Update on
Chronic Myeloid Leukemia

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What is new in CML

- Bosutinib indicated as new front line TKI: 2y follow up.
- Ponatinib, long term follow up: PACE 5 years.
- Treatment free remission get on a TKI label: ENEStop, ENESTfreedom.

CML. The Past and Today

Parameter	Before 2000	Today
• Course	Fatal	Indolent
• Prognosis	Poor	Excellent
• 10-yr survival	10%	84 - 90%
• Frontline Rx	Allo SCT; IFN-α	Imatinib; dasatinib; nilotinib; bosutinib
• Second line Rx	?	Bosutinib, ponatinib ; allo SCT

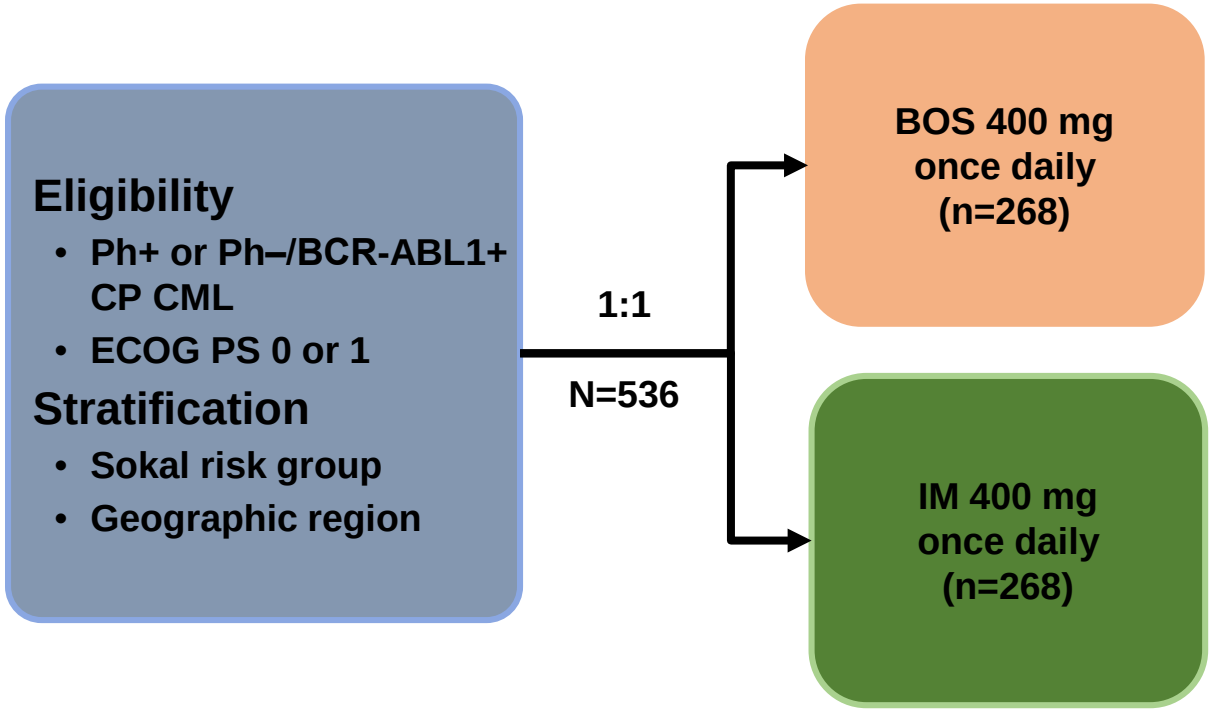
Looking for the perfect TKI for CML

- Very efficacious/ early molecular milestones .
- Low rate of transformation to AP/BC.
- Safety profile/Lack of long term side effects.
- Well tolerated: low rate of discontinuation. 30% on current TKIs at 5y
- Lower dose/optimal effects ratio

Factors Influencing Choice of First-Line Treatment

- Patient dependent.
  - Comorbid conditions
  - Risk stratification
  - Personal expectations
  - Education and compliance.
- TKI dependent
  - Efficacy and time to EMR
  - Side effects
  - Long term safety
  - Cost
- Phsysician dependent
  - Personal experience with the use of a certain TKI

BFORE: BOS vs IM in Frontline CML: Study Design



Primary Endpoint

- MMR rate at 12 mo

Secondary/Other Endpoints

- CCyR by 12 mo
- MMR by 18 mo
- Response duration
- EFS and OS
- MMR at 3, 6, 9 mo
- MR^4, $MR^{4.5}$ at 3, 6, 9, 12 mo
- Time to response
- Time to transformation

- Ongoing, open-label, phase 3 study
- Expected study duration of 5 years

Cortes, J. ASCO Annual Meeting. 2017. Abstract 7002.

Phase 3 Frontline clinical trials outcomes

Phase 3 Trial (Prim. Endpoint)	ENESTND (MMR at 1 yr)		DASISION (CCyR by 1 yr)		BFORE (MMR at 1 yr)	
	Nilotinib	Imatinib	Dasatinib	Imatinib	Bosutinib	Imatinib
CCyR, by 1yr	80%	65%	77%	66%	77%	66%
EMR (3 mo)	91%	67%	84%	64%	75%	57%
MMR at 1 yr by 5 yr	44% 77%	22% 60%	46% 76%	28% 64%	47% **2y 62%**	37% **2y 53%**
MR4.5 by 1 yr by 5 yr	11% 54%	1% 31%	5% 42%	3% 33%	8.1% ------	3.3% ------
Time to MMR (5 yr)	8.3 mo	14 mo	9.3 mo	15 mo	------	------
Progression, % (n) 1 yr 5 yr	<1% (2) <1% (2)	4% (11) 4% (12)	1.9% (5) 5% (12)	3.5% (9) 7% (19)	1.6% (4) ------	2.5% (6) ------
OS by 1 yr by 5 yr	99.3% 93.7%	99.3% 91.7%	97% 90.9%	99% 89.6%	99.6% ------	97.9% ------
OS-CML, 5 yr, % (n)a	97.7% (6)	93.8% (16)	------ (9)	----- (17)	------	------
Disc Due to AE: 1 yr 5 yr	5% 10%	7% 12%	5% 16%	4% 7%	13% **2yr 16%**	9% **2y 10%**

Know Your Tools: Comparing TKI Toxicity in CML

Issue	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Dosing	QD/BID, with food	BID, without food (2h)	QD, w/ or w/o food	QD, with food	QD, w/ or w/o food
Long term safety	Most extensive	Extensive; Emerging toxicity	Extensive; Emerging toxicity	Extensive, No emerging toxicity	More limited but increasing; Emerging toxicity
Heme toxicity	intermediate	least	Most severe; ASA-like effect; lymphocytosis	~dasatinb in 2nd, 3rd line; ~nilotinib in 1st line	↑thrombocytopenia ASA-like effect
Non-Heme toxicity	Edema, GI effects, ↓Phos	↑lipase, ↑bili, ↑chol, ↑glu Black box: QT prolongation; screening req'd	Pleural / pericardial effusions	Diarrhea; transaminitis	↑lipase, pancreatitis; rash; hypertension; Black box: vascular occlusion, heart failure, and hepatotoxicity
Emerging toxicities	early question re: CHF; ?late renal effects	Vascular events (ICVE, IHD, PAD)	PAH (pulmonary arterial hypertension)	? Mild renal effects	Vascular events (ICVE, IHD, PAD, VTE)

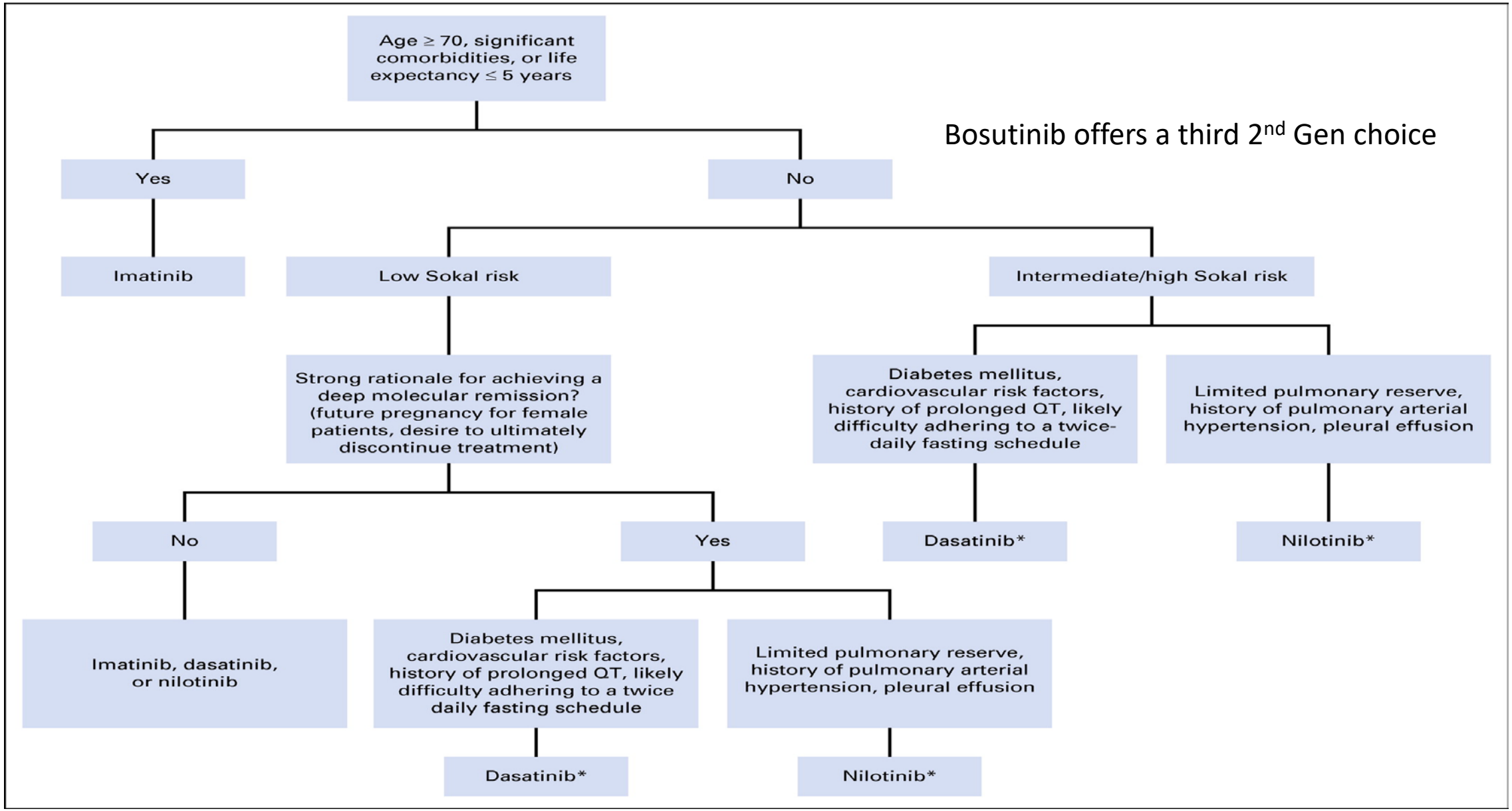
CML Molecular Response Milestones

BCR-ABL1 (IS)	3 months	6 months	12 months	> 12 months
> 10%	YELLOW	RED	RED	RED
1% - 10%	GREEN	GREEN	YELLOW	RED
0.1% - 1%	GREEN	GREEN	GREEN	YELLOW
≤ 0.1%	GREEN	GREEN	GREEN	GREEN

	Clinical Considerations	Treatment options
RED	Evaluate compliance and drug interactions Mutation testing	Switch to alternate TKI Consider screen for HSCT
YELLOW	Same as above	Consider switch to alternate TKI or continue (may increase dose of imatinib to 800 mg)
GREEN	Monitor response and toxicity	Continue same TKI

NCCN 2017 Guidelines

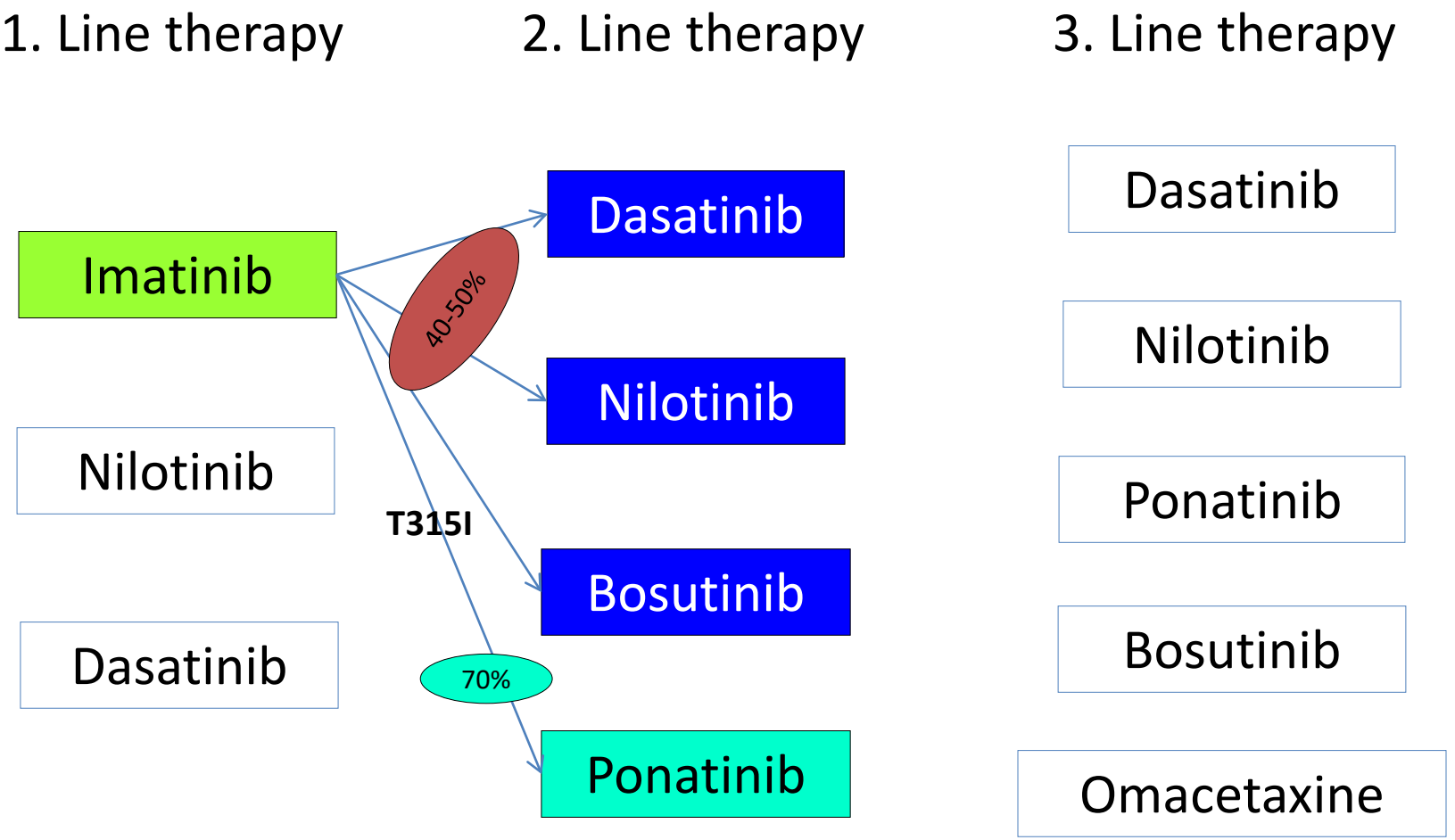
Algorithm for Frontline TKI Therapy in CML



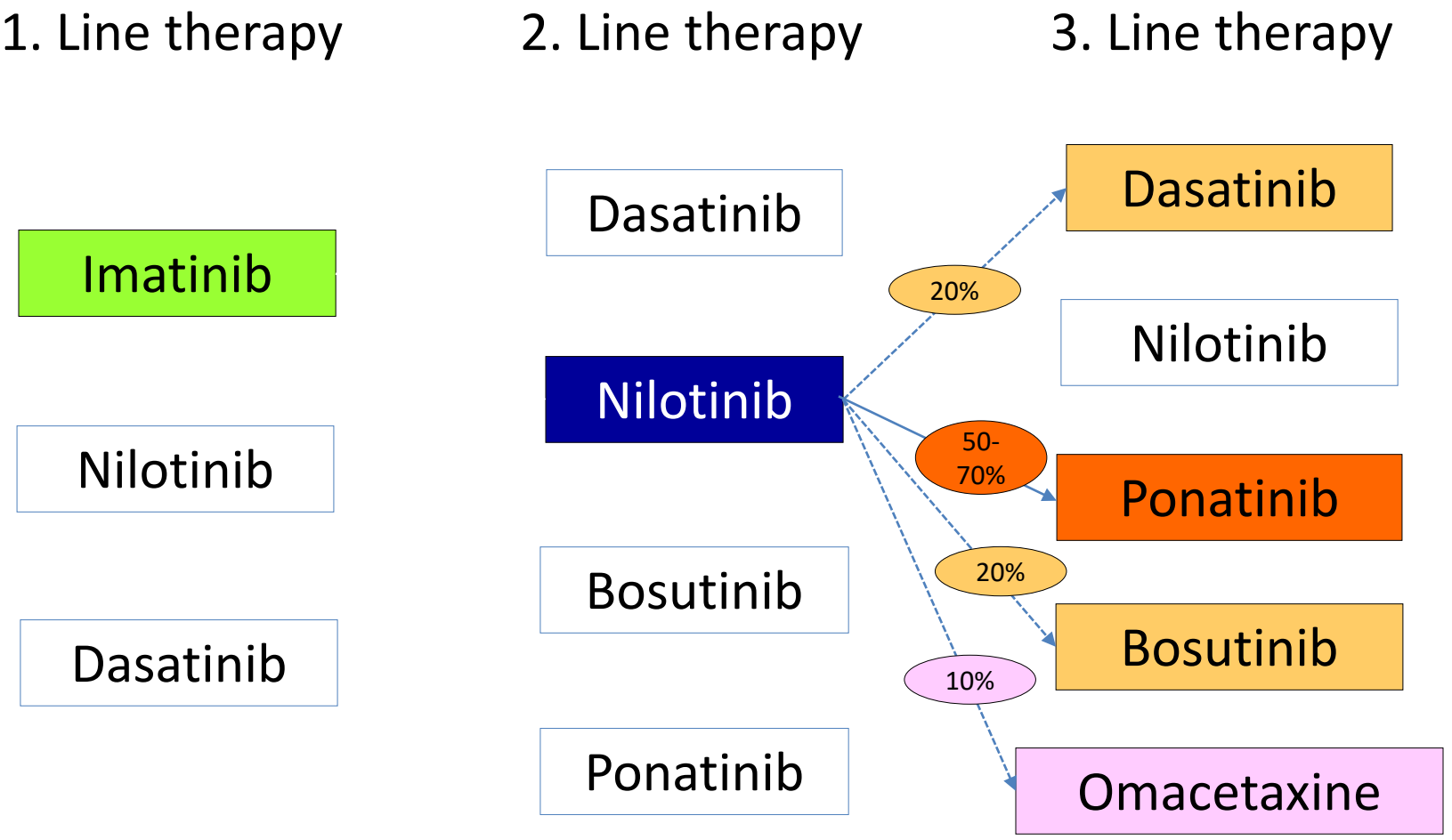
Bosutinib offers a third 2nd Gen choice

Neil P. Shah; *JCO* **2018,** 36, 220-224

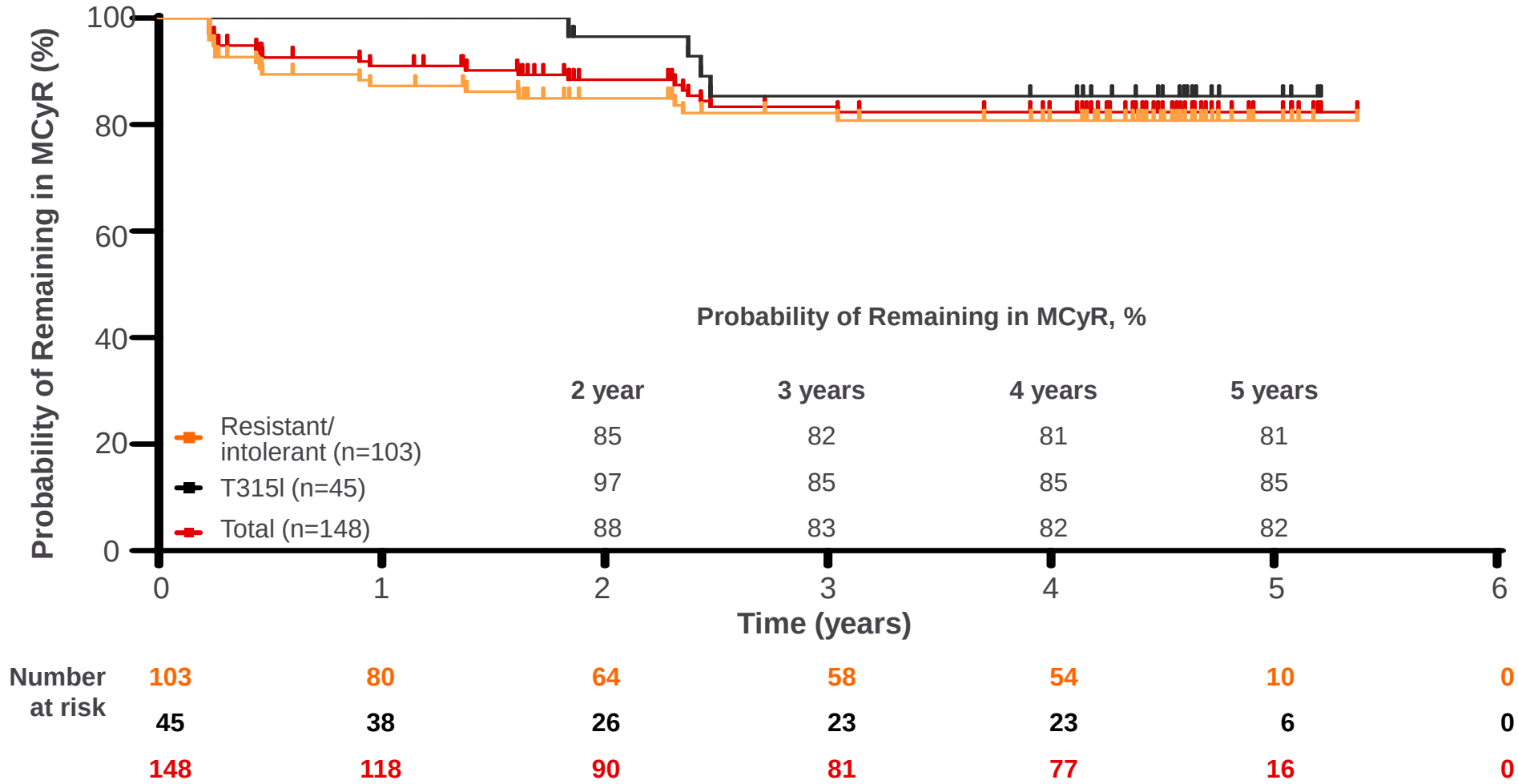
Treatment History and Salvage Therapy – Likelihood of CCyR



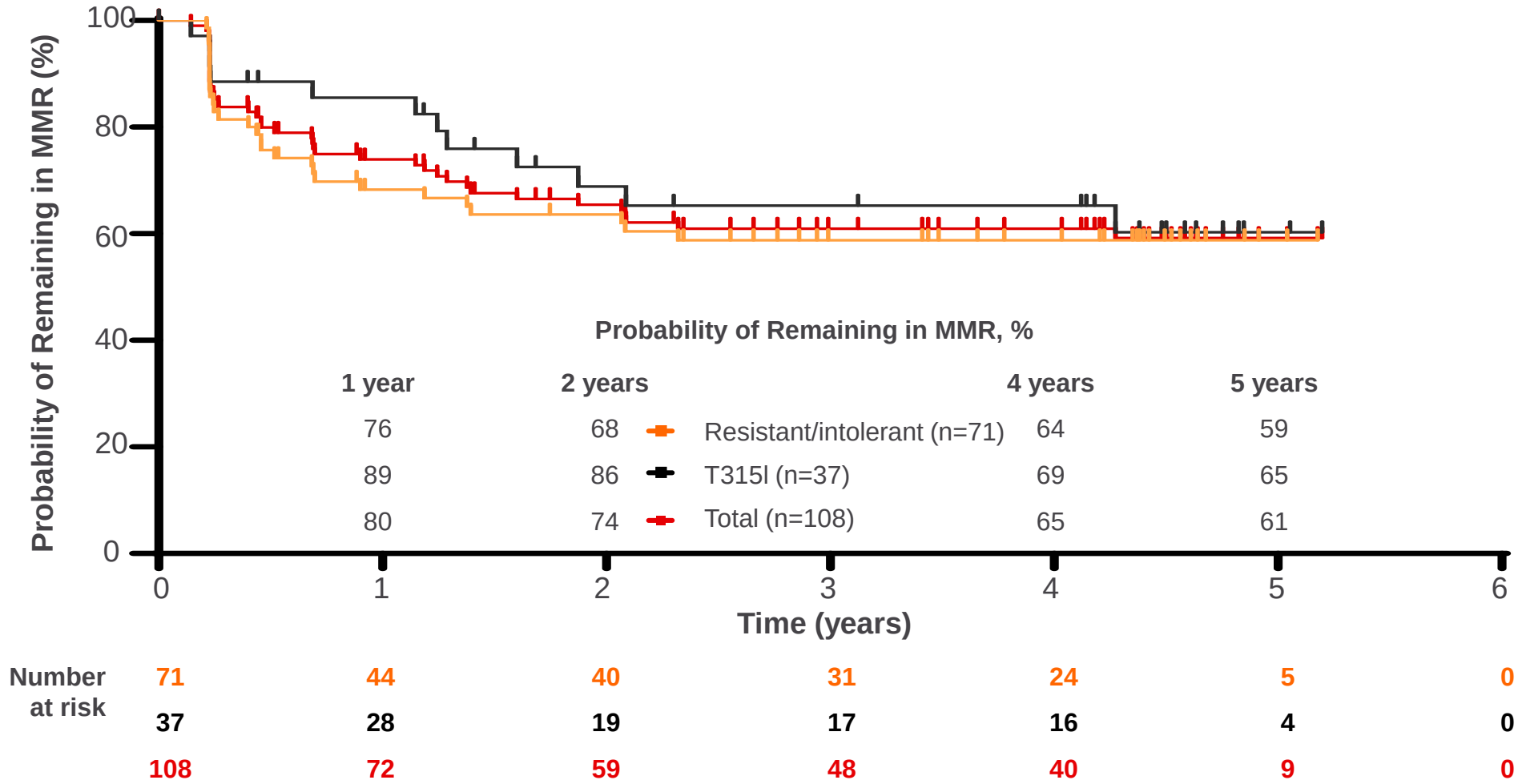
Treatment History and Salvage Therapy – Likelihood of CCyR



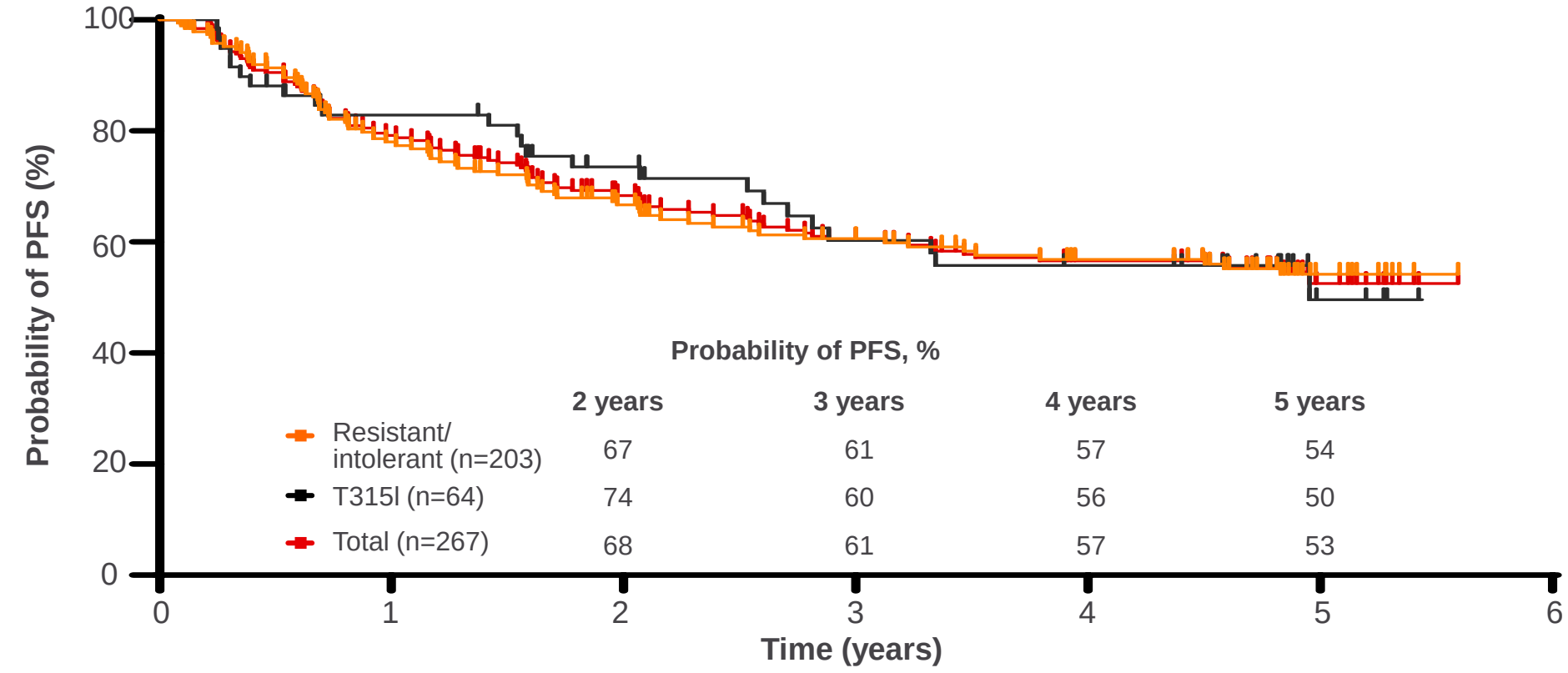
PACE 5y: Estimated Duration of MCyR (Achieved by 12 Months) for CP-CML Patients



PACE 5y: Estimated Duration of MMR (Response at any Time) for CP-CML Patients



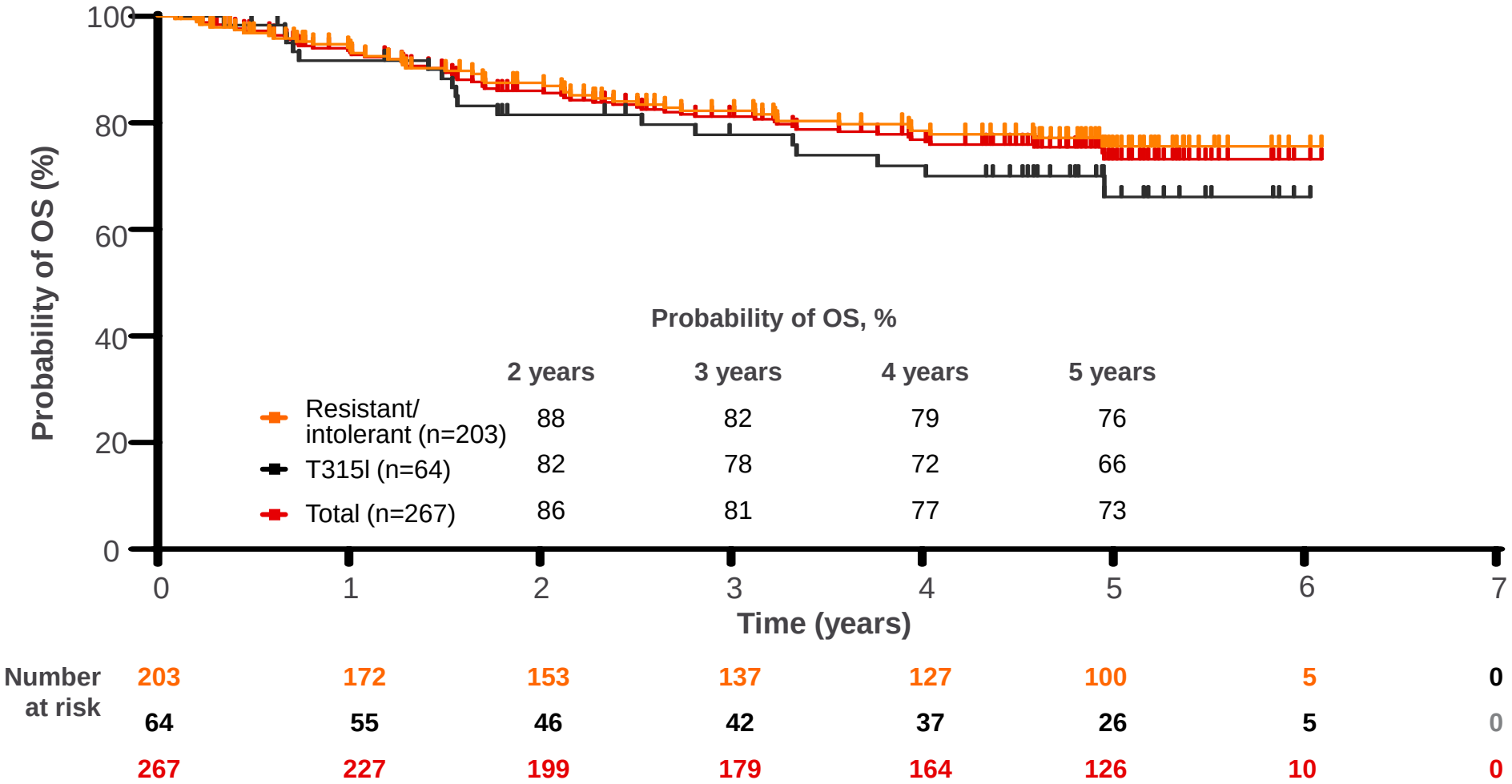
PACE 5y: Estimated PFS for CP-CML Patients



- In patients with advanced phase leukemia:
  - AP-CML (n=83): median PFS was 15.2 months (range, 1.4–69.0)
  - BP-CML/Ph+ ALL (n=94): median PFS was 3.0 months (range, 0.1–60.2)

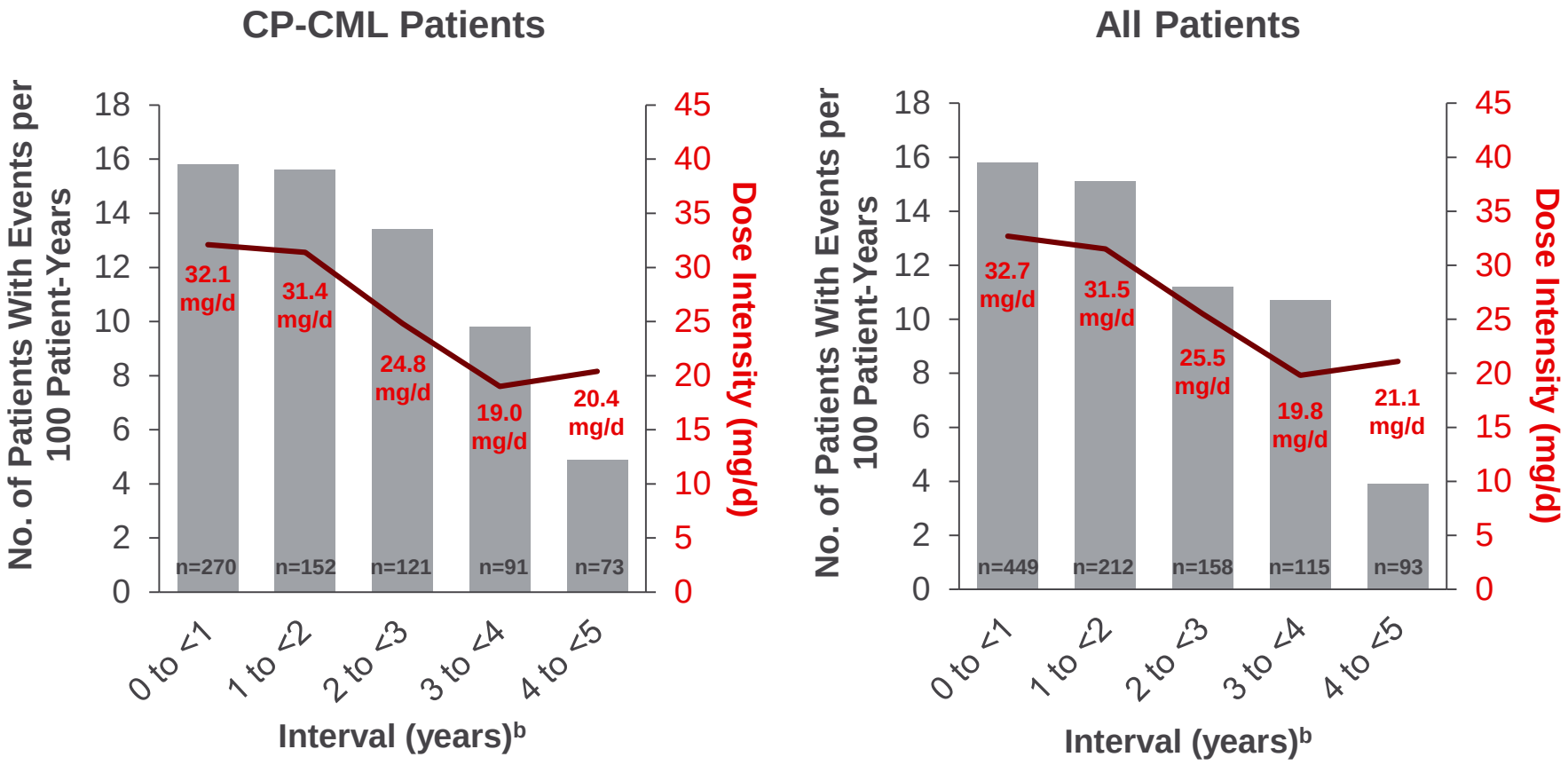
Progression was defined as death, development of accelerated/blast phase–CML, loss of CHR in the absence of CyR, loss of MCyR, or increasing WBC count without CHR. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date

PACE 5y: Estimated OS for CP-CML Patients



- In patients with advanced phase leukemia:
  - AP-CML (n=83): median OS was 55.5 months (range, 4.2–71.3)
  - BP-CML/Ph+ ALL (n=94): median OS was 6.9 months (range, 0.1–66.3)

PACE 5y: Summary of Exposure-Adjusted Incidence Rates for Newly Occurring AOEs[a]



- Exposure-adjusted incidence of new AOEs did not increase over time
- Of all patients who had an AOE (n=111), 40 (36%) were ongoing at initiation of study closure

[a] In the safety population; [b] Later intervals exclude patients with prior events; ongoing patients may have a different risk than those at study start

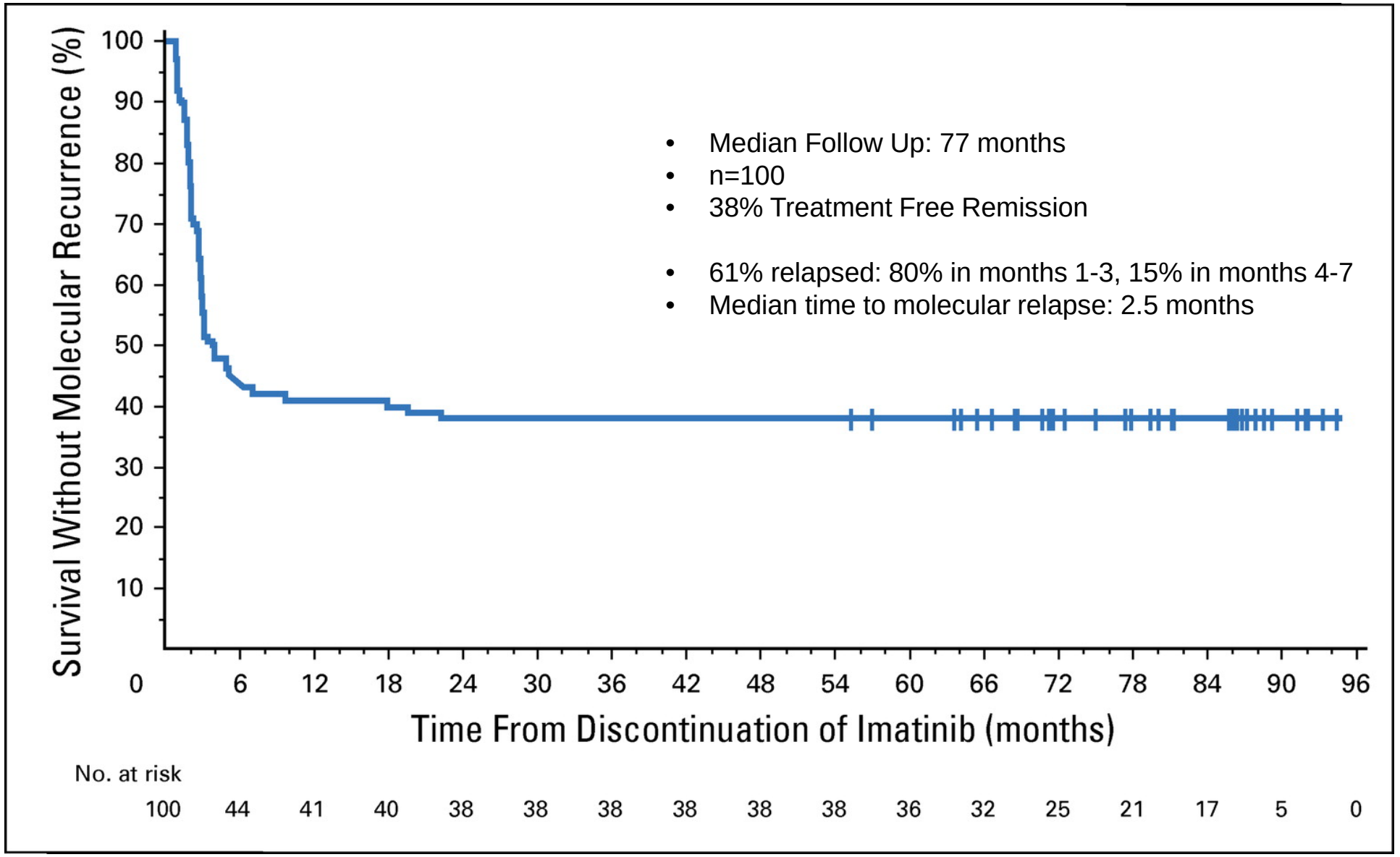
New TKIs Under Development

TKI	Features	Current status
ABL-001	Allosteric inhibitor	• Completed phase 1, single agent and combination • Pivotal phase 3 3rd line v bosutinib started
Radotinib	2nd generation	• Approved in South Korea 1st and 2nd line • Pending studies elsewhere
PF-114	Ponatinib analog, not binding VEGFR	• Nearing MTD Starting phase 2
K0706	3rd generation	• Phase 1 started

Why consider stopping a TKI in CML?

- TKI therapy is associated with reduced QOL
- High cost to patient and society
- Potential for long term toxicity
  - Cardiovascular
  - Pulmonary
  - Thyroid dysfunction
- Children and adolescents:
  - Substantial growth abnormalities
  - Effect on pregnancy/fertility

Long Term Follow Up From STIM

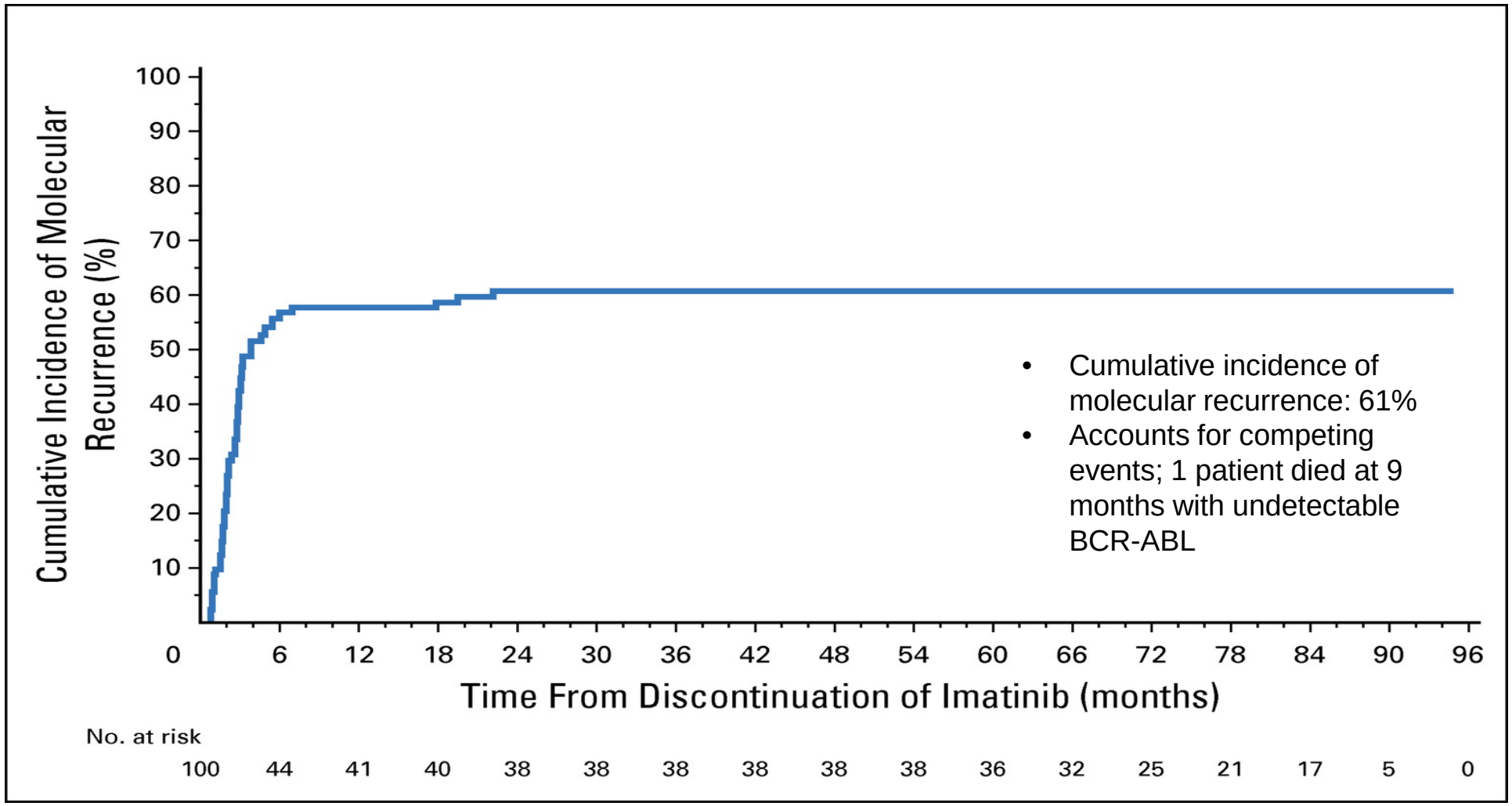


- Median Follow Up: 77 months
- n=100
- 38% Treatment Free Remission

- 61% relapsed: 80% in months 1-3, 15% in months 4-7
- Median time to molecular relapse: 2.5 months

Etienne G. Journal of Clinical Oncology 35, no. 3 (January 2017) 298-305

Cumulative Incidence of Molecular Recurrence on STIM



Etienne G. Journal of Clinical Oncology 35, no. 3 (January 2017) 298-305

Outcomes In Patients With Molecular Relapse

Table 2. MR Patient's Disposition, Treatment, and Molecular Status at the Last Date of Follow-Up

Patient Disposition and Treatment	Patients (n = 61)		No. of Molecular Responses at Last Available Evaluation		
	No.	%	≥ $MR^{4.5}$	≥ MMR to < $MR^{4.5}$	< MMR
Alive with TKI therapy	43	70.5	34	6	3
Imatinib	31	50.8	28	2	1
Dasatinib	7	11.4	3	3	1
Nilotinib	4	6.5	3	1	0
Bosutinib	1	1.6	0	1	0
Alive without TKI therapy	14	22.9	10	3	1
Second or third TKI discontinuation*	9	14.7	8	1	0
Discontinuation for TKI-related AE	2	3.2	0	1	1
Without any TKI resumption	3	4.9	2	1	0
Death	4†	6.5	2	2	0

Abbreviations: AE, adverse event; MMR, major molecular response; MR, molecular response; $MR^{4.5}$, molecular response 4.5-log; TKI, tyrosine kinase inhibitor.
*Twenty-one patients who had achieved a second sustained undetectable molecular residual disease (UMRD) of at least 1 year had a second treatment discontinuation as previously described.[21] Of those patients, 13 had MR leading to treatment resumption, and eight were free from MR with a median follow-up of 11.6 months (range, 0.9 to 21.4 months) after second imatinib discontinuation and without TKIs at last follow-up. Among the 13 MR patients, four achieved a third sustained UMRD and one experienced a third treatment discontinuation without molecular recurrence at the last date of follow-up.
†One patient died as a result of pleural mesothelioma while receiving imatinib. The remaining three patients discontinued TKI therapy because of worsening concomitant disease leading to death (one patient case each of cerebral hemorrhage, metastatic gastric adenocarcinoma, and acute renal failure).

- 57/61 relapsed pts restarted TKIs
- 55 achieved second undetectable status – median time 4.3 months
- No progression to AP/BP
- 14 now alive and off TKIs – 10 in MR4.5
- 4 deaths – none CML related

Etienne G. Journal of Clinical Oncology 35, no. 3 (January 2017) 298-305

Multivariate Analysis From STIM

- Two factors predictive of molecular relapse
  1. High-risk Sokal score at diagnosis
     - HR 2.22
     - 95% CI 1.11-4.42
     - P=0.024
  2. Imatinib duration ≥58.8 months prior to discontinuation
     - HR 0.54
     - 95% CI 0.32-0.92
     - P=0.024

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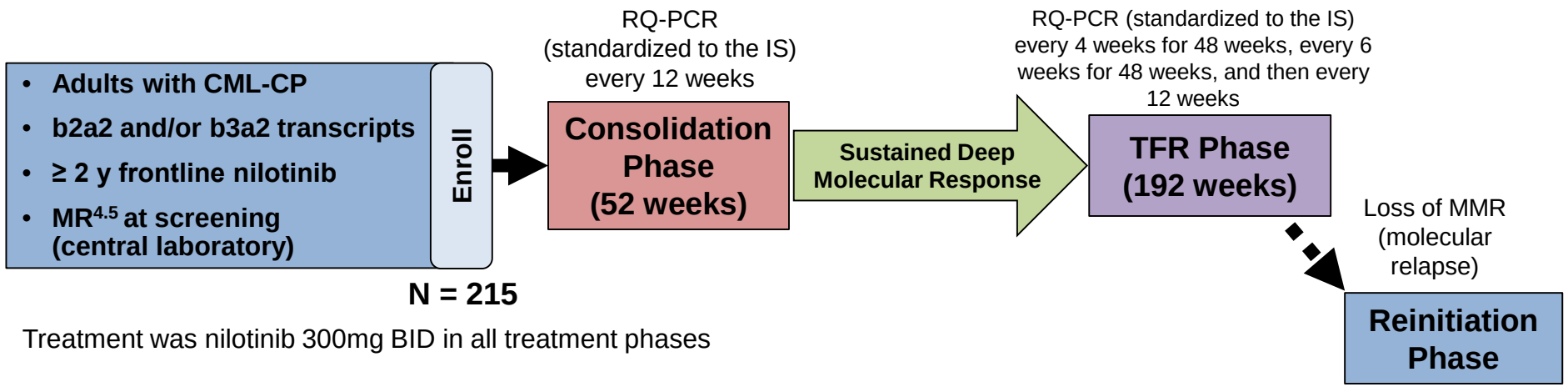
ENESTfreedom

Enrollment and Inclusion Criteria	
Total enrollment	n=215
Minimum treatment duration required prior to discontinuation	≥3 years frontline nilotinib
Minimum response required prior to discontinuation	Sustained $MR^{4.5}$ for at least 1 year

- 37.9% of nilotinib 300mg BID treated patients on ENESTnd met the inclusion criteria for attempting TFR on ENESTfreedom

Study Design

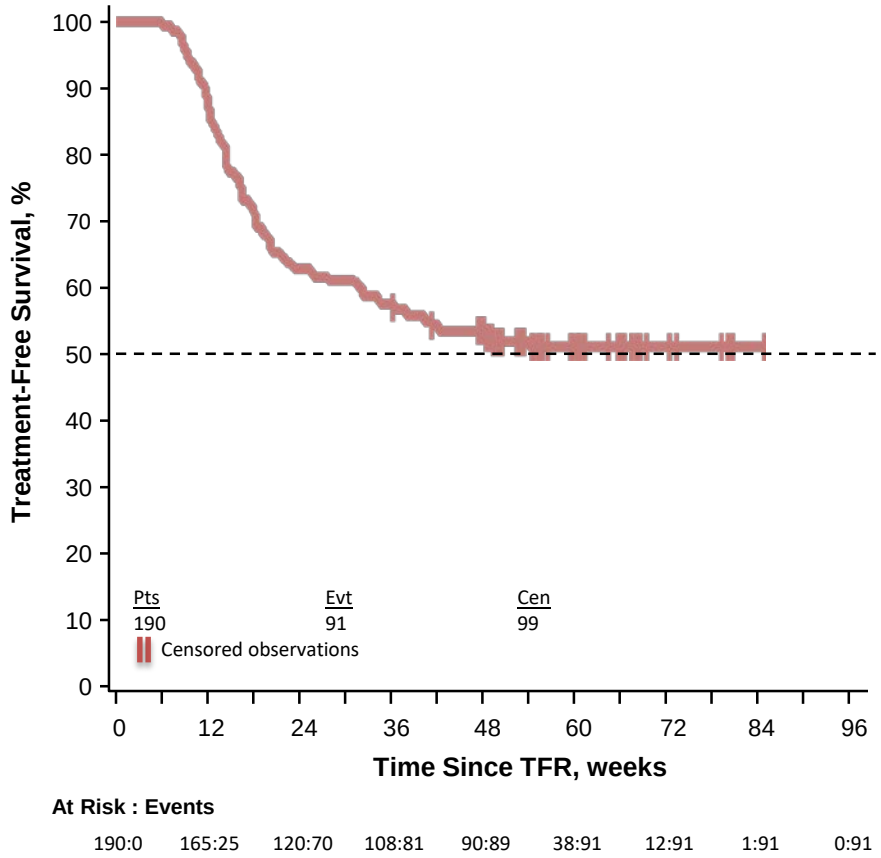


Treatment was nilotinib 300mg BID in all treatment phases

Hochhaus A. ASCO Annual Meeting 2016. Abstract #7001

Primary Endpoint and Treatment-Free Survival

Kaplan-Meier Estimated Treatment-Free Survival[a]

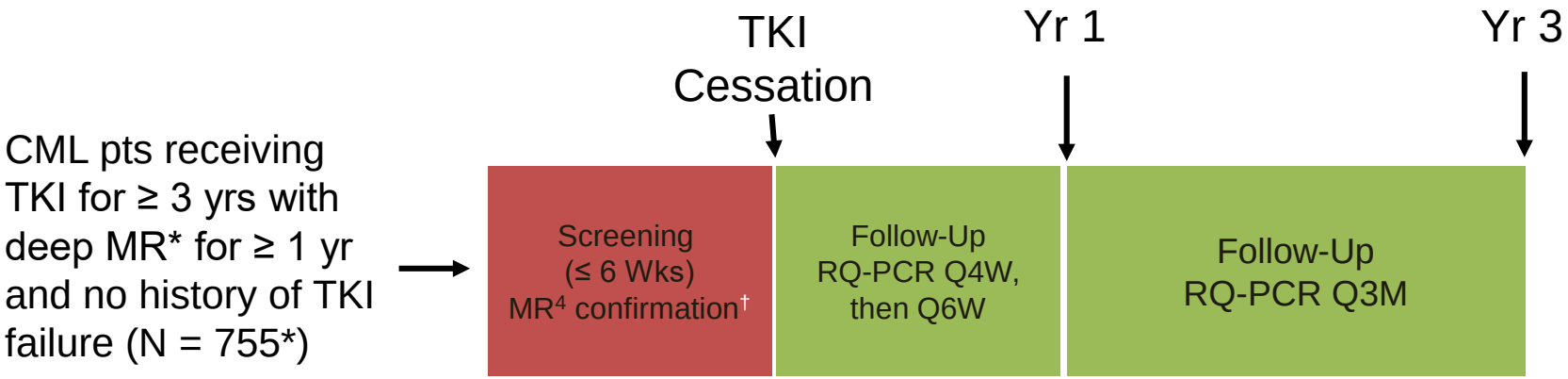


- 190 patients entered the TFR phase
- 51.6% of patients (95% CI, 44.1-58.9%) remained in TFR after 48 weeks

[a] Defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, reinitiation of nilotinib for any reason, progression to accelerated phase/blast crisis, or death due to any cause.

Hochhaus A. ASCO Annual Meeting 2016. Abstract #7001

EURO-SKI: Study Design



*In primary analysis of 868 preregistered pts.
†MR^4, defined as detectable BCR-ABL ≤ 0.01%, or undetectable BCR-ABL in samples with ≥ 10,000 ABL or ≥ 24,000 GUS transcripts, respectively.

Primary endpoint: molecular recurrence (BCR-ABL > 0.1%, ie, loss of MMR)

- Largest TFR study to date
- Goal was to establish criteria for TKI discontinuation

Sauselle S, et al. ASH 2017. Abstract 313.

EURO-SKI: Patient Population

- N = 821 pts recruited
  - Male: 52%
  - Median age: 60 yrs (range: 19-90)
  - 448 imatinib treated patients
- N = 755 included in MRFS analysis
  - MMR loss after TKI cessation: n = 371 (49%)
  - TKI restarted in MMR: n = 13 pts
  - Death in MMR: n = 4 pts

Sauselle S, et al. ASH 2017. Abstract 313.

EURO-SKI: Molecular Recurrence-Free Survival

Month	Pts at Risk, n	MRFS, % (95% CI)
6	457	61 (58-65)
12	396	55 (51-58)
18	333	52 (49-56)
24	219	50 (47-54)
36	31	47 (43-51)

Sauselle S, et al. ASH 2017. Abstract 313.

EURO-SKI: Cutoffs for MMR at 6 Months

- Cutoffs for 6-mo probability of MMR loss (minimal *P* value approach)
  - TKI (imatinib) cutoff: 5.8 yrs
    - MMR loss if discontinued at ≤ 5.8 yrs: 57% (95% CI: 48% to 64%)
    - MMR loss if discontinued at > 5.8 yrs: 34% (95% CI: 29% to 39%)
  - MR^4 cutoff: 3.1 yrs
    - MMR loss if MR^4 duration ≤ 3.1 yrs: 56% (95% CI: 47% to 64%)
    - MMR loss if MR^4 duration > 3.1 yrs: 38% (95% CI: 33% to 44%)

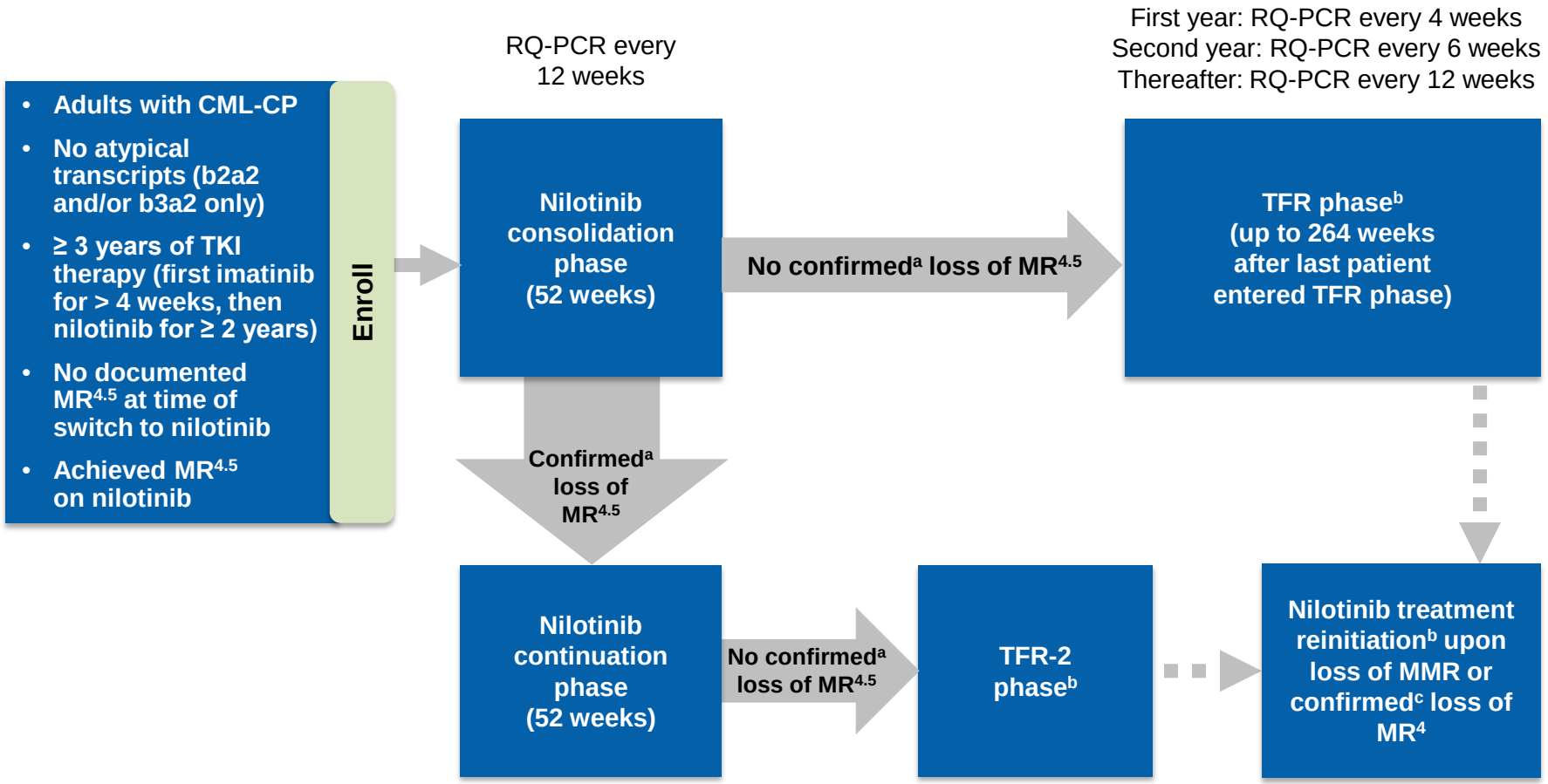
Sauselle S, et al. ASH 2017. Abstract 313.

EURO-SKI: Conclusions

- Study defined stopping criteria for TKI cessation in CML patients who achieve durable deep MR
- Preferred cutoffs for 6-mo probability of MMR loss
  - TKI duration: 5.8 yrs
  - MR^4 duration: 3.1 yrs
- Probability of TFR increased almost linearly per each additional year of first-line imatinib and duration of MR^4

Sauselle S, et al. ASH 2017. Abstract 313.

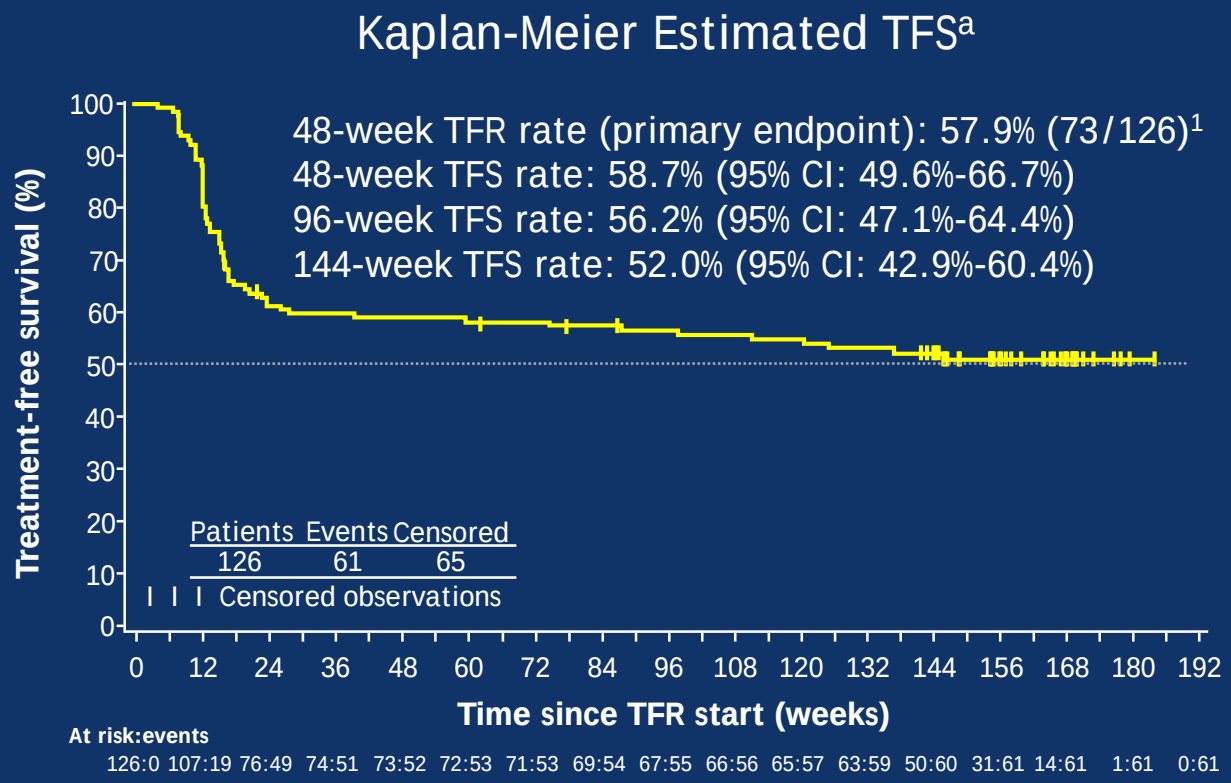
ENESTop Study Design



[a] Confirmed loss of $MR^{4.5}$ was defined as *BCR-ABL1*^{IS} > 0.0032%, confirmed in a second assessment within 4 weeks.
[b] The end of the study was 264 weeks after the last patient entered the TFR phase.
[c] Confirmed loss of MR^{4} was defined as *BCR-ABL1*^{IS} > 0.01%, confirmed in a second assessment within 4 weeks.

Saglio G. ASH Annual Meeting. 2017. Abstract # 1598
Mahon F. ASCO Annual Meeting 2018

Treatment-Free Survival



Of 67 patients in TFR at 96 weeks, 6 were no longer in the TFR phase at 144 weeks

- 3 had confirmed loss of MR^4 at 108, 120, and 144 weeks, respectively
- 2 died (respiratory failure and arthritis bacterial, respectively)
- 1 discontinued the study due to patient decision

A total of 61/126 patients had TFS[a] events by the 144-week data cutoff, including 9 reported after the 48-week data cutoff[b]

AP/BC, accelerated phase/blast crisis; CI, confidence interval; TFS, treatment-free survival.

[a] Defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, confirmed loss of MR^4, treatment re-initiation due to any cause, progression to AP/BC, or death due to any cause. [b] At the 48-week data cutoff, all patients had completed ≥ 48 weeks of TFR, restarted nilotinib, or discontinued the study.

1. Mahon FX, et al. *Ann Intern Med*. 2018;168:461-470.

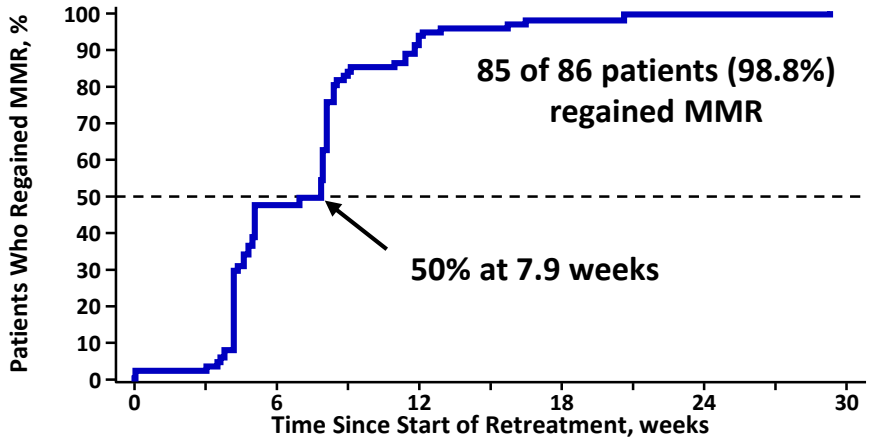
When to Restart?

Trial	Trigger to Restart TKI
STIM1	Loss of MMR or confirmed ≥1-log increase in BCR-ABL
STIM2	Loss of MMR or ≥1-log increase in BCR-ABL
TWISTER	Loss of MMR or two consecutive positive PCR values
A-STIM	Loss of MMR
LAST	Loss of MMR
EURO-SKI	Loss of MMR
KIDS	Confirmed loss of MMR
ENESTfreedom	Loss of MMR

Ross DM, et al. ASH Annual Meeting abstracts 2013.
Mahon FX, *et al.* ASH Annual Meeting abstracts 2013
Mahon FX, *et al.* ASH Annual Meeting abstracts 2016
Atallah et al. ESH 2015
Choi SY et al. ASH Annual Meeting abstracts 2013.
Rousselot P et al JCO 2013

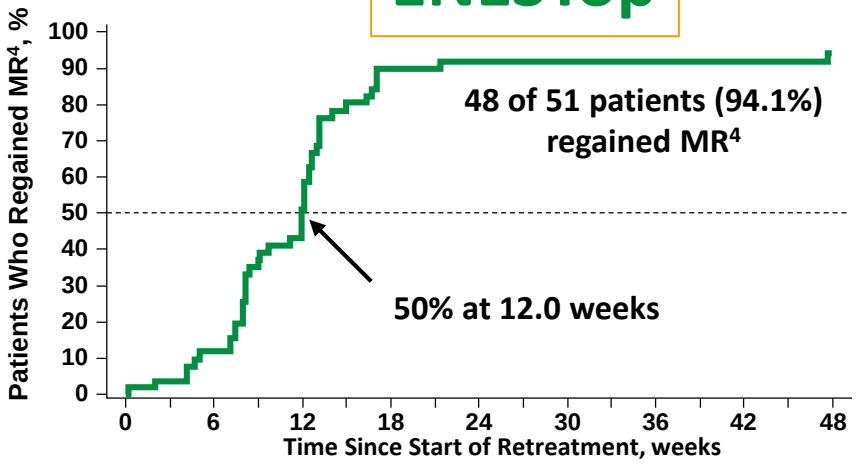
Rates of regained molecular response

ENESTfreedom

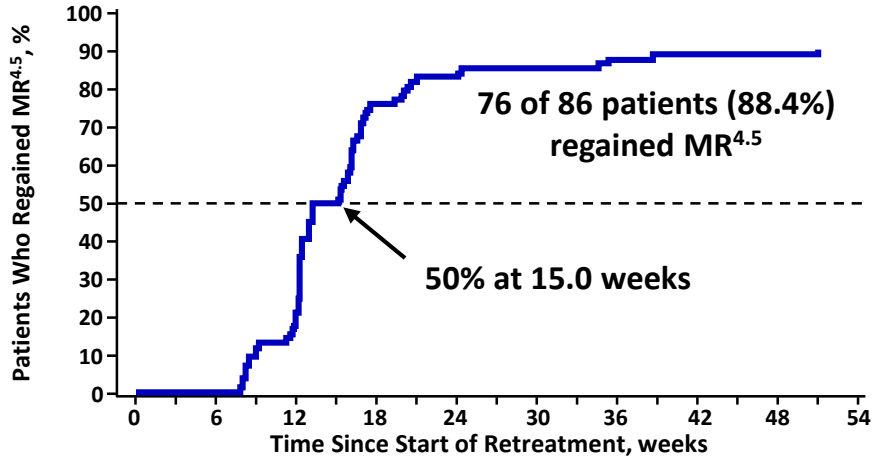


Cumulative n/N	0/86	40/86	79/86	83/86	84/86	85/86
Cumulative %	0.0	46.5	91.9	96.5	97.7	98.8

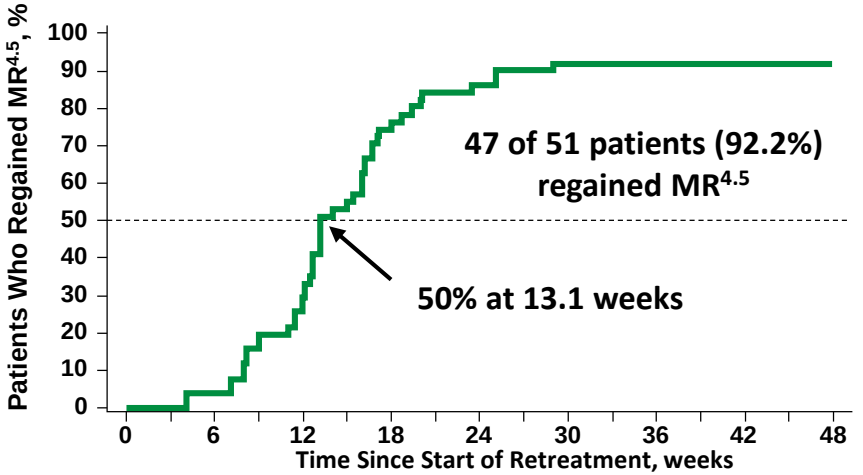
ENESTop



Cumulative n/N	0/51	6/51	26/51	46/51	47/51	47/51	47/51	47/51	48/51
Cumulative %	0.0	11.8	51.0	90.2	92.2	92.2	92.2	92.2	94.1



Cumulative n/N	0/86	0/86	21/86	64/86	71/86	72/86	74/86	75/86	75/86	76/86
Cumulative %	0.0	0.0	24.4	74.4	82.6	83.7	86.0	87.2	87.2	88.4



Cumulative n/N	0/51	2/51	15/51	39/51	44/51	47/51	47/51	47/51	47/51
Cumulative %	0.0	3.9	29.4	76.5	86.3	92.2	92.2	92.2	92.2

Summary of TFR studies

Study	Treatment prior to discontinuation	No. of patients	Depth and duration of MR required for discontinuation	Trigger to resume TKI therapy	Median duration of follow-up	Treatment-free remission (TFR) rate
STIM	Imatinib ± interferon	100	MR5.0 for at least 2 yrs	Loss of MR5.0	65 months	**41% at 24 months**
STIM2	Imatinib	124	MR5.0 for at least 2 yrs	Loss of MR5.0	12 months	**61% at 12 months**
TWISTER	Imatinib ± interferon	40	MR4.5 for at least 2 yrs	Loss of MR5.0	42 months	**47% at 24 months**
HOVON	Imatinib + cytarabine	15	MR4.5 for at least 2 yrs	Loss of MR4.5	36 months	**33% at 24 months**
A-STIM	Imatinib ± interferon	80	MR5.0 for at least 2 yrs	Loss of MMR	31 months	**64% at 24 months** **61% at 36 months**
ISAV	Imatinib	112	CML for at least 18 months	Loss of MMR	22 months	**52%**
KIDS	Imatinib ± interferon	90	MR4.5 for at least 2 yrs	Loss of MMR	27 months	**62% at 12 months** **58.5% at 24 months**
Stop 2G-TKI	Dasatinib /Nilotinib (1L or 2L)	52	MR4.5 for at least 24 months	Loss of MMR	12 months	**61% at 12 months** **57% at 24 months**
DADI	Dasatinib (2L)	63	MR4.0 for at least 2 yrs	Loss of MR4.0	20 months	**49% at 6 months**
ENESTFreedom	Nilotinib (1L)	190	MR4.5 for 12 months	Loss of MMR	12 months	**52%**
ENESTop	**Nilotinib (2L)**	**126**	**MR4.5 for 12 months**	**Loss of MR4.0 or Loss of MMR**	**35 months**	**52% at 36m**
EuroSKI	Imatinib/Dasatinib/ Nilotinib (1L or 2L)	717	MR4.0 for at least 1 yr	Loss of MMR	10 months	**53%**

Discontinuation criteria for TKI therapy as per NCCN 2018

- Age ≥18 years.
- Chronic phase CML. No prior history of accelerated or blast phase CML.
- On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.
- Prior evidence of quantifiable *BCR-ABL1* transcript.
- Stable molecular response (MR4; *BCR-ABL1* ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.
- Access to a reliable qPCR test with a sensitivity of detection at least MR4.5 (BCR-ABL1 ≤ 0.0032% IS) and provides results within 2 weeks.
- **Monthly molecular monitoring for one year, then every 6 weeks for the second year, and every 12 weeks thereafter (indefinitely) is recommended for patients who remain in MMR (MR3; *BCR-ABL1* ≤0.1% IS) after discontinuation of TKI therapy.**
- **Prompt resumption of TKI within 4 weeks of a loss of MMR with molecular monitoring every 4 weeks until MMR is re-established, then every 12 weeks thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after three months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another six months.**
- Consultation with a CML Specialty Center to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Reporting of the following to a member of the NCCN CML panel is strongly encouraged:
- Any significant adverse event believed to be related to treatment discontinuation.
- Progression to accelerated or blast phase CML at any time.
- Failure to regain MMR after three months following treatment reinitiation.

TKI Withdrawal Syndrome

– Diffuse musculoskeletal pain and joint pain

– Occurs in approximately 30% of patients after stopping TKIs

– Median duration 6 months

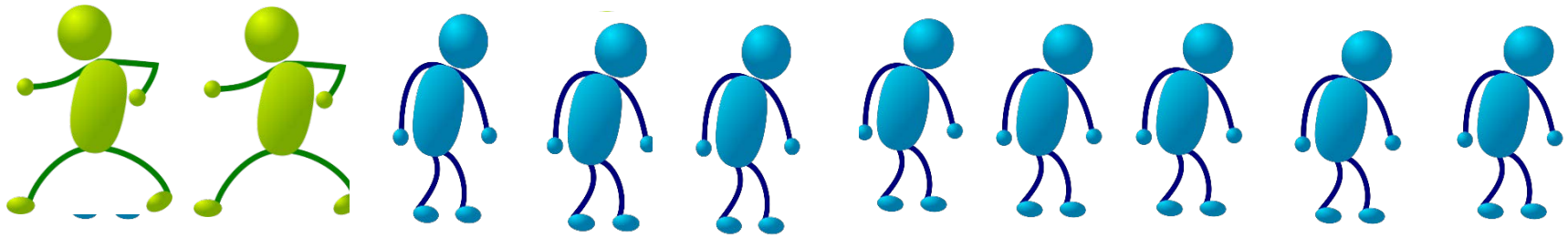
Lee et al. Haematologica. 2016 Jun;101(6):717-23.
Richter et al. J Clin Oncol. 2014;**32**(25):2821–2823.

Financial Impact

- By 2050 the prevalence of CML will plateau at 180,000
- Current prevalence ≅ 30,000 patients
- Current annual cost of TKIs ≅ $100,000
- Annual cost of drugs in the US ≅ $3,000,000,000
- If 25% of patients can discontinue treatment, this annual cost decreases to ≅ $2,250,000,000
- $750,000,000 savings per year

Is Stopping TKI Realistic?

50% achieve MR4 or MR 4.5



50% restart TKI

70-80% of newly diagnosed patients with CML will need long term TKI therapy

Atallah et al EHA iCMLf 2017

Conclusions

- Most patients with chronic phase CML will do well with current therapy
- Stopping TKIs is ready for prime time
  - A select group of patients
  - With proper monitoring
- Multi-team approach is a key component to the success and safety of TFR

Thank you

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