CML & MPN

POST ASH

13th January 2017

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MD, PhD

CML

58 th ASH
ANNUAL MEETING

SAN DIEGO, CALIFORNIA

Imatinib discontinuation studies

Study	# pts	Treatment before discontinuation	Response required to discontinue	Definition of molecular recurrence	%TFR	Ref.
STIM1	100	IM for ≥ 3 yr (±prior IFN)	CMR *($MR^{4.5}$ or $MR^{5.0}$)* ≥ 2 yr	Loss of MMR or ≥ 1-log increase in BCR-ABL	**41** (24 m)	Mahon FX et al. JCO 2010.
STIM2	200	IM for ≥ 3 yr	CMR ≥ 2 yr	Loss of MMR or ≥ 1-log increase in BCR-ABL	**46** (24 m)	Nicolini FE et al. Blood 2013, 122 (abstract)
ALLG CML8 (TWISTER)	40	IM for ≥ 3 yr	UMRD ≥ 2 yr	Loss of MMR or confirmed loss of $MR^{4.0}$	**45** (42 m)	Ross DM et al. Blood 2013.
A-STIM	80	IM for ≥ 3 yr	CMR ≥ 2 yr (occasional pos. sample allowed)	Loss of MMR	**64** (23 m)	Rousselot P et al. JCO 2014
ISAV	112	Imatinib	Undetectable PCR (3 PCRs)	Loss of MMR	**52** (36 m)	Mori S et al. Am J Hematol 2015.
EURO-SKI	809	IM (94%), Nil, Das (TKI ≥ 3 yr)	$MR^{4.0}$ ≥ 1 yr	Loss of MMR	**51** (24 m)	EHA 2016 (abstract); ASH 2016 abstract 787.

2G TKI discontinuation studies

Study	# pts	Treatment before discontinuation	Response required to discontinue	Definition of molecular recurrence	%TFR	Ref.
STOP 2G-TKI	50	NIL or DAS	CMR for median 29 months	Loss of MMR	**63** (12 m)	Rea et al. Blood 2016. (interim analysis)
DADI	63	dasatinib (consolidation for 1 yr within trial)	DMR ≥ 1 yr	Loss of DMR	**49** (6 m)	Imagawa et al. Lancet Haematol 2015.
ENEST-Freedom	175	nilotinib frontline	$MR^{4.5}$ ≥ 1 yr	Loss of MMR		**QOL data shown at ASH 2016 (abstract 3066)**
ENESTpath	1058	IM (≥ 2 yr) then nilotinib	Randomisation $MR^{4.5}$ ≥ 1 yr vs. $MR^{4.5}$ ≥ 2 yr	Confirmed loss of $MR^{4.0}$ or any loss of MMR	on-going	
ENESTGoal	300	IM (≥ 1 yr without MMR) then nilotinib	$MR^{4.5}$ ≥ 1 yr	Loss of MMR	on-going	
DASFree	74	dasatinib > 2 yr	$MR^{4.5}$ ≥ 1 yr	Loss of MMR	on-going	
TIGER	650	nilotinib (≥ 2 yr) vs. nilotinib + PEG-IFN	$MR^{4.0}$ ≥ 1 yr	Loss of MMR	on-going	

Prognostic factors for successful TFR?

	STIM1	TWISTER	EURO-SKI	2G-TKI	DADI
	Imatinib	Imatinib	Im (94%), Nil, Das	Nil, Das	Dasatinib
Sokal score	○	○			
Duration of prior TKI	○		○		
Duration of (D)MR			○		
Duration of previous IFN before TKI	○	○	○		
NK cell number	○	○		○	
Depth of molecular response (MR4.5 vs. not in MR4.5)					

consistent data ?

EURO SKI trial: update

Patients included between May 2012 and December 2014

TKI treatment ≥ 3 years

MR^4 ≥ 1 year

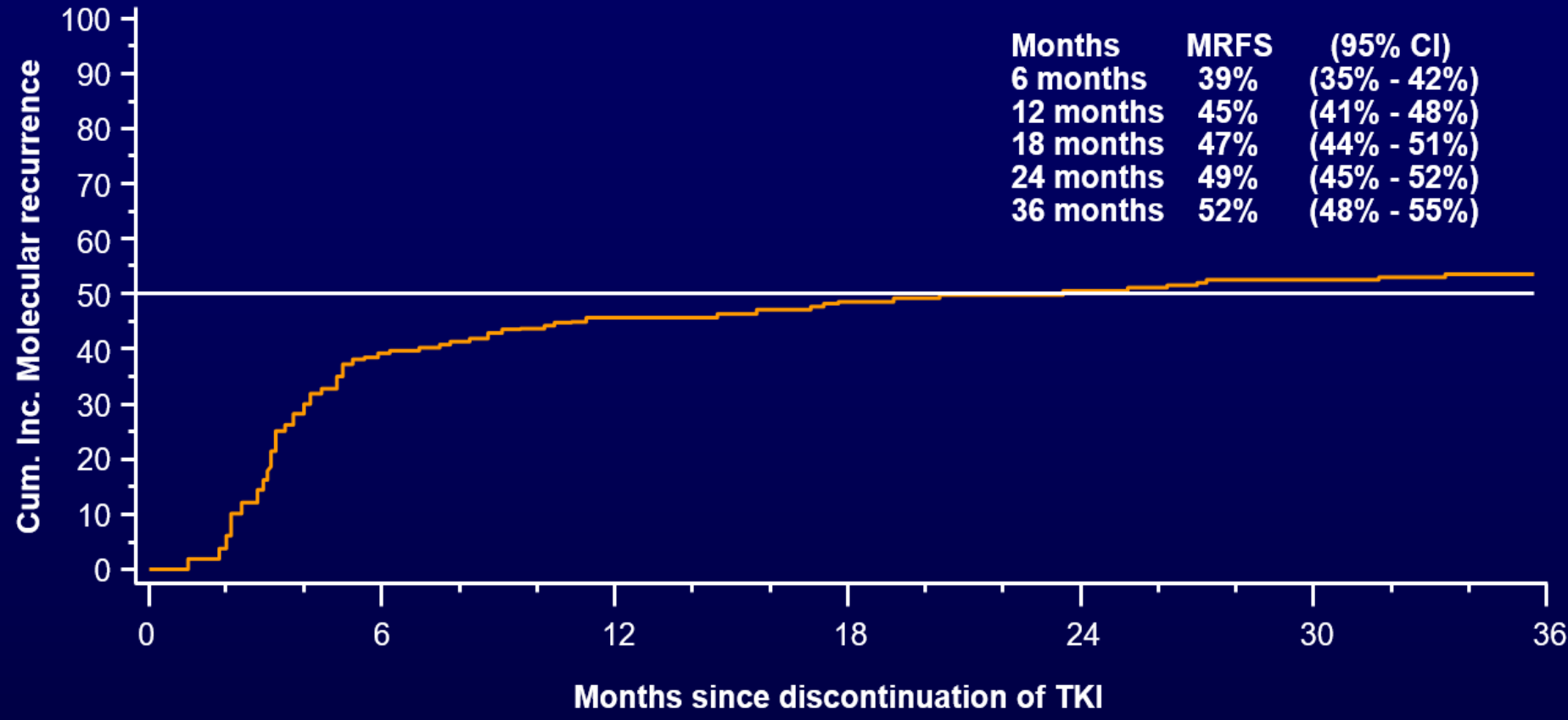
Molecular recurrence defined as BCR-ABL >0.1% (loss of MMR) at one time point

Informed consent

Stop TKI

Follow-up

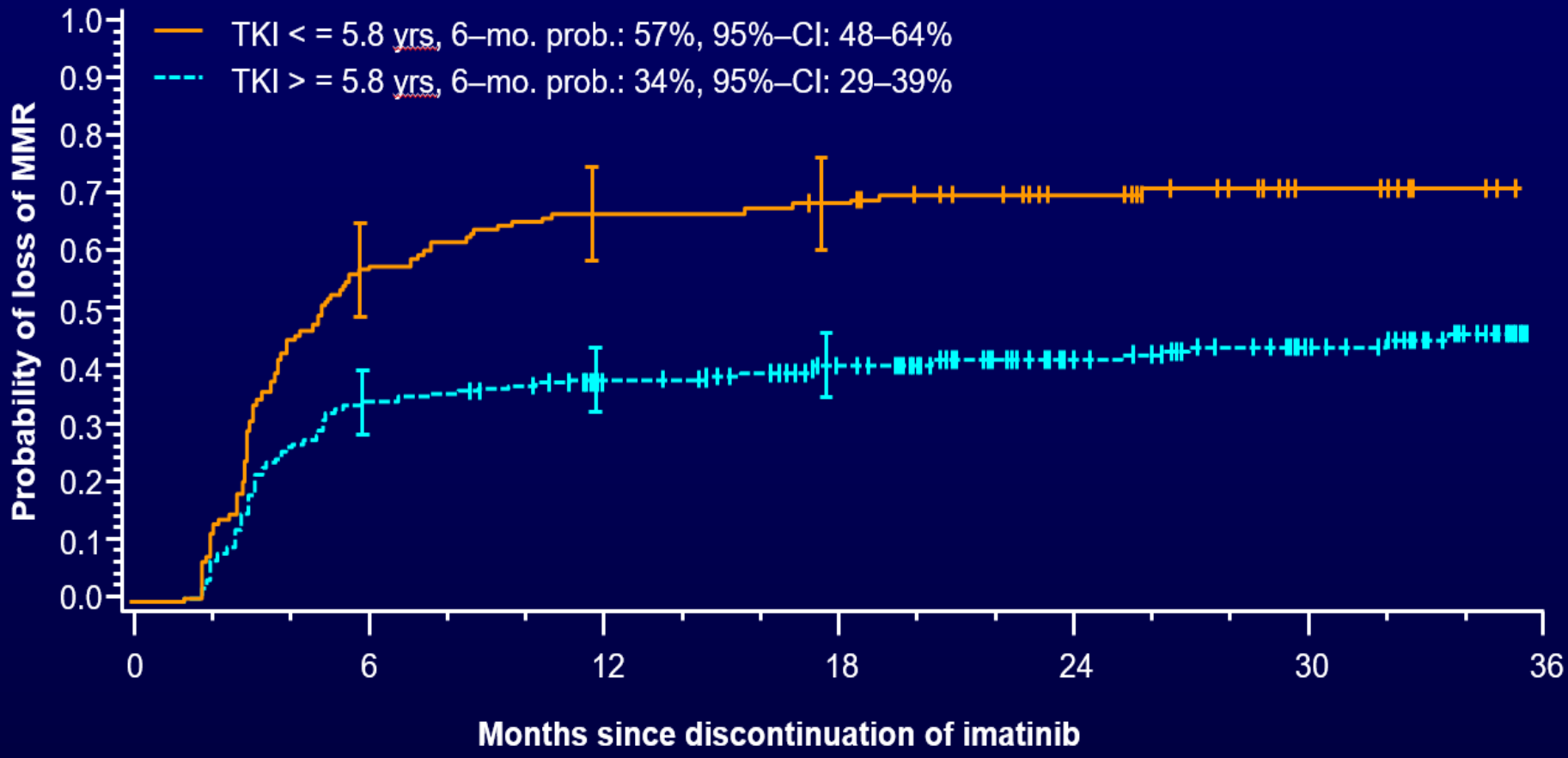
Cumulative incidence of molecular recurrence



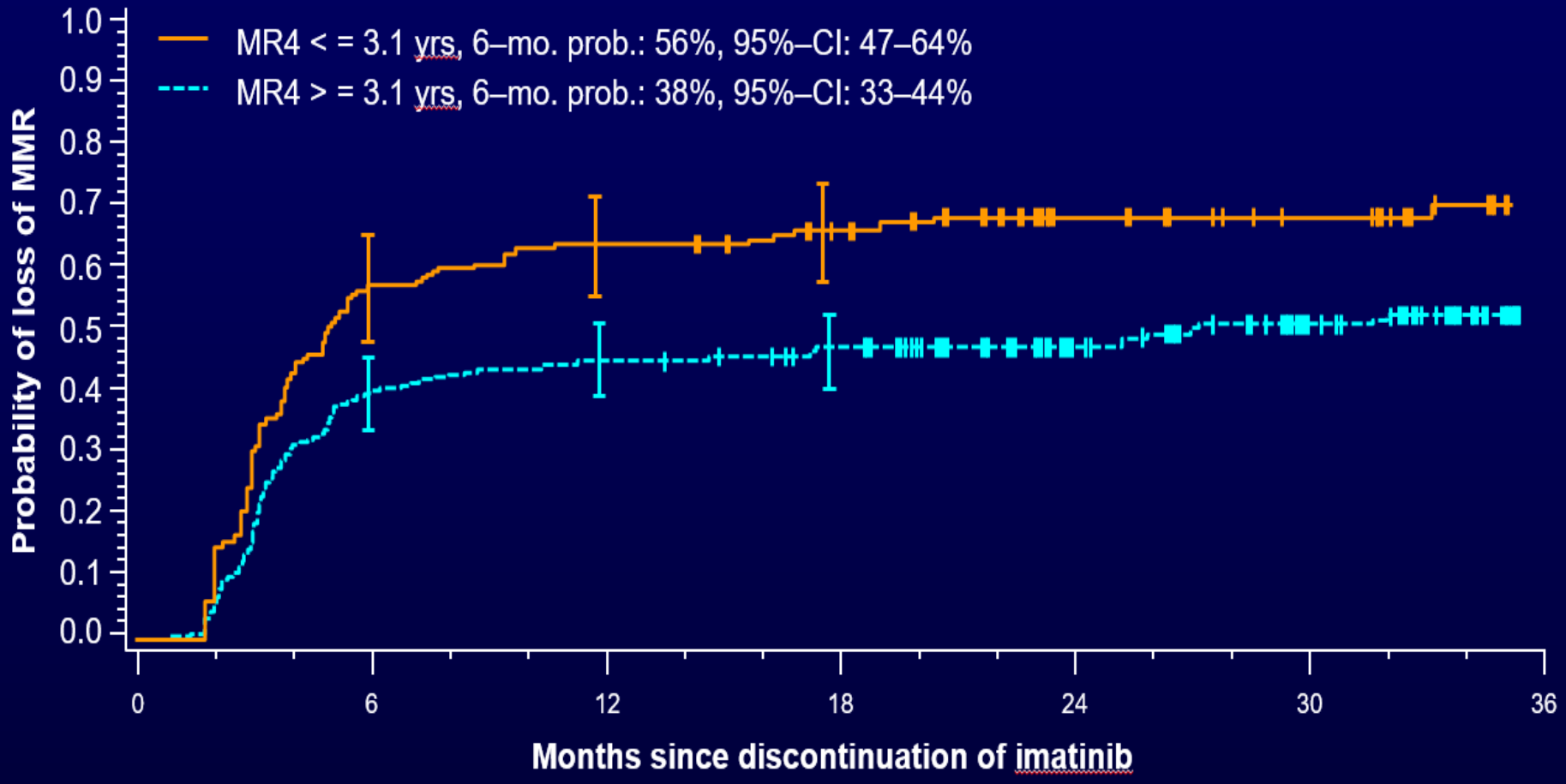
Months	MRFS	(95% CI)
6 months	39%	(35% - 42%)
12 months	45%	(41% - 48%)
18 months	47%	(44% - 51%)
24 months	49%	(45% - 52%)
36 months	52%	(48% - 55%)

At risk	755	457	396	333	219	139	31
Failed	0	291	336	351	362	368	371

EURO-SKI


TKI < = 5.8 yrs, 6–mo. prob.: 57%, 95%–CI: 48–64%
TKI > = 5.8 yrs, 6–mo. prob.: 34%, 95%–CI: 29–39%
Probability of loss of MMR
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
18
24
30
36
Months since discontinuation of imatinib

- Using the minimal p-value approach a 3.1 years cut-off was significant and chosen with respect to patient safety



Partial estimated savings for patients who stopped imatinib

Pre-registered: N=868

Analyzed, overall N=758

Excluded for Imatinib "cost saving evaluation N=162

Not imatinib first line

Imatinib first line but switch to other TKI

Not assessable: missing and/or inadequate information

Assessable N=596

Patients who stopped imatinib and restarted TKI: n=279

1712 months off treatment

Patients who stopped imatinib and have not restarted at last evaluation: n=317

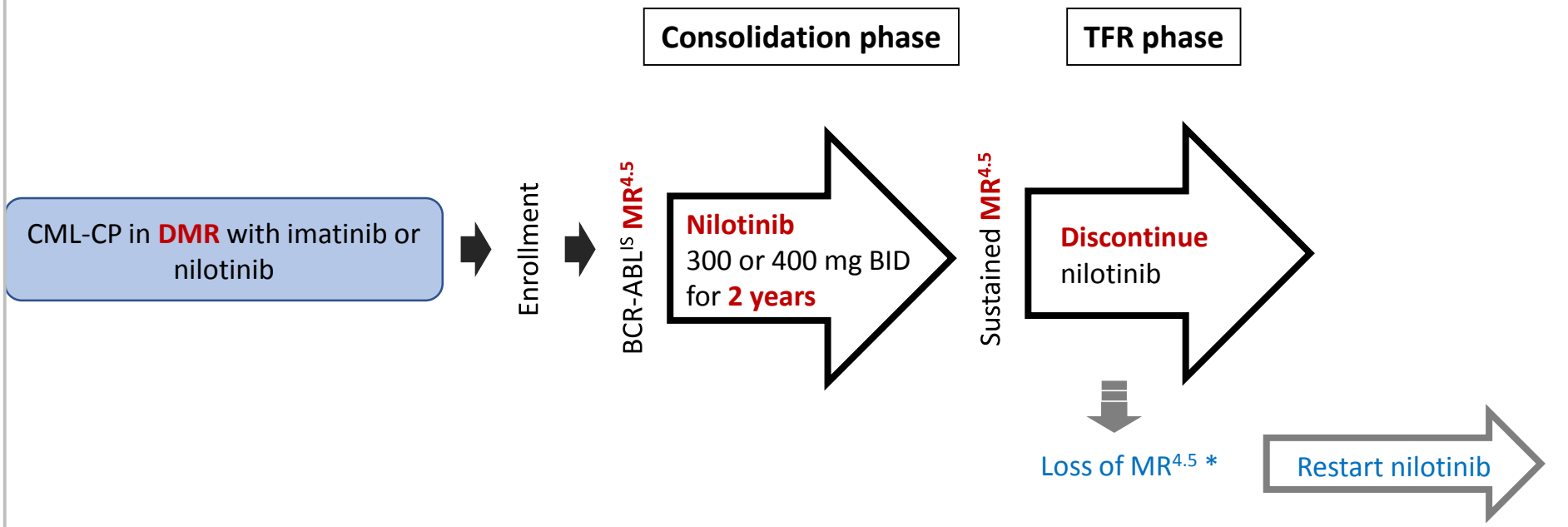
8092 monthts off treatment

Mean value of IM per months in the 11 European countries = 2262€ (before the generics)

Estimated savings more than **22 Millions €**

NILSt trial

Study design



** Loss of MR$^{4.5}$*
> 0.0032% IS with 2 consecutive samples

Primary endpoint

TFR (MR$^{4.5}$) rate 1 year after discontinuation of nilotinib

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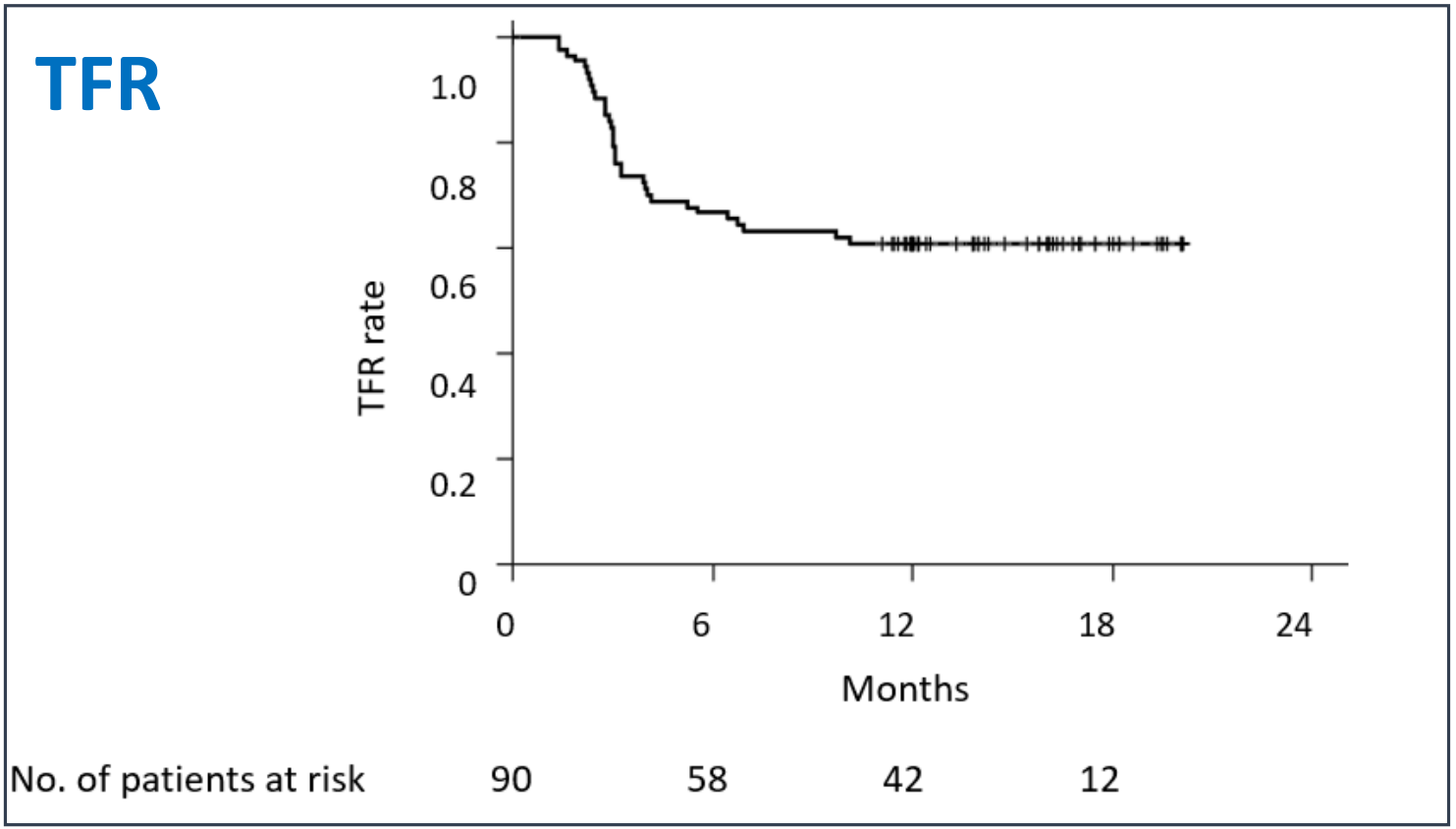
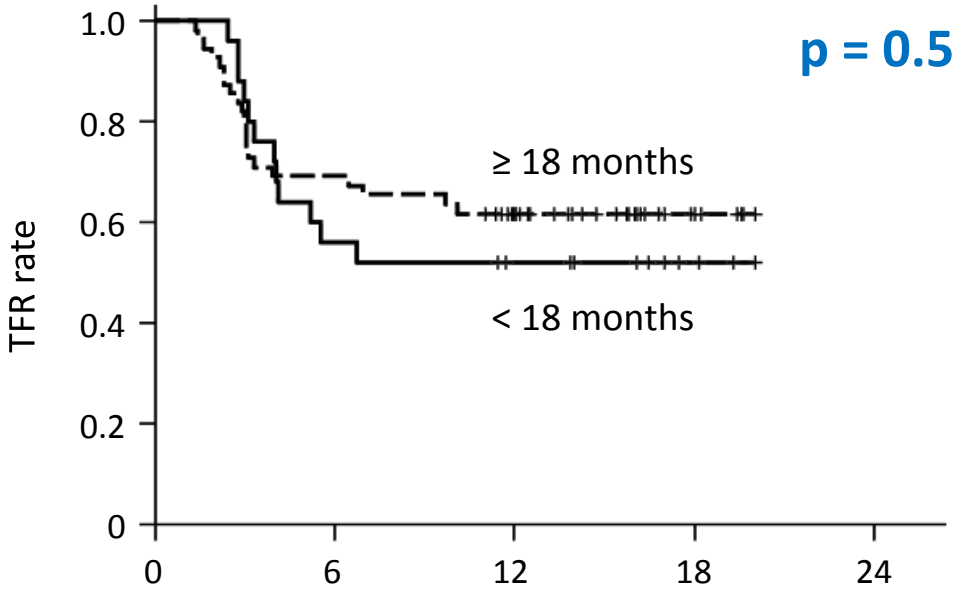
NILSt trial

TFR



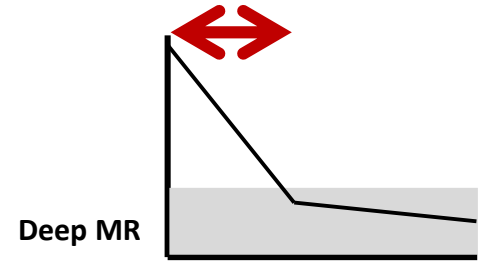
TFR ($MR^{4.5}$) rate 1 year after discontinuation of nilotinib: 62.2%

Time to deep MR

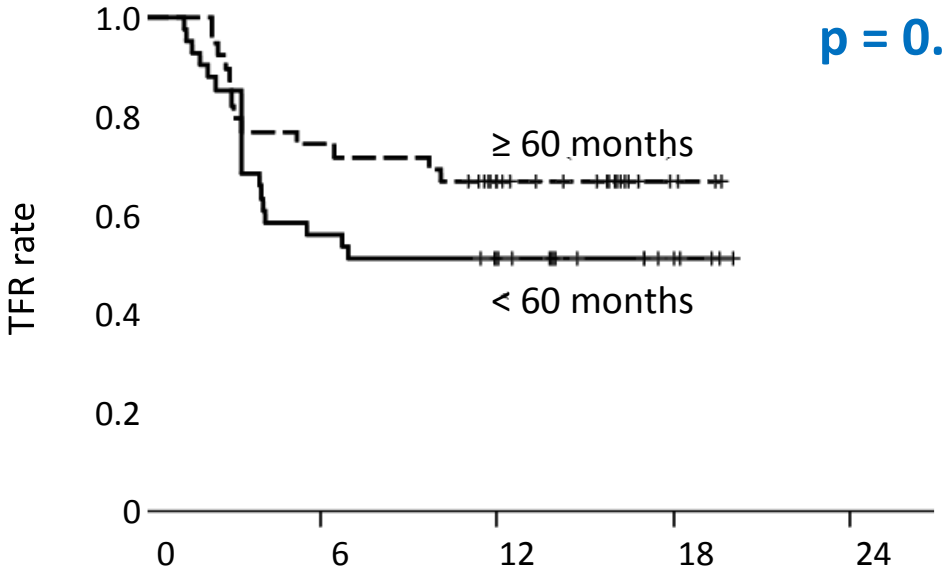


p = 0.56

No. of patients at risk				
< 18 months	26	14	11	5
≥ 18 months	57	38	27	6



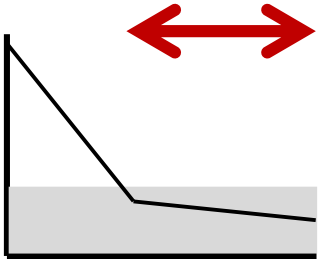
Duration of deep MR



p = 0.15

No. of patients at risk

< 60 months	41	23	18	8
≥ 60 months	39	29	19	3



Prognostic factors for successful TFR?

	STIM1	TWISTER	EURO-SKI	2G-TKI	DADI	NILSt
	Imatinib	Imatinib	Im (94%), Nil, Das	Nil, Das	dasatinib	nilotinib
Sokal score	○	○				
Duration of prior TKI	○		○			
Duration of (D)MR			○			
Duration of previous IFN before TKI	○	○	○			
NK cell number	○	○		○		
Depth of molecular response (MR4.5 vs. not in MR4.5)						

inconsistent !

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ENESTop: Ongoing Single-Arm, Phase 2 Study

- Adults with CML-CP
- ≥ 3 years of TKI therapy (first imatinib for > 4 weeks, then nilotinib for ≥ 2 years)
- No documented $MR^{4.5}$ at time of switch to nilotinib
- Achieved $MR^{4.5}$ on nilotinib

Enroll

RQ-PCR every 12 weeks

Nilotinib consolidation phase (52 weeks)

77% (126/163) of patients entered the TFR phase

No confirmed[a] loss of $MR^{4.5}$

1st year: RQ-PCR every 4 weeks
2nd year: RQ-PCR every 6 weeks
Thereafter: RQ-PCR every 12 weeks

TFR phase (up to 192 weeks after last patient entered TFR phase)

Criteria for reinitiating nilotinib:
- Loss of MMR
or
- Confirmed[b] loss of MR^4

Confirmed[a] loss of $MR^{4.5}$

Nilotinib continuation phase[c] (52 weeks)

No confirmed[a] loss of $MR^{4.5}$

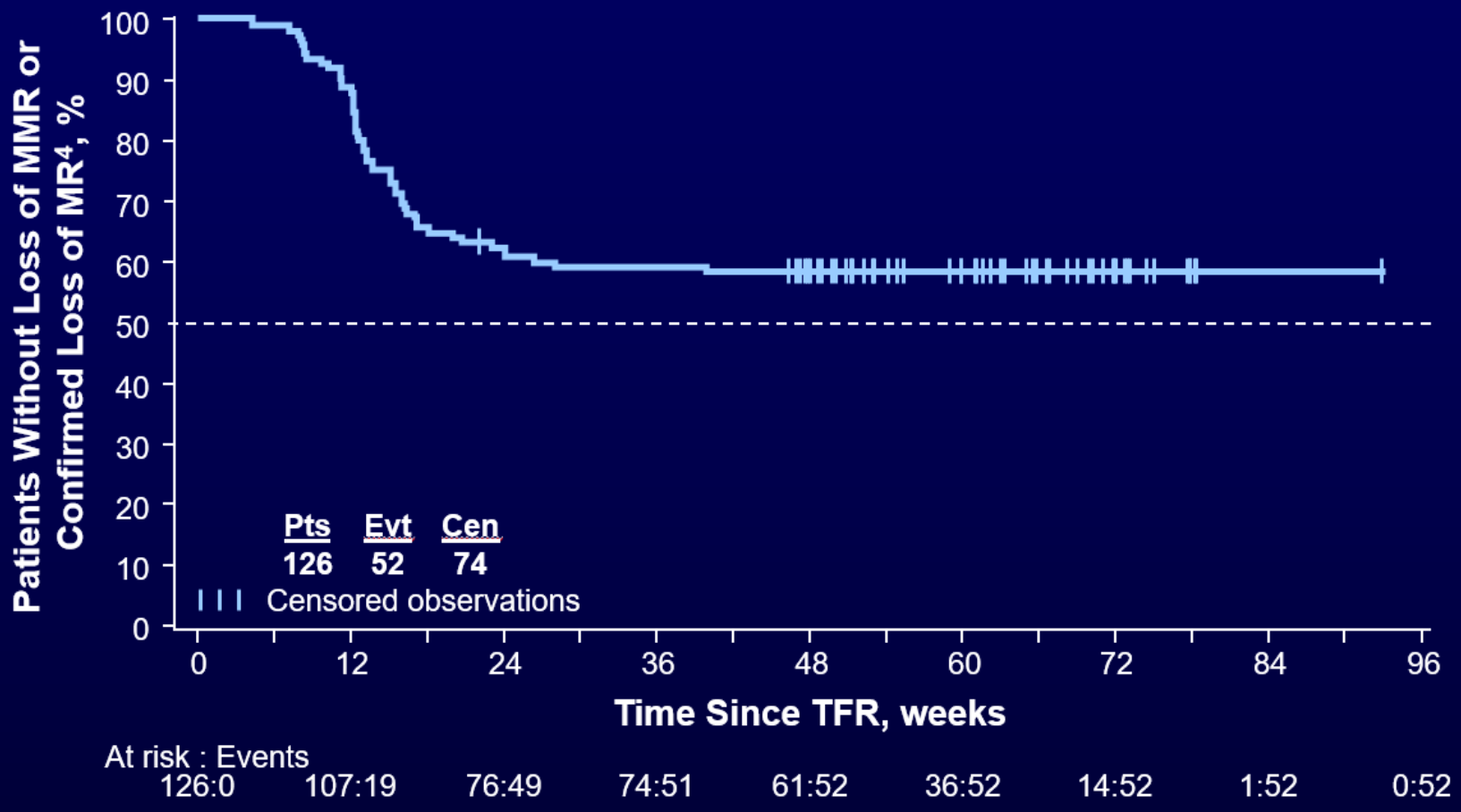
TFR-2 phase (up to 192 weeks after last patient entered TFR phase)

Nilotinib treatment reinitiation phase

Primary endpoint: proportion of patients in TFR (no loss of MMR, no confirmed loss of MR^4, and no reinitiation of treatment) at 48 weeks

TFR Rate at 48 Weeks After Stopping Treatment

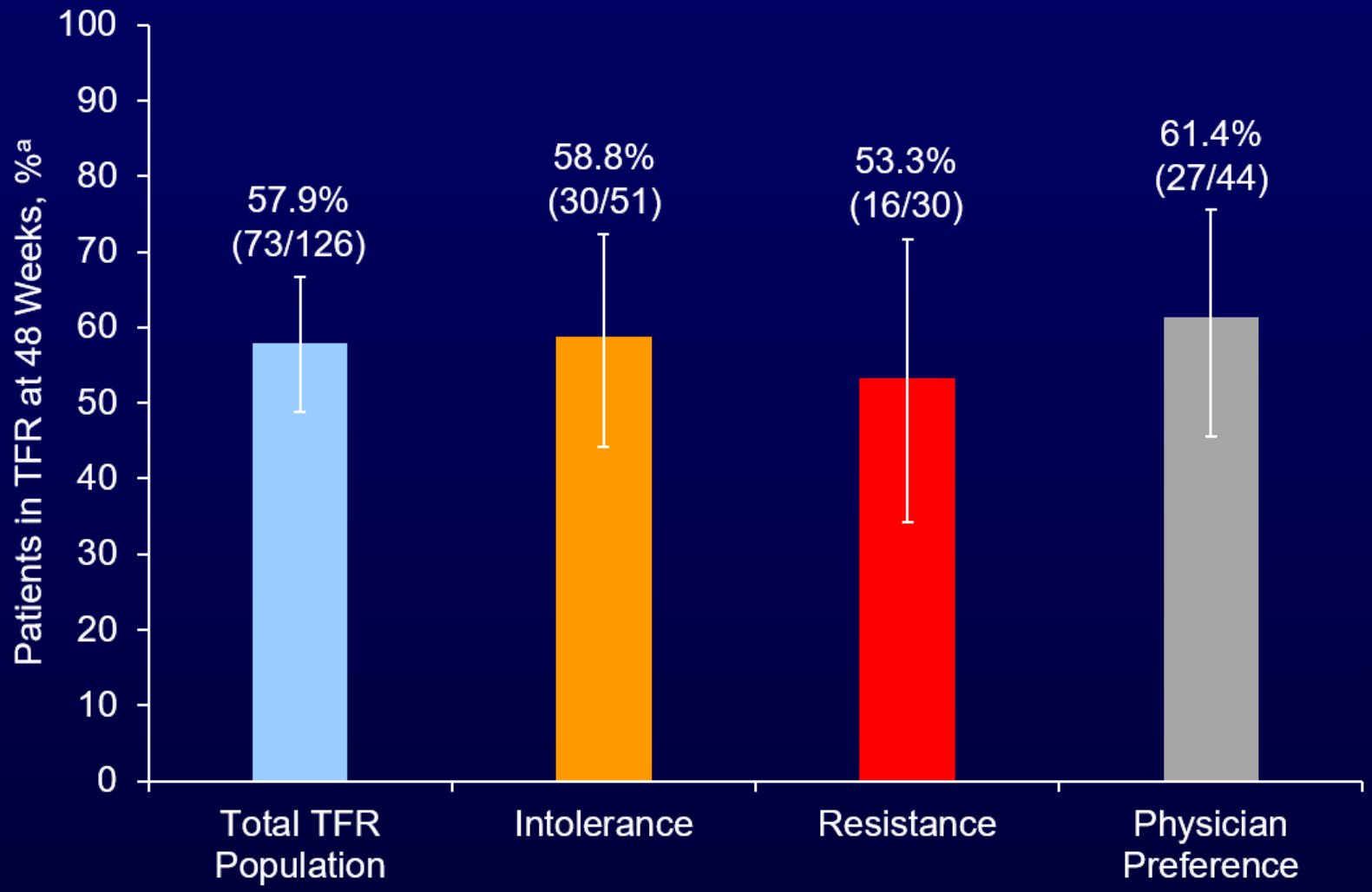
- The TFR rate at 48 weeks (primary endpoint) was 57.9% (73 of 126 patients; 95% CI, 48.8%-66.7%)



Stated Reasons for Switch Among Patients Who Entered the TFR Phase[a]

Categories, n (%)	TFR Population (N = 126)
Intolerance	*51 (40.5)*
AE	50 (39.7)
Intolerance	1 (0.8)
Resistance	*30 (23.8)*
Resistance/treatment failure[b]	16 (12.7)
Cytogenetic suboptimal response	8 (6.3)
Loss of MMR	1 (0.8)
Loss of cytogenetic response[c]	3 (2.4)
Loss of hematologic response[d]	2 (1.6)
Physician preference	*45 (35.7)*
Clinical trial available	22 (17.5)
Molecular suboptimal response	17 (13.5)[e]
New therapy available	5 (4.0)
Unknown	1 (0.8)

TFR Rate at 48 Weeks by Reasons for Switch



Second discontinuation of TKI

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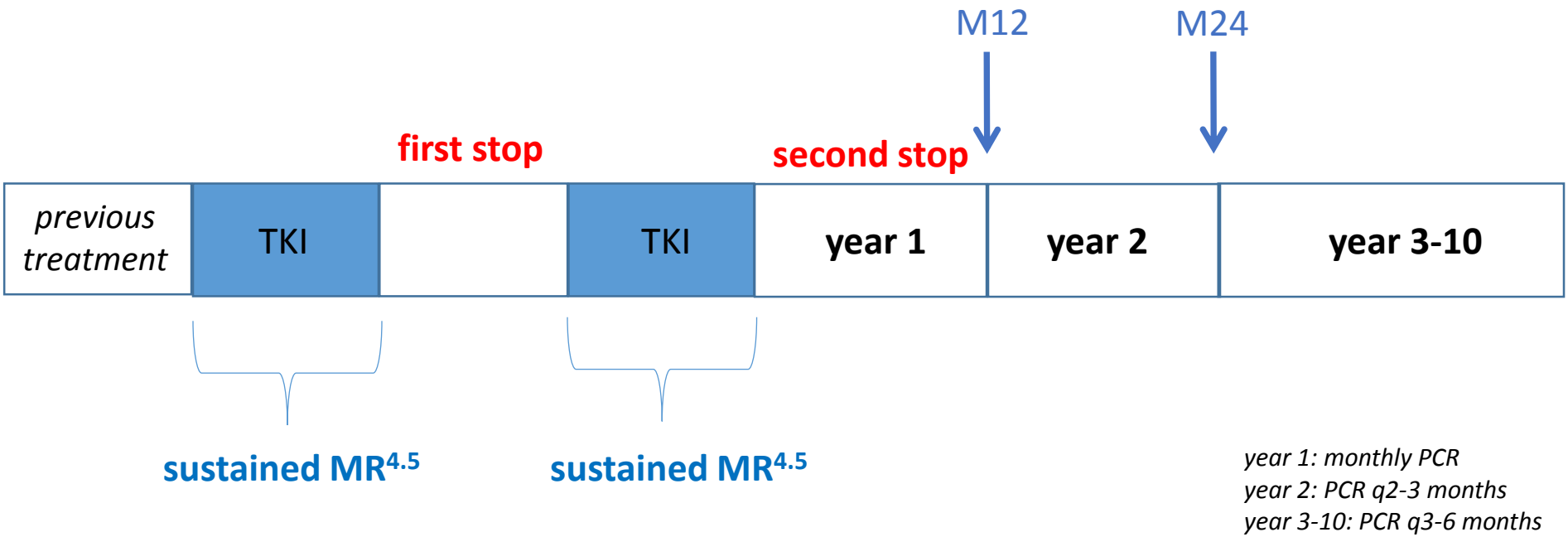


year 1: monthly PCR
year 2: PCR q2-3 months
year 3-10: PCR q3-6 months

Primary objective: TFR at M6, M12 and M24 after second STOP

at 2nd attempt of TKI discontinuation: relapse = MMR loss

#788: results

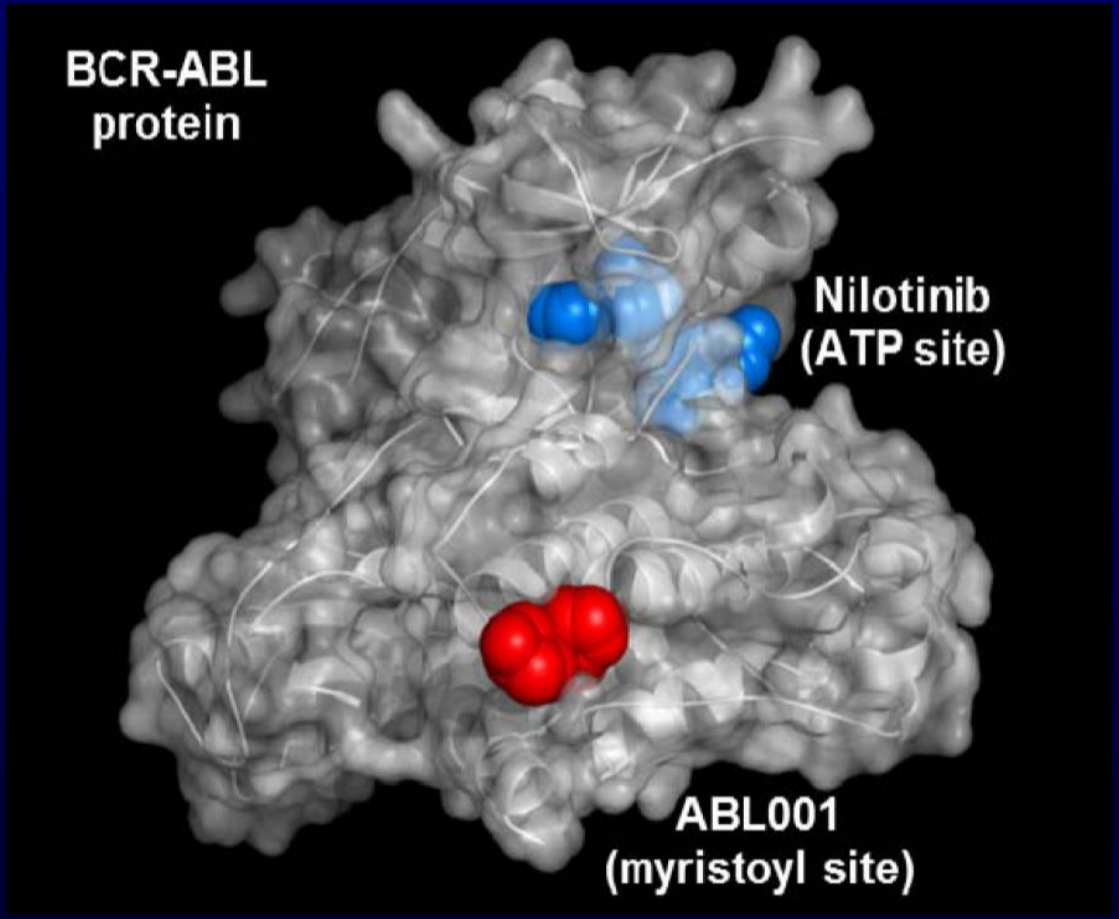
788

TFR rate at M6: 65%
TFR rate at M12: 48%
TFR rate at M24: 40%
TFR rate at M36: 33%

Molecular relapses extended later over time in comparison to other TFR studies leading to a drop to 33% at and beyond 36 months.

ABL001 Is a Potent, Specific Inhibitor of BCR-ABL1 With a Distinct Allosteric Mechanism of Action

- Developed to gain potent BCR-ABL1 inhibition, maintained against BCR-ABL1 mutations that confer resistance to TKIs
- Potential to combine with TKIs to prevent the emergence of BCR-ABL1 mutations, increasing the depth of molecular response in a greater number of patients compared with single-agent treatment



Demographics and Baseline Characteristics

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	N = 123
Median age (range), years	55 (23-79)
Male/female, %	61 / 39
ECOG performance status 0/1 or 2, %	72 / 28
Prior lines of therapy, median (range)	3 (1-5)
1 prior TKI, %	5
2 prior TKIs, %	30
≥ 3 prior TKIs, %	65
CML-CP/CML-AP/CML-BP/ALL, %	88 / 4 / 2 / 6
TKD non-mutated/mutant[a]/not evaluable, %	46 / 30[a] / 24

[a] T315I (17), E255K (3), F317L (3), G250E (3), M244V (2), V299L (2) Y253H (2), E279K (1), L248V/G250E/V299L (1), T315I/F359V (1), T315I/M351T (1), T315I/Y253H (1)

Safety: Adverse Events Suspected of Being Related to Study Drug Occurring in ≥ 5% of Patients (n = 123)

Adverse Event	All Grades, n (%)	Grade 3/4, n (%)
Lipase increase	26 (21)	12 (10)
Rash	19 (15)	0
Thrombocytopenia	16 (13)	7 (6)
Fatigue	15 (12)	1 (1)
Nausea	14 (11)	0
Arthralgia	13 (11)	0
Amylase increased	12 (10)	1 (1)
Headache	12 (10)	0
Pruritus	11 (9)	1 (1)
Anemia	9 (7)	5 (4)
Diarrhea	9 (7)	0
Myalgia	9 (7)	1 (1)
Vomiting	9 (7)	0
Hypophosphatemia	7 (6)	1 (1)
Neutropenia	7 (6)	5 (4)

625: ABL001 - results

625

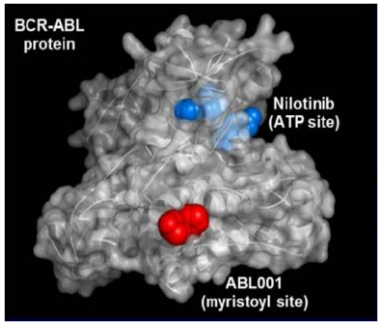
61% of CML patients treated with single-agent ABL001 were resistant to last prior TKI

44% achieved or maintained MMR by 12 months

80% of patients in cytogenetic relapse (>35% Ph+) achieved CCyR by 6 months

14% of CML patients treated with ABL001 BID had T315I mutations

* 40% in cytogenetic relapse (>35% Ph+) at baseline achieved CCyR by 6 months
* 60% have maintained stable disease without achieving CCyR or MMR

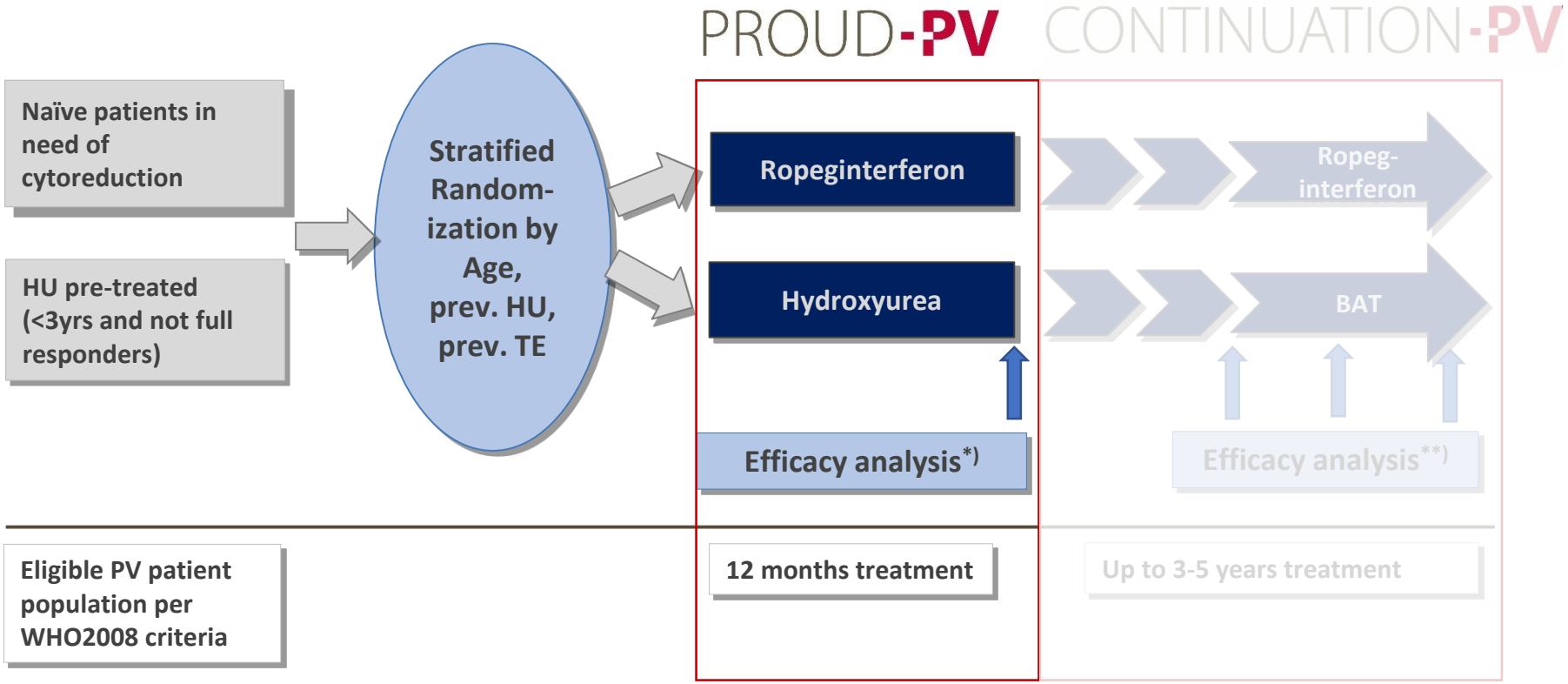


BCR-ABL negative MPN

58 th ASH
ANNUAL MEETING

SAN DIEGO, CALIFORNIA

Ropeginterferon alfa-2b phase III development: PROUD/CONTI-PV



primary objective: demonstration of non-inferiority of ropeginterferon vs. HU for CHR at 12 months.

Courtesy of H.Gisslinger

Complete Hematologic Response at 12 months

475

	AOP2014	HU	Difference % (95% CI)	P-value *)
Complete hematologic response rate (ITT)	43.1%	45.6%	-2.5 (-14.9 to 9.9)	0.0028
Responding patients/n	53/123	57/125		
Complete hematologic response rate (PP)	44.3%	46.5%	-2.2 (-15.2 to 10.7)	0.0036
Responding patients/n	50/113	53/114		

non-inferiority is demonstrated, p=0.0028

Courtesy of H.Gisslinger

All grade AEs in either treatment arm

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Adverse Event	AOP2014 (n=127) n (%)	HU (n=127) n (%)	P-value*
Anaemia	8 (6.3%)	31 (24.4%)	p<0.01
Leukopenia	11 (8.7%)	27 (21.3%)	p<0.01
Thrombocytopenia	19 (15.0%)	36 (28.3%)	p<0.01
Nausea	3 (2.4%)	15 (11.8%)	p<0.01
Fatigue	16 (12.6%)	17 (13.4%)	n.s. (p>0.05)
GGT increased	18 (14.2%)	1 (0.8%)	p<0.01

* Fisher's exact test
n.s. not significant

Courtesy of H.Gisslinger

Adverse Events of special interest

475

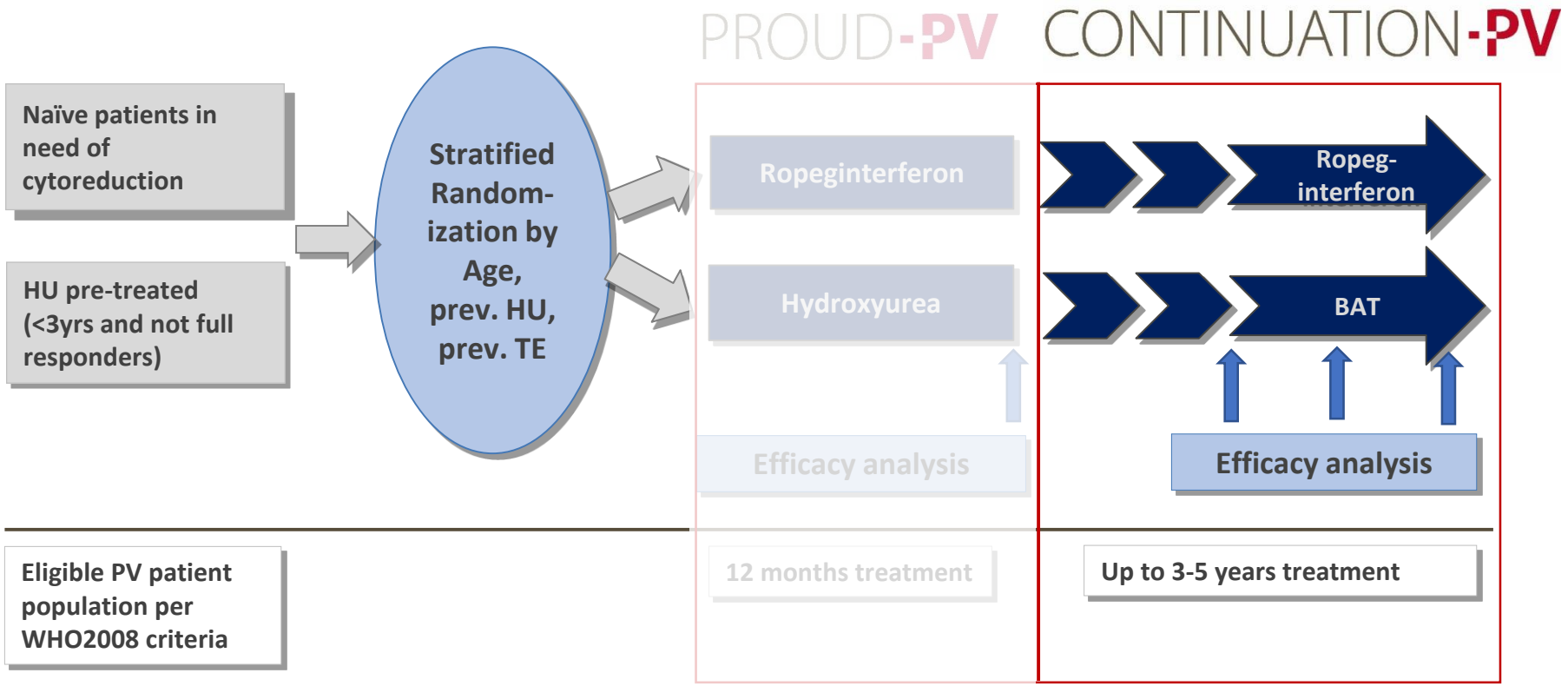
AE	AOP2014 (n=127) n (%)	HU (n=127) n (%)	P-value*
Endocrine disorders*	4 (3.1%)	1 (0.8%)	n.s.
Psychiatric disorders**	2 (1.6%)	0 (0.0%)	n.s.
Cardiac/Vascular disorders***	4 (3.1%)	2 (1.6%)	n.s.
Tissue disorders****	2 (1.6%)	0 (0.0%)	n.s.

* Fisher's exact test
s. significant
n.s. not significant (p>0.05)

* Autoimmune thyroiditis, Hypo-/Hyperthyroidism
** Anxiety, Depression, Mood altered
*** Major cardio-vascular events within different System organ classes (cardiac failure, thrombotic event, stroke)
**** Rheumatoid arthritis, psoriasis

Courtesy of H.Gisslinger

Ropeginterferon alfa-2b phase III development: PROUD/CONTI-PV



Courtesy of H.Gisslinger

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MPD-RC 112

WHO 2008 ET/PV
(n = 168)

High risk:
> 60 yr
thrombosis
thrombocytosis
symptomatic spleen
uncontrolled CV RF

Diagnosis < 5 years

Treatment naive

planned analyis
75 subjects treated
for 1 year

HU n=39

HU n=86

Interim analysis

PEG n=36

PEG n=82

Final analysis to be
Completed once
all subjects enrolled
For 1 year

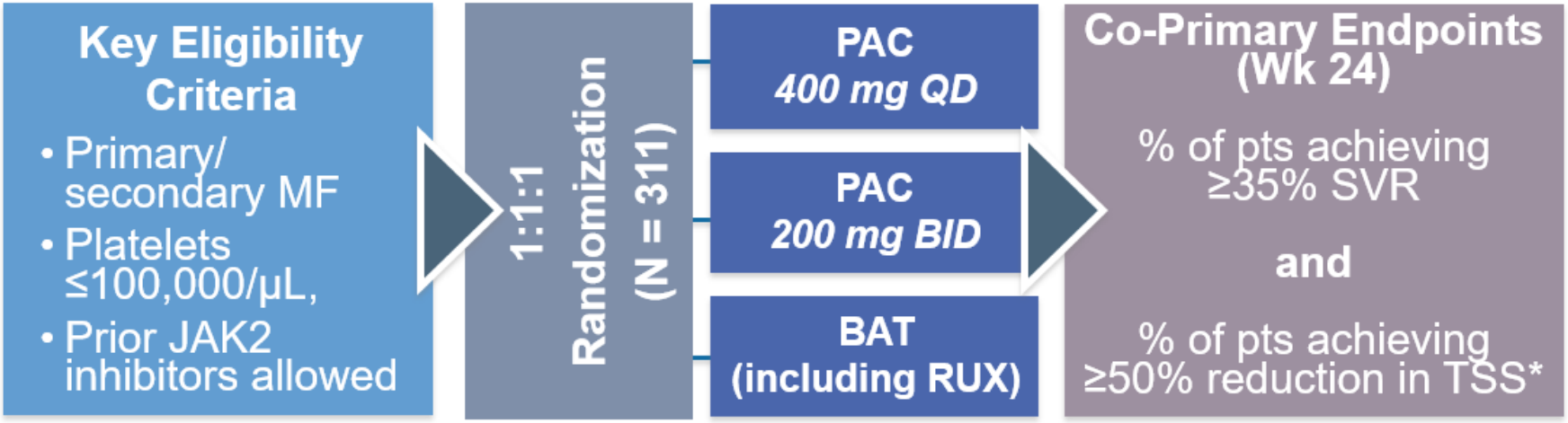
(anticipated date
30 JUN 2017)

Primary endpoint: CHR at 12 months of therapy

MPD-RC 112: overall RR at 12M by treatment arm

	HU (n=39)			PEG (n=36)			P value
	PR n (%)	CR n (%)	ORR n (%)	PR n (%)	CR n (%)	ORR n (%)	
Entire cohort (n=75)	14 (36)	13 (33)	27 (69)	19 (53)	10 (28)	29 (81)	*0.6 **
ET (n=31)	4/16 (25)	7/16 (44)	11/16 (69)	6/15 (40)	6/15 (40)	12/15 (80)	*0,8*
PV (n=44)	10/23 (44)	6/23 (26)	16/23 (70)	13/21 (62)	4/21 (19)	17/21 (81)	*0,6*

PERSIST-2 Phase 3 Study Design



*TSS, total symptom score by MPN-SAF 2.0

- Crossover from BAT allowed after progression (any time) or at Wk 24

- **Study Objectives:**
  - Primary: efficacy of pooled QD and BID PAC vs BAT
  - Secondary: efficacy of QD PAC or BID PAC separately vs BAT

Courtesy of J.Mascarenhas

 # LBA-5

Efficacy Summary

Endpoint	Statistics	PAC QD+BID (n=149)	PAC QD (n=75)	PAC BID (n=74)	BAT (n=72)
Patients with ≥35% SVR from BL to Wk 24	n (%)	27 (18.1)	11 (14.7)	16 (21.6)	2 (2.8)
	95% CI*	12.3-25.3	7.6-24.7	12.9-32.7	0.3-9.7
	P value vs BAT	**0.001**	**0.017**	**0.001**	-
Patients with ≥50% reduction in TSS from BL to Wk 24	n (%)	37 (24.8)	13 (17.3)	24 (32.4)	10 (13.9)
	95% CI*	18.1-32.6	9.6-27.8	22.0-44.3	6.9-24.1
	P value vs BAT	0.079	0.652	**0.011**	-

 # LBA-5

Courtesy of J.Mascarenhas

Serious TEAEs

	PAC QD n=104	PAC BID n=106	BAT n=98
Any SAE, n (%)	48 (46)	50 (47)	30 (31)
SAEs of interest, n (%)			
CHF	1 (1)	4 (4)	2 (2)
Atrial fibrillation	3 (3)	0	3 (3)
Cardiac arrest	2 (2)	0	0
Epistaxis	2 (2)	2 (2)	1 (1)
Subdural hematoma	2 (2)	0	0

10% 6% 6%

LBA-5

Courtesy of J.Mascarenhas

TAKE HOME MESSAGES

- TFR is a feasible and cost-saving strategy in CML-CP patients in different settings. Availability and implementation of a standardized and robust molecular monitoring is the 'conditio sine qua non'.

- The vast majority of TKI-discontinuation studies in CML show a TFR-rate reaching 50 - 60%. Prognostic factors for succesfull TFR are not consistent yet. A better knowledge of the kinetics of molecular recurrence is needed.

- Need for official clinical recommendations on TFR. Difficult because of he variety of the definitions for stopping and re-initiating treatment in the different TFR-trials and publications.

TAKE HOME MESSAGES (2)

- Data of prospective controlled trials of interferon therapy in MPN (PV/ET) were presented at ASH 2016. Ropeginterferon alpha-2b is non-inferior compared to hydroxurea in inducing CHR at 1 year of treatment and shows benefits over hydroxurea in safety and tolerability.

- Pacritinib does effectively reduces spleen volume and symptom burden in MF patients treated with prior JAK-inhibition. The prior safety concerns of the drug were not an issue in the truncated PERSIST-2 trial (truncation because of temporary FDA clinical hold).

Moving TFR into clinical practice

Criteria	Green	Yellow	Red
Institutional criteria met	Yes	–	No
Sokal score at diagnosis	Non-high	High	–
BCR-ABL transcript at diagnosis	Typical: B2A2 or B3A2 (e13a2 or e14a2)	Atypical, but can be accurately quantified	Not quantifiable
CML past history	CP only	Resistance or KD mutation	Prior AP or BC
Response to 1st-line TKI therapy	Optimal	Warning	Failure
Duration of all TKI therapy	> 8 years	3–8 years	< 3 years
Depth of deep molecular response	MR4.5	MR4.0	Not in MR4.0
Duration of deep molecular response monitored in a standardized laboratory	> 2 years	1–2 years	< 1 year

Hughes and Ross. Blood 2016.