

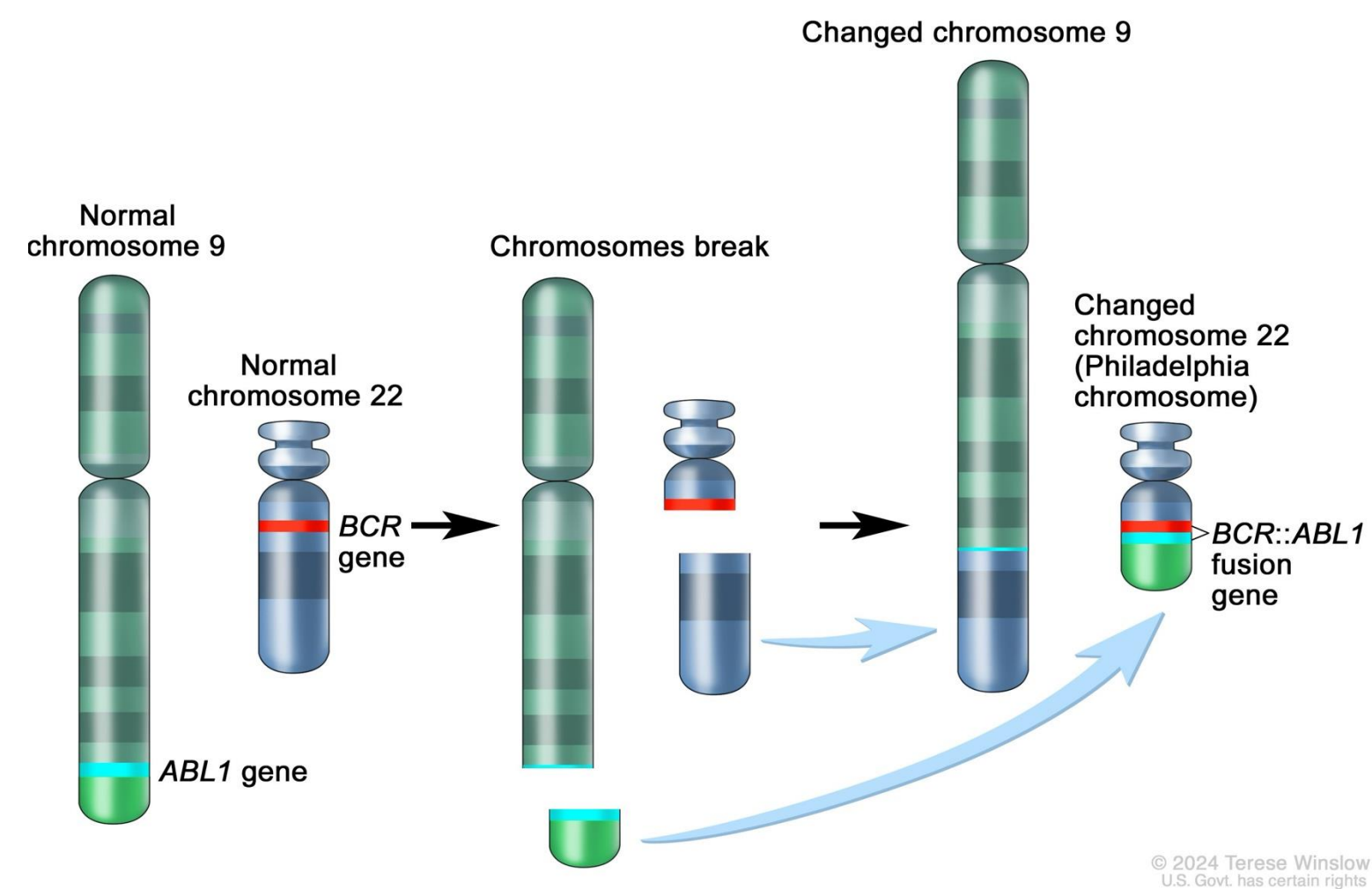
LAM E LAL DAY 2026 - STATO DELL'ARTE DELLE LEUCEMIE ACUTE

NAPOLI 8 APRILE

DALLA DIAGNOSI ALLA MALATTIA REFRATTARIA NEL PAZIENTE PH+

ANGELA GRAVETTI

AORN CARDARELLI - NAPOLI



t(9;22)(q34;q11) → BCR::ABL1

- Presenza di BCR:ABL1 definisce un sottotipo ad alto rischio “storico”.
- Trascritti principali: p190 (più tipico in ALL) e p210 (più tipico in CML, ma possibile in ALL).
- NUOVE PROSPETTIVE:
 Risposta molecolare profonda (MRD-) con combinazioni TKI + immunoterapia.
 Individuare cloni resistenti/mutazioni
 Monitoraggio MRD (PcR vs NGS)
 Aberrazioni citogenetiche e/o molecolari aggiuntive
 (delezione IKZF1, geni CDKN2A e PAX5 – ovvero IKZF1plus)

WORK UP DIAGNOSTICO

Checklist pratica (prime 24–72h)

- Emocromo, striscio, biochimica, coagulazione ($\pm$ DIC)
- Aspirato/biopsia midollare: morfologia + immunofenotipo (flow)
- Citogenetica convenzionale + FISH (t(9;22))
- RT-qPCR per BCR::ABL1 (tipo di transcript + baseline quantitativa)
- MRD baseline (IG/TR e/o NGS se disponibile)
- Profilo mutazionale (NGS, incl. ABL1 KD) – almeno al fallimento
- Valutazione SNC: clinica + profilassi intratecale secondo protocollo
- Valutazione fitness/comorbidità (trapianto, tossicità TKI)

Diagnosi

- Immunofenotipo B-ALL
- BCR::ABL1 confermato (FISH/RT-qPCR)
- Transcript (p190/p210) riportato

Baseline per MRD

- Valore quantitativo BCR::ABL1
- Assay MRD definito e replicabile
- Timepoint programmati (es. fine induzione, post-blina, pre-HSCT)

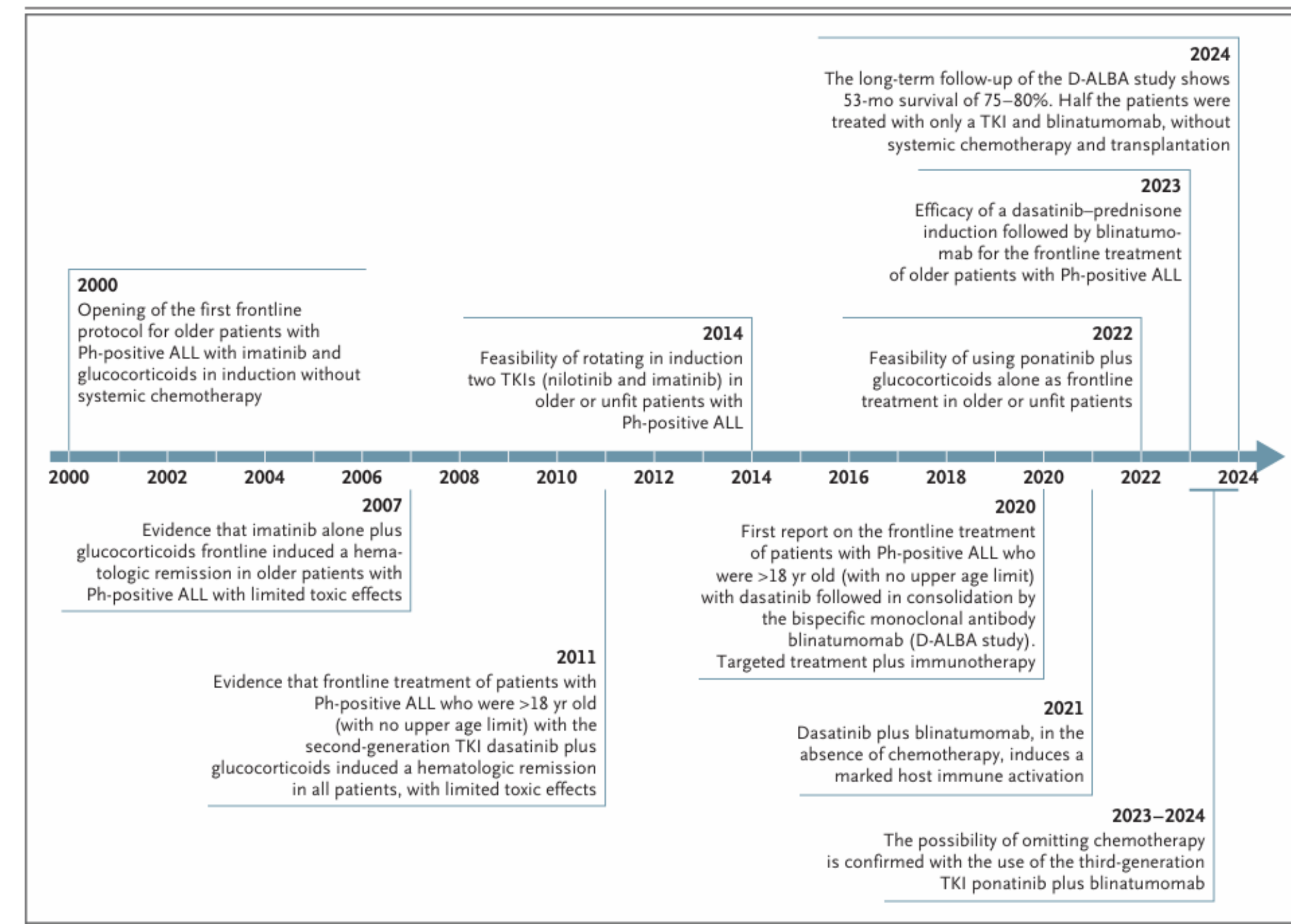
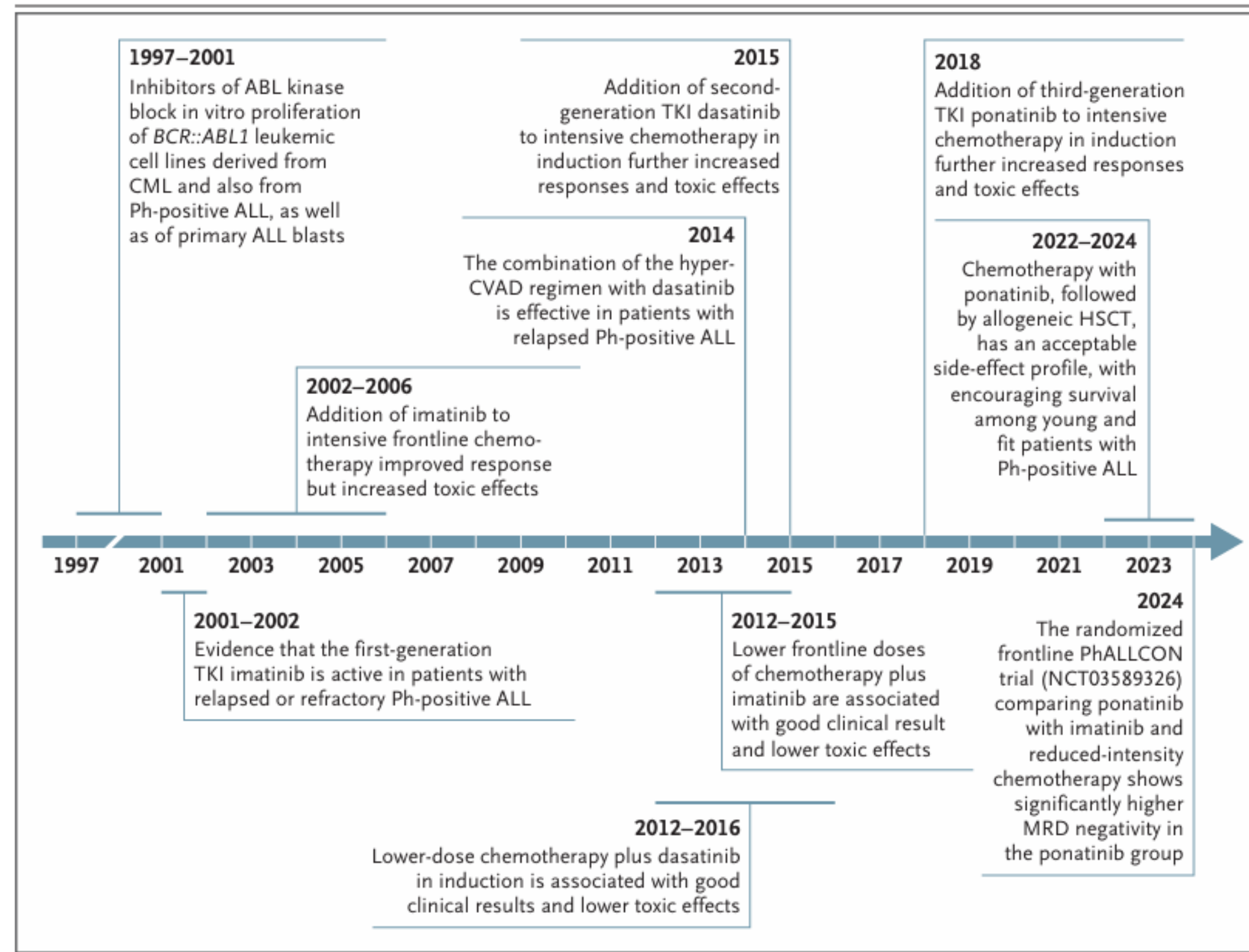
Piano terapeutico iniziale

- Scelta TKI, profilassi SNC, strategia consolidamento / HSCT

Ph-Positive Acute Lymphoblastic Leukemia — 25 Years of Progress

Robin Foà, M.D.¹

EVOLUZIONE del TRATTAMENTO



Da “chemioterapia intensiva” a strategie target + immunoterapia

≈2000
Chemo + imatinib

≈2010
2^a gen TKI
(dasatinib)

≈2015
Ponatinib
(T315I)

2020+
Chemo-free
(TKI + blinatumomab)

2024+
Strategie “risk-adapted”
+ CAR-T / trial

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. The GIMEMA Frontline Strategy without Chemotherapy from 2000 to 2025 in Patients with Ph-Positive ALL.*

Study Protocol	Age yr	Induction Therapy	Complete Remission % of patients
LAL0201-B ³⁰	>60	Imatinib	100
LAL1205 ³¹	>18	Dasatinib	100
LAL0904, 3rd amendment ²⁰	16–60	Imatinib followed by chemotherapy (with or without HSCT)	96
LAL1408 ³²	>60 or unfit	Nilotinib and imatinib	94
LAL1509 ³³	18–60	Dasatinib and total therapy†	97
LAL1811 ³⁴	>60 or unfit	Ponatinib	95
LAL2116 ^{35,36}	>18	Dasatinib plus blinatumomab	98
ALL2820 ^{37,38}	>18	Ponatinib plus blinatumomab	95

* Starting in 2000, tyrosine kinase inhibitors (TKIs) (plus glucocorticoids) were used without chemotherapy for induction therapy. Starting in 2017 (protocols LAL2116 and ALL2820), the bispecific monoclonal antibody blinatumomab was added as consolidation therapy, always without chemotherapy. Patients who were not candidates for chemotherapy or allogeneic hematopoietic stem-cell transplantation (HSCT) were classified as “unfit.” ALL denotes acute lymphoblastic leukemia, GIMEMA Gruppo Italiano Malattie Ematologiche dell'Adulto, and Ph Philadelphia chromosome.

† Dasatinib and glucocorticoids were given in the induction phase, followed by chemotherapy and transplantation in patients who did not have a complete molecular response.

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REVIEW ARTICLE

Ph-Positive Acute Lymphoblastic Leukemia
— 25 Years of Progress

Robin Foà, M.D.¹

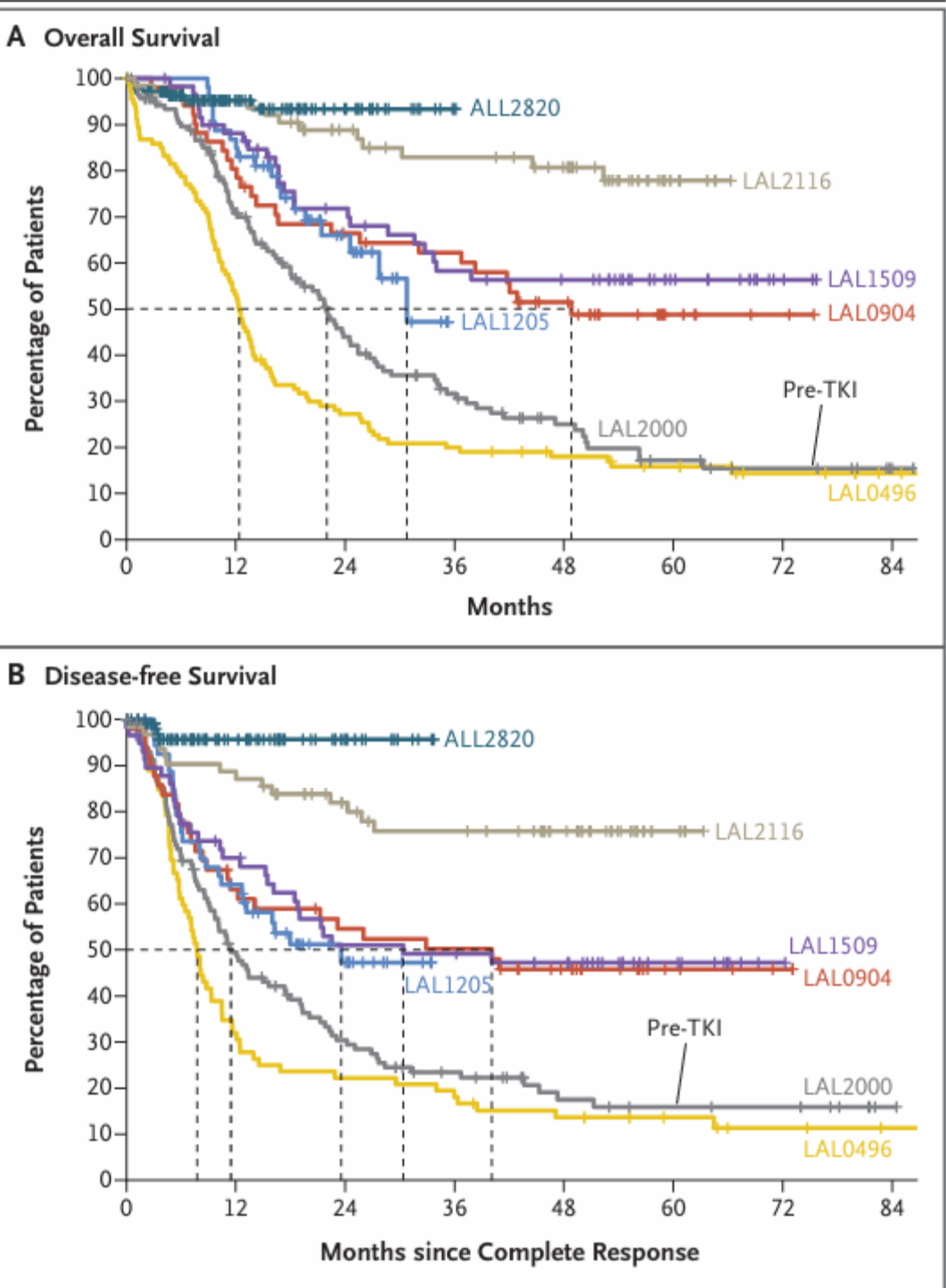
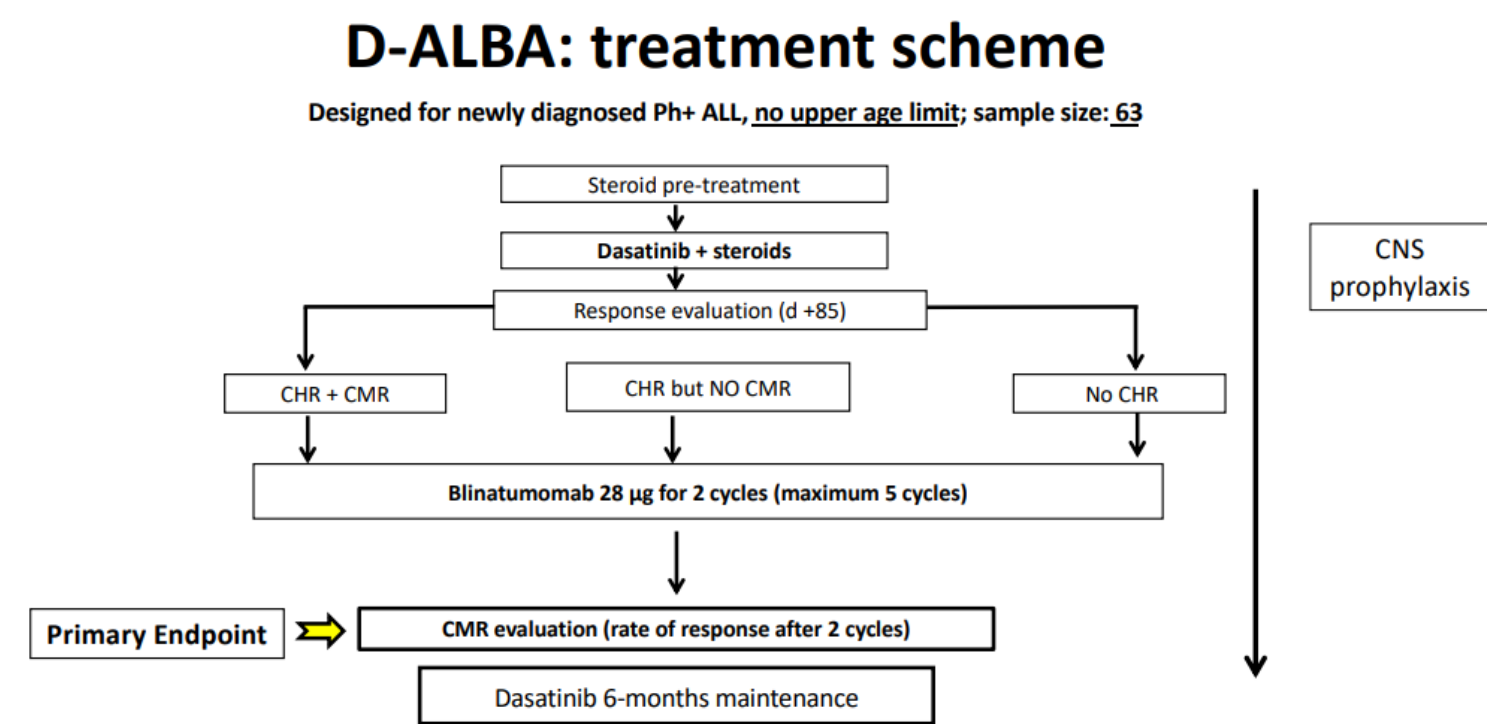


Figure 4. Overall and Disease-free Survival among Adults with Ph-Positive ALL Treated with or without TKIs in the GIMEMA Trials.

Front-line chemo-free:

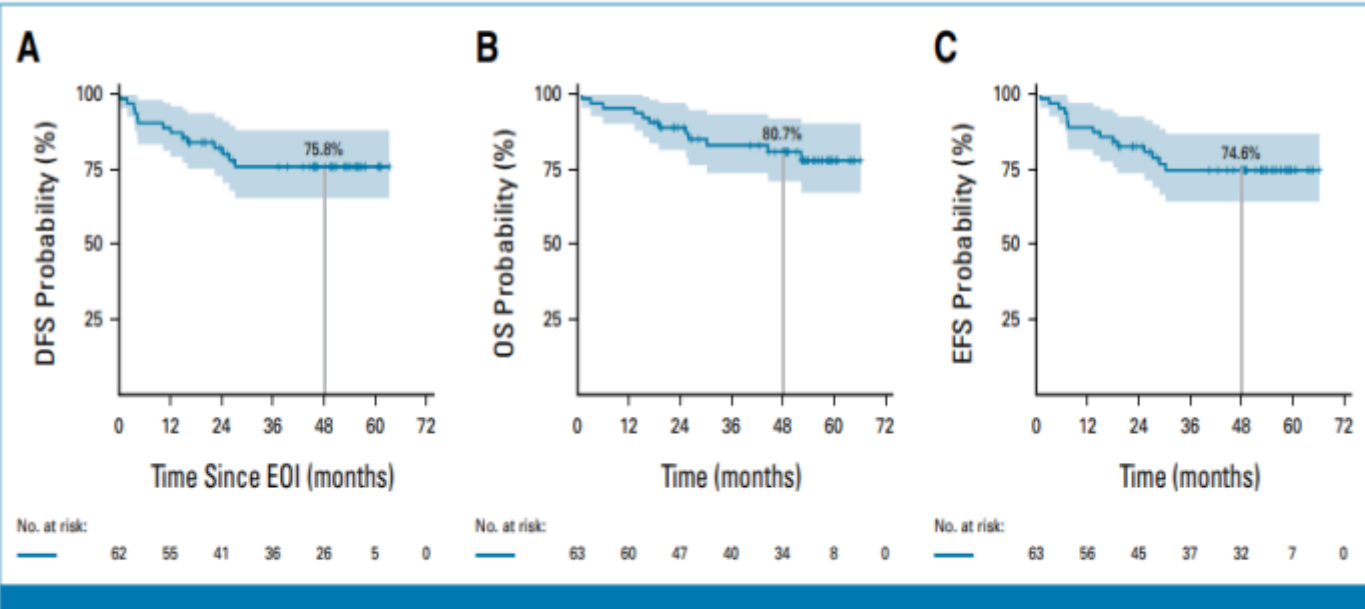
D-ALBA (dasatinib → blinatumomab)

Ph-positive B-ALL



Ph-positive B-ALL

D-ALBA: results



- Median age **54** years (24-82);
- Median follow-up of **53** months;
- DFS, OS, and EFS were 75.8%, 80.7% and 74.6%;
- Worse DFS for **IKZF1^{plus}** patients;
- DFS is 100% in molecular responders at the EOI → **prognostic role of early molecular response in a chemotherapy-free setting.**
- **9 Relapses** (4 CNS-only);*
- **6** patients requiring a TKI switch: **Pleural effusion** was the most common adverse event.

COINVOLGIMENTO CNS

IKZF plus

CMR PRECOCE

STEP UP: ponatinib + blinatumomab



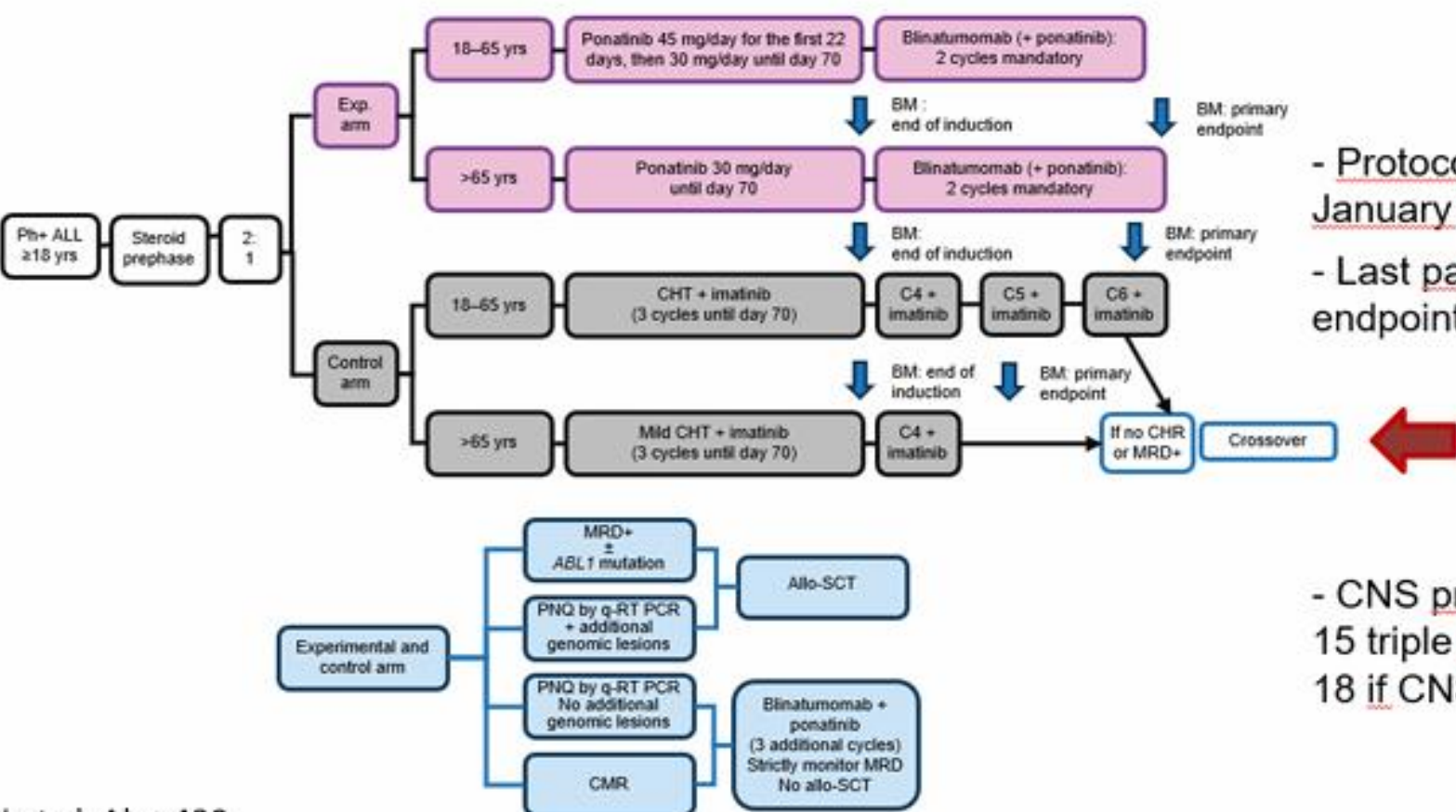
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Torino, 19-21 Febbraio 2026

GIMEMA ALL2820 Phase III Trial

Frontline treatment of adult Ph+ ALL (≥18 years, no upper age limit) with ponatinib plus steroids followed by blinatumomab compared to chemotherapy with imatinib



- Protocol closed to enrolment in January 2025.
- Last patient reached primary endpoint in June 2025.

- CNS prophylaxis strengthened:
15 triple medicated lumbar punctures
18 if CNS+ at diagnosis.

Chiaretti et al, Abs 439

ALL2820



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GIMEMA ALL2820. Patients' features (n=236)

	Experimental arm N=158	Control arm N=78
Age, median (range)	56.5 (19-84)	55 (21-79)
>65 years (%)	44 (28)	21 (27)
Gender: M/F (%)	79/79 (50/50)	48/31(59/41)
WBC x10 ⁹ /l, median (range)	10.5 (0.1-244)	13.4 (0.7-231)
≥30x10 ⁹ /l (%)	43 (27)	27 (31)
≥70x10 ⁹ /l (%)	16 (10)	7 (9.3)
CNS+	15 (9.9)	11(15)
p190 (%)	111 (70)	49 (64)
p210, p190/210 (%)	41 (26), 6 (4)	24 (31.7), 4 (5.2)
IKZF1 ^{plus} (%)	52 (34)	19 (26)

Chiaretti et al, Abs 439

GIMEMA ALL2820. Hematologic responses

End of induction (d +70)	Experimental arm (n=158)	Control arm (n=78)	p
CHR	149 (94.3%)	62 (79.4%)	0.004
Deaths	4 (2.5%)	8 (10.2%)	
Refractory	-	1 (1.3%)	
Off-treatment	5 (2.8%)	7 (8.9%)	



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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)
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)		

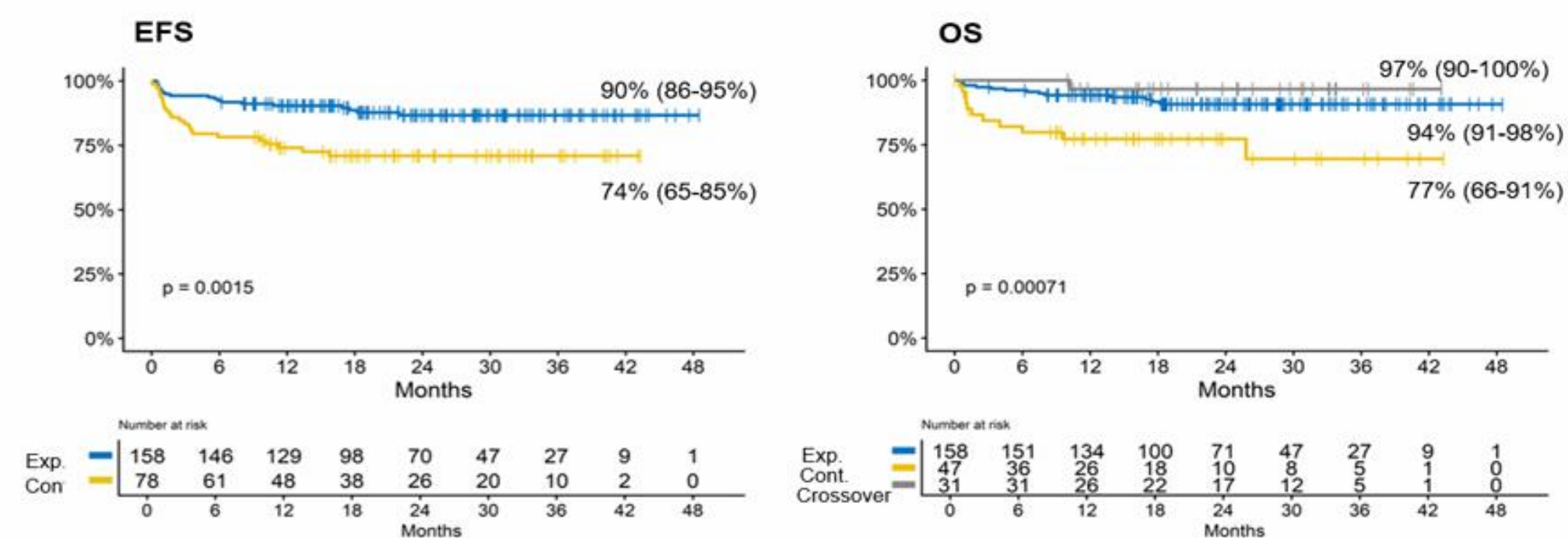
*Depending on age

p= <0.001

Chiaretti et al, Abs 439

ALL2820

GIMEMA ALL2820. EFS and OS



Median follow-up: 23.4 months (0.1- 48.5)

Chiaretti et al, Abs 439

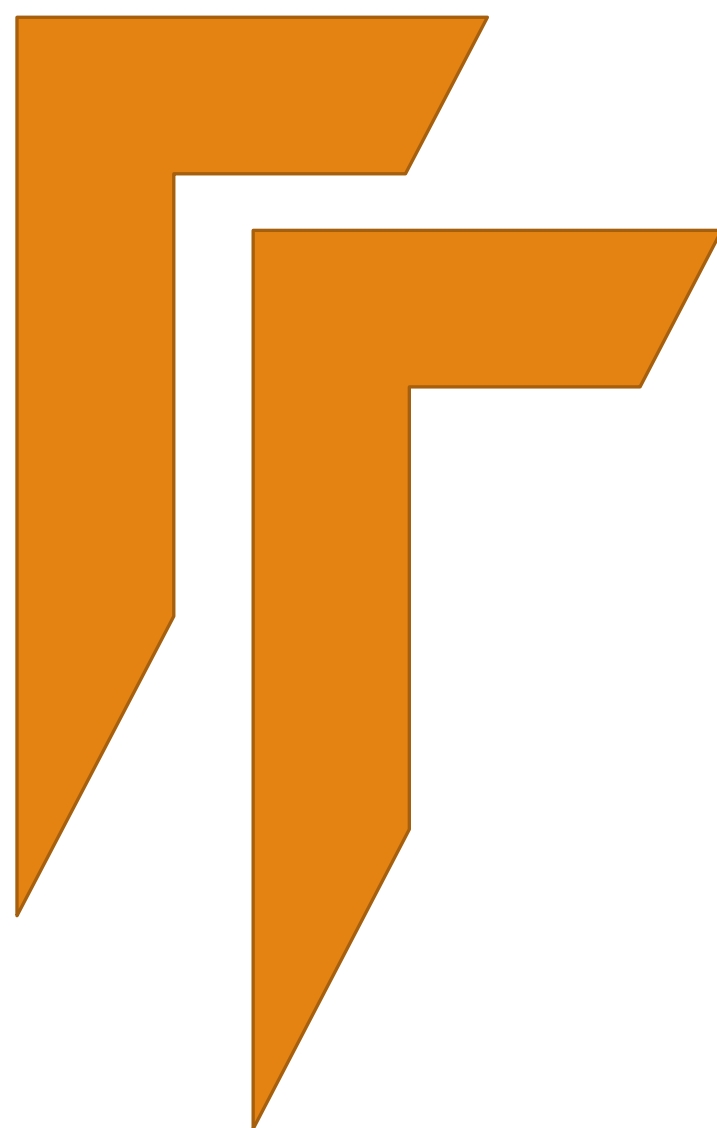
GIMEMA ALL2820. Conclusions

- The first results of the phase III GIMEMA ALL2820 trial show for the first time, in a head-to-head comparison, a significant advantage of a chemo-free, targeted/immunotherapeutic based approach over a TKI/chemotherapy strategy, with higher CHR and MRD responses, fewer deaths and improved EFS and OS.
- An increase in MRD negativity and less relapses have so far been observed compared to the D-ALBA trial.
- A crossover is capable of rescuing MRD+ patients in the control arm.
- A biology-driven transplant allocation strategy appears to be feasible and effective.
- **A chemo-free approach should be the new standard for adult Ph+ ALL.**

Ongoing

- *BCR::ABL1* and IG/TR MRD monitoring by RQ-PCR and ddPCR (NGS in a subset).
- Monitoring of *ABL1* mutations by ddPCR in MRD+ patients.
- Host immune modulation (Ansuinelli M et al, *Leukemia in press*).
- Quality of life.

Chiaretti et al, Abs 439



NOTIZIE DAL FUTURO

FUTURA

Testo e Musica di L. DALLA

Moderatamente

Sax. Chis.

Solm
Do

- sà chis - sà do - ma-ni, su che co - sa met-te-re -

Fa Solm Do7 Fa

- mo le ma - ni se si po - trà con-ta-re an-co-ra le

Sib Do7 Sib Sol

on-de del ma - re e al - za-re la te - sta, non es-ser co-sì

Sib Do7

se - ri - a, ri - ma-ni

Sib Solm7 Do7

rus - si, i rus - si - gli a-me-ri-ca-ni, no la -

Fa Solm 7/7 Do7

- cri-me non fer-mar - ti fi-no a do-ma - ni sa-rà sta -

Fa Fa Re Do7/9

Abstract Title : Primary efficacy analysis of phase II study investigating tyrosine kinase inhibitor (TKI) and inotuzumab ozogamicin-based therapy for newly diagnosed Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL)

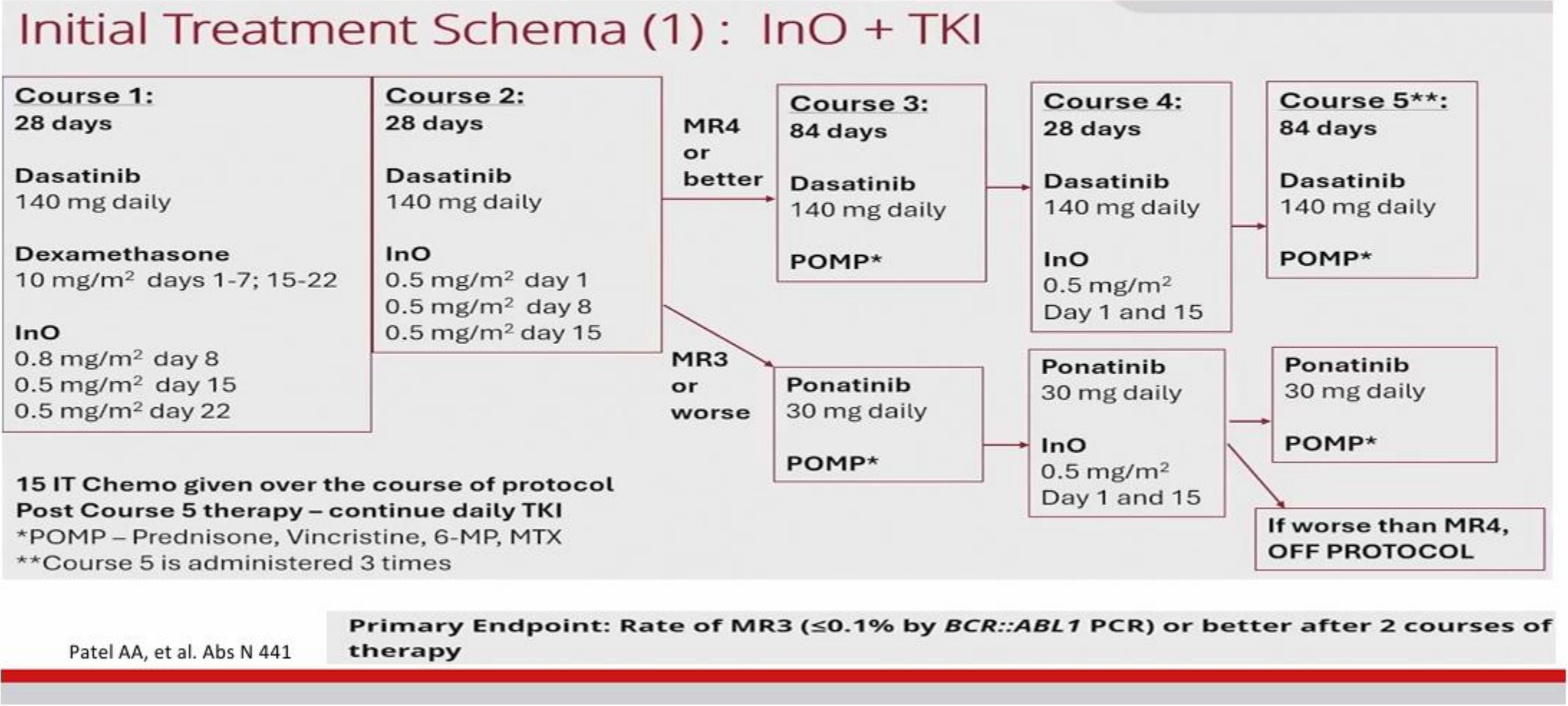
Anand Patel 1, Adam Duvall1, Caner Saygin1, Howard Weiner1, Emily Dworkin2, Afsheen Noorani1, Jamie Mathews1, Angela Lager3, Sandeep Gurbuxani3, Peng Wang3, Rafael Madero-Marroquin1, Austin Wesevich1, Michael Drazer1, Mariam Nawas1, Gregory Roloff1, Satyajit Kosuri1, Michael Thirman1, Richard Larson1, Olatoyosi Odenike1, Theodore Harrison4, Wendy Stock1 1University of Chicago, Section of Hematology-Oncology, Department of Medicine, Chicago, IL, United States, 2 University of Chicago, Department of Pharmacy, Chicago, IL, United States, 3 University of Chicago, Department of Pathology, Chicago, IL, United States, 4 University of Chicago, Department of Public Health Sciences, Chicago, IL, United States

Primary efficacy analysis of phase II study investigating tyrosine kinase inhibitor (TKI) and inotuzumab ozogamicin-based therapy for newly diagnosed Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL)

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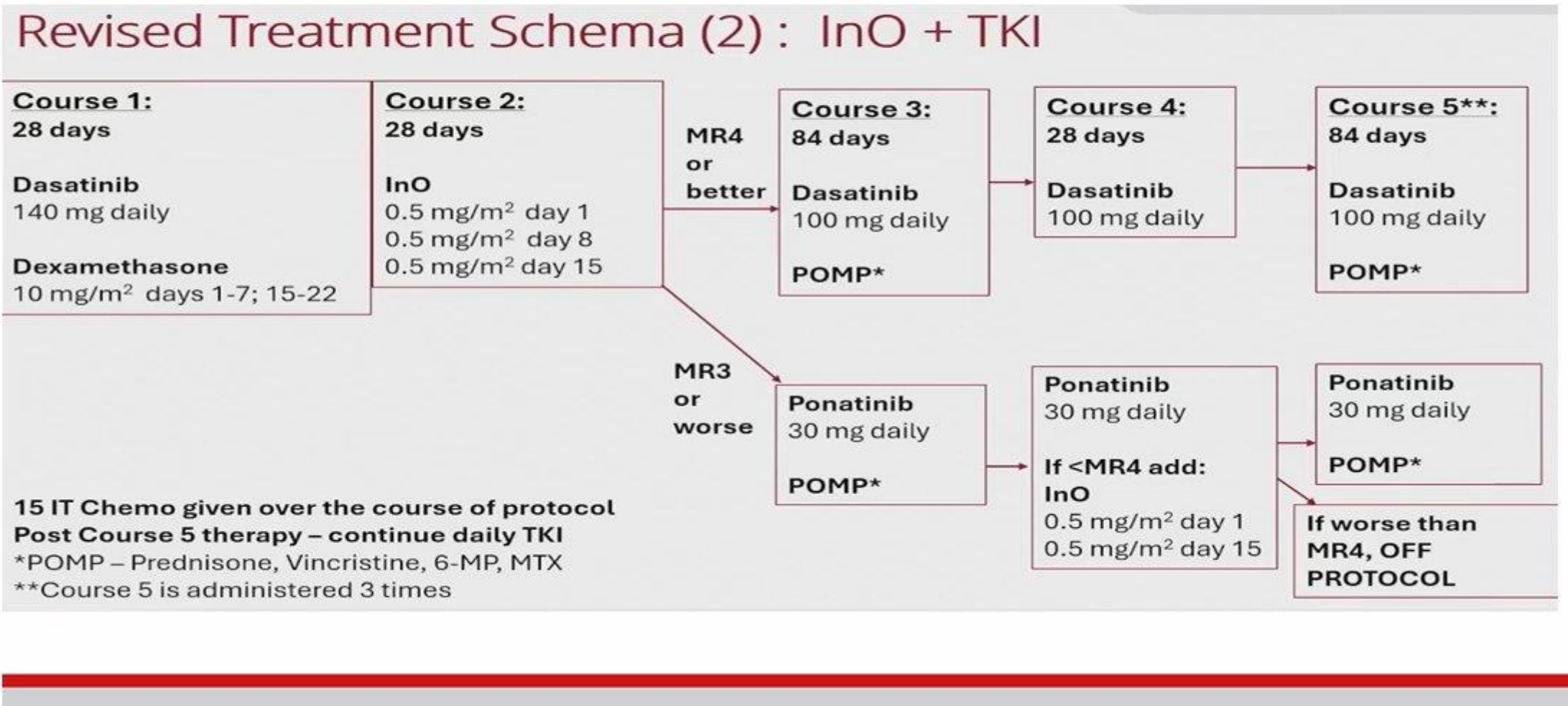
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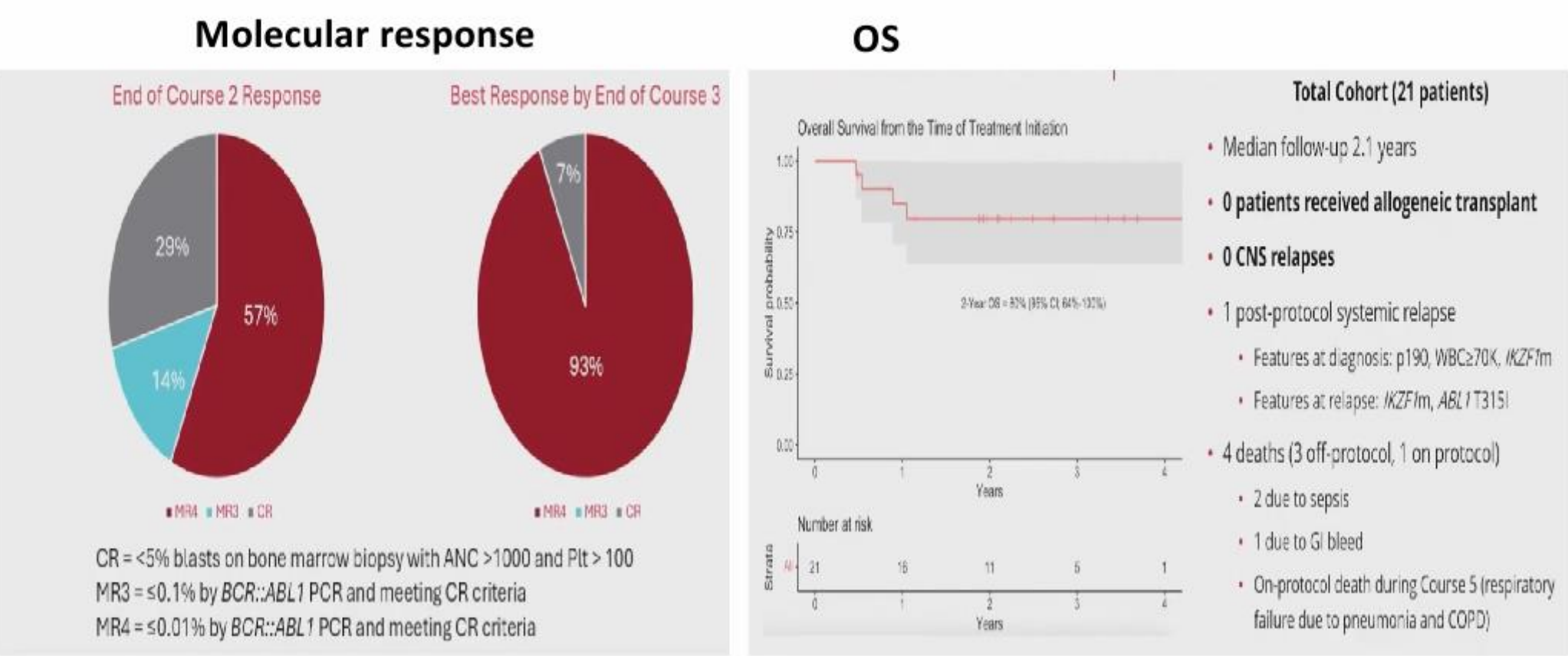
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Patient Characteristics (N=21)

Demographics		Laboratory Values at Diagnosis	
Median Age (range)	60 (21-79)	WBC (10 ³ /μL), median (range)	12.3 (1.2-149.2)
Female	57%	WBC ≥ 70K/μL	19%
Race/Ethnicity		Platelet Count (10 ³ /μL), median (range)	34 (12-224)
Non-Hispanic White	53%	Hemoglobin (g/dL), median (range)	8 (5.9-12.6)
Non-Hispanic Black	24%	% CD22 expression on blasts, median (range)	93 (33-99)
Hispanic	14%	Molecular Aberrations	
Not Reported	10%	IKZF1 aberration	38%
BCR::ABL1 Transcript		IKZF1 ^{plus} *	14%
p190	67%	*defined per Foa et al, NEJM 2020	
p210	29%		
atypical	5%		

Patel AA, et al. Abs N 441

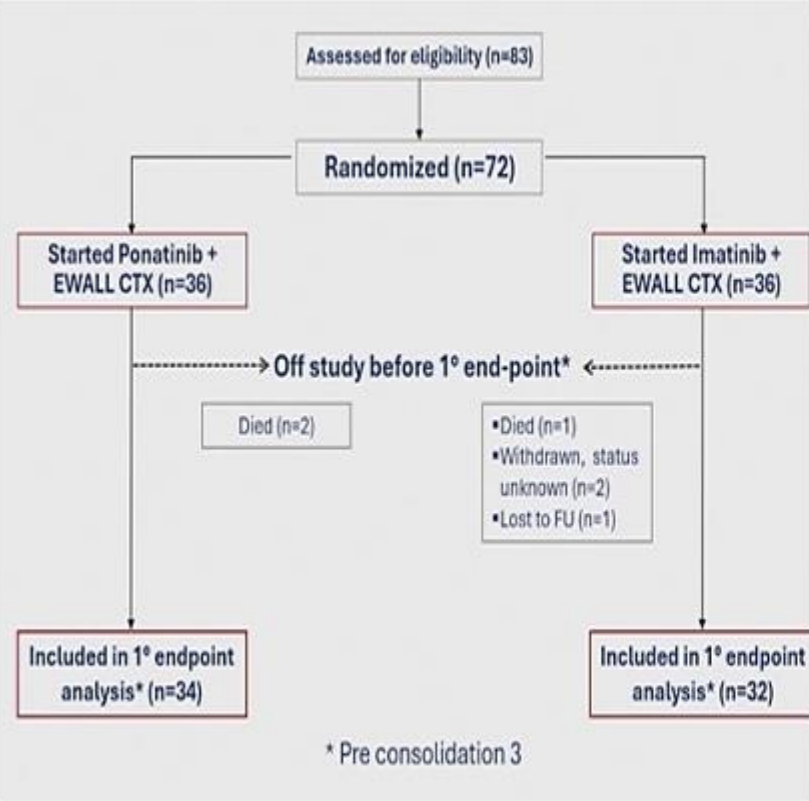


Abstract Title : Randomized comparison of ponatinib versus imatinib in combination with chemotherapy in patients 55 years of age and older with newly diagnosed ph+ ALL: Molecular response and initial outcome analysis of the EWALL PH03 Study

Publication Number: 444

Torino, 19-21 Febbraio 2026

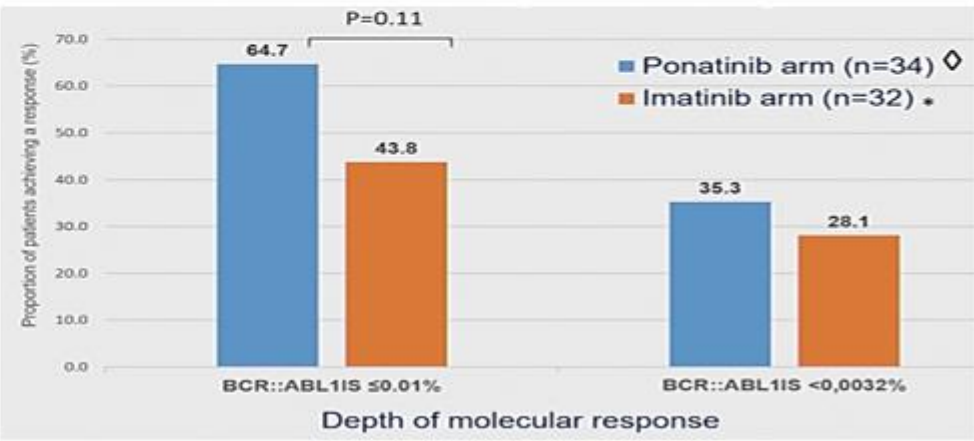
Disposition



Ottmann O, et al. Abs N 440

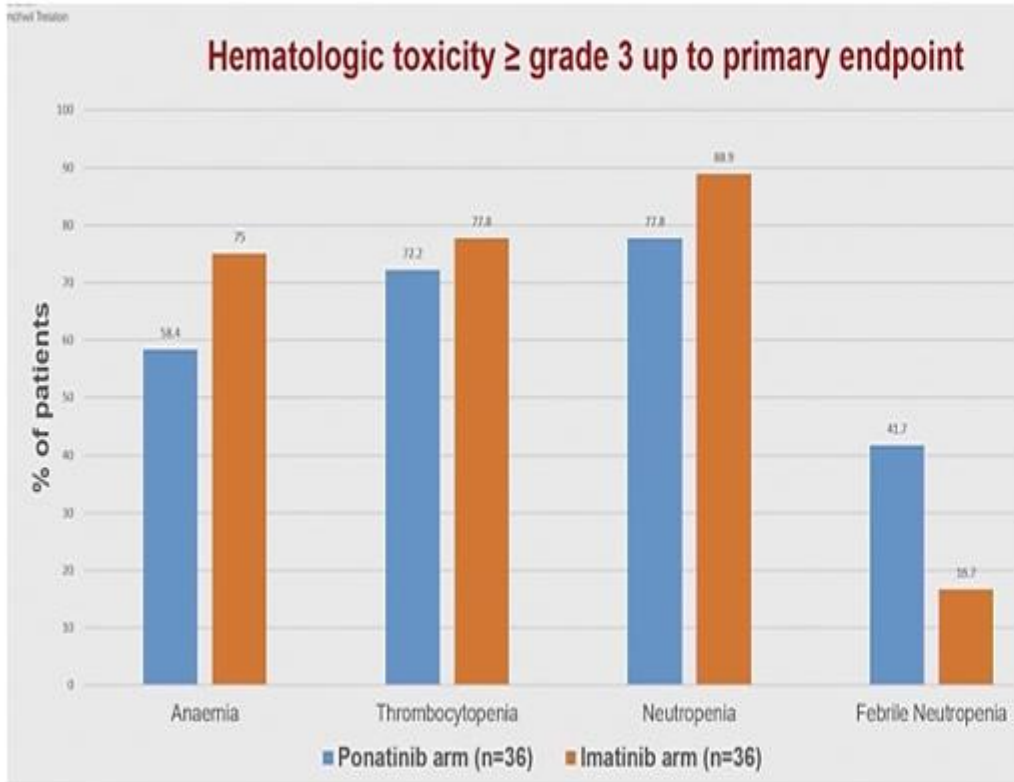
Responses

	End of induction phase 1 n (%)		After consolidation cycle 2* n (%)	
Response	Ponatinib arm (n=36)	Imatinib arm (n=36)	Ponatinib arm (n=36)	Imatinib arm (n=36)
Evaluable (n)	34	34	32	29
CHR	32 (94.1)	31 (91.2)	32 (100)	27 (93.1)
Partial	0 (0)	1 (2.9)	0 (0)	0 (0)
Progression	1 (2.9)	0 (0)	0 (0)	1 (3.4)
Relapse	0 (0)	0 (0)	0 (0)	0 (0)



Torino, 19-21 Febbraio 2026

Toxicity



Ottmann O, et al. Abs N 440

Survival



Conclusion

- In the context of the EWALL chemotherapy backbone, PON induces a non-significantly higher molecular response rate than IM in older patients with de novo Ph+ALL
- The safety profile of PON was consistent with known AEs, with no increase in the rate of withdrawal from study treatment compared to IM
- Overall safety and tolerability of ponatinib and imatinib were equivalent
- Combining PON or IM with mild induction and intensive consolidation chemotherapy was applicable with low toxicity even in an older population
- `CNS-active` ID-MTX and HDAC consolidation cycles may have contributed to the absence of CNS relapses to date
- Assessing the impact on survival will require longer follow-up

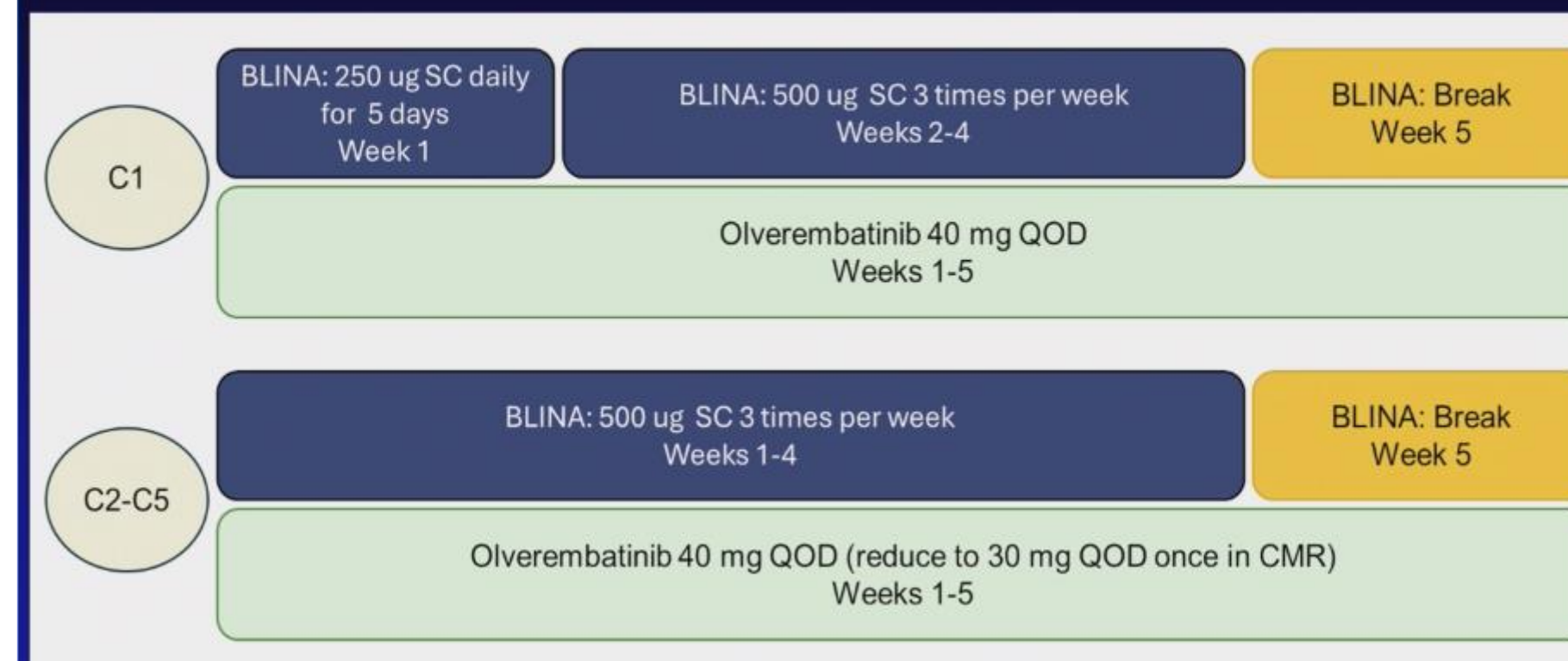
Ottmann O, et al. Abs N 440

Olverembatinib + LD ChemoRx in FL Ph+ ALL: Part A of Phase 3 POLARIS-1

- 55 patients; median age 43 years; p190 65.5%
- Olverembatinib 30–40 mg QOD with 3 cycles of VP–VPD followed by 3 cycles of HD MTX alternating with 3 cycles of HDAC, followed by 12 cycles of maintenance with 6-MP–MTX–VP
- Median duration of Rx: 9.6 months
- Primary endpoint: MR4 CR at 90 days 52.8% (35.8% EOC1)
- Rx well tolerated: 1 patient with G2 CAD
- Subsequent ASCT in 5 patients (9.1%)
- Progression in 4 patients (1 refractory and 3 CNS/BM)
- 9/10 patients with *IKZF1*^{plus}: MRD-neg CR
- No difference between olverembatinib 30 and 40 mg QOD
- Randomization 2:1 of olverembatinib vs dealer choice TKI with LD ChemoRx ongoing

Chen S, et al. ASH 2025; Abstract 1574.

Olverembatinib + SQ Blinatumomab in Ph+ ALL: Regimen

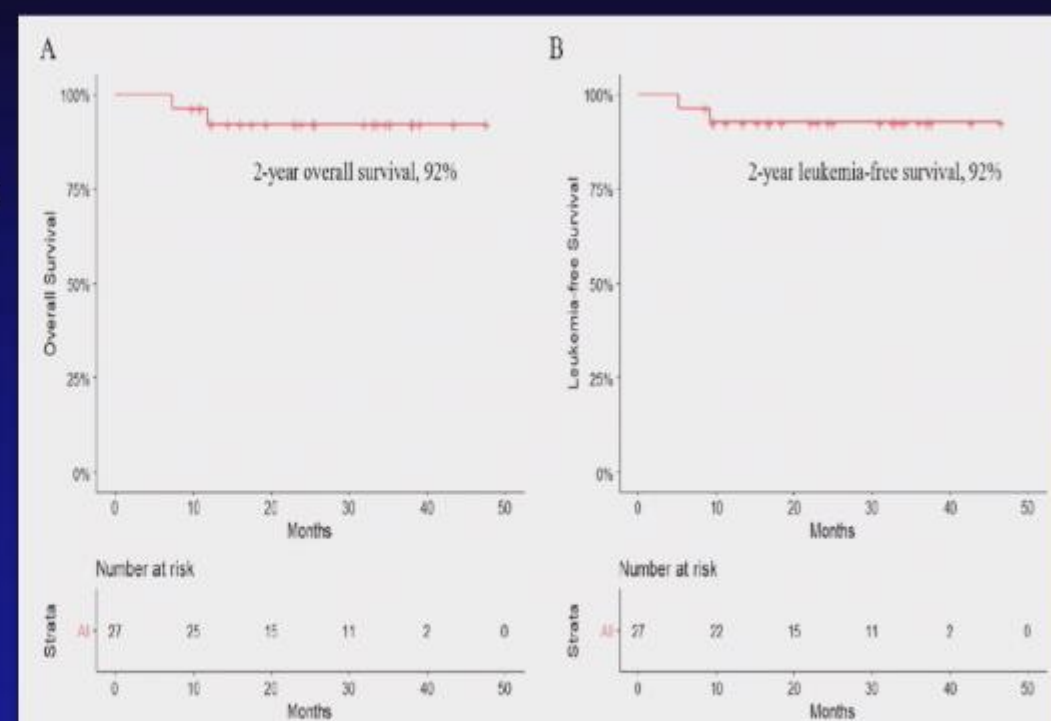


15 IT chemo for all patients

<https://clinicaltrials.gov/study/NCT07178912>

Dasatinib + Sequential CD19 and CD22 CAR-Ts in Ph+ ALL

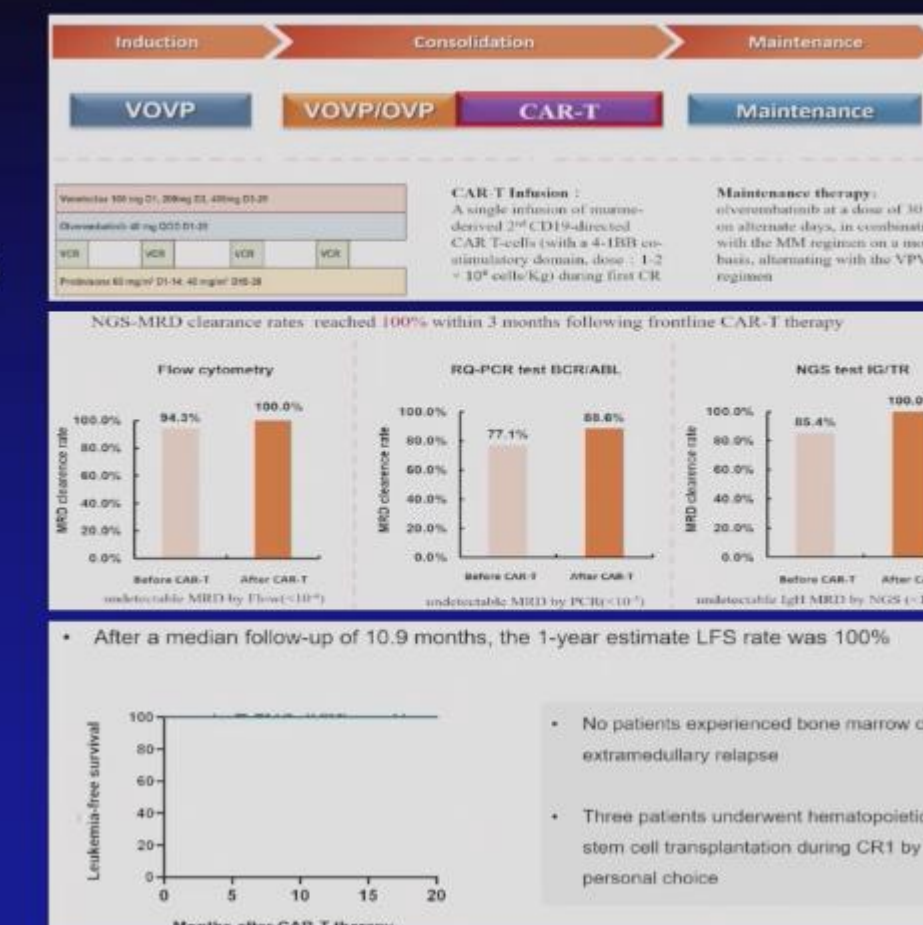
- 28 patients; median age 48.5 years (18–69); Rx with dasatinib 100 mg/d, then sequential CD19 and CD22 CAR-Ts; median FU 24 months
- CMR 25% post induction; 85% post CD19 CAR-T (n=27); 76% post CD22 CAR-T (n=25)
- CD22 CAR-T given for normal B-cell reappearance in 18, and PCR+ in 7
- 2-year OS and LFS: 92%
- 2 relapses/deaths; 21 in CMR, 4 PCR+



Zhang M, et al. JAMA Oncol 2025;11:625–9.

CD19 CAR-T Consolidation in ND Ph+ ALL. Phase 2

- 35 patients; median age 39 years (20–60)
- IT for CNS as SOC
- @LD: 100% CR; 6% MRD+ (MFC); 23% MRD+ (BCR-ABL1); 15% MRD+ (NGS)
- Post-CAR: 100% MRD– (MFC); 11% MRD+ (BCR::ABL1); 100% MRD– (NGS)
- Median F/U: 11 months; 1-year OS: 100%; 1-year LFS: 100%
- No relapses; 3 elected alloSCT by preference
- CRS: 74%, all Grade1; ICANS: 0%



Gu R, et al. ASH 2025; Abstract 442.

Ph+ ALL: new approaches for upfront therapy

Marlise R. Luskin
Adult Leukemia Program, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

TMO IN CR1

Table 3. Select studies evaluating role of alloHCT in Philadelphia chromosome-positive acute lymphoblastic leukemia in first complete remission

Study	Pre-alloHCT regimen	Population (# in CR1, age, transplant allocation)	Outcomes (alloHCT vs no)
GRAALL (SAKK) GRAAPH-2005 ⁹ NCT00327678	IM, chemotherapy	n=254; 18–59 yrs Transplant allocation: 161 allo, 35 auto, 58 no transplant	OS HR 0.64, p=0.02 RFS HR 0.69, p=0.04 In MR4 at MRD2: RFS HR 1.02, p=0.96 Not in MR4 at MRD2: RFS HR 0.62, p=0.03
GRAALL (SAKK) GRAAPH-2014 ²⁸ NCT02611492	NIL, chemotherapy	n=155; 18–59 yrs Transplant allocation: 93 allo, 40 auto, 22 no transplant	alloHCT associated with longer RFS (4-yr 79.4%) vs auto (57.2%; HR 0.46, p=0.018) and vs no transplant (32.0%, HR 0.17, p<0.0001) By randomization: Similar results in arm B (low-intensity consolidation), but improved RFS after alloHCT not seen in arm A (high-intensity consolidation)
KAALLWP (Korea) NCT00844298 ³⁰	NIL, chemotherapy	n=82; 17–71 yrs Transplant allocation: allo 57, no allo 25	OS 80% vs 72%, p=0.23 RFS 78% vs 49%, p=0.045 CIR 19% vs 41%, p=not reported NRM 19% vs 20%, p=not significant In MR5: RFS 65% vs 53%, p=0.78 Multivariable analysis: alloHCT (HR 3.3, p=0.048) and achievement of MR3 (HR 12.3, p=0.038) associated with 2-yr RFS
SWOG (US) SWOG 0805 ³¹ NCT00792948	DAS, hyper-CVAD	n=85; 20–60 yrs Transplant allocation: 41 protocol-specified allo; 44 no protocol-specified allo (8 nonprotocol allo)	Received protocol-specified: RFS 83% (12 mo); 76% (3 yr) Landmark analysis (175 days): protocol allo associated with improved RFS (HR 0.42, p=0.038 and OS HR 0.35, p=0.037)
Retrospective US (5 transplant centers) ³²	IM, DAS, PON, chemo (mostly IM/DAS plus hyper-CVAD)	n=230 all in MR4 by 3 months; 19–73 yrs Transplant allocation: 98 allo; 132 non-allo	OS (5 yr): 58% vs 61% (p=0.63) RFS (5 yr): 63% vs 52% (p=0.42) CIR (5 yr): 15% vs 36% (p=0.001) NRM (5 yr): 21% vs 11% (p=0.06) GRFS (5 yr): 25% vs 52% (p=0.0001)
JALSG (Japan) ³³ Ph+ALL202, Ph+ALL208, Ph+ALL213	IM, DAS plus chemo	n=147 all in MR5 by 3mos; 15–64 yrs Transplant allocation: 101 allo; 46 non-allo	OS (5 yr): 73% vs 50% (aHR 0.54, p=0.04) RFS (5 yr): 70% vs 20% (aHR 0.21, p<0.001) CIR (5 yr): 14% vs 73% (aHR 0.10, p<0.001) NRM (5 yr): 17% vs 5% (aHR 3.49, p=0.03) GRFS (5 yr): 50% vs 20% (p=NS)

Consolidation: role of alloHCT

The ability of alloHCT to cure patients with ALL is established, but indications for transplantation in Ph+ ALL are evolving. In the pre-TKI era, “donor versus no-donor” analyses established the benefit of alloHCT.⁴ Subsequently, studies treating patients with IM or a 2G TKI continued to demonstrate reduced relapse and improved OS with alloHCT (Table 3).^{9,21,30,31}

It is uncertain whether patients who achieve an early, deep MRD response after TKI plus chemotherapy induction still benefit from alloHCT. In the GRAAPH-2005 trial, the benefit of alloHCT could not be confirmed in IM-treated patients who achieved MR3 at an early time point.⁹ In a Korean study of NIL plus chemotherapy, among patients who achieved an MR5 response there was no difference in relapse based on receipt of alloHCT, although alloHCT was associated with superior survival in multi-variable analysis.³⁰

A retrospective multicenter study of 230 patients treated primarily with DAS plus hyper-CVAD showed that among patients who achieved an MR4 response by day 90, there was no improvement in OS (aHR 0.86, p=0.63) or relapse-free survival (RFS, HR 0.80, p=0.42) with alloHCT, although cumulative incidence of relapse (CIR) was lower (aHR 0.37, p=0.01) while non-relapse mortality was higher (aHR 2.29, p=0.06).³² In contrast, a Japanese study reported that alloHCT was associated with superior RFS and OS among 147 patients who achieved MR5 after 3 months of IM or DAS plus chemotherapy, confirmed by multi-variable analysis (OS aHR 0.54, p=0.04; RFS aHR 0.21, p<0.001; nonrelapse mortality [NRM], aHR 3.49, p=0.03; relapse risk aHR 0.10, p<0.001).³³

There are limited data on the benefit of alloHCT in PON-treated patients. MDACC has reported no benefit to alloHCT in the context of PON plus hyper-CVAD, but in their study, alloHCT assignment was at physician discretion, was performed rarely (23%), and occurred late (median of 8 months from diagnosis).³⁴ In contrast, the PONAFL trial, where PON was combined with chemotherapy followed by alloHCT, has reported excellent outcomes among the 30 enrolled patients, of whom 26 were transplanted (median follow-up 4.1 years, treatment-related mortality 7.6%, 4-year EFS and OS 66% and 92%, respectively).³⁴ The GRAAPH-2024 study will randomize PON-treated patients in CMR to alloHCT or no transplant.

The role of alloHCT in the setting of blinatumomab is also not defined. In the GIMEMA LAL2116 study, approximately one-third of patients (24/63) received alloHCT in CR1, enriched in poor molecular responders. On the other hand, half of patients are in ongoing CR without alloHCT (or chemotherapy).²² In the MDACC ponatinib plus blinatumomab study, only 2 of 60 patients were transplanted.²⁵

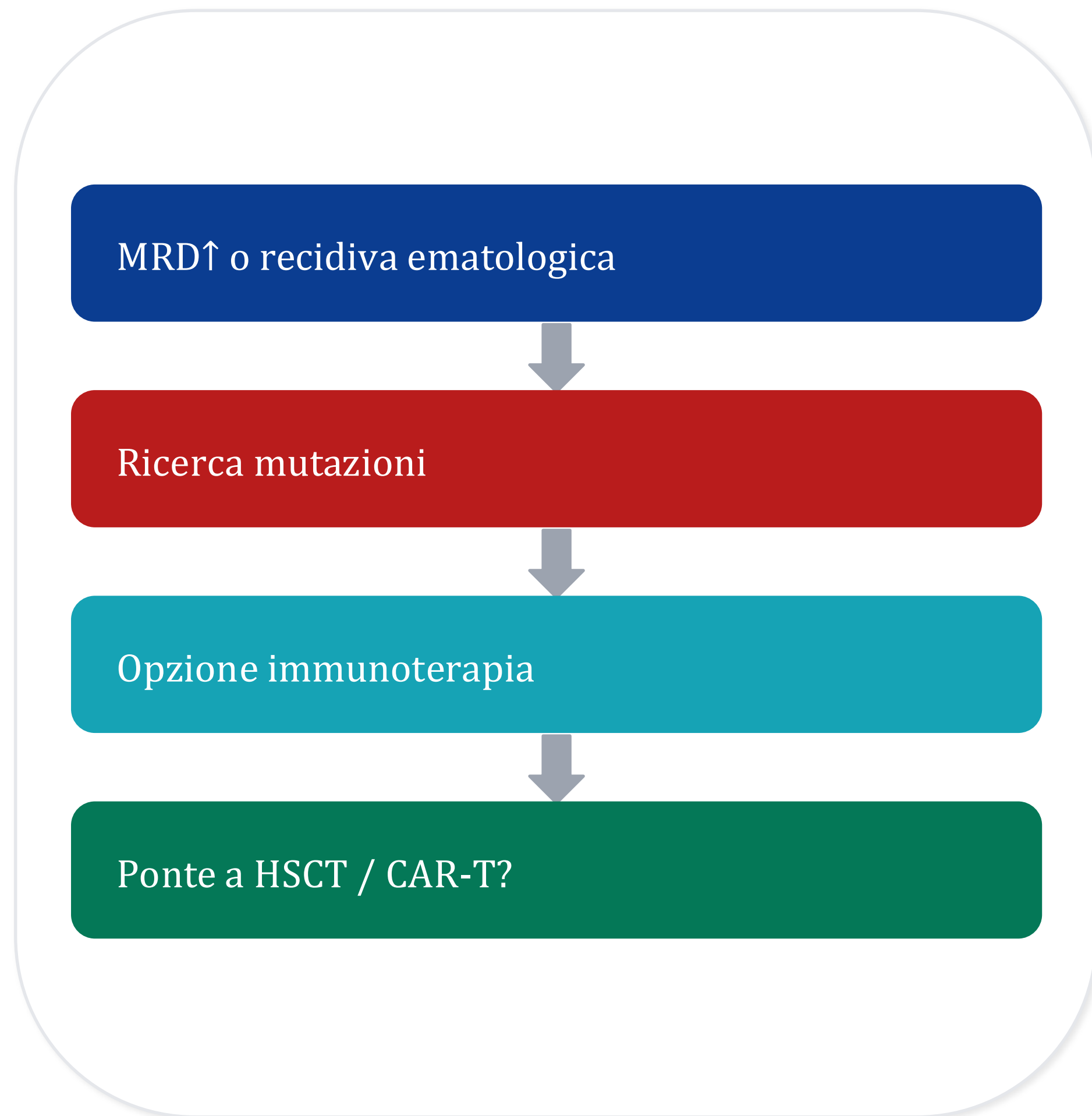
In the future, alloHCT is likely to be deployed strategically. For instance, the GRAAPH-2014 trial suggested that alloHCT benefited high-risk patients as defined by high white blood cell (WBC) at diagnosis and poor early MRD response.²⁸

		x1C							
GIMEMA (Italy) ALL2820 NCT04722848	3 ^a	Ind/cons: PON + blina vs IM + chemo (2:1) CNS: 15 IT chemo	2021-	236 ^a	Eligibility: ≥18	-	Based on IKZF1 plus and MRD	-	-
GRAALL (SAKK) GRAAPH-2024	3 ^a	Ind: PON, blina, chemo Cons: alloHCT vs chemo/blina CNS: IT and systemic chemo	-	-	-	-	Randomize if in CMR (NGS)	-	-

^aongoing/planned.

^bpreviously untreated.

FAILURE



Checklist “failure work-up”

1) Conferma biologica

- Ripetere MRD/RT-qPCR
- Rivalutazione midollare

2) Ricerca di resistenze “on-target”

- Sequenziamento ABL1 kinase domain (al fallimento o risposta subottimale)

3) Valutazione sedi “santuario”

- SNC / extramidollare

4) Revisione terapeutica

- Aderenza, interazioni farmacologiche, tossicità

R/R Ph+ ALL: opzioni di salvataggio

A) Ottimizzare TKI

- Switch guidato da ABL1 KD (es. ponatinib per T315I)
- Gestione interazioni/tossicità → mantenere intensità di dose
- Combinare con immunoterapia quando possibile
- Monitorare MRD stretto (settimane)

B) Immunoterapia

- Blinatumomab in combinazione con TKI
- Inotuzumab ozogamicin (CD22) anche post-CD19
- CAR-T anti-CD19: opzione chiave in R/R (bridge)
- Attenzione a tossicità specifiche (CRS/ICANS, VOD)

C) Consolidare la risposta

- Allo-HSCT
- Trial clinici: nuovi bispecifici / CAR-T multi-target
- Follow-up: sorveglianza molecolare + gestione TKI lungo termine

R/R Ph+ ALL: opzioni di salvataggio

Blinatumomab (CD19)

- MRD-conversion
- R/R con burden controllato
- Spesso in combo con TKI

Inotuzumab (CD22)

- Potente “debulking”
- Bridge a TMO
- Attenzione VOD/SOS

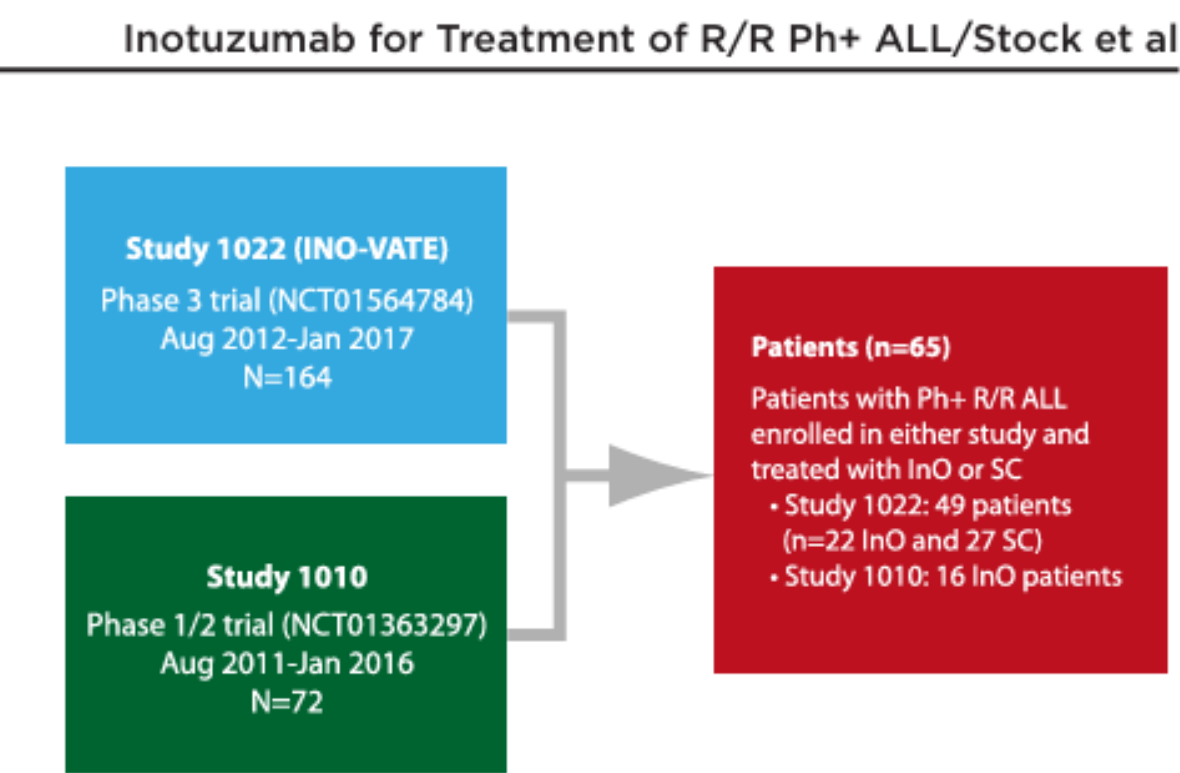
CAR-T (CD19)

- R/R multipla
- Possibile consolidamento
- CRS/ICANS; logistica

TMO

- MRD pre e post
- Mantenimento

Inotuzumab



POSTER

613. ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES EXCLUDING ALLOGENEIC TRANSPLANTATION

Efficacy and safety of a retreatment with inotuzumab ozogamicin in adult patients with relapsed/refractory acute lymphoblastic leukemia: A Campus ALL study

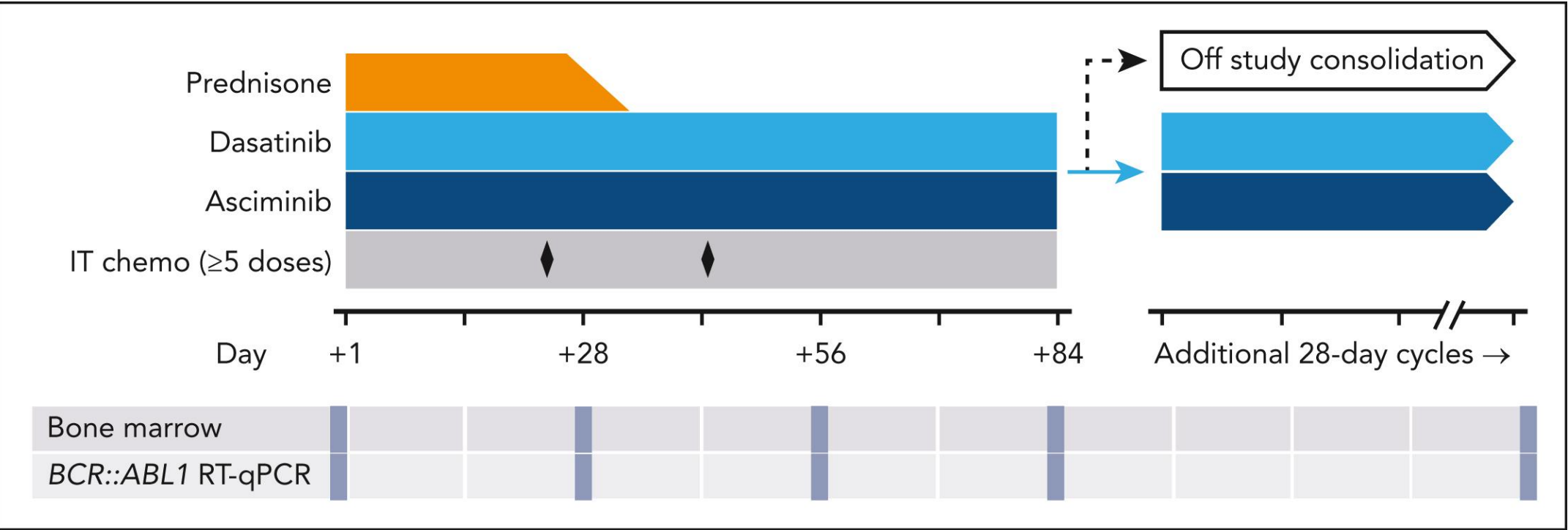
Gianluca Cavallaro¹, Ferdinando Porretto², Patrizia Chiusolo³, Cristina Papayannidis⁴, Mario Delia⁵, Nicola Stefano Fracchiolla⁶, Francesco Grimaldi⁷, Matteo Leoncin⁸, Antonino Mule⁹, Mario Annunziata¹⁰, Immacolata Attolico⁵, Claudia Maria Basilico¹¹, Ilaria Capolsini¹², Daniele G. Mattei¹³, Giovanni Marconi¹⁴, Matteo Piccini¹⁵, Chiara Pavoni¹, Antonio Curti⁴, Robin Foà¹⁶, Federico Lussana^{1,17}

**26 patients
20 had Philadelphia negative
6 Philadelphia positive (Ph+) ALL.**

**median age of the study population was 39 years (range 16-66)
median follow up was 5 months**

Conclusions This study indicates that retreatment with Ino is a valuable option associated with a high CR rate and acceptable safety, even in heavily pretreated relapsed patients. Notably, the clinical outcomes for patients who responded to Ino retreatment and were subsequently bridged to CAR therapy were particularly encouraging.

Asciminib e combinazioni



CLINICAL TRIALS AND OBSERVATIONS

Asciminib plus dasatinib and prednisone for Philadelphia chromosome–positive acute leukemia

Marlise R. Lusk^{1,*}, Mark A. Murakami^{1,*}, Julia Keating², Yael Flamand², Eric S. Winer¹, Jacqueline S. Garcia¹, Maximilian Stahl¹, Richard M. Stone¹, Martha Wadleigh¹, Stella L. Jaekle¹, Ella Hagopian¹, David M. Weinstock³, Jessica Liegel⁴, Malgorzata McMasters⁴, Eunice S. Wang⁵, Wendy Stock⁶, and Daniel J. DeAngelo¹

¹Department of Medical Oncology and ²Department of Data Sciences, Dana-Farber Cancer Institute, Boston, MA; ³Merck & Co, Rahway, NJ; ⁴Division of Hematologic Malignancies and Bone Marrow Transplantation, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA; ⁵Leukemia Service, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY; and ⁶Section of Hematology/Oncology, Department of Medicine, University of Chicago Comprehensive Cancer Center, Chicago, IL

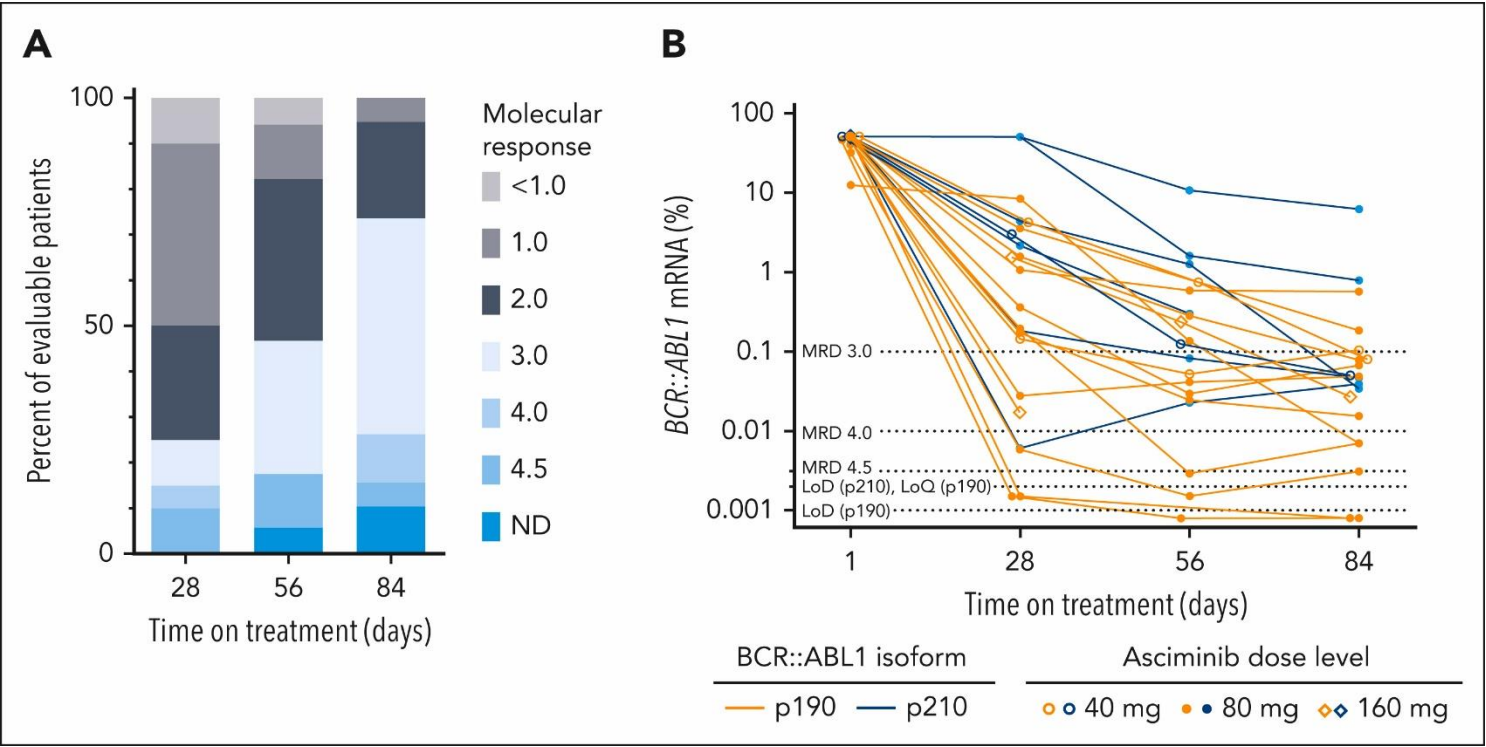
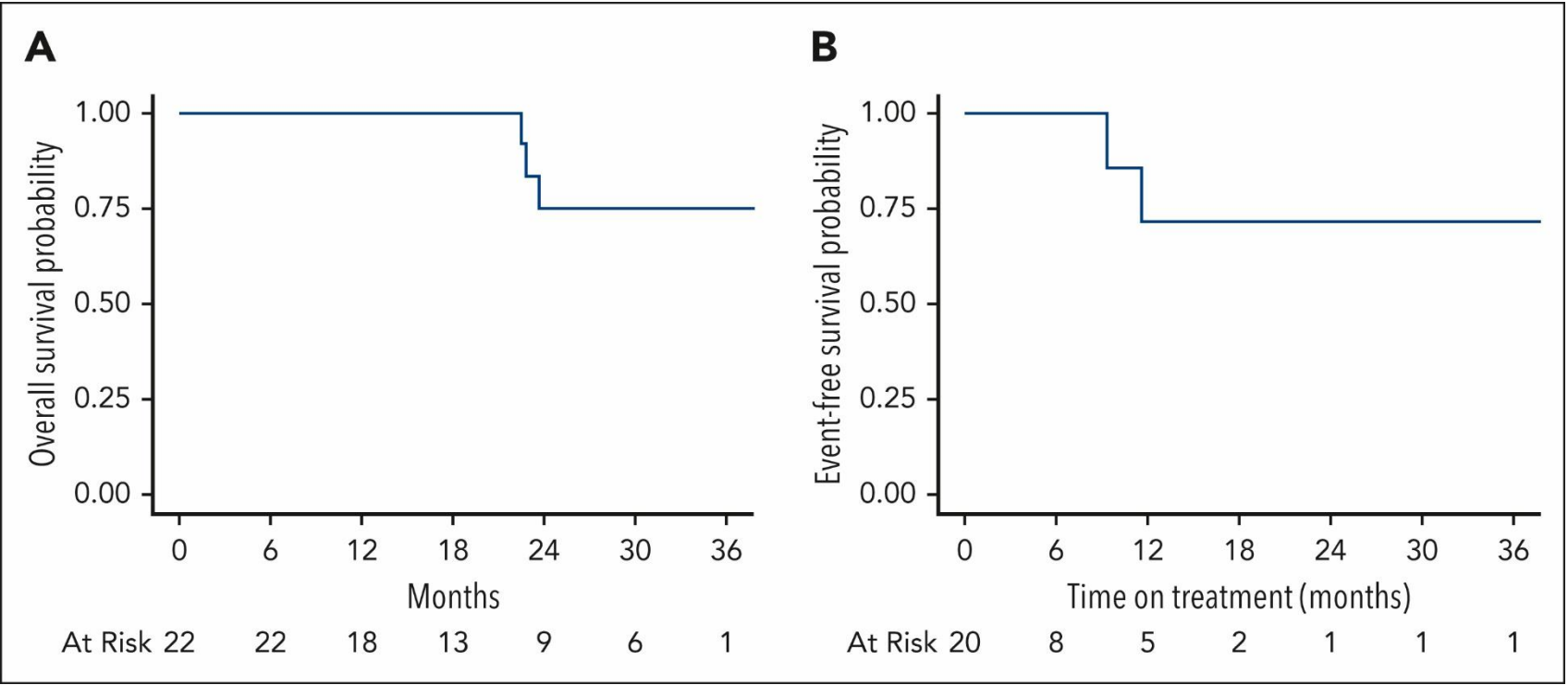


Table 3. Summary of response kinetics for patients with de novo ALL (n = 22)

	No. of patients with response/total evaluable patients (%)		
	Day 28	Day 56	Day 84
Hematologic CR	19/20 (95)	18/18 (100)	18/18 (100)
Cytogenetic CR	14/17 (82)	16/17 (94)	16/16 (100)
Flow-negative MRD (<10 ⁻⁴)	12/20 (60)	15/18 (83)	16/18 (89)
BCR::ABL1 RT-qPCR			
Molecular response 1	18/20 (90)	16/17 (94)	19/19 (100)
Molecular response 2	10/20 (50)	14/17 (82)	18/19 (95)
Molecular response 3	5/20 (25)	8/17 (47)	14/19 (74)
Molecular response 4	3/20 (15)	3/17 (18)	5/19 (26)

Shown are response rates after each cycle of induction treatment for study participants with de novo ALL (n = 22). Of note, the 2 patients with CML-LBC achieved flow-negative MRD, with molecular response 2-log and molecular response 3-log.

RT-qPCR, reverse transcription quantitative polymerase chain reaction.

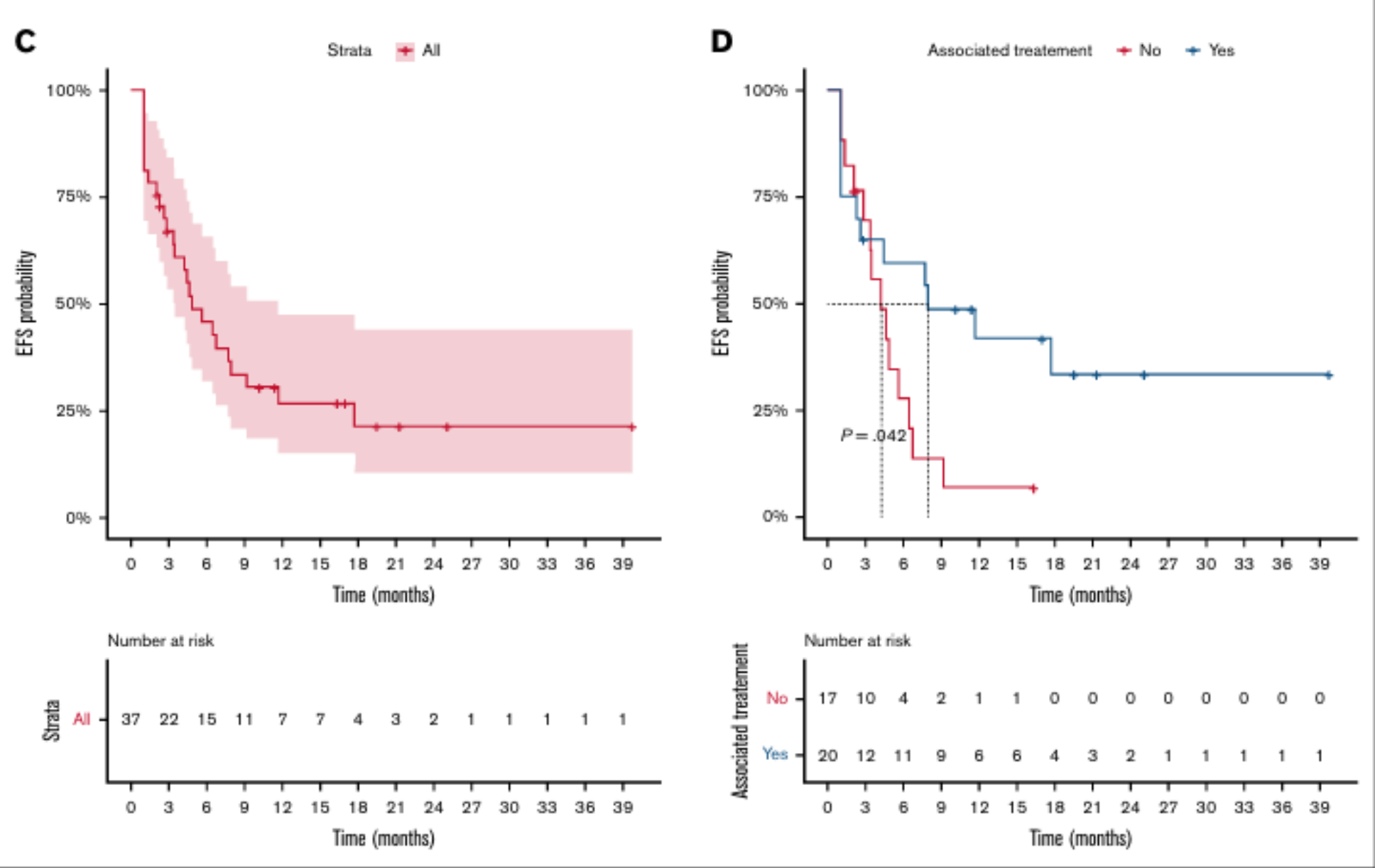
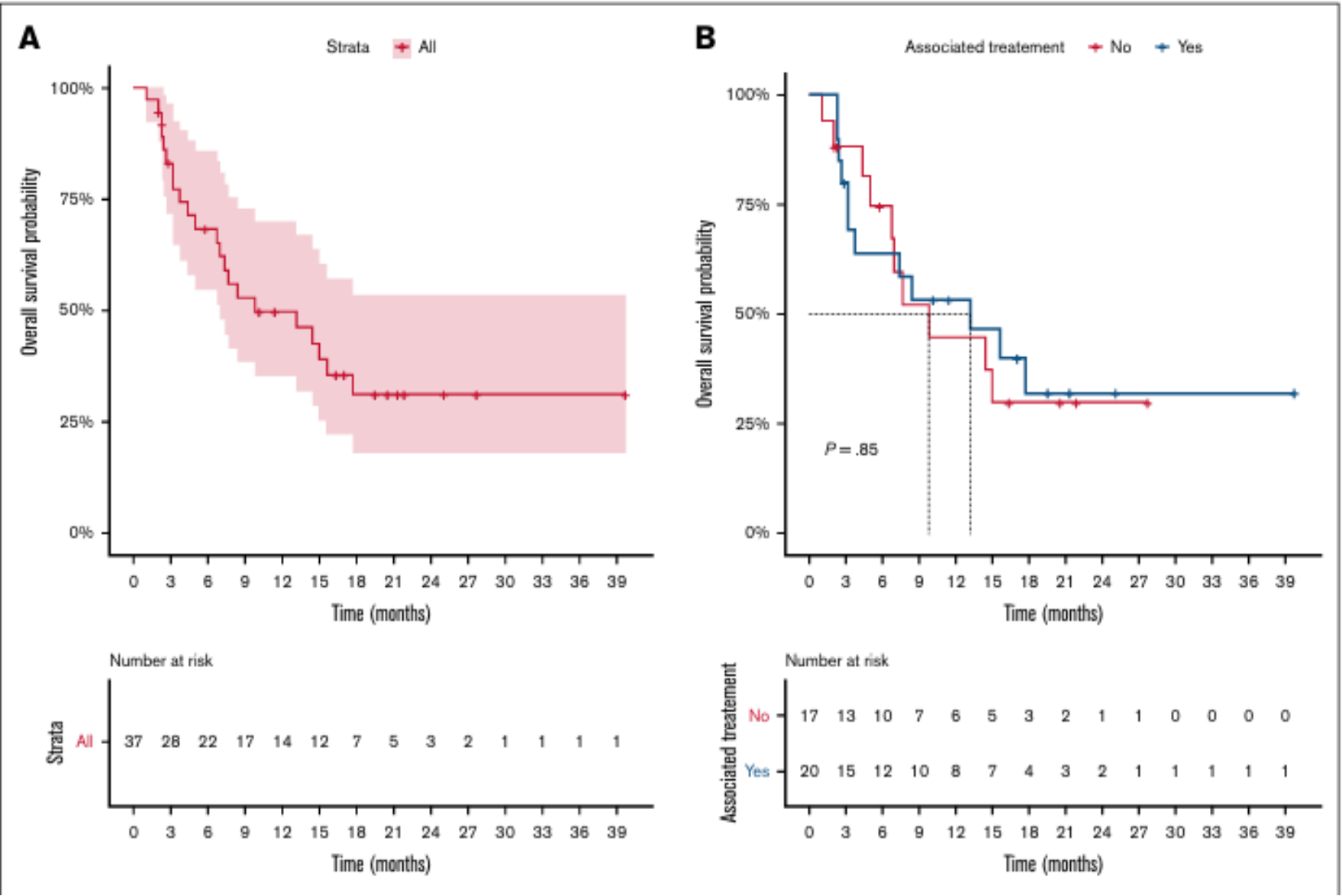


The median follow-up was 26.9 months (95% CI, 15.0-30.7). At 1 and 2 years, the OS was 100% and 75% (95% CI, 51-99), respectively. At 1 and 2 years, the EFS was 71% (95% CI, 38-100) and 71% (95% CI, 38-100), respectively

TO THE EDITOR:

Asciminib for relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia

23 SEPTEMBER 2025 • VOLUME 9, NUMBER 18



Median follow-up was 7.6 months.
Median OS and median EFS were 9.8 months and 4.9 months

Median EFS was higher when ASC was used in combination compared to monotherapy (7.93 months vs 4.23 months respectively). Median remission duration was 4.87 months (95% CI, 3.43-11.70).

Publication Number: 1572

Abstract Title : Asciminib for relapsed or refractory Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) and lymphoid blast crisis of chronic myeloid leukemia (LBC-CML) in Italy: A Campus ALL real life study

Matteo Dragani , Patrizia Chiusolo, Giulia Rivoli, Marco Cerrano, Lara Aprile, Erika Borlenghi, Benedetta Cambò, Eleonora De Bellis, Marzia Defina, Ludovica Fucci, Rachele Giubbolini, Carmela Gurrieri, Cristina Papayannidis, Elisa Roncoroni, Marina Aurora Urbano, Robin Foà, Sabina Chiaretti

- ❖ September 2021 to April 2025, 19 patients (12 Ph+ ALL, 7 LBC-CML)
- ❖ Median age was 55 years (range 20–77) and 12 were male.
- ❖ median of 2 prior TKIs (range 1–3).
- ❖ 6 Blinatumomab, 10 Inotuzumab, 8 relapse after alloTMO and 5 CAR-T therapy.
- ❖ 11 hematologic relapse , 7 with MRD relapse/ recurrence, 1 MRD-negative patient (toxicities during previous therapies).
- ❖ CNS+ 2 patients.
- ❖ median follow-up from asciminib initiation was 10.2 months (95% CI: 3.4–NA) and median duration of asciminib-based therapy was 2.71 months (range, 0.8–25.3).
- ❖ Mutations in ABL1 in 10 patients (66.6%)
- ❖ Asciminib was administered as monotherapy in 63% of cases.
- ❖ 37% combination therapy: one with imatinib (400 mg daily), five with ponatinib (30 mg daily), and one sequentially after high-dose chemotherapy and radiotherapy.

Publication Number: 1572

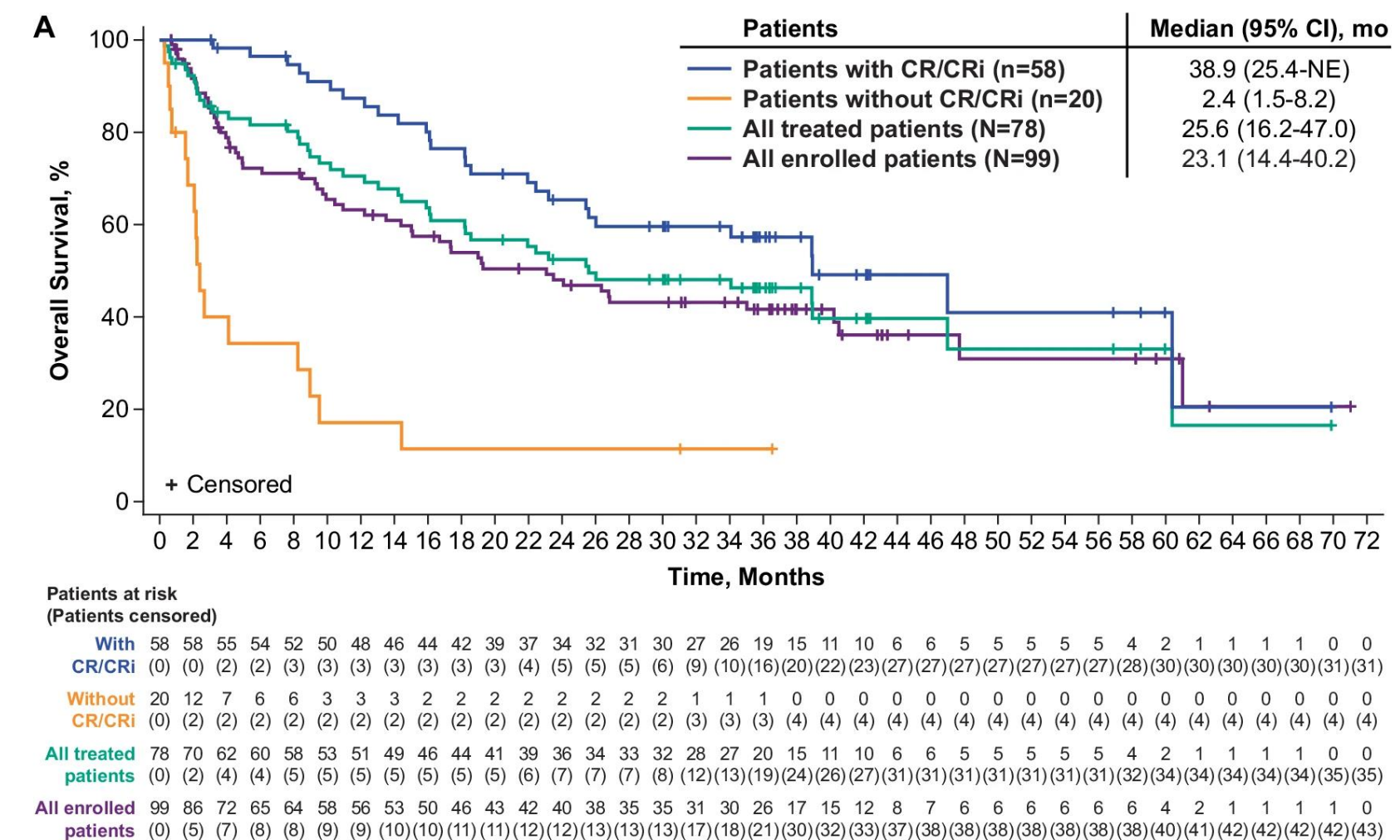
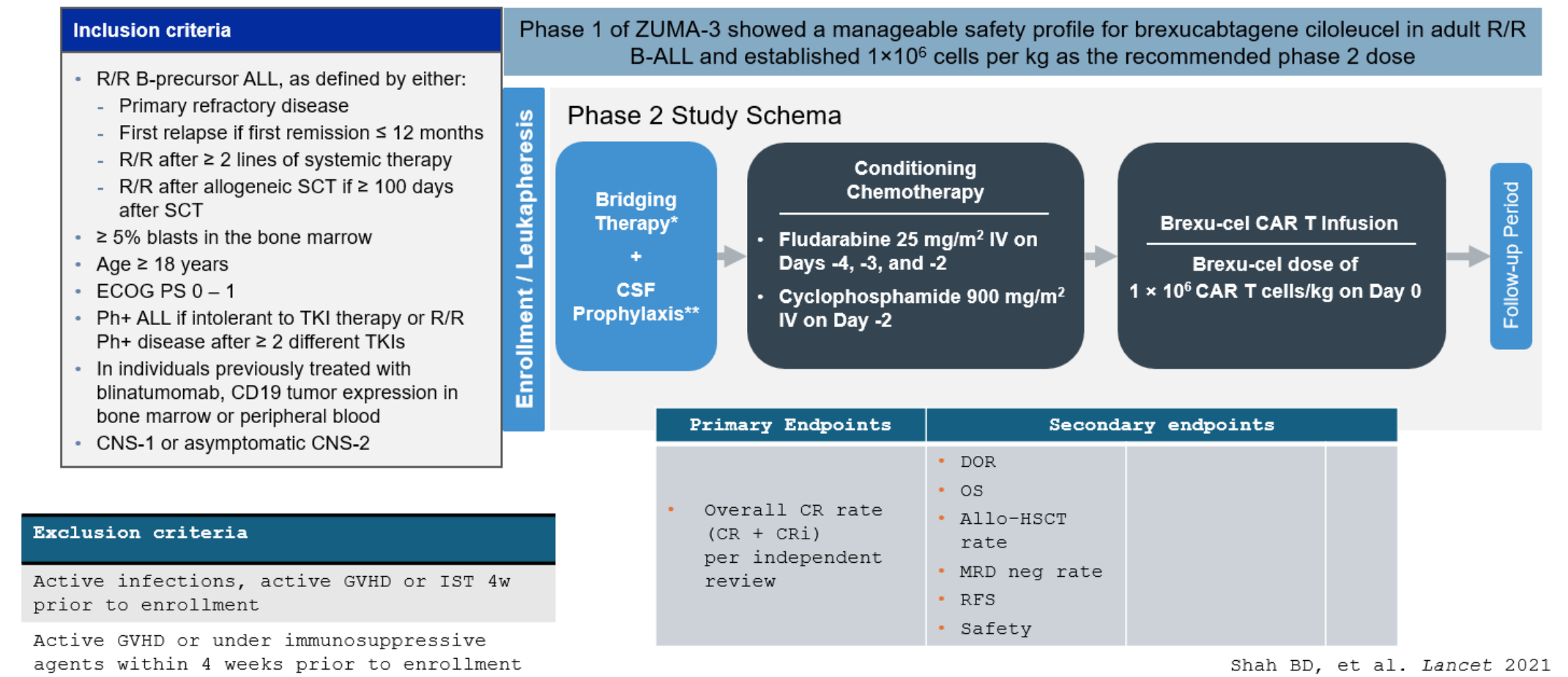
Abstract Title : Asciminib for relapsed or refractory Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) and lymphoid blast crisis of chronic myeloid leukemia (LBC-CML) in Italy: A Campus ALL real life study

- ❖ Daily asciminib doses in combination therapy ranged from 40 mg once daily (1 patient) to 40 mg twice daily (6 patients).
 - ❖ Monotherapy, 11 patients received 200 mg twice daily, and one patient 40 mg once daily.
 - ❖ Thirteen patients (68.4%) achieved complete hematologic remission, 3 achieved partial remission, 1 had a stable disease, and two were refractory, dying shortly after treatment initiation.
 - ❖ Among the responders, seven patients (7/13) achieved a major molecular response.
 - ❖ Asciminib was generally well tolerated, both as monotherapy and in combination.
-
- Median overall survival (OS) was not reached, while the estimated 1-year OS was 62.9%.
 - 5 deaths, 4 were due to disease progression, and 1 occurred in a patient with non-blastic aplasia and BCR-ABL < 0.1%.
- 8 subsequent lines of therapy after asciminib:
- 4 were TMO ,
 - 1 low-dose chemotherapy
 - 3 who progressed under asciminib respectively received inotuzumab, ponatinib, or olverembatinib and subsequent immunotherapy.

CAR-T: dove si colloca nella Ph+ ALL

- Indicazione principale: R/R B-ALL, inclusa Ph+.
- In Ph+ la strategia può includere mantenimento TKI post-CAR-T
- Timing: considerare prima di deterioramento clinico; logistica e bridging.
- Antigeni escape: monitorare CD19/CD22; valutare sequenze con InO/blina.

ZUMA-3: phase II study design



The median OS was 25.6 months for all treated patients and 38.9 months for responders

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ACUTE LYMPHOBLASTIC LEUKEMIA

Three-year analysis of adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with brexucabtagene autoleucel in ZUMA-3

Bijal D. Shah^{1,5}, Ryan D. Cassaday¹⁰, Jae H. Park¹¹, Roch Houot⁴, Aaron C. Logan⁵, Nicolas Boissel¹⁶, Thibaut Leguay⁷, Michael R. Bishop⁹, Max S. Topp², Kristen M. O'Dwyer¹⁰, Dimitrios Tzachanis¹¹, Martha L. Arellano¹², Yi Lin¹³, Maria R. Baer¹⁴, Gary J. Schiller¹⁵, Marion Subklewe¹⁶, Mehrdad Abedi¹⁷, Monique C. Minnema¹⁸, William G. Wierda¹⁹, Daniel J. DeAngelo²⁰, Patrick Stiff²¹, Deepa Jayakumar²², Daqin Mao²³, Sabina Adhikary²³, Lang Zhou²³, Tsveta Hadjivassileva²³, Rita Damico Khalid²³, Armin Ghobadi^{24,26} and Olalekan O. Oluwole^{25,26}

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ACUTE LYMPHOBLASTIC LEUKEMIA

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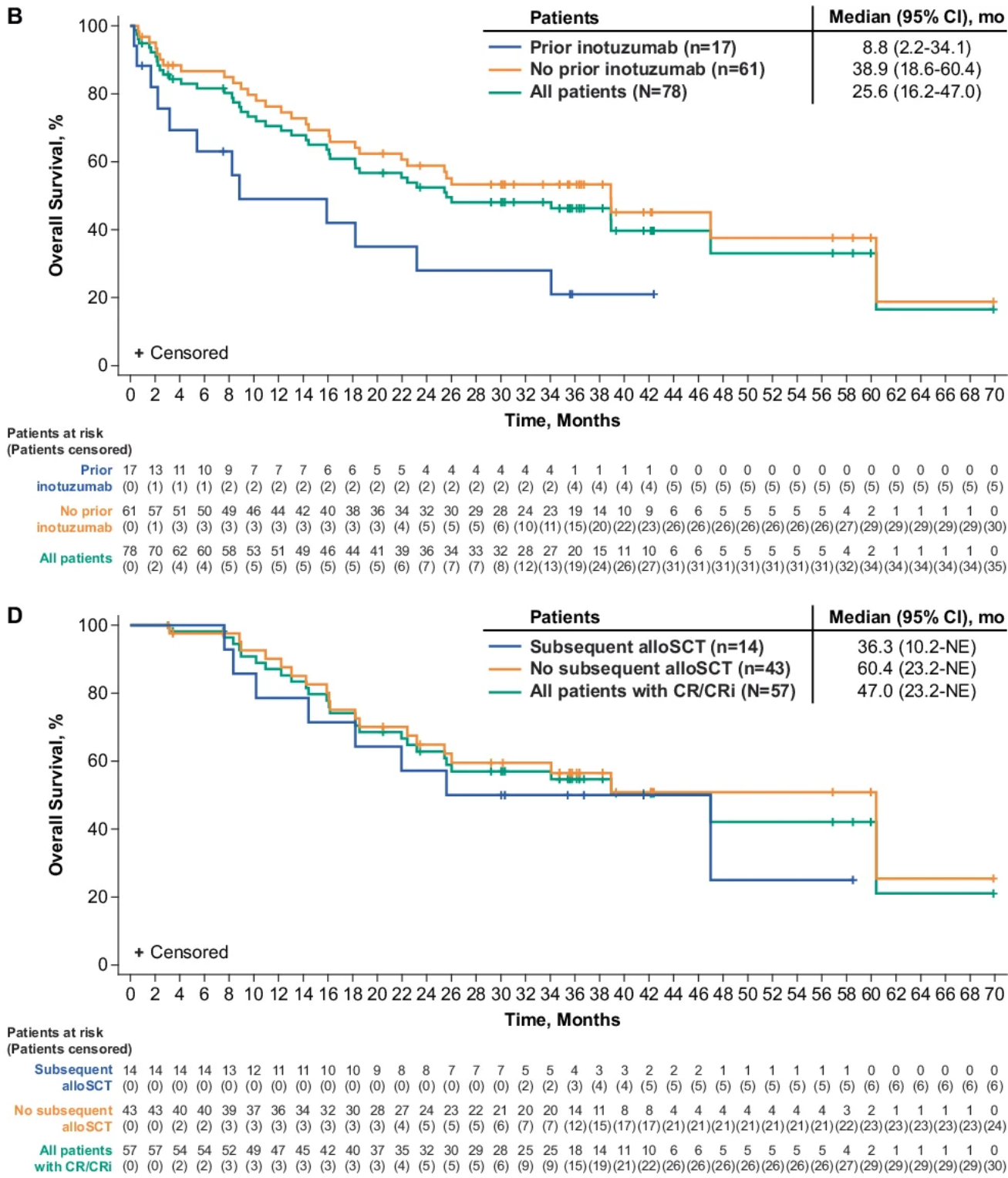
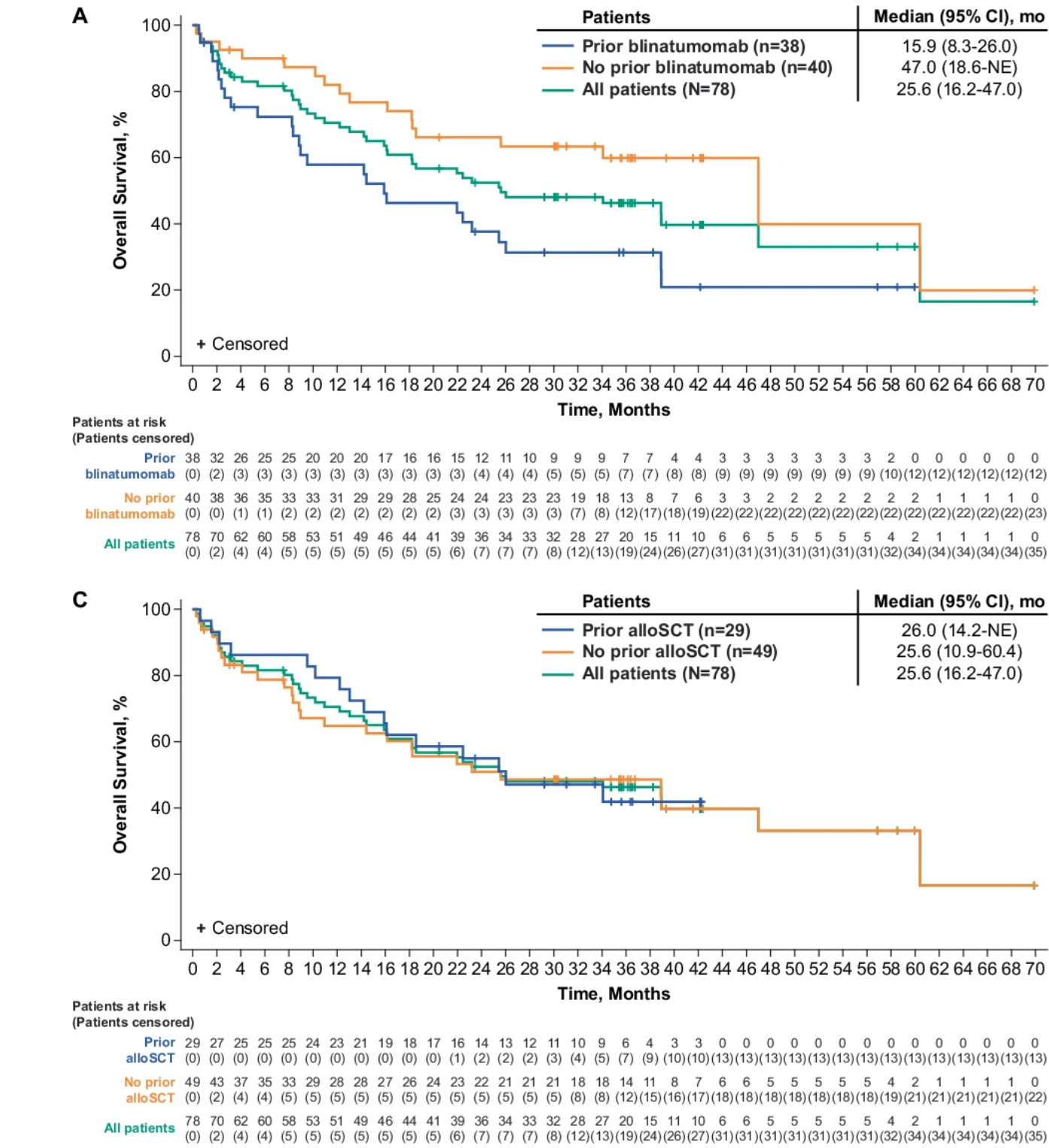


Table 1. Efficacy outcomes in all treated patients by prior blinatumomab, inotuzumab, or alloSCT.

	Phase 1 and 2 patients treated at pivotal dose (N = 78)	Prior blinatumomab		Prior inotuzumab		Prior alloSCT	
		Yes (n = 38)	No (n = 40)	Yes (n = 17)	No (n = 61)	Yes (n = 29)	No (n = 49)
Overall CR/CRi rate per investigator review, n (%) ^a	58 (74)	24 (63)	34 (85)	11 (65)	47 (77)	23 (79)	35 (71)
CR rate, n (%)	49 (63)	19 (50)	30 (75)	9 (53)	40 (66)	17 (59)	32 (65)
CRi rate, n (%)	9 (12)	5 (13)	4 (10)	2 (12)	7 (11)	6 (21)	3 (6)
Median overall survival, months (95% CI)	25.6 (16.2–47.0)	15.9 (8.3–26.0)	47.0 (18.6–NE)	8.8 (2.2–34.1)	38.9 (18.6–60.4)	26.0 (14.2–NE)	25.6 (10.9–60.4)

AlloSCT allogeneic stem cell transplant, CI confidence interval, CR complete remission, CRi complete remission with incomplete hematologic recovery, NE not estimable.

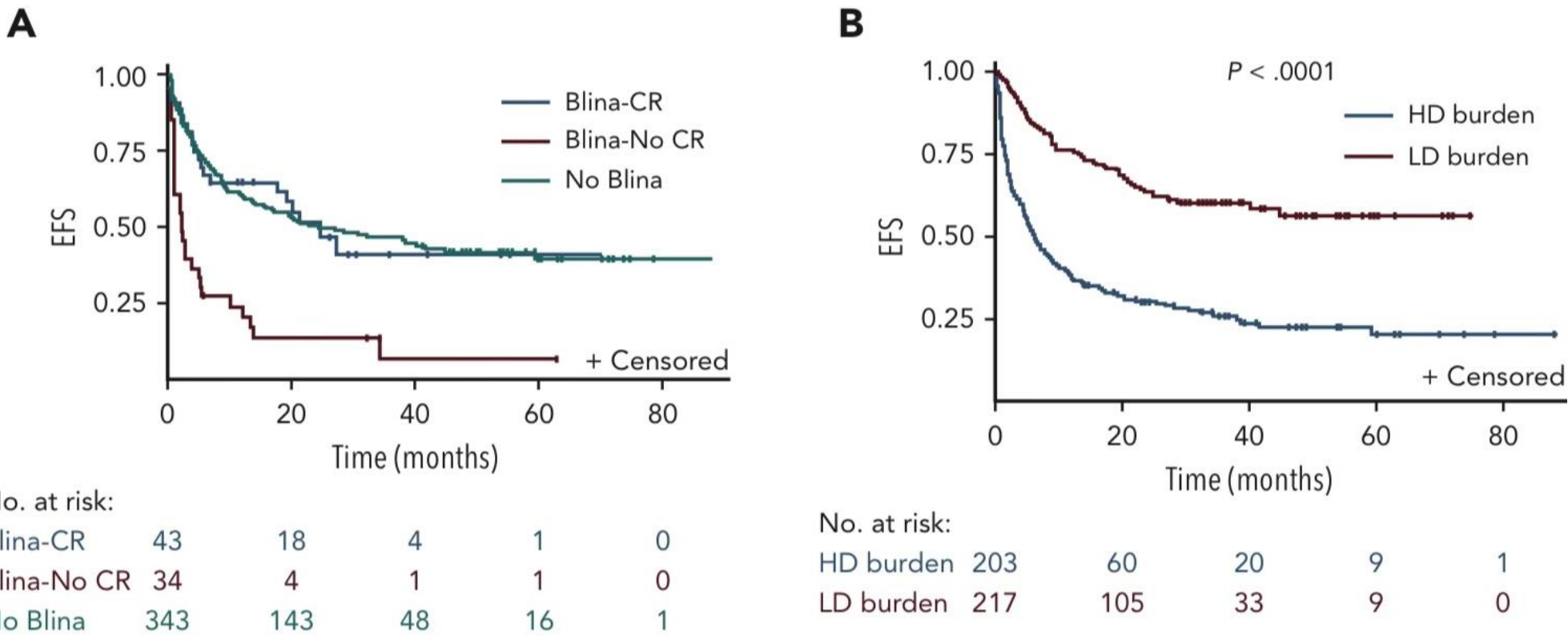
Of the 58 patients with CR/CRi per investigator review, 14 were Ph + at baseline, of whom, 4 patients (29%) started TKI therapy without being censored as permitted by study protocol. One of these patients subsequently died without relapse; 1 patient subsequently relapsed and died; one patient had subsequent alloSCT shortly after TKI start and was censored at last disease assessment per study protocol, prior to TKI start; and 1 patient remained in ongoing remission without additional therapy as of data cutoff

median OS for all treated patients with prior blinatumomab exposure (n = 38) was 15.9 months (95% CI: 8.3–26.0), and was 47.0 months (95% CI: 18.6–NE) for patients without prior blinatumomab exposure (n = 40)

median OS prior reports for all treated patients with prior inotuzumab exposure (n = 17) at 8.8 months (95% CI: 2.2–34.1) and 38.9 months (95% CI: 18.6–60.4) for those without prior inotuzumab exposure

the median OS estimates for patients with and without prior alloSCT were similar at 26.0 months (n = 29; 95% CI, 14.2–NE) and 25.6 months (n = 49; 95% CI: 10.9–60.4), respectively

whereas estimated medians for patients without prior alloSCT appeared higher in a previous report [8].



How I use risk factors for success or failure of CD19 CAR T cells to guide management of children and AYA with B-cell ALL

Regina M. Myers,^{1,*} Nirali N. Shah,^{2,*} and Michael A. Pulsipher³

¹Division of Oncology, Cell Therapy and Transplant Section, Children's Hospital of Philadelphia, Philadelphia, PA; ²Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; and ³Division of Hematology and Oncology, Intermountain Primary Children's Hospital, Huntsman Cancer Institute, Spencer Fox Eccles School of Medicine at the University of Utah, Salt Lake City, UT

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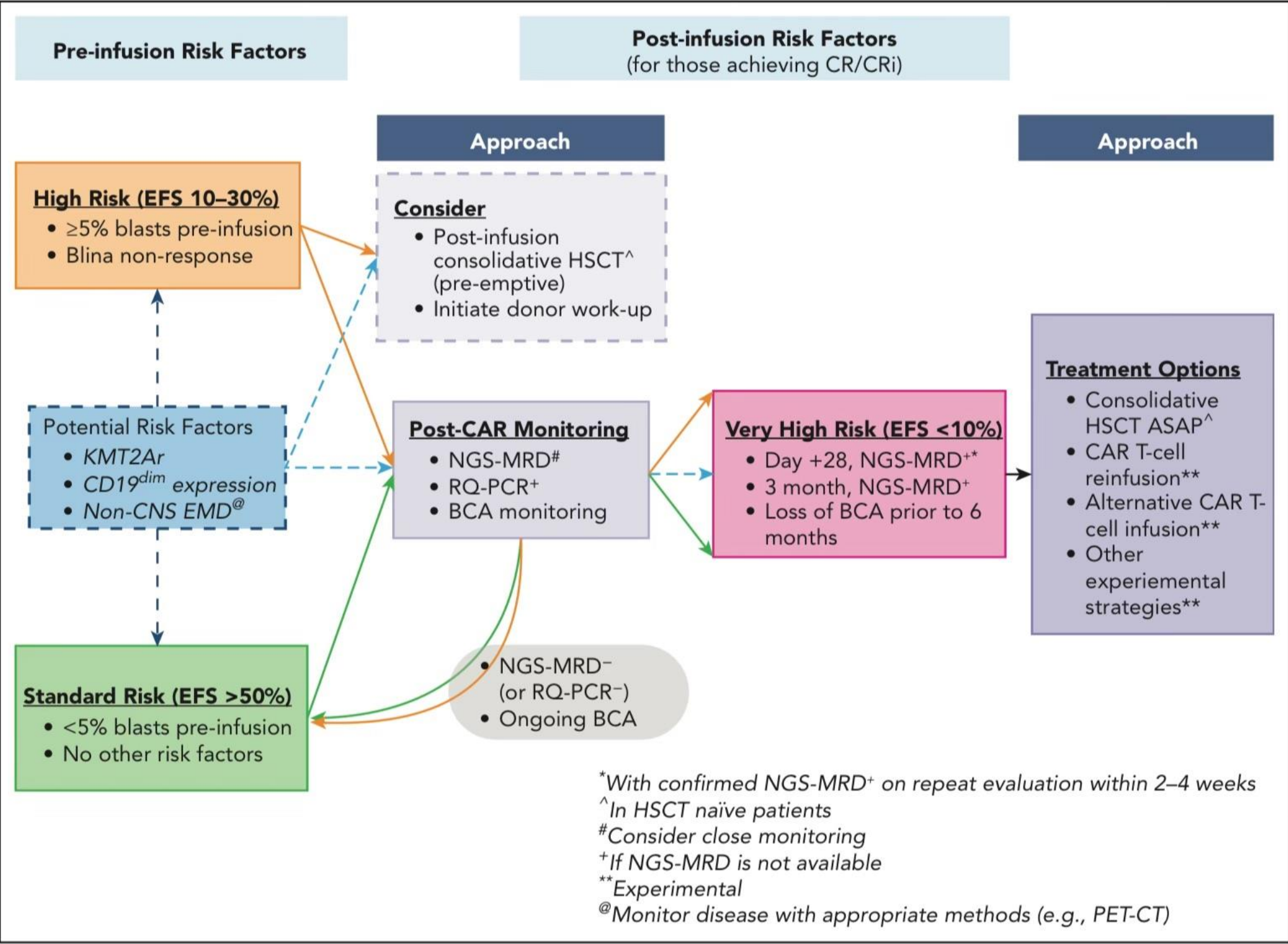
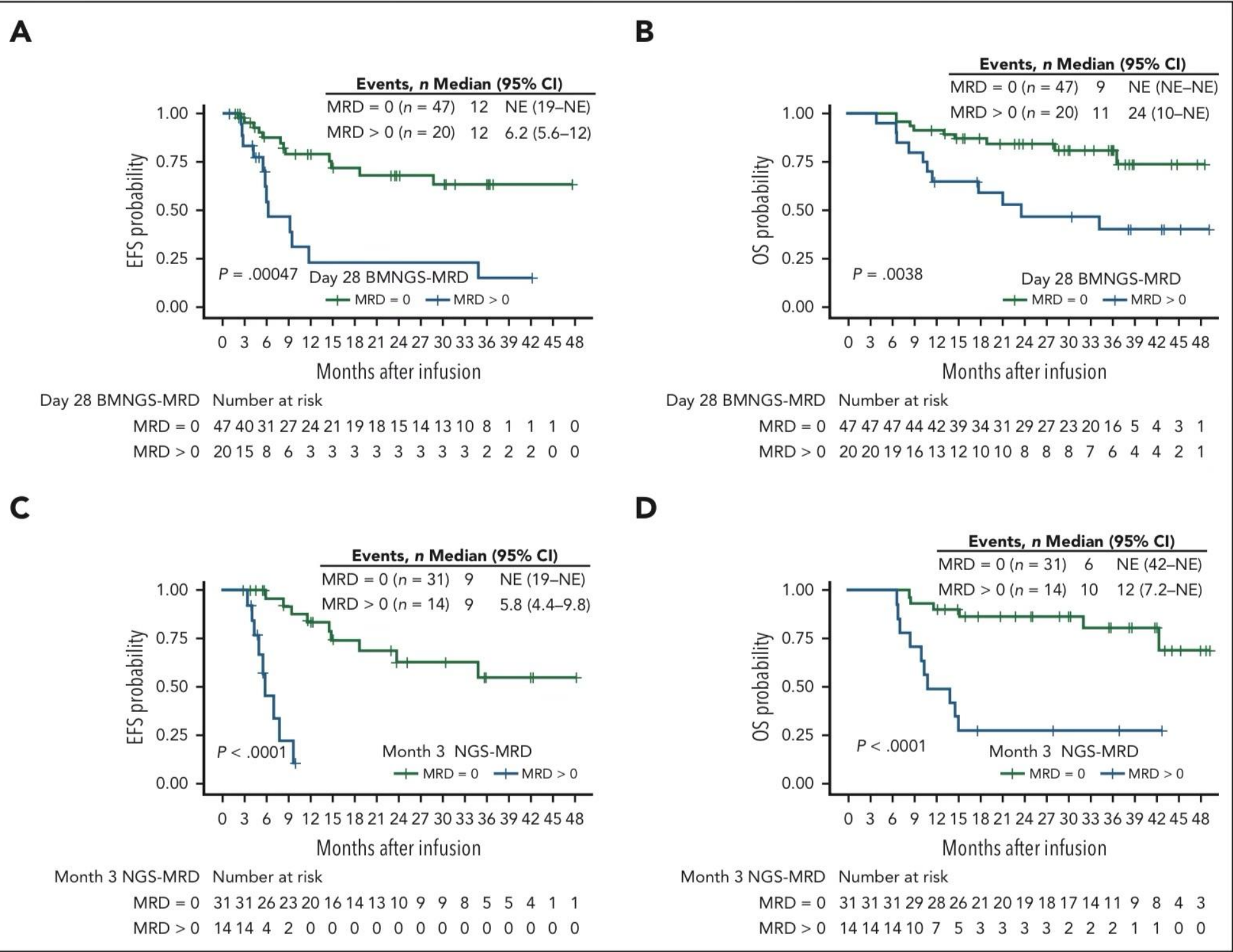
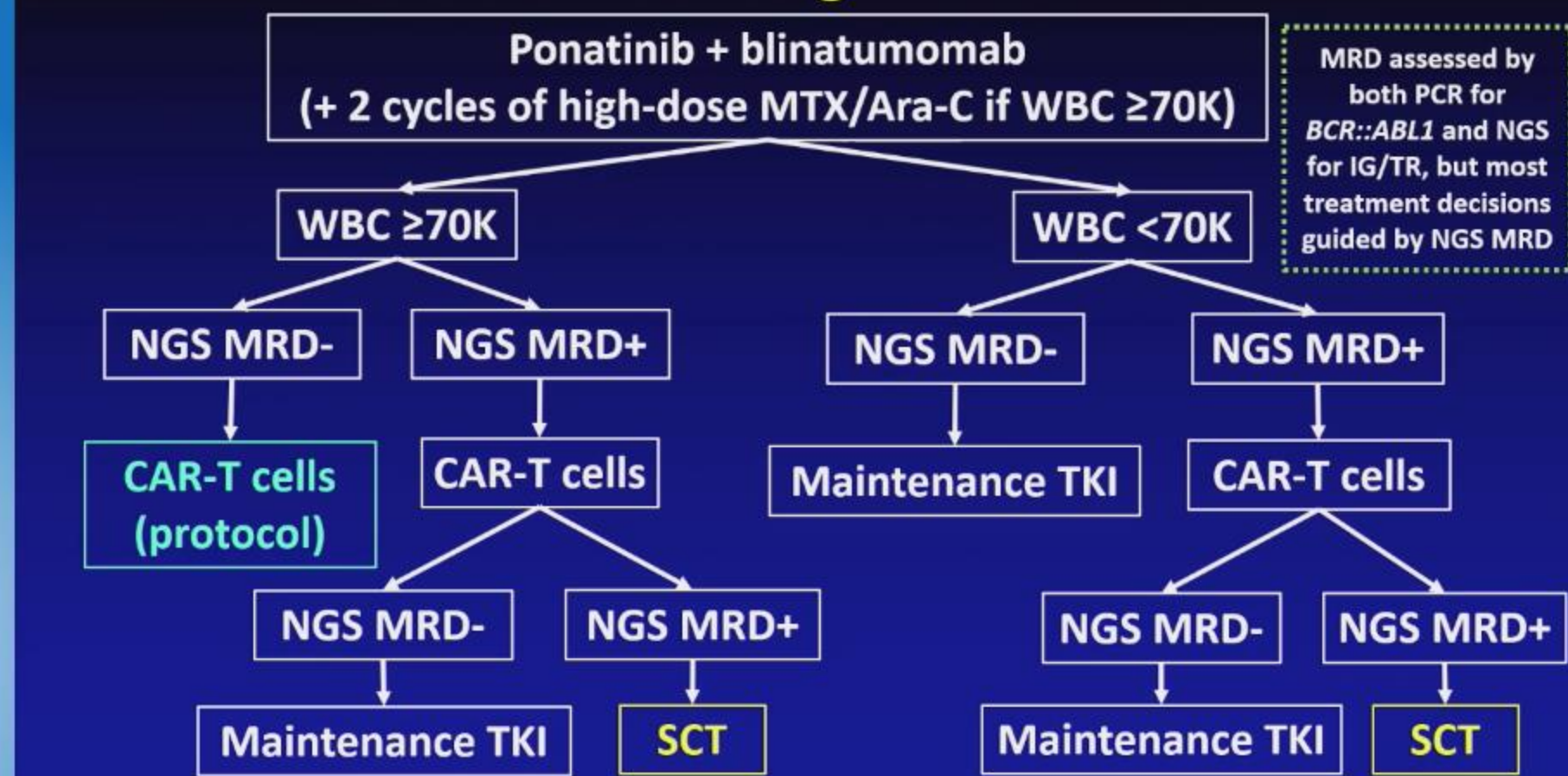


Figure 3. Approach to peri-CAR T-cell risk stratification with monitoring and treatment options. This figure highlights various preinfusion risk factors that may affect long-term EFS, remission durability, and/or OS; and how these factors are further modulated by post-CAR T-cell outcomes, based primarily on NGS-MRD status and loss of BCA. Refer to Table 1 for specific information on risk factors. ASAP, as soon as possible; Blina, blinatumomab; CRi, complete remission with incomplete count recovery.

Which adult patient deserves consolidative allo-HCT after brexu-cel?

BEFORE APHERESIS	BEFORE APHERESIS	AFTER CAR T
Disease-related factors - Genetics? (Ph+ better? KMT2AR?) - EMD? CNS? - Disease burden pre-apheresis? - CD19 weak expression? Disease history Previous alloHCT++ - Number of previous relapses? - Response to previous immunotherapy? Patient characteristics PS/comorbidities+ → NRM Age+ → NRM Expectations / will +	Disease-related factors Disease burden pre-LD+ - HEMATOTOX?	Disease-related factors MRD++ CAR-T related factors - CAR-T persistence?/BCA? - CAR-T expansion ? Other factors Donor features + → NRM

MDACC Research Algorithm for Ph+ ALL



In Conclusion...

- Do we need alloSCT?
 - Identify patients who can be cured without alloSCT; e.g. **3-months CMR, MRD negative by NGS** (lack of *IKZF1*^{plus})
- **Ponatinib** best TKI: 3 months-CMR 86%; 6-year OS rate 76% (HCVAD-ponatinib)
 - **Ponatinib > Imatinib**: Phase III PhALLCON
- How much chemoRx (risk of CNS relapses):
 - **15 IT** vs HDAC/MTX?
 - Consider CAR-T cells?
- New drugs to be explored:
 - **SQ Blinatumomab, Asciminib, Olverembatinib**
- Duration of TKI maintenance → Treatment-free remission
 - At least 4–5 years of MRD-negativity by NGS
 - In patients without HR features (High WBC and/or *IKZF1*^{plus})

E Jabbour, personal communication.

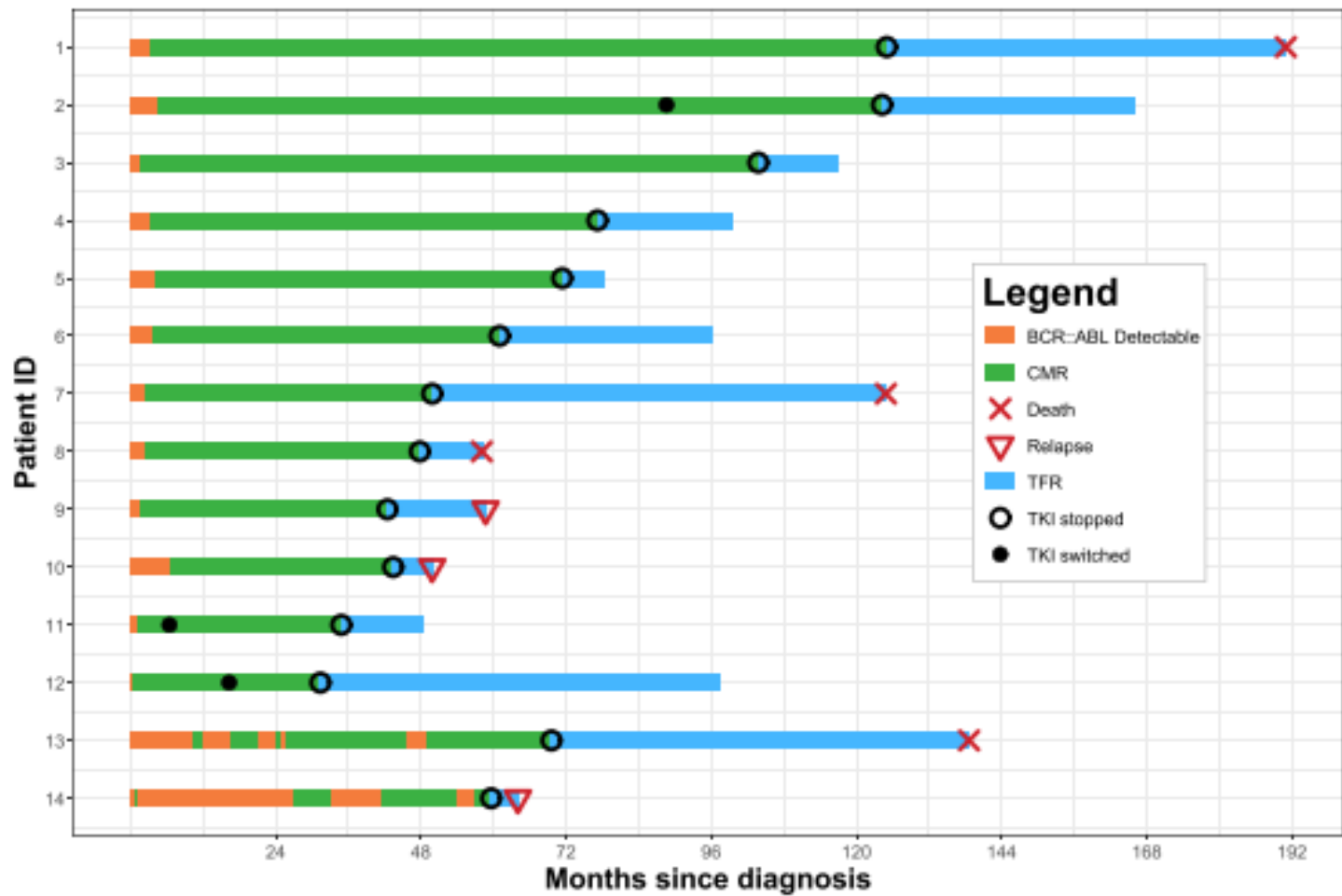
Treatment-Free Remission (TFR)

TABLE 1 Patient characteristics, N = 14.

Variable	No. (%) or median [range]
Sex	
Woman	7 (50.0)
Man	7 (50.0)
Age at diagnosis, years	
Median [range]	61 [20–82]
Age at TKI discontinuation, years	
Median [range]	65 [23–86]
Transcript at diagnosis	
p190	10 (71.0)
p210	4 (29.0)
Induction regimen	
HCVAD + imatinib	2 (14.0)
HCVAD + dasatinib	6 (43.0)
HCVAD + ponatinib	4 (29.0)
Blinatumomab + ponatinib	2 (14.0)
TKI type before discontinuation	
Dasatinib	5 (36.0)
Ponatinib	5 (36.0)
Imatinib	3 (21.0)
Bosutinib	1 (7.0)

TABLE 2 Tyrosine kinase inhibitor treatment and outcome characteristics, N = 14.

Variable	No. (%) or median [range/IQR]
Time to CMR, months	
Median [IQR]	3.1 [1.9–4.3]
Range	0.42–56.5
Duration of CMR before TKI discontinuation, months	
Median [IQR]	46.1 [34.2–72.2]
Range	2.7–121.3
Time on TKI, months	
Median [IQR]	60 [43–77]
Range	31–125
Reason for TKI discontinuation, no. (%)	
Pleural effusion	4 (29.0)
Vascular disease	4 (29.0)
PAH	2 (14.0)
Cytopenia	1 (7.1)
Pancreatitis	1 (7.1)
Other	2 (14.0)
Treatment-free remission duration, months	
Median [IQR]	19 [10–66]
Range	4–75
Relapse status, no. (%)	
No relapse	11 (79.0)
Relapse	3 (21.0)



TKI DC/TFR in Ph+ ALL Without Allo HSCT

- 14/238 patients (6%); median age 61 years; median time on TKI 60 months (31–125); median time in CMR 46 months (2.7–121)
- Rx HCVAD + added TKI: Imatinib (n=2); Dasatinib (n=6); Ponatinib (n=4); Blinatumomab–Ponatinib (n=2)
- Reason for TKI DC: pleural effusions (n=4); AOE/VOE (n=4); PH (n=2); pancreatitis (n=1); cytopenia (n=1); other (n=2)
- 11 patients (79%) remained in TFR. None of 8 in CMR 4+ years prior to TKI DC had relapse

The median duration of TFR was not reached
TFR rates were 85% at 12 months and 75% at 36 months

all three molecular/ clinical relapses occurred in patients with a CMR duration less than 48 months

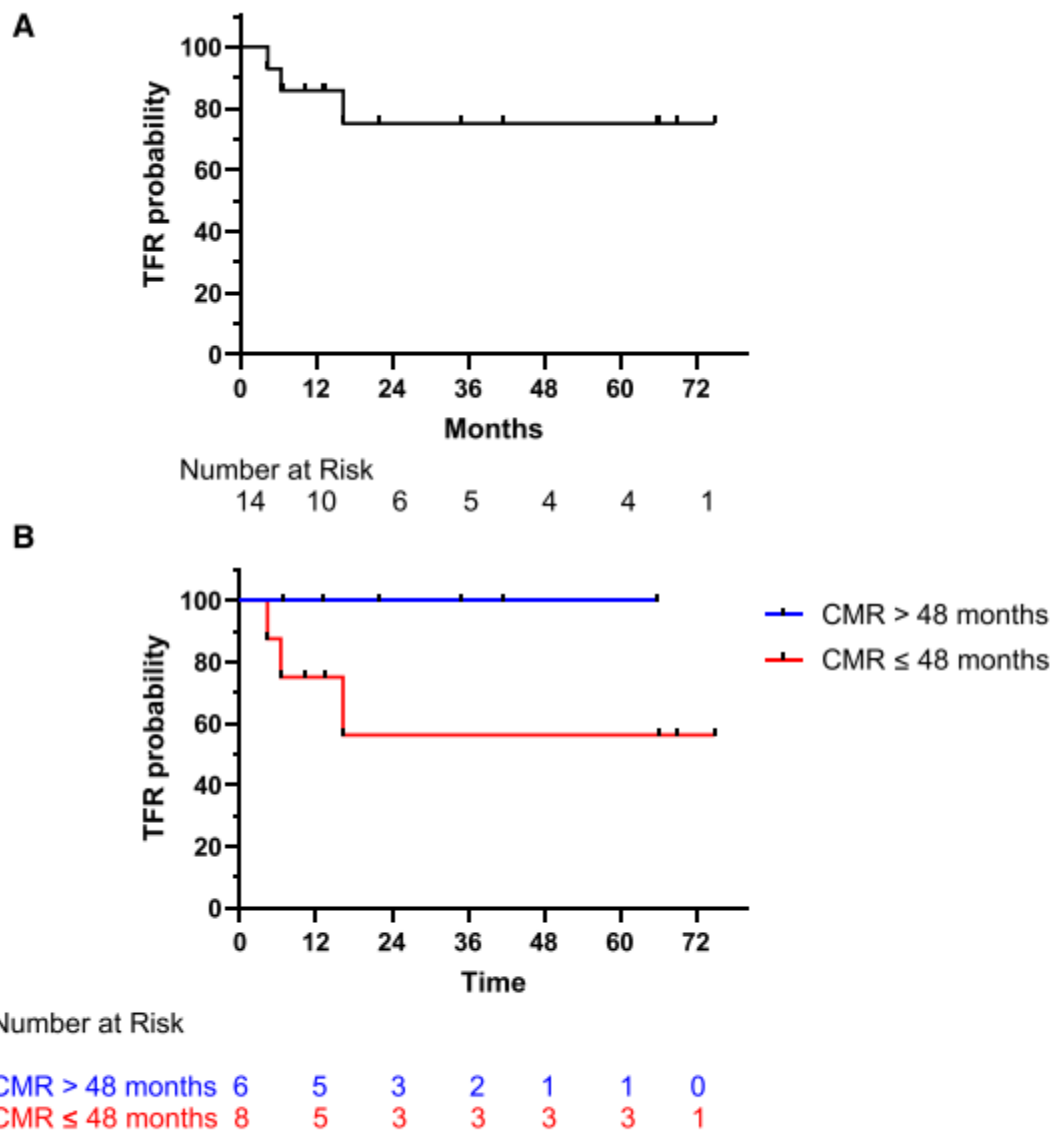


FIGURE 2 A) Kaplan-Meier estimate of the probability of TFR after TKI maintenance discontinuation. (B) TFR probability stratified by CMR duration before TKI discontinuation. CMR indicates complete molecular response; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

DALLA DIAGNOSI ALLA MALATTIA REFRATTARIA NEL PAZIENTE PH+

Table 5. How I treat newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia

Diagnostics/evaluation	Patient: Age, fitness/frailty, cardiovascular risk factors, support Disease: <i>Genetic risk:</i> cytogenetic, molecular (<i>IKZF1</i> ; <i>IKZF1</i> plus) <i>MRD monitoring:</i> RT-PCR p190 vs p210; NGS or PCR for clonal tracking
When possible, (a) enroll on clinical trial, (b) follow published regimen	
Phase: Induction Goal: Complete remission (CR)	TKI: DAS or PON or clinical trial PLUS: Low intensity (steroids, steroids + vincristine, steroids + blinatumomab)
Phase: Consolidation Goal: Prolong CR (indefinitely)	TKI: DAS or PON or clinical trial -If DAS, consider change to PON if inadequate response -If PON, dose reduce to 15 mg after achievement of CMR PLUS: 1. TKI alone (<i>if alloHCT planned or palliative goal</i>) 2. Chemotherapy (<i>age adjusted</i>) 3. Blinatumomab (<i>within 3 months</i>) 4. AlloHCT
AlloHCT, in CR1	Favoring yes 1. High-risk genetic features (chromosomes: complex, "double" Ph; <i>IKZF1</i> plus) 2. No achievement of CMR by 3 months (with TKI+/- chemotherapy) 3. Fit, appropriate donor 4. No blinatumomab available or not tolerated Favoring no 1. No high-risk genetic features 2. Achievement of CMR by 3 months (with TKI+/- chemotherapy) 3. Blinatumomab Unknown 1. Poor response to TKI+/- chemo but CMR with blinatumomab 2. High-risk genetics but optimal MRD response
CNS prophylaxis	IT chemotherapy (12-15) High-dose methotrexate and/or cytarabine
Monitoring	<i>BCR::ABL1</i> RT-PCR NGS, to establish presence of CML-like biology, and if present to supplement <i>BCR::ABL1</i> transcript monitoring

Ph+ ALL: new approaches for upfront therapy

Attilio

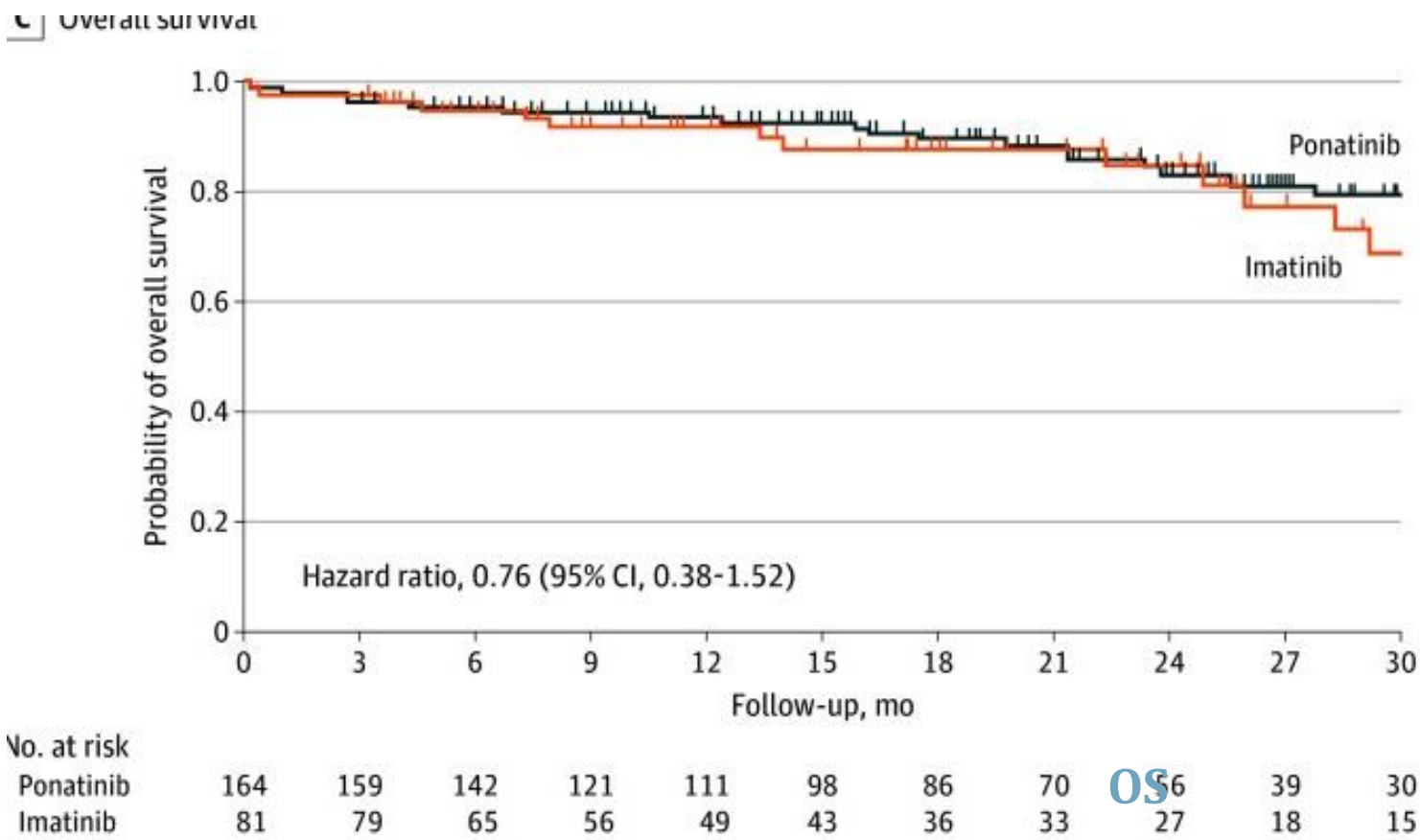


"Il Brutto Anatroccolo
ci insegna che bisogna partire
da ciò che si è per arrivare
a ciò che si vuole fare
e a ciò che si vuole essere
nella propria vita"

IL BRUTTO ANATROCCOLO

PhALLCON — curve di sopravvivenza

Studio di fase 3 in adulti con Ph+ ALL di nuova diagnosi: ponatinib + chemioterapia a intensità ridotta vs imatinib + chemioterapia a intensità ridotta



EFS (endpoint secondario chiave)

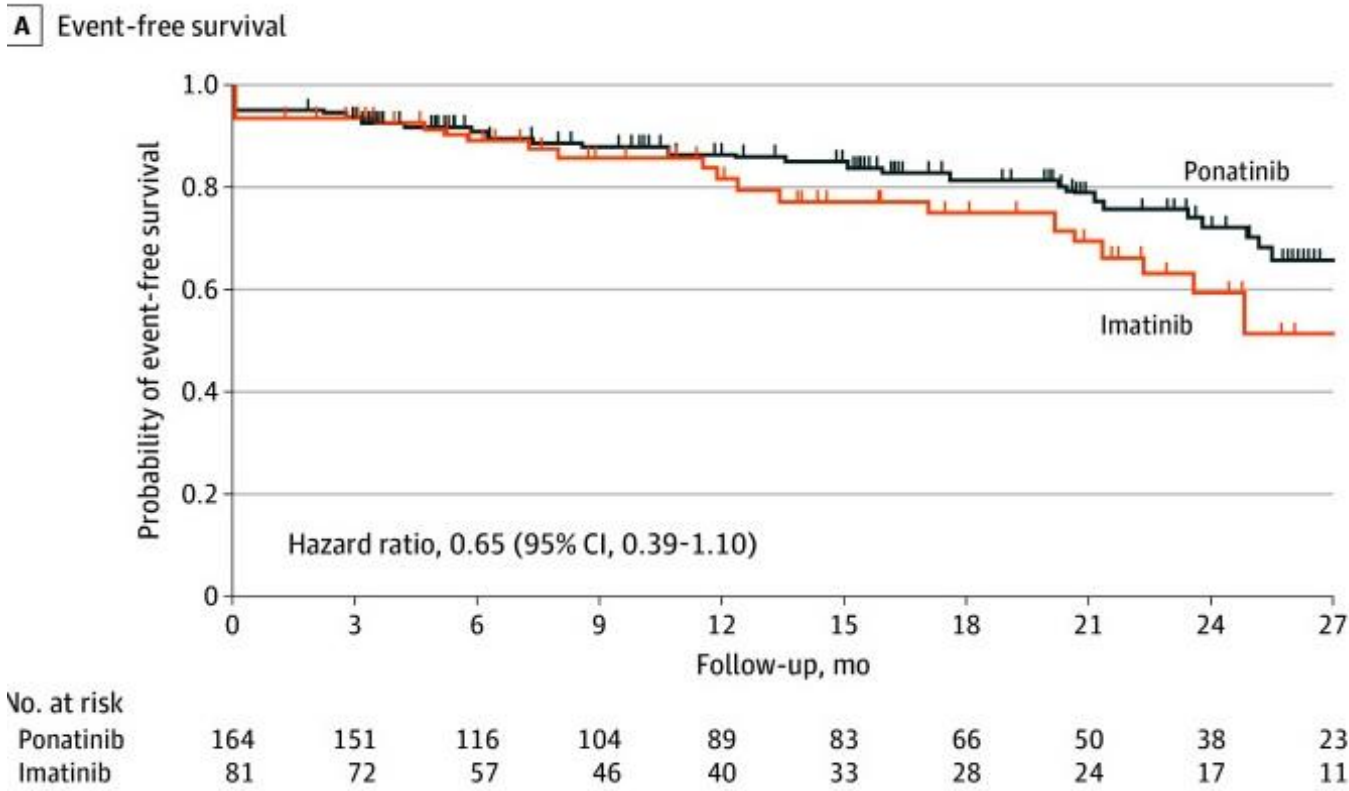
NR vs 29,0 mesi

HR 0,65 (IC 95% 0,39–1,10) — trend favorevole, ma analisi ancora non matura

PFS (analisi post hoc)

20,0 vs 7,9 mesi

HR 0,58 (IC 95% 0,41–0,83) — separazione precoce e sostenuta delle curve

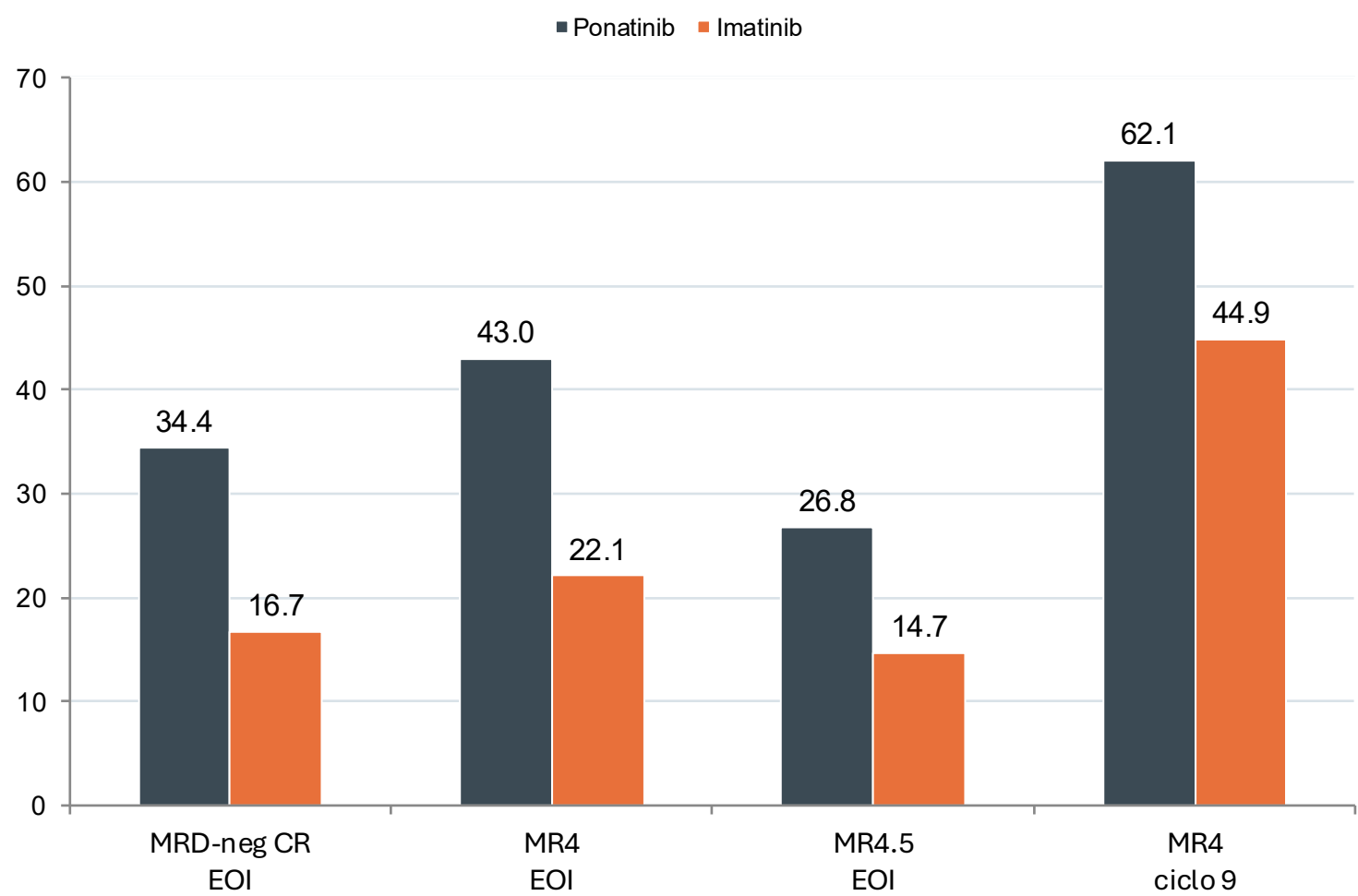


NR vs NR

HR 0,76 (IC 95% 0,38–1,52) — sopravvivenza globale non ancora definita al cutoff

il vantaggio di ponatinib emerge presto sulla profondità di risposta molecolare e si riflette in curve EFS/PFS favorevoli; per EFS e OS serve follow-up più lungo.

PhALLCON — dati di risposta molecolare



EOI = end of induction. MR4 = BCR::ABL1 $\leq 0,01\%$; MR4.5 = $\leq 0,0032\%$. Le percentuali a ciclo 9 mostrano un vantaggio mantenuto nel tempo.

34,4% vs 16,7%

Endpoint primario:
MRD-negative CR a
EOI (P = .002)

NR vs 18,0 mesi

Durata della MRD-negative CR: perdita di risposta 17,0% vs 46,2%

40,0% vs 10,3%

Sottogruppo ≥ 60 anni: beneficio particolarmente marcato su MRD-negative CR a EOI