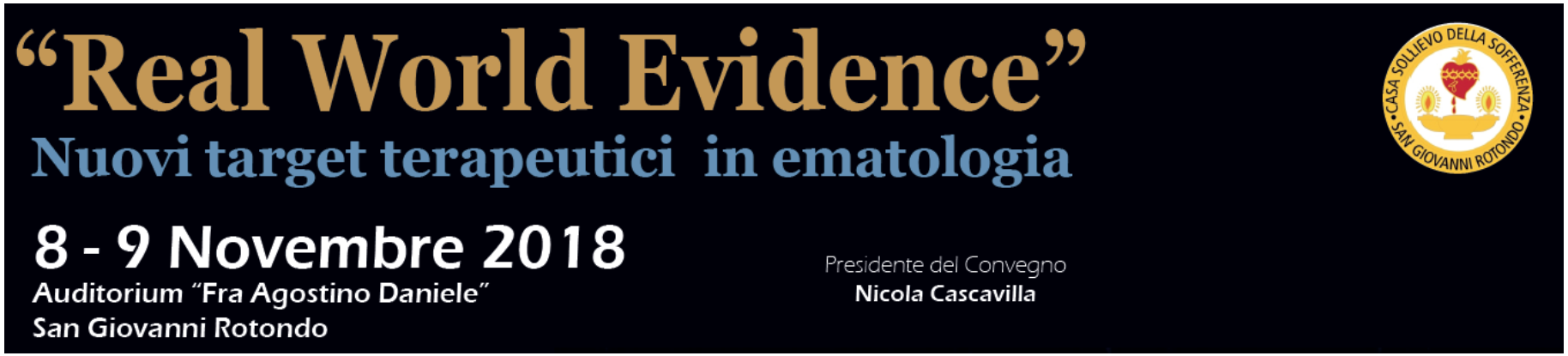
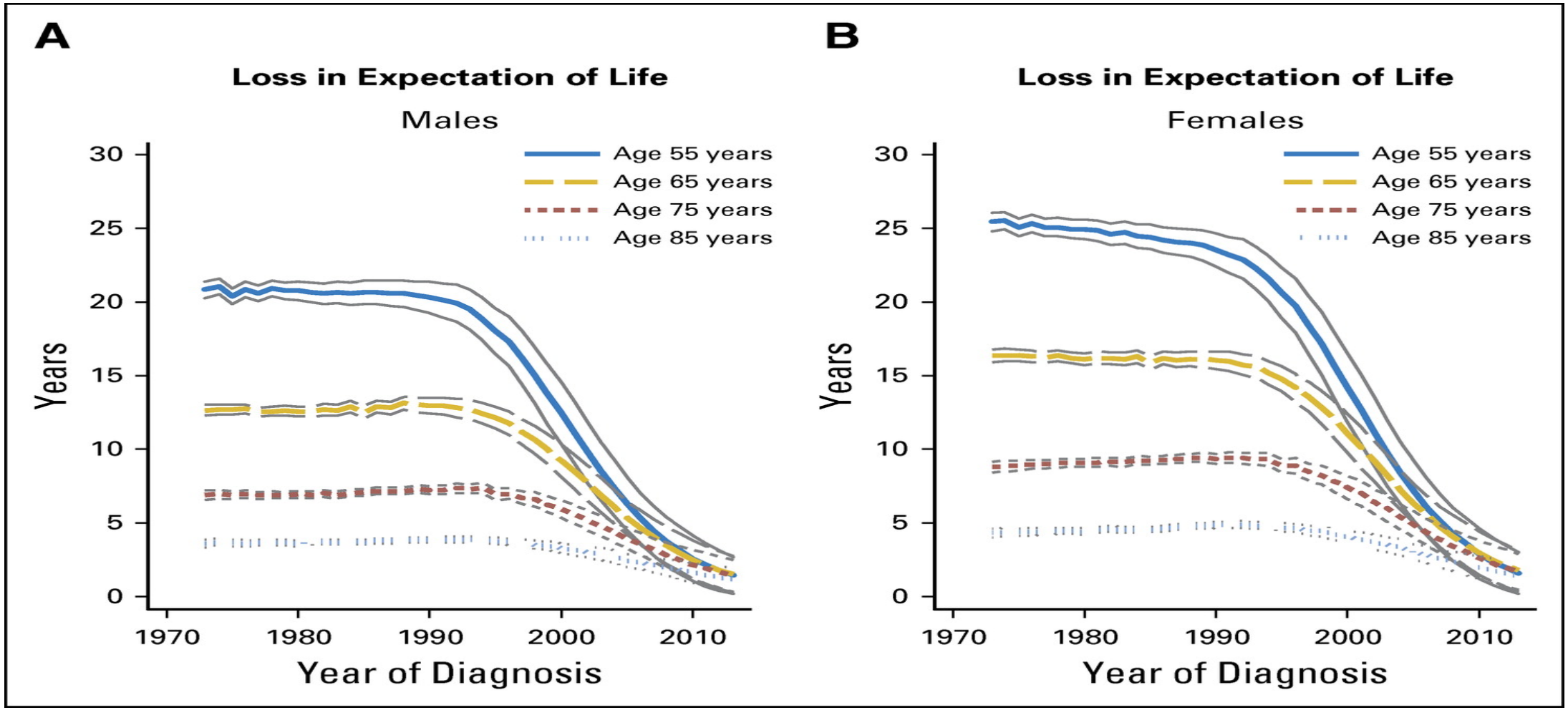


TKIs e LMC: Lo stato dell'arte

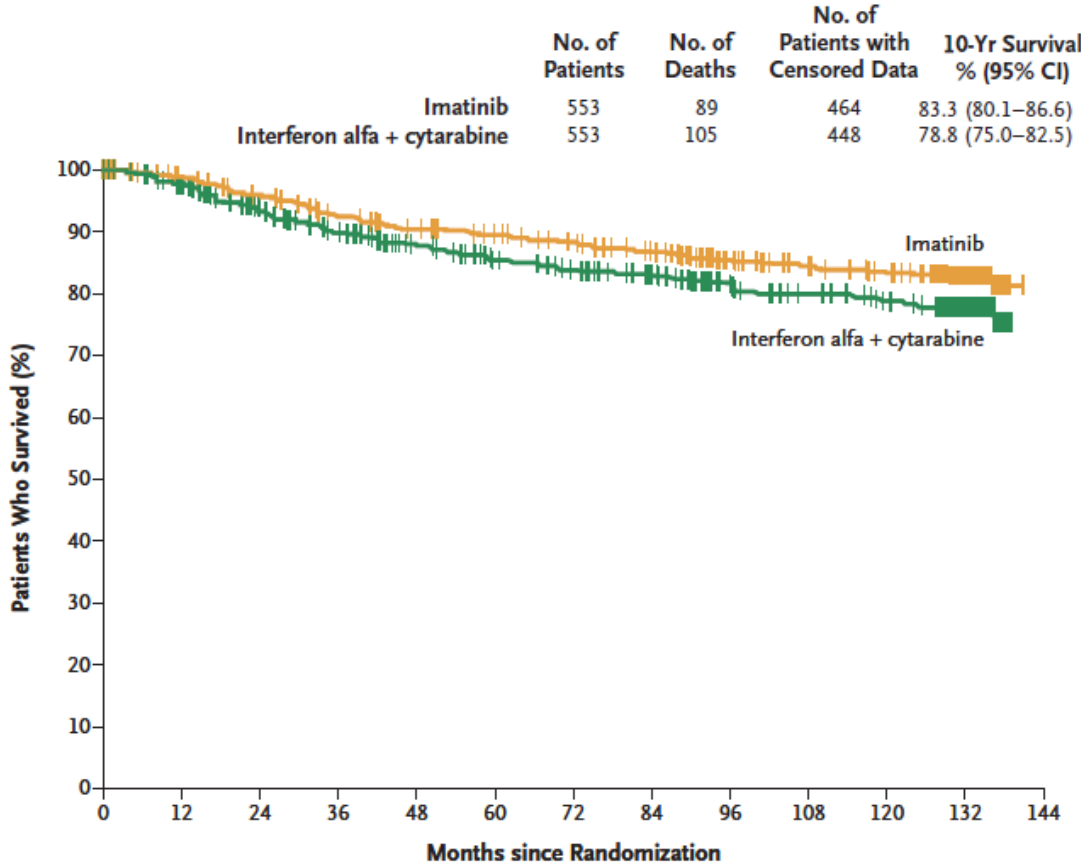
Fabrizio Pane

Loss in life expectancy of patients with CML in Sweden, over year of diagnosis, by age at diagnosis and sex



Long-term Results of Imatinib Treatment in CML

IRIS Trial 11-Year Update



No. at Risk								
Imatinib	553	542	492	461	430	368	250	0
Interferon alfa + cytarabine	553	512	441	388	358	299	199	0
No. of Deaths								
Imatinib	0	6	41	57	71	82	88	89
Interferon alfa + cytarabine	0	12	52	73	83	96	104	105

Variable	All Patients (N = 553)
Median age at baseline (range) — yr	50 (18–70)
Male sex — no. (%)	341 (61.7)
Median duration since diagnosis (range) — mo	2.1 (0–10.4)
Geographic region — no. (%)†	
Europe	277 (50.1)
North America	245 (44.3)
Oceania	31 (5.6)
Completed study treatment — no. (%)	267 (48.3)
Up to end of the core trial in 2006	11 (2.0)
Up to 2007–2008	13 (2.4)
Up to closure of the trial in 2011–2012	243 (43.9)
Discontinued treatment — no. (%)	272 (49.2)
Unsatisfactory therapeutic effect	88 (15.9)
Withdrawal of consent	57 (10.3)
Adverse events	38 (6.9)
No longer required study drug owing to bone marrow transplant	21 (3.8)
Death	19 (3.4)
Protocol violation	17 (3.1)
Loss to follow-up	15 (2.7)
Administrative problems	12 (2.2)
Abnormal laboratory values	3 (0.5)
Abnormal procedure	2 (0.4)
Crossed over to interferon alfa plus cytarabine — no. (%)	14 (2.5)
Imatinib exposure during the trial‡	
Duration of exposure — yr	
Mean	7.5±4.0
Median (range)	8.9 (<0.1–11.7)
Duration of total exposure — patient-yr	4129
Median actual-dose intensity (range) — mg/day	400 (114–770)

Hochhaus A. et al., N Engl J Med 2017;376:917-27

The goals of CML management in 2018

- *Life expectancy*: **Normal**
  - Optimal response (ELN 2013), $MR^{3.0}$ or better?
- *Quality of live*: **Normal**
  - Select treatment for side effects, comorbidities, complications
- *Cure*: **Treatment-free remission**
  - Test and select treatment for deep molecular response

TKIs approved for CML treatment

	Date of FDA approval	
	1st Line	2nd Line
Imatinib	2002	2001
Dasatinib	2010	2006
Nilotinib	2010	2007
Bosutinib	2017	2012
Ponatinib		2013

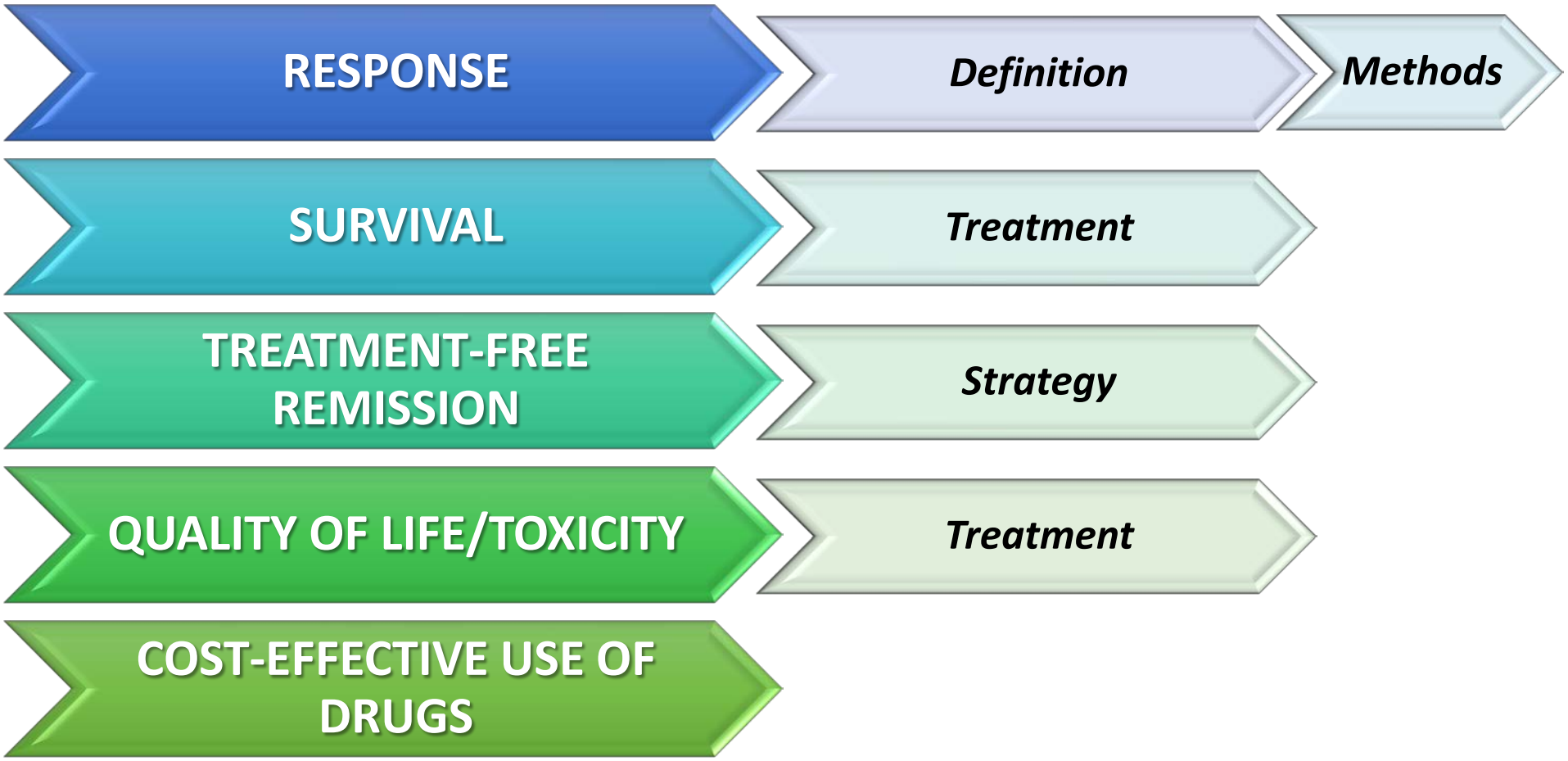
European LeukemiaNet 2013

Treatment recommendations

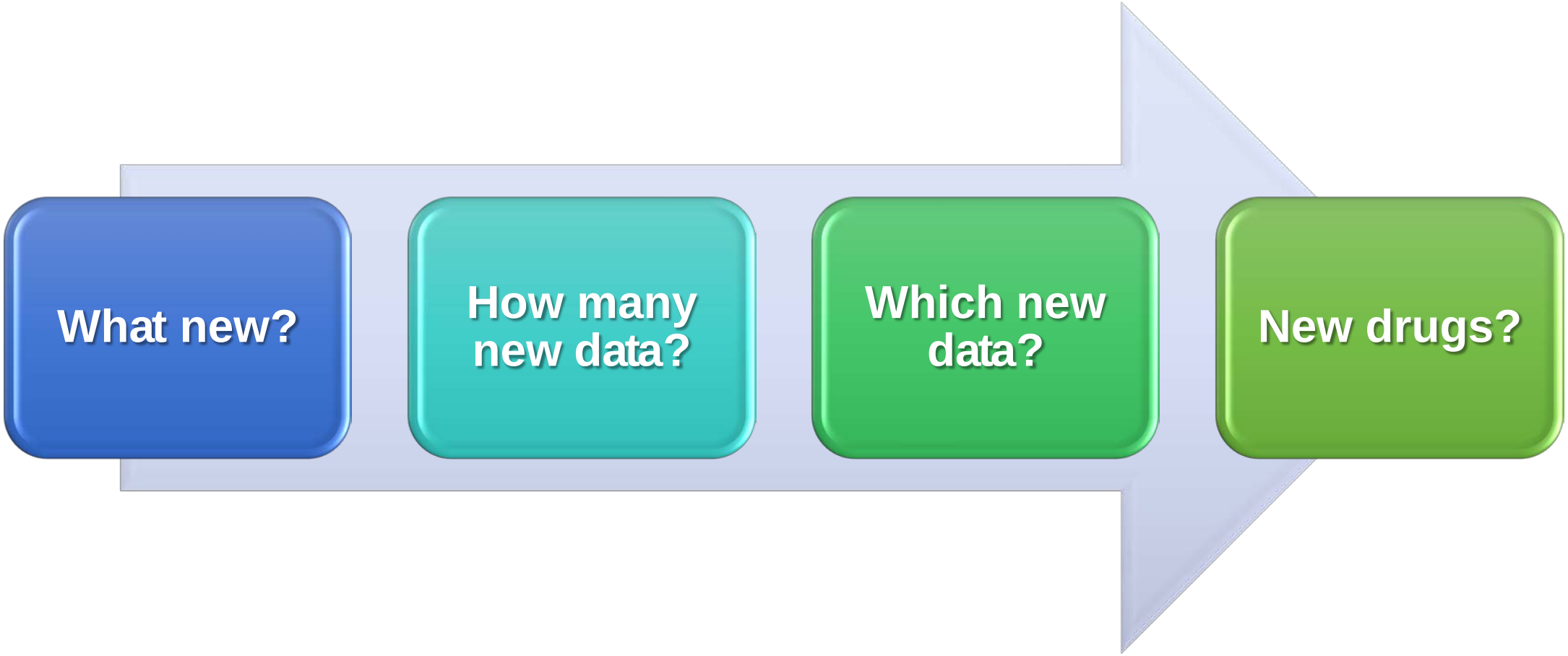
1st LINE	IMATINIB 400 x 1, DASATINIB 100 x 1, NILOTINIB 300 x 2
2nd LINE	
INTOLERANCE	SWITCH TO ONE OF THE OTHER TKIs APPROVED FOR FIRSTLINE TREATMENT, *taking into account comorbidities and side effects*
FAILURE	SWITCH IMATINIB TO OTHER TKIs, *taking into account MUTATIONS, comorbidities and side effects*: - NILO TO DASA, BOSU or PONA (T315I) - DASA TO NILO, BOSU or PONA (T315I)
3rd LINE	SWITCH TO ANOTHER TKI (PONA) ALLOGENEIC SCT EXPERIMENTAL TREATMENT

Perspectives for the 2019 and beyond

THE OBJECTIVES OF TREATMENT OPTIMIZATION



From 2013 to 2018



Treatment of CML in chronic phase 2013 - 2018

1st LINE	IMATINIB	***Generic***
	DASATINIB	
	NILOTINIB	
		Bosutinib
		(Radotinib)
2nd/3rd LINE	IMATINIB	
	DASATINIB	
	NILOTINIB	
	BOSUTINIB	
	PONATINIB	
		(Radotinib)
FAILURE to 2°G TKI	Allo-SCT	
TKI cannot be used (e.g. pregnancy)	INTERFERON-alpha	

First line treatment of CML

Single-arm trials - 2013 / 2018

Imatinib	IRIS	*10-year Update*	Hochhaus A. et al, New Engl J Med 2017;376(10):919-927
	GIMEMA Trials	*7-year Update*	Castagnetti F. et al, Leukemia 2015;29:1823-32
	Italian Registry	*Observational*	Castagnetti F et al, Am J Hematol 2017;92:82-87
	Australian Study of Imatinib		Yeung DT et al, Blood 2015;125(6):915-923
2°G-TKI	Imatinib, Nilotinib, Dasatinib	*Update of 5 MD Anderson Trials*	Jain P et al. Lancet Haematol 2015;2(3):e118- 128
	Imatinib and Nilotinib (ROTATION)	*GIMEMA TRIAL*	Gugliotta G et al, Am J Hematol 2016;91(6):617-622
	ENEST1st Trial	*2-year follow-up*	Hochhaus A et al, Leukemia 2016;30;57-64

First line treatment of CML

Comparative trials - 2013 / 2018

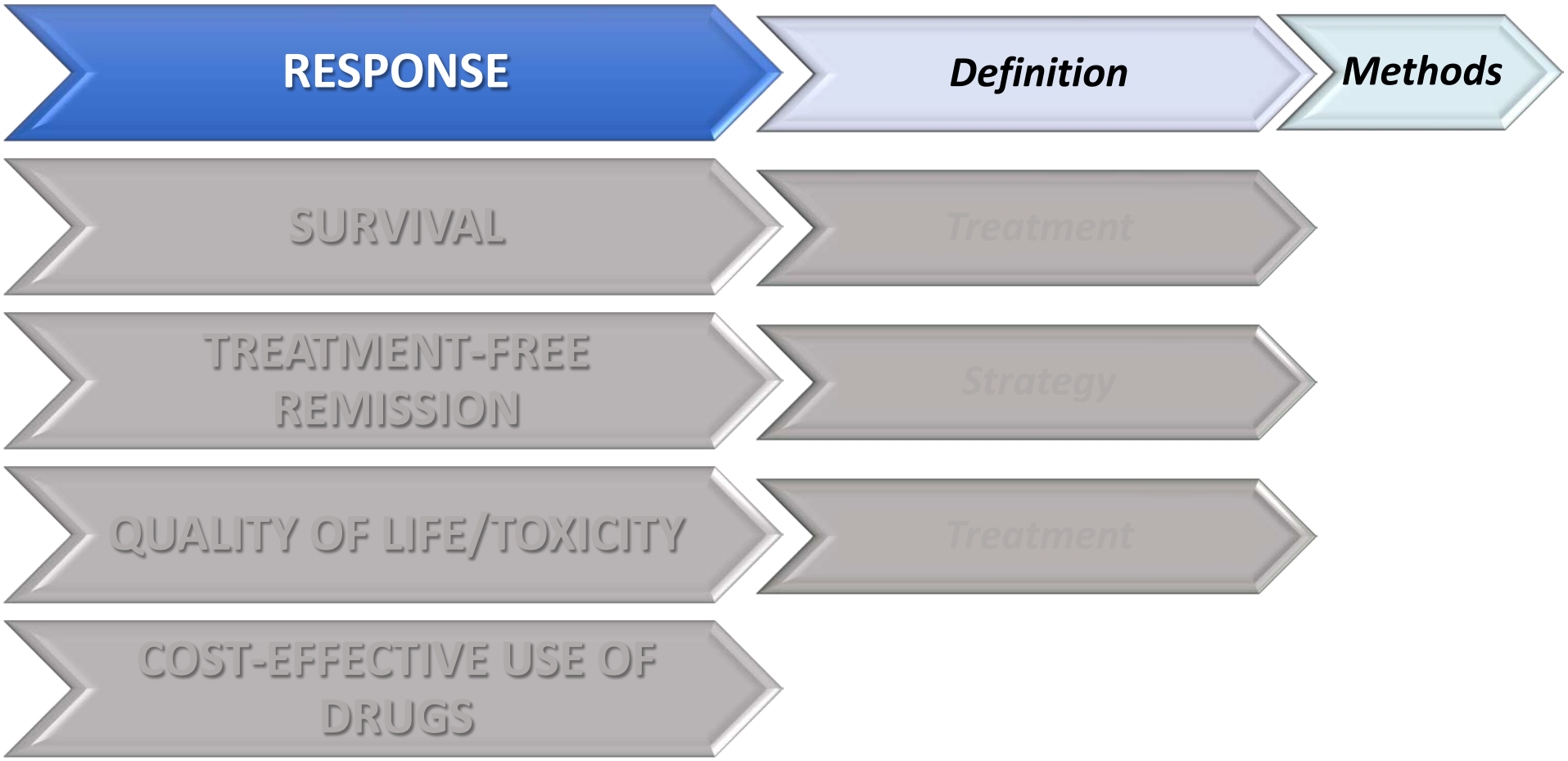
Imatinib 400 vs Imatinib 400 + IFN vs Imatinib 800	*5 - 10-year Update*	Hehlmann R et al, JCO 2014;32(5):415-423 Kalmanti L. et al, Leukemia 2015;29:1123 32 Hehlmann R. et al, Leukemia 2017;31:2398:2406
ENESTnd - Imatinib vs Nilotinib	*5-year Update*	Hochhaus A. et al, Leukemia 2016;30:1044-54
DASISION - Imatinib vs Dasatinib	*5-year Update*	Cortes J et al, JCO 2016;34:2333-2340
BFORE study - Imatinib vs Bosutinib	*1-year Update*	Cortes J et al, JCO 2018;36(3):231-7

Randomized comparative prospective studies in CML

Treatment	Study	Response	Survival	TFR
IMA 800 vs IMA 400	GERMANY CML IV	+	=	NA
IMA 800 vs IMA 400	GIMEMA	=	=	NA
IMA 800 vs IMA 400	TOPS	=	=	NA
NIL vs IMA 400	ENESTnd	+	=	NA
DAS vs IMA 400	DASISION	+	=	NA
BOS vs IMA 400	BFORE	+	NY	NA
NIL vs IMA→NIL	*SUSTRENIM (GIMEMA / HOVON)*	*NY*	*NY*	***NY***
IFN+IMA vs IMA 400	GERMANY CML IV	=	=	NA
IFN+IMA vs IMA 400	FRENCH SPIRIT	+	=	NA
IFN+IMA vs IMA 400	NORDIC	+	NA	NA
NILO+IFN vs NILO	TIGER	NY	NY	**NY**
DAS+IFN vs DAS	NORDIC/FRANCE	+	NA	NA
BOS+IFN vs BOS	NORDIC/FRANCE	NY	NY	**NY**

Perspectives for the 2019 and beyond

THE OBJECTIVES OF TREATMENT OPTIMIZATION



EUROPEAN LEUKEMIANET 2013

Response to treatment firstline (Imatinib, Nilotinib, and Dasatinib)

	Optimal Response	Warnings	Failure
Diagnosis	NA	-HIGH RISK, -ACA/Ph+ (Major route)	NA
3 mos	Ph+ ≤ 35% and/or BCR-ABL ≤ 10%	Ph + 36-95% and/or BCR-ABL ≥ 10%	No CHR and/or Ph + > 95%
6 mos	Ph+ 0 and/or BCR-ABL < 1%	Ph + 1-35% and/or BCR-ABL 1-10%	Ph + > 35% and/or BCR-ABL > 10%
12 mos	BCR-ABL≤ 0.1%	BCR-ABL 0.1-1 %	Ph + ≥ 1%, and/or BCR-ABL > 1%
24 mos	BCR-ABL ≤ 0.1%	BCR-ABL 0.1-1%	BCR-ABL > 1%

EUROPEAN LEUKEMIANET 2013

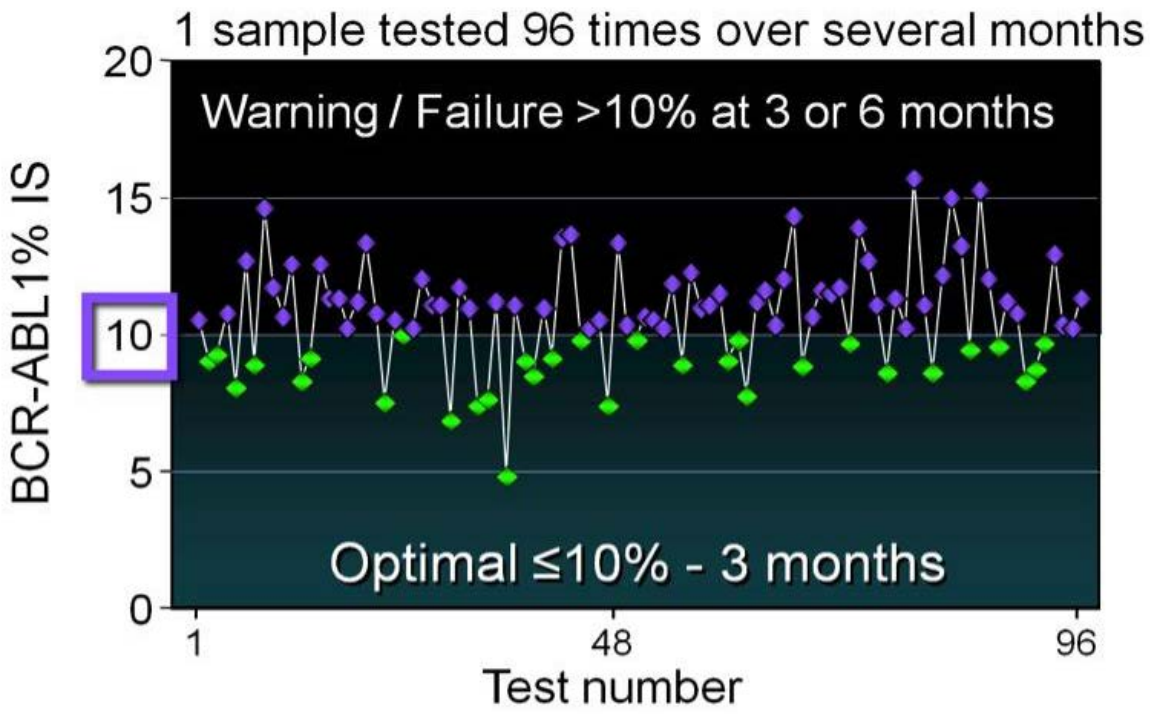
Response to treatment firstline (Imatinib, Nilotinib, and Dasatinib)

	Optimal Response	Warnings	Failure
Diagnosis	NA	-HIGH RISK, -ACA/Ph+ (Major route)	NA
3 mos	Ph+ ≤ 35% and/or BCR-ABL ≤ 10%	BCR-ABL ≥ 10%	No CHR and/or BCR-ABL > 95%
6 mos	Ph+ 0 and/or BCR-ABL < 1%	BCR-ABL 1-10%	Ph + > 35% and/or BCR-ABL > 10%
12 mos	BCR-ABL≤ 0.1%	BCR-ABL 0.1-1 %	Ph + ≥ 1%, and/or BCR-ABL > 1%
24 mos	BCR-ABL ≤ 0.1%	BCR-ABL 0.1-1%	BCR-ABL > 1%

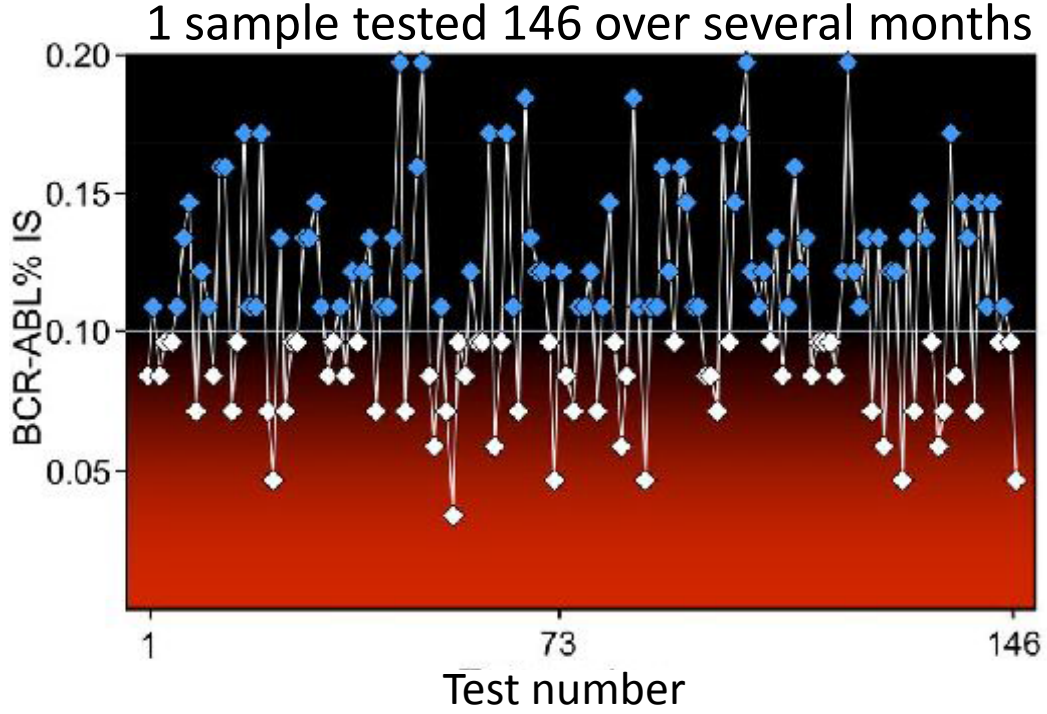
Today response definitions are based on QPCR

Should 2013 definitions be modified?

Imprecision of QPCR assays of CML MRD



BCR-ABL IS = 11% - CV 18%



BCR-ABL IS = 0,11% - CV 32%

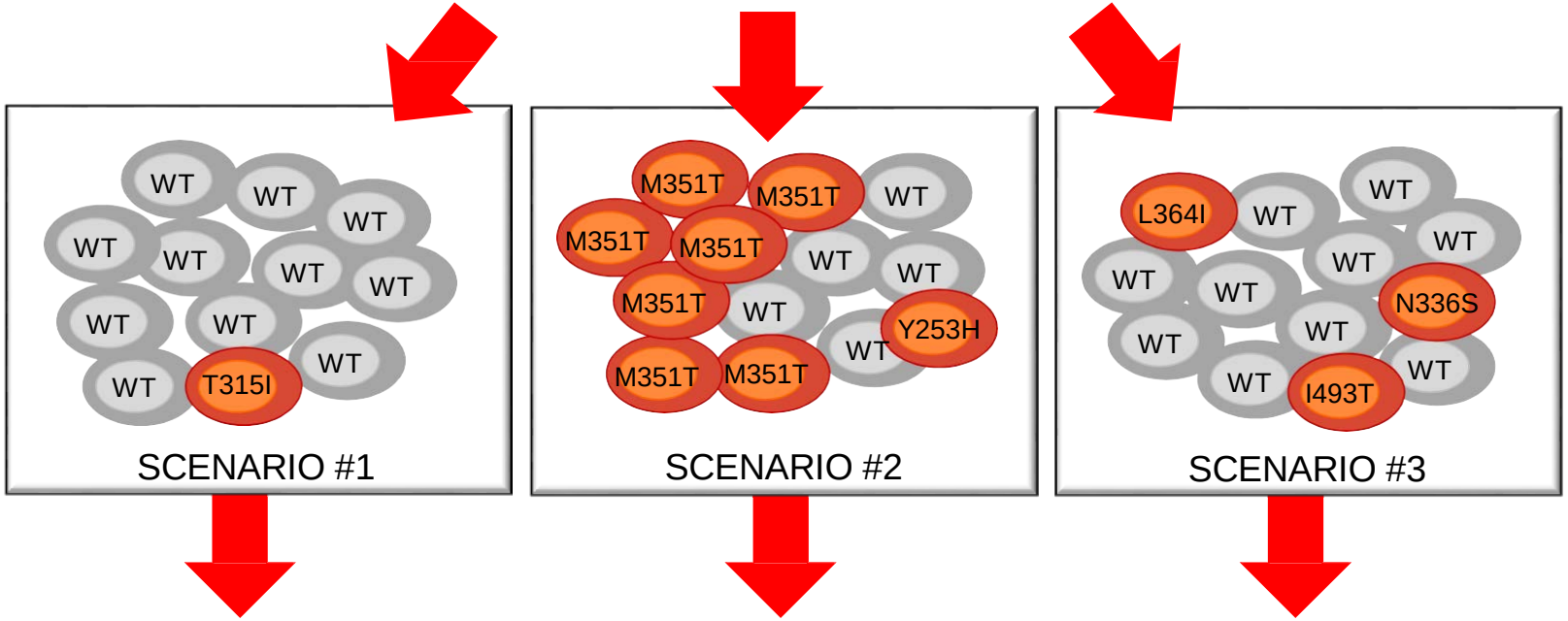
Do we need a range at any given milestone or prompt repetitions for borderline values?

Courtesy from S Branford

The value of low titer ABL-KD mutations

From Sanger to NGS

NGS at the time of FAILURE or WARNING

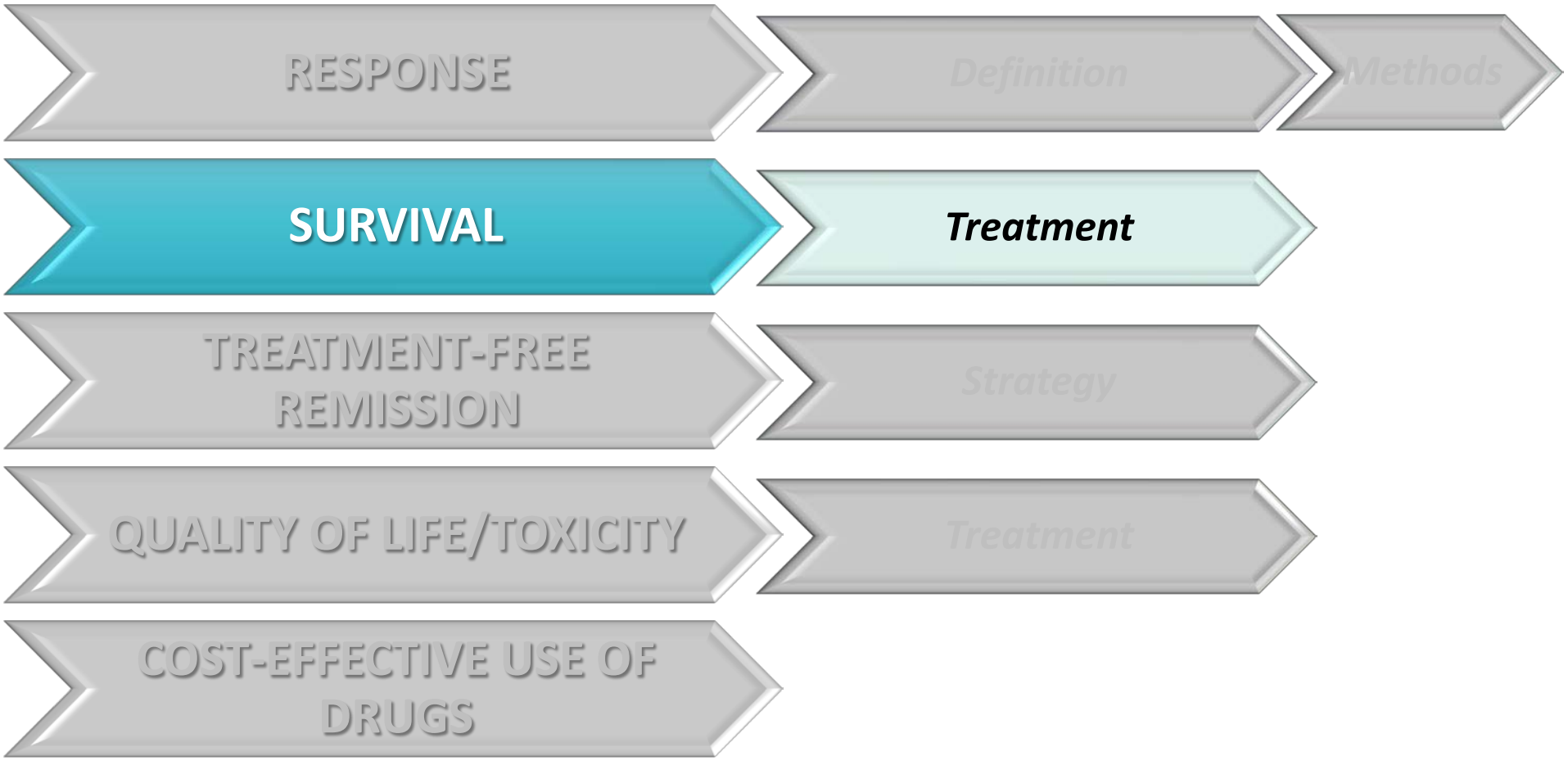


LOW BURDEN CLINICALLY ACTIONABLE MUTATIONS
should be included in therapeutic decision algorithms

LOW BURDEN MUTATIONS OF UNKNOWN SIGNIFICANCE
Should not trigger a therapeutic change (unless failure is observed)

Perspectives for the 2019 and beyond

THE OBJECTIVES OF TREATMENT OPTIMIZATION



ELN 2013
Recommendations for first line treatment

Imatinib	*Dasatinib, Nilotinib*
• More patients/data • Longer observation • Less complications • CHEAPER (generics!)	• Less patients/data • Shorter observation • More complications
• Slower response • Less frequent deep responses • Lower probability of TFR (?)	• Faster response • More frequent deep responses • Higher probability of TFR (?)
• *Survival 80-90%*	• *Survival 80-90%*

***data and follow-up for Bosutinib and Radotinib are not yet sufficient**

Possible choices for CML first-line therapy

- Priority for toxicity and costs
  (e.g. elderly patients) — ***Imatinib***
- Priority for response
  (e.g. high risk and/or young patients) — ***2°G-TKI***
- Priority for TFR achievement — ***????***

Perspectives for the 2019 and beyond

THE OBJECTIVES OF TREATMENT OPTIMIZATION

FIRST-LINE TREATMENT FOR TFR

	ENESTnd Nilotinib (%)	ENESTnd Imatinib (%)	DASISION Dasatinib (%)	DASISION Imatinib (%)
No. Pts in MR4.5 or better by 5 y	54	31	42	33
No. Pts expected in stable MR 4.5@5Y*	40	23	31	25
No. Pts expected in TFR (60% of eligible)	*24*	*14*	*19*	*15*
CVAEs, all grades	7	2	5	2
Pleural effusion, grade ≥ 3	1	0	3	0
Total with AEs	*8*	*2*	*8*	*2*
Net Benefit (TFR - AEs)	16	12	11	13
Difference	+4		-2	

***Estimated as 75% of patients who had achieved MR 4.5 by 5 years**

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

Imatinib discontinuation studies

Study	N	Treatment before discontinuation	Response Required to Stop Therapy	Definition of relapse	TFR (different FU)
STIM 1	100	IFN then Imatinib for 3 years	CMR	Loss of MMR or ≥1-log increase in BCR-ABL	39 %
STIM 2	200	Imatinib for ≥3 years	As for STIM	As for STIM	46 %
ALLG CML8	40	Imatinib for ≥3 years	UMRD 2 years	Loss of MMR or confirmed loss of $MR^{4.5}$	45 %
According to STIM	80	Imatinib for ≥3 years	As for STIM; occasional positive samples eligible	Loss of MMR	64 %
EUROSKI	868	Imatinib, Dasatinib, Nilotinib	MR^4 for ≥1year; TKI for ≥3 years	Loss of MMR	54 %
ISTAV	112	Imatinib	Undetectable PCR (3 PCRs)	Loss of MMR	52%
DESTINY	168	Imatinib, Dasatinib, Nilotinib	MR^4 and stable response under half standard dose for 12 months	Loss of MMR	In progress

2°-G TKI discontinuation studies

Study	N	Treatment before discontinuation	Response Required to Stop Therapy	Definition of relapse	TFR (different FU)
STOP 2G-TKI pilot	50	Nilotinib or Dasatinib	CMR for median 29 mo.	Loss of MMR	61%
ENEST freedom	175	Nilotinib	$MR^{4.5}$ for ≥1year	Loss of MMR	51.6%
ENESTop	117	Nilotinib	$MR^{4.5}$ for ≥1year	Confirmed loos of $MR^{4.0}$ or any loss of MMR	58.7%
ENESTpath	650	Nilotinib	Randomized $MR^{4.5}$ for ≥1year vs ≥2year	Confirmed loos of $MR^{4.0}$ or any loss of MMR	In progress
ENESTGoal	300	Nilotinib	$MR^{4.5}$ for ≥1year	Confirmed loos of $MR^{4.0}$ or any loss of MMR	In progress
DASFREE	75	Dasatinib	$MR^{4.5}$ for ≥1year	Loss of MMR	In progress
DADI	63	Dasatinib	DMR for ≥1year	Loss of MMR	48%

Prognostic factors of TFR in TKI discontinuation studies

Factor category	Factors	Prognostic value
Patient	Age, Sex	No
Disease	Prognostic score at diagnosis	Non high risk sokal best (Imatinib)
Treatment history and response to therapy	History of suboptimal response or resistance	Decreased TFR probability
	TKI treatment duration (total)	Imatinib: yes Dasatinib or Nilotinib: not studied yet
	Deep molecular response duration	Imatinib: yes Dasatinib or Nilotinib: not studied yet
	Depth of deep molecular response (MR4.0, MR4.5 or even deeper)	Difficult to assess with current RT-QPCR techniques
	Type of TKI	**No comparative studies**

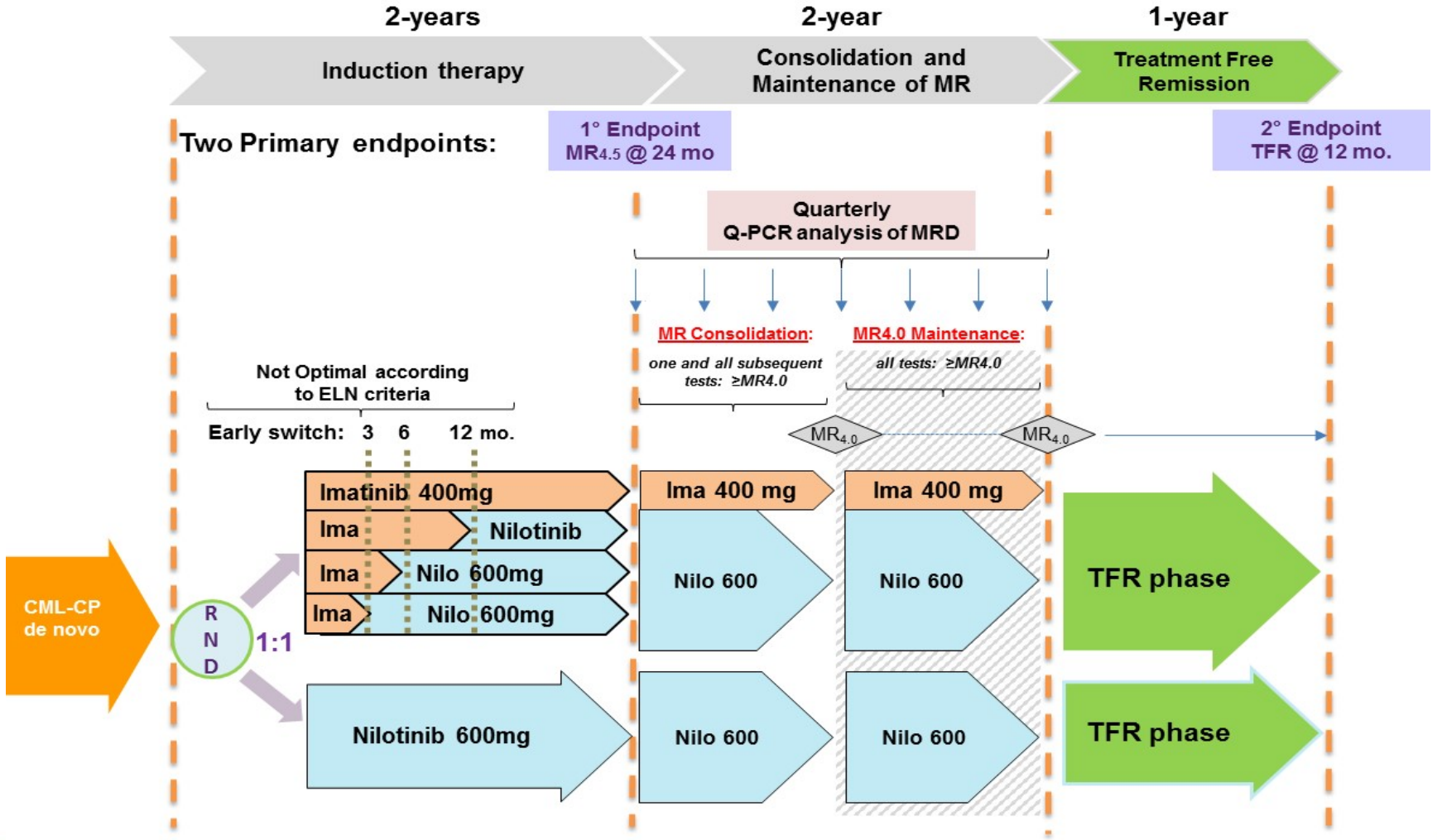
TREATMENT-FREE REMISSION

Which Studies, Which Data 2013-2018

- Many retrospective reports
- Some reports of prospective studies, (mainly the ENEST trials), none in first line
- All reporting the rate of TFR in patients who had achieved a deep molecular response
- None reporting the rate of TFR in newly diagnosed patients
- None comparing the relationship between first-line treatment and the rate of TFR

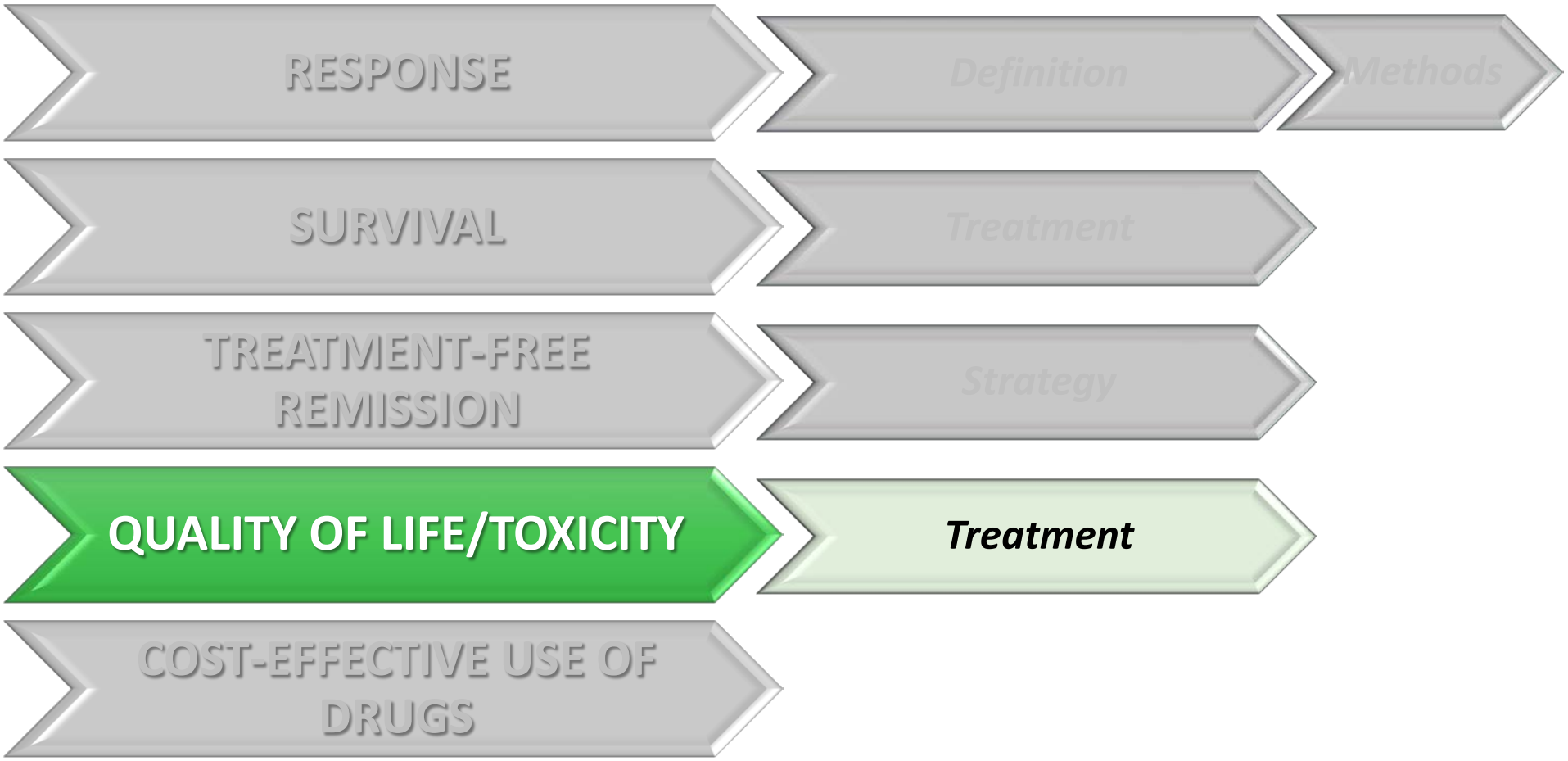
Serching the best cost-effective TFR strategy

GIMEMA SUSTRENIM Study



Perspectives for the 2019 and beyond

THE OBJECTIVES OF TREATMENT OPTIMIZATION



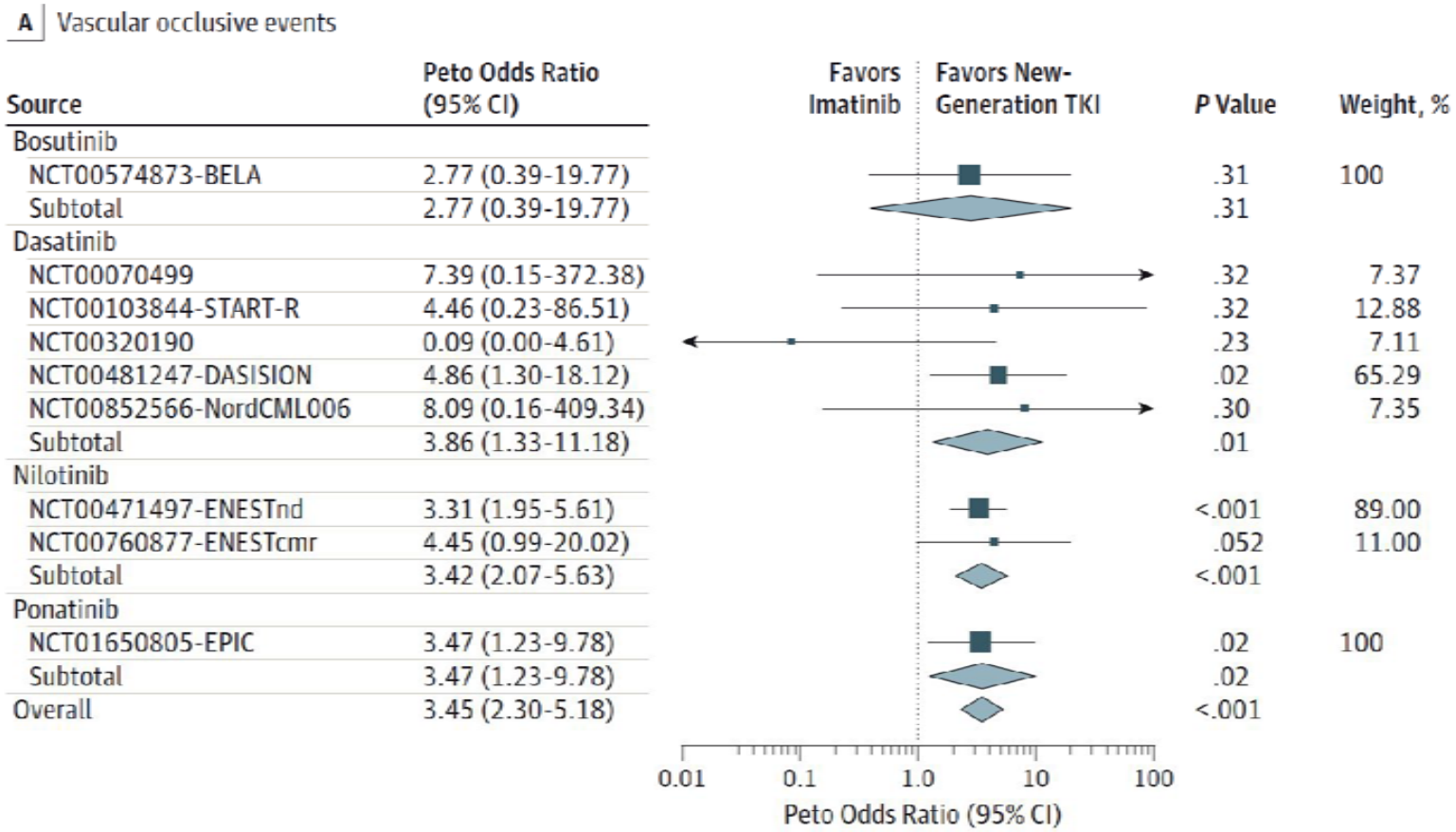
TKI Side effects

- The TKIs have different patterns of side-effects, and this should be considered when choosing amongst these drugs
- Three general categories od side effects
  - Early onset, serious (grade 3/4) side effects
    - **10%** of patients
    - Cause of early discontinuations
  - Minor (grade 1/2), mid / long term side effects
    - **50%** of patients
    - Manageable but affect quality of life also leading to poor adherence
  - Off-target complications
    - Cardiovascular system, vessels, liver, pancreas, metabolism etc.
    - Incidence and seriousness not fully understood

Patient – adapted strategy for TKI treatment optmization

- Age, and type, number and grade of comorbidities influence the choice of the TKI.
- Several “comorbidities” may be even more important than chronic myeloid leukemia itself, both for survival and for quality of life
  - Atherosclerosis, Arterial thrombotic disease, Cerebrovascular disease hypertension, Heart failure, Ischemic heart disease, Thrombophilic state, Diabetes mellitus dyslipidemia, Chronic pulmonary disease (obstructive, enfisema, fibrosis, etc), Autoimmune disease, Other tumors, Psychiatric disorder, Alzheimer, Parkinson

Association Between BCR-ABL Tyrosine Kinase Inhibitors for CML and Cardiovascular Events



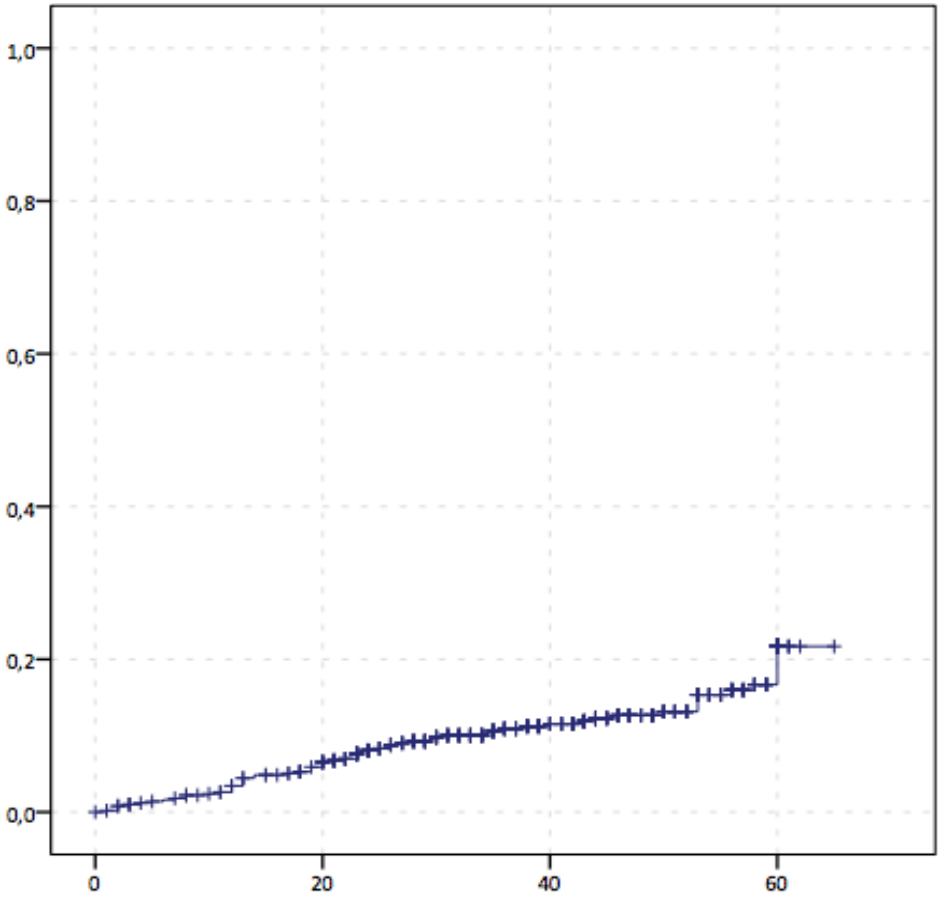
CV events associated with TKI in 896 CML patients and 4438 controls

Table 2. Relative Risks for Arterial and Venous Thromboembolic Events in Patients With CML Compared With the General Population*

Variable	Control Participants (n = 4438)			CML Population (n = 896)			Incidence Rate Ratio Comparing Patients With CML With Control Participants (95% CI)
	Events, *n*	Total Follow-up, *y*	Incidence Rate per 1000 Person-Years	Events, *n*	Total Follow-up, *y*	Incidence Rate per 1000 Person-Years	
All arterial thromboembolic events	185	20 275	9.1	54	4064	13	1.5 (1.1–2.1)
Myocardial infarction	114	20 864	5.5	40	4188	10	1.9 (1.3–2.7)
Cerebrovascular ischemia	89	20 960	4.2	15	4241	4	0.9 (0.5–1.5)
Other arterial thrombosis	10	21 537	0.5	6	4306	1	3.2 (1.2–8.7)
All venous thromboembolic events	54	21 183	2.5	20	4230	5	2.0 (1.2–3.3)
Pulmonary embolism	30	21 421	1.4	10	4317	2	1.8 (0.9–3.6)
Deep venous thrombosis	27	21 330	1.3	11	4261	3	2.2 (1.1–4.4)
All arterial and venous events	250	21 917	11.4	78	3969	20	1.7 (1.3–2.2)

CML = chronic myelogenous leukemia.
* Includes all arterial and venous events; patients with events before diagnosis were censored.

Cardiovascular toxicity in patients with CML treated with “°G-TKI in the real-life practice



The 60-month CV AE cumulative incidence registered in the total cohort of patients was 21.7±2.8%.

Second line treatment

2°G-TKI in CML post-Imatinib Resistance (late switch)

	Percentage		
	Nilotinib	Dasatinib	Bosutinib
F-U (mo)	>24	>24	24*
CHR	77	89	86
MCyR	59	62	54
CCyR	44	50	41
24 mo PFS**	64%	80%	79%
24 mo OS**	87%	91%	92%

*Median; **All patients

Shah NP et al., Haematologica 2010;95:232
Kantarijan HM et al., Blood 2011;117:1141
Cortes J et al., Blood; 2012,118:4567

The second line therapy

- Type of failure
  - From non optimal response (ELN criteria) to blast phase progression
- Paucity of data – mainly registration studies – and limited follow-up
- Previous treatment
  - TKI naive vs TKI treated patients
  - Type of TKI in first line

Conclusions

Excellent prognosis but still possible progressions to advances phases

Long term quality of life and toxicity of patient under TKI therapy

Is it possible to cure CML patients without Allo-SCT?

Yes, but….

- How many patients?
- Which treatment?
- QoL improvement?

- Need of treatment optimization
- Difficult treatment rescue in patients resistant to first line therapy (particularly Nilo and Dasa)