Evolving role of immunotherapy in lymphomas

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Disclosures

- Research Funding to Institution
  - Seagen, BMS, Pharmacyclics, Pfizer
- Consultancy/Advisory Board
  - Seagen, BMS, Merck, Pfizer,
- Speaker Bureau:
  - Seagen, Merck

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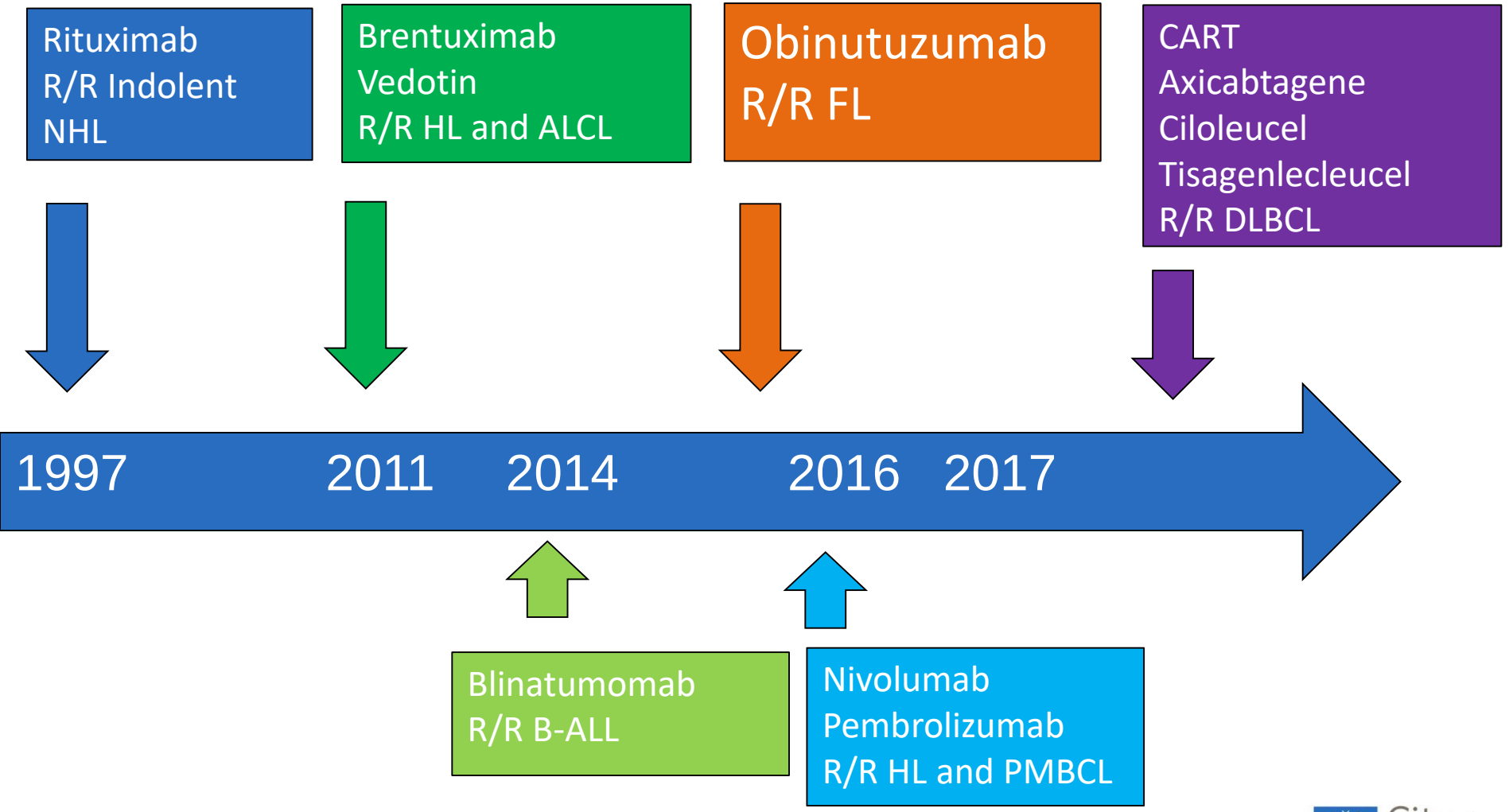
Classes

- Monoclonal antibodies
- Antibody drug conjugates (ADC)
- Checkpoint inhibitors
- Bispecific antibodies
- Chimeric antigen receptor (CAR) T cells

Immunotherapy Landscape



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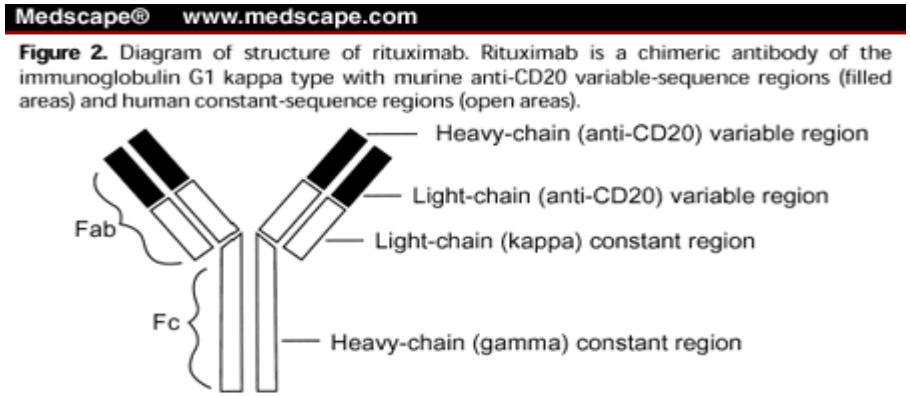
Rituximab

- Chimeric type I anti CD 20 monoclonal ab



- GELA trial in DLBCL
  - RCHOP vs. CHOP, OS survival advantage of 47%

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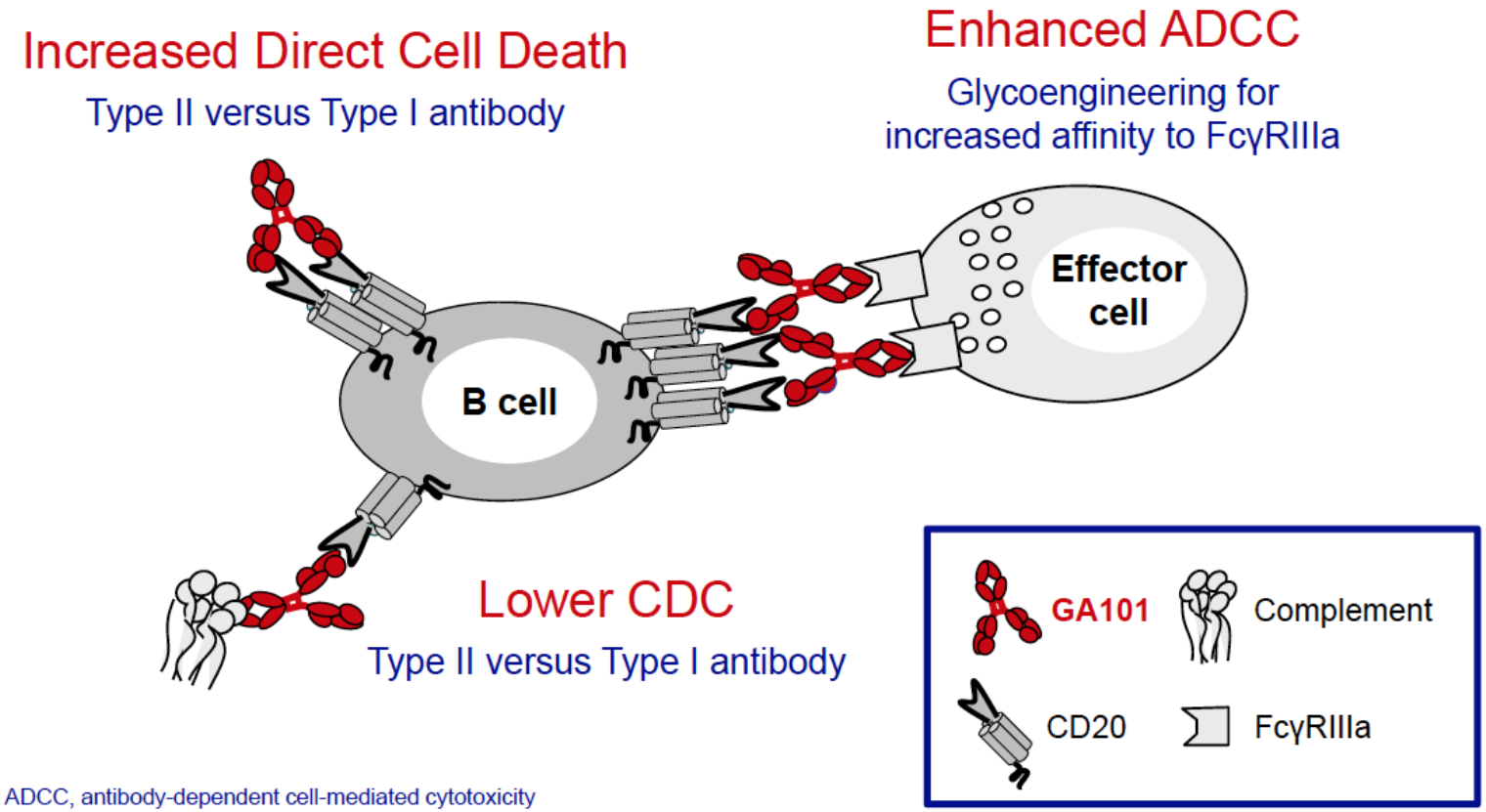
Obinutuzumab

GA101: Mechanisms of action



ADCC, antibody-dependent cell-mediated cytotoxicity
CDC, complement-dependent cytotoxicity
Mössner E, *et al*. *Blood* 2010; 115:4393–4402

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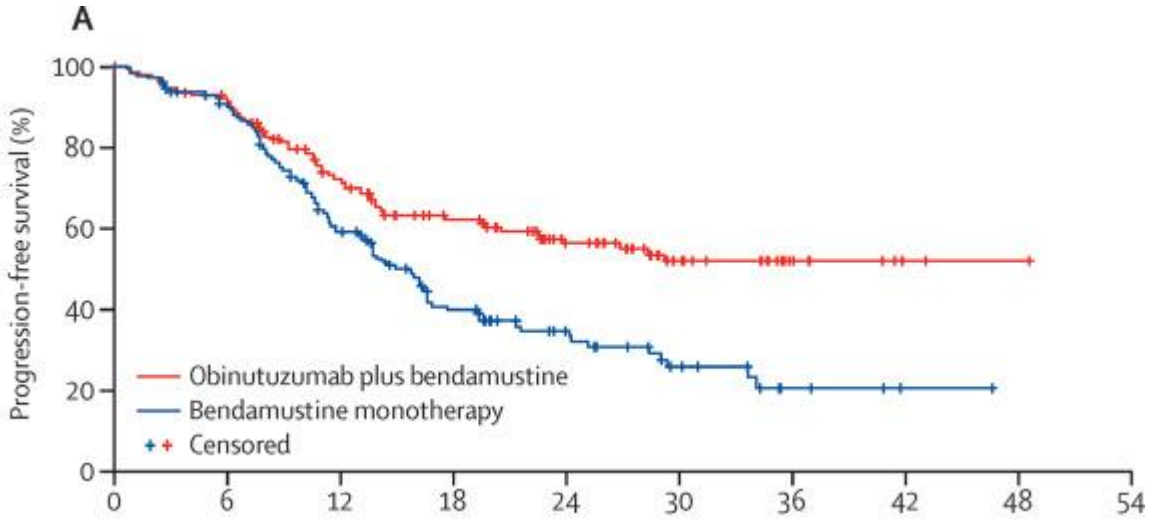
Obinutuzumab (Gadolin)

- Randomized Phase III in rituximab refractory Indolent NHL
- R-bendamustine vs O-bendamustine plus O maintenance
- PFS benefit with O vs. R



Sehn LH et al. Lancet Oncol 2016

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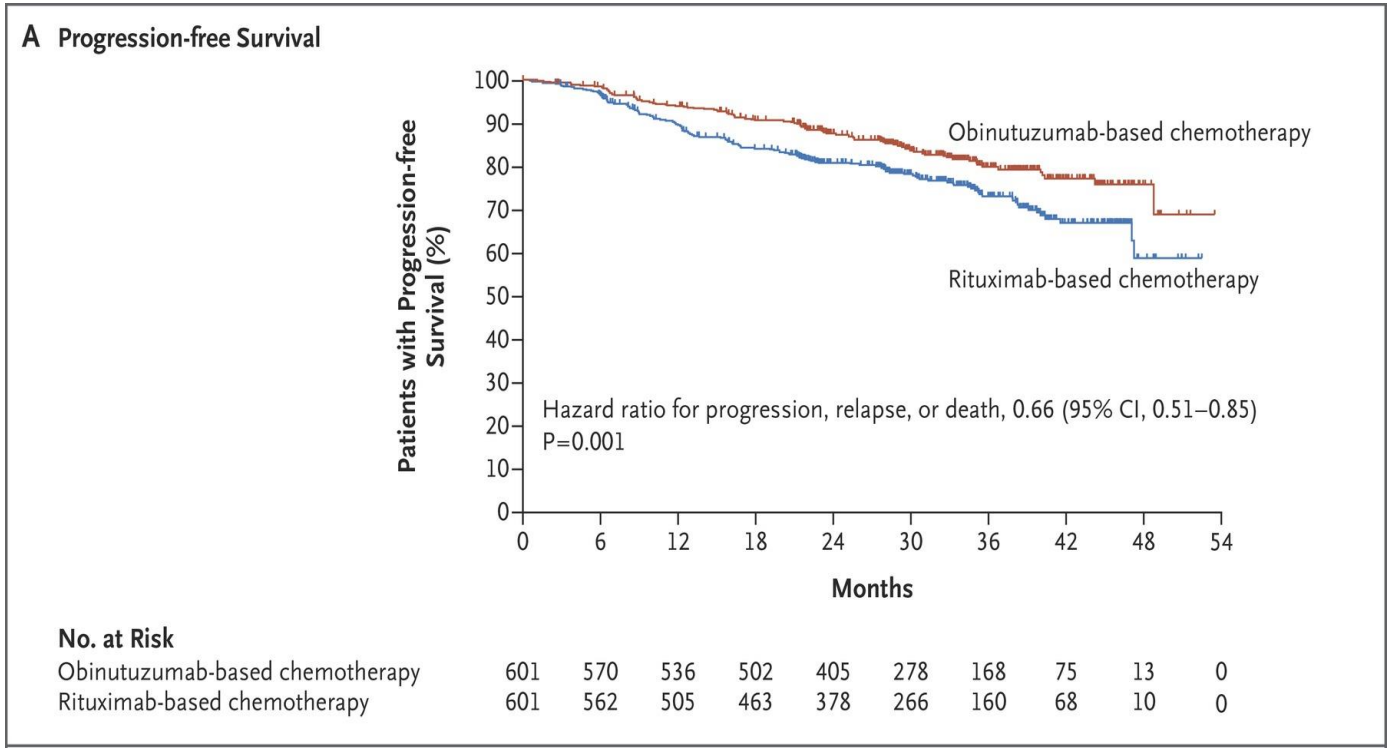
Obinutuzumab (Gallium)

- Randomized Phase III in untreated FL
- R-bendamustine vs O-bendamustine plus O maintenance
- PFS benefit with O vs. R (3 yr PFS 80% vs. 73.3%, p=0.01)



Marcus R et al. NEJM 2017

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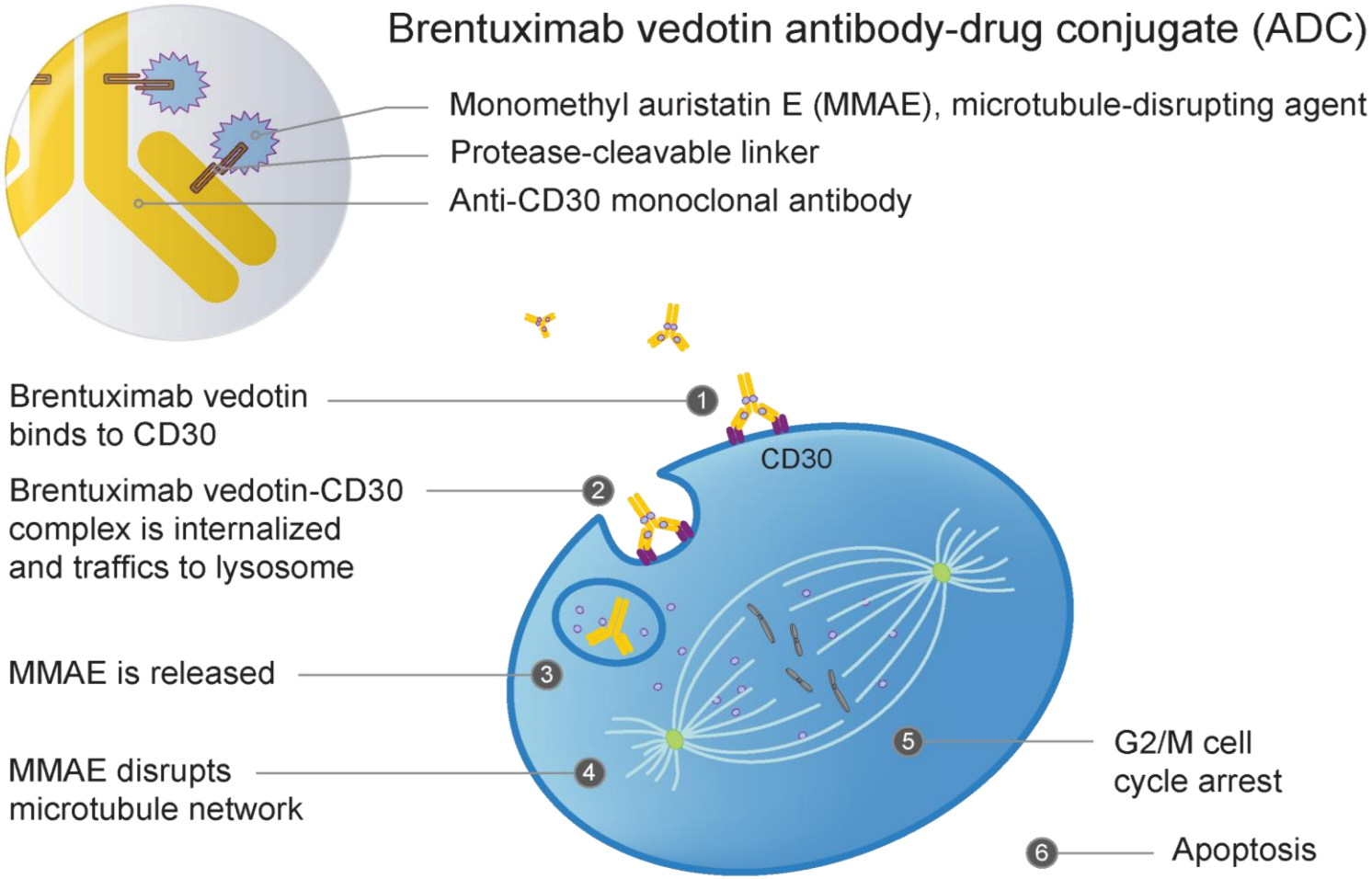
Brentuximab Vedotin



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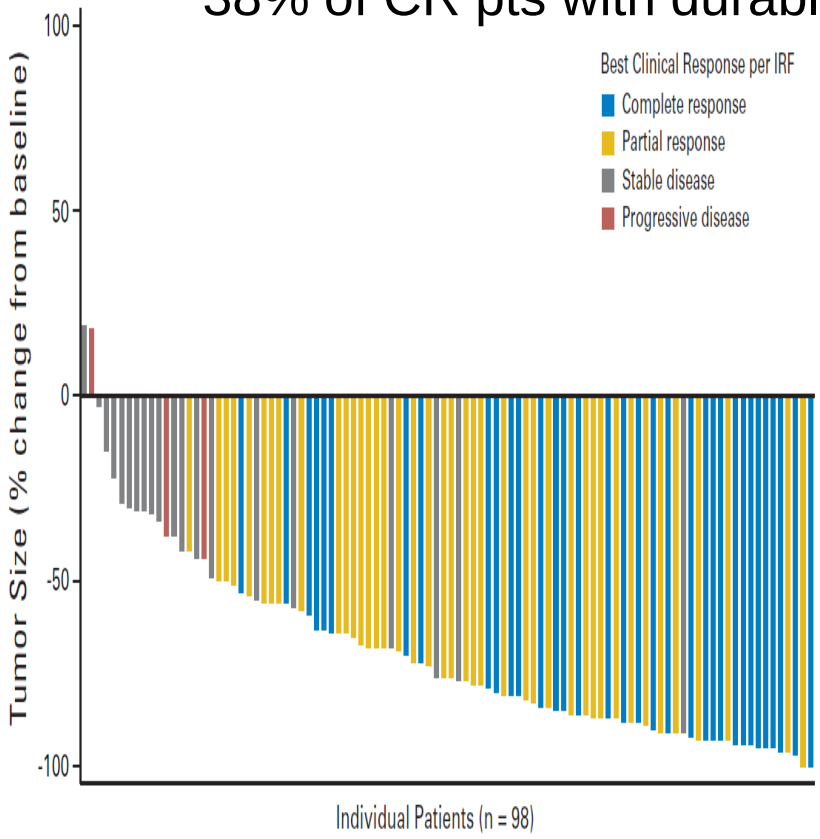
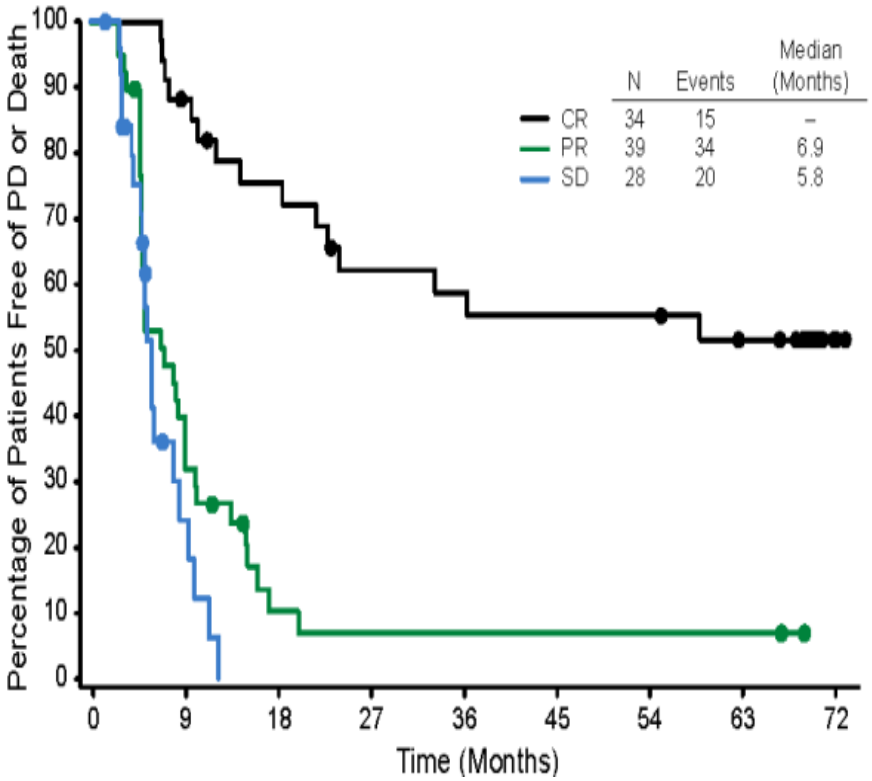
Brentuximab vedotin in Rel/Ref HL

ORR 72% CR 33%
38% of CR pts with durable remission





Younes et al. *JCO* 2012
Chen et al, *Blood 2016*

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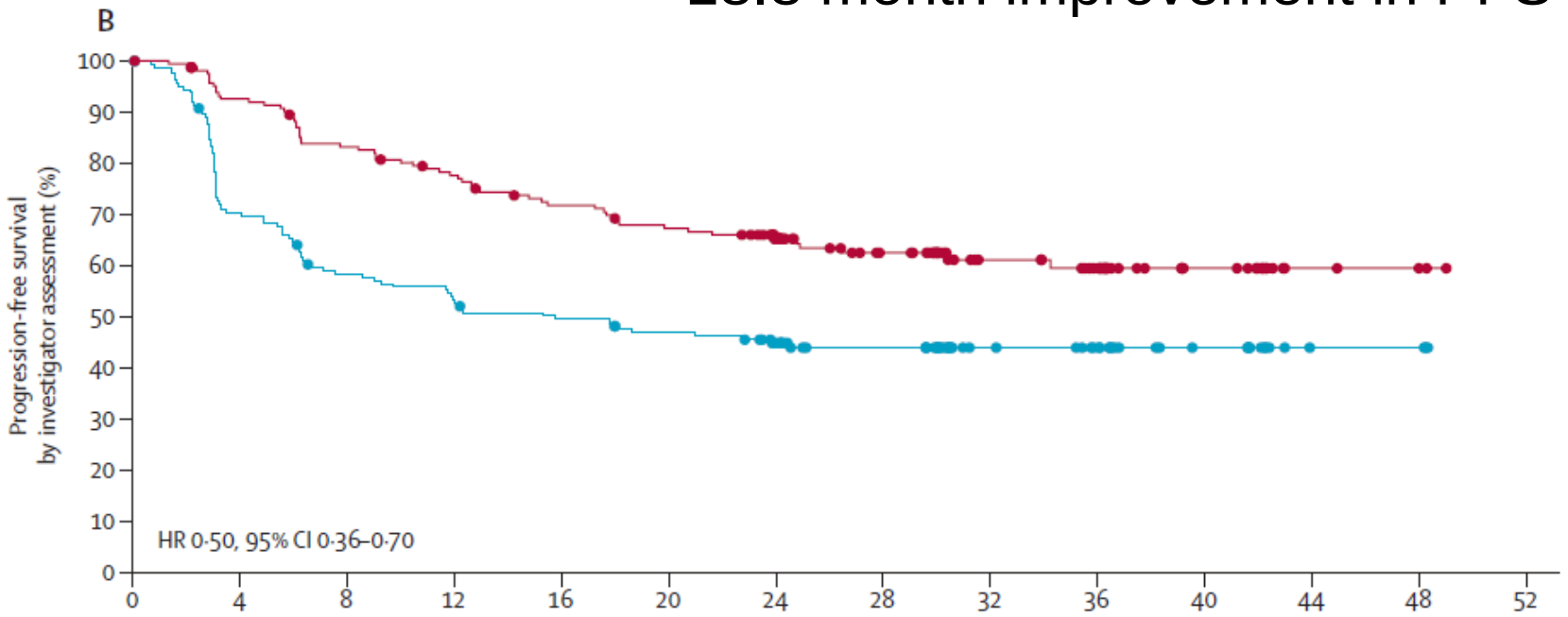
AETHERA: BV consolidation prolongs post-ASCT PFS for rel/ref HL

18.8 month improvement in PFS



Moskowitz C et al. Lancet Oncol 2015

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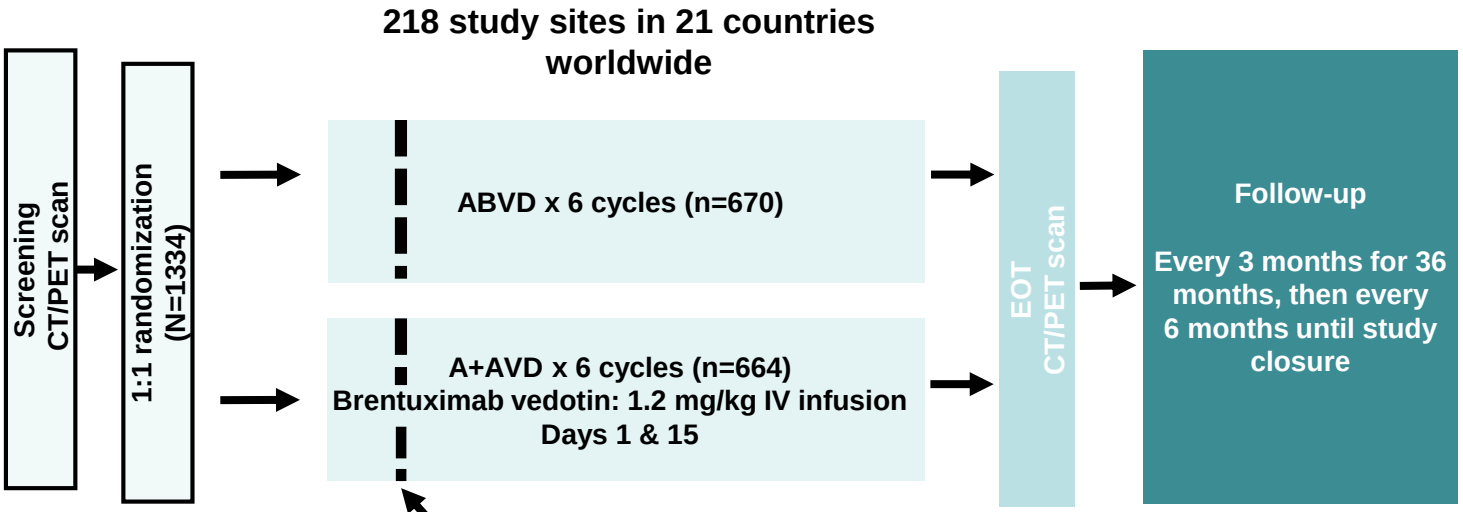
ECHELON-1: Randomized, phase 3 study of A+AVD versus ABVD in patients with newly diagnosed advanced cHL



- **Inclusion criteria**
  - cHL stage
    III or IV
  - ECOG PS
    0, 1 or 2
  - Age
    ≥18 years
  - Measurable disease
  - Adequate liver and renal function

End-of-Cycle-2 PET scan

- Deauville 5; could receive alternate therapy per physician's choice (not a modified PFS event)

cHL, classic Hodgkin lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; PFS, progression-free survival

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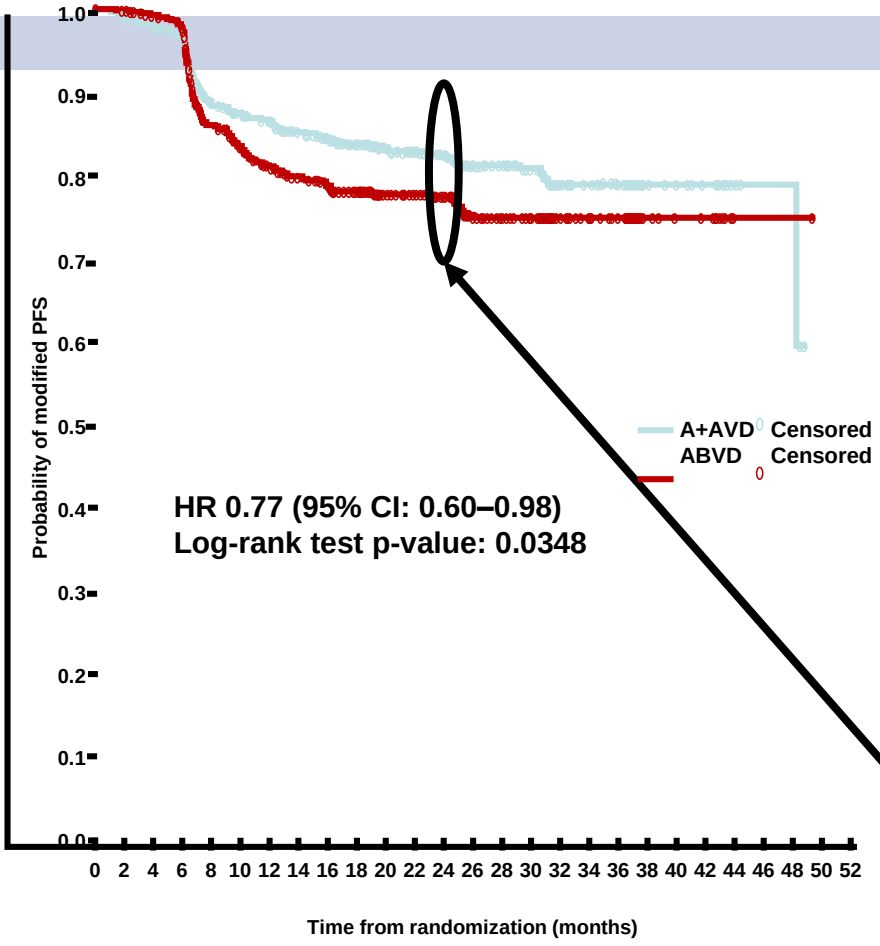
Modified PFS per independent review



No. of patients at risk:

A+AVD	664	640	623	606	544	530	516	496	474	447	350	334	311	200	187	174	99	85	77	27	24	21	6	4	4	0	0
ABVD	670	644	626	613	522	496	476	459	439	415	328	308	294	179	168	153	78	68	62	16	13	12	1	1	1	0	0

Number of events

Category	A+AVD N=117	ABVD N=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

Modified PFS estimates

Time	A+AVD (95% CI)	ABVD (95% CI)
2-year	82.1 (78.7–85.0)	77.2 (73.7–80.4)

Median follow-up (range): 24.9 months (0.0–49.3)

Connors J et al. NEJM 2017

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Brentuximab Vedotin

- R/R HL after 2 lines of therapies
- Consolidation post ASCT
- Upfront combination with AVD for stage III and IV HL
- Also has NCCN recommendations for R/R HL as 1st line salvage therapy option

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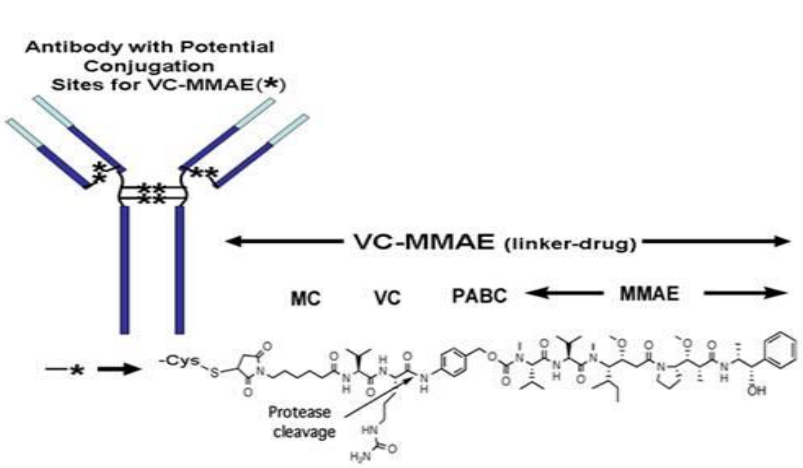
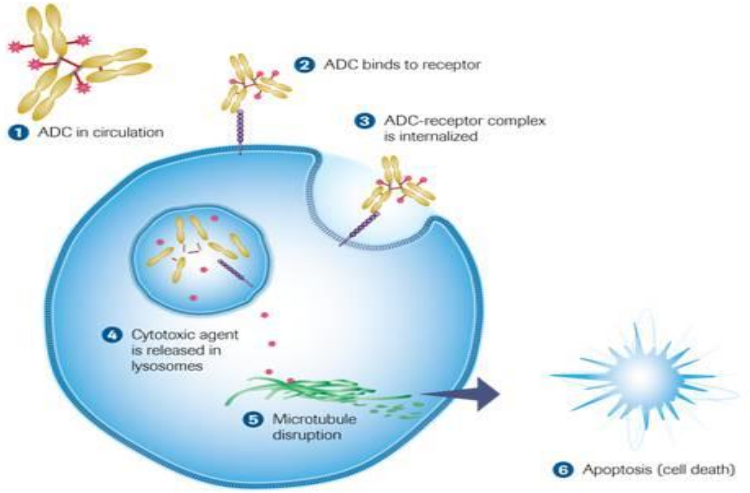
Polatuzumab

Pinatuzumab Vedotin (CD22-ADC)
Polatuzumab Vedotin (CD79b-ADC)

- Antibody drug conjugates (ADC) consisting of the potent microtubule inhibitor monomethyl auristatin E (MMAE) conjugated to anti-CD22 and CD79b monoclonal antibodies via a protease-cleavable peptide linker
- CD22 and CD79b are expressed by most B-cell hematologic malignancies
- Both ADCs have shown clinical activity in Phase I studies





Morschhauser F et al. ASCO 2014

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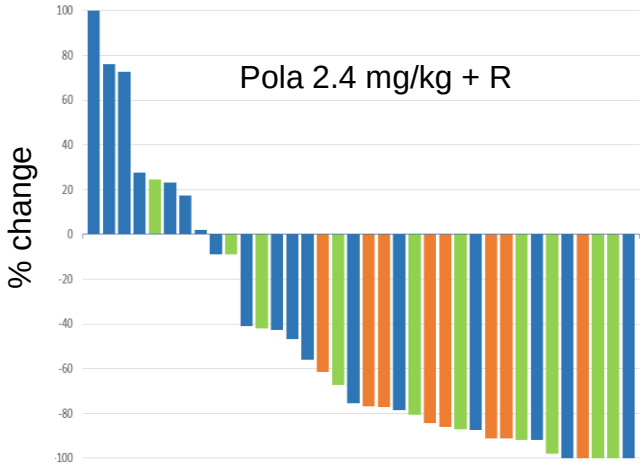
Polatuzumab Vedotin in R/R DLBCL

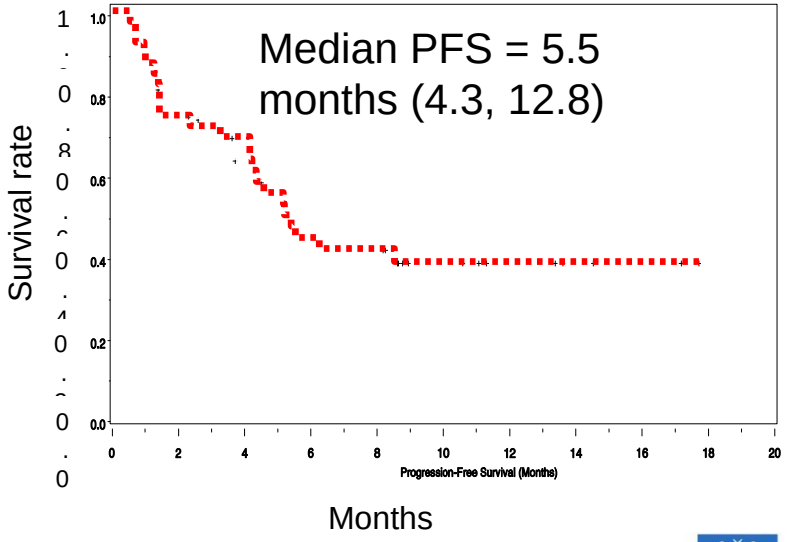
Treatment Regimen	Best Overall Response
Pola 1.8–2.4 mg/kg	51%[1]
Pola 1.8–2.4 mg/kg + rituximab	56%[2]

R/R DLBCL from the ROMULUS trial: pola + rituximab

Best SPD Change from Baseline



Progression-Free Survival



1. Palanca-Wessels MCA, et al. Lancet Oncol 2015; 16: 704-15; 2. Morschhauser F, et al. Blood 2014; 124:4457

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Pola + R/G-bendamustine

Investigator-Assessed Response by PET/CT[a]	FL		DLBCL	
	Pola + BR (n=6)	Pola + BG (n=26)	Pola + BR (n=6)	Pola + BG (n=27)
Best Objective Response				
ORR, n (%)	6 (100)	23 (89)	3 (50)	16 (60)
CR	4 (67)	17 (65)	2 (33)	11 (41)
PR	2 (33)	6 (23)	1 (17)	5 (19)
SD	0	0	0	2 (7)
PD	0	1 (4)	2(33)	6 (22)
UE	0	2 (8)	1 (17)	3 (11)
Objective Response at End of Treatment				
ORR, n (%)	5 (83)	21 (81)	3 (50)	10 (37)
CR	4 (67)	17 (65)	2 (33)	9 (33)
PR	1 (17)	4 (15)	1 (17)	1 (4)
Median duration of response, mo (range)[b]	16.1 (3.8–16.3)	NR (15.2–20.6)	NR (0.03–14.5)	NR (0.03–15.7)
Median PFS, mo (range)[b]	18.4 (7.2–18.9)	NR (1.4–17.1)	NR (1.5–22.7)	5.4 (0.03–17.6)

[a]Modified Lugano 2014 response criteria: for CR, repeat bone marrow biopsy required to confirm clearance of bone marrow if involved at screening. [b]Kaplan-Meier method; range data are at clinical data cut-off.
CT, computed tomography; ORR, objective response rate; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; SD, stable disease; UE, unable to evaluate.

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PV plus RB

- R/R DLBCL (2 prior lines)
- R-bendamustine vs PV + R-bendamustine
- Improvement in CR
  - 40% vs. 15%, p=0.012
- Improvement in median PFS
  - 6.7 months vs. 2 months, p <0.0001
- Improvement in median OS
  - 11.8 months vs. 4.7 months, p = 0.0008
- Toxicities
  - Cytopenia, febrile neutropenia, infection, and peripheral neuropathies

Sehn L et al. ASCO 2018

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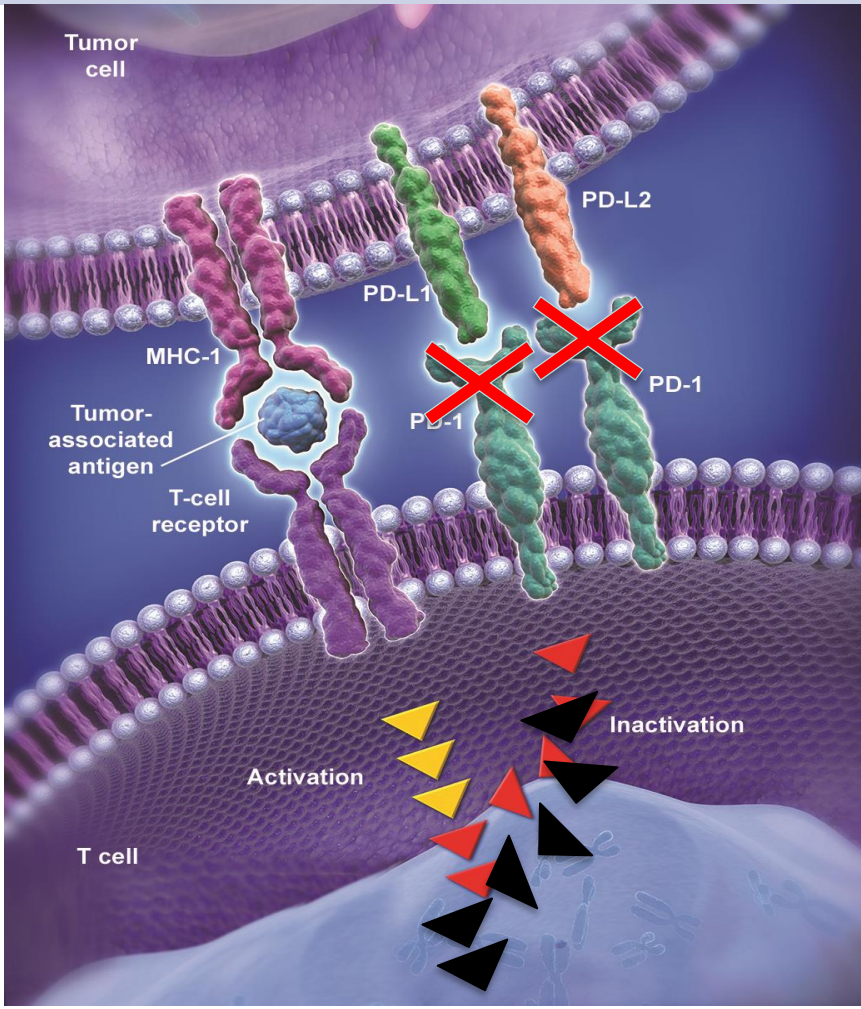
The PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function
- This mechanism is usurped by many tumors
- PD-1 blockade through mAb therapy can restore effective anti-tumor immunity



Topalian et al. *N Engl J Med*. 2012.
Garon et al. *N Engl J Med*. 2015.
Robert et al. *Lancet*. 2014.

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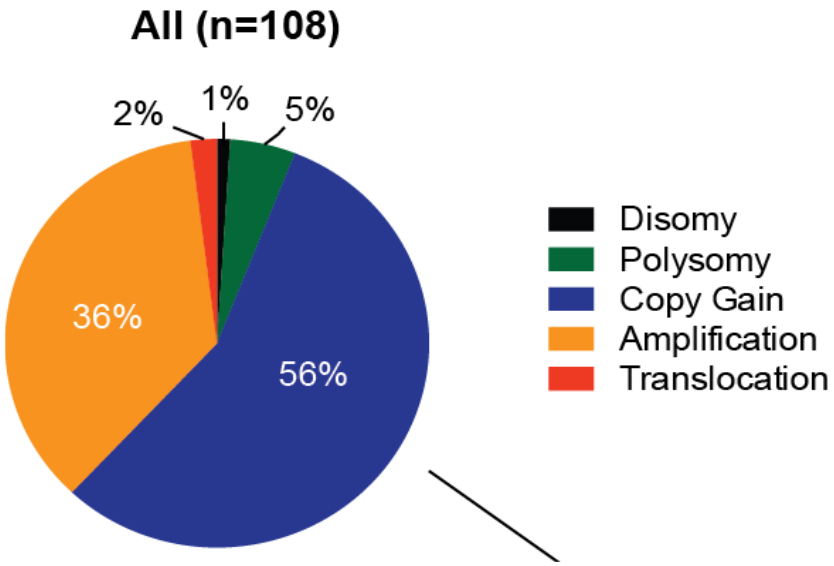
PD-1 pathway in Hodgkin Lymphoma

- Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function
- HL harbors near-universal amplification at 9p24.1, leading to overexpression of PD-L1 and PD-L2
- HL may be uniquely vulnerable to PD-1 blockade



Roemer et al. *J Clin Oncol.* 2016.

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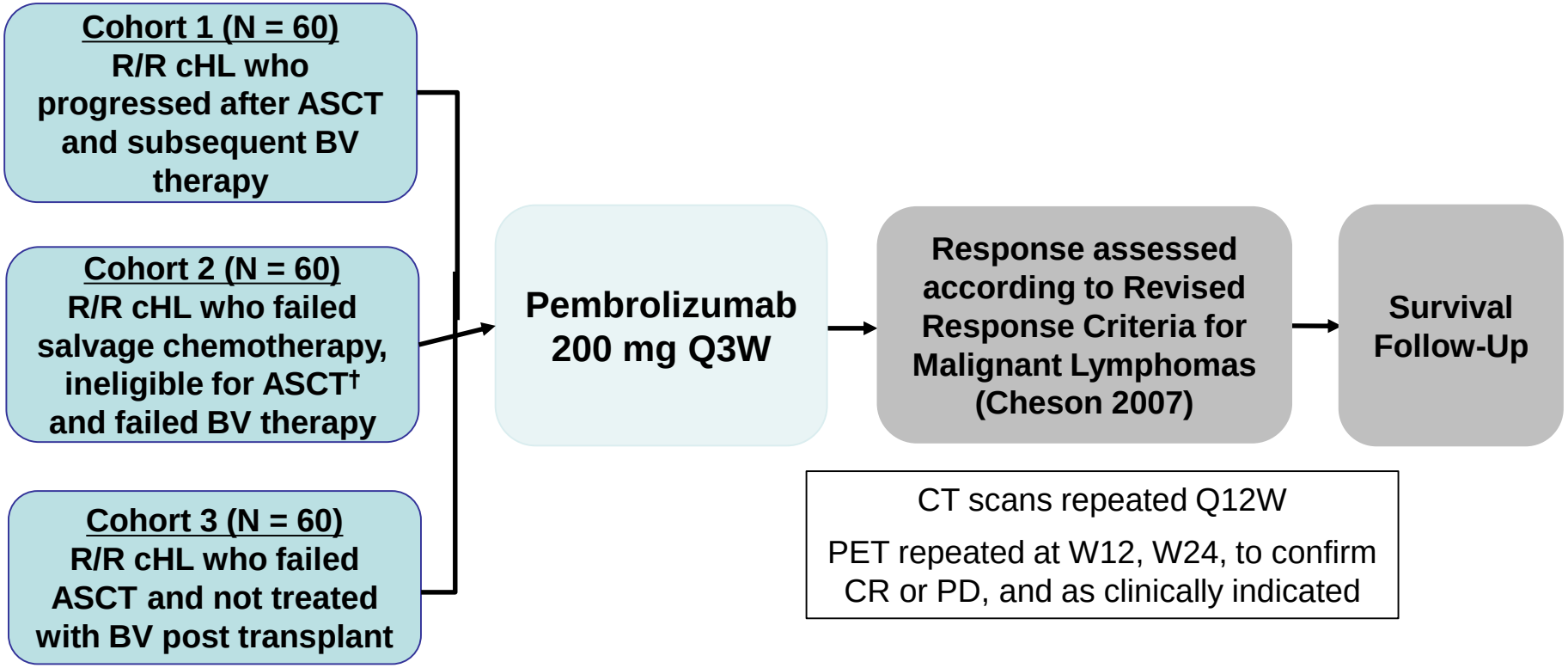
KEYNOTE-087: Study Design



- **Primary end point:** ORR (central review)
- **Secondary end points:** ORR (investigator review), PFS, OS
- Prespecified interim analysis, based on investigator-assessed response, performed after 30 patients in all 3 cohorts reached first response assessment

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Pembrolizumab ORR by Cohort (BICR)

	Cohort 1 Progressed after ASCT and subsequent BV therapy N=69		Cohort 2 Failed salvage chemotherapy, ineligible for ASCT and failed BV therapy N = 81		Cohort 3 Failed ASCT and not treated with BV post transplant N = 60	
	n (%)	95% CI†	n (%)	95% CI†	n (%)	95% CI†
ORR	**51 (73.9)**	**61.9-83.7**	**52 (64.2)**	**52.8-74.6**	**42 (70.0)**	**56.8-81.2**
Complete remission*	15 (21.7)	12.7-33.3	20 (24.7)	15.8-35.5	12 (20.0)	10.8-32.3
Partial remission	36 (52.2)	39.8-64.4	32 (39.5)	28.8-51.0	30 (50.0)	36.8-63.2
Stable disease	11 (15.9)	8.2-26.7	10 (12.3)	6.1-21.5	10 (16.7)	8.3-28.5
Progressive disease	5 (7.2)	2.4-16.1	17 (21.0)	12.7-31.5	8 (13.3)	5.9-24.6
Unable to determine	2 (2.9)	0.4-10.1	2 (2.5)	0.3-8.6	0 (0)	–

Chen et al JCO 2017

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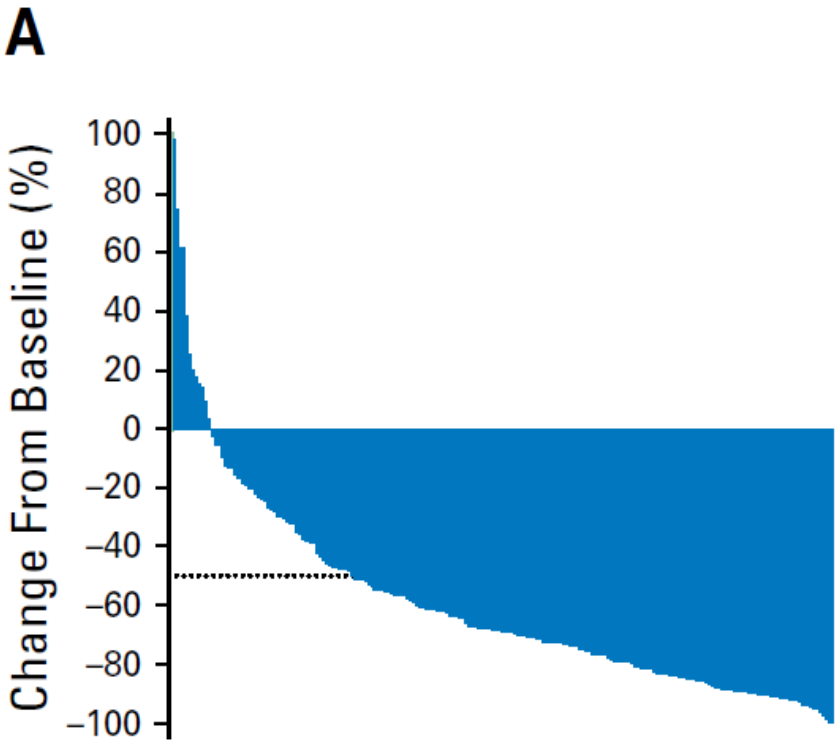
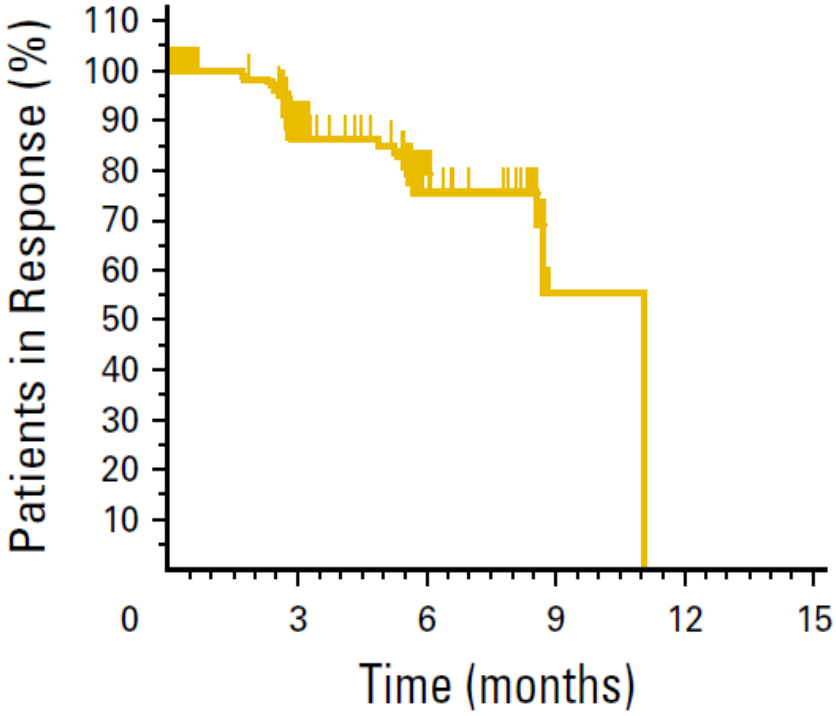
Pembrolizumab in rel/ref HL





Median (range) time to response

- 2.7 months (2.1-8.3)

Median (range) duration of response

- 8.7 (0.0+-11.1)
- Response duration ≥6 months: 82.2%

Chen R et al JCO 2017

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Checkmate 205: Nivolumab

Table 2. Objective and Best Overall Response per IRC

Response	Protocol-Specified Analysis by Cohort: BV Naïve: Cohort A (n = 63)	BV After Auto-HCT: Cohort B (n = 80)	BV Before and/or After Auto-HCT: Cohort C (n = 100)	All patients (N = 243)
ORR, % (95% CI)	65 (52-77)	68 (56-78)	73 (63-81)	69 (63-75)
Best overall response				
Complete remission	18 (29)	10 (13)	12 (12)	40 (16)
Partial remission	23 (37)	44 (55)	61 (61)	128 (53)
Stable disease	15 (24)	17 (21)	15 (15)	47 (19)
Progressive disease	7 (11)	6 (8)	10 (10)	23 (9)
Unable to determine	0	3 (4)	2 (2)	5 (2)

	Exploratory Analyses by Refractory Status (all patients): To First Line (n = 142)	To Last Line (n = 114)	To BV After Auto-HCT (n = 75)
ORR	73	68	68
Best overall response			
Complete remission	25 (18)	15 (13)	5 (7)
Partial remission	78 (55)	62 (54)	46 (61)
Stable disease	25 (18)	22 (19)	13 (17)
Progressive disease	12 (8)	12 (11)	8 (11)
Unable to determine	2 (1)	3 (3)	3 (4)

NOTE. Data presented as No. (%) unless otherwise indicated. Best overall response was unable to be determined for five patients, all because of missing or unknown postbaseline tumor assessments.

Abbreviations: auto-HCT, autologous hematopoietic cell transplantation; BV, brentuximab vedotin; IRC, independent radiology review committee; ORR, objective response rate.

Published in: Philippe Armand; Andreas Engert; Anas Younes; Michelle Fanale; Armando Santoro; Pier Luigi Zinzani; John M. Timmerman; Graham P. Collins; Radhakrishnan Ramchandren; Jonathon B. Cohen; Jan Paul De Boer; John Kuruvilla; Kerry J. Savage; Marek Trneny; Margaret A. Shipp; Kazunobu Kato; Anne Sumbul; Benedetto Farsaci; Stephen M. Ansell; *JCO* **2018,** 36, 1428-1439.

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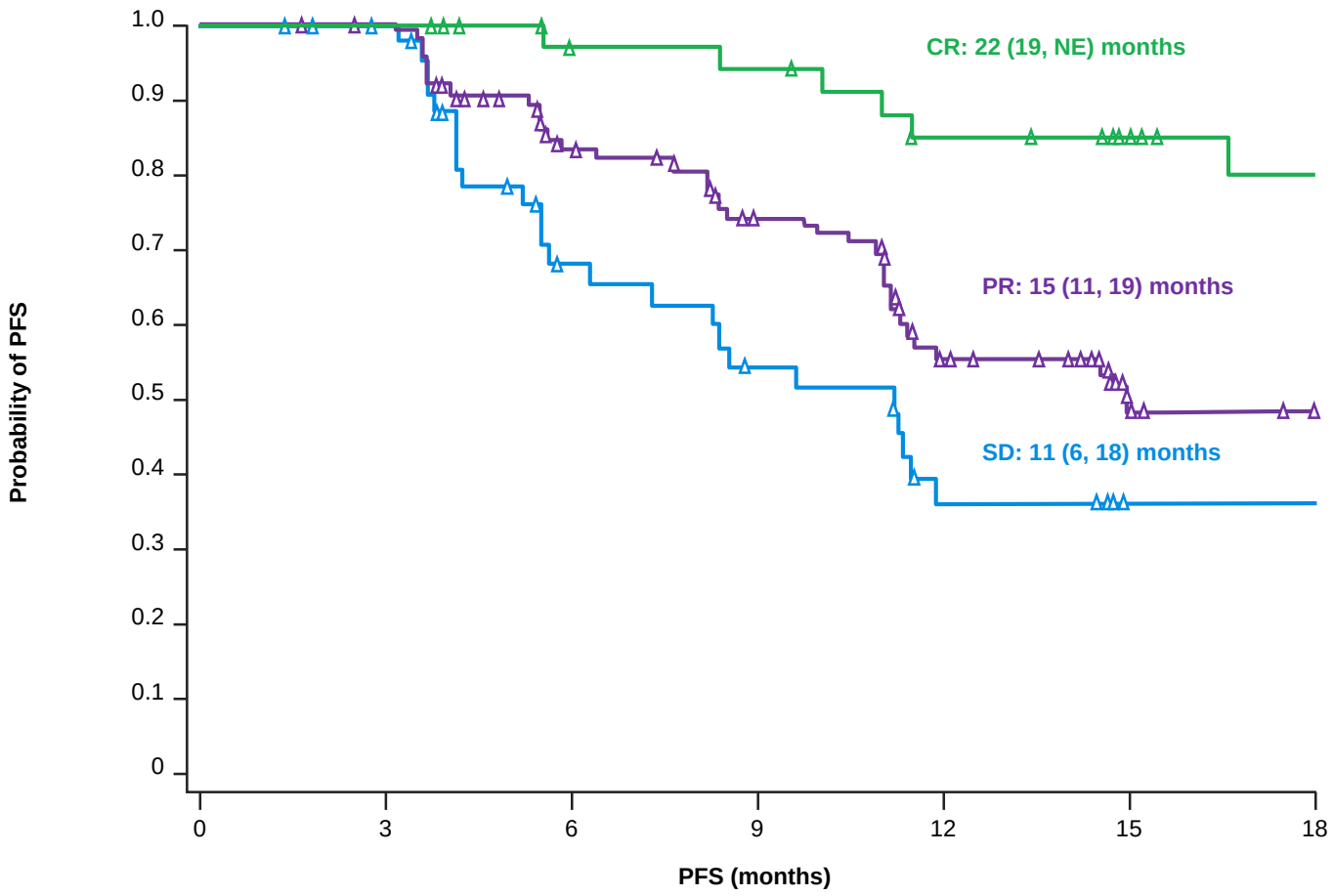
PFS



Median DOR
16.6 months

Median PFS
14.7 months

Armand P et al. Blood 2018

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PD-1/PD-L1 inhibitors in B-NHL

	Objective Response Rate, n (%)	Complete Responses, n (%)	Partial Responses, n (%)	Stable Disease n (%)
B-Cell Lymphoma* (n=29)	8 (28)	2 (7)	6 (21)	14 (48)
Follicular Lymphoma (n=10)	4 (40)	1 (10)	3 (30)	6 (60)
Diffuse Large B-Cell Lymphoma (n=11)	4 (36)	1 (9)	3 (27)	3 (27)
T-Cell Lymphoma† (n=23)	4 (17)	0 (0)	4 (17)	10 (43)
Mycosis Fungoides (n=13)	2 (15)	0 (0)	2 (15)	9 (69)
Peripheral T-Cell Lymphoma (n=5)	2 (40)	0 (0)	2 (40)	0 (0)
Multiple Myeloma (n=27)	0 (0)	0 (0)	0 (0)	18 (67)
Primary Mediastinal B-Cell Lymphoma (n=2)	0 (0)	0 (0)	0 (0)	2 (100)

*includes other B-cell lymphoma (n=8)
†includes other cutaneous T-cell lymphoma (n=3) and other non-cutaneous T-cell lymphoma (n=2)

Courtesy of Alexander Lesokhin. ASH 2014

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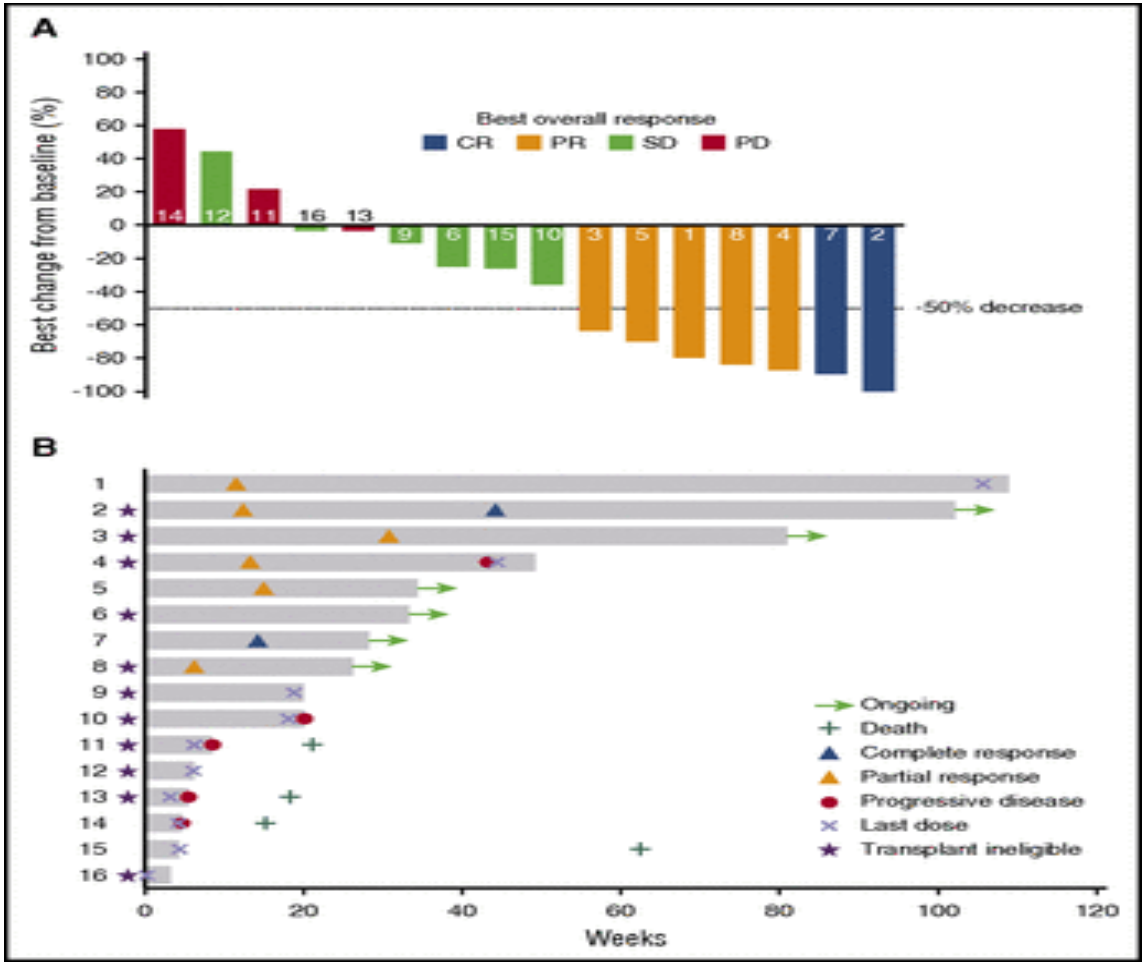
Pembrolizumab in PMLBC



ORR 41%

Zinzani P et al. Blood 2017

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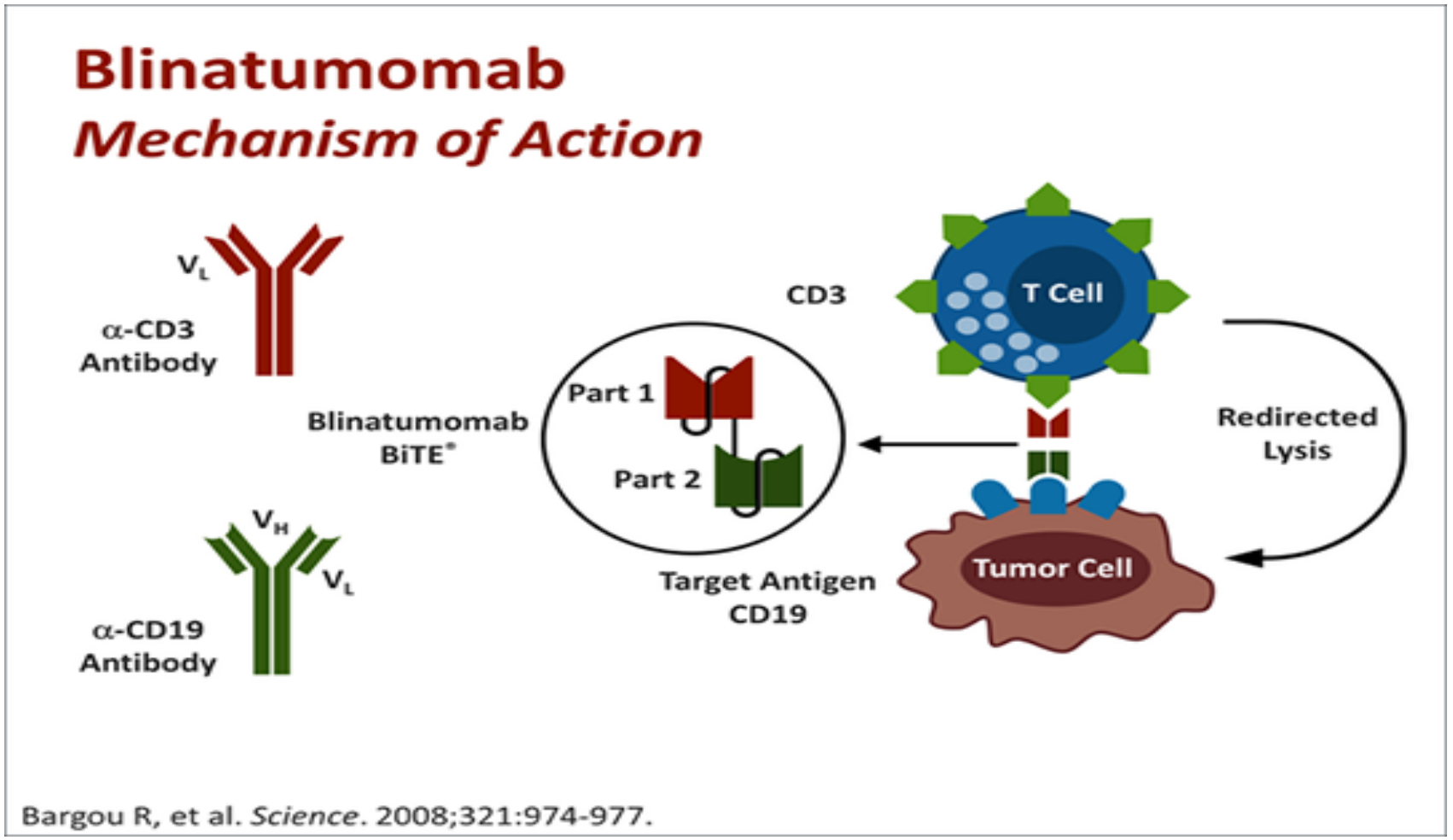
Bispecific Antibodies



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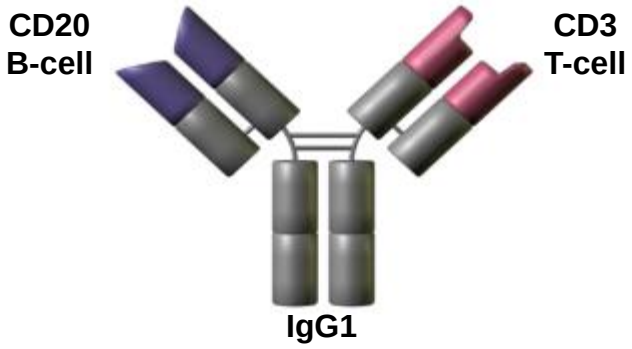
Blinatumomab

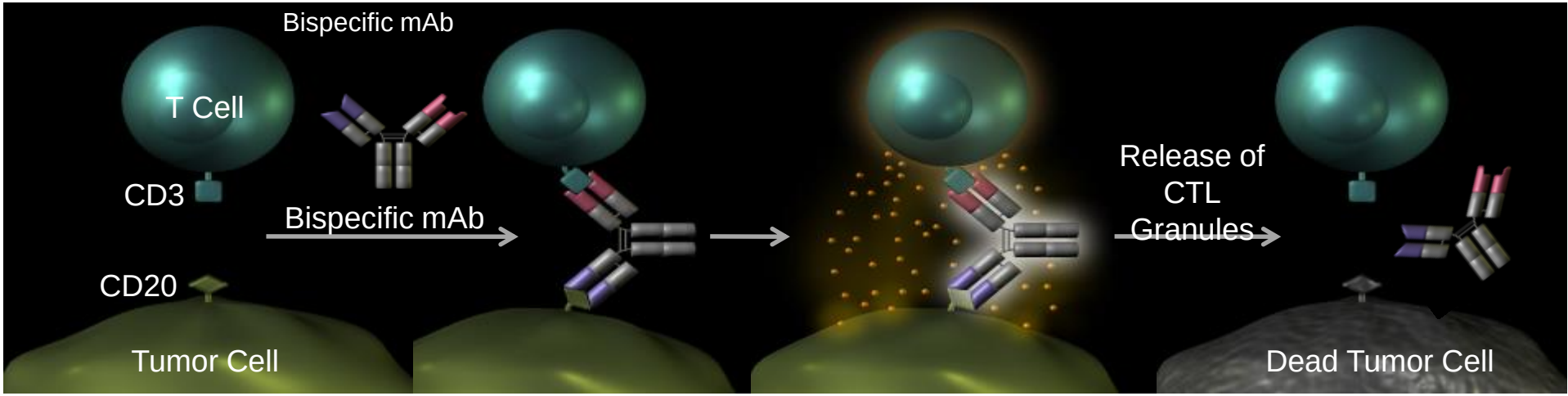
- Phase 1 trial R/R B cell NHL
- 76 pts with FL/MCL/DLBCL
- ORR 69%, CR 37% at 60 ug/m2/day
  - FL, ORR 80%
  - MCL, ORR 71%
  - DLBCL, ORR 55%
- Notable AE
  - Neurological 71%, Grade 3, 22%
  - Encephalopathy 8%, aphasia 4%, Seizure 3%
- Phase II trial shows a CR of 17% and ORR of 36% in patients with relapsed/refractory DLBCL.

Goebeler ME, JCO 2016

The Anti-CD20/CD3 T-Dependent Bispecific (TDB) Antibody BTCT4465A



- **Produced using 'knobs in holes' technology**
  - Full length bi-specific, PK similar to conventional IgG1
  - Glycosylation mutation (N297G) eliminates ADCC function => MOA distinct from rituximab and obinutuzumab
  - Near-natural architecture, low antigenic potential
- **aCD3 arm recruits T-cells to B-cells**
  - Conditional agonist: T-cell activation requires CD20 target engagement
  - Pre-treatment immune response to tumor not a pre-requisite
  - Active against indolent (non-dividing) and chemo-resistant cells



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Submitted to ASH 2018

- **Safety and Efficacy of the Full-Length Bispecific CD20/CD3 Antibody, Mosunetuzumab: Results from a Phase 1 Study in Relapsed/Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (NHL)**

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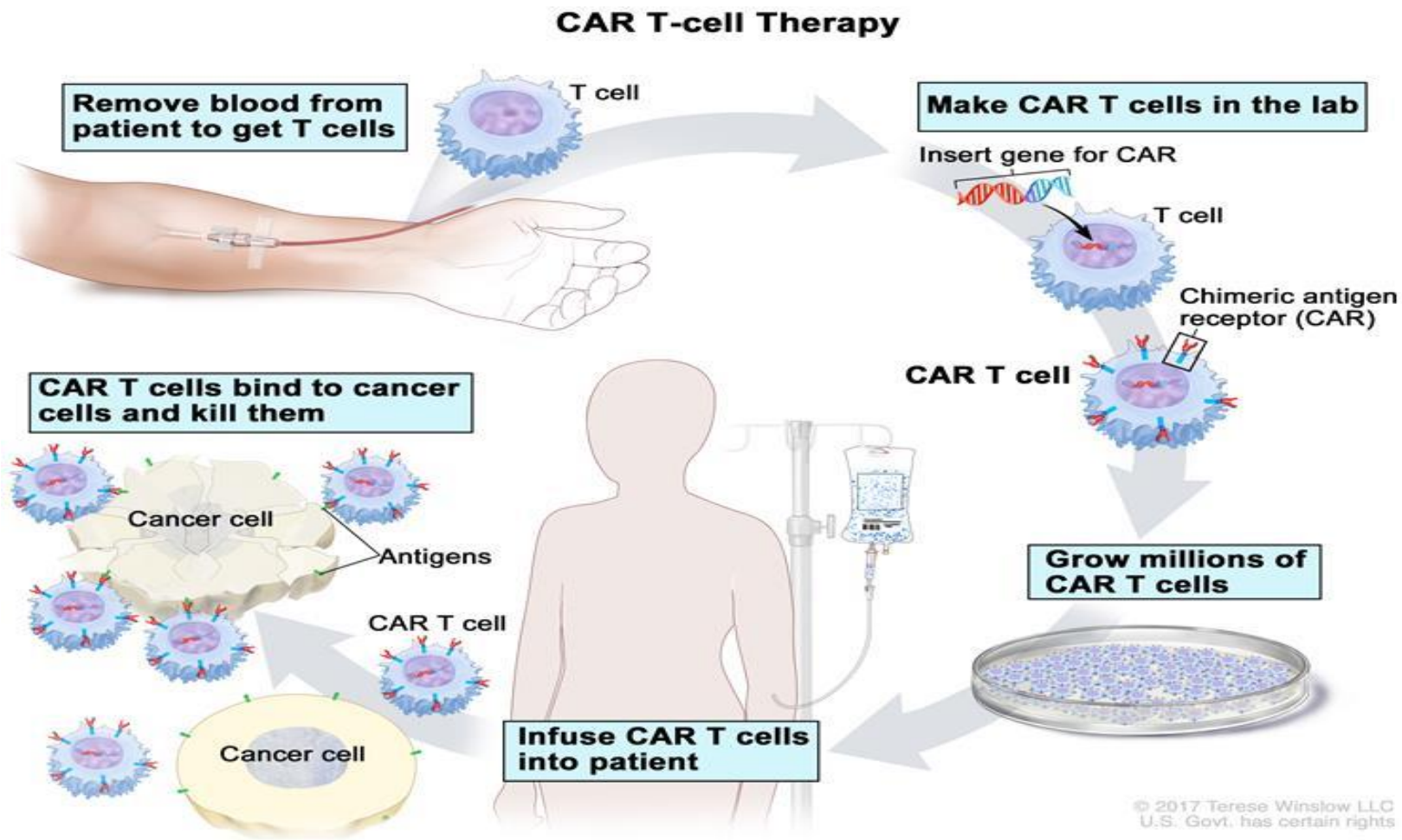
Chimeric antigen receptor (CAR) modified T-cells



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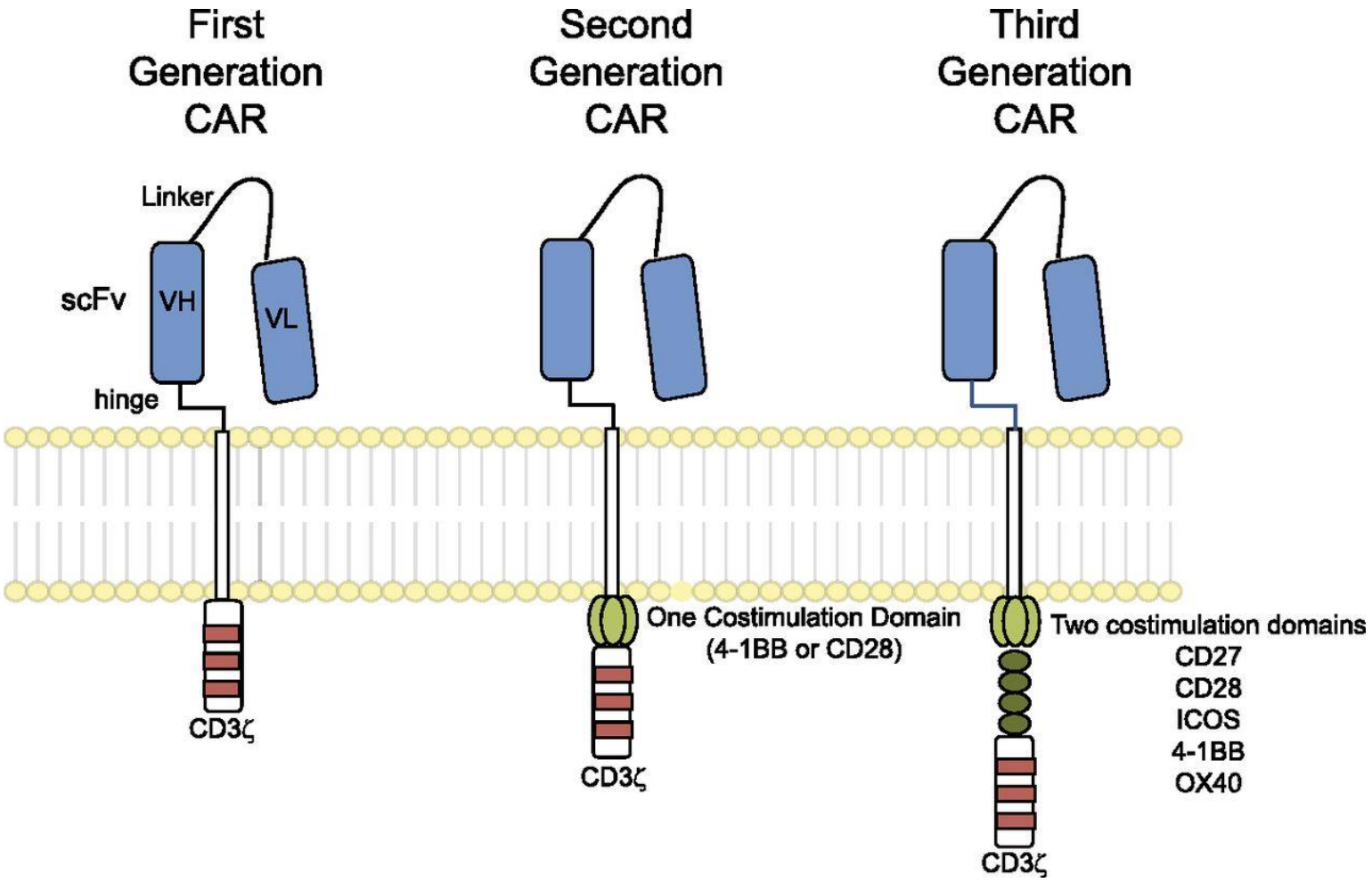

Maus, M et al Blood 2014

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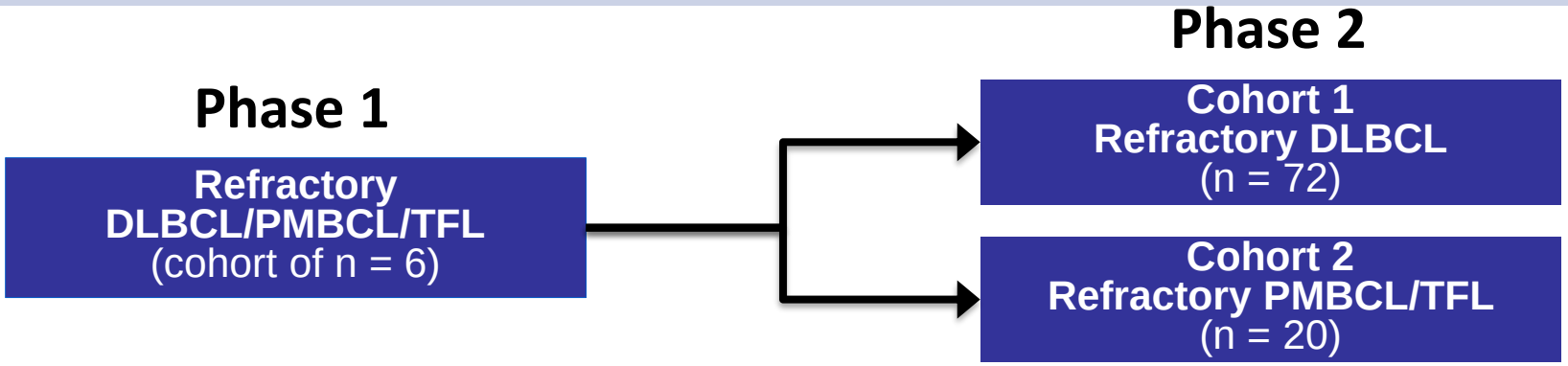
CAR T-cells in Aggressive B-NHL: KiTE (ZUMA-1)



Eligibility criteria

- Aggressive NHL: DLBCL, PMBCL, TFL
- Chemotherapy-refractory disease: no response to last chemotherapy or relapse ≤12 months post-ASCT
- Prior anti-CD20 mAb and anthracycline
- ECOG PS 0-1

Primary end point

- Phase 2: Objective response rate (ORR) tested in the first 92 patients dosed[a]

Key secondary end points

- DOR, OS, safety, levels of CAR T and cytokines

Neelapu SS et al. NEJM 2017

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Responses to CD19-specific CAR T-cells (KiTE)

Axicabtagene Ciloleucel (Yescarta)

Best Response	ZUMA-1 Phase 2					
	DLBCL		TFL/PMBCL		Combined	
	ORR (%)	CR (%)	ORR (%)	CR (%)	ORR (%)	CR (%)
mITT[b]	n = 77		n = 24		n = 101	
	82	49	83	71	82	54

[a] Inferential testing when 92 axi-cel–dosed patients had 6 months of follow-up. ORR 82%, *P*<0.0001. [b] mITT (modified intention-to-treat) set of all patients dosed with axi-cel.
CR, complete response; DLBCL, diffuse large B cell lymphoma; ORR; objective response rate; PMBCL; primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma.

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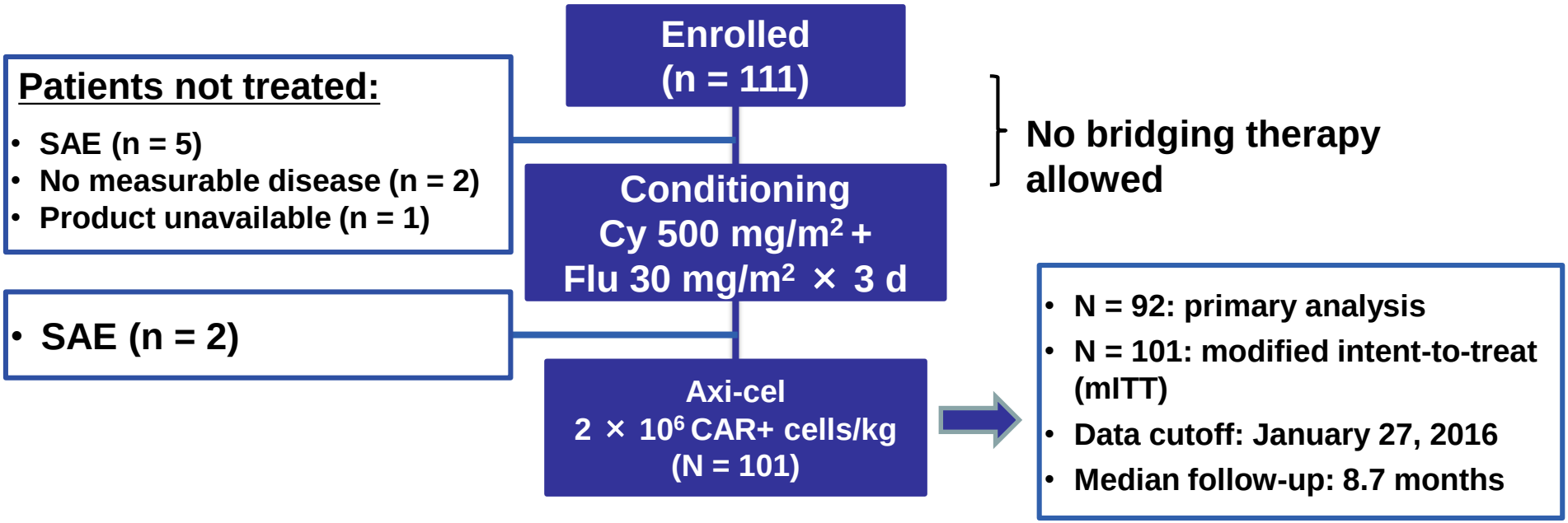
Patient Consort Diagram



- 22 sites enrolled; 99% manufacturing success rate
- 91% of enrolled patients received axi-cel
- 17-day average turnaround time from apheresis to delivery to clinical site

Neelapu SS et al. NEJM 2017

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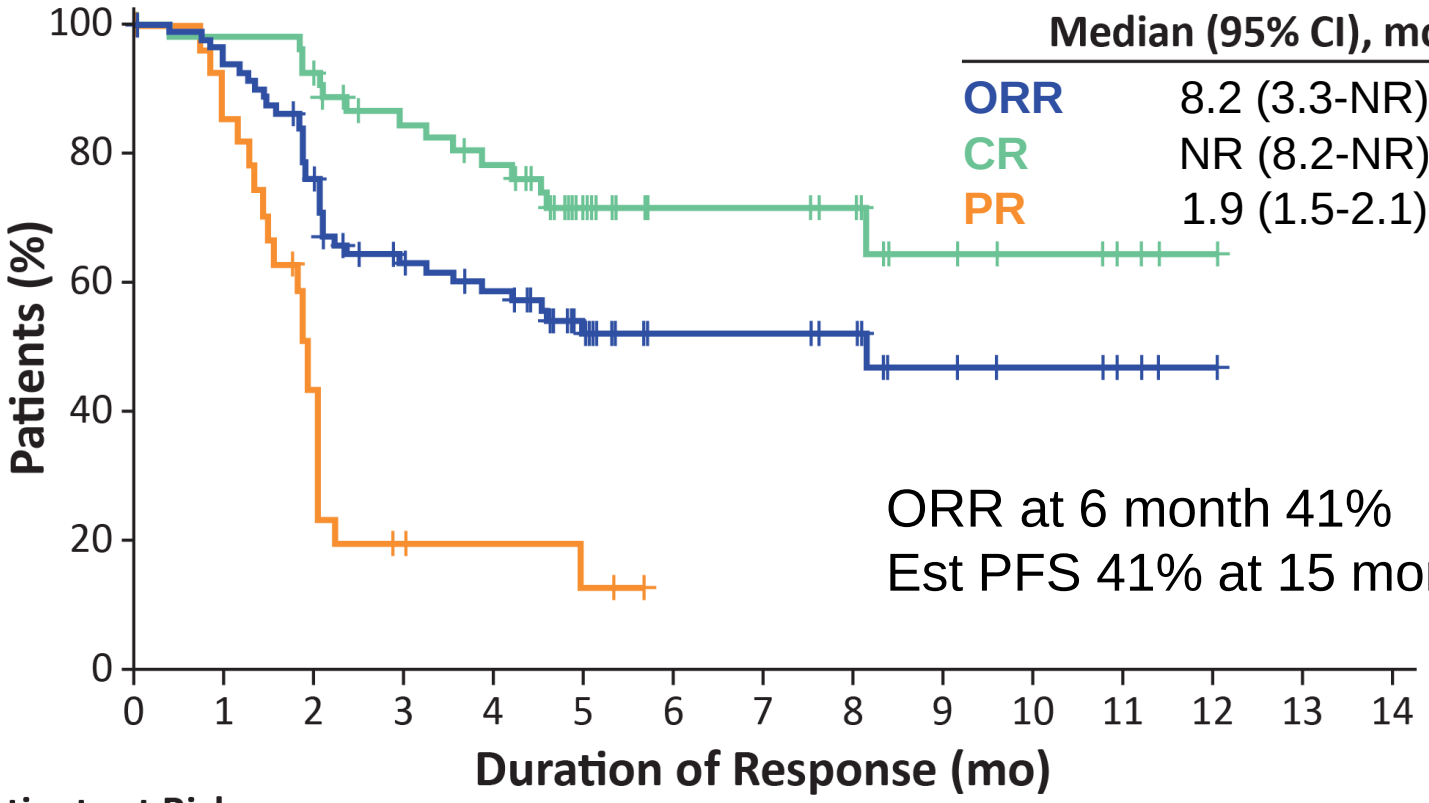
Duration of Responses At a Median Follow-Up of 8.7 Months



Patients at Risk

ORR	83	75	60	45	40	26	14	14	12	7	5	3	1	0
CR	55	52	49	41	37	24	14	14	12	7	5	3	1	0
PR	28	23	11	4	3	2	0							

Neelapu SS et al. NEJM 2017

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Summary of CAR T-cell related AEs

AE, n (%)	Interim Analysis (N = 62)	Primary Analysis (N = 101)
Grade ≥3 AE	59 (95)	95 (95)
Grade ≥3 CRS	11 (18)	13 (13)
Grade ≥3 NE	21 (34)	28 (28)
Grade 5 AE	3 (3)[a]	3 (3)[a]

- CRS and NE were generally reversible
  - All CRS events resolved except 1 case of HLH and 1 case of cardiac arrest
  - All NE resolved except 1 grade 1 memory impairment
- 43% received tocilizumab, 27% received steroids
- No new axi-cel–related grade 5 AEs

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Tisagenlecleucel (Kymriah)

- FDA approval 5/2018
- DLBCL, TFL, High grade B cell lymphoma
- 2 prior therapies
- 147 patients with refractory DLBCL or TFL, 99 infused, 81 evaluated
- Median was 39 days between collection and infusion, bridging chemotherapy allowed
- Median of 5.79 x 10^ 8 CAR cells/kg
- Best ORR 53% and CR 40%, OR at 6 month 37%.
- Grade 3 NT 12%, CRS 23%

Schuster SF et al. ASH 2017

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Combinations

- ADC + Checkpoint inhibitors
  - BV + nivolumab
  - BV + nivolumab + ipilimumab
- ADC + BITE
  - Polatuzumab plus CD20/CD3 Ab
- BITE + PD1 inhibitors
  - Blinatumomab plus pembrolizumab
  - CD20/CD3 Ab + atezolimumab
- CART + PD1 inhibitors

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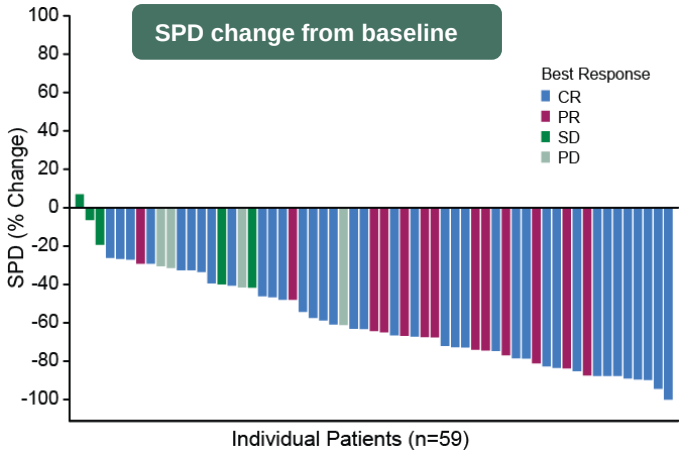
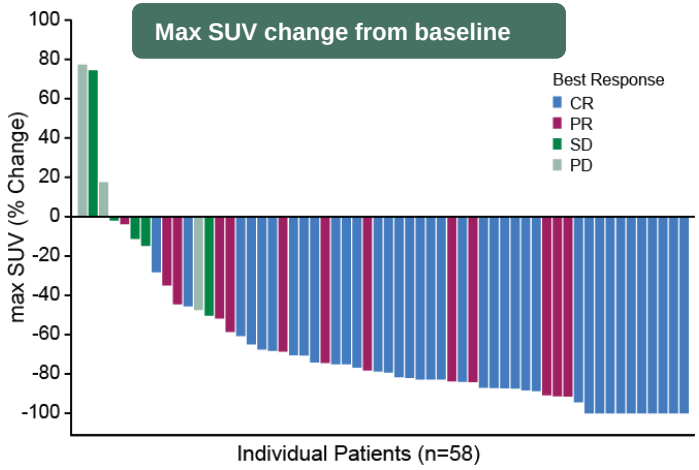
BV plus Nivolumab as 2nd line therapy

85% objective response rate with 63% complete responses





	N = 59 n (%)
Complete response (CR)	**37 (63)**
Deauville ≤ 2	29 (49)
Deauville 3	7 (12)
Deauville 5[a]	1 (2)
Partial response (PR)	**13 (22)**
Deauville 4	7 (12)
Deauville 5	6 (10)
No metabolic response (SD)	**5 (8)**
Deauville 5	5 (8)
Progressive disease (PD)	**3 (5)**
Deauville 5	2 (3)
Missing	1 (2)
Clinical Progression (CP)	**1 (2)**

a. 1 pt had uptake in lymph node, but no evidence of disease was found on biopsy
SPD, sum of the product of the diameters; SUV, standard uptake value

Herrera AF et al. Blood 2017

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