Inotuzumab Oxagamicin in ALL

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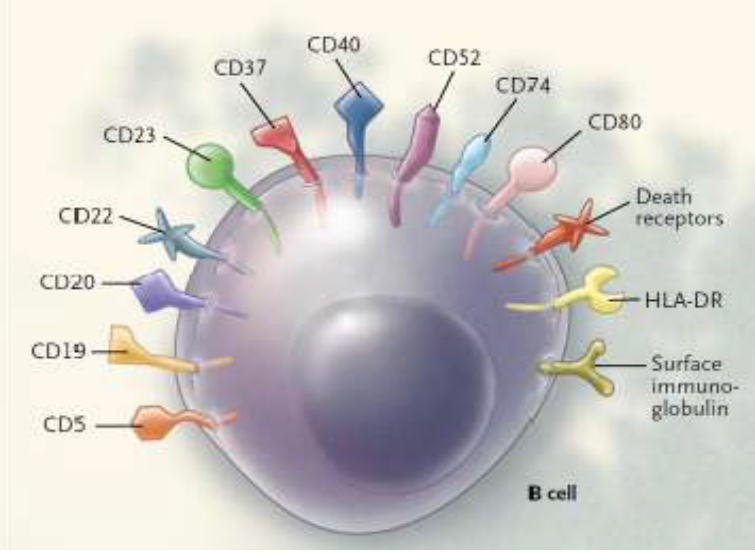
Policlinico S. Orsola-Malpighi

ALL status of the art

- ✓ In contrast with pediatric patients, the outcome in adults remains dismal, despite high initial complete remission (CR) – long term remission @5y 30%, survival @5y after relapse 7%
- ✓ Further intensification of chemo-regimens means increasing already significant toxicity
- ✓ Antibody therapies represent a promising approach



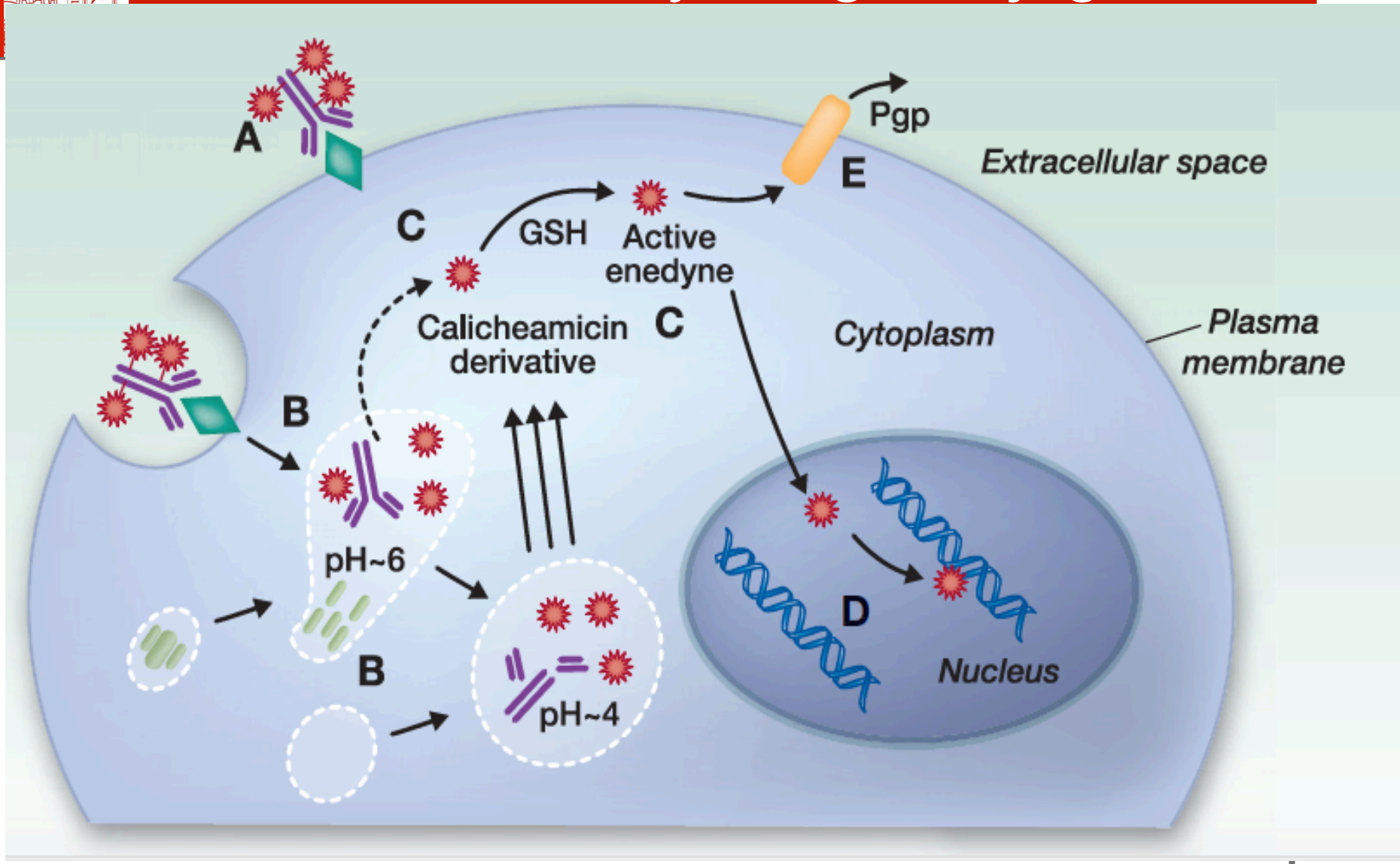
Lymphoblasts express various targetable surface antigens: CD19, CD20, CD22, CD52

Ideal target:

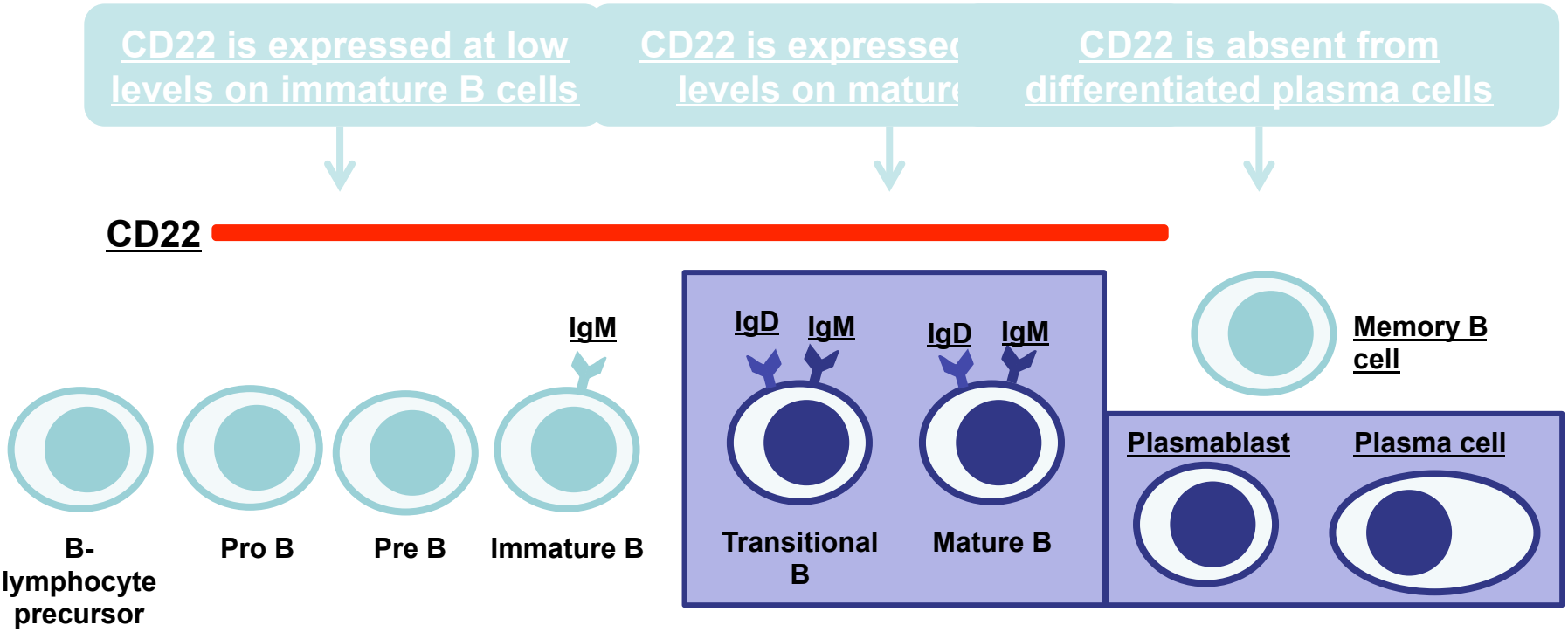
- ➢High percentage of blasts expressing the antigen
- ➢High density of antigen expression
- ➢Lack of expression on normal cells

Cheson et al. *NEJM* 2008; 359:613-626

ADC- Antibody Drug Conjugate



CD22 expression at specific time-points of B-cell development

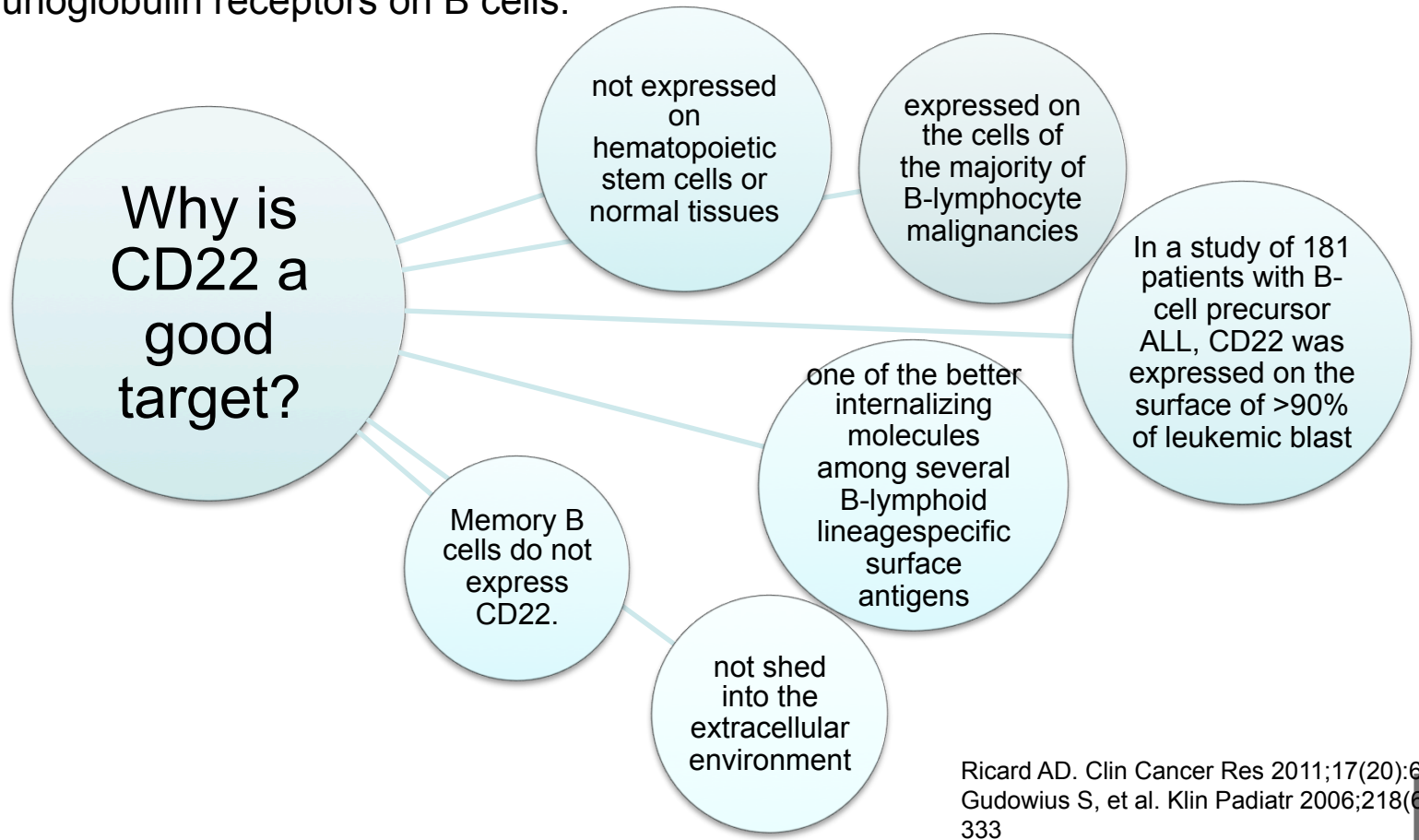


Overall, most circulating IgM-positive, IgD-positive human B cells (including activated B cells and memory B cells) strongly express CD22, whereas differentiated plasma cells do not

Shor B *et al. Mol Immunol* 2015;67;107–116; Blüml S *et al. Arthritis Res Ther* 2013;15 (Suppl 1):S4

CD22: role and therapeutic target

- CD22 is a 135-kDa **B-cell-specific adhesion molecule** preferentially expressed on mature B lymphocytes
- **normal function** of CD22 is to regulate signal transduction of the surface immunoglobulin receptors on B cells.



Ricard AD. Clin Cancer Res 2011;17(20):6417–6427
Gudowius S, et al. Klin Padiatr 2006;218(6):327–333

Inotuzumab Ozagamicin (IO) in ALL

- On the basis of promising pre-clinical data of dose-dependent apoptotic effect on B-ALL cell lines and primary ALL cells IO has been studied in clinical trials in 2 dosing strategies at MDACC:
  - IO 1.8 mg/m^2 IV every 3-4 weeks
  - IO weekly dosing schedule (0.8 mg/m^2 day 1, 0.5 mg/m^2 day 8 and 15) every 3-4 weeks; same cumulative dose

MONTHLY SCHEDULE → up to 8 cycles

Cycle 1 Cycle 2

IO 1.8 mg/m^2 IO 1.8 mg/m^2

⇩ ⇩

D1 D8 D15 D22 D29 D8 D15 D22

WEEKLY SCHEDULE → up to 8 cycles

Cycle 1 Cycle 2

IO 0.8 mg/m^2 IO 0.5 mg/m^2 IO 0.5 mg/m^2 IO 0.8 mg/m^2 IO 0.5 mg/m^2 IO 0.5 mg/m^2

⇩ ⇩ ⇩ ⇩ ⇩ ⇩

D1 D8 D15 D22 D29 D8 D15 D22

Kantarjan et al. *Lancet Oncol* 2012; 13: 403–11
Kantarjan et al. *Cancer* 2013;

Inotuzumab in R/R ALL

- ✓ Phas
- ✓ Shor cycle
- ✓ Pren and 25 mg h
- ✓ Suita
- ✓ Patie ed 2 addi

Characteristics of the Study Group (n=90)

		No. (%) on Inotuzumab Schedule		
Characteristic	**Category**	**Single-dose (n=49)**	**Weekly (n=41)**	**Overall (n=90)**
Age (yrs)	≤ 18	3 (6)	3 (7)	6 (7)
	≥ 60	12 (24)	13 (32)	25 (28)
PS (ECOG)	0-1	44 (90)	37 (90)	81 (90)
	≥ 2	5 (10)	4 (10)	9 (10)
Salvage status	S1	13 (27)	16 (39)	29 (32)
	S1, CRD1 < 12 mos	3 (6)	12 (29)	15 1(7)
	S1, CRD1 ≥ 12 mos	7 (14)	2 (5)	9 (10)
	S2	24 (49)	10 (24)	34 (38)
	≥ S3	12 (24)	15 (37)	27 (30)
Prior HCVAD regimen	Yes	28 (57)	29 (71)	57 (63)
Karyotype	Diploid	12 (24)	9 (22)	21 (23)
	Ph-positive	7 (14)	8 (20)	15 (17)
	T (4;11)	5 (10)	3 (7)	8 (9)
	Other	25 (51)	21 (51)	46 (51)
Prior allo SCT	Yes	7 (14)	3 (7)	10 (11)
% CD22-positive	> 90	28 (57)	31 (76)	59 (66)
	70-89	14 (29)	8 (20)	22 (24)
	50-69	7 (14)	2 (5)	9 (10)

68% ≥ S2

Kantarjian H *et al. Cancer* 2013;119:2728-2736

Inotuzumab in R/R ALL – MDAACC results

Response	Single dose n°=49	Weekly n°=41	Overall n°=90
CR	9 (18)	8 (20)	17 (19)
CRp	14 (29)	13 (32)	27 (30)
CRi, bone marrow CR	5 (10)	3 (7)	8 (9)
PR	0	0	0
Resistant	19 (39)	15 (37)	34 (38)
Death < 4 weeks	2 (4)	2 (5)	4 (4)
ORR	28 (57)	26 (59)	52 (58)

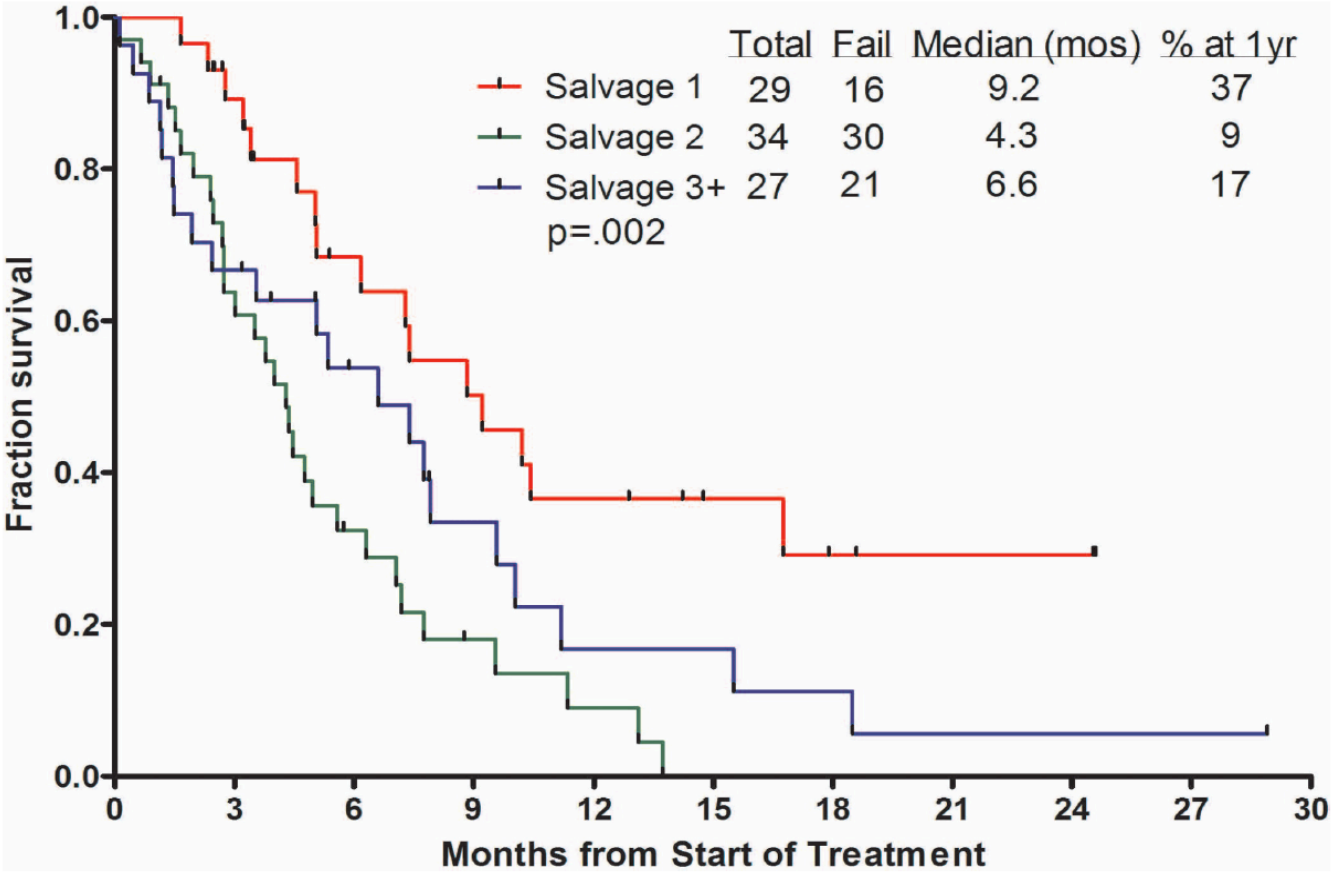
- Respo
- Media
- Best
- ORR 58% MRD 72%

Deep molecular remissions allow opportunity to transplant

n was brief

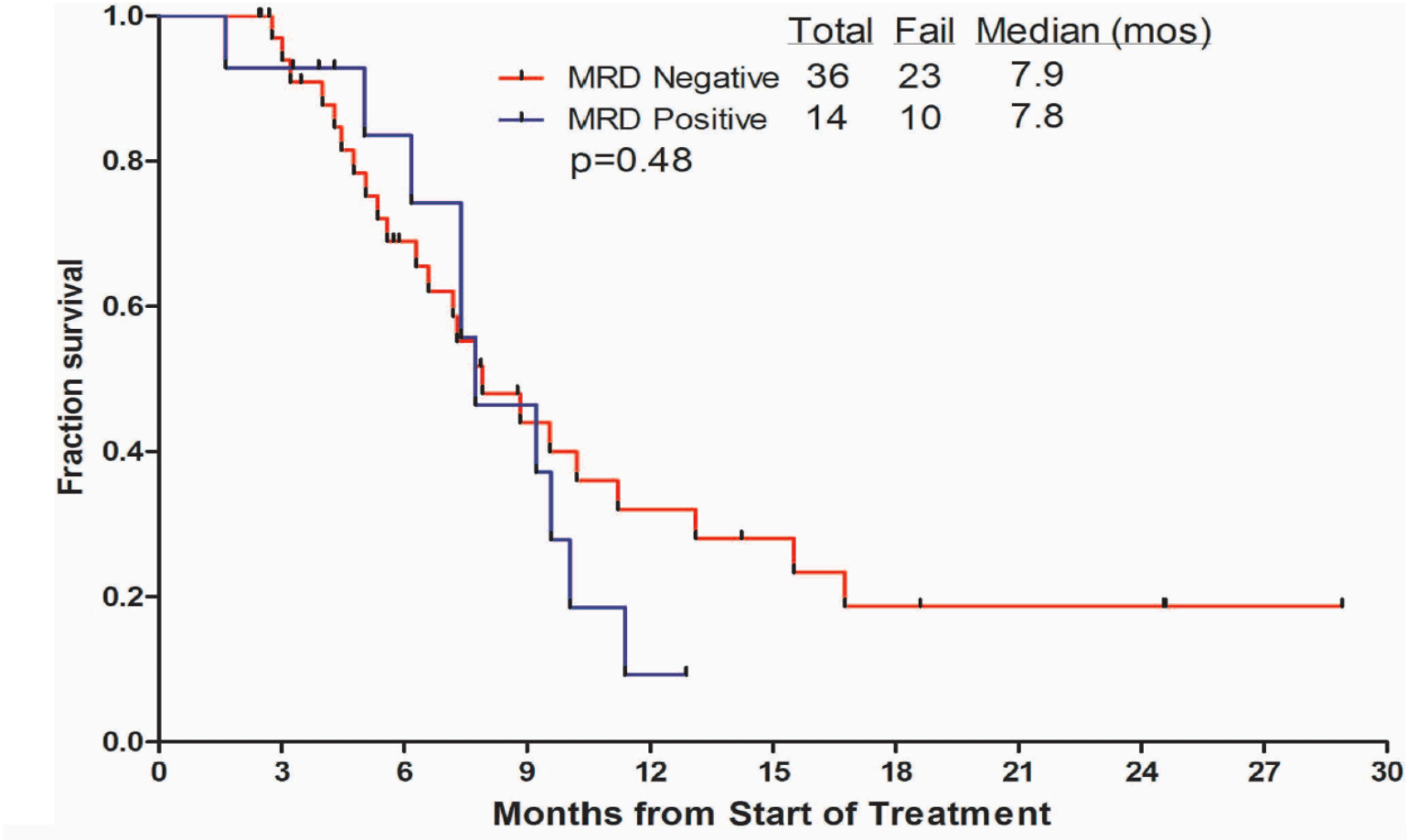
Kantarjian H *et al. Cancer* 2013;119:2728-2736

Survival by salvage status



Kantarjian H *et al. Cancer* 2013;119:2728-2736

Survival by achievement of MRD



Kantarjian H *et al. Cancer* 2013;119:2728-2736

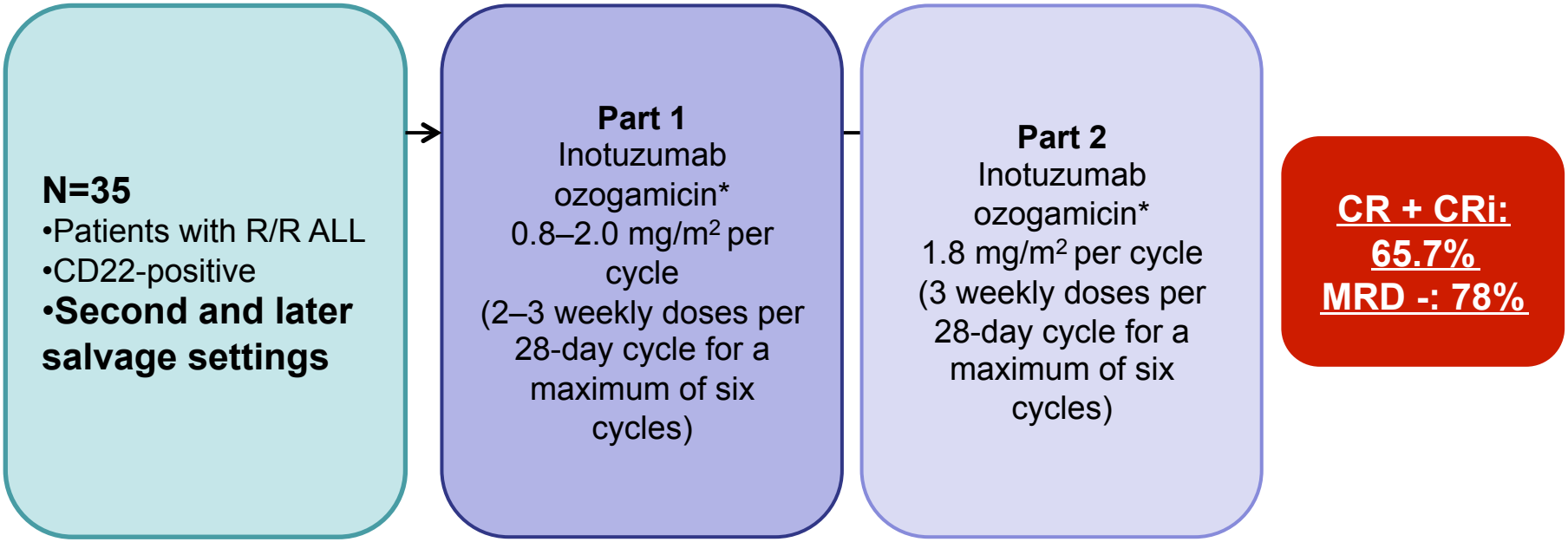
Adverse eventes weekly vs monthly

	Weekly		Single-dose	
	G1-2	G3-4	G1-2	G3-4
Day 1-2 drug-related fever	3	6	20	9
Day 1-2 drug-related hypotension	6	0	12	1
↑ bilirubin	2	0	12	2
↑ AST/ALT	9	2	27	1
↑amylase/lipase	1	0	0	1

- ✓ Less frequent toxicity with weekly dose probably related to peak levels
- ✓ Peak levels not associated with worse response
- ✓ **Weekly IO as effective and less toxic**

Targeting CD22 in R/R ALL phase I/II

Phase I/II B1931010 trial (multi-institution)[2,3]



*Fractionated dosing only

1. Dahl J et *al. Expert Rev Hematol* 2016 [Epub]; 2. Advani AS *et al*. ASH 2014 (abstract 2255)

INO-VATE ALL: IO vs chemo in ALL salvage

- Phase 3 multi-center study
- INO-VATE ALL: NCT 01564784

Relapsed/Refractory CD22positive ALL

Ph+/Ph-

Eligible for 1st or 2nd salvage therapy

Randomization 1:1

Inotuzumab Ozagamicin IO

IO maximum dose 1.8 mg/m^2 per cycle (21-28 day cycle)

- Day 1 IO 0.8 mg/m^2
- Day 8 and day 22 IO 0.5 mg/m

Investigator's choice - SOC:

- FLAG: Fludarabine, cytarabine and G-CSF up to 4 cycles
- Cytarabine and mytoxantrone for up to 4 cycle

HIDAC: high dose cytarabine up to 12 doses

Stratification:

- **Duration of 1st remission >12 mos vs <12 months**
- **S1 vs S2**
- **Age >55 vs <55y**

Allogenic stem cell transplant encouraged afetr CR/CRi

DeAngelo D *et al.* EHA 2015 (abstract LB2073).

INO-VATE results

Primary end-points:
- CR/CRi
- OS

Secondary end-points:
- MRD negat
- Safety
- PFS
- Duration
- Allogenic

Inotuzum

Investigat
FLAG *or*
Cytarabine + mitoxantrone *or*
HiDAC (high-dose Ara-C)

- Most common grade ≥3 AEs were haematological cytopenias
- Grade ≥3 hepatobiliary AEs occurred in 9% of the inotuzumab arm vs 3% in the SOC arm
- Any grade veno-occlusive liver disease occurred in 15 vs 1 patients, respectively

MRD – neg in pts with CR/CRi: 28.1% (95% CI: 14-47)

DeAngelo D *et al.* EHA 2015 (abstract LB2073).

IO and alloSCT – VOD risk

- Monthly INO: VOD suspected in 6 pts (23%): 2 cases confirmed by biopsy; 2 pts were receiving 2nd SCT; 5 cases were fatal (19%)
- Weekly INO: 1 case of VOD confirmed by Doppler, resolved
- SCT Conditioning for 5 VOD cases

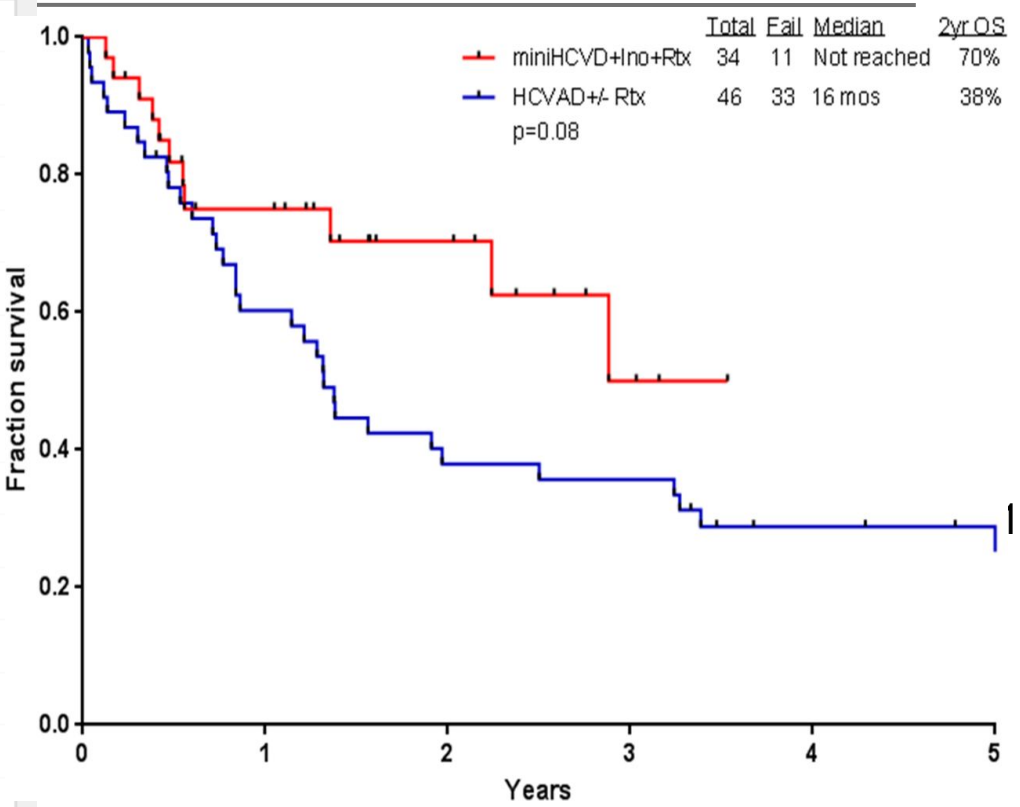
  BU/Clo (n=1), BU/Clo/thiotepa (n=2), flu/mel/thiotepa (n=2)
- Interval between INO and SCT did not appear to influence VOD risk: median, 40 d in VOD group vs. 36 d in non-VOD group.
- No apparent correlation between # INO courses and VOD
- VOD Risk Factors during SCT after monthly INO

1. 2 alkylating agents 5/13
2. 1 alkylating agent 1/19 P = .02

Kebriaei P et al. Clinical Lymphoma, Myeloma & Leukemia, 2013

IO in association with chemotherapy

Characteristic	Median (range) / No. (%) N=34
Age (yrs)	69 [60–79]
Male	21 (62)
Performance Status (ECOG) ≥ 2	4 (12)
WBC at DX	3.5 [0.6–111.0]
WBC at DX ≥ 50	2 (6)
Karyotype	
Diploid	11 (32)
Complex	15 (44)
Misc	5 (15)
IM	3 (9)
CD22 Positivity	97 [72–100]
CD20 ≥ 20	20 (65)
Response	
CR	25/31 (81)
CRp	5/31 (31)
Cytogenetic CR	19/19 (100)
Negative MRD, D21	20/25 (80)
Negative MRD, Overall	33/33 (100)
ORR	30/31 (97)
No response	1/31 (3)
Early death	0



IO with low-intensity mini-hyper-CVD chemotherapy is safe and shows encouraging results (97% CR/CRp) in the frontline setting in older patients with ALL

Jabbour, Blood ASH 2015

Conclusions

- ✓ The cell surface antigen, CD22 is highly expressed in B-cell ALL
- ✓ CD22 exhibits features that make it an ideal therapeutic target in ALL, particularly its ability to internalise on antibody binding
- ✓ Inotuzumab Ozagamicin is being investigated in ALL with promising results both as **single agent** and in **association with chemotherapy**
- ✓ Role of Inotuzumab and VOD in allogenic stem cell transplant remains an issue

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NEXT GENERATION SEQUENCING for Targeted Personalized Therapy of Leukemia

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