New Drugs in Hematology

Bologna
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Nilotinib-based treatments and ABL001

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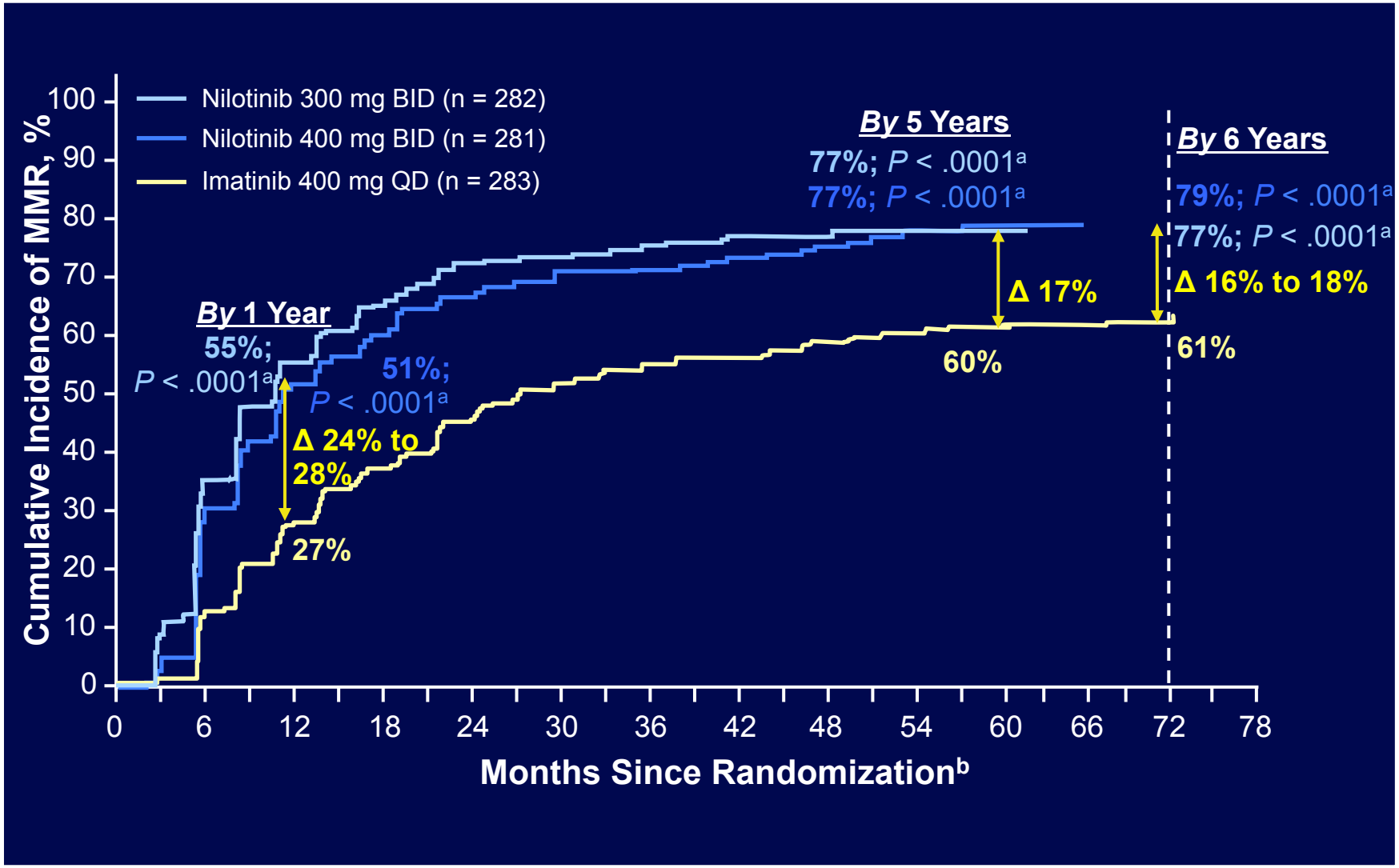
Disclosures of Fausto Castagnetti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board
Novartis	No	No	**Yes**	No	**Yes**	**Yes**
BMS	No	No	**Yes**	No	**Yes**	**Yes**
ARIAD	No	No	**Yes**	No	**Yes**	**Yes**
Pfizer	No	No	**Yes**	No	**Yes**	**Yes**

Cumulative Incidence of MMR



Larson RA, et al. *Blood*. 2014:[abstract 4541]

Deaths Due to CML and Overall Survival

	Nilotinib 300 mg BID (n = 282)	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg QD (n = 283)
Progression on study, n	11	6	21
Deaths due to advanced CML, n	6	4	16
KM-estimated 6-year freedom from death due to advanced CML (95% CI), %	**97.7** (96.0-99.5)	**98.5** (97.1-100)	**93.9** (91.0-96.8)
Nominal *P* value vs imatinib	**.0302**	**.0061**	**–**
Total deaths on study, n[a]	21	11	23
KM-estimated 6-year OS on study (95% CI), %	**91.6** (88.0-95.1)	**95.8** (93.4-98.2)	**91.4** (88.0-94.7)
Nominal *P* value vs imatinib	**.7085**	**.0314**	**–**

[a] Death from any cause at any time (during study treatment or during post-treatment follow-up).

Larson RA, et al. *Blood*. 2014:[abstract 4541]

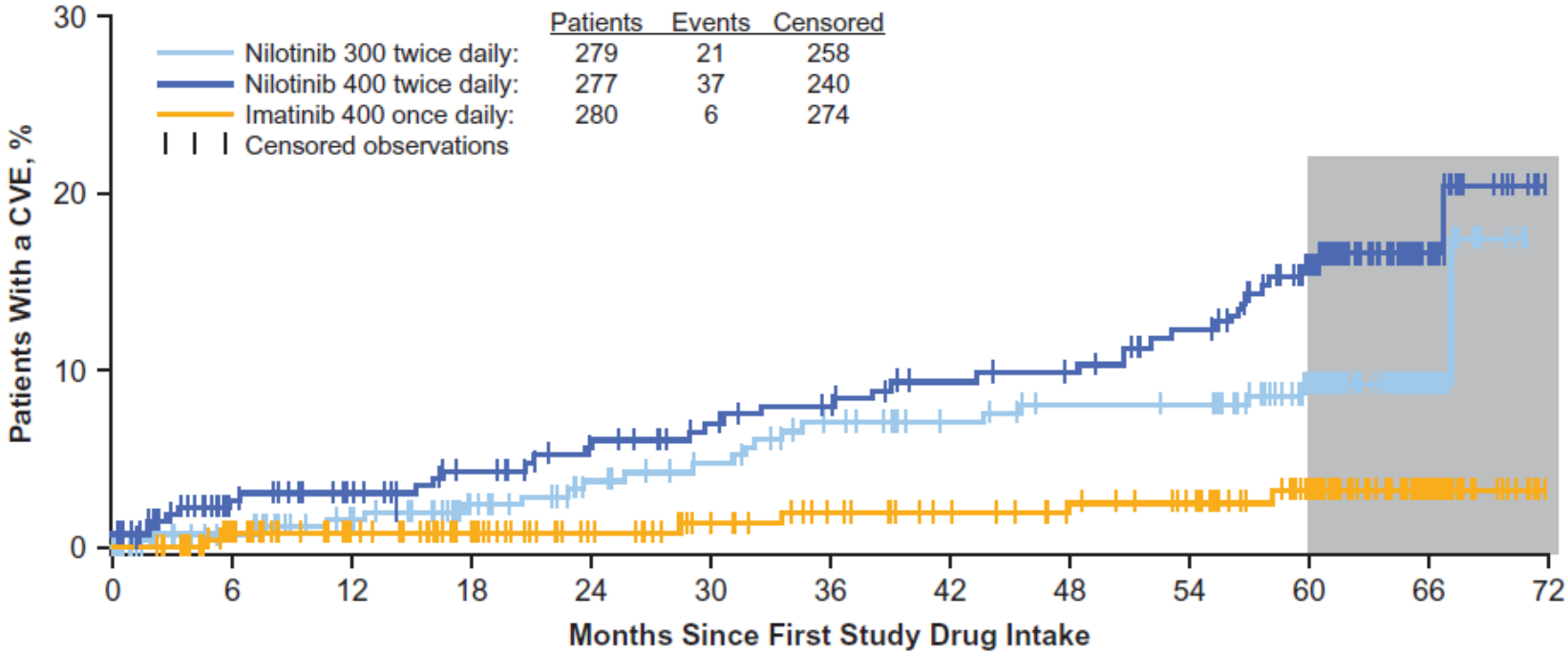
NILOTINIB
Metabolic effects and cardiovascular events

Hyperglycemia

Hypercholesterolemia (both LDL and HDL fractions)

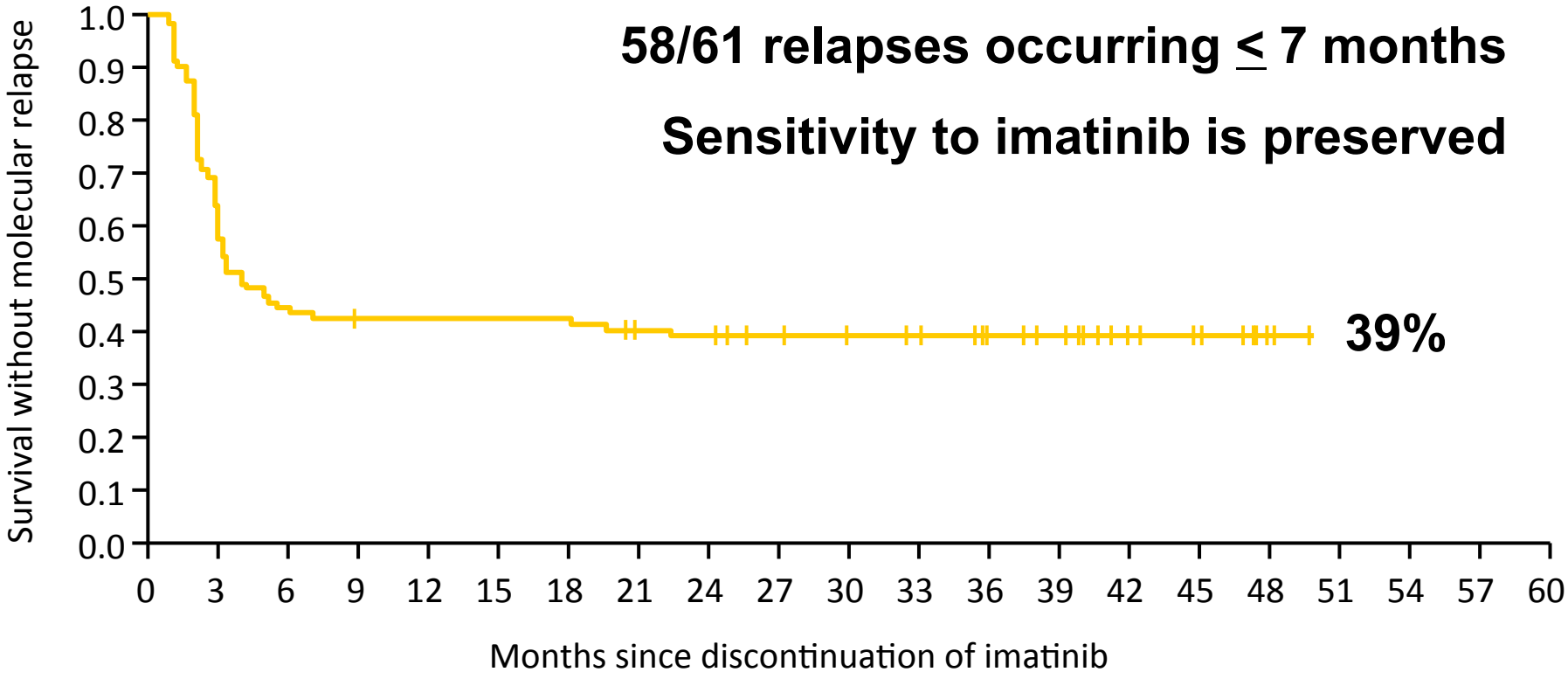
Higher incidence of CV AEs (arterial thrombosis)

Time to first cardiovascular event



GIMEMA 0811 study - Castagnetti F et al. EHA 2015
ENESTnd study - Hochhaus A et al. Leukemia. 2016; 30:1044-54

Emerging treatment goal: Treatment-free remission



Mahon et al. Blood (ASH) 2011; 118: Abstract 603

Deep Molecular Response is the first step to attempting Treatment Discontinuation

Depth of response at discontinuation

	Study	Median Time Off Treatment, mo	N	Patients Relapsing, %[a] (0 – 50 – 100)
CCyR or MCyR	Korea study[1]	7	11	100
	Hammersmith[2]	9	4	100
≥ MMR	STOP study[3]	4-9	12	83
≥ MR4	EURO-SKI[4]	6	200	39
	KID study[5]	3	28	32
	STOP 2G-TKI[6]	4	52	46
	A-STIM[7]	4	80	36
	KEIO STIM[8]	12	40	45
	STIM2[9]	12	124	39
	STIM1[10]	24	69	61
	CML8[11]	33	40	55
	TWISTER[12]	42	40	55

Studies requiring MR4/MR4.5 prior to stopping treatment have demonstrated improved sustained disease remission following treatment discontinuation[1-12]

1. Goh H-G, et al. *Leuk Lymphoma*. 2009;50(6):944-951; 2. Kuwabara A, et al. *Blood*. 2010;116(6):1014-1016; 3. Koskenvesa P, et al. *Eur J Haematol*. 2014;92(5):413-420; 4. Mahon FX, et al. *Blood*. 2014;124(21) [abstract 151]; 5. Lee SE, et al. *Am J Hematol*. 2013;88(6):449-454; 6. Rea D, et al. *Blood*. 2014;124(21) [abstract 811]; 7. Rousselot P, et al. *J Clin Oncol*. 2014;32:424-430; 8. Matsuki E, et al *Blood*. 2012;120(21) [abstract 2788]; 9. Mahon FX, et al. *Blood*. 2013;122(21) [abstract 654]; 10. Mahon FX, et al. *Lancet Oncol*. 2010;11(11):1029-1035; 11. Ross M, et al. *Haematologica*. 2012;97(s1):74 [abstract 0189]; 12. Ross DM, et al. *Blood*. 2013;122(4):515-522.

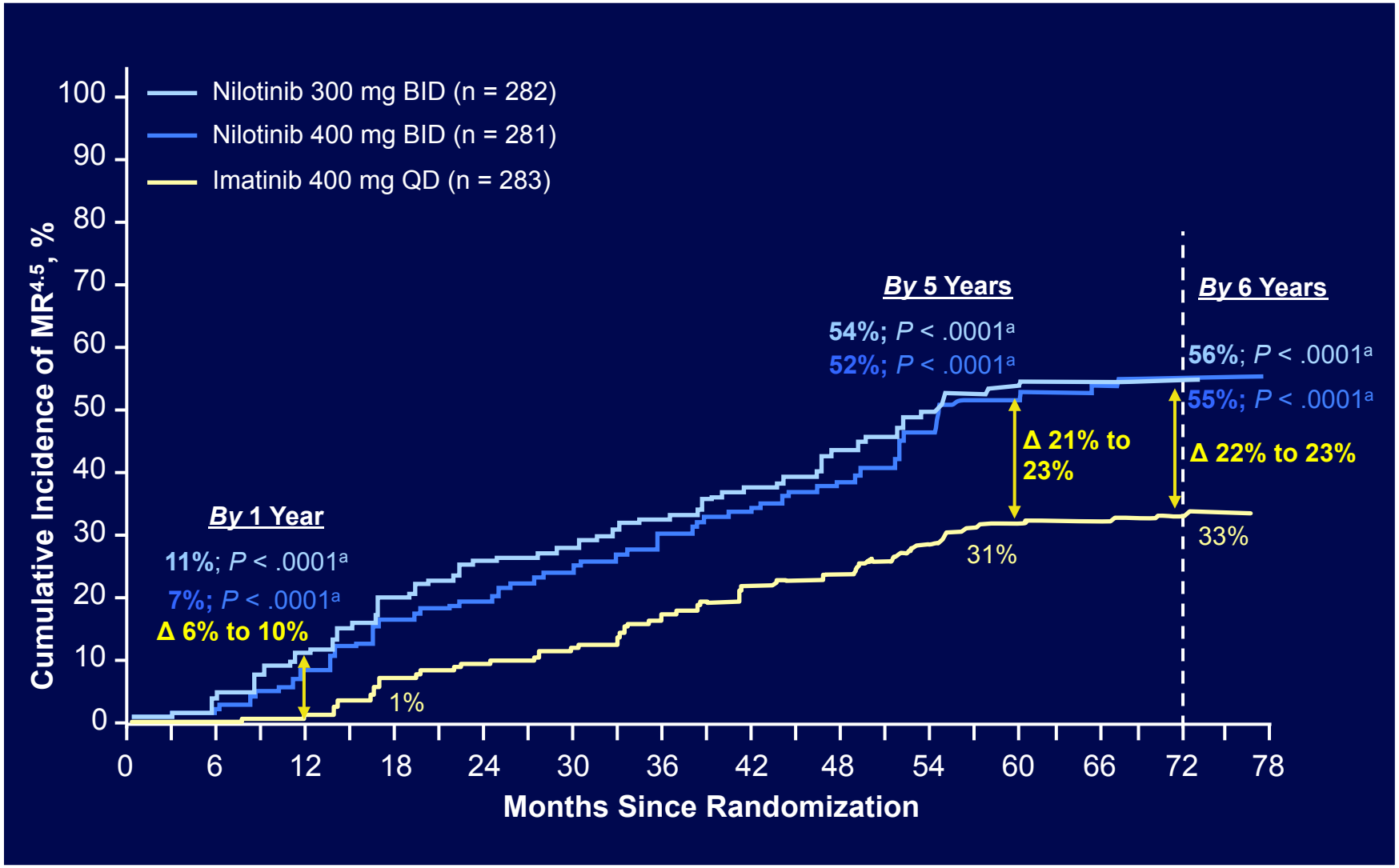
Is Nilotinib able to improve the rate of stable deep molecular response?

We don’t know yet

Is Nilotinib able to improve the rate of stable deep molecular response?

- **Frontline Nilotinib**

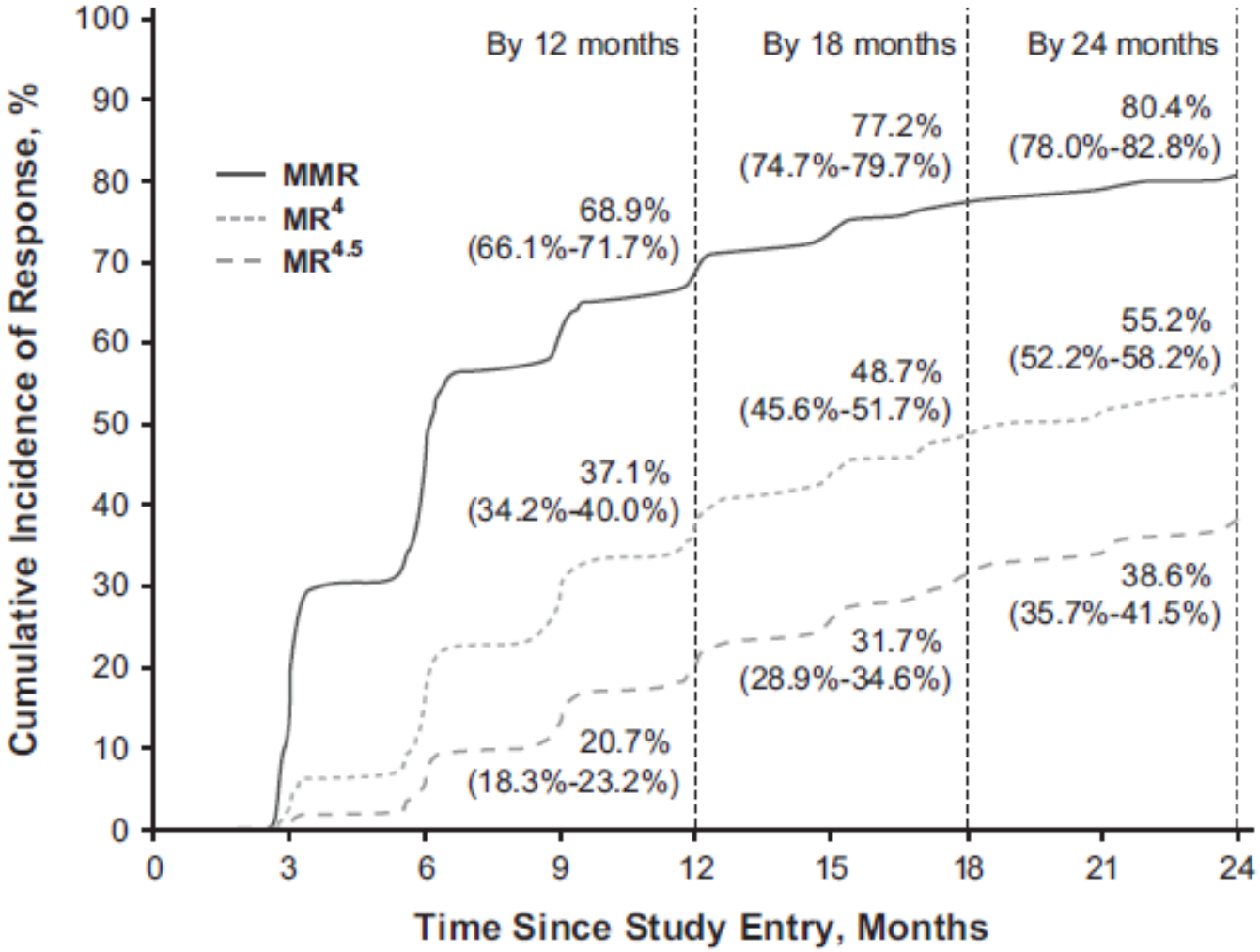
Cumulative Incidence of $MR^{4.5}$



Larson RA, et al. *Blood*. 2014:[abstract 4541]

ORIGINAL ARTICLE

Frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the European ENEST1st study

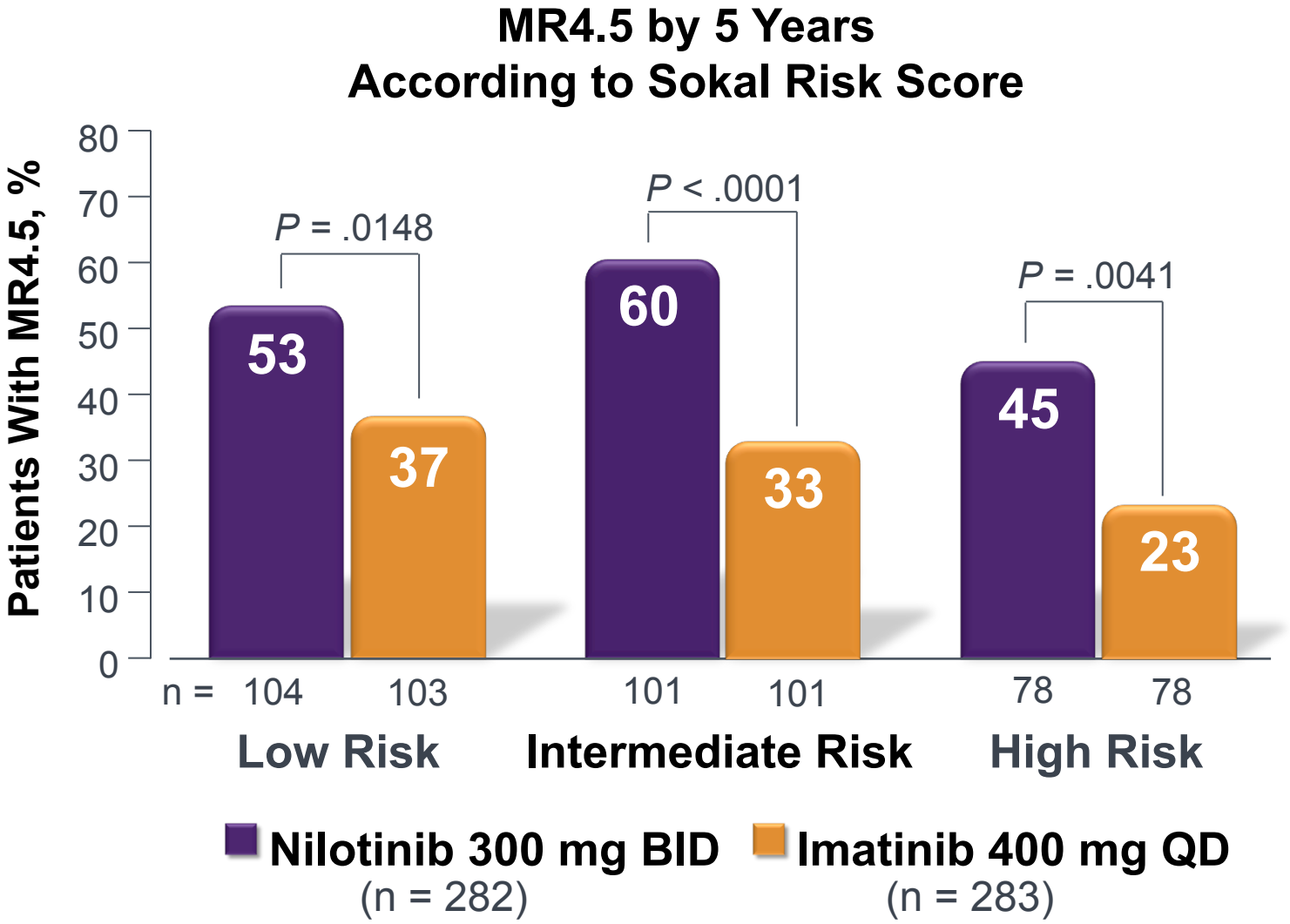


N = 1089

ENEST1st: 2-year results

Hochhaus A et al. Leukemia. 2016; 30:57-64

Rates of MR4.5 by 5 Years Were Higher With Nilotinib vs Imatinib Regardless of Sokal Risk Score



ENESTnd: 5-year update

Hochhaus A et al. Leukemia. 2016; 30:1044-54

Durability of deep molecular responses:
ENESTnd

	Nilotinib 300mg BID N=282	Nilotinib 400mg BID N=281	Imatinib 400mg QD N=283
Patients with MR4.5 at anytime, n(%)	56.4%	56.2%	33.9%
Estimated durability of responses,%			
MR4.5 sustained for ≥ 1 year	81.5%	84.3%	84.4%
MR4.5 sustained for ≥ 2 years	73.1%	77.8%	76.9%
MR4.5 sustained for ≥ 3 years	66.3%	76.7%	70.6%

Hypothesis: TKI cessation Attempt if ≥ 2 years of MR4.5 → 41% | 43.7% | 26%

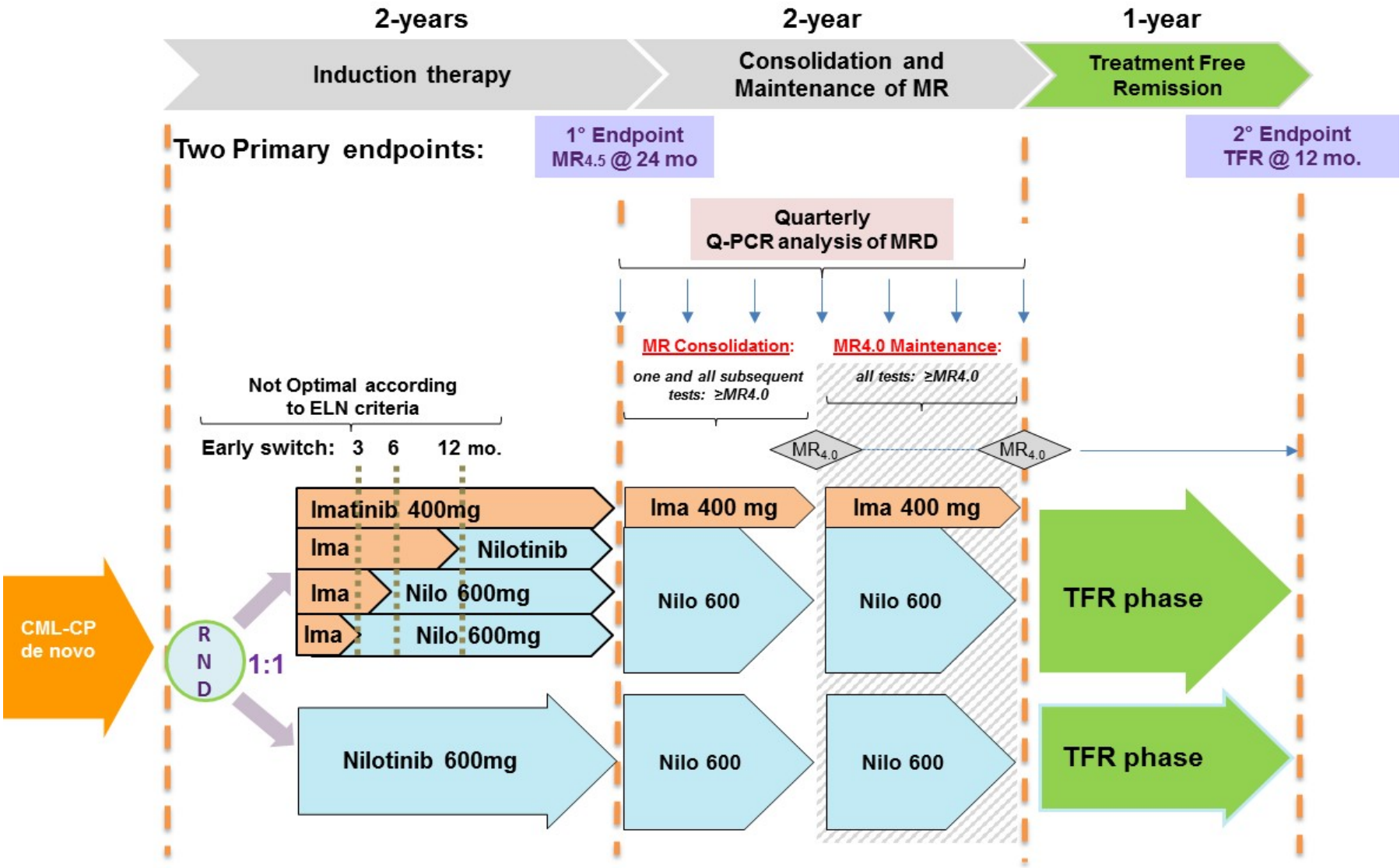
Hypothesis: ~ 50% TFR success rate (loss of MMR as relapse definition) → 20.5% | 21.6% | 13%

Hochhaus et al. ASH Annual Meeting 2015. Abstract 2781.

DR

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche.

SUSTRENIM Study

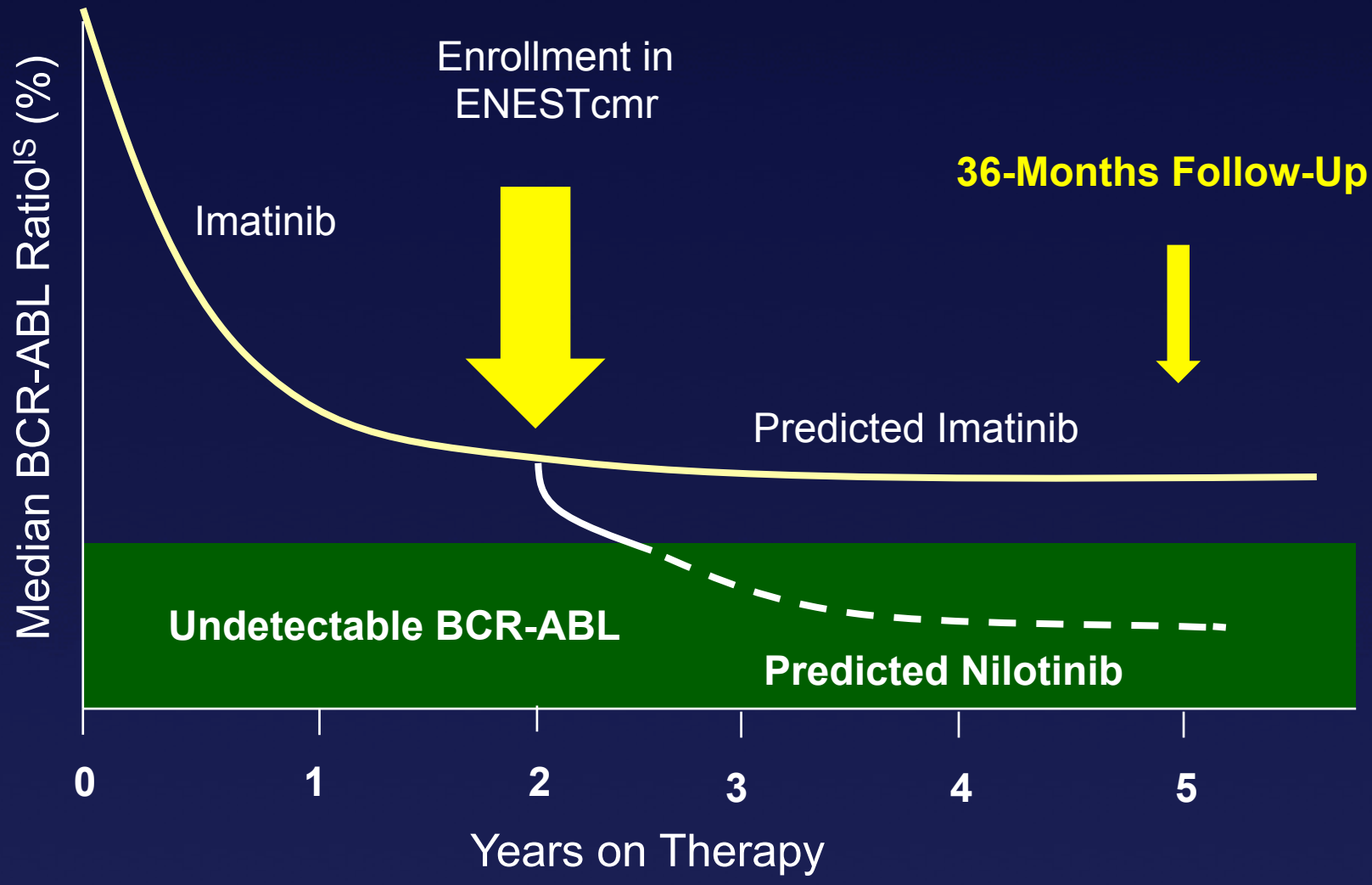


Is Nilotinib able to improve the rate of stable deep molecular response?

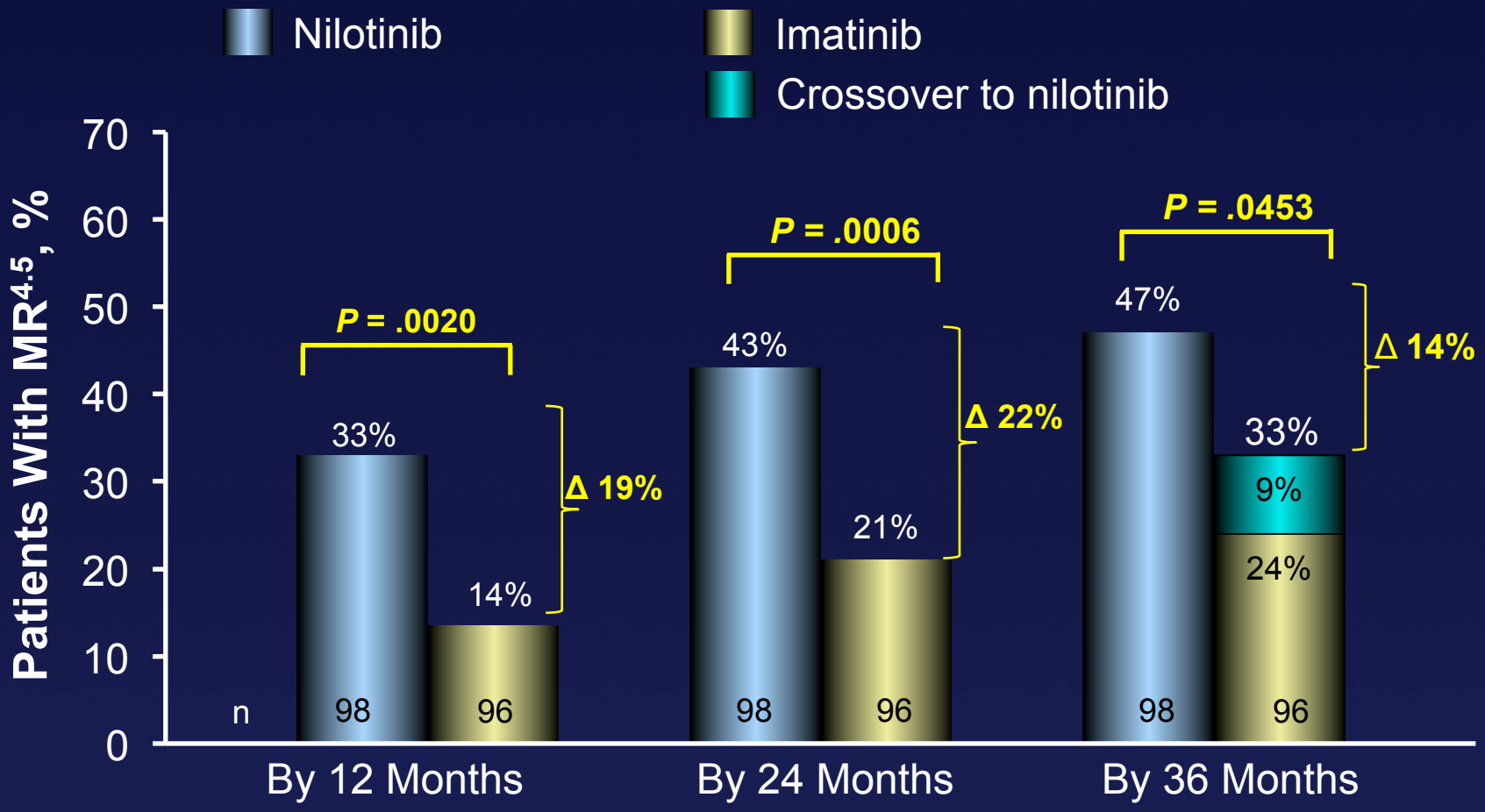
- Frontline Nilotinib

- **Switch to Nilotinib in absence of deep molecular response**

ENESTcmr Hypothesis



Cumulative Incidence of $MR^{4.5}$ in Patients Without $MR^{4.5}$ at Baseline (ITT analysis)



- In a subgroup analysis when only responses up to crossover were counted, 47% versus 24% of patients in the nilotinib and imatinib arms, respectively, achieved $MR^{4.5}$ (*P* = .0003)

Leber B, et al. Blood. 2013:[abstract 94].

Review Article

European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013

Michele Baccarani,[1] Michael W. Deininger,[2] Gianantonio Rosti,[3] Andreas Hochhaus,[4] Simona Soverini,[3] Jane F. Apperley,[5] Francisco Cervantes,[6] Richard E. Clark,[7] Jorge E. Cortes,[8] François Guilhot,[9] Henrik Hjorth-Hansen,[10] Timothy P. Hughes,[11] Hagop M. Kantarjian,[8] Dong-Wook Kim,[12] Richard A. Larson,[13] Jeffrey H. Lipton,[14] François-Xavier Mahon,[15] Giovanni Martinelli,[3] Jiri Mayer,[16] Martin C. Müller,[17] Dietger Niederwieser,[18] Fabrizio Pane,[19] Jerald P. Radich,[20] Philippe Rousselot,[21] Giuseppe Saglio,[22] Susanne Saußele,[17] Charles Schiffer,[23] Richard Silver,[24] Bengt Simonsson,[25] Juan-Luis Steegmann,[26] John M. Goldman,[27] and Rüdiger Hehlmann[17]

outside of clinical trials. Treatment discontinuation may be considered in individual patients, also outside studies, if proper, high-quality, and certified monitoring can be ensured at monthly intervals. This is particularly relevant to fertile women who may have achieved an optimal response, because conception and pregnancy are contraindicated during TKI treatment. In these patients, when the optimal response is stable for at least 2 years, TKI discontinuation with or without the use of rIFNα, can be considered, after informed consent and with very frequent molecular monitoring.

Is Nilotinib able to improve the rate of stable deep molecular response?

- Frontline Nilotinib
- Switch to Nilotinib in absence of deep molecular response
- **Nilotinib plus alpha-interferon**

IFN-α Immune System Activities

Innate Immunity

NK cell
- ↑-proliferation
- ↑-cytolytic activity
- ↑-secretion of IFN-γ
- ↑-trafficking

↑LAK activity

↑Priming activity for IL-2, IFN-γ

Adaptive Immunity

CD4+ T-cell
- ↑-Dendritic cell secretion of IFN-γ
- ↑-balance of Th1 vs Th2
- ↑-trafficking

CD8+ T-cell
- ↑-CTL activity
- ↑-bystander stimulation of memory
- ↑-response to MHC Class I presentation
- ↑-trafficking

B-cell
- ↑-IgG secretion
- ↓-IgE secretion
- ↑-trafficking

Macrophage
- ↑-Ag-dependent cytotoxicity
- ↑-differentiation
- ↑-secretion of IFN-γ
- ↑-NO activity

↑MHC Class I Expression

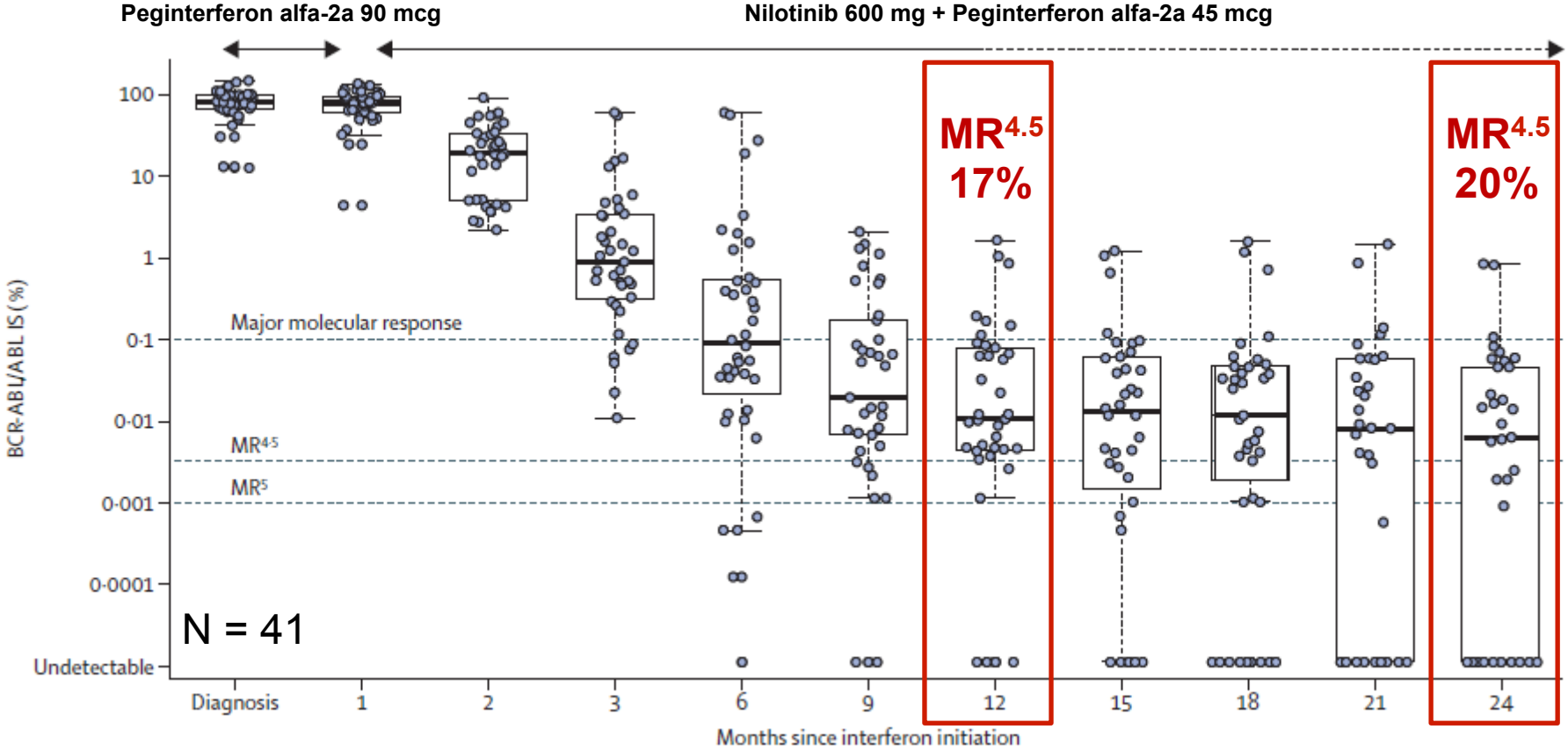
↑MHC Class II Expression

↓Antigen-Stimulated Hypersensitivity

↓Neutrophil activation

↑Up-regulated
↓Down-regulated

Nilotinib and peginterferon alfa-2a for newly diagnosed chronic-phase chronic myeloid leukaemia (NiloPeg): a multicentre, non-randomised, open-label phase 2 study

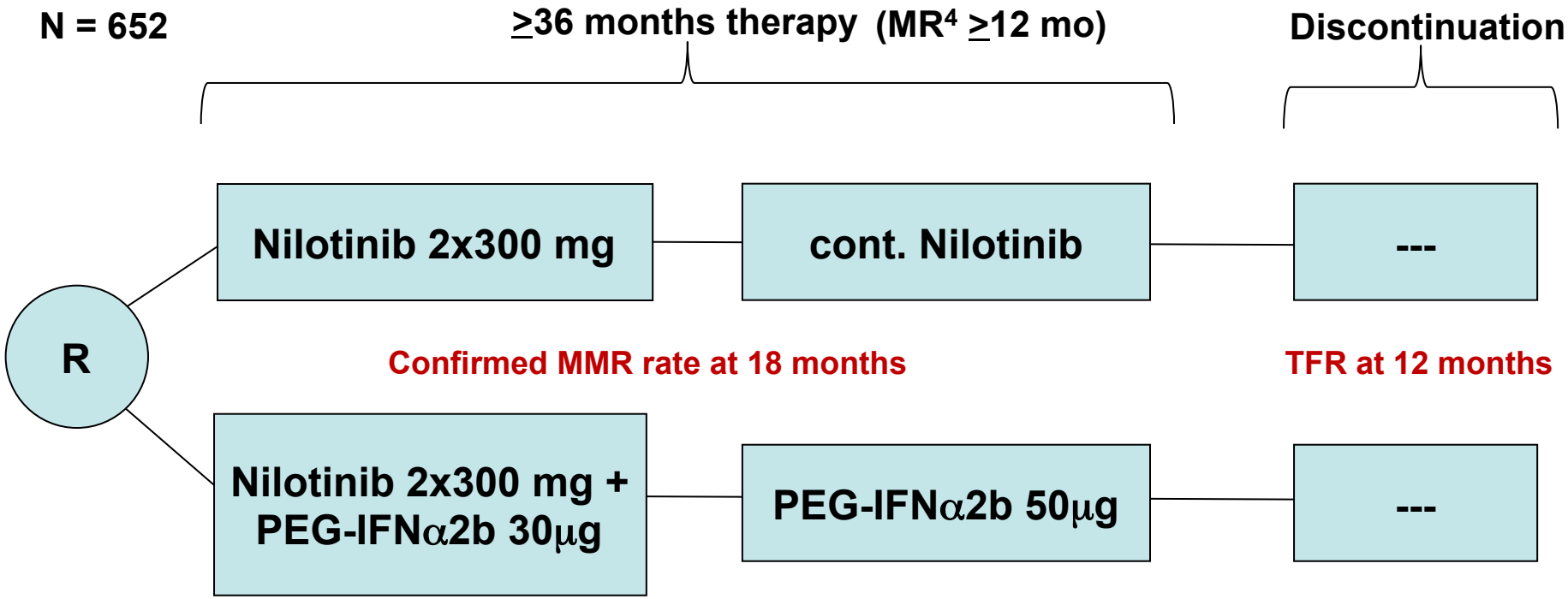


Patients on IFN: 74% at 12 months; 29% at 24 months
Grade 3-4 Hematologic or Non Hematolgic AEs: 68% by 24 months

Nicolini FE et al. Lancet Haematol. 2015;2(1):e37-46

CML study V – TIGER study

TKIs + IFN in GERmany (NCT01657604)



Nilo intolerance -> Imatinib
Nilo resistance -> Transplantation/Dasatinib recommended
Suboptimal response: -> Nilotinib 400 mg BID

Induction therapy **Maintenance therapy** **Cure?**

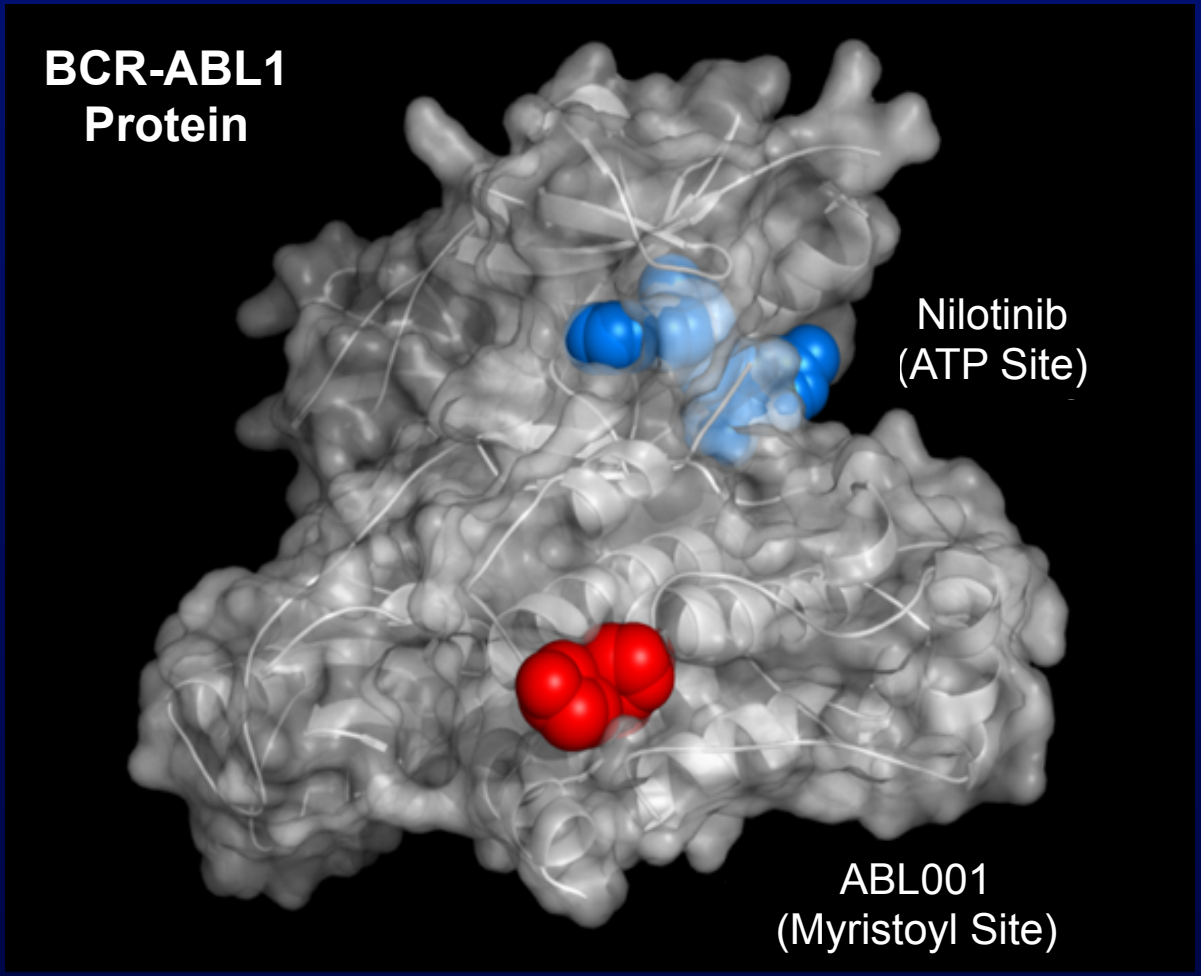
Courtesy of Andreas Hochhaus

Nilotinib – Take home messages

- Higher MMR rates, if compared with imatinib
- Lower number of leukemia-related deaths but no significant survival differences
- CV risk assessment to minimize the incidence and the consequences adverse events
- Higher deep molecular response (DMR) rates in all risk categories
- The benefit of nilotinib over imatinib in terms of stable deep MR and TFR has not been determined yet
- Should any other treatment be added to TKIs to increase the probability of TFR?

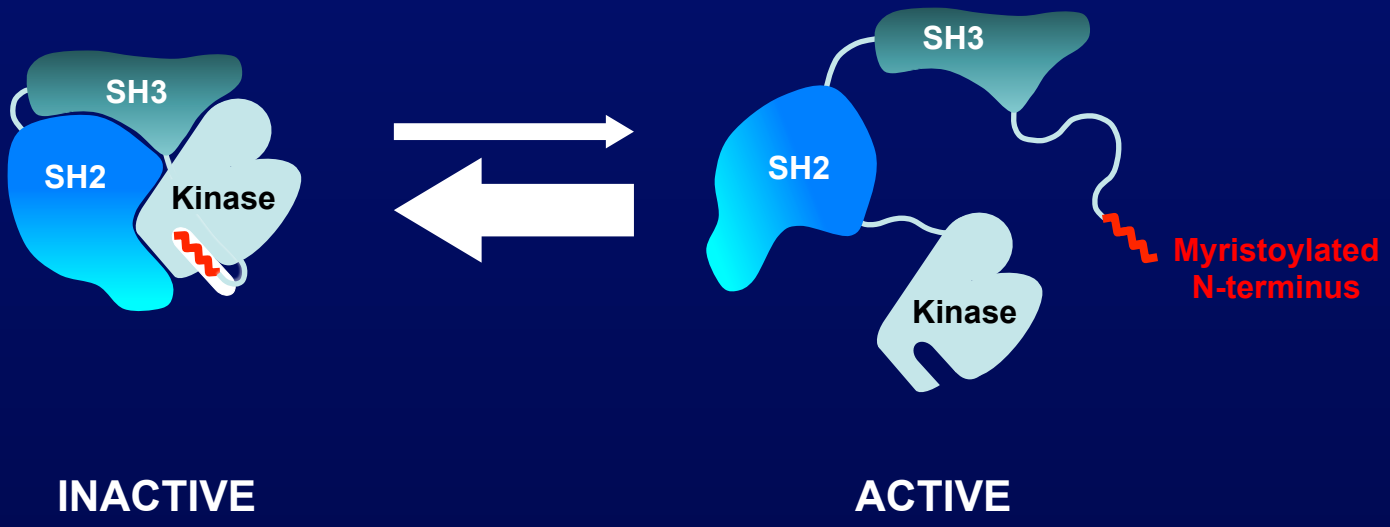
ABL001 Is a Potent, Specific Inhibitor of BCR-ABL1 With a Distinct Allosteric Mechanism of Action

- Developed to gain greater BCR-ABL1 inhibition, with activity against BCR-ABL1 mutations conferring resistance to TKIs
- Potential to combine with TKIs for greater pharmacological control of BCR-ABL1



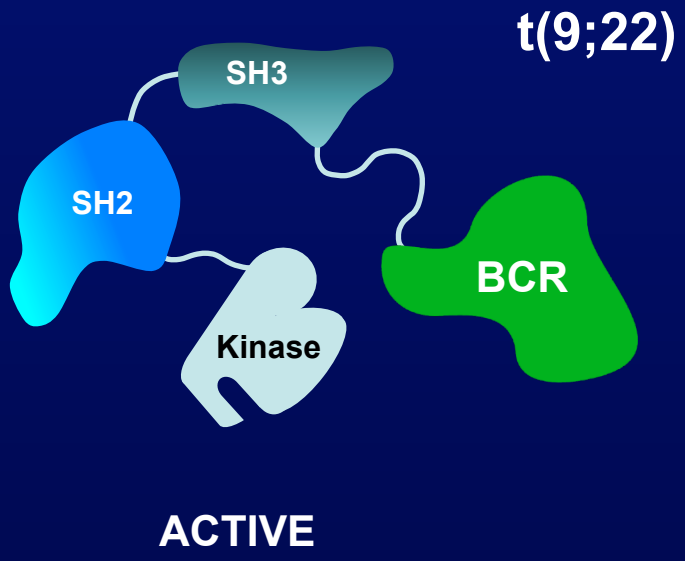
Ottmann O, et al. *Blood*. 2015:[abstract 138].

Autoinhibition of ABL1 by engagement of Myristoyl Binding Site (normal)



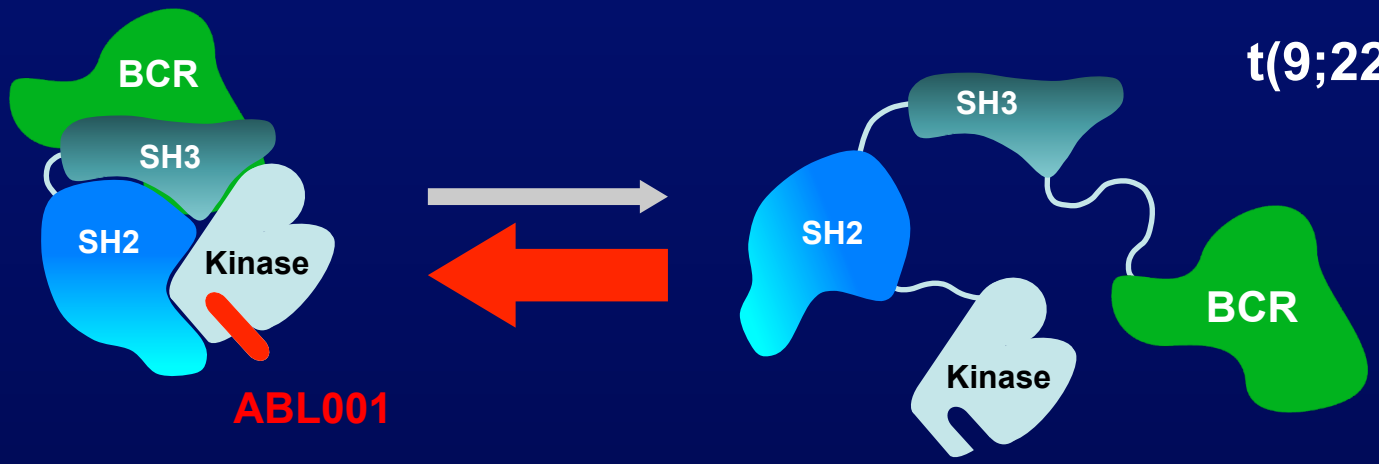
Ottmann O, et al. *Blood*. 2015:[abstract 138].

When fused with BCR, this regulatory element is lost (loss of ABL1 Autoinhibition)



Ottmann O, et al. *Blood*. 2015:[abstract 138].

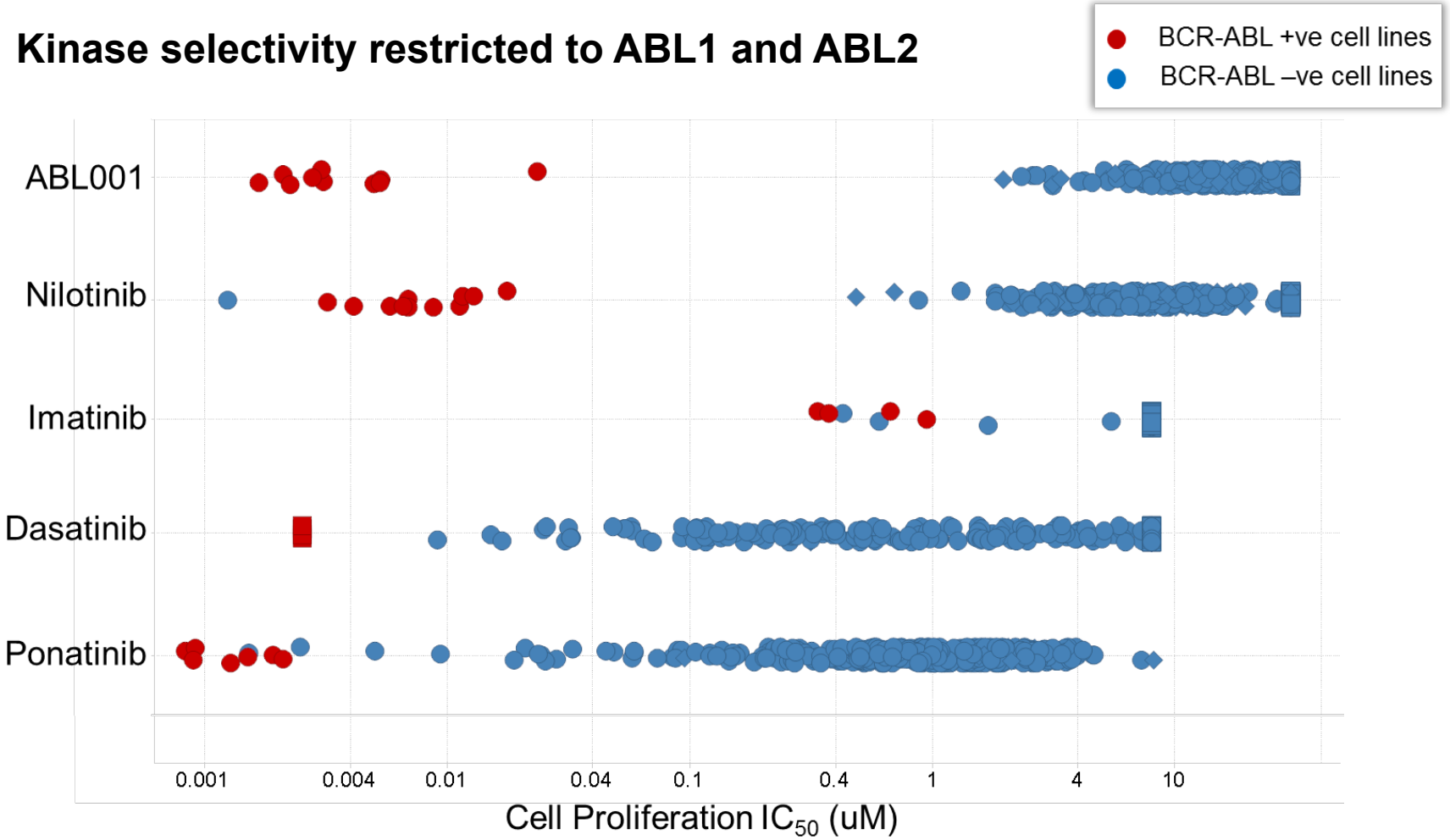
ABL001 functionally mimics myristoylated peptide by occupying its vacant binding site and restoring negative regulation



ABL001

Ottmann O, et al. *Blood*. 2015:[abstract 138].

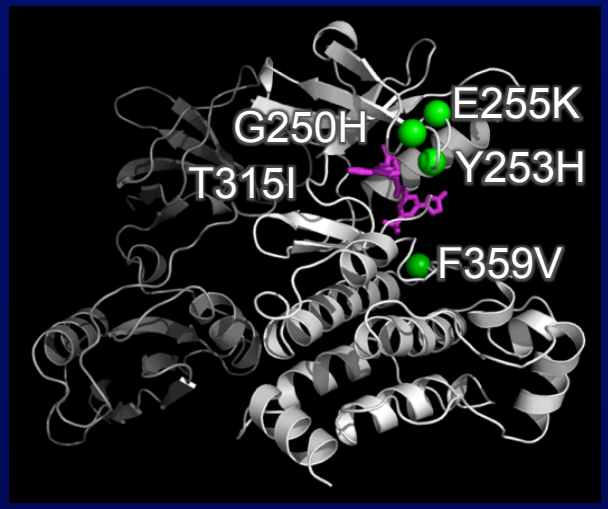
ABL001 selectively inhibits proliferation of cell lines expressing BCR-ABL



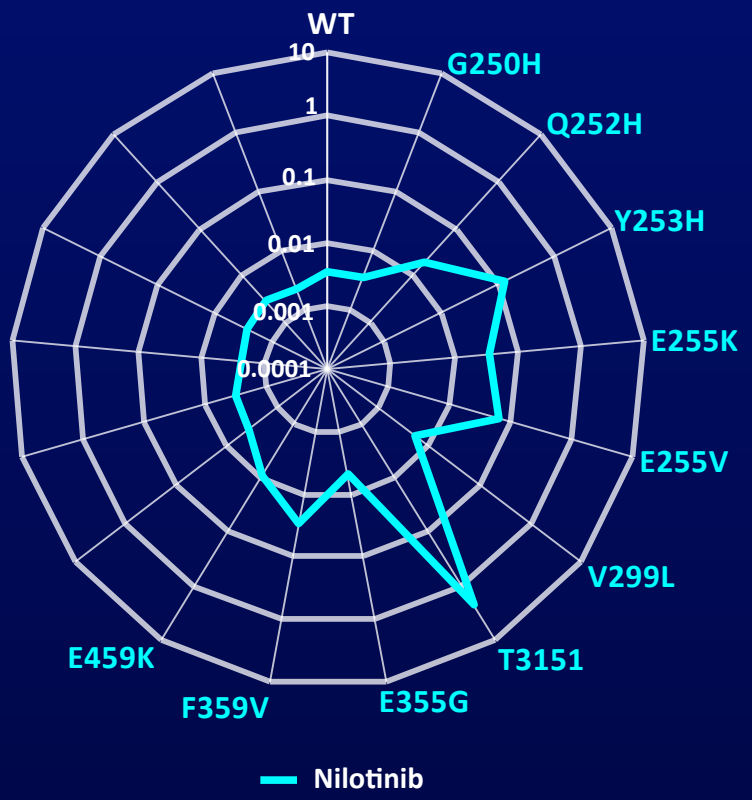
Wylie A, et al. *Blood*. 2014:[abstract 398].

ABL001 and Classical TKIs Exhibit Complementary Mutation Profiles

ATP Binding Site Mutations



Proliferation IC_{50} Profiles in Ba/F3 *BCR-ABL1*–Mutant Lines



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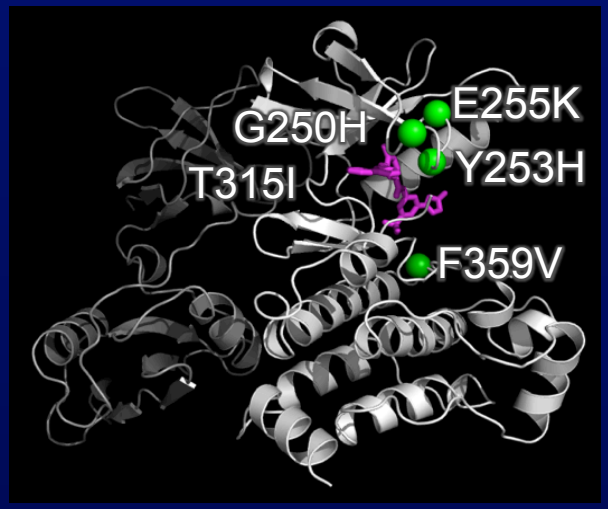
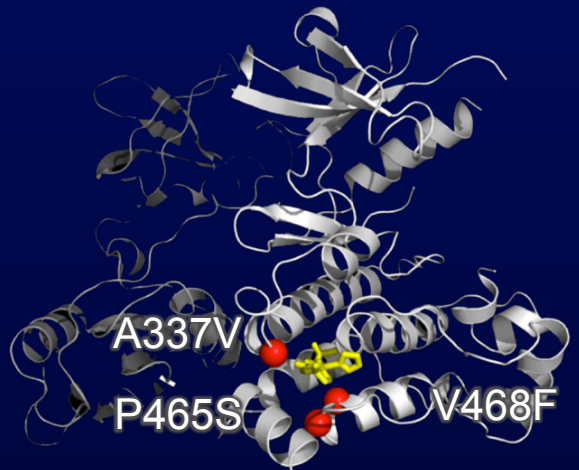


Myristoyl Binding Site Mutations



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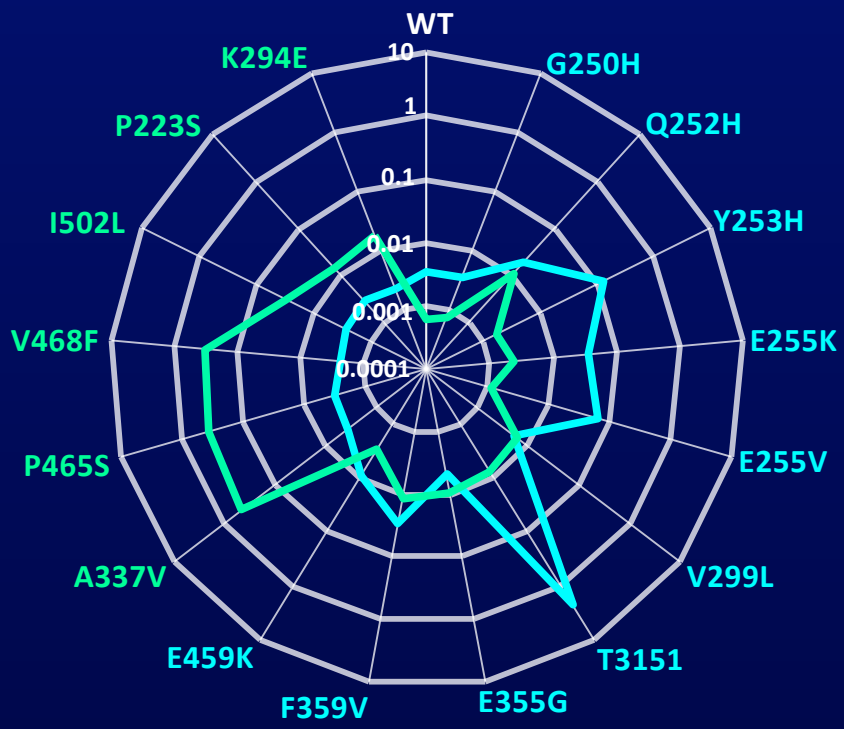


Nilotinib

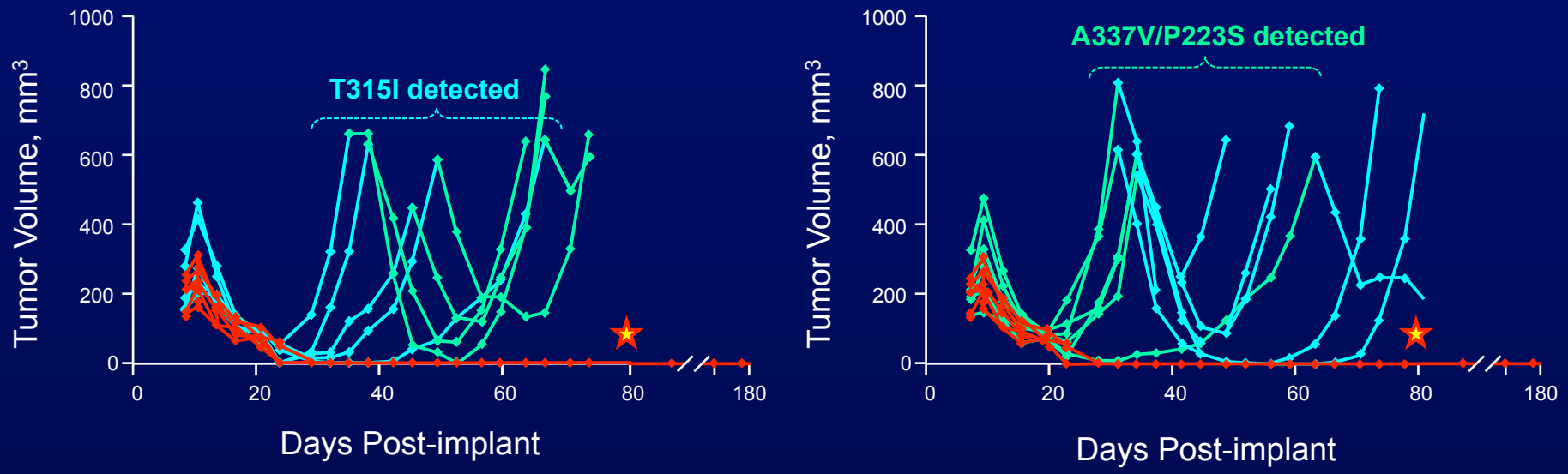
ABL001

ATP binding site mutations

Myristoyl binding site mutations

Ottmann O, et al. *Blood*. 2015:[abstract 138].

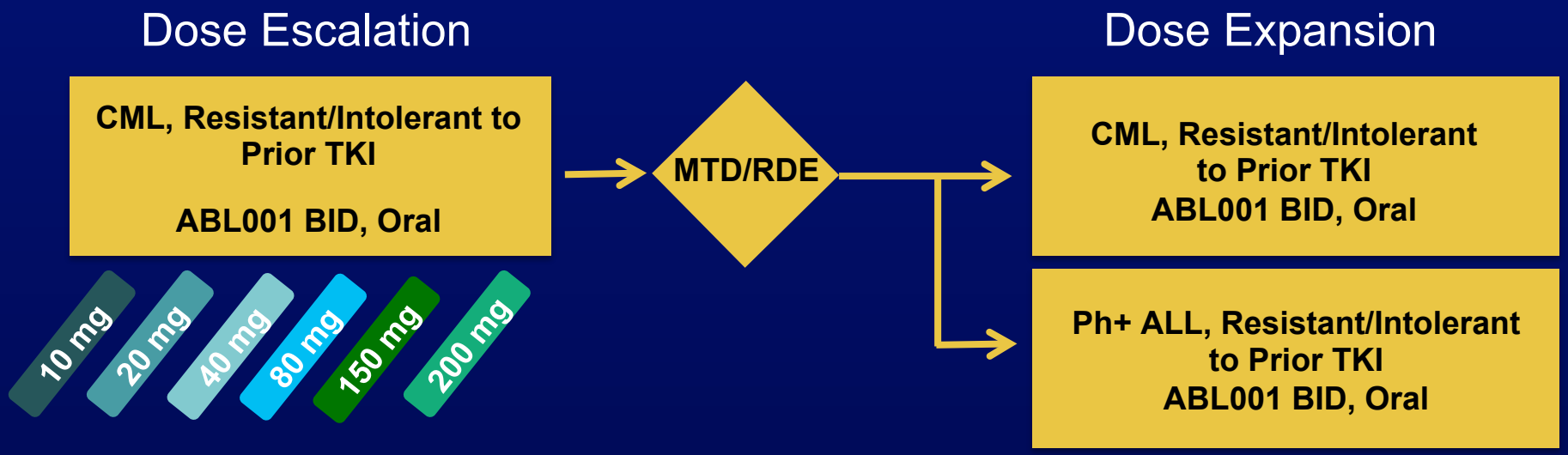
Combination of ABL001 and Nilotinib Prevents the Emergence of Resistance (KCL-22 CML Xenograft)[a]



[a] Each line represents individual animals.

Ottmann O, et al. *Blood*. 2015:[abstract 138].

ABL001X2101: Study Design (NCT02081378)
A multicenter, phase 1, first-in-human study



- **Primary outcome:** estimation of MTD/RDE
- **Secondary outcomes:** safety, tolerability, preliminary anti-CML activity, pharmacodynamics, pharmacokinetic profile

Ottmann O, et al. *Blood*. 2015:[abstract 138].

ABL001X2101: Study Design
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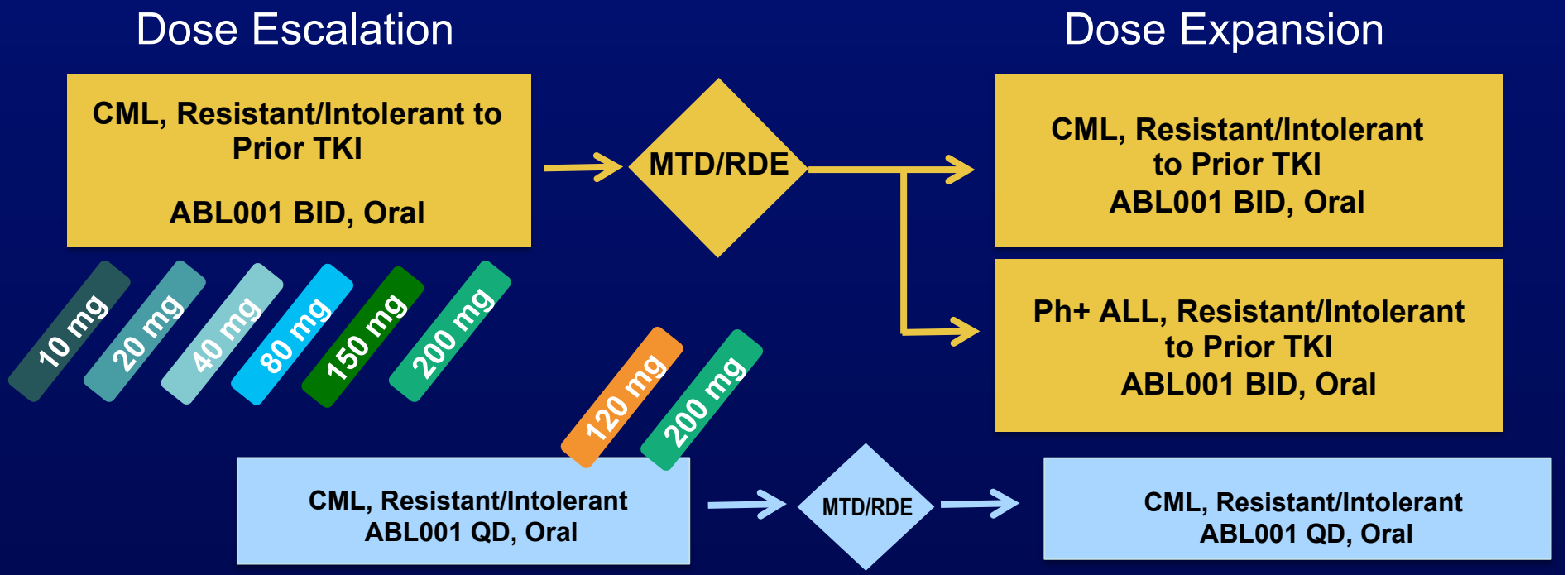

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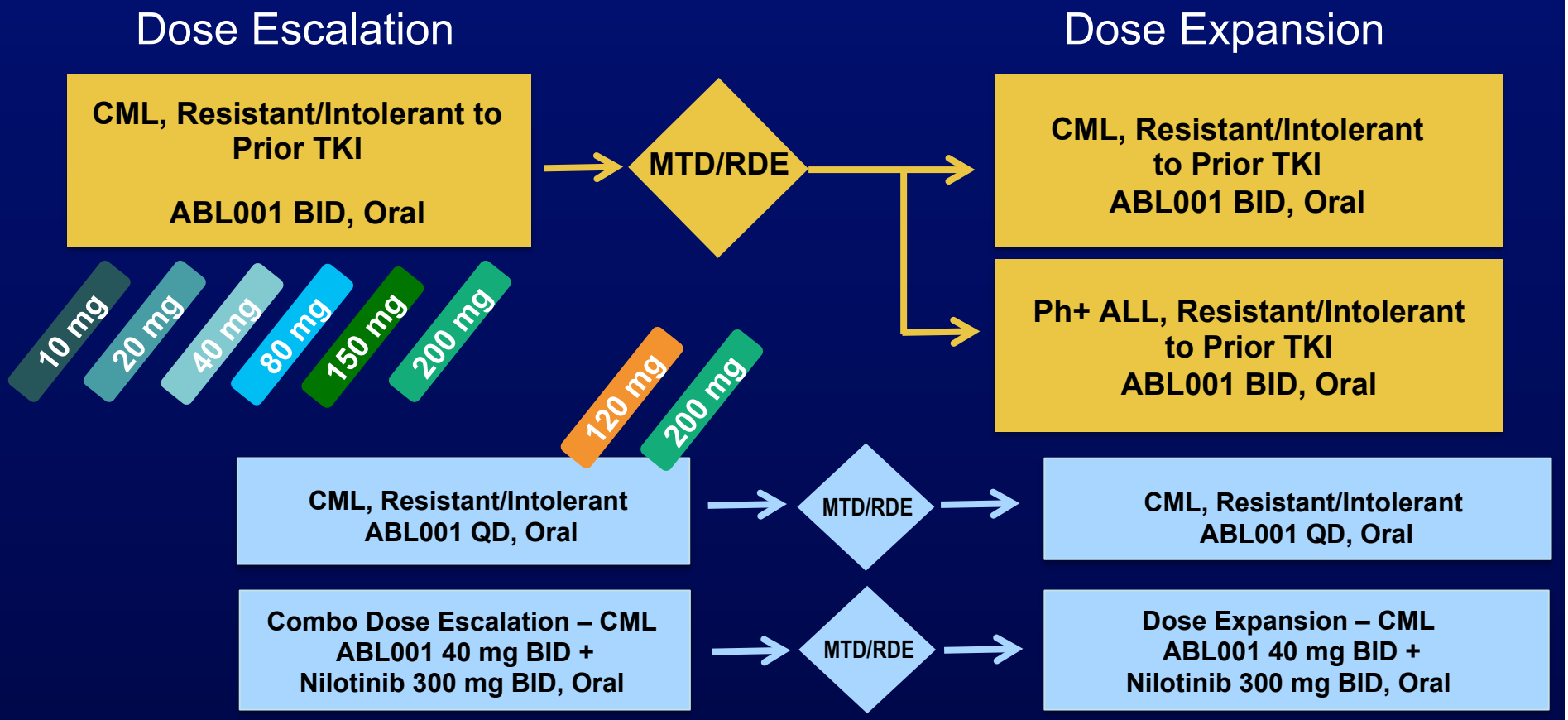

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Ottmann O, et al. *Blood*. 2015:[abstract 138].

Demographics and Baseline Characteristics

	N = 59
Median age (range), years	**56** (23 - 78)
Male / female, n (%)	**36** (61) / **23** (39)
ECOG 0 / 1 or 2, n (%)	**58** (98) / **1** (2)
Prior lines of therapy, median (range)	**3.5 (2-5)**
2 prior TKIs, n (%)	**24 (41)**
≥ 3 prior TKIs, n (%)	**35 (59)**
Resistant to prior TKI, n (%)	**45 (76)**
Intolerant to prior TKI, n (%)	**14 (24)**
CML-CP / -AP, n (%)	**58 (98) / 1 (2)**
TKD nonmutated / mutant / not evaluable, n (%)	**18 (31) / 14 (24) / 27 (46)**

Ottmann O, et al. *Blood*. 2015:[abstract 138].

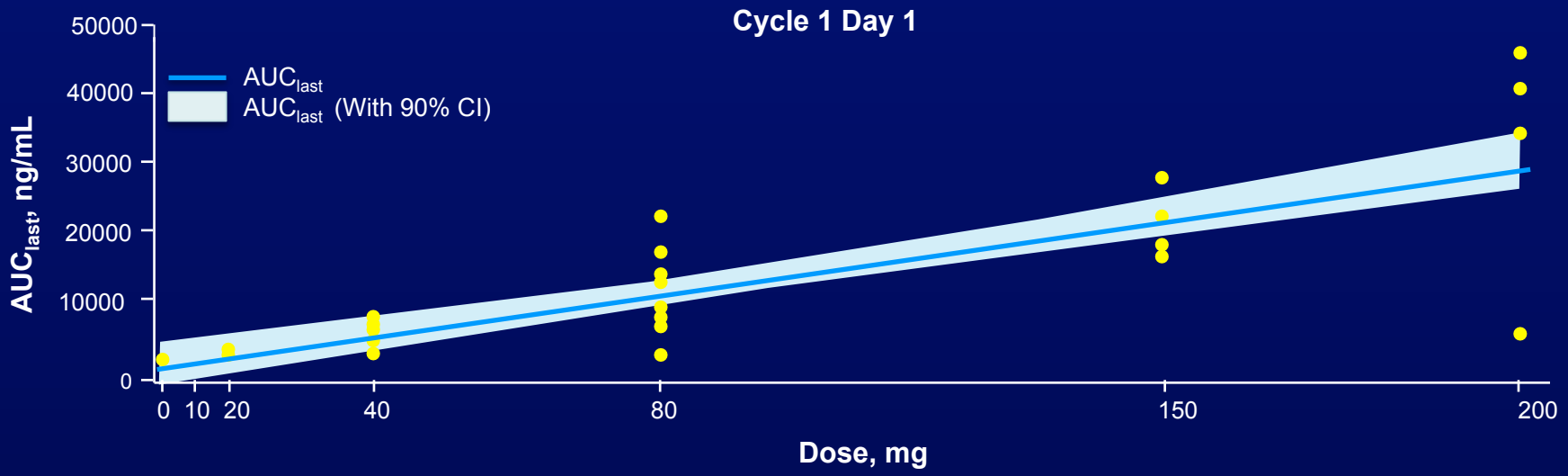
Patient Disposition

	Monotherapy BID						Monotherapy QD		Nilo + ABL BID	Total
mg	10	20	40	80	150	200	120	200	300 + 40	
n	1	5	12	12	8	5	5	6	5	59
Median duration of exposure, weeks	49	67.3	45.4	38.6	28.6	25.1	26	9.8	6.3	26.3
Ongoing, n (%)	0	5 (100)	10 (83)	10 (83)	5 (63)	3 (60)	5 (100)	6 (100)	5 (100)	49 (83)
Discontinued, n (%)	1 (100)	0	2 (17)	2 (17)	3 (38)	2 (40)	0	0	0	10 (17)
Reason for discontinuation, n (%)										
AE	1 (100)	0	1 (8)	2 (17)	2 (25)	1 (20)	0	0	0	7 (12)
Withdrew consent	0	0	0	0	1 (13)	1 (20)	0	0	0	2 (3)
Disease progression	0	0	1 (8)	0	0	0	0	0	0	1[a] (2)

[a] Patient had myristoyl binding pocket mutations (V468H, I502L).

Ottmann O, et al. *Blood*. 2015:[abstract 138].

ABL001 Pharmacokinetic Profile Exhibits Dose Proportionality From 10 to 200 mg BID



Dose proportionality using C1D15 (steady state) AUC_{last} from individual patients: 10 to 200 mg BID

- Rapid absorption (median T_{max} ≈ 2 to 3 h)
- Dose-proportional increase in exposure following single and repeated dosing
- Low (< 2-fold) to moderate (≈ 2-fold) accumulation on repeated dosing
- Short apparent elimination half-life (median ≈ 5 to 6 h)

Ottmann O, et al. *Blood*. 2015:[abstract 138].

Safety: Adverse Events Suspected of Being Related to Study Drug Occurring in ≥ 5% of Patients (n = 59)

Adverse Event	All Grades, n (%)	Grade 3/4, n (%)
Thrombocytopenia	11 (19)	4 (7)
Neutropenia	9 (15)	4 (7)
Anemia	6 (10)	3 (5)
GI (N/V/D)	17 (29)	0
Arthralgia/myalgia	12 (20)	0
Skin (rash)	10 (17)	0
Fatigue	9 (15)	0
Lipase increase	**8 (14)**	**4 (7)**
Headache	8 (14)	0
Pruritus	6 (10)	0
Dry skin	4 (7)	0
Hypophosphatemia	4 (7)	1 (2)
Acute pancreatitis	**3 (5)**	**0**

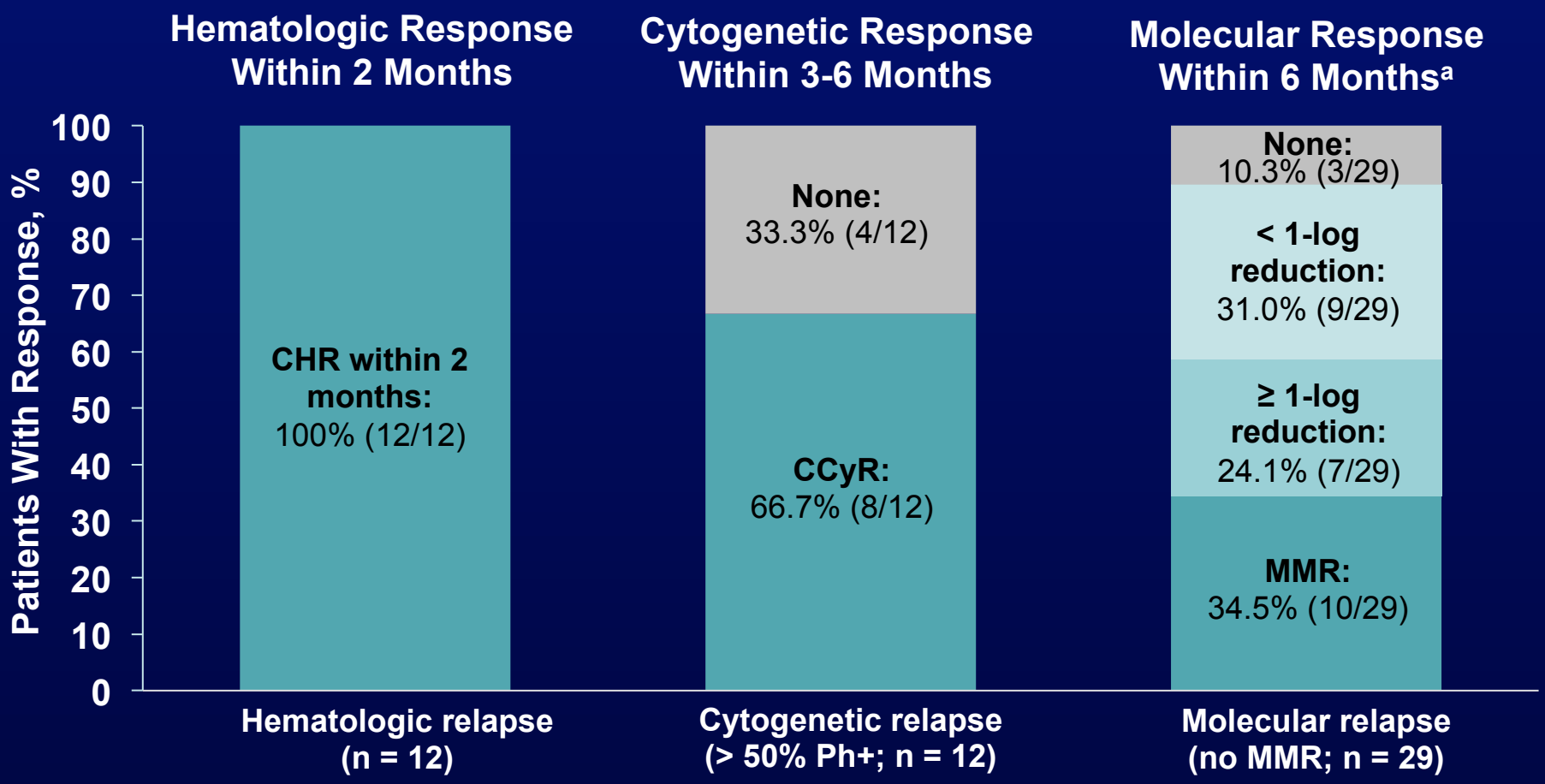
Ottmann O, et al. *Blood*. 2015:[abstract 138].

Safety: Dose-Limiting Toxicities

- All patients had > 1 postbaseline safety assessment
- There were 5 dose-limiting toxicities:
  - Grade 3 lipase increase (n = 2, 40mg BID, 200 mg QD)
  - Grade 2 myalgia/arthralgia (80 mg BID)
  - Grade 3 acute coronary event (150 mg BID)
  - Grade 3 bronchospasm (200 mg BID)
- No deaths occurred on study
- Dose escalation is ongoing

Ottmann O, et al. *Blood*. 2015:[abstract 138].

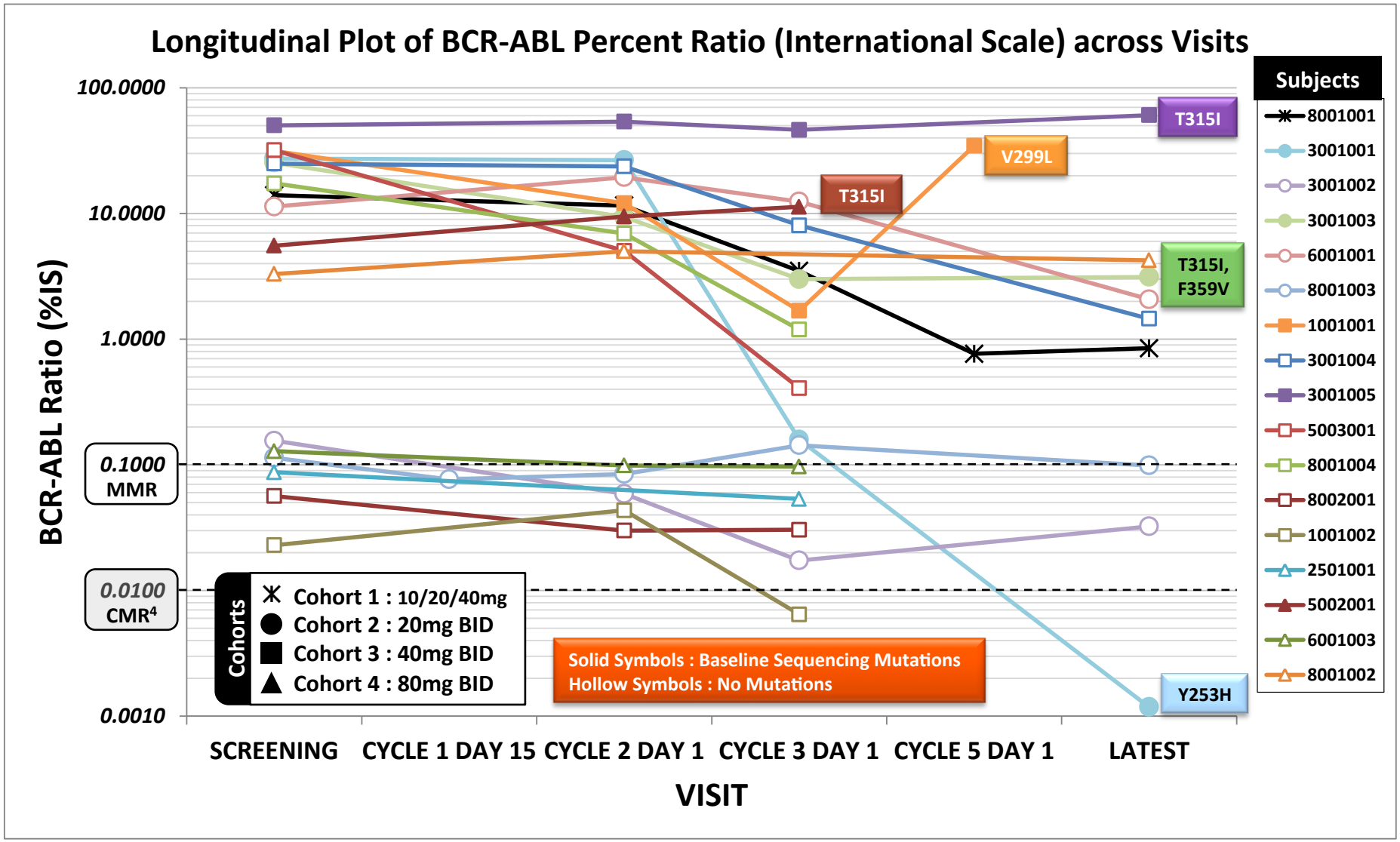
Responses in Patients With ≥ 3 Months of Follow-up on Study (n = 29)



[a] *BCR-ABL1*^{IS} reduction achieved.

Ottmann O, et al. ***Blood***. 2015:[abstract 138].

ABL001 exhibits single agent activity at doses ≥ 10 mg BID



ABL001 – Take home messages

- ABL001 generally well tolerated in heavily treated CML patients resistant to or intolerant of prior TKIs
- Preliminary pharmacokinetic exposures appear linear in the dose range tested
- Early evidence of single-agent efficacy at ≥ 10 mg BID
  - Clinical activity across TKI-resistant mutations (eg, V299L, F317L, Y253H)
  - Myristoyl binding pocket mutations (V468H, I502L) may lead to clinical resistance
- Allosteric inhibition of BCR-ABL1 is a promising approach
- Enrollment ongoing to determine the recommended dose (safety and tolerability)
- Combination with other TKIs (NIL, IM, DAS)?

Thank you for attention!

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Evolution of CML treatment

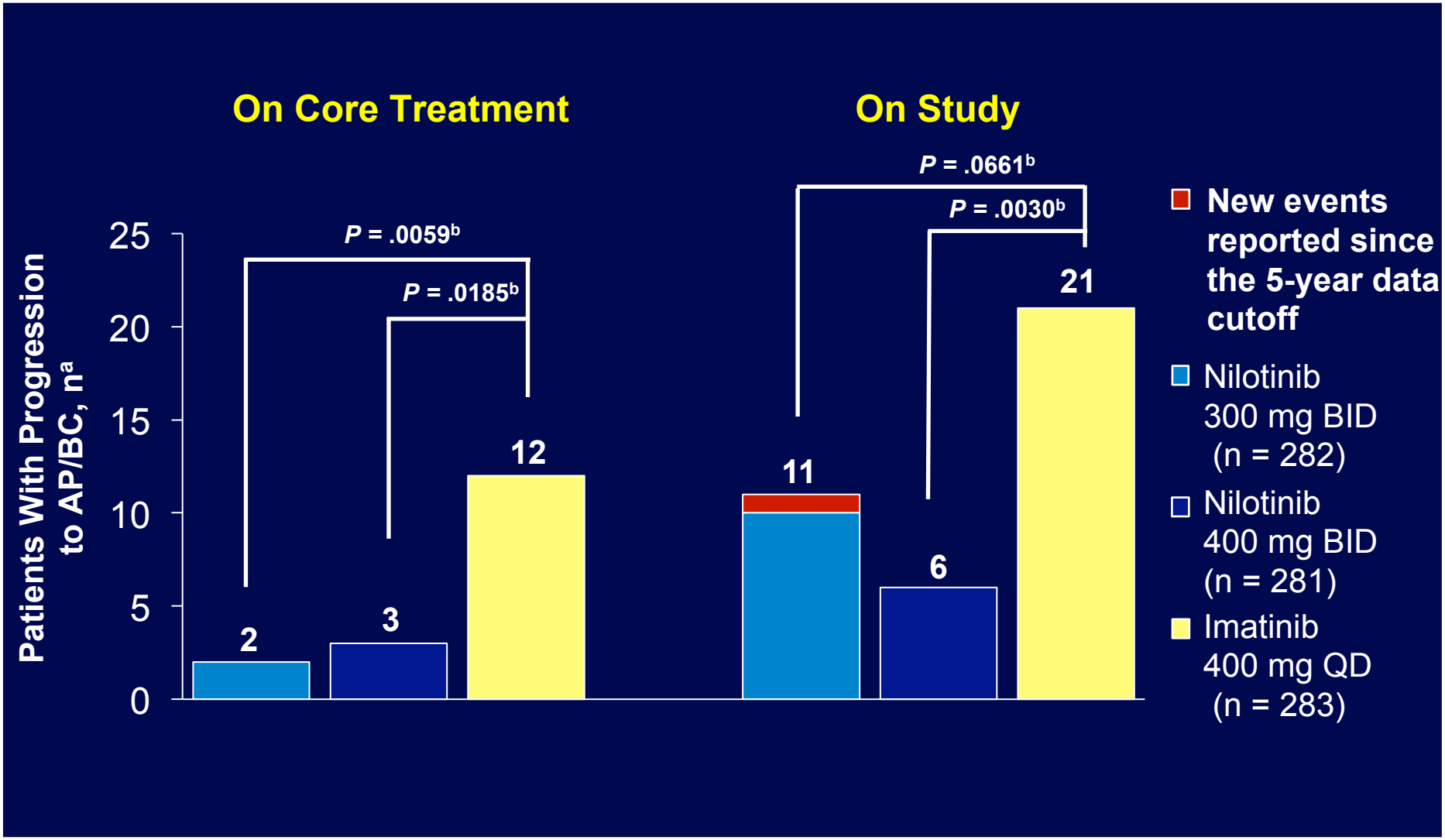
	2006[1]	2009[2]	2013[3]
1st LINE	**Imatinib 400**	**Imatinib 400**	**Nilotinib** **Dasatinib** **Imatinib 400-600-800**
2nd LINE	**Imatinib 600-800** **Allo-SCT**	**Nilotinib** **Dasatinib** **Allo-SCT**	**Nilotinib** **Dasatinib** **Bosutinib** **Ponatinib** **Allo-SCT**
3rd LINE	Palliation	Palliation	Anyone of remaining TKIs Allo-SCT

1) Baccarani M et al, Blood, 2006
2) Baccarani M et al, J Clin Oncol, 2009
3) Baccarani M et al, Blood, 2013

Unanswered clinical questions

- What is the optimum level of MRD and what is the minimum duration of TKI treatment and deep MR before attempting TFR?
- Which patients are the best candidates for a treatment discontinuation?
- Is there a difference in the rate of stable deep MR and TFR after imatinib, nilotinib or dasatinb treatment?
- Any other treatment should be added to TKIs to increase the probability of TFR?

Progression to AP/BC



Larson RA, et al. *Blood*. 2014:[abstract 4541]

2nd Generation TKIs in Early CP

Outcome and Responses By 5 Years

	ENESTnd[1]		Dasision[2]	
Treatment	**Nilotinib**	**Imatinib**	**Imatinib**	**Dasatinib**
Patient N.	**282**	**283**	**260**	**259**
5-year PFS[&]	**92.0%**	**91.1%**	**85.5%**	**85.4%**
5-year OS^	**93.6%**	**91.6%**	**89.6%**	**90.9%**
MMR	**77%**	**60%**	**64%**	**76%**
MR[4.5]	**54%**	**31%**	**33%**	**42%**

Note: Data from different studies, please interpret with care.

[&] ENESTnd: death from any cause or progression to AP/BC.
DASISION: WBC doubling, loss of CHR, increase in Ph+ metaphases to >35%, transformation, or death from any cause

^ ENESTnd Including events occurring on core or extension treatment or during f/u after treatment discontinuation;
DASISION Total n. of deaths on-study treatment and in follow-up after discontinuation of randomized treatment.

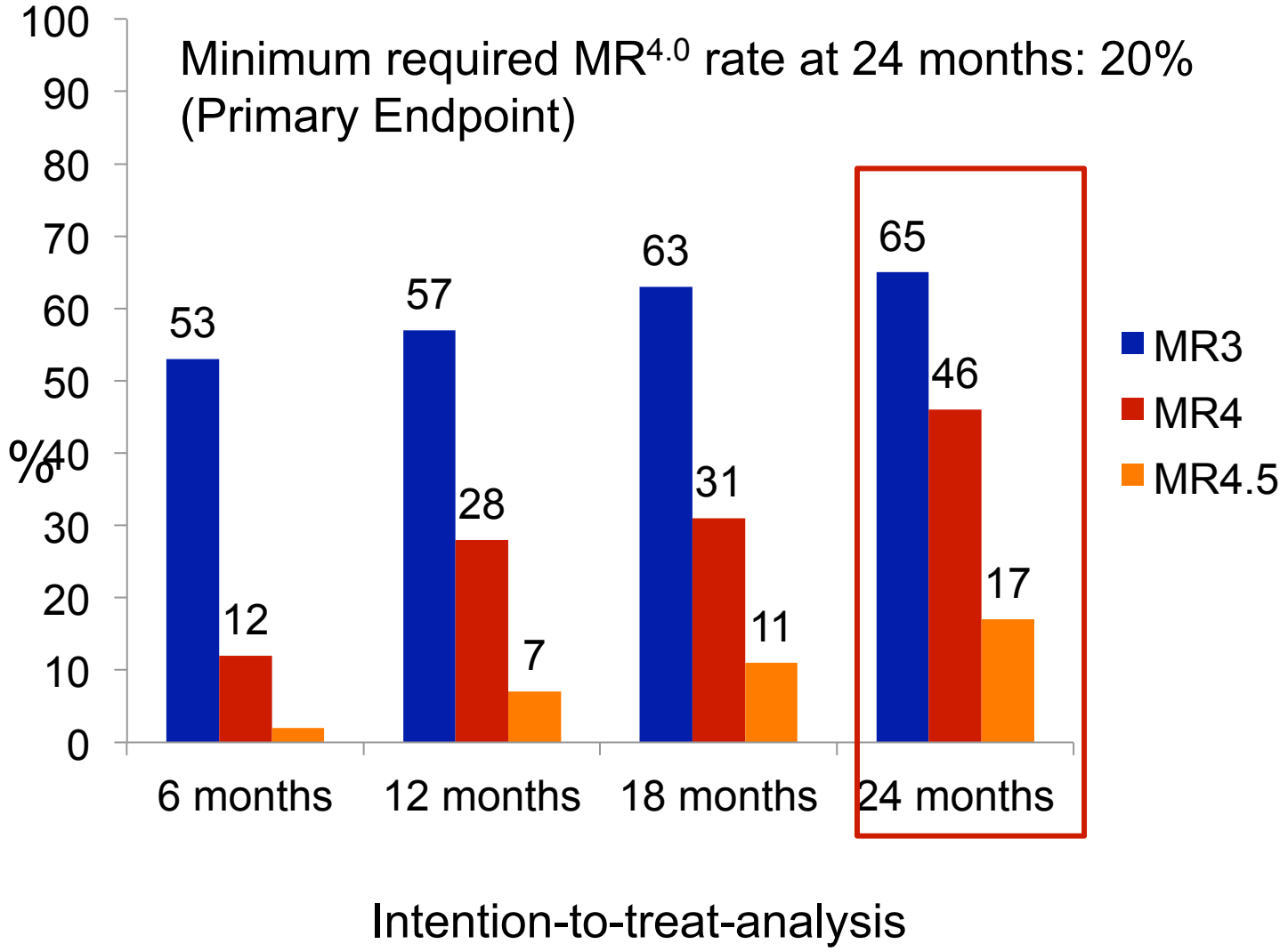
[1] Hochhaus A et al. Leukemia. 2016; 30:1044-54
[2] Cortes J. et al. ESH, iCMLf 2104

Interferon + Imatinib combination studies

	FRENCH SPIRIT[1]	NORDIC[2]	Ger-CML Study IV[3]	MDAnderson[4]
IFN type	PEG	PEG	No PEG	PEG + G-CSF (IMA 800)
MMR	Yes	Yes	No	No
CCyR	No	No	No	No
Survival	No	NA	No	No
Toxicity	Yes	Yes	No	Yes

1. Preudhomme C et al., N Engl J Med. 2010;363(26):2511-21
2. Simonsson B, et al. Blood 2011;118(12):3228-3235
3. Hehlmann R et al., JCO 2011;29:1634-1642
4. Cortes J et al. Cancer. 2011;117(3):572-80

Molecular response at milestones N = 130



Intention-to-treat-analysis

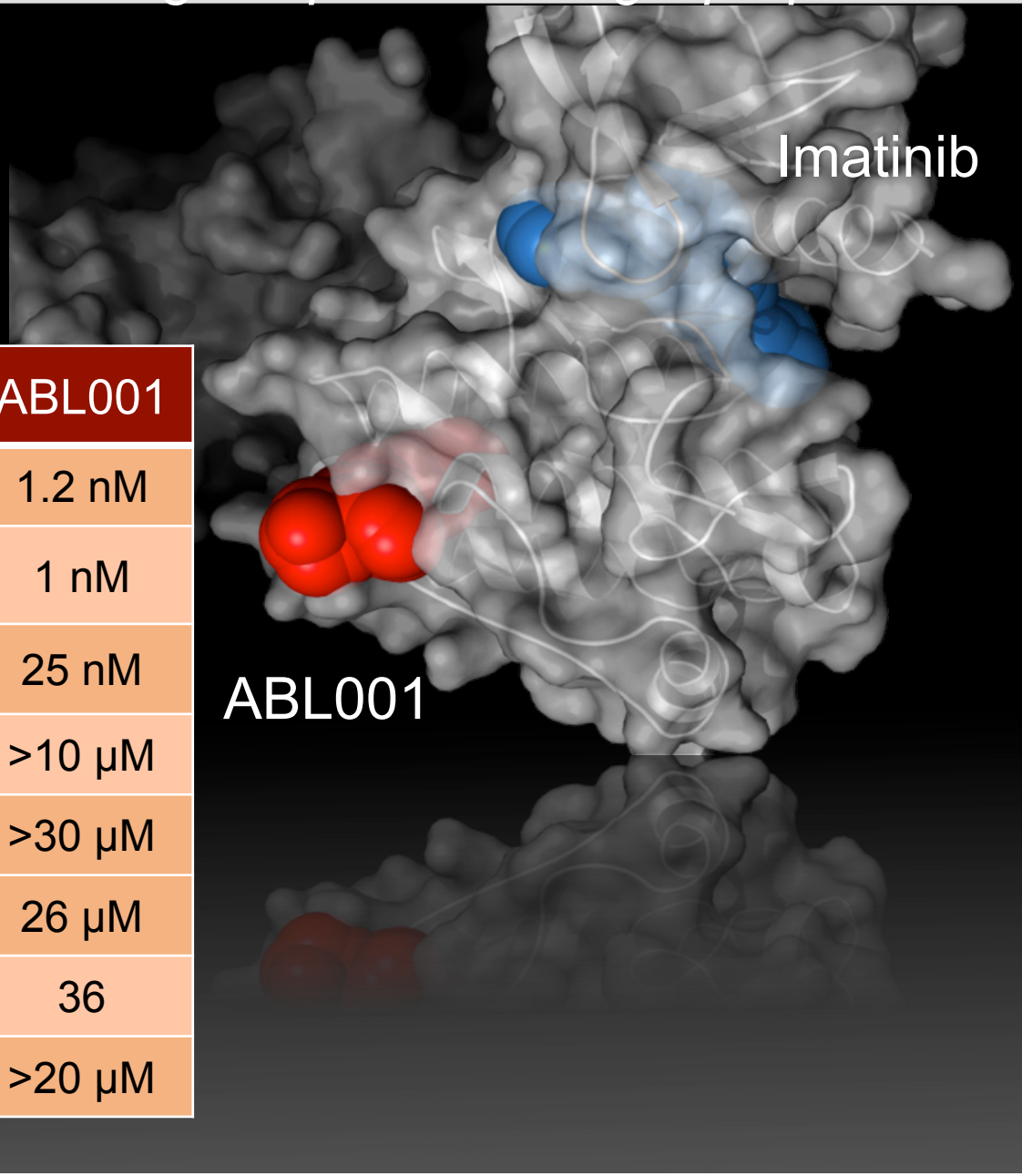
Castagnetti et al. Submitted to Haematologica

GIMEMA CML WP

ABL001

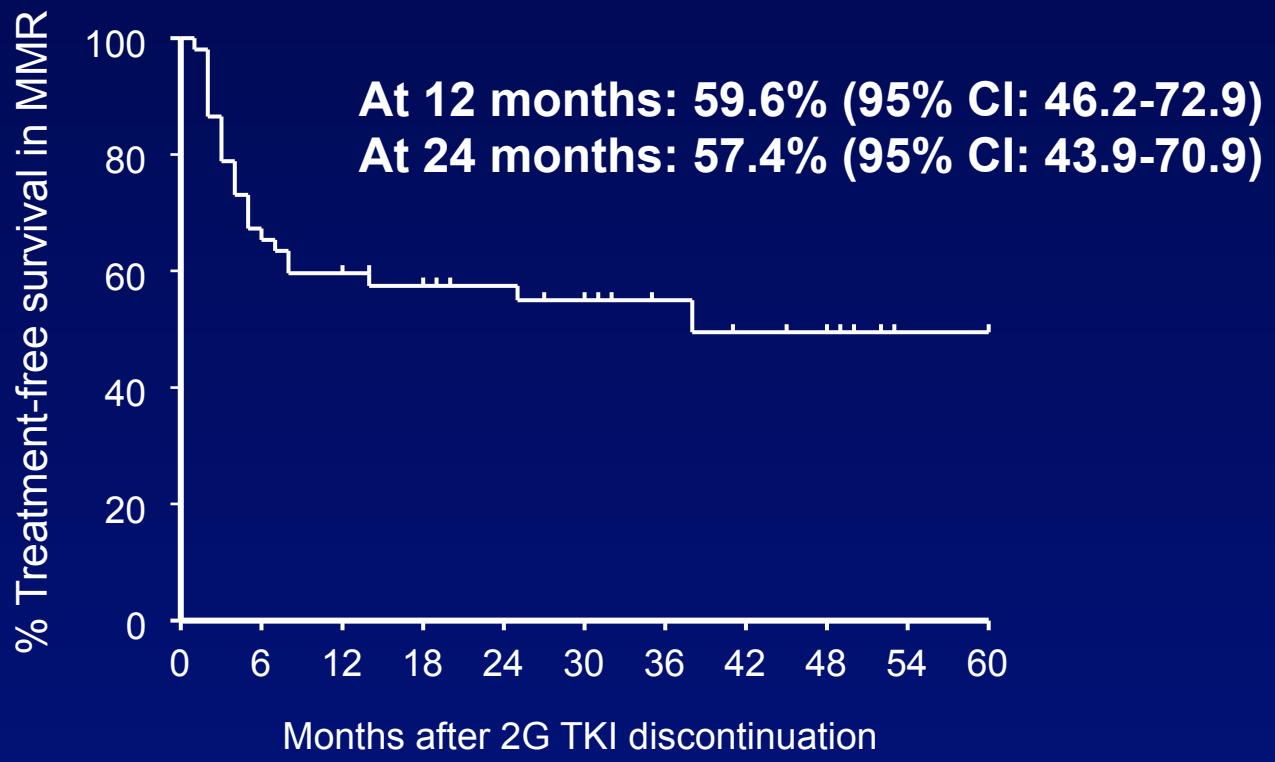
Potent allosteric inhibitor with good pharmacologic properties

Assay	ABL001
Biochemical IC_{50}, ABL^{WT}	1.2 nM
Cellular IC_{50} $BCR\text{-}ABL^{WT}$	1 nM
Cellular IC_{50} $BCR\text{-}ABL^{T315I}$	25 nM
Cellular IC_{50} WT BaF/3	>10 μM
hERG	>30 μM
Qpatch Clamp	26 μM
PAMPA class, F %	36
CYP3A4,2D6,2C9	>20 μM



Dasatinib or nilotinib discontinuation in CP-CML patients with durably undetectable transcripts: interim analysis of the STOP 2G-TKI study (follow-up ≥ 12 months)

- - 2G-TKI frontline or after intolerance/resistance to imatinib
- - TKI therapy for at least 3 years
- - Undetectable BCR-ABL* (CMR4.5) for at least 2 years



KM analysis

Rea et al. Blood (ASH) 2014; Abstract 811.

NILOTINIB 800 MG FRONTLINE

CML 0307

Stable Deep Molecular Response

METHODS

-Stable MR^4: $\geq$ 5 evaluations during the preceding 2 years of treatment

- Minimum follow-up: 60 months

56/73 (76%) patients had a MR^4 at least once

Of the 55 patients still on nilotinib at last contact:
→18 (33%) were in stable MR^4
→24 (44%) fluctuated between 0.1 and <0.01%

42/73 (58%) patients eligible for TFR studies

More patients eligible for TFR studies with 2nd generation TKIs

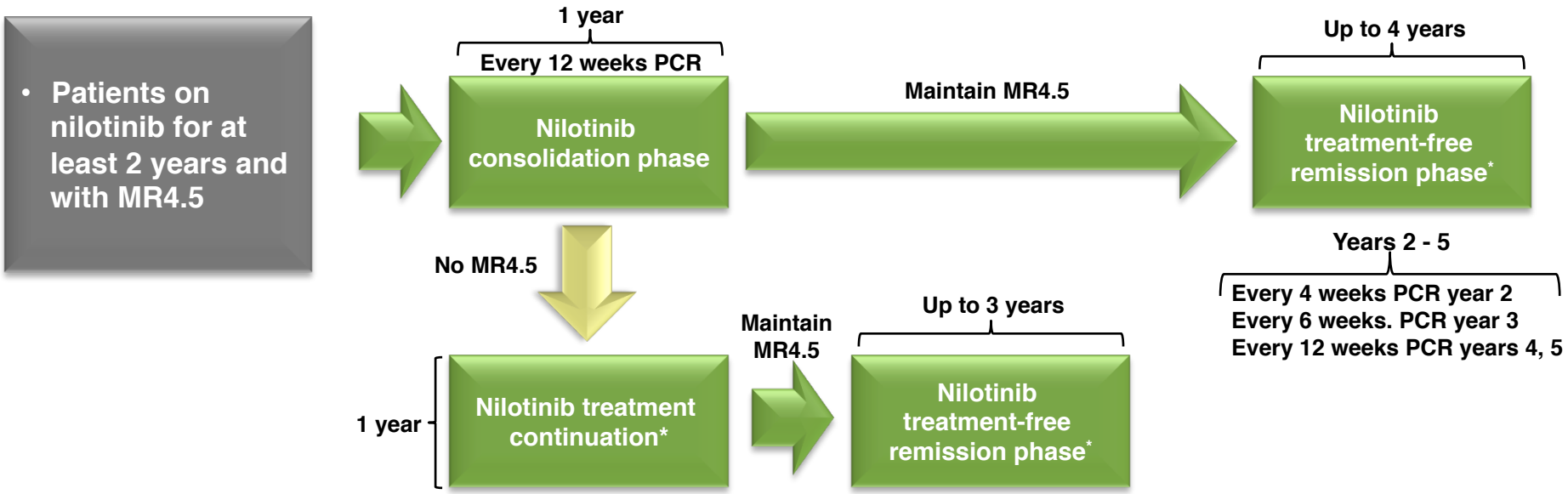
GIMEMA CML WP

Gugliotta G et al. Haematologica. 2015;100(9):1146-50

ENESTfreedom

Global

evaluates stopping nilotinib treatment in adults with Ph+ CML-CP after achieving and maintaining MR4.5 with nilotinib as first-line treatment



- **Primary objective:** Rate of TFR (no loss of MMR and no reinitiation of nilotinib treatment) at 48 weeks from start of the TFR phase

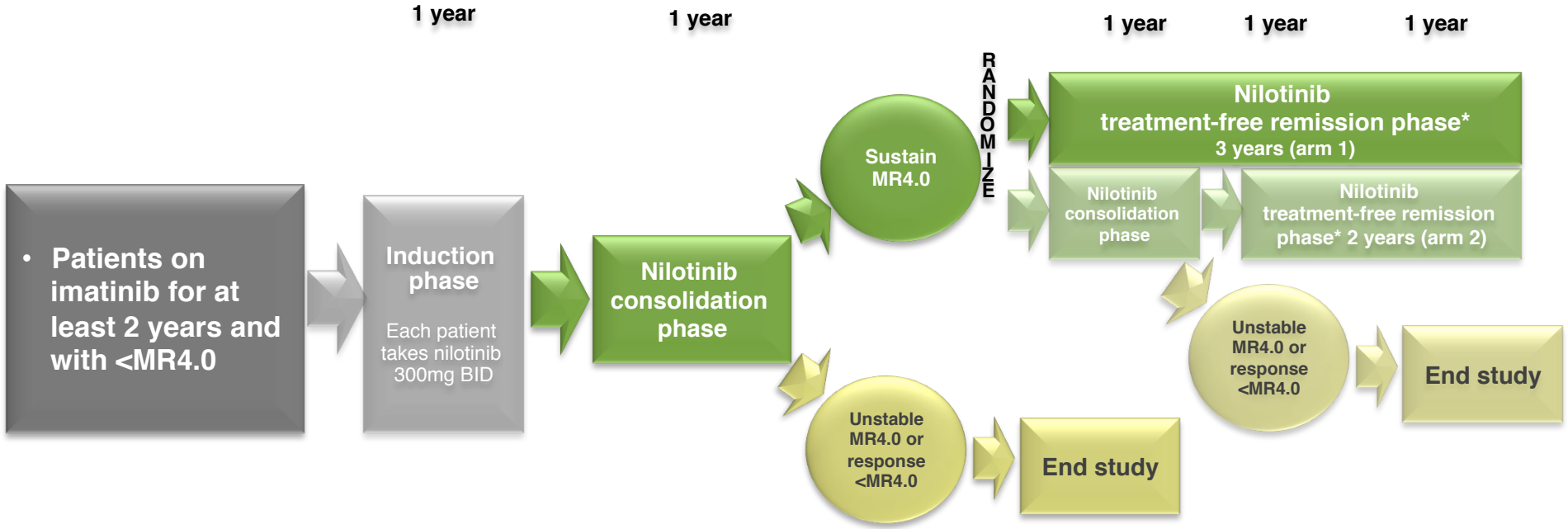
- **Study status**
  - **Fully accrued (N= 217)**
  - **Primary Endpoint Analysis ASCO, EHA 2016**

**If no MR4.5 after this point, continue or reinitiate treatment with nilotinib.*

NOVARTIS

ENESTpath
Europe

evaluates treatment-free remission rate in patients with Ph+ CML-CP after two different durations of consolidation treatment with nilotinib 300mg BID



- **Primary endpoint:** The number of patients who remain in treatment-free remission (≥MR4.0), without molecular relapse, at the end of 12 months in the TFR phase of the study, in the nilotinib 12 months consolidation treatment arm versus the nilotinib 24 months consolidation treatment arm

- **Study status**
  - **Fully accrued (N=602 + 76 still on screening)**
  - **First Interim Analysis: ASH 2015**
  - **Primary Endpoint Analysis ASCO, EHA 2020**

**If patient does not maintain MR4.0, treatment with nilotinib 300mg BID will be restarted.*