Chemo-free approach of Ph+ ALL

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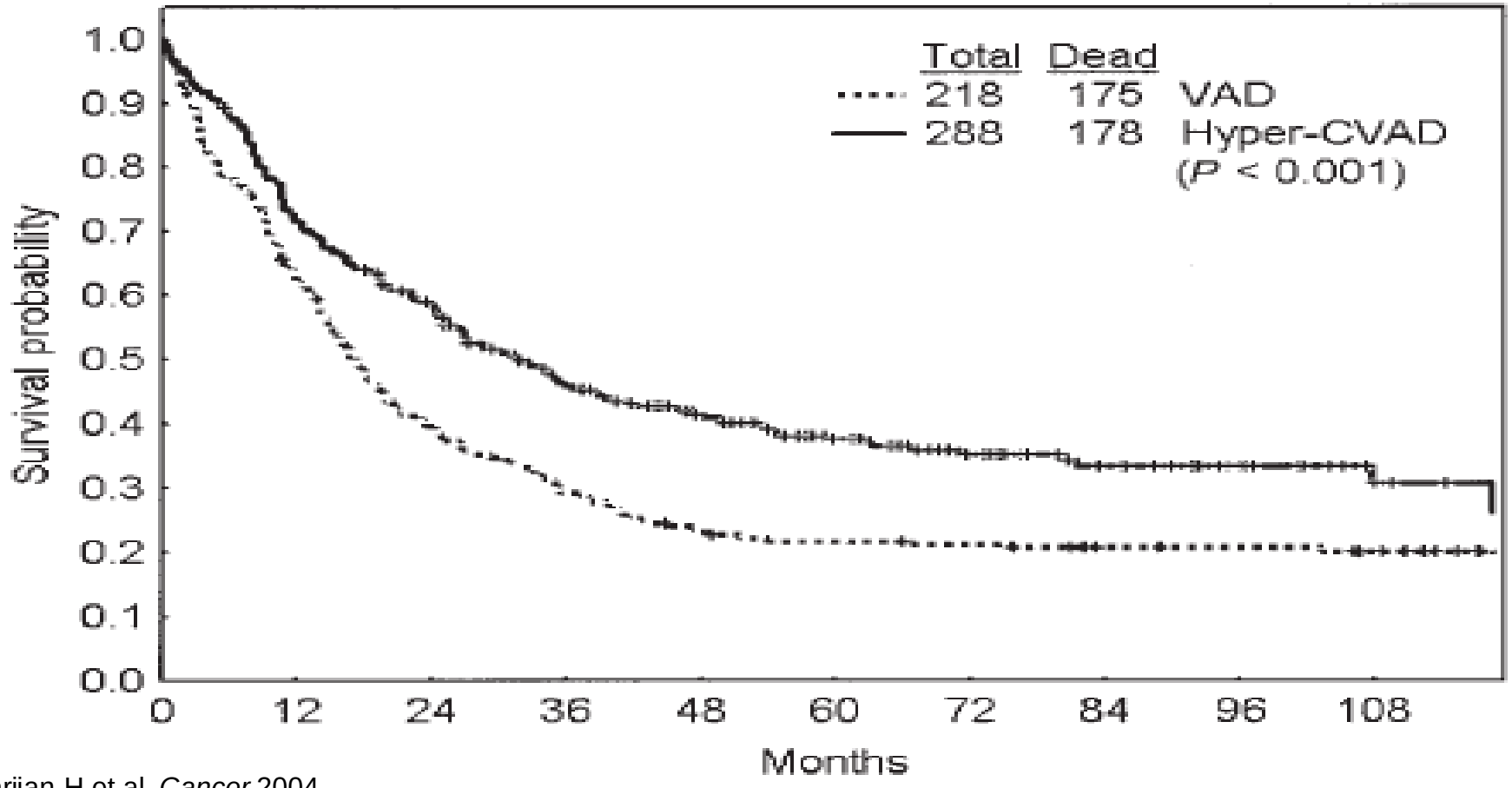
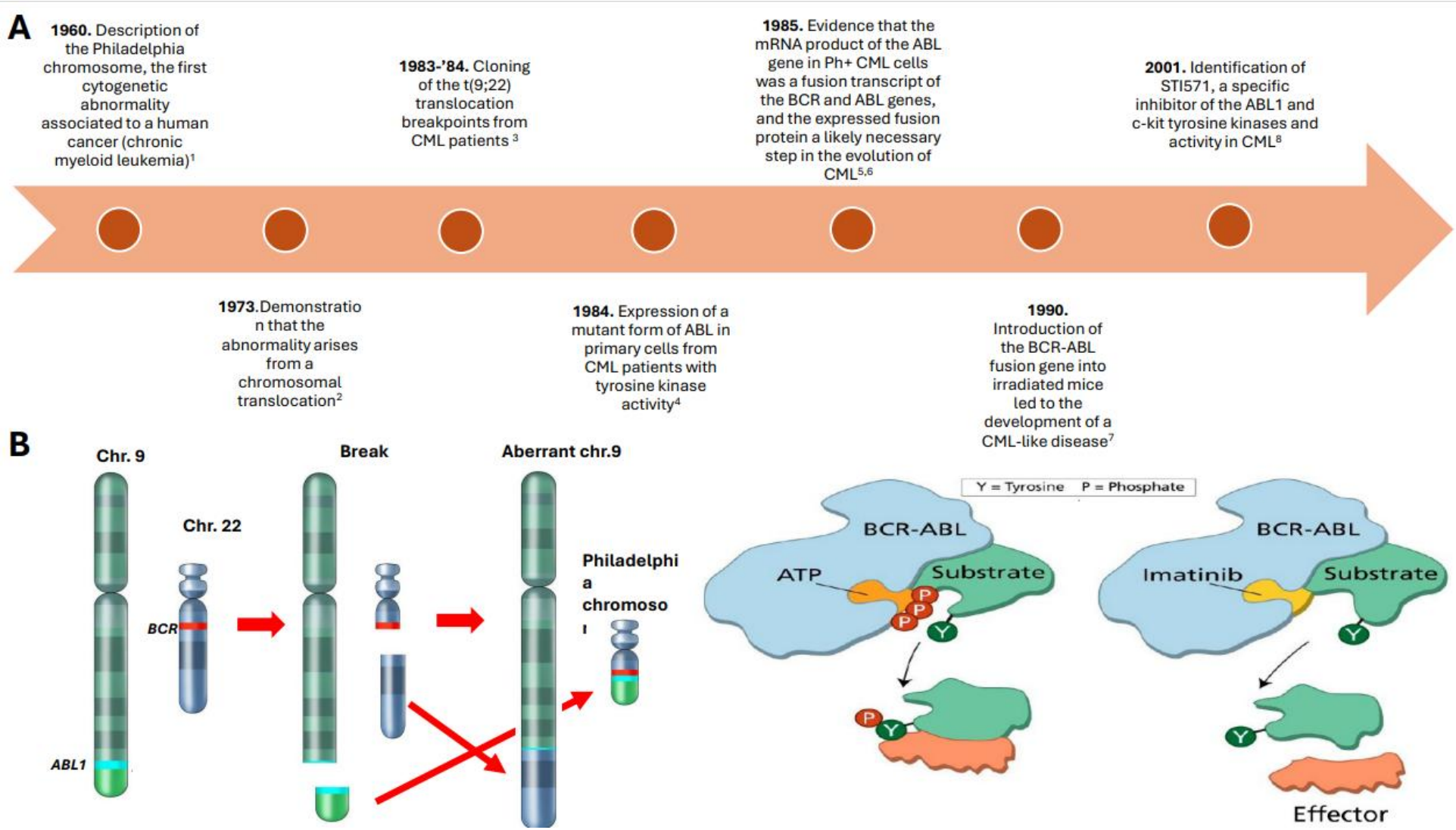
Where did we start from?

Ph+ ALL



Kantarjian H et al. *Cancer* 2004

Ph+ ALL



Foà R, Chiaretti S. *NEJM 2022* Jun 23;386(25):2399-2411

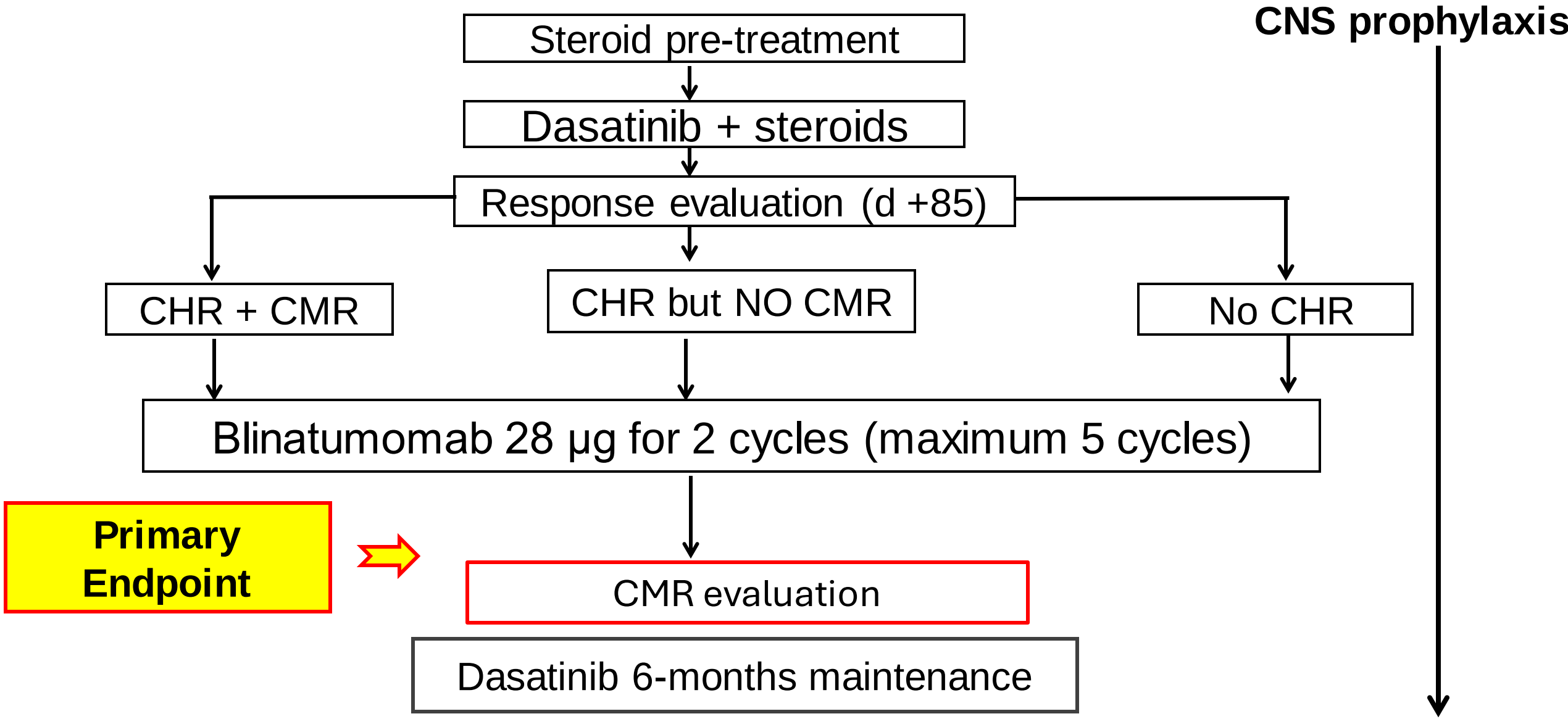
Topics

Dual targeted approaches

Novel TKIs based-strategies

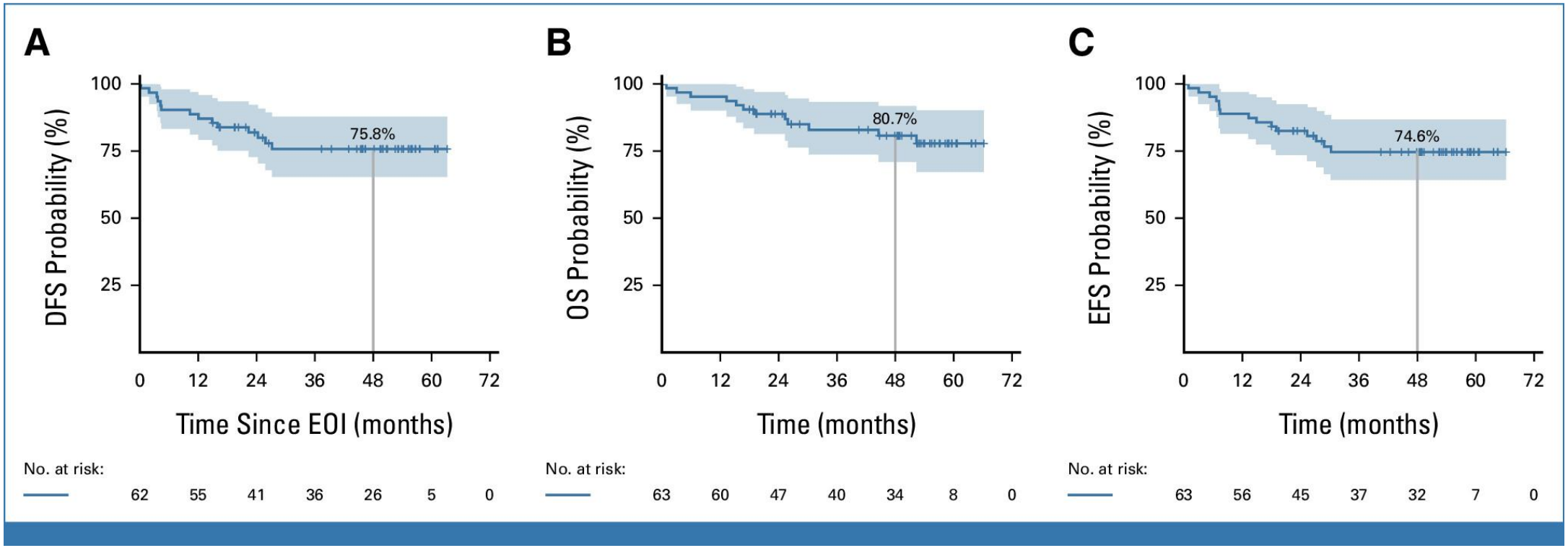
New immunotherapeutic approaches

D-ALBA: treatment scheme



Foà et al; *NEJM* 2020

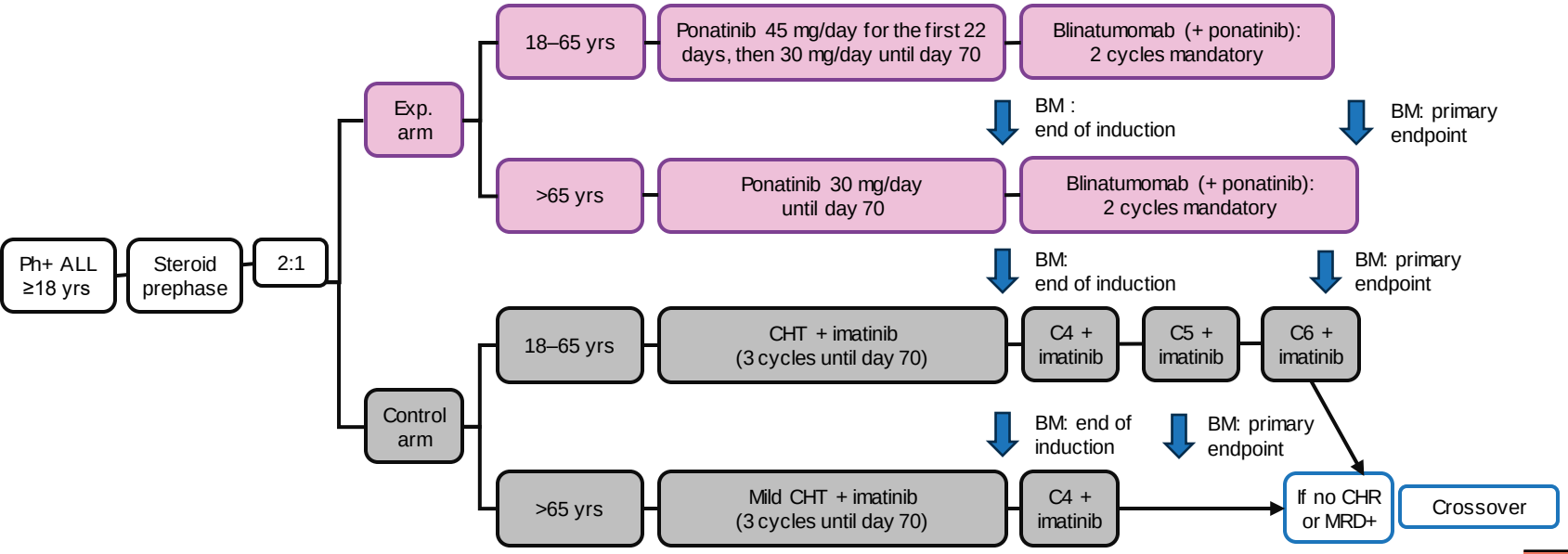
Long-term results of D-ALBA

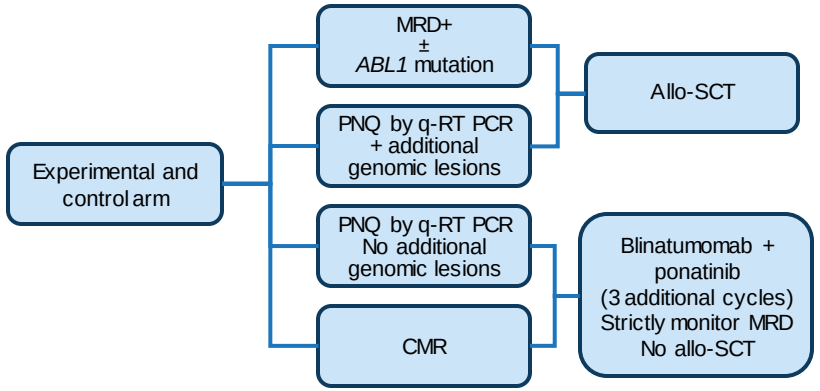


At a median follow-up of 53 months, DFS, OS and EFS are **75.8%** , **80.7%** and **74.6%** respectively.
IKZF1^{plus} emerged as a significant risk factor for relapse

Foà R, et al. *JCO* 2024

Ph+ ALL. GIMEMA ALL2820: Ponatinib-blinatumomab frontline





-Protocol closed to enrolment in January 2025.

- Last patient reached primary endpoint in June.

	Experimental N=158	Control N=78
Age, median (range)	56.5 (19-84)	55 (21-79)
>65 years (%)	47 (30)	21 (26.6)
Gender: M/F (%)	79/79 (50/50)	48/31(61/39)
WBC x10^9/l, median (range)	14 (0.3-356)	13.4 (0.7-250)
≥30 (%)	49 (31)	24 (30)
≥70 (%)	23 (15)	10 (12.7)
p190(%)	110 (69)	50 (63)
p210, p190/210 (%)	40 (25), 8 (4)	25 (31.7)
IKZF1^{plus} (%)	45 (32)	18 (25)

Chiaretti et al, abs 835, ASH 2024

GIMEMA ALL2820. Experimental arm: hematologic & molecular responses

End of induction (d +70)	Experimental arm (N=158)
CHR	151 **(95.6%)**
Deaths	4 **(2.5%)***
Refractory	-
Off treatment	3 **(1.9%)**

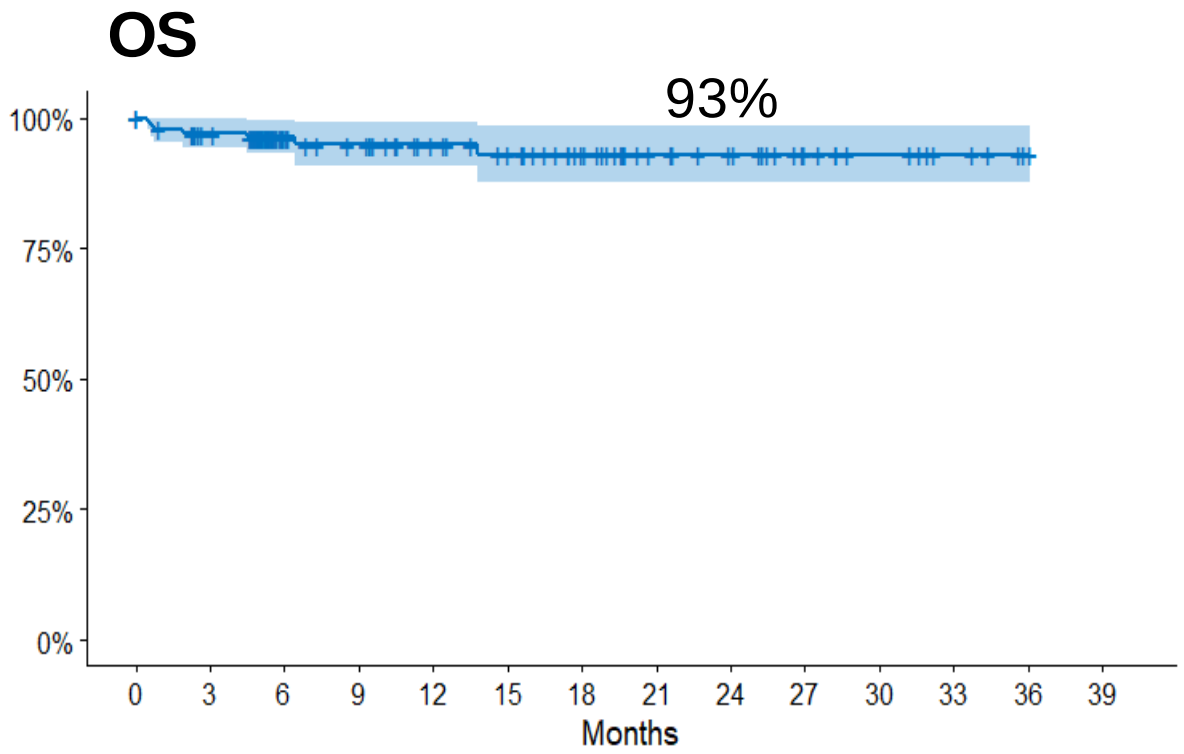
*Median age: 67 yrs

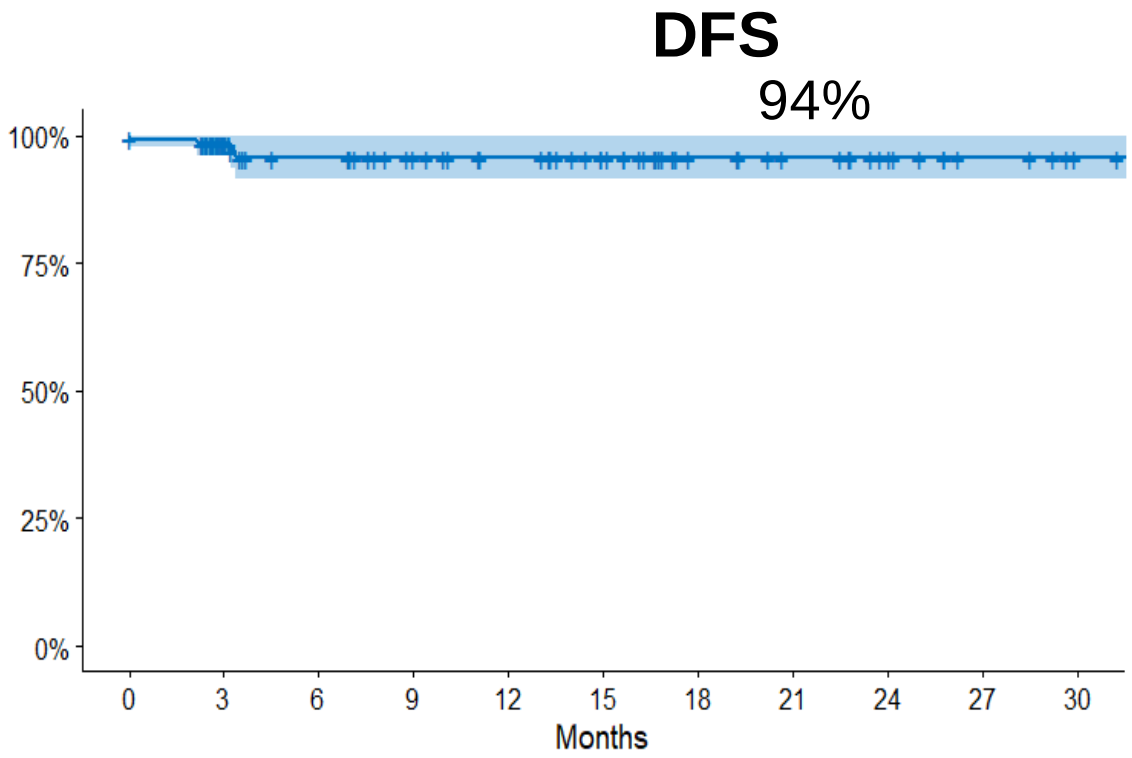
Relapses	Experimental arm (N=151)
Overall	7 (4.6%)
In trial*	4 (2.6%)
Off-treatment	3 (1.3%)

*1 relapse was due to a Ph- clone

Experimental arm N=159	No molecular responses (%)	CMR	PNQ	Overall molecular responses (%)
End induction (d +70)	76/148 (51)	46/148	26/148	72/148 **(49)**
After 2 blina cycles	32/134 (24)	71/134	31/134	102/134 **(76)**

GIMEMA ALL2820. Experimental arm: estimated 18-ms OS & DFS

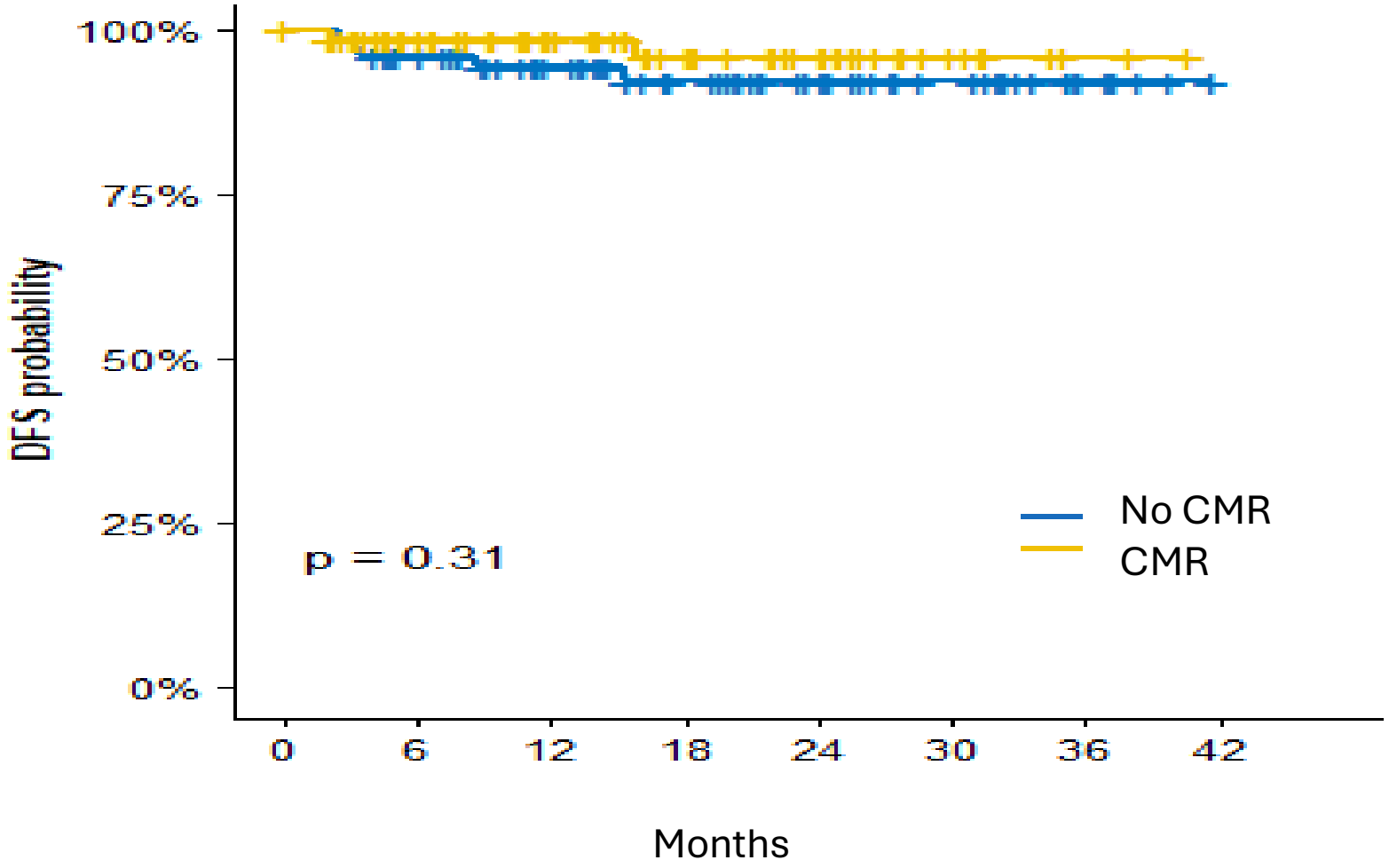




Median follow-up: 19.6 months (0.1 - 44.1)

Chiaretti et al, ASH 2024, updated

GIMEMA ALL2820, experimental arm. Do we still need MRD??



The MDACC study: ponatinib + blinatumomab

- **Blinatumomab** was started at **9 mg daily** continuous intravenous on **days 1-4** of **course 1** and then **increased to 28 mg** daily continuous intravenous on **days 5-28** on a 4-week-on, 2-week off schedule, for up to **five courses**.
- **Ponatinib** was given as **30 mg/d** during induction and **maintained** for at least **5 years**. On achieving **CMR**, the dose was **reduced to 15 mg/d**.
- **12 to 15 doses** of intrathecal chemotherapy (**IT**) were administered.

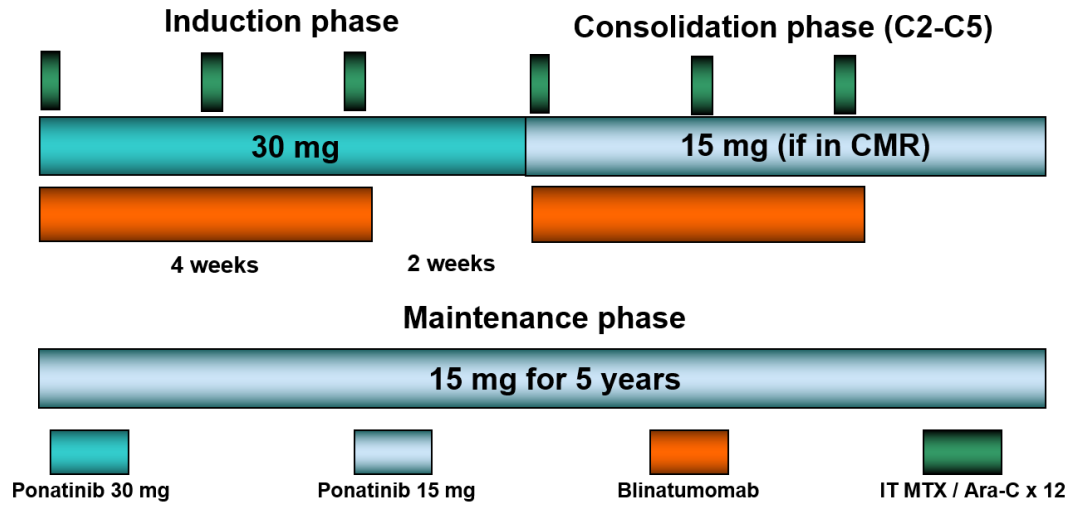


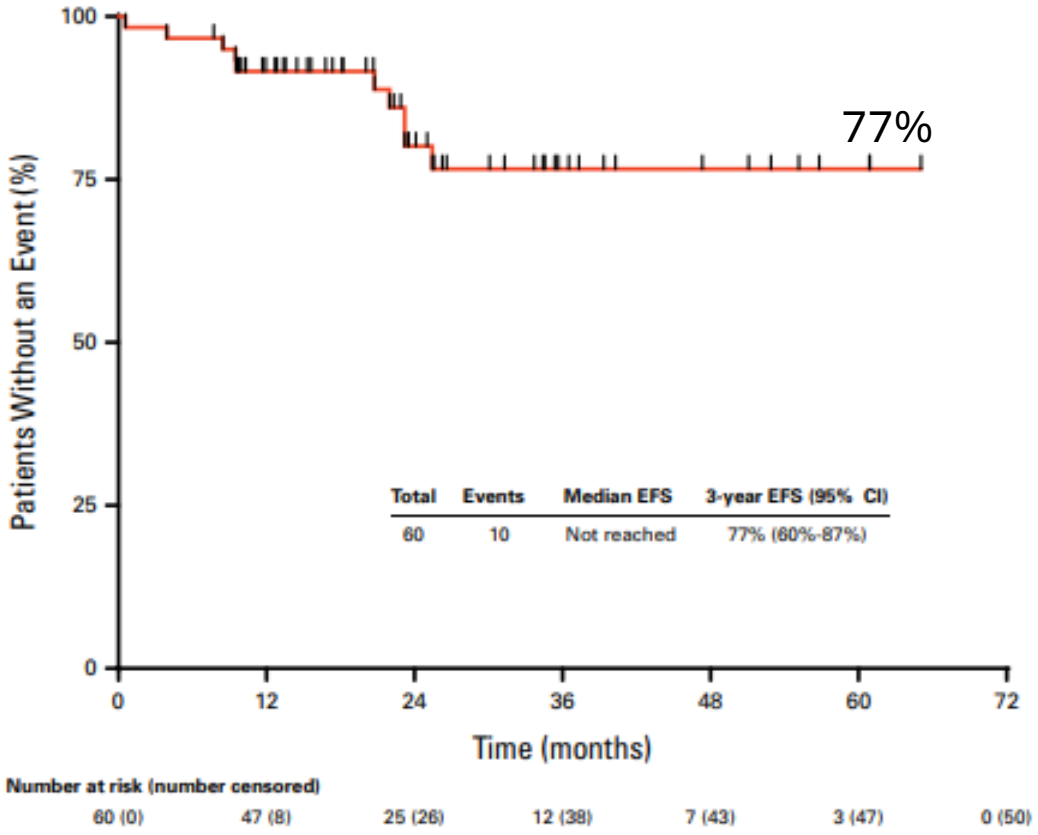
TABLE 2. Hematologic and Molecular Responses

Parameter	n/N (%)
Overall response rate[a]	
CR	37/39 (95)
CRi	1/39 (2)
Early death	1/39 (3)
CMR[b]	
After cycle 1	36/54 (67)
Overall	45/54 (83)
MRD negativity by NGS/ClonoSEQ	
After cycle 1	10/22 (45)
Overall	44/45 (98)
EFS	
3-year rate, % (95% CI)	77 (60 to 87)
No. of events	10 (17)
OS	
3-year rate, % (95% CI)	91 (76 to 97)
No. of events	4 (7)

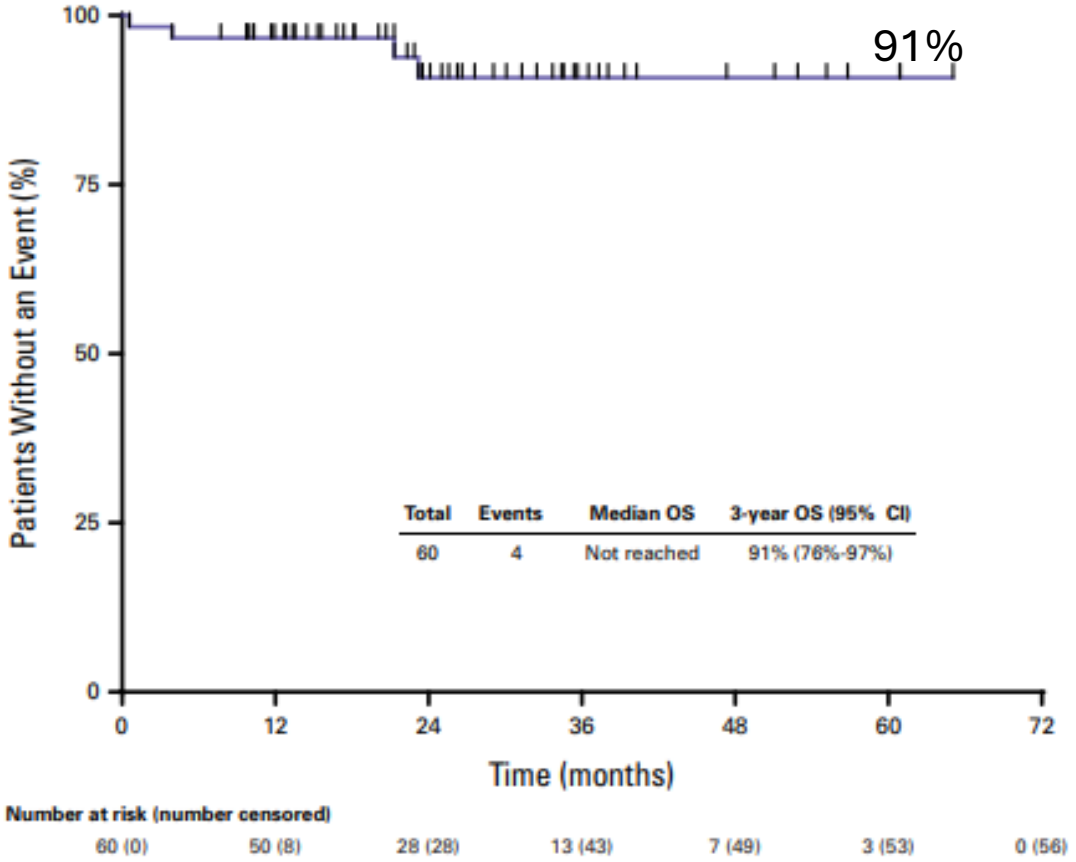
Kantarjian, et al JCO 2024

The MDACC study: ponatinib + blinatumomab

EFS



OS



Median follow-up: 24 months (range: 9-67)

2 patients allografted for BCR::ABL1 persistence (NGS not performed)

7 relapses: 2 systemic, 4 isolated CNS relapses, and 1 extramedullary Ph-negative ALL.

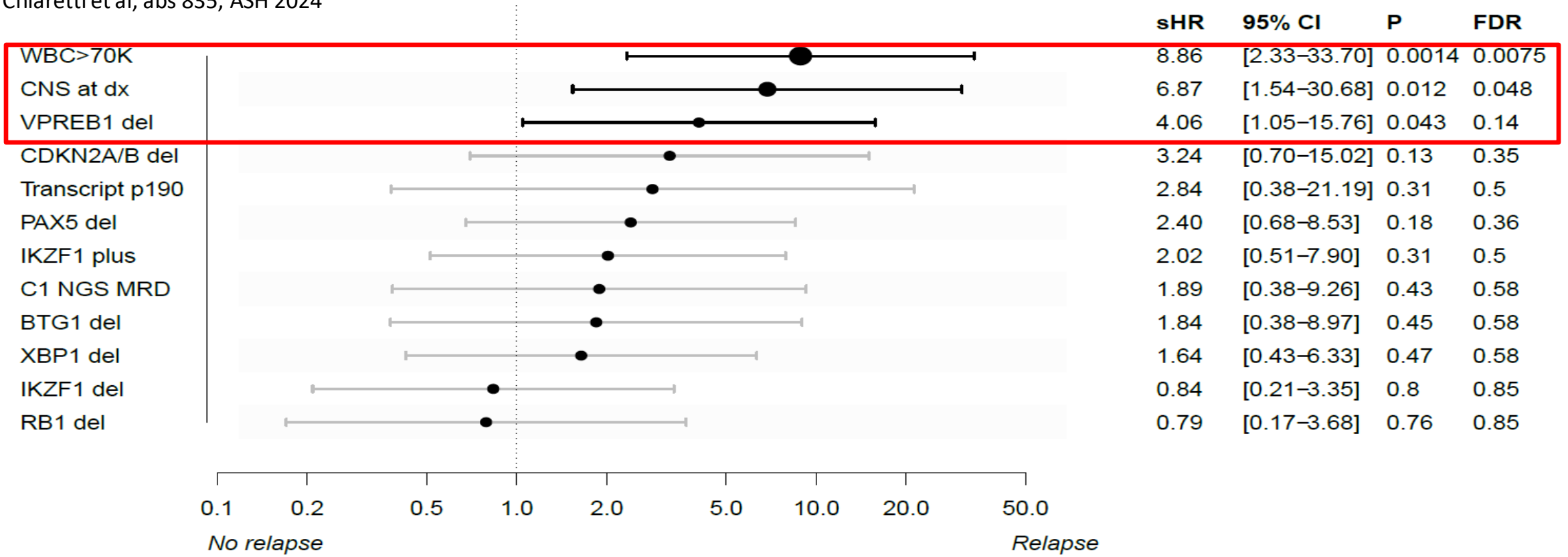
3/7 tested for ABL1 mutation: a new E255V mutation and a T315I mutation after 11 months of switching to dasatinib.

CNS relapse rates: 23% in patients with WBC > $75x10^9$ /L and 2% in patients with WBC < $75x\ 10^9$ /L.

Predictors of inferior response in ponatinib + Blinatumomab

Correlation between molecular response and protein fusion type (p190 *vs* p210) at EOI (p=0.02), and WBC after 2 cycles of blinatumomab (>30x10^9/l and >75x10^9/l, p=0.047 and 0.016, respectively)

Chiaretti et al, abs 835, ASH 2024



Short et al, abs 837, ASH 2024

Topics

Dual targeted approaches

Novel TKIs based-strategies

New immunotherapeutic approaches

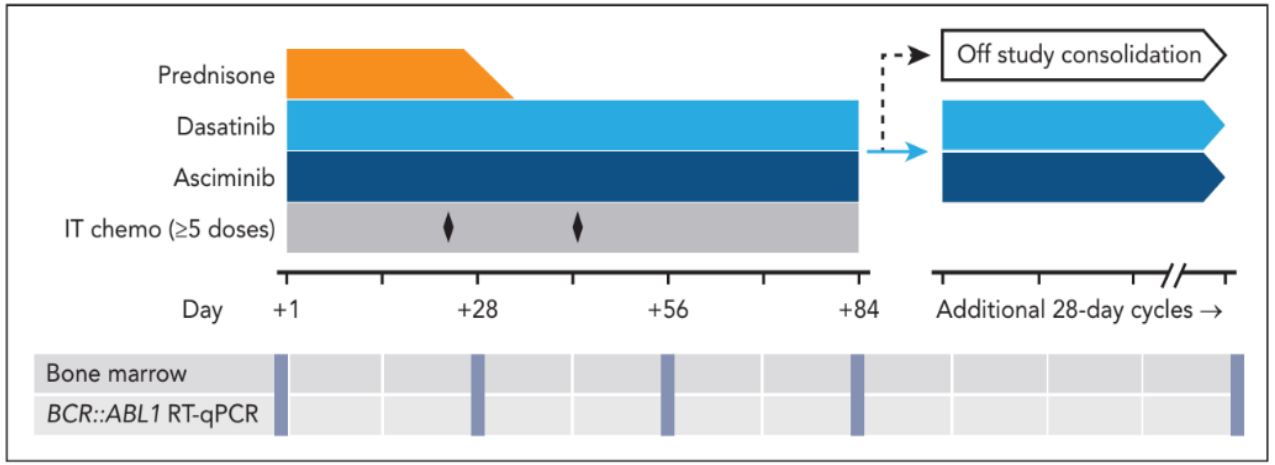
blood Regular Article

CLINICAL TRIALS AND OBSERVATIONS

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

Marlise R. Luskin,[1,*] Mark A. Murakami,[1,*] Julia Keating,[2] Yael Flamand,[2] Eric S. Winer,[1] Jacqueline S. Garcia,[1] Maximilian Stahl,[1] Richard M. Stone,[1] Martha Wadleigh,[1] Stella L. Jaeckle,[1] Ella Hagopian,[1] David M. Weinstock,[3] Jessica Liegel,[4] Malgorzata McMasters,[4] Eunice S. Wang,[5] Wendy Stock,[6] and Daniel J. DeAngelo[1]

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



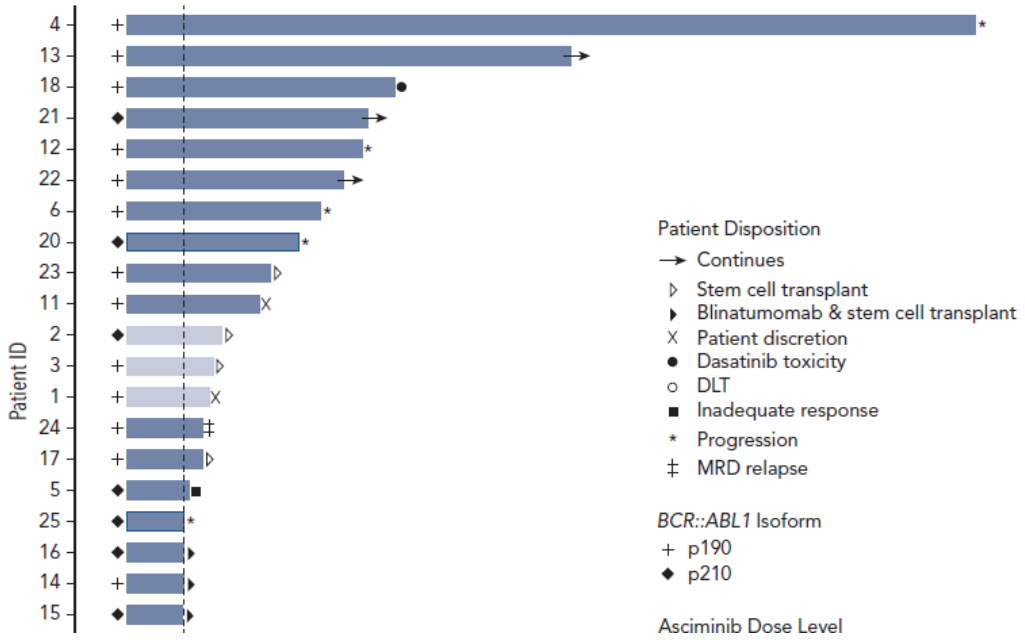
Asciminib dose: 40 mg, **80 mg**, and 160 mg

Luskin MR, et al. Blood. 2025

24 patients enrolled
Median age: 64.5 years (range, 33-85), 12 patients ≥65 years at registration.
22 newly-diagnosed Ph+ ALL, 2 BC CML

p190: 16 pts, p210: 6 ; *IKZF1* deletions: 41%.

CHR and cytogenetic responses by day 84: 100%
Molecular responses (<0.01%): 26%



Median follow-up: 27 months (95% CI, 15.0-30.7). 2 years OS and EFS:75% and 71%

Asciminib + dasatinib: toxicity

Toxicity	All DLs				DL 2			
	Grade 3/4		All grades		Grade 3/4		All grades	
	n	%	n	%	n	%	n	%
Metabolism and nutrition disorders								
Hyperglycemia	4	16.7	8	33.3	3	17.6	4	23.5
Tumor lysis syndrome	2	8.3	2	8.3	1	5.9	1	5.9
Hyperkalemia	1	4.2	3	12.5	1	5.9	2	11.8
Obesity	1	4.2	1	4.2	1	5.9	1	5.9
Hypophosphatemia	2	8.3	5	20.8	0	0.0	1	5.9
Musculoskeletal and connective tissue disorders								
Musculoskeletal pain	3	12.5	12	50.0	3	17.6	10	58.8
Generalized muscle weakness	3	12.5	4	16.7	2	11.8	3	17.6
General disorders and administration site conditions								
Fatigue	1	4.2	17	70.8	1	5.9	15	88.2
Fever	1	4.2	7	29.2	1	5.9	6	35.3
Flu-like symptoms	1	4.2	3	12.5	1	5.9	3	17.6
Opioid induced hyperalgesia	1	4.2	1	4.2	1	5.9	1	5.9
Vascular disorders, hypertension	3	12.5	5	20.8	2	11.8	4	23.5
Gastrointestinal disorders, nausea and vomiting	4	16.7	16	66.7	4	23.5	13	76.5
Investigations								
Alanine aminotransferase increased	1	4.2	6	25.0	1	5.9	4	23.5
Creatinine increased	1	4.2	4	16.7	1	5.9	3	17.6
Lipase increased	1	4.2	9	37.5	0	0.0	6	35.3
Blood and lymphatic system disorders, febrile neutropenia	2	8.3	2	8.3	2	11.8	2	11.8
Respiratory, thoracic, and mediastinal disorders								
Dyspnea	2	8.3	13	54.2	2	11.8	11	64.7
Pulmonary edema	1	4.2	2	8.3	1	5.9	2	11.8
Infections and infestations								
COVID-19 infection	1	4.2	3	12.5	1	5.9	3	17.6
Urinary tract infection	1	4.2	2	8.3	1	5.9	2	11.8
Injury, poisoning, and procedural complications								
Fall	1	4.2	1	4.2	1	5.9	1	5.9
Hand laceration	1	4.2	1	4.2	1	5.9	1	5.9
Eye disorders, optic nerve disorder	1	4.2	1	4.2	1	5.9	1	5.9
Psychiatric disorders, anxiety or agitation	1	4.2	5	20.8	1	5.9	4	23.5
Ear and labyrinth disorders, hearing impaired	1	4.2	1	4.2	0	0.0	0	0.0
Nervous system disorders, paresthesia	1	4.2	3	12.5	0	0.0	2	11.8
Skin and subcutaneous tissue disorders, maculopapular rash	1	4.2	6	25.0	0	0.0	5	29.4

Shown are adverse events per CTCAE version 5 observed in >25% of study participants treated at the RP2D (DL2, asciminib 80 mg once daily) or with grade ≥3 severity in patients treated at any DL. Hematologic adverse events attributed to underlying disease and resolving by the end of induction treatment are excluded.

Luskin MR, et al. Blood. 2025

RESEARCH

Olverembatinib treatment in adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia

Yiyan Zhu[1,2] · Jiayi Huang[1,2] · Ying Wang[1,2] · Yue Han[1,2] · Shengli Xue[1,2] · Yonggong Yang[3] · Yu Zhu[4] · Wenzhi Cai[1,2] · Suning Chen[1,2]

Features

20 patients with *de novo* Ph + ALL

Median age: 32.5 years

Median WBC: 26.6x10^9/L (1.7-260.8)

P190: 65%, p210: 35%

Induction treatment

Olverematinib 40 mg every other day plus vindesine and prednisone (n=14)

Olverematinib 40 mg every other day plus blinatumomab (n=4)

Olverematinib 40 mg every other day plus prednisone (n=2)

Consolidation treatment

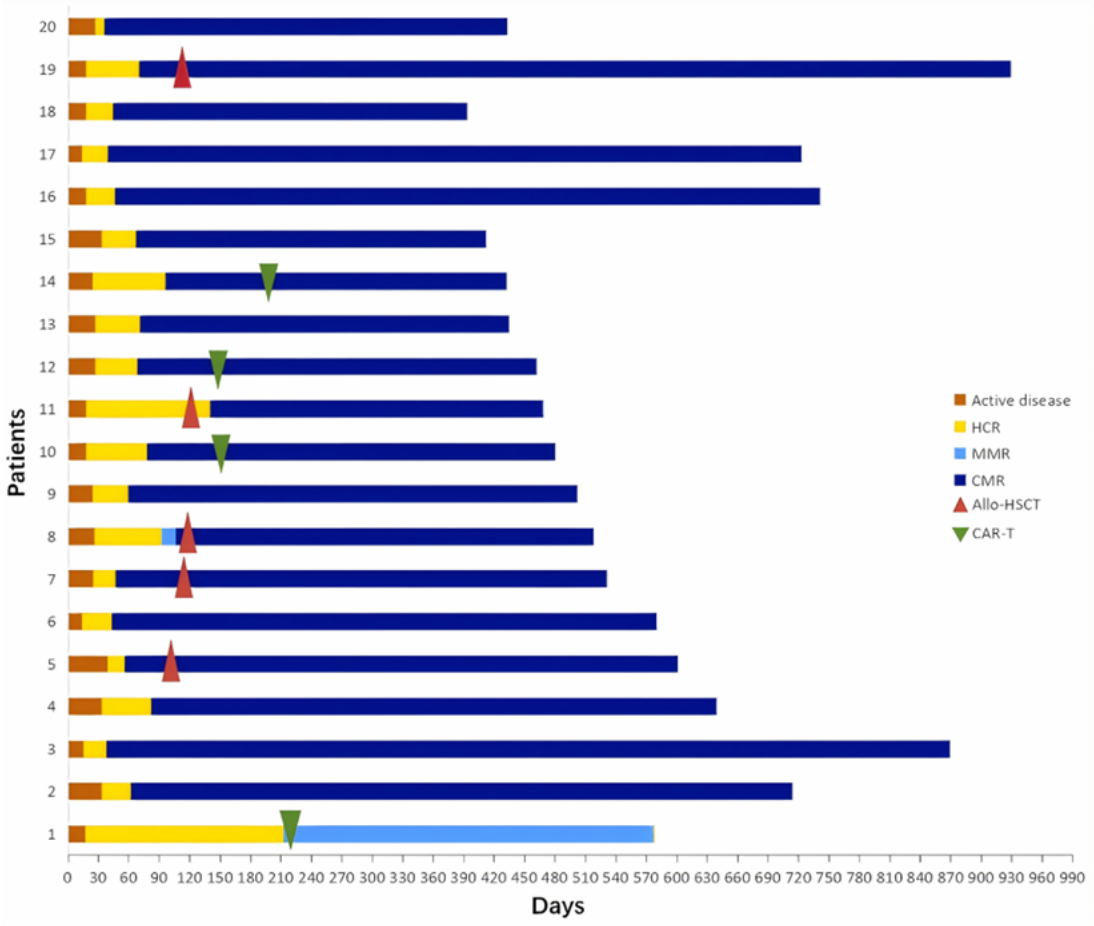
Olverematinib 40 mg every other day plus blinatumomab (n=9)

Olverematinib 40 mg every other day plus Hyper-CVAD (n=4)

High-dose methotrexate and blinatumomab (n=3)

Zhu Y, et al. Ann Hematol. 2024

Olverematinib: follow-up



Median follow-up: 17.2 months (range: 12.9–30.5), no 1-year OS and EFS : 100%.....

Additional procedures carried out
5 underwent allo-SCT, 4 CAR-T

Zhu Y, et al. Ann Hematol. 2024

Received: 1 December 2023 | Revised: 13 February 2024 | Accepted: 4 March 2024
DOI: 10.1002/ajh.27289

CORRESPONDENCE

AJH WILEY

A new chemotherapy-free regimen of olverembatinib in combination with venetoclax and dexamethasone for newly diagnosed Ph+ acute lymphoblastic leukemia: Preliminary outcomes of a prospective study

OVD induction

Olverembatinib 40 mg every other day,

Dexamethasone,

Venetoclax starting from day 4 (ramp-up strategy: 100 mg day 4, 200 mg day 5, and 400 mg on days 6–17).

OVD consolidation

Olverembatinib 40 mg every other day

Venetoclax 400 mg daily for the first 2 weeks of each cycle until progression; maximum 3 years

10 patients

Median age: 41 years (range 27–60).

p190: 8 patients

P210: 2 patients

Tang H, et al. Am J Hematol. 2024

Received: 1 December 2023 | Revised: 13 February 2024 | Accepted: 4 March 2024
DOI: 10.1002/ajh.27289

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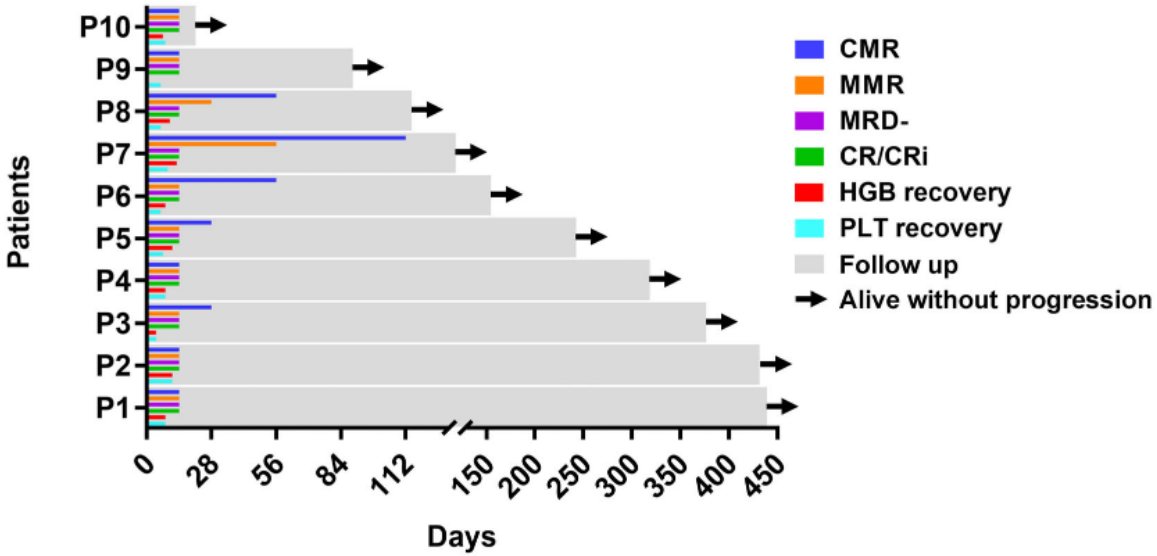

Grade 4 neutropenia in 3 patients

Grade 3 pneumonia in 2 patients

Grade 3 febrile neutropenia in 3 patients

Median follow-up: 7.4 months (range: 1.8–16)

Topics

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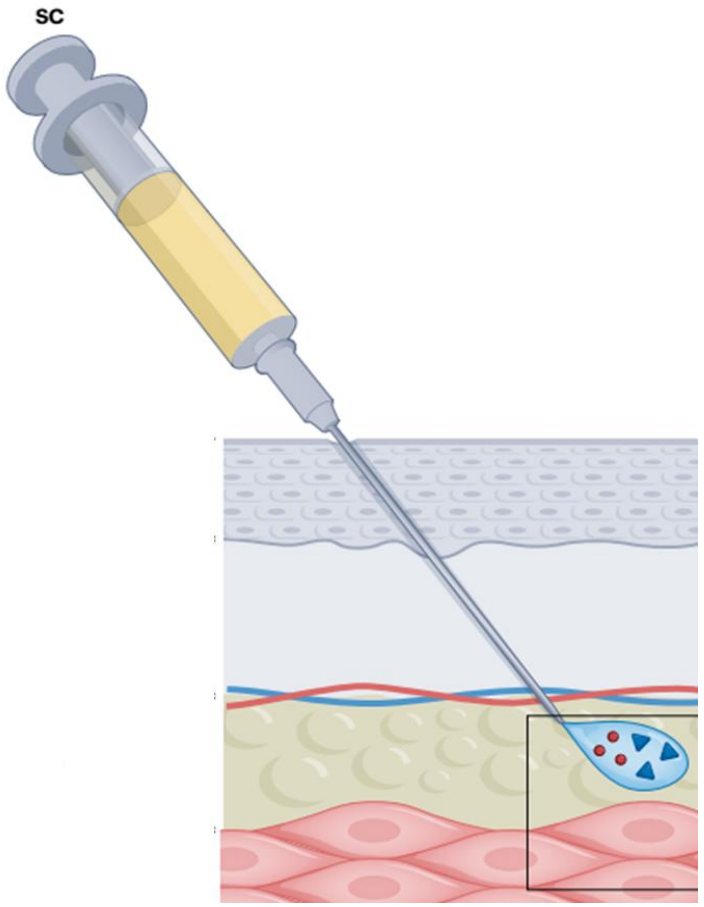
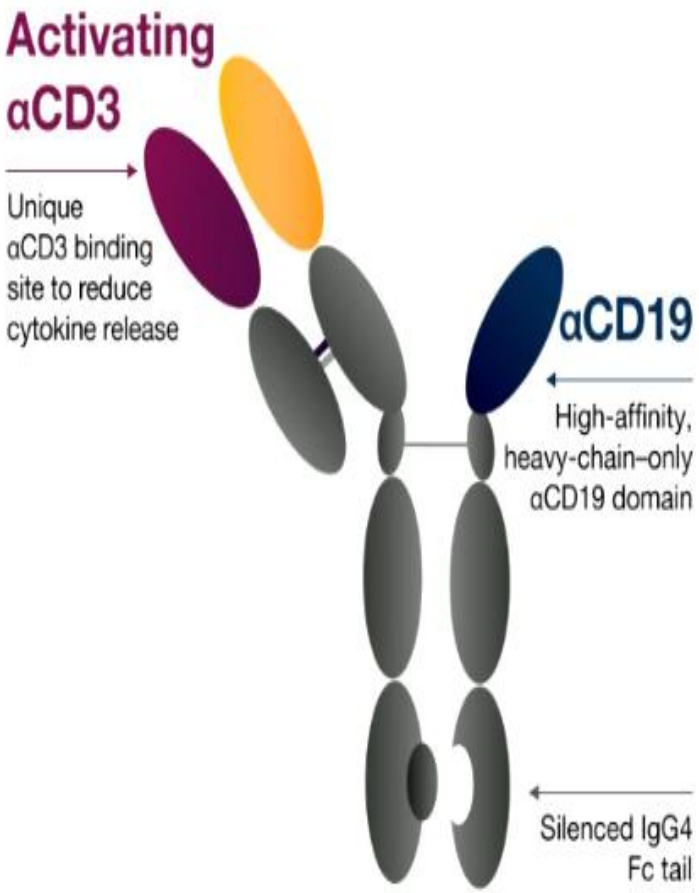
New immunotherapeutic approaches

New immunotherapeutic approaches

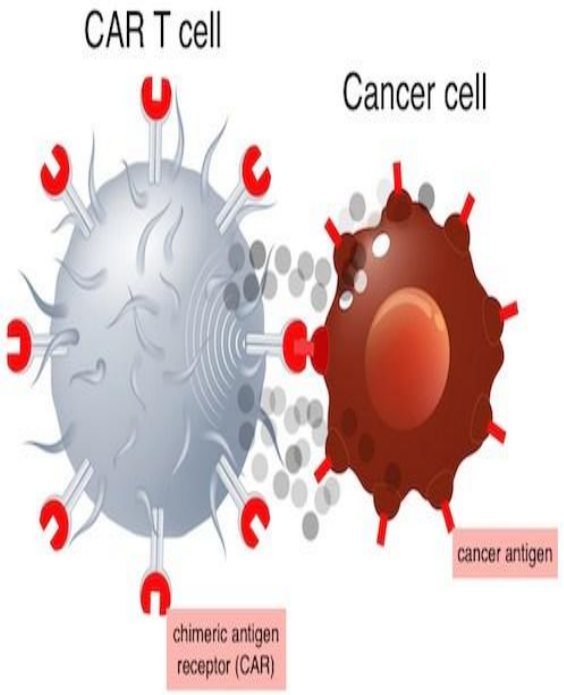
Subcutaneous blinatumomab



Surovatamig



CAR-T



Conclusions

- Ph+ ALL, a history of success: from 20% of survival to about 80%
- Chemo-free approaches: feasibile and effective
- Dual targeted-immunotherapeutic approaches apparently the most effective. Not always feasible

Transplant will disappear?

At relapse?

TKI forever?

MRD monitoring: how?

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Renato Bassan
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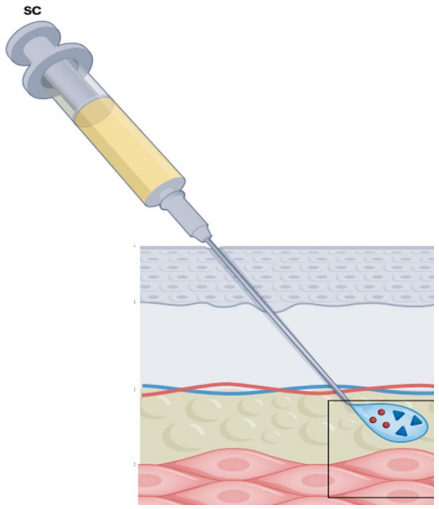
Monica Messina
Valentina Arena
Stefano Soddu
Paola Fazi
Marco Vignetti

And now? The dark after the light???

Subcutaneous (SC)
blinatumomab



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Most likely not, at least in Italy