Imatinib, nilotinib and dasatinib frontline: which and why?

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Juan Luis Steegmann's disclosures

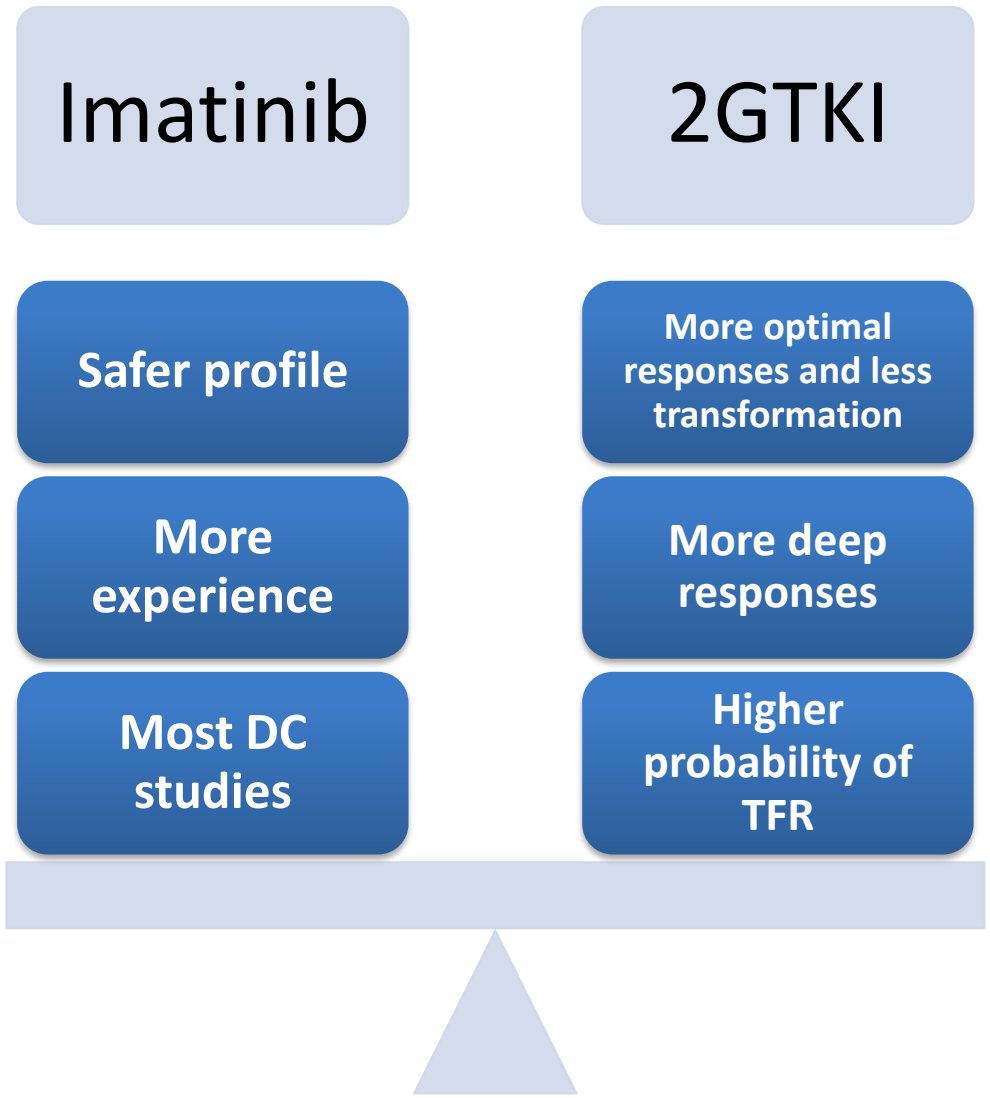
	BMS	Incyte	Novartis	Pfizer
Research grants	x	x	x	x
Educational activities	x	x	x	x
Advisory boards	x	x	x	x
Consultancy	**No**			
Speakers Bureau				
Stock Shares				

TKI: Different designs, different activities

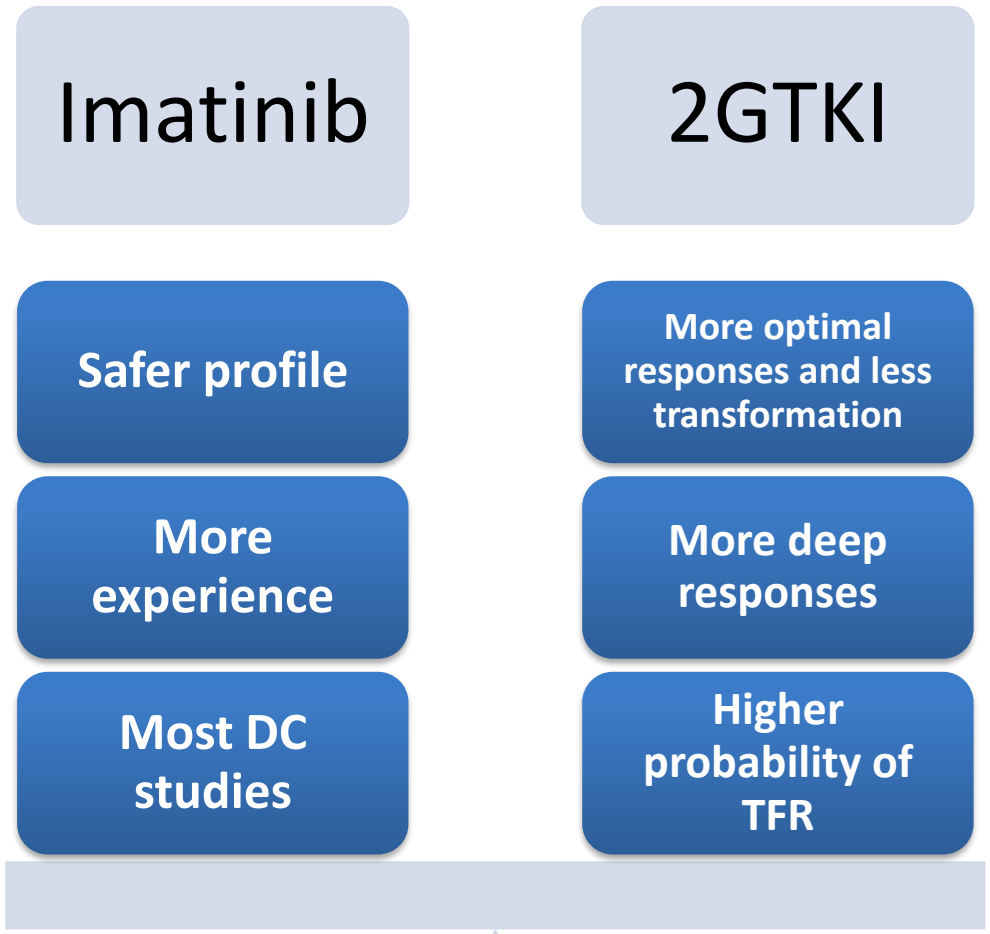
	BCR-ABL	C-KIT	PDGFR	SRC	VEGFR	FGF-R	RET
Imatinib	1						
Nilotinib	30						
Dasatinib	325						
Bosutinib	100						
Ponatinib	250						

JL Steegmann:
Source: Investigators Brochure:
The intensity on column BCR-ABL must be read in vertical.
The other cells' colour intensity must be read in horizontal comparing with the correspondent BCR-ABL cell

Imatinib and 2GTKI, pros and cons

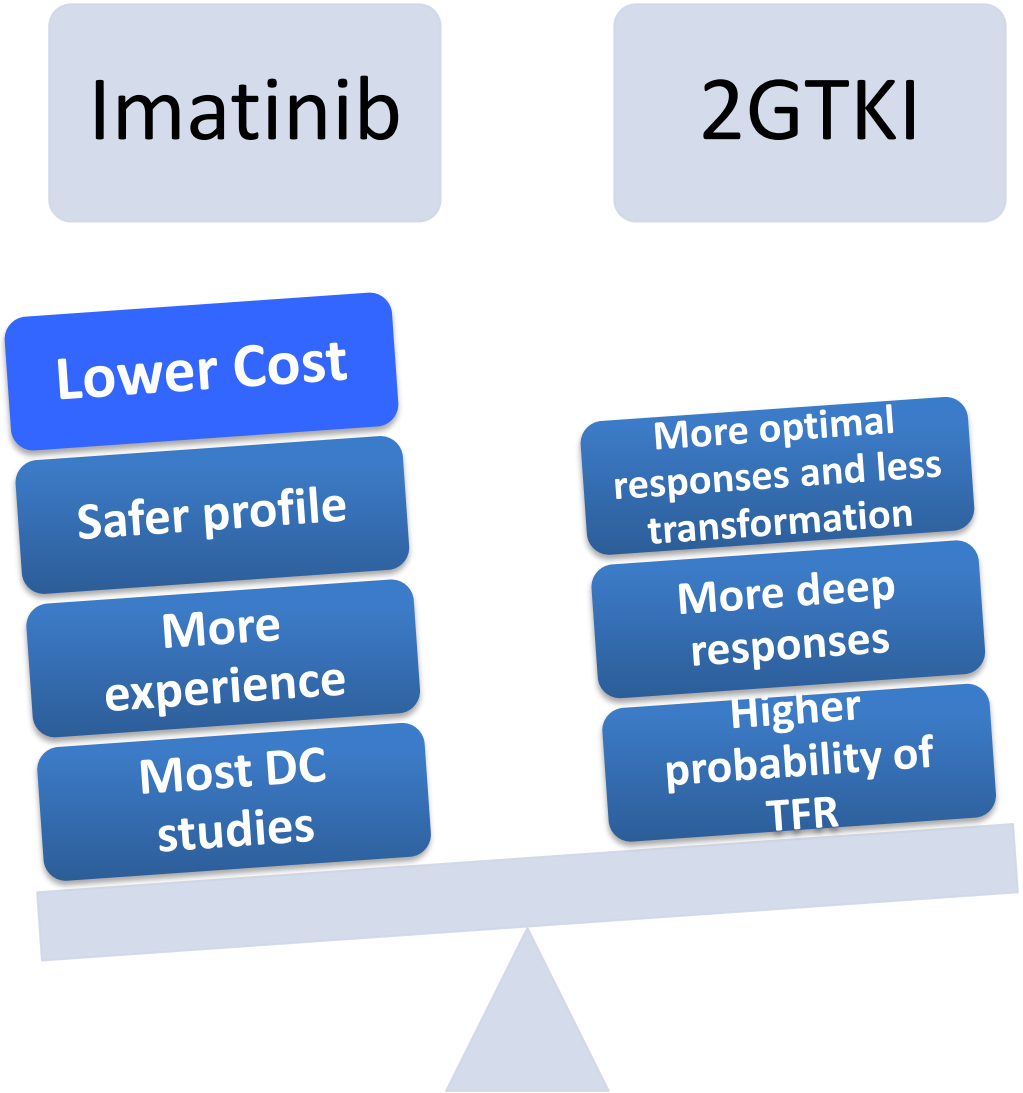


Imatinib and 2GTKI, pros and cons



The probability of survival is similar, probably, at least in part, because more than one third of Imatinib patients are rescued with 2GTKI

Generic imatinib: low price, heavy weight



Major Caveat

There is no large randomized trial comparing 2GTKI head to head

Do we need new TKIs, apart from Imatinib?

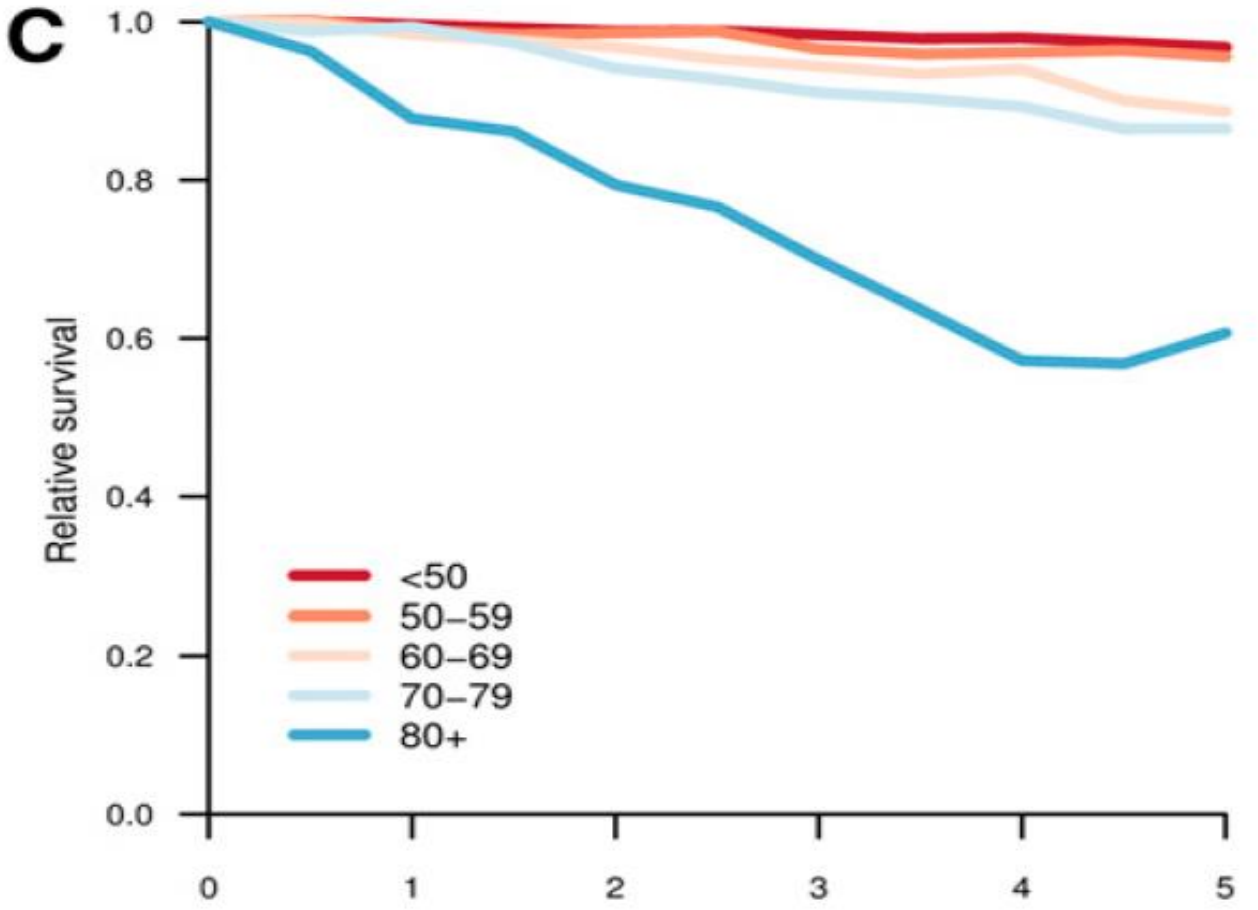
- If our objective is crude overall survival:
  - Yes
- If our objective is cure:
  - Yes
- If our objective is quality of life:
  - Yes.

Do we need new TKIs, apart from Imatinib?

- If our objective is crude overall survival:
  - Yes , because it could be associated to repeated rescues with other TKIs
- If our objective is cure:
  - Yes, because CMR can be achieved by switching to other TKI.
- If our objective is quality of life:
  - Yes, because in front of Aes, cross-tolerance is the rule*

* Exception: Hematologic, Ima→Dasa

TKI-based treatment offers a probability of survival similar to persons of the same age[1], but not in patients > 60 y old, which are 40% of CML patients. [2].



1. Hoglund M, Sandin F, Hellstrom K et al. Blood. 2013;122(7):1284-92
2. Hoffmann VS, Baccarani M, Hasford J et al. Leukemia. 2015.. .. doi:10.1038/leu.2015.73

3. .

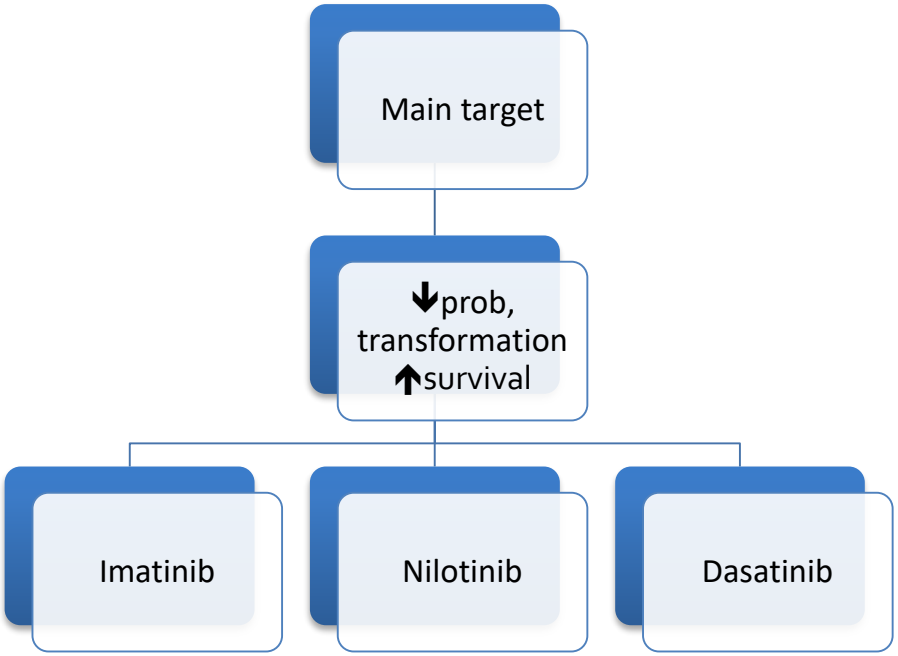
One third of Imatinib treated patients are switched to other TKIs, and there is a huge variety of schemes afterwards

- This data is usually absent from trials
- In our experience, out of 564 patients treated with Imatinib upfront, 30% of the patients were switched to 2GTKI
- … and look the number of combinations

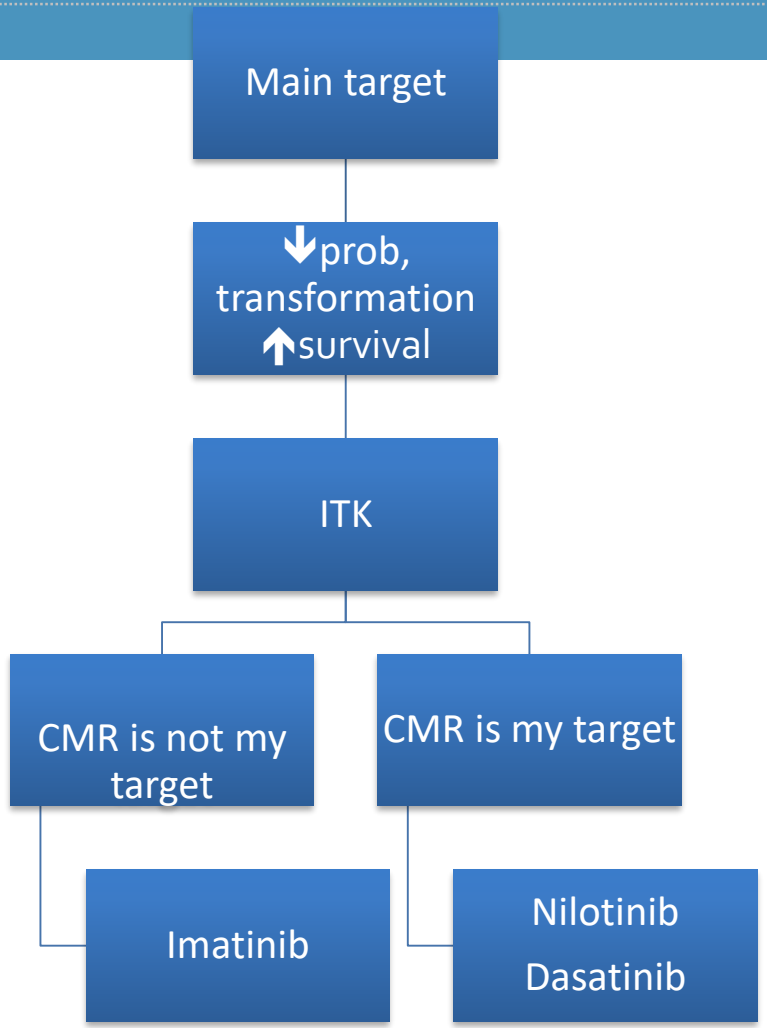
		Number of combinations in sequence
IFN, then Imatinib	138	
IFN→Im→2GTKI	69	8
Imatinib only	394	
Imatinib→2GTKI	170	12
2GTKI	91	10

Casado LF, et al presented to EHA 2018 (pub.only)

Treatment algorithm for CML-CP. ELN 2013 vs GELMC 2014



Baccarani M, Deininger MW, Rosti G, et al.. Blood. 2013;122(6):872-84.

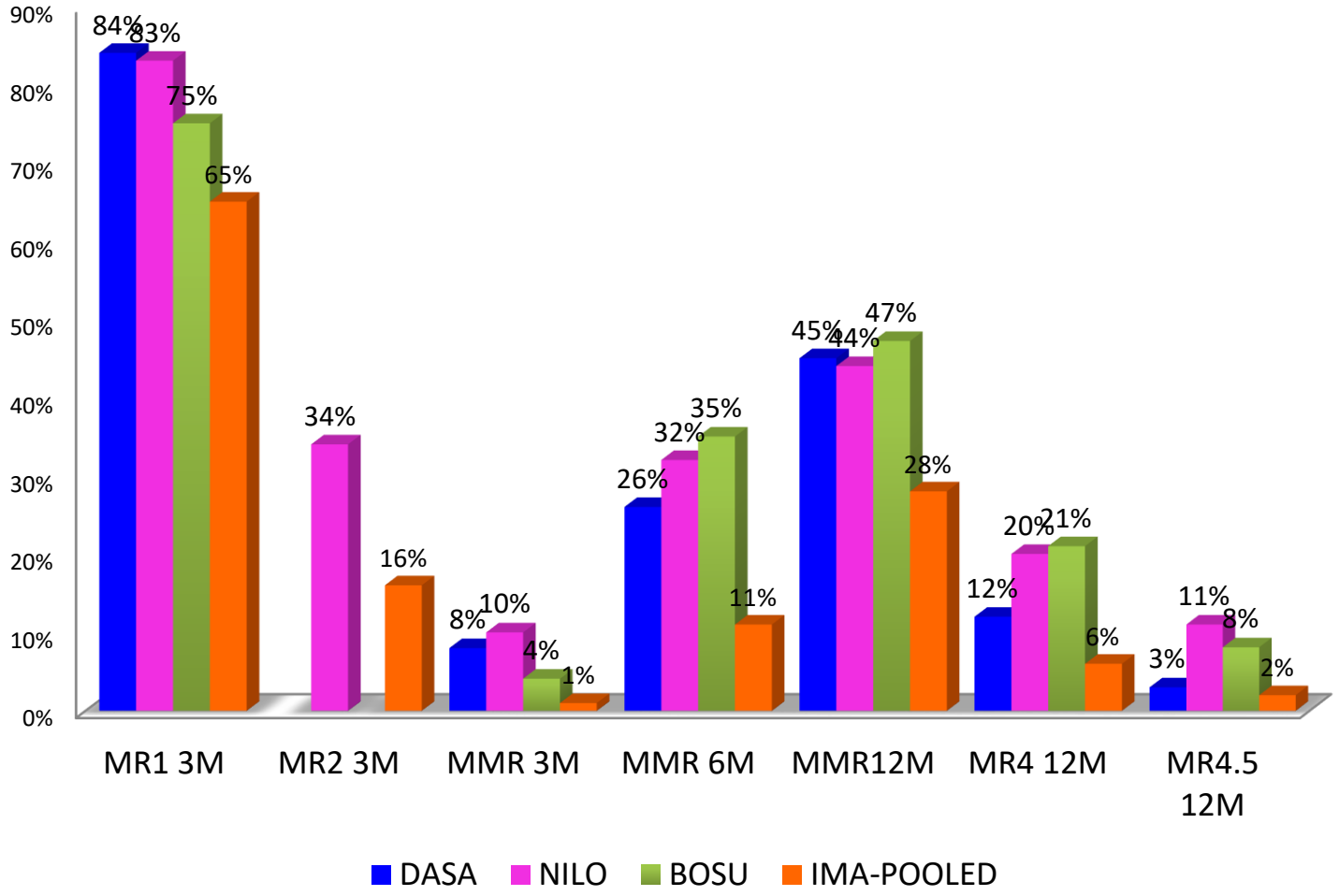


Steegmann, J.L. and L.F. Casado,
Tratamiento de primera línea de la leucemia mieloide crónica en fase crónica, in *Manual para el control y el tratamiento de los pacientes con leucemia mieloide crónica*,
J.L. Steegmann, M.T. Gomez-Casares, and M. Perez-Encinas, Editors. 2014, Euromedice: Badalona (Spain). p. 43-56.

Background of GELMC approach

- In comparison with Ima400, 2nd generation TKI has increased optimal responses and deep molecular responses (1st line and 2nd line)
  - Deep molecular responses are safe havens
  - Less BCR-ABL, lower risk of mutations (single cell and population)

In first line, 2G TKI are more effective than imatinib 400 in inducing any sort of molecular response, in any given time



1. Saglio G, Kim DW, Issaragrisil S, le Coutre P et al. N Engl J Med. 2010 Jun 17;362(24):2251-9.
2. Kantarjian H, Shah NP, Hochhaus A, et al . N Engl J Med. 2010 Jun 17;362(24):2260-70.
3. Cortes JE, Gambacorti-Passerini C, Deininger MW et al. J Clin Oncol. 2017:JCO2017747162 (BFORE study, with Bosu400)

The earlier the MMR, more probable is the obtention of subsequent MR4,5

German CML IV trial

Time of MMR achievement after IM treatment	Cumulative incidence of MR4,5 by 4-y
3 months*	83,3 %
6 months*	55,5 %
12 months*	44,2 %
18 months*	39,0 %

*Window: ± 1,5 m

Hehlmann R, Muller MC, Lauseker M, et al. *J Clin Oncol.* 2014;32(5):415-423.

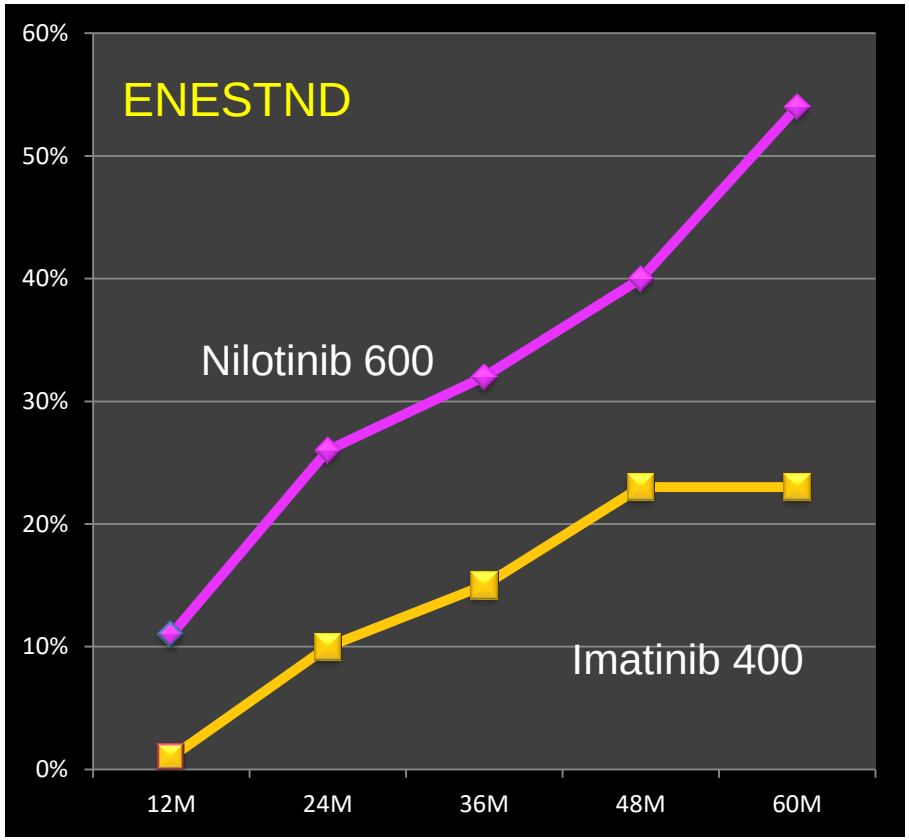
VERY early kinetics of molecular response are relevant

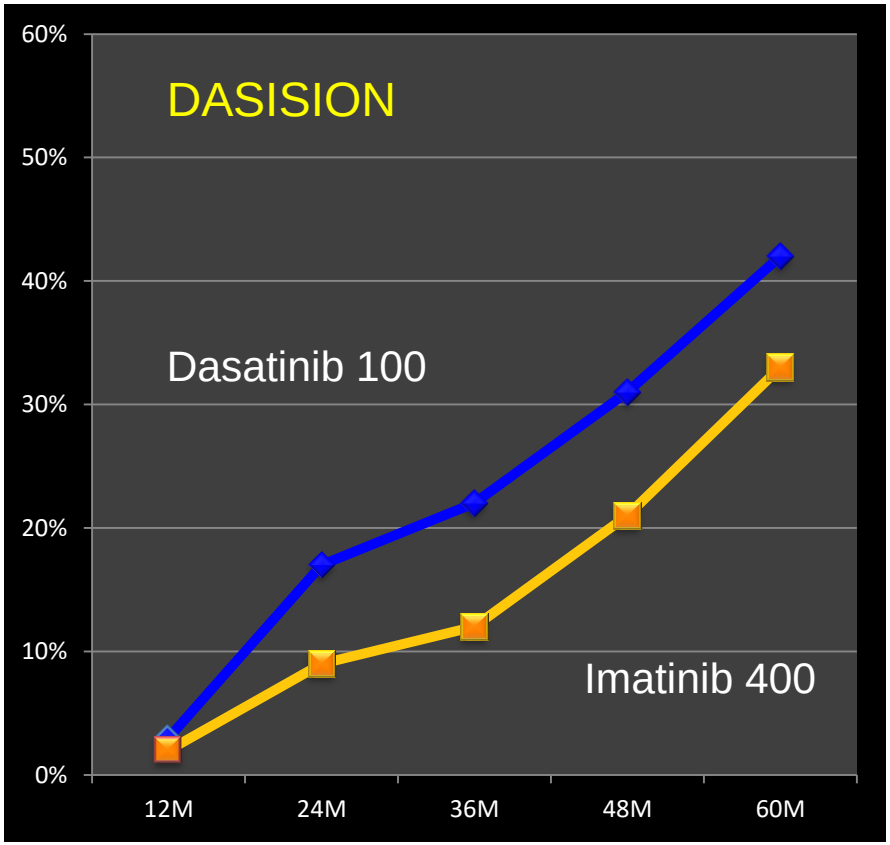
- Associated with higher probability of MMR and deep response.
  - With Dasatinib[1]
    - HT ≤ 14 days, with MMR_{by12m} and $DMR_{by\ 18m}$
  - With Nilotinib[2]
    - HT ≤ 13 days was predictive and independently associated with $MMR_{at\ 12m}$ and $MR^4{}_{at\ 18m}$ [2]

1. Iriyama N, Fujisawa S, Yoshida C, … Sakamaki H (2015) Am J Hematol 90:282–287.
2. Steegmann JL, Colomer D, Gomez-Casares MT, …Casado-Montero LF: J Cancer Res Clin Oncol 2017.

Both nilotinib and dasatinib are superior to imatinib in first line, in lon-term deep molecular respons

MR $^{4.5}$ By 5 years:





54% vs 23% (Δ=21)

42% vs 33% (Δ=9%)

Hochhaus, A., et al.,. Leukemia, 2016. **30**(5): p. 1044-54.
Cortes, J.E., et al.. J Clin Oncol, 2016. **34**(20): p. 2333-40.

JLS: Data coming from different trials. Not for comparison

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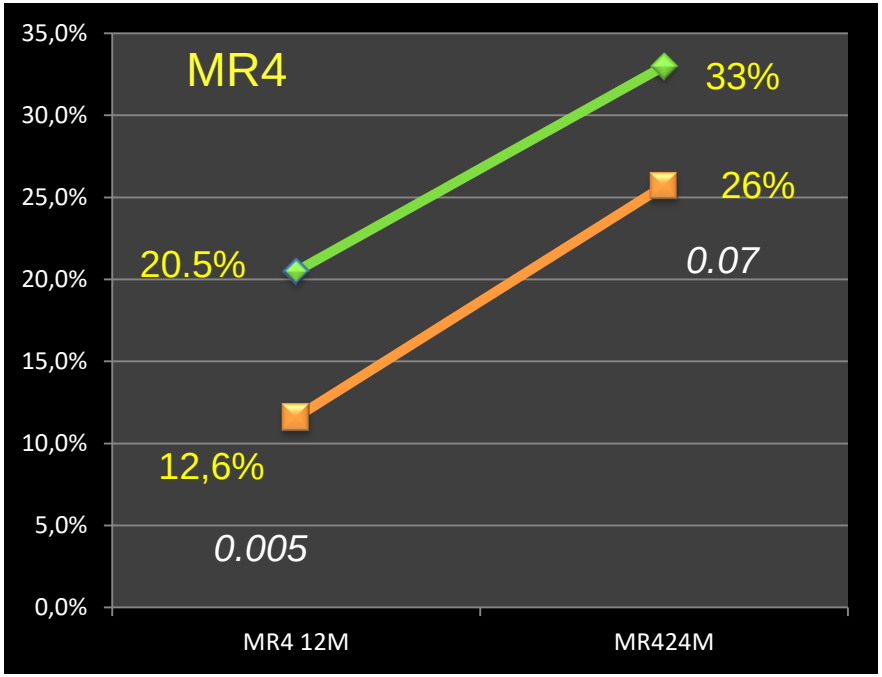
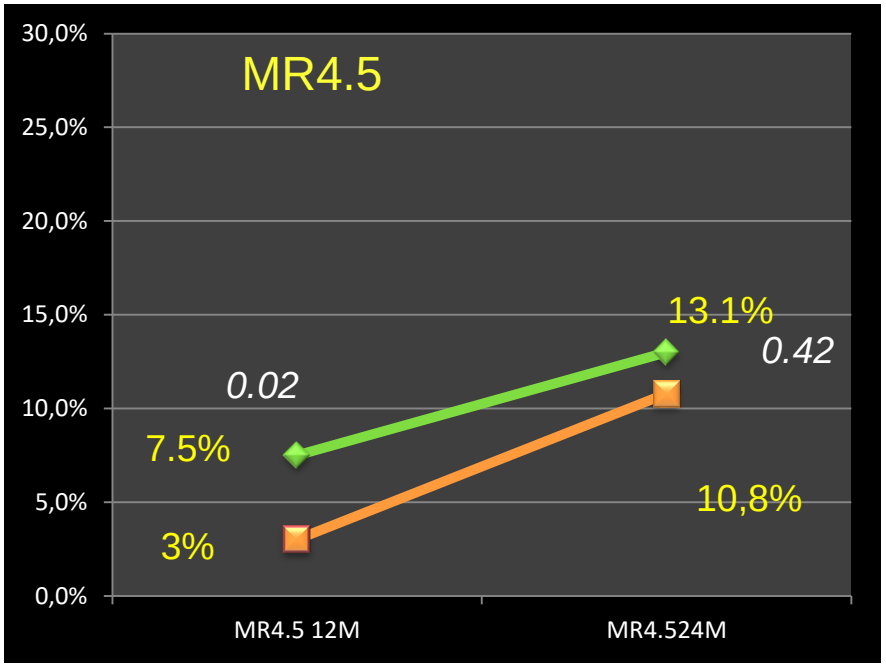
Bosutinib is not showing clear advantage in deep molecular response in the first two years





Δ=8 Δ=7 Δ=4.5 Δ=2.3

BOSUTINIB VERSUS IMATINIB FOR NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA IN THE BFORE TRIAL: 24-MONTH FOLLOW-UP. EHA 2018

Summary of 1st line studies with **2GTKI**

- More efficacious in:
  - Obtaining optimal responses defined by the ELN 2013 recommendations,in every time point
  - Obtaining complete molecular responses
  - Across all the risk groups
- Deep Molecular Responses with Nilotinib **seem** to be more frequent than with Dasatinib or Bosutinib, and faster.

CHOICE OF TKIS

BALANCING EFFICACY , TOXICITY AND COMORBIDITIES

Choice of TKI

- There is no absolute contraindication for using any given TKI
- The more resistant appears to be the disease, the more important is efficacy as the main variable when choosing TKI.
  - *"Overall, imatinib has a good long-term safety profile, although we probably underestimate the burden of AE . Second and third generation TKIs may have higher response rates, but have been associated with unexpected lung and vascular problems, some of which could be irreversible".*

Steegmann JL, Baccarani M, Breccia M, et al.. Leukemia 2016 Apr 28.

Choice of TKI, in first line

The choice must be based, primarily, in the antileukemic effect, and second, in the interaction between comorbidities and potential toxicity with the TKI of primary choice.

By objectives

- Prolong survival
  - *Imatinib, Nilotinib, Dasatinib*
  - *Bosutinib*
- Lower transformation probability
  - *Nilotinib, Dasatinib*
  - *Bosutinib*
- Deep molecular response
  - *Nilotinib, Dasatinib*
  - *Bosutinib*

By comorbidities

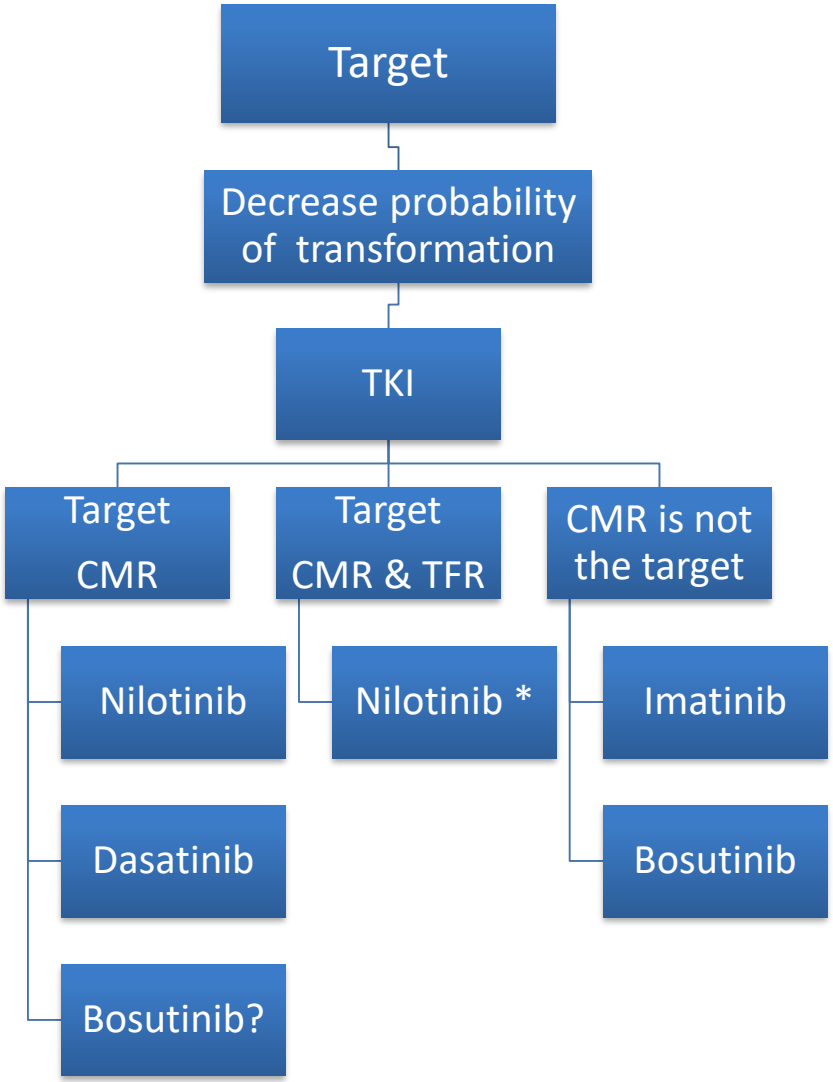
- Very high CV risk
  - *Avoid Nilotinib*
- High CV risk
  - *Nilotinib less advisable*
- Recent infections, COPD, bleeding dyathesis
  - *Dasatinib is not 1st choice*
- Cardiac failure or liver disease
  - *Imatinib is not 1st choice*
- Gut or liver disease
  - *Bosutinib is not 1st choice*

Steegmann, J.L. and L.F. Casado,
Tratamiento de primera línea de la leucemia mieloide crónica en fase crónica, in *Manual para el control y el tratamiento de los pacientes con leucemia mieloide crónica*,
J.L. Steegmann, M.T. Gomez-Casares, and M. Perez-Encinas, Editors. 2014, Euromedice: Badalona (Spain). p. 43-56.

Caveat: Bosutinib not yet approved by EMA in 1st line

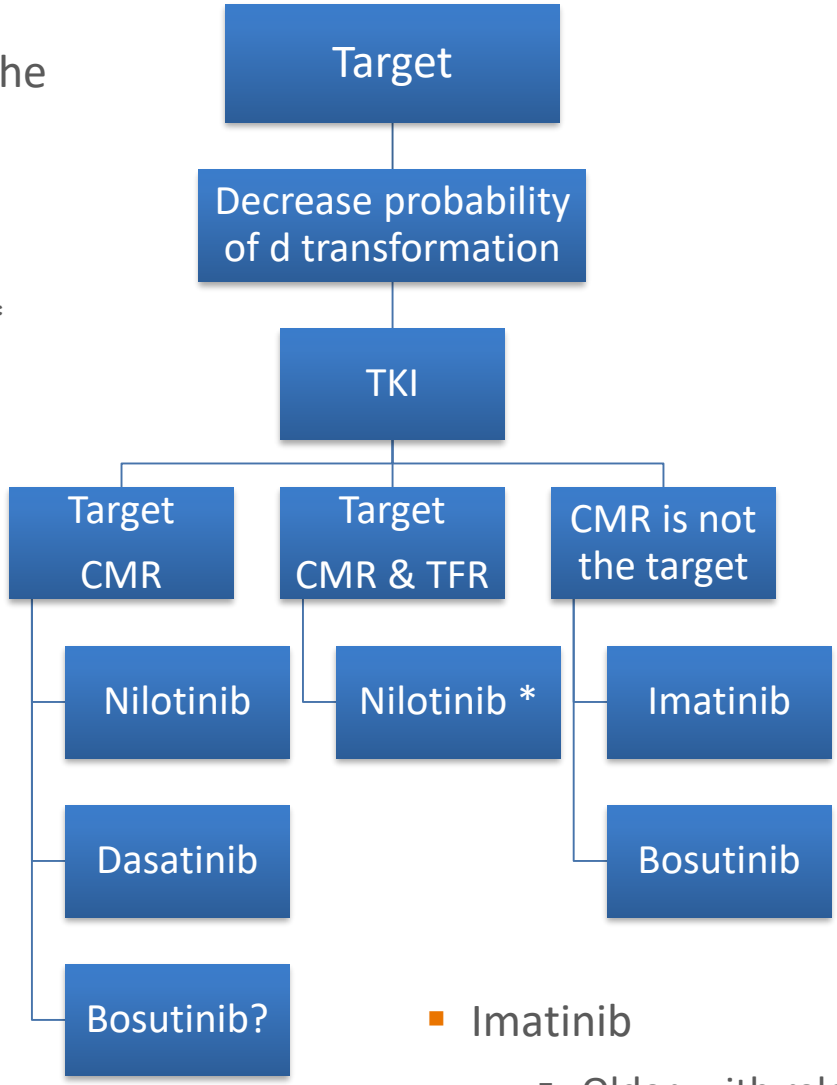
My choice for 2019

To incorporate TFR to the therapeutic objectives



My choice for 2019
To incorporate TFR to the therapeutic objectives

- 2nd generation TKIs: Any of the following:
  - Younger, with no relevant comorbidites
  - With the goal of stopping*
  - High or intermediate risk
  - With major CCA/Ph1+



* Nilotinib authorized by EMA for this target

- Imatinib
  - Older, with relevant comorbidities
  - Low-risk

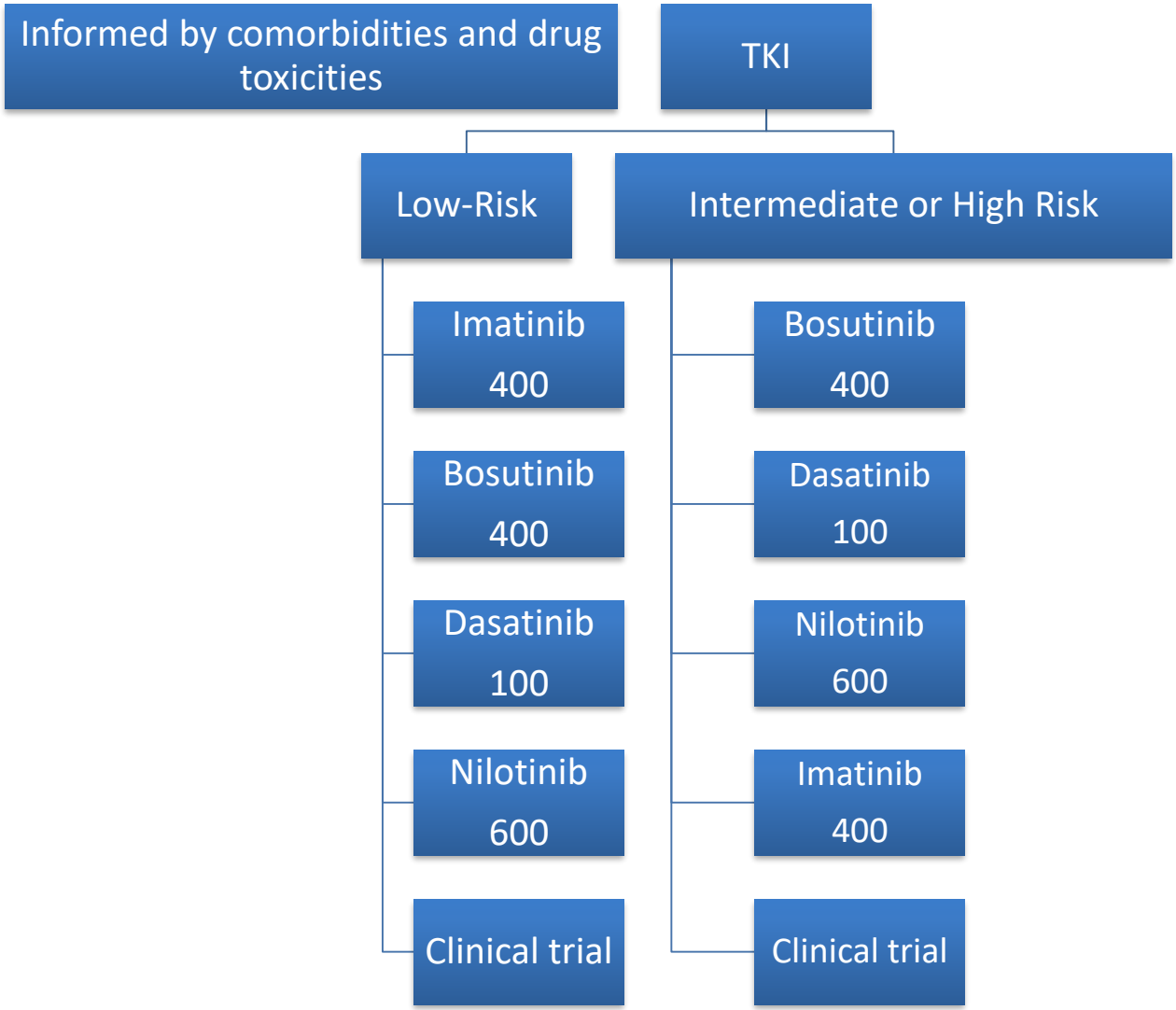
Choosing TKIs considering previous conditions and toxicity

	ITK			
Previous condition	Imatinib	Nilotinib	Dasatinib	Bosutinib
• Heart disease				
• QT vulnerability				
• Arterial HT		1		1
• ↑ Glu, ↑Chol		1		
• Ulcus, Bleeding Dyath.			2	
• Liver disease				
• Pancreatitis risk				
• Renal disease				
• Gut disorders				
• COPD, autoimmunity			3	
• Previous viral hepatitis				

1. CVR (N, B, P, or *per se* (B, P)
2. Bleeding
3. Pleural disease

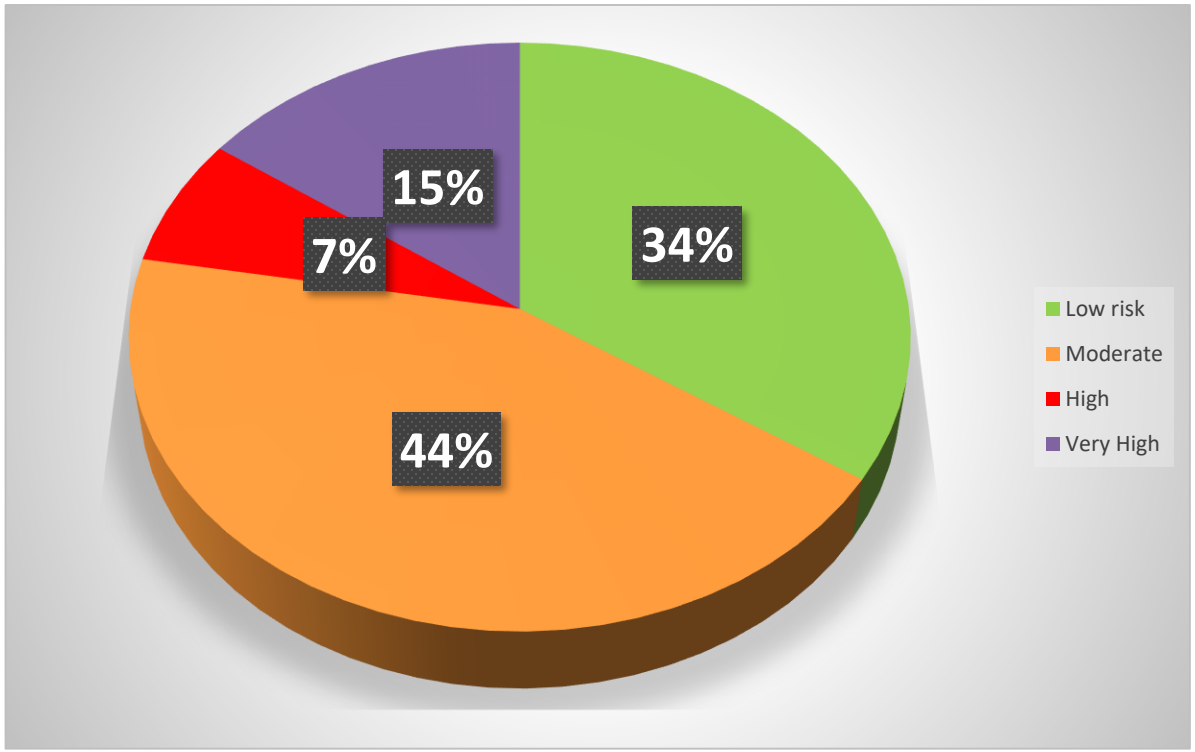
Thank you, Grazie, Gracias

NCCN v. 1-2019 . 08/01/2018
CML Guidelines



Cardiovascular risk in Spanish population, 2009-2010: Only 22% high or very high

- 2310 persons, 100 primary care centers in Spain, 2009-2010
- 40-65 years



Rev Esp Cardiol. 2015;68:417-25 - Vol. 68 Núm.05 DOI: 10.1016/j.recesp.2014.05.023

NCCN Guidelines V 1-2019 Chronic myeloid leukemia

BCR-ABL1(IS)	3 months	6 months	12 months	> 15 months
> 10%	Yellow	Red		
> 1% - 10%	Green		Yellow	Red
≤ 1%	Green			

Color	Concern	Clinical Considerations	2nd line treatment
Red	Resistant	Compliance & interactions Consider mutational analysis	Switch Evaluate for allo HCT
Yellow	Possible resistant	Same, plus Consider BM CG for MCyR at 3m or CCyR at 12m	Switch or continue * Dose escalation of Imatinib (max: 800) Consider eval. for Allo HCT
Green	Sensitive	Monitor response and AEs	Continue

* Other tan imatinib