How did the introduction of low-cost generics change clinical decision making in first-line therapy?

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To be short,

NO CHANGE AT ALL, OR MARGINAL CHANGES

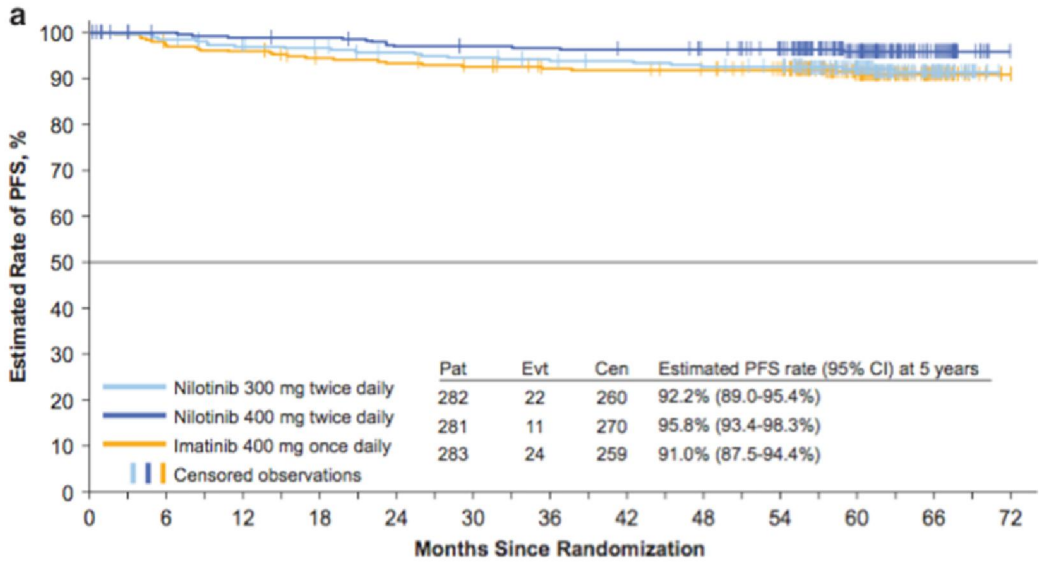
My perception,

In Italy, many (most) CML docs prescribe 2nd Gen TKIs in High Risk and “Young” patients.

Addressing the basic question from a different viewpoint:

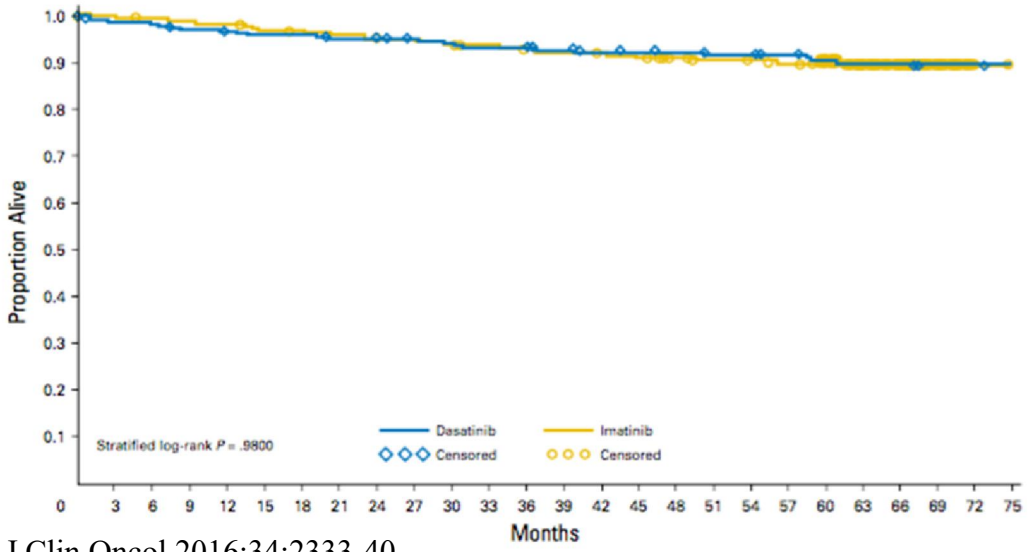
Is there any condition where NOT using 2nd gen front-line can be considered unethical or a “mistake”?

5-years OS is similar in different trials



ENESTnd:
Nilotinib vs Imatinib

DASISION:
Dasatinib vs Imatinib



Hochhaus A et al, Leukemia 2016;30:1044-54; Cortes J et al, J Clin Oncol 2016;34:2333-40.

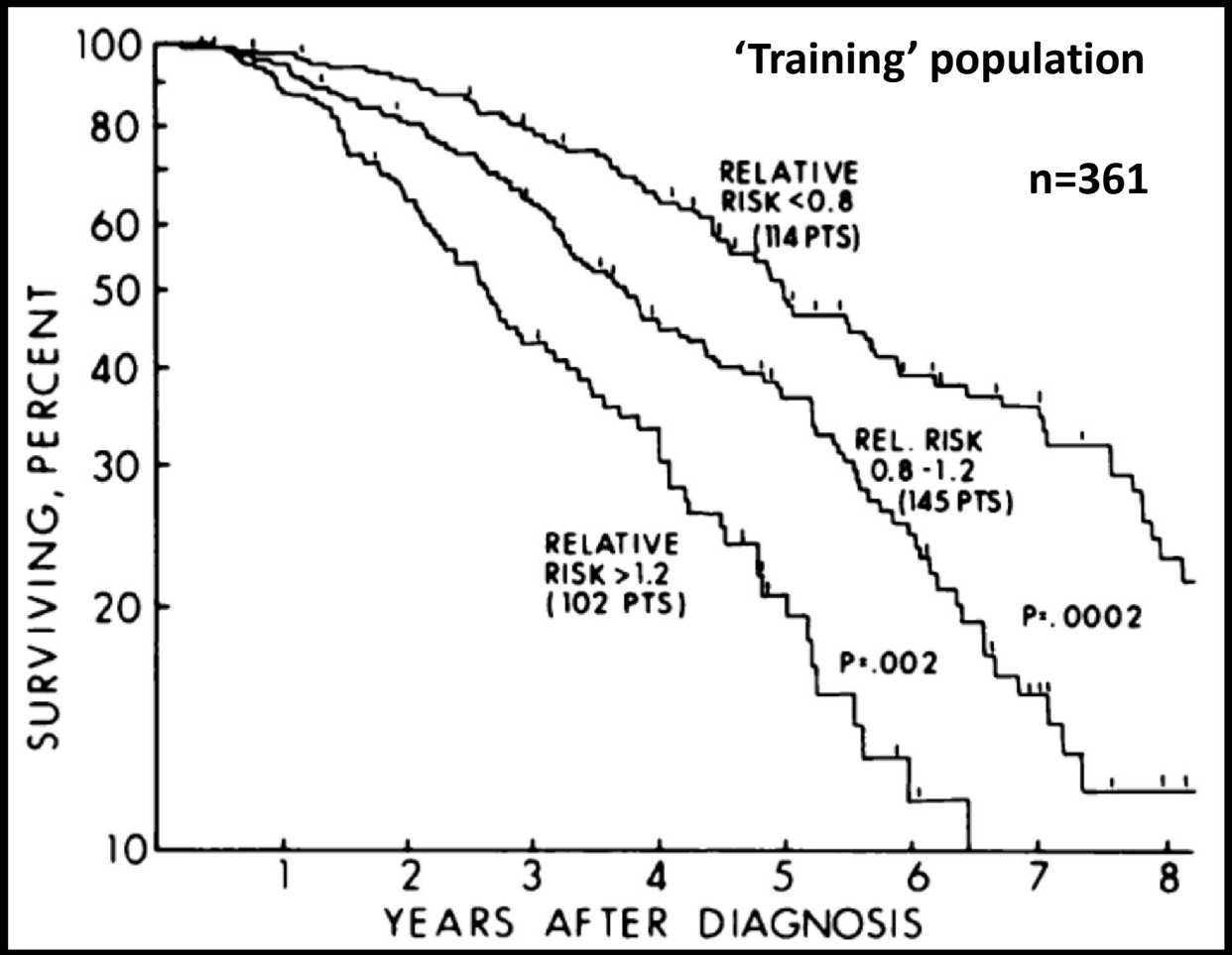
It is CLEAR that only Nilotinib 800 is associated with a tiny, but significant advantage in PFS and OS

	5-years deaths	5-years leuk death	PFS* 5Y %	OS 5Y %
ENESTnd Nilo 600[1]	6,4%	2,1%	92,2	93,7
ENESTnd Nilo 800	3,6%	1,4%	95,8	96,2
ENESTnd Ima 400	7,8%	5,7%	91	91,7
Dasision Dasa[2]	10,0%	3,5%	85	91
Dasision Imatinib	10,0%	6,5%	86	90

PFS IN DASISION is EFS[3]

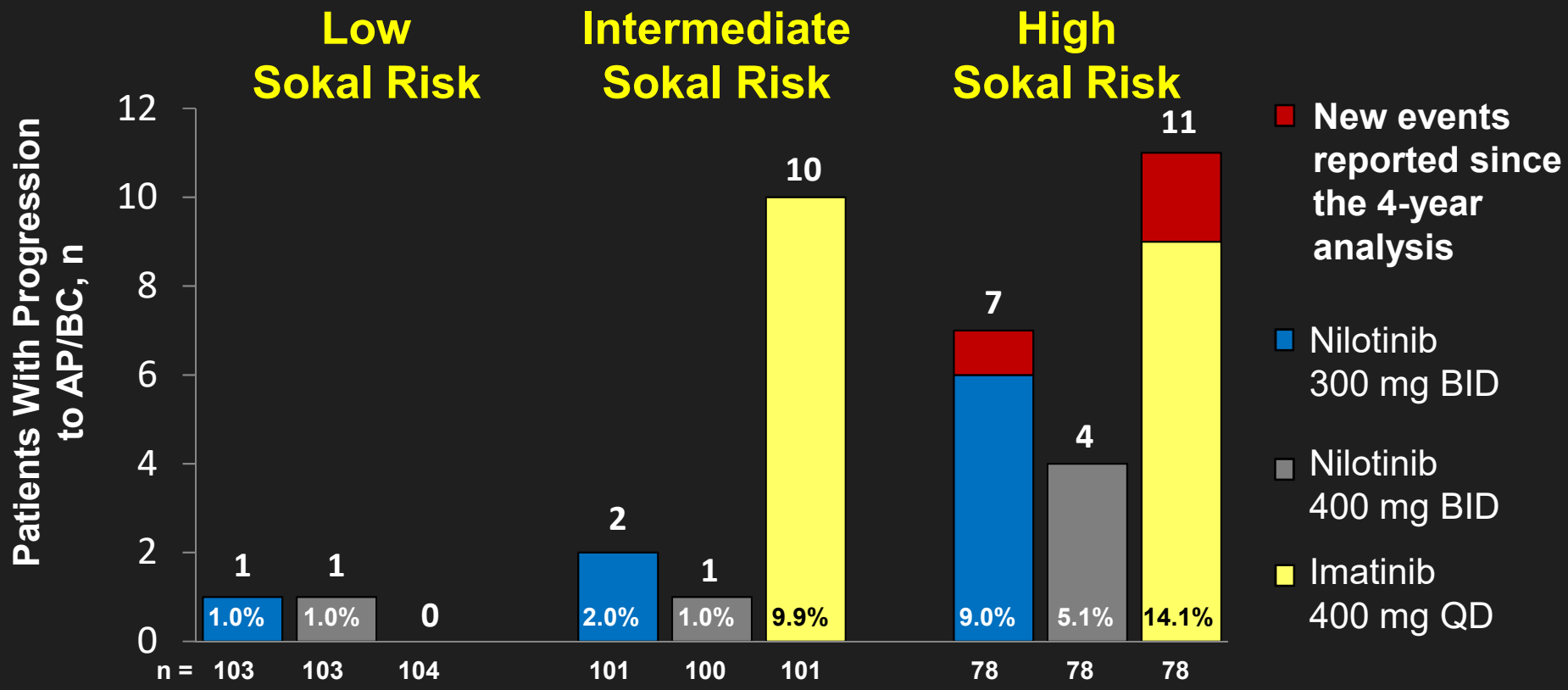
1. Hochhaus A, Saglio G, Hughes TP,, et al. Leukemia. 2016;30(5):1044-54.
2. Cortes JE, Saglio G, Kantarjian HM, et al. J Clin Oncol. 2016;34(20):2333-40.
3. Guilhot J, Baccarani M, Clark RE et alBlood. 2012;119(25):5963-71.

Survival according to relative risk (Cox model analysis)



Sokal JE, et al. Blood 1984;63:789–799.

Progression to AP/BC on Study[a] According to Sokal Risk Score



- All 3 progressions to AP/BC on study reported since the 4-year analysis occurred in patients with high Sokal risk scores at baseline; all 3 patients also had BCR-ABL^{IS} > 10% at 3 months
- All progressions in patients with low/intermediate Sokal risk scores occurred during the first 2 years on study

Data cutoff: September 30, 2013

[a] Progression to AP/BC or death due to advanced CML on core treatment or during follow-up after discontinuation of core treatment.

ELN 2013 – Response to Front-line Treatment (Imatinib, Nilotinib, and Dasatinib)

	OPTIMAL	WARNING	FAILURE
Baseline	NA	**-High risk**, -CCA/Ph+ (Major route)	NA
3 months	Ph+ ≤ 35% and/or BCR-ABL ≤ 10%	Ph+ 36-95% and/or BCR-ABL > 10%	No CHR and/or Ph+ > 95%
6 months	Ph+ 0% and/or BCR-ABL ≤ 1%	Ph+ 1-35% and/or BCR-ABL 1-10%	Ph+ > 35% and/or BCR-ABL > 10%
12 months	BCR-ABL ≤ 0.1%	BCR-ABL > 0.1-1 %	Ph+ > 0% and/or BCR-ABL > 1%
Then	BCR-ABL ≤ 0.1%	BCR-ABL 0.1-1%	BCR-ABL > 1%

Baccarani et al, Blood 2013; 122: 885-892.

2018, the weight of the choice of 1st line Treatment

Patient

- Risk, comorbidities
- Personal Expectations
- Education, compliance
- Advocacies

Drugs

- Efficacy and time to response
- Side Effects
- Long term safety
- Costs

Physician

- Personal Experience
- Experience

ENDPOINTS

CML, Same Endpoints for Everybody?

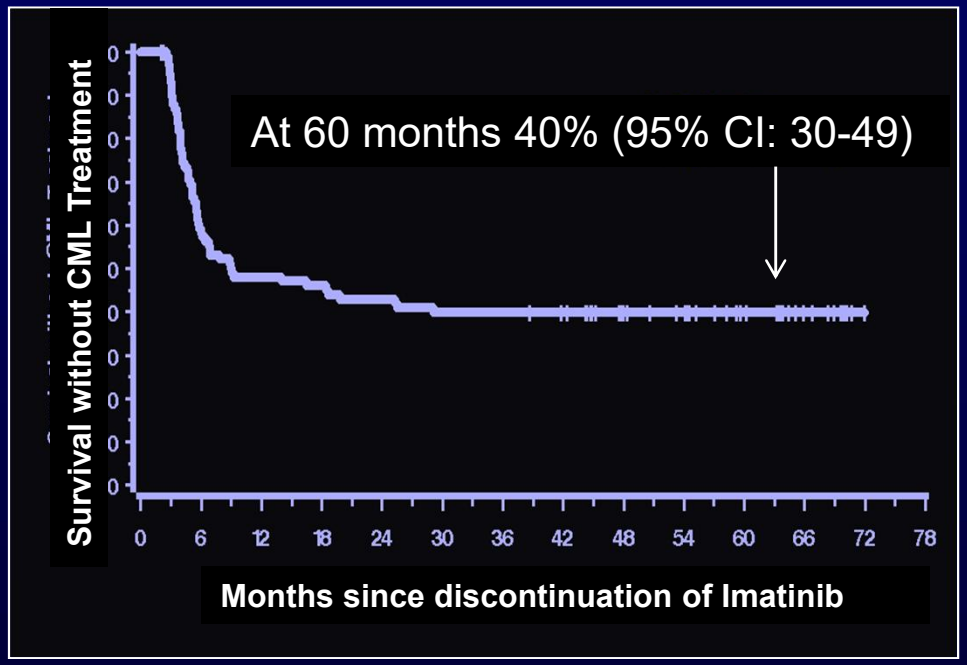
34 yrs old, female, intermediate risk (Sokal), no comorbidities

74 yrs old, male, low risk (Sokal), mild COPD, hypertension, dislipidemia.

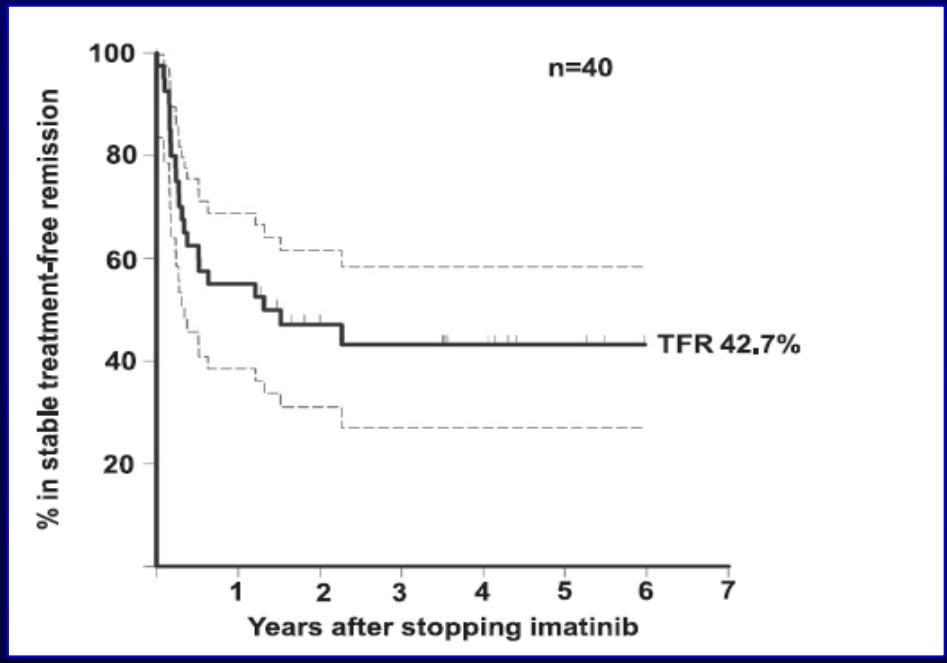
COPD, chronic obstructive pulmonary disease

STIM and TWISTER Studies

STIM



TWISTER

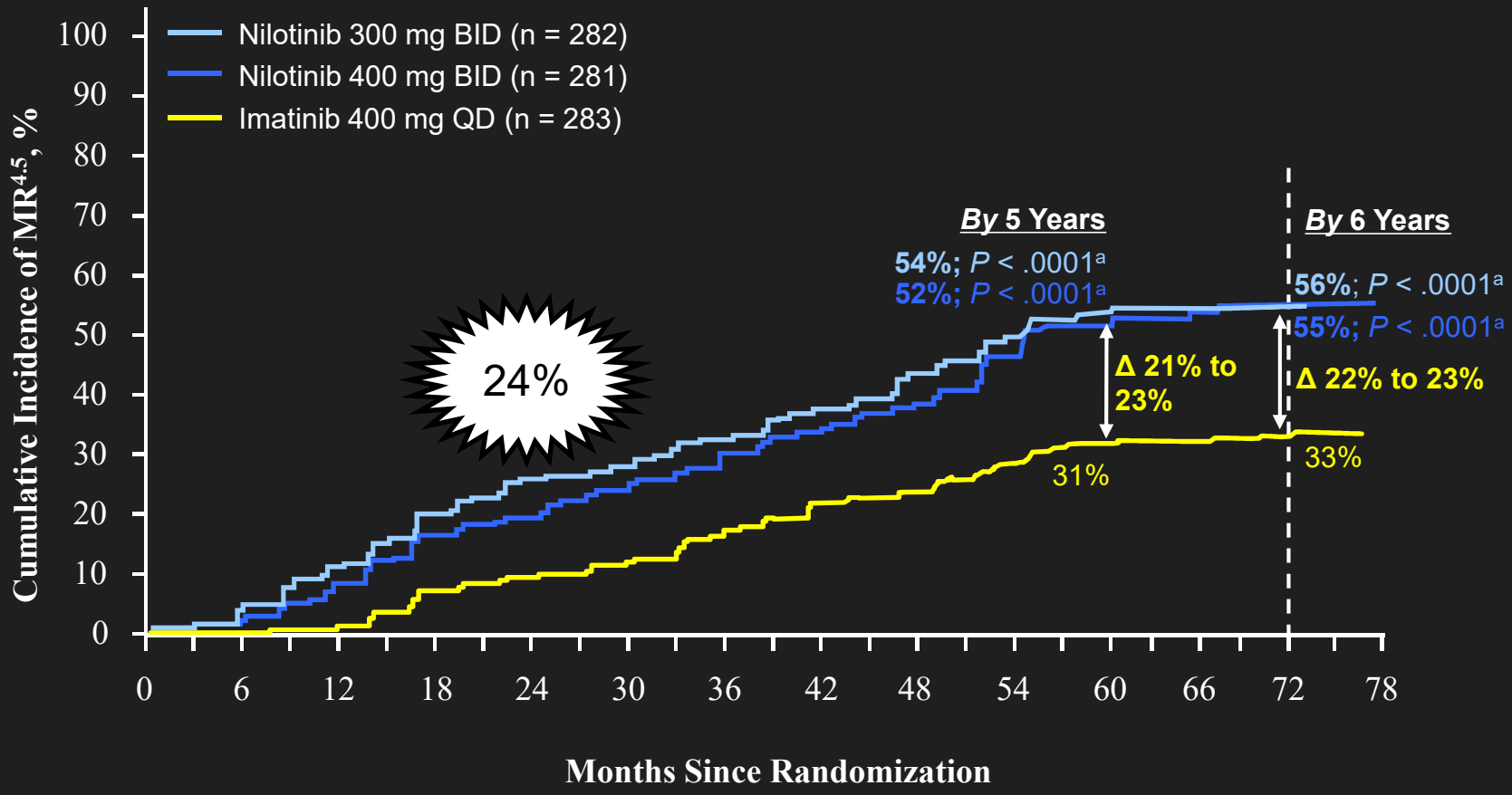


~40% of patients treated for at least 3 years with imatinib and with CMR4.5 for at least 2 years maintain CMR4.5 after imatinib discontinuation.

Hughes TP, et al. *Haematologica.* 2015;100:[abstract P229].

Mahon FX et al. Lancet Oncol. 2010; 11: 1029-1035.
Mahon FX et al. Blood 2013; 122: abstract 255.
Ross DM et al. Blood 2013; 122: 515-522.

ENESTnd: cumulative incidence of MR4.5 by 6 years



KM-estimated median times to first MR4.5 were:

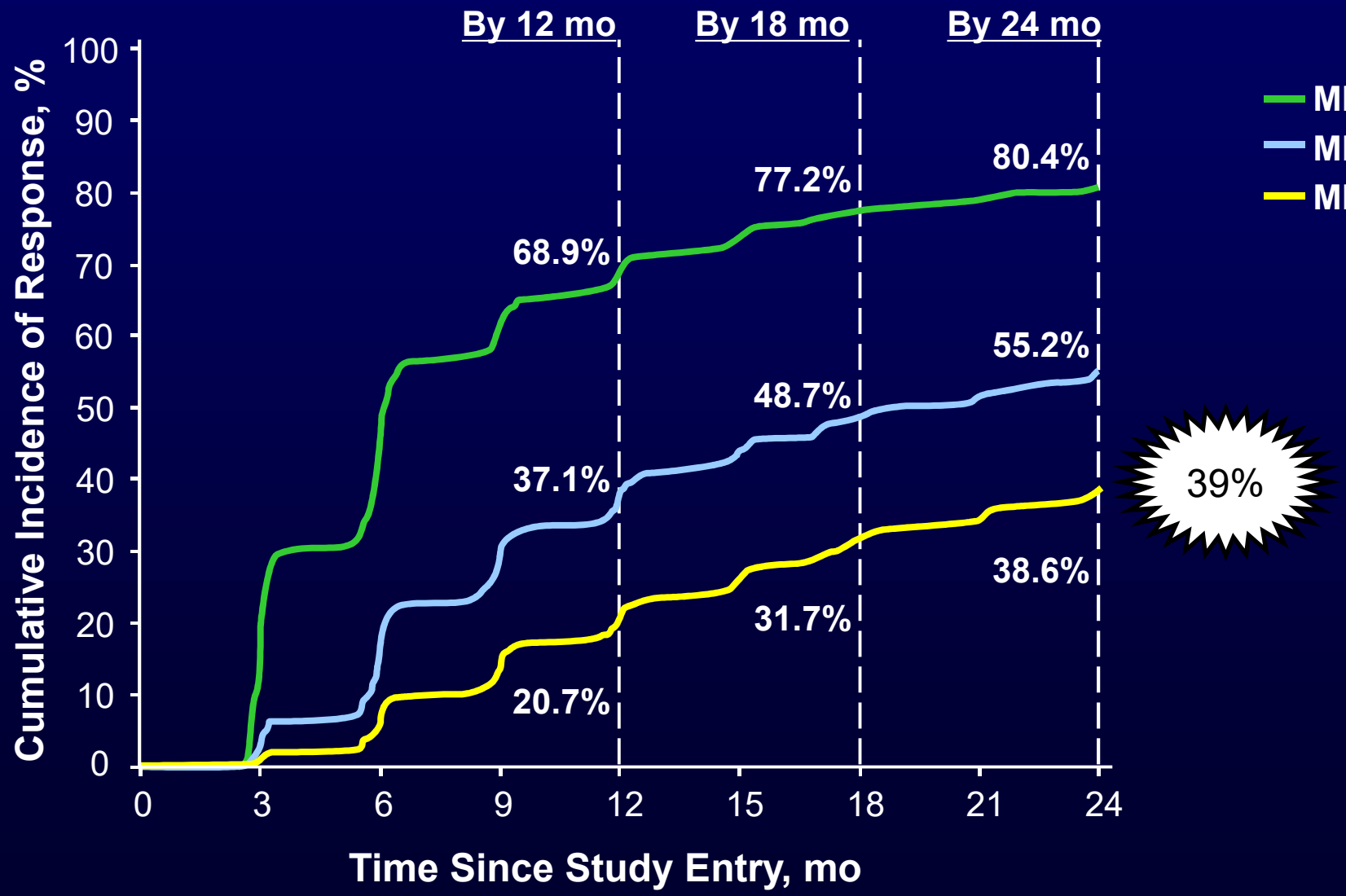
- Nilotinib 300 mg BID: 45.5 months (hazard ratio [HR] vs imatinib, 2.0387 [95% CI, 1.5807-2.6295]; nominal $P < .0001$)
- Nilotinib 400 mg BID: 49.8 months (HR vs imatinib, 1.7770 [95% CI,1.3780-2.2915]; nominal $P < .0001$)
- Imatinib 400 mg QD: 61.1 months

[a] *P* values are nominal.

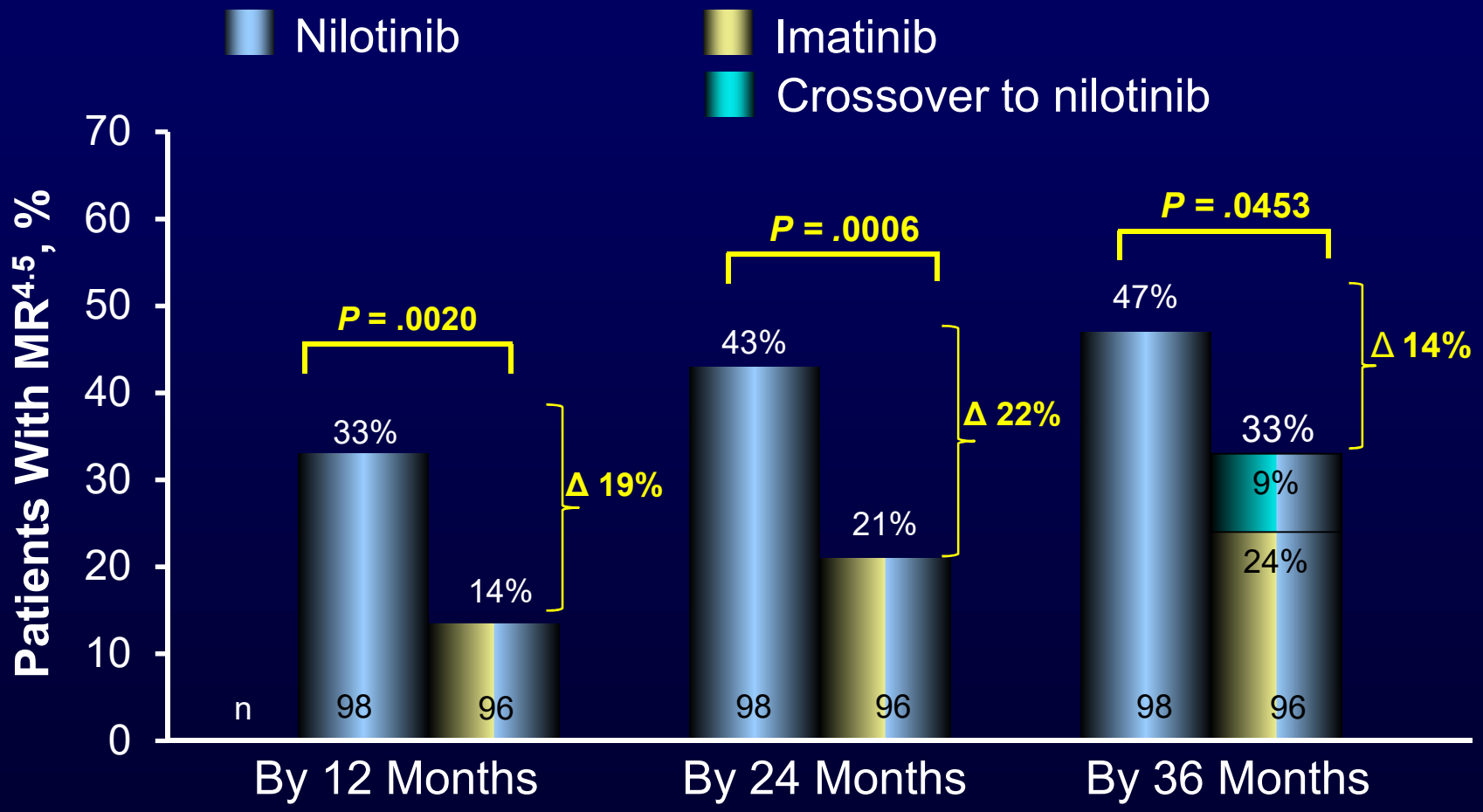
Larson et al. *Blood*. 2014:[abstract 4541].

ENEST1st Final Analysis

Cumulative Incidence of MMR, MR^4, and $MR^{4.5}$



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)

ITT, intention-to-treat.

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

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