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Resistant or recurrent CML and prospective discontinuation

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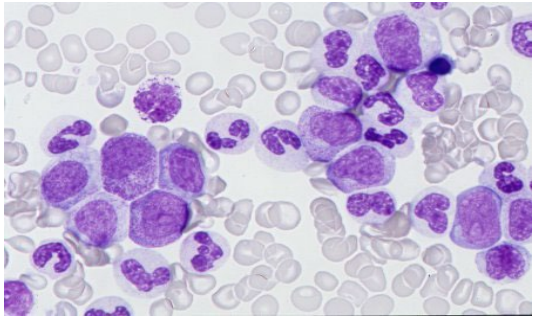
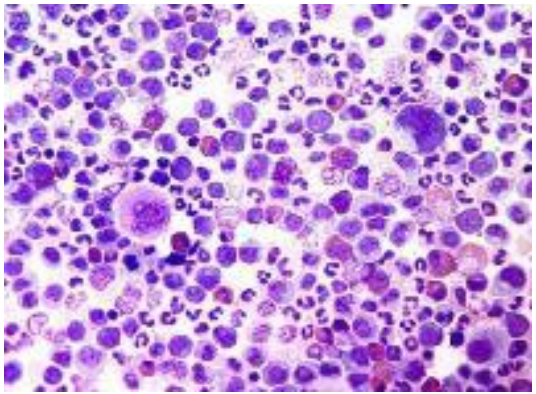
Investigational agents will not be discussed: Olverembatinib HQP1351 (GZD824); ELVN-001 – pure ABL1 inhibitor

Learning Objectives for Chronic Myeloid Leukemia

- Identify common causes of resistance to initial tyrosine-kinase inhibitor (TKI) therapy.
  - Assessments of side-effects and adherence
  - Management strategies
- Describe mechanisms of recurrence of CML in patients with initial good responses.
  - Known acquired resistance mutations
- Attempting treatment-free remission





Comparison of Sokal and ELTS prognostic scores (EUTOS Long Term Survival score)

N = 5154 patients	Low Risk		Intermediate Risk		High Risk	
	Sokal	ELTS	Sokal	ELTS	Sokal	ELTS
% of patients	38%	55%	38%	28%	23%	13%
10-yr OS	89%	88%	81%	79%	75%	68%
6-yr Leukemia-related death	3%	2%	4%	5%	8%	12%

- ELTS: EUTOS score for **long-term survival considering leukemia-related death**; age given in years; spleen size in cm below costal margin measured by palpation; blasts in percent of peripheral blood differential; platelet count 10E9/L. All values are pre-treatment.
- To calculate Sokal and ELTS scores, go to http://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html ; or UpToDate.

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Pfirrmann et al. Leukemia. 2020; 34(8): 2138.

2020 European LeukemiaNet Recommendations for newly diagnosed CML

Time:	Optimal Response	Warning	Failure
3 months	BCR/ABL ≤10%	BCR/ABL >10%	>10% if confirmed
6 months	BCR/ABL <1%	BCR/ABL >1-10%	BCR/ABL >10%
12 months	BCR/ABL ≤0.1% (MMR)	BCR/ABL >0.1-1%	BCR/ABL >1%
Thereafter, >12 months	Major Molecular Response [MMR] or better; Tolerating the drug; good adherence; monitored every 3 mos	BCR/ABL >0.1% -7 or del(7q) in Ph- cells	BCR/ABL >1% ABL mutations. New chromosome abnormalities

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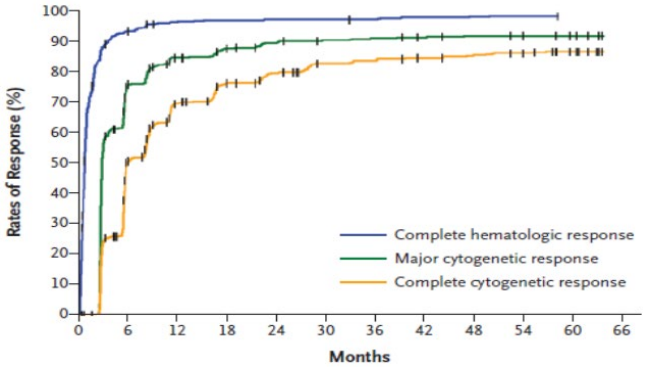
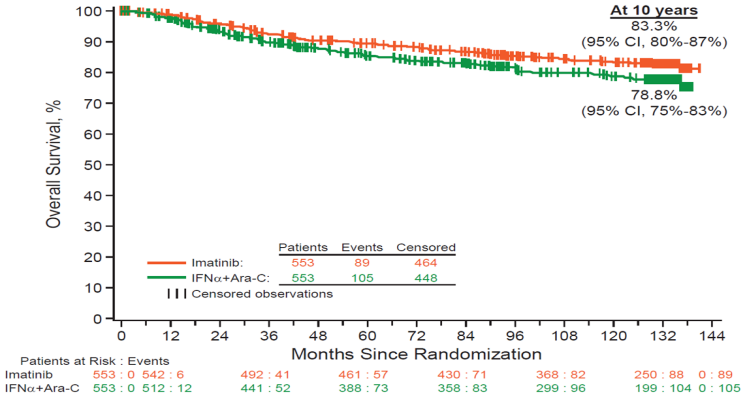
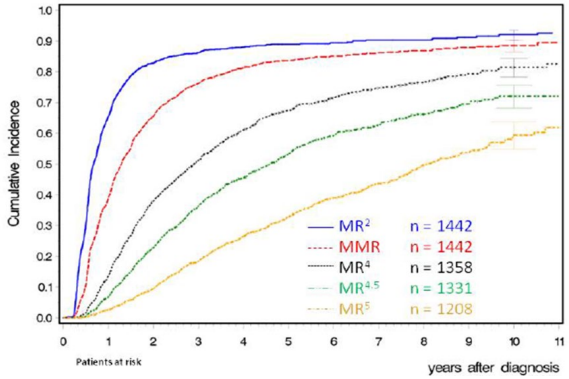
Baccarani et al. Blood 2013 Aug 8; 122(6): 872-884
Hochhaus, et al. Leukemia 2020 Apr; 34(4): 966-984

The IRIS Trial: Imatinib vs Interferon + AraC







German CML IV trial

Efficacy of imatinib over 10 years
Kalmanti et al. German CML Study Group.
Leukemia 2015

BJ Druker et al. New Engl J Med 2006;355:2408-17.
A Hochhaus, RA Larson, F Guilhot, et al. New Engl J Med 2017

Common causes of “clinical failure” within 1 year or afterwards

- Primary resistance (fail to achieve hematologic remission or early molecular response)
  - Stopping TKI therapy for cytopenias
  - Non-adherence
  - Metabolic effects of drug interactions or inhibitors
- Secondary resistance (recurrence after initial response)
  - High-risk features (Sokal or ELTS score)
  - ASXL1 mutation; compound mutations
  - Emergence of resistance mutations

Primary resistance

- Non-adherence by patient or physician
  - Lack of insurance or high out-of-pocket costs (patient-assistance programs)
  - Stopping and restarting TKI therapy due to drop in blood counts
    - “on target” effect since most hematopoiesis is Ph+ at diagnosis
    - Transfusions, growth factors (G-CSF; eltrombopag; romiplostim)
- Toxicity (mostly low grade, but often continuous)
  - Brief drug holiday (3-5 days)
  - Alter dose or schedule (e.g. imatinib, bosutinib)
  - Be slow to switch agents until clear intolerance is established
- Alterations in metabolism (drug-drug interactions)

Shoukier et al. The effect of eltrombopag in managing thrombocytopenia associated with tyrosine kinase therapy in patients with CML. Haematologica 2020

Most common side-effects from TKIs in CML (early and later)

All BCR::ABL1 TKIs	**Fatigue,** (asymptomatic) lipase elevation
Imatinib	Gastritis, diarrhea, rash, myalgia, periorbital edema
Dasatinib	Pleural and pericardial effusions, diarrhea, bleeding; vascular events, (rare) pulmonary hypertension
Nilotinib	Hyperglycemia, hypertension, rash, headache, LFT elevation; vascular events
Bosutinib	Diarrhea, LFT elevation, rash, myalgia; vascular events, effusions
Ponatinib	Dry skin, rash, LFT elevation; vascular events
Asciminib	Hypertension, rash, headache

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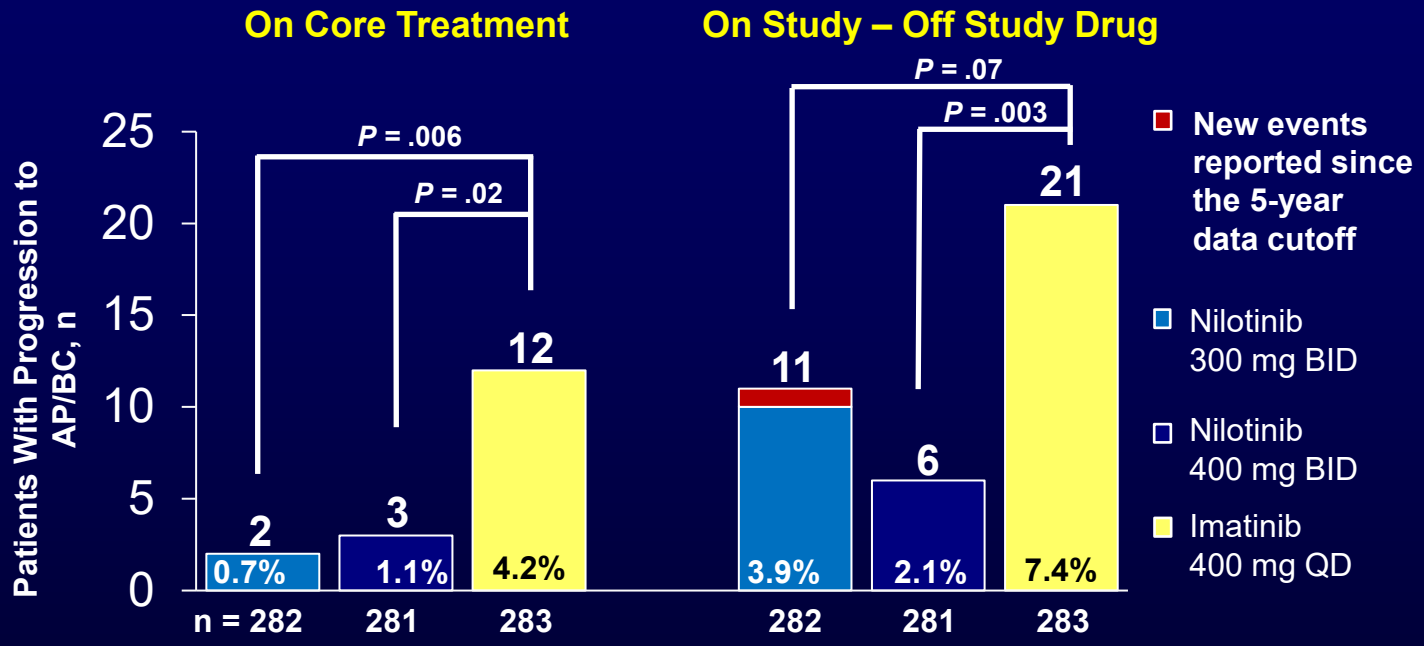
Apperley. Lancet Dec 5, 2014; Steegmann et al. Leuk Lymph 2012; 53:2351.
Lipton et al. Long-term safety review of tyrosine kinase inhibitors in CML - What to look for when treatment-free remission is not an option. Blood Reviews 2022

Secondary resistance: Recurrence of Ph+ cells after initial response

- Non-adherence by patient or physician
  - Lack of insurance or high out-of-pocket costs
  - Stopping TKI therapy due to drop in blood counts
- Emergence of resistance mutations in ABL1
  - Sequence ABL1 kinase domain if transcripts are still >10% at 3-6 months
- Compound mutations on the same allele, or polyclonal
- *ASXL1* mutation
- Switch TKI (combinations are under investigation)

Progression to Accelerated phase or Blast crisis



Phase III randomized trial of nilotinib vs imatinib for newly diagnosed chronic phase CML. ENESTnd. Hochhaus et al. Leukemia 2016; 1-11

Map of mutations in the BCR::ABL1 kinase domain reported to be resistant to imatinib

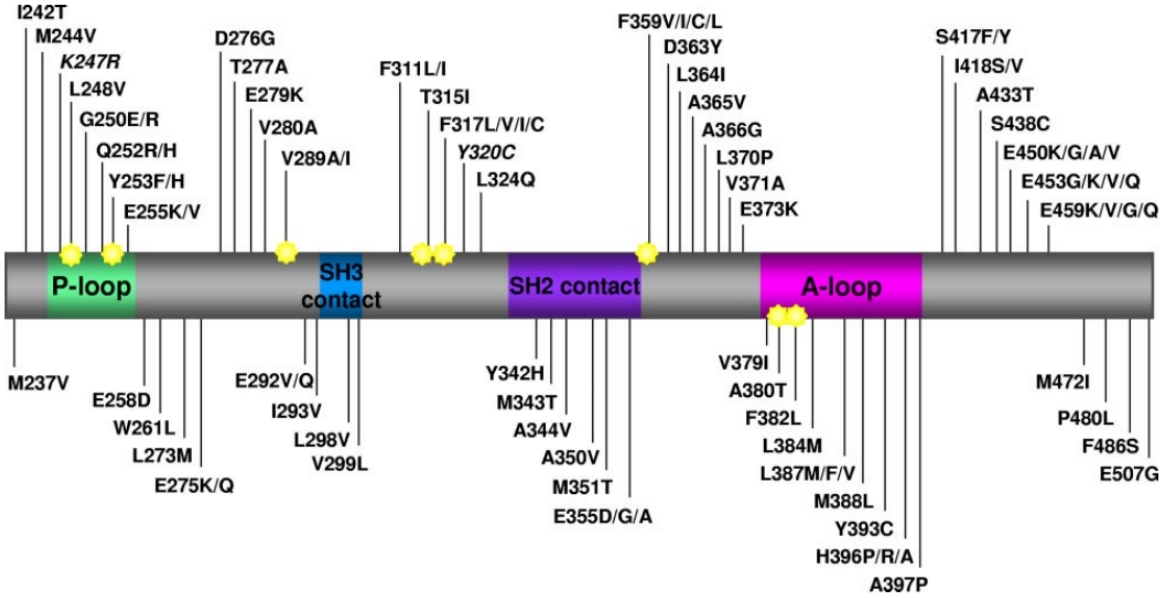


Figure 1. Map of all the amino acid substitutions in the Bcr-Abl KD identified in clinical samples from patients reported to be resistant to imatinib in published papers. Key structural motifs within the KD are indicated. P-loop indicates phosphate binding loop; SH2 contact and SH3 contact, contact regions with SH2 and SH3 domain-containing proteins; and A-loop, activation loop. Star indicates amino acid position reported to be directly involved in imatinib binding via hydrogen bonds or van der Waals interactions.[7] K247R and Y320C are in italic because they have been reported to be single nucleotide polymorphisms. Numbering of residues is according to Abl Ia isoform. Data were collated from 27 studies published between 2001 and 2009.[1-6,14,16,17,28,35,51-53,61,62,72,82-91]

Soverini et al. Blood. 2011;118(5): 1208-1215

Activity of TKIs Against 18 Imatinib-Resistant BCR/ABL Mutations

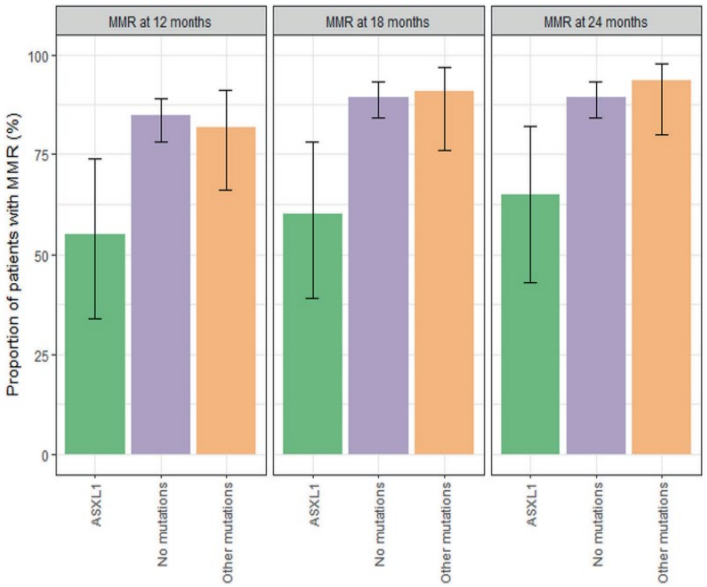
		IC_{50} fold increase (WT = 1)			
		Bosutinib	Imatinib	Dasatinib	Nilotinib
	Parental	38.31	10.78	> 50	38.43
	WT	1	1	1	1
P-LOOP	L248V	2.97	3.54	5.11	2.80
	G250E	4.31	6.86	4.45	4.56
	Q252H	0.81	1.39	3.05	2.64
	Y253F	0.96	3.58	1.58	3.23
	E255K	9.47	6.02	5.61	6.69
	E255V	5.53	16.99	3.44	10.31
C-Helix	D276G	0.60	2.18	1.44	2.00
	E279K	0.95	3.55	1.64	2.05
ATP binding region (drug contact sites)	V299L	26.10	1.54	8.65	1.34
	T315I	45.42	17.50	75.03	39.41
	F317L	2.42	2.60	4.46	2.22
SH2-contact	M351T	0.70	1.76	0.88	0.44
Substrate binding region (drug contact sites)	F359V	0.93	2.86	1.49	5.16
A-LOOP	L384M	0.47	1.28	2.21	2.33
	H396P	0.43	2.43	1.07	2.41
	H396R	0.81	3.91	1.63	3.10
	G398R	1.16	0.35	0.69	0.49
C terminal lobe	F486S	2.31	8.10	3.04	1.85

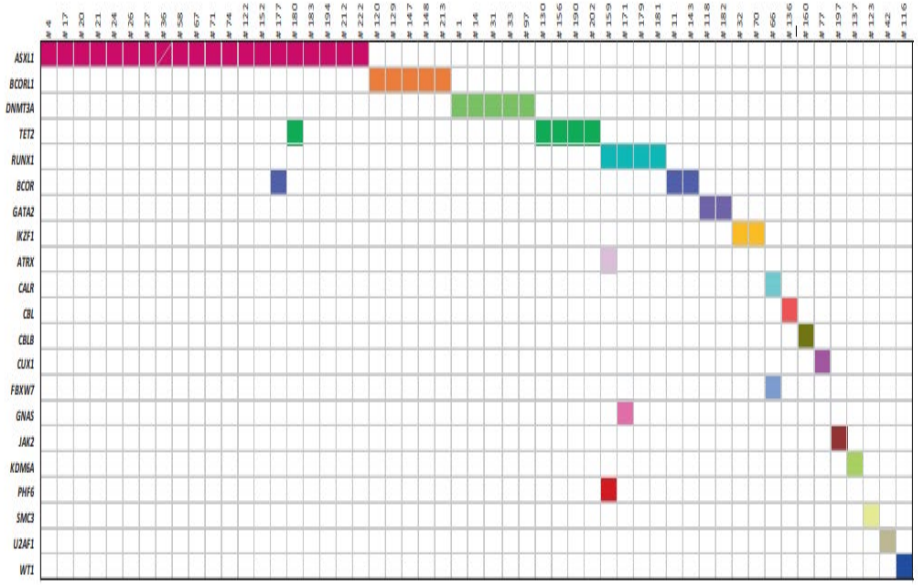
Sensitive	≤ 2
Moderately resistant	2.01–4
Resistant	4.01-10
Highly resistant	> 10

- These mutations are not detectable when chronic phase CML is first diagnosed.
- Occult subclones emerge under selective pressure from TKI therapy.

Redaelli et al.
J Clin Oncol 2009.

Somatic mutations in 222 CML patients at diagnosis with NGS evaluation





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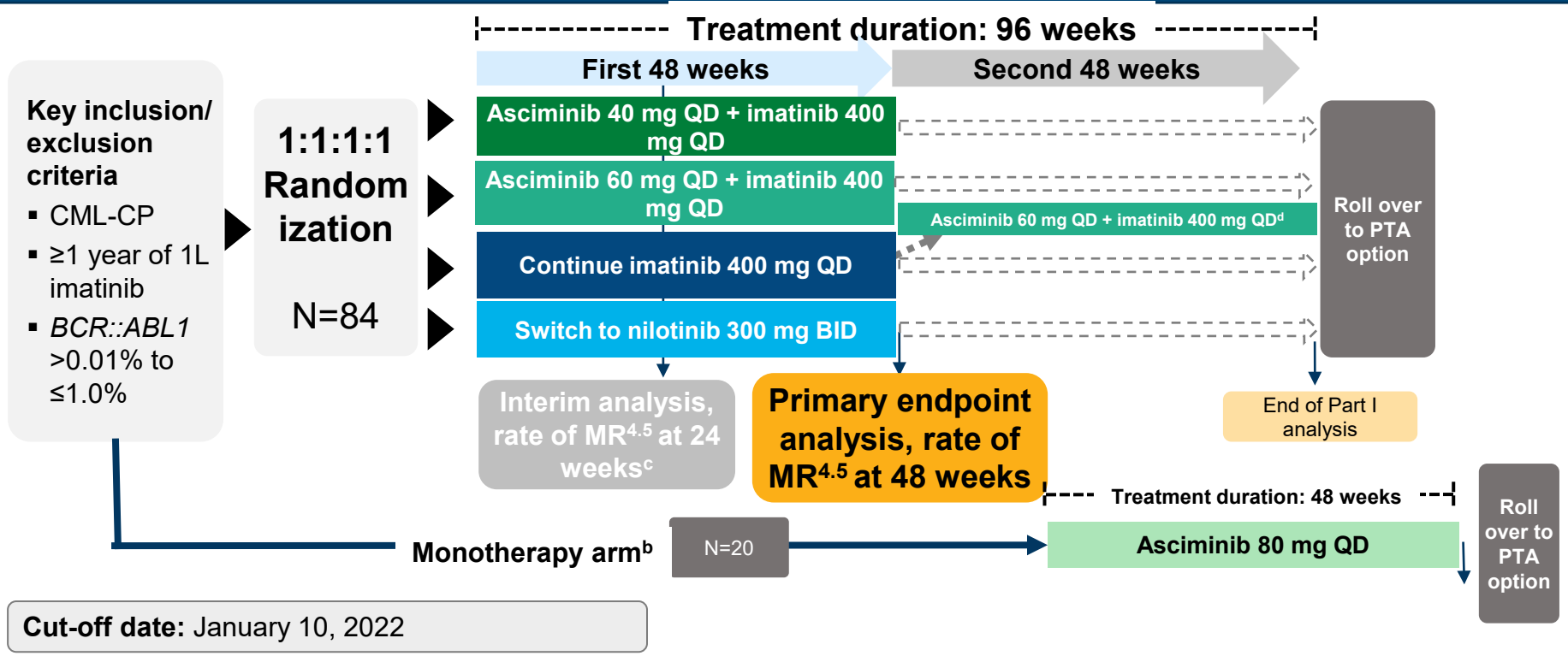
Schonfeld et al -- ASXL1 mutations predict inferior molecular response to nilotinib treatment in CML -- Leukemia 2022; 36: 2242-49

ASC4MORE Study Design (Cortes et al. ASH 2022. Abstract #80)



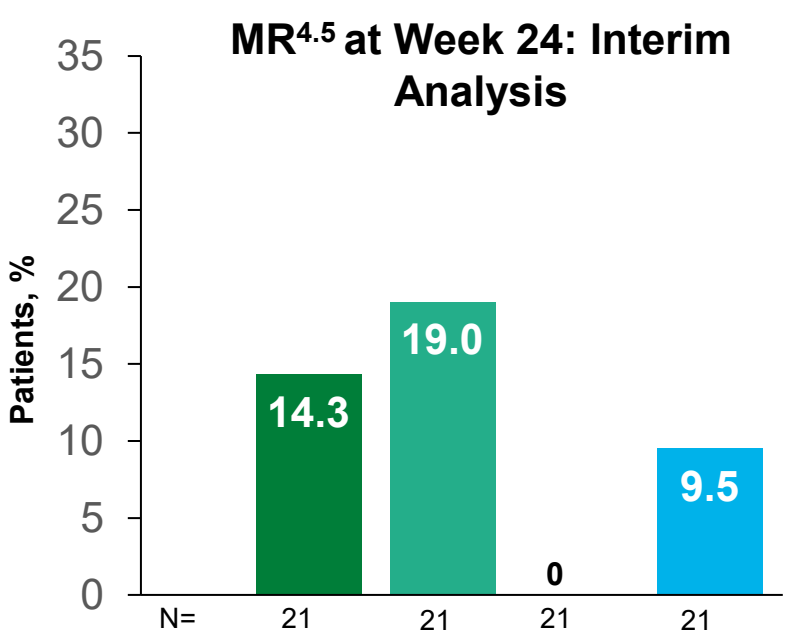
Cut-off date: January 10, 2022

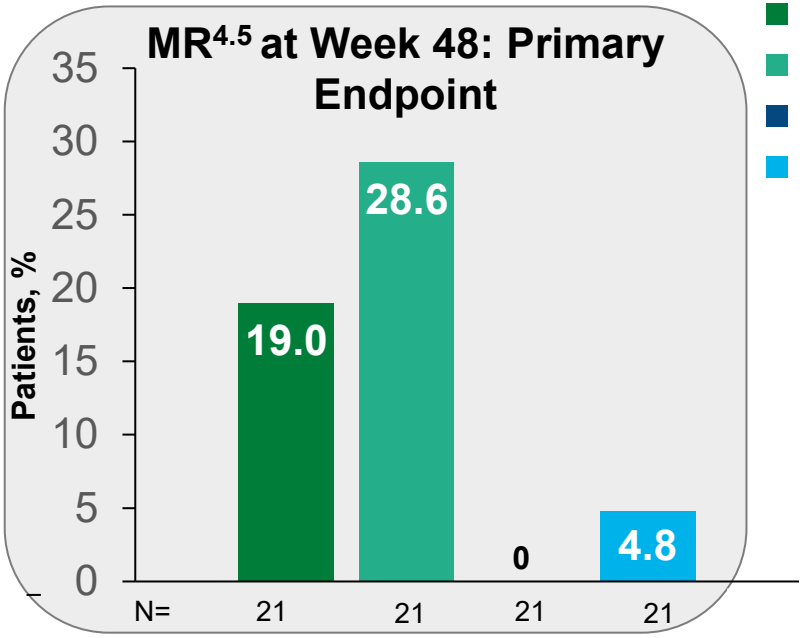
BID, twice daily; IS, International Scale; $MR^{4.5}$, *BCR::ABL1*^{IS} ≤0.0032%; PTA, post-trial access; QD, once daily.

[a] With no change of dose in the past 3 months. [b] The monotherapy arm was added in a protocol amendment on July 12, 2022 to estimate the safety and efficacy of single agent asciminib and is now enrolling. [c] Patients may discontinue treatment at the time of interim analysis if there is excessive toxicity without added benefit is observed in 1 of the observational arms. Patients who choose to discontinue in the asciminib 60 mg add-on arm will have the opportunity to continue the study in the asciminib 40 mg add-on arm if the investigator believes it is in the best interest of the patient. [d] Crossover allowed for patients who have not achieved $MR^{4.5}$ (not included in this analysis).

Oral presentation at: 64th ASH Annual Meeting & Exposition. December 10-13, 2022; New Orleans, LA, and virtual.

Deep Molecular Response ($MR^{4.5}$) at Weeks 24 and 48





ASC 40 + IMA
ASC 60 + IMA
Continued IMA
Switch to NIL

- 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

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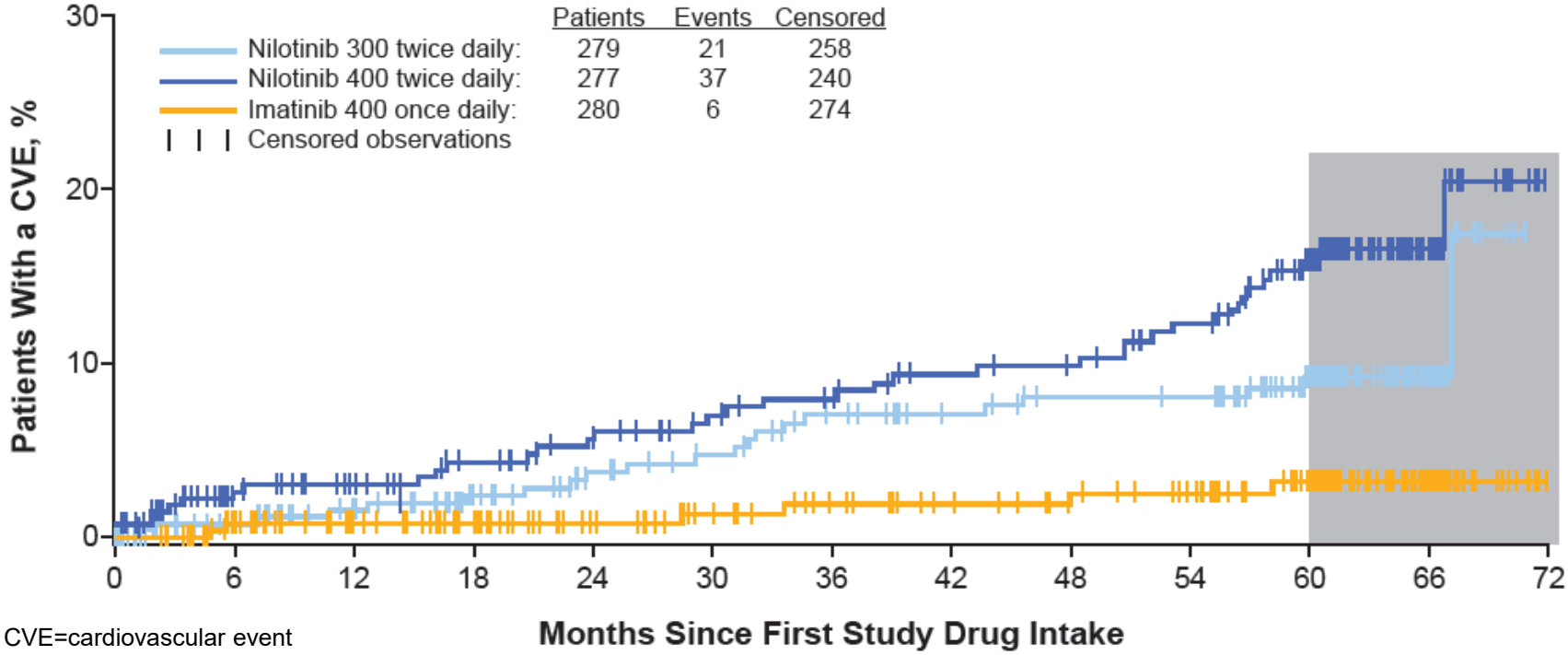
Stopping TKI Therapy in CML

Why discontinue tyrosine kinase inhibitor (TKI) therapy?

Incidence of Adverse Vascular Events on ENESTnd



CVE=cardiovascular event

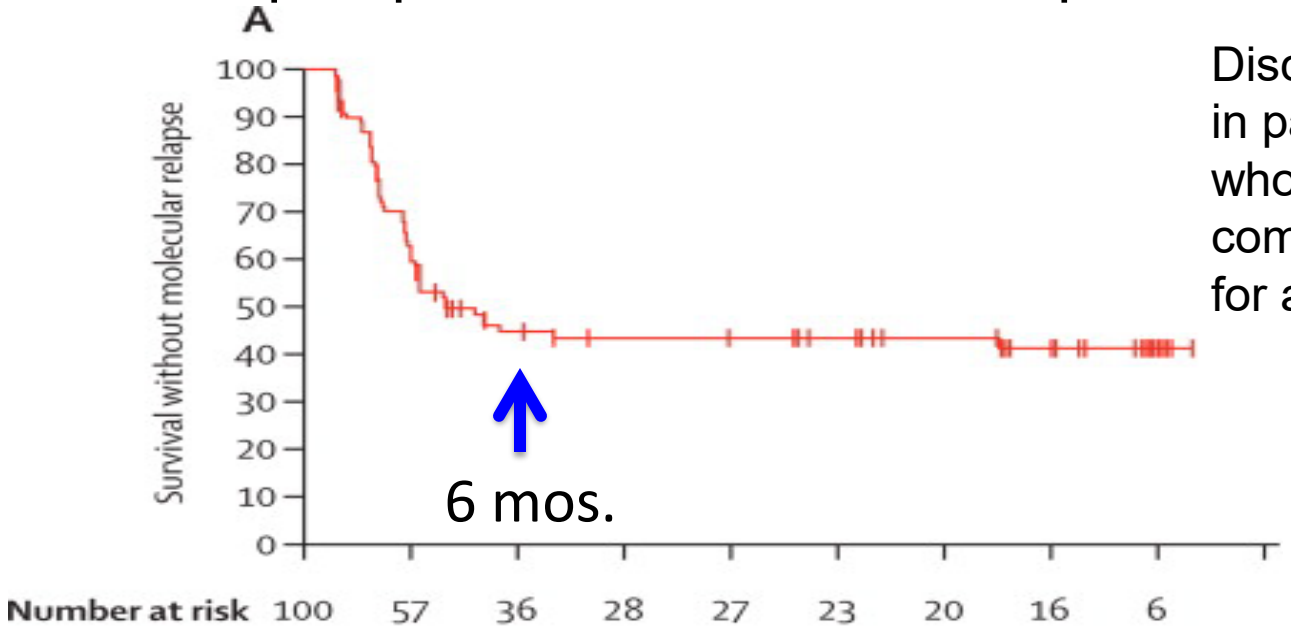
What is “treatment-free remission” (TFR) and when it is appropriate to consider?

- Prospective discontinuation of TKI therapy with more frequent molecular monitoring.
  - Goal is to maintain deep molecular remission without treatment.
  - Eliminate chronic side-effects (e.g. fatigue, rash, GI)
  - Reduce complications of treatment (vascular toxicity)
  - Reduce costs
- Best results are achieved after >5 years of total therapy and >2 years in deep molecular remission (<0.01% transcript level)

TFR – warnings!

- Psychological stress and anxiety
- Non-adherence to follow up (monitoring is mandatory)
- “TKI withdrawal” syndrome
- Molecular recurrence and hematologic relapse
- Need for retreatment

- The prospective, multicenter Stop Imatinib (STIM) Trial



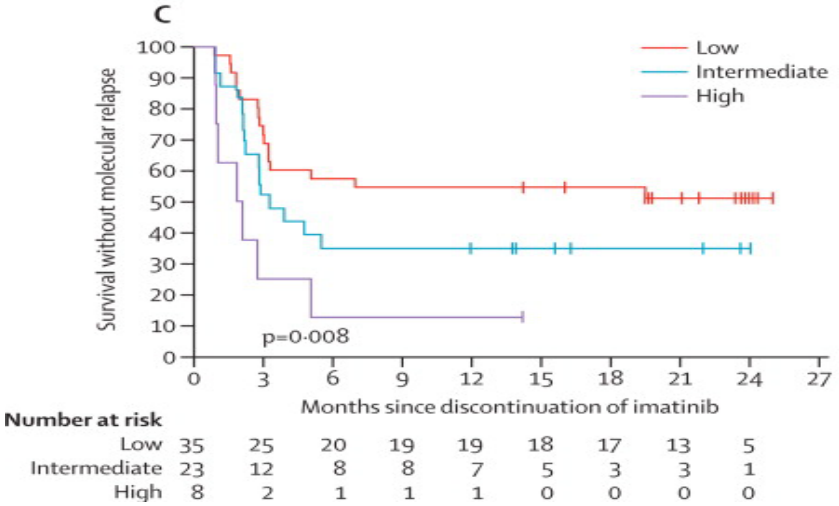
Discontinuation of imatinib in patients with CML who had maintained complete molecular remission for at least 2 years.

For 100 patients, the estimated molecular relapse-free survival was 45% (95% CI 34–55) at 6 months, 43% (33–53) at 12 months, and 41% (34–55) at 24 months.

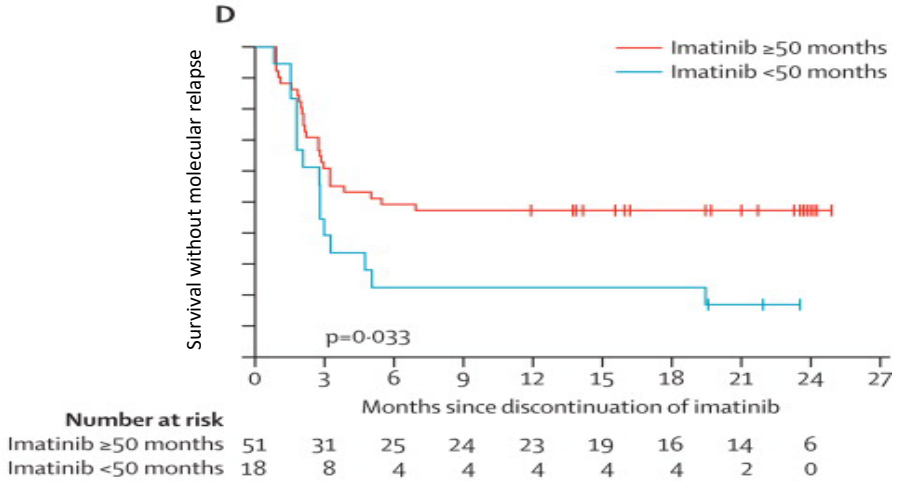
FX Mahon et al. Lancet Oncology 2010; 11: 1029

- The prospective, multicenter Stop Imatinib (STIM) Trial

By initial Sokal Score



By time on Imatinib therapy

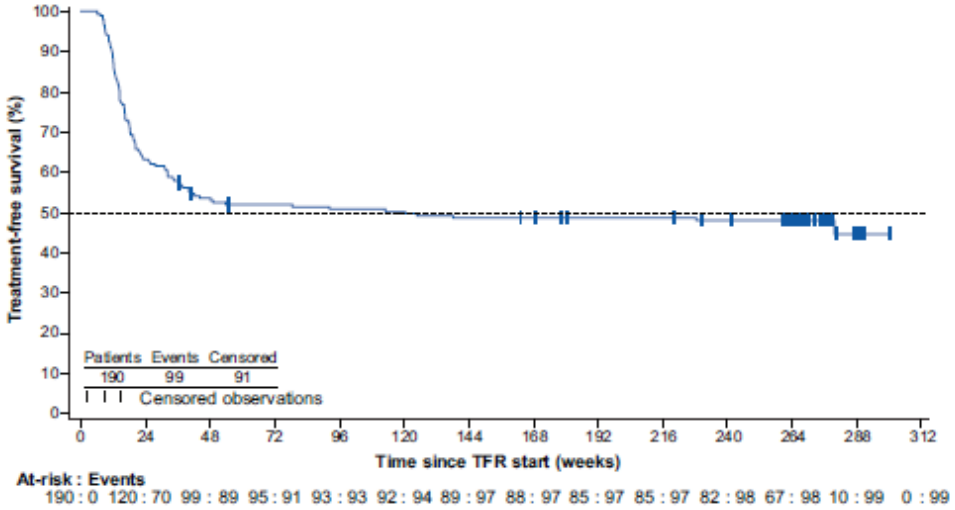


FX Mahon et al. Lancet Oncology 2010; 11: 1029

ENESTfreedom Study: TFR after frontline nilotinib

- Chronic phase CML, n=190
- Frontline nilotinib for >3 years.
- Sustained $MR^{4.5}$ for >1 year.

Sokal score at Diagnosis	TFR at 5 years, n/N (%)	
Low	32/63	51%
Intermediate	19/50	38%
High	8/29	28%
Missing	20/48	42%



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Radich et al. Leukemia 2021

Greatest chance for successful TKI discontinuation

- First-line therapy, or second-line if intolerance was the only reason for changing TKI.
- Low-risk by Sokal or ELTS scores
- No prior treatment failure.
- Duration of TKI therapy >5 years (>4 years for 2nd Gen TKI)
- Duration of Deep Molecular Response (DMR) >3 years, if MR4
- Duration of DMR >2 years, if MR4.5

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Hochhaus, et al. Leukemia 2020; 34: 966–984

Cumulative incidence of deep molecular response (MR^4 and $MR^{4.5}$) with imatinib, nilotinib, and dasatinib by 5 and 10 years

Study		5 Years (%)	10 Years (%)
CML Study IV	Imatinib MR4	68	81
	Imatinib MR4.5	53	72
ENESTnd	Imatinib MR4	42	56
	Imatinib MR4.5	35	45
	Nilotinib MR4	66	73
	Nilotinib MR4.5	54	64
DASISION	Imatinib MR4.5	33	NA
	Dasatinib MR4.5	42	NA

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Hochhaus, et al. Leukemia 2020; 34: 966–984

Take Home Points

- To avoid resistance or recurrence:
  - Ensure daily dosing of TKI
  - Manage and minimize side-effects
  - Monitor adherence and response (every 3 months)

- Consider prospective discontinuation (>4-5 years on TKI):
  - Initial low-risk scores
  - Durable deep molecular remission

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Thank you.

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