Leucemia Linfoblástica Aguda. Sesion Educacional
SEFH, GEDEFO y PETHEMA
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LLA: fisiopatología y tratamiento actual

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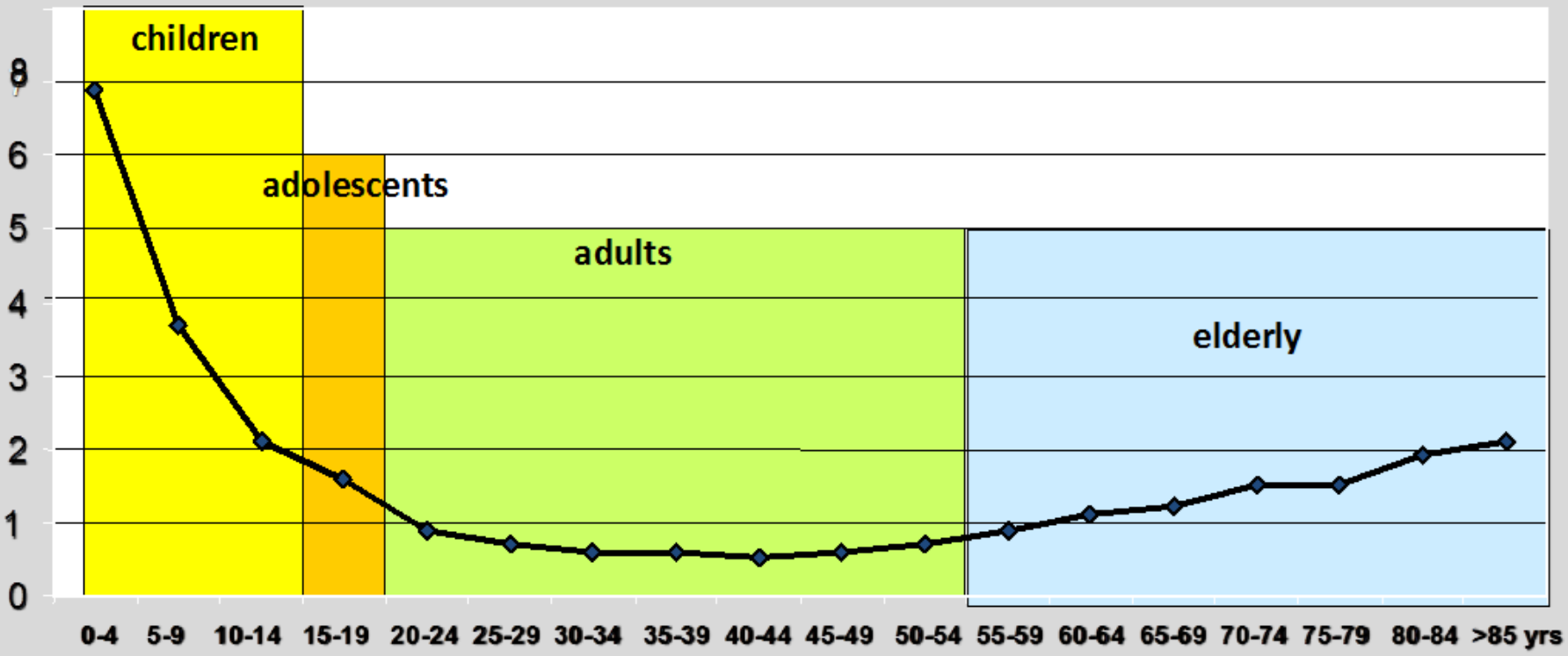
Topics of the presentation

- Etiology and epidemiology
- Response criteria
- Treatment protocols

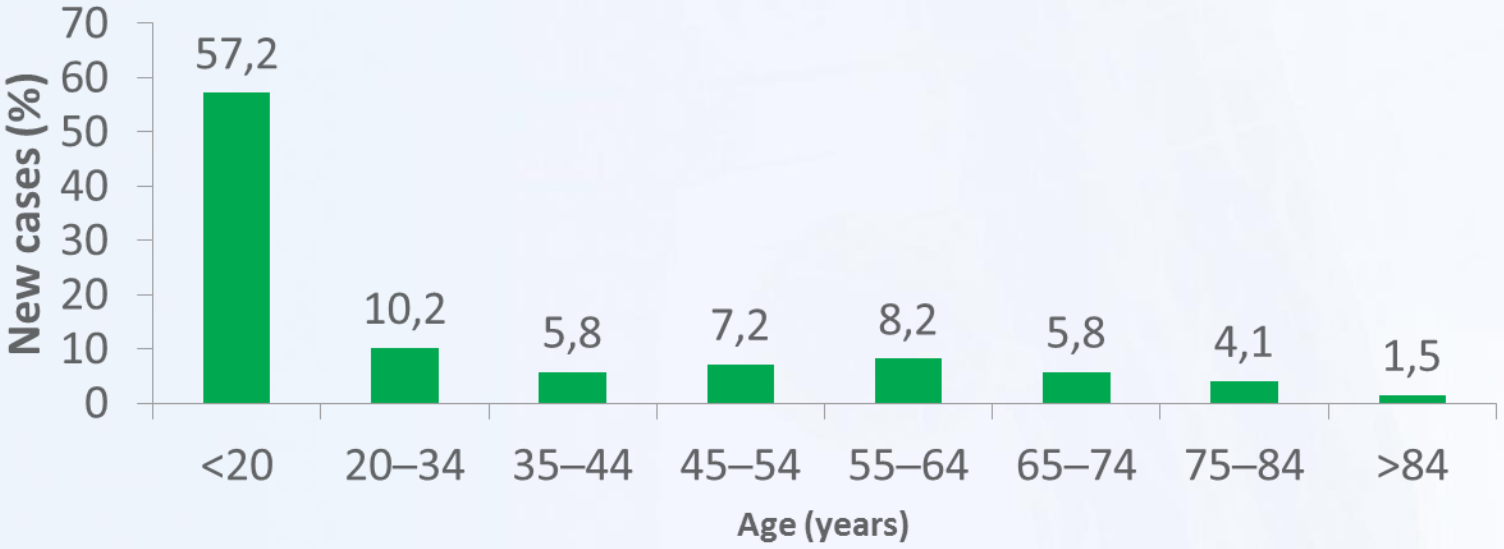
ALL is mainly a disease of children and adolescents



SEER Program (www.seer.cancer.gov)
Public-Use, Nov 2003 (incidences 1992-2001)

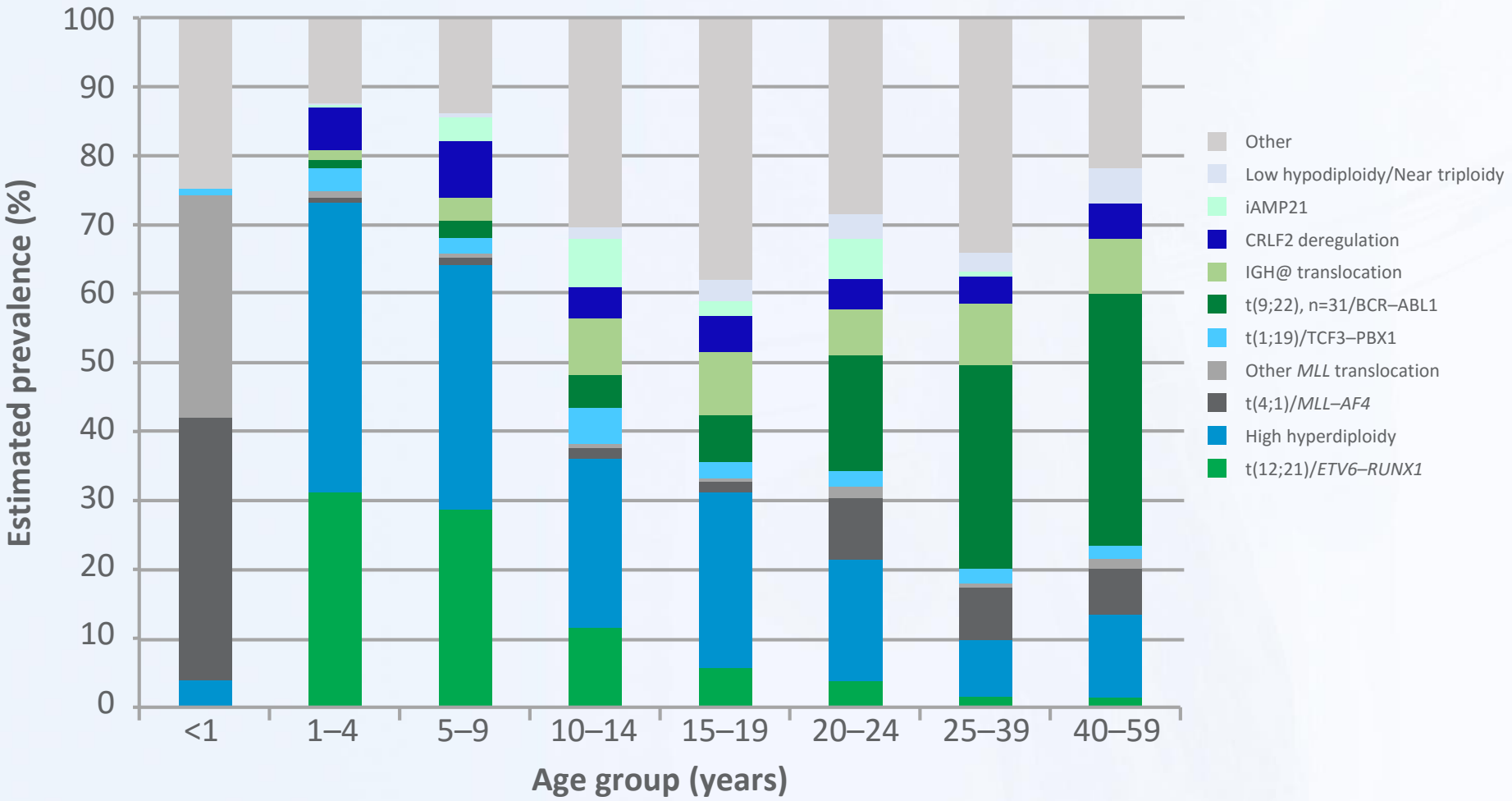
ALL: Background

- ALL represents 0.4% of all new cancer cases
- In 2009–2013, the rate of new cases of ALL was 1.7 per 100,000 persons per year
- Median age at diagnosis: 15 years



National Cancer Institute Surveillance, Epidemiology, and End Results Program. SEER 18 2009–2013, all races, both sexes. Available at: http://seer.cancer.gov/statfacts/html/alyl.html. Accessed 31 May 2016

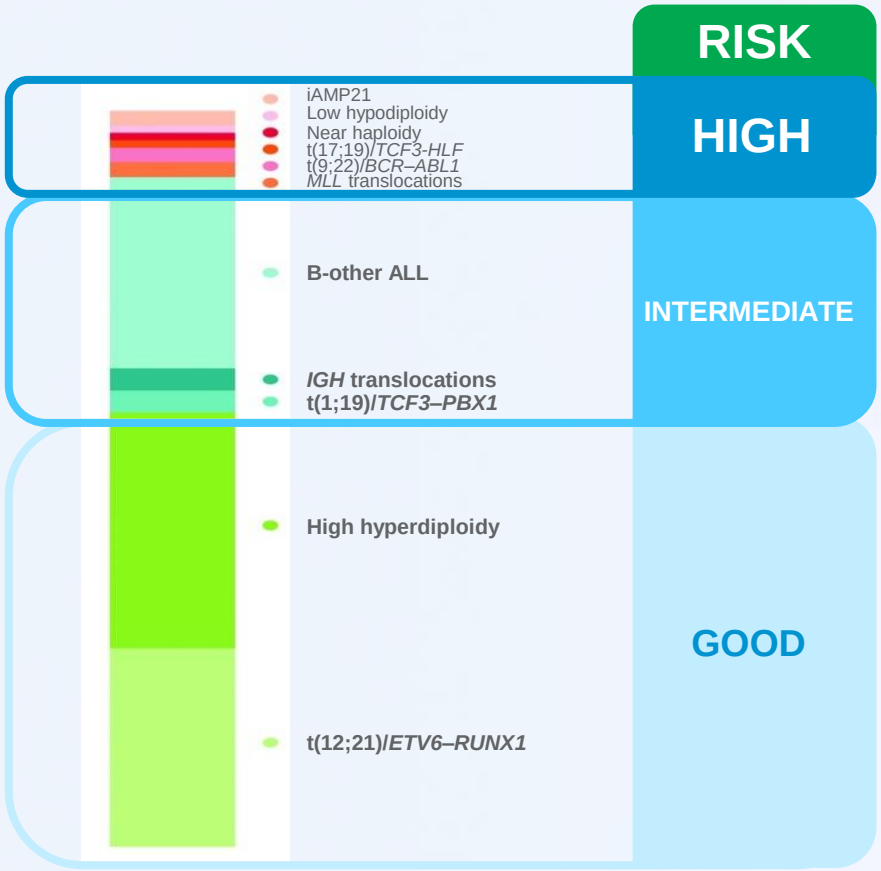
Age-specific frequency of selected chromosomal abnormalities in ALL



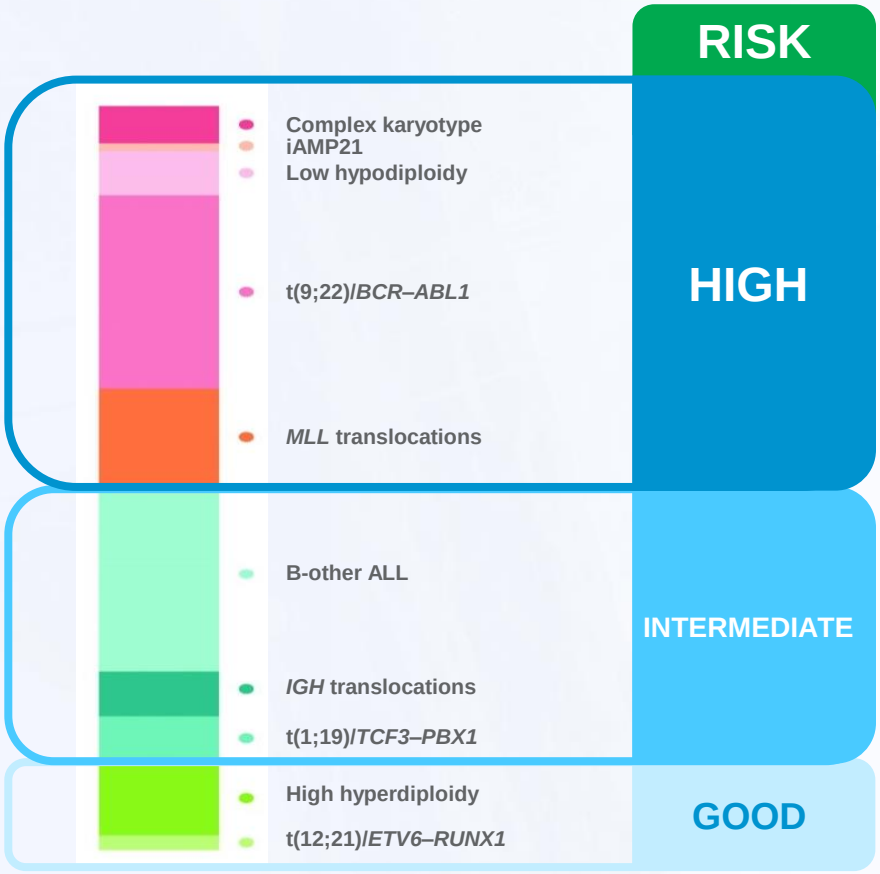
Moorman AV. *Blood Rev* 2012; 26:123–135

Frequency of primary chromosomal abnormalities in children and adults with B-cell precursor ALL

Children and adolescents



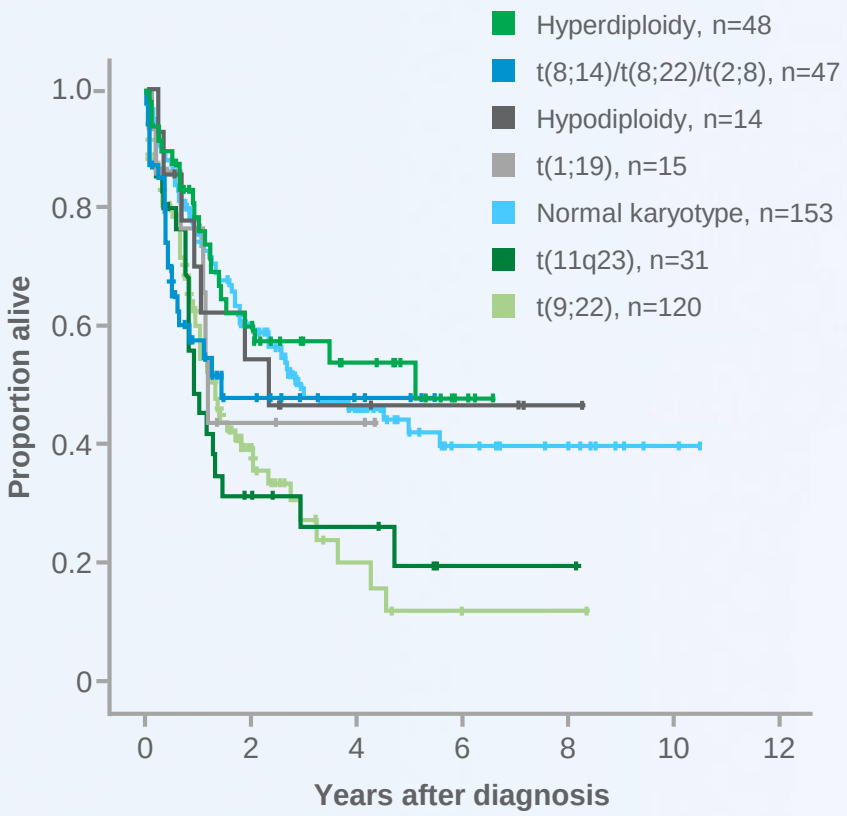
Adults



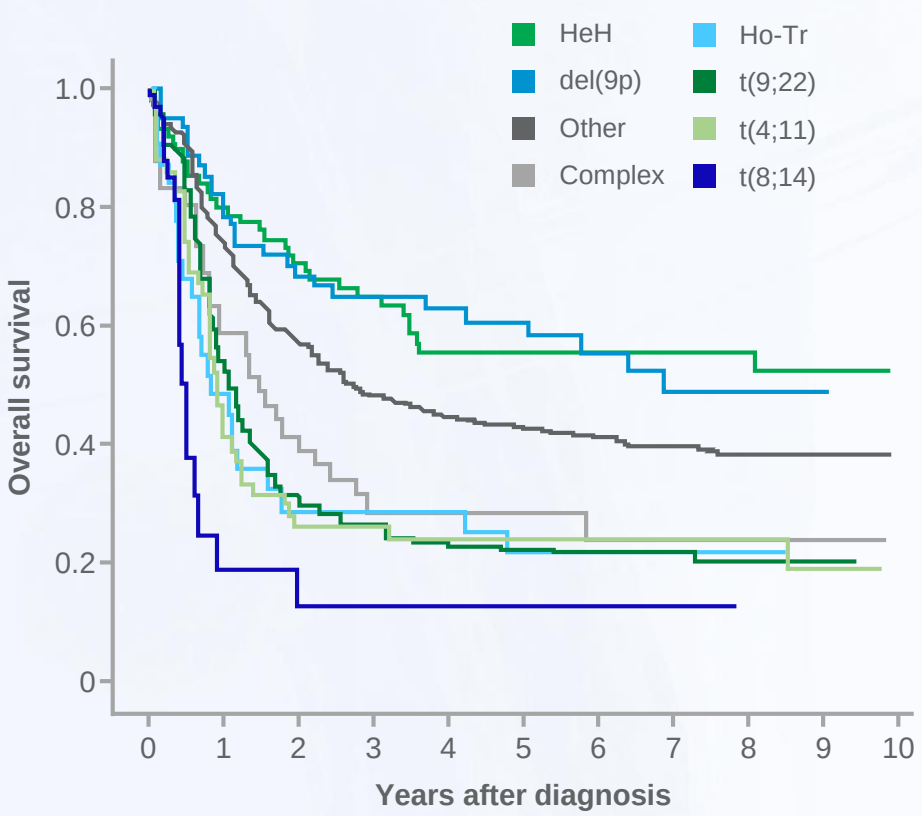
Moorman AV. *Haematologica* 2016;101:407–416

Adult ALL: overall survival by cytogenetics

PETHEMA data[1]



MRC UKALLXII/ECOG 2993, n=1522[2]



1. Courtesy of PETHEMA; 2. Moorman AV, *et al. Blood* 2007;109:3189–3197

Recurring alterations of multiple key pathways in ALL

- Transcriptional regulation of lymphoid development[1]
  - *PAX5, IKZF1, EBF1, ETV6, LMO2, TCF3*[2], *VPREB*[3]
- Tumour suppression and cell cycle regulation[1]
  - *TP53, RB1, CDKN2A/CDKN2B*
- Cytokine receptor, kinase signalling and Ras signalling[1]
  - Cytokine receptor: *CRLF2, EPOR, IL7R*
  - Kinase signalling: *ABL1, ABL2, CSF1R, JAK2, PDGFRB*
  - Ras signalling: *KRAS, NF1, NRAS, PTPN11*
- Lymphoid signalling[1]
  - *BTLA, CD200*
- Epigenetic modification[1]
  - *EZH2, CREBBP, SETD2, MLL2, NSD2*

1. Mullighan CG. *Hematology Am Soc Hematol Educ Program* 2014;2014:174–180; 2. Somasundaram R, *et al. Blood* 2015;126:144–152; 3. Bauer SR, *et al. Blood* 1991;78:1581–1588

Co-operating mutations in relation to distinct genetic subtypes of B-cell precursor ALL

Primary chromosomal abnormality	Co-operating secondary aberrations			
	Lymphoid differentiation	Cell cycle regulation	Proliferation and cell survival	Transcription co-factors
t(12;21)/*ETV6–RUNX1*	*PAX5*			*ETV6, BTG1, TBLXR1*
High hyperdiploidy			*KRAS, NRAS*	*CREBBP*
t(1;19)/*TCF3–PBX1*	*TCF3, PAX5*	*CDKN2A/B*		
IGH translocations	*IKZF1*	*CDKN2A/B*		
B-other ALL	*PAX5, IKZF1*	*CDKN2A/B*	*KRAS, NRAS, CRLF2, JAK2*	
t(9;22)/*BCR–ABL1*	*PAX5, IKZF1*	*CDKN2A/B*		
MLL translocations		*CDKN2A/B*	*KRAS, NRAS, FLT3*	
iAMP21		*RB1*	*RAS, FLT3, CRLF2*	
Complex karyotype		*TP53*		
Near haploidy		*CDKN2A/B*	*KRAS, NRAS, NF1*	
Low hyperdiploidy	*IKZF2*	*TP53, RB1*		

Leukaemogenesis

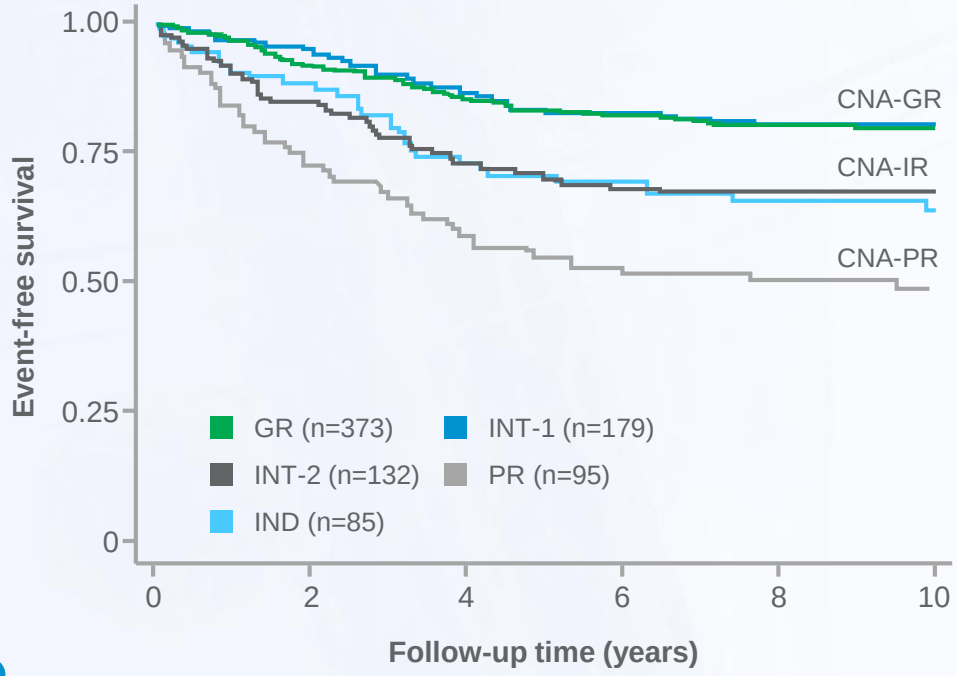
ALL, acute lymphoblastic leukaemia

Moorman AV. *Haematologica* 2016;101:407–416

Genetic risk groups and prognosis in childhood ALL

- **Good risk genetic abnormalities**
  - Good risk cytogenetic abnormalities:
    - *ETV6–RUNX1*/t(12;21)(p13;q22)
    - High hyperdiploidy (51–65 chromosomes)
  - Good risk copy number alteration profiles:
    - No deletion of *IKZF1, CDKN2A/B, PAR1, BTG1, EBF1, PAX5, ETV6* or *RB1*
    - Isolated deletions of *ETV6, PAX5* or *BTG1*
    - *ETV6* deletions with a single additional deletion of *BTG1, PAX5* or *CDKN2A/B*
- **Poor risk genetic abnormalities**
  - High risk cytogenetic subgroups:
    - t(9;22)(q34;q11)/*BCR–ABL1*
    - *MLL*/11q23 translocation
    - Near haploidy (<30 chromosomes)
    - Low hypodiploidy/near triploidy (30–39/60–78 chromosomes)
    - iAMP21
    - t(17;19)(q23;p13)/*TCF3–HLF*
  - Intermediate and poor risk copy number alteration profiles
    - Any deletion of *IKZF1, PAR1, EBF1* or *RB1*
    - All other copy number alteration profiles not mentioned above

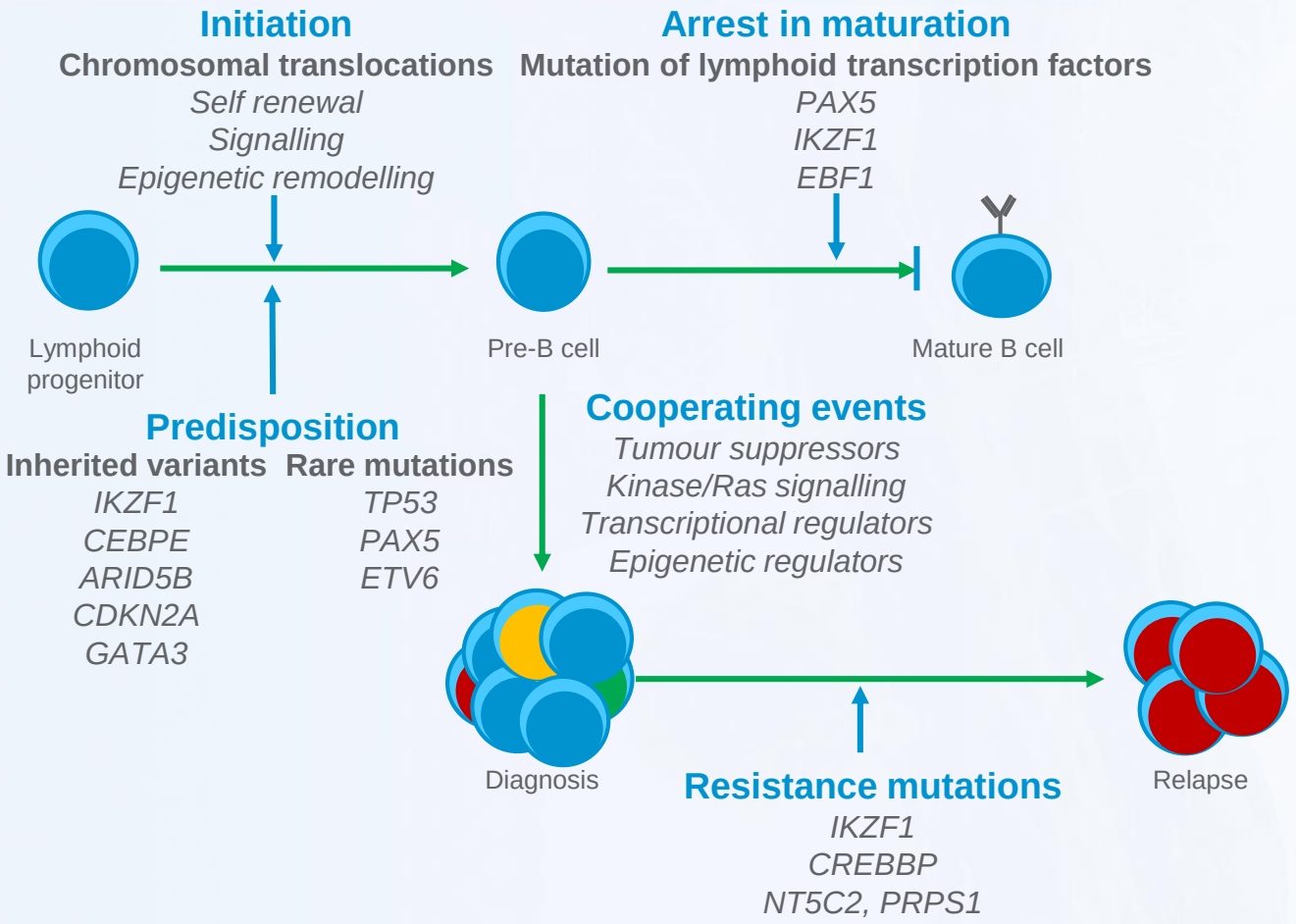
Patients are classified hierarchically with cytogenetic abnormalities taking precedence over copy number alteration profiles



ALL, acute lymphoblastic leukaemia; iAMP21, intrachromosomal amplification of chromosome 21

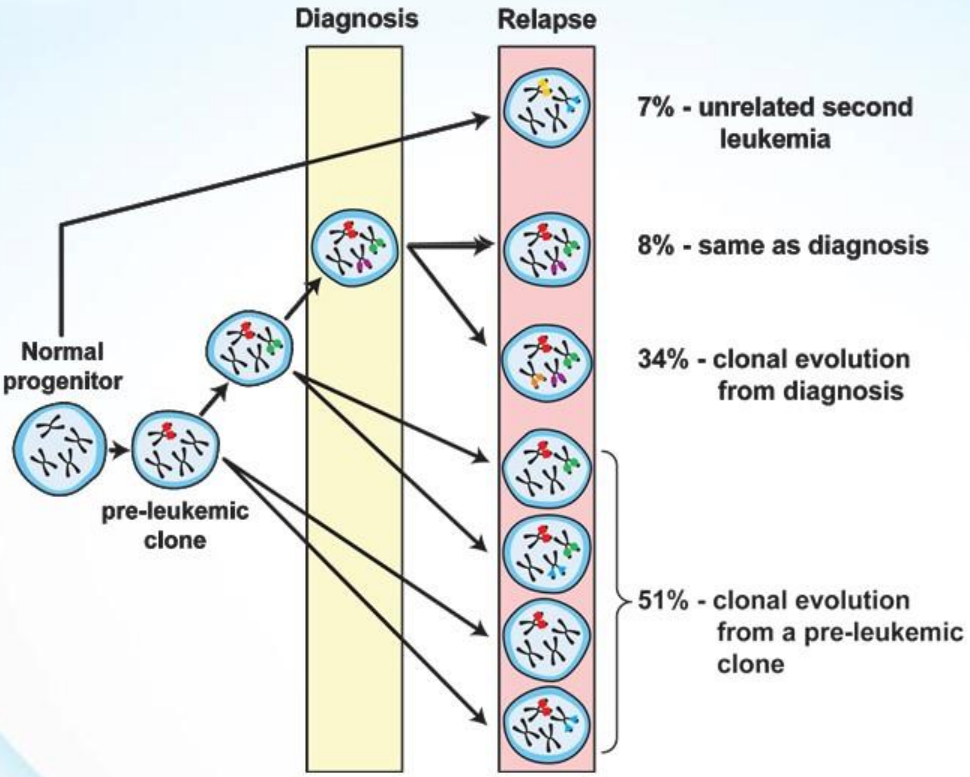
Moorman AV, *et al. Blood* 2014;124:1434–1444

The multistep pathogenesis of ALL



Mullighan CG, *et al. Nature* 2007;446:758–764; Mullighan CG, *et al. Nature* 2008;453:110–114; Mullighan CG *et al. Science* 2008;322:1377–1380; Mullighan CG, *et al. N Eng J Med* 2009;360:470–480; Mullighan CG, *et al. Nature* 2011;471:235–239; Roberts KG, *et al. Cancer Cell* 2012;22:153–166

Patterns of relapse



Mullighan CG, et al. Science 2008;322:1377–80

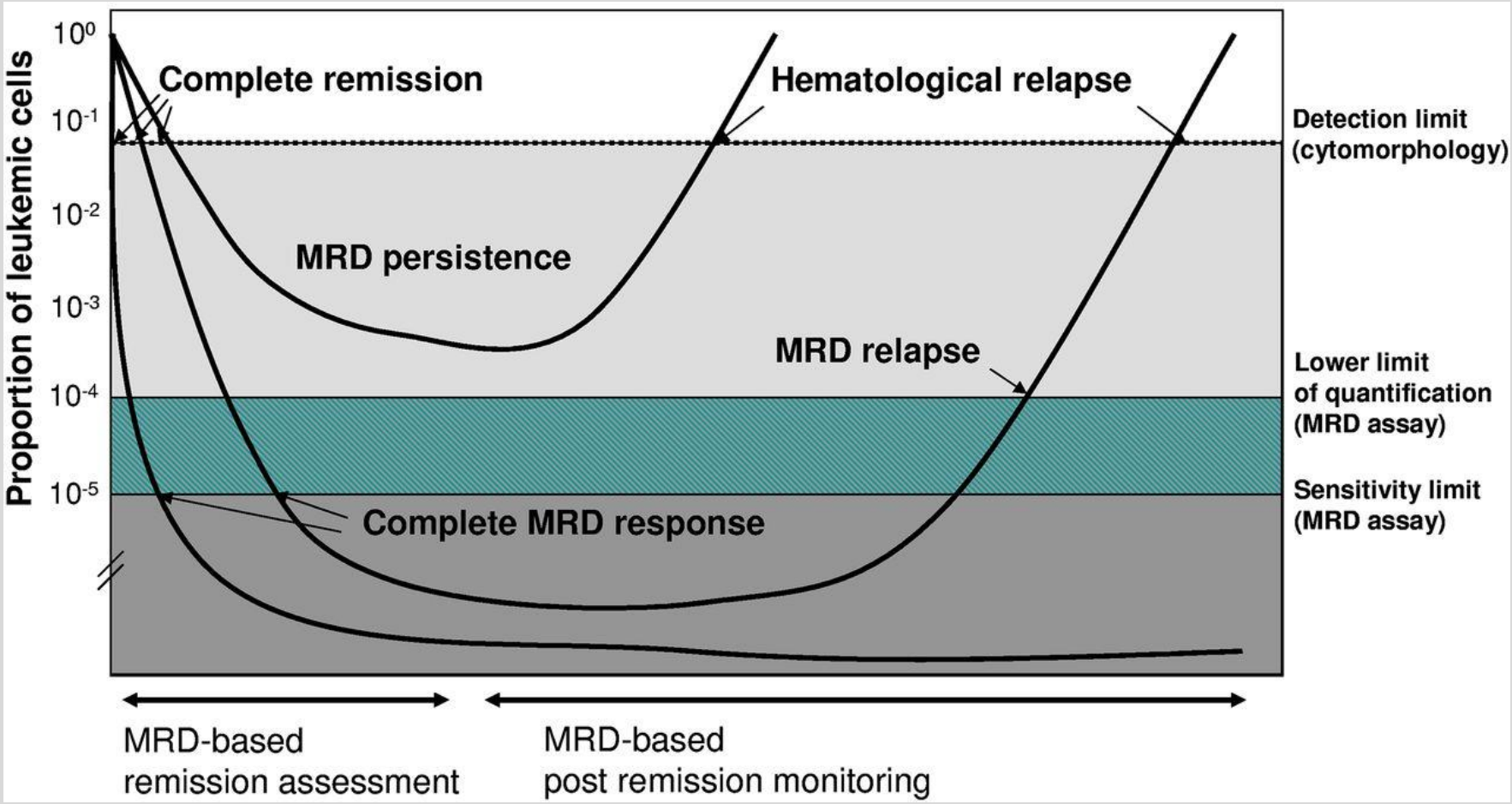
Topics of the presentation

- Etiology and epidemiology
- Response criteria
- Treatment protocols

Definitions of response

CR	≤5% blasts in BM and no evidence of disease, with PB count recovery: platelets >100,000/µL and ANC >1,000/µL
CRh	≤5% blasts in BM with partial PB recovery: platelets >50,000/µL and ANC >500/µL
CRi	≤5% blasts in BM with incomplete PB recovery: platelets >100,000/µL or ANC >1,000/µL)
CRp	≤5% blasts in BM with incomplete platelet recovery (platelets <100,000/µL)
MRD response	$< 10^{-4}$ leukemic cells (Ig/TCR PCR, PCR for specific rearrangements, FCM)

Proposal for definition of MRD terms in ALL



Brüggemann M et al. Blood 2012;120:4470-4481

MRD. Consensus definitions

2nd International Symposium on MRD (Kiel,2009)

- **Molecular response**: MRD $\leq 10^{-4}$ (<0.01%)
- **Complete MRD response**: MRD negativity.
- **MRD persistence**: Quantifiable MRD positivity measurable at at least 2 time-points with one or more relevant treatment elements in between.
- **MRD reappearance**: conversion from MRD negativity to quantifiable MRD positivity (confirmation strongly recommended before drawing clinical conclusions!).

Brüggemann M et al. Leukemia 2010; 24. 521-535

Response parameters according to MRD. Consensus statement EWALL Group

Table 3. Response parameters according to MRD

Terminology	Definitions
CR (complete haematological remission)	– Leukaemic cells not detectable by light microscopy in BM/PB/CSF (BM < 5% blasts)
MolCR (complete molecular remission/MRD negativity)	– Patient in CR – MRD not detectable by sensitive molecular probe(s) (sensitivity $\geq 10^{-4}$)
MolR (molecular/MRD response, less than molCR)	– Patient in CR, not in molCR – Low-level non-quantifiable MRD ($<10^{-4}$/0.01%, i.e. <1 leukaemic cell in 10 000) – Assessable by MFC (lower detection limit, between 10^{-3} and 10^{-4}, higher sensitivity with 8–12 colour techniques)
MolFail (molecular failure/MRD positivity)	– Patient in CR, not in molCR/molR – Quantifiable MRD ($\geq 10^{-4}$/0.01%, i.e. ≥1 leukaemic cell in 10 000) – Assessable by MFC (lower detection limit, between 10^{-3} and 10^{-4})
MolRel (molecular/MRD relapse)	– Patient still in CR, prior molCR/molR – Loss of molCR/molR status ($\geq 10^{-4}$/0.01%, i.e. >1 leukaemic cell in 10 000) – Assessable by MFC (lower detection limit, between 10^{-3} and 10^{-4})
Relapse	– Loss of CR status – Haematological relapse (BM ALL blasts >5%) – Extramedullary relapse (CNS, other site)

MRD, minimal residual disease; BM/PB/CSF, bone marrow/peripheral blood/cerebro-spinal fluid; MFC, multiparameter flow cytometry; ALL, acute lymphoblastic leukaemia; CNS, central nervous system.

Hoelzer D, et al. Ann Oncol 2016 Apr 7. pii: mdw025

Topics of the presentation

- Etiology and epidemiology
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Contemporary management of *de novo* adult ALL

ALL subtype	Management	Cure, %
Mature B (Burkitt)	Rituximab + specific chemotherapy	70–80
ALL in AYA	Pediatric-inspired	60–70
Ph+ ALL	TKI + chemotherapy + allo (or auto?) HSCT	≥50
Ph-neg, CD20+ ALL	Chemotherapy (+ rituximab)	40
Any ALL with MRD+	Allo HSCT in CR1	40

ALL, acute lymphoblastic leukaemia; allo, allogeneic; auto, autologous; AYA, adolescent and young adult; CR1, complete remission 1; HSCT, haematopoietic stem cell transplantation; MRD, minimal residual disease; Ph+, Philadelphia chromosome-positive; Ph-neg, Philadelphia chromosome-negative; T-ALL, T-cell acute lymphoblastic leukaemia; TKI, tyrosine kinase inhibitor

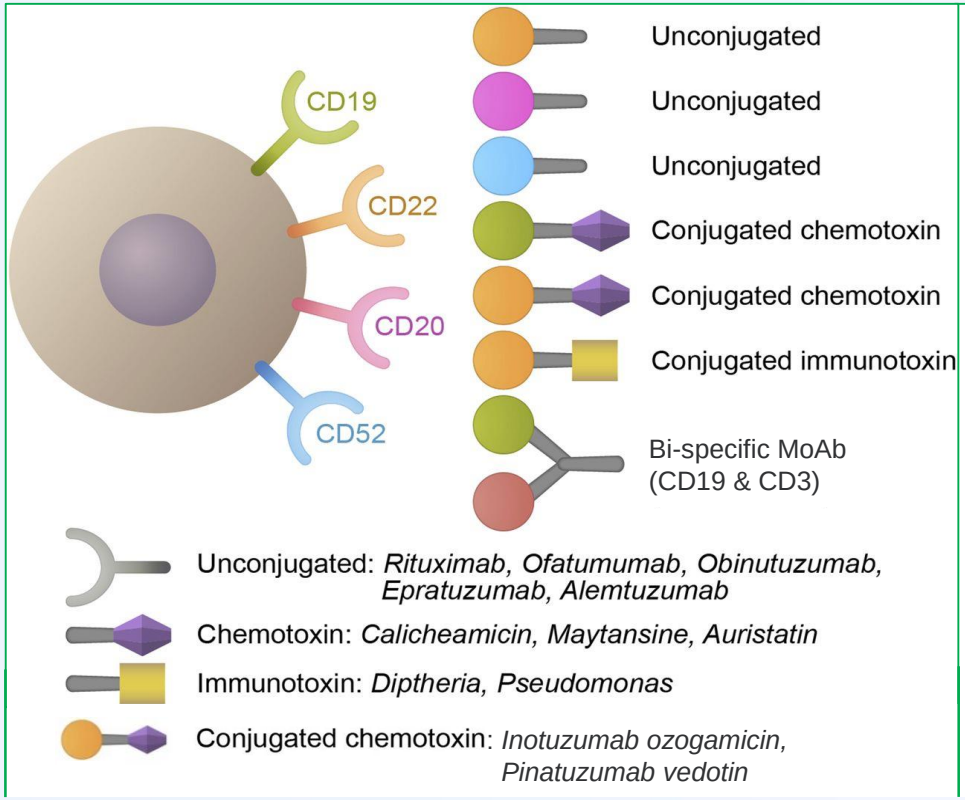
Contemporary management of R/R adult ALL

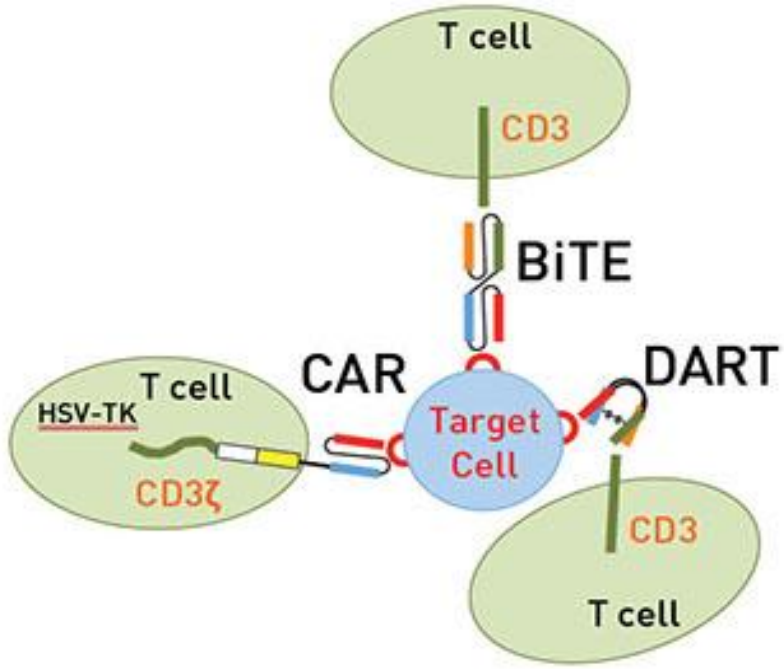
ALL subtype	Management	Allo HSCT
Ph+ ALL	Change TKI ± chemotherapy Immunological therapy (MoAb, CAR-T)	Yes No if CAR-T?
B-cell precursor, Ph-neg	Immunological therapy (MoAb, CAR-T)	Yes No if CAR-T?
T-cell	Nelarabine ± chemotherapy	Yes
Mature B	Experimental	Yes?
Extramedullary relapse	Local therapy + systemic therapy depending on ALL subtype	Yes

ALL, acute lymphoblastic leukaemia; allo, allogeneic; CAR, chimeric antigen receptor; HSCT, haematopoietic stem cell transplantation; MoAb, monoclonal antibody; Ph+, Philadelphia chromosome-positive; Ph-neg, Philadelphia chromosome-negative; R/R, relapsed/refractory; TKI, tyrosine kinase inhibitor

Immuno-oncology in ALL

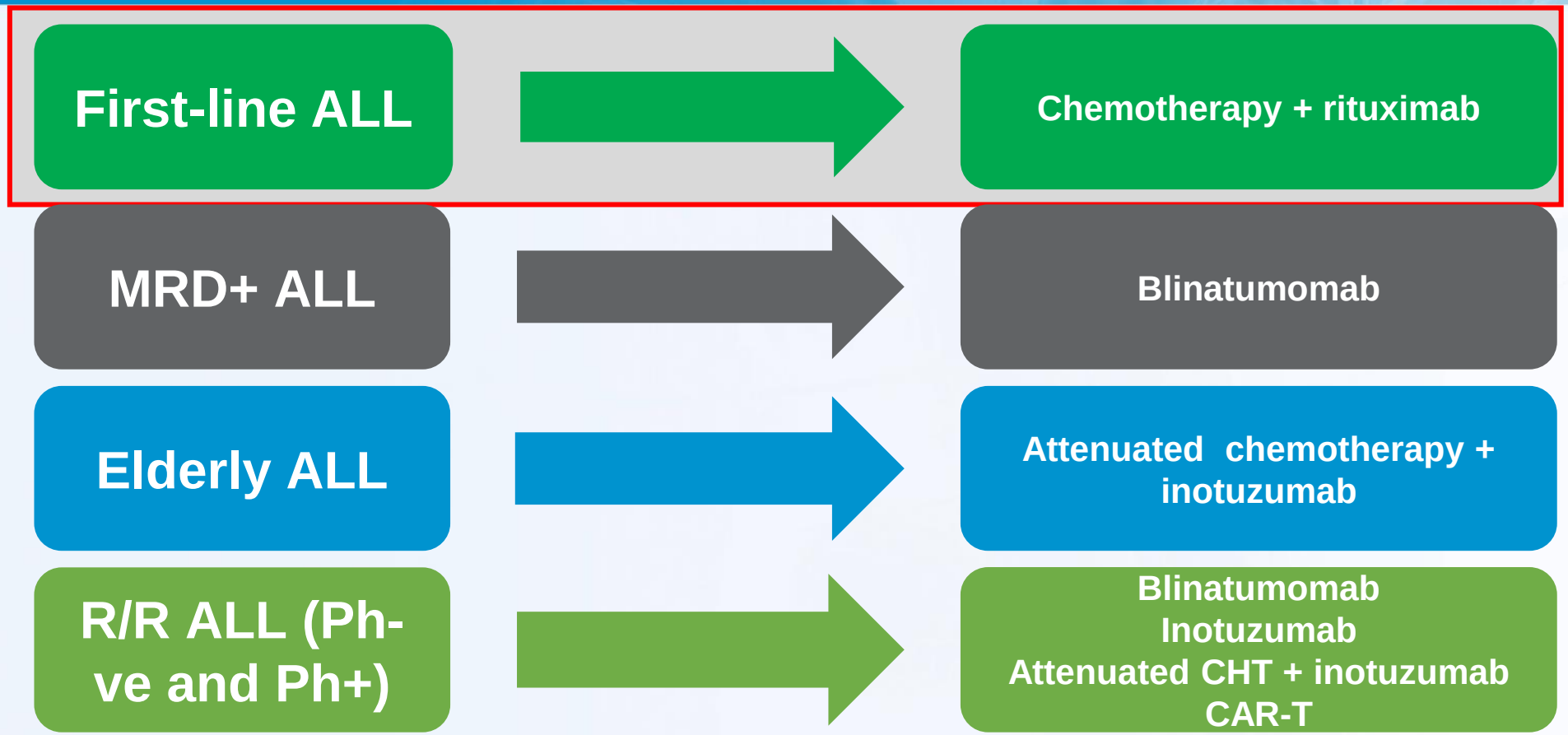
- **Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR-T cells[1,2]**





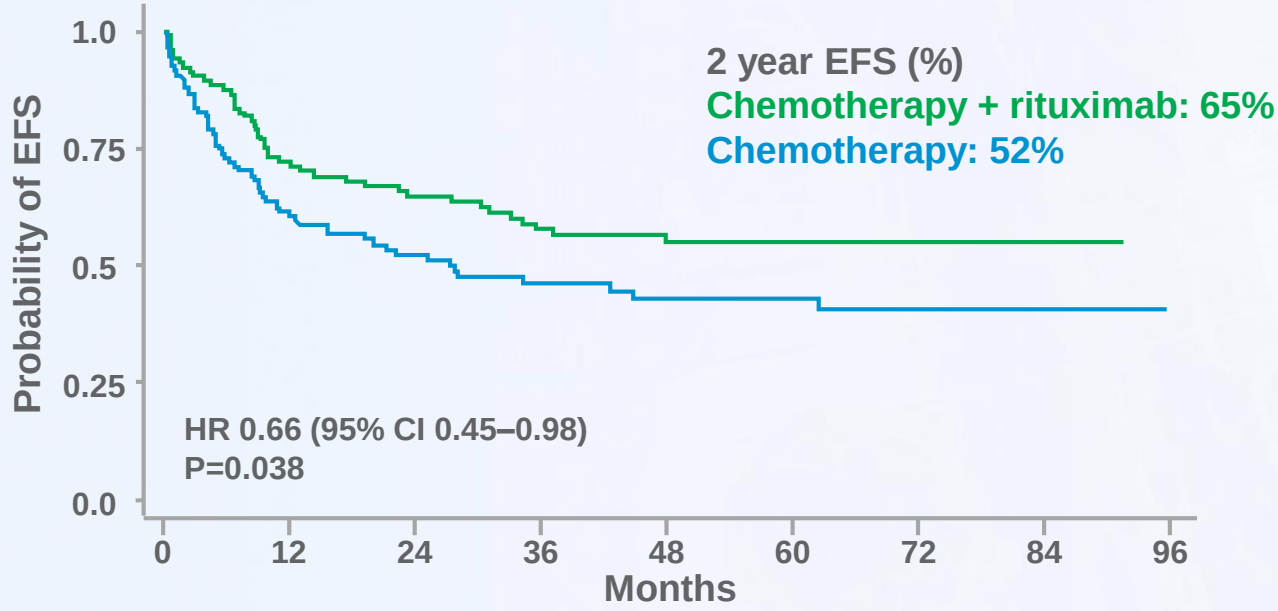
ADC: antibody-drug conjugate; CAR, chimeric antigen receptor; BiTE: bispecific T-cell engagers; DART, dual affinity retargeting molecules; HSV-TK, Herpes Simplex virus thymidine kinase. 1. Adapted from Jabbour. Blood 2015;125:4010; 2. http://www.dipersiolab.org/index.html (accessed 20 March 2016)

Possible new strategies according to the recent results of clinical trials



Chemotherapy ± Rituximab in pre-B ALL: French GRAALL-R, 2005

- 220 pts, median age 40 years (range: 18–59 years) with CD20+ pre-B ALL
- Chemotherapy ± rituximab 375 mg/m^2 for 16–18 doses



- Chemotherapy versus chemotherapy + rituximab:
  - 2-year OS, 71% vs 64% (P=0.095); sensor for SCT, P=0.018
  - CR, 91% vs 92%; MRD-neg*, 61% vs 65%; Allo-SCT, 20% VS 34%

*Defined as MRD <10^{-4} at CR. ALL, acute lymphoblastic leukaemia;
Maury *et al*. ASH 2015. Abstract 1

Blina in MRD-positive ALL

- N=116
- Median follow-up: 30 mos
- Median OS: 37 mos
- Complete MRD response: 79%
- 90 (78%) received HSCT

Median (mos)	Overall	MRD-negative	MRD-positive	P-value
OS	37	40	12	0.001
RFS	19	35	7	0.002
DOR	NR	NR	15	0.015

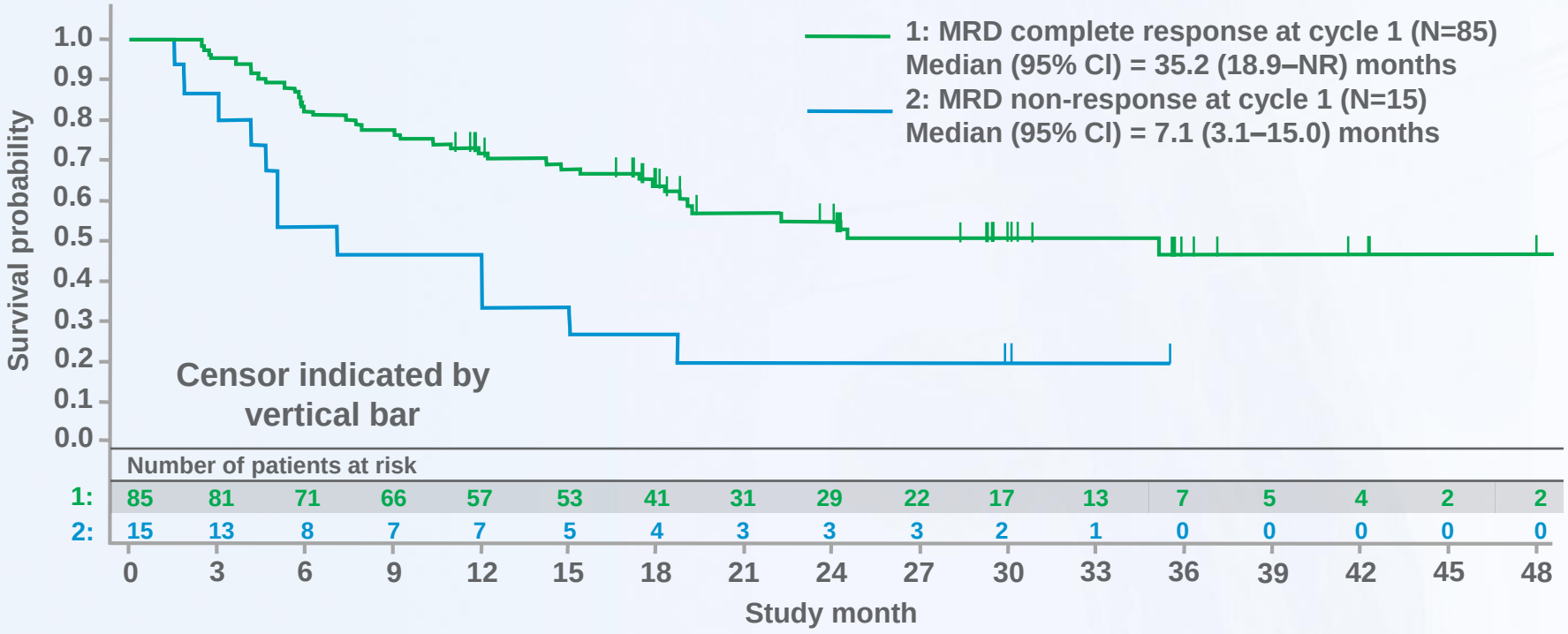
No difference in OS (HR=1.39; P=0.37) and RFS (HR=0.89; P=0.73) between HSCT vs no HSCT

ALL, acute lymphoblastic leukaemia; Allo-SCT, allogeneic stem cell transplant; DOR, duration of response; MRD, minimal residual disease; OS, overall survival; RFS, relapse-free survival

Gökbuget. *Blood* 2015;126. Abstract 680

Long-term outcomes after Blina Rx

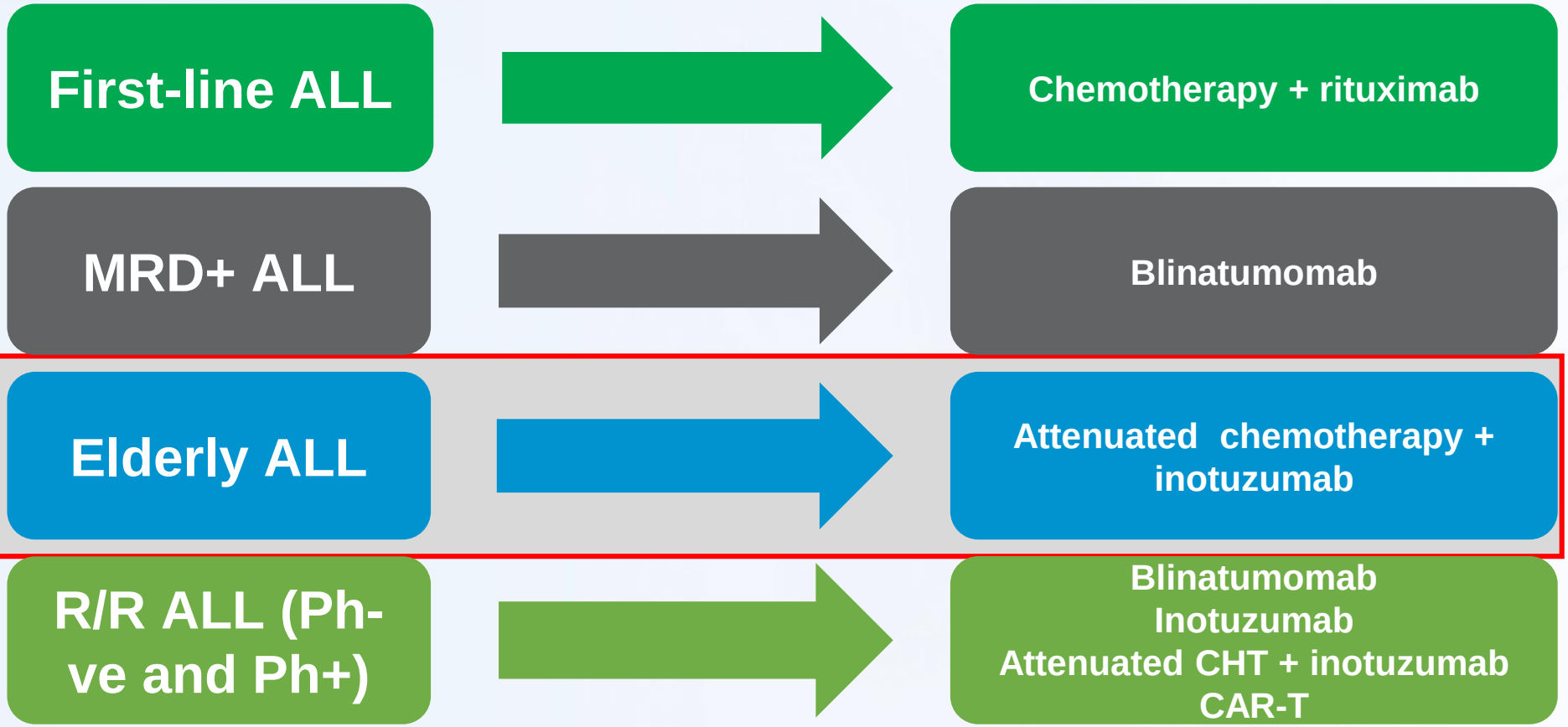
- **Follow-up of a Phase II study in pt MRD+ pre-B ALL (116 pts)**



ALL, acute lymphoblastic leukaemia; CI, confidence interval; MRD, minimal residual disease; RFS, relapse-free survival

Gökbuget. *Blood* 2015; 126:680

Possible new strategies according to the recent results of clinical trials

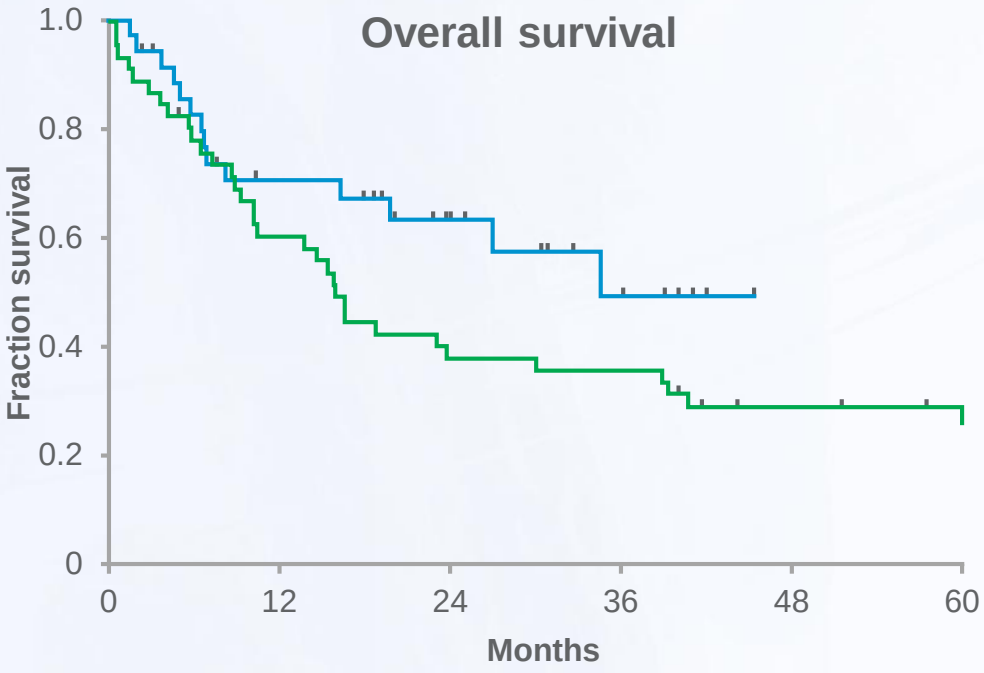


InO plus Mini-HCVD in Elderly ALL

- Median age: 69 years (range: 60–69)
- Median CD22 positivity: 97 (range: 72–100)
- CD20 ≥20: 22 (65%)

Response	N	(%)
CR	28	28/35 (80)
CRp	6	6/35 (17)
ORR	34	34/35 (97)
No response	1	1/35 (3)
Early death	0	0

Response	N	(%)
Cytogenetic CR	19 abn at start	19/19 (100)
Negative MRD*		
D21	21 (6 not done)	21/28 (75)
Overall	36	36/36 (100)



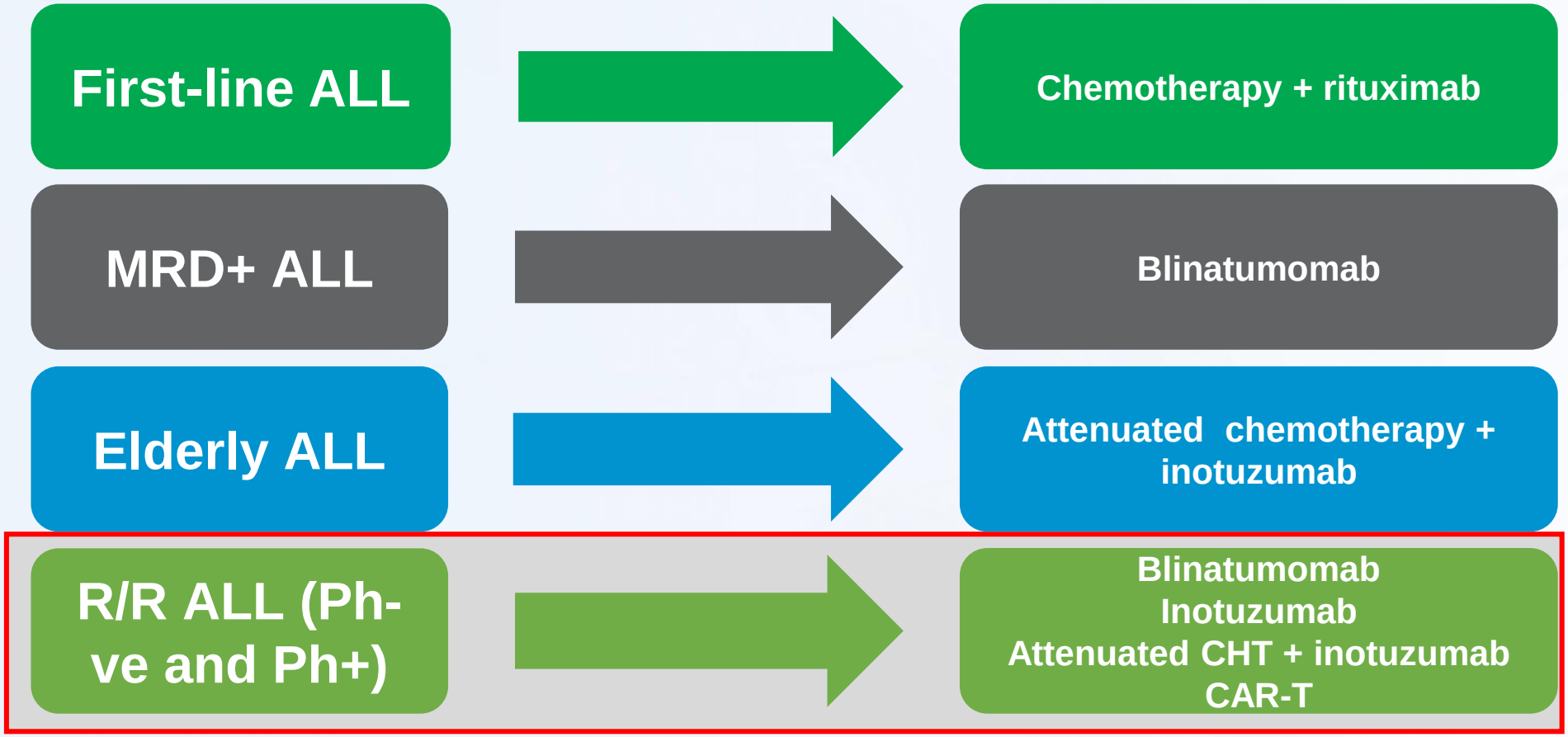
	Total	Fail	2-year OS	Median
HCVD+Ino+/-Rtx	38	14	64%	35 months
HCVAD+/-Rtx	46	33	38%	16 months

p=0.09

*MRD assessed by 6-colour multiparameter flow. ALL, acute lymphoblastic leukaemia; CR, complete remission; CRp, complete remission with incomplete platelet recovery; HCVAD, hyper-cyclophosphamide, vincristine, adriamycin, dexamethasone; HCVD, hyper-cyclophosphamide, dexamethasone, methotrexate and cytarabine; OS, overall survival; PFS, progression-free survival

Jabbour. ASH 2015. Abstract 83

Possible new strategies according to the recent results of clinical trials



Blina Phase II trials

Study (year)	Study	Rx	CR/CRh, %	MRD response, %	Survival
Topp (2011)[1]	MRD+ ALL	21	--	80	78% RFS at 405 days
Gökbuget/ BLAST (2015)[2]	MRD+ ALL	116	--	76	MRD- vs MRD+ RFS: 35.2 vs 7.1 mo OS: 40.4 vs 12 mo
Topp (2014)[3]	R/R ALL	36	69	88	RFS: 7.6 mo OS: 9.8 mo
Topp (2015)[4]	R/R ALL	189	43	82	RFS: 5.9 mo OS: 6.1 mo

ALL, acute lymphoblastic leukaemia; CR, complete remission; CRh, complete remission with partial haematological recovery of peripheral blood counts; HSCT, haematopoietic stem cell transplantation; MRD, minimal residual disease; OS, overall survival; RFS, relapse-free survival; R/R, relapsed/refractory

1. Topp. *J Clin Oncol* 2011;2493; 2. Gökbuget. *Blood* 2015;126; 680a; 3. Topp. *J Clin Oncol* 2014;32:4134; 4. Topp. *Lancet Oncol* 2015;16:57

Phase III InO vs SOC in R/R ALL: Response

	Inotuzumab (n=109)	SOC (n=96)	1-sided P-value
CR/CRi, %	80.7	33.3	<0.0001
S1 CR/CRi, %	87.7	31.3	<0.0001
S2 CR/CRi, %	66.7	37.9	0.0104
MRD-negative in responders, %	78.4	28.1	<0.0001
Median DOR, months (range)	4.6 (3.9–5.4)	3.1 (1.4–4.9)	0.0169
Later Allo-SCT, n	48	20	

ALL, acute lymphoblastic leukaemia; Allo-SCT, allogeneic stem cell transplant; CR, complete remission; CRi, complete remission with incomplete haematological recovery of peripheral blood counts; DOR, duration of remission; MRD, minimal residual disease; R/R, relapsed/refractory; SOC, standard of care

DeAngelo. EHA 2015. Abstract LB2073

Phase III InO vs SOC in R/R ALL: OS

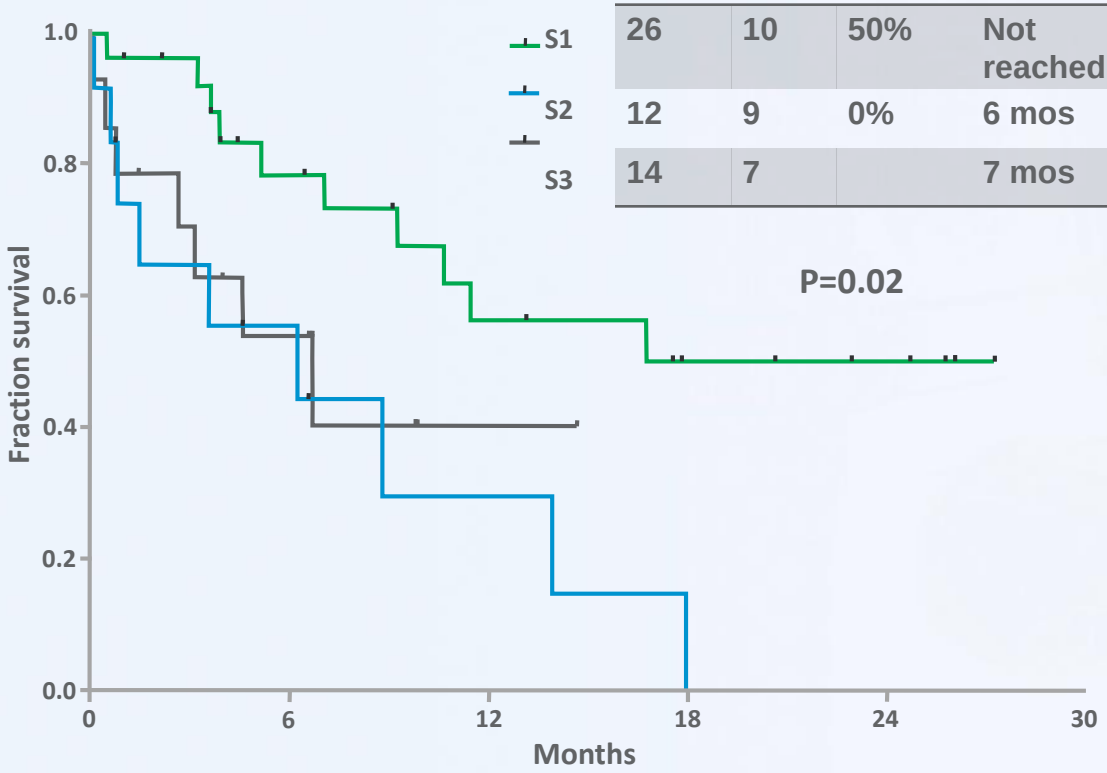
- ITT analysis population included 326 pts
- mOS: 7.7 months (95% CI: 6.0–9.2) for InO vs 6.7 months (95% CI: 4.9–8.3) for SOC
- OS hazard ratio between InO and SOC: 0.77 (97.5% CI: 0.58–1.03; P=0.0203)
- Statistically significant improvement in final OS with InO not met*
- The 2-year OS rate for InO vs SOC was 23% (95% CI: 16–30%) vs 10% (95% CI: 5–16%)
- In a restricted mean OS time analysis, mean OS: 13.9 months for InO vs 9.9 months for SOC, which met statistical significance
- PFS was significantly longer with InO vs SOC (5.0 vs 1.8 months; P<0.0001)

*prespecified significance level of 0.0104

ALL, acute lymphoblastic leukaemia; CI, confidence interval; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; SoC, standard of care

Kantarjian. EHA 2016. Abstract LB2233; N Engl J Med 2016 (online)

Phase I/II MiniHCVD + InO in R/R ALL (n=52)



Total	Fail	2 yr OS	Median
26	10	50%	Not reached
12	9	0%	6 mos
14	7		7 mos

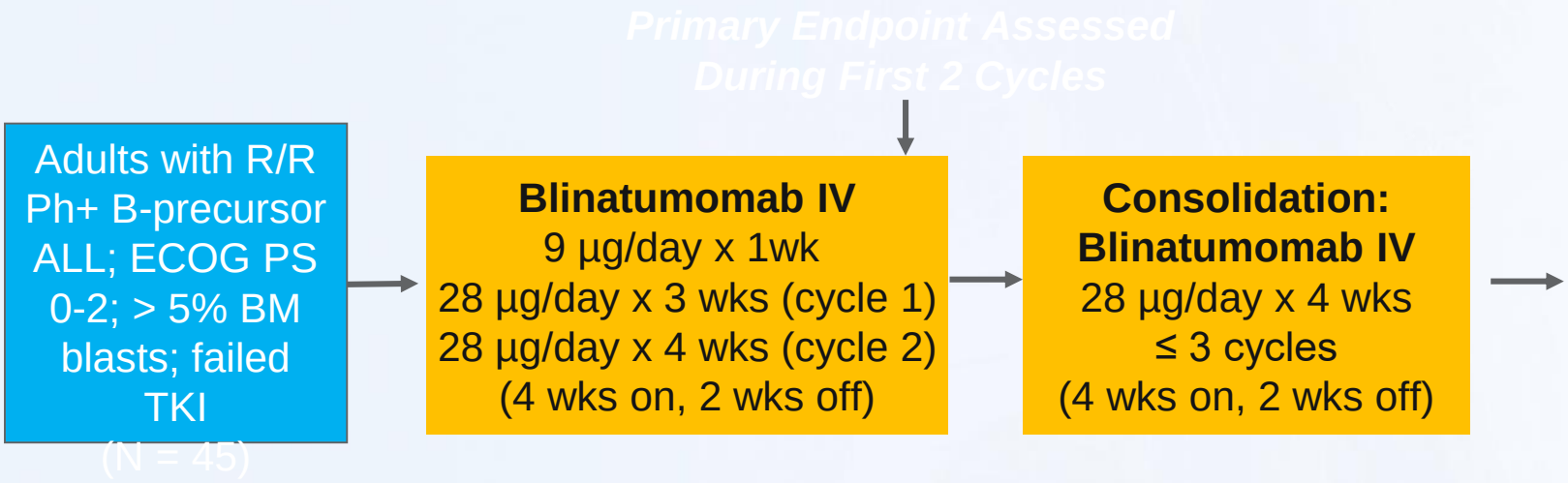
Response	N=52 (%)
CR	24 (52%)
CRp	8 (17%)
CRi	2 (4%)
ORR	34 (74%)

ALL, acute lymphoblastic leukaemia; CR, complete remission; CRi, complete remission with incomplete haematological recovery of peripheral blood counts; CRp, complete remission with partial haematological recovery of peripheral blood counts; HCVD, hyper-cyclophosphamide, dexamethasone, methotrexate and cytarabine; OS, overall survival; R/R, relapsed/refractory

Sasaki. *Blood* 2015;126:3721

ALCANTARA: Study Design

- Phase II single arm study



- **Primary endpoint**: CR/CRh during first 2 cycles
- **Secondary endpoints**: best CR, MRD, RFS, OS, allogeneic HSCT rate, and safety

Martinelli G, et al. ASH 2015. Abstract 679. ClinicalTrials.gov. NCT02000427.

ALCANTARA: Baseline Characteristics

Characteristic	Pts (N = 45)
Median age, yrs (range)	55 (23-78)
Male, n (%)	24 (53)
Prior relapses, n (%)	
▪ 0 (primary refractory)	3 (7)
▪ 1	25 (56)
▪ 2	13 (29)
▪ ≥ 3	4 (9)
Prior allogeneic HSCT, n (%)	20 (44)
Prior TKI, n (%)	
▪ All pts	45 (100)
▪ Imatinib	25 (56)
▪ Dasatinib	39 (87)
▪ Nilotinib	16 (36)
▪ Ponatinib	23 (51)
BM blasts, n (%)	
▪ < 50%	11 (24)
▪ ≥ 50%	34 (76)
ABL kinase domain mutations,* n (%)	17 (46)
▪ T3151 mutation	10 (27)

*n = 37

Martinelli G, et al. ASH 2015. Abstract 679.

ALCANTARA: Efficacy

Parameter	Response, %
Primary endpoint	
CR/CRh (first 2 cycles)	36
▪ T315I mutation	40
▪ ≥ 2 prior 2+ gen TKI	41
▪ Prior ponatinib treatment	35
Secondary endpoints	
Best response (first 2 cycles)	
▪ CR	31
▪ CRh	4
▪ CRi (not including CRh)	4
Complete MRD response†	88
▪ MRD response in pts with ABL-kinase mutations	100
Proceeded to allogeneic HSCT	25

*Number of evaluable pts. †Includes all 4 CR/CRh T315I pts.

- **Median RFS**: 6.7 mos (95% CI: 4.4-NE)
- **Median OS**: 7.1 mos (95% CI: 5.6-NE)

Martinelli G, et al. ASH 2015. Abstract 679.

CAR-T Cells in ALL

Parameter	U Penn[1]	Seattle[2]	U Penn[3]	MSKCC[4]	NIH[5]
Rx, n	59	33	27	46	45
Median age, yrs (range)	4-24	NR (1-25)	44 (21-72)	45 (22–74)	13 (5–27)
CR, %	93	94	59**	82	58
Estimated 12-mo OS, %	79	74	NR	9	40
Severe CRS, %	23	16	78	24	16
Severe neurotoxicity	47	31	NR	28	13

*10/12 pts (83%) in the last cohort

1.Grupp S. Blood 2015; 126, abstract 681. 2. Turtle C. JCO 2016; 34, abstract 102; 3. Frey NV. JCO 2016; 34:, abstract 7002. 4. Park JH. Blood 2015; 126, abstract 682, 5. Lee. Lancet 2015;385:517

Immunologic therapy in adult ALL. Summary

- **Monoclonal antibodies**
  - Naked. Anti CD20 (rituximab, ofatumomab)
    - Clearly indicated in Burkitt ALL
    - Possibly useful in CD20+ Precursor B-ALL
  - Immunoconjugates (inotuzumab)
    - Effective in R/R ALL
  - Bispecific (blinatumomab)
    - Effective in R/R and MRD+ ALL
- CAR T-cells
  - Highly effective in R/R ALL in phase I-II trials

- **Effective and safe bridge to HSCT**
- **First line?**

Bridge to HSCT or cure w/o SCT?

Treatment of adult ALL in the "real world"
Main co-operative groups in adult ALL

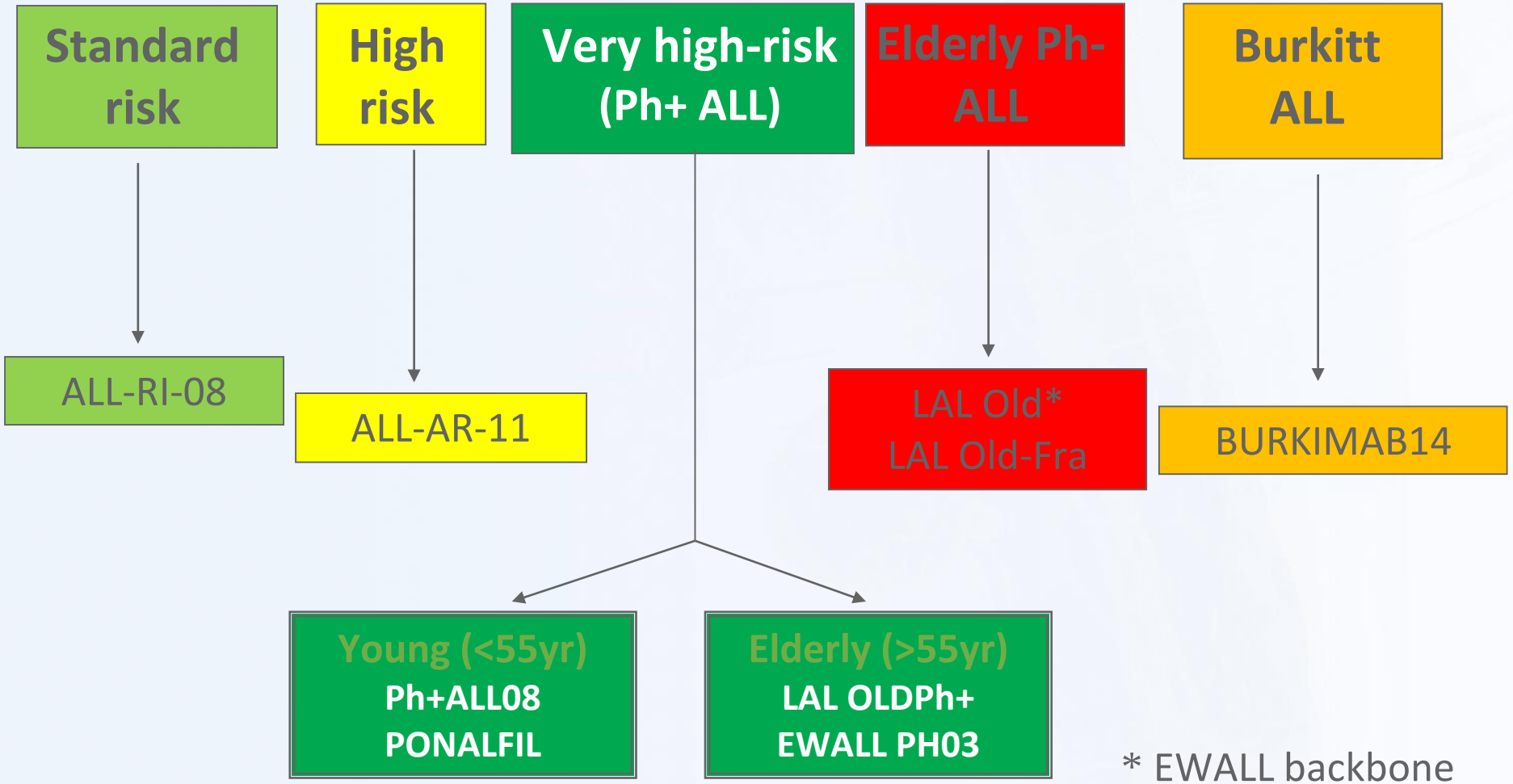
Europe

- GMALL. Germany
- GIMEMA. Italy
- NILG. Northern Italy
- GRAALL. France,Belgium, Switzerland
- HOVON. Holland
- MRC. United Kingdom
- NOPHO. Sweden, Norway, Finland, Denmark
- PALSG, Poland
- PETHEMA. Spain

Rest of the world

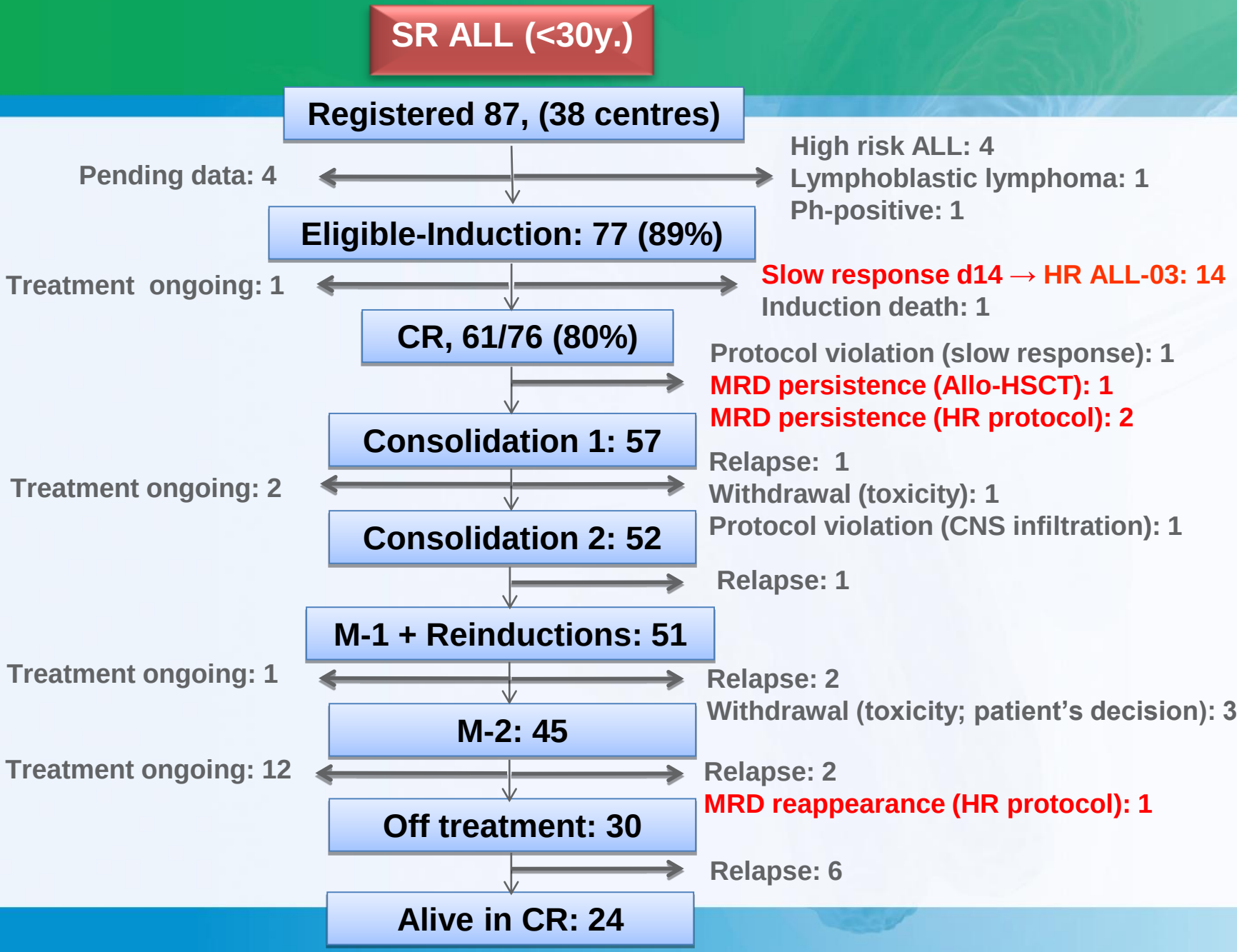
- CALGB. USA
- MDACC. USA
- DFCI Consortium. USA
- JALSG. Japan
- … /…

Overview of the Spanish PETHEMA protocols in adult ALL Front line

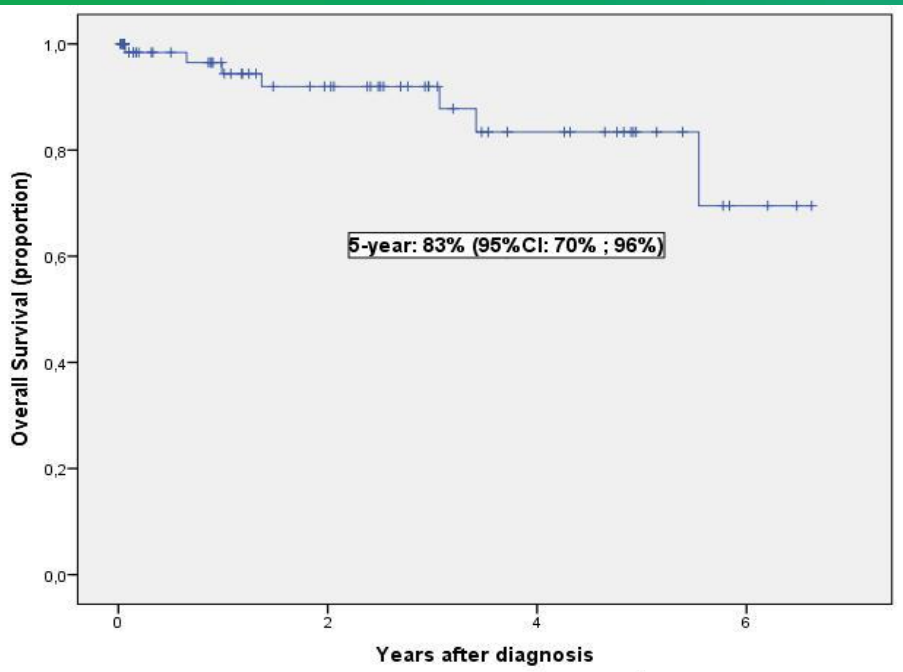


* EWALL backbone

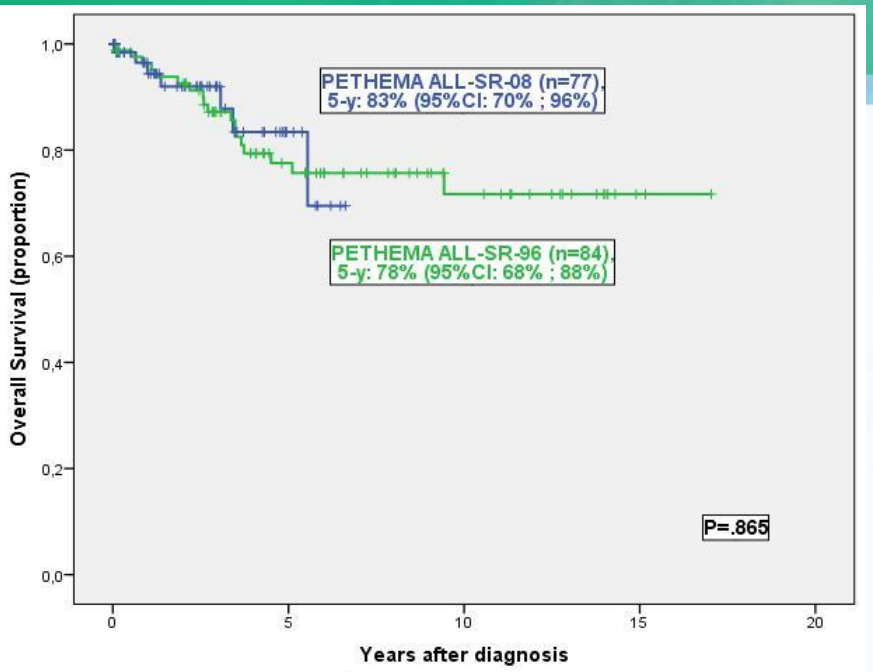
PETHEMA SR ALL-08



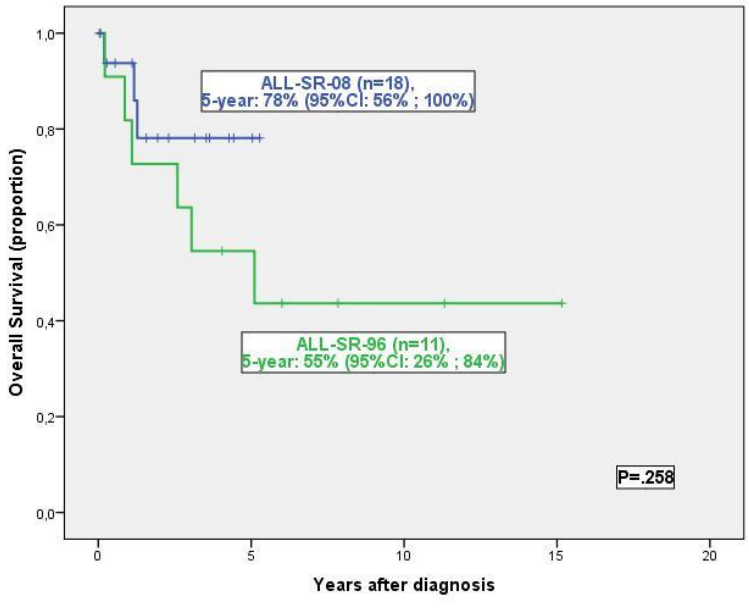
OS (n=77)

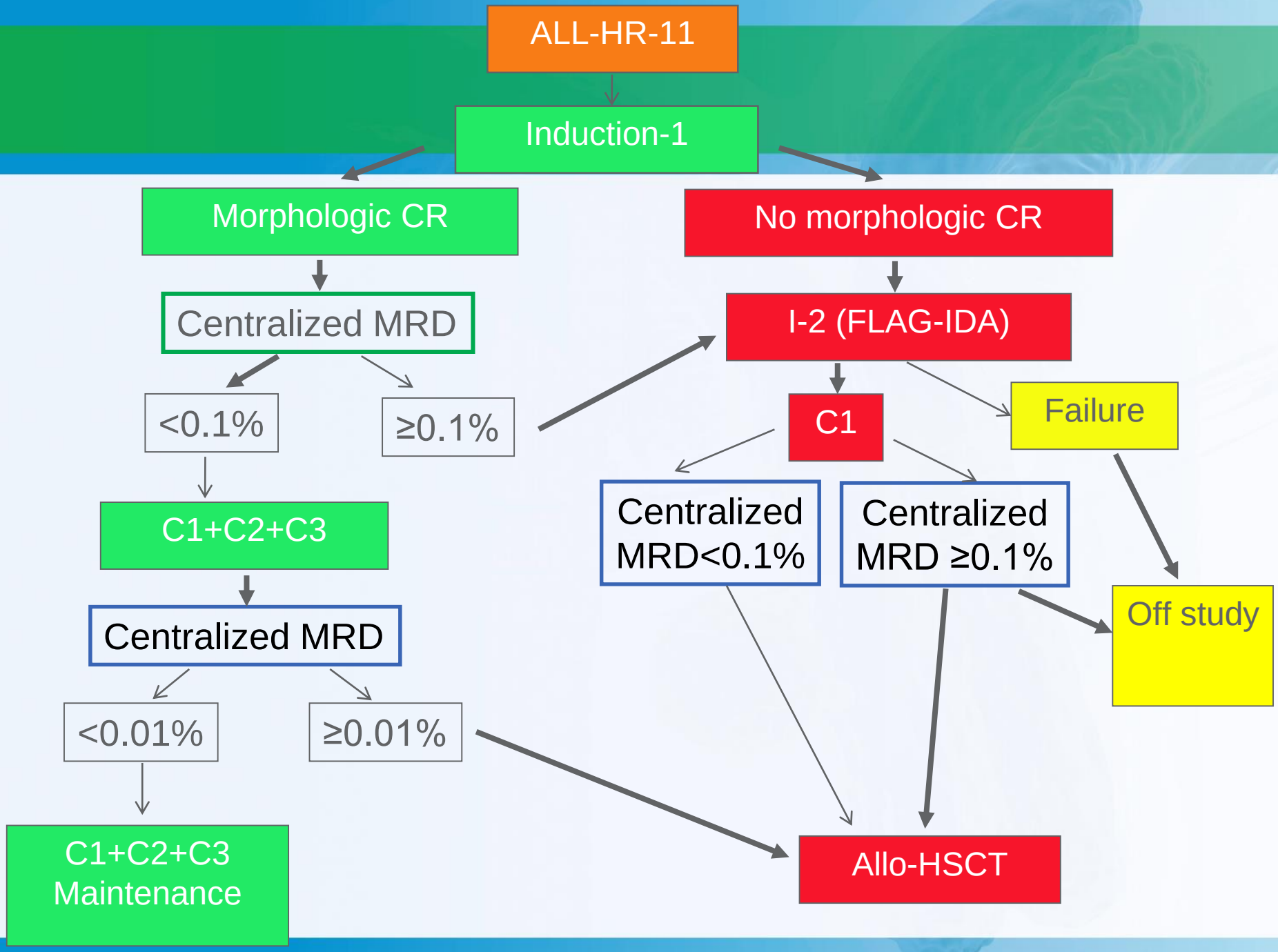


OS by SR PETHEMA protocol

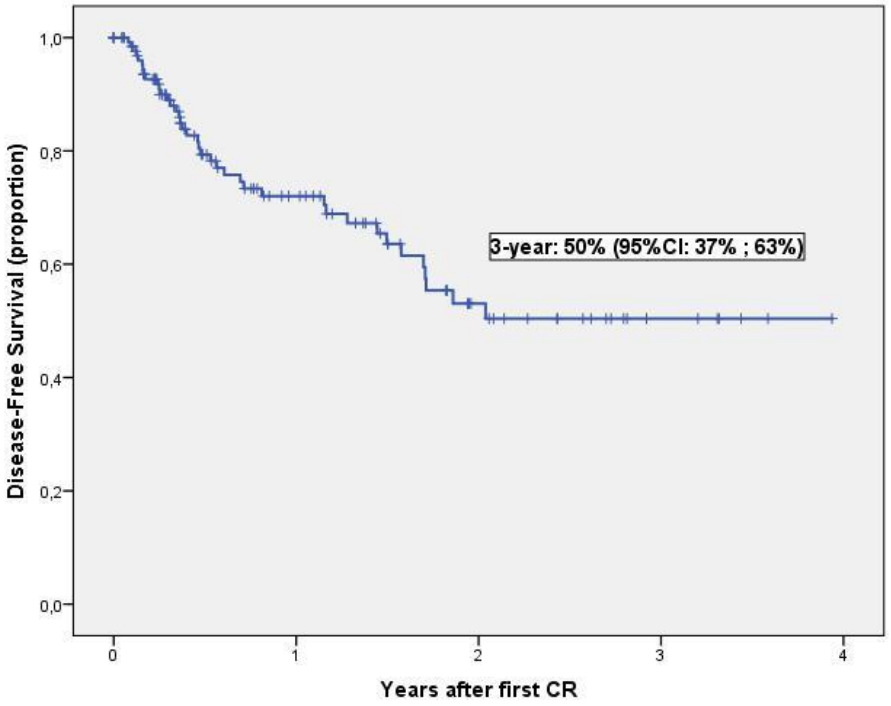


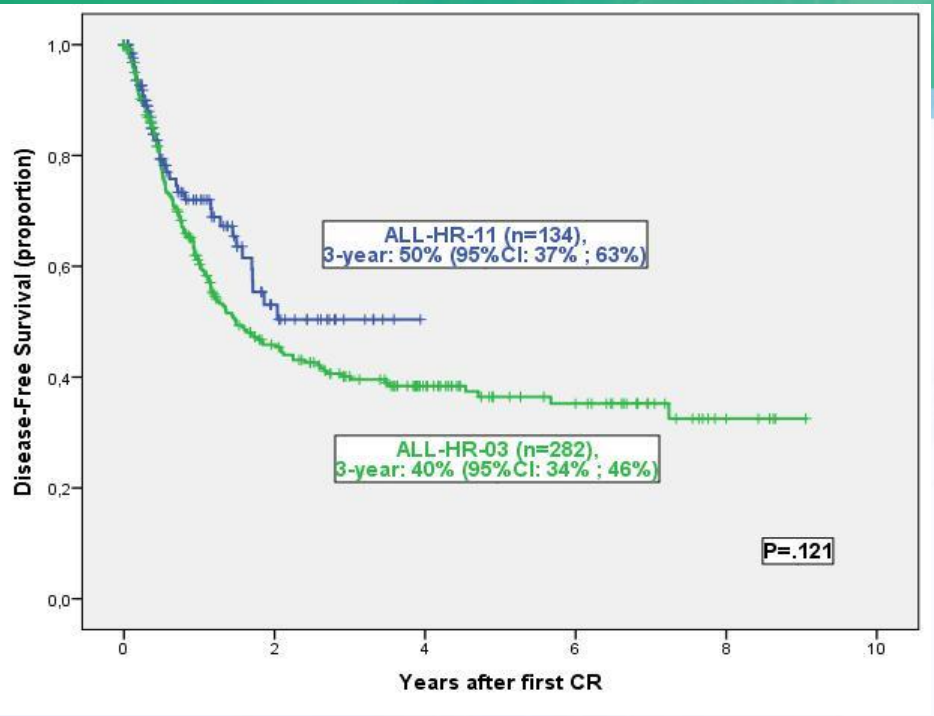
OS in poor responders ALL-SR-96 vs. ALL-SR-08



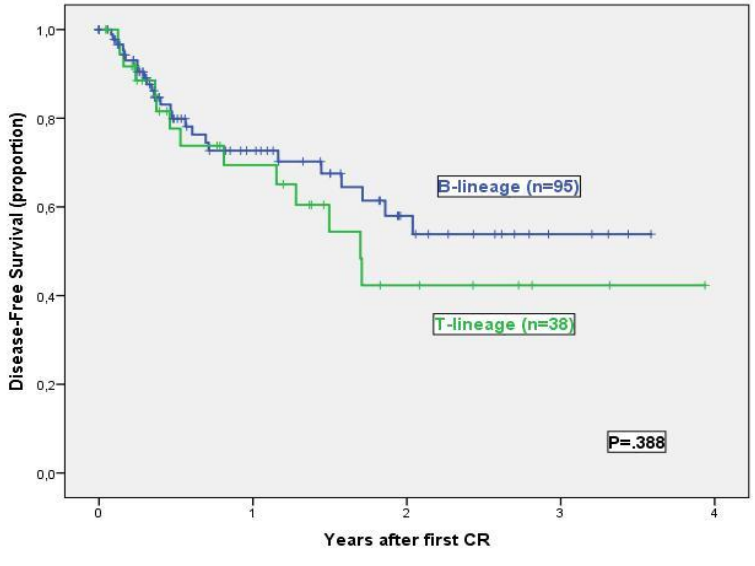

ALL-HR-11
Induction-1
Morphologic CR
No morphologic CR
Centralized MRD
I-2 (FLAG-IDA)
<0.1%
≥0.1%
C1
Failure
C1+C2+C3
Centralized MRD<0.1%
Centralized MRD ≥0.1%
Centralized MRD
Off study
<0.01%
≥0.01%
C1+C2+C3 Maintenance
Allo-HSCT

DFS (n=134)

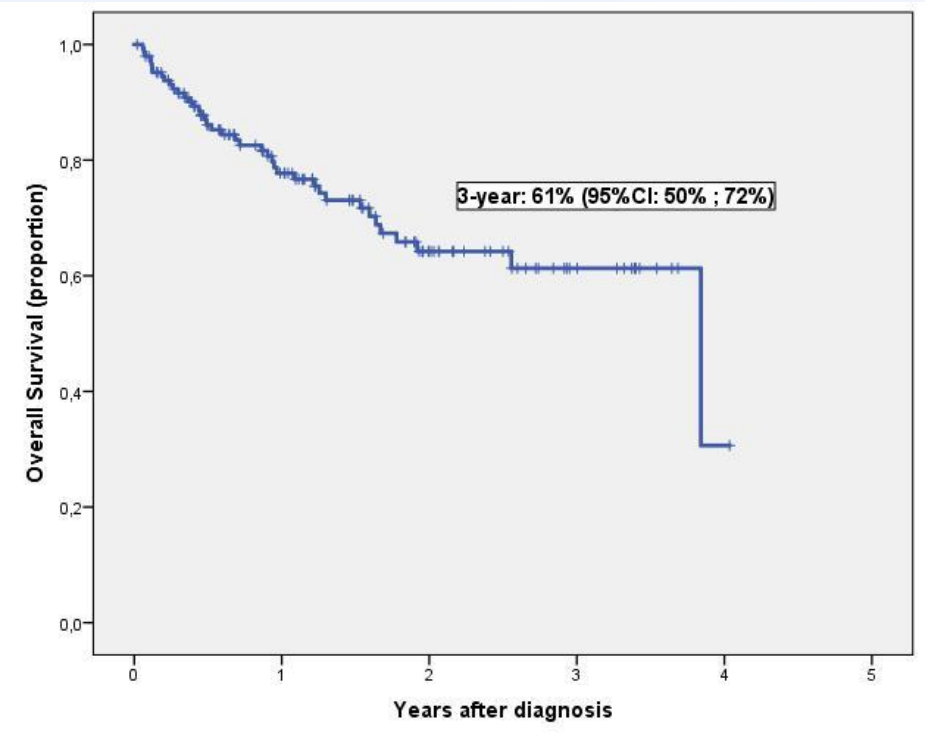


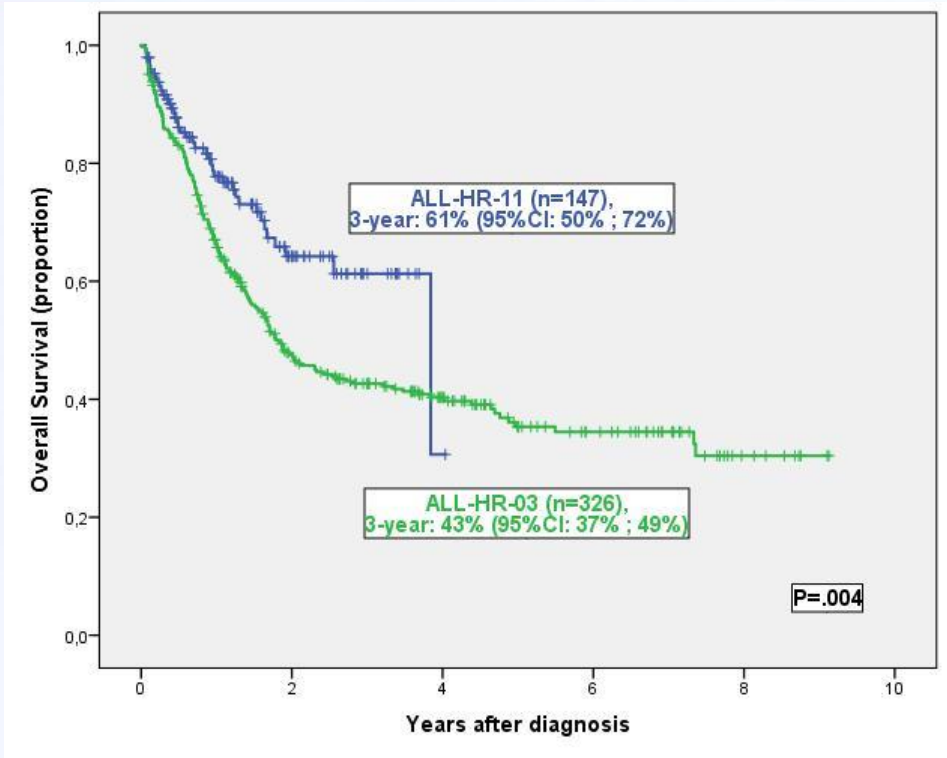


DFS by phenotype



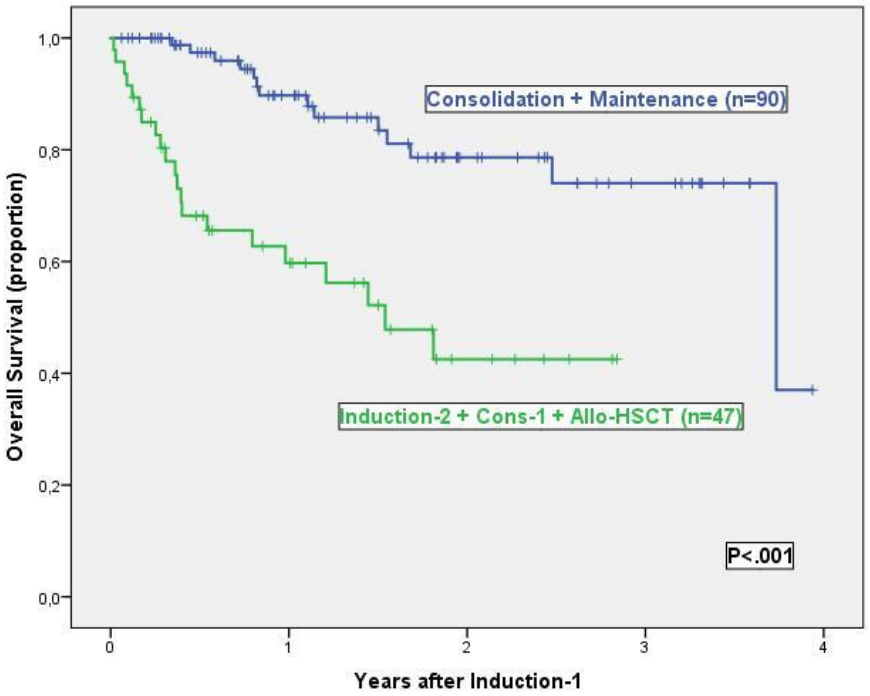
OS (n=147)

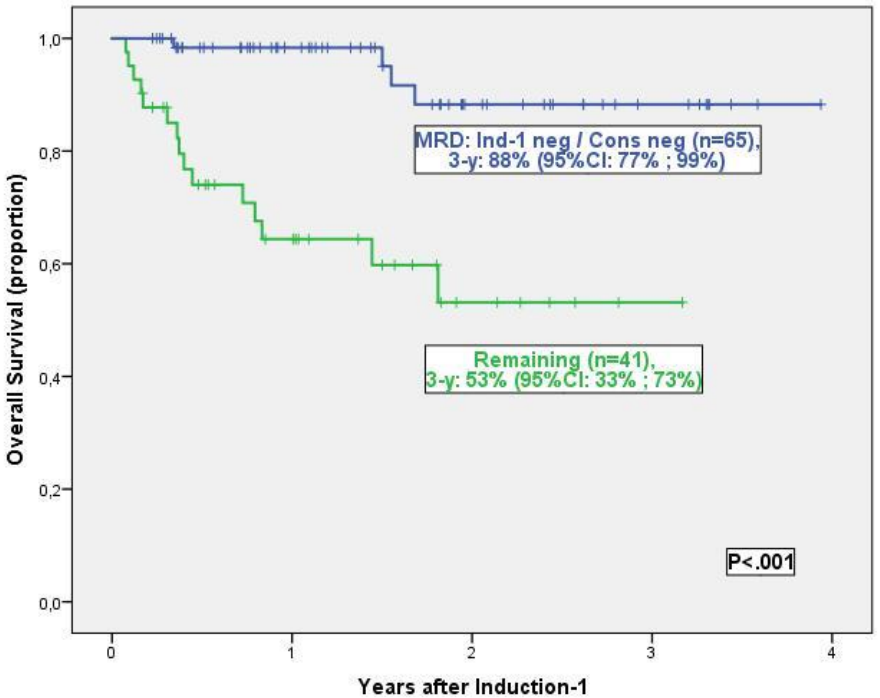




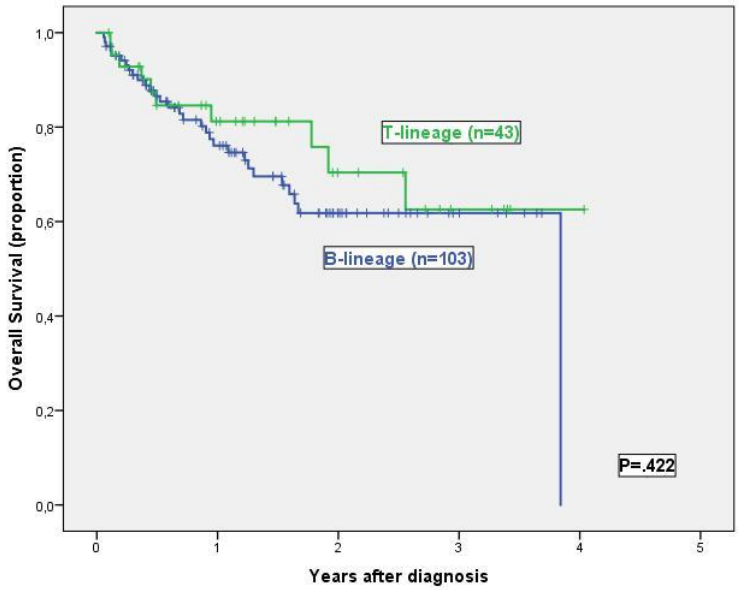
Median follow-up: 1.22 [0.02 ; 4.04] years

OS by intention-to-treat



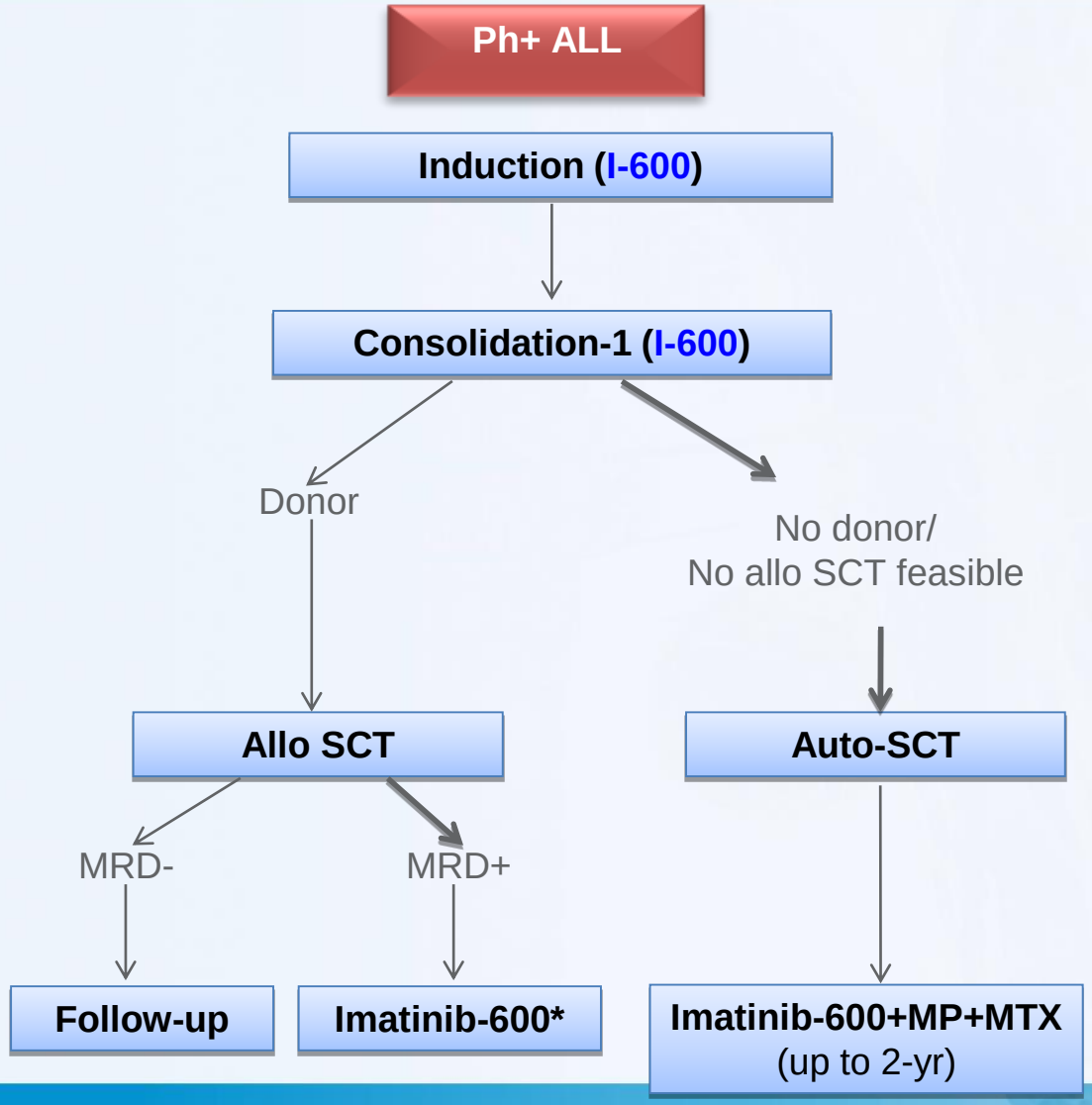


OS by phenotype



Treatment schedule

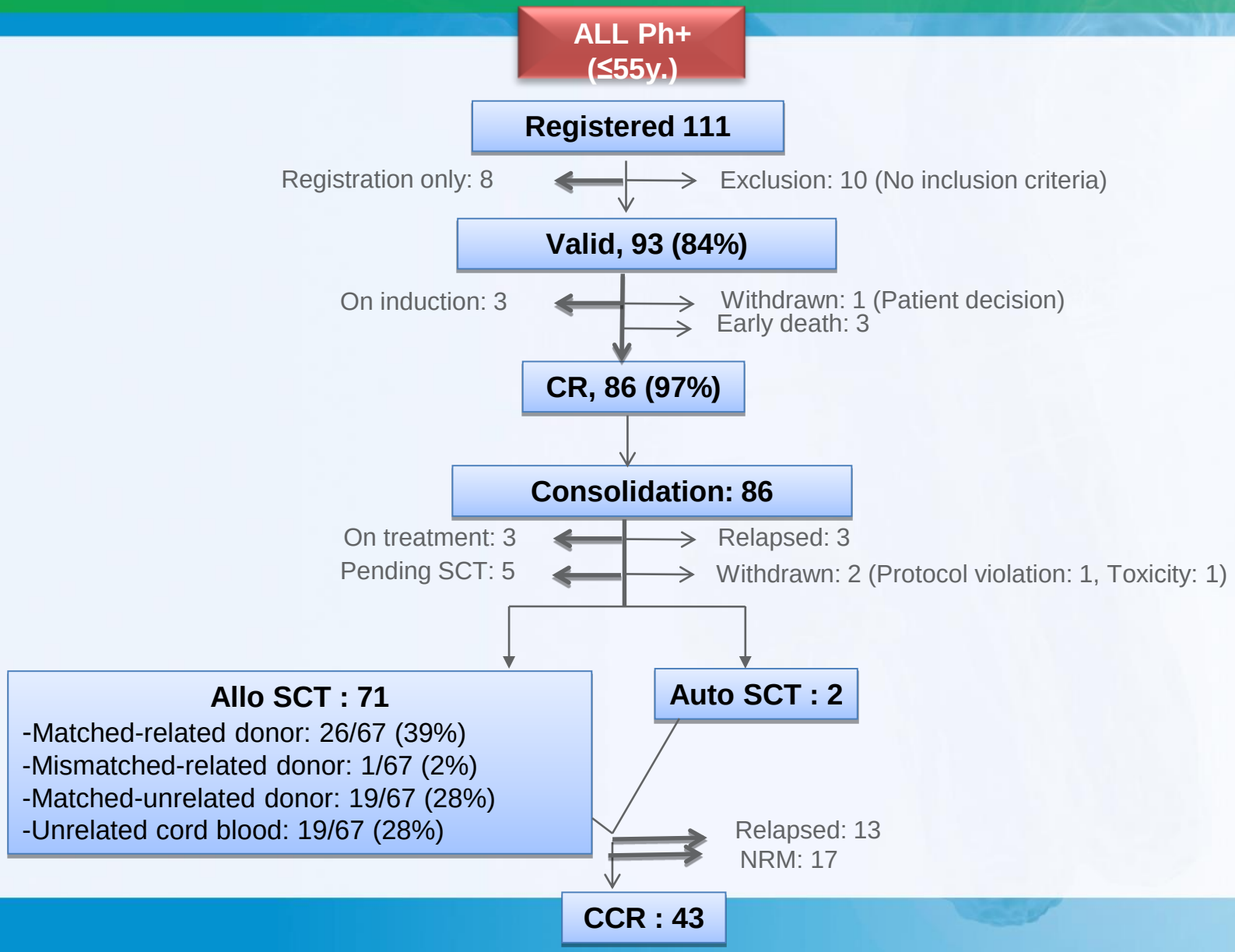
Ph+ ALL < 55 yr. ALL Ph-08



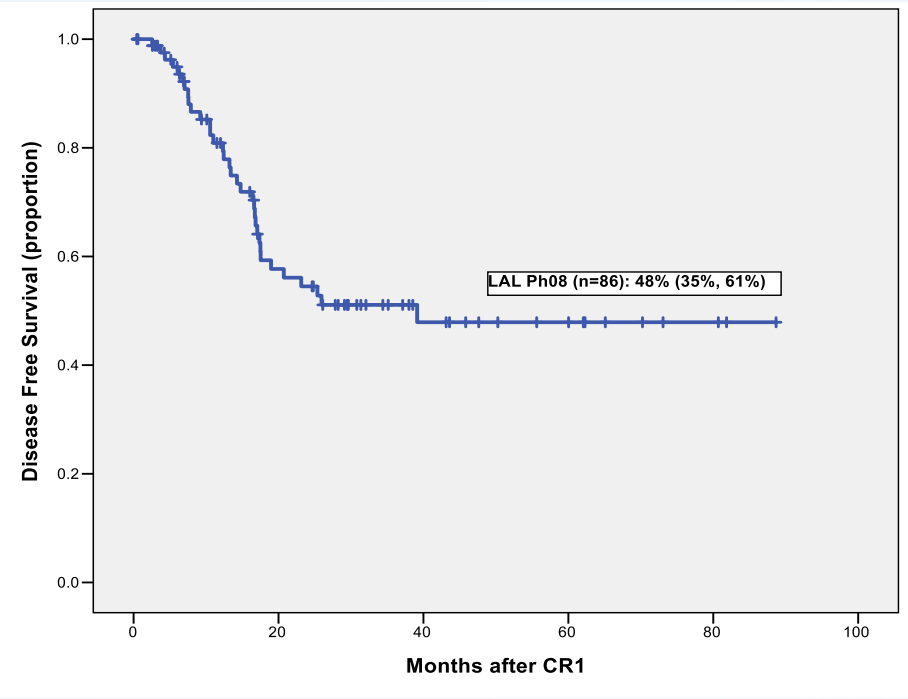
*If no T315I mutation

Flow chart of the study

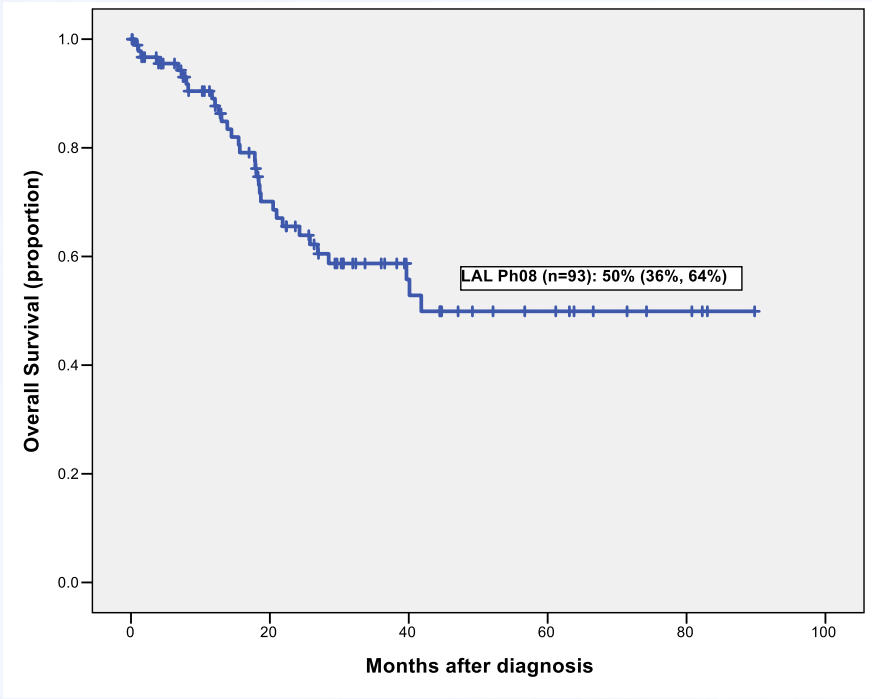
PETHEMA LAL Ph08



Disease-free survival

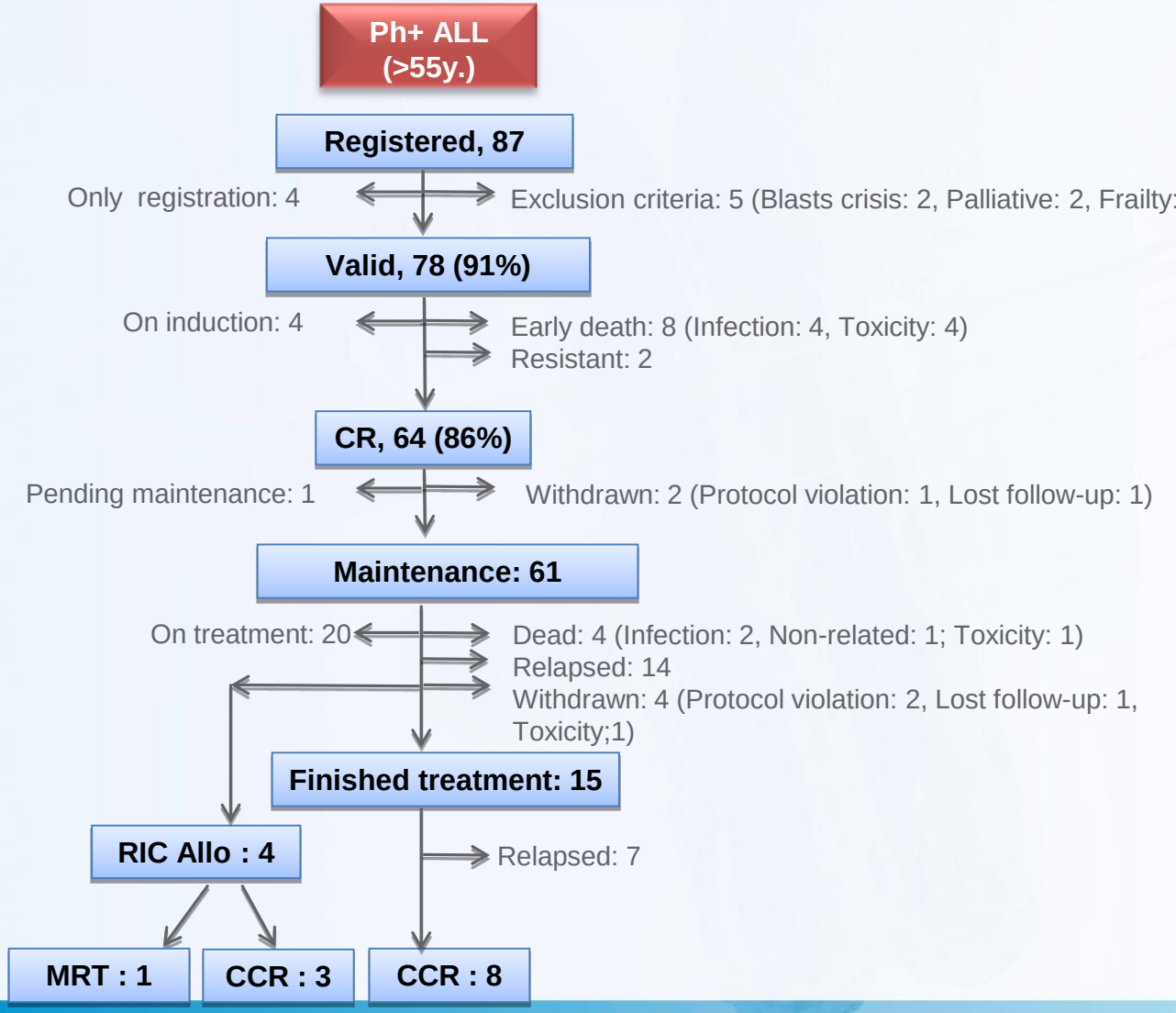


Overall survival

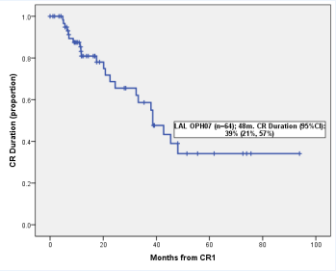


Flowchart

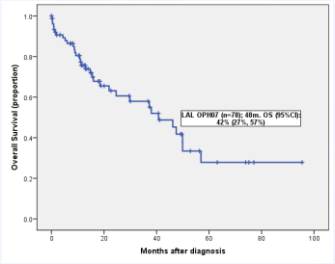
PETHEMA LAL OPH 07



CR duration

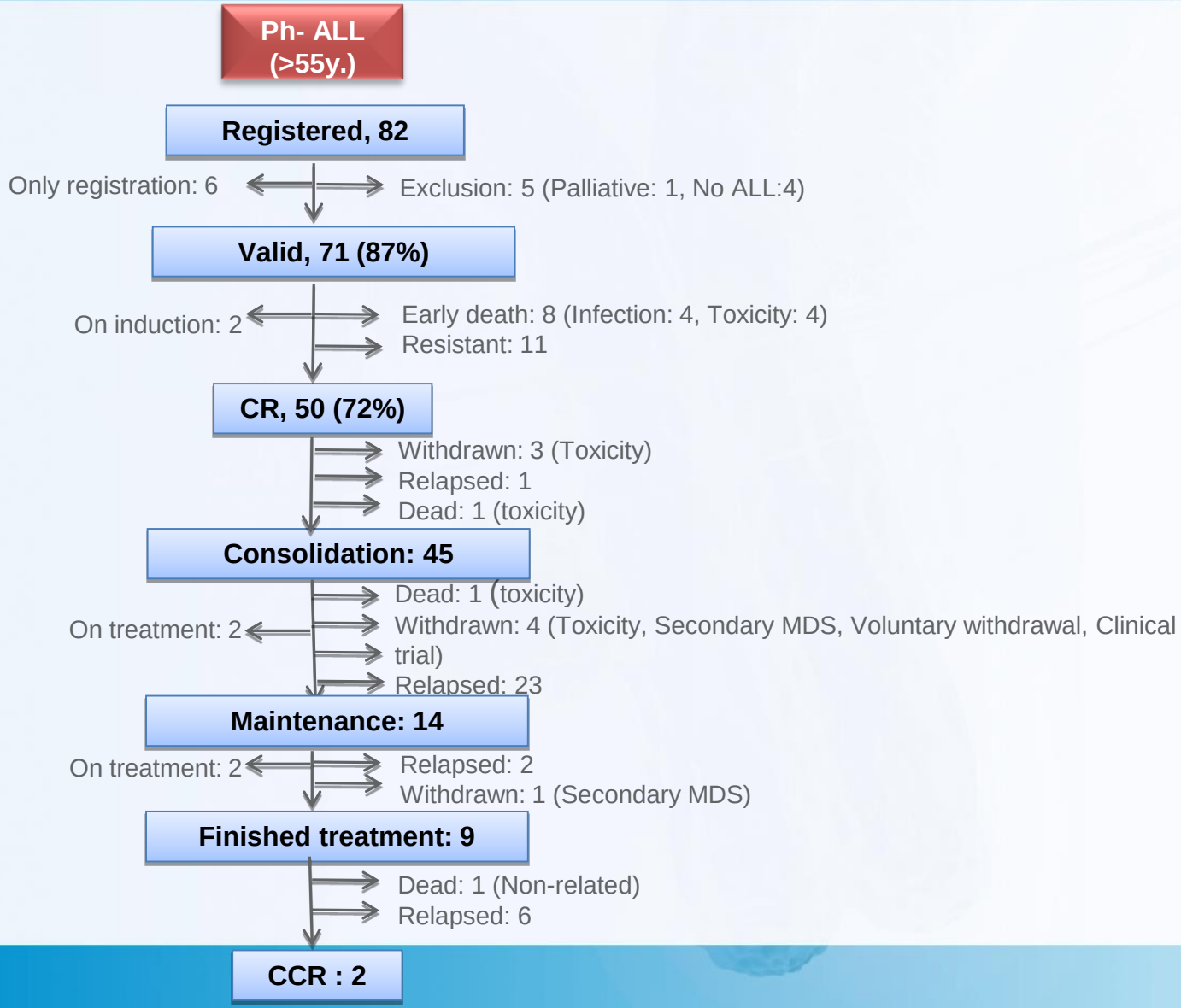


Overall survival

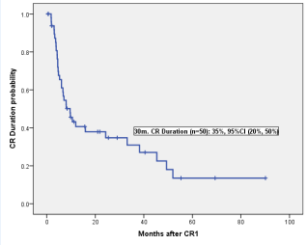


Flowchart

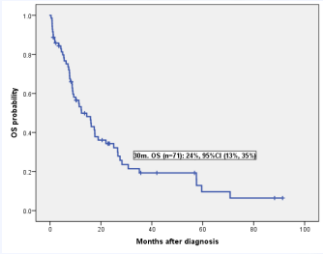
PETHEMA ALL OLD 07



CR duration

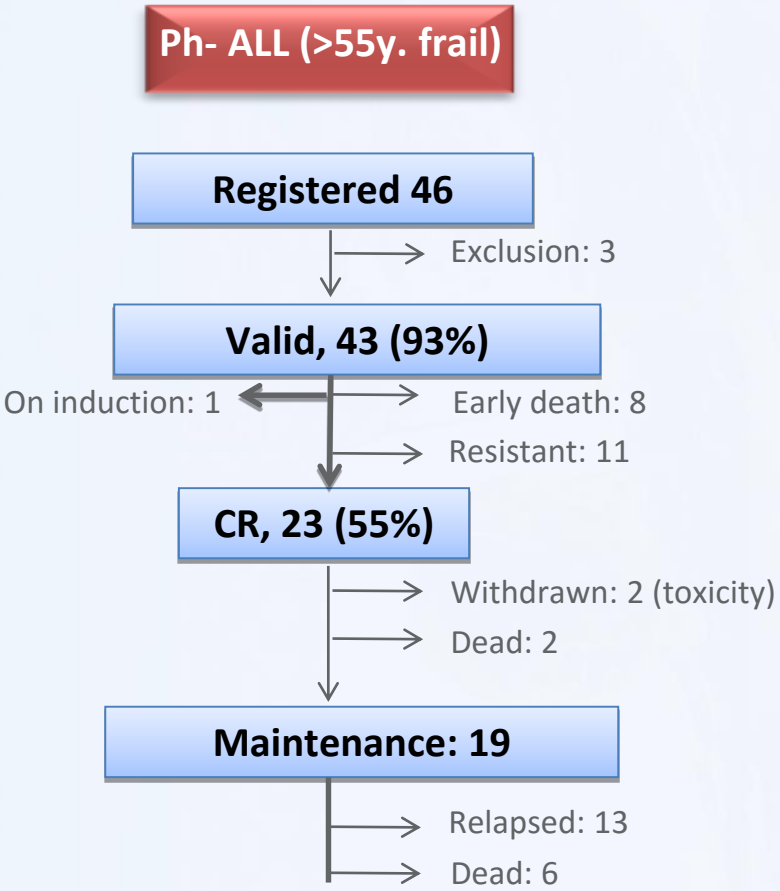


Overall survival

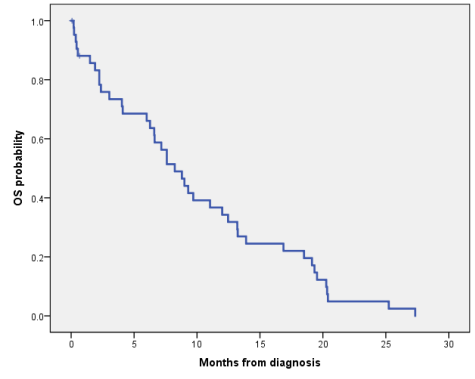


Flowchart

PETHEMA LAL FRAIL 07



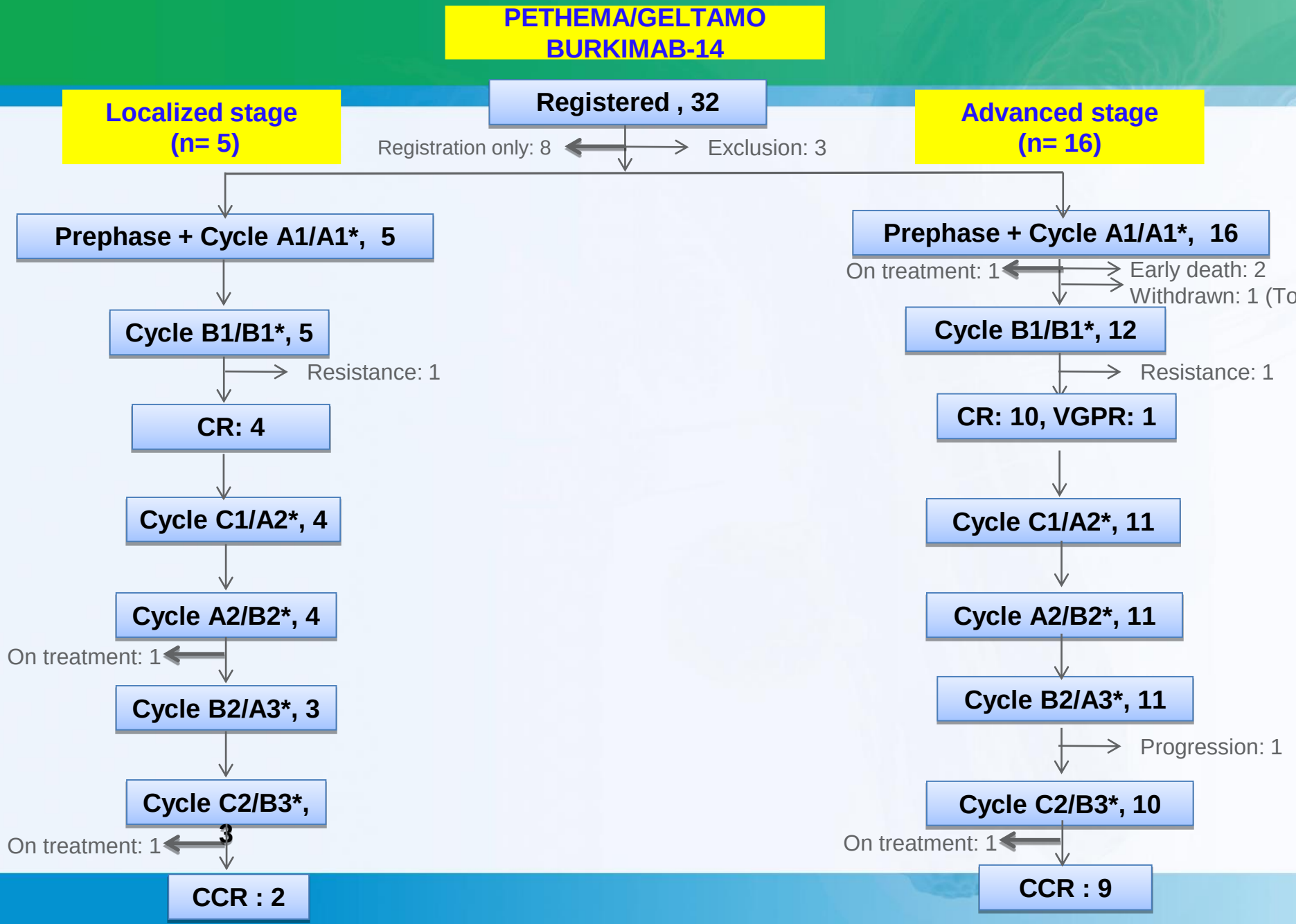
Overall Survival



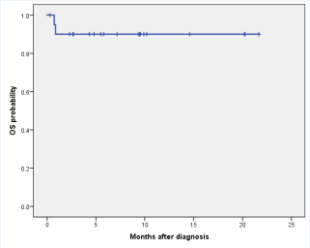
Median Overall Survival (months), 95% CI : 8.2 (5.9 , 10.5)

Median Disease Free Survival (months), 95% CI : 6.9 (2.8 , 11)

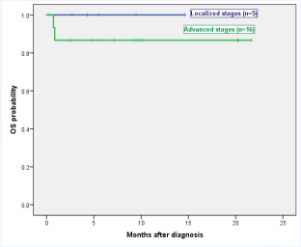
Flowchart for B-mature ALL and Burkitt lymphoma



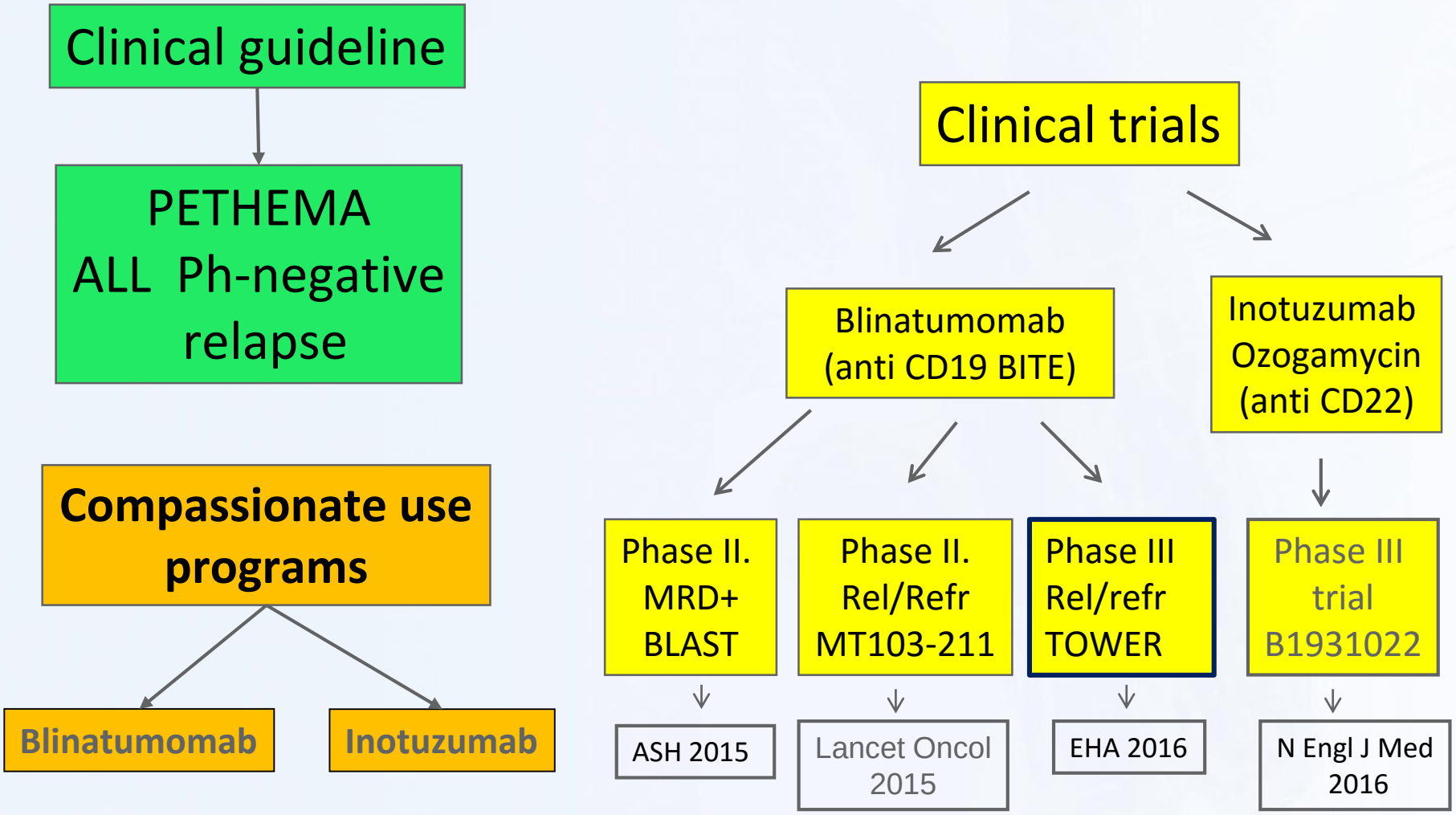
Overall Survival (Mature B-ALL and Burkitt lymphoma)



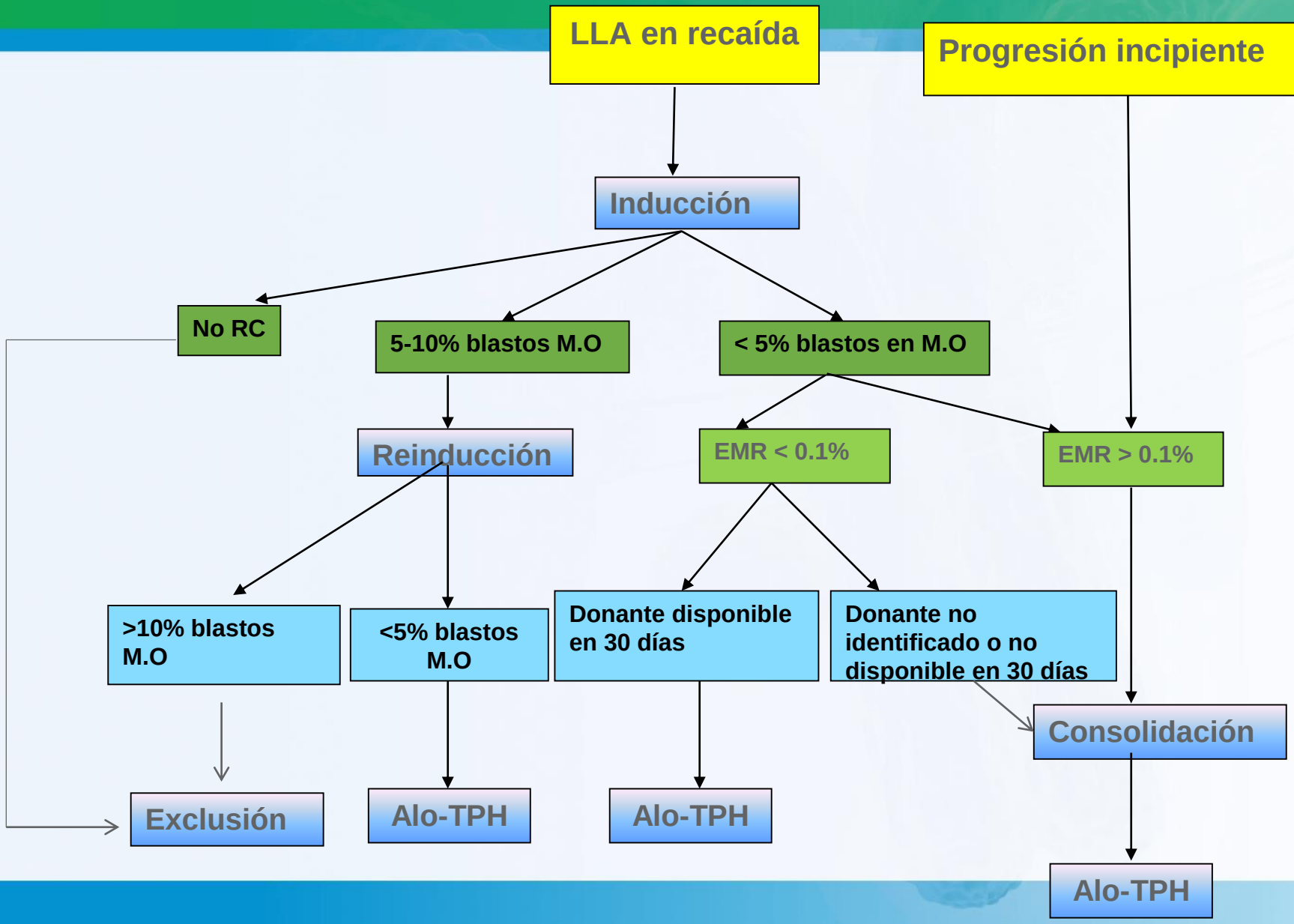
Overall Survival (Mature B-ALL and Burkitt lymphoma) according to stage



Spanish PETHEMA studies in adult ALL Relapse

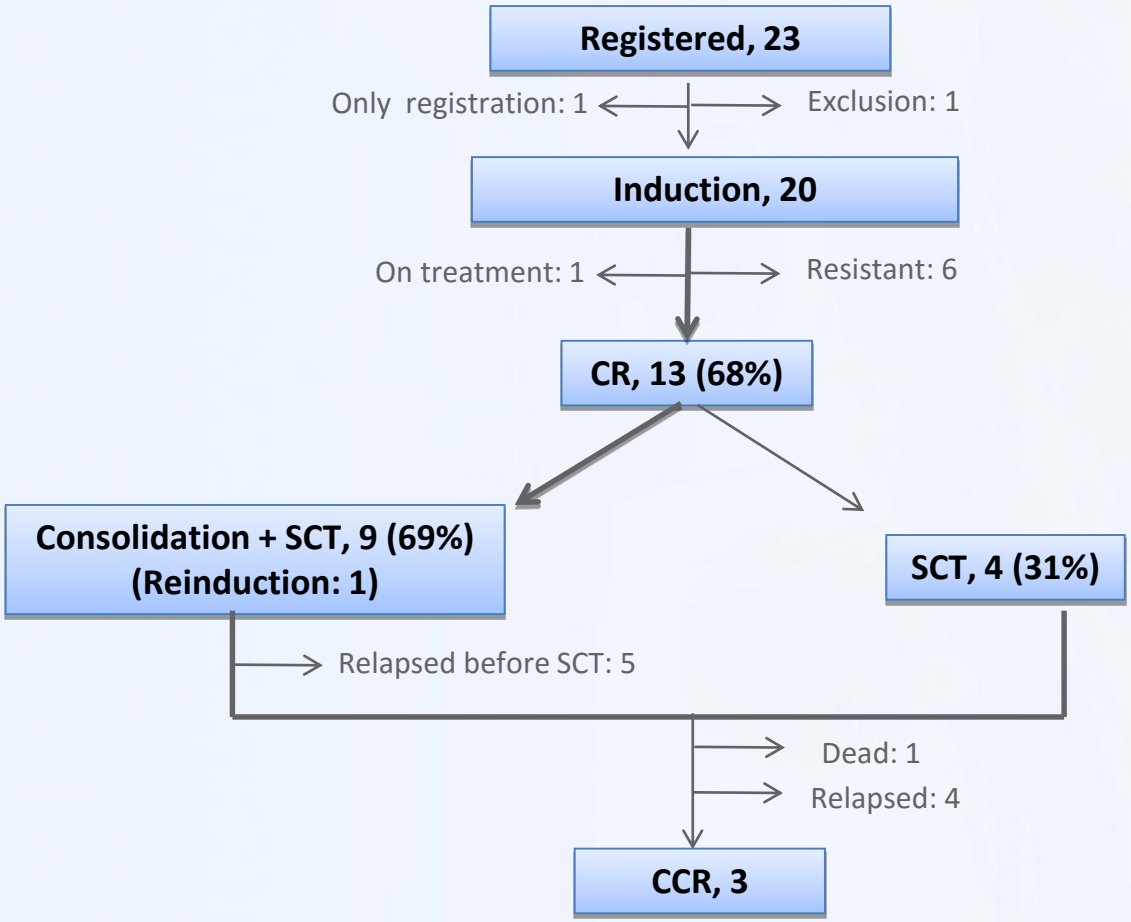


Treatment schedule

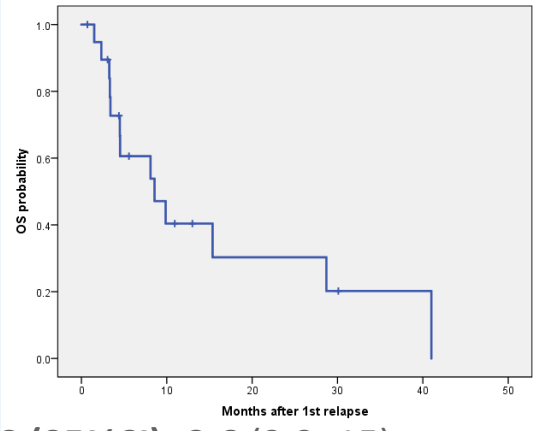


Treatment schedule

CLINICAL GUIDE FOR RELAPSE ALL



Overall Survival



Median OS (95%CI): 8.6 (2.2, 15)

Concluding remarks

- ALL: rare and difficult to treat disease in adults
- Complex genetic background
- Improved results in recent chemotherapy-based, MRD-oriented trials
- Promising results with new targeted and immunological therapies (MoAb, BiTE, CAR T-cells) in R/R setting
- New treatments evaluated in earlier phases of the disease