POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Verona
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Leucemie Acute Linfoidi

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Disclosures of Cristina Papayannidis

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie						X	X
Astellas						X	X
Servier							X
Menarini							X
BMS							X
Pfizer						X	X
Amgen							X
Janssen						X	
GSK						X	
Blueprint						X	
Incyte						X	X
Paladin Labs Inc							X
Jazz pharmaceuticals						X	
Novartis						X	
Delbert Laboratoires						X	

Agenda

- ✓ Ph+ ALL
- ✓ Ph-like ALL
- ✓ Ph- B-ALL:
  - Young patients
  - Elderly patients
- ✓ T-ALL
- ✓ New drugs

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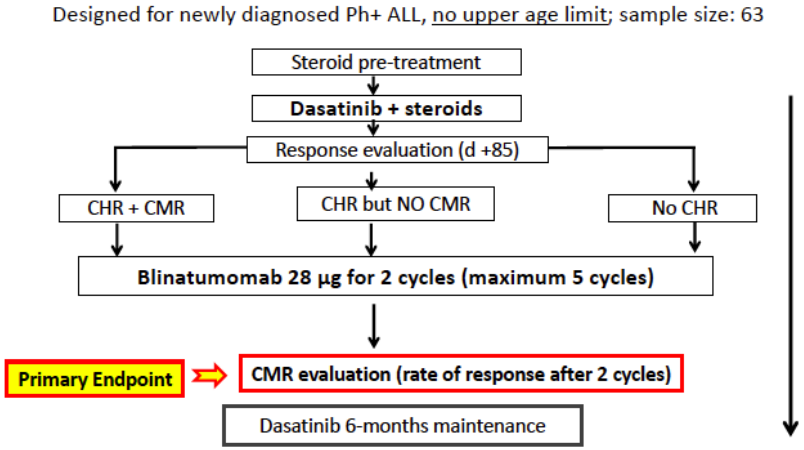
Dasatinib+Blinatumomab in newly diagnosed Ph+ ALL (D-ALBA): long term results



Characteristic	Enrolled Patients (N=63)
Age — yr	
Median	54
Range	24–82
Sex — no. (%)	
Male	29 (46)
Female	34 (54)
White-cell count — per mm^3	
Median	13,000
Range	600–88,000
Fusion protein — no. (%)	
p190	41 (65)
p210	17 (27)
p190 and p210	5 (8)

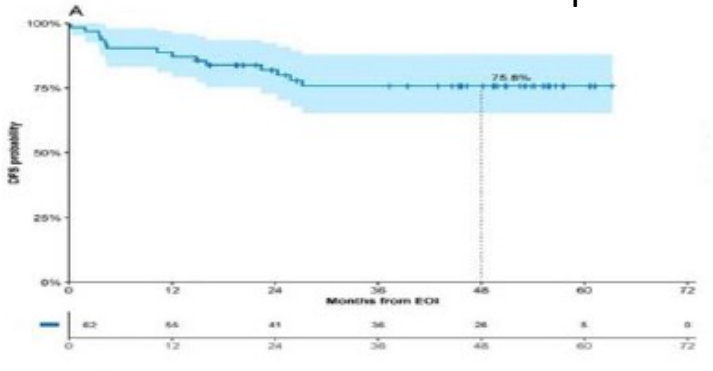
Foà R et al, Abstract 4250; Foà R et al, NEJM 2020; Foà R et al, JCO 2023

Dasatinib+Blinatumomab in newly diagnosed Ph+ ALL (D-ALBA): long term results

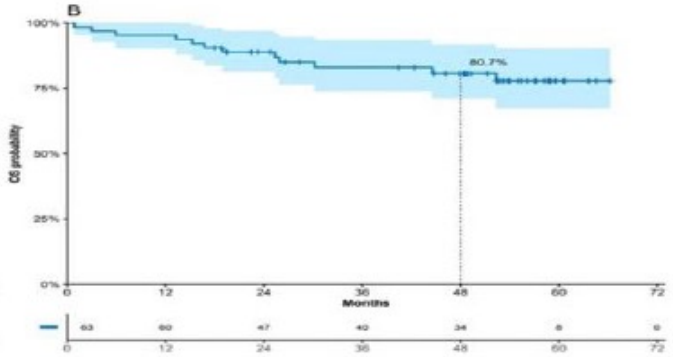
- ✓ 30/59 (51%) who started blina had SCT
- ✓ 53 months **OS 80.7%**, **DFS 75.8%**
- ✓ Outcome **worse if IKZF1+**: DFS 82% vs 45% (p=0.029)
- ✓ Outcome **better if MR (EOI)**: DFS 100% vs 69% (p=0.036)

Median follow up: 53 months

DFS

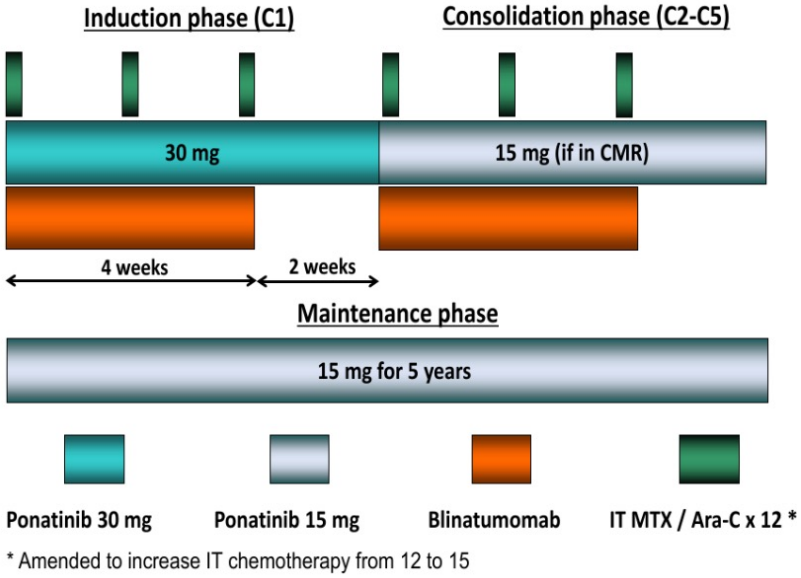


OS



Foà R et al, Abstract 4250; Foà R et al, JCO 2023

Ponatinib+Blinatumomab in newly diagnosed Ph+ ALL



Characteristics N (%) / Median [range]	N = 62
Age (years) ≥ 60	56 [20 - 83] 25 (40)
WBC (x10⁹/L) at start	4.65 [0.4 - 23.7]
Male gender	27 (44)
Performance Status 0-1 2	 52 (84) 10 (16)
Central nervous system involvement	3 (5)
CD19 expression	99.8 [74.9 - 100]
>1 cardiovascular risk factor(s)	36 (58)
BCR::ABL1 Transcript *p190* *p210*	 47/61 (77) 14/61 (23)

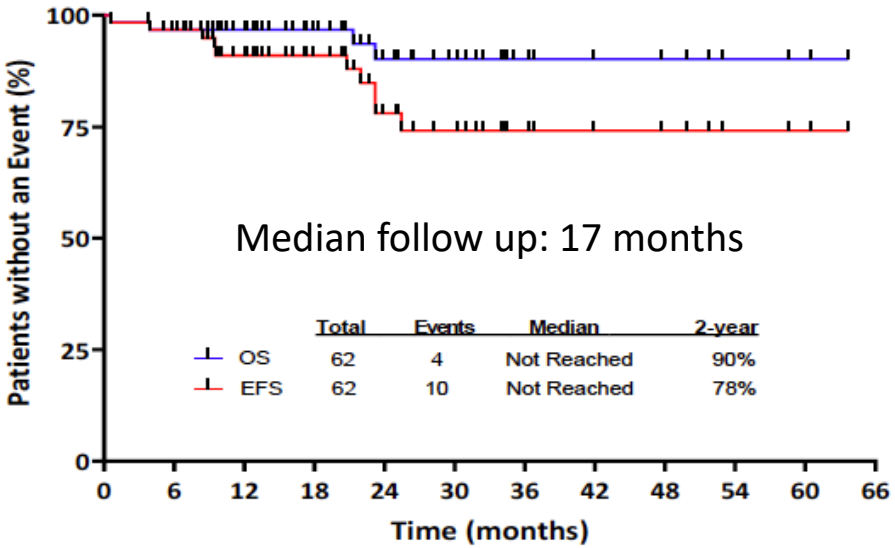
Haddad FG et al, Abstract 2827

Ponatinib+Blinatumomab in newly diagnosed Ph+ ALL

✓ 1 pt had SCT; 7 relapses (all p190): 4CNS, 1 CRLF2+, 2 systemic

Responses n/N (%)	N = 62
CR	38/40 (95)
CRi	1/40 (3)
CR/Cri *	39/40 (98)
PR	0
No response	0
Complete molecular response (CMR) **	
After Cycle 1	37/55 (67)
Overall	46/55 (84)
Negative MRD by NGS	44/47 (94)
Early death	1/62 (2)

* 22 patients were in CR at the start of therapy
** 7 patients were in CMR at the start of therapy



Haddad FG et al, Abstract 2827

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Feasibility and Outcome of Post-Induction Therapy Incorporating Dasatinib for Patients with Newly Diagnosed (ABL-class Fusion B-ALL): Children's Oncology Group AALL1131

- 22 patients, median age 14 years (1-27)
- ABL-class fusions: ABL1 4
  ABL2 4
  PDGRB 12
  CSF1R2

- 5/22 completed therapy
- **MRD neg EOC 40% (Dasa)** vs 87.5% (AALL1131) p=0.0006

Patient Characteristics	Dasatinib Arm(n=22)	All the others on AALL1131 (n=5867)	P-value
Age (median , range)	14 [1,27]	10 [1,30]	0.008
WBC (median , range)	44 [3,360]	19 [1,6200]	0.086
Sex (% male)	17 (77%)	3293 (56.1%)	0.046
DFS at 4-year	52.5 ± 18.1%	86.8 ± 0.7%	<0.0001
OS at 4-year	79.4 ± 13.6 %.	89.2 ± 0.4%	<0.2528

Salzer WL et al, Abstract 961

➡ No indications to add Dasatinib for patients with these genotypes

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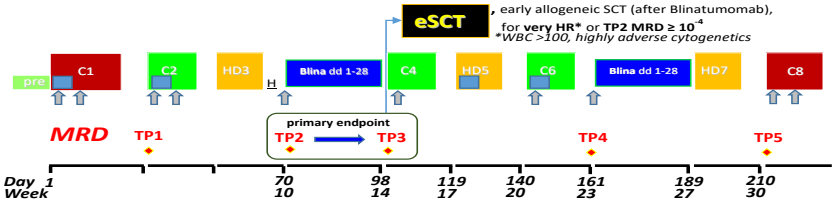
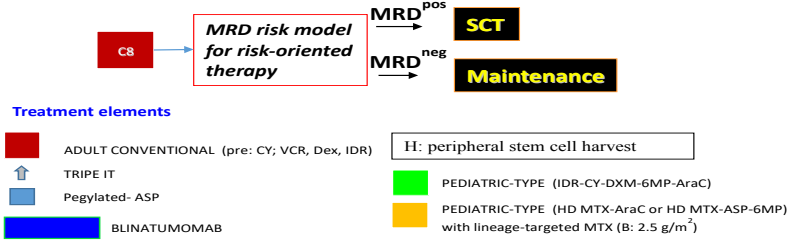
Final results of the phase 2 Gimema trial 2317

A. Induction/consolidation, Blinatumomab, MRD study and early SCT



B. Final MRD-oriented therapy



Enrollment period: August 2018-June 2020
Median follow up 38.1 months (0.5-62.8)

n=149

	n (%)
Sex, n (%)	
M/F	81 (54%)/68 (46%)
Median age (range)	41 (18-65)
>55 years	28 (19%)
Median WBC x10^9/l (range)	4.5 (0.1-474)
Risk, n (%)	
SR	85 (57%)
HR	29 (19%)
VHR	35 (23%)
WBC, n (%)*	
WBC >30x10^-9/L	36 (24%)
WBC <30x10^-9/L	111 (76%)
Immunophenotype, n (%)**	
ALL pro-B/common/pre-B*	23 (16%)/114 (77%)/11 (7.4%)
Molecular findings	
KMT2A/AFF4, n (%)	12 (8.3%)
E2A/PBX1, n (%)	5 (3.4%)
BCR/ABL1-like, n (%)	31 (28%)
Cytogenetics, n (%)***	
Normal	56 (49%)
Adverse (*KMT2A*-rearranged and other)	26 (22%)
Non adverse (*E2A-PBX1*, hyperdiploid and other)	32 (17.5%)
TEL/AML1	1 (0.9%)

Chiaretti S et al, Abstract 826

Final results of the phase 2 Gimema trial 2317

MRD at TP2 (HD3)*	Whole cohort n (%)	Paired samples n (%)	p
MRD-negative	85 (70)	79 (72)	
MRD-positive	37 (30)	30 (28)	
MRD at TP3 (blinatumomab 1)**	**n (%)**	**n (%)**	**<0.001**
MRD-negative	102 (93)	101 (93)	
MRD-positive	8 (7.3)	8 (7.3)	

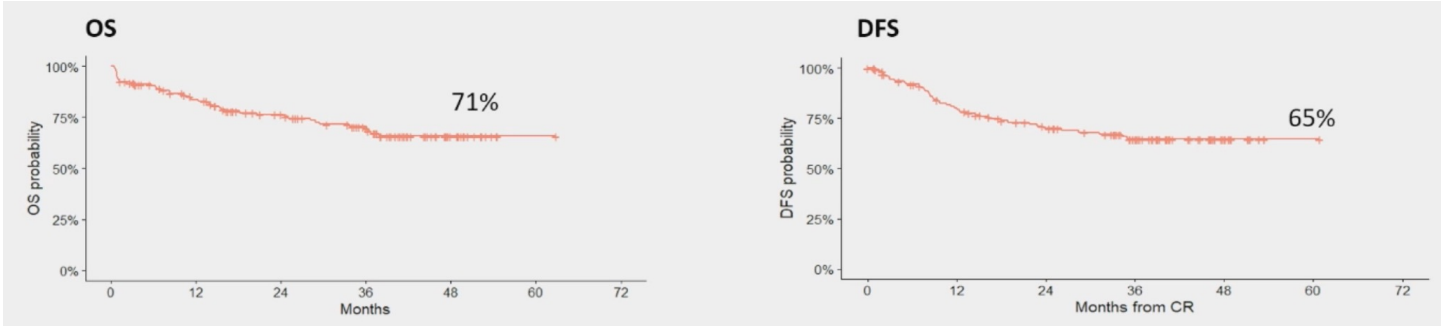
*8 not evaluable; **12 not evaluable

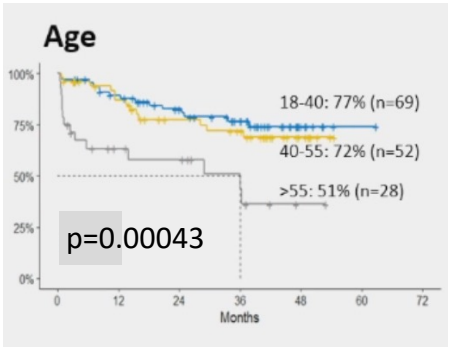
Age class	18-40, n=55 (%)	40-55, n=42 (%)	>55, n=13 (%)	p
MRD at TP3 (blinatumomab #1)				
MRD-negative	49 (89)	40 (95)	13 (100)	0.5
MRD-positive	6 (11)	2 (4.8)	0	
Risk class	**SR, n=65 (%)**	**HR, n=21 (%)**	**VHR, n=22(%)**	**p**
MRD at TP3 (blinatumomab #1)				
MRD-negative	63 (97)	20 (95)	18 (78)	0.02
MRD-positive	2 (3)	1 (4.8)	5 (22)	

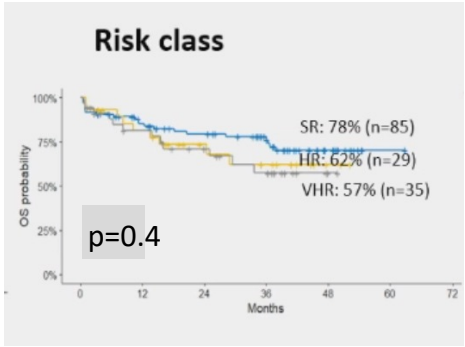
- ✓ Equally effective at all age cohorts
- ✓ Slightly less effective in very high risk group

Chiaretti S et al, Abstract 826

Final results of the phase 2 Gimema trial 2317







- Worse OS for pts>55 years
(in part due to deaths in induction)

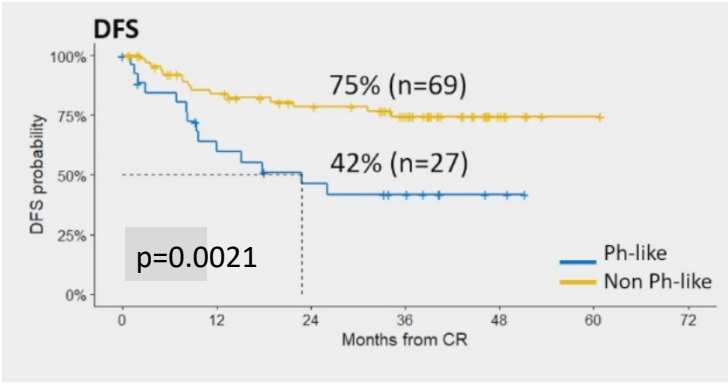
Chiaretti S et al, Abstract 826

Final results of the phase 2 Gimema trial 2317

- ✓ 32 relapses occurred: 6 CNS, 5 extramedullary
- ✓ Median time to relapse: 10 months (1.6-34.3)
- ✓ Biological features: 1 *KMT2A*-r, 3 *E2A-PBX1*, 11 *BCR/ABL*–like, 4 *MEF2D-r*

Focus on Ph-like:

MRD at TP2 (HD3)	Overall (n=81, %	Ph-like (n=22, %)	Non Ph-like (n=59, %)
MRD-negative	59 (73)	15 (68)	44 (75)
MRD-positive	22 (27)	7 (32)	15 (25)
MRD at TP3 (blinatumomab #1)	**n (%)**		
MRD-negative	78 (96)	22 (100)	56 (95)
MRD-positive	3 (3.7)	0	3 (5.1)

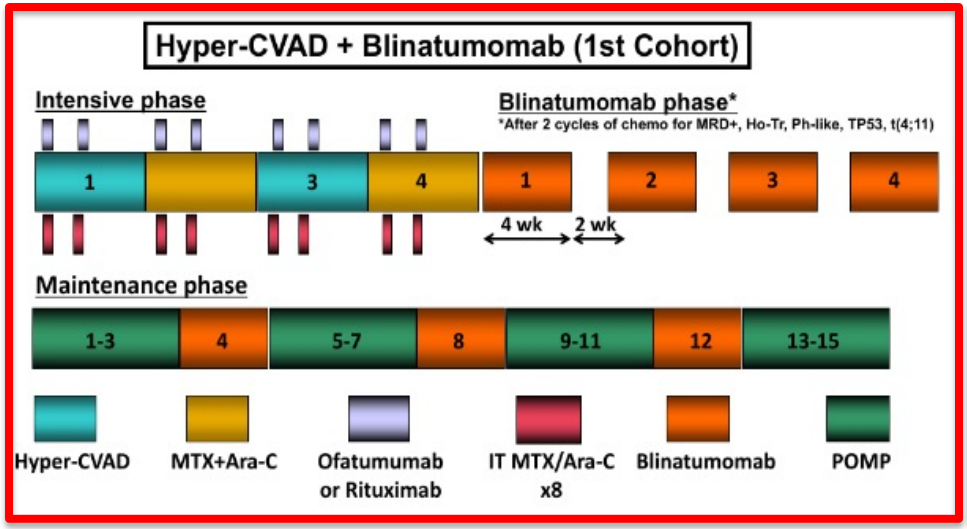


- Ph-like ALL patients need innovative approaches!

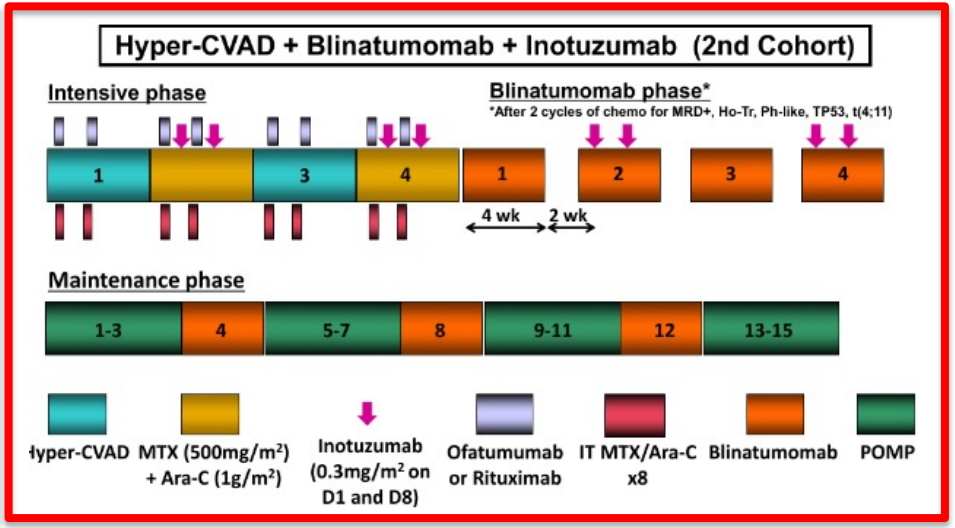
Chiaretti S et al, Abstract 826

Hypercvad with or without Inotuzumab Ozogamicin and sequential blinatumomab in newly diagnosed young ALL

n=38



n=37

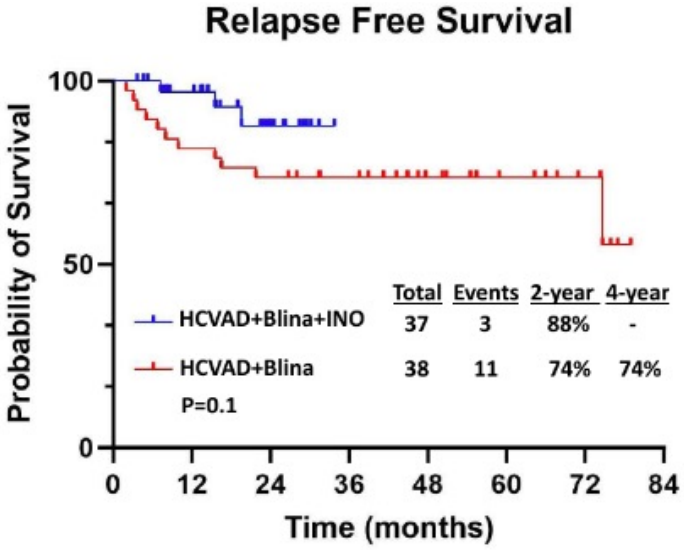


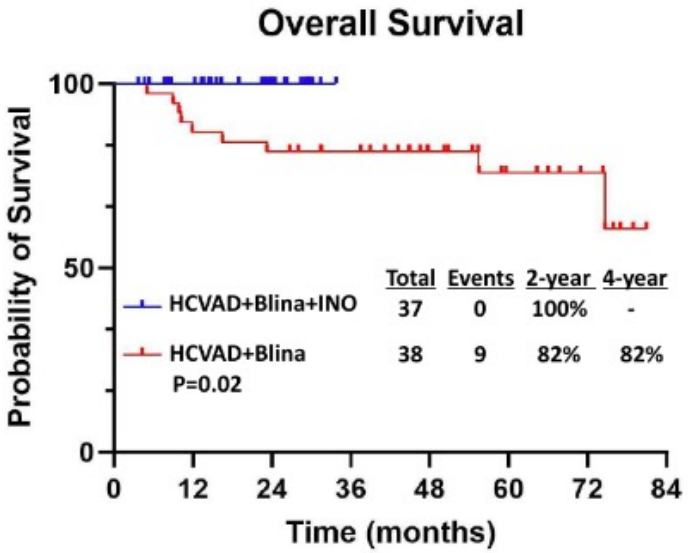
Ngyuen D et al, Abstract 4245

Hypercvad with or without Inotuzumab Ozogamicin and sequential blinatumomab in newly diagnosed young ALL

- ✓ 75 patients; median age 33 years (18-59)
- ✓ CR rate 100%; MRD negative 95%; 60 day mortality 0%; 24 (32%) allo-SCT

Median follow-up: 30 months

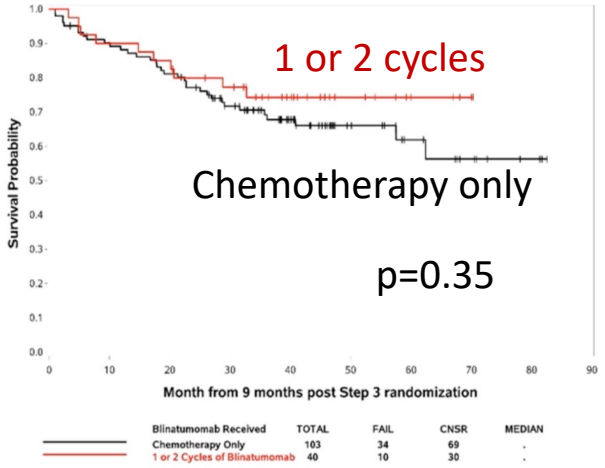


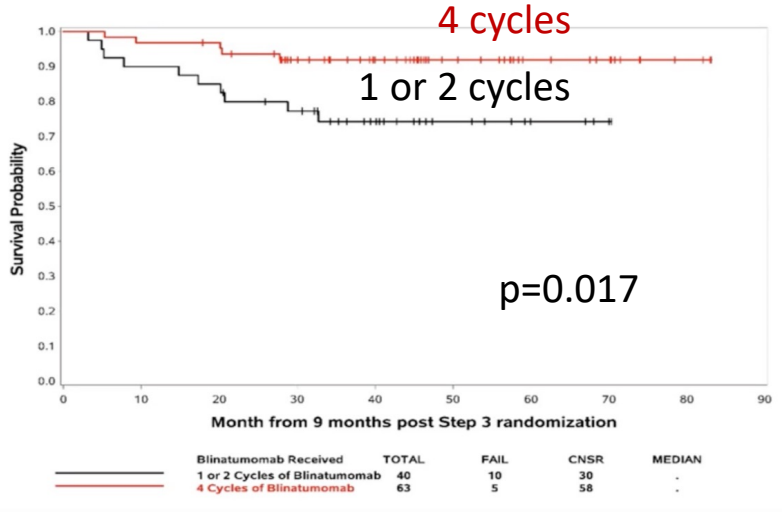


Ngyuen D et al, Abstract 4245

E1910 randomized phase 3 trial: Blina vs SOC as consolidation in MRD negative Outcomes by number of cycles

- ✓ 488 pts, median age 51 yrs (30-70)
- ✓ 224 MRD neg CR randomized 1:1
- ✓ Median follow-up 43 months: median OS NR vs 71.4 months (p=0.003)





Luger SM et al, Abstract 2877

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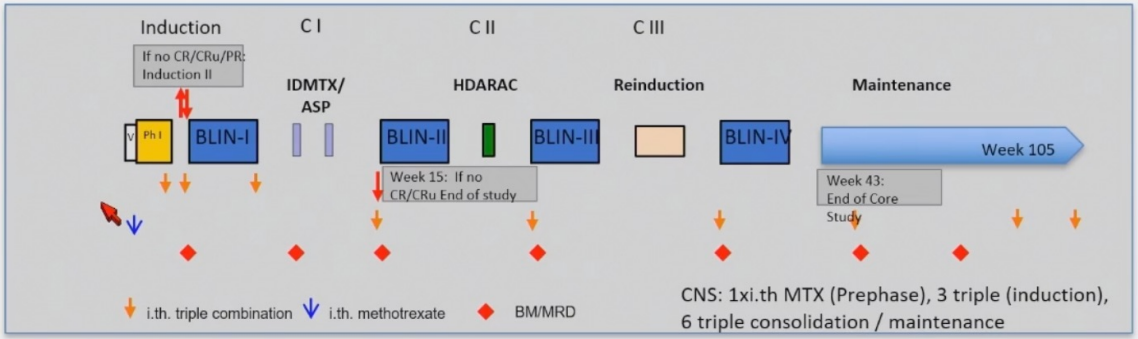
Dose-reduced chemotherapy and Blinatumomab in older pre B ALL: Phase 2 GMALL Bold trial

✓ Age 56-75 years

56-60y:	15 (29 %)
61-65y:	**11 (21 %)**
66-70y:	**14 (27 %)**
71-75y:	11 (21 %)
>75y:	1 (2 %)



Reduction compared to GMALL standard:

- Idarubicin 2x in induction
- Rituximab 1x in induction
- Phase II of induction
- IDMTX/ASP 2x
- HDAC 1x

Primary Endpoint:
Rate of complete hematologic remission after induction (Induction I Chemotherapy and Blinatumab 1)

Key Secondary Endpoint:
Molecular response

Key inclusion criteria: Ph-negative CD19 positive B-precursor ALL aged 56-76 years (NCT 03480438)

Goekbuget N et al, Abstract 964

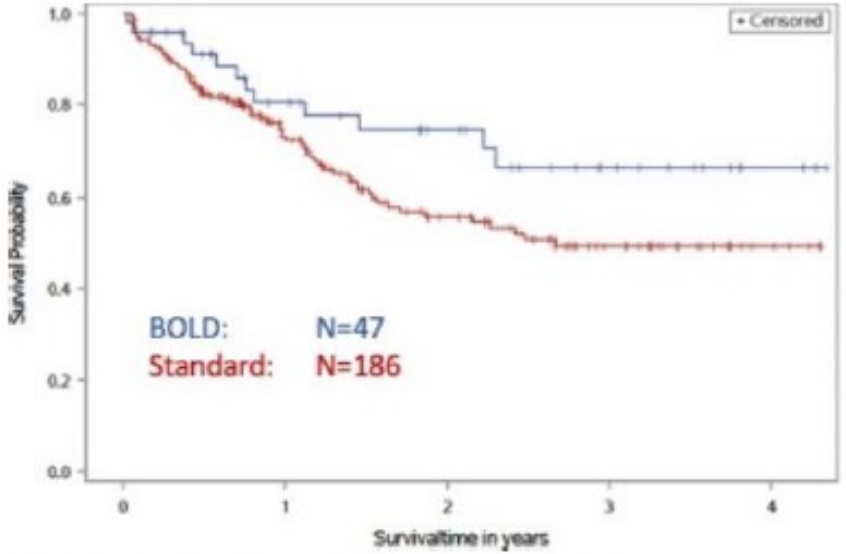
Dose-reduced chemotherapy and Blinatumomab in older pre B ALL: Phase 2 GMALL Bold trial

N=50

	Induction I	Blina I
N Hematologic Response*	50	47
Hematologic CR	38 (76%)	40 (85%)
Early death	2 (4%)	2 (4%)
Failure/PR/Relapse	10 (20%)	5 (11%)
N Molecular Response**	34	37
Molecular CR	6 (18%)	28 (82%)
Molecular IMR	5 (15%)	2 (6%)
Molecular Failure	23 (68%)	4 (12%)

OS@1 year 80%
OS@ 3 years 67% (48% in historical)
ALLOSCT: 3
MolCR 82% (55% in historical)

Median follow up: 757 days (61-1584)



Goekbuget N et al, Abstract 964

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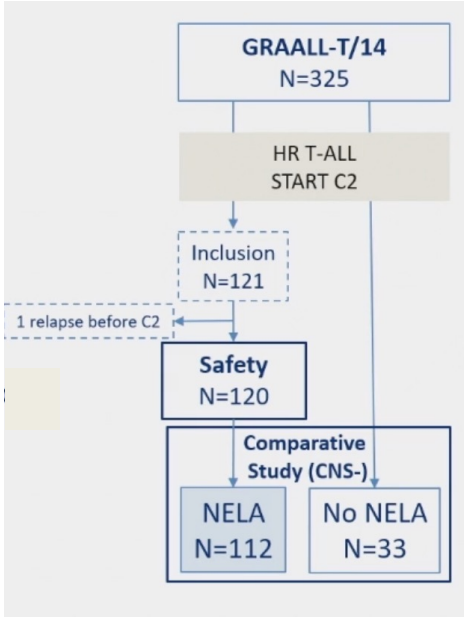
Frontline Consolidation with Nelarabine for Adults with High-Risk T-Cell Acute Lymphoblastic Leukemia. Results of the Graall-2014/T Atriall Phase 2 Study



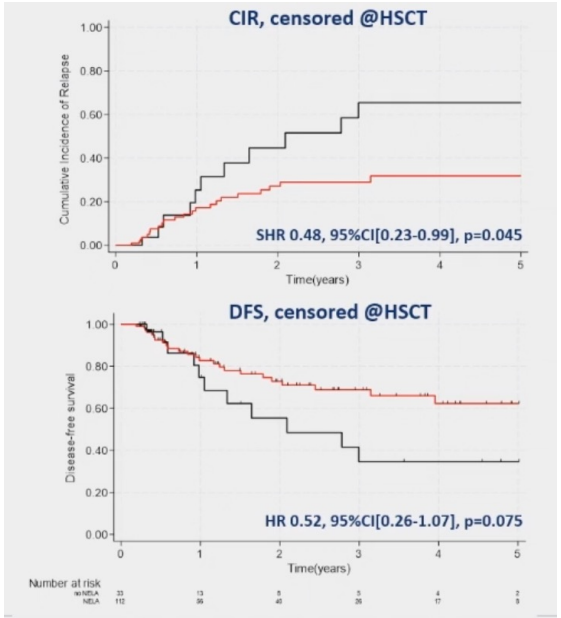
	NELA (ATRIALL) n=112	No NELA N=33	p
MRD response (after conso 2)			
$MRD3_{neg}$, N(%)	75/96 (78)	15/26 (58)	0.05
$MRD3_{neg}$ if MRD1 ≥ 10^{-4} , N(%)	36/55 (65)	5/16 (31)	0.02
Allo-HSCT rate	38/112 (34)	15/33 (45)	0.30
Median follow-up	3.0	5.8	<0.001
3y-CIR (95%CI)	27% (20-37)	47% (31-67)	0.14
3y-CIR, censored at HSCT (95%CI)	29% (20-41)	65% (43-85)	0.045
3y-DFS (95%CI)	67% (56-75)	49% (30-66)	0.32
3y-DFS, censored at HSCT (95%CI)	69% (56-79)	35% (13-57)	0.075
3y-OS (95%CI)	72% (62-80)	76% (56-88)	0.80
3y-OS, censored at HSCT (95%CI)	74% (61-83)	69% (41-86)	0.97

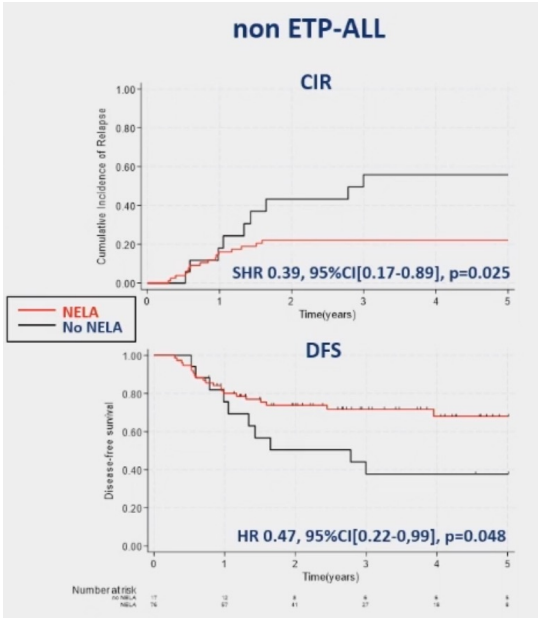
After Nelarabine:

- Significant improvement of MRD response
- No significant reduction in CIR or improvement of DFS
- Significant reduction in CIR censored @HSCT

Boissel N et al, Abstract 962

Frontline Consolidation with Nelarabine for Adults with High-Risk T-Cell Acute Lymphoblastic Leukemia. Results of the Graall-2014/T Atriall Phase 2 Study





- Patients inelegible to HSCT or with a non-ETP phenotype seem to benefit from Nelarabine in terms of relapse risk reduction and DFS
- The role of Nelarabine in T-LBL was not investigated

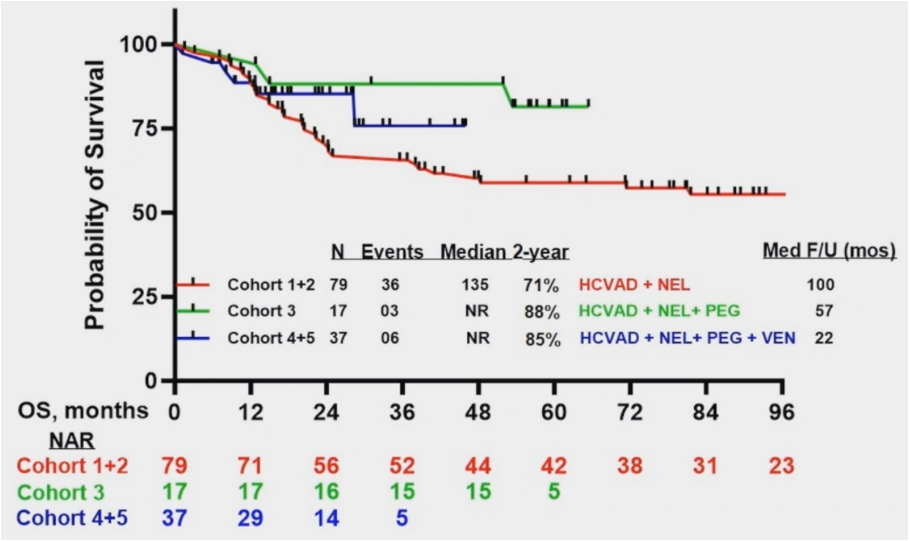
Boissel N et al, Abstract 962

Nelarabine, Pegylated Asparginase and Venetoclax Incorporated to HCVAD Chemotherapy in the Frontline Treatment of Adult Patients with T-ALL/T-LBL

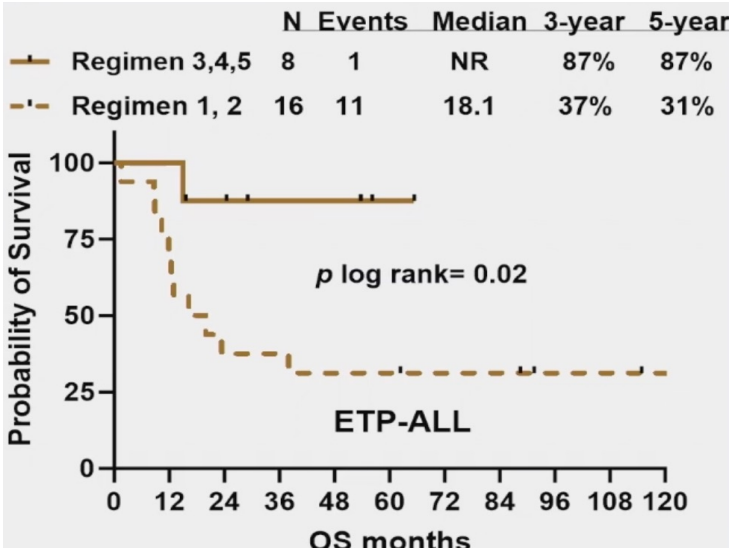
Regimens	N	Year	Hyper-CVAD	Nelarabine (NEL)	Pegasparaginase (PegAsp)	Venetoclax (Ven)	ORR
1	30	2007-2011	Hyper-CVAD 1,3,5,7 MTX/Ara-C 2,4,6,8	After C8 for 2 cycles Cycles 6-7 of maintenance	-	-	96%
2	49	2011-2017		After C4 (4N) and C5 (5N) Cycles 6-7 of maintenance	-	-	98%
3	17	2017-2019			PegAsp with NEL in Cycles 4N and 5N PegAsp with NEL in Cycles 6-7 of maintenance	-	100%
4	16	2019-2021				Days 1-7 of all Induction/ consolidation cycles	100%
5	21	2021-2023				Days 1-7 of C1; Days 1-3 for C2-C8* only for ETP-ALL / MRD+	89%

Jain N et al, Abstract 963

Nelarabine, Pegylated Asparginase and Venetoclax Incorporated to HCVAD Chemotherapy in the Frontline Treatment of Adult Patients with T-ALL/T-LBL



ETP-ALL



- Prolonged thrombocytopenia more common in Ven containing arms

Jain N et al, Abstract 963

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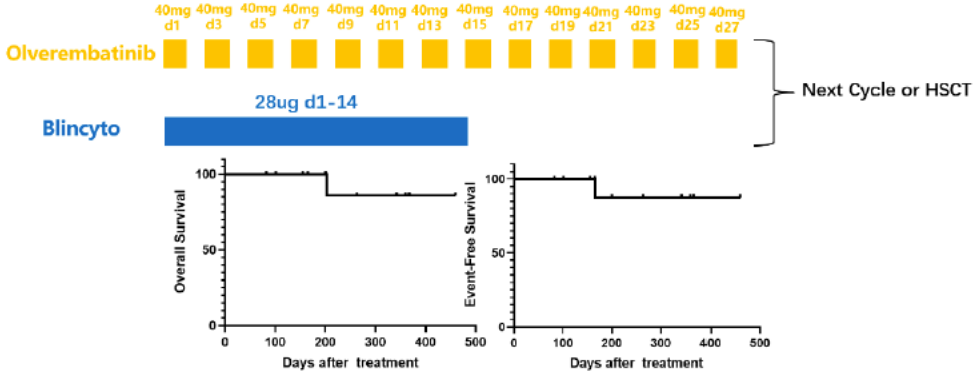
Olverembatinib + Blinatumomab in frontline Ph+ and Ph-like ALL

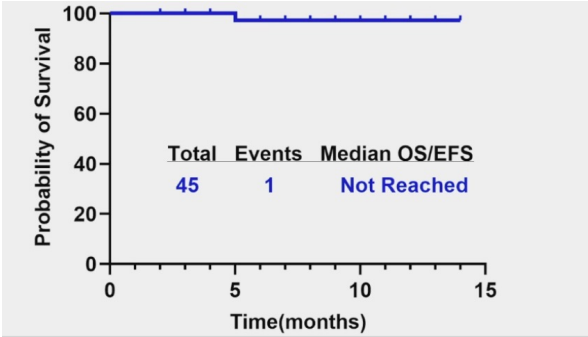
- 13 pts, 2 Ph-like
- 13/13 CR, CMR 71% C1; 90% C2; 100% C3
- 6 months OS 100%; EFS 87.5%
- No cardiovascular event
- Median follow-up: 7 months



Zhang T et al, Abstract 1504

Olverembatinib + Venetoclax and Reduced-Intensity Chemotherapy in frontline Ph+ ALL

- 45 pts; median age 42 (19-74)
- CR/CRi 100%
- CMR 53.3%@1 month; 62.2% @3 months
- No early deaths
- Median follow-up: 8 months

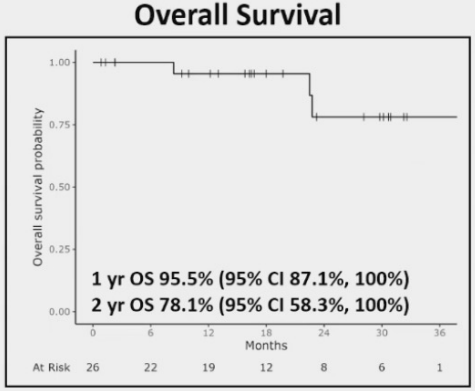


Gong X et al, Abstract 827

A Phase I Study of Asciminib (ABL001) in Combination with Dasatinib and Prednisone for BCR-ABL1-Positive ALL and Blast Phase CML in Adults

- ✓ Asciminib is an allosteric ABL1 inhibitor
- ✓ Combination treatment with an allosteric and an ATP-competitive TKI may deepen responses and limit mutations

De Novo ALL Outcome (n=22)^	
Ongoing Treatment Cycles	**3** 15, 16, 27
HSCT, Time, days, median (range)	**8** 144 (102-233)
Disease progression Cycles	**4** 4#%, 11*, 11$, 45%
Other DLT Patient decision Dasatinib toxicity	 **2** (C1, C1) **2** (C5, C7) **3** (C2, C4, C14)



- ✓ Good safety profile

CR: 100%
MRD-negative Flow: 89%
BCR:ABL1 RT-PCR MR3: 74%
BCR:ABL1 RT-PCR MR4: 26%

- ✓ An expansion cohort incorporating Blinatumomab is now accruing

Luskin MR et al, Abstract 965

Take home messages

- ✓ In **Ph+ ALL** a **chemo-free approach** is hopefully going to become a new standard of care
- ✓ **HSCT** will be likely required only in a **high risk Ph+ ALL patients** (e.g. MRD+@3 months, *IKZF1*+…)

- ✓ In Ph neg ALL, **MRD driven strategies** are mandatory, and **incorporation of antibodies** in the frontline setting is leading to better results both in young and elderly patients
- ✓ **Ph-like ALL** still have a **dismal outcome**, despite sensitivity to Blinatumomab (new strategies are needed)

- ✓ **Blinatumomab** may play a role **also in MRD neg patients**

- ✓ In **T-ALL setting**, where antibodies are not available, Venetoclax is showing clinical activity (ETP)

- ✓ **New TKIs** are in clinical development (olverembatinib, asciminib) in combination strategies

Thank you!

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