Imatinib versus a 2nd generation TKI for the first line of therapy: how we can tip the balance between efficacy and quality of life

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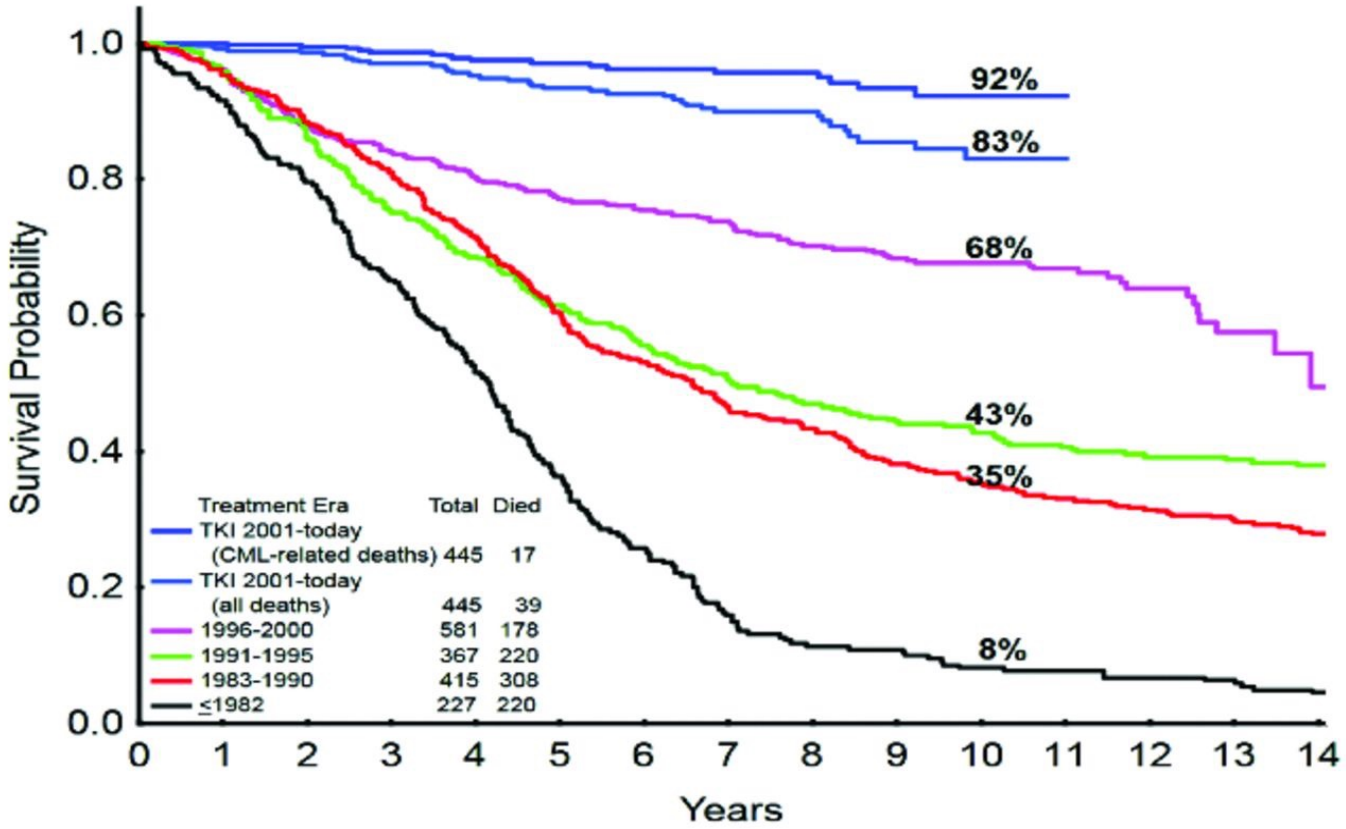
CML: treatment goals in 2022

- **Overall survival**
- Progression free survival
- Quality of life
- Good tolerability
- Lack of long term toxicity
- **Chance to achieve treatment free remission**
- Costs ?

Survival with CML over time



Mughal T. et al. Haematologica 2016

Evolution of scoring systems

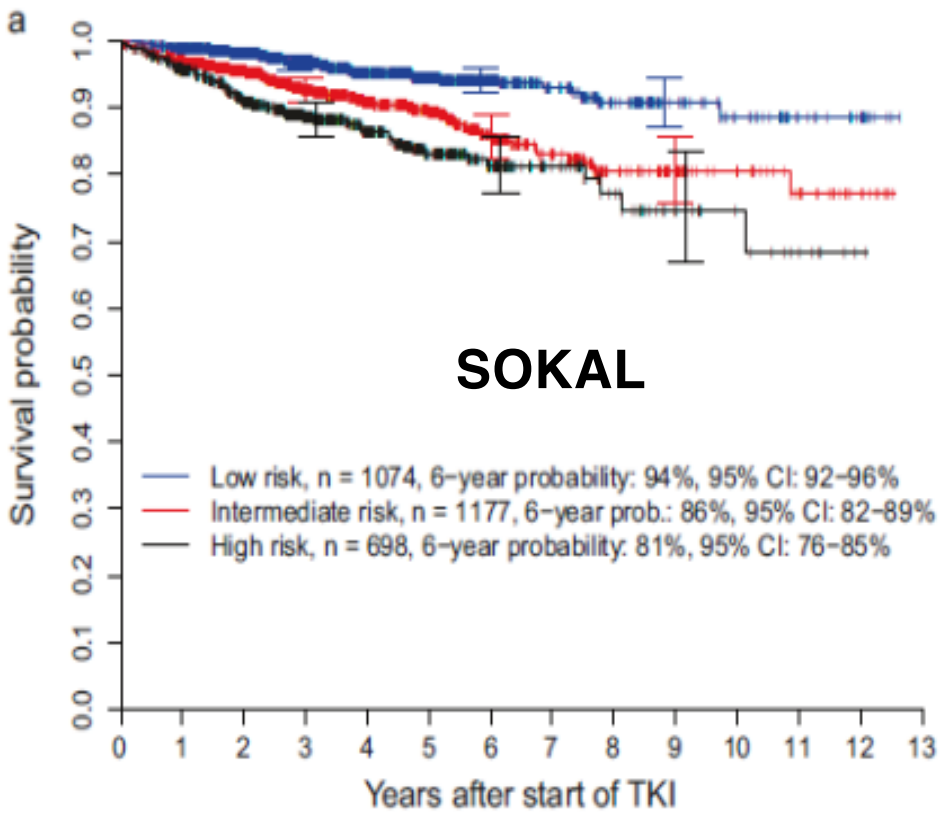
	Sokal 1984	EURO „Hasford“ 1998	EUTOS 2011	European Long Term Survival 2016*
Parameter	Age	Age		Age
	Spleen	Spleen	Spleen	Spleen
	Blasts	Blasts		Blasts
	Platelets	Platelets		Platelets
		Eosinophils		
		Basophils	Basophils	
Therapy	Chemotherapy	IFN	Imatinib	Imatinib
Endpoint	Survival	Survival	CCyR	Survival (CML-rel. deaths)

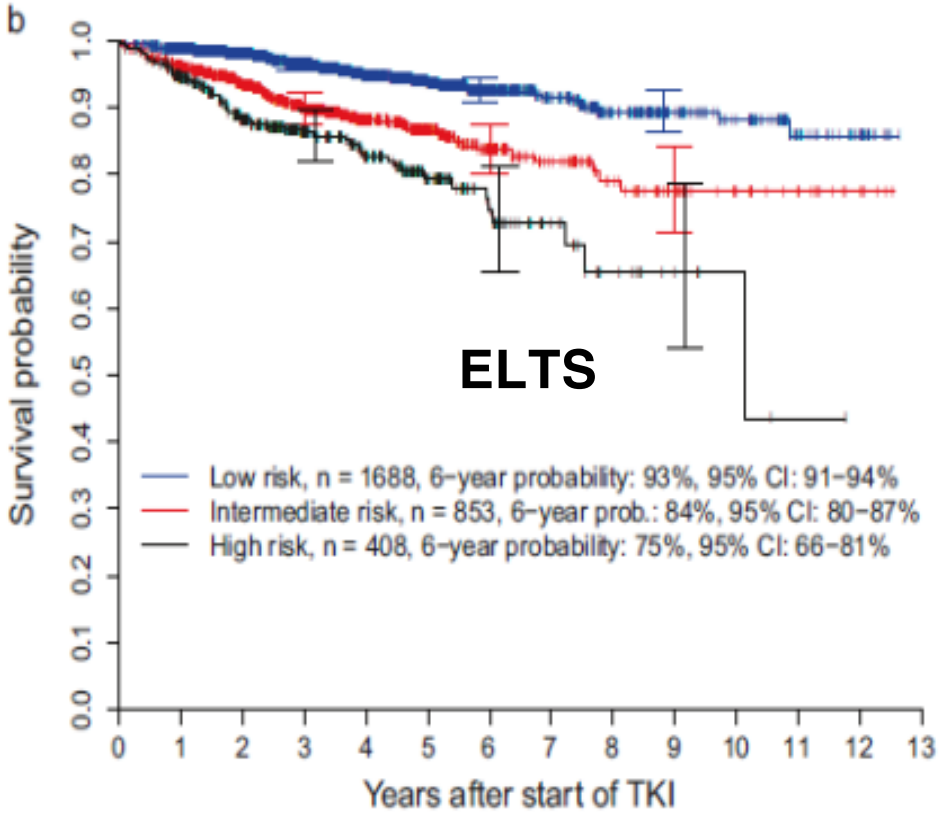
*Pfirrmann et al, Leukemia 2016

Outcome according to risk scores

(b) Risk strata proportions and outcome

	Low risk		Intermediate risk		High risk	
$n = 5154$	Sokal	ELTS	Sokal	ELTS	Sokal	ELTS
%	38	55	38	28	23	13
10-year OS	89%	88%	81%	79%	75%	68%
6-year LRD	3%	2%	4%	5%	8%	12%





Pfirmman M. et al. Leukemia 2020

The ELTS score should be preferred

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

Hochhaus A. et al. Leukemia 2020

Choice of front-line therapy

European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

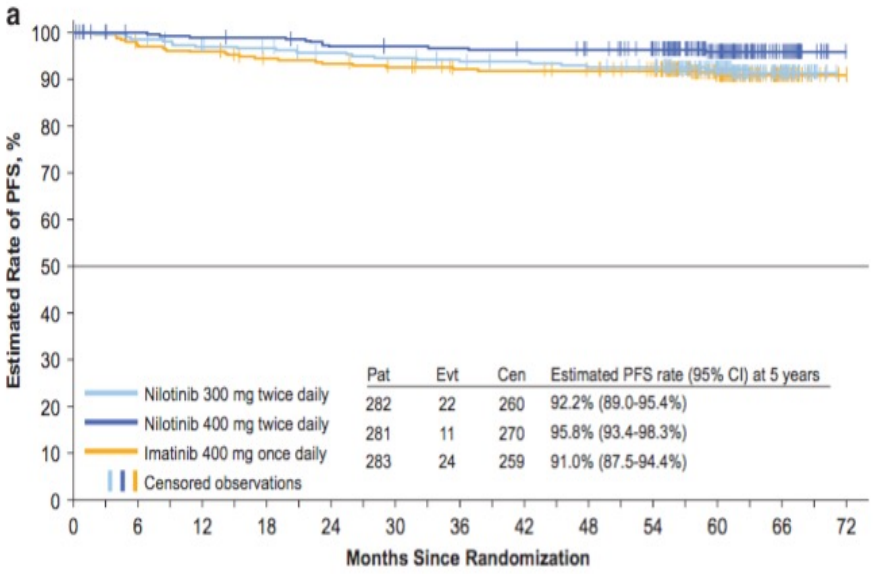
A. Hochhaus[1] · M. Baccarani[2] · R. T. Silver[3] · C. Schiffer[4] · J. F. Apperley[5] · F. Cervantes[6] · R. E. Clark[7] · J. E. Cortes[8] · M. W. Deininger[9] · F. Guilhot[10] · H. Hjorth-Hansen[11] · T. P. Hughes[12] · J. J. W. M. Janssen[13] · H. M. Kantarjian[14] · D. W. Kim[15] · R. A. Larson[16] · J. H. Lipton[17] · F. X. Mahon[18] · J. Mayer[19] · F. Nicolini[20] · D. Niederwieser[21] · F. Pane[22] · J. P. Radich[23] · D. Rea[24] · J. Richter[25] · G. Rosti[2] · P. Rousselot[26] · G. Saglio[27] · S. Saußele[28] · S. Soverini[2] · J. L. Steegmann[29] · A. Turkina[30] · A. Zaritskey[31] · R. Hehlmann[28,32]

- With the exception of pregnancy, **first-line treatment is a TKI**
- Currently, 4 TKIs have been approved for first-line treatment by the FDA and EMA: **imatinib**, **dasatinib**, **nilotinib** and **bosutinib** (**radotinib** approved in South Korea only)
- Second generation TKIs have been tested against imatinib in company-sponsored trials
- They have never been tested against each other
- **Comparisons among these trials, and of these trials with academic studies, are difficult**

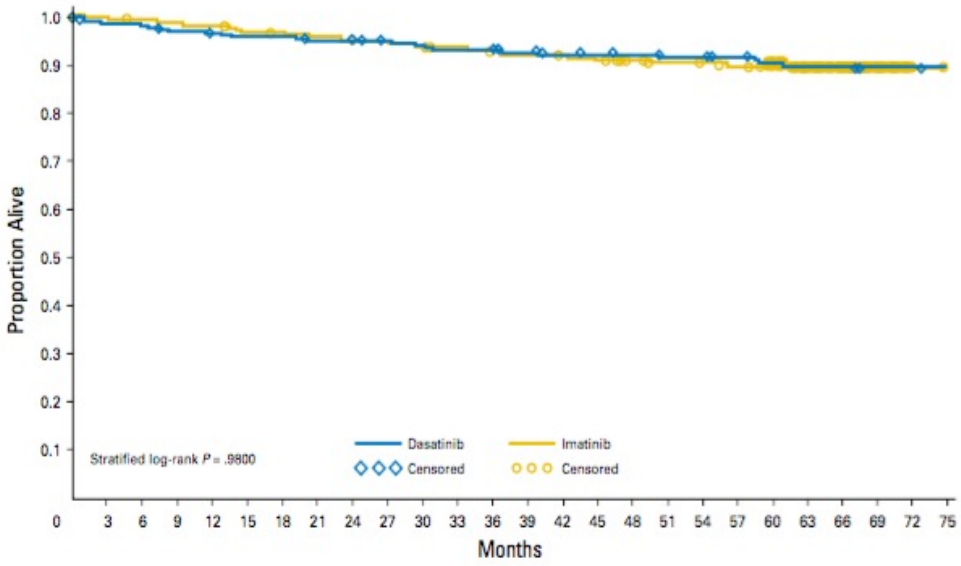
Hochhaus A. et al. Leukemia 2020

RCT of Imatinib vs 2G-TKIs: OS is similar

ENESTnd*: Nilotinib vs Imatinib



DASISION**: Dasatinib vs Imatinib



*Hochhaus A. et al. Leukemia 2016
** Cortes J. et al. J Clin Oncol 2016

RCT of Imatinib vs 2G-TKIs: risk of progression to AP/BC

5-year risk (ITT)	n
Dasatinib vs Imatinib	12 vs 19
Nilotinib vs Imatinib	10 vs 21 (rare in low Sokal risk)

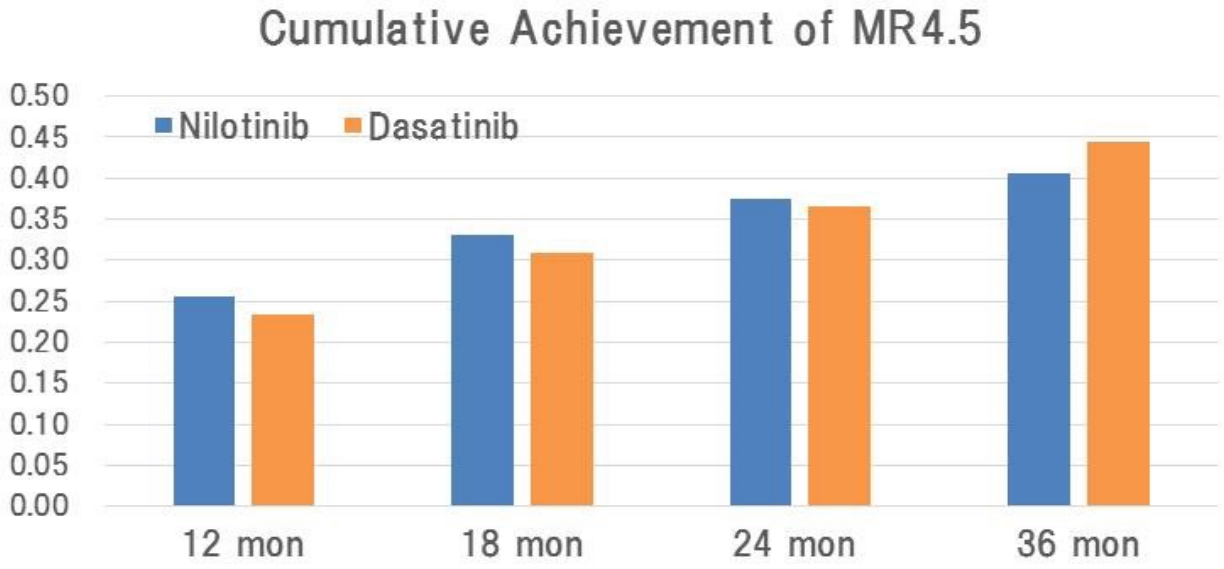
Hochhaus A. et al. Leukemia 2016
Cortes J. et al. J Clin Oncol 2016

RCT of Imatinib vs 2G-TKIs: molecular responses

	MMR by 5 years	$MR^{4.5}$	≤10% at 3 months (EMR)
DAS vs IM	**76%** 64%	**42%** 33%	**84%** 64%
NIL vs IM	**77%** 60%	**54%** 31%	**91%** 67%

Hochhaus A. et al. Leukemia 2016
Cortes J. et al. J Clin Oncol 2016

Nilotinib vs. Dasatinib for newly diagnosed CML: prospective randomized phase III study JALSG CML212



"Based on these results, we consider that nilotinib and dasatinib are equally effective for *de novo* CML-CP patients in achieving $MR^{4.5}$ as well as in achieving CCyR and MMR in terms of both frequencies and times to achievement with similar continuity."

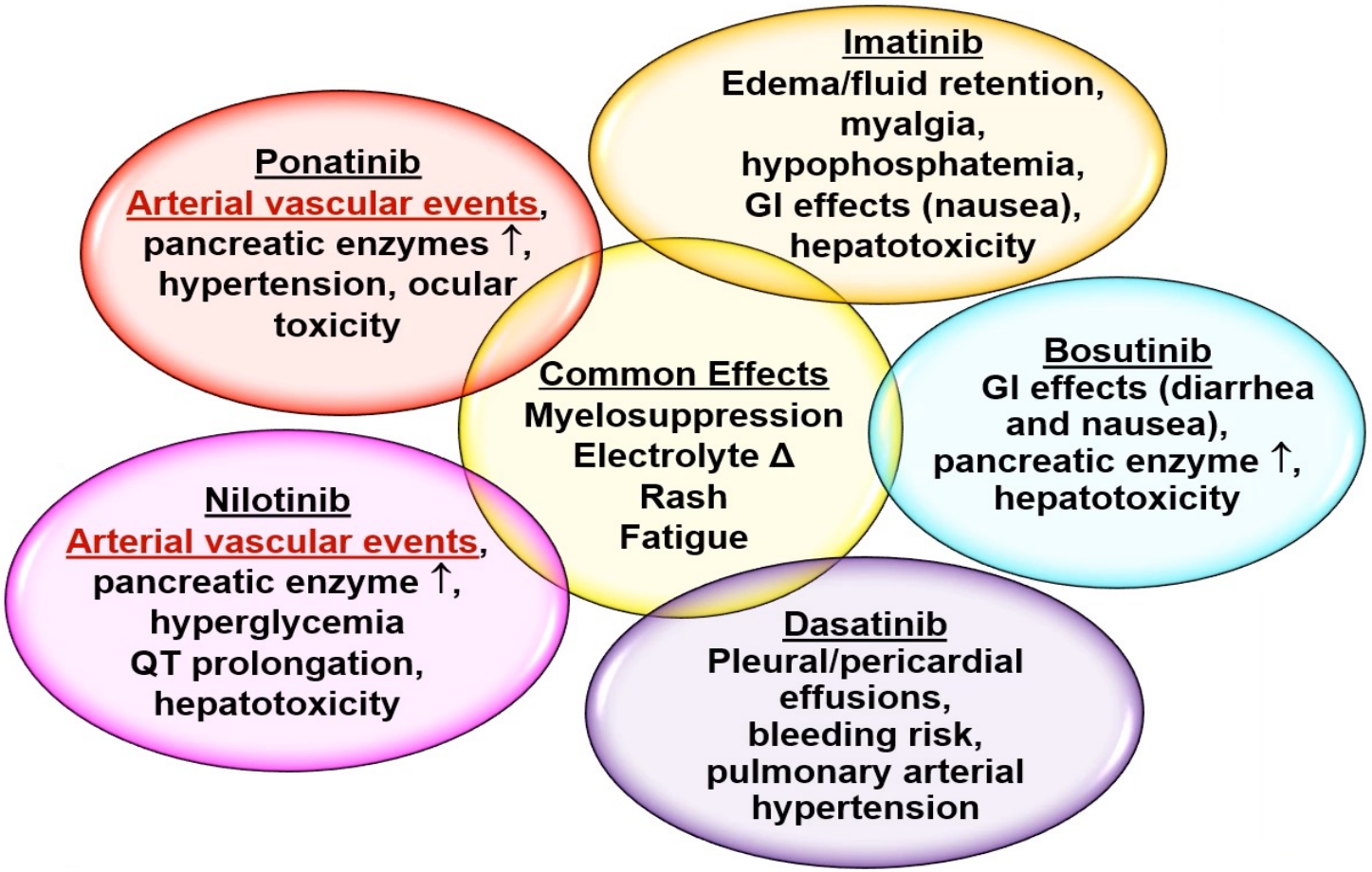
Matsumura I. et al. ASH 2020

First-line Imatinib vs 2G/3G-TKIs: metanalysis

Outcome efficacy*	No. of RCTs	No. of pts	RR†	95% CI†
EMR at 3 mo	6	2182	**1.34**	**1.27-1.41**
MMR at 12 mo	6	2208	**1.52**	**1.32-1.75**
MR4 at any time	7	2331	**1.67**	**1.32-2.11**
CCyR at 12 mo	5	1553	**1.13**	**1.04-1.22**
CCyR by 12 mo	5	2204	**1.15**	**1.09-1.22**
MMR at 3 mo	5	1823	**4.50**	**2.23-9.09**
MR4.5 at any time	6	1930	**2.65**	**1.44-4.88**
AP/BP during study treatment	6	2411	**0.43**	**0.25-0.73**
Discontinued any time	7	2715	1.00	0.81-1.24

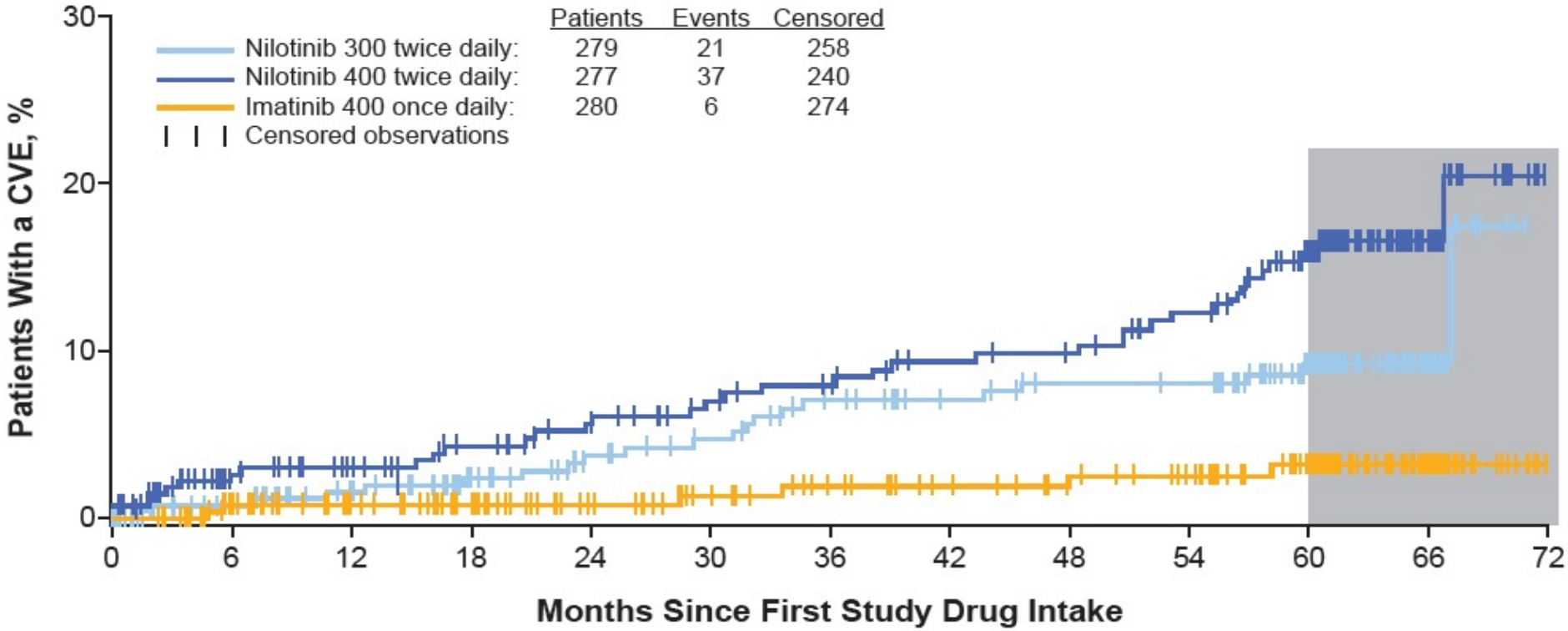
Vener et al. Blood Adv. 2020;4:2723-2735

Common and unique toxicities of TKIs in CML



RCT of Imatinib vs 2G-TKIs: toxicities

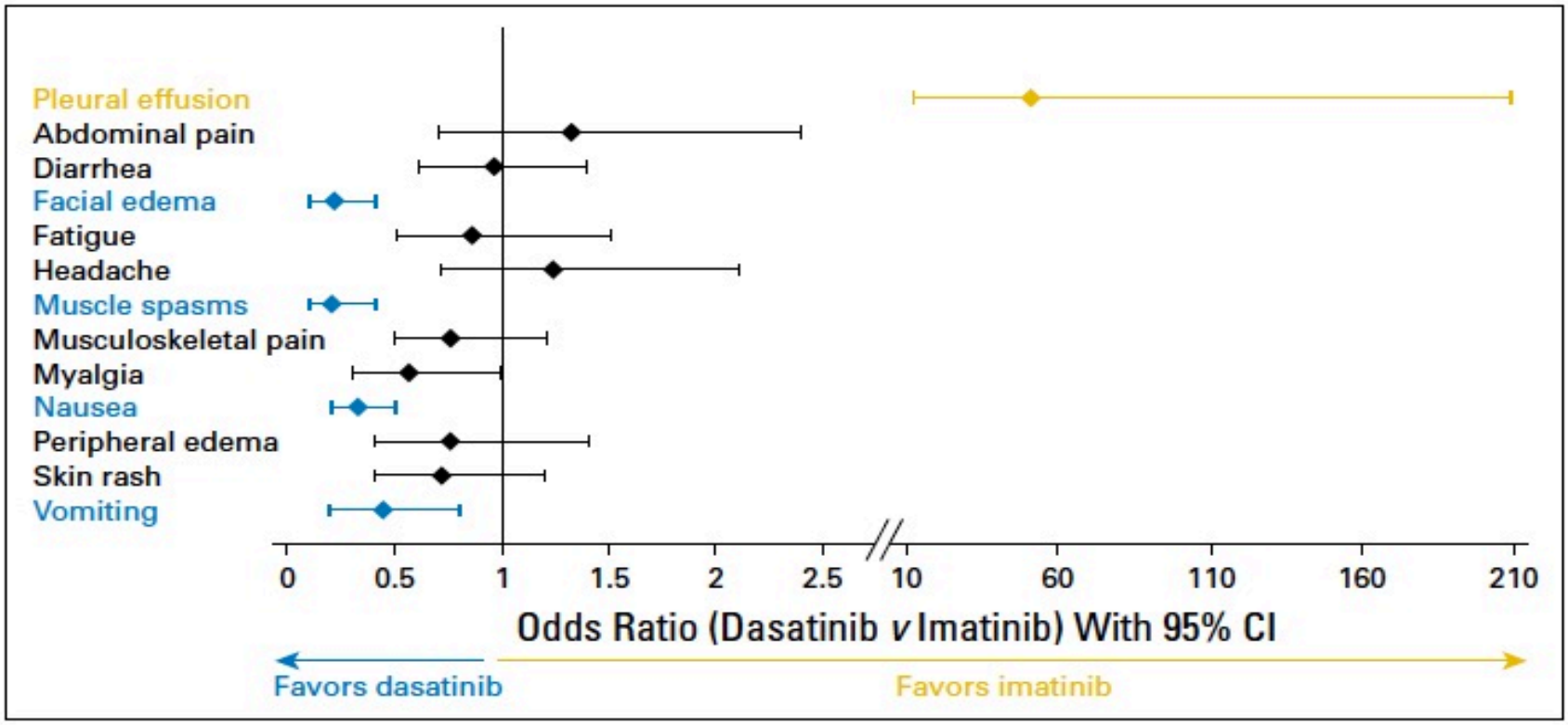
ENESTnd (Nilotinib vs Imatinib): CV events



Hochhaus A. et al. Leukemia 2016

RCT of Imatinib vs 2G-TKIs: toxicities

DASISION (Dasatinib vs Imatinib)



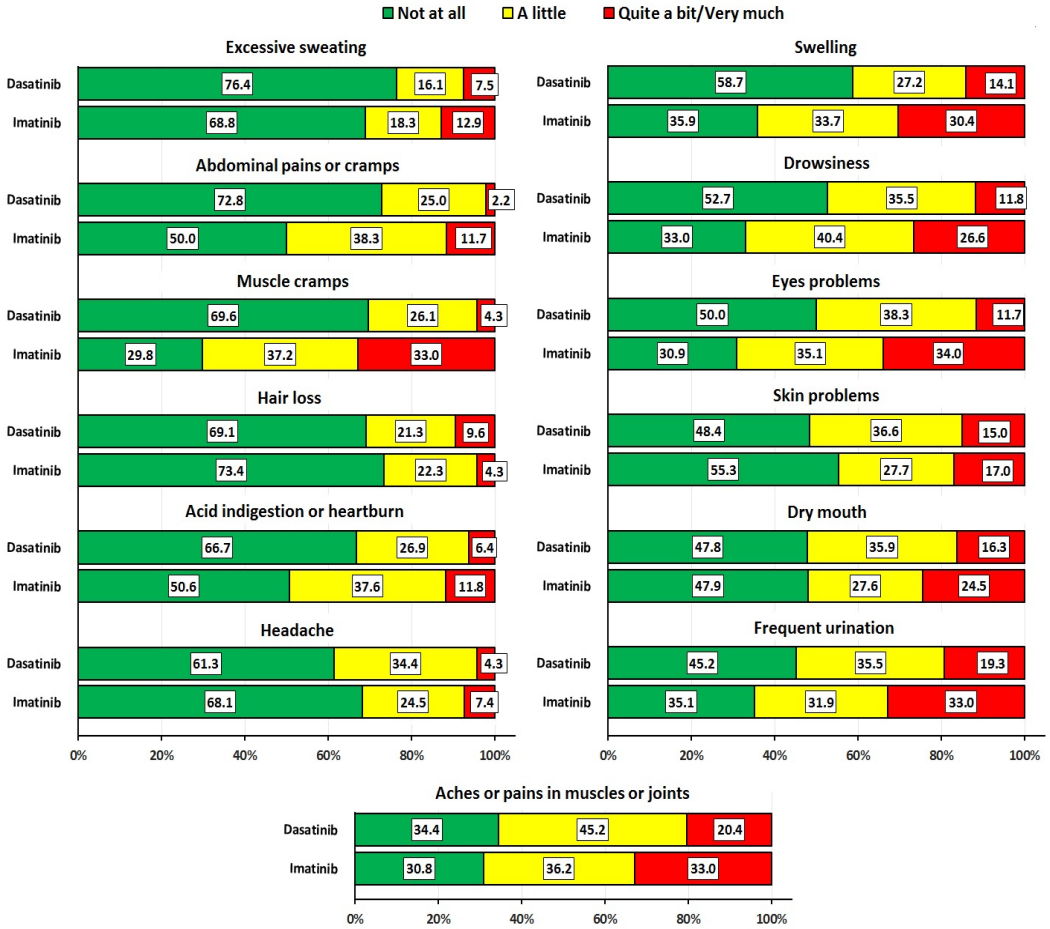
Cortes J. et al. JCO 2016

First-line Imatinib vs 2G/3G-TKIs: metanalysis

Outcome toxicity: grade 3-4*,†	No. of RCTs	No. of pts	RR‡	95% CI‡
Anemia	7	2704	1.17	0.80-1.72
Neutropenia	7	2704	0.69	0.46-1.02
Thrombocytopenia	7	2704	**1.55**	**1.17-2.05**
Cardiovascular events	7	2704	**2.26**	**1.32-3.87**
Cutaneous effects	7	2704	0.73	0.21-2.47
GI effects	7	2704	1.80	0.67-4.84
Fluid retention§	7	2704	**3.21**	**1.09-9.48**
Infectious events	7	2704	1.11	0.54-2.28
Pancreatic effects	5	2413	**2.24**	**1.29-3.87**
Hepatic effects	6	2459	**3.01**	**1.21-7.51**
Musculoskeletal disorders	6	2658	0.76	0.36-1.62
QT prolongation	5	2352	0.82	0.39-1.73

Vener et al. Blood Adv. 2020;4:2723-2735

…but QoL seems superior with 2GTKIs (at least in youngs)



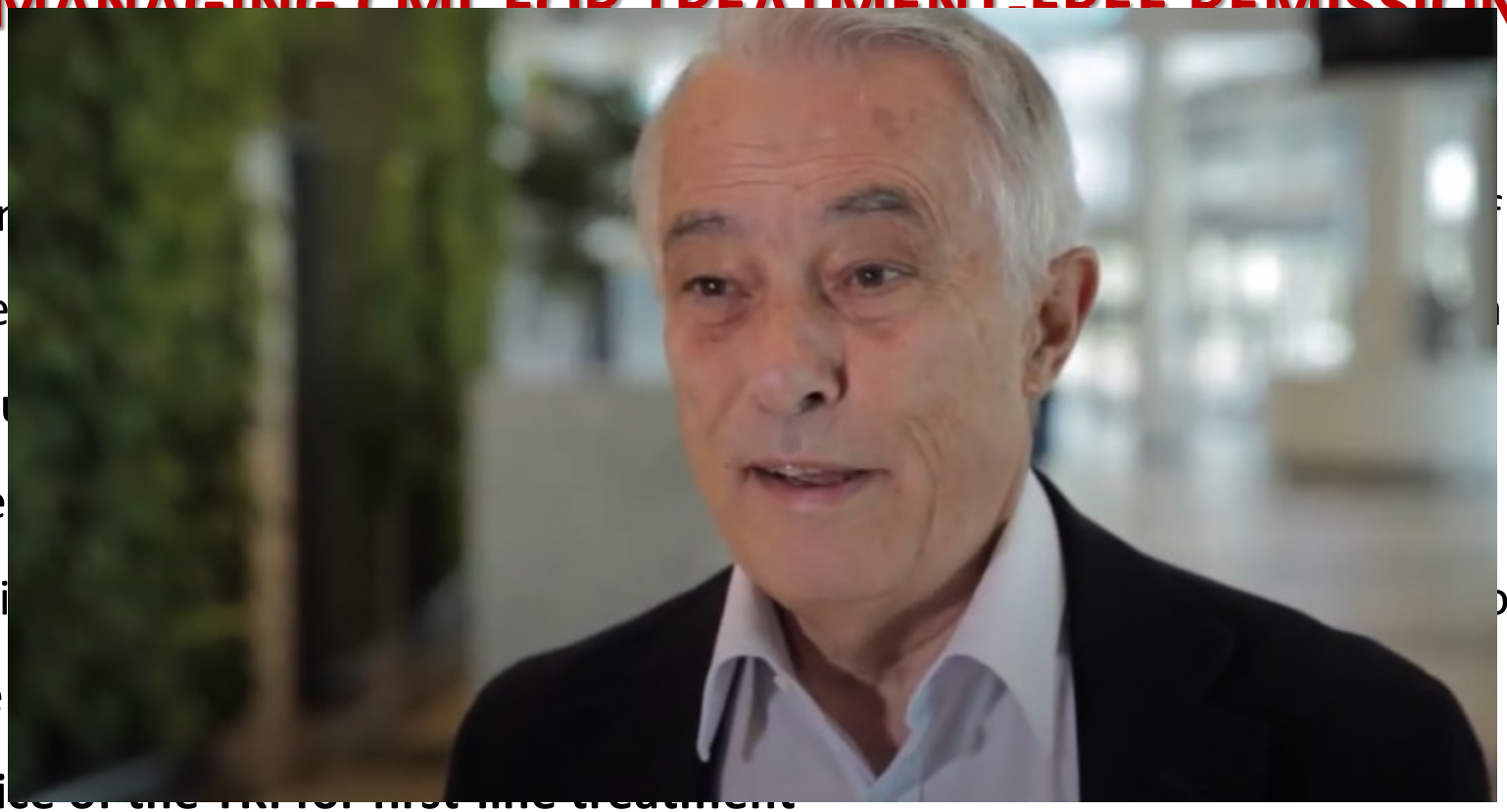
	Impact on daily life		Symptom burden		Impact on worry/mood		Body image problems		Satisfaction with care and information		Satisfaction with social life	
	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p
dasatinib	18.82 (19.98)	0.002	19.12 (14.96)	0.001	22.70 (17.75)	0.346	17.56 (28.91)	0.339	82.62 (22.26)	0.484	70.29 (24.93)	0.001
imatinib	26.22 (23.29)		26.62 (17.23)		24.79 (20.82)		20.15 (28.06)		80.65 (23.22)		56.63 (29.40)	

Efficace F. et al. Leukemia 2020

TKI selection based on comorbidities

Comorbidity	Preferred	Less preferred
Diabetes	Imatinib, Dasatinib, Bosutinib	Nilotinib, Ponatinib
Pulmonary disease	Imatinib, Nilotinib, Ponatinib	Dasatinib, (Bosutinib?)
Gastrointestinal issues	Nilotinib, Dasatinib, Ponatinib	Bosutinib, (Imatinib?)
Cardio-vascular disease	Imatinib, Bosutinib	Nilotinib, Ponatinib, (Dasatinib?)
Peripheral arterial disease	Imatinib, Bosutinib, Dasatinib	Nilotinib, Ponatinib
Liver disease	Dasatinib, (Nilotinib?)	Bosutinib, Ponatinib, (Imatinib?)
Renal disease	Nilotinib, Dasatinib, Ponatinib	Bosutinib, Imatinib

MANAGING CML FOR TREATMENT-FREE REMISSION



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- **the choi**

Baccarani M. et al. Blood Adv 2019

The choice of first-line treatment

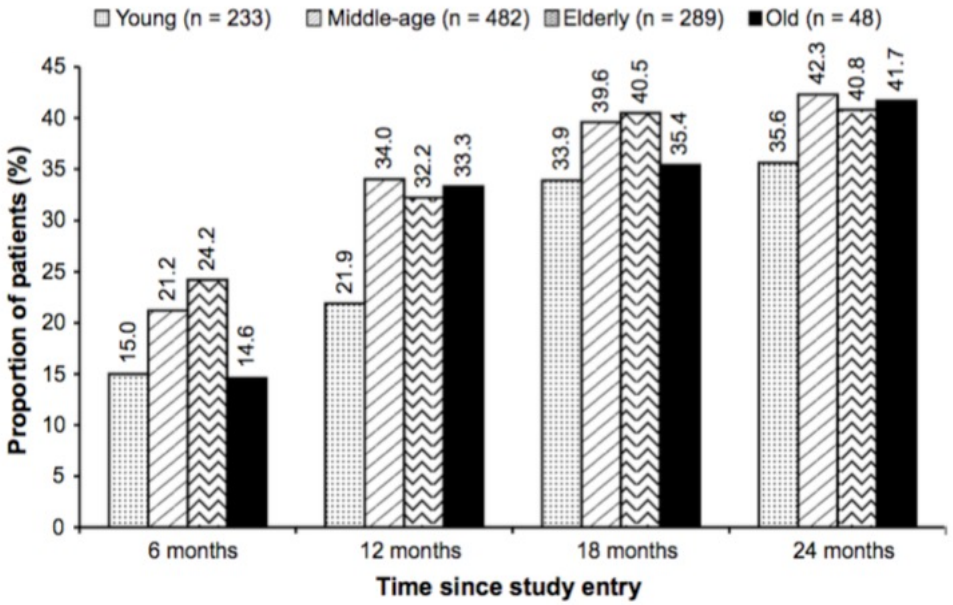
	18-40 yrs	41-65 yrs	66-80 yrs	> 80 yrs
Low risk	2GTKIs	IM – 2GTKIs	IM	IM
Intermediate risk	2GTKIs	2GTKIs	IM – 2GTKIs	IM
High risk	2GTKIs	2GTKIs	IM – 2GTKIs	IM

Baccarani M. et al. Blood Adv 2019

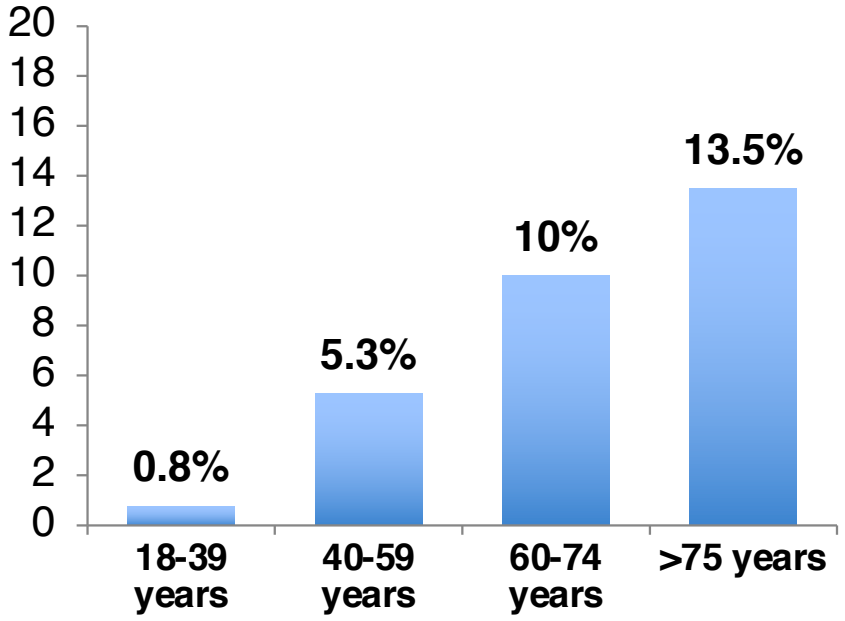
Age or Comorbidities?

Efficacy and toxicity of frontline nilotinib across age groups

Rates of MR^4



CV events



Giles F. et al. J Cancer Res Clin Oncol 2017

LEUKEMIA2022 May 5-6, 2022
AIL President: P. Toro
Coordinators: A.M. Carella, S. Amadori

Determinants of Choice of Front-Line Tyrosine Kinase Inhibitor for Chronic Phase CML: a Study from the "Registro Italiano LMC" & "Campus CML"

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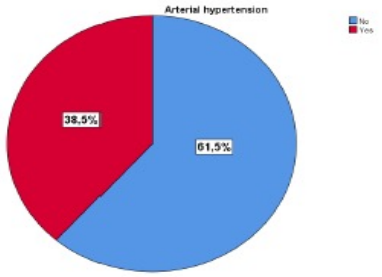
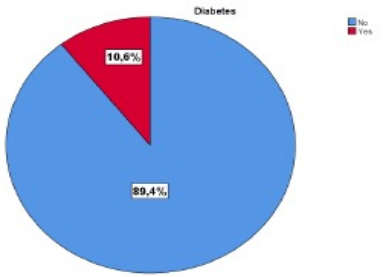
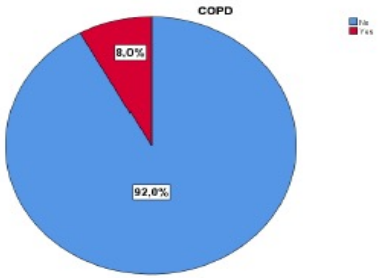
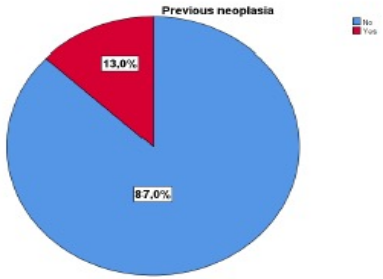
MAIN CONCOMITANT DISEASES

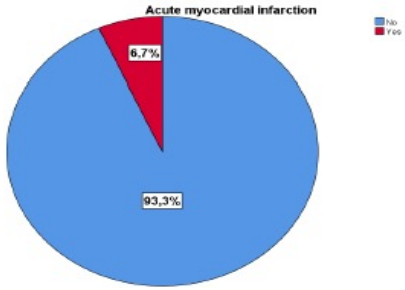
Arterial hypertension	**547/1419 (38.5%)**
Diabetes	**150/1421 (10.6%)**
COPD	**114/1420 (8.0%)**
Previous neoplasia	**185/1420 (13.0%)**
Acute my infarction	**95/1421 (6.7%)**
Stroke	**36/1421 (2.5%)**

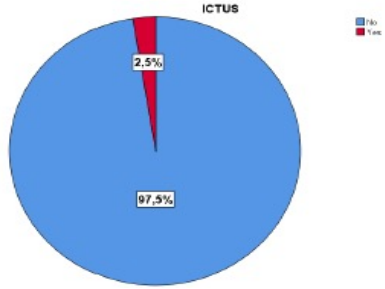












Tiribelli M. et al. ASH 2020

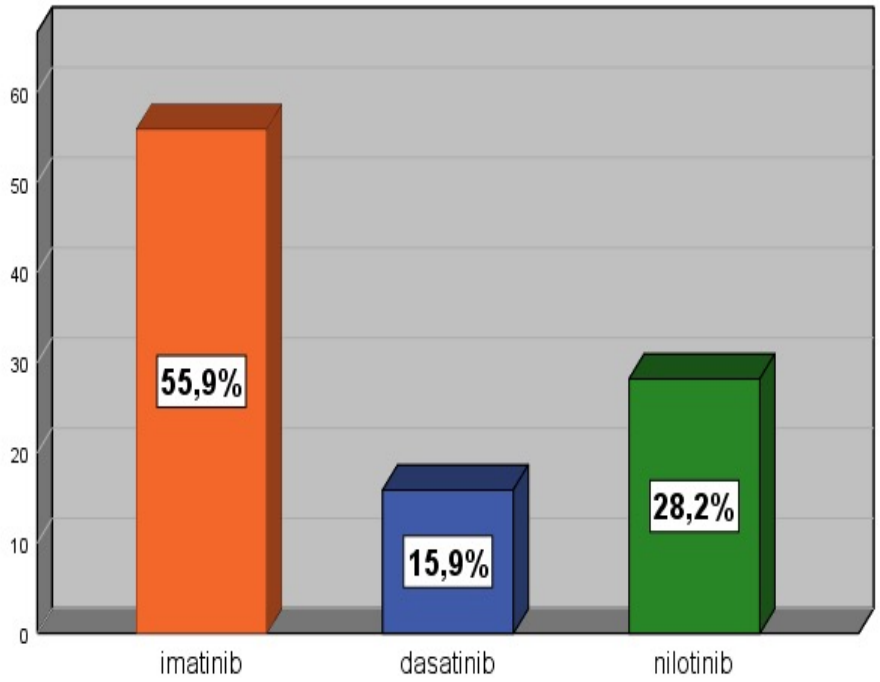
FRONTLINE TREATMENT

Imatinib 794 (55.9)

Dasatinib 226 (15.9)

Nilotinib 402 (28.2)

2G-TKI 628 (44.2)



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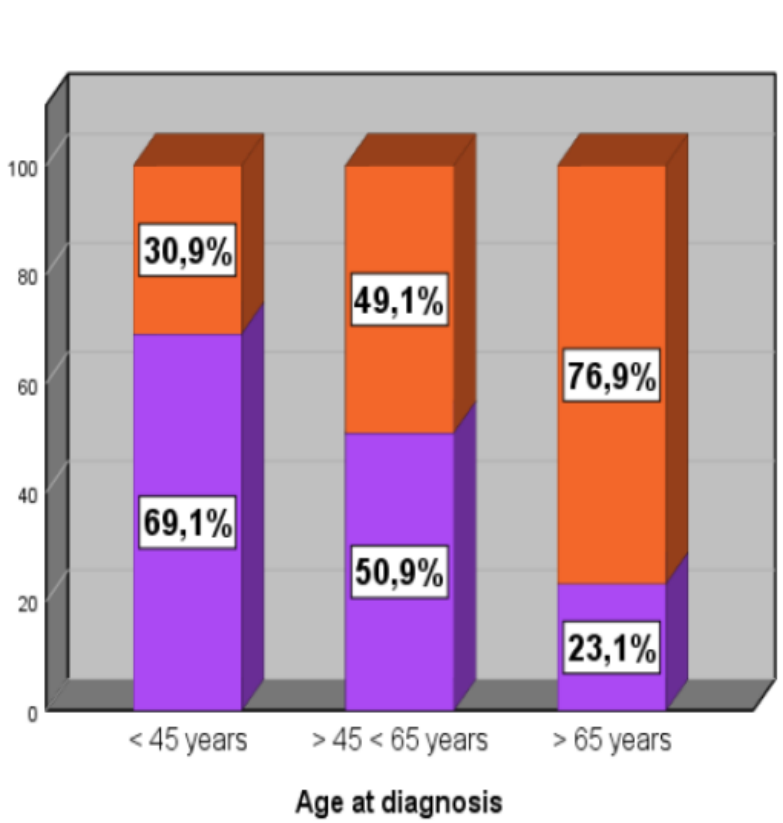

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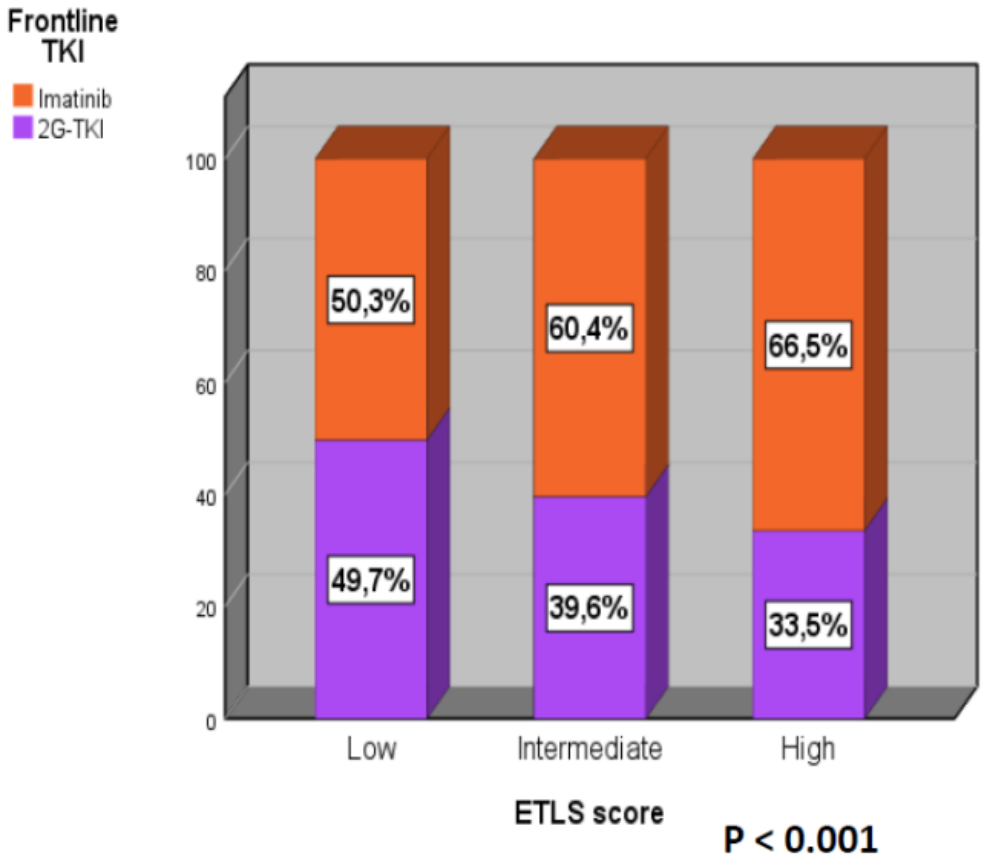

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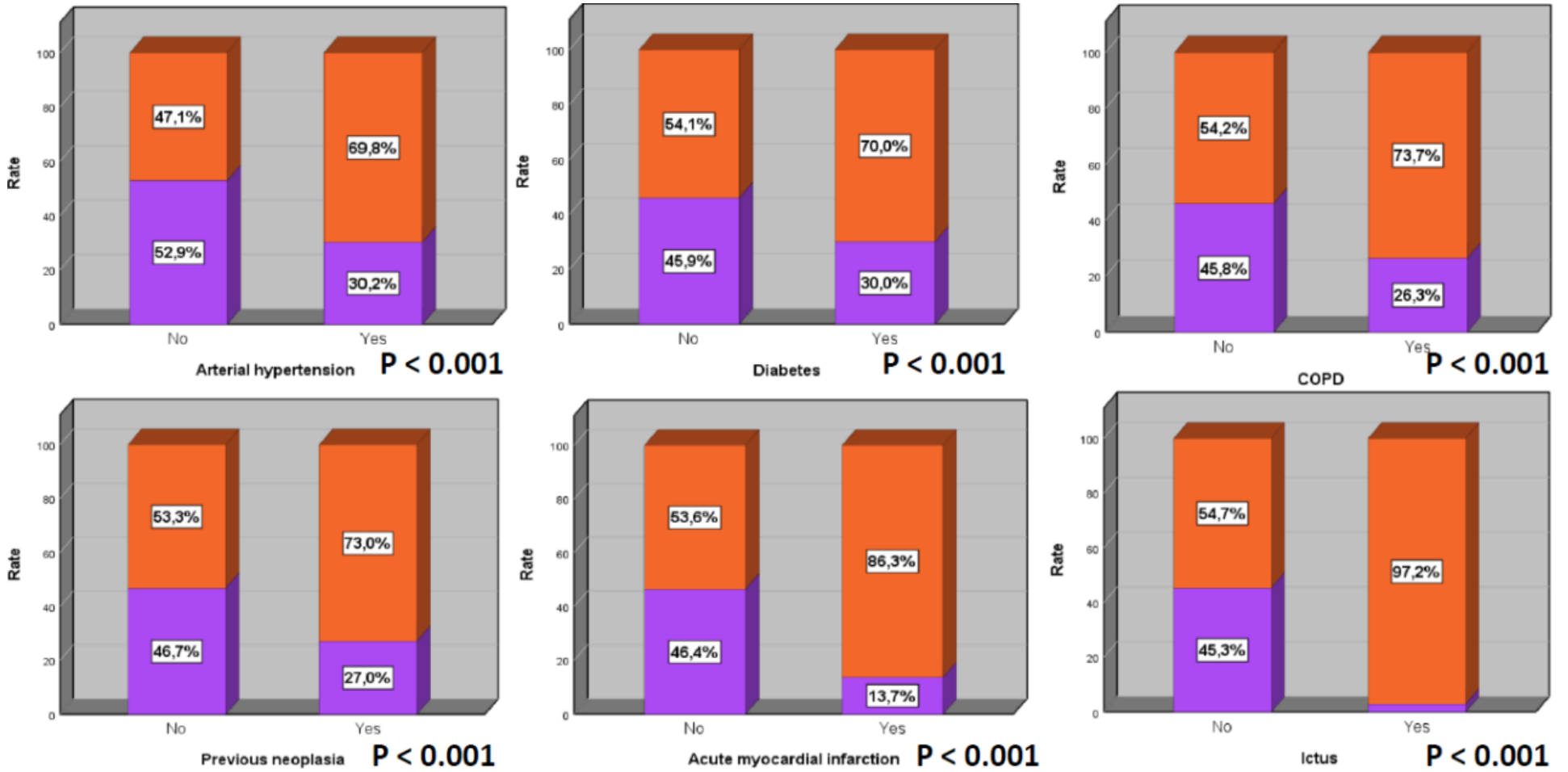

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In the end, selection of first-line TKI is a not so easy task…

Patient

Risk
Comorbidities
Age
Compliance

Drugs

Efficacy
Time to response
Side Effects & long-term safety
Costs?

Physician

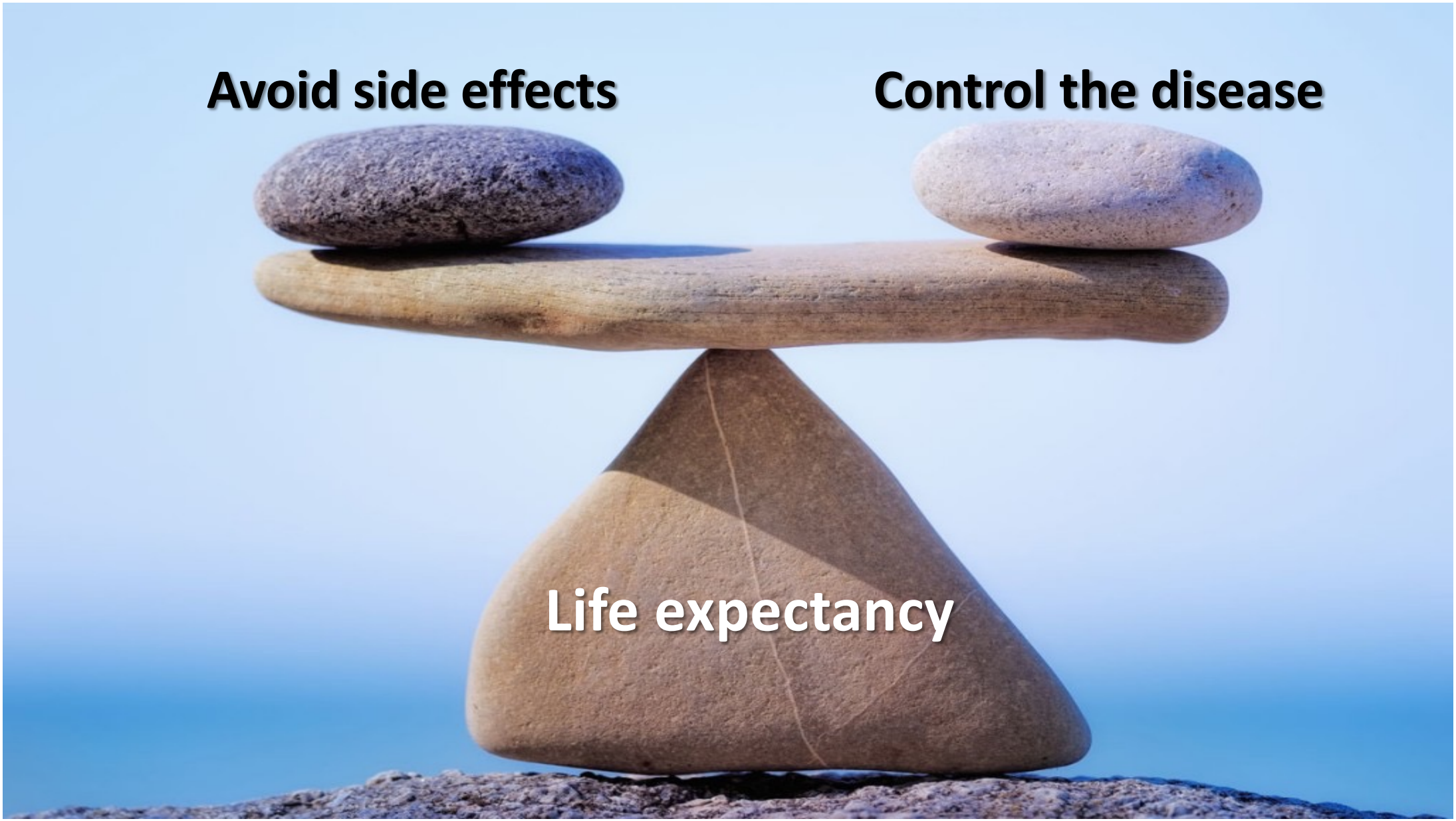
Personal Experience

ENDPOINTS

Overall survival

Treatment-free remission

Quality of life


Avoid side effects
Control the disease
Life expectancy

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