ELN 2025 recommendations

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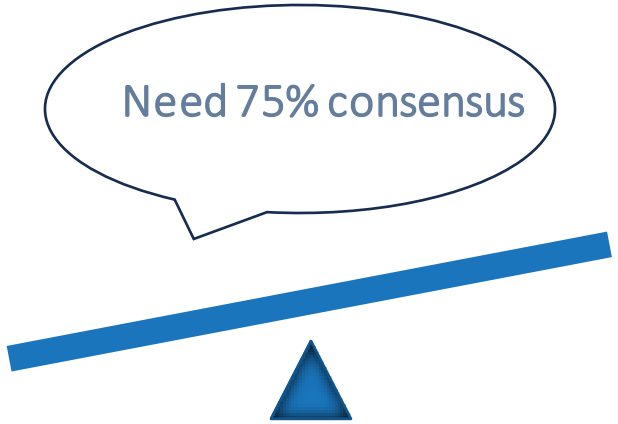
DISCLOSURES OF COMMERCIAL SUPPORT

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board
Incyte	√				√	√
Novartis	√				√	√
Ascentage	√					√
Pfizer					√	
Ascentage						√

Updates (v.5)

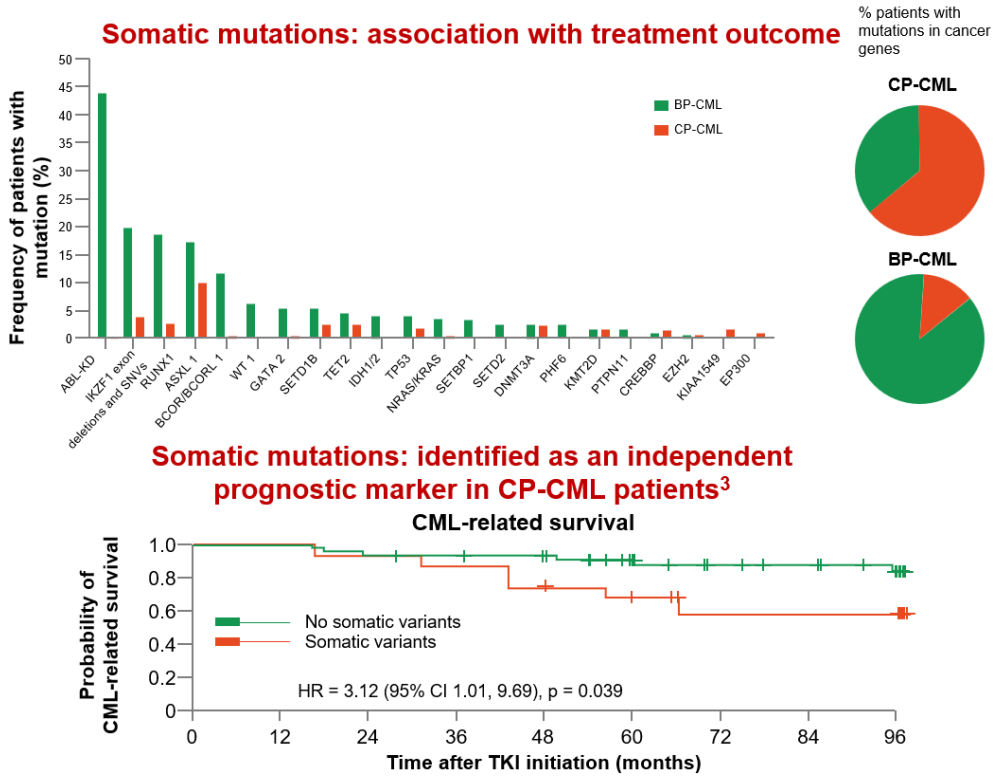
- Diagnosis
- Disease classification
- Prognosis
- Monitoring response to treatment
- Milestones of response
- Resistance and BCR::ABL1 mutations
- First line treatment
- Second line treatment
- Treatment beyond second line therapy
- Advanced phase disease
- Allogeneic stem cell transplantation
- Treatment free remission
- Parenting
- Adverse event (side-effects)

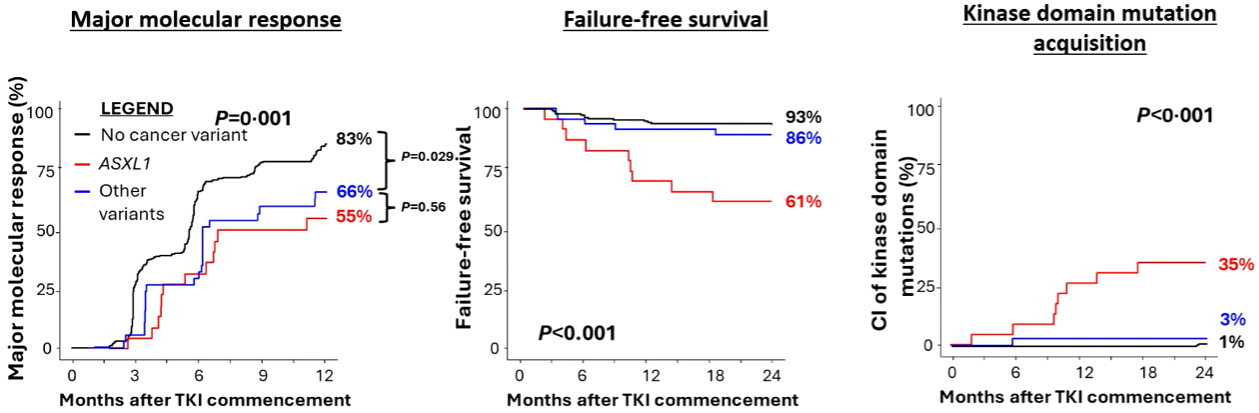


Prognosis

- ELTS √ Sokal/Hasford x
- High risk ACA at diagnosis: 3q26.2,-7/7q-, +8, 11q23, i(17q), +17,+19, +21, +Ph, complex
- (Transcript type, e13a2 *vs* e14a2)
- (Somatic mutations)
    - Currently a research tool
    - Possible impact on depth of response and EFS, but not OS
    - No clear therapeutic implication
    - ASXL1 mutations, 10% of patients

Impact of ASXL1 at diagnosis





Fabarius A, et al. Ann Hematol. 2015;94:2015-24; Adnan-Awad S. Leuk Lymphoma. 2021;62:2064-78, Nteliopoulos G, et al. Haematologica. 2019;104:2400-9, Shanmuganathan N et al, Blood 2025

Molecular response milestones for 1st, 2nd and 3rd line TKI

ELN 2025 recommendations: **No patient is a failure**

- Change in milestone terminology
- At 12 months: personalised approach to BCR::ABL1 of 1-10% [IS]

	FAVOURABLE Treatment switch unnecessary	**WARNING** Treatment switch may become necessary	**UNFAVOURABLE** Treatment switch preferred High risk of resistance
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%-established resistance
12 months	≤0.1%	0.1–1%	>1% (1–10%—see text)
Any time	≤0.1%	>0.1–1% loss of ≤0.1% (MMR)	Loss of a previous response, resistant BCR::ABL1 mutations, high-risk ACA

CML 2025: Therapeutic recommendations

ELN 2025 recommendations

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NCCN Guidelines Version 1.2026
Chronic Myeloid Leukemia

EARLY TREATMENT RESPONSE MILESTONES
CRITERIA FOR RESPONSE AND RELAPSE

BCR::ABL1 (IS)	3 months	6 months	12 months[n]
>10%[o]	YELLOW	RED	
>1%–10%[p]	GREEN		ORANGE
>0.1%–1%	GREEN		LIGHT GREEN
≤0.1%	GREEN		

COLOR	CONCERN	RECOMMENDATIONS[r,i]
RED	TKI-resistant disease[t]	Switch to alternate TKI (CML-5) (other than imatinib) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance[t]	Switch to alternate TKI (CML-5) or Continue same TKI[o]
ORANGE	Possible TKI resistance[t]	Consider switch to alternate TKI[p] (CML-5) or Continue the same TKI if CCyR is achieved
LIGHT GREEN	TKI-sensitive disease	• If optimal: continue same TKI • If not optimal: shared decision-making with patient[q,t]
GREEN	TKI-sensitive disease	Continue same TKI[u]

2G, second-generation; AP, accelerated phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; DMR, deep molecular response; IS, international reporting scale; MMR, major molecular response; TKI, tyrosine kinase inhibitor; TFR, treatment-free remission

Why were the ELN failure milestones revisited ?

- Patients in the ELN 2020 ‘failure’ category included
  - late responders
  - older patients/those with co-morbidities who are at greater risk of significant adverse events with more potent drugs

- Data from a number of studies show that patients in the failure category at 3, 6 and 12 months have similar 10-15yr survival to those meeting the favourable milestones

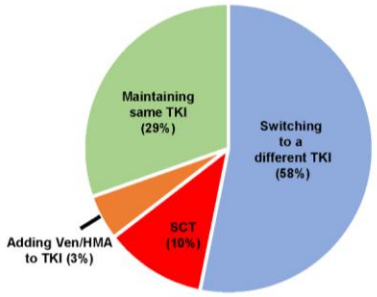
- Meeting optimal milestones may provide more patients with TFR opportunities

CML without MMR after 2 years of TKI treatment (2003-2020)

- 131 patients between 2003-2020 who failed to achieve MMR within 2 years
- Despite not achieving MMR, 79 (60%) patients were maintained on their frontline treatment in the first 2 years
- 13 (10%) received ≥ 3 treatment lines
- At 2 years

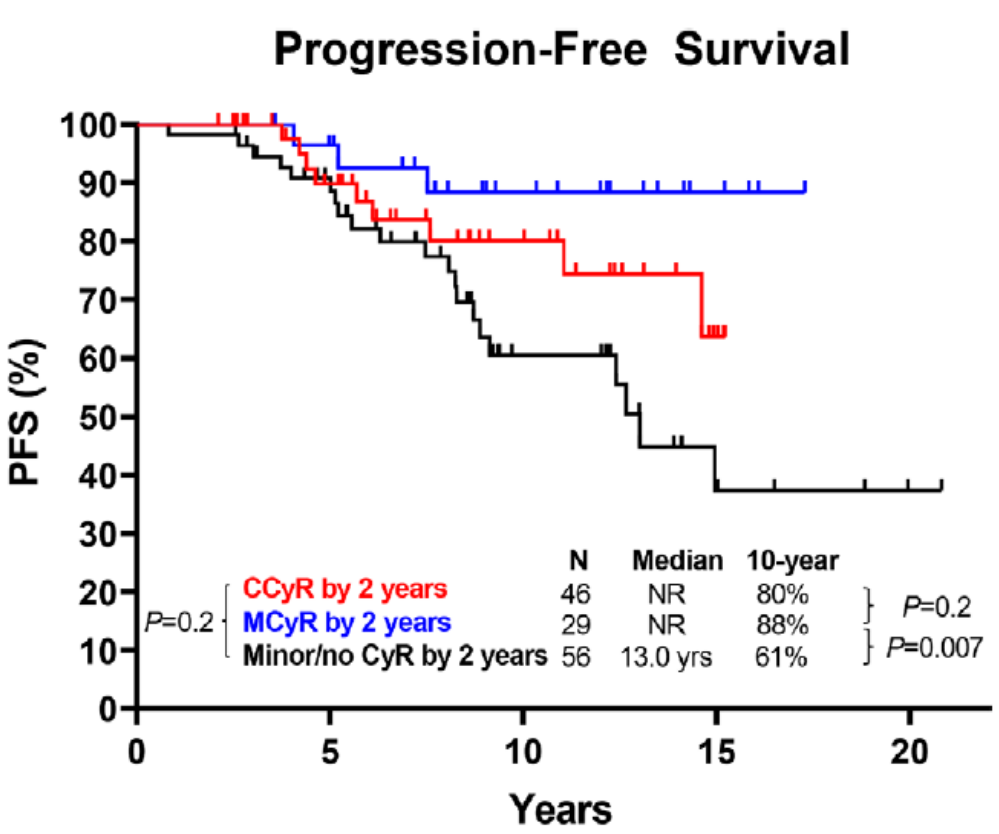
Patient n, %	CyR	RQ-PCR
46, (35)	CCyR	0.1-1%
29, (22)	MCyR	1-10%
56, (43)	no or minor CyR	>10%

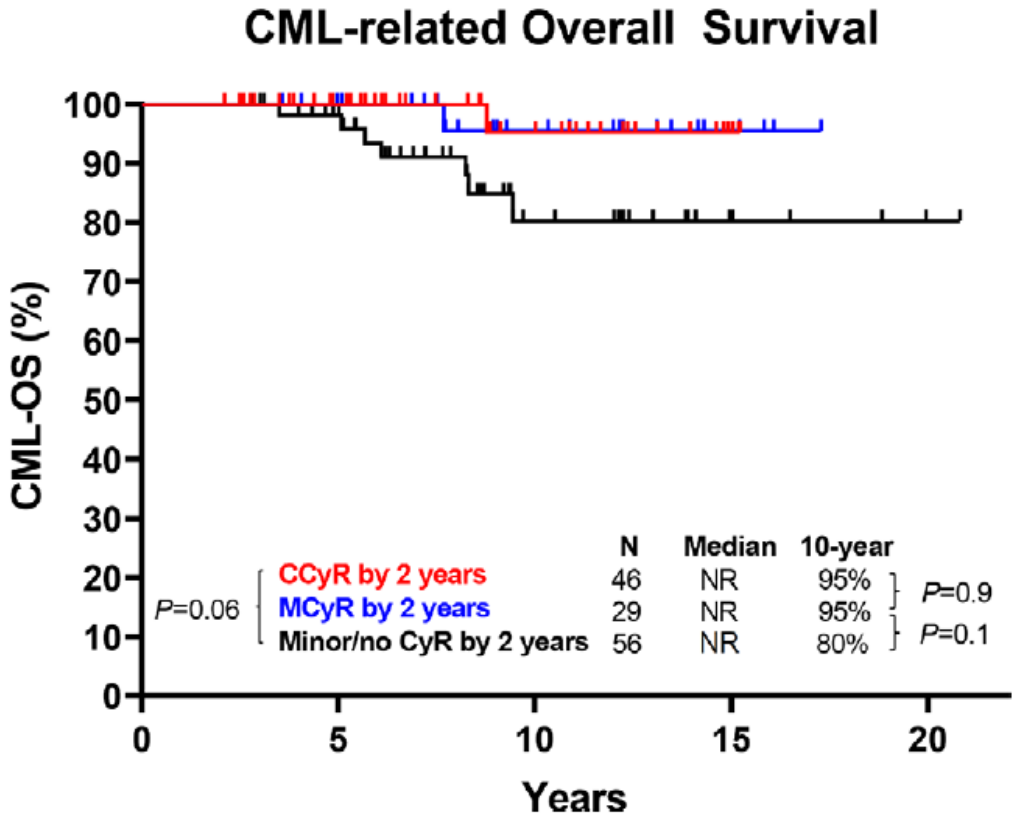
- 15 (11%) patients progressed – 11/15 RQ-PCR >10% at 2 years
- 79/131 eventually achieved MMR, 24 CCyR, 19 MCyR, 9 no or minor CCyR
- 29 MCyR patients: n=13, no change; 16 switched to alternative TKI



Bidikian *et al*, Am J Hematol. 2023; 98(4): 639-644.

CML-CP patients who did not achieve MMR after 2 years of TKI therapy: PFS and OS by 2-year landmark analysis





10-yr CML-OS: 88%

- Patients who achieved CCyR within the first 2 years of TKI treatment had similar 10-year PFS as patients who only achieved MCyR
- The 10-year OS was 95% in patients who had achieved MCyR or CCyR as their best response
  80% in patients who had achieved a minor or no cytogenetic response

MCyR; roughly equivalent to *BCR::ABL1* <10%

Bidikian *et al*, Am J Hematol. 2023; 98(4): 639-644

German CML-study IV: landmark survival analyses according to response levels of ≤0.1%, >0.1–1%, >1–10% and >10% BCR::ABL1^{IS} at 3, 6, 12 and 24 months

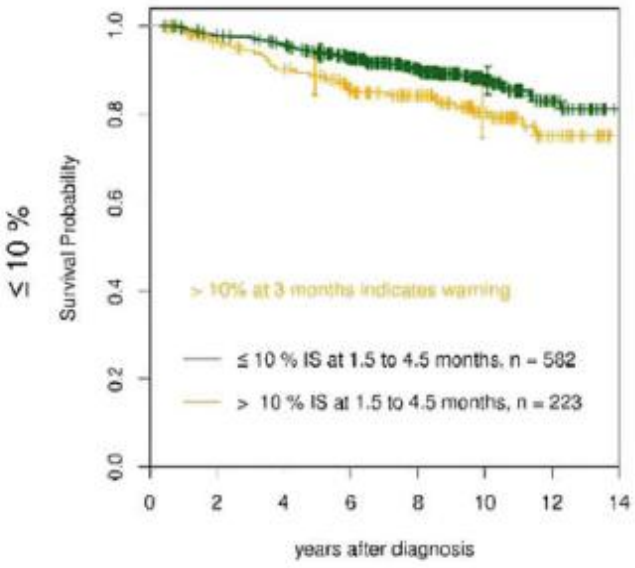
- **CML IV: randomised 5-arm study; 1,536 patients treated with imatinib with or without IFN or Ara-C, 2002-2012**
- **Analysis of 1,342 patients who only received imatinib and with regular RQ-PCR tests: evaluable at one or more timepoints**
- **FU up to 14yrs**

Months after diagnosis	3	6	12	24
Patients (n)	805	891	861	755
>10% BCR::ABL1^{IS}	223 (28%)	104 (12%)	65 (8%)	37 (5%)
Early deaths within 12 months after landmark: after progression / total	2/4	7/7	8/9	3/4

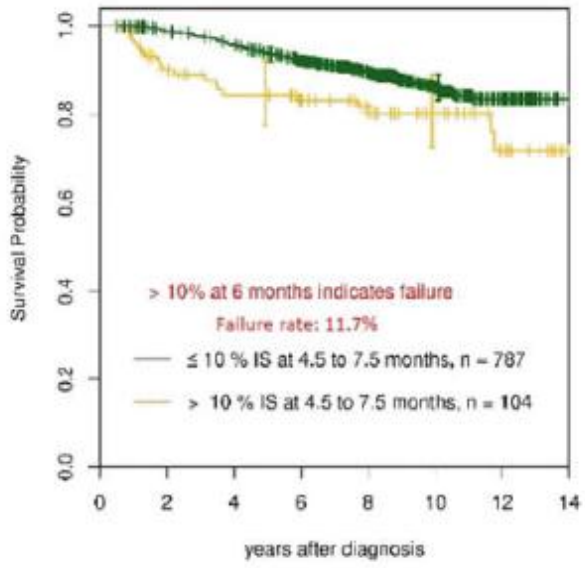
- The number of non-responders > 10% BCR::ABL1^{IS} level decreases from 3 months to 24 mo
- Numbers of deaths within 1 year after the landmarks are low
- Patients with >10% at 3 and 6 months BCR::ABL1^{IS} have late responses and a low risk of early death from CML

Hehlmann, R., Lauseker, M. *Leukemia* **38**, 465–466 (2024)

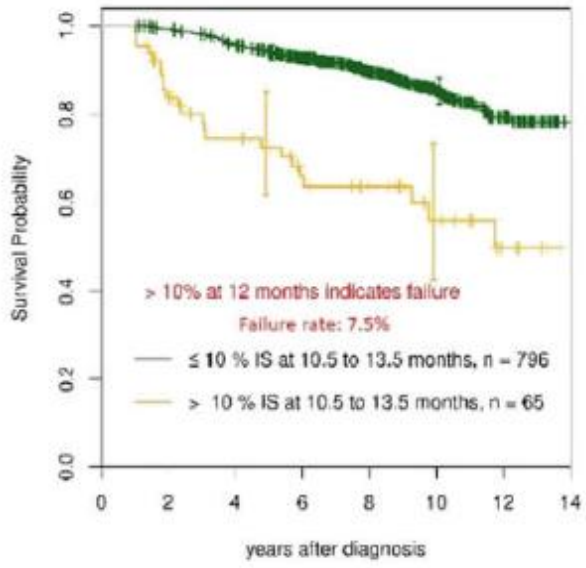
CML-study IV: Outcome by response < or >10%^{IS} at 3, 6, 12 and 24 months



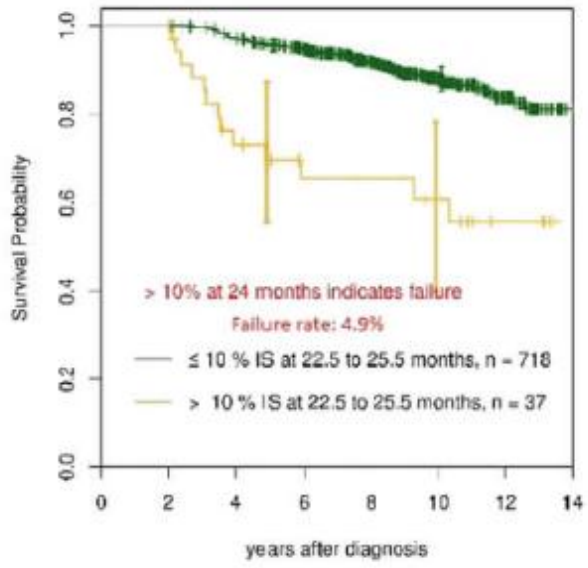
3 months



6 months



12 months

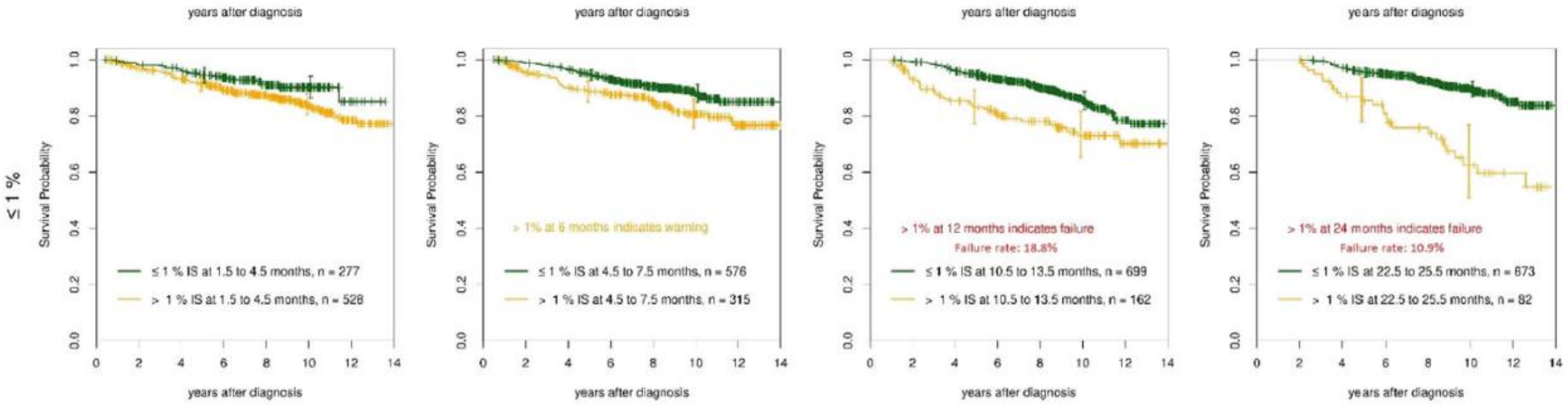


24 months

- Failure at 3–**6 months** (BCR::ABL1 transcripts >10%), had a 10–12 yr survival of about 70% (10% lower than those who met the milestones)
- Worse survival if >10% at **12 and 24 months** with 55–60% 10-year survival rate- argument that this is a more accurate definition of TKI 'failure'?

Lauseker, M *et al*., *Leukemia* 37, 2231–2236 (2023); Kantarjian, *Leukemia* 37,2324–2325((2023)

CML-study IV: Outcome by response < or >1%^{IS} at 3, 6, 12 and 24 months



3 months | 6 months | 12 months | 24 months

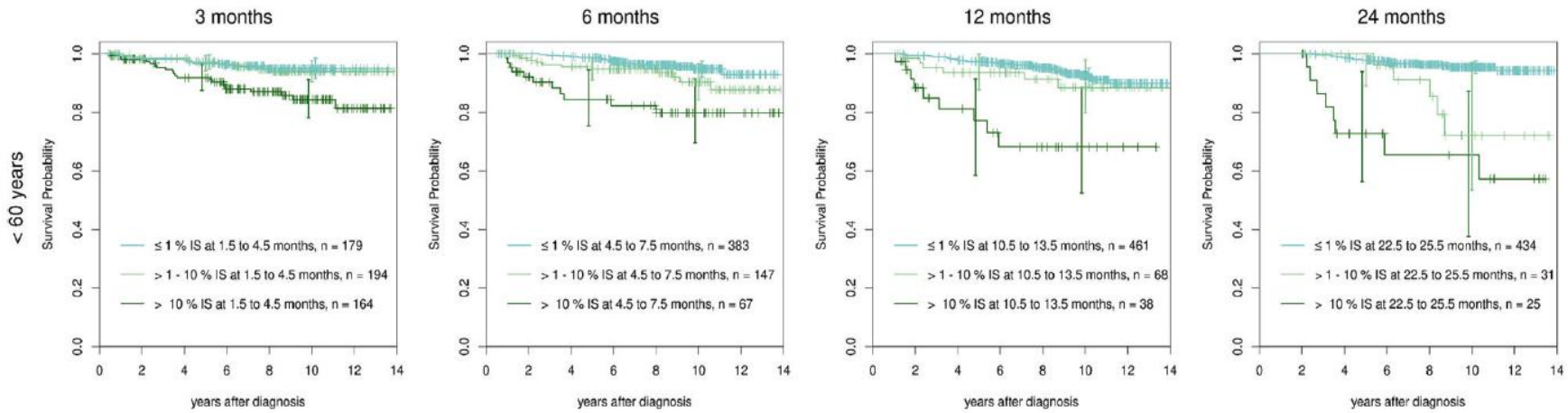
- Previous ELN 2020 failure category at **12–24 months** (BCR::ABL1 transcripts >1%) had a 10–12 yr survival of about 70%
- Patients with BCR:ABL1 transcripts <1% have **almost** the same 5-10 yr survival rates as those with lower values than this
- For 1–10% at **12 months,** the 10-yr survival rate was the same as that of patients with transcripts <1%— around 80%
- Patients with transcripts >1–10% at **24 months** had a 5-yr survival rate similar to those with transcripts <1%, however, the 10-year survival rate was closer to 60%

Lauseker, M *et al*., *Leukemia* **37**, 2231–2236 (2023)

CML-study IV: landmark analyses – outcome by age

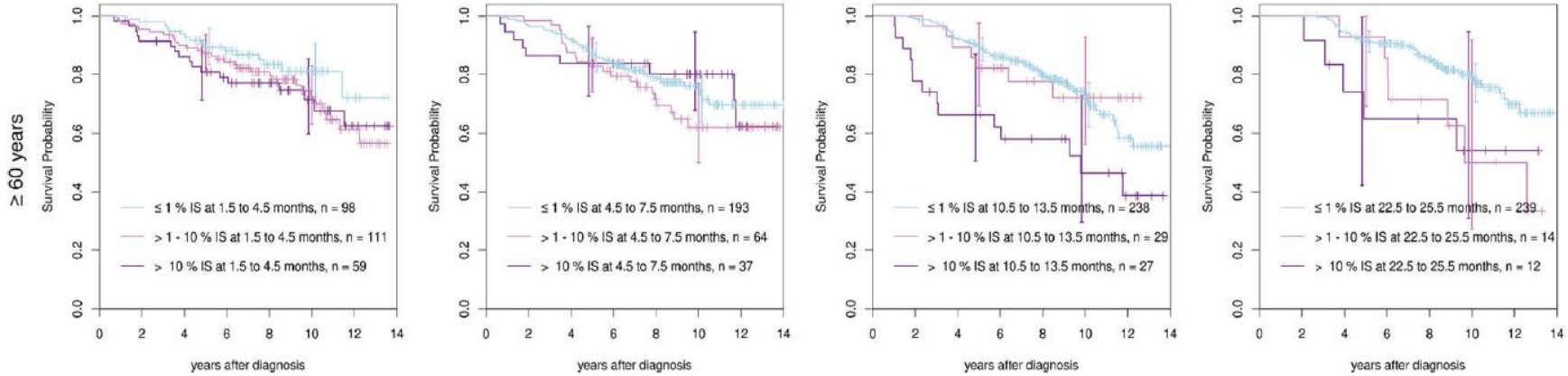
AGE

<60yrs



Survival probability

>60yrs



Survival probability

- Worse survival in age>60 yrs, whereas reaching milestones occurred at a similar rate
- >10% BCR::ABL1^{IS} at 12 months is associated with a fall in 10-yr OS in both age groups
- Worse survival age <60 yrs were mostly CML-related; age >60 yrs, non-CML related

Lauseker, M *et al*., *Leukemia* **37**, 2231–2236 (2023)

EMR (3-mo BCR::ABL^{IS} ≤1% and 6-mo BCR::ABL^{IS} ≤0.1%) is predictive for the achievement of DMR

- CML-CP patients, n=206
- 2010- 2018
- received imatinib or nilotinib

	Cumulative incidence of MR^4 according to BCR::ABL at 3 months		
BCR::ABL1^{IS} at 3 months	**24 months, %**	**36 months, %**	**48 months, %**
>10%	5.7	10.2	18.3
≤10%	28.9	42.7	62.2
≤1%	40.7	55.4	87.3

- EMR achieved more frequently with a more potent TKIs

German population registry for CML

- the rate of pts who could start TFR after achieving the ELN-milestones was 4-5 times higher than of pts who failed milestones

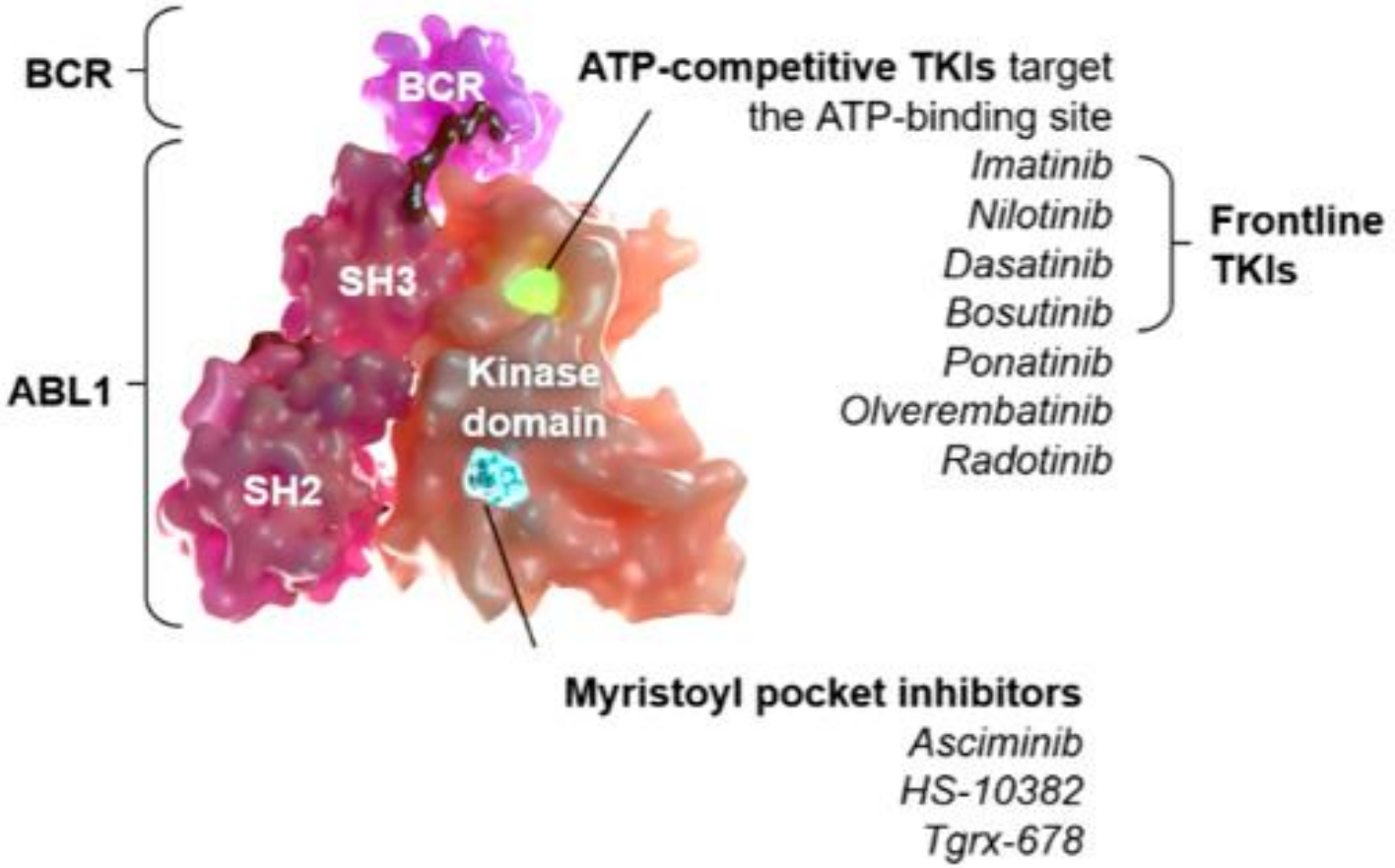
Wang R, et al. *Medicine*. 2019;98(15):e15222. 2. Pennisi MS, et al. *Frontiers in Oncology*. 2019;9:764; ; Kohlbrenner K et al, Hemasphere 2024 8 (supplement 1): 713

First line treatment

- 5 TKI licensed for 1L treatment
- Rates of CCyR, MMR, DMR and progression to advanced phase favour 1L 2G-TKI
- No OS benefit
- No difference in EMR, CCyR, MMR, DMR, discontinuation rates between randomised study of 1L dasatinib and nilotinib
- No role for addition of IFN to TKI in front line therapy (minor benefit is offset by toxicity)
- New lower dose first line approaches for 2G-TKI ; dasatinib 50mg not recommended at present

Matsumura *et al*, Blood Adv (2024) 8 (20): 5237–5247

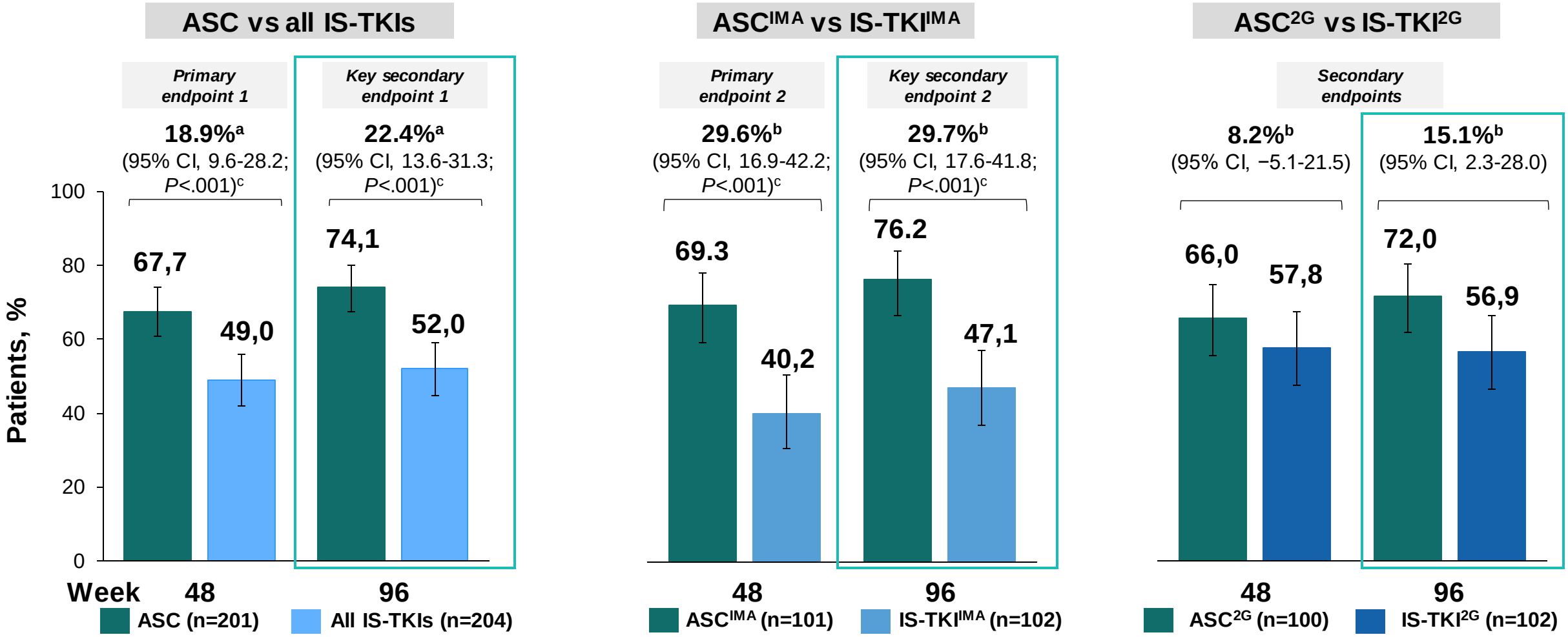
First line treatment



ABL1, Abelson tyrosine kinase 1; ATP, adenosine triphosphate; BCR, breakpoint cluster region; L, line; MOA, mechanism of action; TKI, tyrosine kinase inhibitor.

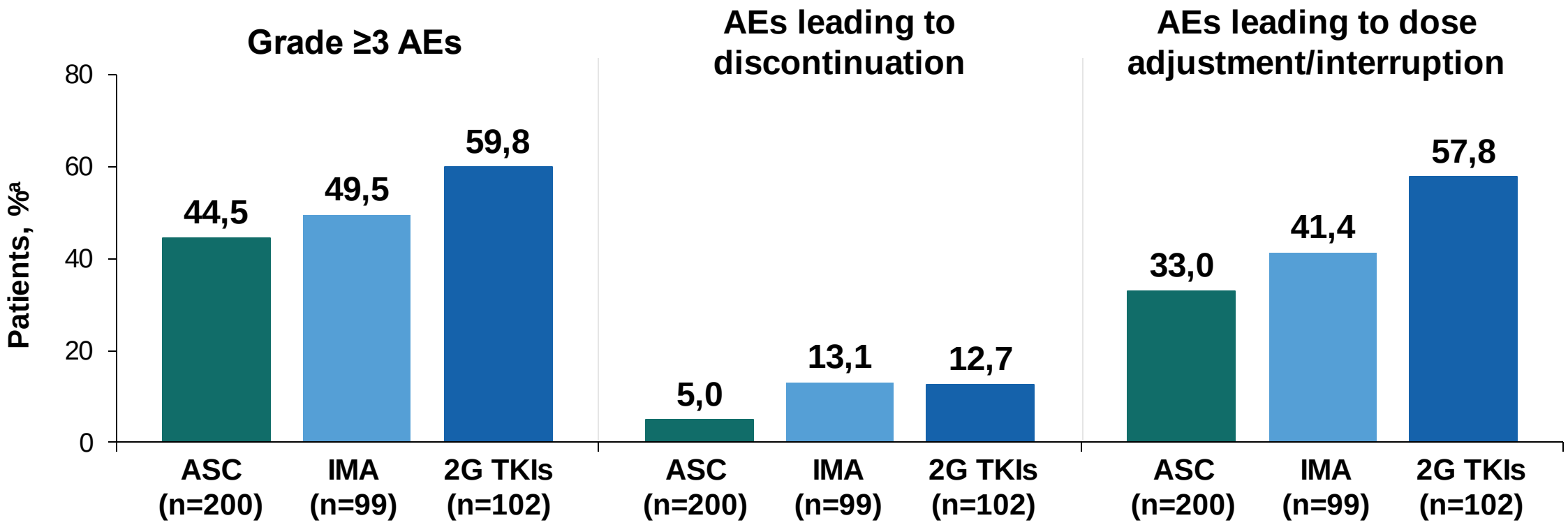
1. Hughes TP, et al. *N Engl J Med*. 2019;381:2315-2326. 2. Wylie AA, et al. *Nature*. 2017;543:733-737. 3. Schoepfer J, et al. *J Med Chem*. 2018;61:8120-8135. 4. Eide CA, et al. *Cancer Cell*. 2019;36:431-443. 5. Roskoski R, et al. *Pharmacol Res*. 2016;103:26-48. 6. Zhao Z, et al. *ACS Chem Biol*. 2014;9:1230-1241. 7. Knight JDR, et al. *PLoSOne*. 2007;2:e982. 8. Eide CA, et al. *Blood*. 2016:128. Abstract 2747. 9. Jabbour EJ, et al. *Clin Lymphoma Myeloma Leuk*. 2013;13:515-529.

First line ascimimib: ASC4FIRST, phase 3, randomized, head-to-head study comparing asciminib vs all standard-of-care TKIs in newly diagnosed CML



Cortes JE, et al. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral 475.

Safety and tolerability



- The median average daily dose was 80 mg/day with ASC, 400 mg/day with IMA, 600 mg/day with NIL, 100 mg/day with DAS, and 316 mg/day with BOS
  - There was a 54% lower risk of discontinuation due to AEs[b] with asciminib compared with 2G TKIs

BOS, bosutinib; DAS, dasatinib; NIL, nilotinib; TTDAE, time to treatment discontinuation due to AE.
[a] Safety analyses were done in patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. A patient with multiple severity grades for an AE is only counted under the maximum grade. [b] Discontinuation for other reasons was a competing event.
Cortes JE, et al. Presented at: 66th ASH Annual Meeting and Exposition; December 7-10, 2024; San Diego, USA. Oral Presentation S632

First line treatment: how to choose

- Goal of therapy, OS or TFR considerations
- High- risk prognostic factors/ELTS at diagnosis- suggest 2G/4G-TKI
- Co-morbidities influence the choice of treatment
- Cost and availability of individual TKI

Dose reduction in 2L treatment (in at least MMR)

TKI	Recommended 1L dose (SMPC)	Dose reduction levels (includes RW evidence)
Imatinib	400mg	100mg – 300mg OD
Dasatinib	100mg	20-50mg OD
Nilotinib	300mg bd	150-200mg OD
Bosutinib	400mg OD	200mg OD

- After dose reduction, patients should be monitored closely to be certain that the level of response is maintained
- Lower dose can be started initially, and then titrated up
- Dose reduction levels also relevant to > 2L therapy

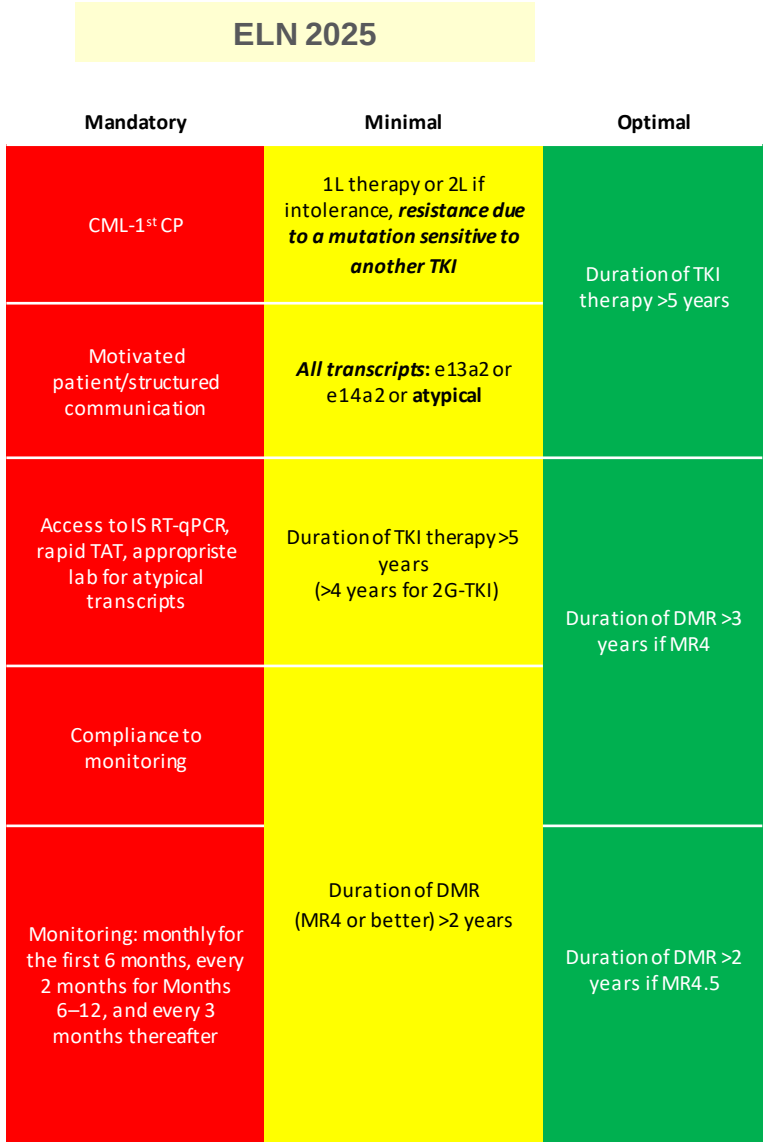
Resistance

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

- Q252H- confers resistance to asciminib

Recommendations/guidelines for specific patients who may be eligible for TFR

Criteria	NCCN	BSH
Disease phase	CP-CML	CP-CML
Age	≥18 years	Not specified
***BCR-::ABL1* transcript type**	Prior evidence of quantifiable *BCR::ABL1* transcript.	Quantifiable transcript
TKI treatment duration	≥3 years	> 3 years
DMR level and duration	MR4 for ≥2 years	MR4 for ≥2 years
Other	No prior history of accelerated or blast phase CML; access to reliable qPCR test (sensitivity: ≥MR 4.5; results within 2 weeks)	No advanced phase/no resistance/no previous TKDM /halve the dose 12 mo pre stopping



National Comprehensive Cancer Network.:NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia ; Apperley *et al*, Leukemia 39, 1797–1813 (2025)

TFR recommendations- decrease in frequency of molecular monitoring post TKI discontinuation

NCCN	ELN 2025	BSH
Every 1–2 months for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; BCR::ABL1 ≤0.1% IS	6 to 8 weekly for the first 6 months, 2 monthly for months 6–12 every 3–6 months thereafter Monitoring should increase in frequency if there is an increase in BCR::ABL1 transcript levels. If TKI-therapy is restarted monitor 4-6 weekly until MMR is regained and then every 3 months until MR4 is regained	Monthly for six months Six-weekly from 7 to 12 months Two-monthly from 13 to 36 months Three-monthly for year ≥ 3

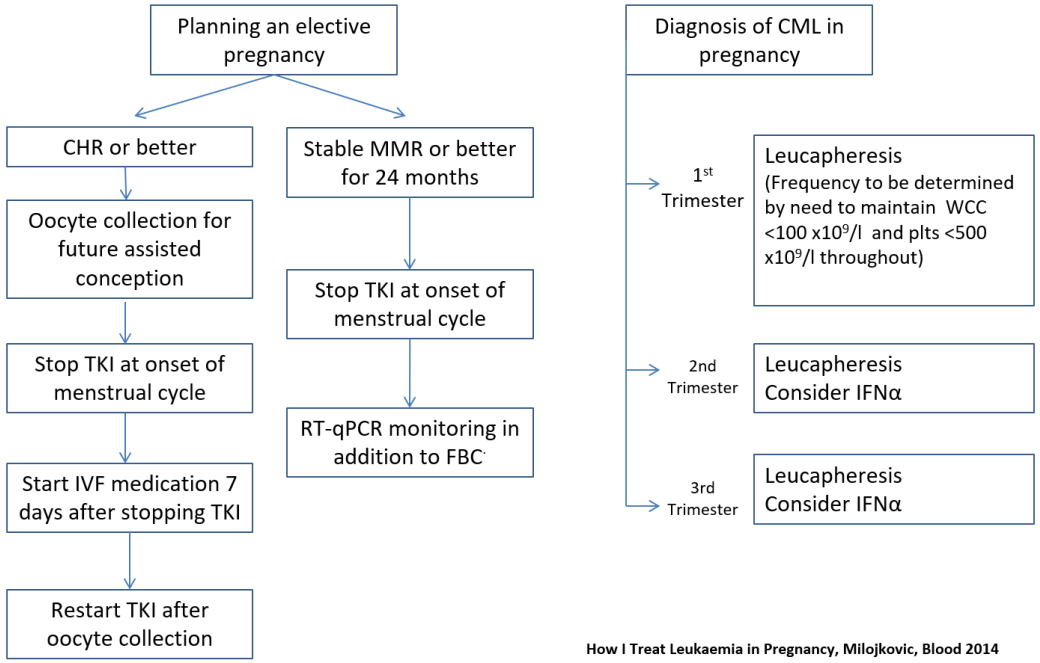
- **Stopping TKI-therapy in patients who failed their first attempt is possible**
- **Long-term monitoring is essential**

A new dawn: planning a pregnancy in women with established CML

Current response	Recommendation
≥ MR^4 **(RT-qPCR ≤0.01% IS)**	Manage as for TFR • Remains in TFR – leave off treatment indefinitely irrespective of pregnancy • Becomes pregnant & loses MMR • Does not become pregnant & loses MMR – restart same or more potent drug.Further attempts at conception possible at a later date
MMR but not MR^4 **(RT-qPCR** **>0.01% IS <0.1% IS)**	Continue TKI to achieve ≥ MR4 and manage as above. If MMR is established with sufficient follow-up to suggest achievement of MR4 is unlikely, then there are 3 possible scenarios 1. Discontinue TKI & manage any subsequent pregnancy 2. Continue TKI with regular pregnancy tests, Discontinue TKI at first positive & manage pregnancy 3. Continue TKI with patient stopping after completion of menses & taking a pregnancy test 2 weeks later. If positive stay off TKI, manage pregnancy • Second and third options only possible if the patient understands the risks, and access to regular molecular monitoring and pregnancy tests
<MMR **(RT-qPCR ≥0.1% IS)**	• Continue on same/ more potent TKI to establish a deeper response before attempting conception. • In older patients consider referral to a local IVF service. TKI can be interrupted to enable a hyperstimulation cycle. Embryos can be implanted fresh or frozen. If implanted immediately, manage as in table 7b. If frozen, try to establish a deeper response before implantation and manage as for ≥MMR • If the patient wishes to pursue pregnancy when not in MMR: manage as in second and third scenarios detailed above for MMR

Managing the pregnancy in established CML- less is no longer more

Previous Hammersmith approach



How I Treat Leukaemia in Pregnancy, Milojkovic, Blood 2014

ELN 2025 recommendations

Discontinue the TKI at confirmation of pregnancy. **Refer to obstetrics and explain need for early and regular fetal scanning** **RT-qPCR & full blood count every 6 – 8 weeks, adjust as clinically indicated**		
Current response	**Recommendation**	
	Weeks 0-16	≥Week 16
MR[4]: RT-qPCR ≤0.01% IS **MMR: RT-qPCR ≤0.1% IS** **MR[2]: RT-qPCR ≤1% IS**	• Continue observation without therapy • IFN can be introduced at any point to control counts. Ability to maintain molecular responses is unproven • If RT-qPCR is increasing rapidly and/or loss of CHR and after week 16, start imatinib 400mg daily. Nilotinib up to 400mg daily can be used in case of imatinib resistance or intolerance	
No MR[2]: RT-qPCR >1%	Commence IFN	If loss of CHR Imatinib 400mg daily Nilotinib up to 400mg daily if imatinib resistant/intolerant

Side-effects of TKI therapy: routine baseline investigations

Minimum requirements

Prior to starting TKI

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib	Olverembatinib
Cardiovascular							
ECG[1]	√	√	√	√	√	√	√
Lipid profile HbAIC	-	-	√	-	√	-	√
Blood pressure	√	√	√	√	√	√	√
Echo	-	-	-	-	-	-	-
Other							
HBV[2] (HBsAg, HBcAb)	√	√	√	√	√	√	√
Thyroid function	-	-	-	-	√	-	√
Lipase+/- Amylase	as clinically indicated						

Additional monitoring investigations

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib	Olverembatinib
Cardiovascular							
ECG	As clinically indicated						
Lipid profile HbA1c	-	-	6-12 monthly	-	6-12 monthly	-	6-12 monthly
Blood pressure	As per good clinical practice						
Echo	As clinically indicated						
Other							
Thyroid	-	-	-	-	6-12 monthly	-	6-12 monthly
Lipase +/- amylase	As clinically indicated						

Summary

- ELN recommendations provide a robust framework for the management of CML patients to prevent or delay progression to improve survival, and allow for TFR
- Molecular monitoring remains essential for evaluation of response and prompt intervention
- No change of TKI therapy should take place on the basis of a single result at a single milestone/time-point
- Toxicity of TKI therapy can be significantly improved/prevented by dose-reduction, with increased vigilance with molecular monitoring
- Recommendations need to be placed in context for individual patients, supported by real-world evidence for a personalised treatment approach
- The aim to be ‘not as bad as predicted’ , ‘or ‘not as dismal’ , but to provide optimal care

Acknowledgements

Jane Apperley, ELN co-authors

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