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New FDA *Approvals*: Update

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Stage Based Approach

- Early Stage = skin only, patches and plaques
- Skin directed therapy only
- Skin directed therapy + other
- "Milder" systemic therapies

- Advanced stage IIB-IV (tumors or disease outside the skin)
- Often include systemic therapy (outside skin-yes)
- Slower growing, less symptomatic, long term approach
- "Milder" medications , little cumulative toxicity
  - retinoids, interferon, hdac inhibitors, immunotherapy,

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2018
Mycosis Fungoides/Sezary Syndrome

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]

SKIN-DIRECTED THERAPIES

For limited/localized skin involvement (Skin-Limited/Local)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard])
- Local radiation (8-12 Gy; 24-30 Gy for unilesional presentation)[c]
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA for thicker plaques)[d]
- Topical imiquimod

For generalized skin involvement (Skin-Generalized)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard])
- Phototherapy (UVB, NB-UVB, for patch/thin plaques; PUVA for thicker plaques)[d]
- Total skin electron beam therapy (TSEBT) (12–36 Gy)[c,e,f]

SYSTEMIC THERAPIES

Category A (SYST-CAT A)
- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)[f]
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)[f]
- Extracorporeal photopheresis[g]
- Methotrexate (≤100 mg q week)
- Brentuximab vedotin[h]

Category B (SYST-CAT B)
- Preferred therapies (alphabetical order)
  - Brentuximab vedotin[h]
  - Gemcitabine
  - Liposomal doxorubicin
  - Low-dose pralatrexate
- Other therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Pembrolizumab[i] (category 2B)
  - Bortezomib (category 3)

SYSTEMIC THERAPIES (continued)

Category C (SYST-CAT C)[j] (alphabetical order)
- Bortezomib (category 3)
- Brentuximab vedotin[h]
- Gemcitabine
- Liposomal doxorubicin
- Low- or standard-dose pralatrexate
- Romidepsin
- See regimens listed on TCEL-B 2 of 5 (PTCL-NOS)[k]

COMBINATION THERAPIES

Skin-directed + Systemic
- Phototherapy + retinoid
- Phototherapy + IFN
- Phototherapy + photopheresis[g]
- Total skin electron beam* + photopheresis[g]

Systemic + Systemic
- Retinoid + IFN
- Photopheresis[g] + retinoid
- Photopheresis[g]+ IFN
- Photopheresis[g] + retinoid + IFN

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Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients With CD30-Expressing Cutaneous T-Cell Lymphoma Versus Physician's Choice (Methotrexate or Bexarotene): the Phase 3 ALCANZA study

ALCANZA investigators

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Belgium: Oliver Bechter (Pascal Wolter), Dominique Bron

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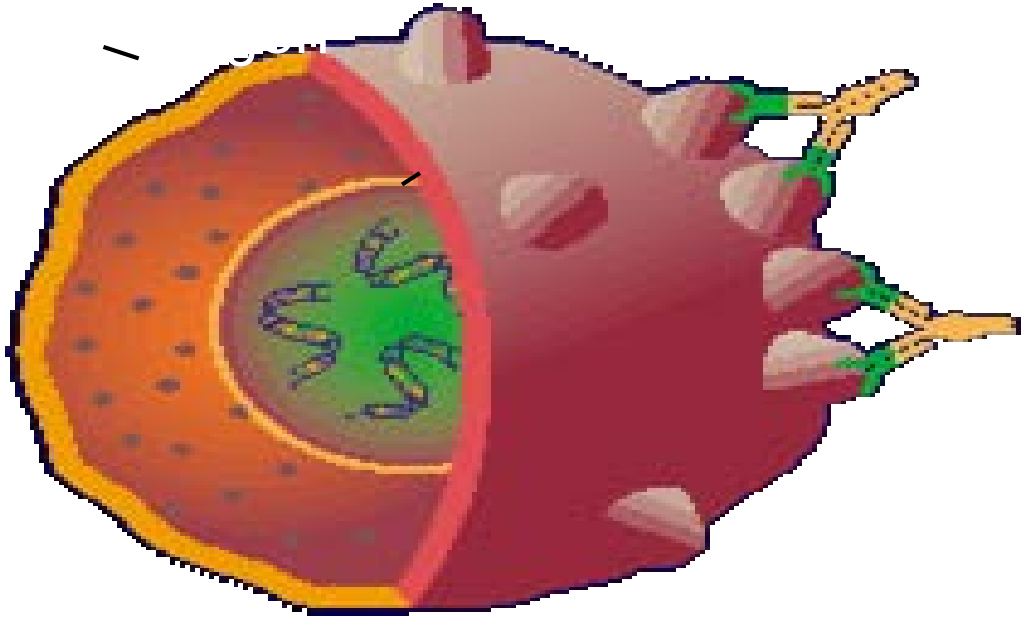
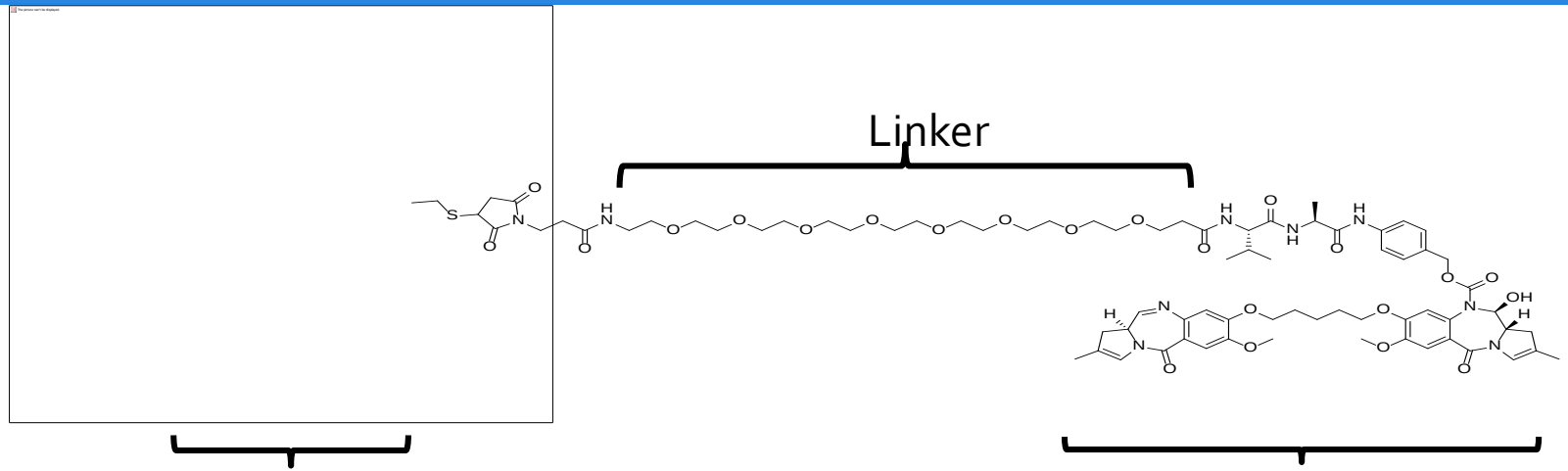
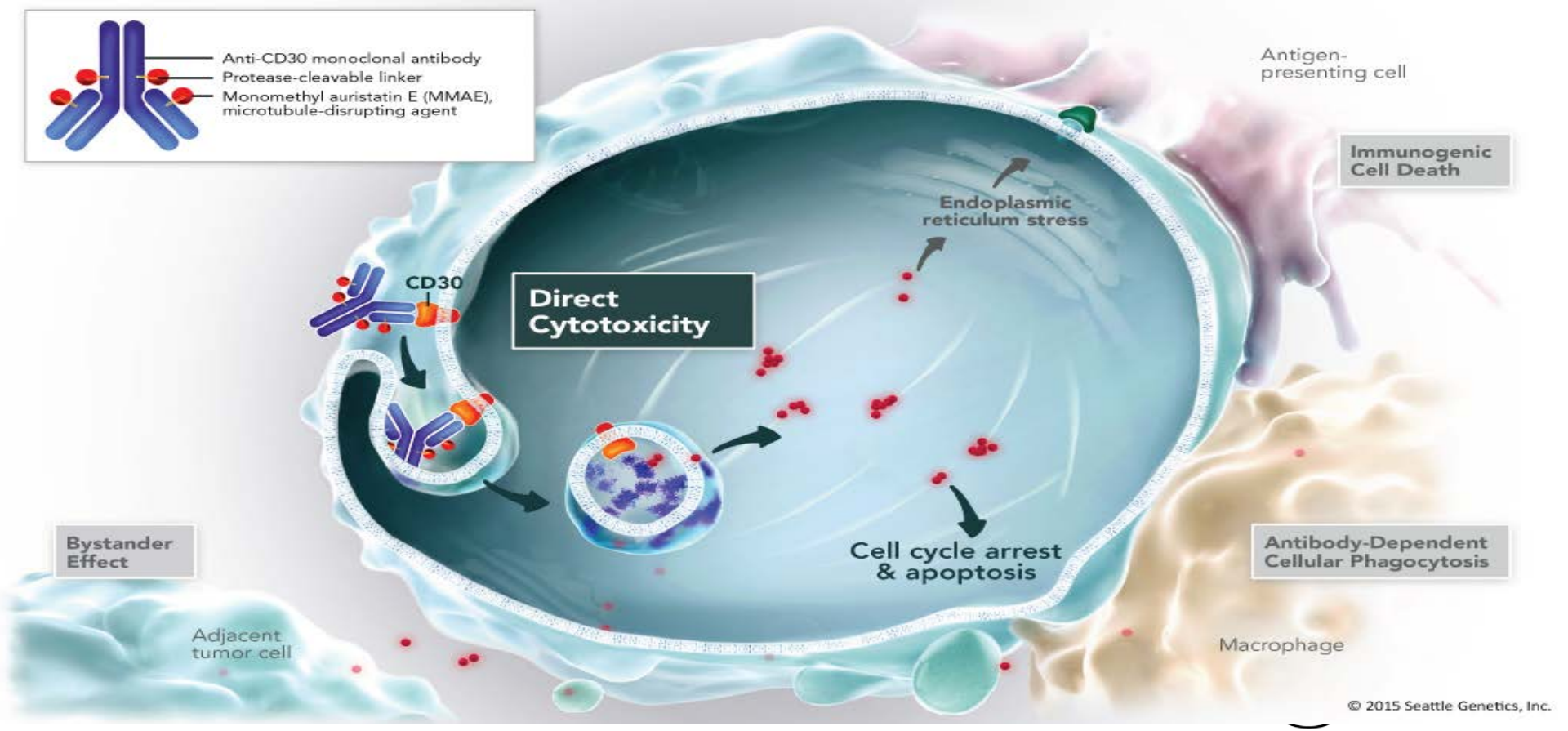
Antibodies



Antibody Drug Conjugates (ADCs)



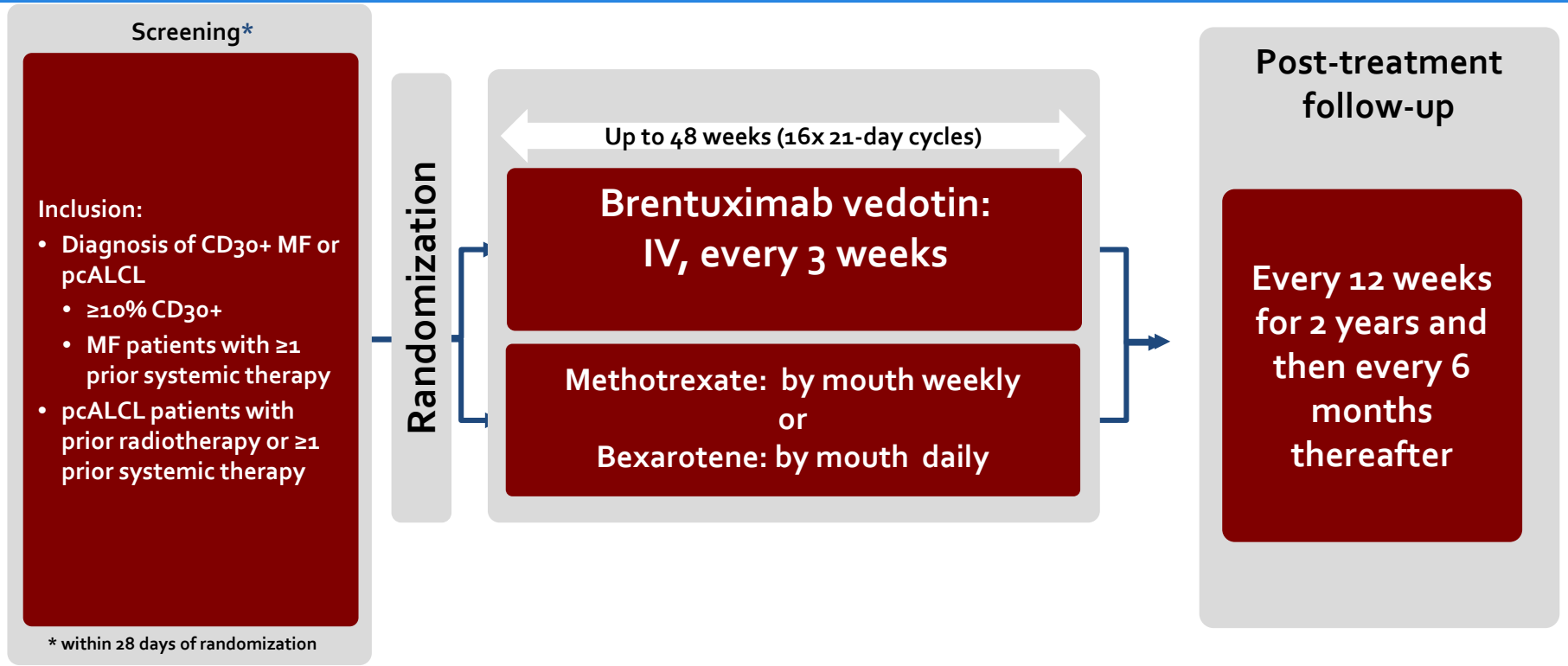
Antibody Drug conjugates



Background and rationale

- Brentuximab vedotin, a CD30 targeting antibody-drug-conjugate
- 2 Phase 2 studies showed promising activity
- This was the first reported phase 3 trial of a new systemic agent tested against standard therapy in CTCL

ALCANZA: a randomized, open-label, phase 3 trial of brentuximab vedotin vs physician's choice (methotrexate or bexarotene) in patients with CD30+ CTCL



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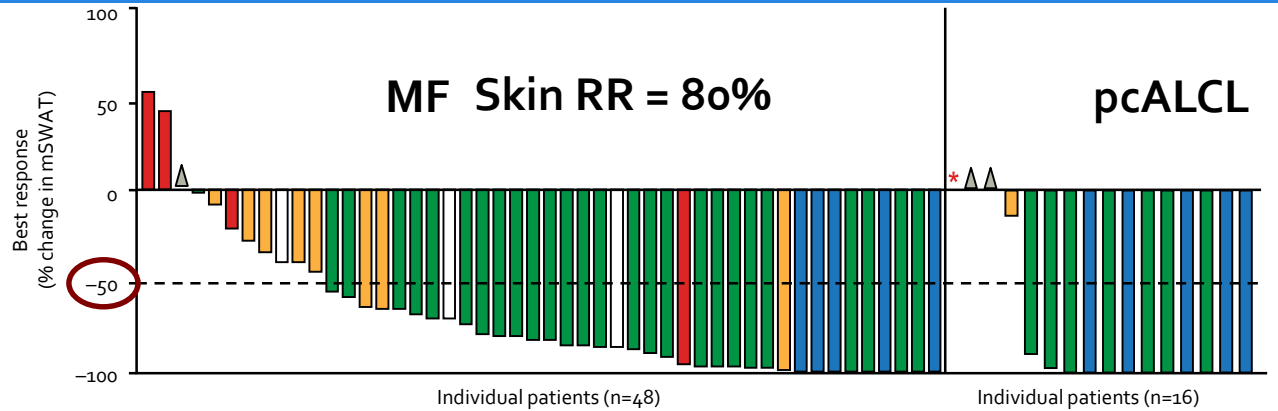
Patient baseline characteristics: ITT population, N=128

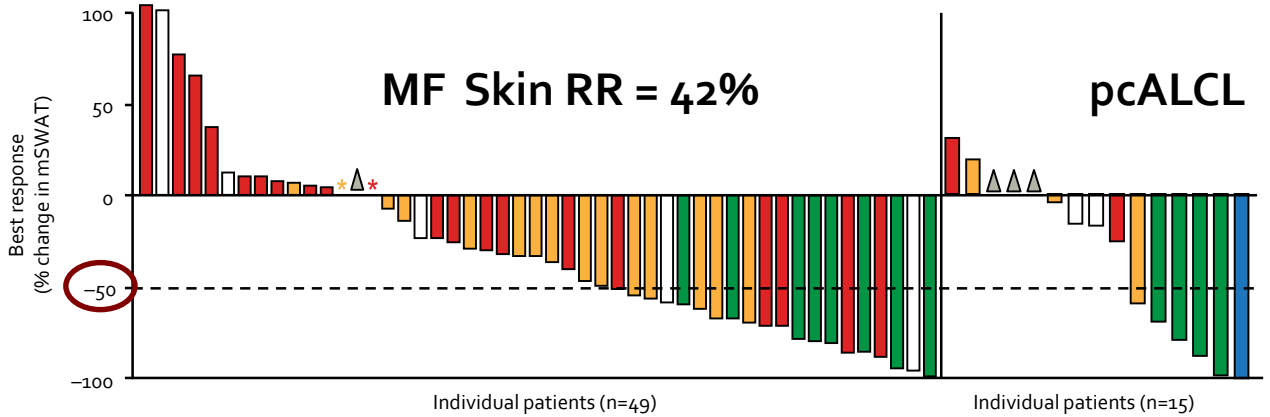
	Brentuximab vedotin (n=64)	Methotrexate or bexarotene (n=64)
Median age, years (range)	62 (22–83)	59 (22–83)
Gender, Male n (%)	33 (52)	37 (58)
Early (IA-IIA)	15 (31)	18 (37)
Advanced (IIB-IVB**)	32 (67)	30 (61)
Prior therapies, median (range)	4.0 (0–13)	3.5 (1–15)
Prior systemic therapies, median (range)	2.0 (0–11)	2.0 (1–8)

Maximum percent change in skin mSWAT score

Brentuximab vedotin



Methotrexate or Bexarotene



Best global response

- Complete response
- Stable disease
- Partial response
- Progressive disease
- No best global response
- No post-baseline assessment

* Indicates % change in mSWAT is o

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Primary and key secondary endpoint analyses (ITT population)

Endpoint	Brentuximab vedotin N=64	Physician's Choice N=64	Statistical Significance
Primary endpoint			
ORR4, n (%)	36 (56.3)	8 (12.5)	p<0.0001
Key secondary endpoints			
CR, n (%)	10 (15.6)	1 (1.6)	p=0.0046 adj
Mean maximum reduction in Skindex-29 symptom domain, points	-27.96	-8.62	p<0.0001 adj

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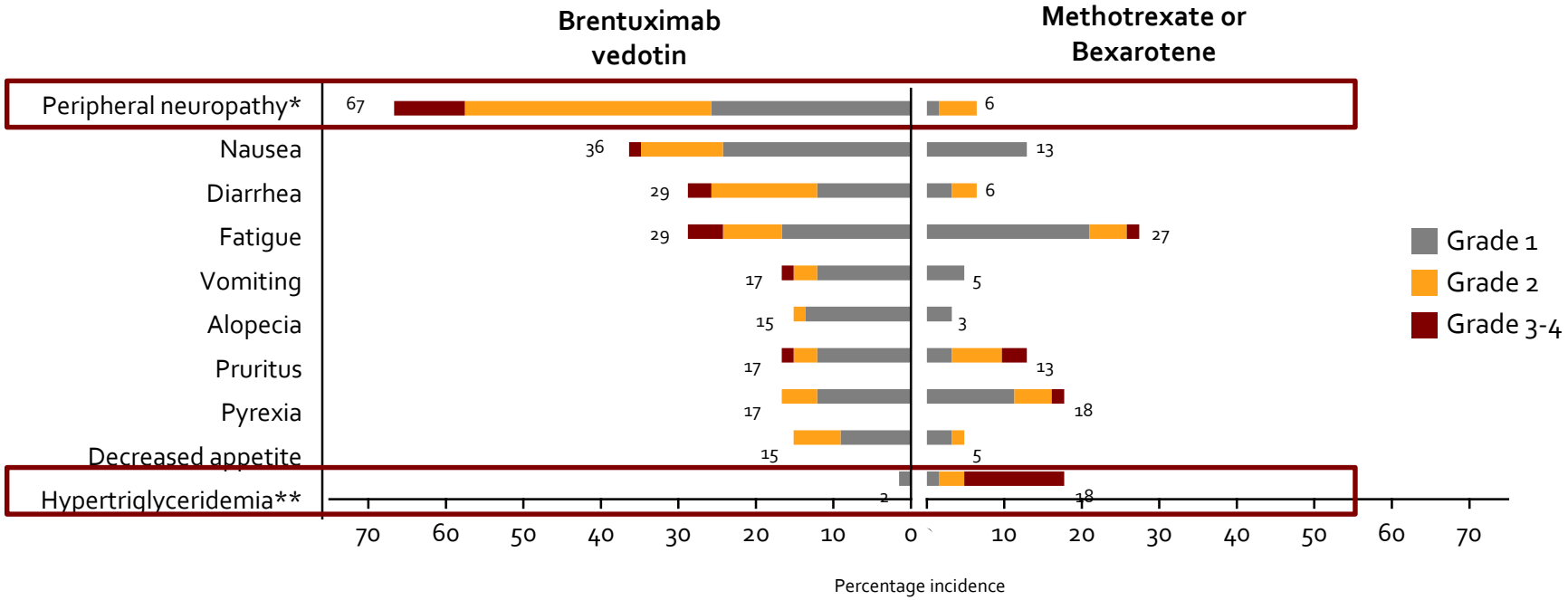
Commonly reported (≥15% of patients) treatment-emergent AEs

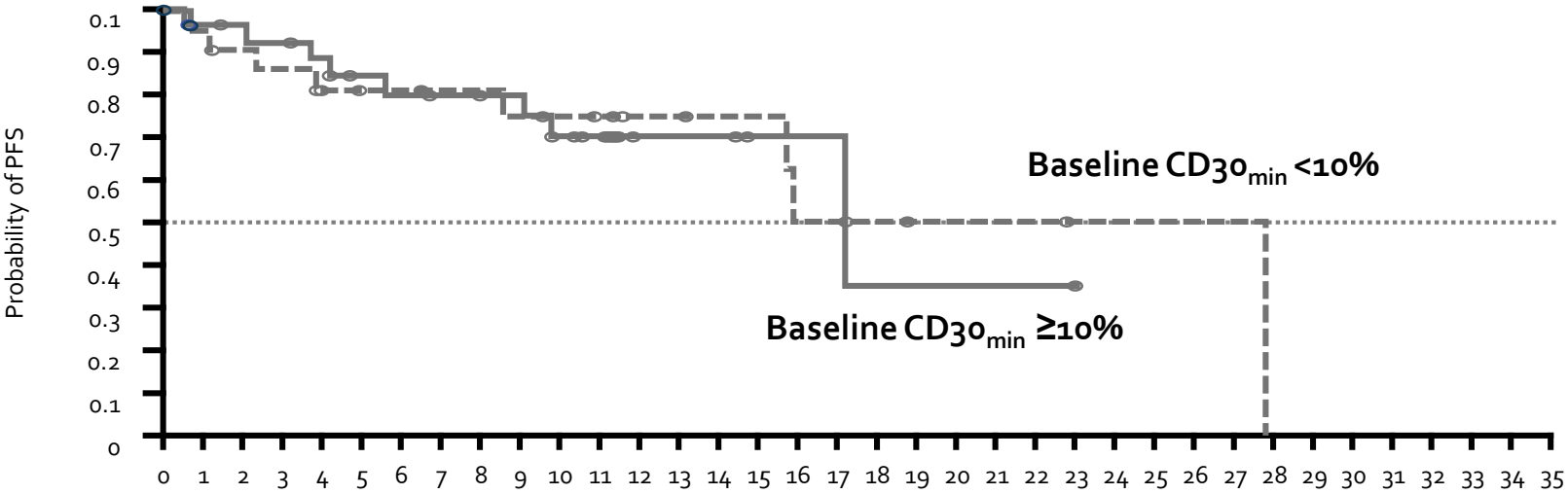


*No Gr 4 peripheral neuropathy was reported in the brentuximab vedotin (26% Gr 1, 32% Gr 2, 9% Gr 3) or physician's choice arms (2% Gr 1, 5% Gr 2). At last follow-up (median 22.9 months), 36/44 (82%) patients in the brentuximab vedotin arm had improvement or resolution of peripheral neuropathy.

**Elevated triglycerides, were reported in 2% of patients receiving brentuximab vedotin versus 30% of patients receiving bexarotene (14% Gr 3, 8% Gr 4)

Length of drug exposure: median 12 cycles (36 weeks) of BV vs. 17 weeks of bexarotene or 9 weeks of methotrexate

ALCANZA:
Results by CD30 expression in MF patients



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Summary and conclusions

- First report of a randomized phase 3 trial in CTCL with convincing demonstration of improved efficacy of a new systemic agent over standard-of-care options

- Brentuximab vedotin showed superior efficacy outcomes over physician's choice of either bexarotene or methotrexate in MF and pcALCL (CD30 expressing CTCL).

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Anti-CCR4 Monoclonal Antibody, Mogamulizumab, Demonstrates Significant Improvement in PFS Compared to Vorinostat in Patients with Previously Treated Cutaneous T-Cell Lymphoma: Results from the Phase 3 MAVORIC Study

MAVORIC Investigators

- **US:** Alison J. Moskowitz, Erin Boh, Amy Musiek, Mary Jo Lechowicz, Francine Foss, Larisa Geskin, S. Onder Alpdogan, Ronald Peter Rapini, John P. Greer, Timothy Fenske, Ellen Kim, Youn Kim, Basem William, Herbert Eradat, Barbara Pro, Lubomir Sokol, Andrei Shustov, Oleg Akilov, Theresa Pacheco, Craig Elmets, Brian Poligone, Michael D. Tharp, Ryan A. Wilcox, Frederick Lansigan, Neil Korman, Lawrence A. Mark, Ahmad Sami Halwani, Adam Lerner, Zanetta Lamar, Sunil Abhyankar, Christiane Querfeld, David C. Fisher, Javier Munoz, Craig Yoshitsugu Okada (Independent Reviewer), Jessica Taft Leonard (Independent Reviewer)
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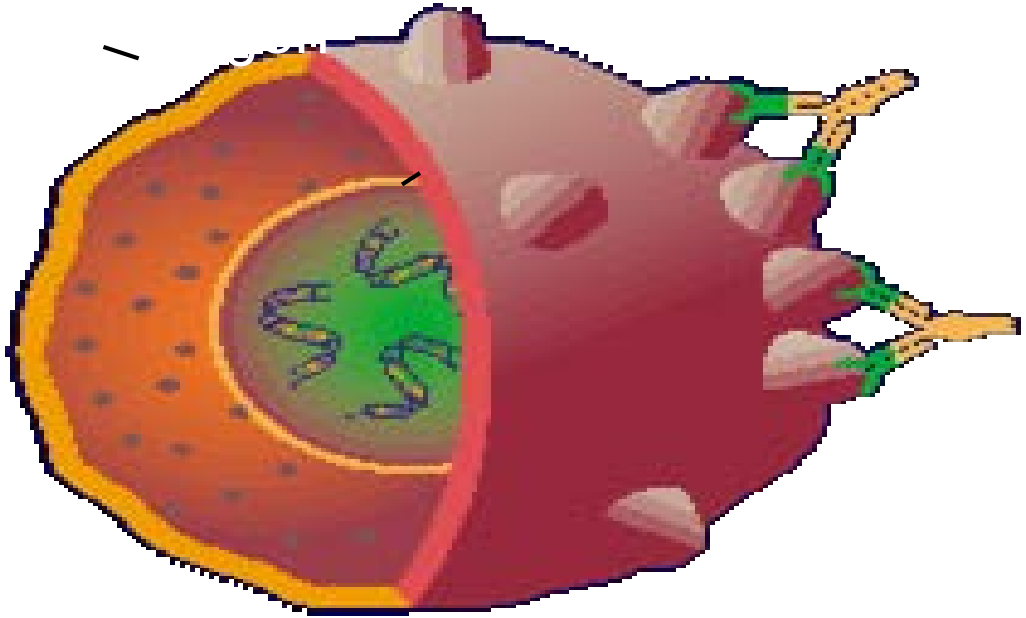
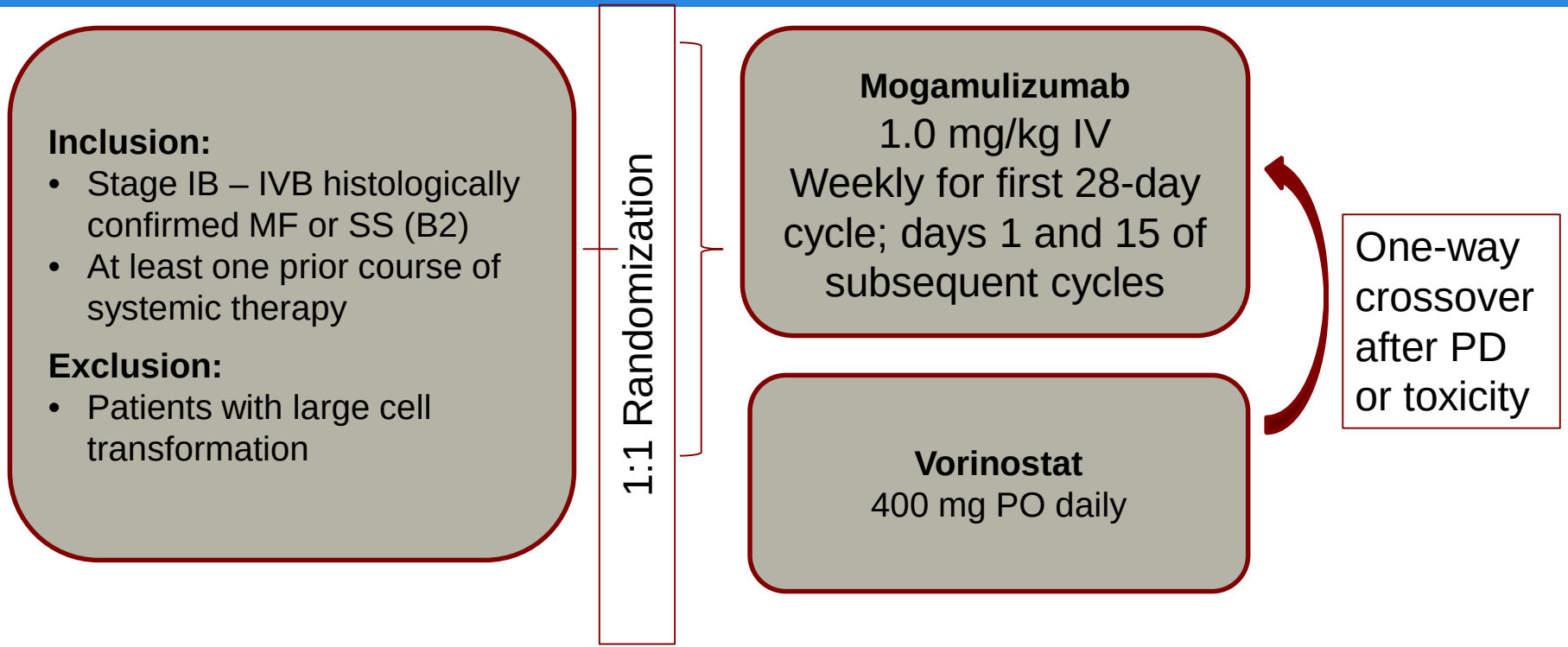
Antibodies



Anti-CCR4
Defucosylated Fc region

MAVORIC Study Design



- 372 patients were randomized at 59 centers across 11 countries

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Background

- In a US-based phase 1/2 study in CTCL, mogamulizumab demonstrated a tolerable safety profile and promising efficacy

- These results led to the development of the MAVORIC trial, a randomized phase 3 study of the efficacy and safety of mogamulizumab versus vorinostat in previously treated patients with CTCL

- MAVORIC is the largest randomized study to compare systemic therapies and the first pivotal trial to use PFS as a primary endpoint in CTCL

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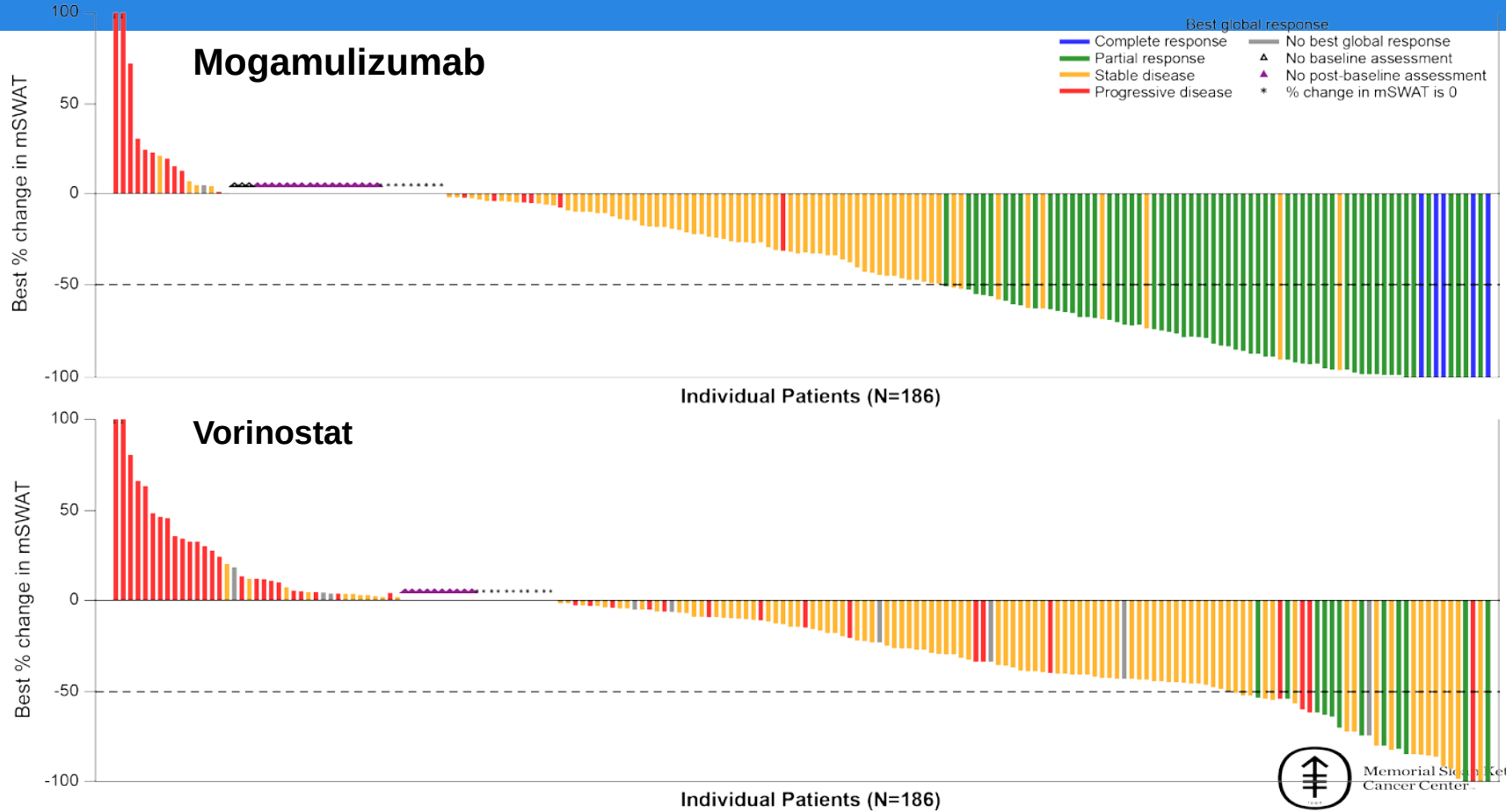
ORR, overall response rate; PFS, progression-free

1. Duvic et al. Blood. 2015;125(12):1883-1889.

Patient Baseline Characteristics: ITT population, N=372

	Mogamulizumab (N=186)	Vorinostat (N=186)
Median age (range), years	63 (25, 101)	65 (25, 89)
Male gender (n, %)	109 (59)	107 (58)
Disease type (n, %)		
MF	105 (56)	99 (53)
SS	81 (44)	87 (47)
Current clinical stage (n, %)		
IB-IIA	36 (19)	49 (26)
IIB	32 (17)	23 (12)
IIIA-IIIB	22 (12)	16 (9)
IVA1	73 (39)	82 (44)
IVA2	19 (10)	12 (6)
IVB[a]	4 (2)	4 (2)
Median number of prior systemic therapies (range)	3 (1, 18)	3 (0, 14)

mSWAT Score and Superior Best Global Response



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Response Outcomes

	Mogamulizumab	Vorinostat
ORR[a,b], n/N (%)	**52/186 (28)**	**9/186 (5)**
MF[c]	22/105 (21)	7/99 (7)
SS[b]	30/81 (37)	2/87 (2)
DOR, median, months	**14**	**9**
MF	13 (n=22)	9 (n=7)
SS	17 (n=30)	7 (n=2)
ORR[a] n (%) mogamulizumab after crossover	**41/136 (30)**	

[a]ORR is the percentage of patients with confirmed CR or confirmed PR; [b]P<0.0001; [c]P=0.004.

ORR=overall response rate; TTR=time to response; DOR=duration of response; PRO=patient-reported outcome.

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Clinical Activity by Compartment

	Mogamulizumab
Compartment response rate, n/N (%)	
Skin	
ORR (CR+PR)	78/186 (42)
CR	8 (4)
Blood	
ORR (CR+PR)	83/124 (67)
CR	54 (44)
Lymph nodes	
ORR (CR+PR)	21/136 (15)
CR	10 (7)

ORR=overall response rate; CR=complete response; PR=partial response.

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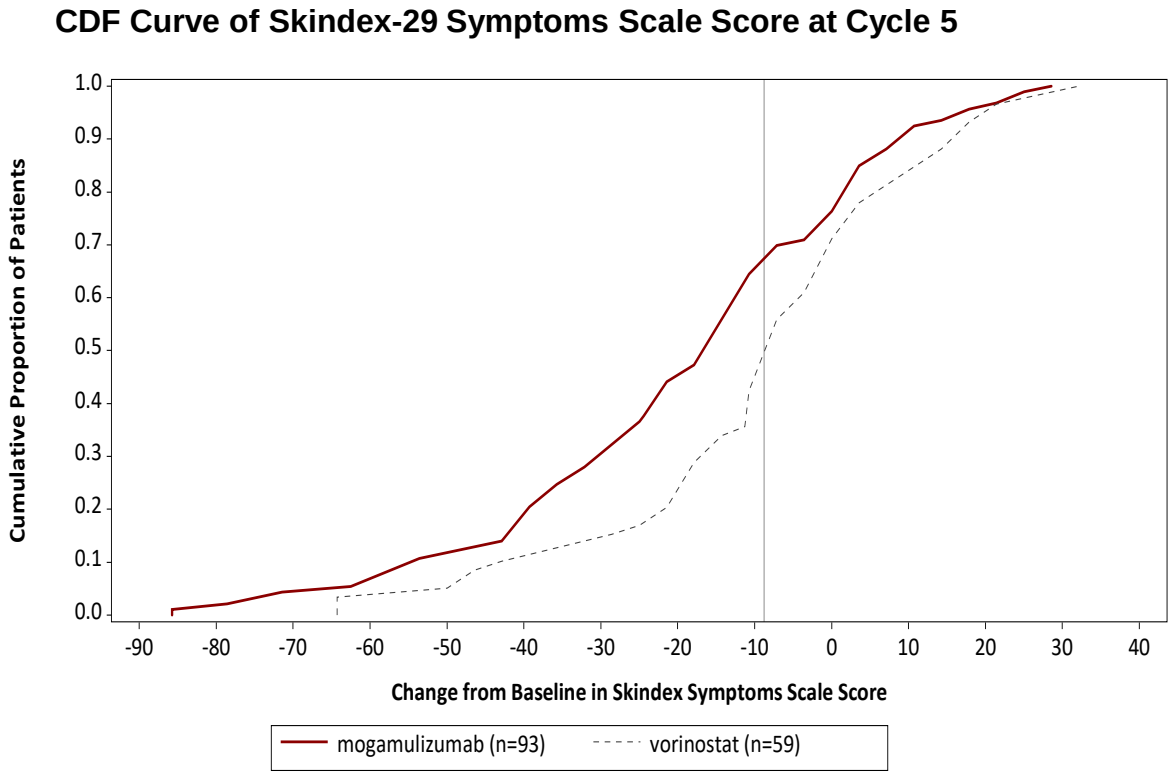
Patient-Reported Symptom Reduction as Measured by the Skindex-29 Scale



CDF, cumulative distribution function.

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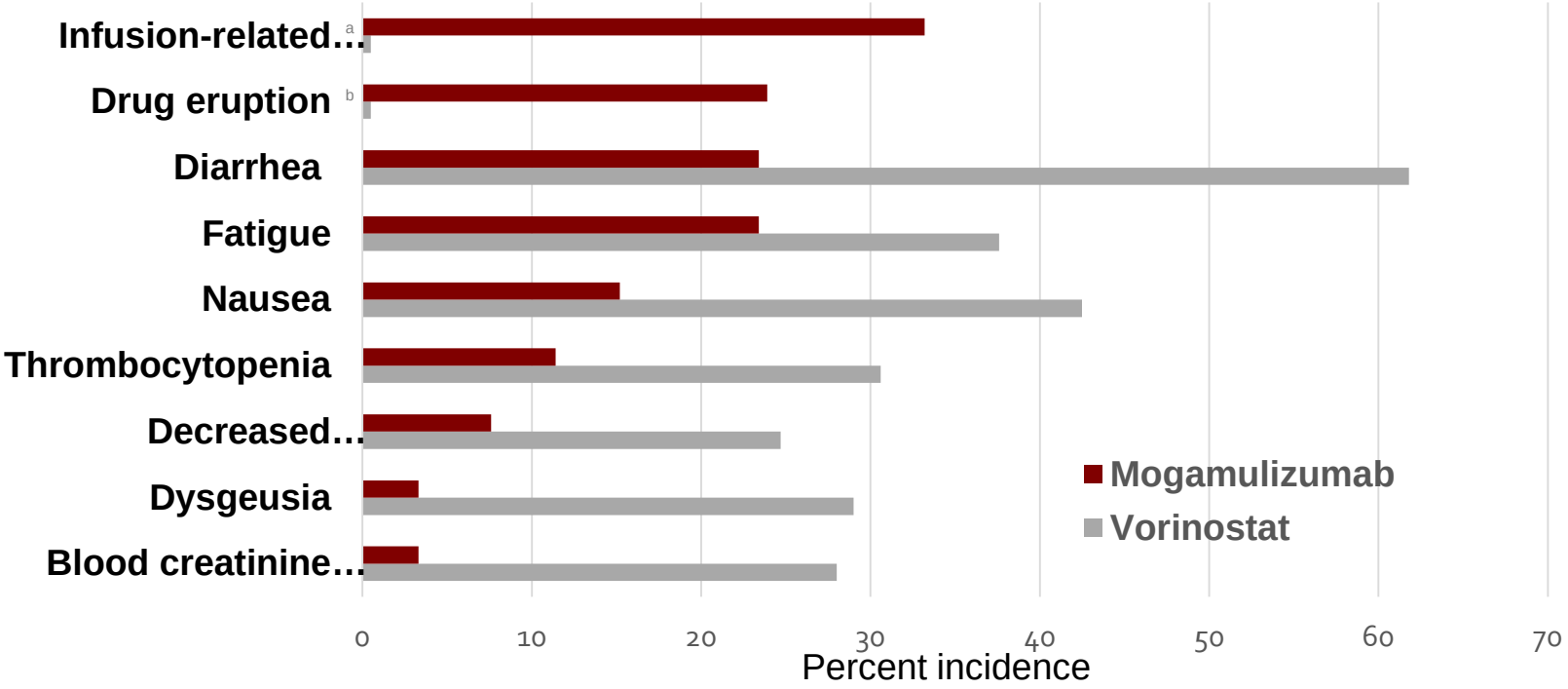
Commonly Reported Treatment-Emergent Adverse Events (≥ 20% of patients)



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Summary and Conclusions

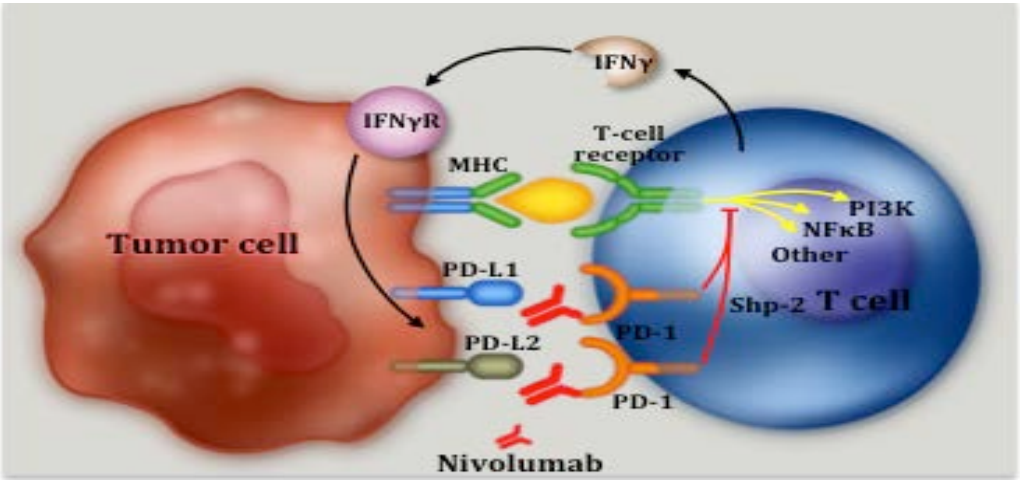
- Mogamulizumab, a novel CCR4-targeting antibody therapy, demonstrated significantly superior efficacy outcomes compared to vorinostat in patients with previously treated CTCL
- Patient-reported outcomes (Skindex-29 and FACT-G) demonstrated significant improvement with mogamulizumab
- The safety profile was consistent with previous reports, and common AEs were manageable
- This study supports mogamulizumab as a valuable new therapeutic option in patients with CTCL

Where would these new drugs fit

- Early Stage –probably not right away
  - Maybe if many things had already been tried
- Advanced stage-another option
  - Brentuximab best in tumors, nodes
    - ?CD30 level
    - Sezary? not include in study
    - Neuropathy-intermittent therapy
  - Mogamulizumab-if/when approved
    - Best in Sezary and Blood
    - ? If CCr4 expression needed
    - Transformed to Large Cell not included
    - Seems ok long term-as best we know

Immune Checkpoint Inhibitors

- PD-L1 expressed on malignant cells and/or in the tumor microenvironment
- It can interferes with host antitumor immunity.[2]



- Nivolumab is a fully human IgG4 monoclonal antibody with anti-PD-1 activity.

[1]Francisco LM et al. J Exp Med 2009;206:3015-29.
[2]Andorsky DJ et al. Clin Cancer Res 2011;17:4232-44

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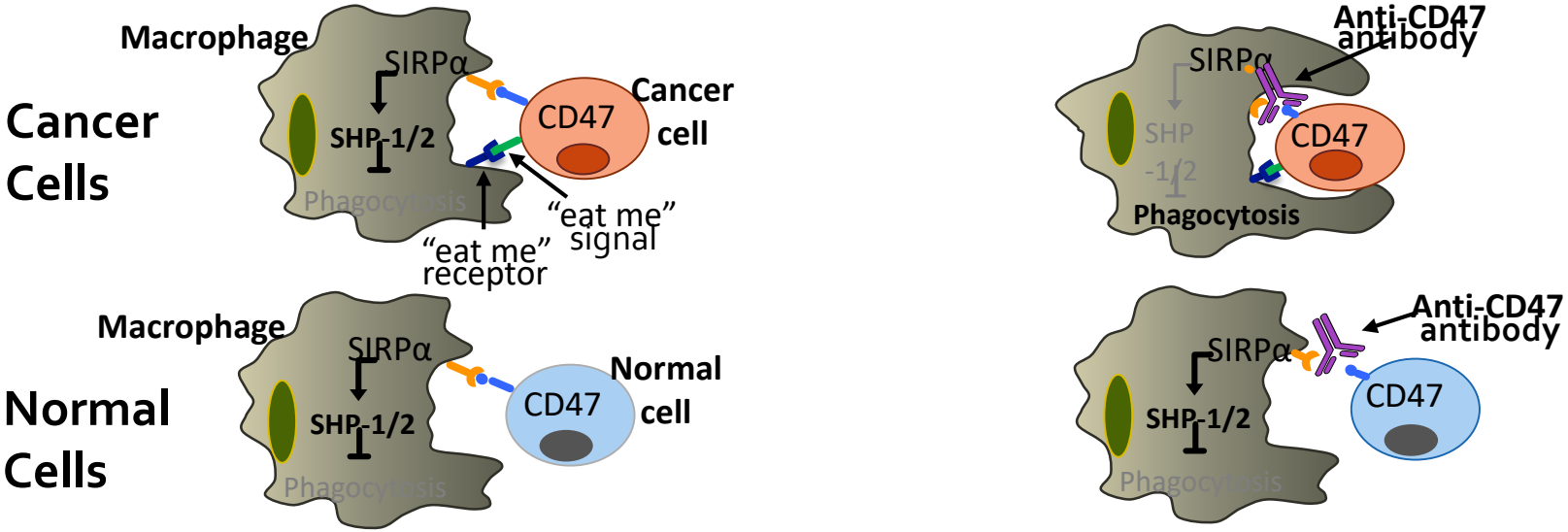
CD47-SIRPα:
A Universal Cancer Immune Checkpoint



- CD47 sends a "don't eat me" signal to macrophages and other immune cells
- CD47 is often up-regulated in a wide variety of cancers
- **Antibodies that block the CD47:SIRPα interaction potently stimulate macrophage phagocytosis (eat) of cancer cells**

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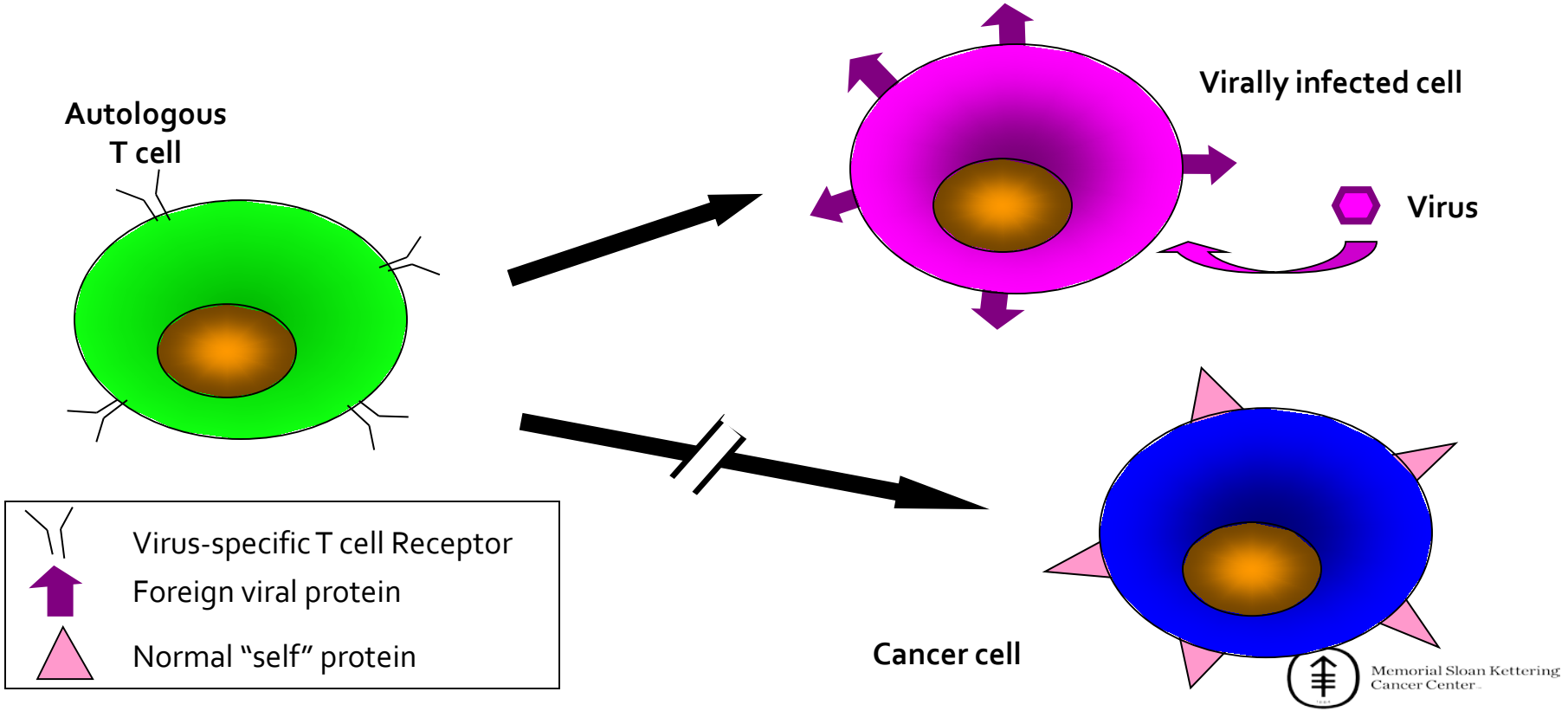
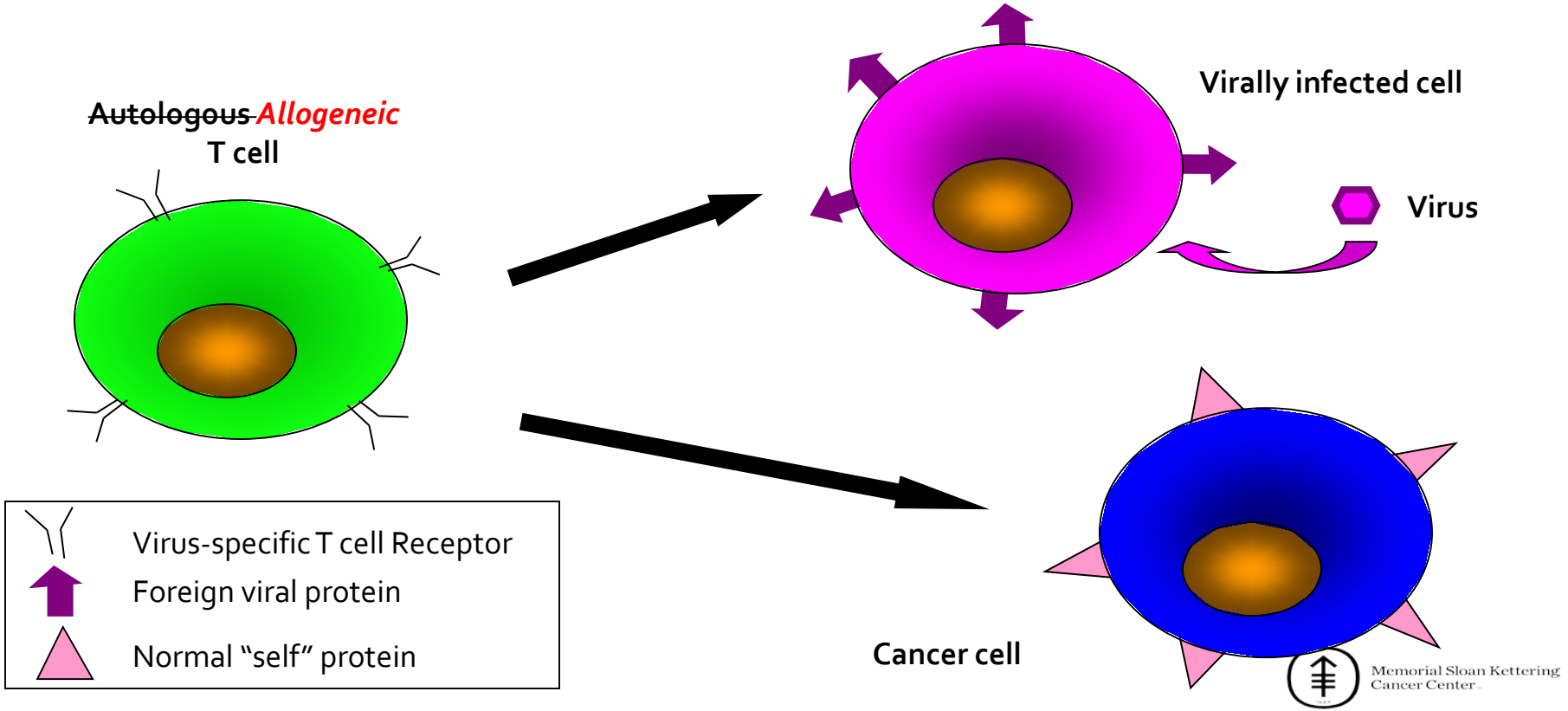
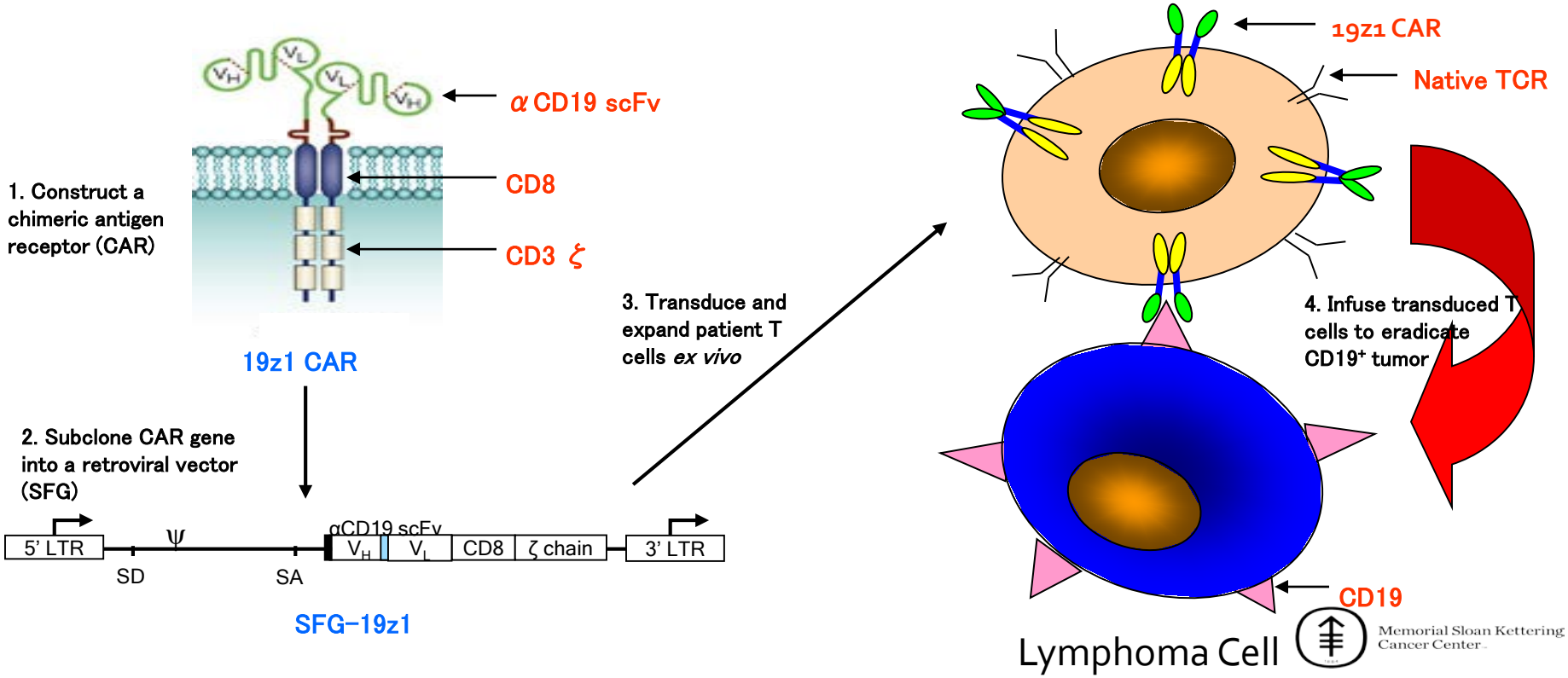
Autologous T cells target foreign proteins on diseased cells, but not self proteins



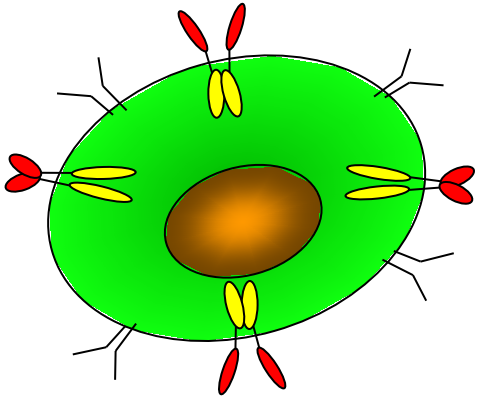
Allogeneic T cells target foreign proteins on diseased cells~~, but not~~ *and* self proteins



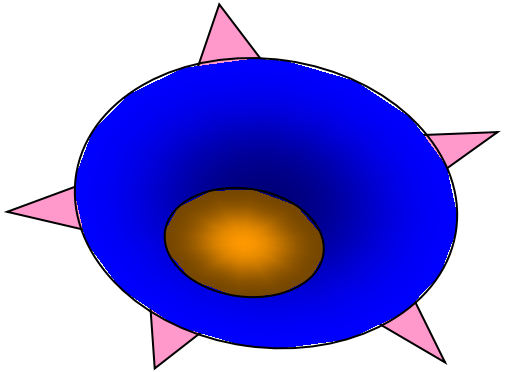
Generation of CD19-targeted Autologous T cells (CAR) for treatment of B cell Lymphoma



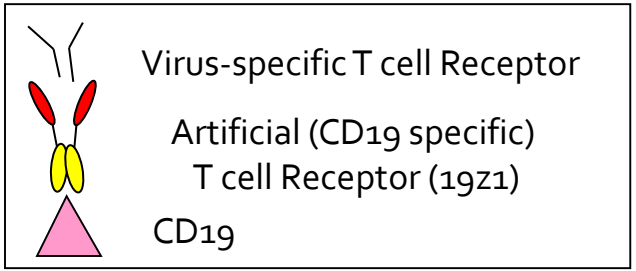
Genetically modified T cells now recognize "non-foreign" tumor cells. . . .



Genetically modified tumor-targeted (CD19 specific) T cell (19z1)



Cancer cell (ie Lymphoma tumor cell)



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Immunotherapy in CTCL

- T-cell checkpoint inhibitors
  - Approved for other cancers-studies in CTCL (pembrolizumab, nivolumab)
- Anti CD47 Strategies-in clincial trials for CTCL now
- CAR-T cells
  - Approved for B-cell leukemia/lymphoma
  - Ideas for T cell lymphomas including CTCL in idea/preclincial stage
  - "may be a more complicated problem than B-cell lymphoma)
  - Early studies starting in T-ALL
  - Other CARs may also work here-also preclinical

Questions?