Deep Molecular Response to Nilotinib As First-Line Treatment of BCR-ABL+ CML in Early Chronic Phase: A Phase 3b Multicenter Study of the GIMEMA CML Working Party

Abstract 4532

Castagnetti F, Gugliotta G, Breccia M, Martino B, Rossi G, Stagno F, Turri D, Tiribelli M, Trabacchi E, Isidori A, Pierri I, Leonardi G, Pregno P, Carella AM, Bochicchio MT, Testoni N, Soverini S, Specchia G, Alimena G, Cavo M, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G,
on behalf of the GIMEMA CML Working Party

Background

- In the ENESTnd trial, nilotinib (NIL) showed higher major molecular response rates with respect to imatinib (IM), with less frequent progression to advanced phases. Based on these results, NIL has been approved as front-line treatment of CML in chronic phase.

- Treatment-free remission (TFR) is an emerging goal of CML treatment and a sustained deep molecular response (DMR, $MR^{4.0}$ or better) is a prerequisite to discontinue TKIs. The 5-year update from the ENESTnd trial showed a superiority of NIL over IM in terms of both $MR^{4.0}$ and $MR^{4.5}$, but differences in the stability of DMR have not been reported yet.

- Despite the efficacy, cost and safety concerns may limit NIL use as first-line treatment in CML. Independent studies are extremely relevant to confirm or to extend the results of company-sponsored trials.

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Study Aims

- **Primary objective**: To assess the efficacy of NIL front line in terms of deep molecular response

  Primary endpoint: rate of $MR^{4.0}$ at 24 months (preliminary results are presented here, because 18/130 patients have not completed the 24-month evaluation)

- **Key secondary objectives**:
  - evaluation of the kinetics of molecular response
  - assessment of the safety profile
  - evaluation of the outcome

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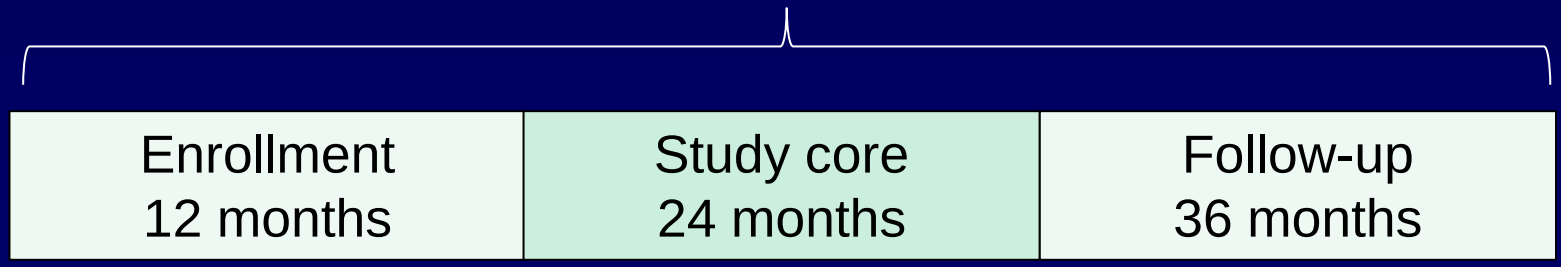
Methods

Open-label, multicentric, prospective phase IIIb study CML in early chronic phase (NCT01535391)

Starting NIL dose: 300 mg BID, with dose escalation to 400 mg BID in case of suboptimal response or failure (ELN 2009 criteria), with the exception of progression to ABP (in absence of toxicity or BCR-ABL mutations insensitive to NIL)

Analysis performed according to the ITT principle

Study duration: 6 years (1 + 5 years)



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Patients

N = 130

Years of age, median (range)	50 (18-85)
65 years or older, n (%)	25 (19)
Sex male, n (%)	86 (66)
Cytogenetics, n (%)	
CCA Ph+	7 (5)
Variant translocations	9 (7)

Relative Risk, n (%)	Sokal	Hasford	EUTOS
• Low	56 (43)	65 (50)	120 (92)
• Intermediate	48 (37)	58 (45)	- 333
• High	26 (20)	7 (5)	10 (8)3

Months of follow-up, median (range) 24 (18-36)

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Sensitivity

Samples with BCR-ABL ratio <0.1% IS

Number of ABL Copies	Percentage of Samples
<10.000 ($MR^{3.0}$)	10%
10.000 - 31.999 ($MR^{4.0}$)	52%
32.000 - 99.999 ($MR^{4.5}$)	27%
≥100.000 ($MR^{5.0}$)	10%

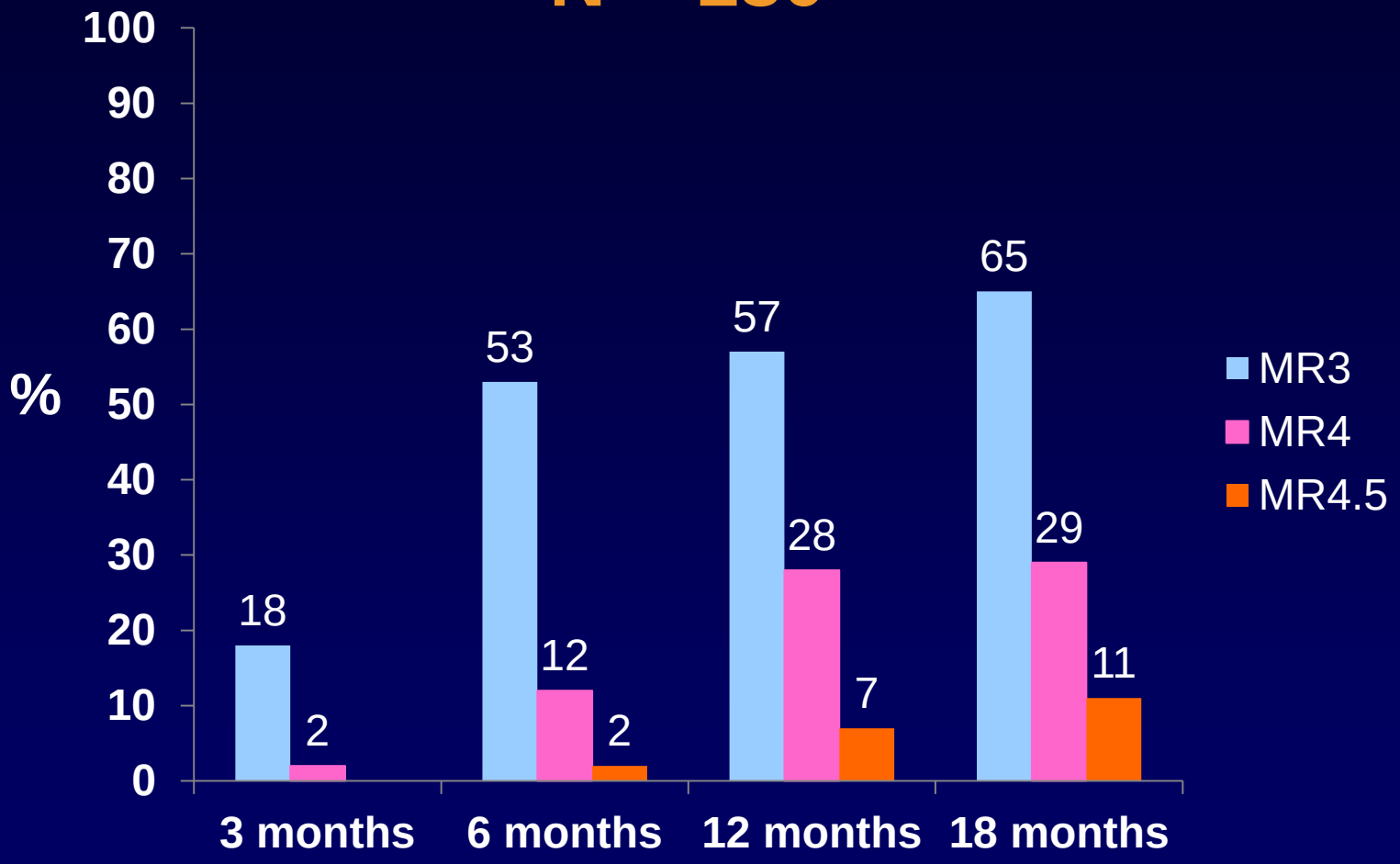
Deep molecular response:

- **$MR^{4.0}$** → detectable disease ≤0.01% BCR-ABL or undetectable disease with ≥10.000 ABL copies
- **$MR^{4.5}$** → detectable disease ≤0.0032% BCR-ABL or undetectable disease with ≥32.000 ABL copies

Cross NC, et al. *Leukemia*. 2012;26(10):2172-5

Castagnetti F, et al. *Blood*. 2014;124: Abstract 4532.

Molecular Response at Each Timepoint
N = 130



Intention-to-Treat Analysis
(not evaluable patients are considered as nonresponders)

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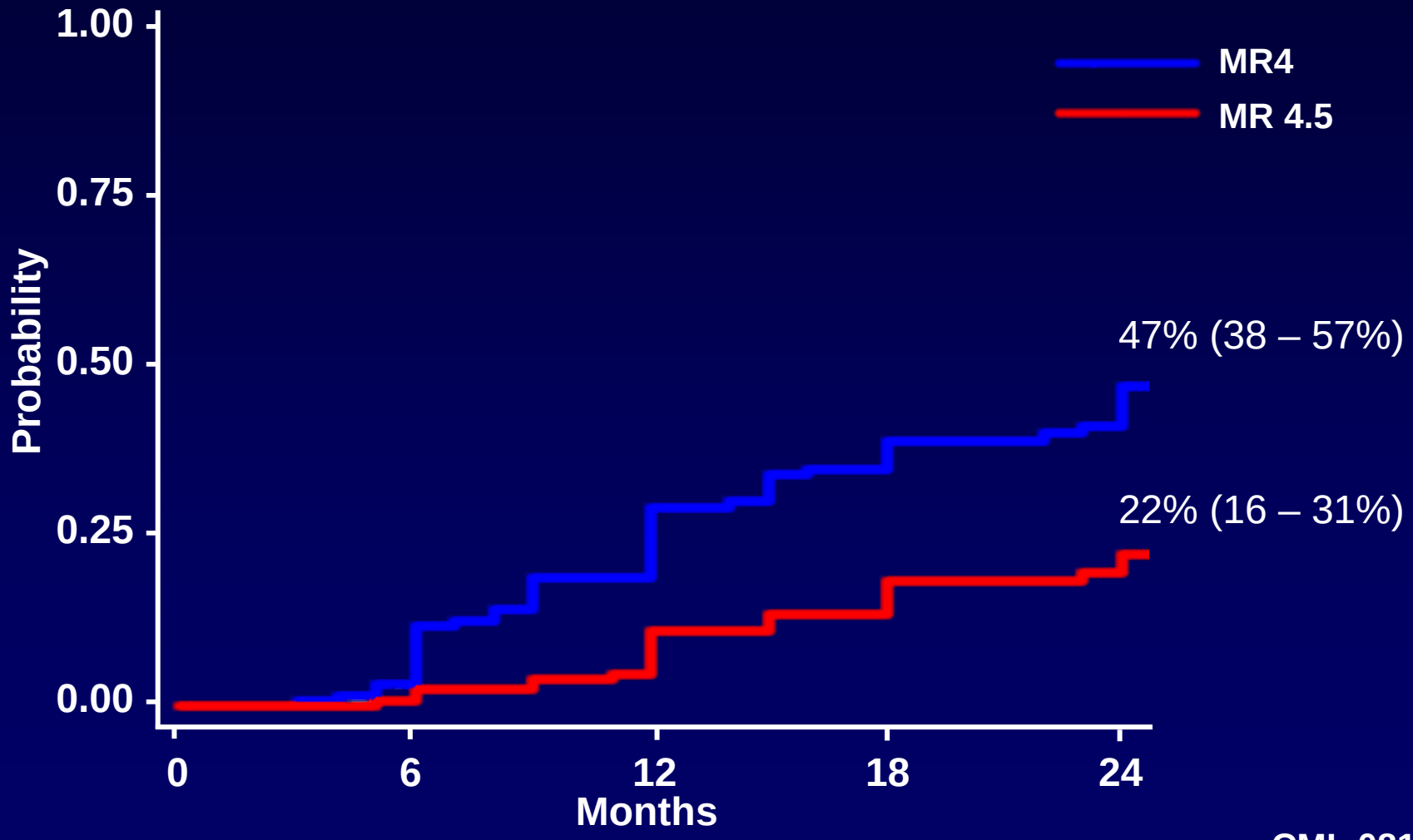
Estimated Cumulative Incidence of Deep MR



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CML 0811

Stability of $MR^{4.0}$

Methods:

- **QPCR every 3 months**
- **$MR^{4.0}$: ≤0.01% $BCR\text{-}ABL^{IS}$ or undetectable BCR-ABL transcript with ≥10,000 ABL transcripts**
- **Sustained $MR^{4.0}$: $MR^{4.0}$ for at least 1 year, with at least 3 evaluable analysis**

Patients achieving an $MR^{4.0}$	**57/130 (44%)**
Sustained $MR^{4.0}$	**27/57 (47%, or 21% of total)**

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Patient Disposition N = 130

Still on study	**107 (82%)**
Off-study	**23 (18%)**
Progression to AP/BP	2 (2%)
Failure	5 (4%)
Toxicity	11 (8%)
Other*	5 (4%)

*Loss to follow-up, consent withdrawal, pregnancy

All the enrolled patients are alive.

At the last contact, the patients still on treatment with NIL were 82%

→75% with 600 mg, 5% with 300 mg or less, 2% with 800 mg daily

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Cardiovascular Events

Overall incidence	**7/130 (5%)**
- Coronary artery disease, n	3
- Arterial thrombosis, n	2
- QTc prolongation, n	1
- Atrioventricular block, n	1

Presence of cardiovascular risk factors at baseline.

The total cholesterol, and both LDL and HDL cholesterol fractions significantly increased during treatment.

Triglyceride concentrations had no significant variations.

A significant increase of HbA1c was not observed.

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Summary

- **The incidence of deep molecular response rates seem to be superior to the historical data of IM.**
- **The duration of observation is still too short to analyze the stability of deep molecular response, but NIL 300 mg BID as front-line treatment of BCR-ABL+ CML, with dose optimization in case of nonoptimal response, may improve the proportion of patients able to discontinue TKI treatment.**
- **Due to the metabolic effects, a baseline evaluation of patients, including comorbidities, is important to maximize the therapeutic benefit and to minimize the cardiovascular risks.**

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