

Aggressive Lymphoma Workshop

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ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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Targeting CD47

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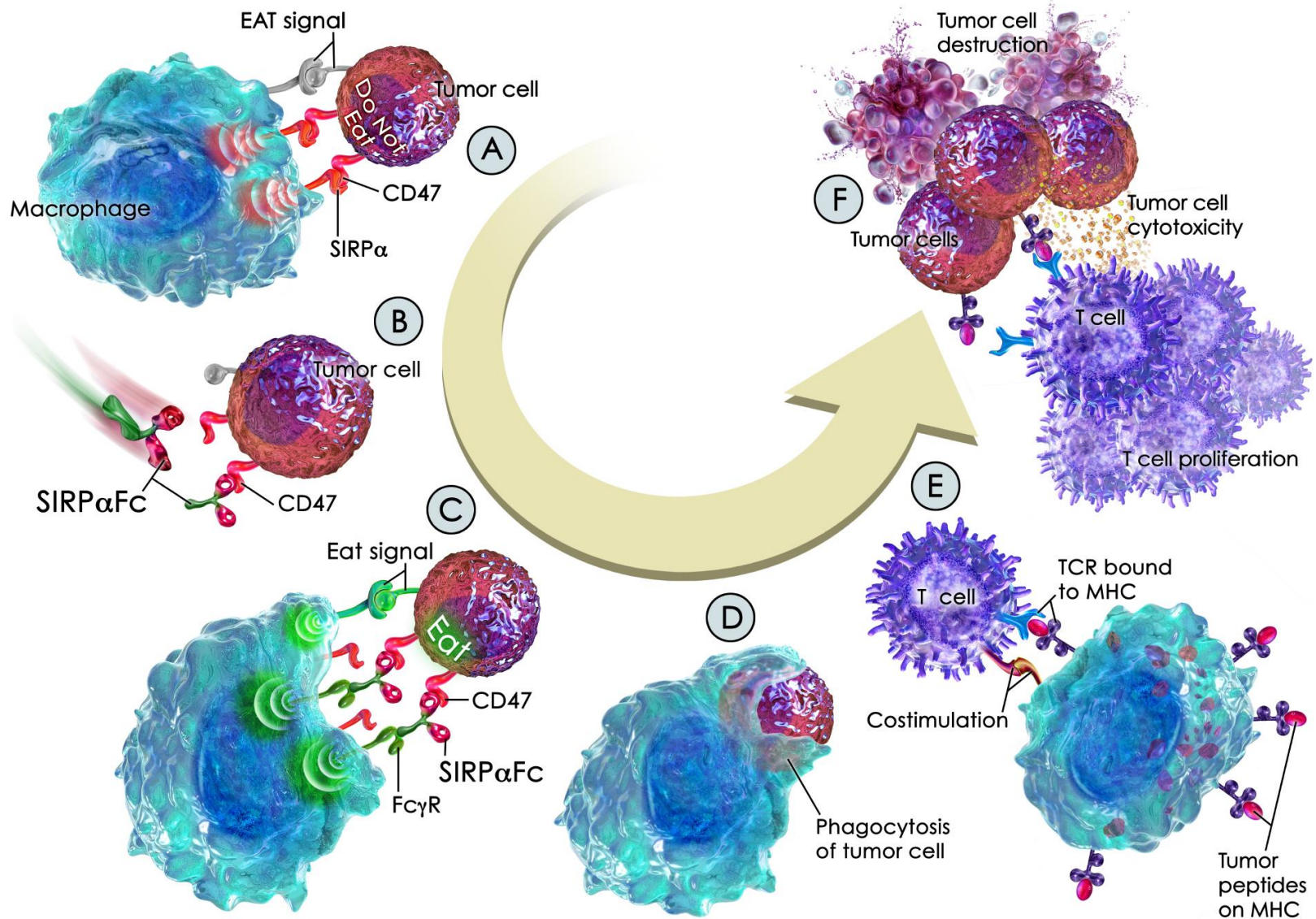
Disclosures for Stephen Ansell, MD, PhD

In compliance with ACCME policy, Mayo Clinic requires the following disclosures to the activity audience:

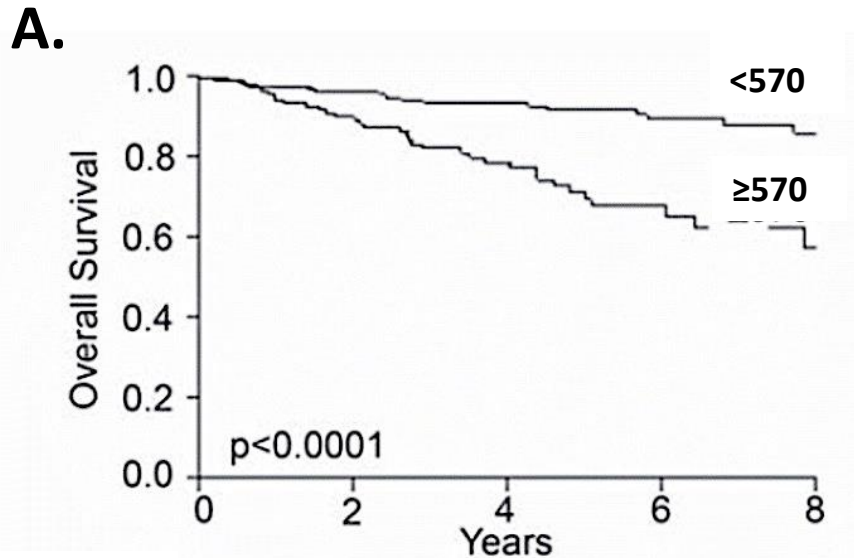
Research Support/P.I.	PI – SeaGen, BMS, Affimed, Regeneron, Pfizer, Takeda, AstraZeneca, ADC Therapeutics for clinical trials
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Speakers' Bureau	N/A
Scientific Advisory Board	N/A

N/A = Not Applicable (no conflicts listed)

Targeting CD47/SIRP α in Lymphoma

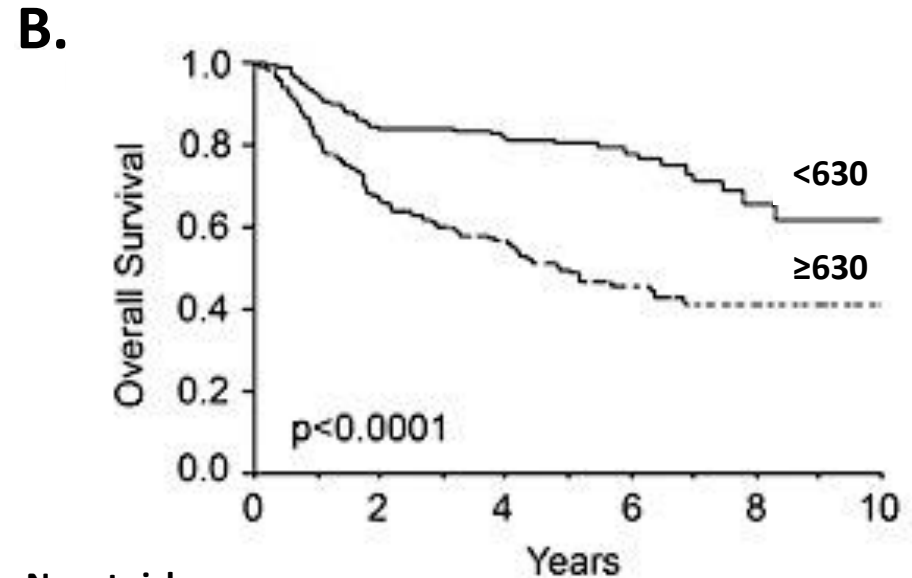


Monocytes and macrophages are typically associated with a poor prognosis



<u>No. at risk</u>					
AMC low	225	198	131	71	39
AMC high	130	101	59	29	12

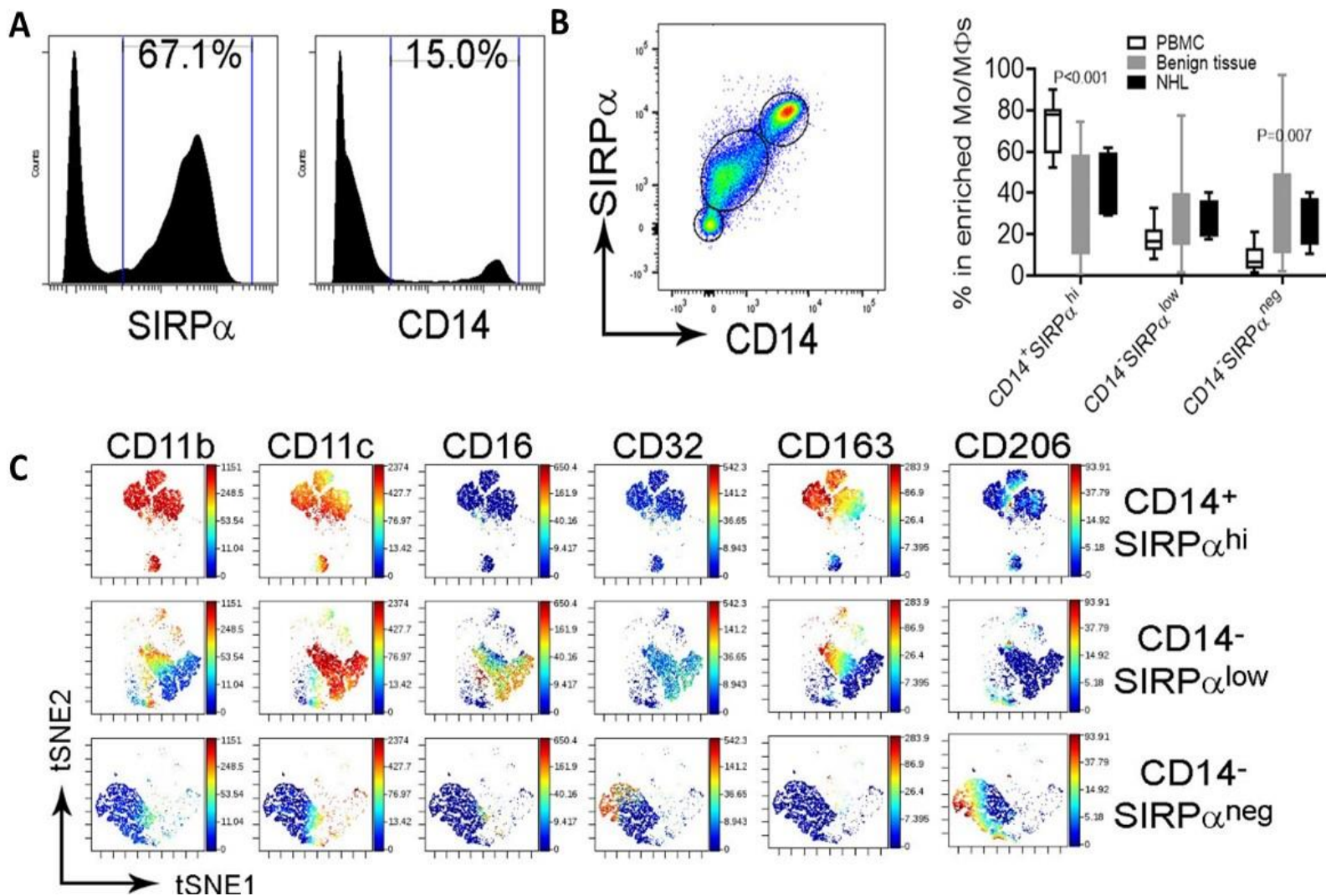
Follicular lymphoma



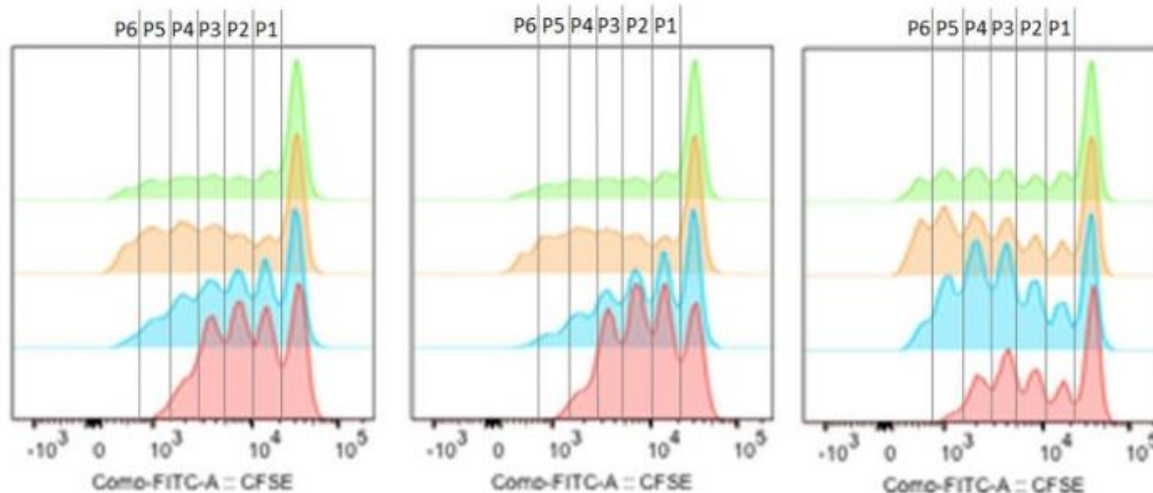
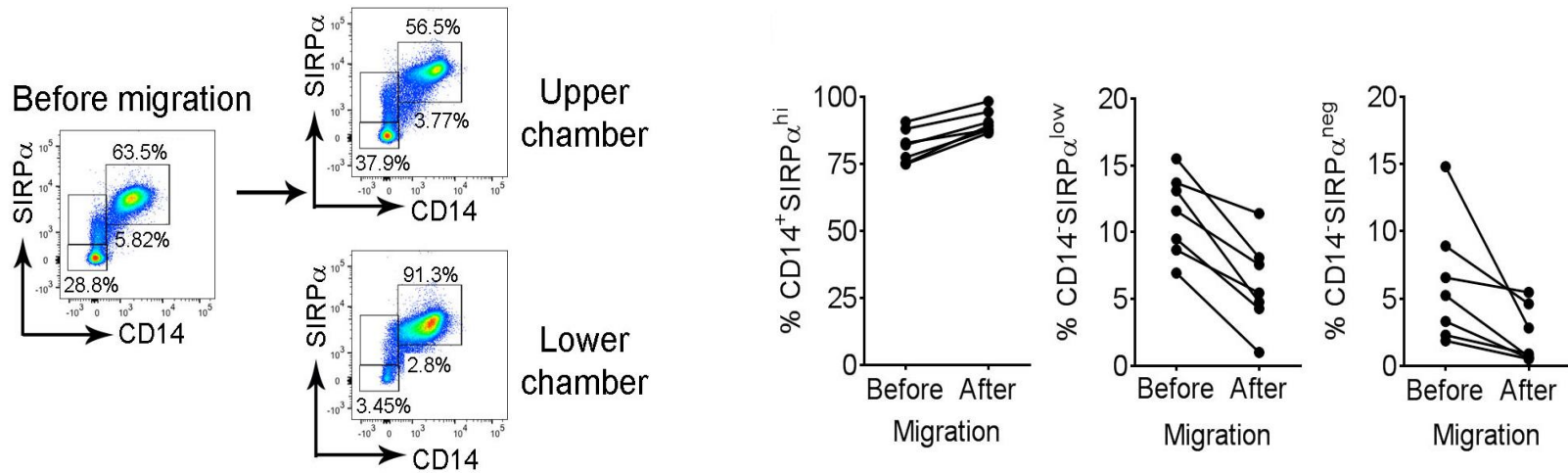
<u>No. at risk</u>						
AMC low	180	148	116	58	22	3
AMC high	186	123	77	36	14	4

DLBCL

Macrophages in lymphoma lymph nodes express variable levels of SIRP α

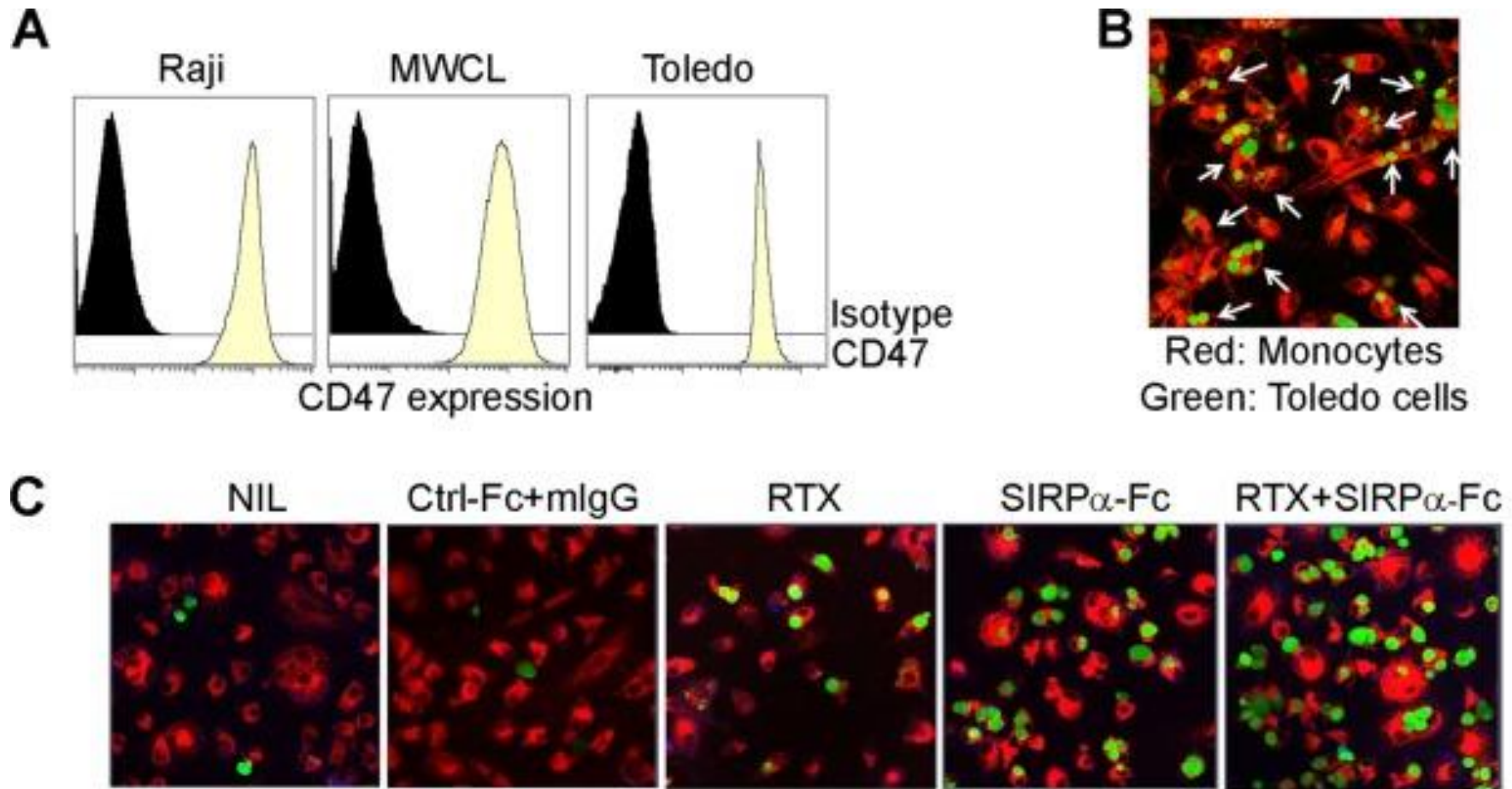


SIRP α expressing macrophages have different migratory abilities and different effects on T-cells

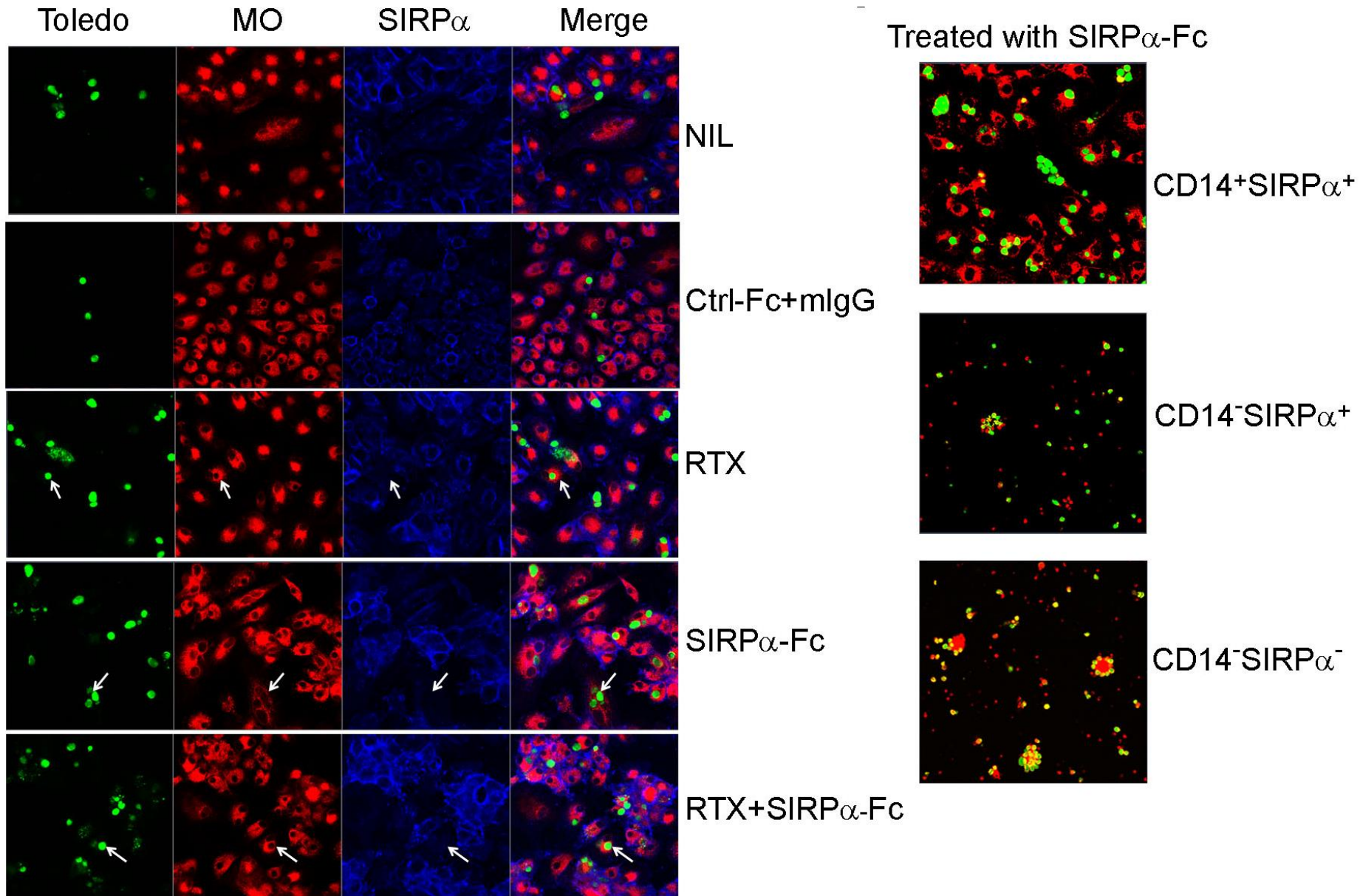


T cell only: green
 CD14-SIRP-: orange
 CD14-SIRP α +: blue
 CD14+SIRP α +: red

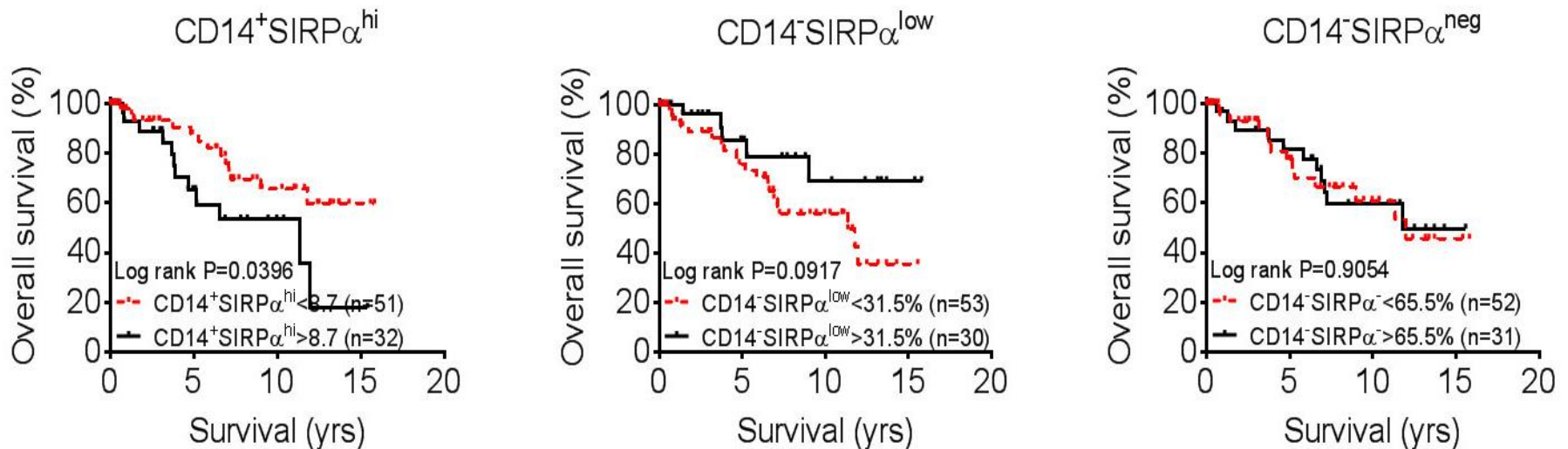
Increased phagocytosis by blocking CD47/SIRP α signaling



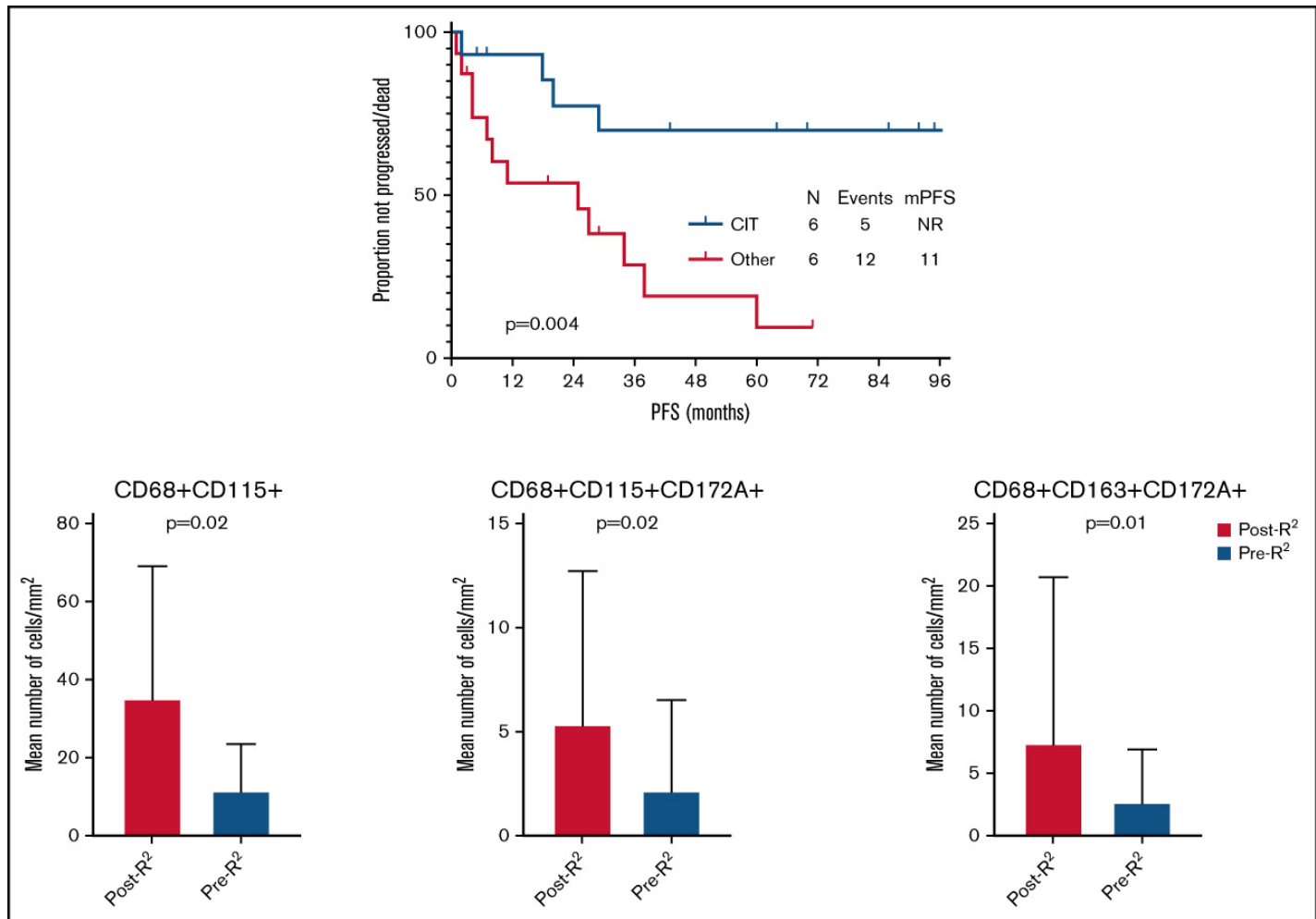
Phagocytosis by macrophages treated with SIRP α -Fc



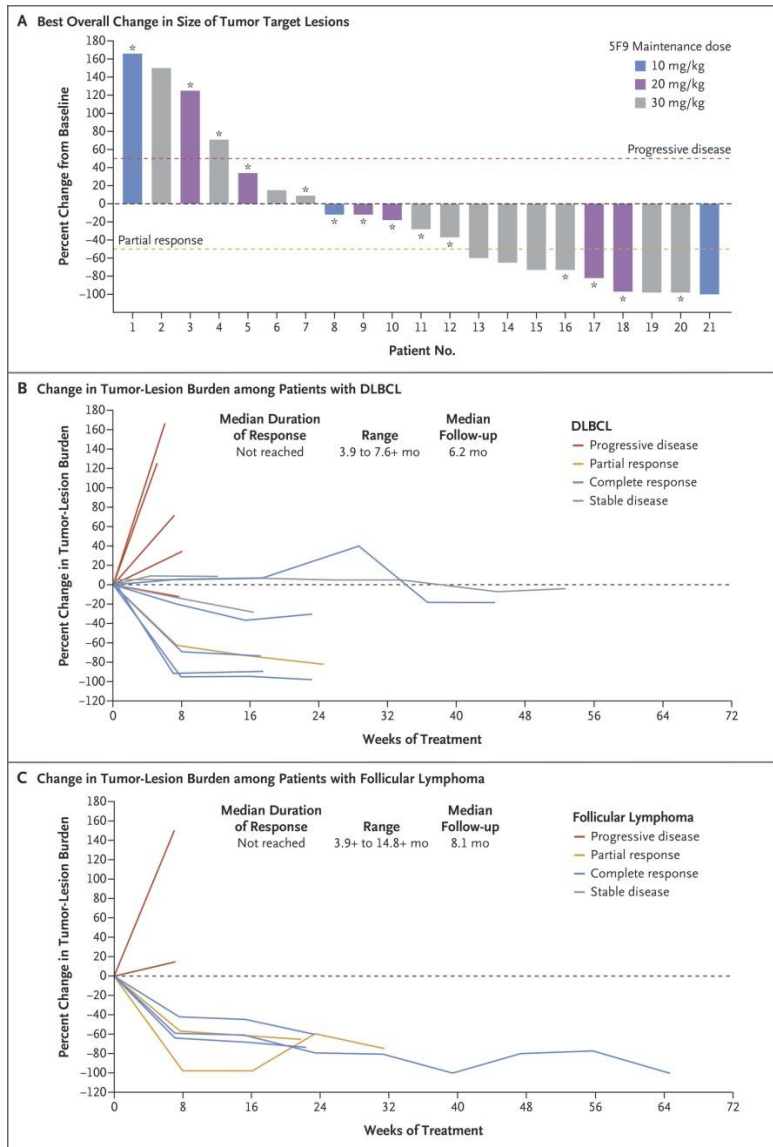
CD14 and SIRP α expressing macrophages have different associations with patient outcome in follicular lymphoma



SIRP α^+ (CD172a) macrophages are increased in patients with Follicular Lymphoma who progress after frontline lenalidomide and rituximab



CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma



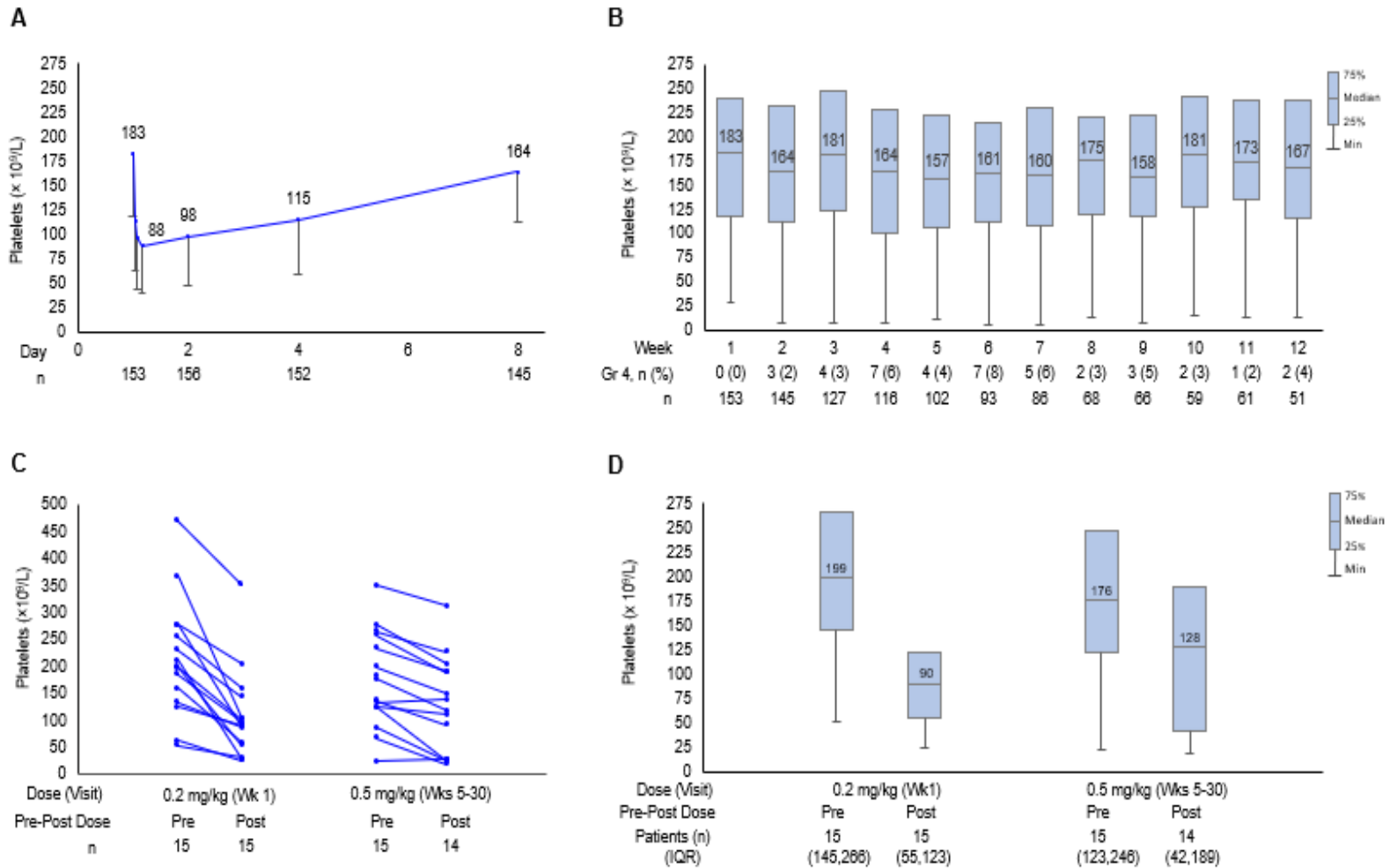
22 patients (15 with DLBCL and 7 with follicular lymphoma)

50% of the patients had an objective response, with 36% having a complete response.

The ORR and CR rates were 40% and 33% among patients with DLBCL and 71% and 43%, respectively, among those with follicular lymphoma.

91% of the responses are ongoing.

Phase 1 Study of TTI-621 in Patients With Relapsed or Refractory Hematologic Malignancies or Solid Tumors

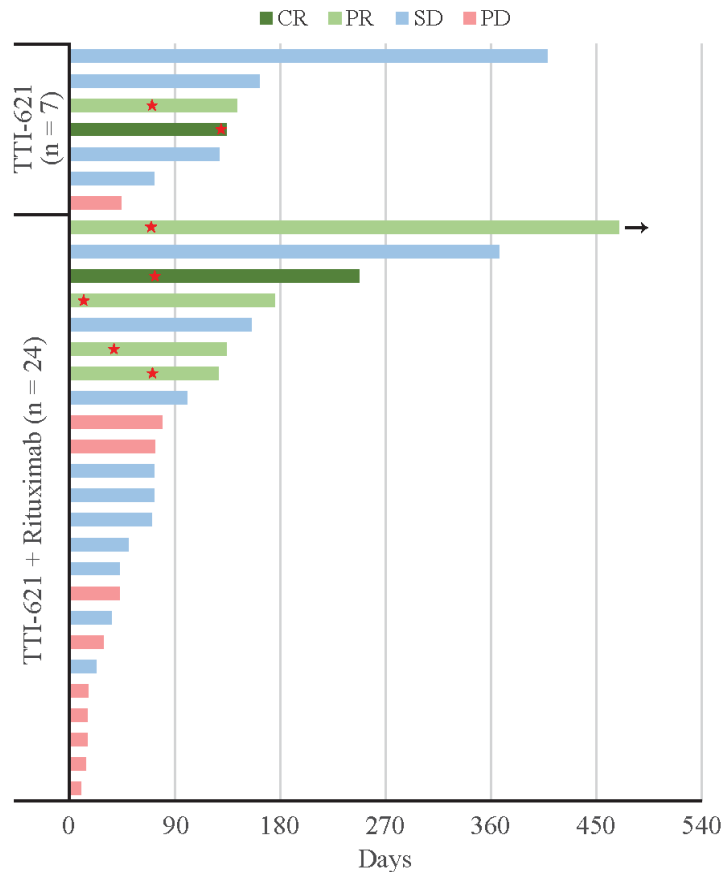


Phase 1 Study of TTI-621 in PTCL and DLBCL

A

Best Response in Patients with DLBCL

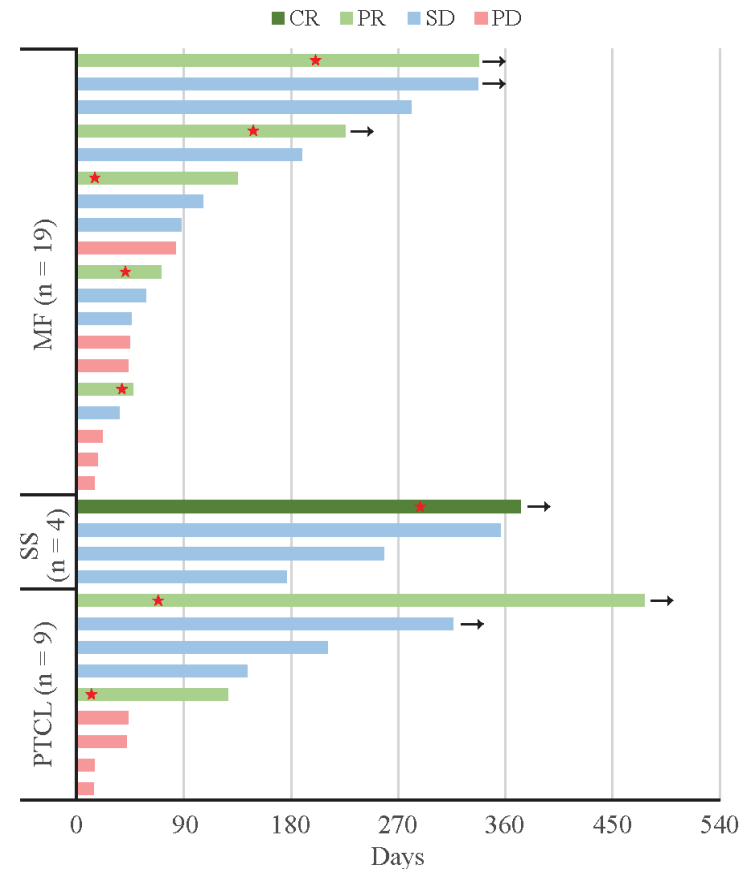
	n	Response, n (%)			Median (Range) Time to Response, d	Median (Range) Treatment Duration, d
		CR	PR	Total		
TTI-621	7	1 (14)	1 (14)	2 (29)	106 (78–133)	139 (134–143)
TTI-621 + R	24	1 (4)	4 (17)	5 (21)	77 (21–78)	175 (127–469)
Total	31	2 (6)	5 (16)	7 (23)	78 (21–133)	143 (127–469)



B

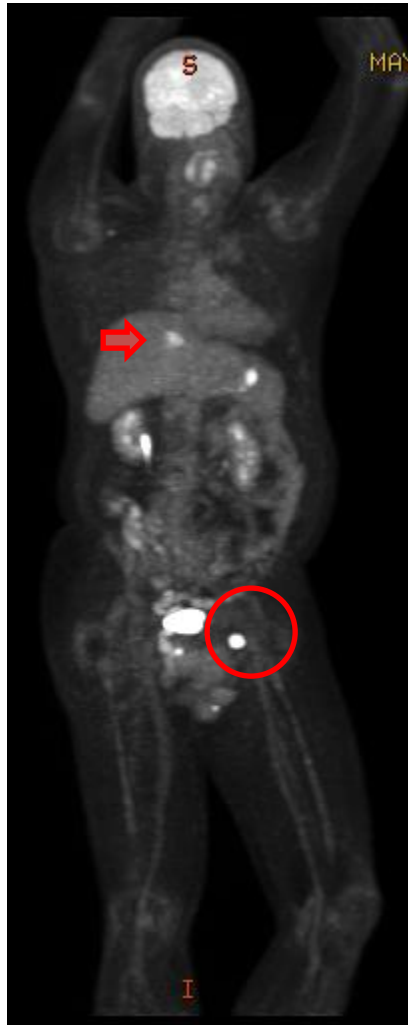
Best Response in Patients with T-Cell Lymphoma

	n	Response, n (%)			Median (Range) Time to Response, d	Median (Range) Treatment Duration, d
		CR	PR	Total		
MF	19	0	5 (26)	5 (26)	50 (23–218)	135 (41–338)
SS	4	1 (25)	0	1 (25)	303 (303–303)	373 (373–373)
PTCL	9	0	2 (22)	2 (22)	50 (20–79)	302 (127–477)
Total	32	1 (3)	7 (22)	8 (25)	65 (20–303)	181 (41–477)



Responses in “Double Hit” lymphoma and DLBCL

Baseline



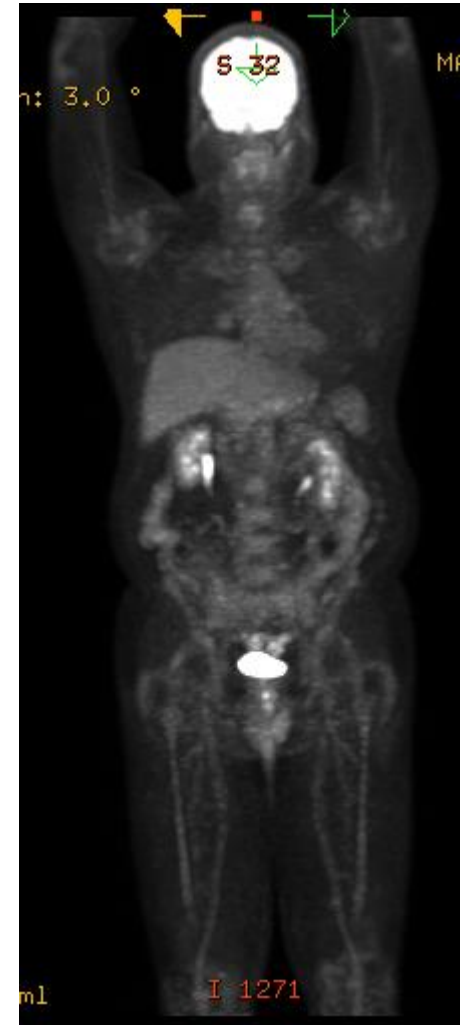
6 weeks



3 months



6 months



Responses to TTI-621 in Mycosis Fungoides and Cutaneous T-Cell Lymphoma



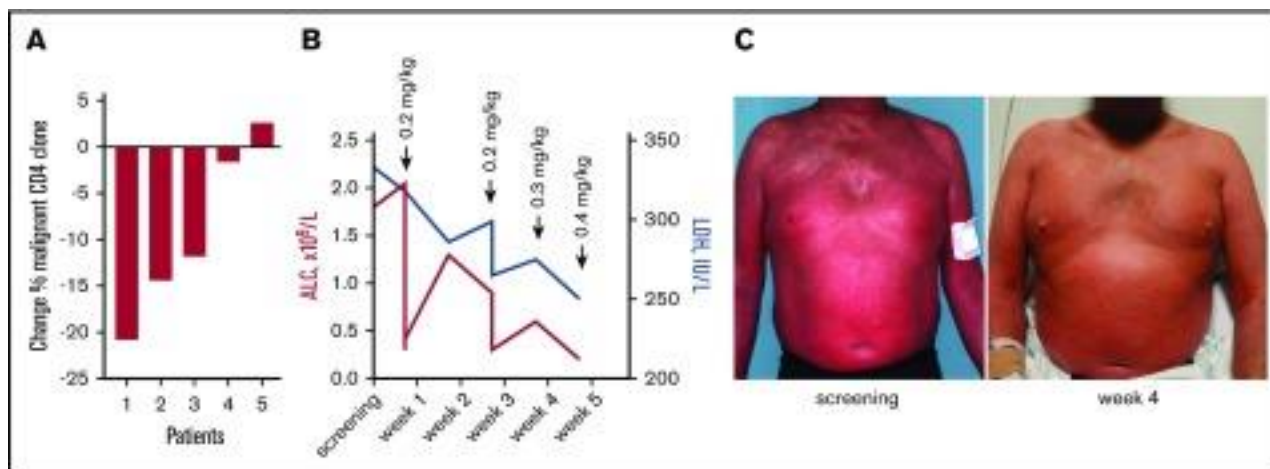
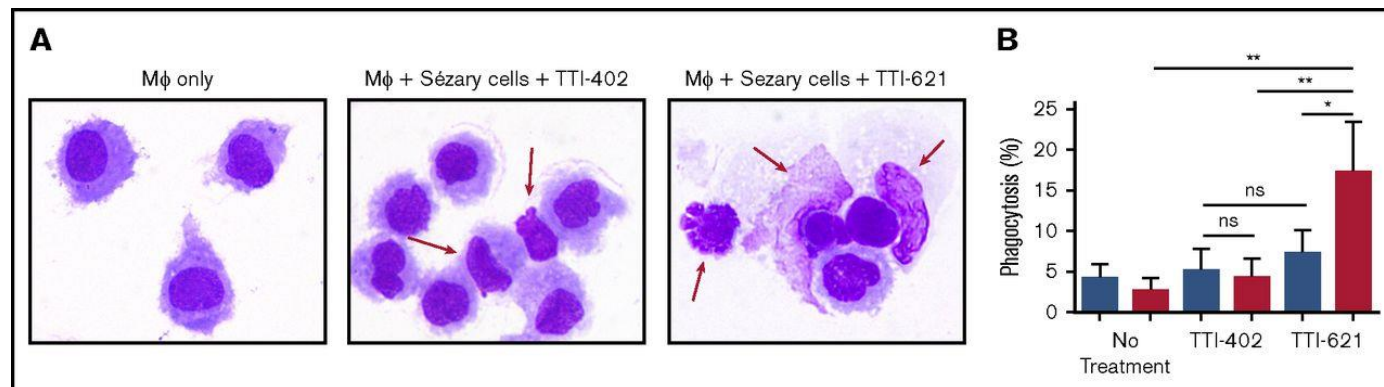
Baseline



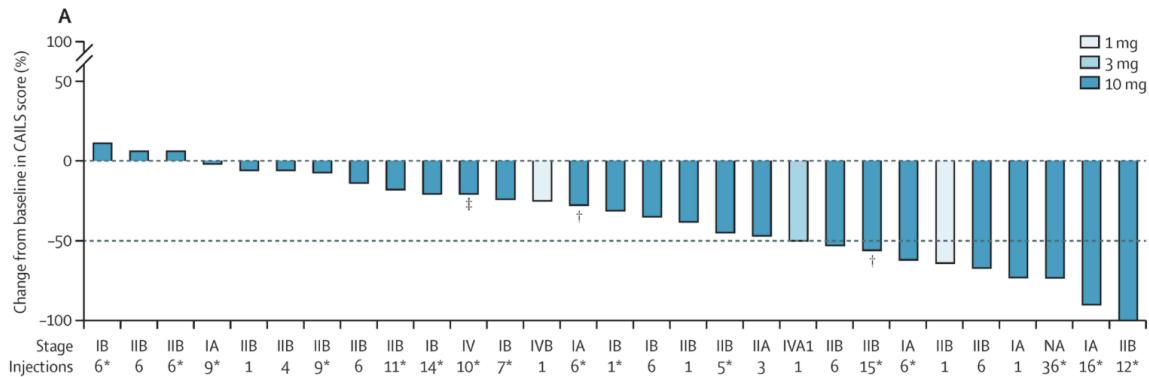
Week 12

Phase 1 trial of TTI-621, a novel immune checkpoint inhibitor targeting CD47, in Hematologic Malignancies

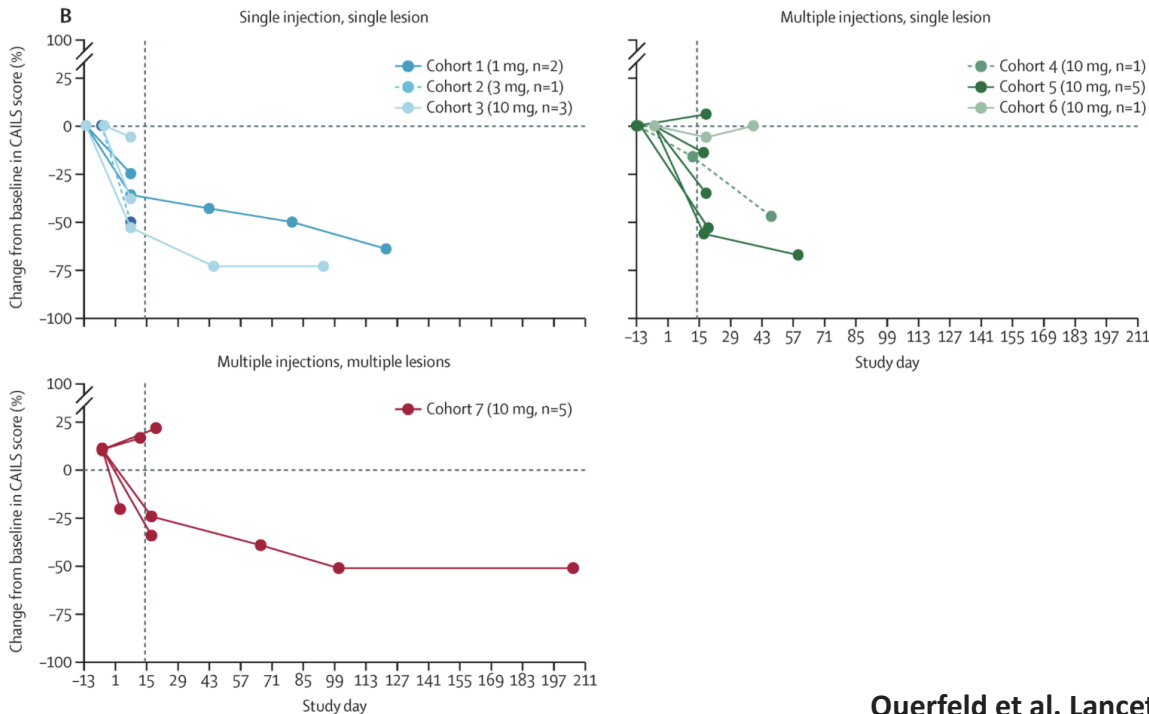
5 patients with Sezary syndrome – 4 of 5 patients had a decrease in Sezary cells



Intralesional TTI-621 in patients with relapsed or refractory mycosis fungoides or Sézary syndrome



35 MF or SS patients received intralesional TTI-621 (escalation, n=13; expansion, n=22).

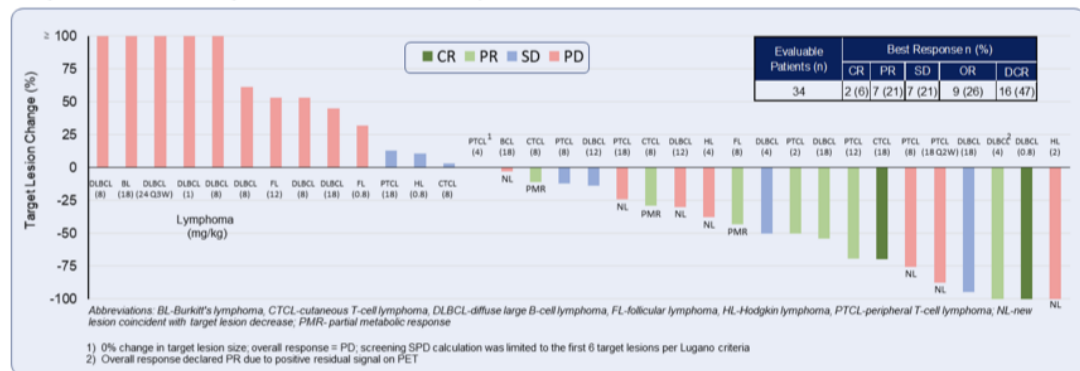


26 (90%) of 29 evaluable patients had decreased Composite Assessment of Index Lesion Severity (CAILS) scores

10 (34%) had a decrease in CAILS score of 50% or more

CD47-Blocker TTI-622 Shows Single-Agent Activity in Patients with Advanced Relapsed or Refractory Lymphoma

Figure 5. Target Lesion Response

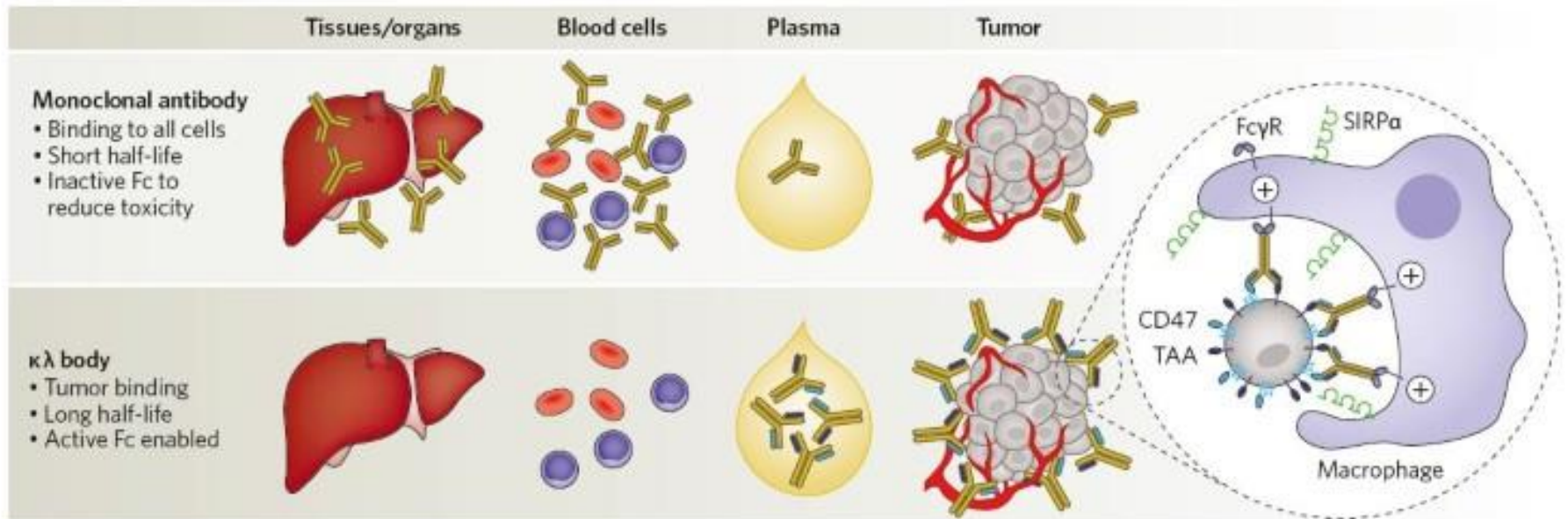


42 patients treated. Objective responses occurred in 33% (9/27) of response-evaluable patients.

Figure 6. Response Onset and Treatment Duration

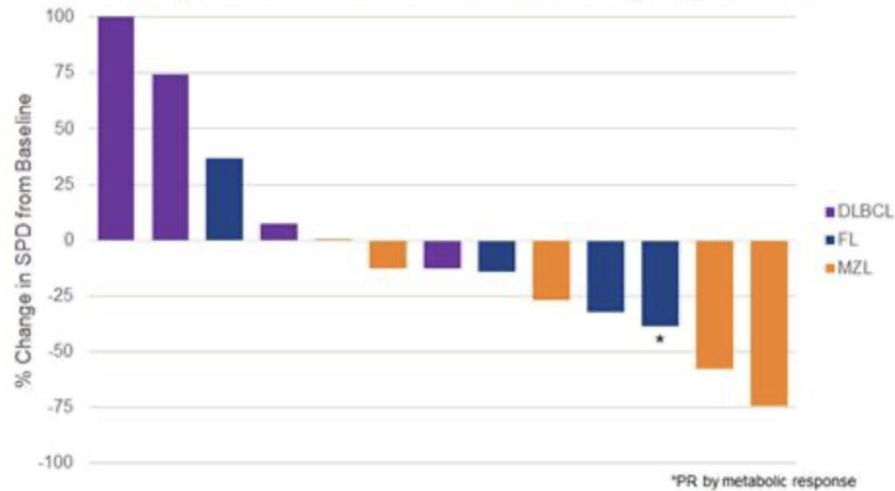


Next-generation immunotherapy with native bispecific antibodies



CD19/CD47 Bispecific Antibody TG-1801 in Patients (pts) with B-Cell Lymphoma

Best Change in Tumor Volume from Baseline: Single Agent Cohort

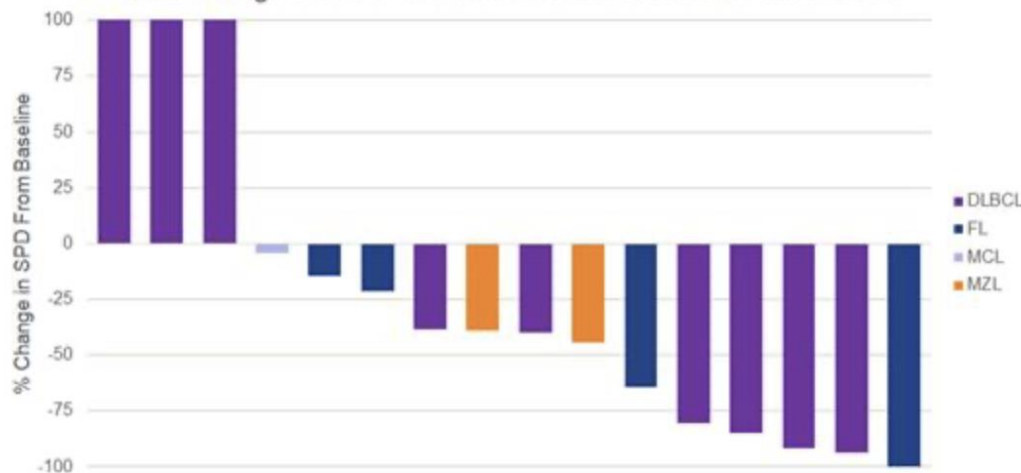


Three partial responses (PR) were observed on monotherapy (n=14)

In the combination arm (n=16), a 44% response rate was observed

56% ORR for DLBCL patients and 50% ORR for FL patients.

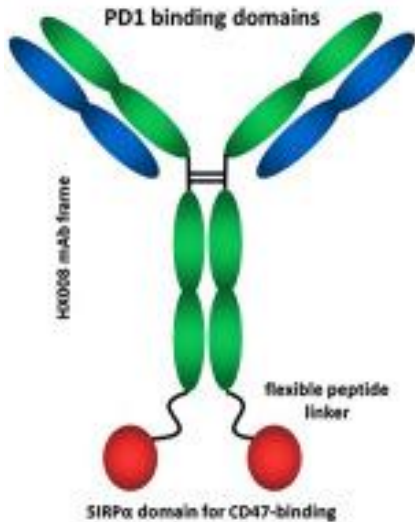
Best Change in Tumor Volume from Baseline: Combination Cohort



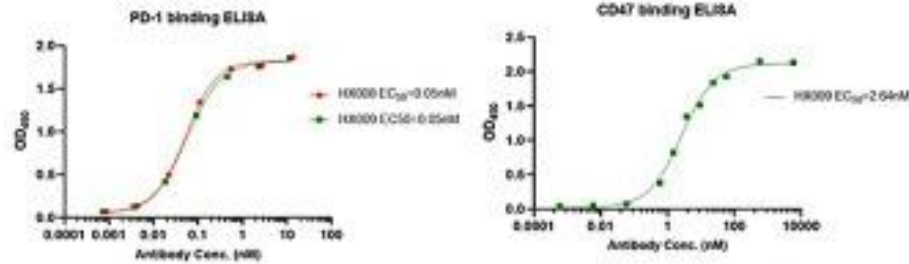
The median duration of combination therapy exposure was 8.7 mo (range of 1-20 mo).

HX009, targeting PD1 x CD47, demonstrates potent anti-lymphoma activity

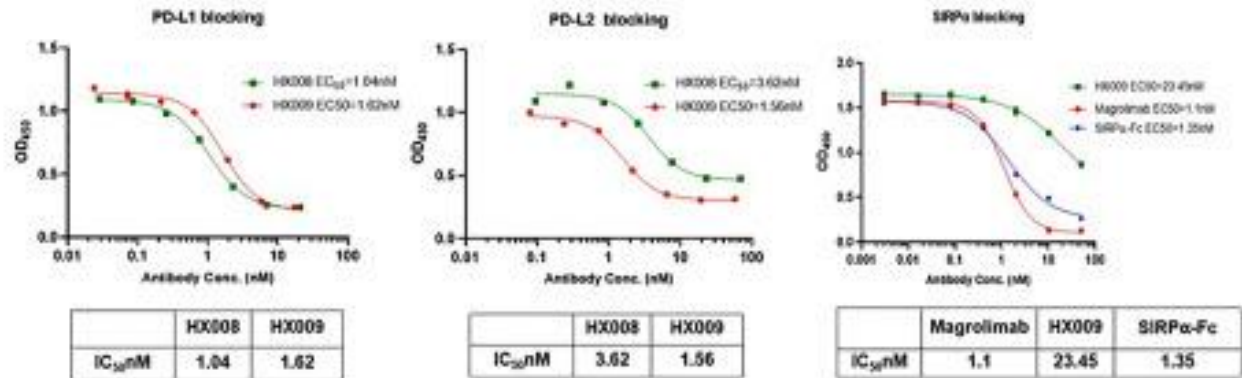
A.



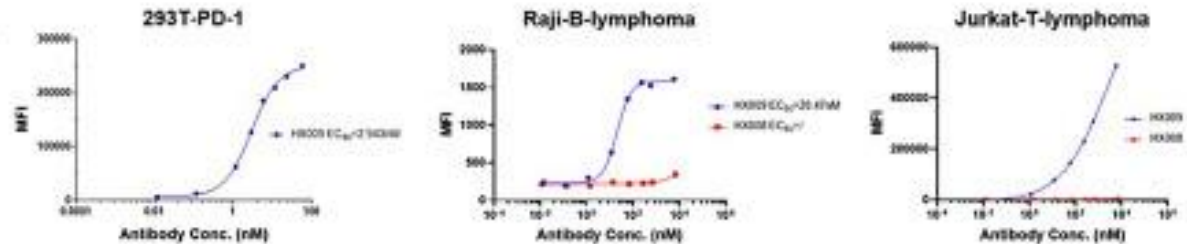
B.



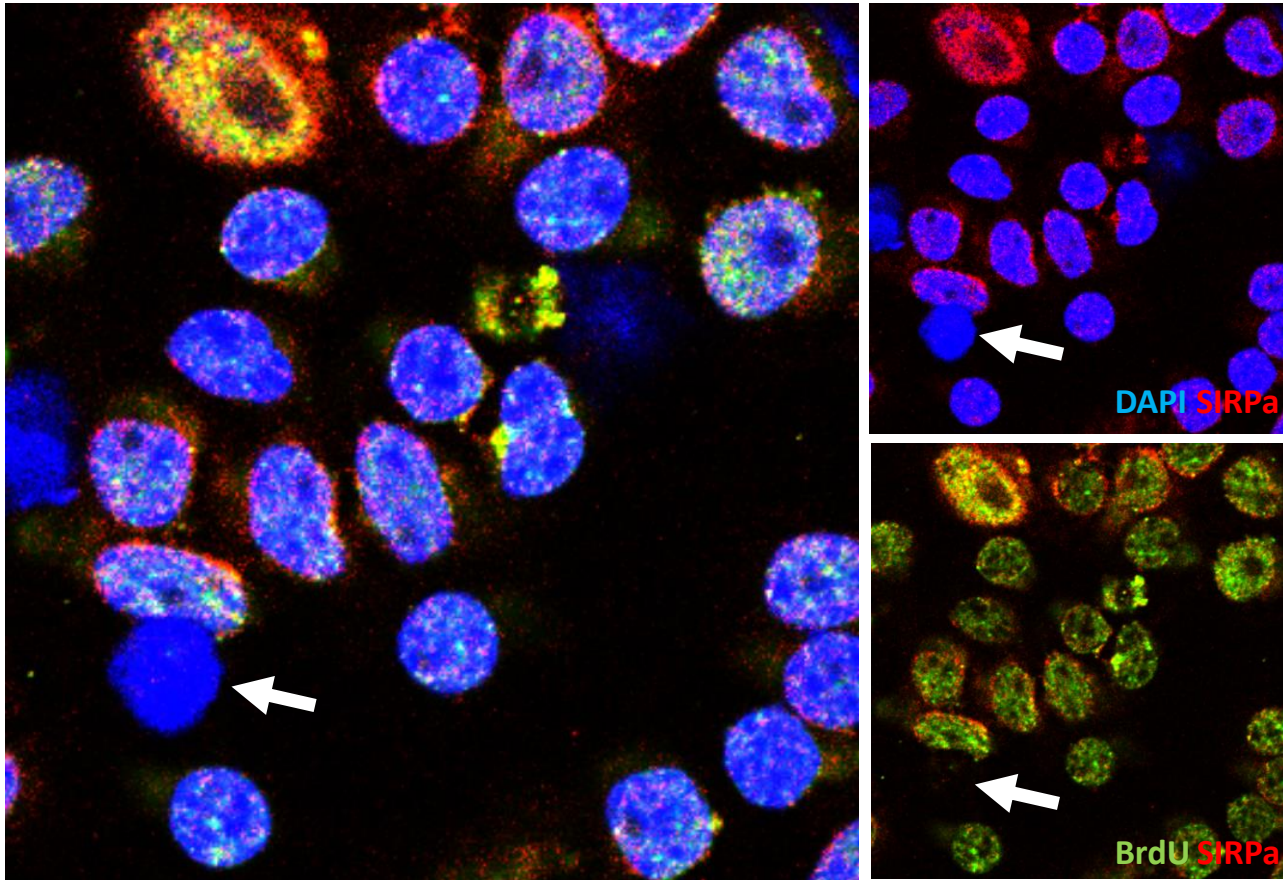
C.



D.

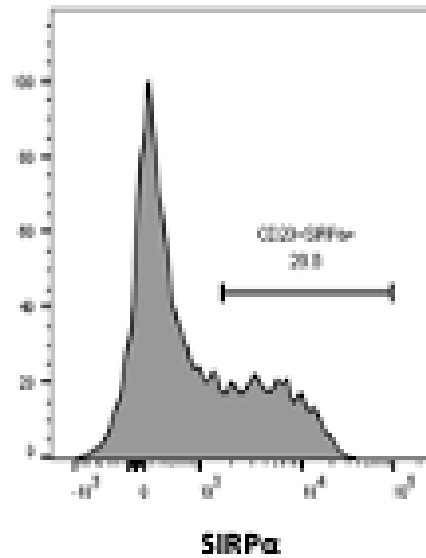


Other issues - SIRP α expressing B- cells are proliferating

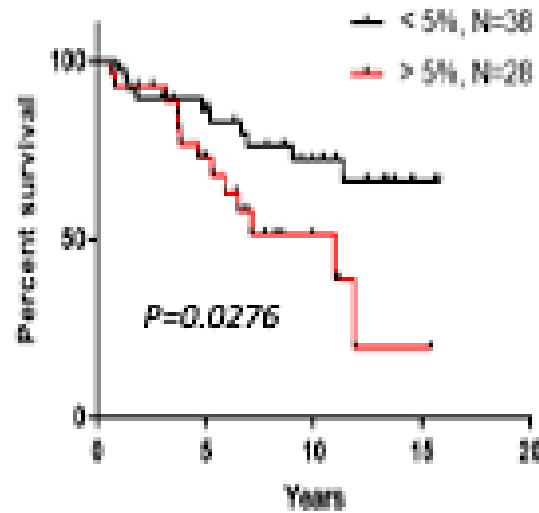


SIRP α expressing B- cells are proliferating

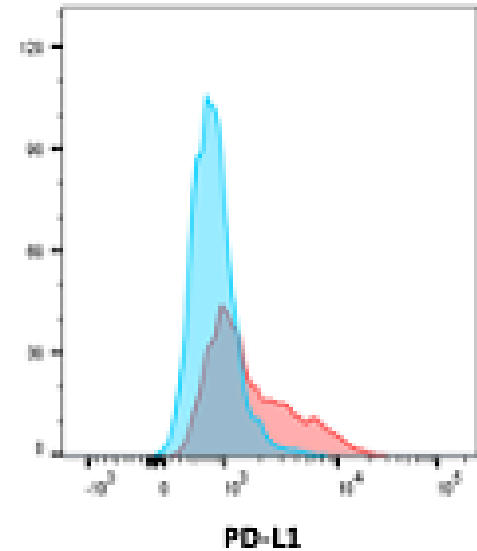
A.



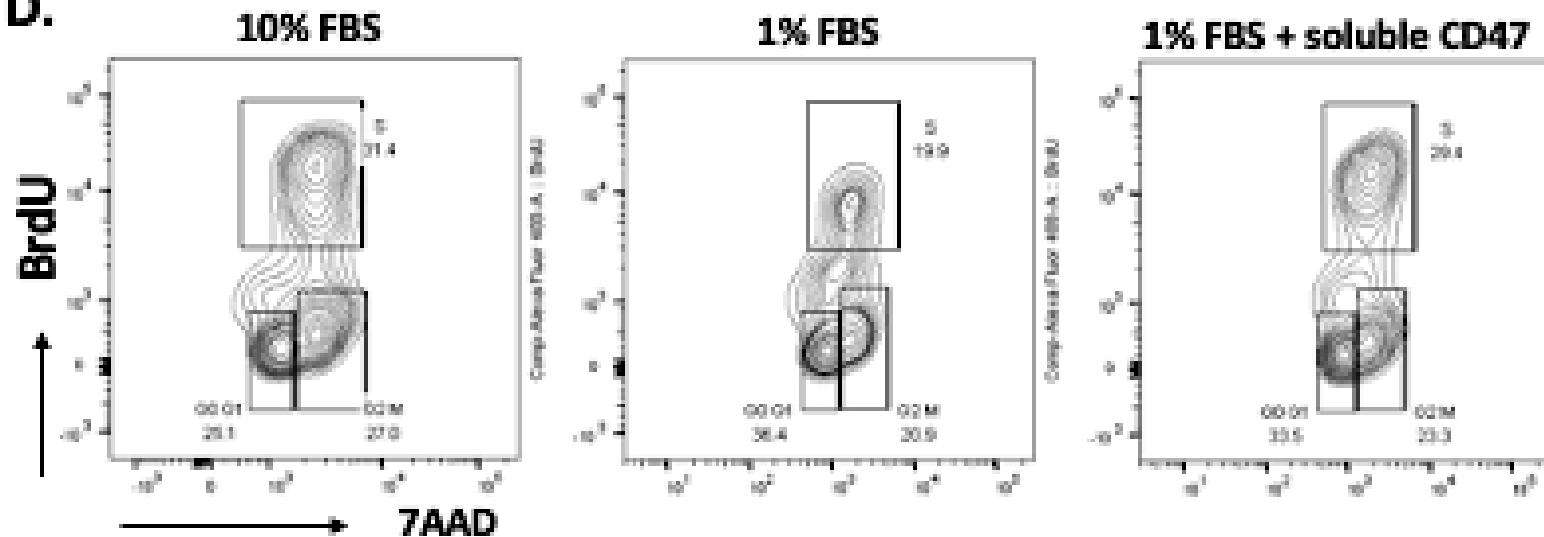
B.



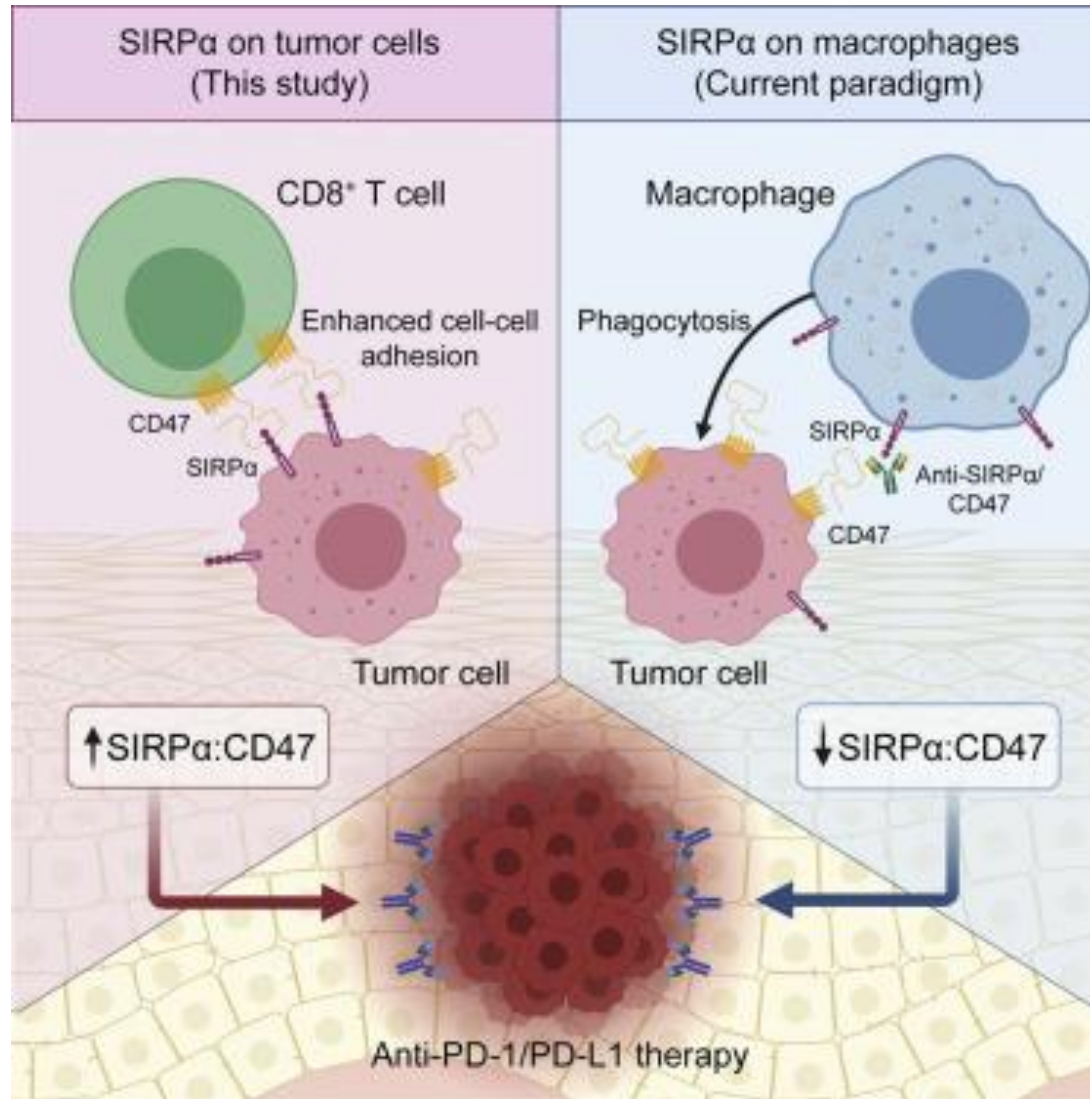
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D.



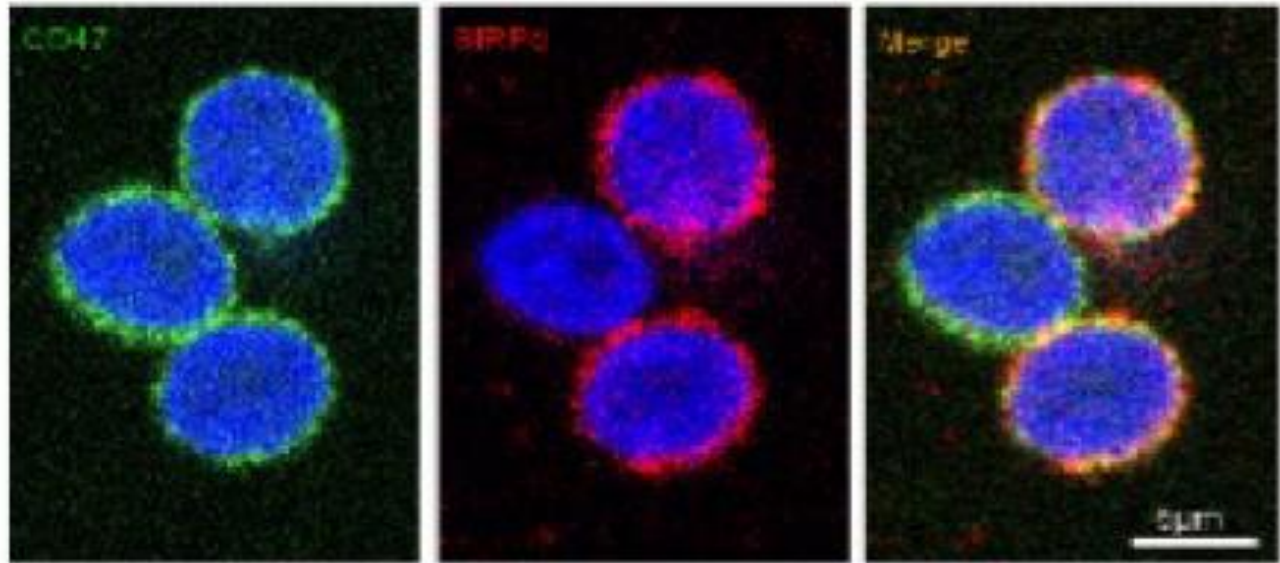
Other issues - SIRP α promotes sensitivity to checkpoint inhibition immunotherapy



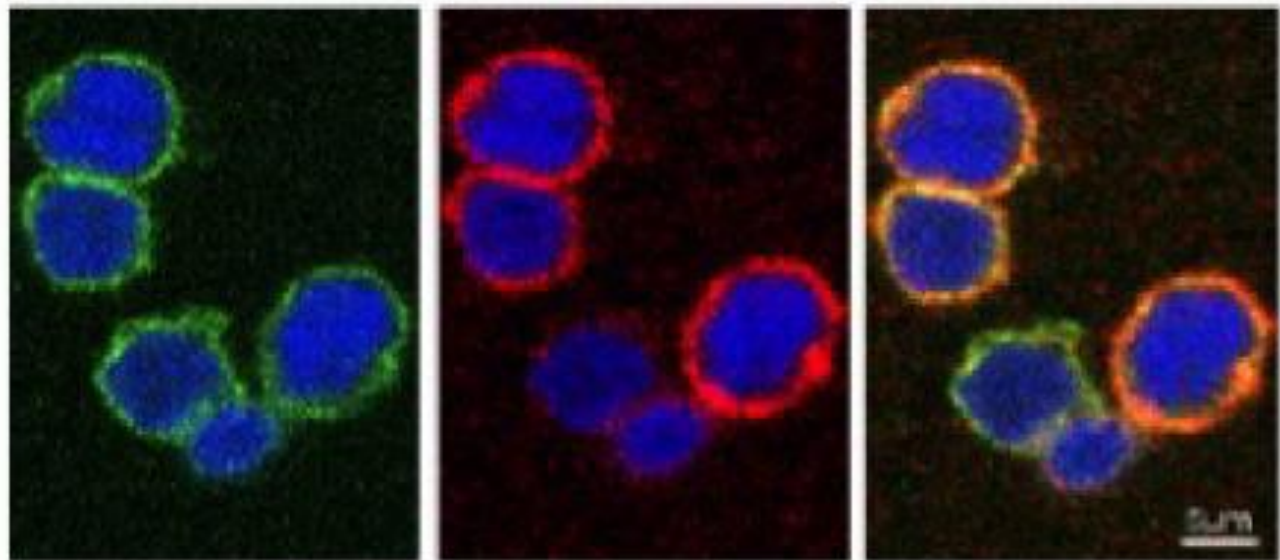
Other issues - SIRP α is also expressed on T-cells

B

Resting
T cells



Activated
T cells



Summary

- Different subtypes of intratumoral macrophages exist in lymphoma defined by SIRP α expression.
- These macrophage subsets have different function and phagocytic ability and present a therapeutic opportunity.
- Inhibition of CD47/SIRP α signaling in patient with T- and B-cell lymphomas is clinically effective.

Acknowledgements

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