Leucemia acuta linfoblastica

F. Ferrara

- **INO-VATE Study**
- **TOWER Study**
- **Long term efficacy and toxicity of CART**
- **Peg-ASP: large German study**
- **NOPHO ALL2008**

Overall Survival in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia Patients Receiving Inotuzumab Ozogamicin vs Standard Care in the Phase 3 INO-VATE Study (EHA 2016: LB2233)

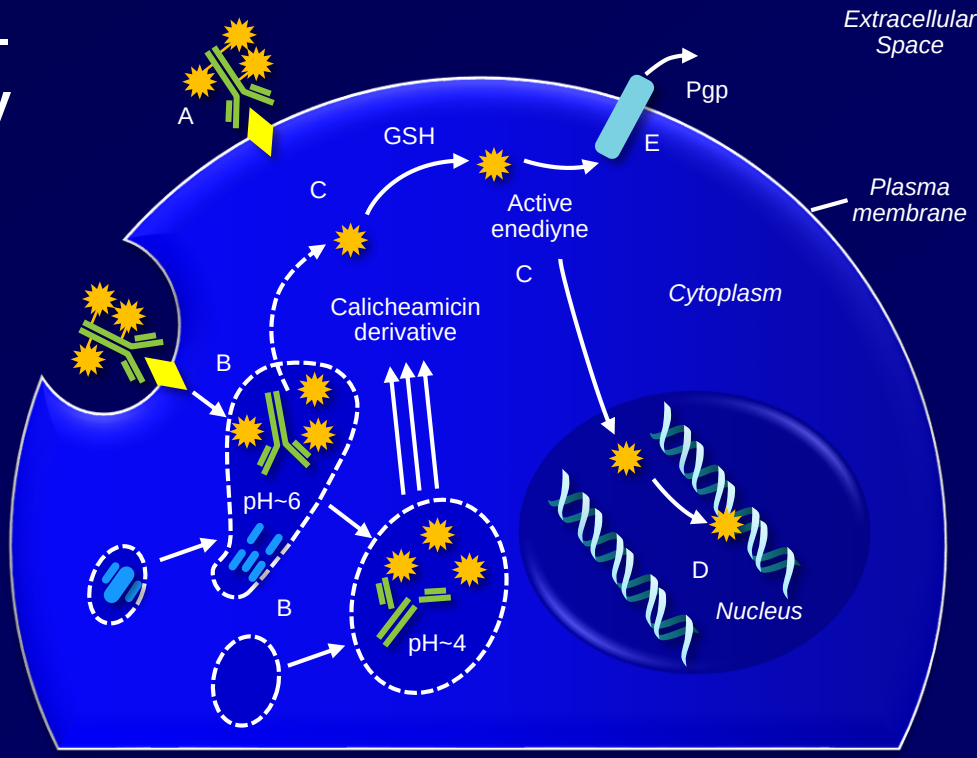
Hagop M. Kantarjian,[1] Daniel J. DeAngelo,[2] Anjali S. Advani,[3] Michaela Liedtke,[4] Wendy Stock,[5] Nicola Gökbuget,[6] Susan O'Brien,[7] Giovanni Martinelli,[8] Kongming Wang,[9] Tao Wang,[10] M. Luisa Paccagnella,[10] Barbara Sleight,[10] Erik Vandendries,[11] Matthias Stelljes[12]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Cleveland Clinic, Cleveland, OH, USA; [4]Standford Cancer Institute, Stanford, CA, USA; [5]University of Chicago, Chicago, IL, USA; [6]Goethe University, Frankfurt, Germany; [7]University of California–Irvine, Orange, CA, USA; [8]Institute Seragnoli, University of Bologna, Bologna, Italy; [9]Pfizer Inc, Pearl River, NY; [10]Pfizer Inc, Groton, CT, USA; [11]Pfizer Inc, Cambridge, MA, USA; [12]Universitätsklinikum Münster, Münster, Germany

Presented at EHA 2016; June 12, 2016; Copenhagen, Denmark

Background

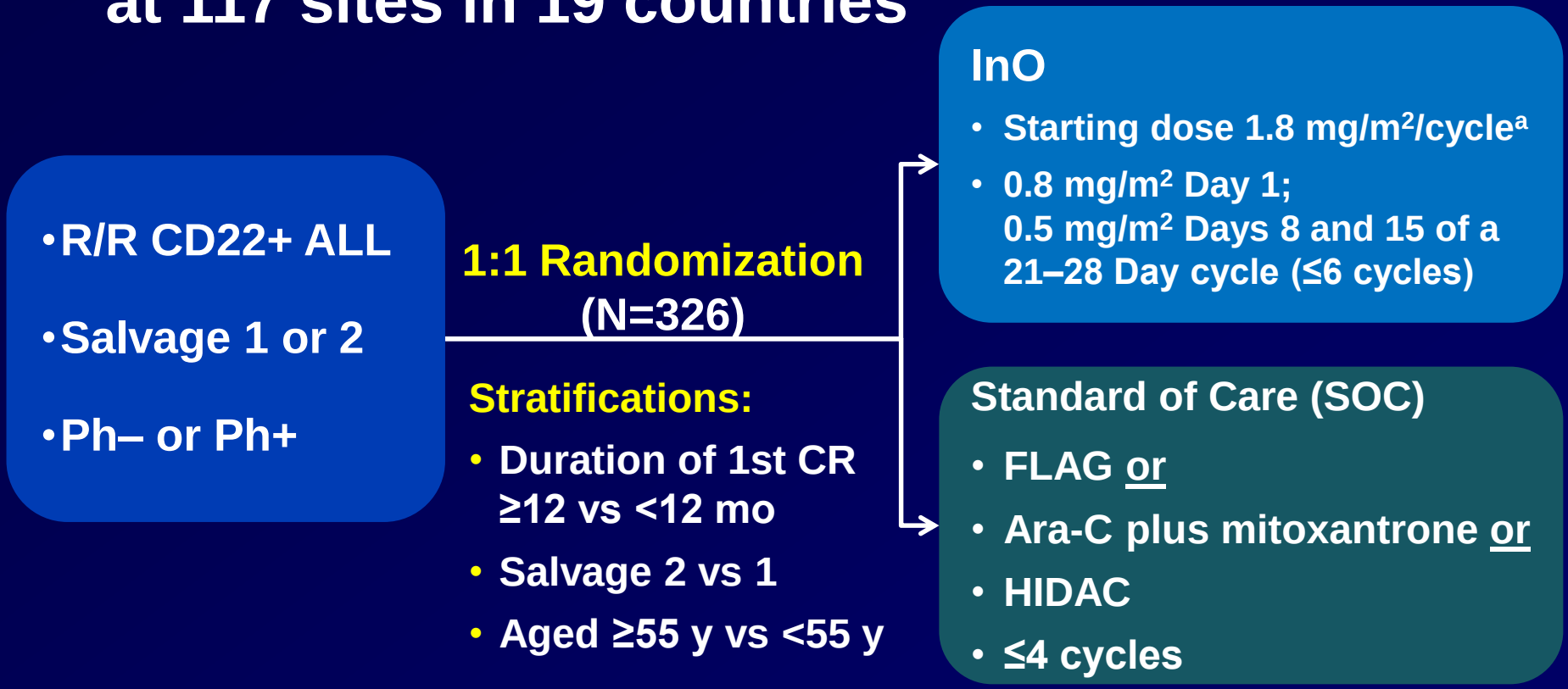
- Relapsed/refractory (R/R) ALL aggressive; 5-year survival <10%[1]
- CD22 expressed on surface of ~90% of B-cell ALL cells[2]
- Inotuzumab ozogamicin (InO) – humanized anti-CD22 antibody conjugated to calicheamicin; potent cytotoxic antitumor antibiotic[3]
- InO demonstrated initial safety and antitumor activity in R/R ALL[4]



1. Fielding A et al. *Blood*. 2006; 944-950. 2. Shah N et al. *Pediatr Blood Cancer*. 2015;62(6):964-969.
3. Shor B et al. *Mol Immunol*. 2015;67(2 Pt A):107-116. 4. Kantarjian H, et al. *Cancer.* 2013;119:2728-2736.

Study Design

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



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

Ara-C=cytarabine; FLAG=fludarabine/ara-C/granulocyte colony-stimulating factor; HIDAC=high-dose ara-C; Ph=Philadelphia chromosome.

Study Endpoints

- Split-α design used for 2 primary endpoints (each at 1-sided α=0.0125)

  1. **CR/CRi**: independent blinded external adjudication committee (EAC); based on first 218 pts randomized; occurred October 2, 2014

  2. **Overall survival (OS)**: prespecified boundary of *P*=0.0104; assessed in all 326 randomized pts after ≥248 events; occurred March 8, 2016

- Key secondary endpoints:
  - Safety (as of March 8, 2016)
  - MRD negativity in pts with CR/CRi (<0.01% by central FCM)
  - Remission duration
  - PFS
  - Transition to SCT

Patient Characteristics

Characteristic	InO (n=164)	SOC (n=162)
Median (range) age, yrs	47 (18–78)	48 (18–79)
Men, n (%)	91 (55)	102 (63)
ECOG PS, n (%)		
0	62 (38)	61 (38)
1	81 (49)	80 (49)
2	21 (13)	20 (12)
Salvage status, n (%)		
1	111 (68)	104 (64)
2	51 (31)	57 (35)
First CR duration, n (%)		
<12 mos	98 (60)	108 (67)
≥12 mos	66 (40)	54 (33)
CR with most recent prior Rx, n (%)	121 (74)	111 (69)
Prior SCT, n (%)	28 (17)	29 (18)
Median (range) WBC, $10^3/\mu L$	4.1 (0−47.4)	4.0 (0.1−68.8)

Patient Characteristics (Continued)

Characteristic	InO (n=164)	SOC (n=162)
Median (range) PB blasts, $10^3/\mu L$	0.1 (0−42.7)	0.03 (0−43.3)
No circulating blasts, n (%)	71 (43)	74 (46)
BM blasts n (%)		
<50%	53 (32)	48 (30)
≥50%	109 (67)	113 (70)
Missing	2 (1)	1 (1)
CD22 on ALL blasts,[a] n (%)		
<90%	35 (21)	36 (22)
≥90%	107 (65)	93 (57)
Missing	22 (13)	33 (20)
Karyotype,[b] n (%)		
Normal	46 (28)	42 (26)
Ph+[c]	22 (13)	28 (17)
t(4;11)	6 (4)	7 (4)
Complex	27 (16)	22 (14)
Other	43 (26)	41 (25)
Unknown/missing	20 (12)	22 (14)

[a] By central laboratory analysis; [b] By local laboratory analysis; [c] By local or central laboratory analysis or medical history.

Treatment Summary

		SOC			
	InO (n=164)	FLAG (n=93)	Ara-C + Mito (n=33)	HIDAC (n=17)	Total (n=143)
Total cycles	464	120	35	21	176
Median (range) n cycles	3 (1–6)	1 (1–4)	1 (1–2)	1 (1–2)	1 (1–4)
Rx ≥2 cycles, n (%)	127 (77)	21 (23)	2 (6)	4 (24)	27 (19)

- Fewer pts in InO arm DC Rx due to resistant disease (11% vs 43%)
- No pts remaining on active Rx as of June 10, 2015

CR/CRi Results in ITT218

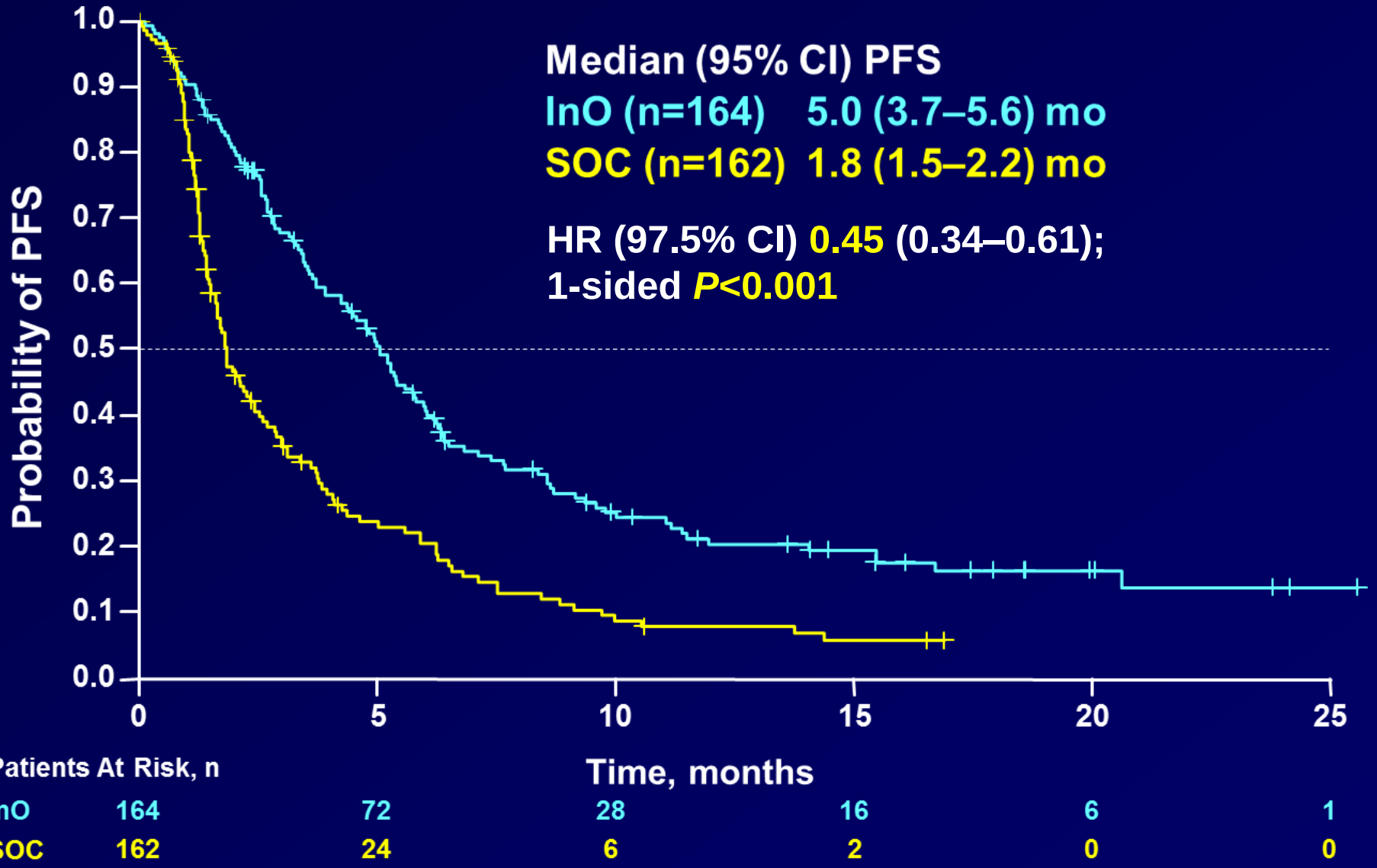
Response,[a] n (%) [95% CI]	InO (n=109)	SOC (n=109)	1-sided *P* Value
CR/CRi	88 (80.7) [72−88]	32 (29.4) [21−39]	<0.0001
MRD neg[b]	69/88 (78.4) [68−87]	9/32 (28.1) [14−47]	<0.0001

- Among the first 218 pts randomized, over 4X more achieved CR/CRi and proceeded directly to SCT after CR/CRi with InO vs SOC (n=41/109 vs n=10/109; *P*<0.0001)[c]

Among the first 218 pts randomized, 41% proceeded directly to SCT after Rx with InO vs 11% in SOC (n=45/109 vs n=12/109; *P*<0.001), including pts not in CR/CRi.

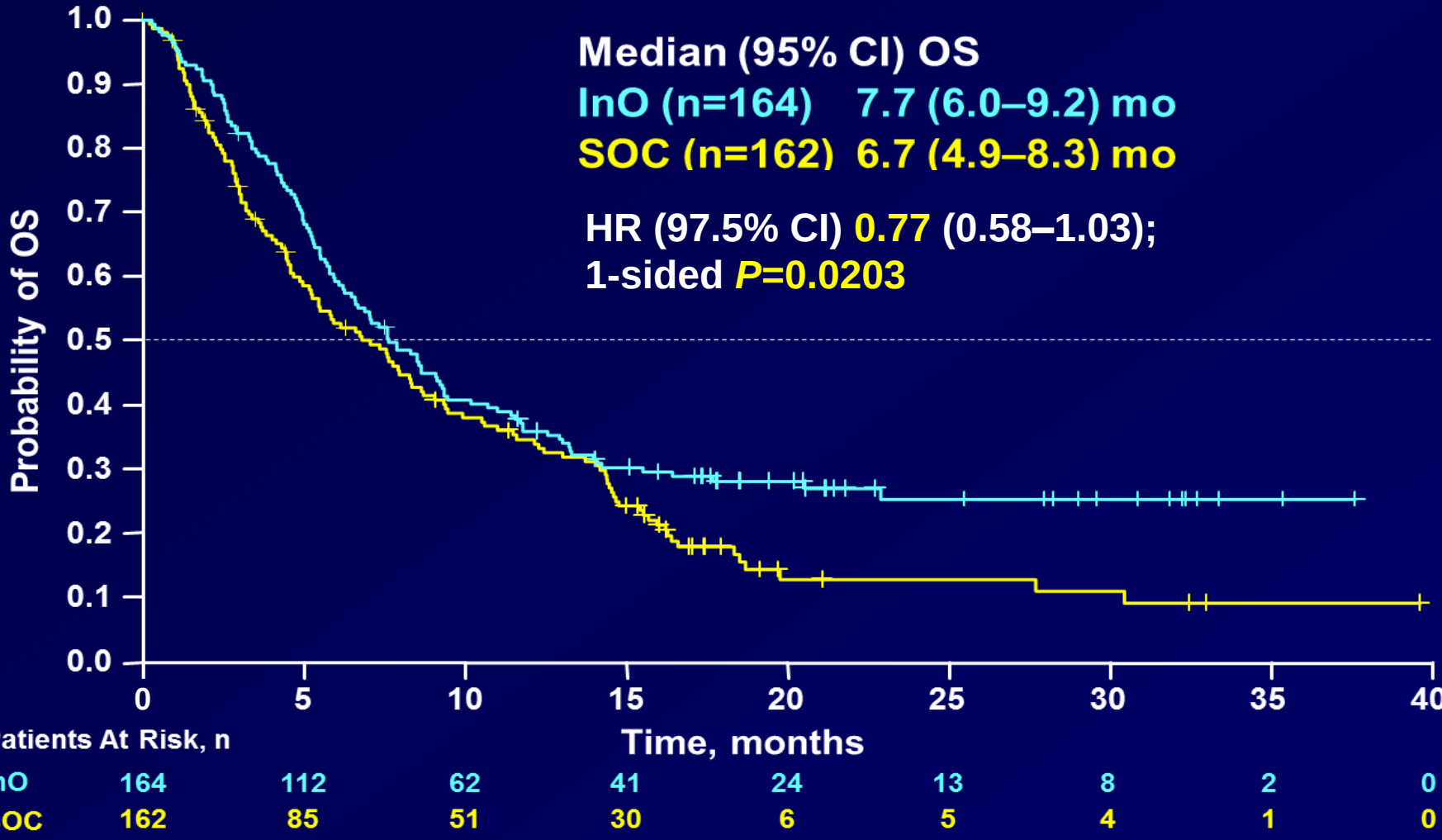
[a]Data as of October 2, 2014 per EAC. [b]Among responders; 13 SOC pts who withdrew prior to dosing were considered nonresponders. [c]Per Investigator's assessment.

Progression-Free Survival



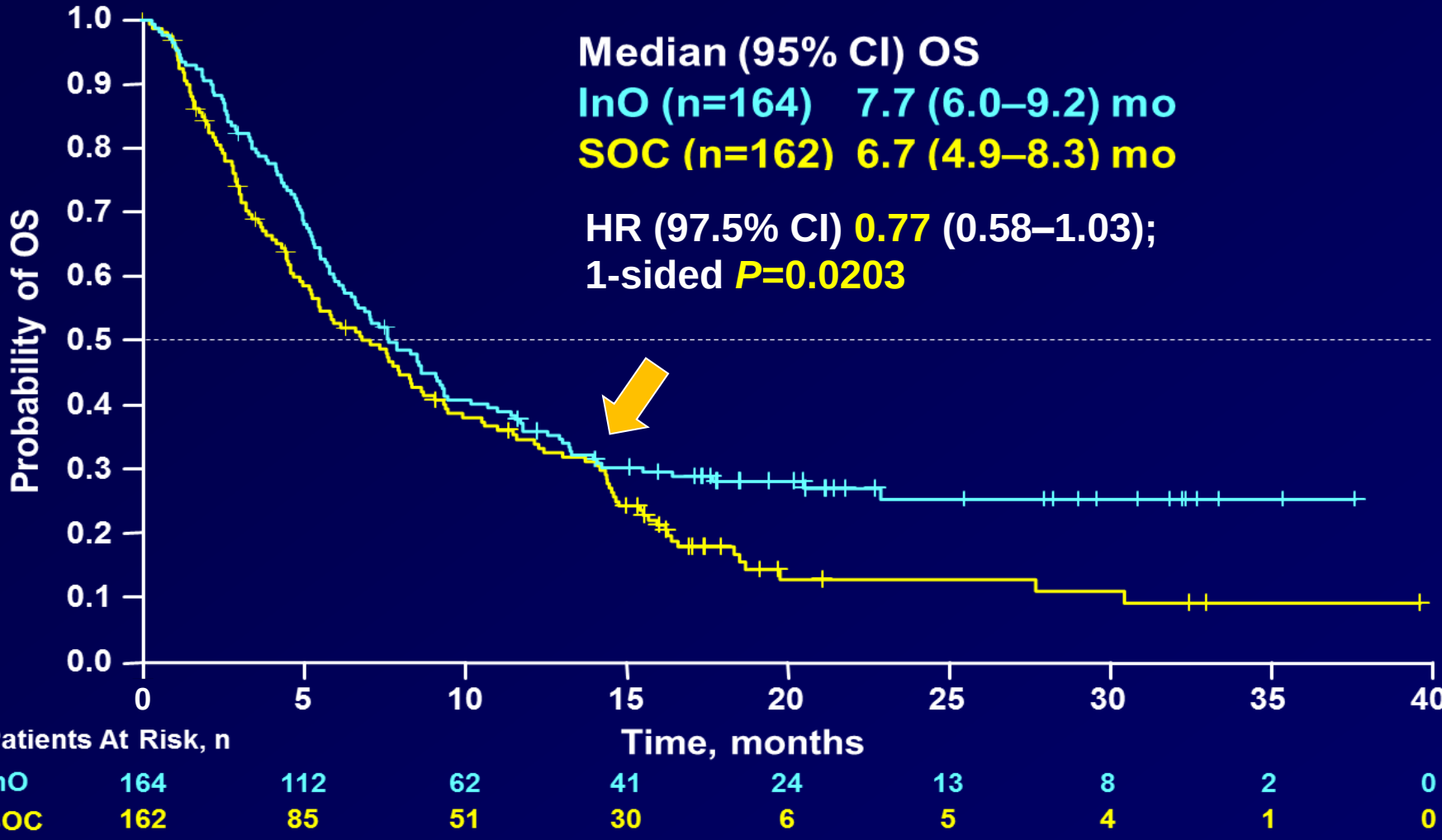
PFS defined as time from randomization to death, disease progression, or start of new induction therapy or post-study SCT.

Overall Survival



- Primary objective to demonstrate significantly improved OS with InO at the prespecified boundary of *P*=0.0104 not met

Overall Survival



- Data appeared to depart from proportional hazards assumption
- 2-yr survival probability higher with InO (23% [95% CI: 16–30] vs 10% [5–16])

Restricted Mean Survival Time (RMST)

- HR may not fully capture the therapeutic impact of Rx in certain situations
- Statistical analysis plan assumed proportional hazards, a condition not met in this study based on the shape of the survival curve
- RMST: alternative to hazard ratio that measures average survival from time 0 to a specific time point; used when proportional hazards assumption does not hold[1]

1. Trinquart L et al. *J Clin Oncol* 2016, 34:1-8.

RMST Analysis

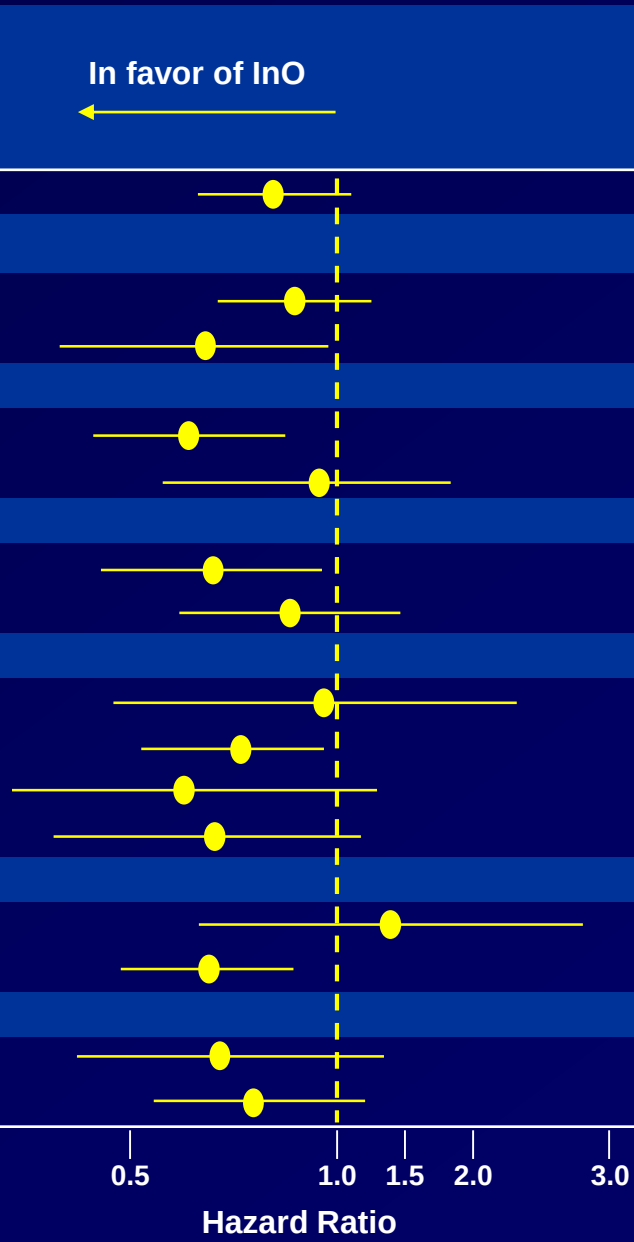
	InO (n=164)	SOC (n=162)
N events	122	130
RMST (SE), mo	13.9 (1.1)	9.9 (0.85)
RMST difference (95% CI)	3.9 (1.2–6.7); 1-sided *P*=0.0023	
RMST ratio (95% CI)	1.4 (1.1–1.8); 1-sided *P*=0.0021	

- Separation of OS curves after ~14 mos suggests survival benefit with InO occurs at later time points
- Truncation time was 37.7 mos (maximum OS time for either arm)

SE=standard error.

Subgroup Analysis of OS

	n (No. of Events)		Median OS, mo		
	InO	SOC	InO	SOC	HR (97.5% CI)
All patients	164 (122)	162 (130)	7.7	6.7	0.77 (0.57, 1.02)
Duration of 1st CR					
<12 Months	109 (89)	107 (89)	6.6	5.3	0.83 (0.59, 1.17)
≥12 months	55 (33)	55 (41)	11.1	9.4	0.59 (0.34, 1.00)
Salvage status					
1	108 (75)	107 (87)	8.6	7.1	0.65 (0.46, 0.93)
2	56 (47)	55 (43)	6.2	5.2	0.97 (0.60, 1.56)
Age at randomization, y					
<55	104 (70)	103 (79)	8.6	8.0	0.68 (0.47, 0.98)
≥55	60 (52)	59 (51)	5.6	5.3	0.90 (0.58, 1.41)
Cytogenetics					
Ph+	22 (18)	28 (22)	8.7	7.7	0.99 (0.48, 2.02)
Ph−	142 (104)	134 (108)	7.4	5.9	0.71 (0.52, 0.97)
Complex	27 (22)	22 (18)	7.2	3.9	0.61 (0.30, 1.25)
Normal w/ ≥20 metaphases	35 (24)	34 (28)	8.6	8.9	0.64 (0.34, 1.19)
Pre-study transplant					
Yes	28 (23)	29 (20)	8.5	13.1	1.31 (0.66, 2.61)
No	136 (99)	133 (110)	7.1	5.5	0.67 (0.49, 0.91)
BM blasts					
<50%	53 (37)	48 (42)	7.4	9.1	0.69 (0.41, 1.15)
≥50%	109 (84)	113 (87)	7.7	5.5	0.77 (0.55, 1.09)



TEAEs (≥20% InO Pts)

	InO (n=164)		SOC (n=143)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any AE,[a] n (%)	163 (99)	149 (91)	143 (100)	137 (96)
Thrombocytopenia	81 (49)	67 (41)	87 (61)	85 (59)
Neutropenia	80 (49)	77 (47)	66 (46)	63 (44)
Anemia	55 (34)	37 (23)	79 (55)	63 (44)
Nausea	53 (32)	3 (2)	68 (48)	0
Pyrexia	52 (32)	5 (3)	60 (42)	8 (6)
Leukopenia	47 (29)	44 (27)	54 (38)	53 (37)
Febrile neutropenia	44 (27)	44 (27)	77 (54)	77 (54)
Headache	45 (27)	4 (2)	38 (27)	1 (1)
Fatigue	42 (26)	4 (2)	24 (17)	3 (2)
↑AST	37 (23)	7 (4)	16 (11)	5 (3)
↑GGT	35 (21)	18 (11)	12 (8)	7 (5)
↑T. Bili	35 (21)	10 (6)	24 (17)	9 (6)

[a]All causality TEAEs among patients in the safety population (any cycle).
TEAE=treatment-emergent adverse event.

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

Conclusions

- OS improved with InO vs SOC: HR 0.77; *P*=0.0203; median OS, 7.7 vs 6.7 mo
  - 2-year survival 23% with InO vs 10% with SOC
  - In restricted mean survival time analysis, mean OS was 13.9 mo with InO vs 9.9 mo with SOC (*P*=0.0023)
- PFS significantly longer with InO vs SOC (5.0 vs 1.8 mo; *P*<0.0001)
- As previously reported, CR/CRi rate (ITT218) significantly higher with InO vs SOC (80.7% vs 29.4%; *P*<0.0001)
- More pts proceeded to SCT with InO vs SOC
- InO well tolerated; VOD post-SCT and liver toxicities more common with InO
- InO may represent an important new Rx option in R/R ALL

Blinatumomab Mechanism of Action

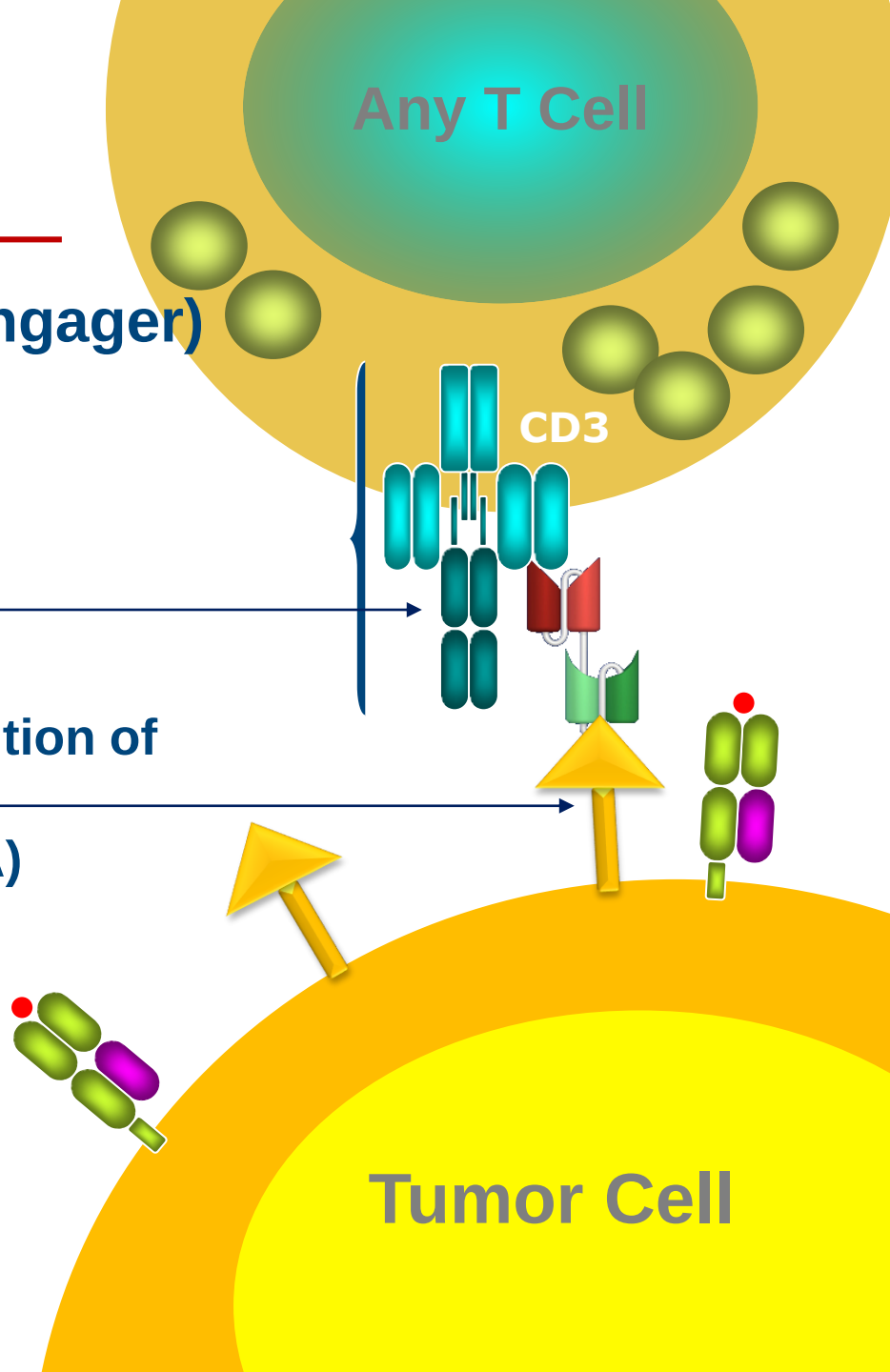
(BiTE® = Bi-specific T-Cell Engager)

Act independently of specificity of T Cell Receptor (TCR)

28 days continuous infusion

Allow T cells recognition of tumor-associated surface antigen (TAA)

Do not require MHC Class I and/or peptide antigen



TOWER study: design

- Phase 3, randomized, open-label study to evaluate the effect of blinatumomab on overall survival (OS) compared with SOC (FLAG± anthracycline; HD-ARA-C, HD-MTX) in adult patients with Ph– r/r BCP-ALL.
- Randomization 2:1
- Blinatumomab given at escalating dose of 9 µg/d in week 1 of cycle 1, then 28 µg/d for 4 weeks) as CIVI with 2 weeks wash-out.
- Primary endpoint: OS
- Secondary endpoints: Complete remission (CR) and combined CR or CR with partial or incomplete hematologic recovery (CR/CRh/CRi)

Topp M et al, EHA 2016

TOWER study: patients' features

	Blinatumomab ITT (N = 271)	SOC ITT (N = 134)	Blinatumomab Treated (N = 267)	SOC Treated (N = 109)
Age, median (range)	37 (18–80)	37 (18–78)	37 (18–80)	36 (18–76)
Female, n (%)	109 (40)	57 (43)	108 (40)	45 (41)
Maximum of central/local bone marrow blasts, n (%)[a]				
> 5% to < 10%	9 (3)	7 (5)	9 (3)	4 (4)
10% to < 50%	60 (22)	23 (17)	60 (22)	19 (17)
≥ 50%	201 (74)	104 (78)	198 (74)	86 (79)
Peripheral blasts, n (%)[a]				
0	117 (43)	51 (38)	116 (43)	43 (39)
1–5,000/µL	72 (27)	47 (35)	70 (26)	40 (37)
> 5,000/µL	32 (12)	15 (11)	31 (12)	12 (11)
WBC at diagnosis, n (%)[a]				
< 30,000/µL	143 (53)	62 (46)	141 (53)	50 (46)
≥ 30,000/µL	71 (26)	40 (30)	69 (26)	34 (31)

TOWER study: previous treatments

Characteristic – n (%)	Blinatumomab ITT (N = 271)	SOC ITT (N = 134)	Blinatumomab Treated (N = 267)	SOC Treated (N = 109)
Prior salvage regimens				
None	114 (42)	65 (49)	112 (42)	55 (50)
1	91 (34)	43 (32)	91 (34)	34 (31)
2	45 (17)	16 (12)	43 (16)	12 (11)
≥ 3	21 (8)	10 (7)	21 (8)	8 (7)
Prior alloHSCT	94 (35)	46 (34)	93 (35)	35 (32)
Primary refractory	46 (17)	27 (20)	44 (16)	23 (21)
Refractory to salvage	87 (32)	34 (25)	84 (31)	25 (23)

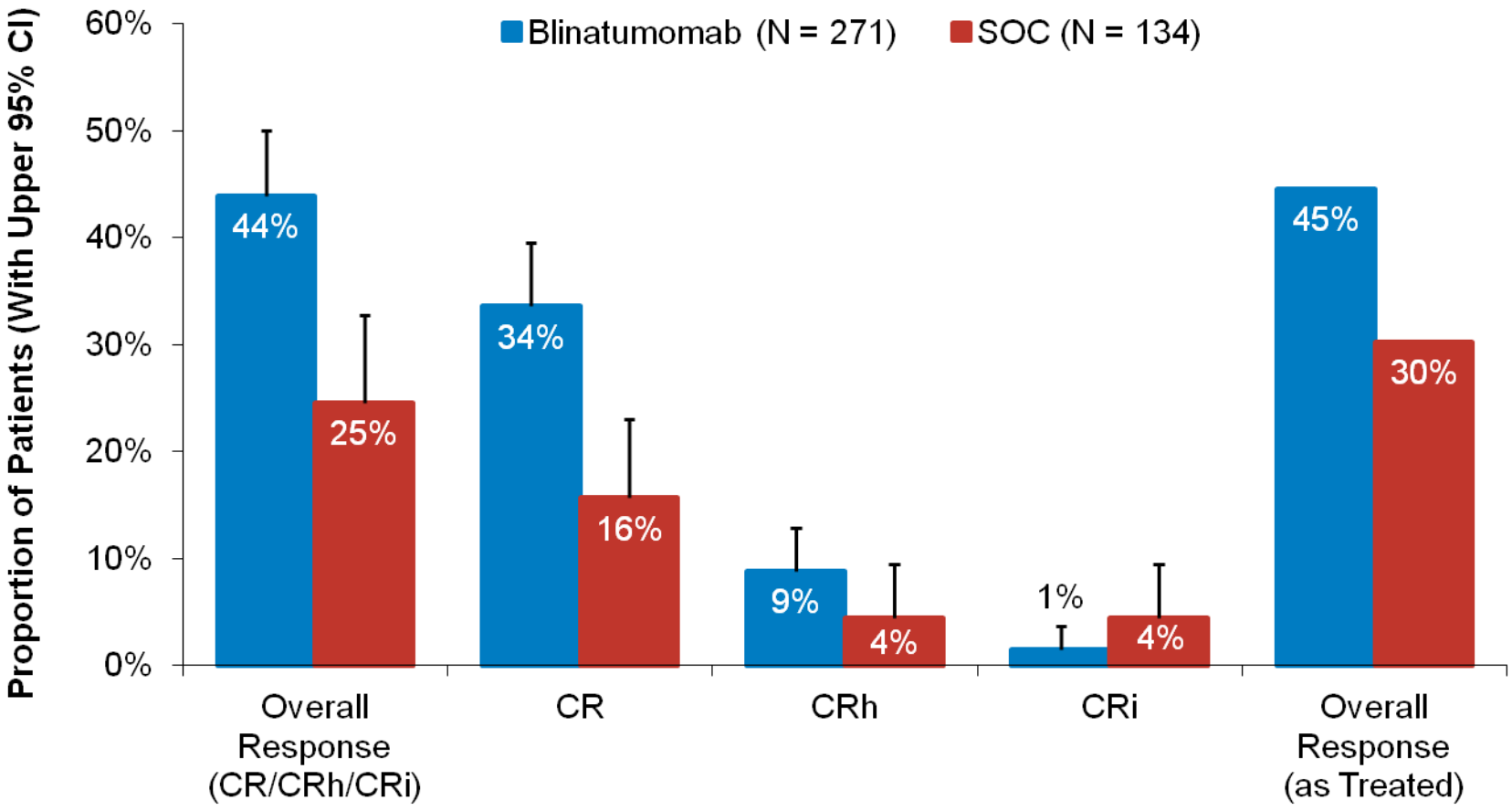
Topp M et al, EHA 2016

TOWER study: toxicty

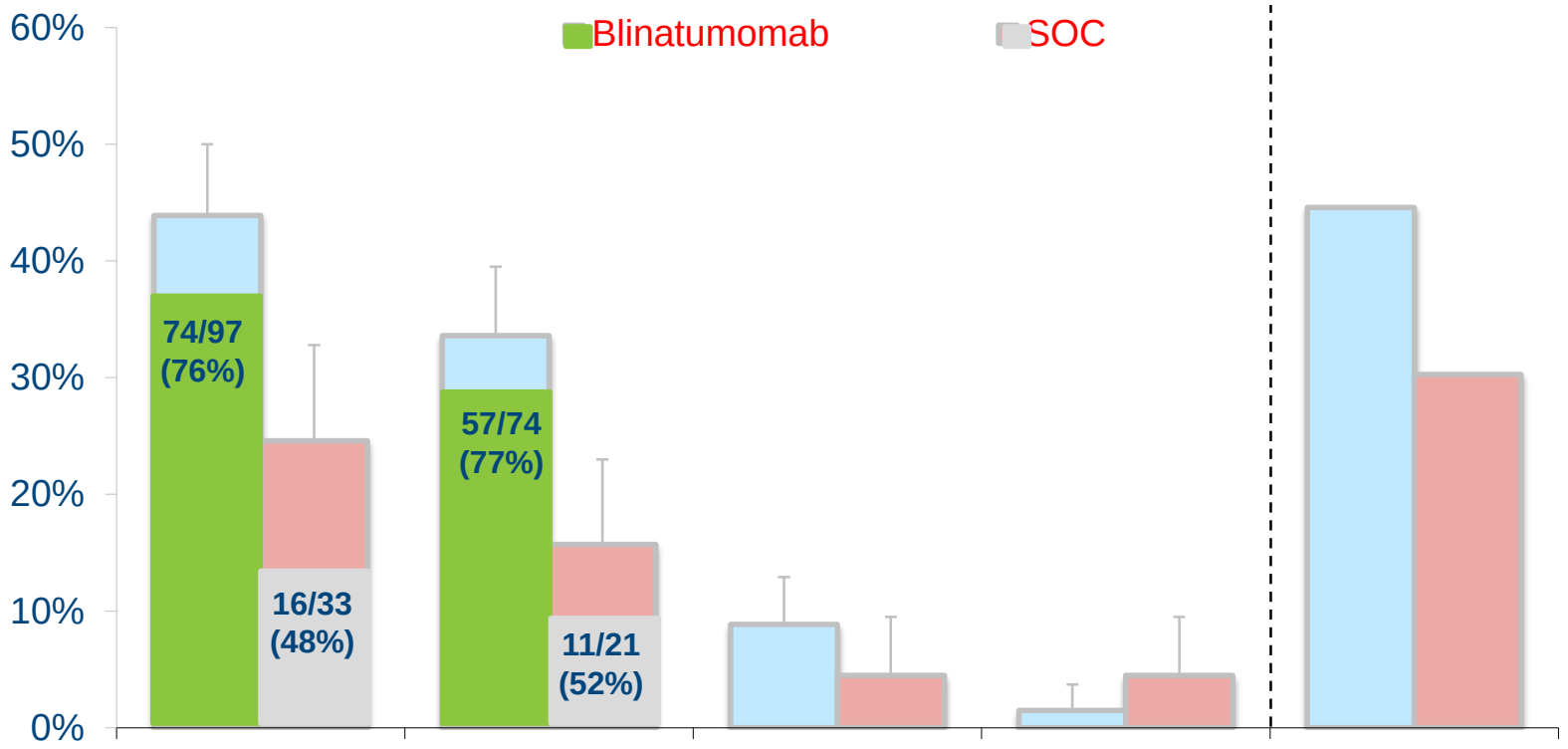
	BLINATUMOMAB (n=266)	SOC (n=107)
Grade≥ 3 AE	86%	93%
Grade 5 infection	11%	12%
Any AE:	62%	45%
Blood/lymphatic	28%	31%
CNS	14%	16%
CRS	3%	0%

Topp M et al, EHA 2016

TOWER study: results (I)



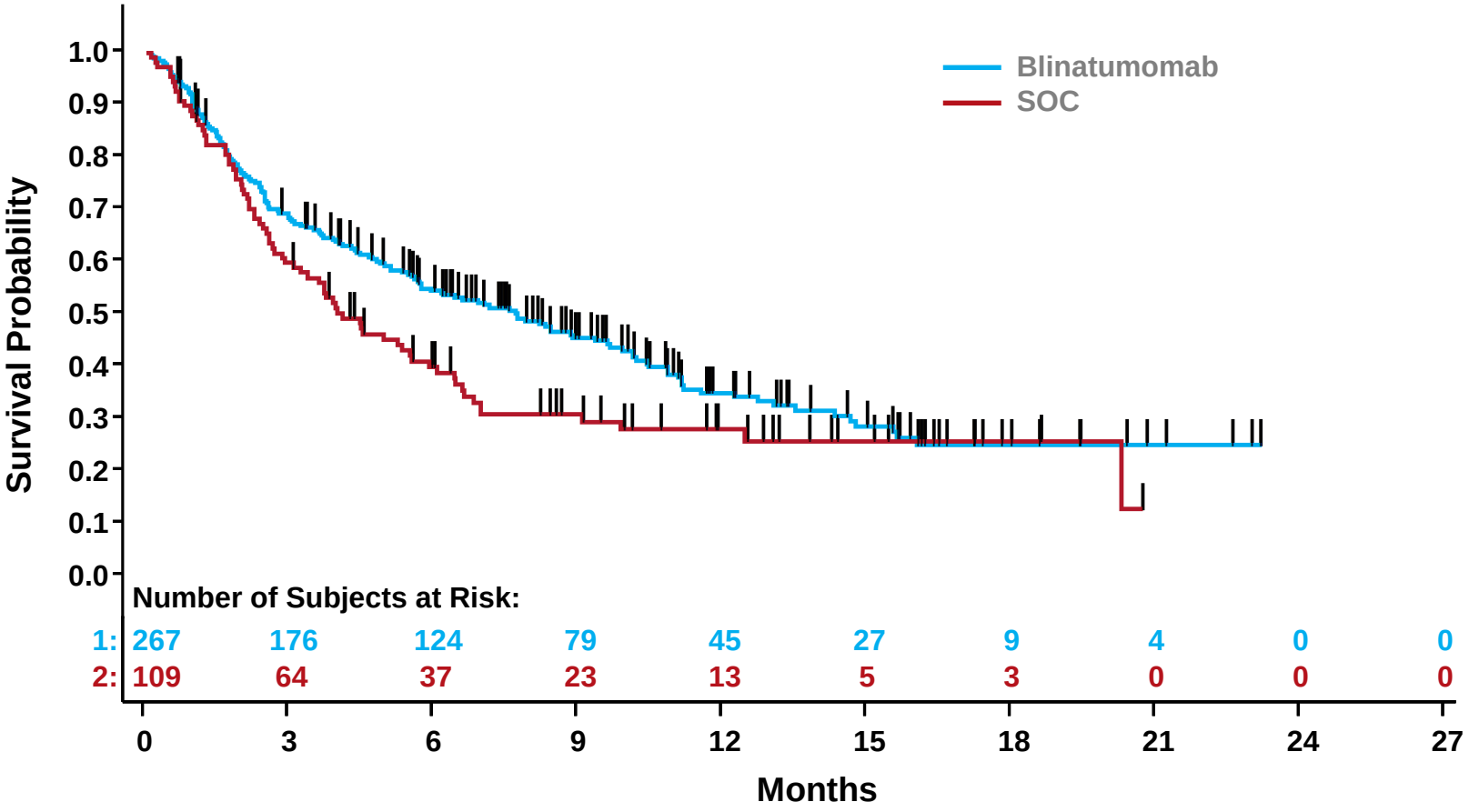
Molecular Remission Among Responders



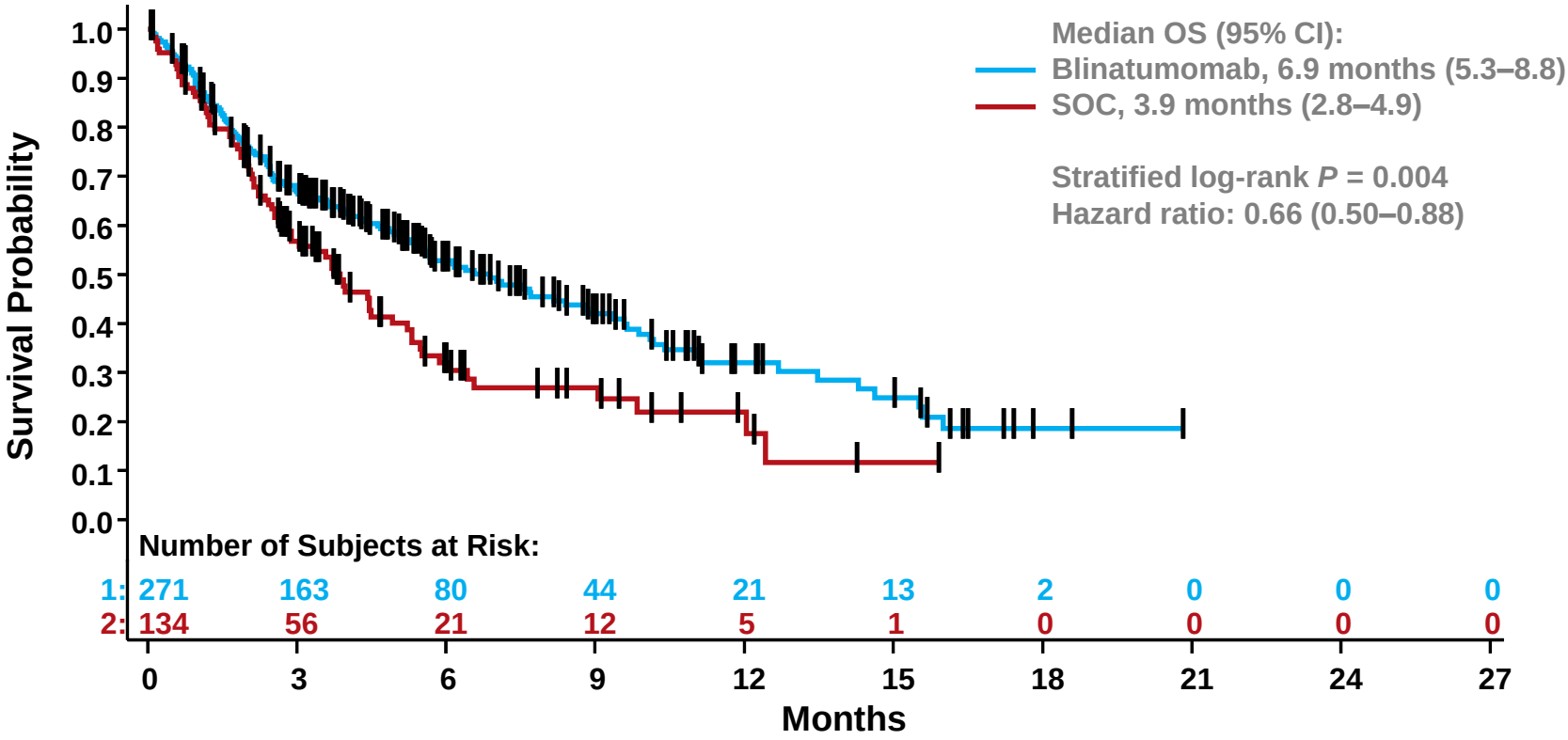
Molecular remission was defined as < 10^{-4} blasts in the first 12 weeks

CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; SOC = standard of care.

Overall Survival (as Treated)



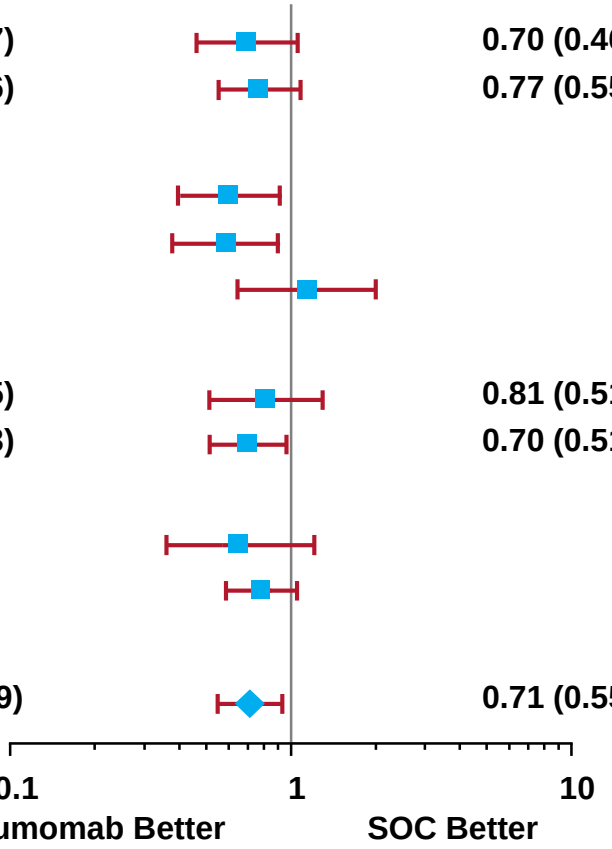
Overall Survival (OS) Censoring for alloHSCT



	Blinatumomab (N = 271)	SOC (N = 134)
alloHSCT post-baseline – n (%) (95% CI)	65 (24%) (19%–30%)	32 (24%) (17%–32%)

Overall Survival by Subgroup

Subgroup	Events/Subjects: Blinatumomab	Events/Subjects: SOC	Hazard Ratio (95% CI)
Age			
< 35 years	68/123 (55.3)	34/60 (56.7)	0.70 (0.46 1.06)
≥ 35 years	96/148 (64.9)	53/74 (71.6)	0.77 (0.55 1.08)
Prior salvage therapy			
Prior alloHSCT			
Yes	58/94 (61.7)	26/46 (56.5)	0.81 (0.51 1.29)
No	106/177 (59.9)	61/88 (69.3)	0.70 (0.51 0.96)
Baseline bone marrow blasts			
Overall	164/271 (60.5)	87/134 (64.9)	0.71 (0.55 0.93)



Pediatric or Pediatric-Inspired Regimens in Recent Adult ALL Clinical Trials

Regimen	Upper Age of Population, Yrs	OS Rate (2-7 Yrs), %
True pediatric		
▪DFCI[1]	50	67
▪CALGB 10403[2]	39	79
Pediatric inspired		
▪PETHEMA[3]	30	69
▪GRAALL-2003[4]	15-45	64
	46-60	47
▪USC[5]	57	51

1. DeAngelo DJ, et al. Leukemia. 2015;29:526-534.
2. Stock W, et al. ASH 2014. Abstract 796.
3. Ribera JM, et al. J Clin Oncol. 2008;26:1843-1849.
4. Huguet F, et al. J Clin Oncol. 2009;27:911-918.
5. Douer D, et al. J Clin Oncol. 2014;32:905-911.

Toft N et al, EHA, 2016

Age group (Median age)		Total	1-9 (3 years)	10-17 (14 years)	18-45 (26 years)	p
Patients		N=1509	N=1022	N=266	N=221	
BCP/T		N=1278/231	N=929/93	N=199/67	N=150/71	<0.001
Induction failure		N=16 0.01(±0.01)	N=10 0.01(±0.00)	N=3 0.01(±0.01)	N=3 0.01(±0.01)	0.9
Death in 1. Remission		N=50 0.03(±0.00)	N=23 0.02(±0.00)	N=15 0.06(±0.02)	N=12 0.06(±0.02)	0.002
Relapse		N=123 0.10(±0.01)	N=60 0.08(±0.01)	N=27 0.12(±0.02)	N=36 0.19(±0.03)	<0.001
Event Free Survival (SE)						
EFS overall		0.84(±0.01)	0.88(±0.01)	0.79(±0.03)	0.73(±0.03)	<0.001
Standard risk (SR)	BCP & WBC<100K & d29 MRD <0.1%	N=673 0.92(±0.01)	N=546 0.92(±0.01)	N=83 0.90(±0.04)	N=44 0.87(±0.07)	0.20
Intermediate risk (IR)	BCP & WBC<100K & d29 MRD <0.1% or T a/o WBC≥100K & d29 MRD <0.1% or dic(9;20), t(1;19), iAMP21[RUNX1]	N=542 0.86(±0.02)	N=345 0.90(±0.02)	N=103 0.82(±0.04)	N=94 0.78(±0.05)	0.002
High risk (HR)	T a/o WBC≥100K & d29 MRD ≥0.1% or KMT2A-r hypodiploidy (<45 or DI<0.85)	N=176 0.66(±0.04)	N=85 0.65(±0.05)	N=46 0.68(±0.07)	N=45 0.66(±0.08)	0.9
High risk + hSCT (HR+hSCT)	d29 MRD ≥5% a/o d79 MRD (≥0.1%)	N=100 0.71(±0.05)	N=35 0.80(±0.08)	N=30 0.74(±0.09)	N=35 0.61(±0.09)	0.12

Table 1. Cumulative risk adjusted for competing events and event free survival.
16 patients with Induction failure and 2 patients not risk grouped due to severe toxicity (1-9 and 10-17 years) were excluded in survival analysis.
N number of patients, EFS event free survival. SE standard error, SR standard risk, IR intermediate risk, HR high risk, hSCT hematopoietic stem cell transplantation.

ADULTS AND CHILDREN (1-45 YEARS) WITH PH-NEGATIVE ALL HAVE ALMOST IDENTICAL OUTCOME IN RISK-STRATIFIED ANALYSIS OF NOPHO ALL2008.

We collected information on 1509 patients from Sweden, Norway, Iceland (children only), Finland (children only), Denmark, Lithuania, and Estonia diagnosed 7/2008-12/2014 with Ph-negative ALL and treated according to the NOPHO ALL2008 protocol.

Figure 1. Risk group distribution for ALL patients 1-45 years .
Six age groups: 1-4, 5-9, 10-14, 15-17, 18-25 and 26-45 years.

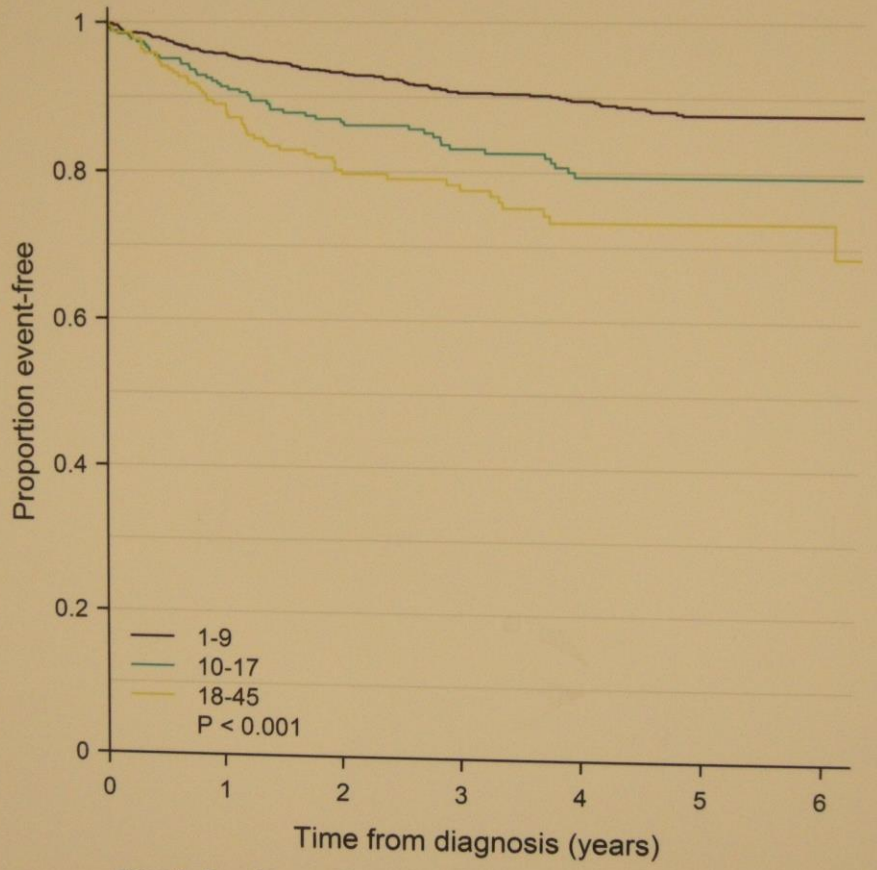
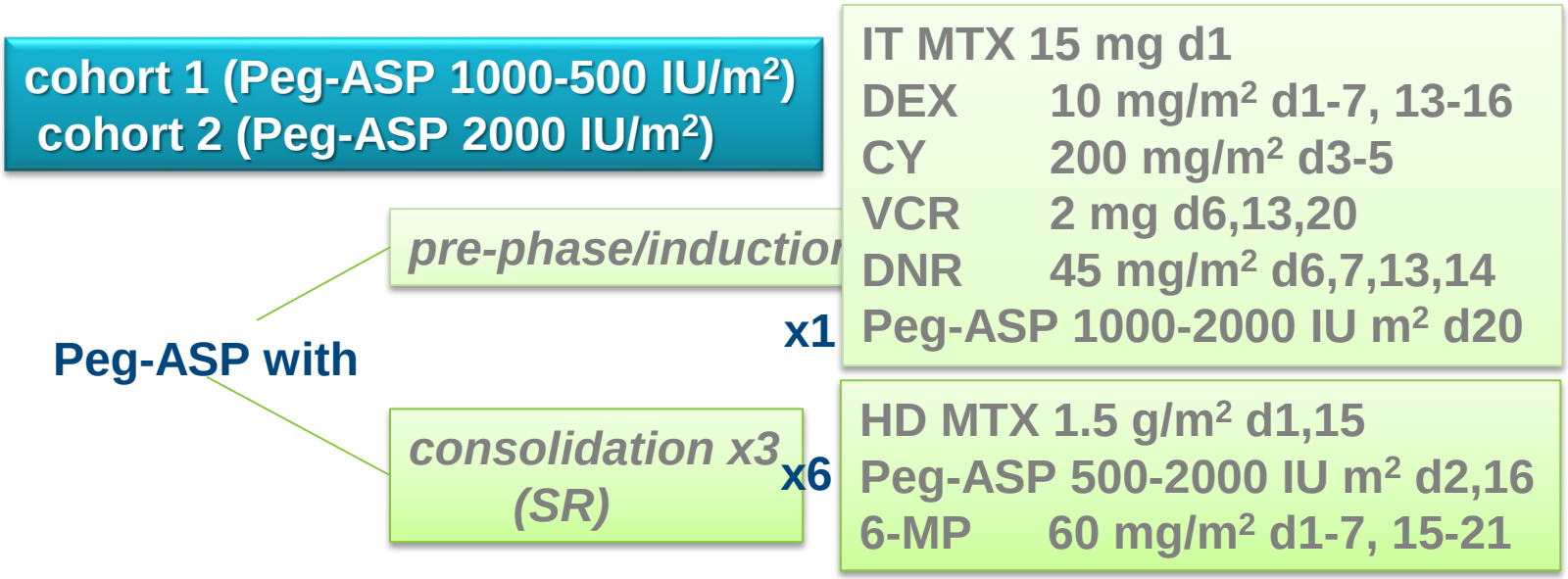


Figure 2. Event free survival (EFS) for 1509 ALL patients 1-45 years.
Three age groups: 1-9, 10-17 and 18-45 years.

Toft N et al, EHA, 2016

Peg-ASP: large German study

- **GMALL 07/2003** (Goekbuget et al, ASH 2010, abstr 494)
- **AGE 15 – 55 years**
- **N 1226**



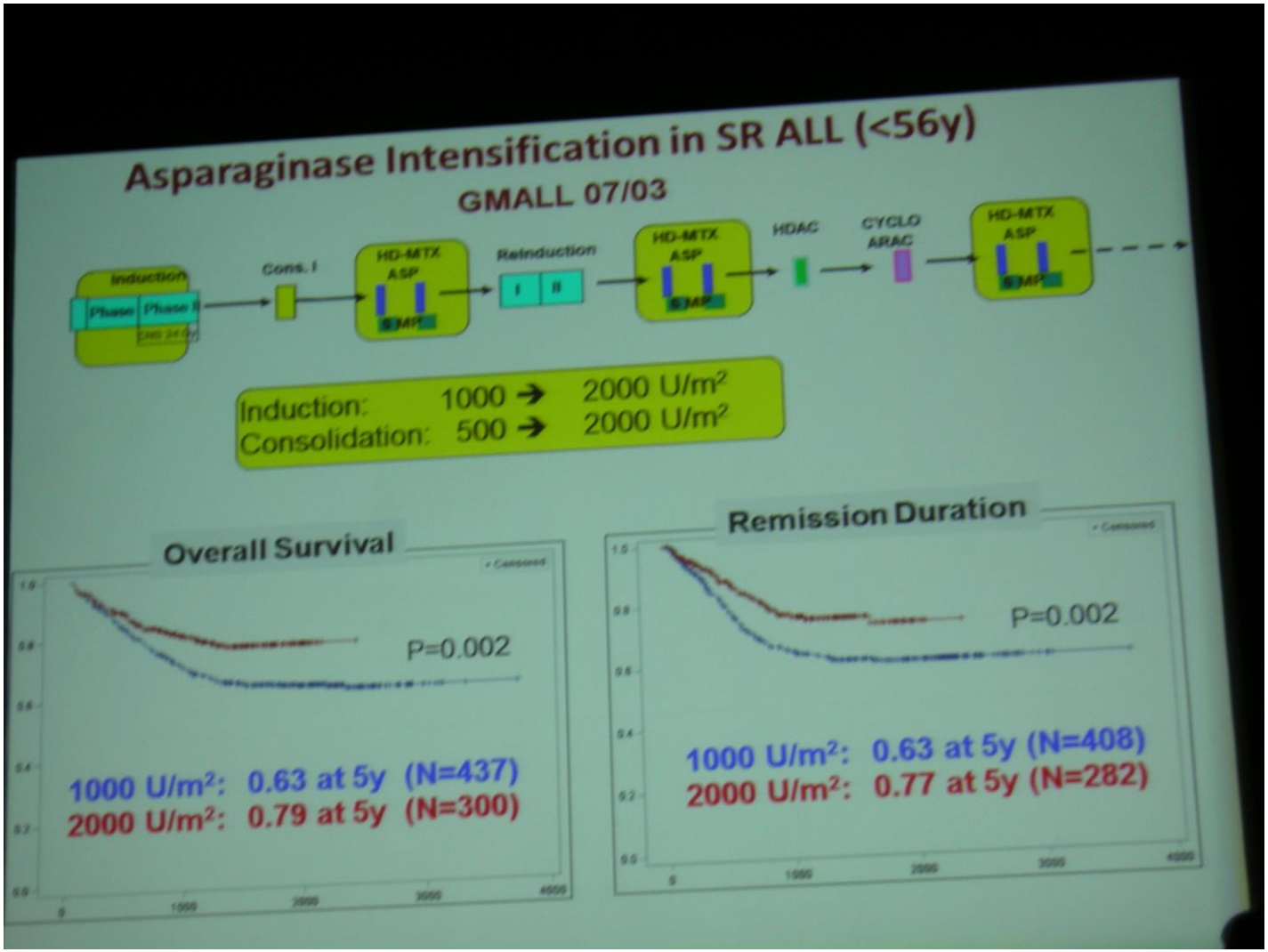
Goekbuget et al, EHA, 2016

	Cohort 1	Cohort 2	P
No.	826	400	
CR (%)	91	91	NS
MRD <10^{-4} (%)	79	82	NS
3-Y OS (%)	60	**67** (+7%)	>0.5
3-Y OS SR	68	**80** (+12%)	**0.02**
3-Y CR duration SR	61	**74** (+13%)	**0.02**
3-Y OS AYA 15-25 (y)	77	**86** (+9%)	>0.5
3-Y CR duration AYA	60	**78** (+18%)	>0.5
GIII-IV tox (%)			
got/gpt	30	30	-
bilirubin	10	16	**0.04****
thrombosis	5	5	-
hypersensitivity	<1	<1	-
amylase	5	13	-
lipase	23	15	-
glucose	10	12	-

**age >45 (P=0.005)

Goekbuget et al, EHA, 2016

Peg-Asparaginase- related effects (GMALL:EHA 2016)



Goekbuget et al, EHA, 2016

Peg-Asparaginase- related effects (GMALL:EHA 2016)

Relevant Correlations and Prognostic Factors for Liver Toxicity (Bilirubine Grade III/IV) in Induction

4 Factors are significantly correlated to liver toxicity

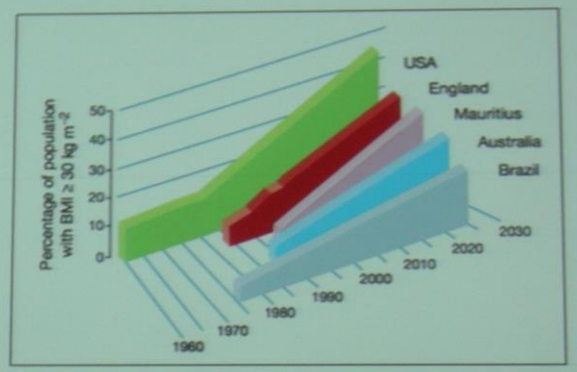
	Incidence
Dose	
1000	11%
2000	14%
Age	
<45 y	11%
>45 y	17%
BMI	
<30	11%
>30	19%
Steatosis	
No	6%
Yes	30%

Multivariate Analysis
BMI and Steatosis

Combined Risk Model:
BMI and / or Steatosis

	N	< 45 y	>45 y
None	92	2%	7%
Either	59	22%	24%

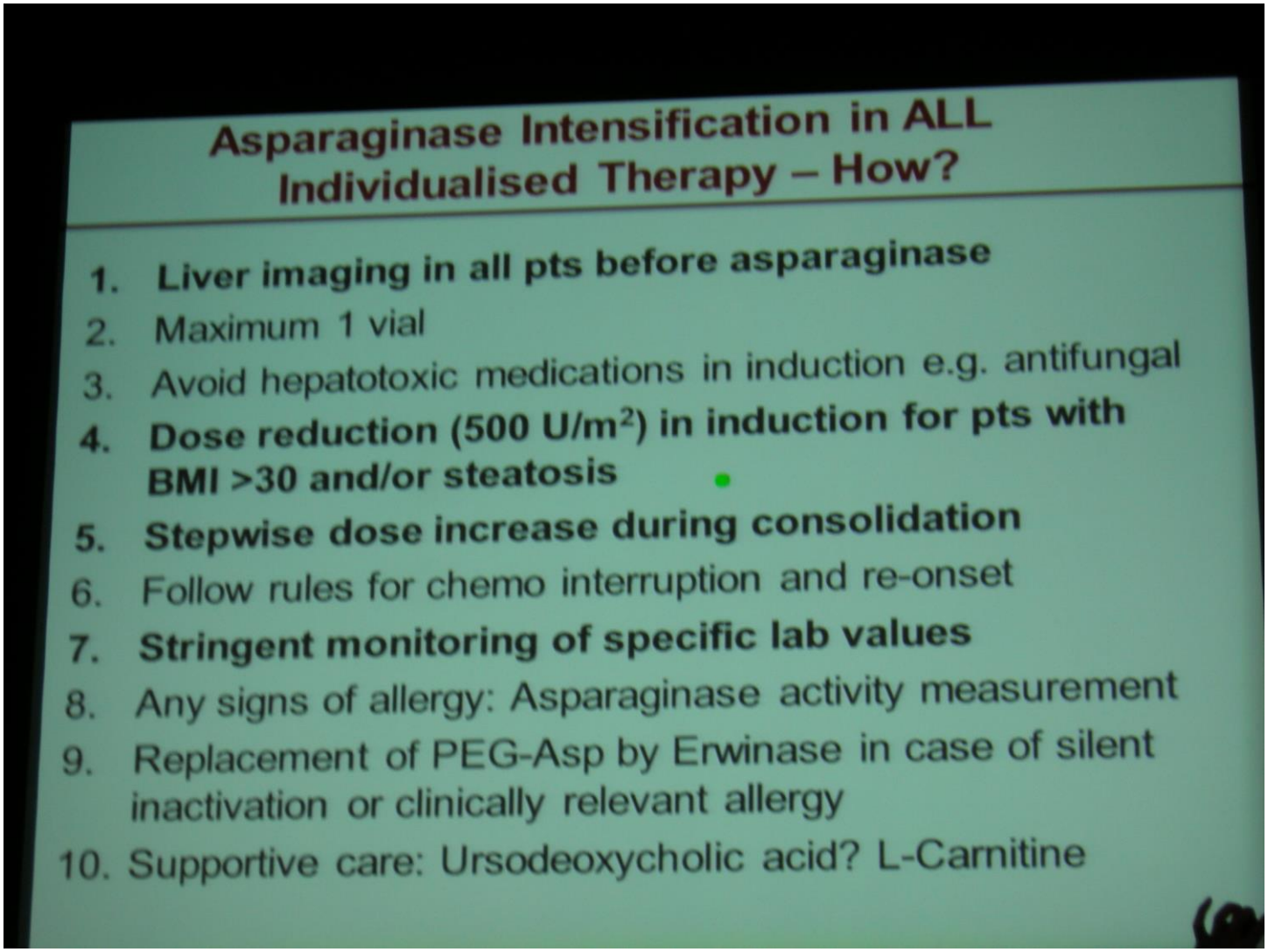
Obesity worldwide: Projection until 2030



Kopelman, Nature 2000

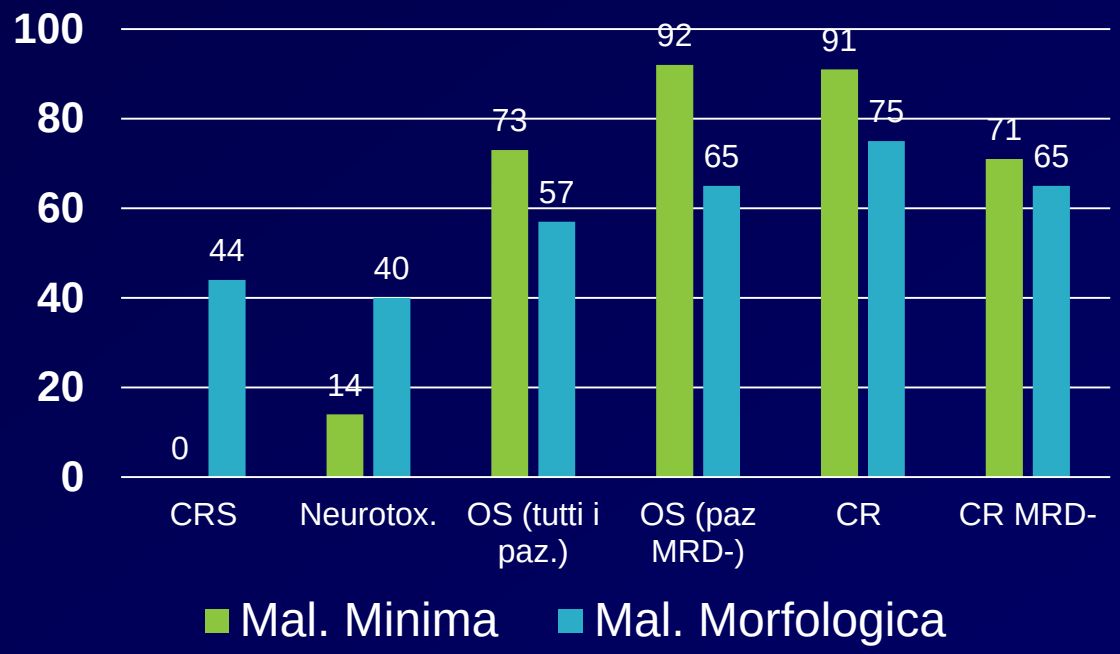
Goekbuget et al, EHA, 2016

Peg-Asparaginase- related effects (GMALL:EHA 2016)



Goekbuget et al, EHA, 2016

IMPACT OF DISEASE BURDEN ON LONG-TERM OUTCOME OF CD19-TARGETED CAR MODIFIED T CELLS IN ADULT PATIENTS WITH RELAPSED B-ALL



Park J, EHA, 2016 Abs S498

- **Ritenete i risultati dello studio Inno-Vate convincenti per la rapida introduzione di Inotuzumab-Ozogamicin nella pratica clinica ?**

- **Qual è il timing ideale dell'impiego di Blinatumomab nella ALL ?**

- **Quale età e quali comorbidità vanno considerate nell'approccio "true pediatric" o "pediatric-like" nella ALL ?**