Lymphoma: Emerging Therapies

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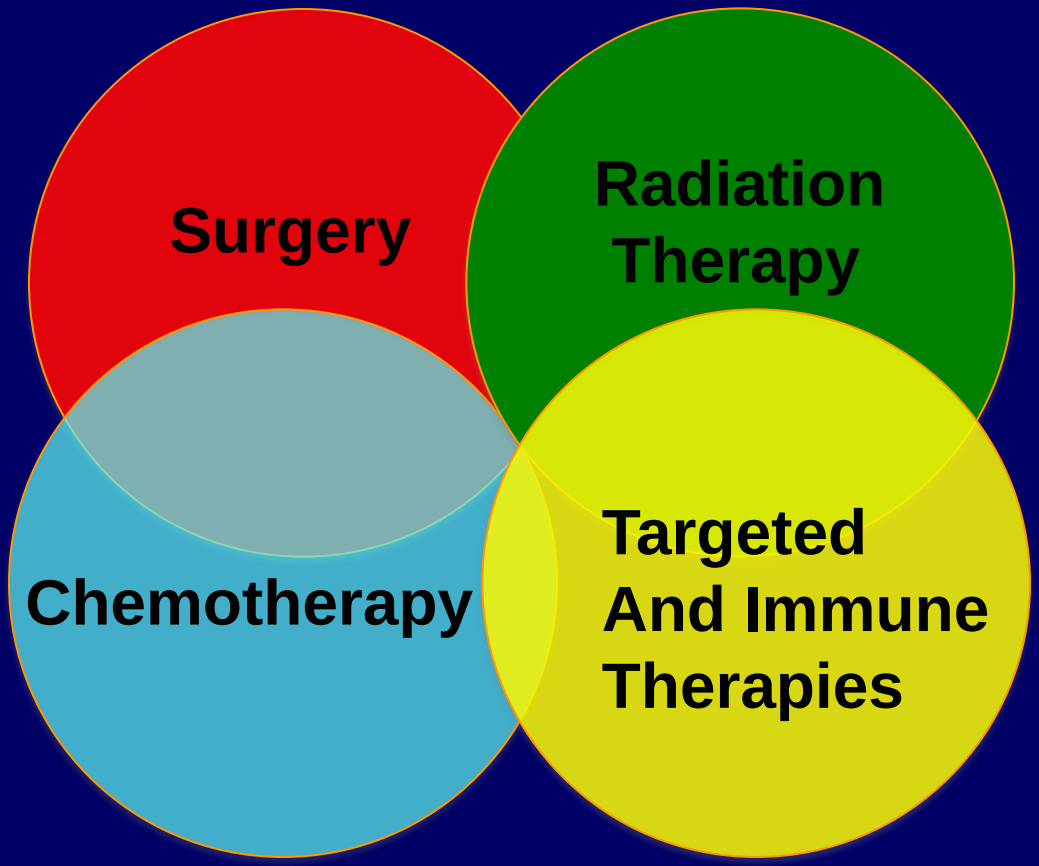
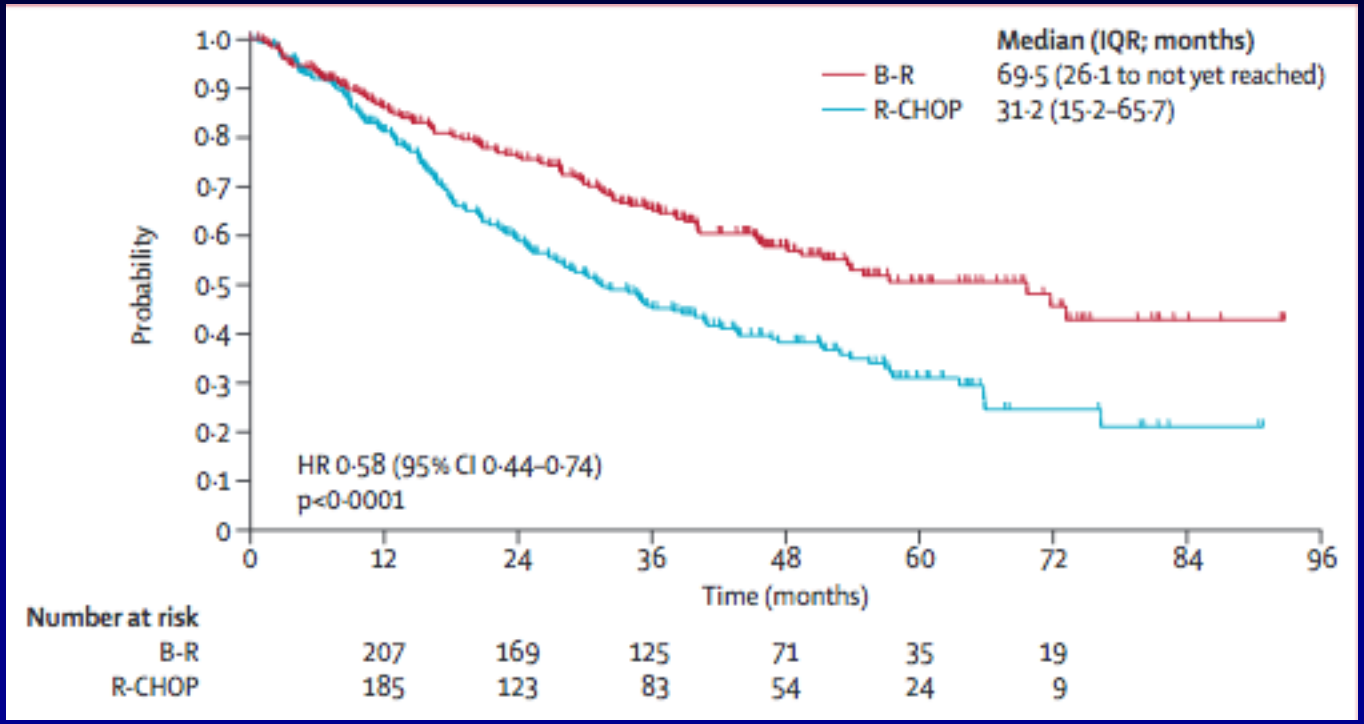
Treatment Modalities in Lymphoma

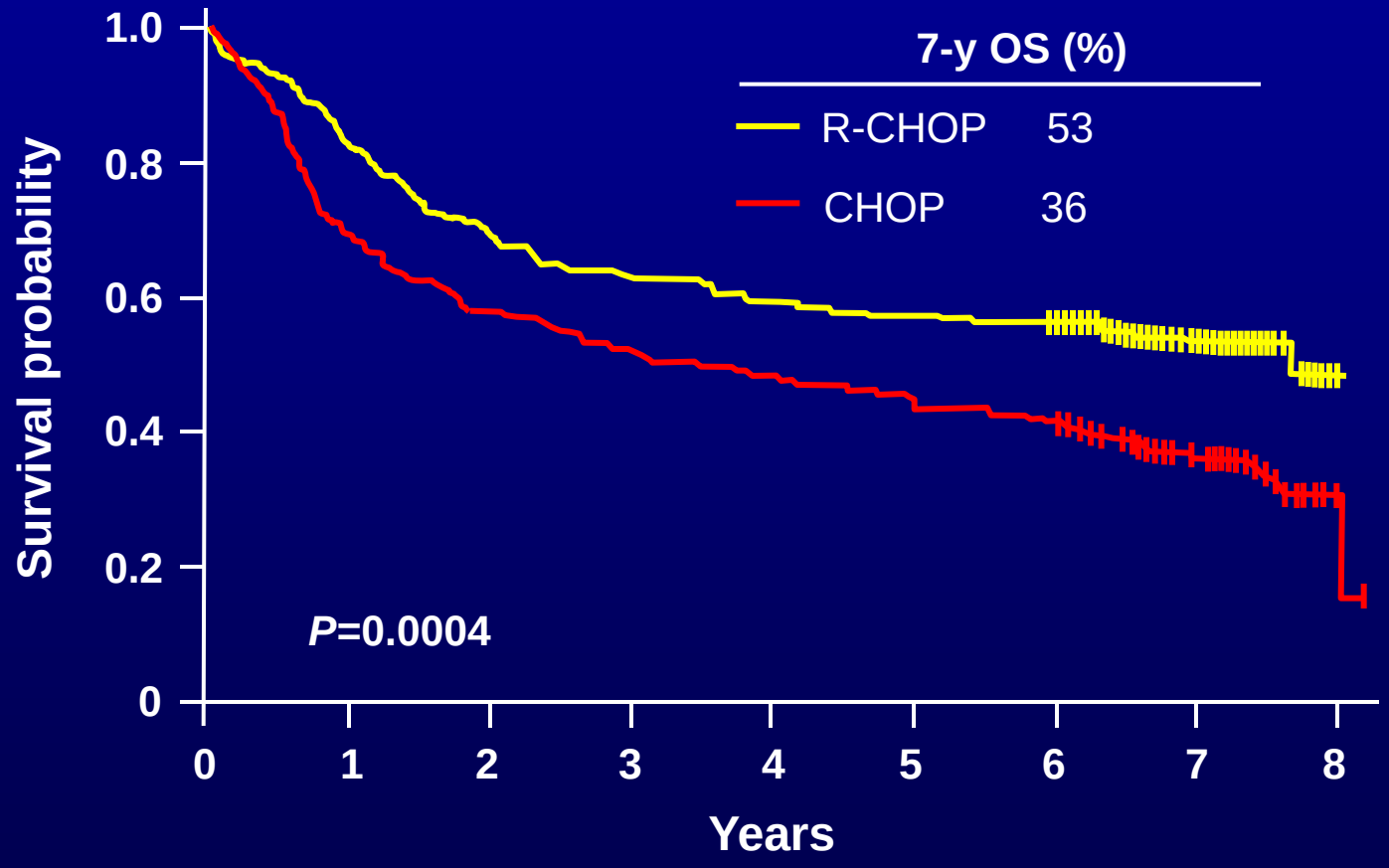


BR vs R-CHOP in Untreated iNHL



Rummel et al, Lancet 381:1203, 2013

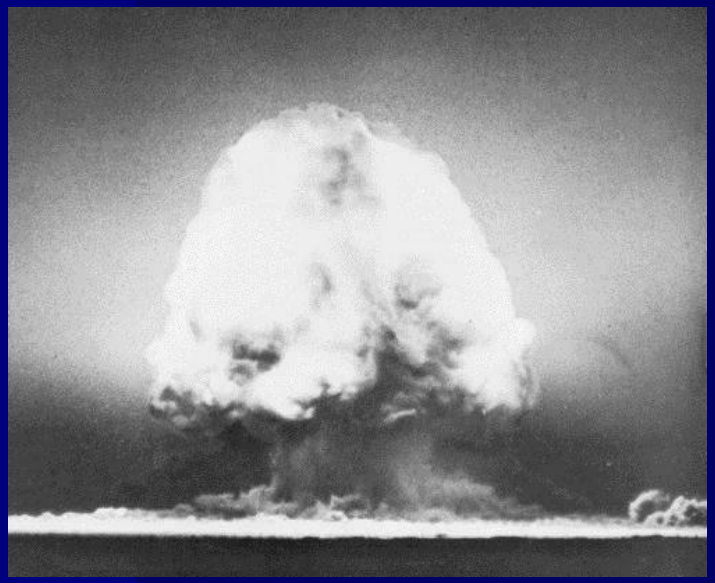
7-Year Results of GELA Study of CHOP ± Rituximab in Older Patients With DLBCL: OS



Coiffier et al. ASCO, 2007. Abstract 8009.

Ways to Kill Cancer Cells

Nuclear Attack



Smart Bomb

Chemotherapy

Drugs attack the "bricks and mortar" of cancer cells (DNA, cell cytoskeleton, etc.)

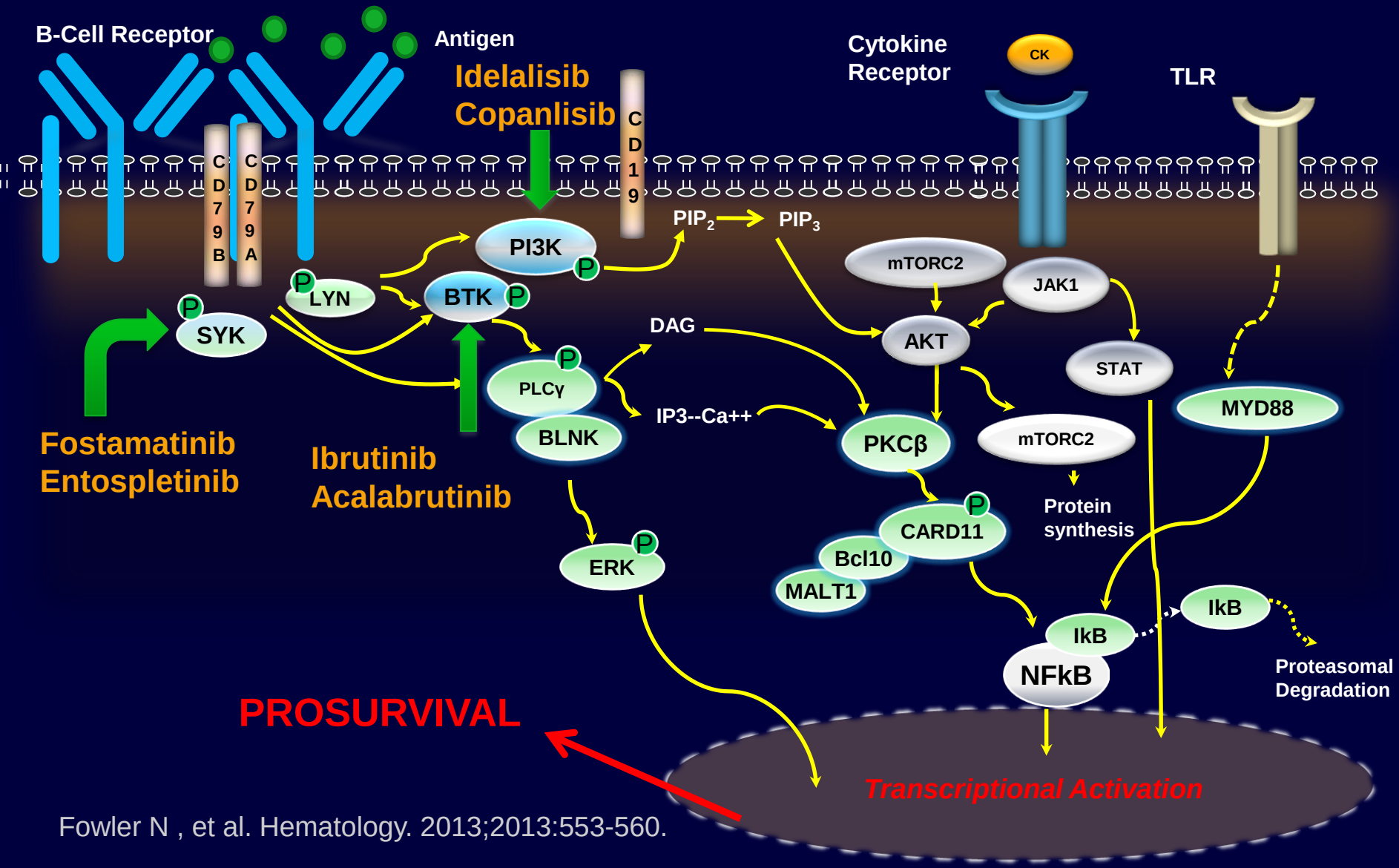
Targeted Therapy

Drugs attack the "electrical wiring system" of cancer cells (receptors, enzymes, cell signaling molecules)

Novel Targeted Agents

Agent	Target
Ibrutinib, Acalabrutinib,	Btk
Idelalisib, Umbralisib, Copanlisib	PI3-K
Venetoclax Tazemetostat	Bcl-2 EZH2
Lenalidomide	Multiple
Nivolumab/Pembrolizumab	PD-1
Atezolizumab	PDL-1

Targets of B-Cell Receptor Signaling



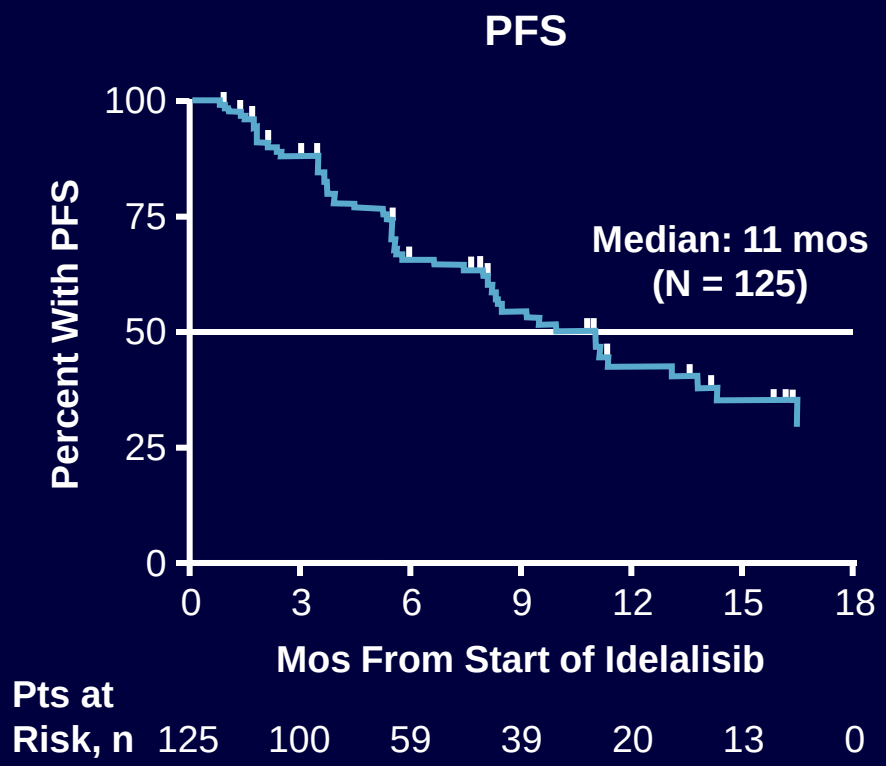
Fowler N , et al. Hematology. 2013;2013:553-560.

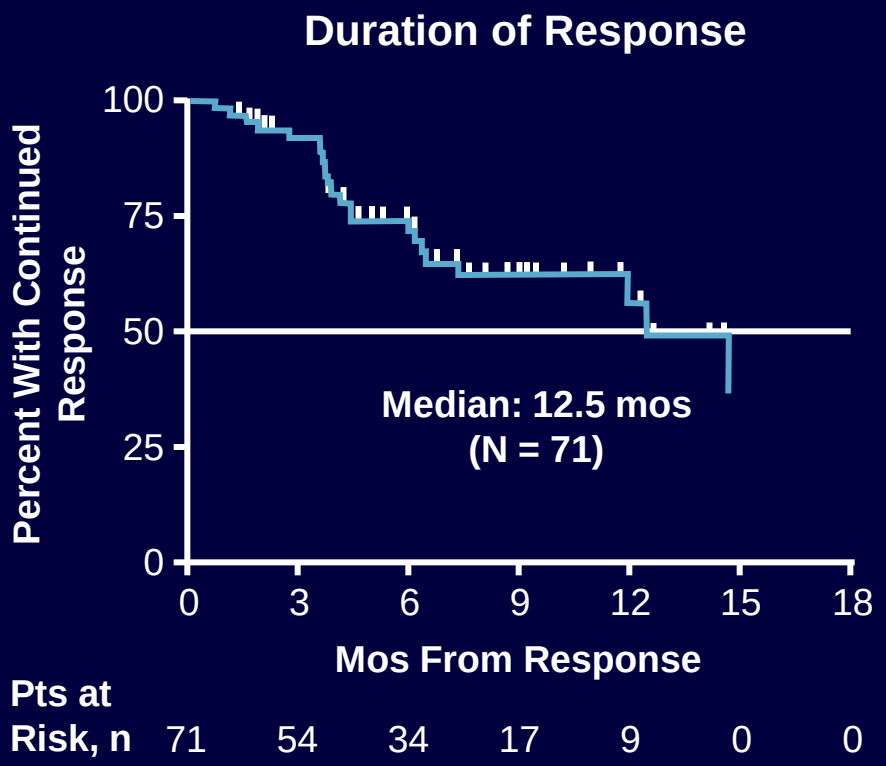
Idelalisib Monotherapy in Refractory iNHL (Phase II): Responses

Characteristic	Patients, n (%) (N = 125)
ORR, n (%)	71 (57)
CR	7 (6)
PR	63 (50)
Minor response*	1 (1)
SD	42 (34)
PD	10 (8)
Not evaluated	2 (2)
Time to response, mos (n = 71)	
Median (interquartile range)	1.9 (1.8-3.7)

Gopal A, et al. N Engl J Med. 2014;370:1008-1018.

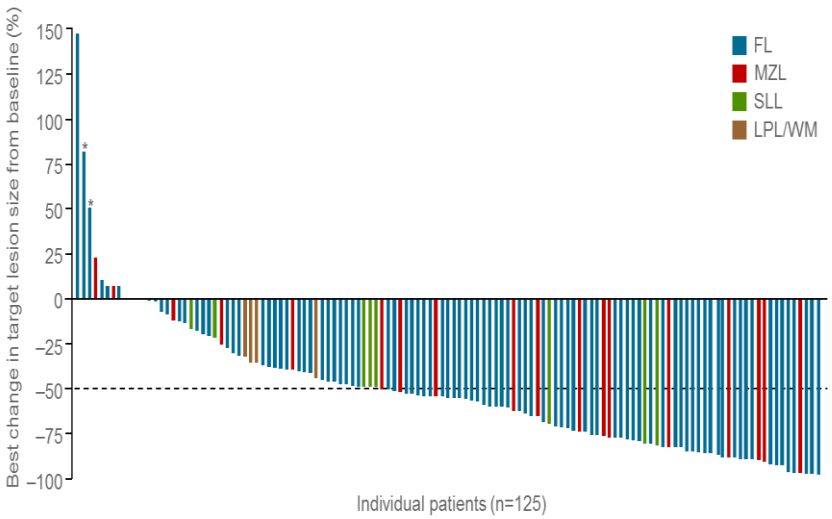
Phase II Study of Idelalisib Monotherapy in Refractory iNHL: PFS and DOR





Gopal A, et al. N Engl J Med. 2014;370:1008-1018.

Copanlisib Demonstrated Anti-Tumor Efficacy in Patients with Relapsed or Refractory iNHL

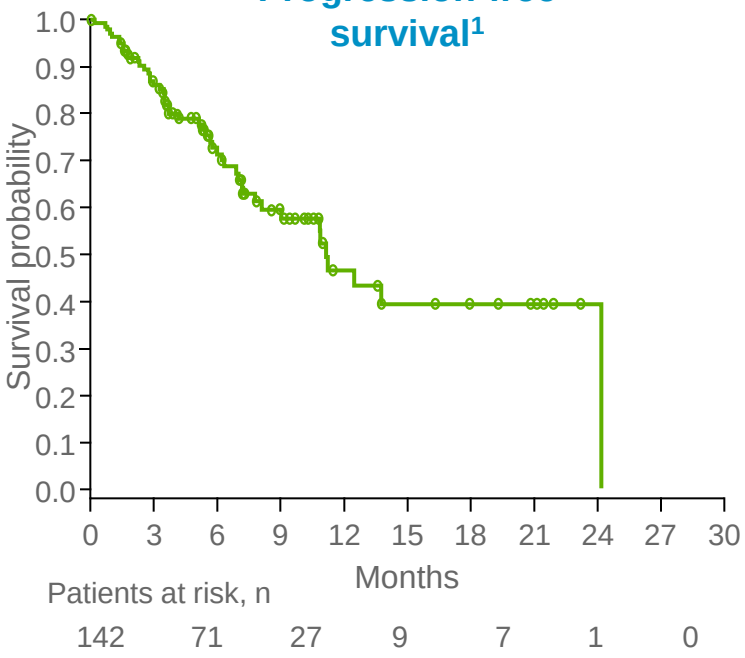


	FL (n=104)	MZL (n=23)	SLL (n=8)	LPL/WM (n=6)	Total[a] (N=142)
Best response, n (%)					
Complete response	15 (14%)	2 (9%)	0	0	17 (12%)
Partial response	46 (44%)	14 (61%)	6 (75%)	1 (17%)	67 (47%)
Stable disease	35 (34%)	4 (17%)	1 (13%)	3 (50%)	42 (30%)
Progressive disease	2 (2%)	0	1 (13%)	0	3 (2%)
NE/NA	6 (6%)	3 (13%)	0	2 (33%)	12 (9%)
ORR, n (%)	61 (59%)	16 (70%)	6 (75%)	1 (17%)	84 (59%)
95% CI	49–68	47–87	35–97	0.4–64	51–67

*Patient was assessed by independent review as having stable disease.
[a]One patient with follicular lymphoma who received treatment was later confirmed by the local investigator to have diffuse large B-cell lymphoma.
CI, confidence interval; **NA**, not available; **NE**, not evaluable; **ORR**, objective response rate.
Dreyling M *et al. J Clin Oncol* 2017; doi: 10.1200/JCO.2017.75.4648.

Copanlisib Demonstrated Durable Responses in Patients with Relapsed or Refractory iNHL

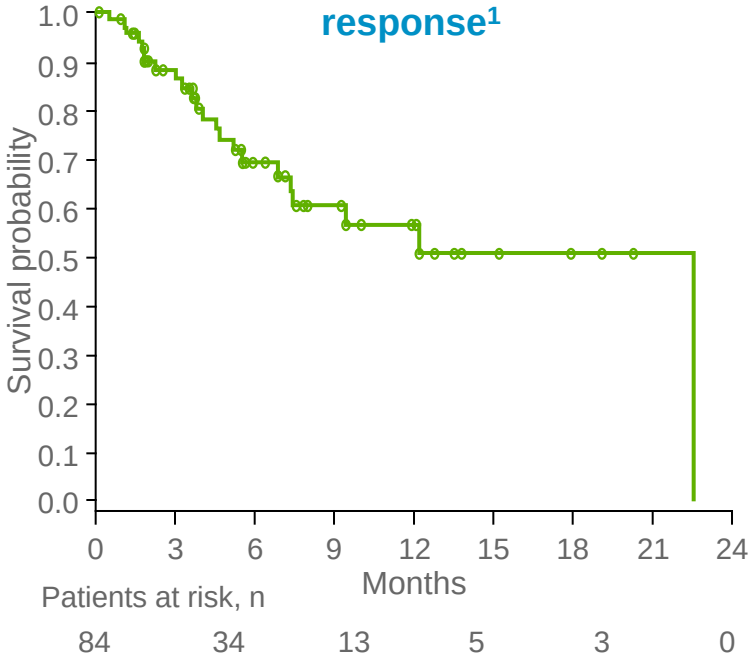
Progression-free survival[1]



Median progression-free survival:

- **Overall:** 11.2 months (95% CI: 8.1–24.0)[1]
- **FL:** 11.2 months (95% CI: 7.8–24.2)[2]

Duration of response[1]



Median duration of response:

- **Overall:** 22.6 months (range 0–22.6; 95% CI: 7.4–22.6)[1]
- **Refractory patients:** 12.2 months (range 0–22.6; 95% CI: 7.4–22.6)[2]
- **FL:** 12.2 months (range 0–22.6; 95% CI: 6.9–22.6)[2]

1. Dreyling M *et al. J Clin Oncol* 2017; doi: 10.1200/JCO.2017.75.4648. **2.** Dreyling M *et al.* Presented at: International Conference on Malignant Lymphoma; June 14–17, 2017; Lugano, Switzerland.

Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Clinical Efficacy

- Responses according to disease type:

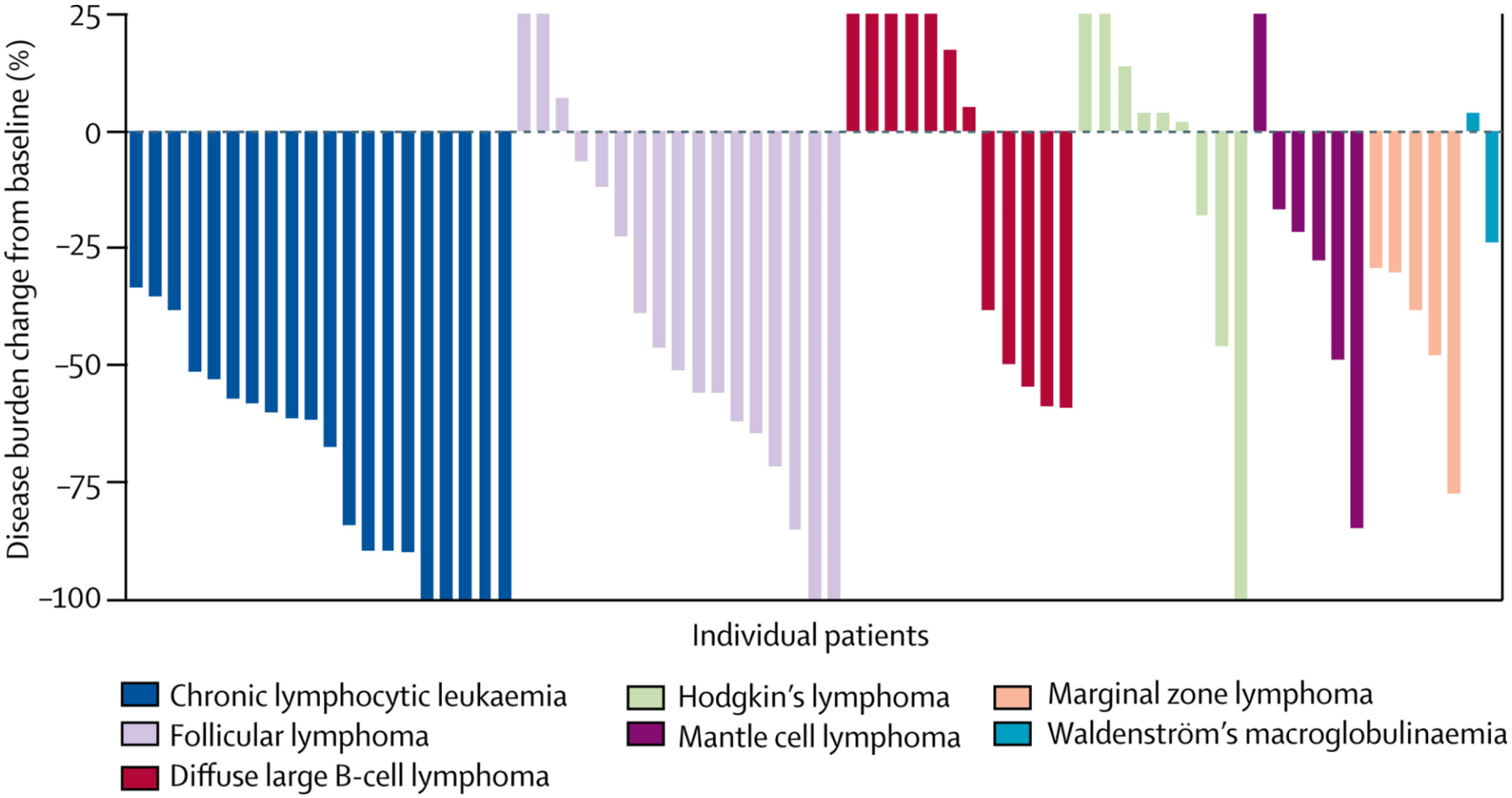
Disease	Objective response, n (%)	CR, n (%)	PR, n (%)	PR-L, n (%)	Duration of Response, mo (n)
CLL, n=20	17 (85)	-	10 (50)*	7 (35)	13.4 (16)
CLL, del 17p/del 11q,n=8	6 (75)	-	4 (50%)*	2 (25%)	-
FL, n=17	9 (53)	2 (12)	7 (41)	-	9.3 (9)
DLBCL, n=13	4 (31)	-	4 (31)	-	6.4 (4)

-HL: 1 CR, 4 SD, 4 PD; MZL: 1 PR, 4 SD; Waldenström macroglobulinemia: 2 SD; MCL: 1 PR, 4 SD, 1 PD.*iwCLL 2008

- Umbralisib was clinically active in most treated patients
  - 56 of 90 (62%) study patients had reductions in disease burden by CT scan
  - ORR 37% (PR 33%) amongst all evaluable patients (N=73)
- Responses increased over time amongst patients with CLL and iNHL

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

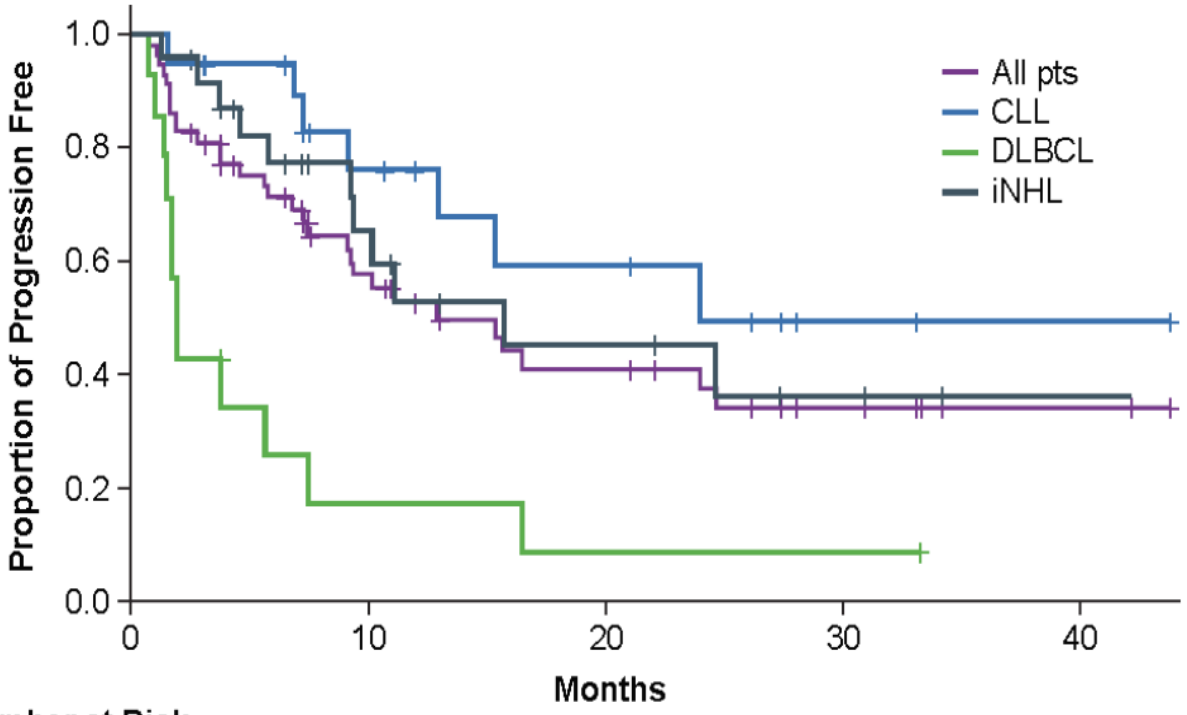
Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Best Percentage Change from Baseline in Disease Burden



mITT, modified intention-to-treat.

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Progression-free Survival (post-hoc analysis)



Number at Risk

All pts	57	38	24	17	14	10	6	2	1
CLL	20	17	11	8	7	5	2	1	1
DLBCL	13	4	2	2	1	1	1	0	0
iNHL	24	17	11	7	6	4	3	1	1

- Median PFS :
  - CLL: 24 mo (95% CI 7.4 – NR)
  - iNHL: 16 mo (95% CI 9.2– NR)
- Tumor reductions in most patients with lymphoma and CLL tended to improve over time

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

DAWN Study: Primary End Point: IRC-Assessed Clinical Response With Single-Agent Ibrutinib

	All Treated Patients (N = 110)	
Clinical response, n (%)		95% CI
Overall response rate (ORR)	**23 (20.9)**	13.7-29.7
Complete response (CR)	12 (10.9)	5.8-18.3
Partial response (PR)	11 (10.0)	5.1-17.2
Stable disease (SD)	34 (30.9)	22.5-40.4
Progressive disease (PD)	47 (42.7)	33.3-52.5
Not evaluable/unknown	6 (5.5)	2.0-11.5

- Disease control rate (ORR + SD for ≥ 6 months) was 33.6% (37/110)

CI, confidence interval.

58th ASH Annual Meeting 2016, DAWN Study, Gopal A, et al.

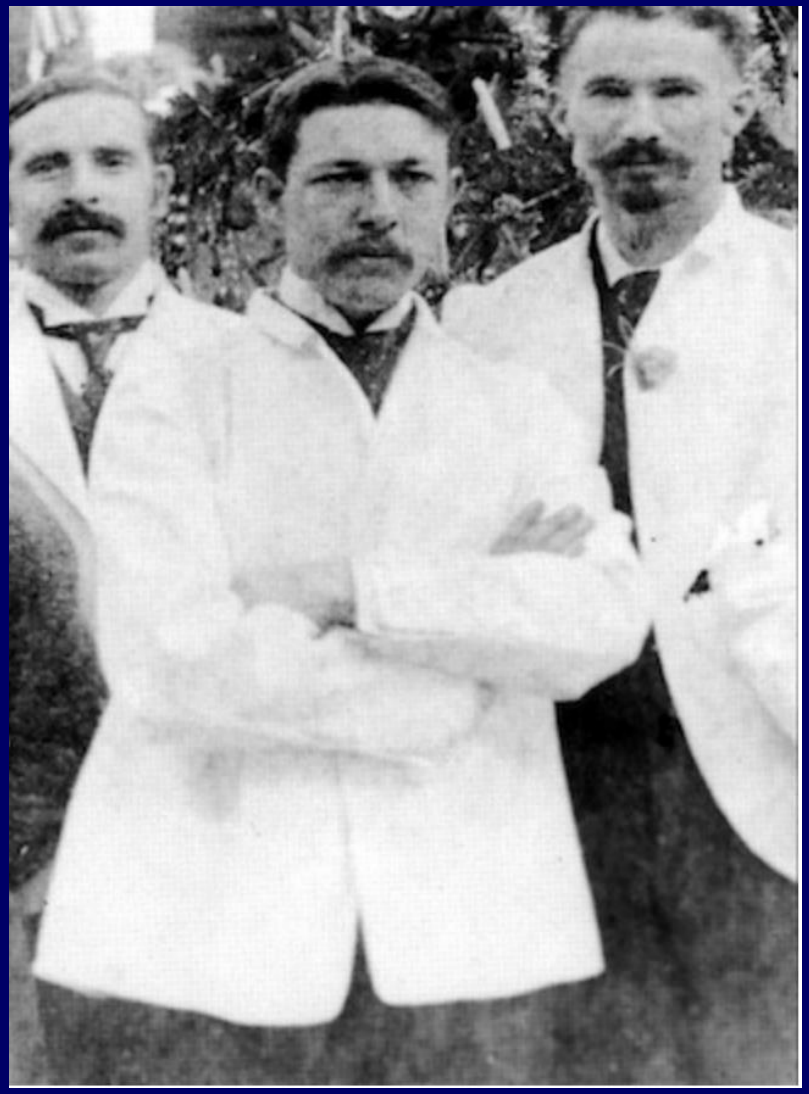
Edward Jenner- Late 18th Century

Figure 1-1 Immunobiology, 6/e. (© Garland Science 2005)

Observed that milkmaids who get a mild viral disease Cowpox (Vaccinia virus) do not get the deadly disease, Smallpox

Inoculation of Cowpox provided protection from Smallpox

William Coley:1892



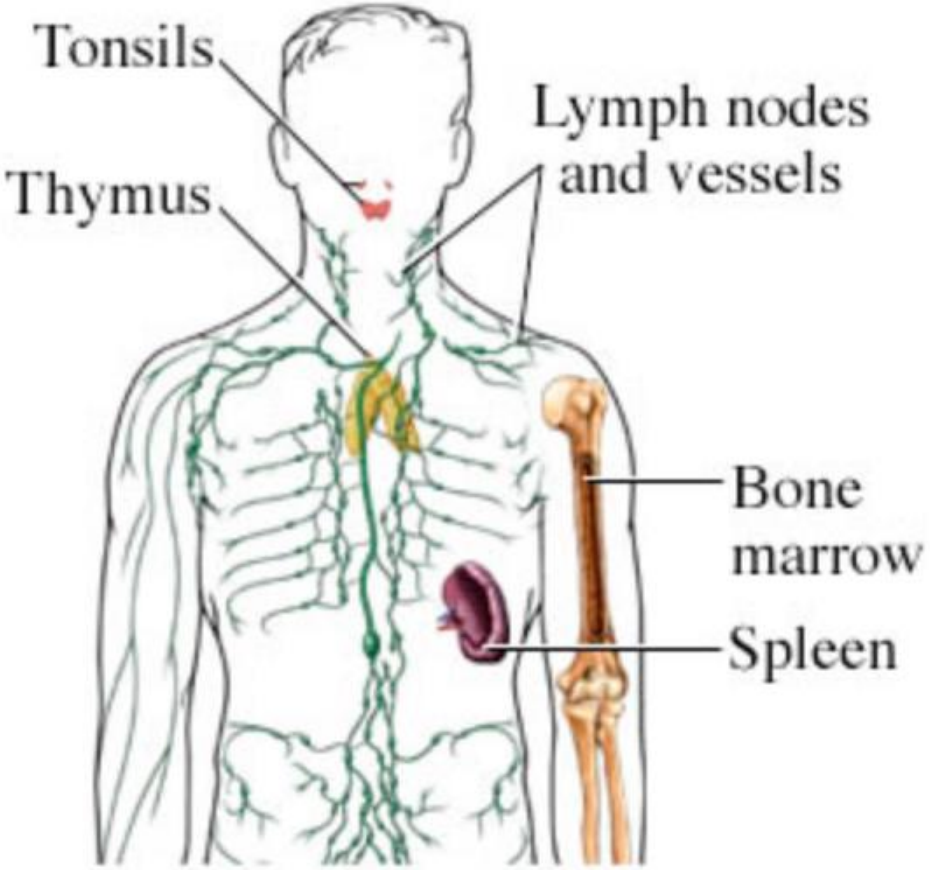
Paul Ehrlich 1854-1915

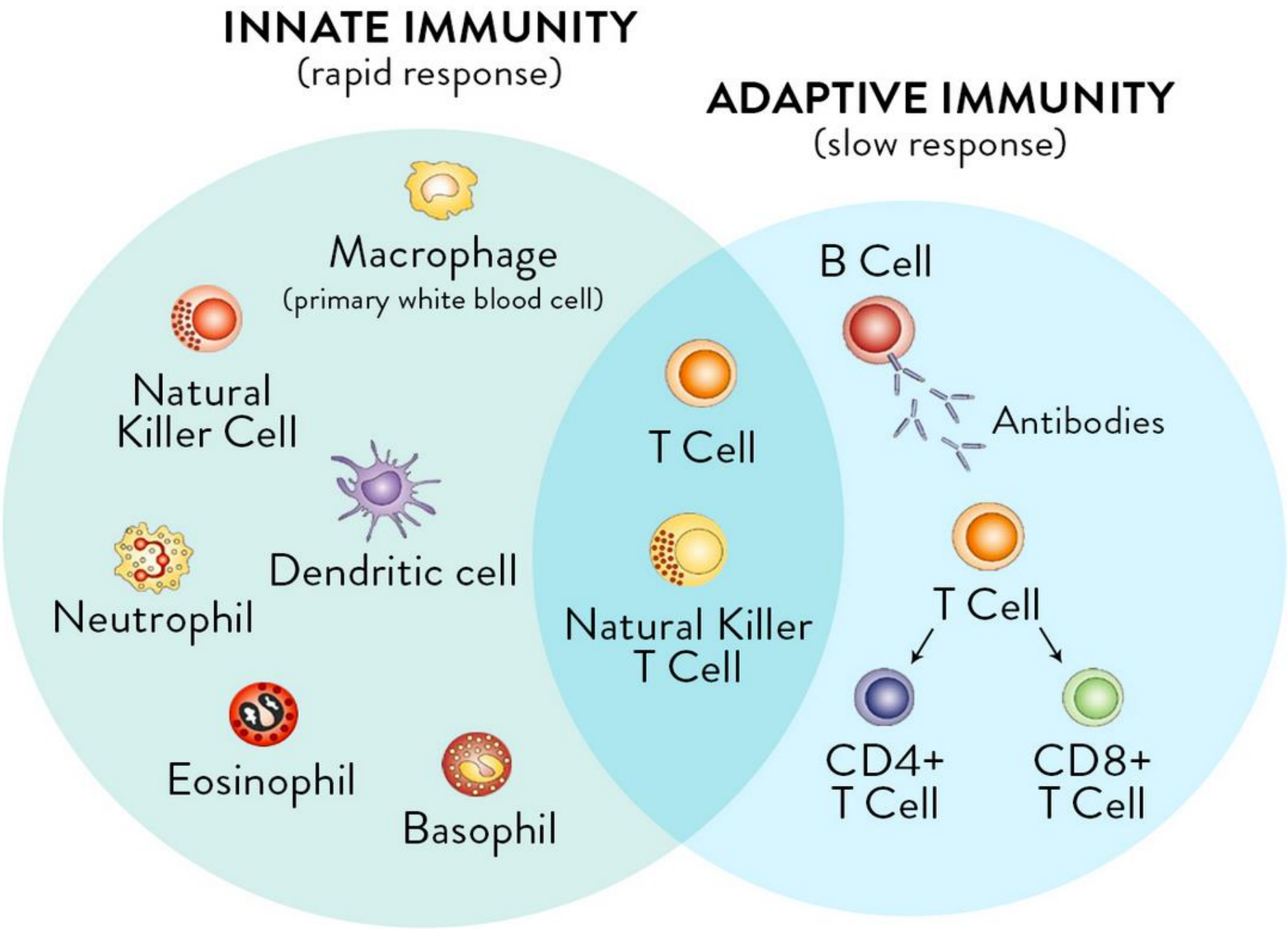
"You see we must take aim - aim by chemical variation! The marvellous effect of an antibody in the serum is due to the fact that in no case it has affinity for the body substances but flies straight onward without deviation, upon the parasites.

The antibodies are therefore MAGIC BULLETS which find the targets themselves… we must therefore concentrate all our powers and abilities on making the aim as accurate as we can contrive, so as to strike the parasites as hard and the body cells as lightly as possible."

circa 1904

Components of the Immune System



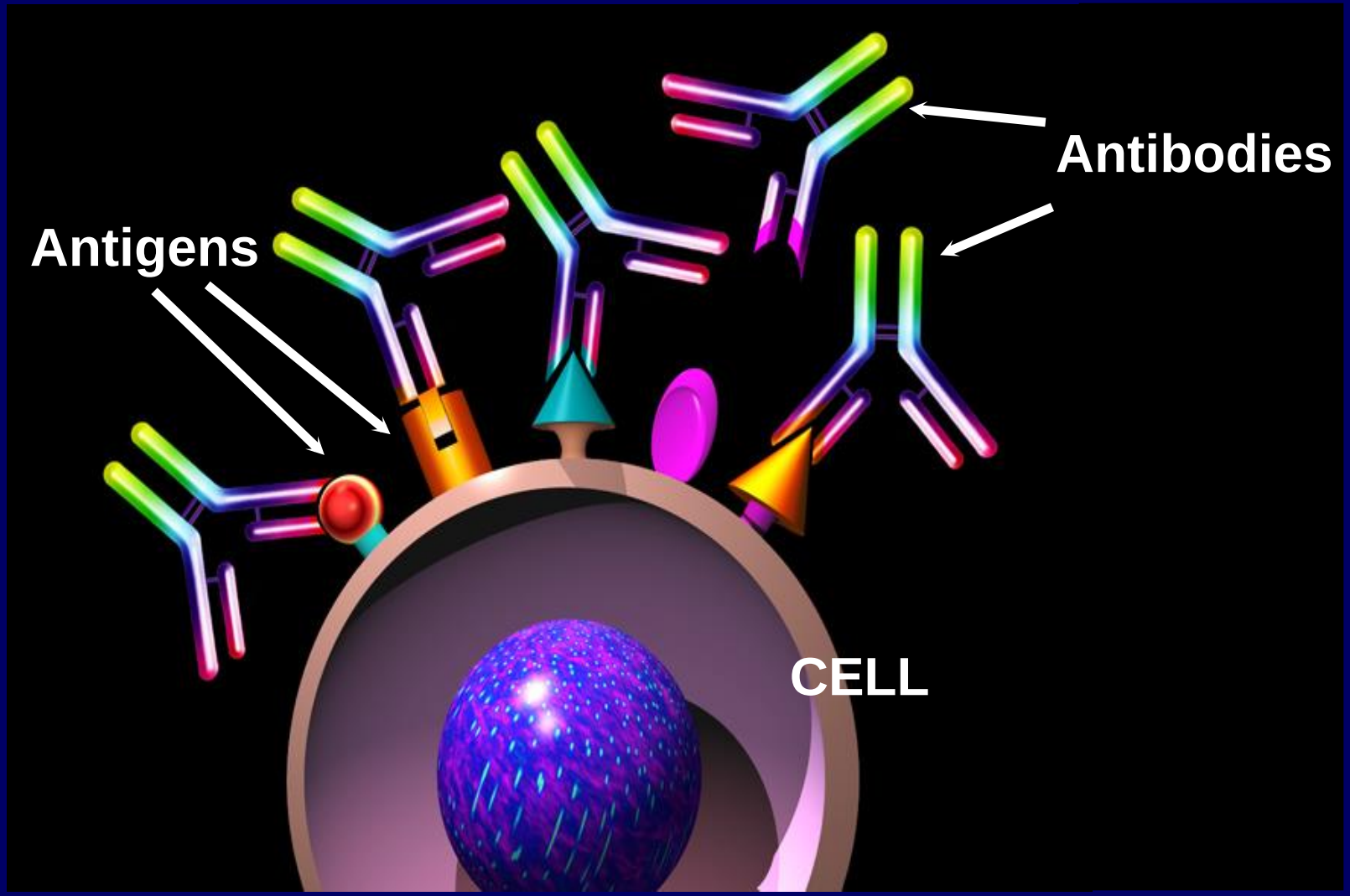

INNATE IMMUNITY
(rapid response)
ADAPTIVE IMMUNITY
(slow response)
Macrophage
(primary white blood cell)
Natural
Killer Cell
Dendritic cell
Neutrophil
Eosinophil
Basophil
T Cell
Natural Killer
T Cell
B Cell
Antibodies
T Cell
CD4+
T Cell
CD8+
T Cell

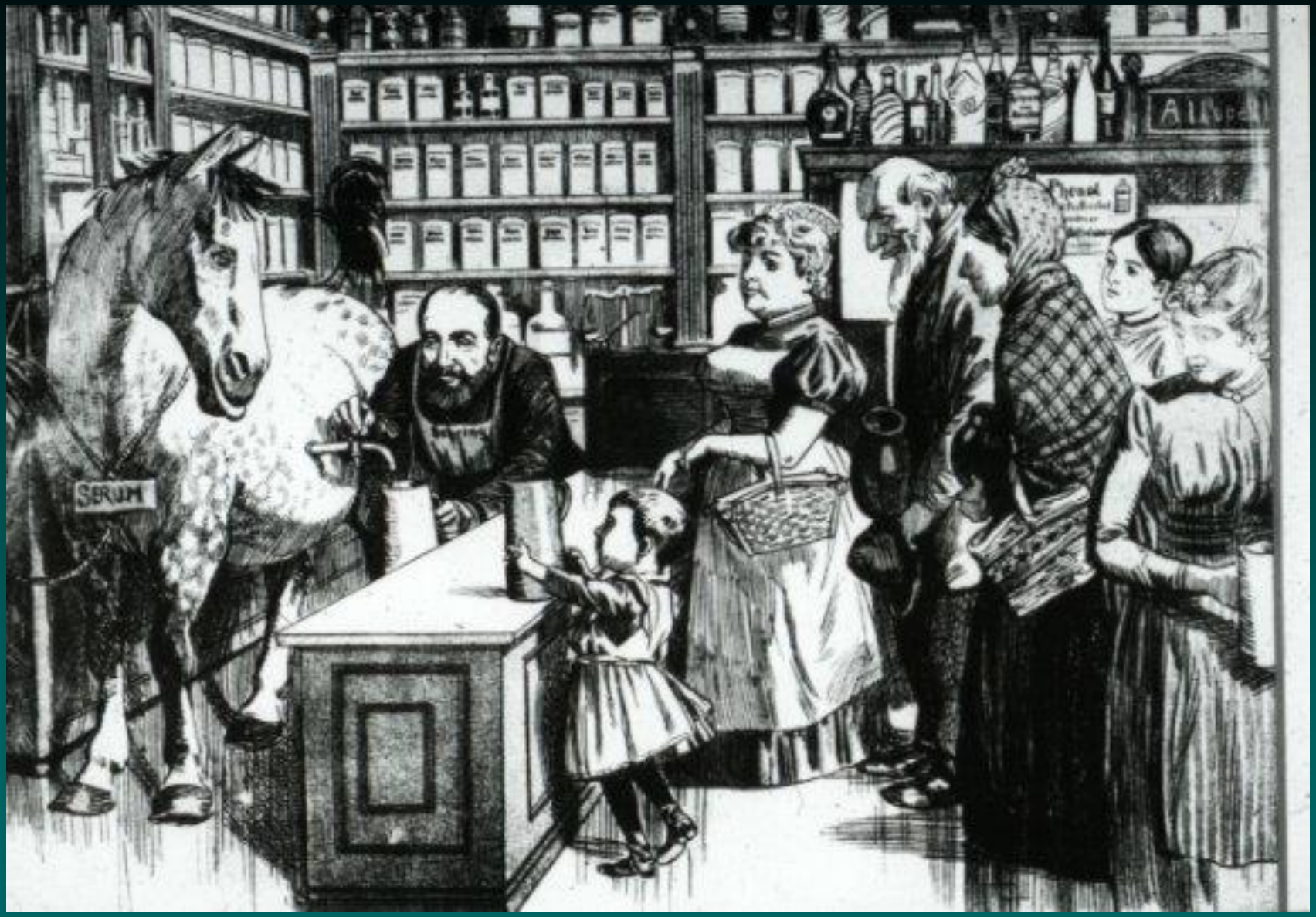
Active vs Passive Immunotherapy*

	Active	Passive
Examples	Vaccines, cellular immunotherapy	Antibodies, checkpoint inhibitors, cytokines
Potential for benefit	Only those who respond	Most all
Timing of response	Slow	Immediate
Immunological memory	Yes	No
Duration of response	Long	Short
Benefit to immunosuppressed pts?	May be a disadvantage	Yes and may improve immunity
Route of administration	Various	Usually systemic

**Immunotherapy*: treatment using certain parts of a person's immune system to fight diseases such as *cancer*

Antibodies/Antigens

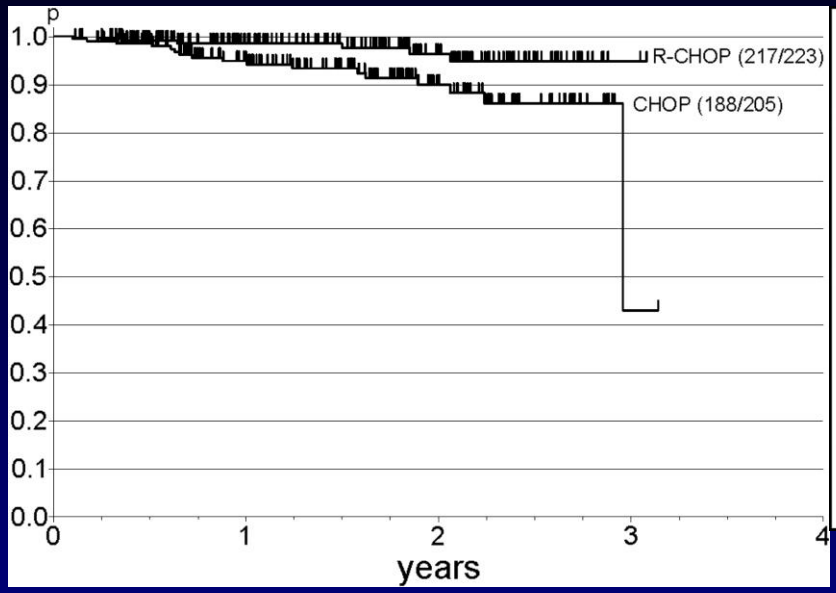



SERUM

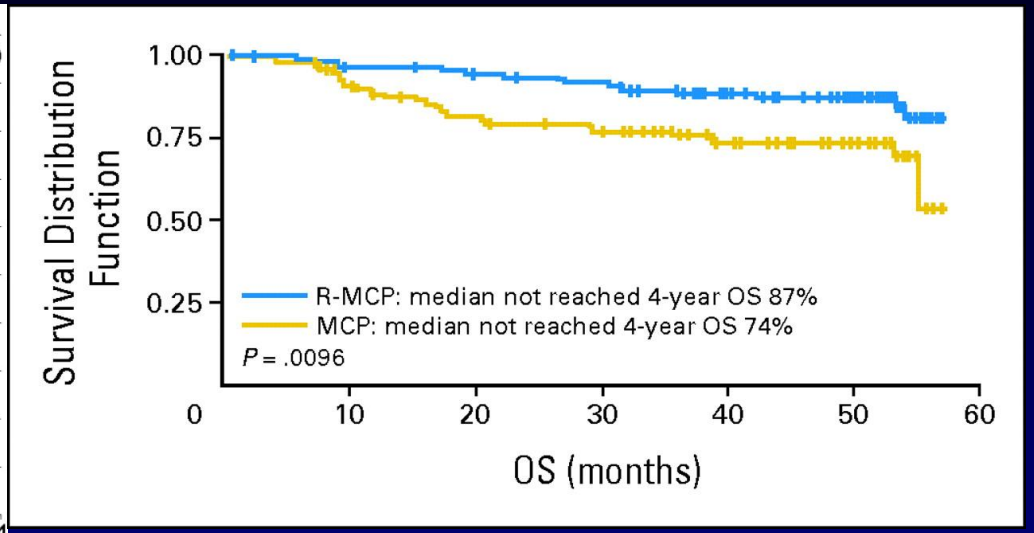
Monoclonal Antibodies in Lymphoma

Antibody	Target	Construct
Rituximab, obinutuzumab, ofatumumab	CD20	Unconjugated
Alemtuzumab	CD52	Unconjugated
Daratumumab	CD38	Unconjugated
MOR-208	CD19	Unconjugated
Nivolumab, pembrolizumab	PD-1	Unconjugated
Atezolizumab	PDL-1	Unconjugated
Y-90 ibrutmomab tiuxetan	CD20	RIT
Brentuximab vedotin	CD30	ADC
Polatuzumab vedotin	CD79b	ADC
Blinatumomab	CD19/CD3	BITE

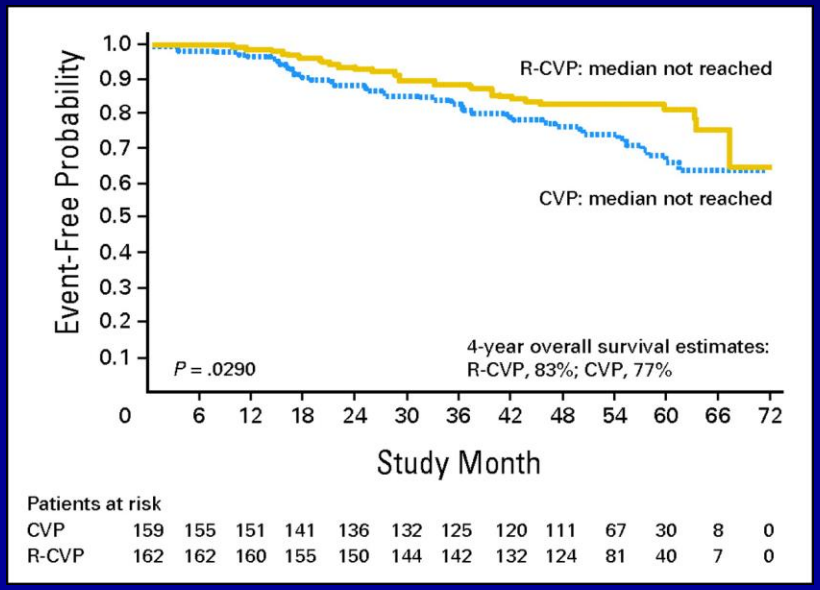
Rituximab in Front-line Follicular NHL



Hiddemann et al. Blood 2005;106:3725-3732

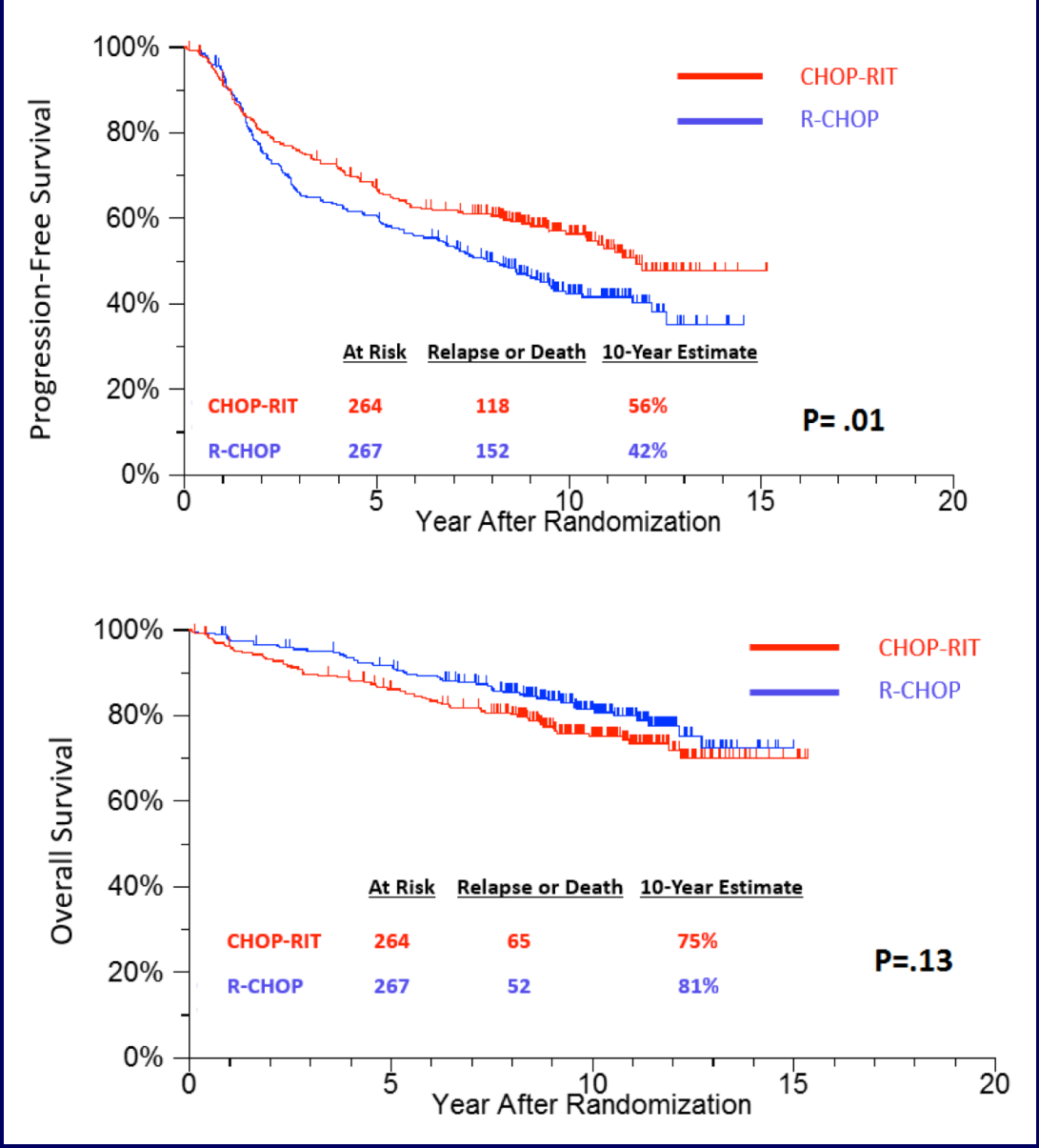


Herold et al. JCO 2007;25:1986-1992



Marcus et al. JCO 2008;26:4579-4586

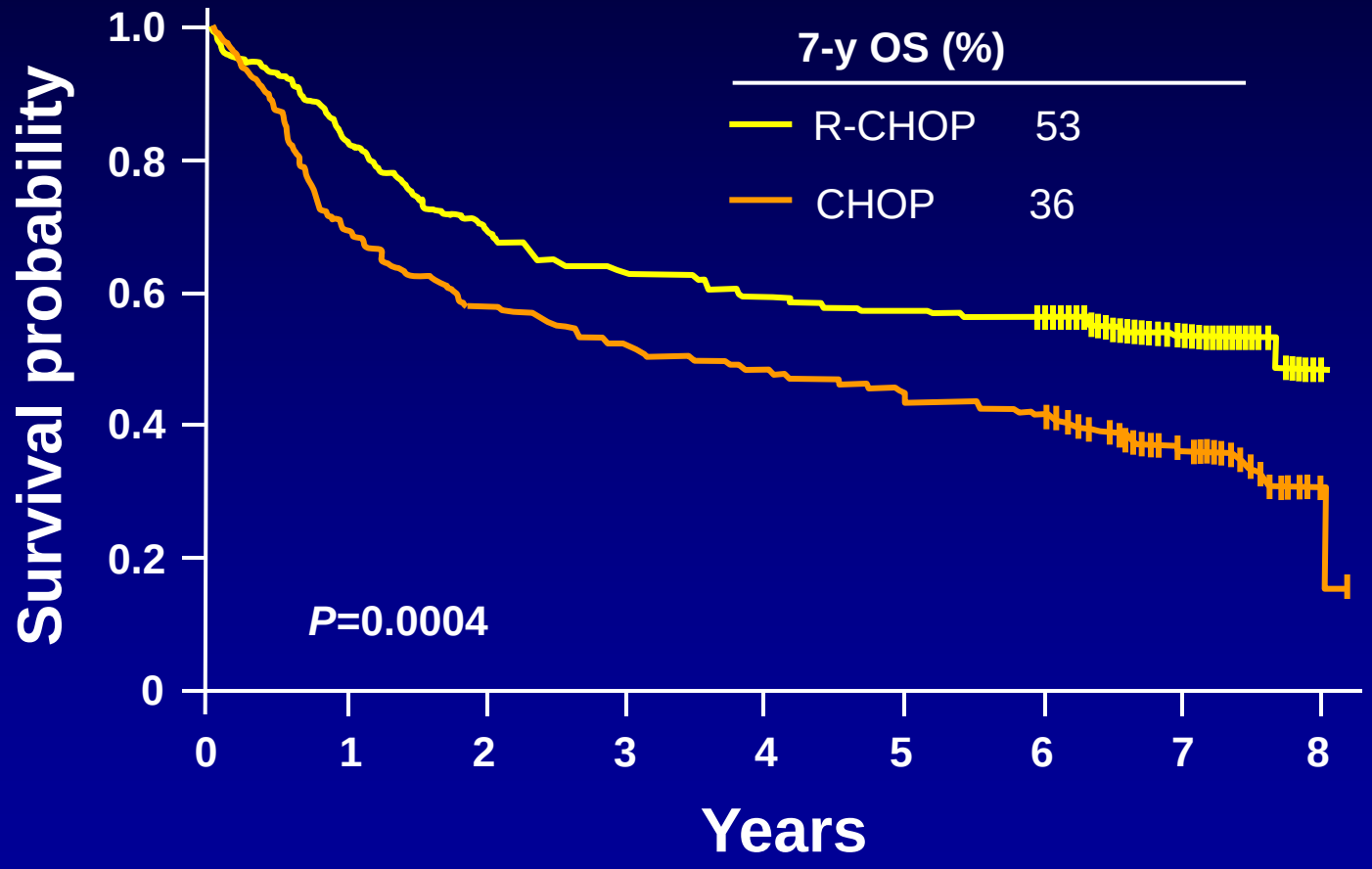
PFS and Survival Curves for S0016



Med f/u 10.3 y

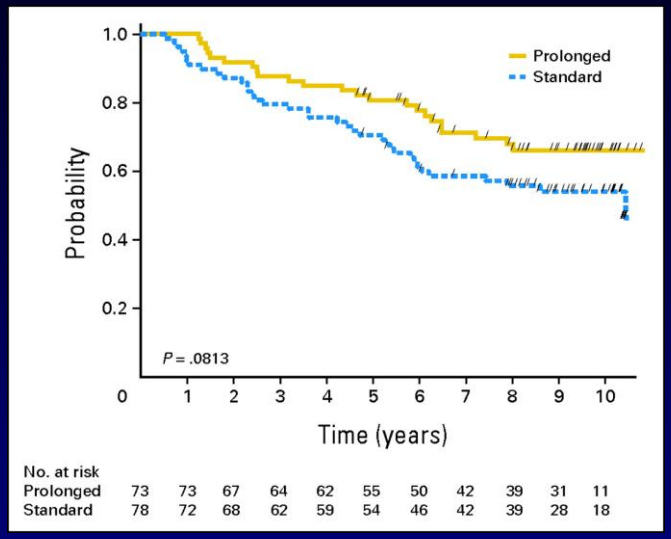
Shadman et al, JCO, e-pub online, 2018

7-Year Results of GELA Study of CHOP ± Rituximab in Older Patients With DLBCL: OS

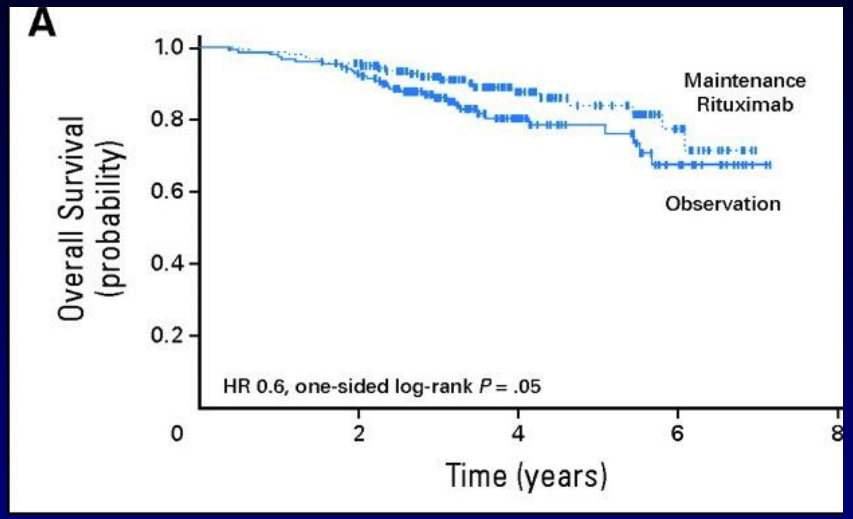


Coiffier et al. ASCO, 2007. Abstract 8009.

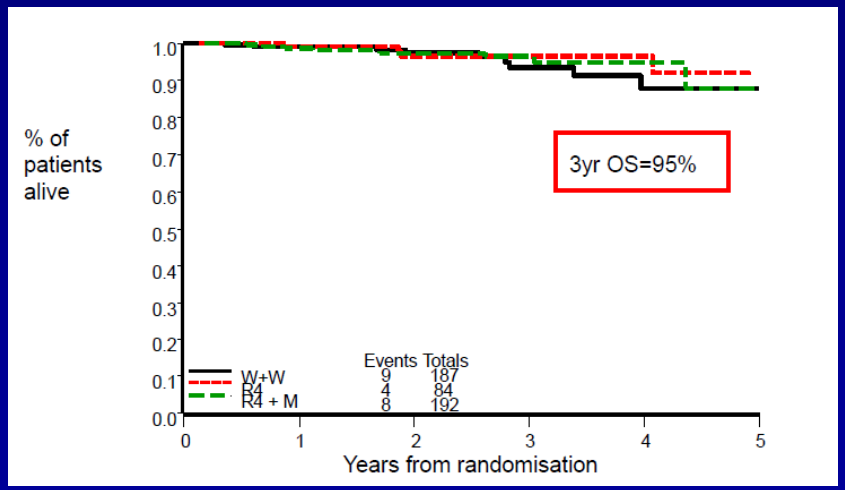
Overall Survival By Maintenance



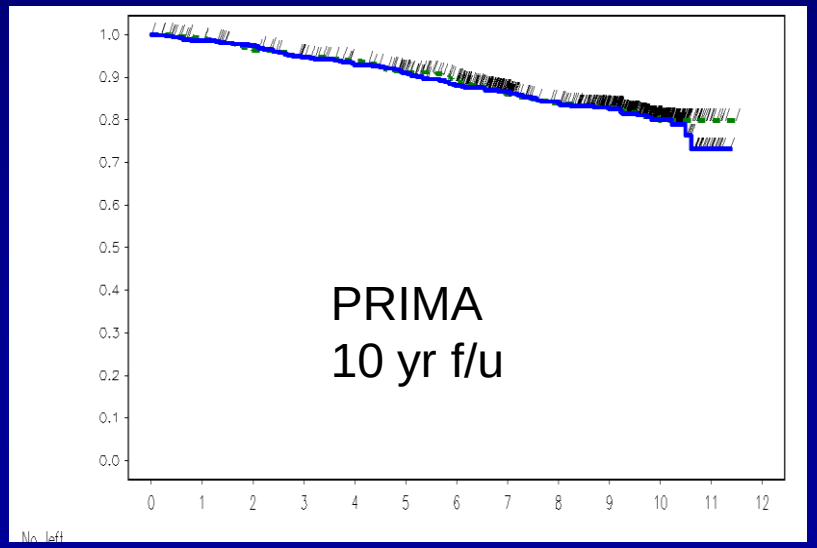
Martinelli G et al. JCO 2010;28:4480-4484



Hochster, H. et al. J Clin Oncol; 27:1607-1614 2009



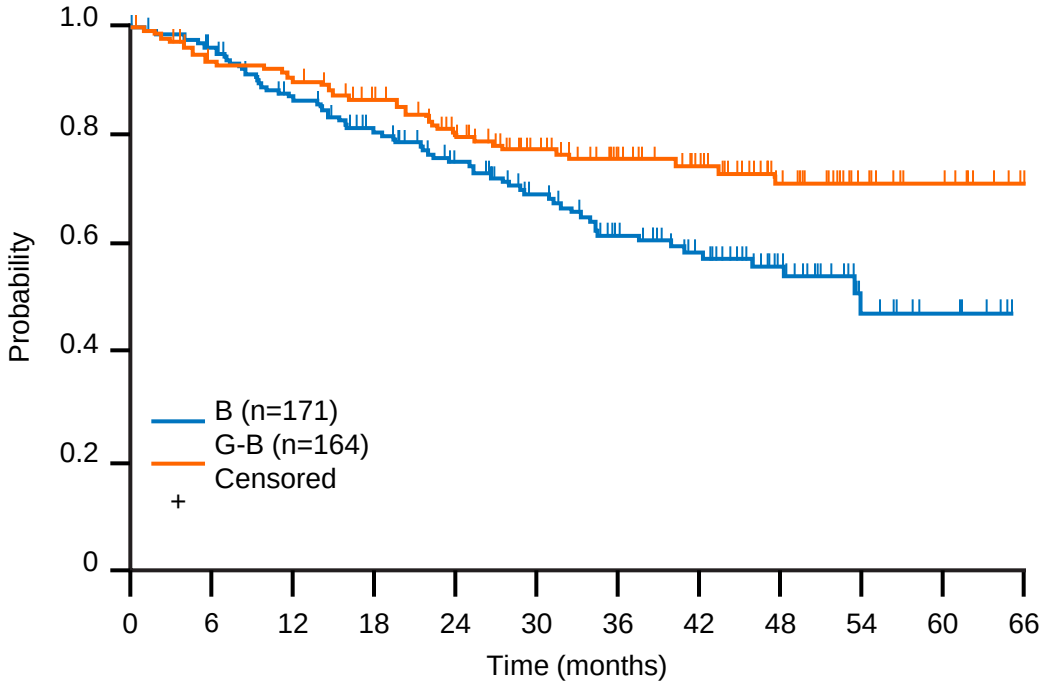
Ardeshna KM et al. *Proc ASH* 2010; Abstract 6



Salles et al, abstr 486, ASH 2017

OS in the FL population

Kaplan-Meier plot of OS by treatment arm (FL)



No. of patients at risk

B	171	159	137	122	103	84	65	49	32	13	7	0
G-B	164	147	141	129	111	90	71	56	38	20	12	0

	G-B, n=164	***B, n=171***
Pts with event, n (%)	39 (23.8)	64 (37.4)
Median OS (95% CI), mo	NR (NR, NR)	53.9 (40.9, NR)
HR (95% CI), p-value*	0.58 (0.39, 0.86), p=0.0061	

Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

NR, not reached

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

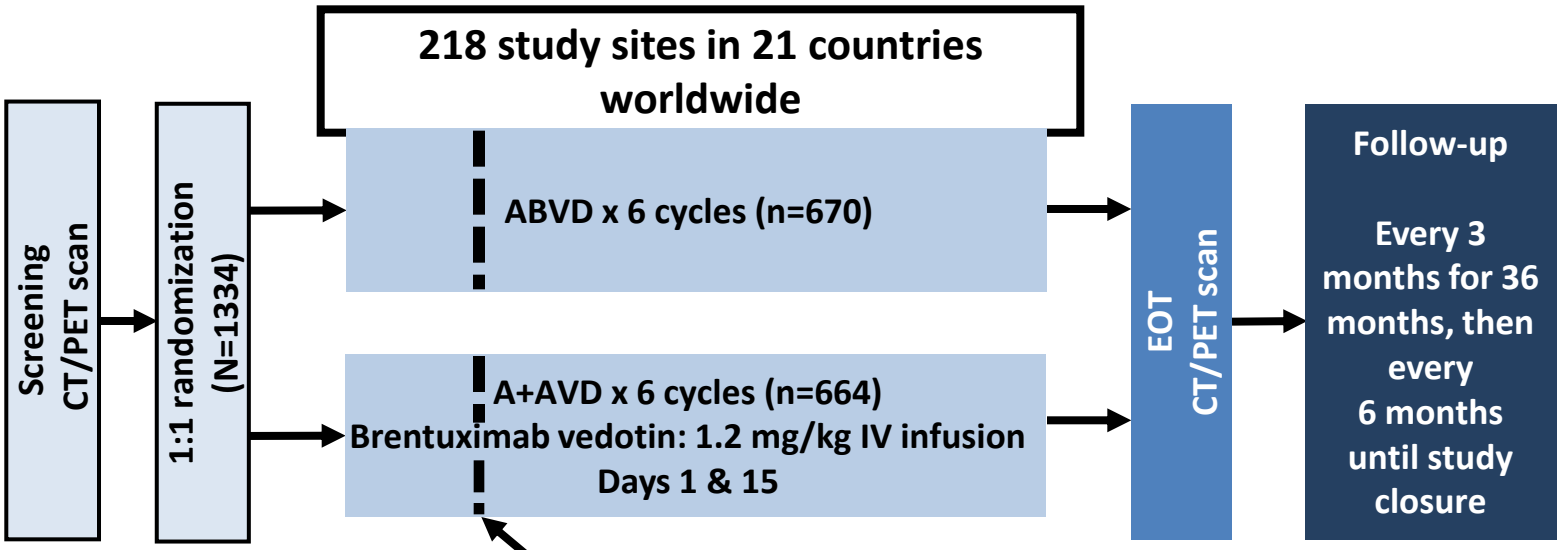
Amping up monoclonal antibodies: Antibody-drug conjugates (ADC)

Sievers Annu Rev Med. 2013;64:15-29

Brentuximab Vedotin in HL: Response Results

	N=102	
	IRF	Investigator
Overall response rate (95% CI)	75% (65, 83)	72% (62, 80)
Complete remission	34%	33%
Partial remission	40%	38%
Stable disease	22%	27%
Progressive disease	3%	0%
Not evaluable	1%	1%

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

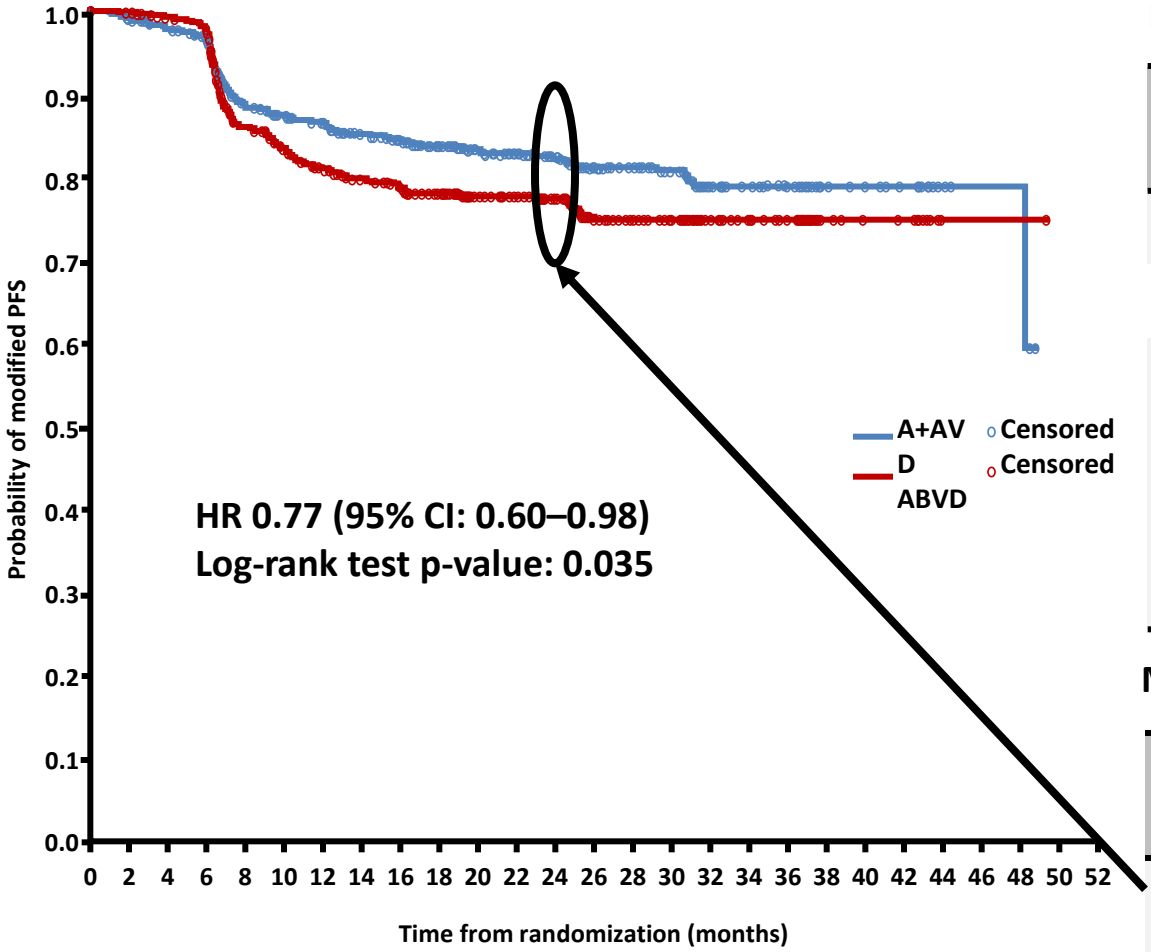


- Inclusion criteria
  - cHL stage — III or IV
  - ECOG PS — 0, 1 or 2
  - Age — ≥18 years
  - Measurable disease
  - Adequate liver and renal function

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

Connors et al, abstr. 6, ASH 2017

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

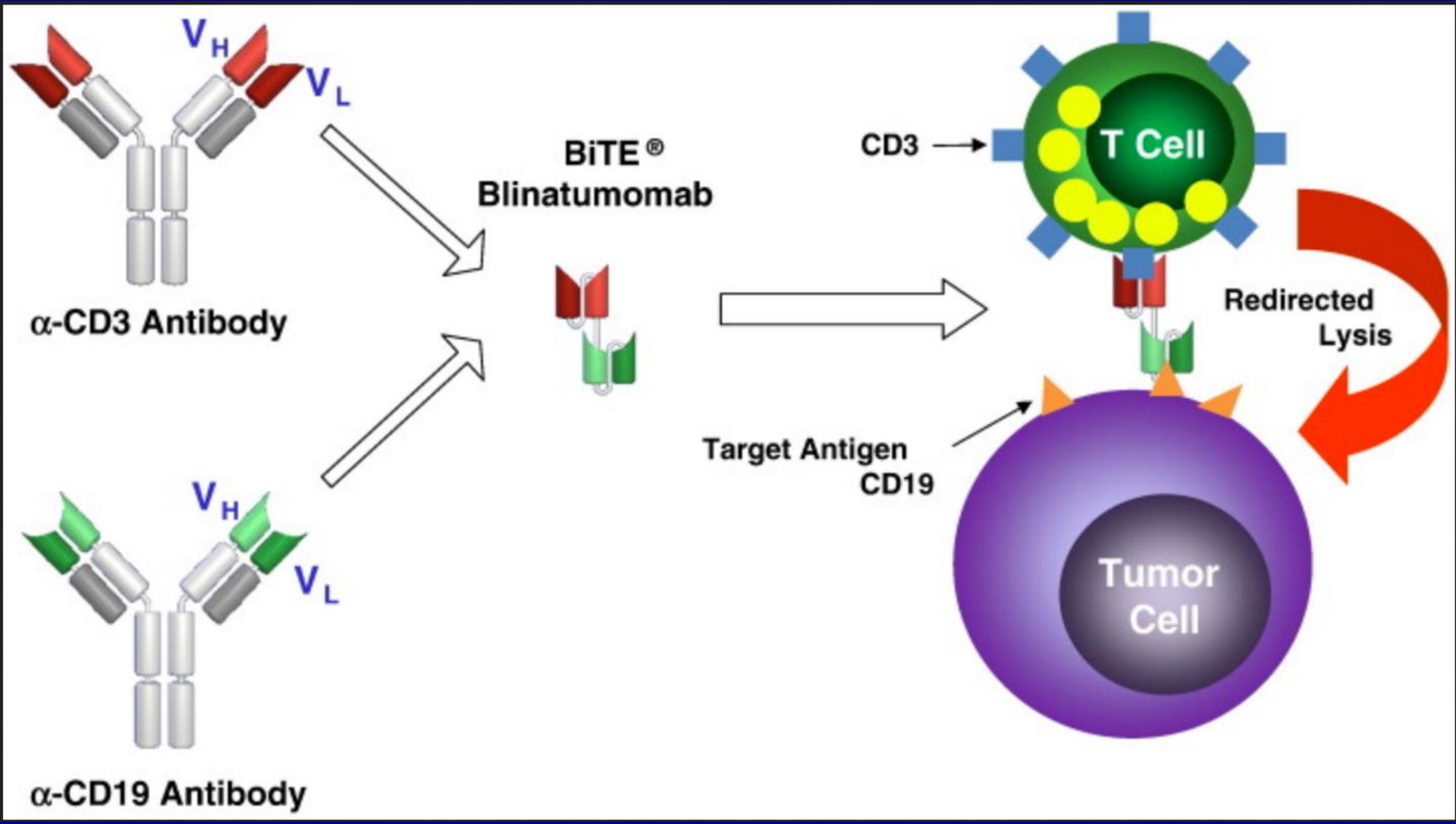
Category	A+AVD N=117	ABVD N=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

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)

Blinatumomab



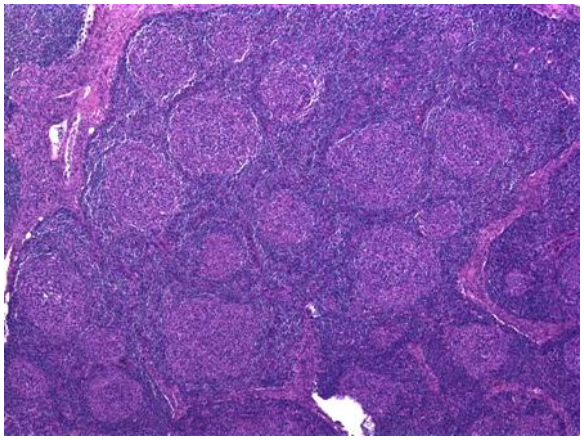
Blinatumomab in Relapsed NHL

	Dose ($\mu g/m^2$/day)	No. of Patients	No. of Responses				
			CR	CRu	CR/CRu	PR	ORR CR + CRu + PR, n (%)
Response at highest actual dose received*	0.5, 1.5	9	0	0		0	0 (0)
	5	7†	0	0		0	0 (0)
	15	15†	1	0		2	3 (20)
	30	6†	1	0		0	1 (17)
	60	35†	8	5		11	24 (69)
	90	4†	1	0		1	2 (50)
Response at target dose*							
By histology							
FL	60	15			6	6	12 (80)
MCL	60	7			3	2	5 (71)
DLBCL‡	60§	11			4	2	6 (55)
Other	60	2			0	1	1 (50)
By early relapse status‖							
Early relapse	60	19			5	5	10 (53)
No early relapse	60	16			8	6	14 (88)

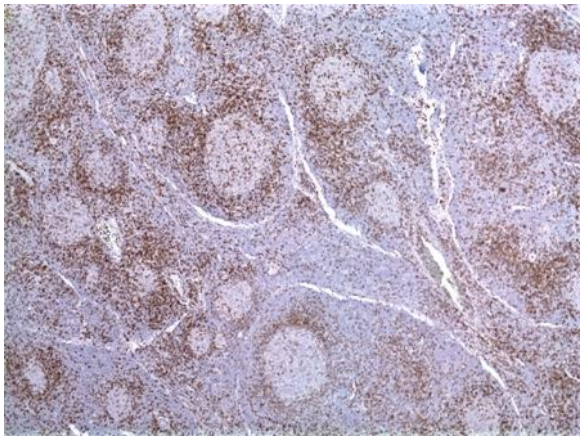
Goebeler et al, JCP 34:1104, 2016

Not all cells in the tumor are cancer cells

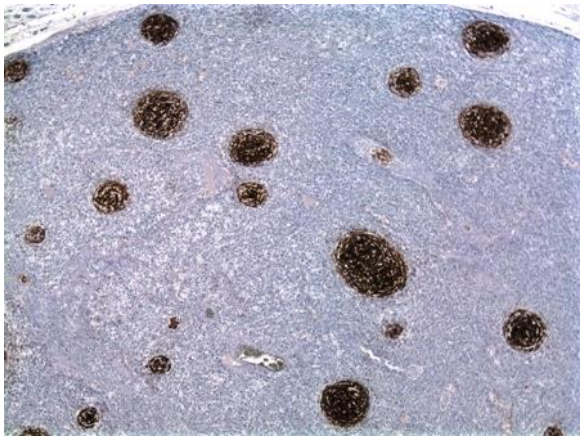
HE stain



CD3 stain

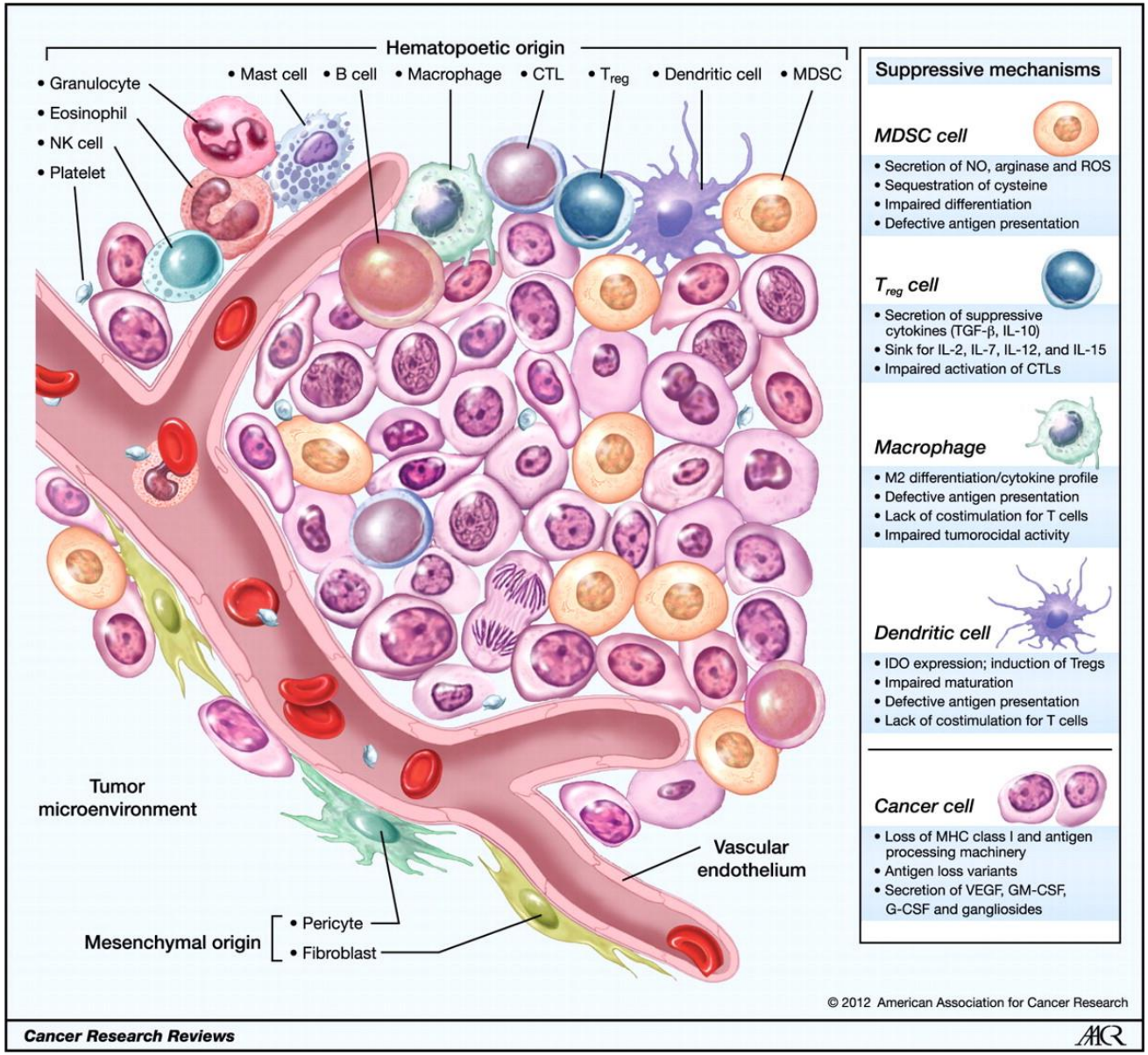


CD21 stain



- 15-40% of intratumoral cells are not malignant cells
- But immune response appears ineffective

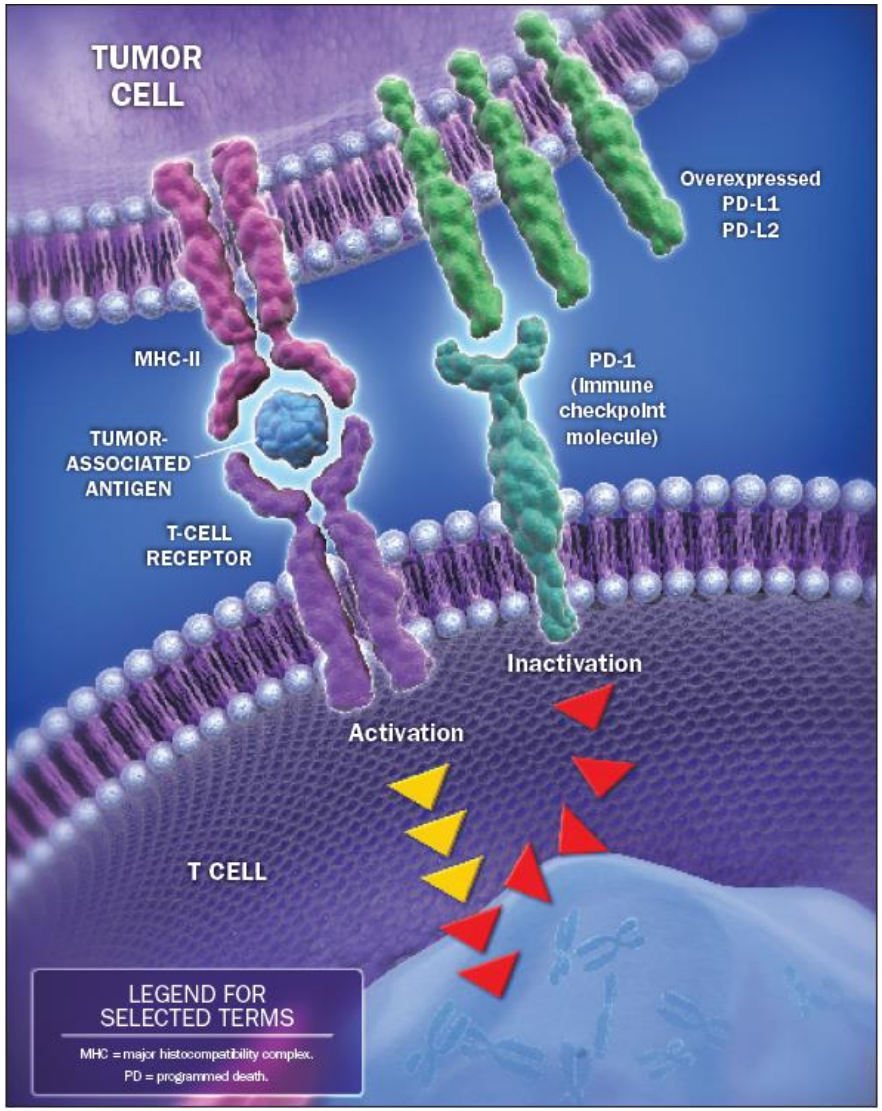
Immunotherapeutic Targets

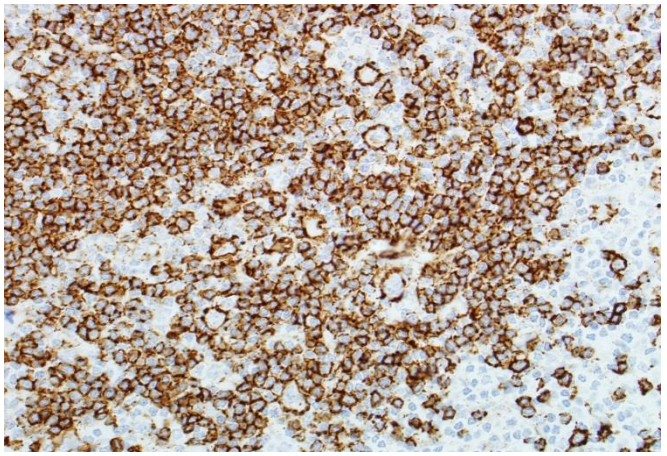


Immunotherapy at present mainly targets ineffective T-cells

- Prevent T-cells from being “switched off”
- Specifically activate T-cells
- Increase T-cell ability to target cancer cells

PD-1 Pathway and Immune Surveillance

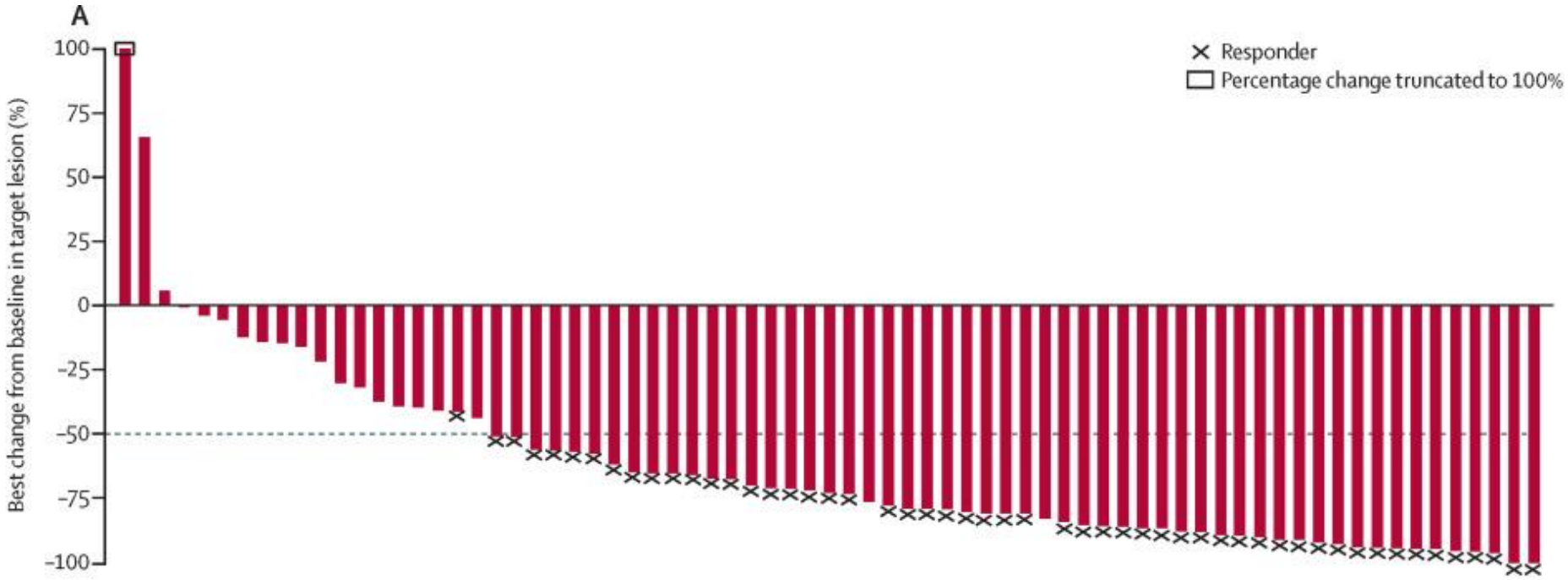




- PD-1 is expressed on the surface of activated T cells
- Its ligands, PD-L1 and PD-L2, are overexpressed in certain tumor cells
- Binding of PD-1 to its ligands inhibits T-cell activation, allowing tumors to evade the immune response

Nivolumab for classical Hodgkin's lymphoma: a multicentre, multicohort, single-arm phase 2 trial (Cohort B).

80 patients – failed ASCT and BV
66% ORR



Younes et al. Lancet Oncol. 2016 2016 Sep;17(9):1283-94.

Interim Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

Alex F. Herrera[1], Alison J. Moskowitz[2], Nancy L. Bartlett [3], Julie M. Vose[4], Radhakrishnan Ramchandren[5], Tatyana A. Feldman[6], Ann S. LaCasce[7], Stephen M. Ansell[8], Craig H. Moskowitz[2], Keenan Fenton[9], Carol Anne Ogden[9], David Taft[9], Qu Zhang[9], Kazunobu Kato[10], Mary Campbell[9], Ranjana H. Advani[11]

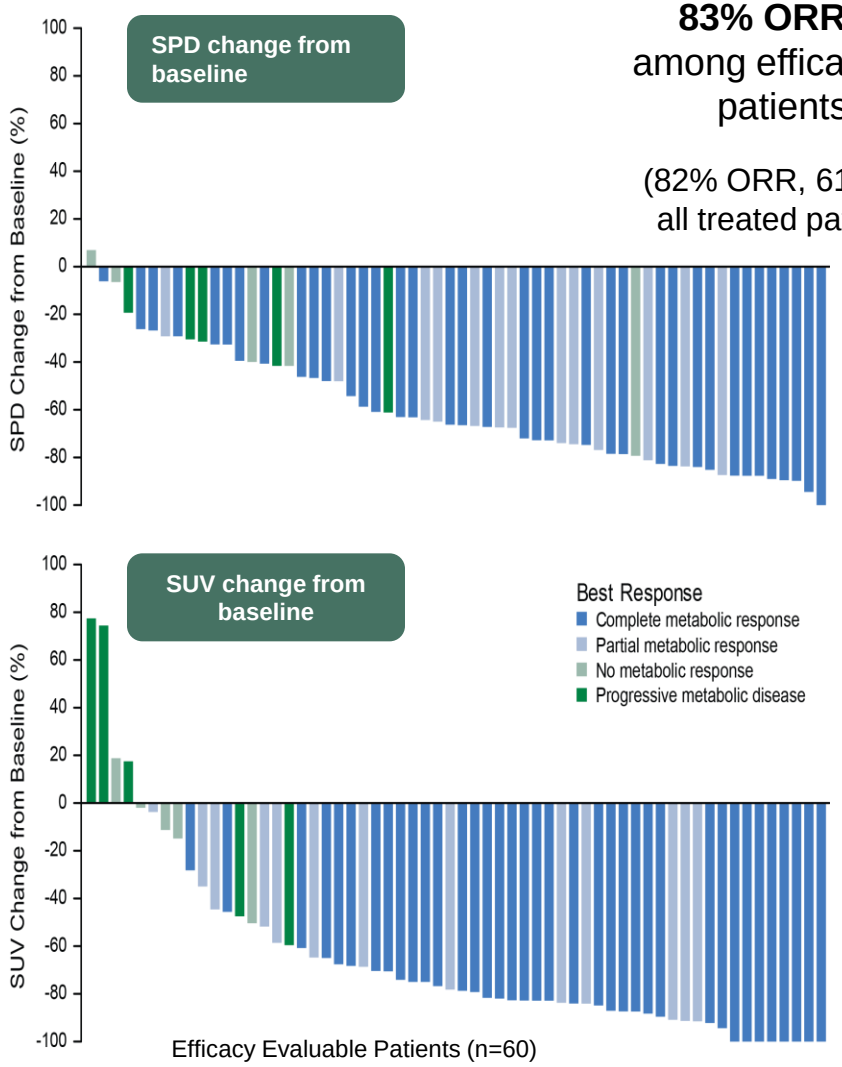
[1]City of Hope National Medical Center, Duarte, CA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Washington University School of Medicine, St. Louis, MO, USA; [4]University of Nebraska Medical Center, Omaha, NE, USA; [5]Karmanos Cancer Institute, Detroit, MI, USA; [6]Hackensack University Medical Center, Hackensack, NJ, USA; [7]Dana Farber Cancer Institute, Boston, MA, USA; [8]Mayo Clinic, Rochester, MN, USA; [9]Seattle Genetics, Inc., Bothell, WA, USA; [10]Bristol-Myers Squibb, Princeton, NJ, USA; [11]Stanford University Medical Center, Palo Alto, CA, USA

American Society of Hematology Annual Meeting; Atlanta, Georgia, December 9–12, 2017, Abstract #649

Tumor Response

	n (%)	95% CI
Objective response rate (CR + PR)	50 (83)	72, 92
Complete response	37 (62)	48, 74
Deauville score = 1	14 (23)	
Deauville score = 2	15 (25)	
Deauville score = 3	7 (12)	
Deauville score = 5*	1 (2)	
Partial response	13 (22)	12, 34
Deauville score = 4	7 (12)	
Deauville score = 5	6 (10)	
Stable disease	5 (8)	3, 18
Deauville score = 5	5 (8)	
Progressive disease	4 (7)	2, 16
Deauville score = 5	4 (7)	
Clinical progression	1 (2)	

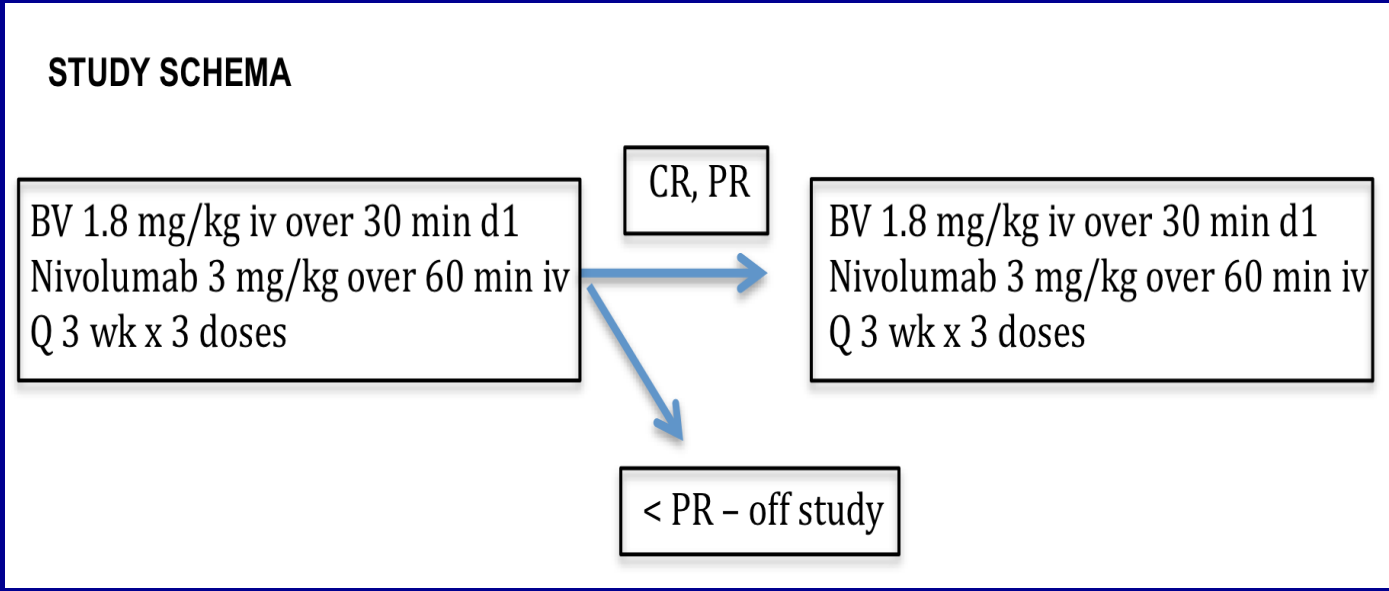
*Residual area of FDG-avidity on PET was biopsied and was not consistent with residual Hodgkin lymphoma



83% ORR, 62% CR
among efficacy evaluable patients (n=60)

(82% ORR, 61% CR among all treated patients,; n=61)

Schema of BV+Nivo in Untreated Hodgkin Lymphoma

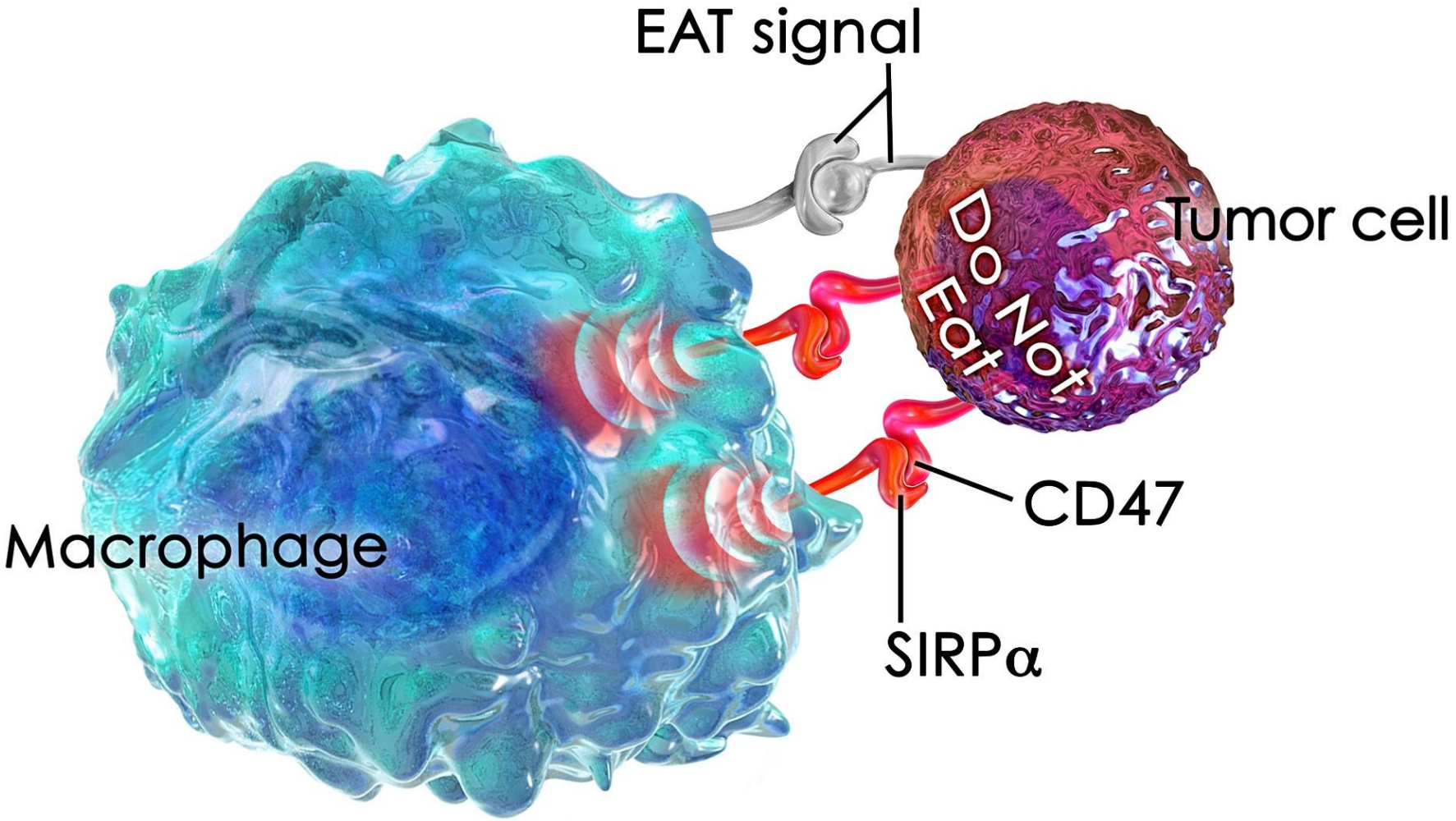


CPI in NHL

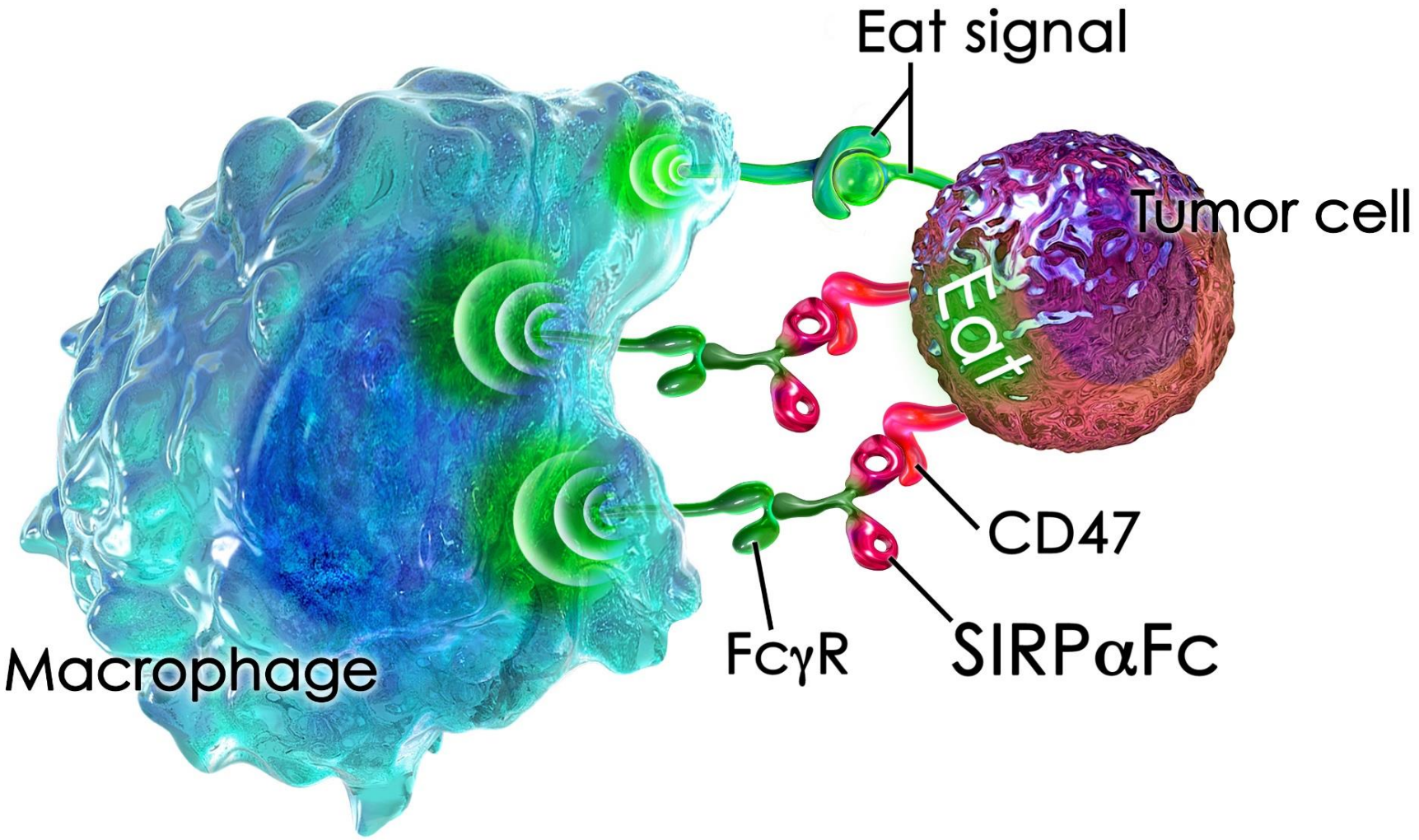
Disease	Drug	Target	Phase	Patients	ORR	PR	CR	PFS	OS	DOR	References
Diffuse large B cell lymphoma (DLBCL)											
DLBCL	Nivolumab	Anti-PD-1	I	11	4 (36%)	3 (27%)	1/11 (9%)	NR	NR	22 weeks	(44)
DLBCL	Pidilizumab 0.2-6.0 mg/kg	Unknown	I	2	0%	0	0	NR	NR	NR	(45)
DLBCL, PMBL, transformed indolent lymphoma, after auto-HSCT	Pidilizumab 1.5 mg/kg every 42 days, 30-90 days after auto-HSCT	Unknown	II	66	51%	6 (17%)	12 (34%)	72% at 16 months	NR	NR	(46)
Follicular lymphoma (FL)											
FL (treatment-naïve)	Pidilizumab 3 mg/kg	Unknown	I	1	100%	0	1 (100%)	NR	NR		(45)
FL	Nivolumab	Anti-PD-1	I	10	40%	3 (30%)	1 (10%)	NR	68% at 24 weeks	MNR	(44)
FL (R/R)	Pidilizumab + rituximab	Unknown, anti-CD20	II	32 (29 evaluable)	19 (66%)	4 (14%)	15 (52%)	NR	NR	Median 20.2 months	(47)
Other B-NHL											
PMBL	Nivolumab	Anti-PD-1	Ib	2	100% (SD)	NR	NR	24 weeks: 100%	NR		(44)
T-NHL											
CTCL	Nivolumab	Anti-PD-1	I	13	15%	15%	0%	NR	NR	MNR	(29)
PTCL	Nivolumab	Anti-PD-1	I	5	40%	0%	0%	NR	NR	MNR	(29)
Sézary Syndrome (SS); Mycosis Fungoides (MF)	Pembrolizumab	Anti-PD-1	II	24 total (SS =18; MF n=6)	SS: 33%; MF: 50%	SS: 33%; MF: 33%	SS: 0; MF 17%	12-month PFS: 69%	MNR	MNR	(48)

Lesokhin et al Stem Cell Inv, epub 2017

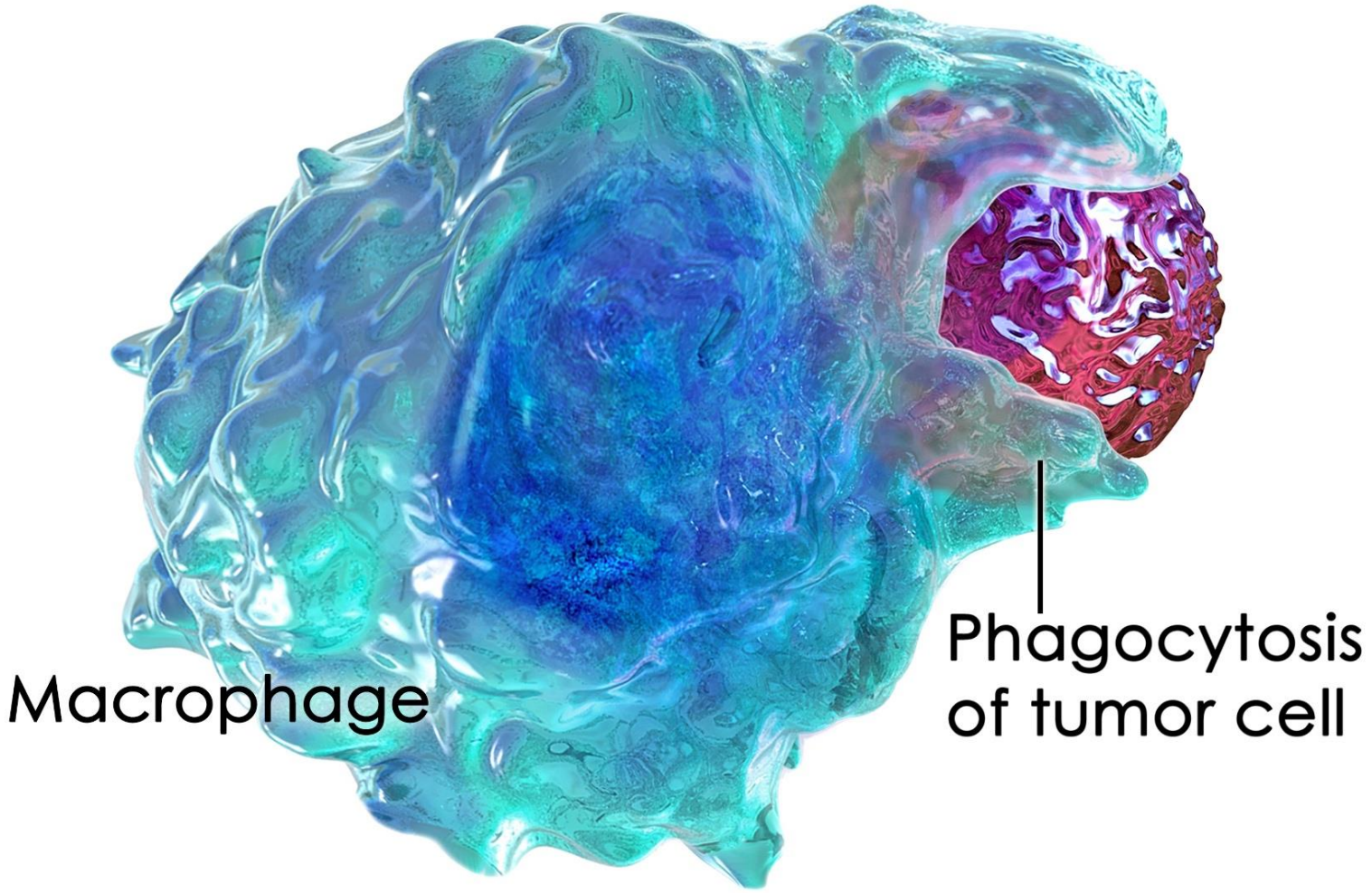
A) CD47 Inhibition of Phagocytosis



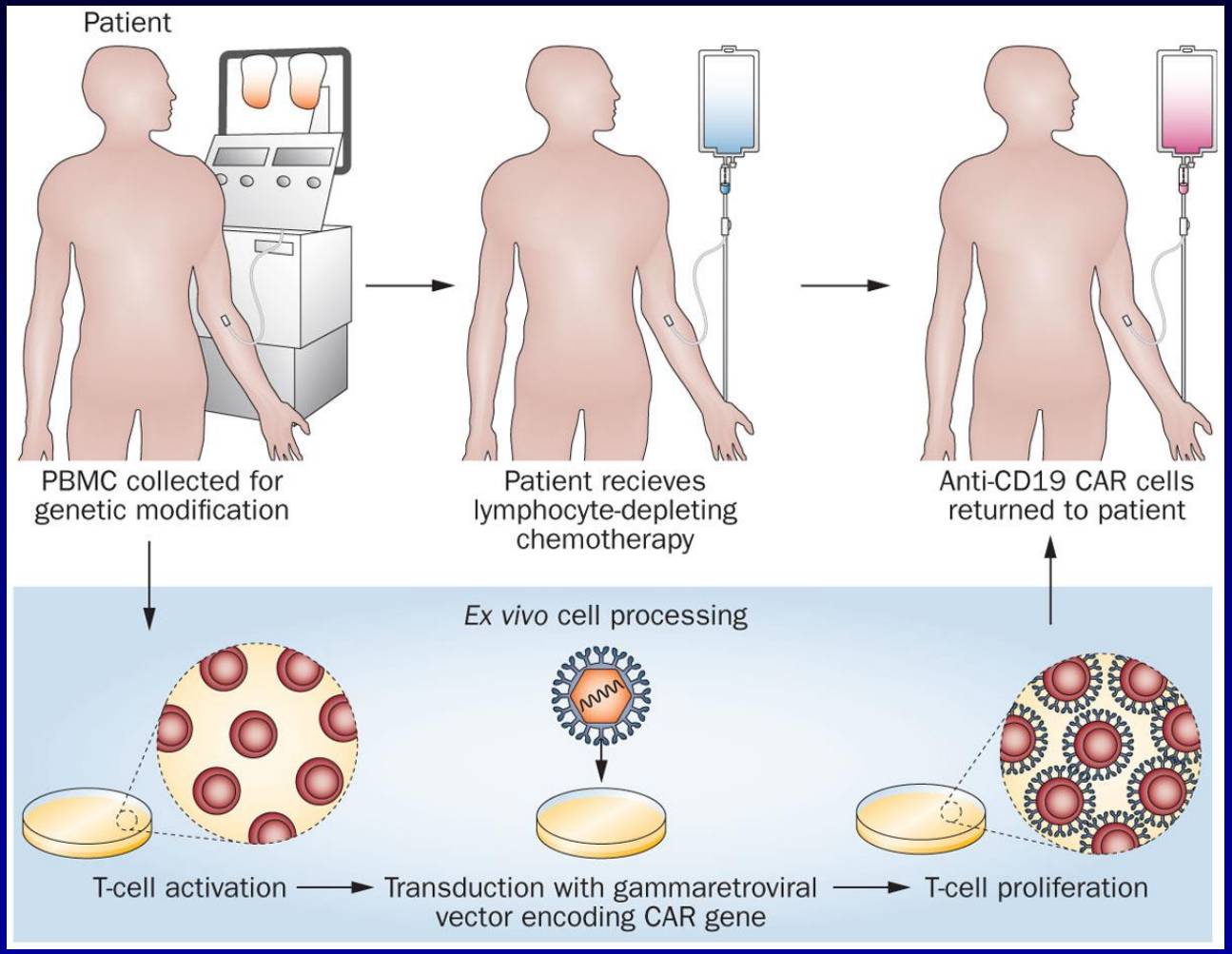
C) SIRPαFc Blockade of the CD47 Signal



D) Macrophage Phagocytosis



Chimeric Antigen Receptor (CAR) T-cells



Kochenderfer et al. Nat. Rev. Clin. Oncol.
doi:10.1038/nrclinonc.2013.46

Targeted Agents and Immunotherapy

- New agents target specific parts of the lymphoma cell and its environment
- Combinations in development
- Potential to replace chemotherapy
- Less toxicity, greater efficacy
- Increase potential for cure

Let's Make Lymphoma Therapy Great (Again?)