Targeting CD47 in Cutaneous T-cell Lymphomas

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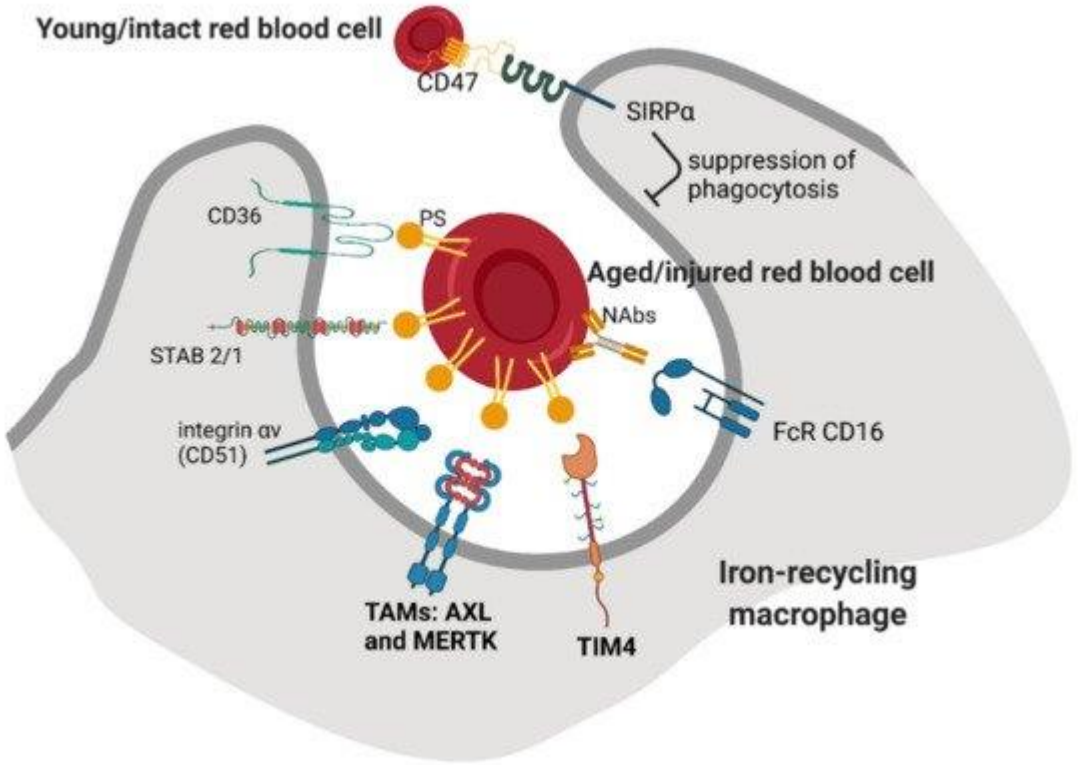
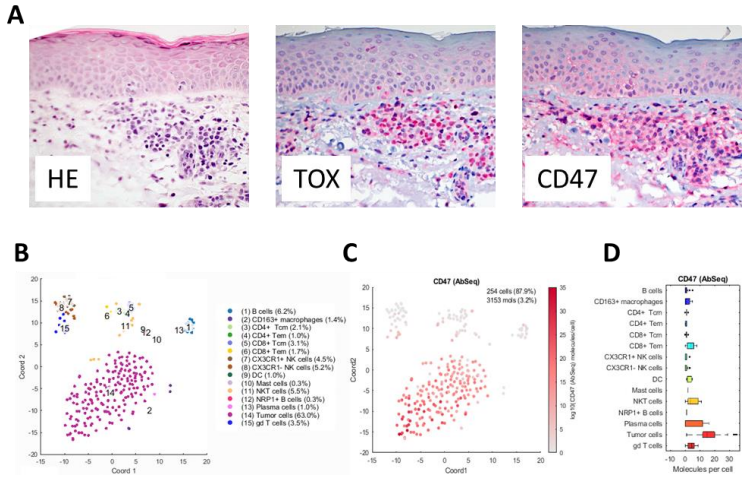
Conflict of Interests

- Research support: Adaptive Biotechnology, Pfizer, Kyowa Kirin, Actelion, Trillium Therapeutics, Mallinckrodt
- Site Principal Investigator: Eisai, Innate Pharma, Tellomak, Corvus
- Advisory Board: Trillium Therapeutics, CHRISPR Therapeutics, SkinJect, Citius Pharma, Castle Bioscience, Bioniz, Almiral
- Speakers Bureau: Kyowa Kirin, Helsin

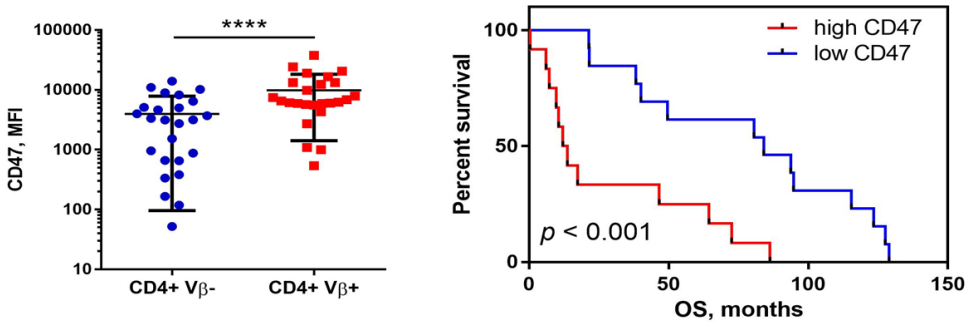
CD47 is a marker of self on all normal cells known to regulate cell turnover



[Slusarczyk et al Genes, 2021]

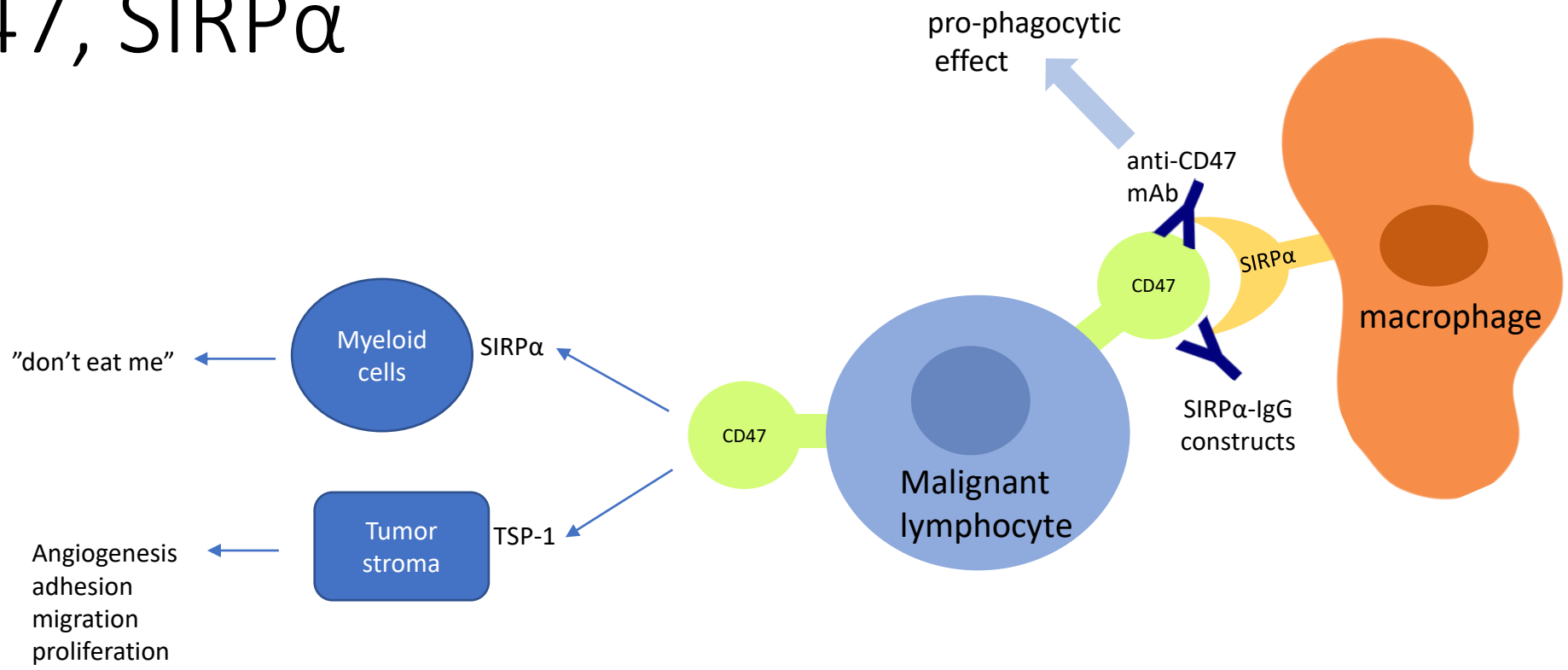


[Kruglov O, … Akilov OE. Cancer Immunol Immunother, 2022]



[Johnson L,…, Akilov OE. Blood Adv. 2019]

CD47, SIRPα


pro-phagocytic
effect
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mAb
SIRPα
CD47
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SIRPα-IgG
constructs
Myeloid
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”don’t eat me”
SIRPα
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Malignant
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Tumor
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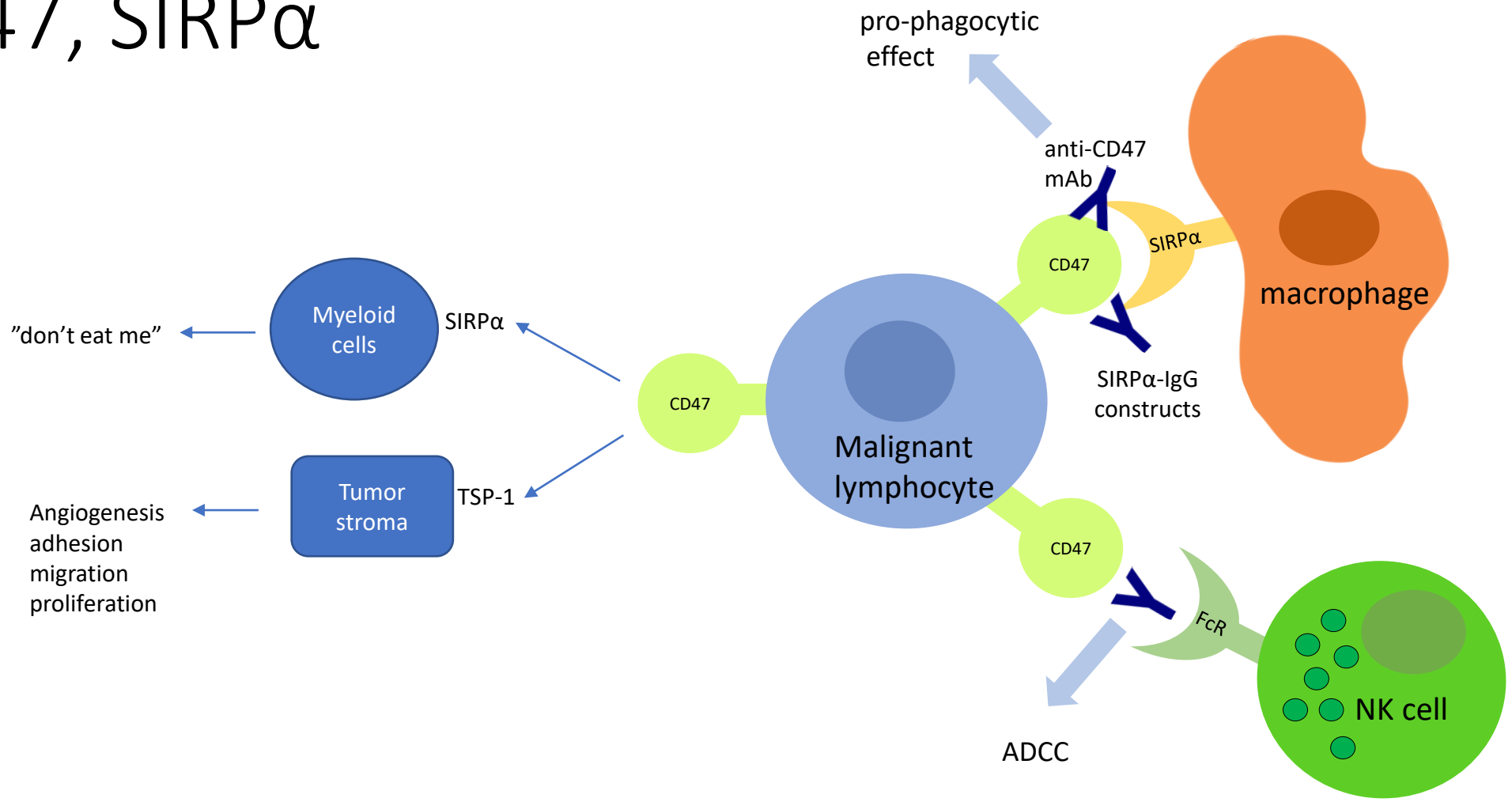
TSP-1
Angiogenesis
adhesion
migration
proliferation

CD47, SIRPα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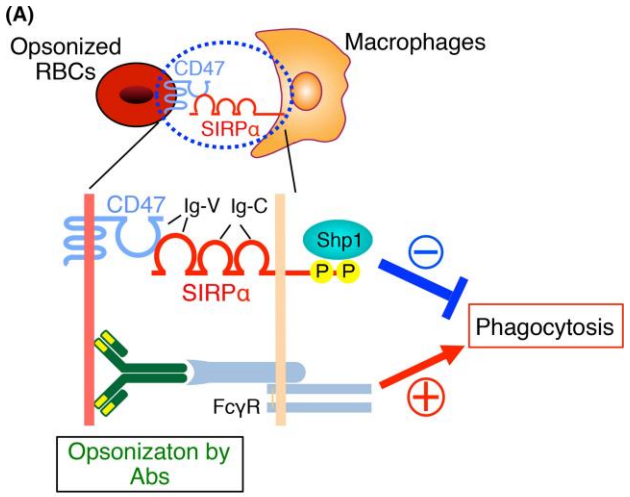
proliferation
CD47
FcR
NK cell
ADCC

Anti-CD47 antibodies

Company	FortySeven/ Gilead	Arch Oncology		I-MAB Biopharma	Cellgene	Surface Oncology	Jiangsu HengRui Medicine
Candidate	Magrolimab (5F9)	AO-176	Ti-061	TJ011133 (TJC4)	CC-90002	SRF231	SHR 1603
Molecule	mAB	mAb	mAb	mAb	mAB	mAb	mAb
Fc isotype	IgG4	IgG2	IgG4	IgG4	IgG4-PE	IgG4	IgG4
Lead indication	MDS/AML; DLBL Solid tumors B cell lymphoma Colorectal cancer Hematologic MF	Solid tumors; MM; Preclinical: lymphoma and TLL	Solid tumors	R/R solid tumors and lymphoma	Not been used as monotherapy R/R NHL in combination	B cell lymphoma, R/R solid tumors	Advanced CA; hematologic CA
RBC binding	yes	low			yes		
Combination	+Rituximab +Cetuximab +Azacitidine + cabazitaxel + mogalizumab	+ Pembro +paclitaxel			+ Rituximab	No CR/PR 4 mg/kg >90% R occupancy	

Efficacy of anti-CD47 antibodies

- Most of the clinical trials in B cell lymphoma
  - Current trial are trying to demonstrate the synergistic effect of the combination of anti-CD47 blockade with rituximab
- Margolimab 63% ORR and 42% CR in AML; no data in CTCL
  - Currently, a trial of margolimab + mogamulizumab run by Dr. Khodadoust at Stanford
- IgG2 based antibody will not be used as monotherapy
- Given the ubiquitous expression of CD47, mAbs targeting CD47 has a high “drug sink” of erythrocytes, platelets, and other CD47-expressing cells, leading to on-target anemia and rapid elimination
  - anti-SIRPα constructs



[Murata et al. Cancer Science, 2018]

SIRPα protein constructs

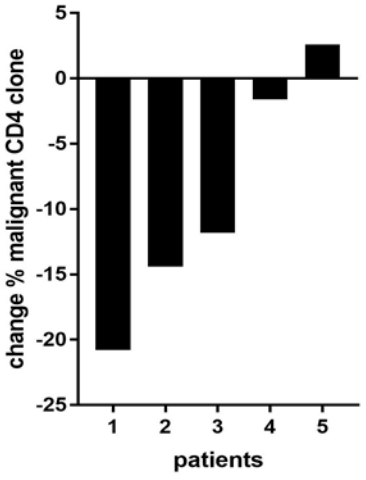
	SIRPα protein constructs			
Company	Trillium Therapeutics		ALX Oncology	Weisskopf's group
Candidate	TTI-621	TTI-622	ALX-148	CV1
Molecule	WT SIRPα-IgG1 Fc fusion	WT SIRPα-IgG4 Fc fusion	WT SIRPα-IgG1 fusion with inactive Fc	Truncated SIRPα protein
Lead indication	PTCL Hematologic malignancies	Advanced Hematologic Malignancies, Including Lymphoma, Leukemia, and Multiple Myeloma.	Head and neck SCC (phase II) HER2+ gastric/gastroesophageal cancer (phase II/III), breast ca, NHL, mylodysplastic syndromes, AML (phase I/II)	Preclinical: lymphoma; breast CA
Rbc binding?	No RBC binding	No RBC binding	+RBC binding	
Combinations in clinical trials	+ PD1/PDL1 + Peg-IFN-α2a		+ pembrolizumab +Trastuzumab	+rituximab + trastuzumab

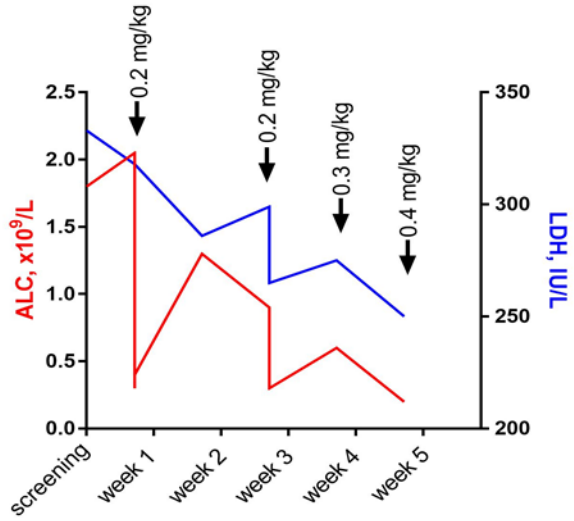
Efficacy

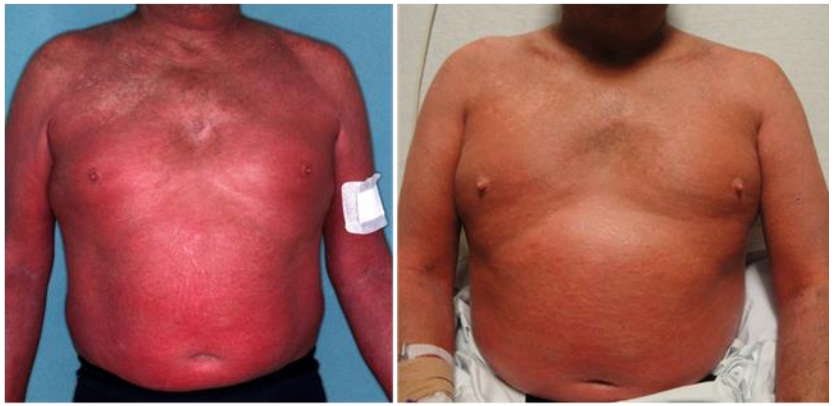
- ALX148: NHSCC trial
  - ALX148 + pembro = ORR 40%
  - Pembro alone = ORR 18%
- ALX148 AE: infusion related reactions, chills, fatigue, nausea, pyrexia, pruritis, diarrhea, and thrombocytopenia
- Abx have poor tissue penetration due to their high molecular weights
  - The solution is a small proteins
    - High-affinity variants of CD47 with N-terminal peptide extension, Velcro-CD47
    - A truncated SIRPα variant, CV1 (Weisskopf's group)

TTI-621 IV trial

Blood response





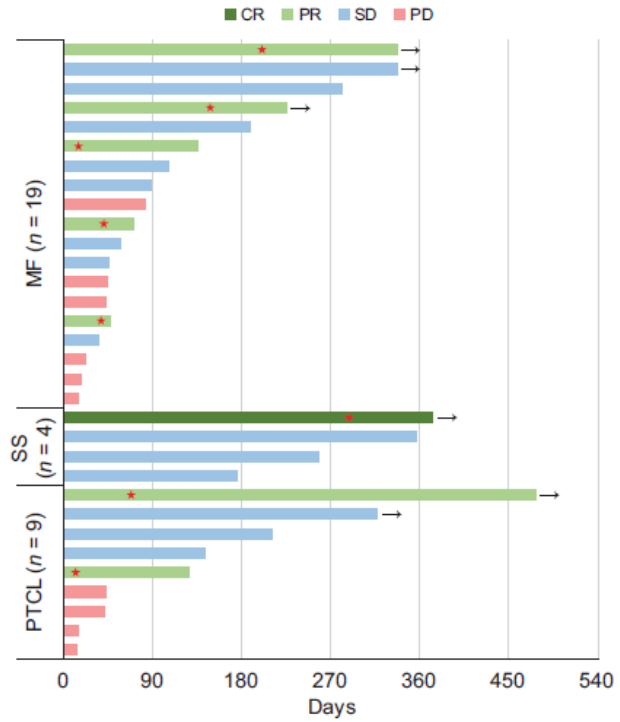


[Johnson L,…, Akilov OE. Blood Adv. 2019]

All compartments

Best response in patients with T-cell lymphoma

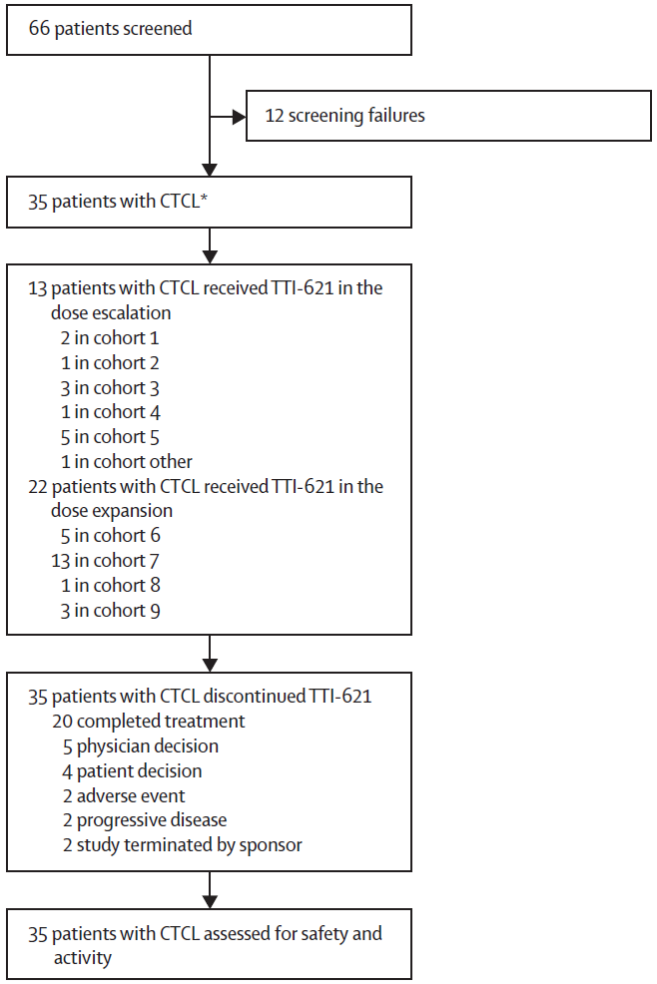
	n	Response, *n* (%)			Median (range) time to response, d	Median (range) treatment duration, d
		CR	PR	Total		
MF	19	0	5 (26)	5 (26)	50 (23–218)	135 (41–338)
SS	4	1 (25)	0	1 (25)	303 (303–303)	373 (373–373)
PTCL	9	0	2 (22)	2 (22)	50 (20–79)	302 (127–477)
Total	32	1 (3)	7 (22)	8 (25)	65 (20–303)	181 (41–477)



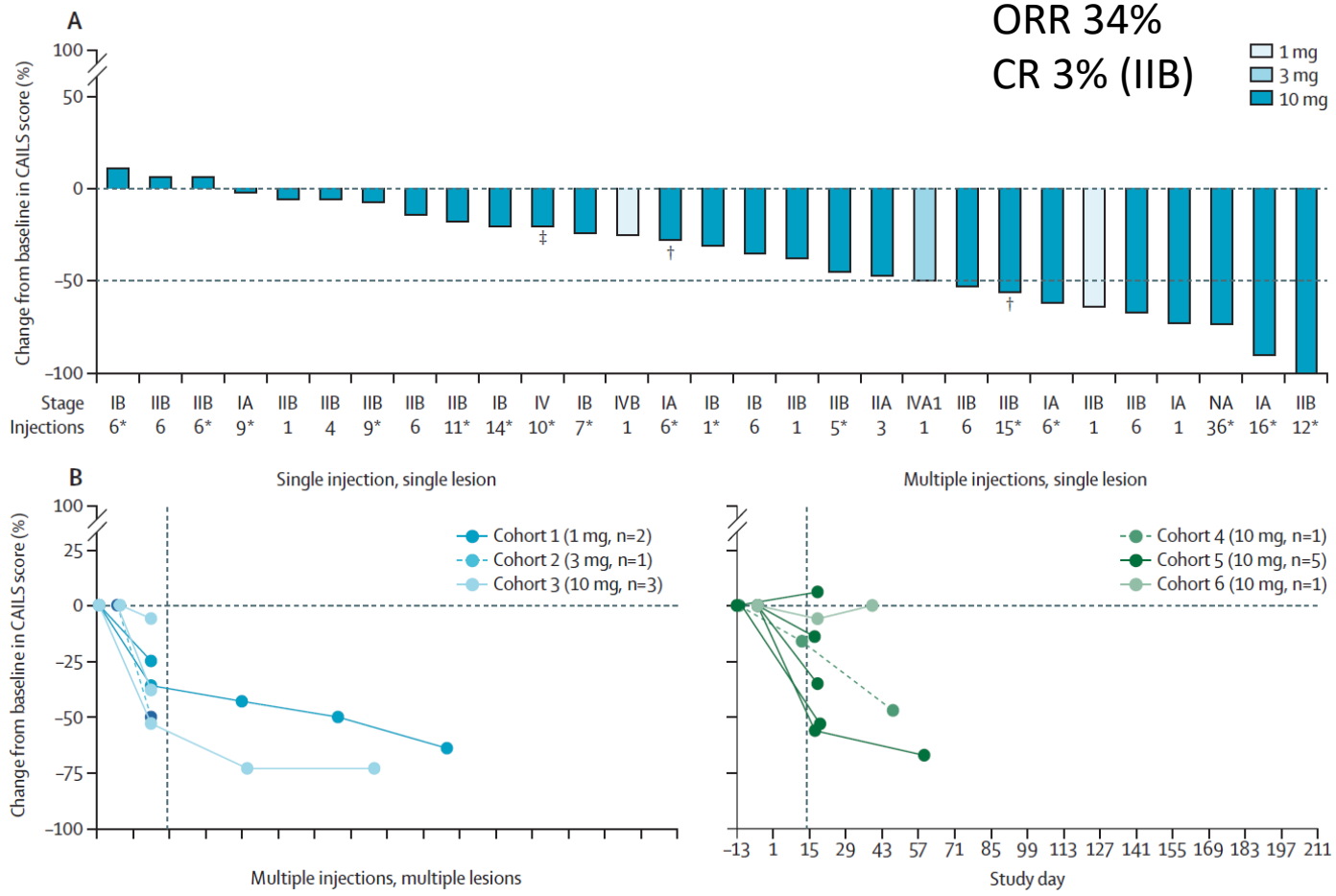
[Ansell S, et all. Clin Cancer Res, 2021]

ORR 21%
CR 3% (SzS)

TTI-621 IL trial



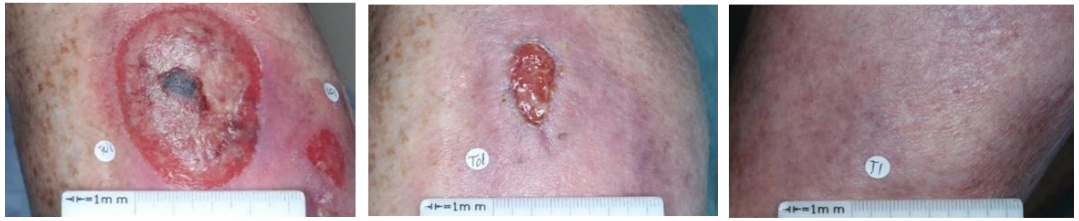
ORR 34%
CR 3% (IIB)



[Querfeld C,…. Akilov OE. Lancet Hematol, 2021]

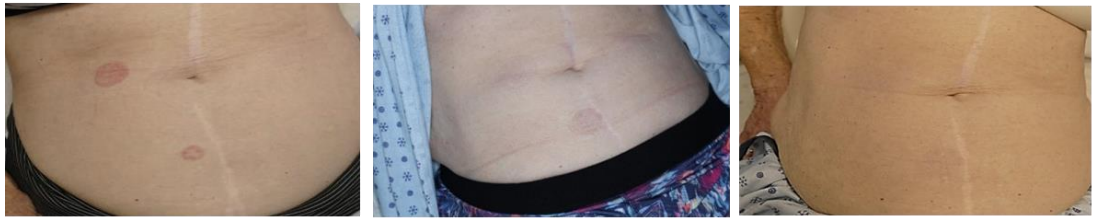
TTI-621 IL trial

Injected Lesion – T01 (Left Calf)



Screening | End of Week 7 | End of Week 11

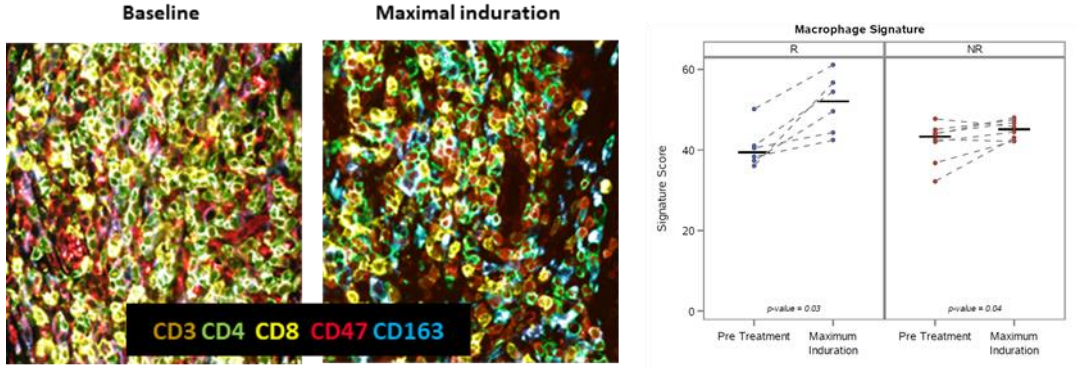
Distal Non-Injected Lesion – Abdomen



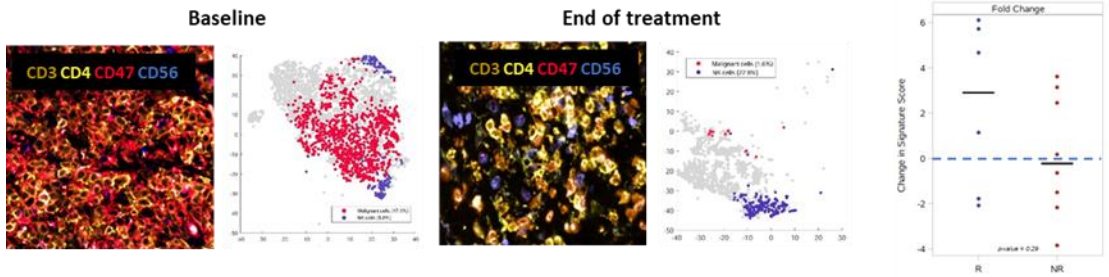
Screening | End of Week 2 | End of Week 9

[Patient of Dr. Querfeld]

Infiltration by CD163+ cells

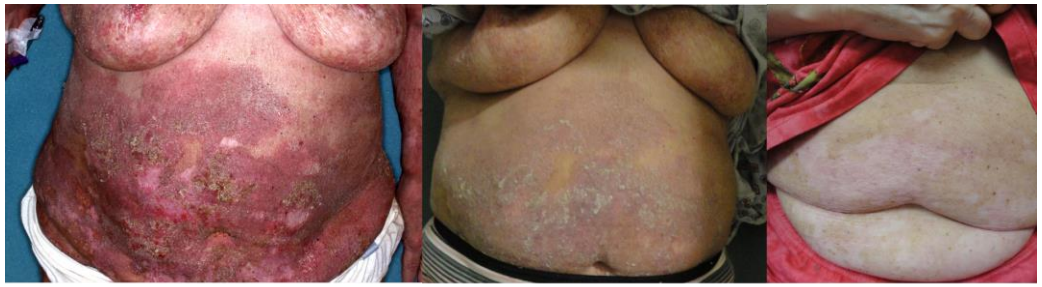


Decrease of CD47 cells and an increase of CD56 cells



[Querfeld C,…. Akilov OE. Lancet Hematol, 2021]

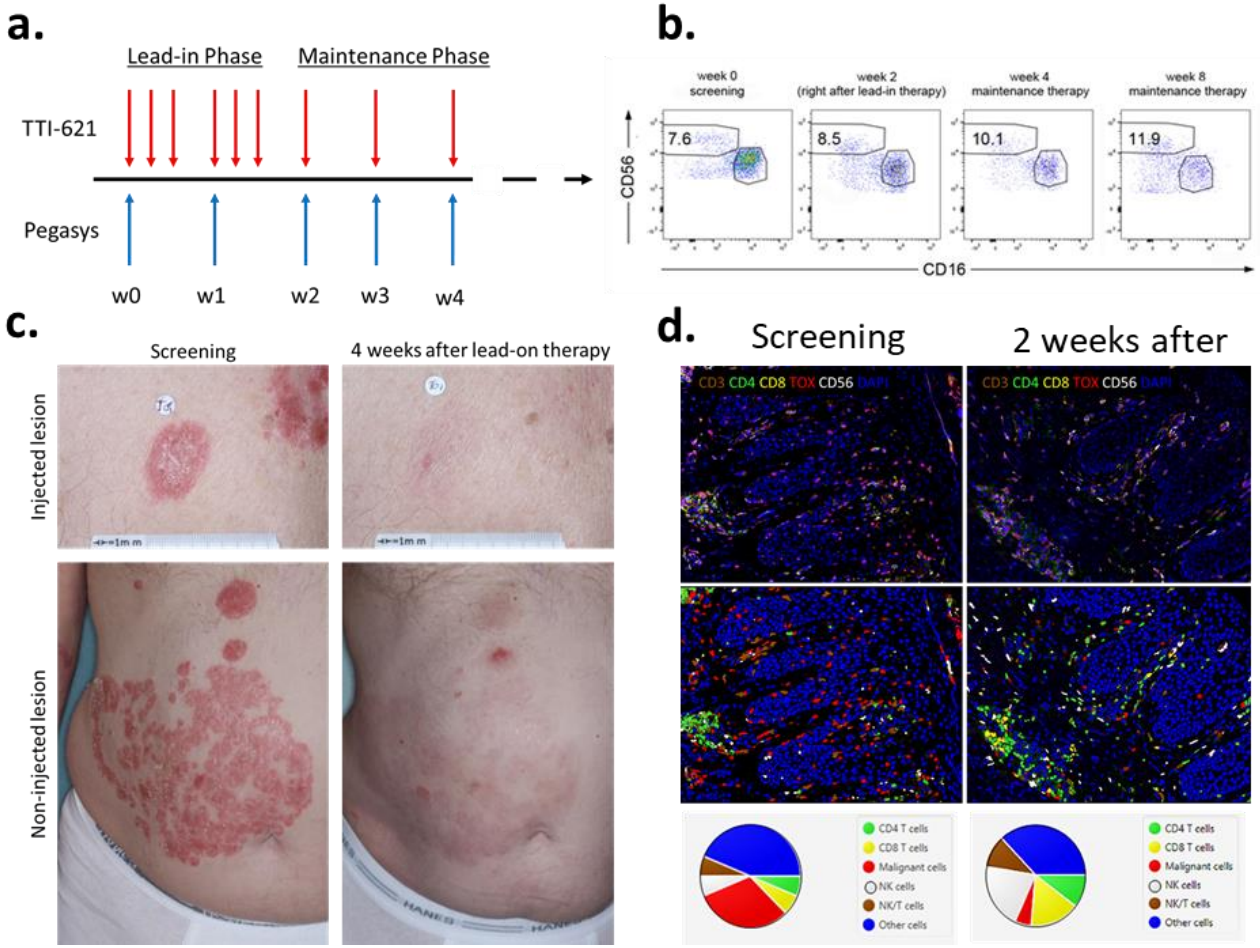
Clinical response to **TTI-621+PEG-IFN-α2a** is associated with an increase of NK cells in the peripheral blood and skin after treatment



Before injection of TTI-621

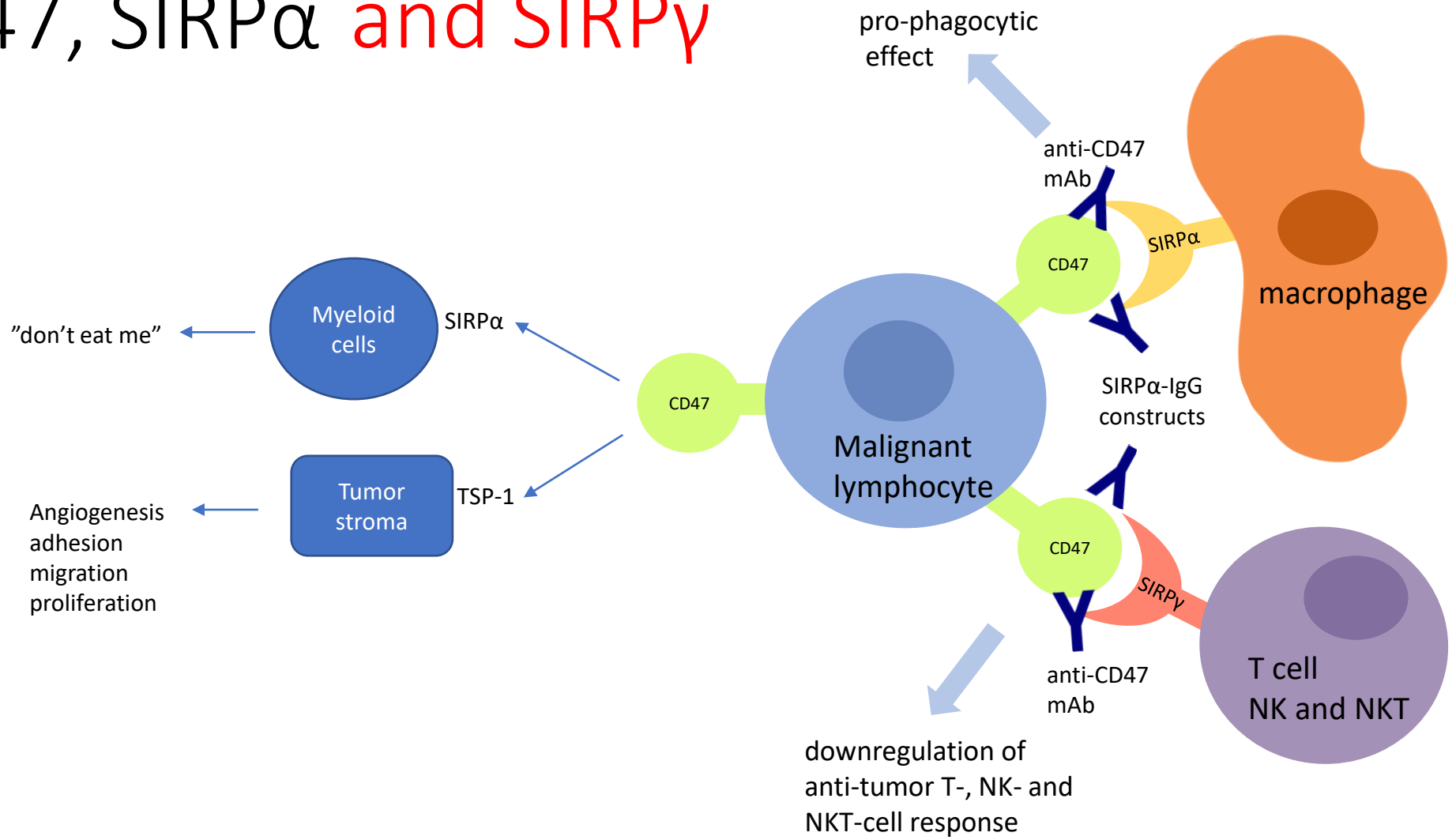
6 injections of TTI-621
+ 2 injections of PEG-IFN-α2a

Maintenance
PEG-IFN-α2a weekly



[Jiang TT,… Akilov OE. Cancers 2021]

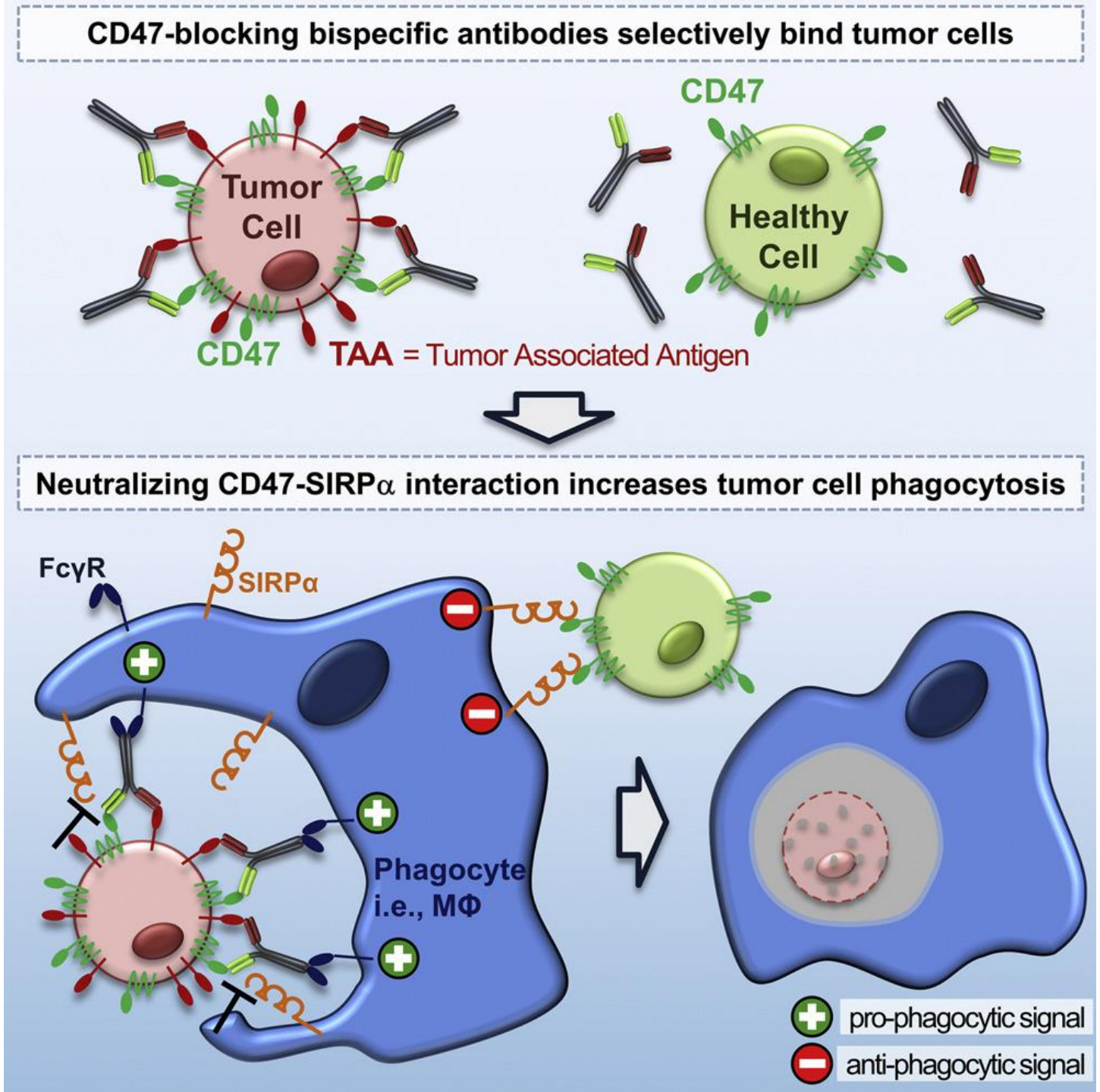
CD47, SIRPα and SIRPγ



Anti-SIRPα antibody

	SIRPα antibody	
Company	Celgene	OSE Immunotherapeutics
Candidate	CC-95251	BI 765063 (OSE-172)
Molecule	mAb	mAb IgG4
Lead indication	Solid tumors, heme CA	Advanced solid tumors
Rbc binding?	No	No
Combinations in clinical trials	+ Rituximab + Cetuximab	+ PD-1 inhibitor (ezabenlimab)

- No anemia/thrombocytopenia
- Stimulate T-cell recruitment in TME
- Work best in tumors rich in TILs
- Anti-SIRPα Abx increase PD-L1 expression on tumor cells 2 weeks after the first dose
- BI 765063 does not increase phagocytosis when used alone
- Explored in combinations



[Dheilly et al Molecular Therapy, 2016]

Bispecific antibody

	Bispecific antibody			
Company	Waterstone Hanxbio Pty Ltd (Australia)	Innovent Biologics (China)	Shattuck Labs	Kahr Medical
Candidate	HX009	IBI322	SL-172154	DSP107
Molecule	CD47/PD1	CD47/PDL1	SIRPα/40L	SIRPα/41BB
Lead indication	advanced solid tumors	lung, cervical, esophageal, HNSCC and liver CA	Platinum-resistant ovarian cancers	Non-small cell lung cancer, SCC, advanced solid tumors
Rbc binding?	1/21 pts had anemia in prelim results	unknown	minimal	unknown
Combinations in clinical trials			Many combinations for future clinical trials	Lymphoma express 41BB (CD137) * preclinical studies in DLBCL* Need PD1 + atezolizumab (PD-L1)

Tumor cells Macrophages T-cells

Conclusions and future directions

- There is no panacea:
  - IMT: multi-target approach (is there hope for tetramers?)
  - IMT: innate and adaptive immune response:
    - APC induction (in vivo expansion with Flt3L, STING or TLR agonist)
    - early engagement of CD8 and NK cells
    - attraction of TILs in TME
    - checkpoint inhibition (Tim3, LAG3, BTLA and other)
    - sustainability of adaptive immune response
  - Combinations