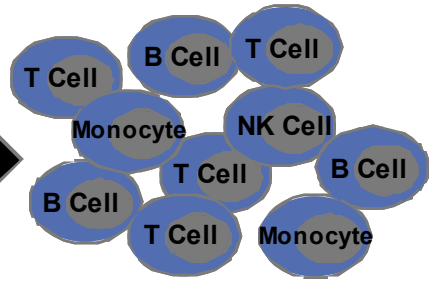
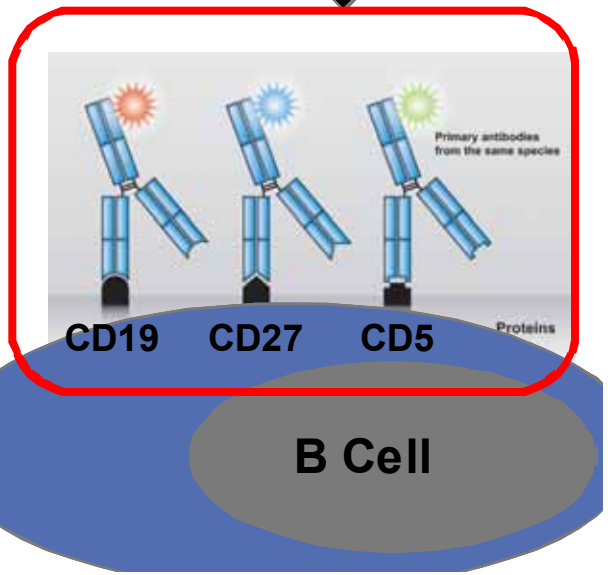
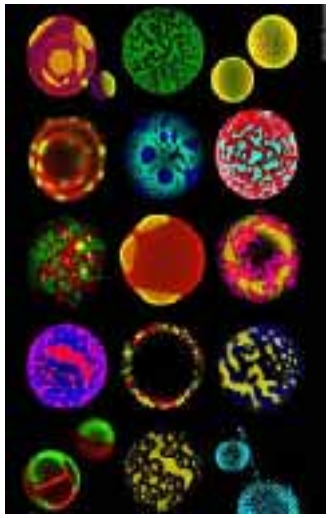
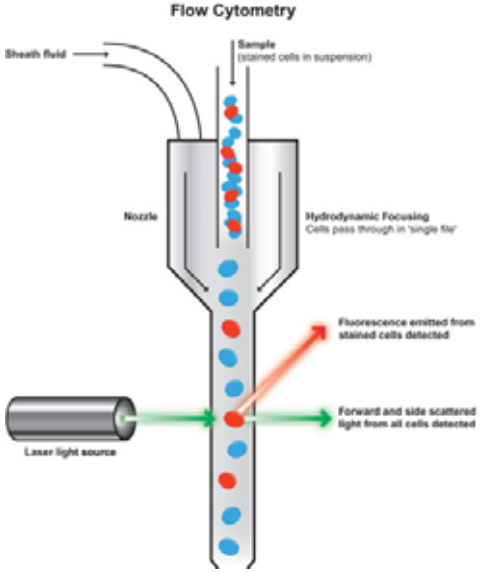










Immune Profiling

B/NK Cell Panel
CD3
CD19
CD5
CD1d
CD27
CD56
CD16

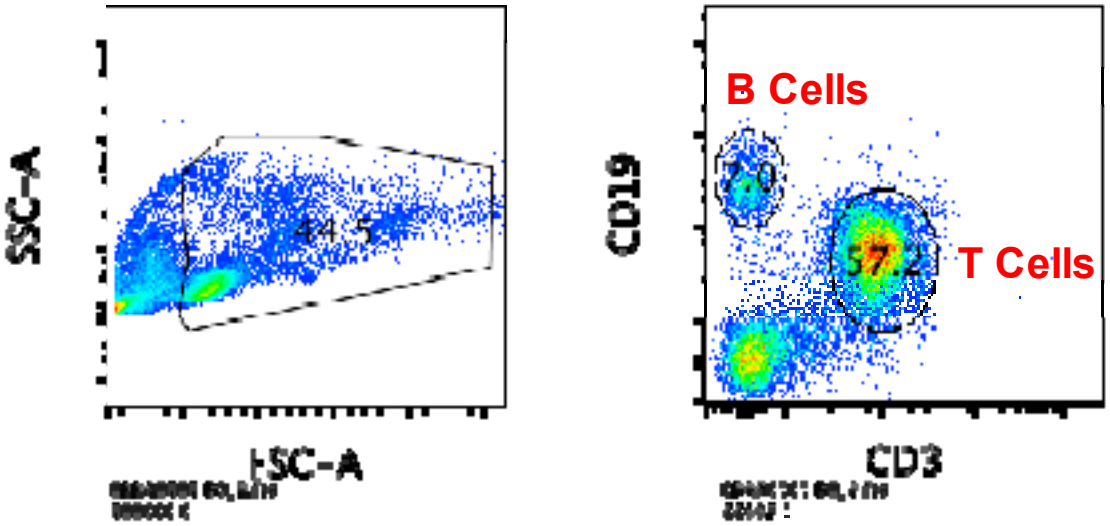
Activated/Reg B Cell Panel (PMA/Ion/CpG)
CD3
CD19
CD5
CD1d
CD27
IL-10
IL-27/35

T Cell Panel
CD3
CD4
CD8
CD45RA
CD27

Treg Cell Panel
CD3
CD4
CD25
FoxP3

Helper T Cell Panel (PMA/Ion)
CD3
CD4
CD45RA
IL-10
IFNγ
GM-CSF
IL-17

B Cell Analysis



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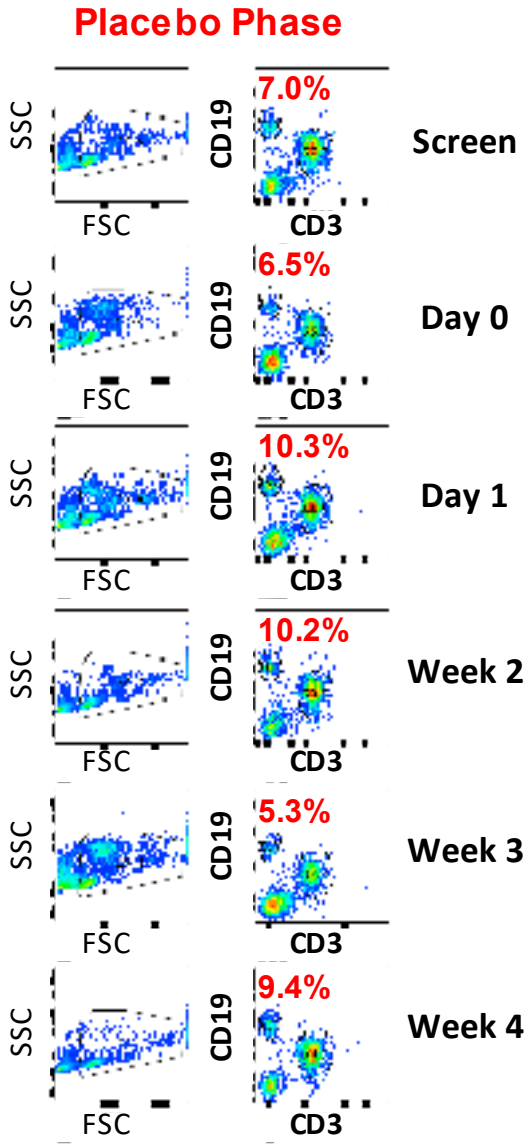

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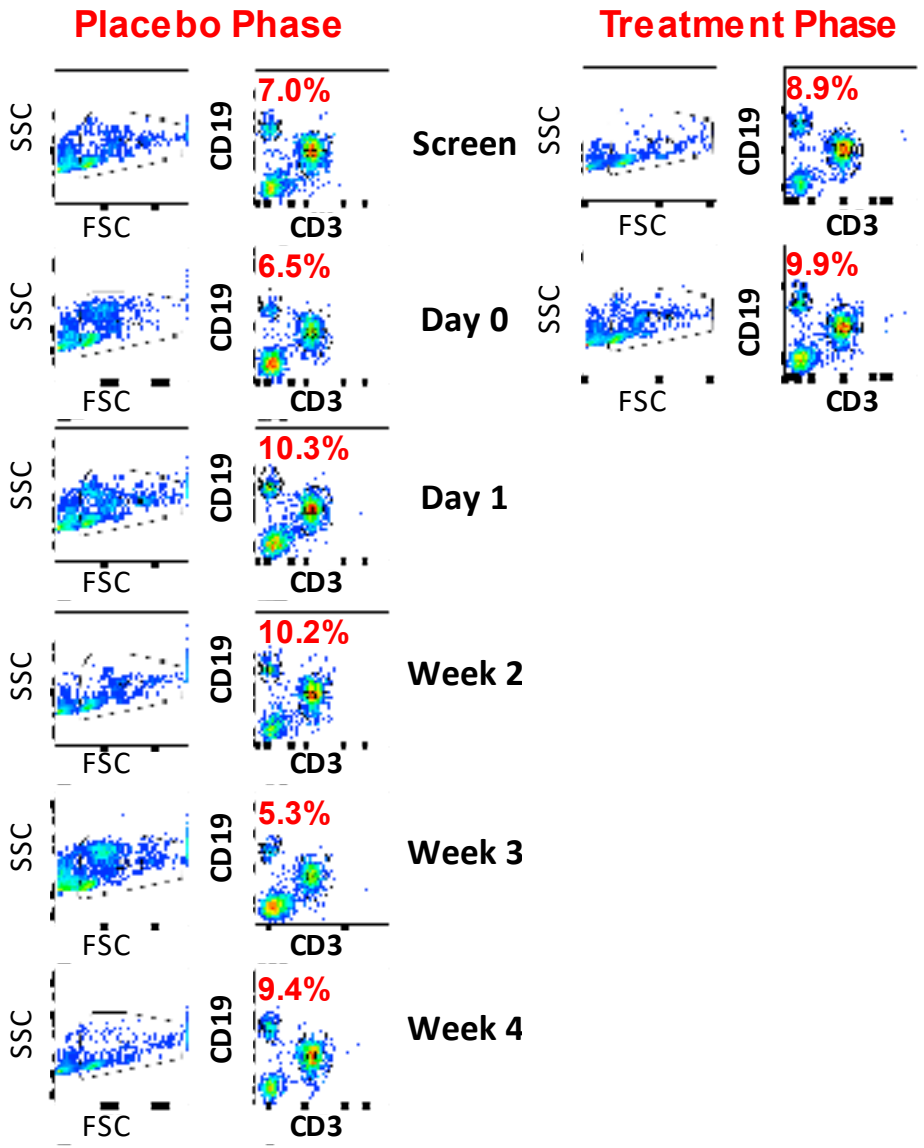

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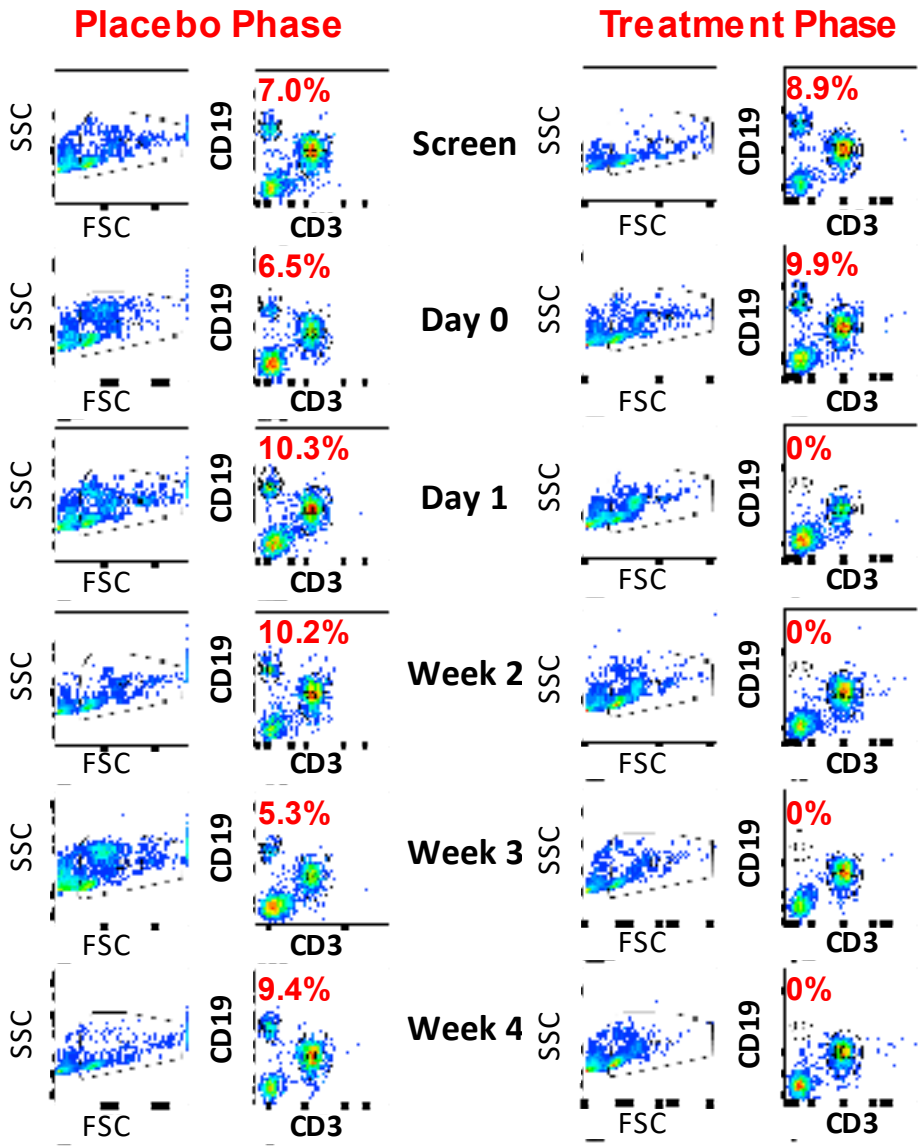

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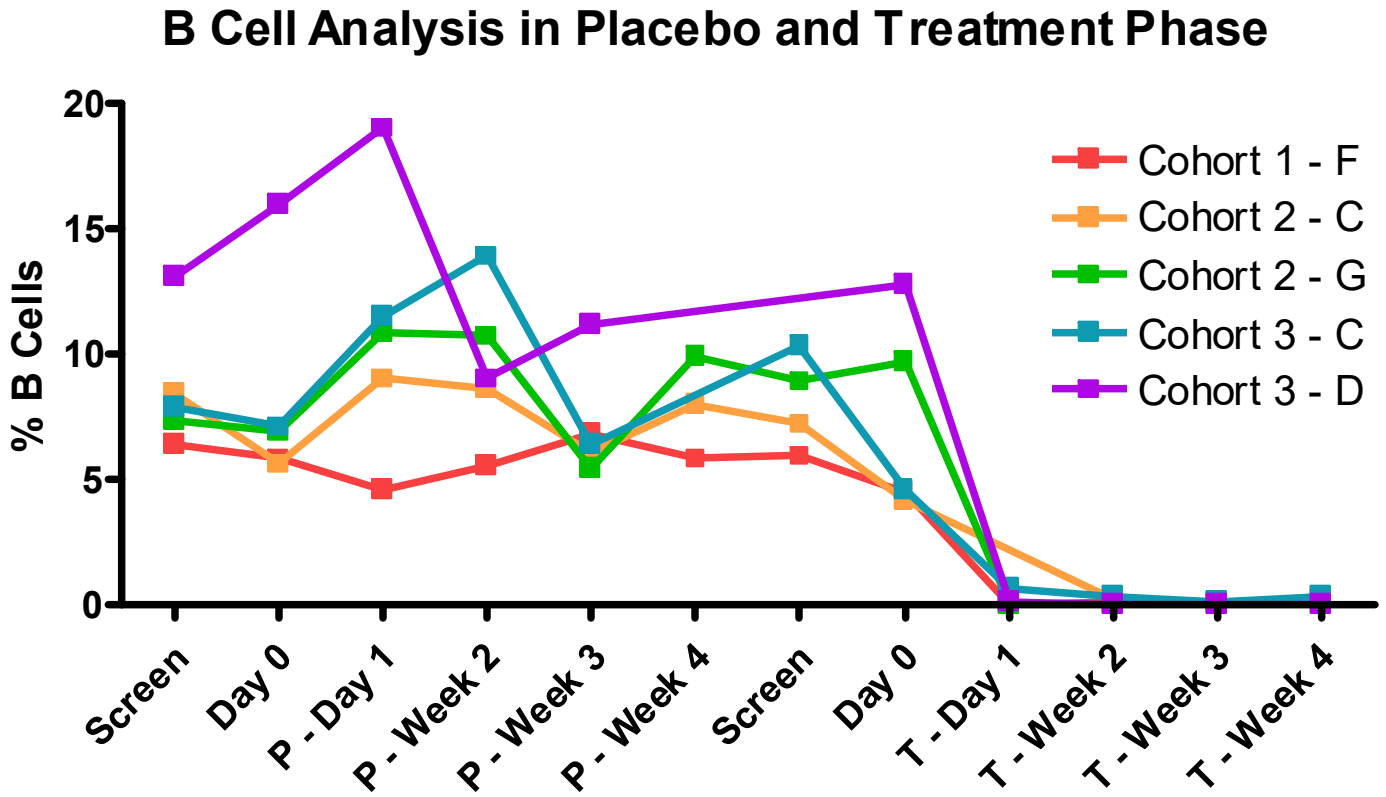

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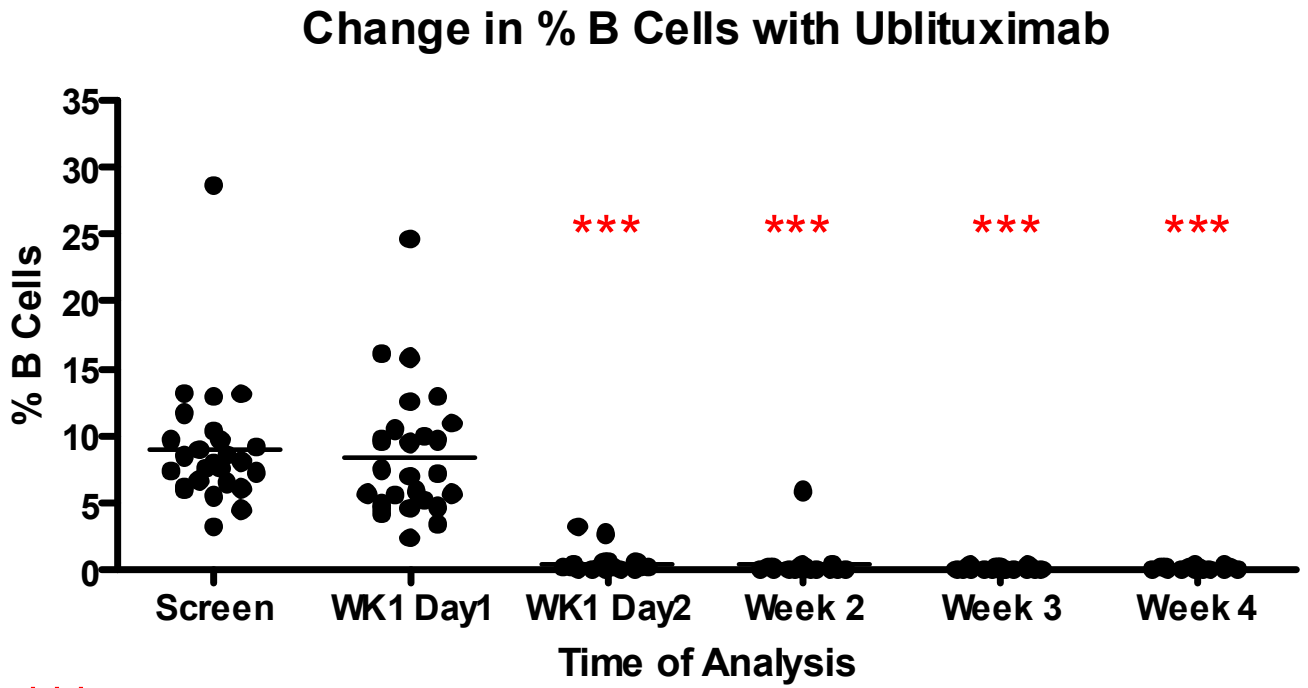
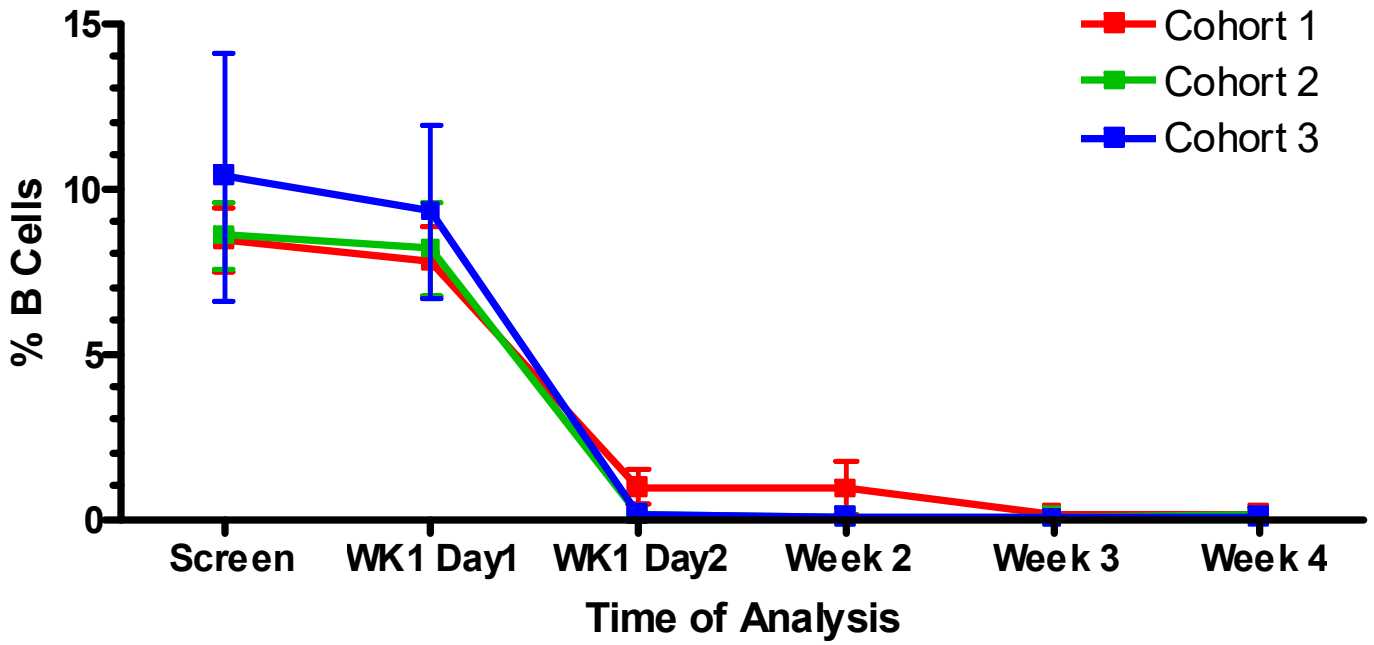


*** p<0.001 Bonferroni's Multiple Comparison Test compared to Screening and Day 0

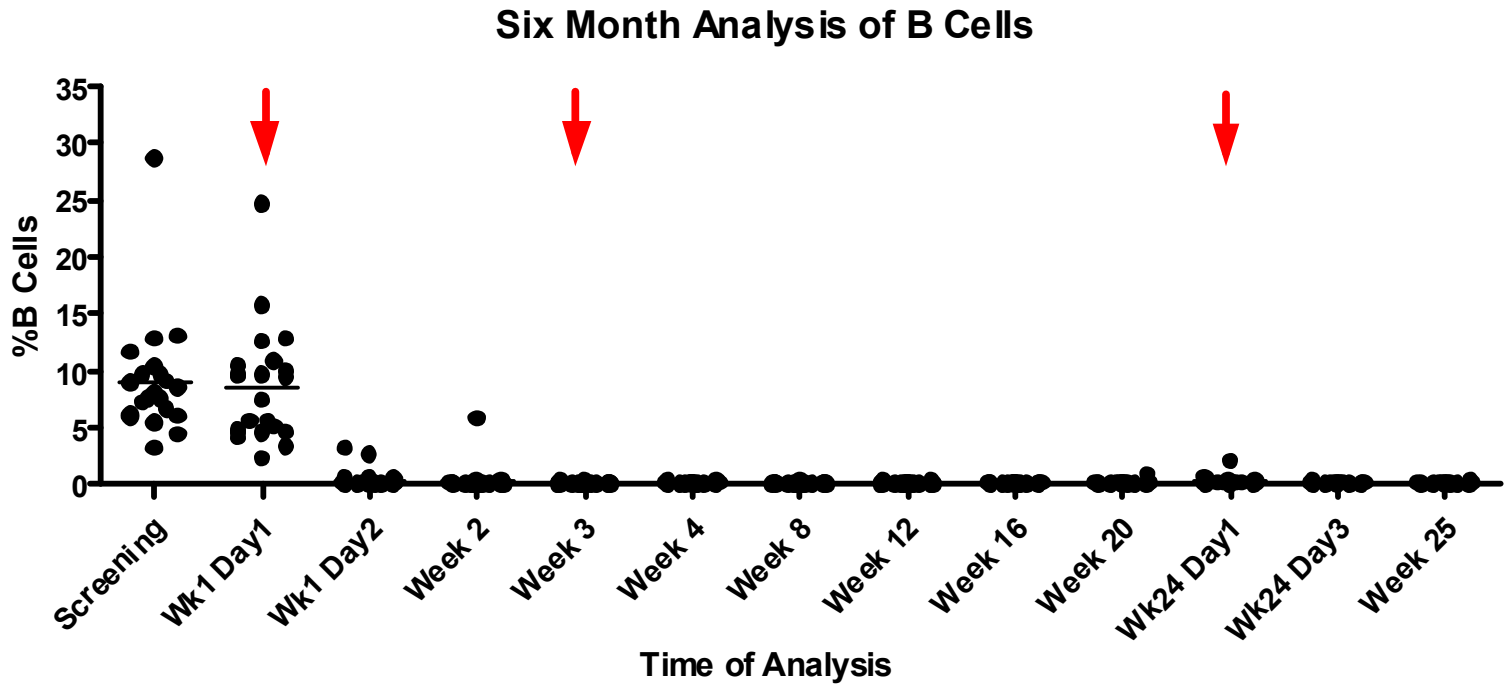
B Cell Analysis



*No statistical difference (ANOVA) between cohorts at each time point.
Error bars are mean±SEM.

All patients received the same total dose of 600 mg, only infusion times differed.

B Cell Analysis



Arrows represent treatment timepoints. Blood analysis was done pre-treatment.

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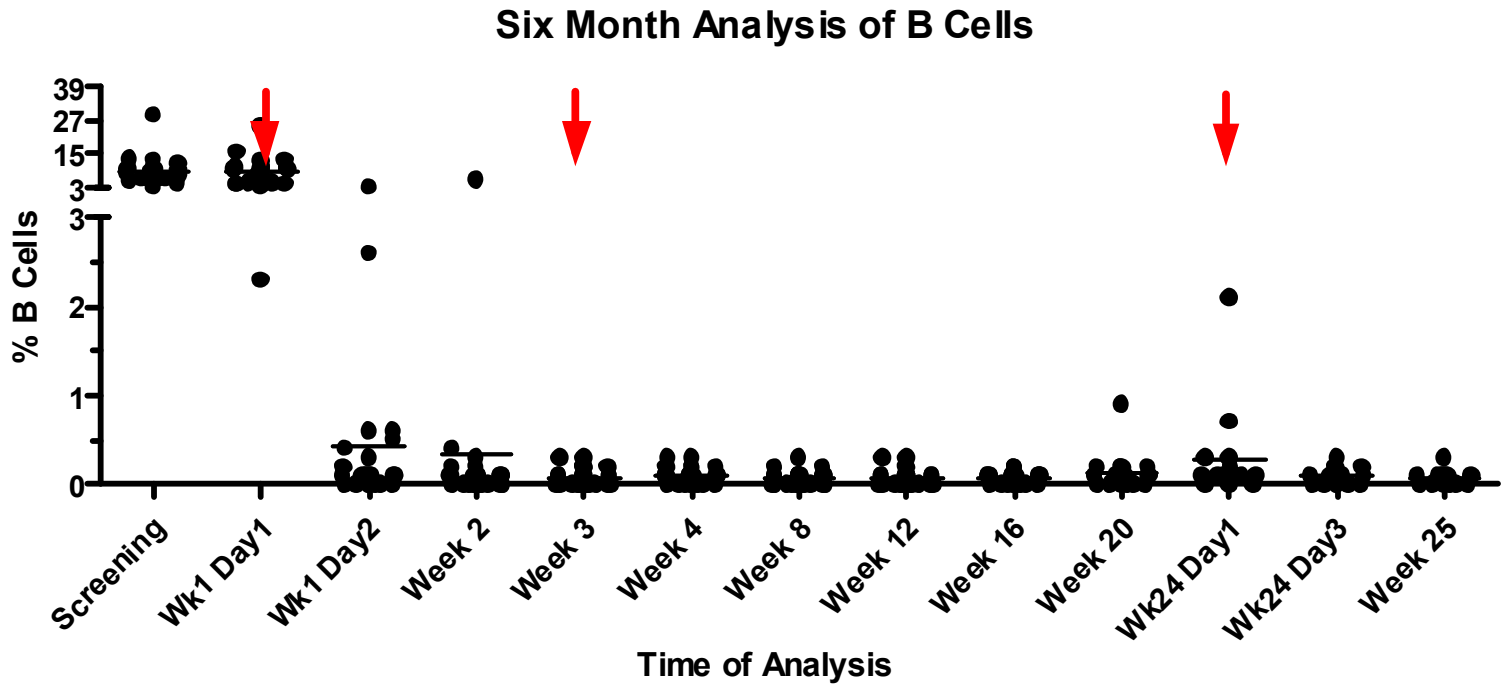

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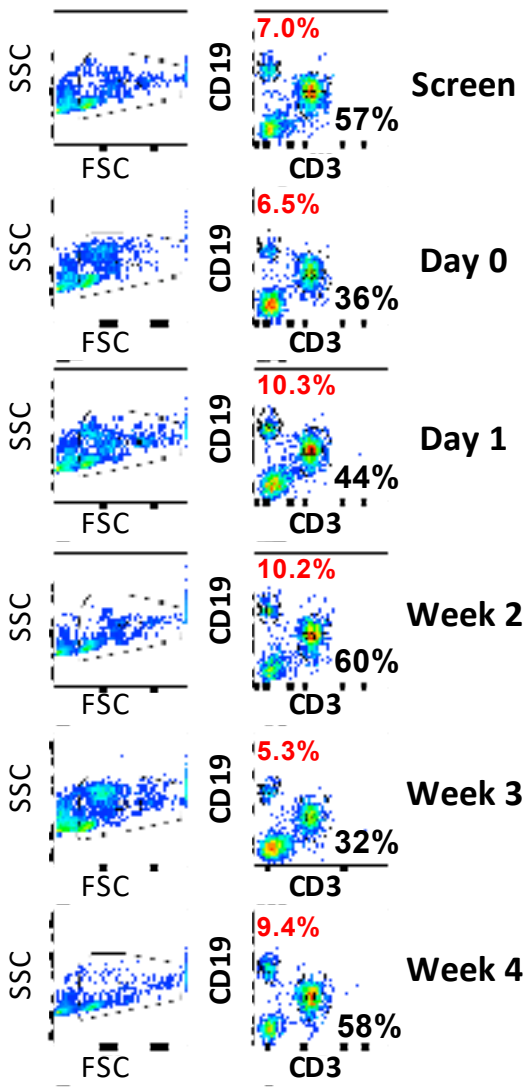
T Cell Analysis

Placebo Phase



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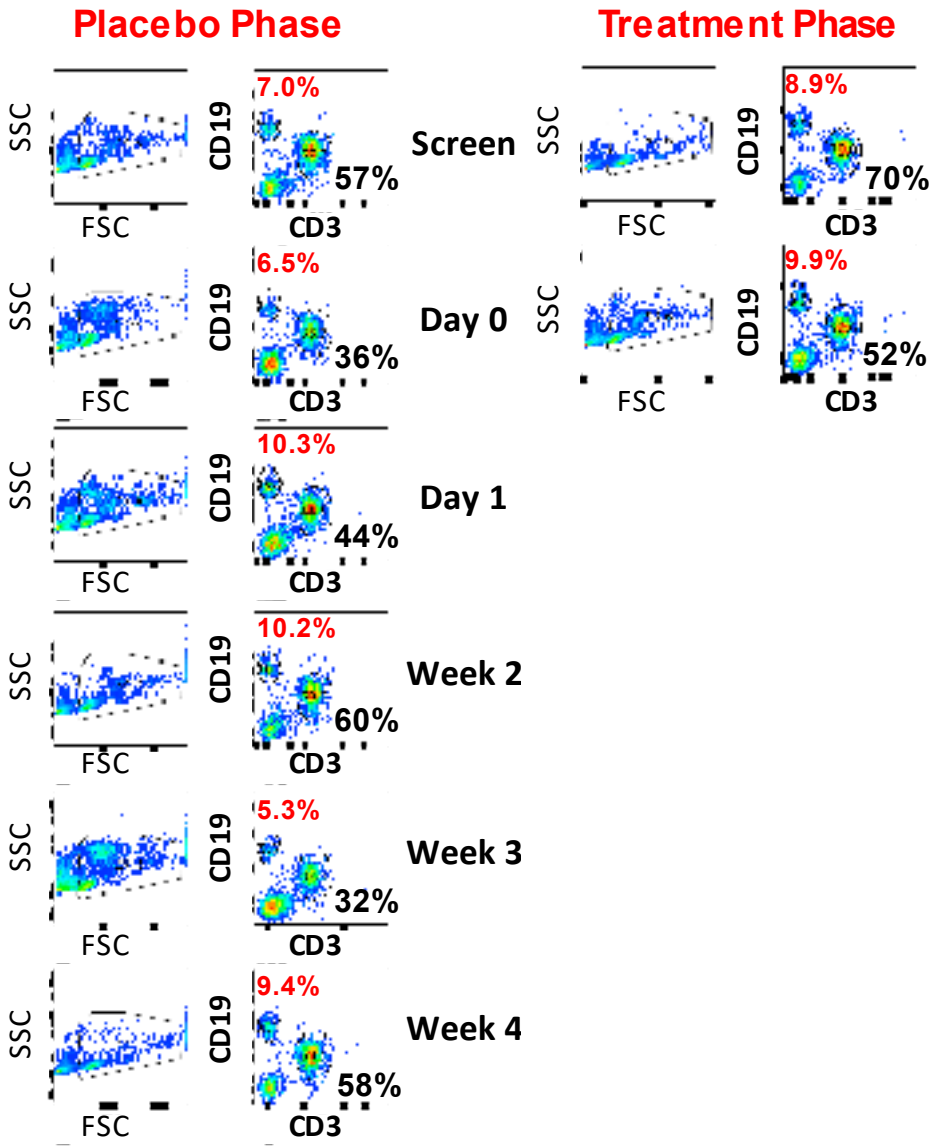

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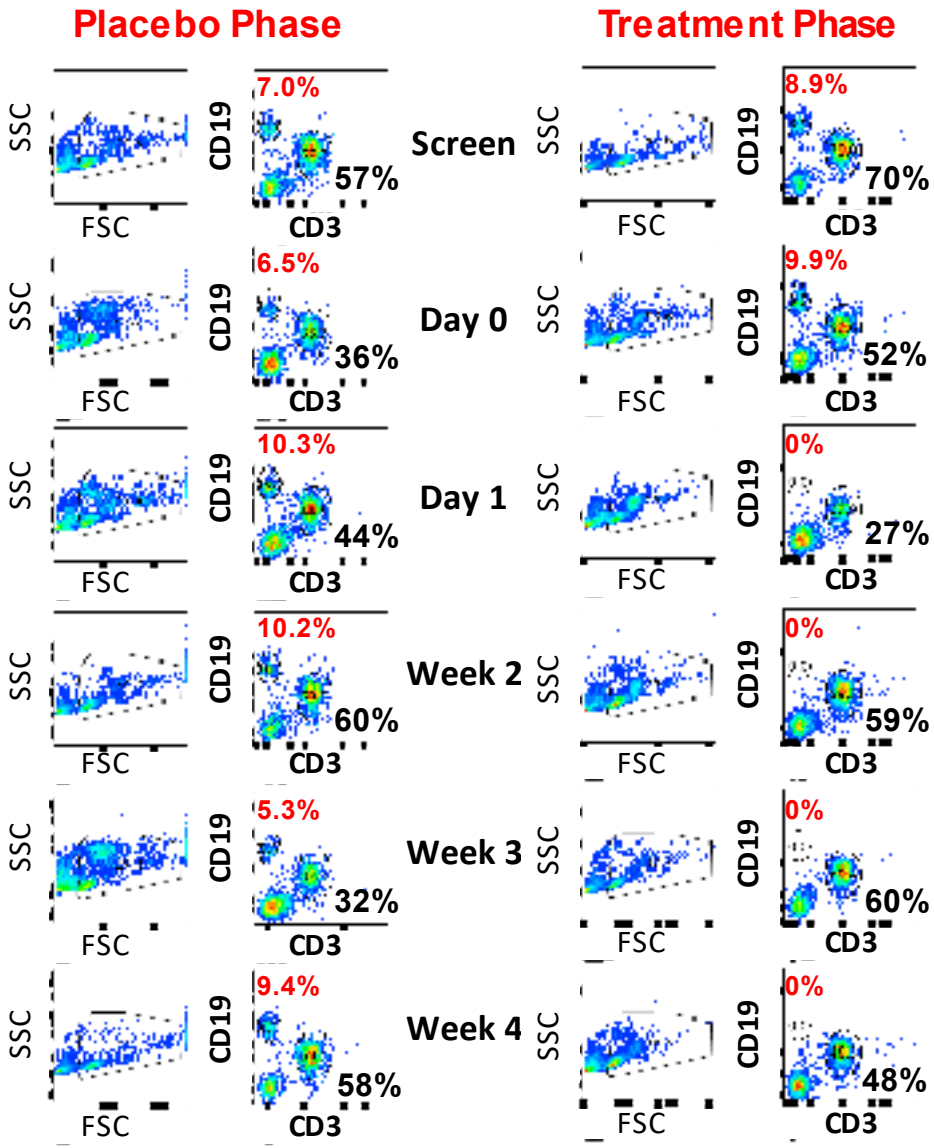

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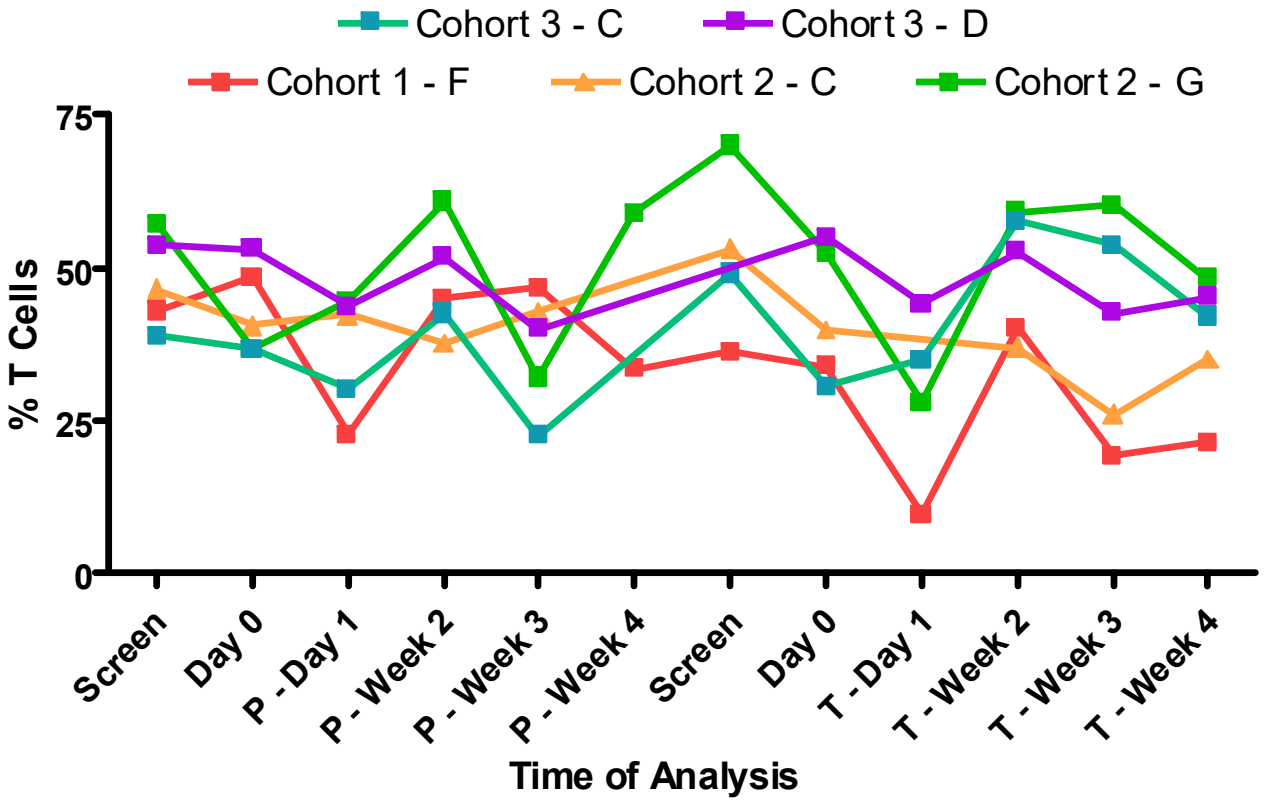

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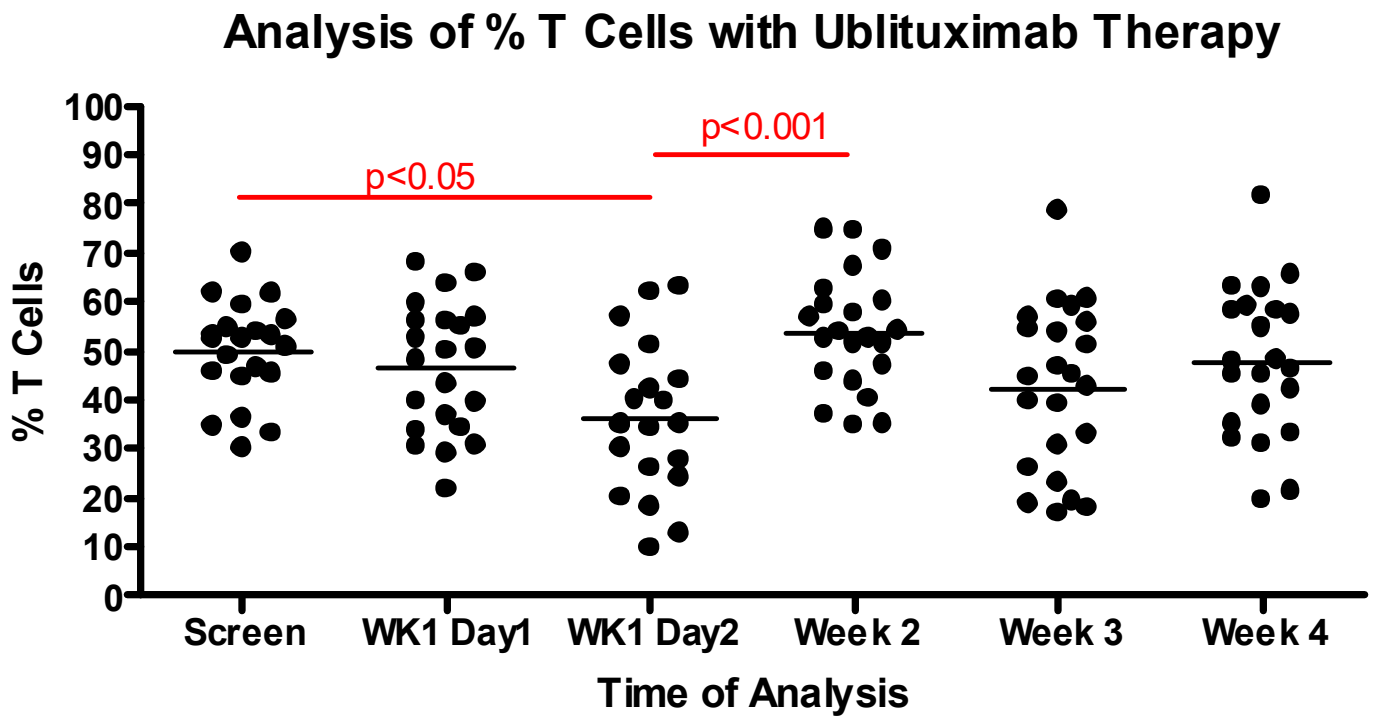
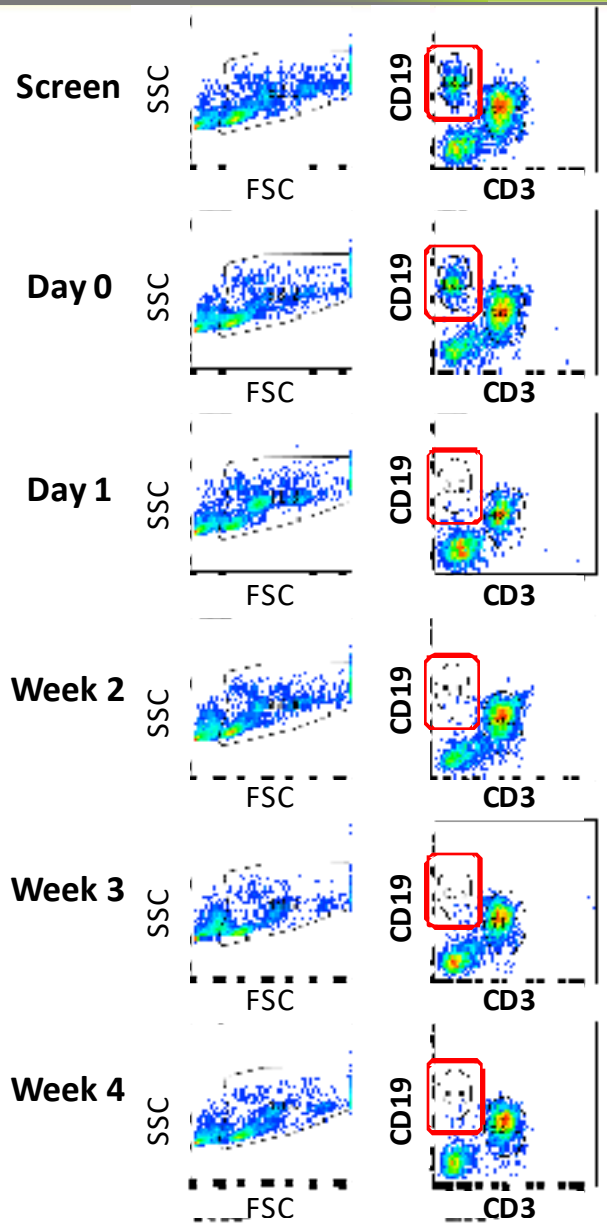


Statistical analysis with Bonferroni's Multiple Comparison Test

B Cell Subset Analysis



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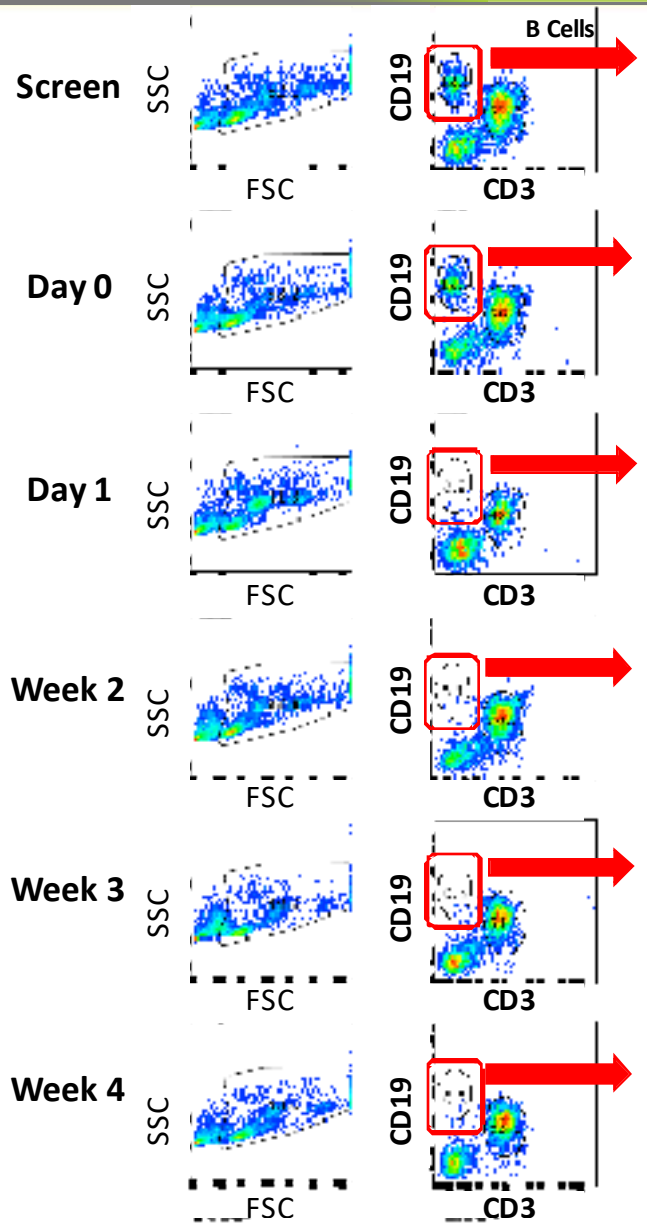

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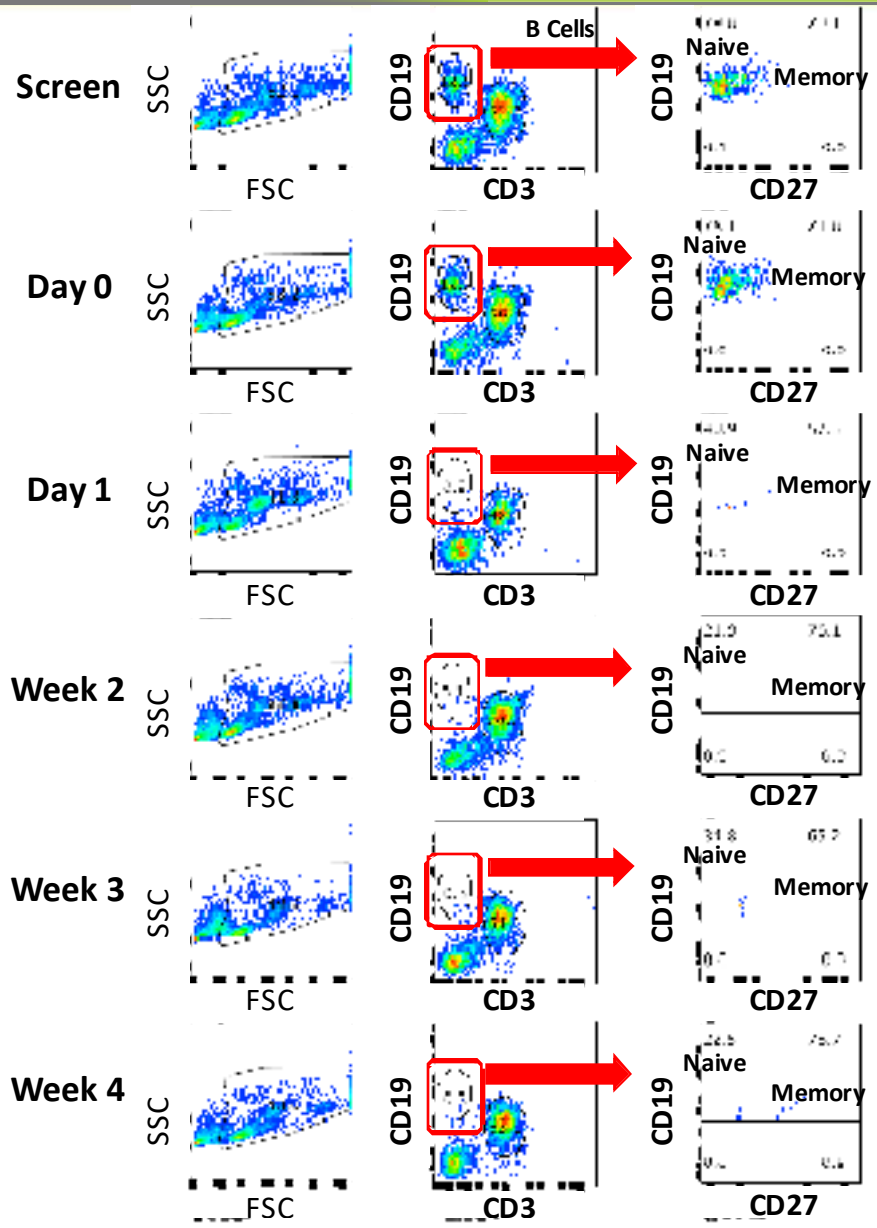

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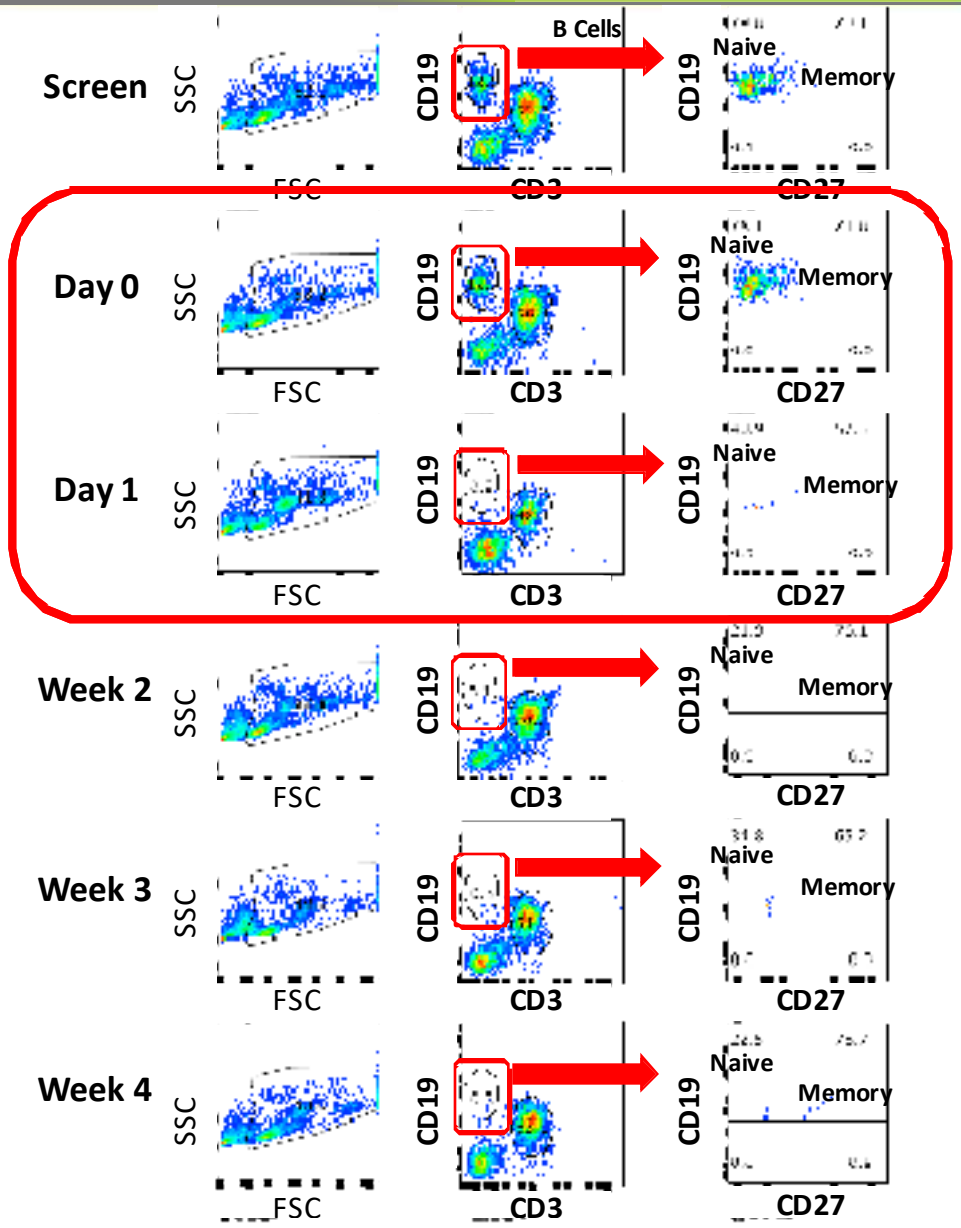

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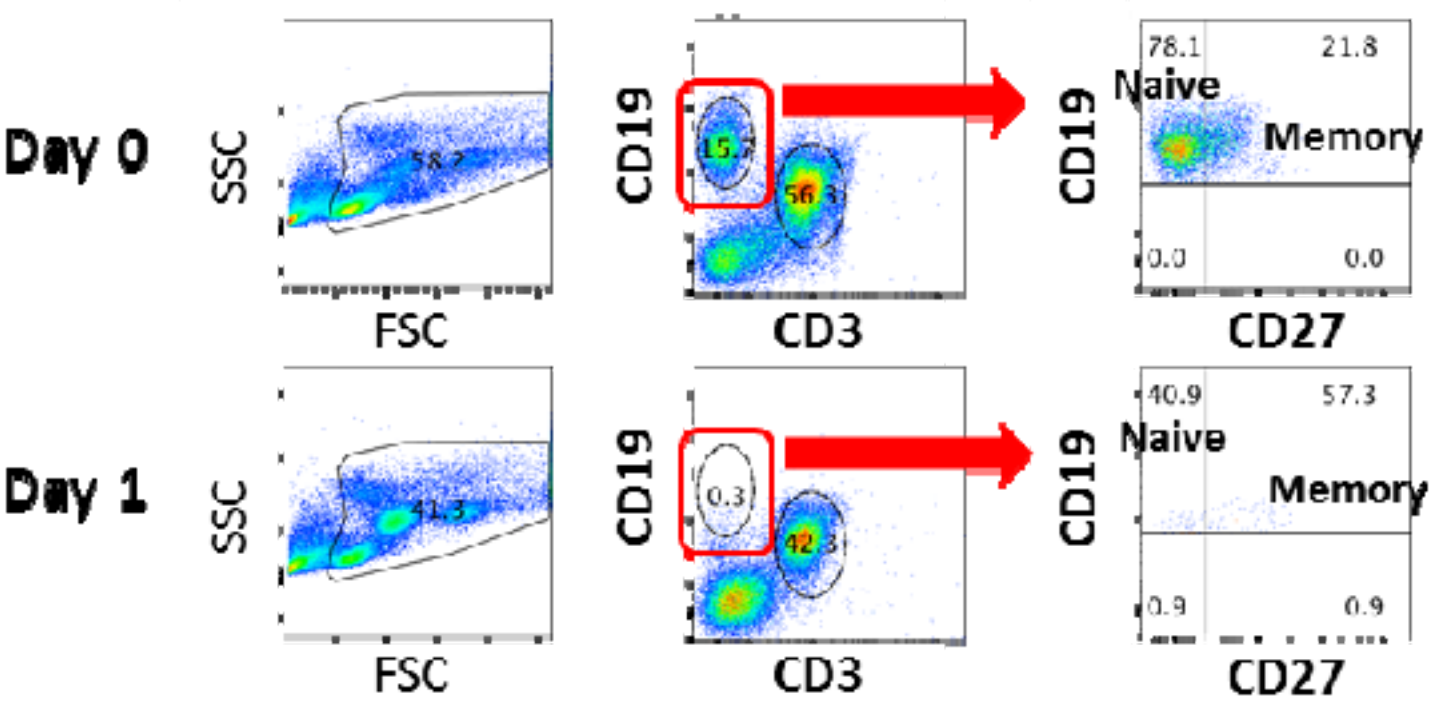

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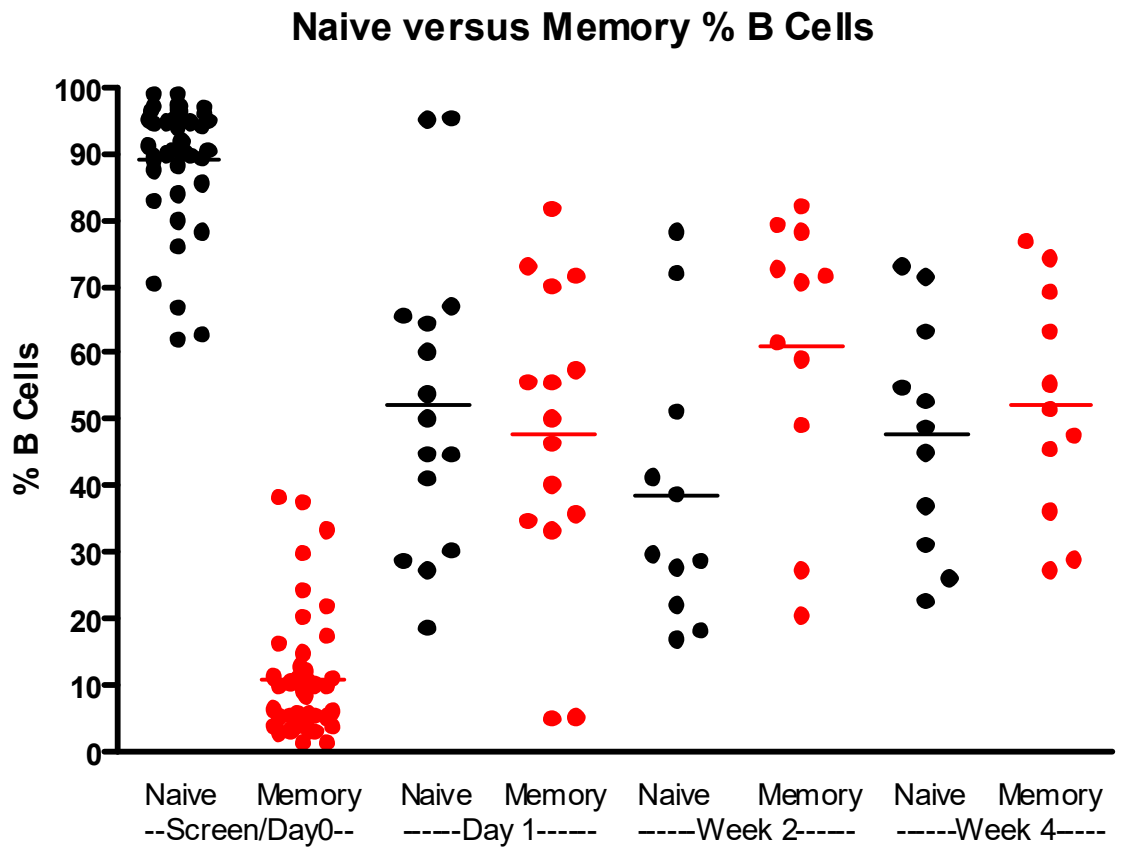

Summary

- Ublituximab is well-tolerated, with only mild infusion reactions (Grade 1-2) being observed, even with infusion times reduced to 1 hour.
- Ublituximab efficiently depletes B cells (98.9%), meeting the endpoint of >95% depletion within two weeks of second dose, comparable to ocrelizumab.
- Although there is a transient decrease in T cells after the initial dose of ublituximab, T cell numbers are fairly stable over time.
- Memory B cells seem slightly more resistant to depletion, but are efficiently depleted in all patients.
- A comprehensive analysis of B and T cell profiles is being performed to understand how B cell depletion influences T cell profiles, and to characterize the B cell repletion.
- This one year study of ublituximab in RMS patients is ongoing and clinical and MRI measures will be reported at future congresses.

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