UNIVERSITÄTS KLINIKUM jena

Next drug or allogeneic transplant - what's the choice?

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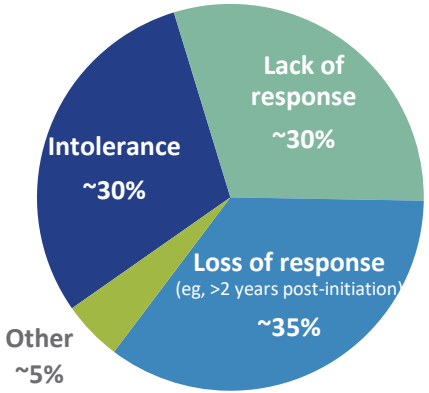
Treatment switch in CML

Rationale for Treatment Switching



In the US and EU[2], majority of treatment switches across lines of therapy and TKIs are driven by intolerance or initial lack of response (~60% combined)

Approximately **20% of patients switch treatment** within the first year (1L & 2L)

Approximately **40% of patients** switch treatment within the first 5 years (1L & 2L)

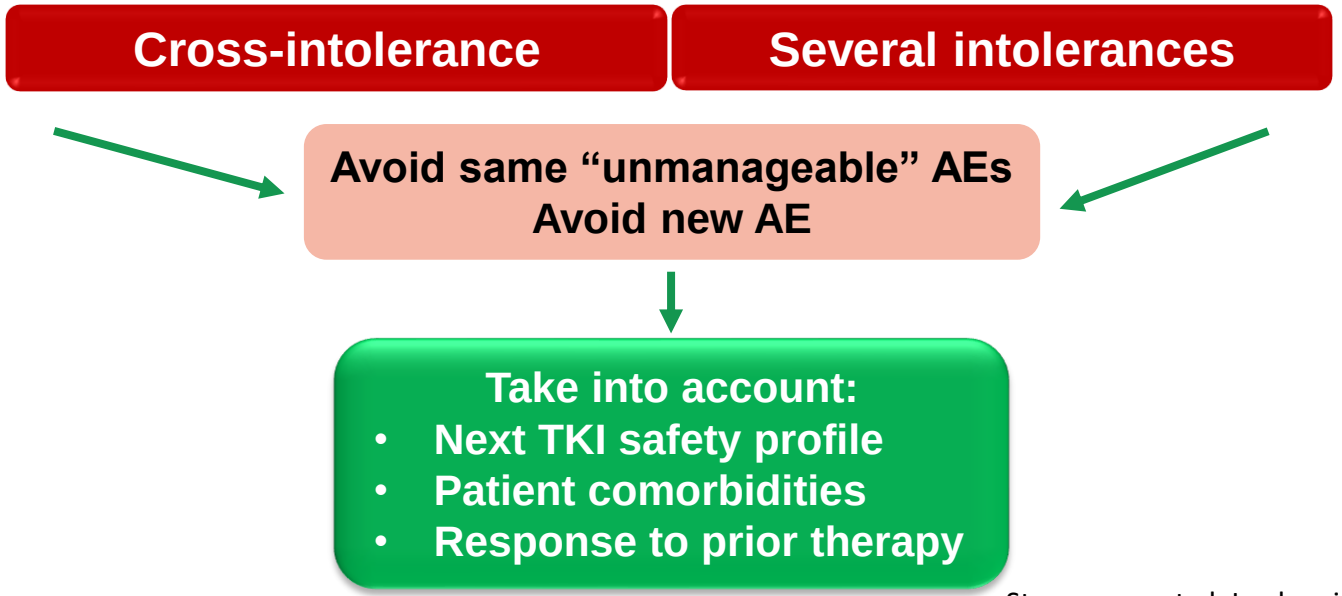
More than **50% of CML patients** require dose modification due to adverse events

Many toxicities of existing TKIs are attributable to off target inhibition such as KDR, FGFR, KIT, RET, FLT3, PDGFR, CSFR1, SRC

1. Henk HJ et al., *J Clin Pathways*. 2020 **2.** Cortes JE et al. *J Clin Oncol*. 2016;34:2333-40. **3.** Hochhaus A et al. *Leukemia*. 2016;30:1044-54.
4. Saglio G et al. *NEJM.* 2010;362:2251-9. **5.** Shah et al. *J Clin Oncol*. 2008;26:3204-12.

Intolerance to ≥2 lines of TKI

- **Intolerance to TKI therapy:** Adverse events (AEs) that cannot be managed through dose reduction or symptomatic treatment
- **Next treatment choice in case of intolerance:**



Rea, EHA 2022
Steegmann et al. Leukemia. 2016;30:1648-71.
Rabian et al. Curr Hematol Malig Rep. 2019;14:492-500.

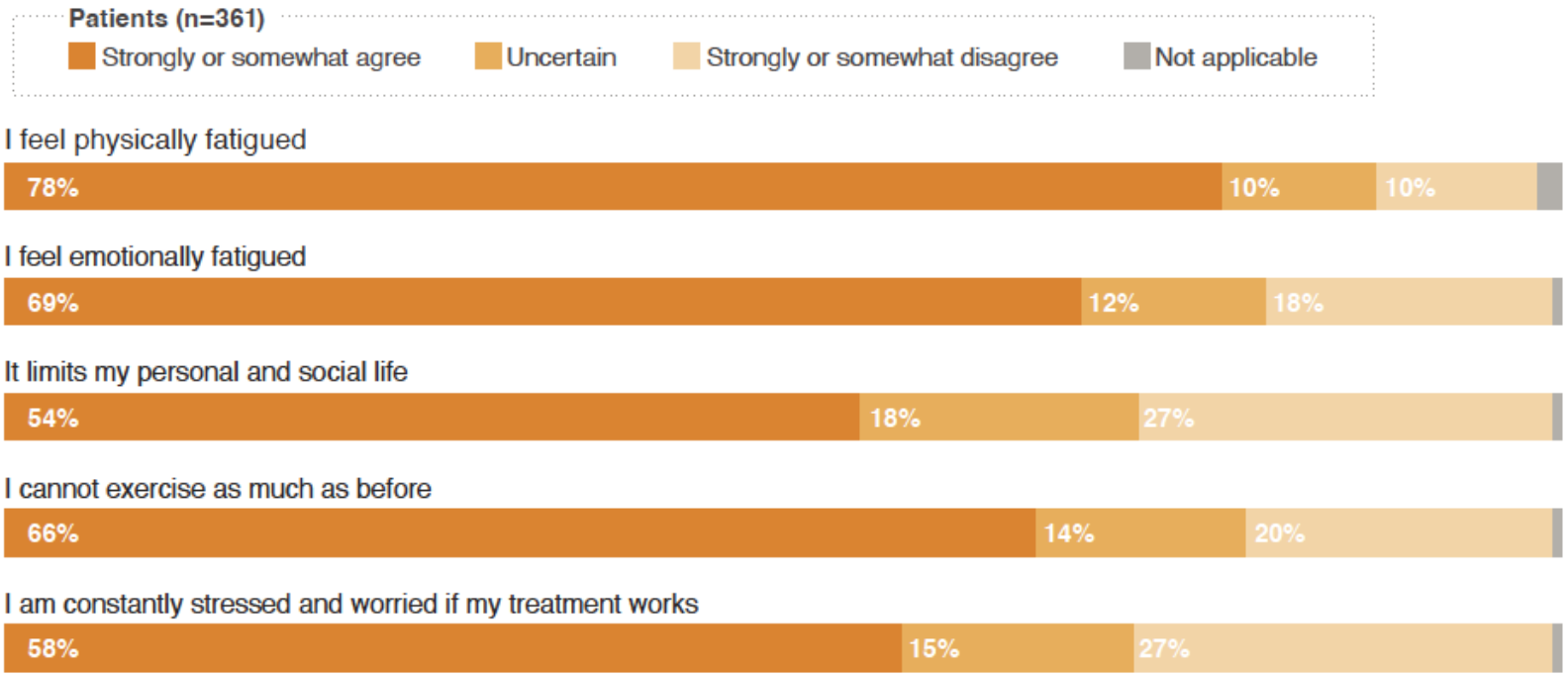
Chronic Myeloid Leukemia Survey on Unmet Needs (CML SUN):

Balancing Tolerability and Efficacy Goals of Patients and Physicians Through Shared Treatment Decision-Making

P668

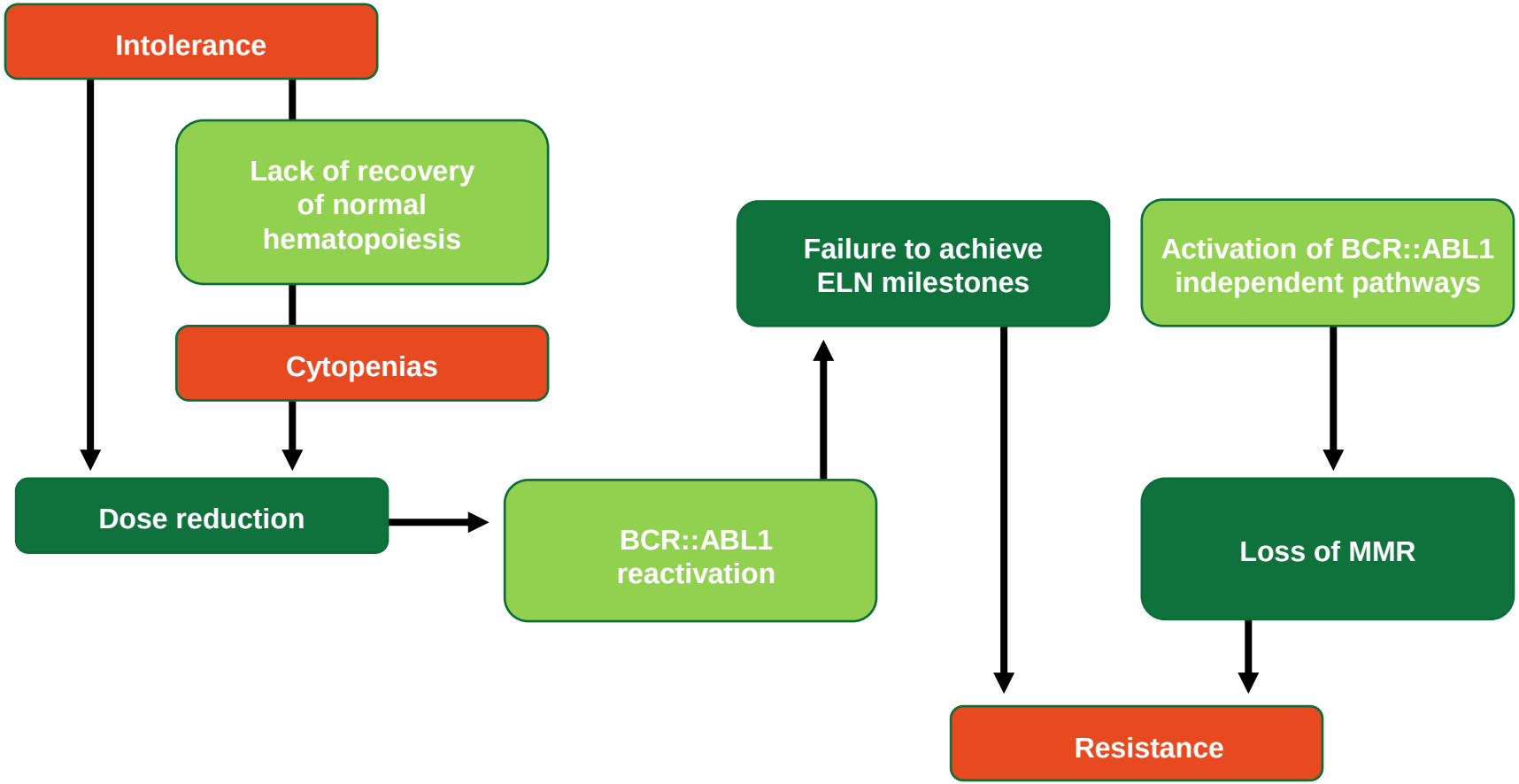
Fabian Lang,[1] Zack Pemberton-Whiteley,[2] Joannie Clements,[3] Cristina Ruiz,[3] Delphine Rea,[4] Lisa Machado,[5] Naoto Takahashi,[6] Sung-Ho Moon,[7] Andrew Grigg,[8] Cornelia Borowczak,[9] Peter Schuld,[10] Pauline Frank,[10] Cristina Constantinescu,[11] Carla Boquimpani,[12,13] Jorge E. Cortes[14]
[1]Department of Hematology and Oncology, Goethe University Hospital, Frankfurt am Main, Germany; [2]Leukaemia Care, Worcester, UK; [3]CML Buster Foundation, Costa Mesa, CA, USA; [4]Hôpital Saint-Louis, Paris, France; [5]Canadian CML Network, Toronto, ON, Canada; [6]Akita University Graduate School of Medicine, Akita, Japan; [7]Korea Leukemia Patients Organization, Seoul, South Korea; [8]Austin Hospital, Melbourne, VIC, Australia; [9]LeukaNET, Hohenbrunn, Germany; [10]Novartis Pharma AG, Basel, Switzerland; [11]Ipsos, Basel, Switzerland; [12]Hemorio, Rio de Janeiro, Brazil; [13]Oncoclínicas, Rio de Janeiro, Brazil; [14]Georgia Cancer Center, Augusta University, Augusta, GA, USA

Patient Perceptions of How CML Treatment Affects Their Life



Lang et al., EHA 2023

Interaction of causes of treatment failure



CML Risk factors

At diagnosis

- High ELTS score
- 10–19% blasts in the peripheral blood and/or bone marrow[ab]
- ≥20% basophils in the peripheral blood
- Additional chromosomal abnormalities in Ph+ cells, including 3q26.2 rearrangements, monosomy 7, isochromosome 17q and complex karyotype
- Additional chromosomal abnormalities in Ph+ cells, including trisomy 8, 11q23 rearrangements, trisomy 19, trisomy 21, additional Ph+ (evidence of association with disease progression less clear)
- Clusters of small megakaryocytes (including true micromegakaryocytes similar to those seen in myelodysplastic syndromes), associated with significant reticulin and/or collagen fibrosis, which is best assessed in biopsy sections.

a. The finding of bona fide lymphoblasts in the peripheral blood or bone marrow (even if <10%) is consistent with the diagnosis of blast phase

b. ≥20% blasts in the peripheral blood or bone marrow, or an infiltrative proliferation of blasts in an extramedullary site, is diagnostic of blast phase

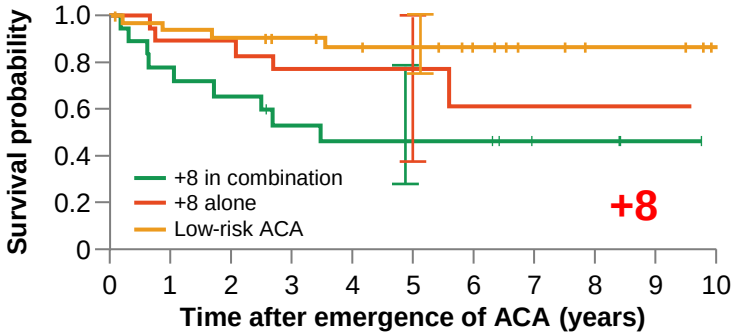
ELTS score	0.0025 × (**age**/10)^3 + 0.0615 × **spleen size** + 0.1052 × **peripheral blood blasts** + 0.4104 × (**platelet count**/1000)$^{-0.5}$	Low-risk: < 1.5680 Intermediate-risk: 1.5680- 2.2185 High-risk: > 2.2185

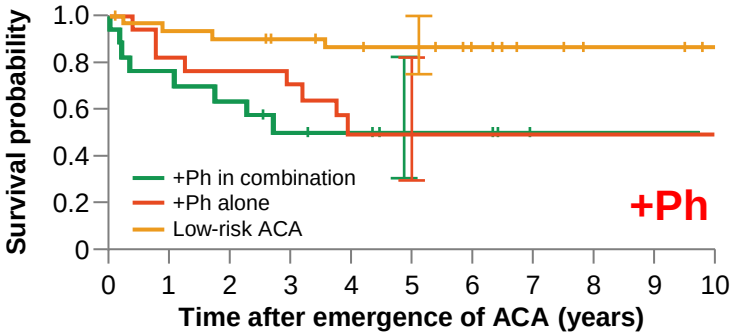
Emerging on treatment

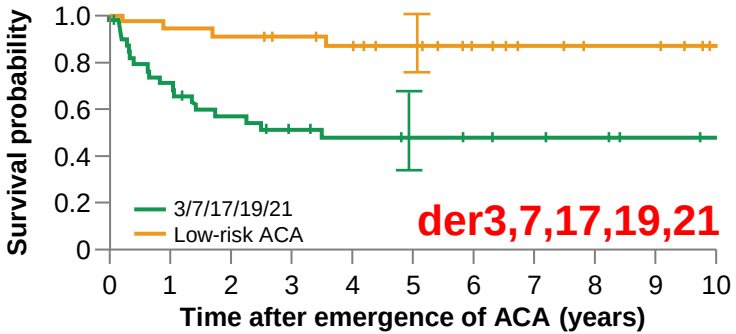
Resistance to TKI as defined by ELN 2020, including loss of prior responses, emergence of ACA and BCR::ABL1 kinase domain mutations.

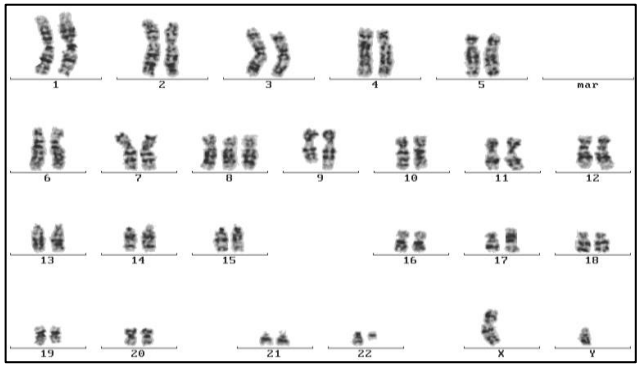
Khoury et al., Leukemia. 2022;36:1703-19

High risk additional chromosomal aberrations herald advanced disease and predict survival probability: CML IV cohort









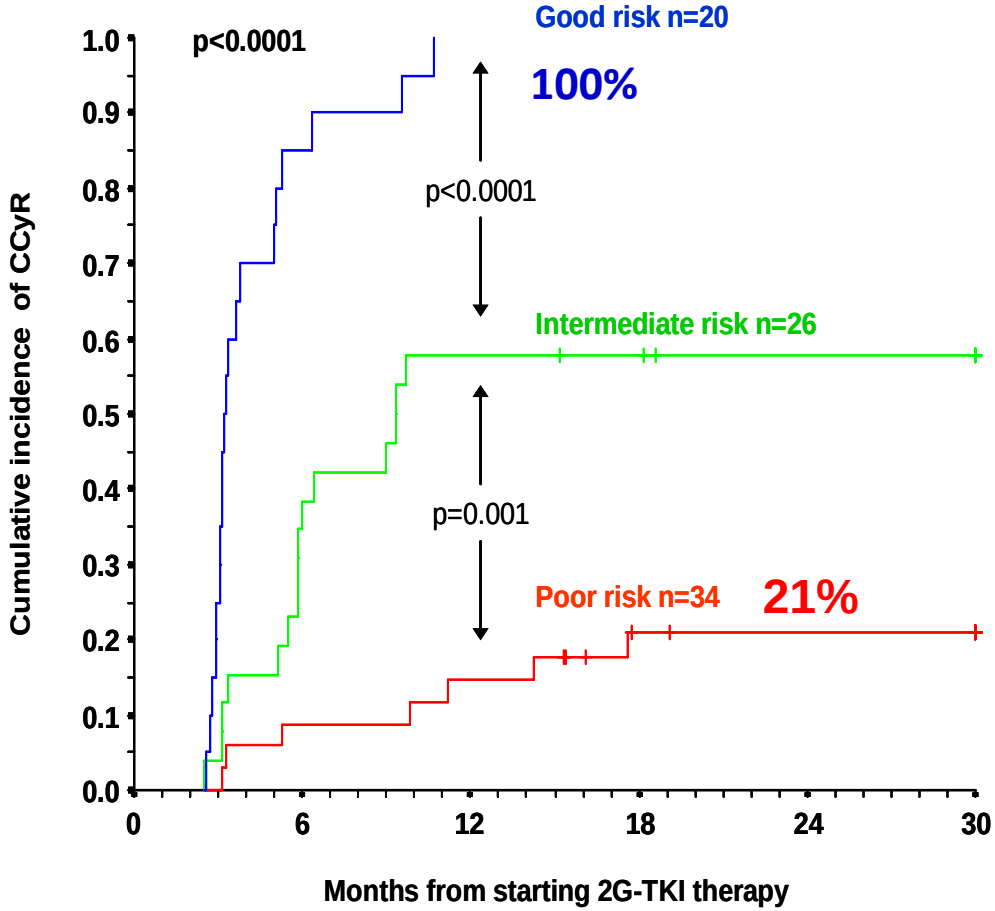
ACA, Additional cytogenetic abnormalities.

Hehlmann R, et al. Leukemia. 2020;34:2074-86

Predicting responses to second line TKI

- **Cytogenetic response to imatinib**
- **Risk score (here: Sokal)**
- **Recurrent neutropenia**

Score	Risk
<1.5	good
≥1.5 <2.5	intermediate
>2.5	poor



Milojkovic et al, Haematologica 2010

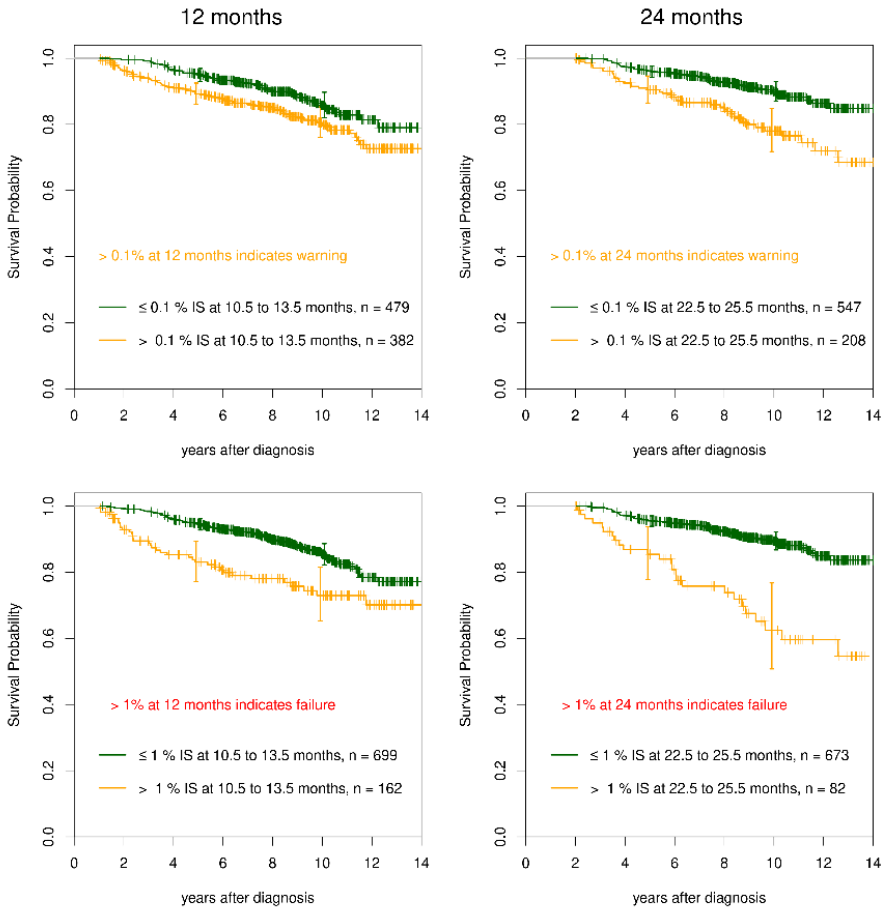
ELN 2020 treatment milestones

	Optimal	Warning	Failure
Baseline		High risk-ACA High risk ELTS score	
3 months	BCR::ABL1 ≤10%	BCR::ABL1 >10%	BCR::ABL1 >10%, if confirmed within 1-3 months
6 months	BCR::ABL1 ≤1%	BCR::ABL1 >1-10%	BCR::ABL1 >10%
12 months	BCR::ABL1 ≤0.1%	BCR::ABL1 >0.1-1%	BCR::ABL1 >1%
Any time	BCR::ABL1 ≤0.1%	BCR::ABL1 >0.1-1%, Loss of MMR	BCR::ABL1 >1%, Resistance mutations, High-risk ACA

For patients aiming at TFR, optimal response (at any time) is MR^4 (BCR::ABL1 ≤0.01%)

Leukemia 2020;34:966-84

Outcome after failing ELN milestones (German CML Study IV)



Hehlmann et al., Leukemia 2023

ELN 2020 recommendations on treatment beyond 2nd line

Treatment beyond second-line

The definition of an acceptable response to third, fourth, or fifth-line treatment cannot be formalized, but a BCR-ABL1 transcript level >1% or a cytogenetic response less than complete (Ph+ >0%) are insufficient for optimal survival. There are no comparative studies and the choice of TKI should be guided by the sensitivity profile of specific BCR-ABL1 KD-mutations if possible, and, in particular T315I where only ponatinib is efficacious. Suboptimal response to two or more TKIs should lead to prompt consideration of an allogeneic stem cell transplantation (allo-SCT).

T315I	Ponatinib
F317L/V/I/C, T315A	Nilotinib, bosutinib[a], or ponatinib
V299L	Nilotinib or ponatinib
Y253H, E255V/K, F359V/I/C	Dasatinib, bosutinib[a], or ponatinib

Leukemia 2020; 34:966-84

Expert opinion—management of chronic myeloid leukemia after resistance to second-generation tyrosine kinase inhibitors

Andreas Hochhaus[1] · Massimo Breccia[2] · Giuseppe Saglio[3] · Valentín García-Gutiérrez[4] · Delphine Réa[5] · Jeroen Janssen[6] · Jane Apperley[7]

Leukemia. 2020;34:1495-502

ELN Recommendations for CML: 2020

	2006	2009	2013	2020
1st line	Imatinib	Imatinib	Imatinib, nilotinib, dasatinib	Imatinib, nilotinib, dasatinib, bosutinib
2nd line	None (high-dose imatinib)	Nilotinib, dasatinib, high-dose imatinib	• Ima → nilo, dasa, bosu • Dasa → nilo, bosu, pona • Nilo → dasa, bosu, pona • T315I: pona	• Ima → nilo, dasa, bosu • Dasa → nilo, bosu, pona • Nilo → dasa, bosu, pona • Bosu → dasa, nilo, pona • T315I: pona
Alt. Options	IFN/allogeneic SCT	None	None	(Asciminib)
Salvage	Allogeneic SCT	Allogeneic SCT, nilotinib, dasatinib	Allogeneic SCT	Allogeneic SCT
Milestones	CCyR	CCyR → MR	MMR, major and stable	MMR → DMR
Concerns/ Considerations	• Short follow-up • Emerging mutations	Risk of emerging mutations ↓	TFR, mainly inside the frame of RCTs	Side effects

Courtesy Gianantonio Rosti

Choices of alternative TKIs

- Swich imatinib → 2G TKI
- Rotation between 2G TKI
- Swich 2GTKI → ponatinib
- Swich after ≥ 2 TKI to asciminib

Choice of an alternative TKI

- Goals of treatment?
- Resistance (Mutations) / intolerance profile?
- Clinical and biological risks?
- Comorbidities vs risk of adverse events?
- Availability of the drug/ reimbursement in the individual country/ financial burden?

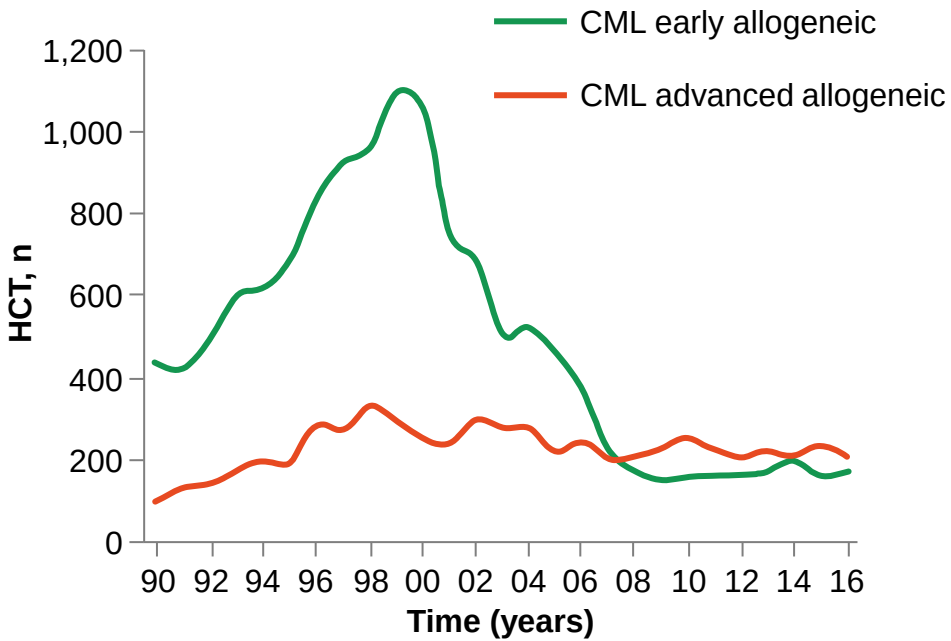
→ **Shared decision-making**

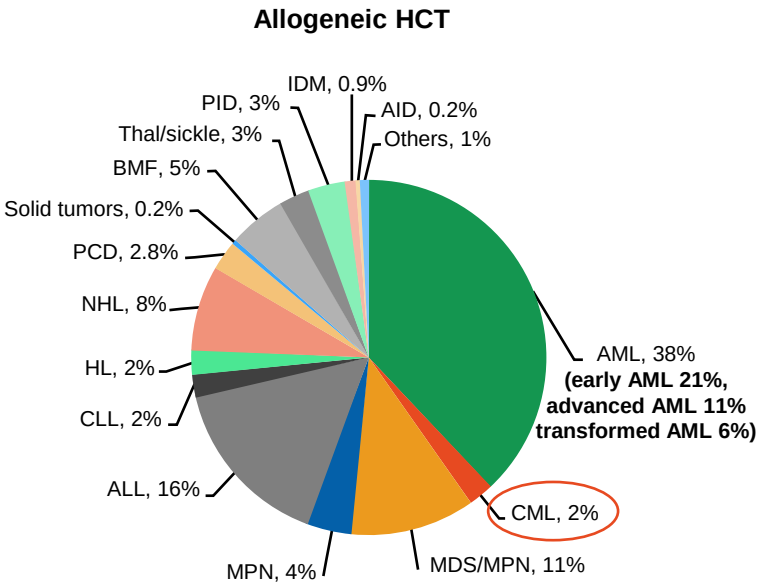
All TKIs have toxicities which may cause clinically relevant complications.
These must be considered when selecting a TKI for a patient with comorbidities:

- Previous or concomitant arteriovascular disease represents a strong contraindication to nilotinib and ponatinib second- or third-line, unless there is a unique need
- Respiratory failure and previous or concomitant pleuro-pulmonary disease are contraindications to dasatinib
- Imatinib should be withheld in patients with significant renal impairment

Hochhaus et al. Leukemia. 2020;34:966-84.

Allogeneic HCT in CML in Europe: EBMT report

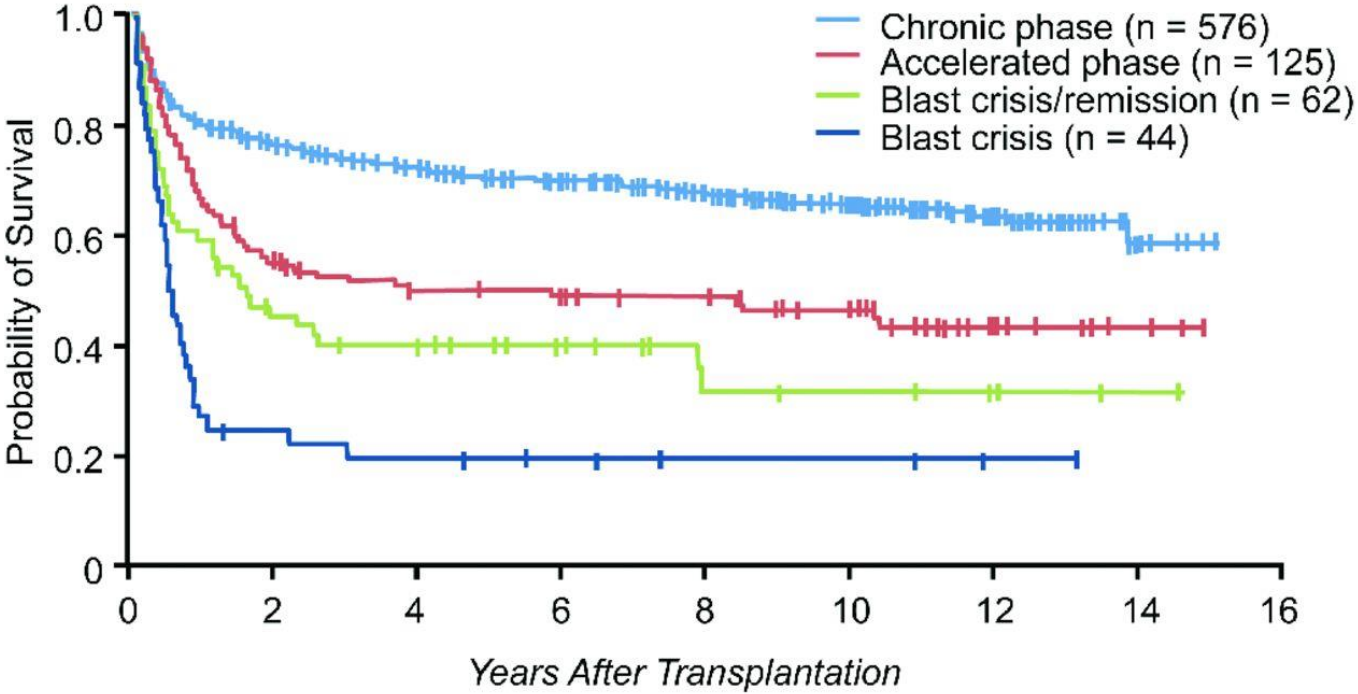




EBMT, European Society for Blood and Marrow Transplantation;
HCT, hematopoietic cell transplantation.

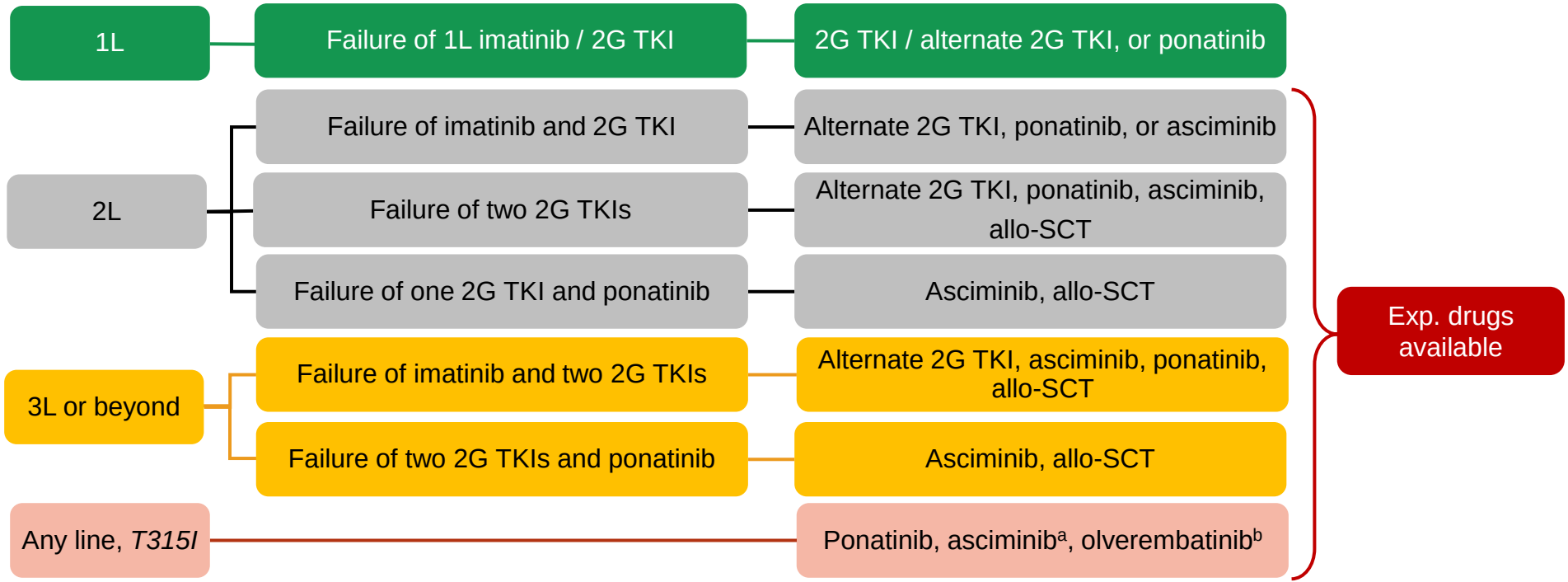
Passweg et al. Bone Marrow Transplantation. 2018;53:1139-48.

Outcome after allogeneic transplantation by phase of CML



Mughal et al. Haematologica. 2016;101:541-58.
Figure is courtesy of Dr Ted Gooley.

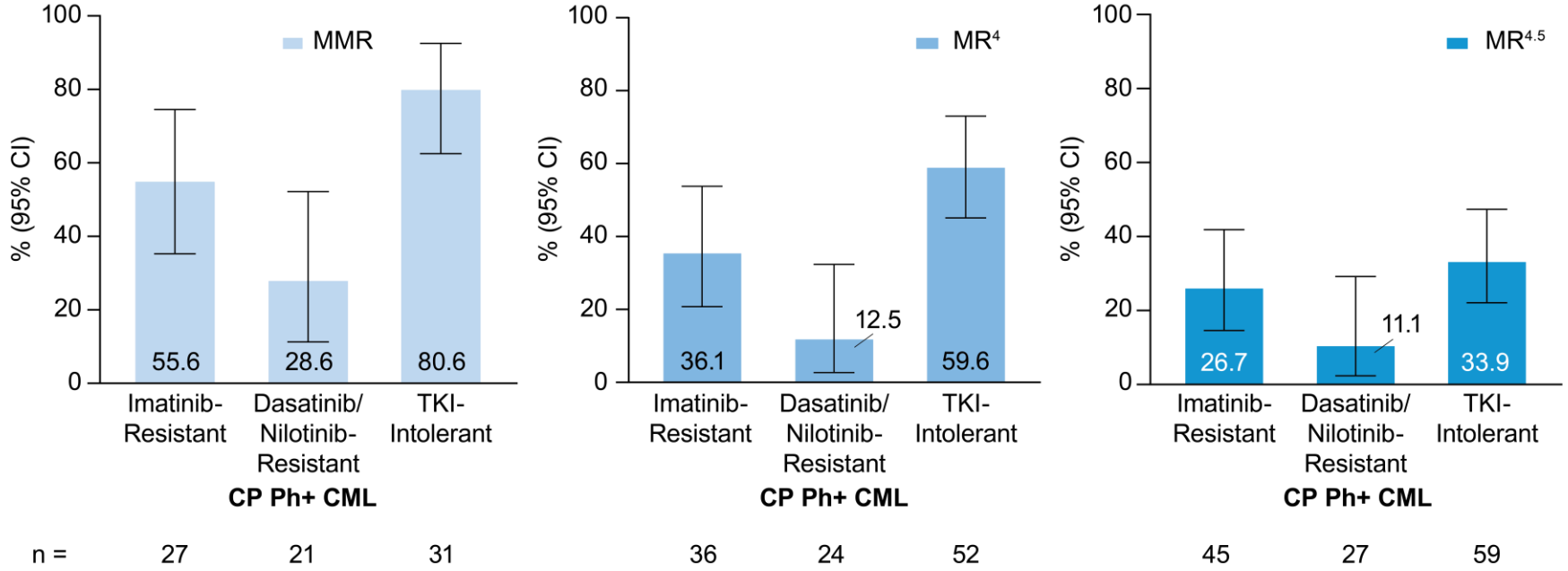
Conclusion: expanding arsenal to fight failure of TKIs



[a]USA approved, [b]China approved.
1L, first-line; 2G, 2nd generation, 2L, second-line; 3L, third-line.

Hochhaus et al. Leukemia. 2020;34:966-84.
NCCN. Chronic Myeloid Leukemia. Version 1.2022.

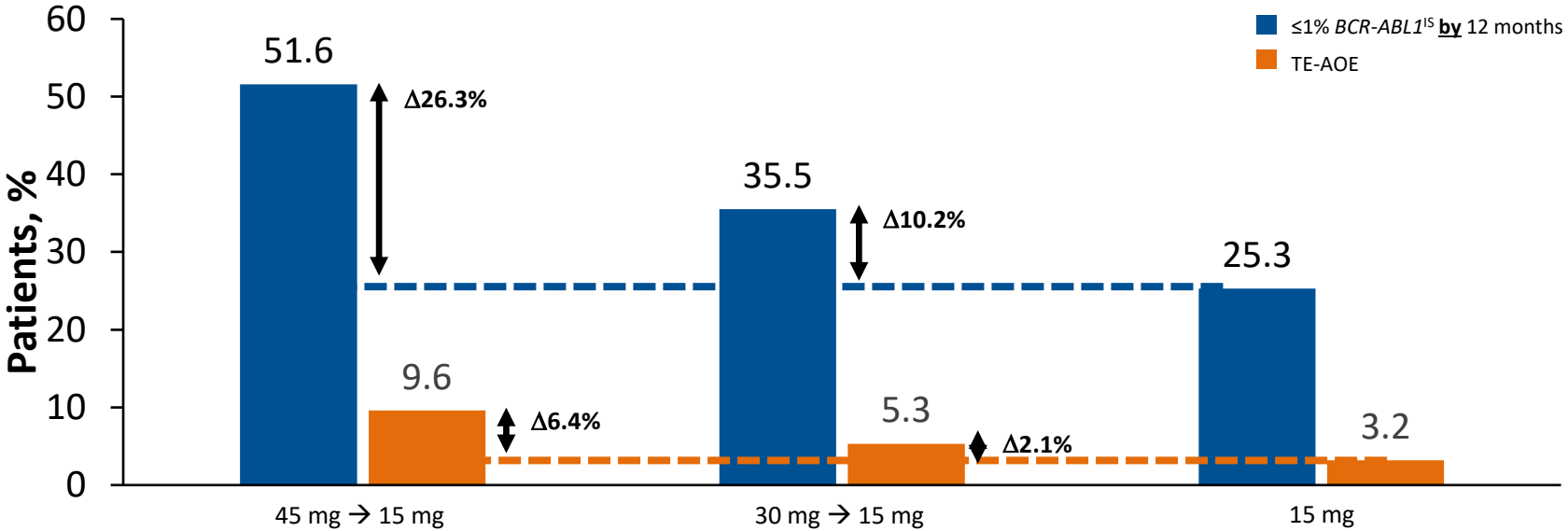
BYOND Study. Bosutinib in late line therapy: Cumulative Molecular Response Rates by 1 year, Excluding Patients With the Respective Baseline Response



Evaluable patients have a valid baseline molecular assessment without the respective endpoint response at baseline.
MMR (*BCR::ABL1* IS ≤0.1%), MR^4 (*BCR::ABL1* IS ≤0.01%), and $MR^{4.5}$ (*BCR::ABL1 IS* ≤0.0032%).
IS=international scale; MMR=major molecular response

Hochhaus et al. Leukemia. 2020;34:2125-37.

OPTIC Study: Overall Safety and Efficacy by Ponatinib Starting Dose

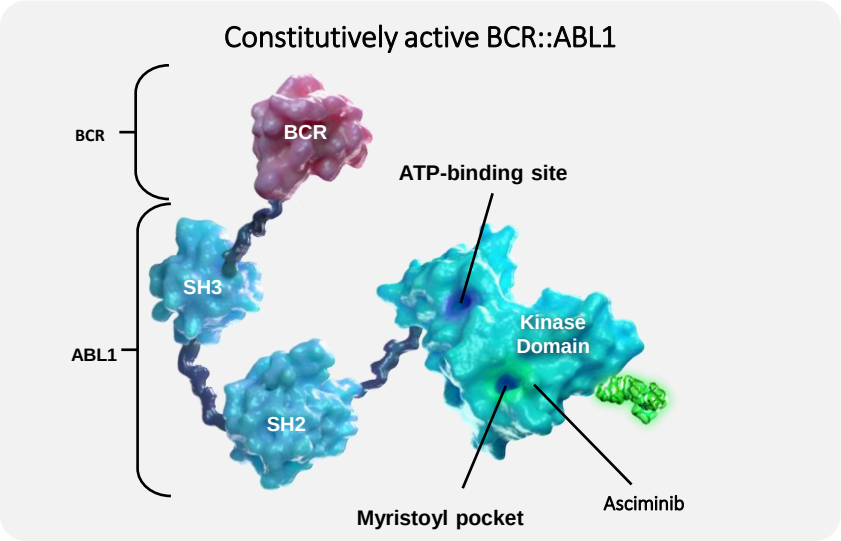


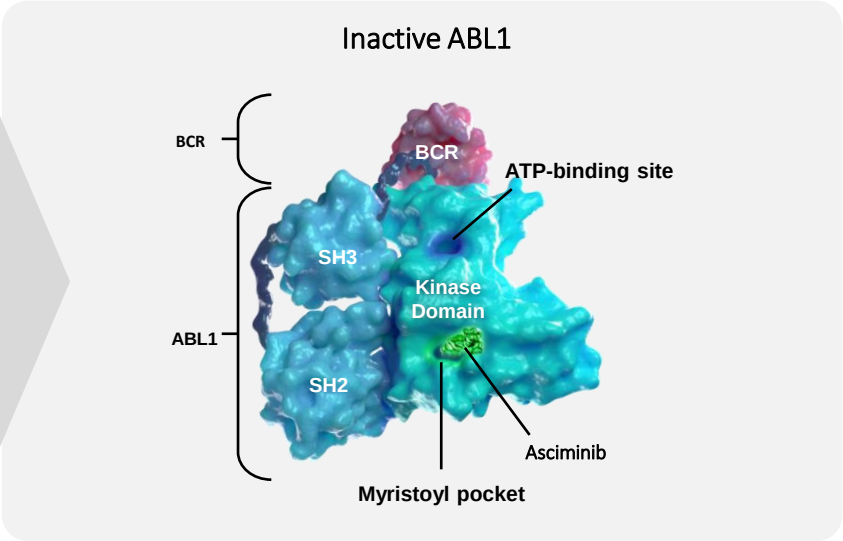
- The percentage of patients with ≤1% *BCR-ABL1*^{IS} decreased with decreasing doses
- The incidence of TE-AOEs decreased with decreasing doses

TE-AOE, treatment-emergent arterial occlusive event

Cortes J, et al. Blood. 2021;138:2042-50.

Asciminib is an investigational first-in-class STAMP (Specifically Targeting the BCR::ABL1 Myristoyl Pocket) inhibitor



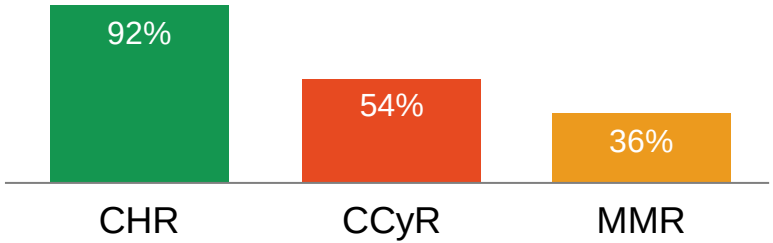


Hughes et al. N Engl J Med. 2019;381:2315-2326.

Asciminib: efficacy in phase 1 study

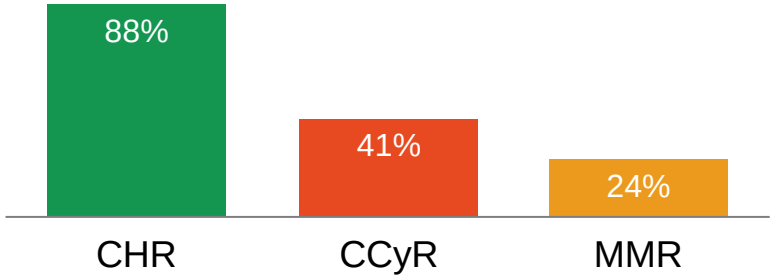
Asciminib was active in **heavily pretreated patients** with CML, including patients **pre-treated with ponatinib** and patients with a **T315I mutation**

12 months
CP patients without T315I



- 87% of patients maintained CCyR by 12 months
- 95% of patients maintained MR3 by 12 months
- MMR in patients with <2 previous TKIs: 47%
- MMR in patients with >2 previous TKIs: 34%
- MMR in patients pretreated with ponatinib: 40%

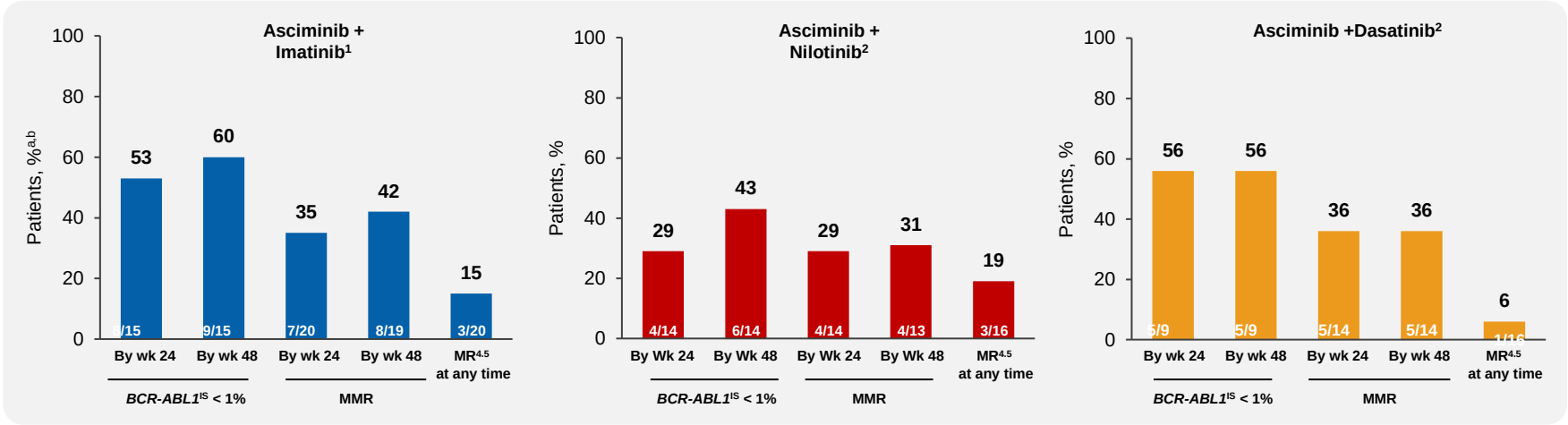
12 months
CP patients with T315I



- 67% of patients maintained CCyR by 12 months
- 1/18 patient maintained MR3 by 12 months
- MMR in patients with <2 previous TKIs: 38%
- MMR in patients with >2 previous TKIs: 11%
- MMR in patients pretreated with ponatinib: 17%

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

Asciminib in combination with imatinib, nilotinib, or dasatinib shows clinical activity in pretreated patients with CML-CP or -AP



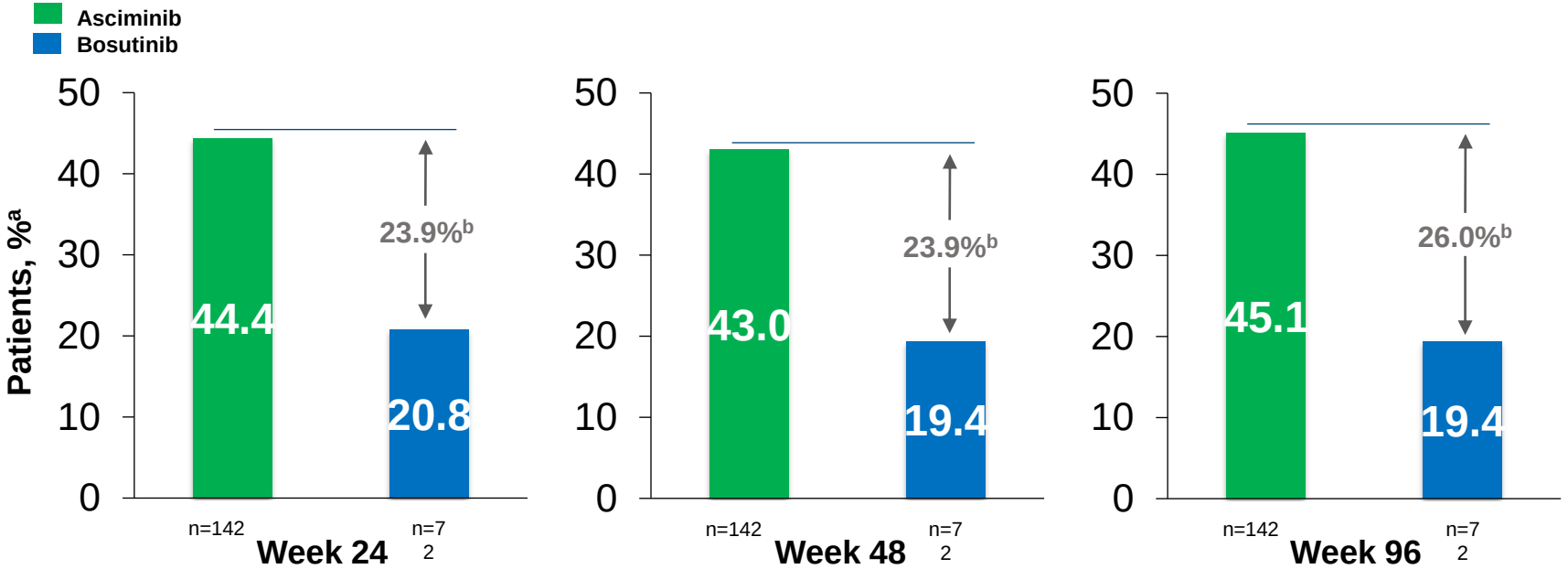
Cumulative molecular responses among evaluable patients without the respective responses at baseline:

Asciminib plus imatinib shows promising efficacy[1]:
- 60% (9/15) achieved *BCR-ABL1*^{IS} < 1% by 48 weeks
- 42% (8/19) achieved MMR by 48 weeks
- 15% (3/20) achieved MR$^{4.5}$ by 48 weeks

Asciminib plus nilotinib or dasatinib shows promising efficacy[2]:
- 43% (6/14) and 56% (5/9), respectively, achieved *BCR-ABL1*^{IS} < 1% with asciminib + nilotinib and asciminib + dasatinib by 48 weeks
- 31% (4/13) and 36% (5/14), respectively, achieved MMR by 48 weeks
- 14% (2/14) and 7% (1/14), respectively, achieved MR$^{4.5}$ by 48 weeks

Cortes et al. Presented at the 24th EHA Annual Congress. Abstract 1685.
Mauro et al. Presented at the 24th EHA Annual Congress. Abstract 1684.

ASCEMBL: Rates of *BCR::ABL1*^{IS} ≤1% at Weeks 24, 48, and 96 and Maintenance



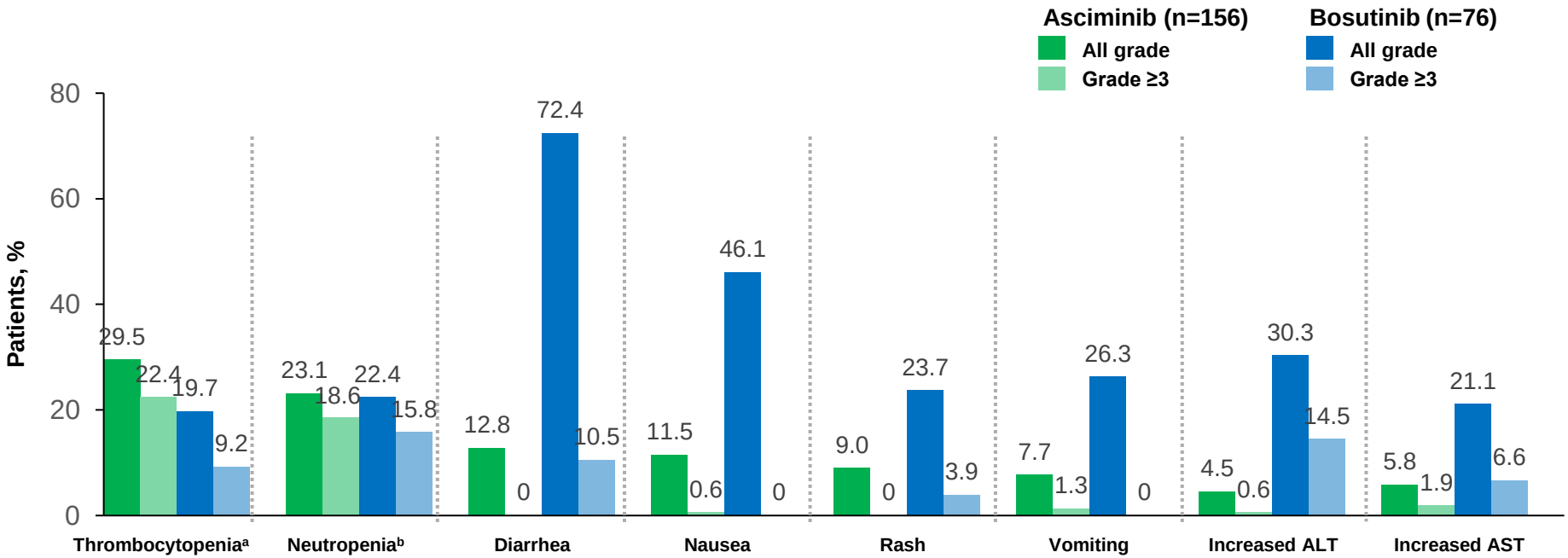
Maintenance of *BCR::ABL1*^{IS} ≤1%[c]

- 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%.

Hochhaus et al. Leukemia. 2023;37:617-26.

ASCEMBL: Most Frequent All-Grade AEs (in ≥20% of Patients in Any Arm)

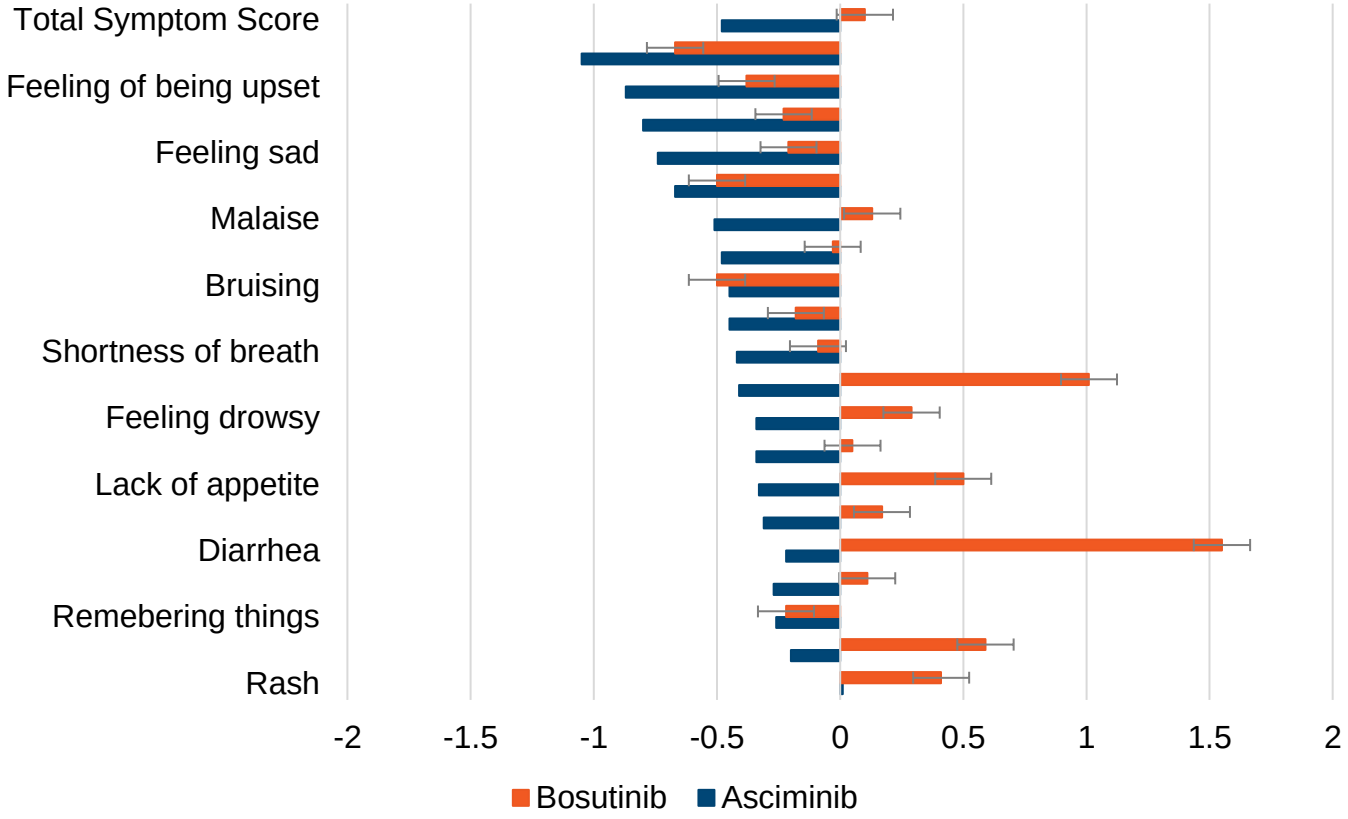


- Regardless of the longer duration of exposure, safety and tolerability of asciminib remained consistent with that at the time of the primary analysis, and continued to be better than with bosutinib with longer follow-up

[a] Includes thrombocytopenia and platelet count decreased.
[b] Includes neutropenia and neutrophil count decreased.

Hochhaus et al. Leukemia. 2023;37:617-26.

ASCEMBL: MDASI-CML Overall Quality of Life change from baseline (MMRM): Symptom items



Mauro et al. Poster presented at the Society of Hematologic Oncology 2021 Annual Meeting

Rough guide to 3L+ therapies

	Rotation of 2G-TKI	Ponatinib	Asciminib	Allo-SCT
Intolerance to ≥ 2 previous TKI	+		+++	
Resistance with BCR::ABL1 mutations	+	+	++	
T315I mutation		++	(+, US only)	++
Resistance without BCR::ABL1 mutations	+	++	++	+
High risk ACAs		+		+++
Recurrent cytopenias	+		++	+++

New ABL1 inhibitors

Olverembatinib (T315I active)

Vodobatinib, limited off-target activity

ELVN-001 (T315I active)

TERN-701 (allosteric, T315I active)

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