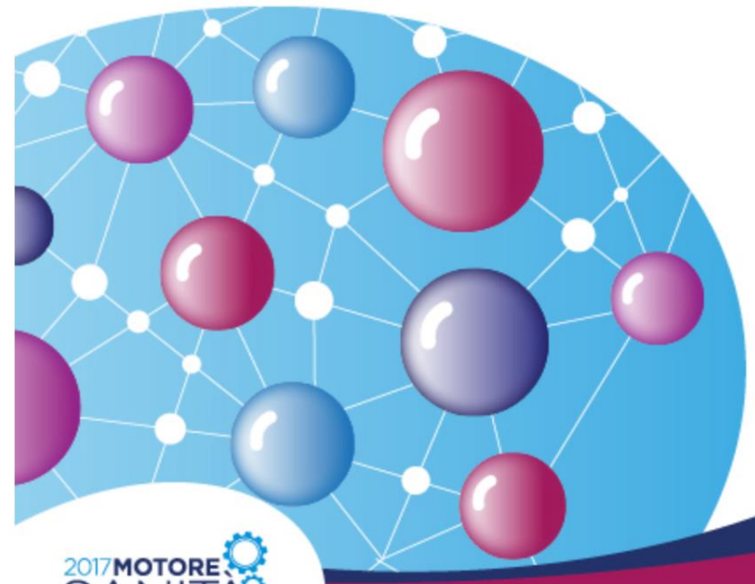


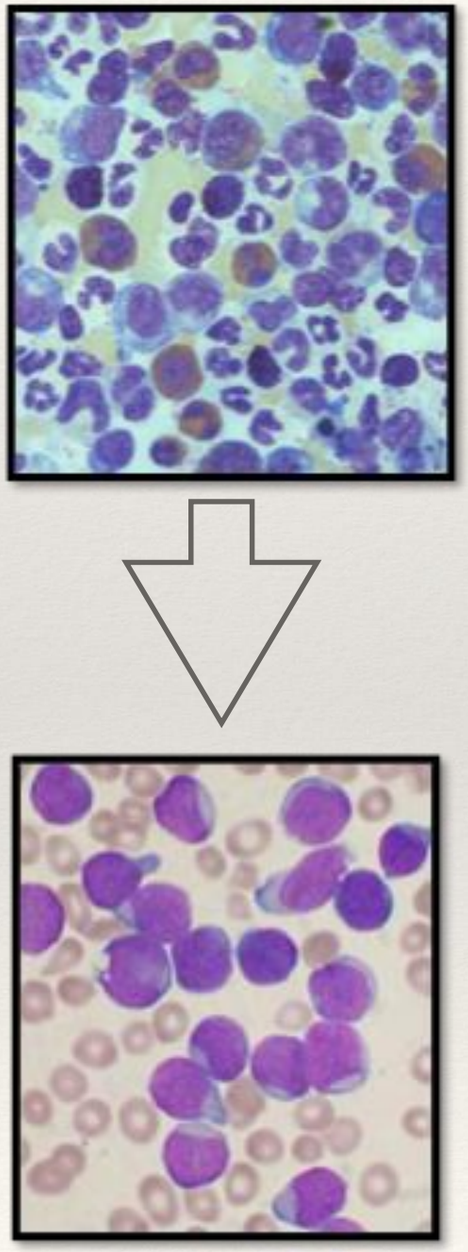
IL FUTURO DELLA RETE EMATOLOGICA NELLA REGIONE DEL VENETO

PADOVA 6 GIUGNO 2017
AZIENDA OSPEDALIERA
AULA MAGNA PALAZZINA DEI SERVIZI - VIA GIUSTINIANI 2

L'EVOLUZIONE DIAGNOSTICO-TERAPEUTICA DELLA LMC: DAGLI OBIETTIVI DELLA TERAPIA AGLI OUTCOME RAGGIUNTI E RAGGIUNGIBILI

Gianni Binotto
Ematologia ed Immunologia Clinica
Dipartimento di Medicina
Università – Azienda Ospedaliera di Padova

La leucemia mieloide cronica: di cosa stiamo discutendo



- **Disordine clonale della cellula staminale emopoietica**
- **Neoplasia rara (incidenza 1,5-2/100.000/anno)**
  Età mediana alla diagnosi: 65 anni
- **Caratterizzata dalla presenza del cromosoma Ph+ da cui origina un gene di fusione BCR-ABL**
- **Il gene chimerico codifica un'oncoproteina con attività tirosin chinasica deregolata, responsabile del fenotipo leucemico**
- **La storia naturale della malattia prevede una trasformazione da una fase cronica in crisi blastica nella quasi totalità dei casi**

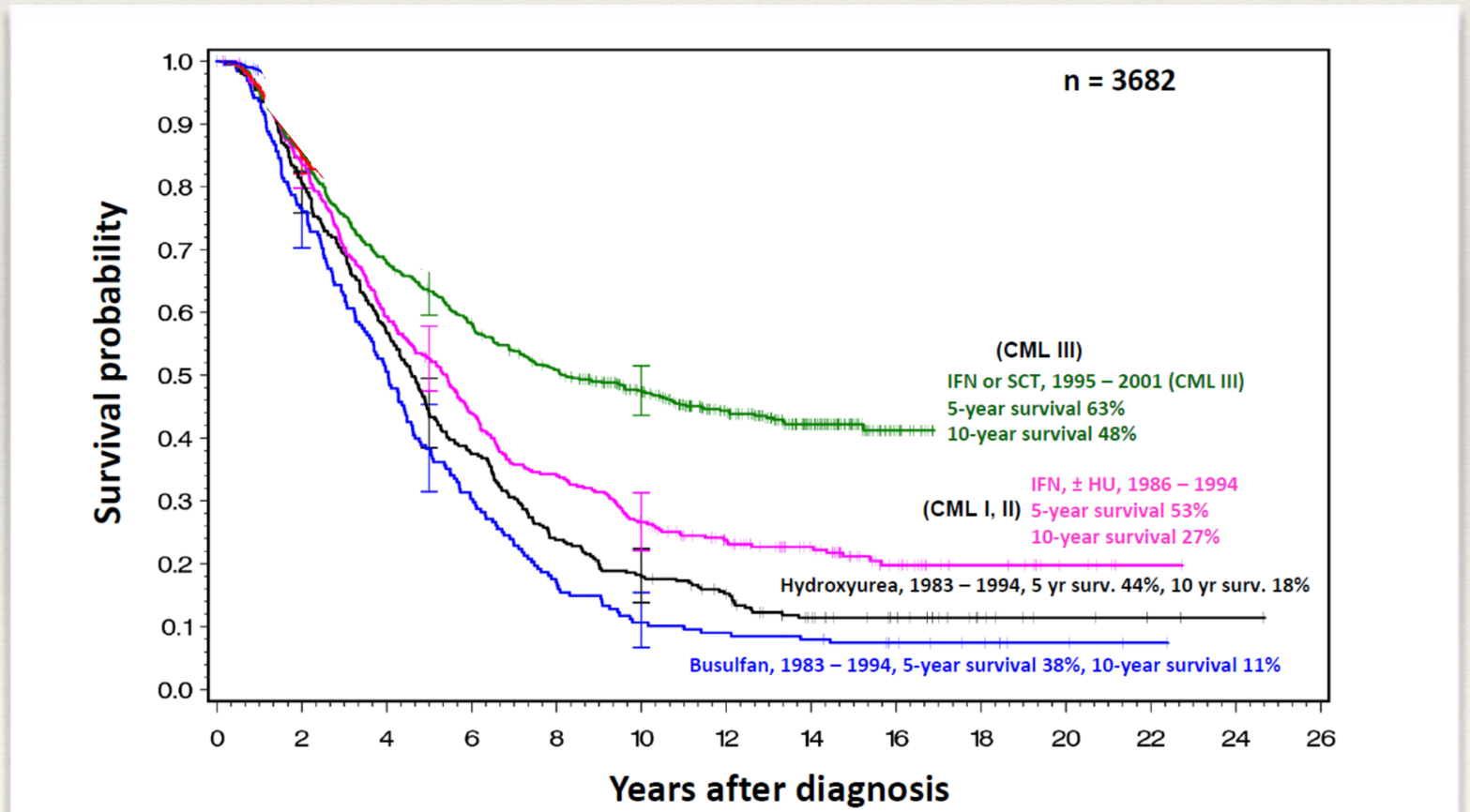
Il rischio di progressione è uguale per tutti pazienti?

Sokal **Hasford** **Eutos**

Comunicazione di diagnosi di LMC fino agli inizi del 2000

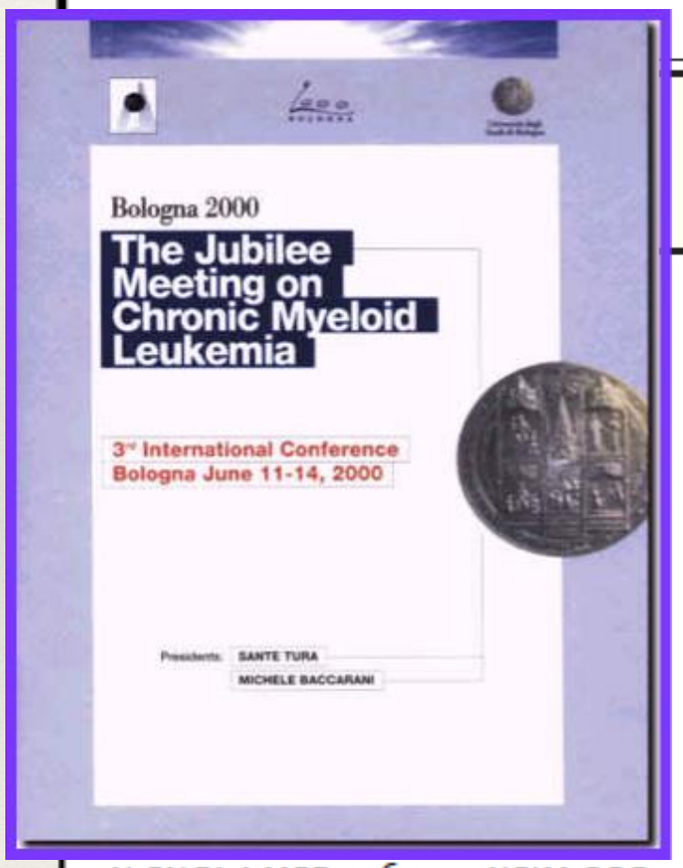
"Gli esami indicano che c'è una malattia seria, per la quale possiamo offrirle **l'interferone** o il **trapianto**… Entrambi con effetti collaterali importanti…."

leucemia mieloide cronica



German study Group

Una svolta epocale



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Imatinib Changed Everything

Dan L. Longo, M.D.

N ENGL J MED 376;10 NEJM.ORG MARCH 9, 2017

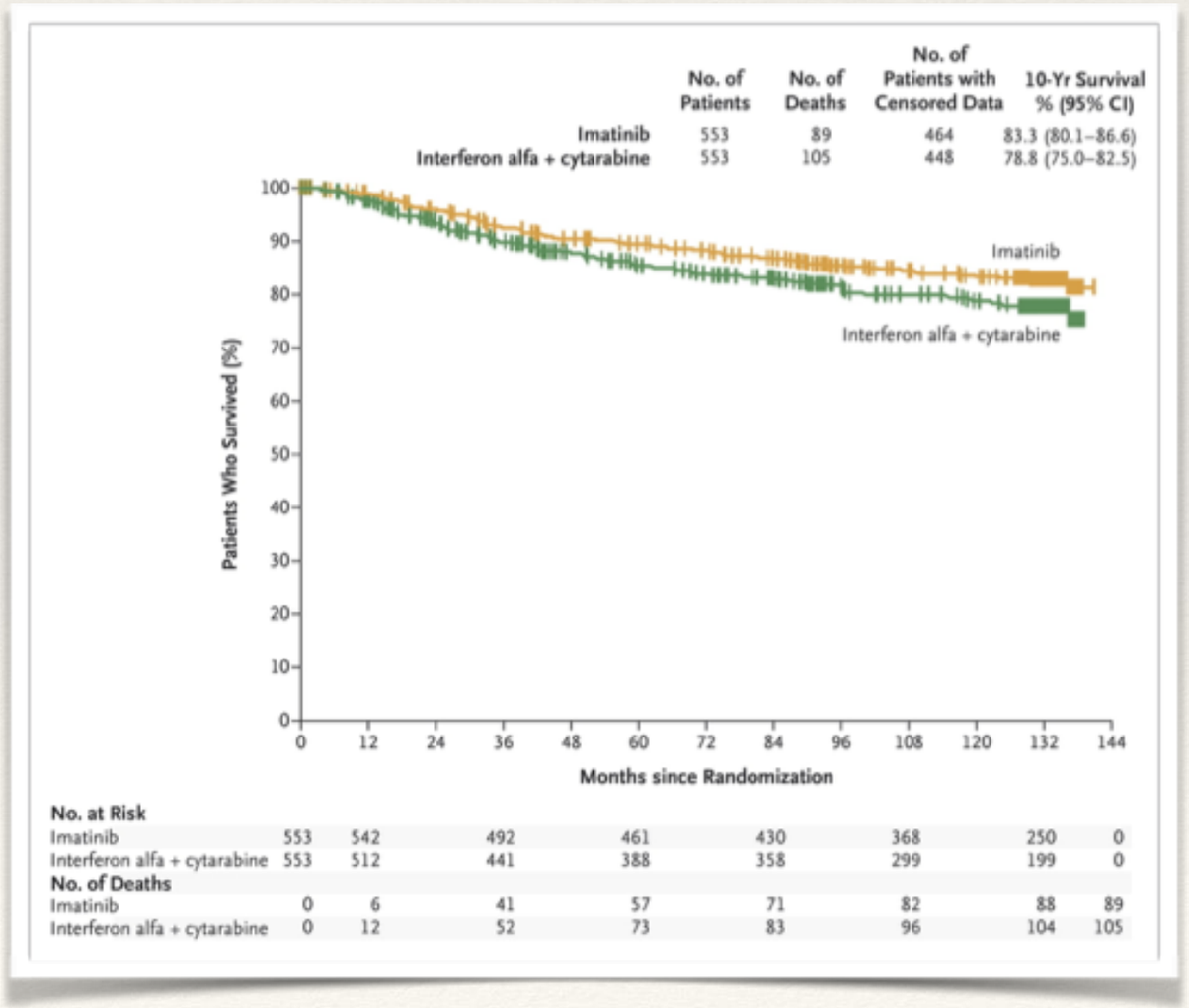
2001

Come è cambiata la comunicazione della diagnosi?

"Gli esami indicano che c'è una malattia seria, per la quale abbiamo però farmaci efficaci in grado offrire una prospettiva di vita pressochè normale…"

leucemia mieloide **cronica**

Perché i pazienti trattati con TKI sopravvivono più a lungo?

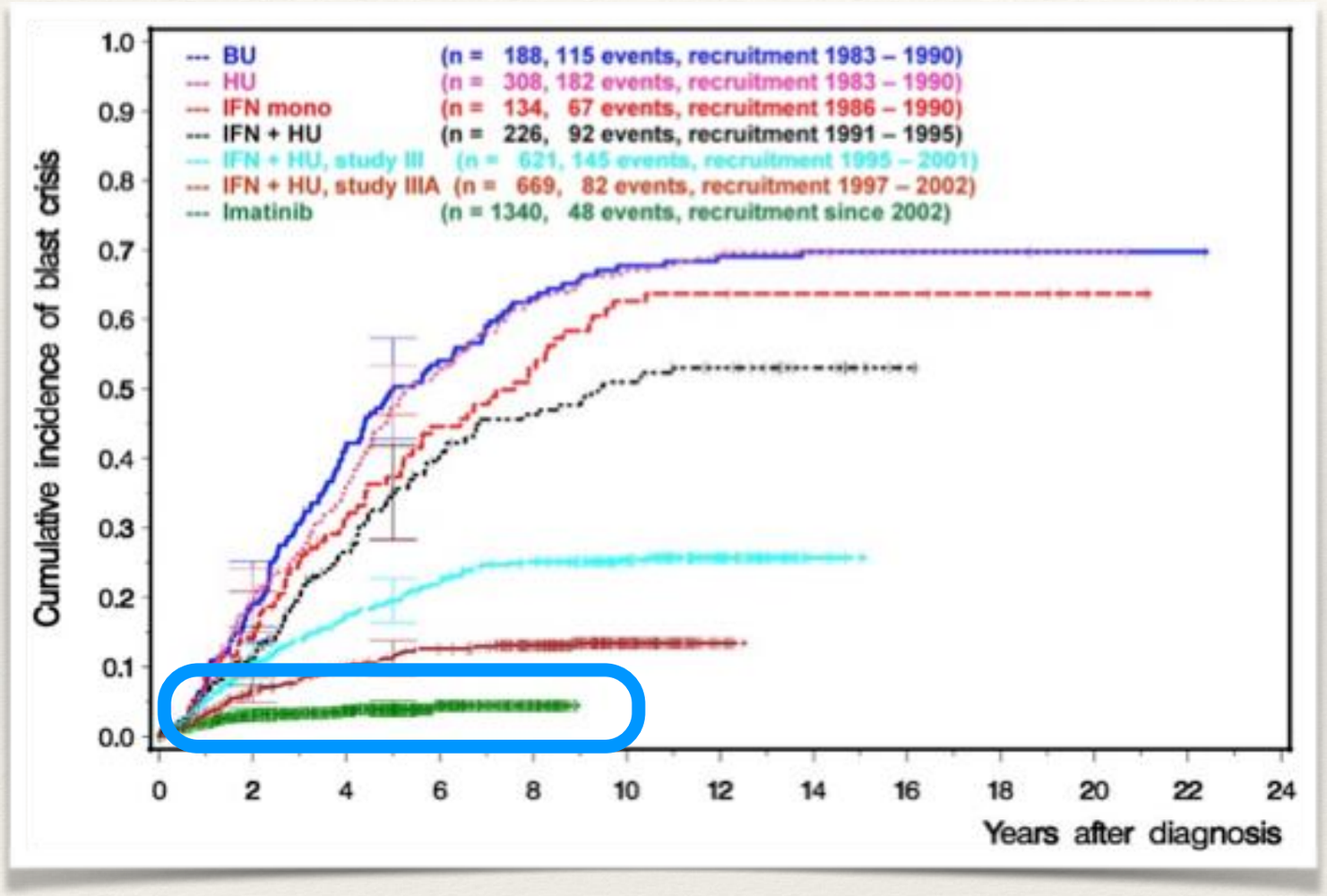


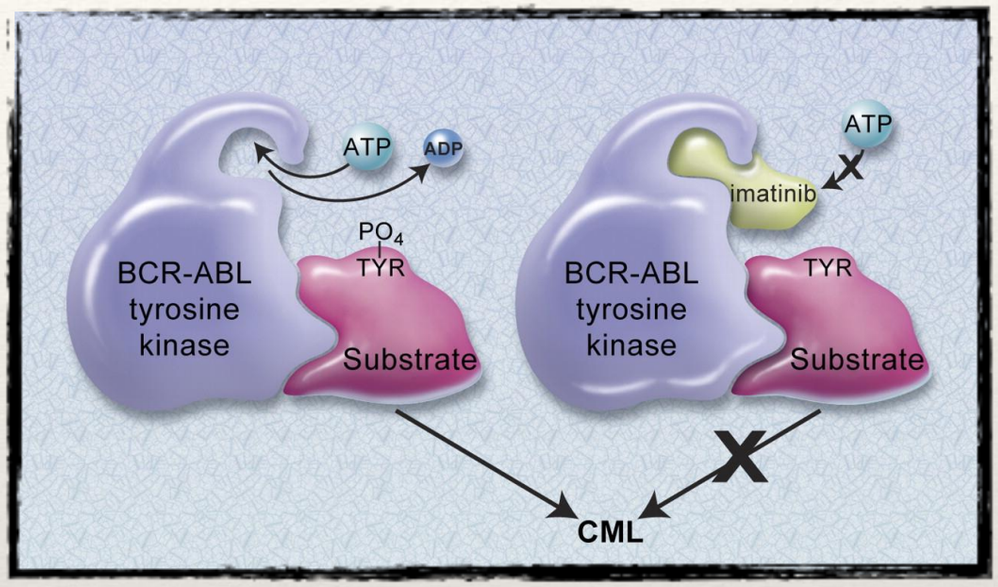
	No. of Patients	No. of Deaths	No. of Patients with Censored Data	10-Yr Survival % (95% CI)
Imatinib	553	89	464	83.3 (80.1–86.6)
Interferon alfa + cytarabine	553	105	448	78.8 (75.0–82.5)

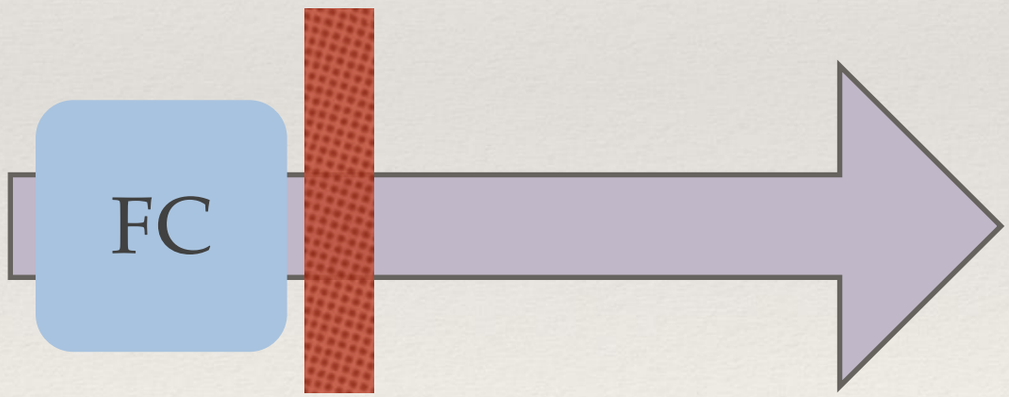
No. at Risk								
Imatinib	553	542	492	461	430	368	250	0
Interferon alfa + cytarabine	553	512	441	388	358	299	199	0
No. of Deaths								
Imatinib	0	6	41	57	71	82	88	89
Interferon alfa + cytarabine	0	12	52	73	83	96	104	105

Hochhaus A et al. N Engl J Med 2017;376:917-927
Druker et al. Blood 2008 112:4808-4817

Prevenzione dell'evoluzione a crisi blastica attraverso trattamenti più efficaci nella fase cronica precoce (German CML Study Group experience 1983-2011).







Hehlmann et al. Blood 2012;120:737-747

La formula del successo

BCR-ABL + TKI − AE =

Monitoraggio molecolare

Disponibilità di diversi inibitori

Gestione eventi avversi

Obiettivi della terapia della LMC nel 2017

1

Sopravvivenza sovrapponibile a soggetti sani di pari età

2

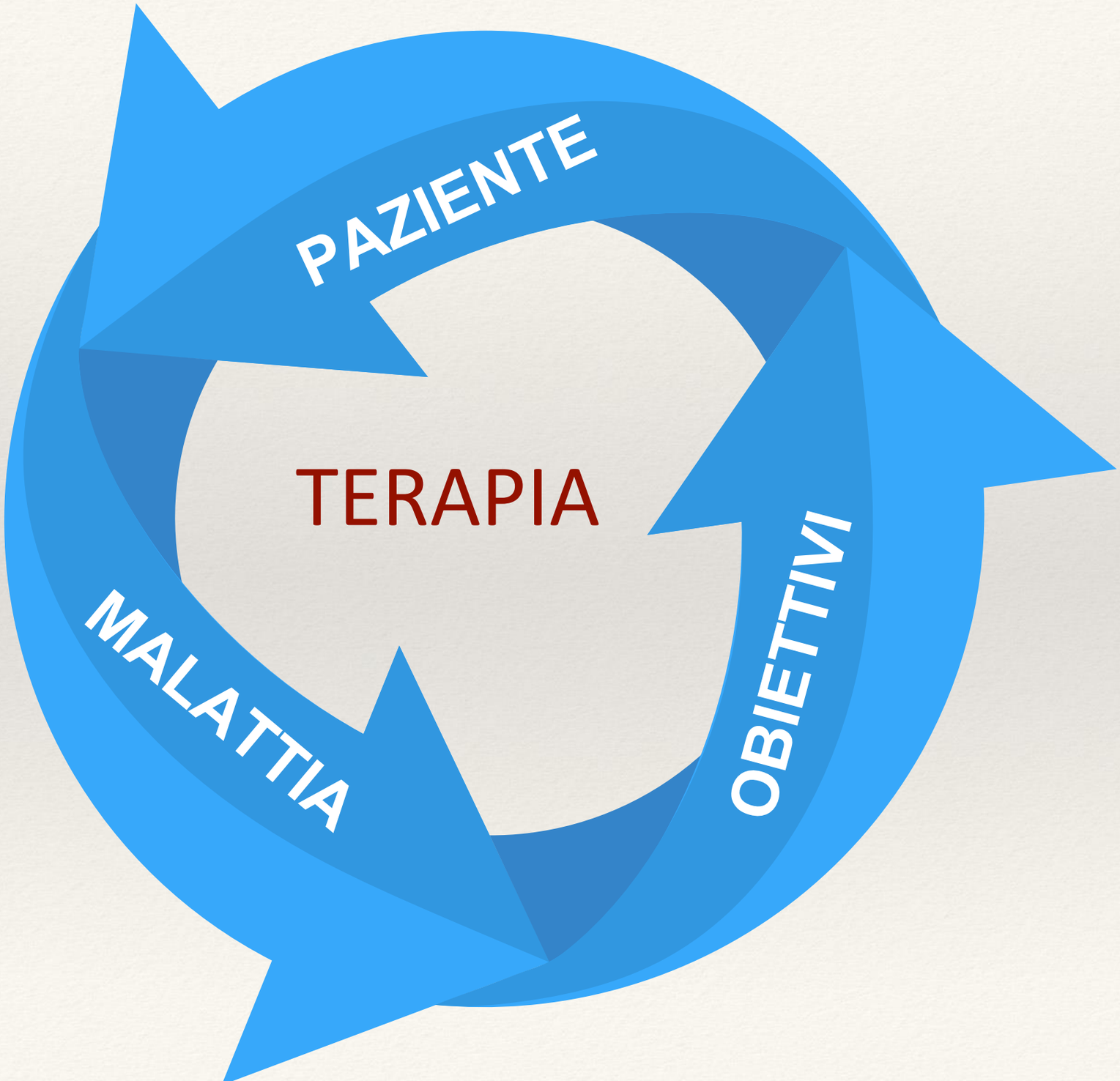
Ottimizzazione della qualità di vita

3

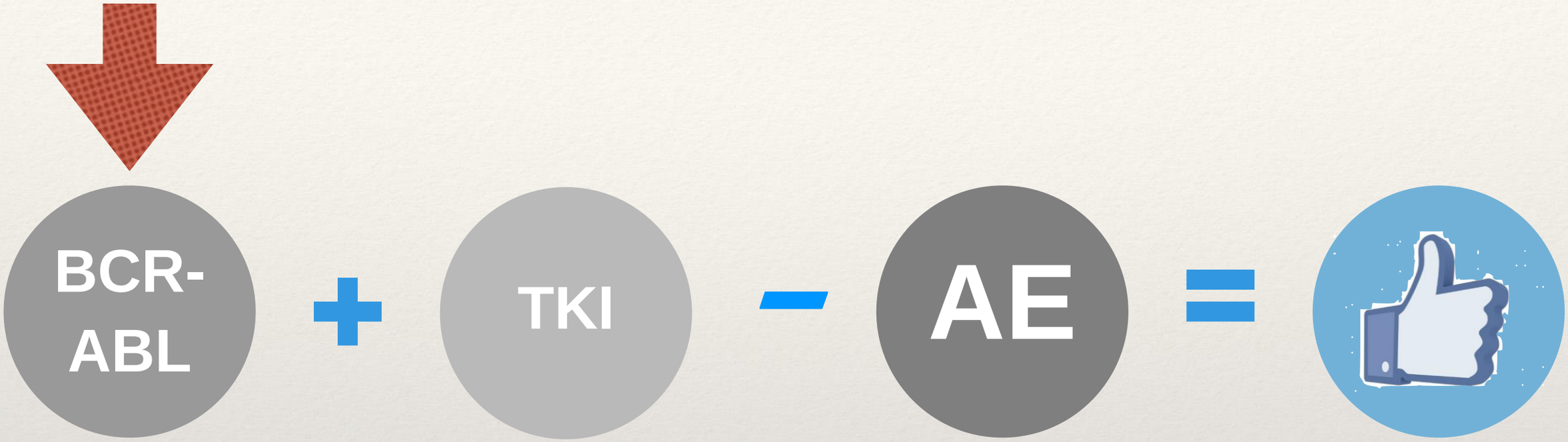
Mantenere una remissione di malattia dopo l'interruzione del trattamento

Per tutti i pazienti?

Quali sono oggi le variabili in base alle quali si decide il trattamento ?



La formula del successo



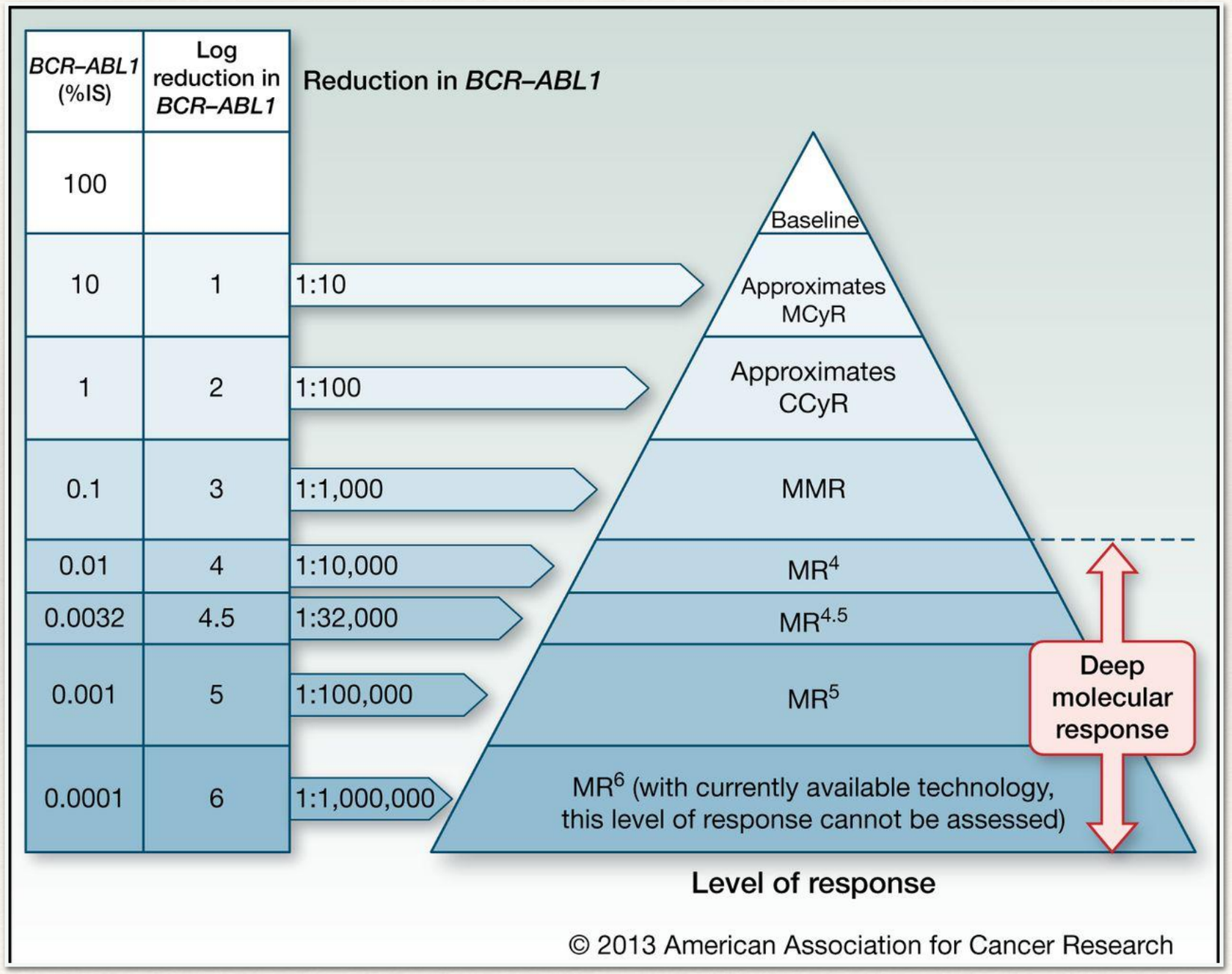
Monitoraggio molecolare

Disponibilità di diversi inibitori

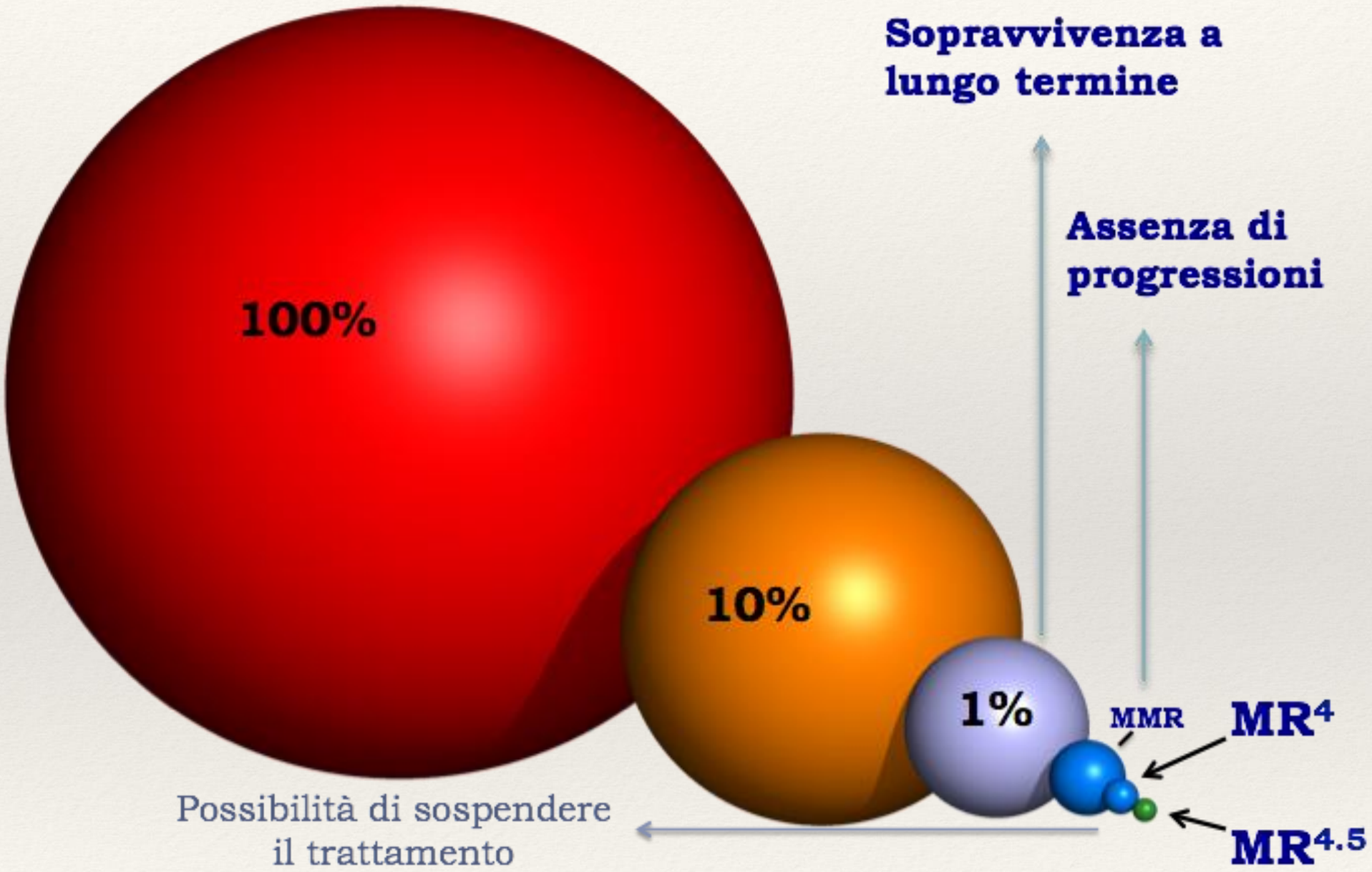
Gestione eventi avversi

Una pietra miliare della LMC

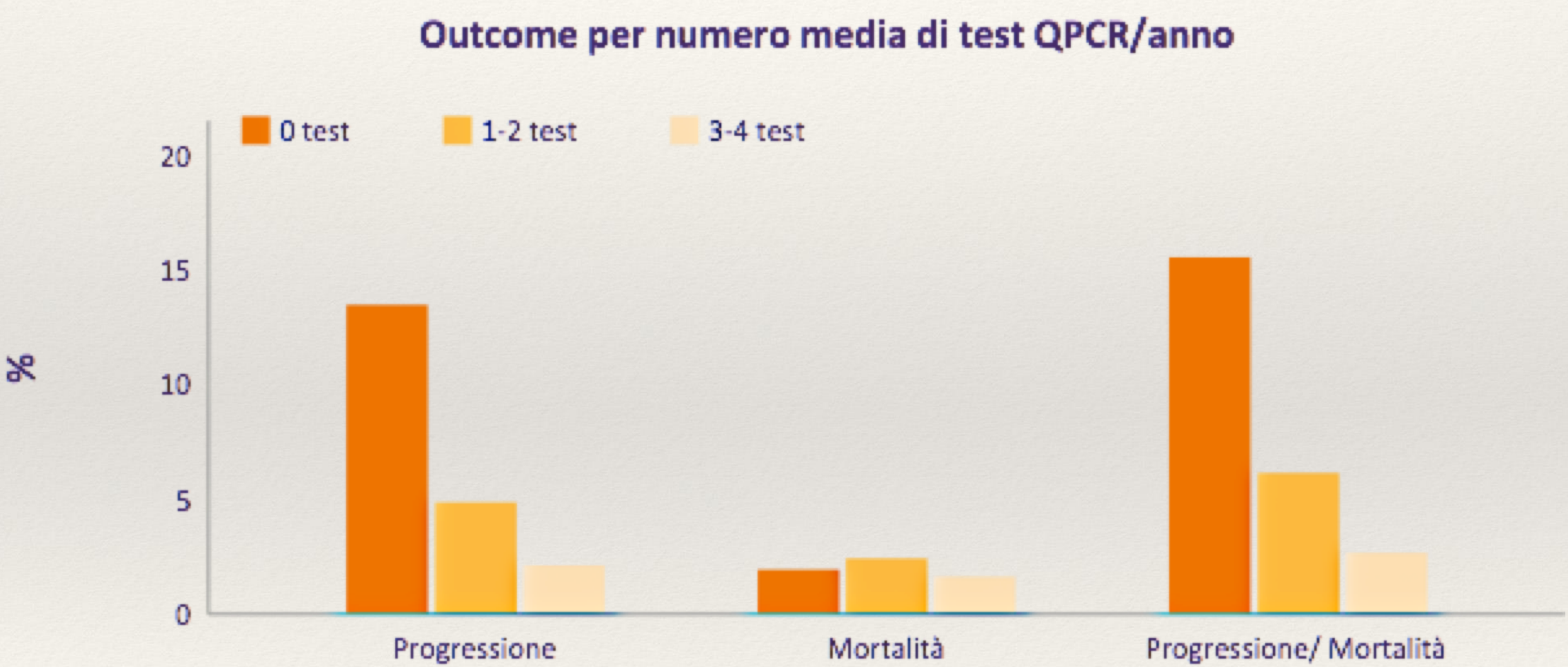
Come quantificare la risposta al trattamento con TKI



Correlazione tra burden leucemico ed obiettivi di trattamento



Un inadeguato monitoraggio molecolare si associa ad un outcome più sfavorevole



Goldberg et al. Curr Med Res Opin. 2013;29:1075-82

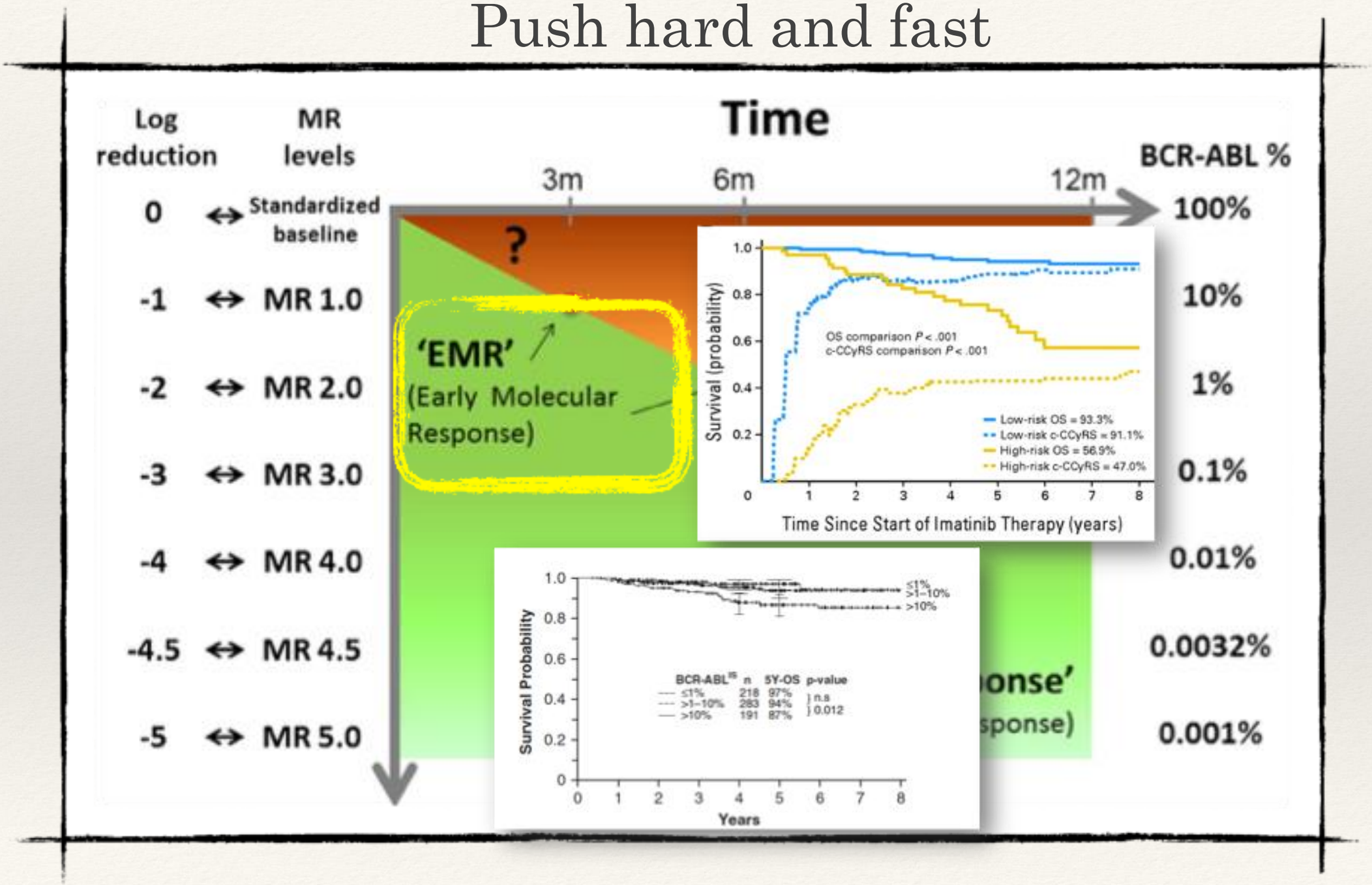
Once upon a time

La scomparsa del cromosoma Philadelphia è la condizione essenziale per la lungosopravvivenza…

“Treatment of chronic phase is a marathon, not a sprint”

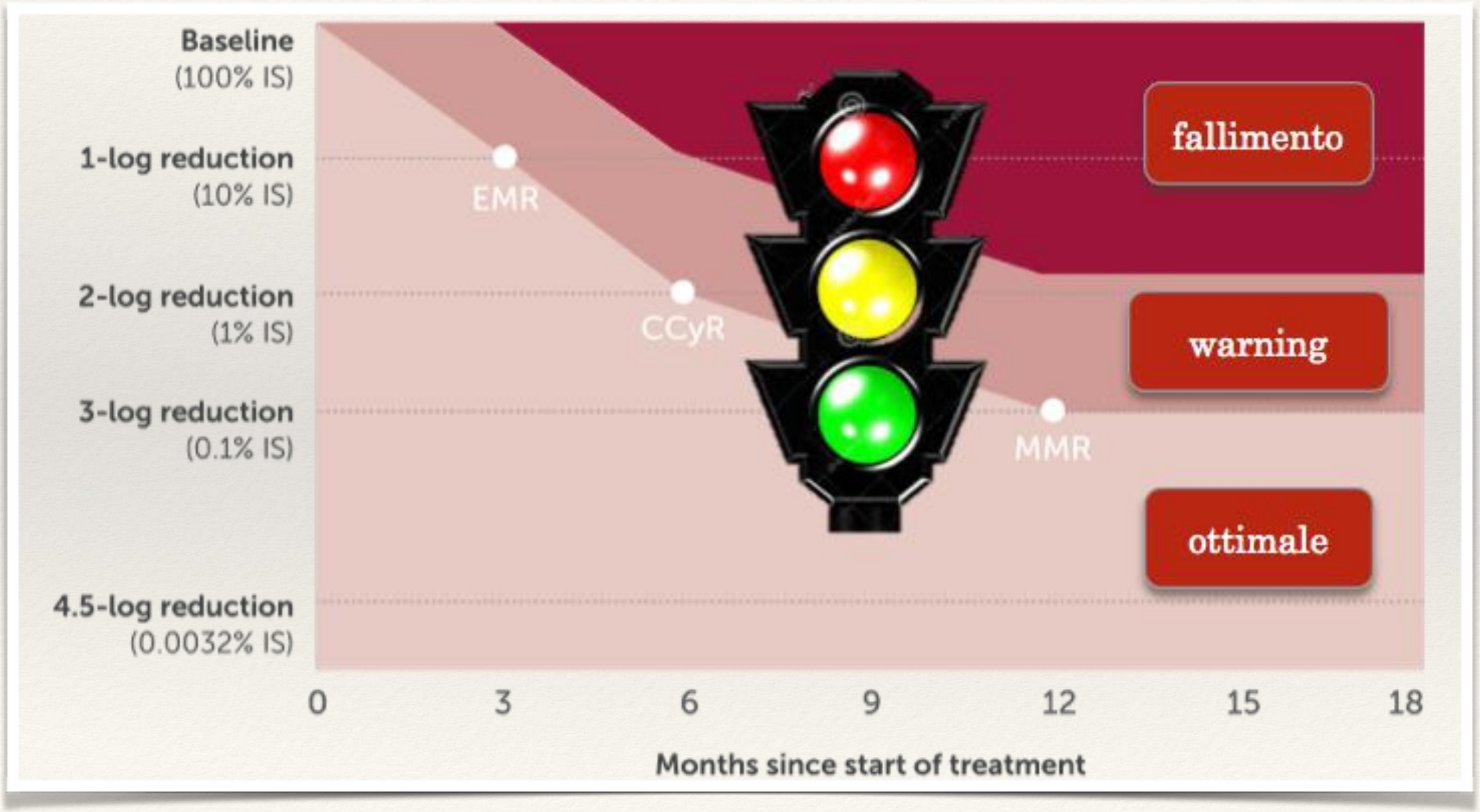
Ora

Push hard and fast



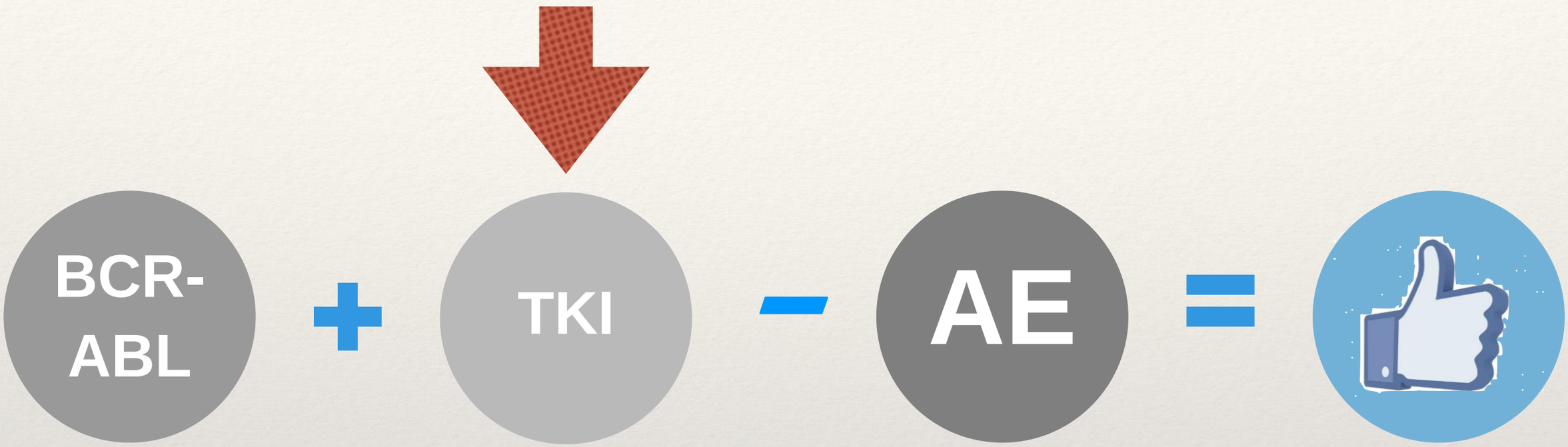
Marin D et al. JCO 2012;30:232-238
Hanfstein et al. Leukemia 2012 26, 2096–2102

Raccomandazioni LeukemiaNet 2013



Baccarani et al. Blood. 2013;122:872-884

La formula del successo



Monitoraggio molecolare

Disponibilità di diversi inibitori

Gestione eventi avversi

Imatinib curriculum vitae

europass

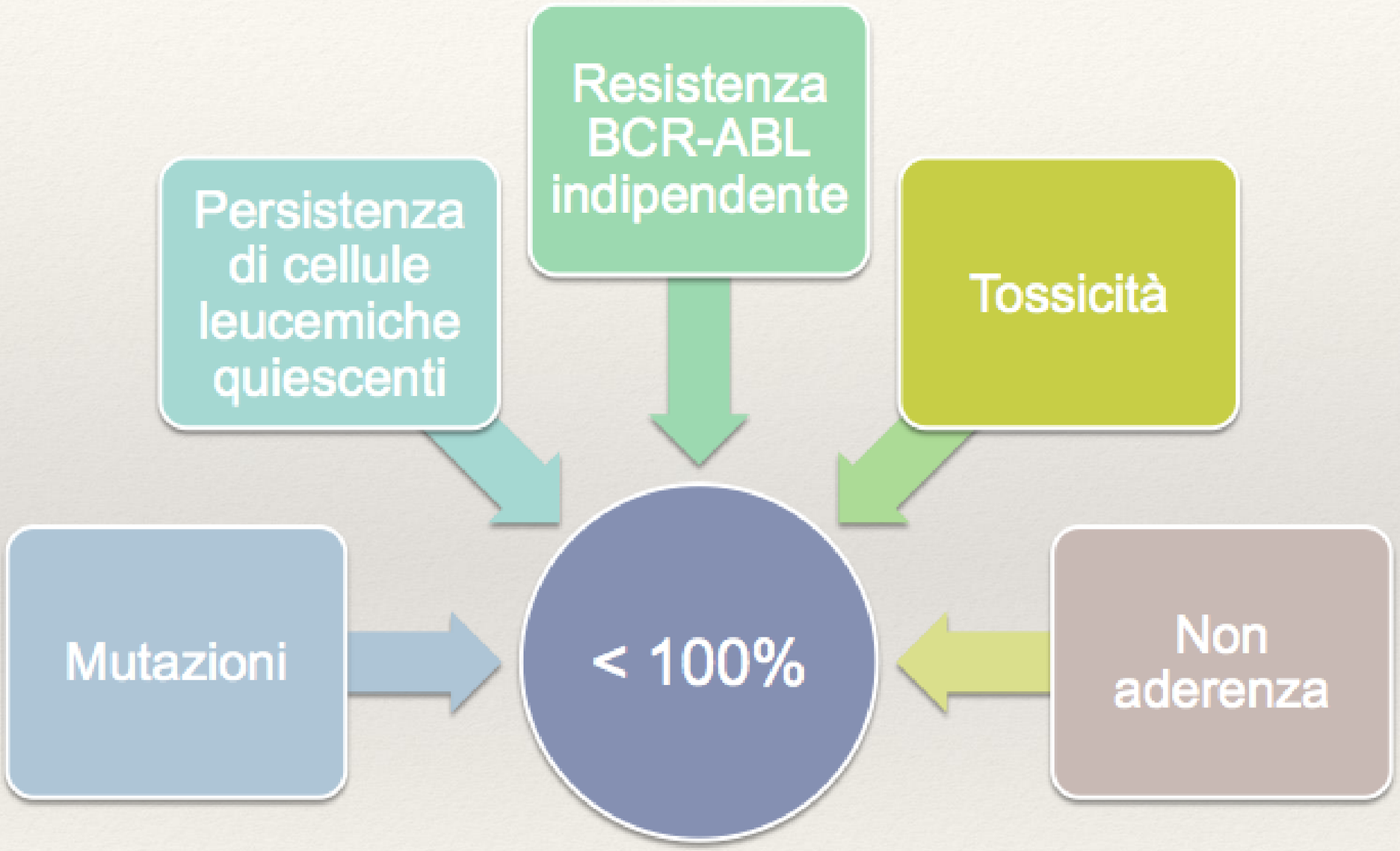
Curriculum Vitae Europass

Informazioni personali

Still on treatment after 8 years	55%
Never achieved CCyR	18%
Failure to maintain stable CCyR	17%
Adverse events leading to discont.	5%
Progression to AP/BP	1-3% per year (during first 4 years)

Deininger M. et al, Blood 2009;111:462, abs #1126

Cause di inefficacia di imatinib



Molte possibilità di scelta

PRIMA LINEA

ALTRA LINEA

48 COMBINAZIONI DI TRATTAMENTO TEORICHE

Perfomance degli inibitori di seconda e terza generazione nei pazienti con intolleranza/resistenza a imatinib

	DASATINIB	NILOTINIB	BOSUTINIB	PONATINIB*
CCyR	50%	44%	48%	46%
MMR	37%	28%	35%	34%
MR^4 / CMR	n.a.	n.a.	28%	15%
EFS at 2 years	n.r.	53%	n.r.	n.r.
PFS at 2 years	80%	64%	81%	80% (@ 1 year)
OS at 2 years	94%	87%	91%	94% (@ 1 year)

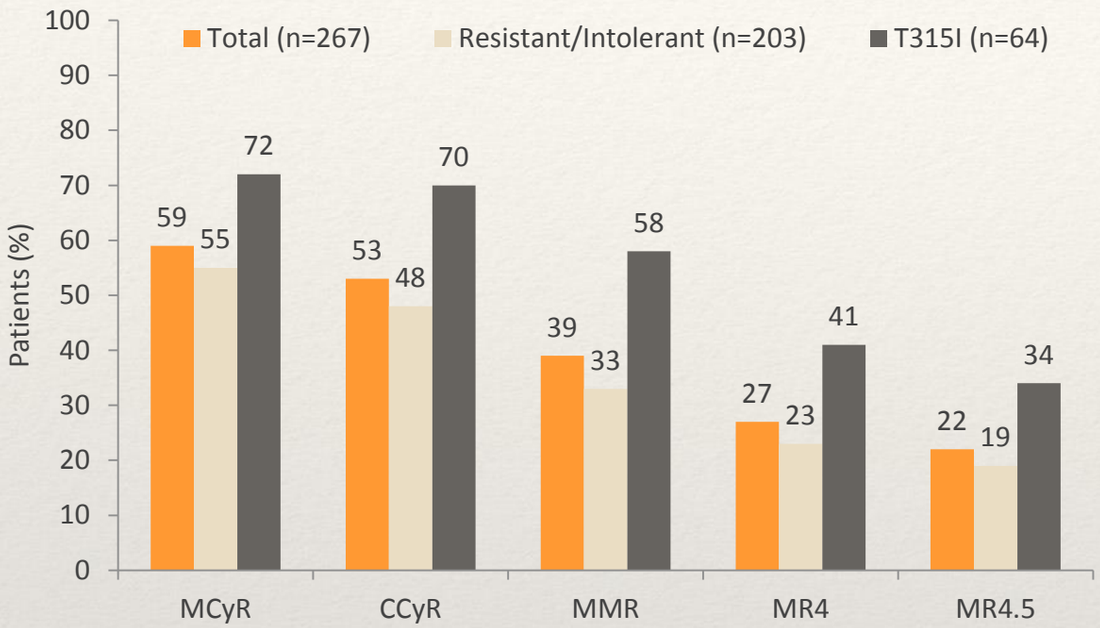
Shah N. et al, Haemotologica 2010;95:232-240. Kantarjian H. et al, Blood 2011;117:1141-1145.
Cortes J.E. et al, Blood 2011;118:4567-4576. Cortes J.E. et al, N Engl J Med 2013;369:1785-1796.

Un meccanismo di resistenza: le mutazioni

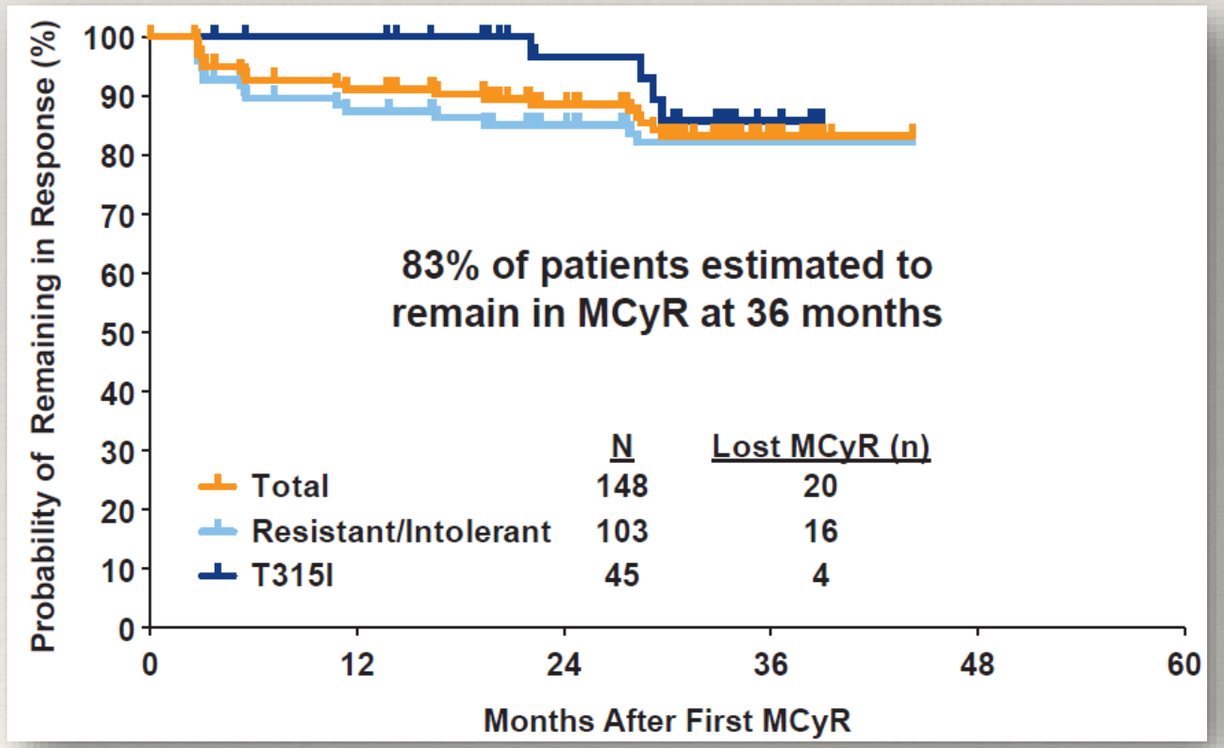
BCR-ABL MUTANT	PONATINIB	IMATINIB	NILOTINIB	DASATINIB	BOSUTINIB
Native	3	201	15	2	71
M244V	3	287	12	2	147
L248R	8	10000	549	6	874
L248V	4	586	26	5	182
G250E	5	1087	41	4	85
Y253H	5	4908	179	3	40
E255K	6	2487	127	9	181
E255V	16	8322	784	11	214
V299L	4	295	24	16	1228
T315A	4	476	50	59	122
T315I	6	9773	8091	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
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).

Ponatinib: una buona alternativa in caso di resistenza ad un inibitore di seconda generazione o in presenza della mutazione T315I



Studio PACE, 270 pazienti con LMC in fase cronica, 60% almeno tre linee di terapia



Cortes et al ASH 2014

Durata del trattamento in seconda linea

Dasatinib IIa linea, F-U 72 mesi

Table 1. Patient disposition

	100 mg once daily (n = 165)	
	No.	%
On treatment	51	31
Reason for discontinuation		
Disease progression*	34	21
Study drug toxicity	34	21
Patient or investigator request	24	15
Adverse event unrelated to drug	7	4
Other†	15	9

≅30%

Nilotinib IIa linea, F-U 48 mesi

Table 1. Patient disposition

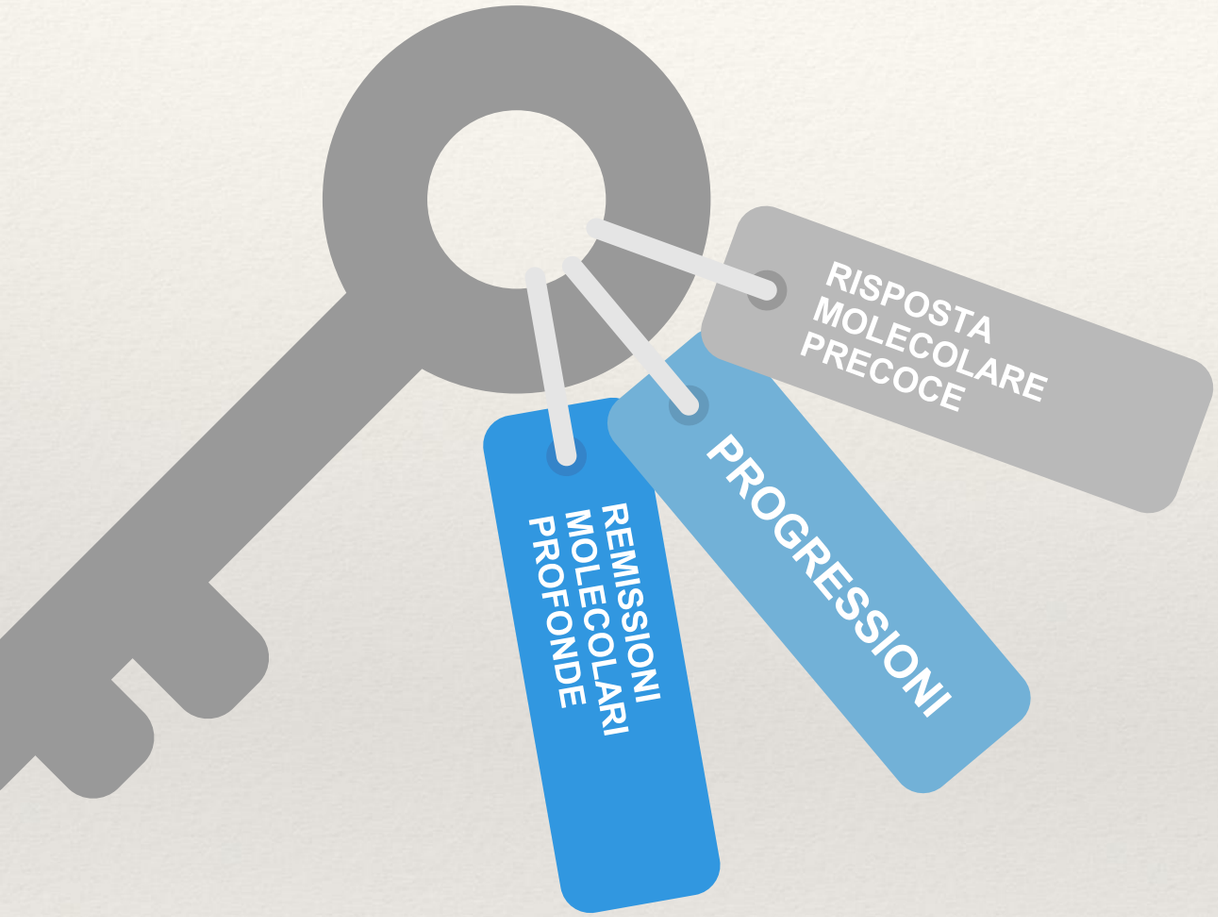
Disposition	*No. of Patients (%) (N = 321)*
Discontinued study	224 (69.8)
Disease progression	96 (29.9)
Adverse events	*66 (20.6)*
Drug-related	53 (16.5)
Subjects who withdrew consent	26 (8.1)
Abnormal test results	4 (1.2)
Death	4 (1.2)
Abnormal laboratory values	3 (0.93)
Lost to follow-up	3 (0.93)
Other[a]	22 (6.9)

[a]Includes administrative issues, protocol violations and not stated.

≅30%

Shah et al. Blood. 2014;123:2317-2324
Giles et al. Leukemia 2013;27:107–112

L’utilizzo di un inibitore più potente in prima linea può migliorare l’outcome del paziente?



ENESTnd

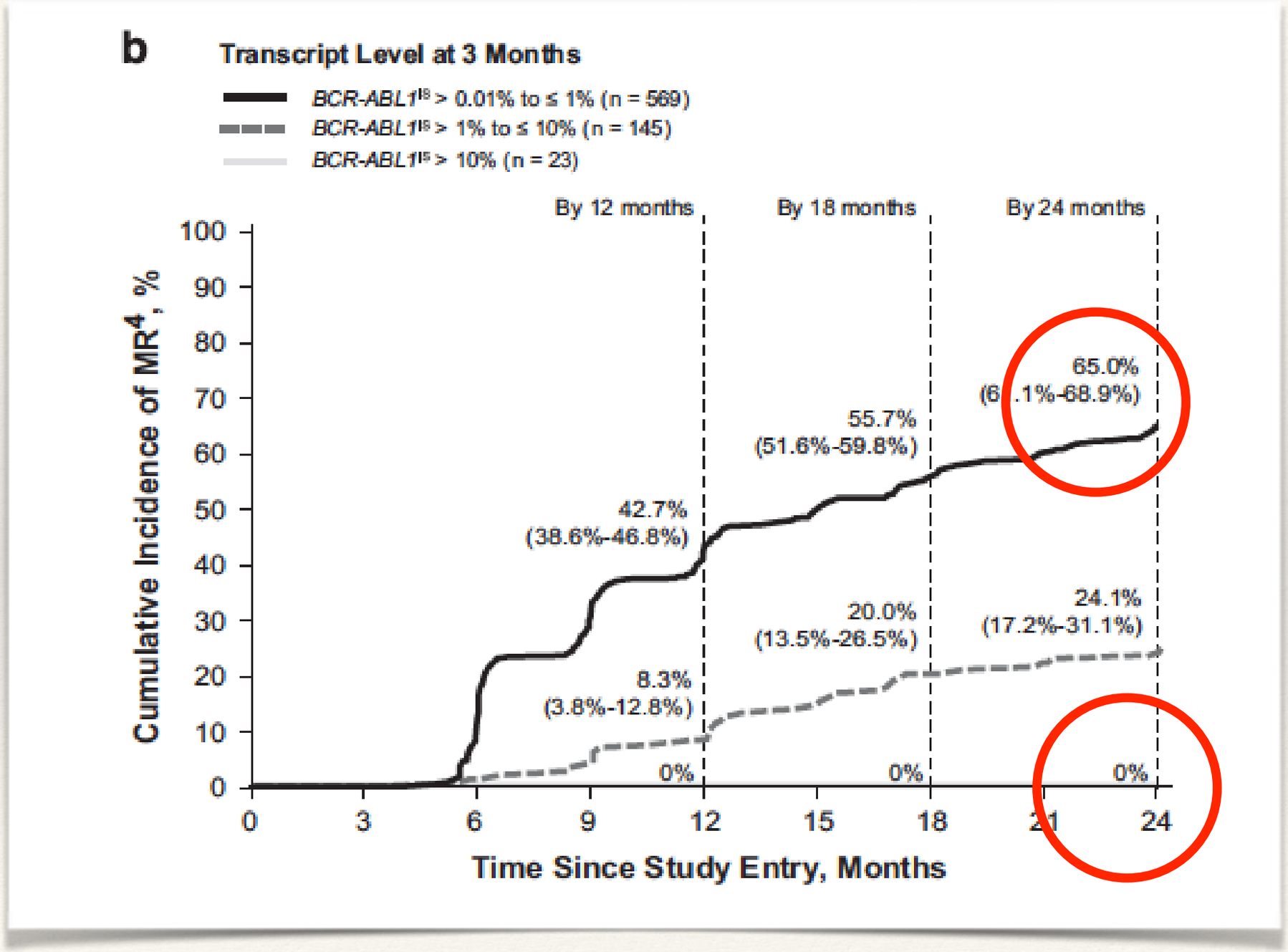
studio randomizzato fase 3

IMA 400 vs NILO 300 bid vs NILO 400 BID

	NILO 300 BID	IMA 400
RISPOSTE MOLECOLARI PRECOCI	91%	67%
PROGRESSIONI	10	21
REMISSIONI MOLECOLARI PROFONDE	66% 54%	42% 31%
MUTAZIONI	7,7%	16,7%

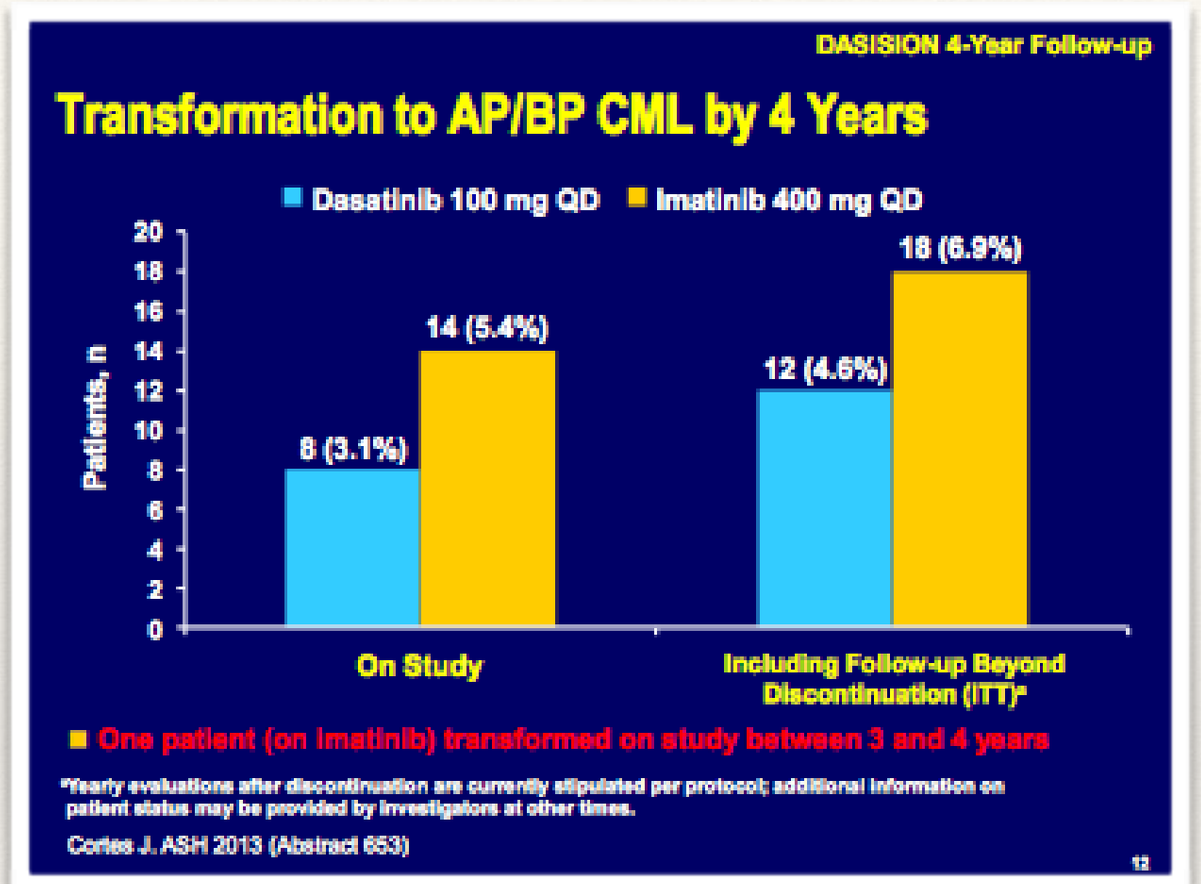
Hochhaus-Leukemia 2016;30: 57–64

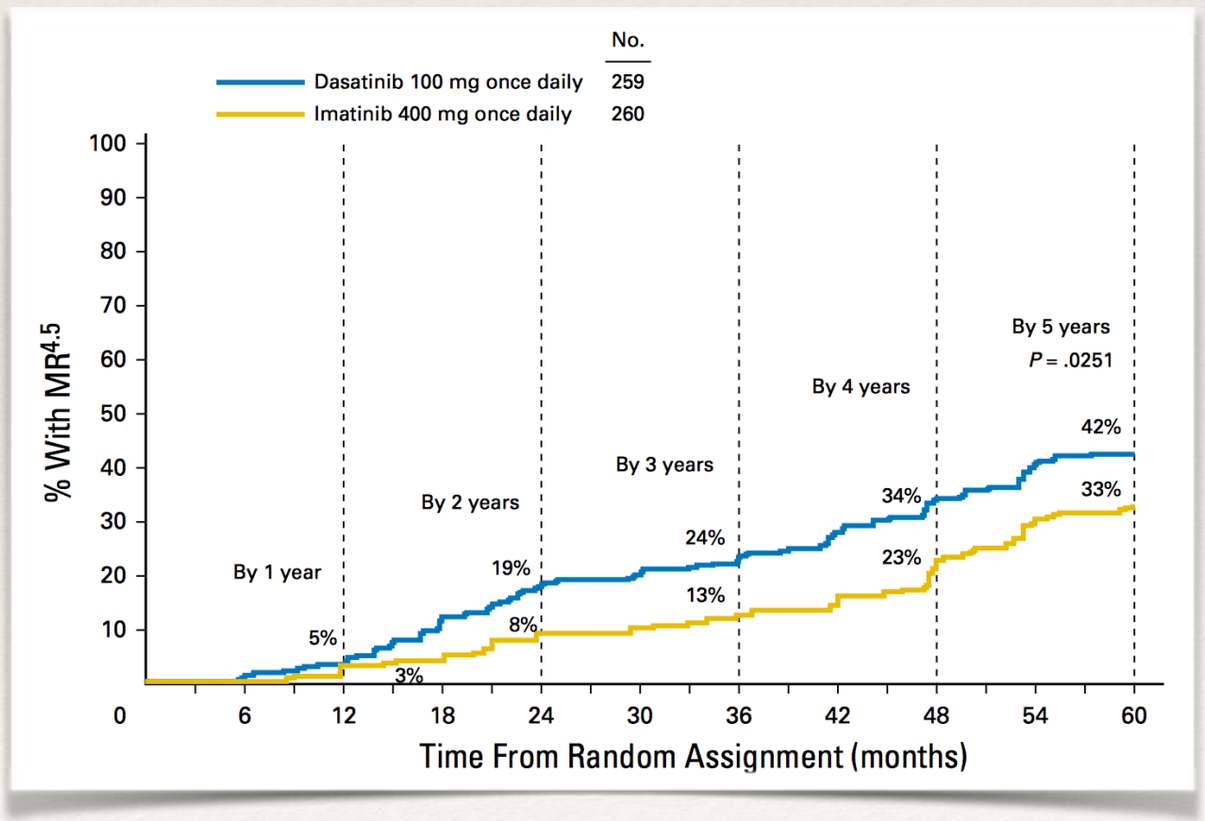
Il mancato ottenimento della risposta molecolare precoce compromette la possibilità di una risposta molecolare profonda



Hochhaus-Leukemia 2016;30: 57–64

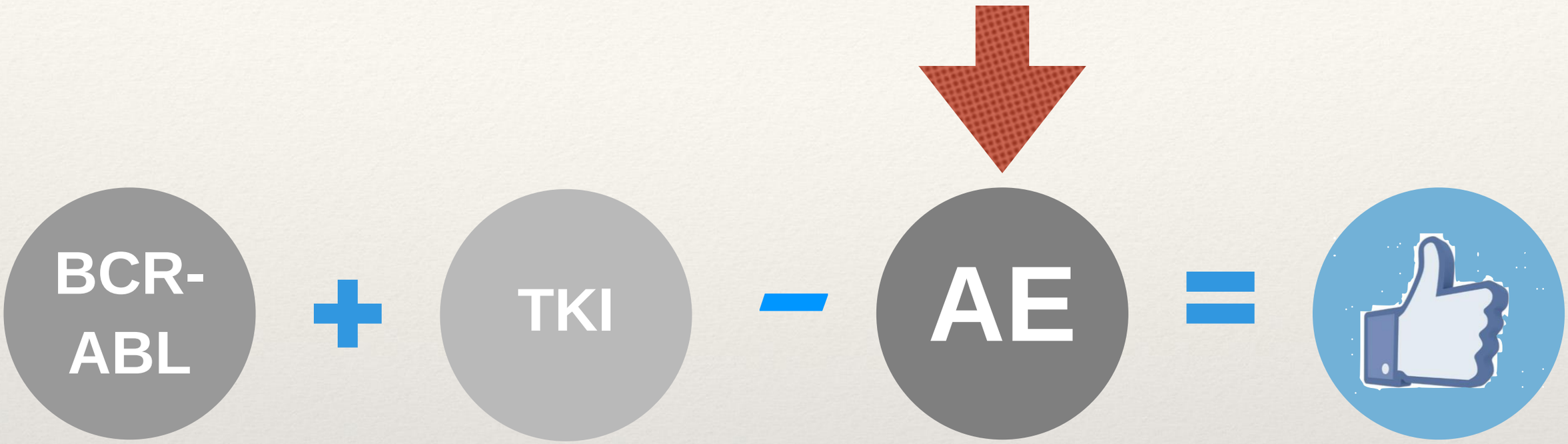
Studio Dasision





Cortes et al. J Clin Oncol. 2016;34:2333-40

La formula del successo

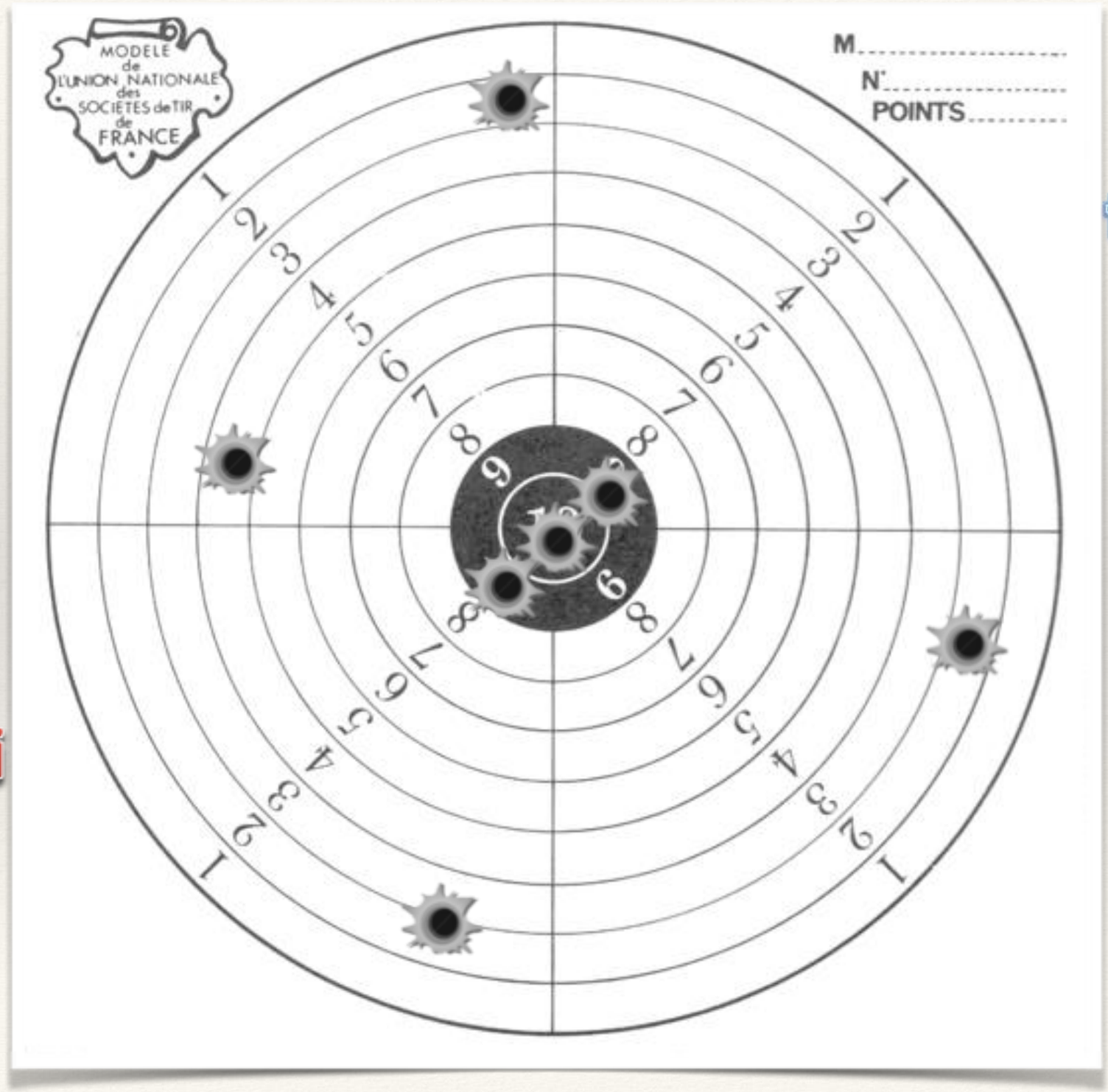


Monitoraggio molecolare

Disponibilità di diversi inibitori

Gestione eventi avversi

Selettività dei TKI



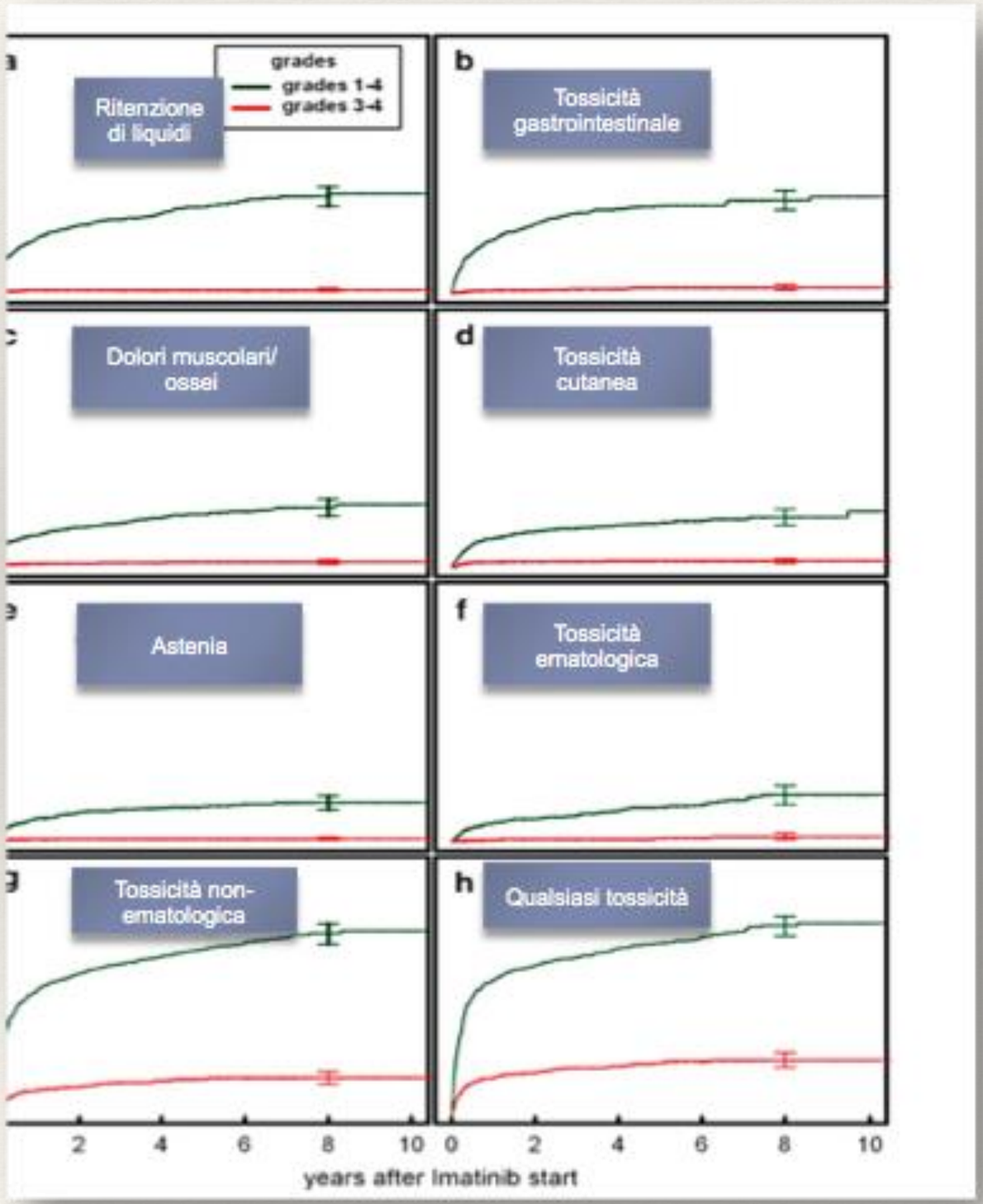
Efficacia terapeutica

Effetti collaterali

Differenti profili di tossicità

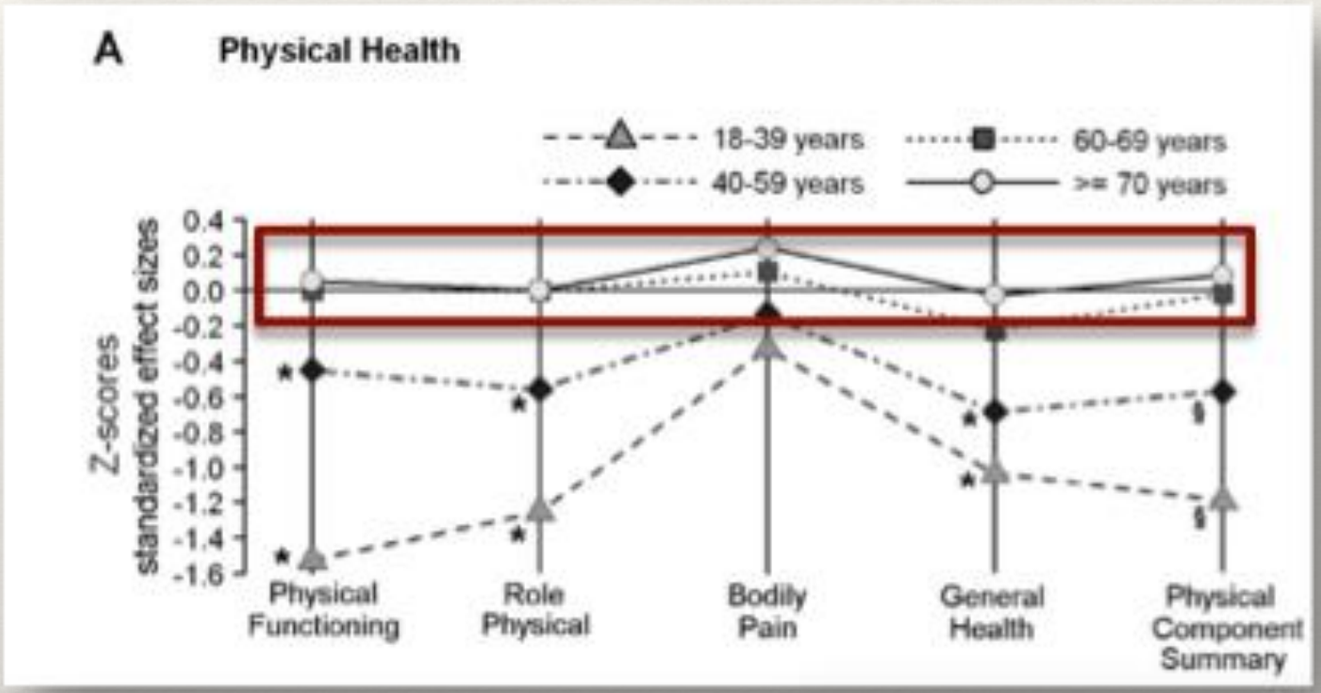
	IMATINIB	NILOTINIB	DASATINIB	BOSUTINIB
Edema	++	+	+	-
Diarrea	++	+	+	++
Rash	+	++	+	+
Cefalea	+	++	++	+
Iperglicemia	-	++	-	+
Iperlipasemia	-	+	-	+
Prolungamento Qt	-	+	+	+
Epatotox	+	+	-	+
Tossicità ematologica	+	++	++	+
Versamento pleurico	-	-	++	+
Ipertensione polmonare	-	-	+	+
PAOD	-	+	-	-

Effetti collaterali nel lungo termine legati al trattamento con imatinib



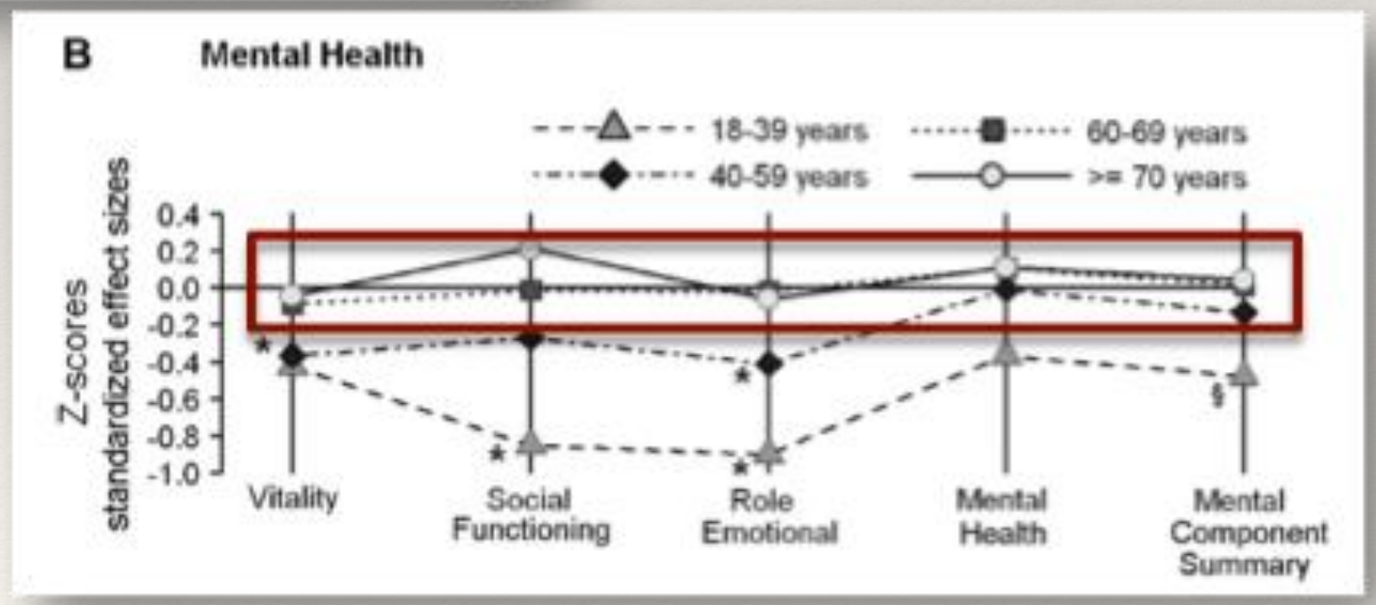
La probabilità di sviluppare un effetto collaterale nell'arco di 8 anni è del 76%.

Qualità di vita con imatinib



448 pazienti
Età mediana: 57 anni(>60y: 40%; >70y: 20%)
Durata mediana del trattamento con IMA: 5 aa

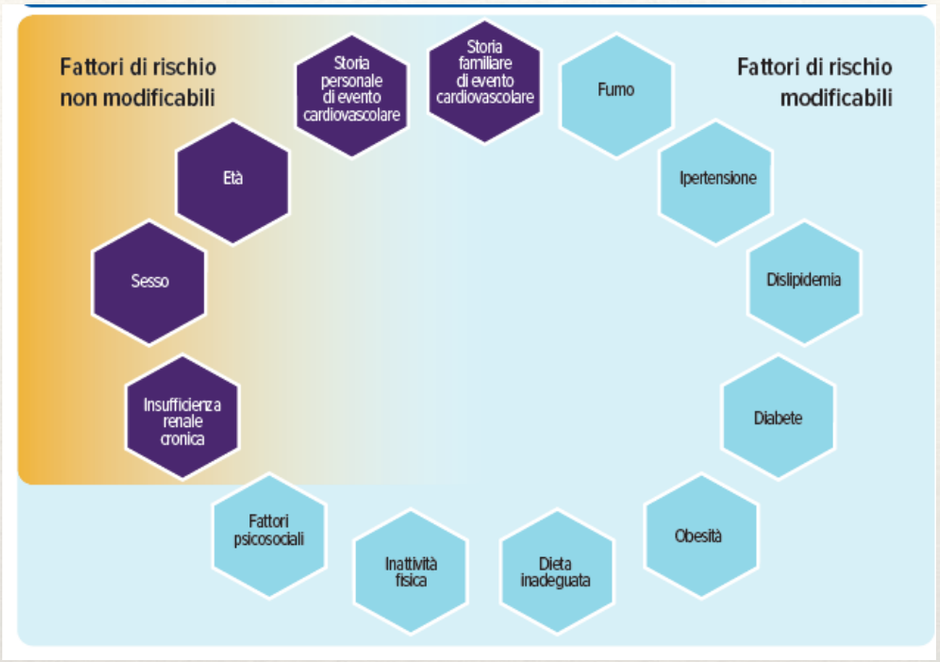
ECOG 0: 67%
CCI 0: 63%

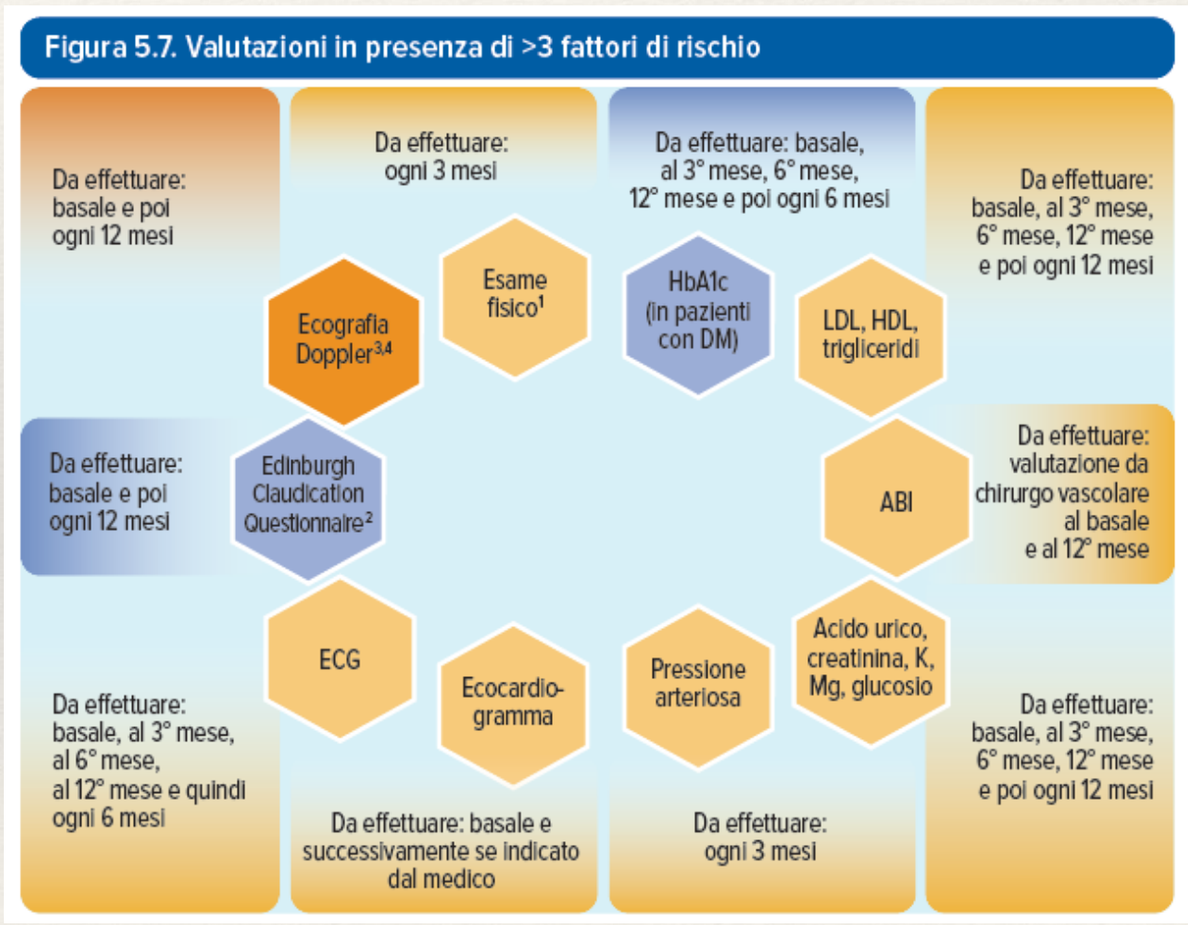


Efficace et al. Blood 2011;118:4554-4560


PAOD
Ipertensione polmonare
Insufficienza cardiaca
Versamento pleurico
Dislipidemia
Iperglicemia

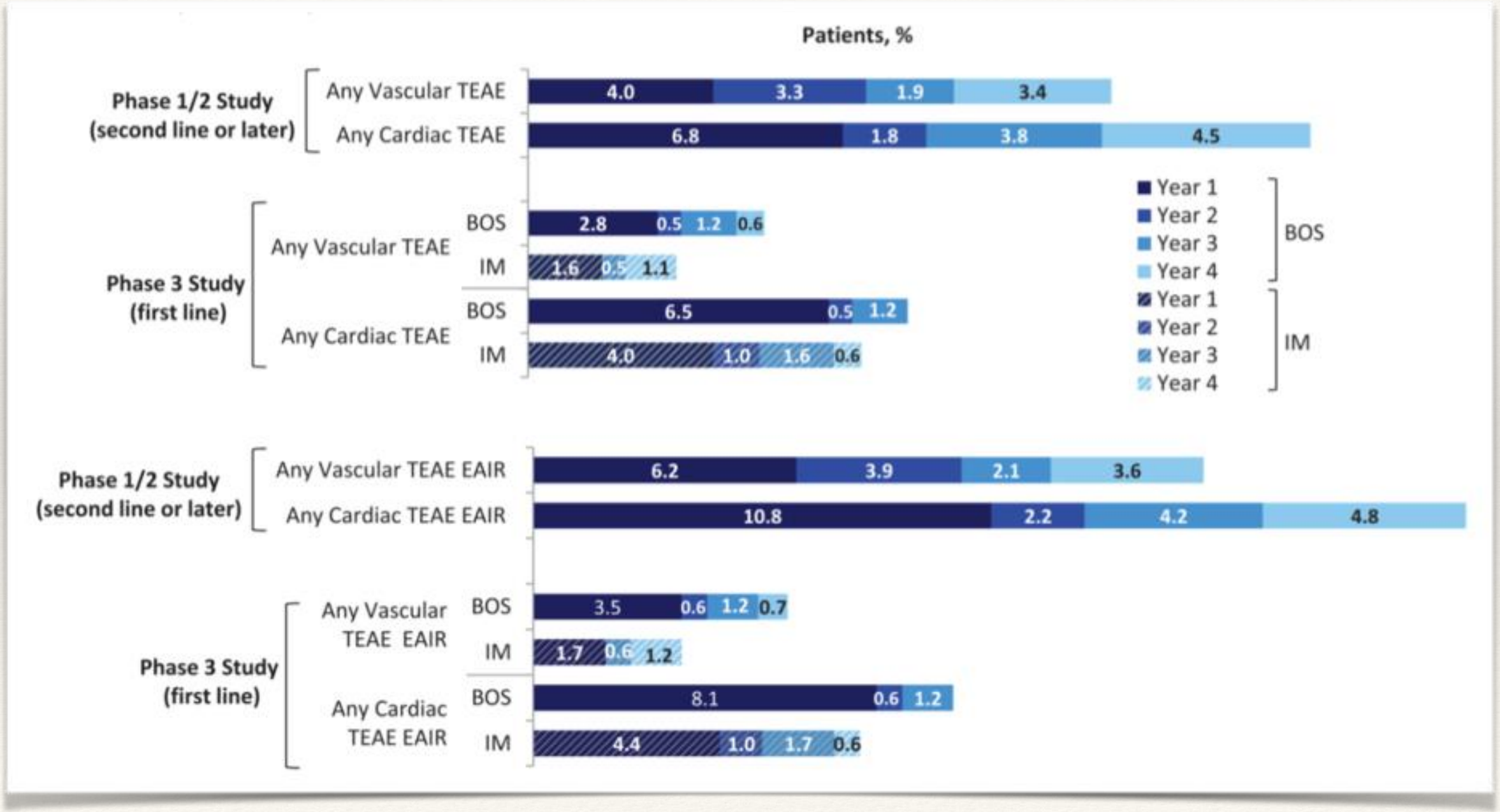
Programmi di prevenzione eventi avversi cardiovascolari





Nilotinib guida pratica, ed Edra 2016

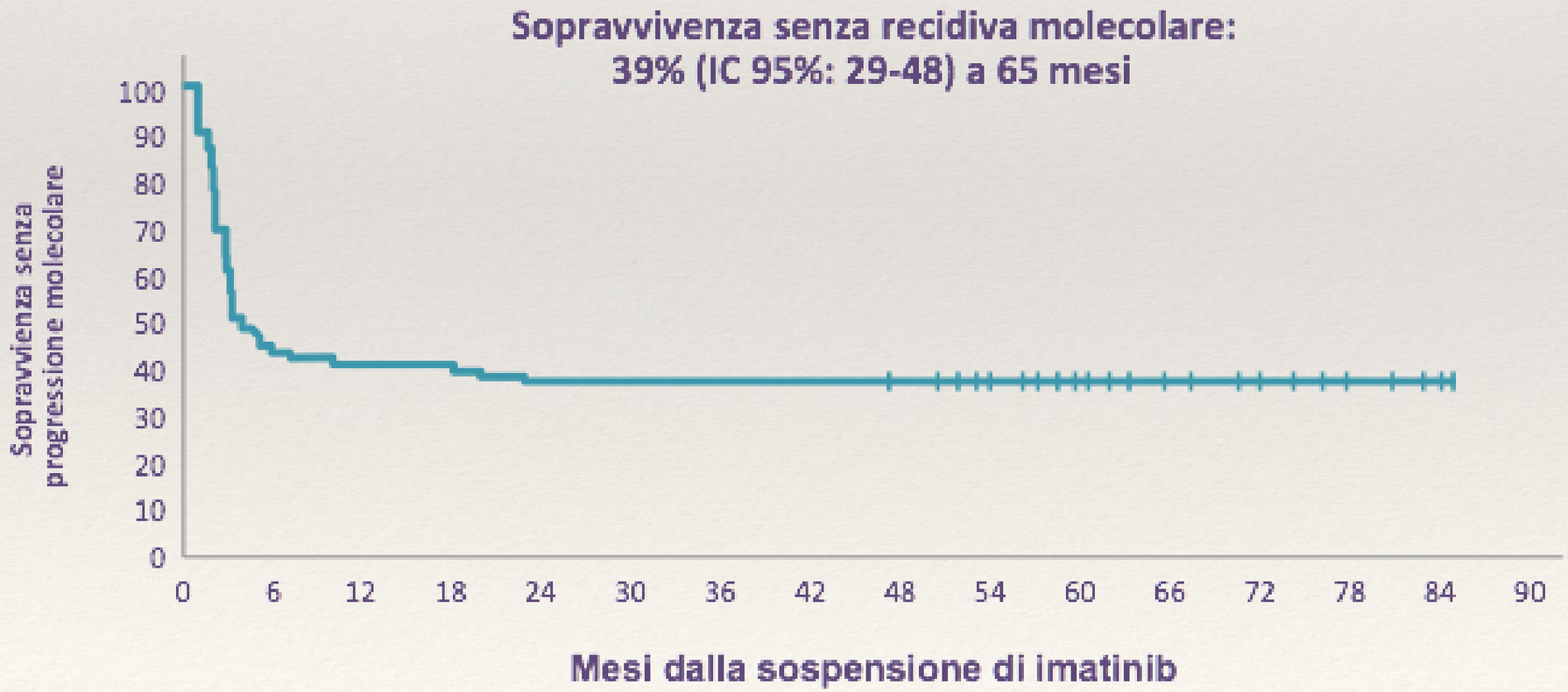
Bosutinib: una buona alternativa in caso di intolleranza



Una seconda rivoluzione

Studio STIM: *follow-up* a 65 mesi

- 61/100 recidive (58 durante i primi 7 mesi e 3 tardive)
- 5 decessi per cause non ematologiche
- Incidenza cumulativa di recidive: 60%
- Tutti i pazienti sensibili al *re-challenge*: 48 con imatinib, 5 con dasatinib e 5 con nilotinib
- Nessuna altra recidiva dopo il 2° anno



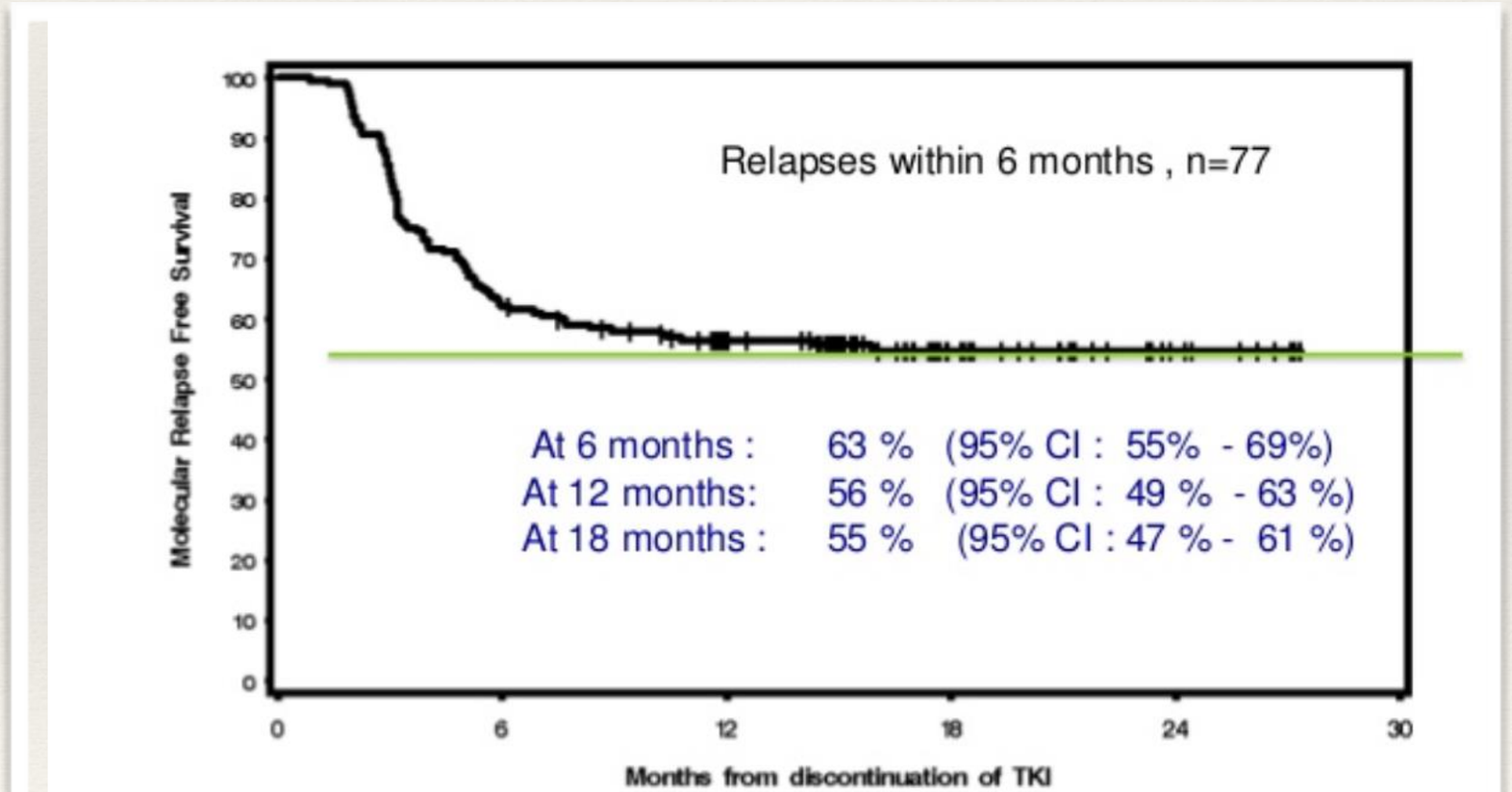
Etienne ASH 2015
Mahon et al. Lancet Oncol. 2010;11:1029-35

Necessità di una risposta molecolare profonda per mantenere la TFR

Risposta al momento dell'interruzione del TKI	Pazienti con ricaduta citogenetica o molecolare, %
CCyR	100%
MMR	100%
MMR, CCyR, MCyR	100%
CMR per ≥ 2 anni con imatinib	~30%-65%

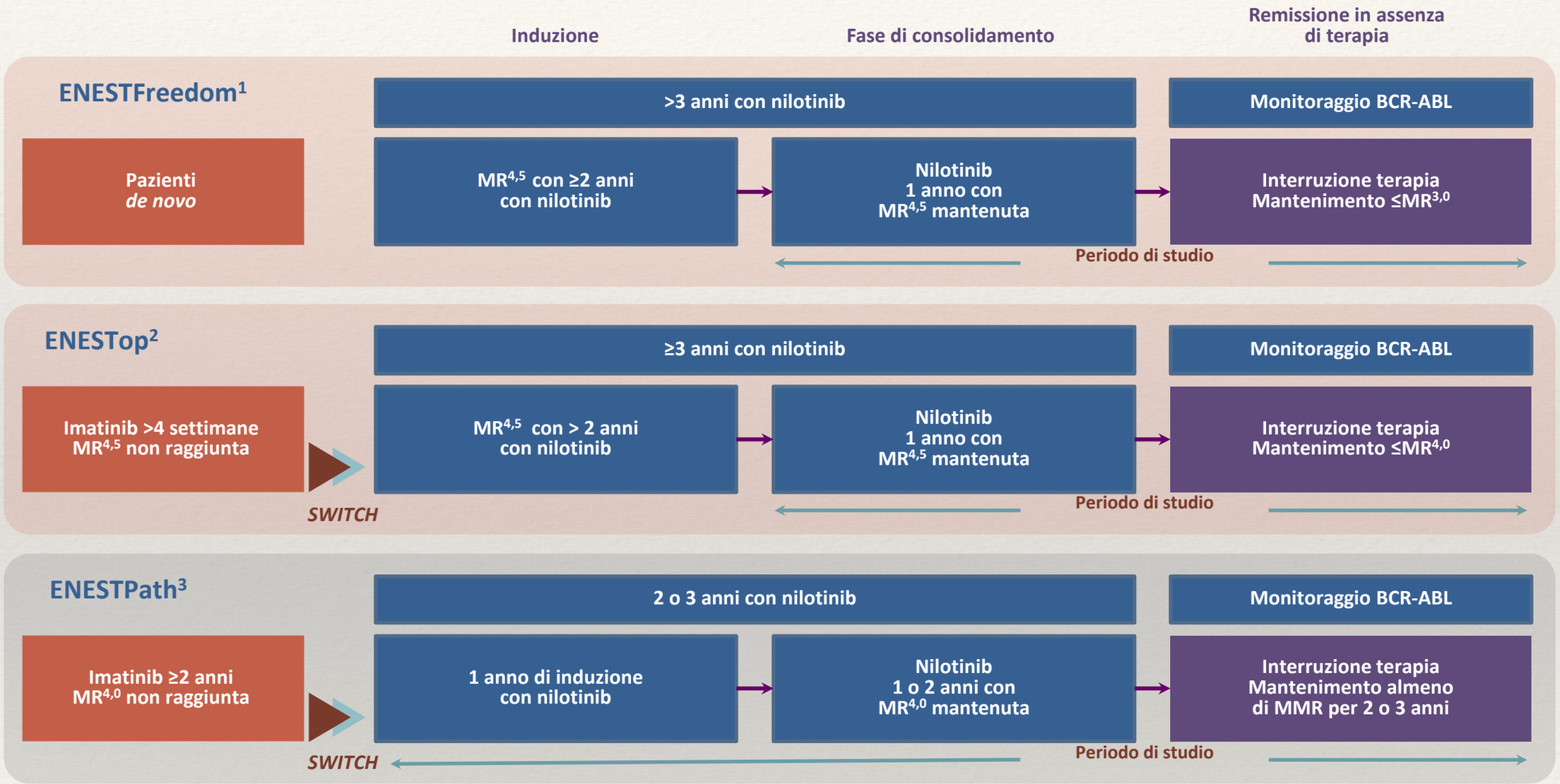
EURO-SKI

806 pazienti
Almeno tre anni di trattamento con TKI
Almeno 12 mesi di risposta molecolare profonda

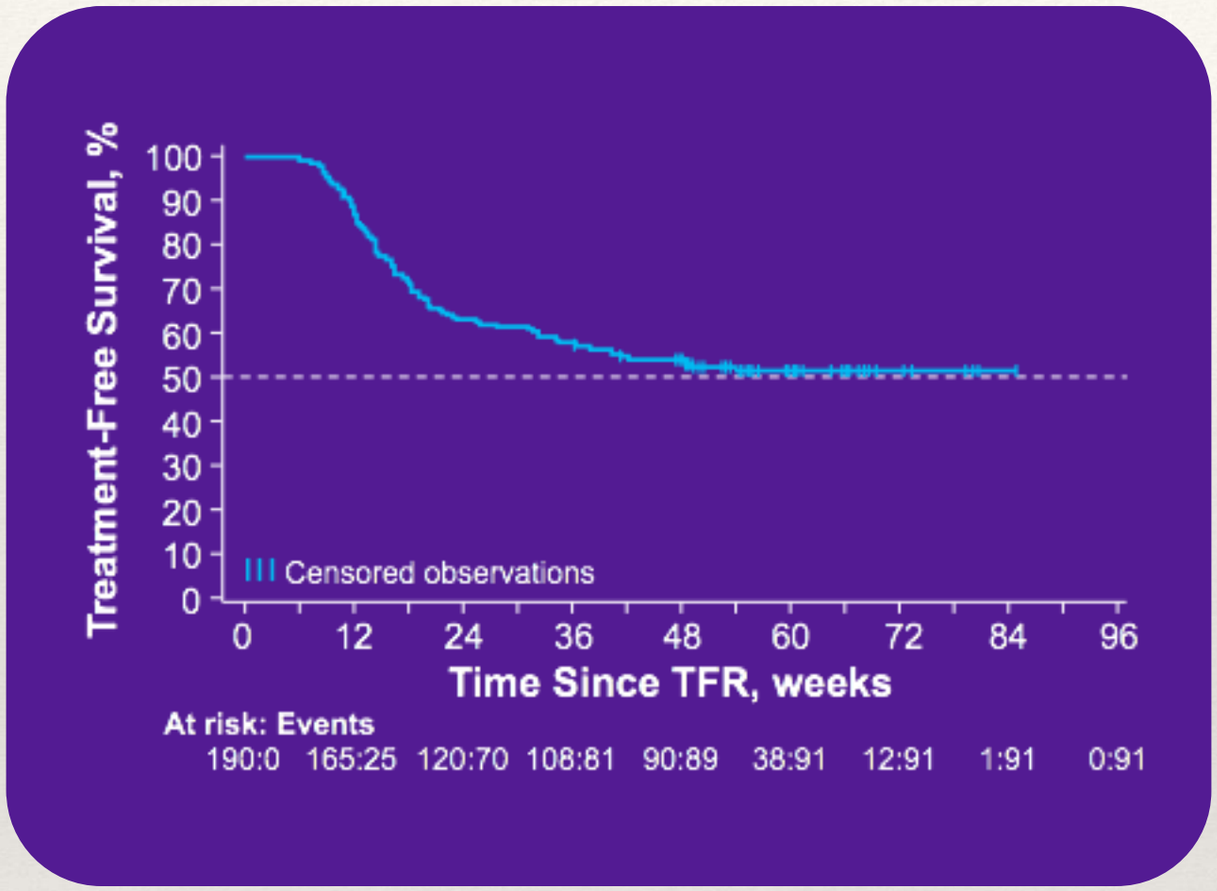


Mahon et al. ASH 2016

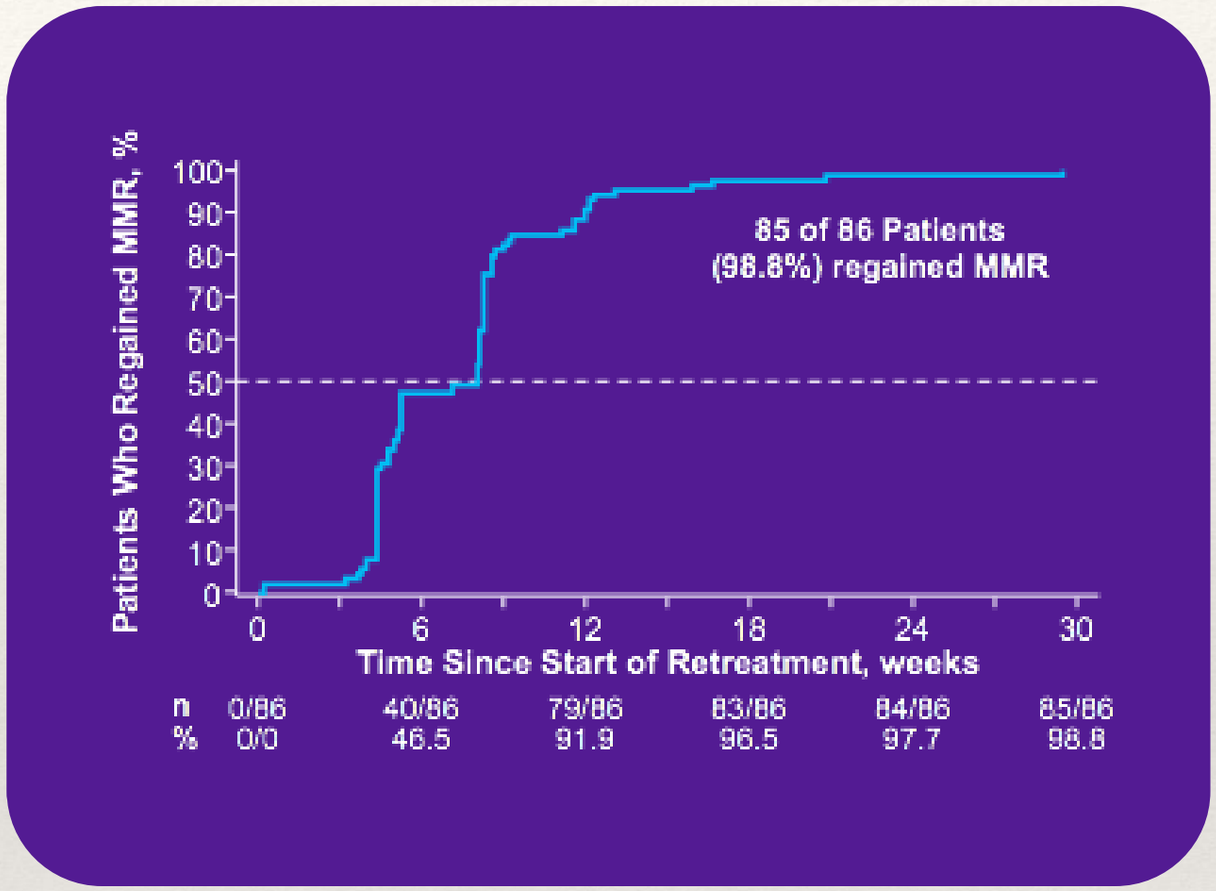
Path to cure


Induzione
Fase di consolidamento
Remissione in assenza di terapia
ENESTFreedom[1]
>3 anni con nilotinib
Monitoraggio BCR-ABL
Pazienti de novo
MR4,5 con ≥2 anni con nilotinib
Nilotinib 1 anno con MR4,5 mantenuta
Interruzione terapia Mantenimento ≤MR3,0
Periodo di studio
ENESTop[2]
≥3 anni con nilotinib
Monitoraggio BCR-ABL
Imatinib >4 settimane MR4,5 non raggiunta
MR4,5 con > 2 anni con nilotinib
Nilotinib 1 anno con MR4,5 mantenuta
Interruzione terapia Mantenimento ≤MR4,0
SWITCH
Periodo di studio
ENESTPath[3]
2 o 3 anni con nilotinib
Monitoraggio BCR-ABL
Imatinib ≥2 anni MR4,0 non raggiunta
1 anno di induzione con nilotinib
Nilotinib 1 o 2 anni con MR4,0 mantenuta
Interruzione terapia Mantenimento almeno di MMR per 2 o 3 anni
SWITCH
Periodo di studio

ENEST freedom



Il 50% circa dei pazienti rimane in TFR dopo 48 settimane

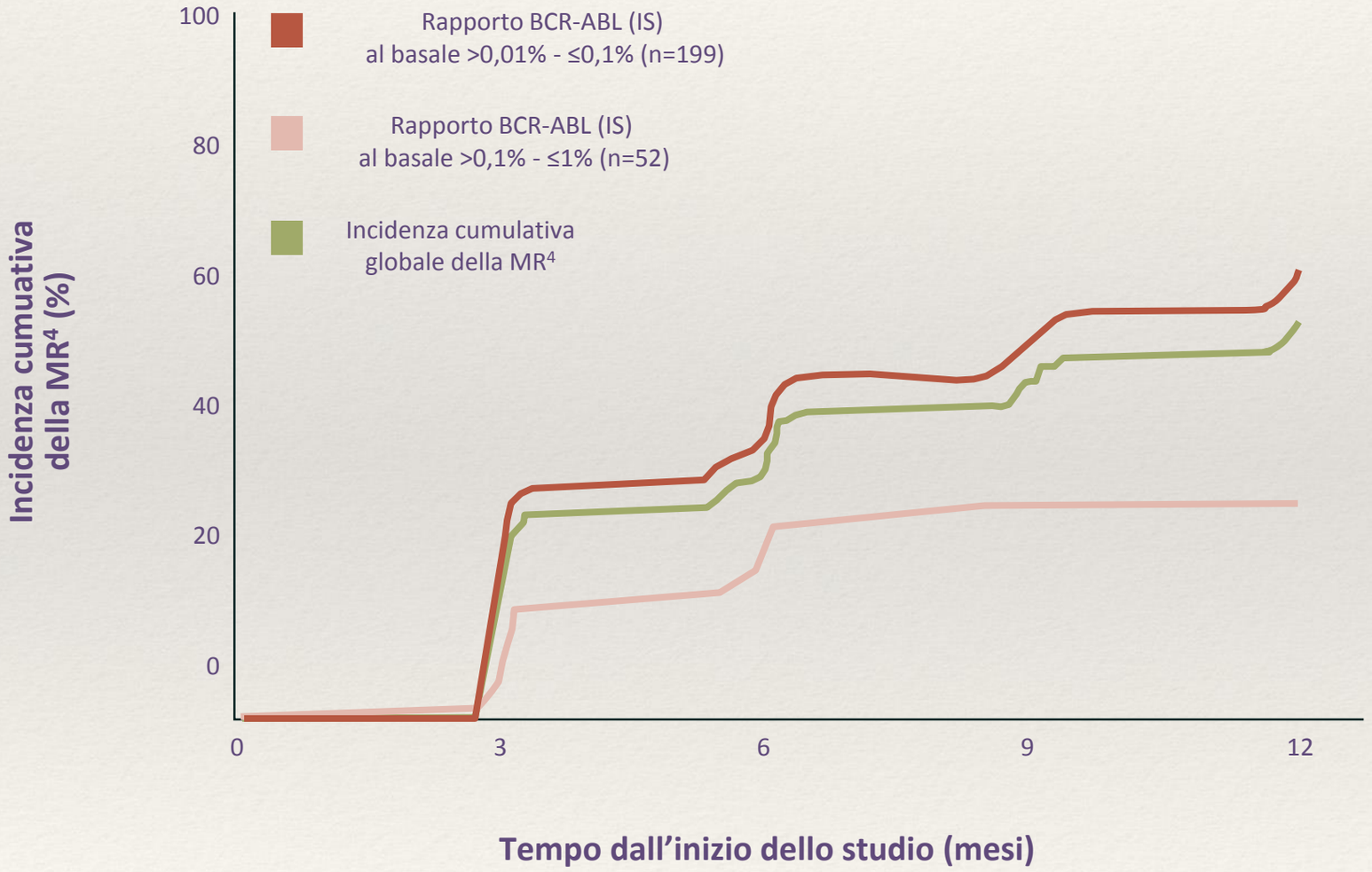


Il 98% dei pazienti recupera la MMR alla ripresa del nilotinib

Hochhaus A, et al. J Clin Oncol. 2016;34 [abstract 7001].

ENEST-path: ottimizzazione del trattamento

- Incidenza cumulativa di MR^4 a 12 mesi
(analisi *ad interim*, 300 pazienti in terapia con nilotinib 300 mg BID da ≥1 anno)



MR^4 ottenuta nel
64,8%
dei pazienti con MMR
al basale

MR^4 ottenuta nel
57,4%
della popolazione totale

MR^4 ottenuta nel
30,8%
dei pazienti senza MMR
al basale

Rea D, et al. Abstract 4040. Blood 2015; 126(23):4040

Studi di sospensione

Study	*Number*	*Treatment before discontinuation*	*Response required for discontinuation*	*Definition of relapse*	*TFR% (median follow-up time)*
Trials of imatinib discontinuation					
STIM1[24,25]	100	IFN then imatinib for ⩾3 years	CMR for ⩾2 years	Loss of MMR or ⩾1-log increase in BCR-ABL	39% (55 months)
STIM2[32]	200	Imatinib for ⩾3 years	As for STIM	Loss of MMR or ⩾1-log increase in BCR-ABL	Preliminary results 46% (95% CI 38–56) at 2 years
ALLG CML8[26,27]	40	Imatinib for ⩾3 years	UMRD ⩾2 years	Loss of MMR or confirmed loss of MR[4.5]	45% (42 months)
According to STIM[30]	80	Imatinib for ⩾3 years	As for STIM; confirmed CMR with occasional weakly positive samples were also considered eligible	Loss of MMR	64% (23 months)
EURO-SKI[33,40]	809	Imatinib, nilotinib and dasatinib	MR4 for ⩾1 year; TKI for ⩾3 years	Loss of MMR	Preliminary results 61% (95% CI 54–68) at 6 months. Trial still in progress
ISAV			able PCR (3 PCRs)	Loss of MMR	51.9% at 36 months (median FU 21 months)
DES			stable response under half standard 2 months	Loss of MMR	In progress
Trials					
STOP 2G-TKI pilot	50	Nilotinib or dasatinib	CMR for median 29 months (range 21–39)	Loss of MMR	Preliminary 61.1% (95% CI 45.6–76.6) but still in progress
ENESTFreedom[36]	175	Nilotinib front line	MR4.5 for ⩾1 year	Loss of MMR	In progress
ENESTop[36]	117	Second-line nilotinib (⩾3 years total; ⩾2 years NIL)	MR4.5 for ⩾1 year	Confirmed loss of MR4 or any loss of MMR	In progress
ENESTPath[36]	1058	Imatinib (⩾2 years) and nilotinib	MR4.5 for ⩾1 year vs MR4.5 for ⩾2 years randomized	Confirmed loss of MR4 or any loss of MMR	In progress
ENESTGoal[36]	300	Imatinib (⩾1 years) without MMR followed by nilotinib	MR4.5 for ⩾1 year	Confirmed loss of MR4 or any loss of MMR	In progress
DADI trial (dasatinib discontinuation)[35]	88 (63 discontinued)	Dasatinib consolidation for 1 year within trial	Deep molecular response, definition unclear	loss of deep molecular response at any assessment	49% (95% CI 36–61) at 6 months
DASFREE[37] dasatinib functional cure CA180-406 Study	~74	>2 years dasatinib treatment	MR4.5 for ⩾1 year	Loss of MMR	In progress
CML V (TIGER)[61] nilotinib +/− PEG-IFN	650	Nilotinib (3 years) vs Nilotinib+PEG-IFN (2 years)	MR4 for >1 year+ PEG-IFN maintenance	Loss of MMR	in progress

Abbreviations: ALLG, Australasian Leukemia & Lymphoma Group; CI, confidence interval; CML, chronic myeloid leukemia; CMR, complete molecular response; Destiny, De-escalation and stopping treatment of imatinib, nilotinib or dasatinib in CML; ENEST, nilotinib treatment-fee remission studies; EURO-SKI, Europe stops tyrosine kinase inhibitor trial; 2G-TKI, second-generation TKIs; IFN, interferon; MMR, major molecular response; MR[4], MR[4.5] molecular response level corresponding to a 4 or 4.5log reduction from the standardized baseline, respectively; PEG, polyethylene glycol; STIM, stop imatinib trial; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor; UMRD, undetectable minimal residual disease.

> 4000 pazienti

Saußele et al. Leukemia 2016; 30;1638–1647

Quali pazienti sono candidati alla TFR?

Criteria	Green	Yellow	Red
Institutional criteria met (per table 1)	Yes	-	No
Sokal score at diagnosis	Non-high	High	-
BCR-ABL transcript at diagnosis	Typical - B2A2 or B3A2 (e13a2 or e14a2)	Atypical, but can be accurately quantified	Not quantifiable
CML past history	CP only	Resistance or KD mutation	Prior AP or BC
Response to first line TKI therapy	Optimal	Warning	Failure
Duration of all TKI therapy	> 8 years	3–8 years	< 3 years
Depth of deep molecular response	MR4.5	MR4.0	Not in MR4.0
Duration of deep molecular response monitored in a standardized laboratory	> 2 years	1–2 years	< 1 year

All green lights: strong recommendation to consider TKI withdrawal

Any yellow lights: only consider TKI withdrawal in high priority circumstances (e.g. significant toxicity or planned pregnancy)

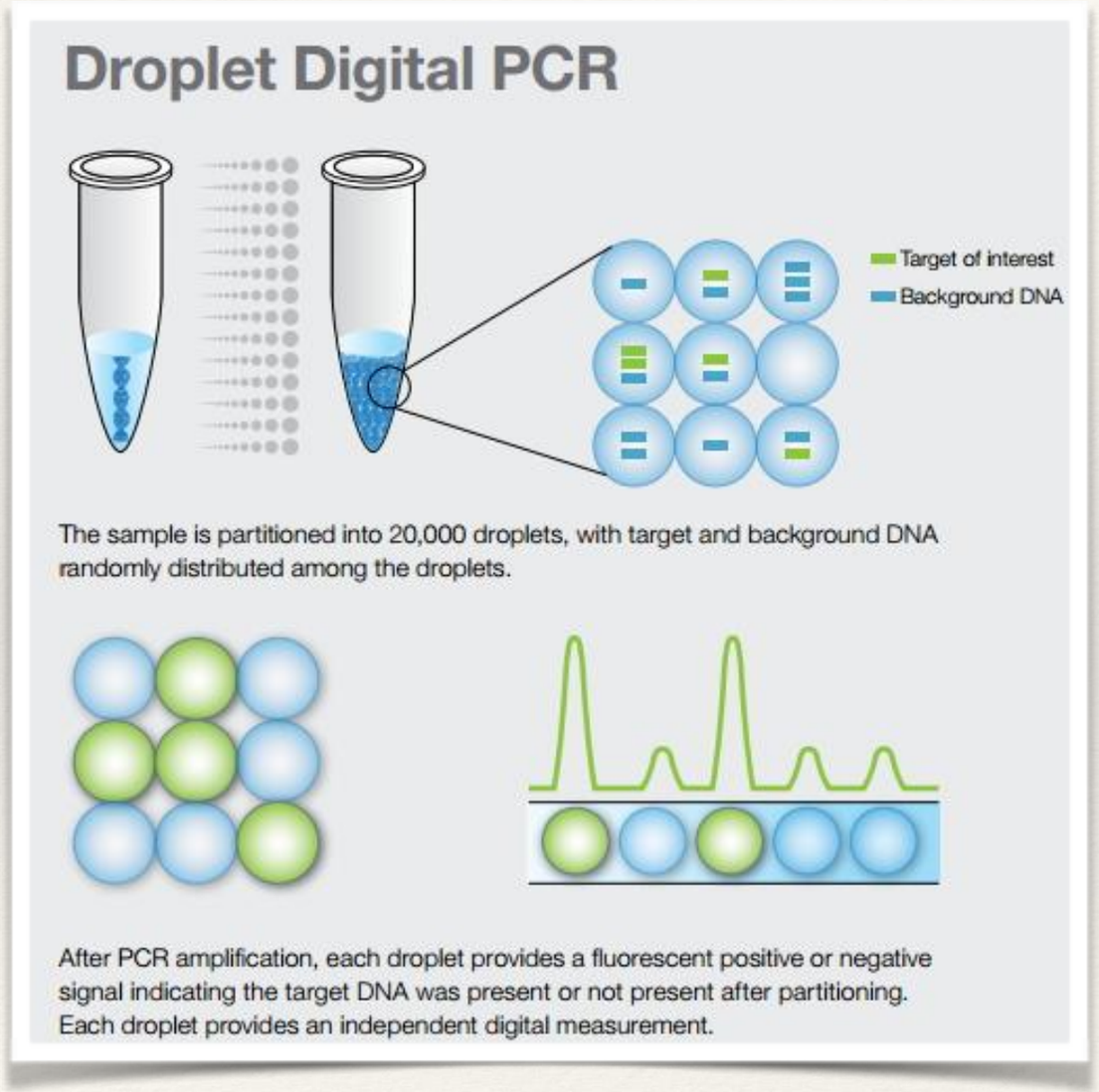
Any red lights: TKI withdrawal not recommended except in clinical trial

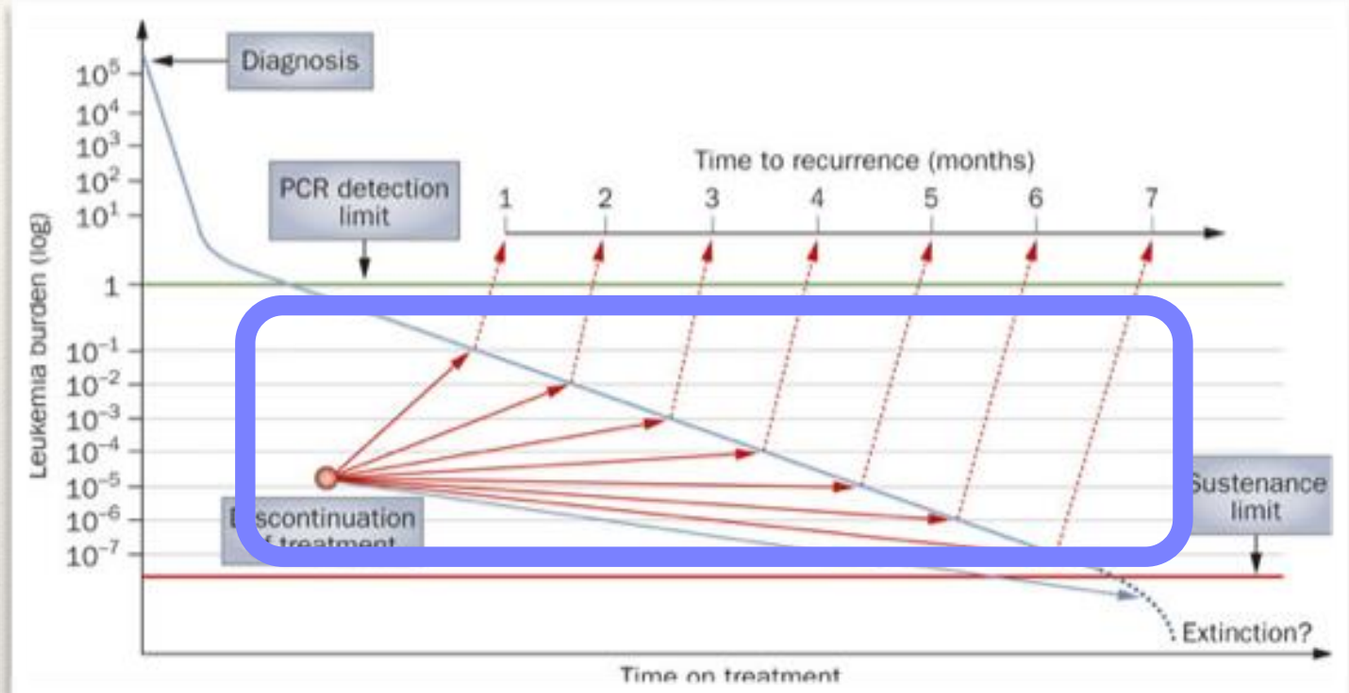
Hughes et al. Blood 2016 128:17-23

Cosa rimane da chiarire sulla sospensione del trattamento?

- Quali sono i fattori più importanti per la sospensione
- Ci sono differenze tra pretrattamento con inibitori di prima o seconda gen
- Qual è il rischio di un secondo tentativo di sospensione dopo la recidiva
- Qual è il miglior monitoraggio

Nuove metodiche all'orizzonte: Digital PCR





- **maggiore sensibilità**
- **maggiore accuratezza**

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EUTOS score predicts long-term outcome but not optimal response to imatinib in patients with chronic myeloid leukaemia

Mario Tiribelli*, Massimiliano Bonifacio, Elisabetta Calistri, Gianni Binotto, Elena Maino, Luciana Marin, Emanuele Guardalben, Antonio Branca, Filippo Gherlinzoni, Giampietro Semenzato, Rosaria Sancetta, Giovanni Pizzolo, Renato Fanin

Division of Hematology and Bone Marrow Transplantation, Azienda Ospedaliera – Universitaria di Udine, Italy

EUTOS score predicts early optimal response to imatinib according to the revised 2013 ELN recommendations

Massimiliano Bonifacio · Gianni Binotto · Elisabetta Calistri · Elena Maino · Mario Tiribelli · Gruppo Triveneto LMC

Received: 12 November 2013 / Accepted: 20 November 2013

Combination of EUTOS Score and 3-month BCR-ABL transcript level identifies a group of good-risk chronic myeloid leukemia patients with favorable response to frontline imatinib therapy

Mario Tiribelli,[1]* Gianni Binotto,[2] Elisabetta Calistri,[2] Elena Maino,[3] Luigi Scaffidi,[3] Marta Medeot,[3] Mitil Narbergis,[3] Achille Ambrosetti,[3] Gianpietro Semenzato,[4] Renato Fanin,[5] Massimiliano Bonifacio,[6] for the Gruppo Triveneto LMC

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Conflict of Interest: The authors report no potential conflicts of interest.

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LETTERS TO THE EDITOR

Imatinib-treated chronic myeloid leukemia patients with discordant response between cytogenetic and molecular tests at 3 and 6 month time-points have a reduced probability of subsequent optimal response

Massimiliano Bonifacio,[1] Gianni Binotto,[2] Elena Maino,[3] Elisabetta Calistri,[2] Luciana Marin,[4] Luigi Scaffidi,[3] Luca Frison,[1] Federico De Marchi,[1] Mauro Krampera,[1] Giampiero Semenzato,[5] Renato Fanin,[6] Achille Ambrosetti[3] and Mario Tiribelli[7] Gruppo Triveneto LMC*

*These authors contributed equally

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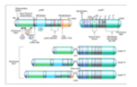
BCR-ABL Fusion Transcript b2a2 Is Associated With A Higher Risk Of Non-optimal Early Response In CP-CML Patients Treated With Standard Dose Imatinib: A Study From Gruppo Triveneto LMC.

Gianni Binotto*,[1], Mario Tiribelli[2], Massimiliano Bonifacio[3], Luca Frison[1], Mitja Narbergis[1], Federico De Marchi[2], Luigi Scaffidi[3], Marta Medeot[2], Elena Maino[4], Elisabetta Calistri[5], Angela Bonalumi[3], Mauro Krampera[3], Achille Ambrosetti[3], Renato Fanin[2], Giampietro Semenzato[1]

[1]Department of Medicine, Hematology and Clinical Immunology, Padua University School of Medicine, Padova; [2]Division of Hematology and Bone Marrow Transplantation, Department of Experimental and Clinical Medical Sciences, AOU Udine, University of Udine, Udine; [3]Department of Medicine, Section of Hematology, University of Verona, Verona; [4]Hematology Unit, Dell'Angelo Hospital, Venezia-Mestre; [5]Hematology Unit, Ca' Foncello Hospital, Treviso

Background

The diagnostic hallmark of CML is represented by the the presence of Philadelphia (Ph) chromosome, which originates from the reciprocal translocation of chromosome 9 and 22 t(9;22)(q34;q11). This genetic lesion generates a chimeric oncogene in which the BCR and ABL genes are fused. The breakpoints within the ABL gene at 9q34 occur over a large (greater than 300 kb) area at its 5' end, while the break on chromosome 22 is restricted in most patients to an area of 5.8-kb termed the M-bcr. M-bcr consists of five exons (b1–b5). Most breaks take place immediately downstream of exon 2 or 3 of the M-bcr region and result in b2a2 or b3a2 fusion transcripts (see Figure) (1).



Early molecular response is a well established predictor of outcome. LeukemiaNet CML 2013 recommendations, highlighting the importance of "time to response" concept, defined the response as optimal, warning, or failure according to the degree and the timing of hematologic, cytogenetic, and molecular results.

The clinical significance of BCR-ABL transcript type in the tyrosine kinase inhibitors (TKI) era has recently been debated (2,3). However, few data concerning the impact of different BCR-ABL transcripts on early response dynamics in chronic phase-chronic myeloid leukemia (CP-CML) patients treated with standard dose imatinib (IM) have been reported.

Aims and Methods

We investigated the probability of optimal response at early timepoints and the impact on long term outcome, according to different p210 BCR-ABL1 transcripts, in a real life population of CML-CP patients treated with standard dose front-line imatinib (400 mg daily).

93 CP-CML patients, diagnosed from 2010 to 2015 were retrospectively analyzed. The type of BCR-ABL1 transcript was determined by multiplex RT-PCR at diagnosis. Complete cytogenetic response (CCyR) was defined as 0% Ph+ metaphases; major molecular response (MMR) was defined as BCR-ABL ≤0.1%IS. Molecular monitoring was performed with quantitative RT-PCR and results were expressed in International Scale (IS) values. Optimal, warning and failure categories were analyzed according to the 2013 ELN recommendations.

Time to imatinib failure (TTF) was measured from the start of imatinib to the date of any of the following events: progression to accelerated or blastic phase, death for any cause at any time, primary or secondary hematologic, cytogenetic or molecular resistance leading to imatinib discontinuation. Progression-free survival (PFS) was calculated from the start of IM to the date of accelerated or blast phase, or death. Overall survival (OS) was calculated from the start of IM to death or date of last follow-up.

Survival probabilities were estimated by the Kaplan-Meier method and compared by log rank test; differences among variables were evaluated by the Fisher's exact test or by Cochran–Mantel–Haenszel test.

Results

Patients with b3a2, b2a2, b3a2/b2a2 BCR-ABL transcript were 44.1%, 36.6% and 19.4%, respectively. The cohorts were comparable for age, sex and risk score (both Sokal and Eutos) (***Table 1***). Forty-three patients (46.2%) switched to second generation TKI (2GTKI). 24 (55.8%) due to primary or acquired cytogenetic or molecular resistance, 19 (44.2%) for intolerance.

Table 1. Baseline patients characteristics

	21/13	22/19	12/6
Age median, years (range)	60.6 (32-85)	62 (21-84)	63 (16-72)
	47.5 (17-68)	43 (13-70)	48 (13-70)
Sokal score, n (%)			
Low	14 (41.2)	16 (39.0)	8 (44.4)
Intermediate	16 (47.1)	20 (48.8)	8 (44.4)
High	4 (11.8)	5 (12.2)	1 (5.6)
			1 (5.6)

Rates of optimal vs non optimal responses at 3 months were different between b3a2 vs b2a2 vs coexpressed transcript groups (75.8% vs 62.2% vs 100% respectively, p=0.018). Interestingly, all failures at 3 months were observed in the b2a2 group (***Table 2***). At 6 months, optimal responses were documented in 80% vs 48.3% vs 78.6% of b3a2, b2a2 and b3a2/b2a2 group, respectively (p=0.027); 80% of warnings and 75% of failures were associated to b2a2 transcript.

At 12 months timepoint, major molecular response (MMR) rate was significantly different between transcripts (81.8% vs 47.8% vs 78.6% respectively, p=0.03). 52% of treatment changes within 12 months, either for resistance or intolerance, were observed in the b2a2 group.

Table 2. Rate of optimal and non-optimal responses at 3, 6 and 12 months according to transcript type.

		b3a2	b2a2	b3a2/b2a2	
3 months (Available pts: 87)	Optimal (%)	75.8	62.2	100	
	Non optimal				p=0.018
	- Warning (%)	20.2	33.4	0	
	- Failure (%)	4	4.4	0	
6 months (Available pts: 64)	Optimal (%)	80	48.3	78.6	
	Non optimal				p=0.027
	- Warning (%)	12	31	21.4	
	- Failure (%)	8	20.7	0	
12 months (Available pts: 74)	Optimal (%)	81.8	47.8	78.6	
	Non optimal				p=0.03
	- Warning (%)	9.1	30.4	7.1	
	- Failure (%)	9.1	21.7	14.3	

*Patients switching to 2G-TKI were excluded from the subsequent timepoint analysis

Differences in early response did not translate into inferior cumulative incidence of complete cytogenetic response (CCyR) (93.9% vs 82.1% vs 83.3% respectively, p=0.30) or different time to CCyR achievement.

Patients with b3a2 and b3a2/b2a2 transcript had comparable rates of cumulative MMR (81.8% and 88.9%, respectively), superior to b2a2 patients (66.7%, p=0.12) with a significantly faster time to MMR achievement, either on IM treatment or with sequential IM>2GTKI approach (***Figure 1A***). Notably, among optimal responders at 3 months, MMR was obtained significantly later by patients with b2a2 transcript (***Figure 1B***).

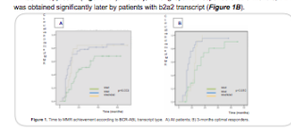


Figure 1. Time to MMR achievement according to BCR-ABL transcript type. A) All patients; B) 3-months optimal responders.

5 years probabilities of treatment failure for patients expressing b3a2, b2a2 and both transcripts were 44.1%, 51.2%, 33.3%, respectively (p=0.441); median time to imatinib failure was not statistically different in the three types of transcripts (***Figure 2A***).

Long term outcomes (PFS, OS) were not affected by transcript type, although this observation may have been influenced by the relatively short follow-up. (***Figure 2B and C***).

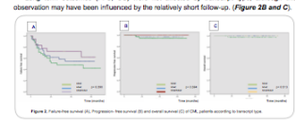


Figure 2. Failure-free survival (A), Progression- free survival (B) and overall survival (C) of CML patients according to transcript type.

Conclusions

This retrospective analysis suggest a different kinetics of early optimal response achievement based on transcript type, with inferior rates in patients expressing b2a2. However, after a median follow-up of almost 4 years, this difference did not translate into unfavourable clinical outcome. Longer time to MMR among optimal responders presenting with b2a2 could partially account for the negative impact of this transcript type on stable deep molecular response, previously observed by our group (4).

References

Disclosures: the Authors declare no competing interests

Presented at the 21st Congress of the European Hematology Association, Copenhagen; June 9-12 2016, Abstract Code: EHA-E1099
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Dynamics Of Response And Impact Of Sokal Score In 3 Months Molecular "Warning" CML Patients treated with imatinib. A Retrospective Study From Gruppo Triveneto LMC.

Gianni Binotto*[1], Mario Tiribelli[2], Massimiliano Bonifacio[3], Elena Maino[4], Elisabetta Calistri[5], Antonio Branca[1], Federico De Marchi[2], Roberta Bortolaso[6], Filippo Gherlinzoni[4], Giovanni Pizzolo[7], Renato Fanin[2] and Giampietro Semenzato[1].

[1]Department of Medicine, Hematology and Clinical Immunology, University of Padova, Padova; [2]Division of Hematology and Bone Marrow Transplantation, Department of Experimental and Clinical Medical Sciences, AOU Udine, University of Udine, Udine; [3]Department of Medicine, Section of Hematology, University of Verona, Verona; [4]Hematology Unit, Dell'Angelo Hospital, Venezia-Mestre; [5]Hematology Unit, Ca' Foncello Hospital, Treviso; [6]Immunology and Molecular Oncology Unit, Istituto Oncologico Veneto, IRCCS, Padova, Italy.

Background

Response to TKI is considered the strongest predictor of long-term outcome in CML patients. Indeed, effective treatment overcomes the negative impact of most prognostic factors, including baseline risk scores (Sokal, Hasford and EUTOS). Early molecular response is a well established predictor of outcome, as a BCR-ABL1 transcript level higher than 10%IS was reported to be associated with inferior overall survival and progression-free survival. LeukemiaNet CML 2013 recommendations, highlighting the importance of "time to response" concept, defined the response as optimal, warning, or failure according to the degree and the timing of hematologic, cytogenetic, and molecular results. "Warning" category represents a "grey zone" where it is not yet clear the best therapeutic strategy to be adopted.

2013 ELN recommendations *

	Optimal	Warning	Failure
3 months	BCR-ABL ≤10% and/or Ph+ ≤35%	BCR-ABL >10% and/or Ph+ 36-95%	Non CHR and/or Ph+ >95%
6 months	BCR-ABL >1% and/or Ph+ 1-35%	BCR-ABL >10% and/or Ph+ 1-35%	BCR-ABL >10% and/or Ph+ >35%
12 months	BCR-ABL ≤0.1%	BCR-ABL 0.1-1%	BCR-ABL >1% and/or Ph+ >0%

* Baccarani M et al. Blood 2013;122:872-884

Aims and Methods

We investigated the response dynamics of 3 months molecular "warning" CML patients at 6 and 12 months timepoints; secondly, we sought to evaluate the impact of Sokal score in the context of this cluster.

A total of 51 patients with BCR-ABL levels >10% at 3 months were identified for the analysis from a cohort of 350 consecutive CML patients, treated with front-line standard dose imatinib (400 mg daily) . "Optimal", "warning" and "failure" responses were stated according to ELN2013 recommendations. Complete cytogenetic response (CCyR) was defined as 0% Ph+ metaphases; major molecular response (MMR) was defined as BCR-ABL ≤0.1%IS. TTF was measured from the start of imatinib to the date of any of the following events: progression to accelerated or blastic phase, death for any cause at any time, primary or secondary hematologic, cytogenetic or molecular resistance leading to imatinib discontinuation. PFS was measured from the start of imatinib to the date of progression to accelerated or blastic phase or death for any cause at any time. Survival probabilities were estimated by the Kaplan-Meier method and compared by log rank test; differences among variables were evaluated by the Fisher's exact test or by Cochran–Mantel–Haenszel test.

Table 1. Baseline characteristics

M/F	33/18
Age median, years (range)	56 (25-81)
Median follow-up, months (range)	45.3 (7-110)
Sokal score, n (%):	
- Low	11 (21.6)
- Intermediate	24 (47.1)
- High	16 (31.3)

Results

The median age of patients was 56 years (range 25–81), with 33 males and 18 females. The median follow-up was 45.3 months (range 7–110). The distribution of patients according to the Sokal score was: 11 (21.6%) in the low risk, 24 (47.1%) in the intermediate and 16 (31.4%) in the high risk group, respectively (***Table 1***). 3 months molecular "warning" patients represented 13.7%, 29.2% and 47% of the original low, intermediate and high risk Sokal Triveneto database (only patients with evaluable tests were included) (***Figure 1***).

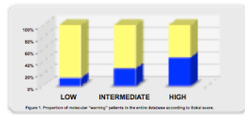

Figure 1. Proportion of molecular "warning" patients in the entire database according to Sokal score.

At 6 months, only 3 of 40 evaluable patients, 1 in each group (11.1%, 5% and 9% respectively), improved their 3 months molecular response, achieving an optimal response. 20 failures, defined as more than 10%IS BCR-ABL transcript level, were recorded (1, 11 and 8 in low, intermediate and high risk group respectively, P=0.008 comparing low vs other risk groups) (***Figure 2***).

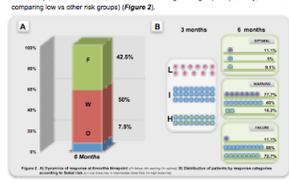

Figure 2. A) Dynamics of response at 6 months timepoint (3% failure, 9% warning, 88% optimal). B) Distribution of patients by response categories according to Sokal risk (Low, Int, High).

At 12 months, 21 of 35 evaluable patients were considered failures (7 new events occurred between 6 and 12 months timepoints); only 1 patient gained an optimal response. No patients failing the 6 month response timepoint improved their response at 12 months, probably because most of them were treated according to ELN2009 recommendations (***Figure 3***).

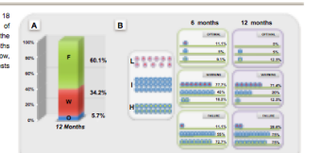

Figure 3. A) Dynamics of response at 12 months timepoint (4% failure, 34% warning, 61% optimal). B) Distribution of patients by response categories according to Sokal risk (Low, Int, High).

27.2%, 50% and 50% of low, intermediate and high Sokal score patients failed to achieve a CCyR at any time (P=0.047), while 72.7%, 45.8% and 31.3% of patients obtained a MMR (P=0.104), respectively.

Imatinib discontinuation rate, albeit remarkable in all Sokal groups, was not significantly different (66.7% vs 78.3% vs 93.8% respectively, P=0.22), as well as PFS (P=0.349), TTF (P=0.321) and OS (P=0.812) (***Figure 4***). 9.1%, 12.5% and 25% of low, intermediate and high Sokal risk patients progressed to AP/BC phase, respectively.

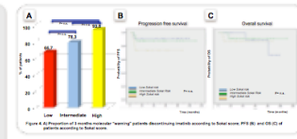

Figure 4. A) Proportion of 3 months molecular "warning" patients discontinuing imatinib according to Sokal score. PFS (B) and OS (C) of patients according to Sokal score.

Conclusions

These data suggest that although non-low Sokal score CML patients may experience a higher probability of early failure, long term outcomes of molecular "warning" patients seem not to be significantly influenced by Sokal risk. Therefore, 3–months BCR-ABL transcript level appears to overcome not only the negative, but also the positive prognostic impact of low Sokal score. These observations warrant further confirmation in larger studies.

Disclosures: the Authors declare no competing interests

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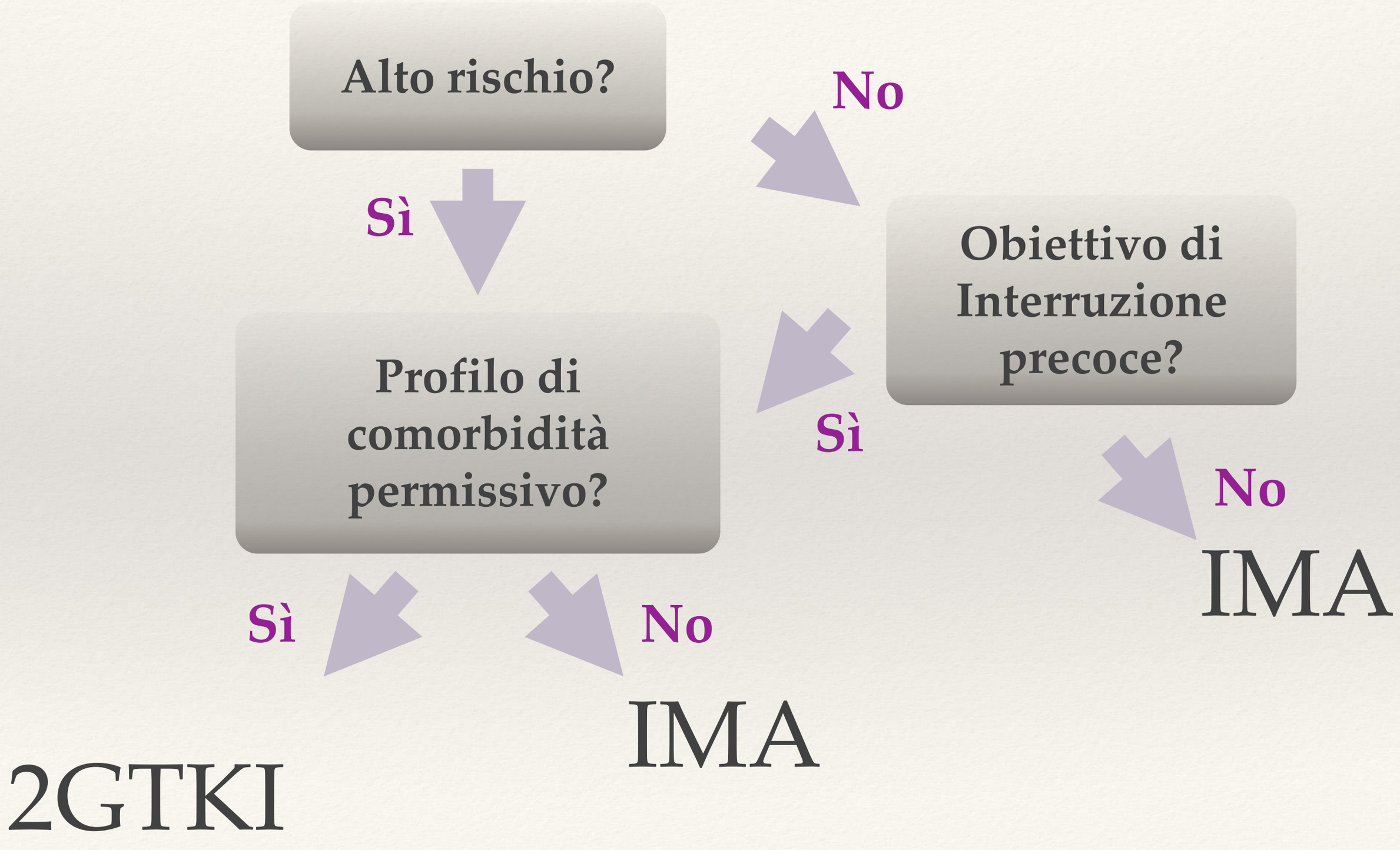
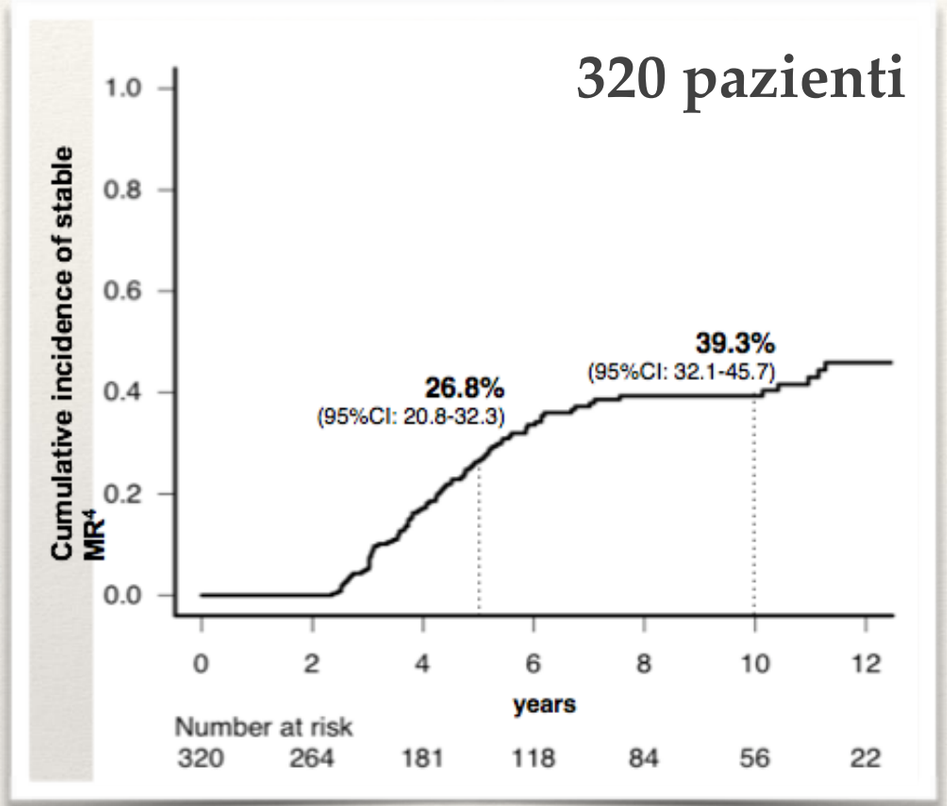
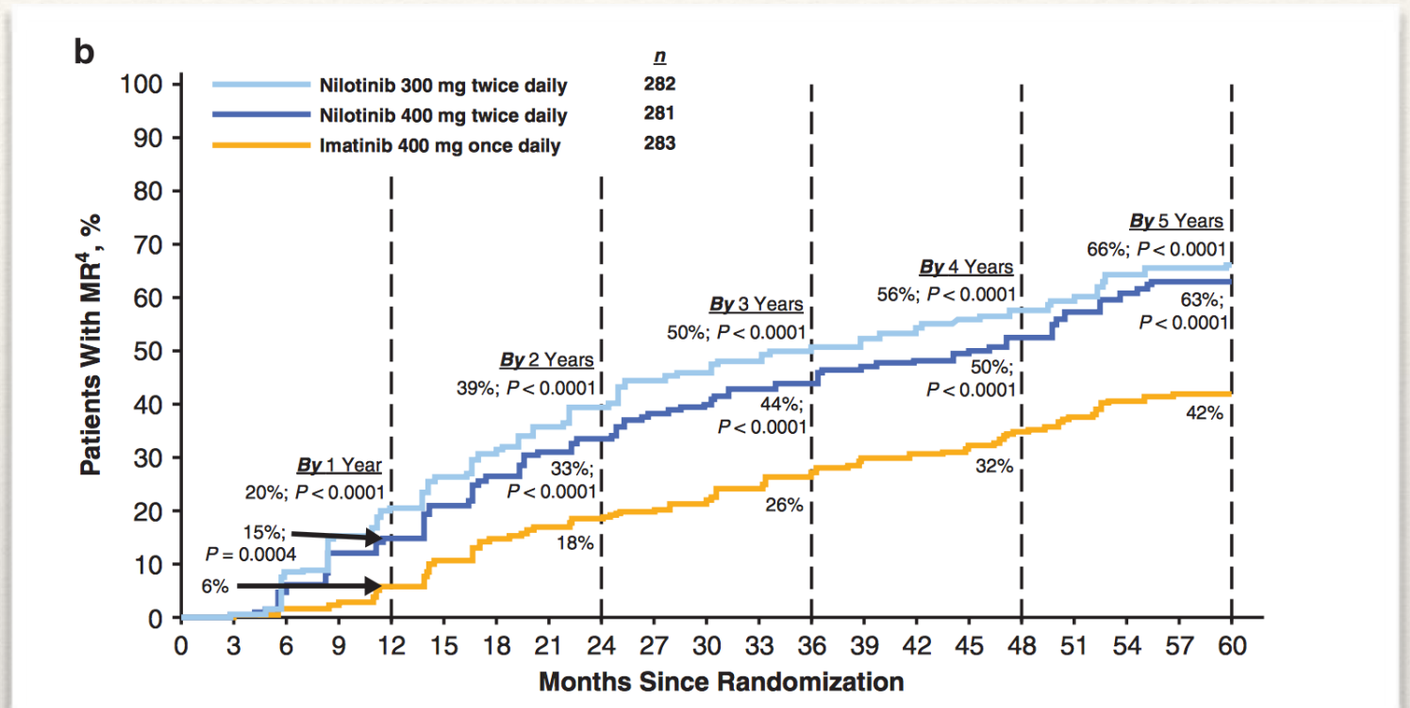


Per chi non può sospendere?



Gruppo Triveneto LMC



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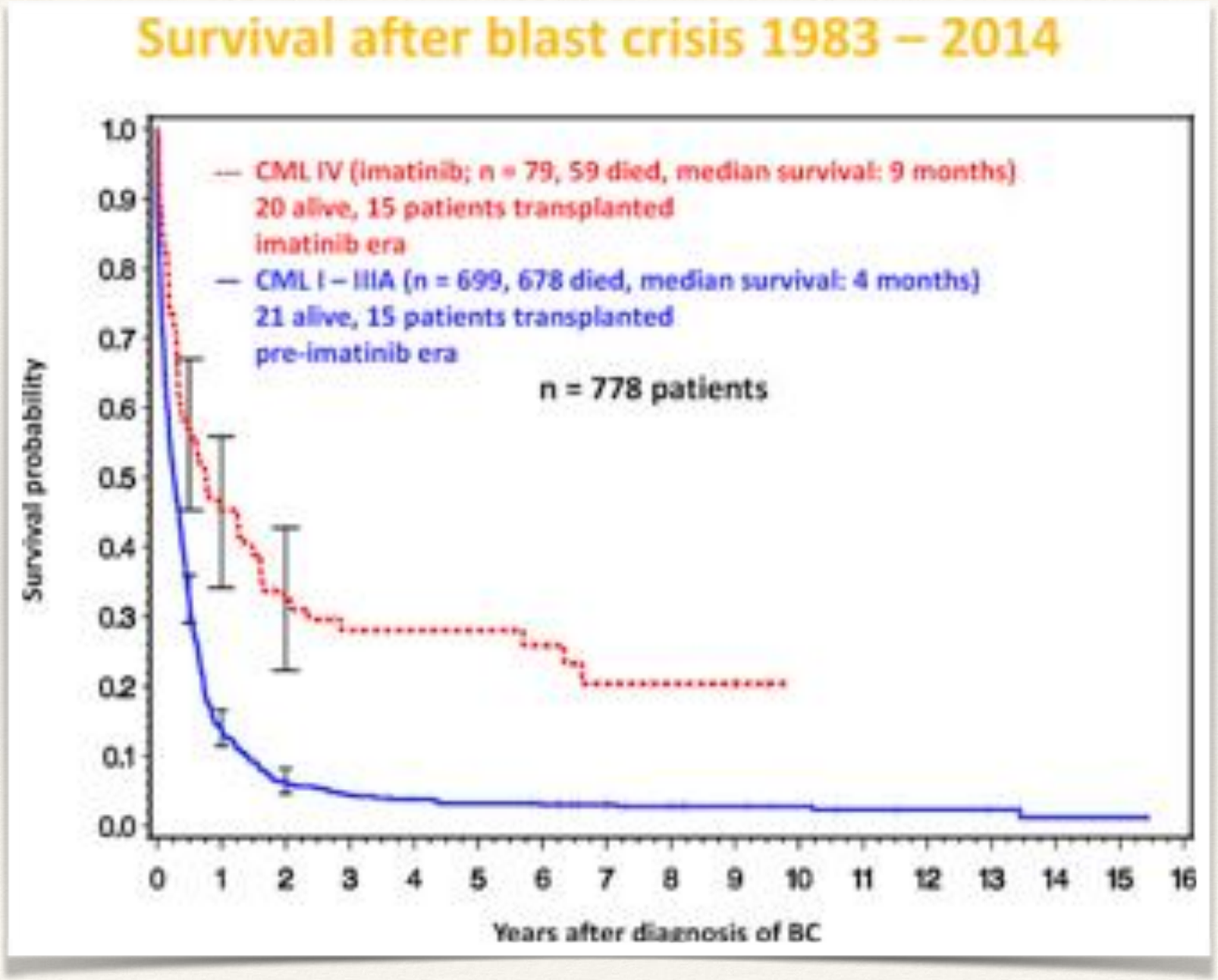

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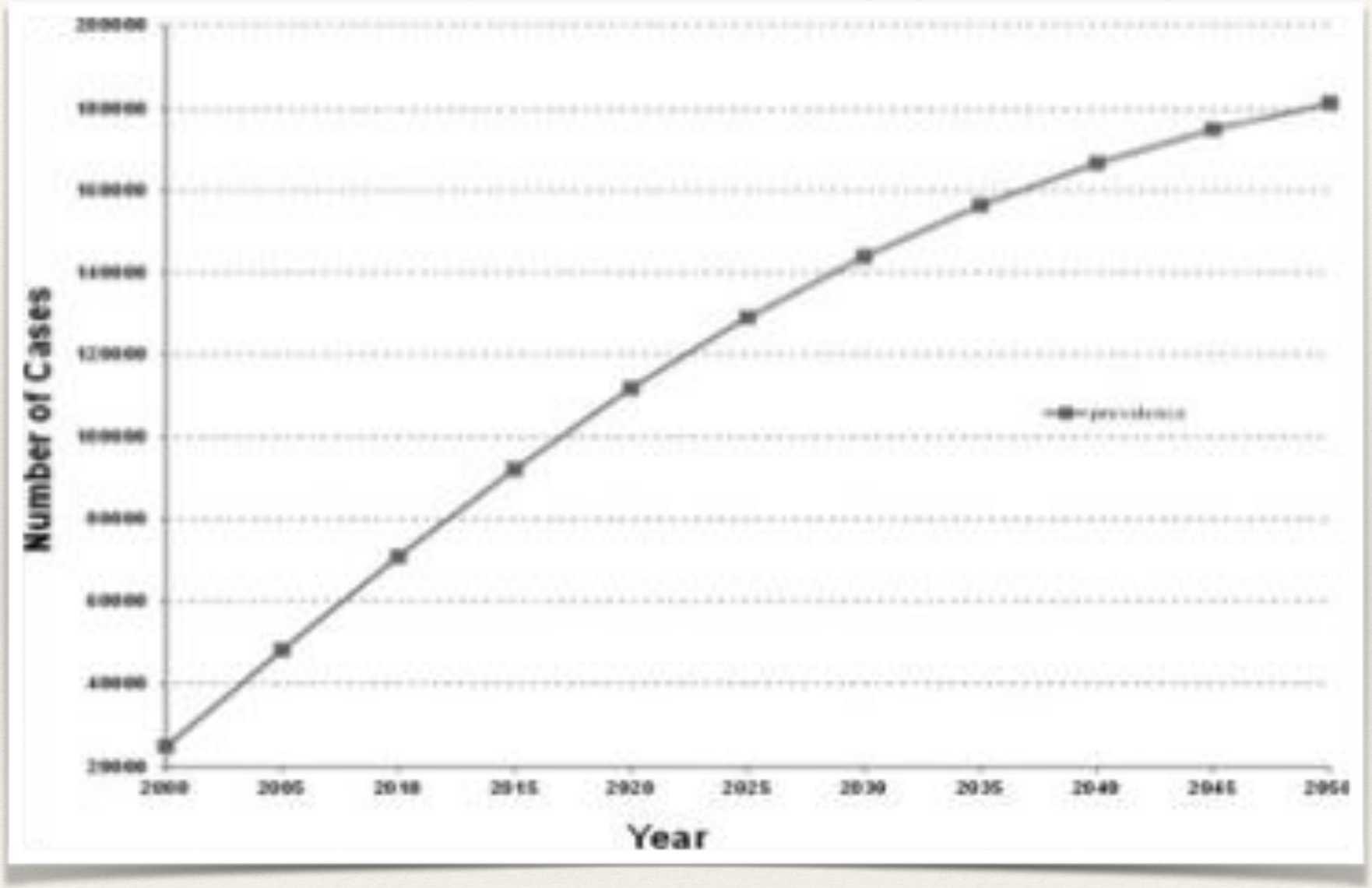
Un dato su cui riflettere....



Il plateau della prevalenza è previsto verso il 2050 (35x incidenza)

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