

I BIOMARCATORI IN ONCOEMATOLOGIA

*TOWARDS AN ALWAYS MORE
BIOLOGICALLY-DRIVEN MANAGEMENT*

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Roma, 17 Maggio 2017



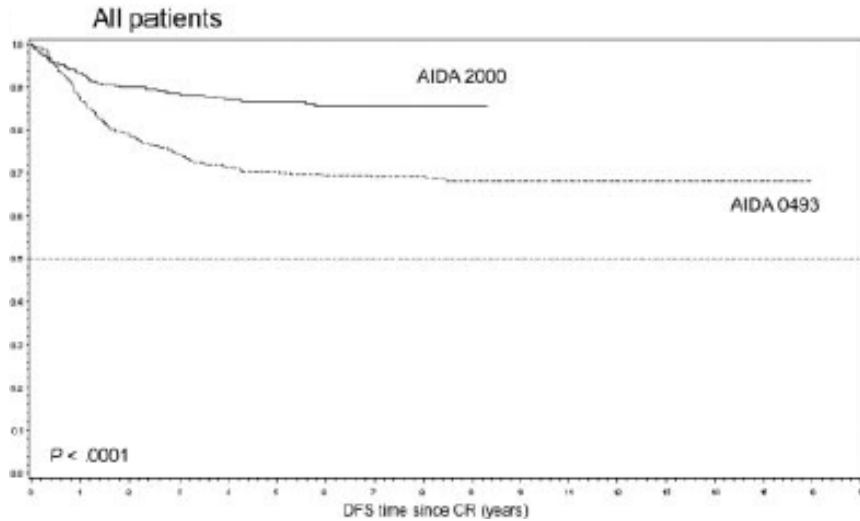
CHANGES OVER TIME IN THE MANAGEMENT OF HEMATOLOGIC DISORDERS

- Diagnosis, dd & prognosis
- Biologically-based risk stratification
- MRD monitoring & therapeutic implications
- Transplant approaches and utilizations
- Definition of response/remission
- Targeted therapies
- Growing use of mechanism-based drugs
- Algorithms of treatment (or non-treatment)
- Progressive use of chemo-free strategies
- Control of the disease vs eradication
- Role of maintenance
- Life expectancy
- Management of 'elderly' patients

HEMATOLOGIC MALIGNANCIES. EXAMPLES OF RADICAL CHANGES IN MANAGEMENT

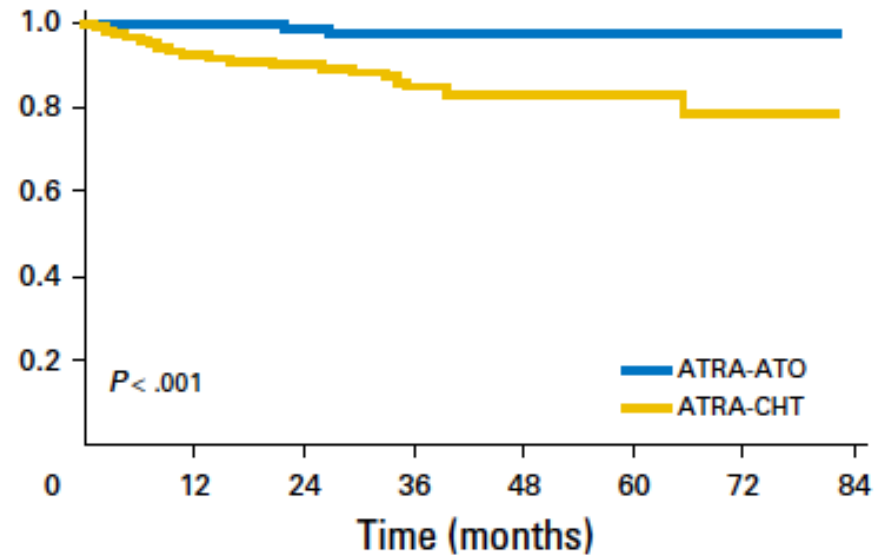
- ALL in childhood (and adolescents/young adults)
- Burkitt ALL (L3)
- APL  from *ATRA* (1st example of targeted therapy) to chemo-free strategies
- Hairy cell leukemia  *IFN, CDA, DCF,...*
- CML  *TK inhibitors (1st, 2nd, 3rd generation)*
- Ph+ ALL  *TK inhibitors (1st, 2nd, 3rd generation)*
- Hodgkin disease
- NHL-CLL-MM  *Chemo-immunotherapy, new drugs*
- Progressive clinical use of MoAb
- Progressive personalization of treatment based on MRD monitoring (APL, ALL, CML, CLL, NHL, MM..)

APL. DFS In ATRA+CHT vs ATO+ATRA ERA



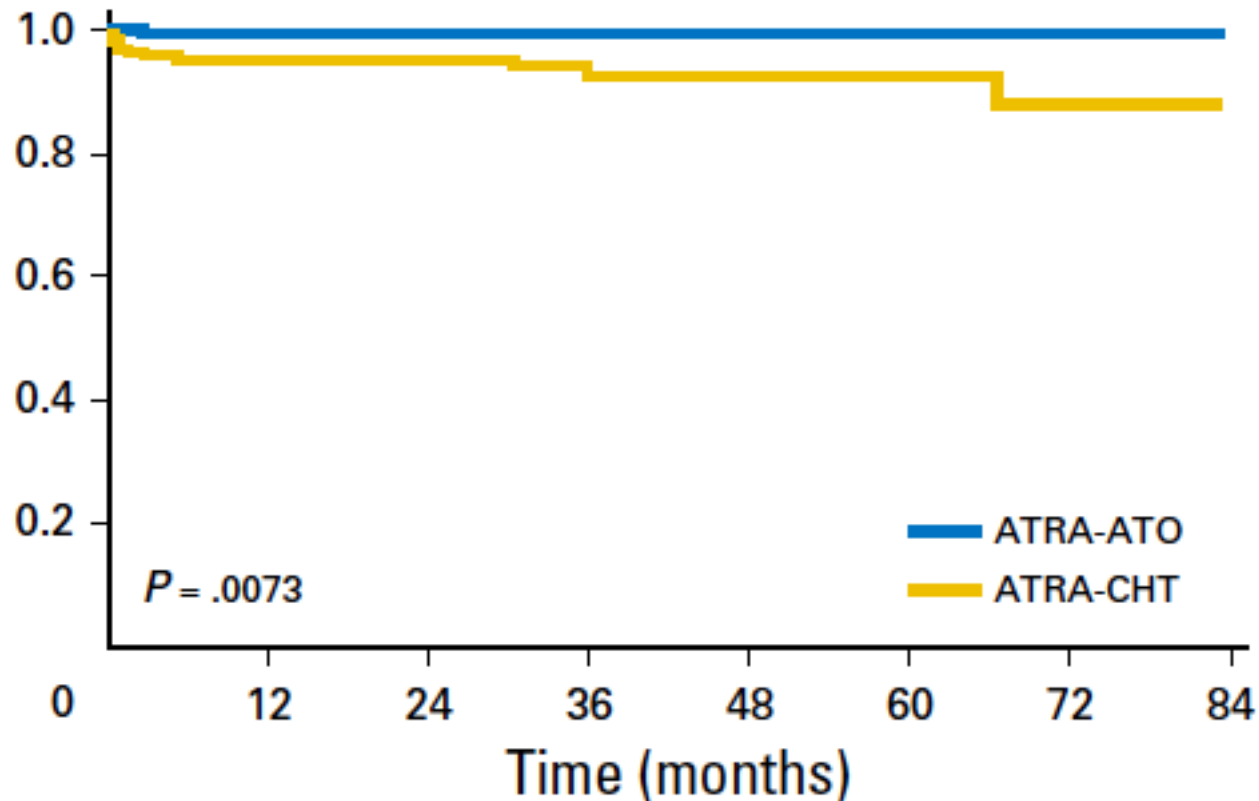
← AIDA trials (ATRA+CHT)

APL 0406 trial (ATRA+ATO) →

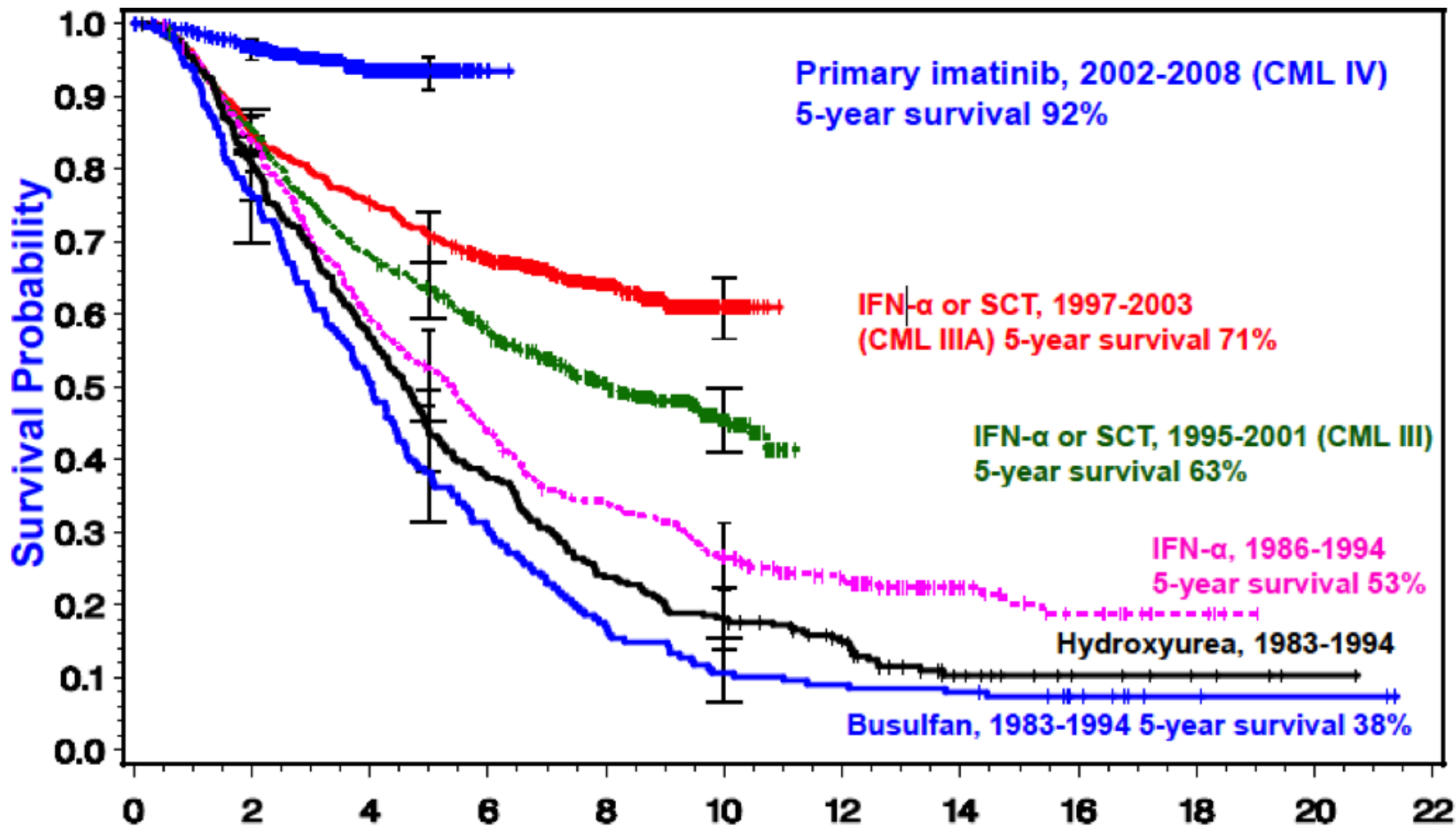


APL. OS in the ATO + ATRA Era

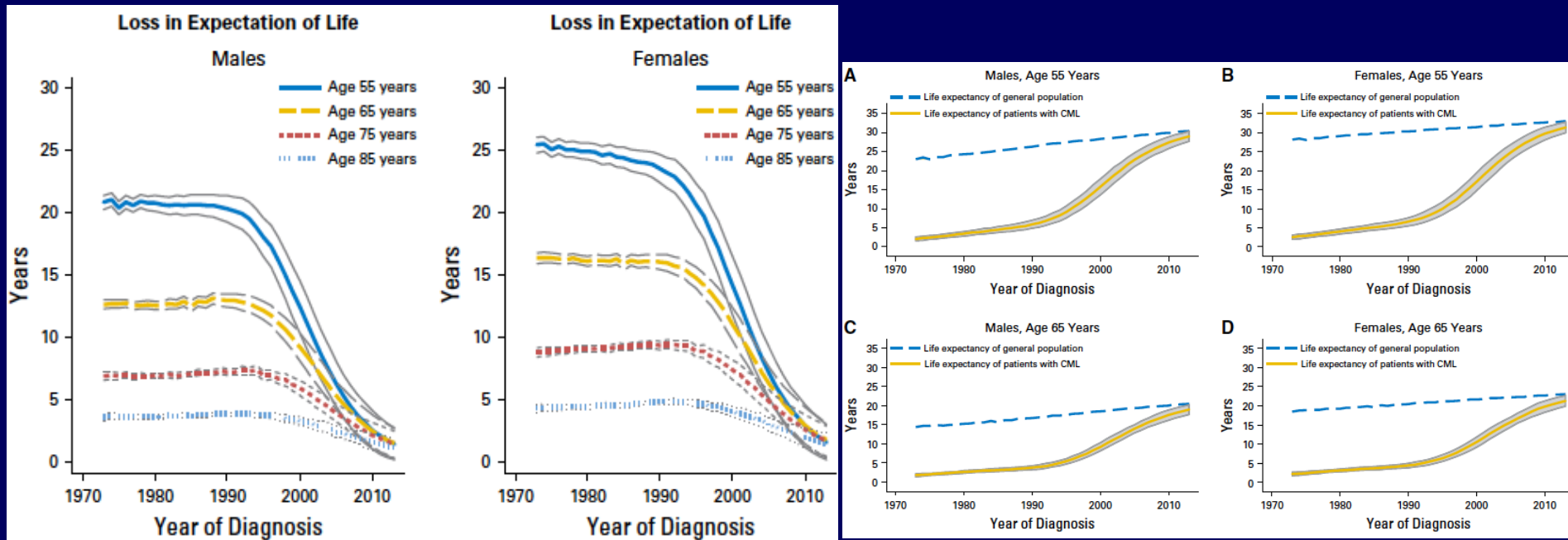
APL 0406 trial (ATRA+ATO)



CML. OS after introduction of TKIs

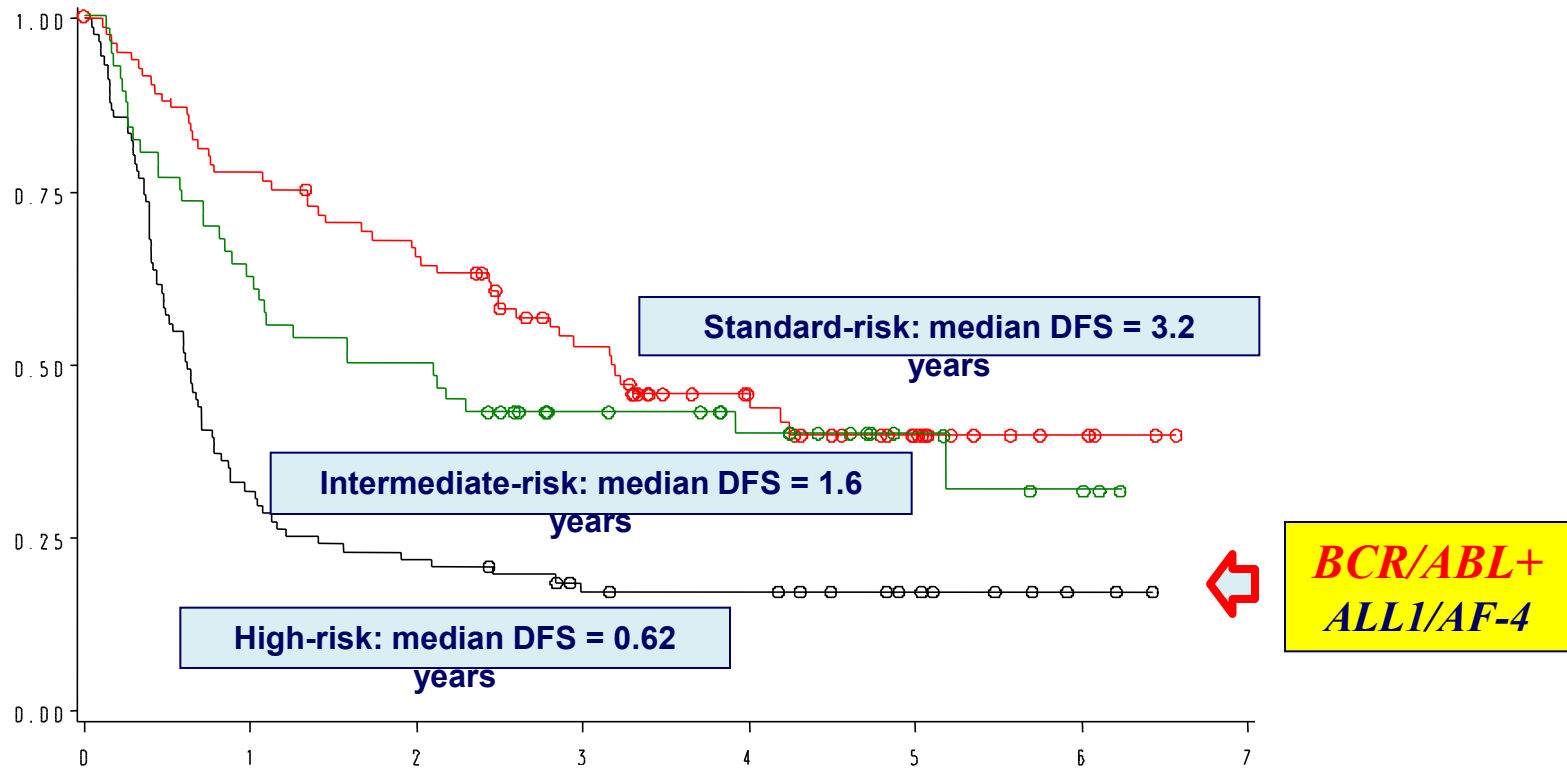


CML life expectancy approaches that of general population



- 4 subset of pts stratified for age: 55, 65, 75, 85 years (2.263 pts)
- Median life improvement reach a peak in 2013 and become similar to that of general population, regardless of sex
- A man of 55 years diagnosed in 1980 had a median life expectancy of 3.5 years, while in 2010 there is a median life expectancy of 27.3 years.

Ph+ ALL. Pre-TKI Era - DFS According to Cytogenetic-Molecular Risk Groups



Standard: 85 events 47
Intermediate: 56 events 34
High: 91 events 75

Ph+ ALL. THE GIMEMA STRATEGY

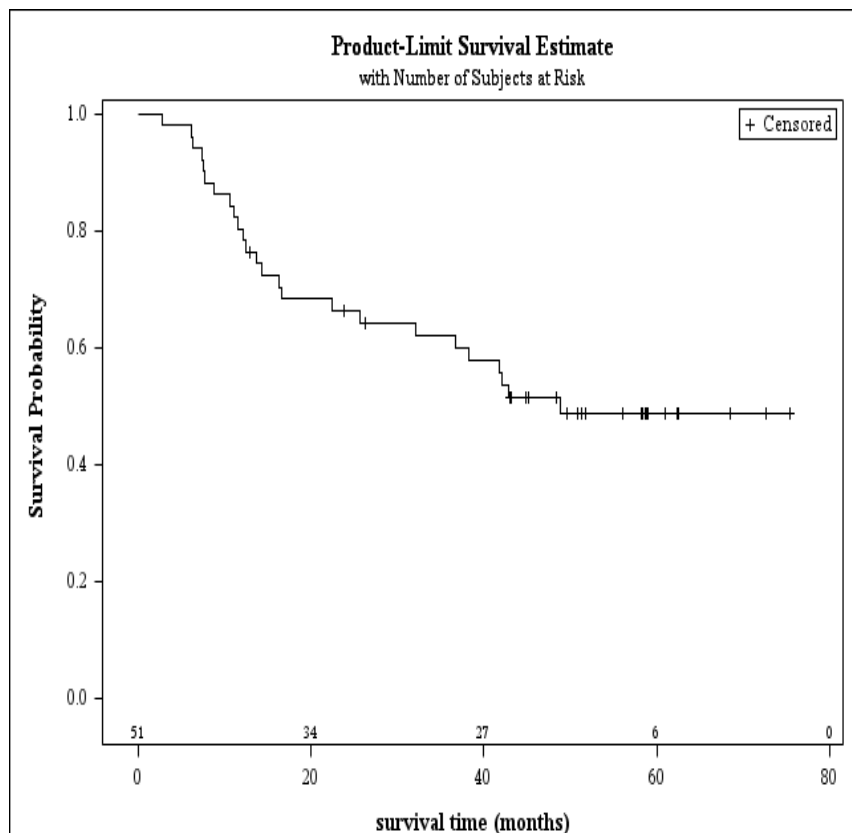
NO SYSTEMIC CHEMO IN INDUCTION

- **LAL 0201B** >60 yrs: Imatinib + PDN: CHR 100% ➡ *Vignetti M et al Blood 2007;109:3676-8*
- **LAL1205** 18 yrs: Dasatinib + PDN: CHR 100% ➡ *Foà R et al ASH, EHA & Blood 2011;15:118:6521-8*
- **LAL 0904 3rd amendment** 16-60 yrs: Imatinib followed by chemo (HAM) ± transplant ➡ *Chiaretti S et al, EHA 2013; Vitale A et al submitted*
- **LAL 1408** >60 yrs: Nilotinib-Imatinib + PDN ➡ *Martinelli G et al, ASCO 2014*
- **LAL 1509** 18-60 yrs: Total Therapy Strategy, Dasatinib ... ➡ *Chiaretti S et al, ASH 2014, 2015*
- **LAL 1811** >60 yrs: Ponatinib + PDN

➡ **97-100% HCR & NO DEATHS IN INDUCTION!**

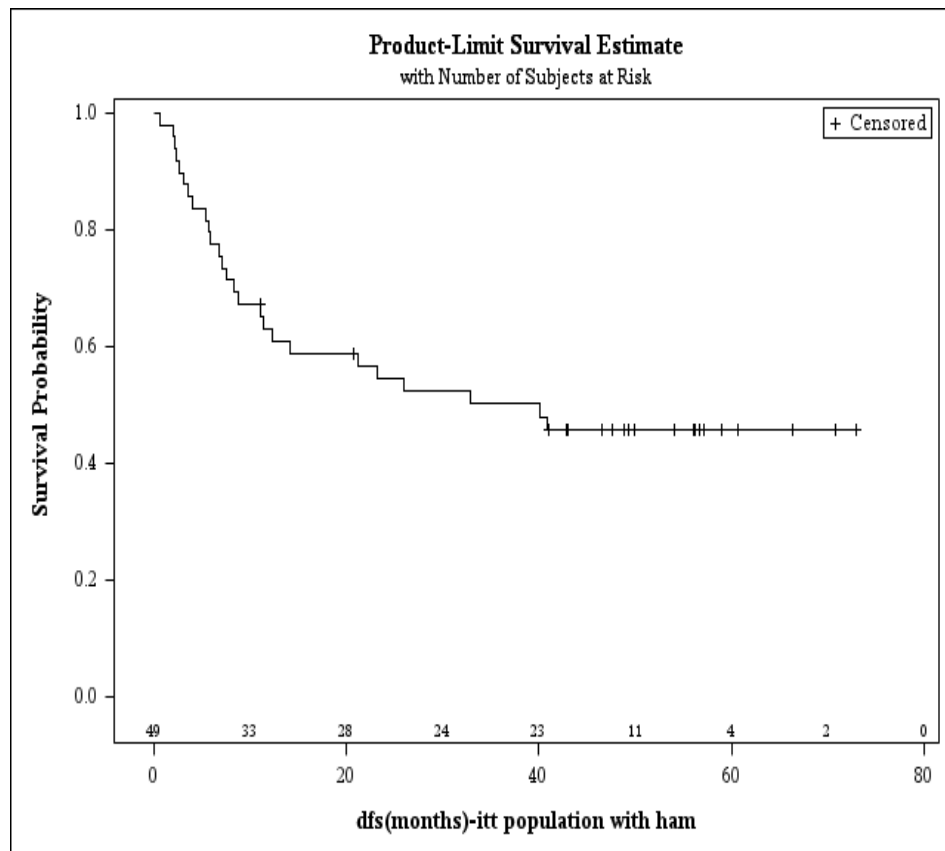
GIMEMA LAL 0904 3rd Amendment: **Long-Term Survival**

Overall Survival



OS at 60 months: 48.8%
(CI 95%: 36.4-65.3)

Disease-Free Survival



DFS at 60 months: 45.8%
(CI 95%: 33.6-62.5)

A 91 YEAR OLD ALL PATIENT...



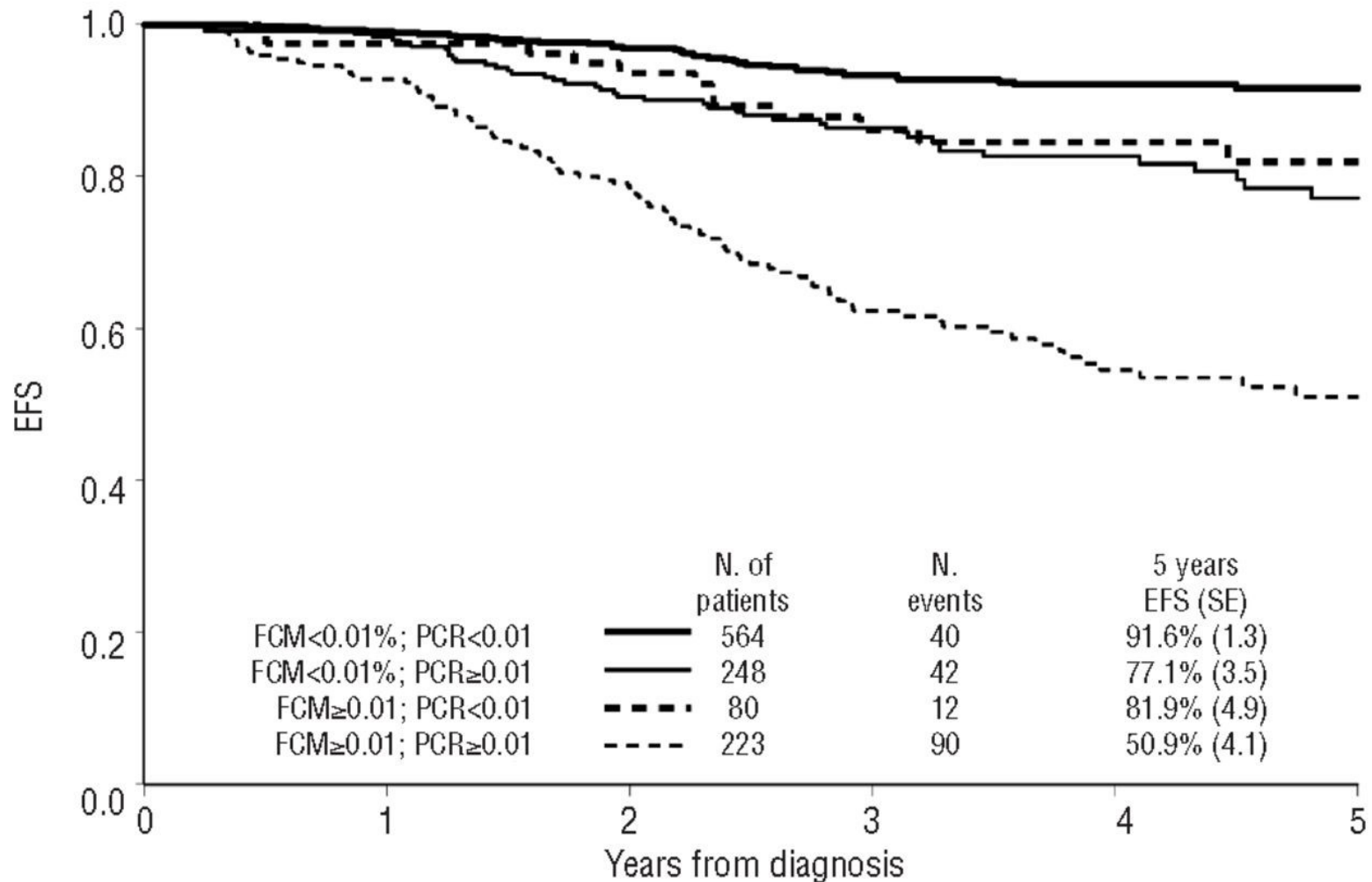
*PC, diagnosed with **Ph+ ALL** in September 2007 at the age of **89**. Treated with Imatinib alone (partly at home...). Obtained a CHR, MRD-, and turned **90**...*

Drived a car and occasionally helped in the family garage...

*Relapse in June 2009. IInd CR with Dasatinib. Relapse in February 2010, responded to VCR. Died March of heart failure, at **91**, 2½ years from diagnosis.*

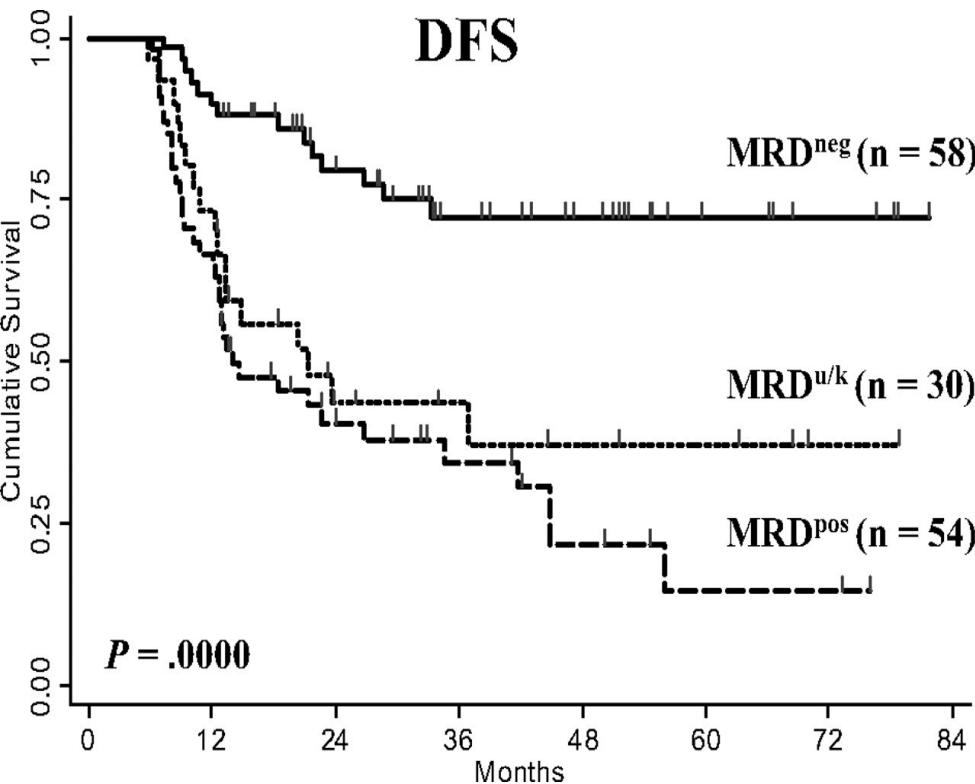
Courtesy of Prof. G. Pizzolo

EFS in 1115 childhood pts treated in the AIEOP BFM-ALL 2000 trial, according to concordant or discordant MRD results on day 33 by the simultaneous application of both PCR and FCM



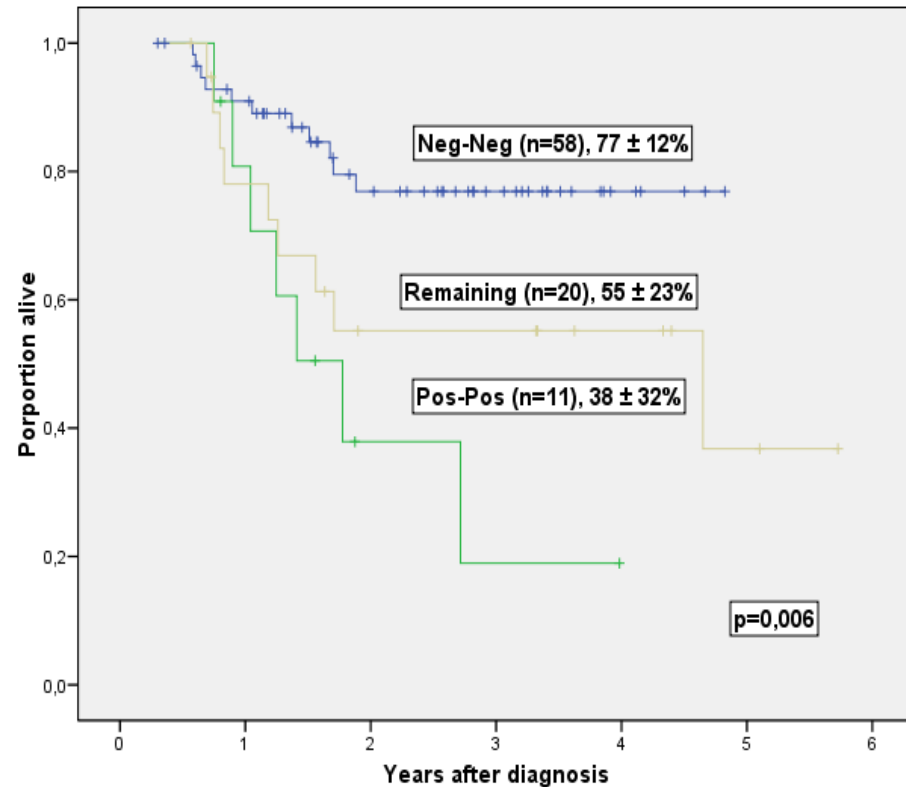
Will MRD negativity stop more allografts?

**NILG Group
(SR & HR ALL)**



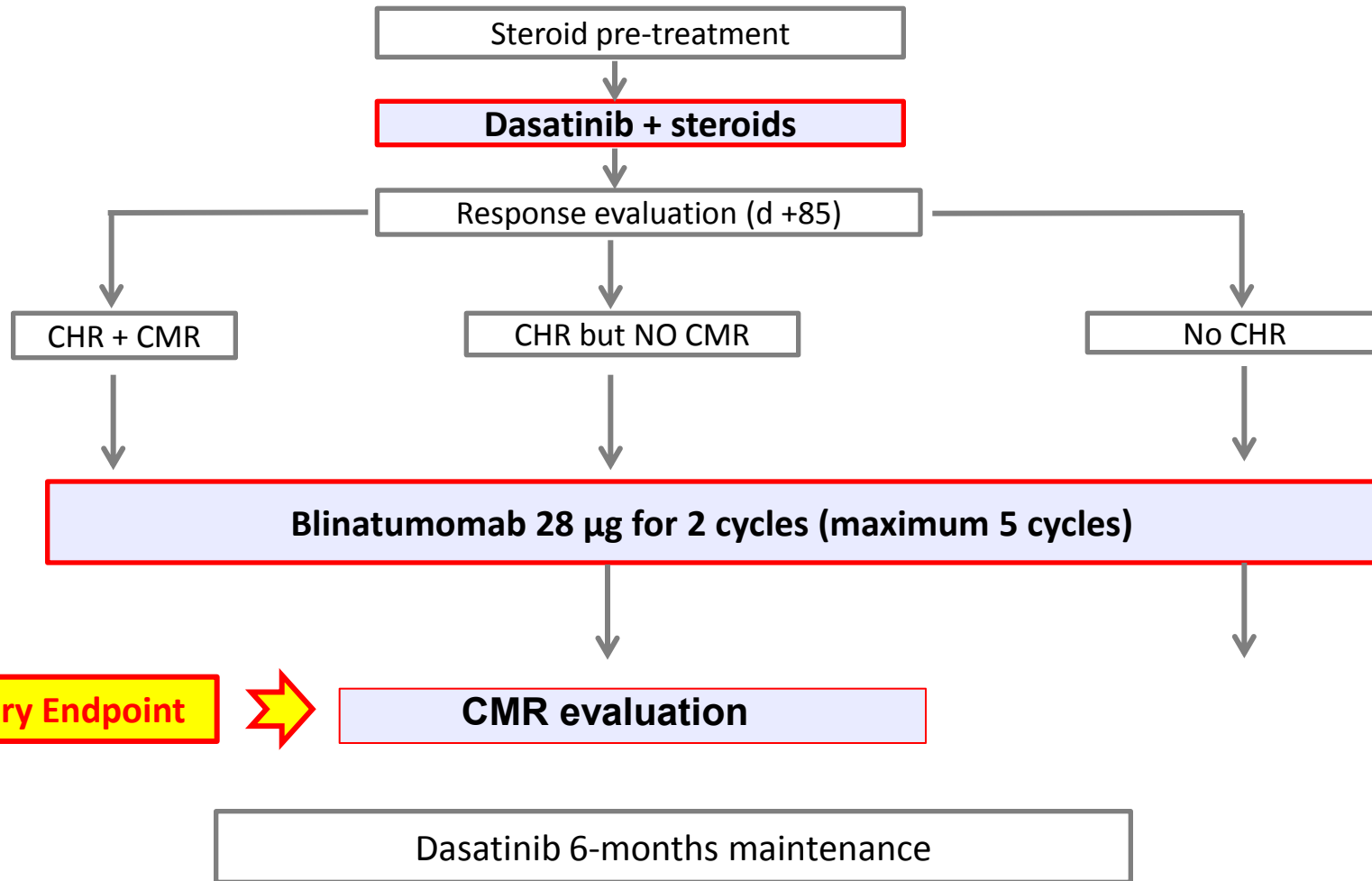
Bassan R, et al. Blood 2009; 113: 4153-4162

**PETHEMA Group
(HRALL only)**



JM Ribera et al, ASH 2009, oral presentation

GIMEMA LAL 2116 Protocol for Ph+ ALL



Primary Endpoint



CMR evaluation

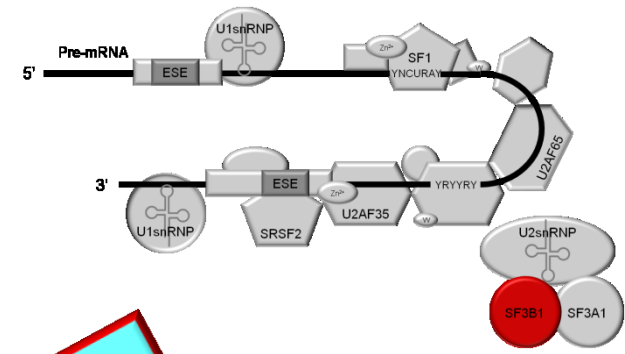
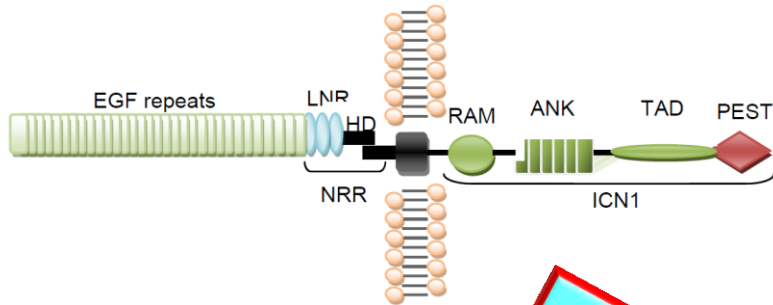
Dasatinib 6-months maintenance

* According to investigator's choice; † additional cycles of Blinatumomab can be administered in case of delayed transplant procedure; ‡ only in case of MRD increase.

PROGRESSIVE DEVELOPMENT OF MORE REFINED TECHNOLOGIES

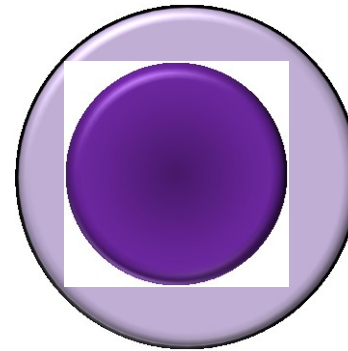
- Further biologic understanding
- Improved management (mainly, prognosis and treatment)
- Continuous advancements in technologies

Novel genes recurrently mutated in CLL

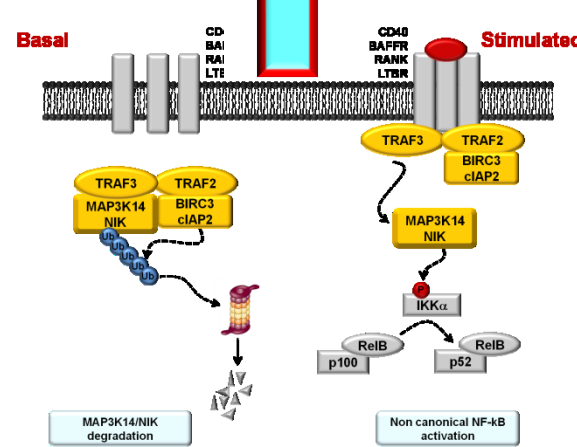


NOTCH signaling
NOTCH1

Splicing regulation
SF3B1



Fabrizi et al, J Exp Med 2011
 Puente et al, Nature 2011
 Quesada et al, Nat Genet 2011
 Rossi et al, Blood 2011
 Wang et al, N Engl J Med 2011
 Rossi et al, Blood 2012
 Rossi et al, Blood 2012
 Rasi et al, Haematologica 2012
 Del Giudice et al, Haematologica 2012
 Landau et al, Cell 2013
 Foà et al, Haematologica 2013

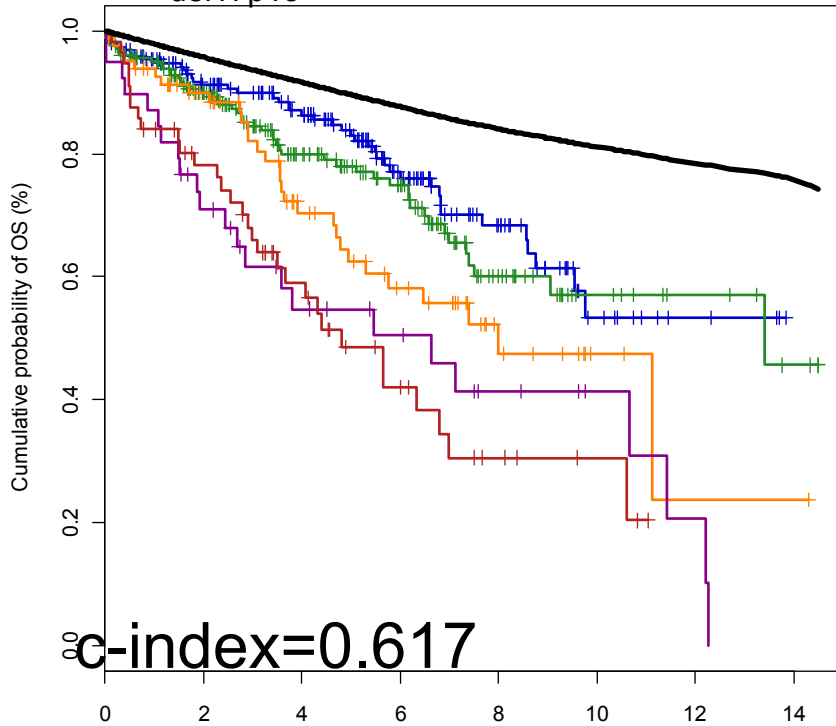


NF-κB signaling
BIRC3
MYD88

Inclusion of mutations in addition to FISH abnormalities significantly improves the accuracy of CLL prognostication

FISH model

- Matched general population
- del13q14
- Normal
- +12
- del11q22-q23
- del17p13

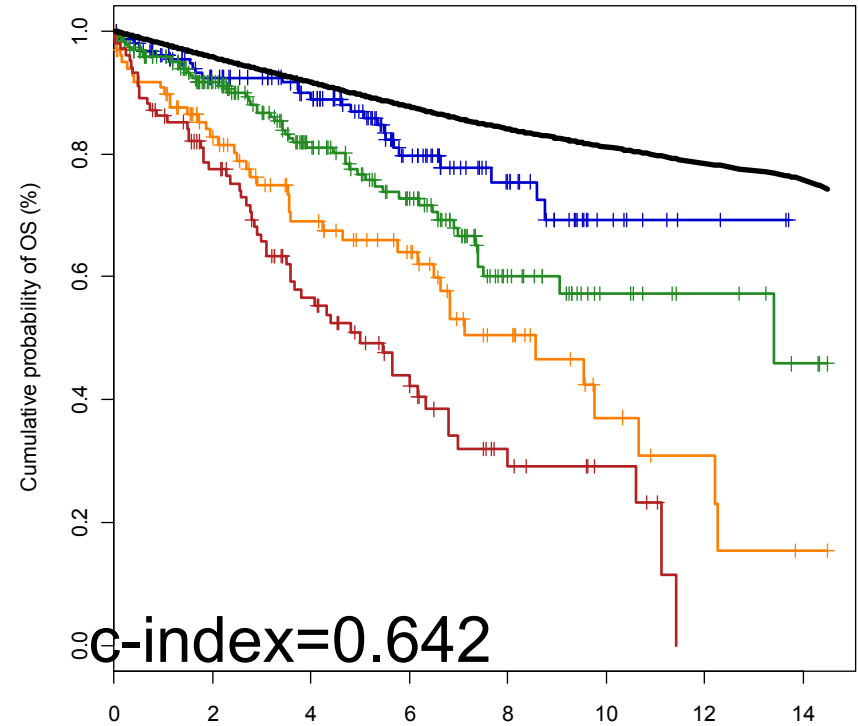


c-index=0.617

	N	Observed events	Expected events*	5-year OS (%)	10-year OS (%)	10-year relative OS*	p*
del13q14	194	44	24.9	83.9	53.3	68.1%	<0.0001
Normal	212	50	24.7	78.0	57.1	72.8%	<0.0001
+12	82	30	12.4	62.5	47.5	62.4%	<0.0001
del11q22-q23	39	23	6.1	54.7	41.3	54.4%	<0.0001
del17p13	56	31	6.1	48.5	30.6	38.1%	<0.0001

Mutational and cytogenetic model

- Matched general population
- del13q14
- Normal/+12
- NOTCH1 M/SF3B1 M/del11q22-q23
- TP53 DIS/BIRC3 DIS

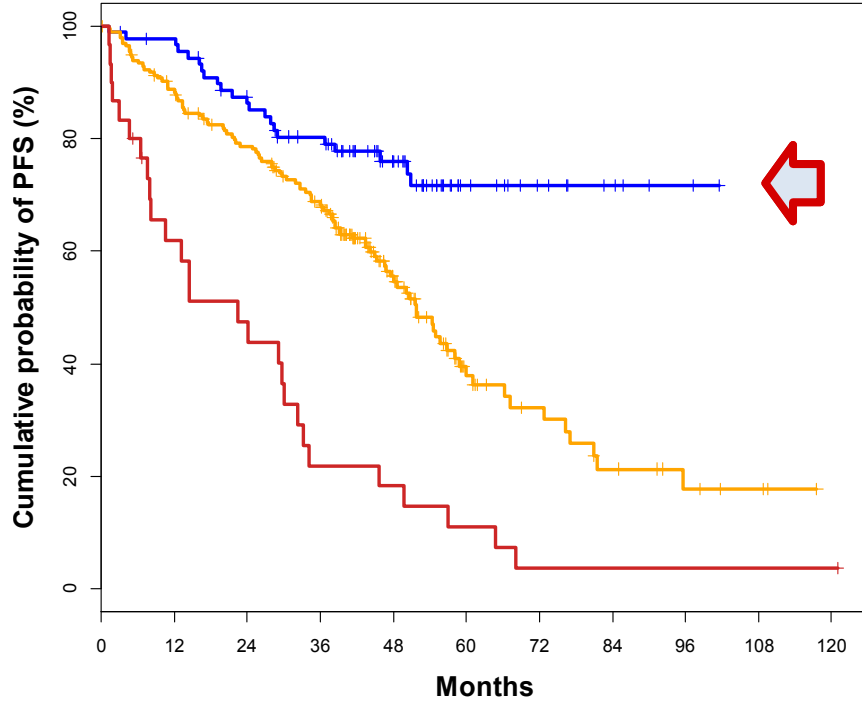


c-index=0.642

	N	Observed events	Expected events*	5-year OS (%)	10-year OS (%)	10-year relative OS*	p*
del13q14	155	27	20.4	86.9	69.3	84.2%	0.1455
Normal/+12	228	53	30.9	77.6	57.3	70.7%	<0.0001
NOTCH1 M/SF3B1 M/del11q22-q23	99	41	10.4	65.9	37.1	48.5%	<0.0001
TP53 DIS/BIRC3 DIS	101	57	12.6	50.9	29.1	37.7%	<0.0001

IGHV-mutated patients devoid of del17p and del11q gain the greatest benefit from FCR chemoimmunotherapy

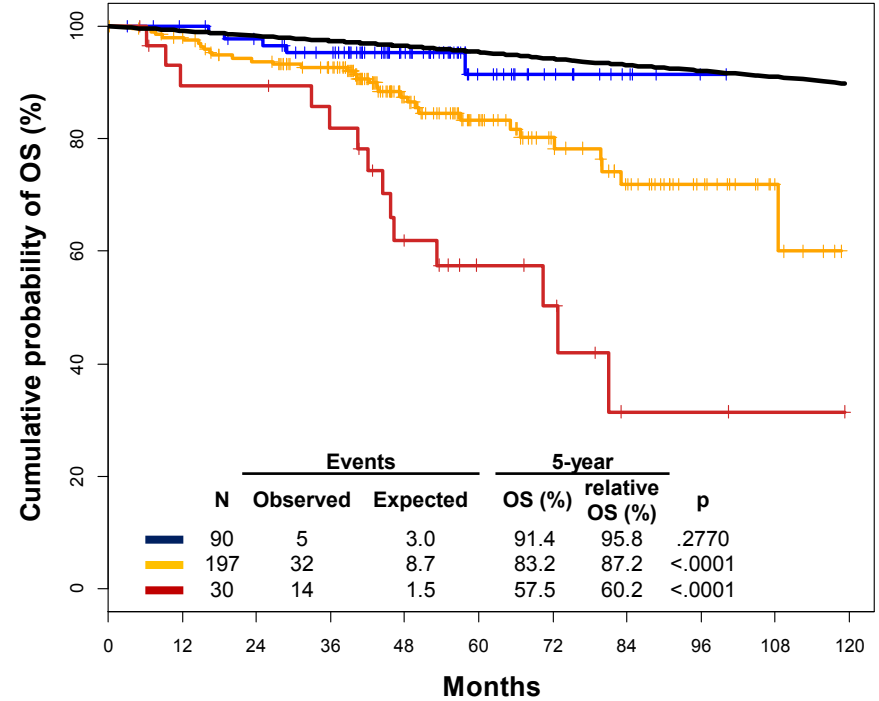
■ Low-risk group (*IGHV* mutated)
 ■ Intermediate-risk group (*IGHV* unmutated and/or 11q del)
 ■ High-risk group (17p del)



Events	Total	Median PFS	95% CI
22	90	nr	na
102	197	51.7	46.1-57.2
27	30	22.5	8.5-36.4

Pairwise comparisons

p	Low-risk vs Intermediate-risk	Low-risk vs High-risk	Intermediate-risk vs High-risk
Low-risk vs Intermediate-risk	-	0.0001	<0.0001
Low-risk vs High-risk	0.0001	-	<0.0001
Intermediate-risk vs High-risk	<0.0001	<0.0001	-



	Events		5-year OS (%)		p
	N	Observed	Expected	relative OS (%)	
Low-risk	90	5	3.0	91.4	.2770
Intermediate-risk	197	32	8.7	83.2	<.0001
High-risk	30	14	1.5	57.5	<.0001

Events	Total	5-years OS	95% CI
5	90	91.4	87.1-95.7
32	197	83.2	80.0-86.4
14	30	57.5	47.6-67.4

Pairwise comparisons

p	Low-risk vs Intermediate-risk	Low-risk vs High-risk	Intermediate-risk vs High-risk
Low-risk vs Intermediate-risk	-	0.0341	<0.0001
Low-risk vs High-risk	0.0341	-	0.0004
Intermediate-risk vs High-risk	<0.0001	0.0004	-

HAIRY CELL LEUKEMIA. BRAF

1. *Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, Pucciarini A, Bigerna B, Pacini R, Wells VA, Sportoletti P, Pettrossi V, Mannucci R, Elliott O, Liso A, Ambrosetti A, Pulsoni A, Forconi F, Trentin L, Semenzato G, Inghirami G, Capponi M, Di Raimondo F, Patti C, Arcaini L, Musto P, Pileri S, Haferlach C, Schnittger S, Pizzolo G, Foà R, Farinelli L, Haferlach T, Pasqualucci L, Rabadan R, Falini B.* BRAF mutations in hairy-cell leukemia. *N Engl J Med.* 364:2305-15, **2011**.
2. *Tiacci E, Schiavoni G, Forconi F, Santi A, Trentin L, Ambrosetti A, Cecchini D, Sozzi E, Francia di Celle P, Di Bello C, Pulsoni A, Foà, Inghirami G, Falini B.* Molecular diagnosis of hairy cell leukemia by sensitive detection of the BRAF-V600E mutation. *Blood,* 119:192-5, **2012**.
3. *Tiacci E, Park JH, De Carolis L, Chung SS, Broccoli A, Scott S, Zaja F, Devlin S, Pulsoni A, Chung YR, Cimminiello M, Kim E, Rossi D, Stone RM, Motta G, Saven A, Varettoni M, Altman JK, Anastasia A, Grever MR, Ambrosetti A, Rai KR, Fraticelli V, Lacouture ME, Carella AM, Levine RL, Leoni P, Rambaldi A, Falzetti F, Ascani S, Capponi M, Martelli MP, Park CY, Pileri SA, Rosen N, Foà R, Berger MF, Zinzani PL, Abdel-Wahab O, Falini B, Tallman MS.* Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. *N Engl J Med.* 373:1733-47, **2015**.



DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS

EMERGING THERAPIES IN CLL AND NHL

- **BCR Pathway Inhibitors**
 - *BTK inhibitors: Ibrutinib*, CC-292
 - *PI3 kinase delta inhibitor: Idelalisib* (GS-1101), PI3g
 - SYK inhibitors
- **BCL-2 Pathway**
 - Navitoclax (ABT-263)
 - *ABT-199*
- **Antibodies other than rituximab**
 - Alemtuzumab: Anti-CD52 antibody
 - Ofatumumab: Anti-CD20
 - Veltuzumumab: Anti-CD20
 - **Blinatumumab: Anti-CD19/CD3**

Blinatumomab

Mechanism of Action

(BiTE[®] = Bi-specific T-Cell Engager)

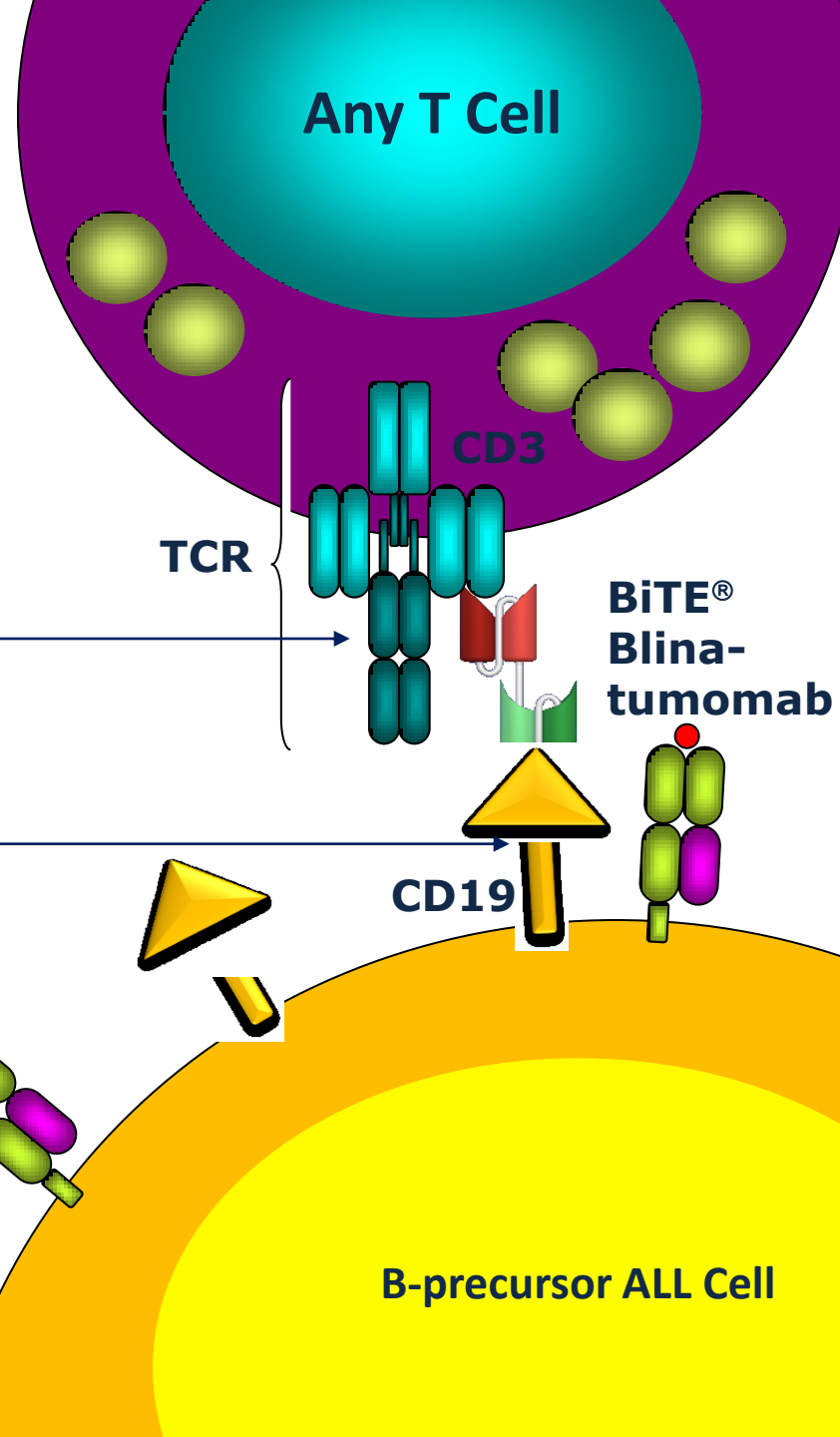
Acts independently of
specificity of T-Cell
Receptor (TCR)

Allows T cell recognition of
tumor-associated
surface antigen (TAA)

Does not require
MHC Class I and/or
peptide antigen

Initially employed in NHL
***It has been largely utilized
for the management of ALL***

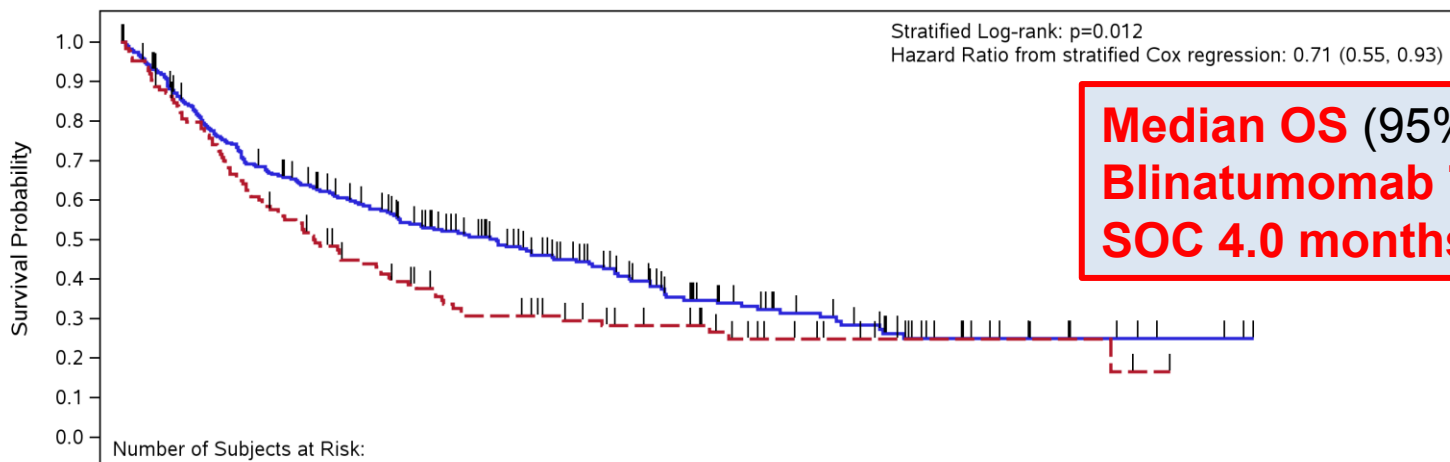
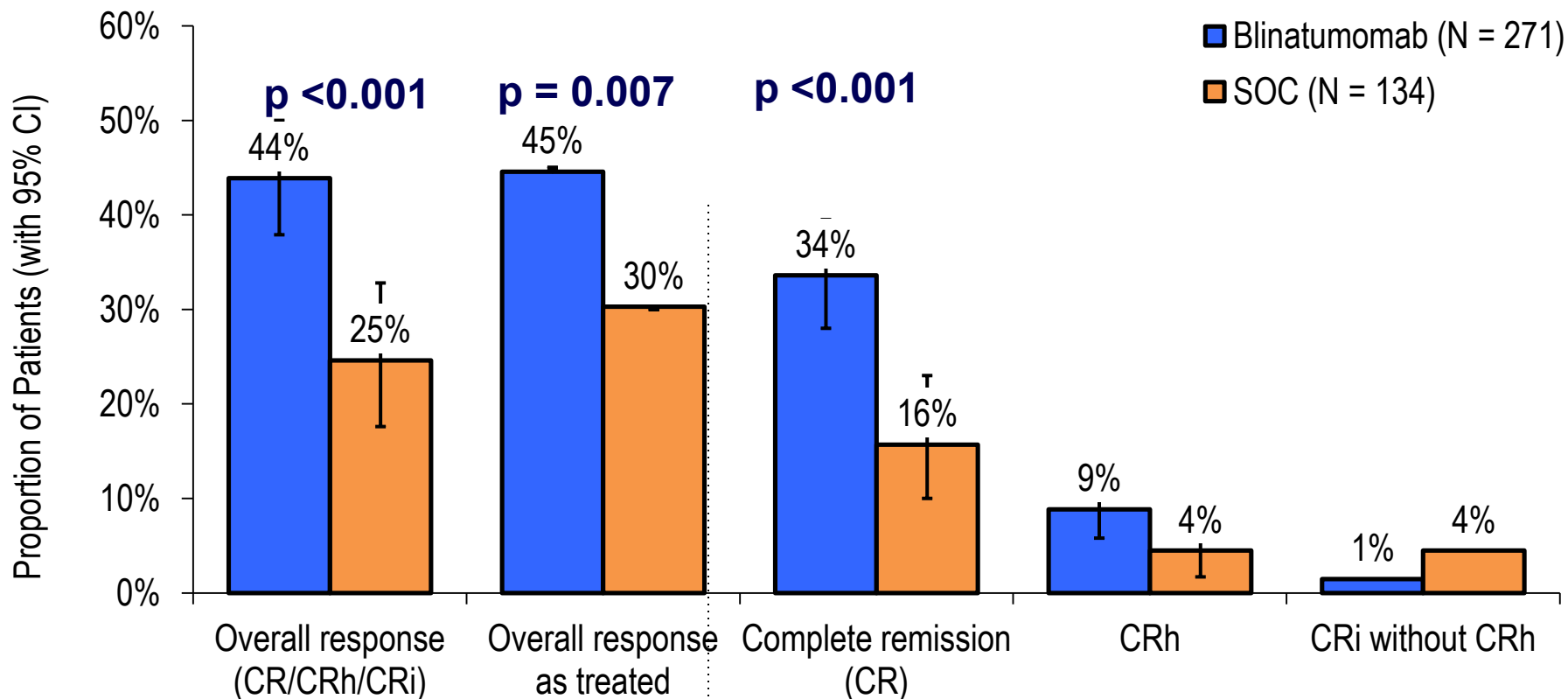
Courtesy of AMGEN



Blinatumomab (MT-103), BiTE



- A bispecific single-chain antibody derivative designed to link B cells and T cells resulting in T-cell activation and a cytotoxic T-cell response against CD19 expressing cells.
- Very encouraging results in relapsed/refractory ALL and for the management of MRD (*Topp et al, JCO 2011; Blood 2012; JCO 2014; Lancet Oncol 2015; Blood 2015*).
- Blincyto approved by FDA and EMA for the treatment of R/R adult Ph- ALL.

Blinatumumab in R/R Ph- B-lin ALL. Hematologic Response



Median OS (95% CI):
Blinatumomab 7.7 months
SOC 4.0 months

OVERALL CONSIDERATIONS


- The management of patients with hematologic malignancies is always more guided by the laboratory and by always evolving technologies
- In terms of diagnosis, prognosis, monitoring and treatment
- Many diseases are being 'chronicized'  *maintenance*
- Always grower impact of non-chemo approaches  *MoAb, inhibitors, small molecules, etc*
- Algorithms of treatment are a reality

NECESSARY CONDITIONS

Some/all of the above advancements that have **translated from the bench to the bedside** possible only through:

- Adequate and accessible laboratories...
- Access to drugs...
- Close interaction between the clinic and the laboratories
- Multicenter networks**
- Central handling of material
- Banking of biologic material
- National and international collaborations
- Adequate funding...
- Interaction with pharma
- Dedicated and motivated individuals/teams...
- Role of physician-scientists

GIMEMA NETWORK FOR ADULT HEMATOLOGIC MALIGNANCIES

- Overall, over 150 centers in Italy
- Central handling of samples at diagnosis (and during the follow-up and at relapse) activated for **ALL** in October 1996
- Aim  broad and uniform characterization of all cases enrolled in the same clinical protocols
- Identification of reference laboratories (*Roma, Ferrara, Perugia, Torino, Napoli, Bologna, etc*)
- Bank of material
- In more recent years extended to other conditions: eg AML, CLL