R/R ALL Ph+

A less frequent but more difficult scenario

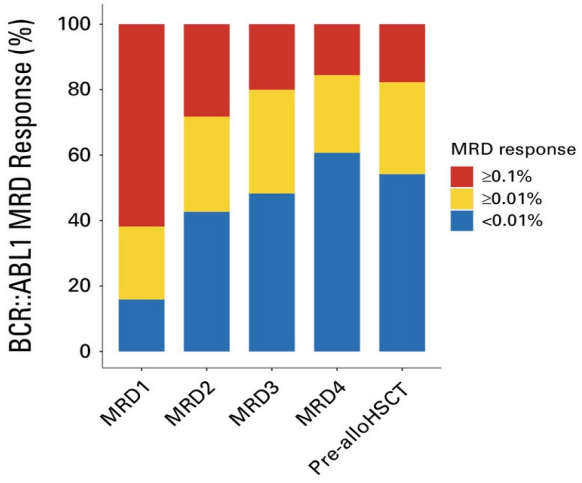
Matteo Leoncin

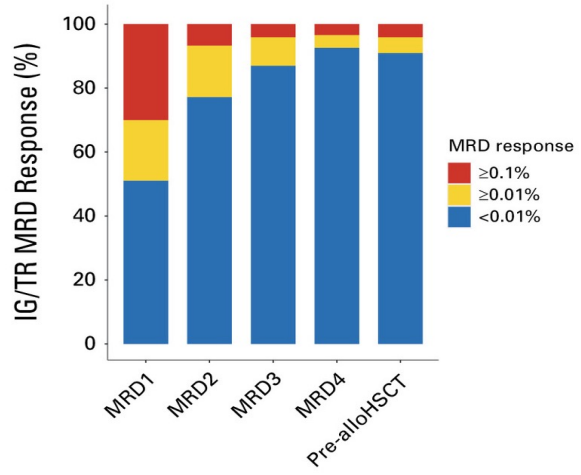
Disclosures of M. Leoncin

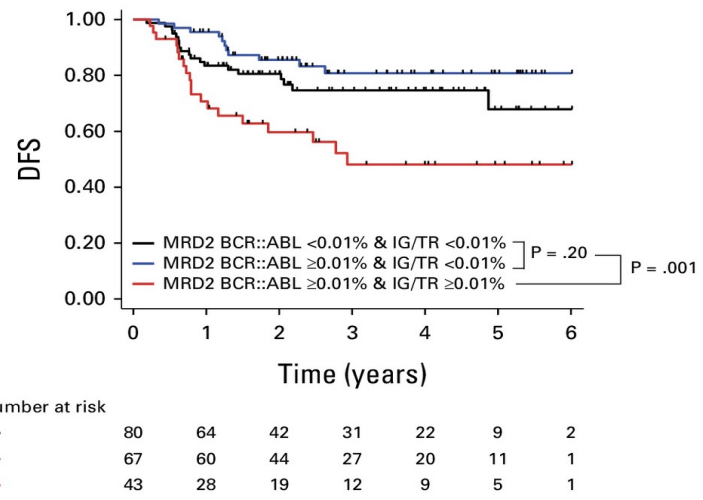
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						x	
Menarini StemLine						x	

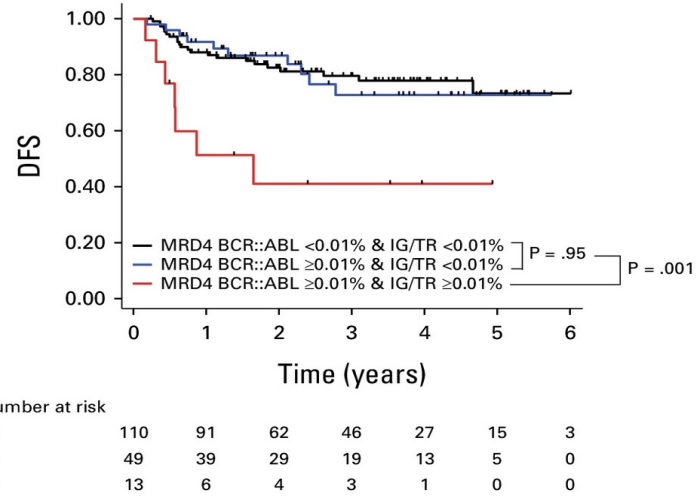
Do we know our enemy?

BCR-ABL or IgH/TCR









Kim R et Al.J Clin Oncol. 2024 Sep 10;42(26):3140-3150.

Short NJ et Al. Blood Adv. 2025 Mar 25;9(6):1442-1451.

Recommendations

- In patients with B-cell ALL, NGS-based MRD quantification of leukemia-specific IG/TR clonotypes is preferred for clinical decision-making over MFC, PCR for IG/TR, or RT-PCR for *BCR*::*ABL1* for MRD assessment, because NGS for IG/TR has superior sensitivity and discrimination for relapse than these other assays.
- In Ph-positive ALL, NGS for IG/TR and RT-PCR for *BCR*::*ABL1* are complementary methods of MRD assessment, although NGS for IG/TR may be more suitable for prognostication and most therapeutic decision-making, because this assay has greater specificity for the leukemic clone than does RT-PCR for *BCR*::*ABL1*.
- In patients with T-cell ALL, NGS for IG/TR and other MRD assays (eg, MFC) are complementary methods of MRD assessment, as NGS for IG/TR provides superior sensitivity to other MRD assays but is not well-validated in T-cell ALL.
- MFC or PCR-based assays may be helpful in select cases, such as when NGS-based MRD for IG/TR is unavailable (eg, towing to the lack of a trackable clonotype) or is too financially costly, or when a very rapid turnaround time is needed for urgent decision-making. MFC may also be complementary to other MRD assays when assessment of antigen expression is needed for selection of antigen-directed immunotherapy. When used, MFC-based MRD should be performed in a validated laboratory that can achieve a sensitivity of 1×10^{-4}.
- In patients with Ph-positive ALL for whom NGS-based MRD for IG/TR is unavailable, PCR for IG/TR is preferred over MFC or RT-PCR for *BCR*::*ABL1*. In cases in which NGS or PCR assays for IG/TR are both unavailable, RT-PCR for *BCR*::*ABL1* is preferred over MFC.

BCR-ABL mutations

When is NGS testing indicated?	Why is NGS testing indicated?	What if a low-level mutation is detected?
At diagnosis	Pretherapy detection of mutations with known resistance profile at low level might allow to identify patients who have a higher risk of MRD persistence and early relapse, and help in planning an individualized molecular and mutation monitoring	Monthly evaluation of mutation kinetics should be performed, until either *BCR-ABL1* levels decrease below 0.1%, or MRD and mutation level increase In the latter case, switching to a different TKI should be considered when the mutation is known to be not sensitive to the TKI currently used
At the end of induction (or consolidation)		
In patients with no CHR	Though few, such patients are highly likely to harbor mutations conferring resistance to TKI-based therapy	Personalized TKI choice should be based on the detectable mutation(s)
In patients with no complete molecular remission[a]	A relatively high incidence of mutations conferring resistance to TKI-based therapy is expected in association with high/rising levels of MRD	Switching to a different TKI should be considered when the mutation is known to be not sensitive to the TKI currently used
At relapse	Accurate assessment of mutation status may be important for personalized TKI choice	Personalized TKI choice should be based on the detectable mutation(s)
Before allo-SCT		
In patients who did not have NGS testing performed at the time of transplant decision[a]	Detection of low-level mutations is likely to affect posttransplantation outcome	Posttransplantation reassessment should be performed for reinstitution of personalized TKI therapy based on MRD and mutation status
After allo-SCT		
Whenever a patient tests MRD+[a]	Persistent mutations associated with MRD positivity may affect posttransplantation outcome	Monthly evaluation should be performed for personalized posttransplantation reinstitution of TKI therapy based on MRD and mutation status

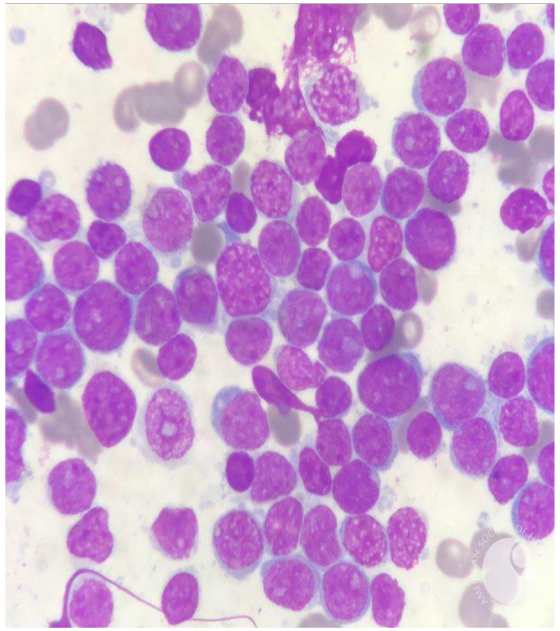
Soverini S et Al. Cancer Med. 2020 May;9(9):2960-2970.

11.10.2017, 45yo Male

- 2 weeks progressive fatigue
- Admitted to ER for syncope
- APR: Mute

EO: ECOG 1, cervical and inguinal lymphogranuly, NO organomegaly, normal pulmonary function

EEC	
WBC	49 x 10^9/L
Hb	4,2 g/dL
PTL	28 x 10^9/L
Blast	83%
Normal renal and hepatic function	
LDH	546 U/L



BM: 95% of small, agranular blasts

IF BM
CD45+, CD19+, CD10+, cyCD79a+, CD34+, HLA-DR+, TdT+, CD22+;

RT-PCR for BCR/ABL1
postivity for p210 transcript

B-ALL with t(9;22)(q34.1;q11.2) sec ICC 2022

- Karyotype: t(9;22) in 16% of metaphases
- Lumbar Puncture: CNS1

1st line: D-ALBA

- 16.10.2017: Enrolled GIMEMA LAL2116 protocol and start PDN + Dasatinib 140 mg/die, well tolerated
- 13.11.2017: d+22 BM evaluation: CR, **MRD (p210) POS 1,2 x 10^-2**, dasatinib continued ad 140 mg/die
- 23.01.2018: d+85 BM evaluation: CR, **MRD (p210) POS 9,8 x 10^-2**; dasatinib continued ad 140 mg/die
- 24.01.2018: Start C1 Blina: coryza, dasatinib continued ad 140 mg/die
- 22.02.2018: BM evaluation: CR, **MRD PNQ (PB+BM)**, dasatinib continued at 140 mg/die
- 06.03.2018: Start C2 Blina: well tolerated, dasatinib continued at 140 mg/die
- 04.04.2018: BM evaluation: CR, **MRD NEG (PB+BM)**, dasatinib continued at 140 mg/die
- 16.04.2018: Start C3 Blina: well tolerated, dasatinib continued at 140 mg/die
- 15.05.2018: BM evaluation: CR, **MRD NEG (PB+BM)**, dasatinib continued at 140 mg/die
- 04.06.2018: Start C4 Blina: well tolerated, dasatinib continued at 140 mg/die
- 26.06.2018: BM evaluation: CR, **MRD NEG (PB+BM)**, dasatinib continued at 140 mg/die
- 09.07.2018: Start C5 Blina: well tolerated, dasatinib continued at 140 mg/die
- 06.08.2018: BM evaluation: CR, **MRD NEG (PB+BM)**, dasatinib continued at 140 mg/die
- **In total 12 TIT performed (required per protocol)**

Start D-ALBA

16/10/2017

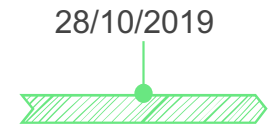
During maintenance with Dasatinib, MRD persistently negative

COMPLICATIONS:

- 02.10.2018: Admission for CMV colitis treated with valgancicolvir, dasatinib continued at 140 mg/die
- 04.02.2019: CMV reactivation treated with valgancicolvir and Ig anti-CMV, dasatinib continued at 140 mg/die
- 08-09.2019: Admission for CMV reactivation with colitis and pneumonia treated with valgancicolvir and foscavir, dasatinib reduced at 100 mg/die
- 24.10.2019: Admission for Pulmonar Hypertension related to dasatinib (CTCAE 3), **STOP DASA, START IMATINIB 600 mg/die**

19.12.2019: BM evaluation: CR, **MRD NEG (PB+BM),** Imatinib continued at 600 mg/die

13.02.2020: BM evaluation: CR, **MRD POS 2,1 x 10-4 (PB+BM),** Imatinib continued at 600 mg/die



CNS Relapse: 2nd line CT + Ponatinib

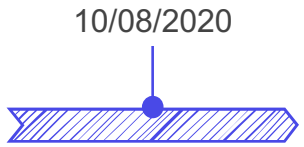
- From 01.03.2020 headeache with poor response to acetaminophen and FANS
- **10.03: diplopia appeared, at LP presence of lymphoblasts, at MRI leukemic meningosis, BM without leukemia localization (CNS only). BCR-ABL wt**
- 11.03.2020: start TIT biweekly (5 total) + Vincristine 2 mg weekly + **start Ponatinib 45 mg/die**
- 02.04.2020: start TIT weekly (4 total) + Vincristine 2 mg weekly (4 total) + Ponatinib 30 mg/die
- 30.04.2020: MTX 2500 mg/mq in 24h + ARA-C 2000 mg/mq for 4 doses, hold Ponatinib 30 mg/die
- From 20.05.2020 start TIT every 2 weeks (4 doses), hold Ponatinib **30 mg/die**
- 28.05.2020: BM evaluation: **CR, MRD neg (SP+SM)**, Ponatinib continued at 30 mg/die
- 22.06-03.07.2020: Craniospinal RT (50 Gy)
- 20.07.2020: BM evaluation: CR, **MRD NEG (PB+BM)**, Ponatinib continued at 30 mg/die

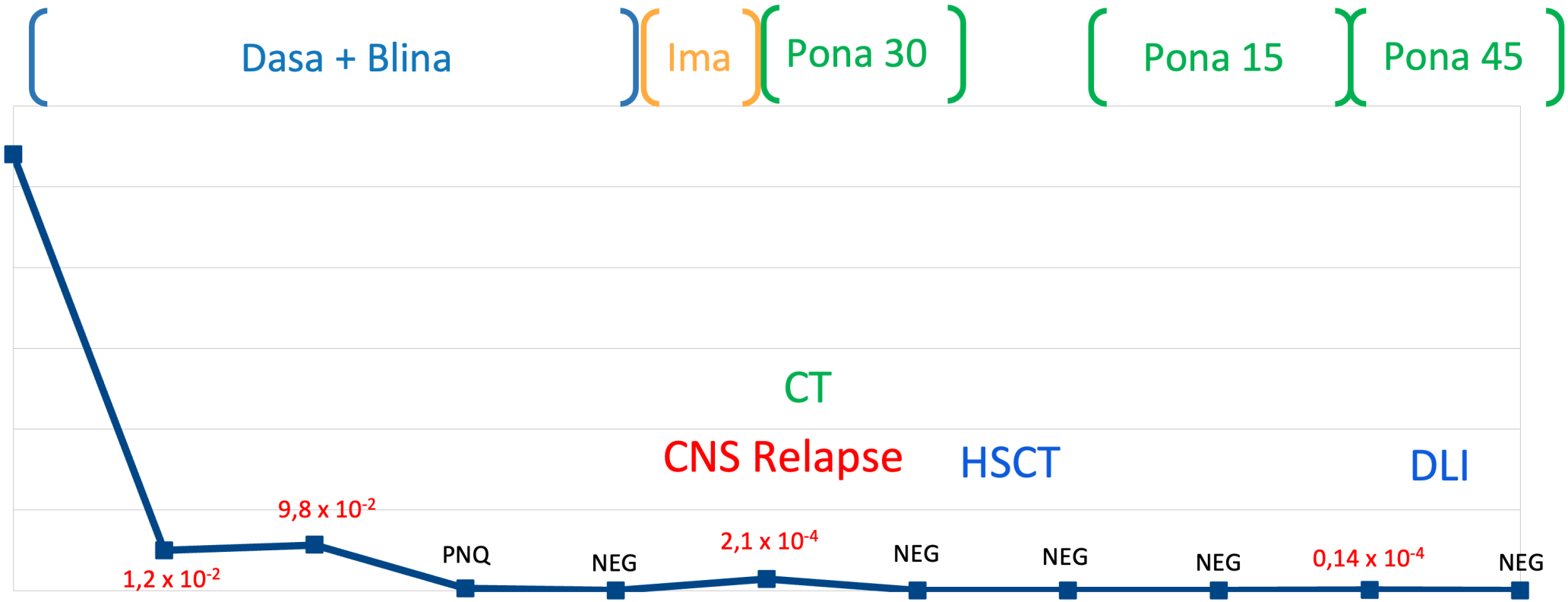
CNS relapse,
start Ponatinib

10/03/2020

Allogenic bone marrow transplantation

- **10.08.2020: Haploindentical HSCT (sister) after conditioning with TBI+Fludarabine at Papa Giovanni XXIII Hematolgy Unit (BG)**
- +30, +60, +90 day BM evaluation: CR MRD NEG (PB+BM)
- From 07.01.2021 start Ponatinib maintenance at 15 mg/die
- 20.07.2021: BM evaluation: **CR, MRD NEG (PB+BM)**, Ponatinib continued at 15 mg/die
- 14.12.2021: BM evaluation: **CR, MRD POS (0,14 x 10^-4) (PB+BM), Ponatinib increased at 45 mg/die**
- 18.01.2022: BM evaluation: **CR, MRD NEG (PB+BM)**, Ponatinib continued at 45 mg/die.
- **02.03.2022: DLI infusion (x 2 infusions)**
- 17.05.2022: BM evaluation: **CR, MRD NEG (PB+BM)**, Ponatinib continued at 45 mg/die.





Start D-ALBA

16/10/2017

28/10/2019

Pulmonary Hypertension, switch to Imatinib

CNS relapse, start Ponatinib

10/03/2020

10/08/2020

HSCT, from 20/01/2021 start Ponatinib maintenance

Increased Ponatinib to 45 mg and DLI infusion

14/12/2021

- From May 2022 to August 2025 MRD persistently negative
- **23.03.2024: Reduced Ponatinib at 30 mg/die, MRD persistently negative**
- **19.02.2025: Admission for VZV encephalitis and secondary polyradicolonevritis AI: Ponatinib suspension and start high dose steroids and acyclovir**
- **Last p210 control (07/08/2025): negative (PB+BM)**
- Last FUP (15.10.2025): Good neurological recovery

Age, Years	WBC (10^9/L)[a]	Type of Relapse	Fusion Type	*IKZF1*	Mutation	Time From CHR to Relapse, ms	Allo-SCT	Last Follow-Up	Previously Reported in Puzzolo et al[24]
71	157.9	Hematologic	p190	*IKZF1*^{plus}	T315I	1.9	No	Dead	Yes
52	0.7	Hematologic	p190	ND	T315I	3.6	Second CHR	Dead	Yes
54	11.2	Nodal	p190	*IKZF1*^{plus}	T315I	3.6	Second CHR	Dead	Yes
30	35.9	CNS + molecular	p190	*IKZF1* loss	E255K	4.2	Second CHR	Alive	Yes
40	10.5	CNS + molecular	p190	*IKZF1*^{plus}	T315I	4	Second CHR	Alive	Yes
81	4.9	Hematologic	p190	No	T315I	12	No	Dead	Yes
53	7.2	CNS + molecular	p210	No	NE	24.3	Second CHR	Dead	No
45	23.9	CNS + molecular	p210	*IKZF1* loss	wt	25.8	Second CHR	Alive	No
67	2.9	Hematologic	p210	*IKZF1*^{plus}	T315I	14.9	First CHR	Dead	No

Foà R et Al. J Clin Oncol. 2024 Mar 10;42(8):881-885.

Not only an italian problem…

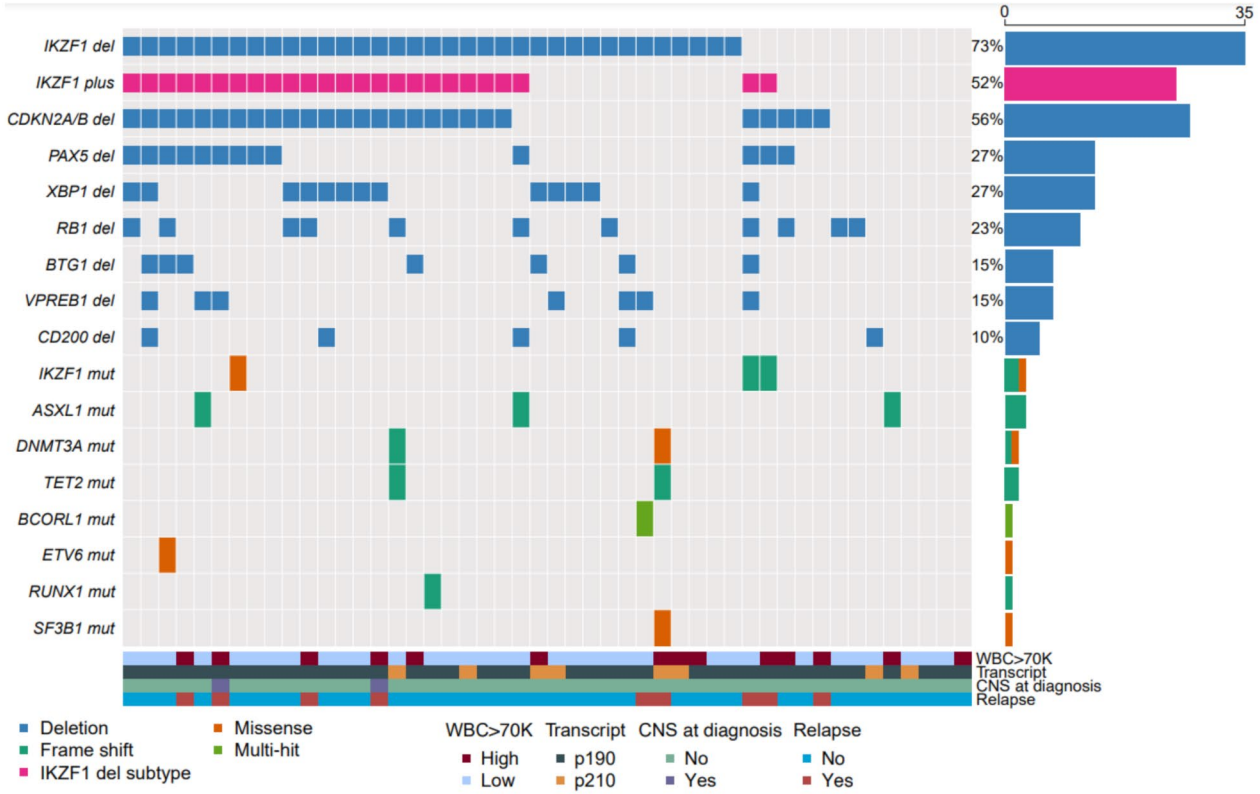
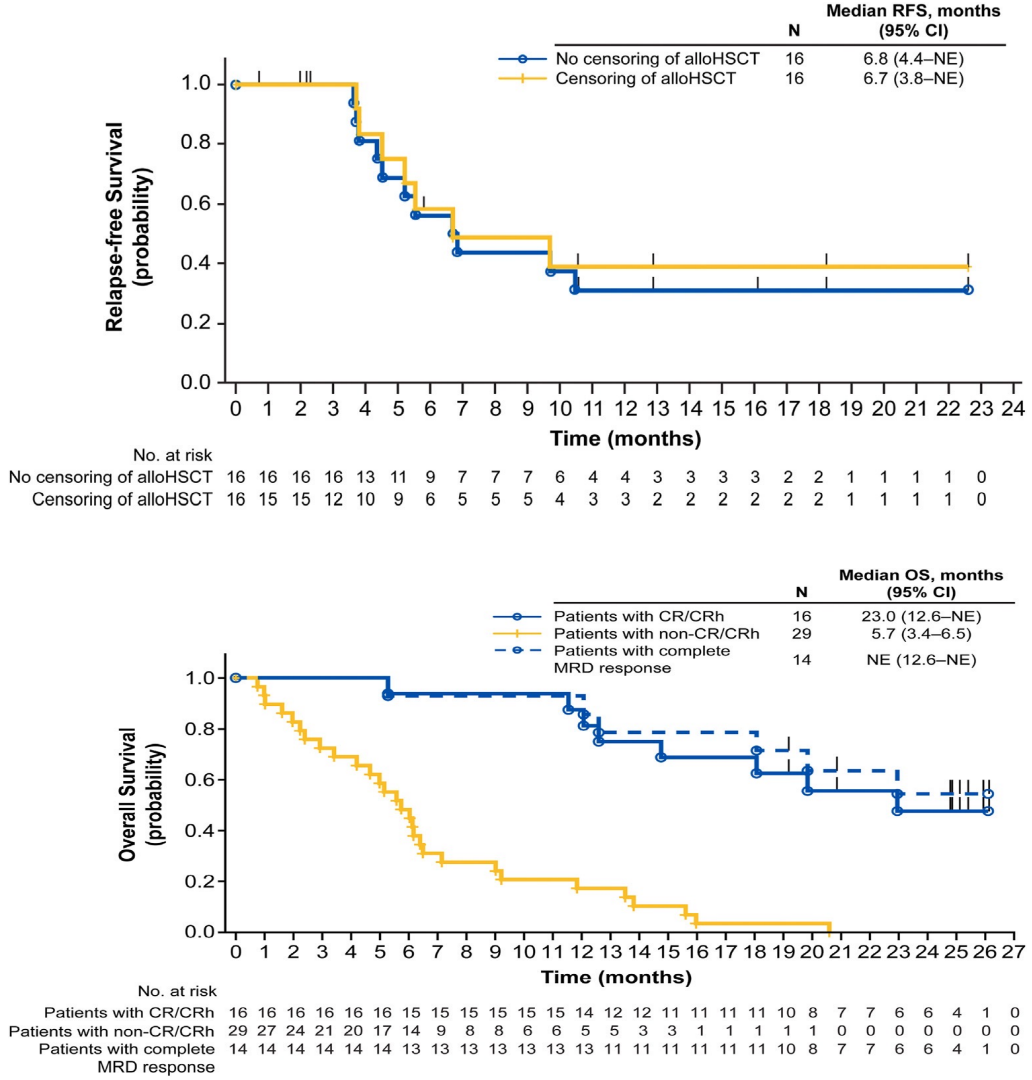


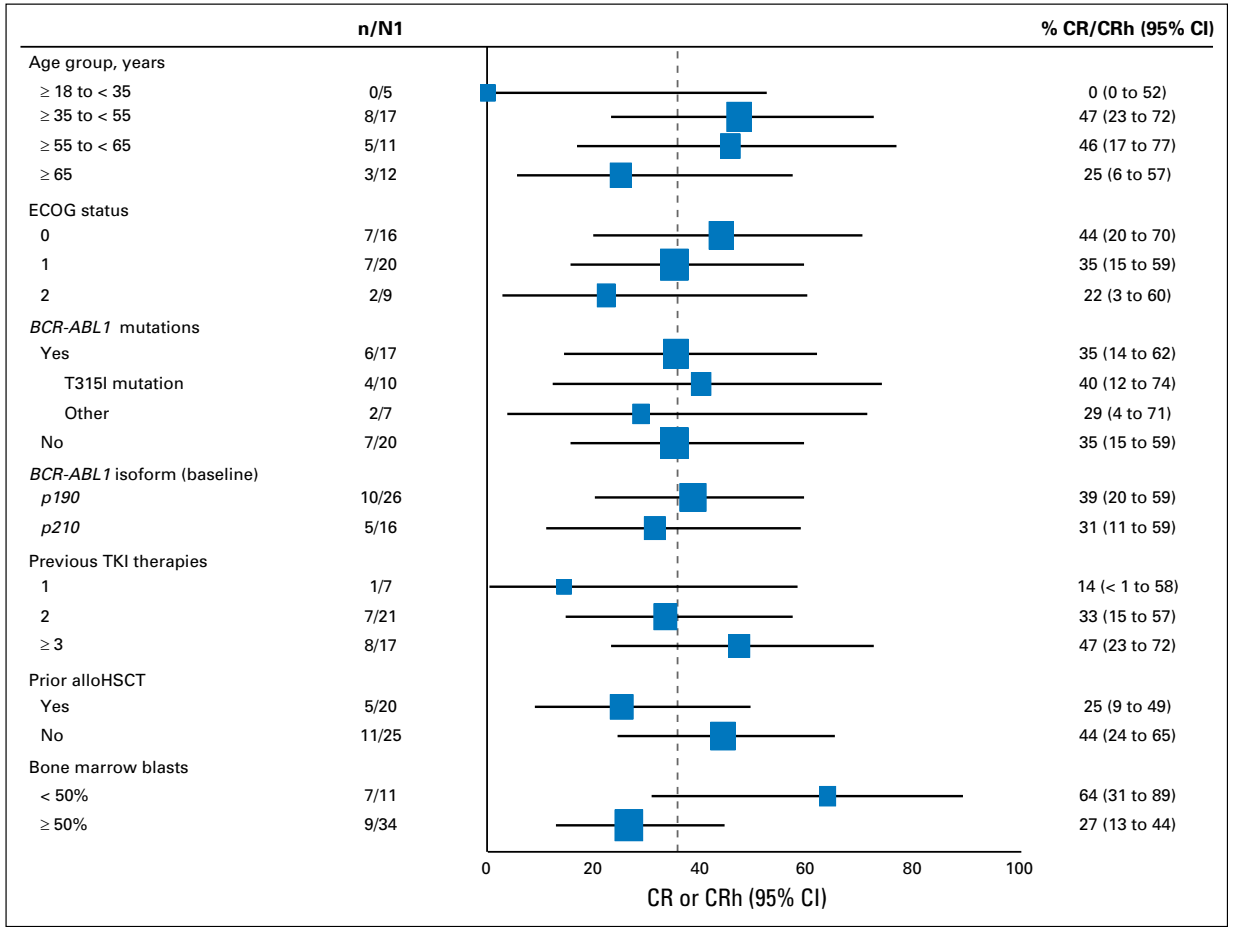
Table 2 – Clinical and molecular characteristics of relapsed patients

Patient	Age	WBC at diagnosis (x 10^9/L)	Transcript type	Mutations (targeted sequencing)	Gene deletions (SNP array)	NGS MRD response after C1	PCR MRD response after C1	Duration of CR1 (months)	Type of relapse
#1	57	2.0	p190	*IKZF1*	*CDKN2A/B, PAX5, VPREB1, BTG1, RB1, XBP1*	Negative	CMR	8.6	Peritoneum and lymph nodes (Ph-negative)
#2	60	322.1	p190	*IKZF1*	*CDKN2A/B, PAX5*	Not done	CMR	24.5	Bone marrow
#3	44	152.6	p190	None	*CDKN2A/B*	Positive (1/million)	CMR	7.6	Bone marrow
#4	18	4.5	p190	None	Not done	Positive (below LOD)	CMR	11.3	Bone marrow
#5	48	95.5	p190	None	*IKZF1, CDKN2A/B, PAX5, BTG1*	Not done	Not done	17.0	Bone marrow + vitreous fluid
#6	28	270.5	p190	Not done	*IKZF1, CDKN2A/B, PAX5, VPREB1*	Not done	CMR	22.0	CNS
#7	43	12.9	p190	*BCORL1*	*IKZF1, VPREB1*	Negative	CMR	19.8	CNS
#8	49	84.9	p190	None	*IKZF1, CDKN2A/B, RB1, XBP1*	Not done	CMR	23.2	CNS
#9	44	236.7	p190	None	*IKZF1, CDKN2A/B, XBP1*	Positive (57/million)	CMR	8.5	CNS
#10	70	181.2	p210	*DNMT3A, SF3B1, TET2*	*IKZF1*	Positive (below LOD)	CMR	20.7	CNS

Short NJ et Al. J Hematol Oncol. 2025 May 14;18(1):55.

BLINATUMOMAB





Martinelli G et Al. Eur J Cancer. 2021 Mar;146:107-114.

Martinelli G et Al. J Clin Oncol. 2017 Jun 1;35(16):1795-1802.

	MRD+ (*N* = 109)				R/R B-cell ALL (*N* = 140)			
Characteristics[a]	**All MRD+ (*N* = 109)**		**Ph− (*N* = 83)**		**Ph+[a] (*N* = 26)**		**R/R Ph− (*N* = 106)**		**R/R Ph+[a] (*N* = 34)**	
Sex, female, *n* (%)	45 (41.3)		39 (47.0)		6 (23.1)		50 (47.2)		16 (47.1)	
Age at blinatumomab initiation, years, median (IQR)	43.0 (27.0–55.0)		35.0 (24.0–56.0)		50.5 (43.0–55.0)		36.5 (24.0–52.0)		51.0 (37.0–64.0)	
Number of salvage therapies										
Median (IQR)	0 (0–1)		0 (0–1)		0 (0–2)		1 (0–2)		1 (1–2)	
Min., max.	0, 4		0, 4		0, 4		0, 5		0, 5	
Prior salvage therapy, *n* (%)	*n* = 77[b]	*n* = 32[c]	*n* = 57[b]	*n* = 26[c]	*n* = 20[b]	*n* = 6[c]	*n* = 64[d]	*n* = 42[e]	*n* = 20[d]	*n* = 14[e]
0	42 (54.5)	18 (56.2)	35 (61.4)	15 (57.7)	7 (35.0)	3 (50.0)	34 (53.1)	11 (26.2)	2 (10.0)	2 (14.3)
1	21 (27.3)	8 (25.0)	14 (24.6)	6 (23.1)	7 (35.0)	2 (33.3)	13 (20.3)	19 (45.2)	8 (40.0)	6 (42.9)
2+	14 (18.2)	6 (18.8)	8 (14.0)	5 (19.2)	6 (30.0)	1 (16.7)	17 (26.6)	12 (28.6)	10 (50.0)	6 (42.8)
Disease status at blinatumomab initiation, *n* (%)										
Full hematologic relapse	NE		NE		NE		64 (60.4)		20 (58.8)	
Refractory	NE		NE		NE		42 (39.6)		14 (41.2)	
Persistent MRD	77 (70.6)		57 (68.7)		20 (76.9)		NE		NE	
MRD relapse	32 (29.4)		26 (31.3)		6 (23.1)		NE		NE	
HSCT before blinatumomab initiation, *n* (%)	17 (15.6)		9 (10.8)		8 (30.8)		43 (40.6)		12 (35.3)	
Time between HSCT and initiation, months, median (IQR)	10.2 (3.8–24.9)		9.5 (3.8–21.3)		13.5 (5.4–36.7)		13.0 (7.2–20.0)		10.4 (7.1–20.6)	
Response before blinatumomab initiation, *n* (%)										
CR/CRh/CRi at frontline therapy	NE		NE		NE		84 (79.2)		25 (73.5)	
Blast count in the bone marrow at blinatumomab initiation, *n* (%)										
≤5	86 (91.5)		65 (91.5)		21 (91.3)		14 (14.6)		2 (7.1)	
>5 and <10	2 (2.1)		2 (2.8)		0 (0.0)		5 (5.2)		0 (0.0)	
≥10 and <50	2 (2.1)		2 (2.8)		0 (0.0)		33 (34.4)		12 (42.9)	
≥50	4 (4.3)		2 (2.8)		2 (8.7)		44 (45.8)		14 (50.0)	
Unknown	15 (NA)		12 (NA)		3 (NA)		10 (NA)		6 (NA)	
Extramedullary involvement, *n* (%)										
Yes	NA		NA		NA		20 (19.2)[f]		5 (14.7)	
Central nervous system	NA		NA		NA		4 (3.8)		5 (14.7)	
Testis	NA		NA		NA		4 (3.8)		0 (0.0)	
Other	NA		NA		NA		12 (11.5)		0 (0.0)	
No	NA		NA		NA		84 (80.8)		—	
Unknown	NA		NA		NA		2 (NA)		—	

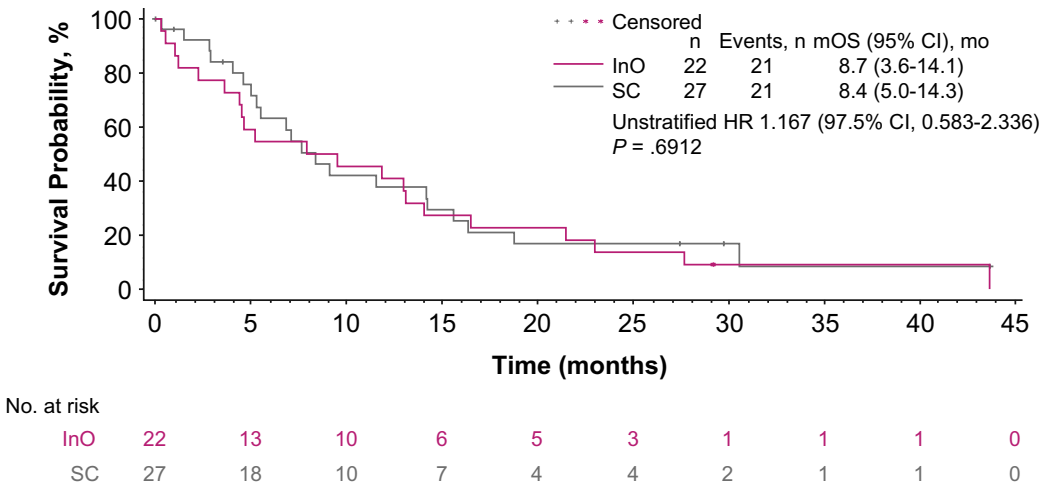
Tyrosine kinase inhibitors, *n* (%)	**MRD+**	**R/R**
	Ph−/ Ph+[a] (*n* = 109)	**Ph+ (*n* = 34)**
Any	13 (12.3)	14 (41.2)
Missing	3 (NA)	0 (NA)
Imatinib	1 (0.9)	1 (2.9)
Dasatinib	8 (7.5)	6 (17.6)
Nilotinib	0 (0.0)	2 (5.9)
Bosutinib	0 (0.0)	1 (2.9)
Ponatinib	4 (3.8)	6 (17.6)

Boissel N et Al. Blood Cancer J. 2023 Jan 4;13(1):2.

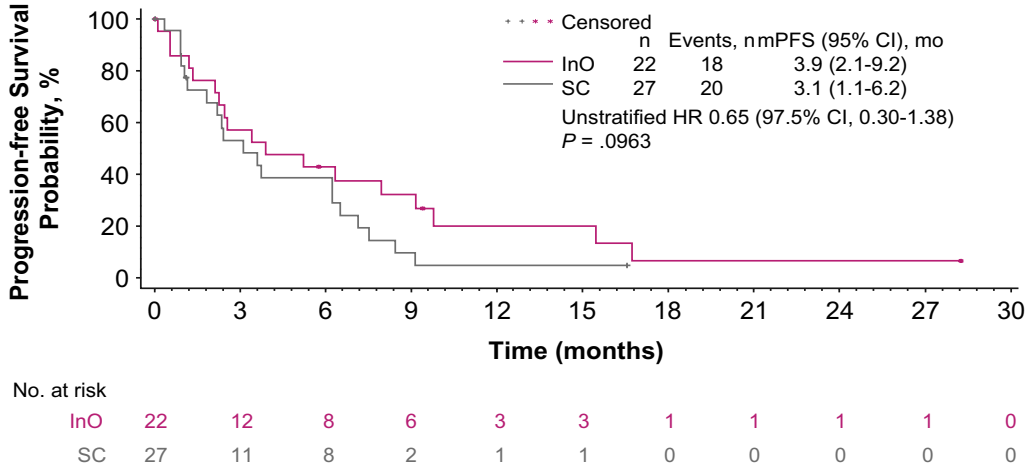
	MRD+			R/R	
	All MRD+[a] (*n* = 109)[b]	Ph–[c] (*n* = 83)[b]	Ph+[d] (*n* = 26)	Ph–[e] (*n* = 106)[f]	Ph+[g] (*n* = 34)[h]
Patients, *n* (%)					
Event (death)	33 (30.3)	28 (33.7)	5 (19.2)	55 (51.9)	15 (44.1)
Censored (alive at end of study, lost to follow-up)	74 (67.9)	53 (63.9)	21 (80.8)	47 (44.3)	16 (47.1)
KM estimate, % (95% CI)					
At 1 month	98.1 (92.7–99.5)	98.8 (91.6–99.8)	96.2 (75.7–99.4)	94.1 (87.3–97.3)	93.5 (76.6–98.3)
At 3 months	96.3 (90.3–98.6)	96.3 (89.0–98.8)	96.2 (75.7–99.4)	84.0 (75.2–89.9)	80.3 (61.3–90.6)
At 6 months	92.4 (85.4–96.1)	95.1 (87.4–98.1)	83.6 (62.0–93.5)	67.5 (57.3–75.8)	60.2 (40.7–75.1)
At 12 months	77.9 (68.0–85.0)	76.4 (64.7–84.7)	83.6 (62.0–93.5)	50.6 (40.0–60.2)	53.1 (34.0–69.1)
At 18 months	66.9 (55.6–75.9)	62.4 (49.3–73.1)	83.6 (62.0–93.5)	42.8 (32.1–53.2)	44.3 (22.5–64.1)
At 24 months	64.7 (52.8–74.2)	62.4 (49.3–73.1)	71.7 (38.6–89.0)	40.0 (28.7–51.0)	44.3 (22.5–64.1)

Boissel N et Al. Blood Cancer J. 2023 Jan 4;13(1):2.

INOTUZUMAB



	Study 1022			Study 1010
Efficacy Endpoints	InO (n = 22)	SC (n = 27)	*P*	InO (n = 16)
CR/CRi, n (% [95% CI])	16 (72.7 [49.8-89.3])	15 (55.6 [35.3-74.5])	.1075	9 (56.3 [29.9-80.3])
CR, n (% [95% CI])	10 (45.5 [24.4-67.8])	8 (29.6 [13.8-50.2])	.1265	4 (25.0)
CRi, n (% [95% CI])	6 (27.3 [10.7-50.2])	7 (25.9 [11.1-46.3])	.4577	5 (31.3)
MRD negativity, n (% [95% CI])[a]	13 (81.3 [54.4-96.0])	5 (33.3 [11.8-61.6])	.009	9 (100.0 [66.4-100.0])
OS				
Median, mo (95% CI)	8.7 (3.6-14.1)	8.4 (5.0-14.3)		7.4 (4.3-11.3)
HR (95% CI)	1.17 (0.64-2.14)		.6912	—
PFS				
Median, mo (95% CI)	3.9 (2.1-9.2)	3.1 (1.1-6.2)		4.4 (1.8-5.9)
HR (95% CI)	0.65 (0.34-1.25)		.0963	—



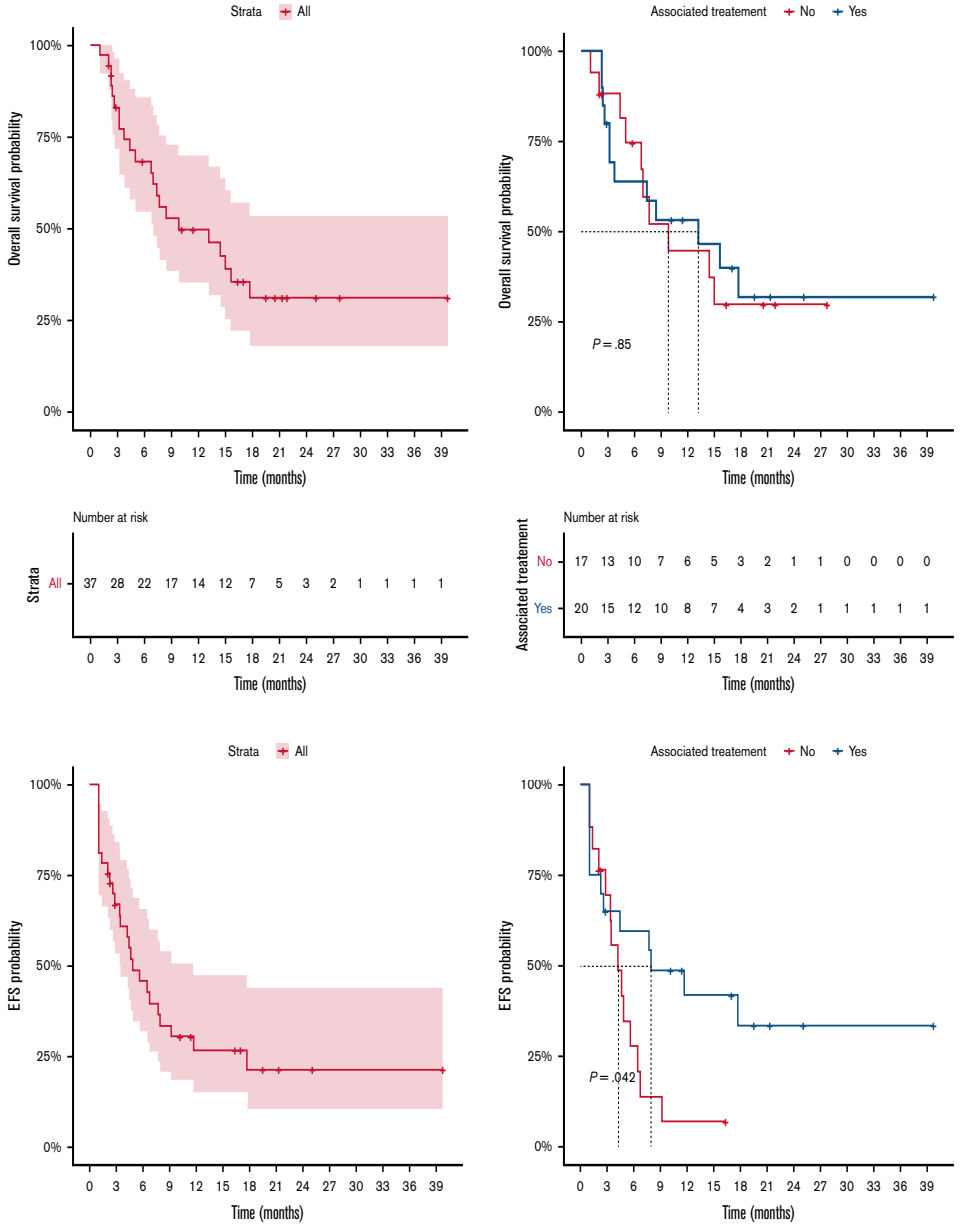
	Study 1022				Study 1010	
	+ Follow-up HSCT		No Follow-up HSCT		+ Follow-up HSCT	No Follow-up HSCT
	InO (n = 9)	SC (n = 5)	InO (n = 13)	SC (n = 22)	InO (n = 3)	InO (n = 13)
PFS, mo, median (95% CI)	9.2 (1.3-NE)	6.5 (2.2-NE)	2.4 (0.6-6.3)	2.4 (1.0-6.2)	5.4 (4.3-NE)	3.5 (1.7-5.9)
OS, mo, median (95% CI)	16.5 (4.7-43.6)	16.4 (11.6-30.6)	4.4 (1.1-8.0)	6.9 (4.1-9.1)	11.3 (4.3-NE)	7.4 (3.5-11.3)

Stock W et Al. Cancer. 2021 Mar 15;127(6):905-913.

ASCIMINIB

Parameters	Value (%) or range (min, max)
Age, median (min-max)	56 (19-84)
Sex male, n (%)	20 (49)
Disease type, n (%)	
R/R Ph+ BCP-ALL	33 (80.5)
LBC-CML	8 (19.5)
No. of previous TKIs, median (min-max)	3 (2-5)
Previous use of ponatinib, n (%)	38 (92.7)
Prior CAR T-cell therapy, n (%)	2 (4.8)
Prior allo-HSCT, n (%)	18 (43.9)
Previous line of therapy, n (%)	41
First line (LBC-CML)	2 (4.9)
Second line of treatment	7 (17.1)
Third line of treatment or more	32 (78)
Disease status, n (%)	
Hematological relapse	24 (58.5)
Refractory	5 (12.2)
CNS-only relapse	1 (2.4)
Molecular relapse	7 (17.1)
Complete remission (intolerance)	4 (9.8)
CNS involvement at time of ASC initiation, n (%)	8 (19)
ASC dose, n (%)	
High dose (200 mg twice daily)	34 (82.9)
Low dose (40 mg twice daily)	7 (17.1)
Associated treatment, n (%)	41
ASC monotherapy, including 2 patients with ITT, n (%)	20 (48.8)
ASC in combination, n (%)	21 (51.2)
High dose chemotherapy	2 (4.9)
Low dose chemotherapy	8 (19.5)
Immunotherapy (blinatumomab or InO)	6 (14.6)
Other TKI	3 (7.3)
DLI	1 (2.4)
CAR T cell	1 (2.4)

Parameters	Value (%) or range (min, max)
Hematological response rate (efficacy population), n (%)	36
CR	28 (77.8)
CRi	2 (5.6)
Failure	6 (16.7)
MRD response in CR + CRi patients with evaluable bone marrow samples, n (%)	23
No CMR	10 (43.5)
CMR (BCR ABL <0.01% in bone marrow)	13 (56.5)
Post ASC treatment, n (%)	37
No HSCT or CAR T cells	27 (73)
Allo-HSCT	3 (8)
CAR T cell	5 (13.5)
Allo-HSCT + CAR T cell	2 (5.4)

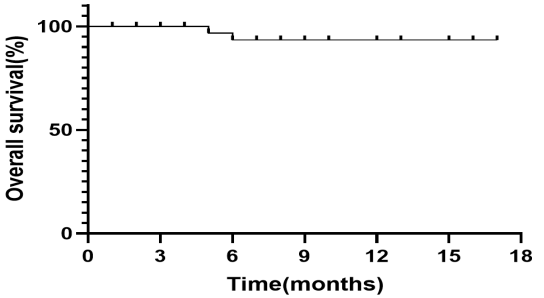


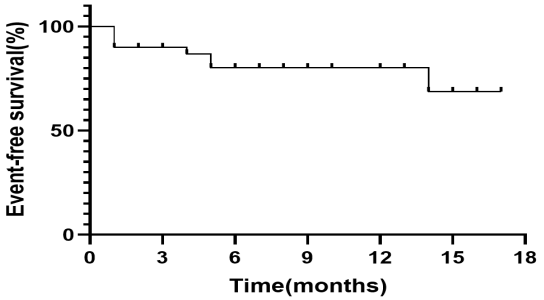
Chanut M et Al. Blood Adv. 2025 Sep 23;9(18):4580-4584.

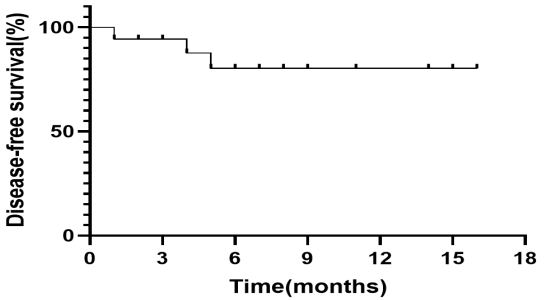
OLVEREMBATINIB

	Total	Ph+ ALL	CML-BP
Patient number	59	40	19
Age (year; median (IQR))	39 (30–48)	38 (28–48)	45 (33–48)
Male (*n* (%))	36 (61.0)	22 (55.0)	14 (73.7)
Female (*n* (%))	23 (39.0)	18 (45.0)	5 (26.3)
ECOG performance status (*n* (%))			
≤ 1	56 (94.9)	38 (95.0)	18 (94.7)
=2	3 (5.1)	2 (5.0)	1 (5.3)
Time from diagnosis to olverembatinib treatment (month; median (IQR))	6.3 (2.5–20.1)	8.2 (2.6-10.8)	20.1 (10.2–87.5)
BCR::ABL1 transcript (*n* (%))			
p210	32 (54.2)	13 (32.5)	19 (100)
p190	27 (45.8)	27 (67.5)	0 (0)
Number of lines of prior TKI therapy (*n* (%))			
0	10 (16.9)	10 (25.0)*	0 (0)
1	22 (37.3)	20 (50.0)	2 (10.5)
2	16 (27.1)	8 (20.0)	8 (42.1)
3	7 (11.9)	1 (2.5)	6 (31.6)
4	4 (6.8)	1 (2.5)	3 (15.8)
Type of prior TKI therapy (n (%))			
Imatinib	12 (20.3)	3 (7.5)	9 (47.4)
Nilotinib	10 (16.9)	1 (2.5)	9 (47.4)
Dasatinib	41 (69.5)	26 (65.0)	15 (78.9)
Flumatinib	9 (15.3)	3 (7.5)	6 (31.6)
Ponatinib	19 (33.9)	10 (25.0)	9 (47.4)
BCR::ABL1 mutation status (n (%))			
Non-T315I BCR::ABL1 mutation	8 (13.6)	2 (5.0)	6 (31.6)
T315I mutation	9 (15.3)	1 (2.5)	8 (42.1)
Receive HSCT before olverembatinib *n* (%)	12 (20.3)	11 (27.5)	1 (5.3)
With CNSL (n (%))	12 (20.3)	9 (22.5)	3 (15.8)

Ph+ ALL	Primary refractory ALL (*n* = 26)	Relapse with CNSL (*n* = 9)	Relapse without CNSL (*n* = 5)	CR/CRi (*n* (%))
VDP ± venclexta	15	5	2	21 (95.5)
Hyper-CVAD	6	2	1	8 (88.9)
Blinatumomab	5	1	2	7 (87.5)
Radiotherapy	0	1	0	1 (100.0)

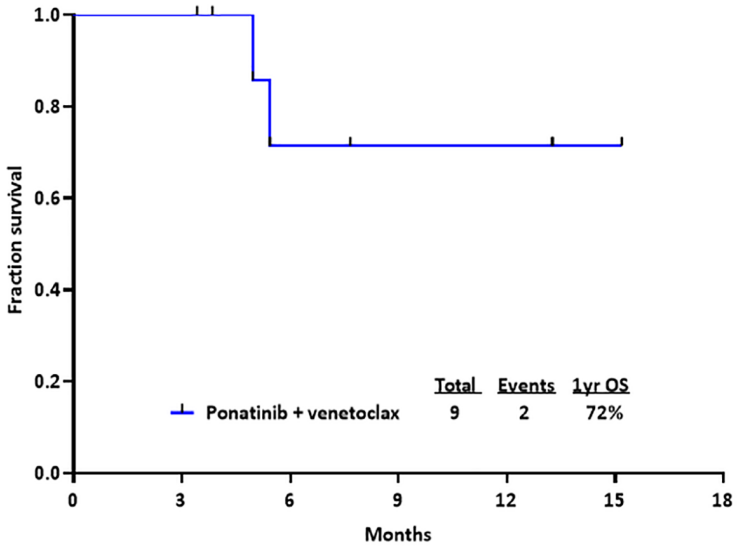


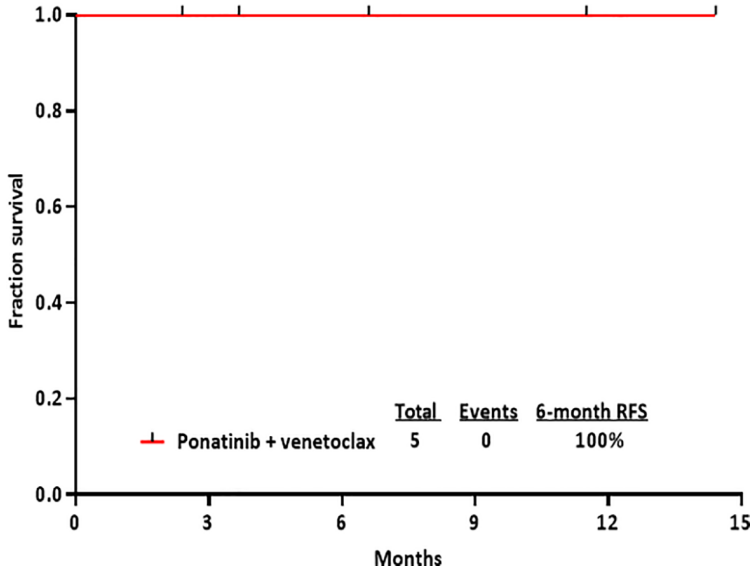


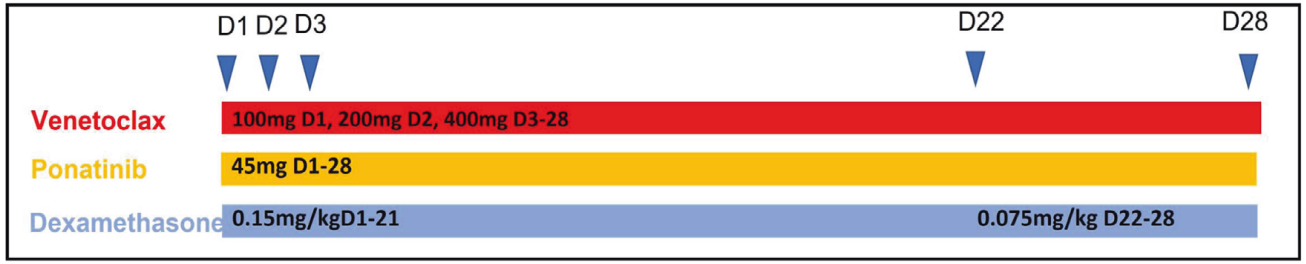


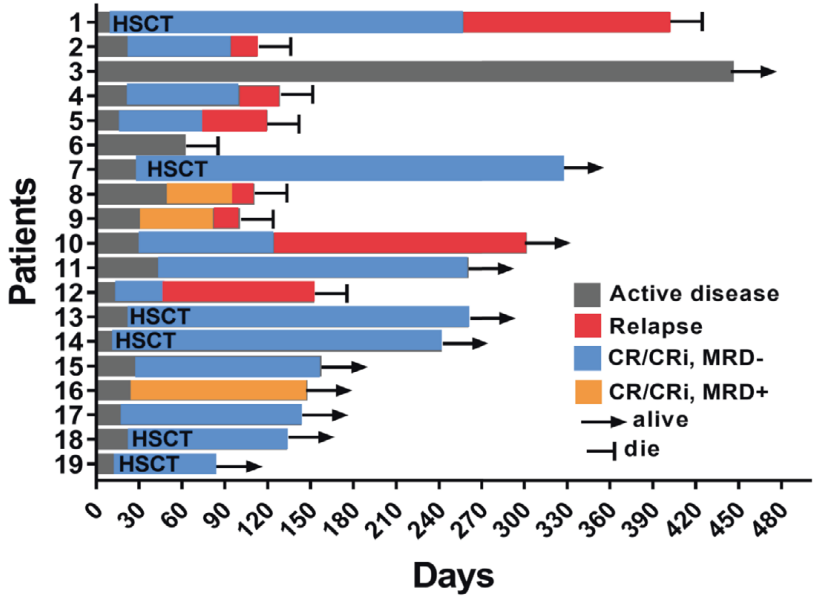
Wen Z et Al. Front Immunol. 2025 May 14;16:1546371.

VENETOCLAX









Short NJ et Al. Am J Hematol. 2021 Jul 1;96(7):E229-E232.

Wang H et Al. Blood Cancer J. 2022 Jan 28;12(1):20.

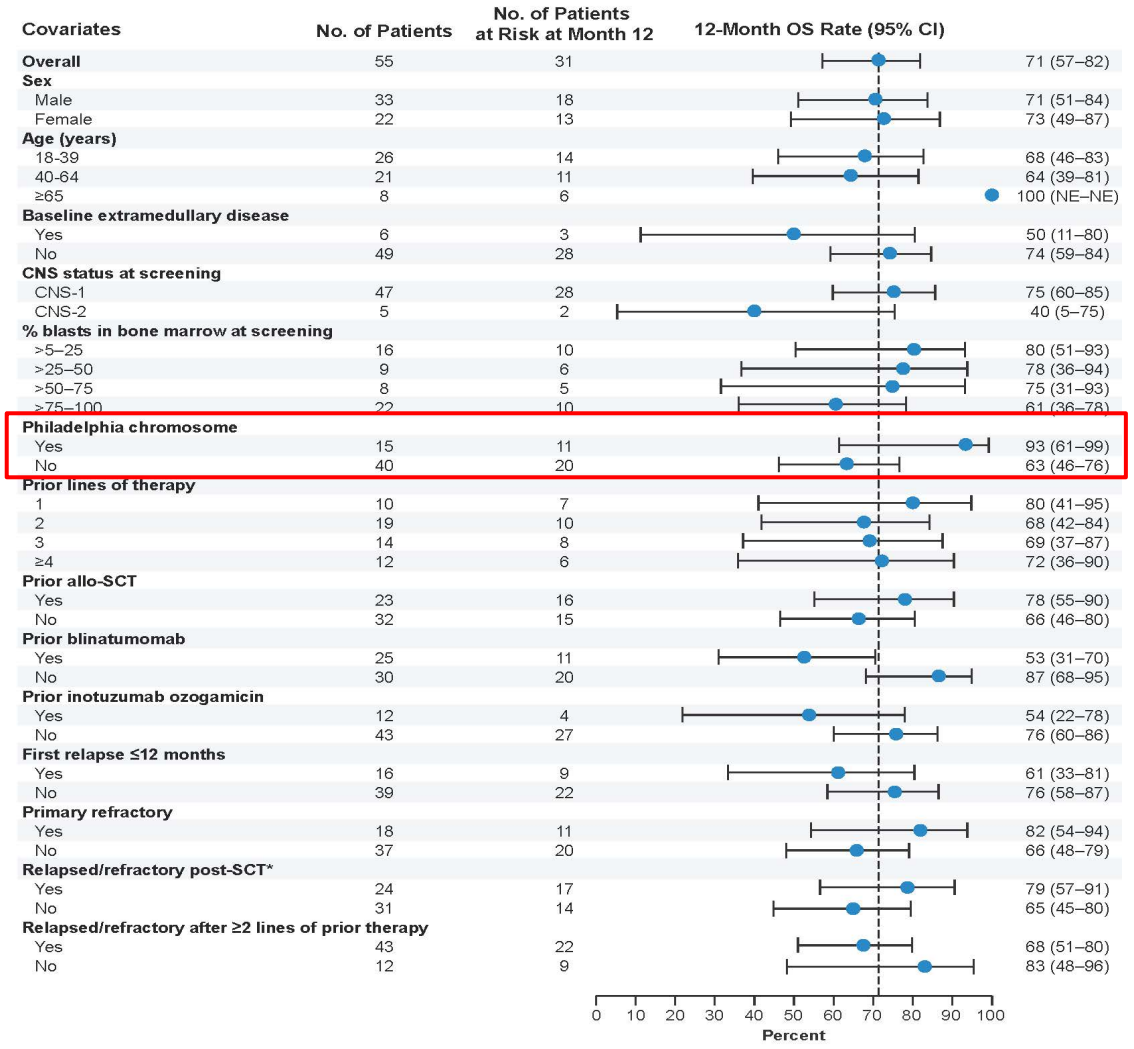
CAR-T

	Patients (N = 75)
Age, median (range), years	11 (3-23)
Male, n (%)	43 (57)
Prior stem cell transplant, n (%)	46 (61)
Previous line of therapies, median (range), n	3 (1-8)
Disease status, n (%)	
Primary refractory	6 (8)
Chemo-refractory or relapsed	69 (92)
Morphologic blast count in bone marrow, median (range), %	74 (5-99)
CNS status classification, n (%)*	
CNS-1	63 (84)
CNS-2	10 (13)
CNS-3	1 (1)
Unknown	1 (1)
High-risk genomic lesions, n (%)†	28 (37)
Down syndrome, n (%)	6 (8)

CNS, central nervous system.

* The most current assessment on or prior to the date of enrollment. † *BCR-ABL1*, *MLL* rearrangement, hypoploidy, lesions associated with *BCR-ABL1*-like gene signature, or complex karyotype (≥5 unrelated abnormalities).

Maude SL et Al. N Engl J Med. 2018 Feb 1;378(5):439-448.



Shah BD et Al. Lancet. 2021 Aug 7;398(10299):491-502.

Table 1. Baseline patient and disease characteristics

Characteristic	Tisa-cel (n = 50)	Brexu-cel (n = 20)	*P* value
Sex, n (%)			.35
M	29 (58)	14 (70)	
F	21 (42)	6 (30)	
Age at CAR T-cell infusion, median (range), y	21 (18-26)	22.5 (18-26)	
Race/ethnicity, n (%)			.81
Non-Hispanic White	24 (48)	9 (45)	
Hispanic	19 (38)	8 (40)	
Black	2 (4)	0	
Asian/Pacific Islander	0	2 (10)	
Other/not reported	5 (10)	1 (5)	
ALL subtype, n (%)			.8
Ph^- ALL*	33 (66)	12 (60)	
Ph^+ ALL	5 (10)	3 (15)	
Ph-like ALL	11 (22)	5 (25)	
Unknown	1 (2)	0	
Marrow disease before CAR T, n (%)			.1
Undetectable MRD	15 (30)	3 (15)	
Detectable MRD with <5% blasts†	12 (24)	11 (55)	
Flow cytometry	12	6	
clonoSEQ	0	3	
qPCR	0	1	
NGS	0	0	
5 to <50% blasts	9 (18)	2 (10)	
>50% blasts	11 (22)	3 (15)	
Unknown	3 (6)	1 (5)	
Extramedullary disease before CAR T, n (%)			.11
Present	5 (10)	5 (25)	
Not present	45 (90)	3 (15)	
Not assessed/unknown	0	12 (60)	
CNS disease status before CAR T, n (%)			.11
CNS 1	41 (82)	11 (55)	
CNS 2	1 (2)	1 (5)	
CNS 3	2 (4)	1 (5)	
Not assessed/unknown	6 (12)	7 (35)	
Therapy before CAR T			
Total lines of therapy, median (range)	3 (1-5)	3 (1-9)	
Blinatumomab, n (%)‡	12 (24)	9 (45)	.08
Inotuzumab, n (%)‡	13 (26)	6 (30)	.73
Allogeneic HCT, n (%)	20 (40)	3 (15)	.04
Bridging therapy between apheresis and lymphodepletion, n (%)	26 (52)	15 (75)	.08
Lymphodepletion regimen, n (%)			.22
Fludarabine/cyclophosphamide	47 (94)	17 (85)	
Other	3 (6)	3 (15)	

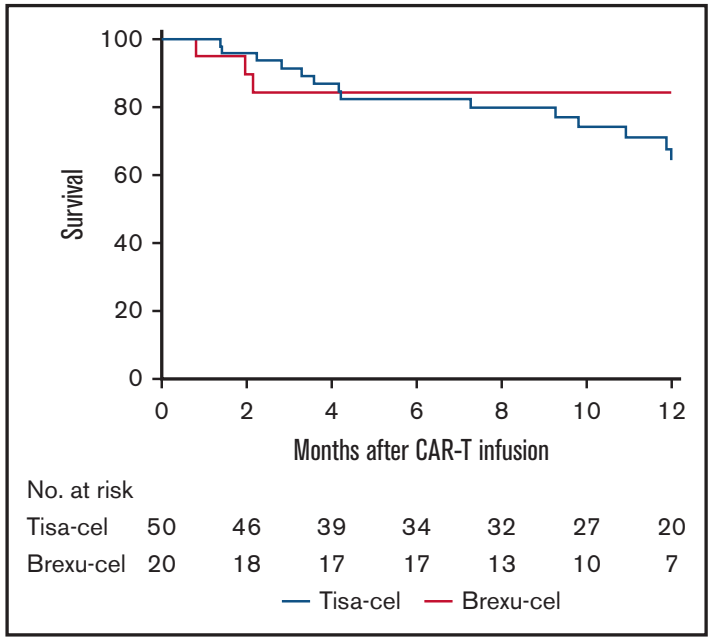


Table 3. Multivariate analysis

	OS			RFS			DOR		
Characteristic	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
CAR T product: brexu-cel vs tisa-cel	0.71	0.18-2.75	.62	1.01	0.40-2.52	.98	0.85	0.26-2.74	.78
Age, >21 vs ≤21 years	1.08	0.36-3.24	.90	1.59	0.68-3.72	.29	1.36	0.46-4.01	.57
ALL subtype, Ph^- vs Ph^+ or Ph-like	1.48	0.46-4.81	.51	0.79	0.34-1.80	.57	0.50	0.19-1.32	.16
Marrow disease before CAR T									
MRD^- or MRD^+ vs ≥5% blasts	0.23	0.06-0.86	.03	0.47	0.20-1.10	.08	0.79	0.29-2.15	.64
Therapy before CAR T									
Allogeneic HCT, yes vs no	0.54	0.20-2.33	.38	0.47	0.17-1.30	.15	0.43	0.12-1.53	.20
Blinatumomab, yes vs no	0.23	0.05-1.17	.08	0.33	0.11-1.02	.05	0.42	0.10-1.75	.23
Inotuzumab, yes vs no	6.32	1.48-27.0	.01	3.65	1.41-9.46	.008	2.17	0.66-7.18	.21

Lust H et Al. Blood Adv. 2025 Jun 10;9(11):2763-2772.

2026 Unmet clinical needs

Early relapse/refractory to Blina + 3 gen TKI

Relapse after CAR-T

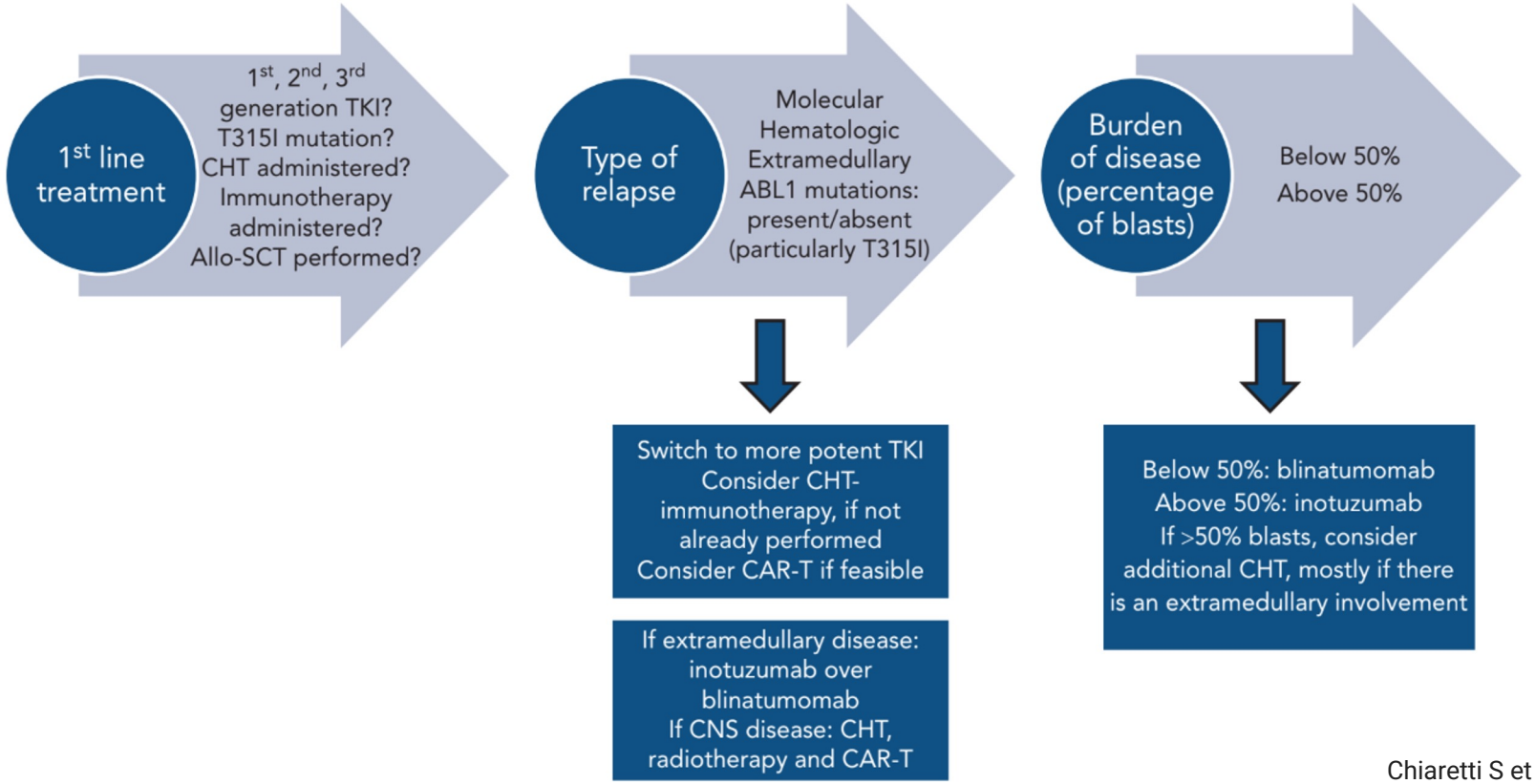
Relapse after HSCT

Extramedullary Relapse

Take home messages

Monitoring MRD with both BCR-ABL and IgH-TCR

Test BCR-ABL mutations



Chiaretti S et Foà R. *Blood*. 2025 Jan 2;145(1):11-19.

Thank you for attention!

Un ringraziamento speciale…

REGIONE DEL VENETO
ULSS3 SERENISSIMA

UO Ematologia
Ospedale dell'Angelo

…and to my Sensei

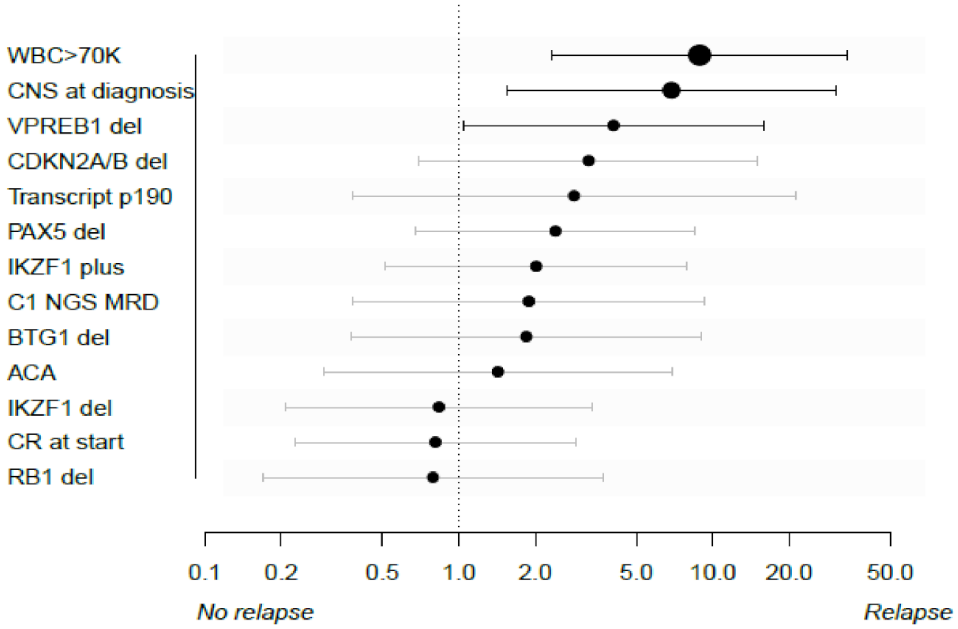
LEUKEMIA UNIT

- Sara Consolo
- Luca Frison
- Matteo Leoncin
- Rosaria Sancetta

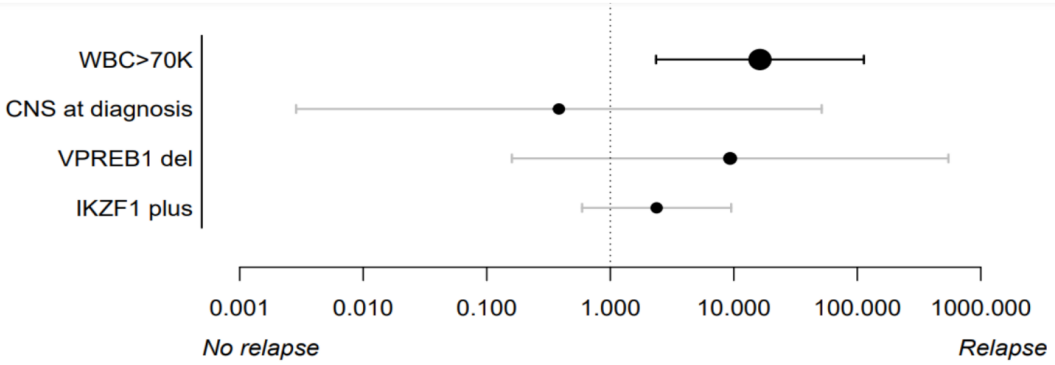
TRANSPLANT UNIT

- Anita Betulla
- Samanta Bonato
- Francesca Carobolante
- Costanza Fraenza
- Giulia Perali

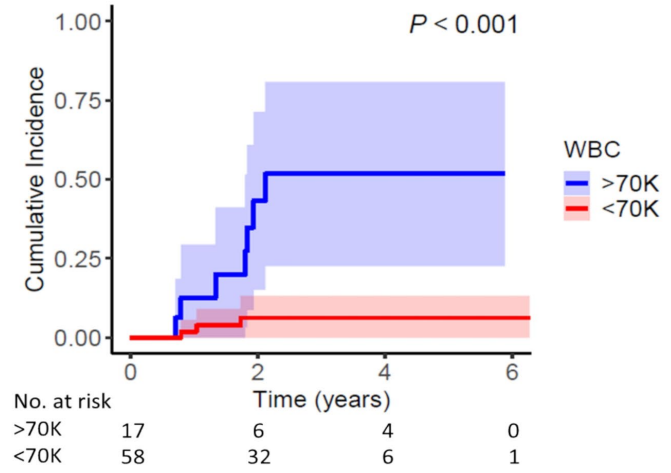
Direttore: Dr.ssa Cristina Skert

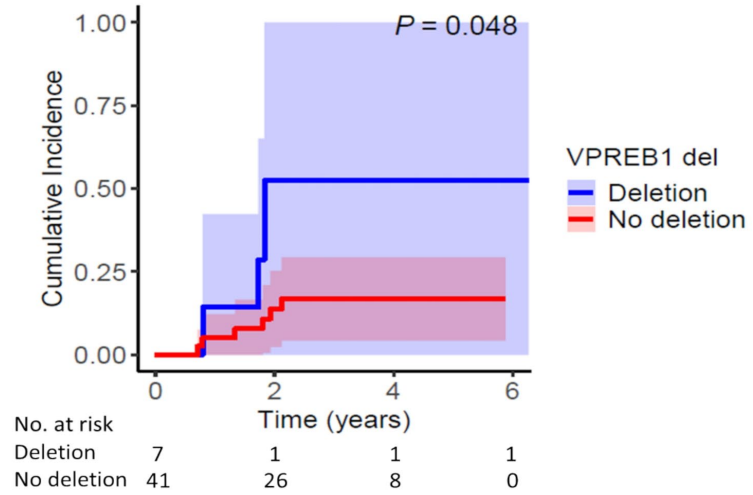


	sHR	95% CI	P	FDR
WBC>70K	8.86	[2.33–33.70]	0.0014	0.0075
CNS at diagnosis	6.87	[1.54–30.68]	0.012	0.048
VPREB1 del	4.06	[1.05–15.76]	0.043	0.14
CDKN2A/B del	3.24	[0.70–15.02]	0.13	0.35
Transcript p190	2.84	[0.38–21.19]	0.31	0.5
PAX5 del	2.40	[0.68–8.53]	0.18	0.36
IKZF1 plus	2.02	[0.51–7.90]	0.31	0.5
C1 NGS MRD	1.89	[0.38–9.26]	0.43	0.6
BTG1 del	1.84	[0.38–8.97]	0.45	0.6
ACA	1.42	[0.29–6.93]	0.66	0.8
IKZF1 del	0.84	[0.21–3.35]	0.8	0.8
CR at start	0.81	[0.23–2.89]	0.74	0.8
RB1 del	0.79	[0.17–3.68]	0.76	0.8



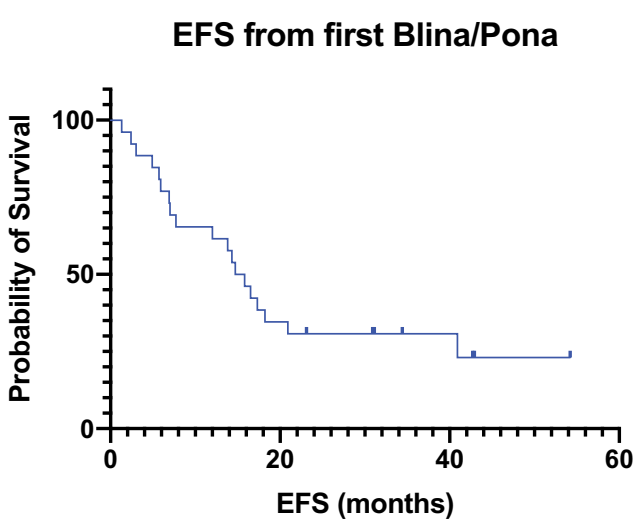
	sHR	95% CI	P
WBC>70K	16.29	[2.35–113.00]	0.0047
CNS at diagnosis	0.38	[0.00–51.50]	0.7
VPREB1 del	9.34	[0.16–546.30]	0.28
IKZF1 plus	2.37	[0.59–9.53]	0.22

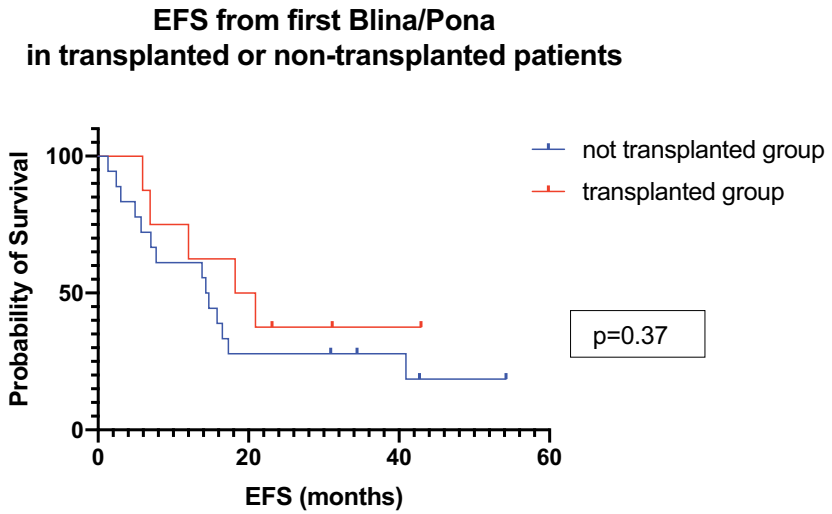


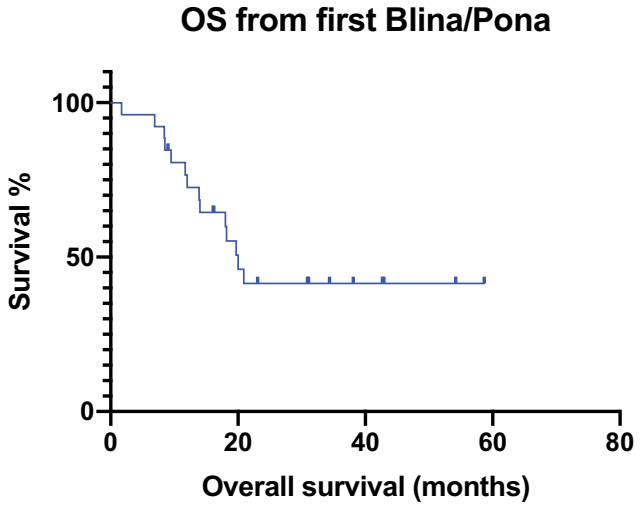


Short NJ et Al. J Hematol Oncol. 2025 May 14;18(1):55.

Blina + Pona







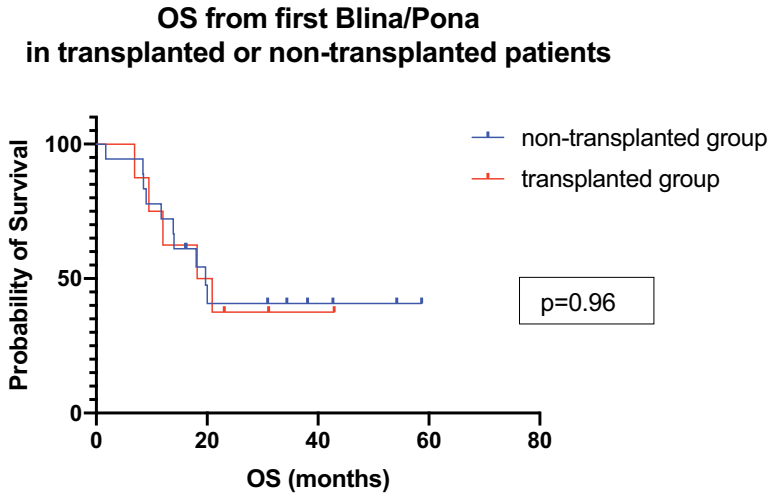
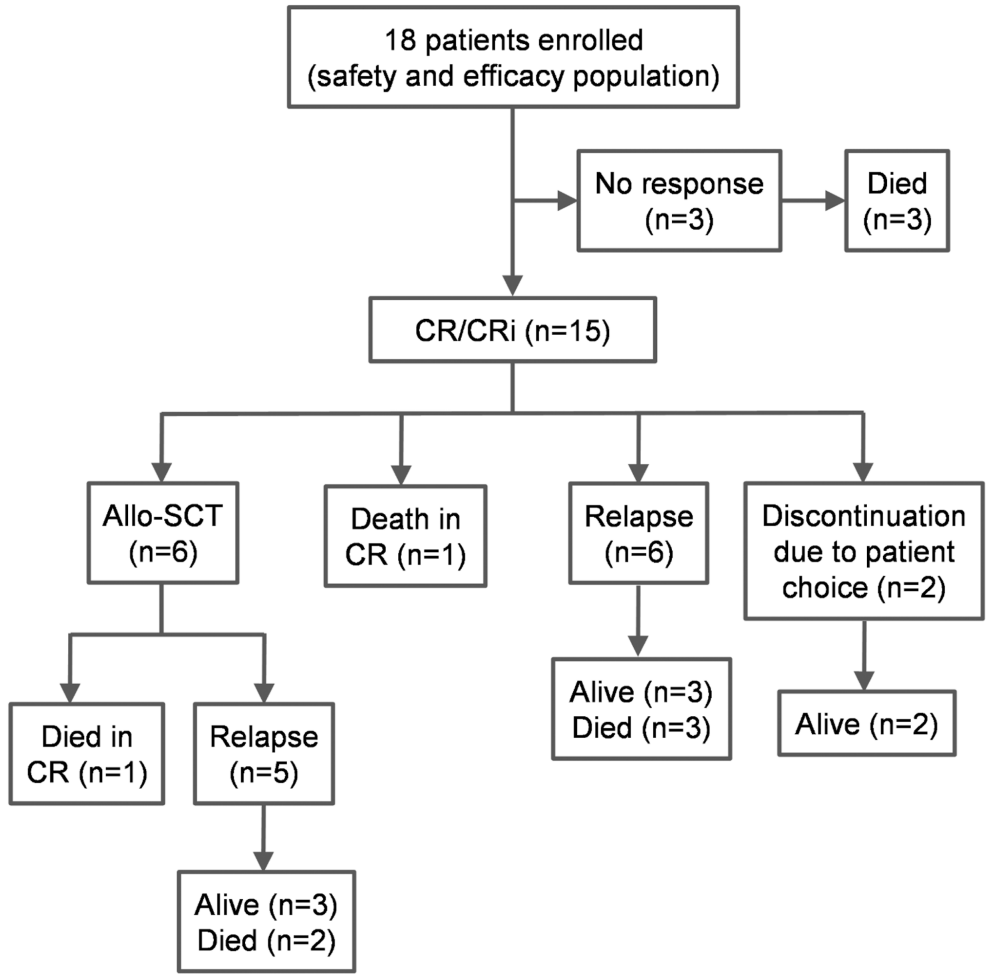


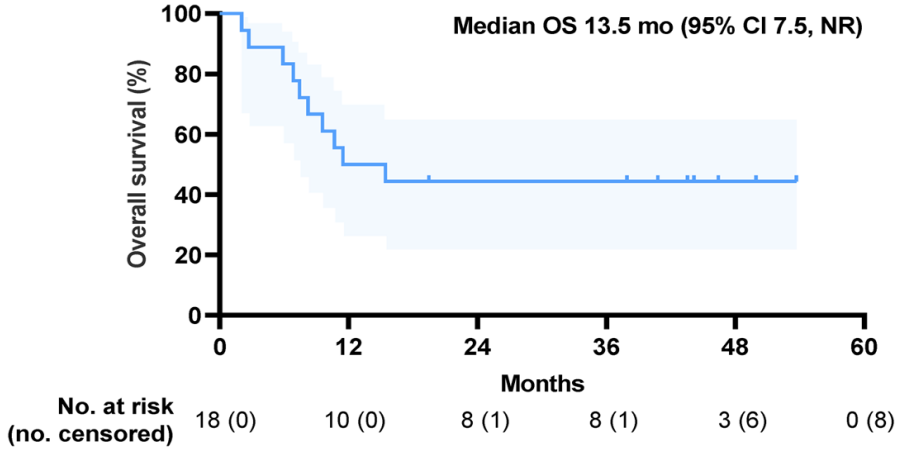
Table 1. Patient characteristics.

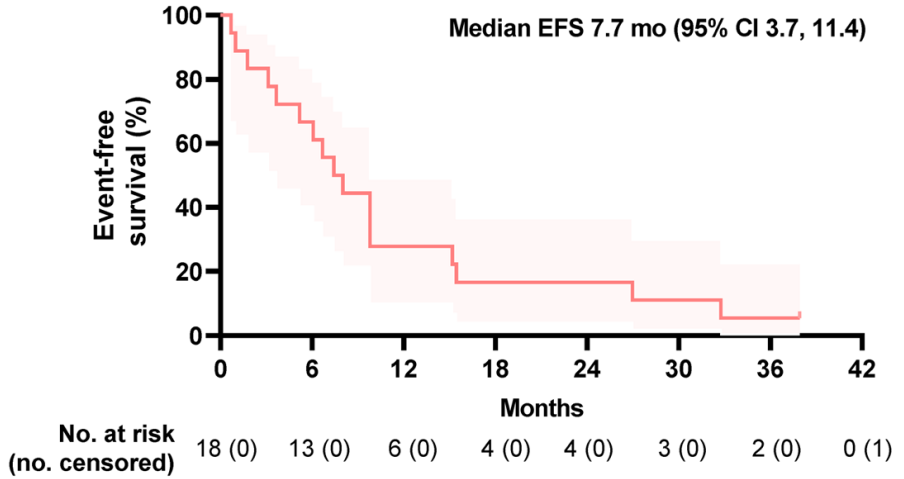
N = 26 Ph + ALL	
Median age: years (range)	58 (18–81)
Gender	
Male/female	14/12
Status at diagnosis	
De novo Ph + ALL/Blast crisis of CML	22/4
Central nervous system disease	1
Extramedullary disease	2
p190 protein/p210 protein/unknown	16/9/1
Status at the time of blina/pona	
First relapse	12
Second relapse or more	13
Primary refractory	1
Previous allograft (sibling/MUD)	9 (4/5)
Previous autograft	5
Molecular status	
No mutation	14
p.T315I mutation	8
p.T315I + p.E255K	1
p.Y253H mutation	1
p.E255K mutation	1
p.F371L + Y253H mutations	1
Previous TKI	
1	8
2	14
3	4

Couturier MA et Al. Leuk Lymphoma. 2021 Mar;62(3):620-629.

Ino + Bosutinib

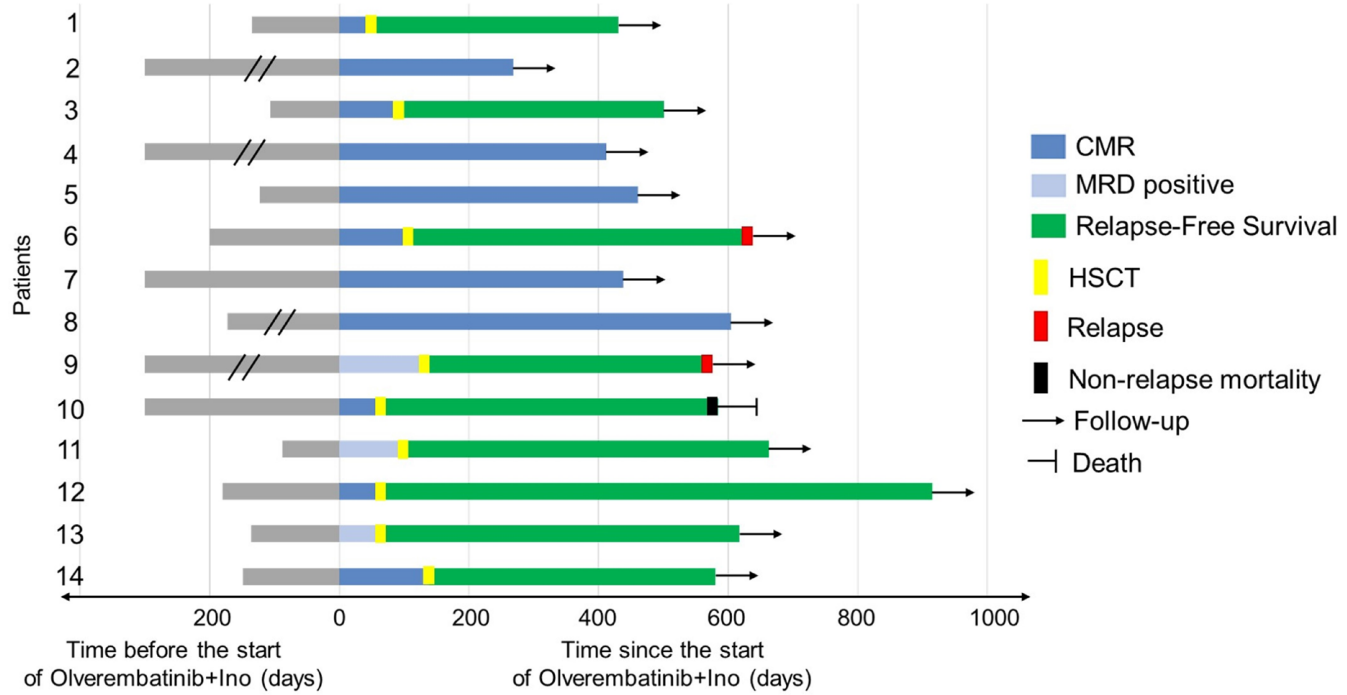


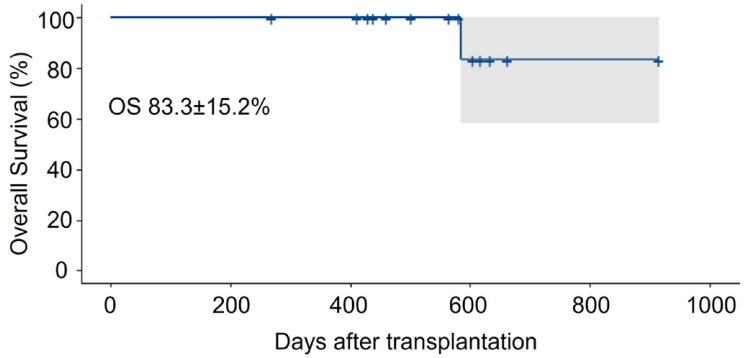


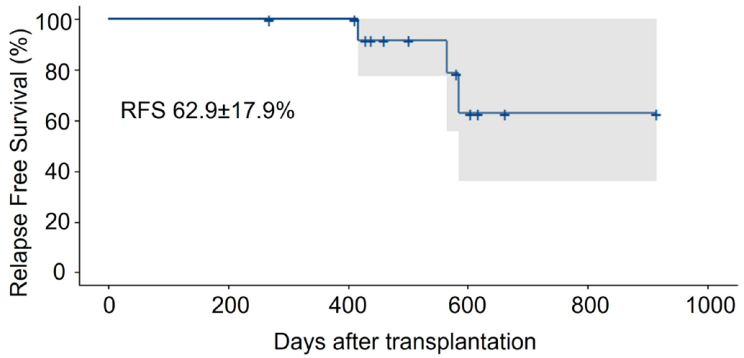


Jain N et Al ia. Am J Hematol. 2021 Aug 1;96(8):1000-1007.

Ino + Olverembatinib



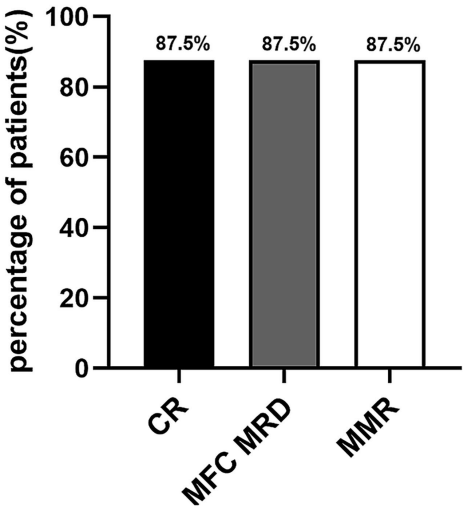


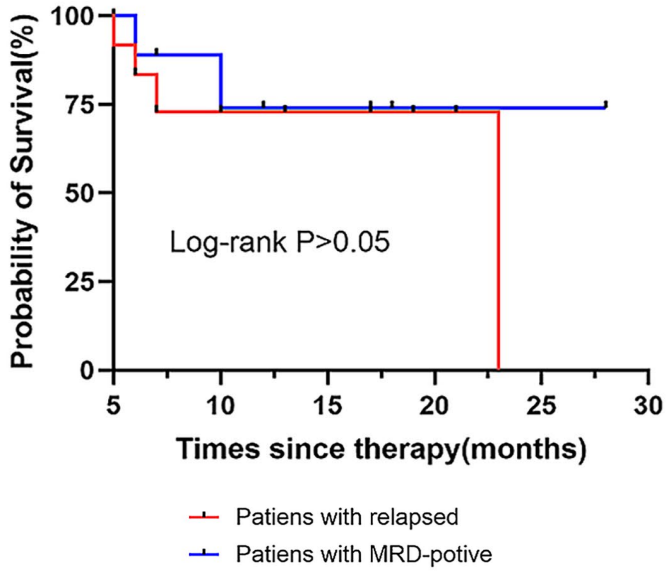


Zhang X et Al. Am J Hematol. 2025 Oct;100(10):1924-1928.

Patient	Cycle 1	BM (%)	MFC (%)	ABL (%)	Cycle 2	BM (%)	MFC (%)	ABL (%)
1	Olv + VIP	0	<0.01	0	Olv + VCP	0	<0.01	$2.9*10^{-7}$
2	Olv + DCME	9	72.71	73.51	Olv + VCP	72	4.86	56.30
3	Olv + CP	0	<0.01	0	Olv + Bli	0	<0.01	0
4	Olv + Bli	0	<0.01	0	Olv + Bli	0	<0.01	0
5	Olv + VP	2	<0.01	2.45	Olv + VP	0	<0.01	0
6	Olv + VP	50	38.97	41.04	N	N	N	N
7	Olv + CVAD	0	<0.01	1.44	Olv + MA	0	<0.01	0.04
8	Olv + VD	0	<0.01	0.003	N	N	N	N
9	Olv + VP + Bli	0	<0.01	0.13	N	N	N	N
10	Olv	4	1.31	26.5	N	N	N	N
11	Olv + VCP	0	<0.01	0.05	Olv	0	<0.01	0.02
12	Olv + VP	0	<0.01	0.08	Olv + Bli	0	<0.01	0.003
13	Olv + IO	0	<0.01	0.037	Olv	0	<0.01	<0.01
14	Olv + Bli	0	<0.01	0	Olv	0	<0.01	0
15	Olv	2	<0.01	0.34	Olv	0	<0.01	0.011
16	Olv + Bli	0	<0.01	0.1	Olv	0	<0.01	0
17	Olv + MTX	0	<0.01	0.52	Olv	0	<0.01	0
18	Olv + VP	0	<0.01	1.2	Olv + VP	0	<0.01	0
19	Olv + Bli	0	<0.01	0	Olv + Bli	0	<0.01	0
20	Olv + Bli	0	<0.01	0.01	Olv	0	<0.01	<0.01
21	Olv	0	<0.01	0.32	Olv + Bli	0	<0.01	0.12
22	Olv	0	<0.01	<0.01	Olv	0	<0.01	<0.01

Olv, Olverembatinib; Bli, blinatumomab; MA, Methotrexate + Cytarabine; IO, inotuzumab ozogamicin; VIP, Vincristine + Idarubicin + Prednisone; DECM, Decitabine + Cyclophosphamide + Etoposide + Mitoxantrone; CVAD, Cyclophosphamide + Vincristine + Doxorubicin + Prednisone; VCP, Vincristine + Cyclophosphamide + Prednisone; N, not tested.





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