

# Old Generics or New Drugs

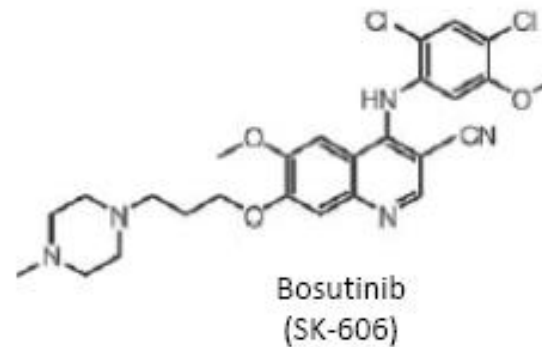
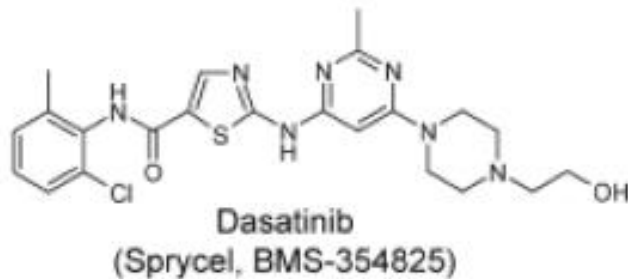
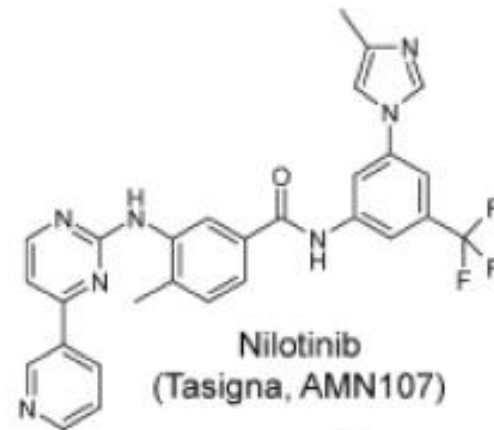
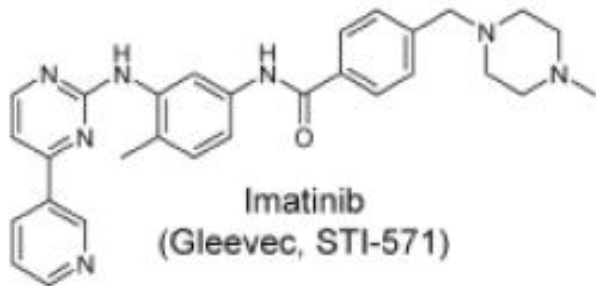
*Gianantonio.rosti@unibo.it*



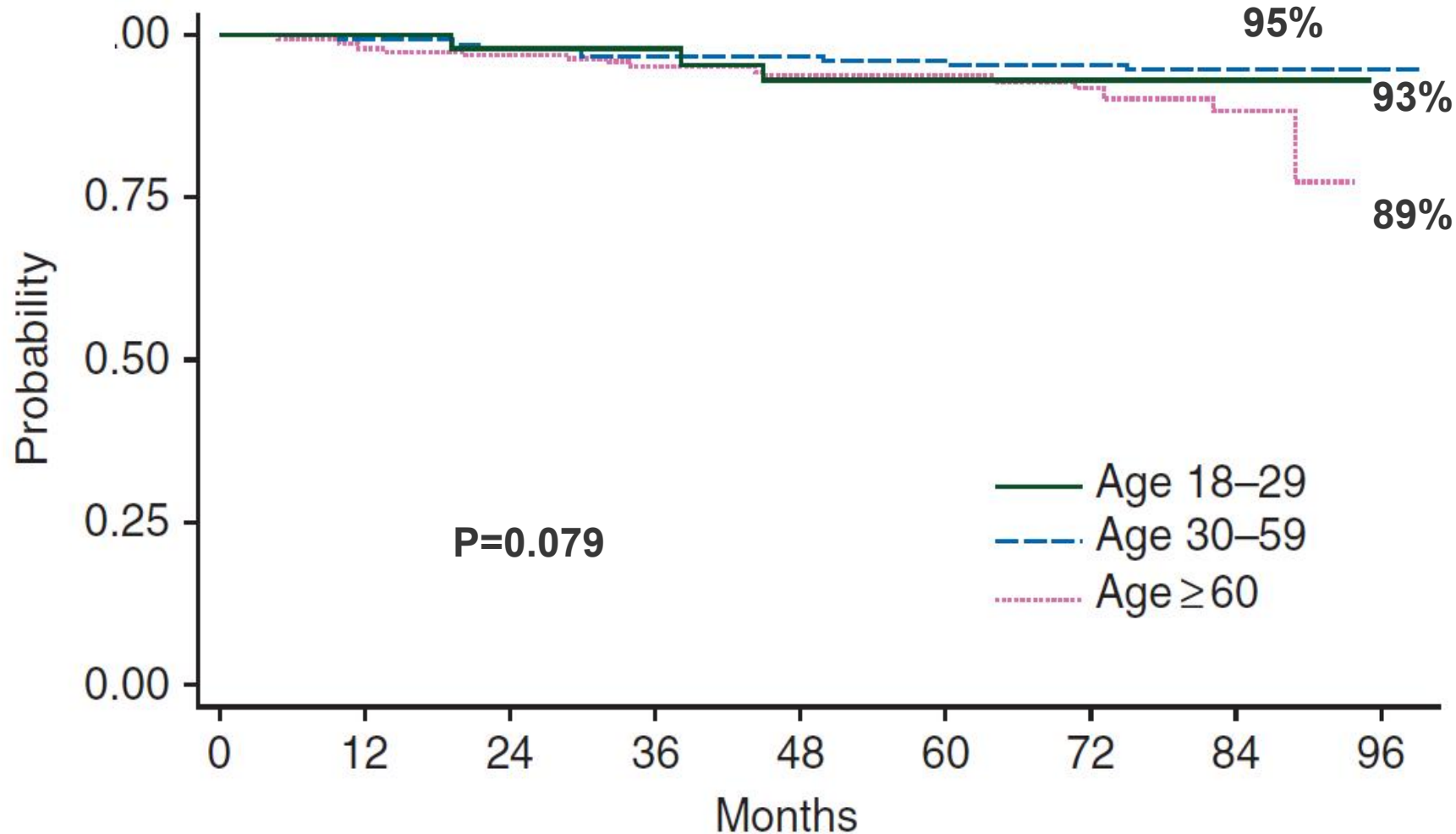
# BCR/ABL Inhibitors

## *Glivec, Tasigna, Sprycell, Bosulif*

*1999-2009*



# CML-related survival by age groups in the TKIs cohort



*Never ever give up!*

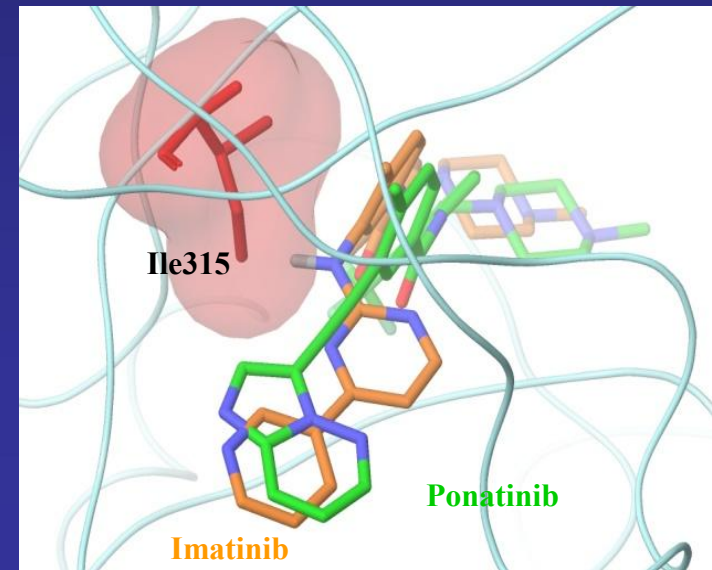
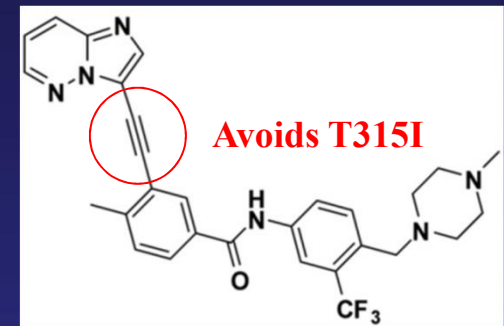




# PONATINIB

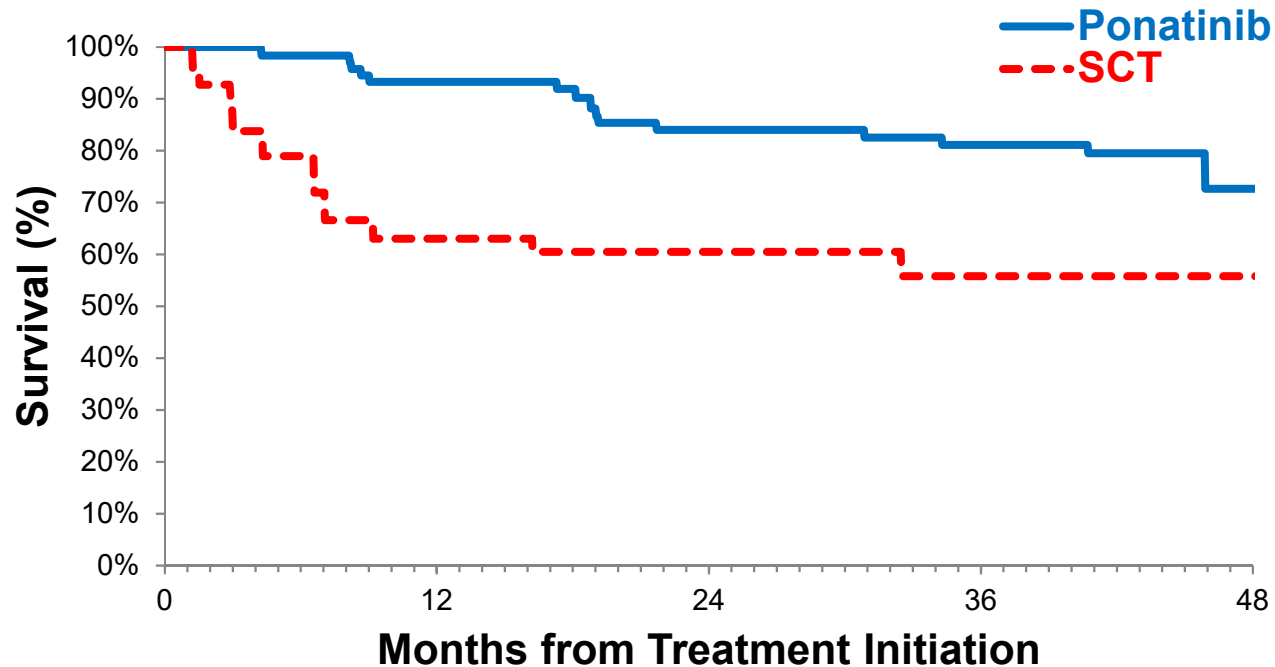
## A PAN-BCR-ABL INHIBITOR

- Rationally designed inhibitor of BCR-ABL
- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
- Potent activity against an array of BCR-ABL variants
- Also targets other therapeutically relevant kinases
  - Inhibits FLT3, FGFR, VEGFR and PDGFR, and c-KIT
- Once-daily oral activity in murine models



FLT3 = FMS-like tyrosine kinase receptor-3; FGFR = fibroblast growth factor receptor; VEGFR = vascular endothelial growth factor receptor  
O'Hare T, et al. Cancer Cell 2009;16:401-412

# Adjusted OS of CP-CML Patients



	Ponatinib (N = 64)	SCT (N = 26)	p-value
Overall survival (months), median (IQR)	NR (45.9 - NR)	103.3 (6.6 - 103.3)	0.013*
Hazard ratio (95% CI)	0.37 (0.16, 0.84)	Ref.	0.017*

\* p-value <0.05. Ref. = reference group; NR = not reached.

*Frank Nicolini et al, ASH 2013*

# NCCN, V.4, 2018

## CLINICAL PRESENTATION

Chronic phase CML

### Treatment Considerations:

- Patient comorbidities and drug toxicities
- Monitor response<sup>c</sup>
- Evaluate patient compliance and drug interactions
- Early toxicity monitoring

Low-risk score  
([See Risk Calculation Table CML-A](#))

Intermediate- or high-risk score  
([See Risk Calculation Table CML-A](#))

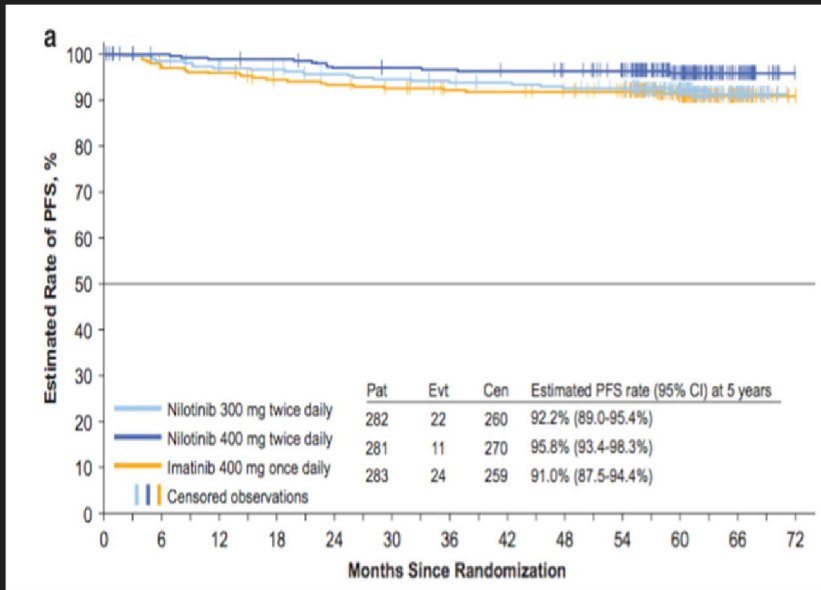
## PRIMARY TREATMENT

First generation TKI ([Imatinib](#) or generic imatinib 400 mg QD) (category 1)  
or  
Second generation TKI ([Bosutinib](#) 400 mg QD [category 1] or [Dasatinib](#) 100 mg QD [category 1] or [Nilotinib](#) 300 mg BID [category 1])  
or  
Clinical trial

[See Evidence Blocks on CML-2A](#)

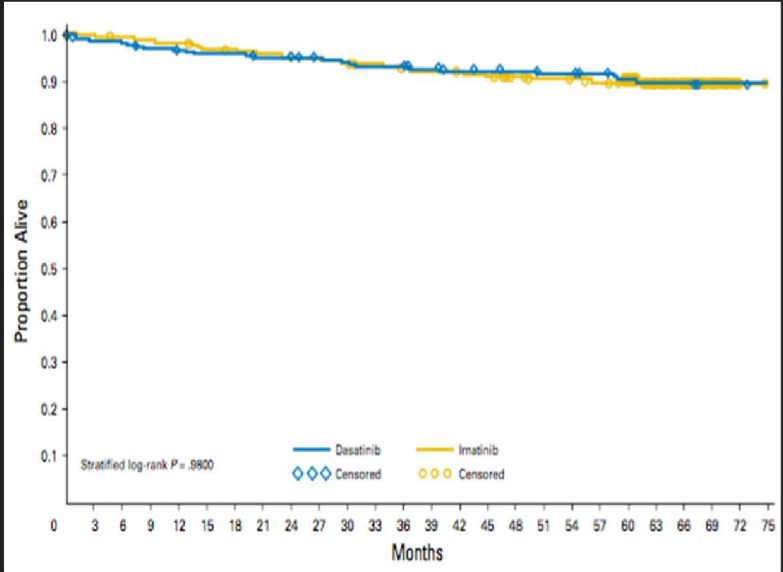
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Clinical trial

# 5-year OS is similar in different trials



ENESTnd:  
Nilotinib vs  
Imatinib

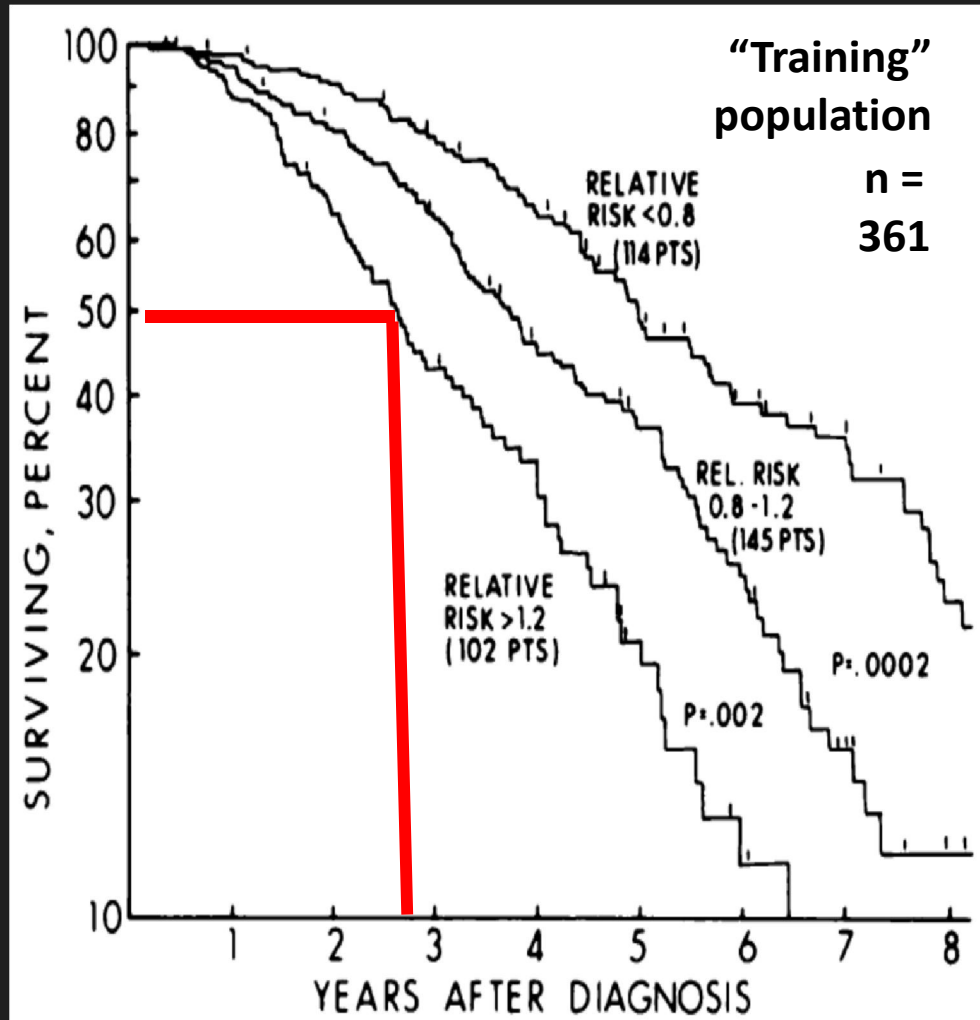
DASISION:  
Dasatinib vs  
Imatinib



Hochhaus A, et al. *Leukemia*. 2016;30:1044-1054; Cortes J, et al. *J Clin Oncol*. 2016;34:2333-2340.

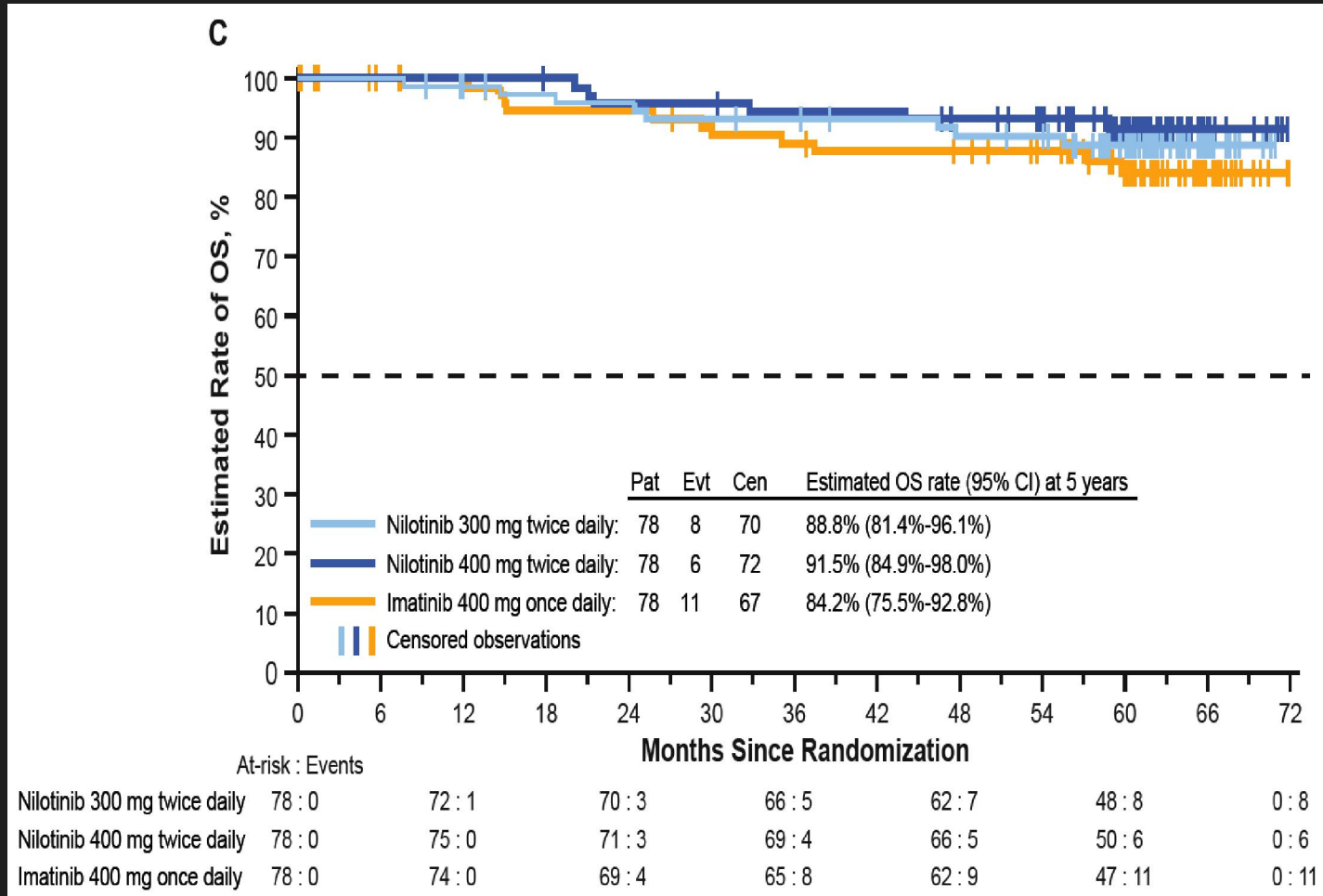


# Survival according to relative risk (Cox model analysis)



# ENESTnd: Nilotinib vs imatinib frontline

KM estimated rates of OS on study among patients with  
(A) low, (B) intermediate, or (C) high Sokal risk

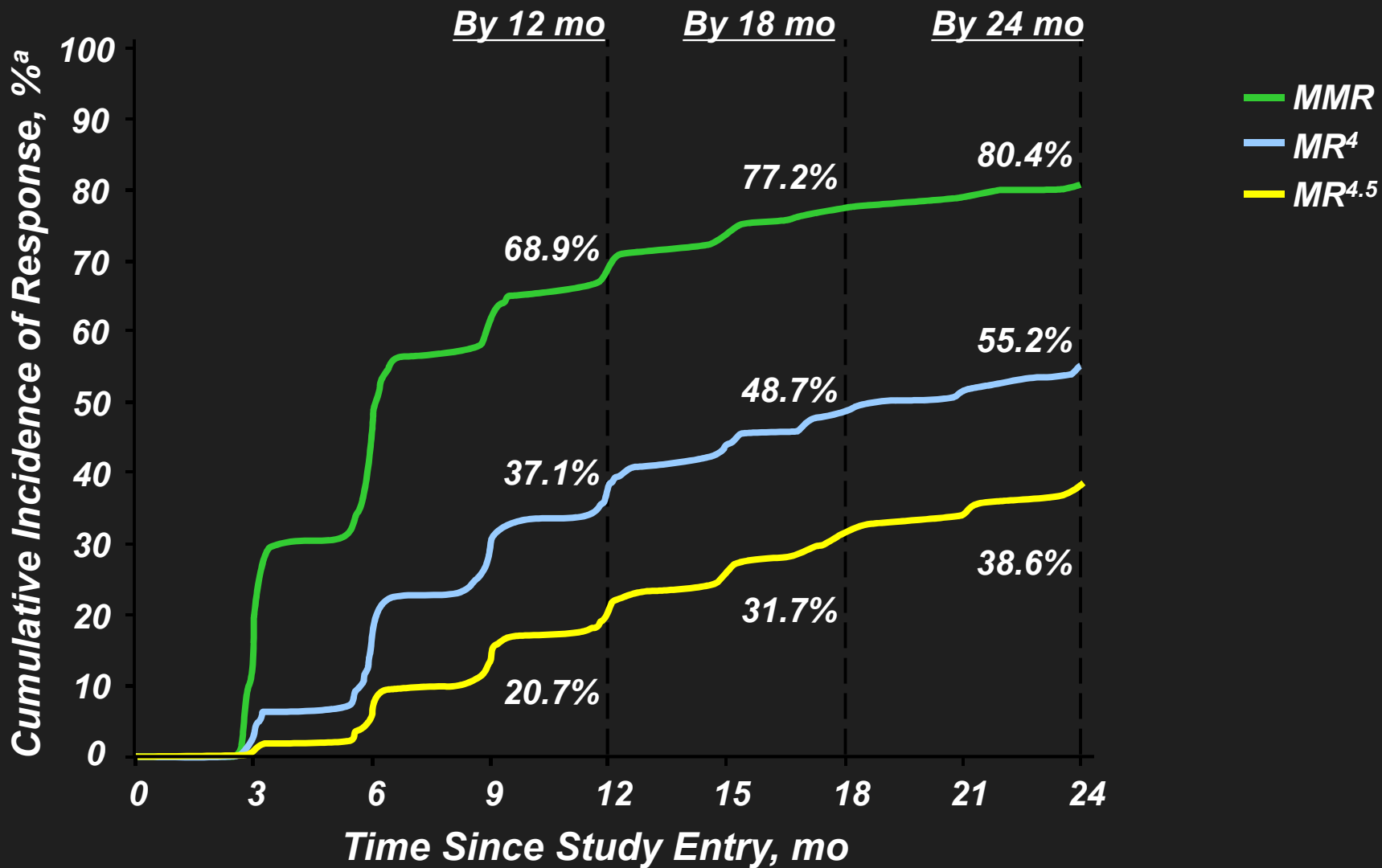


# **Impact of age on efficacy and toxicity of nilotinib in patients with chronic myeloid leukemia in chronic phase (CML-CP): ENEST1st sub-analysis**

**More than 1 thousand patients, Europe, 2010**

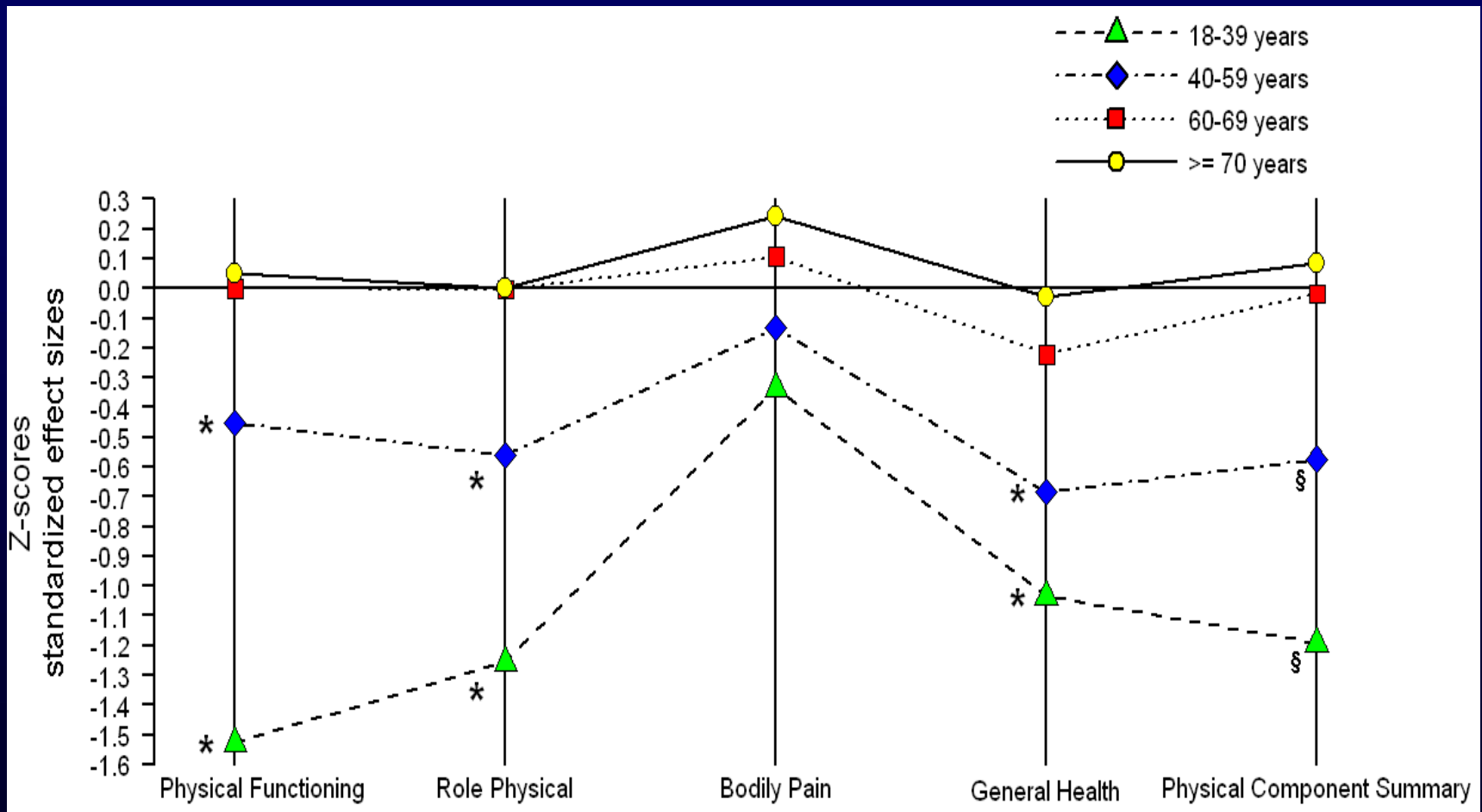
**Francis J. Giles, Delphine Rea, Michele Baccharani, Nicholas C.P. Cross,  
Juan Luis Steegmann, Laimonas Griskevicius, Philipp le Coutre,  
Daniel Coriu, Ljubomir Petrov, Gert J. Ossenkoppele, Francois-Xavier Mahon,  
Martin C. Müller, Andrzej Hellmann, Kimmo Porkka, Tim H. Brümmendorf,  
Gunther Gastl, Angela Pellegrino, Luca Dezzani,  
Gianantonio Rosti, Andreas Hochhaus**

# ENEST1st: Cumulative incidence of MMR, MR<sup>4</sup>, and MR<sup>4.5</sup>



<sup>a</sup> Molecular analysis population (n = 1052).

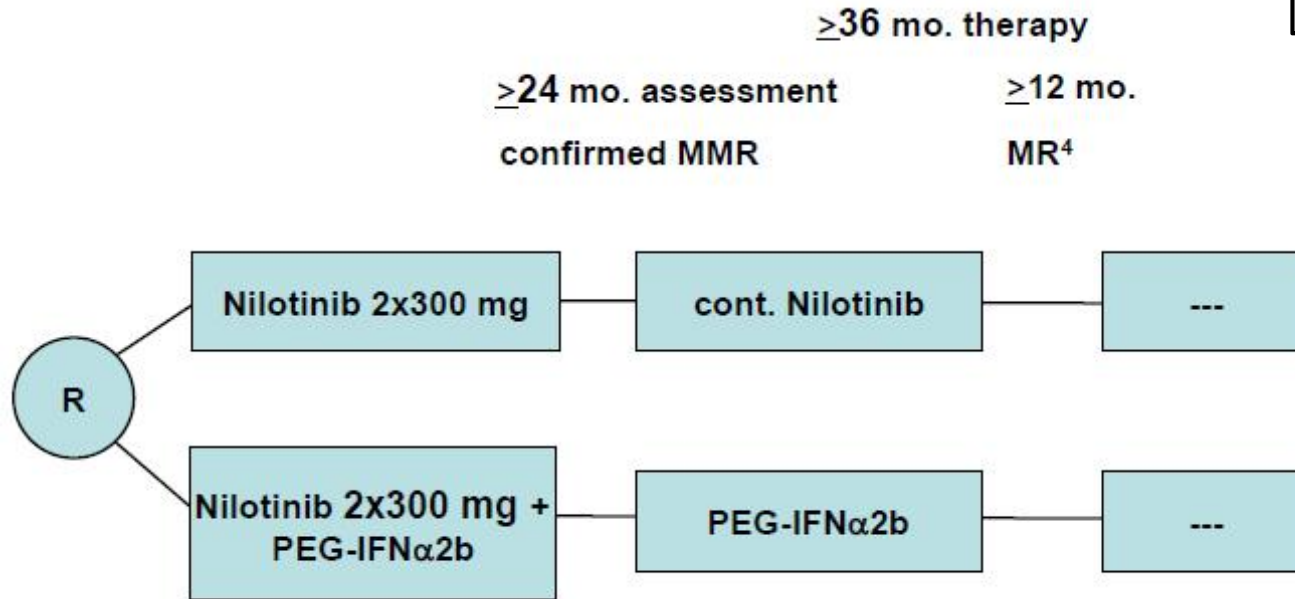
# QOL in CML Patients (n. 456) Receiving Imatinib > 24 months with Compared with the General Population.





# Patients' follow up status

16.04.2018



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

Induction therapy

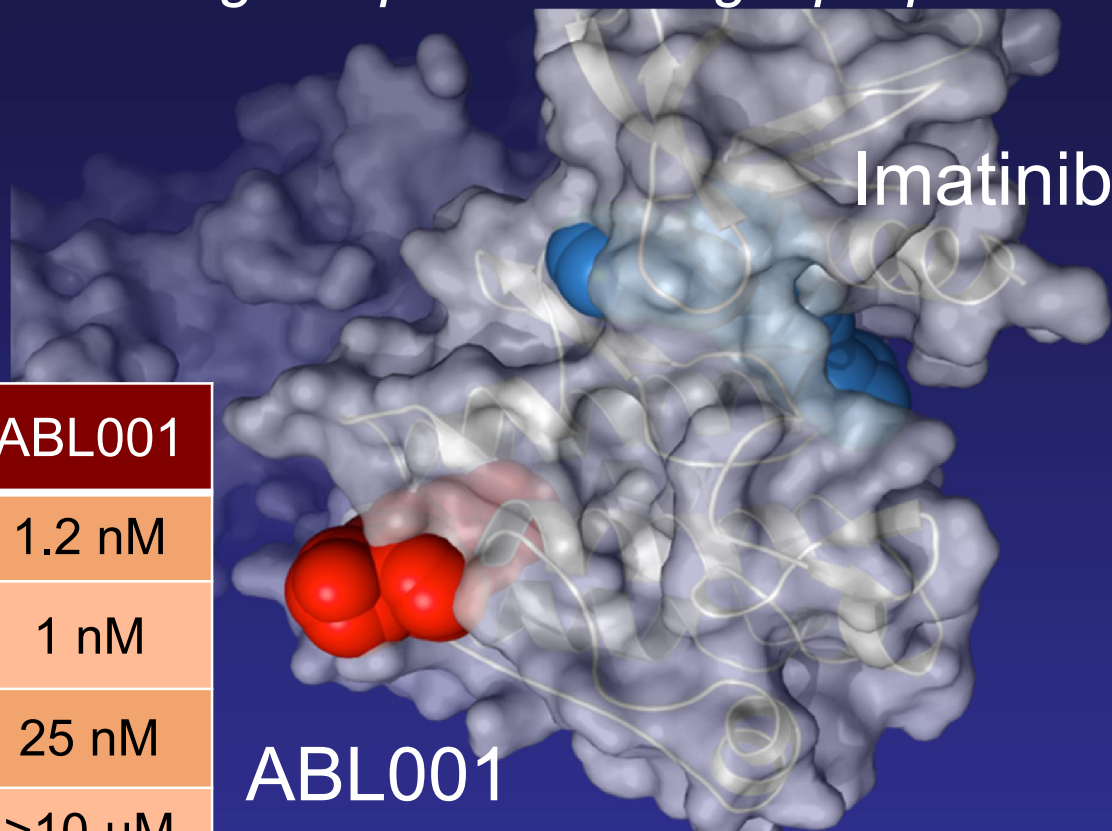
Maintenance therapy

Cure?

Phase of treatments	Induction n=344	Maintenance n=216 (Median 24.6 mo.)	Discontinuation n=116 (Median 37 mo.)

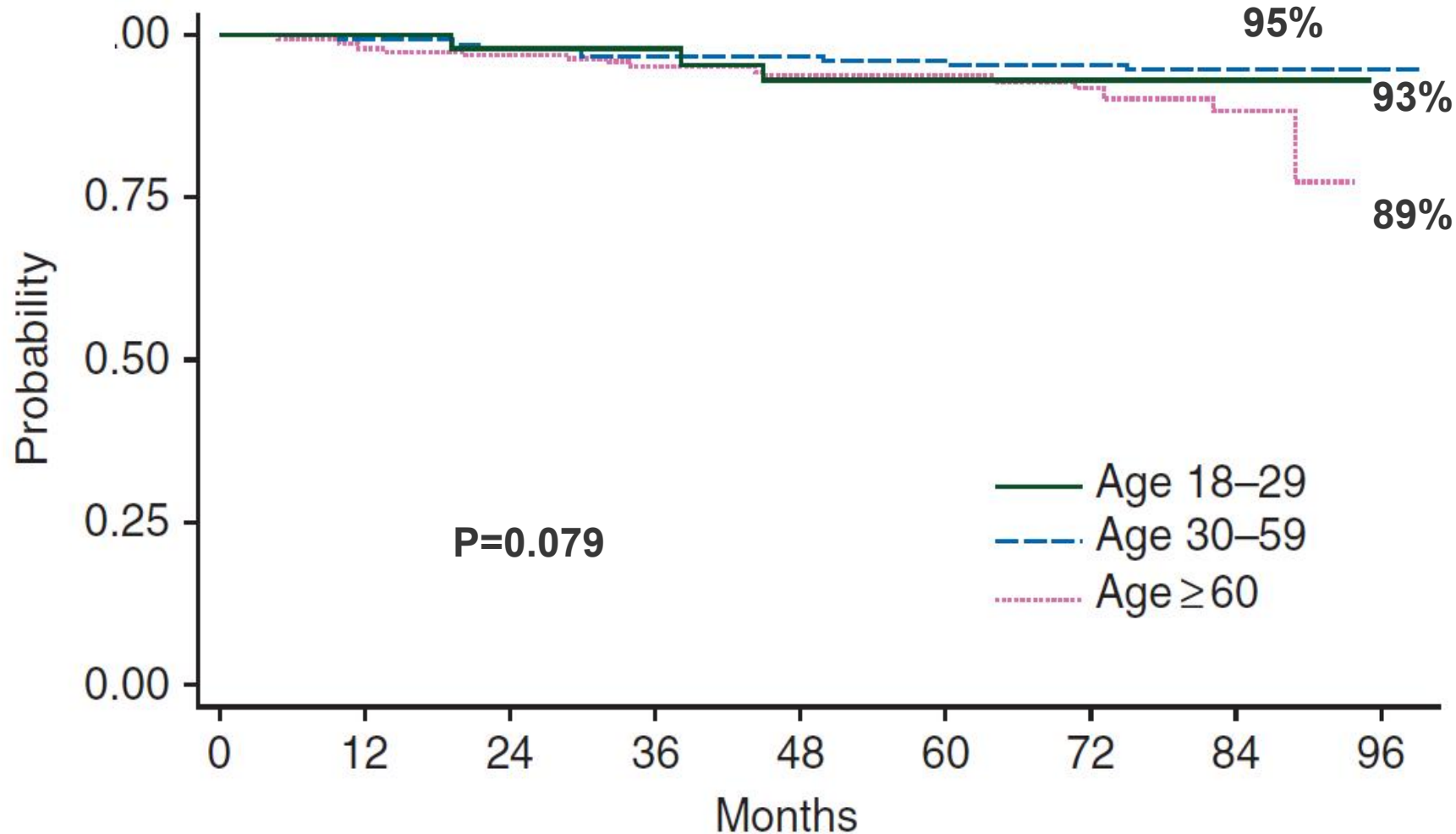
# ABL001

*Potent allosteric inhibitor with good pharmacologic properties*



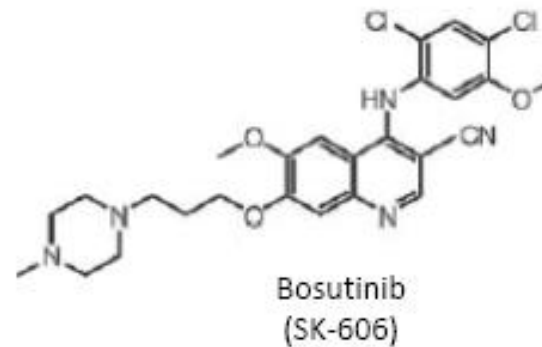
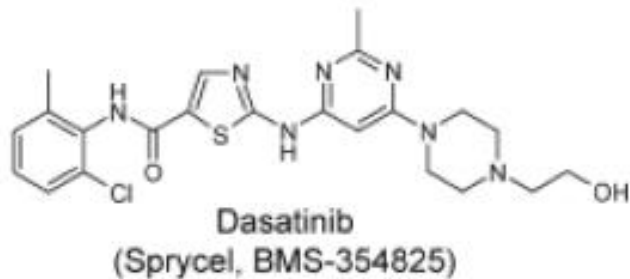
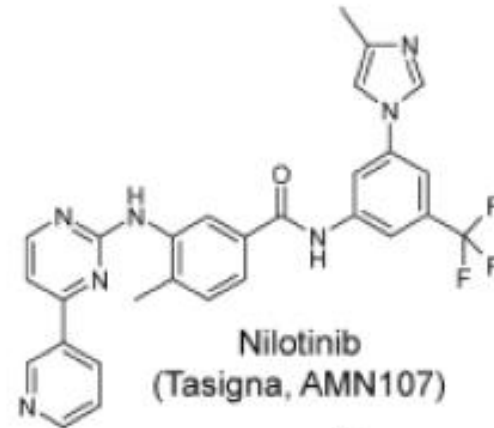
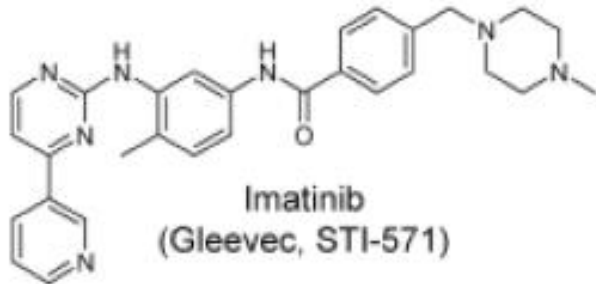
Assay	ABL001
Biochemical IC <sub>50</sub> , ABL <sup>WT</sup>	1.2 nM
Cellular IC <sub>50</sub> BCR-ABL <sup>WT</sup>	1 nM
Cellular IC <sub>50</sub> BCR-ABL <sup>T315I</sup>	25 nM
Cellular IC <sub>50</sub> WT BaF/3	>10 μM
hERG	>30 μM
Qpatch Clamp	26 μM
PAMPA class, F %	36
CYP3A4,2D6,2C9	>20 μM

# CML-related survival by age groups in the TKIs cohort



# BCR/ABL Inhibitors

*Imatinib, dasatinib, nilotinib, bosutinib, ponatinib*



# NCCN, V.4, 2018

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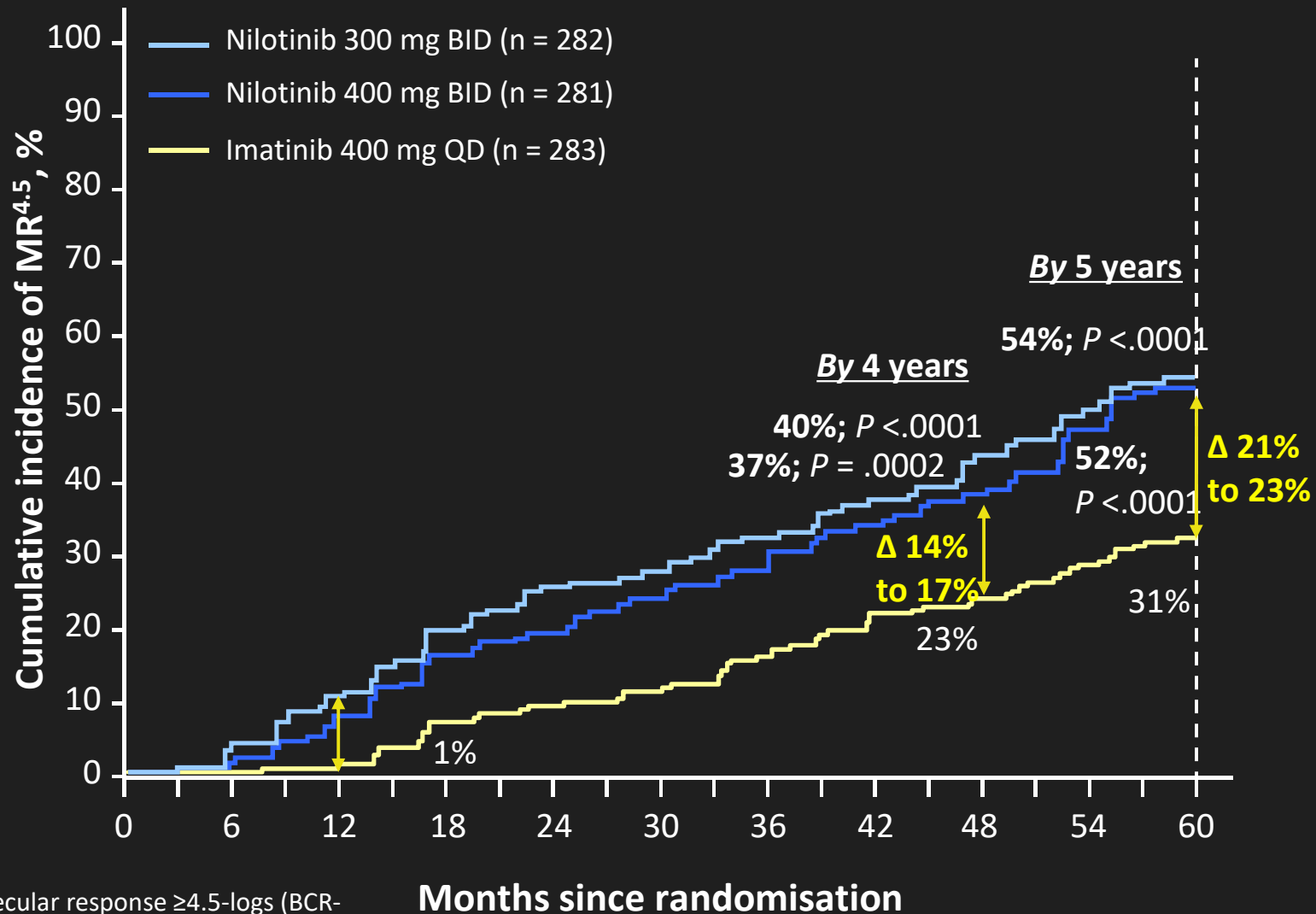
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# Cumulative incidence of MR<sup>4.5</sup>



MR<sup>4.5</sup>, molecular response  $\geq 4.5$ -logs (BCR-ABL<sup>IS</sup>  $\leq 0.0032\%$ ).

Hochhaus A, et al. *Leukemia*. 2016;30:1044-1054.

Data cutoff: September 30, 2013.

# Old Generics

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