2017

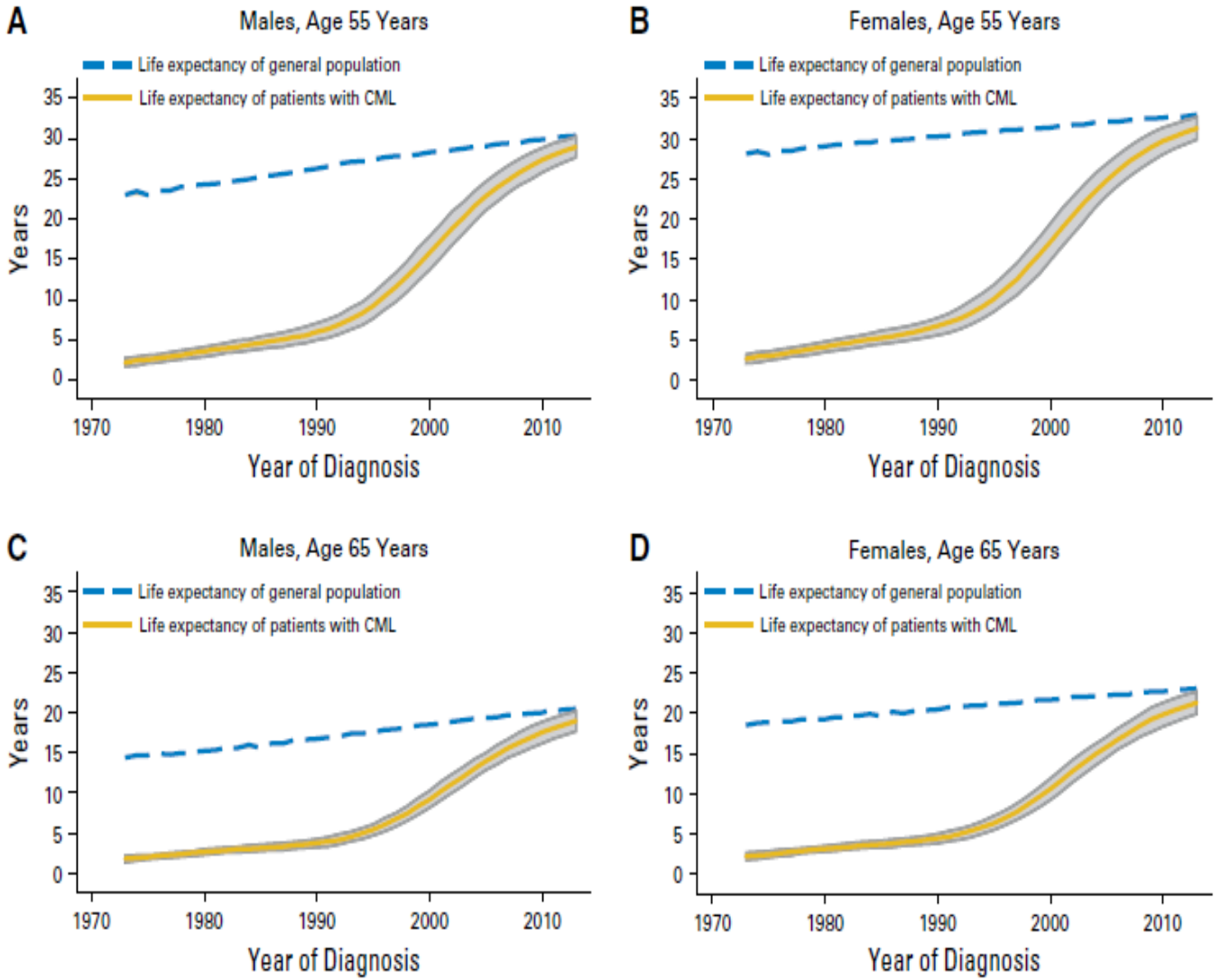
Cesena, 16 Settembre

Progetto Ematologia Romagna

LMC, la malattia resistente
Inquadramento dell'argomento

Fausto Castagnetti

Life expectancy of CML patients and general population



Bower H et al, J Clin Oncol 2016;34:2851-7.

Evolution of CML treatment

	2006[1]	2009[2]	**2013[3]**
1st LINE	Imatinib 400	Imatinib 400	**Imatinib 400-600-800** **Dasatinib** **Nilotinib**
2nd LINE	Imatinib 600-800 Allo-SCT	Nilotinib Dasatinib Allo-SCT	**Dasatinib** **Nilotinib** **Bosutinib** **Ponatinib** **(Allo-SCT)**
3rd LINE	Palliation	Palliation	**Anyone of remaining TKIs** **Allo-SCT**

1) Baccarani M et al, Blood, 2006
2) Baccarani M et al, J Clin Oncol, 2009
3) Baccarani M et al, Blood, 2013

Imatinib – Nilotinib - Dasatinib

Why you may need a 2nd line TKI?

Unsatisfactory therapeutic effect (15-20%)

Intolerance (15-20%)

ELN 2013 Recommendations

Response to first-line treatment

	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.

ELN 2013 Recommendations

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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.

How to predict the response to 1° line therapy

EUTOS long-term survival score

Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia patients

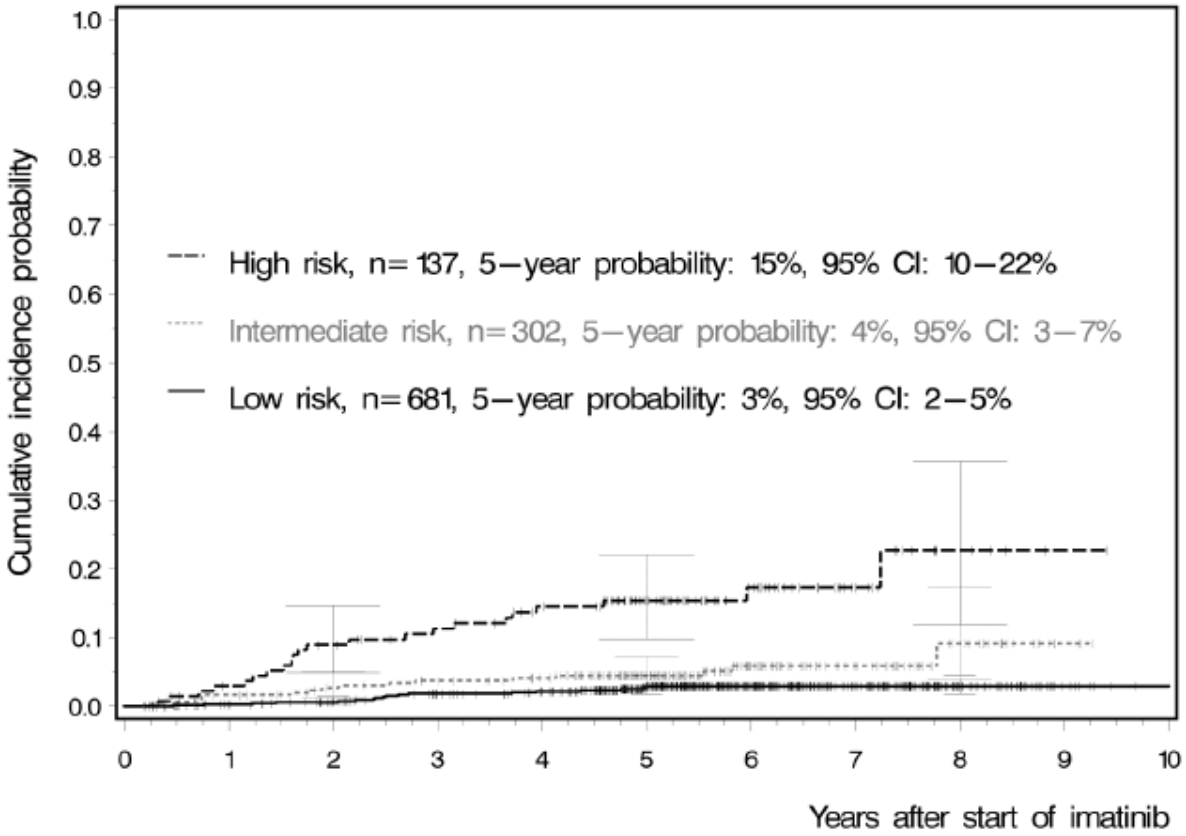
M Pfirrmann, M Baccarani, S Saussele, J Guilhot, F Cervantes, G Ossenkoppele, V S Hoffmann, F Castagnetti, J Hasford, R Hehlmann, B Simonsson

$$0.0025 \times (\textbf{age}/10)^3 + 0.0615 \times \textbf{spleen size} + 0.1052 \times \textbf{blasts in PB} + 0.4104 \times (\textbf{PLT count}/1000)^{-0.5}$$

LOW: < 1.5680

INTERMEDIATE: 1.568 - 2.2185

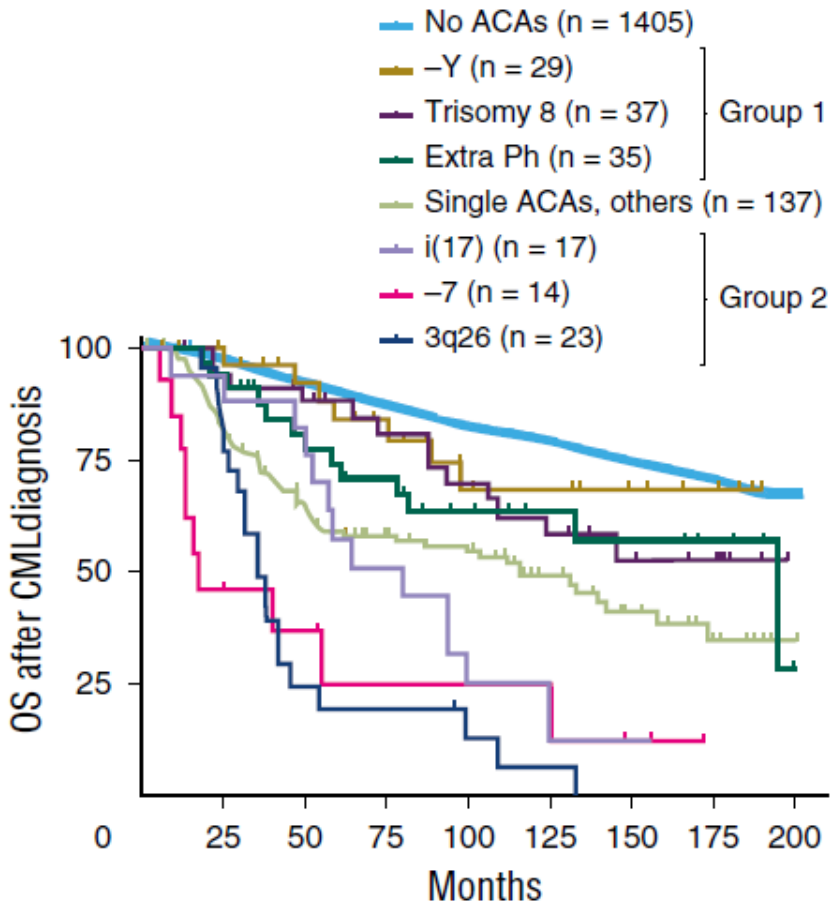
HIGH: > 2.2185

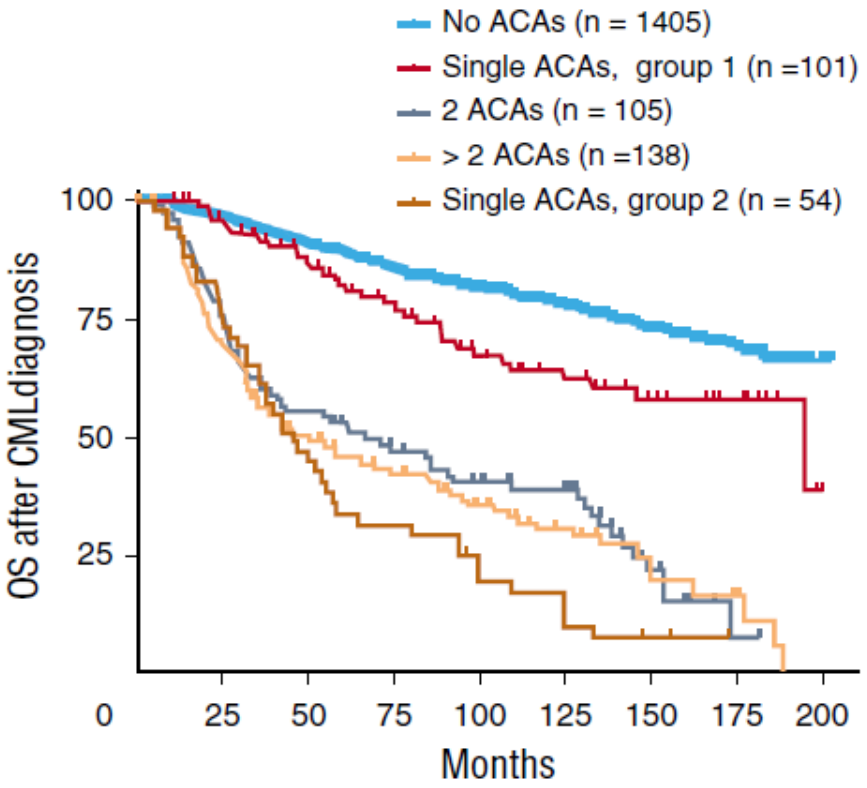


Leukemia. 2016; 30(1):48-56.

How to predict the response to 1° line therapy

CCA IN PH+ CELLS - MDACC Experience





Wang W et al. Blood. 2016; 127:1823-31

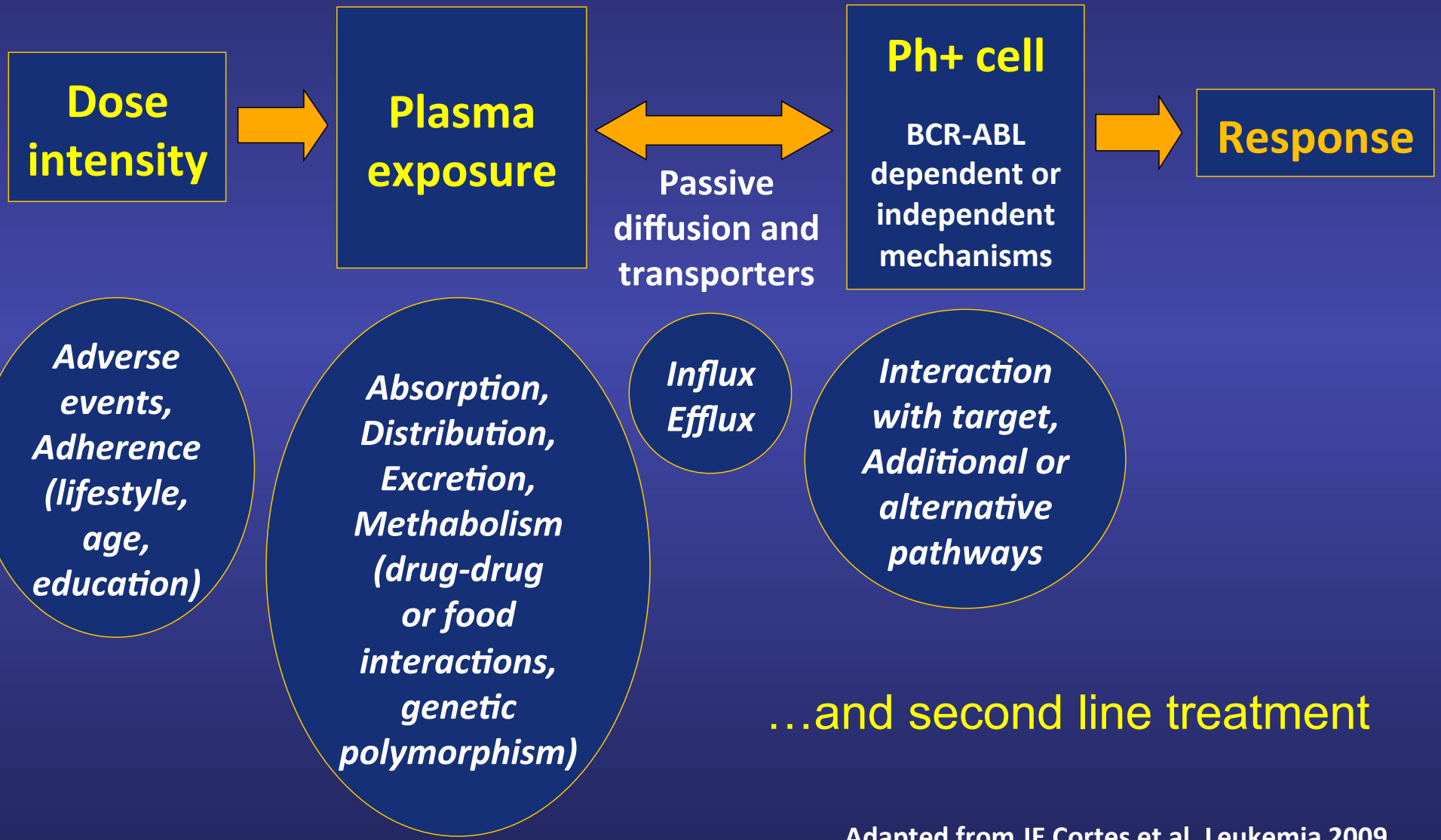
How to predict the response to 2° line therapy

The Hammersmith scoring system - CCyR to 2ndG-TKI

		RR		*Score*
Low Sokal score		1.6	p=0.01	*0 – 0.5*
Best CCyR on IM (% Ph+)	0%	1		*0*
	1-94%	0.3	p<0.0001	*1*
	≥95%	0.006		*3*
Neutropenia G3-G4		0.16	p<0.0001	*0 - 1*

Milojkovic et al. Hematologica 2010; 95 (2):224-31

Factors influencing clinical response



…and second line treatment

Adapted from JE Cortes et al. Leukemia 2009

BCR-ABL Inhibitor Activity Against BCR-ABL Single Mutants

BCR-ABL MUTANT	PONATINIB	IMATINIB	NILOTINIB	DASATINIB	BOSUTINIB
Native	3	201	15	2	71
M244V	3	287	12	2	147
L248R	8	10000	549	6	874
L248V	4	586	26	5	182
G250E	5	1087	41	4	85
Y253H	5	4908	179	3	40
E255K	6	2487	127	9	181
E255V	16	8322	784	11	214
V299L	4	295	24	16	1228
T315A	4	476	50	59	122
T315I	6	9773	8091	10000	4338
F317C	3	324	16	45	165
F317I	7	266	25	40	232
F317L	4	675	21	10	82
F317V	10	1023	26	104	1280
M351T	4	404	15	2	97
E355A	7	441	18	3	74
F359C	6	728	47	2	70
F359I	11	324	64	3	76
F359V	4	346	41	2	59
H396R	4	395	23	2	60
E459K	5	612	38	4	127

Criteria Used to Classify Drug Potency

Effective C_{ave} at rec. dose	28*	444	131	11	159
IC50 <75% of C_{ave}	<21	<333	<98	<8	<119
IC50 75-150% of C_{ave}	21-32	333-500	98-147	8-12	119-179
IC50 150-300% of C_{ave}	33-95	501-1499	148-442	13-37	180-537
IC50 >300% of C_{ave}	>95	>1499	>442	>37	>537

Gozgit, et al. *Blood.* 2013;122 (abstr 3992).

Intolerance to TKIs

	Main Adverse Events	Main Complications
Imatinib	Fatigue Myalgia Fluid retention	None
Dasatinib	Hematologic toxicity Pleural effusion	Pulmonary hypertension
Nilotinib	Skin rash Glucose and lipid metabolism Bilirubin and lipase elevation	Arterial thrombosis*
Bosutinib	Diarrhea Nausea Liver (AST/ALT)	None
Ponatinib	Hematologic toxicity Skin rash Arterial hypertension	Arterial and venous thrombosis* Pancreatitis

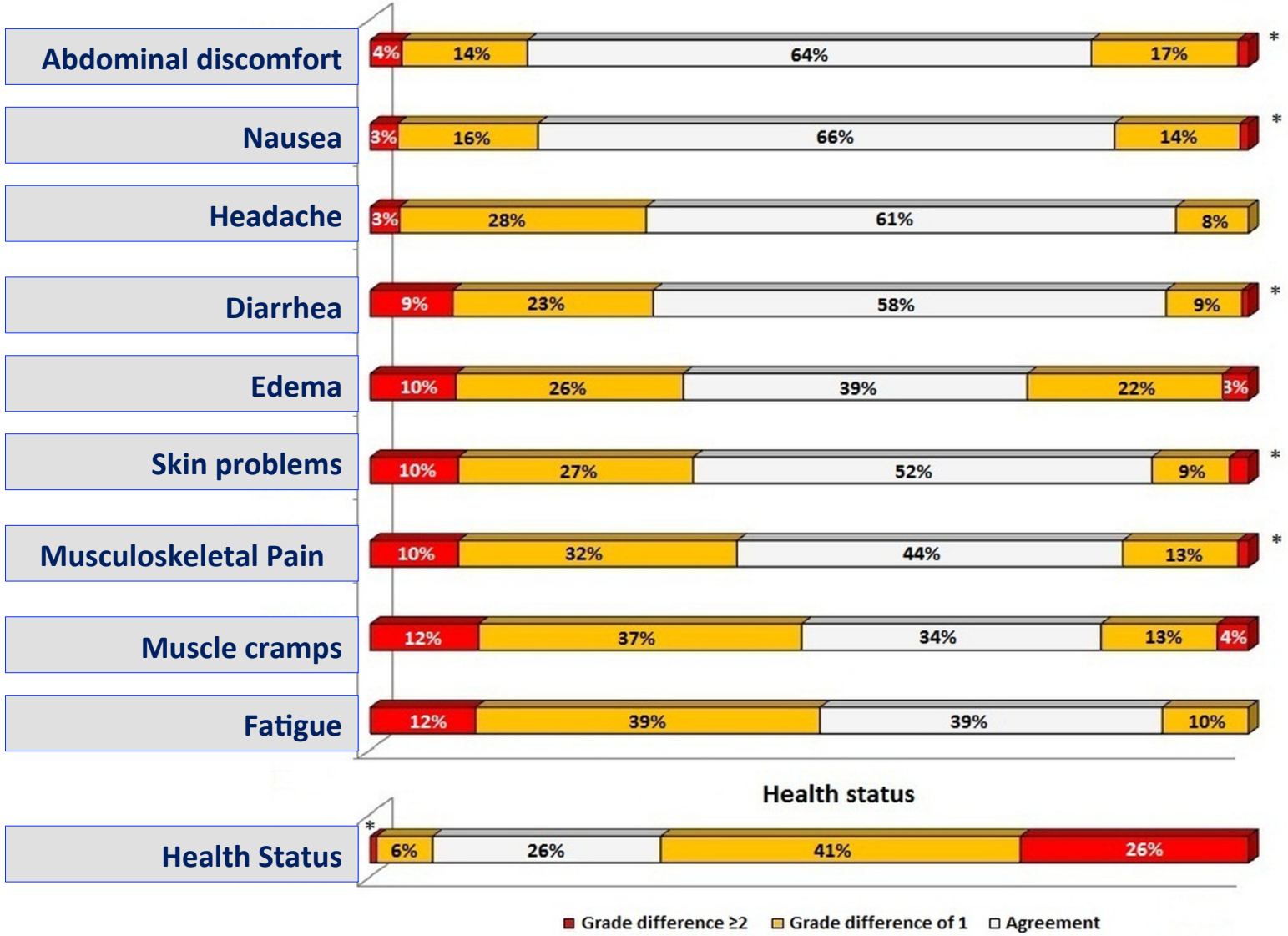
* Mostly in patients with pre-existing CV risk factors

Consider comorbidities, rather than cross-intolerance

N=422 comparison Patient-Physician

Patient graded higł

ʰhysician graded higher



Efficace F, Rosti G, Aaronson , et al, *Haematologica*, 2013

Leukemia (2016) 30, 1648–1671

www.nature.com/leu

OPEN

REVIEW

European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia

JL Steegmann[1], M Baccarani[2], M Breccia[3], LF Casado[4], V García-Gutiérrez[5], A Hochhaus[6], D-W Kim[7], TD Kim[8], HJ Khoury[9], P Le Coutre[8], J Mayer[10], D Milojkovic[11], K Porkka[12,13], D Rea[14], G Rosti[2], S Saussele[15], R Hehlmann[16] and RE Clark[17]

1. Suboptimal management of AEs **must not compromise the efficacy**
2. Most AEs **will resolve spontaneously** or are easily controlled
3. Reduction or interruption must **only** be done if optimal management cannot be accomplished in other ways
4. Attention must be given to **comorbidities** and drug interactions
5. Some **unexpected TKI-related AEs** have emerged

European LeukemiaNet 2013 Treatment Recommendations

First-line	Imatinib 400 x 1, nilotinib 300 x 2, or dasatinib 100 x 1
Second-line	
Intolerance	• **Anyone of the other TKIs approved for first-line, taking into account comorbidities and side effects**
Failure	• Switch from imatinib to another TKI, taking into account mutations, comorbidities, and side effects • Switch from nilotinib to dasatinib, bosutinib, or ponatinib • Switch from dasatinib to nilotinib, bosutinib, or ponatinib • Allogeneic stem cell transplant
Third-line	• Switch to another TKI (ponatinib) • Allogeneic stem cell transplant • Experimental treatment

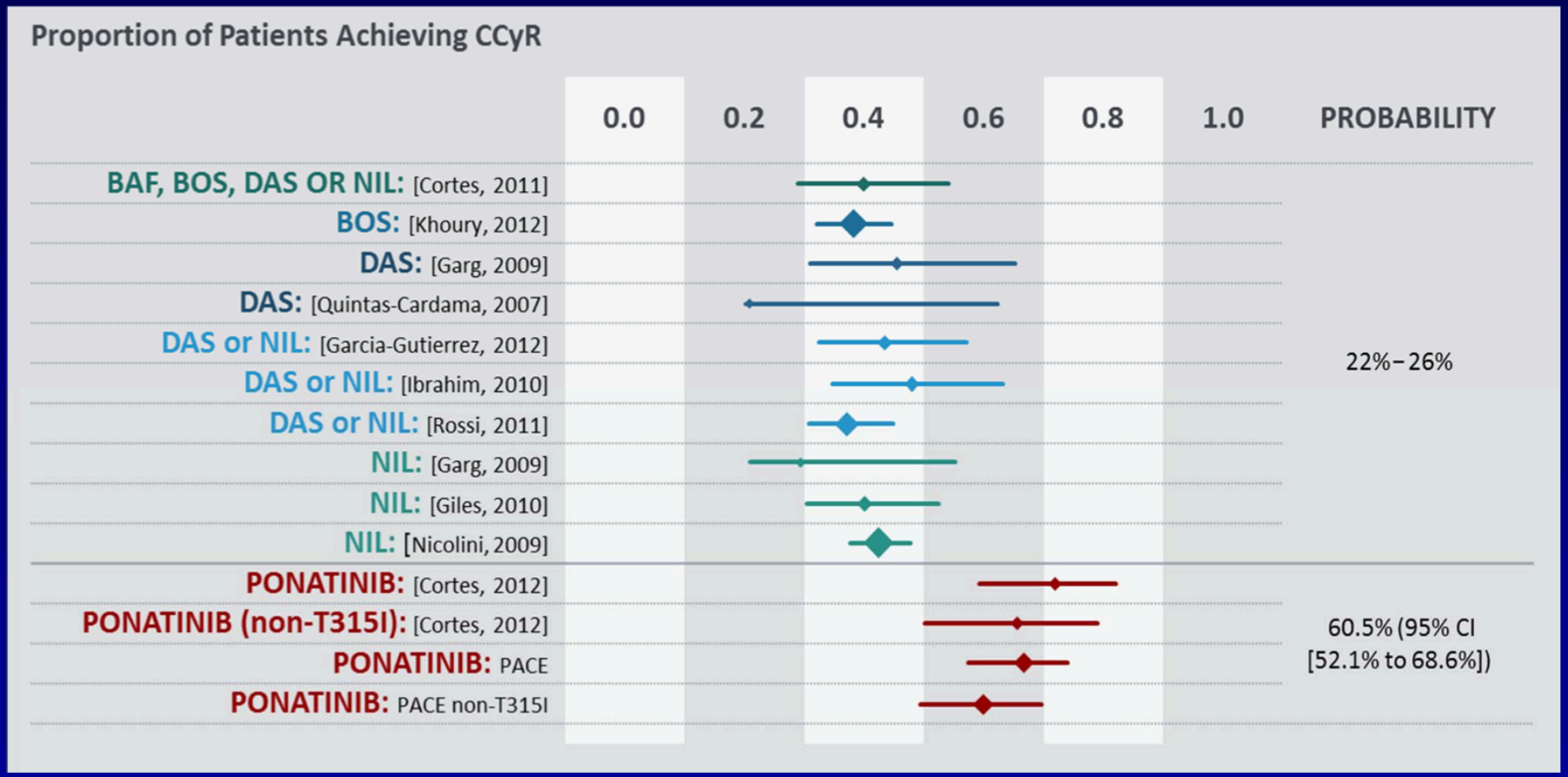
Baccarani et al, Blood. 2013 Aug 8;122(6):872-84.

European LeukemiaNet 2013 Treatment Recommendations

First-line	Imatinib 400 x 1, nilotinib 300 x 2, or dasatinib 100 x 1
Second-line	
Intolerance	• Switch to another TKI, taking into account comorbidities and side effects
Failure	• **Switch from imatinib to another TKI (nilotinib, dasatinib, bosutinib, ponatinib), taking into account mutations, comorbidities, and side effects** • Switch from nilotinib to dasatinib, bosutinib, or ponatinib • Switch from dasatinib to nilotinib, bosutinib, or ponatinib • Allogeneic stem cell transplant
Third-line	• Switch to another TKI (ponatinib) • Allogeneic stem cell transplant • Experimental treatment

Baccarani et al, Blood. 2013 Aug 8;122(6):872-84.

Systematic Review of CP-CML Patients in Third-line Setting: Response to Ponatinib Was Superior to Other TKIs



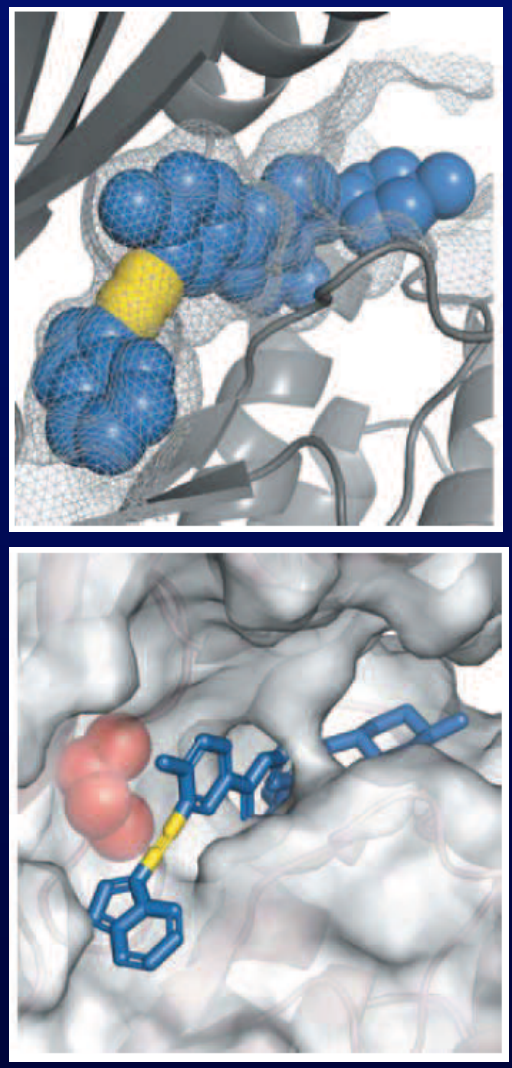
These data suggest sequencing of second-generation TKIs may be a suboptimal treatment approach

NOTE: Node size in graph represents patient numbers; line signifies derived 95% confidence interval.
AF=bafetinib; BOS=bosutinib; DAS=dasatinib; NIL=nilotinib.
Lipton et al, *Blood*. 2013;122(21) (abstr 4010).

Lipton et al. Leuk Res 39 (2015) 58–64

Ponatinib
A Pan-BCR-ABL Inhibitor

- Rationally designed inhibitor of BCR-ABL
- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
- Potent activity against an array of BCR-ABL variants
- Once-daily oral activity
- Half-life ≈ 22 hours
- Also targets other therapeutically relevant kinases:
  - Inhibits FLT3, FGFR, VEGFR and PDGFR, and c-KIT



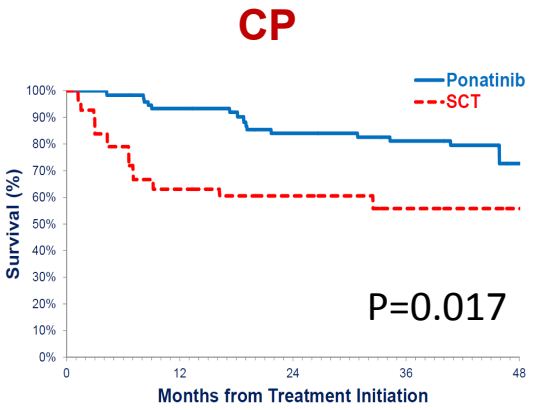
O'Hare T, et al. Cancer Cell. 2009;16:401-412

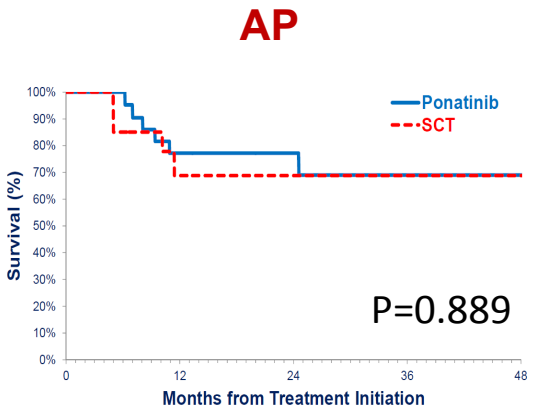
Where we are going

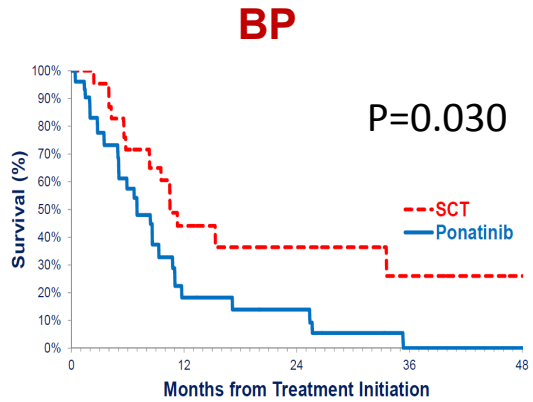
Ponatinib or SCT for T315I CML

- Pts ≥18 yrs with CML *T315I* in any stage enrolled in PACE (n=449) or EBMT (n=222)
- Median age (yr): CP 53 vs 48; AP 55 vs 46; BP 47 vs 44; Ph+ ALL 55 vs 36

Disease phase	Median survival (mo)	
	PACE	EBMT
CP	NR	103
AP	NR	56
BP	7	11
Ph+ ALL	7	32



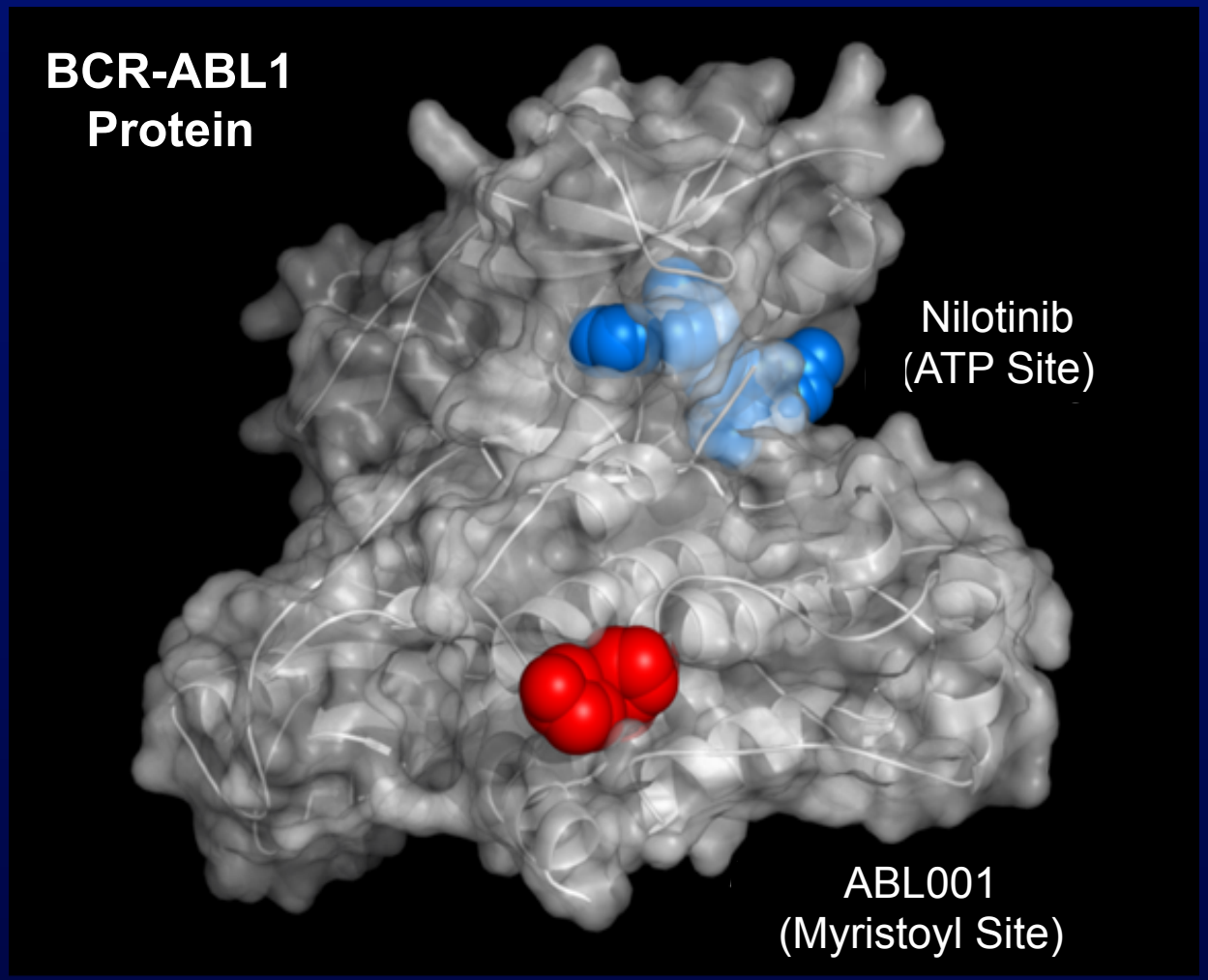




Nicolini FE, et al. Cancer 2017

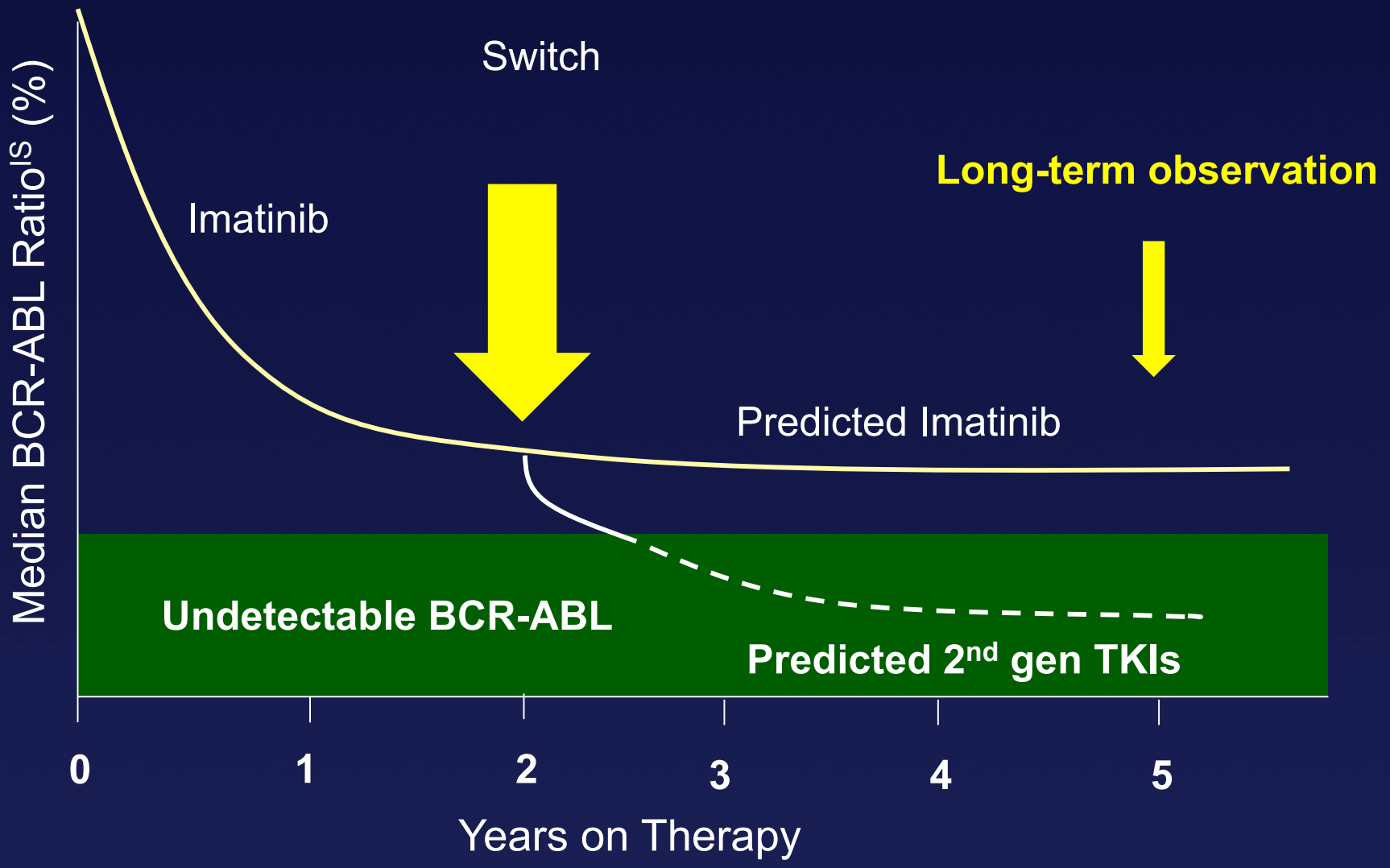
ABL001 Is a Potent, Specific Inhibitor of BCR-ABL1 With a Distinct Allosteric Mechanism of Action

- Developed to gain greater BCR-ABL1 inhibition, with activity against BCR-ABL1 mutations conferring resistance to TKIs
- Potential to combine with TKIs for greater pharmacological control of BCR-ABL1



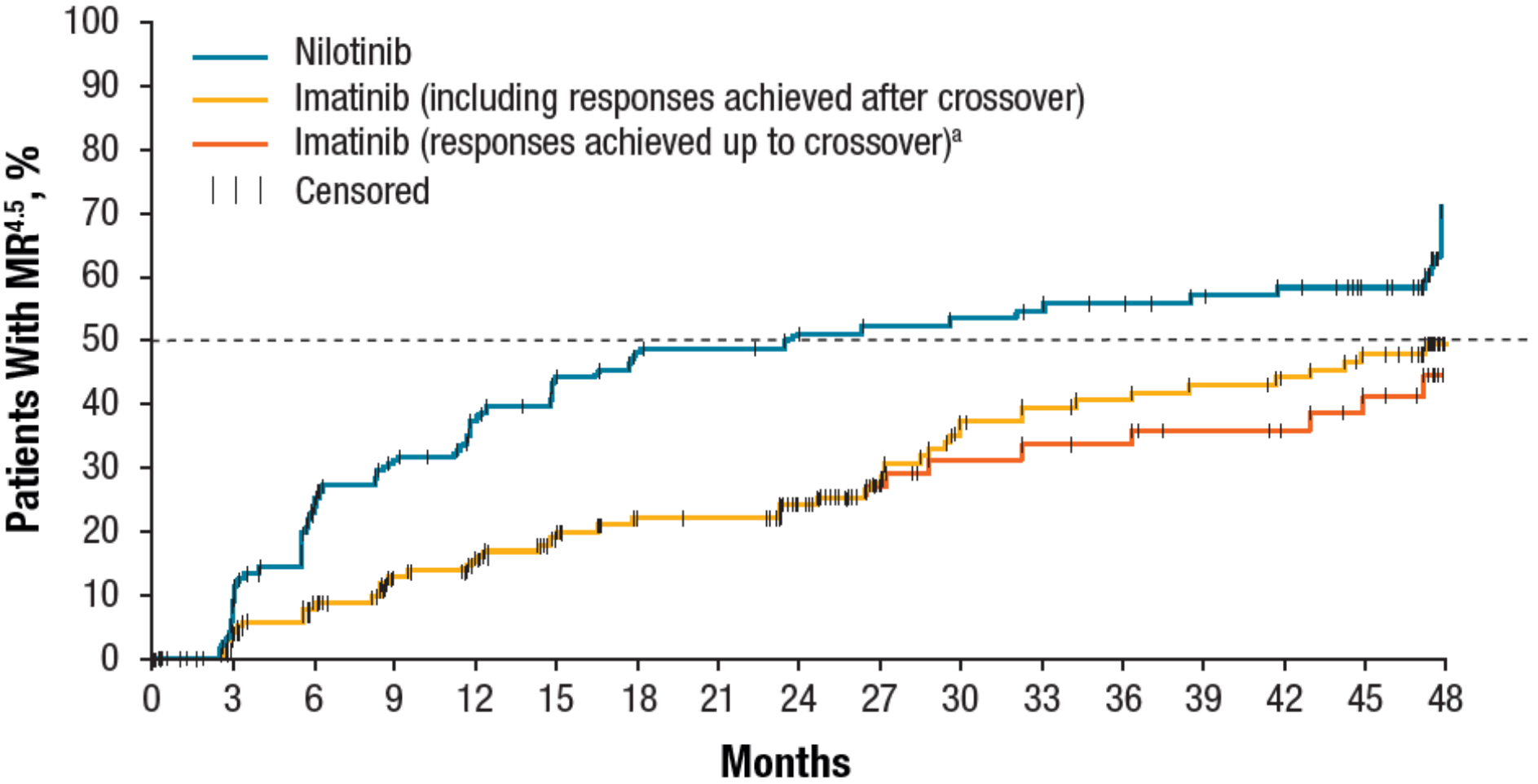
Ottmann O, et al. *Blood*. 2015:[abstract 138].

Achieving a deeper molecular response (TFR) Switch to 2nd gen TKIs



ENESTcmr study

Time to MR$^{4.5}$



48-month follow-up

Hughes et al. ASCO 2016. Abs. 4029

RESEARCH ARTICLE

AJH

A population-based study of chronic myeloid leukemia patients treated with imatinib in first line

First-line IM, with switch to 2nd generation TKIs

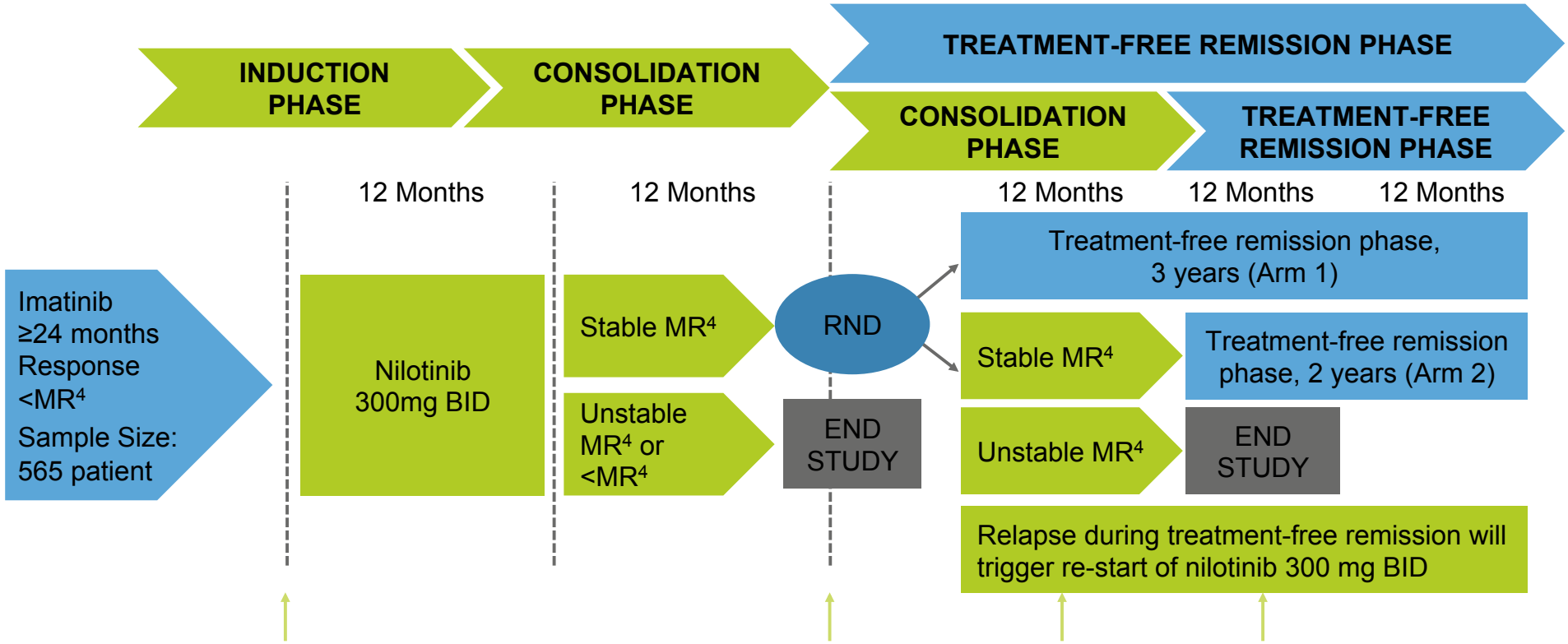
in case of unsatisfying response or intolerance (N=236)

(A) Patients switched from imatinib to second-generation TKIs for failure or suboptimal response	
N. total	63
N. evaluable for a change of molecular response	61
N. who improved by 1 log	14 (23%)
N. who improved by 2 log	11 (18%)
N. who improved by 3–4 log	10 (16%)
N. who improved, total	35 (57%)
(B) Number of patients who achieved a stable $MR^{4.0}$	
With imatinib first-line only, no switch	52/236 (22%)
With imatinib first-line, including switch	78/236 (33%)

Emilia-Romagna and Sicily

Castagnetti et al. Am J Hematol. 92:82-87,2017

ENESTpath study design



BID, twice daily; MR, molecular response; RND, randomization.

CML in 2017: news and changes

GOALS: from survival to cure (treatment-free remission)

HIGH RISK and CCA/Ph+: from “warning” to risk-adapted treatment

MONITORING: from cytogenetics to standardized qPCR

MOLECULAR RESPONSE: from late to early, from MMR to MR 4.0 or better

MUTATIONS: from Sanger Sequencing to Ultra Deep or NGS

T315I: from stem cell transplantation to ponatinib

QUALITY OF LIFE: from one drug to many

COSTS: from GLIVEC to GENERICS

DR

Thank you for attention!