New antibodies in the post-Rituximab-era: Another breakthrough?

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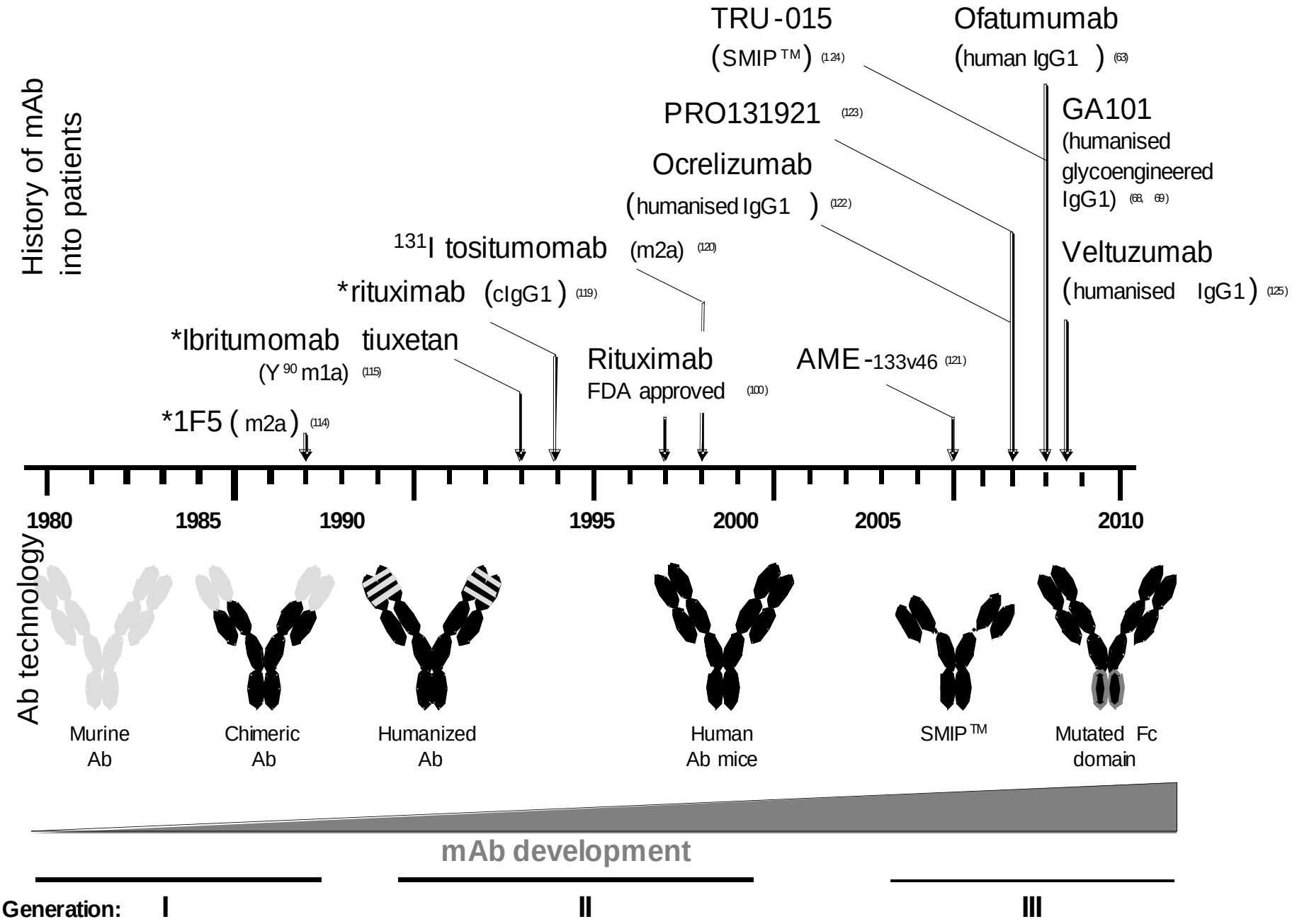
Disclosures: Peter Johnson

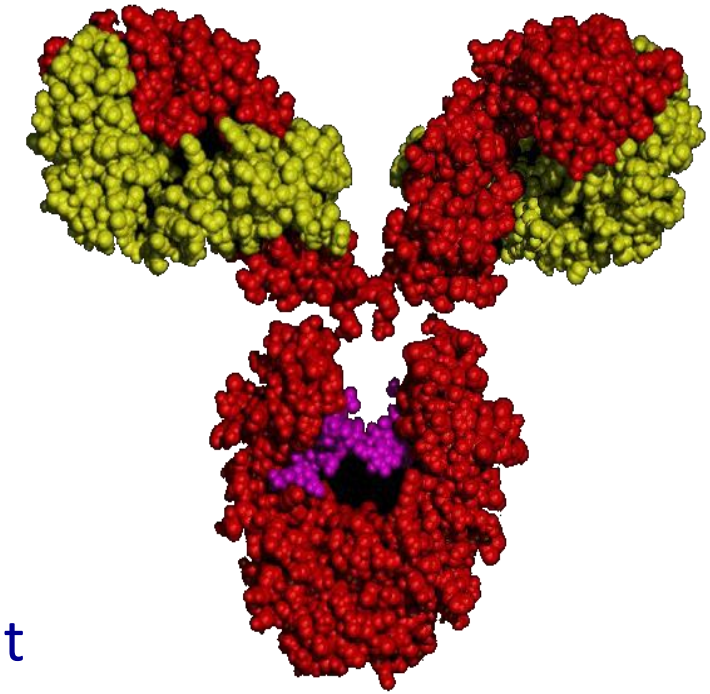
- Advisory Boards
  - Pfizer
  - Millenium Takeda
  - Roche
  - Boehringer Ingelheim
- Research funding
  - Janssen-Cilag

History of CD20 mAb in clinical translation

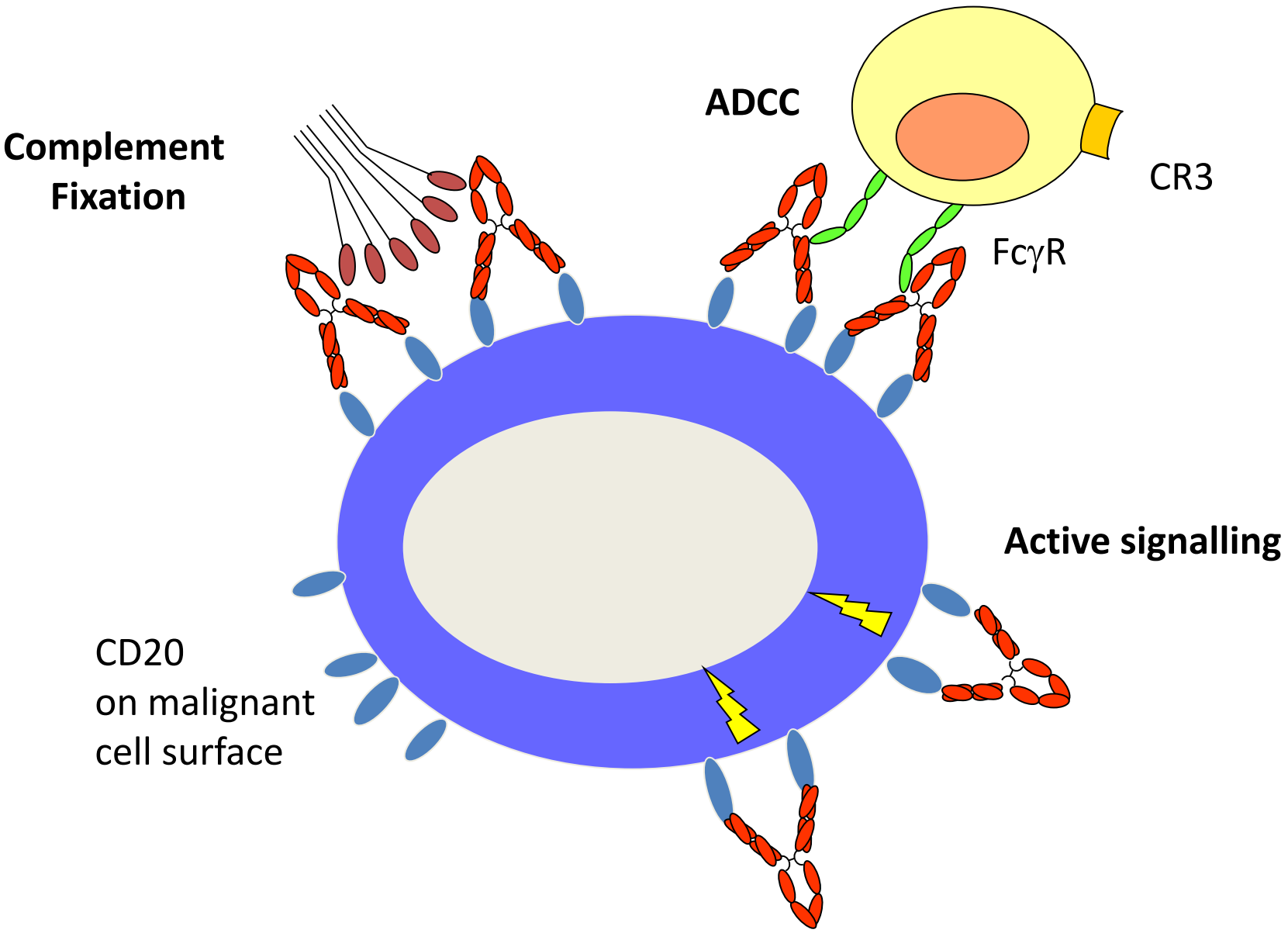


After Rituximab….

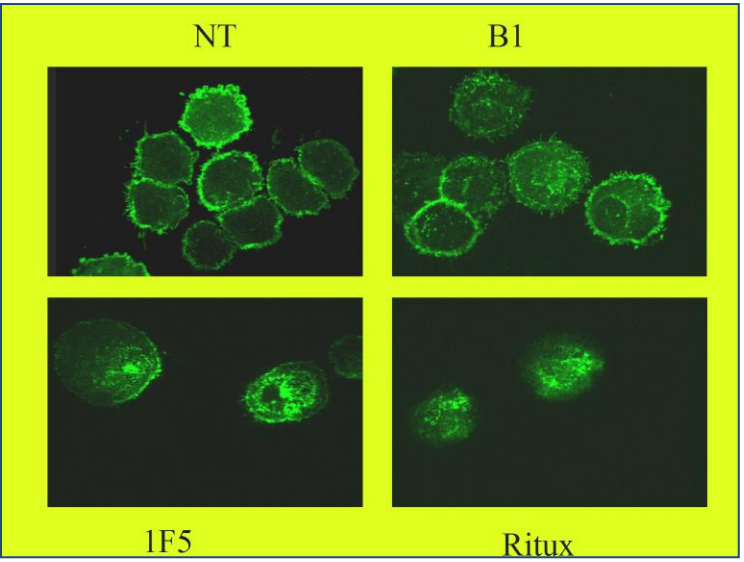
- Target specificity
  - Different anti-CD20 types
  - Different antigens
- Effector mechanisms
  - Host effectors: ADCC, complement
  - Recruitment of other cells: NK, T-cells
  - Payloads: radionuclides, toxins



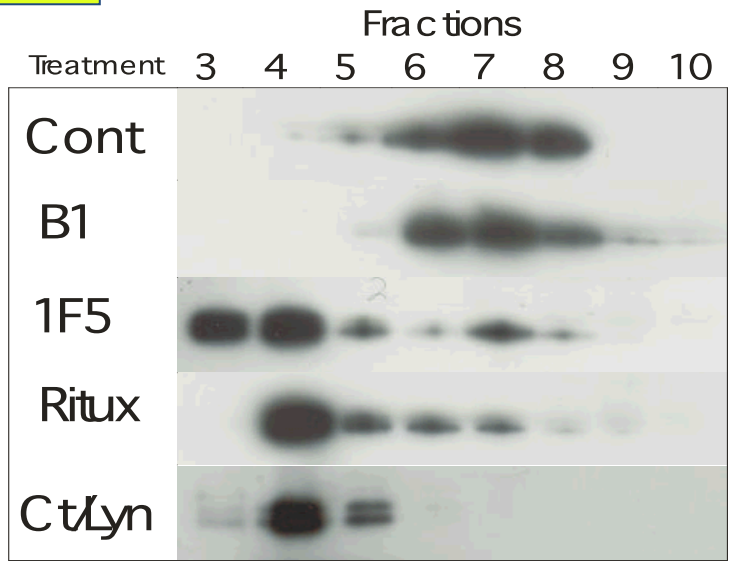
Potential Effects of anti-CD20 on Lymphoma cells



In vitro effects of different anti-CD20 antibody types



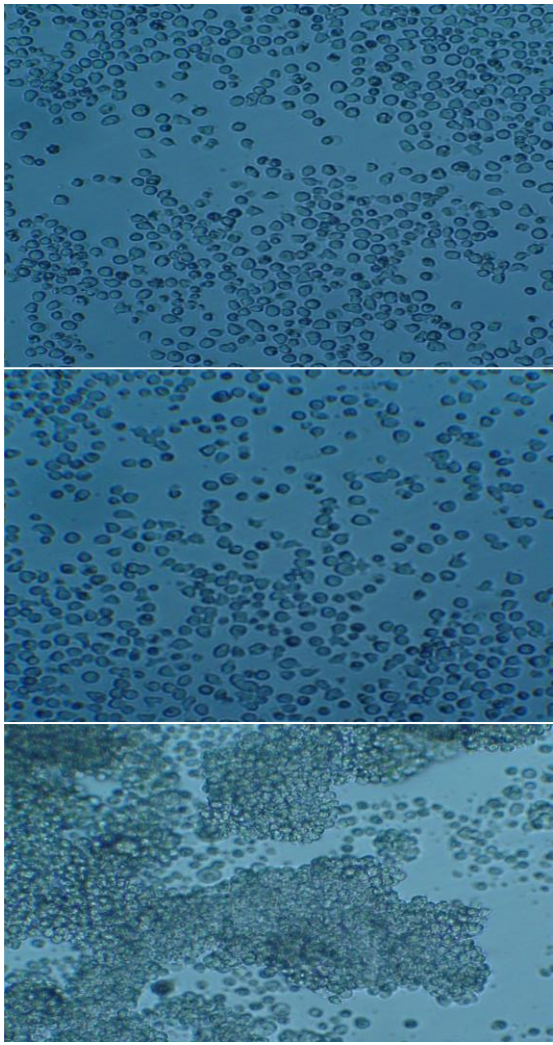
YFP-CD20 in Bcl_1-3B3 cells



Cragg et al., Blood. 2003;101:1045-1052

Homotypic adhesion: Ramos

Control



Type I and type II antibodies

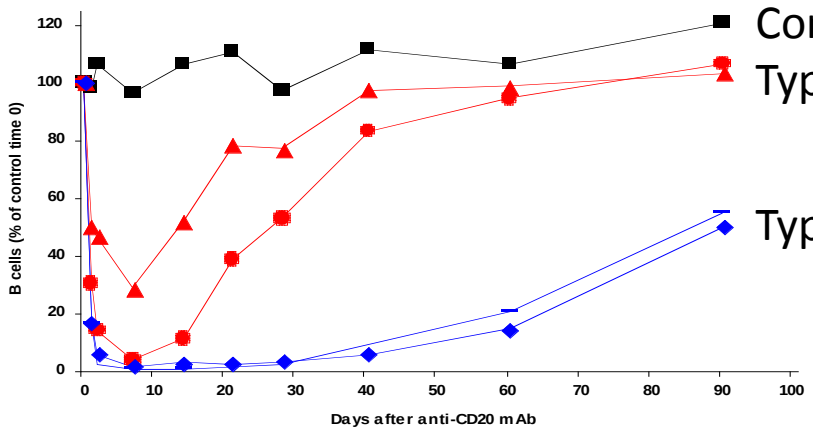
	Type 1	Type II
	Rituximab, Ofatumumab	Tositumomab, GA-101
CDC	++	-
ADCC	++	++
Move CD20 into lipid rafts	++	-
Homotypic adhesion	-	++
Induce cell death	-	++

Why does the half-life differ between antibody types?

(Beers et al., Blood. 2010; 115:5191-5201)

CD20 mAb depletion of circulating B cells in hCD20 Tg mice

C57Bl/6

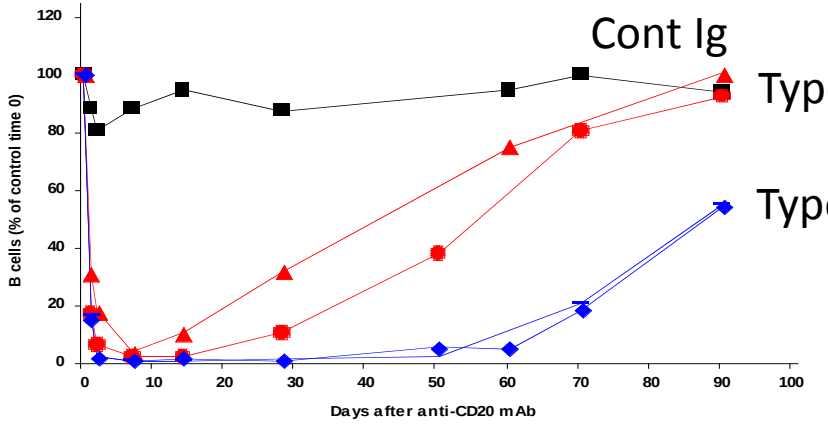


Cont Ig

Type I mAb (rit m2a; 1F5)

Type II mAb (B1; FGM1)

BALB/c



Cont Ig

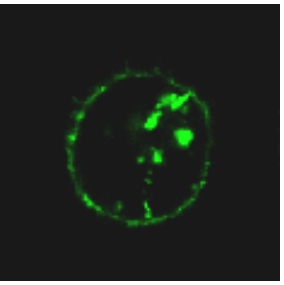
Type I mAb (rit m2a; 1F5)

Type II mAb (B1; FGM1)

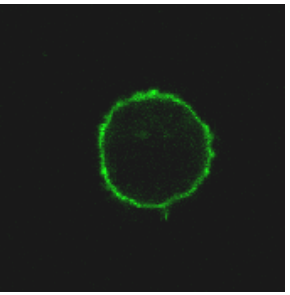
All mouse 2a

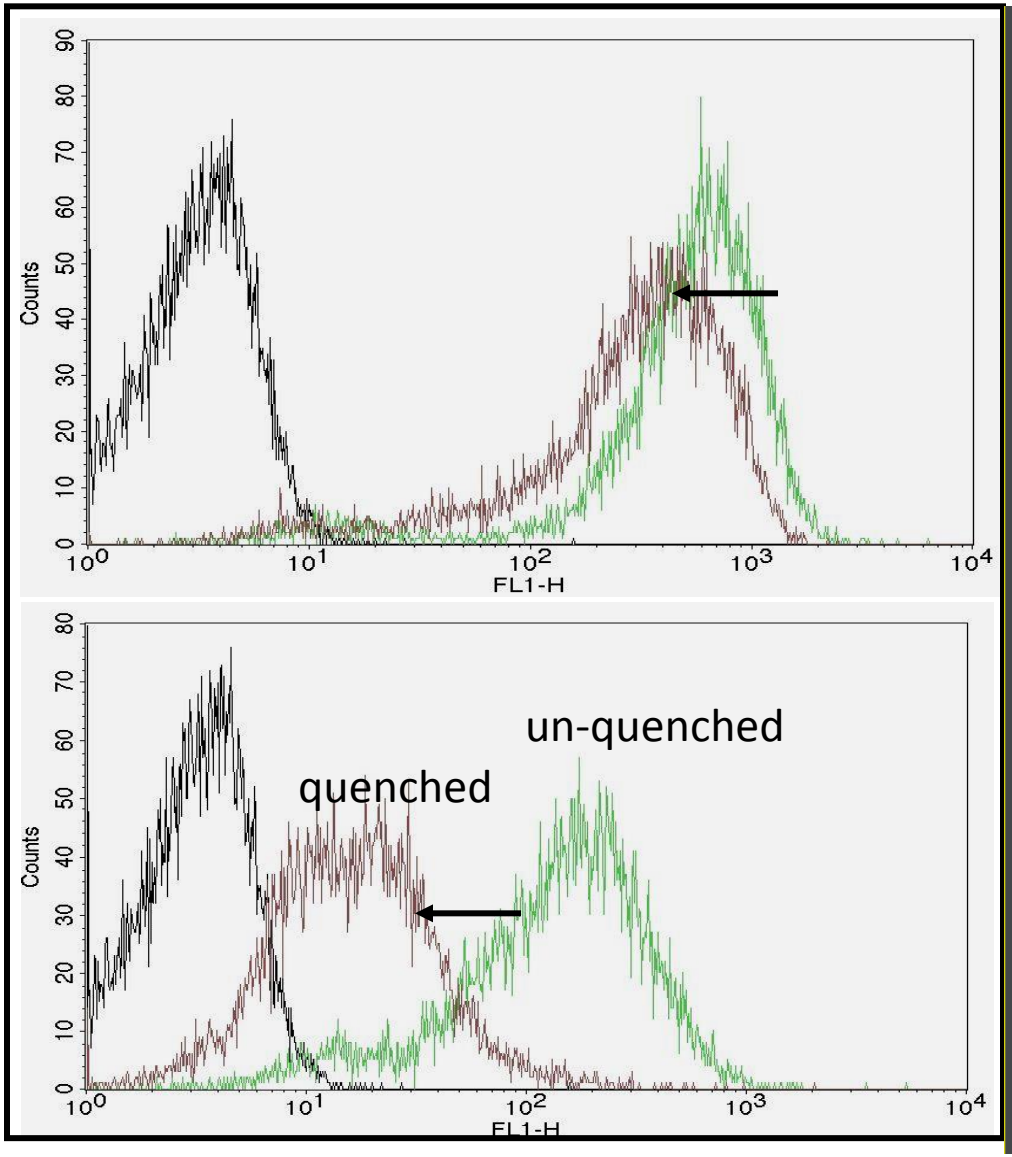
Modulation of surface CD20 mAb by 488 quenching.

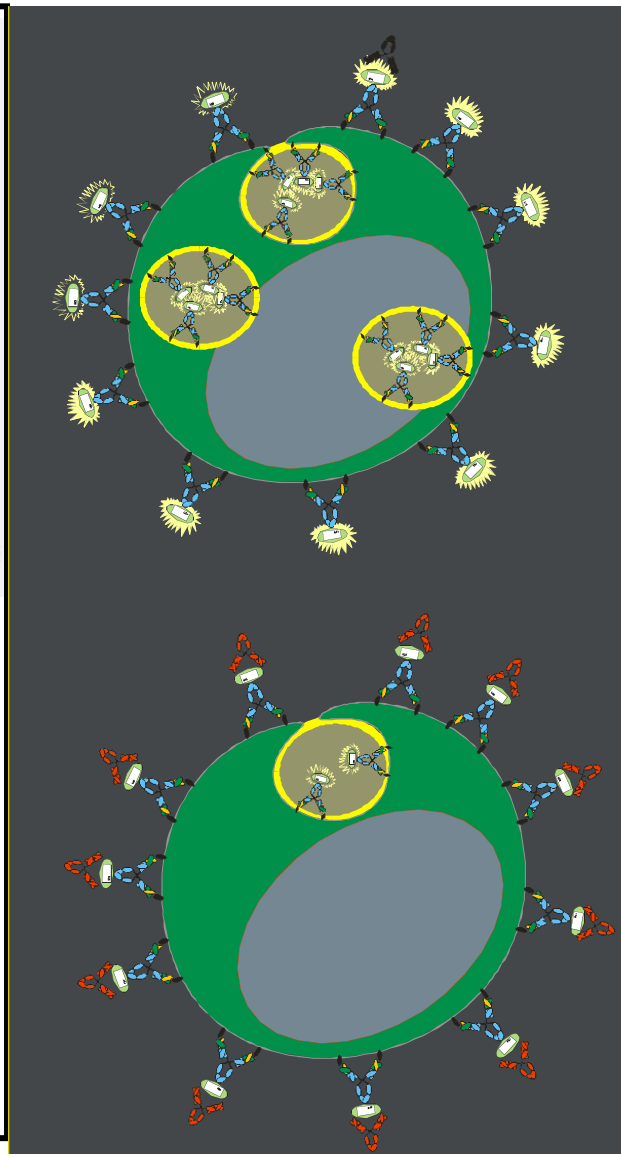
Ritux (type I)



Tosit (Type II)



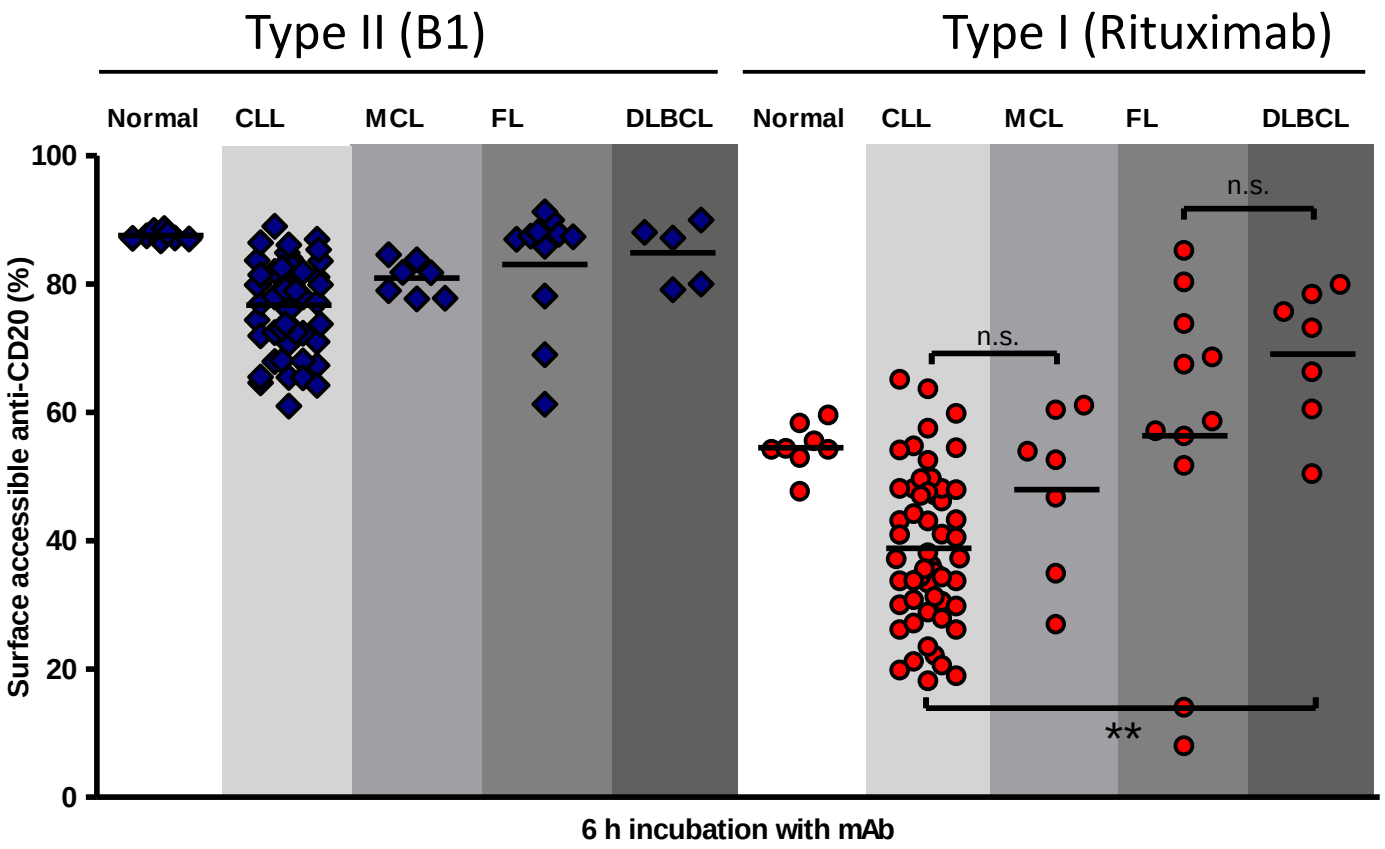




Human CD20 Tg B cells, 24 h, 5 ug/ml, then wash x 2, into FACS tubes and +/- quench

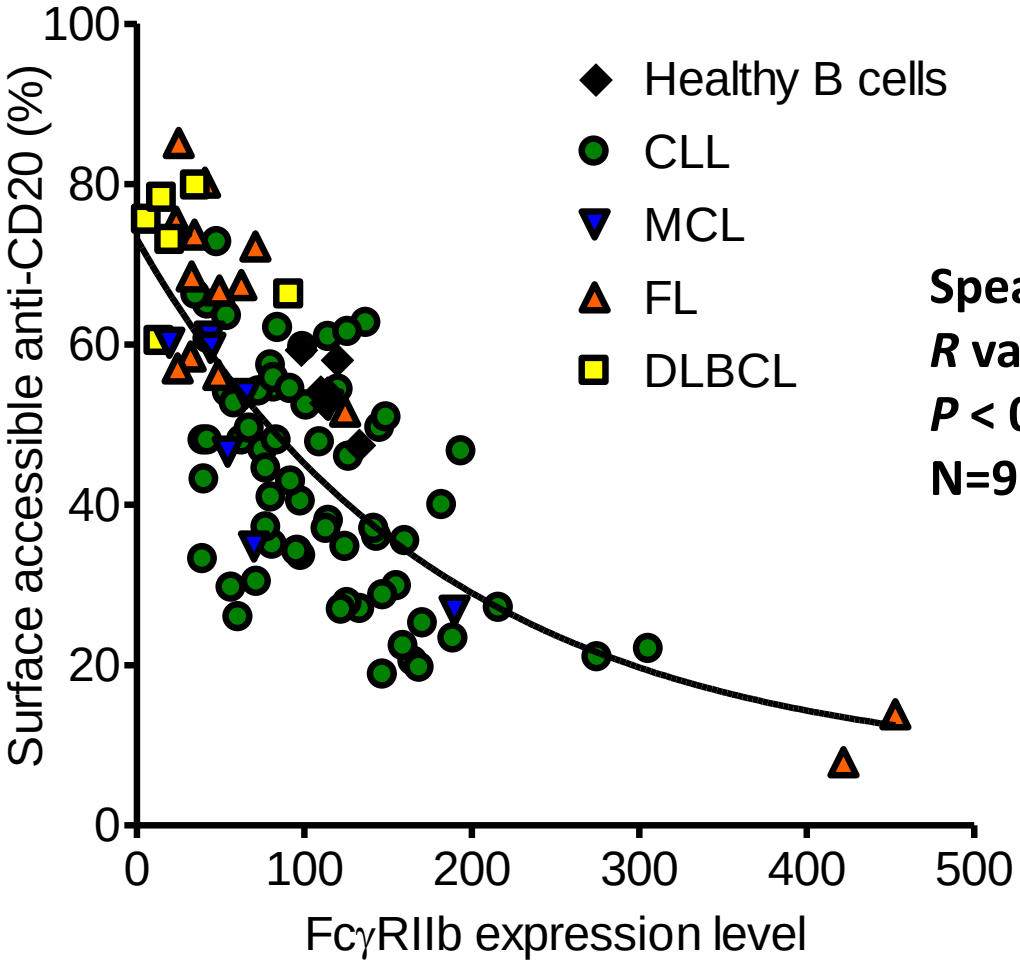
Differences in internalisation an according to type of antibody and type of lymphoma

Lim SH et al., Blood 2011:118:2530-2540



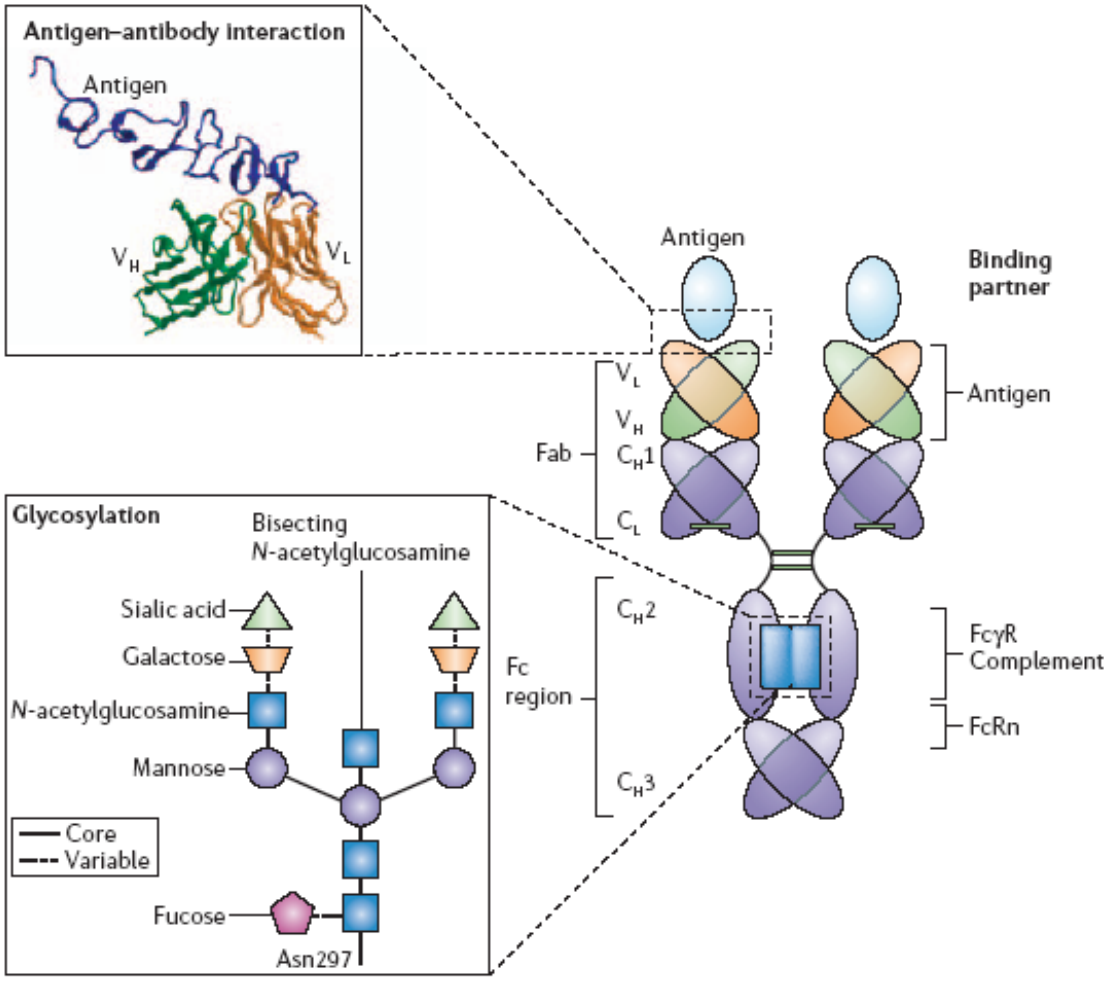
Effect lost with F_{ab} antibodies, occurs with isolated B-cells blocked with anti-CD32

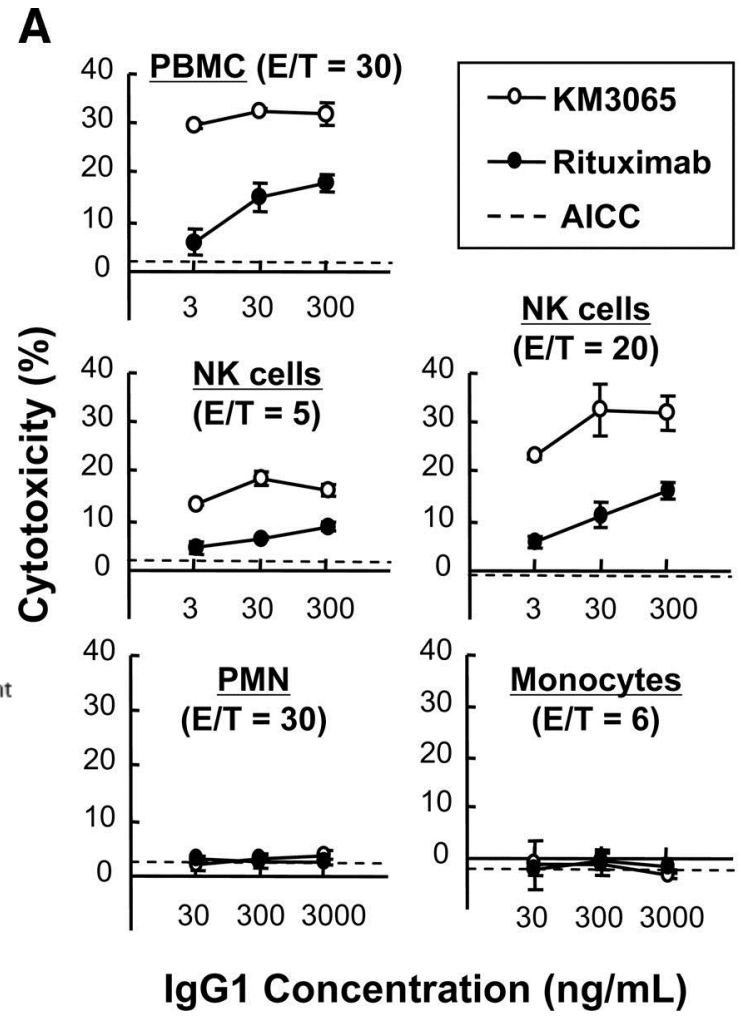
Internalisation correlates with FcγRIIb (CD32b) expression



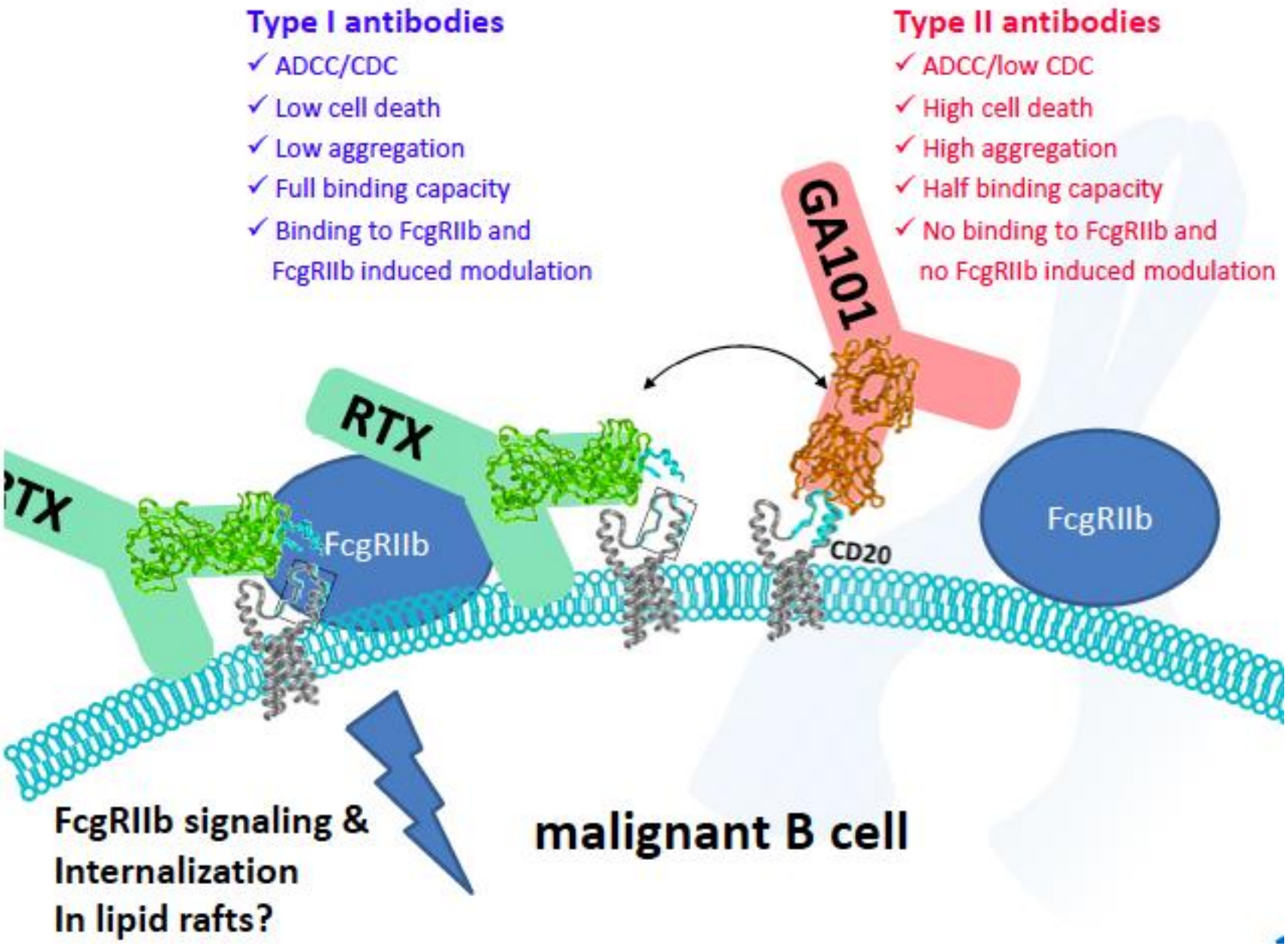
Lim SH et al., Blood 2011:118:2530-2540

Glyco-engineering



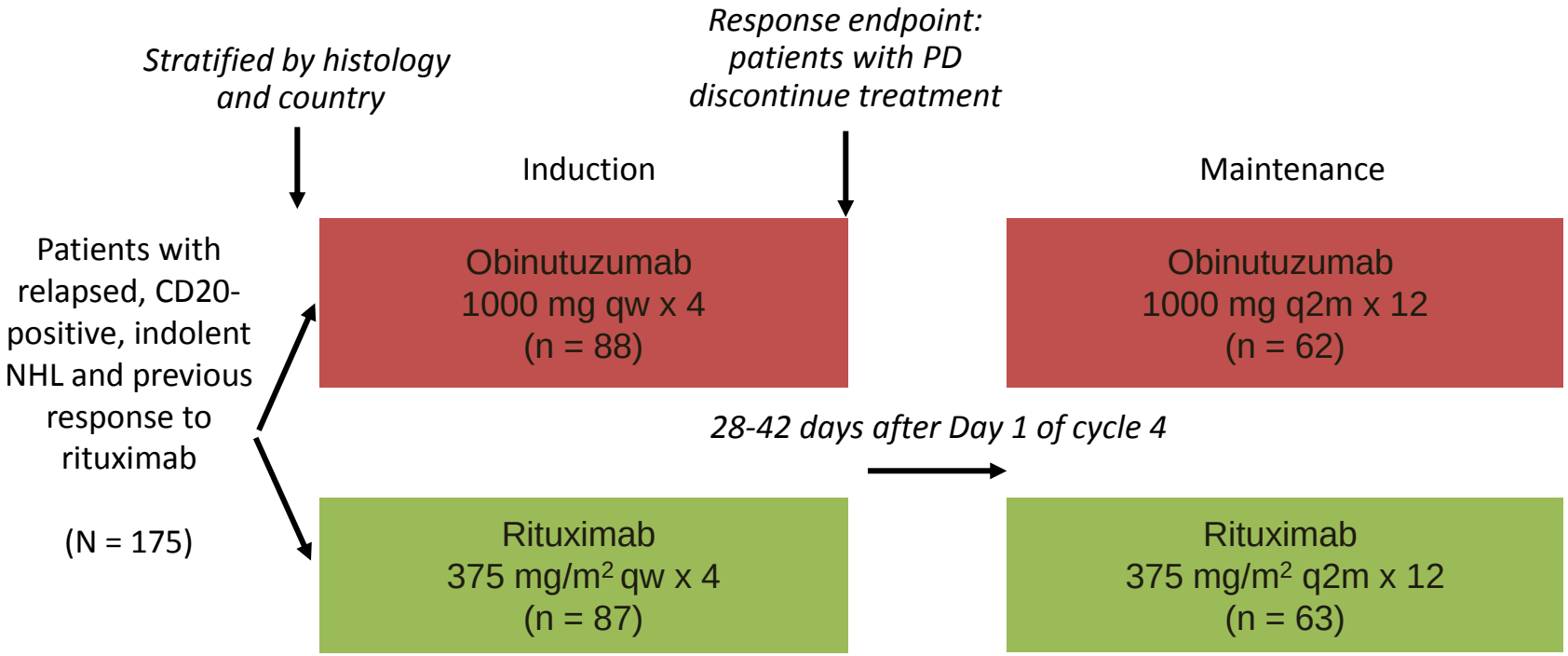


Niwa, R. et al. Clin Cancer Res 2004;10:6248


Type I antibodies
✓ ADCC/CDC
✓ Low cell death
✓ Low aggregation
✓ Full binding capacity
✓ Binding to FcgRIIb and FcgRIIb induced modulation
Type II antibodies
✓ ADCC/low CDC
✓ High cell death
✓ High aggregation
✓ Half binding capacity
✓ No binding to FcgRIIb and no FcgRIIb induced modulation
GA101
RTX
RTX
FcgRIIb
FcgRIIb
CD20
FcgRIIb signaling & Internalization In lipid rafts?
malignant B cell

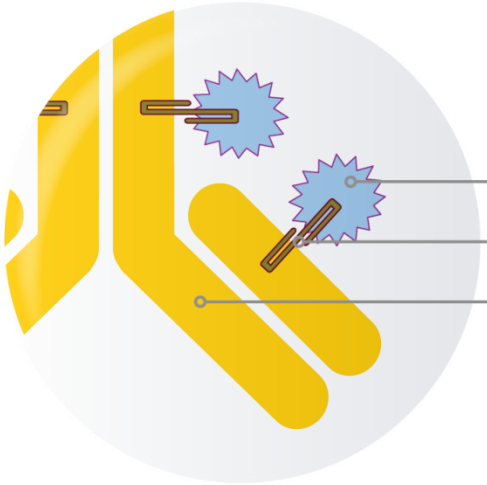
GAUSS: Open-Label Phase II Trial in Relapsed Indolent NHL

Sehn LH, et al. ASH 2011. Abstract 269.



- Primary endpoint: ORR to induction in FL population
- 43.2% [32/74] *v* 28.0% [21/75]: ASH 2011.
- PFS no difference, when reported at ASH
- Large phase III first-line study in progress (GALLIUM)

Brentuximab Vedotin Mechanism of Action

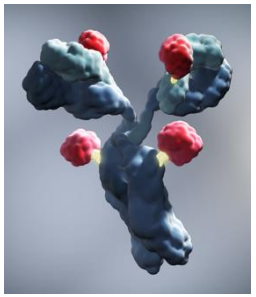


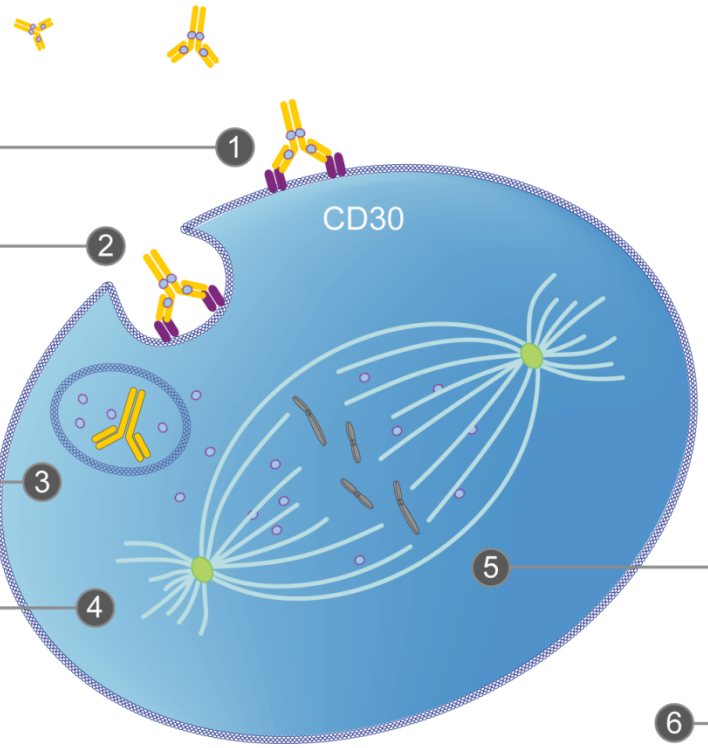
Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

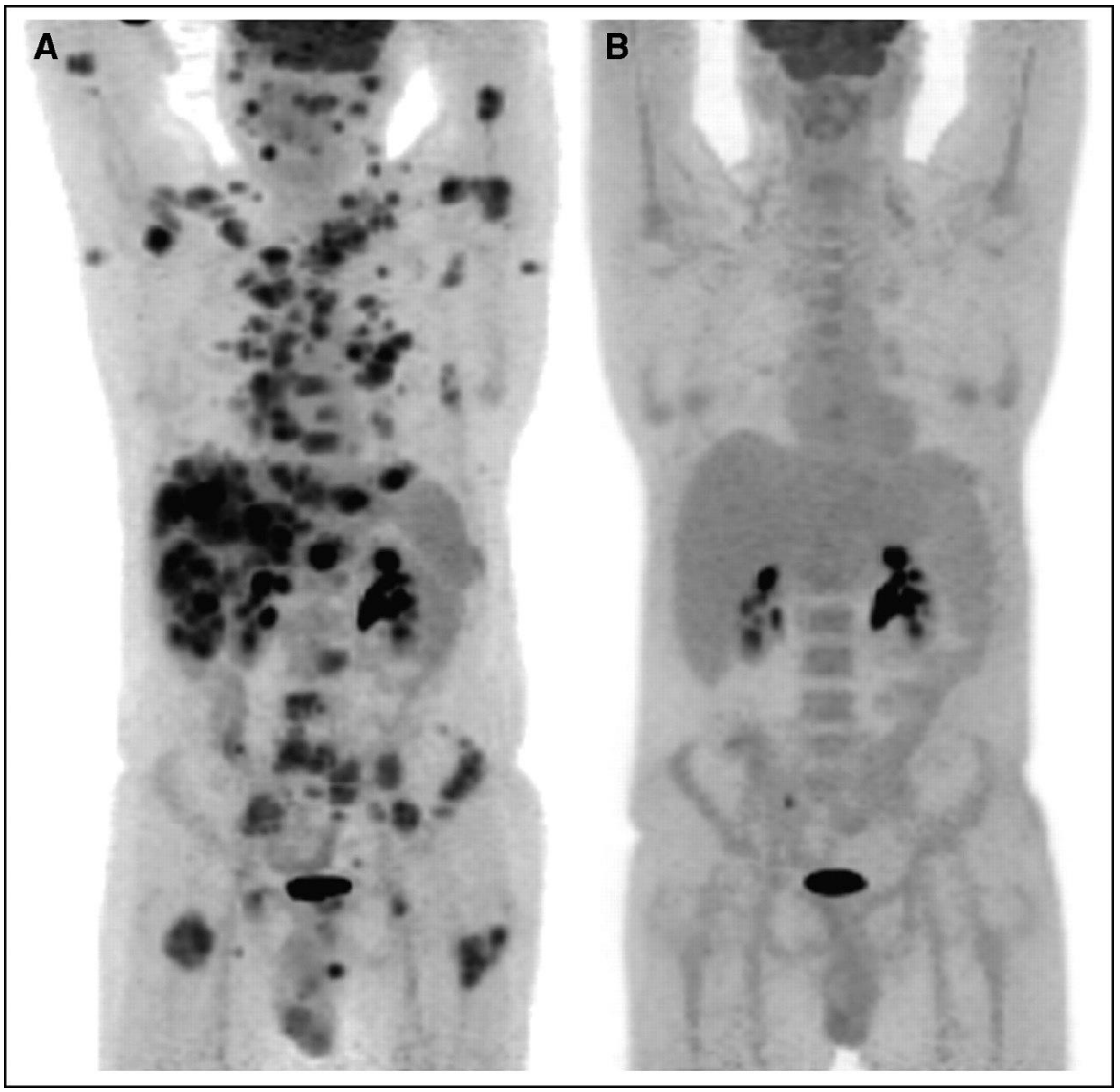
anti-CD30 monoclonal antibody





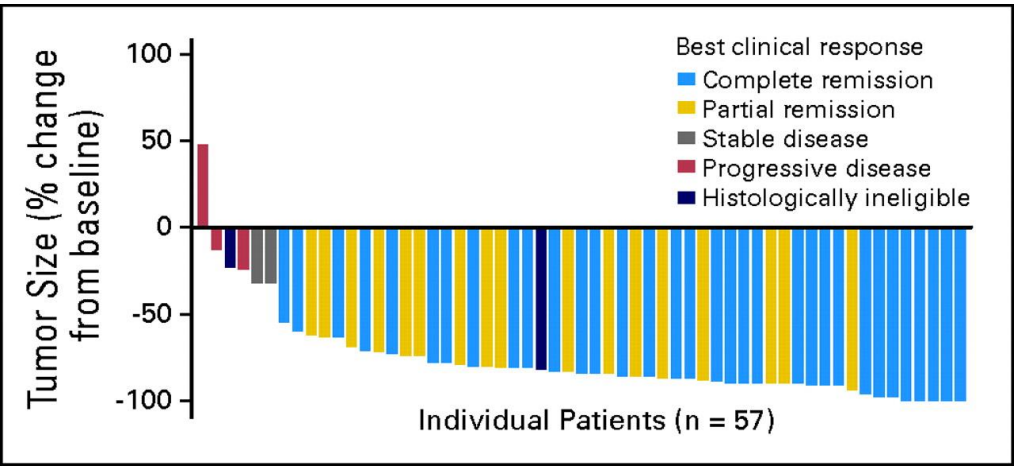
1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

PET scan before/after 4 doses

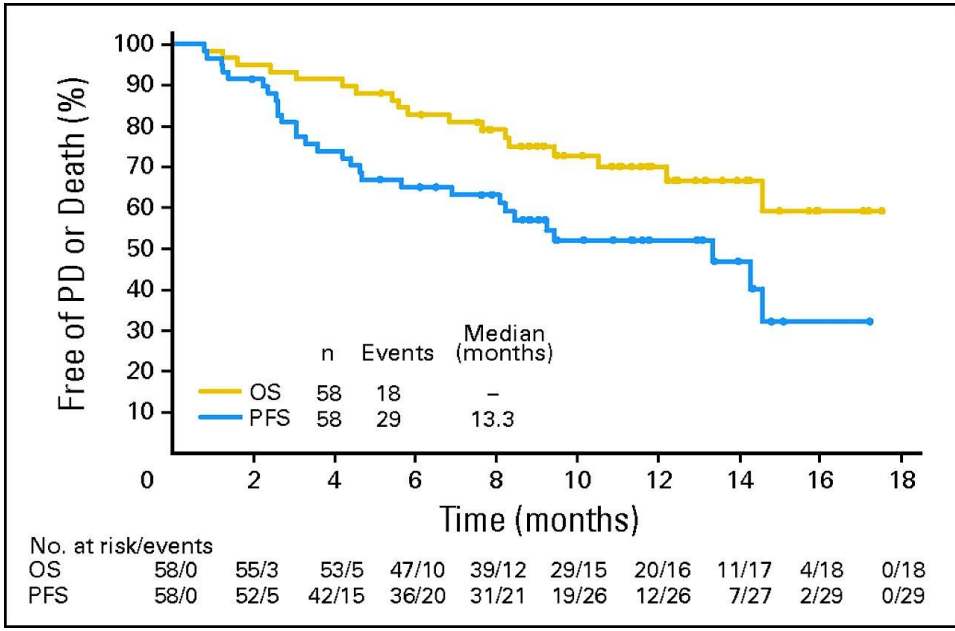


Pro B et al. JCO 2012;30:2190-2196

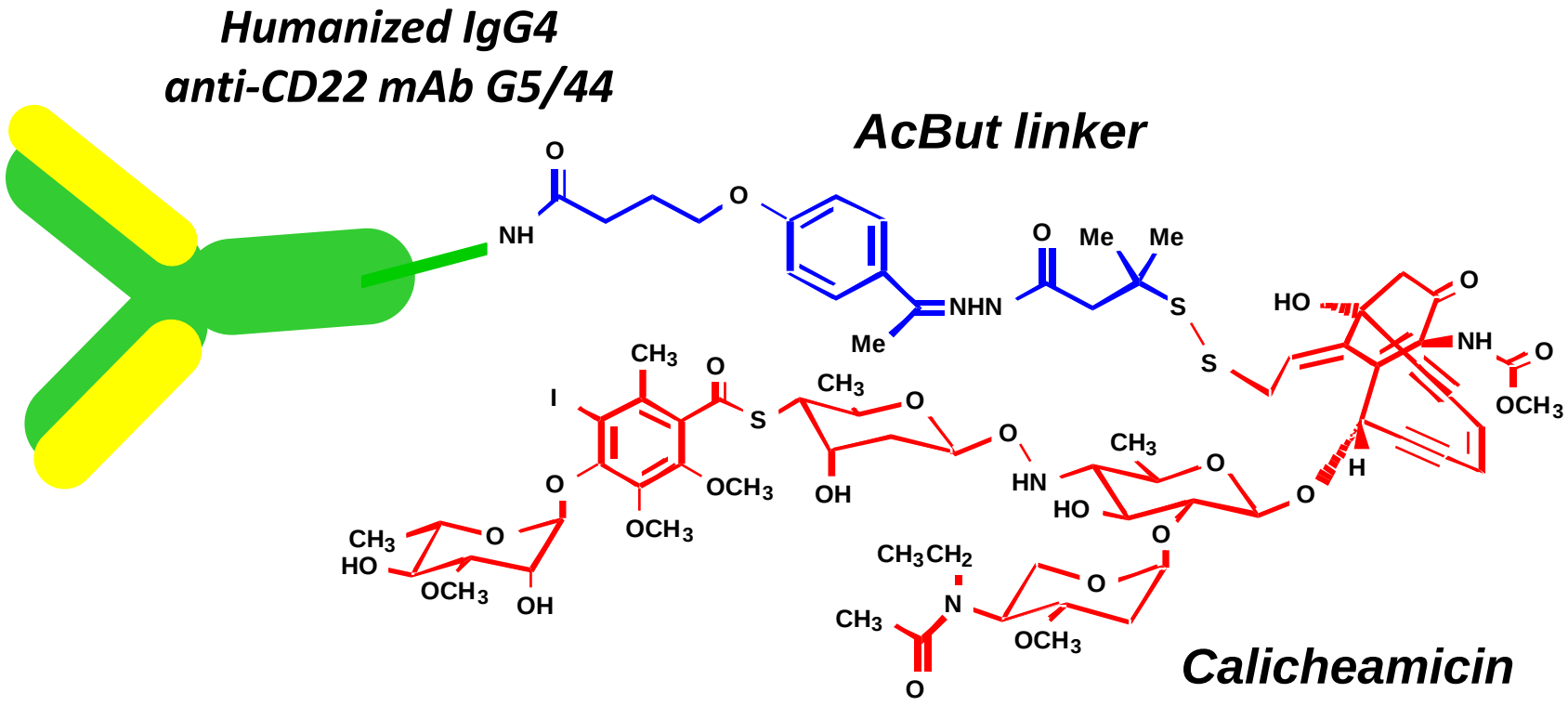
Phase 2 study of Brentuximab Vedotin in 58 patients with relapsed or refractory sALCL



Pro B et al. JCO 2012;30:2190-2196



Inotuzumab ozogamicin (CMC-544)

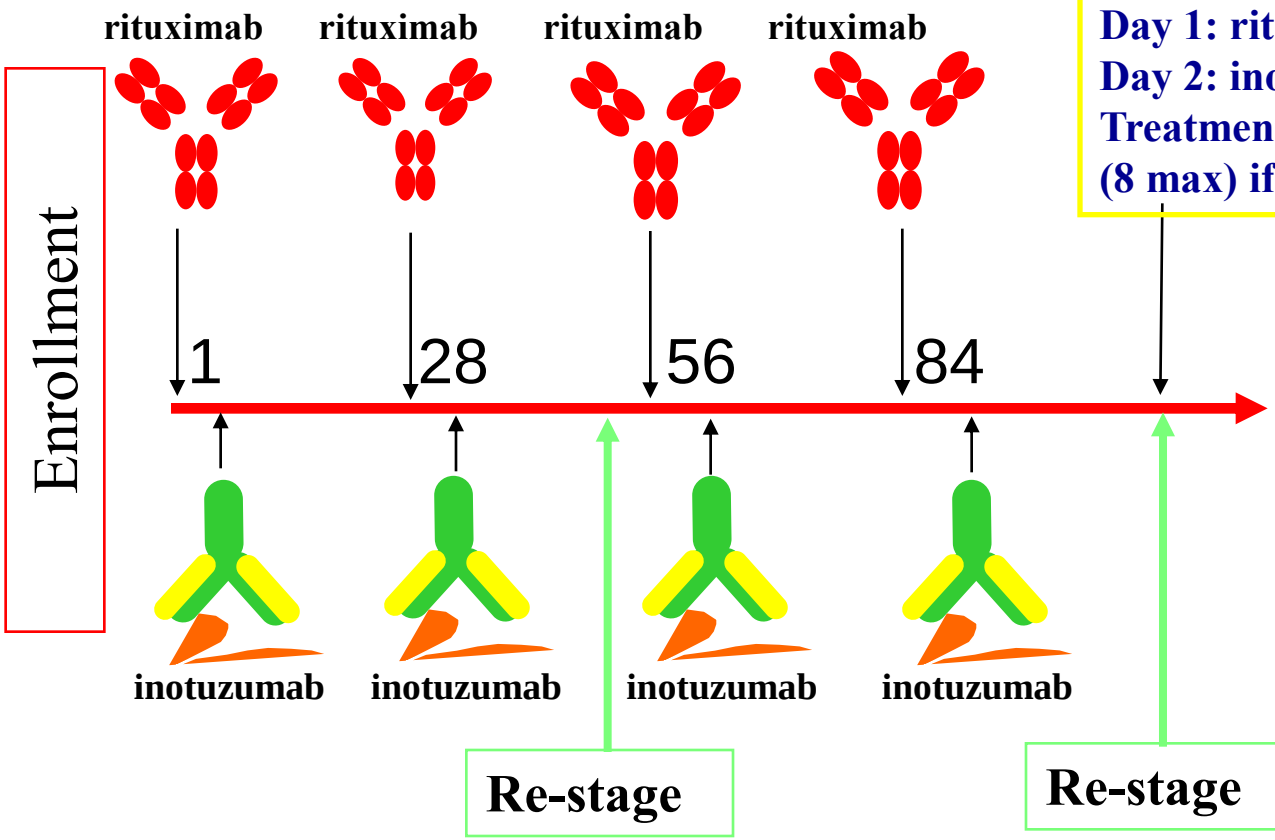


Structure of inotuzumab ozogamicin

Adapted from DiJoseph JF et al. *Blood*. 2004;103:1807-1814.

Phase I/II Inotuzumab + Rituximab in Recurrent B-cell Lymphomas

Recurrent CD22+ B-cell NHL



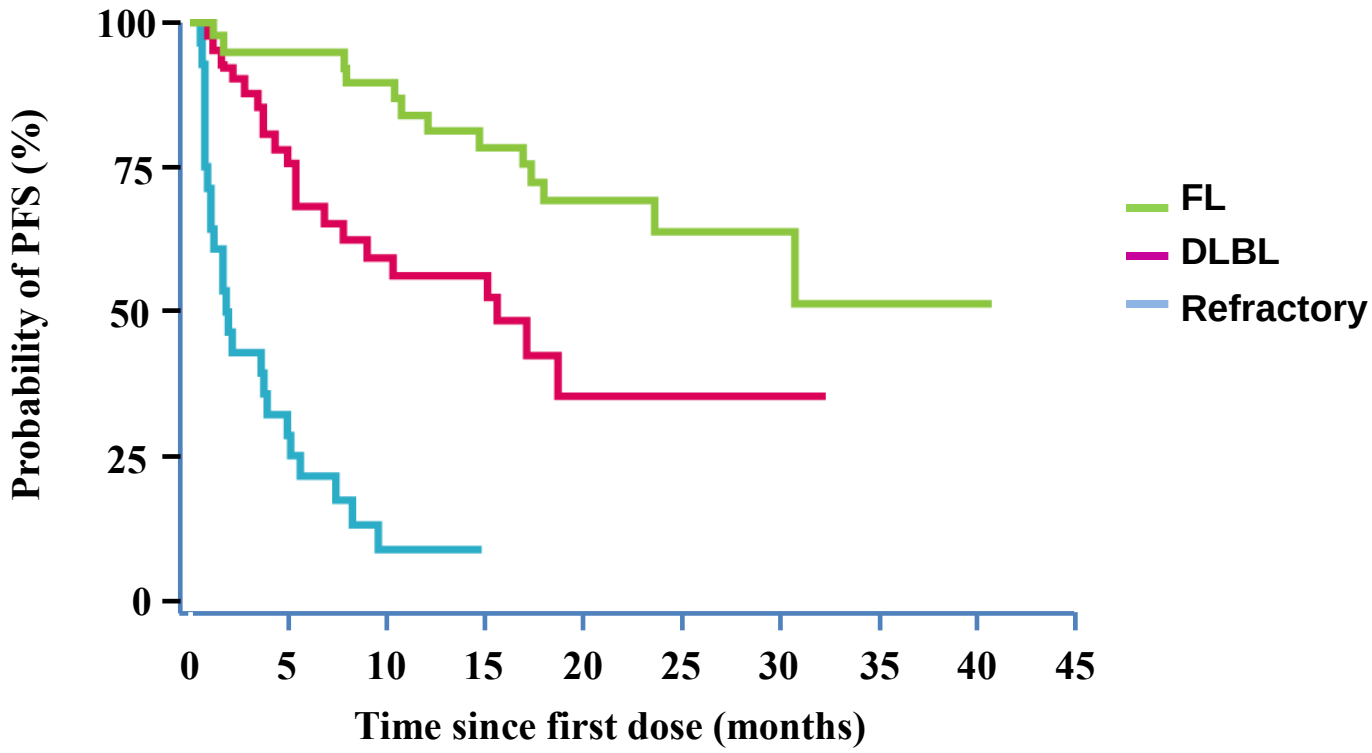
28-day cycle

Day 1: rituximab 375 mg/m²
Day 2: inotuzumab
Treatment: 4 cycles; additional 4 cycles (8 max) if clinical benefit

Dose levels

1 = 0.8 mg/m²
2 = 1.3 mg/m²
3 = 1.8 mg/m²

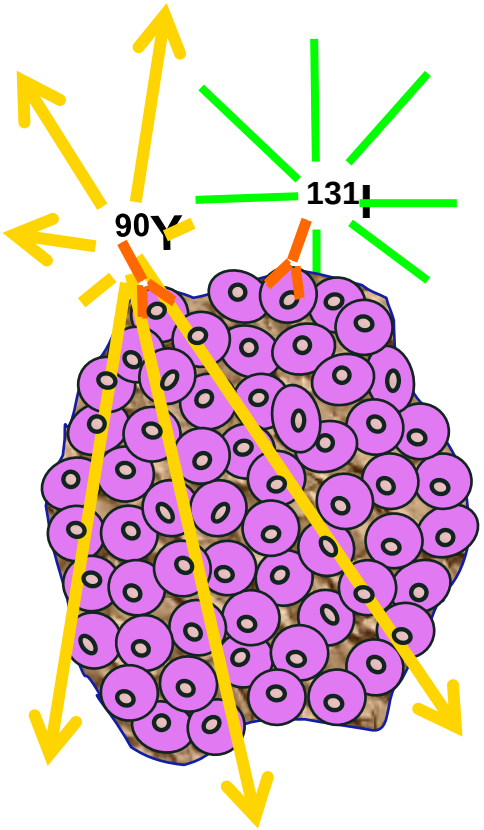
Progression-free Survival

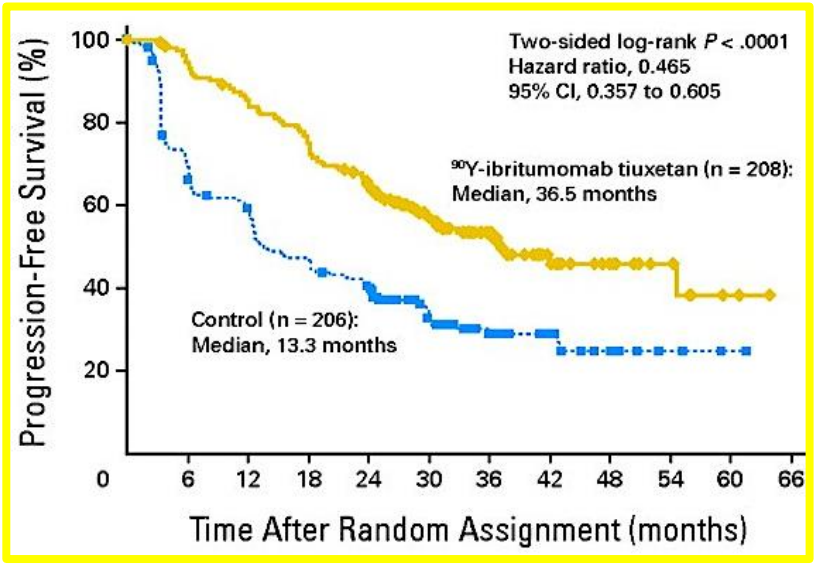


		PFS, mo	
	n	Median	95% CI
FL	39	NR	30.8-NR
DLBCL	42	17.1	7.8-NR
Refractory	30	1.9	1.0-4.8

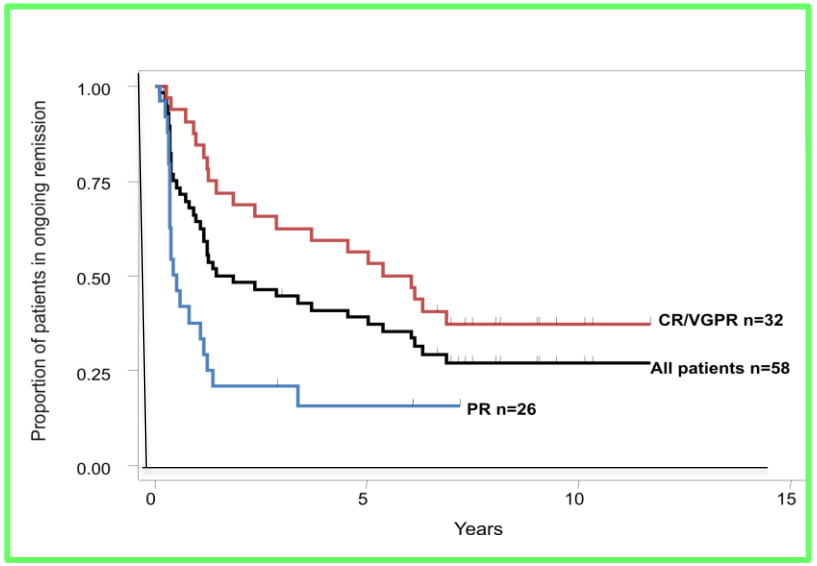
Fayad L et al., J Clin Oncol *in press*

Radioimmunotherapy





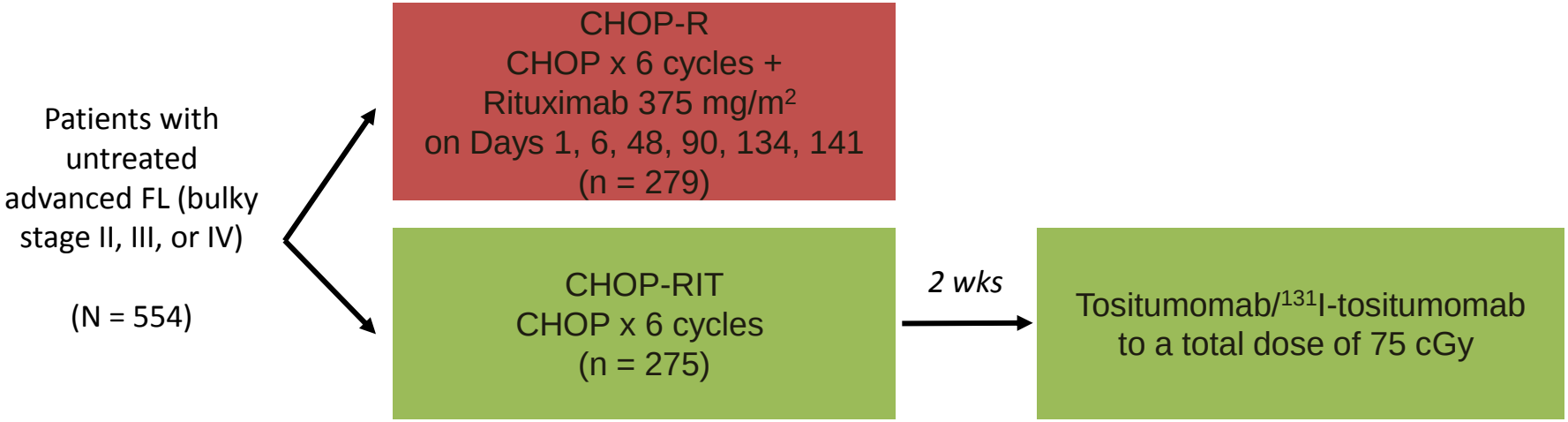
Morschhauser F et al. J Clin Oncol 2008;26:5156-5164



Davies A et al. ICML Lugano 2008

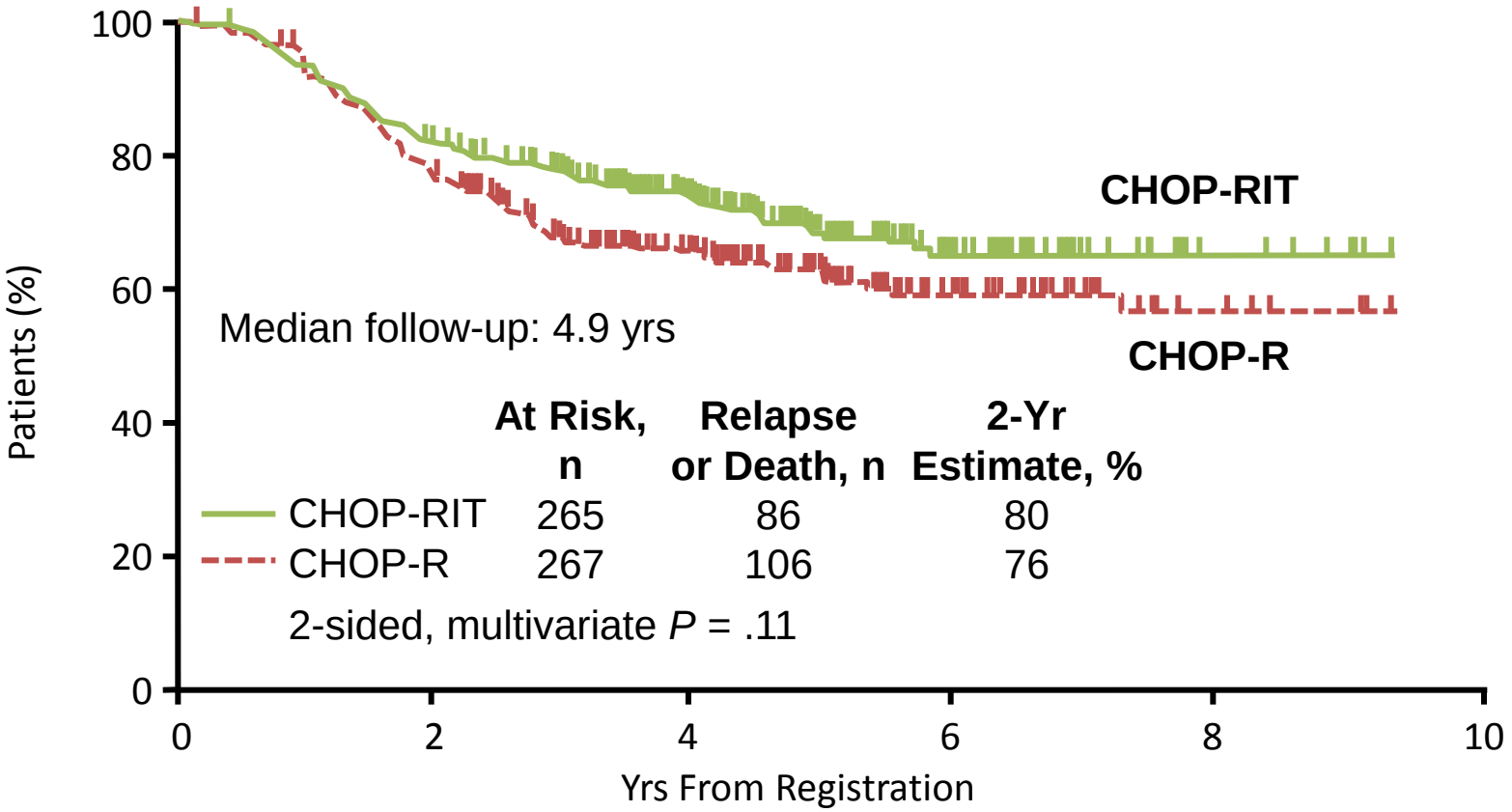
SWOG 0016: R-CHOP vs CHOP + ^{131}I-Tositumomab in Untreated FL

Press OW, et al. ASH 2011. Abstract 98.



Outcome, %	CHOP-R (n = 267)	CHOP-RIT (n = 265)	HR (95% CI)	*P* Value
2-yr OS	97	93	1.55 (0.95-2.54)	.08
2-yr PFS	76	80	0.79 (0.60-1.05)	.11
Response rate	(n = 263)	(n = 260)		
▪ ORR (CR + PR)	85	86	.90	
▪ CR	41	46	.25	

SWOG 0016: PFS With R-CHOP vs CHOP + ^{131}I-Tositumomab in Untreated FL



Press OW, et al. ASH 2011. Abstract 98.

Bispecific constructs

Anti-CD19/CD3ε

Forty patients with relapsed B-NHL requiring treatment

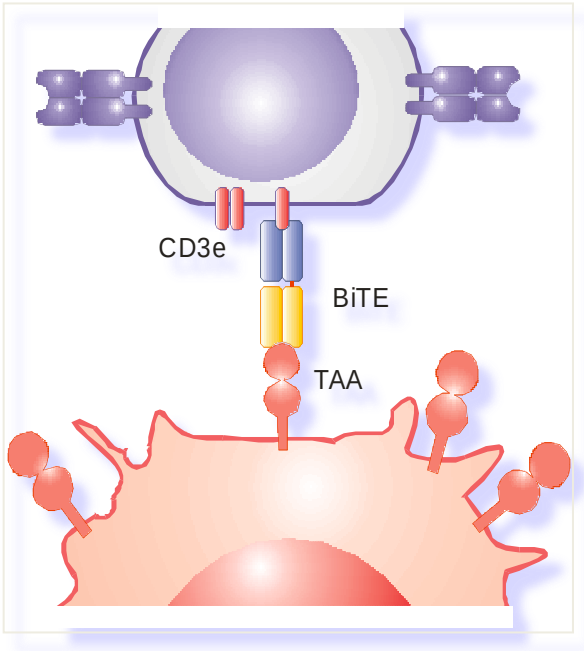
Stages: IV 60%, III: 30%, II: 10%

Number of patients in NHL subtypes*

FL: 16
MCL: 16
CLL/SLL: 3
MW/PL: 2
MZL: 2
DLBCL: 1

Median of 3 previous regimens (range 1 – 12)

90% patients pretreated with rituximab, 45% with fludarabine



Treated with 0.0005 – 0.09 mg/m²/24 h by IVI

Nine of 40 patients permanently discontinued treatment due to adverse events:

Seven with CNS symptoms (all reversible),

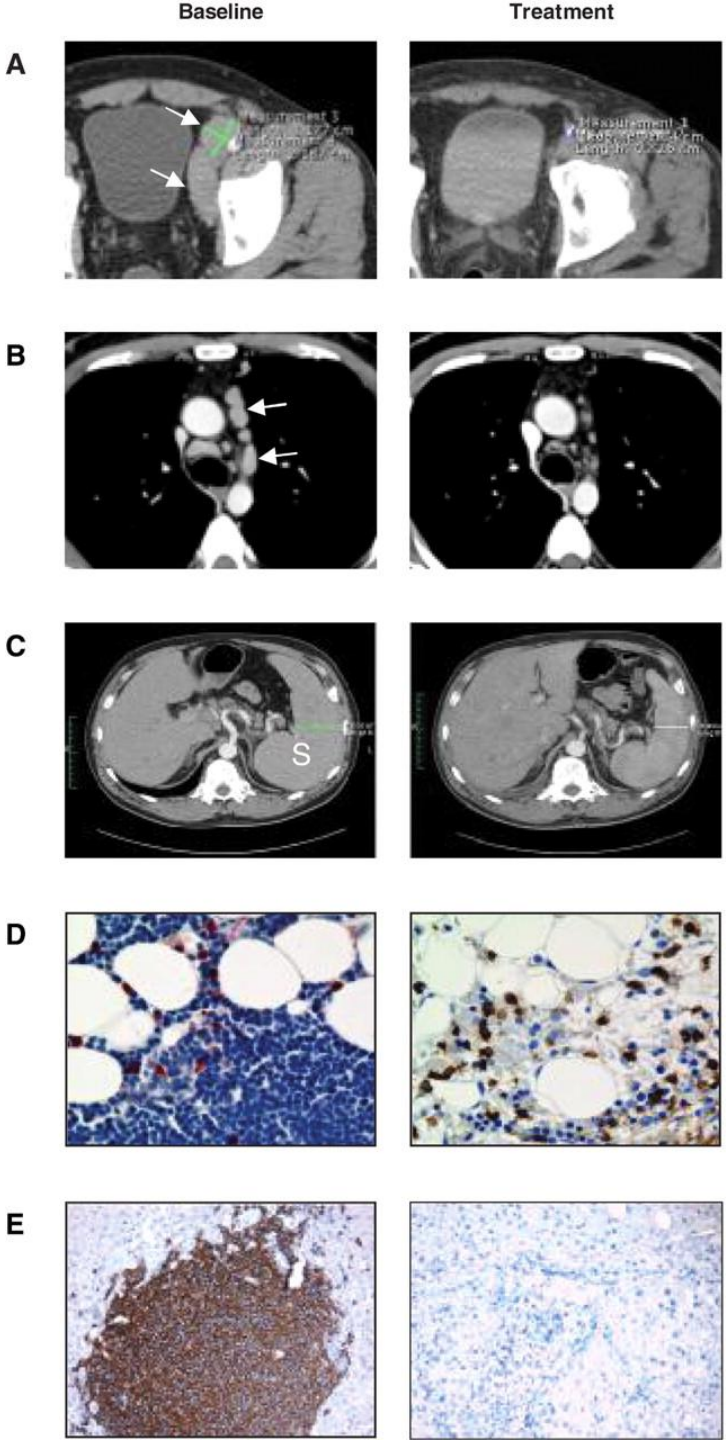
One patient died of sepsis

Blinatumumab Clinical Activity

Dose-dependent CR and PR in FL, MCL, and SLL/CLL

Induction of durable responses with up to 14 months CR in MCL

Complete removal or reduction of tumor load in bone marrow (8 out of 9 patients)



Bargou et al Science 2008 321:974

What comes next?....

- New types of anti-CD20
  - Theoretically attractive
  - Maybe only some sub-types will show benefit
- Immunotoxins
  - Renewed interest, mainly thanks to linker chemistry
  - Combinations being tested
- Radioimmunotherapy
  - Some long term remissions
  - Still to determine place in treatment algorithms
- Bispecific conjugates
  - Highly potent
  - Narrow therapeutic window at present