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Therapiewechsel in fortgeschrittener CML: Wann und Wie?

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14.10.24 Basel

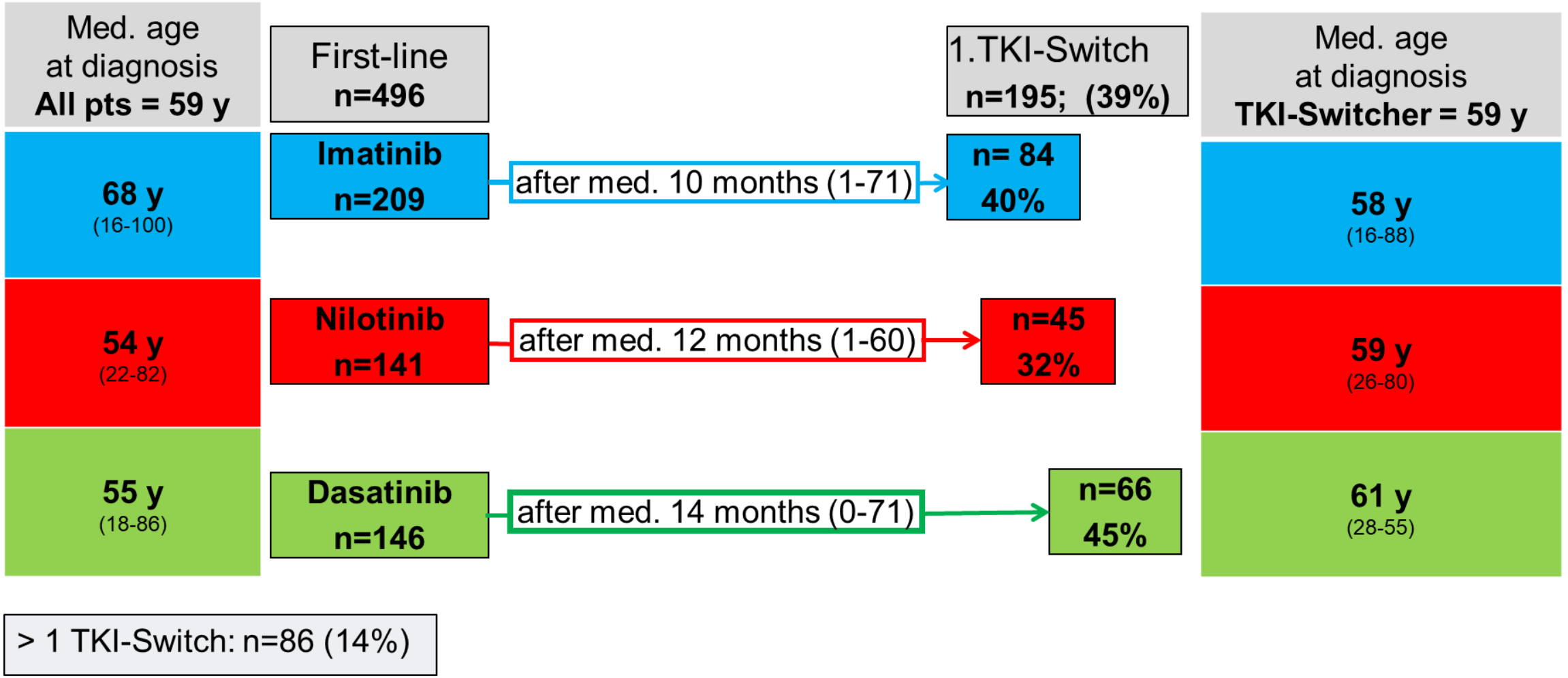
DE/ICLG/P24/0059

Disclosures

Research support / PI	BMS, Incyte, Novartis
Employee	NA
Honoraria	Incyte, Novartis, Pfizer, Roche, Zentiva
Major stockholder	NA
Scientific Advisory Board	Incyte, Novartis

NA, not applicable.

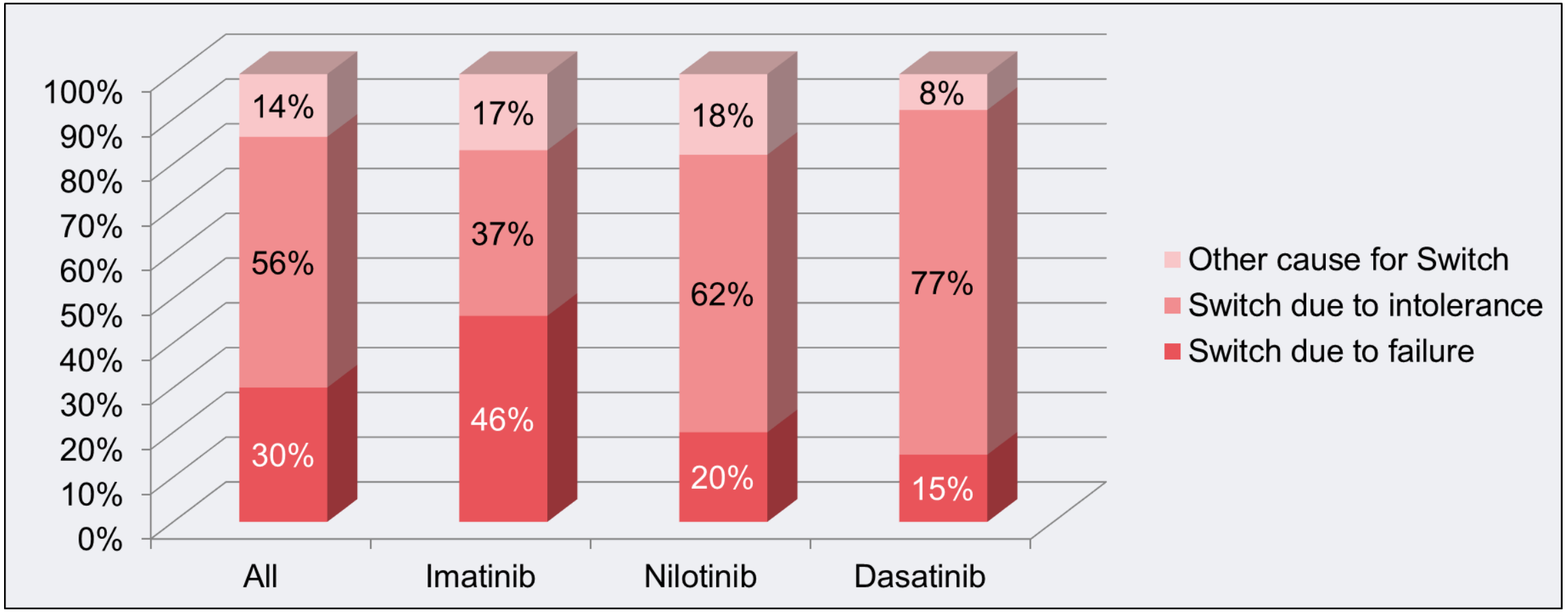
CML VI: Primary endpoint: TKI-Switch



> 1 TKI-Switch: n=86 (14%)

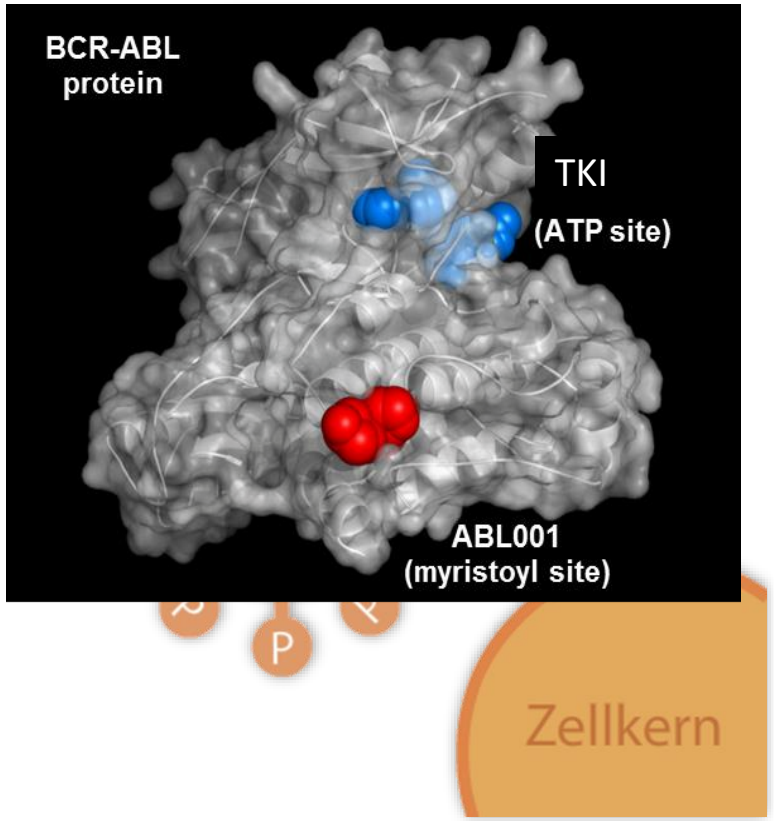
Kohlbrenner et al. ASH 2022

CML VI: Reason for Switch



Kohlbrenner et al. ASH 2022

Tyrosine kinase Inhibitors (TKIs) in CML

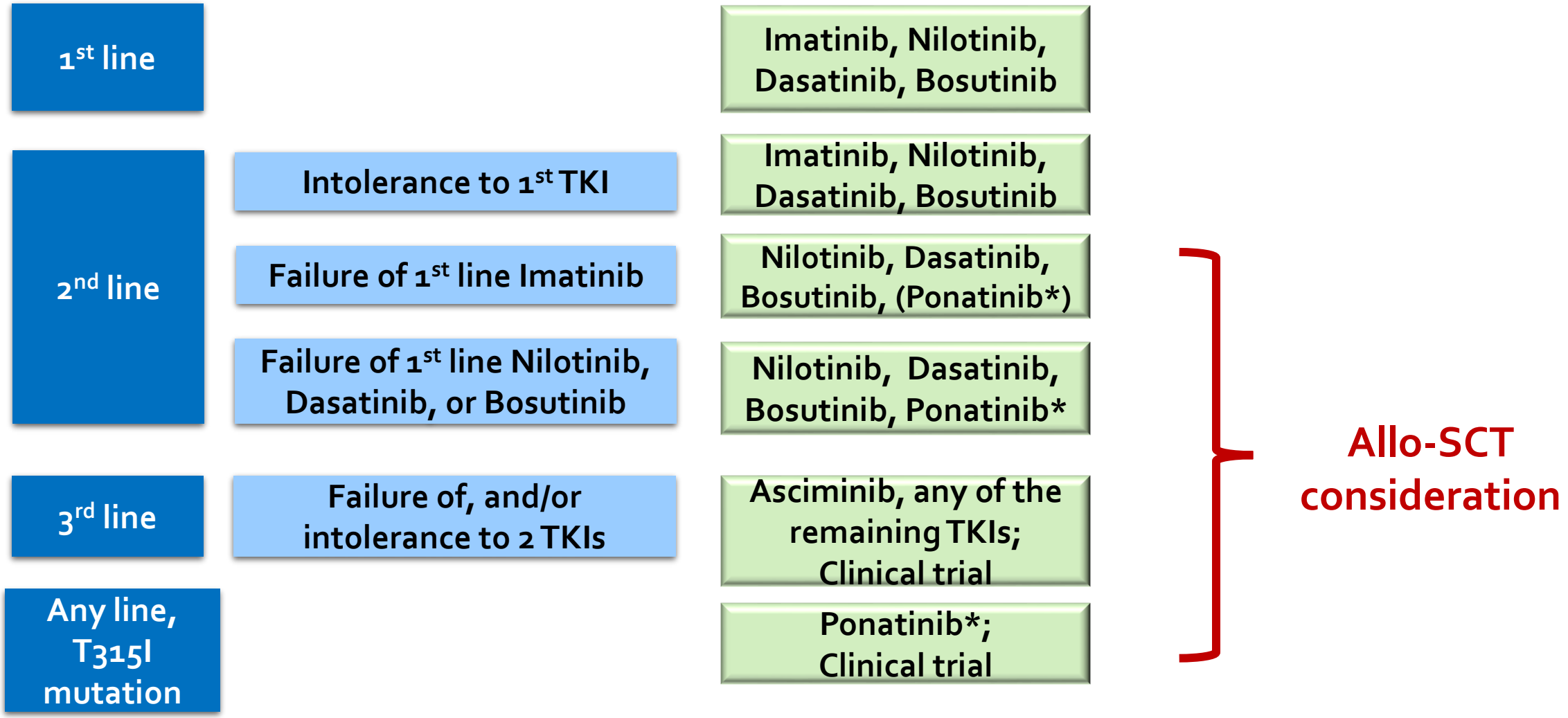


- Imatinib
- Dasatinib
- Nilotinib
- Bosutinib
- Ponatinib
- *ELVN*

- **Asciminib (ABL001)**
- ***TERN***

*Image adapted from Novartis and University of Adelaide, Tim Hughes

Treatment recommendations in CP-CML



Hochhaus et al., Leukemia 2020, 34:1495; * Ponatinibfachinformation, abrufbar unter: https://www.meet-incyte.de/fachinformationen/, 2022.03, Startdosis: 45 mg

What exactly means treatment line?

- Intolerance

OR

- Real resistance?

personal interpretation

ELN 2020 Treatment milestones

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

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

A change of treatment may be considered if MMR is not reached by 36–48 months.

NA not applicable, *ACA* additional chromosome abnormalities in Ph+ cells, *ELTS* EUTOS long term survival score.

[a]Loss of MMR (BCR-ABL1 > 0.1%) indicates failure after TFR

Hochhaus et al. Leukemia. 2020;34(4):966–984

Therapy decision in CML – independent of treatment line

Efficacy

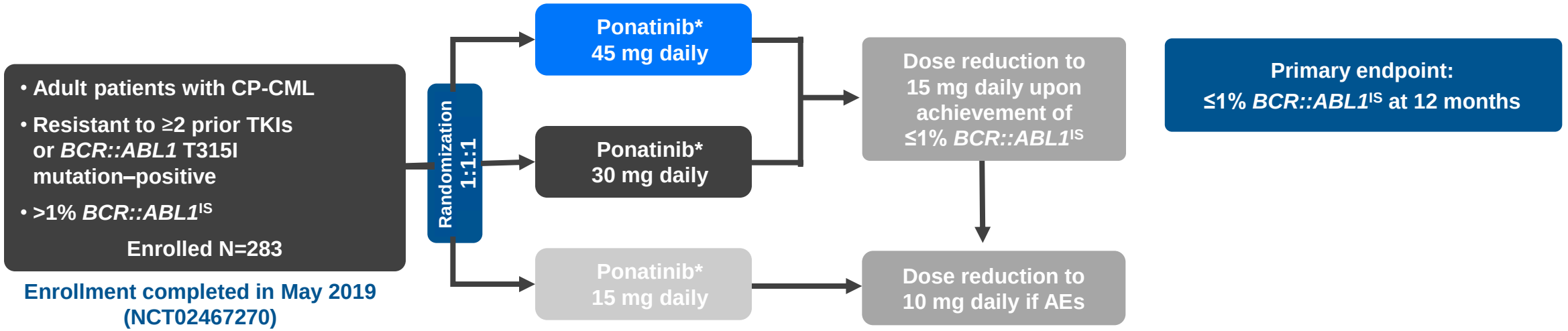
Adverse events
Toxicity
QoL

personal interpretation

Efficacy in focus

OPTIC (Optimizing Ponatinib Treatment In CP-CML): Study design

OPTIC is an ongoing multicenter randomized phase 2 trial

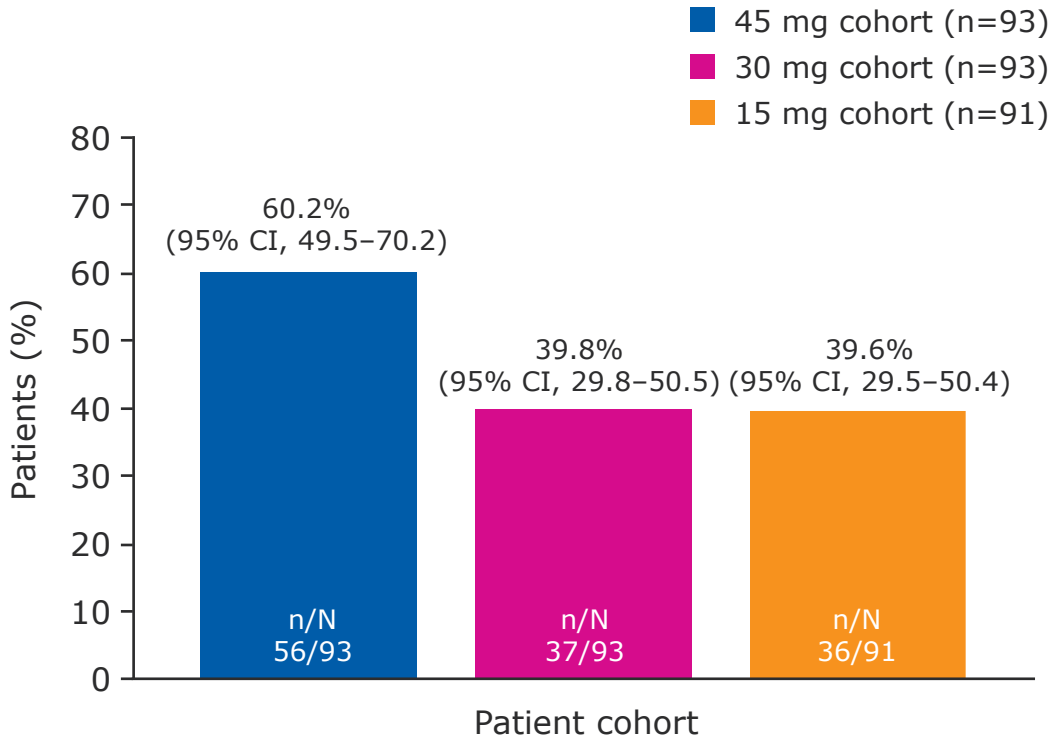


- At the data cutoff for the 4-year analysis (May 8, 2023), median follow-up in patients with the T315I mutation was 60.6, 63.5, and 60.7 months in the 45-mg, 30-mg, and 15-mg cohorts, respectively

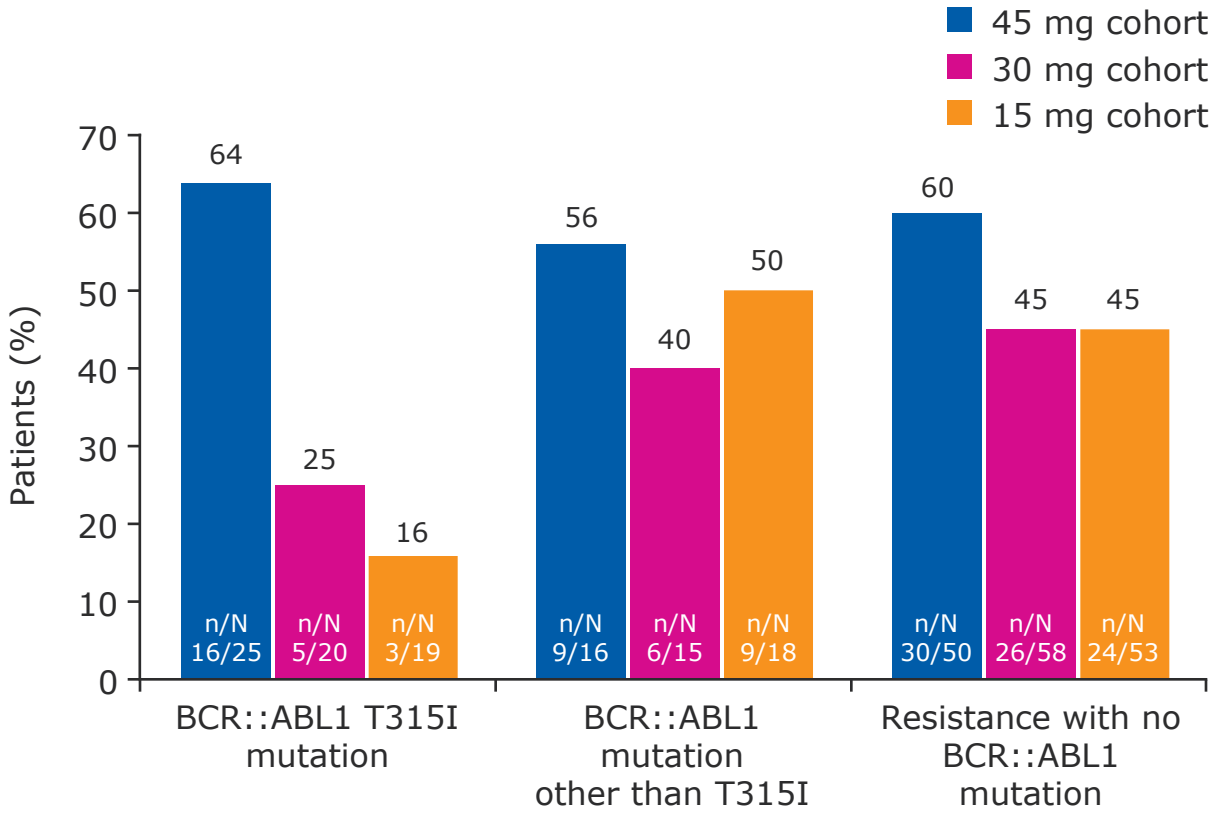
Deininger M, et al. Presented at ASCO2024; abstract #6501.

OPTIC* 3-year data
Remission rates according to dosage and mutation status

Patients achieving ≤1% BCR::ABL1^{IS} by 36 months



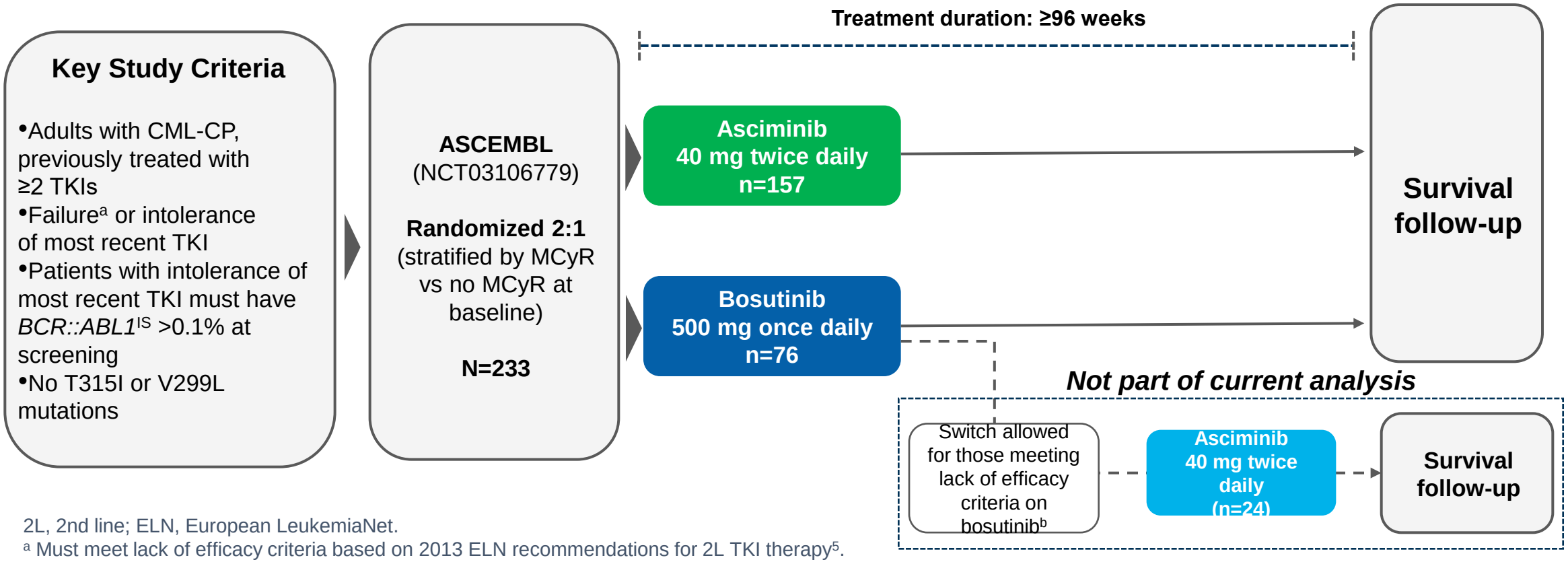
Patients achieving ≤1% BCR::ABL1^{IS} by 36 months by mutation status at baseline



Cortes JE, et al., ASH 2022; Abstract 620.

ASCEMBL Study Design

- **Data cutoff for current analysis:** October 6, 2021
- **Median duration of follow-up:** 2.3 years (120 weeks) from randomization to last contact date
- **Primary endpoint:** MMR rate at week 24
- **Key secondary endpoint:** MMR rate at week 96



2L, 2nd line; ELN, European LeukemiaNet.

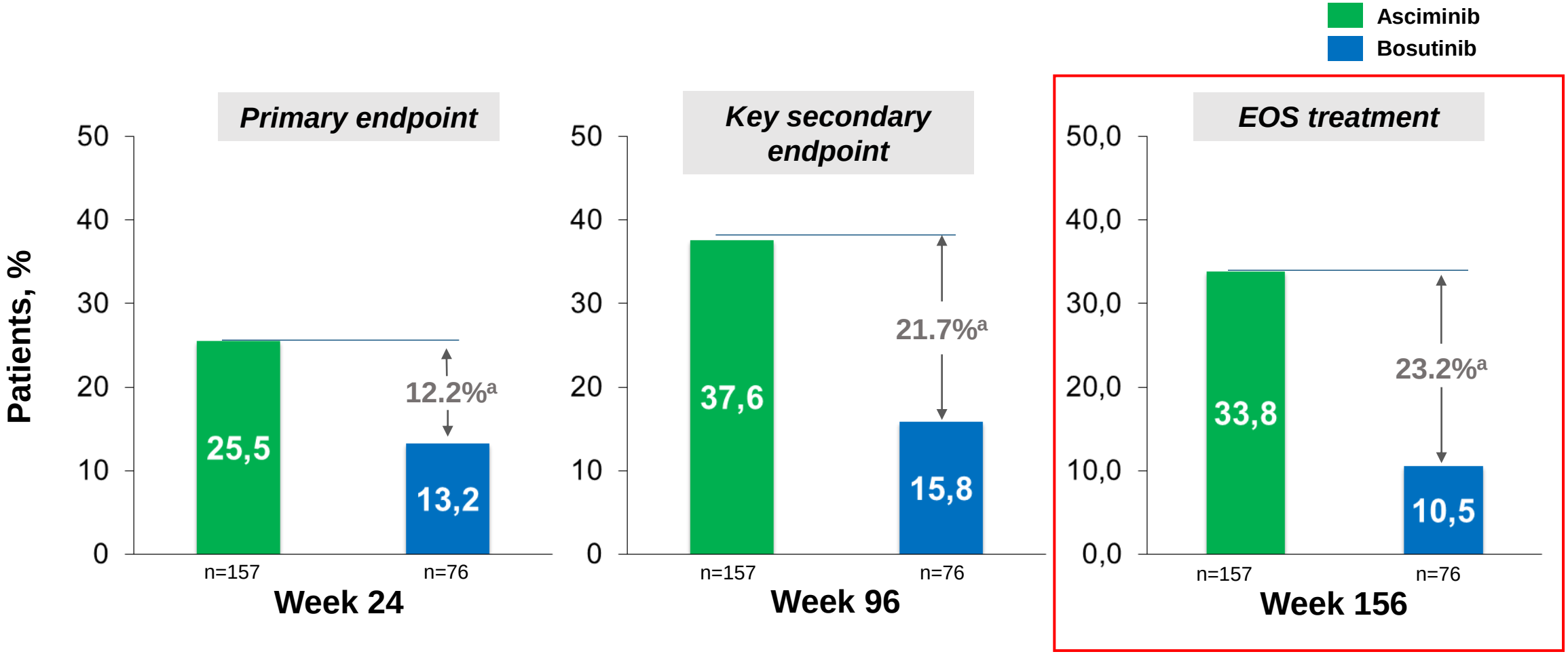
[a] Must meet lack of efficacy criteria based on 2013 ELN recommendations for 2L TKI therapy[5].

[b] Patients who discontinued bosutinib treatment due to intolerance or any reason other than lack of efficacy were ***not*** allowed to switch to asciminib.

Hughes, T et al., ASH 2022, Abstr. 3008

MMR Rates at Weeks 24, 96, and 156

Figure 3. MMR Rates at Weeks 24, 96, and 156



[a] The treatment difference after adjusting for the baseline MCyR status, was 12.2% (95% CI, 2.19%-22.3%; 2-sided *P*=0.029) at Week 24, 21.74% (95% CI, 10.53%-32.95%; two-sided *P*=0.001) at Week 96, and 23.16% (95% CI: 13.14, 33.18; 2-sided *P*<0.001) at Week 156.

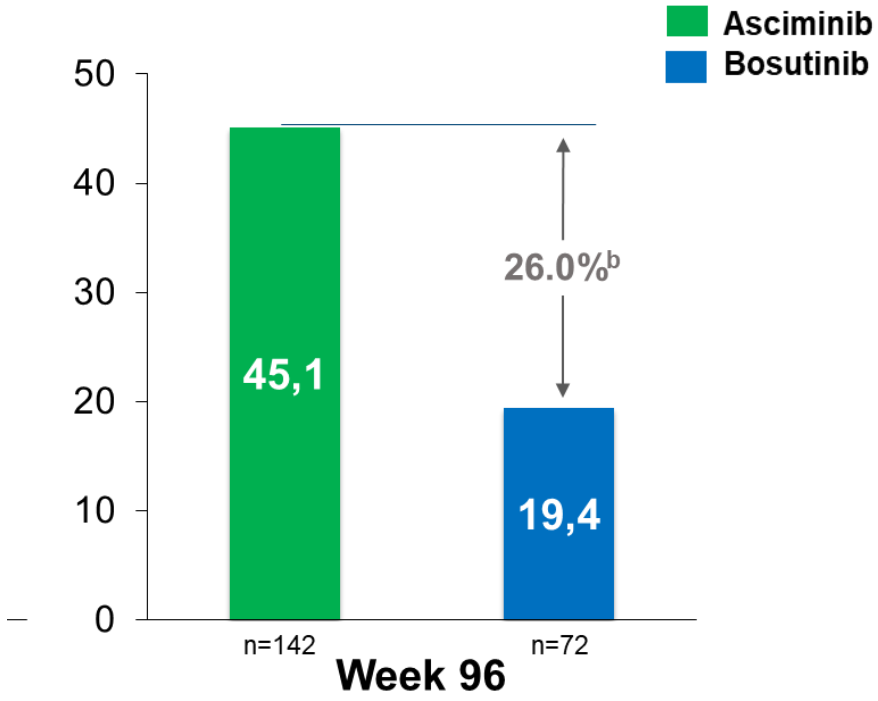
Poster presented at: 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California, & virtual.

Hughes, T et al., ASH 2022, Abstr. 3008

Remission rates Ascembl vs. OPTIC

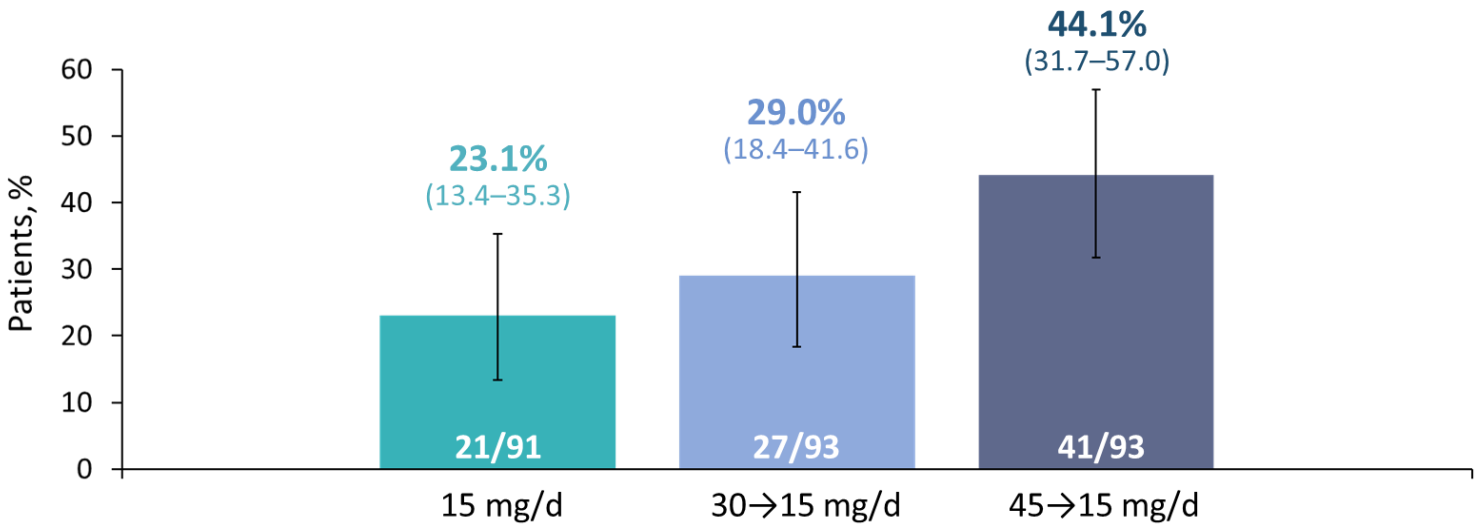
Ascembl

Rates of *BCR::ABL1*^{IS} ≤1% at Week 96



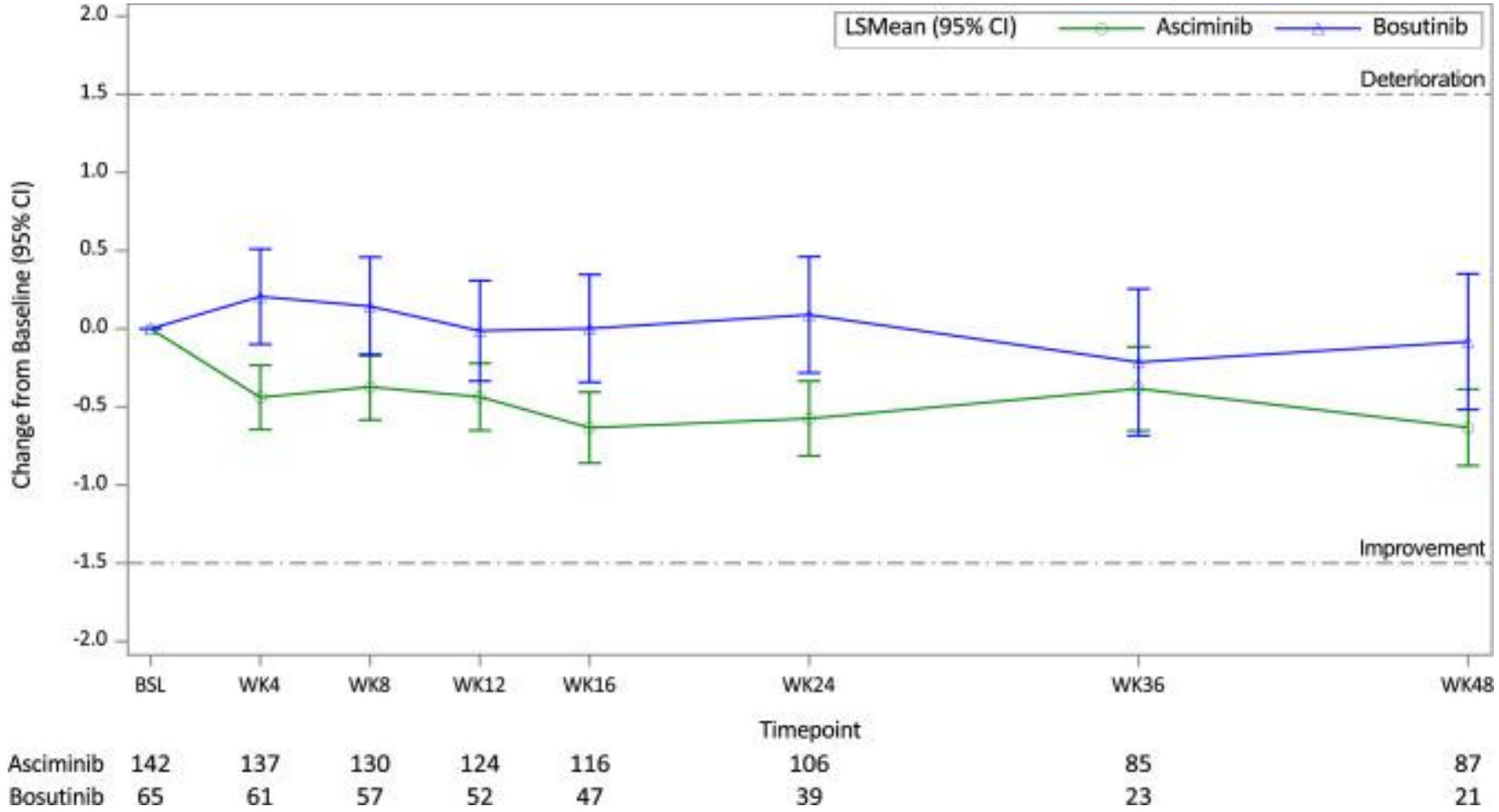
Optic

***BCR::ABL1*^{IS} ≤1% rate *at* 12 months (98.3% CI)**



This is an indirect comparison between Asciminib and Ponatinib, as data are from different clinical trials.

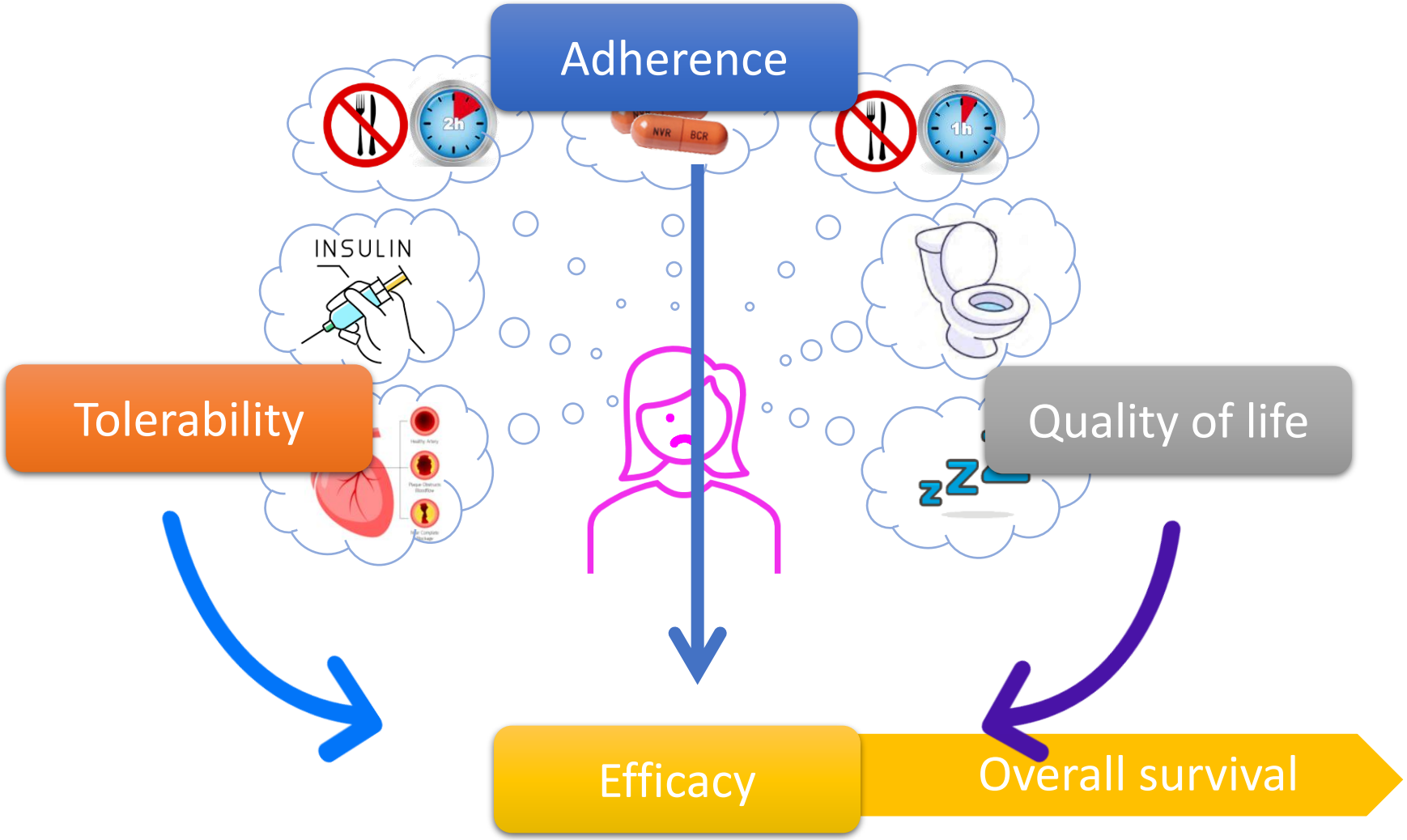
ASCEMBL: Change from Baseline in MDASI-CML Symptom Severity Score



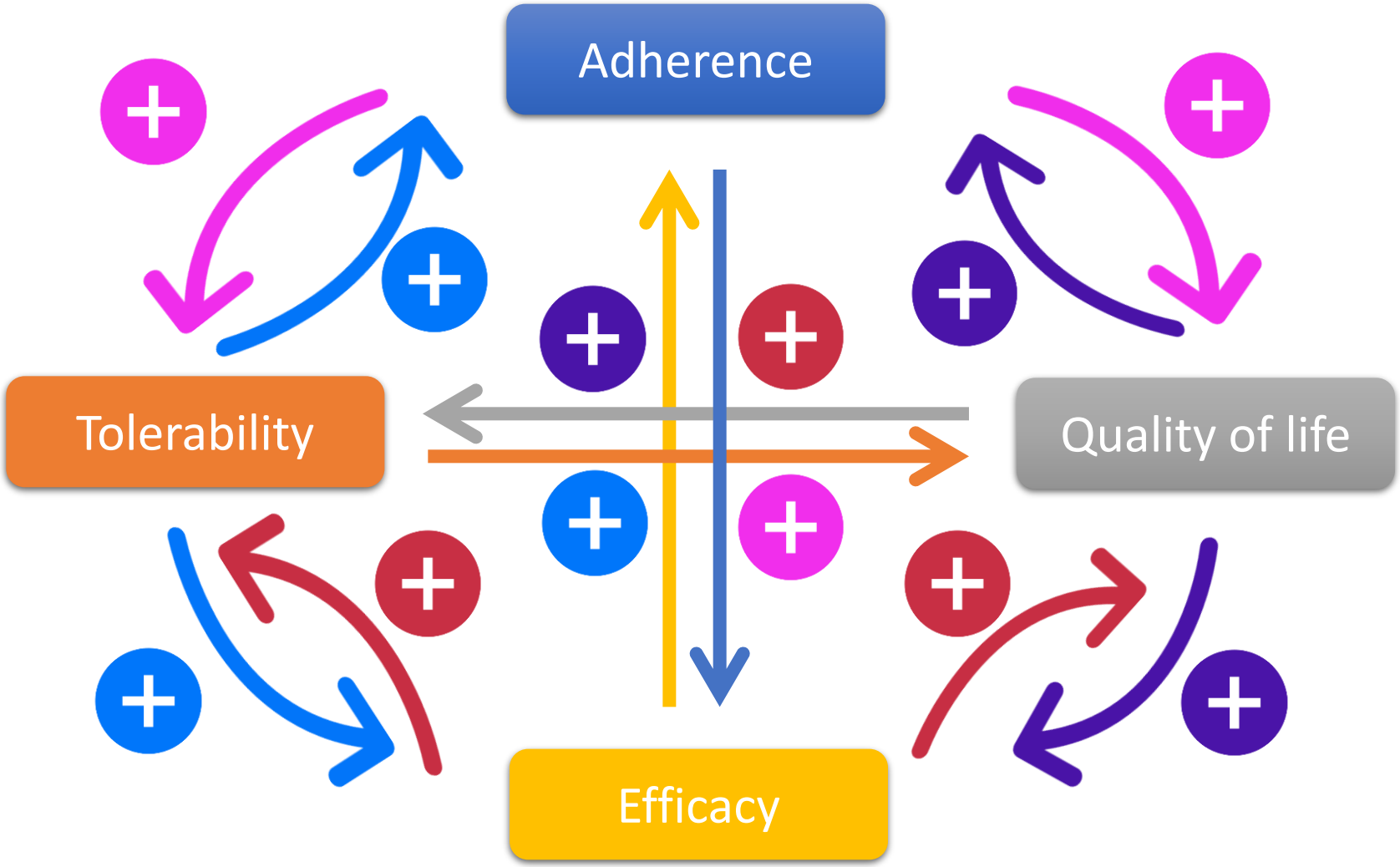
Rea et al., Leukemia. 2023; 37(5): 1060–1067

Intolerance in focus

How is daily life with CML?

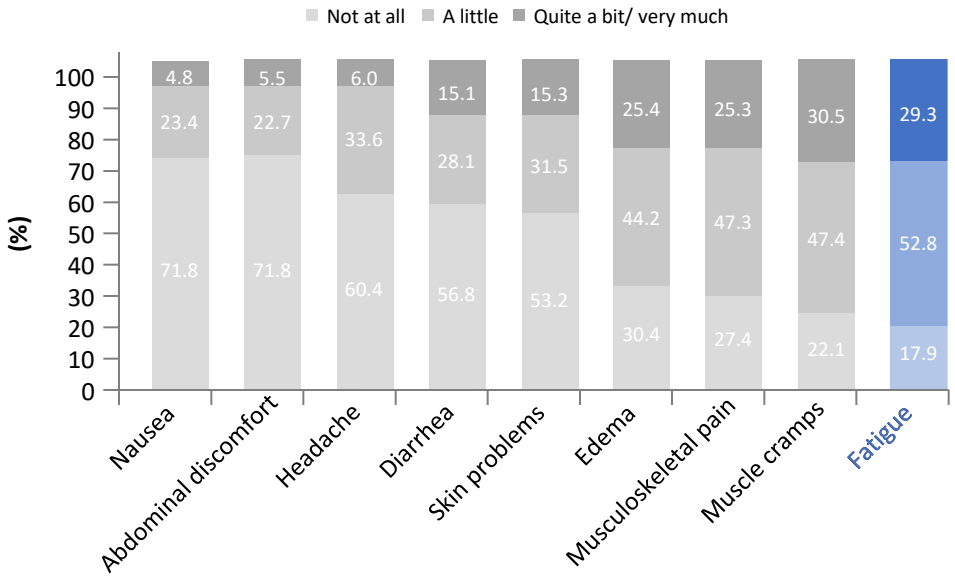


Everything is connected with everything



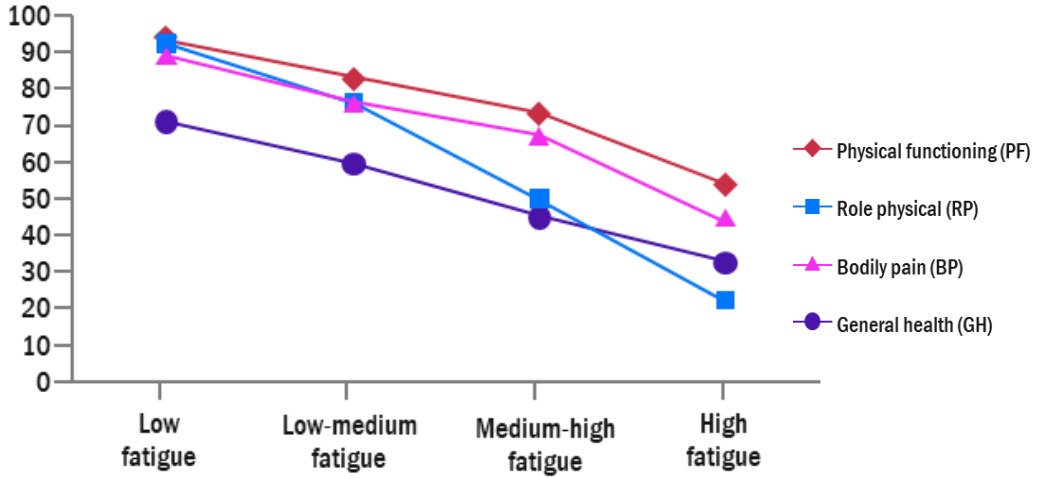
How does (in)tolerance affect QOL?

Non-hematologic AEs reported by patients



- Italy, multicentric, cross-sectional HRQoL study
- CML-CP, IM > 3 years, 1L
- N=448

Physical HRQOL aspects by fatigue severity

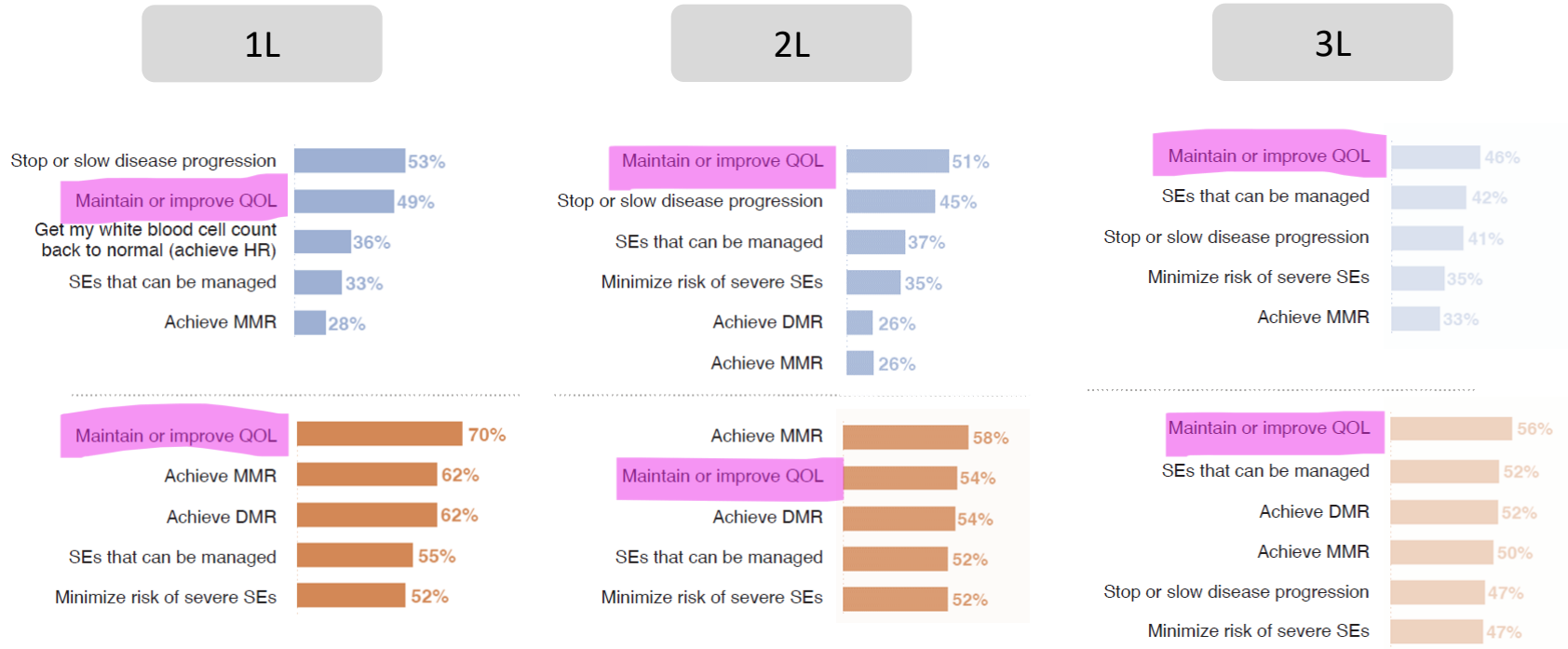


Efficace F, et al. Blood. 2011;118:4554-60. Efficace F, et al. Leukemia. 2013;27:1511-9.

How relevant is QOL to TKI therapy?

- The CML Sun survey
- Online
- 361 patients and 198 physicians; 11 countries

TKI treatment goals perceived by patients and physicians



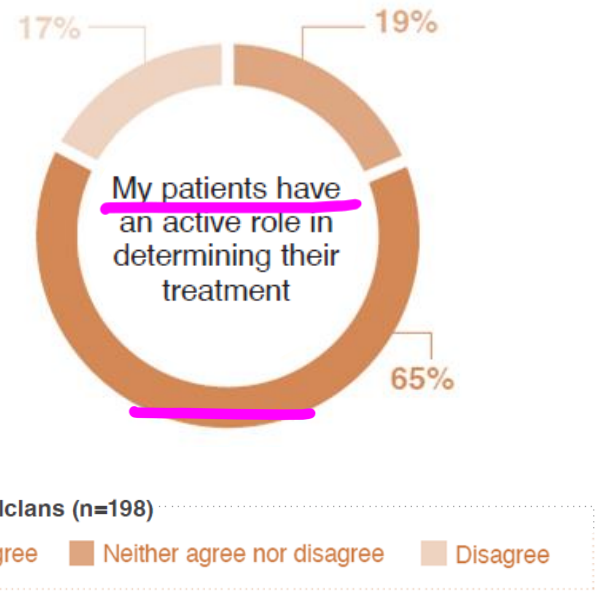
Lang F, et al. Presented at EHA 2023; abstract P668.

Optimizing TKI tolerability by shared decision-making

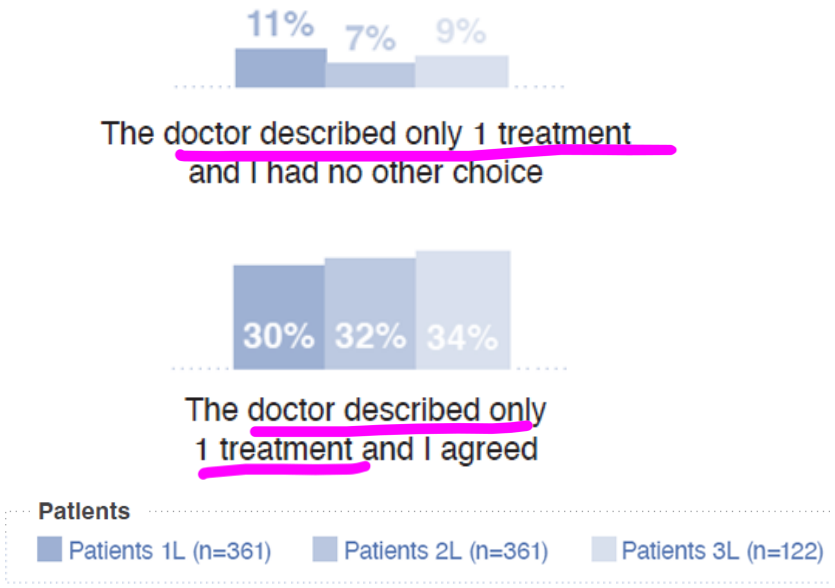
Patient and physician input on treatment selections

- The CML Sun survey
- Online
- 361 patients and 198 physicians; 11 countries

Physicians' expectations



Patients' expectations



Lang F, et al. Presented at EHA 2023; abstract P668.

Relative toxicity of TKIs

Side effects	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib	Asciminib
Myelosuppression	++	+	+	+	+	+
Edema	++	-	++	-	-	-
Muscle/Bone pain	++	-	+	-	+	-
Diarrhea	++	+	+	+++	+	-
Hepatic	+	++	+	+++	+	(+)
Glucose/Cholesterol elevation	-	++	-	-	-	-
Arterial thrombotic events	-	++	(+)	(+)	+++	?
	Nausea	Rash	Hemorrhage	Nausea	Abdominal pain	Hypertension

Lipton et al, Blood Reviews , 2022 Nov:56:100968

Zusammenfassung

- Auswahl des TKI jeweils unter Berücksichtigung von Effizienz und Toxizität/QoL
- Bei Therapieversagen Option mit Ponatinib und Asciminib, bisher kein direkter Vergleich bzgl Effizienz, allo SZT nicht vergessen
- Bei Intoleranz QoL bei Patienten und Ärzten im Fokus, allerdings zeigt sich ein Unterschied in der Wahrnehmung bei gemeinsamen Entscheidungsprozessen (Shared decision making)
- Bzgl Verträglichkeit ergeben sich aus Studiendaten Hinweise für einen Vorteil bei Asciminib, prospektive Real World Studiendaten sind rar