B-CELL LYMPHOMA: NEW THERAPEUTIC APPROACHES

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Leslie Popplewell

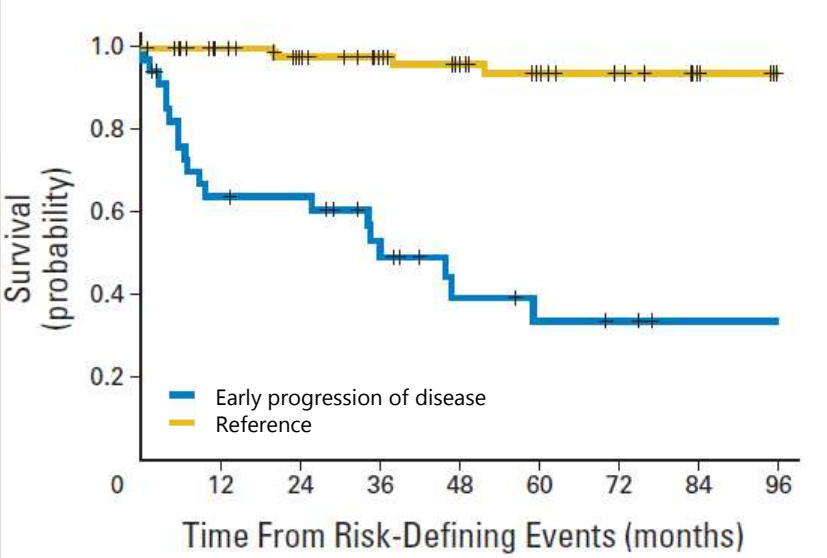
Clinical Director, Division of Lymphoma

Department of Hematology and Hematopoietic Cell Transplantation

City of Hope Medical Center

RELAPSED AND REFRACTORY (R/R) FL: UNMET NEED

- Approximately 20% of patients experience disease relapse within 2 years of initial first-line chemoimmunotherapy[1]
  - Five-year OS is 50% in patients who progressed within the first 2 years vs 90% in those who did not relapse
- First-line therapies typically delay disease progression by several years but are not curative; almost all patients will eventually develop progressive disease



FL, follicular lymphoma; OS, overall survival.
Casulo C et al. *J Clin Oncol.* 2015;33:2516-2522.

NCCN GUIDELINES FOR ≥ SECOND-LINE TREATMENT OF EARLY STAGE GRADE 1/2 FL

First-line treatment can be repeated or alternative anti-CD20 or targeted therapies used

If remission is achieved, maintenance therapy may be considered including SCT

Preferred regimens	Other recommended regimens
• Bendamustine + obinutuzumab or rituximab • CHOP + obinutuzumab or rituximab • CVP + obinutuzumab or rituximab • Rituximab • Lenalidomide ± rituximab	• Ibritumomab tiuxetan • PI3K inhibitors (relapsed or refractory after two prior therapies: Idelalisib, Copanlisib, Duvelisib) • Second-line therapy for DLBCL without regard to transplantability

Elderly or infirm (if none of the above regimes are expected to be tolerable)

- Rituximab (preferred, 375 mg/m^2 weekly for four doses)
- Chlorambucil + rituximab
- Cyclophosphamide + rituximab
- Chlorambucil
- Cyclophosphamide
- Ibritumomab tiuxetan (category 2B)

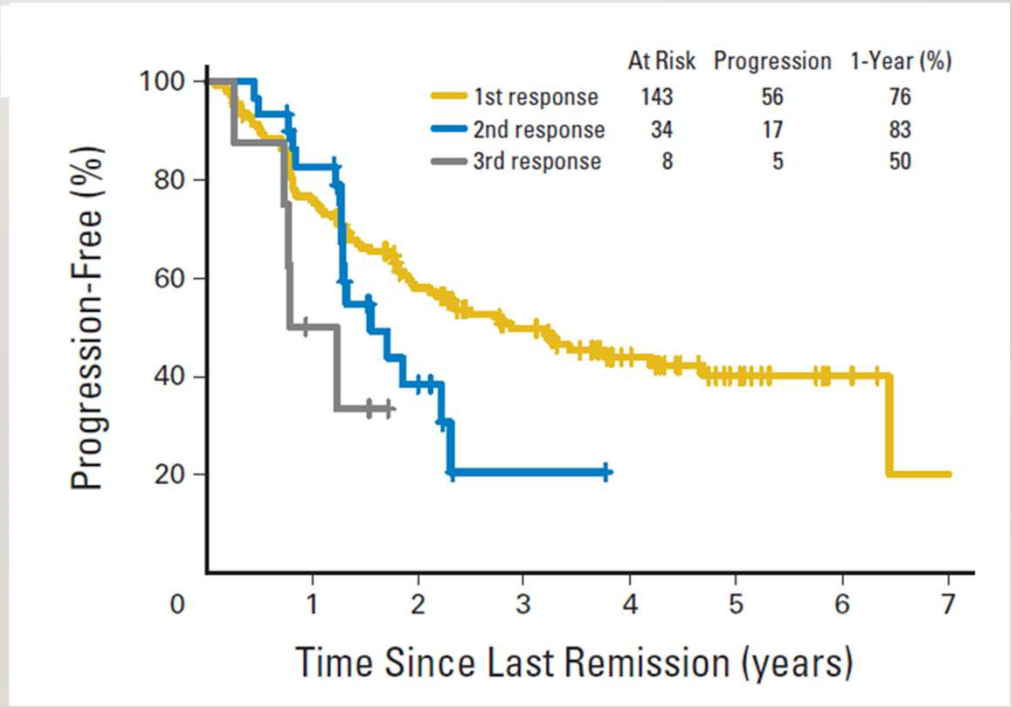
Second-line consolidation or extended dosing (optional)

- Rituximab maintenance (375 mg/m^2 one dose every 12 weeks for 2 years) for patients initially presenting with high tumor burden
- Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for 12 doses)
- High-dose therapy with ASCR
- AlloSCT for highly selected patients

AlloSCT, allogeneic stem cell transplant; ASCR, autologous stem cell rescue; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma. [a] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

RESPONSES DECLINE WITH SUBSEQUENT LINES OF THERAPY

- In an investigation of rituximab maintenance versus as-needed retreatment, the proportion of patients responding decreased with each retreatment



Kahl BS, et al. *J Clin Oncol.* 2014;32(28):3096-3102.

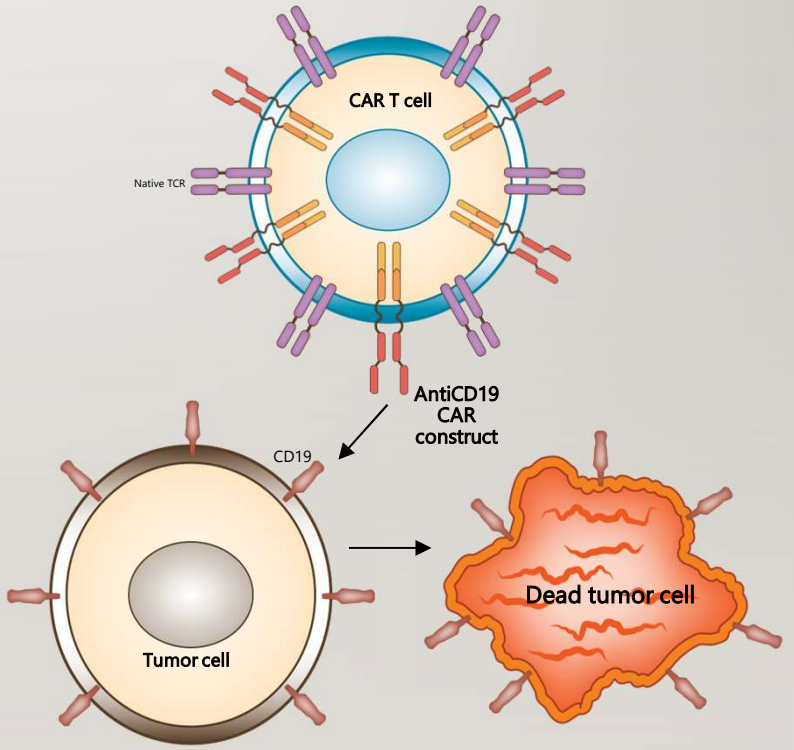
SUMMARY OF CURRENT TREATMENT STRATEGIES FOR FL

Disease Stage	Current Standard Practice	Developing Options
Early-stage disease	➢ Radiotherapy alone	• Low-toxicity ICT and radiotherapy
Advanced-stage, non bulky	➢ Watchful waiting (observation)	• Anti-CD20 monotherapy
Advanced stage, bulky	➢ Immunochemotherapy with rituximab or obinutuzumab	• Rituximab+lenalidomide • Risk-adapted strategies
Early treatment failure	➢ Obinutuzumab-bendamustine (in naïve patients) ➢ Auto- or alloSCT ➢ Clinical trial	• Targeted agents alone or in combination • CAR-T cell therapy
Late (> 2 year) relapse	➢ Conventional approaches (observation, radiotherapy, rituximab, immunochemotherapy)	• ?

CAR-T
Modif

CAR-T CELL THERAPY FOR FL

- Gene-transfer technology is used to stably express a chimeric antigen receptor (CAR) on the surface of the patient's T cells, conferring novel antigen specificity against CD19[1,2]
- CAR-T cells can thus be directed against any cell that expresses the CD19 surface antigen
- Anti-CD19 CAR-T cells have demonstrated safety and efficacy in B-cell malignancies including pediatric and young-adult ALL and in adult r/r DLBCL[3-5]

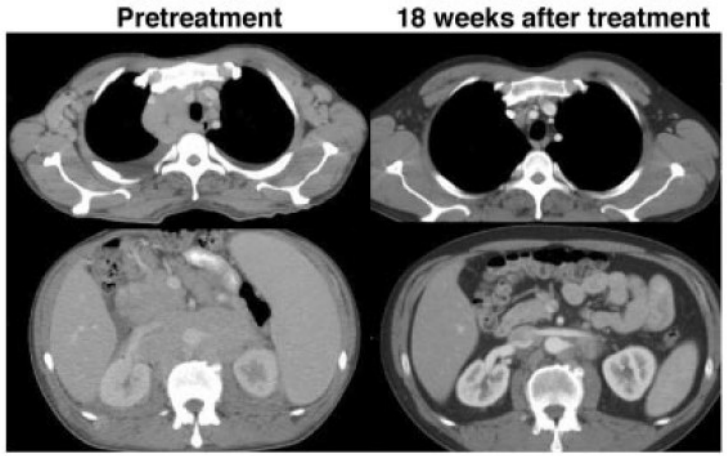


ALL, acute lymphoblastic leukemia; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma.

1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464; 2. Hollyman D, et al. *J Immunother.* 2009;32:169-180; 3. Maude SL, et al. *N Engl J Med.* 2018;378(5):439-448. 4. Schuster SJ, et al. *N Engl J Med.* 2017;377(26):2545-2554. 5. Schuster SJ, et al. *N Engl J Med.* 2019; 380(1):45-56.

TREATMENT OF FL WITH ANTI-CD19 CAR-T CELL THERAPY

Patient History	• **NCT 00924326, Patient #1, 2009** • Diagnosed 2002 with Grade 1, stage IVB FL • Relapsed after multiple rounds of treatment • Last treatment prior to CAR-T cells was EPOCH-R with best response of PR
LD Regimen	• 60 mg/kg cyclophosphamide daily for 2 days then • 25 mg/m^2 fludarabine daily for 5 days
CAR-T cell Therapy	• Day 1: 1 x10^8 anti–CD19-CAR-transduced T cells IV • Day 2: 3 x10^8 anti–CD19-CAR-transduced T cells IV followed by 720,000 IU/kg interleukin-2 (IL-2) IV every 8 hours (8 doses total)
Adverse Events	• Acute cytopenia and fever that lasted 2 days • Pneumonia and herpes zoster with otitis external at 5 and 6 months post-infusion, respectively • Sustained B-cell aplasia
Outcome	• Hospital discharge 11 days post-infusion • Resumed full-time employment • CD19+ PD at 7 mo, re-treated with CAR-T cells • Best response PR of 32 weeks duration



CONTINUED CASE SERIES OF EARLY ANTI-CD19 CAR-T CELL THERAPY-TREATED PATIENTS 2009-2015

8

Patient Histo	Patient #21 48 years old 5 prior lines of therapy	Patient #81 63 years old 7 prior lines of therapy	Patient # 232 63 years old 6 prior lines of therapy	Patient # 362 66 years old 3 prior lines of therapy including autoSCT
LD Regimen	• 60 mg/kg cyc daily x 2 days then • 25 mg/m^2 flu daily x 5 days	• 60 mg/kg cyc daily x 2 days then • 25 mg/m^2 flu daily x 5 days	• 300 or 500 mg/m^2 cyc AND 30 mg/m^2 flu x 2 days	• 300 or 500 mg/m^2 cyc AND 30 mg/m^2 flu x 2 days
CAR T-cell Therapy	• 0.5 x 10^7 CAR-T cells/kg • 9 total doses of IL-2	• 4.2 x 10^7 CAR-T cells/kg • 5 total doses of IL-2	• 1.6 x 10^6 CAR-T cells/kg	• 2.6 x 10^6 CAR-T cells/kg
Adverse Events	• Influenza pneumonia prior to response	• Hypotension, obtundation, acute renal failure, capillary leak syndrome, headache, pleural effusion, abnormal electrolytes • Prolonged B-cell aplasia	• Fever (grade 2) • Febrile neutropenia, encephalopathy, neutropenia (grade 3) • Myelodysplastic syndrome at 20 months post-infusion	• Hypotension (grade 2) • Febrile neutropenia, confusion, somnolence, dysphasia, anemia, cardiac left ventricular systolic dysfunction, urinary tract infection (grade 3) • Dyspnea, dysphasia, hypoxia, neutropenia, thrombocytopenia (grade 4)
Outcome	• Died before response assessment	• PR of 8+ months at cutoff	• CR of 19 months	• CR 11+ months at cutoff

TREATMENT OF FL WITH SPECIFIC CD4:CD8 RATIO OF ANTI-CD19 CAR-T CELLS

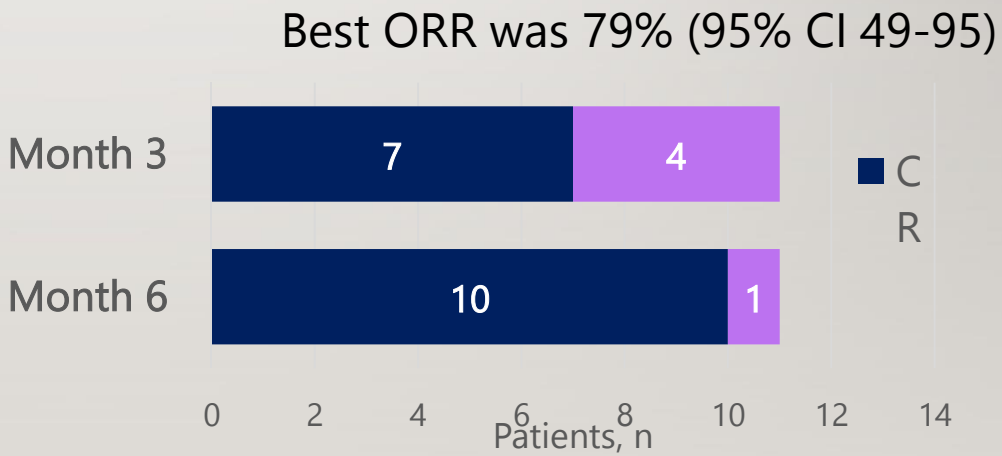
Phase 1 NCT1865617	All Patients (N=32) Median age 57 (range 22-70) Median 5 prior treatments	Patients with FL N=6
LD Regimen	• Cyclophosphamide (Cyc) • Cyc + etoposide • Cyc + fludarabine	• Not specified
CAR T-cell Therapy	• 1:1 CD4 and CD8 CAR-T cells at 2×10^5 CAR-T cells/kg 2×10^6 CAR-T cells/kg 2×10^7 CAR-T cells/kg	• Not specified
Adverse Events	• 4 of 32 (13%) developed severe cytokine release syndrome • 9 of 32 (28%) developed severe neurological adverse events	• Not specified
Outcome	• CR: 10/30 evaluable patients • PR: 9/30 evaluable patients • ORR: 63%	• CR: 2/5 • PR: 2/5 • ORR: 80%

CAR, chimeric antigen receptor; CR, com

Turtle CJ, et al. *Sci Transl Med.* 2016; 8(355):355ra116.

UNIVERSITY OF PENNSYLVANIA CLINICAL TRIAL OF CTL019 ANTI-CD19 CAR-T CELLS

Characteristic	Infused Patients with FL (n=14)
Age, median (range), yrs	59 (43-72)
Previous therapies, median (range), n	5 (2-10)
Stage III/IV disease, n (%)	12 (86)
Elevated LDH, n (%)	9 (64)
Double refractory FL[a], n (%)	8 (57)
Previous SCT, n (%)	4 (28)



Safety data (includes 14 patients with DLBCL who were also treated with CTL019):

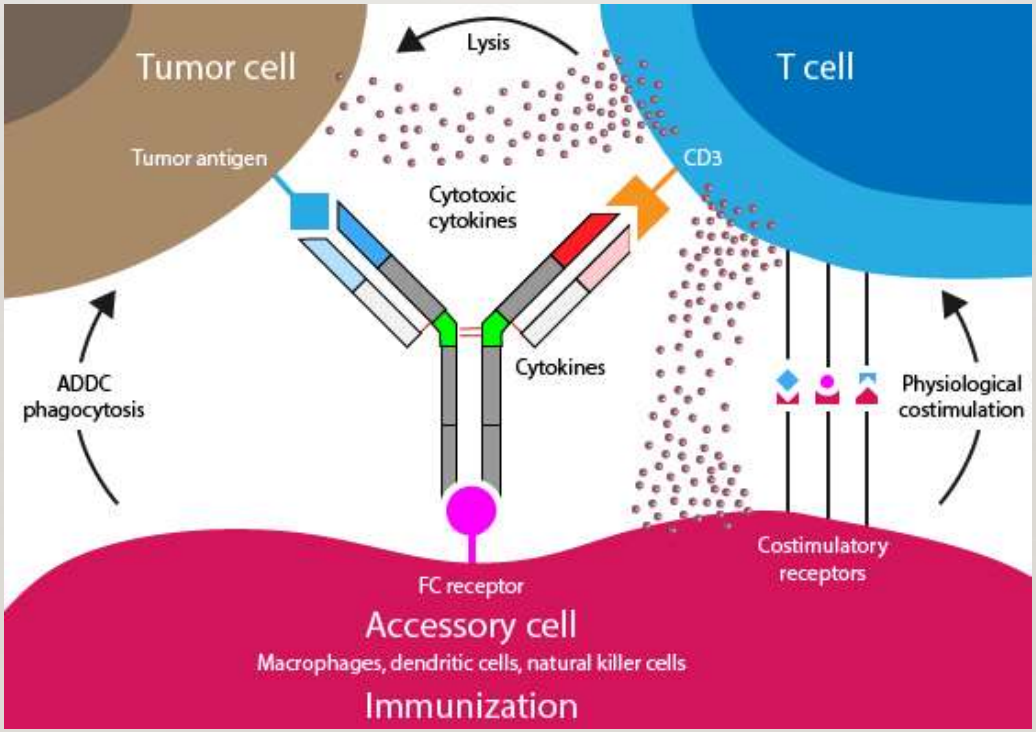
- CRS occurred in 16 of 28 (57%) patients, 5 (15%) were grade ≥3
- Neurological events occurred in 11 of 28 (39%) patients, 3 (11%) were grade ≥3
- One patient with FL suffered from encephalopathy and progressive neurologic deterioration that resulted in death

AE, adverse event; CR, complete response; DLBCL, diffuse large B-cell lymphoma; LDH, lactose dehydrogenase; FL, follicular lymphoma; PR, partial response; SCT, stem cell transplant; yrs, years.
[a] Defined as progressive disease < 6 months after the last dose of rituximab and the last dose of an alkylating agent.
Schuster SJ et al. *New Engl J Med.* 2017; 377(26):2545-2554.

BACKGROUND

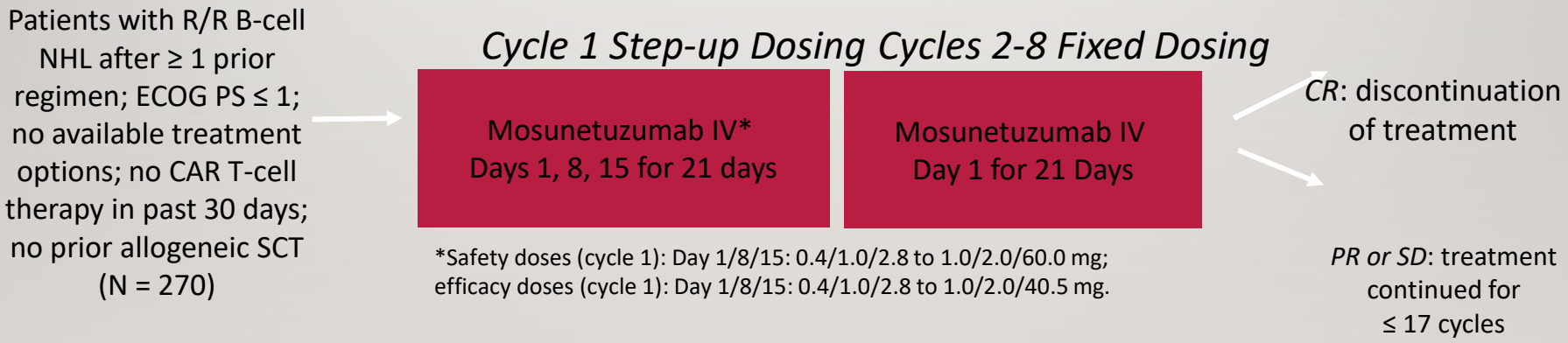
- Mosunetuzumab (BTCT4465A): full-length, fully humanized IgG1 bispecific antibody targeting CD20 on B-cells and CD3 on T-cells
  - Can be used without ex vivo T-cell preparation, allowing immediate treatment
  - Mobilizes T lymphocytes to eliminate B lymphocytes
    - T-cell activation, increase in cytokines, and increase in tumor-infiltrating lymphocytes demonstrated[1]
- Current study investigated mosunetuzumab in heavily pretreated patients with R/R B-cell NHL[2]

BISPECIFIC ANTIBODY DESIGN



STUDY DESIGN

- Open-label phase I/Ib study



- Primary objectives: safety, tolerability, maximum tolerated dose, best objective response

MOSUNETUZUMAB: BASELINE CHARACTERISTICS

Characteristics	N = 270
Median age, yrs (range)	62 (19-96)
Male, n (%)	172 (63.7)
ECOG PS 1, n (%)	164 (61.2)
Aggressive NHL type, n (%) ▪ DLBCL ▪ trFL ▪ MCL ▪ Other	180 (66.7) 117 (43.3) 32 (11.9) 23 (8.5) 8 (3.0)
Indolent NHL type, n (%) ▪ FL ▪ Other	85 (31.5) 82 (30.4) 3 (1.1)
Median no. earlier systemic treatments (range)	3 (1-14)*
Prior CAR T-cell therapy, n (%)	30 (11.1)
Prior autologous SCT, n (%)	77 (28.5)
Refractory† to last therapy, n (%)	194 (71.9)
Refractory† to earlier anti-CD20 therapy, n (%)	233 (86.3)

Characteristics of Patients With Prior CAR T-Cell Therapy	n = 30
Aggressive NHL type, n ▪ DLBCL ▪ trFL ▪ FL	17 8 5
Median no. earlier systemic treatments (range)	5 (3-14)
Refractory to last prior therapy, n (%)	25 (83.3)
Refractory to prior anti-CD20 therapy, n (%)	29 (96.7)
Refractory to CAR-T therapy	22 (73.3)

*N = 268; data not available for 2 patients.

†No PR or CR or progressive disease within ≤ 6 mos of treatment.

GO2971: ADVERSE EVENTS

- Most AEs (95%) in Cycle 1 with no cumulative toxicity
- Neutropenia responsive to GCSF
  - Febrile neutropenia: 3.3%

AE, n (%)	N = 270
Any AE ▪ Treatment-related AE	255 (94.4) 190 (70.4)
Grade 3-5 AE ▪ Treatment-related grade 3-5 AE	170 (63.0) 92 (34.1)
Serious AE ▪ Treatment-related serious AE	107 (36.9) 51 (18.9)
Fatal AE not including neoplasm progression	5* (1.9)
Discontinuation due to AE	7 (2.6)
Dose interruption/modification due to AE	54 (20.0)

*AEs (all n =1): *Candida* sepsis; large intestine perforation; pneumonia; sepsis; volvulus.
†Includes both decreased neutrophil count and febrile neutropenia.

AEs Occurring in > 15% of Patients, n (%)	N = 270
CRS	78 (28.9)
Neutropenia†	65 (24.1)
Fatigue	55 (20.4)
Hypophosphatemia	52 (19.3)
Diarrhea	45 (16.7)
Pyrexia	44 (16.3)
Headache	42 (15.6)
Nausea	41 (15.2)

Grade 3/4 AEs Occurring in > 5% of Patients, n (%)	N = 270
Neutropenia†	59 (21.8)
Hypophosphatemia	36 (13.3)
Anemia	24 (8.9)

GO2971: CRS ADVERSE EVENTS

- Median onset of first CRS event
  - Day 4 (range: 1-43)
- Median duration of CRS event
  - 2 days (range: 1-59)
- CRS events resolved by clinical cutoff date: 96.6%
- CRS adverse events not greater among those with prior CAR T-cell therapy

Adverse Event, n (%)	Total Safety Population (N = 270)	Patients With Prior CAR T-Cell Tx (n = 30)
Any grade AE	78 (28.9)	8 (26.7)
Grade 1 AE	54 (20.0)	6 (20.0)
Grade 2 AE	21 (7.8)	1 (3.3)
Grade 3 AE	3 (1.1)	1 (3.3)
Use of tocilizumab for CRS treatment	8 (3.0)	1 (3.3)

GO2971: NEUROLOGIC ADVERSE EVENTS

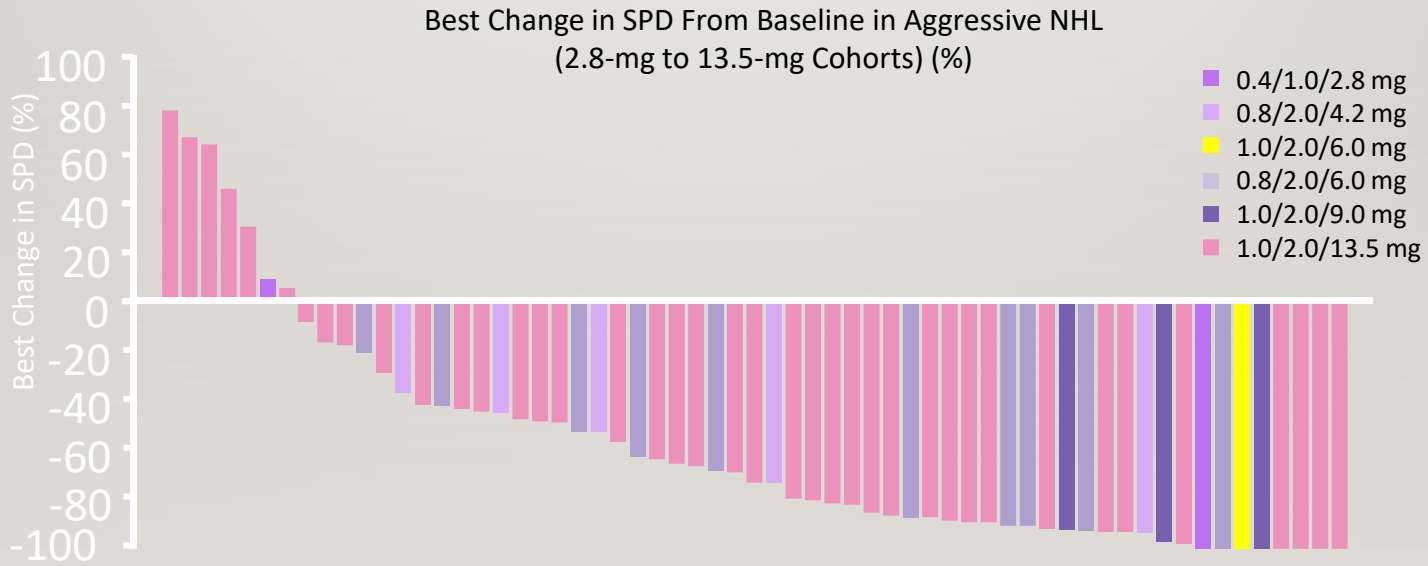
- Neurologic adverse events not greater among those with earlier CAR T-cell therapy

AE, n (%)	Total Safety Population (N = 270)	Patients With Earlier CAR T-Cell Tx (n = 30)
Any grade AE	118 (43.7)	13 (43.3)
Grade 1 AE	74 (27.4)	7 (23.3)
Grade 2 AE	34 (12.6)	3 (10.0)
Grade 3 AE ▪ Grade 3 AE related to Tx	10 (3.7) 3 (1.1)	12 (10.0) 1 (3.3)
ICANS-like neurologic AEs ▪ Grade 1 ▪ Grade 2	3 (1.1) 2 (0.7) 1 (0.4)	0 0 0

- Most common neurologic AEs
  - Headache: 15.6%
  - Insomnia: 9.3%
  - Dizziness: 9.3%
- ICANS-like neurologic AEs
  - Confusion: n = 2 (1 treatment related)
  - Lethargy: n = 1 (treatment related)
- All ICANS-like neurologic AEs resolved in ≤ 3 days

GO2971: RESPONSES IN PTS WITH INDOLENT NHL

- ORR: 62.7% (42/67)
- CR: 43.3% (29/67)



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RESPONSE RATES AMONG PATIENTS WITH INDOLENT NHL

- Patients achieving CR with continuing remission ≥ 26 mos after treatment cessation: n = 24

Response, n (%)	Indolent NHL Patients (n = 67)
Total population with indolent NHL (n = 67)	
▪ ORR	42 (62.7)
▪ CR	29 (43.3)
FL after ≥ 2 lines of therapy (n = 67)	
▪ ORR	39 (63.9)
▪ CR	27 (44.3)
FL after ≥ 2 lines of therapy and refractory to anti-CD20 and alkylating CT (n = 43)	
▪ ORR	28 (65.1)
▪ CR	19 (44.2)
FL after ≥ 2 lines of therapy with history of POD24 (n = 33)	
▪ ORR	20 (60.6)
▪ CR	14 (42.4)
FL after ≥ 2 lines of therapy and PI3Ki refractory (n = 9)	
▪ ORR	8 (88.9)
▪ CR	7 (77.8)

GO2971: RESPONSE RATES AMONG PATIENTS WITH PRIOR CAR T-CELL THERAPY AND RETREATED PATIENTS

Response, n (%)	Patients With Prior CAR T-Cell Therapy
Total population with prior CAR T-cell therapy (n = 18)	
▪ ORR	7 (38.9)
▪ CR	4 (22.2)
DLBCL (n = 9)	
▪ ORR	2 (22.2)
▪ CR	2 (22.2)
trFL (n = 5)	
▪ ORR	1 (20)
▪ CR	0
FL (n = 4)	
▪ ORR	4 (100)
▪ CR	2 (50)

Response, n (%)	Retreated Patients (n = 4)
▪ ORR	3 (75)
▪ CR	1 (25)

- No CRS events occurred during retreatment

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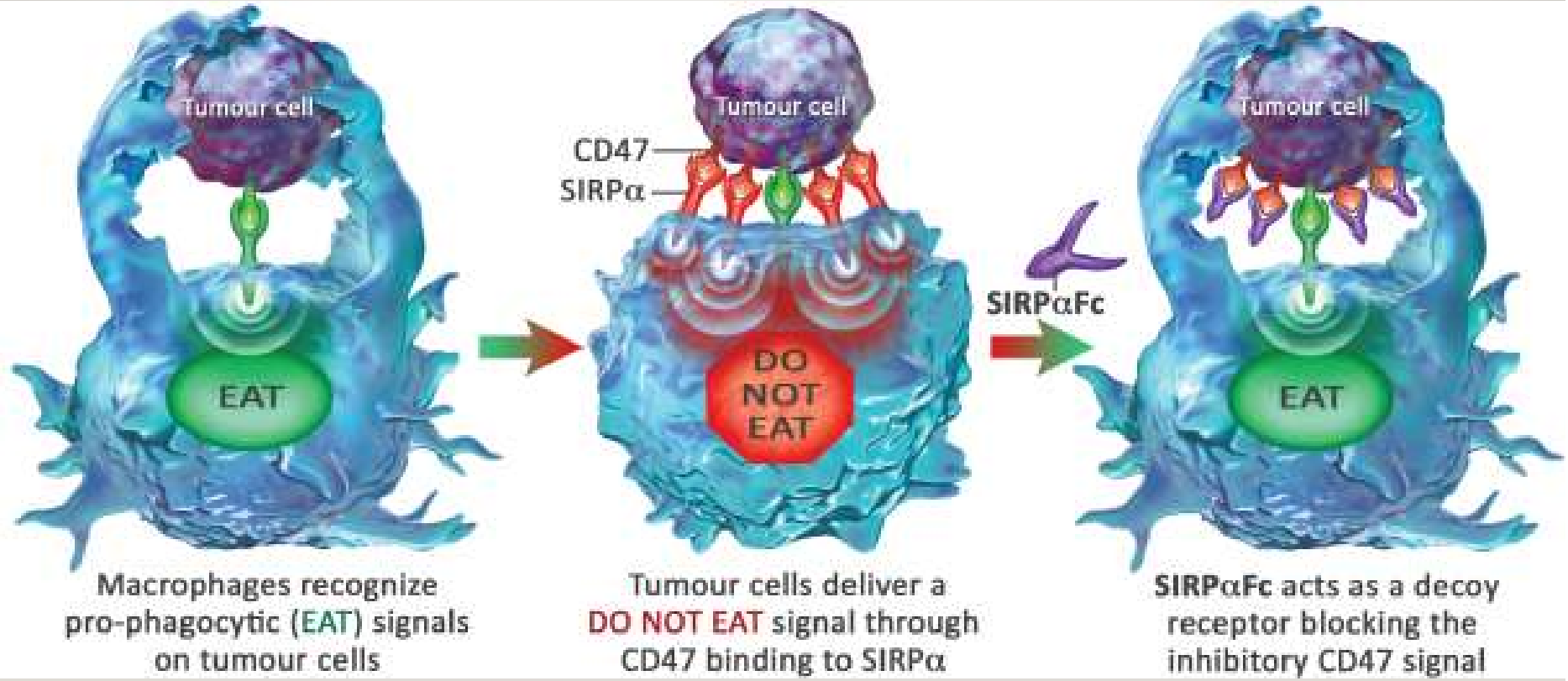
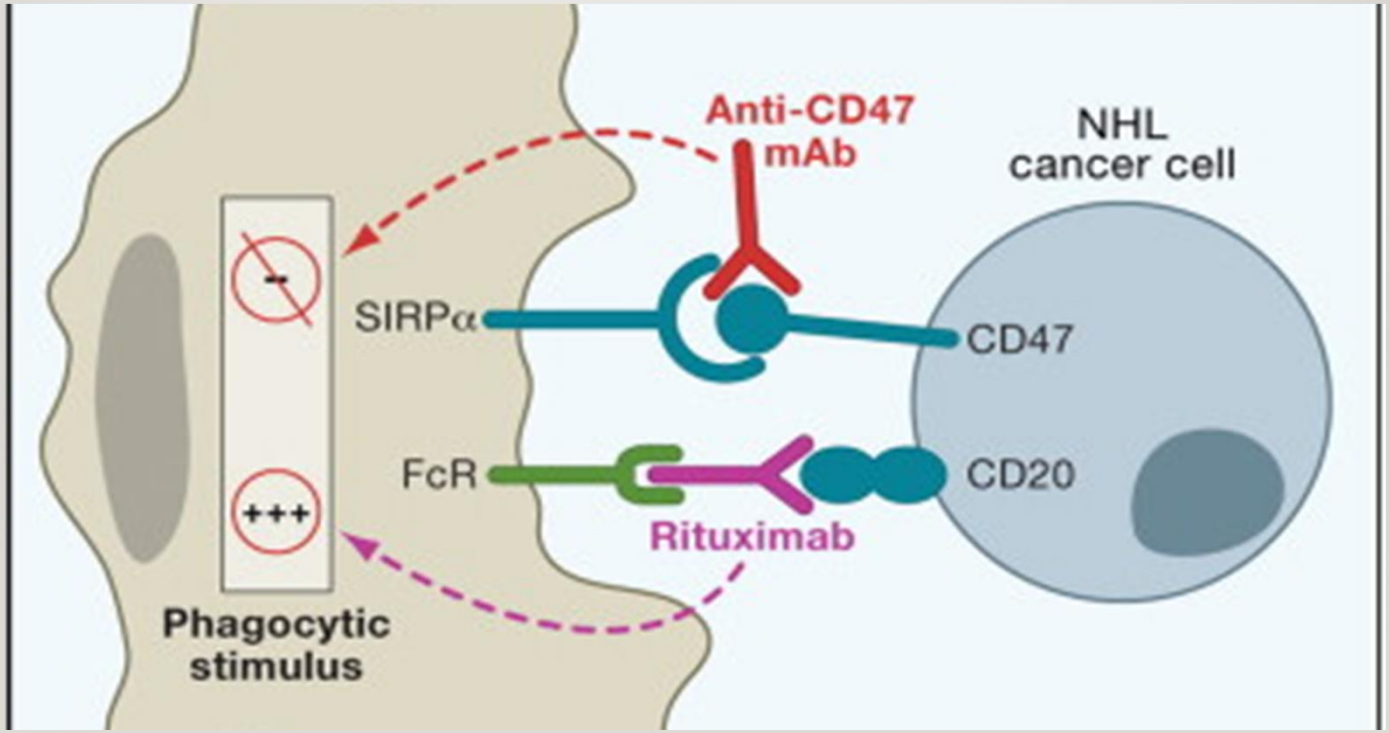
GO2971: INVESTIGATOR CONCLUSIONS

- In patients with R/R B-cell NHL, mosunetuzumab monotherapy associated with CRs, even among patients with aggressive disease, including:
  - Patients previously treated with CAR T-cell therapy
  - Patients with prior autologous SCT and/or CD20-refractory disease
  - Patients with indolent NHL with CD20- and alkylating agent–refractory disease, PI3K inhibitor–refractory disease, or history of disease progression within 24 mos
- CRs durable following cessation of treatment
- Re-treatment can achieve beneficial responses
- Additional monotherapy and combination studies ongoing

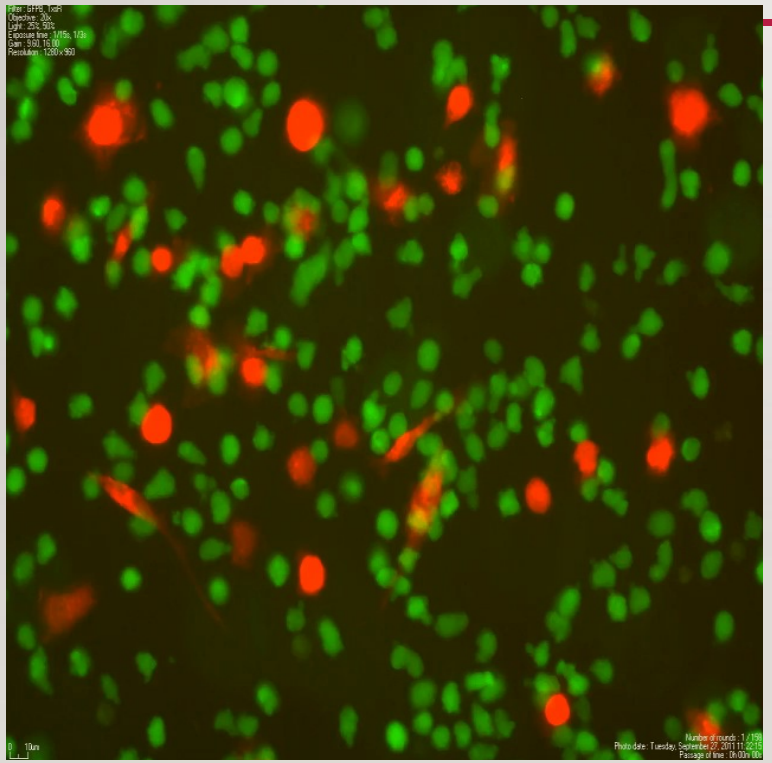
CD47: DON'T EAT ME!



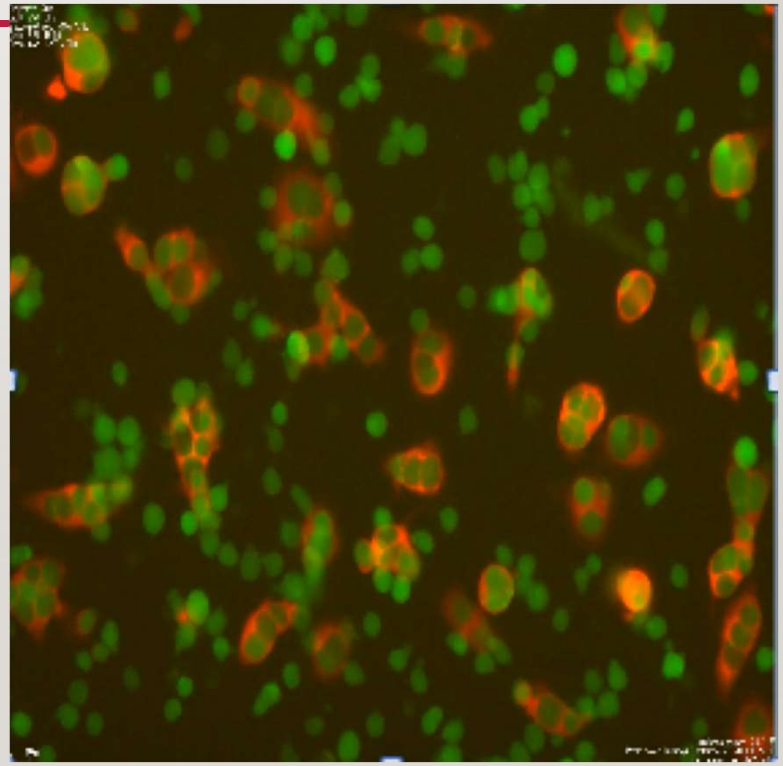

Anti-CD47
mAb
NHL
cancer cell
SIRPα
CD47
FcR
CD20
Rituximab
Phagocytic
stimulus

HU5F9-G4 IS AN ANTI-CD47 ANTIBODY THAT ENABLES CANCER CELLS TO BE EATEN AND DESTROYED

Control treatment



Hu5F9-G4 treatment



Macrophages Lymphoma cells

Hu5F9-G4 blocks the "don't eat me" signal CD47 and uses the body's immune cells To engulf and eliminate cancer cells

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

Ranjana Advani, M.D., Ian Flinn, M.D., Ph.D., Leslie Popplewell, M.D., Andres Forero, M.D., Nancy L. Bartlett, M.D., Nilanjan Ghosh, M.D., Ph.D., Justin Kline, M.D., Mark Roschewski, M.D., Ann LaCasce, M.D., Graham P. Collins, M.D., Thu Tran, B.S., Judith Lynn, M.B.A., James Y. Chen, M.D., Ph.D., Jens-Peter Volkmer, M.D., Balaji Agoram, Ph.D., Jie Huang, Sc.D., Ravindra Majeti, M.D., Ph.D., Irving L. Weissman, M.D., Chris H. Takimoto, M.D., Ph.D., Mark P. Chao, M.D., Ph.D., and Sonali M. Smith, M.D.

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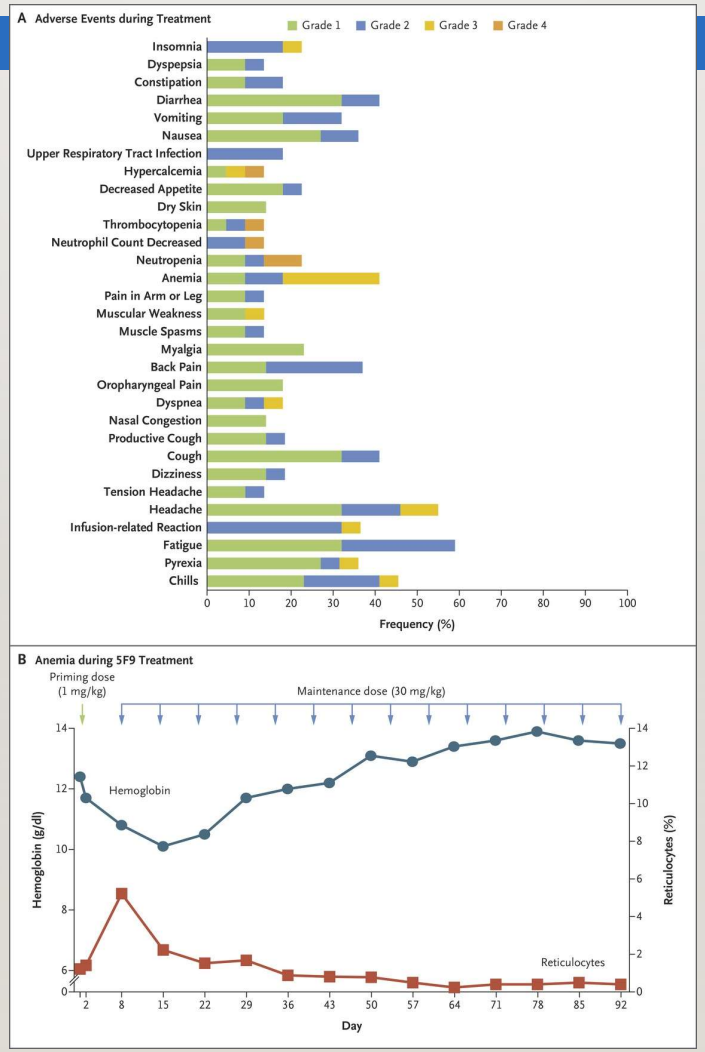
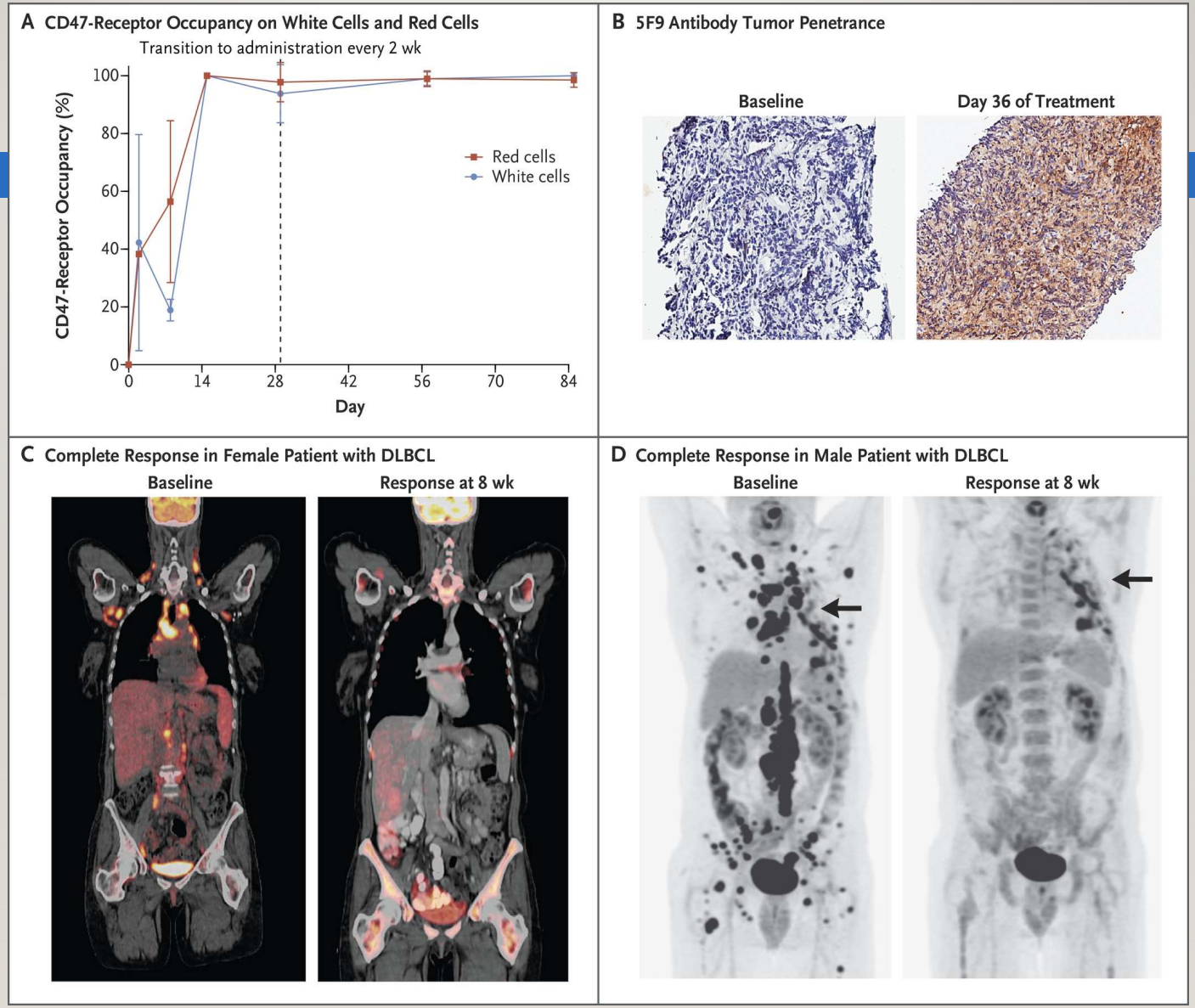
Study Overview

- AN ANTIBODY TO CD47 USED IN COMBINATION WITH RITUXIMAB INDUCED RESPONSES IN HALF OF A SMALL GROUP OF PATIENTS WITH REFRACTORY B-CELL LYMPHOMA.
- INHIBITING THE MACROPHAGE CHECKPOINT OVERCAME RITUXIMAB RESISTANCE BY ACTIVATING MACROPHAGE-MEDIATED TUMOR PHAGOCYTOSIS.

Adverse Events Due to Hu5F9-G4 (5F9), Rituximab, or Both and On-Target Anemia Effect of 5F9.

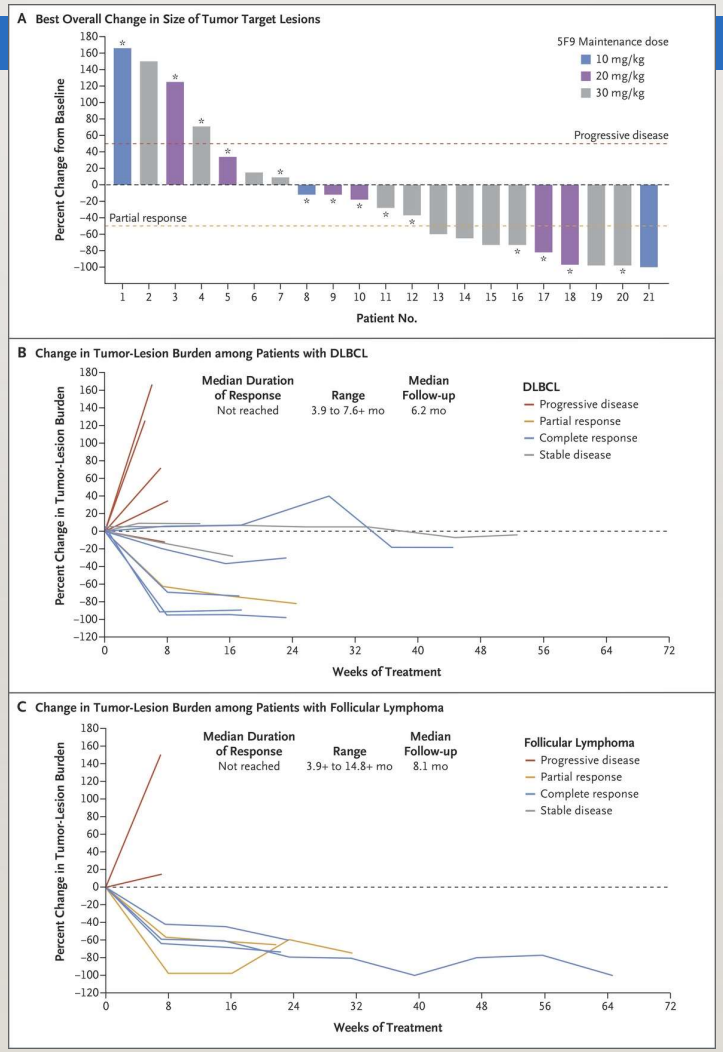


Advani R et al. N Engl J Med 2018;379:1711-1721



Advani R et al. N Engl J Med 2018;379:1711-1721

Change in Tumor-Lesion Size and Duration of Responses with 5F9 and Rituximab.



Advani R et al. N Engl J Med 2018;379:1711-1721

Characteristics of the 22 Patients Who Were Treated.

Table 1. Characteristics of the 22 Patients Who Were Treated.*

Characteristic	All Patients (N=22)	Patients with DLBCL (N=15)	Patients with Follicular Lymphoma (N=7)
Median age (range) — yr	59 (44–82)	60 (44–82)	59 (44–75)
Sex — no. (%)			
Male	12 (55)	7 (47)	5 (71)
Female	10 (45)	8 (53)	2 (29)
Median no. of previous therapies (range)	4 (2–10)	4 (2–10)	4 (2–9)
ECOG performance-status score — no. (%)†			
0	7 (32)	3 (20)	4 (57)
1	14 (64)	11 (73)	3 (43)
2	1 (5)	1 (7)	0
Lugano stage at diagnosis — no. (%)‡			
I or II	4 (18)	3 (20)	1 (14)
III or IV	15 (68)	11 (73)	4 (57)
Unknown	3 (14)	1 (7)	2 (29)
Disease refractory to previous rituximab regimen — no. (%)	21 (95)	14 (93)	7 (100)
Disease refractory to most recent regimen — no. (%)	14 (64)	9 (60)	5 (71)
Previous autologous stem-cell transplantation — no. (%)	4 (18)	2 (13)	2 (29)
5F9 maintenance dose level — no. (%)			
10 mg/kg	3 (14)	2 (13)	1 (14)
20 mg/kg	6 (27)	6 (40)	0
30 mg/kg	13 (59)	7 (47)	6 (86)

* A total of 15 patients (68%) in this study of Hu5F9-G4 (5F9) had received a diagnosis of diffuse large B-cell lymphoma (DLBCL) and 7 (32%) had received a diagnosis of follicular lymphoma.
† Scores for the Eastern Cooperative Oncology Group (ECOG) performance status are assessed on a 5-point scale, with higher numbers indicating greater disability.
‡ A Lugano stage of I indicates disease involving one lymph node or a group of adjacent nodes, II two or more nodal groups on the same side of the diaphragm, III nodes on both sides of the diaphragm or nodes above the diaphragm with spleen involvement, and IV additional noncontiguous extralymphatic involvement.[18]

Advani R et al. N Engl J Med 2018;379:1711-1721

Clinical Responses to Combination Therapy with 5F9 and Rituximab.

Table 2. Clinical Responses to Combination Therapy with 5F9 and Rituximab.*

Response	All Patients (N=22)	Patients with DLBCL (N=15)	Patients with Follicular Lymphoma (N=7)
Objective response	11 (50)	6 (40)	5 (71)
Complete response	8 (36)	5 (33)	3 (43)
Partial response	3 (14)	1 (7)	2 (29)
Stable disease	3 (14)	3 (20)	0
Progressive disease	8 (36)	6 (40)	2 (29)
Disease control	14 (64)	9 (60)	5 (71)

* Objective response was defined as a complete or partial response. Disease control was defined as a complete response, partial response, or stable disease.

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Conclusions

- THE MACROPHAGE CHECKPOINT INHIBITOR 5F9 COMBINED WITH RITUXIMAB SHOWED PROMISING ACTIVITY IN PATIENTS WITH AGGRESSIVE AND INDOLENT LYMPHOMA.
- NO CLINICALLY SIGNIFICANT SAFETY EVENTS WERE OBSERVED IN THIS INITIAL STUDY.