UNIVERSITÄTS KLINIKUM jena

New drugs in CML clinical trials - new data, updated data, any surprises?

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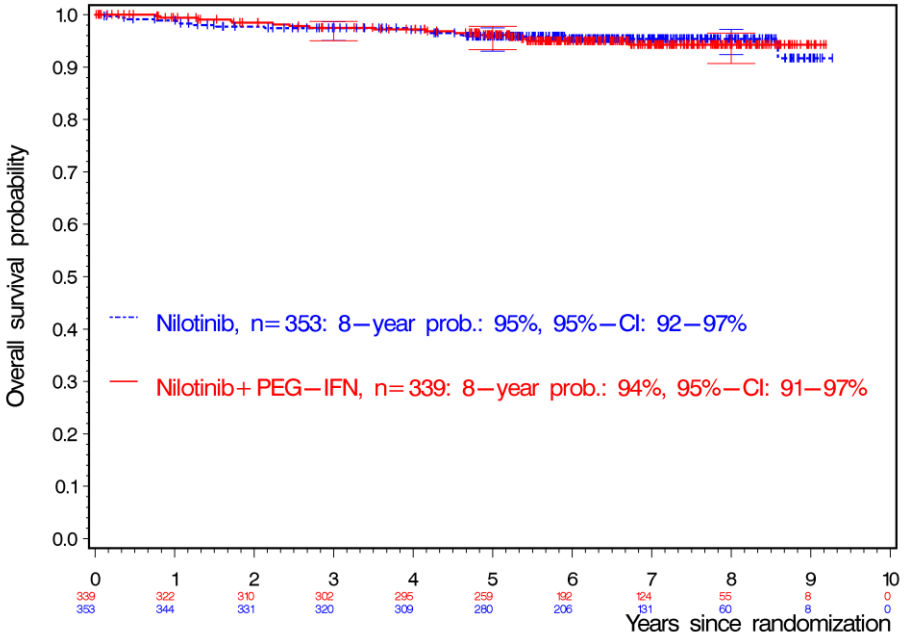
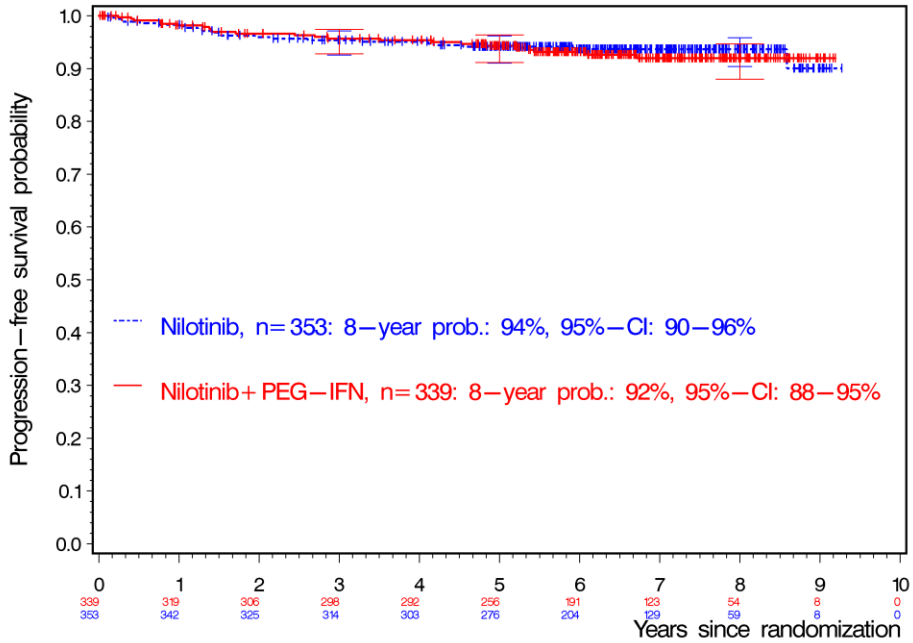
Overall and progression free survival by randomized therapy (TIGER)

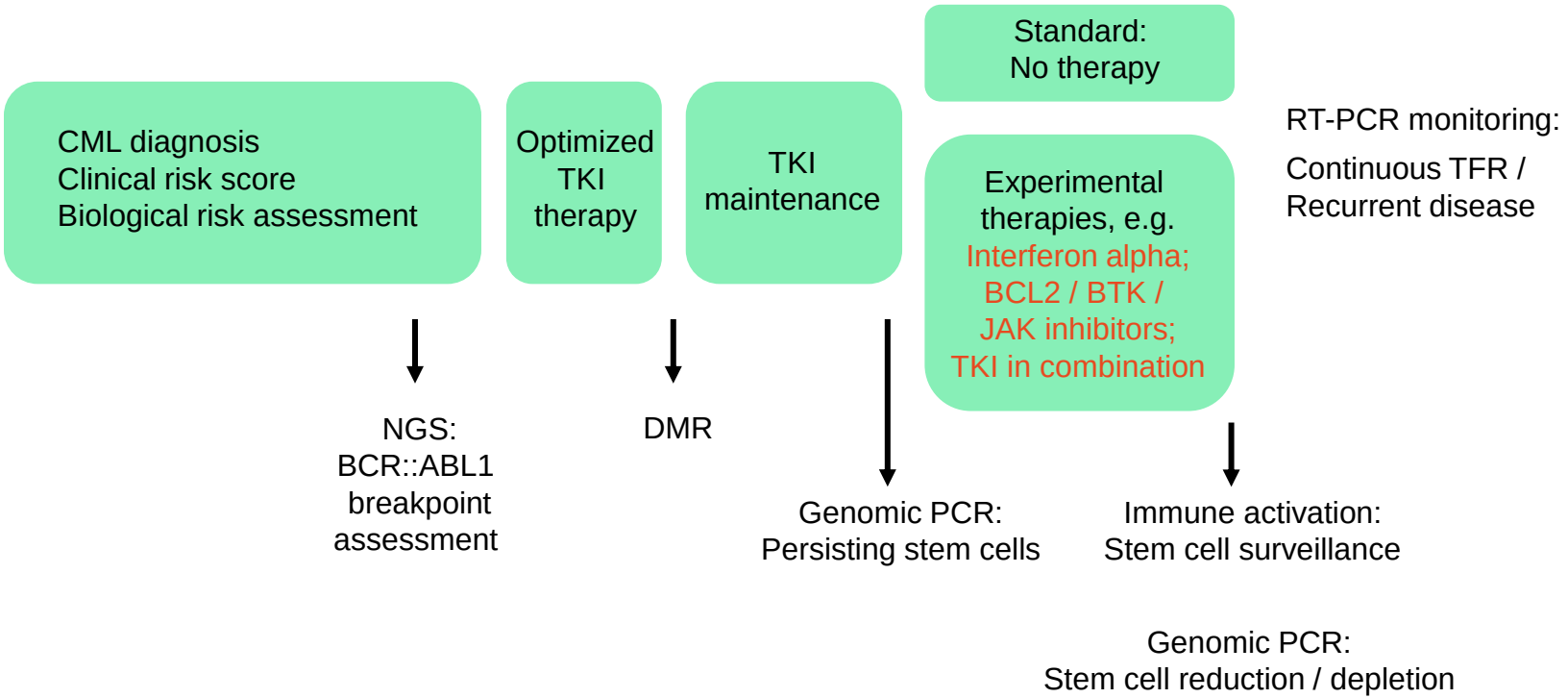


8-year overall survival 95%



8-year progression free survival 93%

Experimental proposals to improve TFR



JAK, Janus kinase; PCR, polymerase chain reaction; RT, real-time.

Hochhaus A, Ernst T. Hematology Am Soc Hematol Educ Program. 2021;2021(1):106-12.

New ABL1 inhibitors

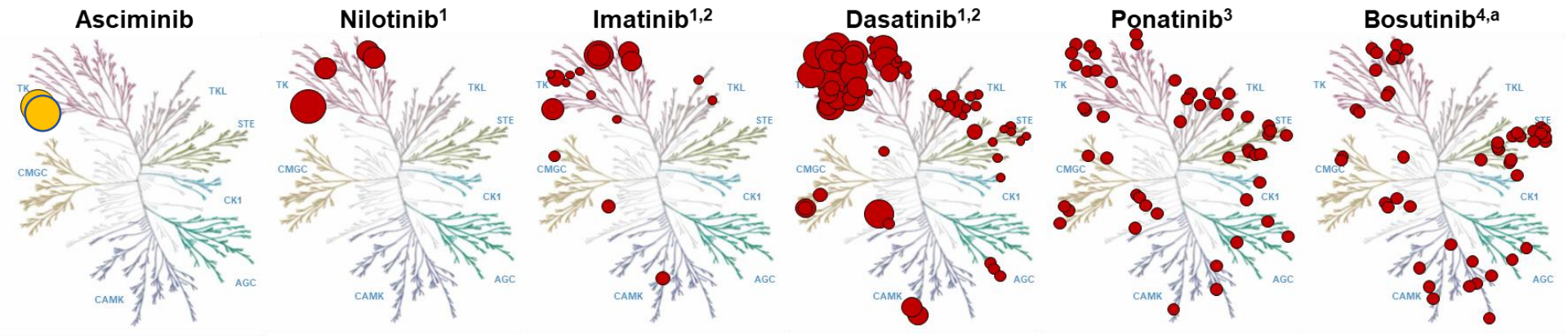
Olverembatinib (T315I active)

Vodobatinib, limited off-target activity

ELVN-001 (T315I active)

TERN-701 (allosteric, T315I active)

Selektivität der Kinase-Inhibitoren



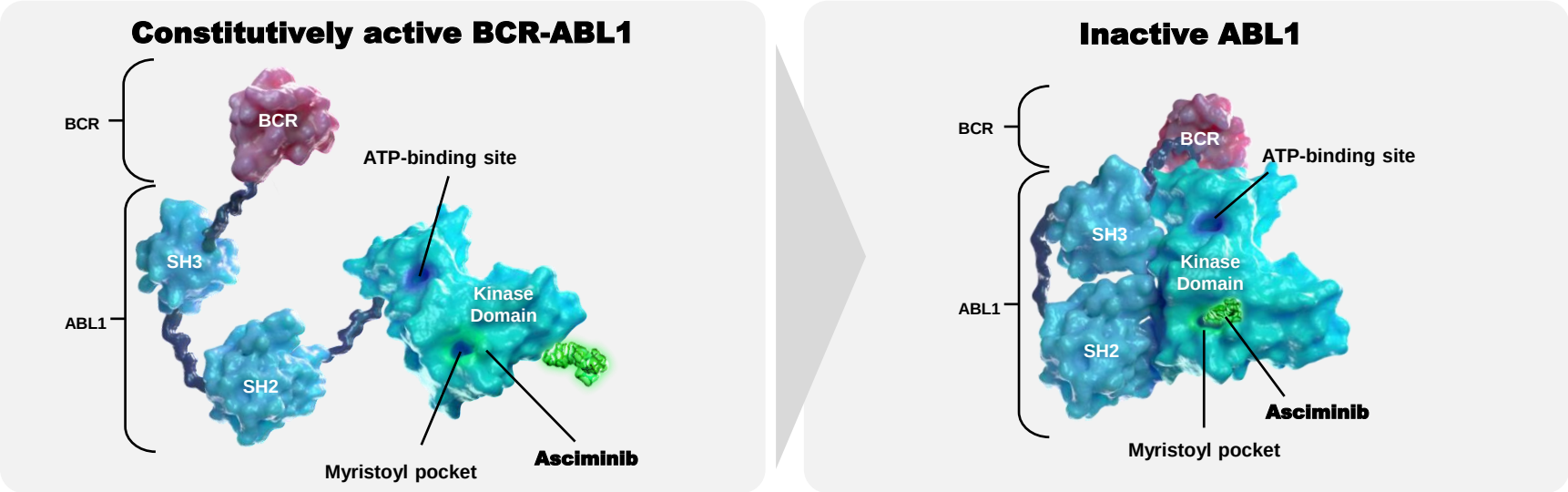
Selectivity of kinase inhibitors:

Kinases bound by ATP-competitive TKIs are indicated by **red** circles.
Kinases bound by STAMP inhibitor are indicated by a **yellow** circles.

[a] Bosutinib inhibits additional kinases that are not depicted in the dendrogram.
ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor;
STAMP, Specifically Targeting the ABL Myristoyl Pocket.

1. Steegmann JL, et al. Leuk Lymphoma. 2012;53:2351-2361.
2. Karaman MW, et al. Nat Biotechnol. 2008;26:127-132.
3. Lang JD, et al. Clin Cancer Res. 2018;24:1932-1943.
4. Remsing Rix LL, et al. Leukemia. 2009;23:447-485.

Asciminib ist ein STAMP Inhibitor (Specifically Targeting the BCR-ABL1 Myristoyl Pocket)

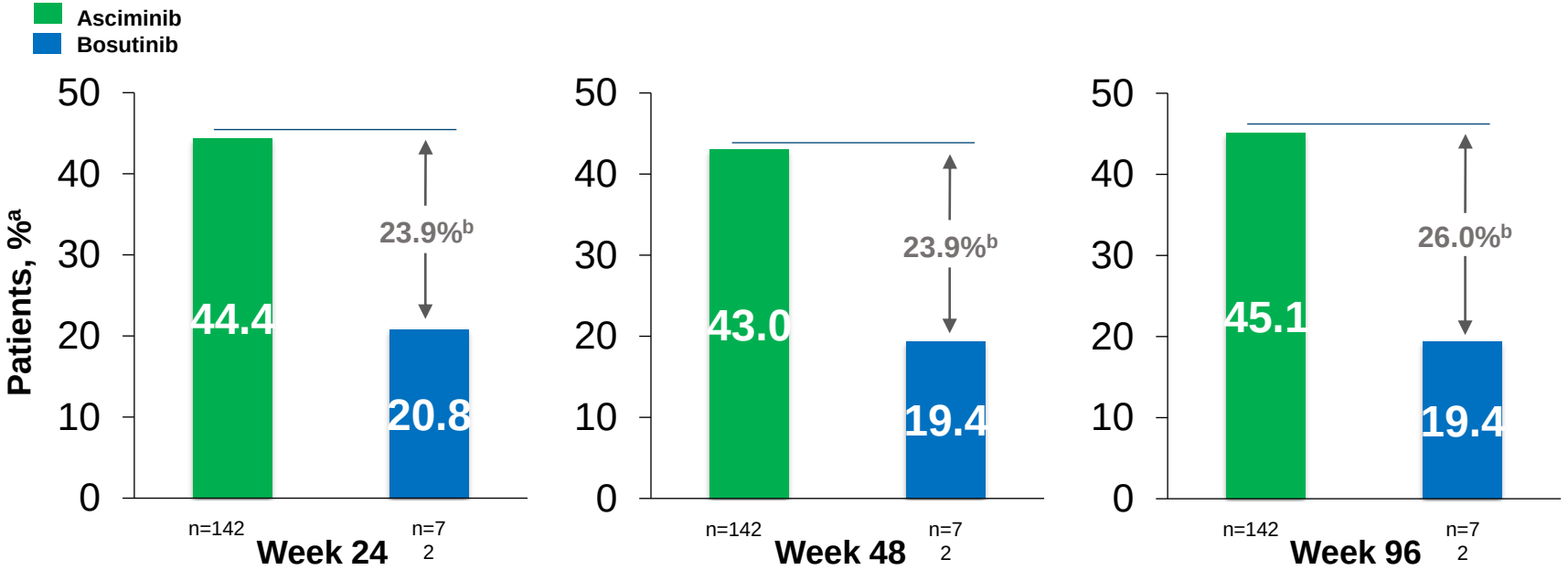


Unlike ATP-competitive TKIs that target the ATP-binding site, asciminib has a unique mechanism of action.[1,2] It is a first-in-class STAMP inhibitor[3]:

- Asciminib mimics myristate by binding the myristoyl pocket of ABL1 (normally bound by the myristoylated N-terminal of ABL1)[4,5]
- Upon binding, asciminib restores inhibition of the ABL1 kinase activity[4-7]

Hughes TP, et al. N Engl J Med. 2019;381:2315-26

ASCEMBL: *BCR::ABL1*^{IS} ≤1%

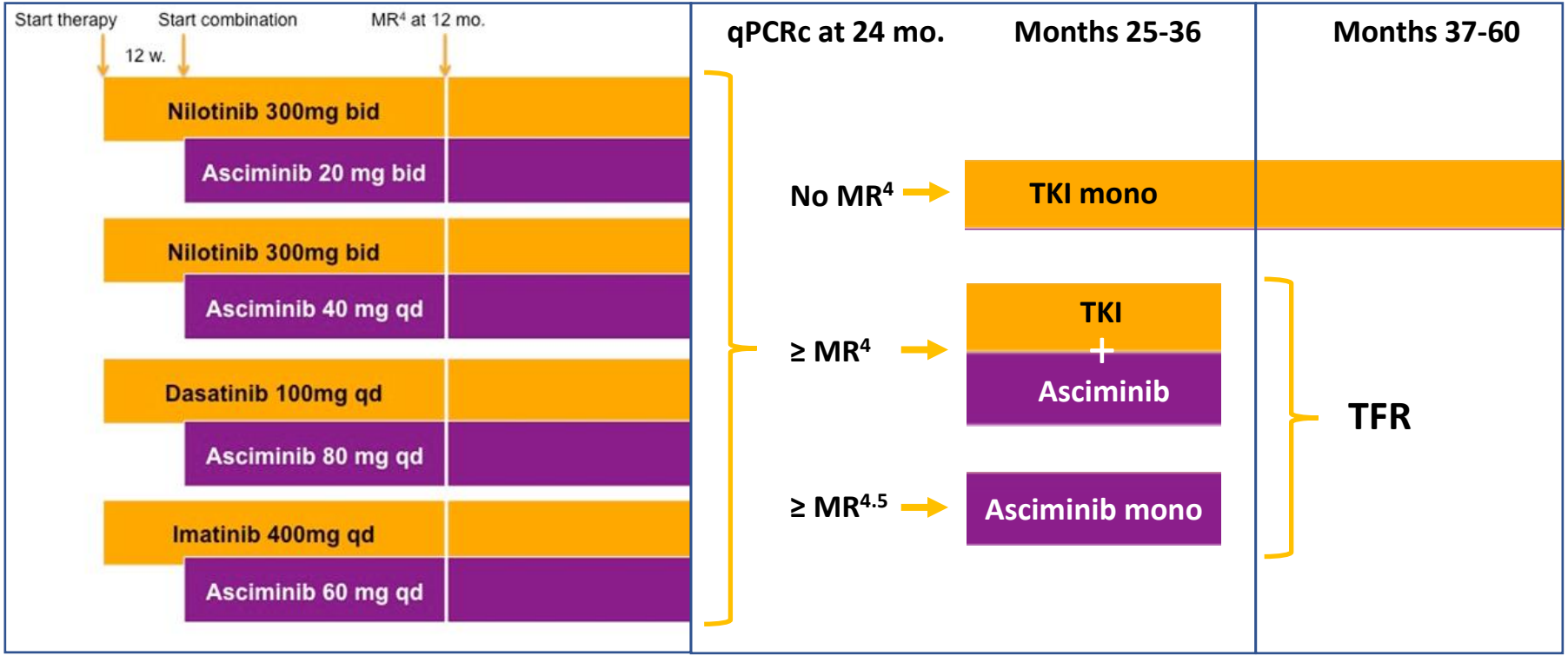


Maintenance of *BCR::ABL1*^{IS} ≤1%[c]

- The probability (95% CI) of maintaining *BCR::ABL1*^{IS} ≤1% for at least 72 weeks was **94.6%** (86.2%-97.9%) with **asciminib** and **95.0%** (69.5%-99.3%) with **bosutinib**

[a] Based on 142 of 157 patients (90.4%) receiving asciminib and 72 of 76 (94.7%) receiving bosutinib with *BCR::ABL1*^{IS} >1% at baseline.
[b] The treatment difference after adjusting for baseline MCyR status was 23.92% (95% CI: 11.36%, 36.49%; 2-sided *P*=0.000) at week 24, 23.85% (95% CI: 11.36%, 36.33%; 2-sided *P*=0.000) at week 24, and 26.02% (95% CI, 13.48%-38.56%; 2-sided *P*=0.000) at week 96.
[c] Based on 78 of 157 patients (49.7%) receiving asciminib and 24 of 76 (31.6%) receiving bosutinib, who achieved *BCR::ABL1*^{IS} ≤1%.

Fascination: Studiendesign

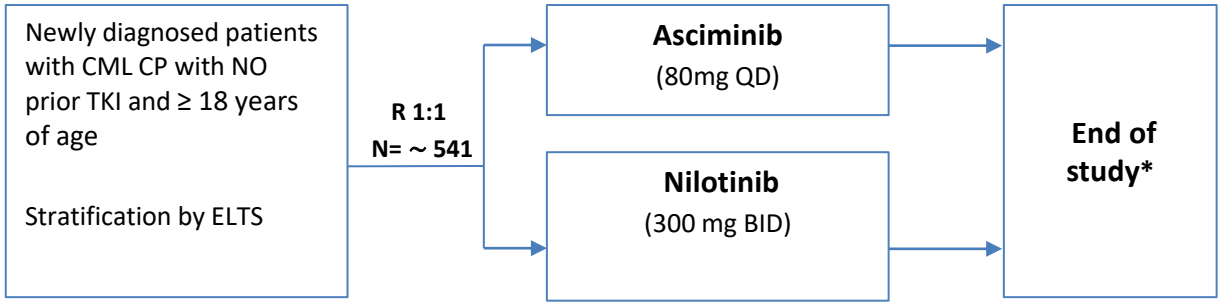


Molecular response

	MMR (%)	MR^4 (%)	$MR^{4.5}$ (%)	MR^5 (%)	$MR^{5.5}$ (%)	N (total)
At month 3	26 (21)	5 (4)	2(2)	1 (1)	0	124
At month 6	69 (57)	28 (23)	13 (11)	6 (5)	2 (2)	121
At month 9	73 (63)	33 (29)	19 (17)	6(5)	3 (3)	115
At month 12	77 (68)	43 (38%)	25 (22)	9 (8)	3 (3)	114

ASC4START: Study Design / Patient Population

A phase IIIb, multi-center, open-label, randomized study of tolerability and efficacy of oral asciminib versus nilotinib in patients with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase



*Participants can be treated in the study until approximately 64 discontinuations of study treatment due to AE (TTDAE) are met. End of study is defined as when the necessary number of events has been reached and when end of treatment and the last assessments as per Table 1-1 are completed. Refer to Section 6.1.5 Treatment Duration for additional details.

N= Approximate number of participants required to achieve 64 events (refer to Section 9.9)

Data on file. Study Protocol No. CABL001J12302 Clinical Trial Protocol.

ELVN-001 is Selective for BCR::ABL1

- ELVN-001 has a very **selective** kinase profile
  - Clean vs. key off-targets in cells
  - 372 kinases screened at 1 µM compound (100 µM ATP)
  - Kinases with >50% inhibition selected for IC_{50} determination
  - >100x window vs. all but 2 kinases profiled
- ELVN-001 is also very **clean** (>10 µM) in an *in vitro* safety panel of >130 receptors

Cellular Phosphorylation IC_{50} (nM)

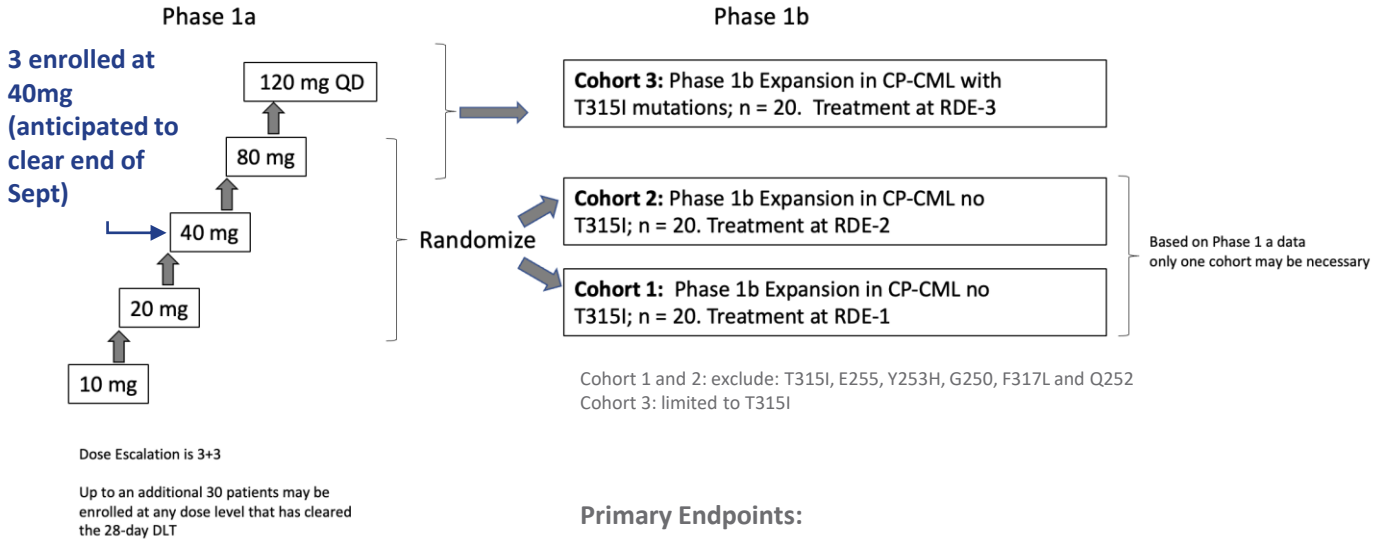
	cKIT	FLT3wt	PDGFRb	VEGFR2	cSRC
ELVN-001	>10,000	>10,000	>10,000	>10,000	>10,000
Ponatinib	30	3.8	89	4.8	630
Nilotinib	200	>10,000	720	2,900	>10,000
Dasatinib	0.6	>1,000	7.1	>1,000	10
Bosutinib	1,000	4,700	7,900	>10,000	16

Ba/F3 Mutant Cell line	Asciminib Fold IC_{50} over Native BCR-ABL1	ELVN-001 Fold IC_{50} over Native BCR-ABL1
Native BCR-ABL1	1	1
M244V	1*	1
G250E	0.2	>10
Y253F	3	8
Y253H	2	>10
E255K	2	>10
T315A	2	1
F317L	>10	>10
F317V	7	1
M351T	7	1
F359V	>10	1
H396P	>10	1

Reference: Abl kinases are required for vascular function, Tie2, and angiopoietin-1-mediated survival. Pendergast et al. *PNAS*. 2013;110(30):12432-7.

ELVN-001-101 Phase 1 Dose Escalation & Expansion in CML

- Chronic Phase CML
- Failed or intolerant to available therapies known to be active for treatment of their CML
  - Failed per 2020 ELN Recommendations
  - Intolerant per Investigator
  - No bone marrow biopsy/aspirate required



Cohort 1 and 2: exclude: T315I, E255, Y253H, G250, F317L and Q252
Cohort 3: limited to T315I

Primary Endpoints:

- Incidence of AEs, ECG and lab abnormalities

Secondary Endpoints:

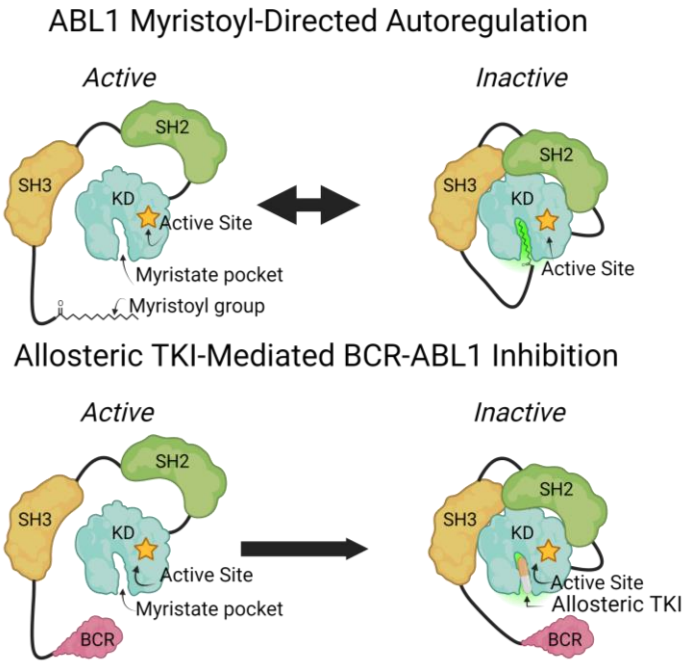
- Molecular response
- PK parameters

CP = chronic phase
AP = accelerated phase
ELN = European Leukemia Net
RDE = Recommended Dose for Expansion
AE = adverse event
ECG = electrocardiogram
PK = pharmacokinetic

TERN-701: Allosteric BCR::ABL1 inhibitor

TERN-701 is an allosteric inhibitor of BCR::ABL1

- Potent allosteric inhibitor of BCR::ABL1, optimized for selectivity and pharmacokinetic parameters, that binds the myristate pocket
- Maintains activity against ATP site mutations which confer resistance to active site-targeting TKIs

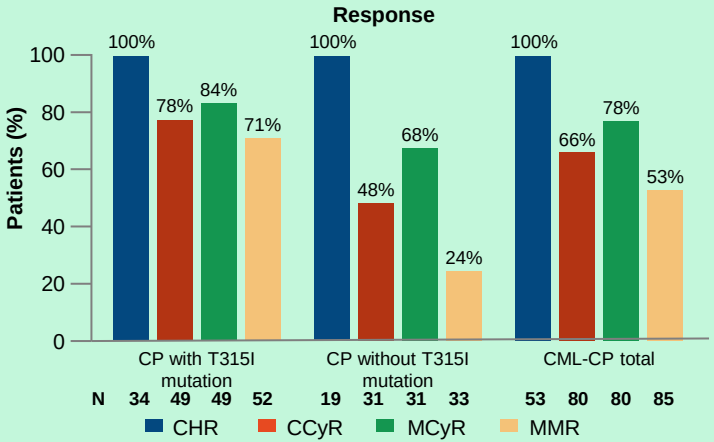


Source: Alves R, et al. Cancers (Basel). 2021.

Olverembatinib: updates of phase 1 and 2

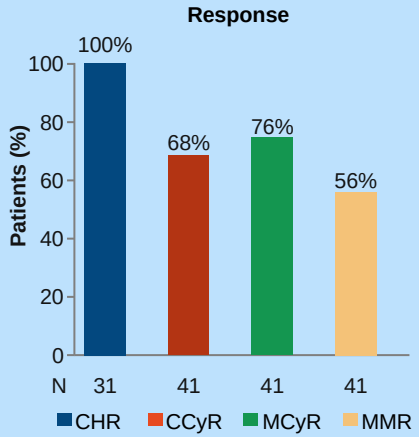
Update of phase 1 study[1]

- 101 patients (86 in CP and 15 in AP)
- 83% treated with 2 prior lines of TKI; **62% harbored the T315I mutation**
- AEs: 86% skin hyperpigmentation; 11% hypertriglyceridemia, 5% proteinuria, 77% thrombocytopenia



Phase 2: CC201 study[2]

- CP with T315I, 40 mg q.d.
- 41 patients, 32 completed 12 cycles
- 78.1% pretreated with > 2 TKIs
- AEs: thrombocytopenia 70.7%, skin pigmentation 56.1%



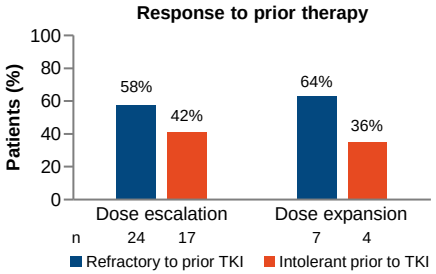
AP, accelerated phase; CHR, complete hematologic response; CP, chronic phase; MCyR, major cytogenetic response; PFS, progression-free survival.

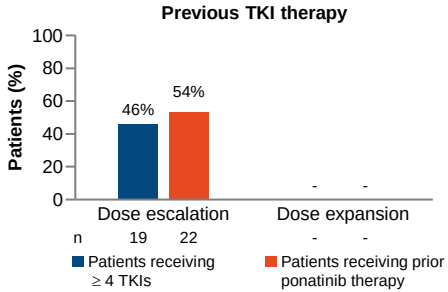
1. Qian J, et al. Presented at ASH 2021, abstract 311.
2. Qian J, et al. Presented at ASH 2021, abstract 3598.

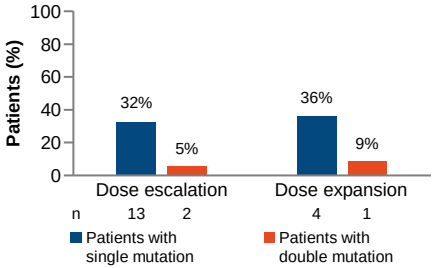
Vodobatinib: phase 1 patient characteristics and results

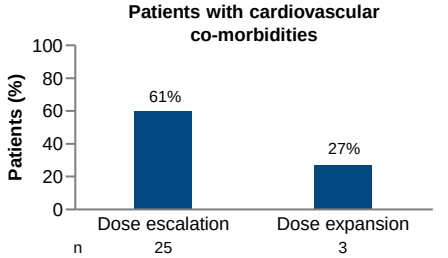
52 patients enrolled

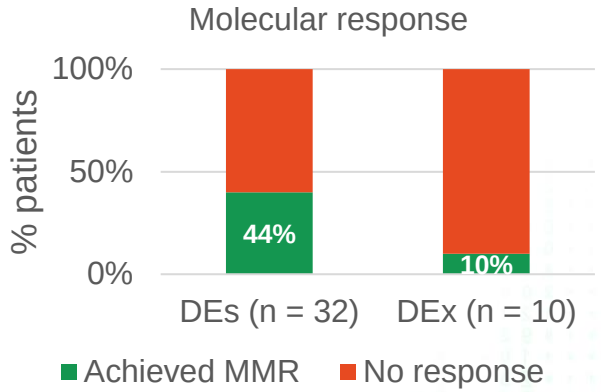
	Dose escalation	Dose expansion
Number of patients	41	11
Median age in years (range)	61 (23–85)	47 (35–60)









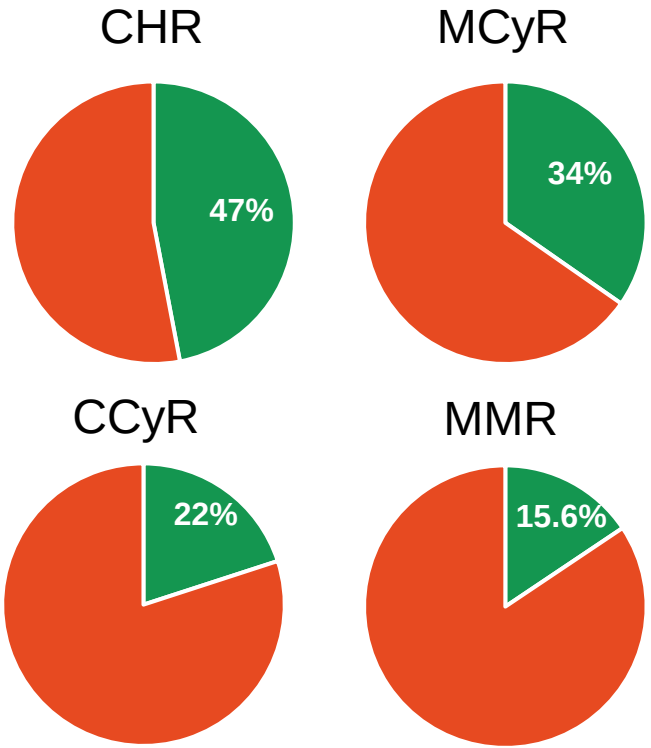


- 17 CP-CML patients had prior ponatinib treatment:
  - 11 (65%) had MCyR
  - 8 (47%) achieved MMR
- Most common any grade TEAEs included thrombocytopenia (33%), cough (19%), anemia & diarrhea (17% each)
- 10 (19%) patients reported cardiovascular TEAEs

TEAEs, treatment-emergent adverse effects.

Cortes JE, et al. Presented at ASH 2021, abstract 309.

PF114: phase 1 study results



- 51 pts enrolled in phase 1 study (11 with T315I), 70% received > 3 lines of therapy
- The MTD was 600 mg with grade-3 psoriasis-like skin AE as the DLT
- No vascular occlusive events or deviations of ankle-brachial index

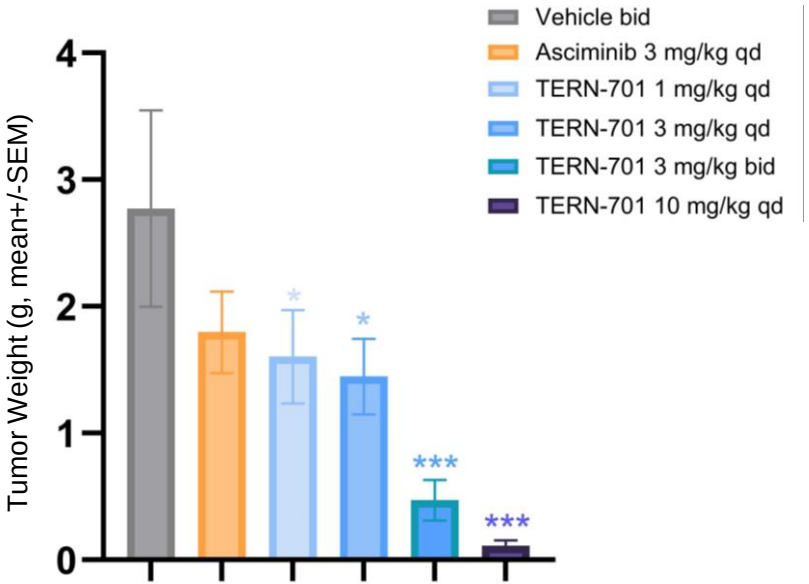
DLT, dose-limiting toxicity.

Turkina AG, et al . Presented at ASH 2021, abstract 1482.

In Preclinical Models of CML, TERN-701 Showed a Greater Anti-Tumor Effect vs. Asciminib at Equivalent Doses & Dosing Frequency

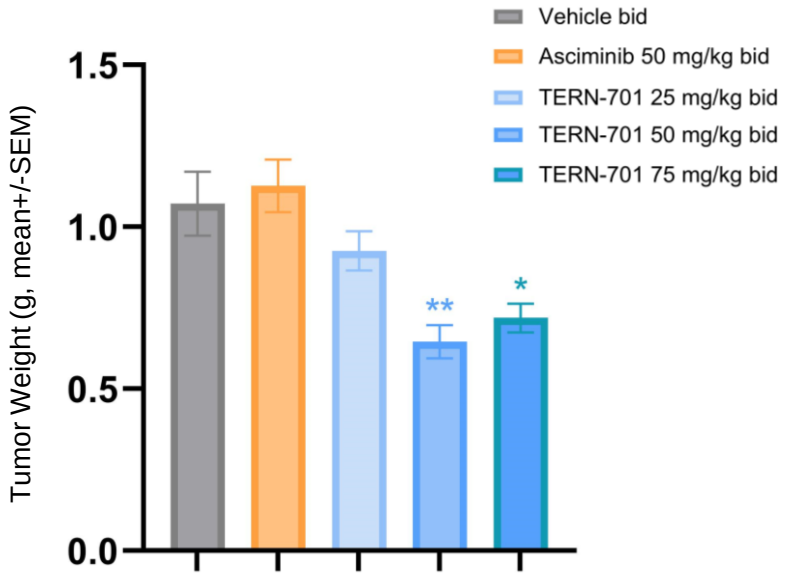
K562 Xenograft

(Day 14)



Ba/F3 BCR::ABL1-T315I Allograft

(Day 15)



Note: NOD-SCID (K562) and BALB/c nude mice (Ba/F3T315I) were implanted with CML cells, randomized, and administered the indicated TKIs once tumor volumes reached a mean size of 110 mm. Mean tumor weights for each of the treatment groups at the conclusion of the study. All error bars represent the SEM. *p<0.05, **p<0.01, ***p<0.001.

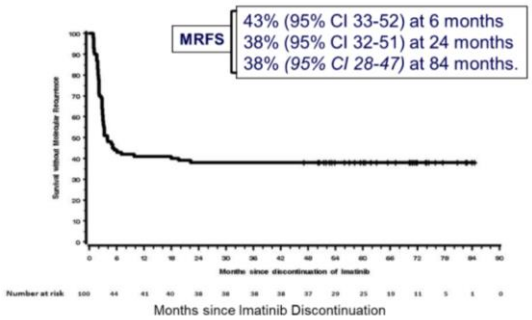
1. asciminib was utilized as the free base, TERN-701 was formulated as an optimized salt form

Source: Zhou et al. ASPET 2023. TERN-701 poster

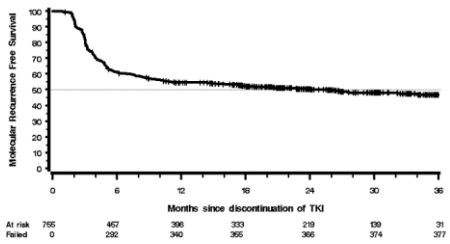
TFR nach Stop von Erst- und Zweitgenerations-TKI

Imatinib

STIM (N=100)[1]

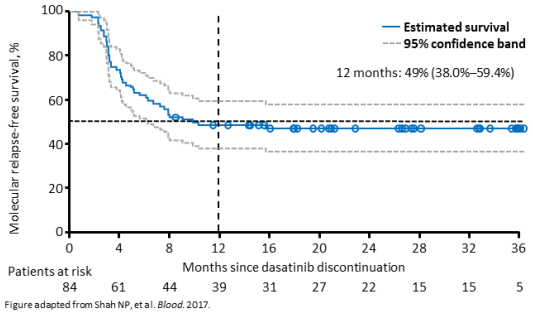


EURO-SKI (N=755)[2]

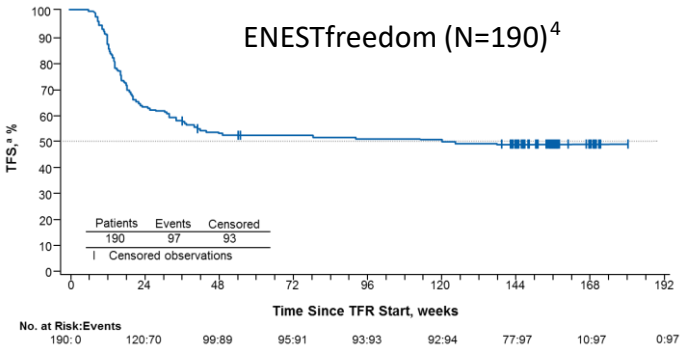


Zweitgenerations-TKI

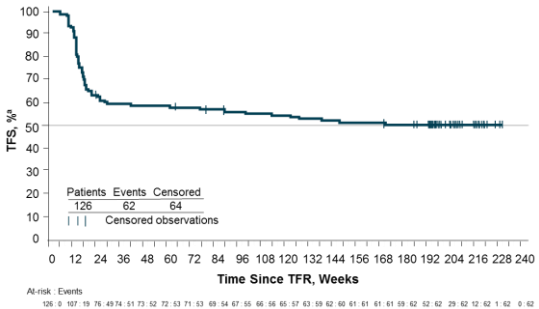
DASFree (N=84)[3]



ENESTfreedom (N=190)[4]

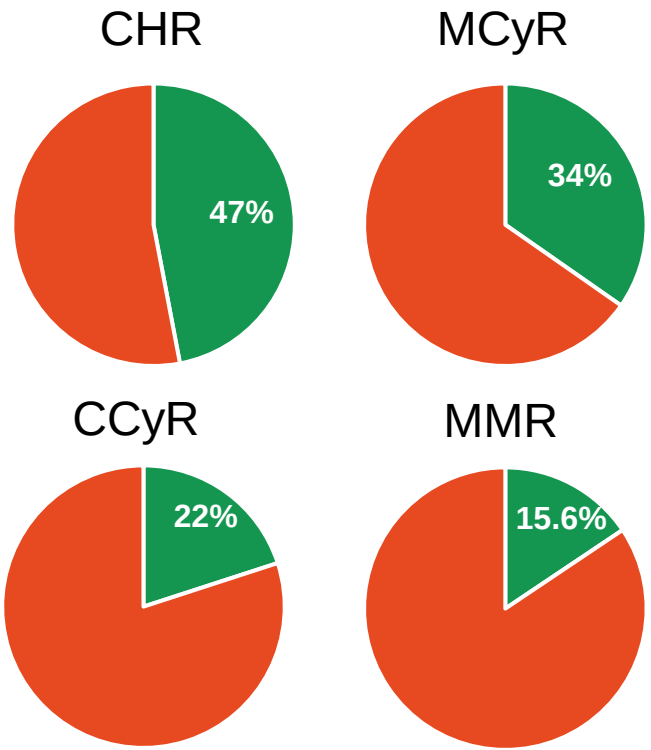


ENESTop (N=126)[5]



ENEST, Evaluating Nilotinib Efficacy and Safety in Clinical Trials. MRFS: molecular relapse-free survival; TKI: tyrosine kinase inhibitor; TFR: Treatment-free remission; TFS: Treatment-free survival1. Etienne G, et al. *J Clin Oncol* 2017;35:298ff.. 2. Saussele S, et al. *Lancet Oncol* 2018;19:747–757. 3. Shah NP, et al. *Blood* 2017;130(suppl 1) [abstract 314].
4. Ross DM, et al. PF409 EHA 2019. 5. Mahon FX, et al. EHA 2019.

PF114: phase 1 study results



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DLT, dose-limiting toxicity.

Turkina AG, et al . Presented at ASH 2021, abstract 1482.

Olverembatinib: updates of phase 1 and 2 (incl. T315I)

Update of phase 1 study[1]

- 101 patients (86 in CP and 15 in AP)
- 83% treated with 2 prior lines of TKI;
  62% harbored the T315I mutation
- AEs: 86% skin hyperpigmentation;
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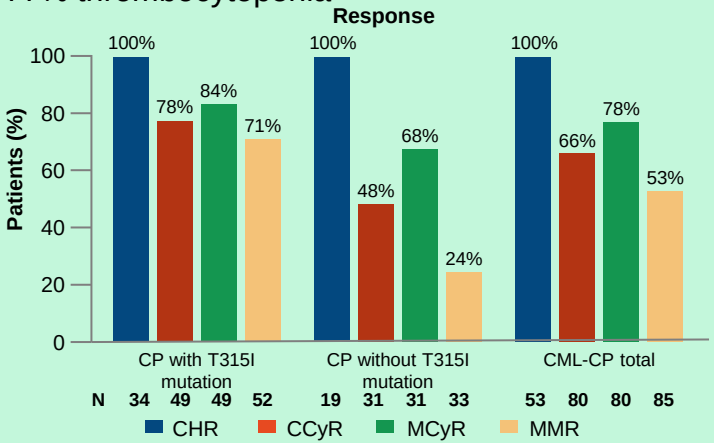

Phase 2: CC201 study[2]

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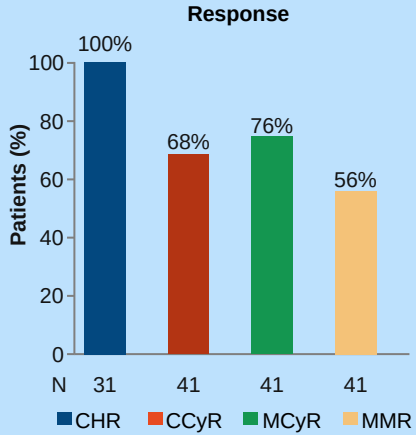

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1. Qian J, et al. Presented at ASH 2021, abstract 311.
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Vodobatinib: phase 1 patient characteristics and results (no T315I)

52 patients enrolled

	Dose escalation	Dose expansion
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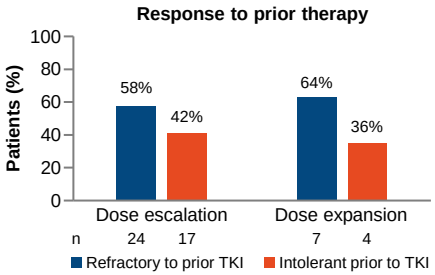
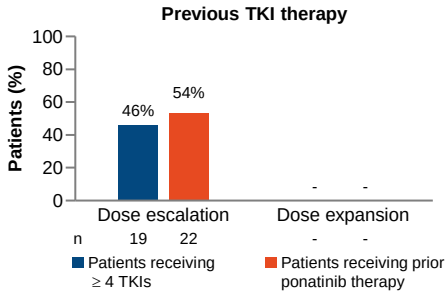
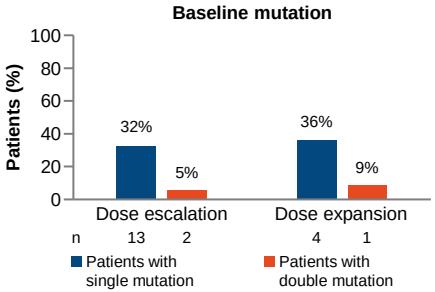
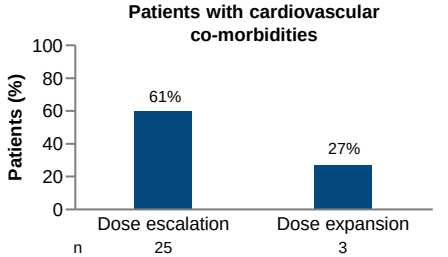
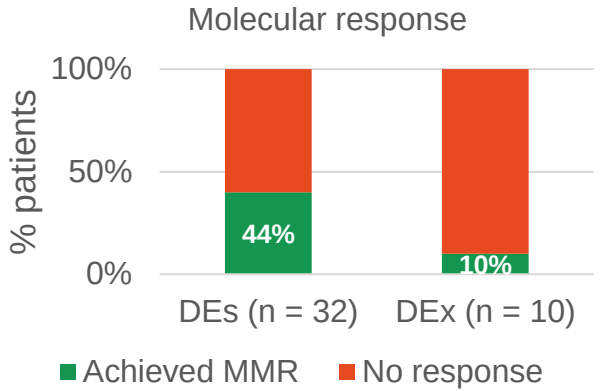
Median age in years (range)	61 (23–85)	47 (35–60)











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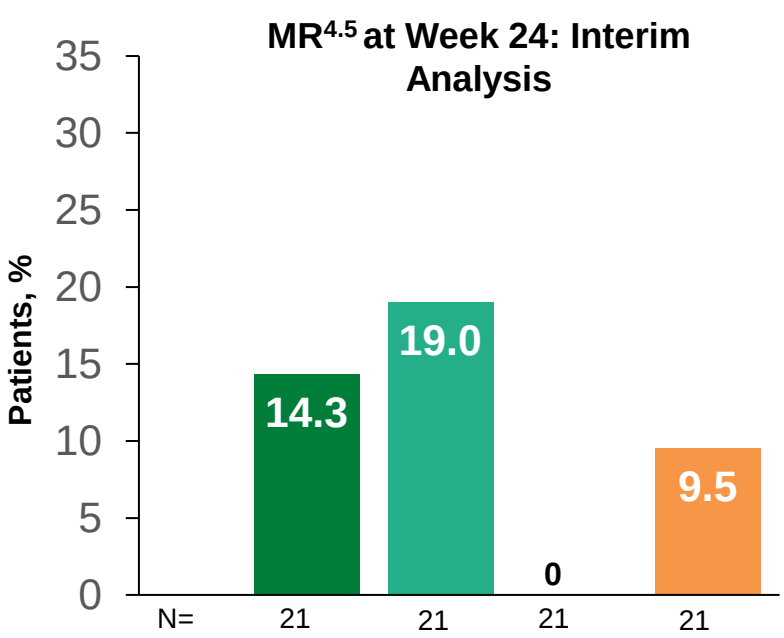
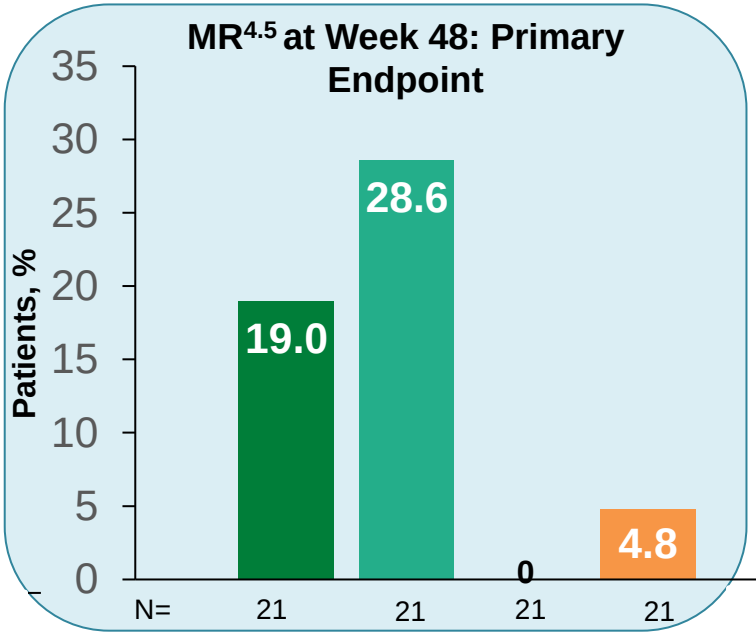
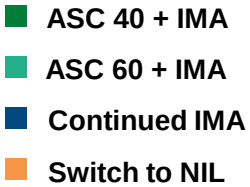
Cortes JE, et al. Presented at ASH 2021, abstract 309.

ASC4MORE: MR$^{4.5}$ at Weeks 24 and 48



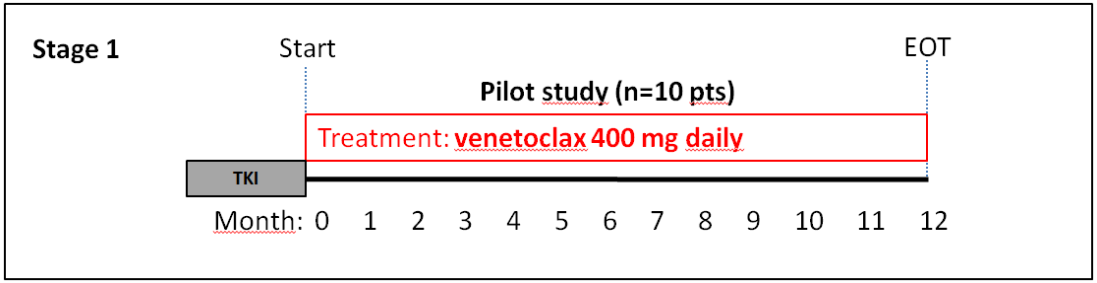


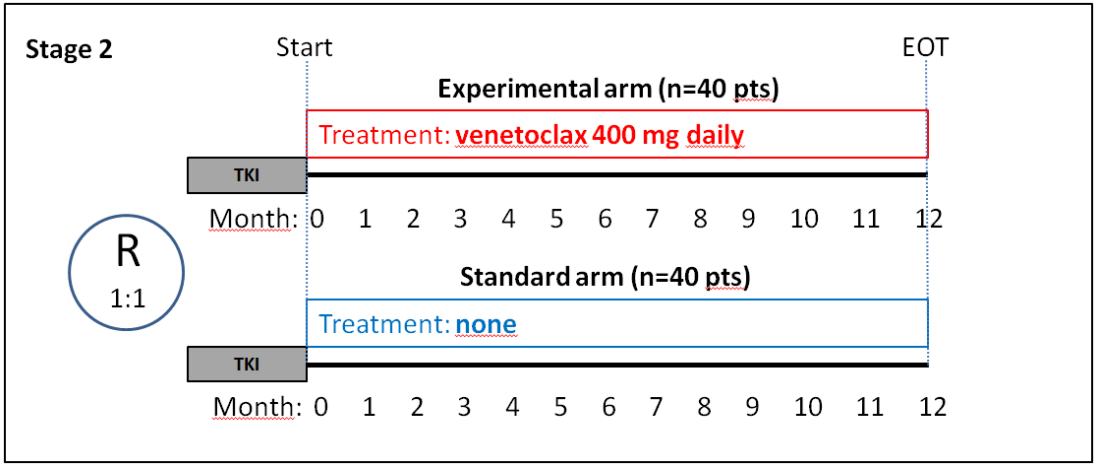


- More patients were able to achieve MR$^{4.5}$ with **asciminib add-on** to imatinib vs continued **imatinib** or switch to **nilotinib**
- No patients in the continued **imatinib** arm were in MR$^{4.5}$ at week 48, although more patients in this arm were in MMR at baseline than in the **asciminib add-on** arms

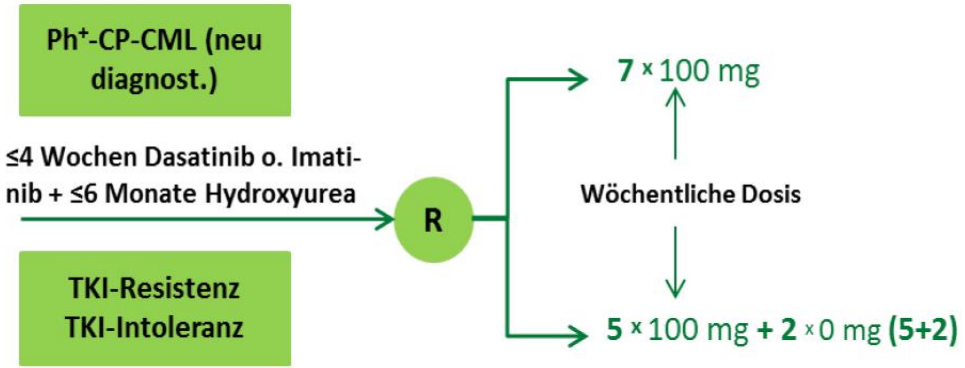
Venetoclax after TKI to target persisting stem cells in CML

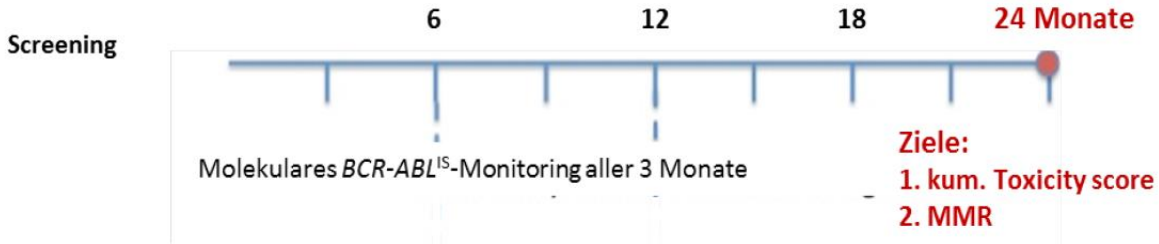
Variant: Pilot study





- **Multicenter, prospective, randomized, unblinded phase III**
- **Non-inferiority (MMR @ 24 ms)**
- **Planned: n = 306**

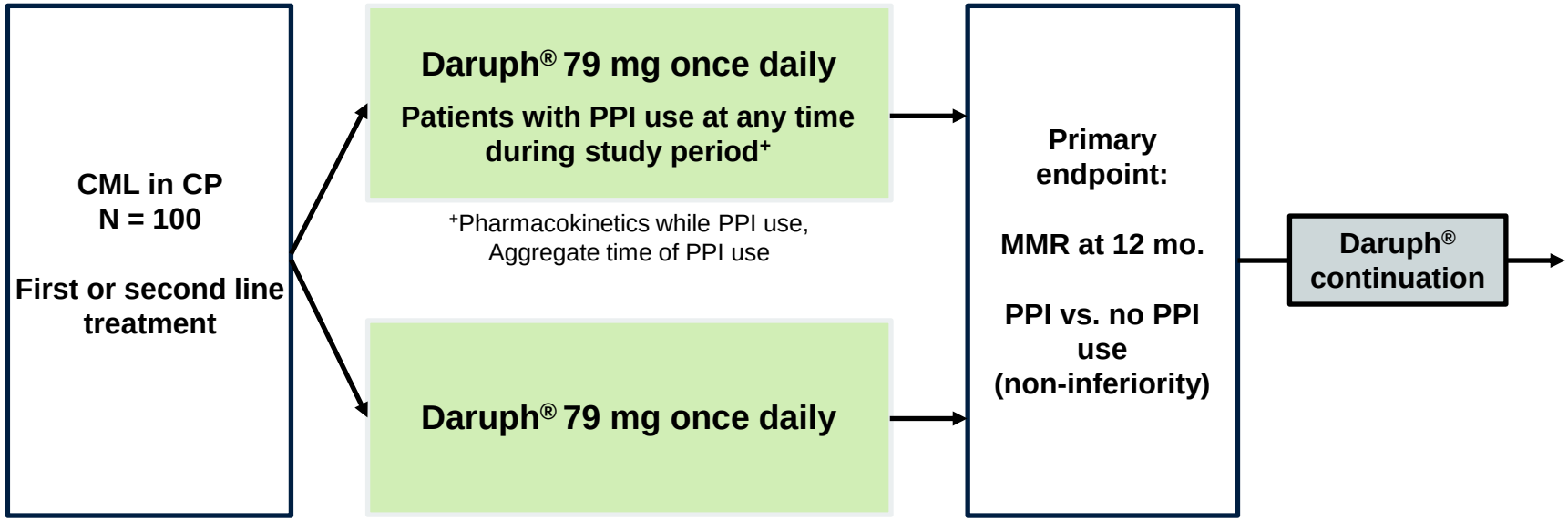




Cumulative Toxicity (24 ms)

1: Pleural Effusion
2: Fluid Retention
3: Hematologic Toxicity
4: Other (GI, Skin, Musculo-skeletal)

Daruph: Proposed Study design



*omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole at any dosage

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