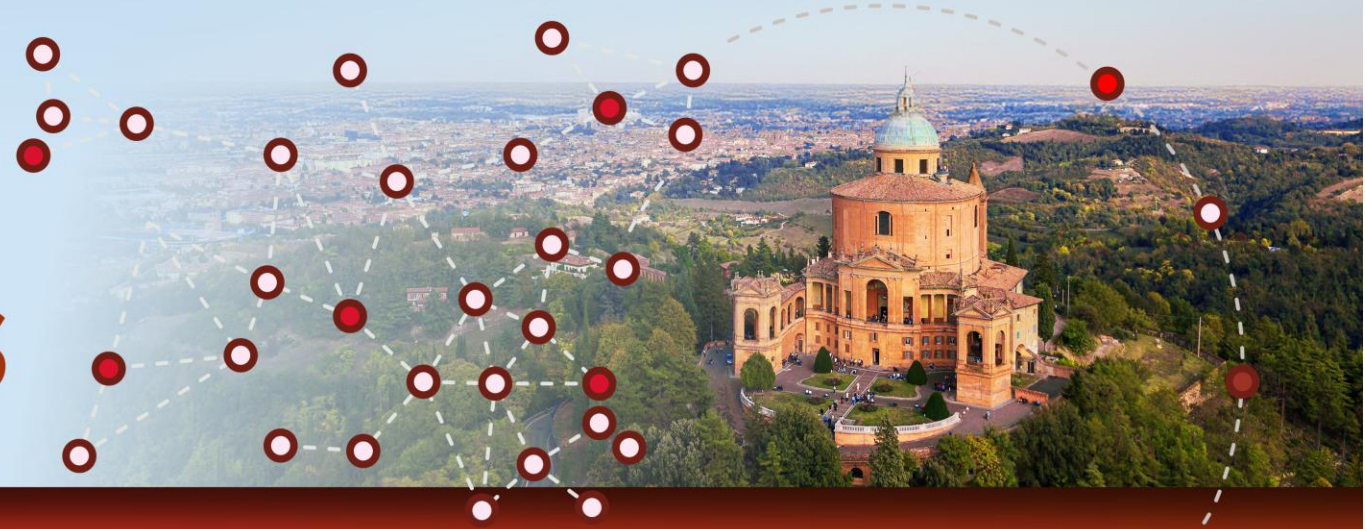
1ST INTERNATIONAL CONFERENCE ON

Ph+Leukemias



Bologna, Royal Hotel Carlton **September 29-30, 2025**

Novel agents for the treatment of CML

Mario Tiribelli

(Division of Hematology - Udine)

Disclosures Mario Tiribelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis					X	X	
BMS					X		
Incyte					X	X	
Jazz Pharmaceuticals					X		
AOP					X		
Abbvie					X		
GSK					X	X	

Agenda

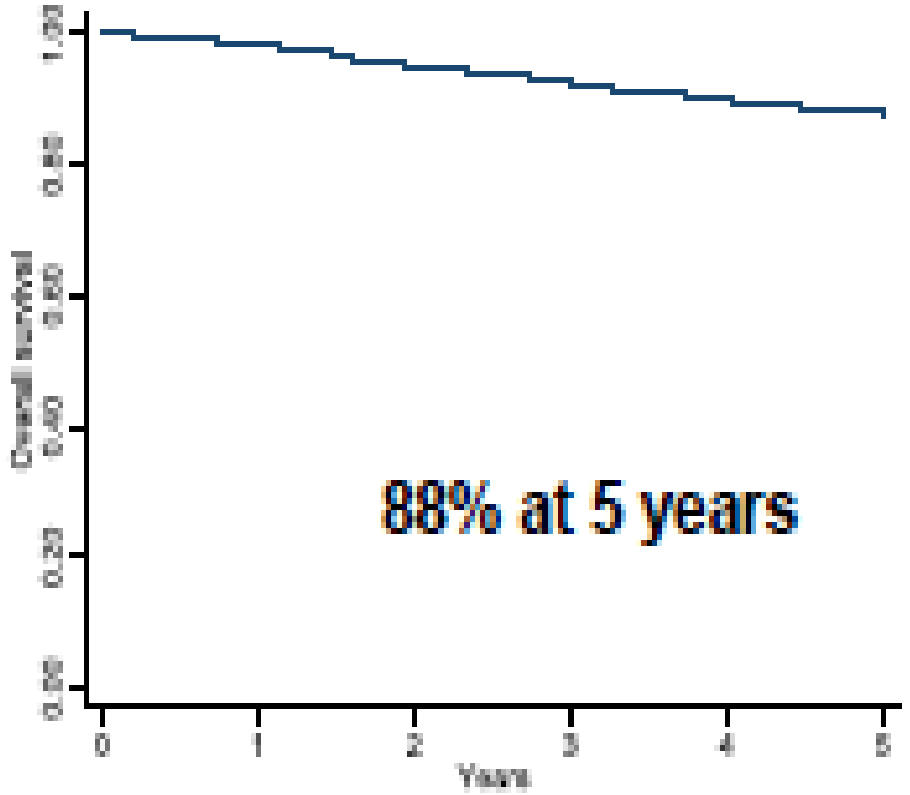
- Do we really need novel drugs in CML?
- Novel agents
- Combination therapies
- Old drugs, new doses
- Something even older…

Agenda

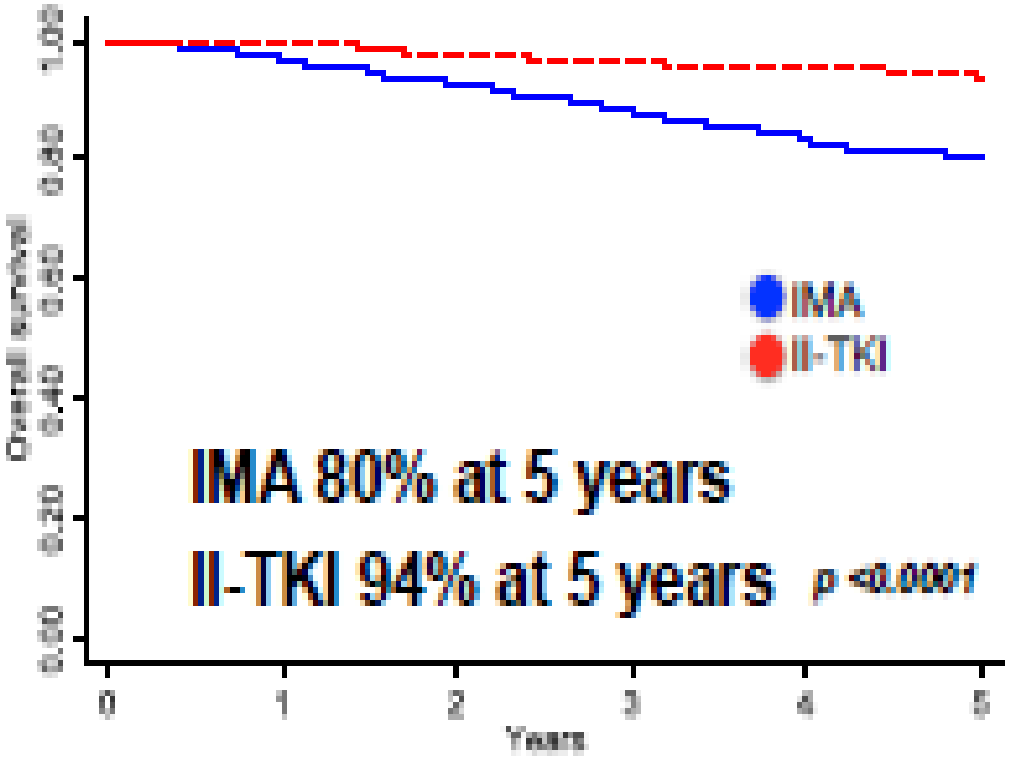
- **Do we really need novel drugs in CML?**
- Novel agents
- Combination therapies
- Old drugs, new doses
- Something even older…

CML survival over time – Italian RWE

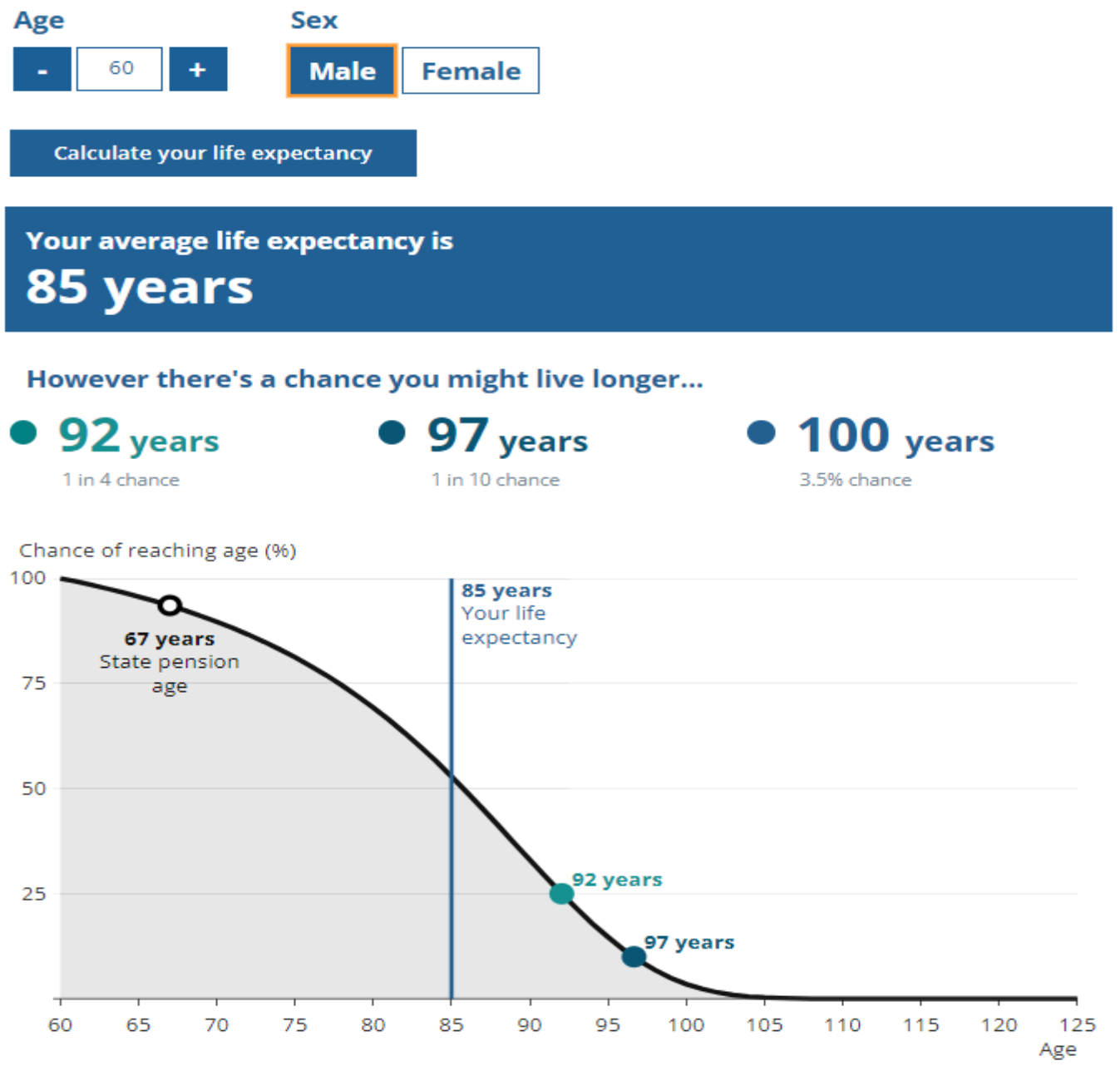
OS of ALL POPULATION (n: 1277)



OS according to first line TKI



Giai V et al., Cancer 2025



- **Median age at CML diagnosis in the Western countries is 60-65 yrs**
- **In the U.K., a 60-yrs old male is expected to live up to 85**

→ **Median OS: 25 yrs**

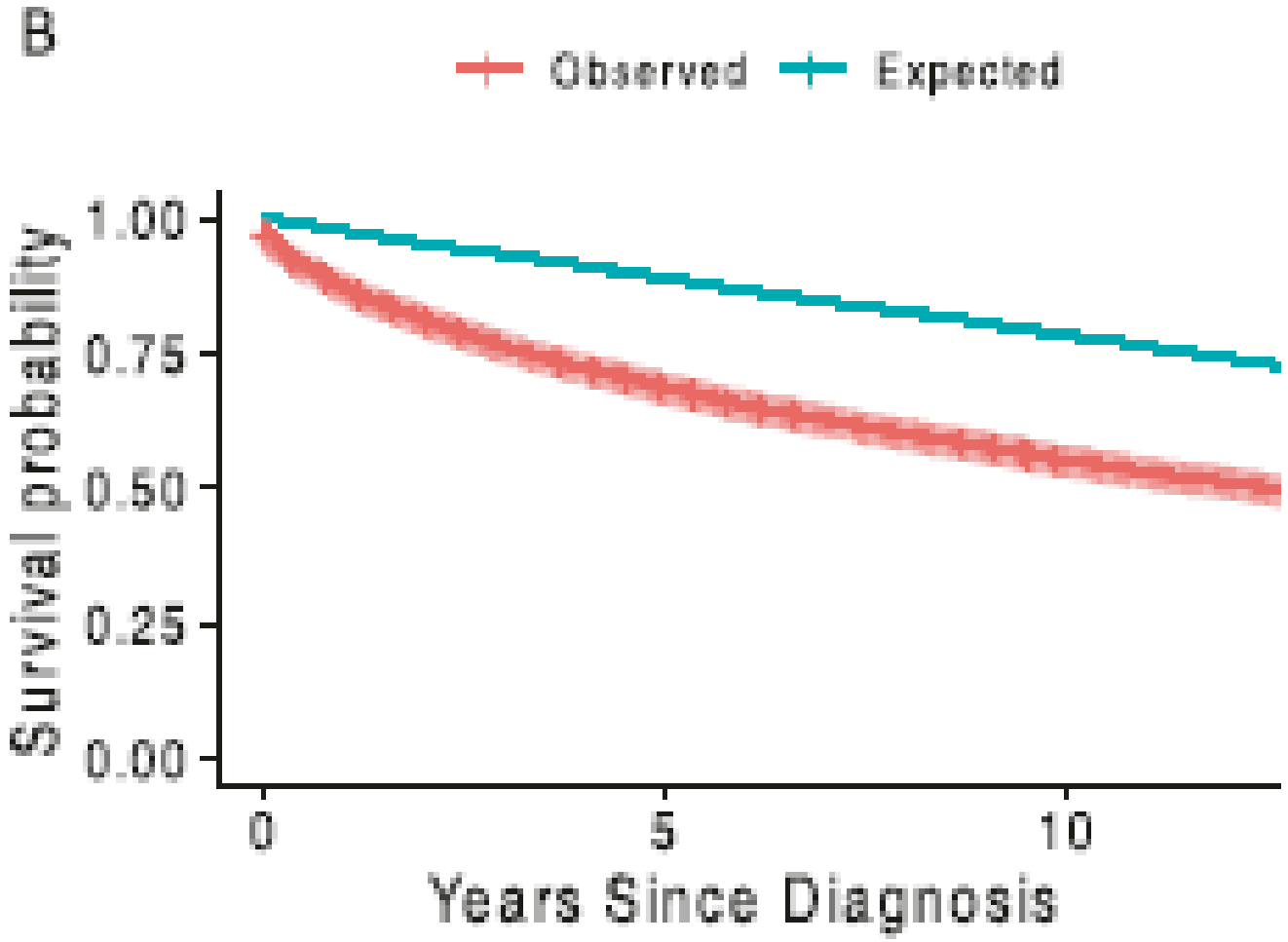
5-yrs OS ≈ 95%

10-yrs OS ≈ 89%

UK Office for National Statistics (ons.gov.uk - access 13/08/25)

Do persons with chronic myeloid leukaemia have normal or near normal survival?

Tomas Radivoyevitch[1] · Davis Weaver[2] · Brian Hobbs[1] · Jaroslaw P. Maciejewski[1] · Rudiger Hehlmann[3] · Qian Jiang[4] · Andreas Hochhaus[5] · Robert Peter Gale[6]



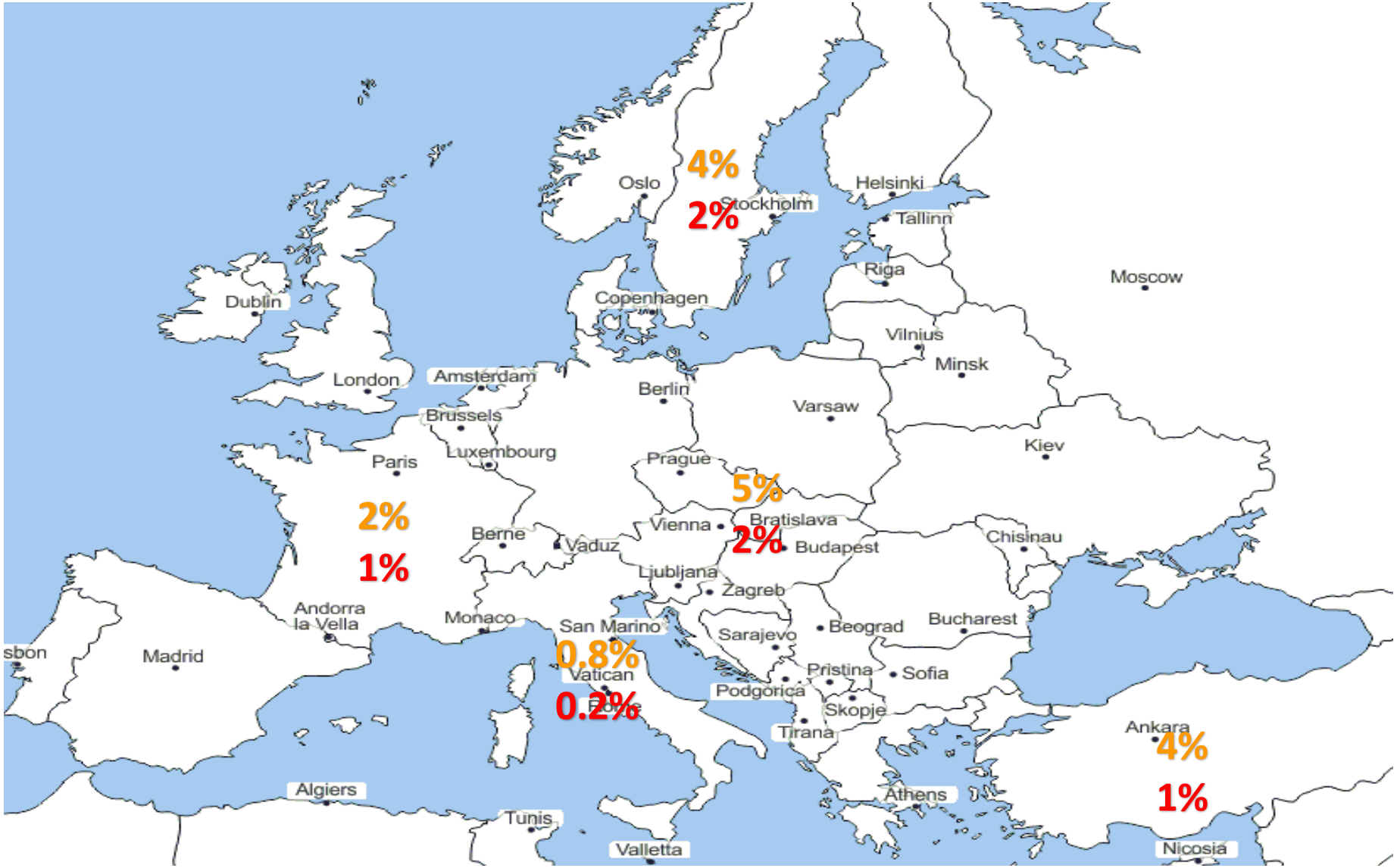
- Unselected cases from US SEER dataset
- **CML patients in the US have a 2.38-fold (95%CI 1.70-3.07; p < 0.0001) higher risk of death than controls**
- Possible explanations: lower access to, compliance with and monitoring of TKI-therapy compared to clinical trials (and data from Europe?)

Radivoyevich T et al., Leukemia 2020

Incidence of A/BP at diagnosis

AP

BP

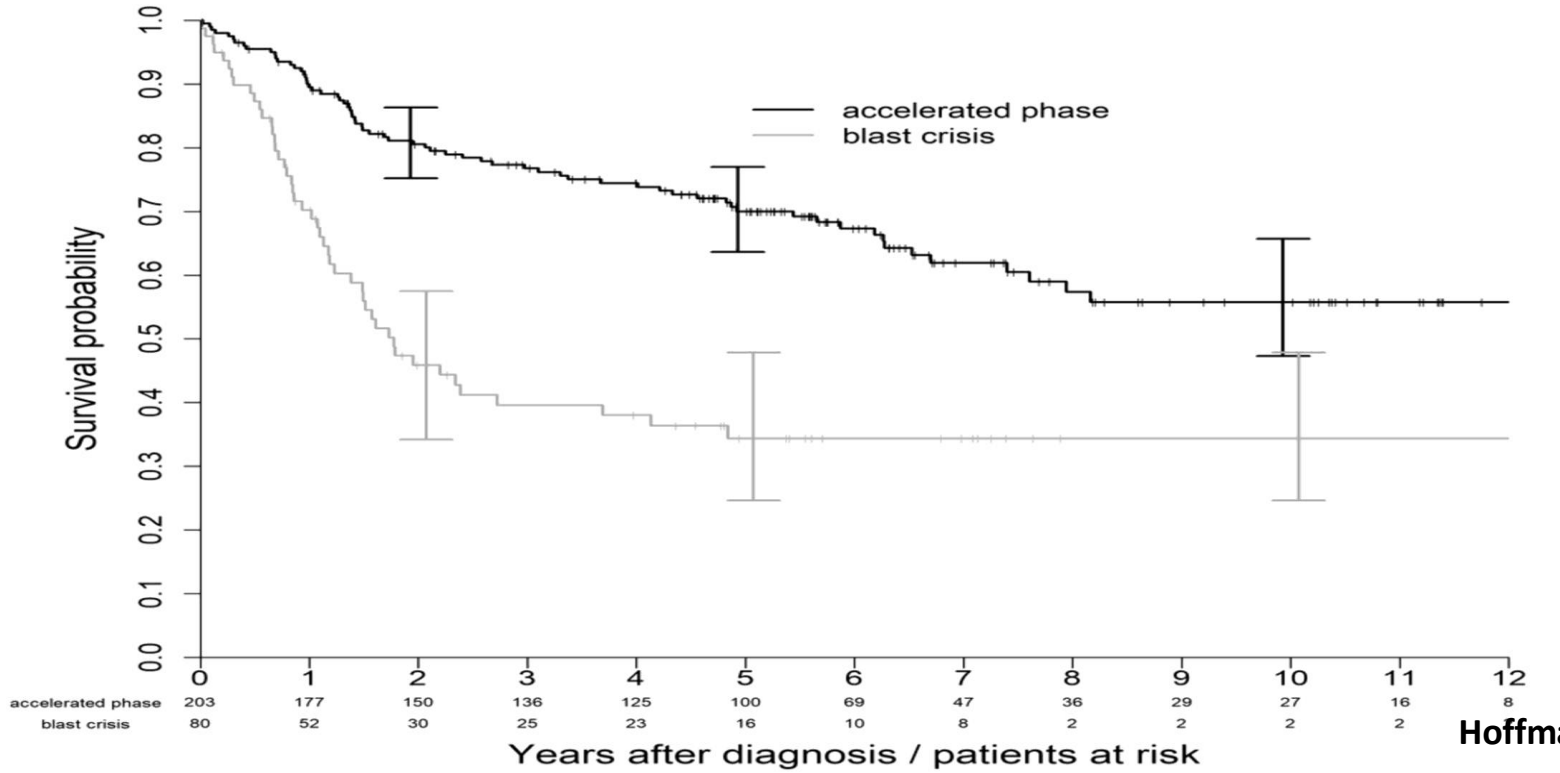


European experience on advanced phase CML

Registry of almost 3,000 CML patients treated with TKIs in European countries

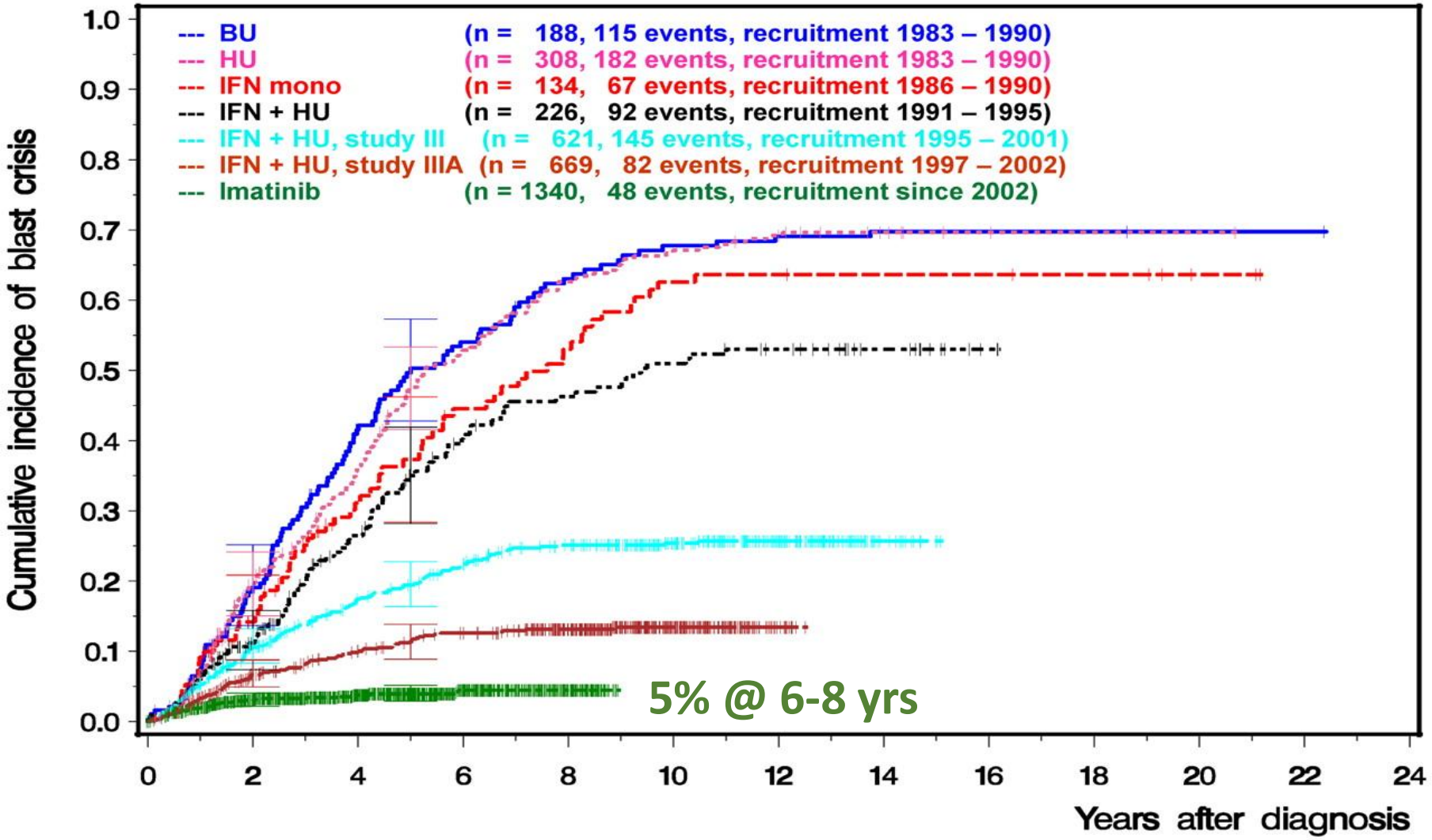
Diagnosis in AP = 3.5% and in BP = 2.2% (according to ELN criteria)

5-yrs OS: ≈70% in AP, ≈35% in BP



Hoffmann VS et al., Leukemia 2015
Lauseker M et al., AJH 2019

Risk of progression under TKI therapy



Hehlmann H, Blood 2012

Does frontline use of 2G-TKIs prevent progression? «conflicting» results

5-year risk (ITT)	n
Dasa vs Ima	12 vs 19
Nilo vs Ima	10 vs 21 (rare in low risk)

	CML related deaths			
	IMA total deaths: 86/607		II-TKI total deaths: 32/670	
	Stayed on IMA	Switched to other	Stayed on II-TKI	Switched to other
	8/58 (14%)	3/28 (10%)	1/15 (7%)	11/17 (65%)
Total CML-rel	11/86 (13%)		12/32 (37%)	

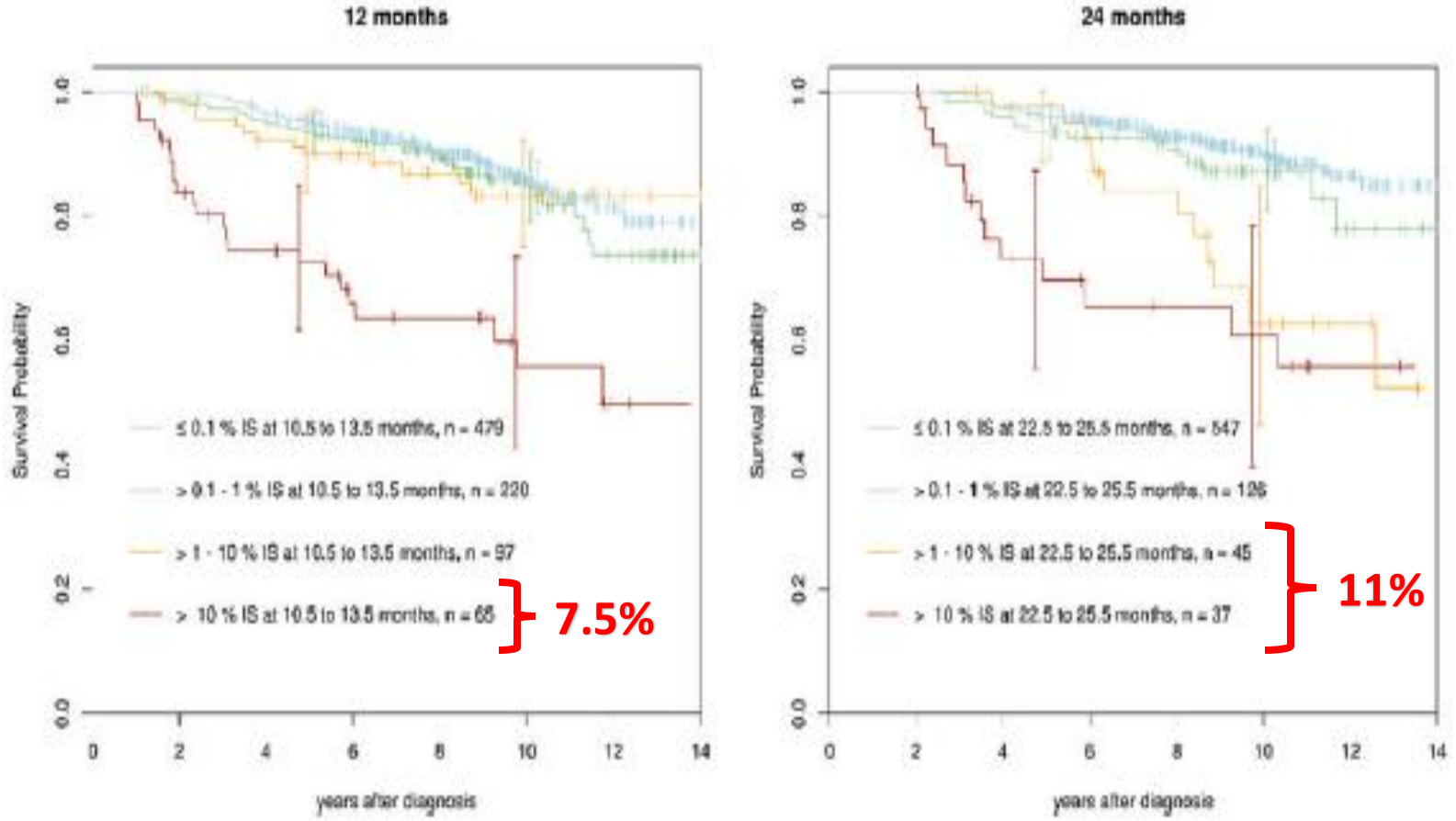
Hochhaus A et al., Leukemia 2016
Cortes J et al., J Clin Oncol 2016

Giai V et al., Cancer 2025

Do patients who fail TKIs really have a «good» prognosis?

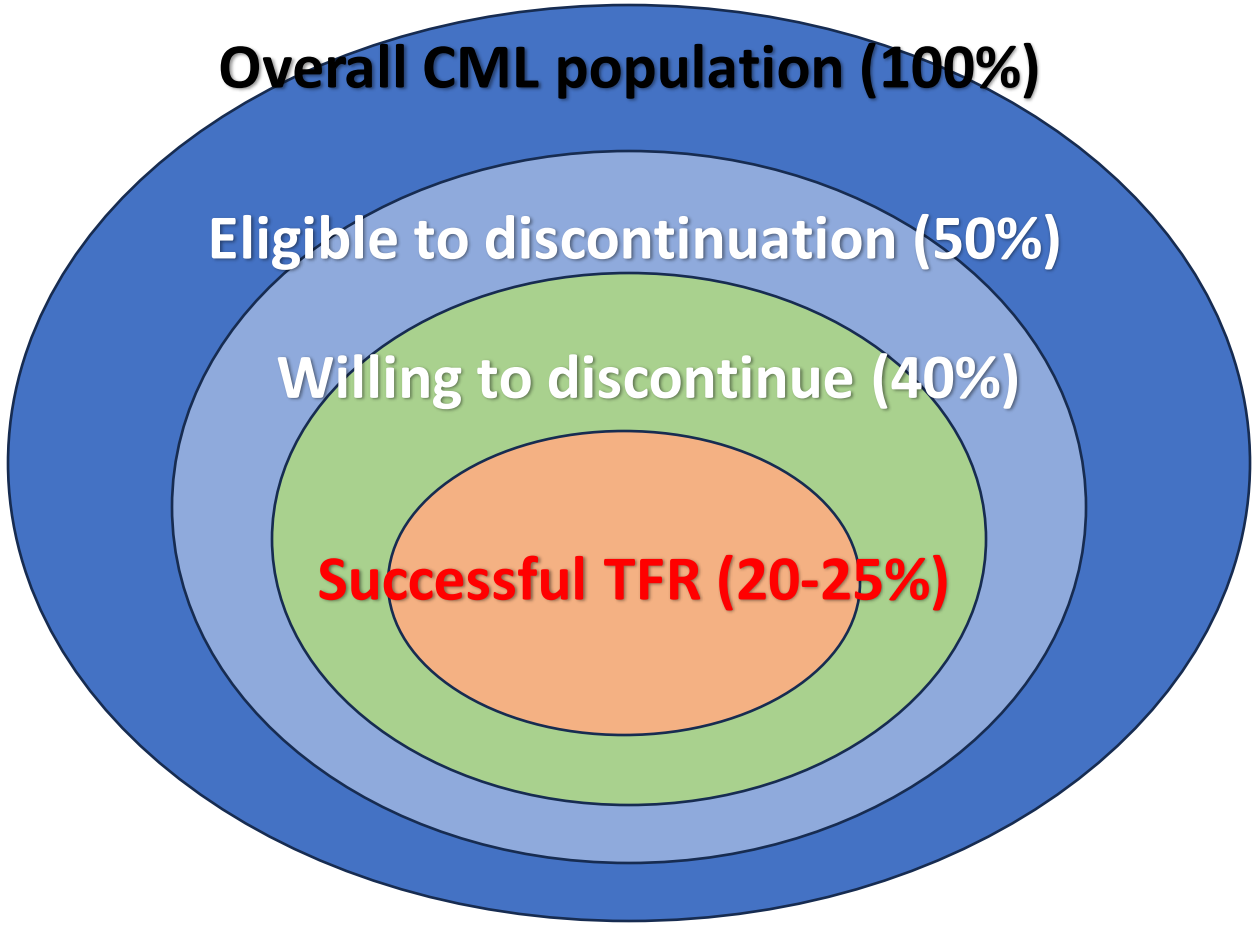
German CML-IV study

- Patients not reaching 10% BCR::ABL1 at 12 months had a 10-year OS of about 55%
- 10-year survival of patients failing >1-10% at 24 months was around 60%
- Censoring for switching therapy did not change the results



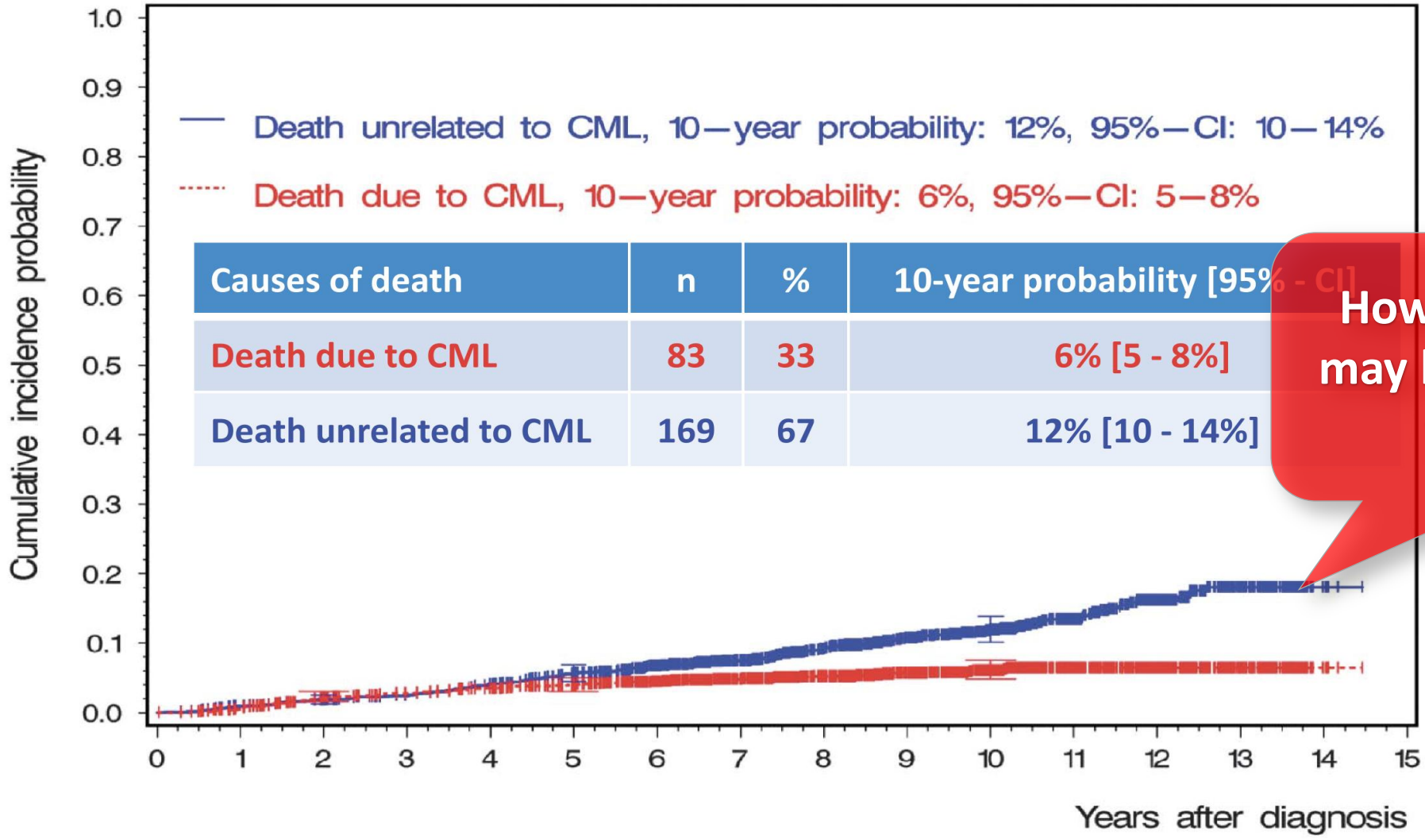
Lauseker M et al., Leukemia 2023

The long and winding road to TFR



Zackova D et al. Leukemia 2024

Survival according to causes of death



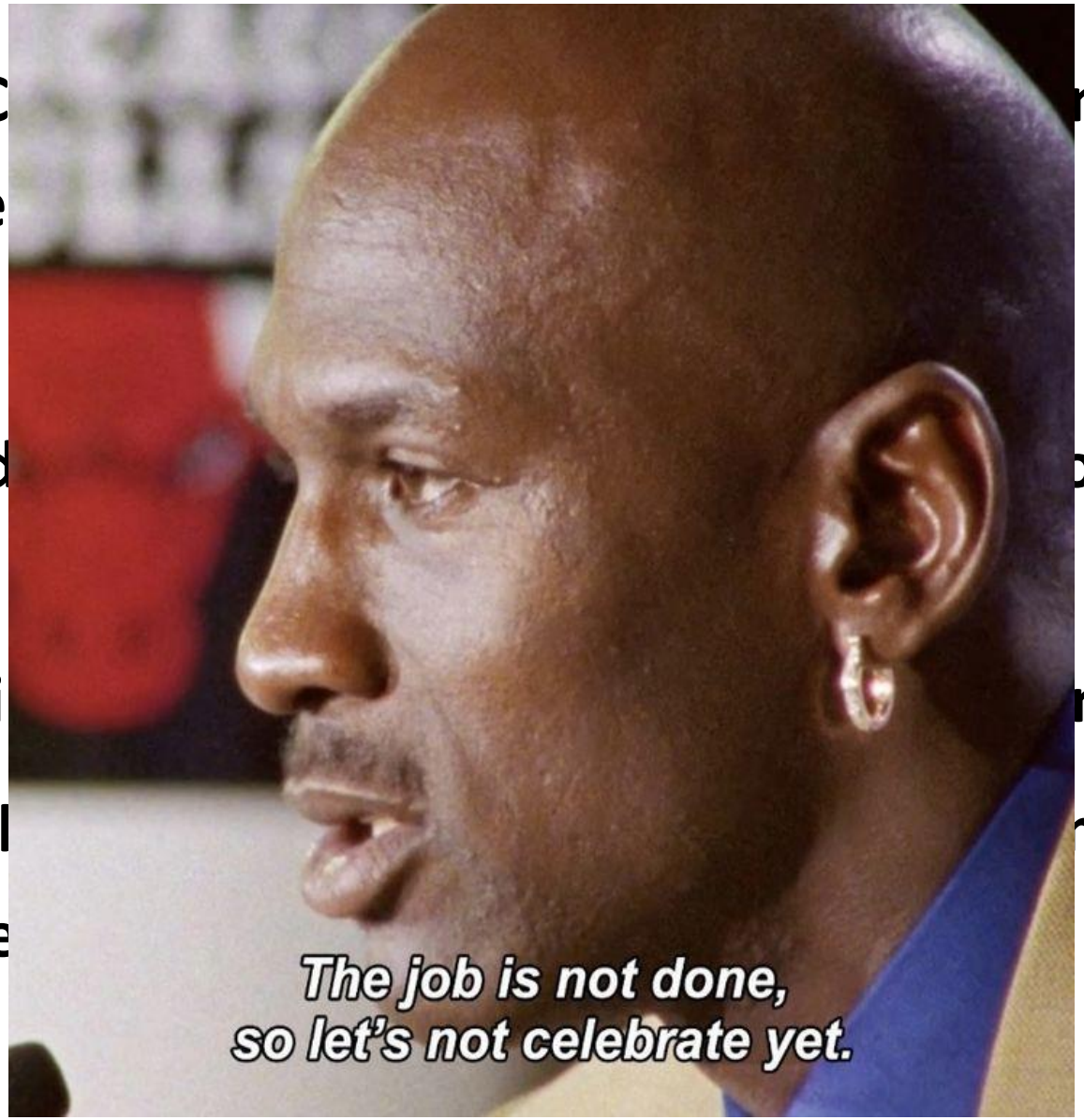
Causes of death	n	%	10-year probability [95% - CI]
Death due to CML	83	33	6% [5 - 8%]
Death unrelated to CML	169	67	12% [10 - 14%]

How many of these may be related to TKI treatment?

Hehlmann H et al., Leukemia 2017

- Undoubtedly, C n the TKI era and now approache

- Prognosis of ad r evolution from CP (≈5%) is still
- Patients «heavi nferior OS
- Sustained TFR l most will receive life-long TKI the

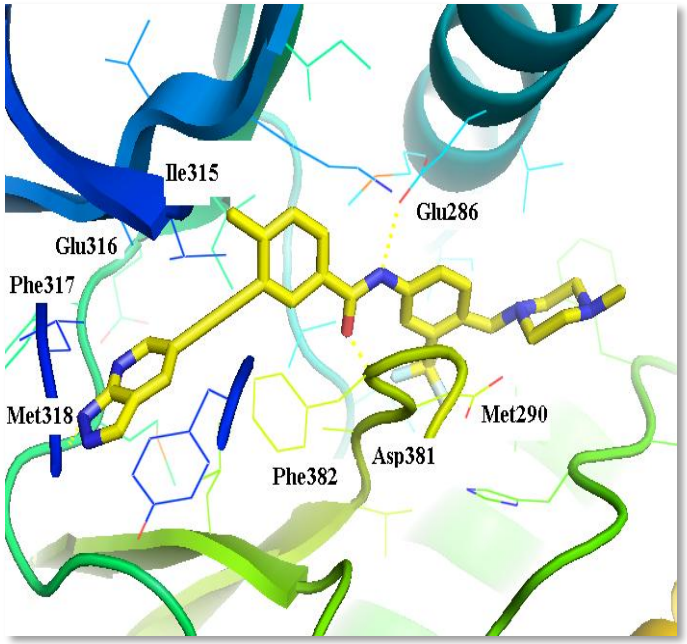


Agenda

- Do we really need novel drugs in CML?
- **Novel agents**
- Combination therapies
- Old drugs, new doses
- Something even older…

Olverembatinib

- **Preliminary favorable safety profile**
- **Highly potent against *BCR::ABL1*^{WT} and *BCR::ABL1*^{T315I} mutant kinases**
- **Significant antiproliferative activity in engineered cells with *BCR::ABL1* compound mutations**



Ren X, et al. J Med Chem. 2013

Olverembatinib Demonstrates Efficacy versus Best Available Therapy in Patients with Tyrosine Kinase Inhibitor-Resistant Chronic Myeloid Leukemia in Chronic-Phase in a Registrational Randomized Phase 2 Study

Jiang Q, et al. ASH 2023

Study Design

Key study criteria

- Adults with CP-CML
- Resistant/intolerant to I, D, and N
- ECOG PS ≤ 2
- Adequate organ function
- Excluded pts had conditions complicating TKI treatment

HQP1351CC203 (NCT04126681)

Randomized 2:1

N = 144*

- **Olverembatinib 40 mg QOD, n = 96**
- **Best Available Therapy** n= 48**

Primary Endpoints:

Event-free survival ***

*2 patients in BAT group had been randomized successfully but not dosed .

** BAT includes interferon, hydroxyurea, and homoharringtonine or TKIs I, D, and N and combinations

*** **Cross-over from BAT was allowed after meet the event criteria**

- **Primary Endpoint:**

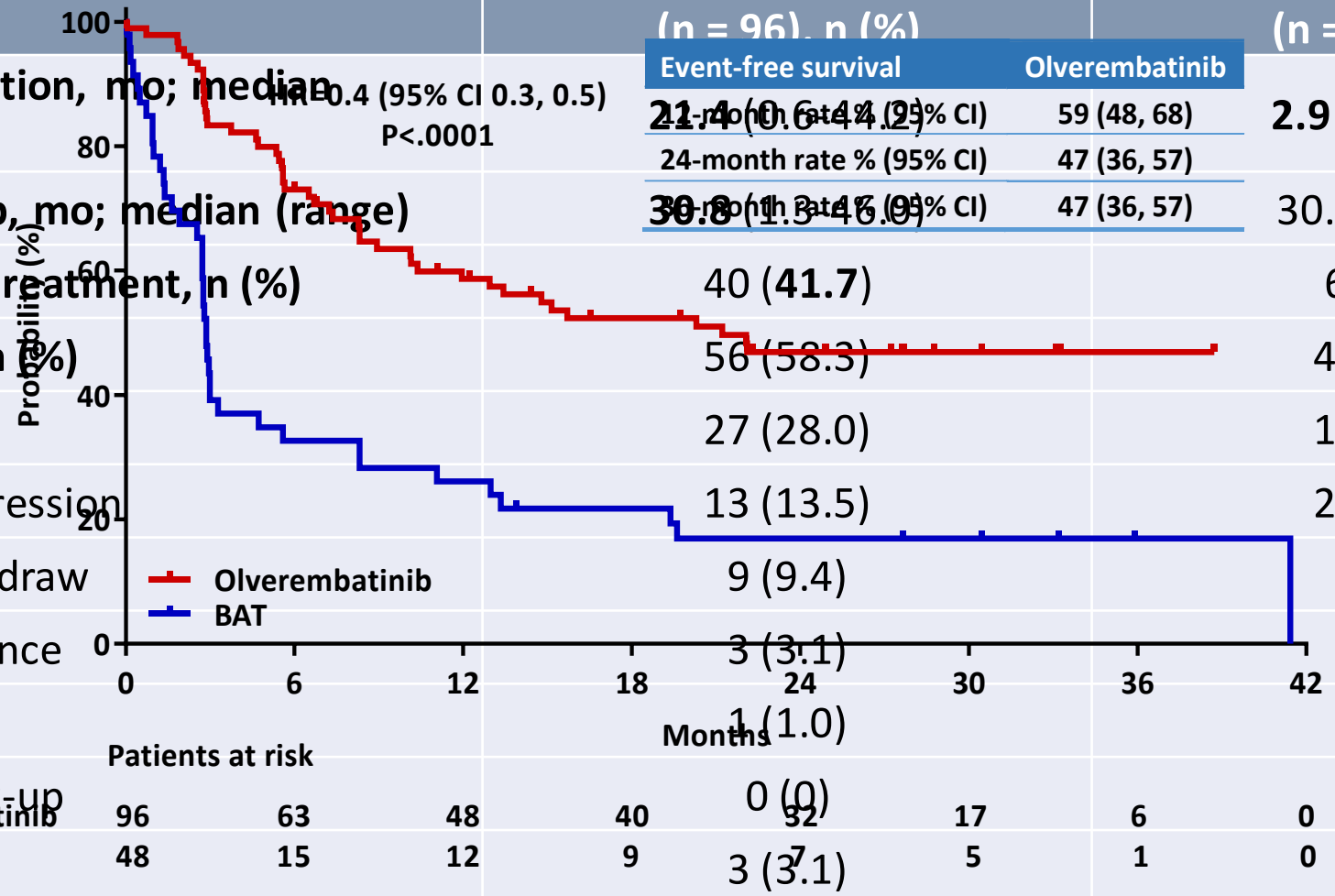
  - **Event-free survival (EFS)**: the time from randomization until an event occurs

  - **Event:** no CHR within 3 cycles, loss of achieved CHR, MCyR or CCyR, disease progression, death from any cause, unacceptable toxicity, whichever comes first

Jiang Q, et al. ASH 2023

Patients' Disposition
Event-free survival

	Olverembatinib (n = 96), n (%)	Best Available Therapy (n = 48), n (%)
Treatment duration, mo; median (range)	**21.4** (0.6-44.2)	**2.9** (0.2-40.5)
Study follow-up, mo; median (range)	**30.8** (1.5-46.0)	30.4 (0-45.8)
Continuing on treatment, n (%)	40 (**41.7**)	6 (**12.5**)
Discontinued, n (%)	56 (58.3)	42 (87.5)
AE	27 (28.0)	15 (31.3)
Disease progression	13 (13.5)	22 (45.8)
Consent withdraw	9 (9.4)	1 (2.1)
Poor compliance	3 (3.1)	1 (2.1)
Death*	1 (1.0)	1 (2.1)
Lost to follow-up	0 (0)	1 (2.1)
Other**	3 (3.1)	1 (2.1)



Event-free survival	Olverembatinib
12-month rate % (95% CI)	59 (48, 68)
24-month rate % (95% CI)	47 (36, 57)
30-month rate % (95% CI)	47 (36, 57)

Jiang Q, et al. ASH 2023

Original Investigation

Olverembatinib After Failure of Tyrosine Kinase Inhibitors, Including Ponatinib or Asciminib

A Phase 1b Randomized Clinical Trial

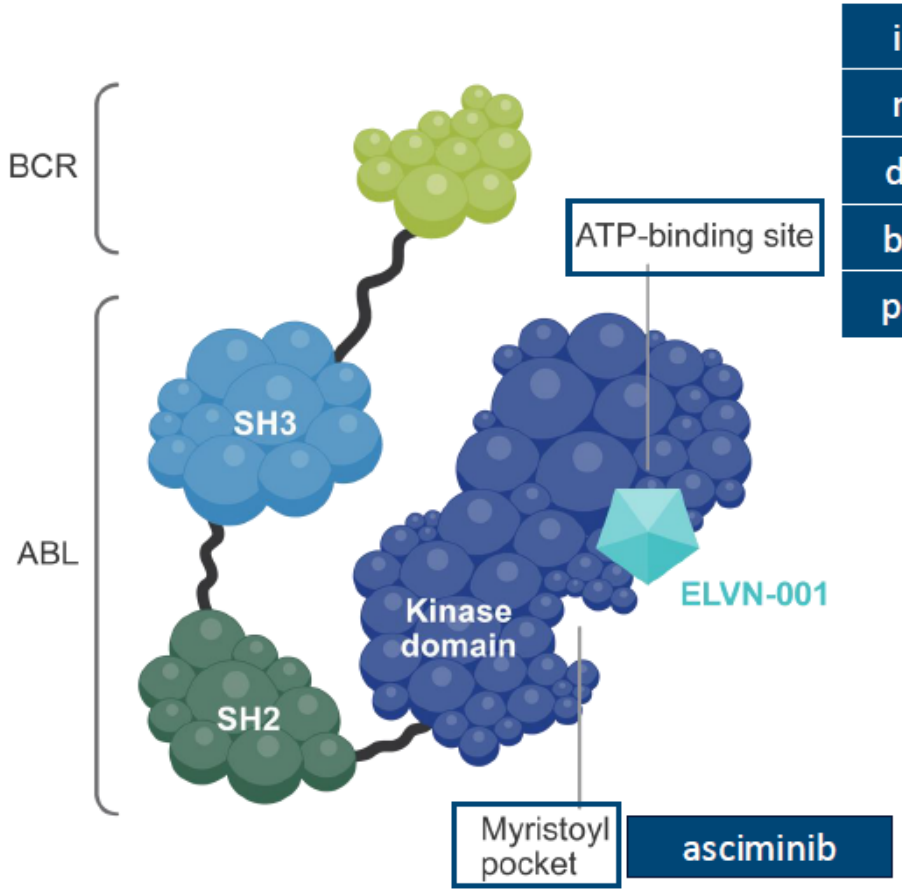
Elias Jabbour, MD[1]; Vivian G. Oehler, MD[2]; Paul B. Koller, MD[3] ; et al

» Author Affiliations | Article Information

Olverembatinib in CML or Ph+ ALL resistant or intolerant to at least 2 TKIs.
Random assignement to 30, 40, or 50 mg of olverembatinib every other day in 28-day cycles.
60 patients (75%) experienced at least 1 treatment-related AE; 32 (40%) experienced grade 3 or higher treatment-related adverse events; and 12 (15%) experienced treatment-related serious adverse events, none of which were fatal.
Frequently reported (10% or more) treatment-emergent adverse events included elevated blood creatine phosphokinase (all grades, 31 [39%]; grade 3 or higher, 10 [13%]) and thrombocytopenia (all grades, 23 [29%]; grade 3 or higher, 14 [18%]).
CML patients: CCyR occurred in 31 of 51 patients (61%), MMR in 25 of 59 patients (42%).
Cytogenetic and molecular responses were similar in patients with or without T315I variants.
Prior ponatinib: 15 of 26 (58%) achieved CCyR, and 11 of 30 (37%)) achieved MMR.
Prior asciminib: 4 of 8 (50%) had CCyR, and 4 of 12 (33%) had MMR.

Jabbour E et al., JAMA Oncol 2025

ENABLE: A Phase 1a/1b Study of ELVN-001, a selective active site inhibitor of BCR::ABL1, in patients with previously treated CML



	KIT	FLT3	PDGFRB	VEGFR2	SRC
ELVN-001	>10,000	>10,000	>10,000	>10,000	>10,000
Ponatinib	30	3.8	89	4.8	630
Nilotinib	200	>10,000	720	2,900	>10,000
Dasatinib	0.6	>1,000	7.1	>1,000	10
Bosutinib	1,000	4,700	7,900	>10,000	16

Fold-Shift in *In Vitro* Cellular Phosphorylation IC_{50} vs. pCRKL in a Panel of Receptor Tyrosine Kinases[1]

	T315I	M244V	A337T	E355G	F359C	F359V	P465S
Asciminib	96	611	173	>2380	>2380	>2380	>2380
ELVN-001	4	2	1	4	3	2	2
Dasatinib	2935	2	1	3	4	2	2
Bosutinib	113	3	1	4	5	5	4
Ponatinib	3	2	1	3	5	5	2
Imatinib	>20	3	1	8	18	10	4
Nilotinib	>341	2	1	5	33	21	3

Fold-Shift Inhibitory Activity vs. Unmutated BCR::ABL1 in a Panel of BCR::ABL1 Resistance Mutants *In Vitro* (BA/F3 Cells)[1]

Hochhaus A et al., EHA 2025

ENABLE: A Phase 1a/1b Study of ELVN-001, a selective active site inhibitor of BCR::ABL1, in patients with previously treated CML

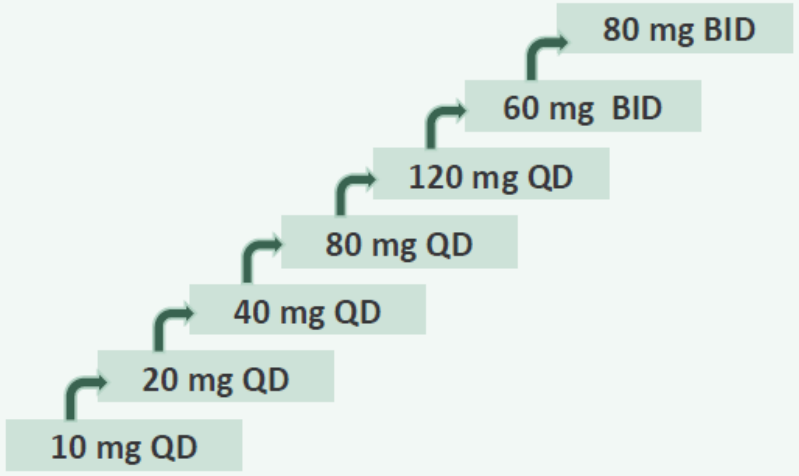
Enliven THERAPEUTICS

Key eligibility criteria:

- Chronic phase CML
- Failed, intolerant to, or not a candidate for available therapies known to be active for treatment of their CML
- Typical or atypical transcripts

Phase 1a Dose Escalation[a]: 3+3

Total N ≈ 80



Up to 10 additional patients per dose level (max n = 50)

Phase 1b Dose Expansion n = 20 each

Phase 1b doses selected based on safety, tolerability, anti-CML activity, and PK/PD

80 mg QD Non-T315I	Completed Enrollment
60 mg QD Non-T315I	Randomized (Enrolling)
120 mg QD Non-T315I	Randomized (Enrolling)
Dose TBD CP-CML with T315I mutations	

Primary Endpoints

- Incidence of DLTs, AEs, clinically significant laboratory and ECG abnormalities

Key Secondary Endpoints

- Molecular response by central qPCR
- PK parameters

Hochhaus A et al., EHA 2025

ENABLE: A Phase 1a/1b Study of ELVN-001, a selective active site inhibitor of BCR::ABL1, in patients with previously treated CML

Parameter	All Patients[a] (N = 90)
Age, years, median (range)	58 (19–79)
Male / female	58%/42%
ECOG PS 0 / 1	74%/26%
Median time since diagnosis, months (range)	58.1 (2.6–281.9)
Typical *BCR::ABL1* transcript (e13a2/e14a2)	93%
Baseline *BCR::ABL1* transcript level[b]	
≤ 0.1%	18%
> 0.1%– ≤1.0%	23%
> 1.0%	52%
Baseline *BCR::ABL1* mutation (central)[c]	
No mutation	54%
T315I mutation	9%[d]
Other mutations	7%
Not available	30%

[a]Includes 3 re-enrolled patients (87 individual patients).
[b]Percentages based on 84 patients with typical transcript.
[c]Only available for patients with typical transcripts.
[d]Includes 2 re-enrolled patients (6 individual patients with T315I).

Parameter	All Patients[a] (N = 90)
Median number of prior unique TKIs, n (range)[e]	3 (1–7)
1–2 prior	32%
3–4 prior	41%
≥ 5 prior	26%
Prior TKI	
Dasatinib	73%
Imatinib	67%
Asciminib	58%
Nilotinib	54%
Ponatinib	43%
Bosutinib	38%
Reason for discontinuation of last TKI	
Lack of efficacy	72%
Lack of tolerability	23%
Other	3%

[e]Median lines of prior TKIs is 4 (range 1-9).

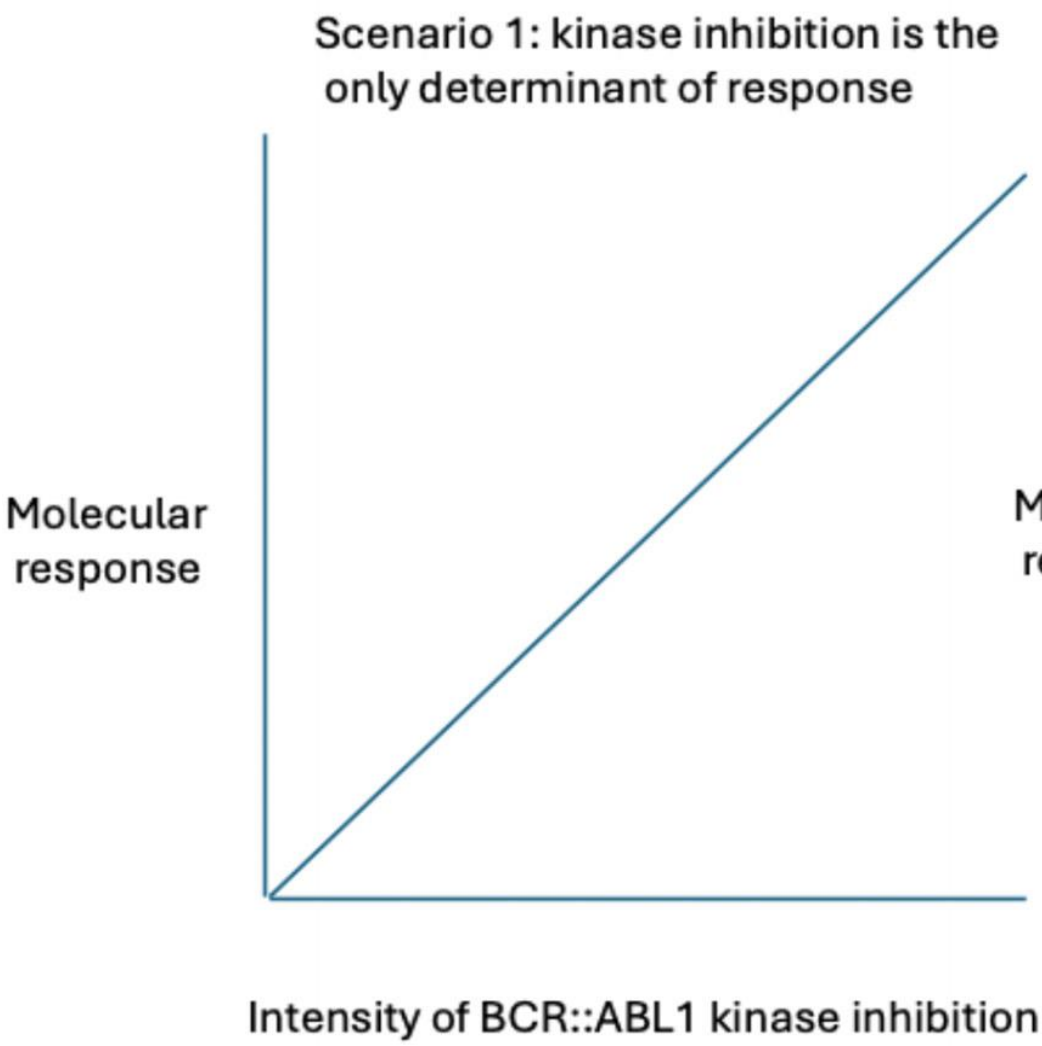
BCR::ABL1 ≤ 0.1% (MMR) by 24 weeks	
Overall MMR by 24 weeks	25/53 (47%)
Achieved (not in MMR at baseline)	13/41 (32%)
Maintained (in MMR at baseline)	12/12 (100%)
Key subgroups	
Post asciminib	9/28 (32%)
Post ponatinib	7/20 (35%)
Lack of efficacy to last TKI	14/34 (41%)
Intolerant to last TKI	9/17 (53%)

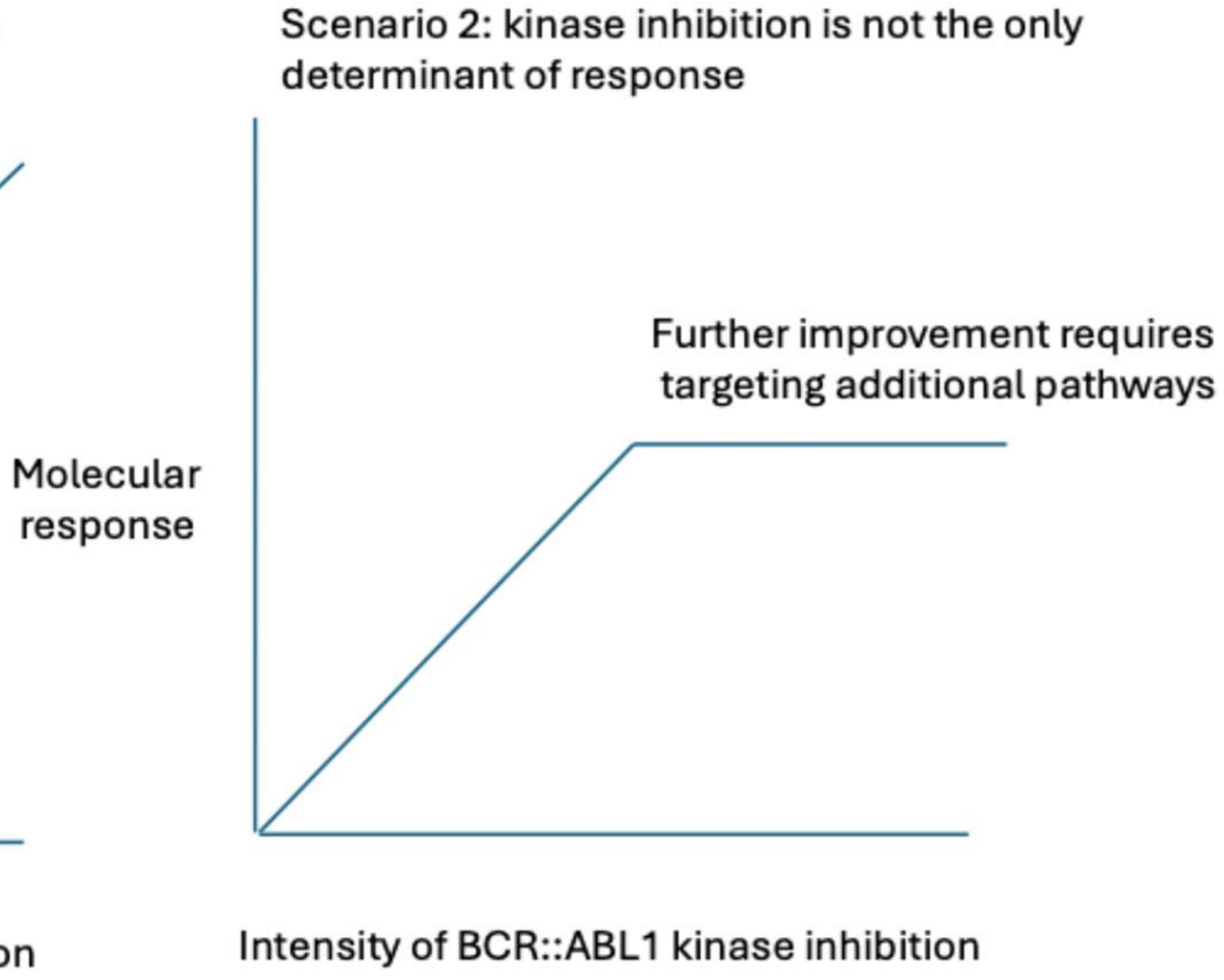
- 80% of patients remain on study with a median duration of exposure of 29 weeks
- 4 patients discontinued due to AEs:
  - Alcoholic pancreatitis (10 mg QD)
  - Thrombocytopenia (20 mg QD and 80 mg QD)
  - Dyspnea (80 mg QD; confounded by pulmonary comorbidities)

Hochhaus A et al., EHA 2025

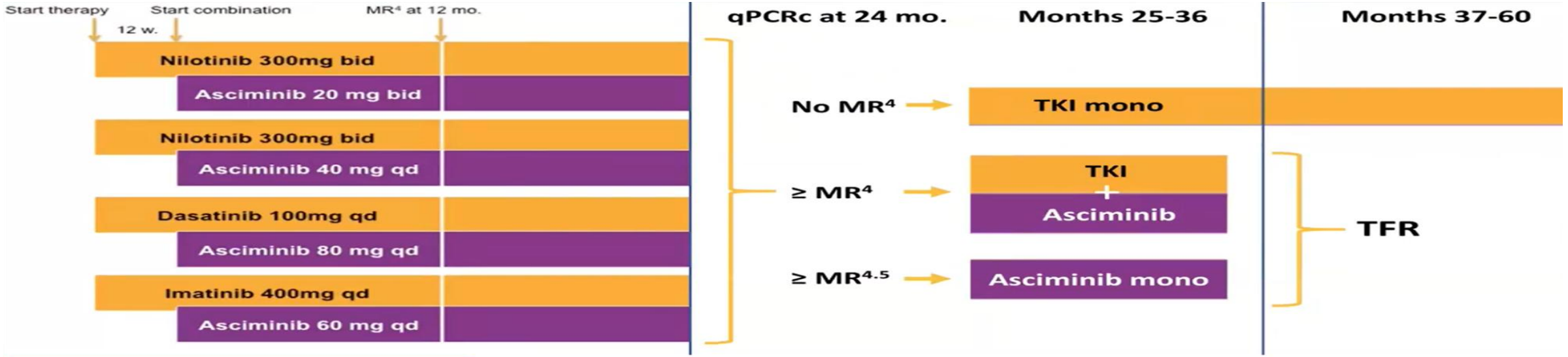
Agenda

- Do we really need novel drugs in CML?
- Novel agents
- **Combination therapies**
- Old drugs, new doses
- Something even older…


Scenario 1: kinase inhibition is the only determinant of response
Molecular response
Intensity of BCR::ABL1 kinase inhibition


Scenario 2: kinase inhibition is not the only determinant of response
Further improvement requires targeting additional pathways
Molecular response
Intensity of BCR::ABL1 kinase inhibition

Asciminib + TKIs: FASCINATION Study

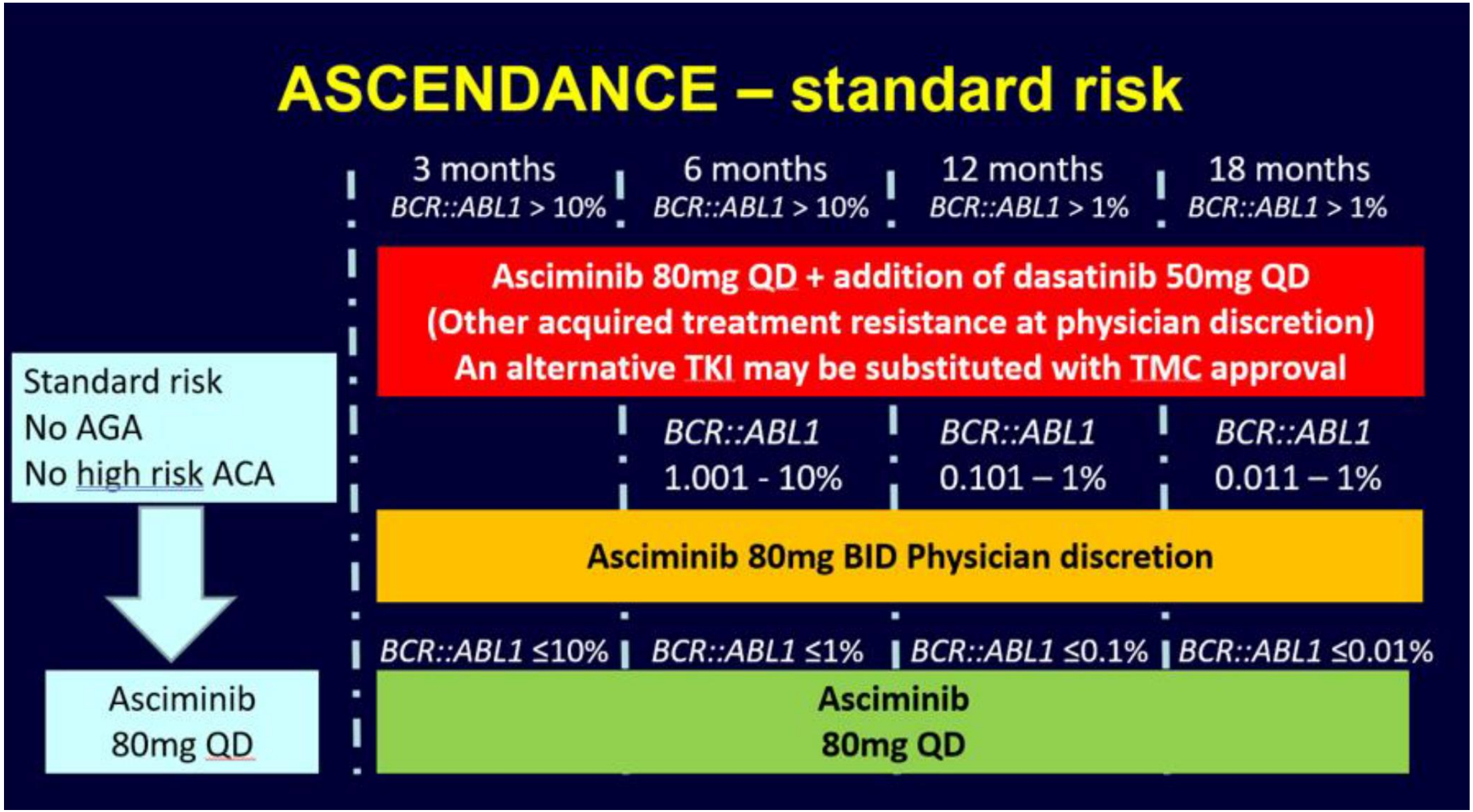


Primary endpoint: MR4 at month 12

Cohort	Patients recruited, n (%)	Patients eligible for MR at 12 mo, n (%)	Patients with MR4 at 12 mo, n (%)
NIL 300 mg BID + ASC 20 mg BID	30 (24)	28 (22)	9 (32)
NIL 300 mg BID + ASC mg 40 QD	32 (26)	31 (25)	13 (42)
DAS 100 mg QD + ASC 80 mg QD	32 (26)	27 (22)	9 (33)
IMA 400 mg QD + ASC 60 mg QD	31 (24)	28 (22)	12 (43)
Total	125 (100)	114 (91)	43 (38)

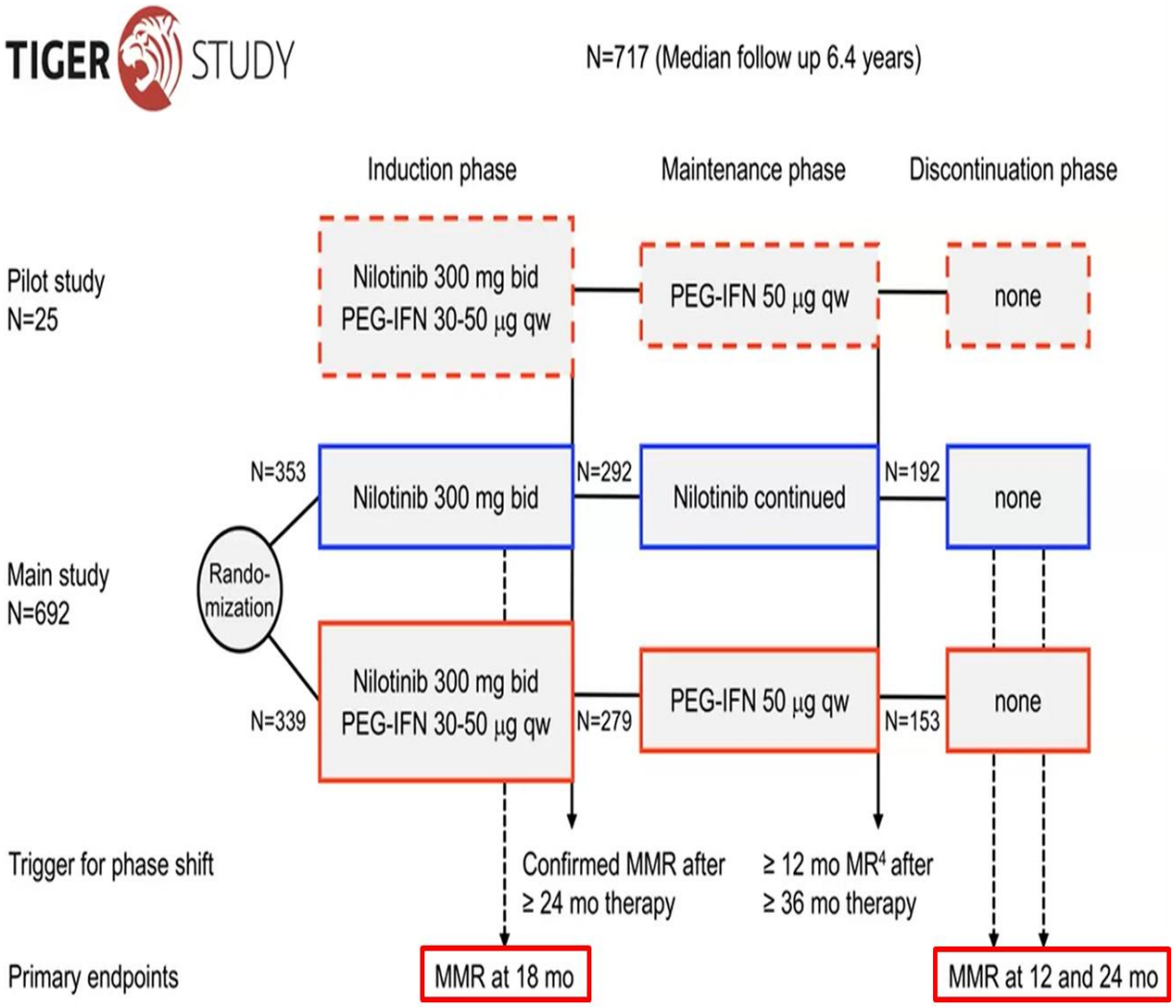
21 patients (17%) discontinued tx within 12 months due to AEs (n=18) or failure/progression (n=3)

Ernst T et al., EHA 2023



Courtesy of N. Shanmuganathan

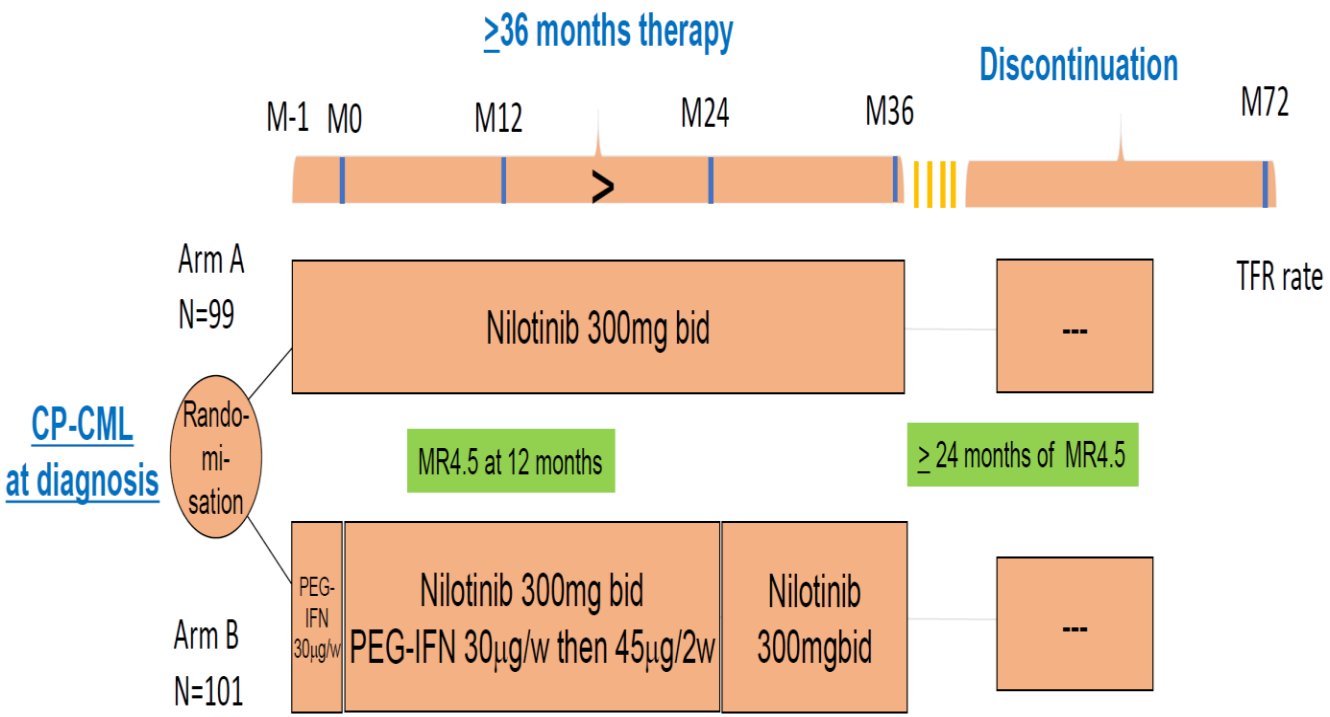
Nilotinib + Peginterferon: TIGER Study

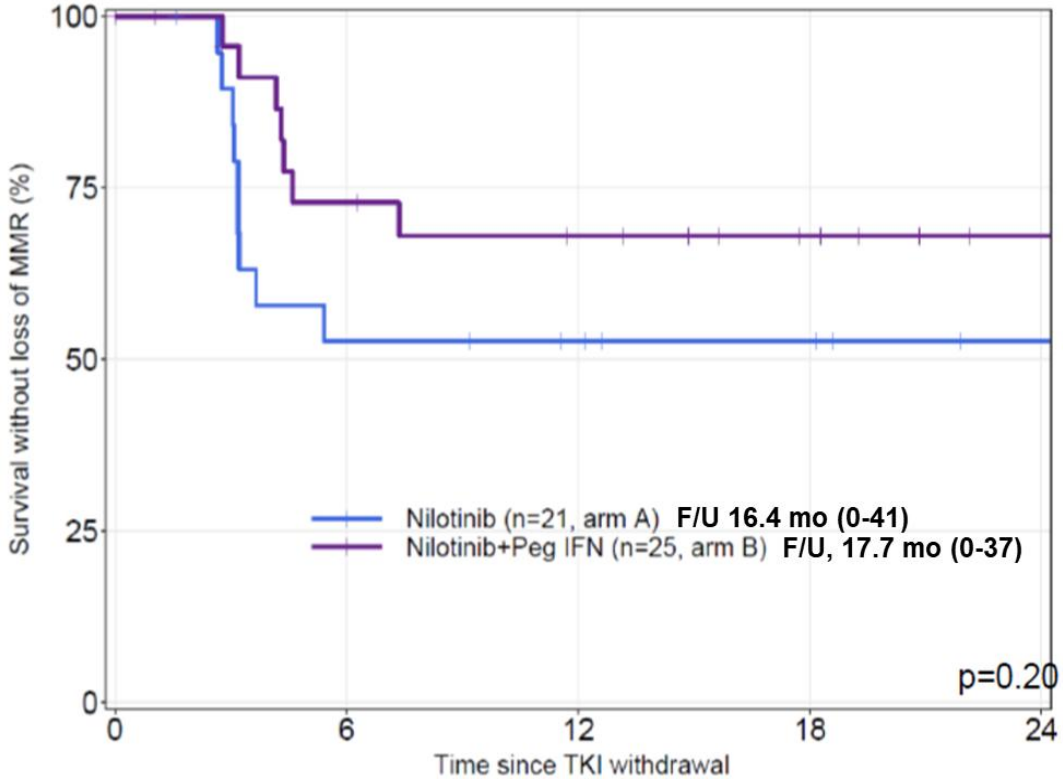


Responses % (95% CI)	Nilotinib	Nilotinib + Peg-IFN	*P*
At 12 mo of therapy			
MMR	76 (72-81)	83 (79-87)	0.035
At 18 mo of therapy			
MMR	81 (76-85)	88 (83-91)	0.021
MR4	51 (46-57)	64 (58-69)	0.0018
MMR at 12 mo of discontinuation	60 (53-67)	69 (60-76)	0.12
MMR at 24 mo of discontinuation	48 (40-56)	57 (48-65)	0.13
8-year PFS	94 (90-96)	92 (88-95)	n.s.
8-year OS	95 (92-97)	94 (91-97)	n.s.

Hochhaus A et al., EHA 2023

Nilotinib + Peginterferon: PETALS Study

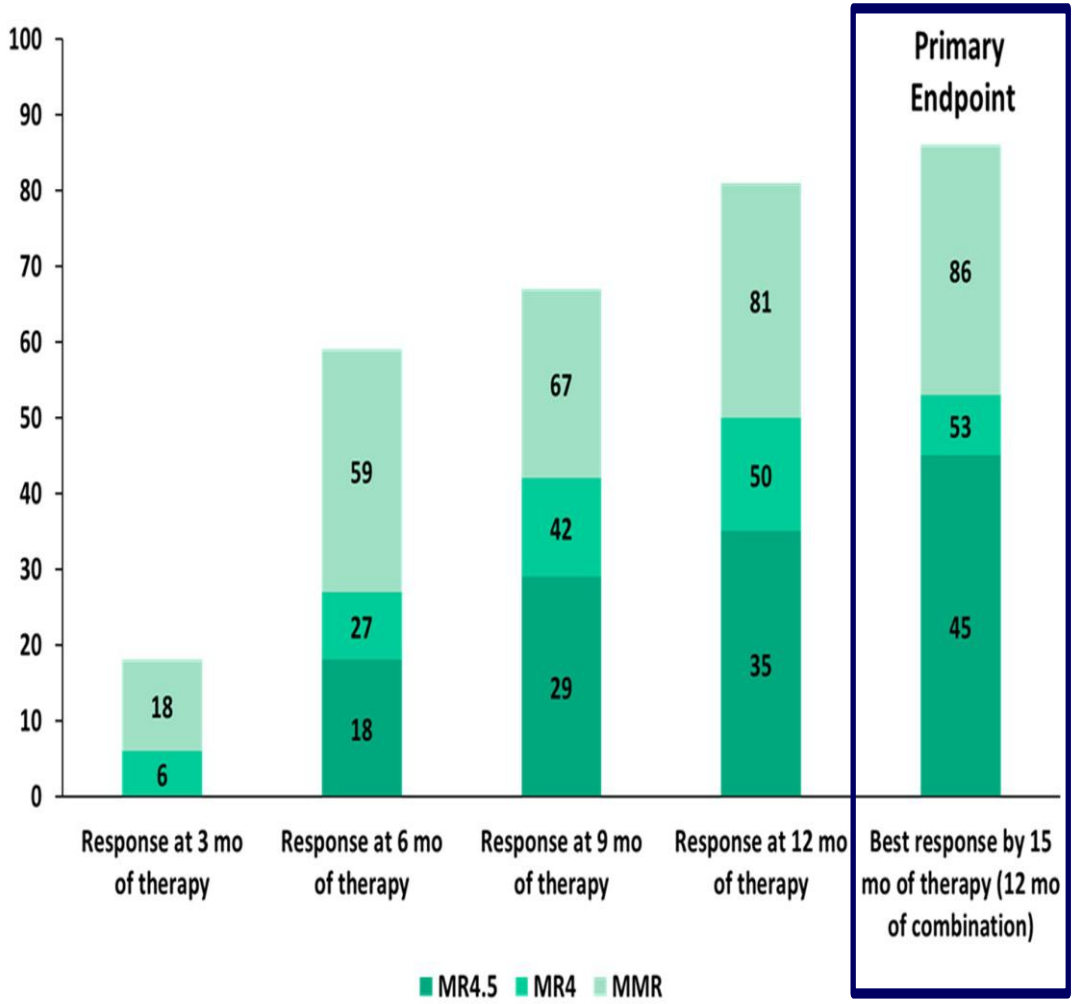


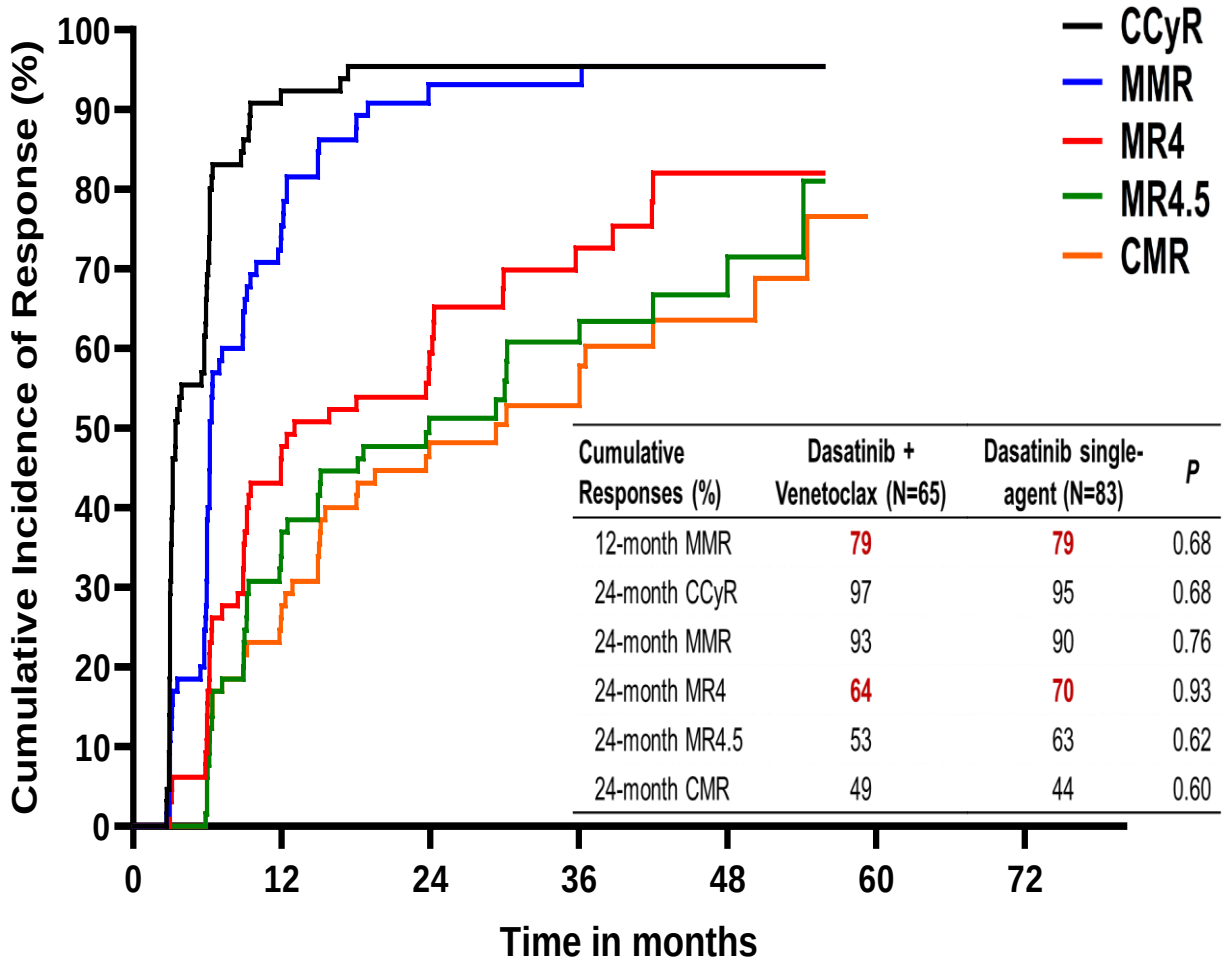


Endpoints, %	Nilotinib	Nilotinib + Peg-IFN	*P*
MR4.5 by 12 mo	16	22	0.049
Overall cumulative incidence of MR4.5	44	55	0.05

Nicolini FE et al., ASH 2021

Dasatinib + Venetoclax





Cumulative Responses (%)	Dasatinib + Venetoclax (N=65)	Dasatinib single-agent (N=83)	*P*
12-month MMR	79	79	0.68
24-month CCyR	97	95	0.68
24-month MMR	93	90	0.76
24-month MR4	64	70	0.93
24-month MR4.5	53	63	0.62
24-month CMR	49	44	0.60

Jabbour E et al. *Cancer* 2024

TKIs + Ruxolitinib

- 75 patients with CML-CP; median time on prior TKI = 3.2 years
- Detectable *BCR::ABL1* transcripts [0.0032-1%]
- At least 6 months on last TKI (DAS 61%; NIL 19%; BOS 10%; IMA 9%); >2 TKIs allowed
- Randomized to continue TKI (N=38) or add ruxolitinib 15 mg BID for 12 months (N=37)

Treatment Arm	TKI only (N=38)	Ruxolitinib + TKI (N=37)	*P*
12-month MR4.5	3%	14%	0.09
12-month cumulative MR4.0	37%	63%	0.048
NCCN criteria for TKI discontinuation met	11%	29%	0.08
Grade 3-4 related AEs	5% (2/38)	11% (4/37)	NA

Sweet K et al. EHA 2024

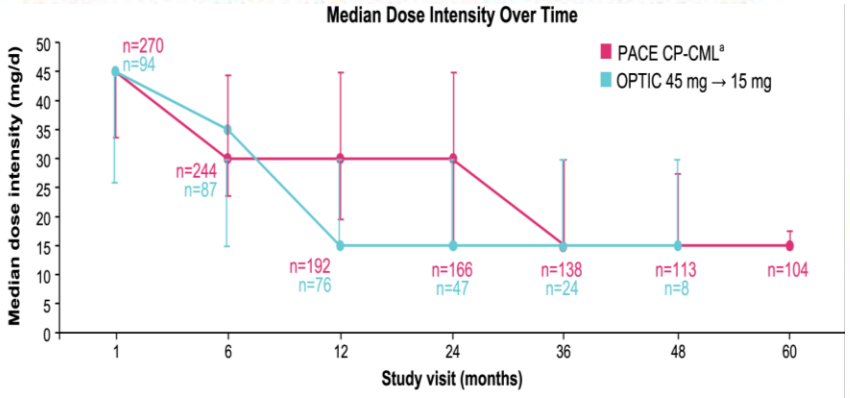
Agenda

- Do we really need novel drugs in CML?
- Novel agents
- Combination therapies
- **Old drugs, new doses**
- Something even older…

Dose modification dynamics of ponatinib in patients with chronic-phase chronic myeloid leukemia (CP-CML) from the PACE and OPTIC trials

Trial Design

- Outcomes for patients with CP-CML who received ponatinib 45 mg/day in the PACE (n=270) and OPTIC (n=94) trials were assessed to evaluate the dose-response relationship and effect on ponatinib safety using 2-year data cutoffs



- A propensity score analysis was used to control for potential bias from differences in baseline demographics and characteristics, disease parameters, and drug exposure comparing AOE rates across both trials

Conclusion

- The response-based dose-reduction strategy in OPTIC provided comparable or higher efficacy than a fixed-dose approach while mitigating AE and AOE risk in patients receiving ponatinib

Results

- A greater proportion of patients had dose reductions due to AEs in PACE (65%) vs OPTIC (45%), with median time to dose reduction 2.9 vs 3.6 months
- Median dose intensity at 24 months: PACE: 30 mg/day; OPTIC, 15 mg/day

Efficacy

- Median time to ≤1% *BCR::ABL1*[15]: 5.6 vs 6.0 months in PACE vs OPTIC, with median duration of response not reached in either trial
- 2-year PFS was 80% in OPTIC and 67% in PACE; 2-year OS was 88% in PACE and 91% in OPTIC
  - Rates were similar regardless of T315I mutation status

Safety

- Rate of grade 3/4 treatment-emergent AEs was higher in PACE (84%) than in OPTIC (68%)
- Grade 3-4 treatment-emergent AOEs occurred in 12% of patients in PACE and 5% in OPTIC
- The propensity score analysis showed an overall risk reduction of approximately 60% for AOEs in OPTIC compared with PACE

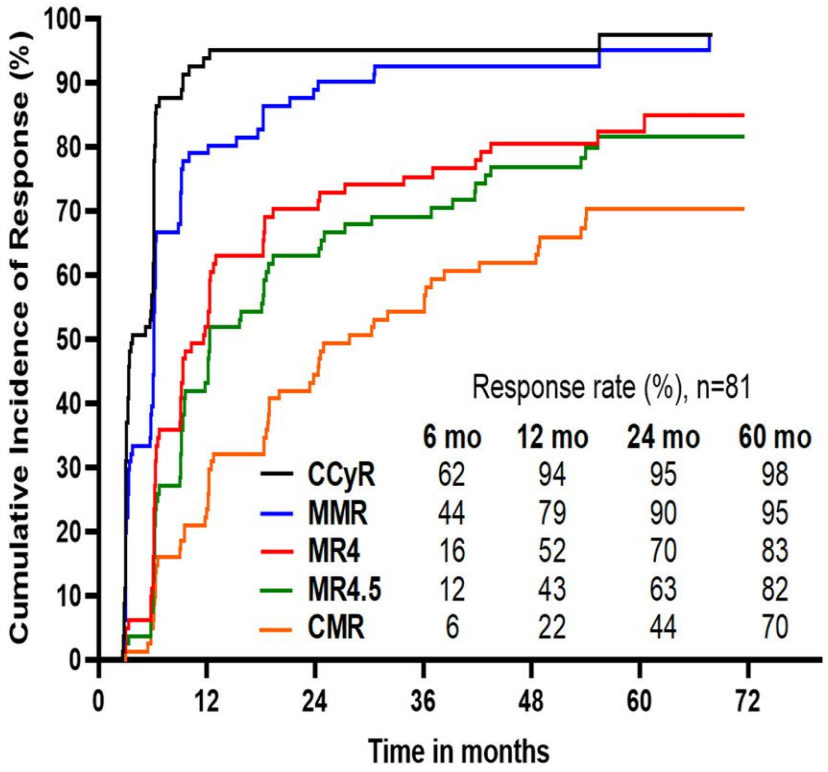
Jabbour E et al. *Leukemia* 2024

Low-Dose Dasatinib in Frontline CML

83 patients with newly diagnosed CML-CP received **dasatinib 50 mg daily**
Patients in suboptimal response increased dose of up to 100 mg daily

Response, %	12 Mo (n = 81)	24 Mo (n = 81)	60 Mo (n = 81)
CCyR	94	95	98
MMR	79	90	95
MR4	52	70	83
MR4.5	43	63	82
CMR	22	44	70

5-Yr Survival, % (95% CI)	Patients (n = 81)
OS	98 (94.6-100)
EFS	92 (85.6-98.4)
TFS	100
FFS	86.2 (78.4-94)



Naqvi K et al. *Cancer* 2020
Gener-Ricos G et al, ASH 2022

Low-Dose Dasatinib in Frontline CML

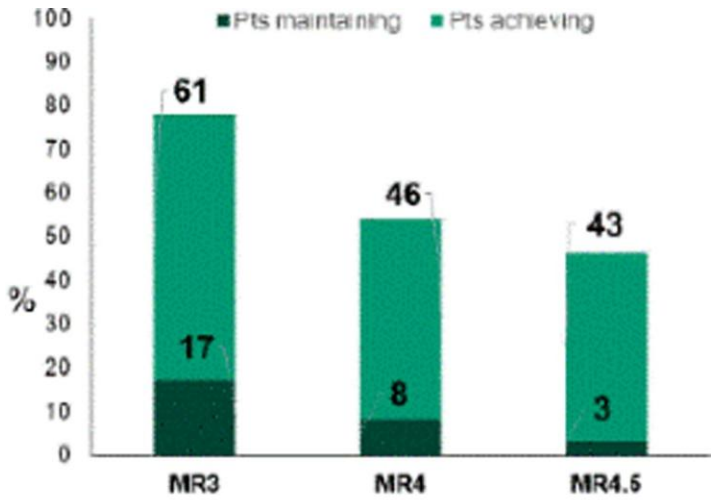
AEs, n (%)	Patients (n = 81)	
	Any Grade	Grade 3/4
Hematologic		
▪ Leukopenia	31 (38)	1 (1)
▪ Neutropenia	23 (28)	6 (7)
▪ Anemia	54 (67)	4 (5)
▪ Thrombocytopenia	27 (33)	5 (6)
Hyperbilirubinemia	5 (6)	0
Increased ALT	53 (65)	2 (2)
Increased ALP	11 (13)	0
Increased creatinine	15 (18)	0

AEs, n (%)	Patients (n = 81)	
	Any Grade	Grade 3/4
Fatigue	11 (13)	0
Musculoskeletal	6 (7)	0
Gastrointestinal	2 (2)	0
Skin	2 (2)	0
CV/pulmonary	0	1 (1)
Neurologic	3 (2)	1 (1)
Edema	3 (2)	1 (1)
Pleural effusion	10 (12)	2 (2)

Naqvi K et al. *Cancer* 2020
Gener-Ricos G et al, ASH 2022

Low-Dose Bosutinib strategies in CML

2L



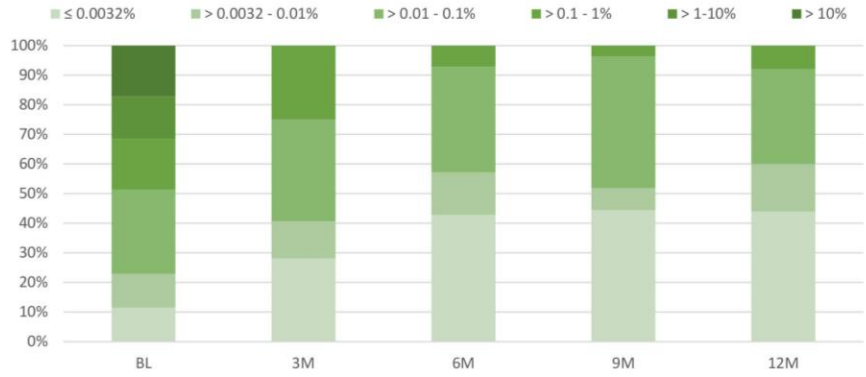
Castagnetti F et al., EHA 2022

2-3L

Table 1. Treatment status and reasons for discontinuation in study patients

	n (%)	
Received treatment	35	(100)
Continued treatment	26	(74.3)
Discontinued treatment	9	(25.7)
Drug-related adverse event	4	(11.4)
Treatment failure or Disease progressed	2	(5.7)
Withdrew consent	2	(5.7)
Other	1	(2.9)

Figure 1. Efficacy of bosutinib treatment

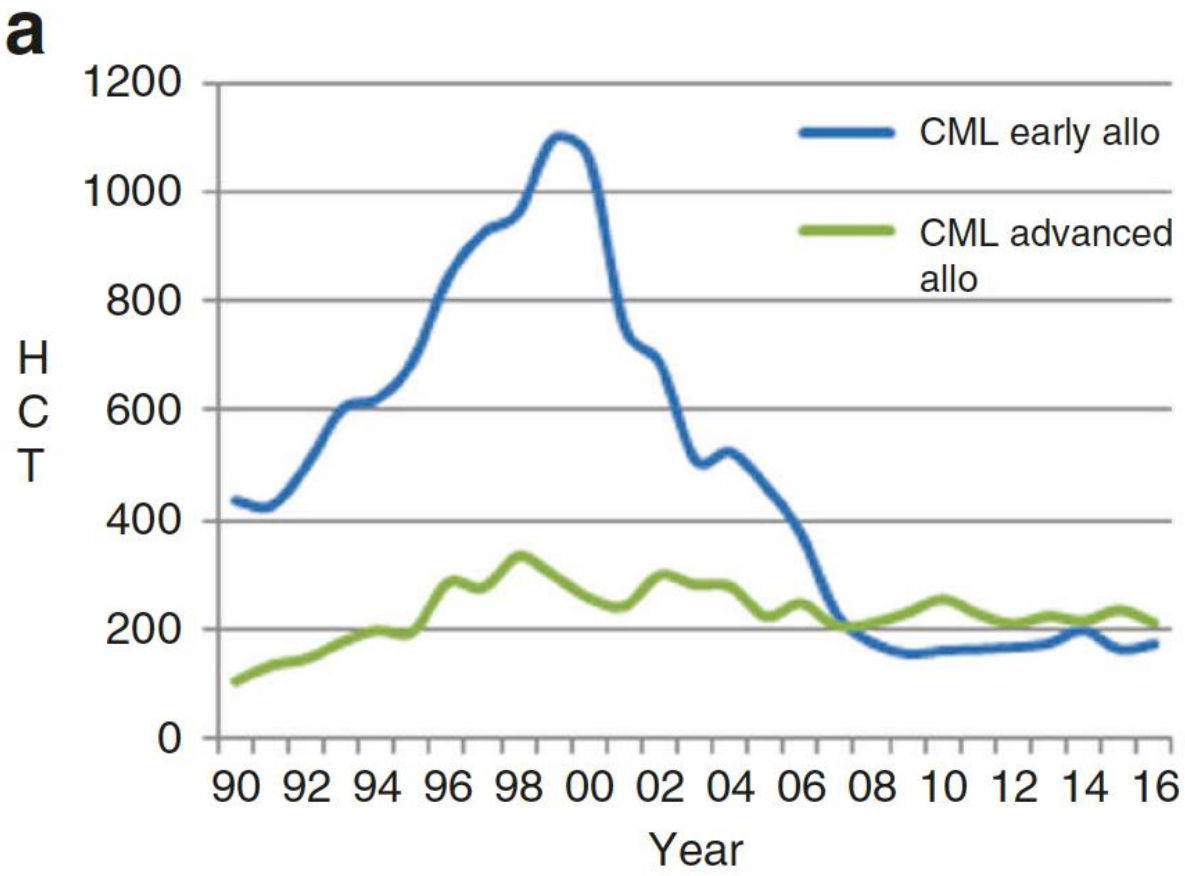


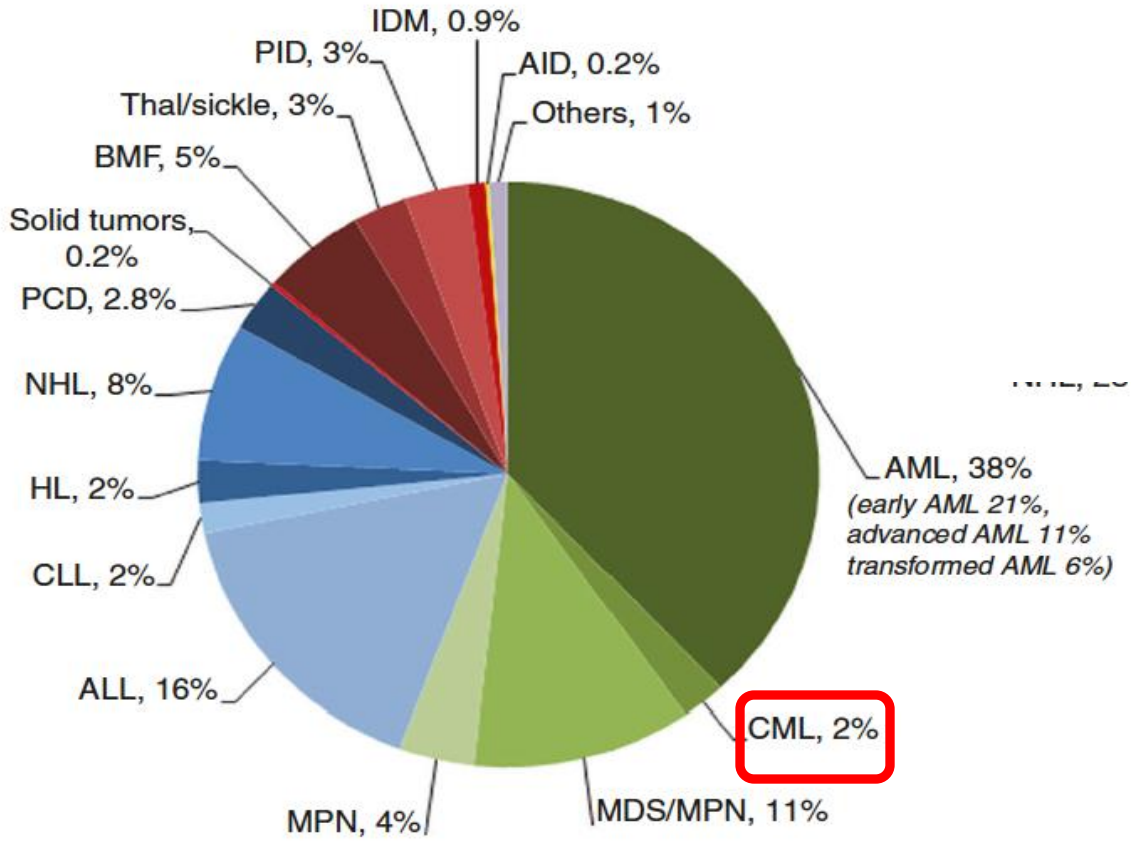
Ureshino H et al., ASH 2023

Agenda

- Do we really need novel drugs in CML?
- Novel agents
- Combination therapies
- Old drugs, new doses
- **Something even older…**

Allo-HCT for CML in Europe (EBMT)





Passweg et al. BMT 2018

Actual “indications” for allo-HCT

- CML in advanced phases: BC «always», AP «often»
- Failure to multiple lines of TKI therapy (≥2? ≥3?)
- «unacceptable» TKI toxicity, mainly hematologic (cytopenias)
- Extremely young patients (?)

…

Conclusions

- Patients in A/BP have poor prognosis
- Failure to 2G-TKI or multiple TKIs may be challenging, with reduced OS
- Novel TKIs are entering the clinical arena
- Results of combos (TKI + TKI or TKI + «other») are preliminar
- TKIs at reduced dose could be equally effective but safer: however, no large trials have been performed yet
- Do not forget the transplant option in selected cases!

mario.tiribelli@uniud.it