ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI
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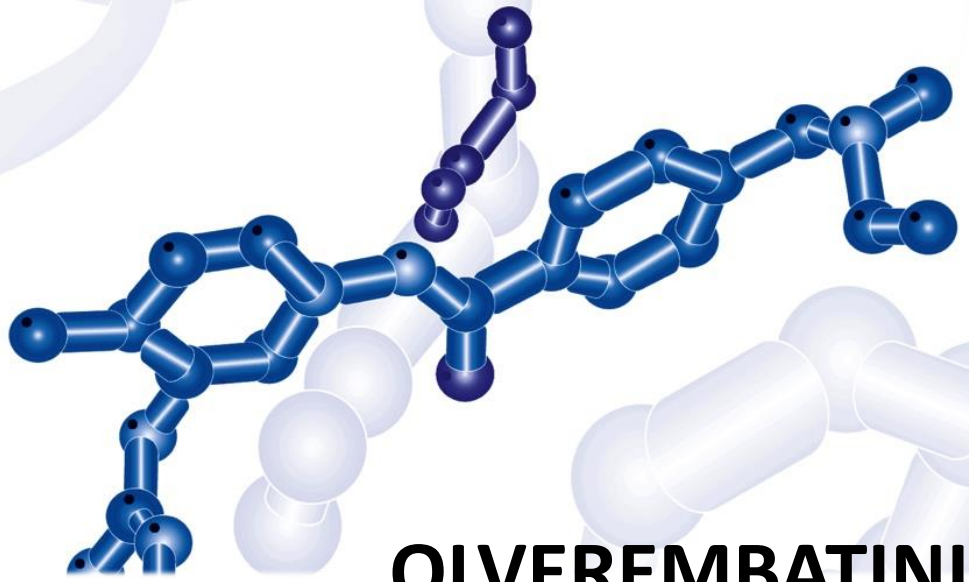
New Drugs in Hematology



OLVEREMBATINIB

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Bologna,
Royal Hotel Carlton
May 18-19-20, 2026

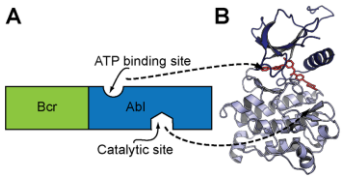
Disclosures of Rea Delphine

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Ascentage Pharma						x	
Enliven Therapeutics						x	
Incyte						x	
Novartis			x			x	
Terns pharma			x			x	

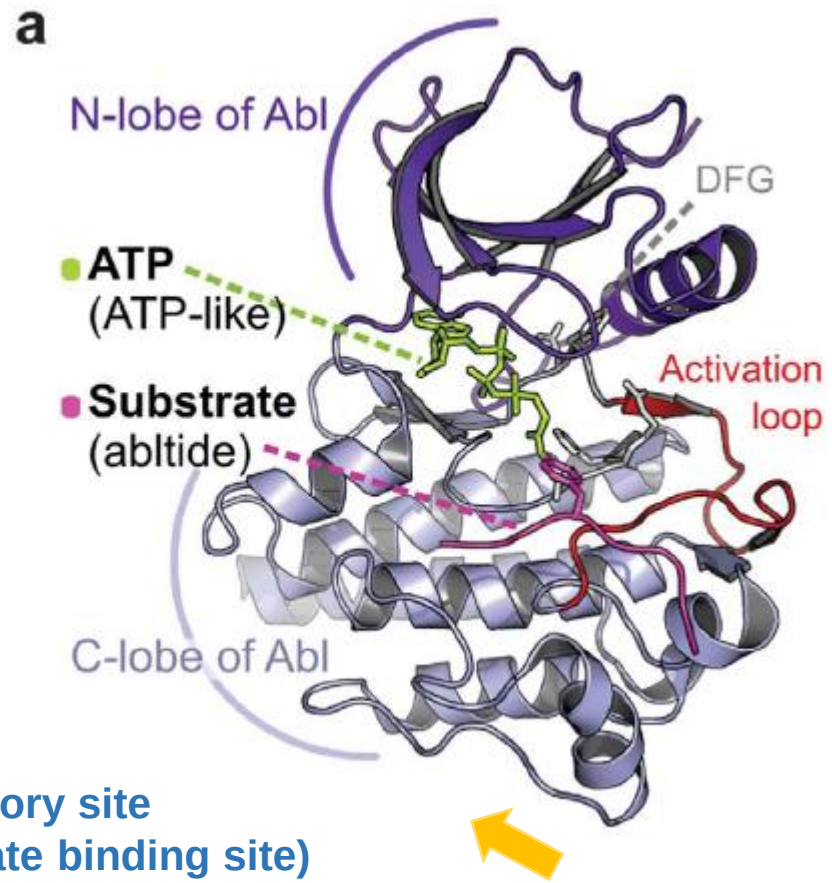
Targeted therapies in CML

Kinase domain

- ATP-competitive inhibitors



Catalytic site



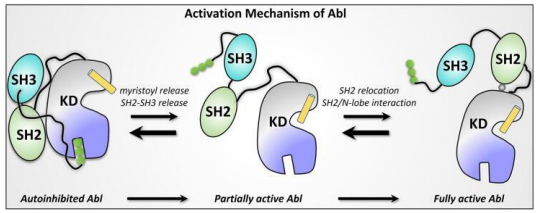
Regulatory site
(Myristate binding site)

- Allosteric inhibitors

P-loop =
ATP-binding loop

A-loop:
regulates the access of ATP and substrate to the catalytic cleft

Myristate pocket:
Hydrophobic regulatory pocket responsible for fatty acid myristate binging



Huang YH, et al. Sci Rep 2015; 5: 12974.

Olverembatinib

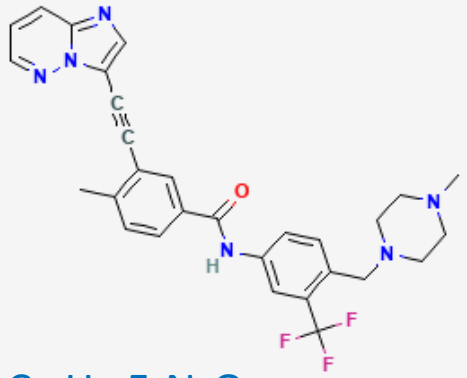
- Formerly named GZD824 and HQP1351
- Non-selective multi-kinase ATP-competitive inhibitor including ABL, b-RAF, DDR1, FGFR, Flt3, Kit, PDGFRα, PDGFRβ, Ret, Src, Tie1, Tie2
- 3rd generation BCR::ABL1 ATP-competitor
  - Active against a broad spectrum of BCR-ABL1 mutations including T315I
- Approved in China in CP- or AP-CML-CP with T315I mutations and CML-CP resistant and/or intolerant to first- and second-generation TKI
- International development ongoing

Liu , et al. Cell Biosci 2019; 9: 88.
Wang Y, et al. Translational Oncology 2020; 100766.
Ren X, et al. J Med Chem2013; 56: 879-894.
Sadati S, et al. Discover Oncology 2026; 17: 291.
https://pubchem.ncbi.nlm.nih.gov/compound/gzd824
https://pubchem.ncbi.nlm.nih.gov/compound/Ponatinib

Olverembatinib

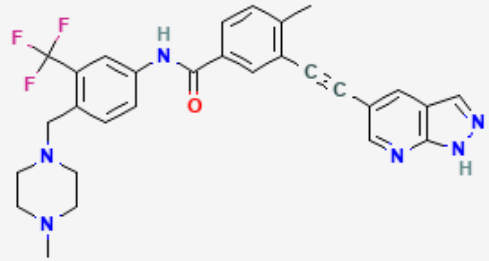
Reengineered ponatinib
Goal: to increase BCR::ABL1 binding affinity

Ponatinib



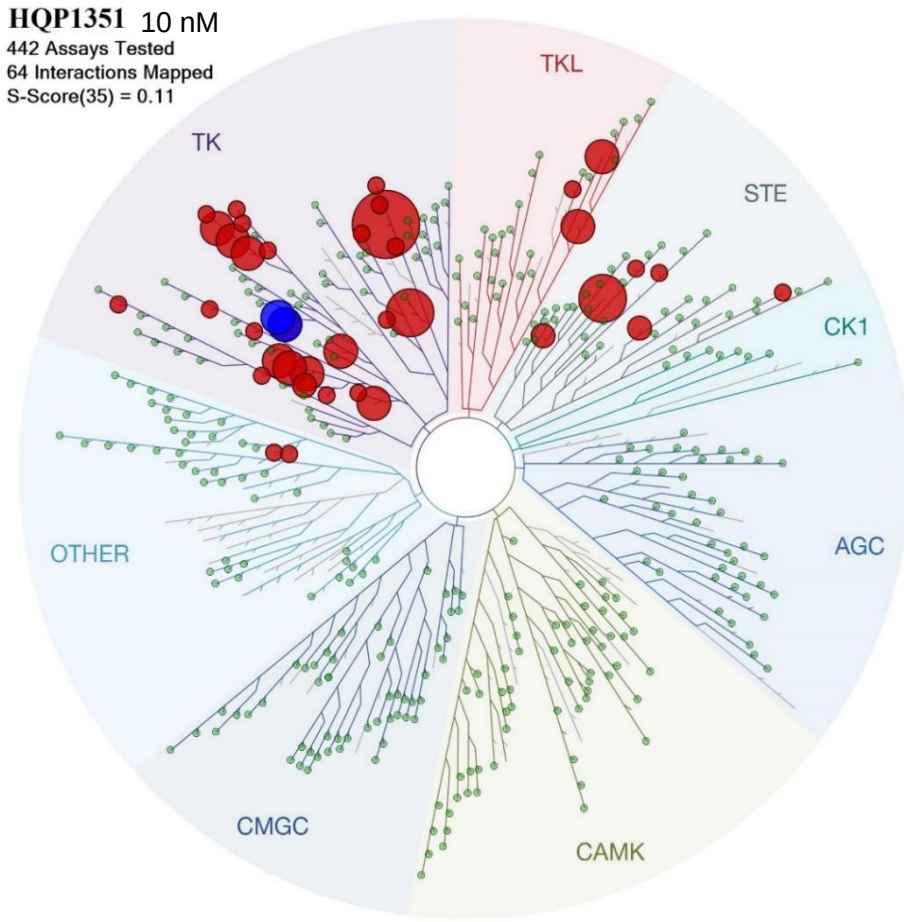
$C_{29}H_{27}F_3N_6O$

Olverembatinib



$C_{29}H_{27}F_3N_6O$

Large spectrum of kinase inhibition



BCR::ABL1 inhibition

Inactive conformation

Inactive and active conformation

Ren X, et al. J Med Chem2013; 56: 879-894.

https://pubchem.ncbi.nlm.nih.gov/compound/gzd824
https://pubchem.ncbi.nlm.nih.gov/compound/Ponatinib

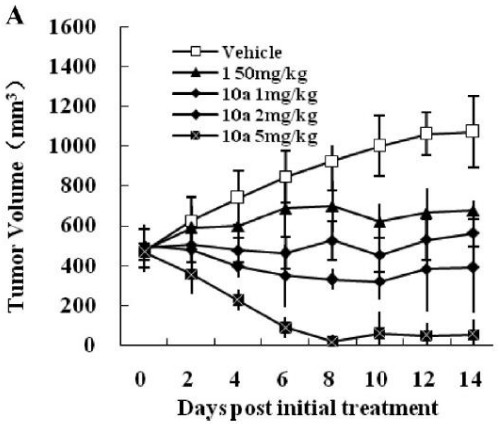
Olverembatinib : *BCR::ABL1* point mutations

Mutated region	BaF3 (*BCR::ABL*) Mutant Cells	Anti-proliferation Assay (IC_{50}, nM)					
		Imatinib	Nilotinib	Dasatinib	Asciminib	Ponatinib	HQP1351
Wild-type	-	565±656	31±4	10±3	31±4	11±0	6±3
SH2-contact region	M351T	1298±542	37±4	8±4	47±34	13±1	9±1
Substrate-binding region	F359V	>10000	1710±635	598±624	6066±355	466±73	50±16
P-loop	E255K	8222±484	648±395	14±1	10±0	49±4	22±13
	Y253H	8936±1774	497±122	11±2	28±13	37±4	7±1
	E255V	7565±3268	587±151	29±15	24±4	56±1	27±11
	M244V	2963±83	236±152	40±1	5223±4899	75±42	41±8
Gate keeper	T315I	>10000	3425±650	2525±322	148±14	33±11	24±10
Hinge region	F317L	526±56	89±8	11±1	6±3	7±1	8±3
	F311I	3547±223	226±122	13±0	107±1	30±8	23±13
SH3-contact region	V299L	1987±1237	103±6	118±2	562±552	10±4	8±4
T315I + Other Compound Mutation	T315I/E255V	>10000	6467±4431	3571±1385	93±86	244±125	26±11
	T315I/F359V	>10000	4586±1397	3392±211	6631±1201	101±22	20±10
	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
	T315/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/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
Other Compound Mutation	G250E/V299L	6486±2622	641±368	570±559	2601±2903	12±3	14±2
	F317L/F359V	7195±1729	926±24	50±12	5214±810	24±12	25±13
	Y253H/E255V	>10000	7026±2183	231±92	5014±2920	772±220	122±0
	Y253H/F359V	>10000	>10000	110±1	>10000	432±23	311±35

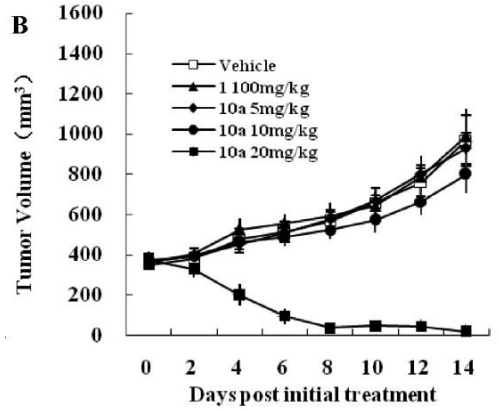
	Sensitive: IC_{50} ≤ 100 nM
	Intermediate sensitive: IC_{50} = 100-1000 nM
	Insensitive: IC_{50} > 1000 nM

Ren X, et al. J Med Chem2013; 56: 879-894.
Kantarjian H, et al. Cancer 2025; e35832
Liu X, et al. Cell Biosci 2019; 9: 88.

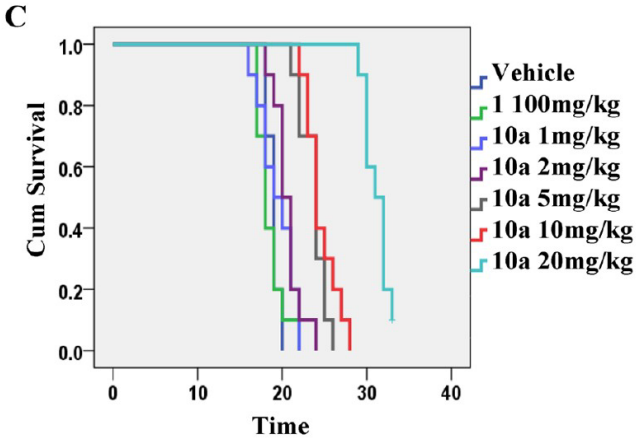
Ba/F3 wt BCR::ABL1



Ba/F3 T315I BCR::ABL1



Ba/F3 T315I BCR::ABL1



Olverembatinib in CML patients: FIH phase 1/2 in China

- **TKI-resistant or refractory CP- or AP-CML**
  - ***Phase 1****:* 3+3: 1 to 60mg QOD: 11 cohorts – TKI-resistant to 3rd line or higher
    - Primary endpoint: RP2D, MTD
  - ***Phase 2:*** T315I+ CP- and AP-CML at RP2D, resistant to 2nd line or higher
    - Primary endpoint: MajCyR (CP-CML) and MaHR (AP-CML)

- 165 pts enrolled (CP-CML: 127 AP-CML: 38) median age 42 (20-74), 67% males no prior exposure to ponatinib or allosteric TKI, 61.8% had a T315I mutation
  - ***Phase 1:*** 101 pts: 86 CP-CML, 15 AP-CML
  - ***Phase 2:*** 64 pts: 41 CP-CML, 23 AP-CML, 60% received olverembatinib in 2nd line

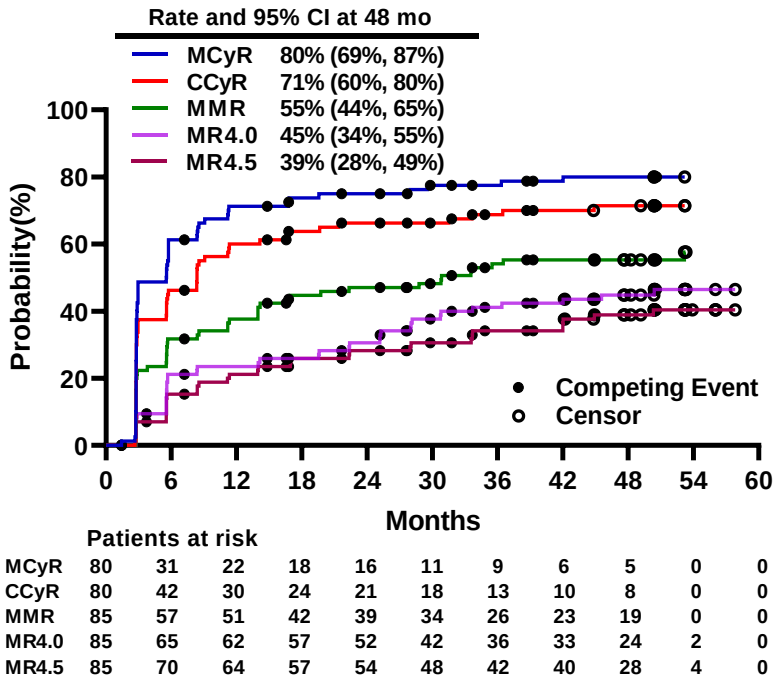
Phase 1

No DLT below 60mg QOD
2 DLTs at 60mg QOD (thrombocytopenia G4 and myocardial infarction)
MTD: 50mg QOD
40mg QOD in phase 2

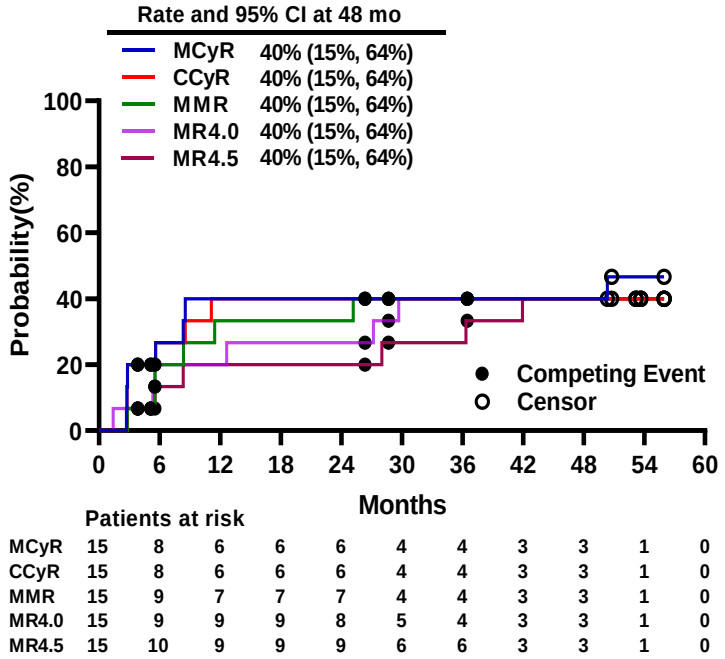
Jiang Q, et al. J Hematol Oncol. 2022;15(1):113.

Olverembatinib in CML patients: efficacy

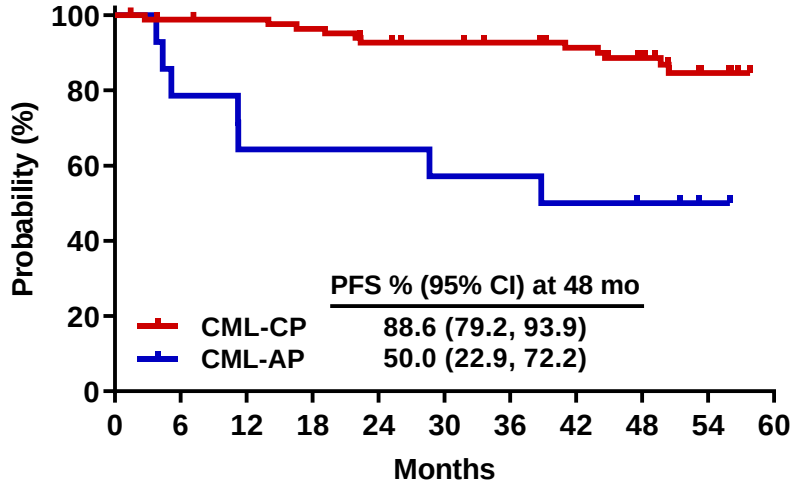
Chronic Phase



Accelerated Phase



Progression-free Survival



Jiang Q, et al. J Hematol Oncol. 2022;15(1):113.
Jiang Q et al. ASH abstract #81, 2022

Courtesy of Dr Qian Jiang

Olverembatinib in CML patients: safety

- **Most frequent TRAE:**
  - Thrombocytopenia
  - Skin pigmentation
  - Hypertriglyceridemia

- **Cardiovascular events: 32%**
- Hypertension
- Pericardial effusion

Prevalence of AE overtime

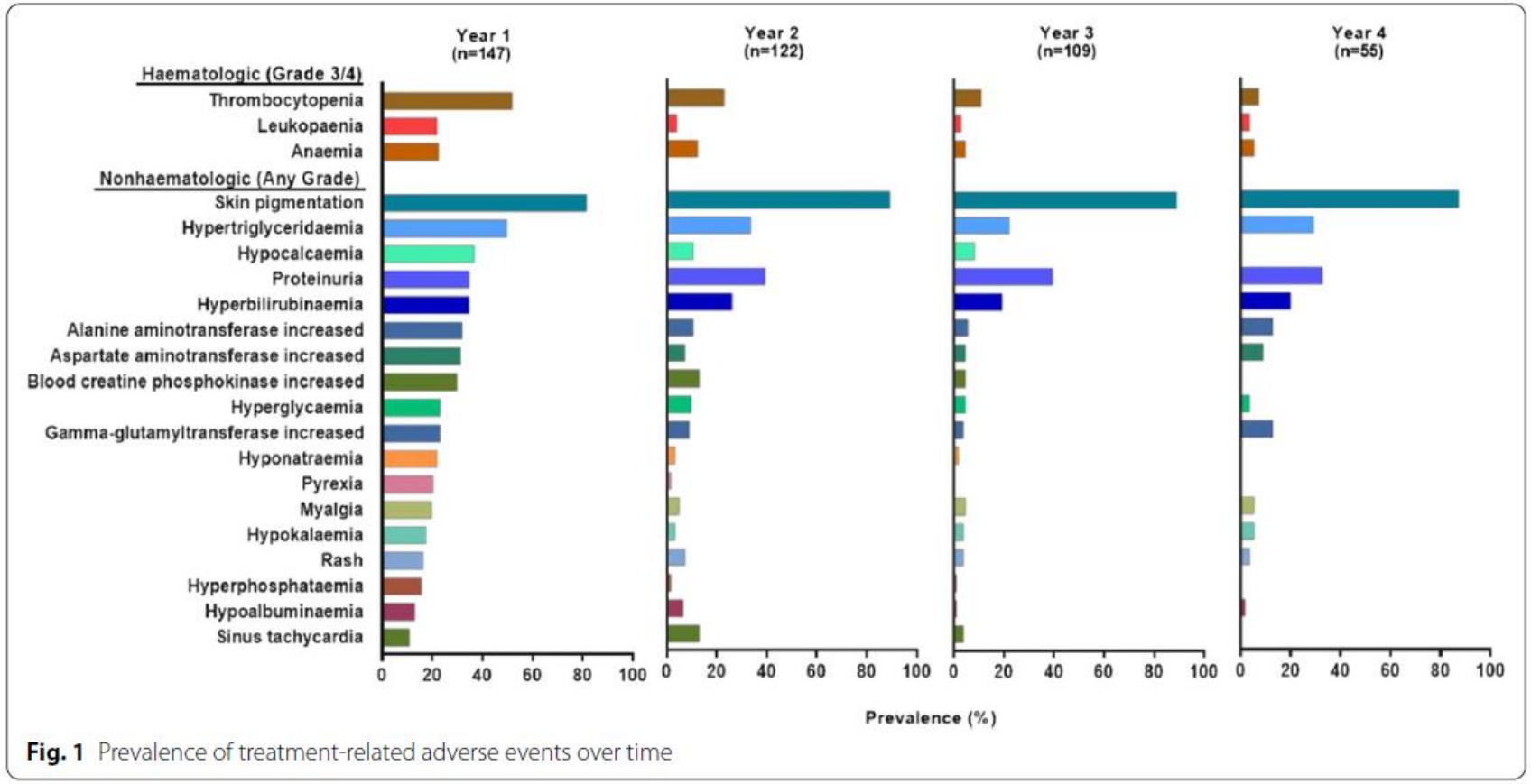


Fig. 1 Prevalence of treatment-related adverse events over time

Jiang Q, et al. J Hematol Oncol. 2022;15(1):113.

Olverembatinib: metabolism and pharmacokinetics

- Rapidly absorbed, slowly eliminated
- Peak plasma concentration (Tmax) 6h
- Half life 20-32.7h (17.5-36.5h)
- No food effect
- Caco-2 cells assay: no substrate for P-glycoprotein efflux transporters
- Liver metabolism
  - Cytochrome P450 assay
    - inhibition of CYP2C9 and CYP2C19
    - induction of CYP1A2, 2B6, 2C9
  - DDI potential in PBPK models:
    - Exposure may be increased by CYP3A4 inhibitors and decreased by inducers
    - Exposure may be increased by liver function injury
- Feces elimination

Ren X, et al. J Med Chem 2013; 3: 879-894.
Yu Z, et al. Frontiers in Pharmacology 2022; DOI 10.3389/fphar.2022.1065130
Jiang Q, et al. Journal of Hematology&Oncology 2022; 1: 113
Jabbour E, et al. JAMA Oncol 2025; 11(1): 28-35

Olverembatinib in CML patients: global phase 1

- Global Phase 1b trial HQP1351CU101; NCT04260022 in CML or Ph+ ALL resistant or intolerant to at least 2 TKI
  - 3 cohorts: 30, 40 or 50mg QOD
  - Randomization into 4 strata: CP- or AP-CML T315I+, CP-CML T315I-, AP-CML T315I-, BC-CML or Ph+ ALL

- 80 pts enrolled (CP-CML: 62) median age 54 (21-80), 58% males
  - Median FU: 48 weeks (0-166)
  - Prior ponatinib: 57.5%, prior asciminib: 31.3%

In CP-CML patients:
Pharmacokinetics comparable to that in Chinese patients
MMR: 42% regardless of T315I status, or prior asciminib or ponatinib exposure
Main >=grade 3 TEAE: CPK elevation, thrombocytopenia, fatigue, nausea, ALAT/ASAT elevation

Jabbour E, et al. JAMA Oncol 2025; 11(1): 28-35
Kantarjian H, et al. Cancer 2025

Olverembatinib in CML patients with prior ponatinib exposure: global phase 1

Outcome	No. With T315I variant	No T315I variant	Resistant	Intolerant	Total previously treated	Total study population
Ponatinib						
Ponatinib pretreated						
Efficacy population	13	17	21	6	30	60
Cytogenetic response						
Evaluable patients	13	13	19	4	26	51
Complete cytogenetic response, No. (%)	8 (61.5)	7 (53.8)	10 (52.6)	3 (75.0)	15 (57.7)	31 (60.8)
Molecular response						
Evaluable patients	13	17	21	6	30	59
Major molecular response, No. (%)	6 (46.2)	5 (29.4)	9 (42.9)	1 (16.7)	11 (36.7)	25 (42.4)

Jabbour E, et al. JAMA Oncol 2025; 11(1): 28-35

Olverembatinib optimization: analyses

- ***Objective:*** to find balance between safety and efficacy

- ***Rationale:***
  - Approval at 40mg QOD in CP- or AP-CML T315I+
  - TRAE leading to drug interruption or dose reduction in 52% and 30% of pts in phase 1 and 2 trials
  - > 70% had grade ≥3 TRAE including thrombocytopenia, hyperpigmentation, increased triglycerides and/or proteinuria. Cardiovascular adverse events occurred in 32% of subjects.

- ***Design:*** multicenter retrospective study with propensity score matching between 40mg QOD and 30mg QOD, 3rd line or beyond.

Zhang X, et al. Haematologica 2025; 110: 2986

Olverembatinib optimization: overall results

- 282 pts (from trials or real life) with matches: 66 at 30mg QOD, 216 at 40mg QOD
- Median FU: 28 and 25 months, respectively

Table 1. Comparative summary of clinical outcomes for olverembatinib 30 mg QOD *versus* 40 mg QOD in the propensity score matched population.

Outcomes	30 mg QOD	40 mg QOD	*P*	Favors
Molecular response at 12 months, % of patients				
MMR	36	42	0.49	Equal
MR4	22	25	0.28	
Cytogenetic response at 12 months, % of patients				
MCyR	67	69	0.89	Equal
CCyR	56	61	0.80	
Overall survival at 12 months, % of patients	95	92	0.60	Equal
Dose reduction/discontinuation due to TRAE, % of patients	18	38	0.003	30 mg QOD
Maintained initial dose, % of patients	67	47	0.009	30 mg QOD

QOD: every other day; MMR: major molecular response; MR4: four-log reduction in molecular *BCR:ABL1*; MCyR: major cytogenetic response; CCyR: complete cytogenetic response; TRAE: treatment-related adverse events.

Comparable AE profile and % in both groups

Perusini MA, Kim DDH. Haematologica 2025; 110: 2284.
Zhang X, et al. Haematologica 2025; 110: 2986

Olverembatinib optimisation: focus on cardiovascular tolerance

Any grade	30 mg	40 mg
Cardio- and cerebro-vascular toxicity	**29**	**30**
Hypertension	**13**	**19**
Sinus tachycardia	**11**	**8**
Arterial and/or venous obstructive events	**5**	**8**
Pericardial effusion	3	3
Sinus bradycardia	2	2
Atrial fibrillation	2	2
Heart failure	2	2
Pulmonary arterial hypertension §	2	2

Perusini MA, Kim DDH. Haematologica 2025; 110: 2284.
Zhang X, et al. Haematologica 2025; 110: 2986

Courtesy of Dr Qian Jiang

Olverembatinib: developments

- CML:
  - US: Phase II Study of Olverembatinib Monotherapy in newly diagnosed CP-CML
  - Global: Olverembatinib (HQP1351) versus bosutinib in patients with CP-CML previously treated with at least two TKIs.

- Outside CML :
  - FGF-R1-related syndromes
  - GIST
  - (AML)
  - Ph+ ALL

Yan Y, et al. Leukemia & Lymphoma 2023; 64:9, 1605-1610
Kantarjian H, et al. Cancer 2025; e35832

Conclusion

- Reengineering TKIs for varying purposes—such as minimizing toxicity, enhancing specificity, or increasing activity—is possible.
- Olverembatinib is derived from ponatinib and has a broader binding capacity to its target, enhanced inhibitory properties *in vitro*, and expanded activity against ABL1 mutations.
- In humans, olverembatinib appears able to overcome ponatinib resistance; however, no head-to-head comparison between the two drugs has been performed.
- Whether olverembatinib retains the cardiotoxic potential of ponatinib still needs to be investigated.
- The precise role of olverembatinib within the current therapeutic landscape will have to be established