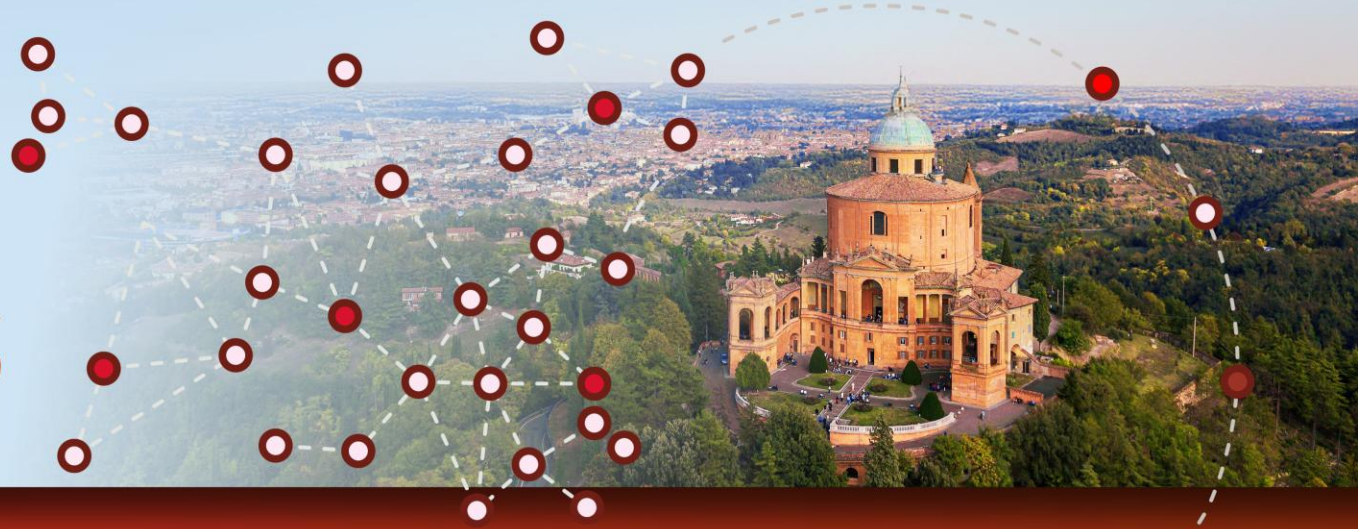
1ST INTERNATIONAL CONFERENCE ON

Ph+ Leukemias



Bologna, Royal Hotel Carlton **September 29-30, 2025**

TKI BASED APPROACH IN R/R PH+ ALL

Massimiliano Bonifacio

UNIVERSITÀ di VERONA

European Reference Network | Hematological Diseases (ERN EuroBloodNet)

Disclosures of MASSIMILIANO BONIFACIO

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						X	
Ascentage Pharma						X	
Blueprint Medicines						X	
Bristol Myers Squibb						X	
Glaxo Smith Kline						X	
Incyte						X	
Novartis						X	
Pfizer						X	

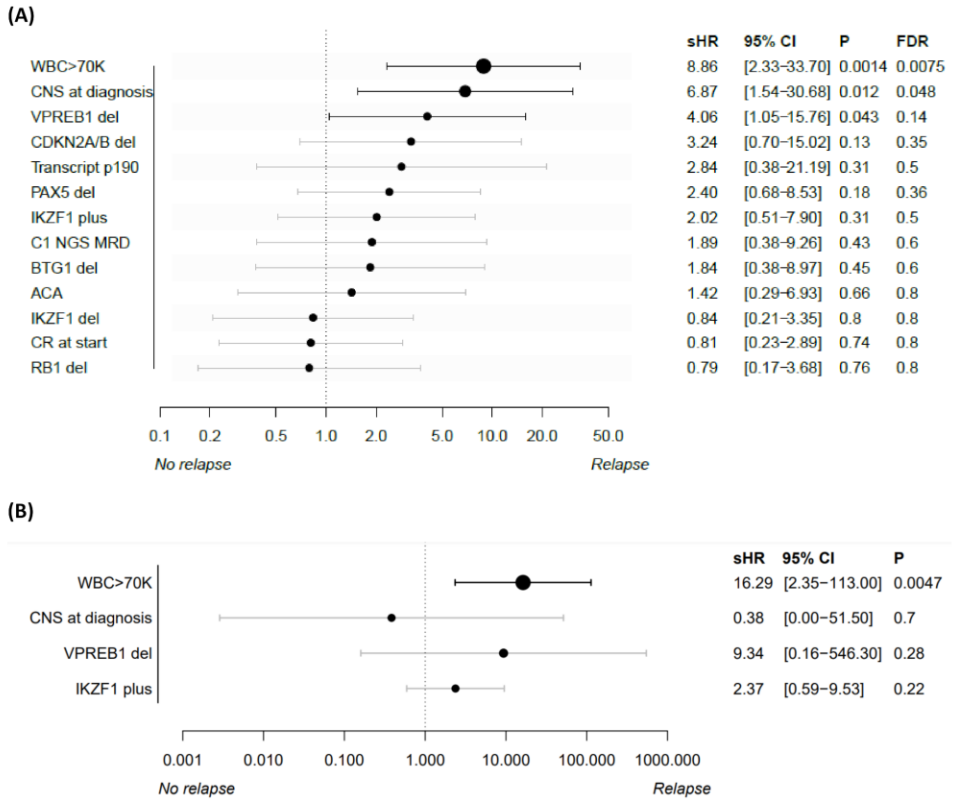
How big is the problem of resistance to TKI in Ph+ ALL?

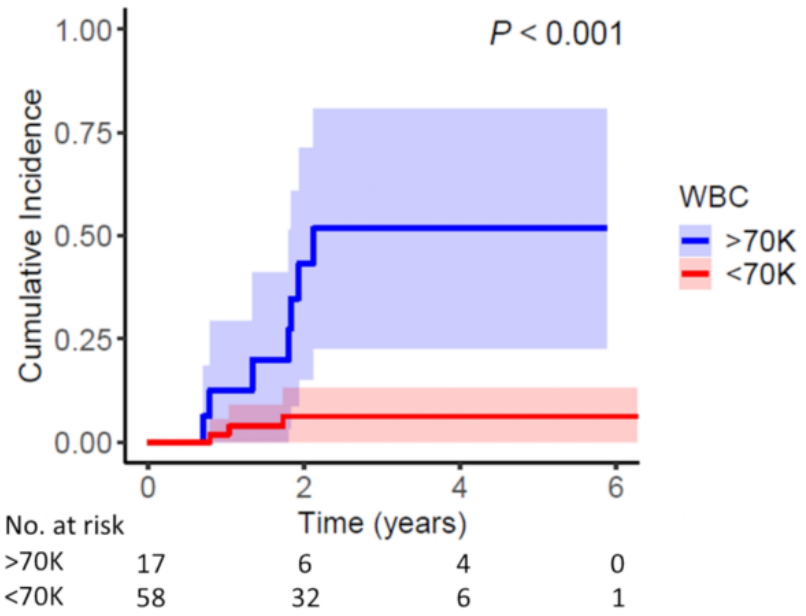
Regimen	CHR rate	CMR rate	Relapse rate	OS
Imatinib monotherapy[1]	100%	4%	46%	median 20 months
Imatinib and chemotherapy[2,3,4,5,6,7,8]	92% - 97%	3% - 57%	30% - 46%	33% - 46% at 5 yrs
Dasatinib monotherapy[9]	100%	15%	42%	median 31 months
Dasatinib and chemotherapy[10,11,12]	96% - 97%	18% - 65%	28% - 50%	36% - 56% at 5 yrs
Dasatinib and blinatumomab[13]	98%	60%	14%	81% at 4 yrs
Ponatinib monotherapy[14]	95%	82%	14%	54% at 3 yrs
Ponatinib and chemotherapy[8,15,16]	94% - 100%	34% - 87%	17%	75% - 80% at 5 yrs
Ponatinib and blinatumomab[17,18]	96% - 98%	74% - 86%	3% - 12%	95% (1 yr) - 91% (3 yrs)

[1] Vignetti et al. *Blood* **2007**;109:3676-3678. [2] Yanada et al. *J Clin Oncol* **2006**;24:460-466. [3] De Labarthe et al. *Blood* **2007**;109:1408-1413. [4] Bassan et al. *J Clin Oncol* **2010**;28:3644-3652. [5] Fielding et al. *Blood* **2014**;123:843-850. [6] Daver et al. *Haematologica* **2015**;100:653-881. [7] Chiaretti et al. *Haematologica* **2016**;101:1544-1552. [8] Jabbour et al. *JAMA* **2024**;331:1814-1823. [9] Foà et al. *Blood* **2011**;118:6521-6528. [10] Ravandi et al. *Cancer* **2015**;121:4158-4164. [11] Rousselot et al. *Blood* **2016**;128:774-782. [12] Chiaretti et al. *Haematologica* **2021**;106:1828-1838. [13] Foà et al. *N Engl J Med* **2020**;383:1613-1623. [14] Martinelli et al. *Blood Adv* **2022**;6:1742-1753. [15] Ribera et al. *Blood Adv* **2022**;6:5395-5402. [16] Kantarjian et al. *Am J Hematol* **2023**;98:493-501. 17 Jabbour et al. *Lancet Haematol* **2023**;10:e24-34. [18] Chiaretti et al. *Blood (ASH annual meeting)* **2024**;abs#835.

Risk factors for resistance to ponatinib / blinatumomab frontline in Ph+ ALL

- Phase II clinical trial of the combination of blinatumomab and ponatinib in 76 patients with newly diagnosed Ph+ ALL.
- Ten patients (13%) relapsed, with a median time to relapse of 18 months (range, 8–24 months).
- Six relapses occurred only in **extramedullary sites** (CNS, *n* = 5; peritoneum and lymph nodes, *n* = 1).

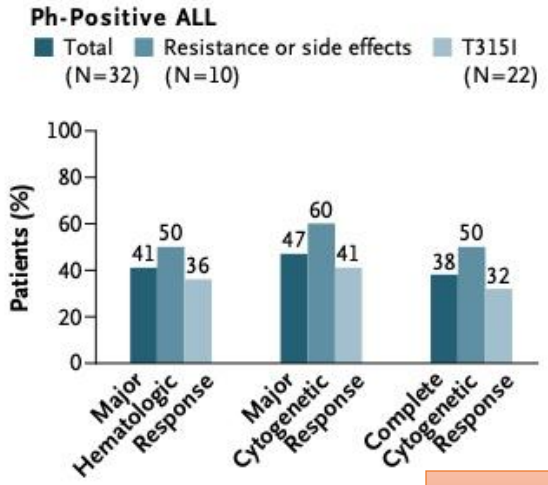


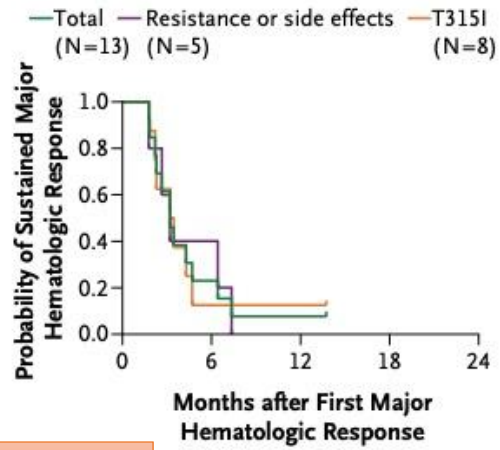


Short et al. *J Hematol Oncol* **2025**;18:55.

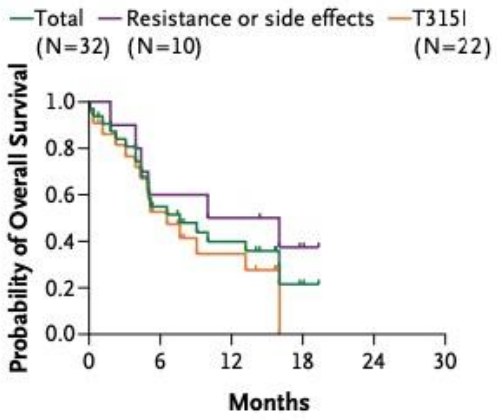
Ponatinib is an effective rescue treatment but responses are short

PACE study
(ponatinib monotherapy,
pts failed ≥2 previous TKIs)





CR rate 41%

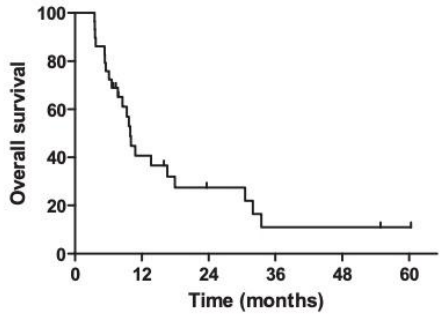


Median OS 8 months

French retrospective study
(ponatinib monotherapy or
associated to mild chemotx,
pts failed at least one TKI)

	Mutated		
Mutational status before PON	All mutations	T315I	Non mutated
N=	12	8	9
CR at day 30	12	8	4/5 Evaluable
Relapse	8	6	2/4 Evaluable
Mutation at relapse post-PON	2/2 Evaluable	2/2 Evaluable	2/2 Evaluable
T315I at relapse	2/2 Evaluable	2/2 Evaluable	0/0 Evaluable

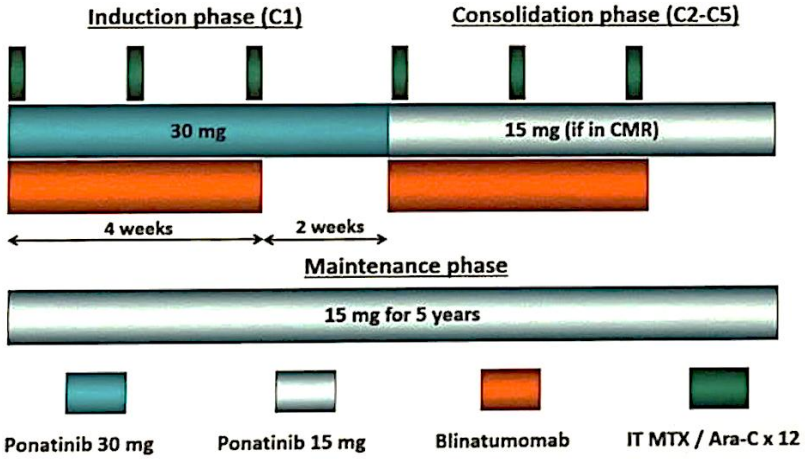
CR rate 90%



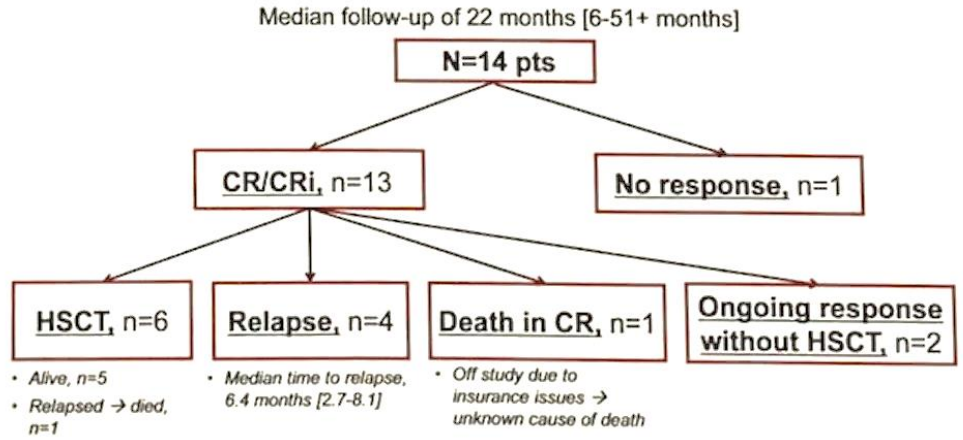
Median OS 9.9 months

Cortes et al. *N Engl J Med* **2013**;369:1783-1796. Tavitlan et al. *Leuk Lymphoma* **2020**;61:2161-2167.

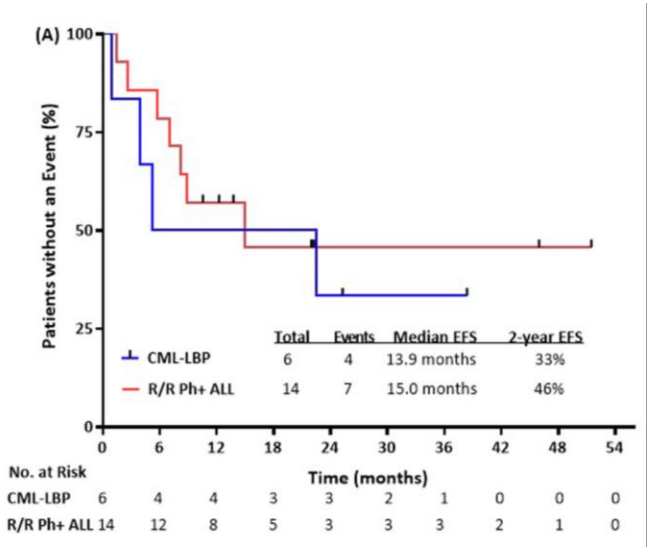
Ponatinib and blinatumomab for patients with R/R Ph+ ALL

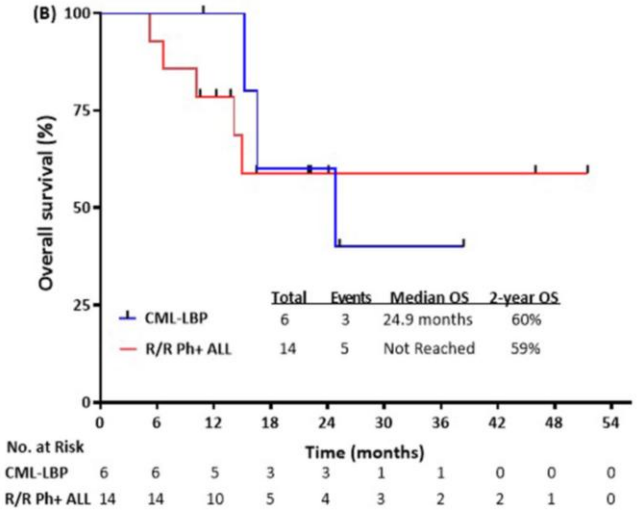


Characteristic N (%) / median [range]	Category	R/R Ph+ ALL N = 14	CML-LBP N=6
Age (years)		38 [24-61]	69 [29-82]
WBC (x10^9/L) at start		4.7 [2.1-10.4]	5.7 [2-28.5]
Performance status	0 – 1 2	13 (93) 1 (7)	3 (50) 3 (50)
CNS involvement		0	2 (33)
CD19 expression		99.9 [98.6-100]	99.7 [98.3-99.9]
Baseline cardiovascular risk factors	Hypertension Diabetes Dyslipidemia Coronary artery disease	4 (29) 0 0 0	4 (67) 2 (33) 1 (17) 1 (17)
BCR::ABL1 transcript	p190 p210	13 (93) 1 (7)	0 6 (100)
Line of therapy	Frontline Primary refractory Salvage 1 Salvage 2+	0 2 (14) 6 (43) 6 (43)	5 (83) 0 1 (17) 0



- CR rate 92%
- CMR rate 71%
- OS 2-yrs 59%

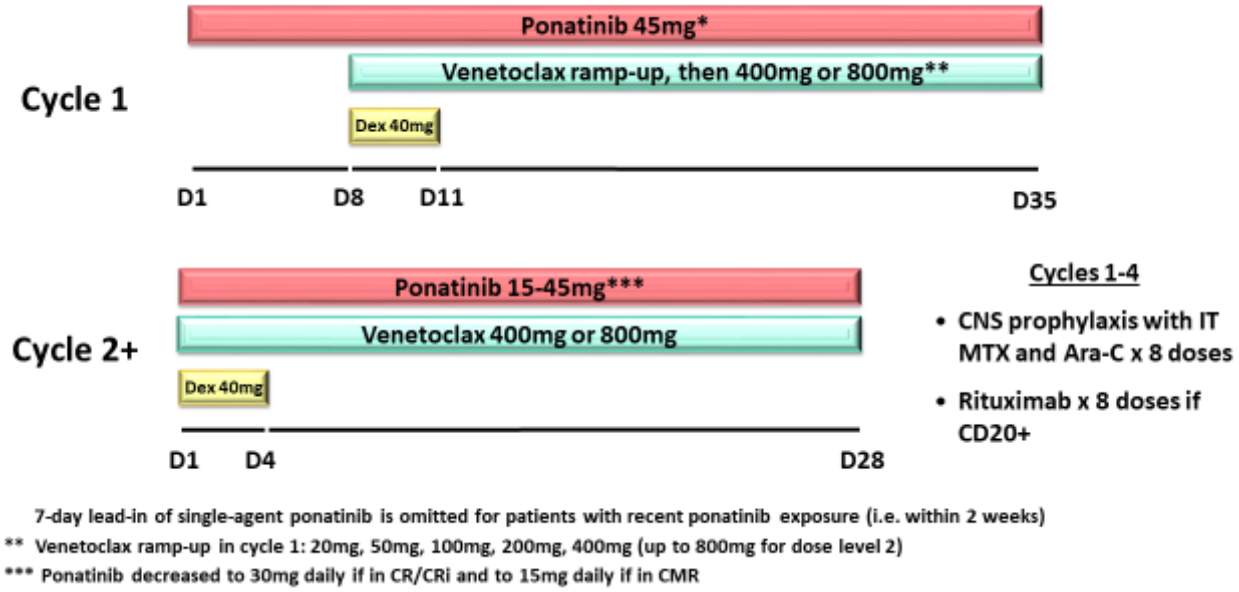


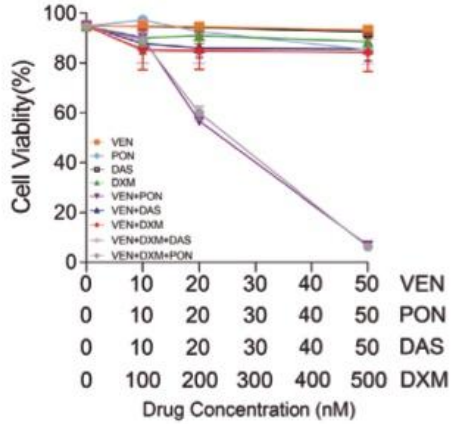


Macaron et al. *Blood (ASH annual abstract)* **2022**;abs#4046.

Ponatinib and venetoclax act synergistically in R/R Ph+ ALL

- Patients = 9.
- Median number of prior TKI lines: 2 (range 1-3); prior **ponatinib** 78%; prior **blinatumomab** 56%; prior **alloHSCT** 67%.
- Mutations: **T315I** (4 patients, 50%).





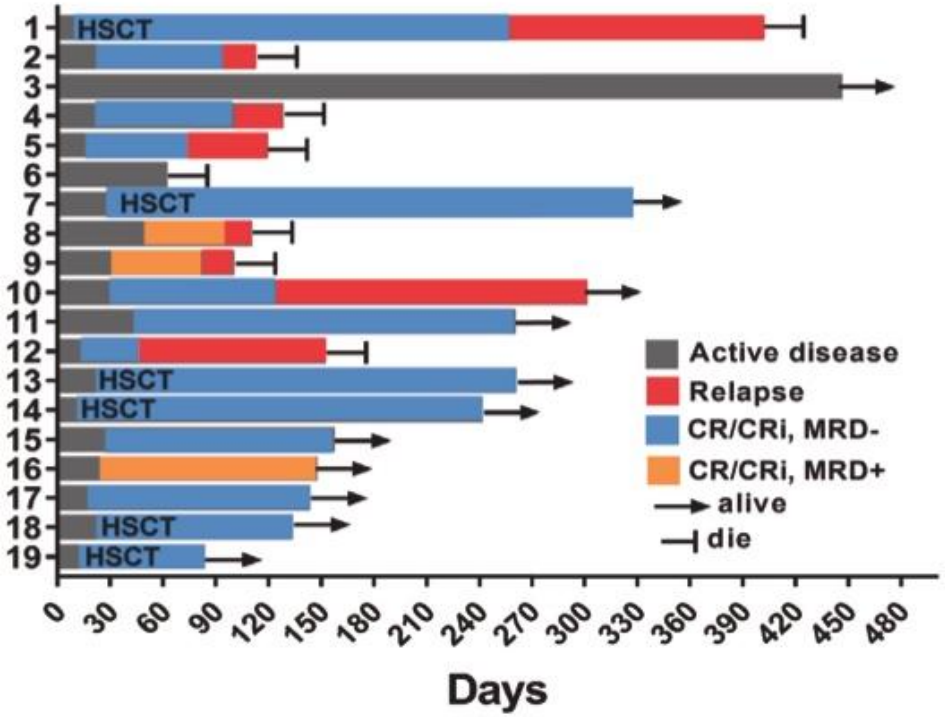
- CR rate 59%*
- CMR rate 44%
- RFS 6-mo: 100%
- OS 1-yr 72%

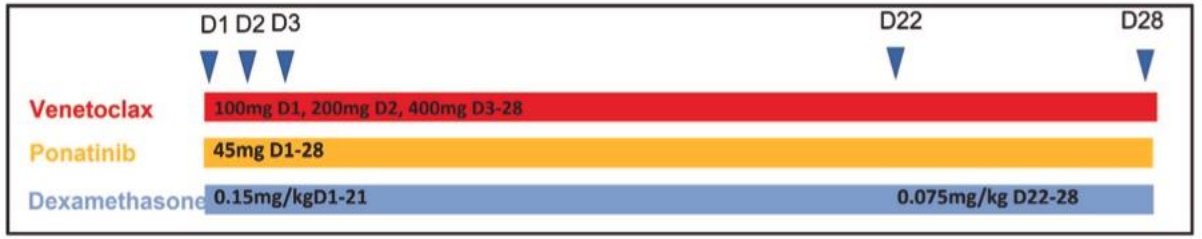
**all treated with venetoclax 800 mg*

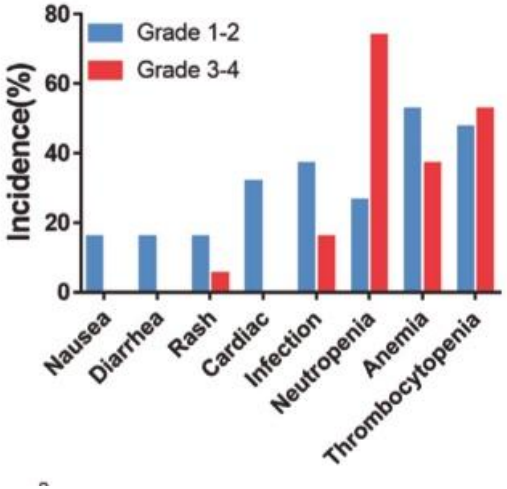
Short et al. *Am J Hematol* **2021**;96:e229-232.

Ponatinib and venetoclax for T315I/compound-mutated Ph+ ALL

- 19 patients (17 Ph+ ALL; 2 CML-BP) with **T315I** alone (n=15) or **compound** T315I+E255K/V, T315I+E279K, T315I+Y253H, G250E/F359V (1 each)
- Median number of prior salvage lines: 3 (range 1-6); prior **TKIs ± CT** 100%; prior **CAR-T** 26%; prior **alloHSCT** 5%.



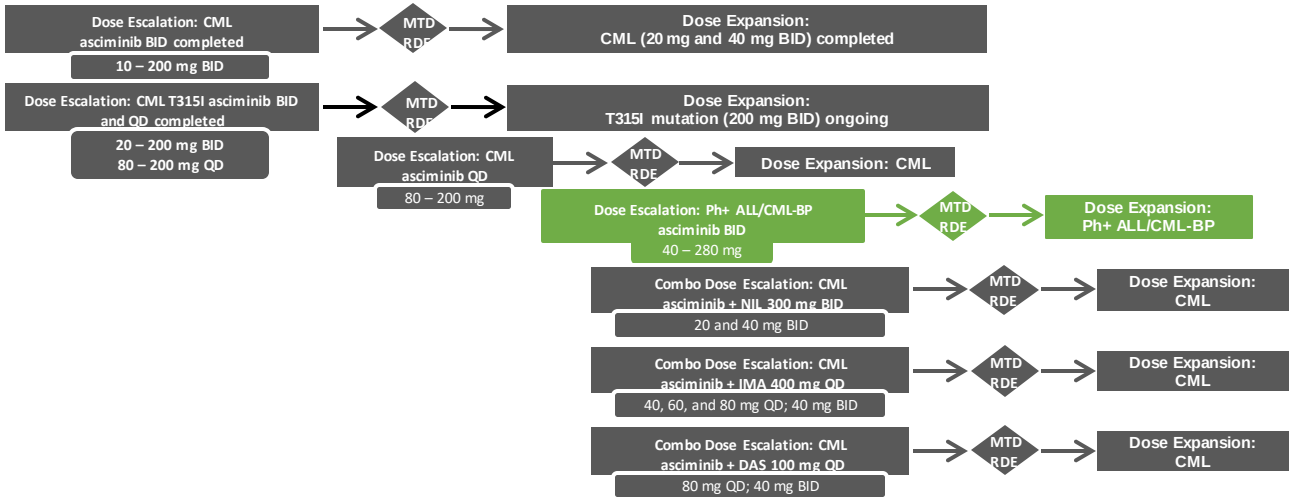


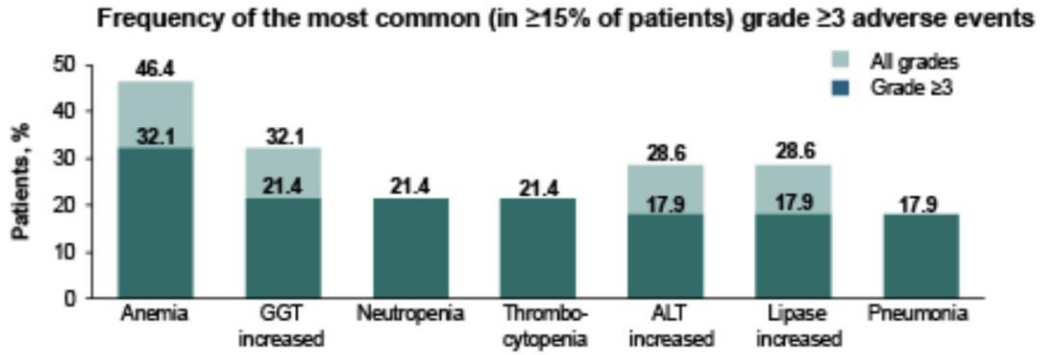


- CR rate 89% (after 1 cycle)
- MRD-FCM neg 82%
- CMR rate 47% (after 1 cycle) and 63% (with further cycles)
- Relapse after alloHSCT: 16%
- Relapse w/o alloHSCT: 64%

Wang et al. *Blood Cancer J* **2022**;12:20.

Asciminib monotherapy in R/R Ph+ ALL: evidences from first-in-human phase 1 study





ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; NA, not available.
[a] n is the number of patients with the specified response; N is the number of patients with screening data available.
[b] n is the number of patients with the specified response; m is the number of evaluable patients at the specific timepoint. Evaluable patients had at least one post baseline value by week 4.

- Asciminib dose: 40 mg bid to 280 mg bid
- Patients: n=28
- Prior **TKIs ≥2** 89.3%; prior **ponatinib** 53.6%; prior **alloHSCT** 46.4%
- Mutations: T315I (7 pts), compound mutations (3 pts)

Median exposure to asciminib: 9.5 weeks

Molecular assessment results in patients with Ph+ ALL treated with asciminib monotherapy

Molecular responses at screening and by week 4			
	Patients with *p210* (*BCR::ABL1*^{i6} %), n	Patients with *p190* (*BCR::ABL1* %), n	
Molecular response at screening			All patients, n/N (%)[a]
>10%	**3**	**2**	**5/28 (17.9%)**
≤10%	**8**	**11**	**19/28 (67.9%)**
≤0.0032%	5	0	5/28 (17.9%)
≤0.01%	6	1	7/28 (25.0%)
≤0.1%	7	6	13/28 (46.4%)
Missing	**NA**	**NA**	**4/28 (14.3%)**
Molecular response by week 4			Evaluable patients, n/m (%)[b]
>10%	**2**	**3**	**5/24 (20.8%)**
≤10%	**8**	**7**	**15/24 (62.5%)**
≤0.0032%	4	0	4/24 (16.7%)
≤0.01%	6	2	8/24 (33.3%)
≤0.1%	7	6	13/24 (54.2%)
Missing	**NA**	**NA**	**4/24 (16.7%)**

Mauro et al. *HemaSphere (EHA annual meeting)* **2025**;abs#S119.

Efficacy of asciminib as monotherapy or in combination with other treatments

- Retrospective study, compassionate use program: 41 patients (33 Ph+ ALL, 8 ly-BP-CML)
- Median number of prior TKIs: 3 (range 2-5); prior **ponatinib** 92.7%; prior **CAR-T** 4.8%; prior **alloHSCT** 43.9%.
- Disease status: refractory or relapse (n=29; 70.7%), CNS-only relapse (n=1; 2.4%), molecular relapse (n=7; 17.1%), intolerance (n=4; 9.8%)

ABL mutations analyzed before ASC treatment, n (%)	35 (85.4)
Absence of mutations, n (%)	8 (22.9)
Presence of mutations, n (%)	27 (77.1)
T315I	14 (51.9)
E255V/K	2 (7.4)
T315I + E255V	3 (11.1)
T315I + E255K + M244T	1 (3.7)
T315I + V299L	1 (3.7)
E255K + G250E + Y253H	1 (3.7)
F311L	1 (3.7)
F317L	1 (3.7)
Y253H	1 (3.7)
E255K + E255V	1 (3.7)
T315A + V299L	1 (3.7)

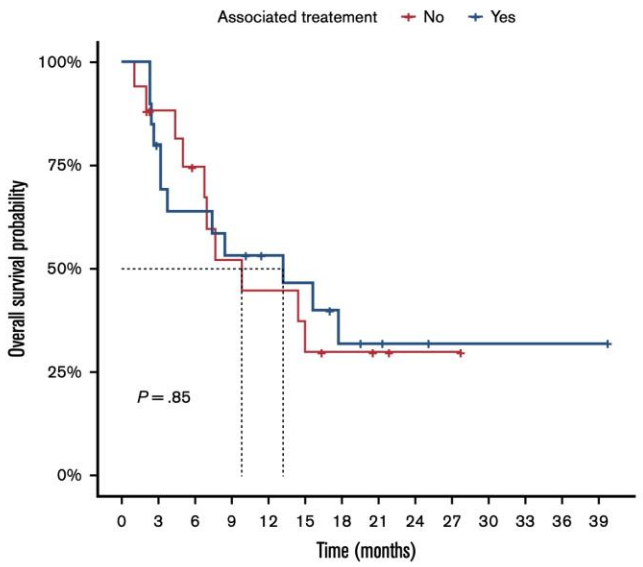
ASC dose, n (%)	
High dose (200 mg twice daily)	34 (82.9)
Low dose (40 mg twice daily)	7 (17.1)
Associated treatment, n (%)	41
ASC monotherapy, including 2 patients with ITT, n (%)	20 (48.8)
ASC in combination, n (%)	21 (51.2)
High dose chemotherapy	2 (4.9)
Low dose chemotherapy	8 (19.5)
Immunotherapy (blinatumomab or InO)	6 (14.6)
Other TKI	3 (7.3)
DLI	1 (2.4)
CAR T cell	1 (2.4)

Chanut et al. *Blood Adv* **2025**;9:4580-4584.

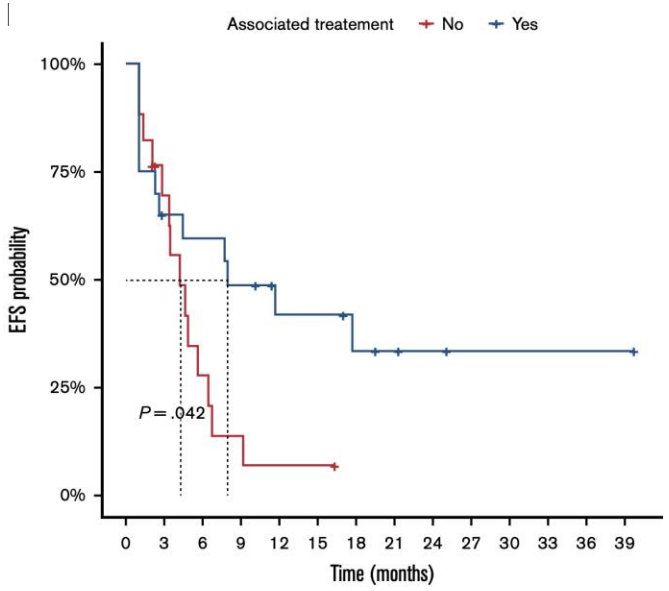
Efficacy of asciminib as monotherapy or in combination with other treatments

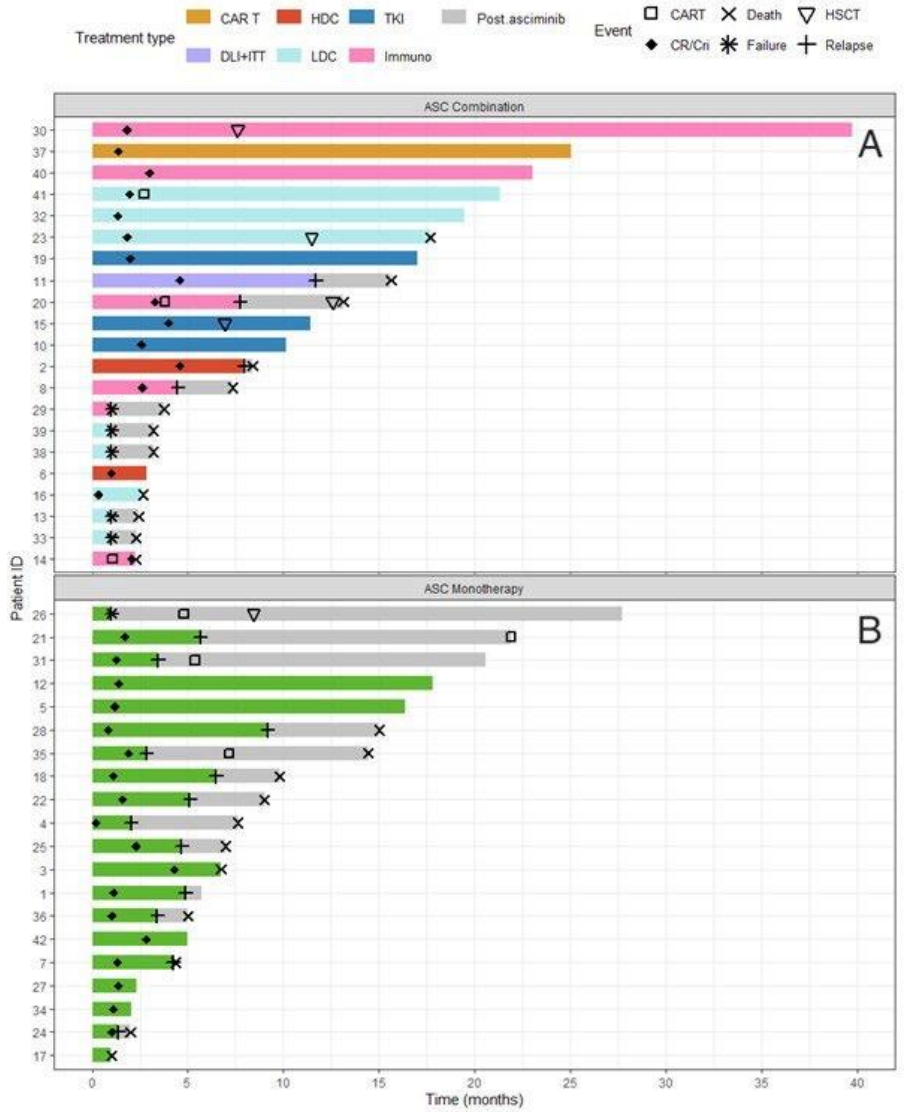
- CR/CRi rate: 83% (ASC **monotherapy**: **88%**; ASC **combination**: **79%**)
- CMR rate 56.3%
- Further treatment after ASC (allo-HSCT and/or CAR-T cells): 29%

Median OS: 9.8 months



Median OS: 4.9 months





Chanut et al. *Blood Adv* **2025**;9:4580-4584.

Olverembatinib is effective in patients resistant to multiple TKIs

- Phase 1b randomized clinical trial: patients were randomly assigned to 30, 40, or 50 mg of olverembatinib every other day.

Characteristic	No. (%)		
	Chronic-phase CML (n = 62)	Advanced leukemia (n = 18)	Total (N = 80)
Age, median (range), y	51.0 (21-80)	58.0 (30-74)	54.0 (21-80)
Sex			
Female	27 (43.5)	7 (38.9)	34 (42.5)
Male	35 (56.5)	11 (61.1)	46 (57.5)
ABL1 T315I variant	18 (29.0)	7 (38.9)	25 (31.3)
BCR::ABL1 levels at baseline, %			
<1	5 (8.1)	1 (5.6)	6 (7.5)
1-10	13 (21.0)	0	13 (16.3)
>10	43 (69.4)	15 (83.3)	58 (72.5)
Prior TKI treatment			
1	0	1 (5.6)	1 (1.3)
2	12 (19.4)	2 (11.1)	14 (17.5)
3	18 (29.0)	4 (22.2)	22 (27.5)
≥4	32 (51.6)	11 (61.1)	43 (53.8)
Prior ponatinib treatment	31 (50.0)	15 (83.3)	46 (57.5)
Resistant[c]	21 (33.9)	11 (61.1)	32 (40.0)
Intolerant[d]	7 (11.3)	3 (16.7)	10 (12.5)
Other[e]	3 (4.8)	1 (5.6)	4 (5.0)
Prior asciminib treatment	17 (27.4)	8 (44.4)	25 (31.3)
Resistant[c]	12 (19.4)	7 (38.9)	19 (23.8)
Intolerant[d]	3 (4.8)	1 (5.6)	4 (5.0)
Other[e]	2 (3.2)	0	2 (2.5)

	n	MCyR	CCyR	MMR
Tot. evaluable population	17	35.7%	21.4%	17.6%
T315I-mutated	6	33.3%	16.7%	16.7%
Non-T315-mutated	11	37.5%	25%	18.2%
Ponatinib-resistant	10	37.5%	25%	20%
Ponatinib-intolerant	3	0	0	0
Asciminib-resistant	7	16.7%	0	0
Asciminib-intolerant	1	0	0	0

Jabbour et al. *JAMA Oncol* **2025**;11:28-35.

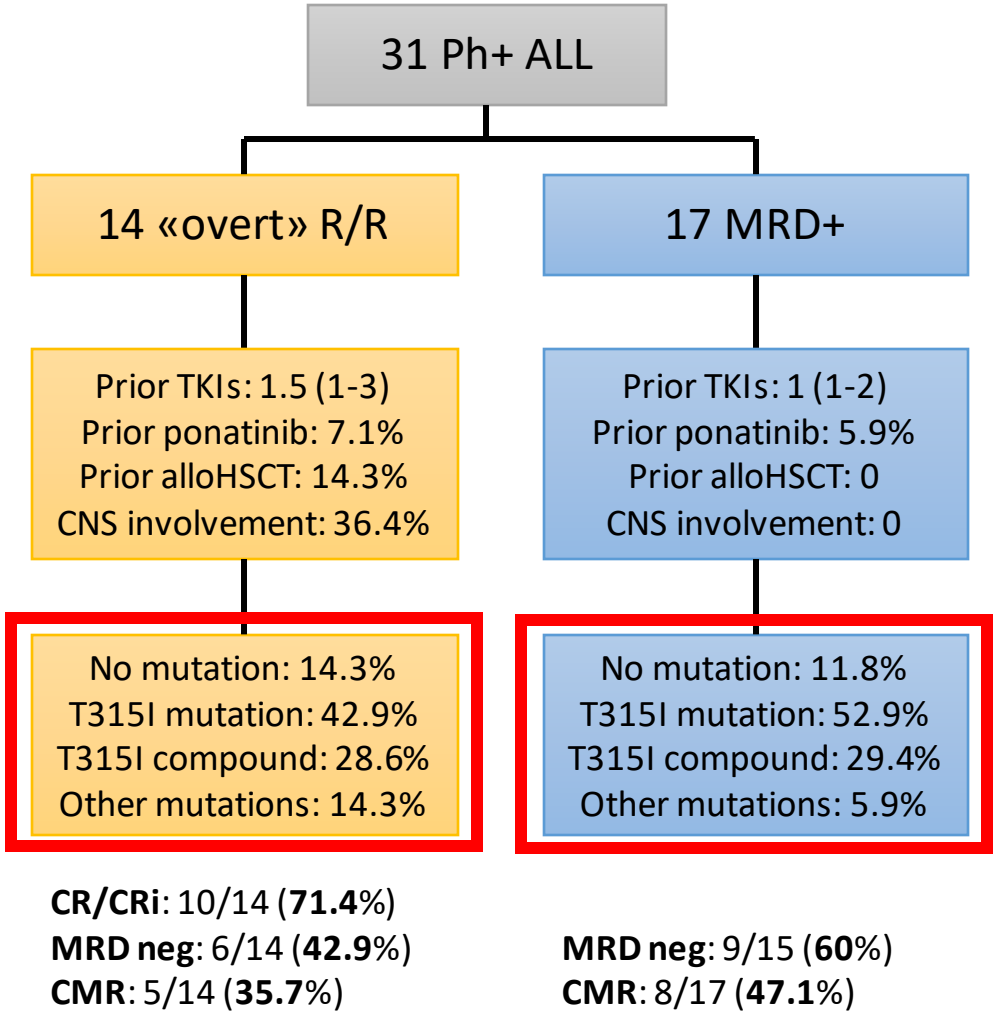
Olverembatinib is effective in patients with T315I or compound mutations

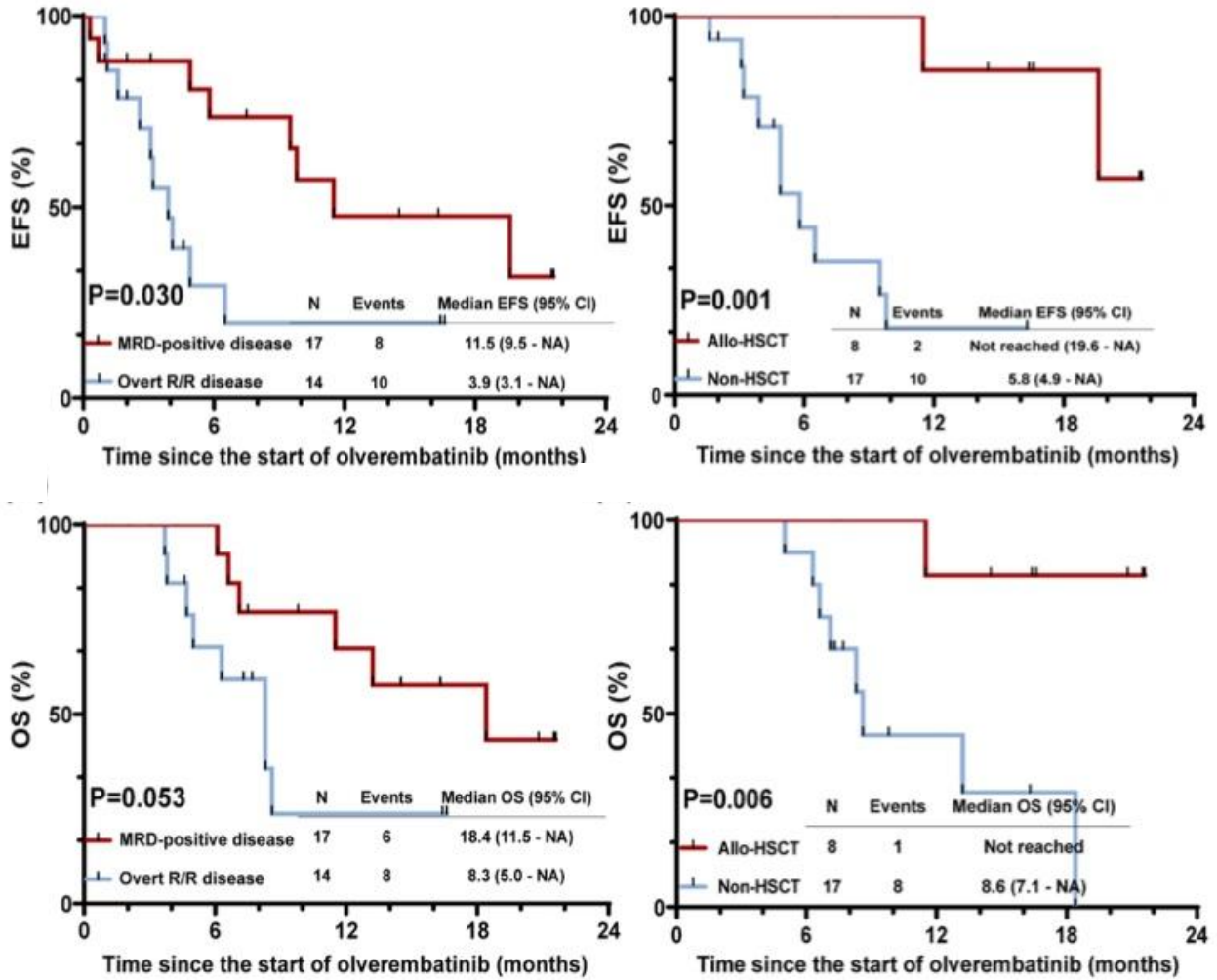
	Imatinib	Nilotinib	Dasatinib	Asciminib	Ponatinib	Olverembatinib
BCR-ABL1 wild-type	565±656	31±4	10±3	31±4	11±0	6±3
BCR-ABL1 gate keeper mutant **T315I**						
	>10000	3425±650	2525±322	148±14	33±11	24±10
BCR-ABL1 compound mutants, T315I-inclusive						
T315I+F359V	>10000	4586±1397	3392±211	6631±1201	101±22	20±10
T315I+E255V	>10000	6467±4431	3571±1385	93±86	244±125	26±11
T315I+G250E	>10000	8511±5599	5001±2939	7451±3057	130±16	33±2
T315I+E255K	>10000	>10000	4706±803	8944±748	339±12	40±5
T315I+E453K	8466±1628	>10000	4724±155	2931±74	130±5	61±27
T315I+M351T	7603±1498	>10000	7683±3645	>10000	127±5	67±44
T315I+M244V	>100000	>100000	3067±904	7242±211	136±15	76±53
T315I+F311I	7144±2459	>10000	4789±1739	7061±1423	438±88	78±46
T315I+H396R	8953±5314	>10000	9286±3386	>10000	211±134	79±54
T315I+E459K	>100000	>100000	4869±702	6001±833	104±1	109±4
T315I+Y253H	>10000	>10000	7080±3233	6981±2481	889±100	114±1
T315I+F317L	>10000	>10000	>10000	860±96	688±412	117±23
*T315M**	>10000	>10000	>10000	996±405	1987±1414	217±131
BCR-ABL1 compound mutants, non-T315I						
Y253H/E255V	>10000	7026±2183	231±92	5014±2920	772±220	122±0
F317L/F359V	7195±1729	926±24	50±12	5214±810	24±12	25±13
Y253H/F359V	>10000	>10000	110±1	>10000	432±23	311±35
G250E/V299L	6486±2622	641±368	570±559	2601±2903	12±3	14±2
F317L/M351T	3088±88	346±16	114±6	6101±5060	122±18	73±51
V299L/F359V	3099±6	2143±1160	344±31	8029±2251	213±151	68±42

Sensitive: $IC_{50} \leq 100$ nM
Moderate: $IC_{50} = 100\text{-}1000$ nM
Highly resistant: $IC_{50} > 1000$ nM

Senapati et al. *Blood Cancer J* **2023**;13:58.

Olverembatinib-based therapy in patients with T315I or compound mutations





Liu et al. *Br J Haematol* **2024**;205:2228-2233.

Safety of olverembatinib in R/R Ph+ ALL

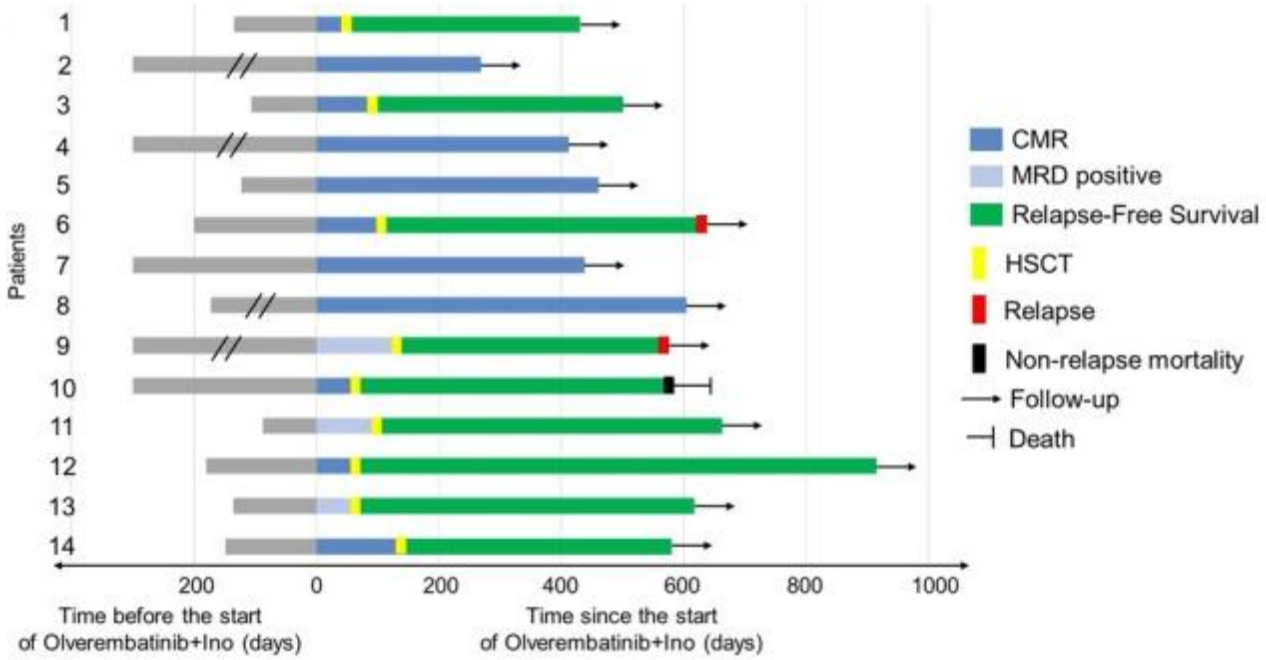
Event, n (%)	Any grades	Grade 3/4
Treatment-related Adverse events	31 (100)	22 (71.0)
Nonhaematologic		
Increased γ-glutamyl transferase	21 (67.7)	6 (19.4)
Increased alanine aminotransferase	16 (51.6)	2 (6.5)
Hypokalemia	15 (48.4)	3 (9.7)
Skin pigmentation	15 (48.4)	0
Hyperglycemia	15 (48.4)	1 (3.2)
Hyperuricemia	15 (48.4)	0
Increased aspartate aminotransferase	13 (41.9)	1 (3.2)
Infection	12 (38.7)	10 (32.3)
Hypoalbuminemia	11 (35.5)	0
Hypertriglyceridemia	10 (32.3)	3 (9.7)
Constipation/diarrhea	10 (32.3)	0
Edema	10 (32.3)	0
Hypocalcemia	9 (29.0)	0
Hyperphosphatemia	9 (29.0)	0
Increased alkaline phosphatase	8 (25.8)	1 (3.2)
Increased creatine kinase	8 (25.8)	0

Event, n (%)	Any grades	Grade 3/4
Arrhythmia	6 (19.4)	0
Pleural effusion	6 (19.4)	0
Asthenia	6 (19.4)	0
Hyperbilirubinemia	5 (16.1)	0
Pericardial effusion	4 (12.9)	0
Hypertension	3 (9.7)	0
Proteinuria	3 (9.7)	0
Pain in extremity	2 (6.5)	0
Cardiac failure	2 (6.5)	0
Hyponatremia	2 (6.5)	0
Hemorrhagic Infarct of the intestine	1 (3.2)	1 (3.2)
Headache	1 (3.2)	0
Cerebral infarction	1 (3.2)	1 (3.2)
Haematologic		
Neutropenia	20 (64.5)	17 (54.8)
Anemia	20 (64.5)	5 (16.1)
Leukopenia	19 (61.3)	11 (35.5)
Thrombocytopenia	16 (51.6)	7 (22.6)

Liu et al. *Br J Haematol* **2024**;205:2228-2233.

Olverembatinib in combination with Inotuzumab Ozogamicin

- Prospective phase II study: 5 patients with «overt» R/R status, 9 patients with persistently positive / relapsed MRD
- Treatment: **olverembatinib** 40 mg every other day + **InO** 0.6 mg/m^2 d1 and d8, every 28 days (13/14 patients received a single cycle)
- 1 patient with V299L mutation, no other BCR::ABL1 mutations
- Prior CD19-directed therapy: 14.3%
- Prior venetoclax-based therapy: 57.1%



Complete remission (CR)	14/14 (100)
Complete cytogenetic response	14/14 (100)
Complete molecular response	11/14 (78.6)
MRD negative by flow cytometry	14/14 (100)
Bridged to alloHSCT	9/14 (64.3)

The probabilities of RFS and OS at 2 years were 62.9% and 83.3%.

Zhang et al. *Am J Hematol* **2025**;100:1924-1928.

Real-world data of olverembatinib-based therapy in R/R Ph+ ALL

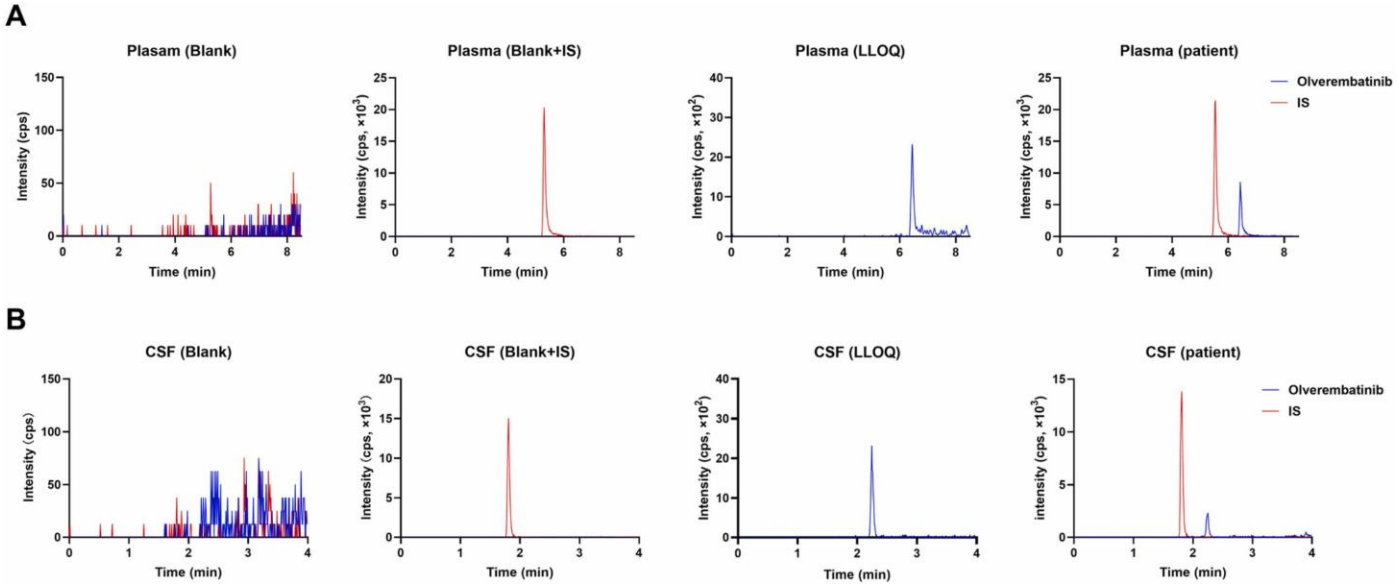
- 40 Ph+ ALL (26 primary refractory, 9 relapse with CNS involvement, 5 relapse without CNS involvement).
- Median number of prior TKI lines: 1 (range 1-4); median time from diagnosis to olverembatinib: 8.2 months (IQR 2.6-10.8)
- Last TKI treatment: imatinib (7.5%), nilotinib (2.5%), dasatinib (65%), flumatinib (7.5%), **ponatinib** (25%).
- Mutations: **T315I** (1 case, 2.5%), non-T315I (2 cases, 5%).
- Received **HSCT** before olverembatinib: 11 patients (27.5%).

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)

- The probabilities of DFS, EFS and OS at 12 months were 80.3%, 80.2% and 93.3%.

Wen et al. *Front Immunol* **2025**;16:1546371.

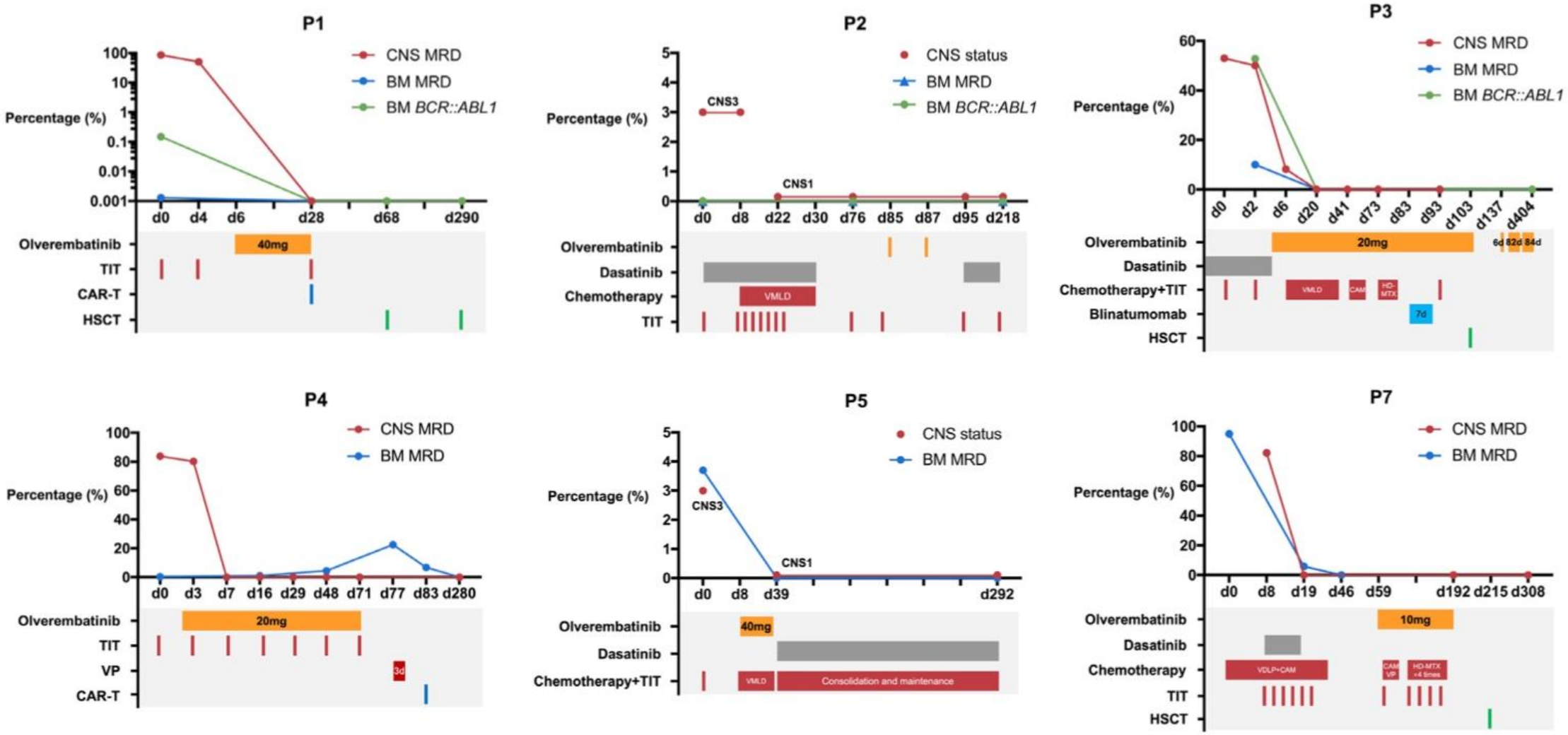
Successful detection and measurement of olverembatinib in CSF



Patients	Dosage regimen	Matrix	Sampling time	Concentration (ng/mL)
1	40 mg per two days	plasma	2 h after the dose	18.8
		CSF	Unknown	0.176
2	40 mg per two days	plasma	2 h after the dose	24.1
		CSF	Unknown	0.453
3	40 mg per two days	plasma	2 h after the dose	10.1
		CSF	Unknown	0.138
4	40 mg per two days	plasma	2 h after the dose	6.61
		CSF	Unknown	0.207
5	40 mg per two days	plasma	2 h after the dose	1.72
		CSF	Unknown	0.293

Xiang et al. *J Pharm Biomed Anal* **2023**;230:115382.

Efficacy of olverembatinib in relapsed Ph+ pediatric patients with CNS disease



Li et al. *Clin Lymphoma Myeloma Leuk* **2023**;23:660-666.

Conclusions

- Patients with relapsed/refractory Ph+ ALL are a very difficult-to-treat population, particularly if exposed to frontline ponatinib and blinatumomab (high WBC count, high incidence of CNS / extramedullary disease, unfavorable genetics).

- Ponatinib, asciminib and olverembatinib may be used as salvage treatment in relapsed/refractory Ph+ ALL, depending on previous treatments, mutational status, and availability.

- Hematologic and molecular response rates to TKI monotherapy are generally high, but their duration is short. Combination with chemotherapy, immunotherapy (blinatumomab or inotuzumab ozogamicin) and venetoclax is feasible and allows a higher number of patients to be transplanted in molecular remission.

- High-dose asciminib- and olverembatinib-based treatment are effective in patients with T315I and/or compound mutations.

- Olverembatinib crossed the blood-brain barrier and may be useful in treating patients with CNS disease.