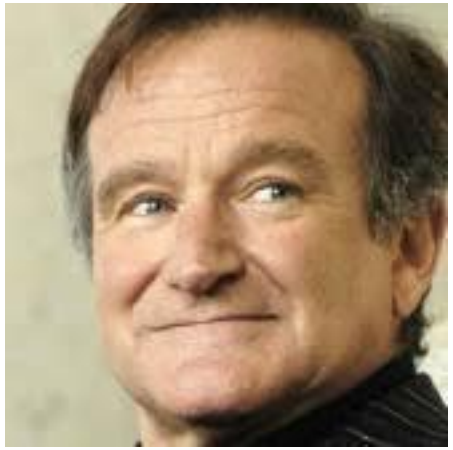


Advances in ALL (2008-2017)

- Pediatric or pediatric like approaches in young/adults
- MRD driven treatment in either Ph+ or Ph- ALL
- Different approaches for other subtypes (Ph like ALL)
- New MoAbs (RTX, Blina and Ino)
- CAR-T cells

Novità dall'EHA >> [Leucemie acute linfoidi]

ALL

Relatore: **R. FOÀ**

27-28 ottobre 2008

Borgo S. Luigi – Monteriggioni (Siena)

1. *Treatment of adults with newly diagnosed ALL with multiple doses of intravenous pegylated asparaginase in an intensified pediatric regimen. P. Srivastava, Los Angeles*

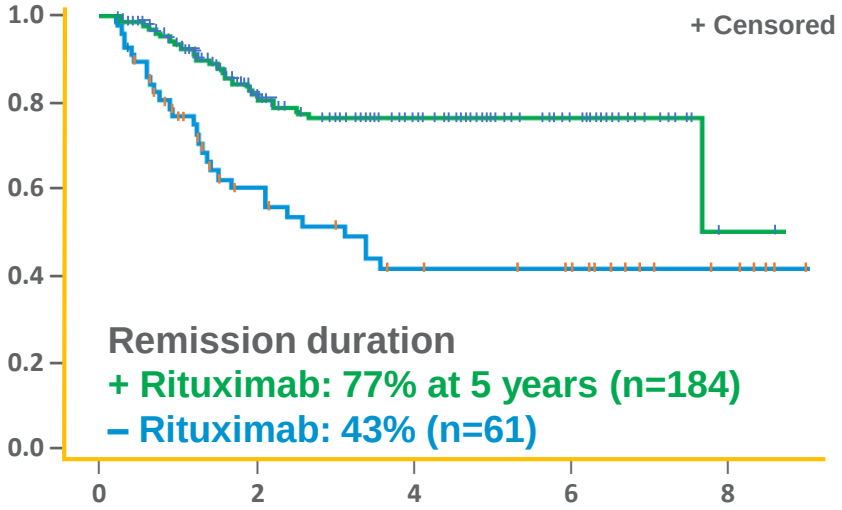
- Aim: Assess feasibility of using an intensive pediatric regimen containing multiple doses of PEG-ASP in adults with newly-diagnosed ALL
- Results: Administration of multiple doses of PEG-ASP IV to adults (ages 19-57 years) in an intensified BFM-based pediatric-like strategy is feasible and provides long term asparagine depletion.

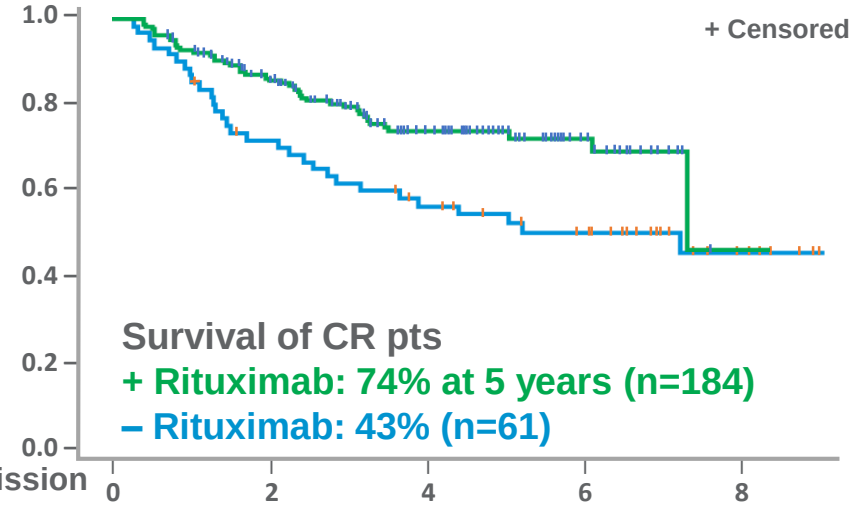
9 INTERIM ANALYSIS OF GIMEMA LAL1205. CONCLUSIONS I

- Feasible with overall good compliance, also in old(er) patients
- No deaths
- Together with Imatinib protocol for patients >60 yrs, over 70 Ph+ ALL treated with a TK inhibitor alone as 1st line treatment with no deaths in induction
- 100% HCR, with early HCR achievement in most patients (94.12%)
- Marked and rapid debulking of disease documented by immunophenotypic and molecular monitoring
- Evidence of immunophenotypic and molecular negativity

Results of Induction Therapy ± Rituximab in CD20+ SR ALL: GMALL, 07/2003

	N=264	
Characteristics	**- R**	**+ R**
Patients (n)	66	198
Median age (years)	31	34
Results (%)		
CR	92	93
MolCR, week 16	62	89
PR/failure	5	3
Death in induction	3	5



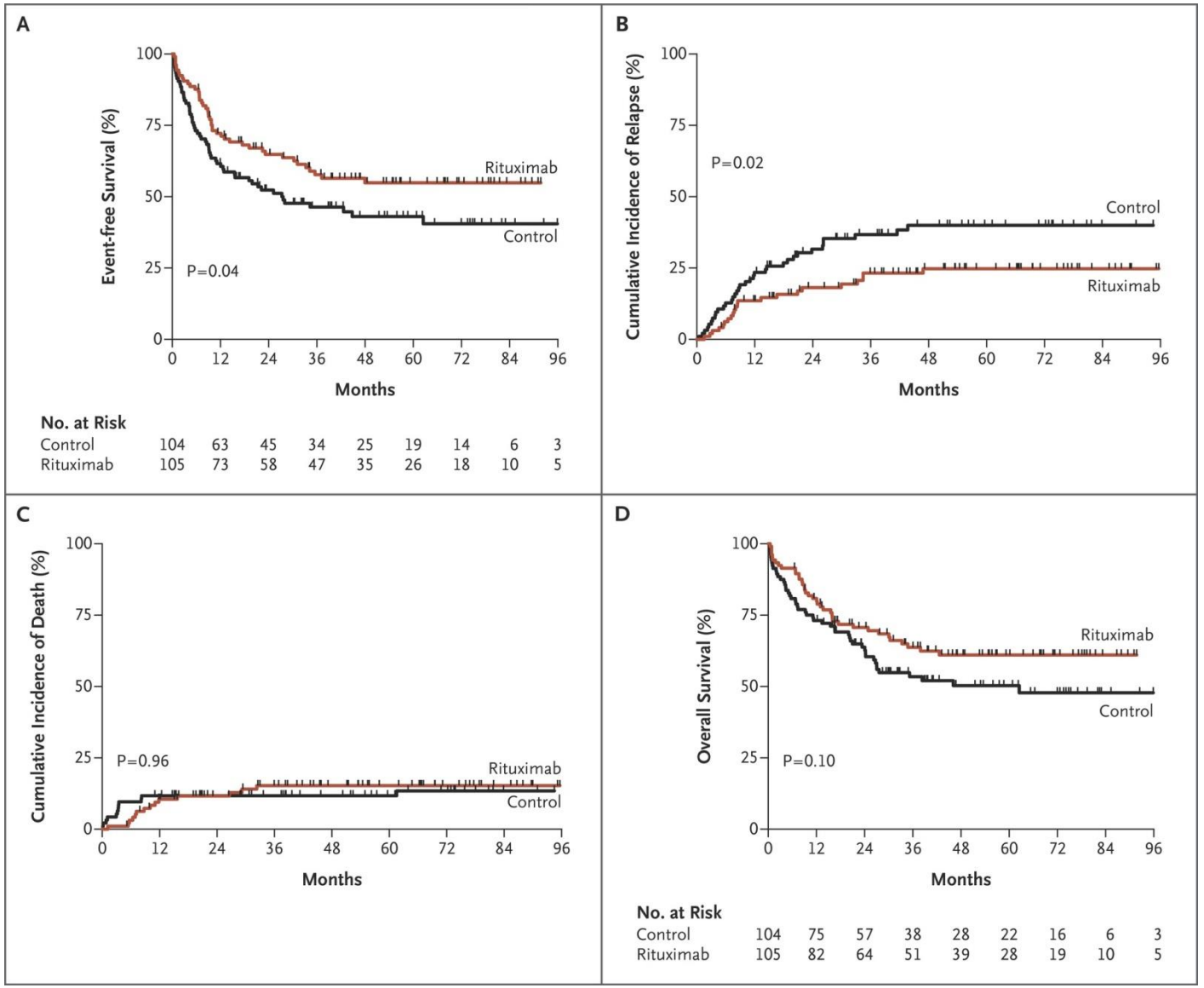


2009 – Foà, Gubbio

ALL, acute lymphoblastic leukaemia; CR, complete remission

Hoelzer. SOHO 2015

- Prospettico randomizzato (GRAAL)
- 209 pz
- CD20 blast positivity >20%
- 16-18 RTX infusions
- 2-y EFS 65% vs 52%



Maury et al, NEJM 2016

Prognostic Significance of MRD in Adults with Ph-negative ALL Clinical Trials Without Therapeutic Consequences

Author	Year	Group	Method	N	Prognostic Model	DFS
Holowiecki	2008	PALG	Flow	115 SR & HR	< 10^{-3} (4 wks)	61%
					> 10^{-3} (4 wks)	17%
Patel*	2010	UKALL	PCR	161 B-lin SR & HR	Neg or <10^{-4} wk10*	71%
					>10^{-4} wk 10*	15%
Beldjord	2009	GRAALL	PCR	212 SR & HR	Neg or <10^{-4} wk6	80%
					>10^{-4} wk6	40%

* Prognostic significance for SR patients, or patients randomised to autologous SCT, but not for those allocated to allogeneic SCT. Prognostic significance also seen in other time-points (wk 5, wk 17, 6-9 mo.)

2010 – Ferrara, Stresa

SCT for MRD positivity: worse if $\geq 10^{-3}$

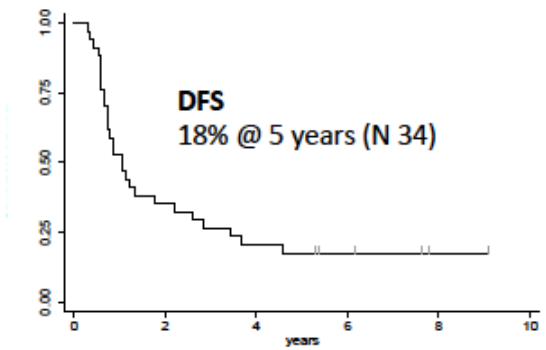
2010 – Ferrara, Stresa

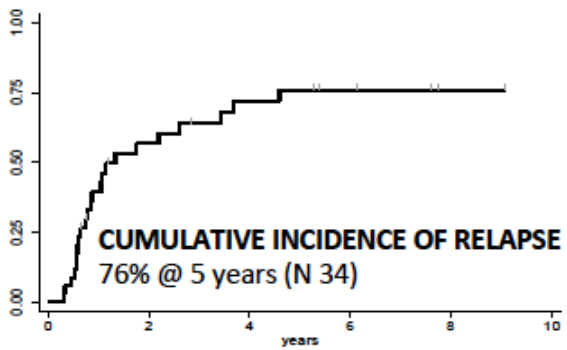
a) *GOEKBUGET et al, Blood 2012 [in press]*

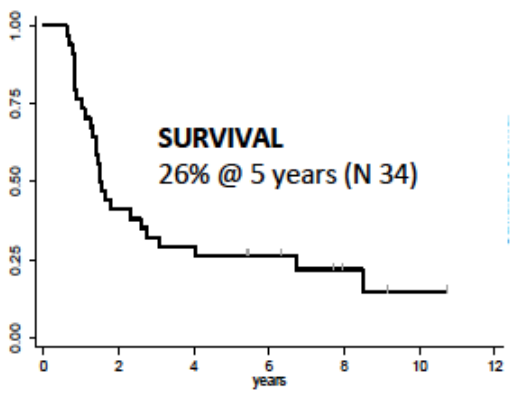
	N	Median time from MRD failure to hematological relapse (without SCT)
MRD failure (unselected)	63	7.6 mos.
MRD failure ($>10^{-3}$)	41	4.9 mos.

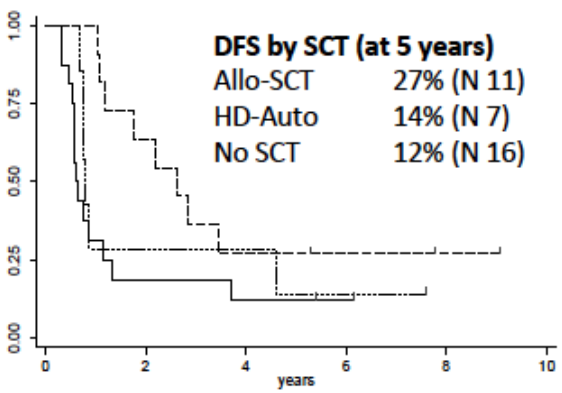
b) *BASSAN et al, Blood 2009 [updated]**

**Ph-, age ≥18 years, only B-lineage, MRD wk 10-22*



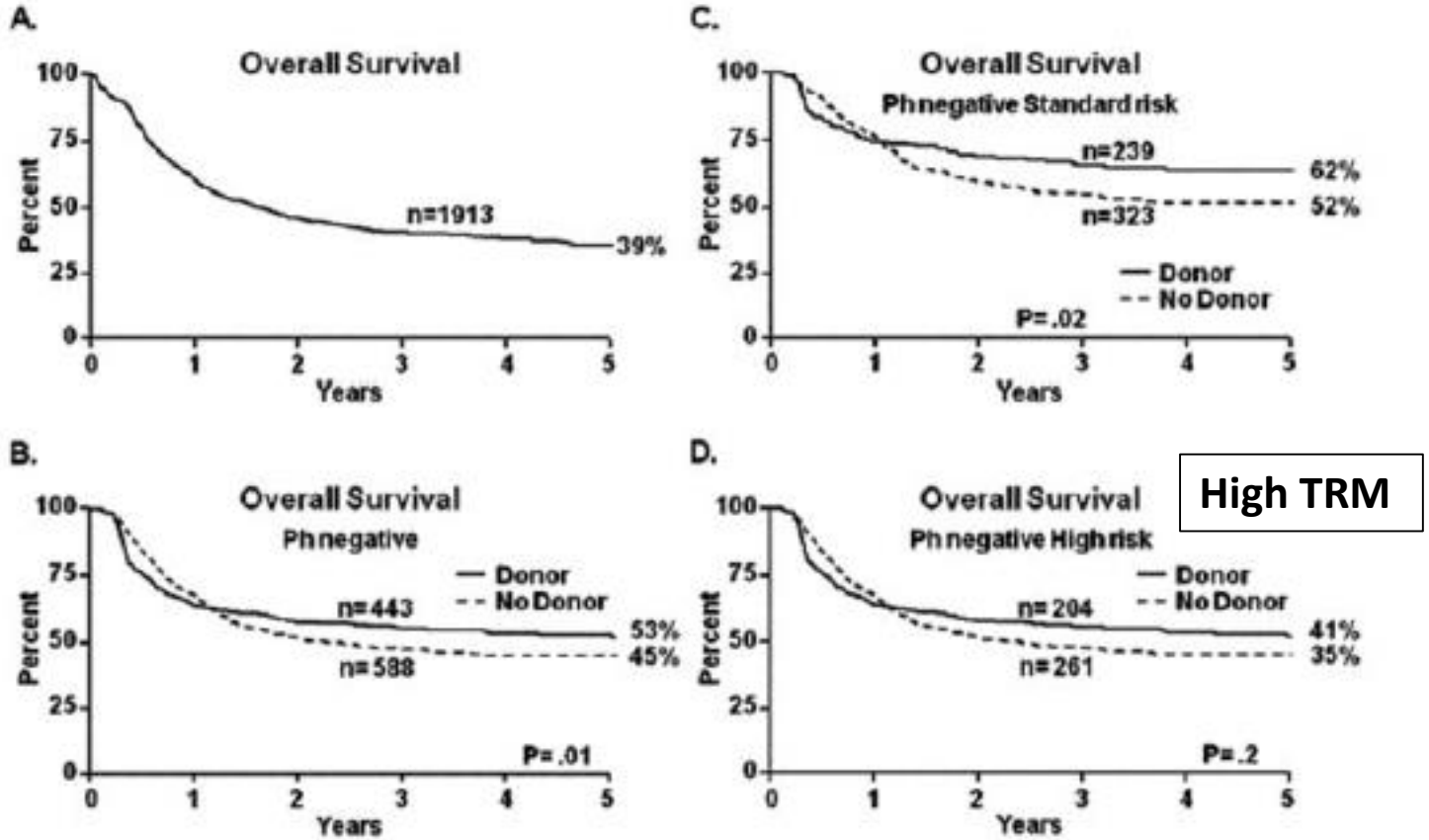






The MRC/ECOG international ALL Trial

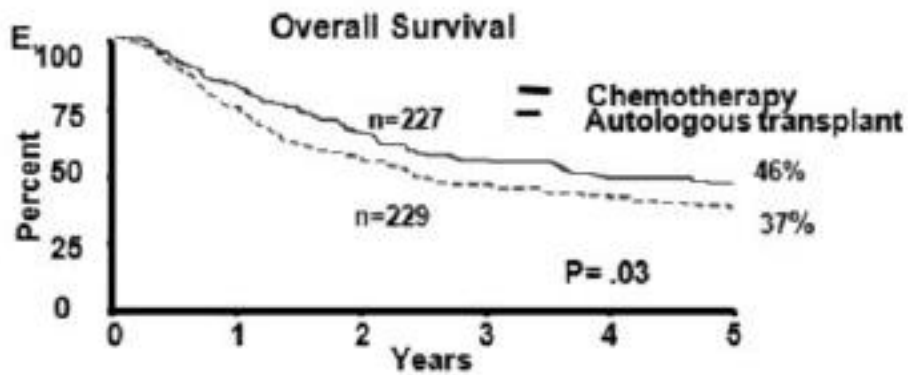
2011 – Ferrara, Gubbio



High TRM

Risk factors:

Age > 35
WBC count
Response to IND



J. Rowe & C. Ganzel

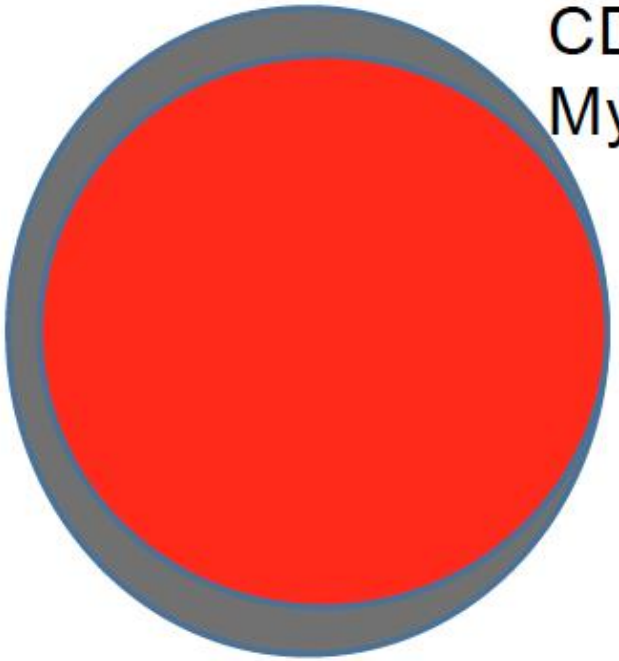
Hot questions

- Which patients with ALL should receive allo-SCT in CR1 ?
- Should post-CR therapy be driven by MRD results ?
- Are there clinically useful new biologic markers (apart from BCR/ABL) ?

Early T precursor ALL

2012 – Ferrara
Matera

CD1a neg
CD8 neg
CD5 weak or neg
MyAg +



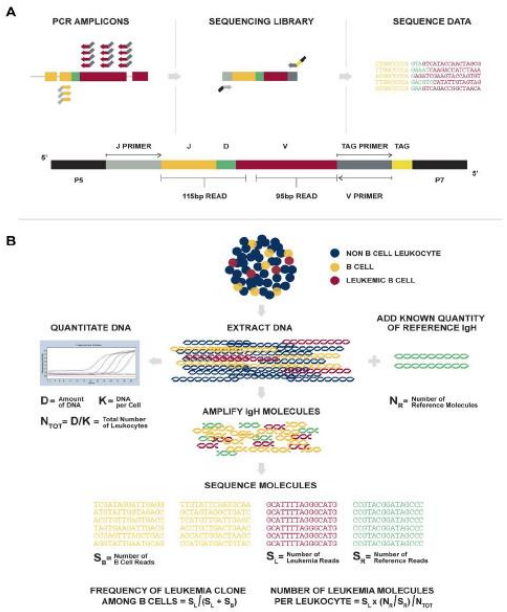
15 % of T-ALL
Poor prognosis

Hot questions

- Should patients with early T-ALL receive a different therapy ?
- Which treatment (if any) for relapsed patients with high levels of MRD before and/or allo-SCT ?
- Shoul we consider an age limit for SCT in high risk ALL (Ph+ or Ph-) ?

2013 – Ferrara

COMPARISON OF NEXT-GENERATION SEQUENCING AND ASO-PCR METHODS FOR MRD DETECTION IN ACUTE LYMPHOBLASTIC LEUKEMIA



Faham M et al, Blood 2012

Malnassy et al, et al. EHA 2013, Abst S537

Table 2. Examples of molecular biomarkers in ALL.

Type of molecular biomarker	Examples in ALL
Diagnostic and prognostic	*BCR-ABL1* *ETV6-RUNX1* *MLL*-rearrangement *TCF3*-rearrangement *IKZF1* deletions *BCR-ABL1*-like gene expression signature *JAK2* mutations and translocations deregulated CRLF2 expression
Surrogate response	Minimal residual disease
Predictive (for selecting drugs)	*BCR-ABL1* and mutation status (imatinib, dasatinib, nilotinib, ponatinib) *FLT3* expression levels and mutation status (midostaurin, lestaurtinib, sunitinib) *JAK2* mutations and translocations (ruxolitinib) RAS-MEK pathway activating mutations (selumetinib, trametinib)
Pharmacodynamic (for monitoring response)	pABL1, pCRKL (ABL1 tyrosine kinase inhibitors) pFLT3 (FLT3 inhibitors) pSTAT5 (JAK inhibitors) pERK (MEK inhibitors)
Pharmacokinetic	*TPMT*

den Boer ML, EHA 2013, Educational Program

2013 – Ferrara

HOT QUESTIONS

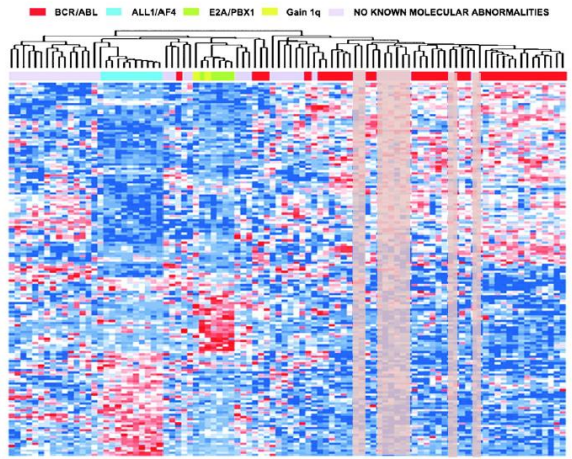
- Which are the most promising new drugs in ALL ?
- Will NGS be the future standard for MRD ?
- What about allo-SCT in Ph ALL ?

Ph-like ALL

- Similar gene expression profile to Ph+ ALL
- Peak incidence in young adults
  - 12% (<15 years)
  - 20.6% (16-20 years)
  - 27.4% (21-39 years)
- Poor prognosis
- Actionable genetic lesions
  - Ruxolitinib, dasatinib, crizotinib

2014 – Ferrara

Gene expression profile of 94 B-ALL enrolled in the GIMEMA 0496 protocol



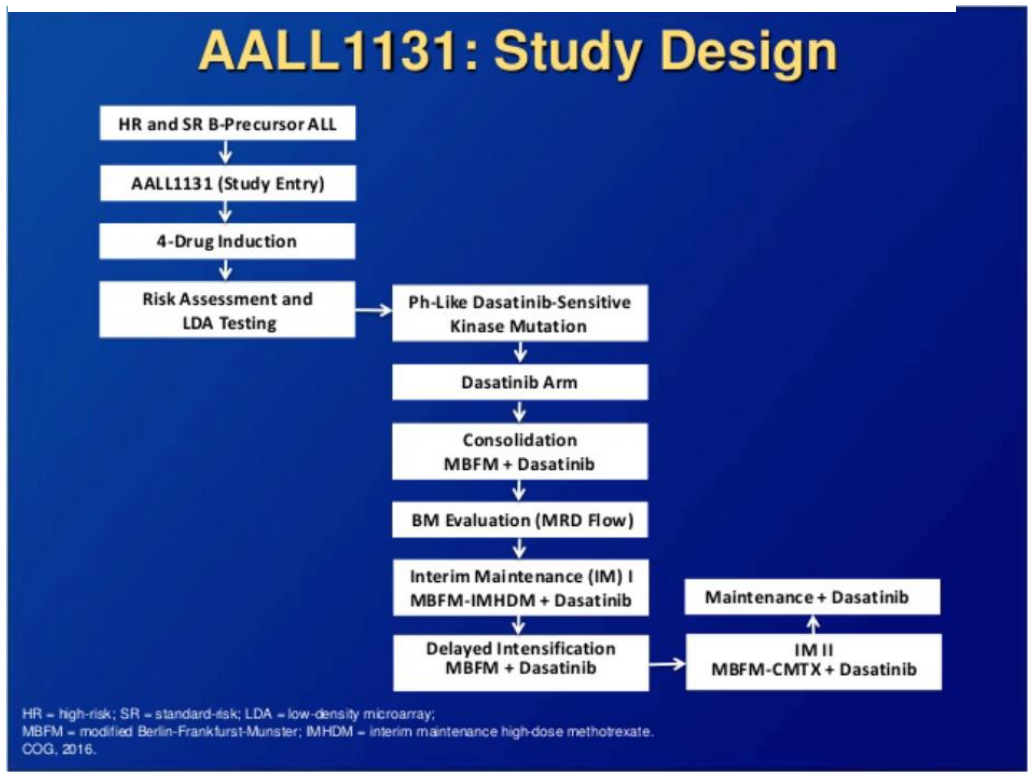
Chiaretti S et al. Clin Cancer Res 2005;11:7209-7219

10 *ALL1/AF4*, 5 *E2A/PBX1*, 37 *BCR/ABL*, 42 without molecular aberrations.

Array type: U95Av2 (~12,625 probe sets).
167 differentially expressed probe sets.
Tight clustering of *ALL1/AF4* and *E2A/PBX1* + cases.
Less homogeneous profile was observed for *BCR/ABL*1+.

Remarkably, 10 cases (23%) without molecular aberration clustered with *BCR/ABL*1+.

Similar findings were simultaneously reported in other adult cohorts (Haferlach et al, Blood 2005).



2014 – Ferrara

QUESTIONS

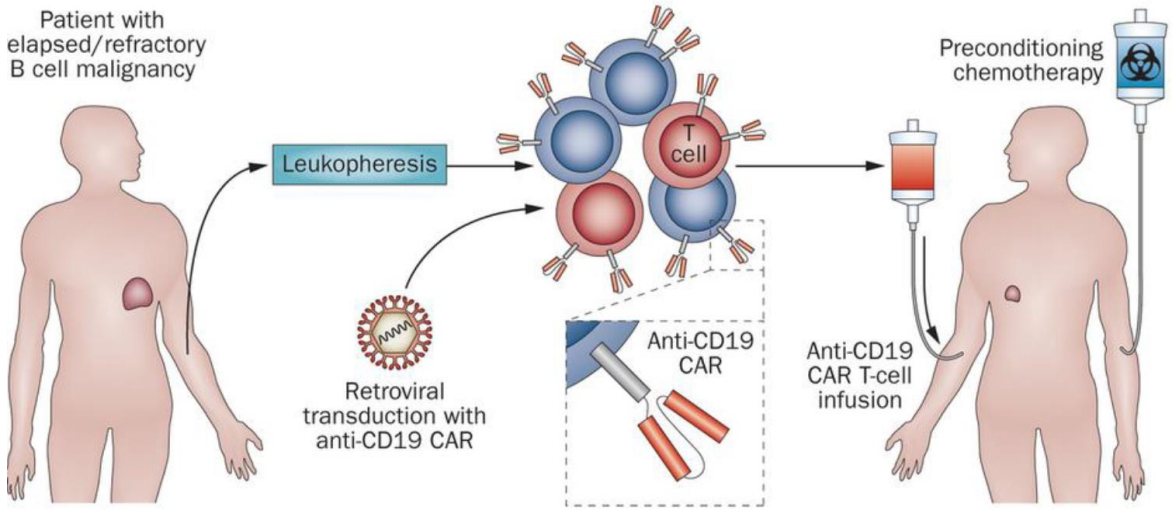
1) Should Ph-like ALL considered as a separate entity in the clinics?

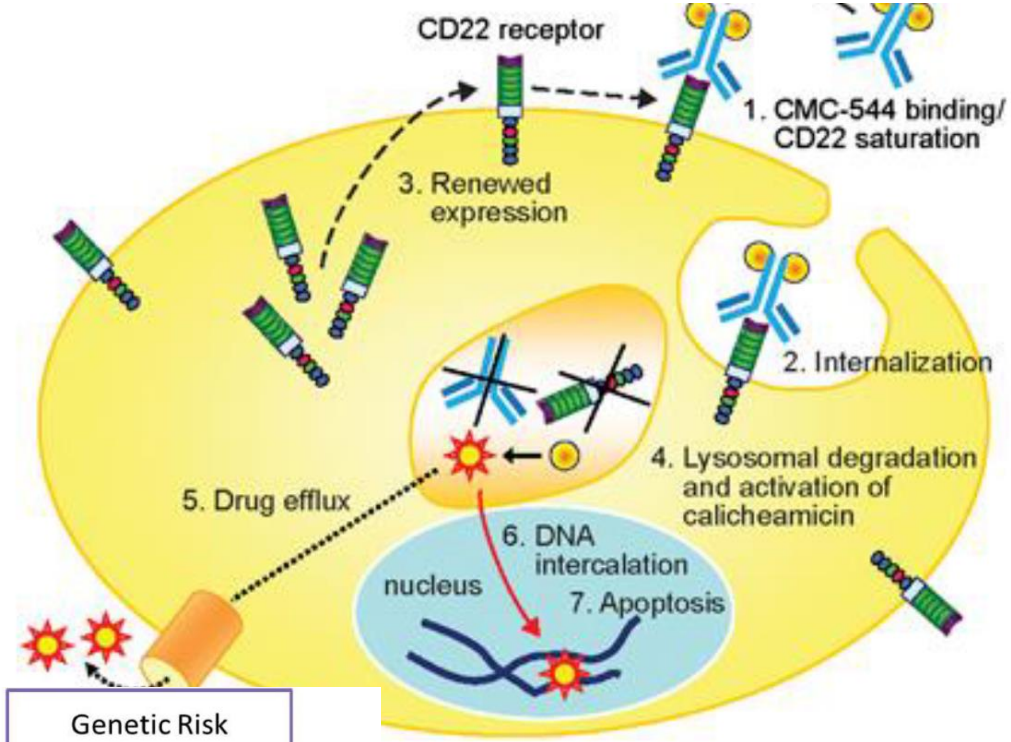
2) Should IKZ1 mutations be considered in the prognostic stratification of ALL ?

3) Blinatumumab in ALL:
- 1° or subsequent relapse ?
- treatment of MRD ?
- 1° line in very high risk patients

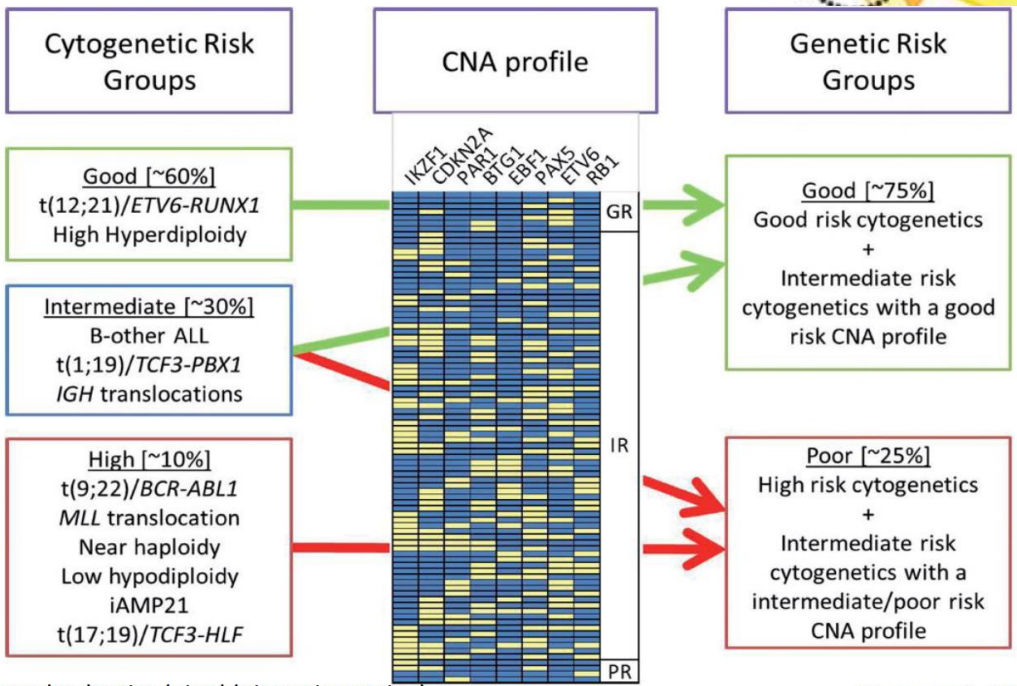
4) Has Ponatinib a role in the treatment of Ph+ ALL ?

T Cells Engineered with a Chimeric Antigen Receptor (CAR) Targeting CD19 Have Long Term Persistence and Induce Durable Remissions in Relapsed, Refractory ALL.





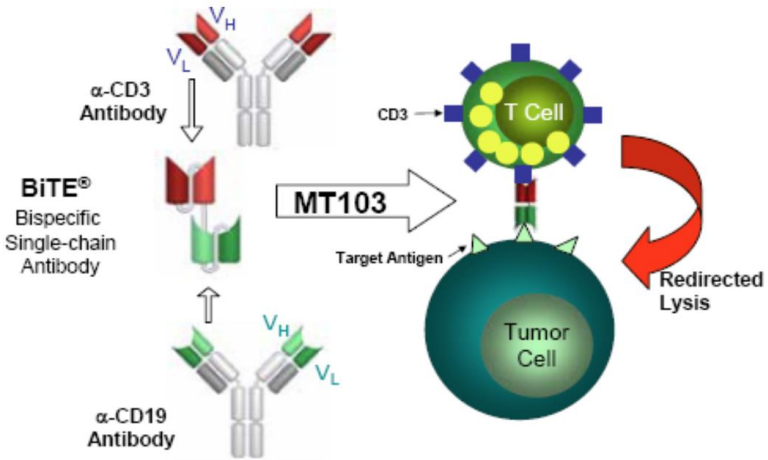
2015 – Ferrara



: copy number alterations (microdeletions, point mutations)

Moorman A, EHA, 2015

OPEN-LABEL, SINGLE-ARM, MULTICENTER CONFIRMATORY PHASE 2 STUDY OF THE BITE® ANTIBODY BLINATUMOMAB IN PATIENTS WITH RELAPSED/ REFRACTORY B-PRECURSOR ACUTE LYMPHOBLASTIC LEUKAEMIA



Topp M et al., EHA, 2014

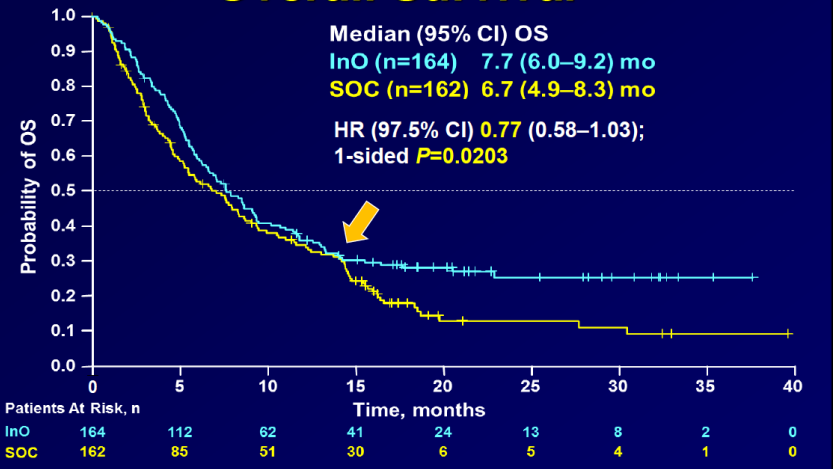
2015 – Ferrara

QUESTIONS

- **Is it time for a new integrated diagnostic/prognostic classification (MOL/GEN BASED) in ALL (either for children or adults) ?**
- **Which is the role of new monoclonal antibodies (Blinatumomab, Inotuzumab-GO) in the treatment of ALL ?**
- **Which patiens should receive CART therapy ?**

INO-VATE: InO vs SOC in R/R ALL

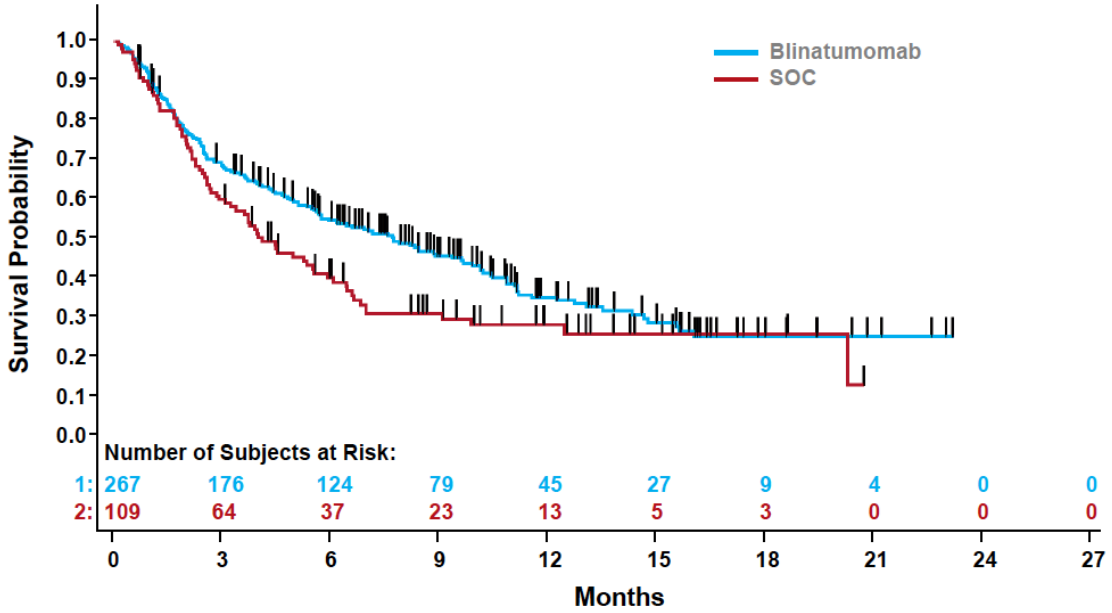
Overall Survival



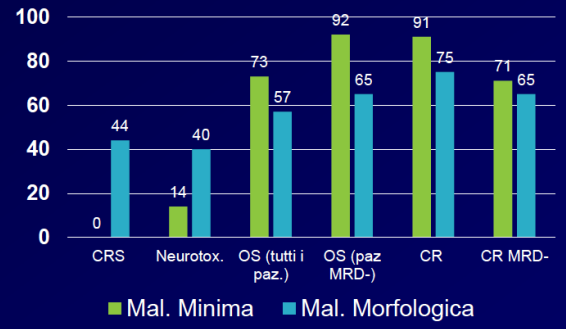
- Data appeared to depart from proportional hazards assumption
- 2-yr survival probability higher with InO (23% [95% CI: 16–30] vs 10% [5–16])

13

Overall Survival (as Treated)



IMPACT OF DISEASE BURDEN ON LONG-TERM OUTCOME OF CD19-TARGETED CAR MODIFIED T CELLS IN ADULT PATIENTS WITH RELAPSED B-ALL



Park J, EHA, 2016 Abs S498

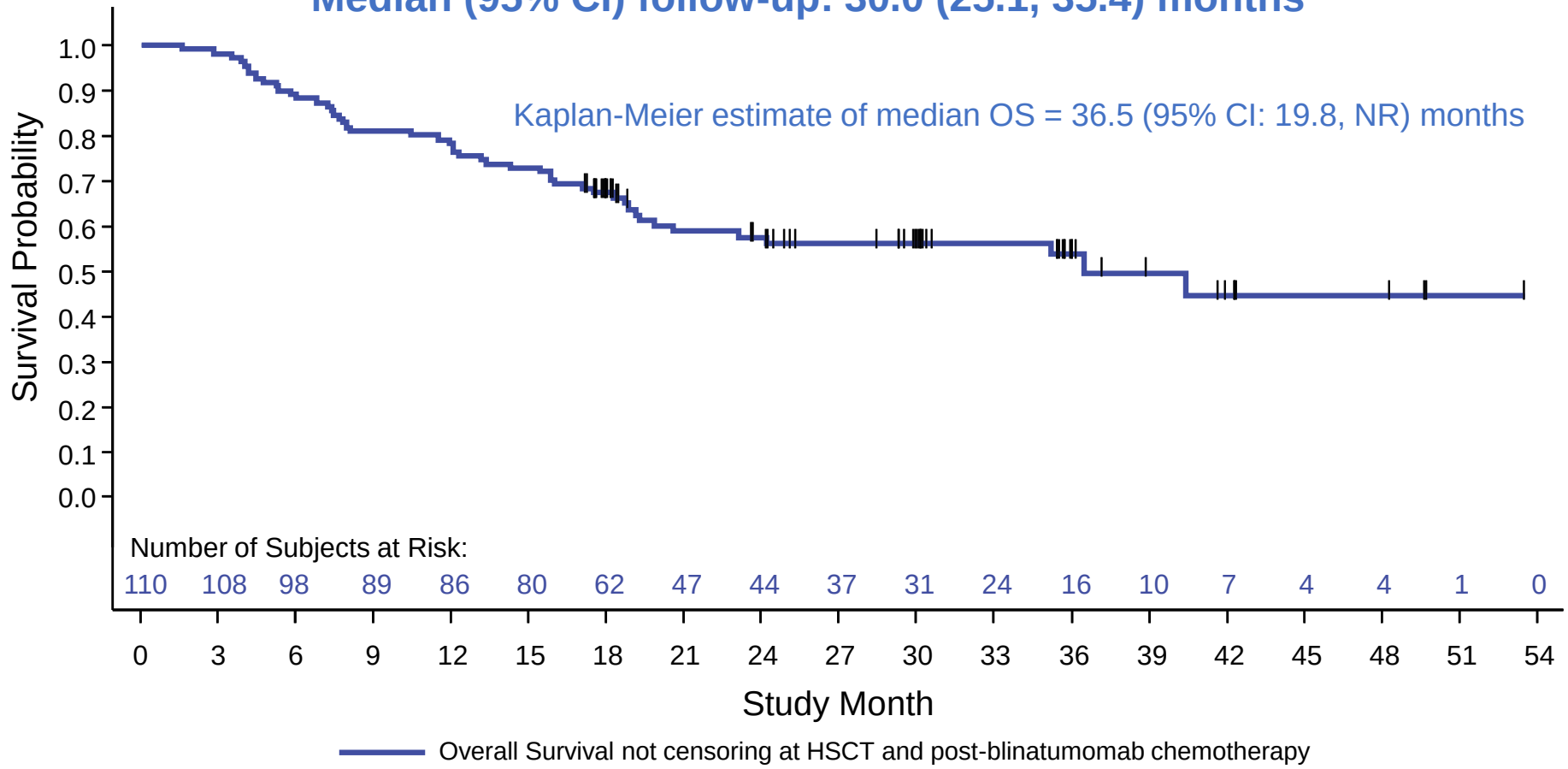
2016 – Ferrara

BLINA for MRD+ pts.

Overall Survival

Median age: 45 (18-76) yrs

Philadelphia-negative patients in hematologic CR
Median (95% CI) follow-up: 30.0 (25.1, 35.4) months



NR = not reached.

2016 – Ferrara

- **Ritenete i risultati dello studio Inno-Vate convincenti per la rapida introduzione di Inotuzumab-Ozogamicin nella pratica clinica ?**
- **Qual è il timing ideale dell'impiego di Blinatumomab nella ALL ?**
- **Quale età e quali comorbidità vanno considerate nell'approccio "true pediatric" o "pediatric-like" nella ALL ?**

Highlights from EHA 2016
Gruppo lavoro LAL

Felicetto Ferrara
Giovanni Pizzolo
Enrico Attingenti
Marinella Veltroni
Sabina Chiaretti
Paola Ursoleo
Anna Rita Guarini
Michela Ansuinelli
Andrea Camera
Federica Barone
Arianna Fani
Catello Califano
(Angelo Michele Carella)

Topics

- **European Working Group on ALL (EWALL) “Adult ALL first line therapy: Major results and future approaches of national ALL study groups”**

-GRAAL - Hervet Dombret

-GIMEMA - Sabina Chiaretti

-UKALL - Adele Fielding

-GMALL - Nicola Goekbuget

- Novel treatments:

  -focus on CAR-T

  -updates on blinatumomab and inotuzumab treatment

GRAALL-2014 trial options

- Dose adaptations:
  - Reduce L-asparaginase and steroids doses in patients aged ≥45 years.
  - Higher MTX dose (5 g/m²) in those aged <45 years.
- CNS prophylaxis:
  - No CNS irradiation, with more triple ITs.
- L-asparaginase Tx monitoring:
  - L-aspa immunization and activity to guide switch from *E. Coli* asparaginase to erwiniase.
- Rapid centralized diagnosis of actionable Ph-like BCP-ALL cases.
- New agents front-line in high-risk patients:
  - Blinatumomab in BCP-ALL patients (QUEST Phase 2 study)
  - Nelarabine in T-ALL patients (ATRIALL Phase 2 study)
- Allogeneic SCT in first CR restricted to poor early MRD responders.
- Allow enrollment of patients aged 55y+ into innovative older ALL trials
  - EWALL-INO
  - EWALL-BOLD

Dombret H

UKALL: moving forward

UKALL14

Specific Aims

Aged 25-65

Aim 1B. (precursor-B ALL) MONOCLONAL ABS
Does the addition of rituximab to standard induction chemotherapy result in improved EFS in patients with precursor B-cell ALL?

Aim 1T (T ALL) NELARABINE
Does the addition of nelarabine improve outcome for patients with T cell ALL?

Aim 2. ASPARAGINSE
To determine the tolerability of pegylated asparaginase in induction and to compare anti-asparaginase antibody levels between patients in the rituximab randomisation groups from aim 1.

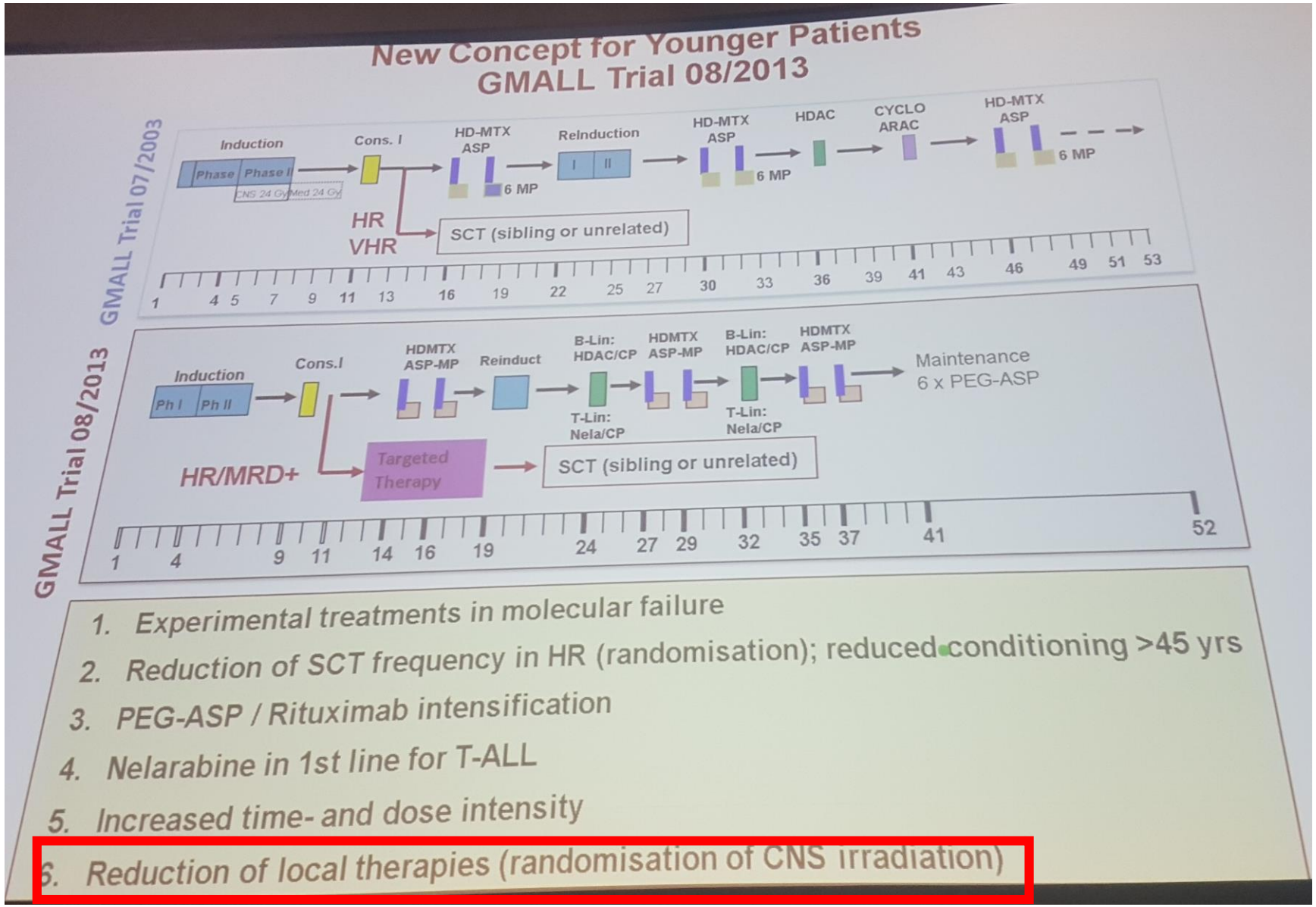
Aim 3. ROLE OF BMT IN HIGH RISK
To determine whether risk-adapted introduction of unrelated donor HSCT (myeloablative conditioning in patients <40 years old and non-myeloablative conditioning in patients >40 years old) improves EFS in patients at highest risk of relapse.

NCRI National Cancer Research Institute

UCL

Fielding A

GMALL: moving forward

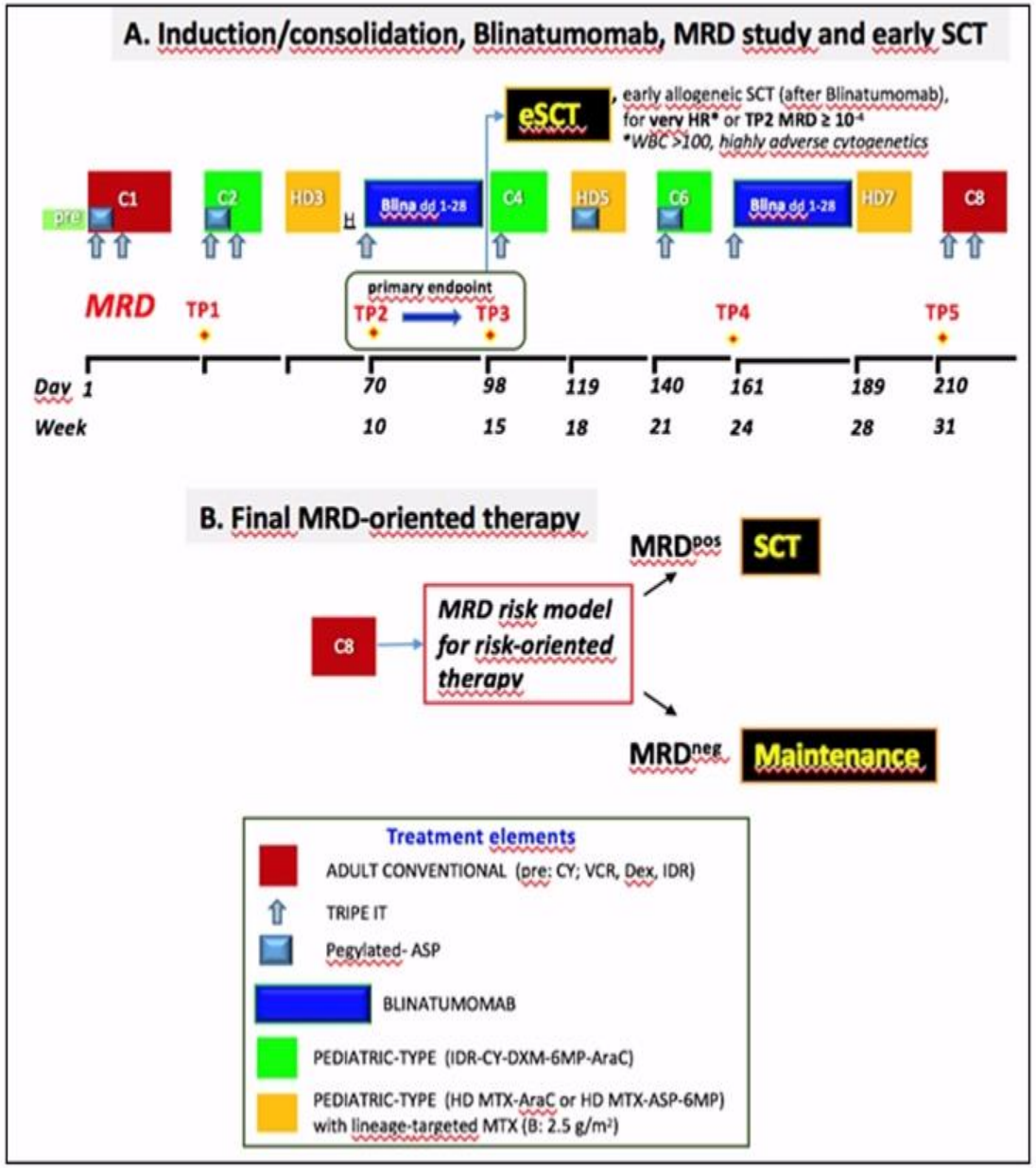


Goekbuget N

Ph- ALL (B-ALL): the forthcoming future

National Treatment Program with Sequential Chemotherapy and Blinatumomab to Improve Minimal Residual Disease Response and Survival in Philadelphia Chromosome-Negative B-Cell Precursor Adult Acute Lymphoblastic Leukemia

Nuova Proposta GIMEMA 16-272

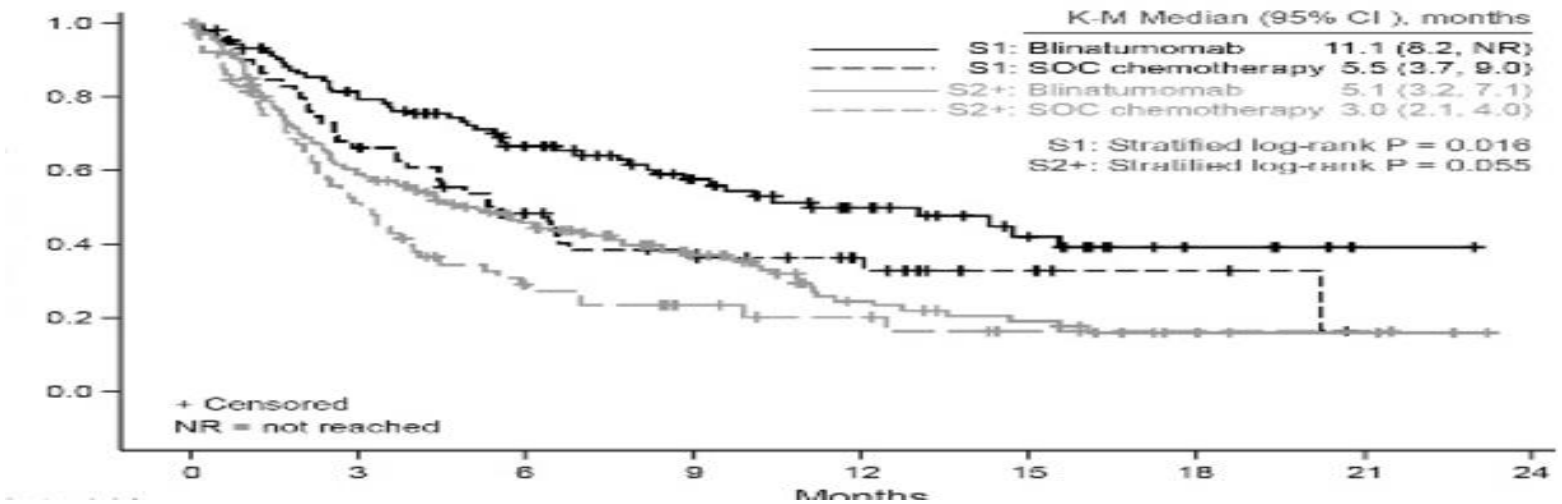


Chiaretti S

- **Atriance in 1 linea- Protocollo lineage adapted**
- **Blina in 1 linea (indipendente da MRD)**
- **Quale profilassi per SNC ?**

Blinatumomab vs SOC chemotherapy in first salvage compared with second or greater salvage in a Phase 3 study

	No prior salvage (S1)		Any prior salvage (S2+)	
	Blinatumomab (n=104)	SOC (n=63)	Blinatumomab (n=167)	SOC (n=71)
Age ≥35 years, n (%)	65 (62.5)	37 (58.7)	82 (49.1)	37 (52.1)
Prior HSCT, n (%)	29 (27.9)	20 (31.7)	65 (38.9)	26 (36.6)
First relapse with remission duration <12 mo, n (%)	58 (55.8)	30 (47.6)	51 (30.5)	19 (26.8)
Maximum blasts ≥50% by central/local lab, n (%)	78 (75.0)	45 (71.4)	123 (73.7)	59 (83.1)
K-M Median OS, mo (95% CI)	11.1 (8.2, NR)*	5.5 (3.7, 9.0)	5.1 (3.2, 7.1)	3.0 (2.1, 4.0)
	HR 0.59 (95% CI 0.38, 0.91) P=0.016		HR 0.72 (95% CI 0.51, 1.01) P=0.055	
Best response (CR/CR/CRi), n (%) [95% CI]	53 (51.0) [41.0, 60.9]	23 (36.5) [24.7, 49.6]	66 (39.5) [32.1, 47.4]	10 (14.1) [7.0, 24.4]
	P=0.07		P<0.001	



<u>Earlier</u> use of blinatumomab is more effective also in the R/R setting

Dombret H et al, abst#S478

Blina – problemi aperti

- **Fattori predittivi della risposta - % linfociti T, Tregs, necessità di studi biologici**
- **Necessità di criteri condivisi di impiego del farmaco (RR/ALL)**

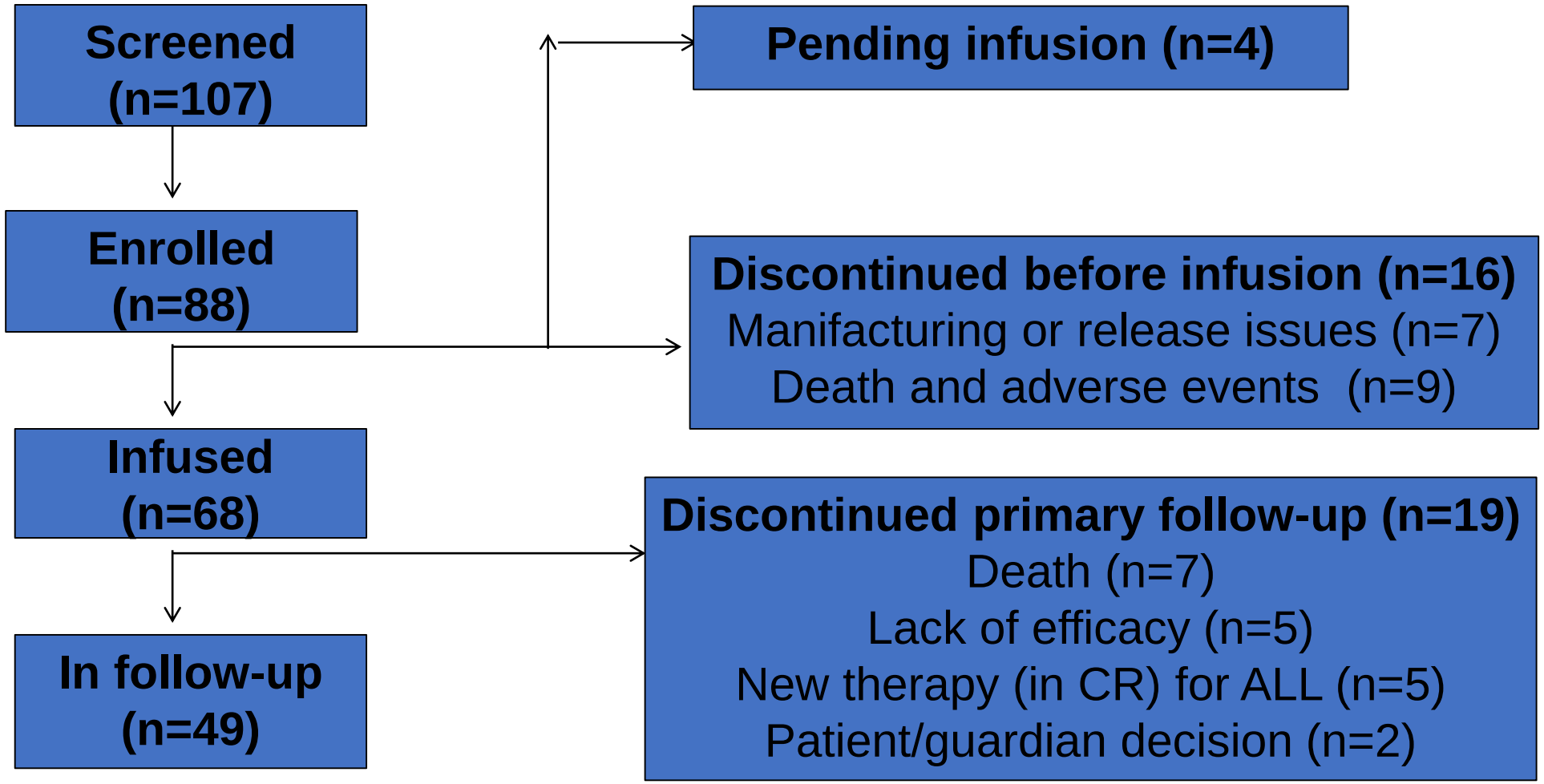
T-cell receptor β (TRB) repertoire characteristics in relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (BCP-ALl) on blinatumomab treatment.

- Aims: To compare the differences in TRB repertoire diversity and composition between two groups of patients with r/r ALL

Blin responders have significantly higher TRB repertoire diversity at screening compared to persisters and that the repertoire expansion during Blin treatment is sharper in responders.

Kotrova M et al, abs# S803

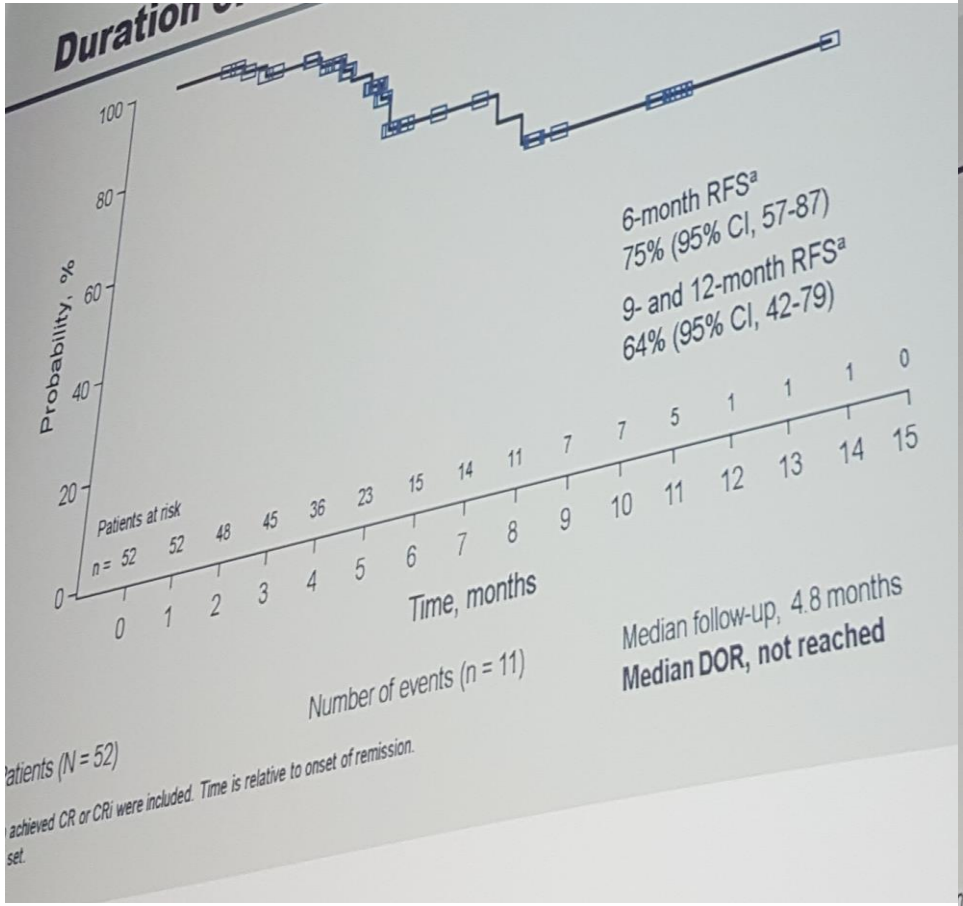
Global registration trial of efficacy and safety of CTL019 in pediatric and young adult patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL): update to the interim analysis

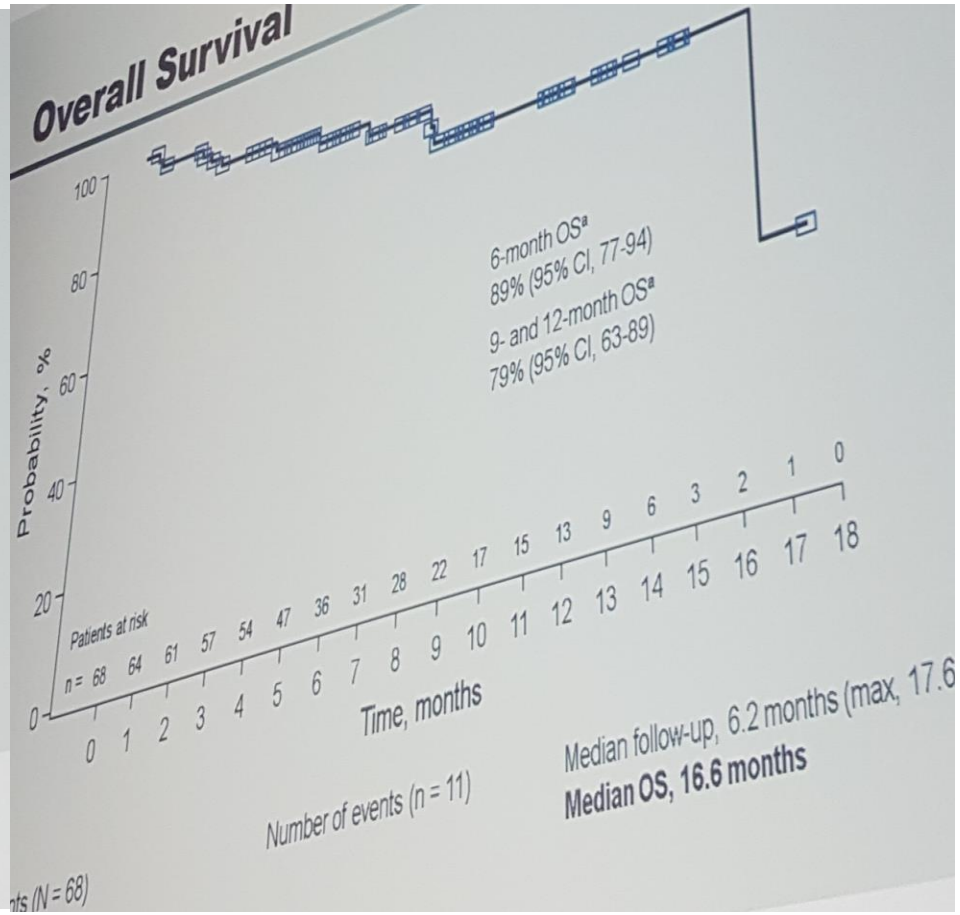


Median time from infusion to cut-off: 8.8 months (range: 0.3-18.5)

Buechner et al, abs#S476

RFS and OS





6 months RFS: 75%

6 months OS: 89%

Buechner et al, abs#S476

Overall safety

AE	%
Grade 3-4 AE, suspected to be drug related	85, 72
Most common AE	*Overall (G 3-4)*
CRS	78 (21-27)
Fever	40 (12-3)
Decreased appetite	37 (13-2)
Febrile neutropenia	37 (34-3)
Hypotension	31 (12-10)
↑GOT-GPT	28 (12-4)
Hypokalemia	24 (12-3)
Hypoxia	24 (12-6)
Infections	43 (24-3)
Neurologic events	44 (15-0)

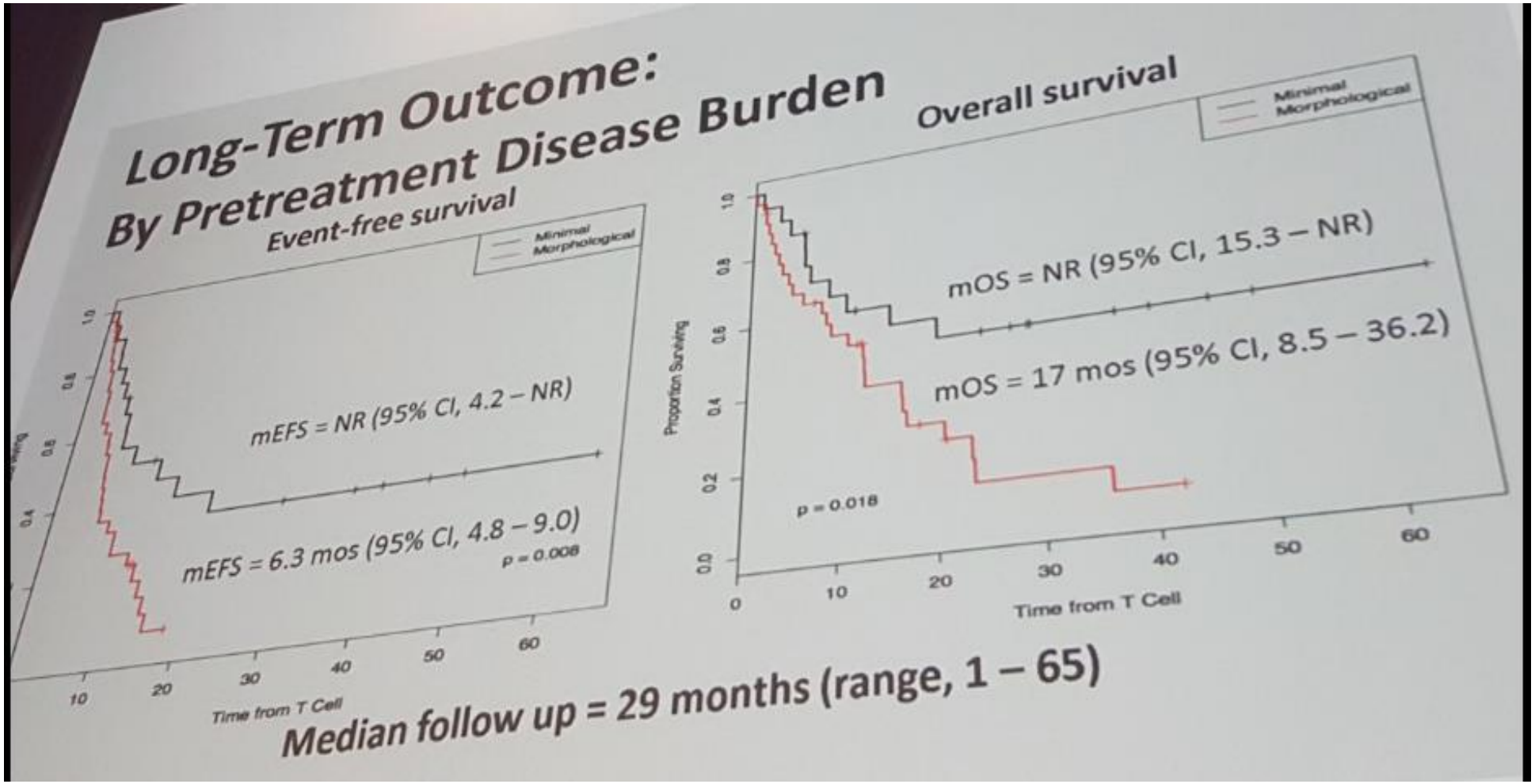
	CRS
Days of duration	8 (1-36)
ICU admission,%	46
Anticytokine therapy,%	38
Hypotension requiring intervention,%	51
HD vasosuppressors,%	25
Intubation,%	15
Dialysis,%	10

CRS	Any neurologic event,%	G3 neurologic event,%
No CRS (n=15)	27	7
G1/2 (n=21)	33	5
G3 (n=14)	50	14
G4 (n=18)	67	33

2 deaths within 30 days of infusion (1 cerebral hemorrage)
No deaths for CRS or neurologic events
Neurologic events: encefalopathy (12%), confusional state (10%) and delirium (10%)
Association between CRS and neurologic events

Buechner et al, abs#S476

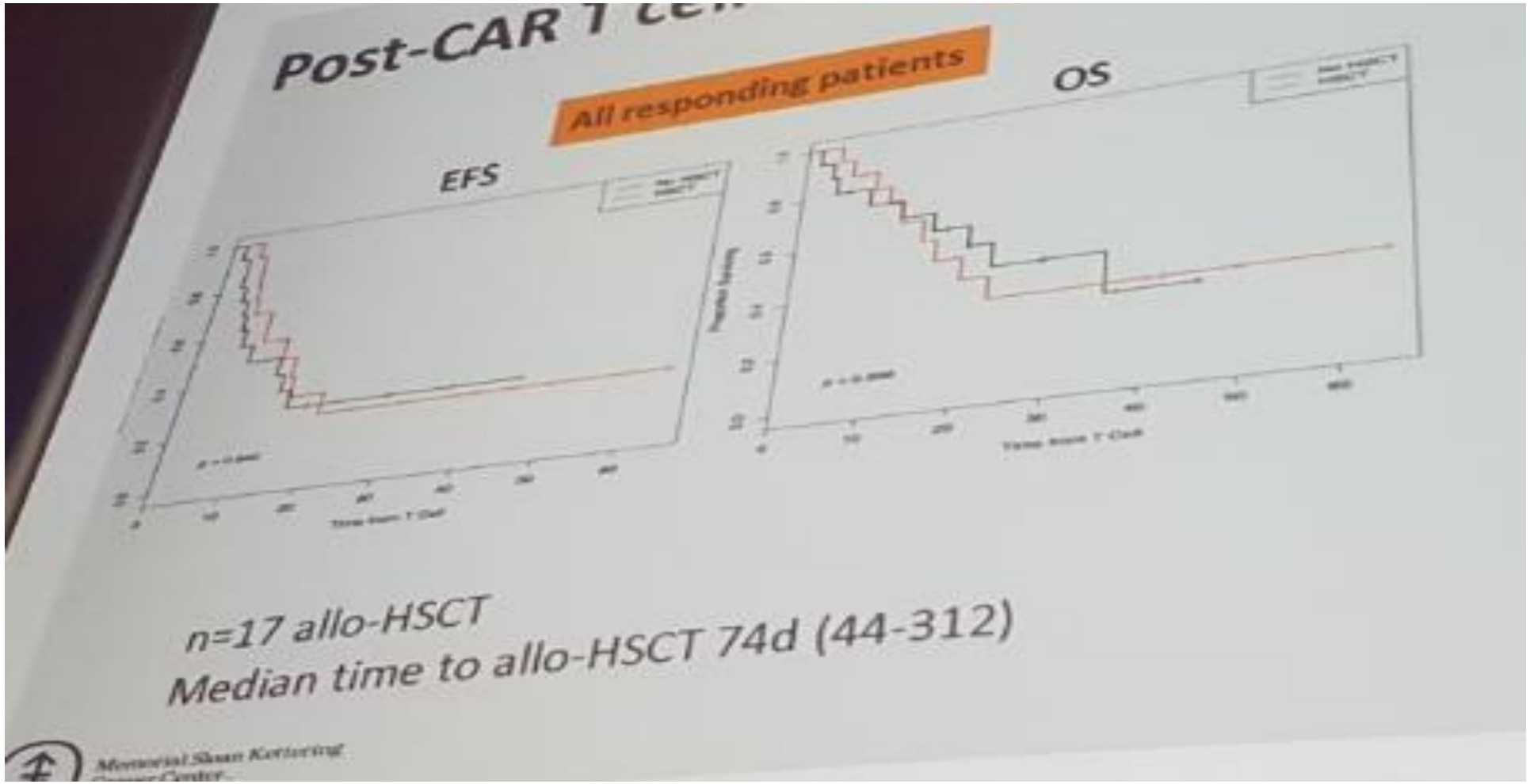
Long-term outcome by disease burden



Better outcomes in MRD+ vs morphological

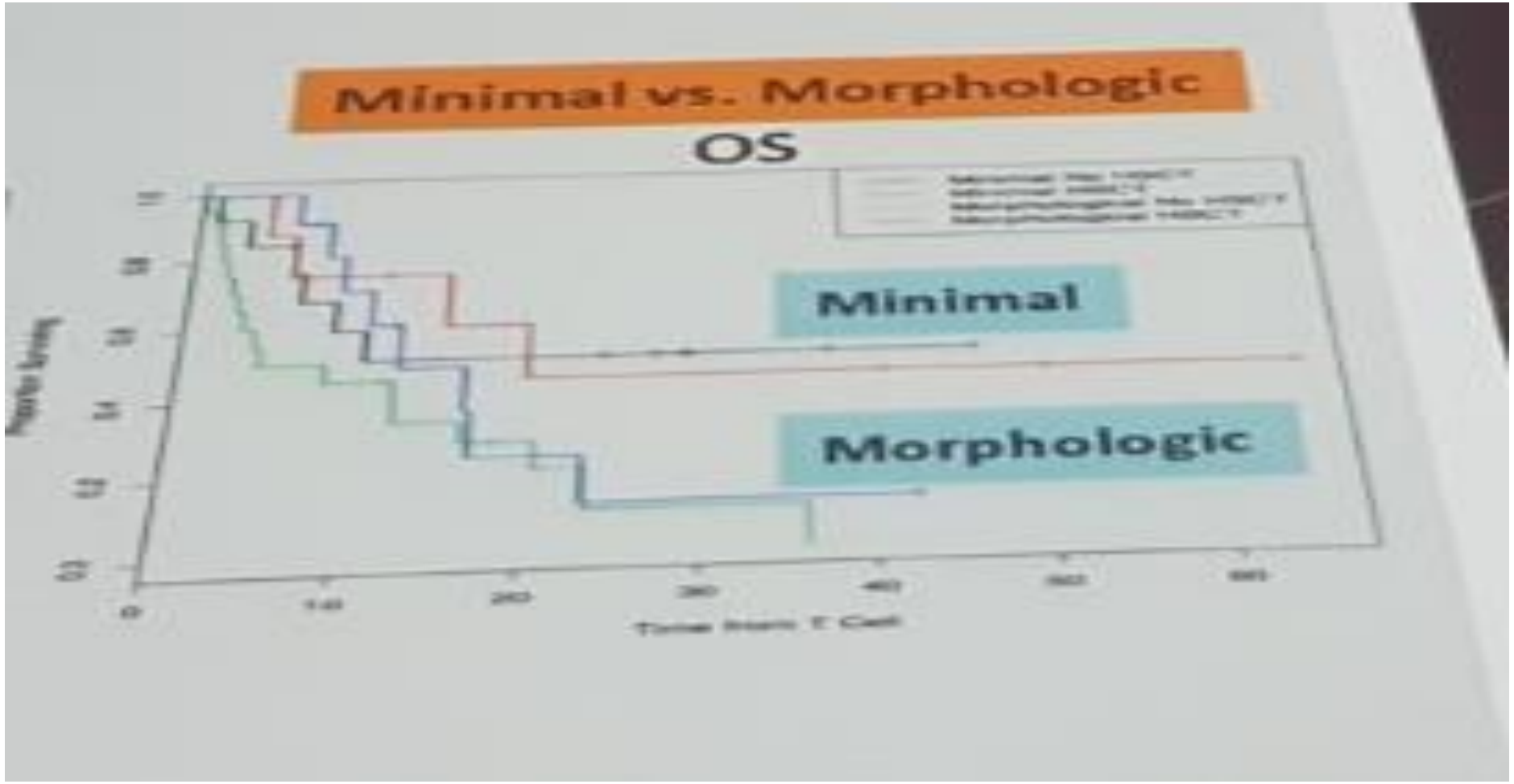
Smith E et al, abs#S479

Role of allo-SCT after CAR T (I)



Smith E et al, abs#S479

Role of allo-SCT after CAR T (II)



No advantages in performing allo-SCT post CAR T.
Observation based on 17 patients

Smith E et al, abs#S479

Conclusions on CAR T therapy

- CAR T therapy appears promising in the R/R setting, both in children and adults.
- Management of patients is still an important concern, thought we are learning!
- Allo-SCT post CAR-T????

Burning questions

- In case of molecular relapse, what therapy is the best (considering that in the forthcoming future blinatumomab /ino will be incorporated in the front-line setting?
- In case of hematologic relapse, what therapy is the best?

- Who is the ideal candidate for CAR T ?

- Sequential use of different Moabs or CAR-T Moabs ?