Inotuzumab for Adult Acute Lymphocytic Leukemia

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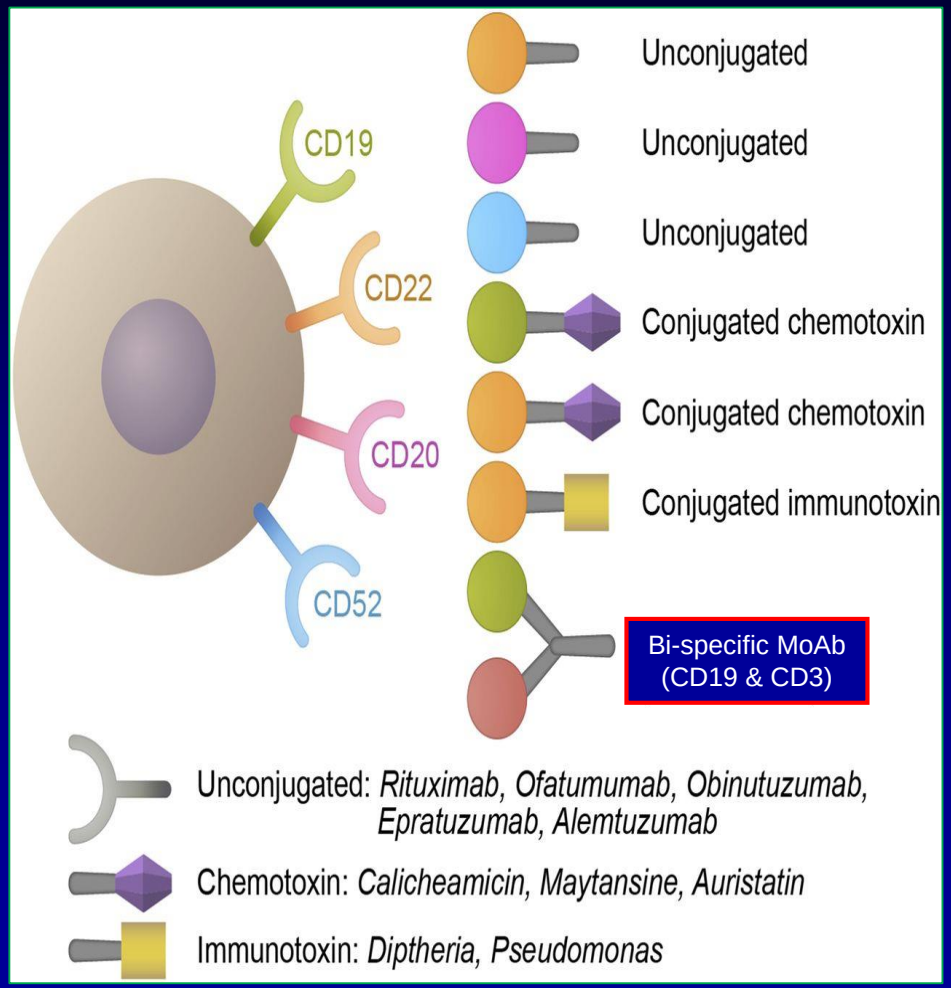
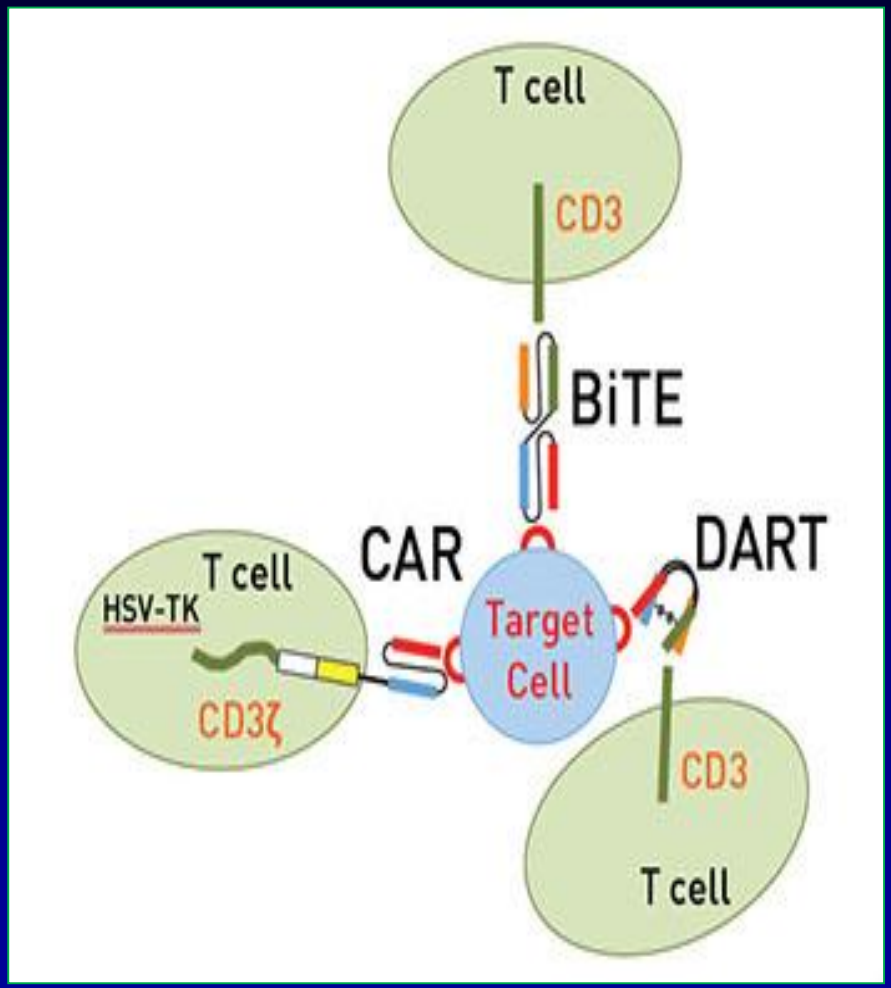
Reasons for Recent Success in Adult ALL Rx

- Addition of TKIs to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Potential benefit of addition of CD19 antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx

Immuno-oncology in ALL

- **Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR-T cells**





Jabbour E. Blood 125: 4010; 2015

Historical Results in R/R ALL

- Poor prognosis in R-R ALL Rx with standard of care (SOC) chemotherapy

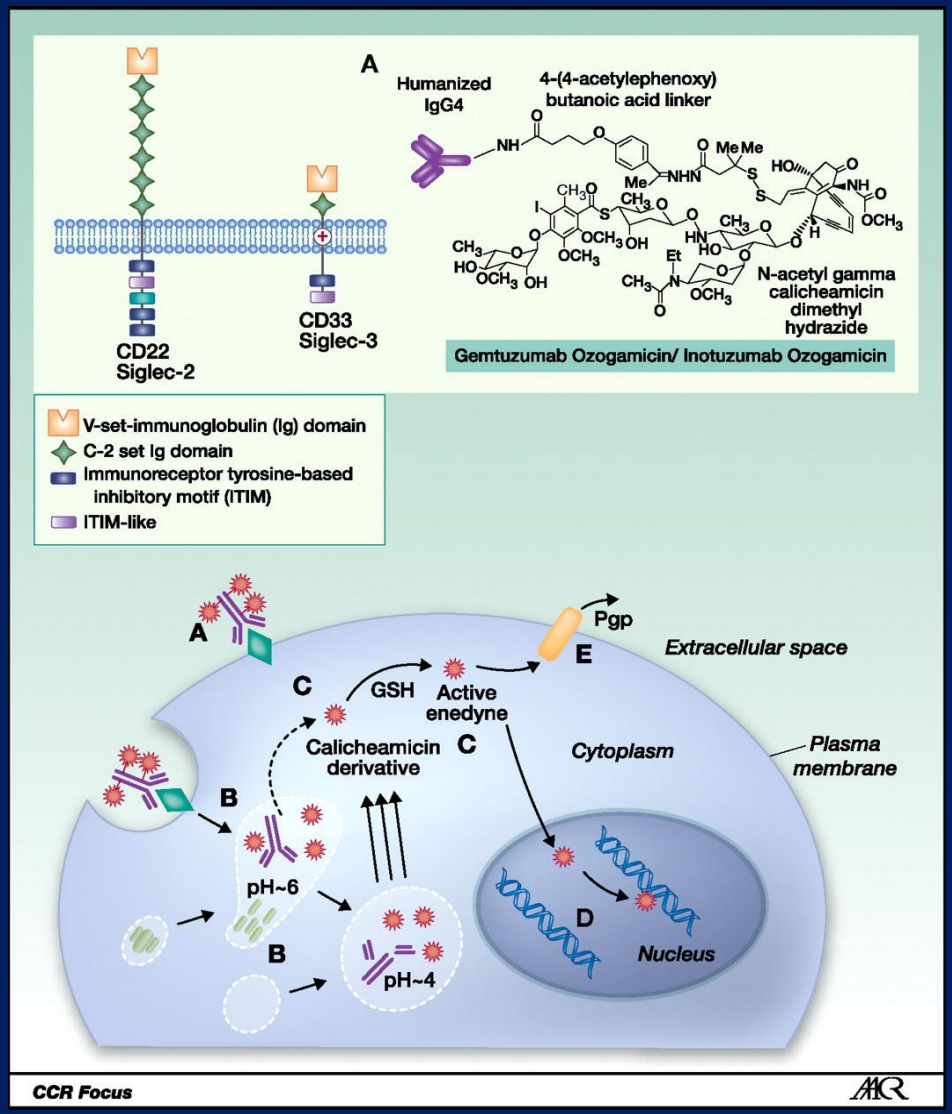
Rate (95% CI)	No prior salvage (S1)	One prior salvage (S2)	≥2 prior salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.8	3.4	2.9

Gökbuget N, et al. *Haematologica*. 2016;101:1524–33.

ALL Salvage Standards of Care in 2018

- Refer for investigational therapies-- MoAb + ChemoRx; CAR-T
- Ph-positive ALL-- TKIs+ chemoRx; blinatumomab
- Pre-B ALL--
  - Blinatumomab (FDA approval 12.2014)
  - Inotuzumab (FDA approval 8.2017)
  - CART (FDA approval 8.2017)
- T ALL: nelarabine
- ChemoRx: FLAG IDA, Hyper CVAD, augmented HCVAD, MOAD

Inotuzumab in ALL. Mechanisms of Action



- The antibody-antigen complex is rapidly internalized upon binding to CD22
- Calicheamicin is released inside the tumor cell
  - Calicheamicin is more potent than other cytotoxic chemotherapeutic agents
- Calicheamicin binds to DNA, inducing double-stranded DNA breaks
- Development of DNA breaks is followed by apoptosis of the tumor cell

Ricart. Clin Cancer Res. 2011; 17:6417–27

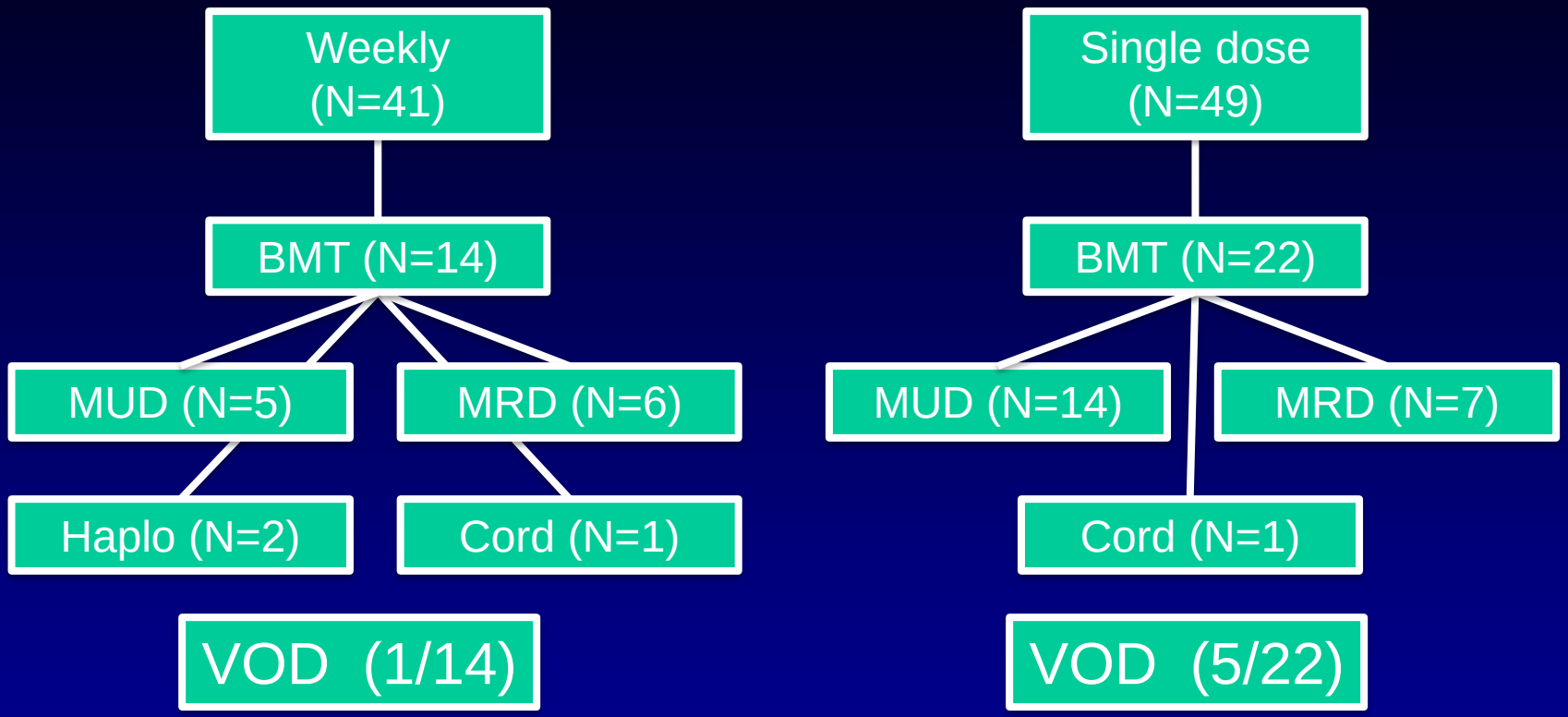
Inotuzumab in ALL. Response

Response No. (%)	Monthly, N=49	Weekly, N=40	Overall, N=90
CR	9 (18)	8 (20)	17 (19)
CRp	14 (29)	13 (32)	27 (30)
CRi (marrow CR)	5 (10)	3 (7)	8 (9)
Resistant	19 (39)	15 (37)	34 (38)
Death < 4 wks	2 (4)	2 (5)	4 (4)
OR	28 (57)	24 (59)	52 (58)

- Median CRD 5-6 mos;Median survival 5-7.3 mos
- Better results in S1-S2

Kantarjian, Cancer. 119: 2728-2736; 2013

Inotuzumab Disposition & VOD



Conditioning regimen	Dual Alkylating (N=13)	Single Alkylating (N=21)
VOD Cases	5	1

Kantarjian et al. Cancer. 2013; 119(15): 2728-36.

Inotuzumab vs ChemoRx in R-R ALL. Design

- Open-label, phase 3 study; 326 pts randomized at 117 sites in 19 countries

- R/R CD22+ ALL
- Salvage 1 or 2
- Ph– or Ph+

1:1 Randomization (N=326)

Stratifications:

- Duration of 1st CR ≥12 vs <12 mo
- Salvage 2 vs 1
- Aged ≥55 y vs <55 y

InO

- Starting dose 1.8 mg/m^2/cycle[a]
- 0.8 mg/m^2 Day 1; 0.5 mg/m^2 Days 8 and 15 of a 21–28 Day cycle (≤6 cycles)

Standard of Care (SOC)

- FLAG or
- Ara-C plus mitoxantrone or
- HIDAC
- ≤4 cycles

[a]InO dose reduced to 1.5 mg/m^2/cycle once patient achieved CR/CRi.

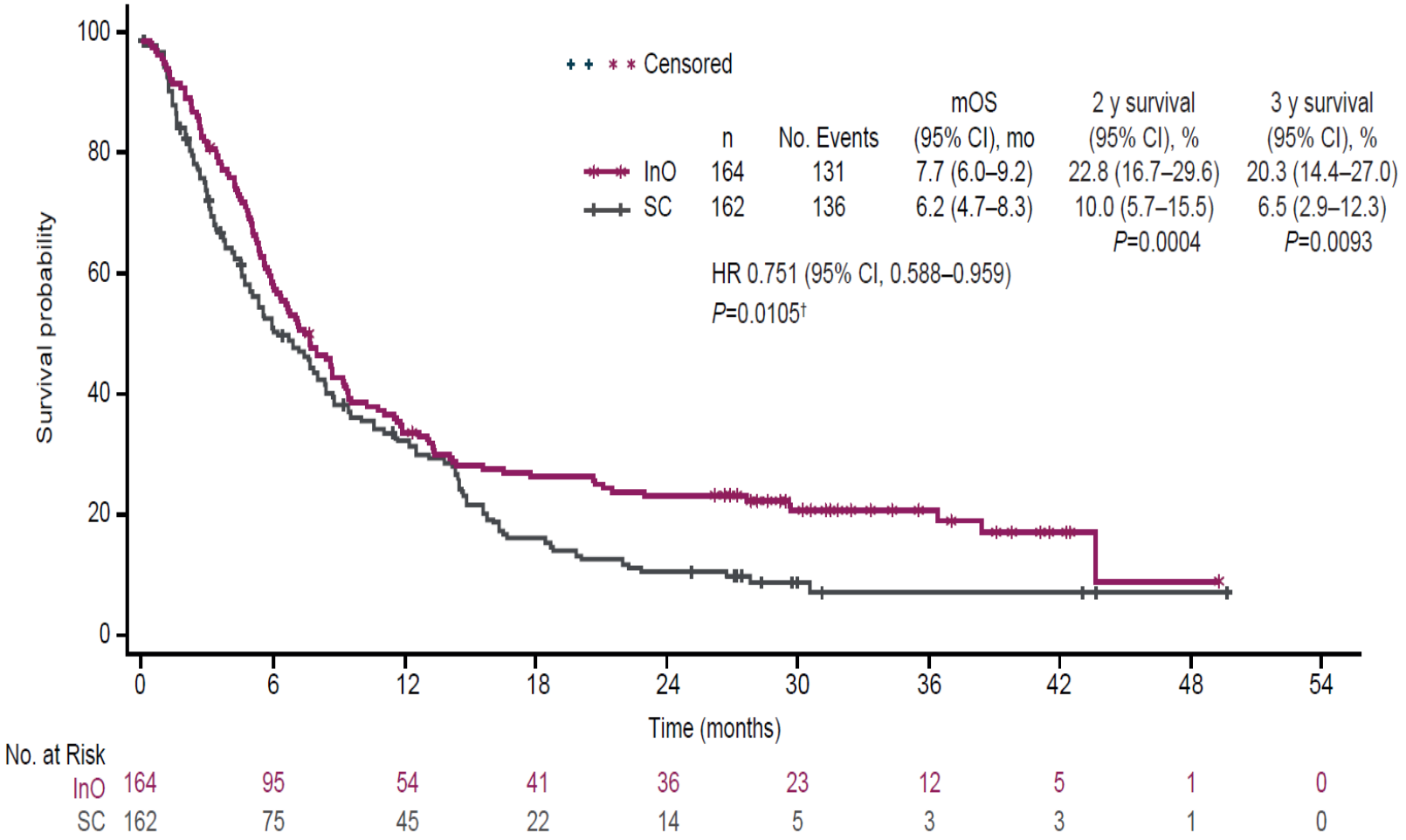
Kantarjian. NEJM. 375: 740; 2016

Inotuzumab vs ChemoRx in R-R ALL (Phase 3 INOVATE Trial)

Parameter	INO	Chemo Rx	p value
% CR/CRi	81	29	<.0001
% MRD negative in CR	78	28	<0.0001
Median OS (mos)	7.7	6.2	.01

Kantarjian. NEJM. 375: 740; 2016

Overall Survival. 2-yr F/U



Kantarjian. Blood. 130: abst 1099; 2017

VOD/SOS Among InO-Treated Pts

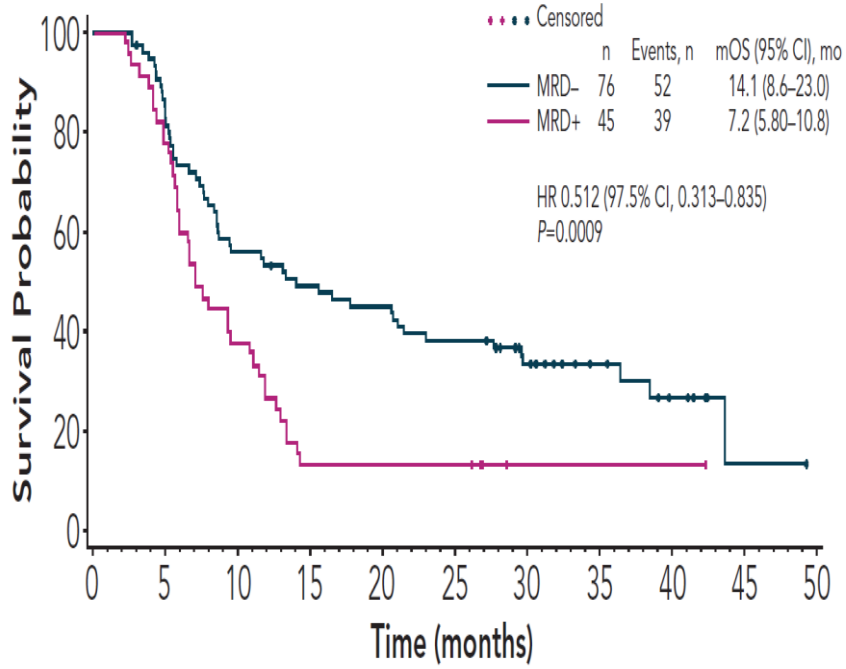
- VOD incidence: InO, 13% (n=22) vs SOC, 1% (n=1)
- 5 (3%) pts had VOD during study Rx (2 with pre-study SCT)
- 77/164 (47%) on InO had post-study SCT vs 33/162 (20%) in the SOC arm
  - 17/77 (22%) on InO had VOD post-SCT (5/17 also had pre-study SCT)
- Median (range) time to VOD after SCT: 15 (3–57) days

MVA Analysis of Factors Associated With Post-SCT VOD

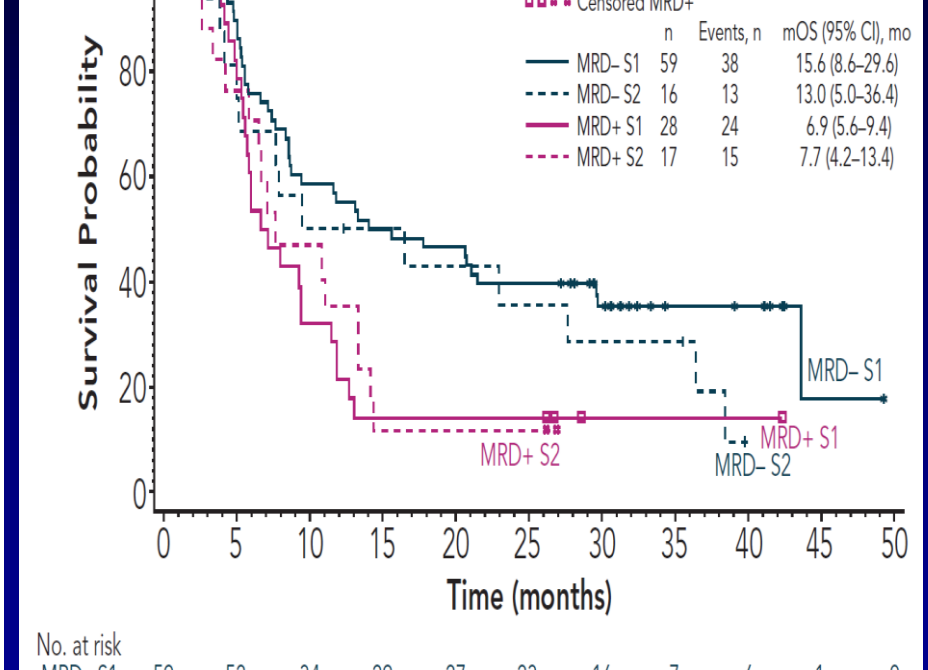
Factor	OR (95% CI)	*P* value
Alkylator conditioning (dual vs single)	7.6 (1.7–33.8)	0.008
Age (≥55 vs <55 y)	4.8 (1.0–22.0)	0.043

[11] Kantarjian. NEJM. 375: 740; 2016

Impact of MRD in R-R ALL Rx with INO



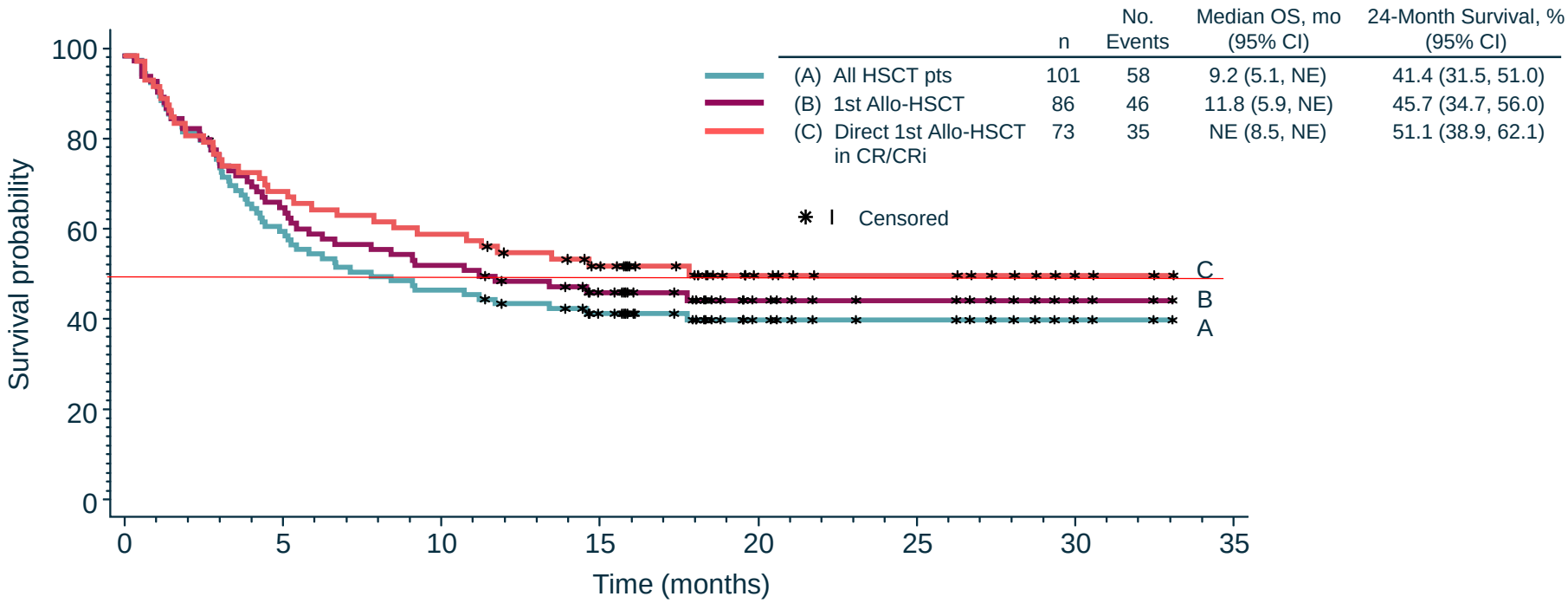
CI=confidence interval; HR=hazard ratio; InO=inotuzumab ozogamicin; mOS=median overall survival; MRD=minimal residual disease



CI=confidence interval; Ino=inotuzumab ozogamicin; MRD=minimal residual disease; S1=first salvage status; S2=second salvage status

Jabbour. ASCO 2018: abst 7013

Allo SCT Post Inotuzumab in R-R ALL



	n	No. Events	Median OS, mo (95% CI)	24-Month Survival, % (95% CI)
(A) All HSCT pts	101	58	9.2 (5.1, NE)	41.4 (31.5, 51.0)
(B) 1st Allo-HSCT	86	46	11.8 (5.9, NE)	45.7 (34.7, 56.0)
(C) Direct 1st Allo-HSCT in CR/CRi	73	35	NE (8.5, NE)	51.1 (38.9, 62.1)

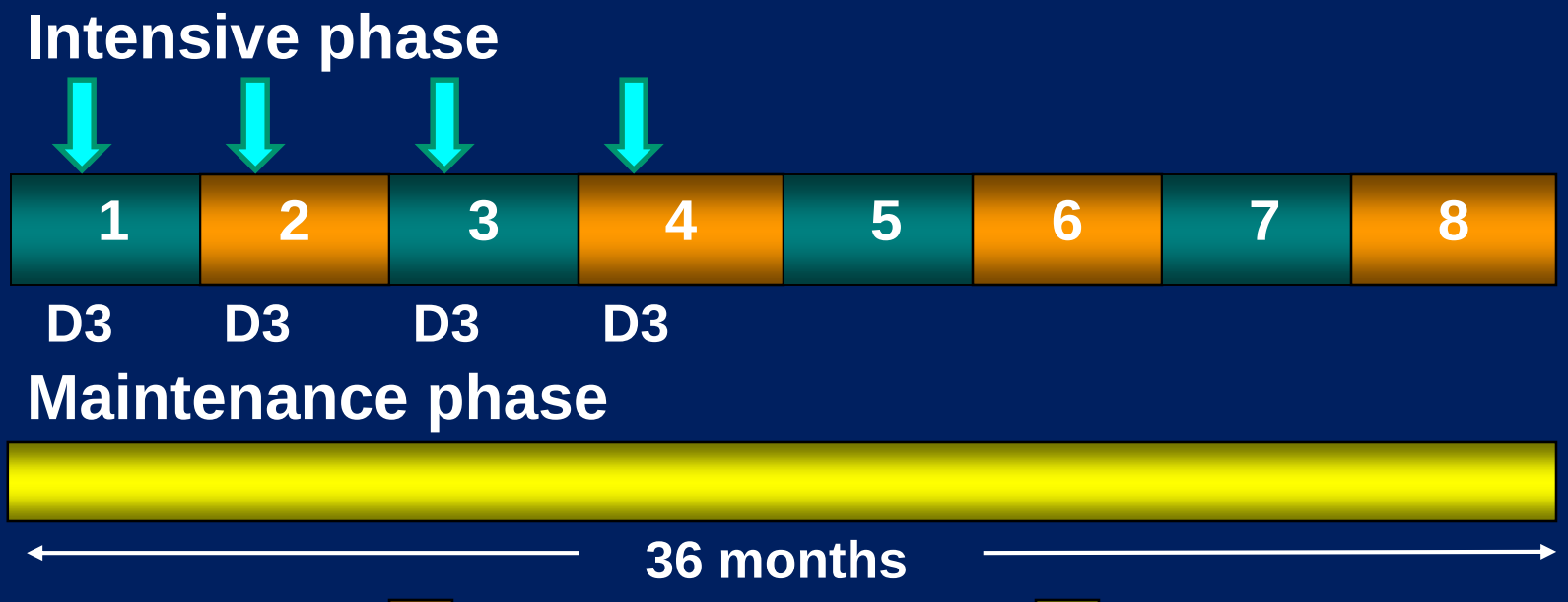
Kebriaei. Blood 130: abst 886; 2017

MiniHCVD-INO in ALL. Design

- Dose reduced HyperCVD for 8 courses
  - Cyclophosphamide (150 mg/m^2 x 6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 x 4) 83% dose reduction
- **Inotuzumab on D3 (first 4 courses)**
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- POMP maintenance for 3 years

Jabbour. JAMA Oncology. 2018;4(2):230-234

MiniHCVD-INO in ALL. Design



Inotuzumab	First 6 pts	7 to 34	35 and beyond
First cycle (mg/m^2)	1.3	1.8	1.3
C2-4 (mg/m^2)	0.8	1.3	1.0

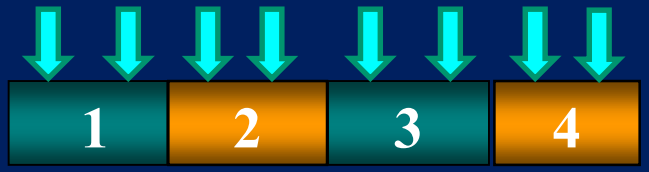
MiniHCVD-INO-Blina in ALL. Design

- Dose reduced HyperCVD for 4-8 courses
  - Cyclophosphamide (150 mg/m^2 x 6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 x 4) 83% dose reduction
- Inotuzumab on D3 (first 4 courses)
  - Modified to 0.9 mg/m^2 C1 (0.6 and 0.3 on D1&8) and 0.6 mg/m^2 C2-4 (0.3 and 0.3 on D1&8)
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- Blinatumomab 4 courses and 3 courses during maintenance
- POMP maintenance for 3 years, reduced to 1 year

Jabbour. April 2018 update

MiniHCVD-INO-Blina in ALL.

Intensive Phase



Consolidative Phase

Maintenance phase

MiniHCVD

Mini-MTX-cytarabine

Blinatumomab

POMP Maintenance

Inotuzumab	Total dose	Dose per day
C 1 (mg/m^2)	0.9	0.6 D2 & 0.3 D8
C 2- 4 (mg/m^2)	0.6	0.3 D2 & D8

MiniHCVD-INO-Blina in R/R ALL. (N=84)

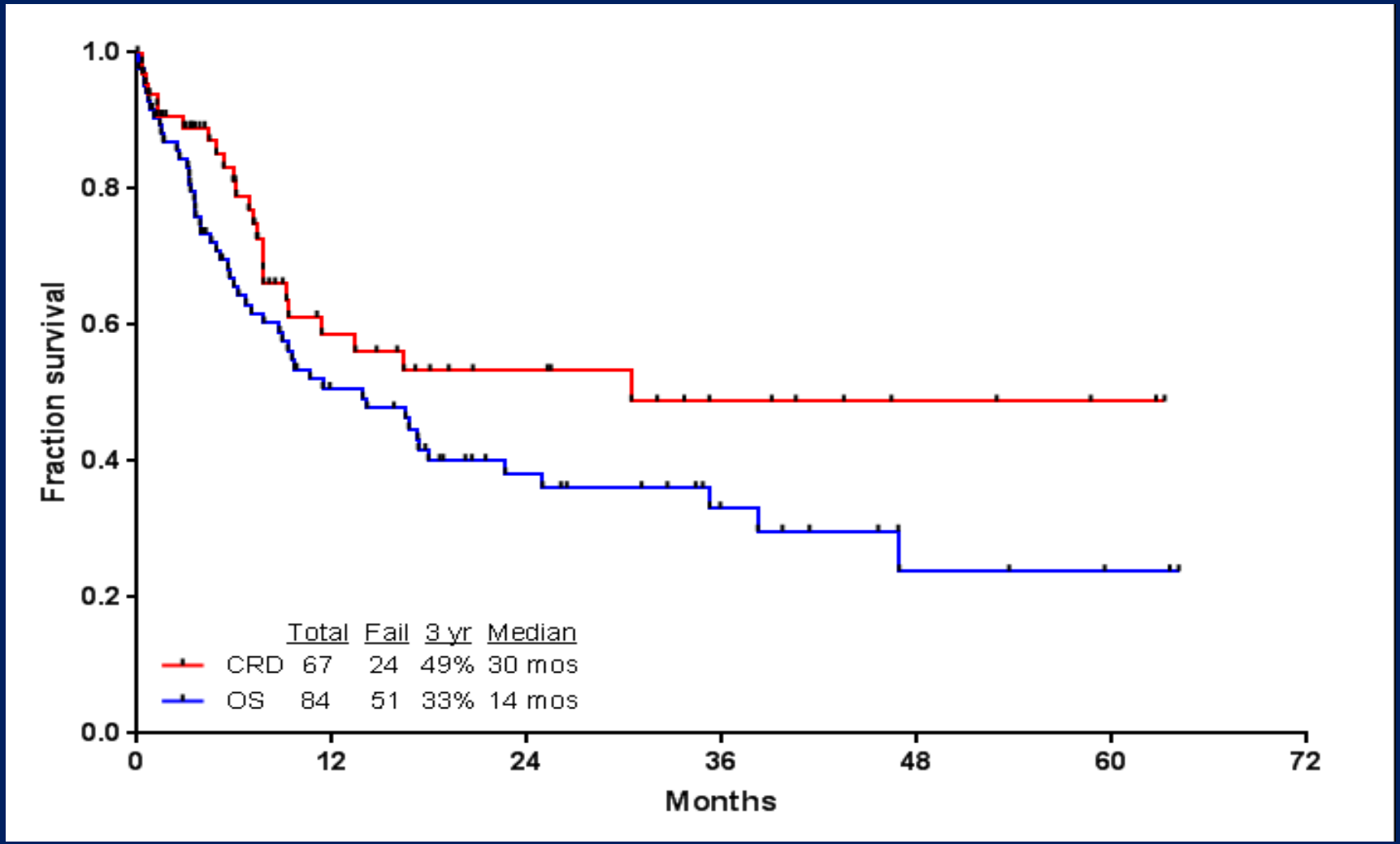
Characteristic	Category	No. (%)
Age (yrs)	Median [range]	35 [9-87]
Gender	Male	37 (44)
Performance Status (ECOG)	2+	16 (19)
Salvage Status	S1	53 (63)
	S1, Primary Ref	5
	S1, CRD1<12m	22
	S1, CRD1≥12m	26
	S2	16 (19)
	≥S3	15 (18)
Prior ASCT		19 (23)
Karyotype	Diploid	19 (23)
	T(4;11)	8 (10)
	Misc	44 (52)
	IM/ND	13 (15)
CD22	Median [range]	96 [14-100]
CD20	≥ 20%	19 (23)

MiniHCVD-INO-Blina in R/R ALL. Response By Salvage (N=84)

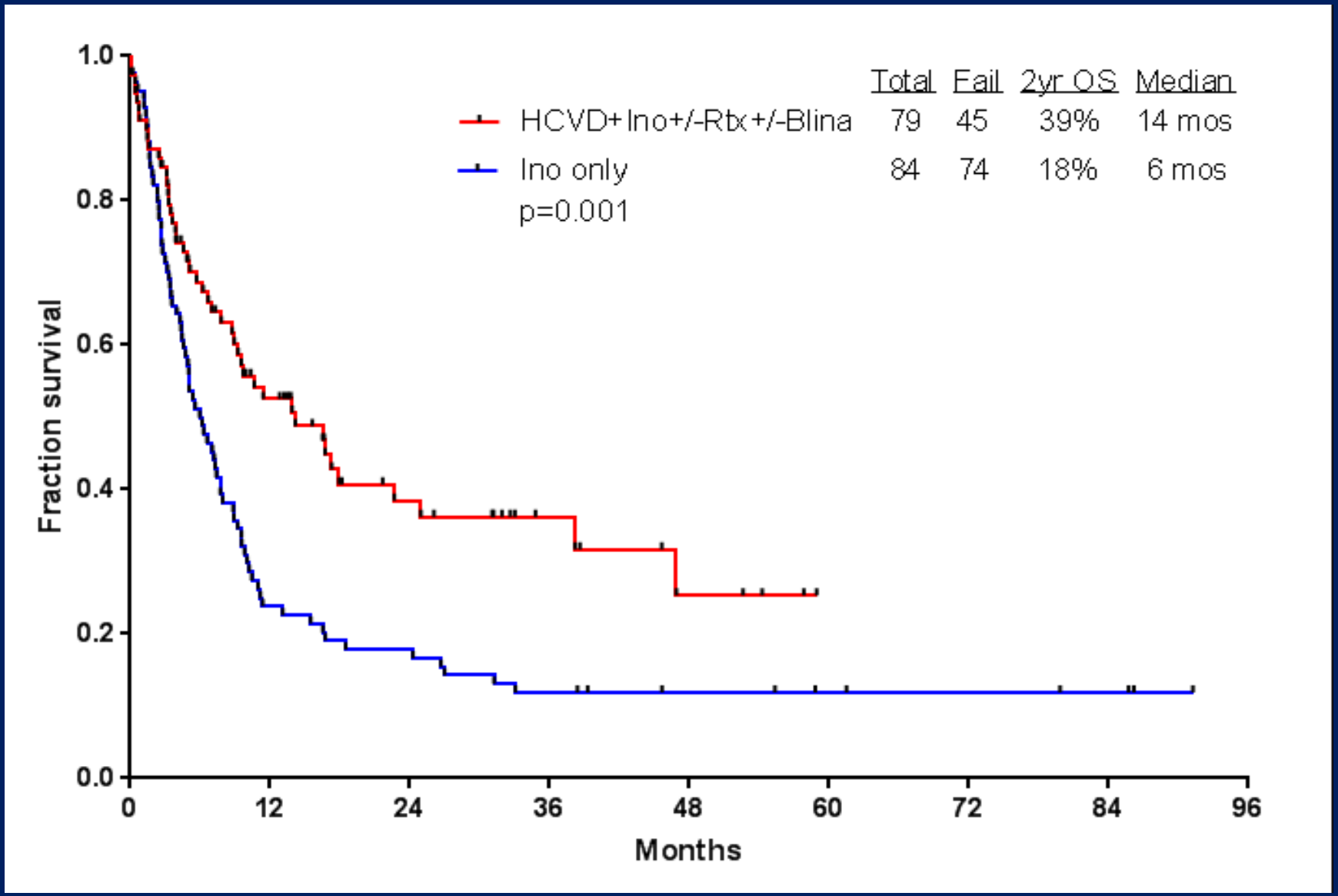
Response	N	(%)
Salvage 1	49/53	92
S1, Primary refractory	5/5	100
S1, CRD1 < 12 mos	18/22	82
S1, CRD1 ≥ 12 mos	26/26	100
Salvage 2	9/16	56
≥ Salvage 3	9/15	60
Overall	67/84	80
MRD negativity	51/64	80
Salvage 1	39/46	85
≥ Salvage 2	12/18	67

MiniHCVD-INO-Blina in R/R ALL. Survival

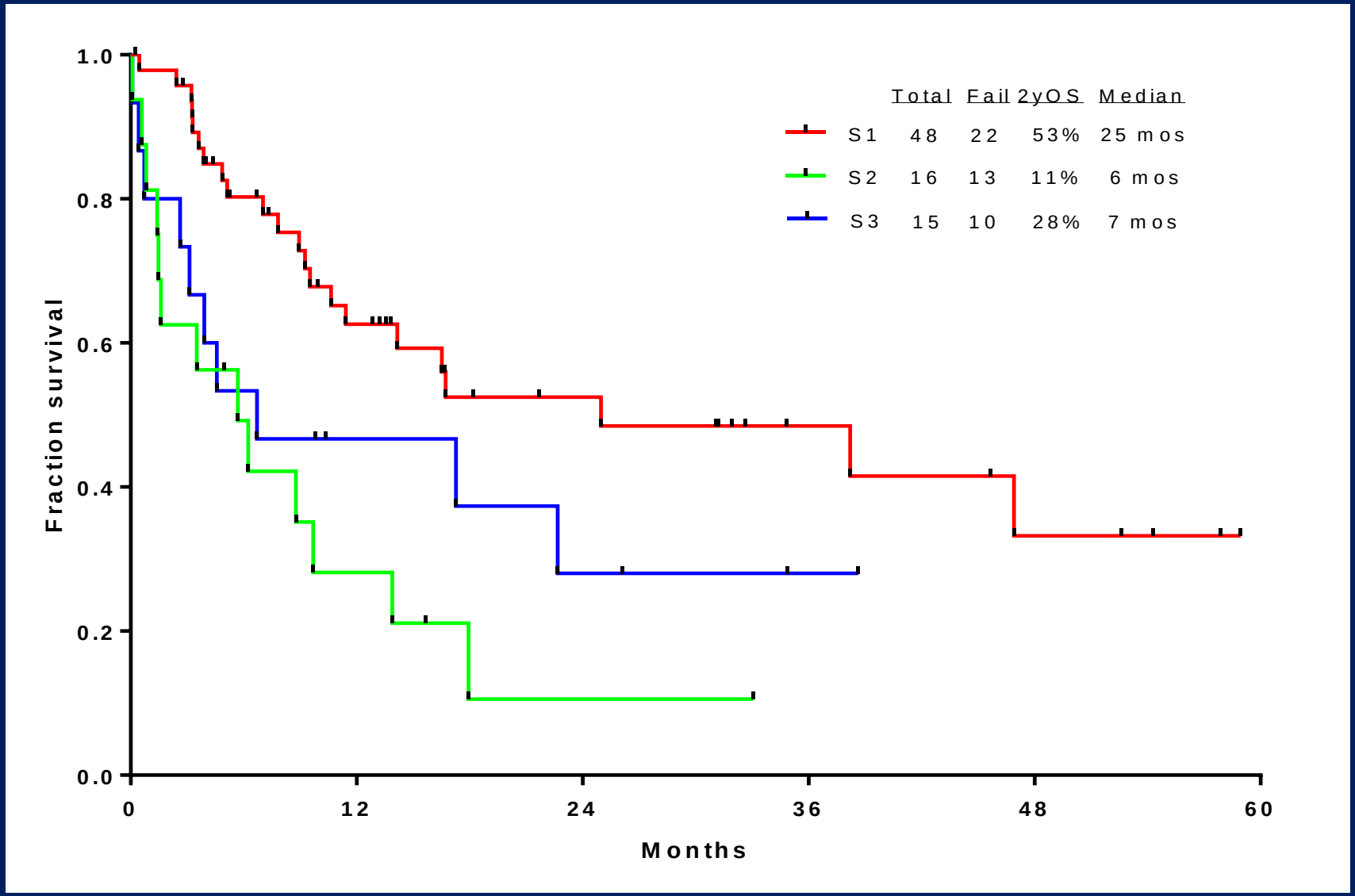
- 3-yr CRD and OS rates 49% and 33%, respectively



MiniHCVD-INO-Blina vs INO in R/R ALL. Survival



MiniHCVD-INO-Blina in R/R ALL. Survival by Salvage

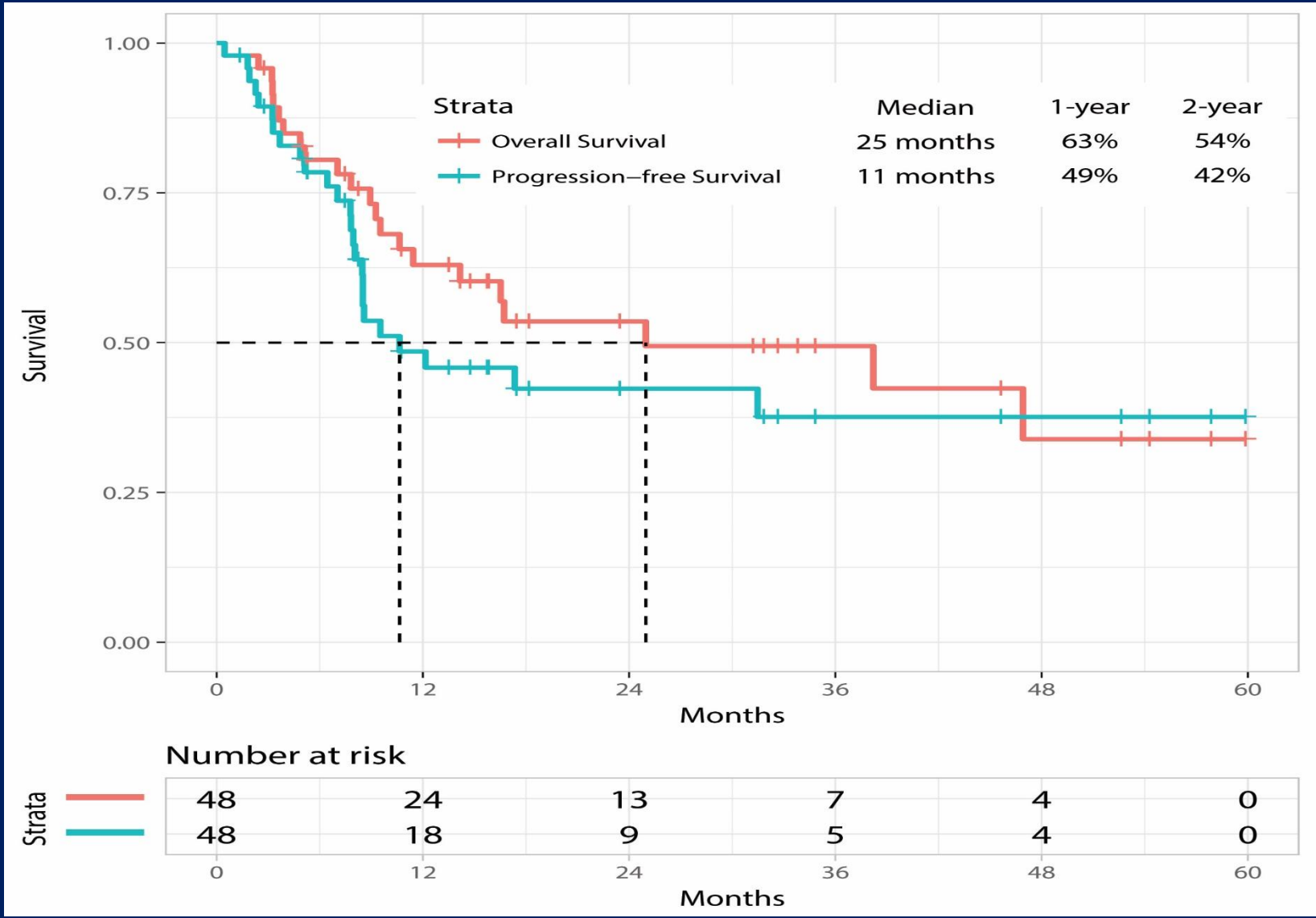


MiniHCVD-INO-/+Blina in ALL S1. Response (N=48)

Response	N	(%)
CR	35	73
CRp	8	17
CRi	1	2
ORR	**44**	**92**
MRD negativity		
at response	28/41	68
Overall	38/41	93
CCyR	19/21	90
No response	3	6
Early death	1	2

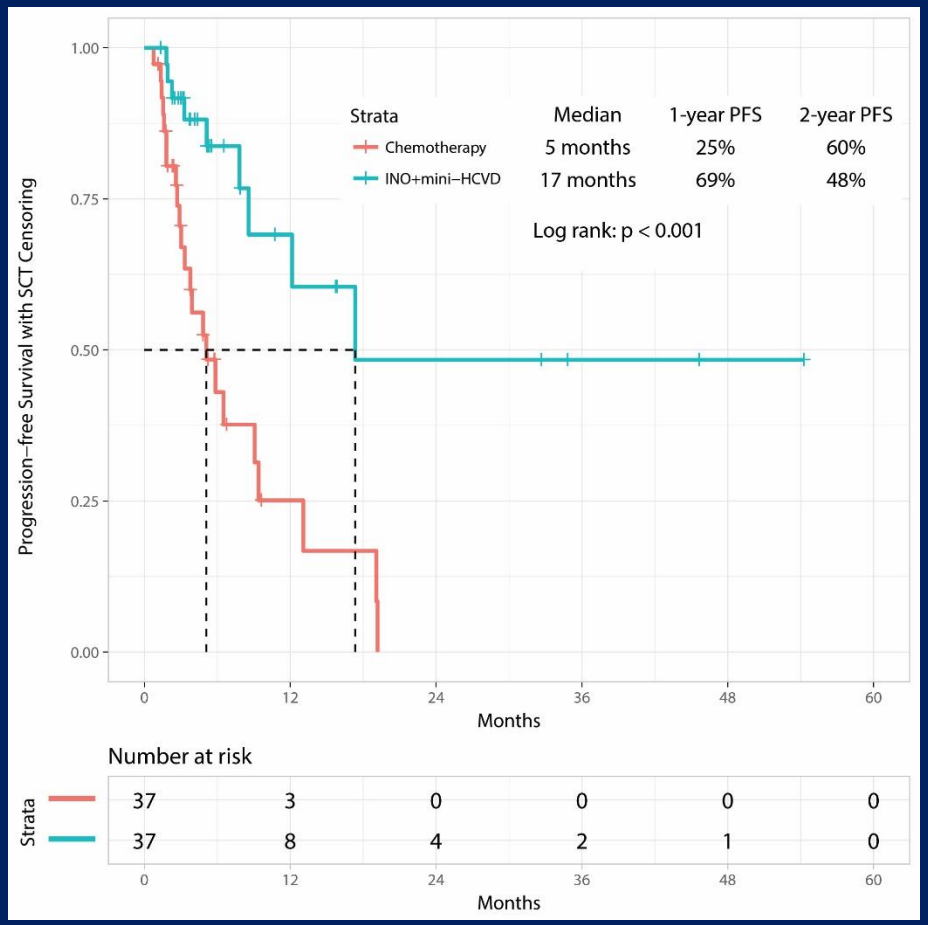
Jabbour. Cancer. 2018; In press

INO + mini-HCVD +/- Blinatumomab in S1. Overall Survival / Progression-free Survival

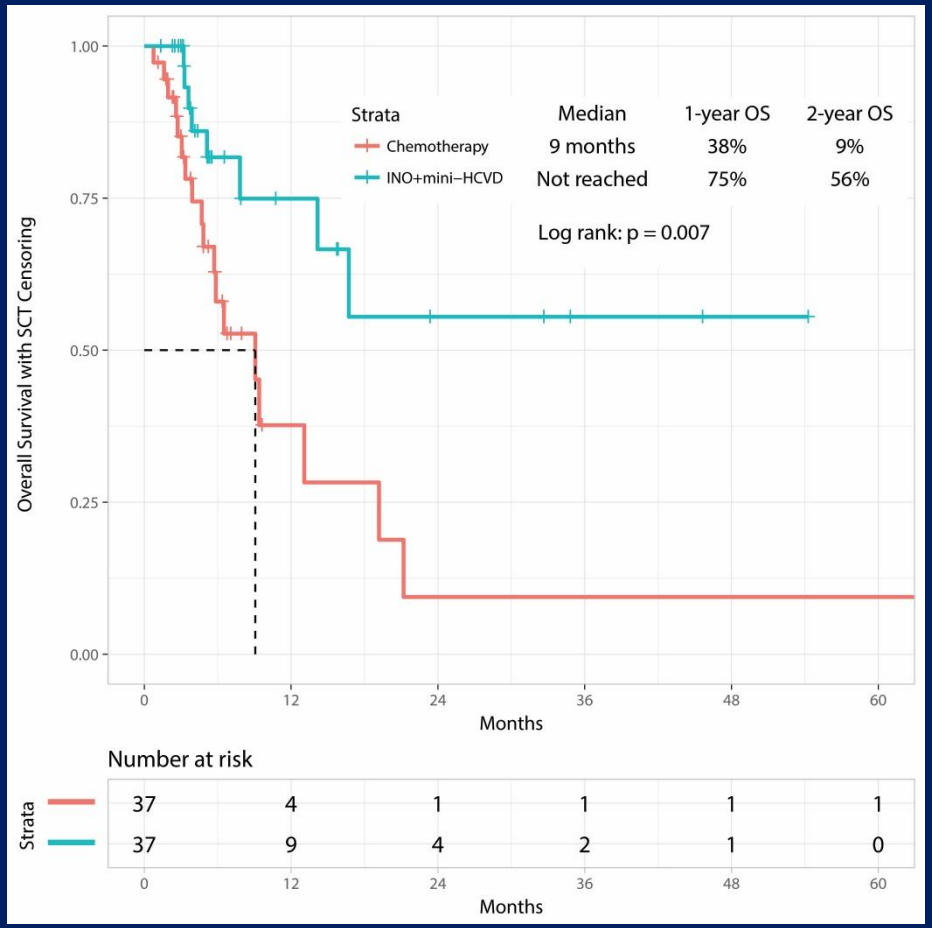


INO + mini-HCVD vs. Chemo in S1. PFS/OS with SCT Censoring

PFS

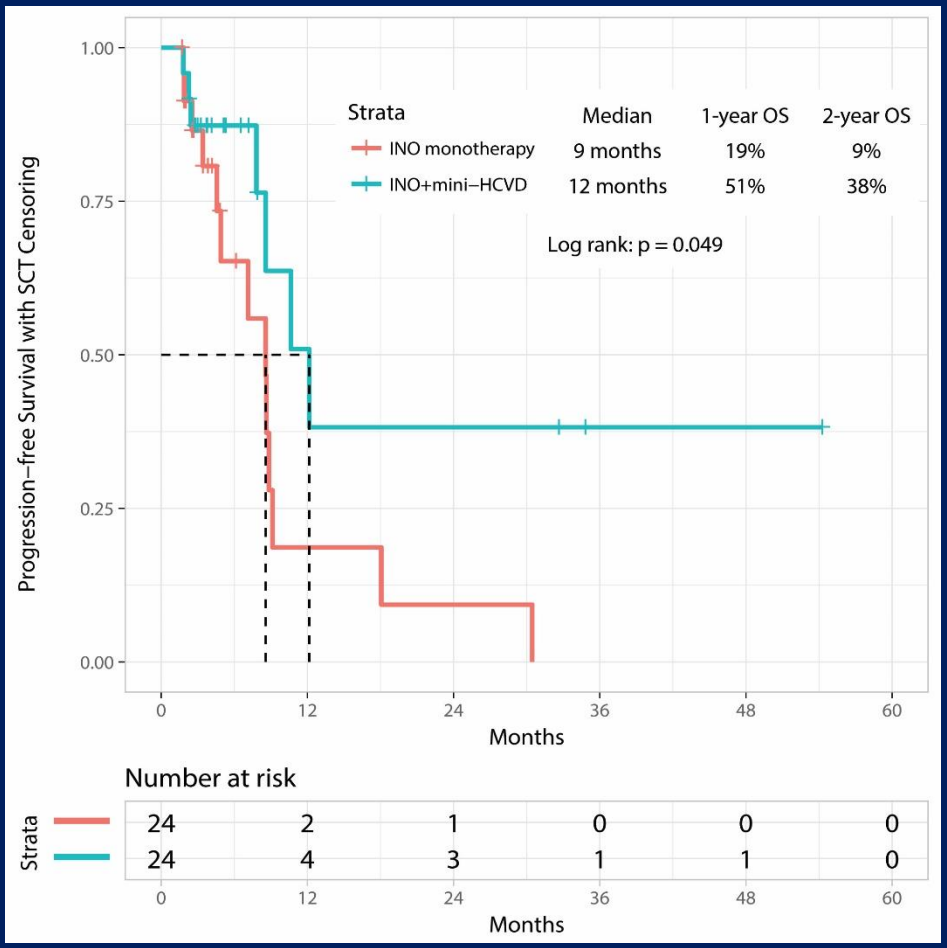


OS

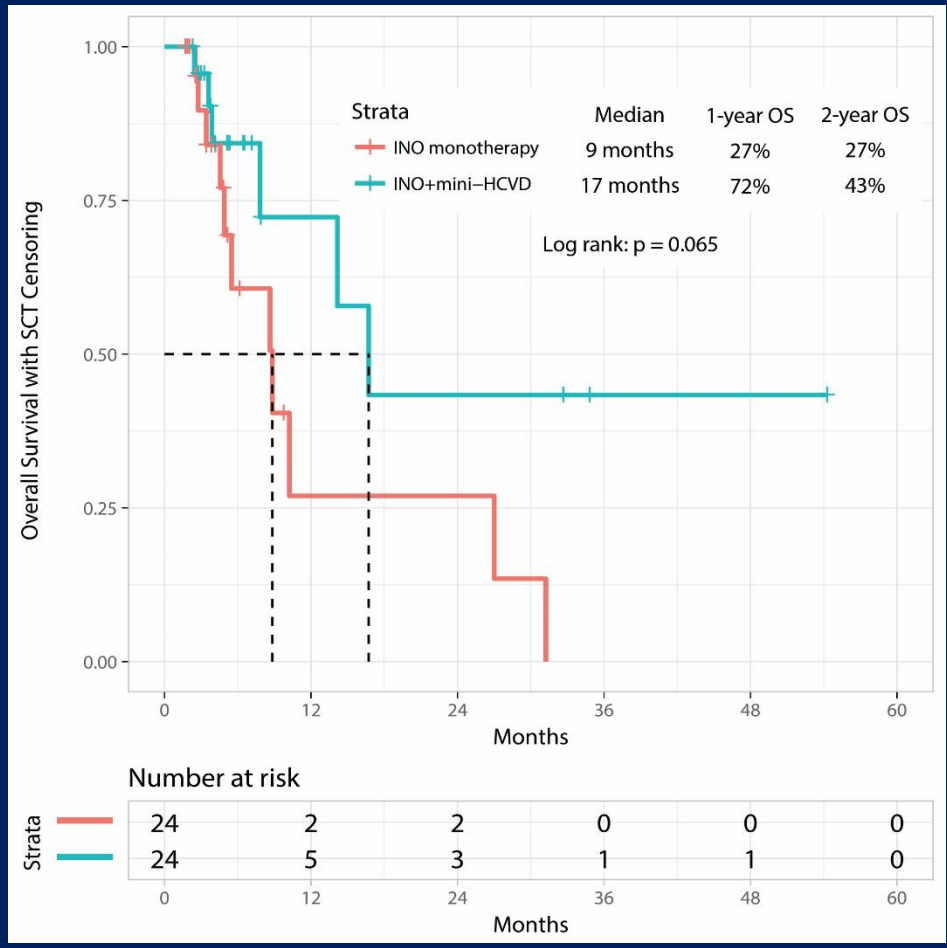


INO + mini-HCVD vs. INO monotherapy in S1. PFS/OS with SCT Censoring

PFS



OS



Elderly ALL. Historical Results

	MDACC	GMALL	SEER	Medicare
N	122	268	1675	727
Median Survival (mos)	15	NA	4	10
OS (%)	20 (3-yr)	23 (5-yr)	13 (3-yr)	NA

O'Brien. Cancer 113: 2097, 2008; Gökbuget. Blood. 2013;122:1336; Li S. Blood. 2016;128:3981; Geyer. Blood 2017;129:1878

MiniHCVD-INO in ALL. Response (N=58)

Response	N	(%)
CR	47	(87)
CRp	5	(9)
CRi	1	(2)
ORR	53	(98)
No response	1	(2)
Early death	0	0

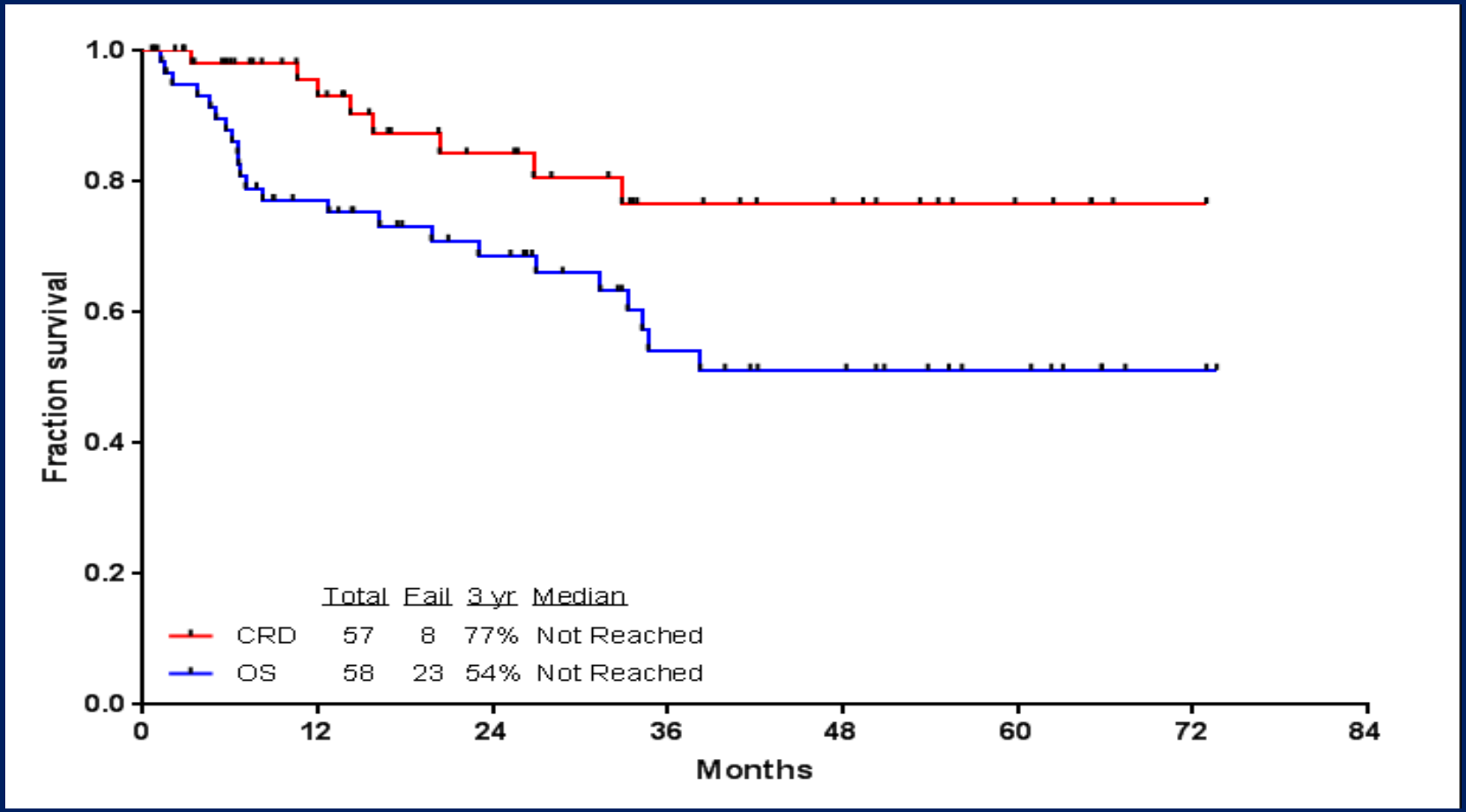
- Four patients were enrolled with CR

Kantarjian. Lancet Oncology. 2018;19(2):240-248

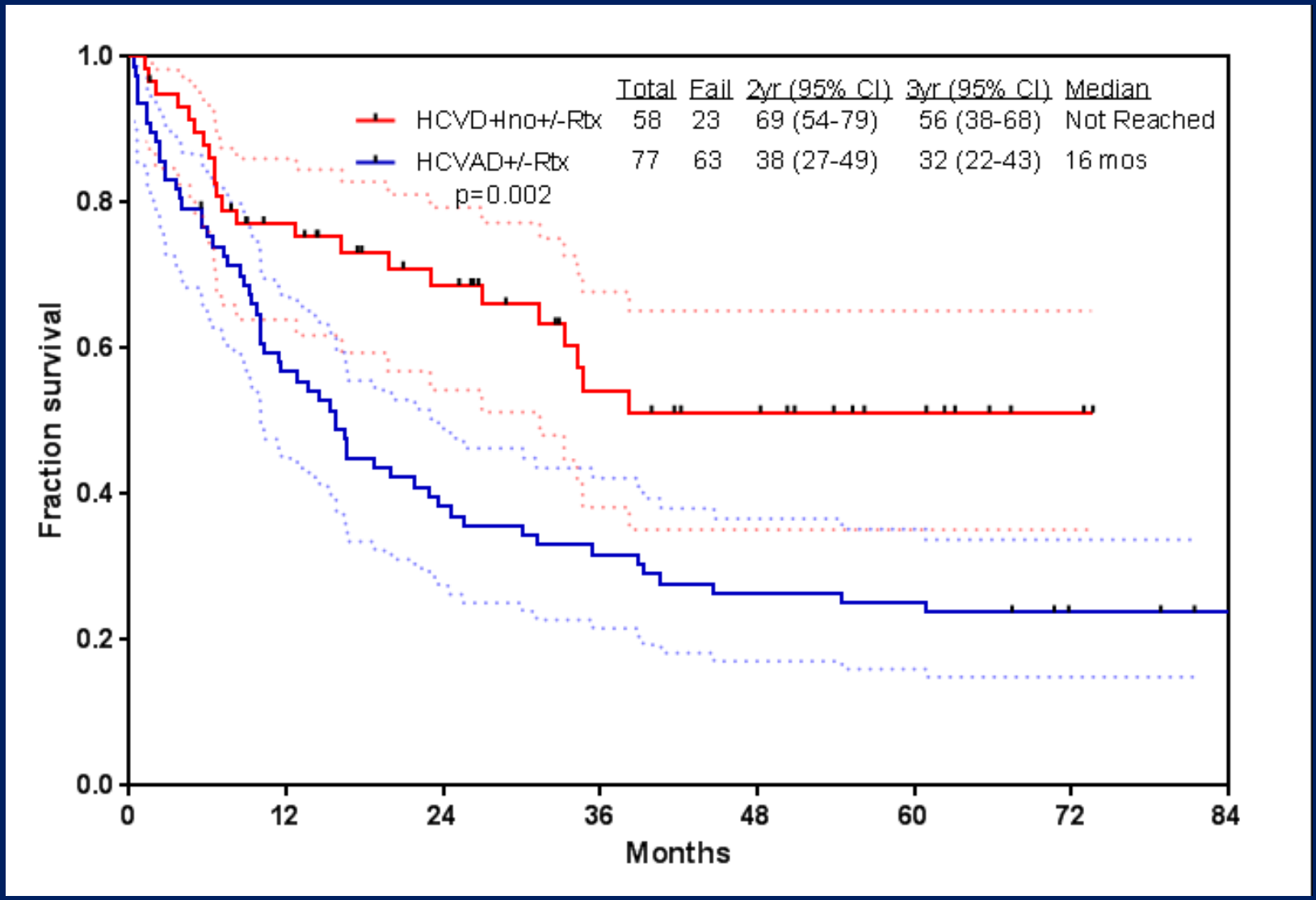
MiniHCVD-INO in ALL. Survival

- Median follow up of 28 months (2-68)

CRD & OS



MiniHCVD-INO vs HCVAD in ALL.



MiniHCVD-INO in ALL. VOD

- **Overall 14/135 (10%)**
  - **R-R 9/79: 9/61 (Single) vs 0/18 (weekly LD)**
  - **FL 5/57: 4/46 (Single) vs 1/11 (weekly LD)**

Inotuzumab + Bosutinib in R-R Ph-positive ALL or Lymphoid CML-BP

- 16 pts (14 ALL; 2 CML-BP) Rx with inotuzumab 0.8-0.5-0.5mg/m^2 weekly then 1mg/m^2 Q4 wks; bosutinib 300-500 mg/D
- 13/16 CR-CRi = 81%; 12/13 CGCR; 9/13 FCM-MRD negative; 8/13 (**55%**) PCR negative
- Median EFS 8.8 mos; median OS 10.7 mos
- 5/6 post allo SCT alive in CR

Jain. Blood 130: abst 143; 2017

Inotuzumab in ALL

- Inotuzumab
  - Highly effective in R/R ALL
    - Best outcome in Salvage 1
  - Combination of Ino with mini-HCVD: Safe and effective
    - R/R Median survival of 14 months; Salvage-1 24 months (2-year OS rate >50%)
    - High efficacy in newly diagnosed elderly ALL (3-year survival rate of 56%
  - VOD: Lower dose Ino schedules being explored
  - Sequential combination with blinatumomab ongoing

Thank You

Leukemia Questions?

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