AIH – Marseille
28/09/2013

Stratégies innovantes
-
Leucémies aiguës lymphoblastiques

Nicolas Boissel

Unité d'Hématologie

Adolescents et Jeunes Adultes

Hôpital Saint-Louis

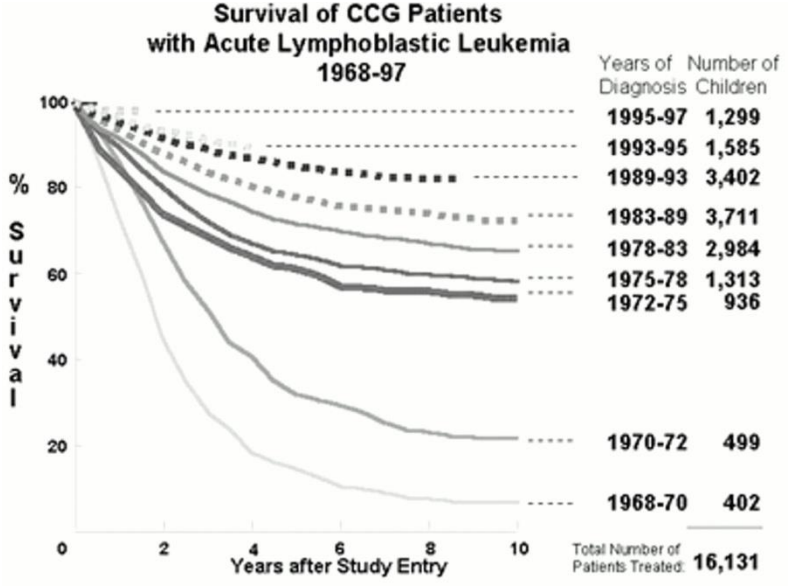
centre hospitalo-universitaire et de recherche

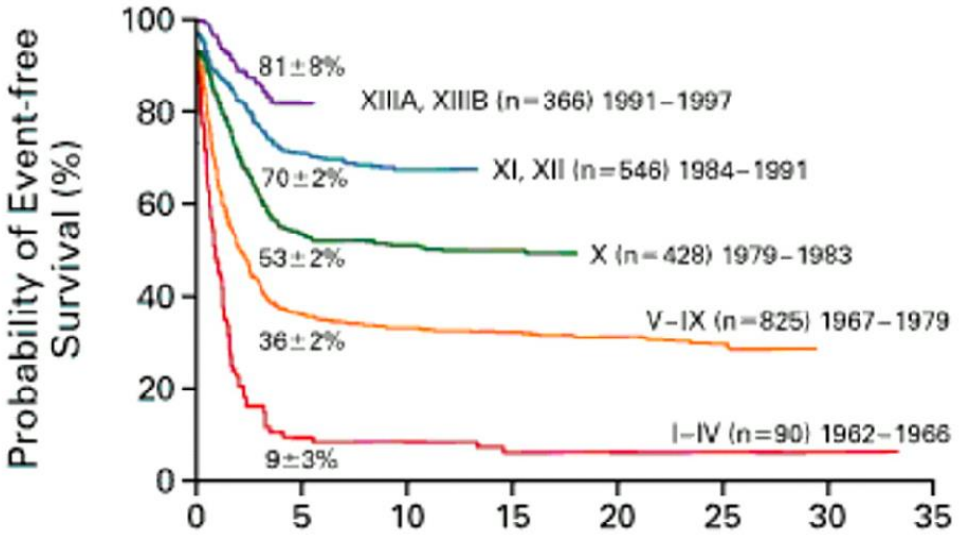
Conventional drugs in ALL

- Steroids
- Vincristine
- Anthracyclines
- L-asparaginase
- Cyclophosphamide

- Methotrexate
- Aracytine
- VP16, VM26,
- 6TG, 6MP

Advances in childhood ALL (1)





Pui, Evans, NEJM 1998
ASH Education Program Book, 2000

Advances in childhood ALL (2)

- 4/5-drug induction including anthracyclin
- Treatment of subclinical CNS involvement
  - DXM, IT chemotherapy
  - High-dose MTX
- Late intensification (delayed reinduction)
- Maintenance therapy up to 2 years

Adult ALL - The old years

- 4/5-drug induction w/o asparaginase
- High-dose consolidation
  - HAM
  - HD-MTX
- Early allogeneic SCT if a sibling donor
  - All patients
  - High-risk patients (standard old criteria, including Ph+)
- Autologous SCT or CTx/maintenance if no donor
- One famous exception
  - The Hyper-CVAD protocol

Adult ALL – Old results

Trial	Ref.	Pts (N)	Period	Median age	CR rate	DFS	OS
CALGB-9111	*Larson Blood 1998*	185	1991-1993	35 years	85%	40% (3y)	43% (3y)
JALSG-93	*Takeuchi Leukemia 2002*	263	1993-1997	31 years	78%	30% (6y)	33% (6y)
GIMEMA-0288	*Annino Blood 2002*	769	1988-1994	27.5 years	82%	29% (9y)	27% (9y)
LALA-94	*Thomas JCO 2004*	992	1994-2002	33 years	84%	30% (5y)	33% (5y)
GOELAL-02	*Hunault Blood 2004*	198	1994-1998	33 years	86%	NA	41% (6y)
UKALL-XII ECOG-E2993	*Goldstone Blood 2008*	1,913	1993-2006	NA	90%	NA	39% (5y)
HyperC-VAD	*Kantarjian Cancer 2004*	288	1992-2000	40 years	92%	NA	38% (5y)

- CR rate, 80-90%
- 5-year OS, 35 to 40%

Major breakthroughs since 2000 in adult ALL

- Comparative Adolescents and Young Adults (AYAs) studies and pediatric-inspired ptotocols in Ph-negative adult ALL.

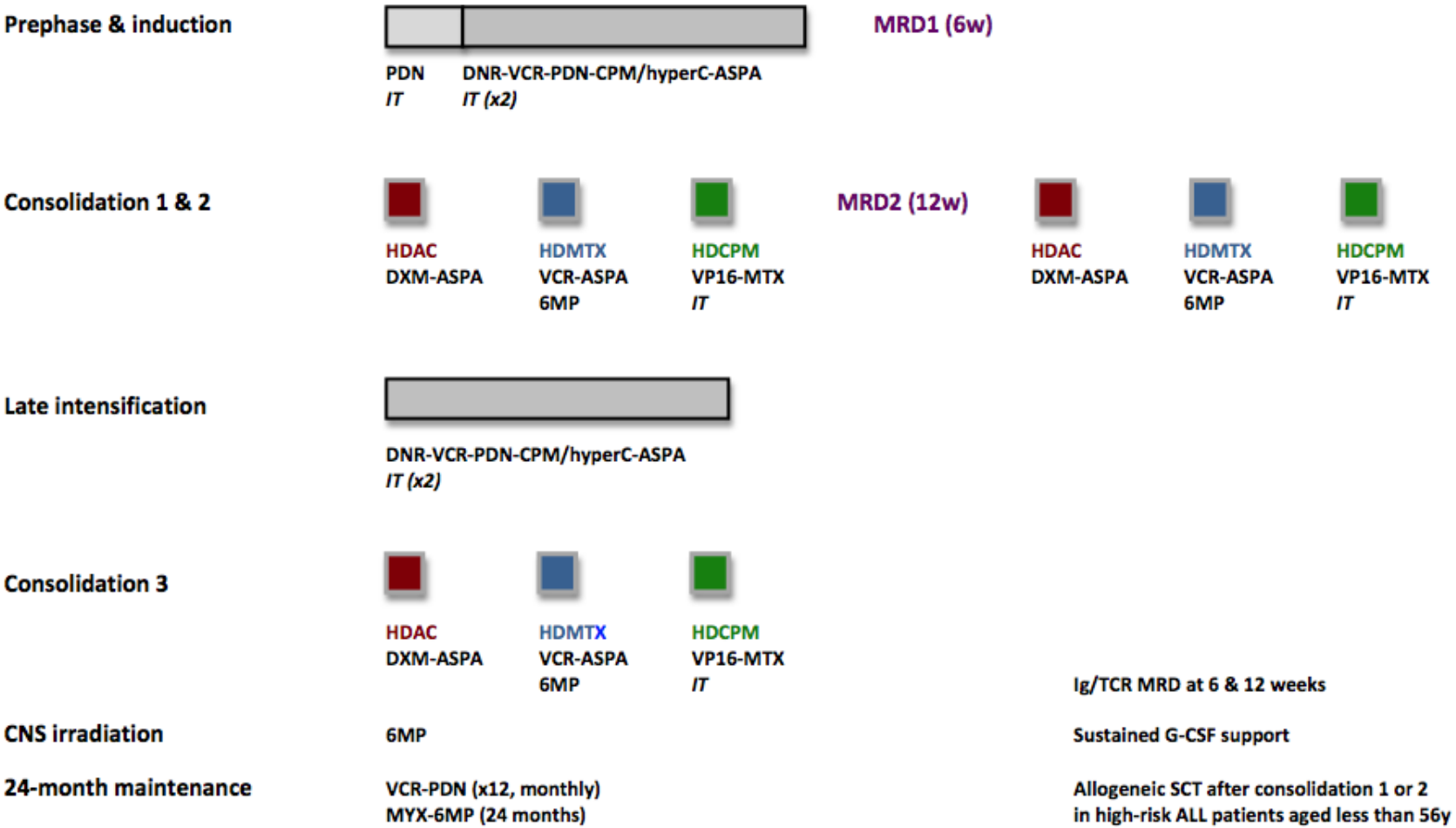
- Imatinib, then 2nd generation TKIs, in Philadelphia chromosome (Ph)-positive ALL.

GRAALL-2003 Pediatric-inspired trial

- *Pediatric approach*
  - Steroid prephase
  - High cumulative doses of PDN, VCR, and L-aspa
  - High dose-intensity consolidation
  - Late intensification
  - 2-year maintenance
- *Adult approach*
  - HyperC sequence
  - CNS irradiation
  - Allogeneic SCT for high-risk patients
  - Early G-CSF

Huguet, JCO 2008

The GRAALL protocol

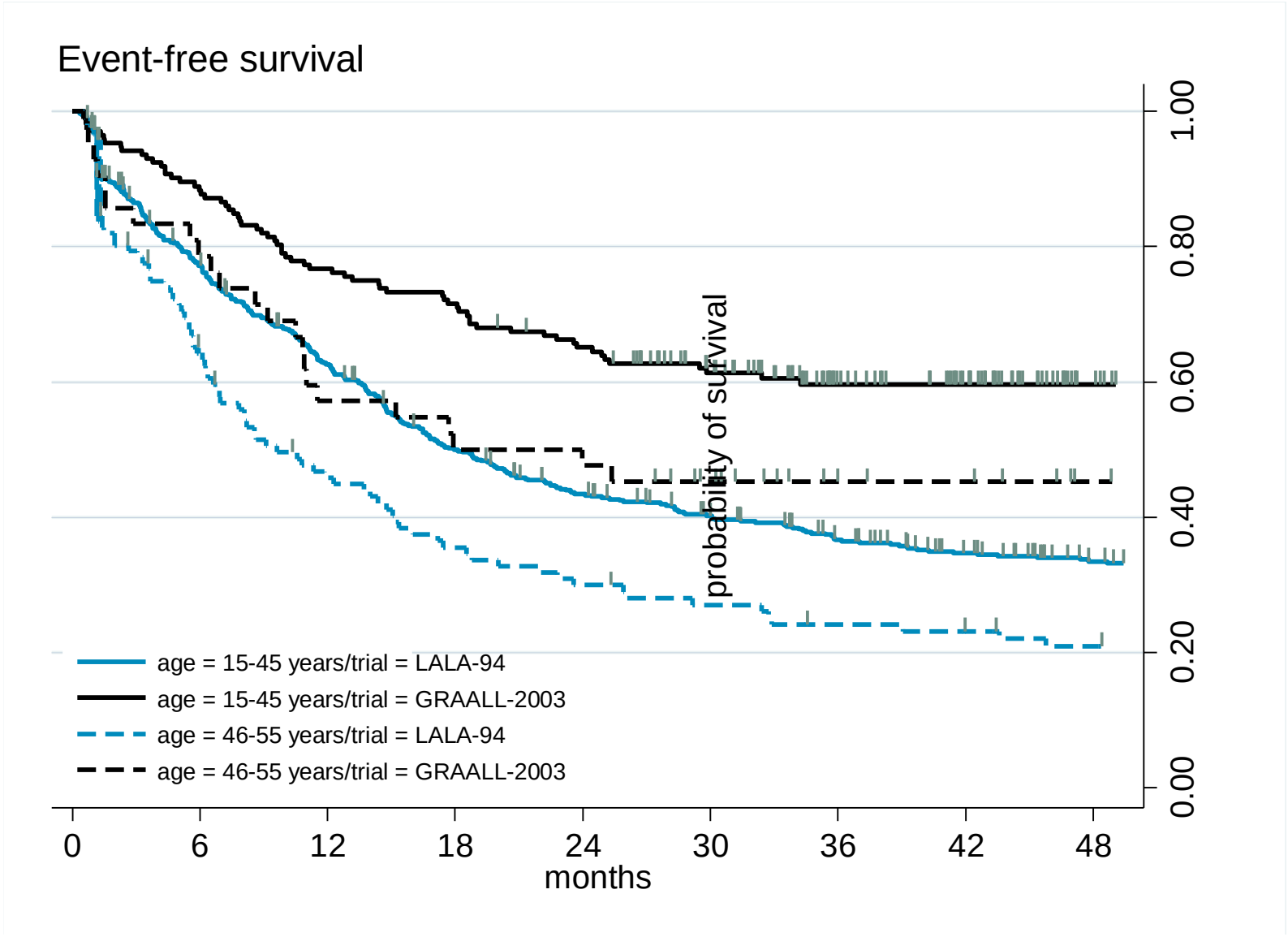


GRAALL-2003 vs LALA-94 : cumulative doses (/sqm)

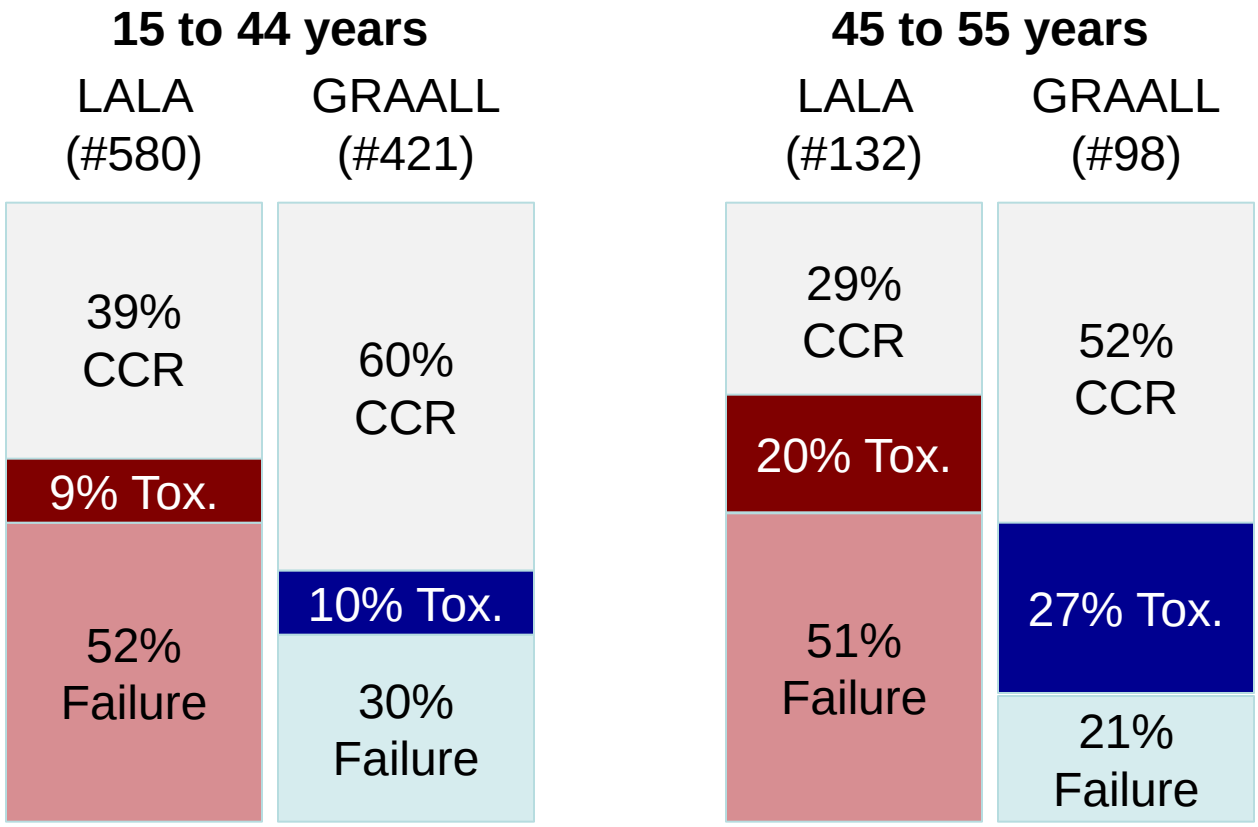
	LALA-94	GRAALL-2003	FRALLE 93
PDN (mg)	840	7,260	4,340
VCR (mg)	6	22	19
L-ASPA (IU.10^3)	9	144	180
VP16 (mg)	0	450	1,200
CPM (g)	12.5	6 or 7*	0
Ara-C (g)	4,3 or12**	24	0.96

** single dose or repeted bolus*

*** without or with intensive consolidation*


Event-free survival
probability of survival
1.00
0.80
0.60
0.40
0.20
0.00
0
6
12
18
24
30
36
42
48
months
age = 15-45 years/trial = LALA-94
age = 15-45 years/trial = GRAALL-2003
age = 46-55 years/trial = LALA-94
age = 46-55 years/trial = GRAALL-2003

LALA-94 *vs* GRAALL-2003/05
3-year cumulative incidences of events



Toxicity: includes induction deaths and deaths in first CR
Failure: includes remission induction failures and relapses

New strategies

- **Improve risk stratification**
- **Decrease treatment-related mortality**
- **Improve old treatment efficacy**
- **Introduce risk-adapted new therapeutics**

Improve risk stratification

From historical risk factors…

- **Baseline factors**
  - WBC ≥ 30,000/μL for B-lineage ALL
  - CNS disease
  - Pro-B ALL *
  - t(4;11) a/o MLL-AF4, t(1;19) a/o E2A-PBX1
  - Low hypo-diploidy, near tri-ploidy
  - Complex karyotype (≥ 5 abns.) *
- **Poor early response**
  - Peripheral blood resistance to steroid (CsR) after the 1-week prephase
  - Bone marrow resistance to chemotherapy (ChR) at day 8 of CTx
  - No hematological CR after the first induction course

Do not include age
**: introduced in the GRAALL-2005 study*

… to current relapse predictors

(in GRAALL trials)

- **B-lineage ALL**
  - WBC
  - t(4;11) translocation or MLL+
  - **IKZF1 deletion ***
  - **Post-induction MRD ***
- **T-lineage ALL**
  - WBC
  - CNS disease
  - **Oncogenetics (4 genes) ***
  - **Post-induction MRD ***

**: independent relapse predictors in multivariate analysis*

GRAALL
LALA GOELAMS SAKK

Improving old treatment efficacy

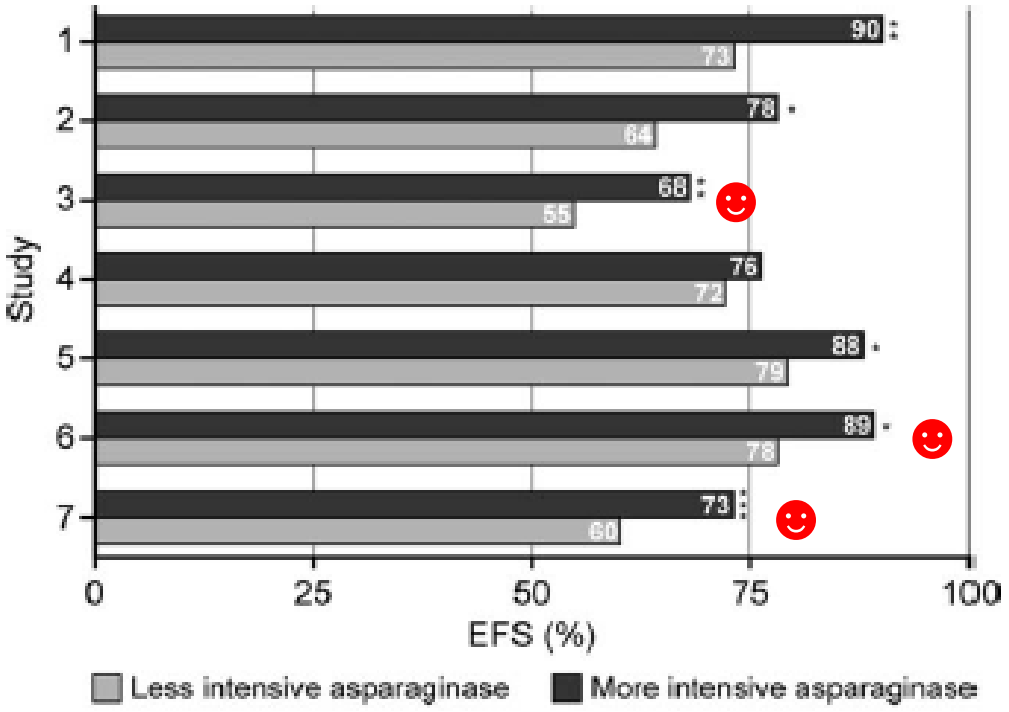
Asparaginase

- Asparaginase available :
  - Native asparaginase derived from *Escherichia coli* (L-ASPA)
  - Pegylated form of the native E. coli asparaginase (PEG-ASPA)
  - Asparaginase derived from Erwinia chrysanthemi, referred to as Erwinia asparaginase (ERW)

- Asparaginase under investigation :
  - asparaginase encapsulated into homologous red blood cells (GRASPA)
  - Pegylated form of Erwina (PEG-ERW)

- Activity = deamination of asparagine +/- glutamine in the plasma and cerebrospinal fluid

L-Asparaginase : More is better (1)
Pediatric studies



Intensification studies

1 Less than or greater than 25 weeks of treatment
2–5 Additional 20 weeks of treatment
6–7 *Erwinia* vs *E.Coli*-ASP

*p<0.05; **p<0.01; ***p<0.001

1 Silvermann Blood 2001 DFCI
25 000UI/w EColi
vs
2500 UI Peg / 2/w 30 sem
2 Amylon Leukemia 1999
3 Amylon Leukemia 1999
4 Rizzari JCO 2001
5 Pession JCO 2005 DFCI
6 Moghrabi Blood 2007 DFCI
7 Duval Blood 2002 EORTC

EFS improvement in children treated with more L-asparaginase,
mostly during consolidation

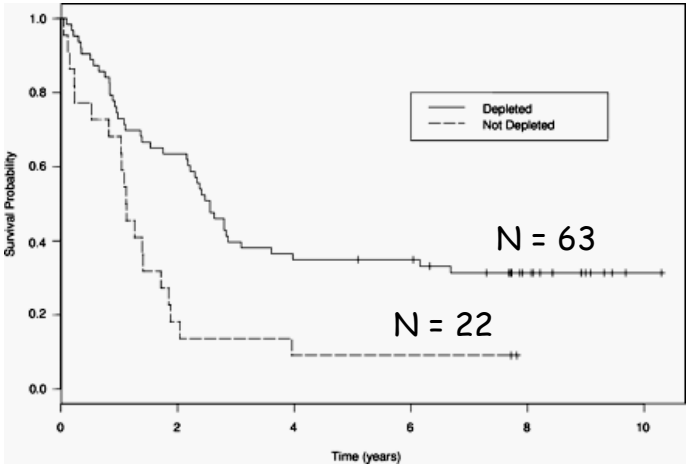
Pieter, Cancer review 2010

L-Asparaginase : More is better (2) Adult studies

- Asparagine depletion associated with improved OS (*Wetzler M, Blood 2007)*

  CALGB 8811 Peg-Aspa 2000U/m²d5,22 induction and d15,43 first intensification

  Asparagine depletion defined by < 0.03 U/ml

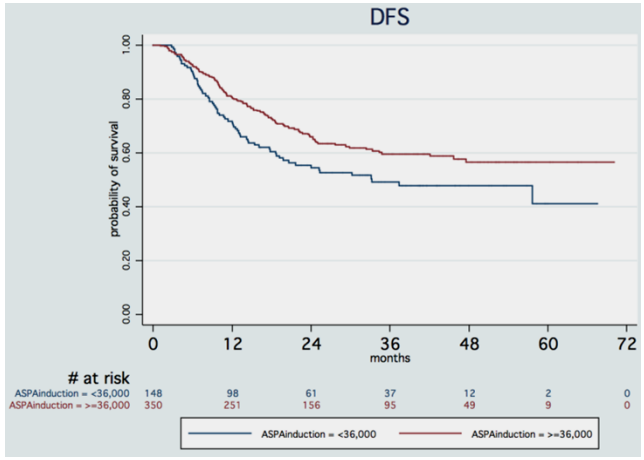


- GRALL2003 results compared to historical LALA-94 controls *(Huguet JCO 2009)*

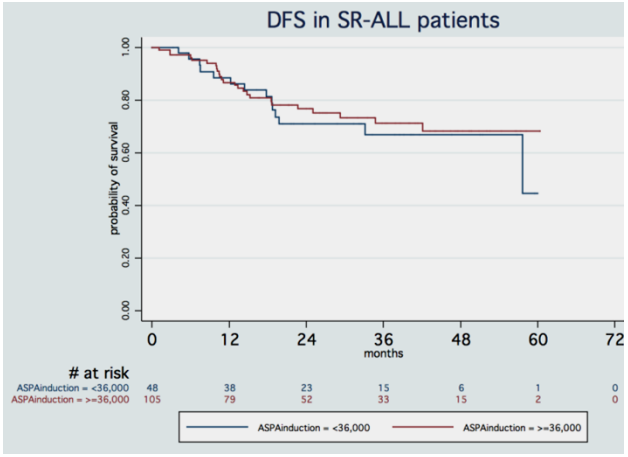
Induction	Kidrolase 8 x 6 000 U/m²
Consolidation	kidrolase 6 x 10 000U/m²
Late intensification	Kidrolase 8 x 6 000 U/m²

GRALL 2003-2005

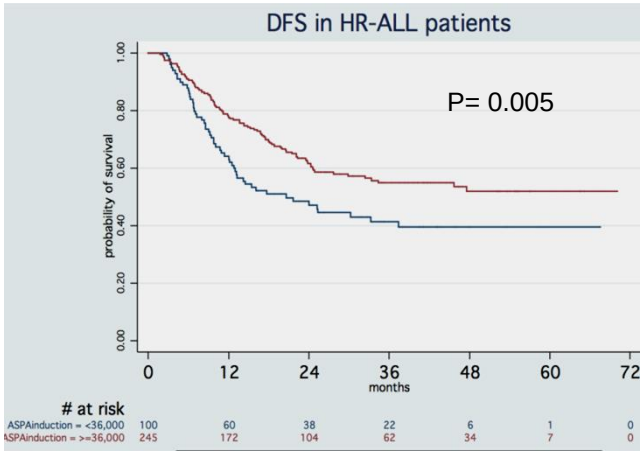
25% of pts < 36 000/m² for any reasons

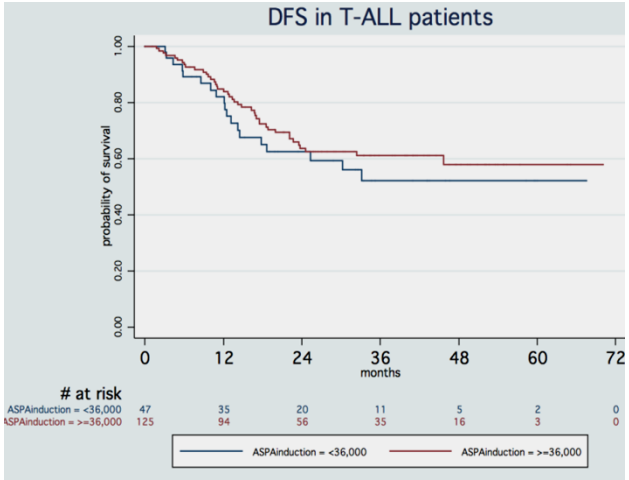


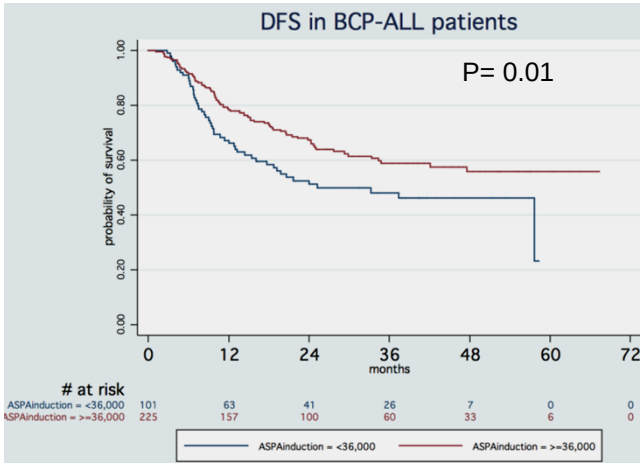
≥ 36 000 350
< 36 000 148



Asparaginase beneficial effect mostly in high risk and B-ALL







Hypersensitivity and silent inactivation

- Analysis of 280 pts with follow up > 30 months, CCG 1961
  E. Coli ASPA 9 x 6000 U/m² x 3/week during induction

94% neutralizing antibodies

Group	Allergy	Antibody (+)	n (%)	Events	Hazard ratio
A	No	No	57 (20)	3/57 (5.2%)	1.0
B*	Yes	No	27 (10)	2/27 (7.4%)	1.3
C*	Yes	Yes	115 (41)	3/115 (2.6%)	0.6
D†	No	Yes	81 (29)	13/81 (16%)	3.2
Total			280 (100)	21/280 (7.5%)	

* Patients treated with Erwinase once allergy symptoms appeared;
† Silent inactivation patients continued to receive E.Coli asparaginase

Panosyan J Pediatr Hematol Oncol 2004

Hypersensitivity and silent inactivation

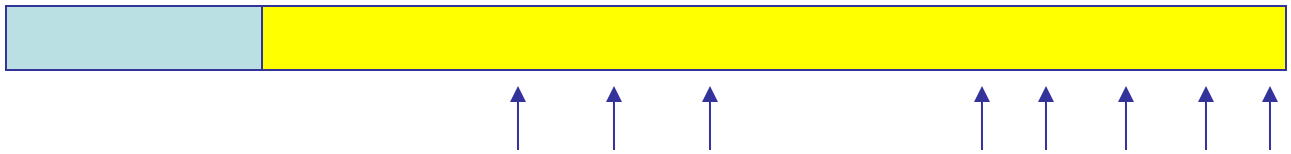
- Hypersensitivity reactions rates differ according to
  - treatment schedule (induction, consolidation),
  - doses,
  - associated drugs.

- E. coli L-asparaginase 45-70%
- Peg-Aspa (also Ab anti-PEG) 2-30%
  - 28% after allergic reaction to E.Coli Aspa
  - In naive children, 26% after Kidrolase vs 2% after Peg-Aspa

    Avramis Blood 2002
- Erwinia 30%
  - 33% after allergic reaction to Aspa

    Vrooman Ped Blood Cancer 2010

Asparaginase
GRAALL 2005 / Induction course

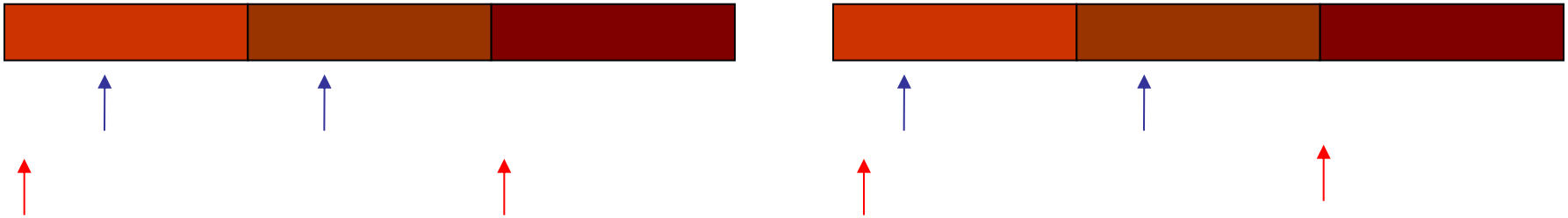


- Median asparagine basal level at Day 8 was 39 µMol/L (25-60)
- No patient with antibody at day 8 before L-Asparaginase infusion

	Day 13	Day 20	Day 29
Asparagine full depletion	97% 28/29	100% 30/30	100% 26/26
Antibodies detection	0% 0/29	0% 0/29	4% 1/26

Hunault, EHA 2013

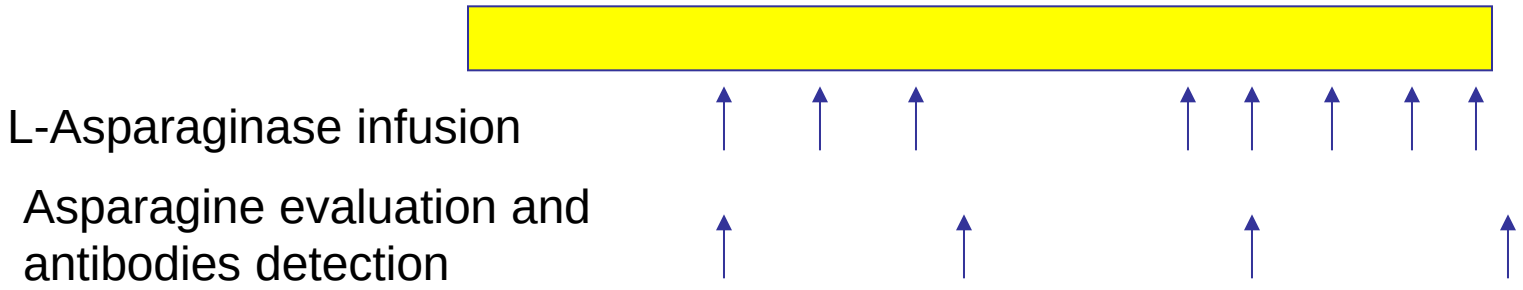
Asparaginase
GRAALL 20005 / Consolidation



- Allergic reaction:
  - 11/23 patients (48%)
  - 10/11 patients with antibodies
- Antibodies detection:
  - 11/23 patients (48%)
  - One patient without clinical reaction= silent antibodies
  - One patient with depletion= no biological relevance
- Asparagine depletion :
  - 7/10 evaluable patients
  - 3 patients received L-Asparaginase without depletion

Hunault, EHA 2013

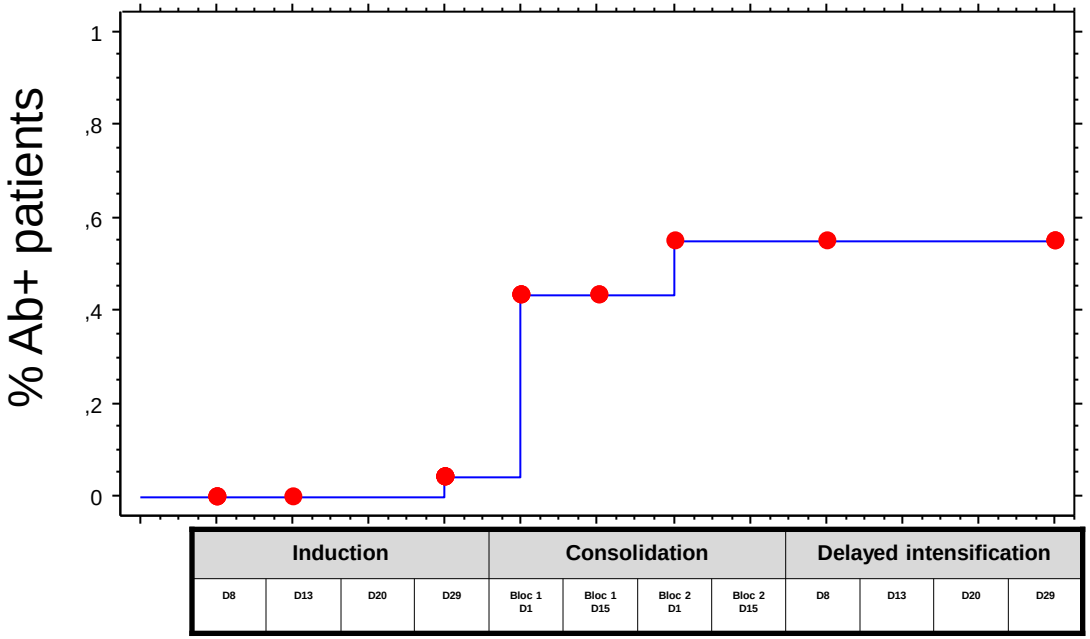
Asparaginase
GRAALL 20005 / Late intensification



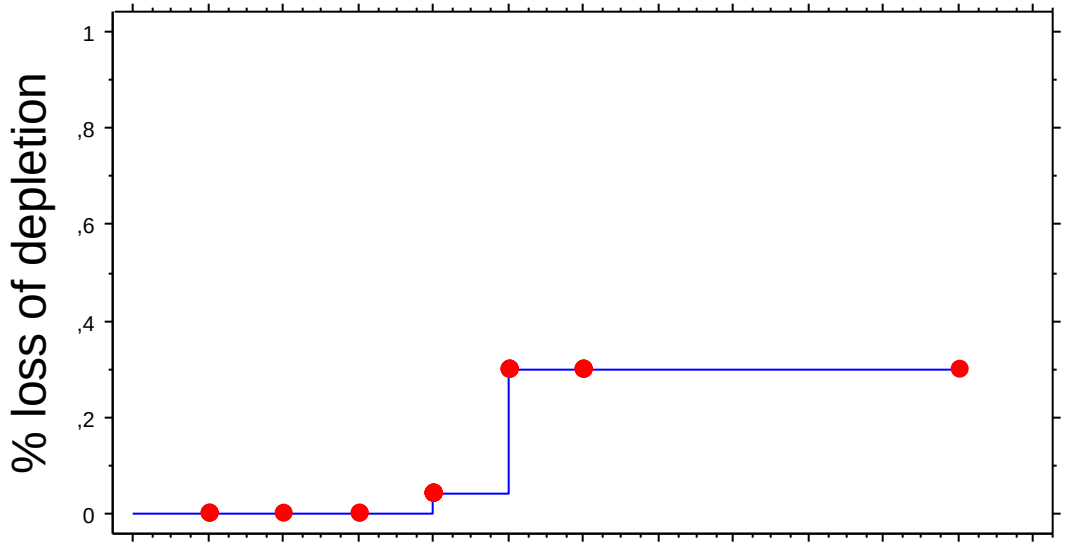
- 6 patients received ERW 12000UI/m2 for late intensification:
  - 5 for anaphylactic reaction during consolidation with Ab detection
  - 1 for encephalitis post kidrolase.
- Two patients received L-ASPA as during late induction.
- All these 8 patients experienced full depletion.

Hunault, EHA 2013

Time to immunization / loss of depletion



Induction				Consolidation				Delayed intensification			
D8	D13	D20	D29	Bloc 1 D1	Bloc 1 D15	Bloc 2 D1	Bloc 2 D15	D8	D13	D20	D29



GRAALL-2013
How to improve asparaginase activity ?

- Protocol design :
  - Asparaginase during induction and late intensification (6 to 9 infusion/cycle)
  - No asparaginase during consolidation (to decrease anti-asparaginase immunization)

- Activity monitoring :
  - During induction and late intensification
  - 48 hours after the 3rd infusion (n°3 & 6)
  - Activity target : 100 UI/L

- Antibody detection :
  - During consolidation (D1, D21 and D45)

GRAALL-2013
How to improve asparaginase activity ?

- ERW substitution if :
  - Clinical allergy to L-ASPA
  - Antibody detection
  - Loss of activity of L-ASPA during late intensification

- GRASPA substitution if
  - Clinical allergy to ERW
  - Loss of ERW activity of during late intensification

Introduce risk-adapted new therapeutic strategies

GRAAPH 2005
Treatment schedule

Steroid prephase
Ph+ and/or BCR-ABL diagnosis

Randomization

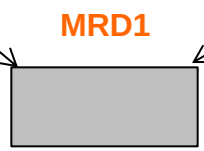
Cycle 1
First induction

IM-based
IM (800mg for 28d)

IM-HyperCVAD
IM (800mg for 14d)

MRD1

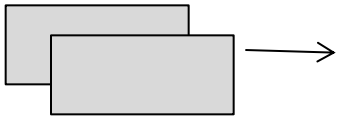
Cycle 2
Consolidation/2nd induction



HD-MTX + HD-AraC + IM (800mg for 14d)

MRD2

Interphase
Two cycles



PBSC collection if Auto-SCT

6MP+ MTX+ IM (600mg for 14d)

SCT

Donor sibling or 9-10/10 MUD	no donor MMolR at MRD2	no donor no MMolR at MR2
Allo-SCT ***MAC:CY-TBI RIC (>55 y)***	**Auto-SCT** ***CY-TBI*** *IM+6MP+MTX maintenance*	*further even and odd IM-HyperCVAD cycles and maintenance*

GRAALL
LALA GOELAMS SAKK

Patients

- **N= 270 patients randomized between 05/2006 and 08/2011**
- **N= 268 patients evaluable**
  - 1 consent withdrawal
  - 1 lost of follow-up
  - **– Median age, 47 years**
  - **– Median follow-up, 40 months**
- **Median age = 47y[18-60]**

Hematological response

	IM-based (n= 135)	IM-HyperCVAD (n=133)	p	Total (n=268)
CR	**133 (98.5%)**	**121 (91.7%)**	**0.006**	**254 (94.8%)**
Courses to CR				
one	132 (97.8%)	118 (88.7%)	0.003	250 (93.2%)
two	1 (0.7%)	3 (2.2%)	-	4 (1.5%)
Resistance after 2 cycles	1 (0.7%)	3 (2.2%)	0.35	3 (1%)
D60 mortality	**1 (0.7%)**	**9 (6.7%)**	**0.01**	**10 (3.7%)**

Molecular response

Bone marrow samples only

	IM-based (n= 135)	IM-HyperCVAD (n= 133)	p	Total (n=268)
MRD1 Tested	116 (86%)	102 (77%)	0.06	218 (81%)
MMolR	**50 (43%)**	**46 (45%)**	**0.79**	**96 (44%)**
Undetectable	11 (9%)	10 (10%)	0.99	21 (10%)
MRD2 Tested	112 (83%)	94 (71%)	0.02	206 (77%)
MMolR	**74 (66%)**	**60 (64%)**	**0.77**	**134 (65%)**
Undetectable	32 (29%)	21 (22%)	0.34	53 (26%)

MMolR= BCR-ABL/ABL < 0.1% in the bone marrow

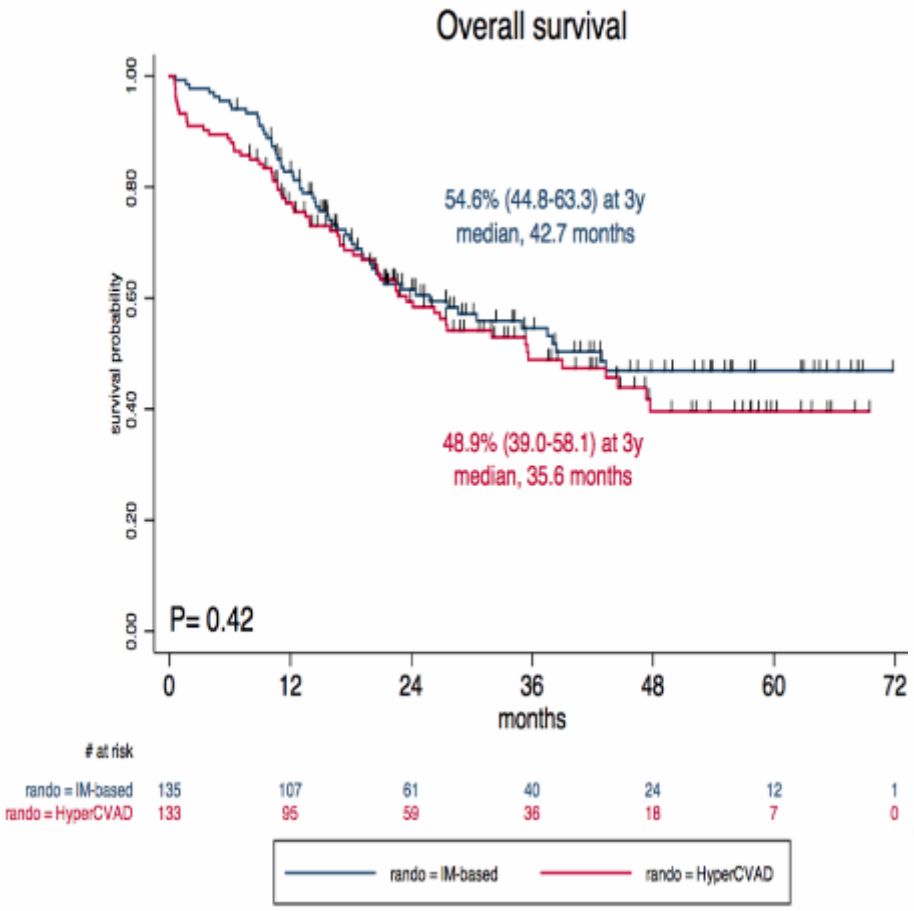
Toxicity during Cycle 1-2

	IM-based (n= 135)	IM-HyperCVAD (n=133)	p
During Cycle 1			
Neutrophils < 0.5 G/L, median	5.5 days (-14)	13.5 days (10-17)	<0.001
Platelets < 20 G/L, median	0 day (0-2)	2.5 days (0-6)	<0.001
Grade 3-4 infectious event, pts	50 (37%)	77 (58%)	0.001
Other Grade 3-4 event, pts	56 (41%)	61 (46%)	0.54
During Cycle 2			
Neutrophils < 0.5 G/L, median	7 days (5-9)	5 days (3-7)	<0.001
Platelets < 20 G/L, median	1 day (0-2)	1 day (0-4)	0.14
Grade 3-4 infectious event, pts	60 (44%)	42 (32%)	0.03
Other Grade3-4 event, pts	41 (30%)	22 (17%)	0.01

Overall survival and EFS

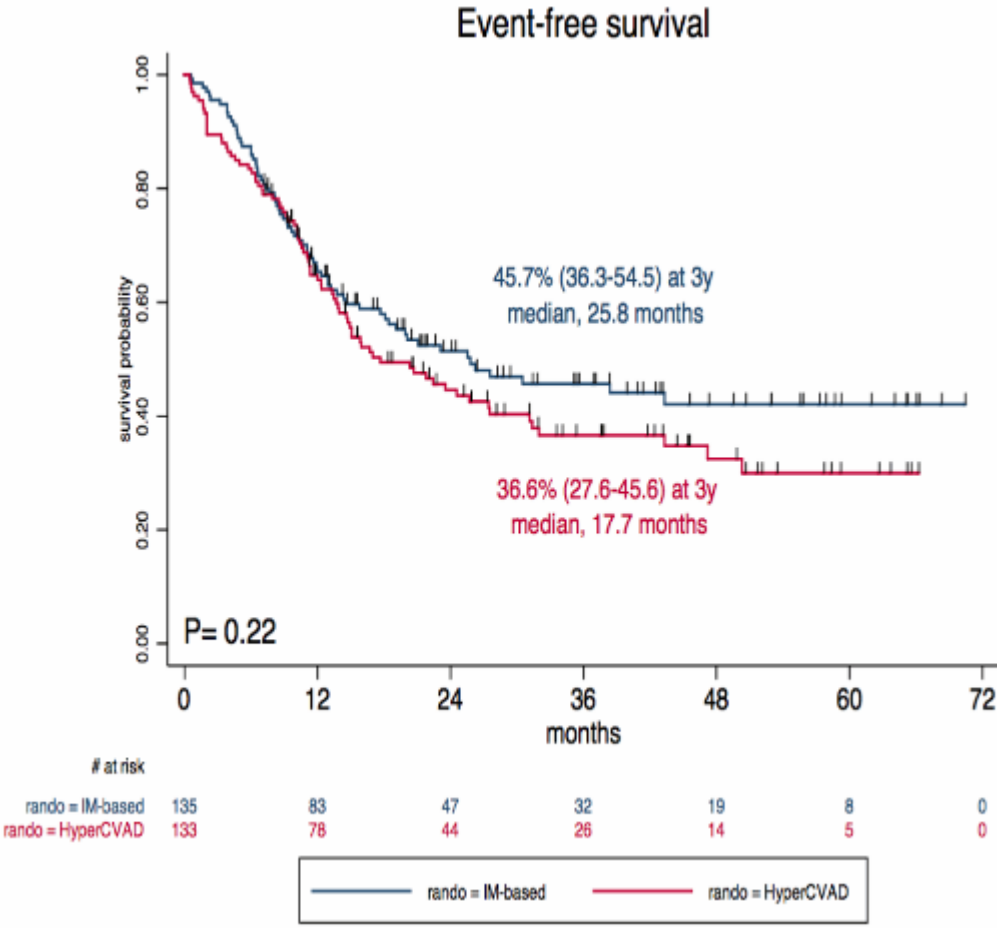
Median OS, 3.2 years

3-y OS, 51.7% (44.8-58.2)



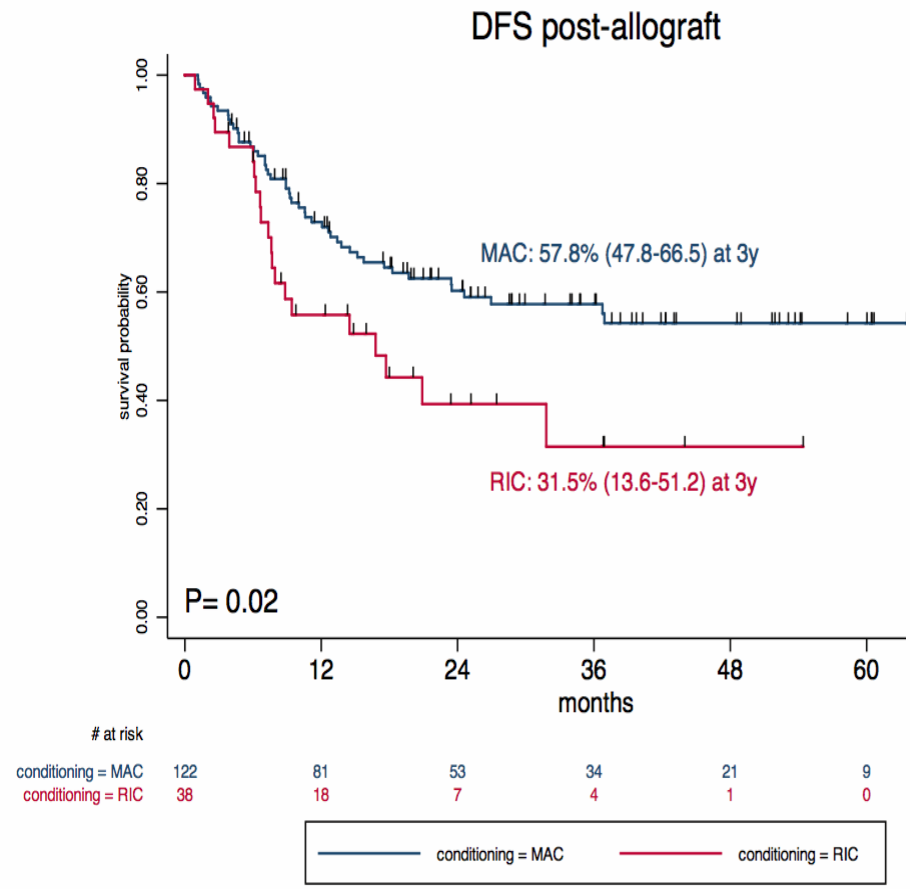
Median EFS, 1.8 years

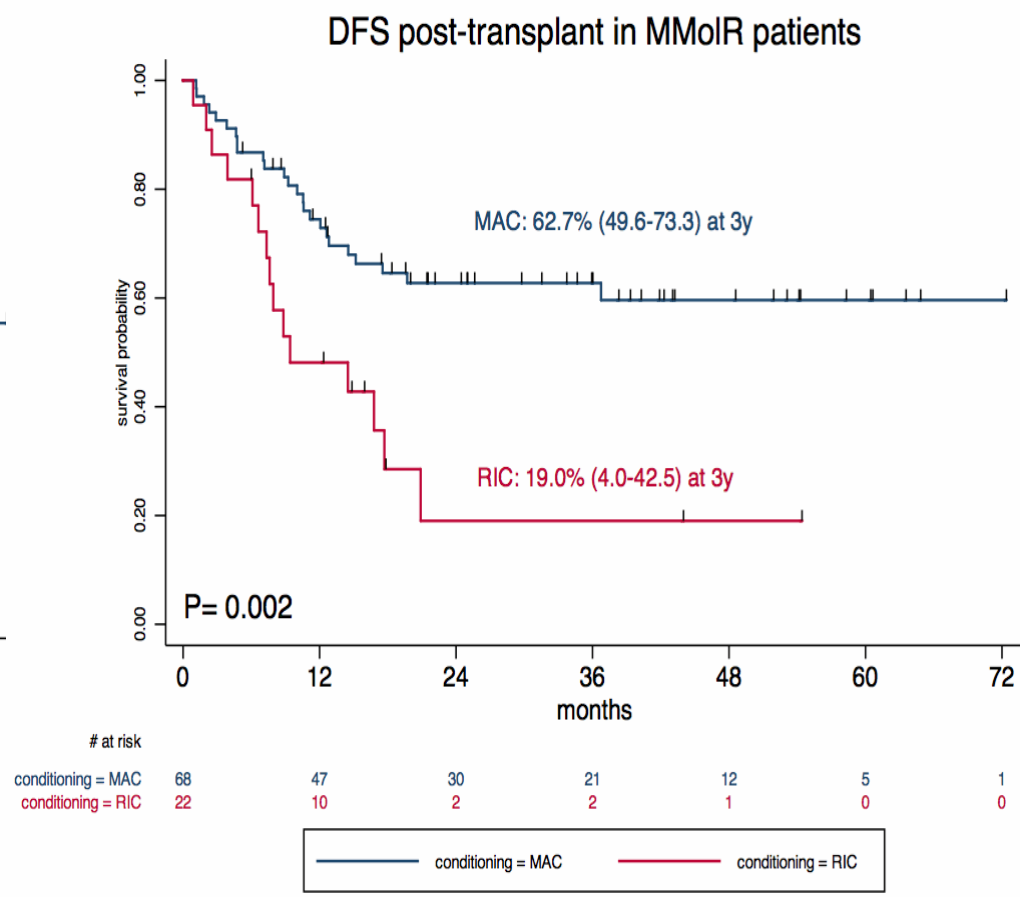
3-y EFS, 41.1% (34.6-47.5)



DFS after allogeneic SCT

RIC *versus* MAC

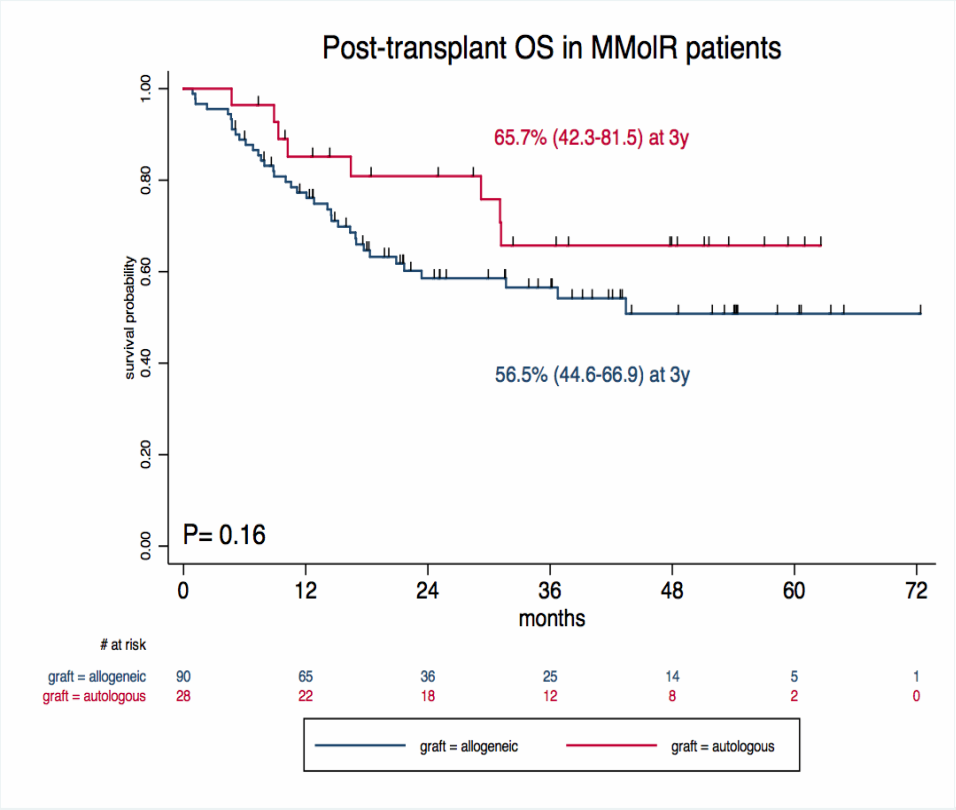


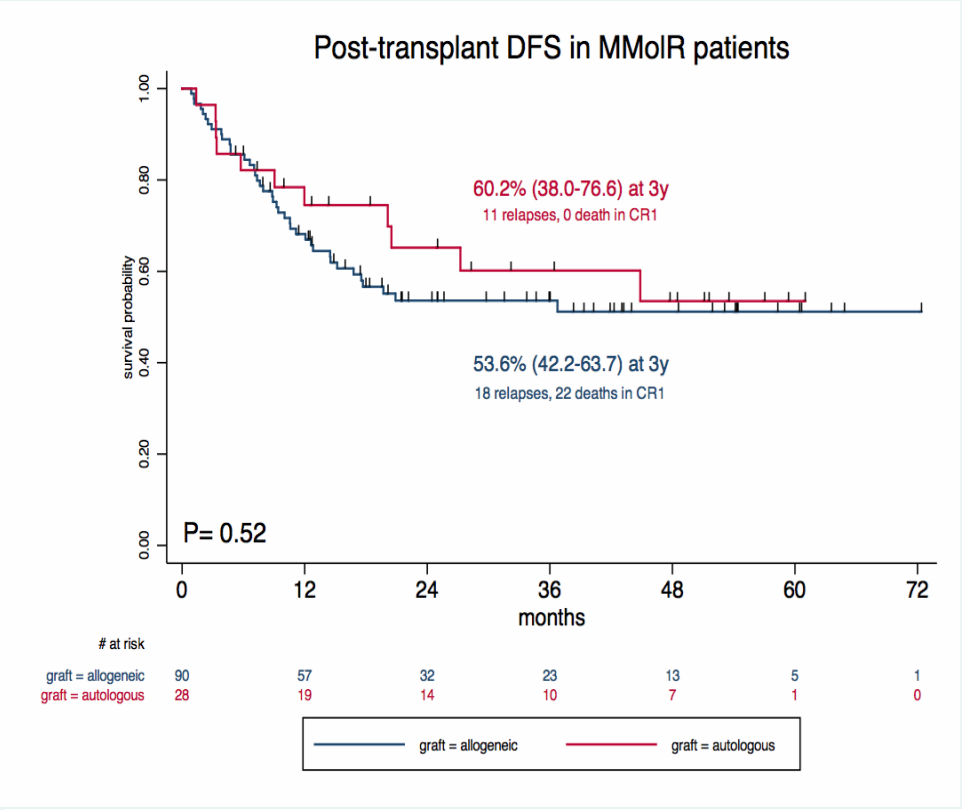


- **Similar results were observed for OS**

MMolR patients

autologous *versus* allogeneic SCT

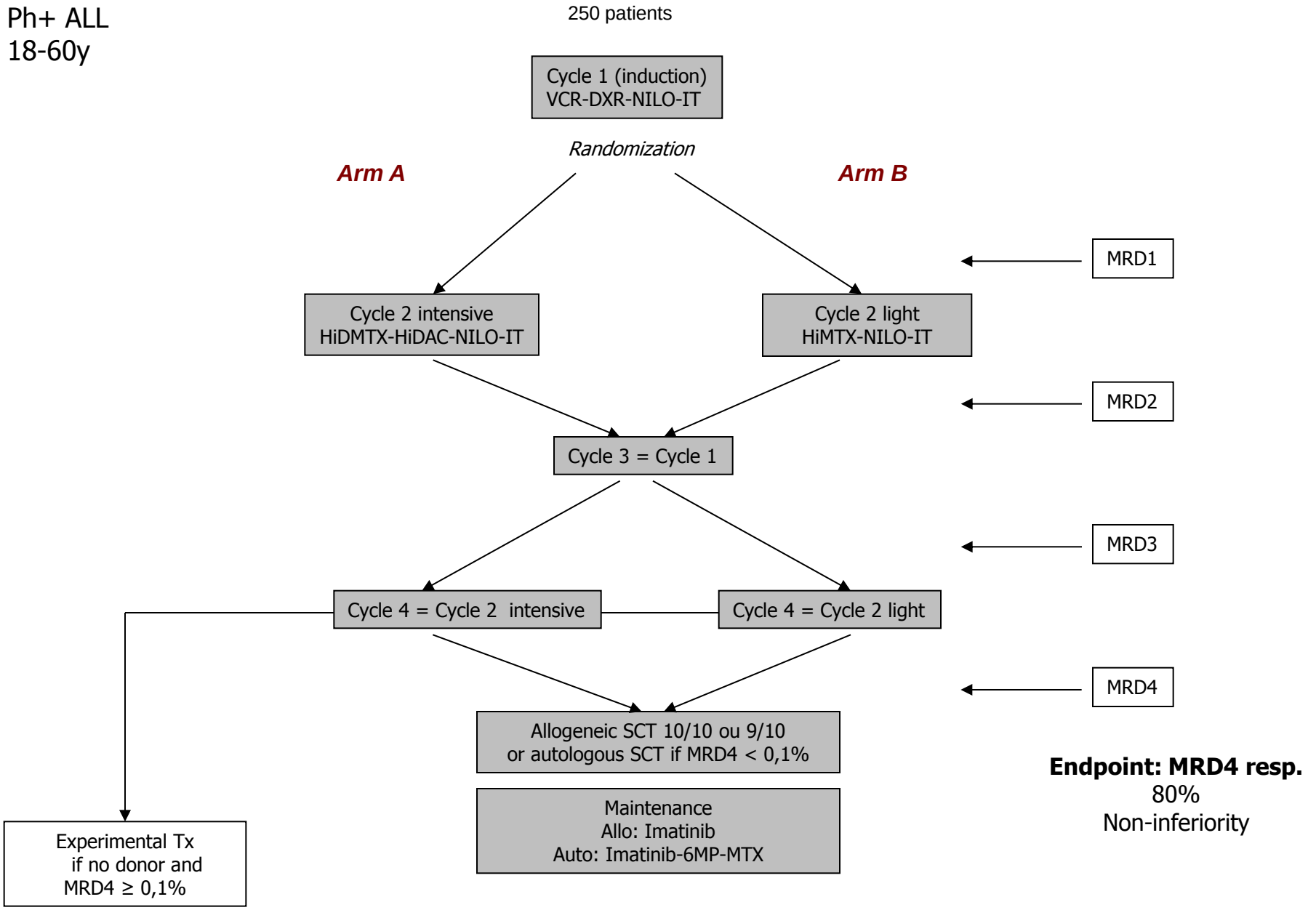




Conclusion

- **In adult patients with Ph+ ALL, treatment with imatinib allows to safely reduce the intensity of CTx prior to SCT.**
- **This reduction was even associated with a lower early mortality rate and a higher CR rate, without impacting, however, on the SCT rate and allogeneic TRM.**
- **In MMolR patients, similar outcome were observed after autologous and allogeneic SCT, validating MRD as an important early surrogate marker for treatment stratification and new drug investigation.**

GRAAPH-2013
Ph+ ALL
18-60y



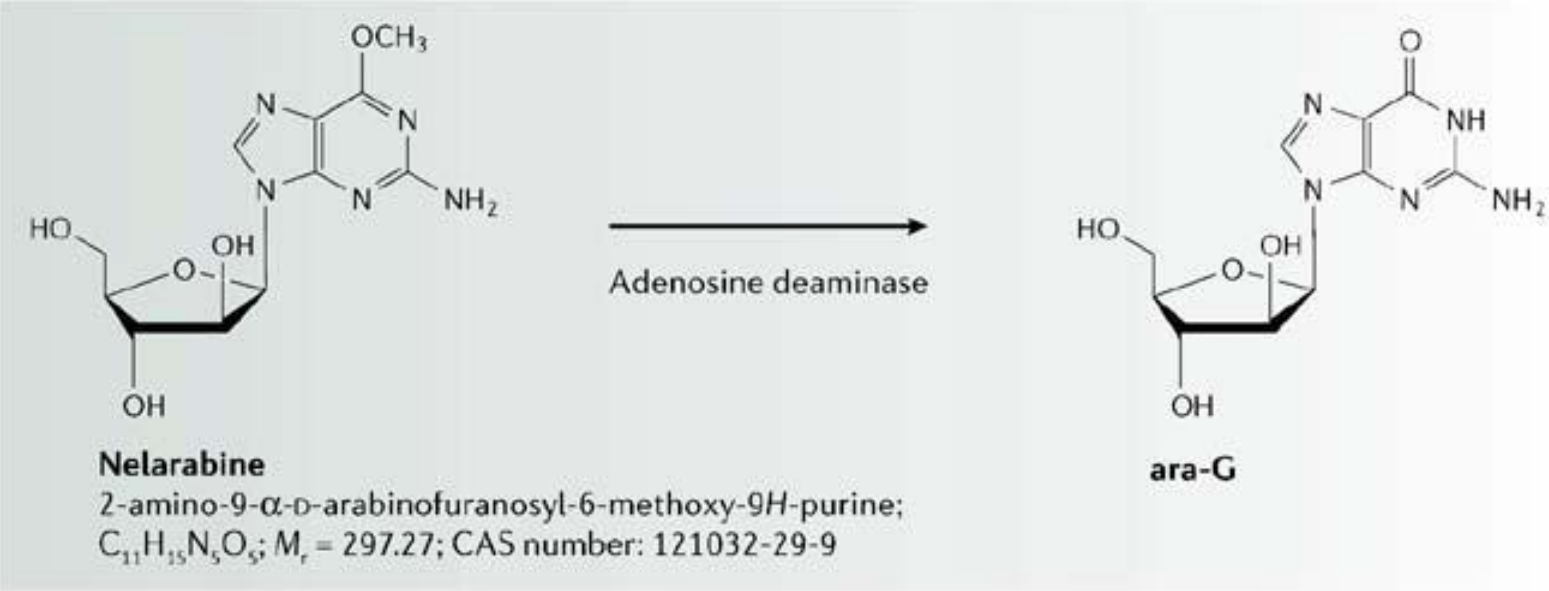
Endpoint: MRD4 resp.
80%
Non-inferiority

Emerging new agents
(TKI excluded)

- B-lineage
  - Clofarabine
  - Antibodies
    - HER2-Neu
      - Trastuzumab
    - CD20
      - Rituximab
      - Obinutuzumab
      - Ocaratuzumab
    - CD19
      - MEDI-551
      - Blinatumomab
      - SAR3419
      - Genetically targeted T cells
    - CD22
      - Epratuzumab
      - Inotuzumab ozogamicin
      - Moxetumomab pasudotox
    - CD127

- T-lineage
  - Clofarabine
  - Nelarabine
  - Forodesine
  - NOTCH inhibitors
  - Antibodies
    - CD127

Ara-G and nelarabine.



Nelarabine
2-amino-9-α-D-arabinofuranosyl-6-methoxy-9*H*-purine;
$C_{11}H_{15}N_5O_5$; M_r = 297.27; CAS number: 121032-29-9

ara-G

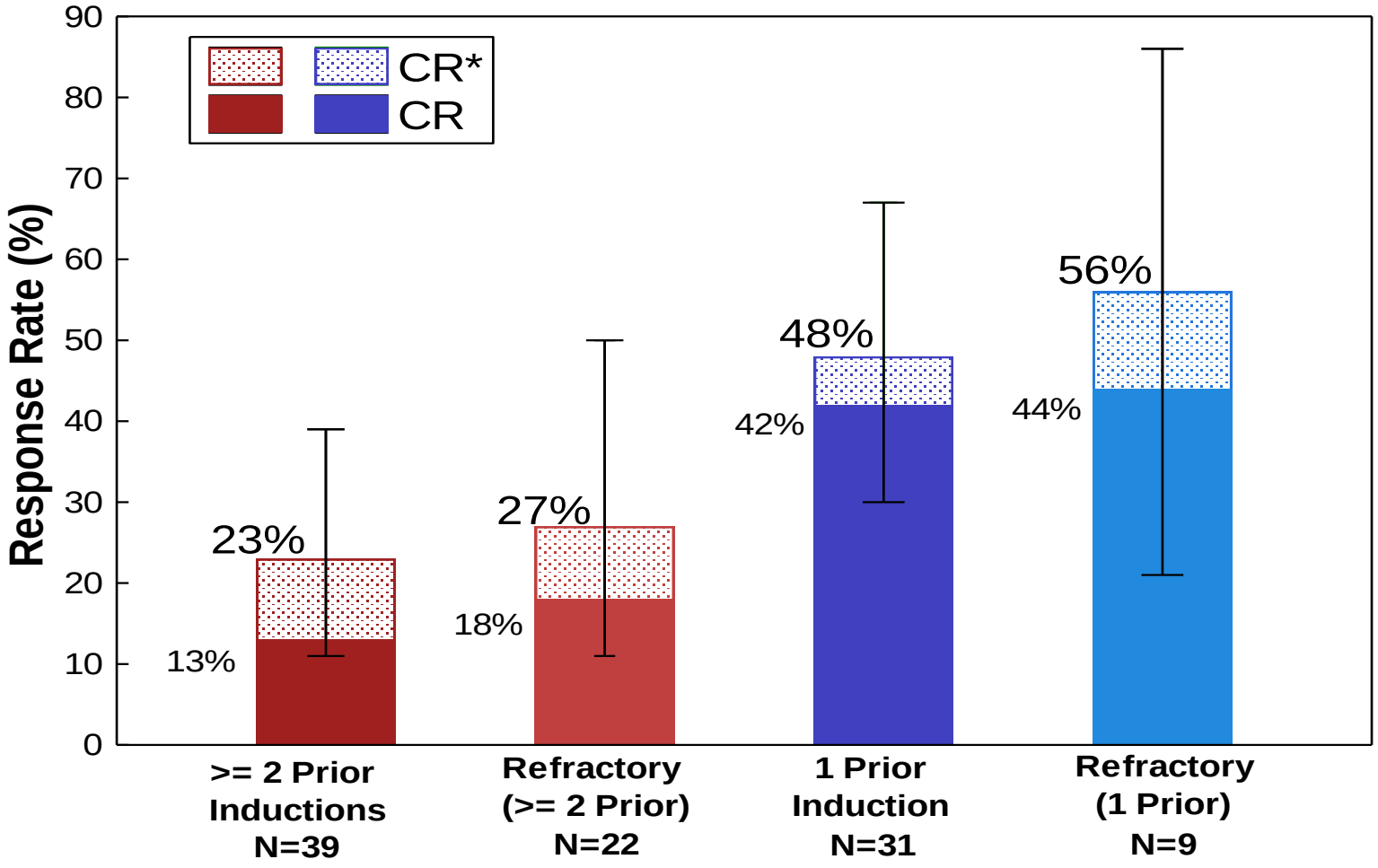
Gandhi V *et al.* Nelarabine
Nature Reviews Drug Discovery
2006

Nelarabine en rechute

Study	Treat.	Disease	N	Age	CR	OR	PFS	OS
DeAngelo et al.	Nelarabine	T-ALL T-LBL	26 13	34 (16–66)	10 (26%)	16 (41%)	20wks	7 (28%) at 1 year
Kurzberg et al.	Nelarabine	Pediatric T-ALL	26	NR	27%	42%	NR	NR
		Adult T-ALL	13		15%	80%		
		B-ALL/Pre-B-ALL	10		0	10%		
Berg et al.	Nelarabine	Refractory or recurrent T-ALL	106	11.5 years (0.6–21.7)	35	45 (33%)	NR	NR
Gökbuget et al.	Nelarabine	Relapsed/refractory T-ALL/LBL	126	18–81	42 (36%)	54 (46%)	37% at 3 years	24% at 1 year
Commander et al.	Nelarabine + VP16 + Cy	Relapsed/refractory pediatric T-ALL/LBL	7	2–19 years	5	7	NR	NR

Robak, Cancer Treatment Reviews 2013

Pediatric: COG P9673 CR+CR* Rates



CR = complete response with full hematologic recovery
CR* = complete response without full hematologic recovery

Relpased/refractory T-ALL/T-LBL N=126

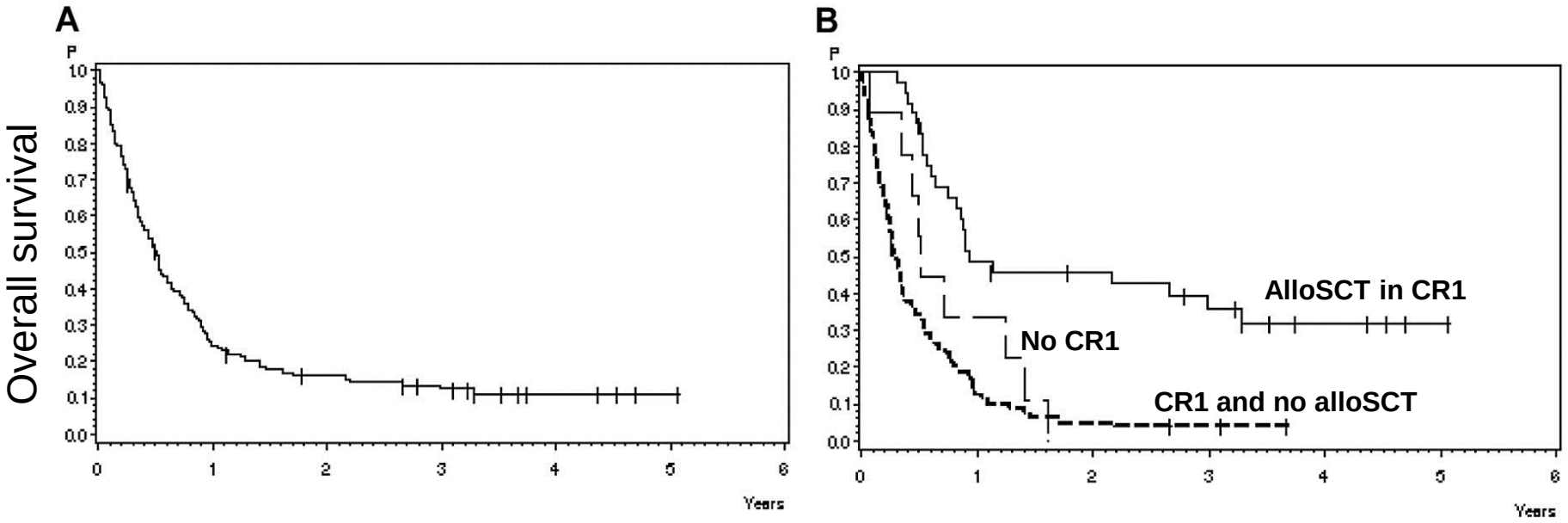
	Result after cycle 1, N (%)	Overall result after 1-3 cycles,* N (%)
CR	40 (32)	45 (36)
PR	24 (19)	12 (10)
Failure	59 (47)	66 (52)
Death on therapy	1 (1)	1 (1)
Withdrawal	2 (2)	2 (2)

Gökbuget, Blood 2011

Prognostic factors for achievement of CR and survival

Factor	Category	N	CR rate, N (%)	*P*	Survival probability		*P*
					1 year, %	3 years, %	
Sex	Male	93	28 (30)	.03	26 ± 5	12 ± 54	.99
	Female	33	17 (52)		21 ± 7	12 ± 6	
Age	18-45 y	98	37 (38)	.17	30 ± 5	16 ± 4	.0007
	> 45 y	28	8 (29)		7 ± 5	0	
Diagnosis	T-ALL	107	45 (42)	.0004	26 ± 4	13 ± 3	.16
	T-LBL	19	0		16 ± 8	11 ± 7	
Phenotype (N = 91 T-ALL)	Thymic	45	45 (56)	.02	36 ± 7	17 ± 6	.03
	Early or mature	46	14 (30)		18 ± 6	10 ± 5	
Disease status	Refractory	13	3 (7)	.65	38 ± 13	38 ± 13	.42
	First relapse	73	27 (37)		21 ± 5	12 ± 4	
	Second relapse	13	6 (46)		9 ± 8	0%	
	Relapse after SCT	27	9 (33)		33 ± 9	7 ± 5	
Involvement	BM only	83	36 (43)	.01	25 ± 5	15 ± 4	.38
	Extramedullary ± BM	43	9 (21)		23 ± 6	7 ± 4	
Pretreatment	No pretreatment	29	11 (38)	.78	34 ± 9	4 ± 4	.98

Patient outcome

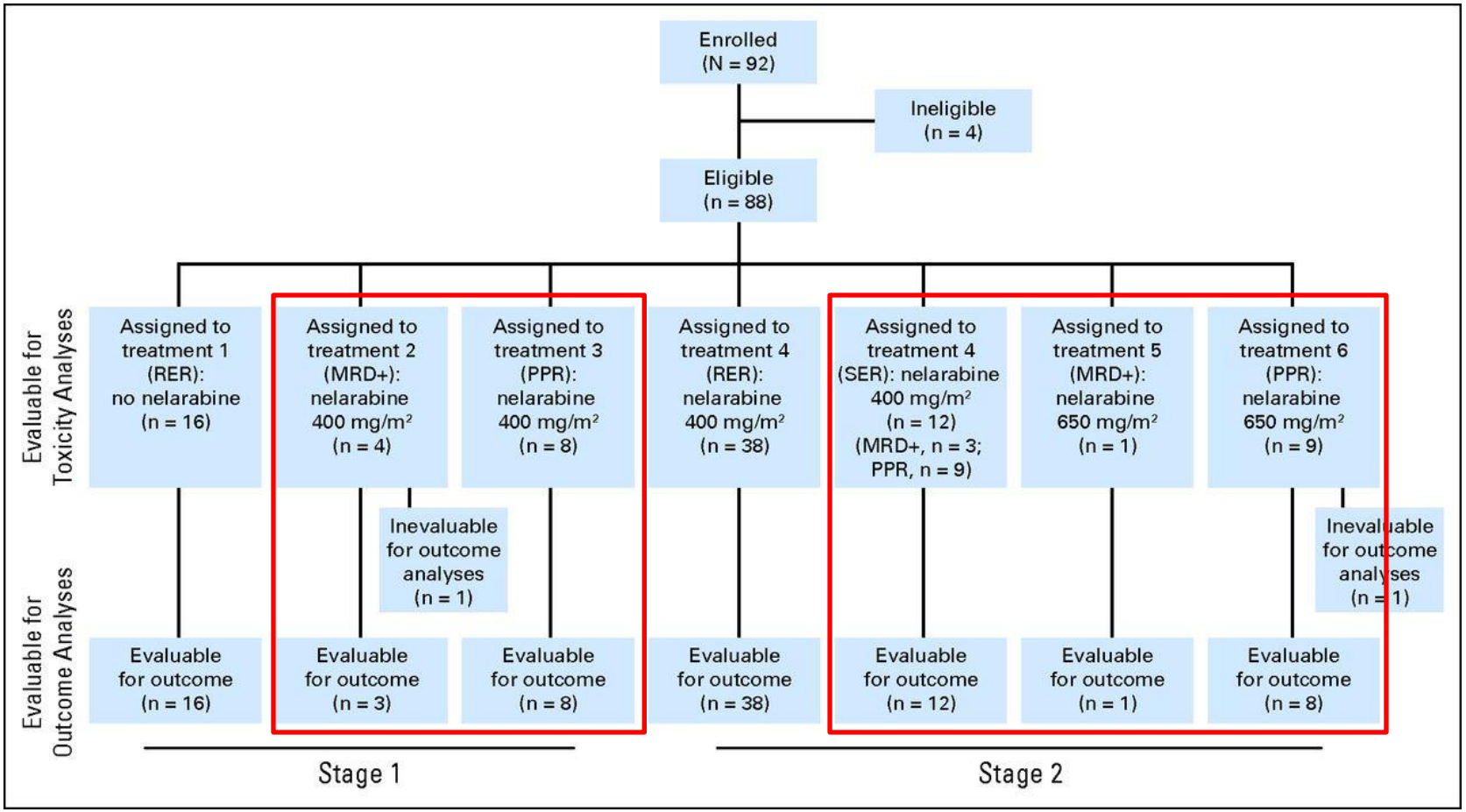


Gökbuget N et al. Blood 2011

Neurotoxicities in adult patients with clinical relapse (N=201 cycles)

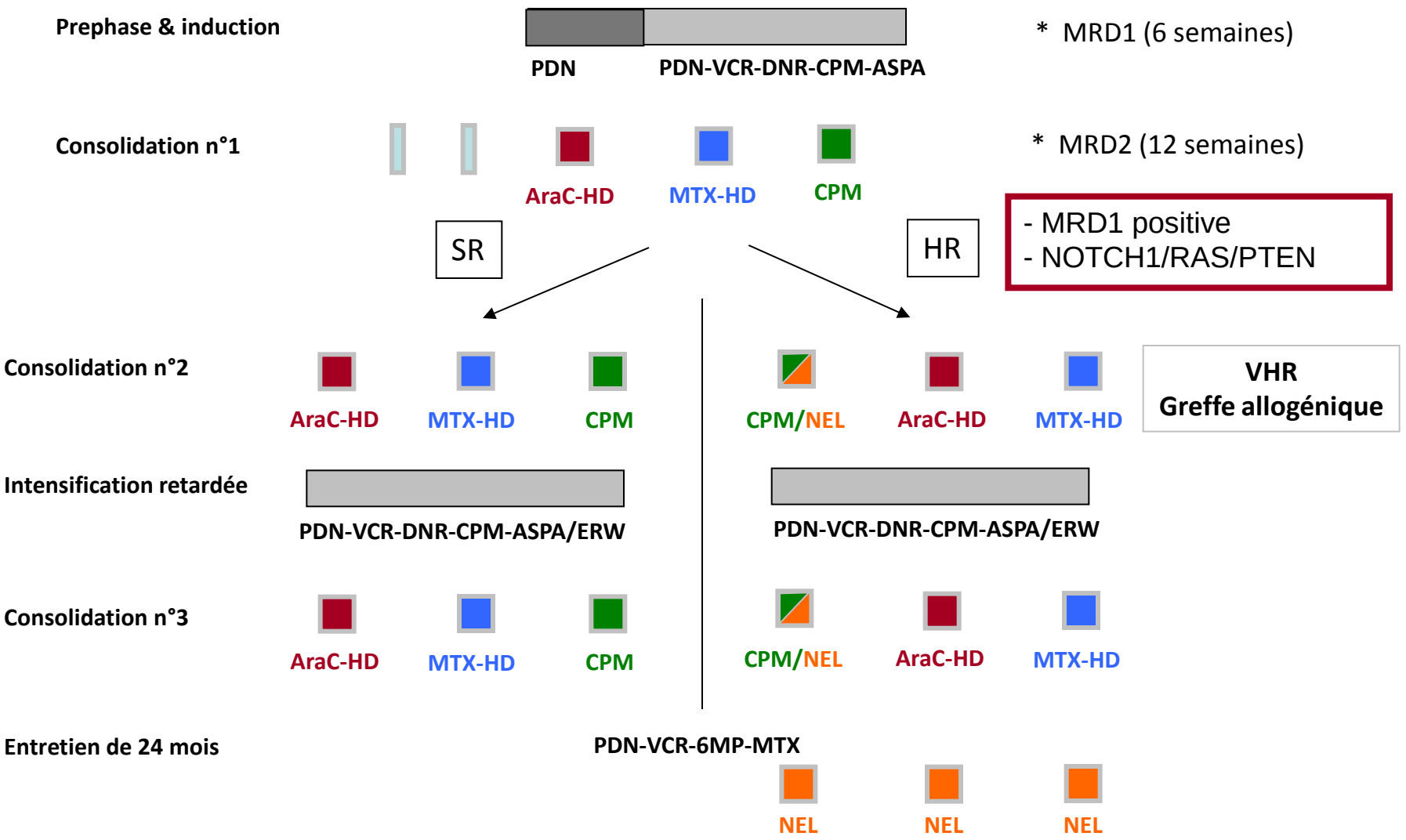
	Incidence, N (%) of cycles	Grade I, no. of cycles	Grade II, no. of cycles	Grade III, no. of cycles	Grade IV, no. of cycles
Cognitive disturbance	9 (4)	3	0	1	5
Confusion	9 (4)	3	0	3	3
Consciousness impaired	1 (0.5)	0	0	1	0
Dizziness	13 (6)	7	2	2	2
Fatigue	1 (0.5)	1	0		0
Guillain-Barré–like syndrome	1 (0.5)	0	0	1	0
Hallucination	4 (2)	0	0	2	2
Insomnia	2 (1)	1	0	1	0
Memory impaired	7 (3)	2	1	1	3
Mood alteration	12 (6)	7	1	4	0
Neuropathy increased	5 (2)	2	2	1	0
Restlessness	4 (2)	1	2	0	1
Somnolence	1 (0.5)	0	0	1	0
Tremor	4 (2)	1	1	2	0

Pilot Study of Nelarabine in Combination With Intensive Chemotherapy in High-Risk T-Cell Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group



Dunsmore, JCO 2012

GRAALL 2013-T (LAL/LL)

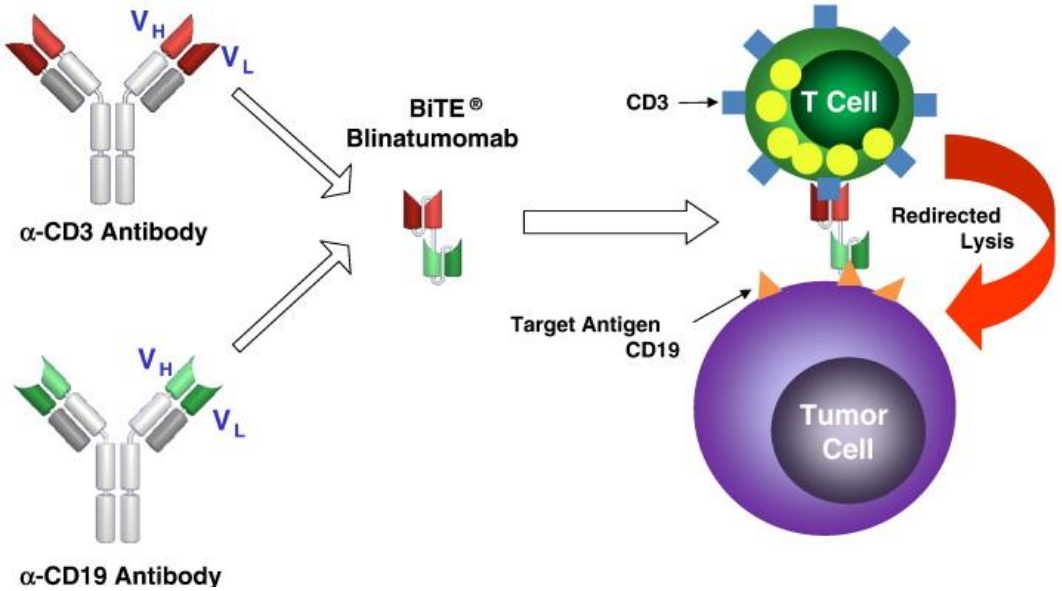


Ab-targeted immunotherapy

Name	Target	Company	Status in ALL
Blinatumomab	CD19 Anti-CD3 BiTe	Amgen	Two German Phase II (MRD, R/R) Two Int'l Phase II (MRD, R/R) ongoing One Int'l pediatric Phase II ongoing One Int'l Ph+ ALL Phase II planned One Int'l Phase III planned for 2013 (R/R)
CART-19	CD19 Transfected autologous T-cells	Amgen	Int'l Phase Ib/II planned

Blinatumomab

- Bispecific T-cell engaging antibody (BiTE) with specificity for CD19



- Targeted Therapy With the T-Cell–Engaging Antibody Blinatumomab of Chemotherapy-Refractory Minimal Residual Disease in B-Lineage Acute Lymphoblastic Leukemia Patients Results in High Response Rate and Prolonged Leukemia-Free Survival

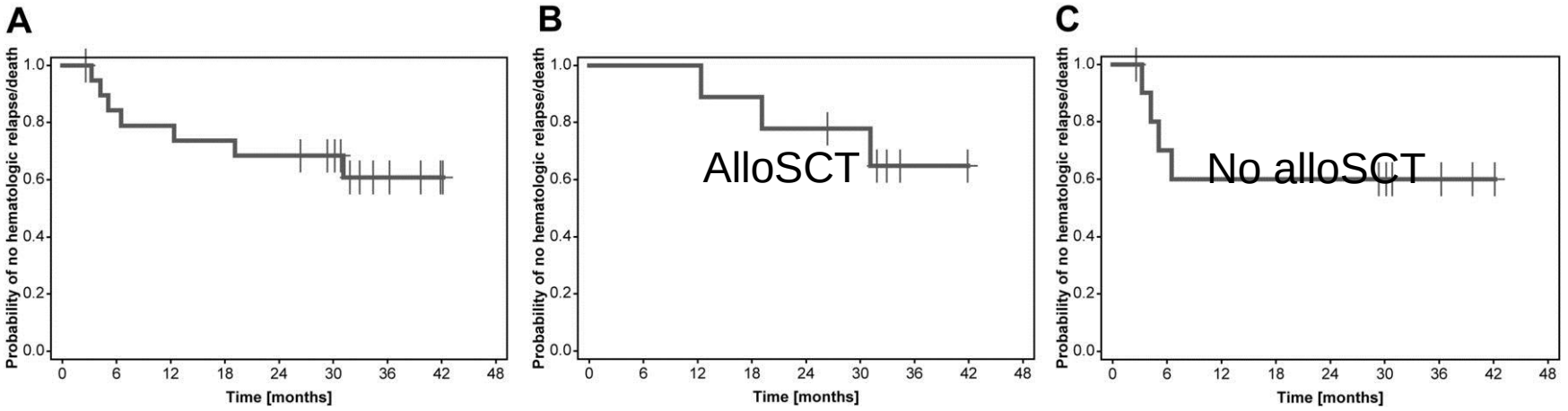
Max S. Topp, Peter Kufer, Nicola Gökbuget, Mariele Goebeler, Matthias Klinger, Svenja Neumann, Heinz-A. Horst, Thorsten Raff, Andreas Viardot, Mathias Schmid, Matthias Stelljes, Markus Schaich, Evelyn Degenhard, Rudolf Köhne-Volland, Monika Brüggemann, Oliver Ottmann, Heike Pfeifer, Thomas Burmeister, Dirk Nagorsen, Margit Schmidt, Ralf Lutterbuese, Carsten Reinhardt, Patrick A. Baeuerle, Michael Kneba, Hermann Einsele, Gert Riethmüller, Dieter Hoelzer, Gerhard Zugmaier, and Ralf C. Bargou

Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL

*Max S. Topp,[1,2] *Nicola Gökbuget,[3] *Gerhard Zugmaier,[4] Evelyn Degenhard,[4] Marie-Elisabeth Goebeler,[1,2] Matthias Klinger,[4] Svenja A. Neumann,[5] Heinz A. Horst,[5] Thorsten Raff,[5] Andreas Viardot,[6] Matthias Stelljes,[7] Markus Schaich,[8] Rudolf Köhne-Volland,[9] Monika Brüggemann,[5] Oliver G. Ottmann,[3] Thomas Burmeister,[10] Patrick A. Baeuerle,[4] Dirk Nagorsen,[4] Margit Schmidt,[4] Hermann Einsele,[1] Gert Riethmüller,[11] Michael Kneba,[5] Dieter Hoelzer,[12] Peter Kufer,[4] and *Ralf C. Bargou[1,2]

Blinatumomab studies MRD persistence (N=20)

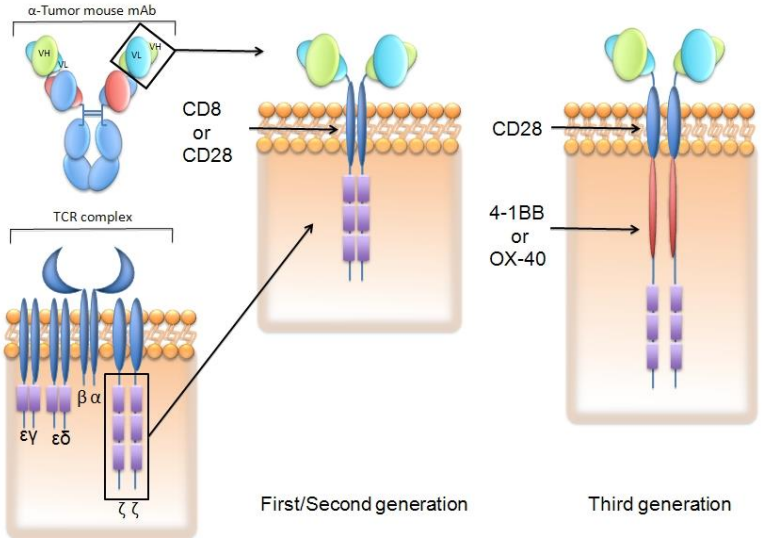
- Inclusion crietria : MRD>10^{-3}
- Complete molecular response in 80% of patients
- DFS :



Topp et al, Blood 2012

CART-19

- Chimeric antigen receptor-modified T cells with specificity for CD19



Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachey, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia

Michael Kalos[1,2,*], Bruce L. Levine[1,2,*], David L. Porter[1,3], Sharyn Katz[4], Stephan A. Grupp[5,6], Adam Bagg[1,2], and Carl H. June[1,2,†]

Immunotoxins

Name	Target	Company	Status in ALL
Inotuzumab ozogamicin	CD22 Calicheamicin	Pfizer	Two Phase II (MDACC, US) One Int'l Phase III ongoing (R/R)
SAR-3419	CD19 Maytansine derivative	Sanofi	Phase Ib/II ongoing (MDACC + GRAALL)
Moxetumomab pasudotox	CD22 Pseudomonas exotoxin A	MedImmune	One pediatric Phase I (US) One Int'l pediatric Phase II planned for 2013 (R/R)

Inotuzumab ozogamicin

- CD22 dans 90% des patients avec LAL
- **Inotuzumab ozogamicin :**
  - Monoclonal anti-CD22 couplé à la calicheamicin
- **Patients** (N=83)
  - LAL de l'enfant et de l'adulte
  - Réfractaire ou en rechute
- **Modalités d'administration**
  - N=49 : 1,3-1,8 mg/m2 IV, /3-4 sem.

    puis
  - N=34 : 0,8 mg/m2 J1, 0,5 mg/m2 J8 et15 / 4 sem

    (Plus efficace *in vitro*, moins toxique *in vivo*)

O'Brien, ASH 2012, #671
Kantarjian, Cancer 2013

Inotuzumab / Tolérance

- **Patients et LAL (N=83)**
  - Age ≥ 60 ans 29%
  - Rattrapage n°1 10%
  - Rattrapage n°≥ 2 71%
  - Ph+ or t(4;11) 28%
  - Post-allogreffe 12%

- **Réponse**
  - RC 17%
  - RCp 28%
  - RCi 11%

  55% de réponse

  (71% si rattrapage n°1, 62% si non Ph+ et non t(4;11))

  - Réponse moléculaire compléte 64% des répondeurs
  - Survie médiane 5,4 mois

Inotuzumab / Tolérance

	1 dose	3 doses
• **Toxixité hépatique biologique**		
– Hyperbilirubinémie (gr1/2)	24%	3%
– Hyperbilirubinémie (gr3/4)	4%	0%
– Hypertransaminasémie (gr1/2)	55%	21%
– Hypertransaminasémie (gr3/4)	2%	6%
• **Maladie veino-occlusive après allogreffe**	5/22 (23%)	1/9 (11%)

- **Conclusion :**
  - Inotuzumab efficace en monothérapie
  - Schéma hebdomadaire aussi efficace et mieux toléré

Concluding remarks on monoclonal antibodies

- We have a lot of very promising new options, especially immuno-conjugates and targeted immunotherapy in B-lineage ALL.
- Fortunately, we probably do not have enough R/R patients to evaluate these options simultaneously.
- Not to mention combination trials that will be required to elaborate new standards of care.
- Future trials should focus on :
  - young patients with high-risk patients in first CR
  - old patients with expected high toxicity upon conventionnal chemotherapy

Merci !

Is less chemotherapy detrimental in adults with Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) treated with high-dose imatinib?

Results of the prospective randomized GRAAPH-2005 study

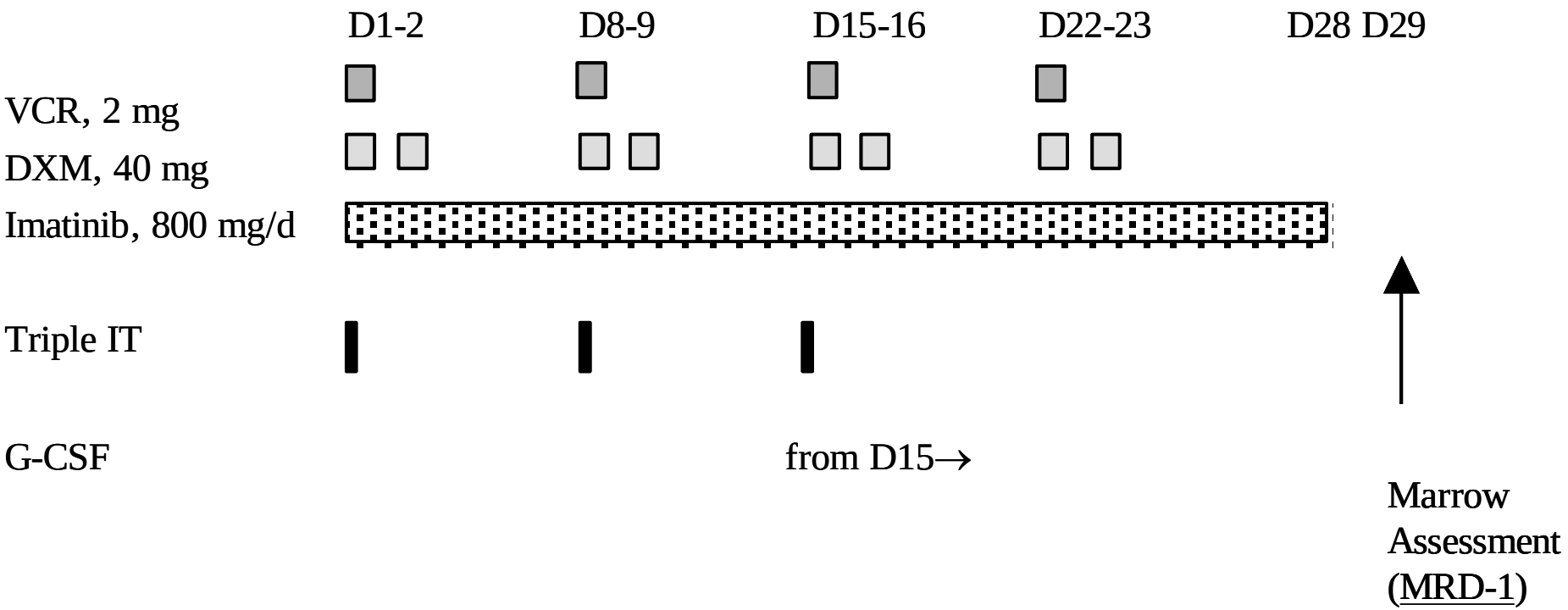
(ClinicalTrials.gov ID, NCT00327678)

Y. Chalandon, X. Thomas, S.Hayette, J-M. Cayuela, C. Abbal, F. Huguet, E. Raffoux, T Leguay, S. Lepretre, M. Escoffre-Barbe, S. Maury, C. Berthon, E Tavernier, J-F. Lambert, M. Lafage, V. Lhéritier, S Chevret, N. Ifrah and H. Dombret

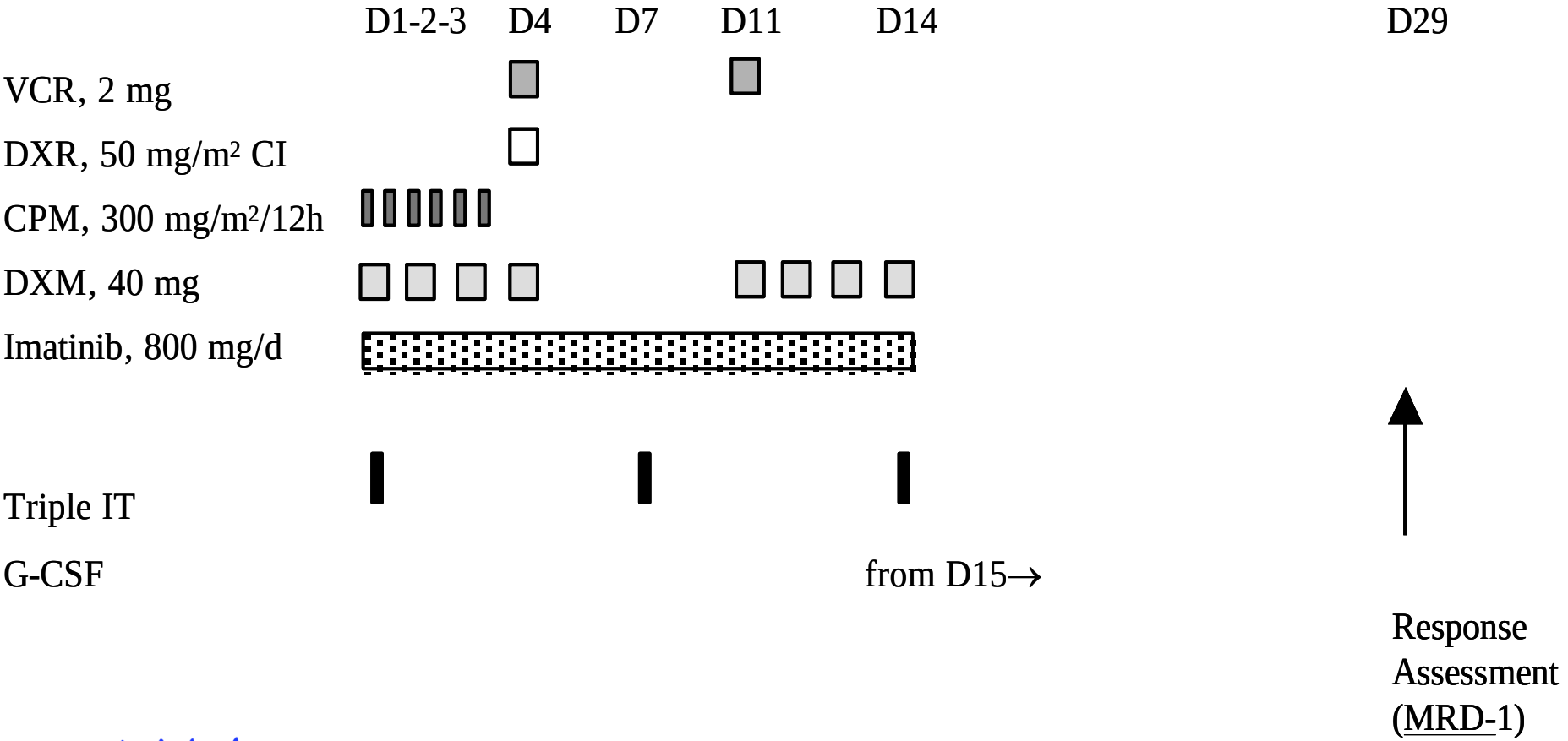
GRAALL

LALA GOELAMS SAKK

First cycle
arm A, IM-based



First cycle
arm B, IM/HyperCVAD



Maintenance after SCT

- **After autologous SCT**
  - **Alternating IM and chemotherapy cycles**
    - Imatinib, 600 mg/d
    - 6-MP/MTX
- **After allogeneic SCT**
  - **No systematic maintenance**
    - TKI in case of molecular relapse
    - Not detailed in the protocol

SCT in CR1 patients

	IM-based (133 CR1)	IM-HyperCVAD (121 CR1)	p	Total (254 CR1)
All CR1 patients				
Allo-SCT	82	78	0.99	**160 (63%)**
Auto-SCT	17	17		**34 (13.4%)**
MMolR patients				
Allo-SCT	51	39	0.39	90
Auto-SCT	13	15		28
CR to SCT time				
Allo-SCT	4.6 mths	4.5 mths	0.8	4.6 mths
Auto-SCT	5.3 mths	4.5 mths	0.14	5.1 mths

Allogeneic SCT modalities

	IM-based (n= 82)	IM-HyperCVAD (n= 78)	p	Total (n=160)
MRD	33	43		76
MUD	40	31	0.12	71
CB	9	4		13
MAC	60	62	0.36	122
RIC	22	16		38

Adult: CALGB 19801

- Open-label, multicenter Phase II study
- Median age: 34 years (range: 16-66 years)
- Refractory or relapsed T-ALL or T-LBL
- Dose*: 1500 mg/m^2 days 1, 3, 5, every 21 days
- Two cycles for induction plus two for consolidation
- 39 patients treated:
  - 11 patients with 1 prior multi-agent induction/regimen
  - 28 patients with ≥ 2 prior multi-agent inductions/regimens
- Enrolled over 37 months

* Recommended Dose

Adult: CALGB 19801 CR+CR* Rates