Inotuzumab Ozogamicin in ALL

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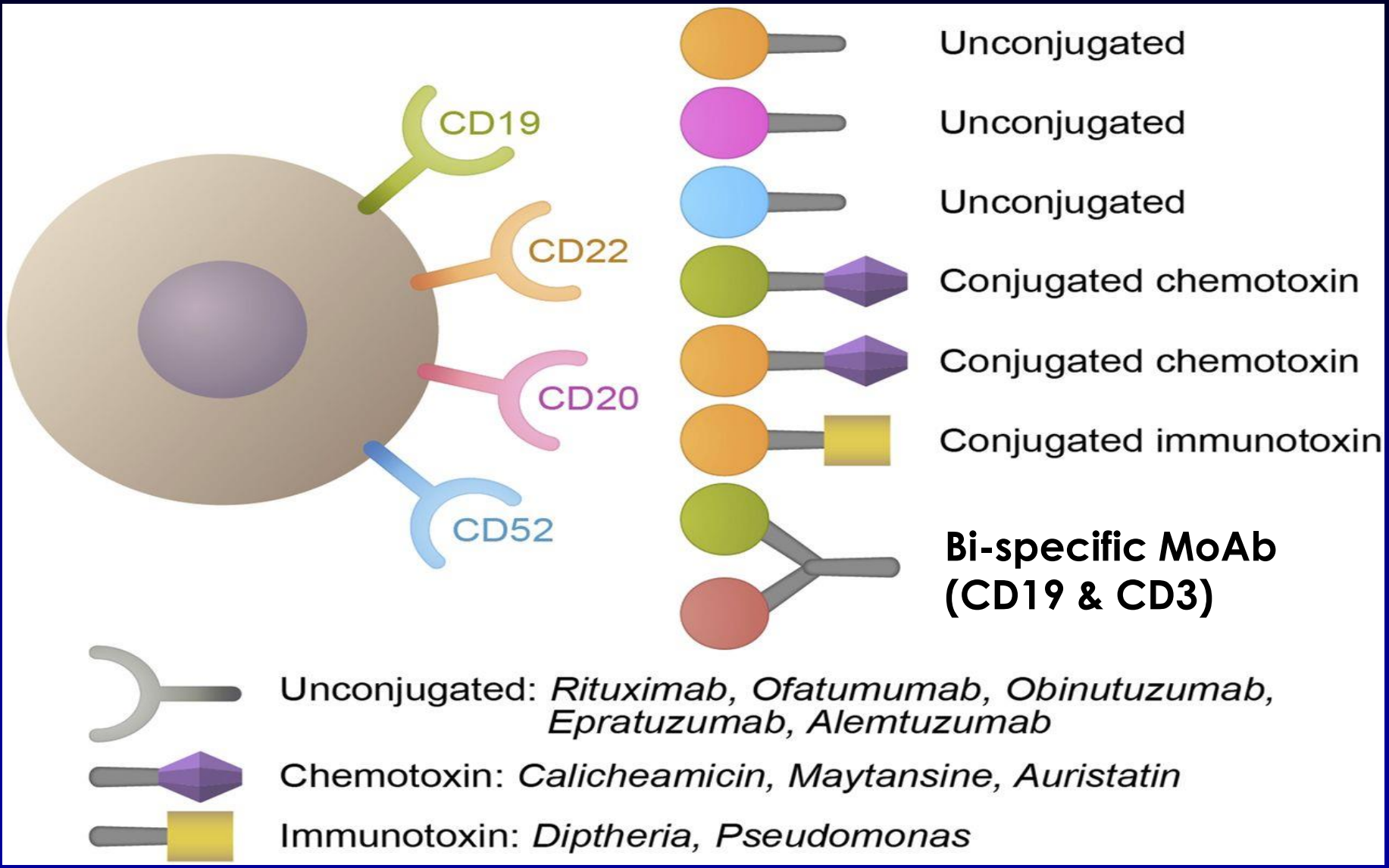
Immuno Oncology in ALL

- Monoclonals + cytotoxic agents—e.g.inotuzumab
- Bispecific monoclonals (CD3 + CD19)– e.g.blinatumomab
- Modified expanded Tcells—

  CART cells

Monoclonal Antibodies in ALL

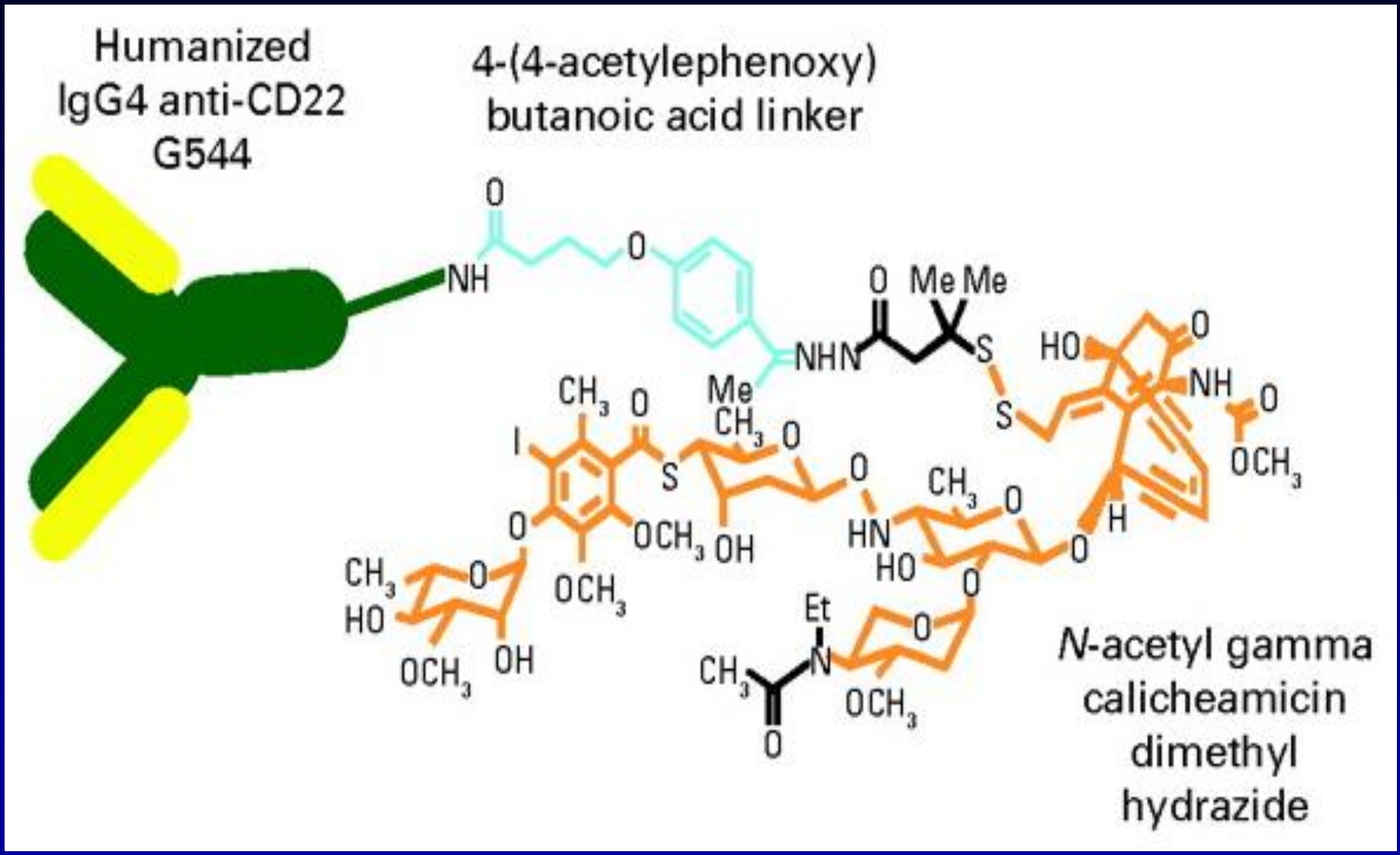


Jabbour E. Blood 125: 4010; 2015

Monoclonal Antibodies in ALL

- Rituximab – established role in Burkitt and pre B CD20-positive ALL in combination with chemoRx
- Inotuzumab – anti-CD22 + calicheamicin
- Epratuzumab – anti-CD22
- Blinatumomab – CD19 + CD3
- Alemtuzumab – anti-CD52
- SAR3419 – anti CD19 + mytansin
- SNG19A – anti-CD19 + auristatin
- Anti-CD22 + auristatin

Inotuzumab ozogamicin



Advani et al. JCO 2010

Inotuzumab in ALL: Schedule

Monthly:

Cycle 1 1.8mg/m²

Cycle 2 1.8mg/m²

up to 8 cycles

Weekly:

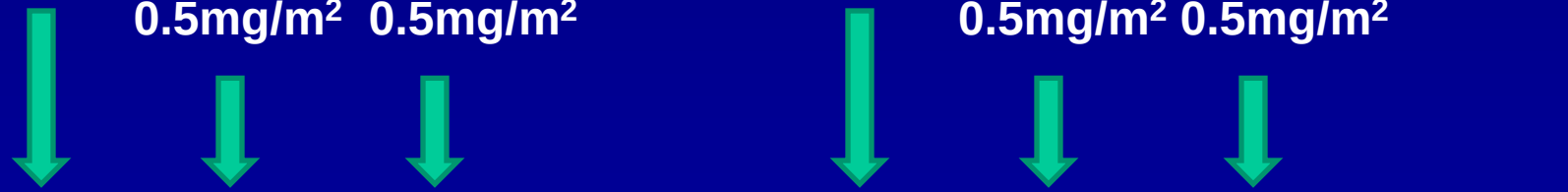
Cycle 1 0.8mg/m²

0.5mg/m² 0.5mg/m²

Cycle 2 0.8mg/m²

0.5mg/m² 0.5mg/m²

up to 8 cycles



Kantarjian, Lancet Oncology 13: 403;2012, Kantarjian, Cancer. 119: 2728-2736; 2013

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

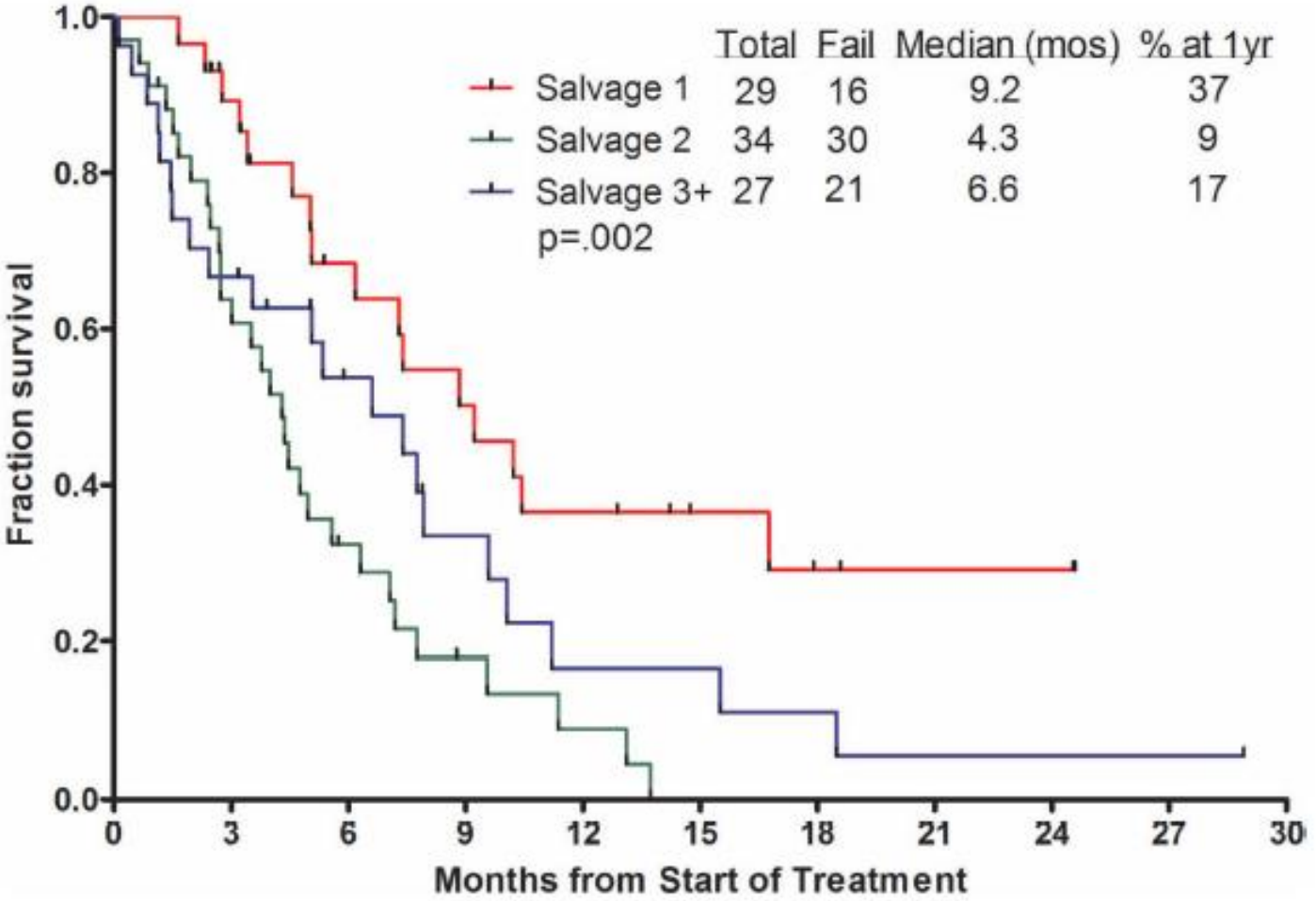
Kantarjian, Cancer. 119: 2728-2736; 2013

Inotuzumab in ALL. Efficacy Comparison to MDACC Data Base for CR/CRp

% Resp.	% ORR				
	Inotuzumab			Chemo n=292	P
	Overall N=89	Monthly N=49	Weekly N=40		
Overall	**47**	**47**	**48**	**29**	**<0.001**
S1	61	69	53	40	0.03
S2	44	38	60	16	<0.001
≥ S3	37	42	33	16	0.02

O'Brien, Blood 120: abst 671;2012

Inotuzumab-Survival By Salvage



Kantarjian. Cancer. (2013) 119: 2728-2736.

Inotuzumab Experience

Reference	Rx	Ino dose-schedule	ALL Status	Comment	CR/CRp/ CRi (%)	Overall Response (%)
MDACC	49	1.8mg/m^2 D1	Relapsed, refractory	*Rituximab 375mg/m^2	18/ 29/ 10	57
MDACC	41	0.8mg/m^2 D1 0.5mg/m^2 D8, 15	Relapse, refractory	Monotherapy	20/ 32/ 7	59
Advani	35	0.8mg/m^2 D1 0.5mg/m^2 D8, 15	Relapsed, refractor (Salvage 2 or greater)	Monotherapy	31.4/ NR/ 12	65.7
DeAngelo	218 total 109 Ino	0.8mg/m^2 D1 0.5mg/m^2 D8, 15	Relapsed, refractory (Salvage 1 or 2 only)	Monotherapy (COMPARED to SOC)	36/ NR/ 45	81
MDACC	24	1.8mg/m^2 C1D3 1.3mg/m^2 D3 during Cycles 2 - 4	Relapsed, refractory	Mini-hyperCVD-R	46/ 25/ 4	75
MDACC	33	1.8mg/m^2 C1D3 1.3mg/m^2 D3 during Cycles 2 - 4	New Dx	¥Mini-hyperCVD-R	80/ 17/ NR	97

1. Kantarjian I, Cancer. (2013) 119: 2728-2736.
2. Advani I abstract 2255. (ASH 2014)
3. DeAngelo Haematologica. (2015) 100:S1 abstract LB2073 (EHA 2015)
4. Jabbour . J Clin Oncol 32:5s, (2014) suppl; abstr 7019 (ASCO 2014)
5. Jabbour . Haematologica. (2015) 100:S1 abstract S114 (EHA 2015)

Inotuzumab Ozogamycin in ALL ≥ Salvage 2

- 35 pts Rx with ino 1.8 mg/m^2
- ORR 24/35 = 69% - 10 CR + 14 CRi
- MRD negative in 18/24 = 75%
- Post Rx SCT 8/35 (23%)
- Median survival 6.4 mos
- VOD 3 (2 post allo SCT)

Advani. Blood 124: abst ___; 2014

Inotuzumab vs Chemo Rx in ALL Salvage

Phase 3 study; 326 pts randomized; 117 sites in 19 countries (INO-VATE ALL; NCT01564784)

- Relapsed/refractory CD22+ ALL
- Due for salvage 1 or 2 therapy
- Ph– or Ph+

1:1 Randomization (N=326)

Stratifications:

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

Inotuzumab ozogamicin (InO)

- Starting dose 1.8 mg/m^2/cycle
- 0.8 mg/m^2 on day 1; 0.5 mg/m^2 on 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

- InO dose was reduced to 1.5 mg/m^2/cycle once the patient achieved CR/CRi

EHA 2015

Ino vs. Chemo Rx. Endpoints

Primary endpoints

- Split-α design used for 2 primary endpoints (1-sided α=0.0125)
  - 1. CR/CRi --Based on first 218 patients randomized
  - 2. Overall survival (OS)-- assessed in all 326 randomized patients after ≥248 events

Key secondary endpoints

- MRD-negativity in CR/CRi (<0.01% by FCM)
- Safety
- Duration of remission
- Progression-free survival
- Stem cell transplant (SCT) rate

Invo vs. Chemo Rx. Study Group

Population	InO	SOC	Total	Definition
ITT	141	138	279	• All randomized patients up to October 2, 2014
ITT218	109	109	218	• The first 218 patients randomized • Primary population for final CR/CRi analysis • 13 patients randomized to SOC refused to start treatment
Safety	139	120	259	• All randomized patients who received ≥1 dose

- Second interim analysis of OS (for futility and efficacy)-- February 20, 2015

Ino vs. Chemo Rx. Study Group

Characteristic	InO (n=109)	SOC (n=109)
Median (range) age, y	47 (18–78)	47 (18-79)
Men, n (%)	61 (56)	73 (67)
ECOG PS, n (%)		
0	43 (39)	45 (41)
1	50 (46)	53 (49)
2	15 (14)	10 (9)
Salvage , n (%)		
1	73 (67)	69 (63)
2	35 (32)	39 (36)
CRD1 at baseline, n (%)		
<12 months	62 (57)	71 (65)
≥12 month	47 (43)	38 (35)
CR to most recent prior Rx, n (%)	78 (72)	74 (68)

Ino vs Chemo Rx. Study Group (2)

Characteristic	InO (n=109)	SOC (n=109)
Median WBC count	3.5 (0−47.4)	3.8 (0.1−51.0)
Median peripheral blasts	0.2 (0−42.7)	0.4 (0−31.5)
No circulating peripheral blasts, n (%)	42 (39)	48 (44)
CD22 expression on ALL blasts, n (%)		
<90%	24 (22)	24 (22)
≥90%	74 (68)	63 (58)
Missing	11 (10)	22 (20)
Karyotype, n (%)		
Normal	27 (25)	23 (21)
Ph+	14 (13)	18 (17)
t(4;11)	3 (3)	6 (6)
Other abnormalities	49 (45)	46 (42)
Unknown/missing	16 (15)	16 (15)

Ino vs Chemo Rx in ALL Salvage. Response

	InO	SOC	1-Sided *P* Value
N	109	96	
CR/CRi,%	81	33	<0.0001
CR	36	20	0.0056
CRi	45	13	<0.0001
MRD-negativity among responders			
CR/CRi, %	78	28	<0.0001

EHA. 2015

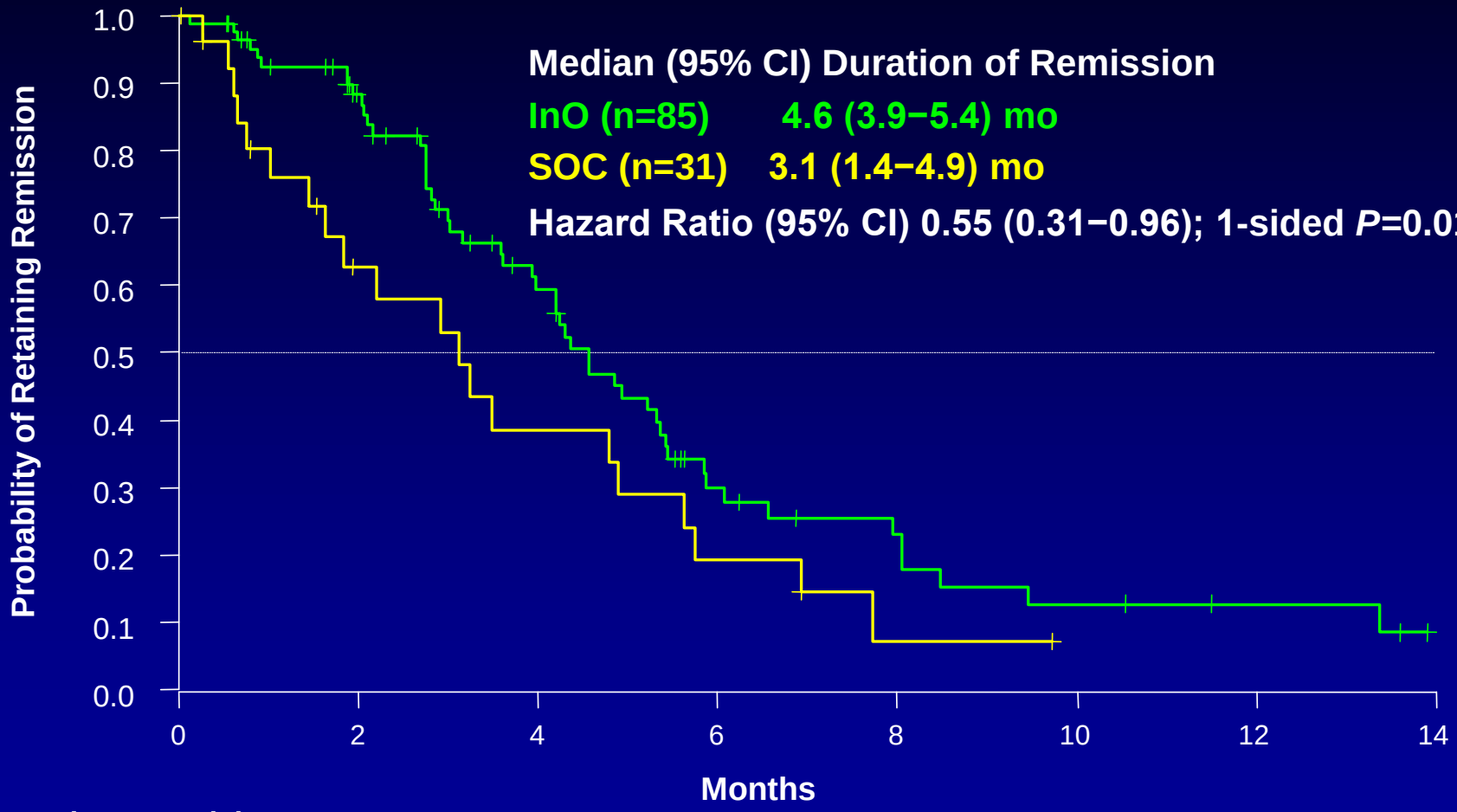
Ino vs. Chemo Rx. CR/CRi by Stratification Factors

	CR/CRi, %				
	InO (n=109)	SOC (n=96)	1-Sided *P* value	In favor of InO	% Rate Difference (97.5% CI)
All patients	80.7	33.3	<0.0001		47.4 (34−61)
Duration of 1st Remission					
<12 mo	77.5	27.0	<0.0001		50.5 (34−67)
≥12 mo	86.8	45.5	0.0001		41.4 (18−64)
Salvage 1	87.7	31.3	<0.0001		56.3 (41−72)
Salvage 2	66.7	37.9	0.01		28.7 (2−56)
Age <55	80.3	36.1	<0.0001		44.2 (27−62)
Age ≥55	81.4	28.6	<0.0001		52.8 (31−75)

Ino vs. Chemo Rx. CR/CRi by Baseline Factors

Characteristic	CR/CRi[a] InO (n=109)	CR/CRi[a] SOC (n=96)	1-Sided *P* Value
Peripheral blasts, n (%)			
≤1000	61/74 (82)	27/72 (38)	<0.0001
>1000	26/34 (77)	5/23 (22)	<0.0001
CD22 expression,[b] n (%)			
<90	19/24 (79)	6/22 (25)	0.0002
≥90	61/74 (82)	23/58 (40)	<0.0001
Karyotype, n (%)			
Normal	19/20 (95)	6/16 (38)	0.0003
Ph+	11/14 (79)	8/15 (53)	0.1498
t(4;11)	1/3 (33)	2/5 (40)	0.8214
Other abnormalities	42/49 (86)	12/42 (29)	<0.0001
Previous SCT, n (%)			
Yes	13/17 (77)	6/19 (32)	0.0085
No	75/92 (82)	26/77 (34)	<0.0001

Ino vs Chemo Rx in ALL Salvage. CRD



Median (95% CI) Duration of Remission

InO (n=85) 4.6 (3.9−5.4) mo

SOC (n=31) 3.1 (1.4−4.9) mo

Hazard Ratio (95% CI) 0.55 (0.31−0.96); 1-sided *P*=0.0169

Patients At Risk, n

InO	85	59	34	14	9	5	3	0
SOC	31	13	8	4	1	0	0	0

EHA. 2015

Ino vs. Chemo Rx. Hepatotoxicity AEs

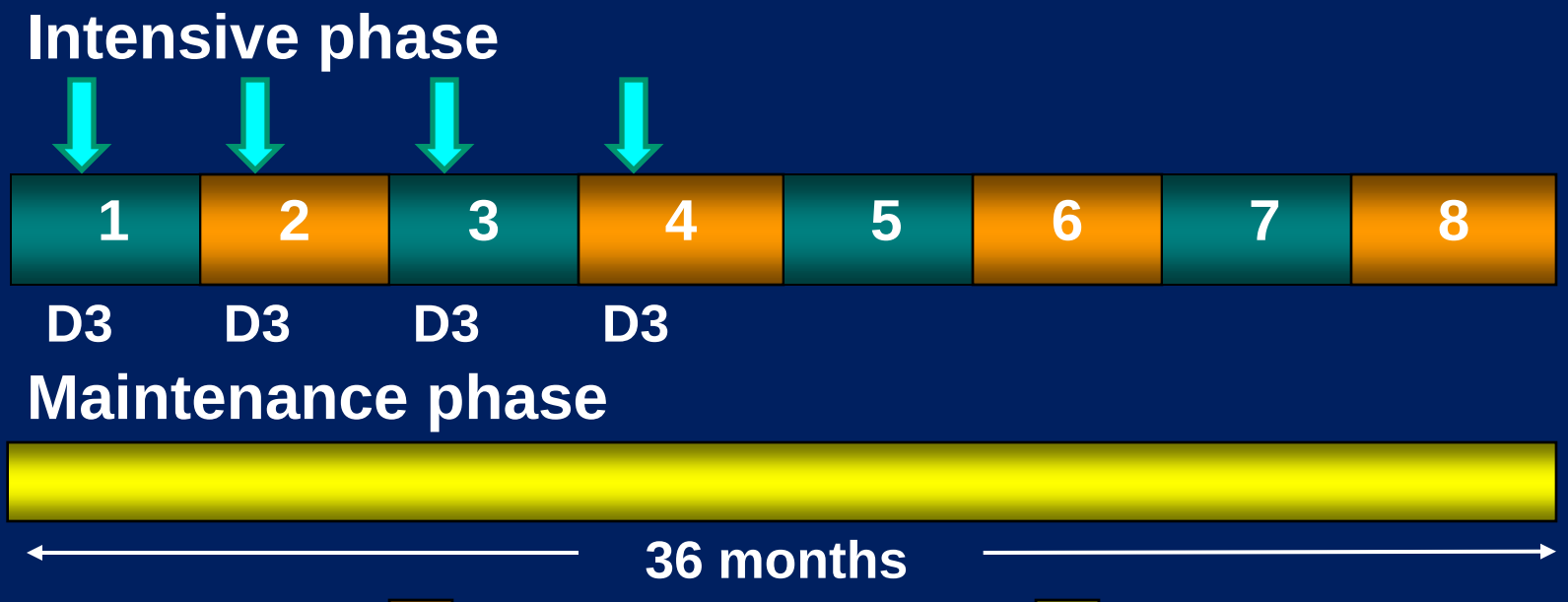
	InO (n=139)	SOC (n=120)
Patients with all causality hepatobiliary TEAEs,n (%)		
Hyperbilirubinemia	21 (15)	12 (10)
VOD/SOS	15 (11)	1 (1)

- In the InO arm, 10 patients had VOD/SOS after post-study SCT, while 5 had VOD/SOS during Rx (2 with and 3 without pre-study SCT)
- Median (range) time to VOD/SOS after SCT in the InO arm 16 (3–39) days
- Multivariate analysis-- dual alkylator conditioning (yes vs no) was the only significant covariate of VOD/SOS (*P*=0.039)

Rx of Elderly ALL

Author/ Group/Study	Age	No. of pts	CR rate (%)	OS
Kantarjian 2000 MD Anderson	>60	44	79	17% (at 5 yrs)
Annino 2002 GIMEMA 0208	50-60	121	68	15% (at 8 yrs)
Larson 2005 CALGB	>60	129	57	12% (at 3 yrs)
Sancho 2007 PETHEMA ALL96	56-67	33	58	39% (at 5 yrs)
Pullarkat 2008 SWOG 9400	50-65	43	63	23% (at 5 yrs)
Hunault-Berger 2010 GRAALL	55-77	31	90	35% (at 2 yrs)
Gökbuget 2012 GMALL	55-85	268	76	23% (at 5 yrs)
Sive 2012 UK NCRI	55-64	100	70	19% (at 8 yrs)

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

Combination therapy Mini-hyper-CVD + Inotuzumab

- Dose reduced HyperCVD for 8 courses
  - Cyclophosphamide 50% dose reduction
  - Dexamethasone 50% dose reduction
  - No anthracycline
  - Methotrexate 75% dose reduction
  - Cytarabine 0.5 g/m2 x 4 doses
- Inotuzumab on day 3 (first 4 courses)
  - 1.8 mg/m2 course 1
  - 1.3 mg/m2 courses 2-4
- Rituximab days 2 and 8 (first 4 courses)
- Intrathecal chemotherapy days 2 and 8 (first 4 courses)
- POMP maintenance for 3 years

Jain. Blood 122: abst 1432; 201

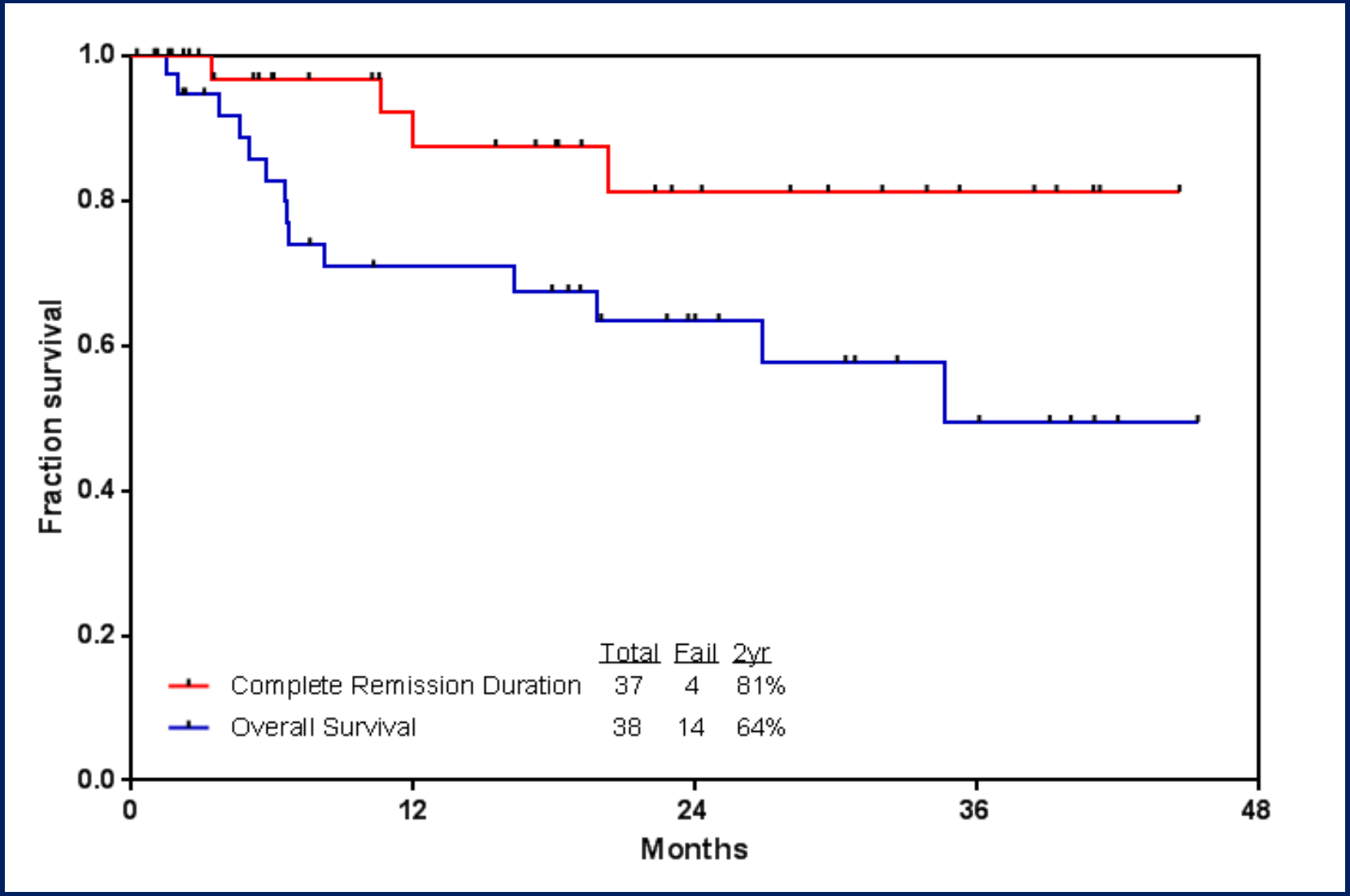
MiniHCVD-INO in ALL. Response (N=35)

Response	N	(%)
CR	28	28/35 (80)
CRp	6	6/35 (17)
ORR	34	34/35 (97)
No response	1	1/35 (3)
Early death	0	0

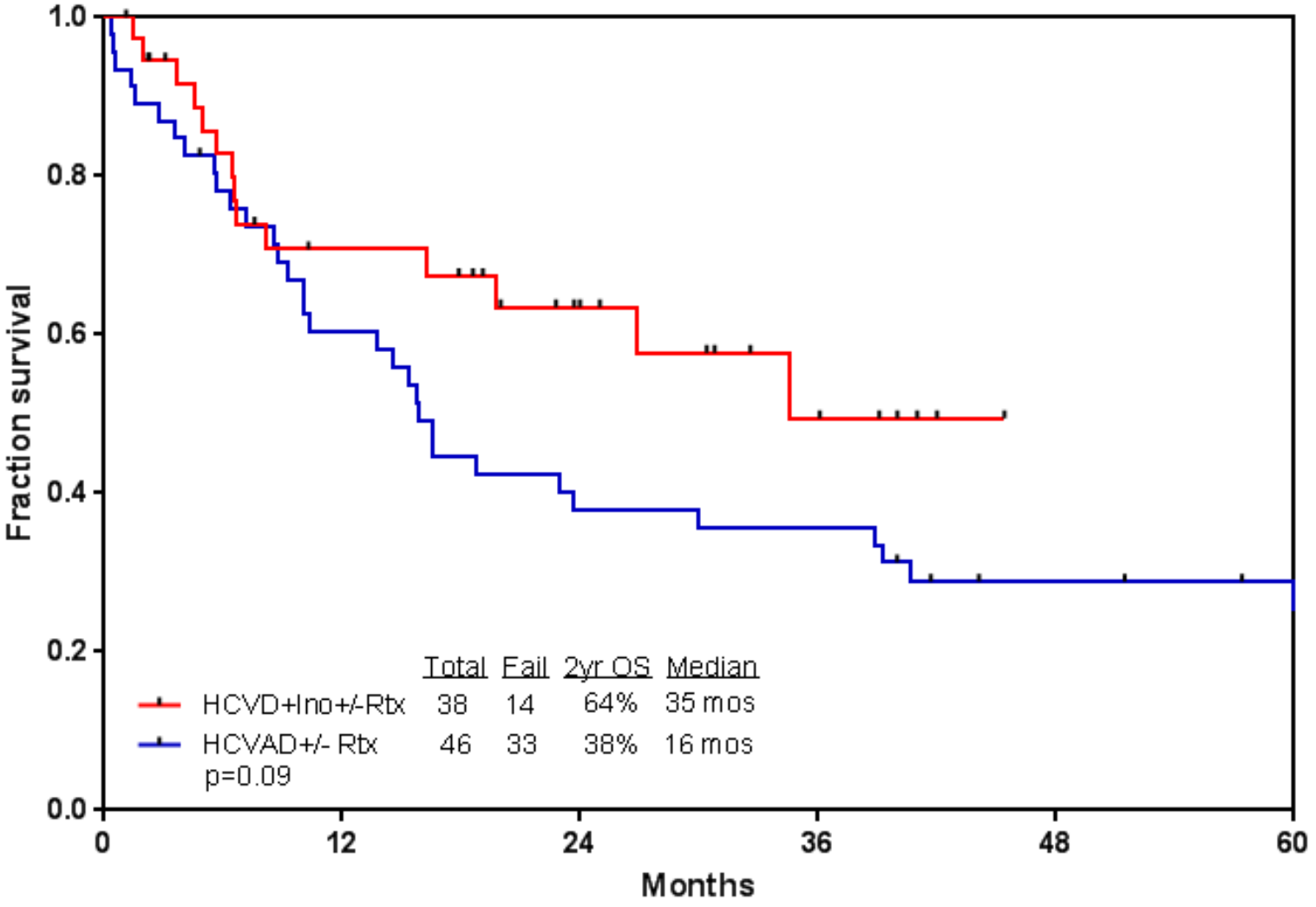
- Three patients were enrolled with CR

MiniHCVD-INO in ALL. Outcome

- 2-yr CRD and OS rates 81% and 64%, respectively



MiniHCVD-INO vs HCVAD in ALL. Overall Survival



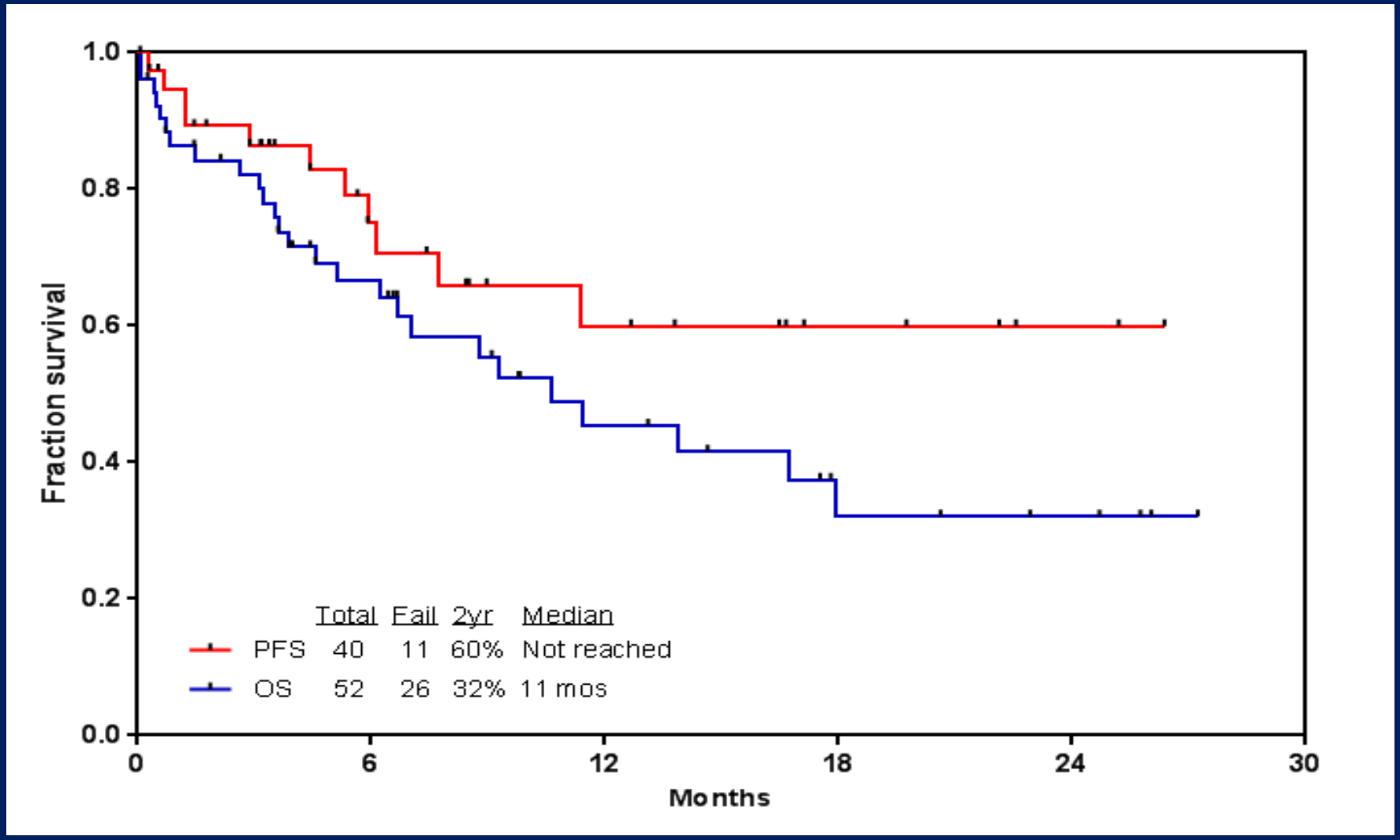
MiniHCVD-INO in R/R ALL. Response (N=52)

Response	N	(%)
CR	27	53
CRp	10	19
CRi	3	6
ORR	40	77
MRD negativity		
at response	13/35	37
Overall	33/40	82
No response	5	10
Early death	7	14

Sasaki. Blood. 2015; 126: Abst # 3721

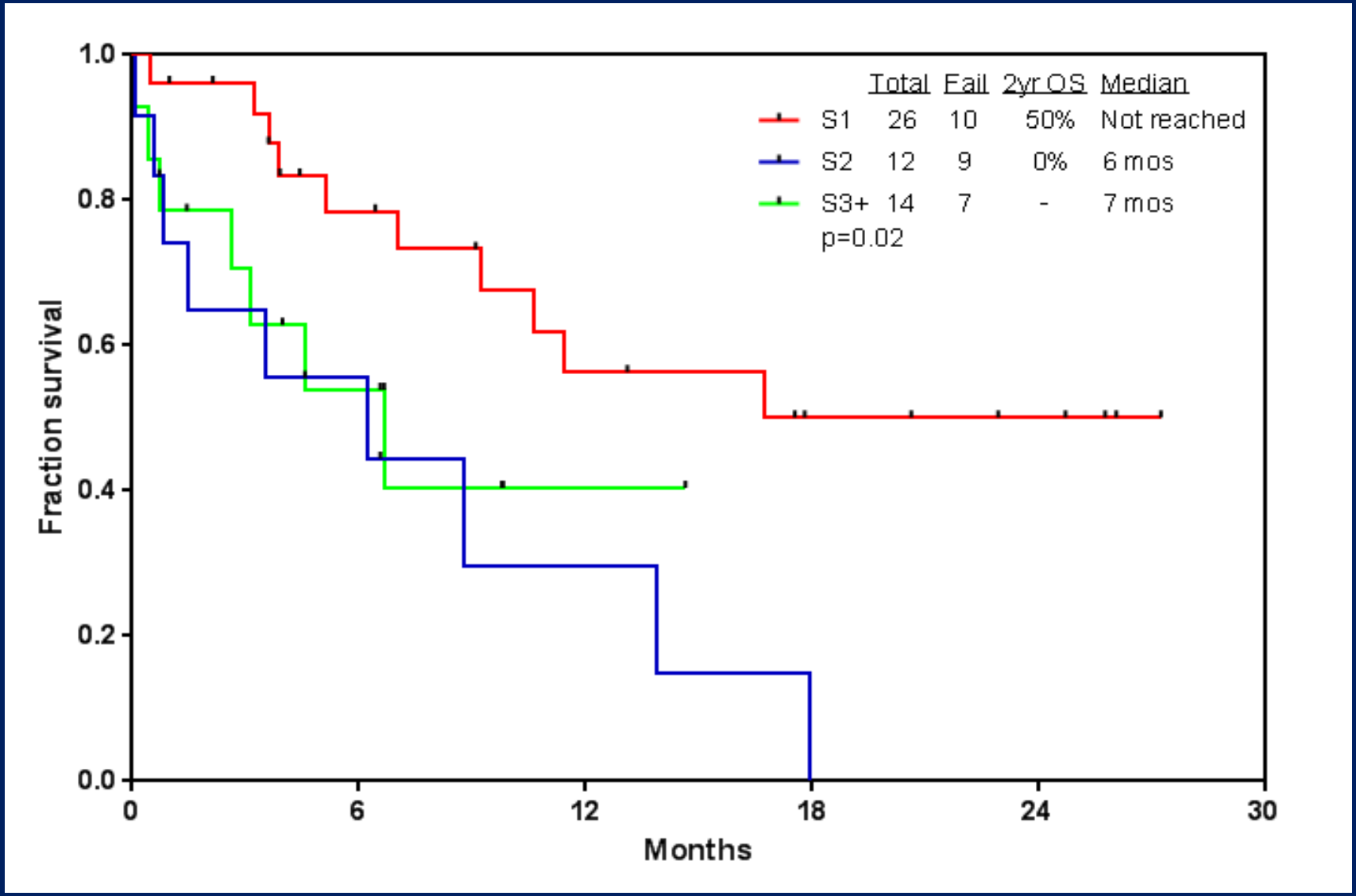
MiniHCVD-INO in R/R ALL. Survival

- 2-yr PFS and OS rates 60% and 32%, respectively



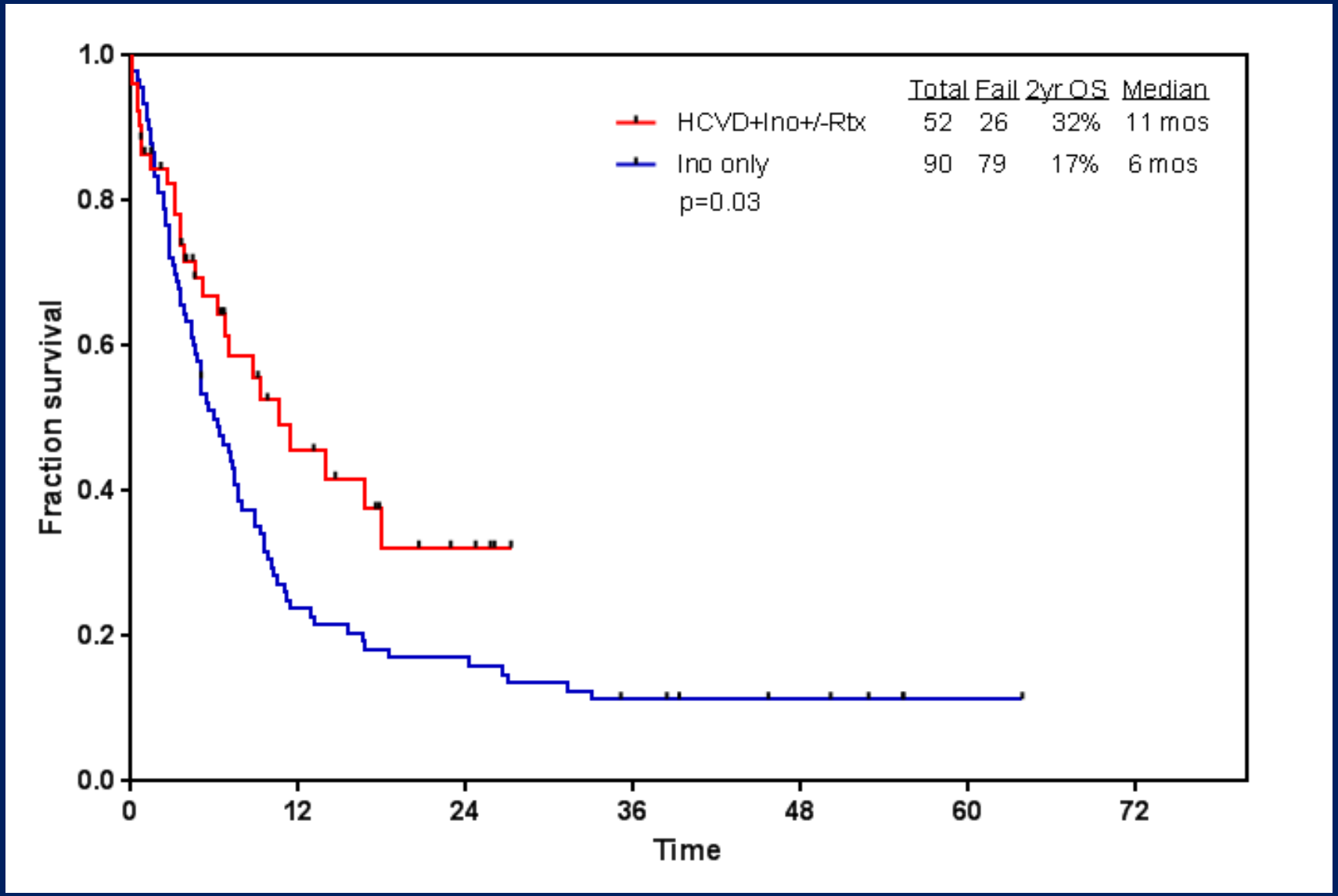
Sasaki. Blood. 2015; 126: Abst # 3721

MiniHCVD-INO in R/R ALL. Survival



Sasaki. Blood. 2015; 126: Abst # 3721

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



Sasaki. Blood. 2015; 126: Abst # 3721