SITC Cancer Immunotherapy Winter School, January 2022

# Industry Session: New Agents CD47/SIRPα Targeting Agents In Clinical Development

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IGM Biosciences

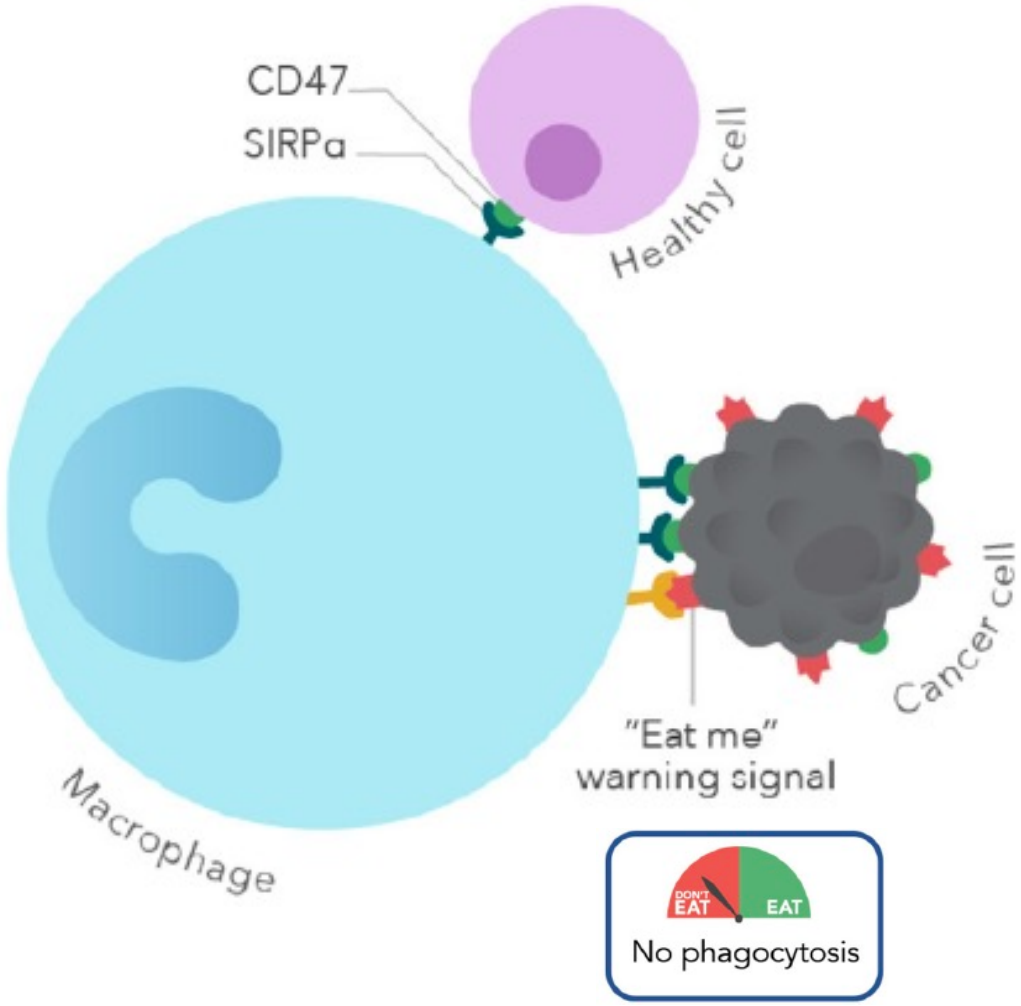
## Disclosures

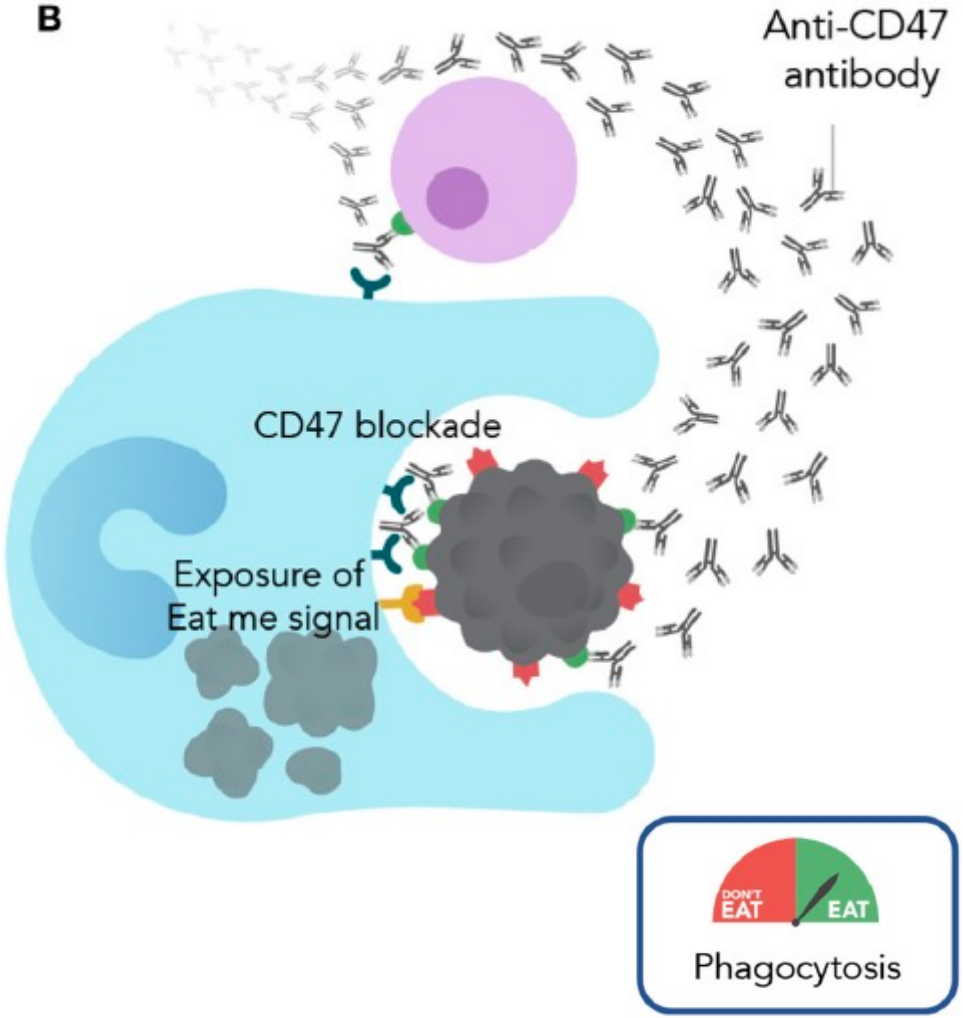
- I am a current stockholder and employee of IGM Biosciences
- I am a former employee and current stockholder of Johnson & Johnson and Gilead Sciences
- The views you hear today are my own and do not represent those of any other individuals or organizations
- This presentation only contains publicly available information

## CD47, A Don't Eat Me Signal for Phagocytic Cells and A Target for Cancer Immunotherapy

- CD47 is a 50 kDa cell surface glycoprotein ubiquitously expressed on normal and malignant tissues
- Engagement with its receptor, SIRPα on macrophages, and other effector cells delivers a potent "Don't Eat Me" signal
- Frequently overexpressed in a wide range of solid tumors and hematological malignancies,
- High expression in various tumor types is associated with a worse clinical prognosis
- Cancer cells utilize CD47 to evade surveillance by the innate immune system
- Blockade of CD47/SIRPα signaling on tumor cells in the presence of prophagocytic signals can induce phagocytosis

## CD47, A Don’t Eat Me Signal for Phagocytic Cells and A Target for Cancer Immunotherapy



# CD47's Therapeutic Potential Discovered by The Weissman Lab at Stanford

## CD47 Is Upregulated on Circulating Hematopoietic Stem Cells and Leukemia Cells to Avoid Phagocytosis

Cell

Siddhartha Jaiswal,[1,*] Catriona H.M. Jamieson,[2] Wendy W. Pang,[1] Christopher Y. Park,[1] Mark P. Chao,[1] Ravindra Majeti,[1] David Traver,[3] Nico van Rooijen,[4] and Irving L. Weissman[1,*]

Jaiswal et al. Cell 2009

## CD47 Is an Adverse Prognostic Factor and Therapeutic Antibody Target on Human Acute Myeloid Leukemia Stem Cells

Cell

Ravindra Majeti,[1,3,7,*] Mark P. Chao,[3,7] Ash A. Alizadeh,[1,3] Wendy W. Pang,[3] Siddhartha Jaiswal,[3] Kenneth D. Gibbs, Jr.,[4,5] Nico van Rooijen,[6] and Irving L. Weissman[2,3,*]

Majeti and Chao et al. Cell 2009

## Anti-CD47 Antibody Synergizes with Rituximab to Promote Phagocytosis and Eradicate Non-Hodgkin Lymphoma

Cell

Mark P. Chao,[1,10,*] Ash A. Alizadeh,[1,2,3,10] Chad Tang,[1] June H. Myklebust,[3,9] Bindu Varghese,[3] Saar Gill,[5] Max Jan,[1] Adriel C. Cha,[1] Charles K. Chan,[1] Brent T. Tan,[4] Christopher Y. Park,[1,4] Feifei Zhao,[1] Holbrook E. Kohrt,[2,3] Raquel Malumbres,[6] Javier Briones,[7] Randy D. Gascoyne,[8] Izidore S. Lossos,[6] Ronald Levy,[3] Irving L. Weissman,[1,4,10] and Ravindra Majeti[1,2,10]

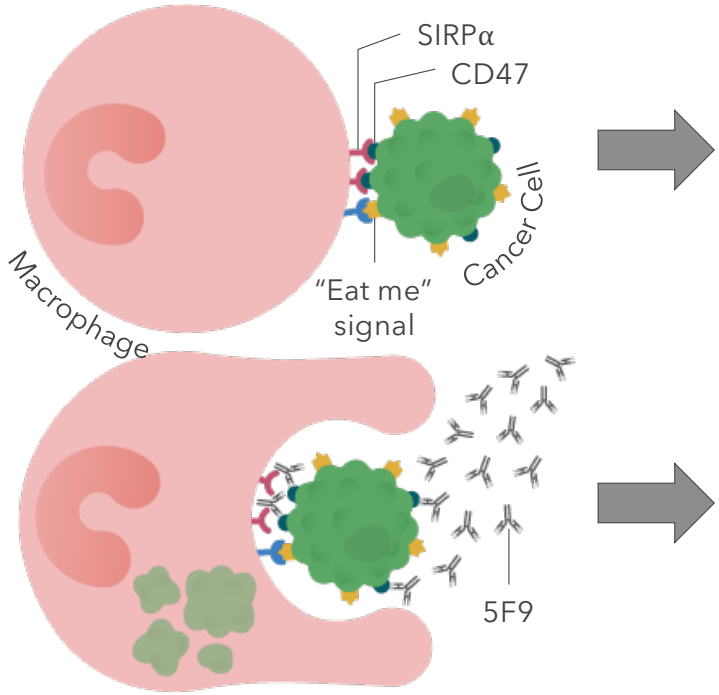
Chao and Alizadeh et al. Cell 2009

Irv Weissman

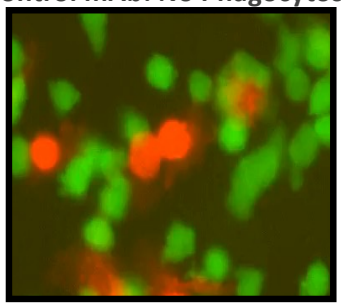
Ravi Majeti

Mark P. Chao

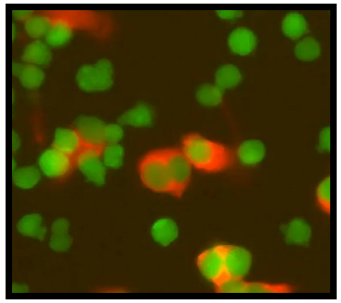
# Targeting CD47 Represents Novel Macrophage Immune Checkpoint Inhibitor Strategy




**Control mAb: No Phagocytosis**



**Anti-CD47 mAb: Phagocytosis**



**Macrophages (Red)**
**Cancer cells (Green)**

- Anti-CD47 antibodies enables macrophages to phagocytose cancer cells by blocking the binding of the "don't eat me" signal CD47 to its receptor SIRPα
- Normal cells are not phagocytosed as they do not express "eat me" signals, except for aged red blood cells
- Additional external "eat me" signals can be provided by cancer-specific antibodies

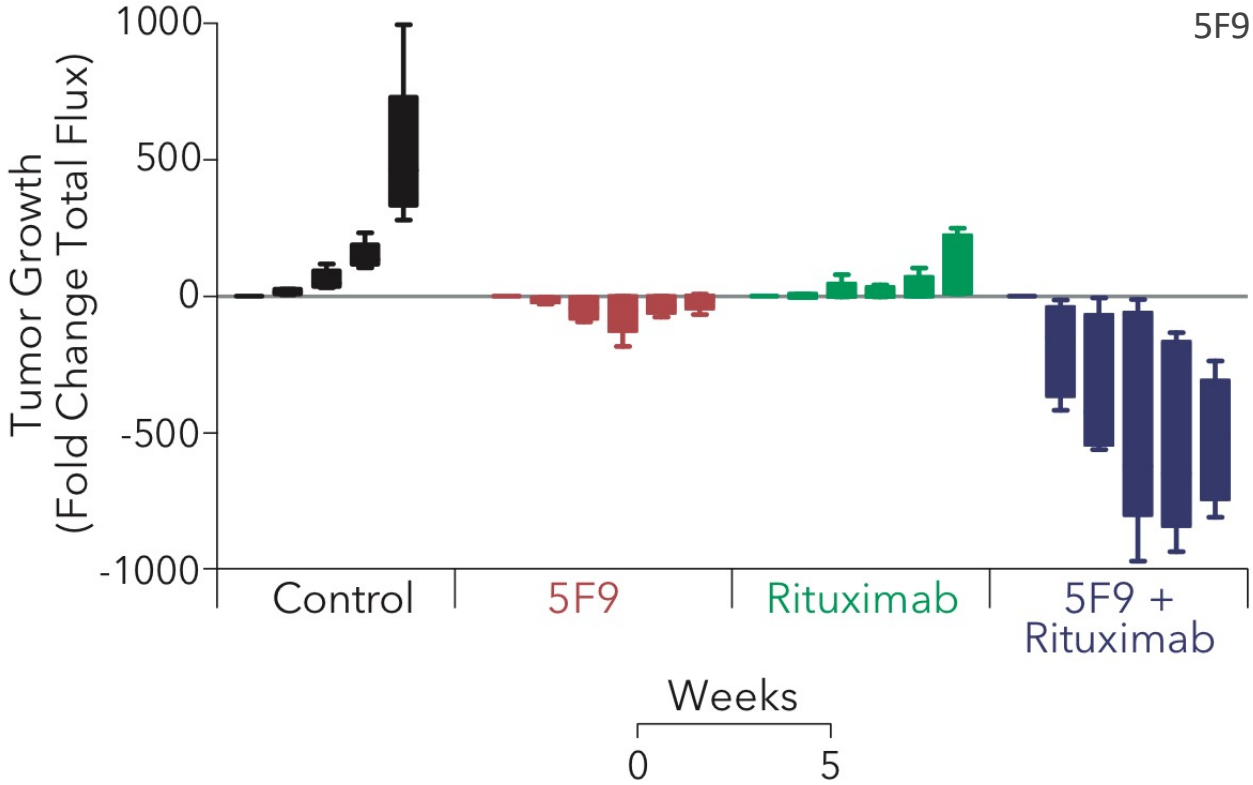
## Key Mechanistic Observations that Impact Guide Drug Development Strategies

- Antitumor activity associated with CD47 blockade generally requires additional prophagocytic signals
  - Monotherapy activity of CD47/SIRPα blocking agents may be modest
  - Combinations can optimize antitumor activity by enhancing the pro-phagocytic "Eat Me" signals on tumor cells

- Pro-Phagocytic Strategies
  - Antitumor antibodies with active Fc domains that engage Fc-receptors on macrophages
  - Cell stressors/cytotoxic agents that up regulate endogenous pro-phagocytic signals such as calreticulin, phosphatidylserine, and others

- Activation of the innate immune response (first responder cells) can enhance tumor antigen presentation and cross priming of T-cells, bringing the adaptive immune system into play
  - Targeting CD47 is a holistic approach to Immunotherapy
  - Both M1 and M2 macrophages can be induced to phagocytose tumor cells after CD47 blockade

# Rationale for Combinations with Antitumor Antibodies That Provide Additional Pro-phagocytic Signals

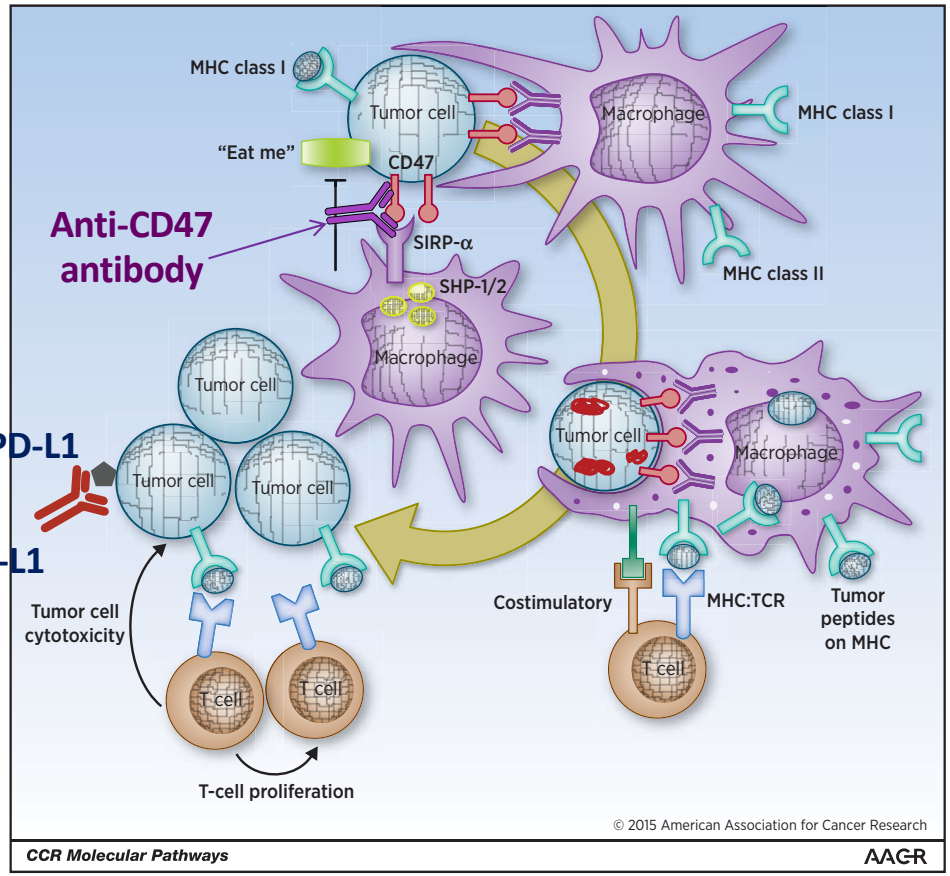



5F9 = Anti-CD47 antibody

Data generated by Jens-Peyer Volmer and colleagues at Forty Seven, Inc.

--Takimoto et al, Ann Oncol 2019

# Rationale for Combination with T Cell Checkpoint Inhibitors




- CD47 blockade can enhance phagocytic cell digestion of tumor cells
- Can potentiate tumor antigen cross priming of T Cells
- Potential to synergize with with Anti-PD-L1 Antibodies
- Currently being evaluated in clinical trials

--McCracken, Cha, Weissman, 2015, Clin Cancer Res

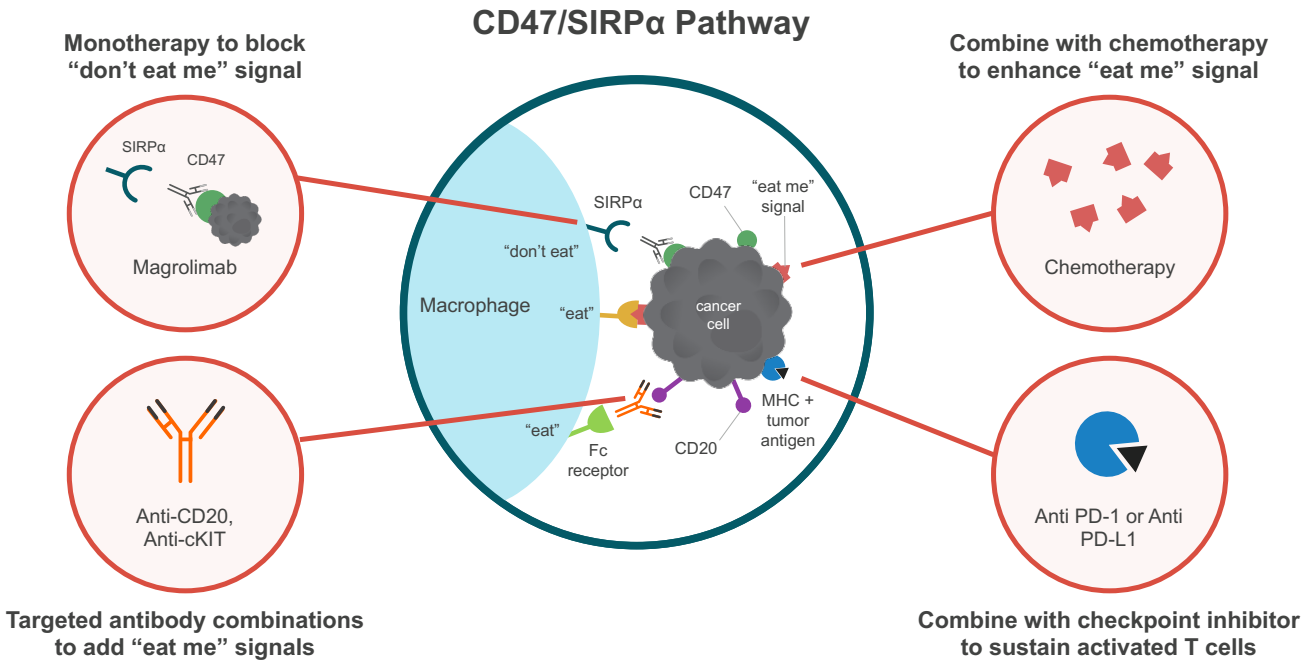
COMPETITORS NOT EXHAUSTIVE

# CD47 Targeting Agents in Clinical Development

| Sponsor | Gilead (acquired Forty Seven) | Pfizer (acquired Trillium Therapeutics) | | ALX Oncology | I-Mab/ AbbVie | Innovent | Arch Oncology | Zai Lab | ImmuneOncia Therapeutics |
|---|---|---|---|---|---|---|---|---|---|
| **Compound name** | Magrolimab (Hu5F9-G4) | TTI-621 | TTI-622 | Evorpacept (ALX148) | Lemzoparlimab (TJ011133 or TJC4) | Letaplimab (IBI-188) | AO-176 | ZL-1201 | IMC-002 |
| **Type of molecule** | mAb | WT SIRPα fusion protein | WT SIRPα fusion protein | High affinity SIRPα fusion protein | mAb | mAb | mAb | mAb | mAb |
| **Class** | IgG4 | IgG1 | IgG4 | Inactive Fc | IgG4 | IgG4 | IgG2 | IgG4 | N/A |
| **Clinical start date** | August 2014 | January 2016 | May 2018 | February 2017 | May 2019 | January 2019 | February 2019 | June 2020 | June 2020 |
| **Study stage (highest)** | Ph 3 | Ph 1b/2 | Ph 1b/2 | Ph 2 | Ph 1/2 | Ph 2 with Ph 3 planned in 1H 2022 | Ph 1/2 | Ph 1 | Ph 1 |
| **Indications** | MDS, AML Heme, solid tumors | DLBCL, PTCL, Leiomyo-sarcoma | Lymphoma, myeloma, AML, MDS, Ovarian, Solid tumors | HNSCC, Gastric, Breast, MDS, AML, NHL | MDS & AML (China & US), NHL, Myeloma, and solid tumors (WW) | MDS, AML, solid tumor, lymphoma | Solid tumor Multiple myeloma | Lymphoma, solid tumor | Solid tumors, lymphomas |

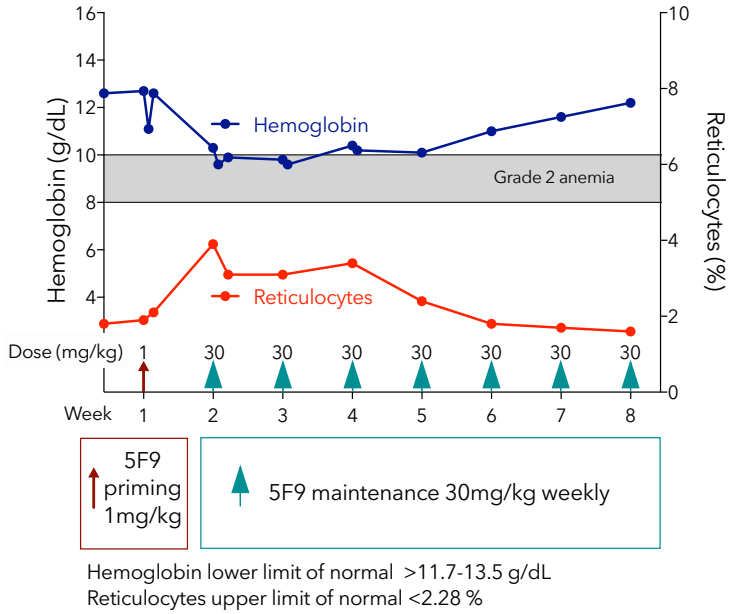
# Magrolimab (5F9; Gilead)

- Magrolimab, an IgG4 Anti-CD47 antibody that initiated clinical trials in August 2014
  - First-in-class program with >500 patients treated with hematological and solid tumor malignancies
  - Clinical development initiated at Stanford, then by Forty Seven, Inc. and now, Gilead Sciences
- Currently in Ph 3 trials in higher risk MDS and demonstrated activity in AML including TP53 mutant, NHL, and solid tumors patients



# Anemia is Mitigated with a Proprietary Prime and Maintenance Dosing Regimen

## Anemia with Compensatory Reticulocytosis




Hemoglobin lower limit of normal >11.7-13.5 g/dL
Reticulocytes upper limit of normal <2.28 %

--Sikic et al, JCO 2019

## Key Points:

- Proprietary priming dose results in an early, temporary decline in hemoglobin levels corresponding to mild to moderate anemia
- Hemoglobin levels return to baseline even with continued treatment with 5F9 at significantly higher doses (up to 45mg/kg)
- Mild to moderate anemia during the first two weeks of starting therapy
- Associated with a temporary and a reversible reticulocytosis that resolves during the dosing period

# Magrolimab Monotherapy Adverse Event Profile

| Solid Tumor Summary (n = 73) | | | |
|---|---|---|---|
| Adverse Event (AE) Term<br>Patients treated at 10 (3 pts), 20 (39 pts), 30 (25 patients), or 45 (6 patients) mg/kg weekly | AE Grade | | |
| | Any | 3 | 4 |
| **Anemia** | 36 (49%) | 8 (11%) | 0 |
| **Hemagglutination** | 22 (30%) | 1 (1%) | 0 |
| **Hyperbilirubinemia/Blood bilirubin increased** | 11 (15%) | 3 (4%) | 0 |
| **Thrombocytopenia** | 9 (12%) | 0 | 0 |
| **Neutropenia** | 2 (3%) | 0 | 0 |
| **Lymphopenia/Lymphocyte count decreased** | 12 (16%) | 7 (10%) | 3 (4%) |
| **Fatigue** | 36 (49%) | 0 | 0 |
| **Headache** | 33 (45%) | 1 (1%) | 0 |
| **Chills** | 28 (38%) | 0 | 0 |
| **Pyrexia** | 26 (36%) | 0 | 0 |
| **Infusion-related reaction** | 16 (22%) | 4 (5%) | 0 |
| **Nausea** | 13 (18%) | 0 | 0 |
| **Photopsia** | 7 (10%) | 0 | 0 |
| **Back pain** | 7 (10%) | 1 (1%) | 0 |
| **Myalgia** | 7 (10%) | 0 | 0 |
| **AST elevation** | 4 (5%) | 1 (1%) | 1 (1%) |
| **ALT elevation** | 4 (5%) | 0 | 1 (1%) |

## Key Points:

- Expected red blood cell findings are easy to manage using a priming dose regimen
- Well tolerated at high and extended exposures
- Magrolimab AE profile comparable as monotherapy or in combination
- MTD not reached with dose escalation up to 45 mg/kg and >250 patients treated as monotherapy or in combination

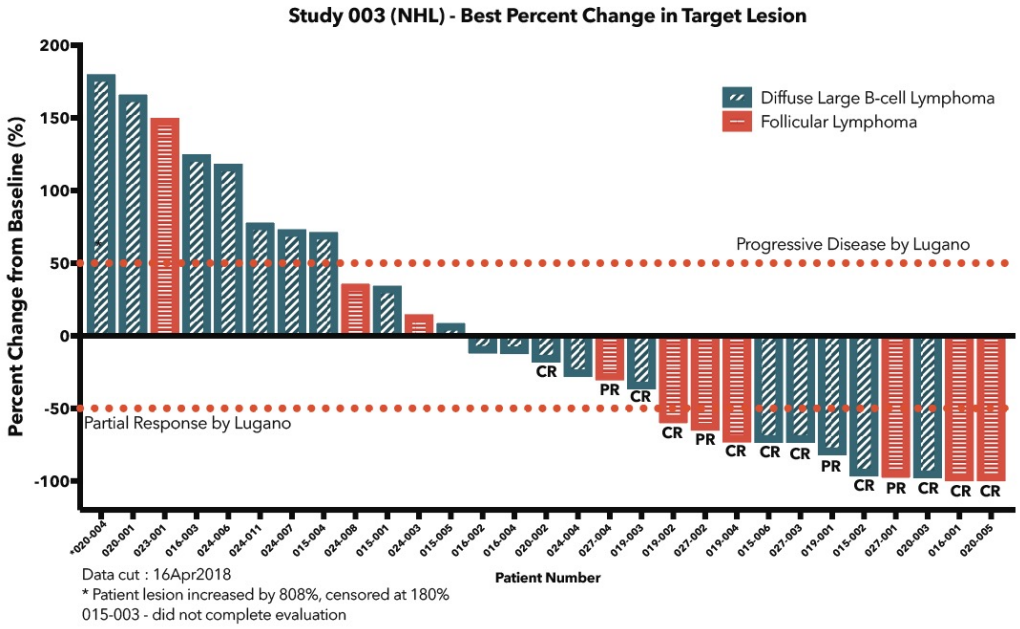


*AEs observed in ≥ 10% or selected for clinical interest; Data cutoff 24 Jul 2018*

# Antitumor Activity Observed with Rituximab Combination in Relapsed or Refractory NHL

| Response | All Patients n=30 | DLBCL n=20 | Follicular Lymphoma n=10 |
|---|---|---|---|
| Objective Response Rate (ORR) | 47% (14) | 35% (7) | 70% (7) |
| Partial Response (PR) | 13% (4) | 5% (1) | 30% (3) |
| Complete Response (CR) | 33% (10) | 30% (6) | 40% (4) |
| Disease control rate (CR+PR+SD) | 57% (17) | 50% (10) | 70% (7) |

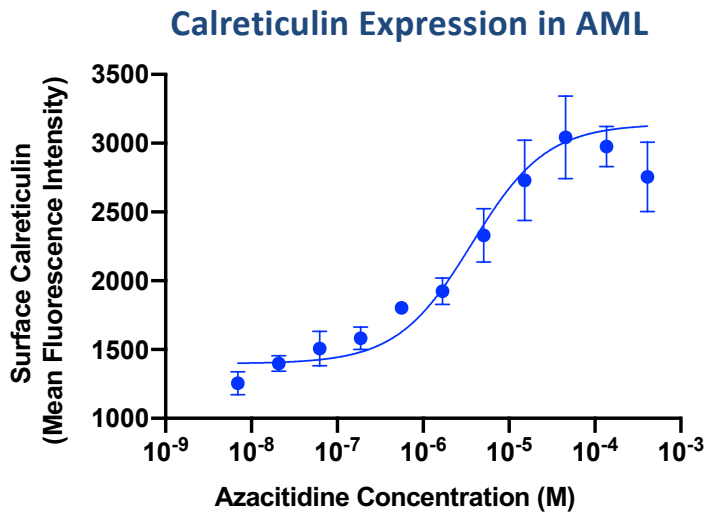
*Data cut 16 Apr 2018 from Phase 1b/2 trial*

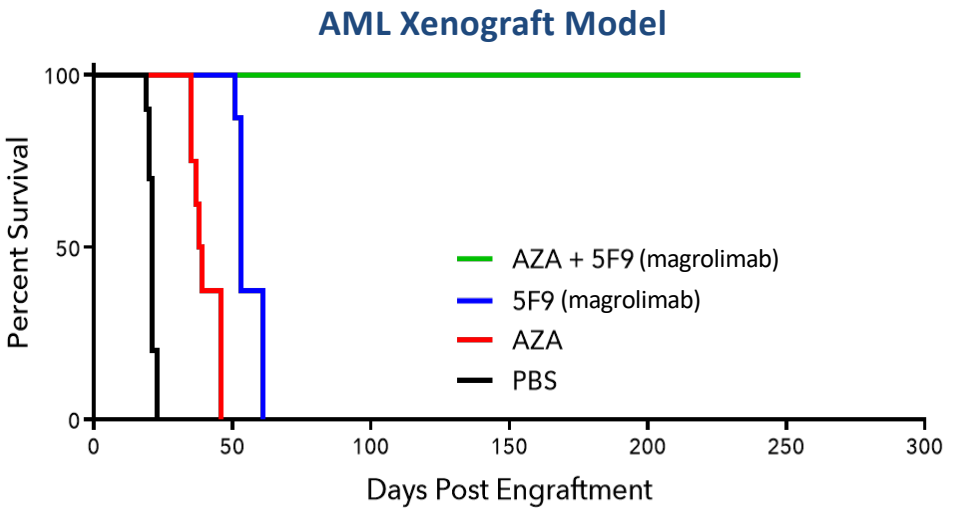



- Clinical activity is observed in rituximab-refractory patients (more than 90% of patients evaluated were rituximab-refractory)
- Approximately 90% of the patients who had an initial response, maintained their response, suggesting durability. One patient continues on therapy in complete remission after 14 months of treatment

--Advani ASCO 2019

# Magrolimab Synergizes With Azacitidine to Induce Remissions in AML Xenograft Models

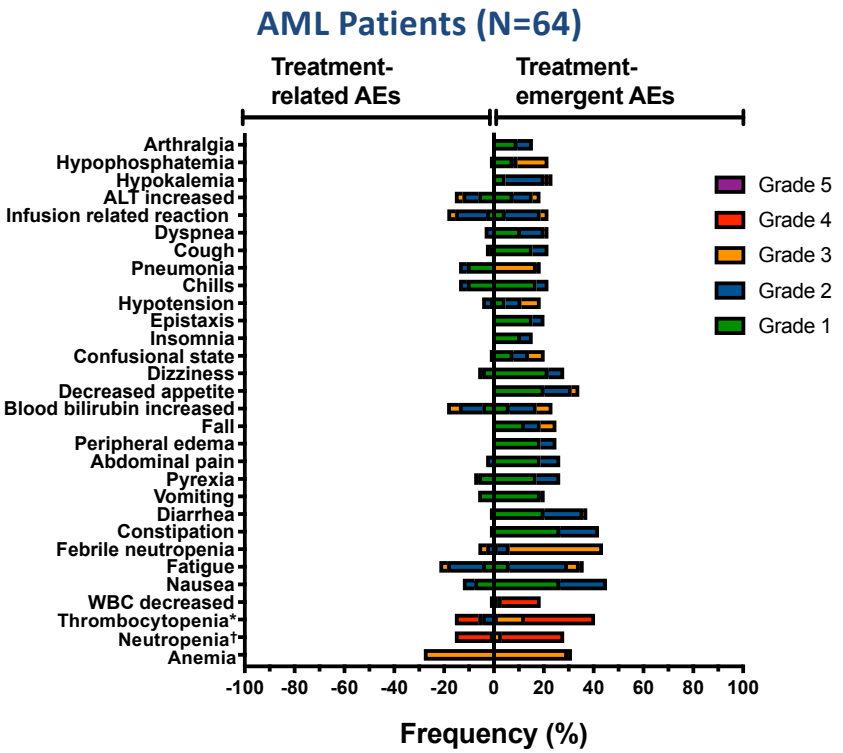



- Azacitidine (AZA) induces prophagocytic "eat me" signals, such as calreticulin, on cancer cells
- Increased "eat me" signals induced by AZA synergize with CD47 blockade of the "don't eat me" signals, leading to enhanced phagocytosis

Feng D, et al. Poster presented at: 60th ASH Annual Meeting and Exposition; December 1-4, 2018; San Diego, CA. Abstract 616 with adaptations.

# Magrolimab in Combination With AZA is Well Tolerated




- No maximum-tolerated dose was reached; magrolimab + AZA profile is generally consistent with AZA monotherapy
- No significant increases in cytopenias, infections, or immune-related adverse events (AEs) were observed (most patients were cytopenic at baseline)
- 30-day all-cause mortality was 4.7%, and 60-day mortality was 7.8%
- 4.7% of patients had an AE leading to magrolimab dose reduction
- Treatment discontinuation due to drug-related AEs occurred in 4.7% of all patients

AEs ≥15% or AEs of interest are shown. All patients with at least 1 magrolimab dose are shown.

*Includes thrombocytopenia and platelet count decreased. †Includes neutropenia and neutrophil count decreased.

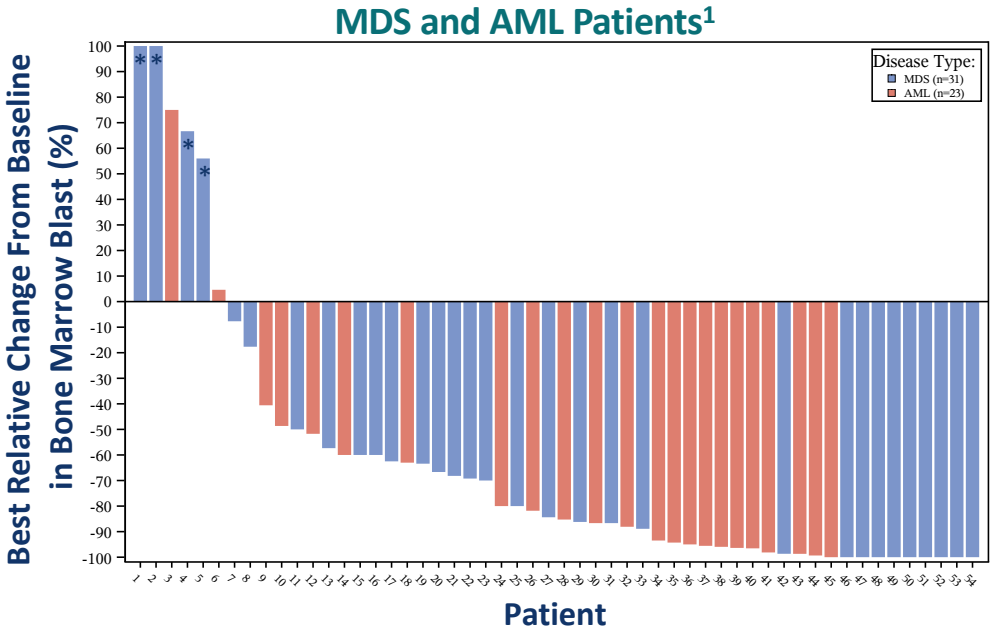


--Sallman ASH 2020

# Magrolimab in combination with azacitidine is effective in myelodysplastic syndrome and acute myeloid leukemia

| Best Overall Response | 1L MDS[1] N=33 | 1L AML[2] N=43 |
|---|---|---|
| ORR | 30 (91%) | 27 (63%) |
| CR | 14 (42%) | 18 (42%) |
| CRi | NA | 5 (12%) |
| PR | 1 (3%) | 1 (3%) |
| MLFS/marrow CR | 8 (24%)<br>4 with marrow CR + HI | 2 (7%) |
| Hematologic improvement (HI) | 7 (21%) | NA |
| SD | 3 (9%) | 8 (28%) |
| PD | 0 | 1 (4%) |

[1]Sallman et al., ASCO 2020; [2]Sallman et al., ASH 2020
Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).

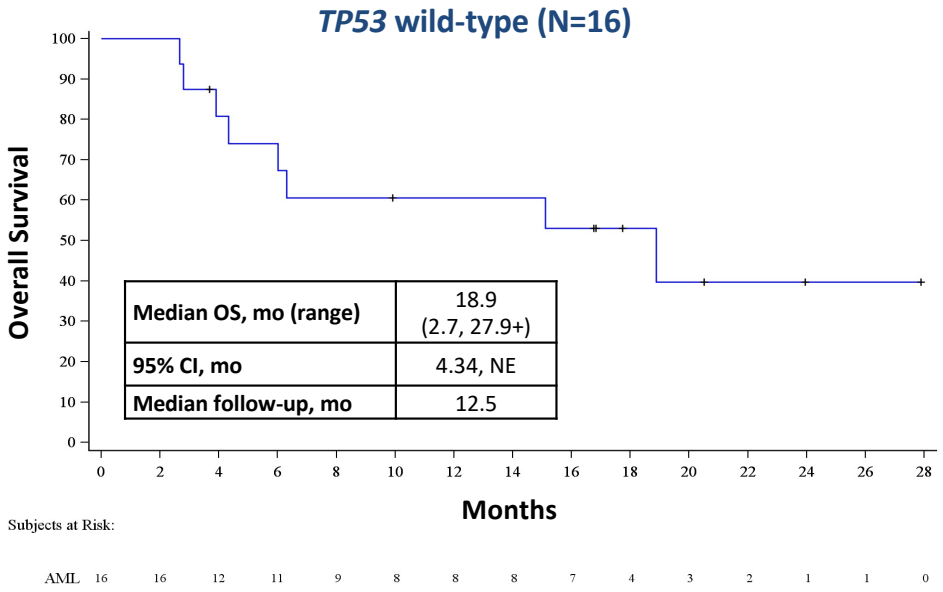


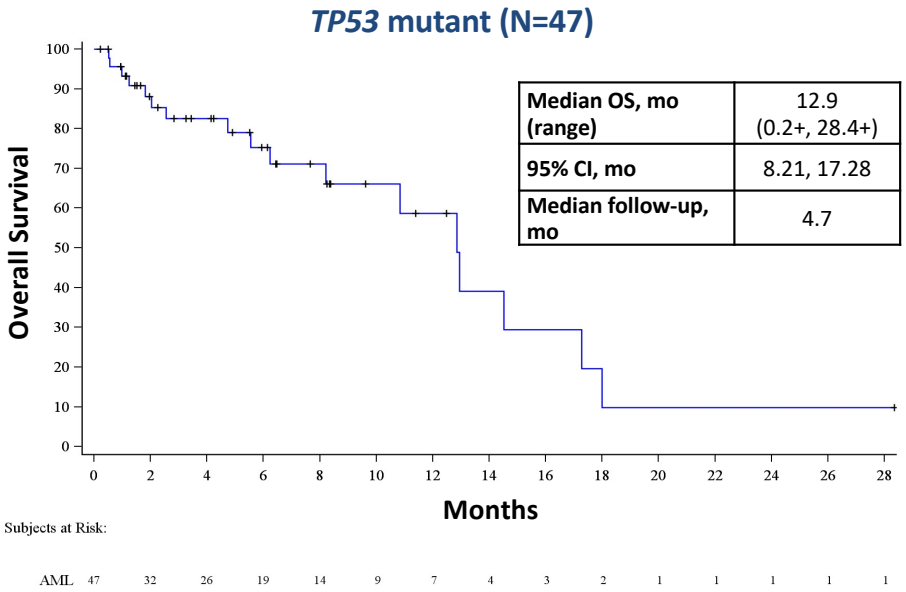
Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 63% ORR (42% CR) in AML
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy in MDS and AML (CR rate 6-17%)
- Magrolimab has been granted Breakthrough Therapy Designation and PRIME Designation for Higher Risk MDS
- Registrational trials are in progress

--Sallman ASH 2020

# Preliminary Median Overall Survival Is Encouraging in Both *TP53* Wild-Type and Mutant 1L AML Patients



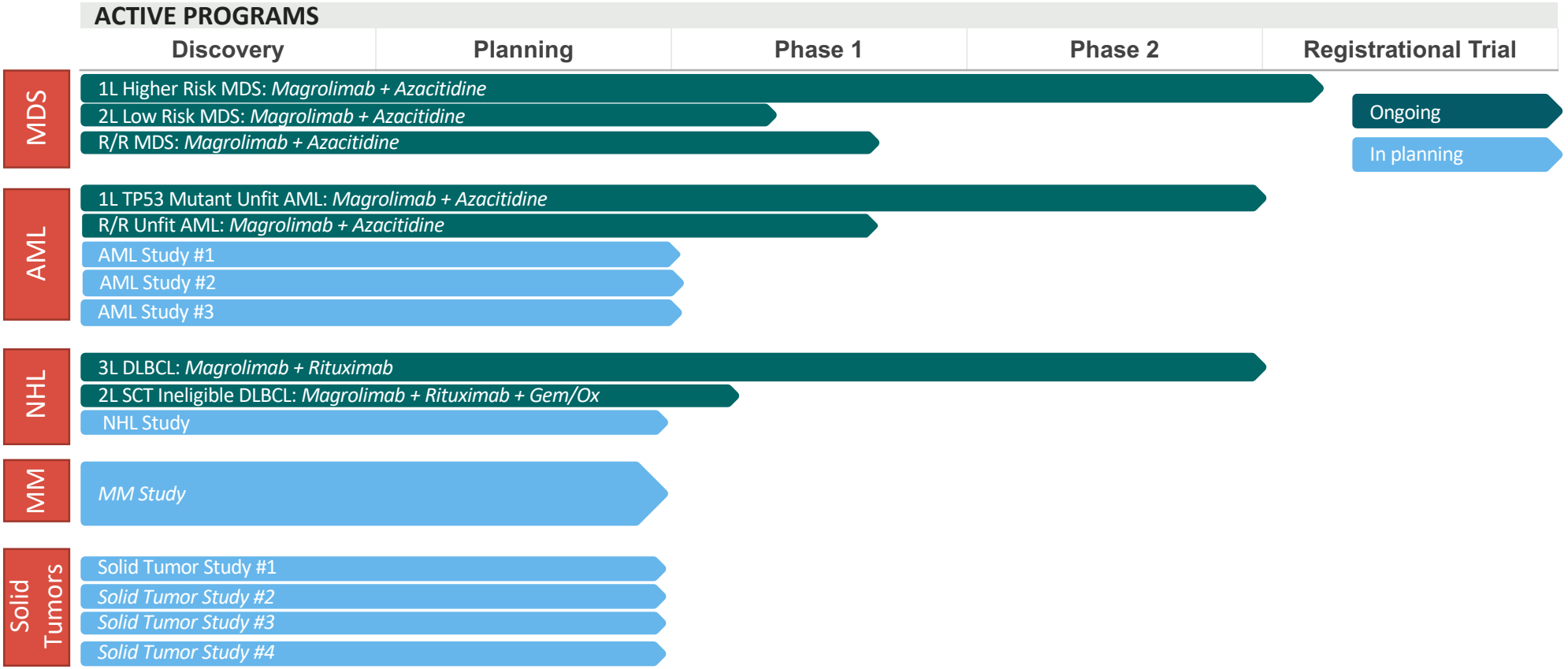




- The median OS is 18.9 months in *TP53* wild-type patients and 12.9 months in *TP53*-mutant patients
- This initial median OS data may compare favorably to venetoclax + hypomethylating agent combinations (14.7-17.5 mo in all-comers,[1,3] 5.2–7.2 mo in patients who are *TP53* mutant[2,3])
- Additional patients and longer follow-up are needed to further characterize the survival benefit

NE, not evaluable.

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.

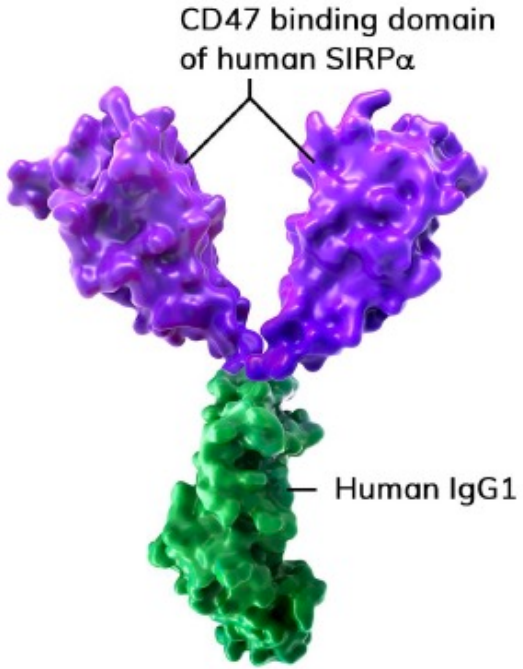
# Broad Magrolimab Development Plan in Hematological Malignancies and Solid Tumor Indicaitons




AML: acute myeloid leukemia; CRC: colorectal cancer; DLBCL: diffuse large B-cell lymphoma; Gem: gemcitabine; MDS: myelodysplastic syndrome; MM: multiple myeloma; NHL: non-Hodgkin's lymphoma;; R/R: relapsed/refractory; SCT: stem cell transplant

# TTI-621 (Pfizer*) CD47-Binding Fusion Protein

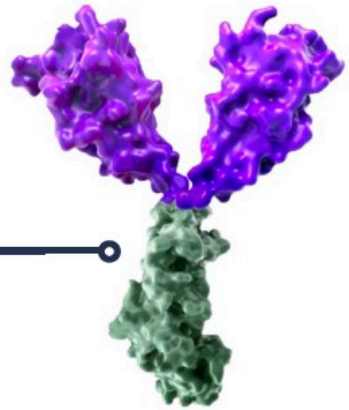
- TTI-621 is a wild type SIRPα-IgG1 Fc fusion protein
  - Binds to human CD47 with micromolar affinity (Petrova Clin Cancer Res 2017)
  - IgG1 provides a potent prophagocytic signal via Fc-gamma receptors on effector cells
  - Minimal binding to human RBCs, but it does bind to human leukocytes and platelets
- Ph 1 trial of weekly intravenous TTI-621 initiated Jan 2016 (NCT02663518)
  - AEs include mild to moderate infusion related reactions but no clinically significant anemia
  - DLT thrombocytopenia initially noted at 0.3 mg/kg, but later dose intensification allows for higher dosing, currently exploring 2.0 mg/kg
    - Revised DLT definition for thrombocytopenia
  - Intratumor injection also explored




* Pfizer acquired Trillium in Aug 2021

# 622 & 621: TWO NOVEL CD47 BLOCKING AGENTS WITH BUILT-IN ACTIVATING SIGNALS

## TTI-622
(SIRPα-**IgG4** Fc)

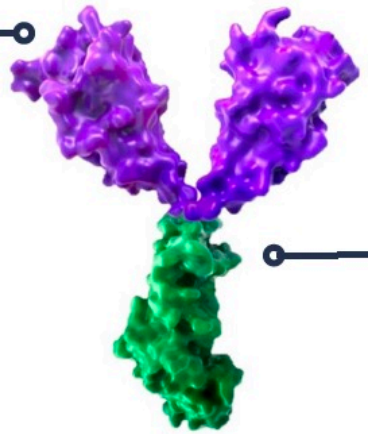


**IgG4 Fc:** Delivers **moderate EAT ME** signal

**SIRPα domain:**
Blocks CD47
**DON'T EAT ME**
signal

Neither binds to RBC CD47

## TTI-621
(SIRPα-**IgG1** Fc)



**IgG1 Fc:** Delivers **strong EAT ME** signal & activates **NK cells**

**Designed to:**
- Achieve high exposure in patients and high level of CD47 blockade
- Deliver moderate eat me signal

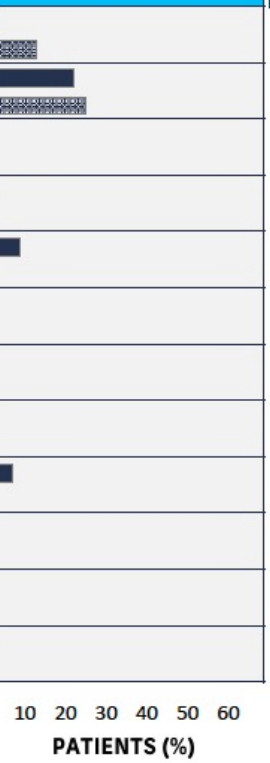
**Designed to:**
- Achieve moderate exposure in patients and moderate level of CD47 blockade
- Deliver strong eat me signal
- Activate NK cells



--Trillium Corp Presentation June 2021

# 621 (IV) HAS GOOD TOLERABILITY AND MANAGEABLE TOXICITIES

| Related Adverse Events n (%) | Parts 1-3 n=218 | | Part 4 n=24 | | Total n=242 | Related Adverse Events ≥Gr3 |
|---|---|---|---|---|---|---|
| Grade | 1-2 | 3-4 | 1-2 | 3-4 | | |
| IRR | 87 (40) | 6 (3) | 9 (38) | 3 (13) | 105 (43) | |
| Thrombocytopenia | 17 (8) | 48 (22) | 2 (8) | 6 (25) | 73 (30) | |
| Chills | 48 (22) | | 2 (8) | | 50 (21) | |
| Fatigue | 34 (16) | 2 (1) | 2 (8) | | 38 (16) | |
| Anemia | 10 (5) | 20 (9) | | | 30 (12) | |
| Pyrexia | 26 (12) | | 1 (4) | | 27 (11) | |
| Nausea | 23 (11) | | 2 (8) | | 25 (10) | |
| Diarrhea | 19 (9) | 1 (0.5) | 2 (8) | | 22 (9) | |
| Neutropenia | 4 (2) | 15 (7) | 3 (13) | | 22 (9) | |
| Headache | 16 (7) | | 3 (13) | | 19 (8) | |
| Vomiting | 14 (6) | 1 (0.5) | 1 (4) | | 16 (7) | |
| Hypotension | 10 (5) | 2 (0.9) | | | 12 (5) | |




IRR = Infusion Related Reaction;
Based on data in clinical database as of 12 April 2021; data are subject to change

## KEY POINTS

- Acceptable tolerability with transient and manageable toxicities
- IRRs occur mostly at first dose and are very manageable with prophylactic treatment
- No dose dependent increase in frequency of thrombocytopenia, but increasing magnitude of platelet drop without clinical bleeding
- Mild chills and fever reflective of active effector function
- All other related AEs occurred in <5% of patients

Parts 1-3: Dose escalation/initial expansion
Part 4: Dose optimization with redefined platelet DLT grading

# 621 (IV) MONOTHERAPY ACTIVITY OBSERVED IN T AND B-CELL LYMPHOMA INDICATIONS

| Indication | Response evaluable n | CR | PR | OR |
|---|---|---|---|---|
| CTCL | 62 | 2 (3%) | 10 (16%) | 12 (19%) |
| PTCL | 22 | 2 (9%) | 2 (9%) | 4 (18%) |
| DLBCL | 7 | 1 (14%) | 1 (14%) | 2 (29%) |

Based on the data in clinical database as of 12 Apr 2021; data are subject to change prior to final database lock

# 622 MONOTHERAPY ACTIVITY OBSERVED IN MULTIPLE LYMPHOMA INDICATIONS, WITH 33% ORR

At doses 0.8-18 mg/kg

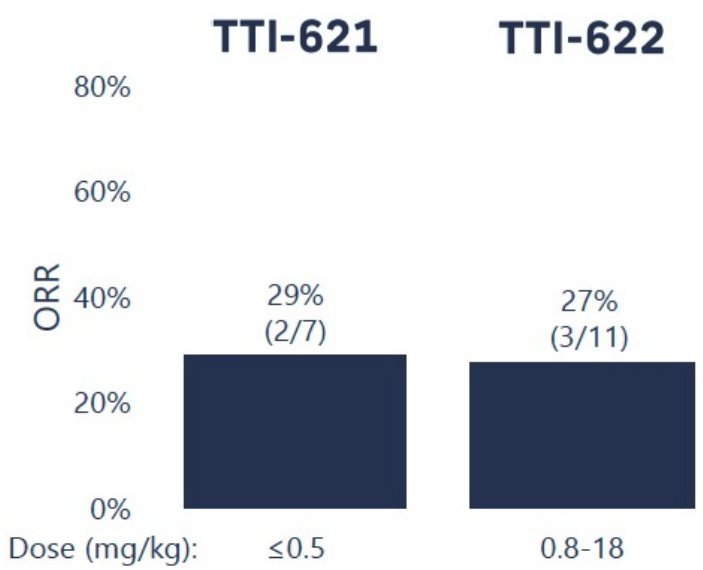
| Indication | Response evaluable N | CR | PR | OR |
|---|---|---|---|---|
| DLBCL | 11 | 1 (9%) | 2 (18%) | 3 (27%) |
| PTCL | 6 | 0 (0%) | 2 (33%) | 2 (33%) |
| CTCL | 4 | 1 (25%) | 2 (50%) | 3 (75%) |
| FL | 3 | 0 (0%) | 1 (33%) | 1 (33%) |
| HL | 3 | 0 (0%) | 0 (0%) | 0 (0%) |
| **TOTAL** | **27** | **2 (7%)** | **7 (26%)** | **9 (33%)** |

Based on the data in clinical database as of 12 Apr 2021; data are subject to change prior to final database lock

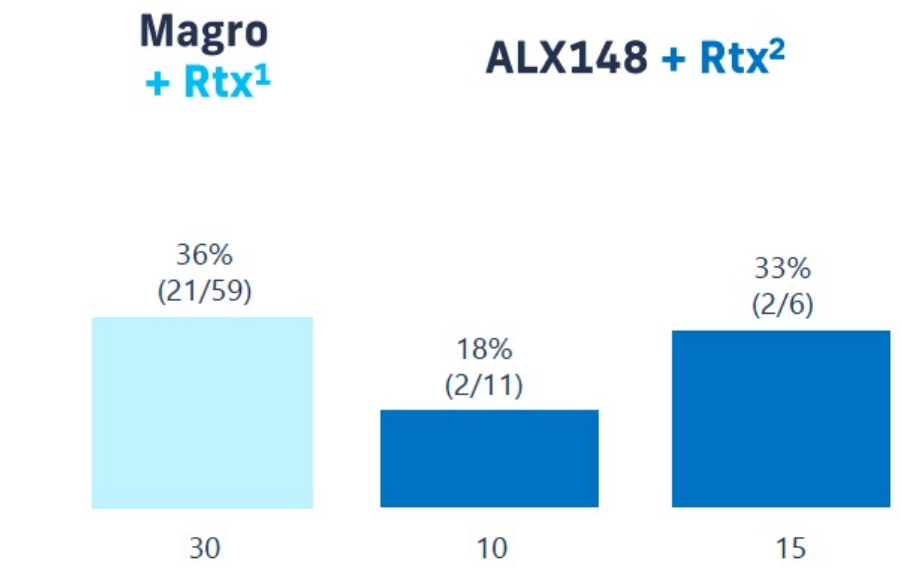
# IN R/R DLBCL, 622 & 621 OBSERVED COMPARABLE MONOTX ORRs AS MAGRO & ALX148 IN COMBINATION WITH RITUXAN

*No head-to-head data**

## DLBCL Monotherapy




## DLBCL Rituxan® (Rituximab) Combinations




[1]Roschewski, EHA 2019

[2]Kim, EHA 2020

*These trials were not designed to be head-to-head, so direct comparisons are not possible

# PIPELINE: INITIATING P1B/2 STUDIES IN NINE SETTINGS

| PROGRAM | INDICATION | COMBINATION AGENT | STAGE OF DEVELOPMENT | SPONSOR | STATUS |
|---|---|---|---|---|---|
| | | | PRECLINICAL / IND ENABLING / EARLY-STAGE CLINICAL / LATE-STAGE CLINICAL | | |
| 622 | MM | Carfilzomib+dex | | Trillium | First patient dosed |
| | AML p53 mut. | Azacitidine | | Trillium | Enrolling |
| | AML unfit | Aza+Ven | | Trillium | Enrolling |
| | DLBCL (IST) | PD-1 | | Mayo Clinic | Finalizing protocol |
| | Ovarian | Chemotx | | Trillium | Design stage* |
| | [Solid tumor #2] | [TBA] | | Trillium | Design stage* |
| 621 | PTCL | -- [Monotx] | | Trillium | P2 design stage* |
| | DLBCL (IST) | PD-1 | | Mayo Clinic | Finalizing protocol |
| | Leiomyosarcoma | Doxorubicin | | Trillium | Protocol submitted to FDA |

**Additional studies:**

- 622 Q2/3W dose escalation study in lymphomas (enrolling)
- 621 Q2/3W dose escalation study in CTCL (enrolling)
- 622 & 621 in combination with daratumumab P1b/2 IST in multiple myeloma (finalizing protocol); Memorial Sloan Kettering

--Trillium Corp Presentation April 2021

*Study design to be announced later this year
Abbreviations: Aza+Ven – Azacitidine + Venetoclax; AML – Acute Myeloid Leukemia; DLBCL – Diffuse Large B-Cell Lymphoma; IST – Investigator-Sponsored Trial; MM – Multiple Myeloma; PTCL – Peripheral T-Cell Lymphoma; TBA - To Be Announced

## TTI-621 and TTI-622 SIRPα-Fc Fusion Proteins Targeting CD47

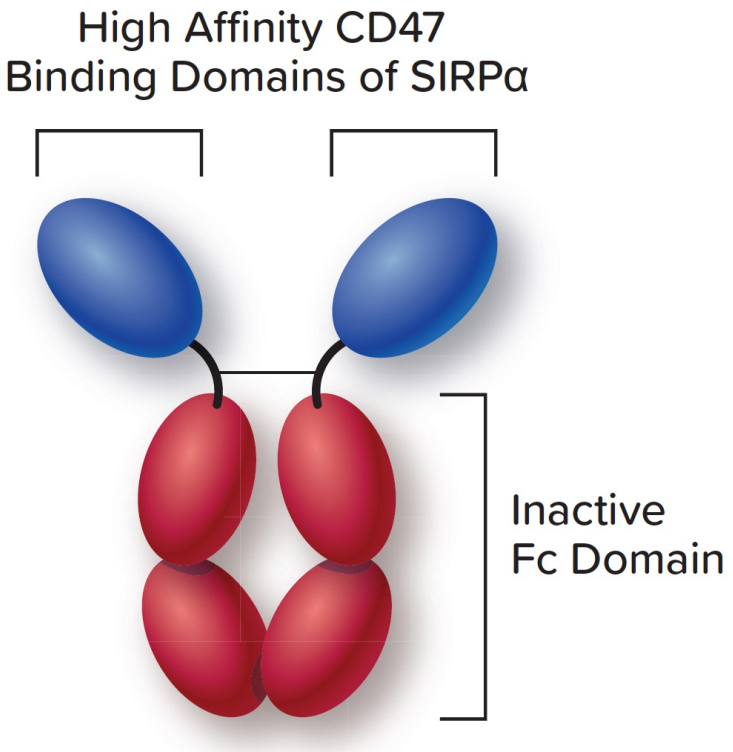
- Activity observed as monotherapy in CTCL/PTCL and as monotherapy and in combination with rituximab in DLBCL
  - Monotherapy activity of the Fc-enhanced TTI-621 is not surprising, but early data with Fc-attenuated TTI-622 is interesting

- TTI-621 Initial dose limiting thrombocytopenia appears to be managed by dose adjustments
  - Now exploring dosing of 2.0 mg/kg
  - Minimal anemia: Gr 3+ anemia 9% (20/214 in early dose escalation studies)

- TTI-622, SIRPα-IgG4 Fc fusion protein also in clinical trials
  - Minimizes ADCC activity to decreased thrombocytopenia
  - Clinical activity differentiation from TTI-621 is unclear, but broad development plan in progress in hematological malignancies and solid tumors
    - Behind magrolimab in hrMDS, AML, but (perhaps) not in multiple myeloma

# Evorpacept (ALX148; ALX Oncology): A Unique High Affinity SIRPα Fusion Protein

- Potently and selectively binds CD47 to blocks its interaction with SIRPα
- Picomolar binding affinity for CD47 is greater than wild-type SIRPα constructs (i.e., TTI-621/622)
- Molecular weight is half the size of a typical antibody allowing higher molar concentrations to be delivered to tumor
- Fc domain is modified to eliminate binding to all Fc gamma receptors minimizing toxicity
- Fc domain retains binding to neonatal Fc receptor for pharmacokinetic half-life extension

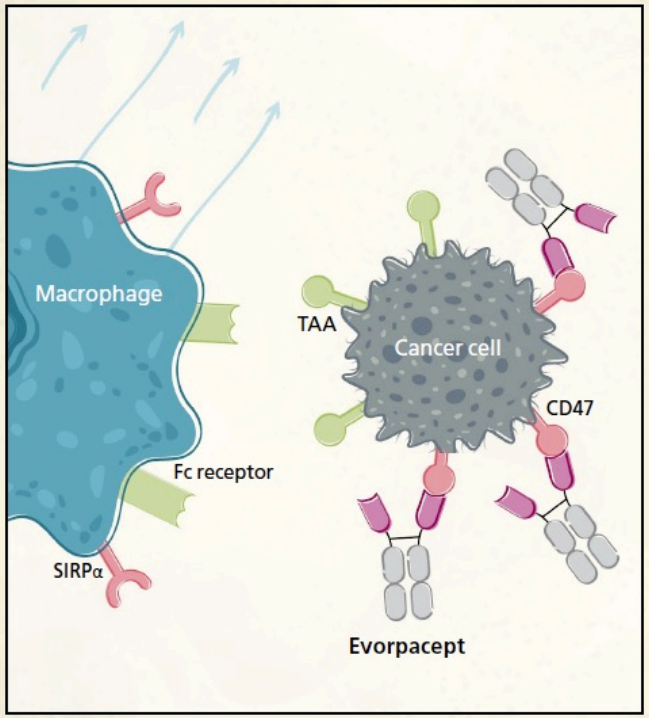



Approximate MW. = 77-78 kDa

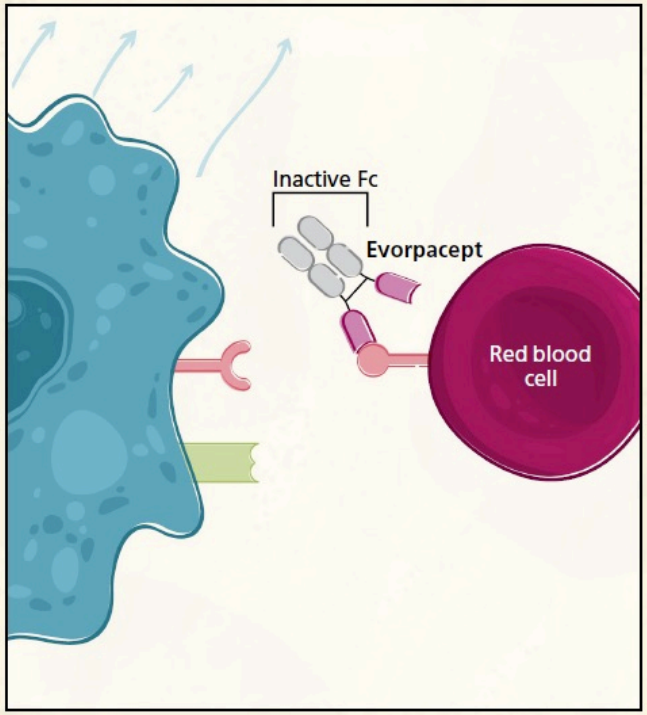
--Lakhani et al, SITC 2018

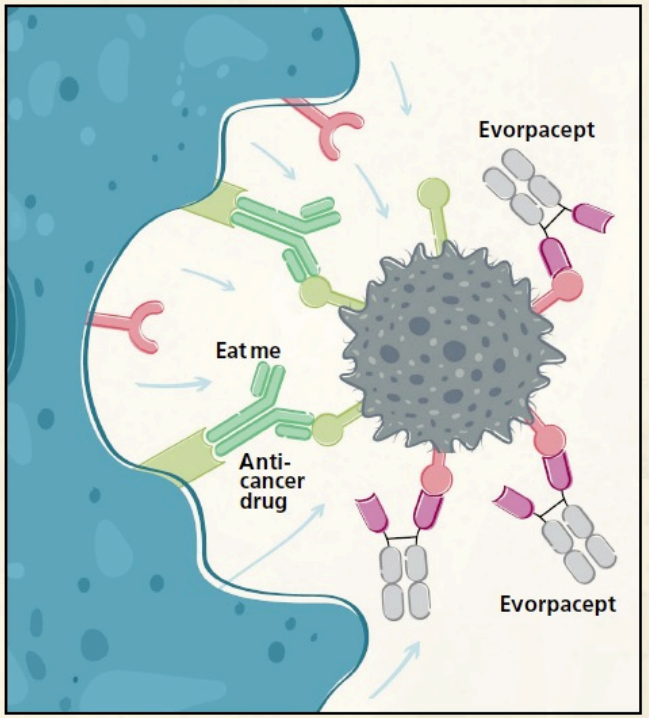
# TARGETING CD47 AS CHECKPOINT: ALX ONCOLOGY'S APPROACH

It spares normal cells




Anti CD47 with inactive Fc binds and block CD47-SIRPα interaction




High dose allows full blockade of CD47 and maximizes activity of combo drug

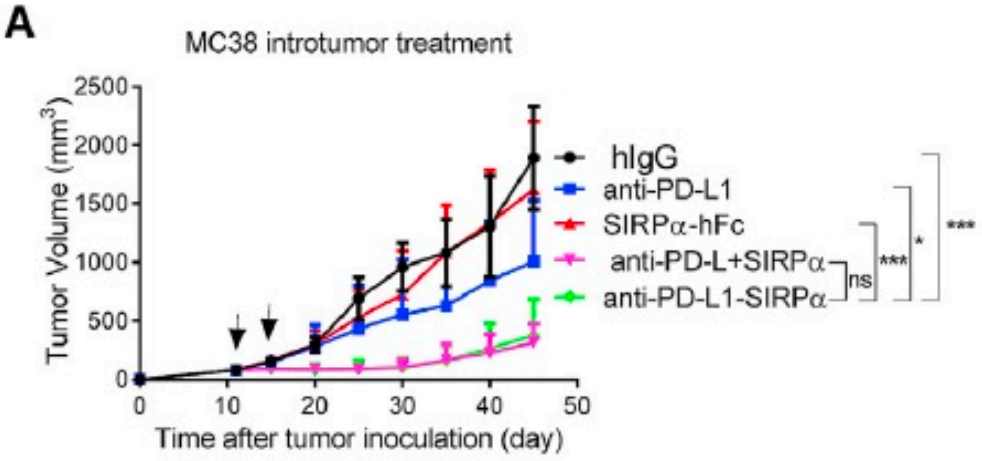
Monotherapy activity expected to be modest, predominantly in combination development

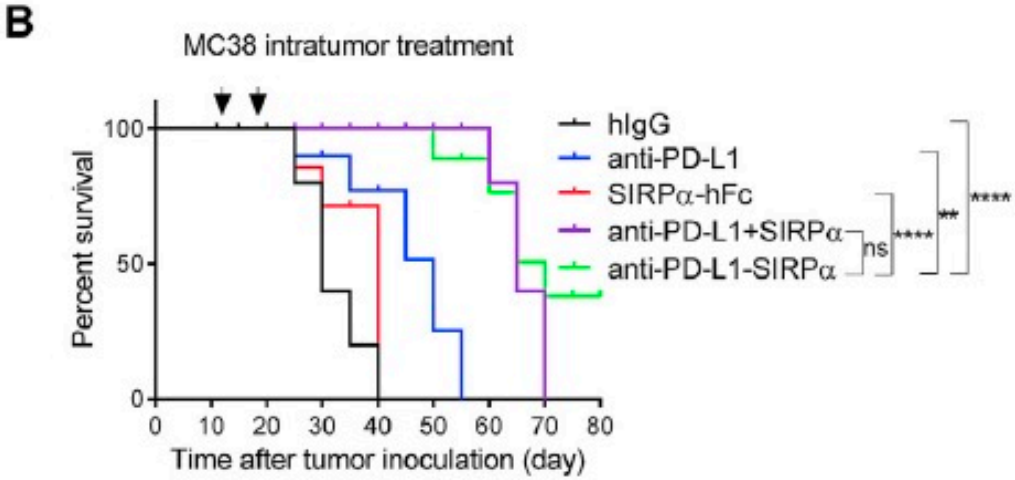
--ALX Oncology Corp Presentation Jan 2021

Cell Reports

# Dual Targeting of Innate and Adaptive Checkpoints on Tumor Cells Limits Immune Evasion

Xiaojuan Liu,[1,2,5] Longchao Liu,[3,5] Zhenhua Ren,[3] Kaiting Yang,[1] Hairong Xu,[1] Yan Luan,[4] Kai Fu,[4] Jingya Guo,[1] Hua Peng,[1] Mingzhao Zhu,[1,2,*] and Yang-Xin Fu[1,3,6,*]




Dual Targeting of CD47/SIRPα and T-Cell Immune Checkpoints shows enhanced antitumor activity



--Liu Cell Reports 2018

# ALX148 DEMONSTRATES CONSISTENT TOLERABILITY PROFILE

| Treatment related adverse events* | ALX148 + Herceptin + Cyramza + chemo (N=14) | | ALX148 + Herceptin (N=30) | | ALX148 + Keytruda + chemo (N=5) | | ALX148 + Keytruda (N=52) | | ALX148 + Rituxan (N=33) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total n (%) | ≥Grade 3 | Total n (%) | ≥Grade 3 | Total n (%) | ≥Grade 3 | Total n (%) | ≥Grade 3 | Total n (%) | ≥Grade 3 |
| Fatigue | 2 (14.0%) | - | 9 (30.0%) | - | - | - | 6 (11.5%) | - | 4 (12.1%) | - |
| Rash | 3 (21.0%) | - | - | - | - | - | 5 (9.6%) | - | 8 (24.2%) | - |
| AST increased | - | - | - | - | - | - | 9 (17.3%) | - | - | - |
| Platelets decreased | - | - | 5 (16.7%) | 2 (6.7%) | - | - | 4 (7.7%) | 2 (3.8%) | - | - |
| ALT increased | - | - | - | - | - | - | 7 (13.5%) | 1 (1.9%) | - | - |
| Pruritus | 2 (14.0%) | - | 3 (10.0%) | - | - | - | 5 (9.6%) | - | 2 (6.1%) | - |
| Pyrexia | - | - | 3 (10.0%) | - | - | - | 3 (5.8%) | - | - | - |
| Decreased appetite | - | - | 3 (10.0%) | - | - | - | 2 (3.8%) | - | - | - |
| Anemia | - | - | 2 (6.7%) | - | - | - | 5 (9.6%) | 1 (1.9%) | 2 (6.1%) | 1 (3.0%) |
| Infusion reaction | - | - | - | - | - | - | 4 (7.7%) | - | - | - |
| Neutropenia / Neutrophil count decr | - | - | 2 (6.7%) | 2 (6.7%) | - | - | 2 (3.8%) | 1 (1.9%) | 2 (6.1%) | 2 (6.1%) |
| Nausea | - | - | 2 (6.7%) | - | - | - | 2 (3.8%) | - | 2 (6.1%) | - |
| Alkaline phosphatase incr | - | - | - | - | - | - | 3 (5.8%) | - | - | - |
| Arthralgia | - | - | - | - | - | - | 3 (5.8%) | - | - | - |
| WBC decreased | - | - | - | - | - | - | 3 (5.8%) | - | - | - |
| Myalgia | - | - | - | - | - | - | 2 (3.8%) | - | 2 (6.1%) | - |
| Diarrhea | 3 (21.0%) | - | - | - | - | - | - | - | - | - |
| Urticaria | 3 (21.0%) | - | - | - | - | - | - | - | - | - |

Treatment related adverse events occurring in ≥2 subjects in all histologies at 10 & 15 mg/kg QW.

*Data cut off: April 1, 2020 for combination cohorts of ALX148 plus Keytruda and Herceptin; October 1, 2020 for combination cohorts of ALX148 plus Rituxan, Keytruda and chemotherapy (5FU, platinum) and Herceptin and chemotherapy (ramucirumab, paclitaxel).

**Tolerability profile enables broad combination potential**

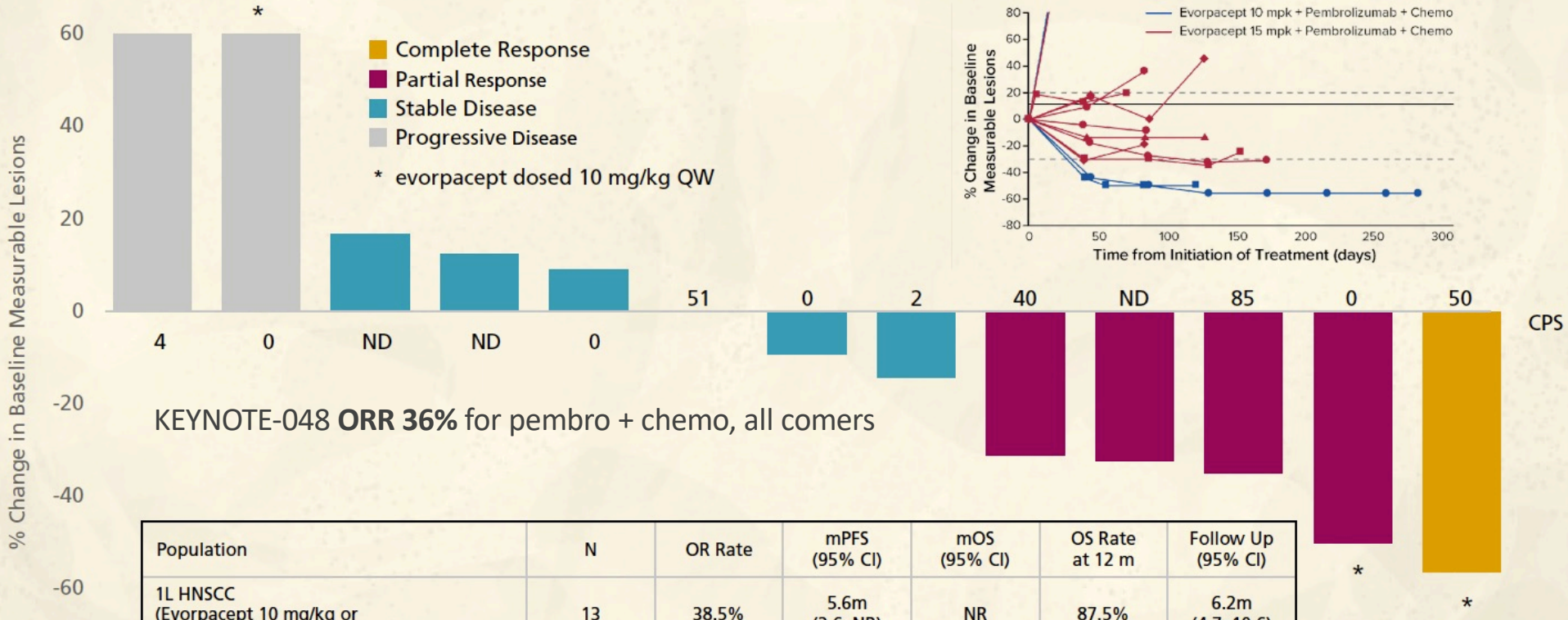
--ALX Oncology Corp Presentation Jan 2021

# PHASE 1B HNSCC: EVORPACEPT + KEYTRUDA + 5FU/PLATINUM FIRST LINE CHECKPOINT NAIVE

Evorpacept = ALX-148

evorpacept in HNSCC

## Evorpacept + Keytruda + 5FU/platinum in 1L HNSCC







KEYNOTE-048 **ORR 36%** for pembro + chemo, all comers

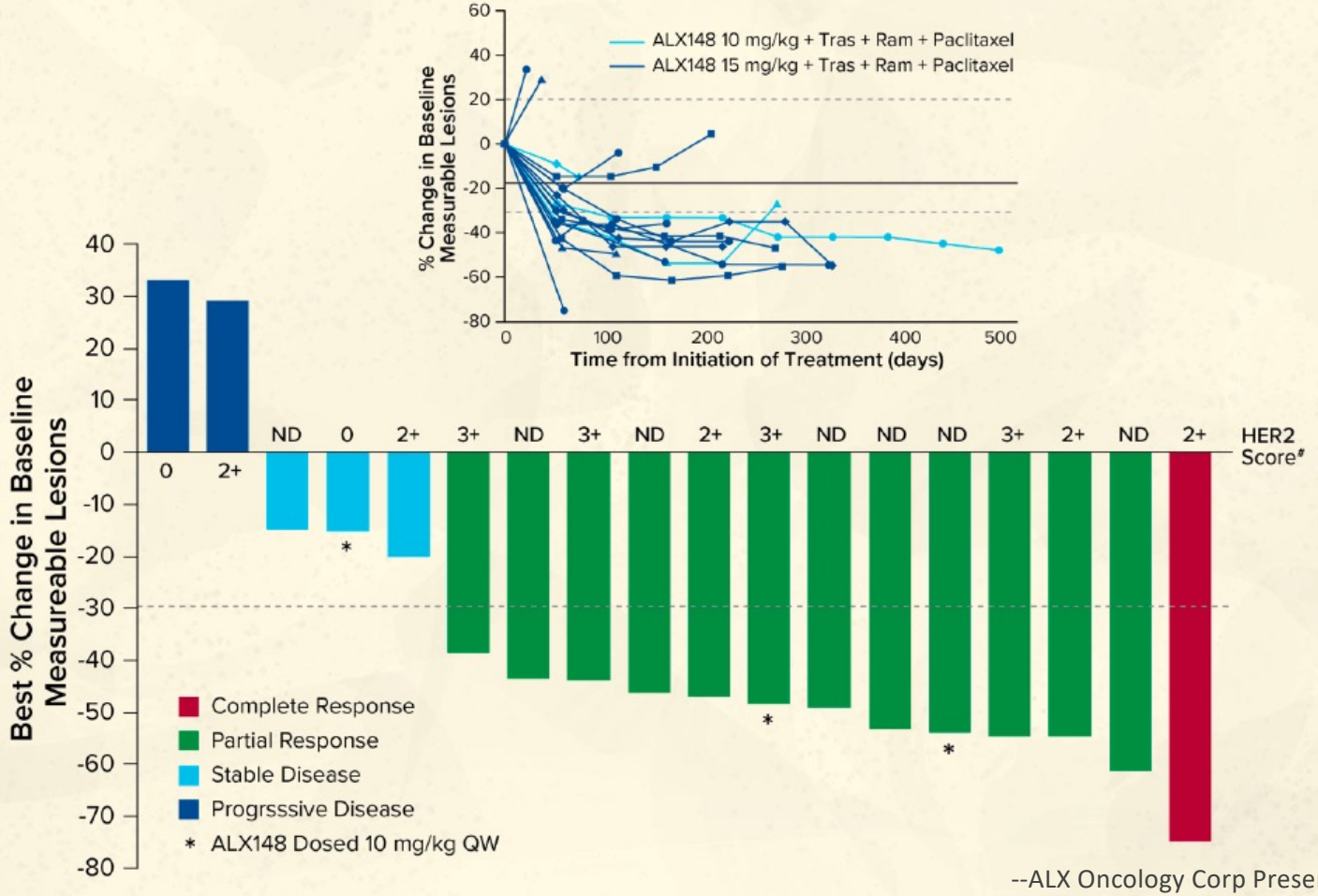
| Population | N | OR Rate | mPFS (95% CI) | mOS (95% CI) | OS Rate at 12 m | Follow Up (95% CI) |
|---|---|---|---|---|---|---|
| 1L HNSCC (Evorpacept 10 mg/kg or 15 mg/kg + Keytruda + chemo) | 13 | 38.5% | 5.6m (3.6; NR) | NR | 87.5% | 6.2m (4.7; 10.6) |
| ≥2L HNSCC (CPI naïve) (Evorpacept 10 mg/kg + Keytruda) | 10 | 40% | 4.6m (0.5; 7.5) | 24.5m (3.1; NR) | 80% | 32.5m (26.9; NR) |

Data Cutoff September 1, 2021. NR = not reached. ND = not done.



--ALX Oncology Corp Presentation Jan 2021

# CLINICAL ACTIVITY OF ALX148 + TRASTUZUMAB + RAMUCIRUMAB + PACLITAXEL IN PATIENTS WITH GC




ESMO-GI 2021



--ALX Oncology Corp Presentation Jan 2021

# CLINICAL ACTIVITY OF ALX148 COMBINATIONS IN RESPONSE EVALUABLE PATIENTS WITH ≥2L HER2 POSITIVE GC CANCER

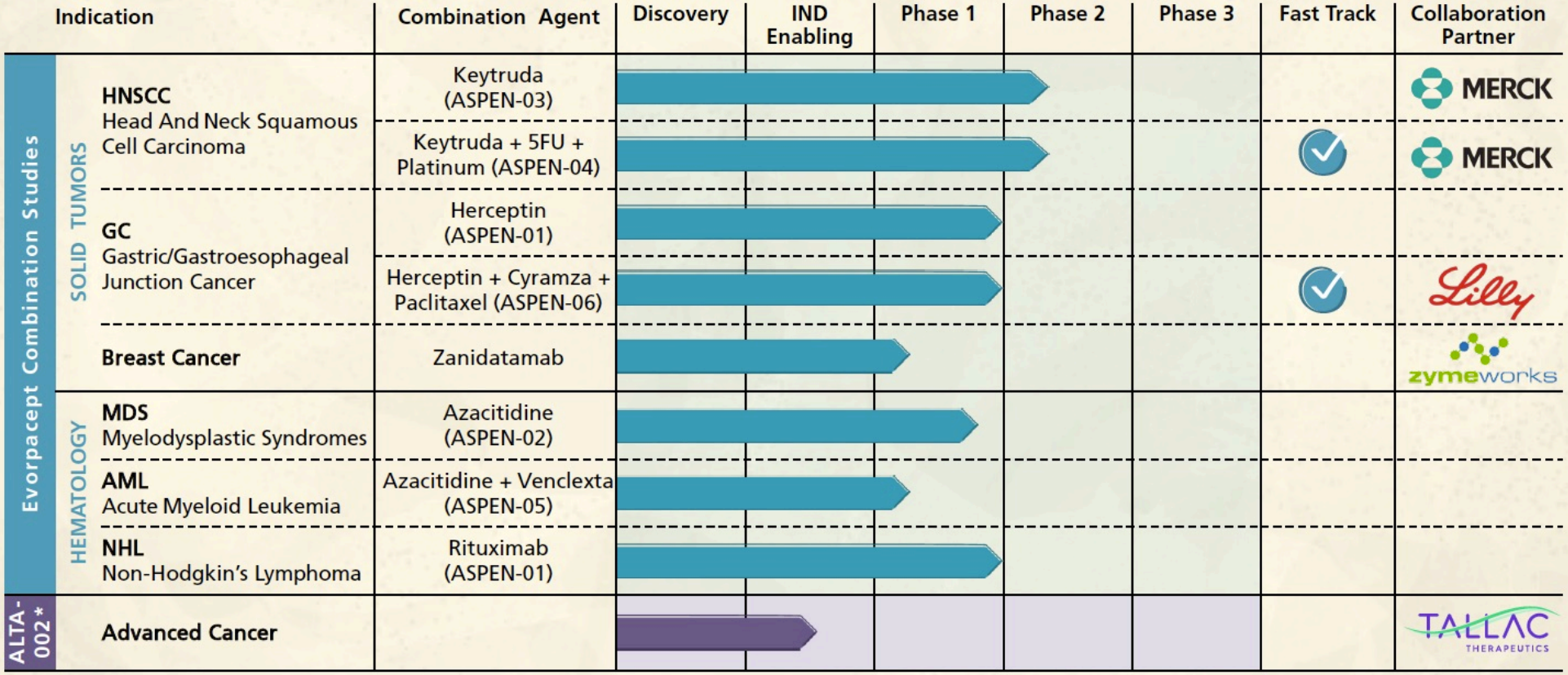
| Population | N (EVAL) | ORR (%) [95% CI] | DOR (m) [95% CI] | PFS (m) [95% CI] | PFS rate at 6 m | OS (m) [95% CI] | OS rate at 12 m | Follow up (m) [95% CI] |
|---|---|---|---|---|---|---|---|---|
| ≥2L Gastric (ALX-10 mg/kg or 15 mg/kg + tras/ram/pac) | 18 | 72.2 [ 49.1% ; 87.5%] | NR | 9.1 [3.8 ; NR] | 74.5% | NR | 75.8% | 10.5 [4.8 ; 12.5] |
| Gastric (ALX-10 mg/kg + TRP) | 3 | 66.7 [20.8% ; 93.9%] | NR | NR | 100% | NR | 66.7% | 14.3 [12.0;NR] |
| Gastric (ALX-15 mg/kg + TRP) | 15 | 73.3 [48.1% ; 89.1%] | NR | NR | 68.3% | NR | 80.8% | 9.4 [4.2 ; 12.5] |
| ≥2L Gastric tras/ram/paclitaxel Rha et al ASCO 2021[3] | 50 | 52 | 5.1 | 7.4 | - | 13.6 | - | 22.9 |
| 3L Gastric Enhertu DESTINY 01[1] | 126 | 41 | 11.3 | 5.6 | 43% | 12.5 | 52% | - |
| ≥2L Gastric ramucirumab/paclitaxel RAINBOW-ASIA Region3[2] | 109 | 34 | - | 5.5 | - | 12.1 | - | 7.9 |
| ≥2L Gastric (ALX-10 mg/kg + tras) | 19 | 21.1 [8.5% ; 43.3%] | 8.7 [5.6; NR] | 2.2 [1.9 ; 5.5] | 16.7% | 8.1 [3.4 ; 12.6] | 38.2% | 27.0 [NR] |
| ≥3L Gastric Irinotecan or Paclitaxel DESTINY 01ControlArm[1] | 62 | 11.3 | 3.9 | 3.5 | 21% | 8.4 | 29% | - |

[1]Enhertu product insert, and Shitara et al, NEJM June 18, 2020; [2]Wilke et al, Lancet October 2014; [3] Rha et al #4063 ASCO 2021



--ALX Oncology Corp Presentation Jan 2021

# ALX PIPELINE




*SIRPα Toll-like receptor agonist antibody conjugate (TRAAC)



--ALX Oncology Corp Presentation Jan 2021

## Other Agents With Emerging Clinical Data

- **Lemzoparlimab (I-Mab/Abbvie)**
  - Anti-CD47 IgG4 mAb targeting huCD47 but spares RBCs
  - Preliminary Clinical Data (Mehta ASH 2021) from Ph 1 study in solid tumors/lymphoma
    - Minimal cytopenias
    - Activity in r/r NHL with rituximab: ORR 57% (3 CR + 1 PR in 7 patients; DLBCL + Indolent lymphoma)

- **Letaplimab (IBI-188; Innovent)**
  - Anti-CD47 IgG4 mAb
  - Preliminary Clinical Data (Company Presentation January 2022) from Ph 1b study with azacytidine in hr MDS patients
    - Activity in 12 patients with hrMDS: ORR 83.3% (2 CR, 2 marrow CR+Heme Improvement, 2 HI, 4 mCR)

# Other CD47/SIRPα Targeting Agents With Emerging Clinical Data

- Other Anti-CD47 Agents in Active Clinical Development (excluding bispecific molecules)
  - AO176 (Arch Oncology)
  - ZL-1201 (Zai Labs)
  - IMC-002 (ImmuneOncia Therapeutics)
  - Ligufalimab (AK117; Akeso)

- Anti-CD47 Agents Presumed to Not Be in Active Development
  - CC-90002 (Celegene/BMS): IgG4 anti-CD47 mAb
  - SRF231 (Surface Onc): IgG4 anti-CD47 mAb
  - TI-061 (Arch Onc): IgG4 anti-CD47 mAb

- Anti-SIRPa Agents in Development
  - CC-95251 (BMS)
  - GSI-189 (Gilead)

COMPETITORS NOT EXHAUSTIVE

# CD47 Targeting Agents in Clinical Development

| Sponsor | Gilead (acquired Forty Seven) | Pfizer (acquired Trillium Therapeutics) | | ALX Oncology | I-Mab/ AbbVie | Innovent | Arch Oncology | Zai Lab | ImmuneOncia Therapeutics |
|---|---|---|---|---|---|---|---|---|---|
| **Compound name** | Magrolimab (Hu5F9-G4) | TTI-621 | TTI-622 | Evorpacept (ALX148) | Lemzoparlimab (TJ011133 or TJC4) | Letaplimab (IBI-188) | AO-176 | ZL-1201 | IMC-002 |
| **Type of molecule** | mAb | WT SIRPα fusion protein | WT SIRPα fusion protein | High affinity SIRPα fusion protein | mAb | mAb | mAb | mAb | mAb |
| **Class** | IgG4 | IgG1 | IgG4 | Inactive Fc | IgG4 | IgG4 | IgG2 | IgG4 | N/A |
| **Clinical start date** | August 2014 | January 2016 | May 2018 | February 2017 | May 2019 | January 2019 | February 2019 | June 2020 | June 2020 |
| **Study stage (highest)** | Ph 3 | Ph 1b/2 | Ph 1b/2 | Ph 2 | Ph 1/2 | Ph 2 with Ph 3 planned in 1H 2022 | Ph 1/2 | Ph 1 | Ph 1 |
| **Indications** | MDS, AML Heme, solid tumors | DLBCL, PTCL, Leiomyo-sarcoma | Lymphoma, myeloma, AML, MDS, Ovarian, Solid tumors | HNSCC, Gastric, Breast, MDS, AML, NHL | MDS & AML (China & US), NHL, Myeloma, and solid tumors (WW) | MDS, AML, solid tumor, lymphoma | Solid tumor Multiple myeloma | Lymphoma, solid tumor | Solid tumors, lymphomas |

## Conclusions

- Targeting CD47, a dominant "don't eat me" signal for macrophages, is a promising novel strategy for treating cancer, especially hematological malignancies
  - Now a validated therapeutic target, although no approved agents in this class as of yet
- CD47 blockade can be well tolerated with an acceptable safety profile
- Activity observed both as monotherapy and in combinations with antitumor antibodies, checkpoint inhibitors, and chemotherapeutics that can augment prophagocytic signals
  - Strongest signals emerging in combination regimens
- Promising clinical activity in patients with hrMDS, AML, refractory NHL, CTCL/PTCL and solid tumors
- Harnessing the power of the innate immune system and first responder cells such as macrophages has the potential to extend the impact of cancer immunotherapies