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Understanding and addressing the challenges in CML in 2024

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University of Chicago
February 2024

Disclosures – Richard A. Larson, MD

- Research funding to the University of Chicago:
  - Astellas
  - Cellectis
  - Daiichi Sankyo
  - Forty Seven/Gilead
  - Novartis (asciminib)
- Equity ownership: none
- Royalties: UpToDate, Inc

- Consultancy/ Honoraria:
  - AbbVie
  - Ariad/Takeda (DSMB)
  - CVS/Caremark
  - Epizyme (DSMB)
  - Jazz Pharmaceuticals
  - Kling Pharmaceuticals
  - Novartis (DSMB)
  - Rigel Pharmaceuticals
  - Servier

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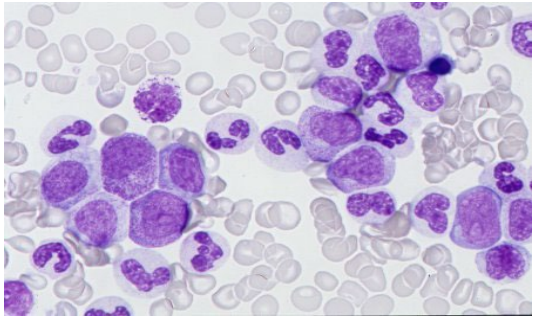
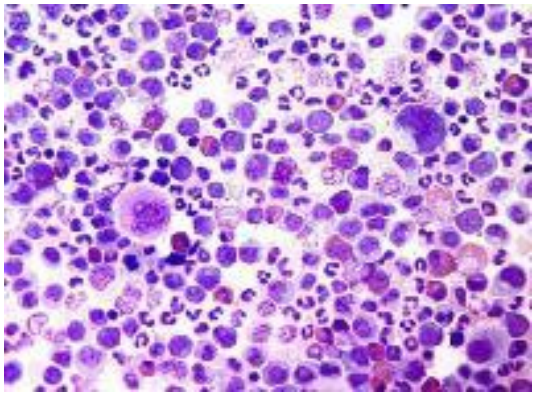
Investigational agents will not be discussed: Olverembatinib HQP1351 (GZD824); ELVN-001 – pure ABL1 inhibitor

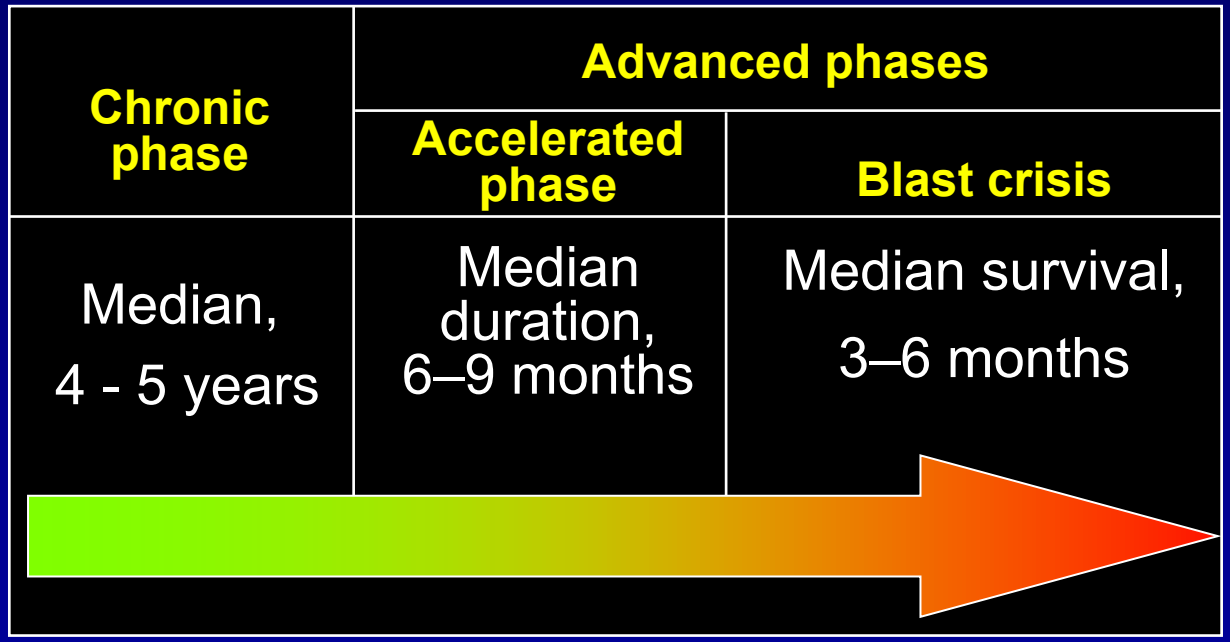
Agenda: addressing remaining challenges

- What is accelerated phase?
- Importance of Risk Assessment
- Clarifying patient goals (Survival &/or TFR)
- Minimizing toxicity; improving adherence & Quality of Life (QOL)
- Consider Treatment-free remission (TFR)
- Learn the role for asciminib





Clinical Course (Historical): Phases of Chronic Myeloid Leukemia

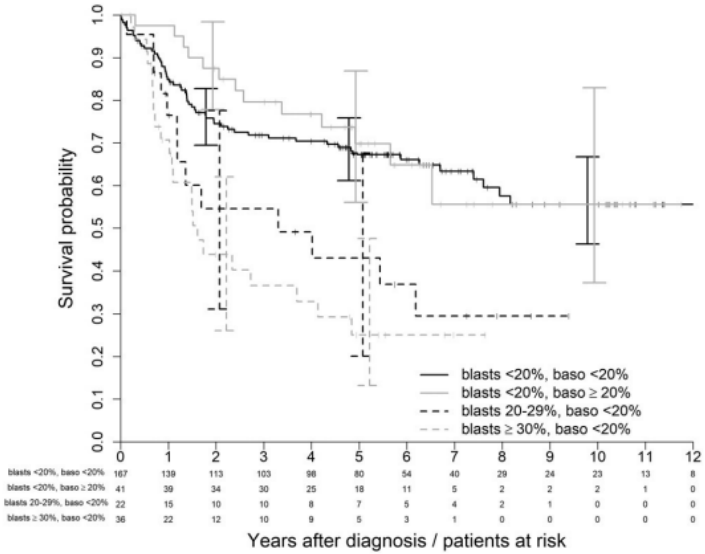


Is Accelerated Phase a real thing?

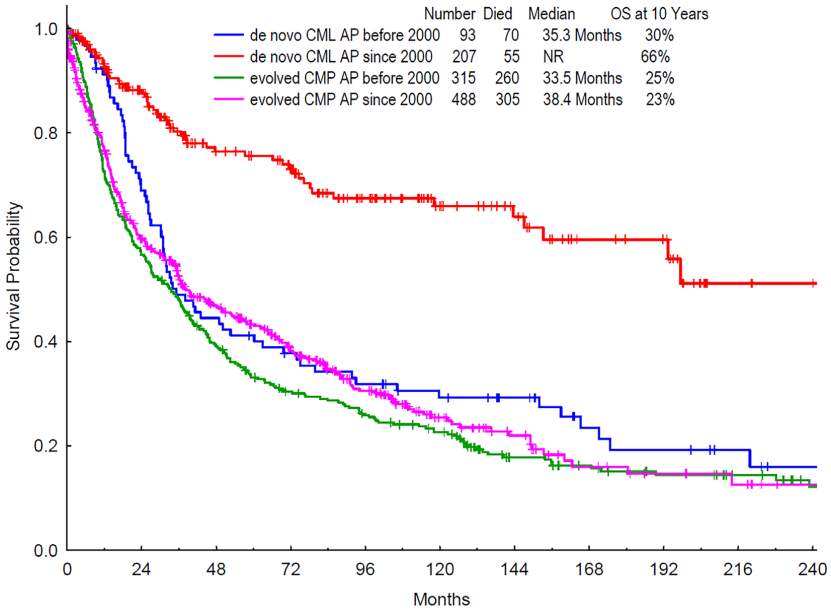
- WHO, 5th Edition: “No”
  - High-risk chronic phase with poor response to TKI therapy
  - +8,+Ph,i(17p),+19,+17,+21,3q26.2,-7/del(7q); complex karyotype
  - mutations in *ASXL1*, *RUNX1*, or *TP53*
- ICC (International Consensus Classification): “Yes”
  - 10-19% blasts in marrow or blood;
  - basophils ≥20%;
  - ACA (additional chromosome abnormalities in Ph+ cells)
  - Blast Phase defined by ≥ 20% blasts in marrow or blood; extramedullary disease; any lymphoblasts

Arber et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood 2022; 140; 1200-1228.
Khoury et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022; doi.org/10.1038/s41375-022-01613-1

Survival in CML differs if 10-19% (AP) or ≥20% blasts (MyBP)



Prognosis of patients with CML presenting in advanced phase is defined mainly by blast count, but also by age, chromosomal aberrations and hemoglobin. Lauseker et al. Am J Hematol 2019; 94:1236-1243.



Survival of de novo CML in AP before and after 2000 and after progression from Chronic Phase. Kantarjian & Tefferi. Am J Hematology 9 June 2023

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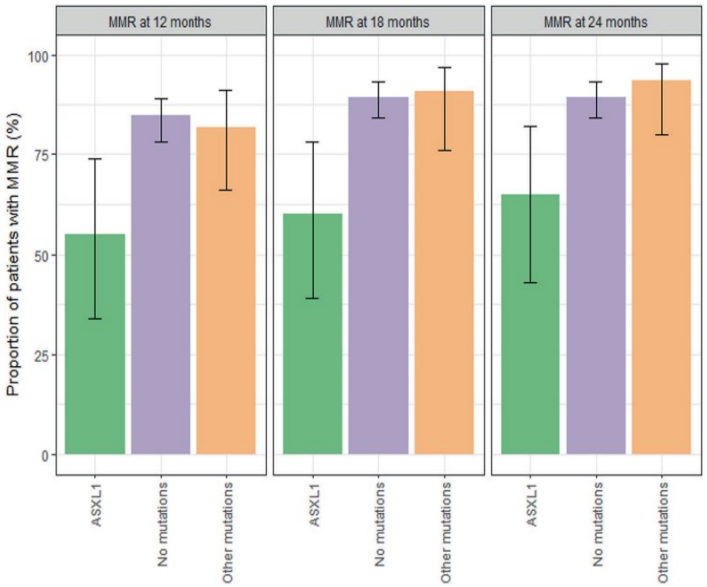
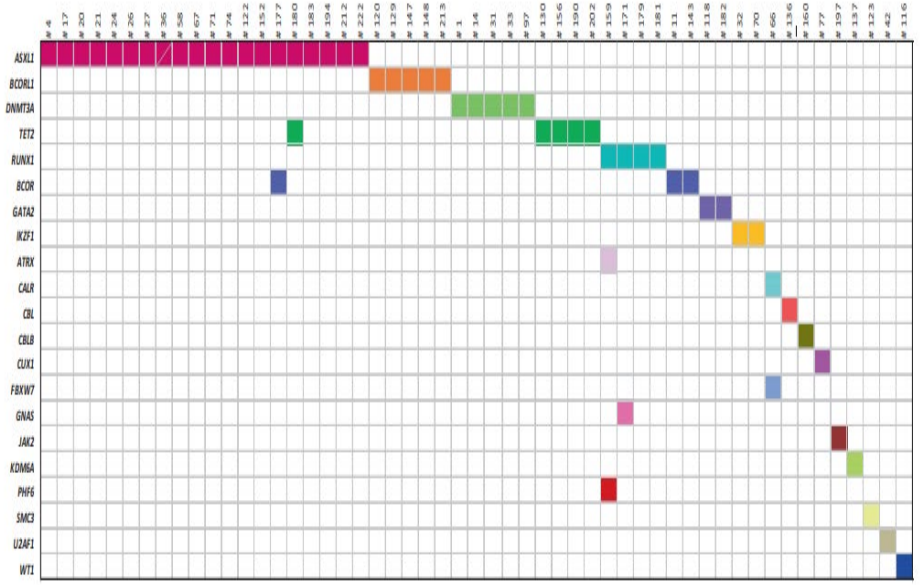
Somatic mutations in 222 CML patients at diagnosis with NGS evaluation





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

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.

Outcomes from major randomized frontline chronic phase CML trials

Trial (FU)	N=	Therapy	CCyR	MMR	MR4.5	PFS	OS
IRIS (10.9 y)	553	IM 400	83%			92%	83%
TOPS (42 mos)	157	IM 400	80%	52%		94%	94%
	319	IM 800	82%	50%		96%	93%
ENESTnd (10 yr)	282	NIL 600		77%	54%	96%	92%
	281	NIL 800		77%	52%	98%	96%
	283	IM 400		60%	31%	93%	92%
DASISION (5 yr)	259	DAS 100		76%	33%	85%	91%
	260	IM 400		64%	42%	86%	90%
BFORE (5 yr)	246	BOS 400	77%	74%	47%	93%	95%
	241	IM 400	66%	65%	37%	91%	95%

Regardless of frontline TKI, Overall Survival is now >90%.

Deininger et al. Chronic Myeloid Leukemia, version 2.2021. NCCN.org; 18: 1385-1408.

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

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

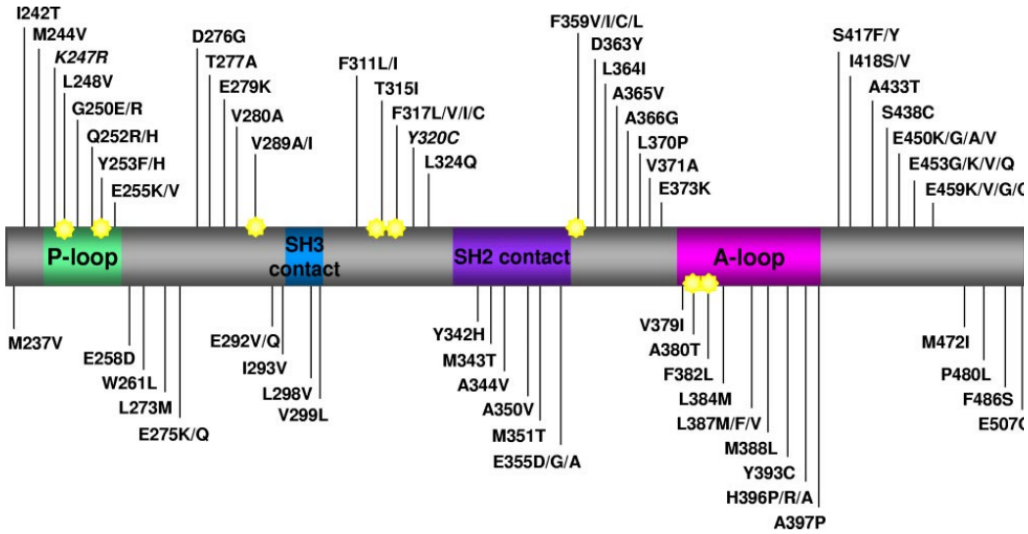
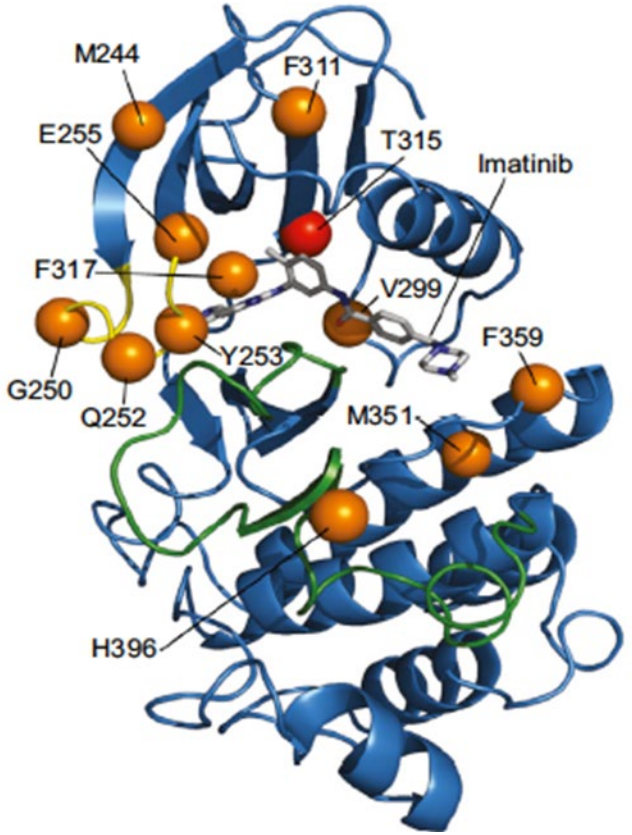


Figure 1. Map of all the amino acid substitutions in the Bcr-Abl KD identified in clinical samples from patients reported to be resistant to imatinib in publish papers. Key structural motifs within the KD are indicated. P-loop indicates phosphate binding loop; SH2 contact and SH3 contact, contact regions with SH2 and S 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 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 Ab 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



Patel AB, et al. Hematol Oncol Clin North Am. 2017;31(4):589-612.

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Mutations conferring resistance to TKIs

Resistance to:	**Due to mutation in:**
Dasatinib	V299L, **T315I/A**, F317L/V/I/C
Nilotinib	Y253H, E255K/V, **T315I**, F359V/I/C, G250E
Bosutinib	E255K, V299L, **T315I**, G250E
Ponatinib	**T315M/L**
Asciminib	G109D, Y115N, M244V, V289I, A337V/T, E355G, F359V, E462K, G463D/S, P465S, V468F, S501R, I502L

Stopping TKI Therapy in CML

Why discontinue tyrosine kinase inhibitor (TKI) therapy?

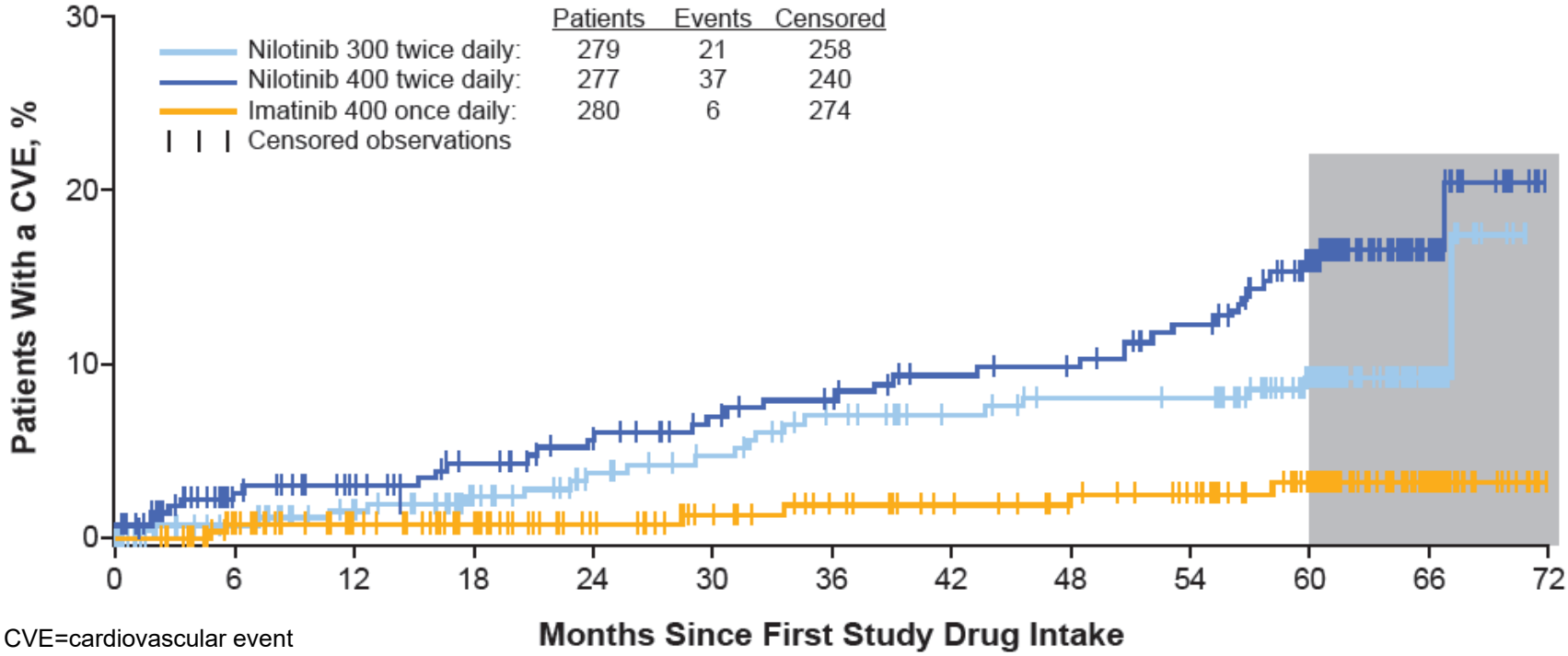
- Avoid chronic toxicities
- Avoid late complications
- Reduce costs

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**, pulmonary hypertension
Nilotinib	Hyperglycemia, 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

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

Incidence of Adverse Vascular Events on ENESTnd



CVE=cardiovascular event

Hochhaus et al. ENESTnd. Leukemia 2016

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

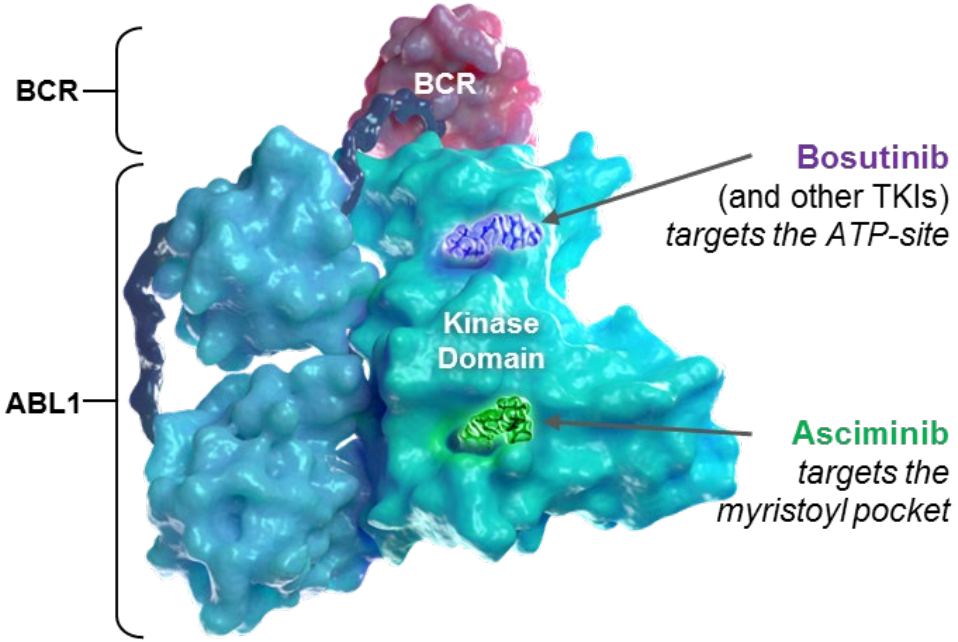
Study		5 Years (%)	10 Years (%)
CML Study IV	Imatinib MR4	68	81
	Imatinib MR4.5	53	72
ENESTnd	Imatinib MR4	42	56
	Imatinib MR4.5	35	45
	Nilotinib MR4	66	73
	Nilotinib MR4.5	54	64
DASISION	Imatinib MR4.5	33	NA
	Dasatinib MR4.5	42	NA

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

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

Will Asciminib and its novel mechanism of action change outcomes in CML?

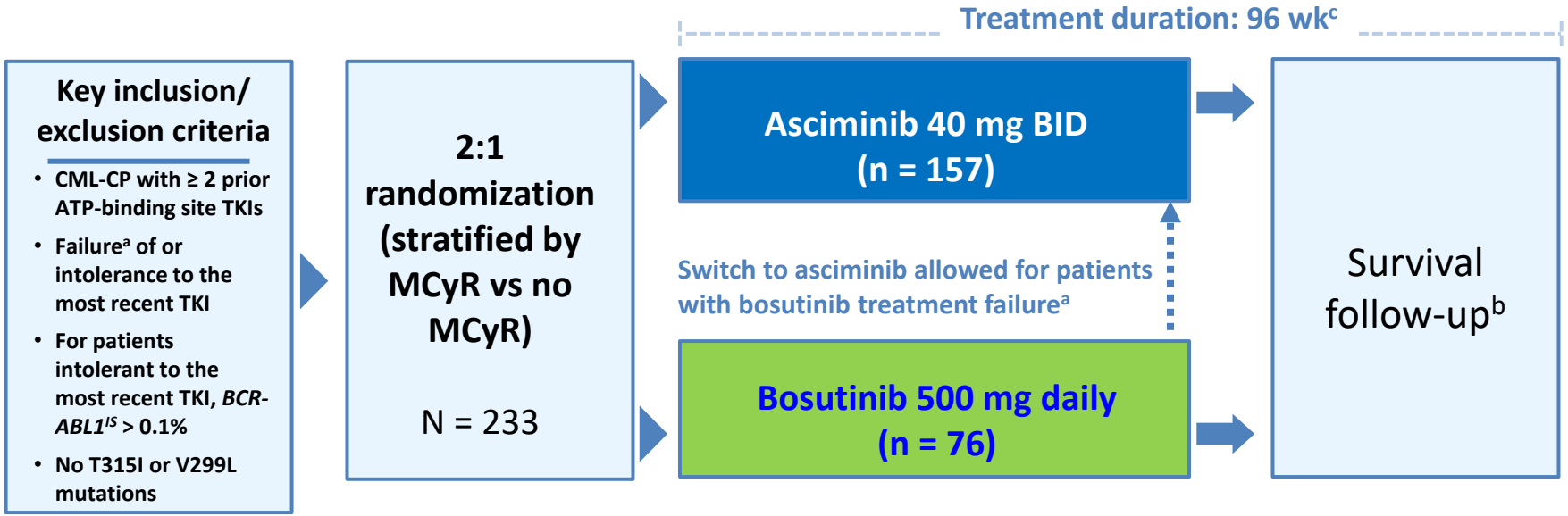


ATP-competitive binding site

Non-ATP-competitive binding site – myristoyl pocket locks the inactive isoform

Manley PW, et al. *Leuk Res* 2020; 98:106458

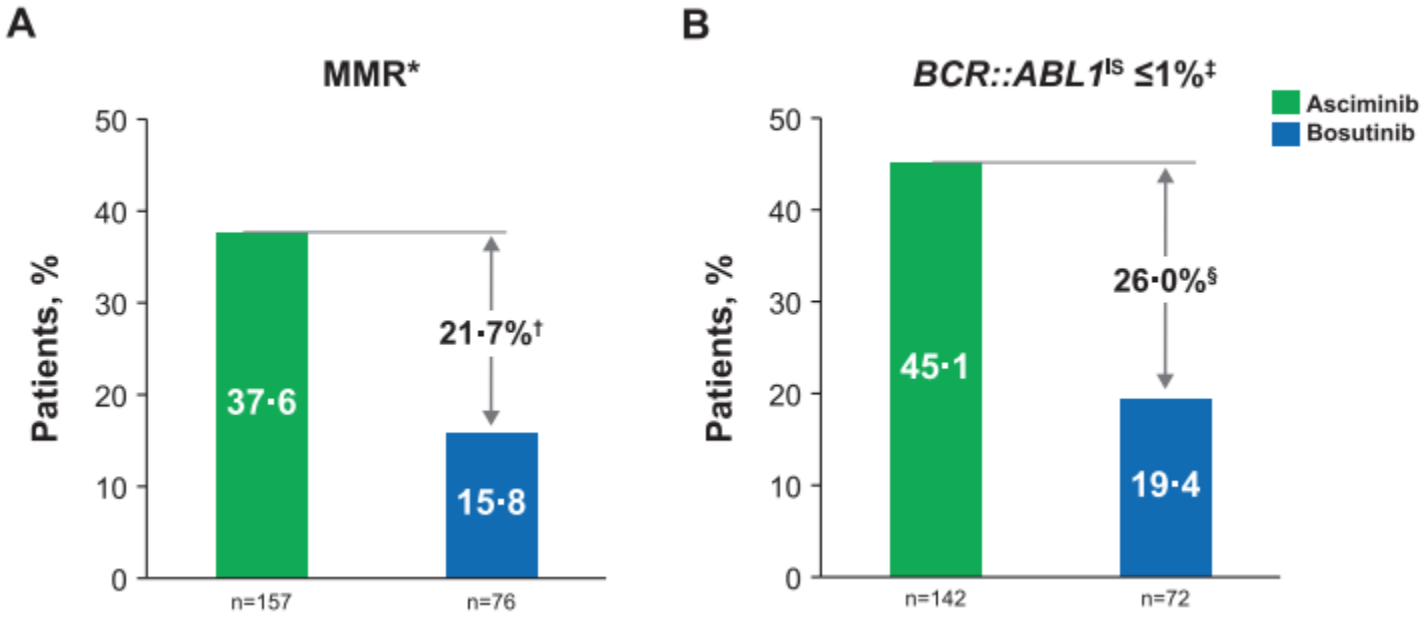
ASCEMBL 3rd Line Study Design and Key Eligibility Criteria



- Data cutoff for current analysis: May 25, 2020 (all patients completed the Week 24 visit or discontinued before)
- Median duration of follow-up: 14.9 months from randomization to cutoff

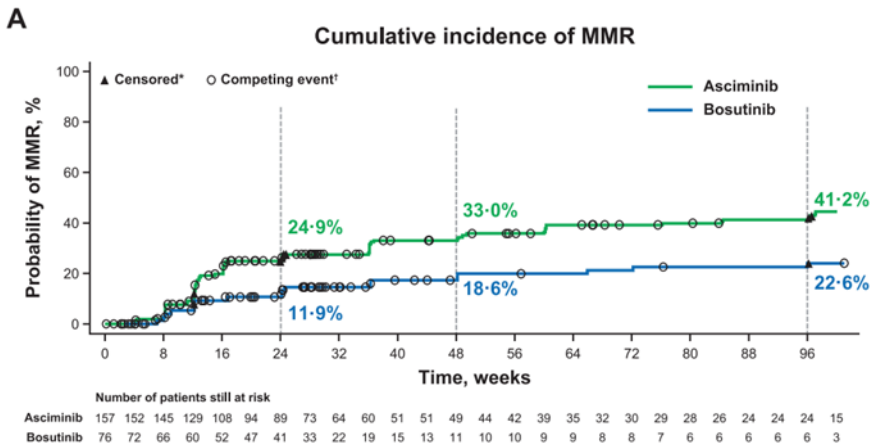
AP, accelerated phase; BC, blast crisis; BID, twice daily; CP, chronic phase; IS, international scale; MCyR, major cytogenetic response; QD, once daily.
[a] Must meet the definition of treatment failure per the 2013 European LeukemiaNet guidelines (Baccarani M, et al. Blood. 2013;122[6]:872-884); [b] Patients who discontinue study treatment at any time will continue to be followed up for survival and progression to AP/BC for up to 5 years after the last patient's first dose; [c] Patients will continue to receive study treatment for up to 96 weeks after the last patient's first dose. Presented by Hochhaus A, et al. ASH 2020. Abstract LBA4.

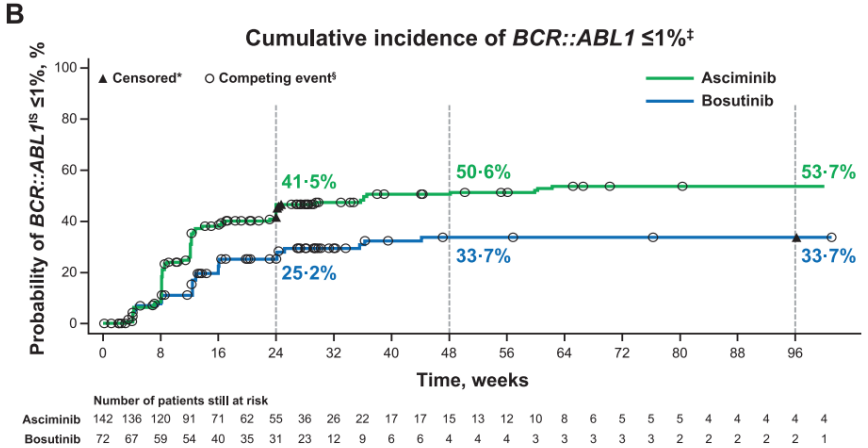
ASCEMBL: MMR and BCR::ABL1 ≤ 1% (IS) at week 96



Hochhaus 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; 37: 617-626.

ASCEMBL: MMR and BCR::ABL1 ≤ 1% (IS) at week 96





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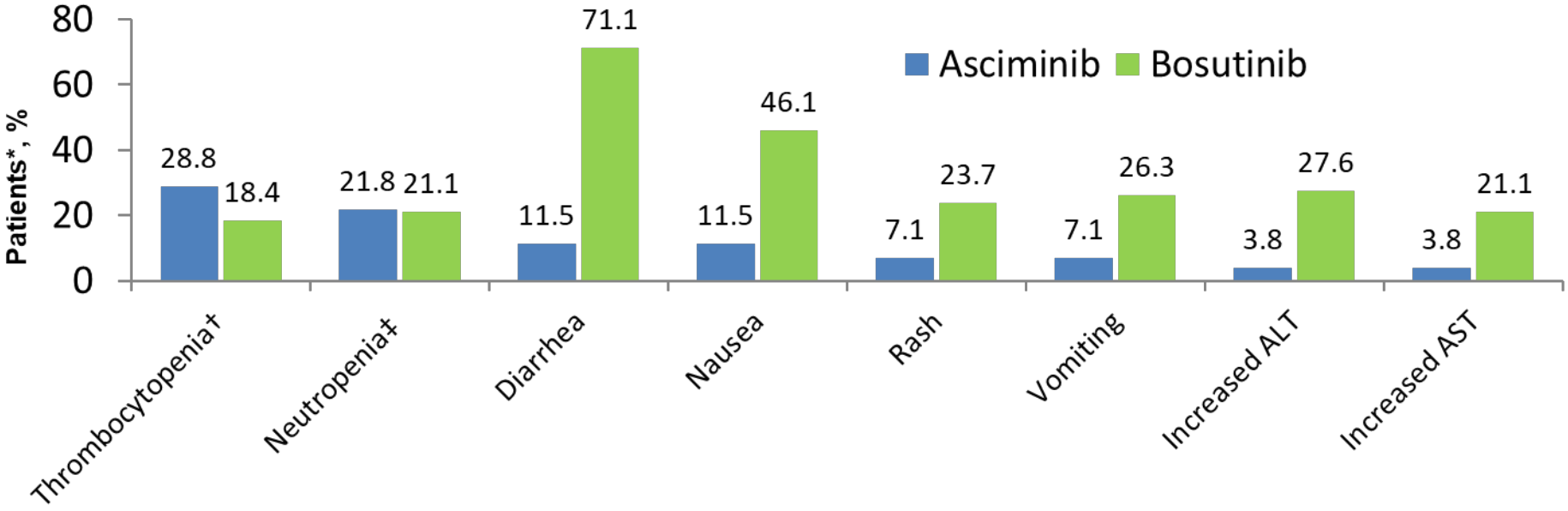
Hochhaus et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia 2023; 37: 617-626.

Most Frequent All-Grade Adverse Events (AEs occurring in ≥20% of patients in either treatment arm)



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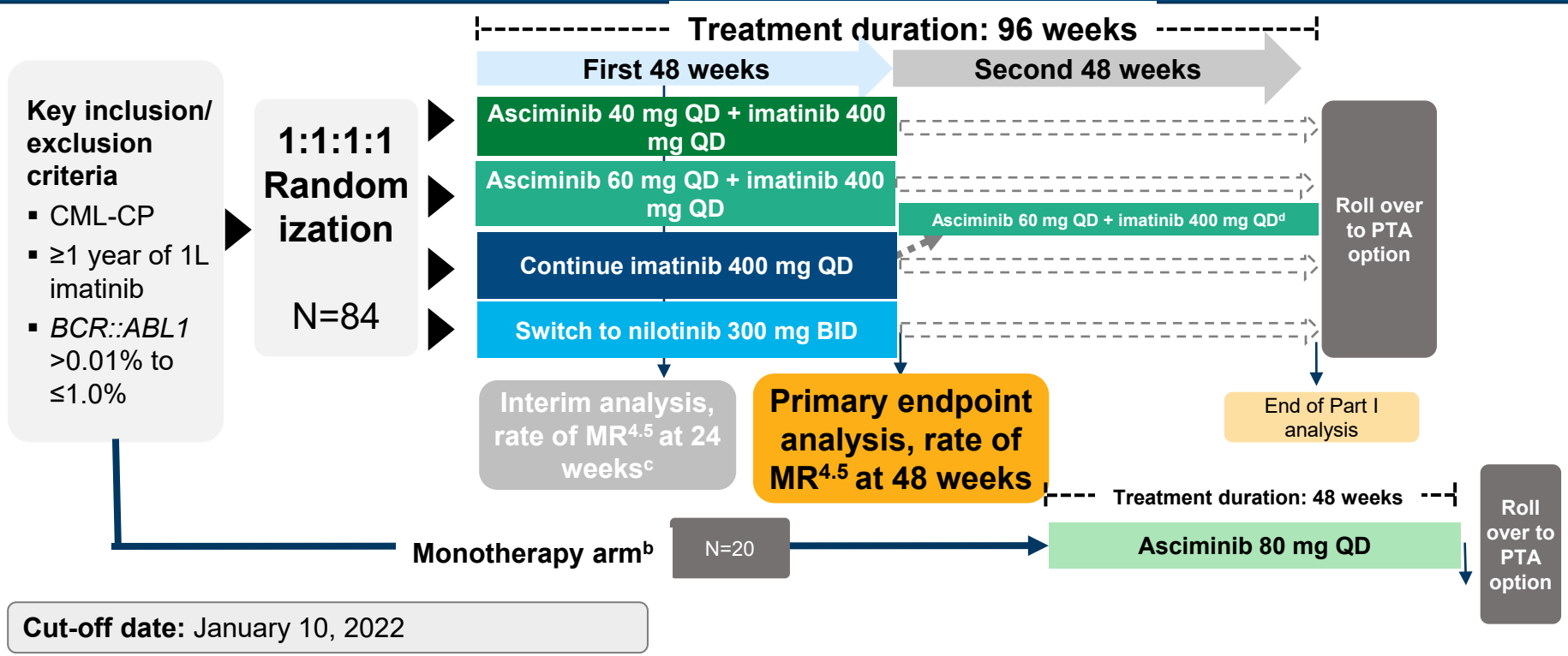
Hochhaus et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia 2023; 37: 617-626.

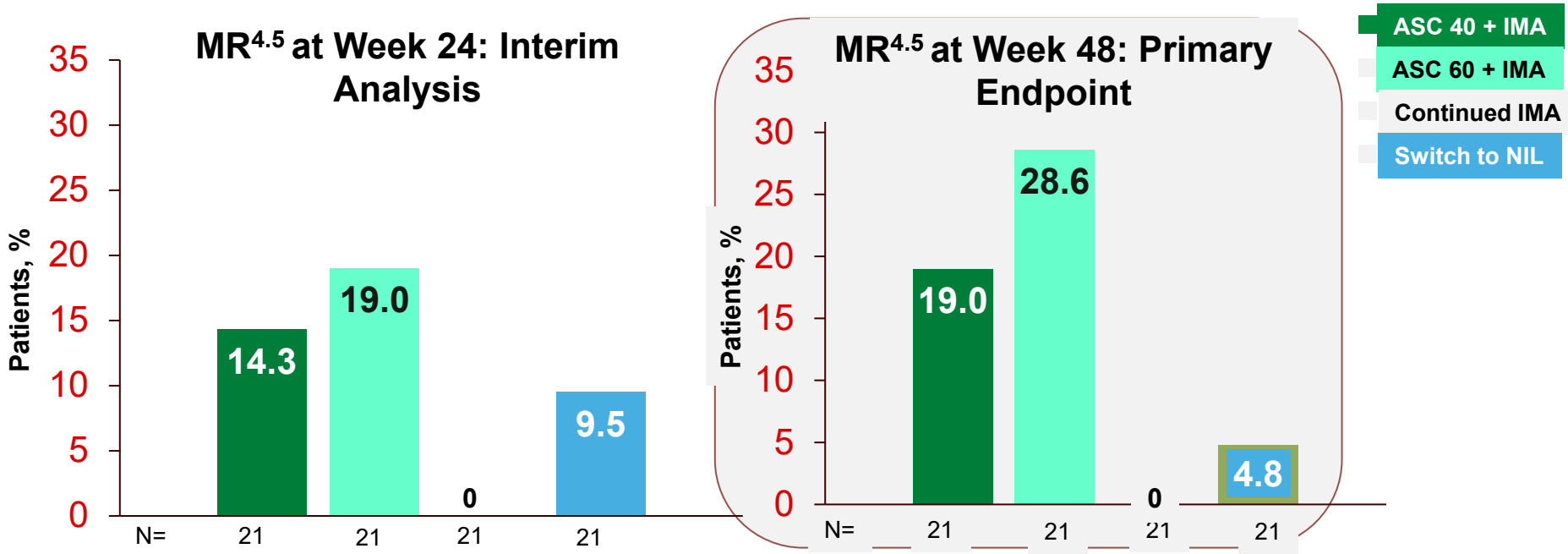
ASC4MORE Study Design



Cut-off date: January 10, 2022

Cortes et al. Blood 2022; 140 (Suppl 1): abstract #80

ASC4MORE: Deep Molecular Response ($MR^{4.5}$) at Weeks 24 and 48

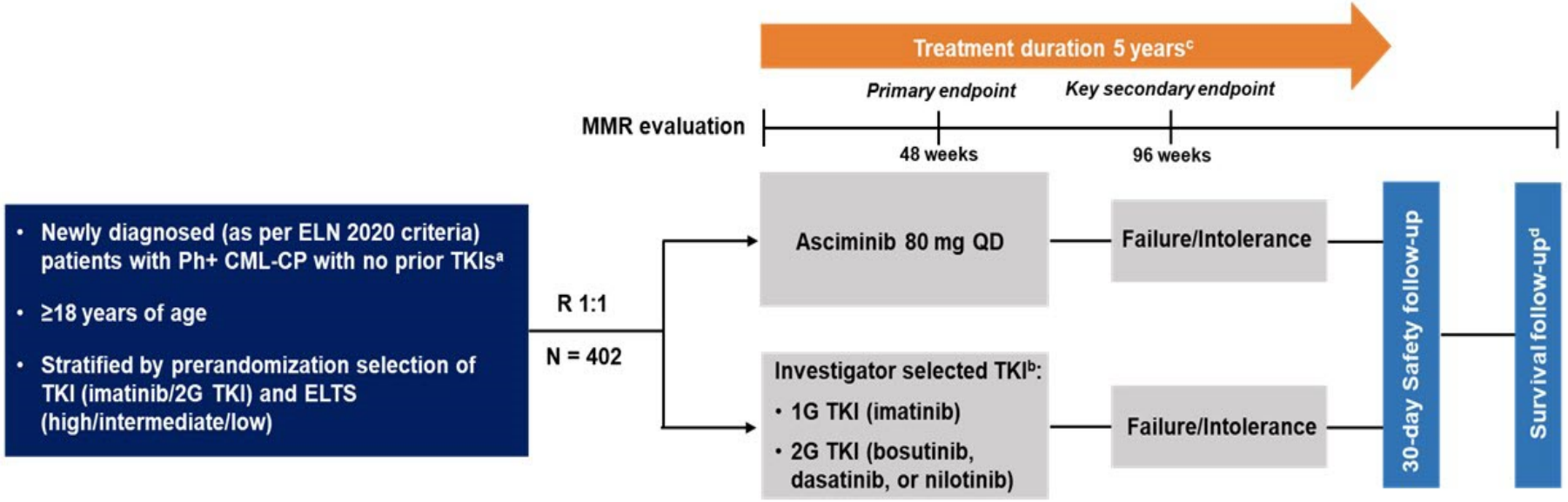


- More patients were able to achieve $MR^{4.5}$ with **asciminib add-on** to imatinib vs continued **imatinib** or switch to **nilotinib.**
- No patients in the continued **imatinib** arm were in $MR^{4.5}$ at week 48, although more patients in this arm were in MMR at baseline than in the **asciminib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

Cortes et al. Blood 2022; 140 (Sup 1): 195-197

ASC4FIRST trial

Figure: Study Design of the Phase III 1L CML-CP Trial (NCT04971226)



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Early and Deep Molecular Responses Achieved with Frontline Asciminib in Chronic Phase CML – Interim Results from the ALLG CML13

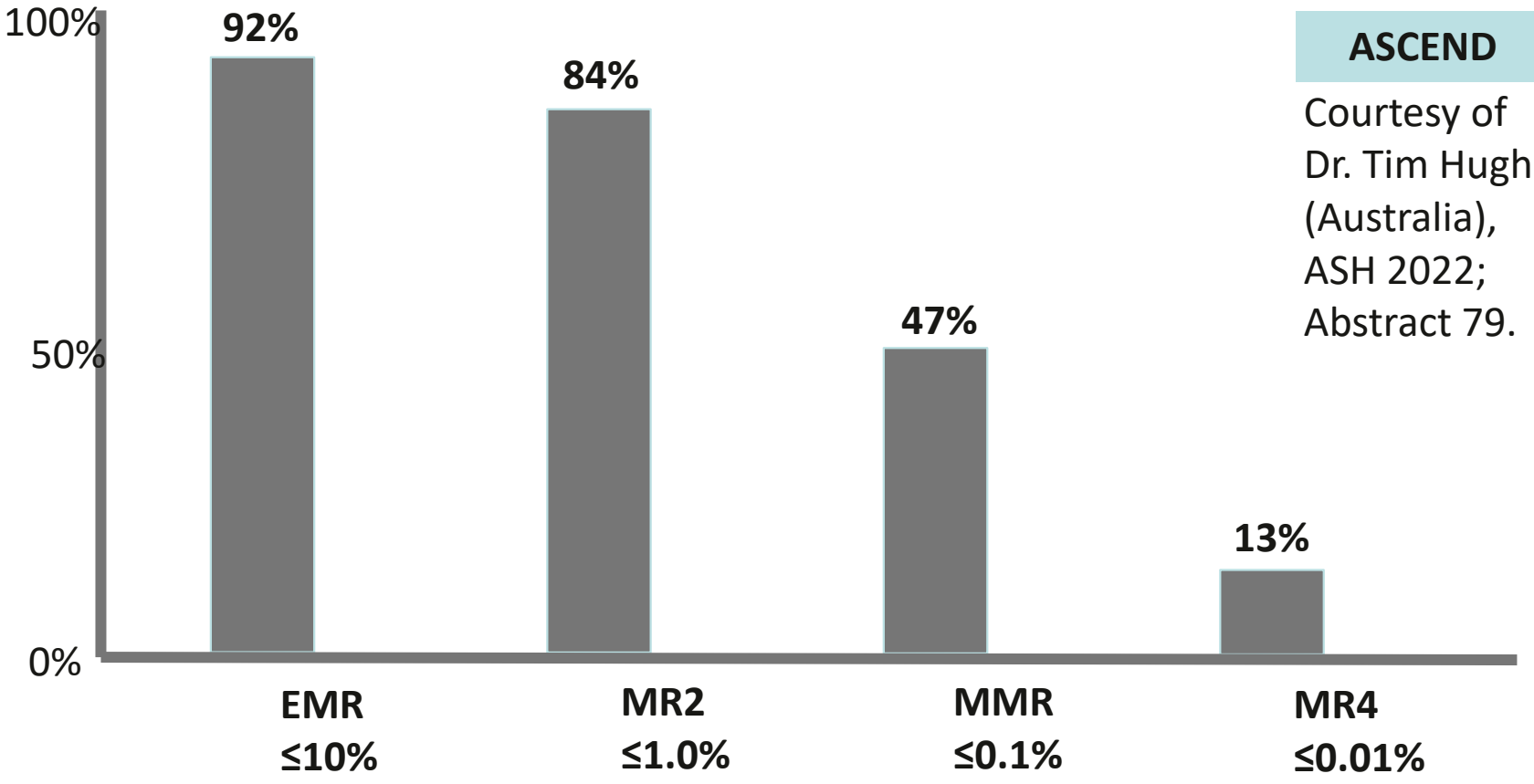
ASCEND-CML

David T Yeung, Naranie Shanmuganathan, John Reynolds, Susan Branford, Mannu Walia, Agnes Yong, Jake Shortt, Kate Burbury, Nicholas Viiala, Ilona Cunningham, David Ross, Rosemary Harrup, Matthew Wright, Cecily Forsyth, Alwyn D'Souza, Robin Filshie, Peter Browett, Steven Lane, Carolyn Grove, Andrew Grigg, Timothy Hughes

SAHMRI South Australian Health & Medical Research Institute | Cancer Research

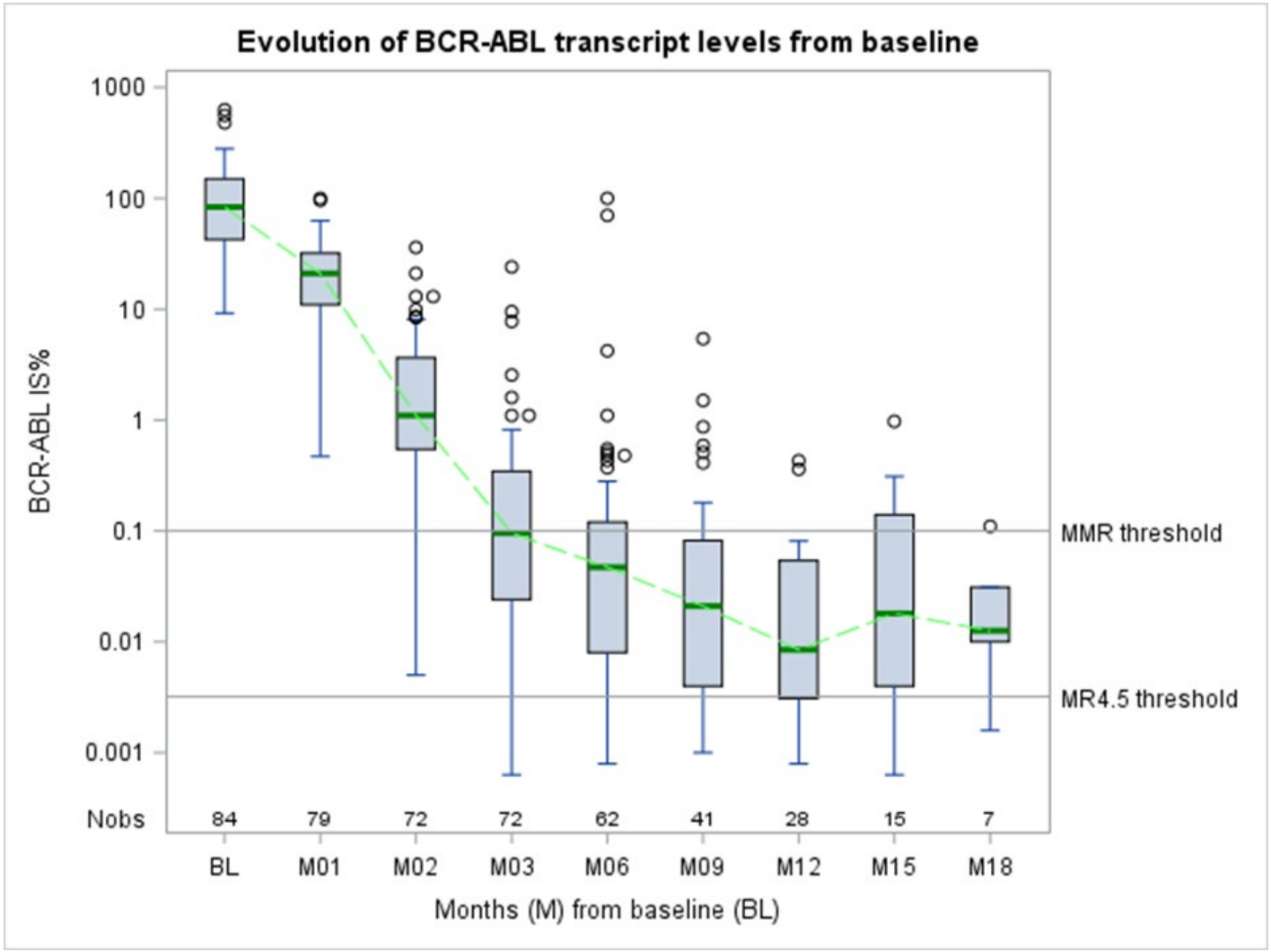
ALLG Australasian Leukaemia & Lymphoma Group

Molecular response at 3 months N=76



ASCEND

Courtesy of Dr. Tim Hughes (Australia), ASH 2022; Abstract 79.



Courtesy of Dr. Tim Hughes (Australia), ASH 2022; abstract 79

ALLG
Australasian Leukaemia & Lymphoma Group

Take Home Points

- Design treatment around the patient's goals
- 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 (>5 years on TKI):
  - Initial low-risk scores
  - Durable deep molecular remission
- Await results of asciminib trials

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Thank you.

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