LAL Ph+ dell'adulto

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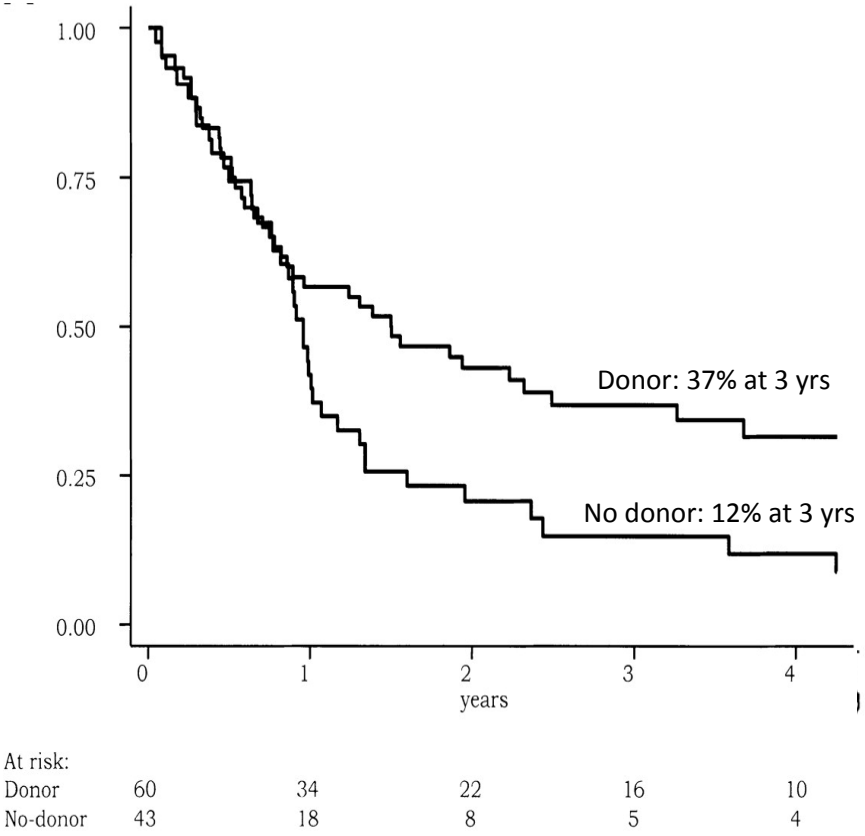
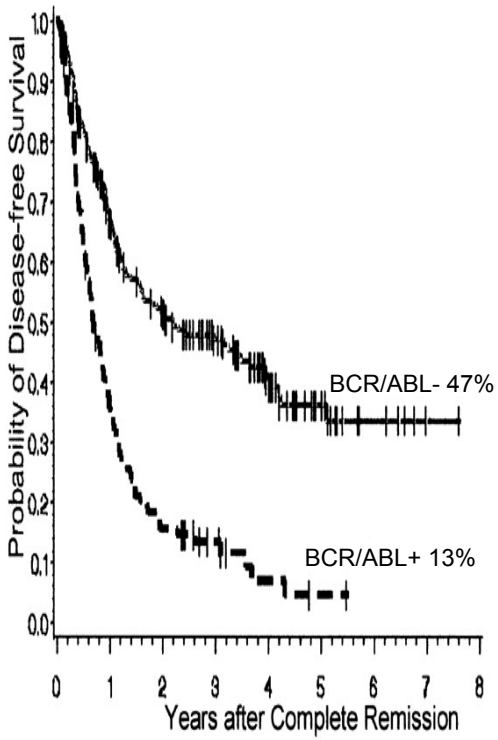
Pre-imatinib era

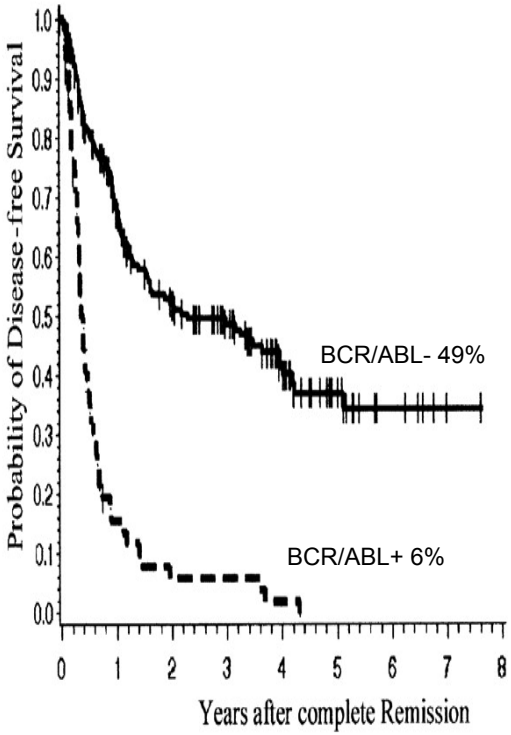
3-yrs estimated survival



Dombret et al, Blood 2002

3-yrs DFS with transplant w/o transplant





Gleissneret al, Blood 2002

Topics

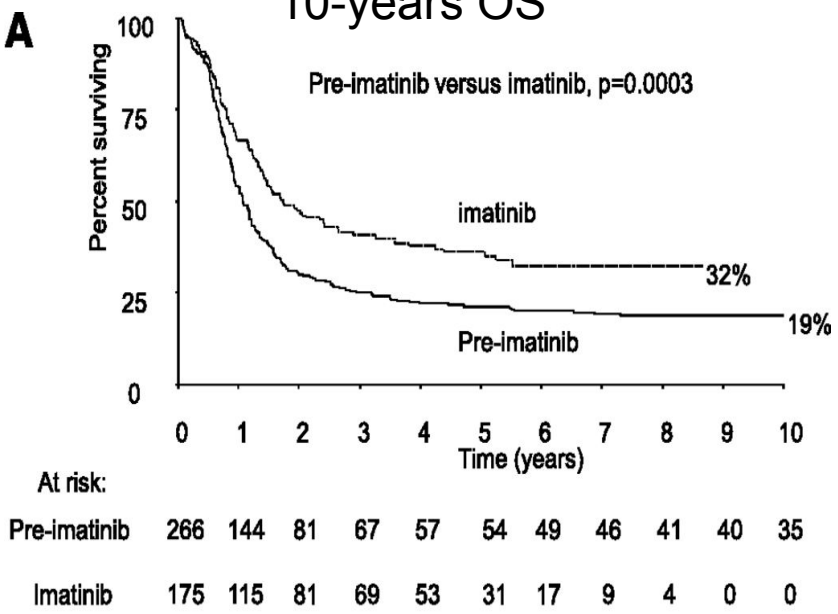
- Induction treatment: TKI with/with low dose / without chemotherapy?
- MRD and consolidation
- Relapses and mutations
- Allo-SCT?

Topics

- Induction treatment: TKI with/with low dose / without chemotherapy?

Intensive regimens in combination with imatinb

10-years OS

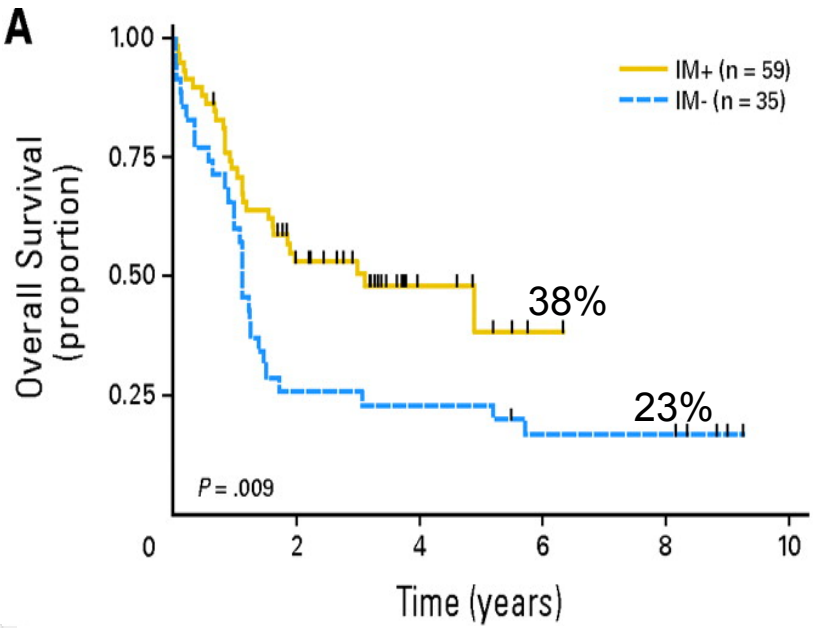


	Preimatinib cohort (N = 266)	Imatinib cohort		
		Any imatinib (N = 175)	Late imatinib (N = 86)	Early imatinib (N = 89)
	Percent at 4 y (95% CI)			
OS	22 (17-27)	38 (31-45)	33 (23-43)	43 (32-53)
EFS	18 (13-22)	33 (26-40)	28 (18-37)	37 (27-48)
RFS	33 (26-41)	50 (41-58)	46 (33-58)	53 (41-66)
Survival free from death in remission	64 (55-73)	72 (64-80)	66 (53-80)	76 (66-86)

Death in induction: 5% in both cohorts
CR rate: 92%

Fielding et al. Blood 2014

5-years OS



Death in induction: 4% vs 7%
in imatinib + vs imatinib-
(partly sustained by L-ASP)
CR rate: 92%

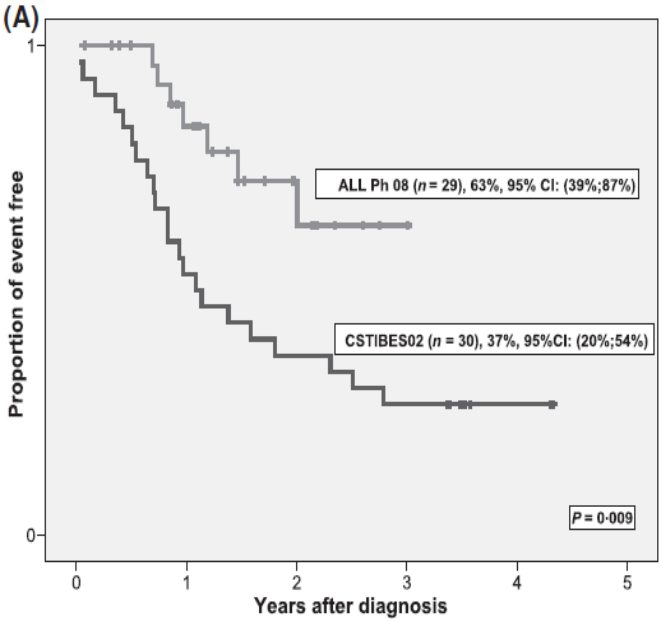
Bassan et al, JCO 2010

De-intensified therapy *vs* intensified treatment

CR rate: 90% intensified vs 100% de-intensified
Death in induction: 2 in intensified treatment *vs* 0 in de-intensified

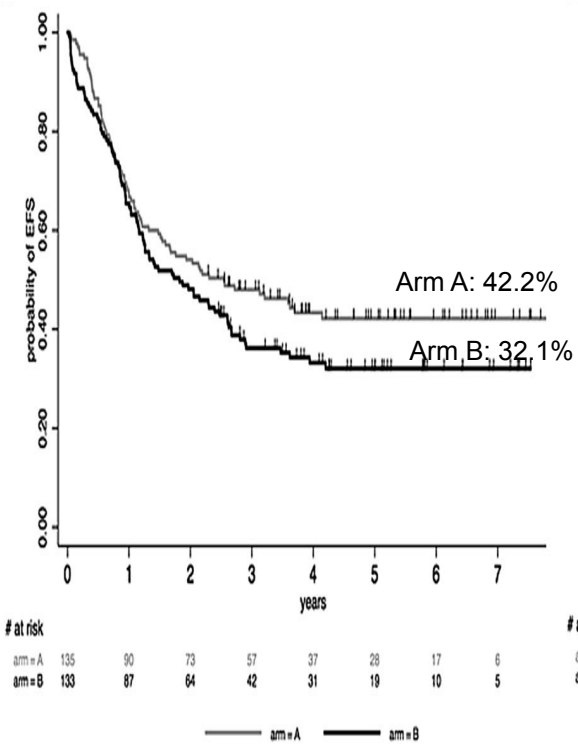
CR rate 98% vs 91% in deintensified vs intensified therapy,
Death in induction: 3.7% in intensified treatment *vs* 0.7%

2-yrs EFS

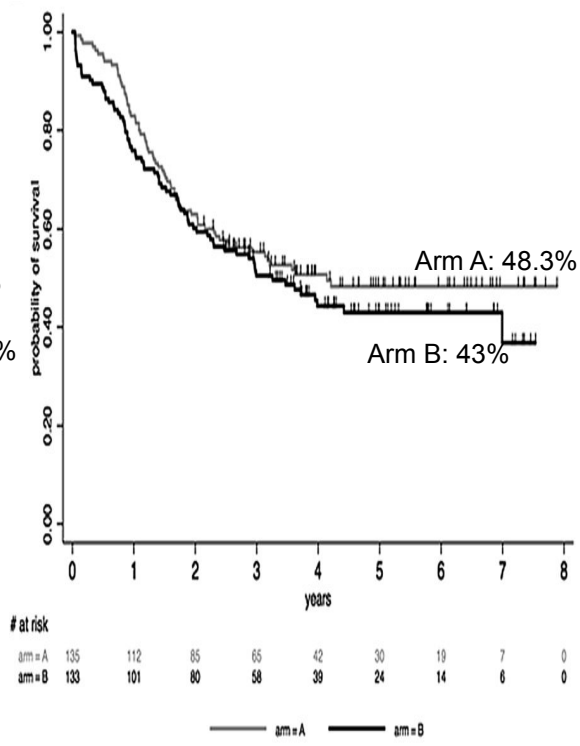


Ribera et al, BJH 2012

5-yrs EFS



5-yrs OS



Chalandon et al, Blood 2015

Ph+ ALL - THE GIMEMA STRATEGY

- **LAL 0201B** >60 yrs (60-89): Imatinib + PDN: CHR 100%
  - ⇨ *Vignetti et al Blood 2007;109:3676-8*
- **LAL1205** 18-84 yrs: Dasatinib + PDN: CHR 100%
  - ⇨ *Foà et al ASH, EHA & Blood 2011,* 15;118:6521-8
- **LAL 0904 3rd amendment** 16-60 yrs: Imatinib followed by chemo (HAM) ± transplant ⇨ *EHA 2013 and under revision*
- **LAL 1408** >60 yrs: Nilotinib-Imatinib + PDN ⇨ *Martinelli G et al, ASCO 2014*
- **LAL 1509** 18-60 yrs: Total Therapy Strategy, Dasatinib…
  - ⇨ *Chiaretti et al, ASH 2014, ASH 2015 (N. 81)*
- **LAL 1811** >60 yrs: Ponatinib + PDN

⇨ ***CHR: 97-100%. NO DEATHS IN INDUCTION***

Topics

- MRD and consolidation

Minimal residual disease

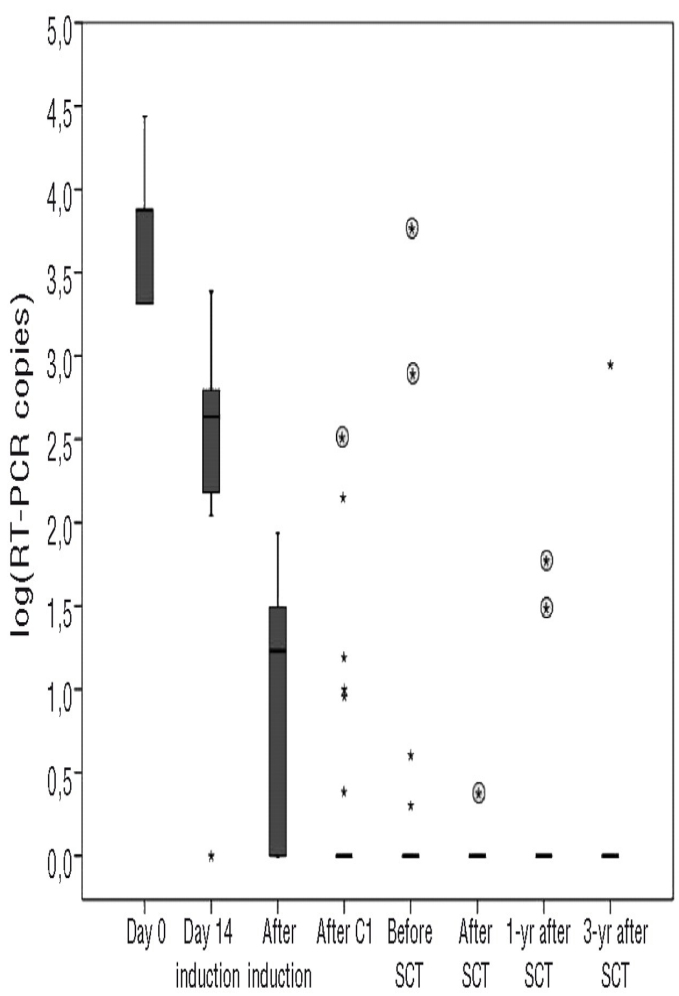
- MRD: how? when and why? therapeutic implications?

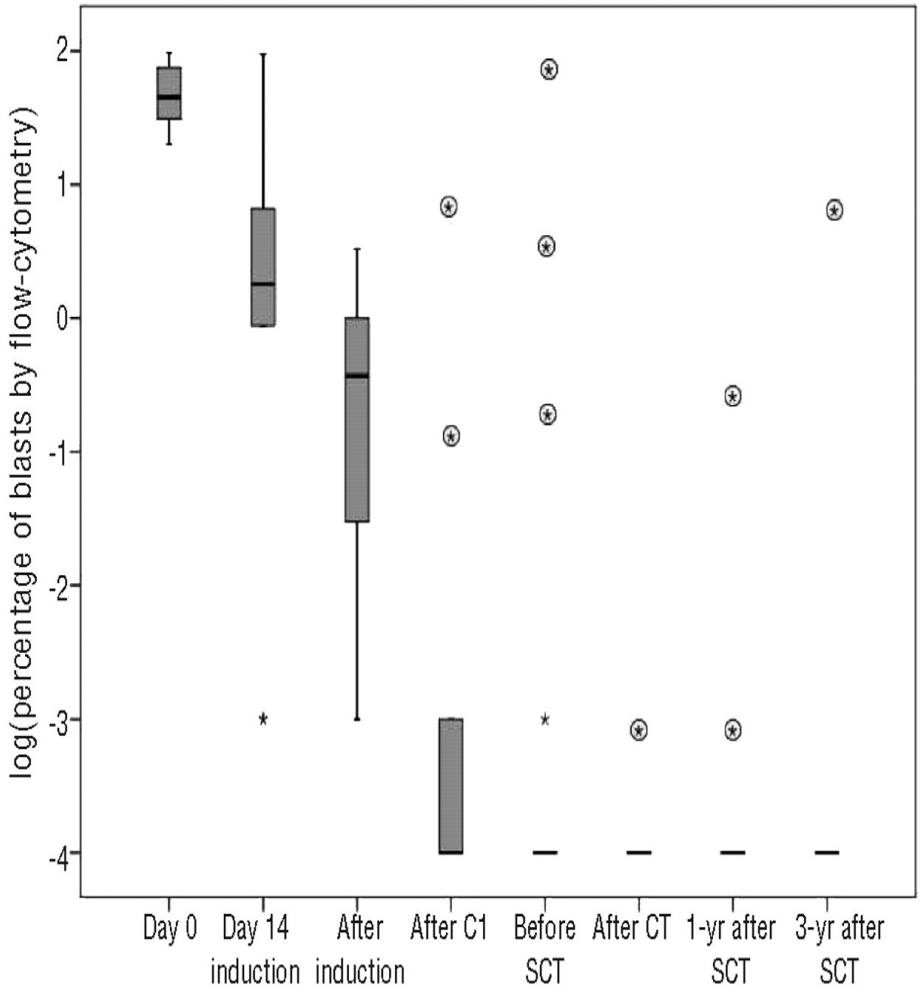
MRD: how?

	PCR analysis of Ig and TCR gene rearrangements	PCR analysis of BCR-ABL transcripts	Multiparameter FCM
Sensitivity	RQ-PCR: 10^{-4}-10^{-5}	10^{-4}-10^{-6}	3- to 4-color: 10^{-3}-10^{-4} 6- to 9-color: 10^{-4}-10^{-5} Also depends on cell input
Quantitative range	RQ-PCR: 10^{-2}-10^{-4}	Not yet defined	Not yet defined
Applicability	pcB-ALL: 90%-95% T-ALL: 90%-95%	Ph^+ ALL (5%-8% of children with pcB-ALL, 30%-35% of adults with pcB-ALL)	pcB-ALL: 80%-95% T-ALL: 90%-95% Depends also on number of colors
Advantages	• High sensitivity • High degree of standardization reached • Well-established stratification tool in various clinical protocols • Most published data for evidence-based treatment decisions • Applicable for almost all ALL patients • Stability of DNA (multicenter setting)	• High sensitivity • Stability of target during course of treatment • Fast • Relatively easy/cheap	• Applicable for almost all ALL patients • Rapid • Quantitative • Additional information on benign cells • Additional information on malignant cells • Growing standardization throughout Europe
Disadvantages	• Time-consuming marker characterization • Pretreatment sample required to sequence the patient-specific diagnostic clone • Potential instability of targets (clonal evolution phenomena) • Extensive knowledge and experience needed • Relatively expensive	• Applicable only in Ph^+ patients • Instability of RNA • Differences in expression levels possible • Standardization necessary • Risk of false positivity due to contamination	• Immunophenotypic shifts • Expanded pcB-cell compartment during regeneration • Low cellularity during/after induction • Relatively expensive (depends on number of markers/colors and ulterior cytometer utilizations) • Limited sensitivity/applicability using 3- to 4-color FCM • ≥ 6-color FCM: extensive knowledge and experience for sensitive and standardized analysis needed

Schrappe M. *Blood* 2012

Spanish CSTIBES02 trial

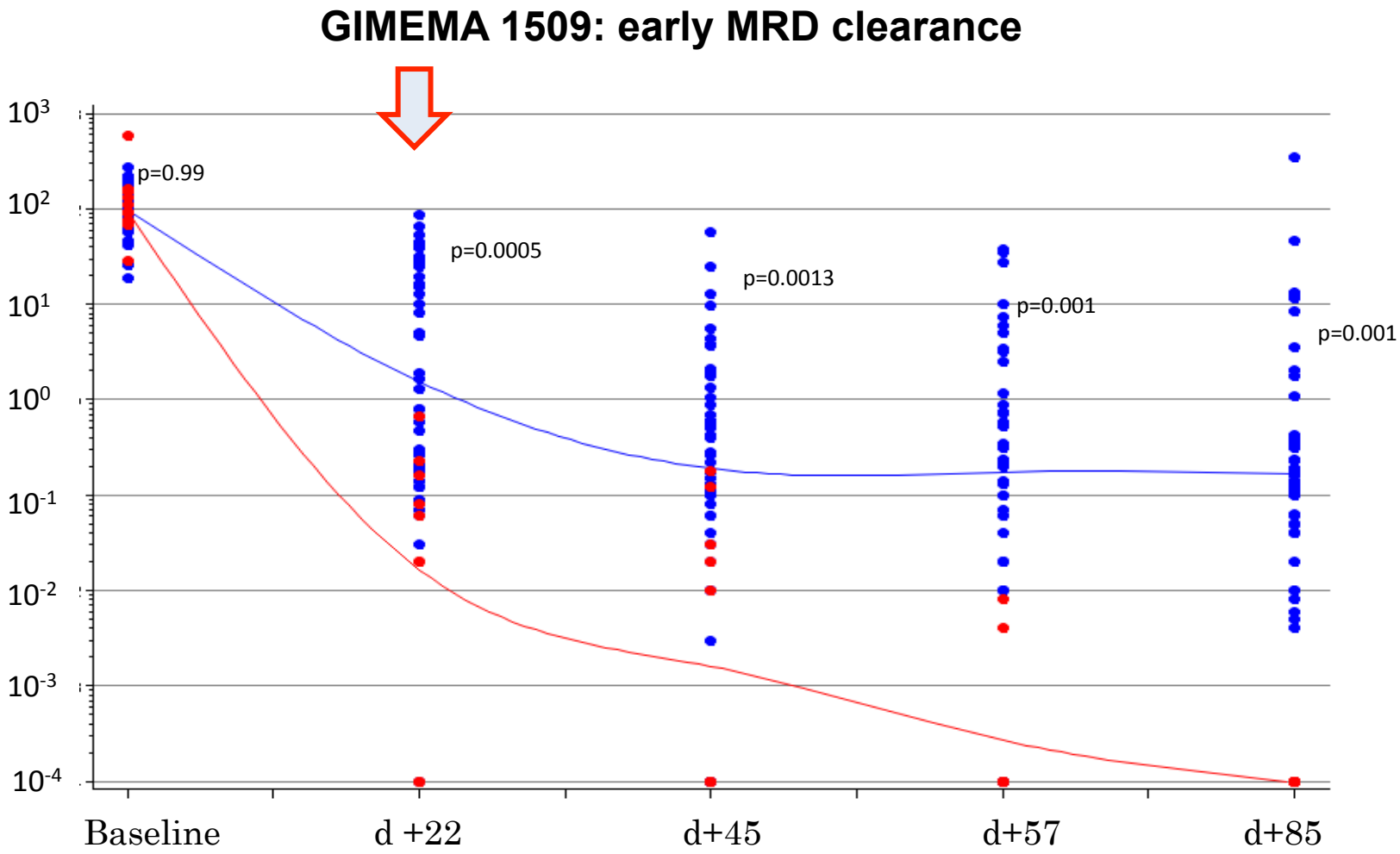




Ribera J et al. Haematologica 2010;95:87-95

Both techniques show that MRD clearance occurs early and provide comparable results.

MRD: when and why ? (I)

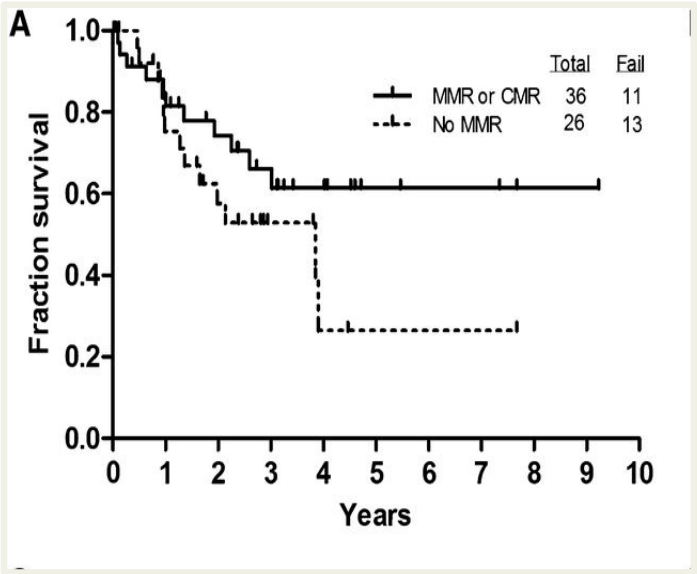


Significant differences are recorded from day +22

Chiaretti et al; ASH 2014

MRD: when and why ? (III)

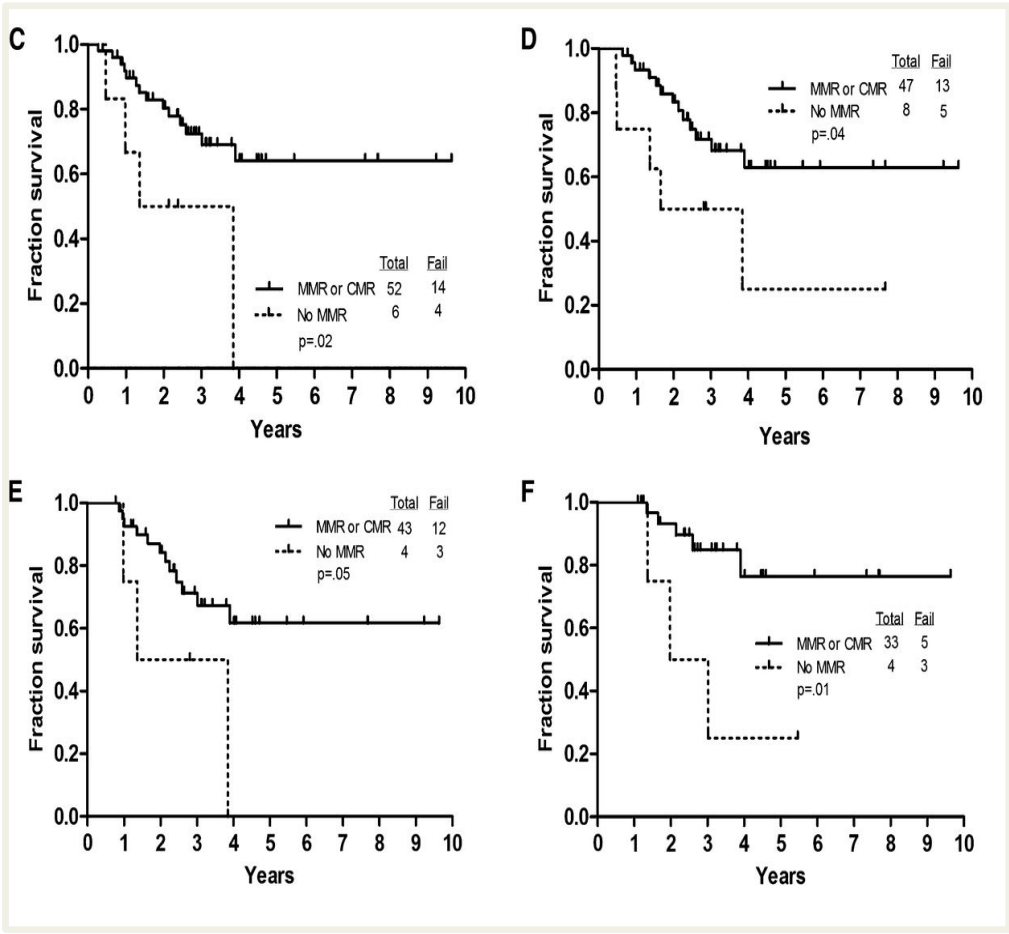
MDACC experience



At CR

Starting from 3° month onwards, MRD is predictive of reduced OS

At 3 mths **At 6 mths**



At 9 mths **At 12 mths**

Ravandi F et al. Blood 2013;122:1214-1221

Topics

- MRD and consolidation

Consolidation

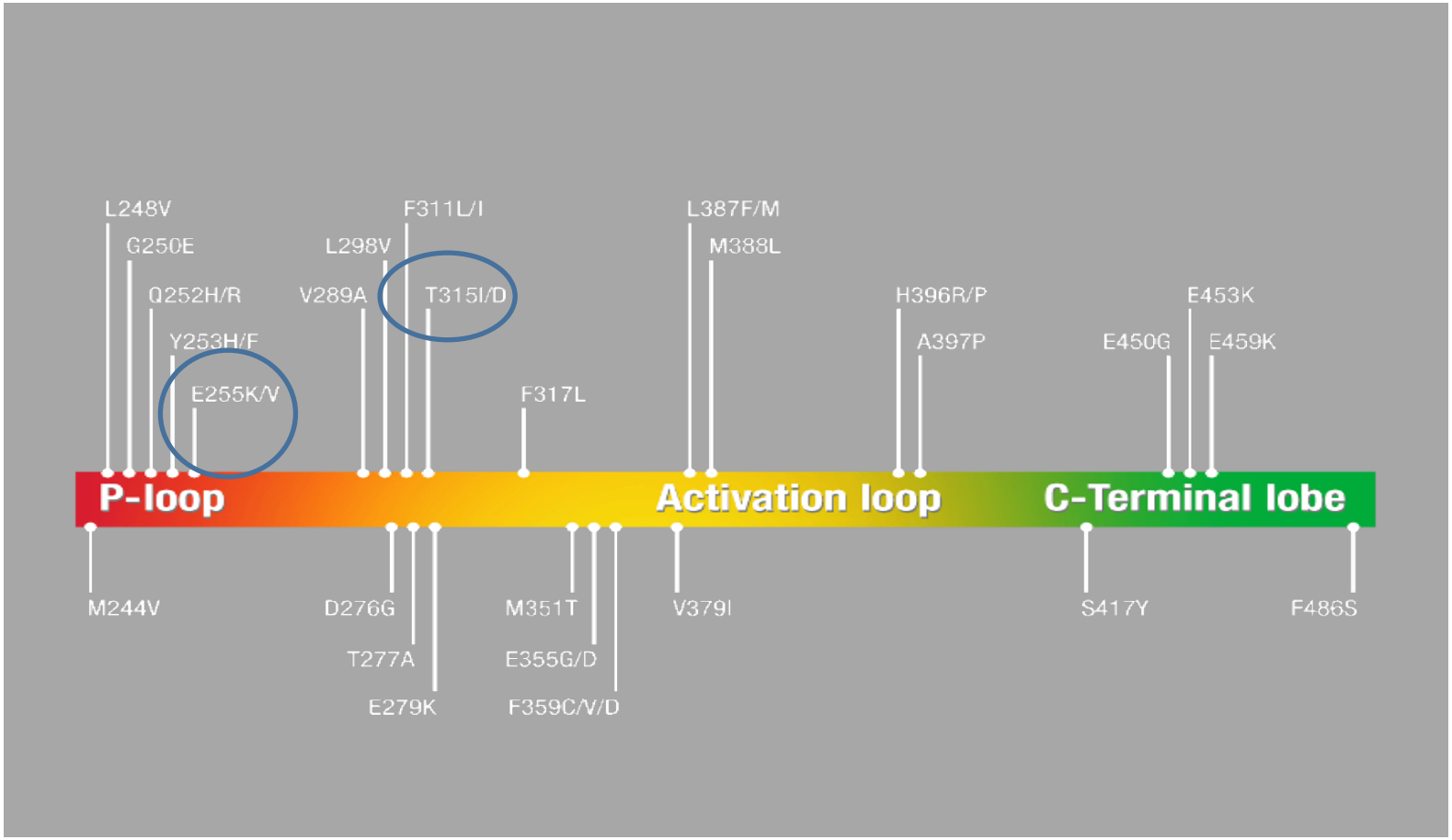
Study group	Consolidation scheme	Ref
GRAAPH2003	HAMI if ALLO-SCT not feasible	Delabarthe, Blood 2007
UKALLXII/ECOG2993	HD-MTX if ALLO-SCT not feasible	Fielding, Blood 2014
PETHEMA: CSTIBES02 ALL Ph08	ID-MTX, Teniposide, ID-ARAC and DX, VCR,DXM CTX if ALLO-SCT not feasible	Ribera, Haematologica 2010 Ribera, BJH 2012
NILG	Pulses CHT and HD-MTX if ALLO-SCT not feasible	Bassan, JCO 2010
GIMEMA 0904	HAM followed by ALLO-SCT	Vitale, under revision
GIMEMA 1509	Clofa+CTX if ALLO-SCT not feasible	Chiaretti, in preparation

Do all patients nowadays need consolidation chemotherapy and transplant?

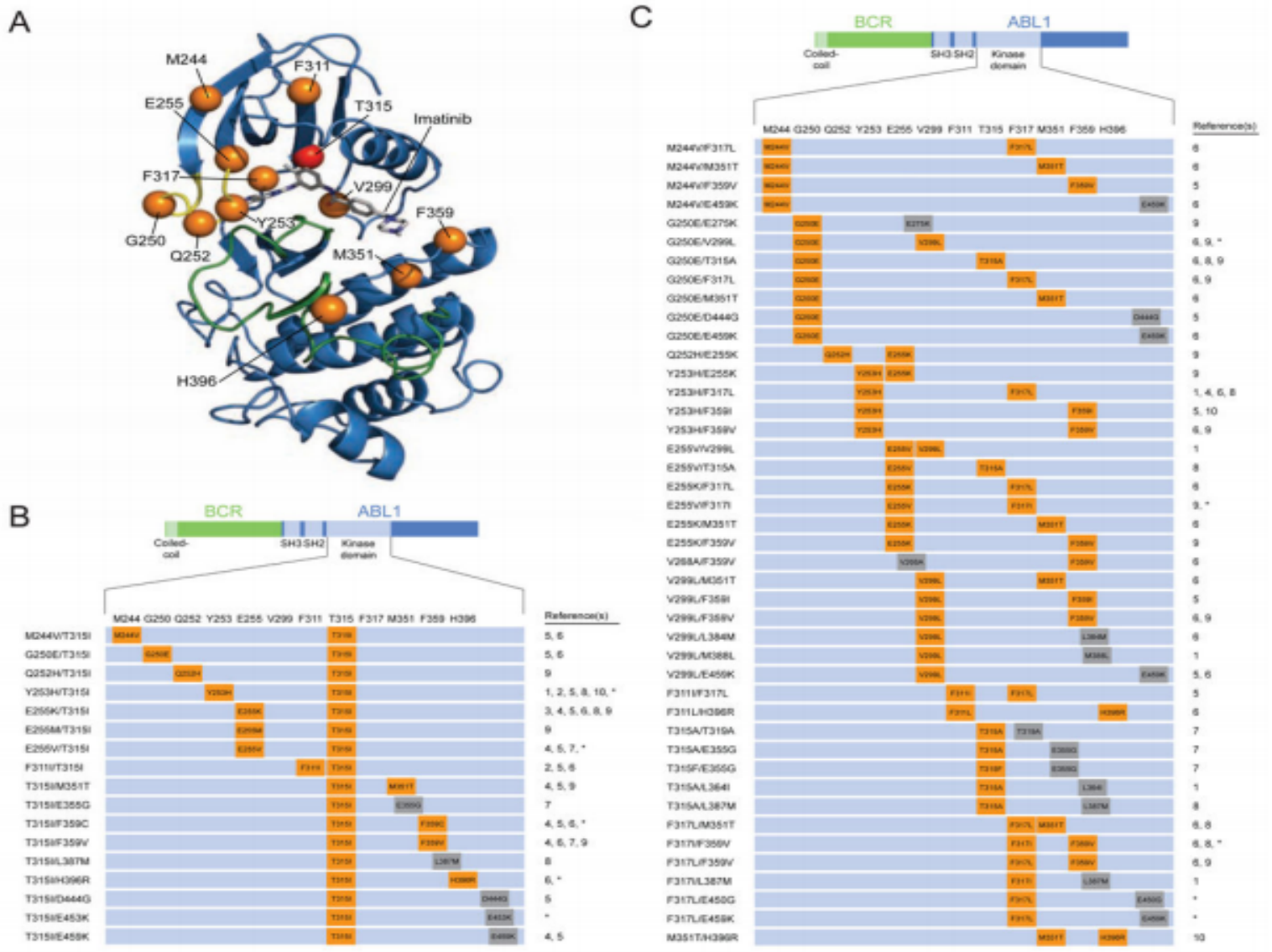
Topics

- Relapses and mutations

MRD and mutations

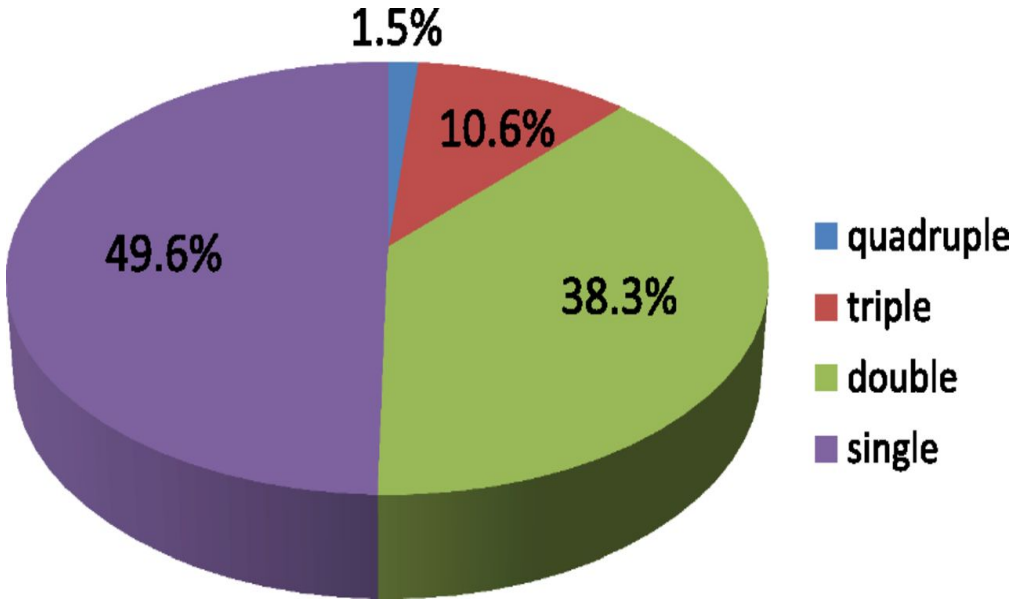


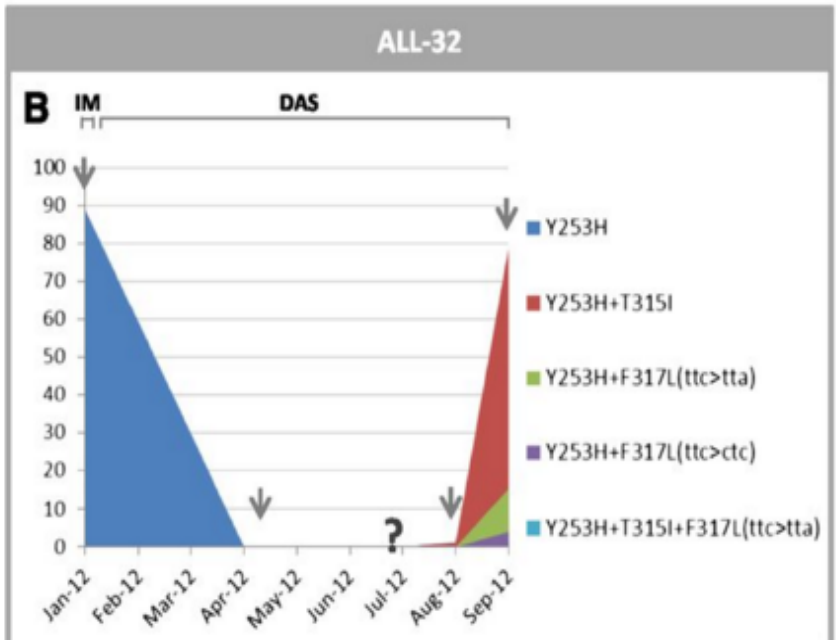
Compound mutations



Zabriskie et al, Cancer Cell 2014

Mutations





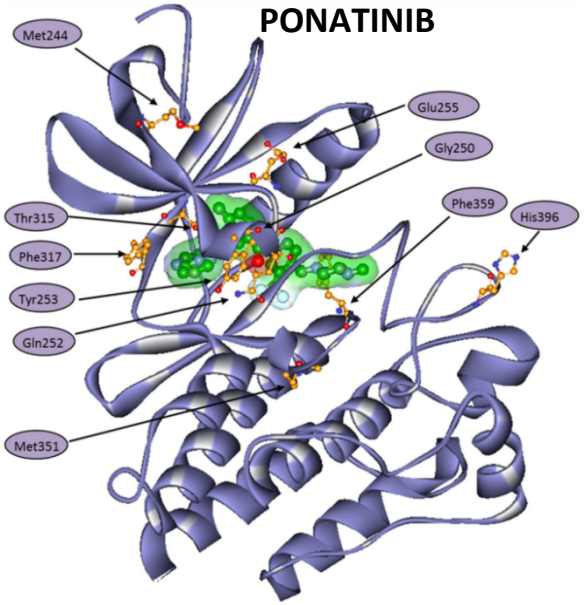
Soverini et al, Blood 2013

Many *BCR-ABL1* compound mutations reported in chronic myeloid leukemia patients may actually be artifacts due to PCR-mediated recombination

BCR-ABL1 kinase domain (KD) mutations are the most common known cause of treatment failure in chronic myeloid leukemia (CML). Emerging evidence suggests that compound mutations (>1 KD mutation in the same molecule) confer resistance to ponatinib[1,2] and combination therapy (GNF-5/nilotinib).[3] Several recent studies, including 2 published in *Blood*, employed nested polymerase chain reaction (PCR) amplification of the *BCR-ABL1* KD, followed by cloning and Sanger sequencing[4] or next-generation sequencing,[5,6] and found a high incidence of compound mutations in imatinib-resistant CML patients with multiple KD mutations. These studies would imply that even a combination approach to therapy would be futile in this setting. Furthermore, they argue strongly against the sequential use of different tyrosine kinase inhibitors in high-risk settings. Surprisingly, however, in most cases reported, the same mutations were found both as compound mutations and as individual mutations in the same patient,[4-6] suggesting that the same nucleotide substitution occurred independently multiple times within an individual patient. This complexity is difficult to explain phylogenetically. Based on extensive evidence that PCR frequently mediates recombination between highly similar templates

Parker et al, Blood 2014

New compounds for “old” targets



Pan-BCR-ABL inhibitor with activity against all IM-resistant mutants, including the T315I mutation.

Reddy E. P. and Aggarwal A. K. Genes & Cancer, 2012 3(5-6) 447–454

Hyper-CVAD + Ponatinib in Ph-Positive ALL (n=37, 34 at onset of disease)

	Participants (n=37)
Age	
Median (years)	51 (27–75)
≥50 years	20 (54%)
≥60 years	12 (32%)
Males	20 (54%)
ECOG performance status	
0–1	31 (84%)
2	6 (16%)
White blood cells (×10⁹ per L)	8 (1–630)
CNS disease	3 (8%)
CD20-positive	11 (30%)
BCR-ABL1 transcript	
p190	27 (73%)
p210	10 (27%)
Cytogenetics	
Diploid	5 (14%)
Philadelphia chromosome-positive	32 (86%)
Baseline cardiovascular risk factors	
Hypertension	18 (49%)
Dyslipidaemia	4 (11%)
Coronary artery disease	4 (11%)
Peripheral arterial disease	1 (3%)

Data are n (%) or median (range). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Patient characteristics**

	Number of patients (%)
Complete response*	36/36 (100%)
Complete cytogenetic response†	32/32 (100%)
Major molecular response	35/37 (95%)
Complete molecular response	29/37 (78%)
Flow cytometry negative‡	35/36 (97%)

Data are n/N (%). *One patient in complete response at beginning of study. †Five patients were diploid by conventional cytogenetics at beginning of study. ‡One patient had no sample sent to flow cytometry.

Table 2: **Best overall response**

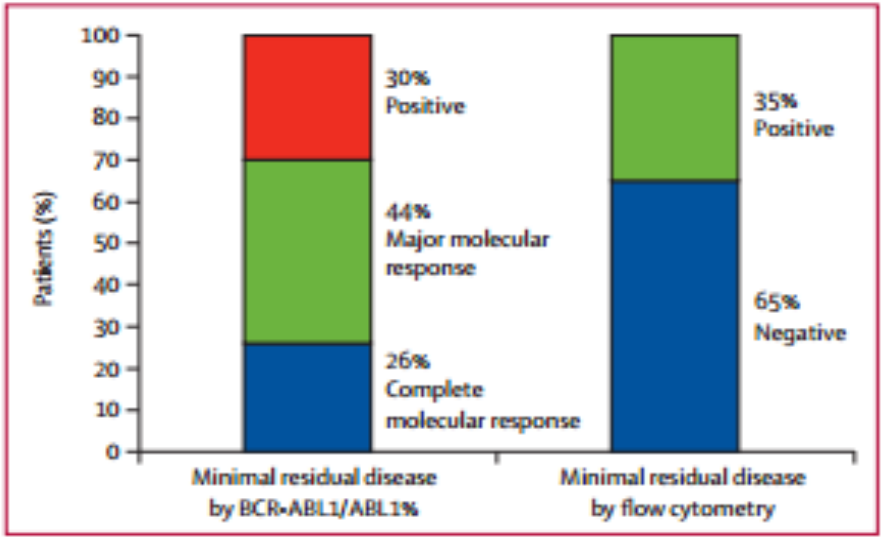


Figure 1: **Levels of residual disease after one cycle of protocol therapy in complete response**
Minimal residual disease after one cycle at complete remission by BCR-ABL1/ABL1 percentage and flow cytometry.

Jabbour et al, Lancet Oncology 2015

Hyper-CVAD + Ponatinib in Ph-Positive ALL. Outcome

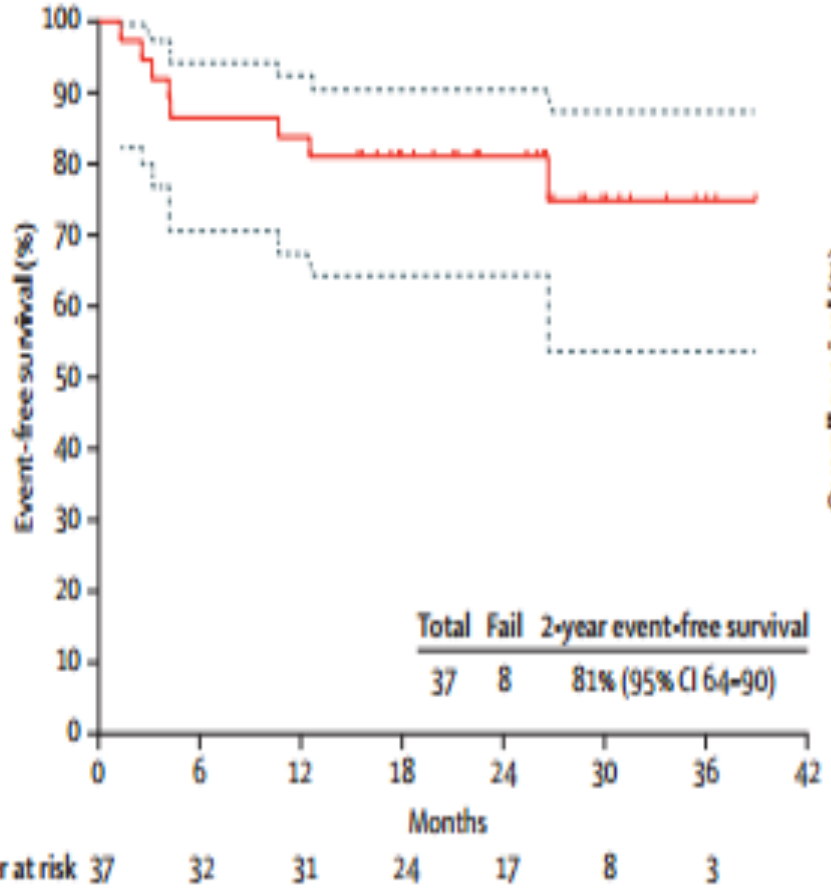
- Median follow up of 26 months (15–39)
- 31 pts are alive and in CR
- **6 pts died in CR:**
  - Unrelated:
    - 1 from an unrelated cardiac event (4 months after being taken off therapy)
    - 1 from MOF post sepsis (C2D13)
    - 1 from head injury sustained after a fall (C4D13)
    - 1 from sepsis and MOF post ASCT
  - Related:
    - 1 from non-ST elevation MI (NSTEMI) (C2D41)
    - 1 from potential MI (C4D42)
- 9 pts (24%) have undergone ASCT after a median of 4 courses (3-10)

- 2 pts relapsed at a median of 18 months (range 10–26).
- 49% of patients reduced dose to 30 mg or less

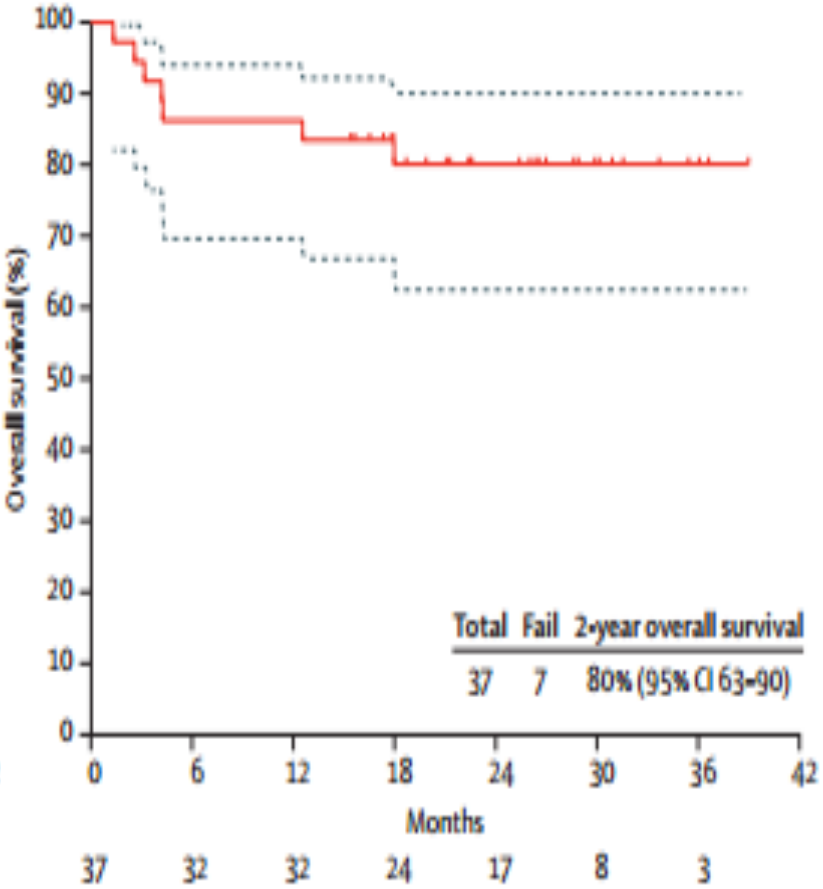
Jabbour et al, Lancet Oncology 2015

Hyper-CVAD + Ponatinib in Ph-Positive ALL: survival

2-yrs EFS:81%



2-yrs OS: 80%



"*Beginning on Aug 1, 2014, the protocol was amended; ponatinib was given at 45 mg daily for 14 days during induction therapy, then at 30 mg daily continuously starting with the second cycle, and then further reduced to 15 mg daily continuously once a complete molecular response was achieved*."

Topics

- Allo-SCT?

The open question: Allo-SCT

- What is the best approach for MRD negative patients?

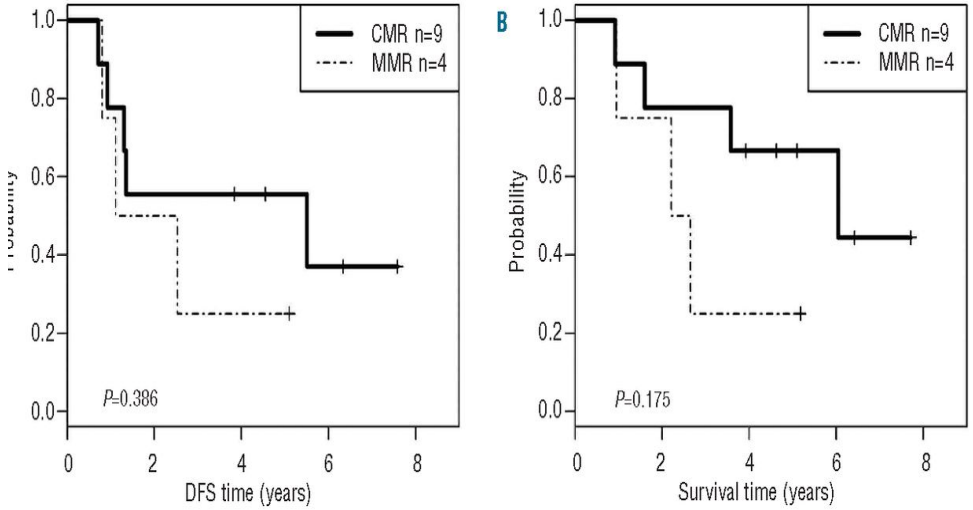
✓ Do these patients really need transplant??

✓ If so, is allo-SCT the only answer???

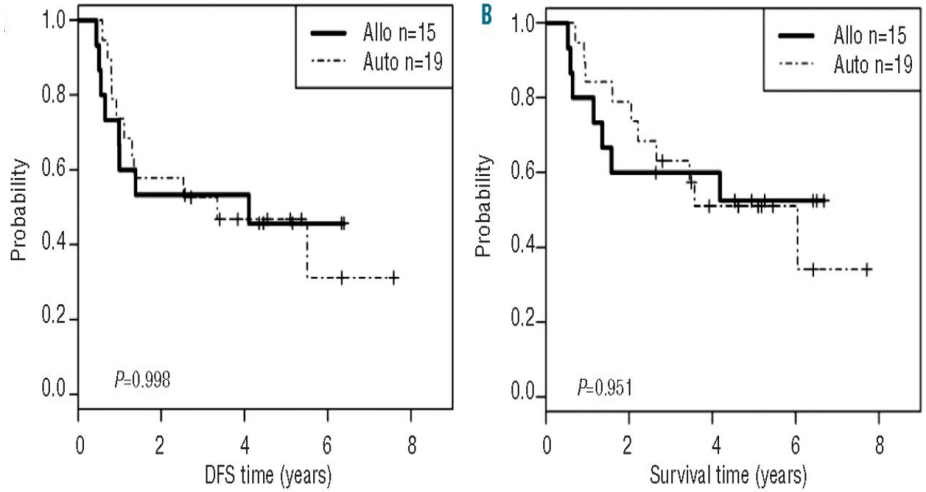
✓ Could auto-SCT an alternative answer??

Autologous BMT in TKI era: a new role (I)?

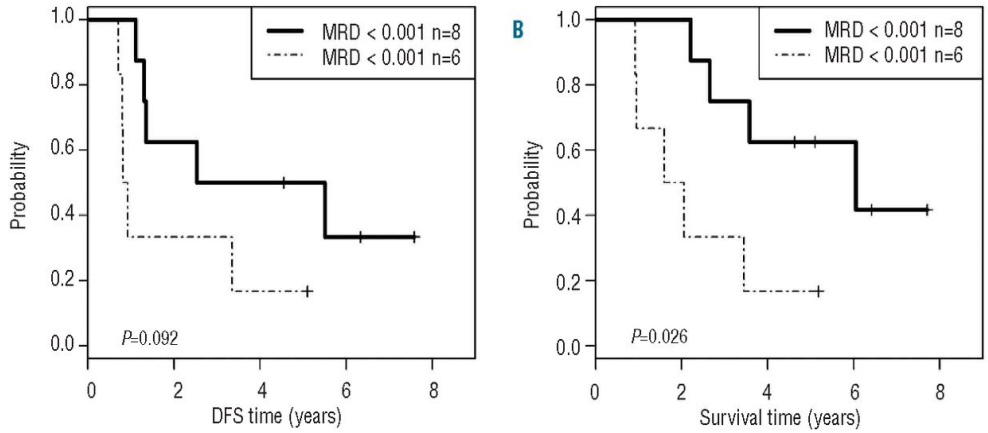
On MRD on stem cell collection

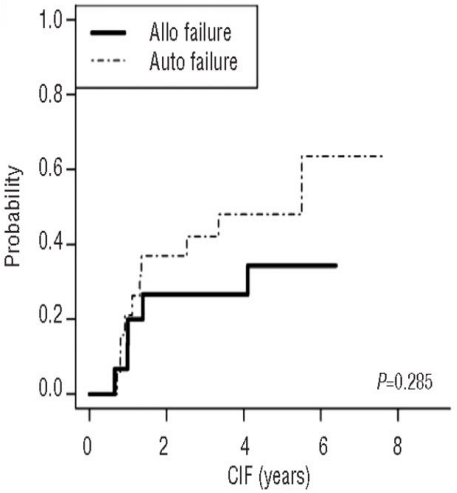


Comparison between Allo and auto-HSCT



On MRD on day +120 post aBMT





Wetzler et al, Haematologica 2013

Autologous BMT in TKI era: a new role (II)?

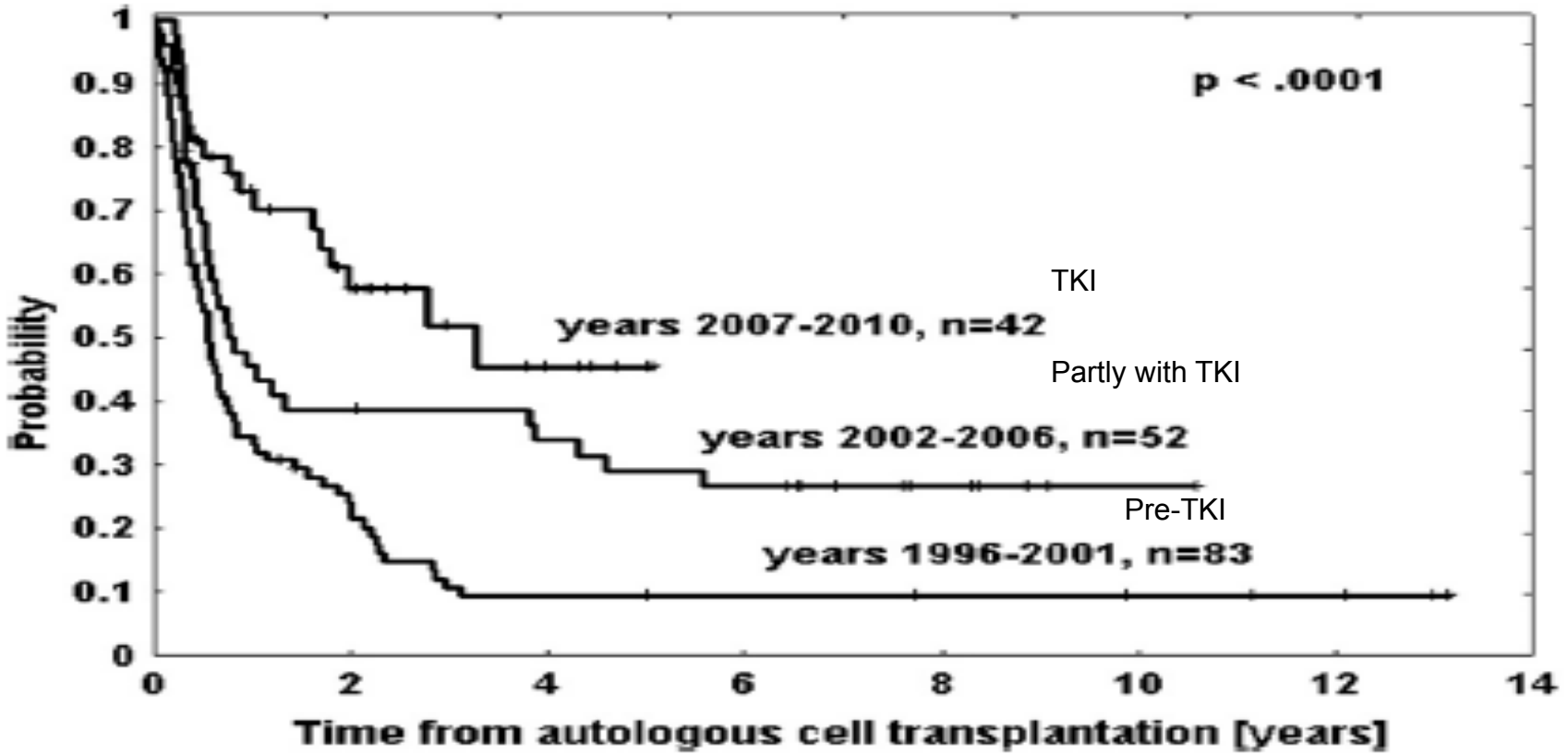


Fig. 1. Leukaemia-free survival after autologous stem cell transplantation in adults with Philadelphia-positive acute lymphoblastic leukaemia according to year of transplantation.

Giebel s, et al. EJC 2014

Concluding remarks

- Induction: TKI alone proved sufficient and spares deaths in induction.
- MRD negativity: nowadays must be considered the major goal.
- Mutations still represents the biggest problem in these patients.
- Allo-SCT: possibly not necessary in all cases

Thank you!