Chronic Myeloid Leukemia
Treatment in Evolution

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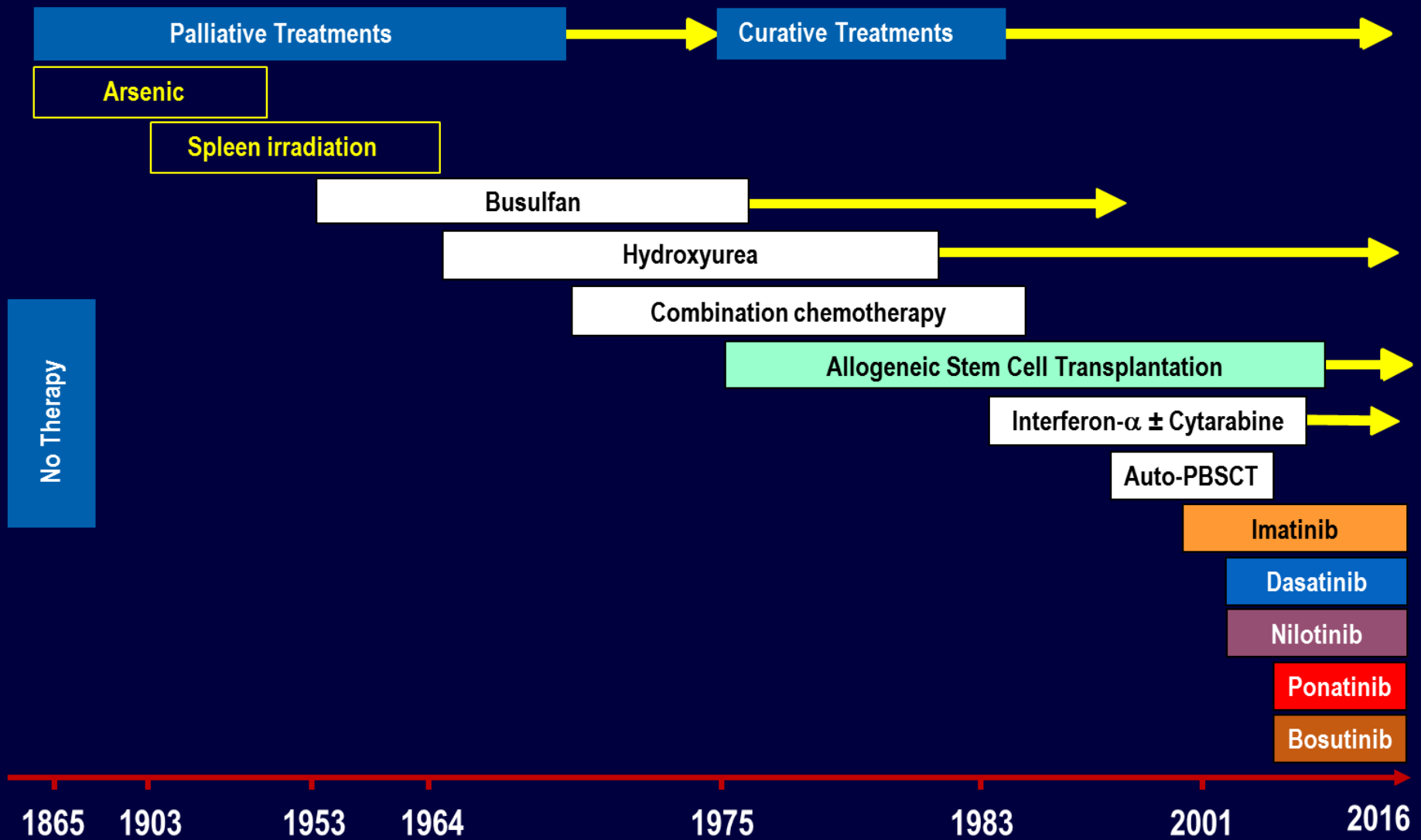
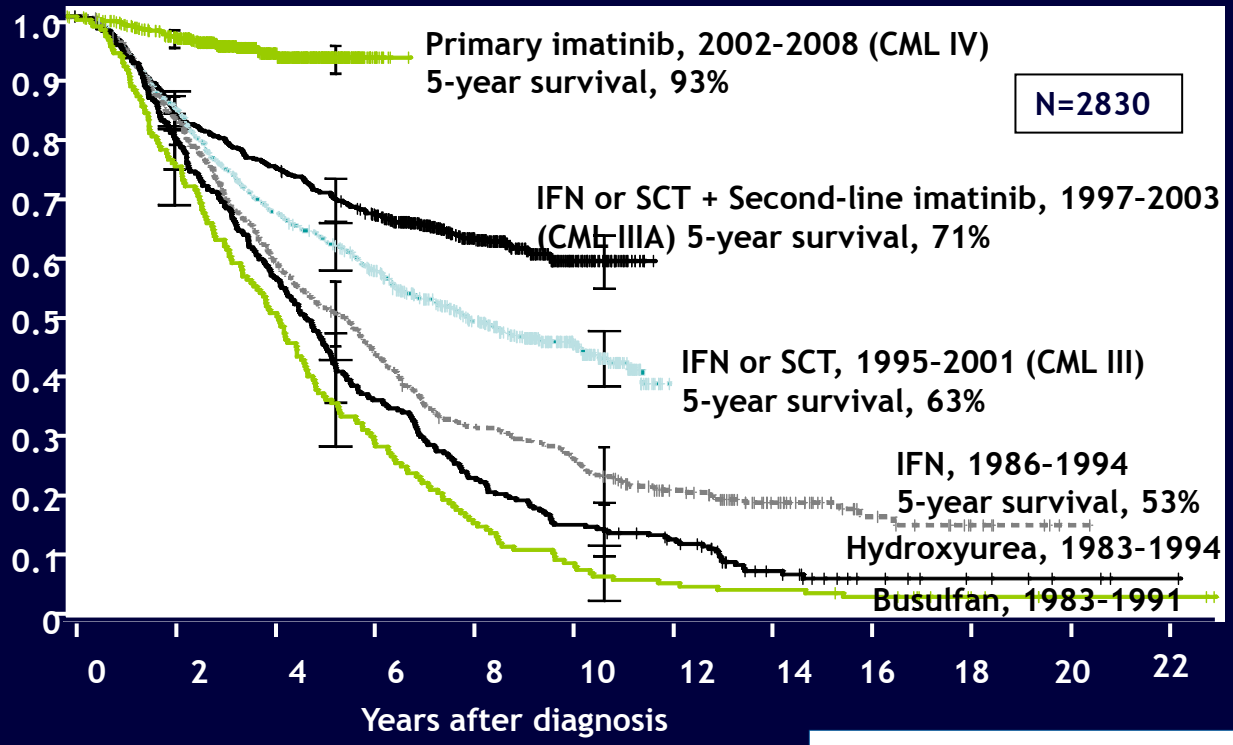
Chronic Myeloid Leukemia: Treatment in Evolution

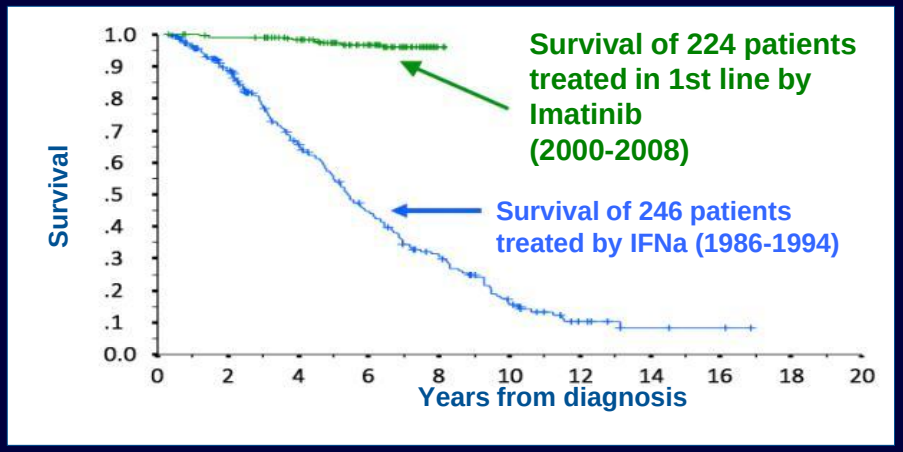


Chronic Myeloid Leukemia: Treatment in Evolution



German CML Study Group 2008

Gambacorti – Passerini C et al. Natl Cancer Inst. 2011



	2006	2009	2016
1st line	Imatinib 400	Imatinib 400	Imatinib 400 Nilotinib (Dasatinib)
2nd line	Allo-HSCT	Nilotinib Dasatinib Allo-HSCT	Nilotinib Dasatinib Bosutinib Allo-HSCT
3rd line	Palliative TT	Palliative TT	Ponatinib Bosutinib Allo-HSCT
Competitors	Allo-HSCT IFNa	none	TKI + IFNa
Milestones	CCyR	CCyR MMR	Early MR CMR

- **First Line of Treatment**
  - ***- Age***
  - ***- Co-Morbidities***
  - ***- Scores : Sokal, Hasford, Eutos***
- **Evaluation according to time**
  - ***- Hematological Response***
  - ***- Cytogenetic Respons***
  - ***- Molecular Response***

The EUTOS Long-term Survival (ELTS) Score

- **2,205 adult patients with Ph+ and/or BCR-ABL1+ CML, imatinib-based treatment within six months from diagnosis.**
- **All patients had been enrolled in controlled clinical trials and became part of the in-study section of the EUTOS registry**

ELTS Score

$$0.0025 \times (\text{age in completed years}/10)^3 + 0.0615 \times \text{spleen size below costal margin} + 0.1052 \times \text{blasts in peripheral blood} + 0.4104 \times (\text{platelet count}/1000)^{-0.5}$$

All variables should be evaluated at diagnosis of the patient.
Age should be given in completed years. The score was validated for patients above 18 years
Spleen size should be inserted in cm below costal margin.
The percentage of blasts in peripheral blood should be rounded to an integer, e.g. 0, 2 or 7.
The platelet count should be given in 10^9/L.

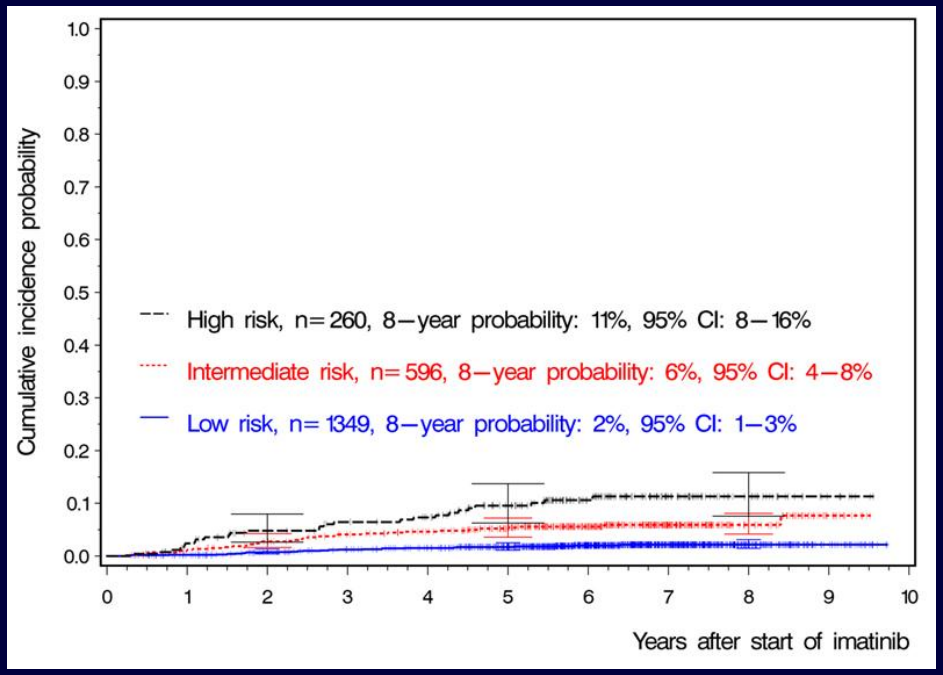
Pfirrmann et al. Leukemia 2016

The EUTOS Long-term survival (ELTS) Score

The ELTS score is rounded to four decimal places.

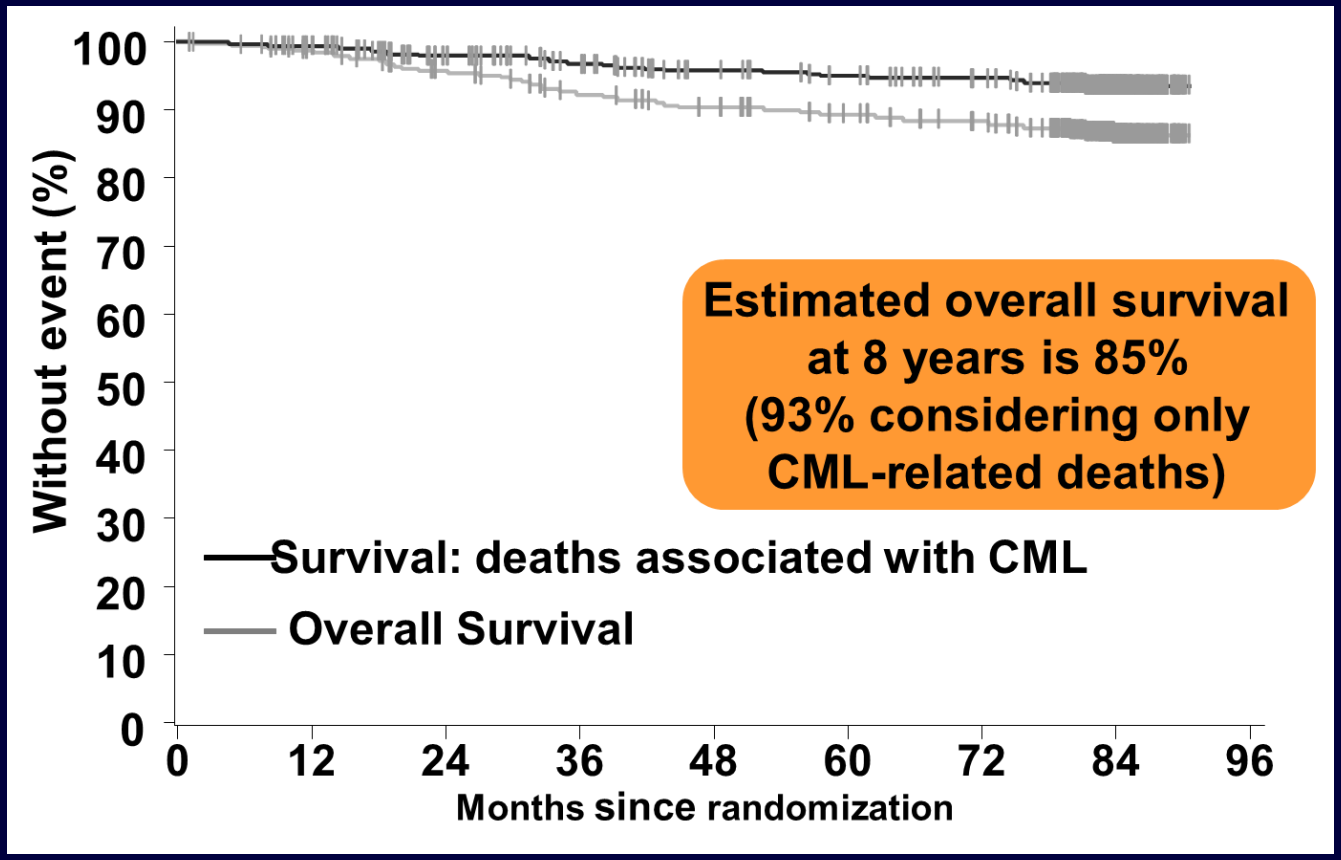
An ELTS score value ≤ 1.5680 defines the low-risk group
An ELTS score value > 1.5680 but ≤ 2.2185 defines the intermediate-risk group
An ELTS score value > 2.2185 defines the high-risk group

Cumulative incidence probability of dying because of CML



Pfirrmann et al. Leukemia 2016

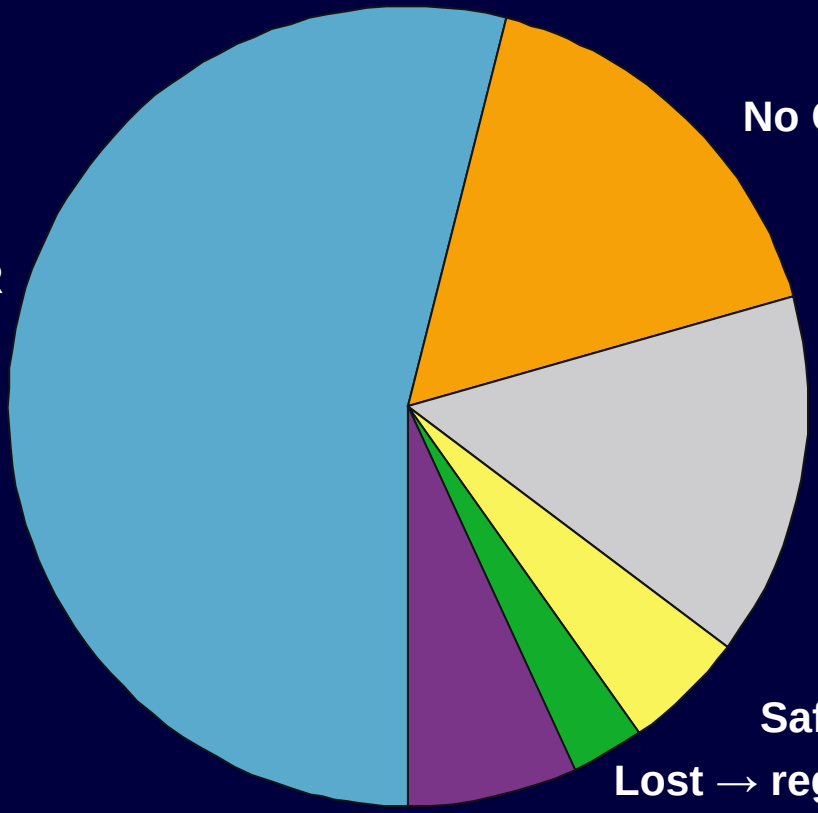
Update of newly-diagnosed Chronic Phase CML patients treated with 400 mg daily imatinib (IRIS trial)



CML patients have almost the survival of the normal population !

Deininger M, et al. Blood 2009

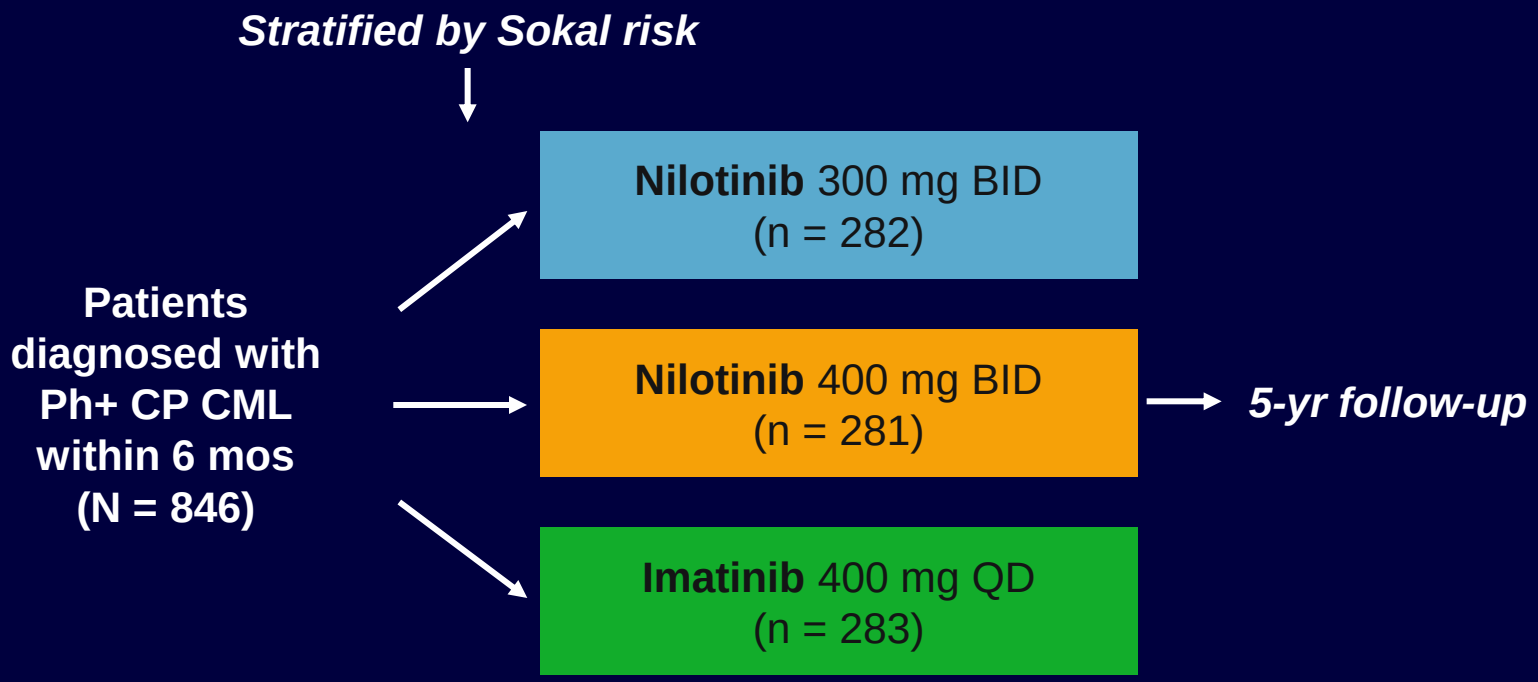
Expectations on Imatinib: IRIS 8-Yr Update Shows 37% Have Unacceptable Outcome



*Unacceptable outcome.

Deininger M, et al. ASH 2009. Abstract 1126.

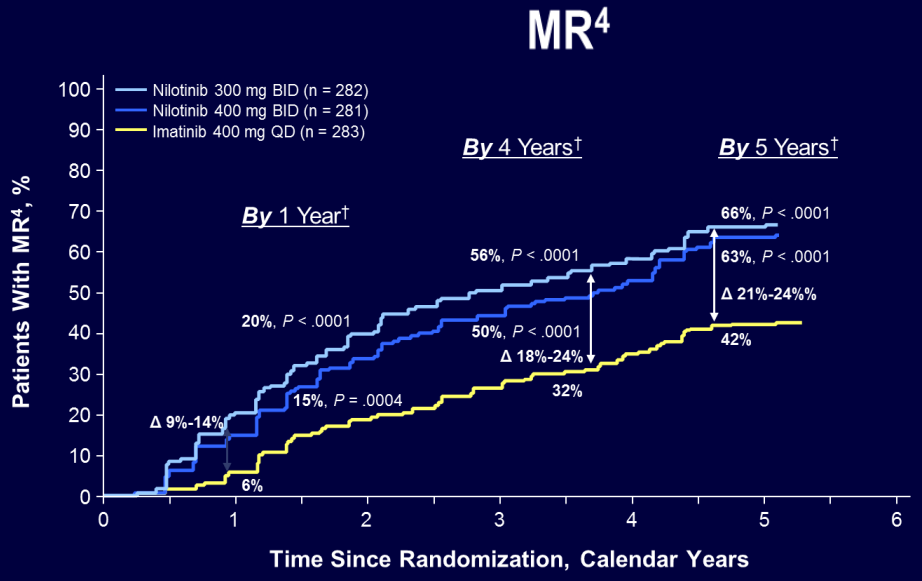
ENESTnd: Comparison of Nilotinib and Imatinib in Newly Diagnosed CP CML

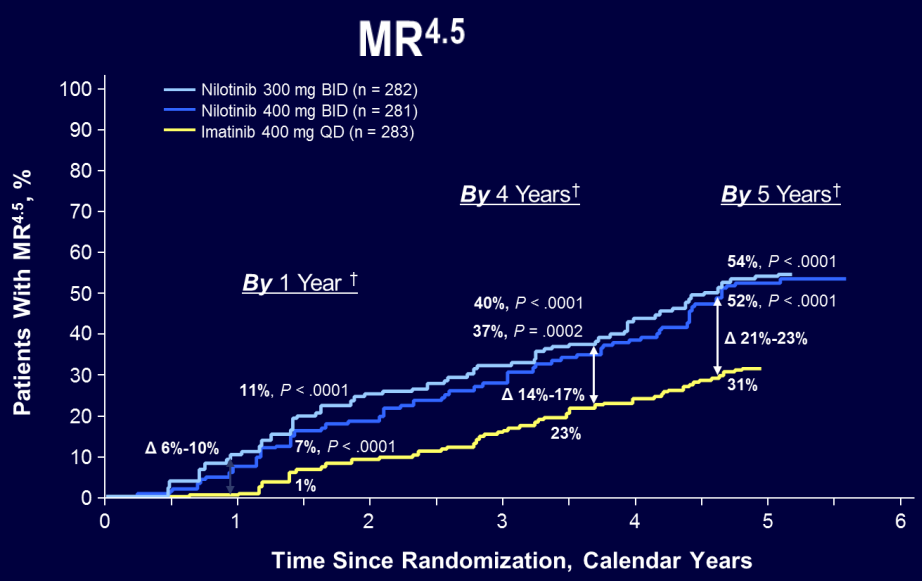


- *Primary endpoint: MMR at 12 mos*
- *Secondary endpoint: durable MMR at 24 mos*
- *Other endpoints: time to MMR, CCyR by 12 mos, time to CCyR, EFS, PFS, OS, time to AP/BC*

Saglio G, et al. N Engl J Med. 2010;362:2251-2259.

ENESTnd: Comparison of Nilotinib and Imatinib in Newly Diagnosed CP CML

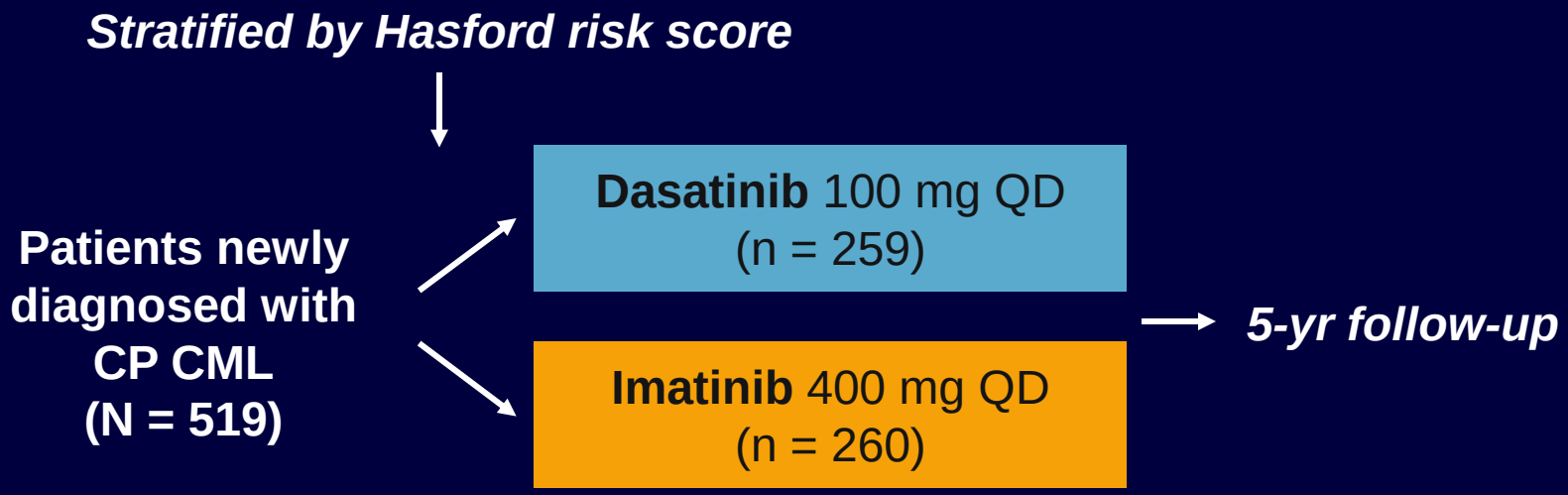




	Imatinib 400 mg QD n = 283	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281
Number of PFS events†	23	22	11
Estimated 5-year PFS, %	91.1	92.0	95.3
Hazard ratio (95% CI)	—	0.92 (0.51-1.65)	0.46 (0.23-0.95)
P value		0.77	0.03
Total deaths [deaths in patients with advanced CML‡]	21 [15]	18 [6]	10 [4]
Estimated 5-year OS, %	91.6	93.6	96.0
Hazard ratio (95% CI)	—	0.84 (0.45-1.58)	0.46 (0.22-0.98)
P value	—	0.58	0.04

Saglio et al. Blood 2013

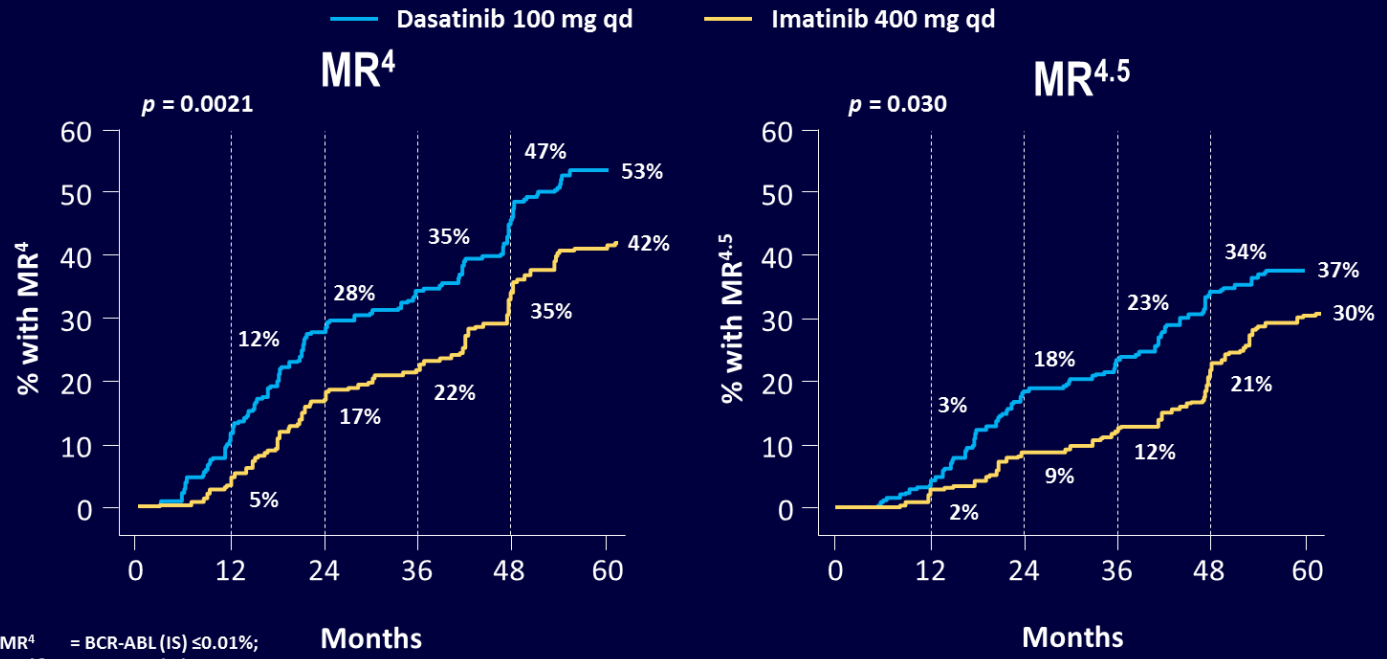
DASISION: Comparison of Dasatinib and Imatinib in Newly Diagnosed CP CML



- *Primary endpoint: confirmed CCyR at 12 mos*
- *Key secondary endpoints: MMR, time in confirmed CCyR, time to confirmed CCyR and MMR, PFS, OS*

Kantarjian HM, et al. N Engl J Med. 2010;362:2260-2270.

DASISION: Comparison of Dasatinib and Imatinib in Newly Diagnosed CP CML

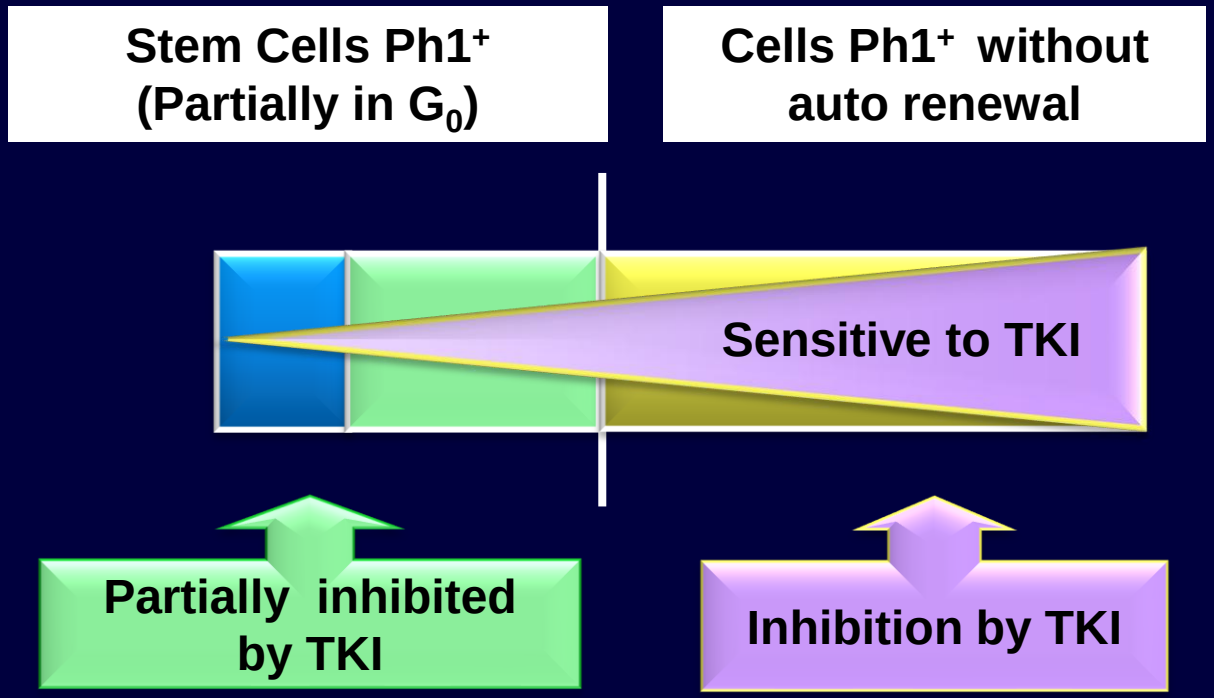


MR[4] = BCR-ABL (IS) ≤0.01%;
MR[4.5] = BCR-ABL (IS) ≤0.0032%;
IS = International Scale.

	Dasatinib 100 mg QD (n=259)	Imatinib 400 mg QD (n=260)	Hazard ratio
Total number of deaths,[a] n	19	21	-
Estimated 4-year OS, %	92.9 (89.7-96.1)	92.1 (88.7-95.4)	HR=0.91 (0.49-1.69)
Estimated 4-year PFS,[b]%	90.0 (86.0-93.9)	90.2 (86.3-94.1)	HR=1.04 (0.58-1.87)

Cortes JE et al. Blood 2013

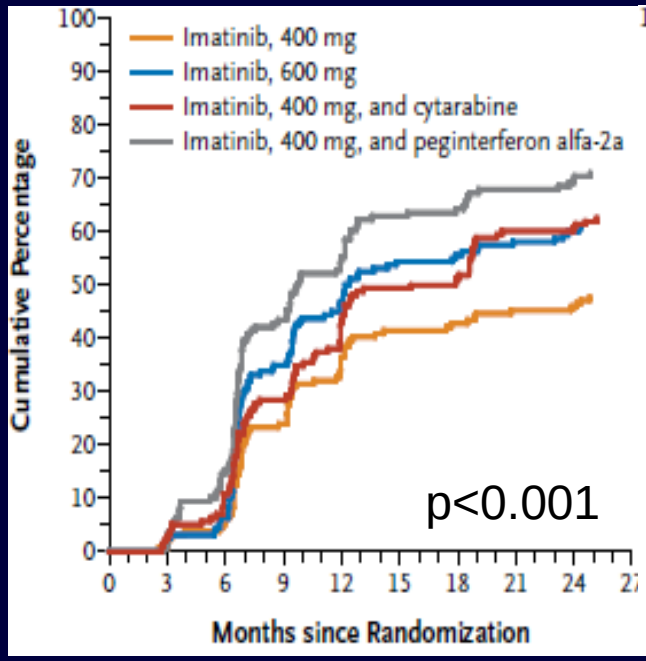
Combination of TKI and IFN-α /: Rationnal



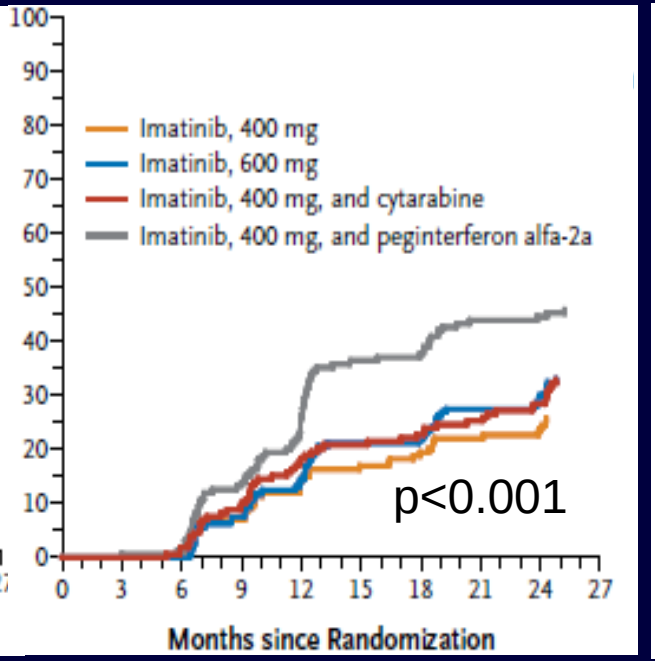
Peg-IFNa 2a + IM first line - SPIRIT study

Cumulative incidences

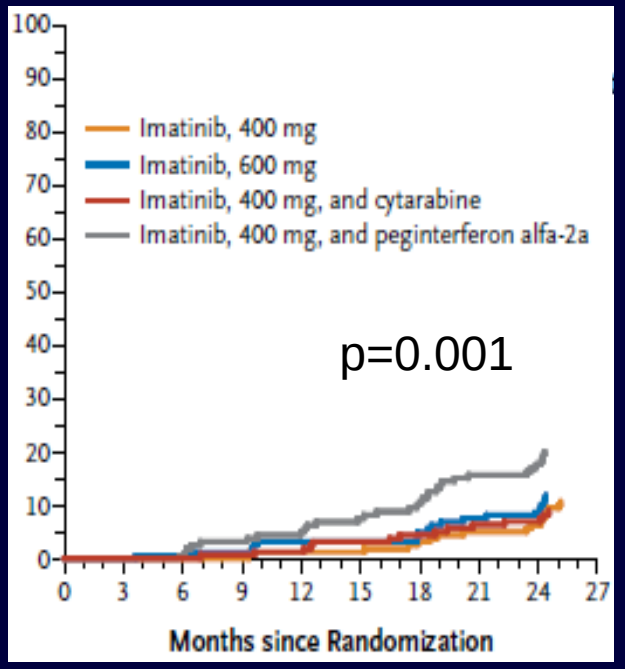
MMR



MR4



>MR4.5



SPIRIT

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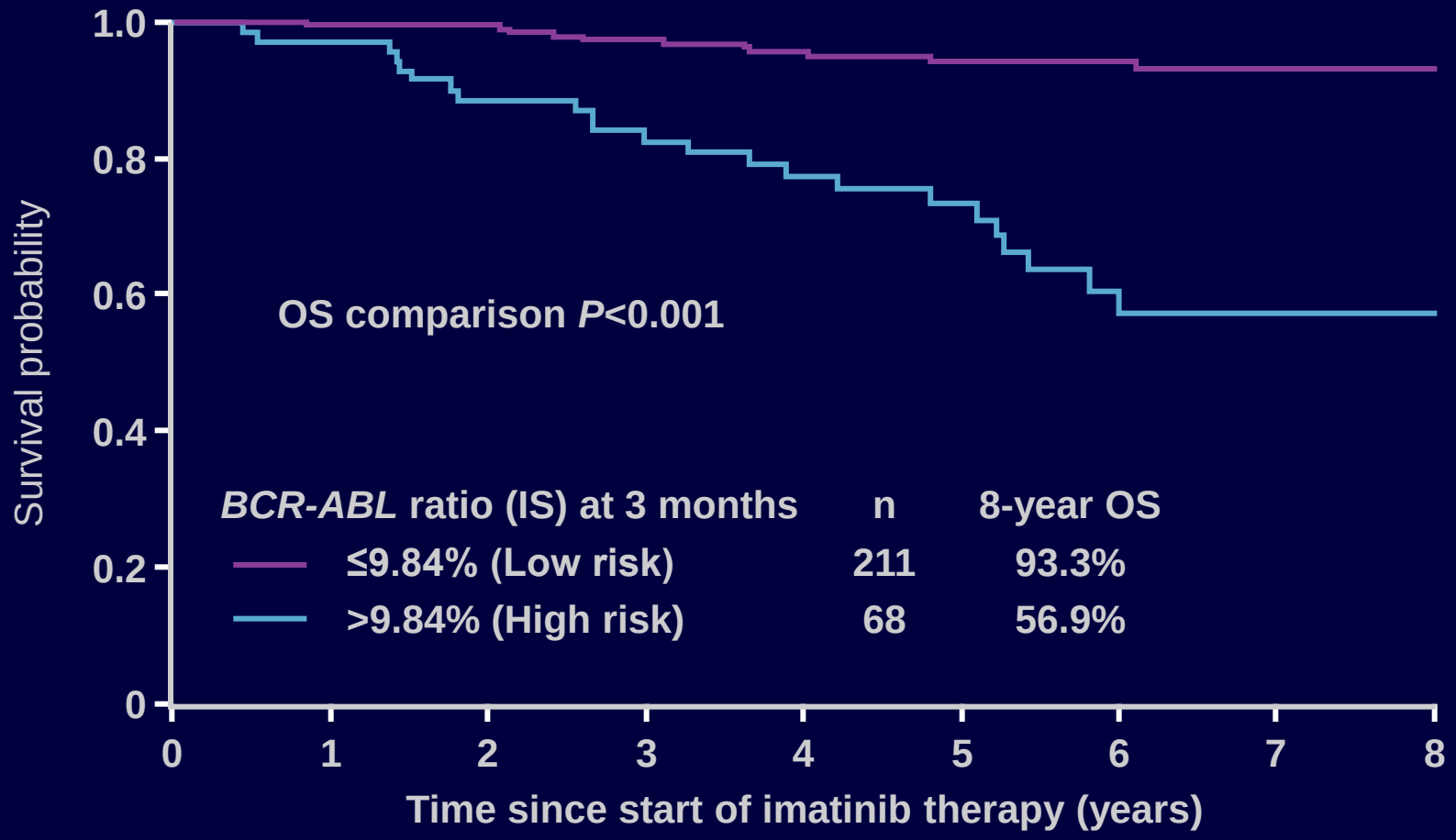
C. Preudhomme et al. N Engl J Med 2010

- **First Line of Treatment**
  - ***- Age***
  - ***- Co-Morbidities***
  - ***- Scores : Sokal, Hasford, Eutos***
- **Evaluation according to time**
  - ***- Hematological Response***
  - ***- Cytogenetic Response***
  - ***- Molecular Response***
  - **- EMR**
  - **- Adverse Events / Mutationnal Status**

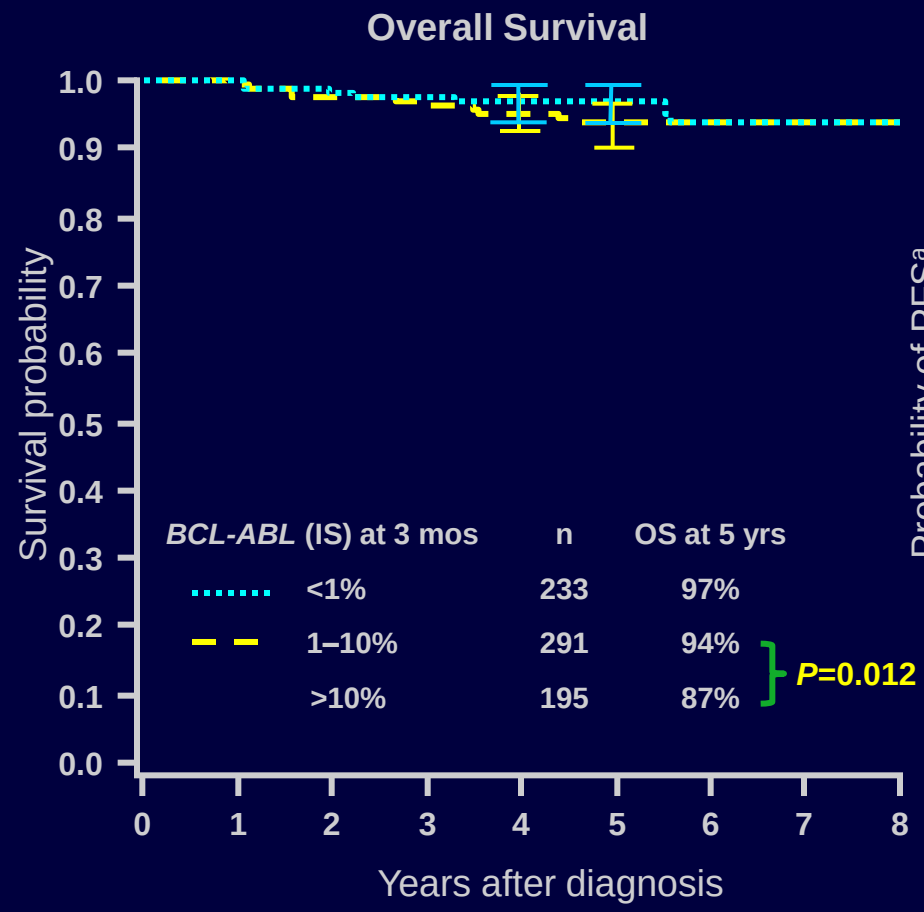
Hammersmith, UK Retrospective Analysis
8 yr OS by 3 month BCR-ABL level

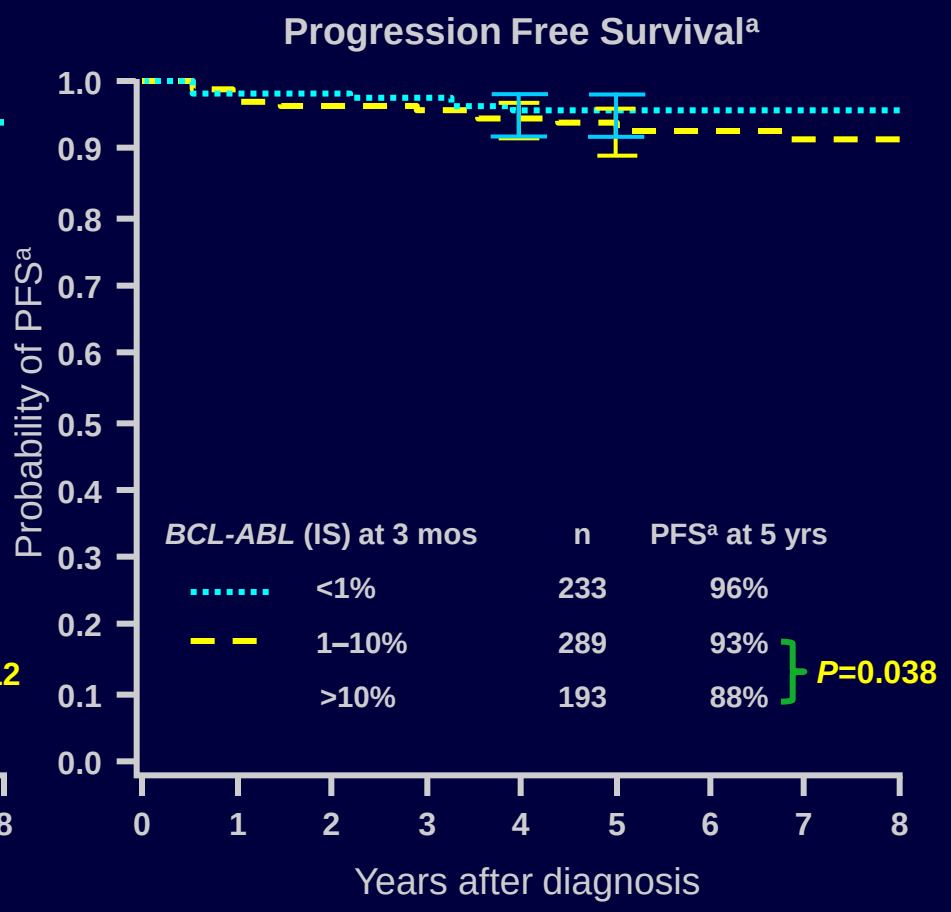


Marin D et al. J Clin Oncol. 2012;30:232-238

German CML IV Study: Long-term Outcomes According to BCR-ABL Levels at 3 Months

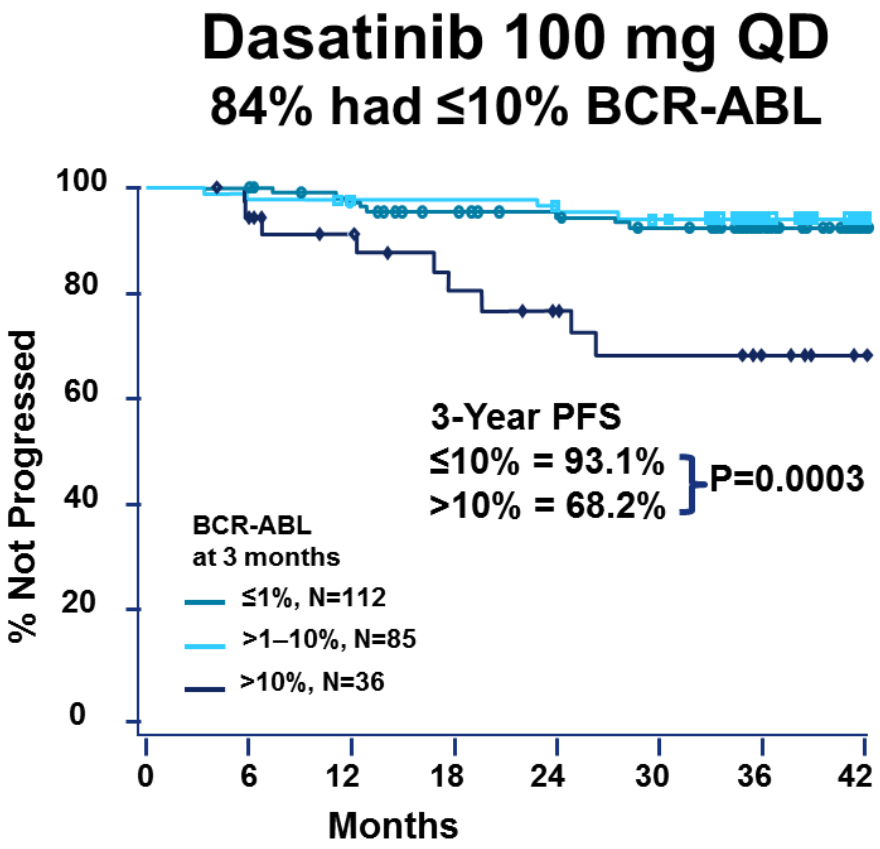
Randomized study of 1340 imatinib-treated patients (median follow-up 4.7 years)

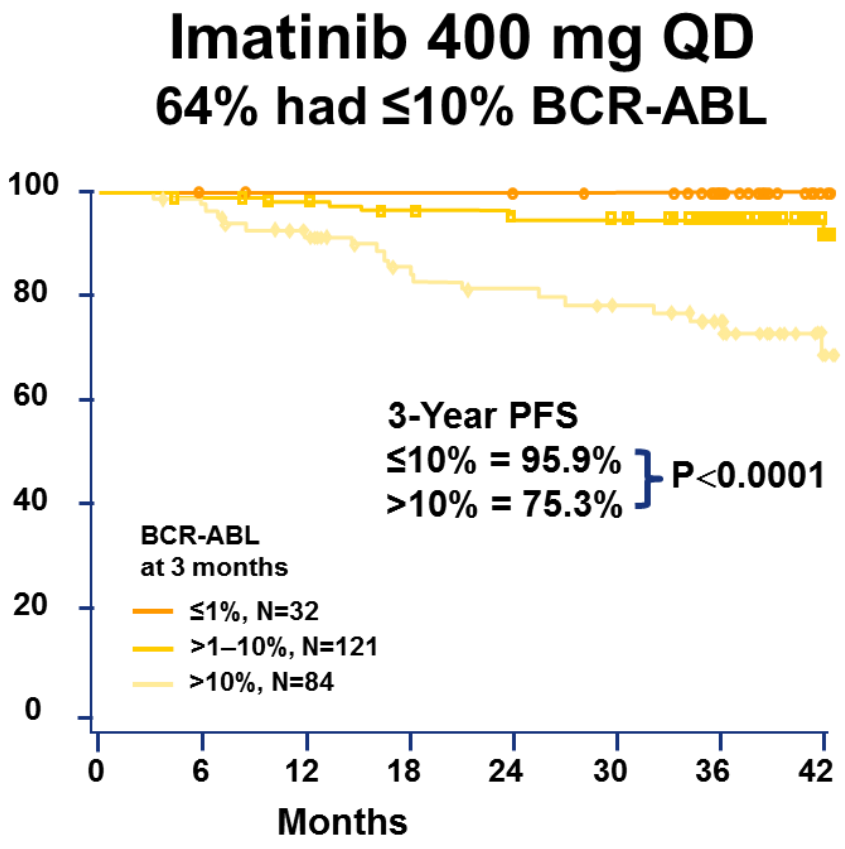




Hanfstein B et al.: ESH-iCML; 2011 (Estoril, Portugal)

DASISION 3 yr update
PFS According to BCR-ABL Level at 3 Months





Evènements Indésirables

Communs aux différents ITK

- Les troubles hématologiques:
- Anémie (baisse de l'hémoglobine)
- Neutropénie (baisse des neutrophiles)
- Thrombopénie (baisse des plaquettes)
- L'asthénie
- Les céphalées
- L'hypophosphatémie

Imatinib

- Les troubles digestifs
- Diarrhées
- Nausées et vomissements
- Douleurs abdominales
- Les hémorragies conjonctivales
- Les œdèmes
- Les troubles musculaires
- crampes
- myalgies
- inflammations

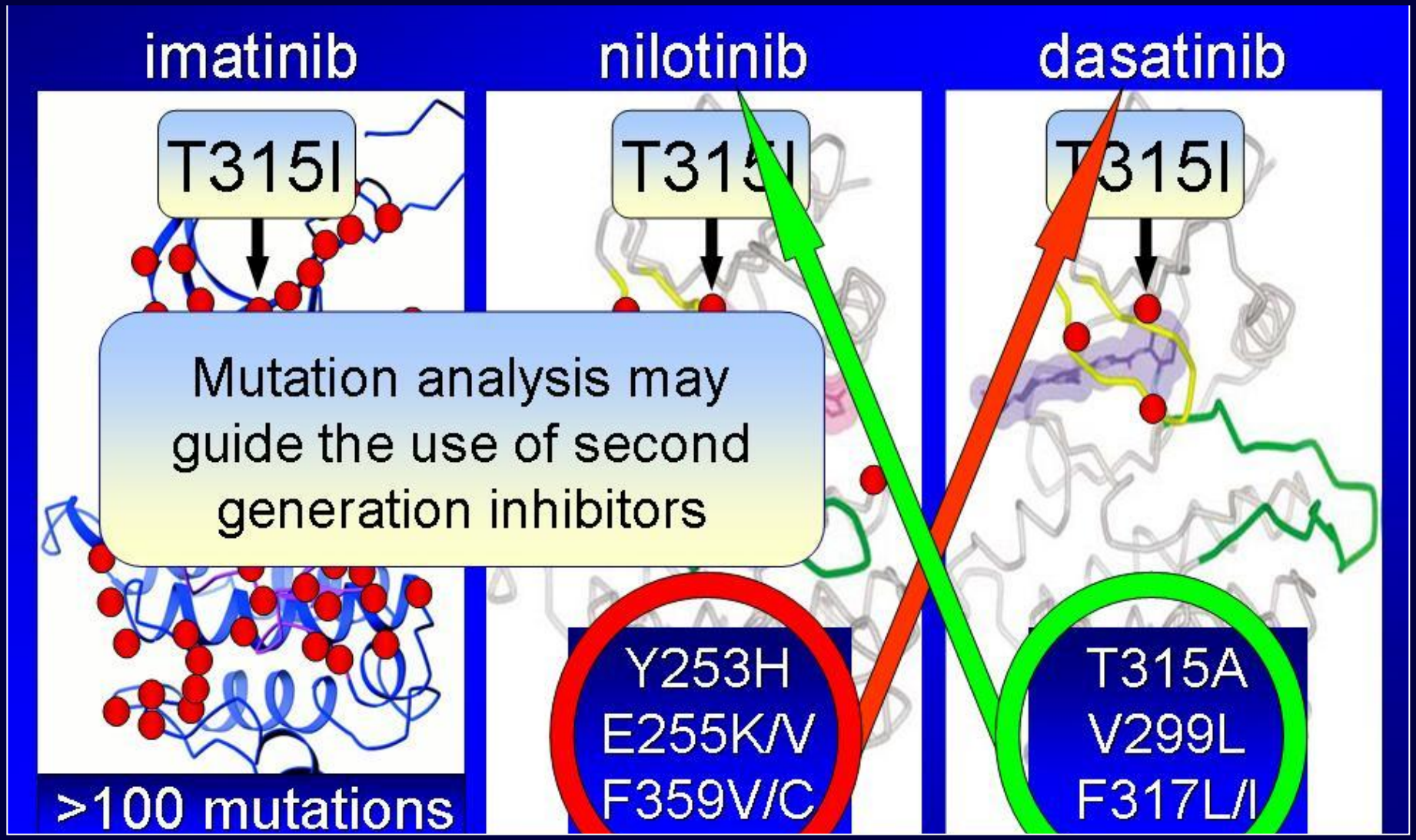
Nilotinib

- Non hématologiques
– Hypokaliémie
– Hypocalcémie
– Hyperglycémie
– Hypercholestérolémie
– Hyperlipasémie
– Perturbations du bilan hépatique
- Troubles cutanés
– Eruption cutanée
– Prurit
– Sécheresse cutanée
- Risque d'accidents artériels

Dasatinib

- Les épanchements de la plèvre (présence de liquide dans la Plèvre)
- L'hypertension artérielle pulmonaire

Impact of mutations on the chance of response to ITK2



- **First Line of Treatment**
  - *Age*
  - *Co-Morbidities*
  - *Scores : Sokal, Hasford, Eutos*
- **Evaluation according to time**
  - *Hematological Response*
  - *Cytogenetic Respons*
  - *Molecular Response*
  - EMR
  - Adverse Events / Mutaionnal Status
- **Second Line of Treatment**
  - *Imatinib to Dasatinib or Nilotinib*
  - *Dasatinib to Nilotinib / Nilotinib to Dasatinib*
  - *Dasatinib or Nilotinib to Bosutinib or Ponatinib*

Bosutinib in TKI-Resistant Setting: Response Rate

CP CML		
Response at Wk 24, n (%)	Prior imatinib (n = 266)	Prior imatinib and dasatinib or nilotinib (n = 108)
MCyR	90 (33.8)	29 (26.9)

Response Rate by Wk 48, n (%)	AP CML (n = 69)	BP CML (n = 60)
CHR	21 (30.4)	9 (15)
OHR	38 (55.1)	17 (28.3)

- **≥ 18 mos MCyR duration in 52.8% of patients with CP CML who received imatinib and achieved MCyR**
- **≥ 9 mos MCyR duration in 51.4% of patients with CP CML who received imatinib and ≥ 1 additional TKI and achieved MCyR**

PACE Trial: Efficacy, Safety Outcomes (Median Follow-up: 10.1 Mos for CP CML)

Patients withCML or Ph-positive ALL resistant or intolerant to dasatinib or nilotinib or with emergent T315I mutation (≥ 2 TKIs: 93%, ≥ 3 TKIs: 58%)

Response, %	CP CML (n = 271)		AP CML (n = 79)		BP CML/ALL (n = 94)	
	R/I	T315I	R/I	T315I	R/I	T315I
CHR or MaHR*	94	91	60	50	35	33
MCyR	49	70	34	56	27	35
CCyR	37	66	20	33	23	26
MMR	23	50	9	17	19	4

Generally well tolerated: grade ≥ 3 AEs in ≥ 10% of patients: elevated lipase (10%), thrombocytopenia (28%), neutropenia (17%). But Problem of Cardiovascular Toxicity !

Cortes JE, et al. ASCO 2012. Abstract 6503

New highlights from ASH 2015

ASH | 57th Annual Meeting & Exposition
Orlando, FL · December 5-8, 2015

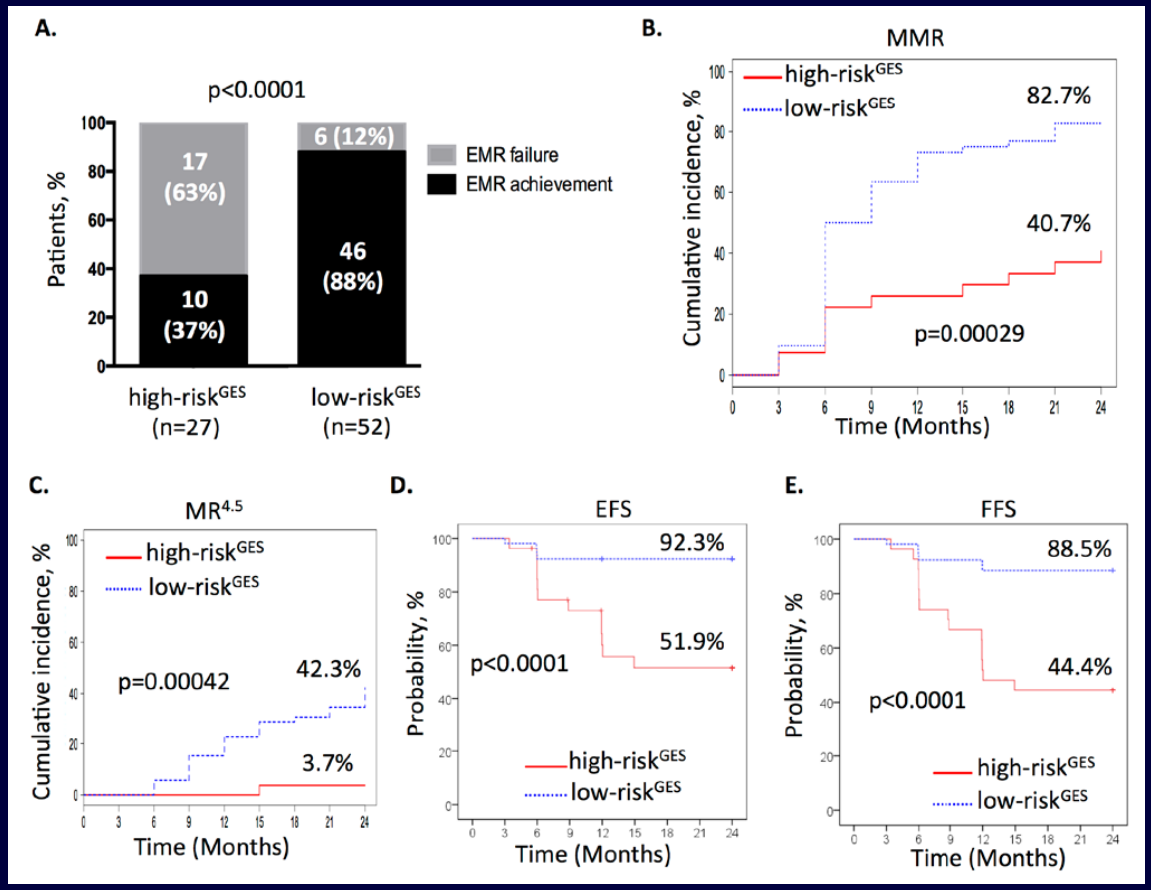
A 20 Gene Expression Signature That Predicts Early Molecular Response Failure in Chronic Phase CML Patients Treated with Frontline Imatinib

PBSC from 119 patients

20 genes detected at diagnosis

IGFBP2, CD3E, RASGRP1, BNIP3L, ETS1, PDK1, METTL7A, HECA, COL8A2, PRSS57, TMEM167A, SPAST, FZD7, VPS41, CDKN1B, CPXM1, SEPT7, RPS28, SLX4IP, & SRSF11

Early molecular response (EMR) failure
BCR-ABL1 >10% @ 3 months



Kok et al. Abstract 596

CD93 is a Novel Biomarker of Leukemia Stem Cells in Chronic Myeloid Leukemia

- **CD93 is a biomarker downregulated in myeloid malignancies (AML)**
- **It is a biomarker of Leukemic Stem Cells in CMLwhich resists to TKI**
- **Could be a good biomarker of MRD (BCR-ABL+)**
- **Some studies are on going to inhibit Leukemic Stem Cells CD93+**

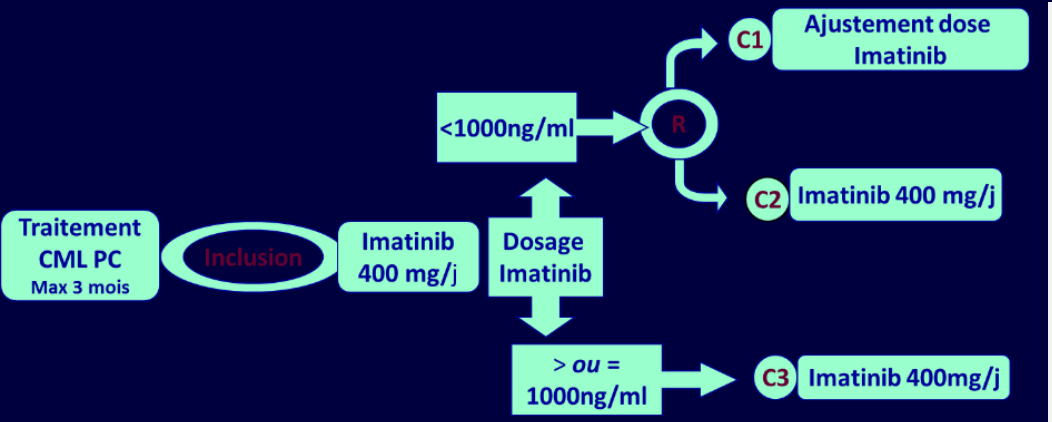
Kinstrie et al. Abstract 49

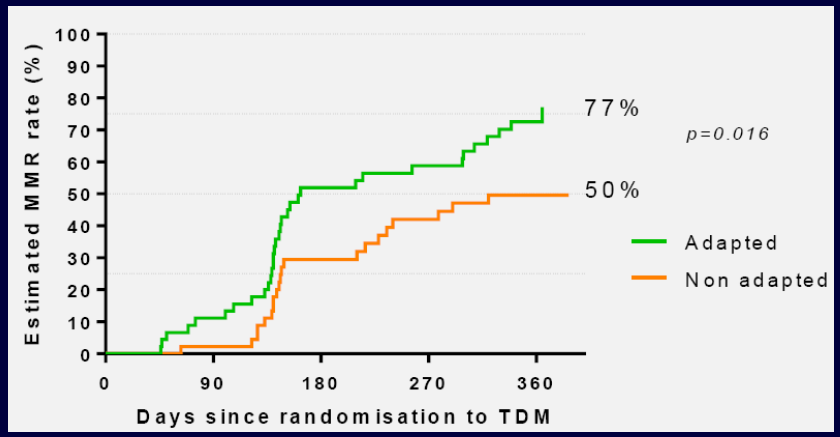
OPTIM study

- Pharmacological Monitoring of Imatinib
- Dose adjustment of 2/3 of patients
- Ameliorate MMR rates at M12
- Important for new Imatinib generics

MMR by 12 months
(post randomization)

Improved MMR in a magnitude similar to 2nd gen TKI

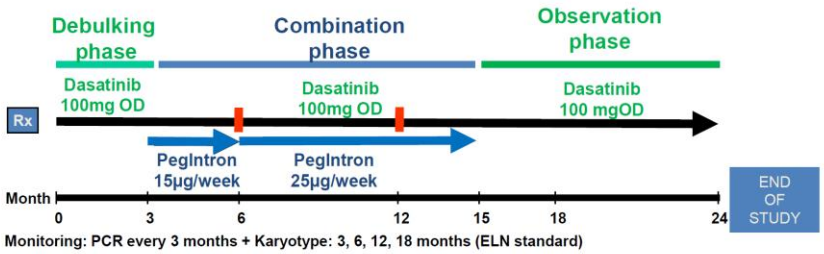




Rousselot P, et al. ASH Annual Meeting 2015. Abstract #133.

Dasatinib+ IFN-α peg (Nordic group)

NordCML007- Outline
CP-CML at debut



Monitoring: PCR every 3 months + Karyotype: 3, 6, 12, 18 months (ELN standard)

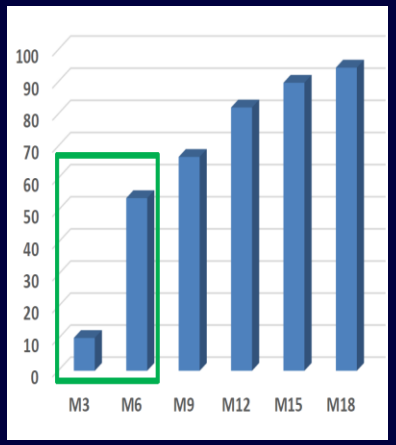
Primary endpoint
Rate of MMR at M12
Study stops if excessive tox in run-in phase M6 (Phase IB)

Secondary endpoints:
CCyR, MMR, MR4 MR4.5 at standard time points.
Safety

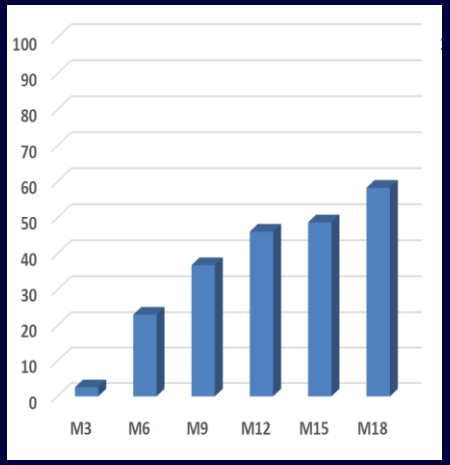
Included from : Feb2013 - May 2014

Historical reference population: DASISION

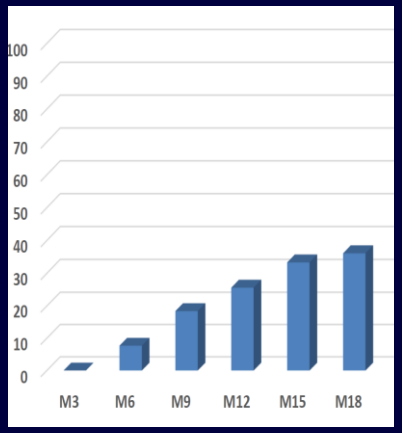
ncml STUDY GROUP



MMR



MR4



MR4.5

No progressions

5 pts failures (ELN): No mutations

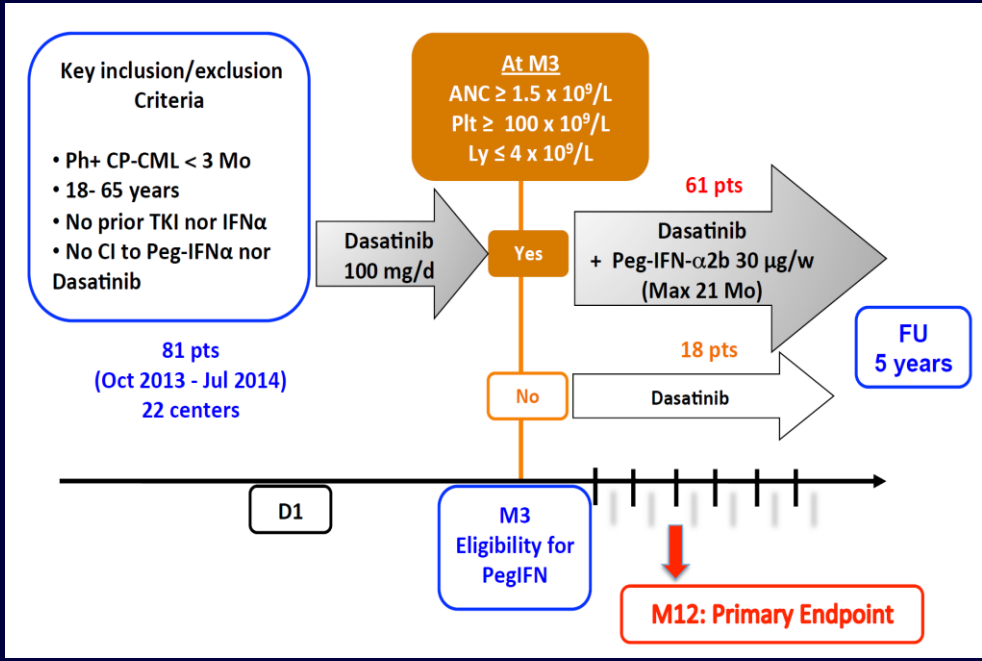
3 patients switched to NIL

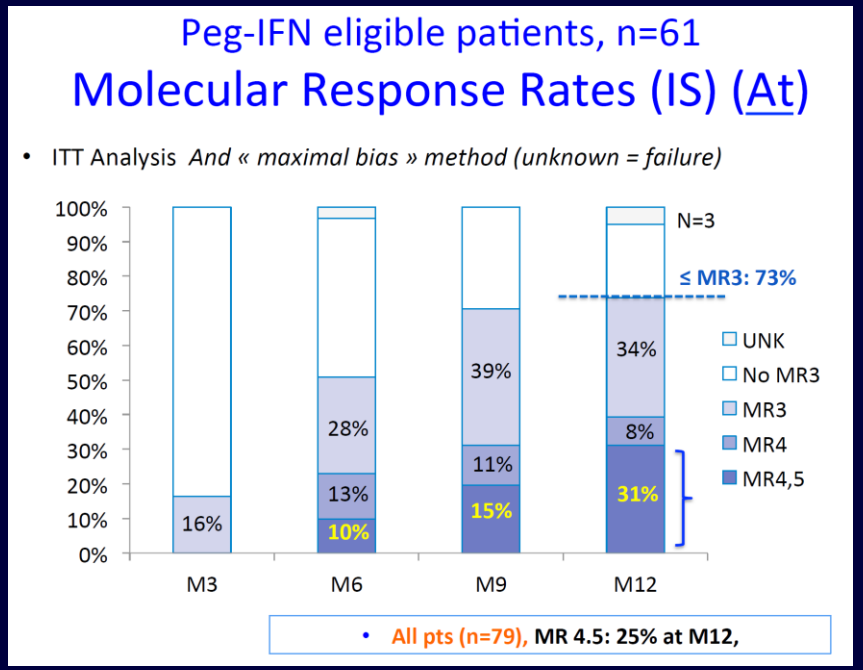
1 SCT

Hjörth-Hansen H. et al. Abstract 477

Dasatinib + IFN-α peg (French group)

DASA-PegIFN





Primary endpoint: Cumulative rate of MR4.5 by 12 months.

Secondary endpoints: Safety, doses, discontinuation, efficacy

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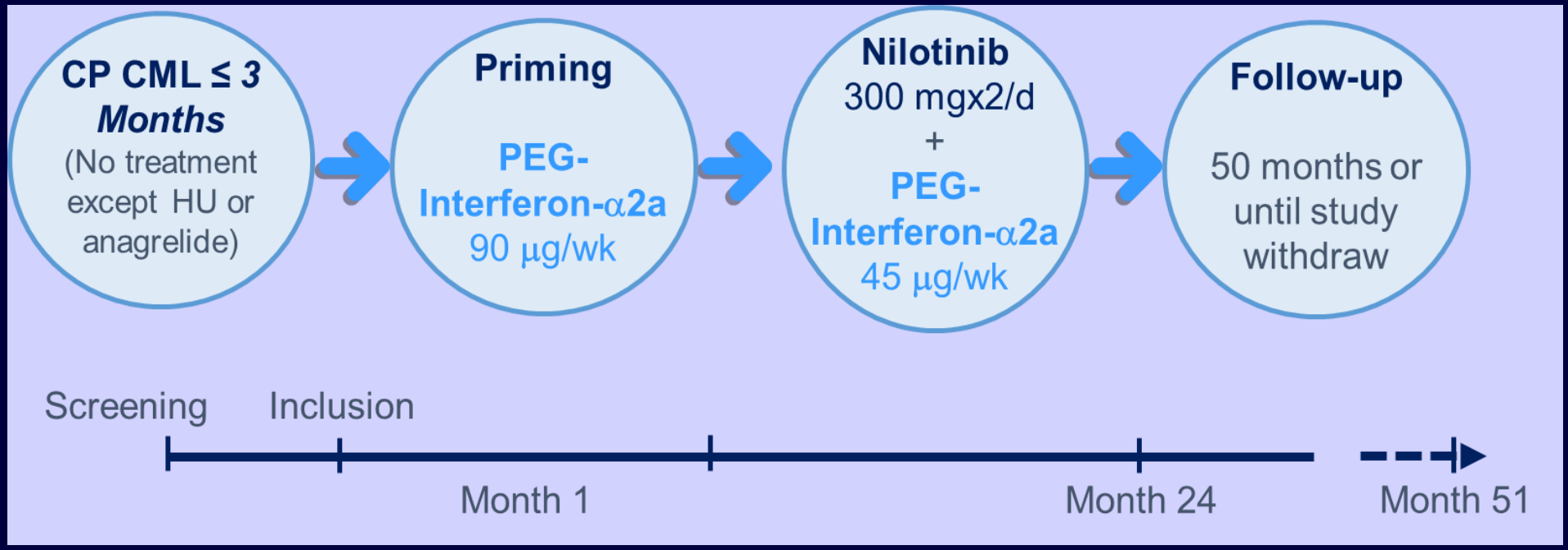
Roy L et al. Abstract 137

Nilotinib + IFN-α peg (French group)

Median FU : 48 months



Primary endpoint : Rate of confirmed molecular response 4.5 (MR4.5) at 12 months

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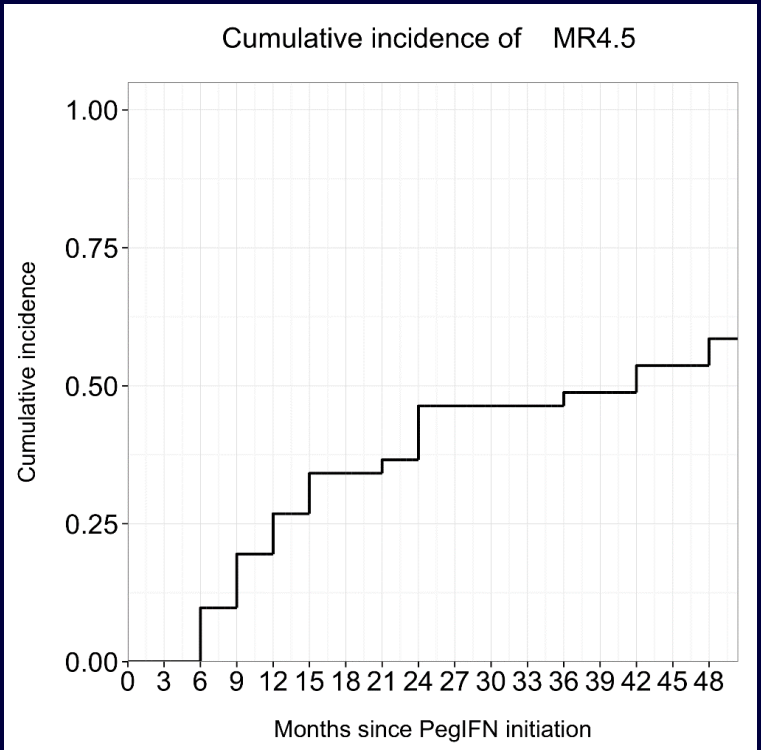
Nicolini FE et al. Abstract 1578

Nilotinib + IFN-α peg (French group)

Median FU : 48 months



At last FU:

- **8 patients (19.5%) were in TFR for a median of 6.8 (0.5-9.5) months after 2-year consecutive MR4.5, and none lost MMR.**
- **One lymphoid blast crisis (died after allo-SCT).**
- **No additional grade 3-4 hematologic or biochemical toxicities occurring after 24 months**
- **10 patients (24%) switched for another TKI for insufficient cytogenetic or molecular response (2 patients) or for toxicity (8 patients)**
- **5 patients presented cardio-vascular events (3 coronary stenosis, 1 brain stroke 1 PAOD)**

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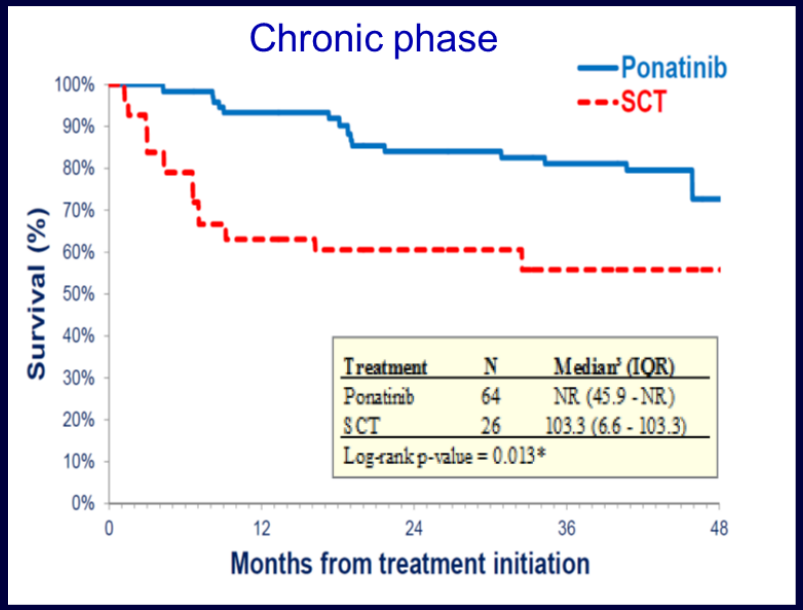
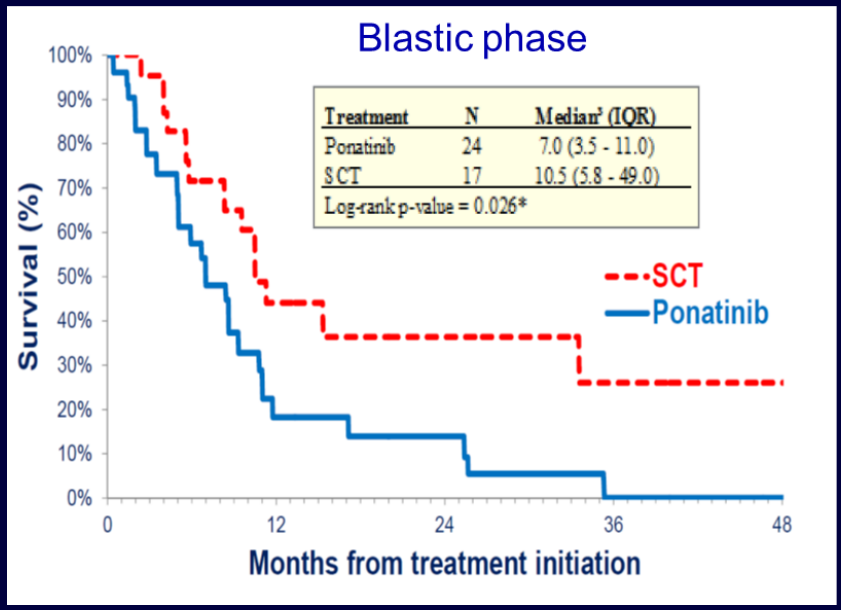
FRANCE INTERGROUPE DE LA LEUCEMIE MYELOIDE CHRONIQUE

Nicolini FE et al. Abstract 1578

T315I : Allo-HSCT or Ponatinib ?

Matching patients T315I PACE versus EBMT Registry

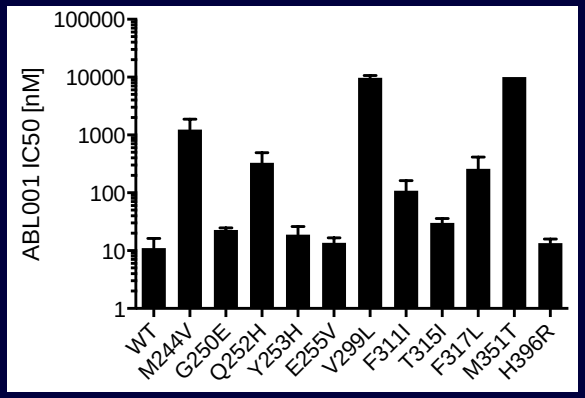


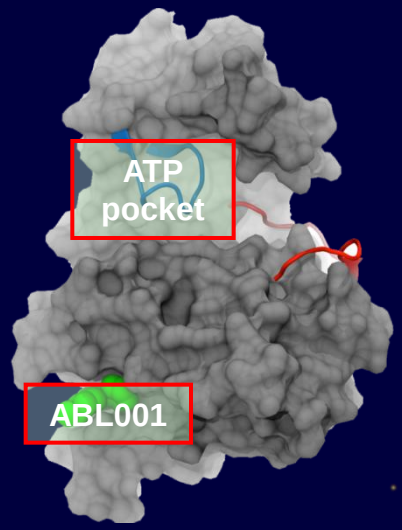


Nicolini FE et al. Abstract 480

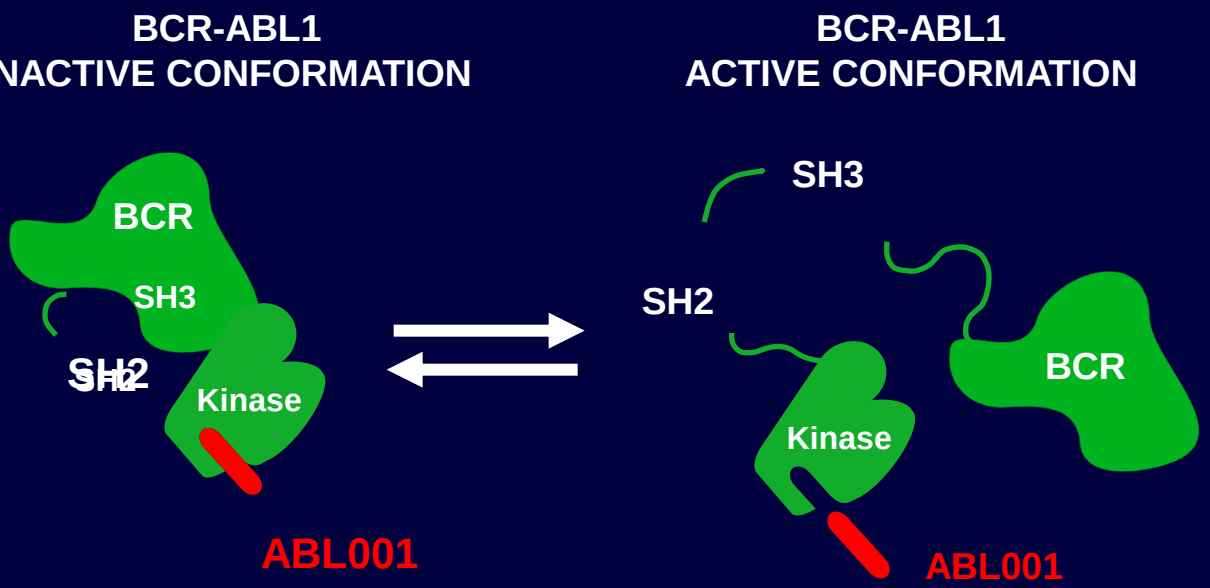
ABL001

- Potent and selective allosteric inhibitor of BCR-ABL1 and ABL1/2
- Active against cell lines with ATP binding site BCR-ABL1 mutants and in murine BCR-ABL1+ tumor model
- Phase I trial ongoing
- Rapid absorption in humans
- Short half life: median 5-6h





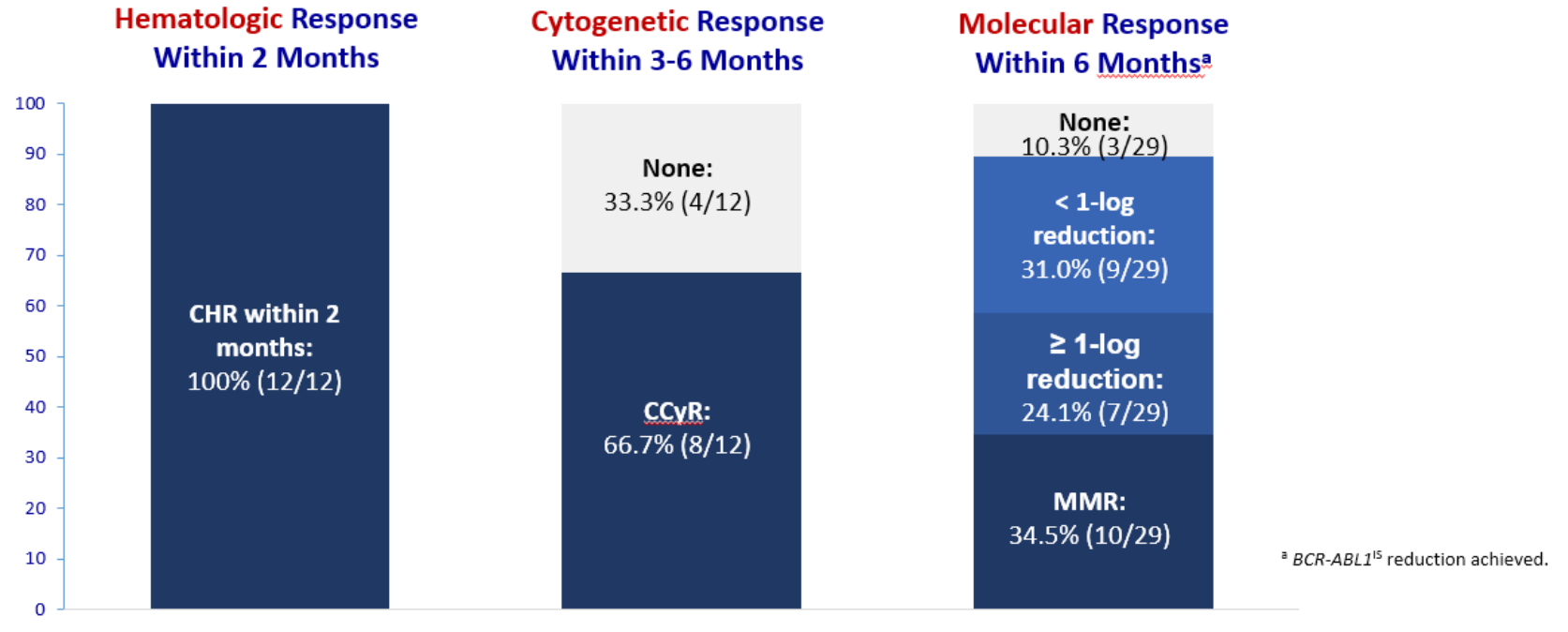
BCR-ABL1 kinase domain



O'Hare T. et al. ASH Annual Meeting 2015. Abstract #1565.

Ottmann O. et al. ASH Annual Meeting 2015. Abstract #138.

Responses in patients with ≥ 3 months of follow-up on study (n = 29)



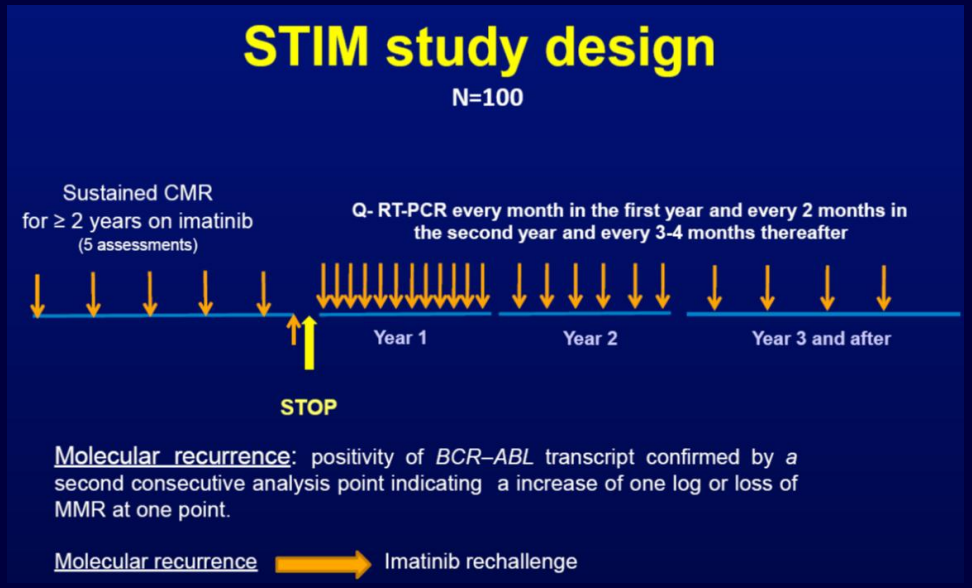
- No death on study
- Dose escalation is o occurred ngoing
- 5 dose-limiting toxicities:
  - *Grade 3 lipase increase n=2 /Grade 2 myalgia/arthralgia n=1*
  - *Grade 3 acute coronary event n=1 /Grade 3 bronchospasm n=1*

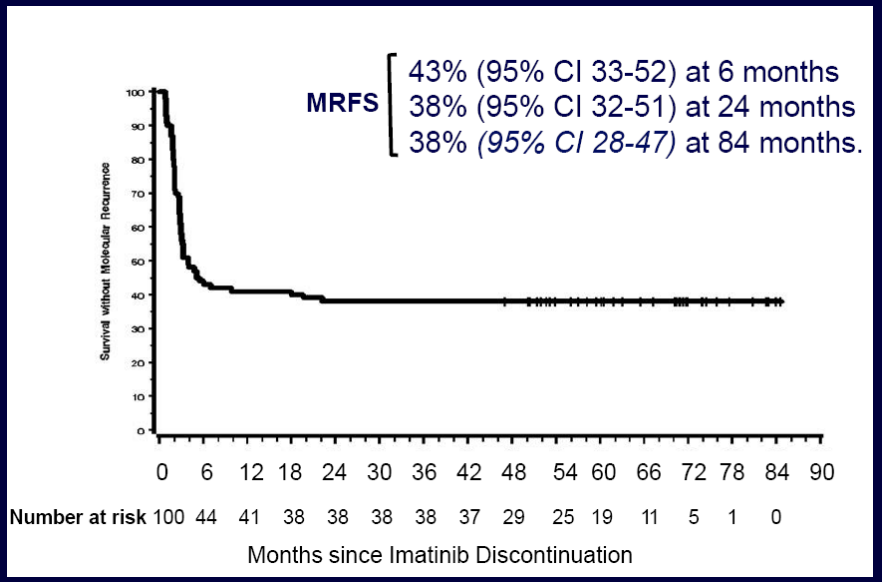
Ottmann O. et al. ASH Annual Meeting 2015. Abstract #138.

Molecular Reccurence-Free Survival (MRFS)

after imatinib discontinuation – Median follow-up = 65 months.

(



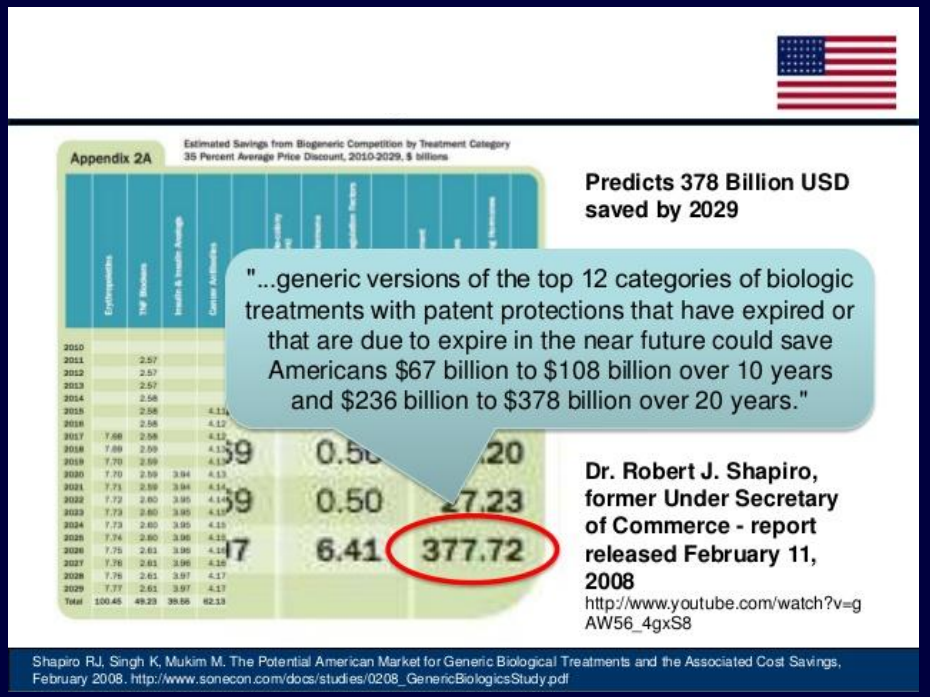


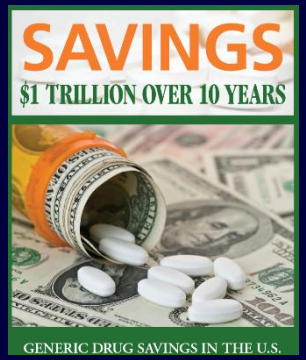
Saving more than 10 Millions Euros !!!

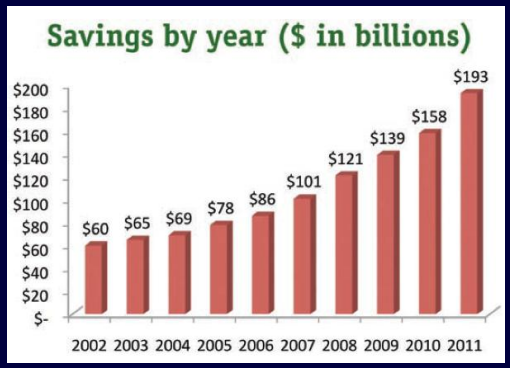
Etienne G. et al. ASH Annual Meeting 2015. Abstract #345.

Annual price of TKI

Country	Price in thousands of US dollars (rounded to nearest $0.5 thousand)		
	Imatinib	Nilotinib	Dasatinib
United States	92	115.5	123.5
Germany*	54	60	90
United Kingdom	33.5	33.5	48.5
Canada	46.5	48	62.5
Norway	50.5	61	82.5
France	40	51.5	71
Italy	31	43	54
South Korea	28.5	26	22
Mexico	29	39	49.5
Argentina	52	73.5	80
Australia	46.5	53.5	60
Japan	43	55	72
China	46.5	75	61.5
Russia	24	48.5	56.5
South Africa	43	28	54.5





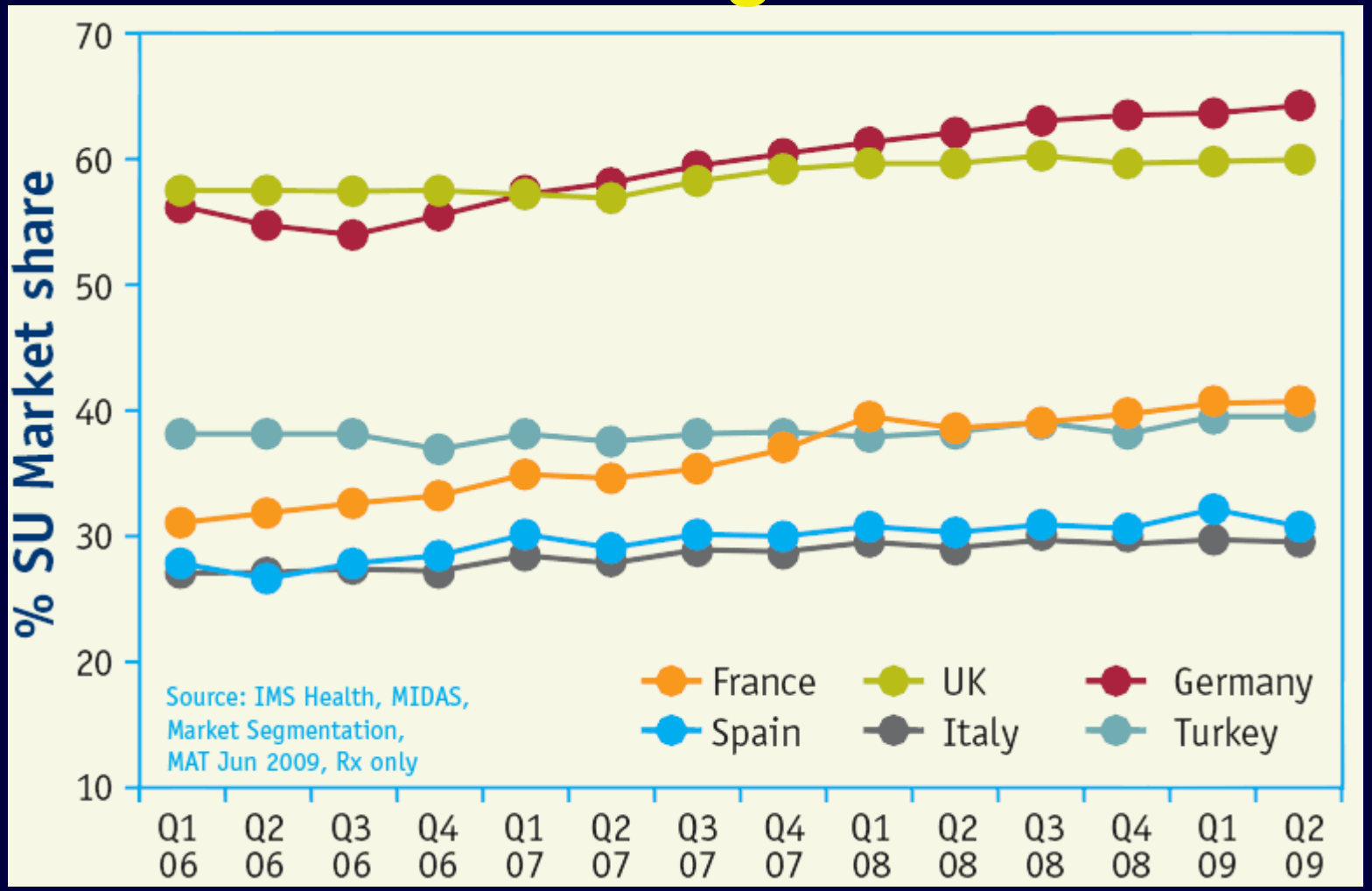


Experts in CML, Blood 2013

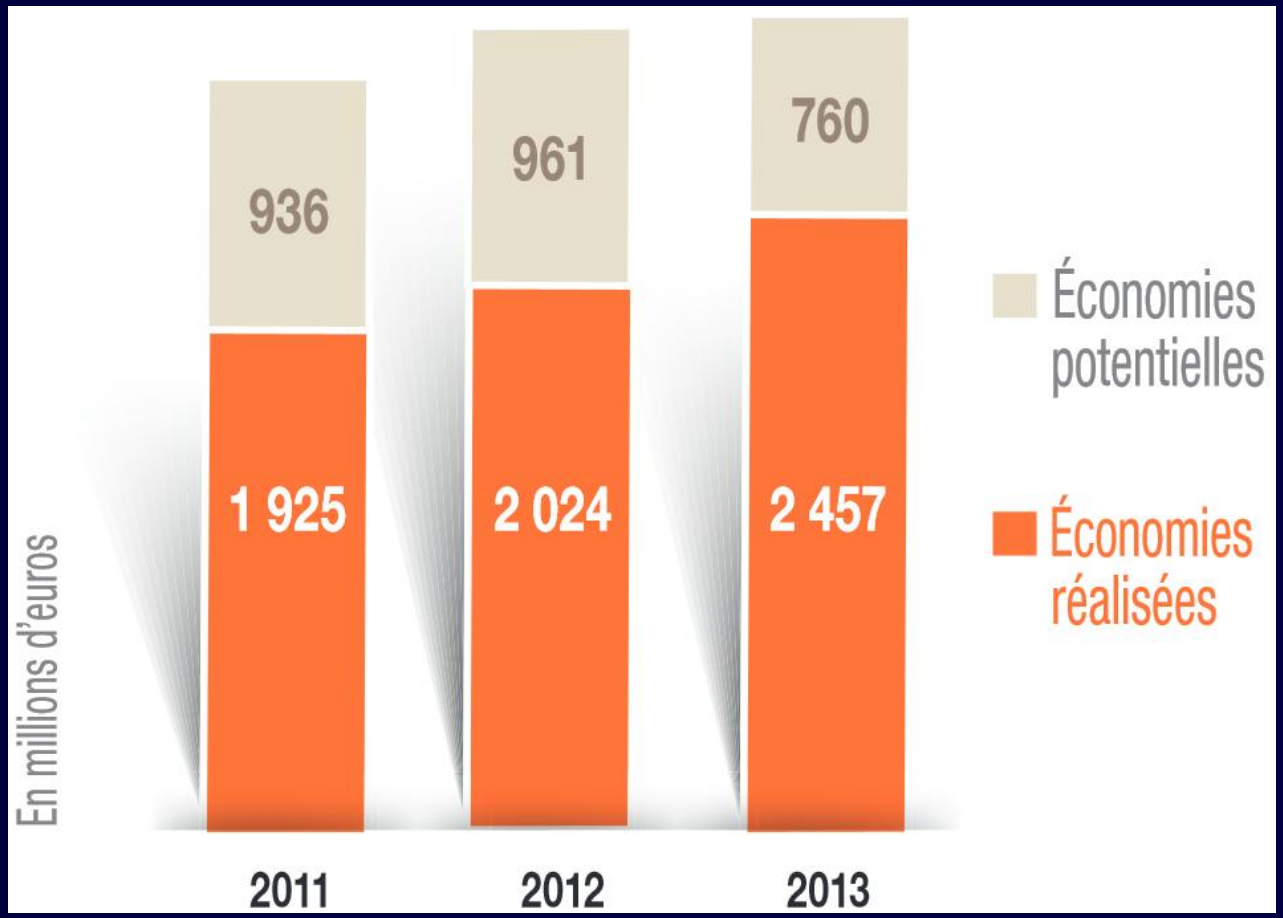
Marketing opening for Imatinib generic

PROTECTION EXPIRY YEAR	US		JAPAN	UK	FRANCE	GERMANY
2012	Plavix® Seroquel® Singulair® Actos® Lexapro®	Diovan® Diovan HCT® Geodon® Boniva®	Nu Lotan Myslee® Preminent Haigou Seroquel®	Lipitor® Amias Seroquel® Aricept® Singulair®	Tahor Singulair® Pariet® Ixprim Aprovel	Seroquel® Atacand® Atacand® Plus Sortis® Aricept®
2013	Oxycontin® Aciphex® Zometa®	Xeloda® Opana®ER Asacol®	Diovan® Plavix® Livalo® Elplat®	Viagra® Xeloda®	Seretide® Coaprovel Xeloda® Micardis® Viagra®	Viani® Zometa® Atmadisc® Coaprovel Viagra®
2014	Nexium® Cymbalta® Celebrex® Symbicort®	Lunesta® Restasis® Evista® Sandostatin® LAR Actonel®	Prograf® Glivec® Abilify®	Abilify® Cipralex® Risperdal® Consta®	Seroplex® Abilify® Ebixa® Risperdal® Consta® LP	Axura Risperdal® Consta® Blopress Plus®
2015	Abilify® Copaxone® Gleevec® Namenda®	Provigil® Combivent® Zyvox® Prezista® Avodart®	Zyprexa® Adoair® Alimta® Spiriva® Symbicort®	Spiriva® Cymbalta® Alimta®	Alimta® Spiriva® Copaxone® Protelos® Cymbalta®	Spiriva® Copaxone® Alimta® Cymbalta®
2016	Crestor® Benicar® Benicar HCT® Cubicin®		Blopress Baraclude®	Glivec® Vfend®	Glivec® Cancidas® Vfend®	Glivec® Zyvoxid Vfend®

Generic drugs market



In 2013, the estimated benefit from using generic drugs in France is more than 2,5 Billion Euros !



Imatinib generics in Poland – economical considerations

Regulation (Pharma Law): the price should be < 50% of original medicament

12 generic preparations available

No.	Generic's Name	Pharma Company
1	Imakrebin	Alvogen
2	Imatenil	Biofarm
3	Imatinib Accord	Accord Healthcare
4	Imatinib Actavis	Actavis Polska
5	Imatinib Apothex	Apothex
6	Imatinib medac	Medac
7	Imatinib Polfa	Polfa S.A.
8	Imatinib Teva	Teva Pharmaceuticals
9	Imatinib Zentiva	Zentiva
10	Meaxin	Krka
11	Nibix	Adamed
12	Telux	Nobilus Ent

Initial price in many hospitals (result of a tender): app. 2%-5% of original imatinib

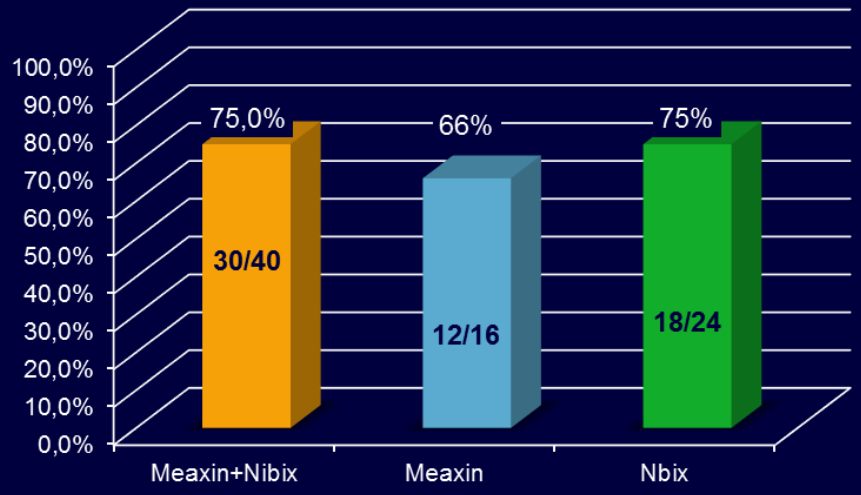
Current price in majority of hospitals (result of a tender): app. 5%-10% of original

Polish Imatinib Generics Registry

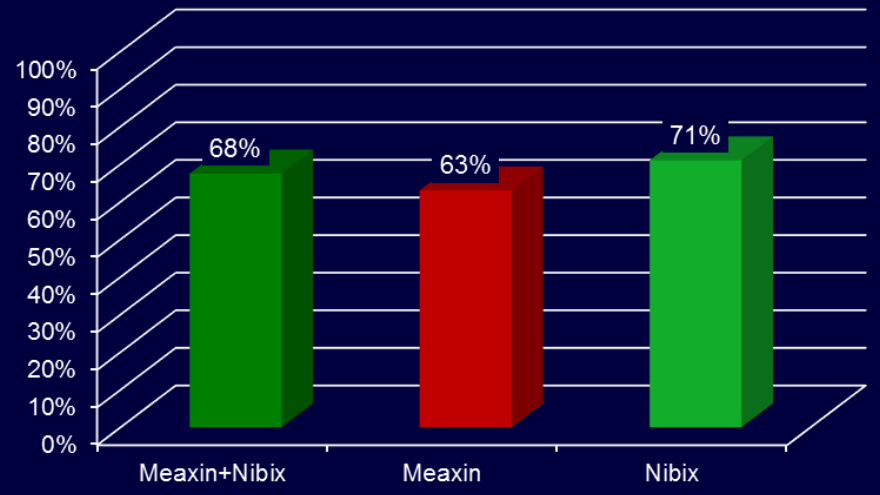
1. **The efficacy of imatinib generics at one-year**

A. „de novo" patients; n = 40, (Nibix: 24, Meaxin:16)

Early molecular response RQ < 10% at 3 mo



Reduction of BCR/ABL to <1% at 6 mo

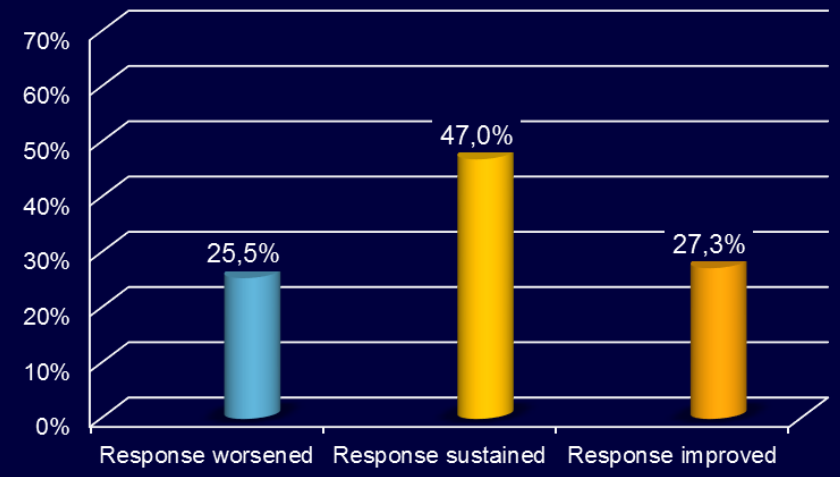


Polish Imatinib Generics Registry

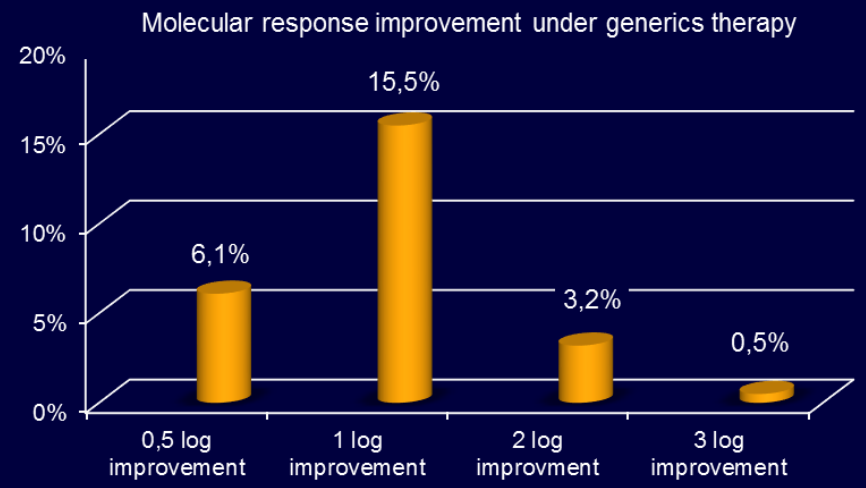
1. **The efficacy of imatinib generics at one-year**

B. „switched” patients; n = 461, (Nibix: 343, Meaxin: 118)

Molecular response under generics therapy



Molecular response improvement under generics therapy

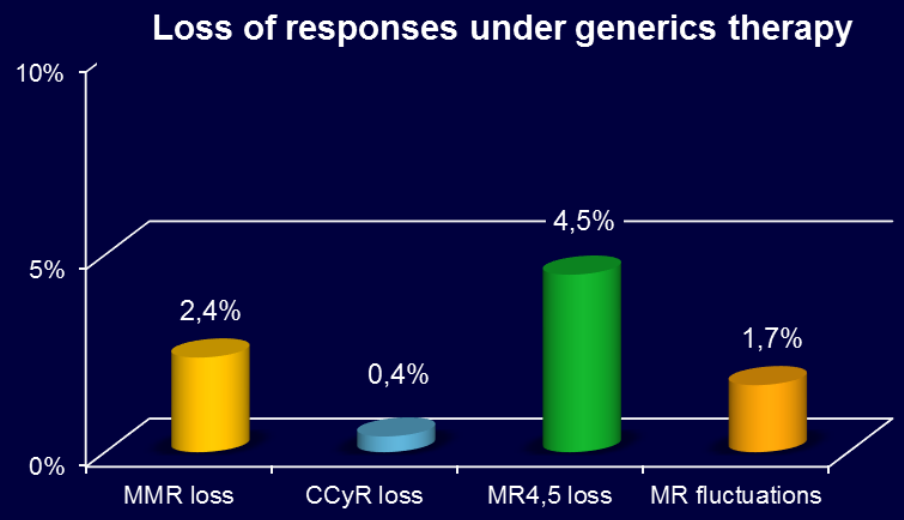


Polish Imatinib Generics Registry

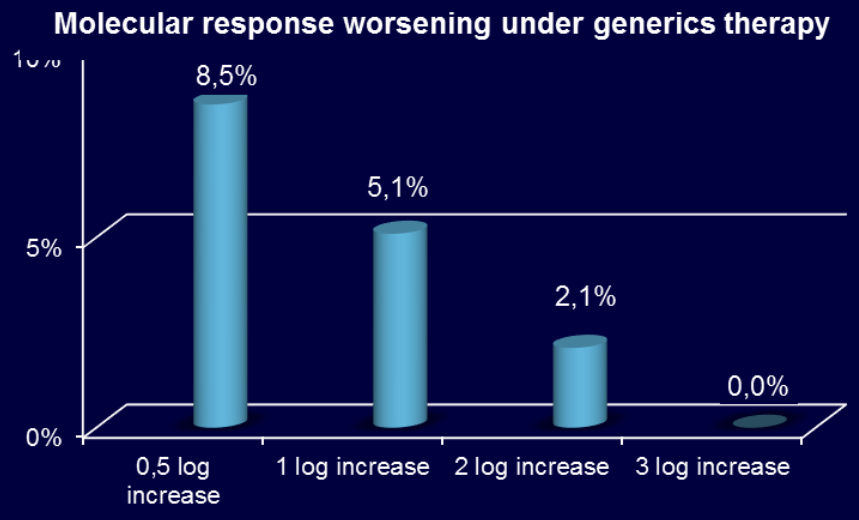
1. **The efficacy of imatinib generics at one-year**

B. „switched" patients; n = 461, (Nibix: 343, Meaxin: 118)

Loss of responses under generics therapy



Molecular response worsening under generics therapy



Questions / difficultés soulevées avec les génériques

- **Liberté de prescription du médecin**
  Importance de la galénique
  Changement de produit fréquent par le pharmacien : patient perturbé

- **Prix faible du produit : suspicion de moindre efficacité**

- **Dans de nombreux pays :base du remboursement est le prix du générique pas en France !**

- **Prix des génériques en France : 2 à 10 fois plus chers (GB et USA) car prix fixé par administration donc pas de concurrence**

- **Générique de l'imatinib en France: dossier du groupe FI LMC**
- **Importance du suivi moléculaire des patients Accompagner la prescription**
- **Enjeu économique énorme : 10 milliard d'euros en 10 ans**
- **L'arrivée du générique fait aussi baisser le prix du princeps**

Imatinib generic

Science

Submitted 12.10.09 | Revisions Received 3.3.10 and 3.29.10 | Accepted 3.29.10

Hematologic and Molecular Responses to Generic Imatinib in Patients With Chronic Myeloid Leukemia

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DOI: 10.1309/LMR1KA61JYKUXRDX

Abstract

Background: Imatinib mesylate is a drug used in treating chronic myeloid leukemia (CML). It induces apoptosis and inhibits cell proliferation. This study aimed to evaluate hematologic and molecular responses to Imatib (Cipla Limited, Mumbai, India) in 30 chronic phase CML patients.

Methods: Physical examination, CBC test, and peripheral blood smear were performed in order to assess the hematologic response in patients. Molecular response was evaluated through quantitative assessment of BCR-ABL fusion gene expression by real-time reverse transcriptase polymerase chain reaction (RT-PCR). The correlation of molecular and hematologic responses with the patient's age and sex and also with dosage and duration of Imatib consumption was analyzed statistically.

Results: Ninety percent of the patients showed some sort of hematologic response that had no significant correlation with a patient's age or sex, dosage, or duration of Imatib consumption ($P>0.05$). Overall, 46.7% of patients showed complete molecular response (CMR), 43.3% showed partial molecular response, and 10% showed no molecular response (NMR) to Imatib. A reverse significant correlation was noted between the type of molecular response and patient's age ($P<0.05$). In contrast, no significant correlation was found between the type of molecular response and patient's sex, dosage, or duration of Imatib consumption ($P>0.05$).

Conclusion: Our study results indicate that molecular and hematologic responses to Imatib were acceptably good and therefore its efficacy is comparable to that of more expensive brands like Gleevec.

Keywords: chronic myeloid leukemia, molecular response, hematologic response, Imatib

Observational Study of Cemivil® (Imatinib) in Chronic Myeloid Leukaemia Patients in Jordan

AIKMA QUALITY

PHASE IV OBSERVATIONAL CLINICAL STUDY

Chronic Myeloid Leukemia: Treatment in Evolution