ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy of Hematologic Malignancies

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

- Celgene Corporation, Pharmacyclics LLC, Sanofi, Contracted Research
- Celgene Corporation, Sanofi, Fees for Non-CME/CE Services Received Directly from a Commercial Interest *or their Agents*
- I will be discussing non-FDA approved indications during my presentation.

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Patient Selection Criteria for Immune-Based Approaches

- Expression of the desired antigen for CAR-T therapy:
  - e.g. CD19 or BCMA for CAR-T cells
- Disease burden
  - <30% in certain CAR-T trials to minimize the risk of cytokine release syndromes
- Expression of the ligand for checkpoint inhibition
  - e.g. PD-L1 expression for anti-PD-1 therapy
- Presence of co-morbidities:
  - e.g. Presence of active autoimmune diseases which could be worsened

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Lymphomas

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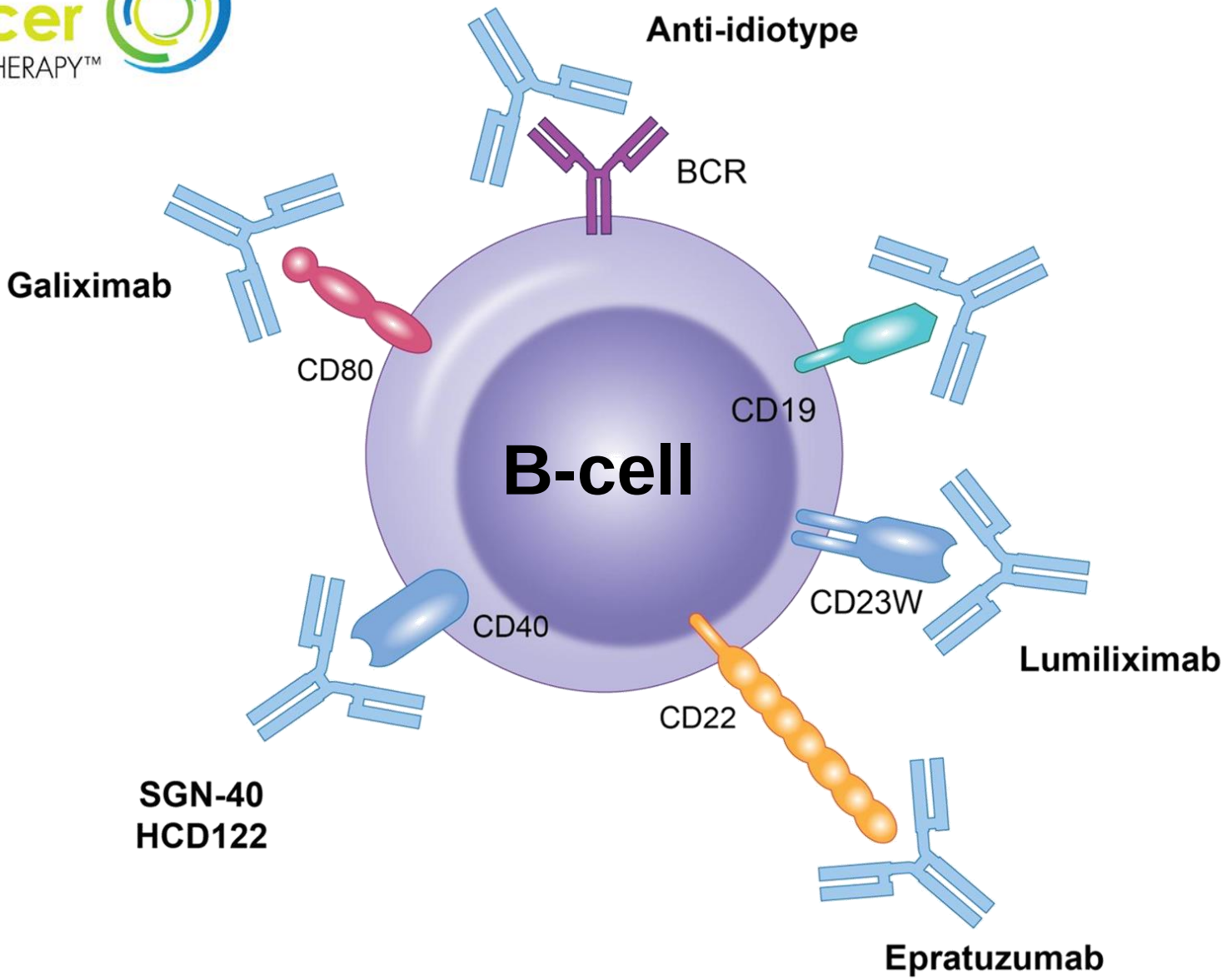
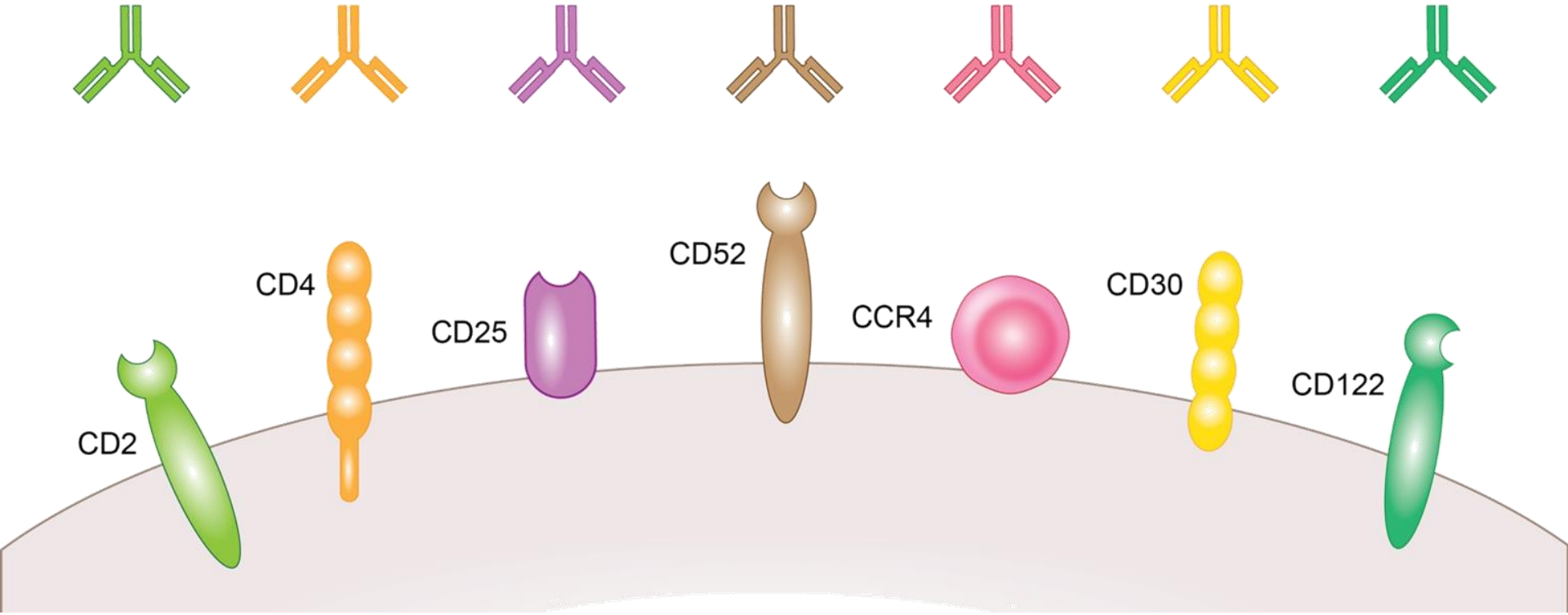
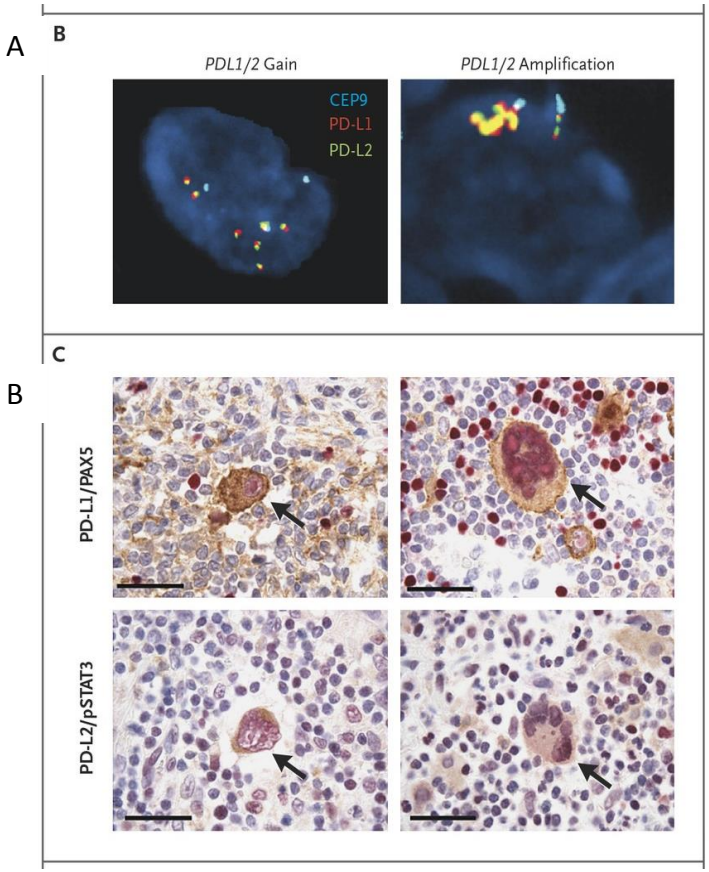

Anti-idiotype
BCR
Galiximab
CD80
CD19
B-cell
CD23W
Lumiliximab
CD40
CD22
SGN-40
HCD122
Epratuzumab

Several monoclonal antibodies targeting T-cell lymphomas



PD-L1 Expression in Hodgkin's Lymphoma

- Reed-Sternberg cells express both PD-L1 and PD-L2
- Expression of ligands increases with advanced disease
- Unclear whether PD-L1/L2 expression correlates with response to treatment



Ansell SM et al. N Engl J Med 2015;372:311-319

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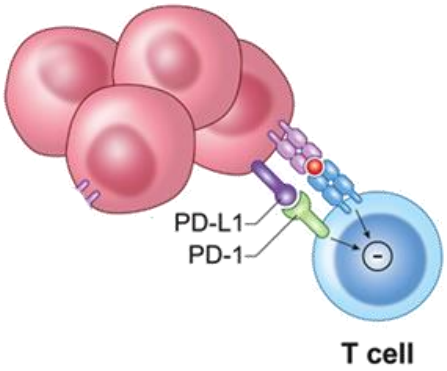

Anti-PD-1 in Hodgkin's Lymphoma

Table 3. Clinical Activity in Nivolumab-Treated Patients.*

Variable	All Patients (N=23)	Failure of Both Stem-Cell Transplantation and Brentuximab (N=15)	No Stem-Cell Transplantation and Failure of Brentuximab (N=3)	No Brentuximab Treatment (N=5)†
Best overall response — no. (%)				
Complete response	4 (17)	1 (7)	0	3 (60)
Partial response	16 (70)	12 (80)	3 (100)	1 (20)
Stable disease	3 (13)	2 (13)	0	1 (20)
Progressive disease	0	0	0	0
Objective response				
No. of patients	20	13	3	4
Percent of patients (95% CI)	87 (66–97)	87 (60–98)	100 (29–100)	80 (28–99)
Progression-free survival at 24 wk — % (95% CI)‡	86 (62–95)	85 (52–96)	NC§	80 (20–97)
Overall survival — wk				
Median	NR	NR	NR	NR
Range at data cutoff¶	21–75	21–75	32–55	30–50

* NC denotes not calculated, and NR not reached.
† In this group, two patients had undergone autologous stem-cell transplantation and three had not.
‡ Point estimates were derived from Kaplan–Meier analyses; 95% confidence intervals were derived from Greenwood's formula.
§ The estimate was not calculated when the percentage of data censoring was above 25%.
¶ Responses were ongoing in 11 patients.

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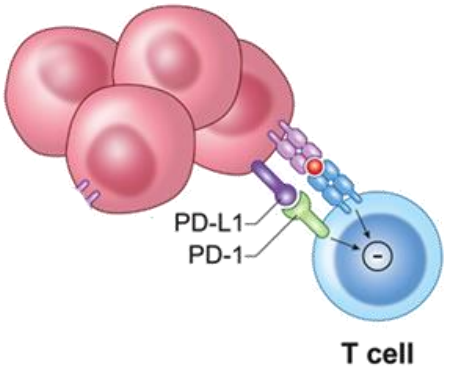

Anti-PD-1 in Hodgkin's Lymphoma

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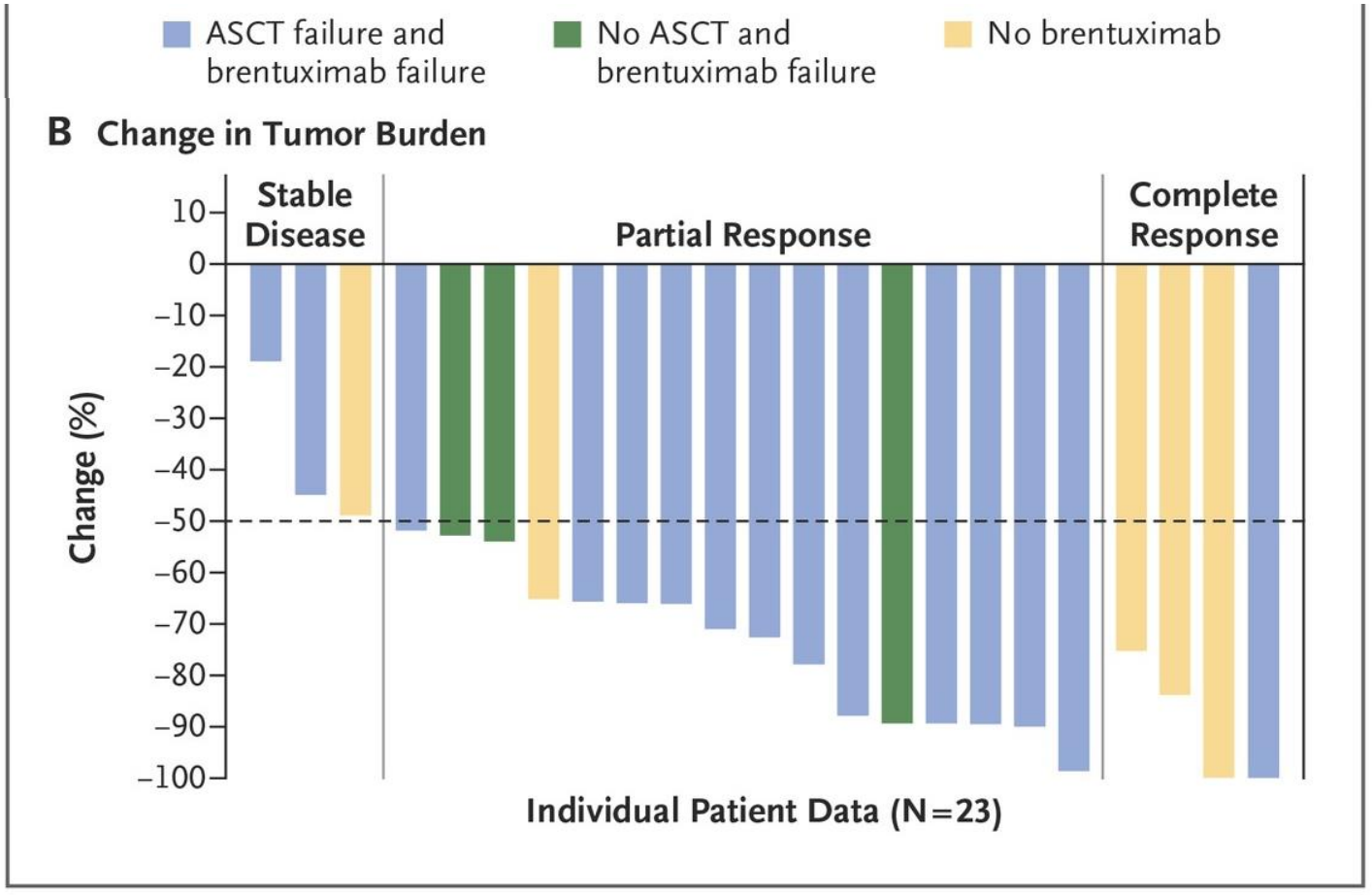

* NC de
† In this
‡ Point e
§ The estimate was not calculated when the percentage of data censoring was above 25%.
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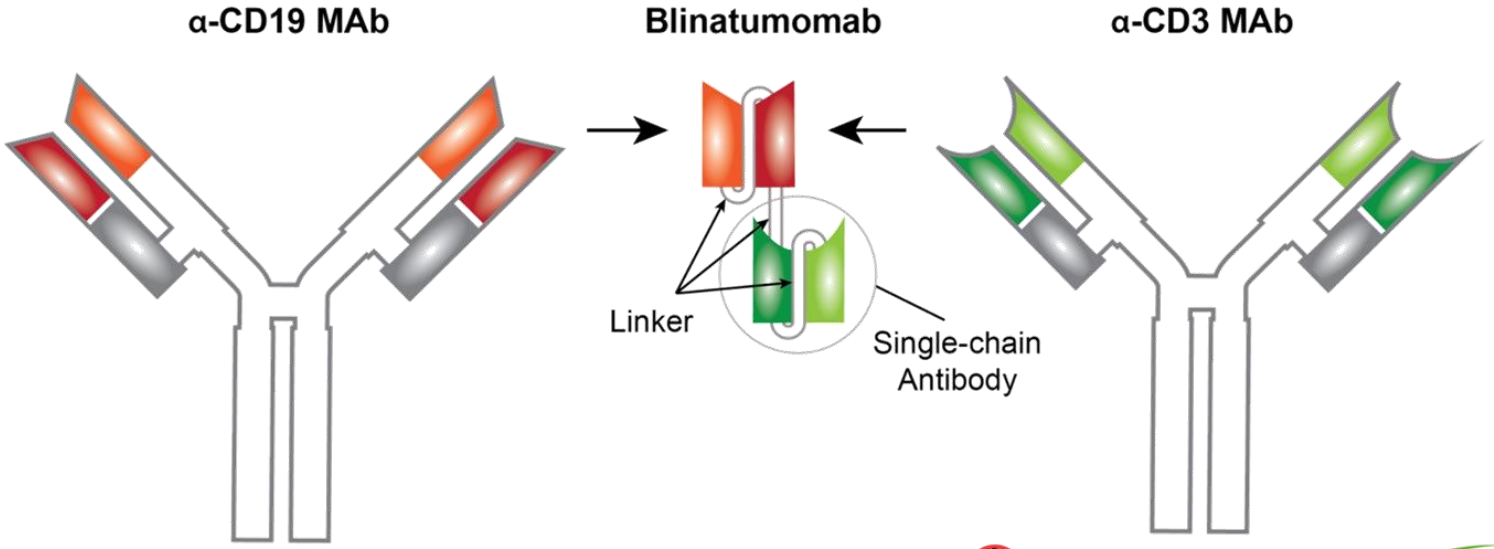
Nivolumab in R/R B Cell Malignancies: Efficacy

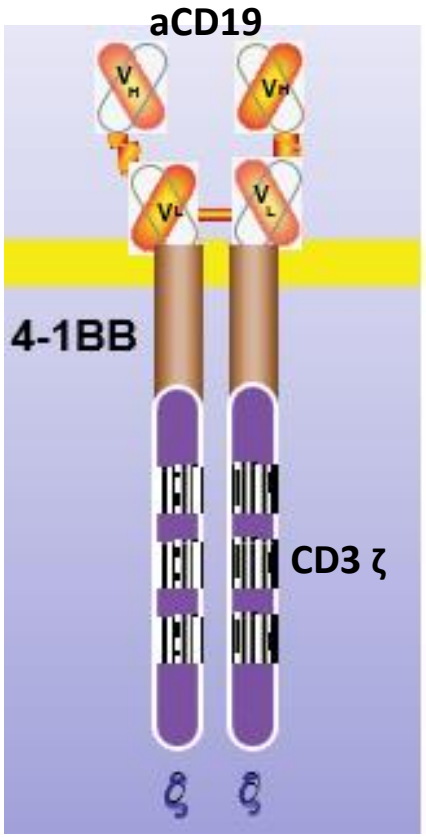
Types	N	ORR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)
B cell lymphoma	29	8 (28)	2 (7)	6 (21)	14 (48)
DLBCL	11	4 (36)	1 (9)	3 (27)	3 (27)
FL	10	4 (40)	1 (10)	3 (30)	6 (60)
T cell lymphoma	23	4 (17)	0	4 (17)	10 (43)
Mycosis fungoides	13	2 (15)	0	2 (15)	9 (69)
PTCL	5	2 (40)	0	2 (40)	0
Multiple myeloma	27	0	0	0	18 (67)
Primary mediastinal B-cell lymphoma	2	0	0	0	2 (100)

BiTE: Blinatumumab

- Combines the F(ab) of an antibody with an anti-CD3 F(ab)
- Lacks the Cf region
- Requires continuous infusions
- Shown considerable activity in:
    - Follicular NHL
    - DLBCL
    - ALL



Chimeric Antigen Receptor for CD19 (CTL019)



Extracellular domain

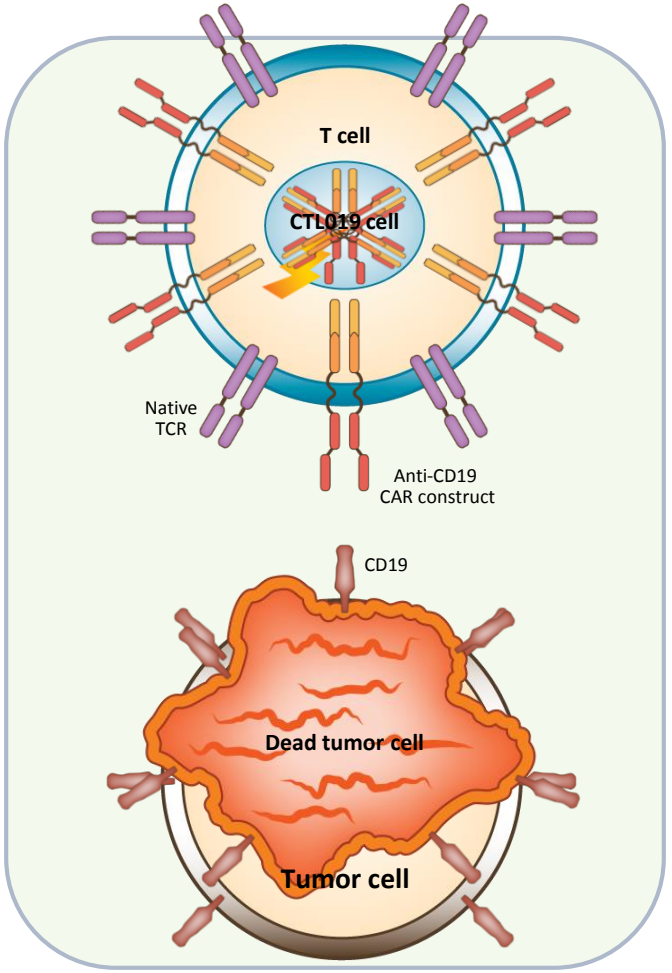
- FMC63 **mouse** hybridoma derivative

Intracellular domain

- Fusion protein

Redirecting the Specificity of T cells

- Gene transfer technology stably expresses CARs on T cells[1,2]
- CAR T cell therapy takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner[1,3]
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells[3]
- **T cells are *non-cross resistant* to chemotherapy**



1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
2. Hollyman D, et al. *J Immunother.* 2009;32:169-180.
3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

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CAR T-cell therapies in DLBCL

Efficacy and safety

	CTL019[1]	KTE-C19[2,3]		JCAR017[4,5]
Disease state	r/r DLBCL	r/r DLBCL	r/r TFL/PMBCL	r/r DLBCL, NOS, tDLBCL, FL3B
Pts treated, n	85	77	24	28
Follow-up, median	NR	8.7 mo		NR
Efficacy				
ORR (best response)	59%	82%	83%	80%[a]
CR (best response)	**43%**	**54%**	**71%**	**60%[a]**
CR (3 months)	37%	NR	NR	45%
CR (6 months)	NR	31%	50%	NR
Safety				
CRS	31% grade 1/2; 26% grade 3/4	13% grade ≥3		36% grade 1/2; 0% grade 3/4
Neurotoxicity	13% grade 3/4	28% grade ≥3		4% grade 1/2; 14% grade 3/4

[a]20 pts with DLBCL were evaluated for efficacy.

CR, complete response; CRS, cytokine release syndrome; NR, not reported; ORR, overall response rate.

1. Schuster, SJ, et al. ICML 2017 [abstract 007]. 2. Locke FL, et al. AACR 2017 [abstract CT019]; 3. Locke FL, et al. ASCO 2017 [abstract 7512]; 4. Abramson JS, et al. *Blood*. 2016;128(22) [abstract 4192]; 5. Abramson JS, et al. ASCO 2017 [abstract 7513].

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CAR T-cell therapies in DLBCL

UPENN Single Institution Study

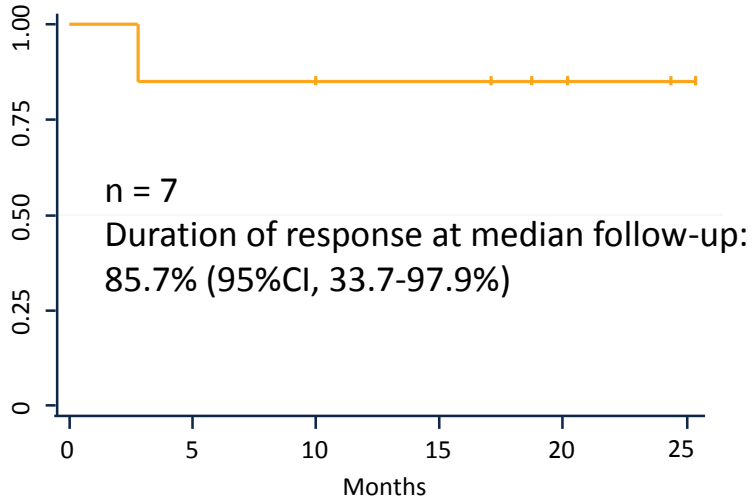
- Results from a single-center, phase 2 study at the University of Pennsylvania showed durable remissions with a single infusion of CTL019 in r/r DLBCL (Cohort A)[1,2]
  - No patient in CR at 6 months has relapsed (median follow-up, 23.3 months)

Response Rates (N = 15)

	Month 3	Month 6
ORR	7 (47%)	7 (47%)
CR	3 (20%)	6 (40%)
PR	4 (27%)	1 (7%)

CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response.

Duration of Response (n = 7; CR + PR)



1. Schuster SJ, et al. *Blood*. 2015;126(23):[abstract 183].
2. Schuster SJ, et al. *Blood*. 2016;128(22):[abstract 3026].

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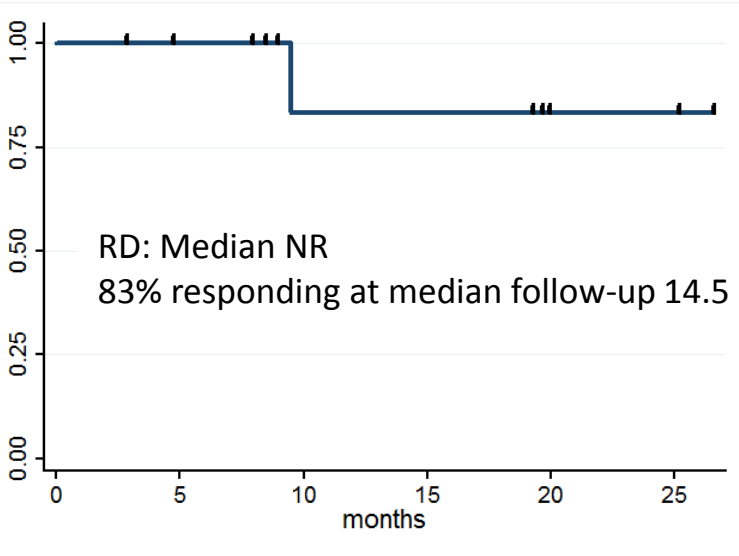
CAR T-cell therapies in FL

UPENN Single Institution Study

FL: ORR at 3 mo. 79% (N = 14)	FL: Best Response Rate 79% (N = 14)
- CR: 7 (50%)	- CR: 10 (71%)
- PR: 4	- PR: 1
- PD: 3	- PD: 3

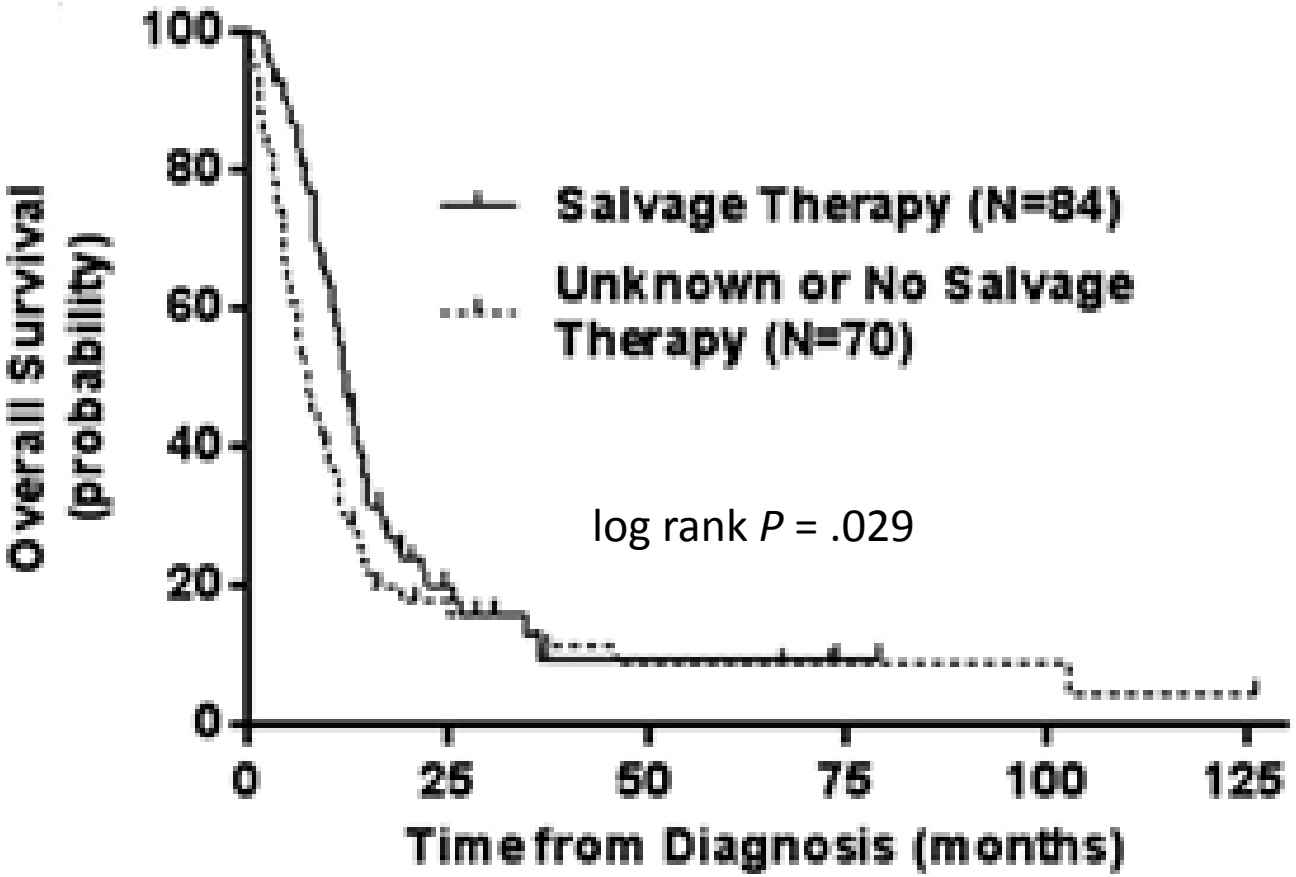
- 3 patients with PRs by anatomic criteria at 3 months converted to CRs by 6 months
- 1 patient with PR at 3 months who remained in PR at 6 and 9 months had PD

Duration of Response (n = 11; CR + PR)



Chong EA, et al. *Blood*. 2016;128:abstract1100.

Survival for relapsed/refractory double-hit lymphoma: salvage therapy vs palliative care



Petrich AM, et al. *Blood*. 2014;124:2354-2361.

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Leukemia

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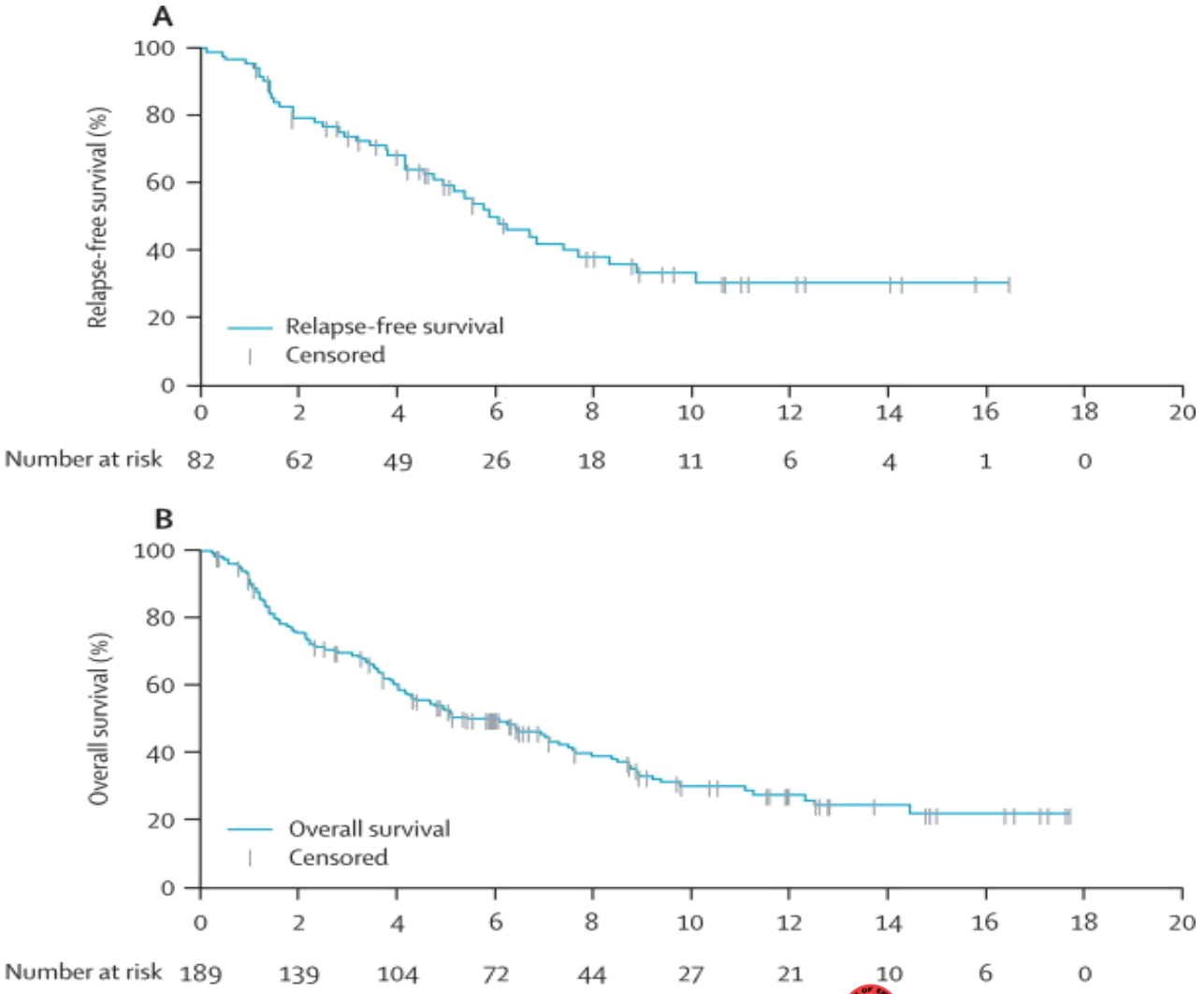
Blinatumumab in ALL



Topp, Max S et al., The Lancet Oncology , Volume 16 , Issue 1 , 57 - 66

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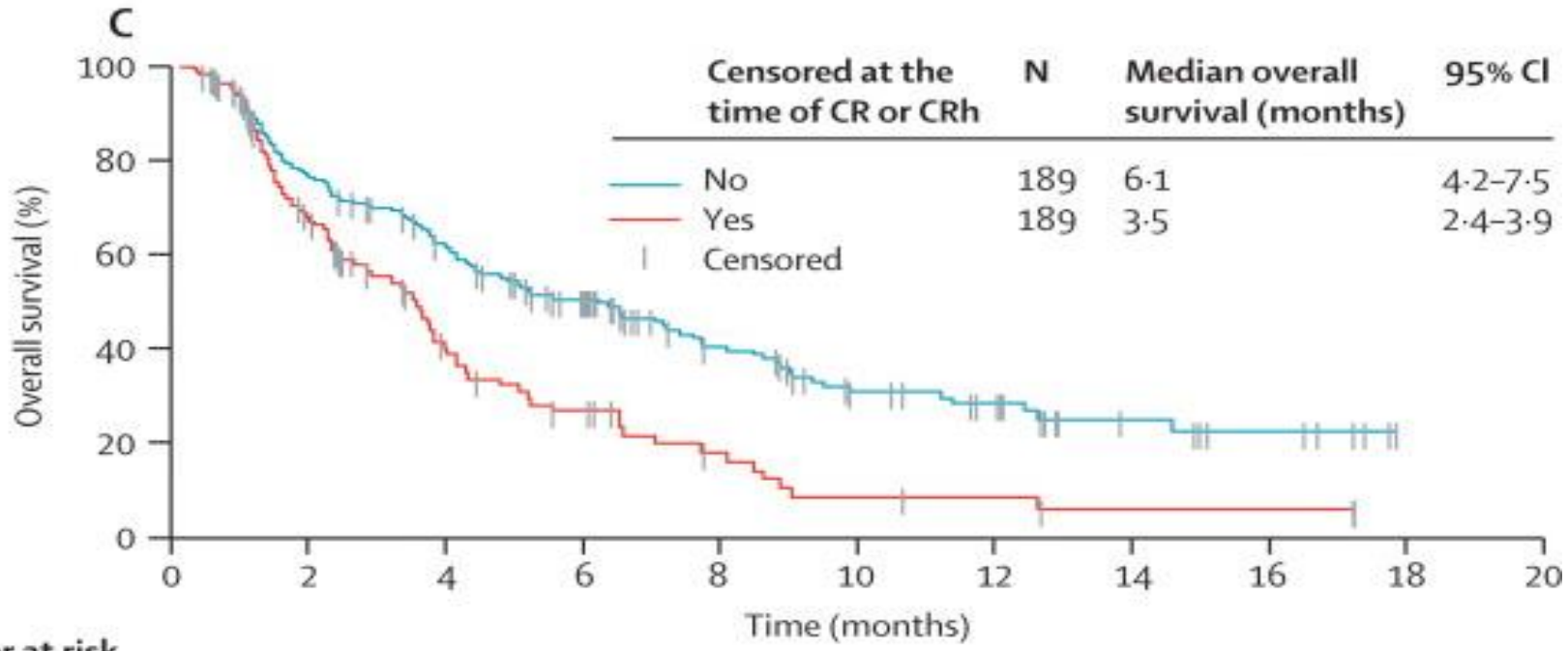
Blinatumumab in ALL



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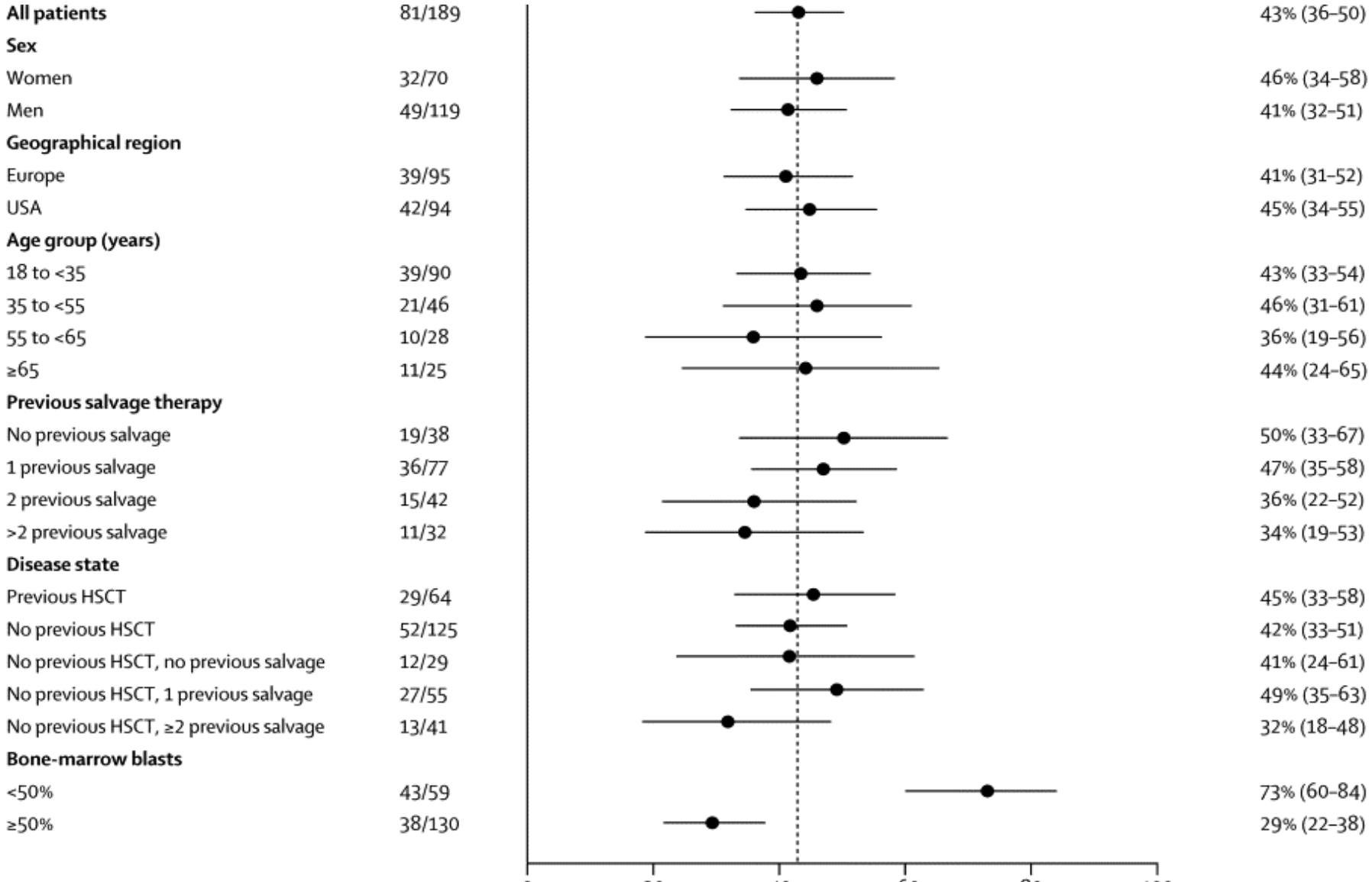
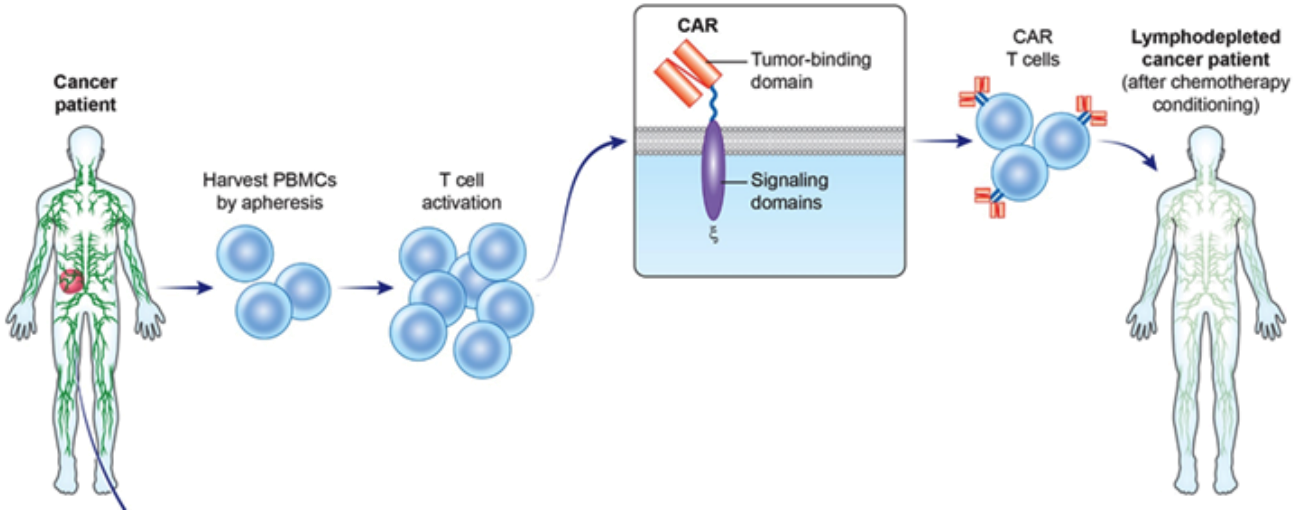
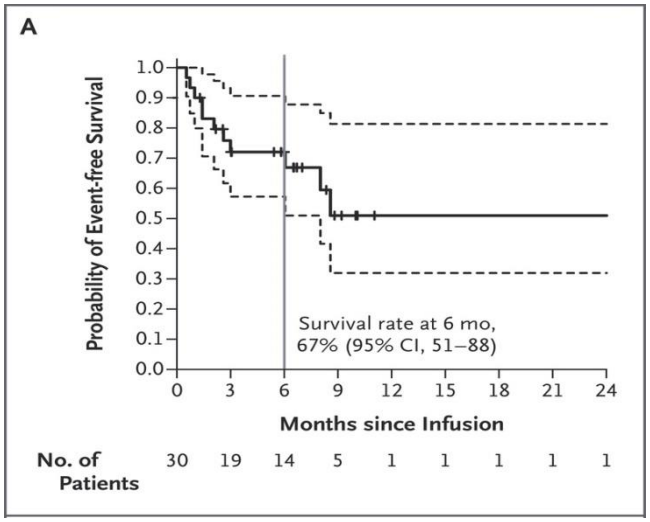
Blinatumumab in ALL

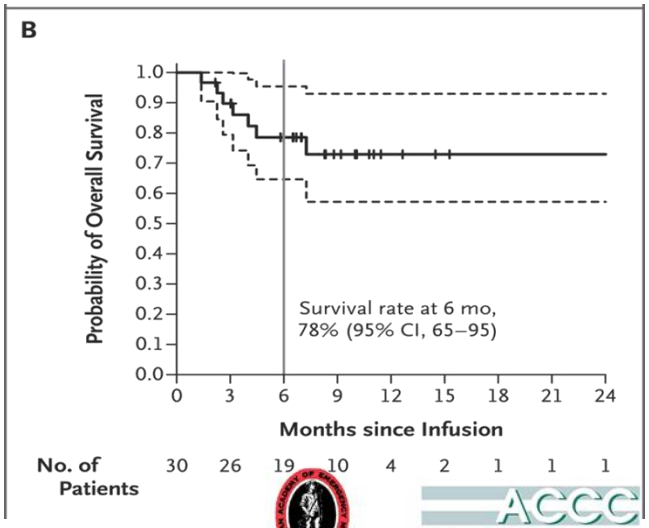


CD-19 CAR-T in ALL

Probability of Event-Free and Overall Survival at Six Months.







Maude SL et al. N Engl J Med 2014;371:1507-1517.

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Antigen-specific Approaches in ALL

Technology:	CART	ADC	BiTE
Example	CART-19	Inotuzumab (anti-CD22 + toxin)	Blinatumumab (anti-CD3/CD19)
Dosing	One infusion	Every 3 weeks	Continuous 28 days
Complete Response	90%	19%	66%
Survival	78% 6 mos OS	5-6 months median	9 mos median
Major toxicity	Cytokine release	Hepatotoxicity	Cytokine release
Antigen loss relapse?	Yes	No	Yes
Challenges	Complex manufacturing, individualized	Lower response rates	Burdensome infusion

Gill Immunol Rev Dec 2014

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Myeloma

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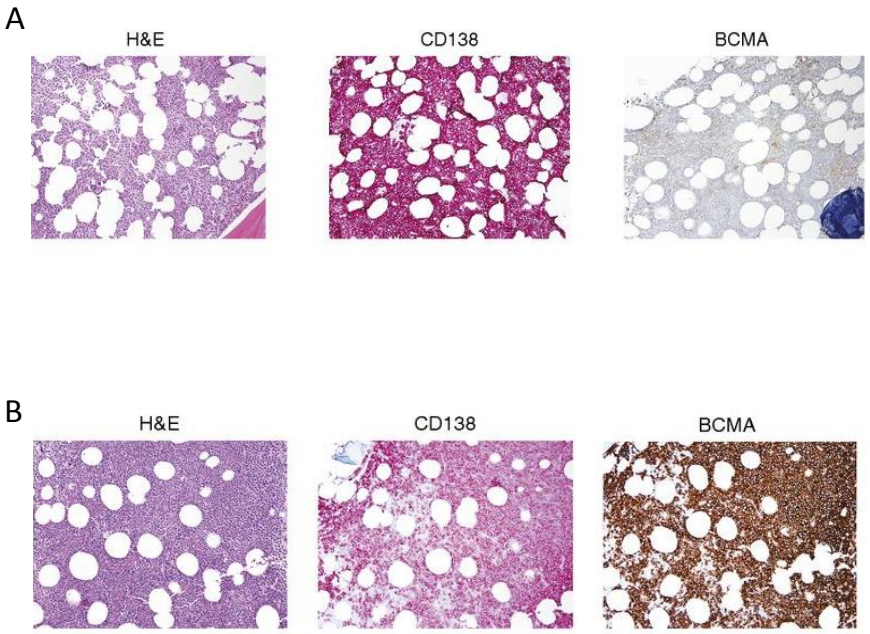
Case Study

Two patients with multiply relapsed myeloma considering participation in a BCMA CAR-T cell trial.

Enrollment BM biopsy shows the following staining



Syed Abbas Ali et al. Blood 2016;128:1688-1700

Case Study

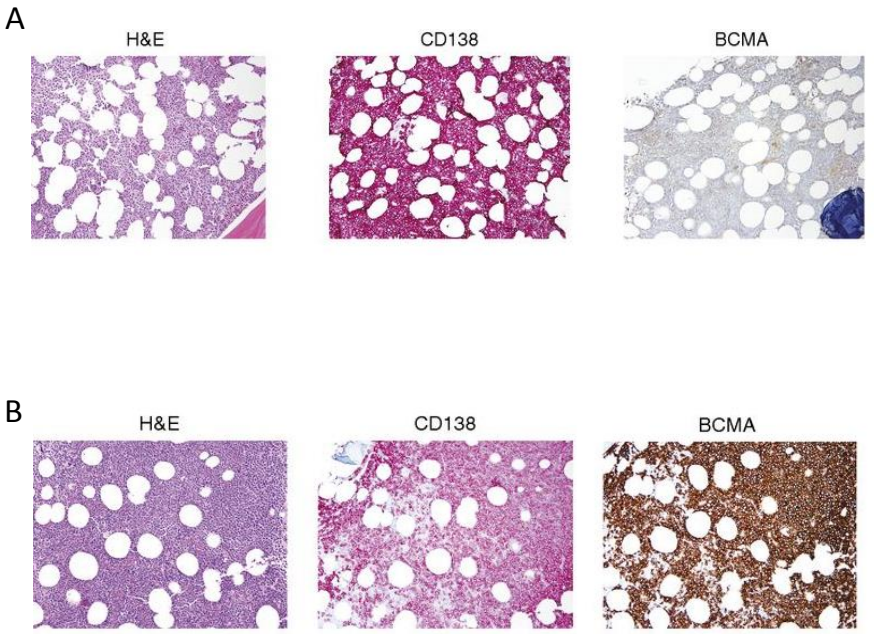
Which of the following statements is true?

A.Pt A more likely to respond to BCMA CAR-T cell therapy

B.Pt B more likely to suffer from cytokine release syndrome (CRS) following BCMA CAR-T cell therapy

C.CRS is independent of disease burden

D.CRS is only seen in ALL



Syed Abbas Ali et al. Blood 2016;128:1688-1700

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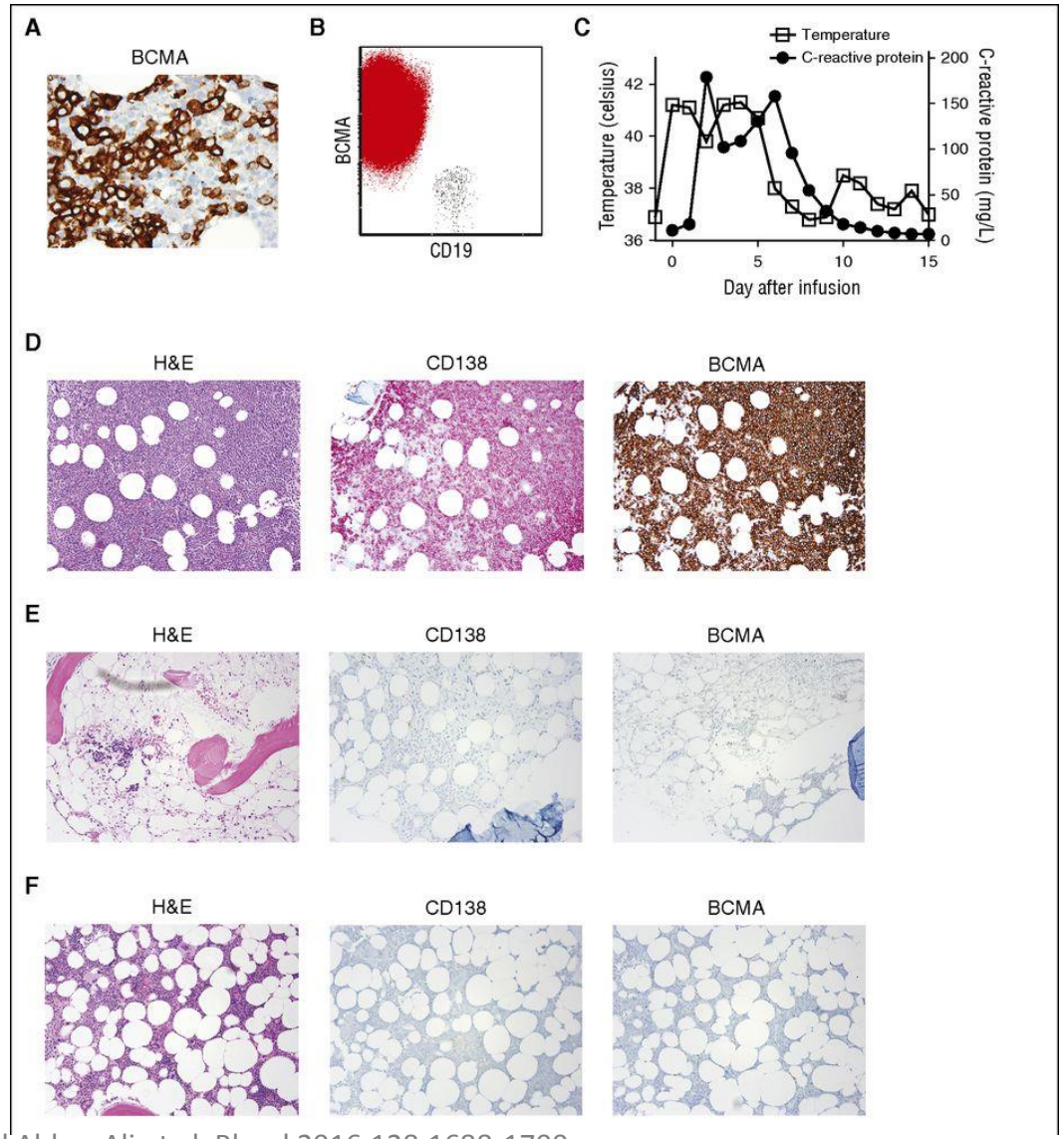
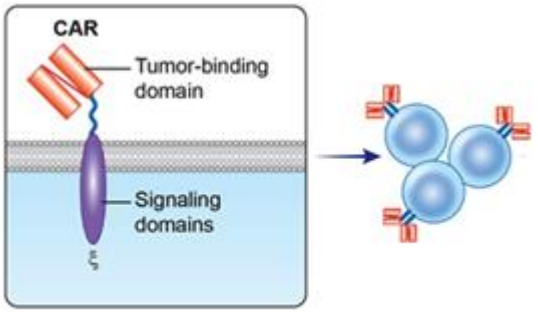
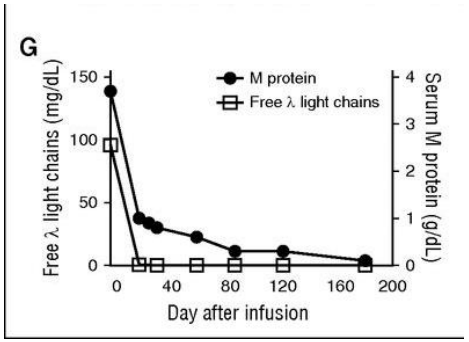
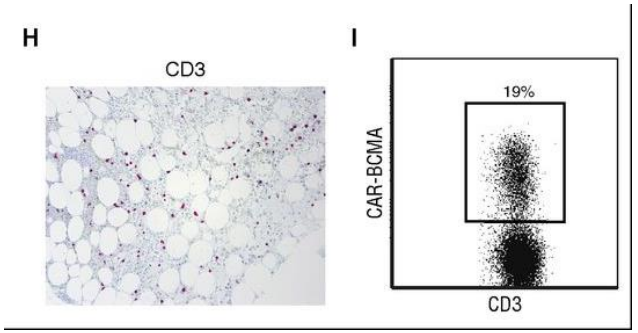
Efficacy of BCMA CAR-T in Myeloma









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Syed Abbas Ali et al. Blood 2016;128:1688-1700

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Types of Vaccines Used in Myeloma

- Non-Antigen Specific
  - Attenuated measles
  - Whole cell - GM-CSF
  - Dendritic – tumor fusions
- Antigen Specific
  - Idiotype: RNA, DNA, protein
  - Pulsed dendritic cells
  - Tumor-specific peptides

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Resources:

Boyiadzis *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:90
DOI 10.1186/s40425-016-0188-z

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of hematologic malignancies: multiple myeloma, lymphoma, and acute leukemia

Michael Boyiadzis[1†], Michael R. Bishop[2†], Rafat Abonour[3], Kenneth C. Anderson[4], Stephen M. Ansell[5], David Avigan[6], Lisa Barbarotta[7], Austin John Barrett[8], Koen Van Besien[9], P. Leif Bergsagel[10], Ivan Borrello[11], Joshua Brody[12], Jill Brufsky[13], Mitchell Cairo[14], Ajai Chari[12], Adam Cohen[15], Jorge Cortes[16], Stephen J. Forman[17], Jonathan W. Friedberg[18], Ephraim J. Fuchs[19], Steven D. Gore[20], Sundar Jagannath[12], Brad S. Kahl[21], Justin Kline[22], James N. Kochenderfer[23], Larry W. Kwak[24], Ronald Levy[25], Marcos de Lima[26], Mark R. Litzow[27], Anuj Mahindra[28], Jeffrey Miller[29], Nikhil C. Munshi[30], Robert Z. Orlowski[31], John M. Pagel[32], David L. Porter[33], Stephen J. Russell[5], Karl Schwartz[34], Margaret A. Shipp[35], David Siegel[36], Richard M. Stone[4], Martin S. Tallman[37], John M. Timmerman[38], Frits Van Rhee[39], Edmund K. Waller[40], Ann Welsh[41], Michael Werner[42], Peter H. Wiernik[43] and Madhav V. Dhodapkar[44*]

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Immunotherapy case #1

Classical Hodgkin lymphoma

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Sequence of events

- 27 yr old male, diagnosed at age 21 with classical Hodgkin lymphoma
- **March 2011:** Initial presentation with n/v, weight loss, fevers, night sweats. Stage IV-B disease, high risk (4/7 on IPS)
- **March – Aug 2011:** ABVD x 6 cycles with partial response
- **Nov 2011 – Jan 2012:** ICE x 3 with partial response but persistent disease on PET. Autologous PBSC collection
- **Feb – March 2012:** GVD x 2 cycles: progression
- **March – May 2012:** COPP x 2 cycles: good PR
- **May – June 2012:** BEAM /auto HCT. July 2012: Progression
- **Aug – Nov 2012:** Brentuximab x 5 doses with good PR after 3 cycles

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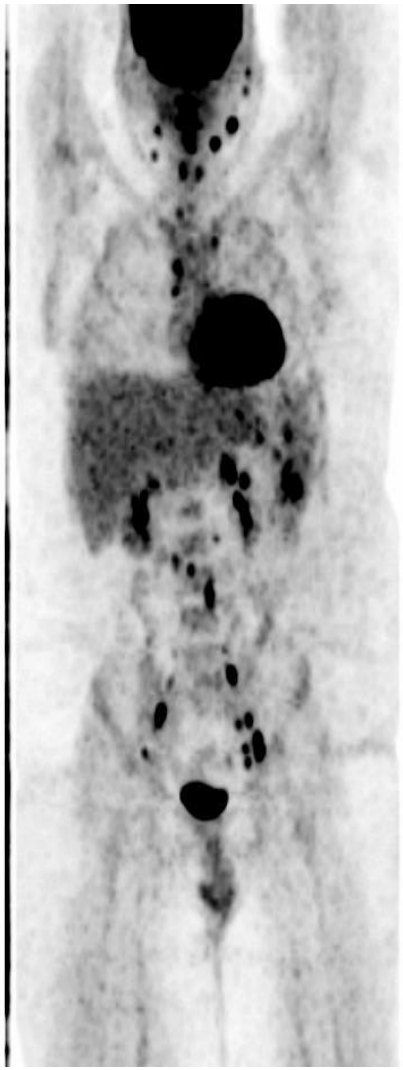
Response to brentuximab



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Sequence of events

- **Dec 2012:** RIC AlloHCT (FCR conditioning)
- **June 2013:** relapsed lymphoma AND liver GVHD. GVHD treated with sirolimus. HL retreated with brentuximab but developed severe neuropathy after 2-3 doses.
- **Oct 2014 – Dec 2014:** Lenalidomide + Bendamustine. Dec 2014: Progression, including extensive liver involvement.
- **Jan 2015:** One cycle of Gem/Cis/Dex given but severe cytopenias limited further treatment.
- **Feb 2015:** Start nivolumab.
- **May 2015:** Complete remisison by PET. Continued nivolumab through remainder of 2015 and all of 2016.
- **Oct 2015:** Vitiligo. Start nb-UVB treatment
- **Oct 2016:** Some progression of disease. Added lenalidomide 10 mg po qd
- **Feb 2017:** Overall improvement in disease burden. Continue Lenalidomide + nivolumab

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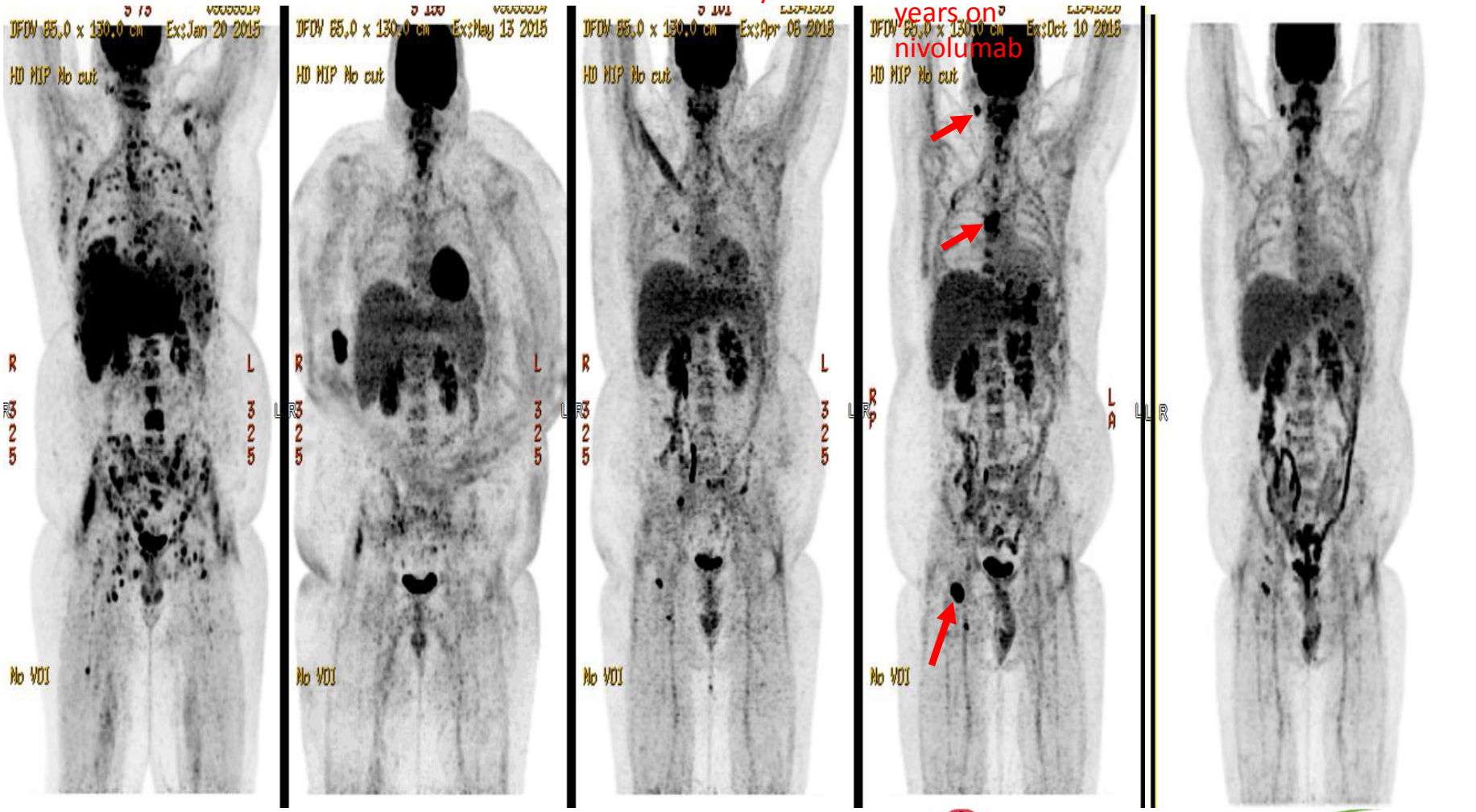
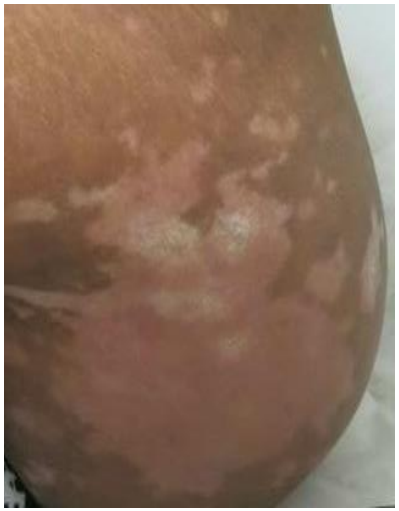
Response to nivolumab



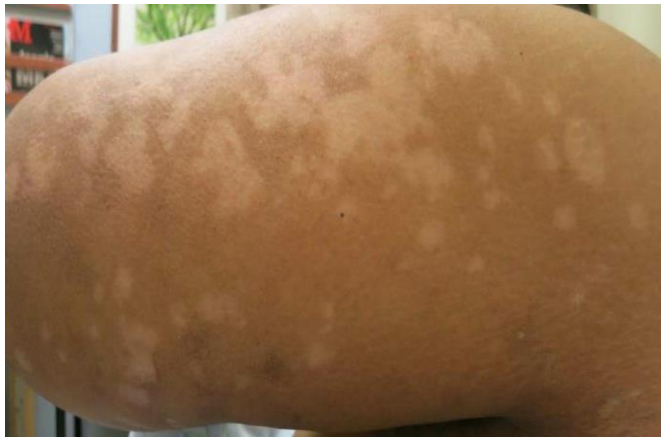
(Despite clear progression on a len- based regimen in the

Oct 2015 (8 months on nivolumab)

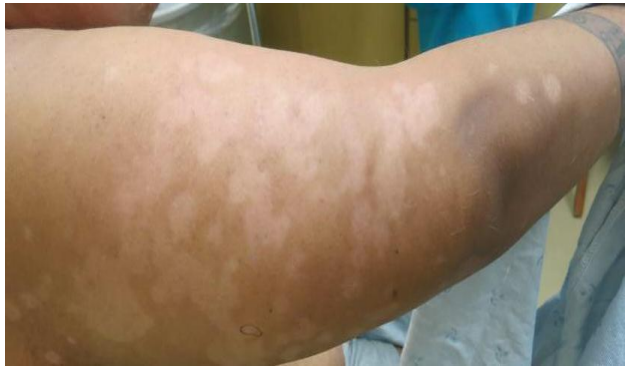
Flank

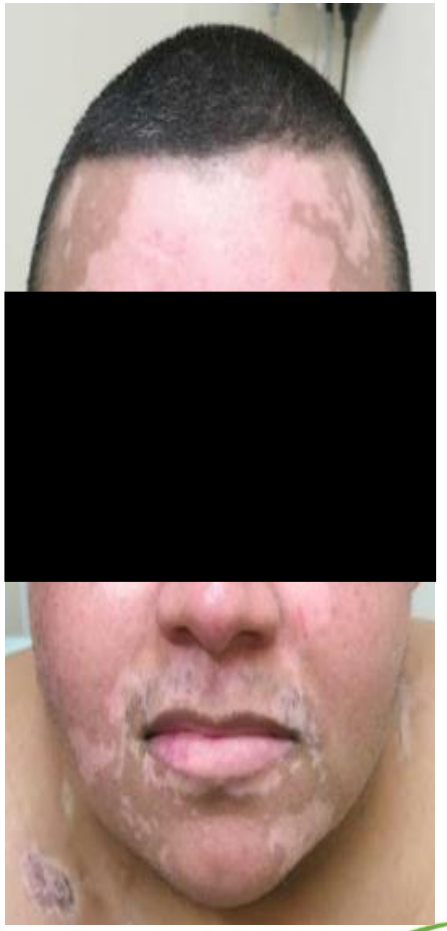


Left arm



Right arm





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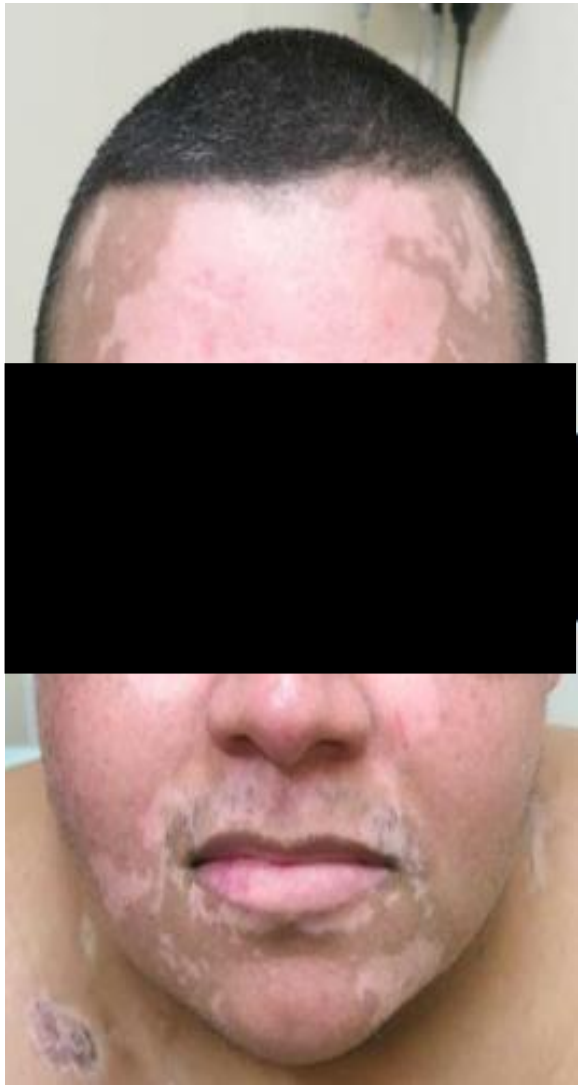
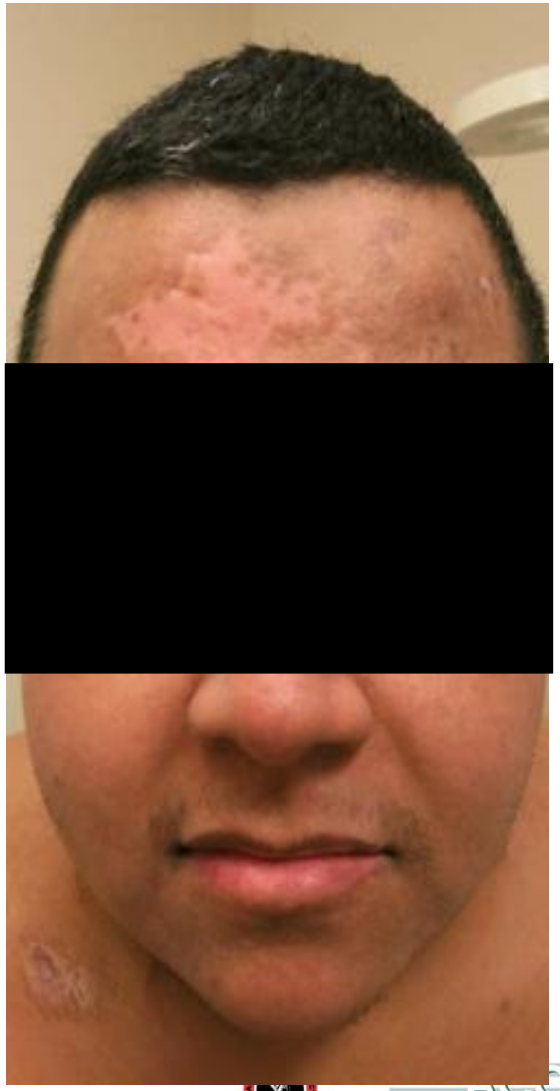
Oct 2015



Aug 2016
(after nbUVB therapy)



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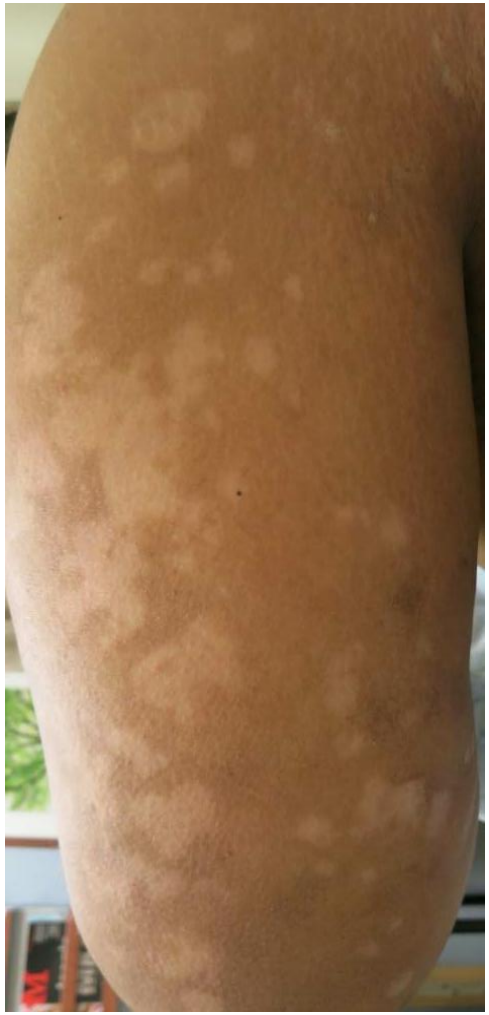
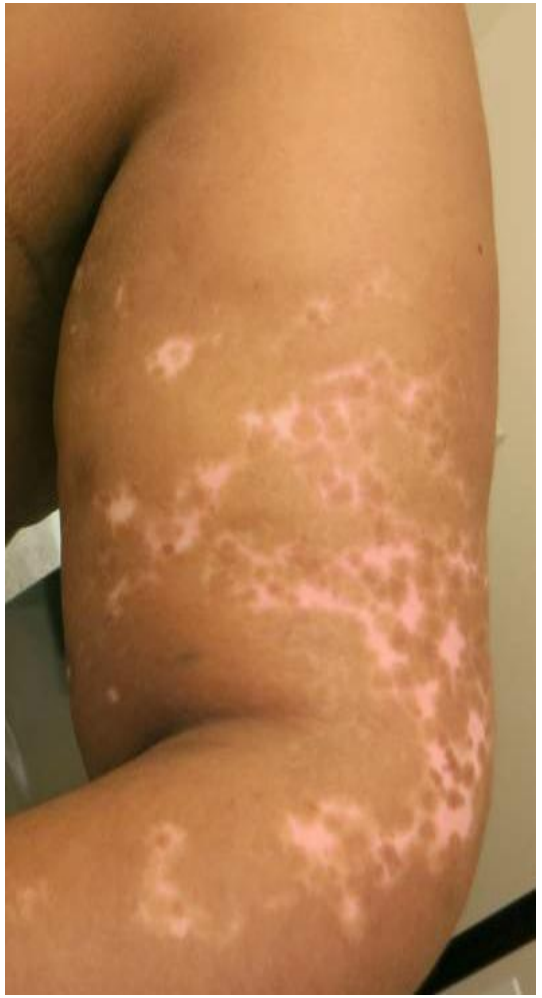
Oct 2015



Aug 2016
(after nbUVB therapy)



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Immunotherapy case #2

Classical Hodgkin lymphoma

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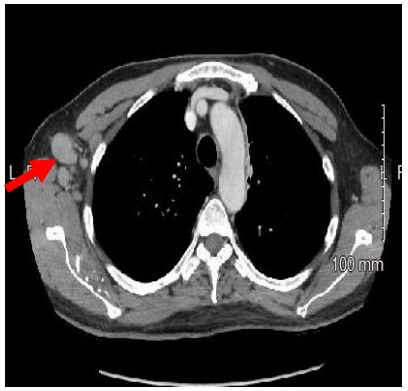
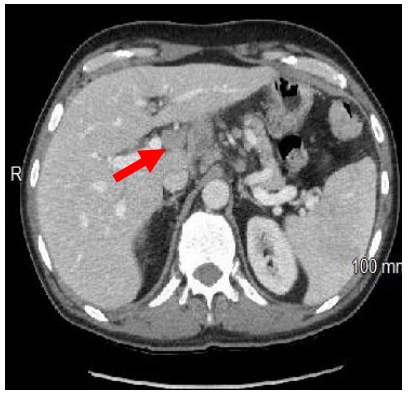
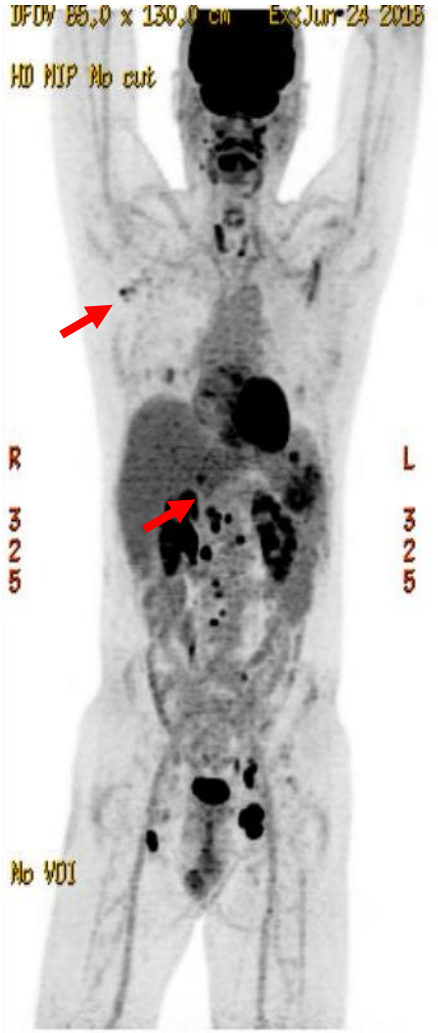
44 yr old male with cHL s/p multiple relapses, autoHCT, alloHCT, DLI, RT, brentuximab, Len, benda, TGR-1202…

Prior to nivolumab

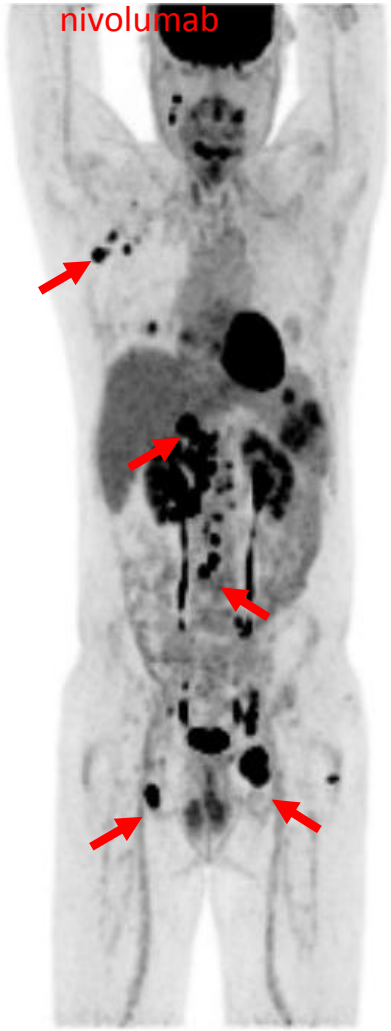




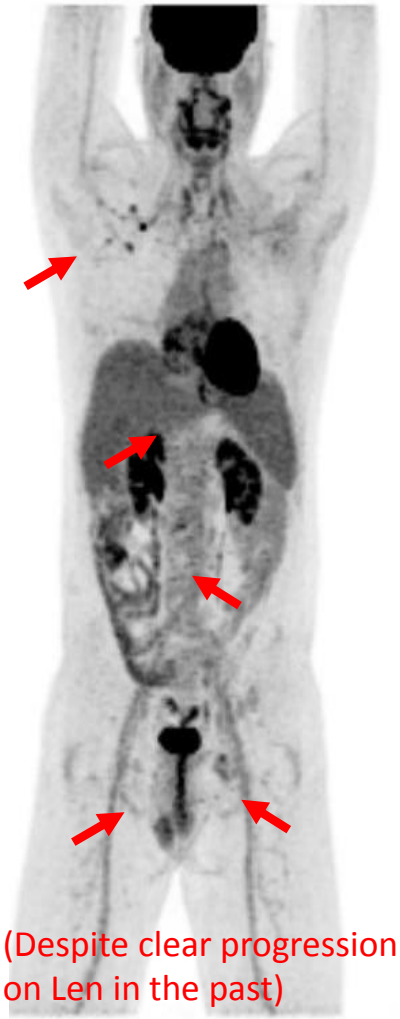
Response to nivolumab



Starting to progress, after 10 mo on nivolumab



6 months after adding lenalidomide 10mg QD



(Despite clear progression on Len in the past)

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Immunotherapy case #3

Low grade B-cell non-Hodgkin lymphoma

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Sequence of events

- 82 yr old female, noted right submandibular mass.
- CT neck showed right parotid mass. CT CAP showed diffuse adenopathy
- right submandibular needle biopsy: extranodal marginal zone lymphoma
- She had some fatigue and abdominal bloating along with some night sweats, so treatment was recommended
- Despite large disease burden, given her age, treated with single agent rituximab (as opposed to rituximab + chemotherapy), followed by maintenance rituximab (one dose every 8 weeks for 2 years)

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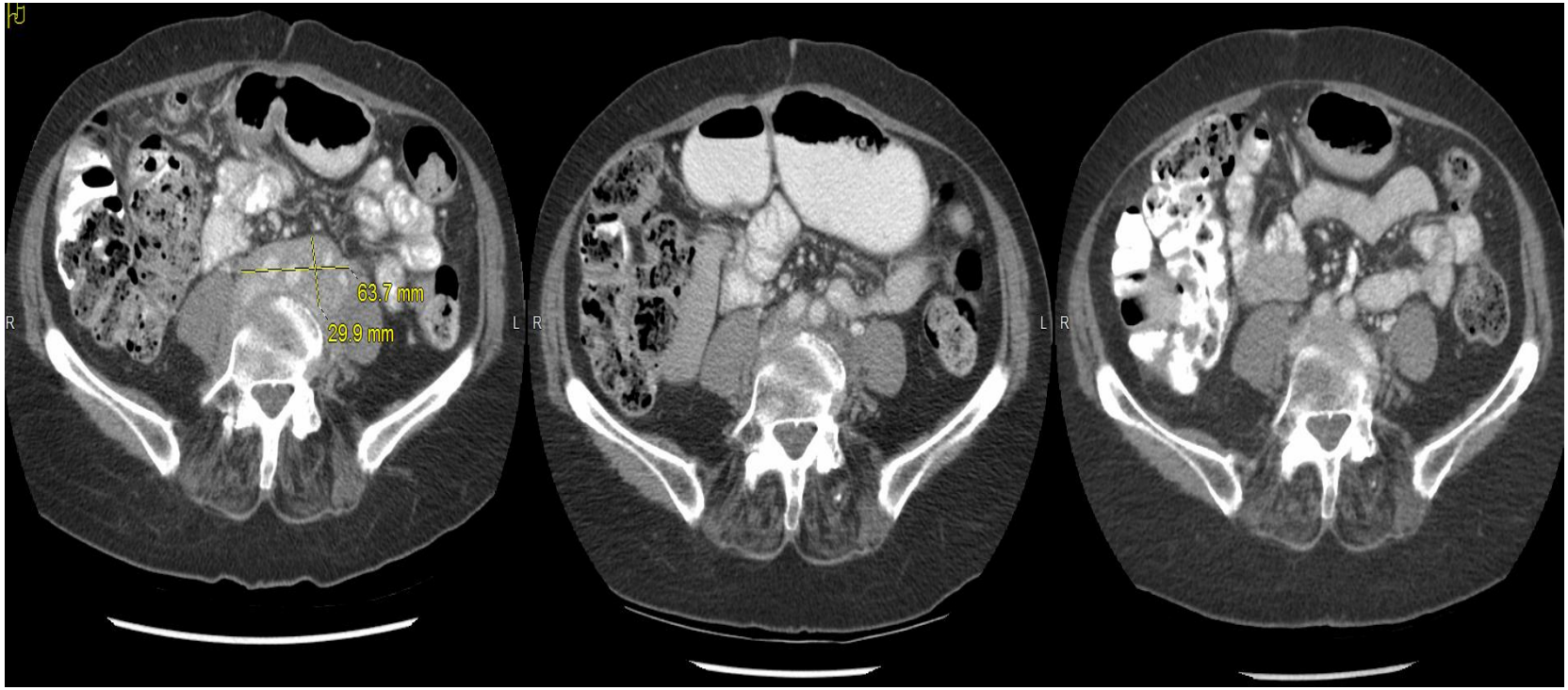
Pre-treatment

After 4 weekly doses of rituximab

After 2 years of maintenance rituximab



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Pre-treatment

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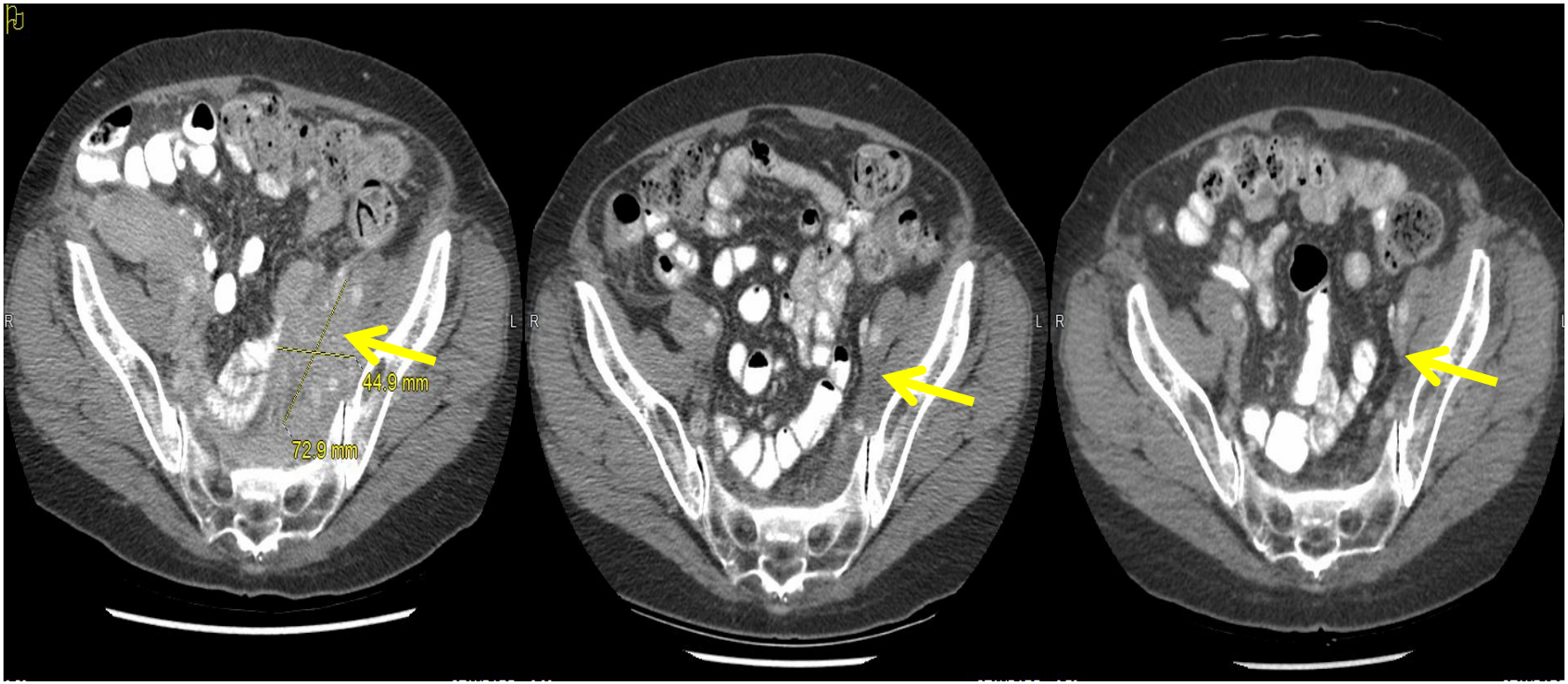
After 2 years of maintenance rituximab



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Pre-treatment

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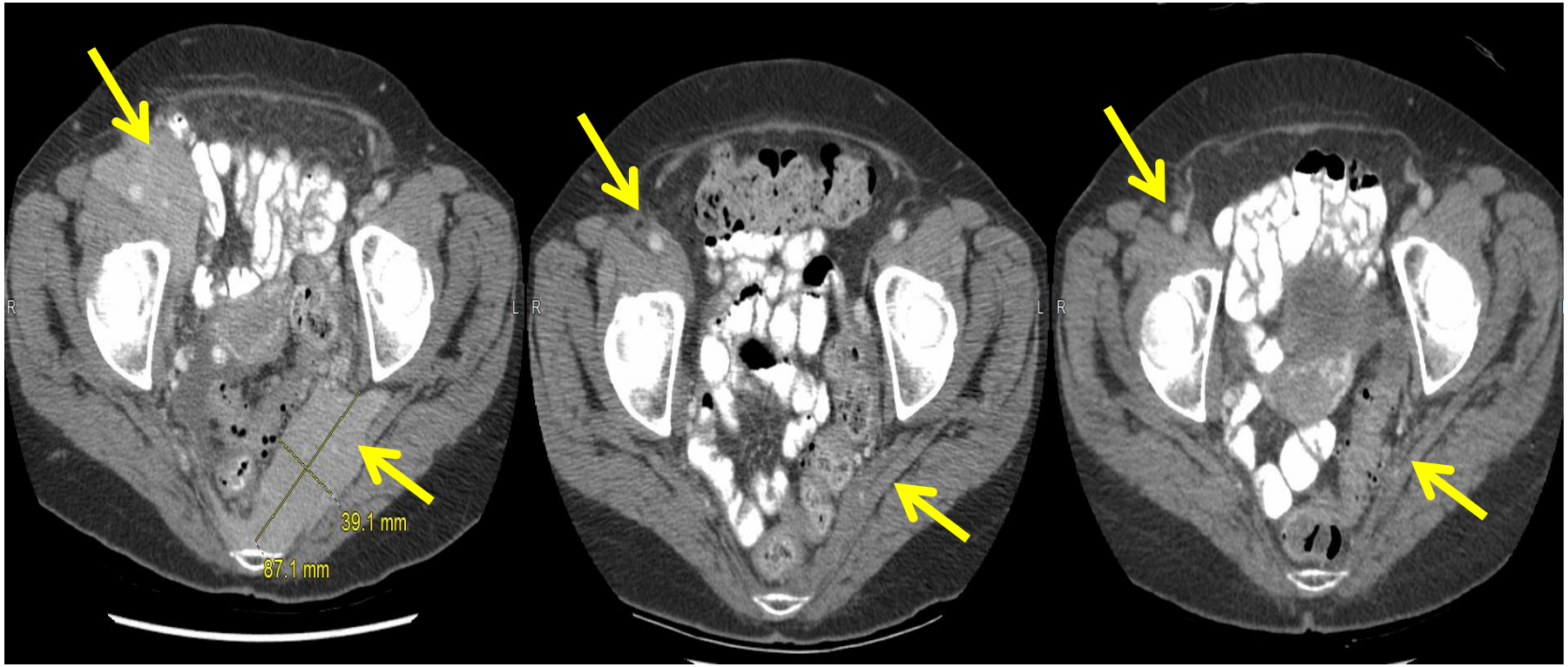
After 2 years of maintenance rituximab



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