

LAL e LAM : DAY

Stato dell'arte delle Leucemie Acute

ED. CENTRO

31 marzo 2026 Roma

Dalla diagnosi alla malattia refrattaria nel paziente Ph+

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SAPIENZA
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The history of a success

1960. Description of the Philadelphia chromosome, the first cytogenetic abnormality associated to a human cancer (CML)¹

1983-'84. Cloning of the t(9;22) translocation breakpoints from CML patients³

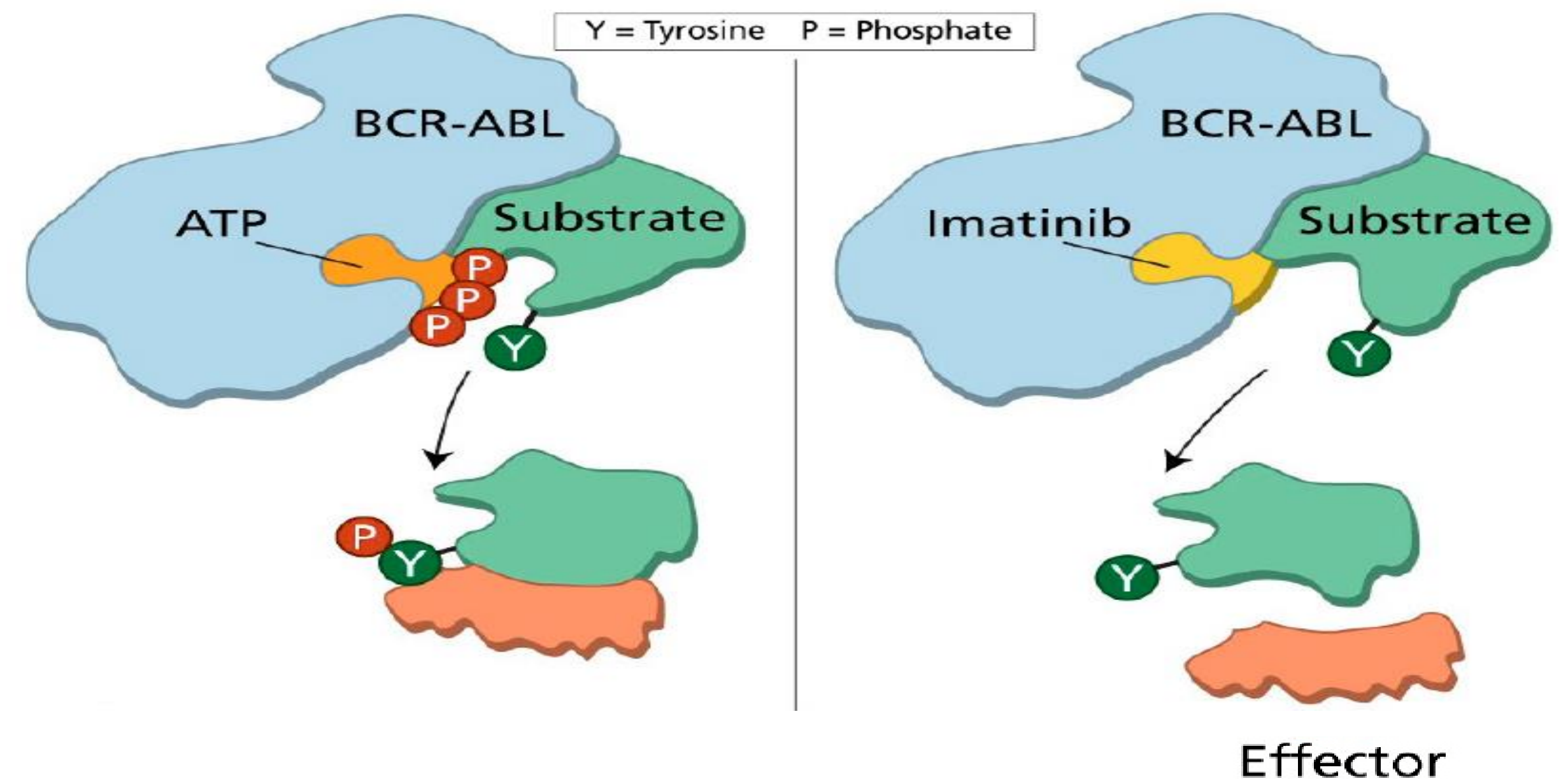
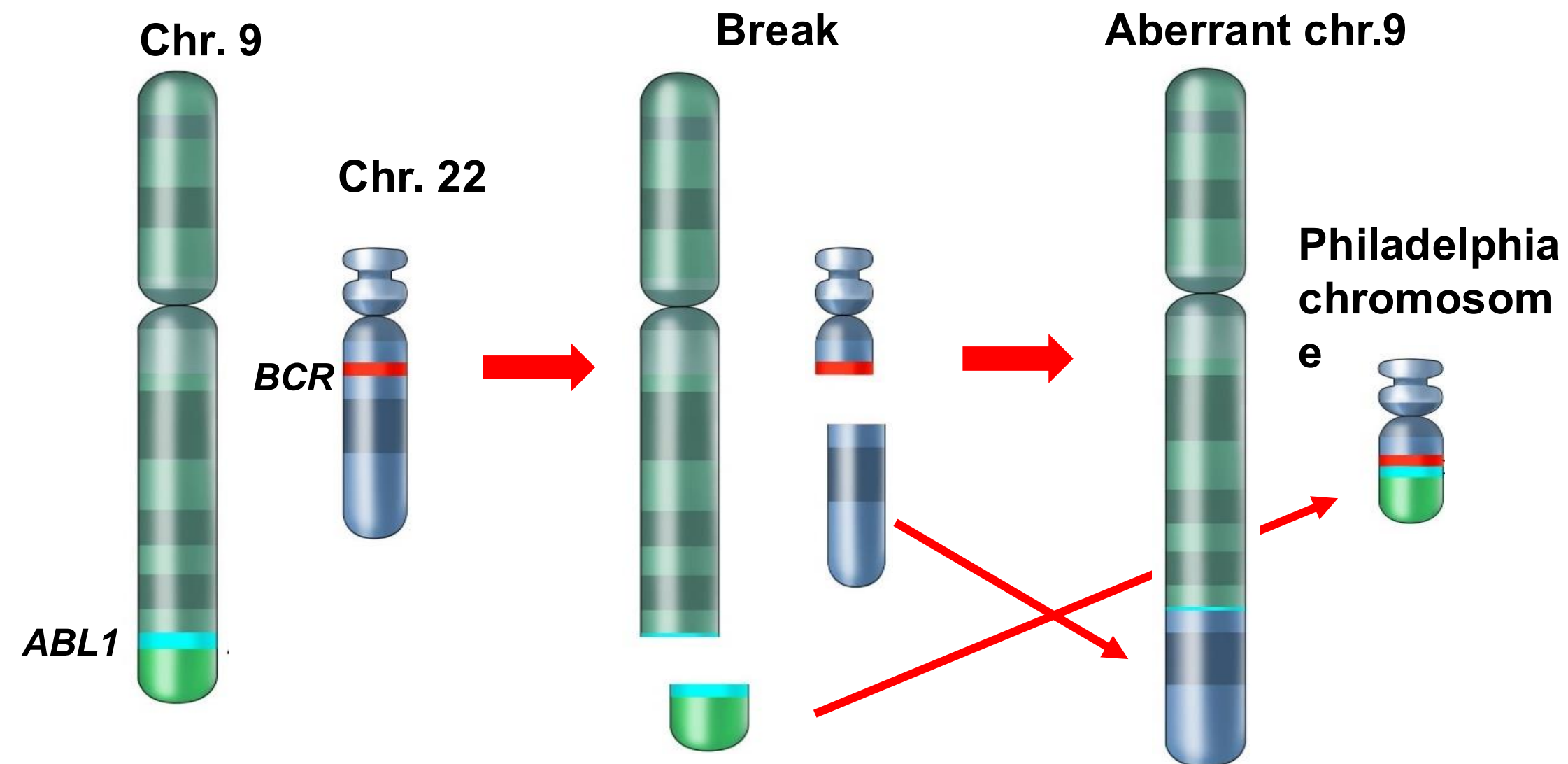
1985. Evidence that the mRNA product of the ABL gene in Ph+ CML cells was a fusion transcript of the BCR and ABL genes, and the expressed fusion protein a likely necessary step in the evolution of CML^{5,6}

2001. Identification of ST1571, a specific inhibitor of the ABL1 and c-kit tyrosine kinases and activity in CML⁸

1973. Demonstration that the abnormality arises from a chromosomal translocation²

1984. Expression of a mutant form of ABL in primary cells from CML patients with tyrosine kinase activity⁴

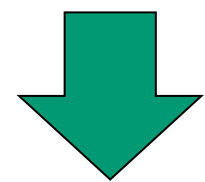
1990. Introduction of the BCR-ABL fusion gene into irradiated mice led to the development of a CML-like disease⁷



Overview

Diagnosis and first-line setting

- Pretty easy
- TKI & immunotherapy



Fusion type
IKZF1

MRD

- When and how to diagnose
- Therapeutic approach

Relapse

- A stiff way

GIMEMA ALL2820. Hematologic responses

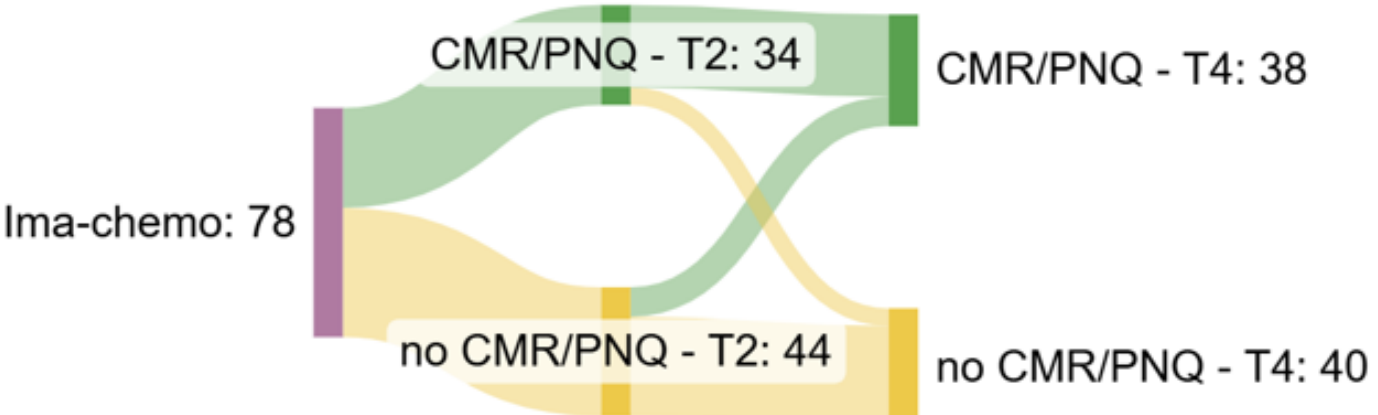
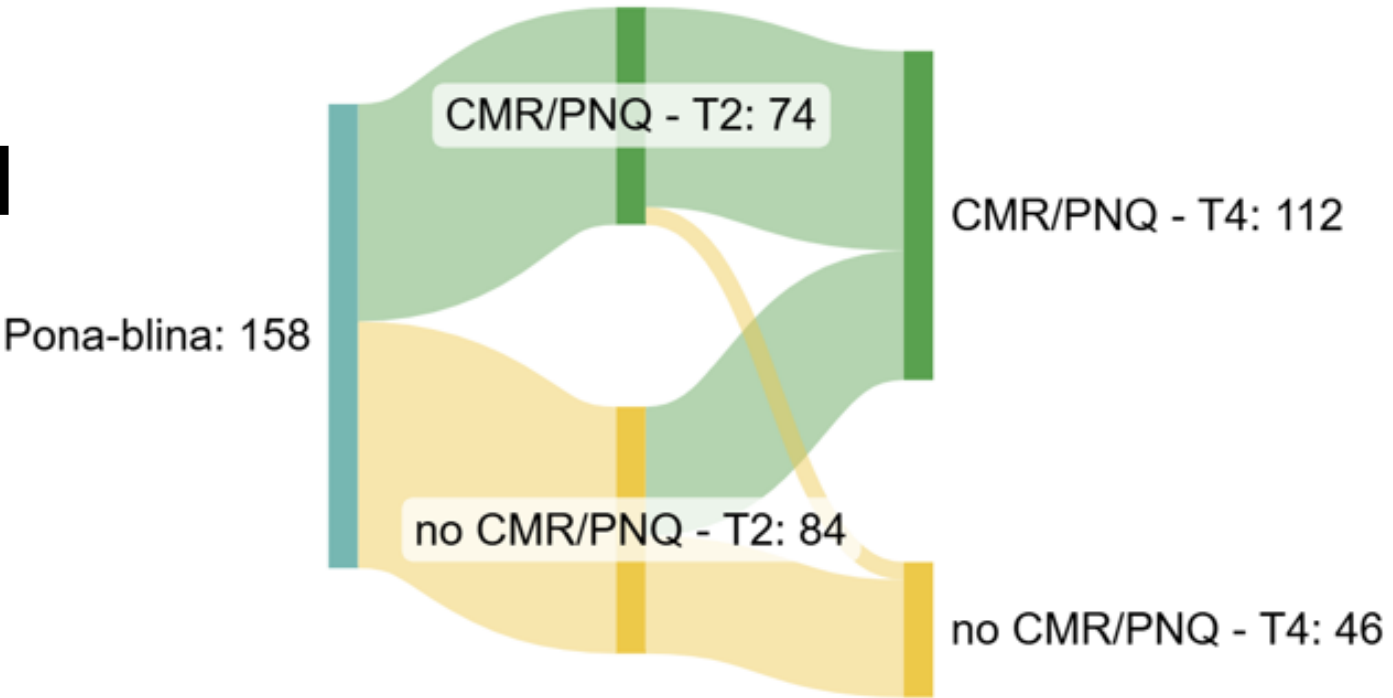
End of induction (d +70)	Experimental arm (n=158)	Control arm (n=78)	
CHR	149 (94.3%)	62 (79.4%)	p=0.001
Deaths	4 (2.5%)	7 (8.9%)	
Refractory	-	2 (2.5%)	
Off-treatment	5 (2.8%)	6 (7.6%)	
Early relapse	-	1 (1.3%)	

GIMEMA ALL2820. Molecular responses by ITT

Experimental arm (n=158)	No molecular responses (%)	CMR	PNQ	Overall molecular responses (%)	D-ALBA (n=63):	Overall molecular responses (%)
End of induction	84 (53.2)	48 (30.4)	26 (16.5)	74 (46.8)	End of induction	17 (26.9)
After 2 blina cycles	46 (29.1)	82 (51.9)	30 (19)	112 (70.9)	After 2 blina cycles	33 (52.4)
$p=ns$						
Control arm (n=78)						
End of induction	44 (56.4)	28 (35.9)	6 (7.7)	34 (43.6)		
After 4/6 CHT cycles*	40 (51.3)	29 (37.2)	9 (11.5)	38 (48.7)		

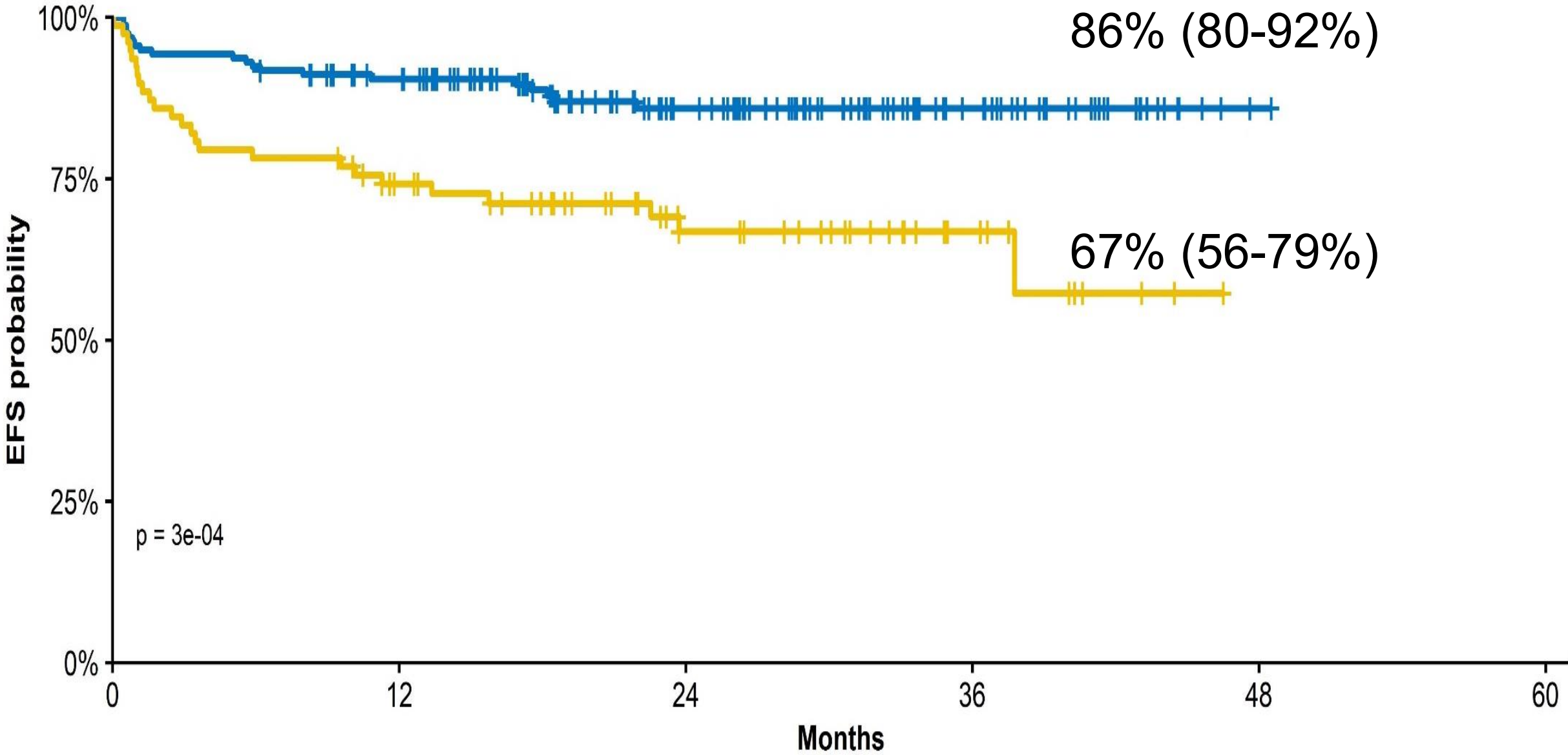
*Depending on age

$p= <0.001$

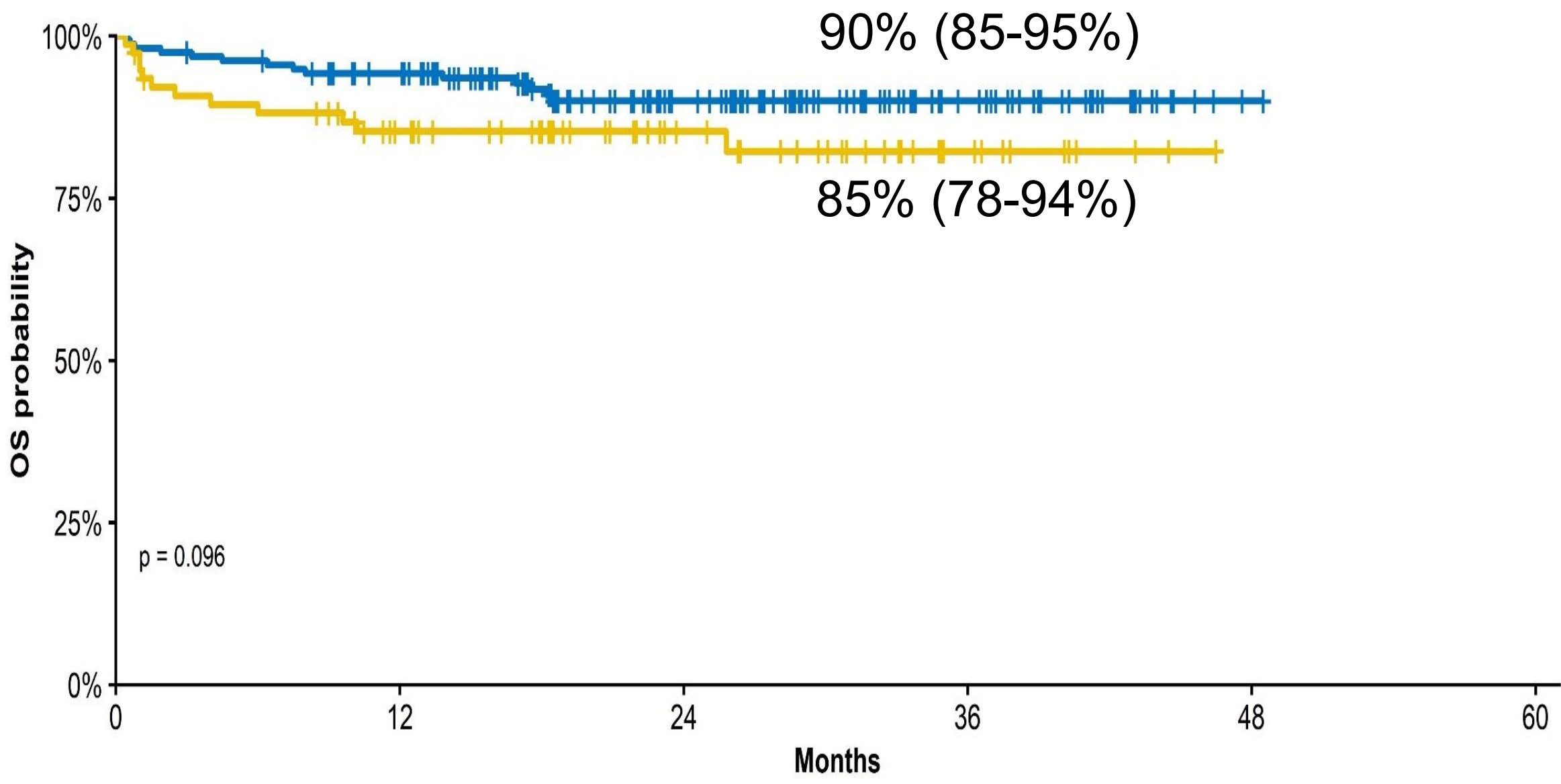


GIMEMA ALL2820. EFS and OS

EFS

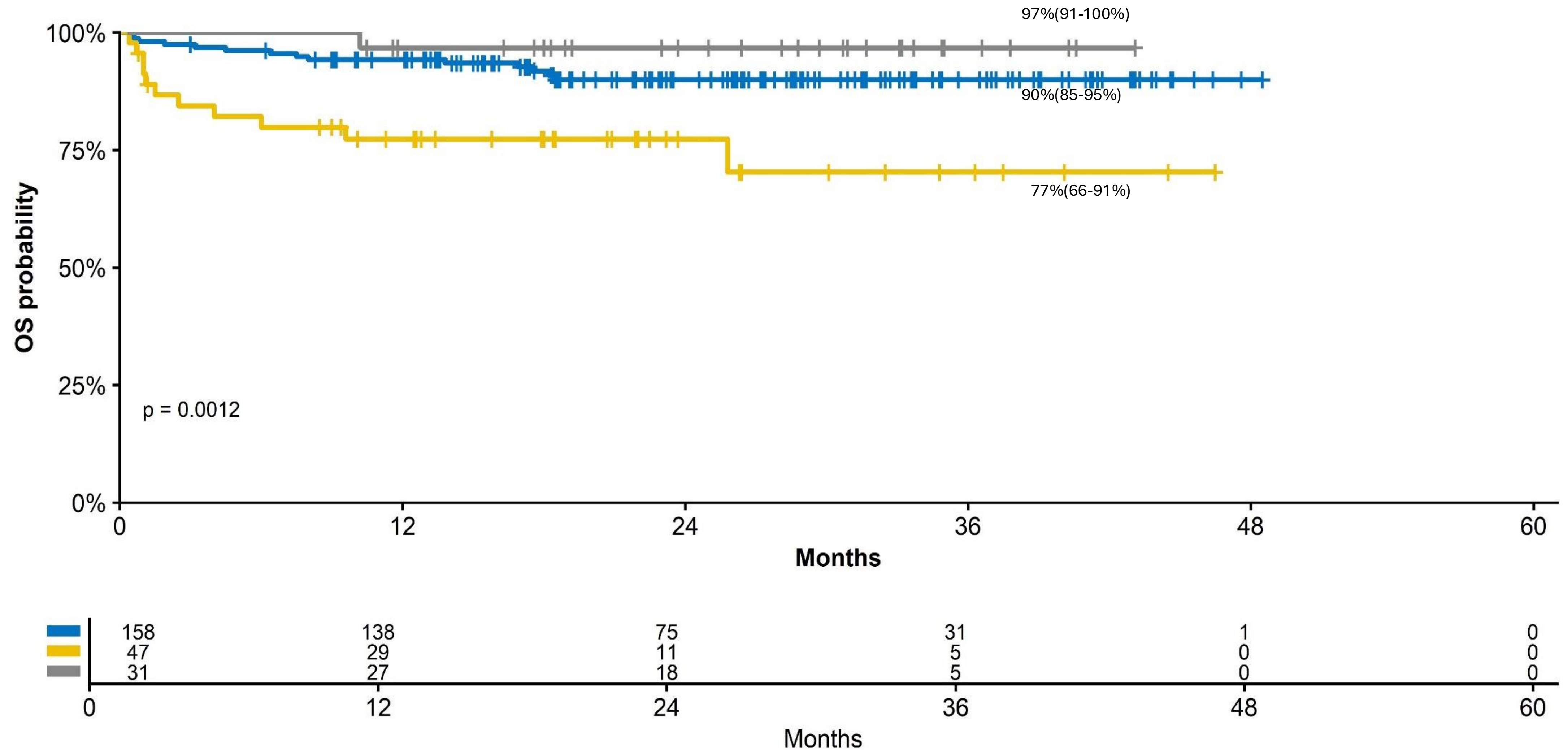


OS



Median follow-up: 23.7 months (0.1- 48.5)

GIMEMA ALL2820. OS considering crossover



— Experimental arm; — control arm; — cross over

Primary Efficacy Analysis of Phase II Study Investigating TKI and Inotuzumab Ozogamicin-Based Therapy for Newly Diagnosed Ph+ ALL (1/8)

Patel AA et al. (ASH Oral Presentation)

Methods

- This was an investigator-initiated, single-center, Phase 2 study
- Eligibility criteria: newly diagnosed Ph+ ALL, age ≥ 18 years, ECOG ≤ 2 , CD22+ on $\geq 20\%$ blasts, no CNS disease at enrollment
- Response definitions used:
 - CR = $<5\%$ blasts on bone marrow biopsy with ANC >1000 and Plt >100
 - MR3 = $\leq 0.1\%$ by *BCR::ABL1* PCR and meeting CR criteria
 - MR4 = $\leq 0.01\%$ by *BCR::ABL1* PCR and meeting CR criteria
- Primary endpoint: rate of MR3 or better after 2 courses of therapy
- DLT assessment window was Course 1

Figure 1. Initial Treatment Schema: InO + TKI

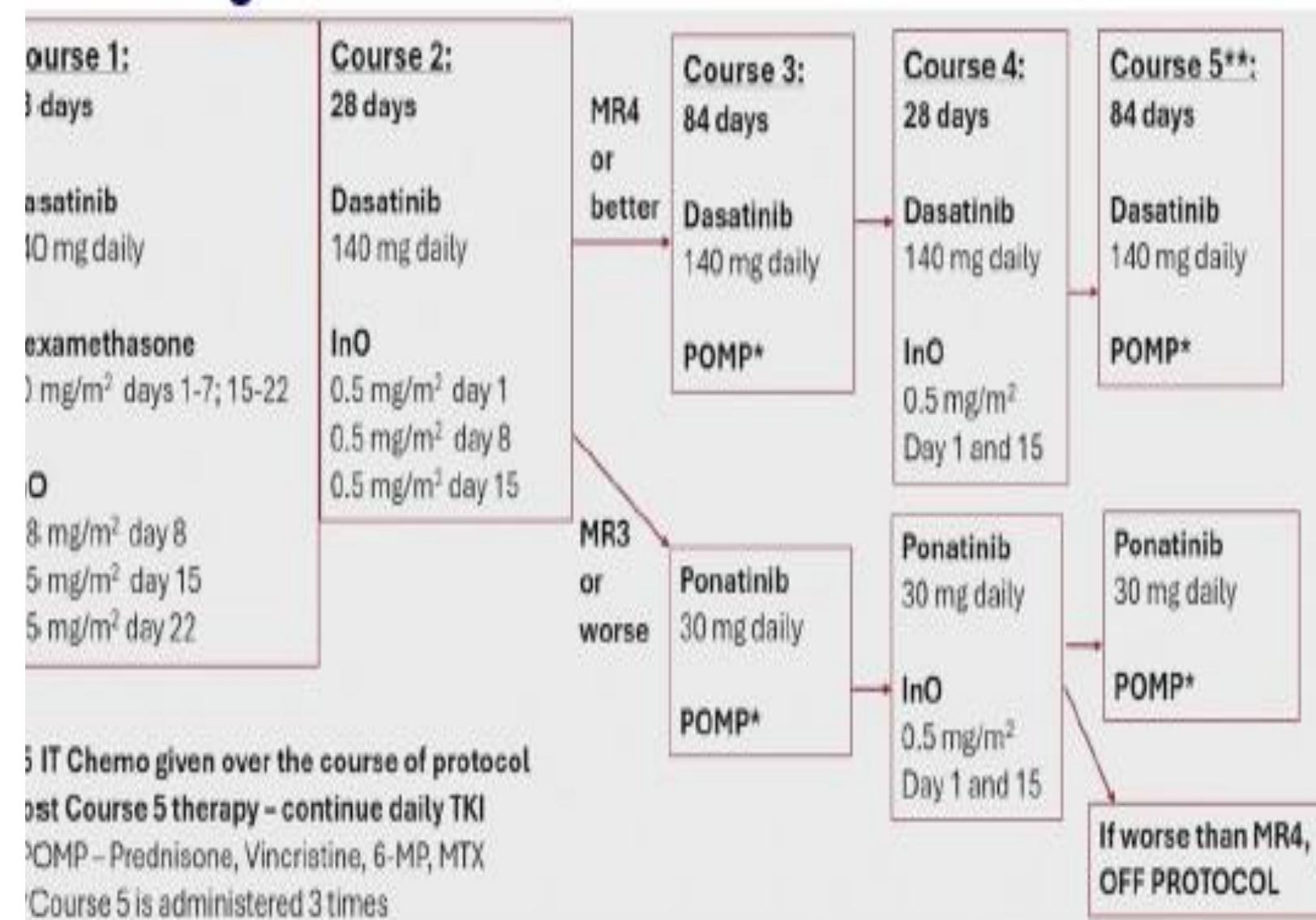
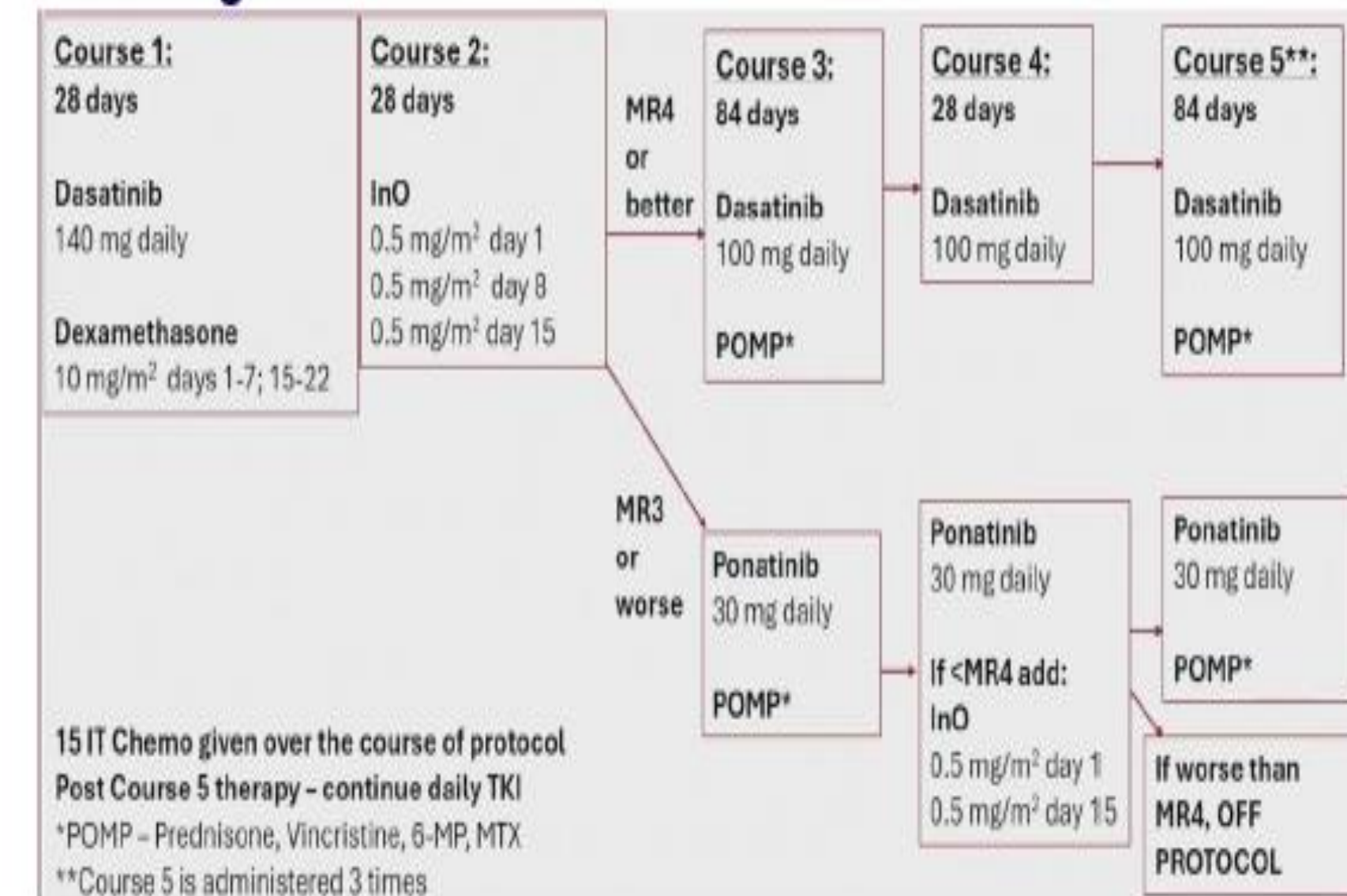


Figure 2. Revised Treatment Schema: InO + TKI



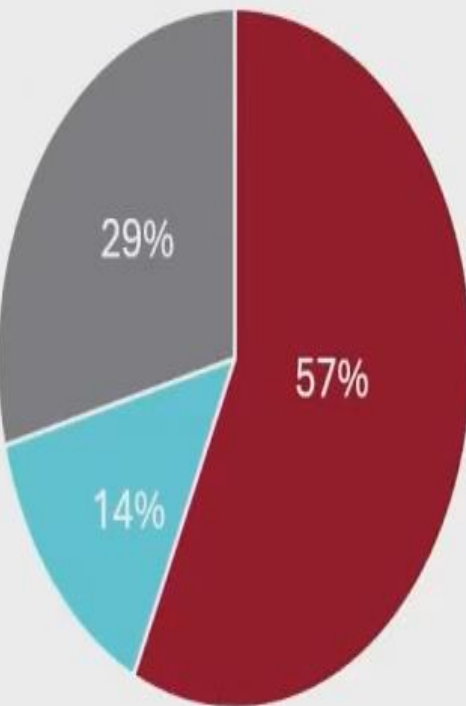
Primary Efficacy Analysis of Phase II Study Investigating TKI and Inotuzumab Ozogamicin-Based Therapy for Newly Diagnosed Ph+ ALL (1/8)

Patel AA et al. (ASH Oral Presentation)

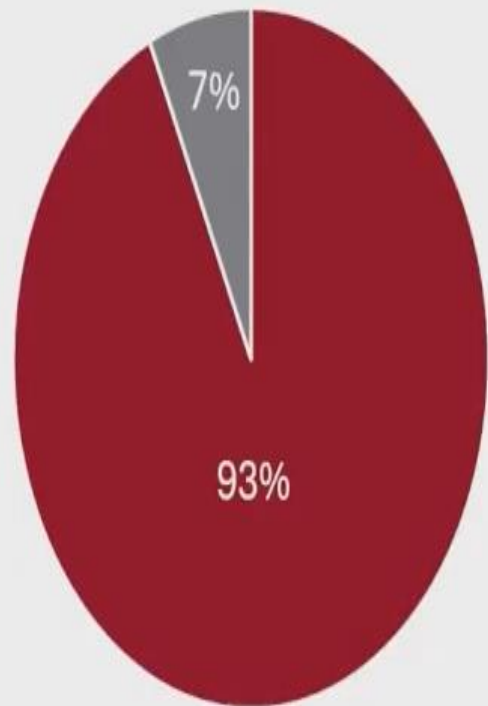
N=21	
Median (range) age, years	60 (21–79)
Female, %	57
Race/ethnicity, %	
Non-Hispanic White	53
Non-Hispanic Black	24
Hispanic	14
Not reported	10
<i>BCR::ABL1</i> transcript, %	
p190	67
p210	29
Atypical	5

Efficacy by RT-PCR – Schema 2 (n=14)

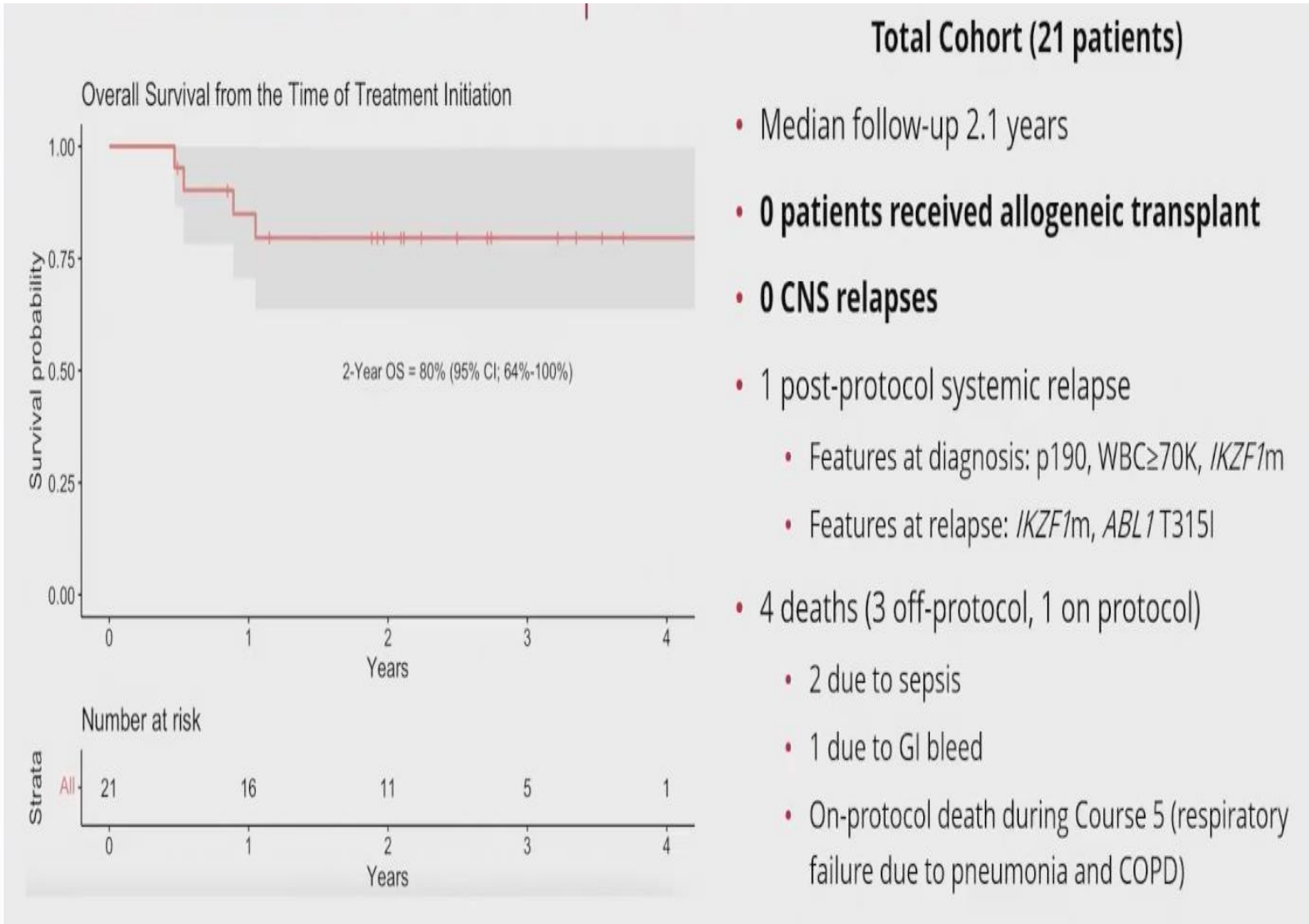
End of Course 2 Response



Best Response by End of Course 3



CR = <5% blasts on bone marrow biopsy with ANC >1000 and Plt > 100
MR3 = ≤0.1% by *BCR::ABL1* PCR and meeting CR criteria
MR4 = ≤0.01% by *BCR::ABL1* PCR and meeting CR criteria



Primary Efficacy Analysis of Phase II Study Investigating TKI and Inotuzumab Ozogamicin-Based Therapy for Newly Diagnosed Ph+ ALL (1/8)

Patel AA et al. (ASH Oral Presentation)

Toxicity Profile – Grade 3+ Events

Adverse Event	Incidence*
Anemia	19%
COVID-19	19%
Dyspnea	19%
Pneumonia	19%
Fatigue	14%
GI Bleed	14%
Nausea/vomiting	14%
Thrombocytopenia	14%

Adverse Event	Incidence*
Abdominal Pain	10%
Anorexia	10%
Bacteremia	10%
Elevated Transaminase	10%
Encephalopathy	10%
Fever	10%
Intracranial hemorrhage	10%

Adverse Event	Incidence*
Muscle Weakness	10%
Neutropenic Fever	10%
Neutropenia	10%
Pancreatitis	10%
Respiratory Failure	10%
Upper Respiratory Infection	10%
Veno-Occlusive Disease**	10%

*Grade 3+ events noted in ≥2 patients are listed

**VOD occurred 9 days after Course I and 24 days after Course II, both patients treated on Schema 1

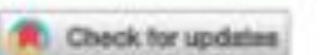
Overview

MRD

- When and how to diagnose
- Therapeutic approach

Consider previous therapy
Consider MRD fluctuations!

LEUKEMIA & LYMPHOMA
2023, VOL. 64, NO. 11, 1884–1887
<https://doi.org/10.1080/10428194.2023.2235450>



LETTER TO THE EDITOR

Digital droplet PCR for T315I BCR::ABL1 KD mutation assessment in adult Ph-positive acute lymphoblastic leukemia with a minimal residual disease increase

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A Phase IIA Study of Feasibility and Effectiveness of Inotuzumab Ozogamicin (IO) in Adult Patients with B-Cell Acute Lymphoblastic Leukemia with positive Minimal Residual Disease before any Hematopoietic Stem Cell Transplantation

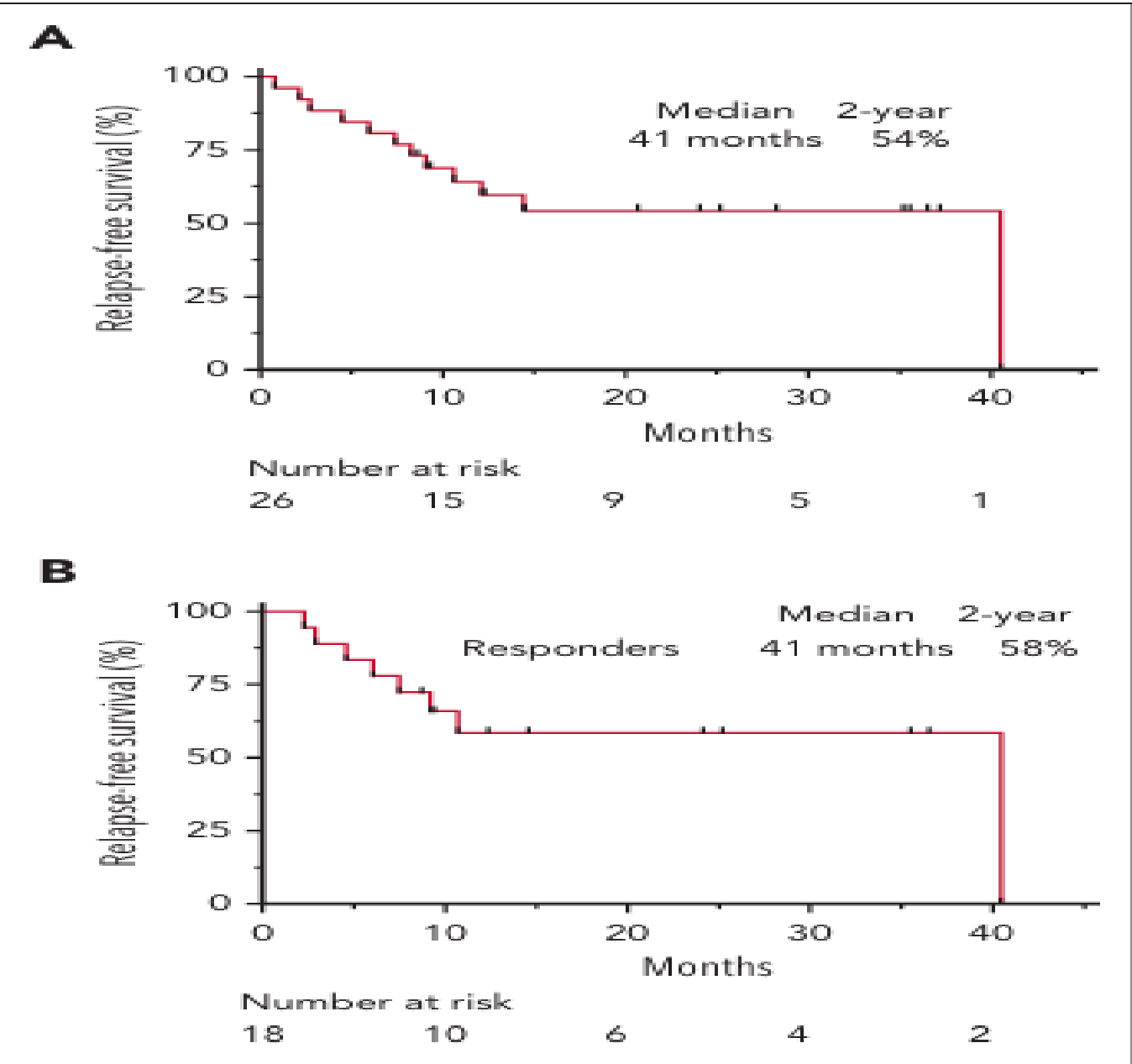
GIMEMA Study ALL2418

EudraCT number 2018-003006-32
NCT number 03610438

Trial closed to enrollment.
Both Ph- and Ph+ALL cases.
Results awaited.

Table 1. Patient characteristics

Characteristics N (%) / median [range]	Full cohort N = 26	Ph-negative B-ALL N = 10	Ph-positive B-ALL N = 16
Age (y)	46 [19-70]	43 [19-67]	46 [26-70]
Sex			
Males	12 (46)	5 (50)	7 (44)
Females	14 (54)	5 (50)	9 (56)
Remission status			
CR1	19 (73)	5 (50)	14 (88)
≥CR2	7 (27)	5 (50)	2 (13)
Prior therapy			
Blinatumomab	13 (50)	4 (40)	9 (56)
ASCT	5 (19)	3 (30)	2 (13)
CAR T cells	1 (4)	1 (10)	0
Preinotuzumab MRD			
MFC (%)	0.03 [0-1.24]	0.21 [0.05-1.24]*	0.001 [0-1.15]
BCR::ABL1 (%)	—	—	0.22 [0-18.97]†
BCR::ABL1 TKI‡			
Ponatinib			14 (88)
Dasatinib			2 (13)
CD22 on flow MRD	96.6 [62.9-99.9]	93.3 [65-99.9]	97.1 [62.9-99.9]
Median number of cycles on therapy	3 [1-6]	3 [1-5]	4 [1-6]



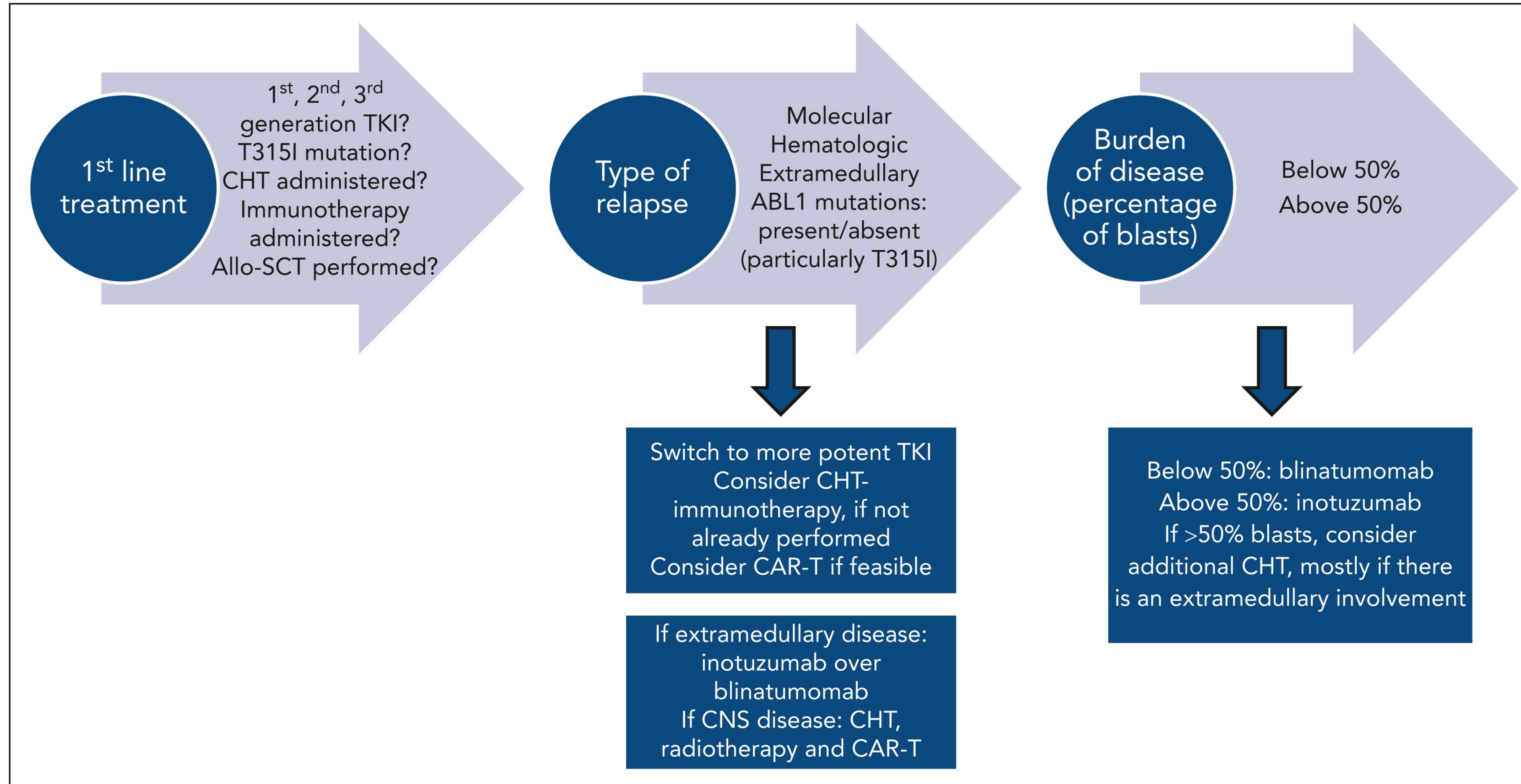
2 VOD occurred, both
in Ph+ ALL cases

Overview

Relapse

- A stiff way

General considerations



CHR re-achievement

How to reinduce it
(and bridging)?

CAR-T?

Not a definitive must,
but an effective
option

Allogeneic
transplant?

Depending on patient's features
(fitness, etc) and on previous
transplant

INO-TRANSIT: Inotuzumab Ozogamicin Treatment Prior to Chimeric Antigen Receptor T-Cell Therapy in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia: Real-World Patient Characteristics and Outcomes in Spain, the UK and US (1/7)

Martínez-Cibrian N et al. (ASH Poster Presentation)

Objective

To describe real-world demographics, clinical characteristics, and treatment outcomes in patients with R/R B-ALL treated with InO prior to CAR-T

Results: Patients

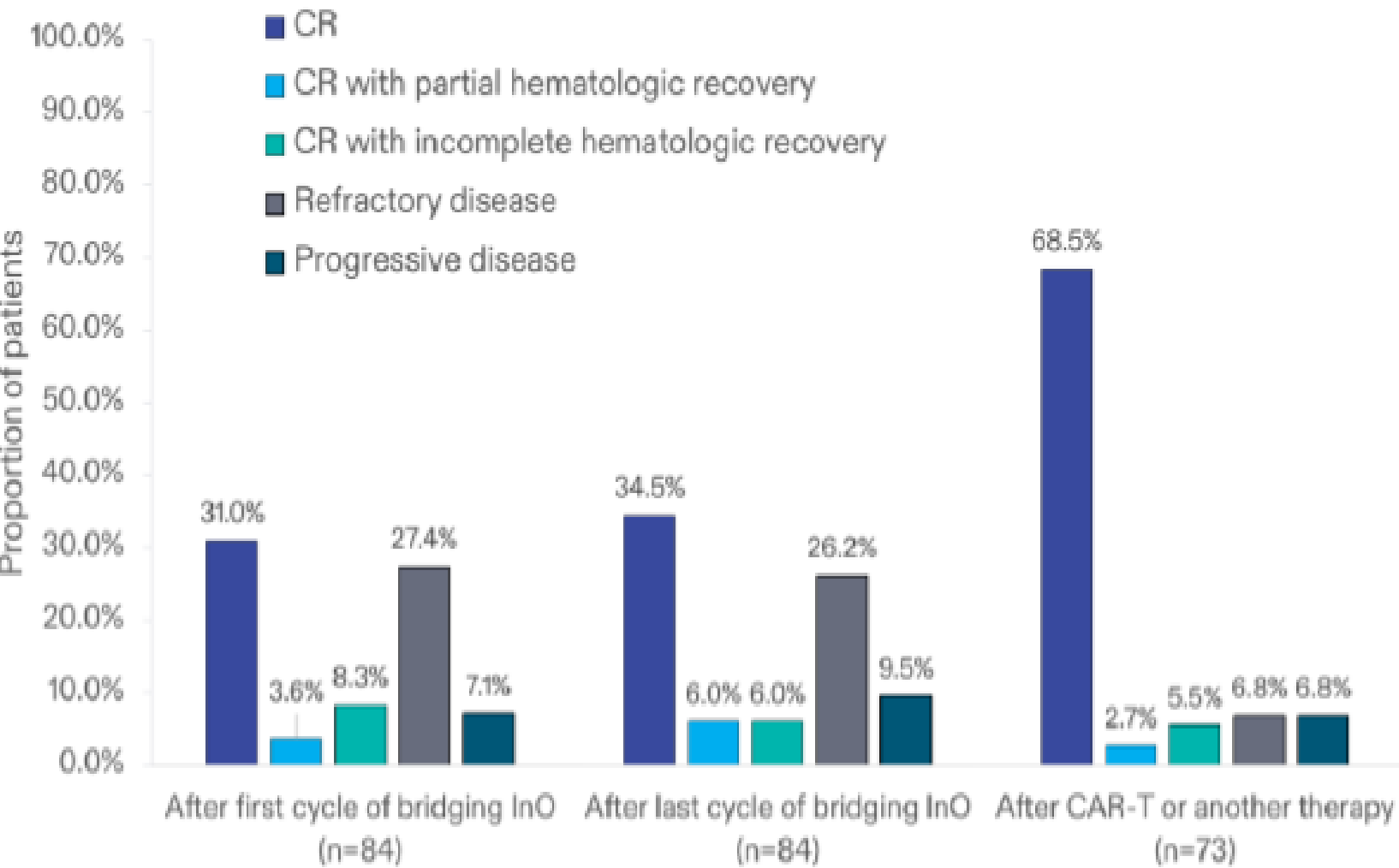
- Overall, 84 patients were analyzed
 - Patients received a median (range) of 2.0 (1–9) lines of salvage therapy
 - 14.3% of patients were Philadelphia chromosome-positive

Table. Patient Clinical Characteristics

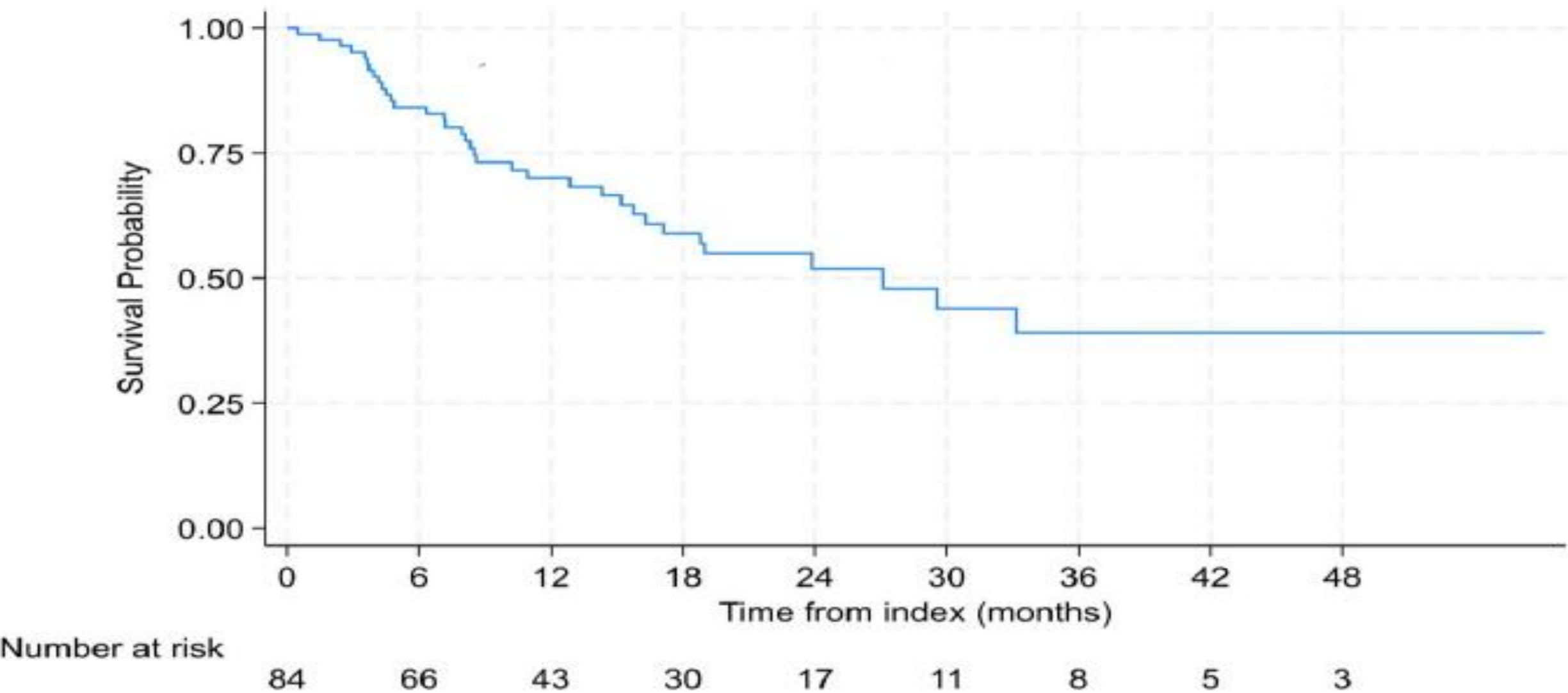
	N=84		N=84
Median (range) age, years	40.0 (18–76)	Treatments received prior to bridging InO,* n (%)	
Male, n (%)	48 (57.1)	Vincristine	70 (83.3)
Ethnicity,* n (%)		Dexamethasone	58 (69.0)
White	66 (78.6)	Cytarabine	57 (67.9)
Other†	15 (17.9)	Methotrexate	56 (66.7)
Not known	4 (4.8)	Intrathecal chemotherapy	56 (66.7)
Patient disease status at receipt of salvage therapy,‡ n (%)	n=149§	Daunorubicin	42 (50.0)
Relapsed	109 (73.2)	Cyclophosphamide	42 (50.0)
Refractory	38 (25.5)	L-asparaginase	38 (45.2)
EMD at R/R ALL diagnosis, n (%)	17 (20.2)	Prednisolone	36 (42.9)
Cytogenetic/molecular features at index,* n (%)		Hematopoietic stem cell transplant	30 (35.7)
Philadelphia chromosome-positive	12 (14.3)	Blinatumomab	26 (31.0)
BCR-ABL1-like ALL	5 (6.0)	Mercaptopurine	26 (31.0)
Other cytogenic abnormalities¶	33 (39.3)	InO (not including InO prescribed as bridge therapy to HSCT or CAR-T)	4 (4.8)
None/not recorded	7 (8.4)		

INO-TRANSIT: Inotuzumab Ozogamicin Treatment Prior to Chimeric Antigen Receptor T-Cell Therapy in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia: Real-World Patient Characteristics and Outcomes in Spain, the UK and US (1/7)

Martínez-Cibrian N et al. (ASH Poster Presentation)



>40%OR after ino



1-yr OS after CAR-T: 72.5%

Results: Safety

- At any point during diagnosis and treatment, 7.1% of patients had VOD, 4.8% had suspected VOD, and 46.4% were diagnosed with neutropenic sepsis
- There were 35 deaths, 82.9% of which were related to ALL disease progression and 11.4% were related to ALL treatment-related causes

VOD

VOD/SOS grading (1)

Endpoints	VOD Grade			
	Mild ^b	Moderate ^b	Severe ^b	Very Severe ^c
Time since first clinical symptoms of VOD ^d	>7 days	5–7 days	≤4 days	Any time
Bilirubin, mg/dL	≥2 and <3	≥3 and <5	≥5 and <8	≥8
Bilirubin, μmol/L	≥34 and <51	≥51 and <85	≥85 and <136	≥136
Bilirubin kinetics	Doubling within 48 h			
Transaminases	≤2× normal	>2 and ≤5× normal	>5 and ≤8× normal	>8× normal
Weight increase	<5%	≥5% and <10%	≥5% and <10%	≥10%
Renal function	<1.2× baseline at transplant	≥1.2 and <1.5× baseline at transplant	≥1.5 and <2× baseline at transplant	≥2× baseline at transplant or other signs of MOD/MOF

Prophylactic measure to prevent VOD/SOS (1)

Preventing VOD

- Avoid HCT conditioning regimens containing dual alkylating agents, thiotepa, or both
- Use prophylactic agents (e.g., ursodiol)
- When possible, avoid hepatotoxic agents (e.g., azoles) in combination with high-dose alkylator-condition administration
- In patients proceeding to HCT, limit treatment with InO to 2 cycles

Monitoring for VOD

- In patients who have experienced prior confirmed severe or ongoing VOD, follow recommendations in country-specific prescribing information to determine appropriate use of InO
- Monitor patient weight for fluid retention daily
- More frequently monitor LFTs and look for clinical signs and symptoms of hepatotoxicity in patients who develop abnormal LFTs
- Before and after each InO dose, monitor ALT, AST, total bilirubin, and alkaline phosphatase levels and adjust InO dose as recommended (Table 3)
- In patients proceeding to HCT, closely monitor LFTs during the first month post-HCT, then less frequently thereafter based on standard practice

ALT alanine aminotransferase, AST aspartate aminotransferase, HCT hematopoietic cell transplantation, InO inotuzumab ozogamicin, LFT liver function test, ULN upper limit of normal, VOD veno-occlusive disease

Predictive markers of VOD/SOS (2)

Biomarker	Reference(s)
Broad-spectrum/multiple mechanism	
Panel of changes in tumorigenicity-2, angiopoieten-2, L-ficolin, hyaluronic acid, and VCAM-1	[68]
↓ L-ficolin plasma level	[83]
Genetic polymorphisms	
MTHFR C677T/A1298C	[84]
Heparanase single nucleotide polymorphisms	[85]
Hematologic and endothelial	
↓ Protein C levels	[86–88]
↓ Antithrombin III levels	[13,87]
↓ Type III procollagen and tPA	[88]
↑ PAI-1 antigen levels	[13,65–67]
↑ Extra-cellular endothelial vesicles CD144 ⁺	[13]
↑ vWF, thrombomodulin, soluble IAM-1 ⁺	[89]
Hepatic/splenic	
↑ Maximum total serum bilirubin/bilirubin increase at any point in time	[90]
↑ Total bilirubin, D-dimer	[67]
↑ Hepatocyte growth factors/with/without IL-6	[91]
↑ APRI	[70]
↑ Splenic volume	[71]
↑ Panel of liver fibrosis indices: API, APRI, PSR, FIB-4 [†]	[69]
Inflammatory/immune response	
↑ IL-6, IL-10, TNF-α plasma levels [†]	[92]
↑ IL-6 plasma level at + day 7 post-HSCT	[93]
↓ IGF and IGFBP-3 plasma levels	[94]

API indicates age-platelet index; APRI, aspartate aminotransferase-to-platelet ratio; FIB-4, fibrosis-4; IAM, intercellular adhesion molecule; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; PAI, plasminogen [84] activator inhibitor; PSR, platelet-to-spleen ratio; tPA, tissue plasminogen activator; vWF, von Willebrand factor; VCAM, vascular cell adhesion molecule.

+ Stiffness

1 Kebriaei P et al, BMT 2018; 2 Corbacioglu S et al, BBMT 2019

Points of improvement

Incidence and outcome of peri-Allo SCT VOD/SOS after inotuzumab

Correlation with disease features (disease status, molecular features, previous treatment)

Correlation with patients' features (age, gender, BMI/weight)

Prophylactic therapeutic measures (ursodeoxycholic acid, carnitine, N-acetylcysteine)

Subsequent or previous allogeneic transplant

Take home messages

1° line therapeutic approach should be based on TKI plus immunotherapy. Allo-SCT reserved to selected cases

MRD/relapse: different options depending on previous therapy and type of relapse

For CAR-T in overt relapse: inotuzumab represents a valuable option; high debulking power, no target competition, most patients leukemia-free at CAR-T infusion

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