1ST INTERNATIONAL CONFERENCE ON

Ph+Leukemias

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

Is BCR::ABL1 the key target in all CML patients?

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Disclosures: Katerina Machova Polakova

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis	YES					YES	

25 Years of TKIs: A Timeline of Transformation

iCMLf 25 years of TKIs

The development of TKIs for CML revolutionised cancer treatment, offering a targeted therapy model for other malignancies. Each generation of TKIs improved upon the last, addressing resistance, intolerance, and specific mutations. Continued innovation, including the new allosteric inhibitors, ensures further advancements in managing CML.

"The identification of BCR::ABL1 and its ability to cause leukemia was a key moment to understanding this disease. It was a moment of hope as I realised we had the potential to change the trajectory of the disease."
– Professor Brian Druker

Pre-TKI Era

1959

Philadelphia Chromosome

The discovery of the Philadelphia (Ph) chromosome in CML patients was the first chromosomal abnormality linked to cancer.

1973

BCR::ABL Fusion Gene

Identification of the BCR::ABL1 fusion gene, resulting from the Ph+ translocation (t(9;22)(q34;q11)).

1985

BCR::ABL Oncoprotien

Discovery that the BCR::ABL1 fusion protein has constitutive tyrosine kinase activity, driving uncontrolled cell growth.

First-Generation TKI

1990

Targeting BCR::ABL1

Collaboration between academia and Novartis began on a drug discovery program to target BCR::ABL

1992

STI571

STI571 (imatinib) is shown to specifically target and kill CML cells.

"The approval of imatinib was more than a milestone; it was a lifeline for patients around the world."
– Professor Jorge Cortes

1998

Phase I trials

Phase I trials showed unprecedented response rates for a cancer treatment, with minimal toxicity.

2000

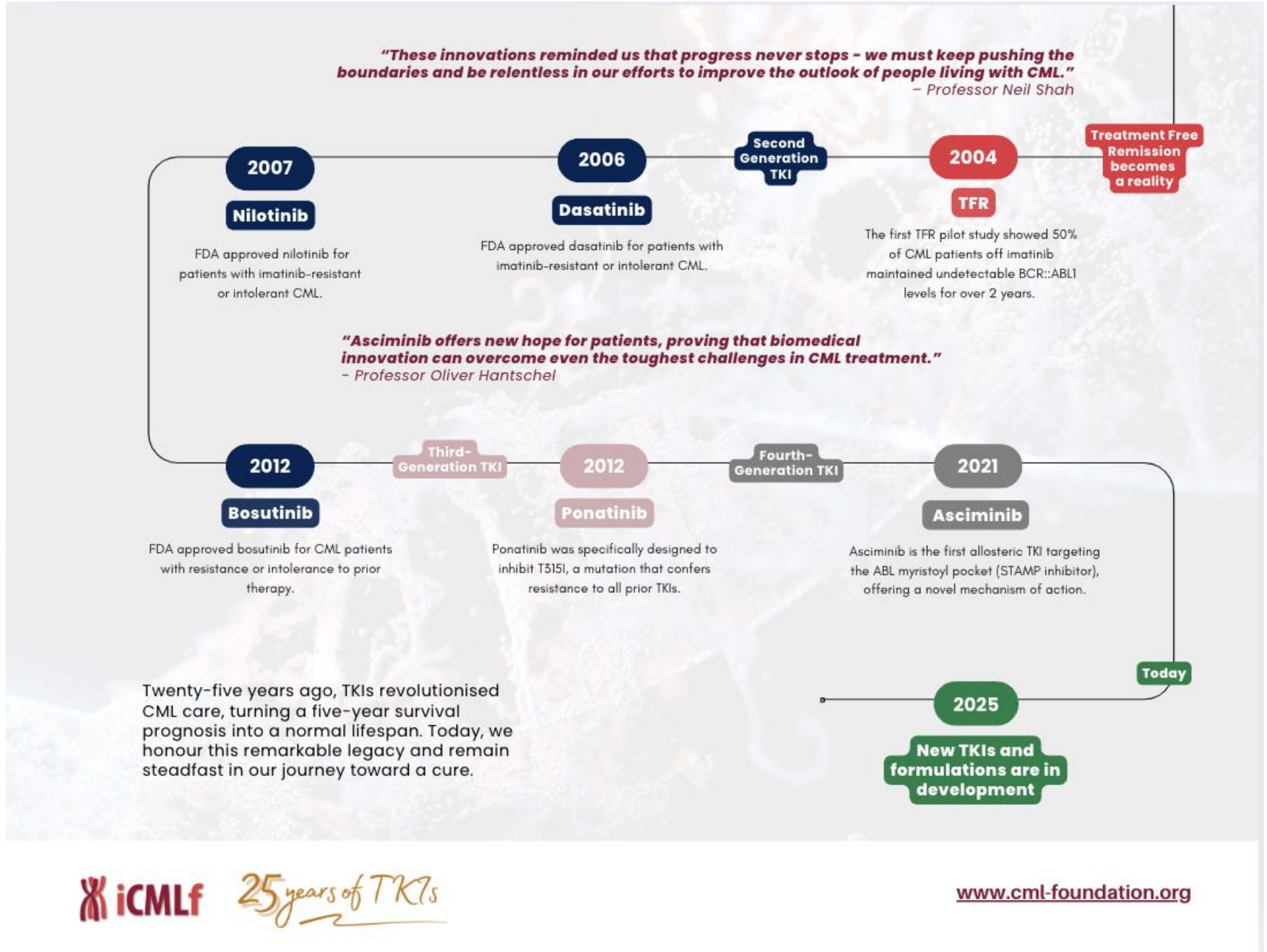
Phase II & III trials

Phase II and III trials demonstrated dramatic improvements in major molecular response and complete cytogenetic response rates in chronic-phase CML patients.

2001

Imatinib

FDA approved imatinib for the treatment of CML.



iCMLf 25 years of TKIs

www.cml-foundation.org

Advanced-Phase Challenges

Treating blast-phase CML is complex and requires combining Tyrosine Kinase Inhibitor (TKI) with advanced therapies—a challenge in low-resource areas.

#CureCML #WCMLD25

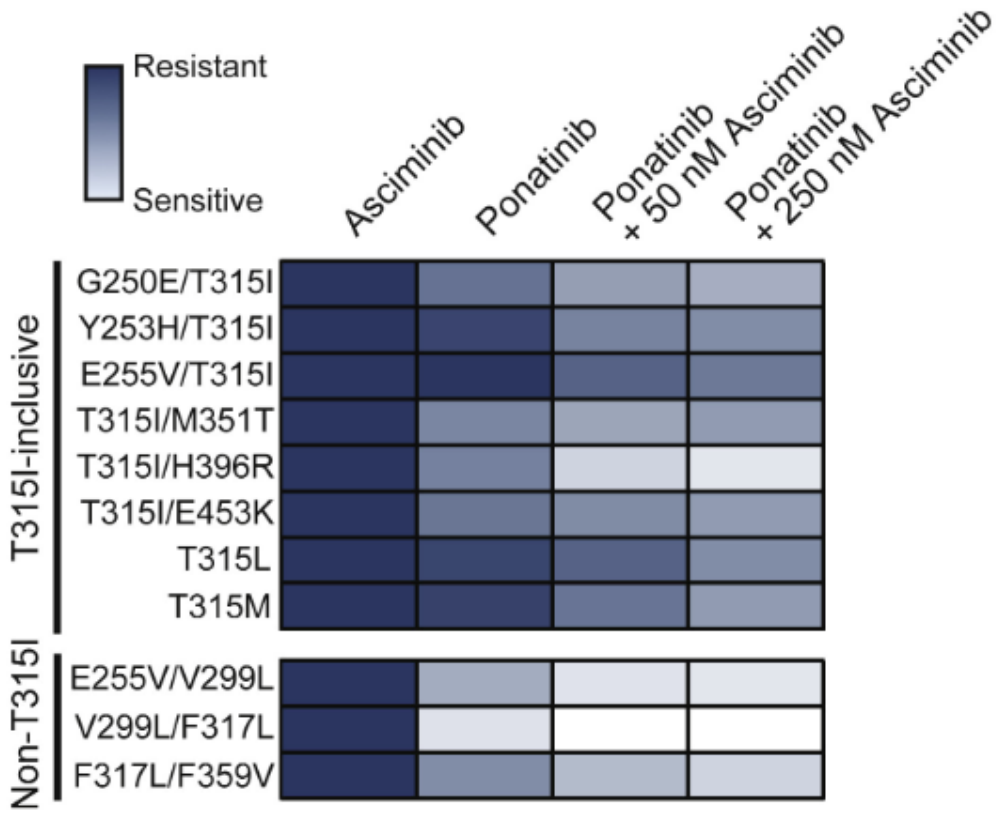
World CML Day
22 SEPTEMBER

ASCIMINIB

STAMP inhibitor (Specifically Targeting the ABL Myristoyl Pocket)

- Effectiveness in heavily pretreated CML patients in CP, including those with the BCR::ABL1 T315I mutation or those who experienced ponatinib failure
- Efficacy in patients who progressed to blast phase while on ponatinib
- A robust synergistic antileukemic effect was observed with the combination of ponatinib and asciminib in CML-BC cell lines and CML-BC stem cells carrying the BCR::ABL1 T315I mutation
  - Evidence also in murine Ba/F3 cells expressing T315I-inclusive BCR::ABL1 compound mutations, both *in vitro* and *in vivo*.

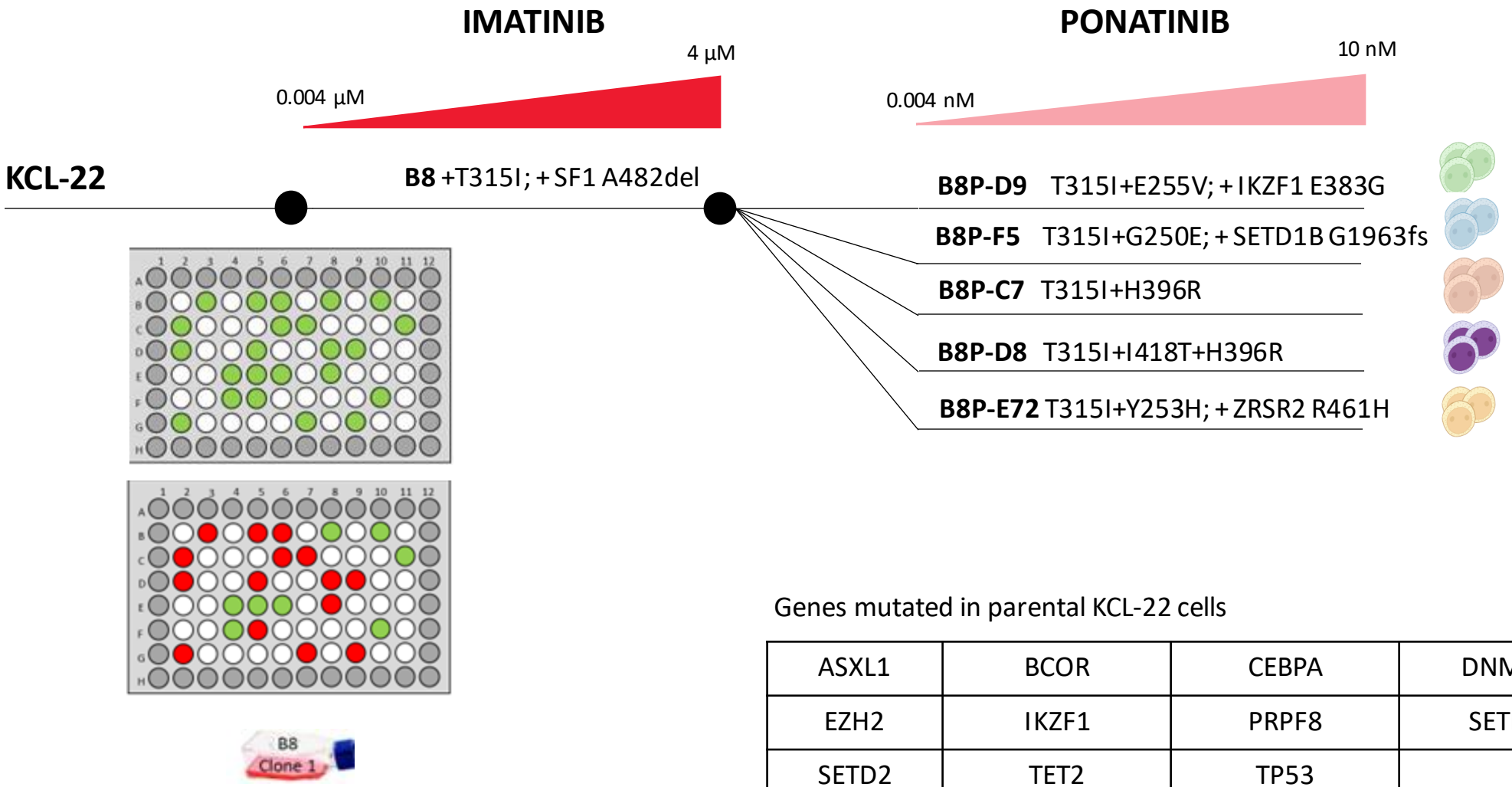
Heatmap summary of TKI sensitivities in cellular proliferation assays for Ba/F3 cells expressing BCR::ABL1 compound mutants.



Hughes T eta al. N. Engl J Med. 2019;381:2315–26; Tomassetti S et al. Clin Case Rep. 2022;10:e6478; Gleixner KV, et al. Am J Cancer Res. 2021;11:4470–84;

Eide CA, et al. Cancer Cell. 2019;36:431–43.

Establishment of imatinib/ponatinib- cross-resistant clones of myeloid CML-BC

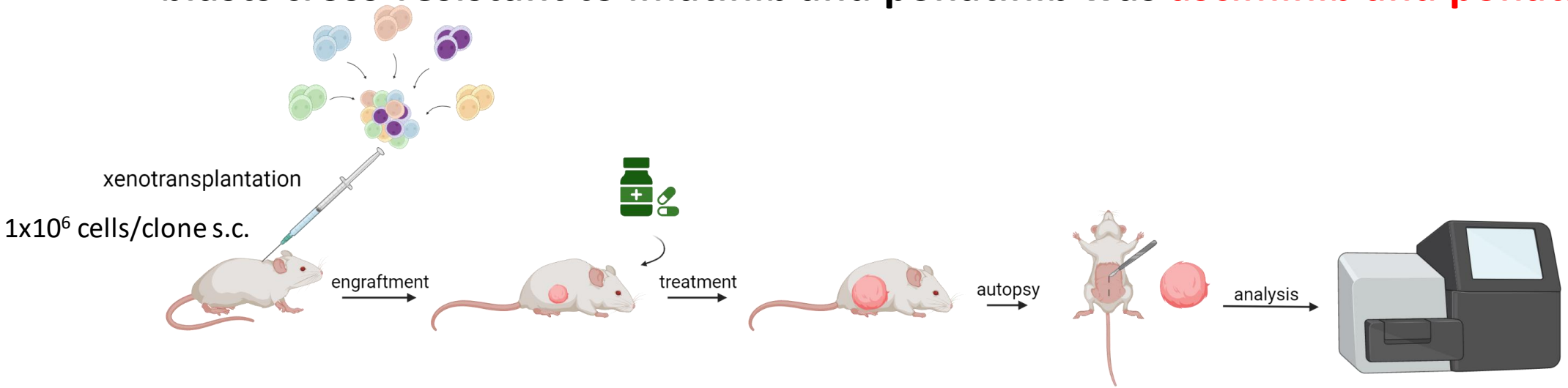


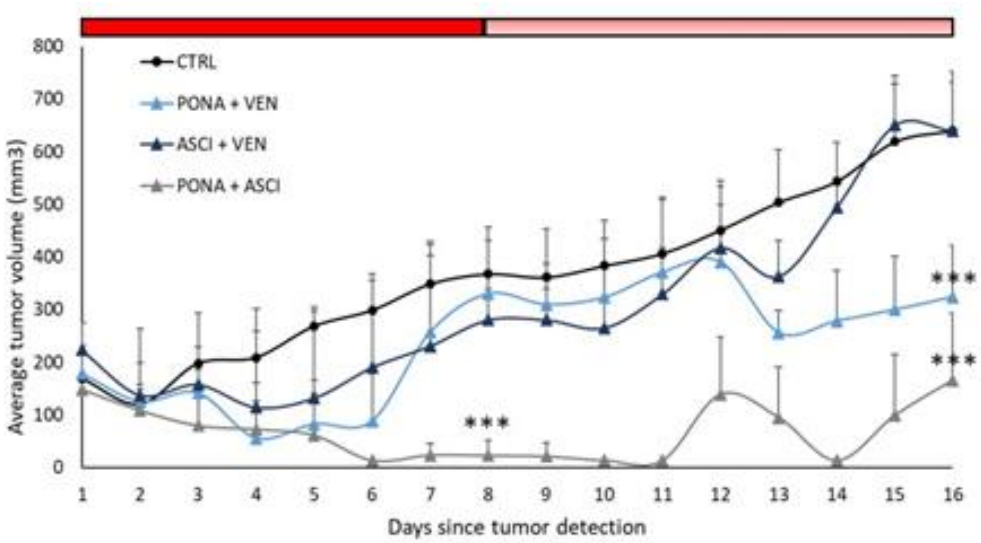
Genes mutated in parental KCL-22 cells

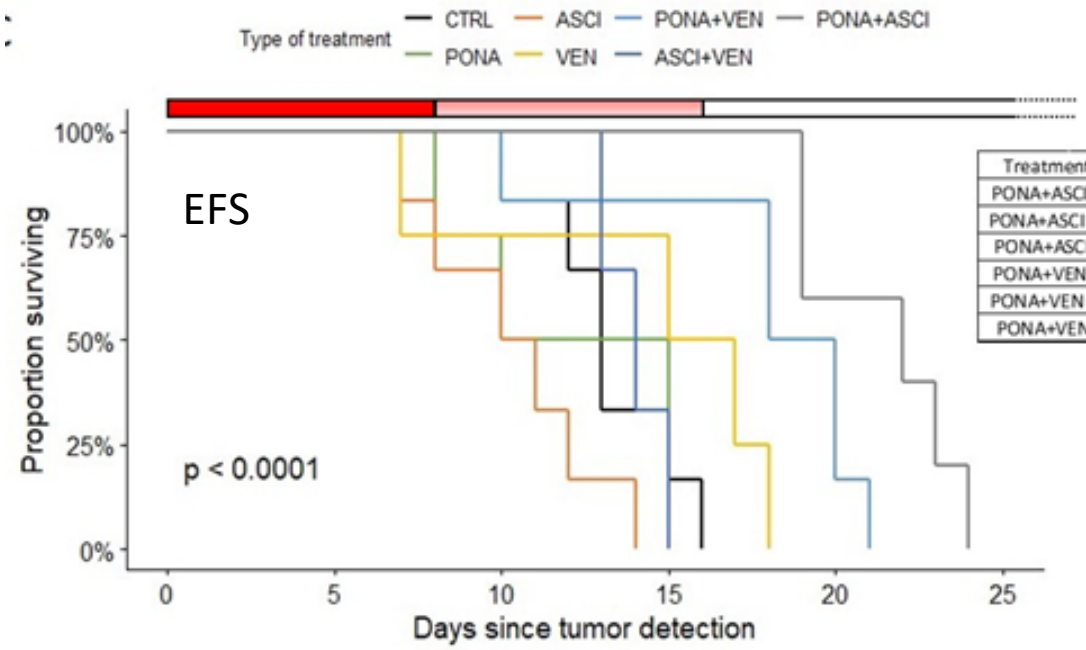
ASXL1	BCOR	CEBPA	DNMT3A
EZH2	IKZF1	PRPF8	SETD1B
SETD2	TET2	TP53	

Curik N et al. Leukemia 2024

The most effective combination therapy of CDX model of mixed clones of myeloid CML blasts cross-resistant to imatinib and ponatinib was asciminib and ponatinib







Treatment groups	Hazard ratio	P value
PONA+ASCI vs. CTRL	0.022 [0.003;0.161]	0.0002
PONA+ASCI vs. PONA	0.018 [0.002;0.147]	0.0002
PONA+ASCI vs. ASCI	0.007 [0.001;0.061]	<0.0001
PONA+VEN vs. CTRL	0.064 [0.012;0.356]	0.0017
PONA+VEN vs. PONA	0.053 [0.008;0.332]	0.0017
PONA+VEN vs. VEN	0.221 [0.052;0.939]	0.0409

The full red line - indicates the daily dosing period.
The paler red line indicates the period of intermittent regime.
The white line indicates the period without treatment.

Curik N et al. Leukemia 2024

Asciminib shows clinical benefit as initial therapy and in subsequent lines following TKI failure

- Hochhaus A, et al. **Asciminib in newly diagnosed** chronic myeloid leukemia. N Engl J Med. 2024
- Yeung DT, et al. **Asciminib** monotherapy **as frontline treatment** of chronic-phase chronic myeloid leukemia: results from the ASCEND study. Blood.
- Hochhaus A et al.: **Asciminib vs bosutinib** in chronic-phase chronic myeloid leukemia **previously treated with at least two tyrosine kinase inhibitors**: longer-term follow-up of ASCEMBL. Leukemia 2023
- Mauro MJ, et al. **Asciminib** monotherapy in patients with CML-CP **without BCR::ABL1 T315I mutations treated with at least two prior TKIs**: 4-year phase 1 safety and efficacy results. Leukemia 2023.

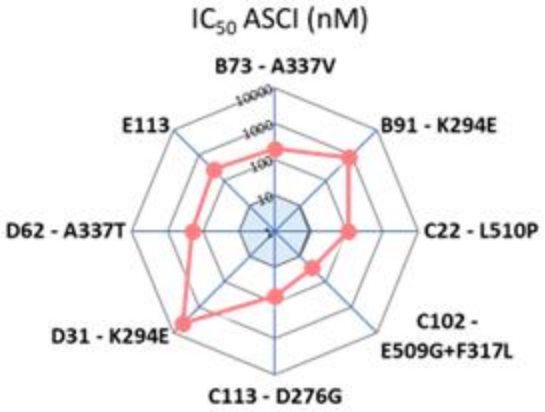
Recommended tyrosine kinase inhibitors in case of BCR::ABL1 mutations

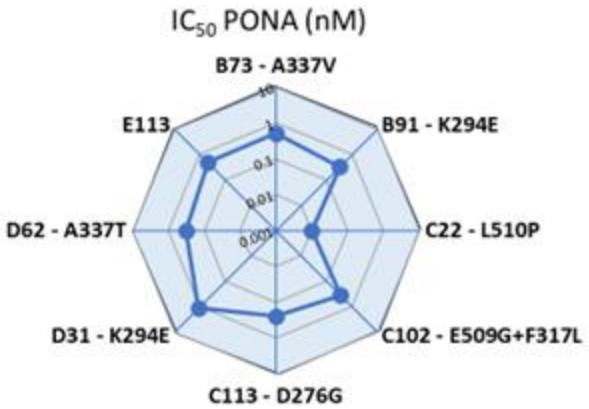
M244V	Nilotinib, dasatinib, bosutinib, ponatinib
Y253H	Dasatinib, bosutinib, ponatinib, asciminib
E255K/V	Dasatinib, ponatinib, asciminib
V299L	Nilotinib, ponatinib, asciminib
T315I	Ponatinib, asciminib
F317L/V/I/C, T315A	Nilotinib, bosutinib, ponatinib, asciminib
F359V/I/C	Dasatinib, ponatinib
A337V/T, L340Q, A344P, A433D, G463D/S, P465S/Q, V468F, F497L, I502L/N, V506L/M	Any ATP-competitive TKI

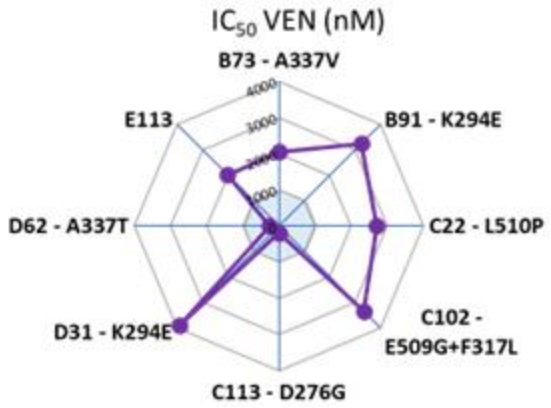
Apperley J et al. Leukemia 2025

Establishment of asciminib resistant myeloid CML blast cells

Clone	BCR::ABL1 mutations (transcript)	BCR::ABL1 mutations (HGVS)	Mutations in other leukemia-related genes (DNA custom panel)	Mutations in other leukemia-related genes (HGVS)
C22	L510P	L510P ABL1(NM_005157.6):c.1529T>C		
E113	-		**NOTCH1 Q862X**	NOTCH1(NM_017617.5):c.2584C>T
C102	E509G + F317L	E509G ABL1(NM_005157.6):c.1526A>G; F317L ABL1(NM_005157.6):c.951C>G		
D31	K294E	K294E ABL1(NM_005157.6):c.880A>G	**GATA2 A257D**; **EZH1 A279T**; ASXL1 S663R; TET2 P20Q	GATA2(NM_032638.5):c.770C>A; EZH1(NM_001991.5):c.844G>A; ASXL1(NM_015338.6):c.1989C>G; TET2(NM_001127208.3):c.59C>A
B73	A337V	A337V ABL1(NM_005157.6):c.1010C>T		
D62	A337T	A337T ABL1(NM_005157.6):c.1009G>A	**SF3B1 Q891R**; **TP53 M340V**; **ZRSR2 Y271C**	SF3B1(NM_012433.4):c.2672A>G; TP53 (NM_000546.6):c.1018A>G; ZRSR2(NM_005089.4):c.812A>G
B91	K294E	K294E ABL1(NM_005157.6):c.880A>G	**GATA2 R396Q**	GATA2(NM_032638.5):c.1187G>A
C113	D276G	D276G ABL1(NM_005157.6):c.827A>G	ASXL1 S663R; ZRSR2 H369L	ASXL1(NM_015338.6):c.1989C>G; ZRSR2(NM_005089.4):c.1106A>T







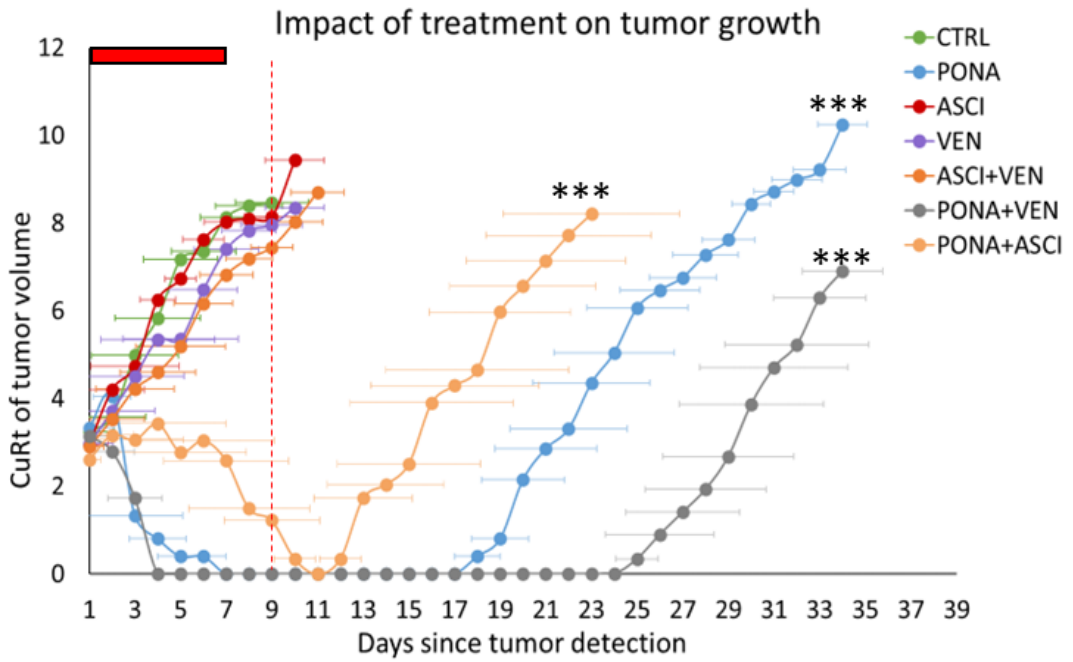
Curik N et al. Leukemia 2025

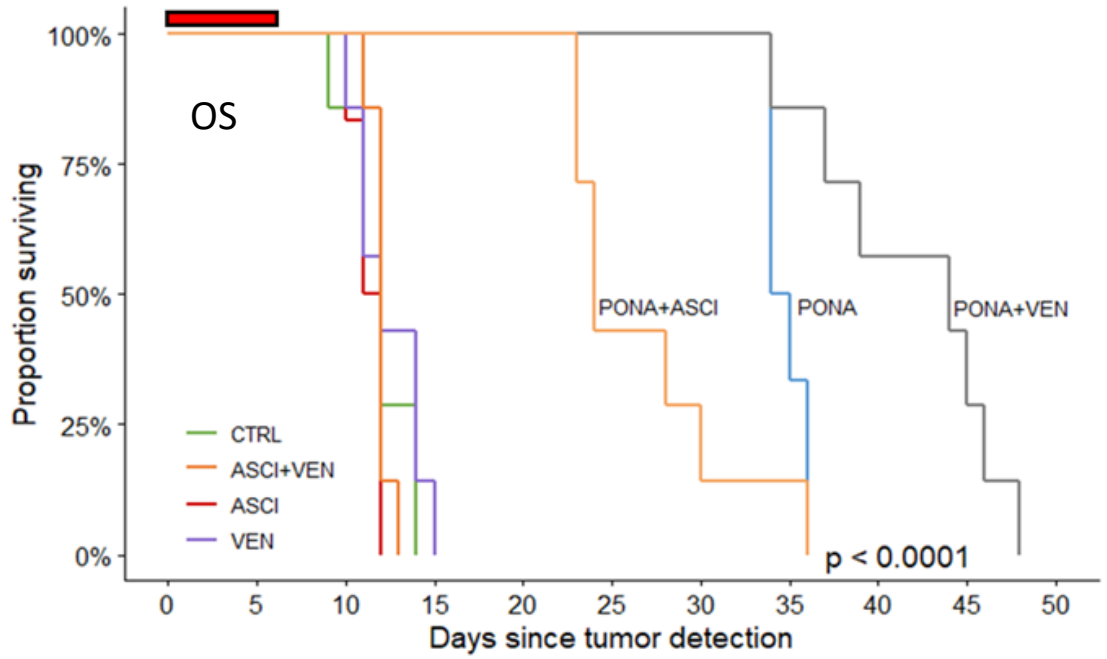
Treatment of preclinical CDX model of mixed asciminib-resistant CML myeloid blasts

- **Ponatinib** showed efficacy, significantly delaying tumor growth and improving overall survival.
- The most effective therapy was combination **ponatinib and venetoclax**

Venetoclax monotherapy was ineffective

➢ Highliths the necessity to target **BCR::ABL1**





The full red line - indicates the daily dosing period.

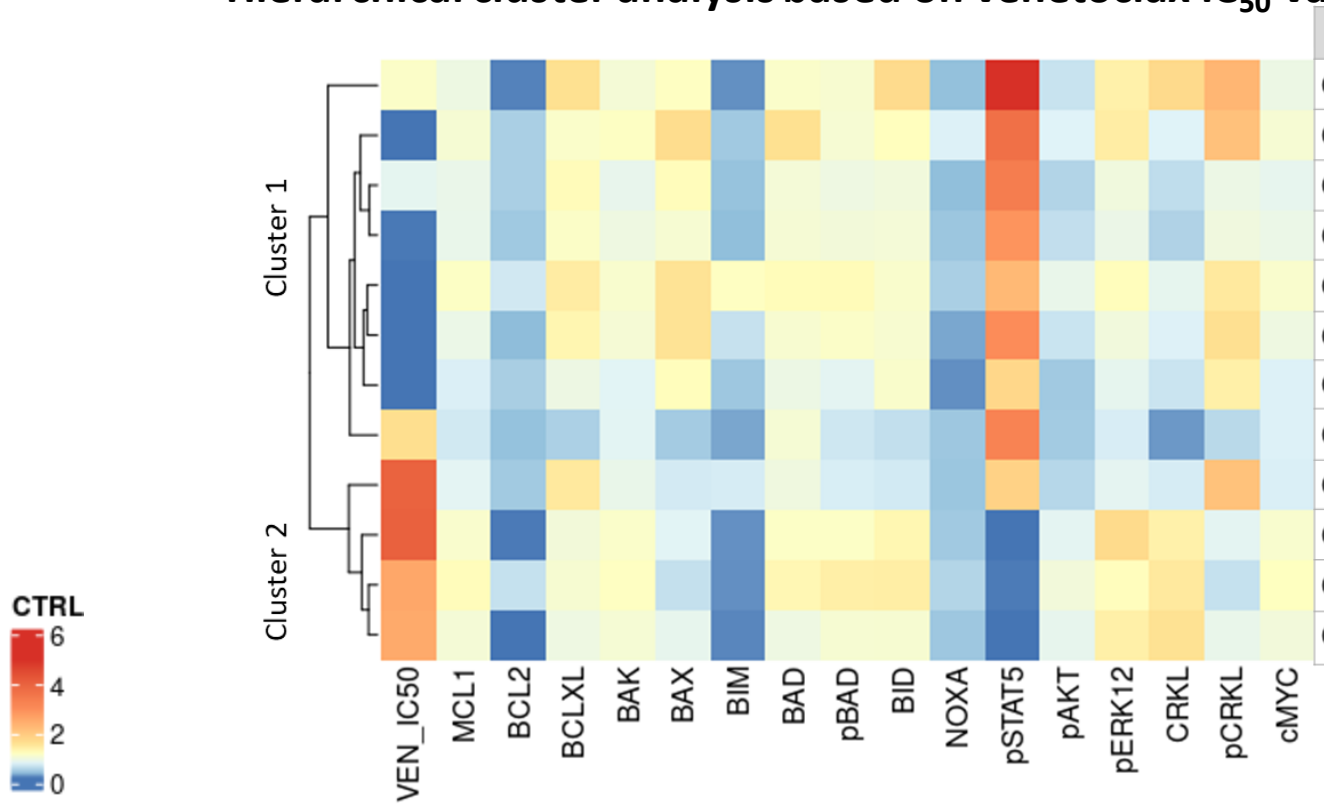
Curik N et al. Leukemia 2025

Sensitivity of CML myeloid blast cells to venetoclax

- Sensitivity varies depending on the **oncogenic driver.**

- Apoptotic panel mass cytometry was used to analyze protein expression in:
  - **Imatinib-resistant clones (Clones 1–4)**
  - **Imatinib/ponatinib cross-resistant clones (Clones 1P1–1P6, 3P2, 3P3)**
- Analysis performed **prior to venetoclax** *in vitro* testing.

Hierarchical cluster analysis based on venetoclax IC_{50} values and protein expression profiles



Clone	BCR::ABL1	KRAS
Clone 1P5	T315I + G250E	
Clone 1P4	T315I + H396R	
Clone 1P3	T315I + E255V	
Clone 1	T315I	
Clone 1P2	T315I + I418T + H396R	
Clone 1P6	T315I + Y253H	
Clone 1P1	T315I	
Clone 4	E255K	
Clone 2	Y253H	
Clone 3P2		G12D
Clone 3P3		G12D
Clone 3		G12D

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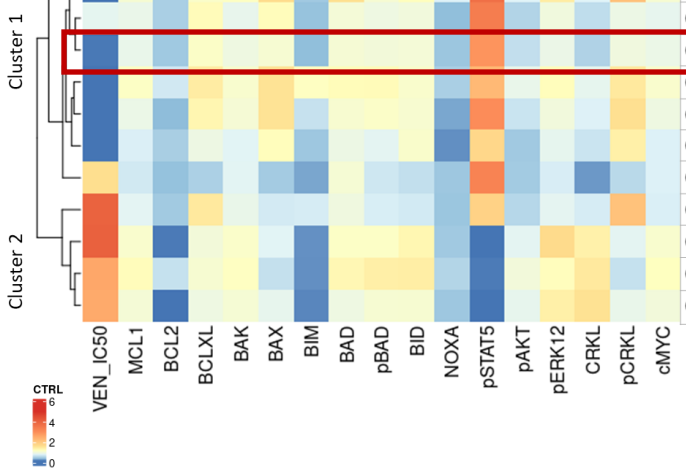
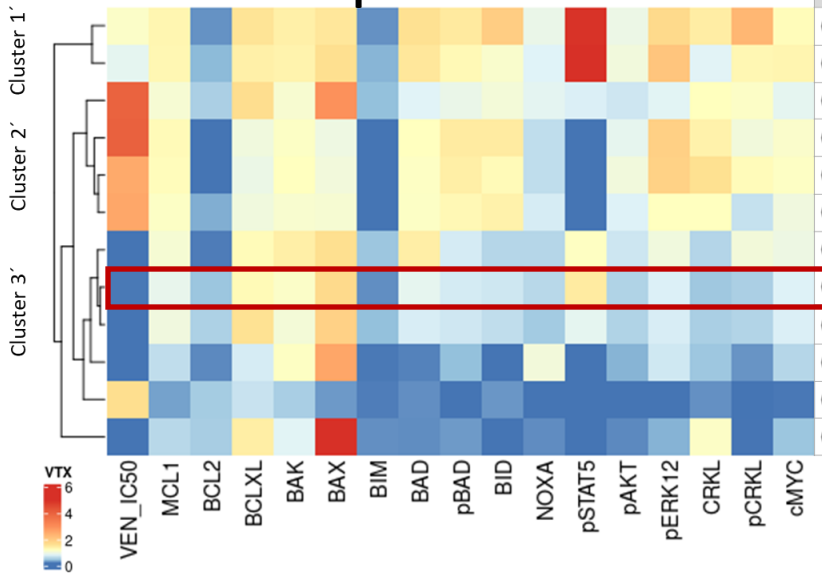
Prior to venetoclax exposure



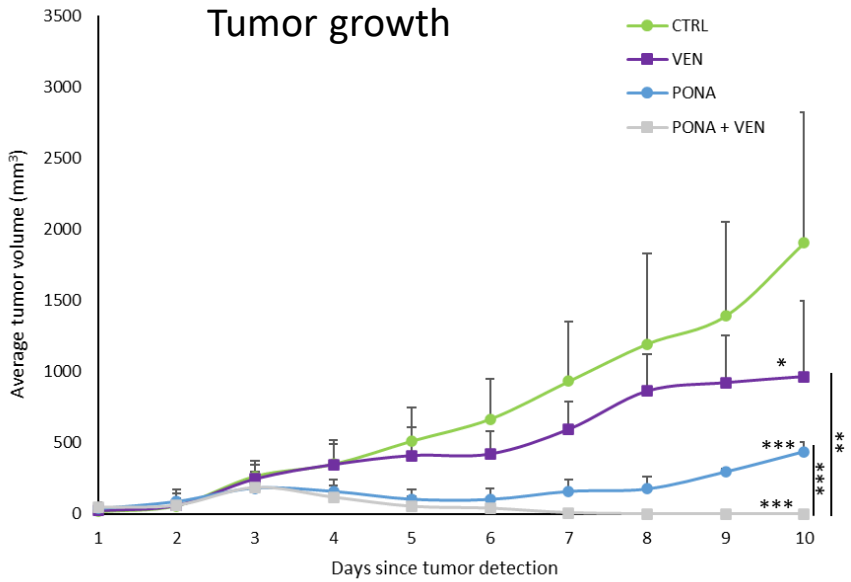
Clone	BCR::ABL1	KRAS
Clone 1P5	T315I + G250E	
Clone 1P4	T315I + H396R	
Clone 1P3	T315I + E255V	
Clone 1	T315I	
Clone 1P2	T315I + I418T + H396R	
Clone 1P6	T315I + Y253H	
Clone 1P1	T315I	
Clone 4	E255K	
Clone 2	Y253H	
Clone 3P2		G12D
Clone 3P3		G12D
Clone 3		G12D

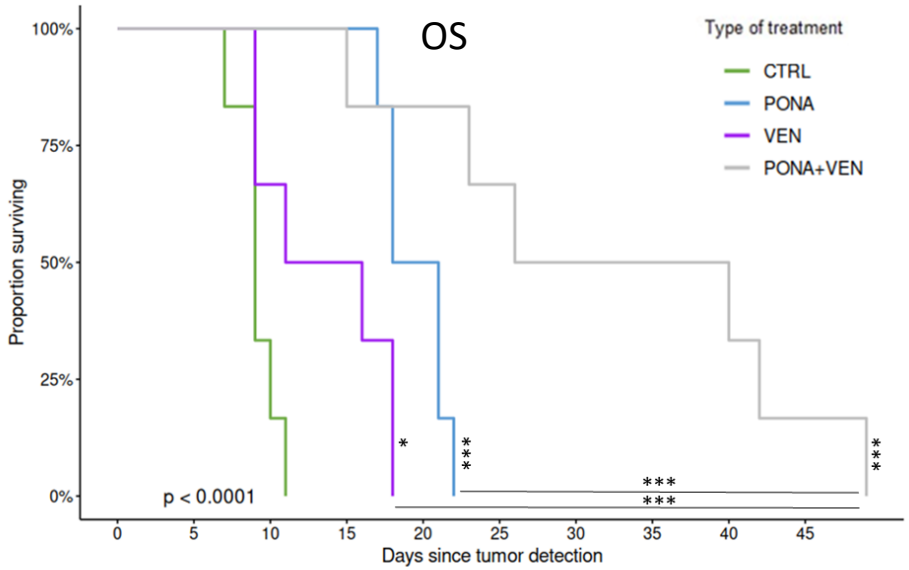
After venetoclax exposure



Clone	BCR::ABL1	KRAS
Clone 1P5	T315I + G250E	
Clone 1P3	T315I + E255V	
Clone 2	Y253H	
Clone 3P2		G12D
Clone 3		G12D
Clone 3P3		G12D
Clone 1P6	T315I + Y253H	
Clone 1	T315I	
Clone 1P2	T315I + I418T + H396R	
Clone 1P4	T315I + H396R	
Clone 4	E255K	
Clone 1P1	T315I	

Treatment of CDX model with T315I-mutated BCR::ABL1 (Clone 1, imatinib-resistant)

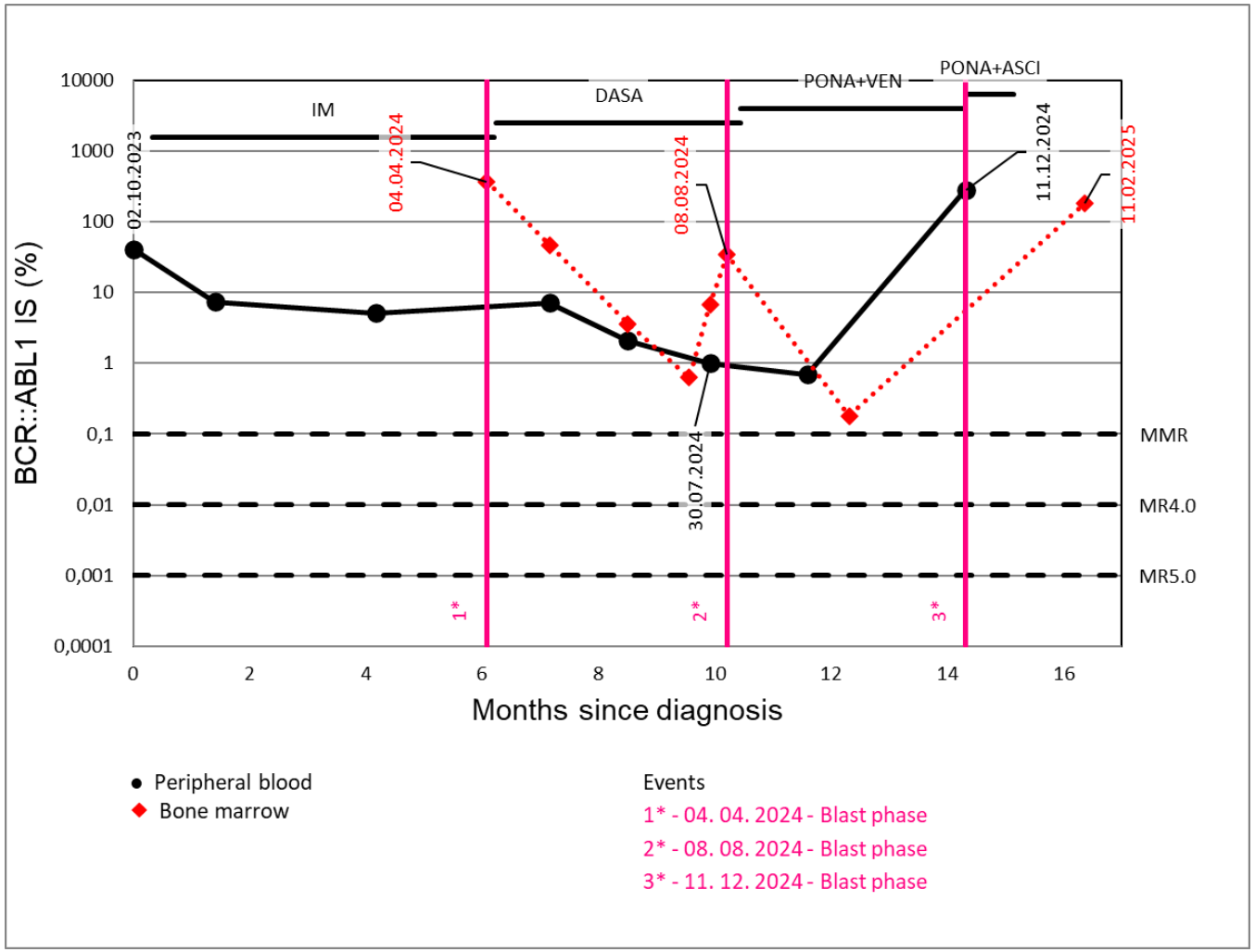




Laznicka et al. manuscript in preparation

Combination therapy of the 2nd and 3rd relapses

- A 57-year-old male was diagnosed with CML in the chronic phase
- EUTOS, ELTS, Sokal, and Hasford scores were all low
- Karyotype of 46,XY,t(9;22)(q34;q11.2)



The 3rd blast phase therapy:

Detected mutations in BCR::ABL1 – compound mutation T315I + E255V and mutation F311L

- Treatment was modified to asciminib 40 mg/day and ponatinib 15 mg/day leading to a reduction in peripheral blasts to 1.7% within three weeks.
- Unfortunately, the patient developed severe pancytopenia and was later admitted with influenza A pneumonia and sepsis that were successfully treated.
- The patient continued on solo therapy with asciminib 40 mg/day.
- 0.6 % blasts were found in PB at 04/03/2025.

Is BCR::ABL1 the key target in all CML patients?

- Yes, BCR::ABL1 is the primary target in all CML patients.
- Effective inhibition of BCR::ABL1 activity is necessary.

However, in advanced stages of CML:

- BCR::ABL1 is not the only oncogenic driver.
- Example: mutated **KRAS**.
  - KRAS G12C can be targeted by **sotorasib** or **adagrasib**.
  - Pan-KRAS inhibitors are under development (Kim D et al., *Nature*, 2023).
- The effectiveness of dual targeting **BCR::ABL1 and KRAS G12D** requires investigation (e.g., Clone 3).

***In vitro* and *in vivo* data show effectiveness of combination therapy:**

1. Asciminib + Ponatinib

Targets BCR::ABL1 with compound mutations.

2. TKI + Venetoclax

Effective BCR::ABL1 inhibition (mutated or unmutated) sensitizes CML cells to venetoclax.

Clinical trials on combination therapy TKI and venetoclax

NCT04188405 (M.D. Anderson Cancer Center)
Decitabine, Venetoclax, and Ponatinib for the Treatment of Philadelphia Chromosome-Positive Acute Myeloid Leukemia or Myeloid Blast Phase or Accelerated Phase Chronic Myelogenous Leukemia

NCT02689440 (M.D. Anderson Cancer Center)
Dasatinib and Venetoclax in Treating Patients With Philadelphia Chromosome Positive or BCR-ABL1 Positive Early Chronic Phase Chronic Myelogenous Leukemia

NCT05701215 University of Jena
Venetoclax After TKI to Target Persisting Stem Cells in CML (VARIANT)

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European Treatment & Outcome Study
EUTOS 2022
Chronic Myeloid Leukemia