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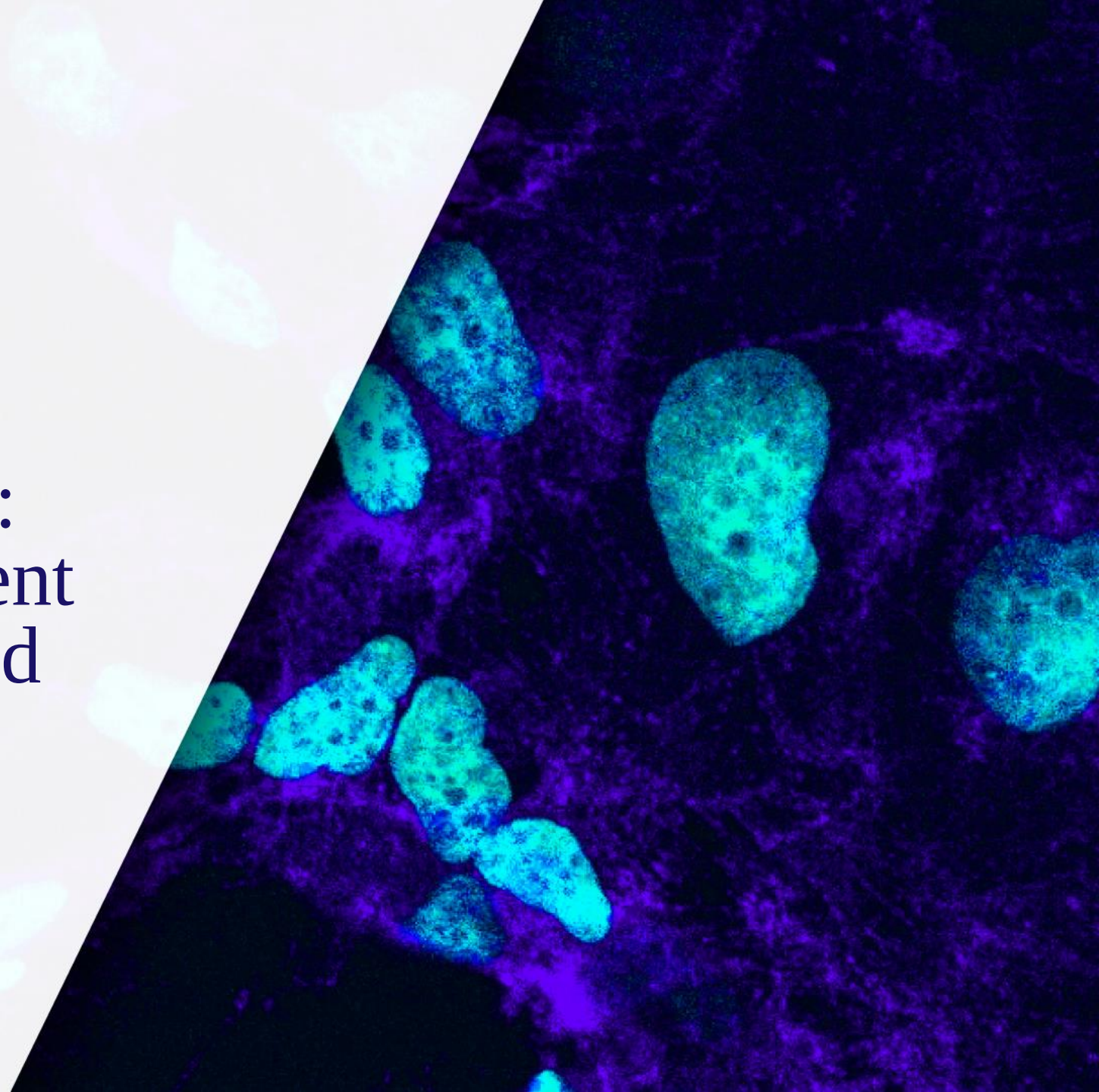
KOL Webinar on CD47 Therapeutics: A Potential Treatment For Solid Tumor and Hematological Malignancies



December 2021

AGENDA

Welcome and Introduction	**Yaron Pereg, PhD**, CEO, KAHR, Jerusalem, Israel
Therapeutic potential of CD47 therapies for solid tumors	**Ezra Cohen, MD, FRCPSC, FASCO,** Chief of Hematology-Oncology at UC San Diego Moores Cancer Center, and o-Director of the San Diego Center for Precision Immunotherapy, San Diego, California
Unmet need in MDS and AML and CD47 landscape	**Naval G. Daver, MD,** Associate Professor of Leukemia at MD Anderson Cancer Center, Houston, Texas
KAHR Pipeline Overview	**Yaron Pereg, PhD**, CEO, KAHR, Jerusalem, Israel
DSP107 Initial Phase 1 Data	**Adam Foley-Comer, MD**, CMO, KAHR, Jerusalem, Israel
Q&A Session	

EZRA COHEN, MD, FRCPSC, FASCO

CHIEF OF HEMATOLOGY-ONCOLOGY AT UC SAN DIEGO MOORES CANCER CENTER, AND CO-DIRECTOR OF THE SAN DIEGO CENTER FOR PRECISION IMMUNOTHERAPY

Ezra Cohen, MD, FRCPSC, FASCO is a board-certified oncologist and an internationally renowned cancer researcher. Dr. Cohen serves as co-director of UC San Diego Health's Precision Immunotherapy Clinic, which offers the most promising investigational immunotherapy treatments for many types of cancer, including head and neck cancers. At UC San Diego Health's Moores Cancer Center, he is associate director for translational science and the leader of the Solid Tumor Therapeutics research program. As a physician-scientist, Dr. Cohen also leads a laboratory that studies novel cancer treatments, including immunotherapy, with a particular focus on squamous cell carcinomas and cancers of the thyroid, salivary gland, and HPV-related oropharyngeal cancers. A frequent speaker at national and international meetings, he has authored more than 170 peer-reviewed papers and has been the principal investigator of multiple clinical trials of new drugs for head and neck cancer and other solid tumors in all phases of development. Dr. Cohen completed a hematology/oncology fellowship at the University of Chicago, where he was named chief fellow. He completed residencies in family medicine at the University of Toronto and in internal medicine at Albert Einstein College of Medicine. Dr. Cohen earned his medical degree at University of Toronto. He is board certified in medical oncology, and a fellow of the Royal College of Physicians and Surgeons of Canada (FRCPSC) and the American Society of Clinical Oncology (FASCO).

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NAVAL G. DAVER, MD

ASSOCIATE PROFESSOR OF LEUKEMIA AT MD ANDERSON CANCER CENTER, HOUSTON, TEXAS

Naval G. Daver, MD is an Associate Professor in the Department of Leukemia at MD Anderson Cancer Center. He completed his medical school from Grant Medical College and Sir J group of Hospitals Mumbai, followed by a residency and fellowship in hematology-oncology from Baylor College of Medicine. He is a clinical investigator with a focus on molecular and immune therapies in AML and Myelofibrosis and is principal investigator on >25 ongoing institutional, national and international clinical trials in these diseases. These trials focus on developing a personalized therapy approach by targeting specific mutations or immune pathways expressed by patients with AML, evaluating novel combinations of targeted, immune and cytotoxic agents, and identifying and overcoming mechanism of resistance. He is especially interested in developing monoclonal and bispecific antibodies, immune checkpoint and vaccine based approaches in AML, MDS, and myelofibrosis and is leading a number of these trials at MDACC. Dr. Daver has published >150 peer-reviewed manuscripts and is on the editorial board of numerous hematology specific journals. He has also authored numerous abstracts at national and international conferences.

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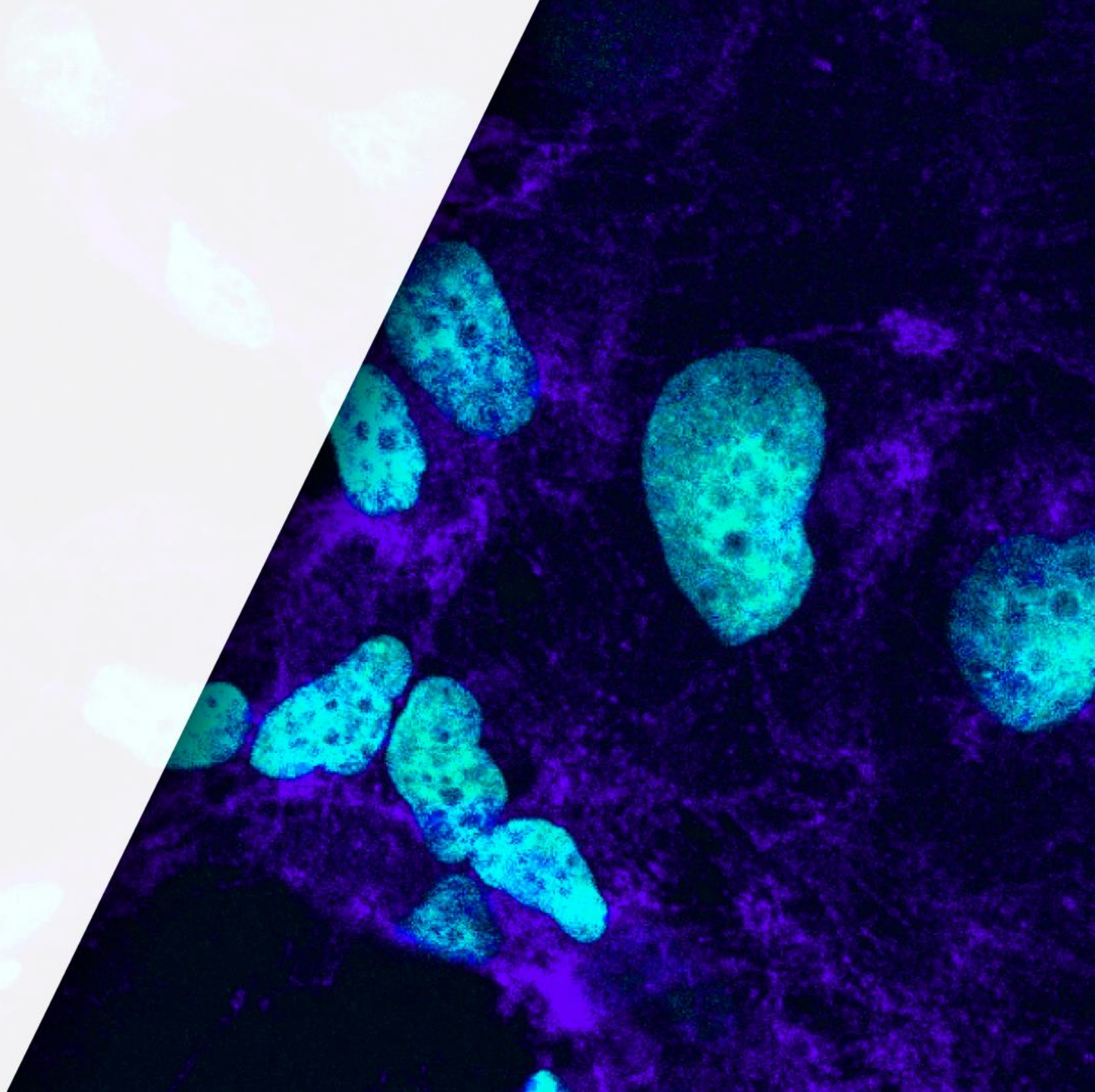
UNMASKING CANCER CELL CAMOUFLAGE

COMPANY PRESENTATION | Dec. 2021



SPECIAL NOTE REGARDING FORWARD LOOKING STATEMENTS

This presentation contains forward-looking statements about our expectations, beliefs and intentions regarding, among other things, our product development efforts, business, financial condition, results of operations, strategies, plans and prospects. In addition, from time to time, we or our representatives have made or may make forward-looking statements, orally or in writing. Forward-looking statements can be identified by the use of forward-looking words such as “believe”, “expect”, “intend”, “plan”, “may”, “should”, “could”, “might”, “seek”, “target”, “will”, “project”, “forecast”, “continue” or “anticipate” or their negatives or variations of these words or other comparable words or by the fact that these statements do not relate strictly to historical matters. Forward-looking statements relate to anticipated or expected events, activities, trends or results as of the date they are made. Because forward-looking statements relate to matters that have not yet occurred, these statements are inherently subject to risks and uncertainties that could cause our actual results to differ materially from any future results expressed or implied by the forward-looking statements. Many factors could cause our actual activities or results to differ materially from the activities and results anticipated in forward-looking statements.

We believe these forward-looking statements are reasonable; however, these statements are only current predictions and are subject to known and unknown risks, uncertainties and other factors that may cause our or our industry’s actual results, levels of activity, performance or achievements to be materially different from those anticipated by the forward-looking statements.

All forward-looking statements speak only as of the date hereof, and we undertake no obligations to update or revise forward-looking statements to reflect events or circumstances that arise after the date made or to reflect the occurrence of unanticipated events, except as required by applicable law. In evaluating forward-looking statements, you should consider these risks and uncertainties.

MULTIFUNCTIONAL CANCER IMMUNOTHERAPIES TARGETING INNATE AND ADAPTIVE IMMUNE SYSTEMS

NOVEL MIRPs

Multifunctional Immuno-Recruitment Proteins – versatile platform targeting both innate & adaptive immunity across cancers

UNIQUE PIPELINE

- First-in-class potential across 3 programs
- Lead candidate DSP107 –
  CD47 inhibition (Cancer specific)
  4-1BB activation (CD47-conditional)

UPCOMING MILESTONES

- **DSP107**| Initial Ph I/II combo data H1 2022
- **DSP502 & DSP216** | IND 2023
- **Multiple future candidates** in research pipeline

MARKET

Immuno-therapeutics
$56.5B by 2025
(Source: Allied Market Research)

IP

13 families
4 granted (US and other territories),
73 pending (NP worldwide and PCT stage)

Experienced Leadership

Management team, BOD and SAB comprised of leading experts including technology inventor, Prof. Mark Tykocinski, Dean of the School of Medicine and Provost, Jefferson University.

EXPERIENCED LEADERSHIP TEAM

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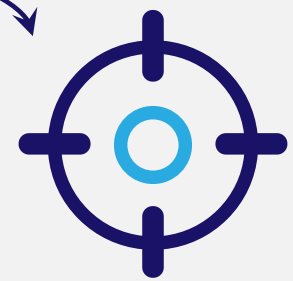
Co-Founder & Managing General Partner at ALIVE Israel HealthTech Fund; 20+ yrs investing in biotech

EFFECTIVELY TREATING CANCER REQUIRES A MULTIFACETED APPROACH

Selectively disabling cancer defense mechanism

WHILE



Recruiting a local targeted immune attack

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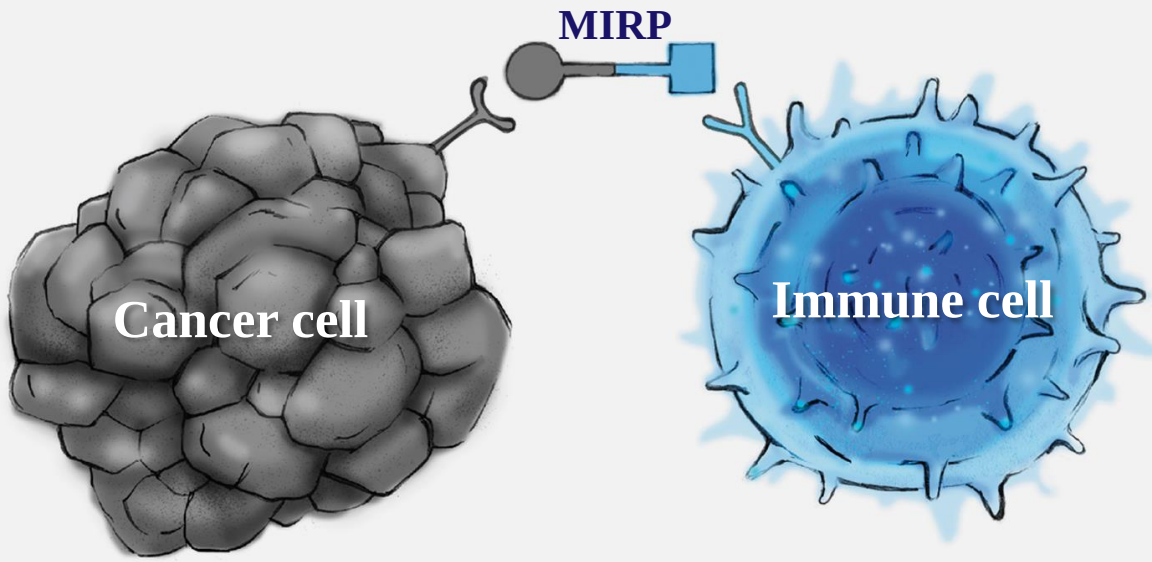
MULTIFUNCTIONAL IMMUNO-RECRUITMENT PROTEIN (MIRP) VERSATILE IMMUNO-THERAPEUTIC PLATFORM DESIGNED TO SAFELY OVERCOME CANCER EVASION

MIRPs trigger a multilayered immune response by:

1. Inhibiting key evasion markers on cancer cells
2. Activating innate and adaptive anti-tumor immunity



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MIRP STRATEGIES FOR IMMUNE RECRUITMENT & ACTIVATION

Two configurations utilize different target-dependent strategies designed to improve safety and efficacy

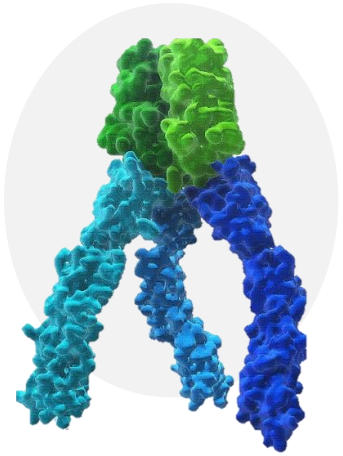
DSP (Dual Signaling Protein)

Combined checkpoint inhibition and immune co-stimulation

DSP107

4-1BB activator – *CD47-conditional T-cell activation*

CD47 inhibitor – *Trimeric binding for cancer specific blocking*



DSP-Fc (Dual Signaling Protein With Fc Domain)

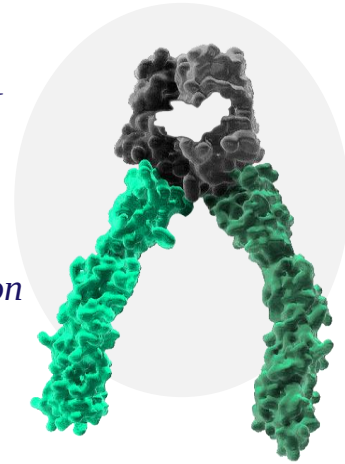
Dual checkpoint inhibition for diverse immune modulation

DSP502

PVR inhibitor – *Dual PD1/TIGIT inhibition with DNAMI potentiation*

PD-L1 inhibitor – *T and NK cell activation*

Active IgG1 Fc – *Half-life extension, ADCC activity*

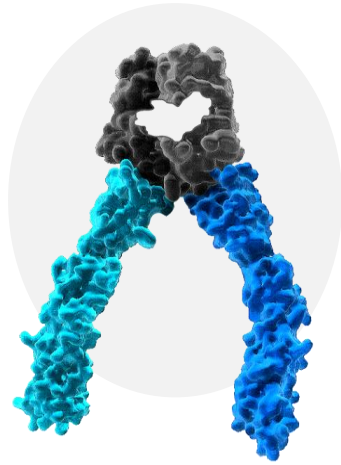


DSP216

CD47 inhibitor – *Avidity driven for cancer specific blocking*

HLA-G inhibitor – *Inhibition of LILRB1,LILRB2*

Inactive Fc – *Half-life extension*



FOCUSED AND DIFFERENTIATED PIPELINE

MIRP Type	Program	Targets	Indications	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Upcoming Milestones	Commercial Rights
DSP	DSP107	CD47 4-1BB	Solid Tumors, NSCLC			DSP107 ± atezolizumab*			Initial Ph I/II combo results 1H 2022	
			AML / MDS			DSP107 ± azacitidine + venetoclax			Initial Ph Ib results Q4 2022	
DSP-Fc	DSP502	PVR PD-L1	Oncology						IND Filing 1H 2023	
	DSP216	HLA-G CD47	Oncology						IND Filing 2H 2023	

Roche *Clinical trial collaboration and supply agreement with Roche for the PD-L1 inhibitor atezolizumab (TECENTRIQ®)

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DSP107

MIRP Type	**DSP**
Targets	**CD47, 4-1BB**
Primary Cell Target	**mϕ macrophages, T-effector cells**
Mechanistic Effect	**Unleash mϕ via ‘Don’t Eat Me’ blockade, Activate T-eff**

DSP107
UNIQUE TRIMERIC STRUCTURE ENABLES TUMOR SELECTIVITY

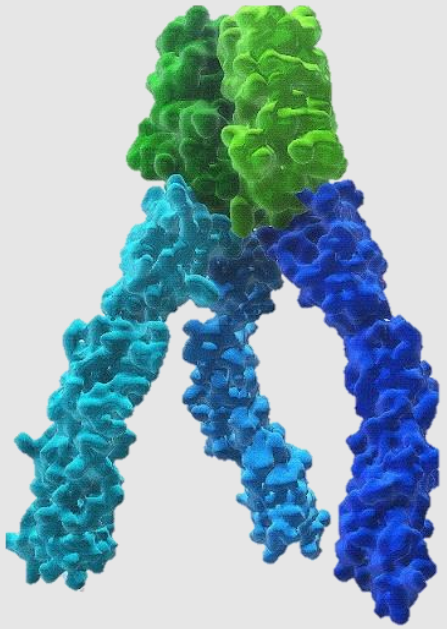
DSP107 Structure

Trimeric ligand ends enable:

1. Cancer selective binding driven by high affinity and avidity to overexpressed CD47

2. Conditional 4-1BB mediated T cell activation dependent on trimeric binding to CD47 on cancer cells

Trimeric 4-1BBL



3 SIRPα for
CD47 Checkpoint Targeting

Cytolytic T cell activation

T cell Proliferation

Checkpoint inhibition

Tumor microenvironment modulation

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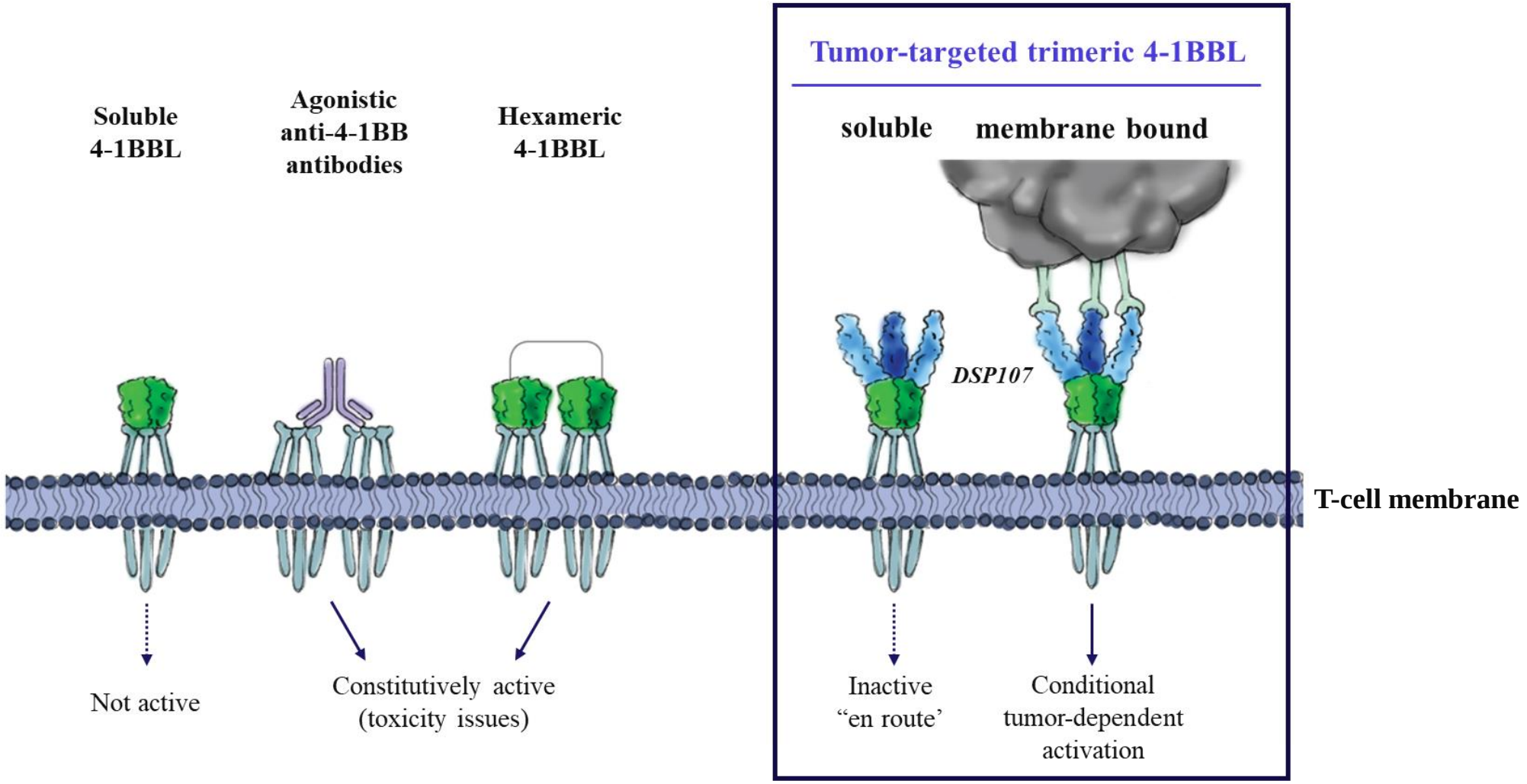
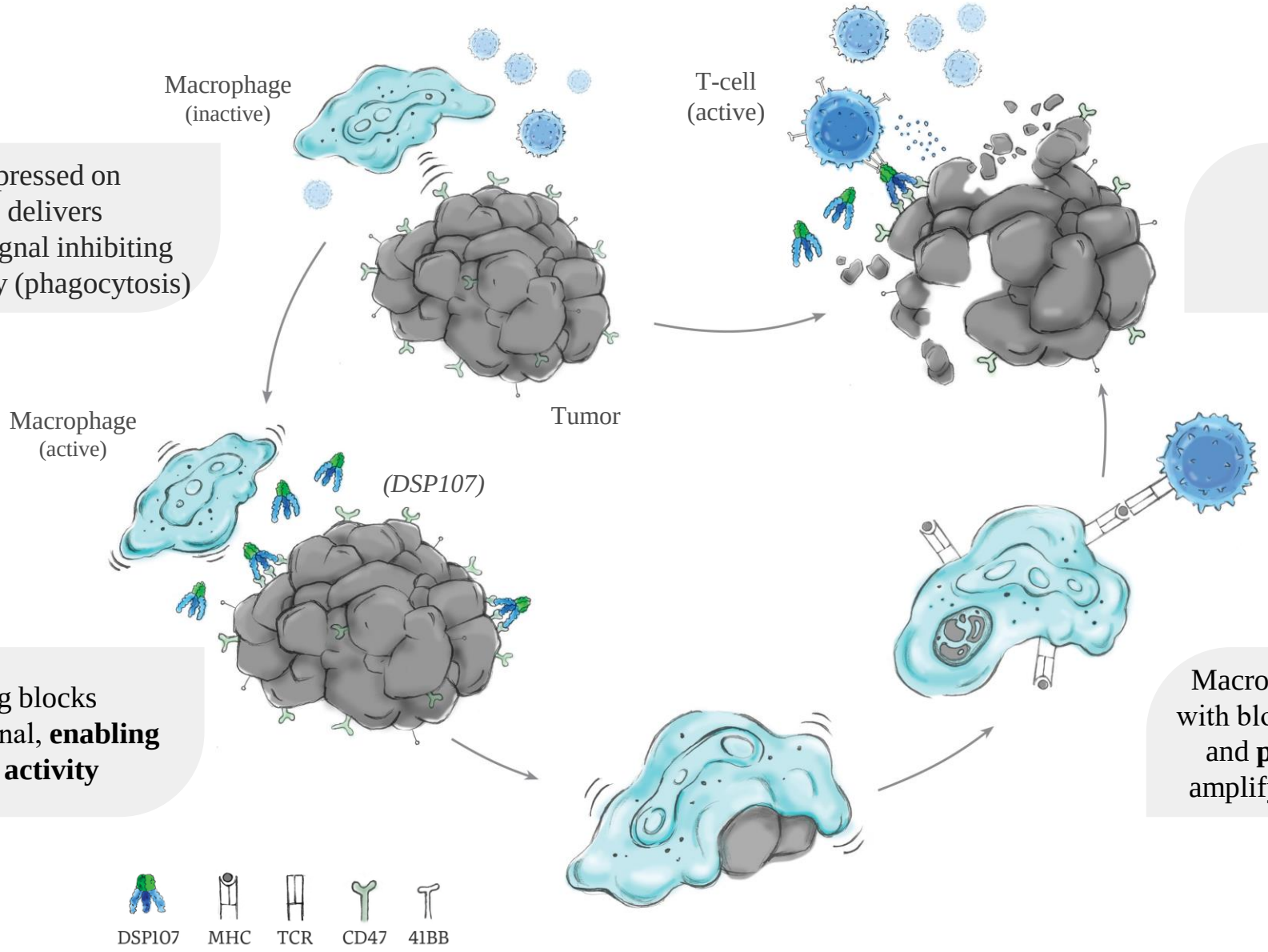
UNIQUE TRIMERIC STRUCTURE ENABLES TUMOR TARGETED 4-1BB CONDITIONAL ACTIVATION



Modified from: Bremer E.; ISRN Oncology; Volume 2013, Article ID 371854

SYNERGISTIC INNATE & ADAPTIVE IMMUNE ACTIVATION

CD47 overexpressed on cancer cells, delivers **“don’t eat me”** signal inhibiting macrophage activity (phagocytosis)



4-1BB mediated **T-cell** binding stimulates their **activation**

CD47 binding blocks “don’t eat me” signal, **enabling macrophage activity**

Macrophages ingest cancer cells with blocked “don’t eat me” signal and **present cancer antigens**, amplifying the immune response

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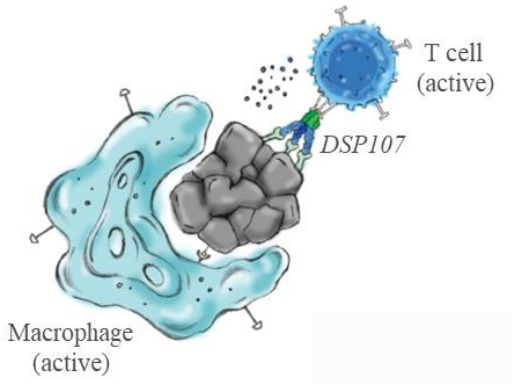
DSP107 WELL POSITIONED TO SHOW ANTI-CANCER ACTIVITY AS MONOTHERAPY AND IN COMBINATION THERAPIES

DSP107 monotherapy

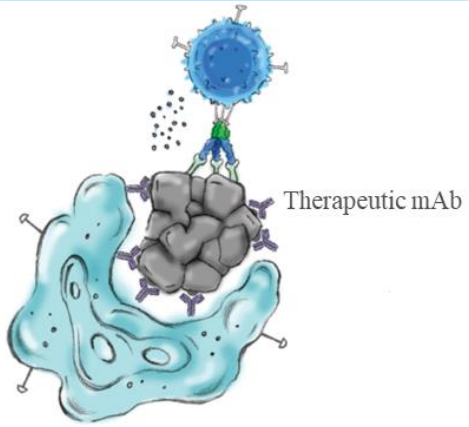
Triggers macrophage mediated phagocytosis and T cell cytotoxicity



DSP107 combination with therapeutic Antibodies IgG1 mAb's

(cetuximab, trastuzumab..)

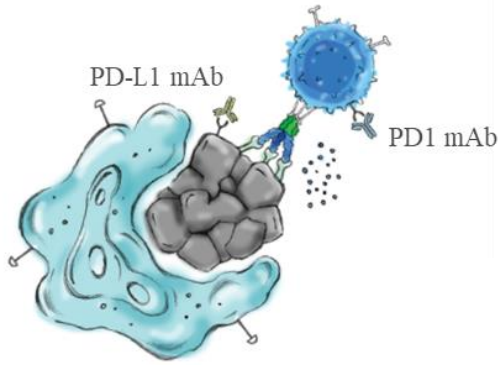
Enhances antibody-dependent cellular phagocytosis (ADCP)



DSP107 combination with PD1/PD-L1 Checkpoint Inhibitors

(atezolizumab, pembrolizumab…)

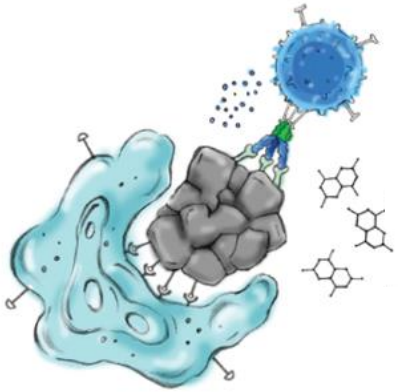
Enhances T cell activation



DSP107 combination with pro-apoptotic agents

(chemotherapy, hypomethylating agents and BCL2 inhibitors)

Increases "eat me" signals



DSP107 - DIFFERENTIATED CD47 TARGETING COMPOUND

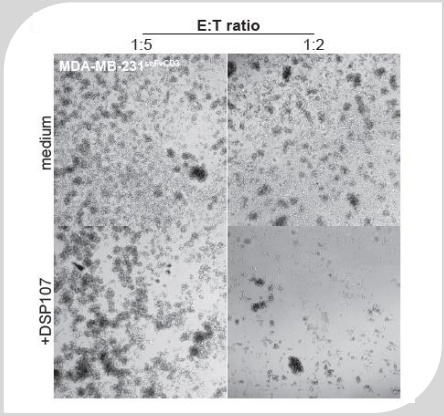
Next generation capabilities

Dual MOA
activates innate and adaptive immunity

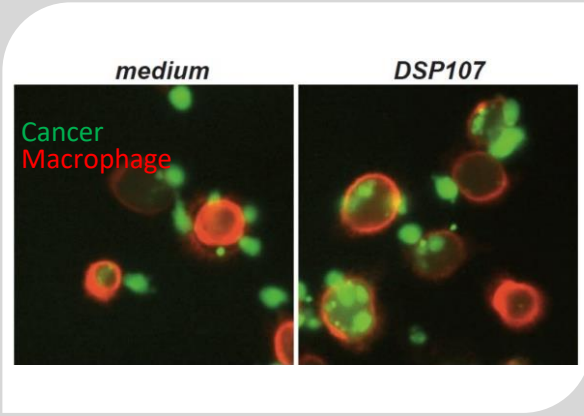
Excellent safety
without hematological toxicities

Strongly positioned
for treatment of solid and hematological malignancies

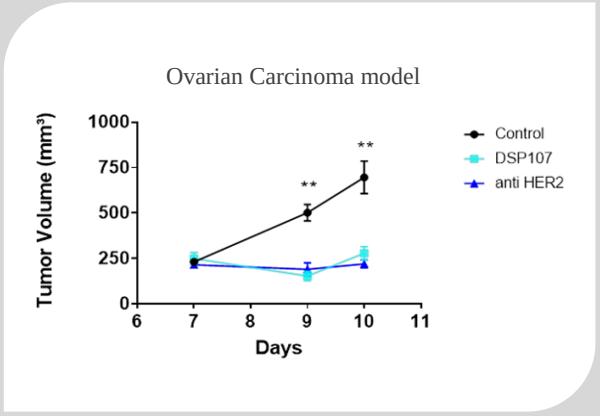
Unique and differentiated features



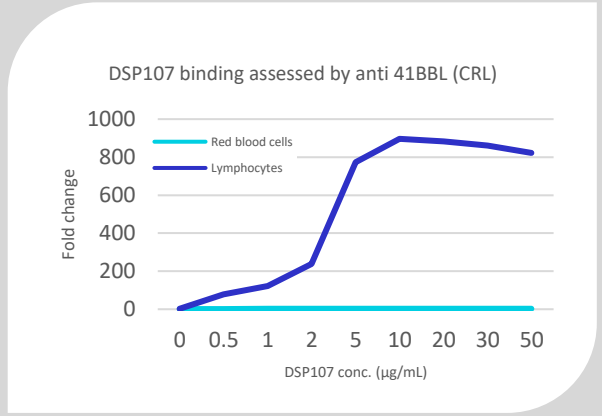
Activates T cells to secrete IFN-γ and augments their cancer cell killing potential



Augments macrophages-mediated phagocytosis of tumor cells as a single agent and synergizes with mAb's



Strong anti tumor activity as a single agent in solid tumors and liquid tumors in-vivo models



Does not bind red blood cells, avoiding antigen sink issues, resulting in a best-in-class safety profile

DSP107 – CLINICAL DEVELOPMENT

DSP107 – CLINICAL DEVELOPMENT STRATEGY

Advanced Solid Tumors

Phase 1 – Dose escalation (n = 30)

Accelerated dose escalation; Then 3+3

- DSP107
- DSP107 + atezolizumab

RP2D

Phase 2 – Expansion Cohort (n = 70)

- DSP107
- DSP107 + atezolizumab

Potential regulatory path

2L NSCLC patients who progressed on PD1/PD-L1 therapies

Enrolling sites: Pittsburgh, Colorado, Kansas, Thomas Jefferson; Sites under evaluation: San-Diego, Augusta, Chapel Hill, University of Texas

Hematological Malignancies

Phase I Dose escalation (n = 36)

Dose escalation N=6-8/cohort

- DSP107 ± azacytidine
- DSP107 + azacytidine + venetoclax

High risk R/R MDS/CMML and AML who failed up to 2 prior therapeutic regimes

RP2D

Phase 2 – Expansion
Details to be announced following EOPI meeting with the FDA

Lead site: MD Anderson Cancer Center

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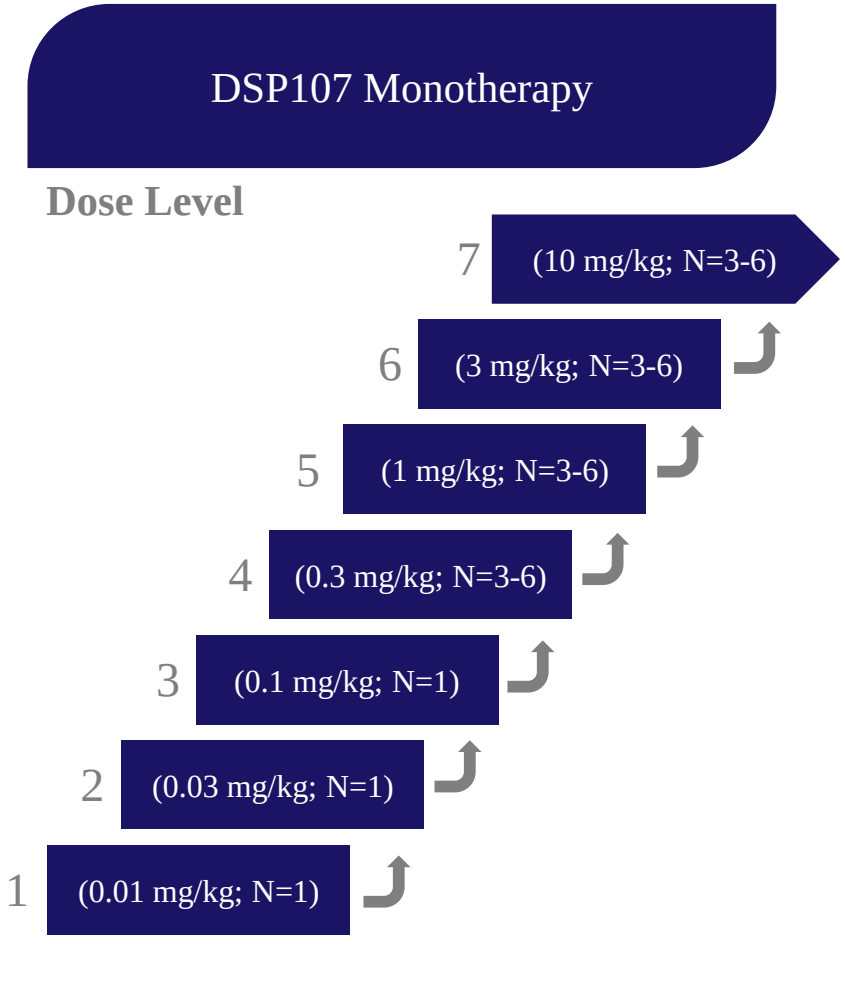
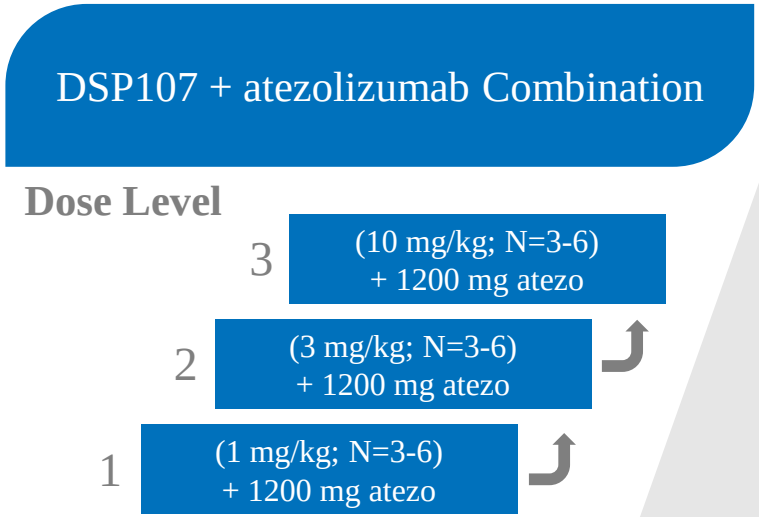
RP2D: Recommended Phase 2 dose; NSCLC: Non-small cell lung cancer; MDS: Myelodysplastic syndromes; AML: Acute myeloid leukemia

TRIAL DESIGN AND KEY INCLUSION CRITERIA

Part 1 – Monotherapy and Combination Dose Escalation





Trial Design:

- Patients with advanced solid tumors (N=30) not suitable for curative therapy and without approved treatment options
- IV administration once weekly
- Accelerated dose escalation in single patient cohorts followed by standard 3+3 design

Key Inclusion Criteria:

- Histologically confirmed advanced solid tumor with no approved therapeutic options
- Age 18 years or older
- ECOG performance status 0 or 1
- Measurable disease per RECIST v 1.1

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PATIENTS WITH ADVANCED SOLID TUMORS – NEARLY HALF FAILED PRIOR IMMUNOTHERAPY AND/OR COLD TUMORS

Characteristics	
Total number of patients	N = 17
Sex	6 (35%) ♀; 11 (65%) ♂
Age	Median 62 (Range 29-78)
Tumor types	
Colorectal	4 (24%)
Pancreas	4 (24%)
Head and Neck	3 (18%)
NSCLC	1 (6%)
Ovarian	1 (6%)
Rare tumor types	4 (24%)
Previous lines of therapy	Median 2 (Range 2-8)
PD1/PD-L1 experienced	8 (47%)

NO DLTs, HEMATOLOGICAL TOXICITIES OR HEPATO-TOXICITIES

Summary

- DSP107 doses up to and including 3 mg/kg considered safe and tolerated
- No DLTs and no treatment-related SAEs
- No hematological toxicities
- No hepato-toxicities
- Very few AEs considered related to DSP107 and almost all mild or moderate in severity
- Most related AEs Grade 1-2 in severity. Only 2 related Grade 3 AEs – transient hypertension and fatigue (at EOT visit)

Now enrolling patients to Dose Level 7 (10 mg/kg)

Treatment-Related AEs in ≥ 2 Patients	
Total No of Patients	**N = 17**
Treatment-related AEs (any grade)	**n (%)**
Any	12 (71)
Diarrhea	4 (24)
IRR*	3 (18)
Fatigue	3 (18)
Nausea	3 (18)
Constipation	2 (12)

*IRRs Grade 1-2 in severity. Easily abrogated in subsequent infusions by reduced rate of infusion and concomitant IV fluids.

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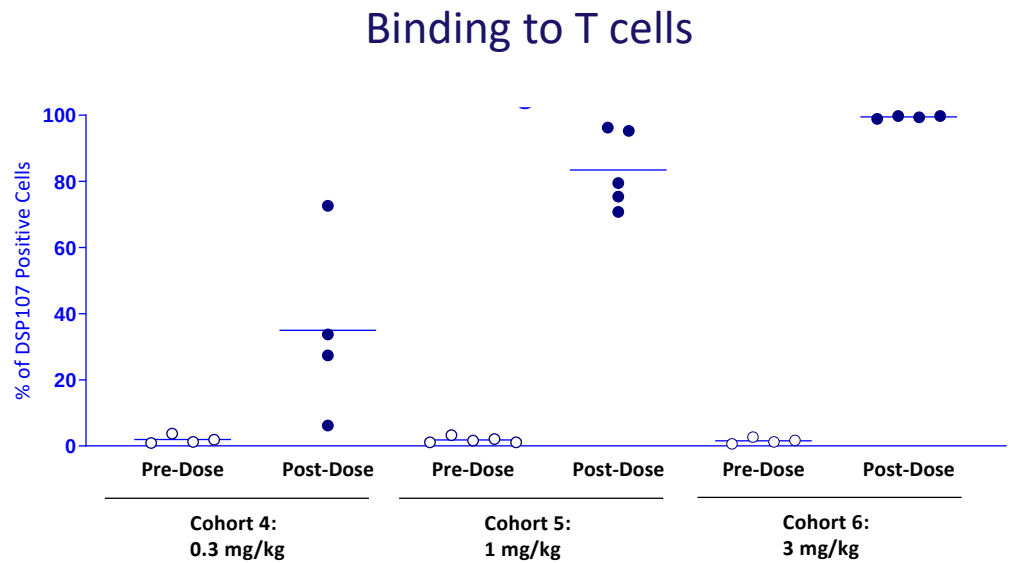
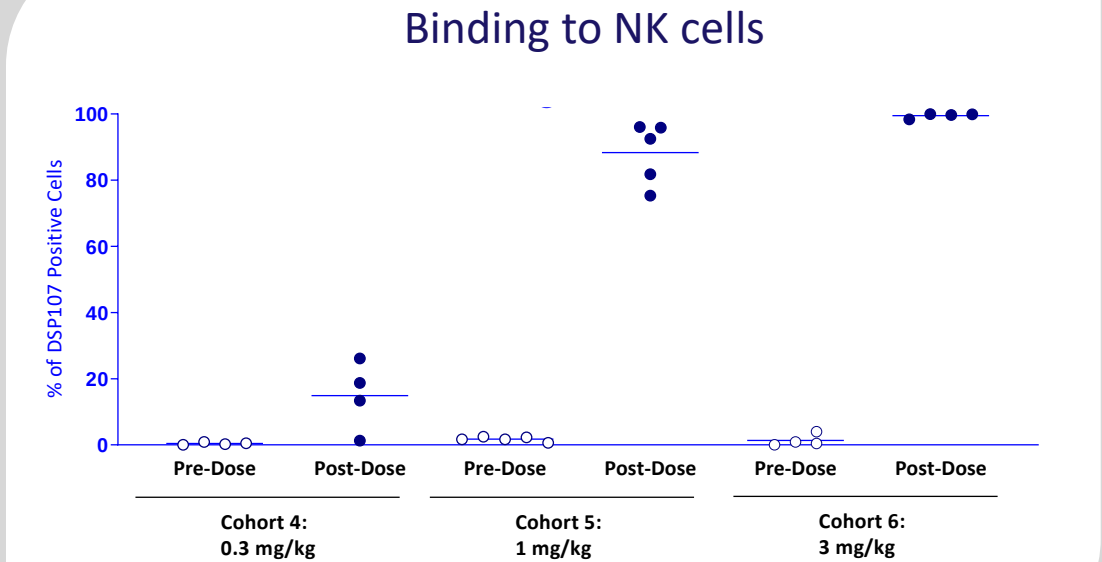
FULL TARGET ENGAGEMENT ON CIRCULATING IMMUNE CELLS

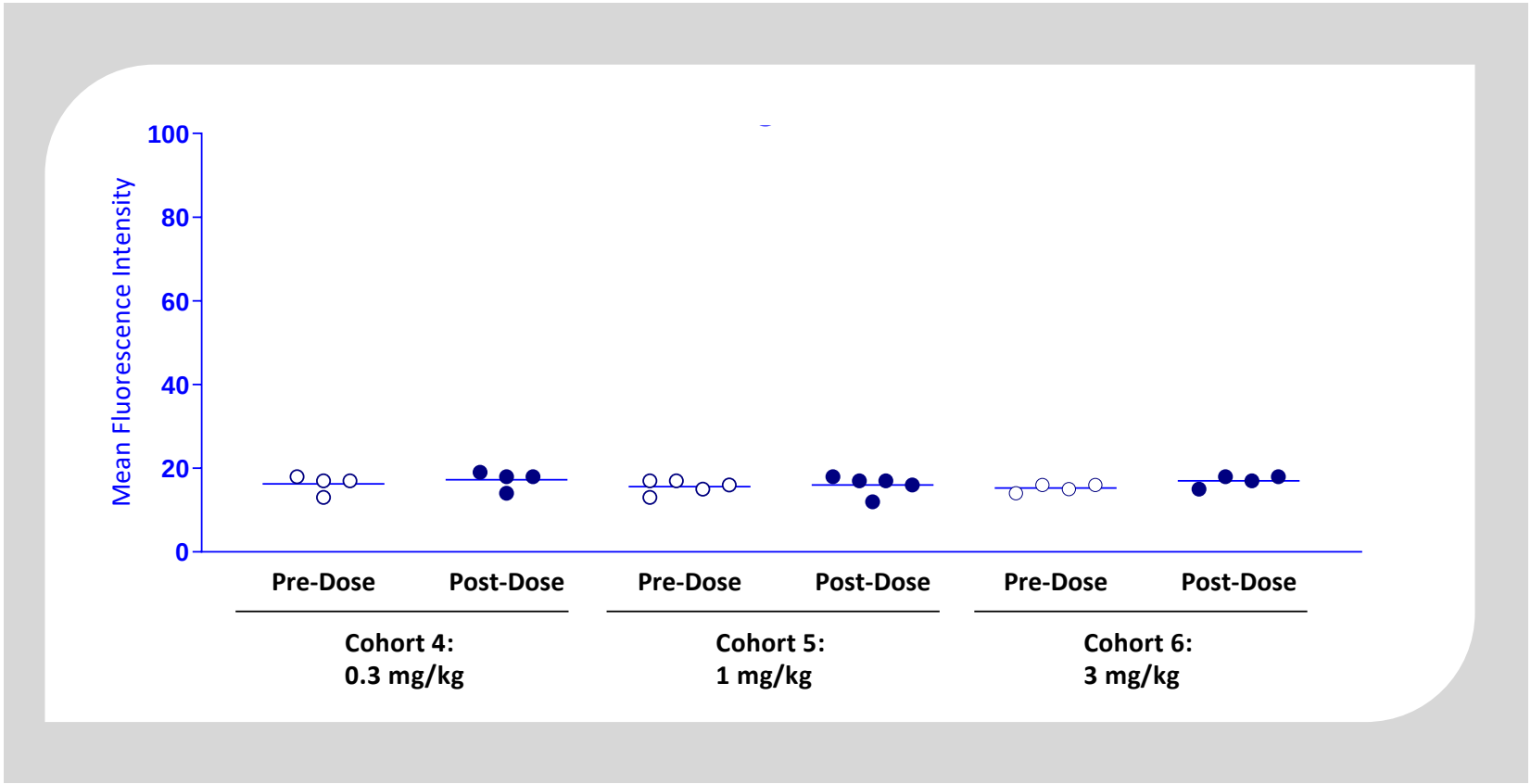
- Dose dependent target engagement achieved across T cells and NK cells
- 100% receptor occupancy on circulating immune cells observed at ≥3 mg/kg



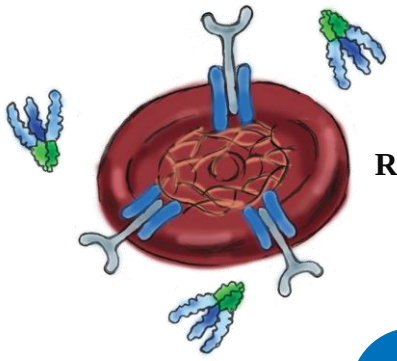


RECEPTOR OCCUPANCY DATA CONFIRMS LACK OF RBC BINDING

No binding to red blood cells at doses 0.3, 1 and 3 mg/kg

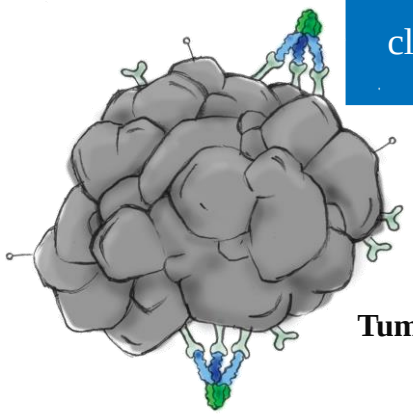


On RBCs CD47 protein complex is anchored to cytoskeleton resulting in its immobilization and low affinity of DSP107 to the monomeric CD47



Red Blood Cell

High affinity/avidity of DSP107 to CD47 clusters on cancer cells



Tumor

INCREASED NECROSIS IN PAIRED BIOPSIES AFTER DSP107

Key Findings:

- Notable increase in necrotic tumor tissue was observed in 3 out of 4 paired biopsies compared to screening
- Necrosis was associated with immune cell infiltration
- No evidence of vascular necrosis

Patient Number	Dose (mg/kg)	Tumor Type	Timepoint	% Necrosis
11-001	0.3	Colorectal	Screening	0
			6 weeks	**65**
11-002	0.3	Colorectal	Screening	2
			6 weeks	**35**
10-003	1	Pancreatic	Screening	10
			6 weeks	**50**
13-005	1	Pancreatic	Screening	4
			6 weeks	3

All biopsies collected from hepatic metastases pre-treatment and following cycle 2 (6 doses). H&E stained slides assessed by independent, blinded pathologist.

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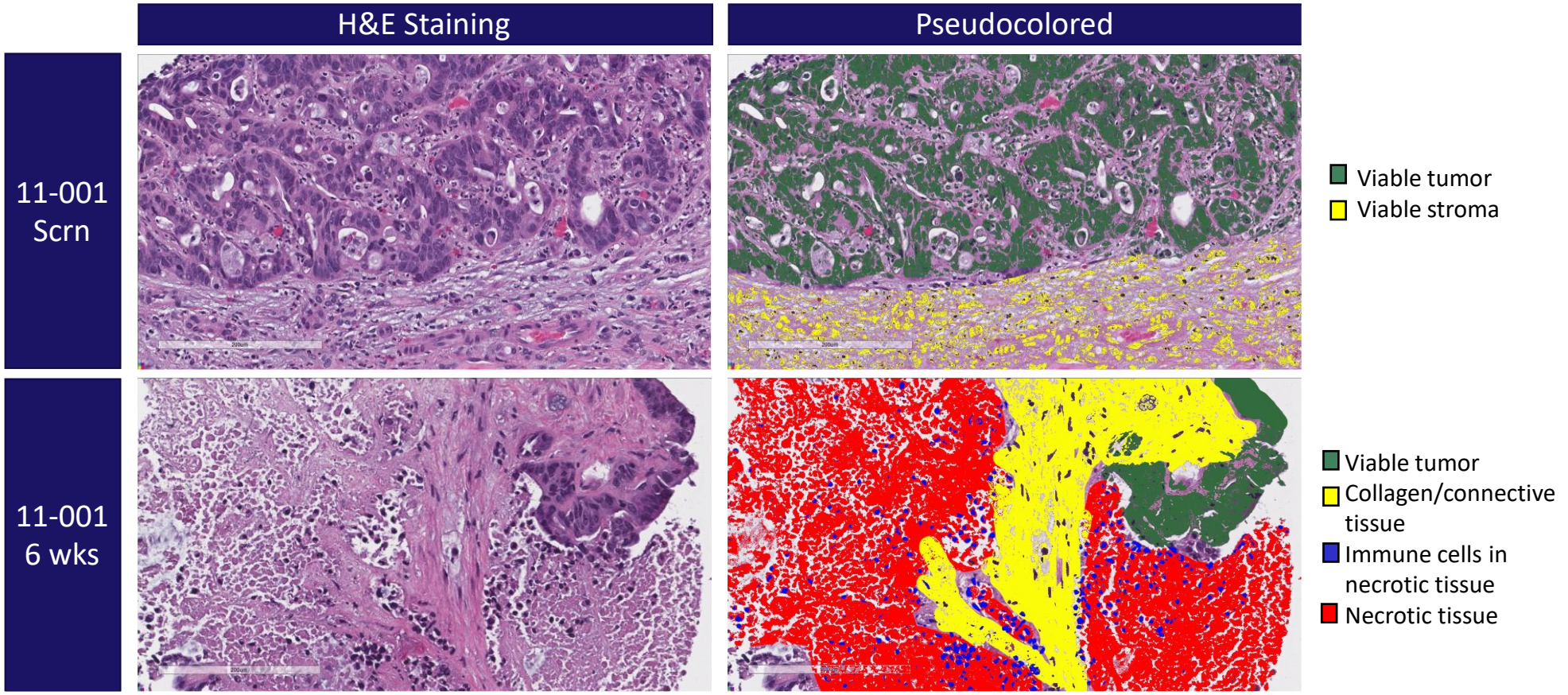
CASE STUDY: NECROSIS ASSOCIATED WITH INCREASED IMMUNE CELL INFILTRATION AFTER DSP107



~ 65%

Necrotic tumor tissue

6-wks post DSP107 treatment

Paired biopsy from colon carcinoma patient (11-001) in dose level 4 (0.3 mg/kg) pre- treatment and following cycle 2 (6 doses). No necrosis at baseline.

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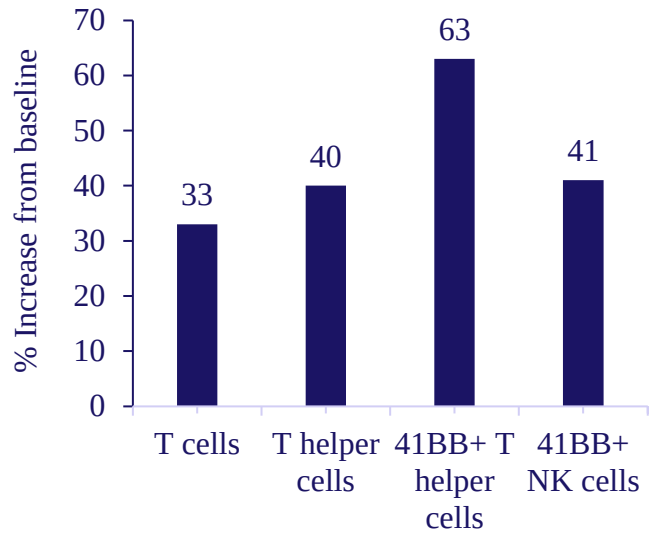
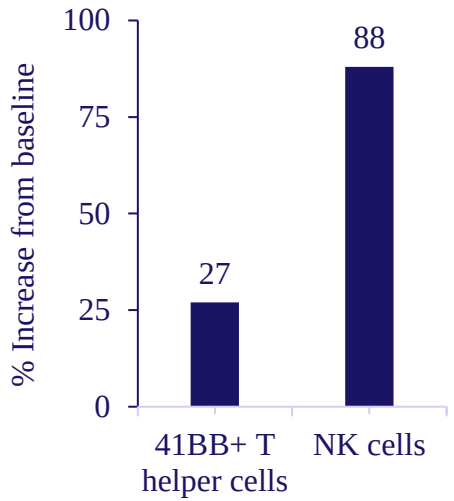
CASE STUDY: INCREASED IMMUNE INFILTRATION AFTER DSP107

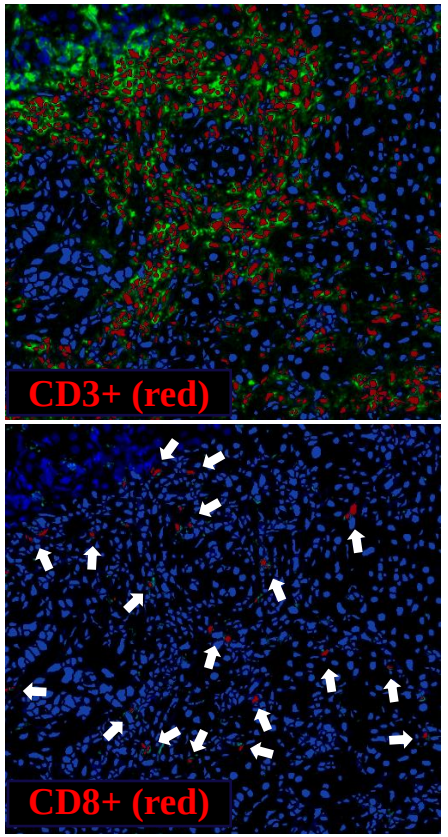
6-wks post DSP107 treatment

Infiltration in tumor compartment



Infiltration at tumor margin





Paired biopsy from colon carcinoma patient (11-001) in dose level 4 (0.3 mg/kg) pre- treatment and following cycle 2 (6 doses). Quantification of multiplex image analysis from biopsy stains.

Significant infiltration of T cells and NK cells in both the tumor compartment and at the tumor margin following DSP107 treatment

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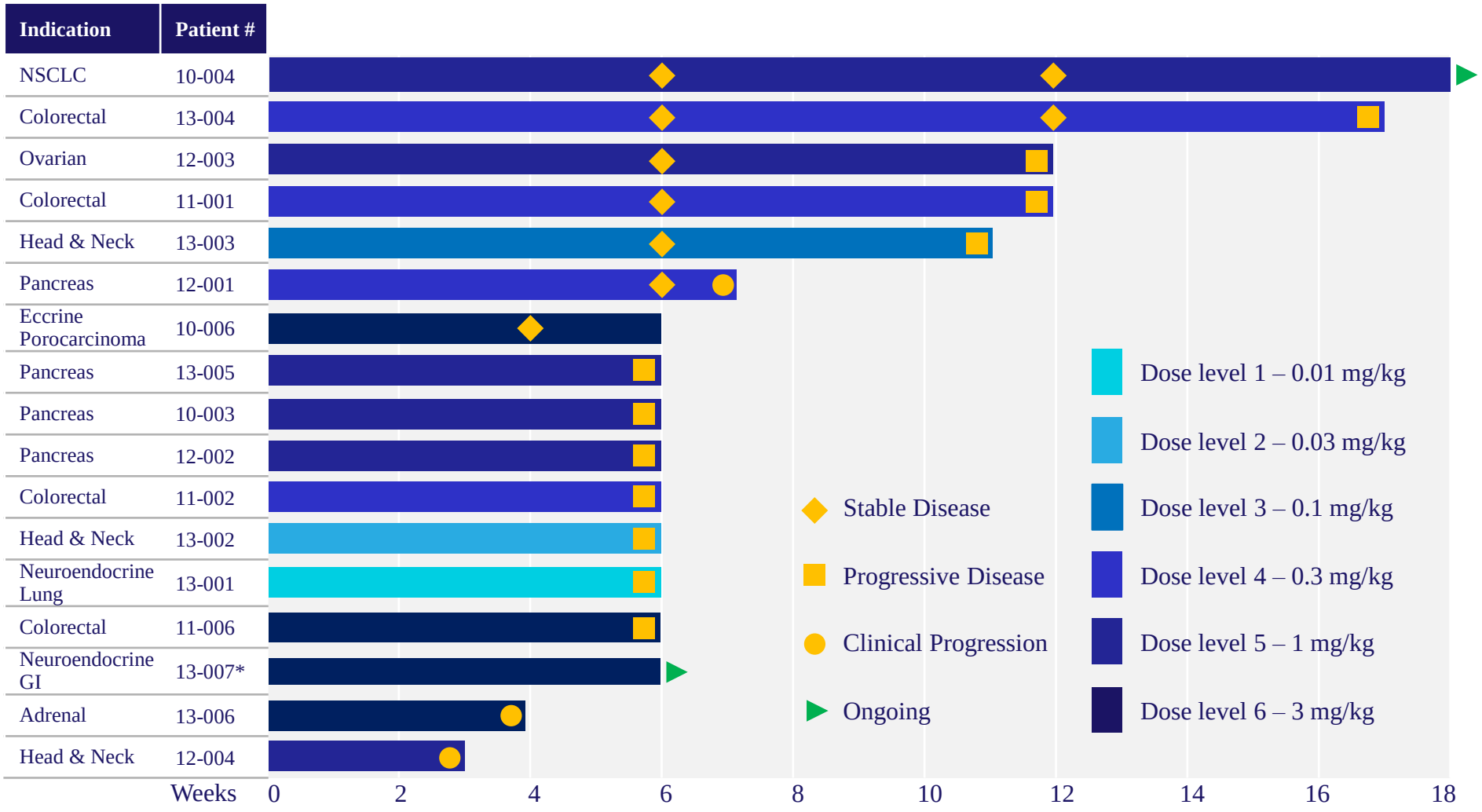
BEST OVERALL RESPONSE TO DATE AFTER DSP107 MONOTHERAPY



Summary

Best response from 16 patients evaluable to date:

SD = 7 (44%)

PD = 9 (56%) incl. 2 patients withdrawn before 1st CT scan due to clinical progression

*Has not reached first CT scan evaluation. †Includes two patients withdrawn before first CT scan due to clinical progression.

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DSP107 PHASE 1 DATA: FAVORABLE SAFETY AND PRELIMINARY ACTIVITY IN SOLID TUMORS

Clinical Overview

- DSP107 alone and in combination with atezolizumab is being evaluated in a dose escalation trial
- 17 patients with diverse solid tumors have been treated as of data cut-off on Nov. 4th 2021, with 16 patients evaluable for efficacy analysis
- Now enrolling patients to cohort 7 (10 mg/kg)

Key Findings

- Mostly low-grade AEs with no DLTs, no hematological toxicities and no hepato-toxicities
- Receptor occupancy data confirming lack of RBC binding and immune cell engagement
- Increase immune cell infiltration into the tumor with increased tumor necrosis

Further evaluate safety and preliminary efficacy of DSP107 alone up to dose level 7, as well in combination with atezolizumab

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KEY UPCOMING MILESTONES

Program MOA	Indication	2021	2022		2023	
		2H	1H	2H	1H	2H
DSP107 CD47 inhibitor 4-1BB activator	**Solid Tumors, NSCLC**	Initial Ph I/II mono data	Initial Ph I/II combo data	Ph I/II NSCLC Interim results		Ph I/II NSCLC Topline results
	AML/MDS			Ph I AML/MDS Interim results		Ph I AML/MDS Topline results
DSP502 PVR inhibitor PD-L1 inhibitor Active IgG1 Fc	**Oncology**		IND-enabling activities		File IND	
DSP216 CD47 inhibitor HLA-G inhibitor Inactive Fc	**Oncology**		IND-enabling activities			File IND

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Q&A

CD47 potential in AML/MDS

NOVEMBER 2021

Naval Daver, MD

Director, Leukemia Research Alliance Program,
Associate Professor
Department of Leukemia
MD Anderson Cancer Center

Disclosures | Naval Daver, MD

Research Funding

Pfizer, BMS, Novartis, Servier, Daiichi-Sankyo, Karyopharm, Incyte, Abbvie, Genentech, Astellas, Immunogen, Forty-Seven, Amgen, Trovagene, Novimmune

Advisory/Consulting

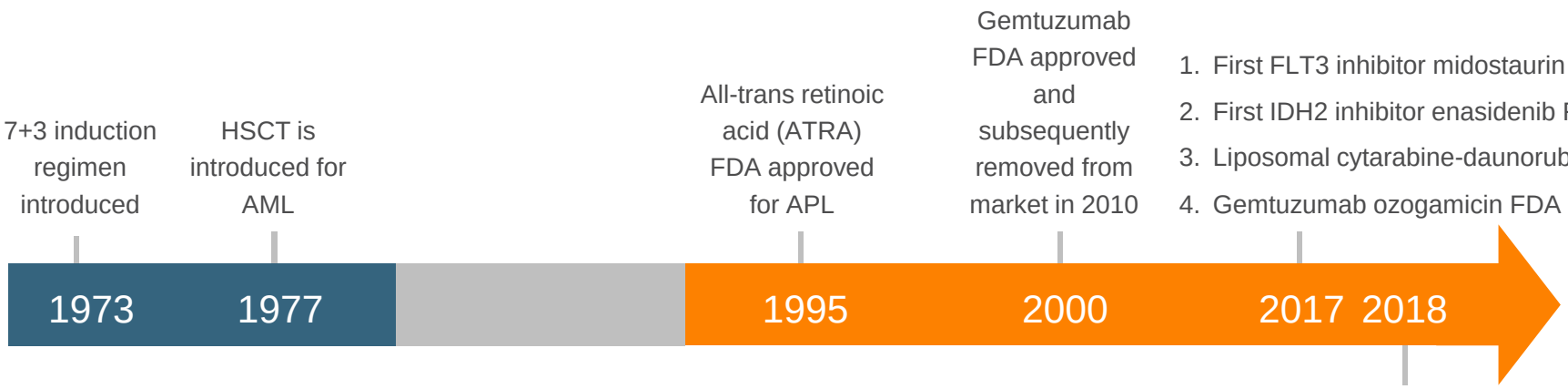
Pfizer, BMS, Daiichi-Sankyo, Novartis, Jazz, Astellas, Abbvie, Genentech, Agios, Servier, Immunogen, Forty-Seven, Gilead, Syndax, Trillium

Disclaimer

Data will include medications not yet approved or with indications still under clinical study

Treatment of AML (accelerated progress 2017–2019): History

Since its introduction in the early 1970s, 7+3 therapy (cytarabine for 7 days + anthracycline for 3 days) has been the standard of care for AML

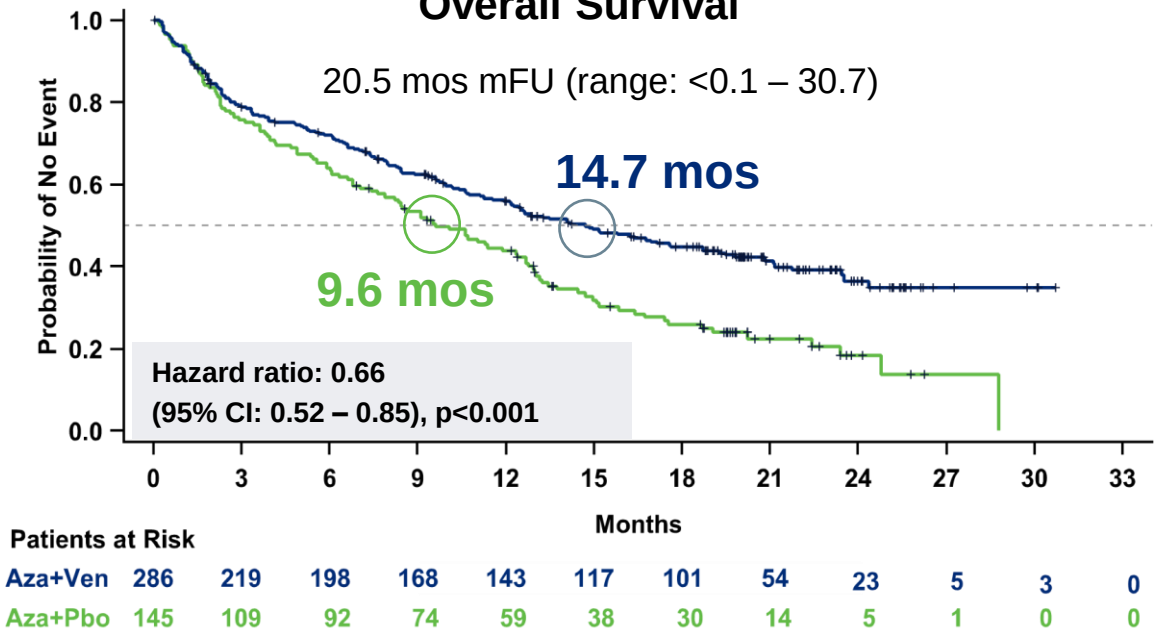


1. Ivosidenib is FDA approved in 2018 for r/r AML with a susceptible *IDH1m*
2. AZA + VEN and LDAC + Ven approved for older AML (Nov 21, 2018)
3. LDAC + glasdegib approved for older AML (Nov 21, 2018)
4. Gilteritinib for relapsed *FLT3* AML (Dec 2018)

Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

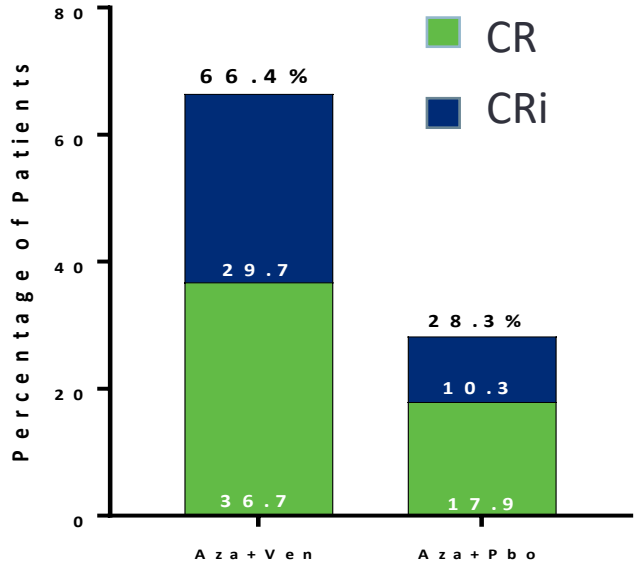
AZA+/- VEN in AML – Clinical Responses

Overall Survival



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

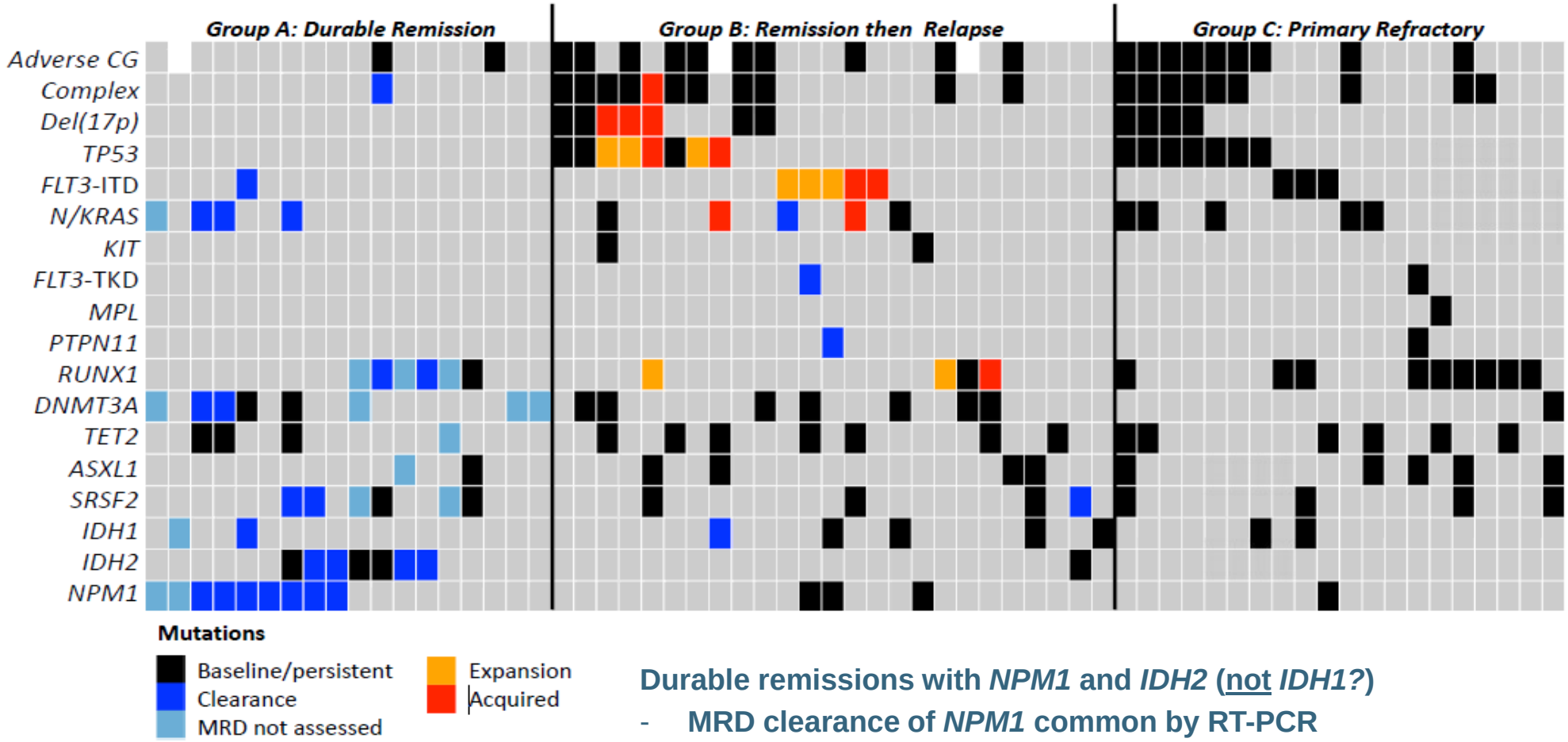
Composite Response Rate (CR+CRi)



	No. cycles, Median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza+Ven (n=286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza+Pbo (n=145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

DiNardo EHA 2019 *CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 by CMH test

Molecular Determinants of Outcome With Venetoclax Combos: Several Molecular subsets with sub-optimal benefit from HMA+VEN (TP53, RAS, CBL, KIT, FLT3, others…



Durable remissions with *NPM1* and *IDH2* (not *IDH1?*)

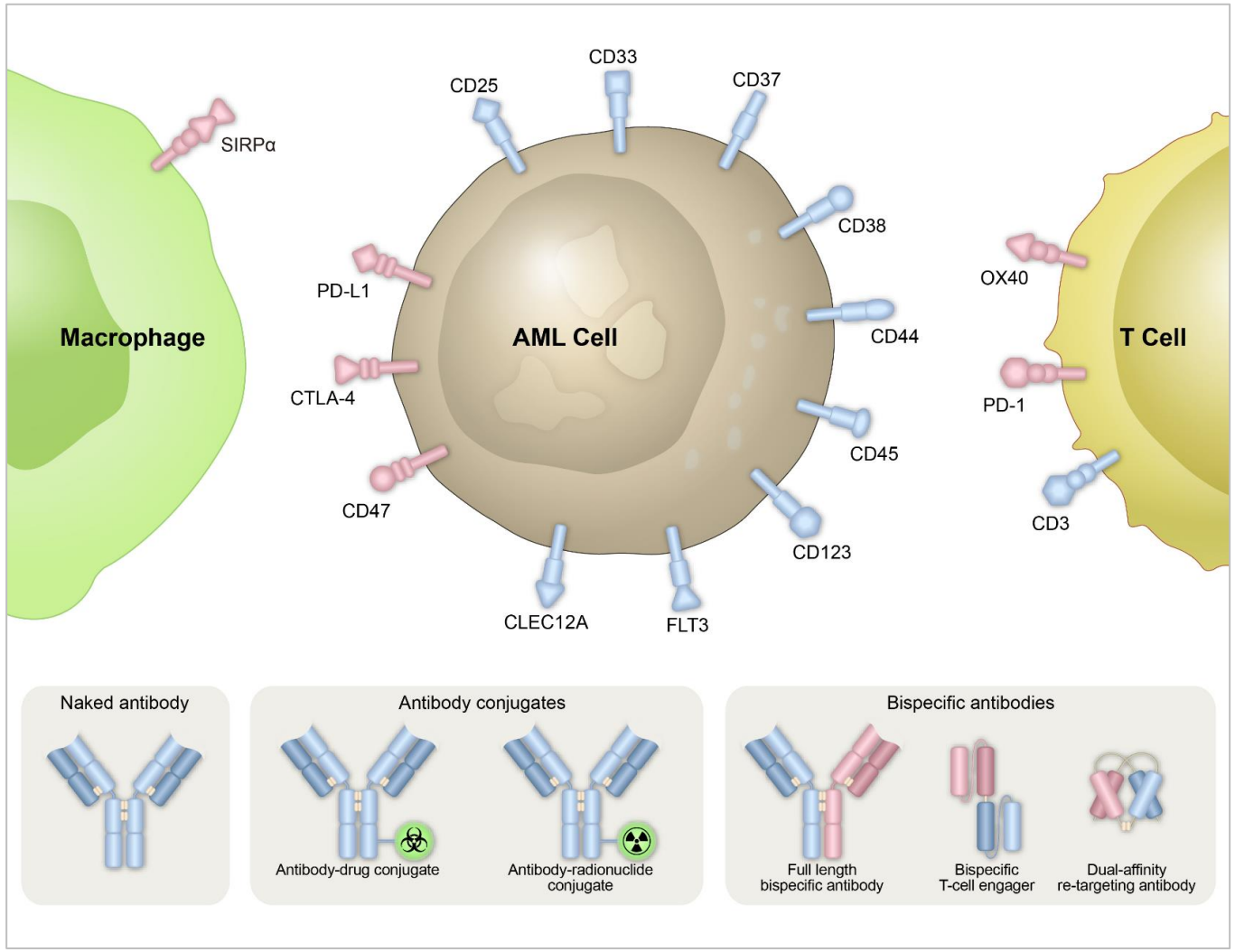
- **MRD clearance of *NPM1* common by RT-PCR**

Resistance commonly associated with expansion or acquisition of *TP53* or signaling mutations including *K/NRAS* and *FLT3*-ITD

Patients treated at MDACC and The Alfred (n = 81)

DiNardo CD, et al. *Blood.* 2020;135(11):791-803.

Heavy Shift in Focus to Developing Immune Based Approaches in AML



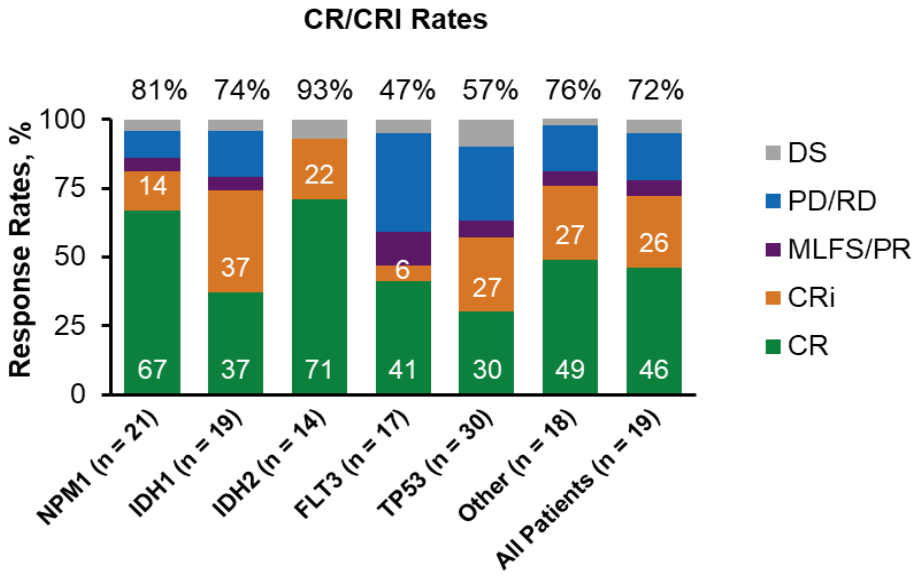
Short N….Daver N, et al, Cancer Discovery 2020

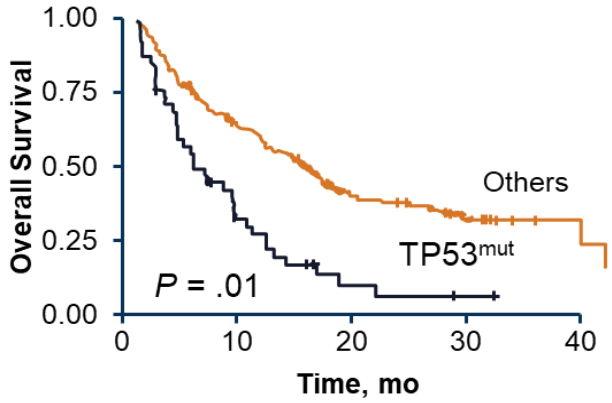
Two major approaches:

1. Antibody drug conjugates (CD33, CD123, CLL1)
2. Adaptive or Innate immune system harnessing therapies:
   a. Bi-specific antibodies (CD3 x AML antigen; CD47 x CD3, others)
   b. Immune checkpoint based approaches: T-cell and macrophage checkpoints
   c. CART, CAR NK, High volume hn-NK cells
   d. Vaccines

Very Poor Outcomes in *TP53* Mutant AML, Even With Venetoclax-Based Treatment

Venetoclax + LDAC or HMA
(Phase IB study)[1]

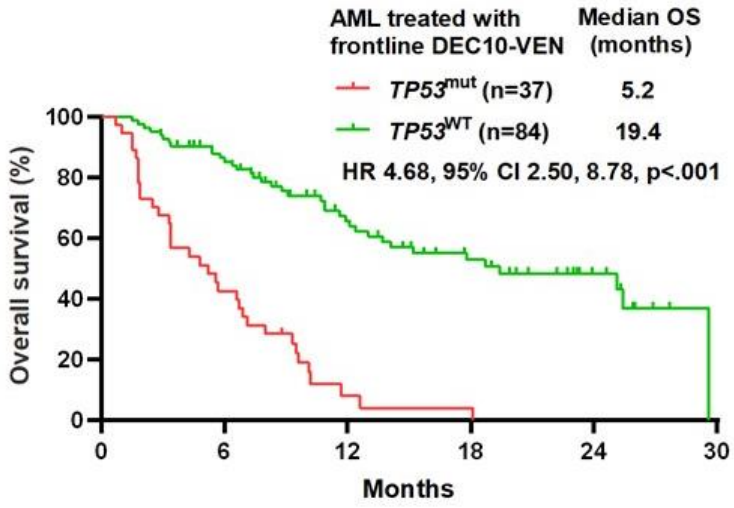




Median OS = 6.4 months

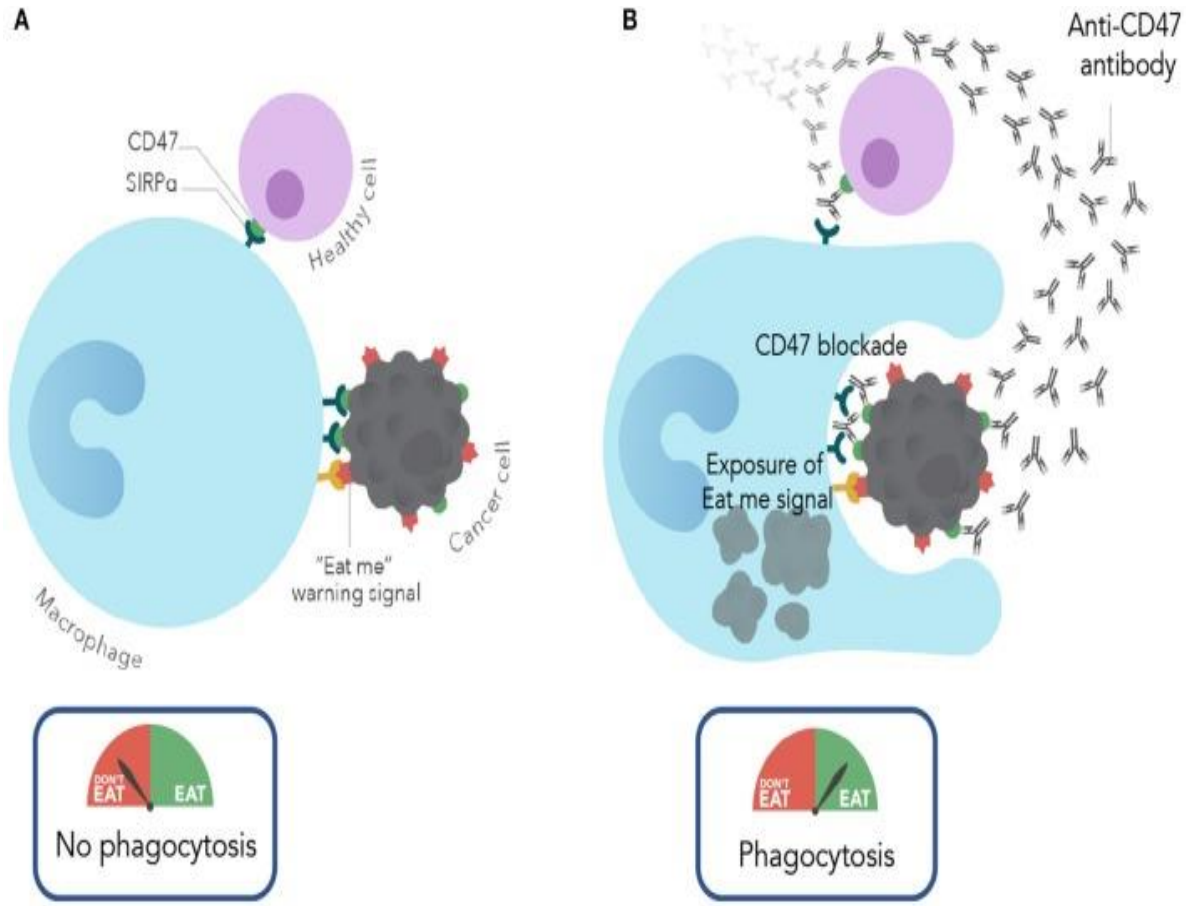
N = 121 patients with newly diagnosed AML receiving decitabine + venetoclax[2]

- Those with *TP53*^{mut} (N=35) had a lower rate of CR at 35% vs 57% in pts with *TP53*^{WT} (N=83) (P = 0.026)
- Lower rate of CR/CRi (54% vs. 76%; *P* .015),



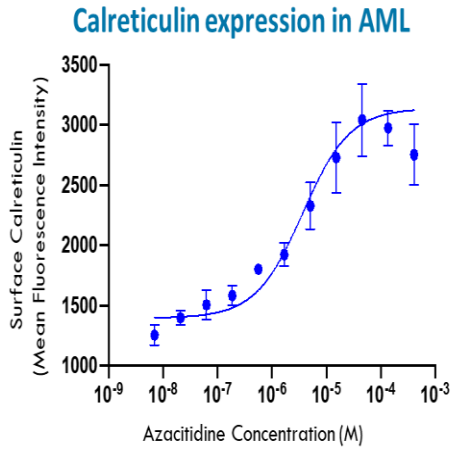
1. Chyla BJ et al. ASH 2019. Abstract 546. 2. Kim K, et al. ASH 2020. Abstract 693

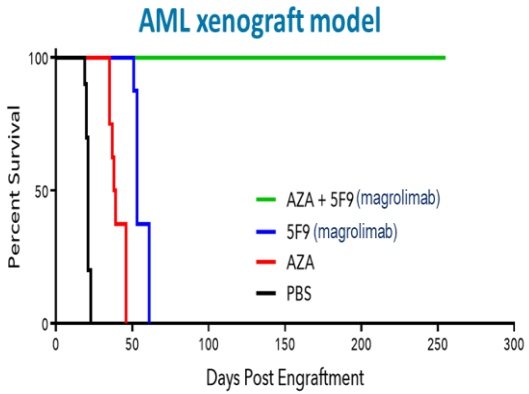
Mechanism of Action of CD47 Blocking Antibodies



Magrolimab Synergizes With Azacitidine to Induce Remissions in AML Xenograft Models

- Azacitidine (AZA) induces prophagocytic "eat me" signals, like calreticulin on cancer cells
- Increased "eat me" signals induced by AZA synergize with CD47 blockade of the "don't eat me" signal, leading to enhanced phagocytosis

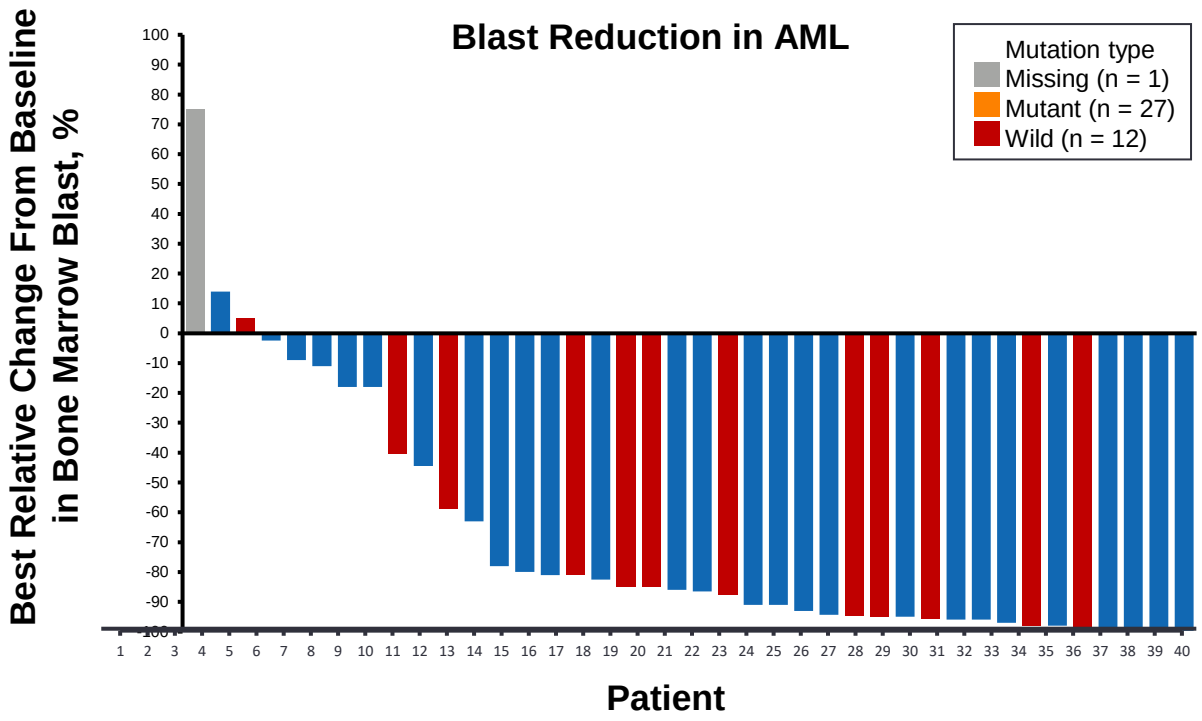




Feng D, et al. ASH 2018, Abstract #616 (with adaptations).

Magrolimab + AZA in Newly Diagnosed AML

Best Overall Response	All AML (N = 43), n (%)	*TP53*-Mutant AML (n = 29), n (%)
ORR	27 (63)	20 (69)
CR	**18 (42)**	**13 (45)**
CRi	5 (12)	4 (14)
PR	1 (2)	1 (3)
MLFS	3 (7)	2 (7)
SD	14 (33)	8 (28)
PD	2 (5)	1 (3)

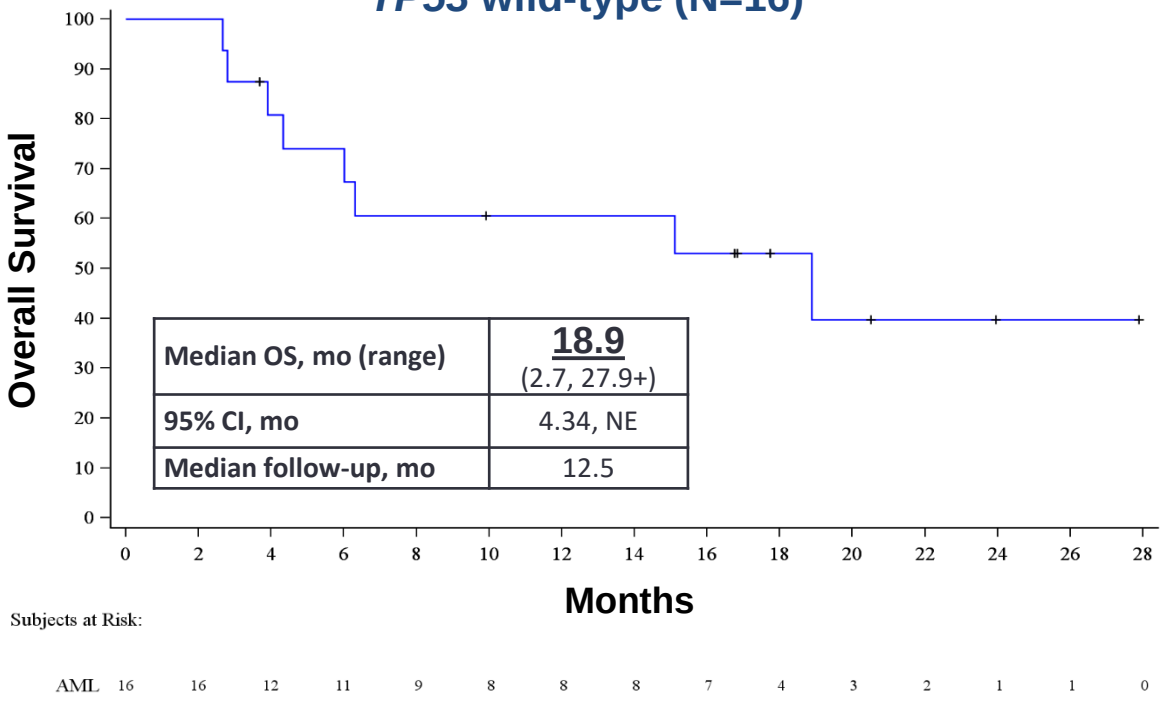


- Magrolimab + AZA with 63% ORR and **42% CR rate** in AML (similar responses in *TP53*-mutant disease)
- Median time to response is 1.95 months (range, 0.95-5.6 mo); more rapid than AZA monotherapy
- Magrolimab + AZA efficacy compares favorably with AZA monotherapy (CR rate: 18%-20%)
- No significant cytopenias, infections, or immune-related AEs were observed; on-target anemia
- Median TP53 VAF burden at baseline: **73.3% (range 23.1% - 98.1%)**

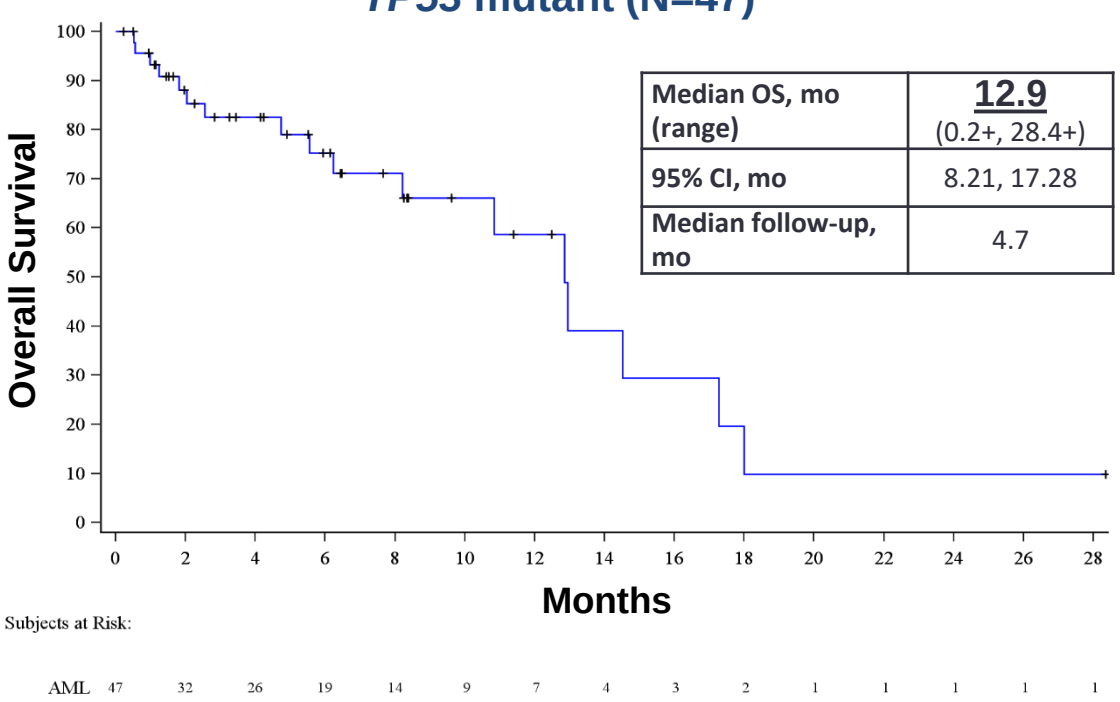
1. Daver N et al. EHA 2020. Abstract 2. Sallman D et al. ASH 2020. Abstract 330.

Preliminary Median Overall Survival with Magrolimab + AZA Is Encouraging in Both *TP53* Wild-Type and Mutant Patients

TP53 wild-type (N=16)



TP53 mutant (N=47)



- 18.9 mos mOS in *TP53* wild-type patients vs 12.9 mos in *TP53*-mutant patients
- mOS with venetoclax + hypomethylating agent combinations (**14.7-18.0 mos** in all-comers,[1,3] **5.2–7.2 mos** in *TP53m*[2,3])
- Additional patients and longer follow-up needed

NE, not evaluable. Sallman D et al, ASH 2020, abst #330

1. DiNardo CD, et al. *N Eng J Med*. 2020;383(7):617-629. 2. Kim K, et al. Poster presented at: 62nd ASH Annual Meeting; December 5-8, 2020 (virtual). 3. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

Novel Immune Strategies to Kill AML, Potentially Mutation Agnostic

ADAPTIVE

Recruiting **CD3** T cell -- **BiTEs** linking to CD3 and targeting CD33/123; **CARTs** with modified CD3 killer cells (success in ALL, lymphoma, MM)

Targets beyond CD33/123 e.g. **CLL1,** IL1RAP, TIM3, CD70, others

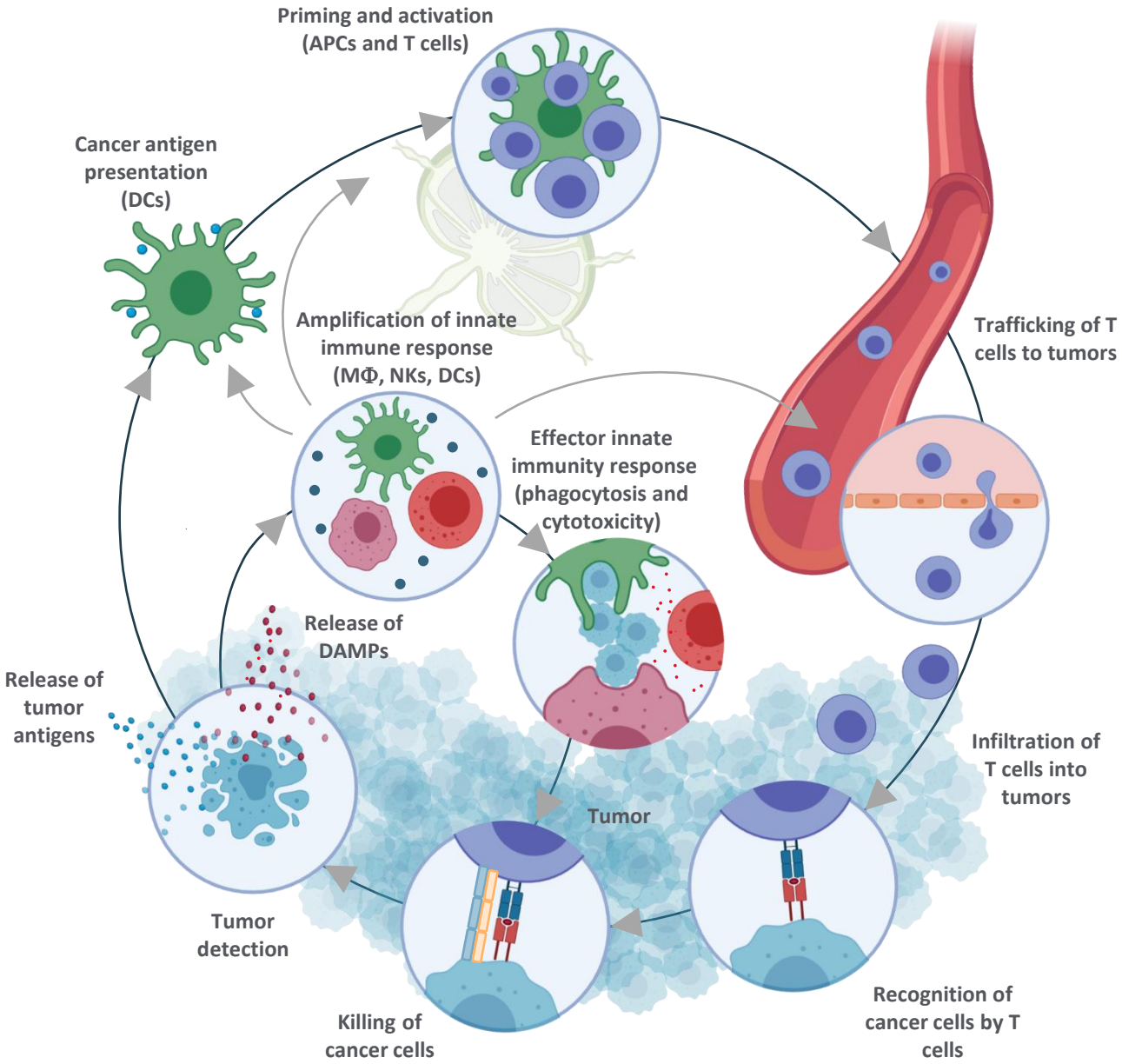
INNATE
(Appears to be more resilient and preserved in AML)

Recruiting **macrophages** -- targeting CD47 on AML (Magrolimab, Lemzo, TTI-622, Evorpacept, DSP107)

Recruiting **NK cells** -- allo NK-CARTs; NK engineered cells (hn, CD38 ko, IL15)

Innate Anti-Tumor Immune Responses

- The adaptive T-cell immune response to tumors does not progress in isolation
- The innate immune response supports and is inter-connected with the adaptive immune response
- Innate immune cells exert effector functions such as phagocytosis (macrophages, polymorphonuclear cells) and natural cytotoxicity (NK cells)



APCs, antigen-presenting cells; DAMPS, damage-associated molecular patterns; DCs, dendritic cells; MΦ, macrophage; NK, natural killer

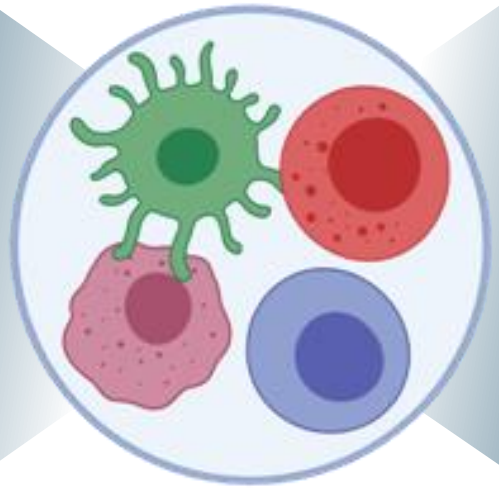
1. Demaria O, et al. *Nature* 2019;574:45-56.

Selected Innate Immune Checkpoint Targets

Investigational agents in development targeting innate immune cell effector functions

Phagocytosis Checkpoint Targets

Target	Cell Expression
CD47	Tumor cells, normal cells
SIRPa	MF, DCs, mast cells, neutrophils



Broad-spectrum Checkpoint Targets

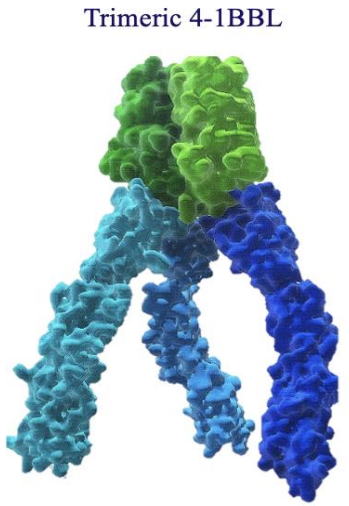
Target	Cell Expression
NKG2A	NK cells, T cells
TIGIT	NK cells, T cells
TIM-3	T cells, NK cells, NKT cells, DCs, and MFs
LAG-3	T_{reg} cells, CD8+ TILS, NK cells

DCs, dendritic cells; LAG-3, lymphocyte activation gene-3; MΦ, macrophage; NK, natural killer; NKG2A, NK group 2 member A; NKT cells, natural killer T cells; SIRPα, signal-regulatory protein α; TIGIT, T-cell immunoglobulin and ITIM domain; TILS, tumor infiltrating lymphocytes; TIM-3, T-cell immunoglobulin and mucin-domain containing 3; T_{reg} cells, regulatory T cells

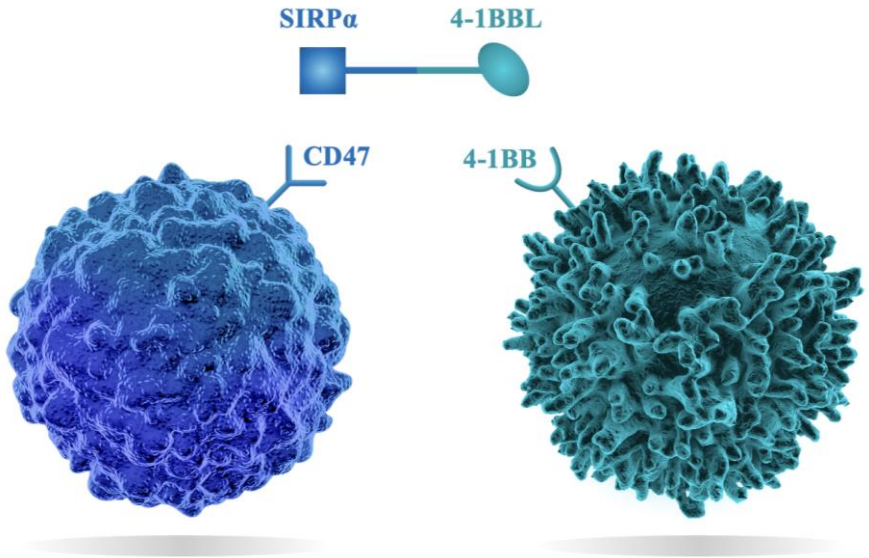
1. Demaria O, et al. *Nature* 2019;574:45-56.

Bispecific CD47-SiRPα and T-cell (4-1BB) engaging approaches (DSP107)

Activating the innate and adaptive immune systems

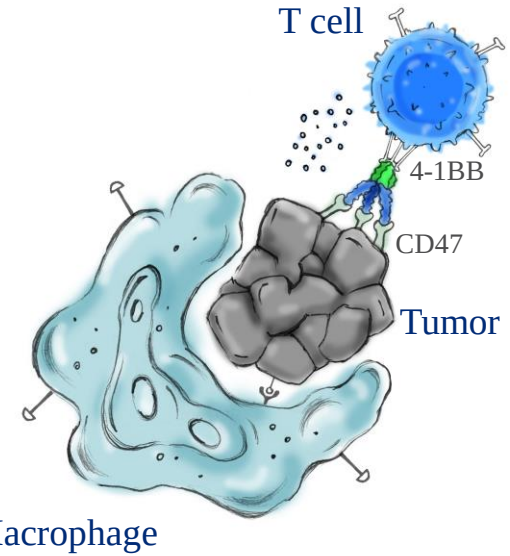


3 SIRPα for
CD47 Checkpoint Targeting



SIRPα binds to **CD47** overexpressed on cancer cells, disabling their 'don't eat me' signal

4-1BBL binds to **4-1BB** on tumor-antigen specific T cells, stimulating their expansion, cytokine production and development of cytolytic effector functions



Next-generation CD47 Programs Will Be Differentiated By Improved Safety

Clinical safety profile of CD47 mAbs

Company	Gilead/ Forty Seven	Surface Oncology	Trillium Therapeutics	Trillium Therapeutics	Celgene	ALX Oncology
Candidate	Magrolimab (n = 48)	SRF231 (n = 46)	TTI-621 (n = 89)	TTI-622 (n = 19)	CC-90002 (n = 28)	Evorpacept (n = 28)
Indication	r/r solid tumors and lymphomas	r/r solid tumors and lymphomas	r/r lymphoma	r/r heme malignancies and select solid tumors	r/r AML or MDS	r/r solid tumors and lymphoma
Dose Levels	0.1 - 45 mg/kg	0.1 - 12 mg/kg	0.1 - 0.2 mg/kg	0.1 - 8 mg/kg	0.1 – 4 mg/kg	0.3 – 30 mg/kg
Anemia (Grade All, ≥3)	56%, 10%	24%, 17%	11%, 9%	<10%, 0%	7%, 7%	≤4%, 0%
Thrombocytopenia (Grade All, ≥3)	13%, 0%	<10%, --	24%, 19%	5%, 0%	7%, 7%	11%, 7%
Neutropenia (Grade All, ≥3)	4%, 0%	22%, 20%	<10%, --	11%, 11%	0%, 0%	4%, 4%

Hematological toxicity safety advantage including lack of on target anemia and transfusion requirements can differentiate next generation CD47 programs vs competitors

Source: LifeSci report August 2020

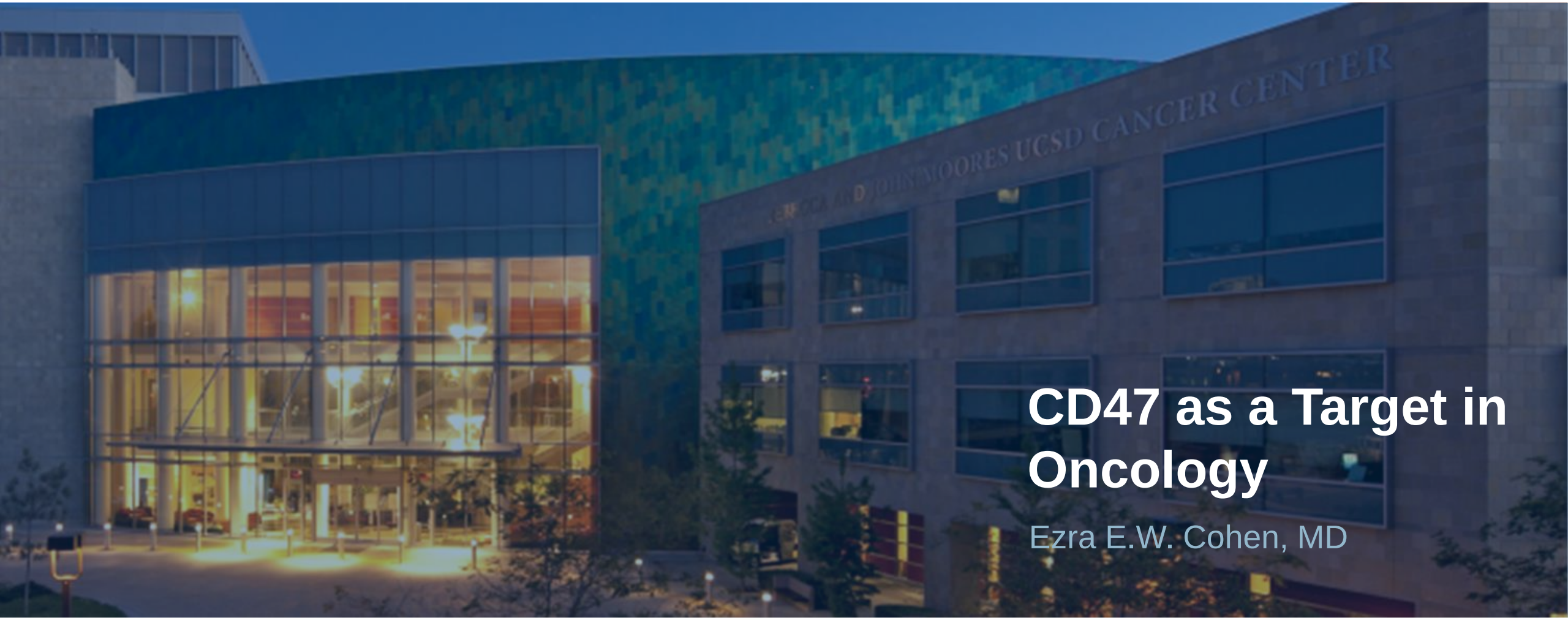
CD47 Monotherapy Lacks Clinical Activity In AML/MDS

- Clinical experience to date with the majority of CD47 mAbs suggests lack of monotherapy activity in solid and hematological malignancies
- In patients with AML/MDS, responses were mostly observed when CD47 mAbs were combined with azacytidine
- Next generation CD47 programs with activity as a monotherapy will be differentiated in AML/MDS
- Effective treatments in R/R AML and R/R MDS remains an unmet need, with majority of responses to date occurring in the frontline setting

Source: LifeSci report August 2020

Summary and Unmet Needs in AML/MDS

- Entrance of venetoclax and other targeted therapies into the market has improved survival rates
- TP53-mutant patients with high-risk MDS and AML have dismal outcomes with standard therapy
- Long-term efficacy and efficacy in patients with high-risk molecular features remains an unmet need
- Targeting CD47 is an immune based approach that has demonstrated clinical responses in combination with azacitidine in both the frontline setting and in patients with high-risk features
- Current majority of CD47 mAbs lack therapeutic activity as a monotherapy and have hematological safety issues
- Novel strategies targeting both the adaptive and innate immune systems may help achieve mutation agnostic clinical responses with durable benefits
- Next-generation CD47-targeted therapeutic in development, including SIRPα/CD47 bi-specific inhibitors, with potential for more robust activity and improved safety



CD47 as a Target in Oncology

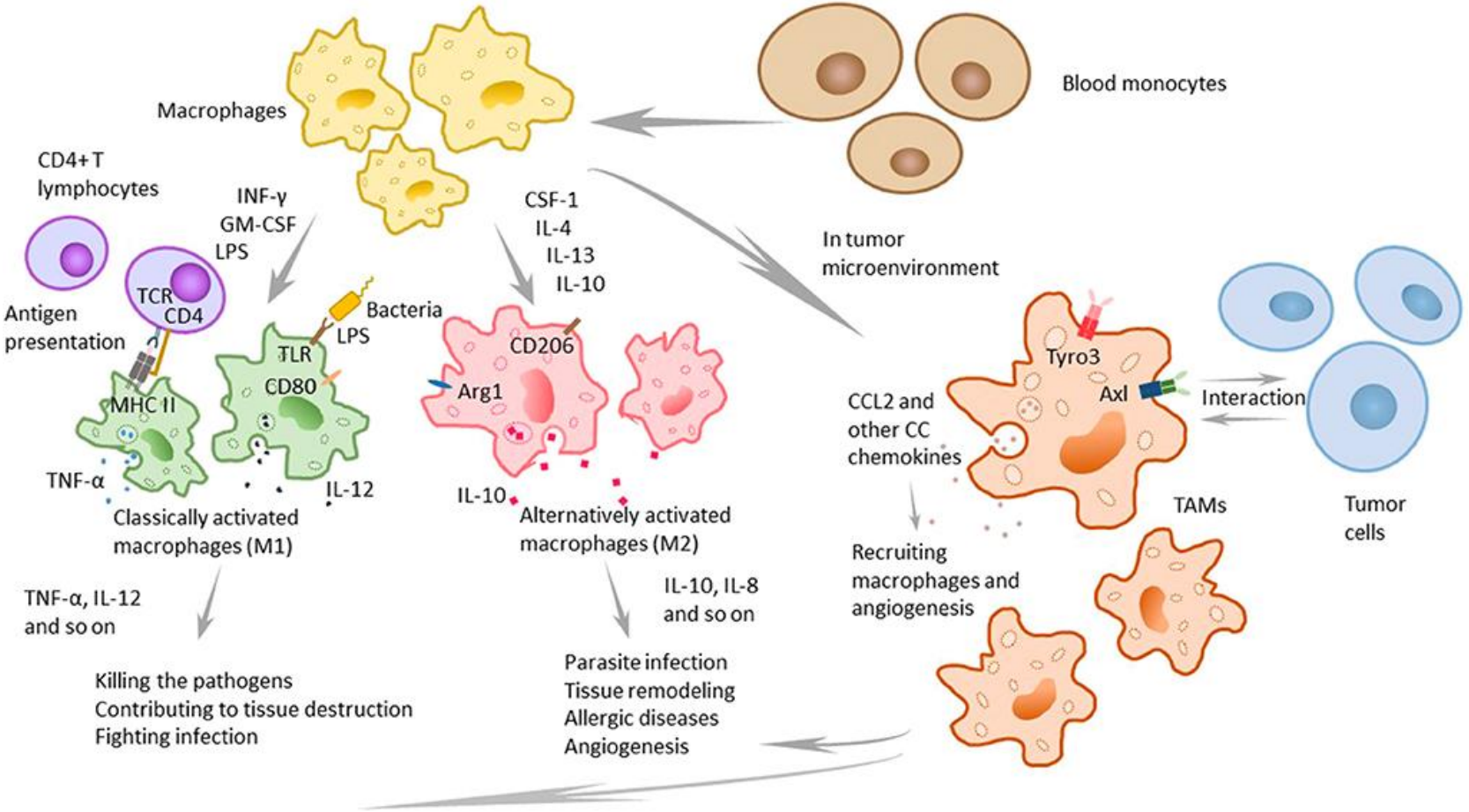
Ezra E.W. Cohen, MD

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

UC San Diego
Moores Cancer Center

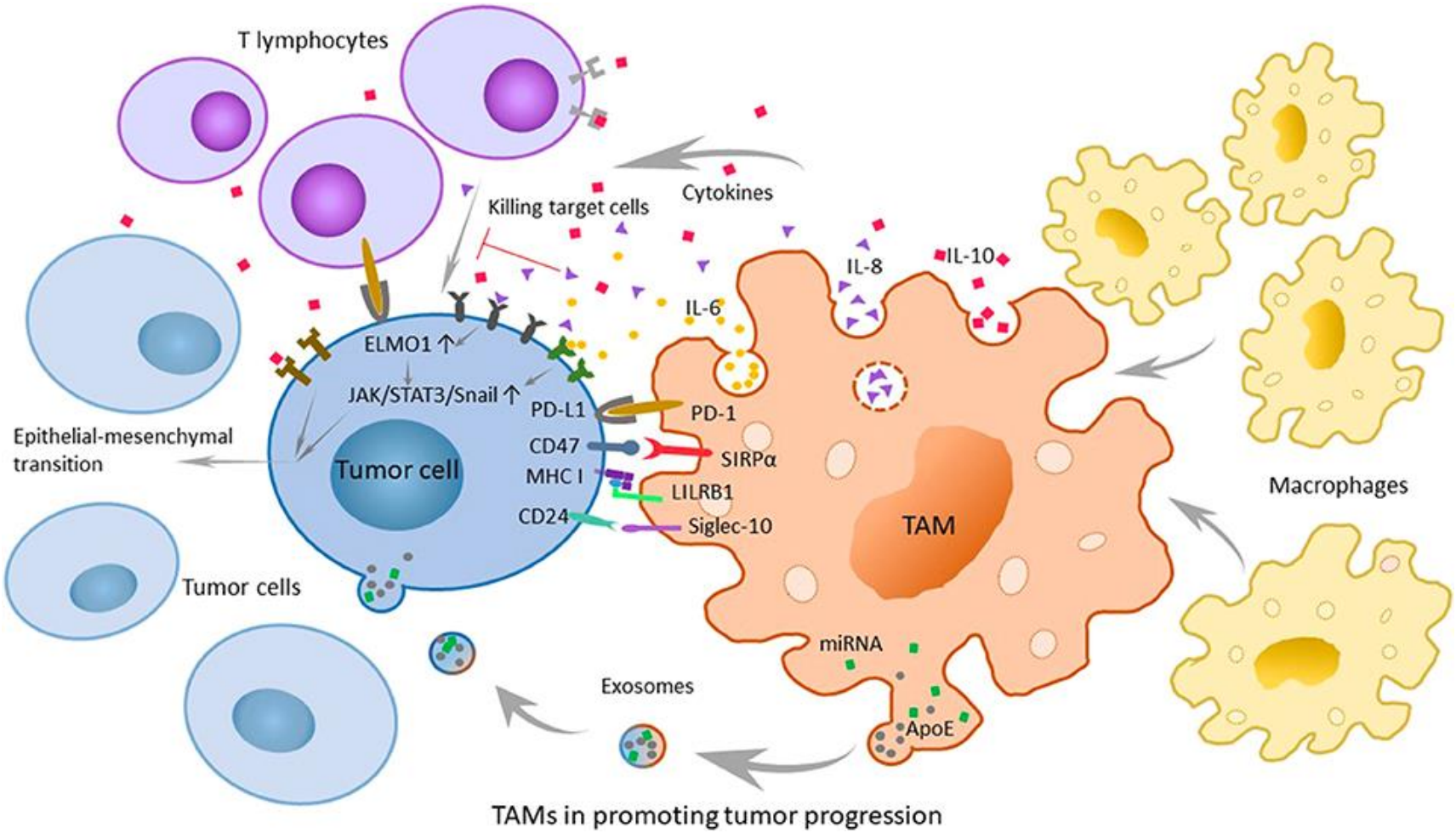
The Innate Immune System

Two of the main subpopulations of macrophages (M1 and M2) and tumor associated macrophages (TAMs)



Front. Oncol., 25 February 2020 | https://doi.org/10.3389/fonc.2020.00188

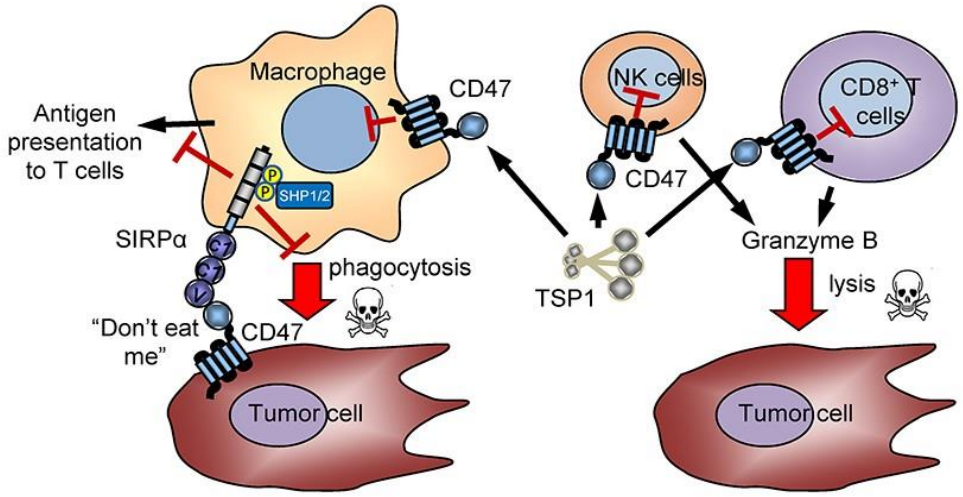
Tumor-Associated Macrophages: Insights and Therapies



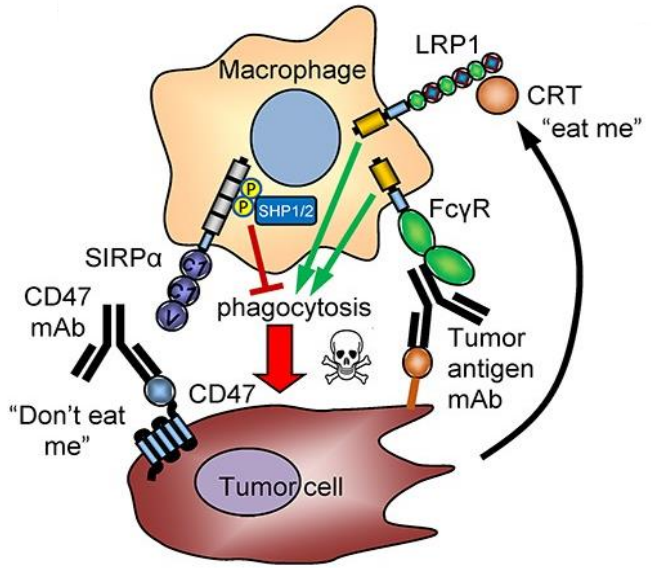
Front. Oncol., 25 February 2020 | https://doi.org/10.3389/fonc.2020.00188

CD47 Functions In The Tumor Microenvironment

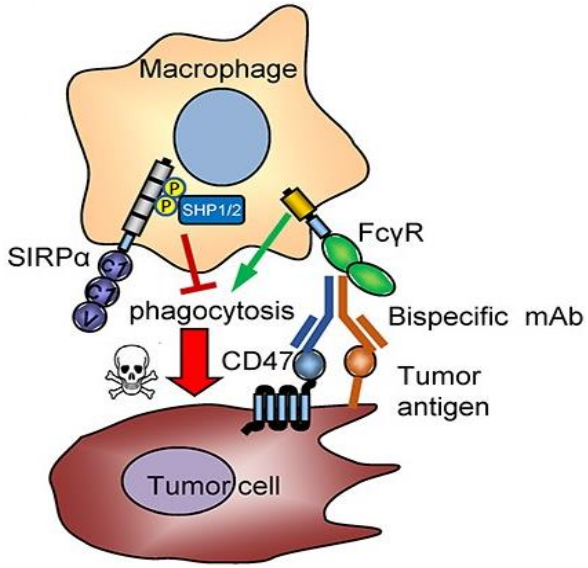
CD47-dependent inhibition of phagocytosis and antigen presentation



Anti-CD47-antibody-dependent phagocytosis and ADCP/ADCC



Bispecific CD47 antibody-dependent ADCP and/or ADCC

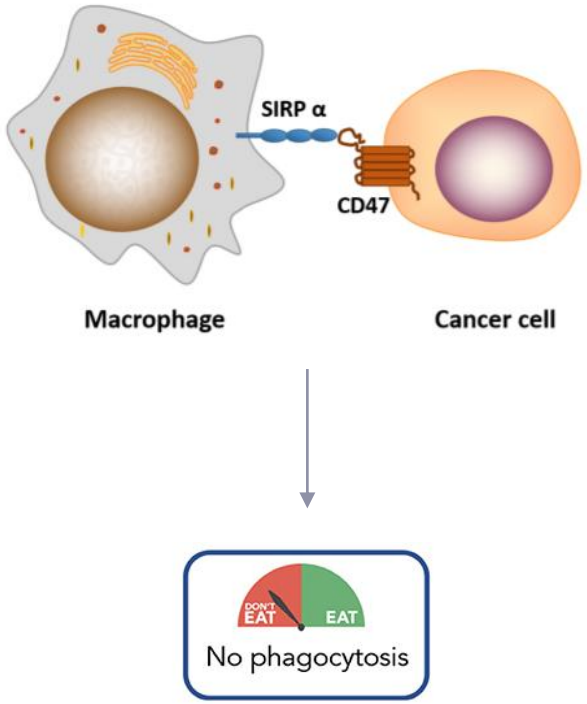


CD47 Interaction With SIRPα Prevents Innate Immune Cells From Attacking Host Cells

Healthy Cells

CD47 protects healthy cells from destruction

- CD47 is a surface protein widely expressed on healthy cells
- Interacts with SIRPα expressed on macrophages and dendritic cells
- Regulates innate immune cell phagocytic activity and cell migration



Tumor Cells

CD47 overexpression evades immune destruction of tumor cells

- CD47 is over-expressed across solid tumors and hematological malignancies
- Serves as a camouflage to avoid clearance by macrophages
- Elevated CD47 is associated with a poor prognosis

Lu Q et al.; Onco Targets Ther. 2020; Chao MP et al.; Front. Oncol., 2020

CD47 Is A Clinically Validated Innate Immunity Check Point Inhibitor

CD47 inhibition impairs tumor growth, inhibits metastatic spread, and leads to tumor regression in preclinical models

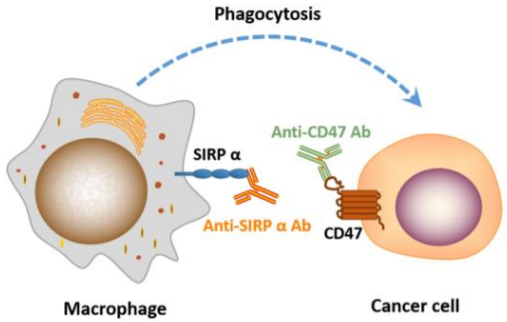
Evidence supports CD47 blockade may help **bridge innate and adaptive immunity** by

1. Reactivating macrophages against cancer cells
2. Enhancing APC presentation of tumor antigens
3. Inducing anti-tumor T-cell activity

Therapeutic considerations for targeting CD47

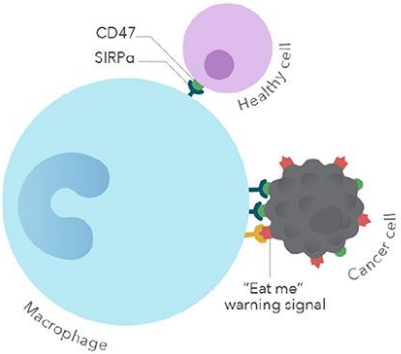
Enhanced activity in combination

CD47 inhibition in combination with antibodies targeting macrophages **enhances phagocytosis and anti-tumor activity** in preclinical models



Healthy cells are spared

An **additional 'eat me signal'** expressed on cancer cells and RBC is required for phagocytosis during CD47 blockade



Lu Q et al.; Onco Targets Ther. 2020; Chao MP et al.; Front. Oncol., 2020; Jalil et al., Antibody Therapeutics, 2020; Takimoto et al., Annals of Oncology, 2019; Tseng T et al., PNAS, 2013

CD47i Monotherapy: Lack of Clinical Responses In Solid Tumors

Company	I-MAB Biopharma/ AbbVie	Innovent	Gilead/ Forty Seven	Surface Oncology	ALX Oncology
Candidate	Lemzoparlimab	Letaplimab	Magrolimab	SRF231	ALX148
MOA	Anti-CD47 Monoclonal Antibody	Anti-CD47 Monoclonal Antibody	Anti-CD47 Monoclonal antibody	Anti-CD47 Monoclonal Antibody	SIRPα-Fc fusion protein
Clinical stage	Phase 1	Phase 1	Phase 1	Phase 1	Phase 1
Indication	Solid Tumors	Solid Tumors	Solid Tumors	Solid Tumors	Solid tumors
N	20	20	62	46	25
Efficacy	6% ORR (1/16)	0% ORR (0/15)	6% ORR (2/35)	0% ORR (0/38)	0% ORR (0/25)
Anemia	30%	15%	57%	24%	-

CD47 Therapies For Solid Tumors – Future Directions

1. Combination with therapeutic mAb's (IgG1-based preferred)

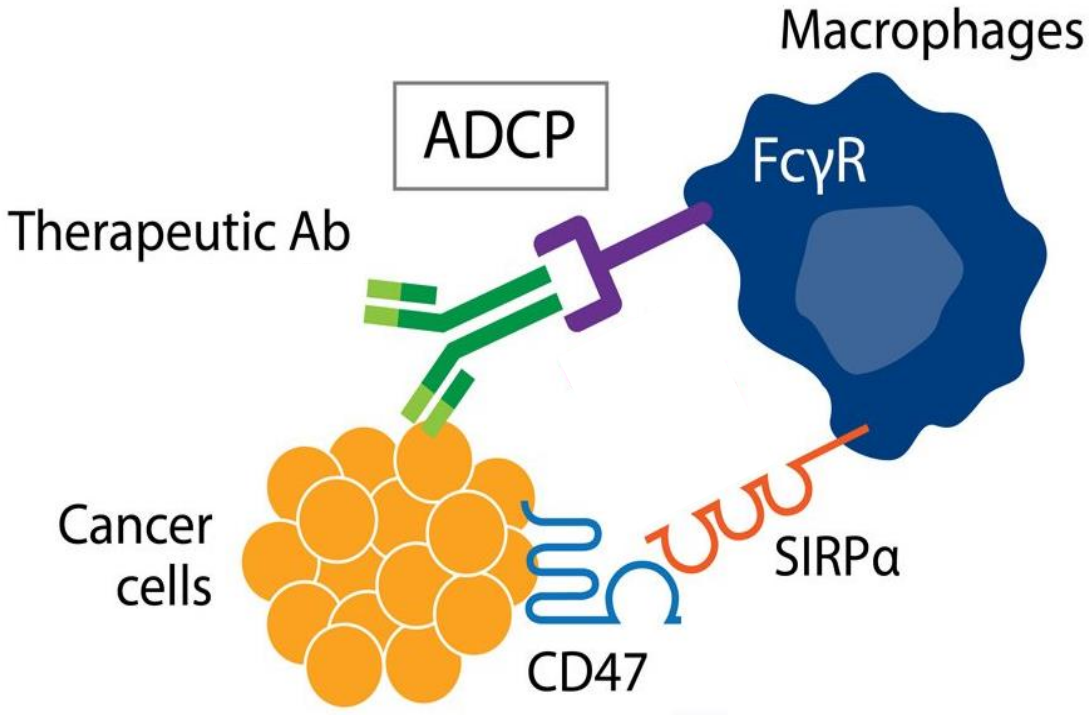
2. Combination of innate and adaptive immunity

3. Combination with Chemotherapy/ Radiotherapy

Combination With Therapeutic mAb's

Combination With Therapeutic mAb's

- CD47 blockade on tumor cells triggers phagocytosis by macrophages which may be opsonized with tumor antigen-specific therapeutic Abs such as cetuximab or trastuzumab
- The mechanism is called antibody-dependent cellular phagocytosis (ADCP) elicited by the interaction of the Fc region of tumor-bound Abs with the macrophage Fcγ receptor (FcγR)



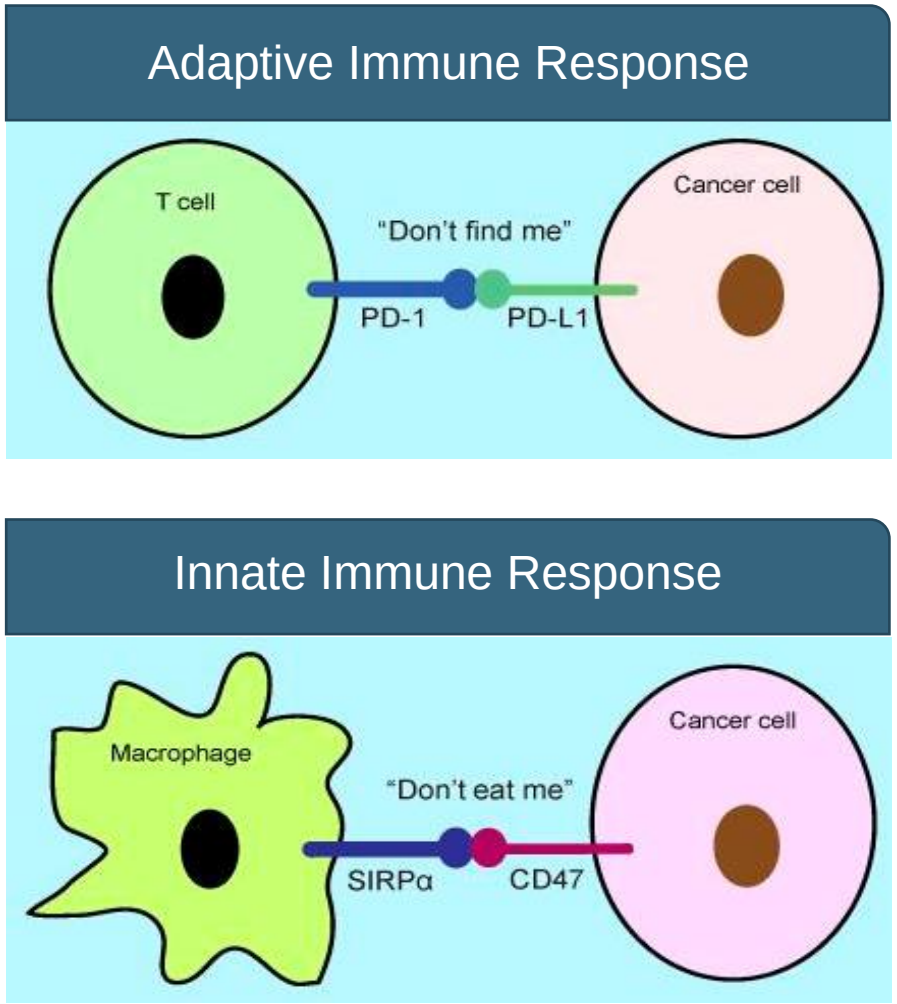
https://doi.org/10.1111/cas.13663

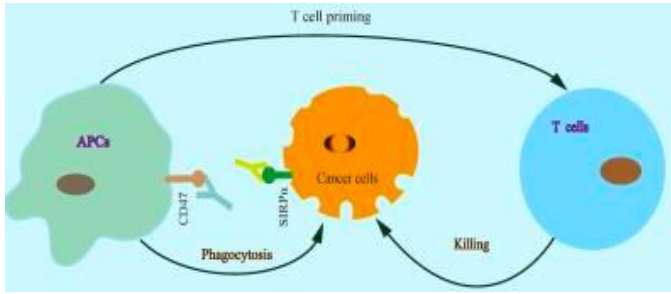
CD47i Combinations: Therapeutic mAb's Improve Clinical Responses

Company	Gilead/ Forty Seven	Gilead/ Forty Seven	Alx Oncology	Alx Oncology	Alx Oncology
Candidate	Magrolimab	Magrolimab	Evorpacept	Evorpacept	Evorpacept
MOA	Anti-CD47 Monoclonal Antibody	Anti-CD47 Monoclonal Antibody	SIRPα-Fc Fusion Protein	SIRPα-Fc Fusion Protein	SIRPα-Fc Fusion Protein
Clinical stage	Phase 1	Phase 1	Phase 1b	Phase 1b	Phase 1b
Additional drug	Cetuximab	Avelumab	Pembrolizumab + 5FU + Platinum	Trastuzumab	Trastuzumab Ramucirumab Paclitaxel
Indication	KRASwt, KRASmut Colorectal Cancer	Ovarian Cancer	HNSCC	HER2+ G/GEJ	HER2+ G/GEJ
N	30	18	13	19	18
Efficacy	7% ORR	6% ORR	**38.5% ORR**	21% ORR	**72% ORR**
Anemia	22%	24%	10%	7%	6%

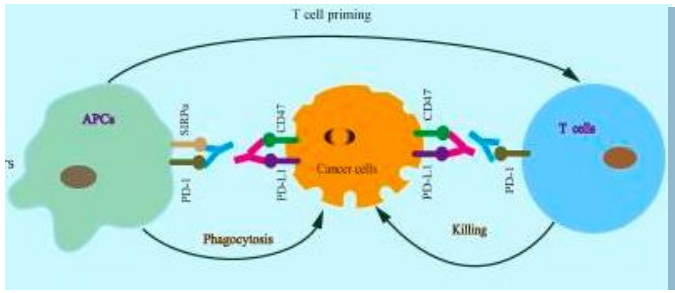
Combination Of Innate And Adaptive Immunity

Combination Of Innate And Adaptive Immunity

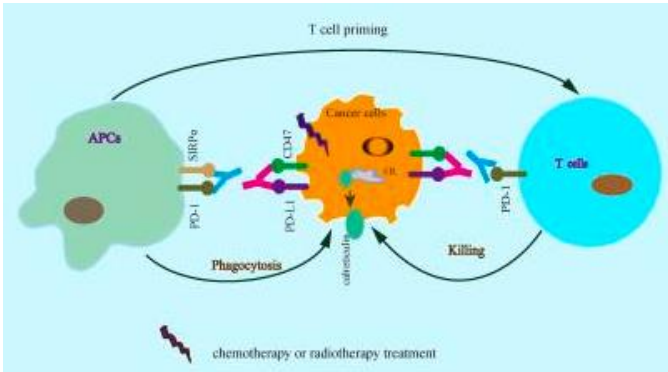




I: SIRPα/CD47 inhibitors



II: Combination with PD-1/PD-L1 inhibitors



III: Combination with chemotherapy or radiotherapy

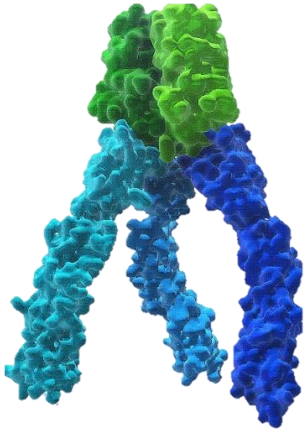
Int J Biol Sci. 2021; 17(13): 3281–3287

Combination Of Innate And Adaptive Immunity In Clinical Development

- Bi-specific fusion proteins combining anti-CD47 and TNF superfamily ligand for immune co-stimulation
- Combination of anti-CD47 and other immune checkpoint inhibitors such as PD-1/PD-L1
- Bi-specific Ab's aiming to both CD47 and PD-1/PD-L1

DSP107
CD47x41BB

Trimeric 4-1BBL for
T cell co-stimulation



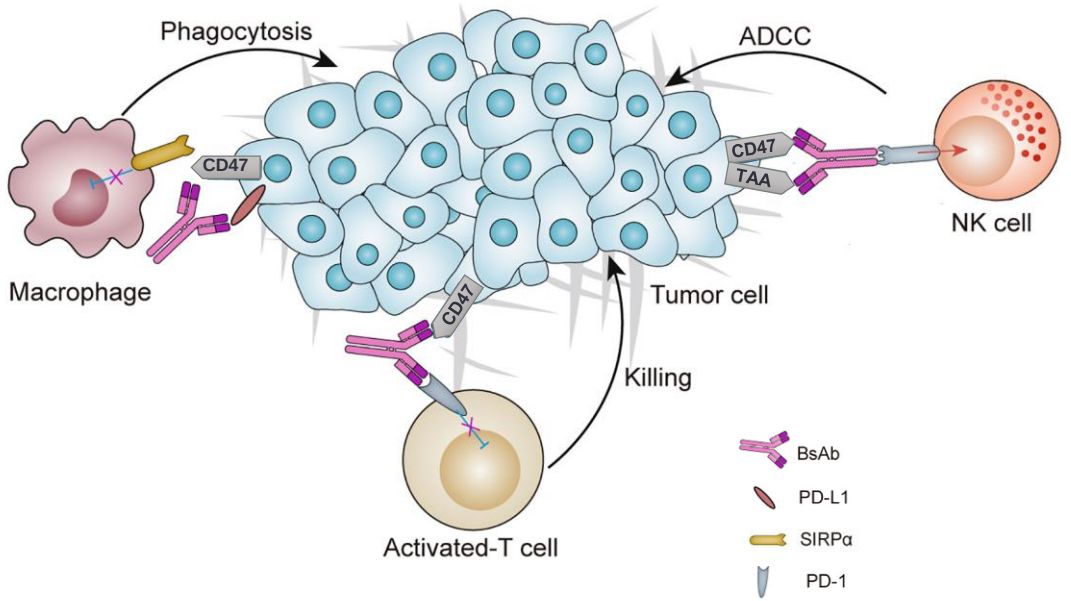
3 SIRPα for CD47 blockade

SL-172154
CD47xCD40

Hexameric CD40L for
antigen presentation

6 SIRPα for CD47 blockade

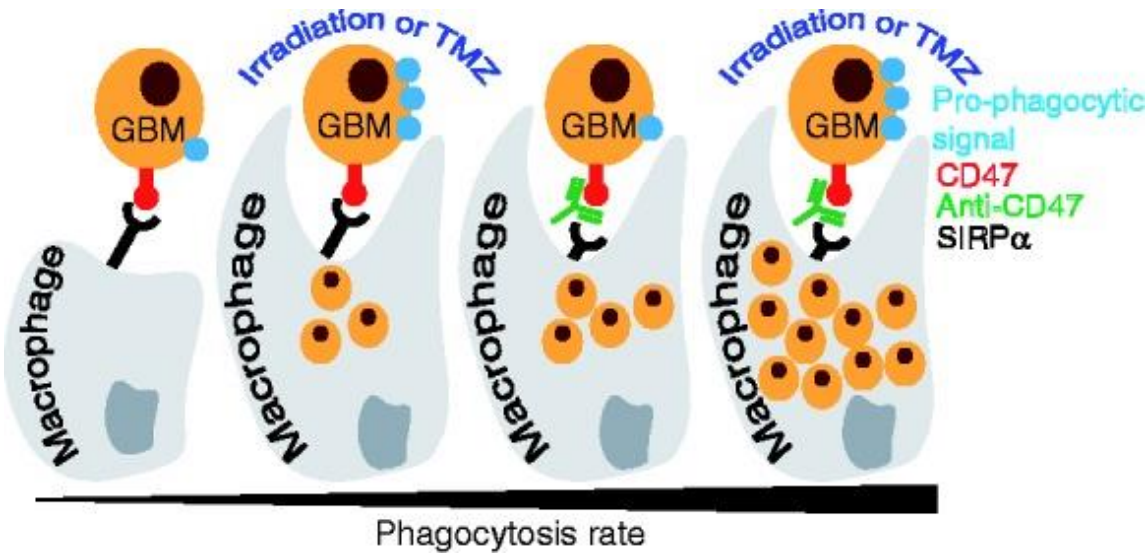
HX009, PF-07257876, IBI322
CD47xPD-1/PD-L1



Combination With Chemotherapy/Radiotherapy

Combination With Chemotherapy/Radiotherapy

- Anti-CD47 immunotherapy in combination with irradiation or chemotherapy may enhance macrophage-dependent phagocytosis and antigen presentation
- Tumor cell death triggered by immunogenic chemotherapeutic such as anthracyclines, cyclophosphamide and taxanes may lead to exposure of calreticulin on the cell surface where it serves as a de novo “eat-me” signal enhancing phagocytosis



Innate Immun. 2020 Feb; 26(2): 130–137.
doi: 10.1177/1753425919876690

Summary and Conclusions

- CD47 is well-established as a critical immune mediator within the tumor microenvironment, as CD47 overexpression leads to poor clinical outcomes across solid tumors and hematologic malignancies
- CD47 is a clinically validated innate immunity checkpoint inhibitor, but lacks robust clinical responses as a monotherapy
- Combination of anti-CD47 antibodies with therapeutic monoclonal antibodies have shown improved clinical efficacy
- Several CD47-targeted therapeutic considerations are currently in development, including SIRPα/CD47 bi-specific inhibitors, combination with adaptive immune activators, and combination with chemotherapy or radiotherapy