QUARTO EVENTO NAZIONALE

SIE incontra i pazienti

Nuovi farmaci nei linfomi

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26 maggio 2025

Bologna, Royal Hotel Carlton

DISCLOSURES

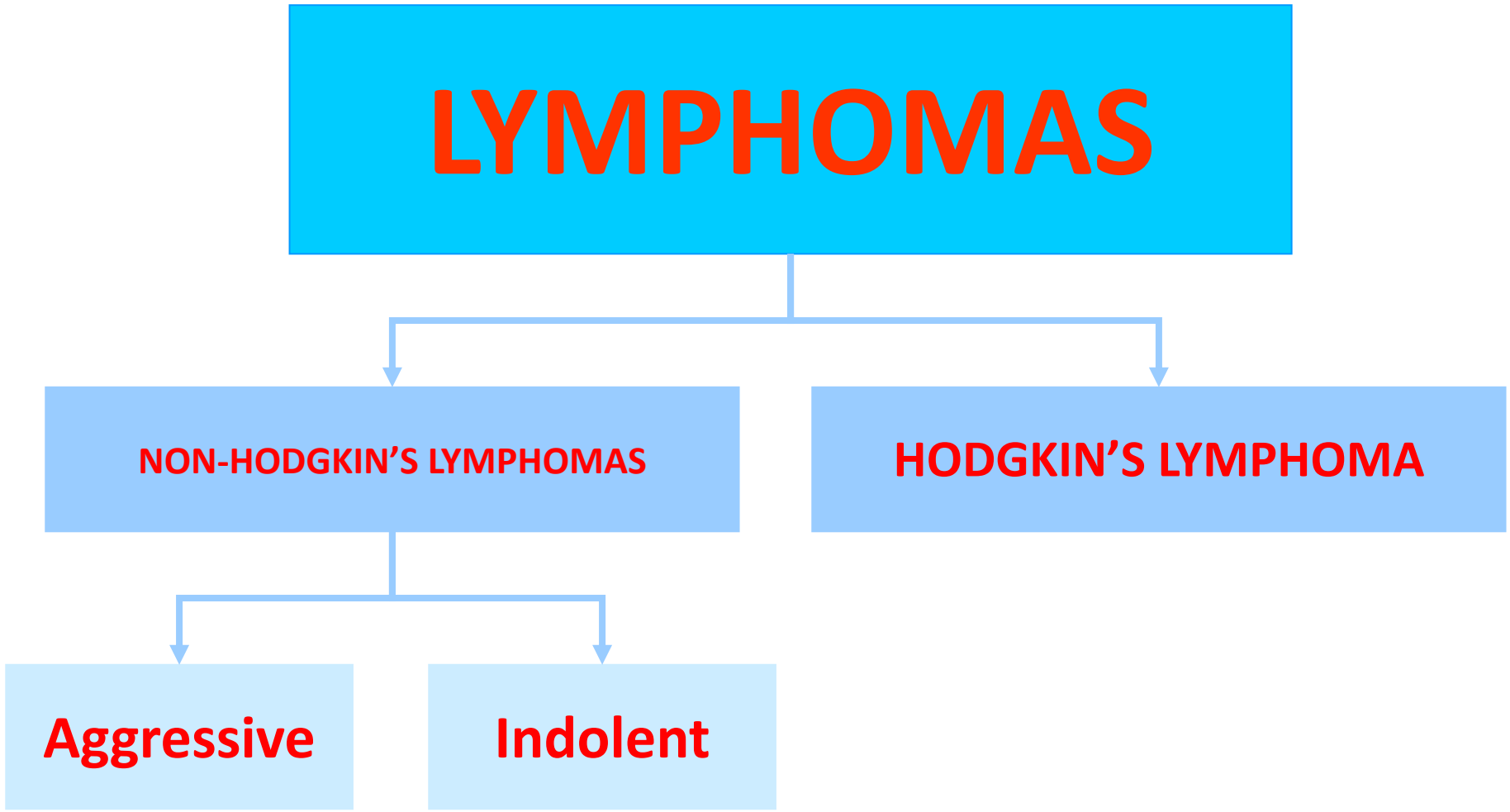
Consultant or advisory role	Advisory board: Roche, Janssen-Cilag, Verastem, Incyte, EUSA Pharma, Celgene/Bristol Myers Squibb, Kite/Gilead, ADC Therapeutics
Speakers' Bureau	EUSA Pharma, Novartis
Research funding	Gilead Sciences

LYMPHOMAS

Lymphomas

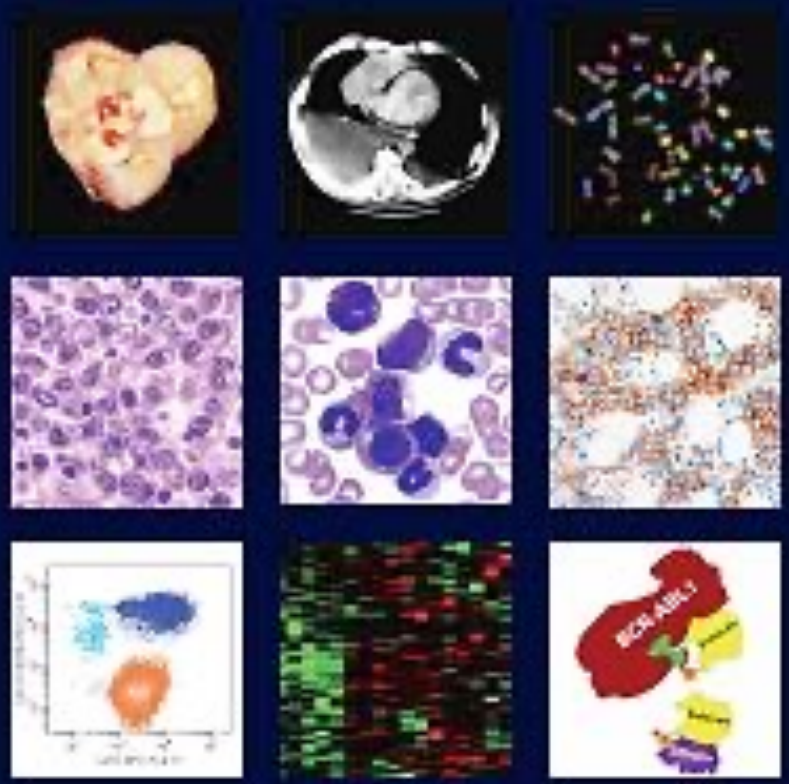
Heterogeneous group of lymphoid neoplasms characterized by proliferation and accumulation of neoplastic lymphoid cells (clonal proliferation)

- From B and T cells
- **Different clinical presentation, natural history, response to therapy and outcome**


LYMPHOMAS
NON-HODGKIN'S LYMPHOMAS
HODGKIN'S LYMPHOMA
Aggressive
Indolent

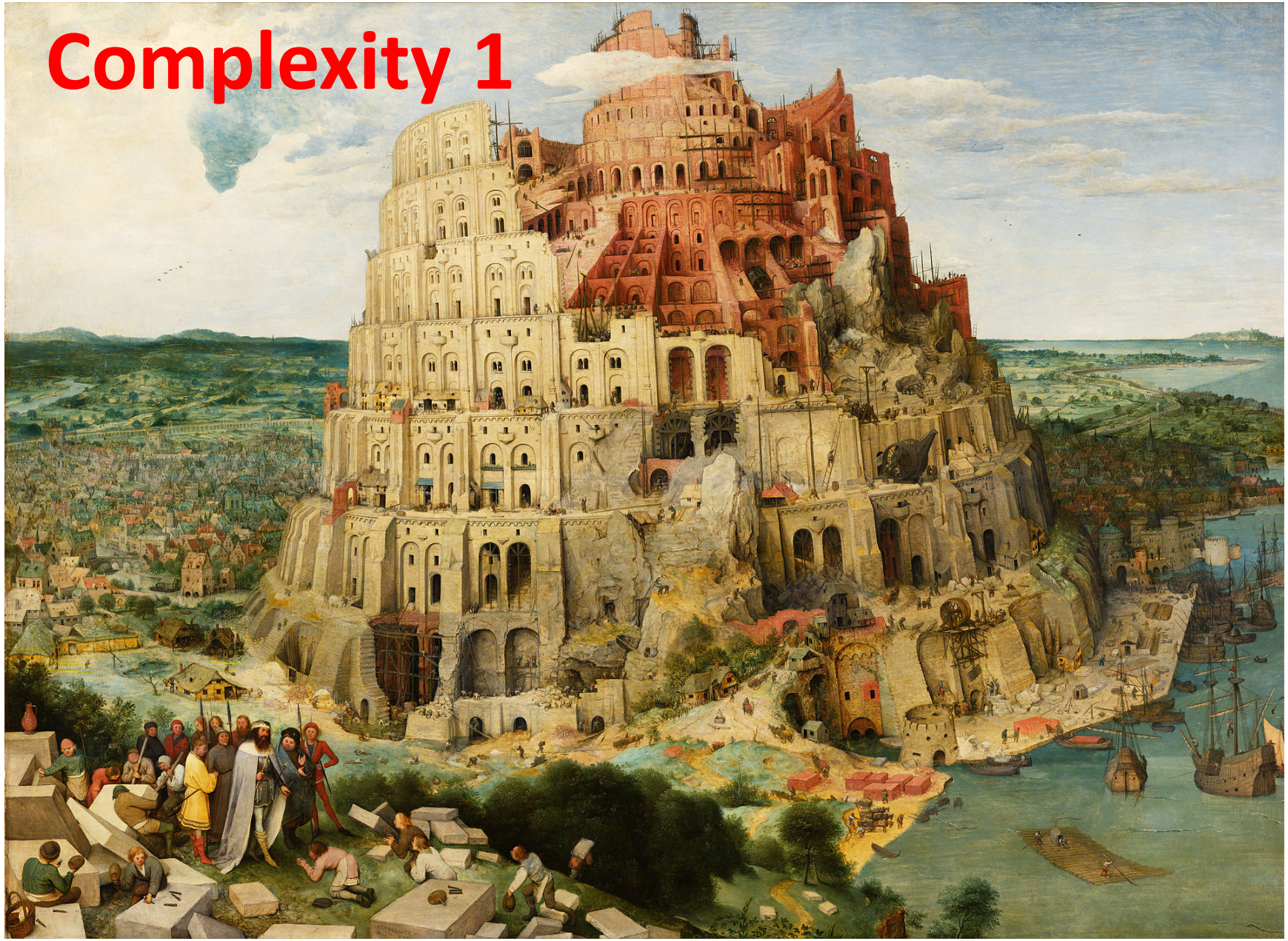
WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Edited by Steven H. Swerdlow, Elias Campo, N. Lynn Harris, Elaine S. Jaffe, Sverre A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman



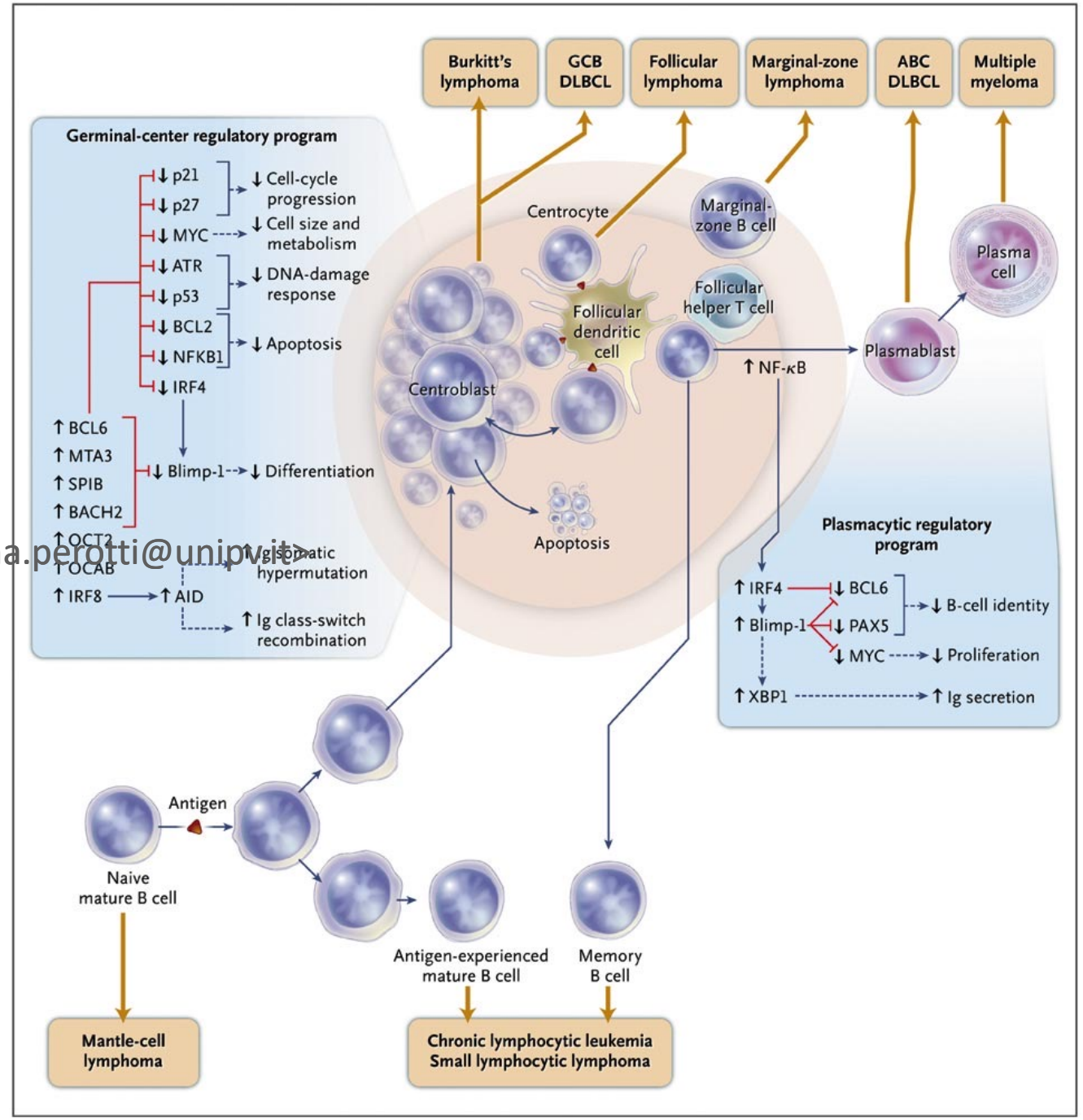
WHO

Complexity 1



Pieter Brueghel il Vecchio, Torre di Babele ''Grande Torre'', (114x155 cm), Kunsthistorisches Museum, Vienna

Complexity 2

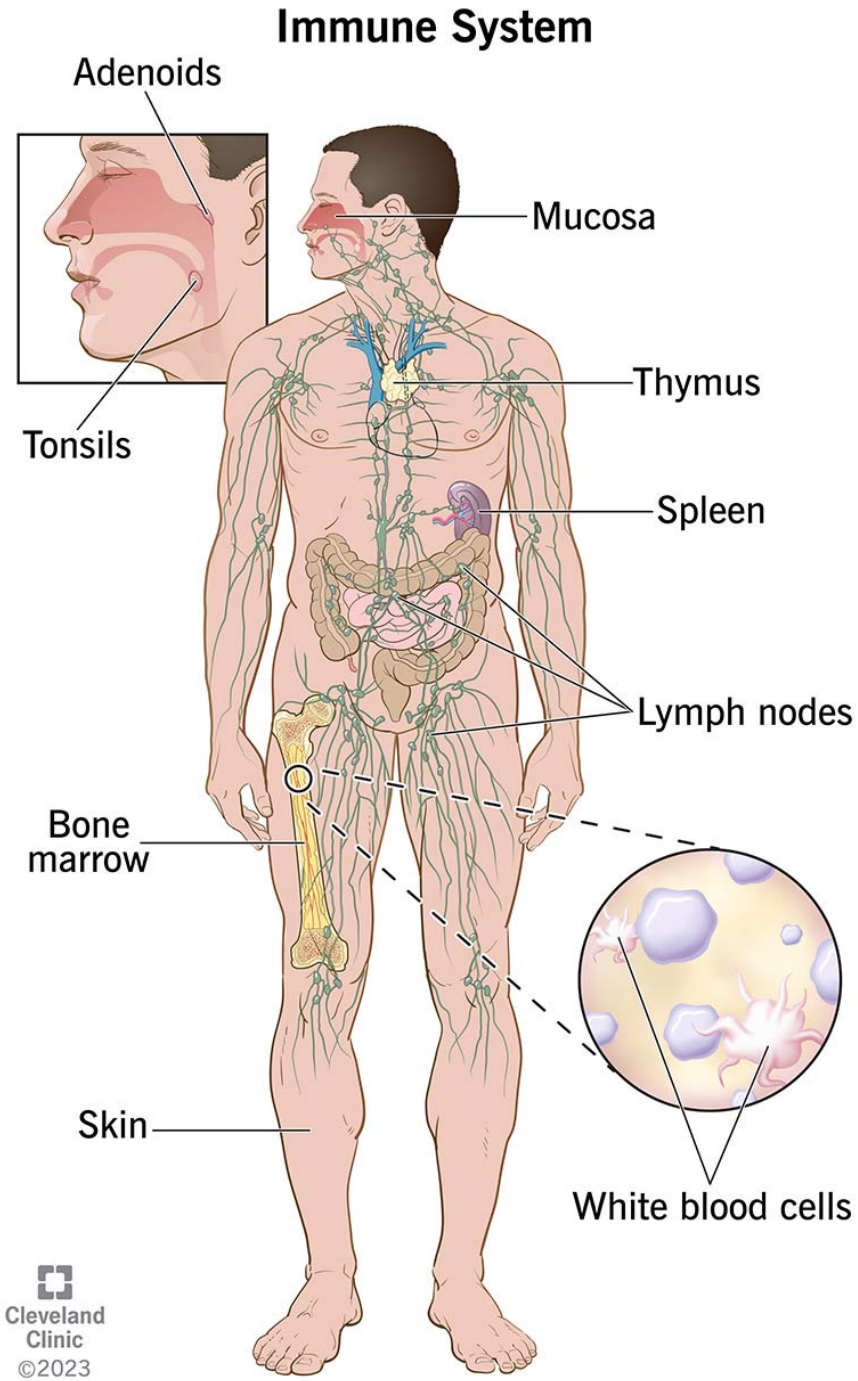


rosamarina.perotti@unipv.it

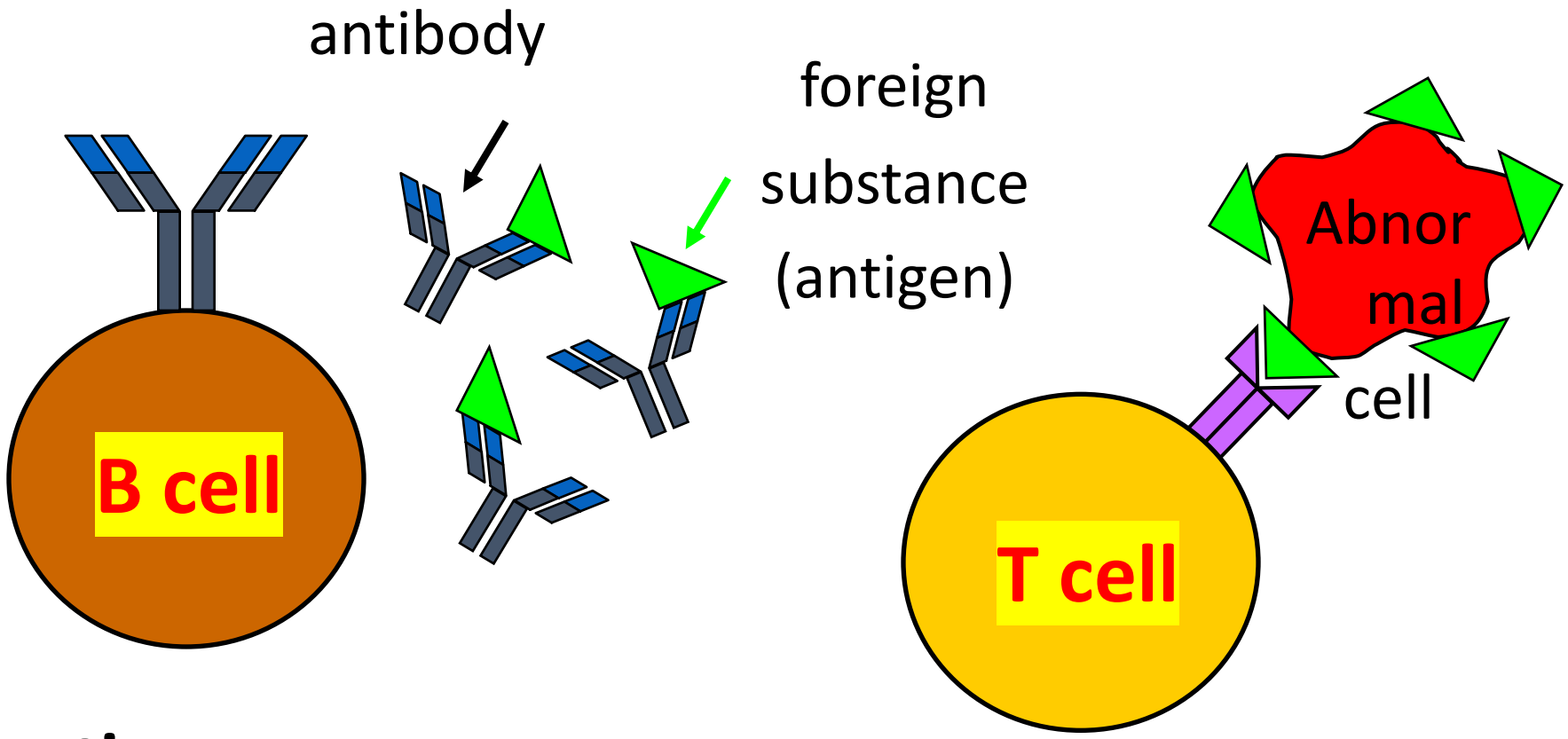
NEW DRUGS

Immune system

Site of disease
Defense against disease



Two arms of the immune system



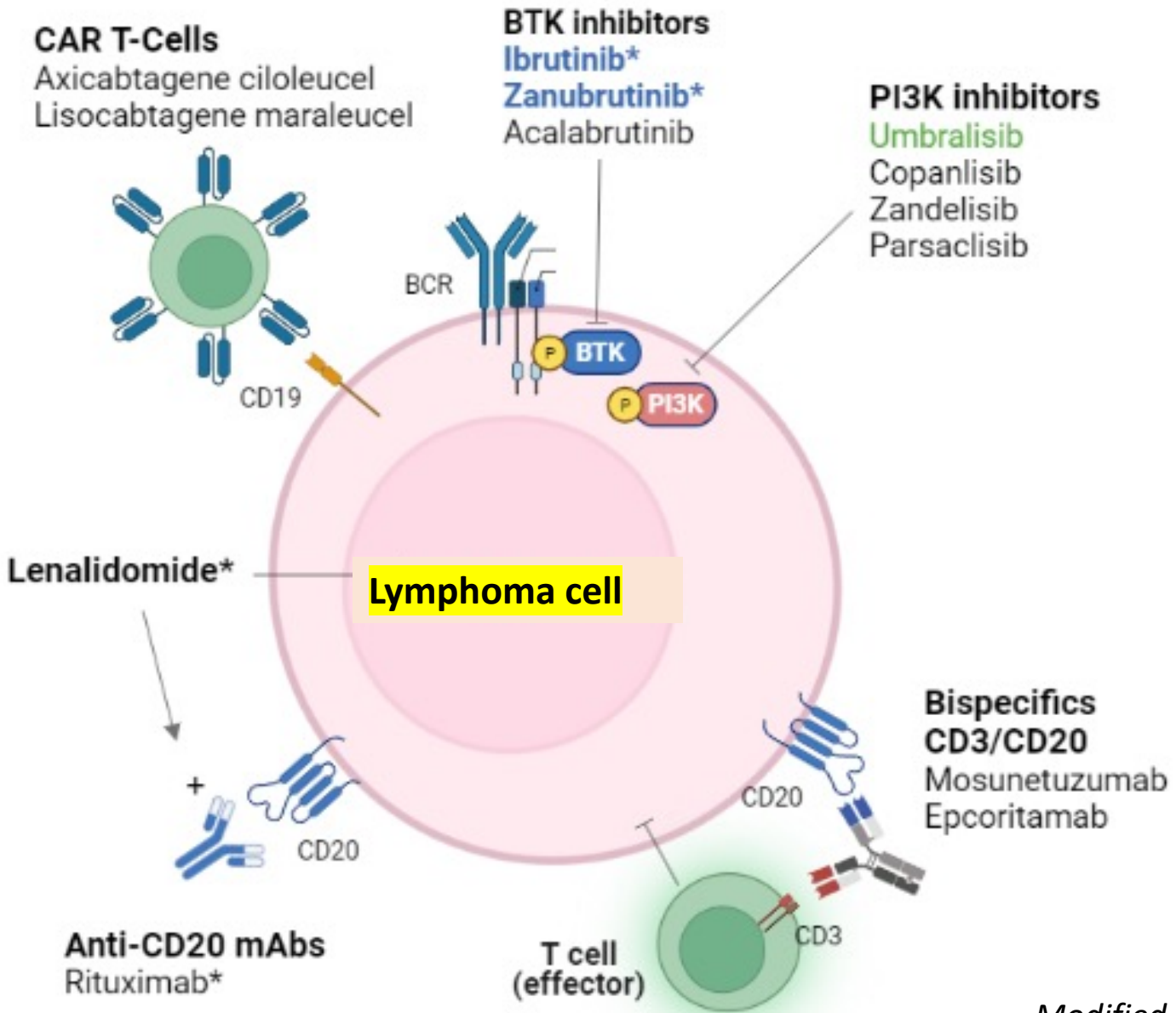
Function

Make Antibodies

Kill abnormal cells

Make cytokines

Toward a chemo-free therapy ?



(*approved drugs)

Modified from ASH Educational Book 2022

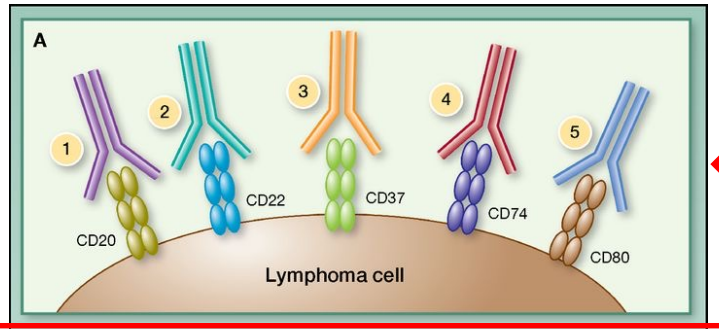
Bachy Clin Cancer Res 2014

mAbs

Epratuzumab Otlertuzumab Milatuzumab

Rituximab
Ofatumumab
Obinutuzumab
Veltuzumab

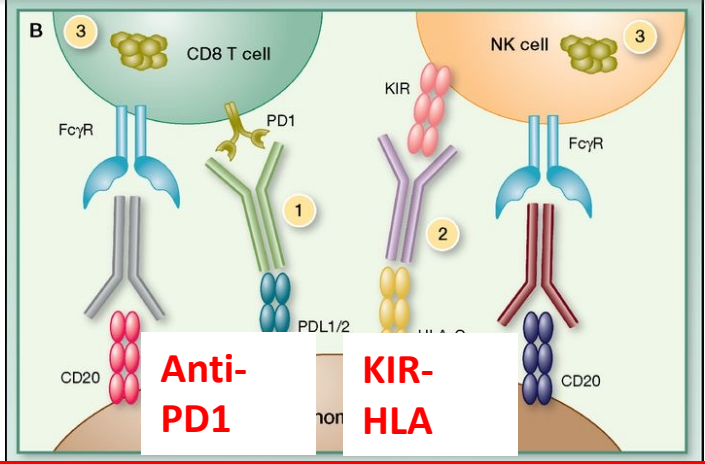
Galiximab



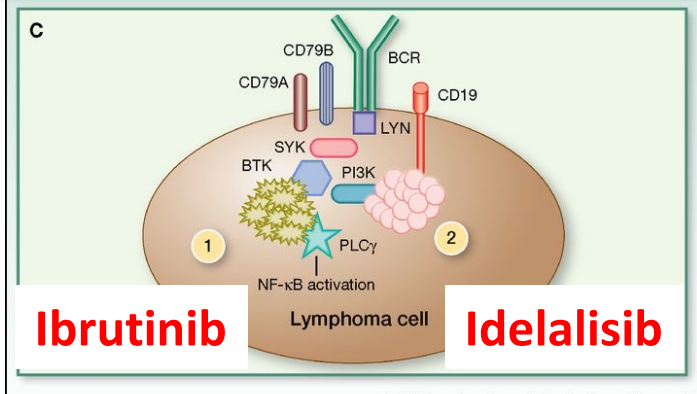
Immunomodulation

Lenalidomide

Lenalidomide



Intracellular targeted therapy

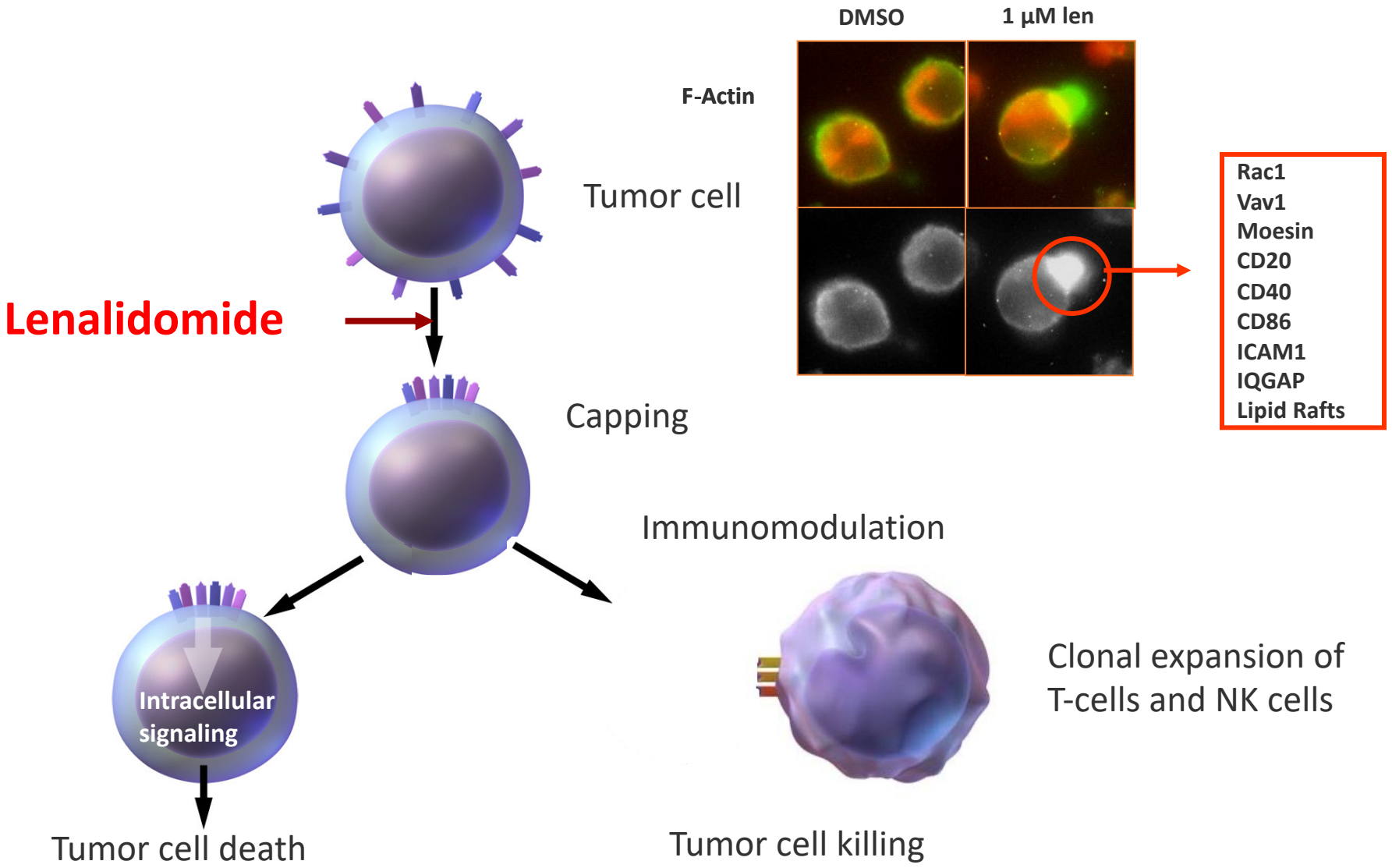


Immunomodulators and targeted treatment

- Lenalidomide (oral drug)

- BTK inhibitors (oral drugs)

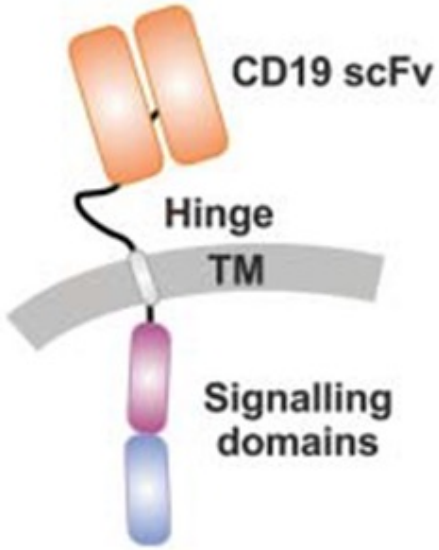
Lenalidomide couples tumoricidal & immunomodulatory activity



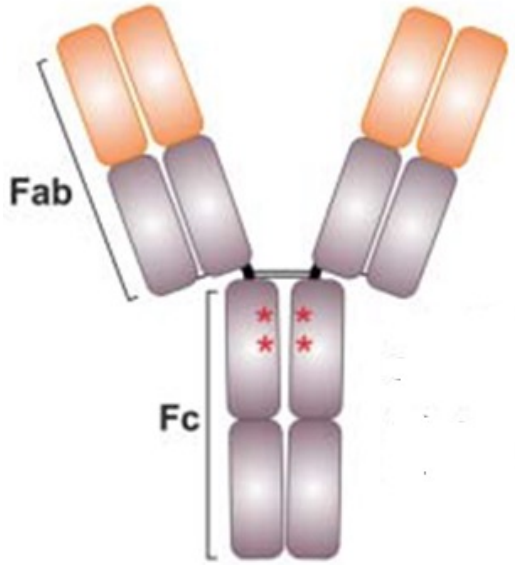
CD19 TARGETING STRATEGIES

Tnb-486 (BITE)

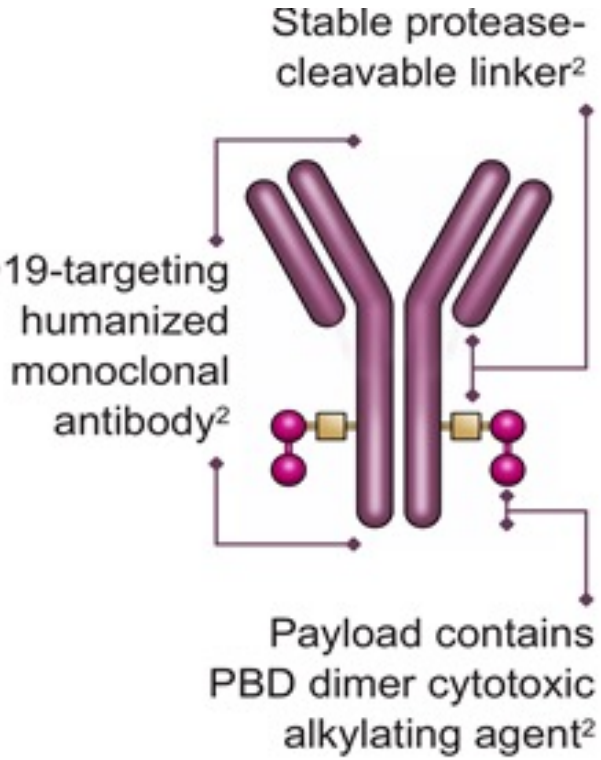
CAR-T cells



TAFASITAMAB (engineered antibody)



ADC (Loncastuximab tesirine)



Mode of actions provide the rationale for tafasitamab + lenalidomide combination

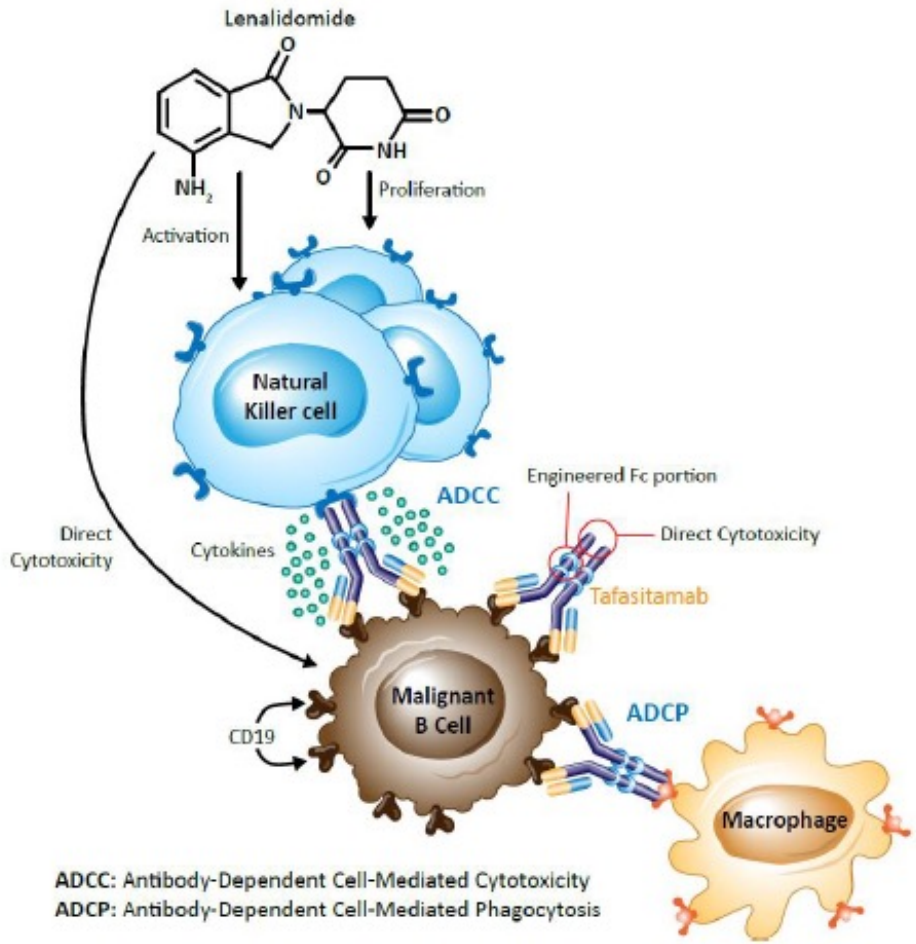
Tafasitamab MoA

- Antibody Dependent Cellular Cytotoxicity via NK cells (ADCC)
- Antibody Dependent Cellular Phagocytosis (ADCP)
- Direct cytotoxicity

Lenalidomide MoA

- Direct cytotoxicity
- Increase NK cell numbers (ADCC)
- Activate NK cells

Increased anti-tumor effects

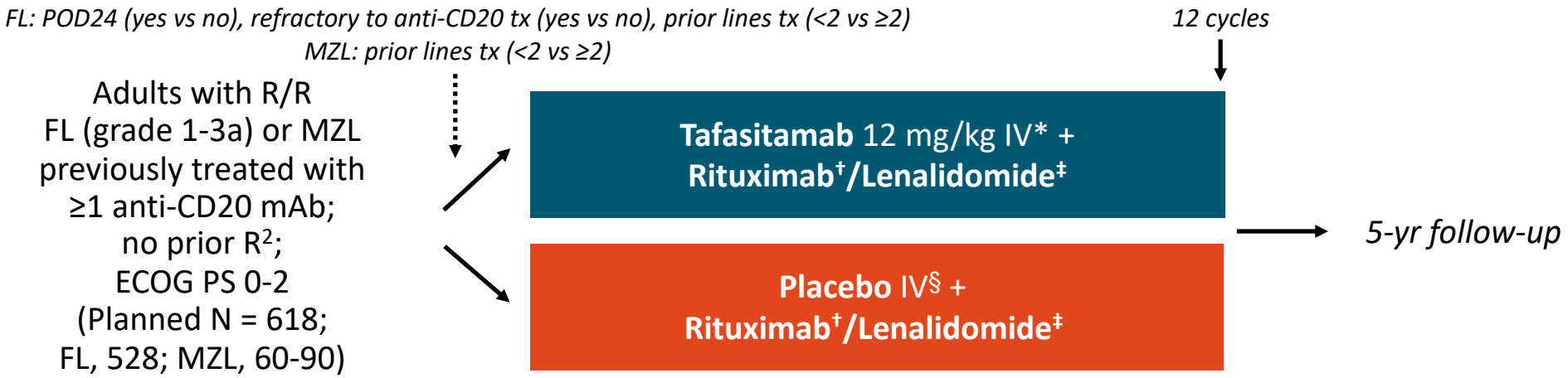


Salles 2020

InMIND: Tafasitamab + R^2 vs R^2 Alone in R/R FL or MZL

ASH 2024; Abstract LBA-1

- Global, double-blind, placebo-controlled, randomized phase III trial
  - Tafasitamab: Fc-engineered humanized anti-CD19 mAb



*Tafasitamab given Days 1, 8, 15, 22 of cycles 1-3 and Days 1, 15 of cycles 4-12 on 28-day cycle.
†Rituximab dosed at 375 mg/m^2 IV; given on Days 1, 8, 15, 22 of cycle 1, then Day 1 of cycles 2-5.
‡Lenalidomide dosed at 20 mg PO QD given on Days 1-21 for 12 cycles. §Placebo given as 0.9% saline solution IV.

- **Primary endpoint:** PFS by investigator per Lugano 2014 criteria in FL population
- **Key secondary endpoints:** PFS in overall population, PET/CR at EOT and OS in FL population

Data cutoff June 22, 2018. ITT, intention to treat; NR, not reached; R-placebo, R plus placebo.

Sehn et al. ASH 2024

PFS by investigator assessment

*
**
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New therapeutic agents and their targets

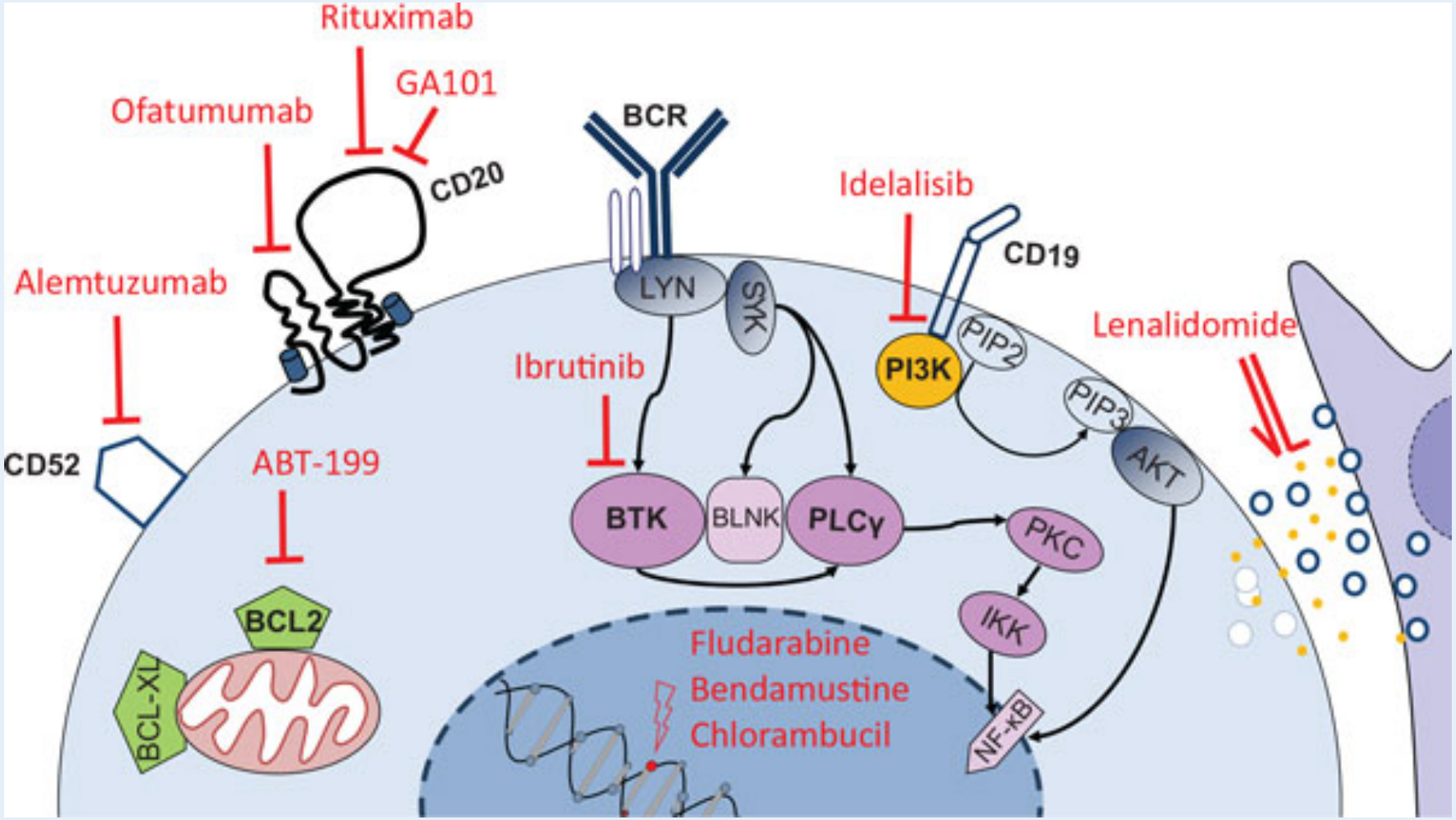


Figure 1.

New therapeutic agents and their targets in a chronic lymphocytic leukemia cell

BCL2, B-cell lymphoma 2; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; NFκB, nuclear factor kappa B; PI3K, phophoinositide 3-kinase; PKC, protein kinase C; PLC, phospholipase C.

B-cell receptor (BCR) inhibitors

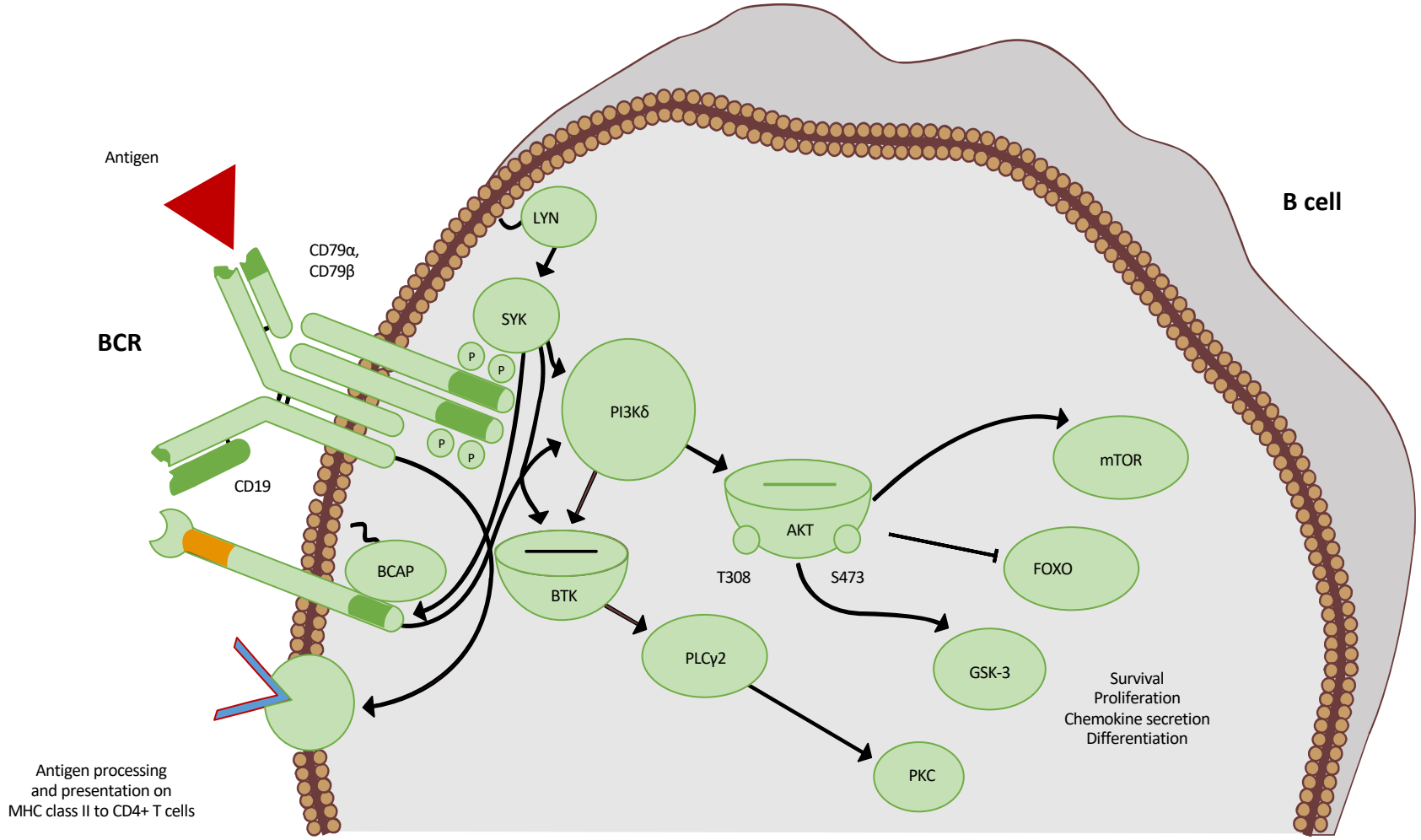
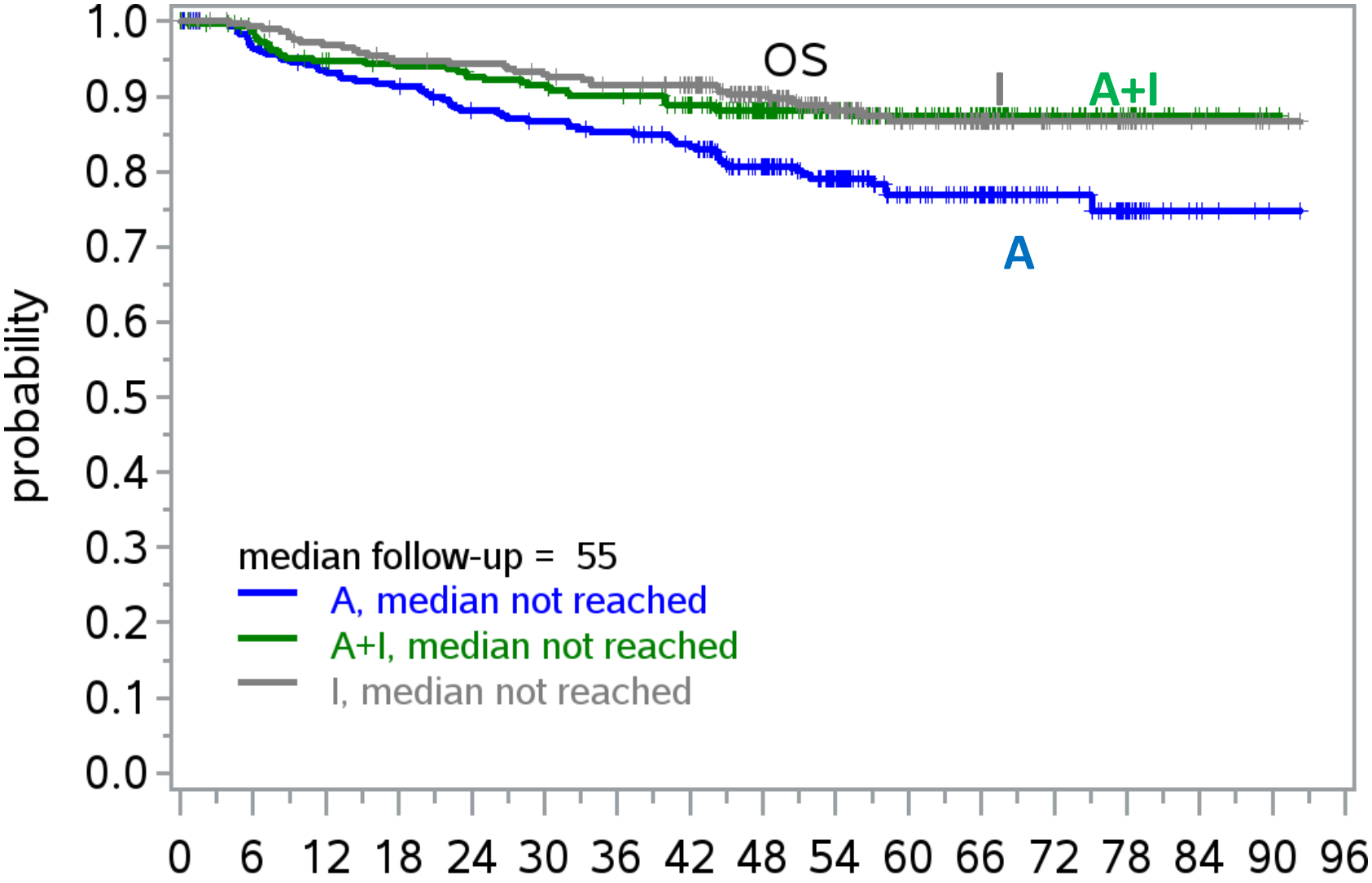


Figure adapted from: Davids MS & Brown J. *Leuk Lymphoma* 2012; 53:2362–2370;
Wiestner A. *Haematologica* 2015; 100:1495–1507; Young RM & Staudt LM. *Nat Rev Drug Discov* 2013; 12:229–243

TRIANGLE: Overall survival



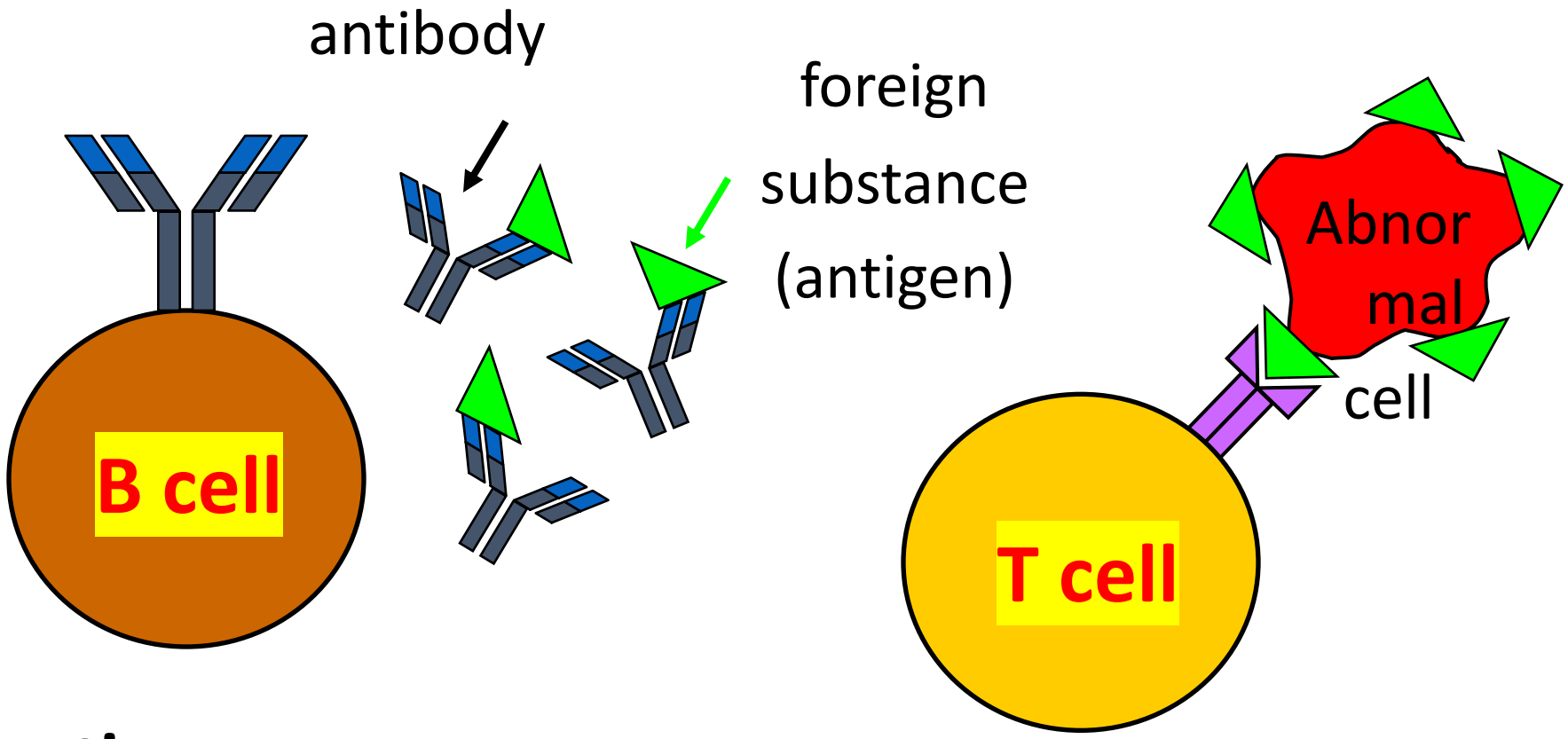
- 4-year OS:
  - A: 81%
    (MCL Younger exp.: 80%)
  - A+I: 88%
  - I: 90%

- two-sided test, (⍰ = 5%):
  - **A vs. I: p=0.0019**, HR: 0.565
  - **A vs. A+I: p=0.0036**, HR I: 0.587
  - **A+I vs. I: ongoing**

Dreyling et al. ASH 2022

IMMUNE SYSTEM AGAIN

Two arms of the immune system



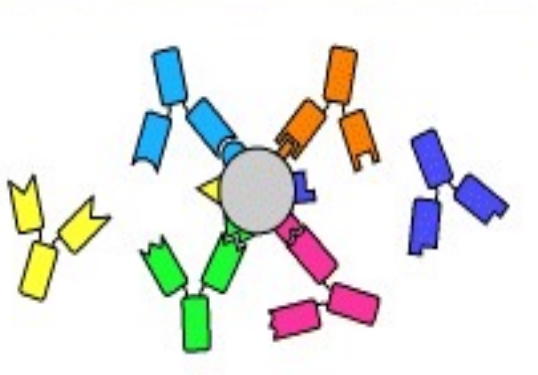
Function

Make Antibodies

Kill abnormal cells

Make cytokines

Antibodies as biological drugs



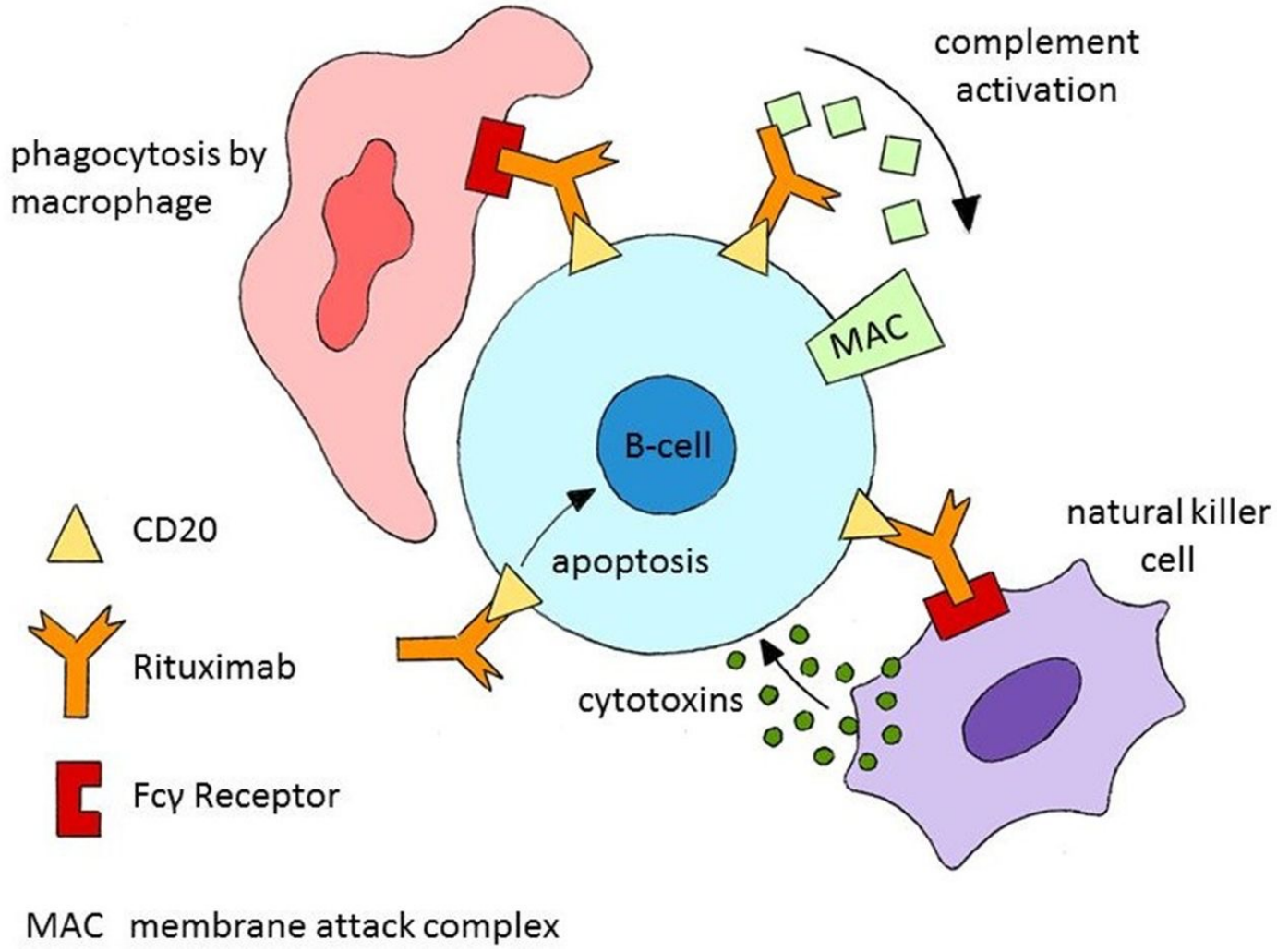
Antibodies are natural glycoproteins with high affinity and specificity for an antigen

Monoclonal antibodies

- Naked
- (Radioimmunoconjugates)
- Bispecific
- Drug-conjugated

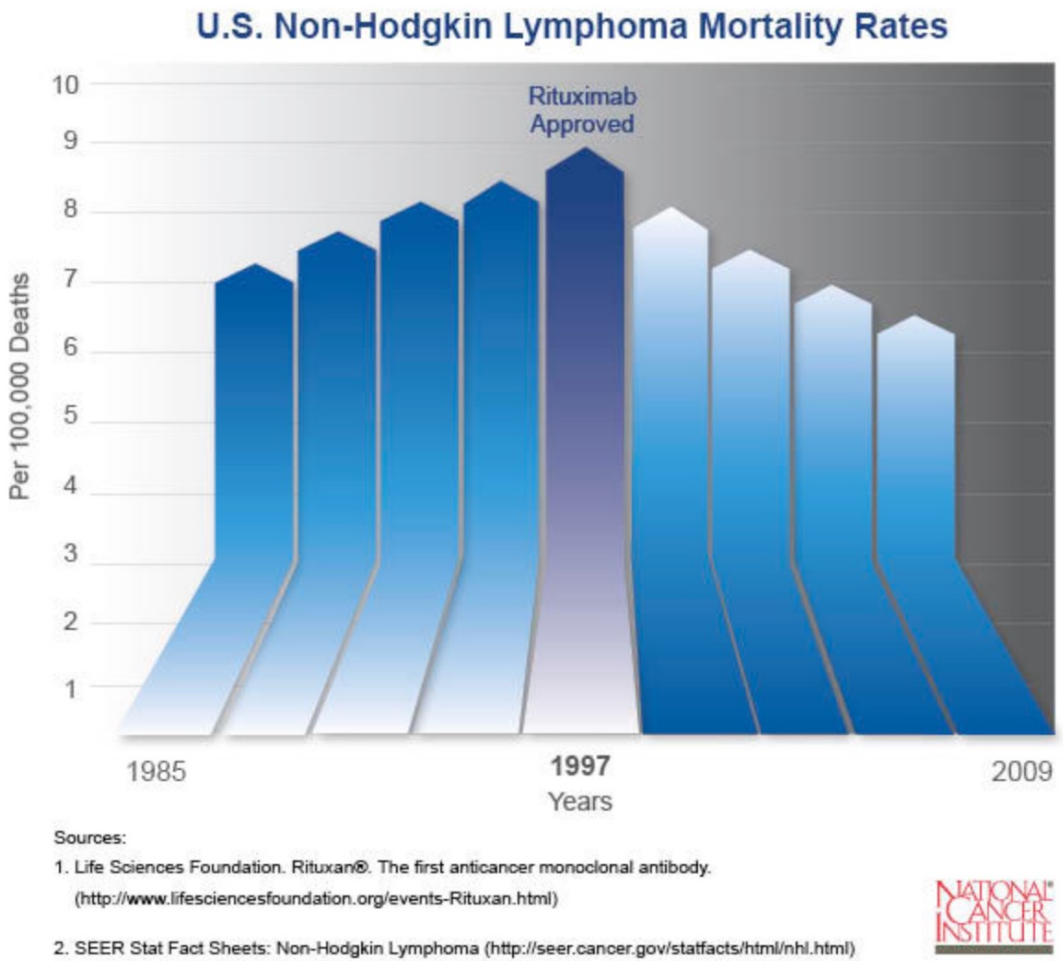
NAKED ANTIBODIES

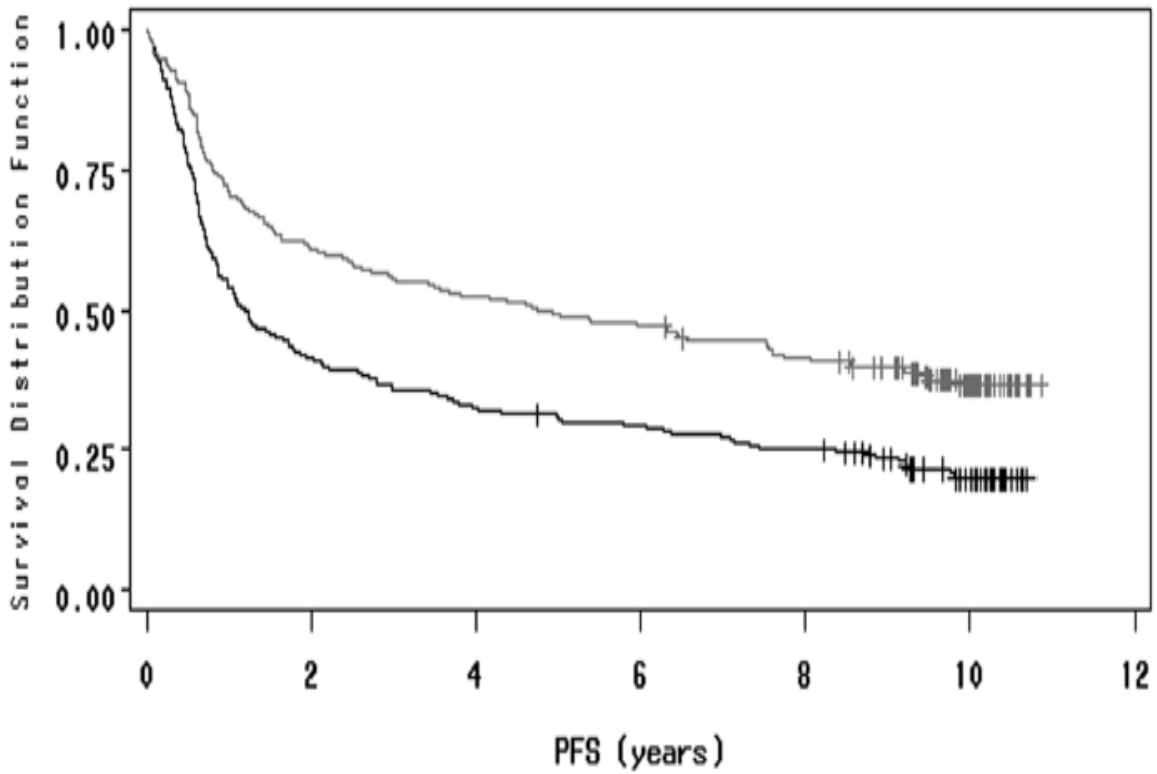
Rituximab



Daniel et al. Pract Neurol 2019

Rituximab

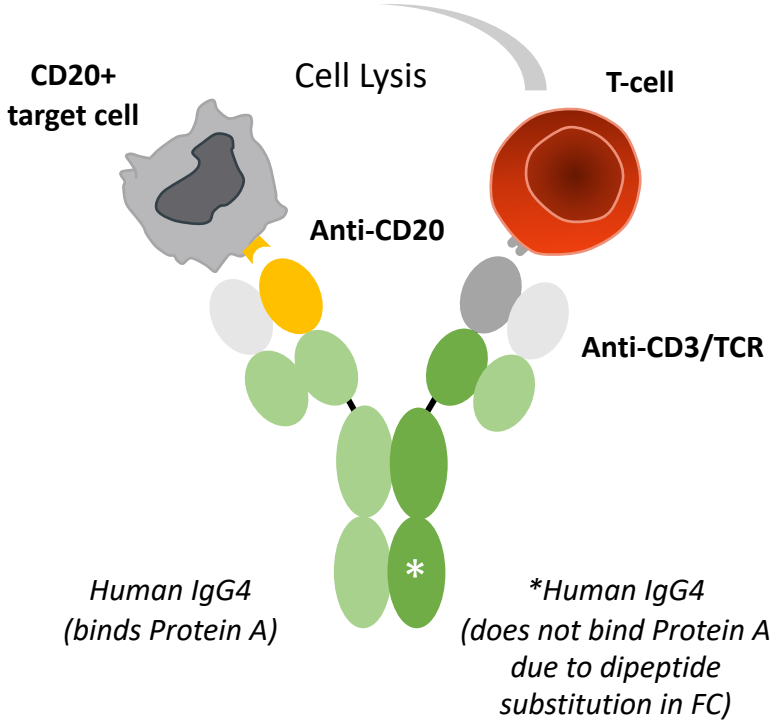




Coiffier et al, Blood 2010

BISPECIFIC ANTIBODIES

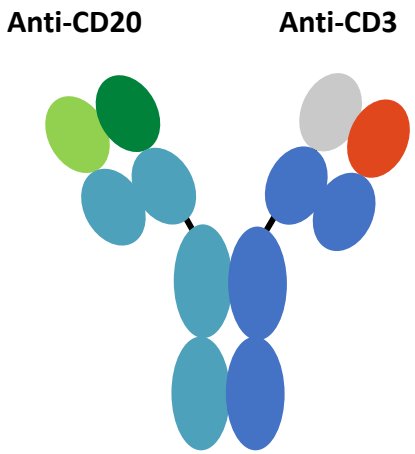
CD20/CD3 bispecific antibodies in B-cell lymphomas



Odronextamab (IV)

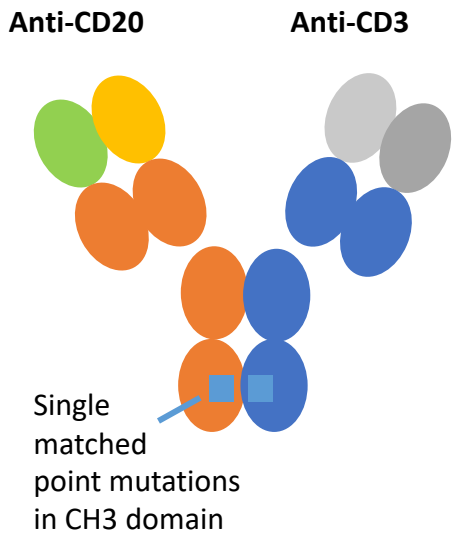
Approval Status: Under FDA Review for 3L+ R/R FL and DLBCL

Humanized mouse IgG1-based mAb



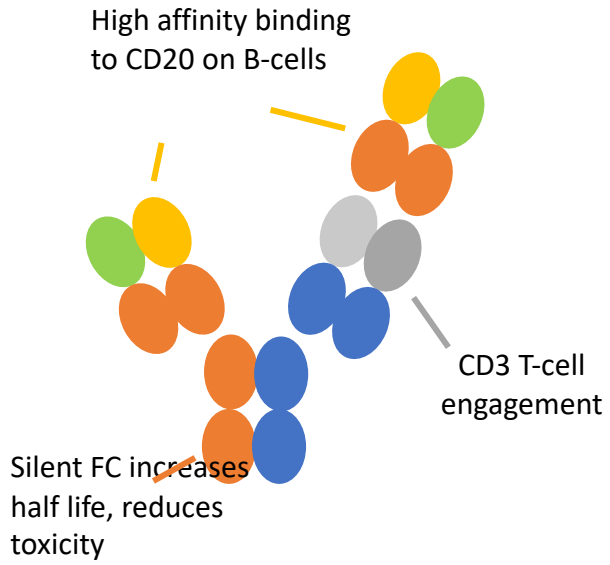
Mosunetuzumab (IV*)

FDA approved: 3L+ R/R FL



Epcoritamab (SC)

FDA approved: 3L+ R/R FL

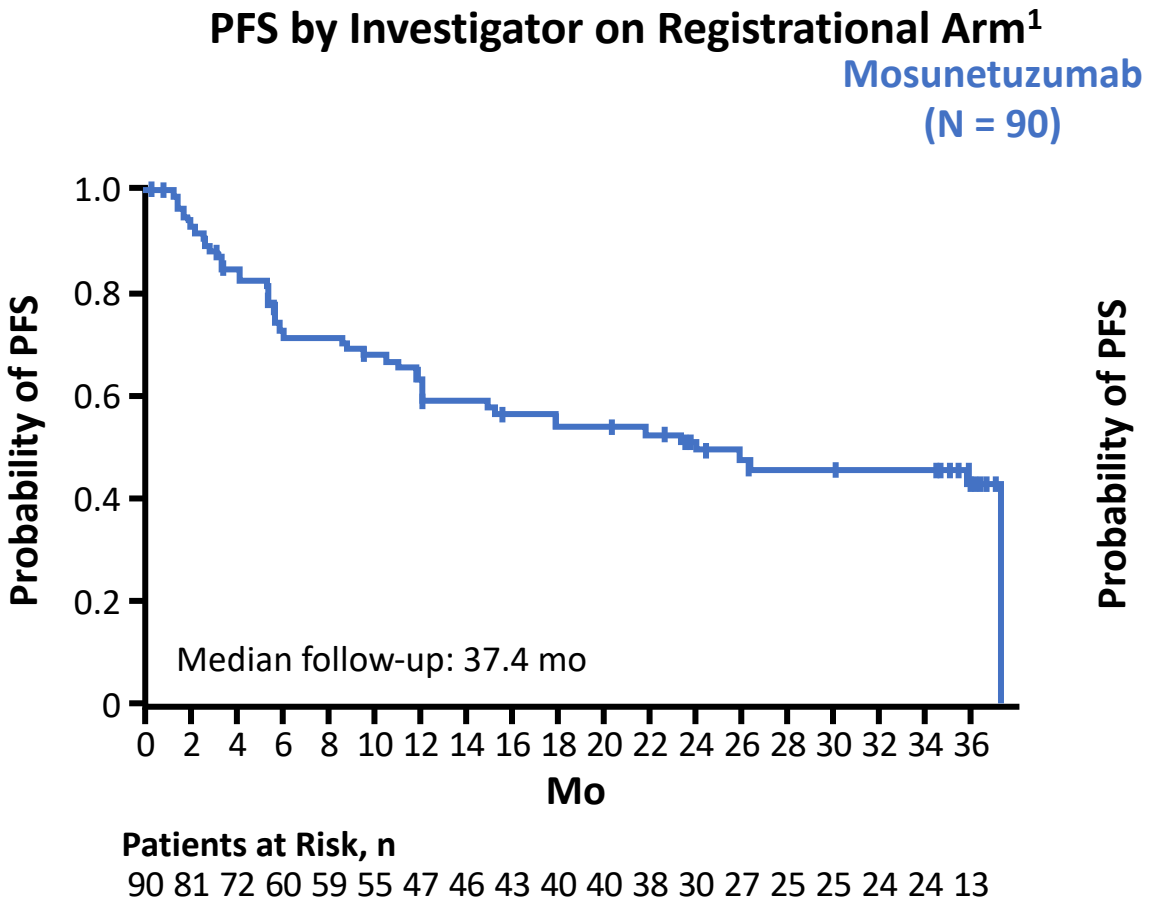


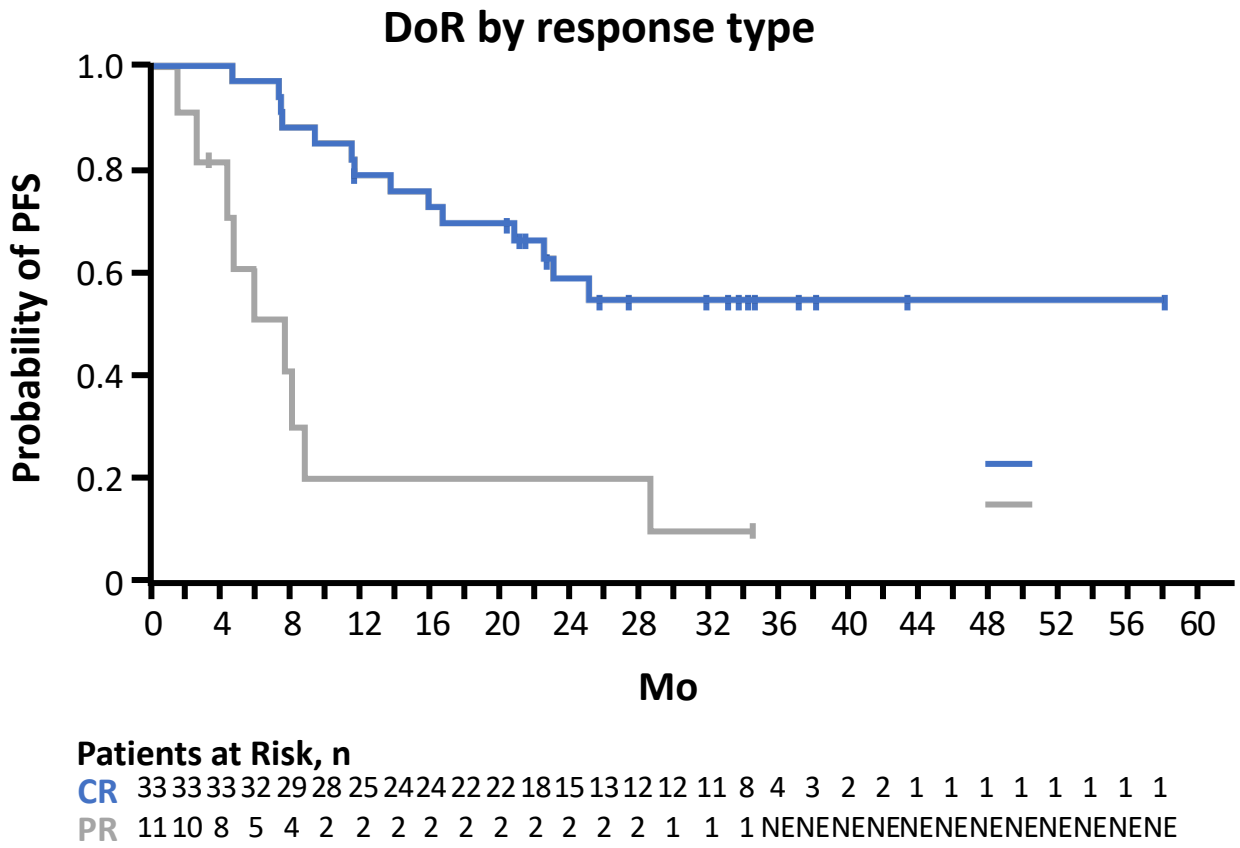
Glofitamab (IV)

3L+ R/R DLBCL

Castaneda-Puglianni. Drugs Context. 2021;10:2021. Bannerji. ASH 2020. Abstr 42. Budde. ASH 2018. Abstr 399. Hutchings. Lancet. 2021;398:1157. Engelberts. eBioMedicine. 2020;52:102625. Hutchings. JCO. 2021;39:1959. Mosunetuzumab PI. Epcoritamab PI. Glofitamab PI.

Mosunetuzumab Phase II Study (updates): efficacy

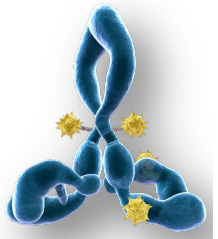




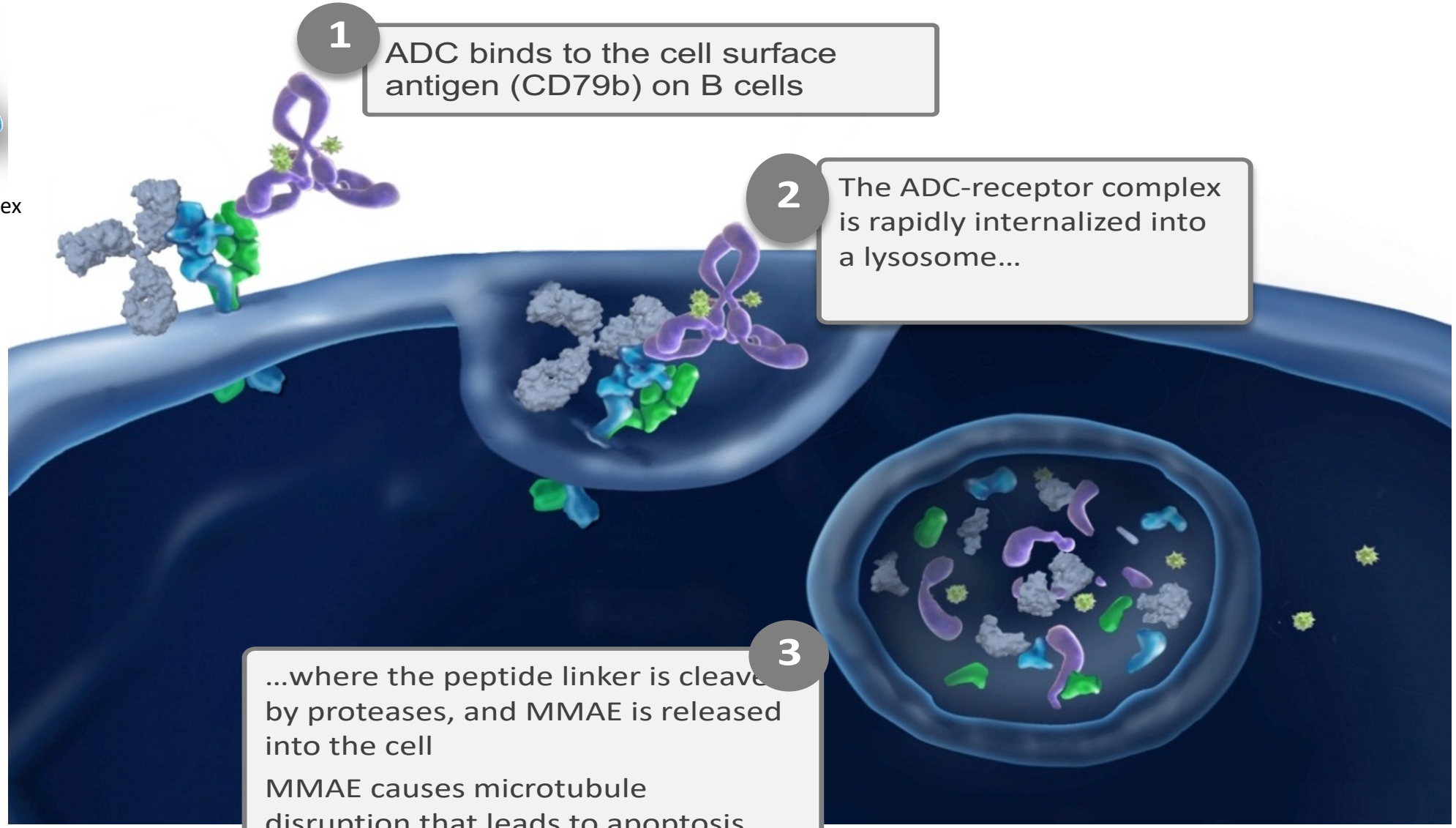
1. *Schuster. ASH 2023. Abstr 603. 2. Budde. JCO. 2024.*

DRUG-CONJUGATED

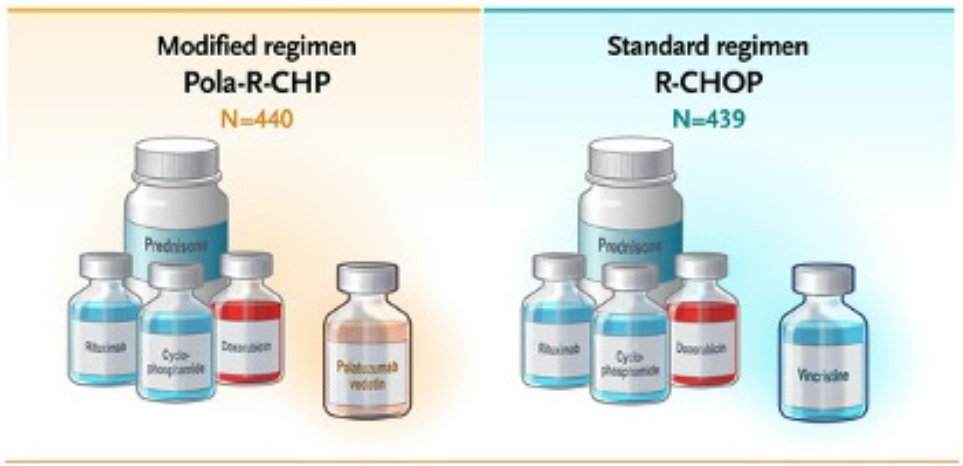
Polatuzumab vedotin: proposed mechanism of action



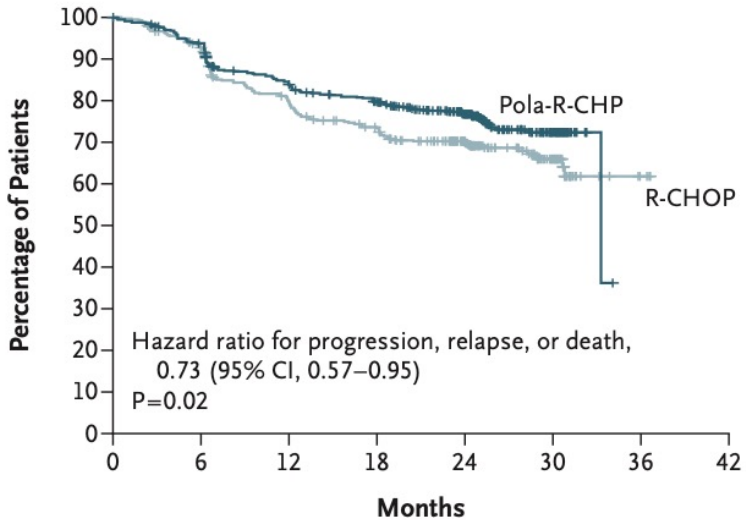
Binds CD79b and ADC-receptor complex internalized



Polarix



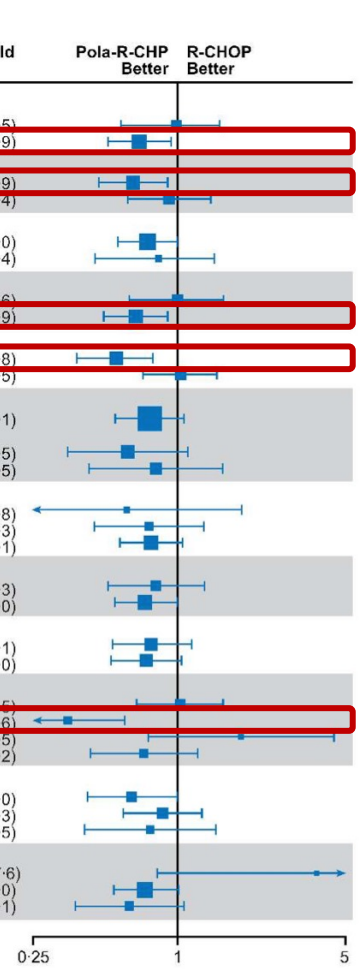
A Investigator-Assessed Progression-free Survival



No. at Risk

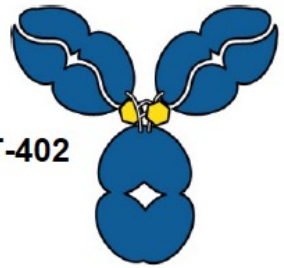
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
<60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·2	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)



Tilly et al. NEJM. 2022

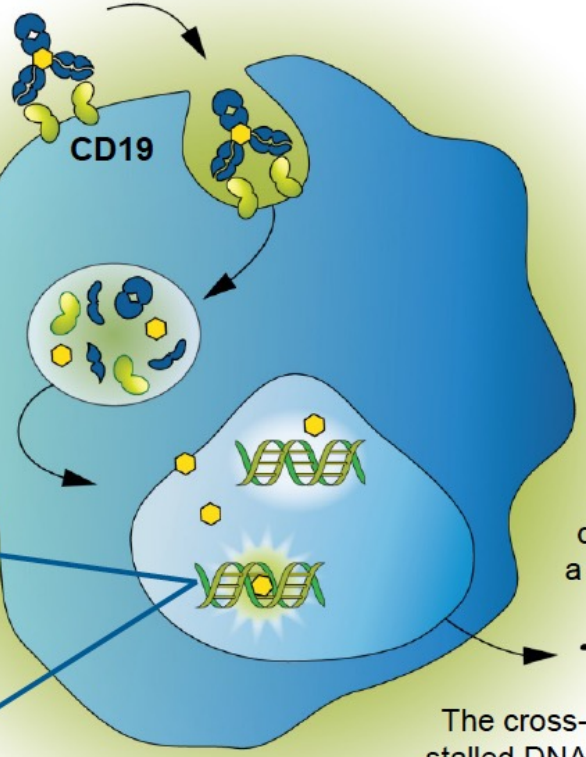
Loncastuximab Tesirine (ADCT-402)



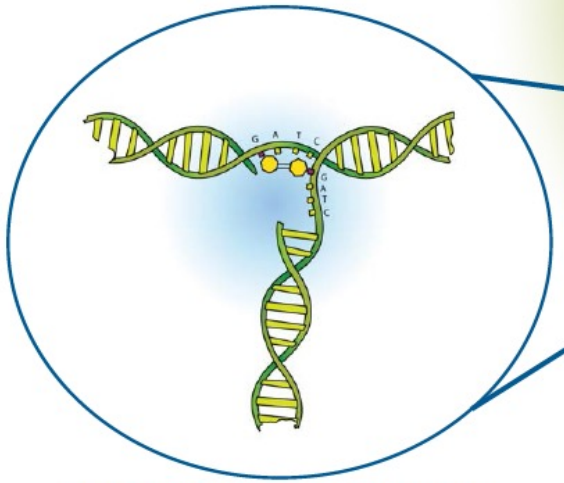
ADCT-402

Anti-CD19 Ab

ADCT-402 binds to the CD19 antigen on the tumor cell surface



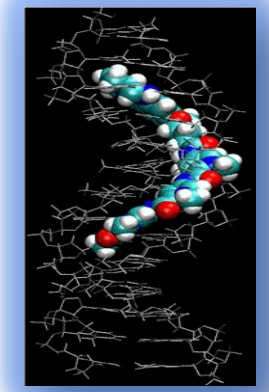
Following internalization of the ADC, the protease-sensitive linker is cleaved and the cytotoxic PBD dimer is released inside the cell



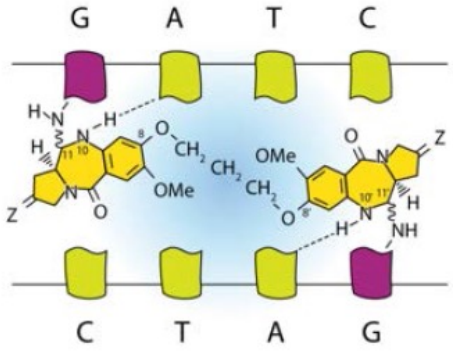
Stalled DNA replication fork

The free PBD dimers bind in the minor groove of the cell DNA and forms potent cytotoxic DNA cross-links in a sequence-selective fashion.

The cross-links result in a stalled DNA replication fork, blocking cell division and causing cancer cell death



Pyrrolobenzodiazepine (PBD)



Cytotoxic cross-links

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