Leucémie Myéloïde Chronique

Questions en 2024

Journées Interrégionales d'Hématologie de l'Est (IHE) 2024

Pr Philippe Rousselot

Service d'Hématologie, Centre Hospitalier de Versailles

Inserm UMR1184, UVSQ-CEA, Université Versailles Paris-Saclay

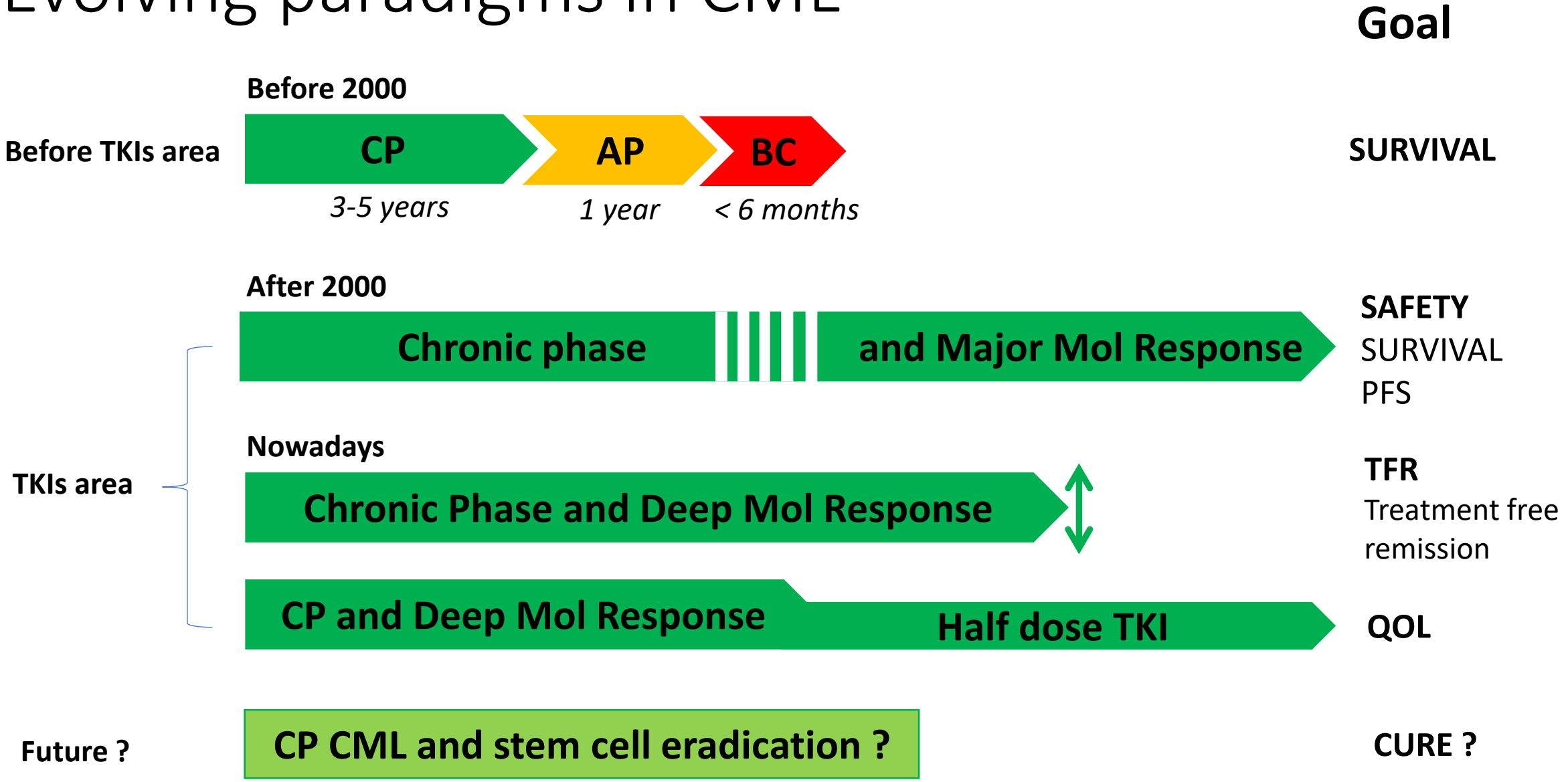
Disclosures

- Research grants from
  - Pfizer
  - Incyte

Open topics

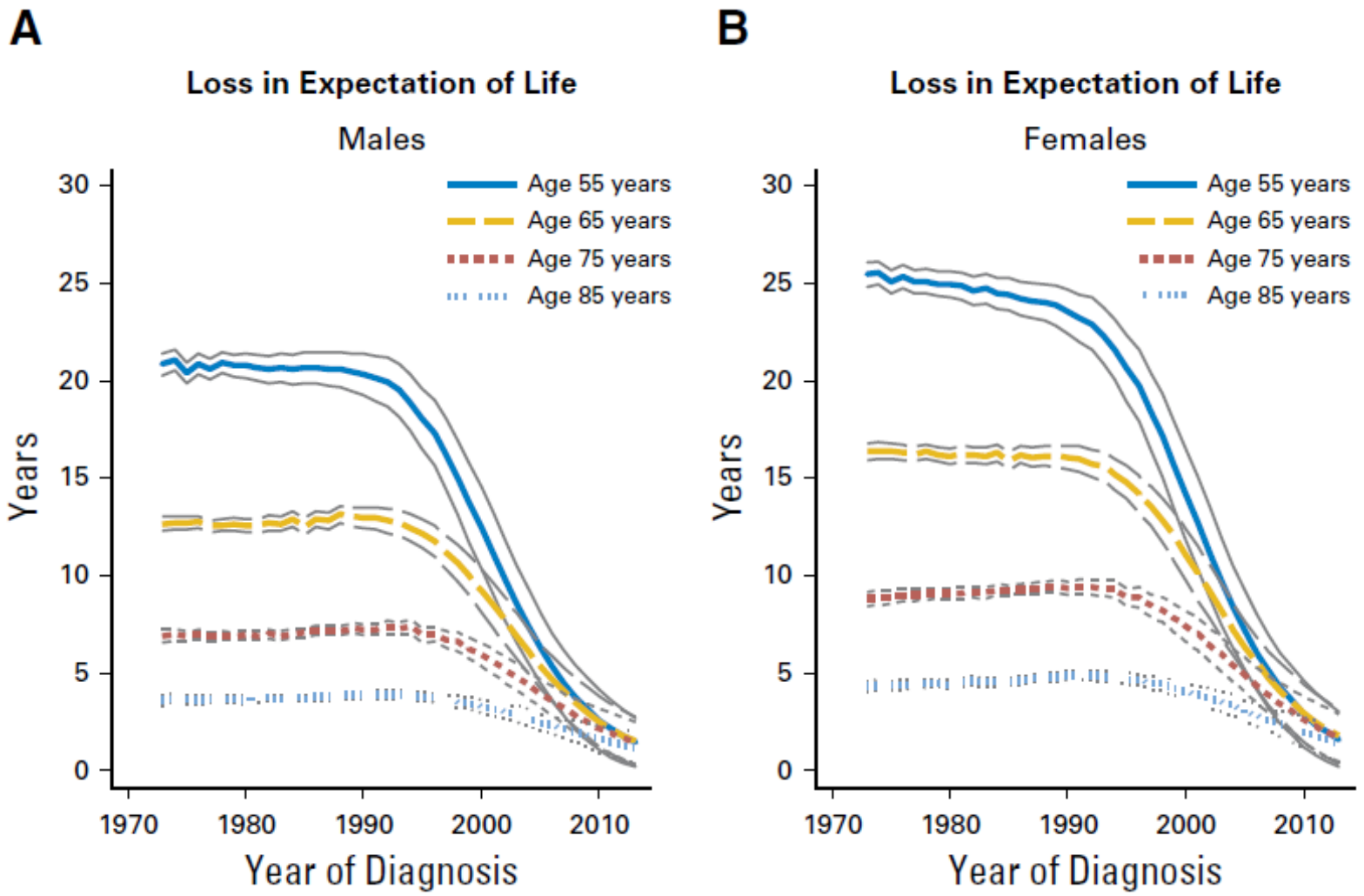
1. First line therapy
2. Resistance, Non-ABL mutations
3. Late molecular relapses in TFR, half dose before TFR
4. Advances phases CML

Evolving paradigms in CML



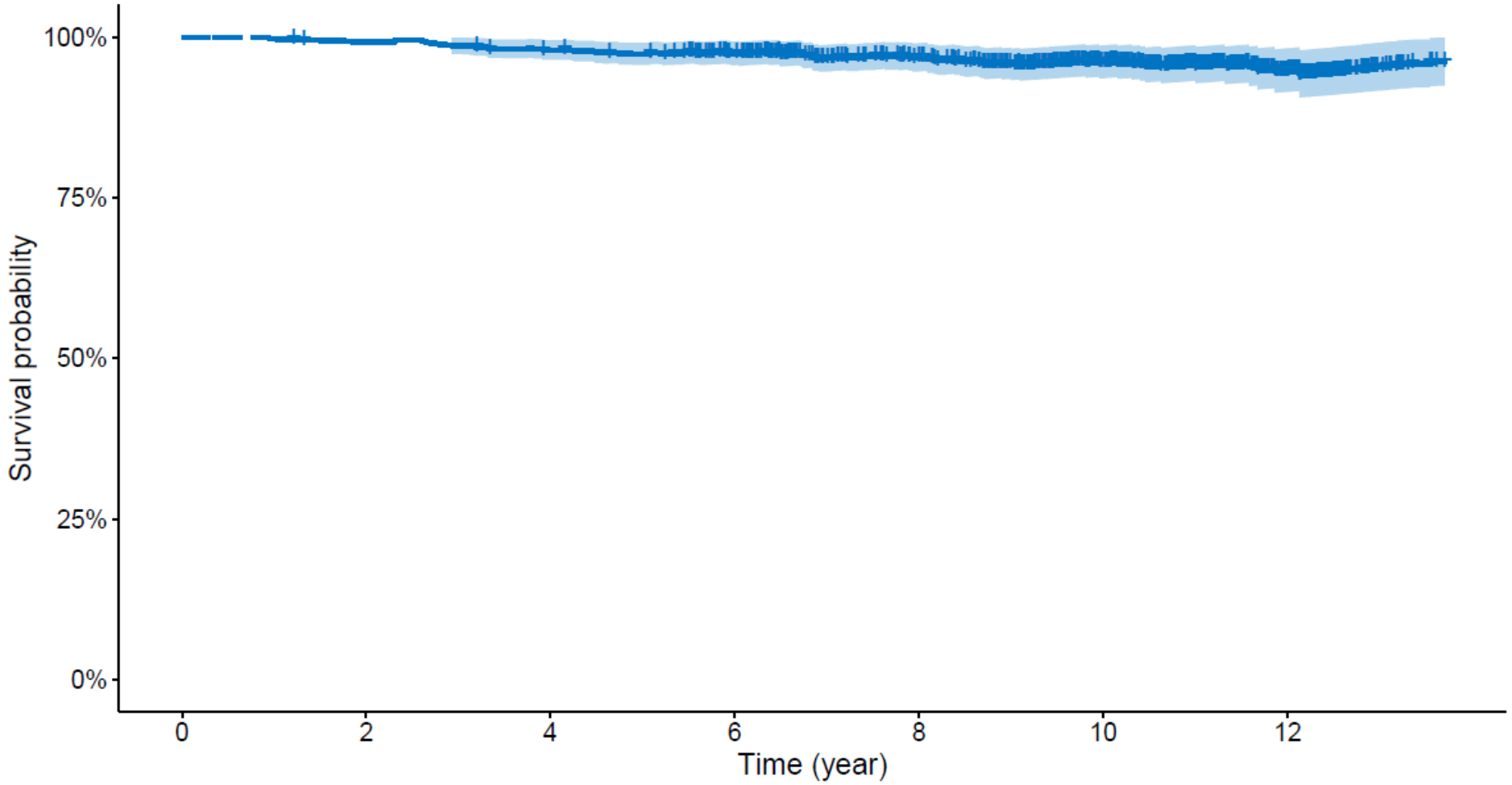
Adapted from J Goldman

Long term survival in CML



Bower H et al., J Clin Oncol 2016;34:2851-2857

Survie relative : essai SPIRIT, n=787



95%

Guilhot F. ESH Bordeaux, 2019

Open topics

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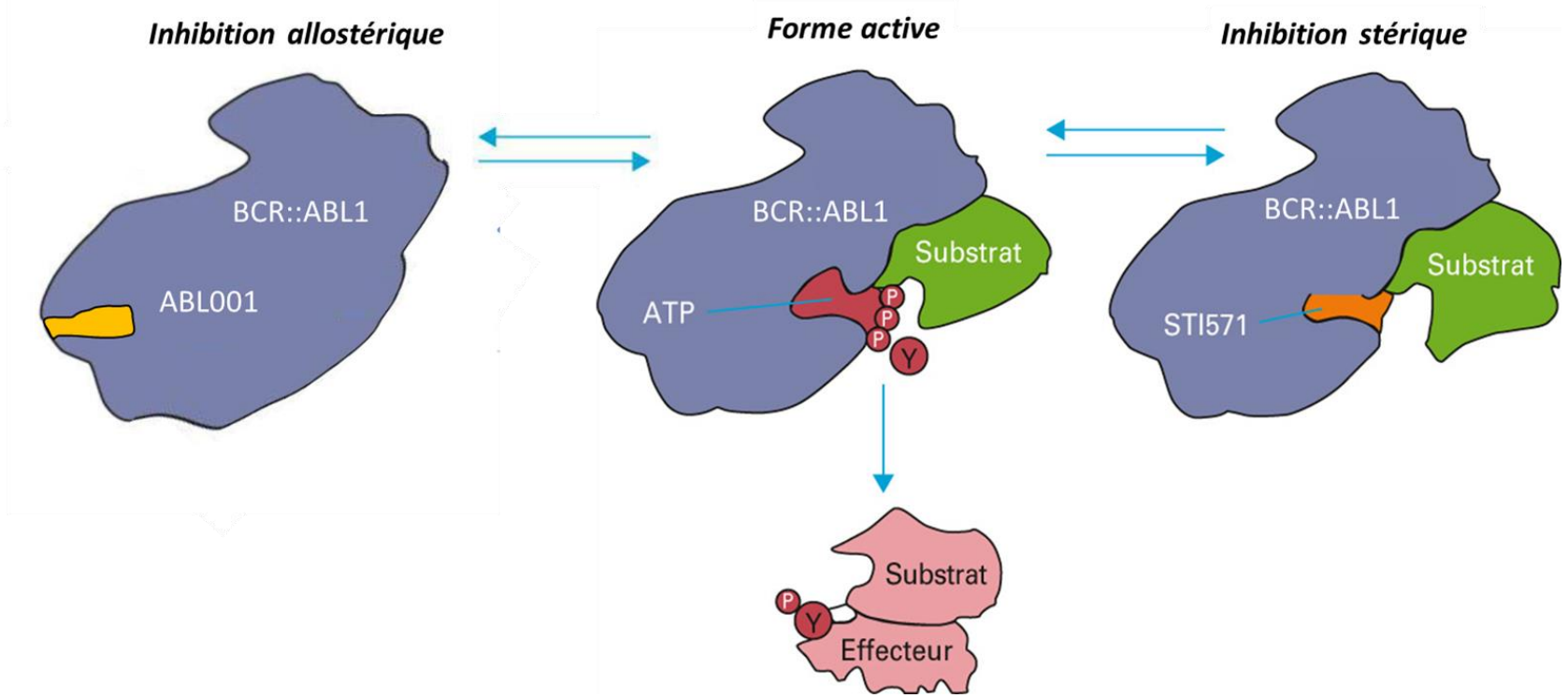
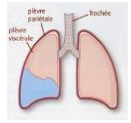
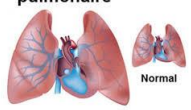
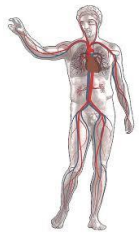
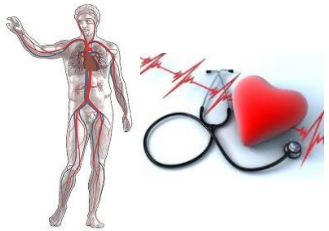
Two classes of BCR::ABL1 inhibitors

Allosteric TKI

ATP-competitive TKIs

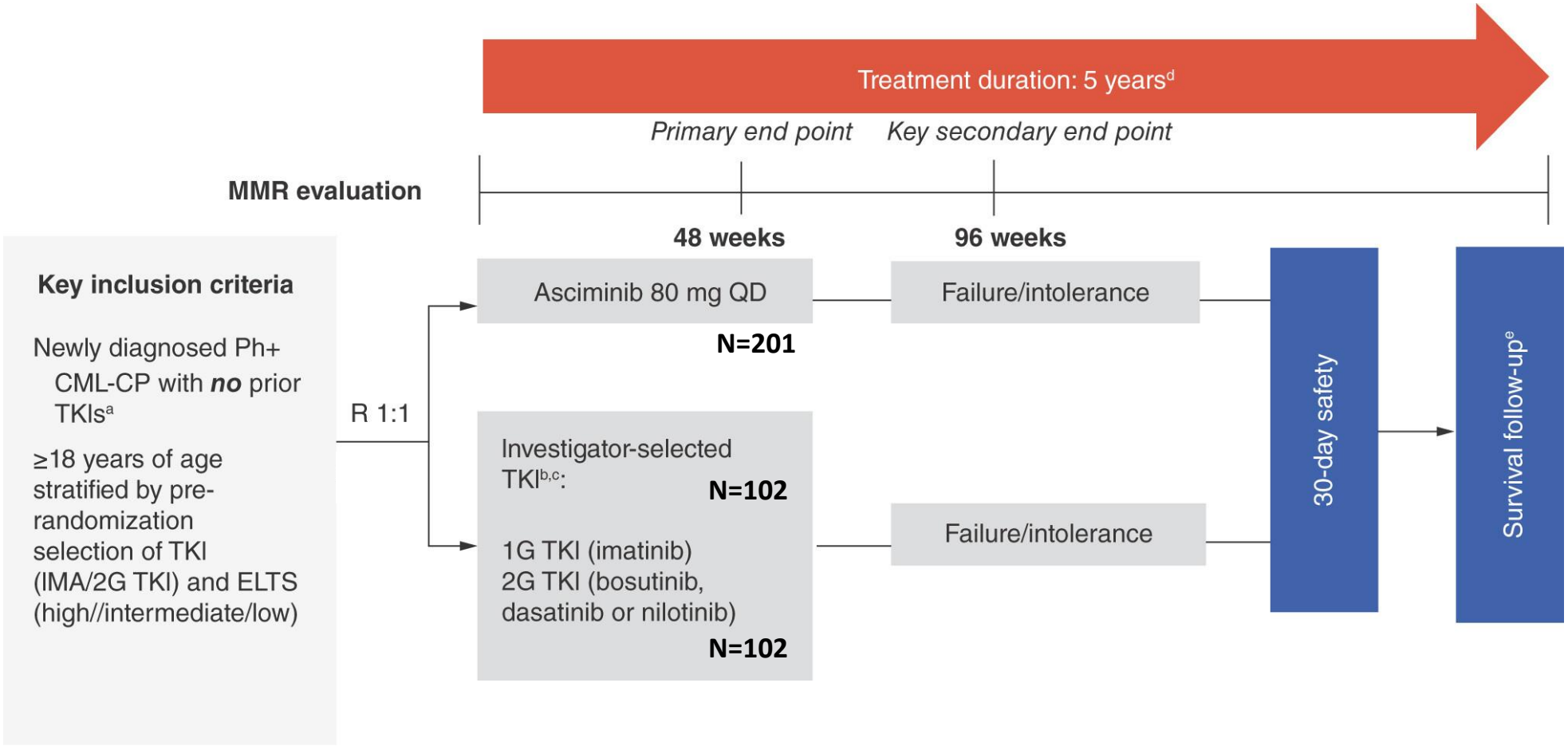


6 registered molecules

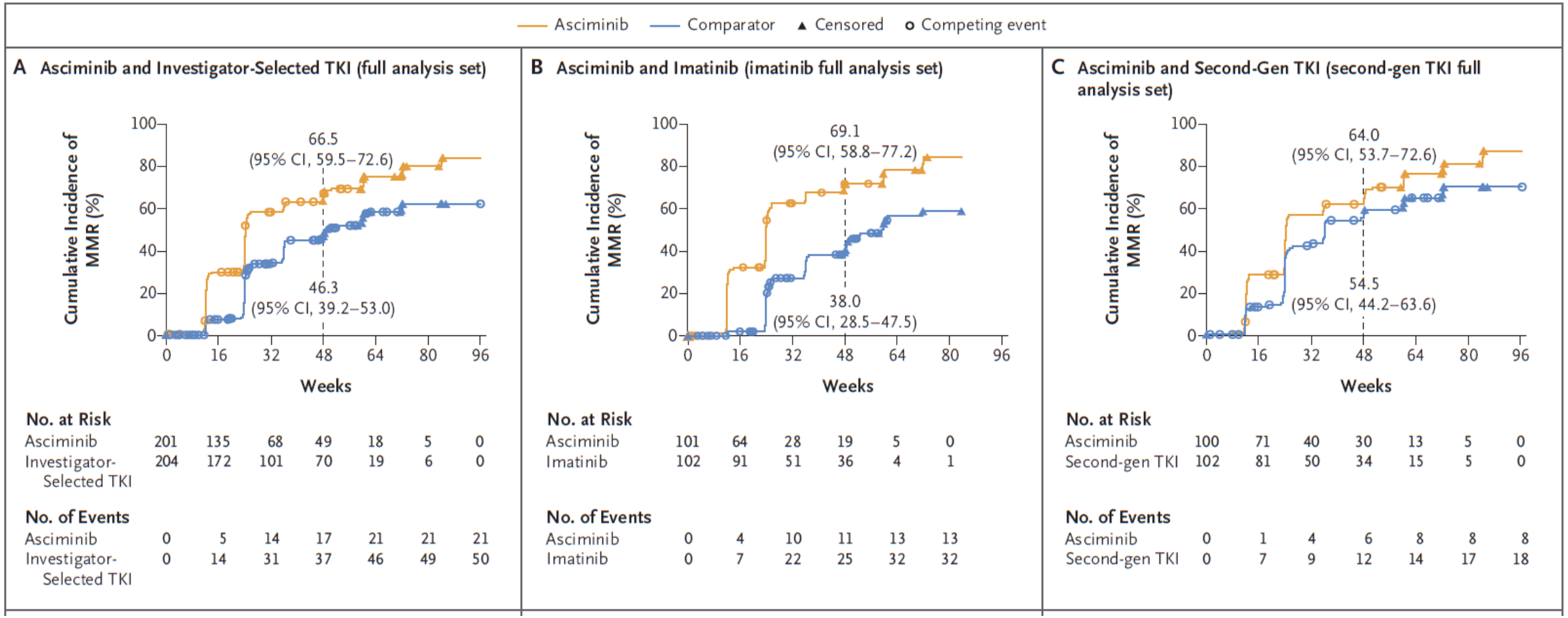
	First Generation	Second Generation			Third Generation	Allosteric
Brand		  				
Generic						
Daily doses **Used doses**	**400 mg** **200 – 300 mg**	**100 mg** **50 – 70 mg**	**600 mg** **300 – 400 mg**	**400 mg** **200 – 300 mg**	**45 mg** **15 – 30 mg**	**80 mg** **?**
Lines	**First**	**Second**	**First Second Third**	**First Second Third**	**Third T315I**	**Third**
Long term SAEs	**No**	 Hypertension pulmonaire 	 			**?**

ASC4FIRST

Asciminib vs investigator-selected TKIs in patients with newly diagnosed CML

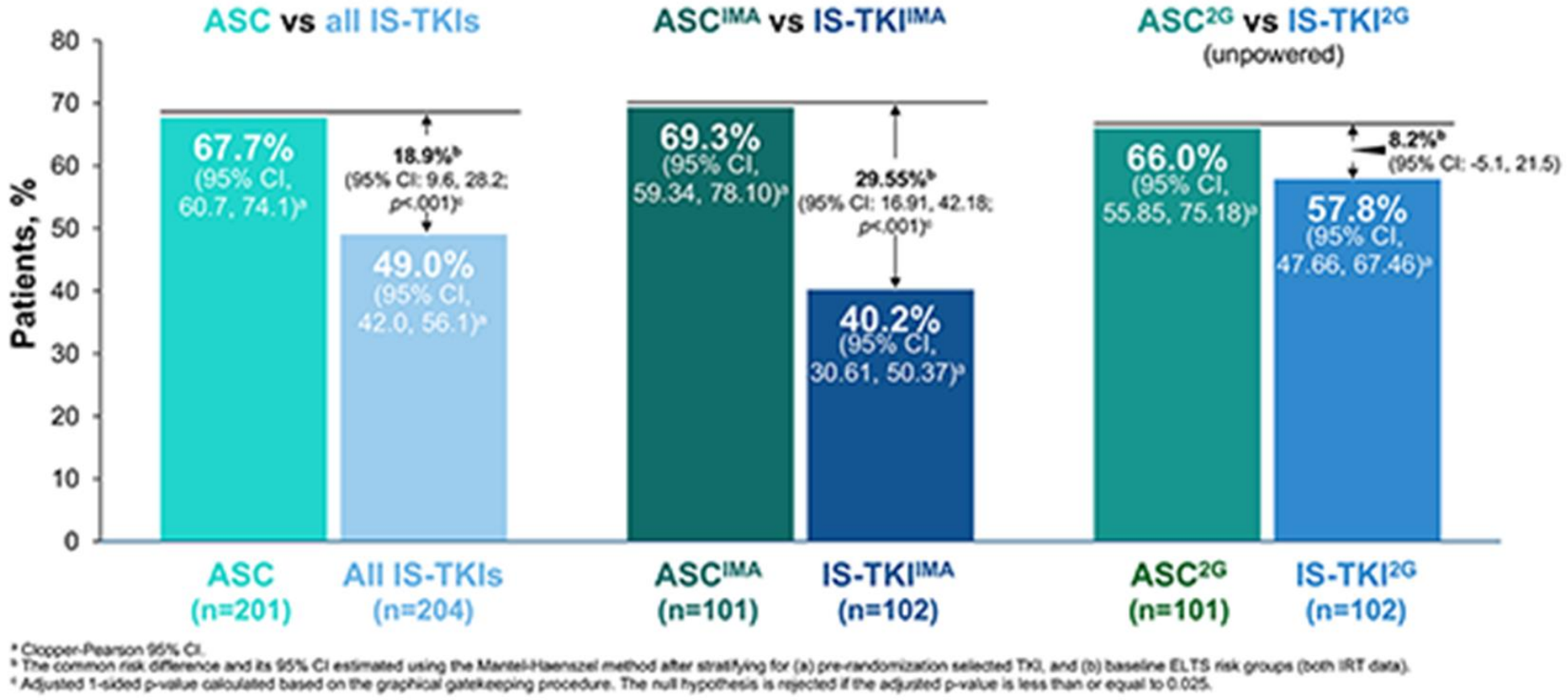


ASC4FIRST : results (primary end-point)



Hochhaus A, et al. N Engl J Med. 2024 Sep 12;391(10):885-898.

ASC4FIRST : results (primary end-point)



[a] Clopper-Pearson 95% CI.
[b] The common risk difference and its 95% CI estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data).
[c] Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p-value is less than or equal to 0.025.

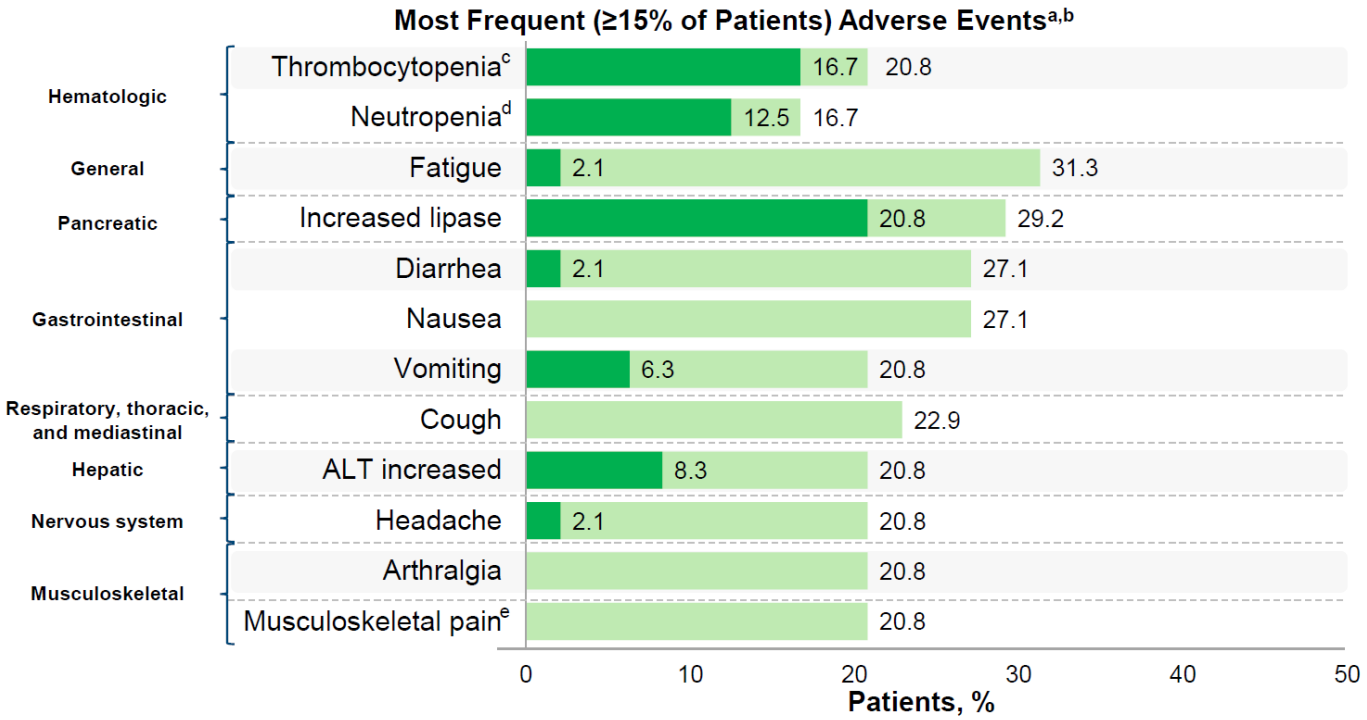
Hochhaus A, et al. N Engl J Med. 2024 Sep 12;391(10):885-898.

Table 2. Most Frequent Adverse Events That Occurred in at Least 10% of Patients (Safety Set).*

Adverse Event	Asciminib		Investigator-Selected TKI					
	All Asciminib (N=200)		Imatinib (N=99)		Second-Generation TKI (N=102)		All Comparators (N=201)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)							
At least one adverse event	187 (93.5)	76 (38.0)	93 (93.9)	44 (44.4)	102 (100)	56 (54.9)	195 (97.0)	100 (49.8)
Thrombocytopenia†	56 (28.0)	26 (13.0)	28 (28.3)	6 (6.1)	35 (34.3)	14 (13.7)	63 (31.3)	20 (10.0)
Neutropenia‡	50 (25.0)	20 (10.0)	31 (31.3)	17 (17.2)	35 (34.3)	18 (17.6)	66 (32.8)	35 (17.4)
Leukopenia§	38 (19.0)	4 (2.0)	29 (29.3)	10 (10.1)	20 (19.6)	5 (4.9)	49 (24.4)	15 (7.5)
Coronavirus disease 2019	35 (17.5)	0	18 (18.2)	0	21 (20.6)	1 (1.0)	39 (19.4)	1 (0.5)
Diarrhea	31 (15.5)	0	26 (26.3)	0	26 (25.5)	1 (1.0)	52 (25.9)	1 (0.5)
Fatigue	28 (14.0)	1 (0.5)	14 (14.1)	1 (1.0)	18 (17.6)	0	32 (15.9)	1 (0.5)
Headache	27 (13.5)	1 (0.5)	8 (8.1)	0	22 (21.6)	0	30 (14.9)	0
Myalgia	26 (13.0)	1 (0.5)	17 (17.2)	0	15 (14.7)	0	32 (15.9)	0
Rash	26 (13.0)	0	10 (10.1)	2 (2.0)	22 (21.6)	1 (1.0)	32 (15.9)	3 (1.5)
Anemia	23 (11.5)	3 (1.5)	26 (26.3)	5 (5.1)	23 (22.5)	6 (5.9)	49 (24.4)	11 (5.5)
Increased lipase	23 (11.5)	6 (3.0)	14 (14.1)	1 (1.0)	11 (10.8)	4 (3.9)	25 (12.4)	5 (2.5)
Constipation	19 (9.5)	0	4 (4.0)	0	13 (12.7)	1 (1.0)	17 (8.5)	1 (0.5)
Nausea	18 (9.0)	0	21 (21.2)	0	18 (17.6)	0	39 (19.4)	0
Increased alanine aminotransferase	14 (7.0)	4 (2.0)	6 (6.1)	2 (2.0)	19 (18.6)	8 (7.8)	25 (12.4)	10 (5.0)
Upper respiratory tract infection	14 (7.0)	0	10 (10.1)	1 (1.0)	8 (7.8)	0	18 (9.0)	1 (0.5)
Lymphopenia¶	12 (6.0)	5 (2.5)	16 (16.2)	5 (5.1)	7 (6.9)	1 (1.0)	23 (11.4)	6 (3.0)
Increased blood alkaline phosphatase	11 (5.5)	0	13 (13.1)	0	6 (5.9)	0	19 (9.5)	0
Vomiting	11 (5.5)	0	12 (12.1)	0	6 (5.9)	0	18 (9.0)	0
Increased blood bilirubin	5 (2.5)	0	2 (2.0)	1 (1.0)	11 (10.8)	0	13 (6.5)	1 (0.5)
Increased aspartate aminotransferase	4 (2.0)	1 (0.5)	6 (6.1)	1 (1.0)	15 (14.7)	3 (2.9)	21 (10.4)	4 (2.0)
Muscle spasms	4 (2.0)	0	19 (19.2)	0	5 (4.9)	0	24 (11.9)	0
Periorbital edema	2 (1.0)	0	10 (10.1)	0	1 (1.0)	0	11 (5.5)	0
Facial edema	0	0	10 (10.1)	1 (1.0)	0	0	10 (5.0)	1 (0.5)

* The safety set comprised all patients who received at least one dose of a trial drug. Adverse events listed occurred during treatment or within 30 days after receiving the last dose of trial medication. A patient with adverse events of multiple severity grades is counted only under the maximum grade.
† The category of thrombocytopenia ncludes thrombocytopenia and decreased platelet count.
‡ The category of neutropenia includes neutropenia and decreased neutrophil count.
§ The category of leukopenia includes decreased white blood cell count and leukopenia.
¶ The category of lymphopenia includes decreased lymphocyte count and lymphopenia

6 years follow-up from the ASC phase 1 study



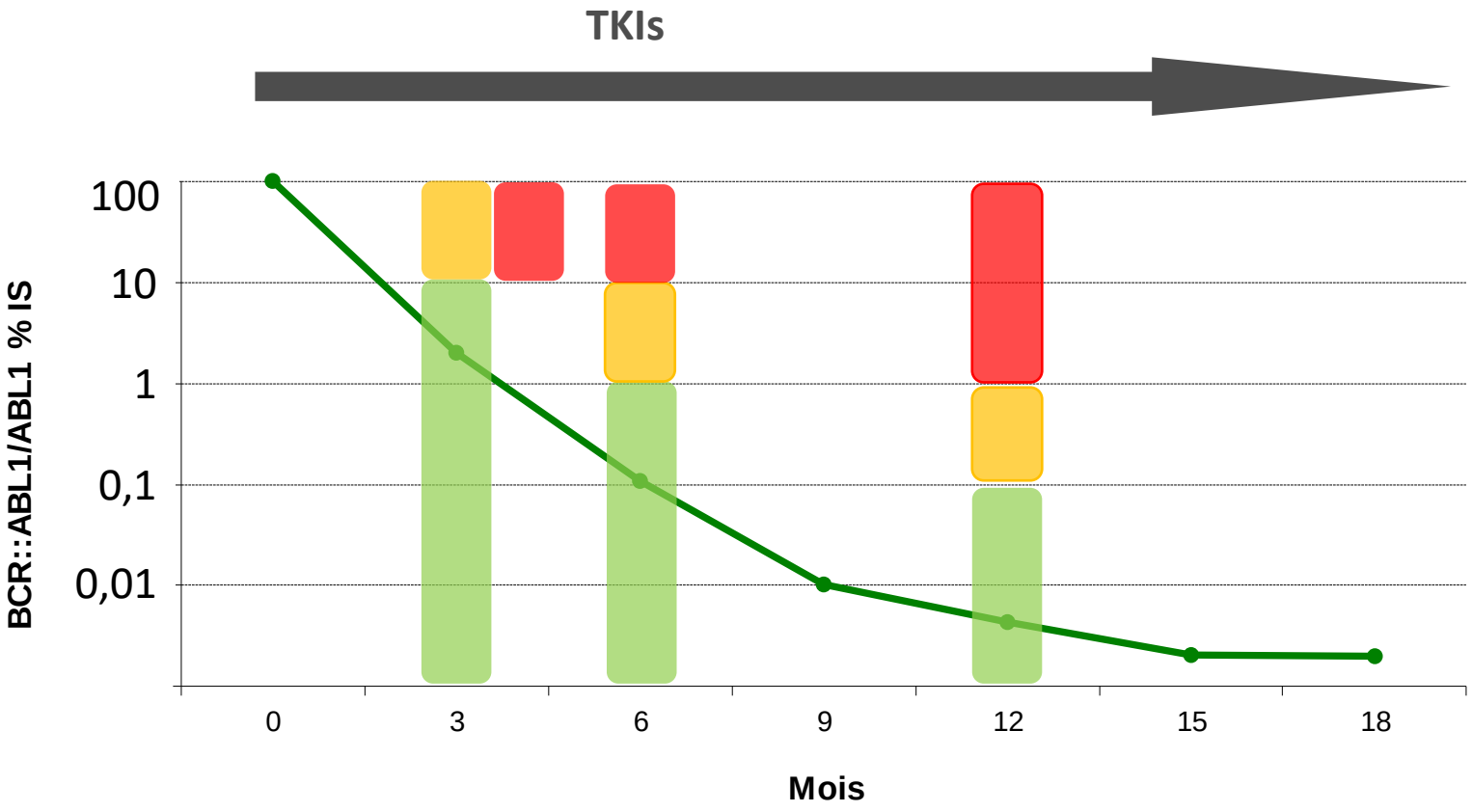
Patients, n (%)	All patients (n=48) All grades	Grade ≥3
Arterial occlusive events	6 (12.5)	3 (6.3)
Cerebrovascular accident	3 (6.3)	2 (4.2)
Carotid artery disease	1 (2.1)	0
Coronary artery disease	1 (2.1)	1 (2.1)
Peripheral arterial occlusive disease	2 (4.2)	1 (2.1)
Peripheral artery occlusion	1 (2.1)	0
Acute coronary syndrome	1 (2.1)	0
Myocardial infarction	1 (2.1)	1 (2.1)
Ischemic stroke	1 (2.1)	1 (2.1)

- Since the previous analysis,[12] 2 additional patients, both with prior ponatinib exposure, experienced AOEs
- Most (5 of 6) patients had prior exposure to ≥3 TKIs,[a] and all had ≥1 past or active cardiovascular risk factor at baseline
- No AOE led to dose adjustment/interruption/discontinuation[b]

CV, cardiovascular; AOE, arterial occlusive event.
[a] Prior TKIs included imatinib (n=5), nilotinib (n=4), ponatinib (n=5), dasatinib (n=3), and bosutinib (n=2). [b] Cerebrovascular accident and myocardial infarction (both grade 4) occurred in 1 patient 23 days after completing the trial while continuing to receive asciminib in post-trial access and resulted in death. The investigator did not suspect a relationship between asciminib and these events.

Cortes J et al. ESH 2024

Molecular response : ELN criteria



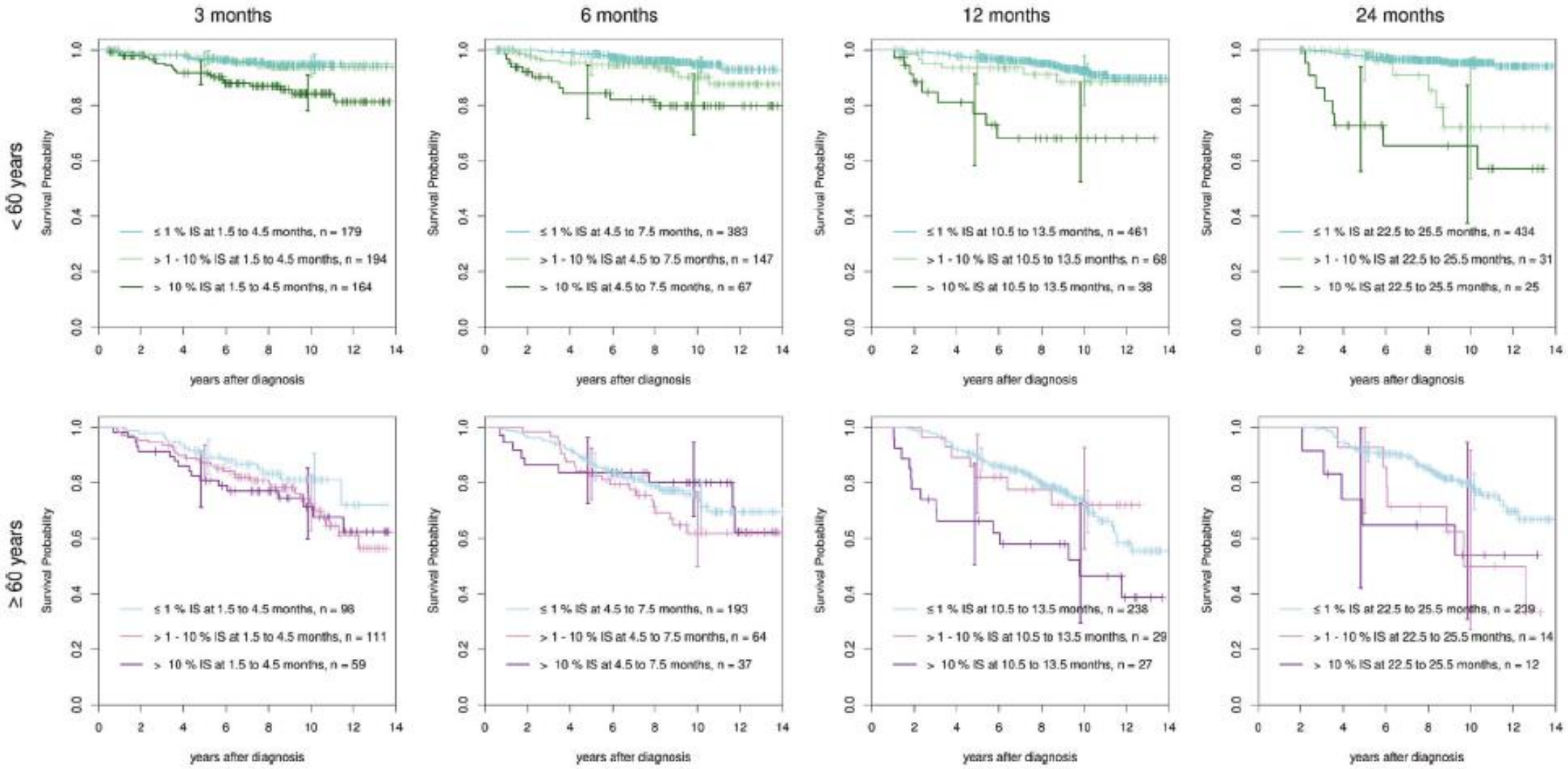
BCR::ABL1 ≤ 1%

BCR::ABL1 ≤ 0,1% = RMM

BCR::ABL1 ≤ 0,01% = RM4

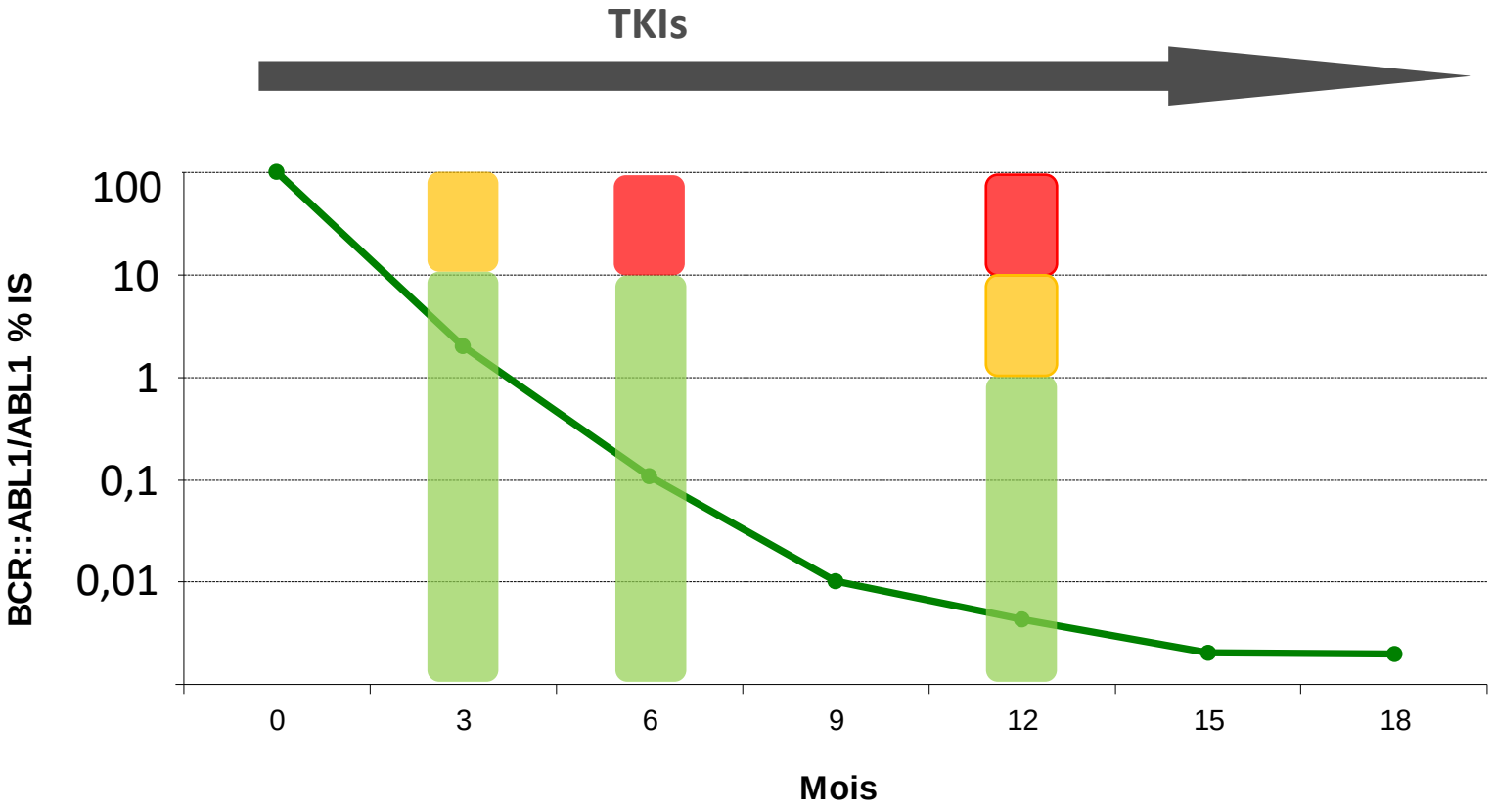
BCR::ABL1 ≤ 0,0032% = RM4.5

Survival with chronic myeloid leukaemia after failing milestones



Lauseker et al. Leukemia. 2023 Nov;37(11):2231-2236.

A revised proposal ?



BCR::ABL1 ≤ 1%

BCR::ABL1 ≤ 0,1% = RMM

BCR::ABL1 ≤ 0,01% = RM4

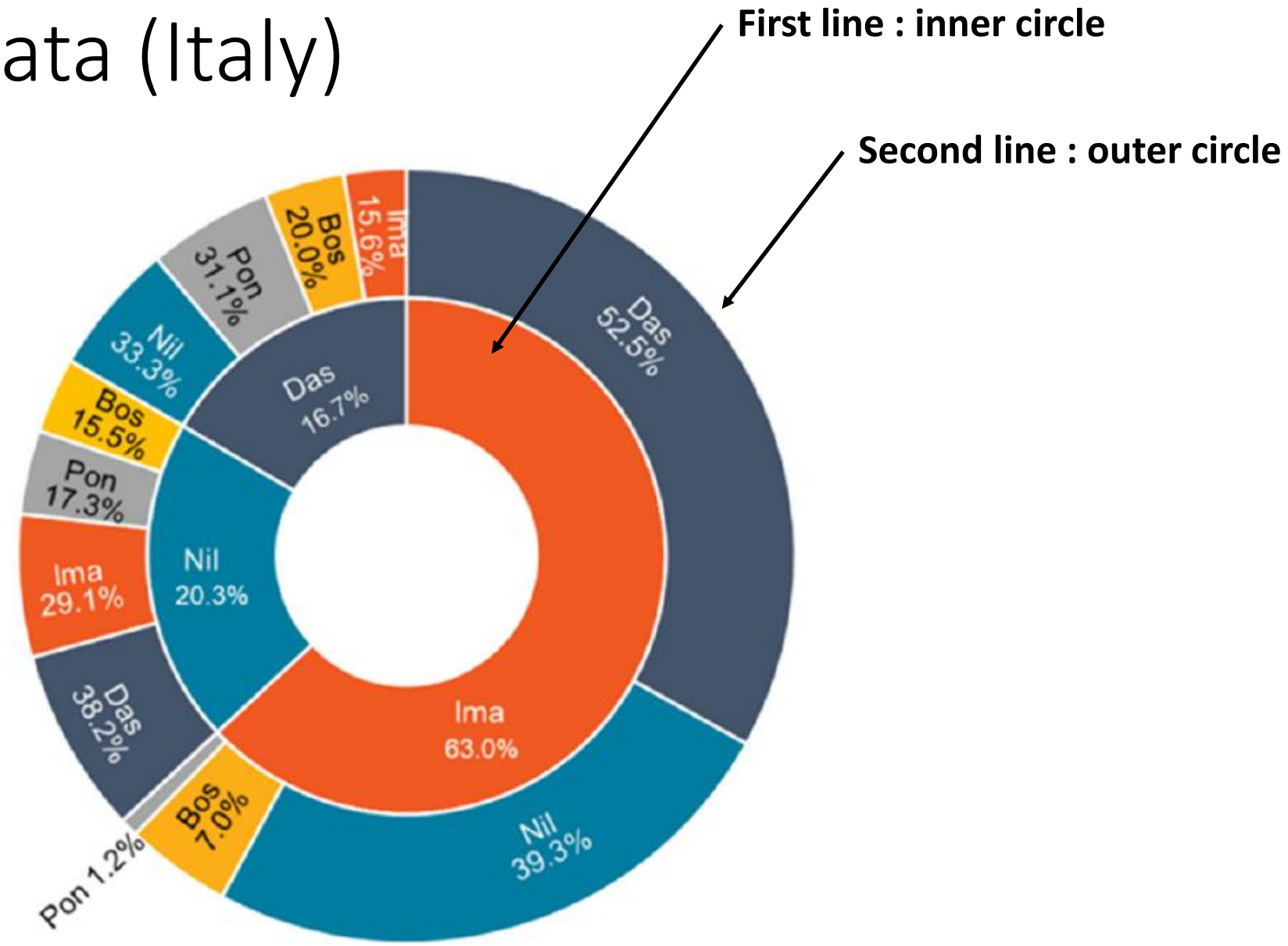
BCR::ABL1 ≤ 0,0032% = RM4.5

Do we need 2nd G-TKI and new agents in first line CP CML ?

- Pro
  - Faster molecular response
  - Higher efficacy in high-risk patients ?
  - Higher TFR rate ?
- Cons
  - No survival advantage
  - No PFS advantage
  - Much higher prices
  - Higher occurrence of severe AEs (cardiovascular, pleural, metabolic)

Walia A and Prasad V. Blood Cancer Journal (2023) 13:36

Real life data (Italy)



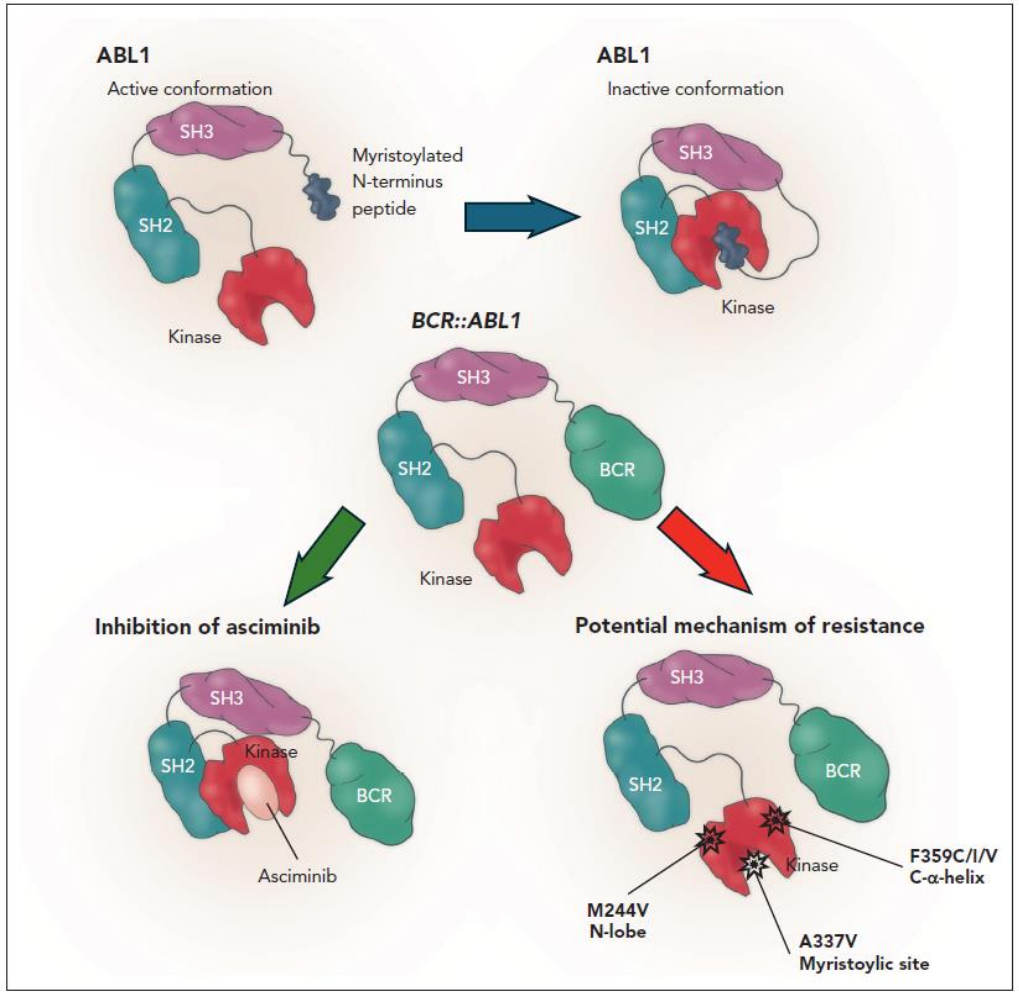
Breccia M et al. J Clin Med. 2022 Jun 22;11(13):3597

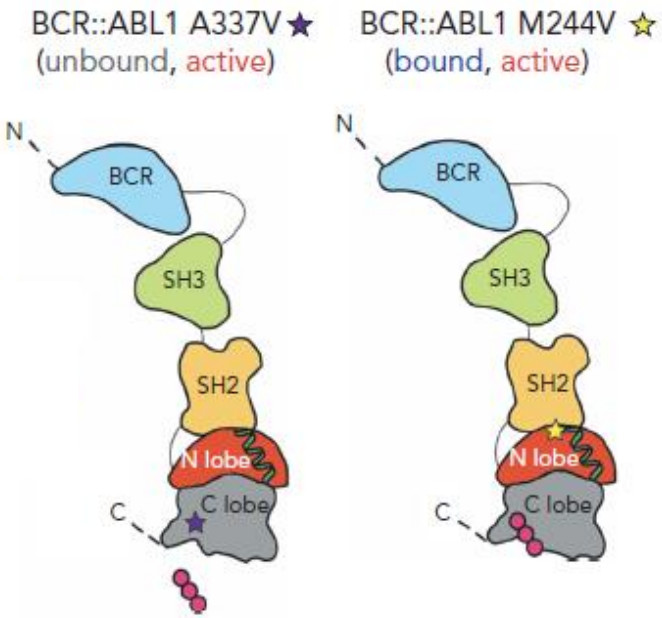
Open topics

1. First line therapy
2. Resistance, Non-ABL mutations
3. Late molecular relapses in TFR, half dose before TFR
4. Advances phases CML

Asciminib : emerging mutations (M244V / A337V)

"Newly emerging BCR::ABL1 mutations were identified in 8 patients (4.0%) receiving asciminib and in 4 patients (2.0%) receiving investigator-selected TKIs"





Breccia M. Blood. 2024 Aug 8;144(6):594-595.

Leyte-Vidal A, et al. Blood. 2024 Aug 8;144(6):639-645

BCR::ABL1 independent mutations at diagnosis

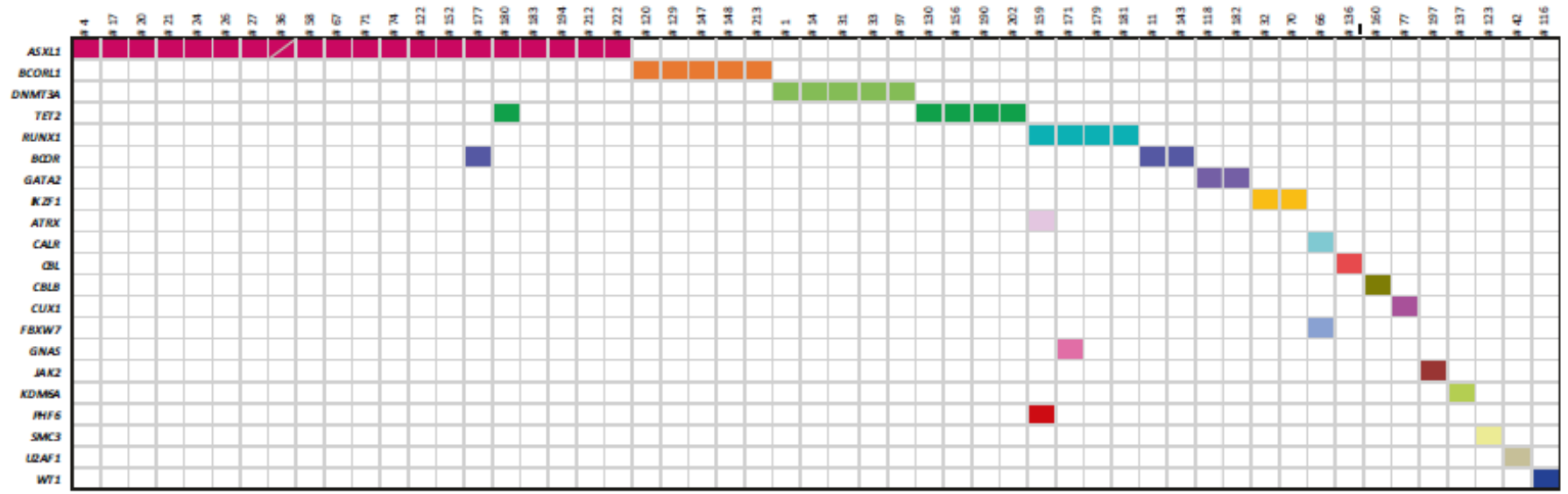


Fig. 1 Landscape of somatic mutations in 222 chronic phase CML patients at diagnosis by targeted next-generation sequencing. Mutations were found in 53/222 patients (24%) with *ASXL1* being the most commonly affected gene ($n = 20$). Patients and genes are displayed in columns and rows, respectively. A unique color is assigned to each mutated gene. Bisected cell represents two variants in the same gene and patient.

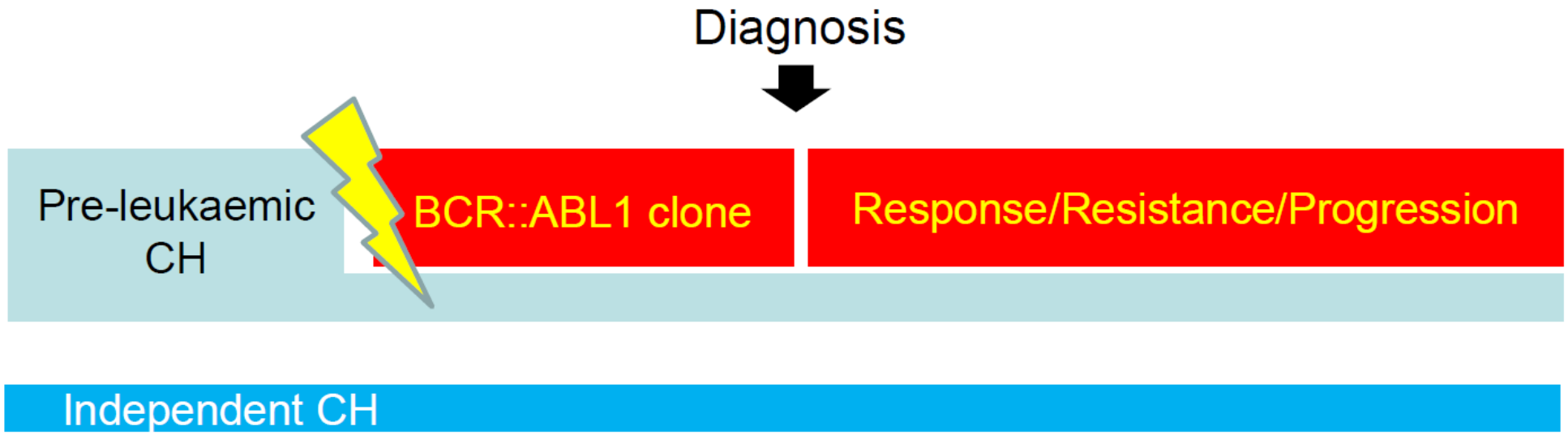
Through – 1/3 of CML patients carry such additional mutations, they have not been included into clinical scoring systems

Are certain mutations associated with an increased risk in term of TKI response and progression ?

Which mutations are bystanders or part of age-related clonal hematopoiesis ?

Schönfeld et al., Leukemia 2022.

CML genomics



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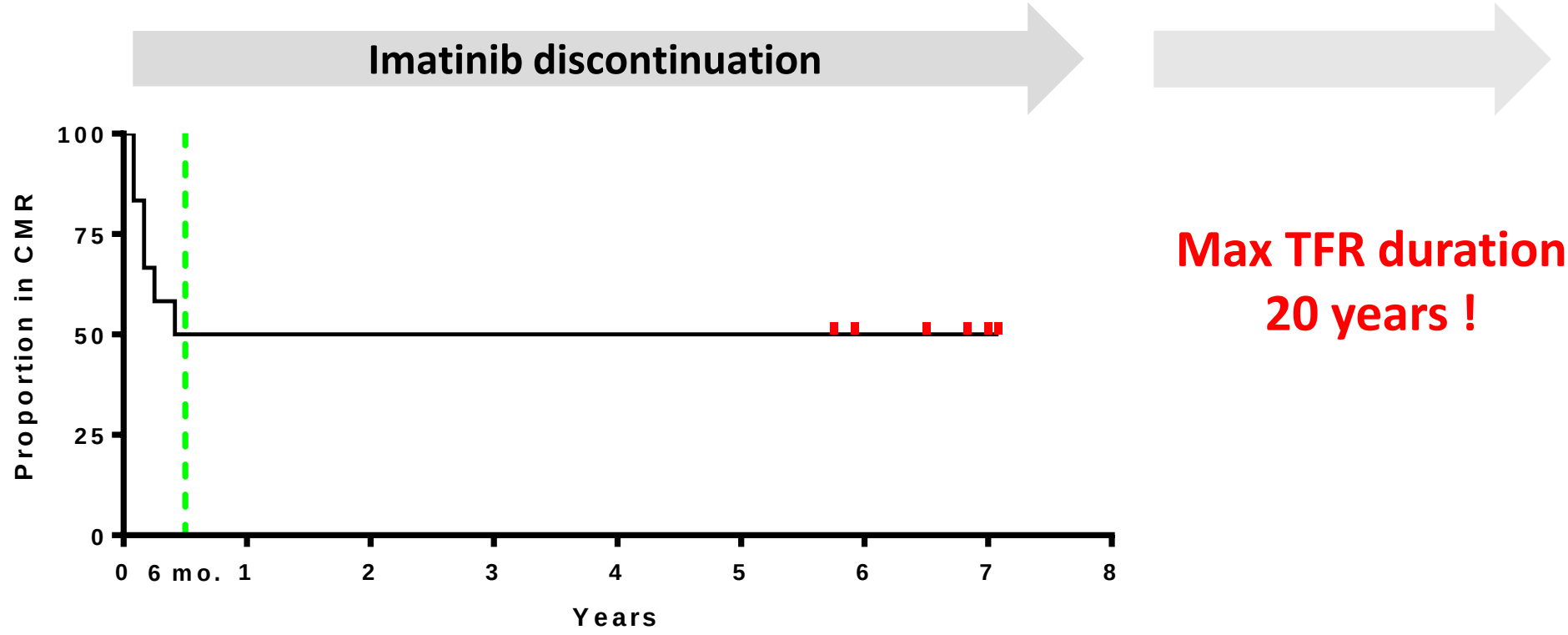
The Pilot Stop IMatinib (STIM) Study more than 20 Years Ago…

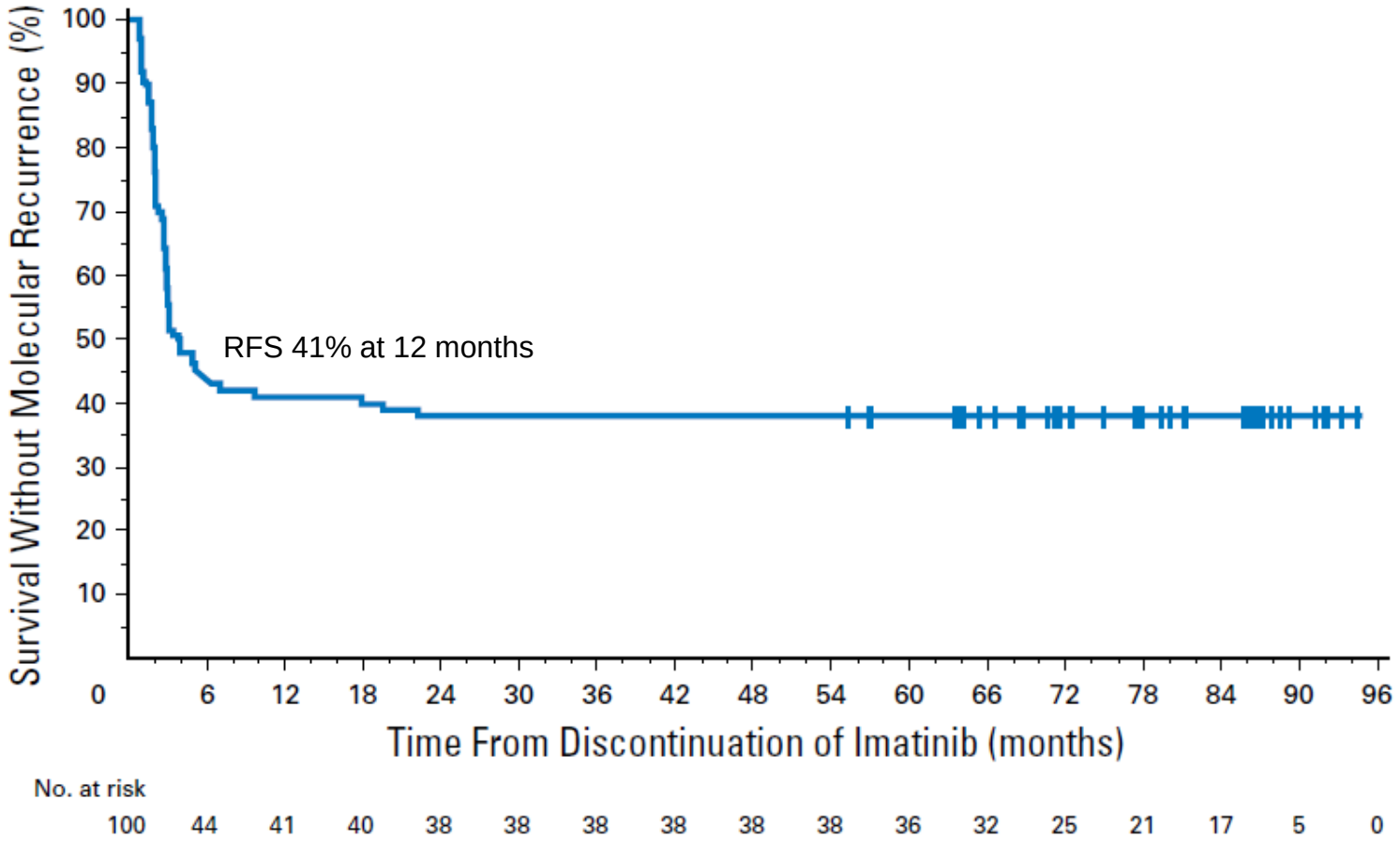
1. Twelve patients in long term CMR with imatinib : STOP imatinib
2. Definition of CMR : CMR 4.5 during 2 years
3. Definition of relapse : Two consecutive positive RQ-PCR
4. Six patients remain treatment free on the very long term



Max TFR duration 20 years !

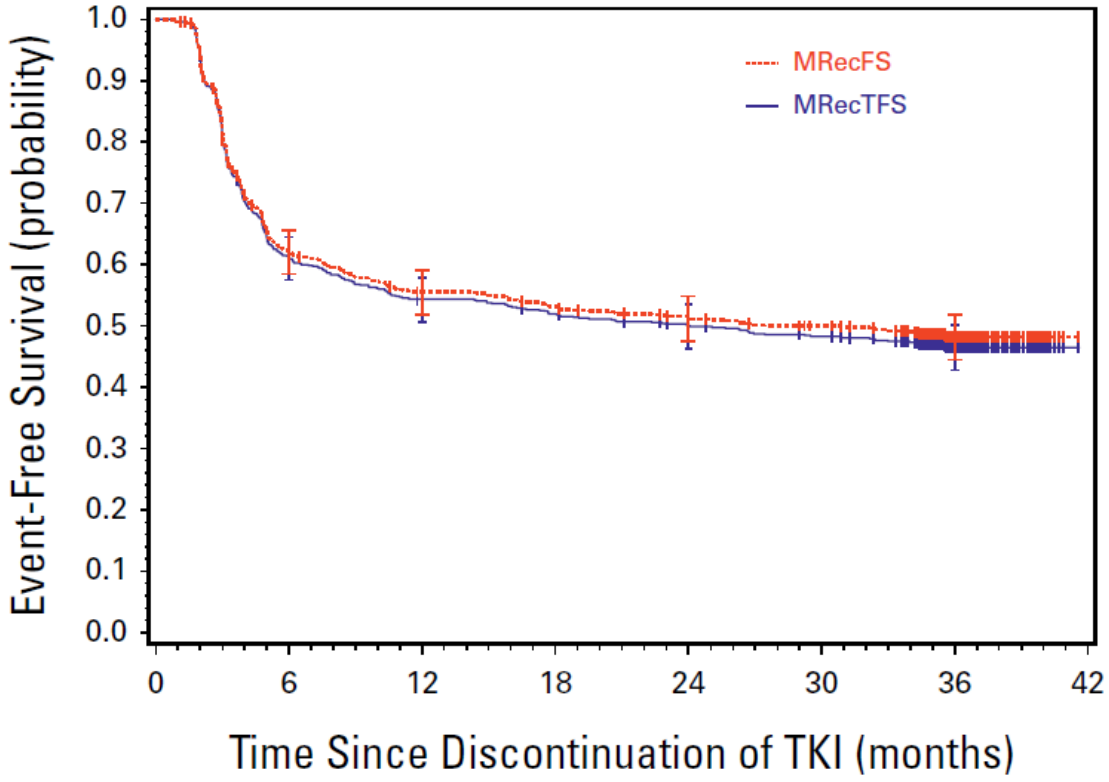
Rousselot P et al., *Blood*. 2007;109:58–60; and personal data.

The multicentric STIM study: an update



STIM1. Etienne G and Mahon FX, J Clin Oncol 2016.

Euroski : n=727 (Mrec = Loss of MMR)



No. at risk:
(cases censored before)

MRecFS	727 (0)	442 (13)	392 (16)	374 (17)	356 (22)	342 (27)	177 (181)
MRecTFS	727 (0)	442 (3)	392 (4)	374 (5)	356 (9)	342 (11)	177 (164)

Probability to Maintain MMR 36 Months After TKI Stop

	EURO-SKI			
Multiple Models	N	OR	95% CI	*P*
Model A				
Duration of TKI treatment, years	413	1.127	1.038 to 1.224	.0043
Blasts in peripheral blood, %	413	0.882	0.800 to 0.972	.0116
Model B				
Duration of TKI treatment, years	392	1.106	1.019 to 1.200	.0163
Transcript, e14a(+e13a2) *v* e13a2	392	2.090	1.254 to 3.484	.0047
Model C				
DMR duration under TKI, years	413	1.119	1.022 to 1.225	.0149
Time to DMR under TKI, years	413	1.142	1.016 to 1.284	.0261
Blasts in peripheral blood, %	413	0.881	0.800 to 0.972	.0112

Mahon FX et al. J Clin Oncol. 2024 Jun 1;42(16):1875-1880.

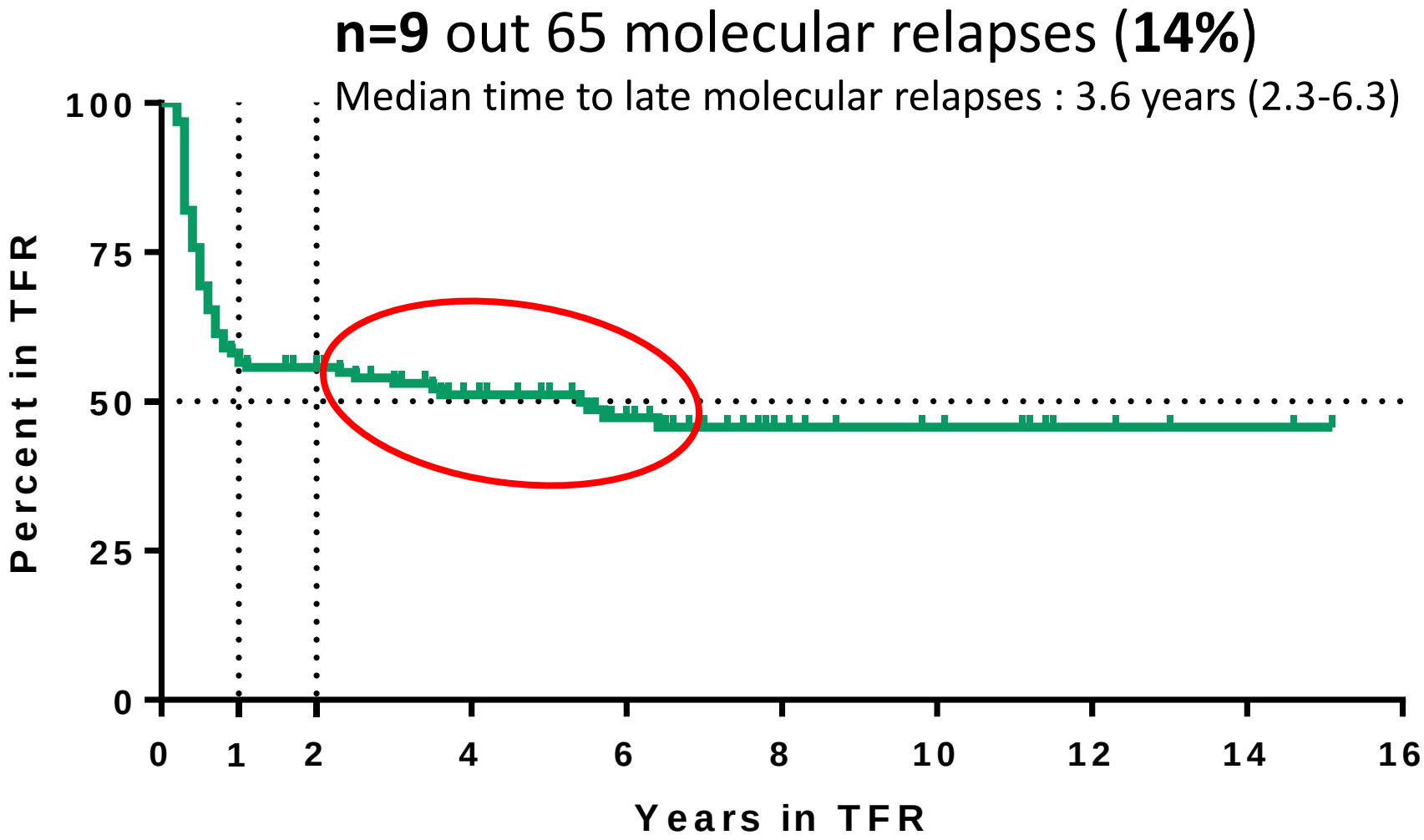
Eligibility, current recommendations

TFR eligibility criteria	FiLMC 2018[1]	ELN 2020[2]
Age	≥ 18 years	Not taken into account
CML phase	CP only	In first CP only 1st line or 2nd line if intolerance only
Pronostic score at diagnosis	Not taken into account	Not taken into account
BCR::ABL1 transcript	Typical (e13a2, e14a2 or e13a2 + e14a2)	Typical (e13a2, e14a2)
TKI treatment duration	≥ 5 years	> 5 years imatinib 4 years with a 2GTKI
Type of DMR	$RM^{4.5}$ at least	$MR^{4.0}$ or better
DMR duration	≥ 2 years	≥ 2 years with any TKI
Prior treatment history	No allogeneic HSCT, progression,resistance, suboptimal response, or warning	No prior treatment failure
Monitoring after treatment discontinuation	CBC and RT-PCR monthly until month 6, every 2 months from month 7 to 12, quarterly from month 13-24 Then every 3 to 6 months	Monitored monthly for the first 6 months, every 2 months for months 6-12, and every 3 months thereafter

1.Rea et al. Cancer 2018 ; 2. Hochhaus et al. Leukemia 2020

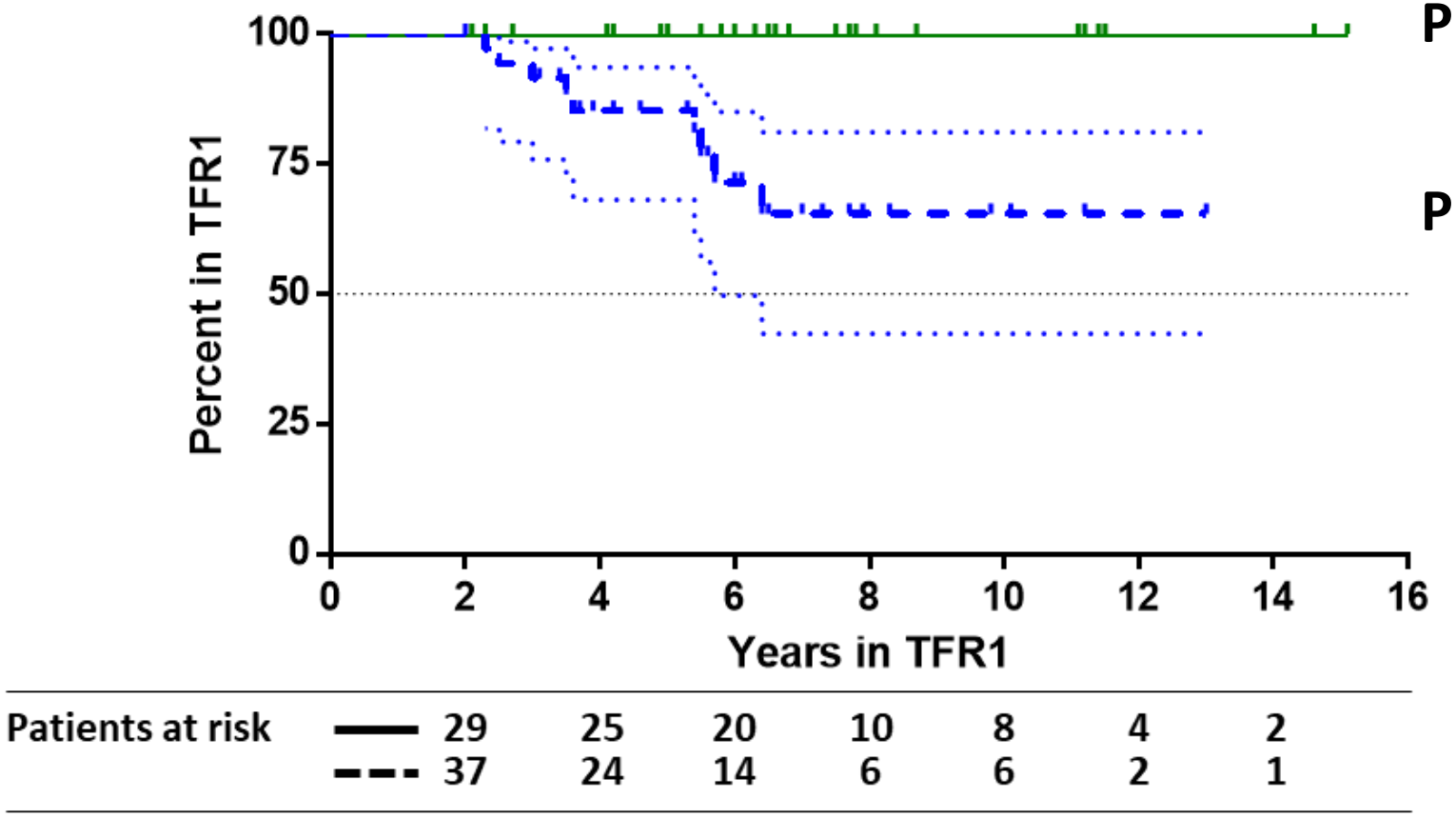
Late molecular relapses (> 2 years in TFR1)

128 patients in TFR, median follow-up in TFR 6.5y



Rousselot P, et al. Blood Adv. 2020 Jul 14;4(13):3034-3040

Stable versus unstable molecular remission



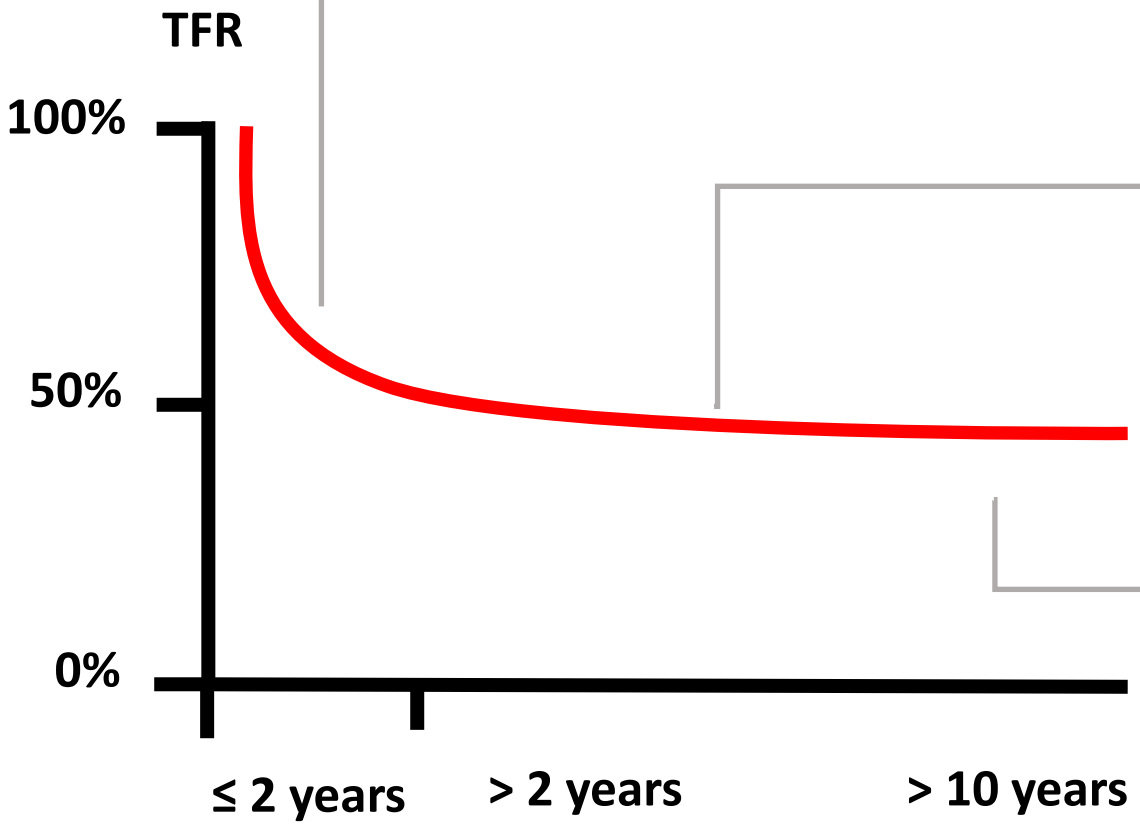
Proportion in TFR1 : 100%

Proportion in TFR1 : 65.4%

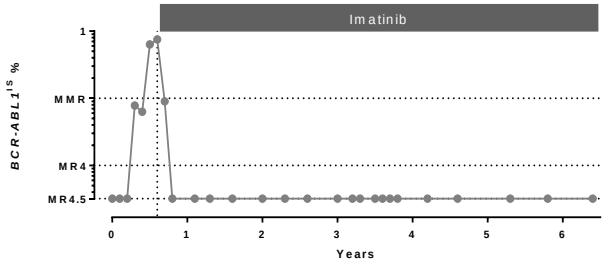
P = 0.02

Rousselot P, et al. Blood Adv. 2020 Jul 14;4(13):3034-3040

Molecular recurrences during treatment free remission (TFR)

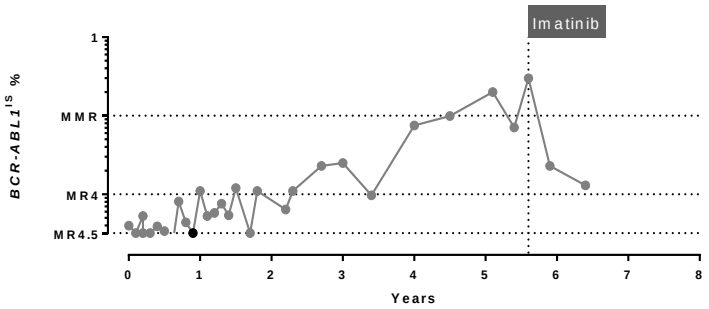


Early molecular recurrences **37%**



55%

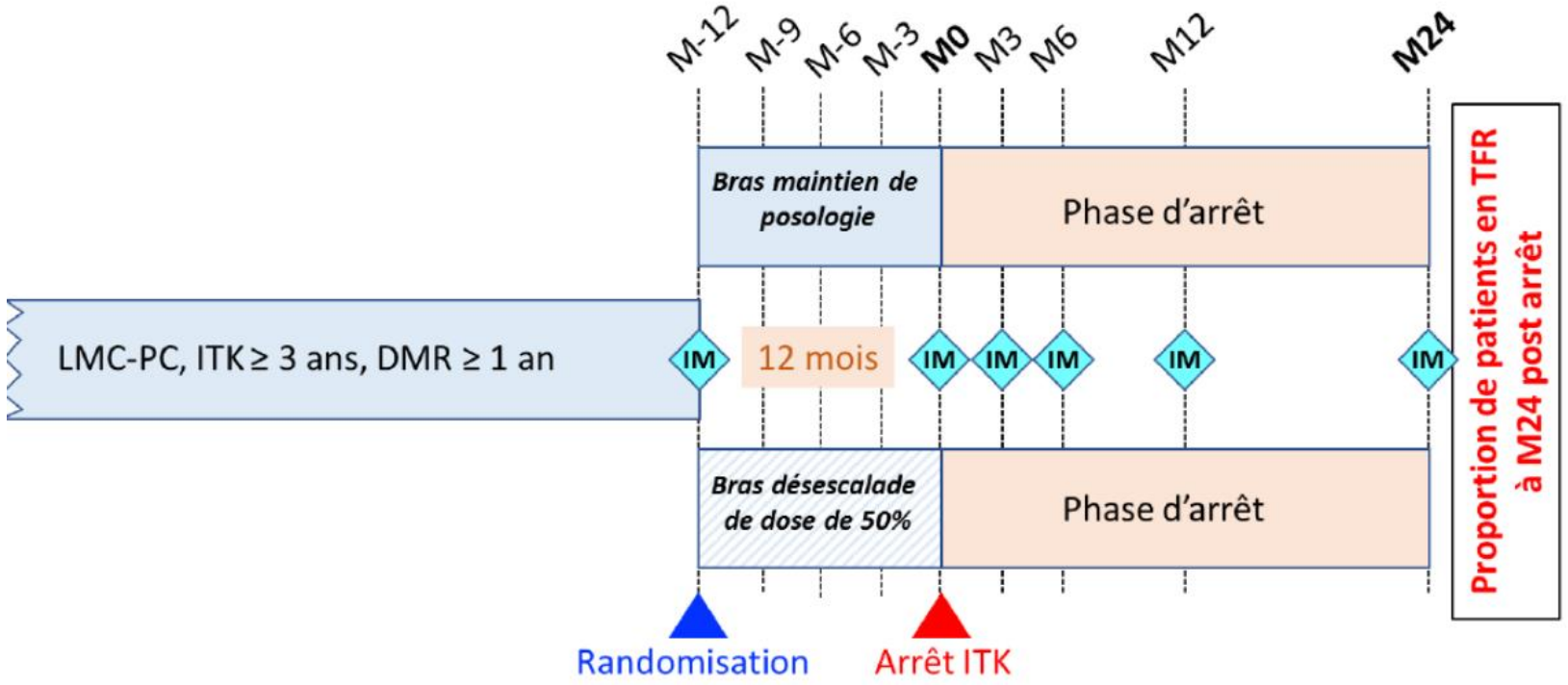
Late molecular recurrences **18%**



Long term treatment free remissions **45%**

Rousselot P, et al. Blood Adv. 2020 Jul 14;4(13):3034-3040

Dose reduction before TFR



Evaluation de la qualité de vie : M-12, M-6, M0, M3 et M6

Evaluation de la concentration résiduelle de l'ITK : M-12 et M0

IM **Immunomonitoring** → *Signature sanguine LT CD8 innés prédictive d'un succès d'arrêt*

Dr Emilie CAYSSIALS-CAYLUS
CHU POITIERS

Dose reducing strategy

❑ Stratégie de désescalade de dose à 50%

ITK	IMATINIB* *Glivec® ou générique*		DASATINIB *Sprycel® ou générique*		NILOTINIB *Tasigna®*		BOSUTINIB *Bosulif®*	
Désescalade	ITK à 100% →	ITK à 50%	ITK à 100% →	ITK à 50%	ITK à 100% →	ITK à 50%	ITK à 100% →	ITK à 50%
Posologie (mg)	400mg/j	200mg/j	100mg/j	50mg/j	300mg/2xj	300mg/j	400mg/j	200mg/j
	300mg/j	200mg/j	80mg/j	40mg/j	200mg/2xj	200mg/j	300mg/j	200mg/j
			70mg/j	40mg/j	300mg/j + 150mg/j	200mg/j	200mg/j	100mg/j
			50mg/j	20mg/j	200mg/j + 150mg/j	150mg/j		
					150mg/2xj	150mg/j		

Dr Emilie CAYSSIALS-CAYLUS

Open topics

1. First line therapy
2. Resistance, Non-ABL mutations
3. Late molecular relapses in TFR, half dose before TFR
4. Advances phases CML

Chemotherapy + TKIs for MBP-CML

2011: AFR01 trial, 3+7 (dose escalated) + imatinib 600 mg/d

Leukemia Research 35 (2011) 777–782

Contents lists available at ScienceDirect

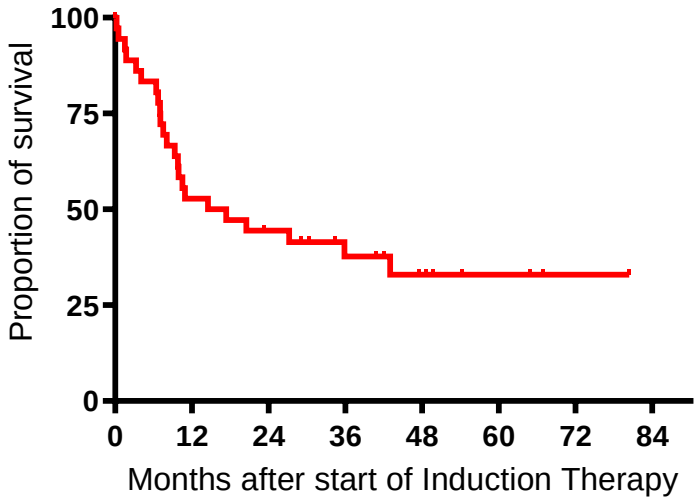
Leukemia Research

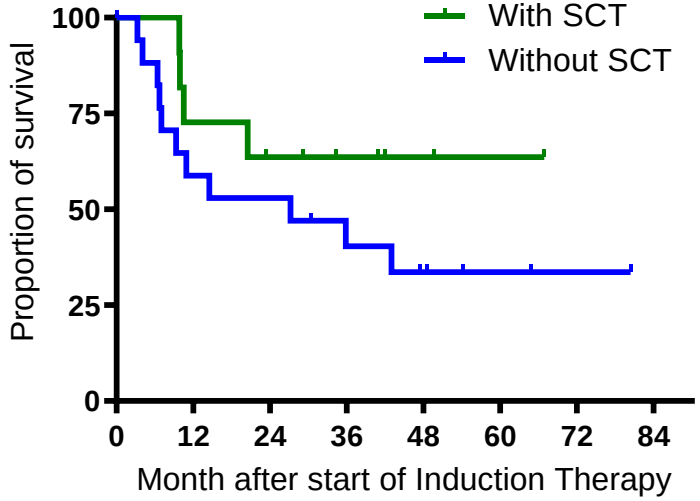
journal homepage: www.elsevier.com/locate/leukres

The addition of daunorubicin to imatinib mesylate in combination with cytarabine improves the response rate and the survival of patients with myeloid blast crisis chronic myelogenous leukemia (AFR01 study)

Bénédicte Deau[a,1], Franck E. Nicolini[b,1], Joelle Guilhot[c,1], Françoise Huguet[d,1], Agnès Guerci[e,1], Laurence Legros[f,1], Cécile Pautas[g,1], Christian Berthou[h,1], Denis Guyotat[i,1], Pascale Cony-Makhoul[j,1], Martine Gardembas[k,1], Mauricette Michallet[b,1], Sandrine Hayette[b,1], Jean Michel Cayuela[l,1], Isabelle Radford Weiss[a,1], Delphine Réa[l,1], Sylvie Castaigne[n,1], François-Xavier Mahon[m,1], François Guilhot[c,1], Philippe Rousselot[n,*,1]

- **45 patients**
- **Median follow-up : 4 years**
- **Median age: 53y (22-74)**
- **TRM before SCT: 14%**
- **Hematological response: 68.9%**
- **HSCT: 29%**



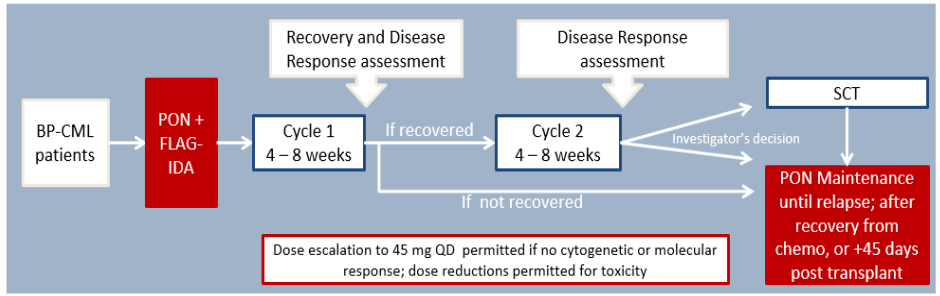


2y OS : 41%

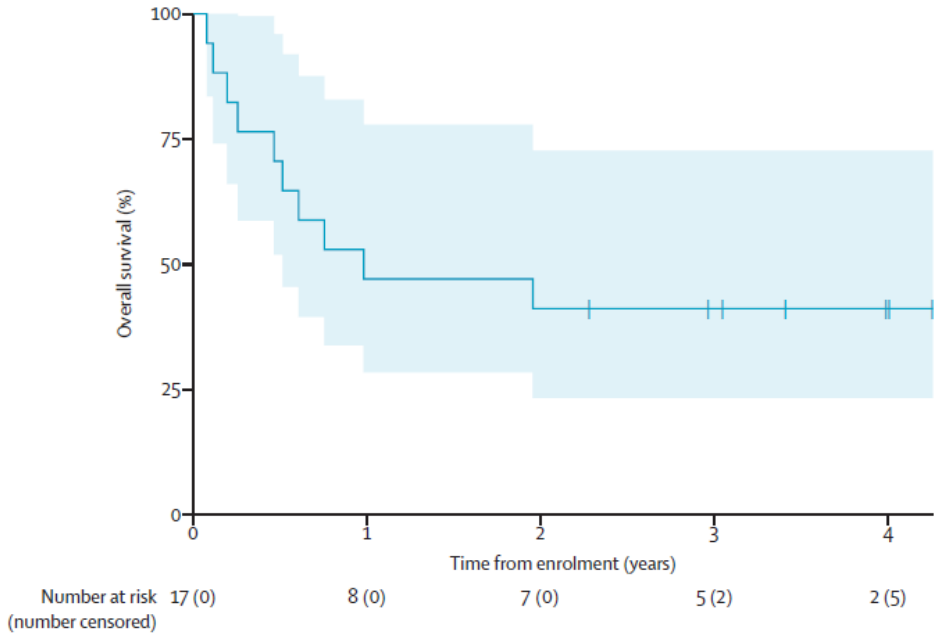
Deau B. Leuk Res. 2011; 35(6):777-782

Chemotherapy + TKIs for MBP-CML

2022: Matchpoint trial, FLAG-IDA + ponatinib (dose finding)



- **17 patients (16 evaluable, 4 LBP-CML)**
- **Median follow-up : 41 months**
- **Median age: 33y (12-48)**
- **TRM before SCT: 17.6%**
- **Hematological response: 69%**
- **HSCT: 71%**

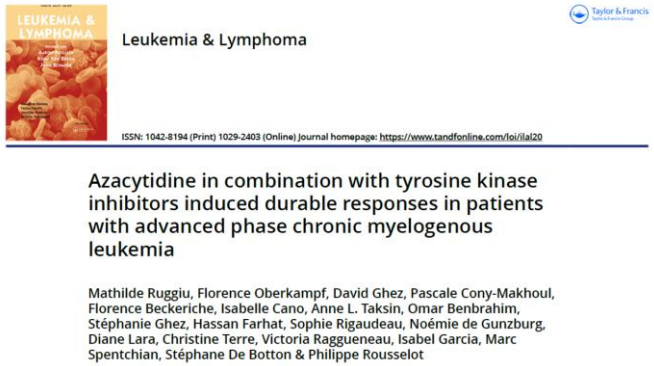


3y OS : 43%

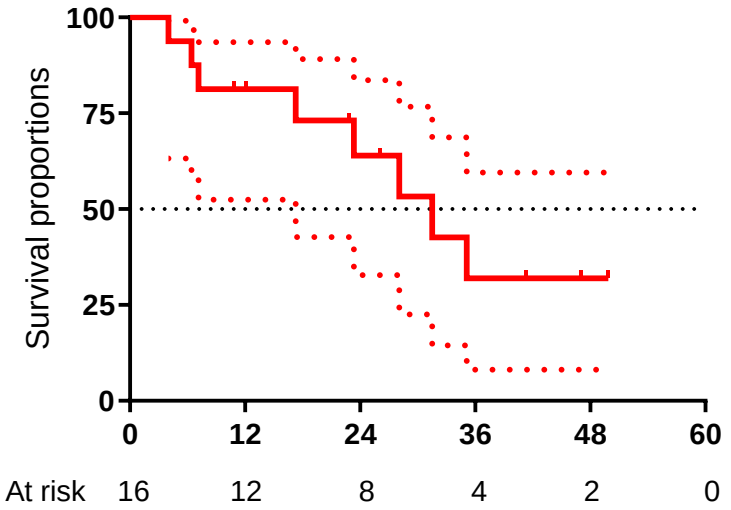
Copland M et al. Lancet Haematol. 2022 Feb;9(2):e121-e132.

Alternative approach for MBP-CML

2018: HMA (Azacytidine) + TKIs (nilotinib, dasatinib, ponatinib)



- **16 patients (4 accelerated phases)**
- **Median follow-up : 23.1 months**
- **Median age: 64.9y (24-89)**
- **TRM before SCT: NO**
- **Hematological response: 81.3%**
- **HSCT: 31.3%**



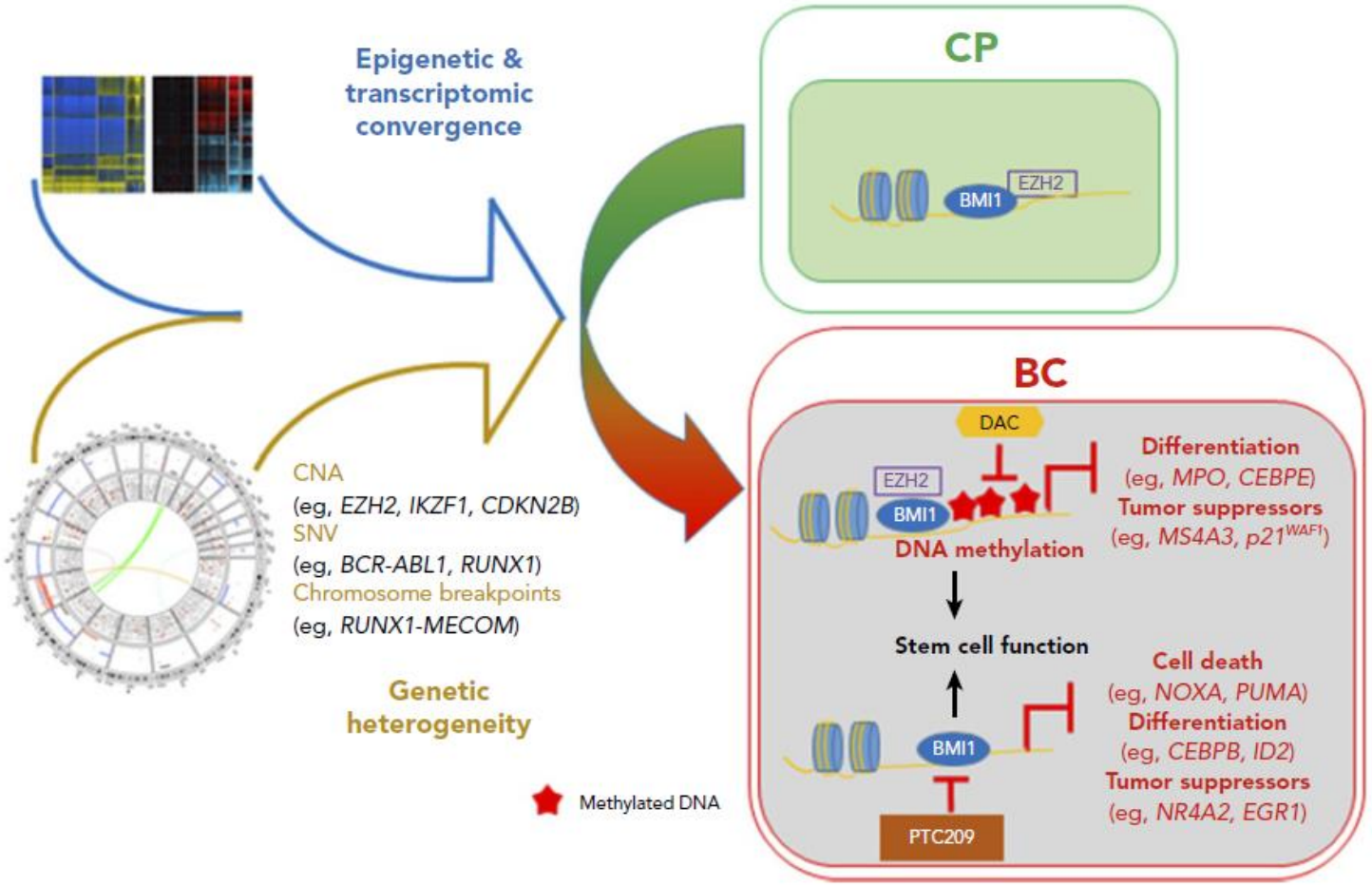
2y OS : 64%

Ruggiu M, et al. Leuk Lymphoma. 2018 Jul;59(7):1659-1665.
Abaza Y, et al. Am J Hematol. 2020 Nov;95(11):1288-1295.

New interest for an old mechanism

The polycomb repressive complex (PRC)-related gene mutations as a complementation group associated with CML progression

PRC1 (BMI1) and PRC2 (EZH2) complexes act as potential mediators of transformation through an epigenetic reprogramming of the CML-BC core transcriptional signature



Ko TK, et al. Blood. 2020 Jun 25;135(26):2337-2353

OPEN LABEL PHASE 2 STUDY ON THE EFFICACY AND TOLERANCE OF A COMBINATION OF PONATINIB AND 5-AZACITIDINE IN CHRONIC MYELOGENOUS LEUKAEMIA IN ACCELERATED PHASE OR IN MYELOID BLAST CRISIS

Sponsor :

Délégation à la Recherche Clinique et à l'Innovation
Centre Hospitalier de Versailles

Principal investigators :

Pr Philippe ROUSSELOT
Dr David GHEZ
Dr Stéphane DE BOTTON

Treatment schedule

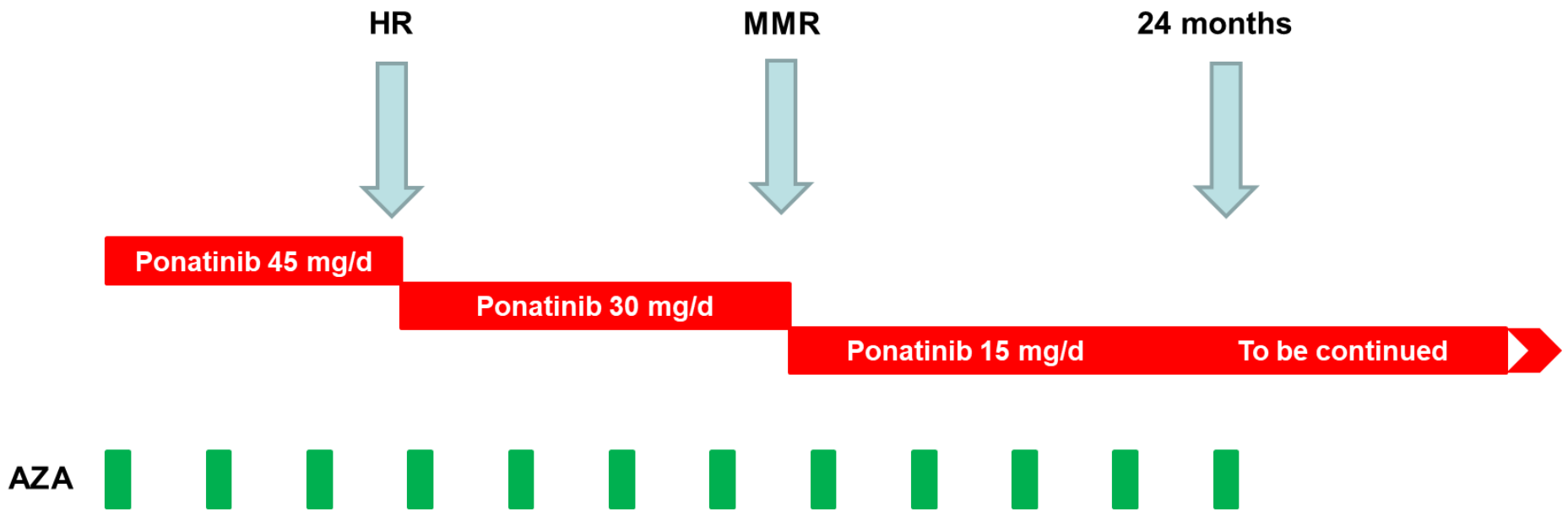
Cycle:
from day 1 to day 28

Induction
max 3 months
(extended up to 6 months if clinically indicated)

Maintenance : stop if progression or allo HSCT
Stop Vidaza at month 24

Ponatinib (Iclusig®)
orally from day 1 to day 28

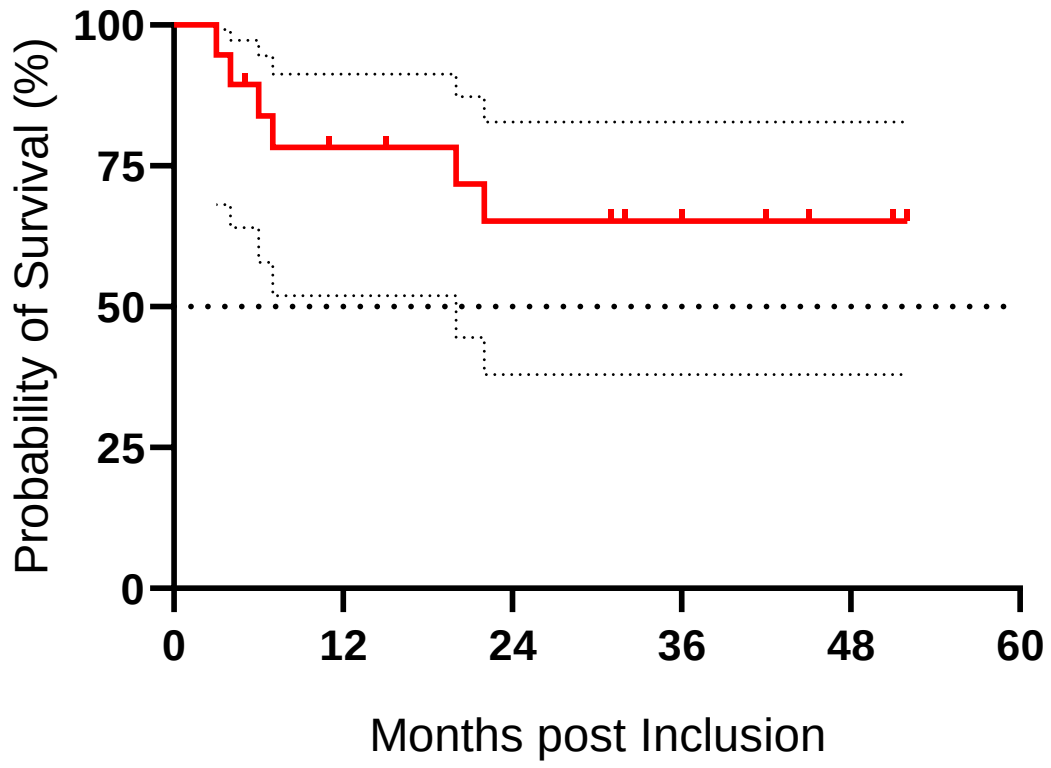
5-Azacitidine
(Vidaza®): 75 mg/m^2 subcutaneously from day 1 to day 7



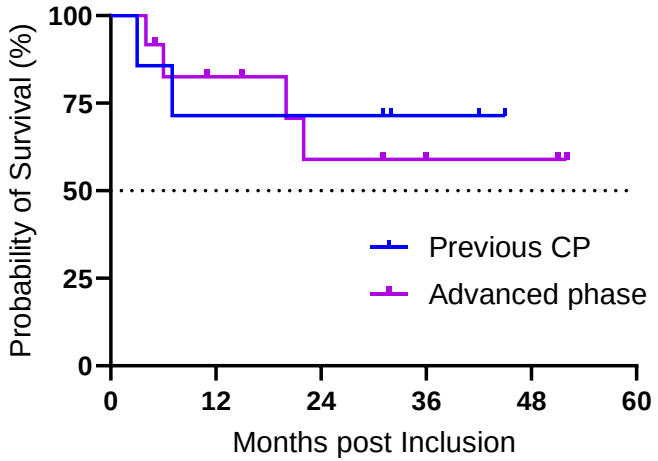
Survival analysis

Median follow-up: 32 months

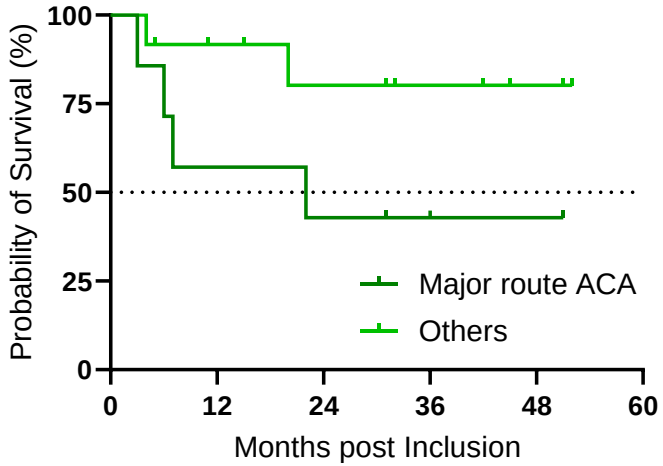
2 years OS : 65.5% (95% CI: 37.9-82.8)



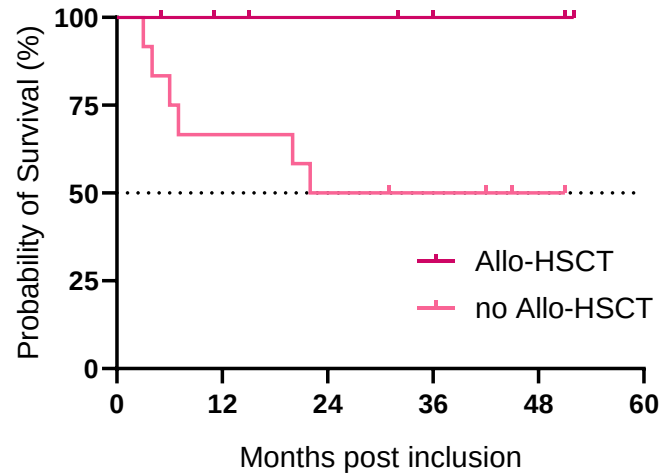
Previous CP



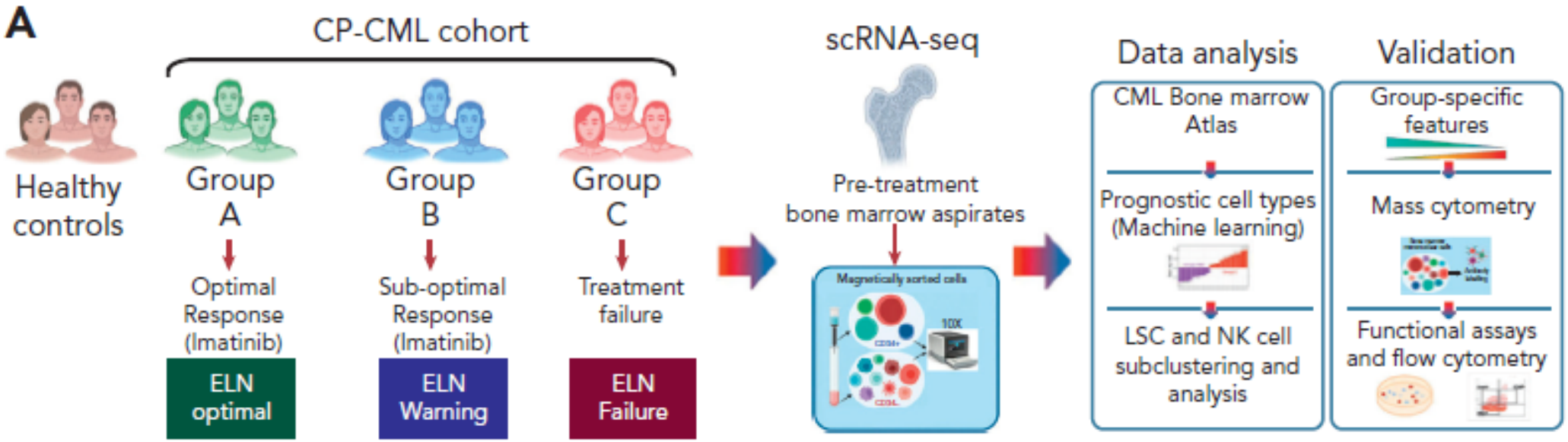
Major route ACA



Allo-HSCT

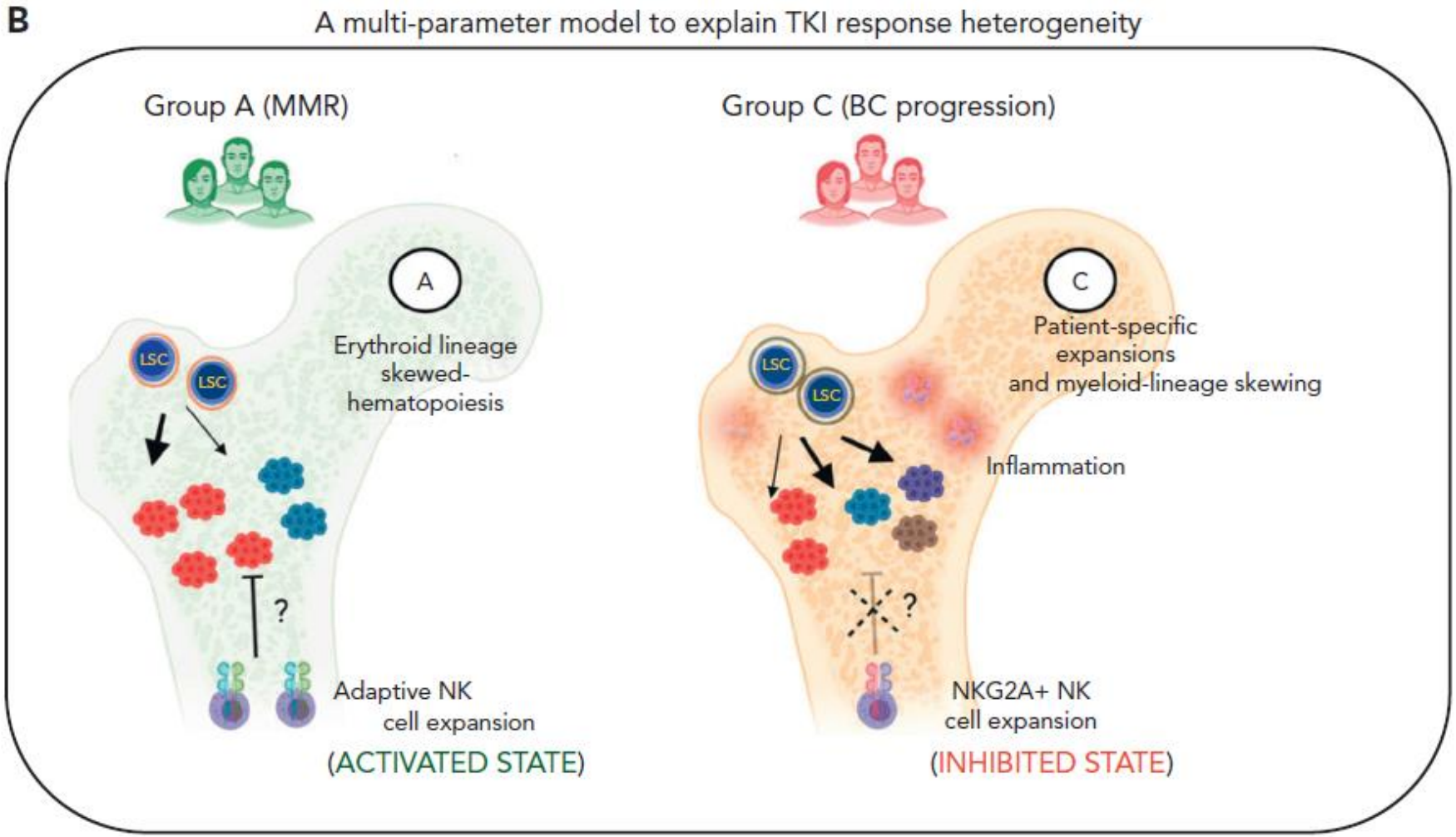


A single-cell atlas identifies pretreatment features of primary imatinib resistance in chronic myeloid leukemia



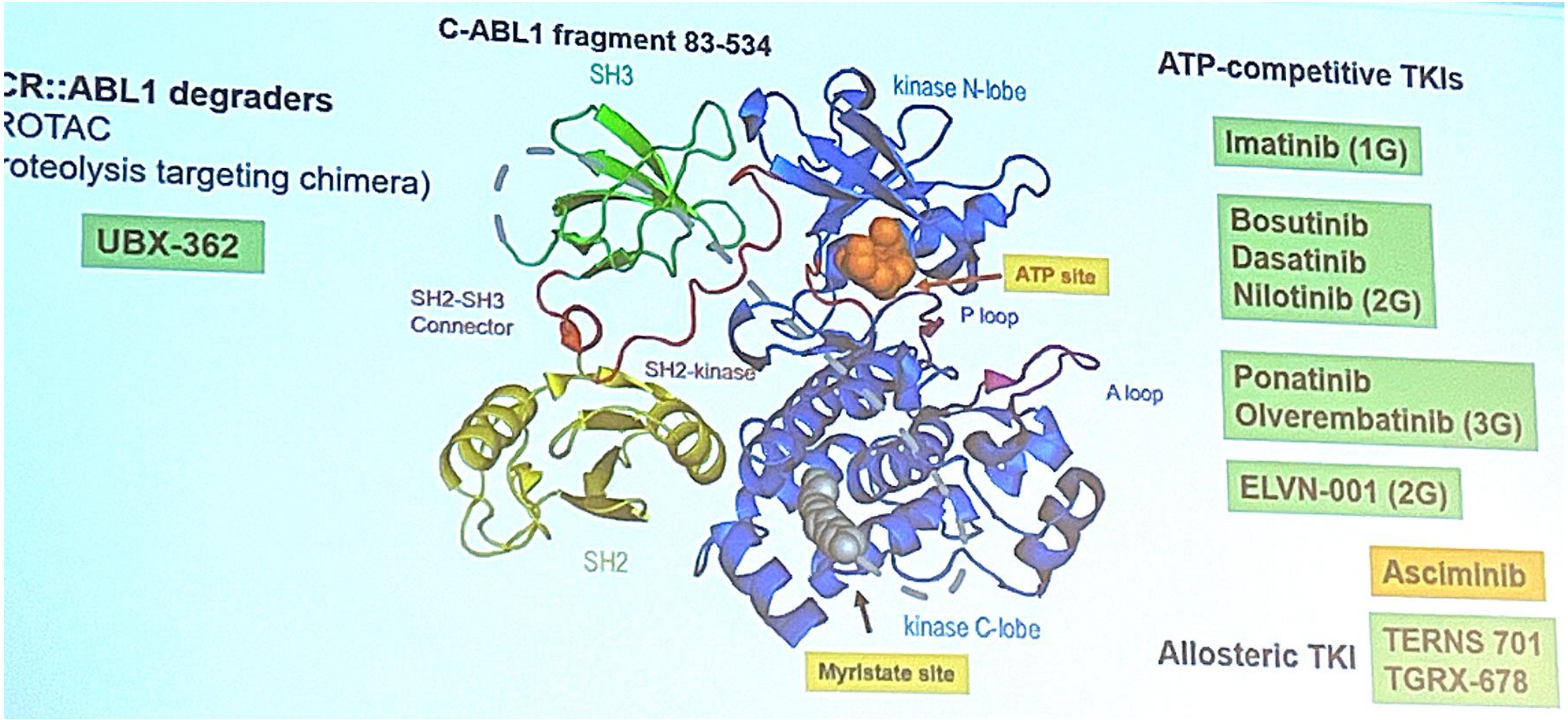
Krishnan V, et al. Blood. 2023 Jun 1;141(22):2738-2755.

Who will progress ???



Krishnan V, et al. Blood. 2023 Jun 1;141(22):2738-2755.

Conclusions



Acknowledgments

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M Delord, Paris

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JM Cayuela