Leucemia acuta linfoide

Sabina Chiaretti, MD, PhD

Division of Hematology
'*Sapienza*' University of Rome

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

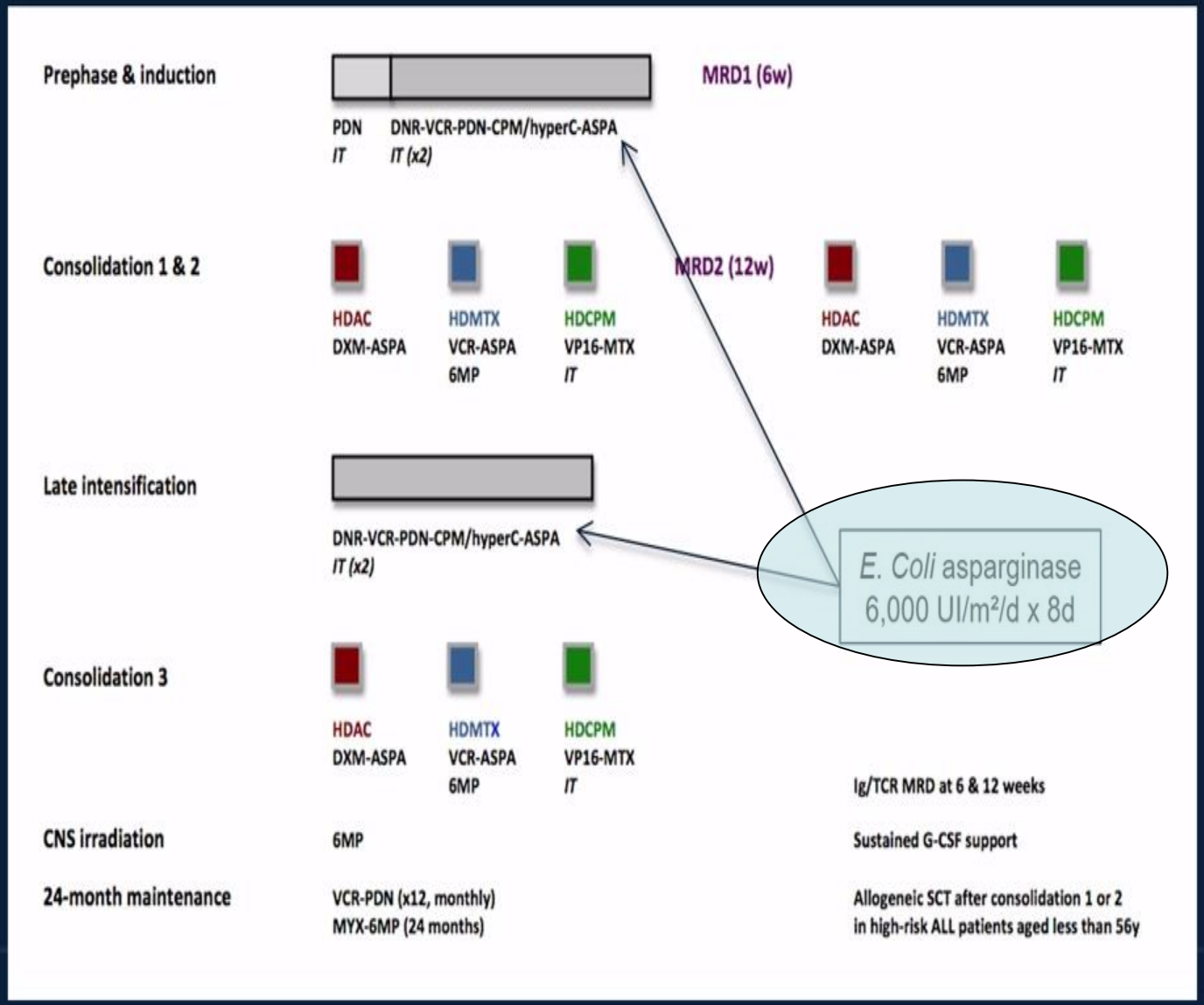
France, Belgium, Switzerland

Hervé Dombret

University Research Institute of Haematology

Hôpital Saint-Louis, Paris, France

GRAALL for Ph-negative ALL



Dombret H

How to manage Asp toxicity

Prevention of Venous Thrombotic Events in Adult Patients with ALL Treated in a Pediatric-Inspired Protocol -a GRAALL Study

Orvain C, et al. *Blood*. 2016:128:Abstract 2776

Methods;

8x native *E.coli* ASP IV (6.000 UI/m² / injection)
2x L-ASP IV (10.000 UI/m²/ injection)
prophylactic heparin was recommended

Results;

787 pts. with newly diagnosed Ph neg. ALL
14.4% (N=113) Venous Thrombotic Events (VTE)
64% (N= 72) Deep Vein Thromboses (DVT)
28% (N= 32) Cerebral Venous Thrombosis (CVT)
12% (N= 13) Pulmonary Embolism (PE)

Conclusion;

appropriate AT prophylaxis associated with less VTE

25 pts. with VTE-after reexposure with *E.coli* ASP or Erwinase-ASP no recurrence of VTE

Fibrinogen concentrates may increase the risk of thrombosis and should be restricted to pts. with hemorrhage

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

Major Results and Future of Italian ALL study groups

Sabina Chiaretti, MD, PhD
on behalf of GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto)

22nd Congress of the European Hematology Association,
Madrid 22-25 June, 2017

STVDIVM VRBIS

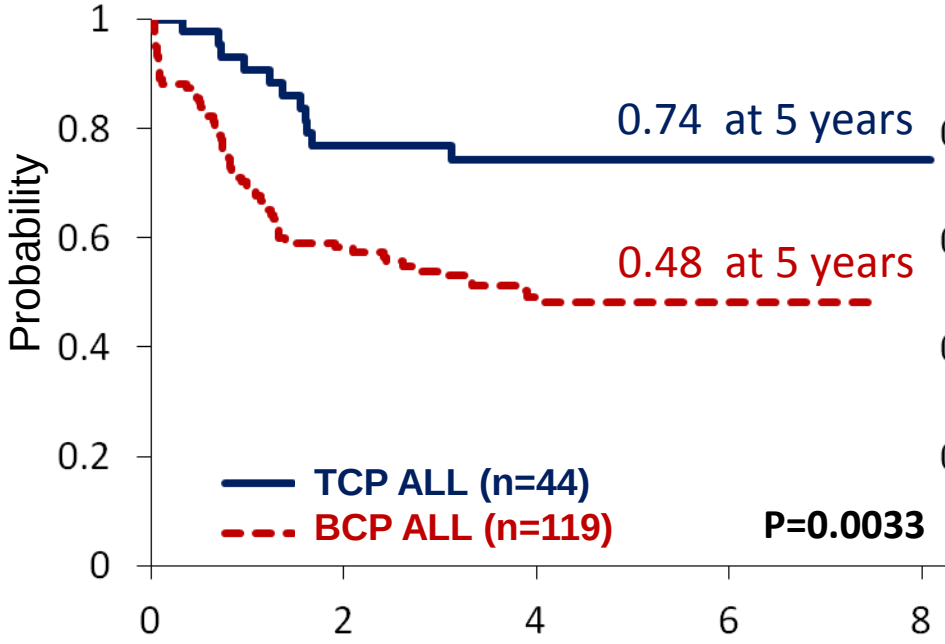
fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

NILG 10/07: CR, OS and DFS

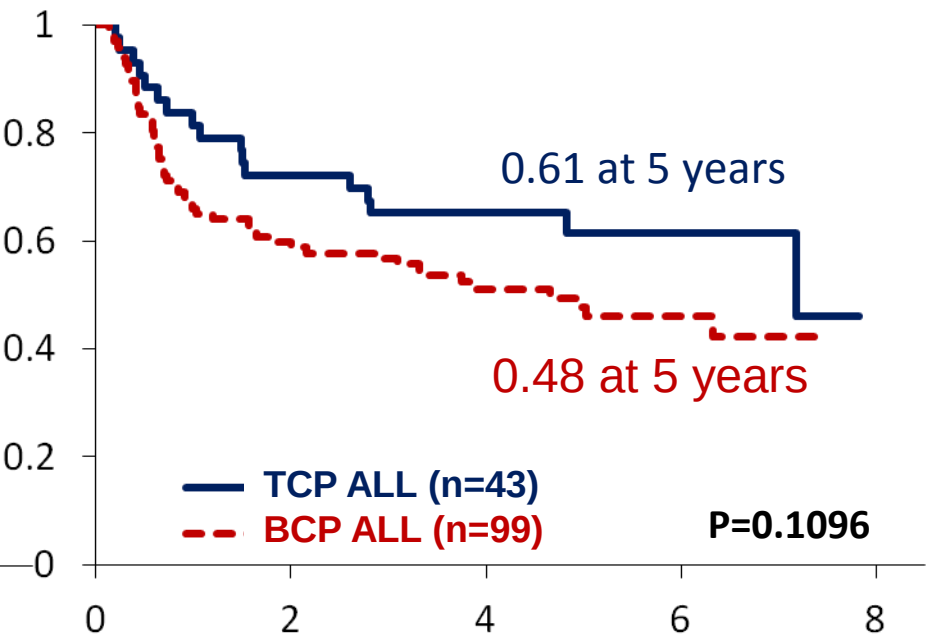
	All (Ph-) n=163	TCP ALL n=44	BCP ALL n=119
CR	142 (87%)	43 (98%)	99 (83%)*
NR	7 (4%)	1 (2%)	6 (5%)
ED	14 (9%)	0	14 (12%)

*Age ≤ 60 vs >60 years:
CR 88% vs 58% (P < .0038)

OS (55% for the whole population)



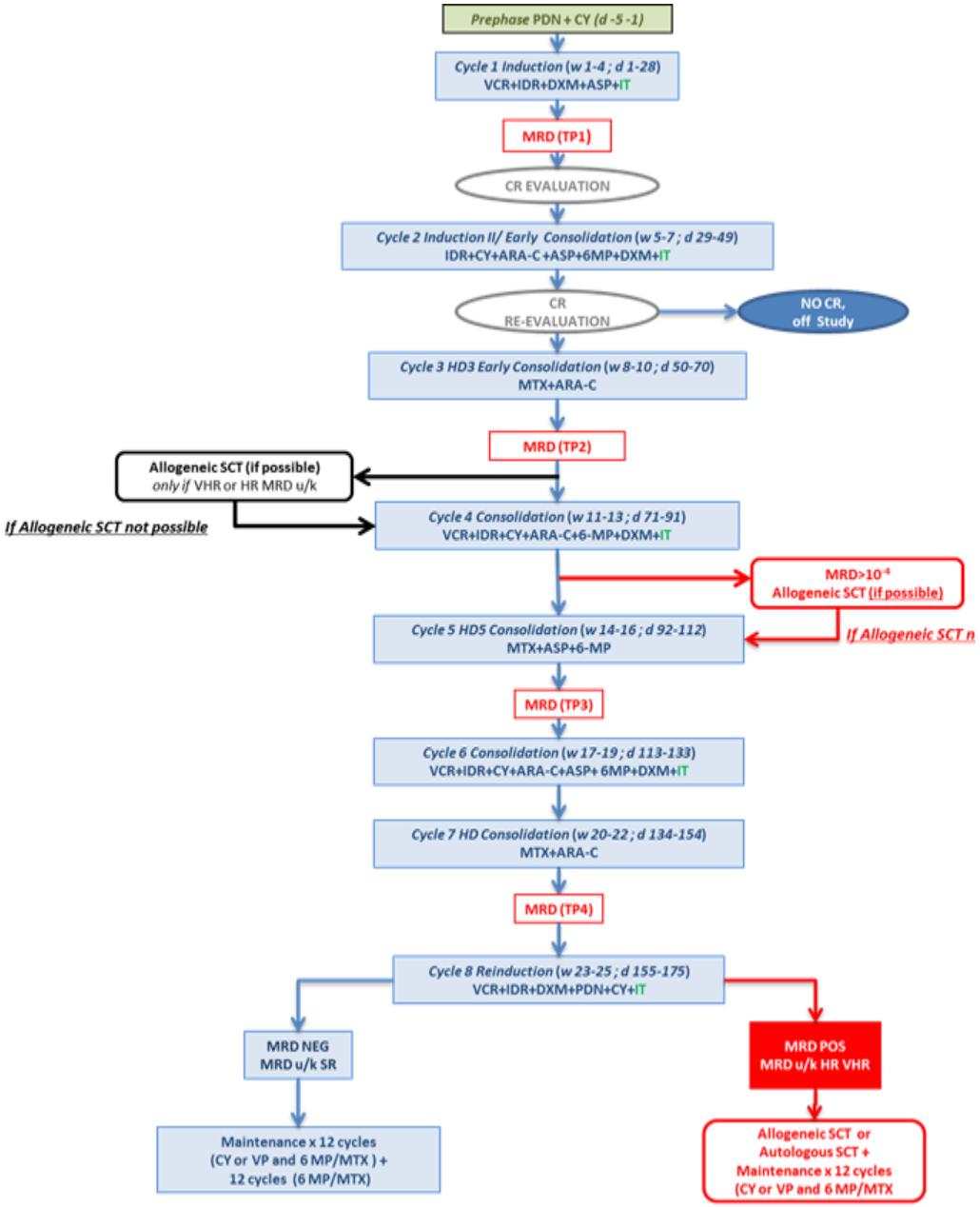
DFS (52% for the whole population)



Bassan R, et al, ASH 2016, abs#176

Chiaretti S

GIMEMA LAL 1913



Same backbone of NILG10/07

Sample dimension: 204 patients

Extended to whole Italy

PEG-ASP introduced

Estimated recruitment period: 24 months

Real recruitment period: 22 months

Chiaretti S

PEG-ASP toxicity and dose adjustments

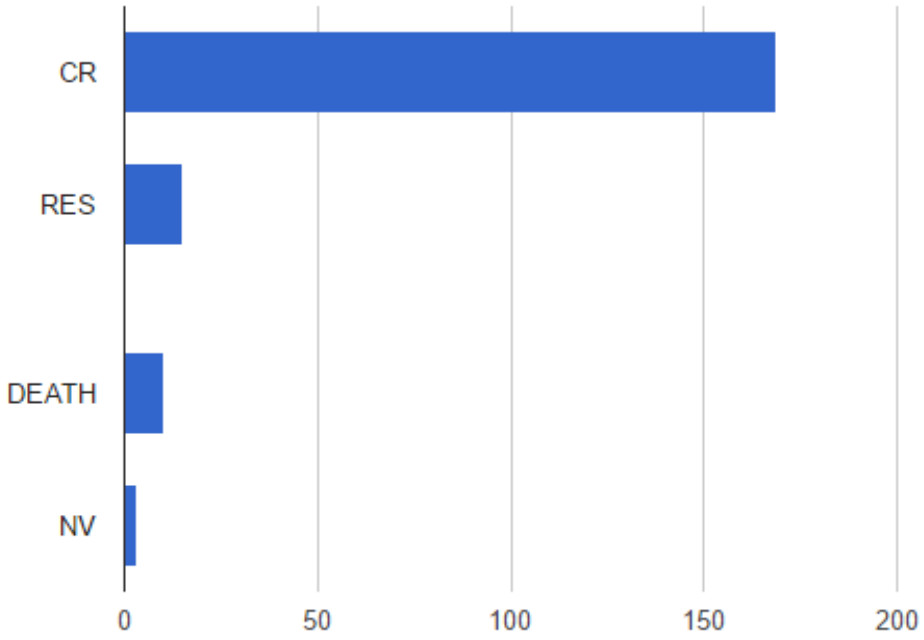
Most frequent complications: alterations of coagulative profile (laboratoristic and/or clinical), hepatic and pancreatic dysfunction

Age group (years)	Cycle no.[1]	Risk factors[1]	Peg-ASP related G3-4 toxicity at prior cycle[2,3]	Peg-ASP IU/m^2 (max cumulative)
≤ 55	1	no	-	1500 (3000)
		yes	-	1000 (2000)
	2, 5, 6	no	No	2000 (3750)
			Yes	1000 (2000)
		yes	No	1500 (3000)
			Yes	500 (1000)
> 55	1	no	-	1000 (2000)
		yes	-	500 (1000)
	2, 5, 6	no	No	1000 (2000)
			Yes	500 (1000)
		yes	No	1000 (2000)
			Yes	No Peg-ASP[4]

Chiaretti S

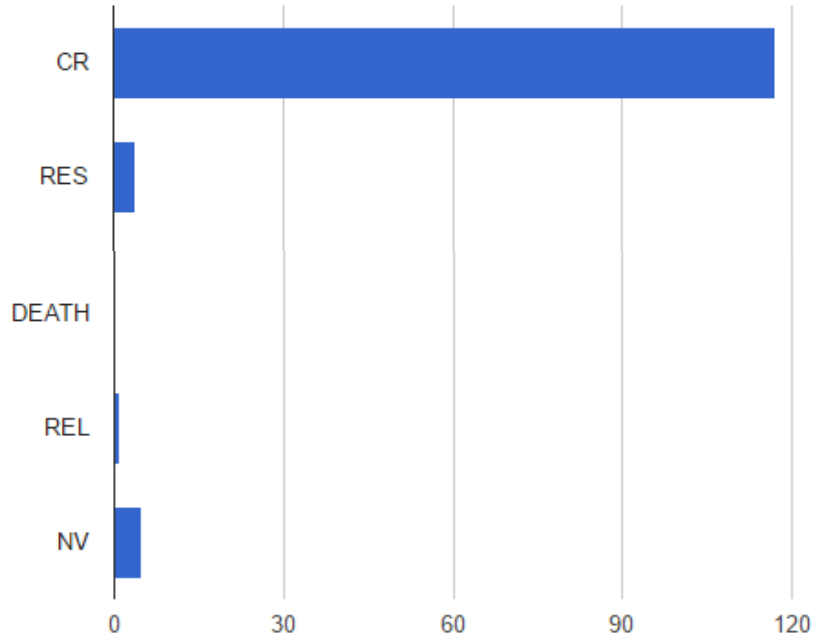
GIMEMA LAL 1913: response to induction

197 evaluable for C1 response



CR (**169**, 85.8%), RES (15, 7.6%), DEATH (10, 5.1%), NV (3, 1.5%)

173 started C2
127 evaluable for response



CR (**117**, 92.1%), RES (4, 3.1%), DEATH (0, 0%), REL (1, 0.8%), NV (5, 3.9%)

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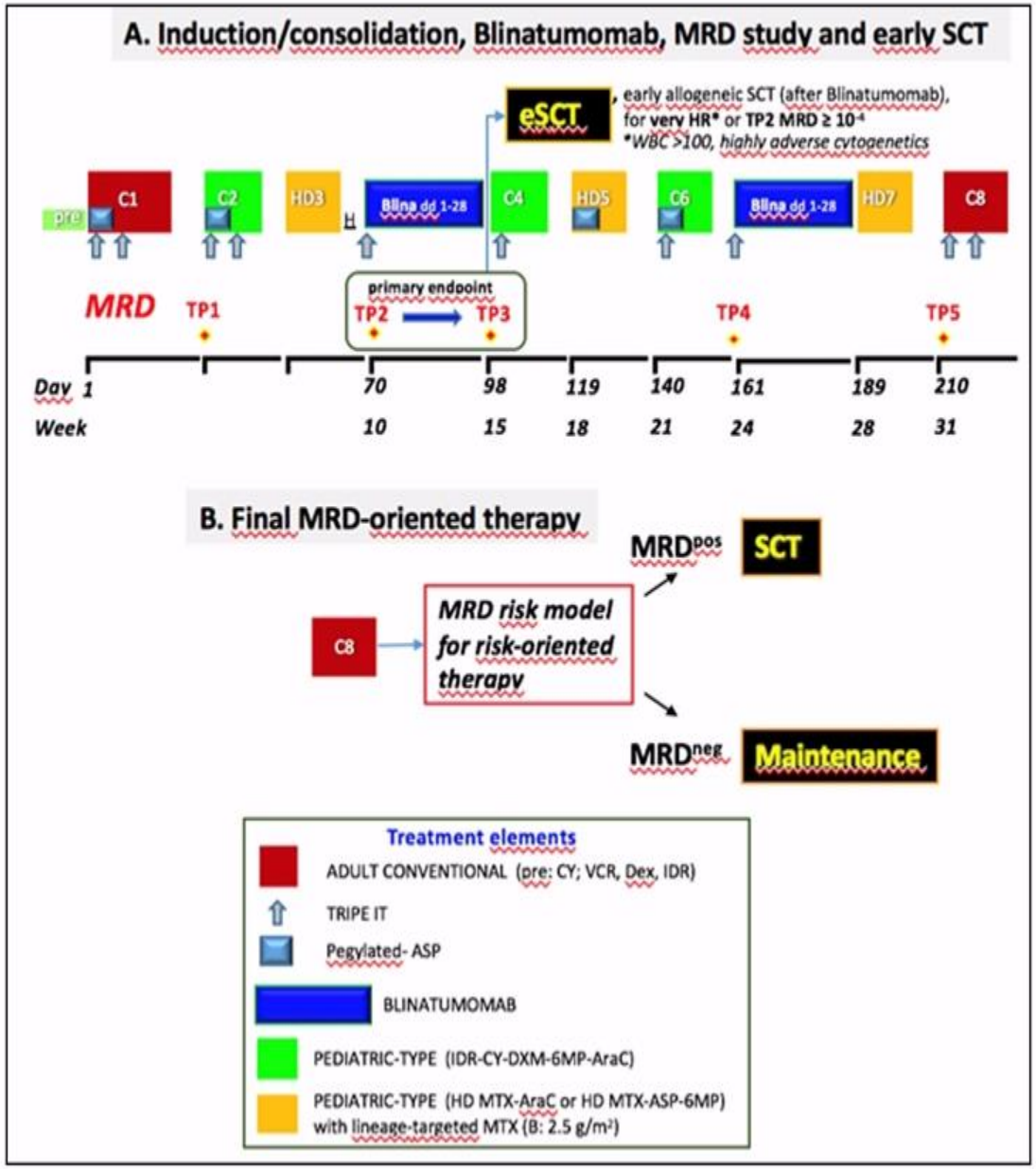
Ph- ALL (B-ALL): the forthcoming future

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



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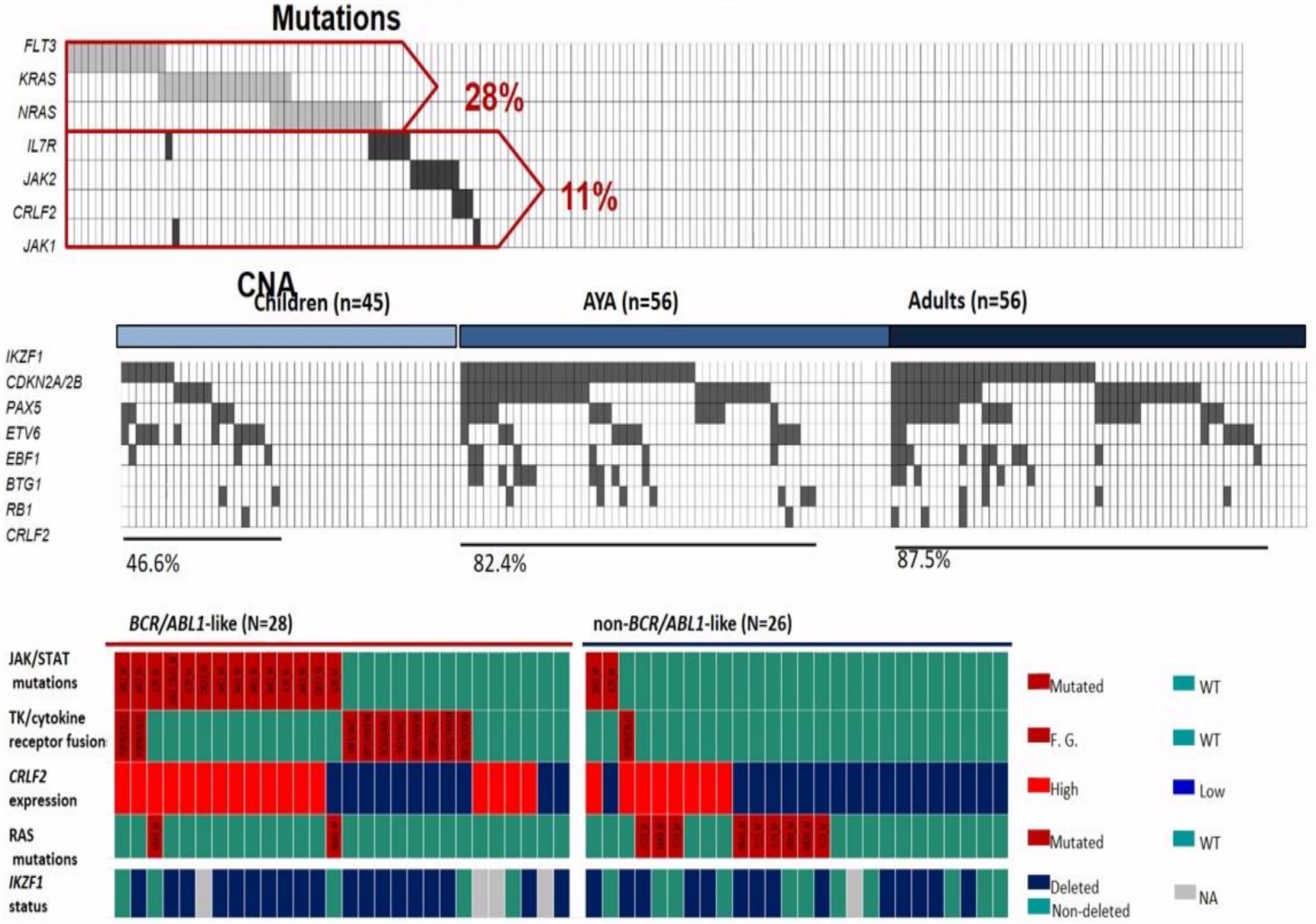
Integrating biology into the clinic



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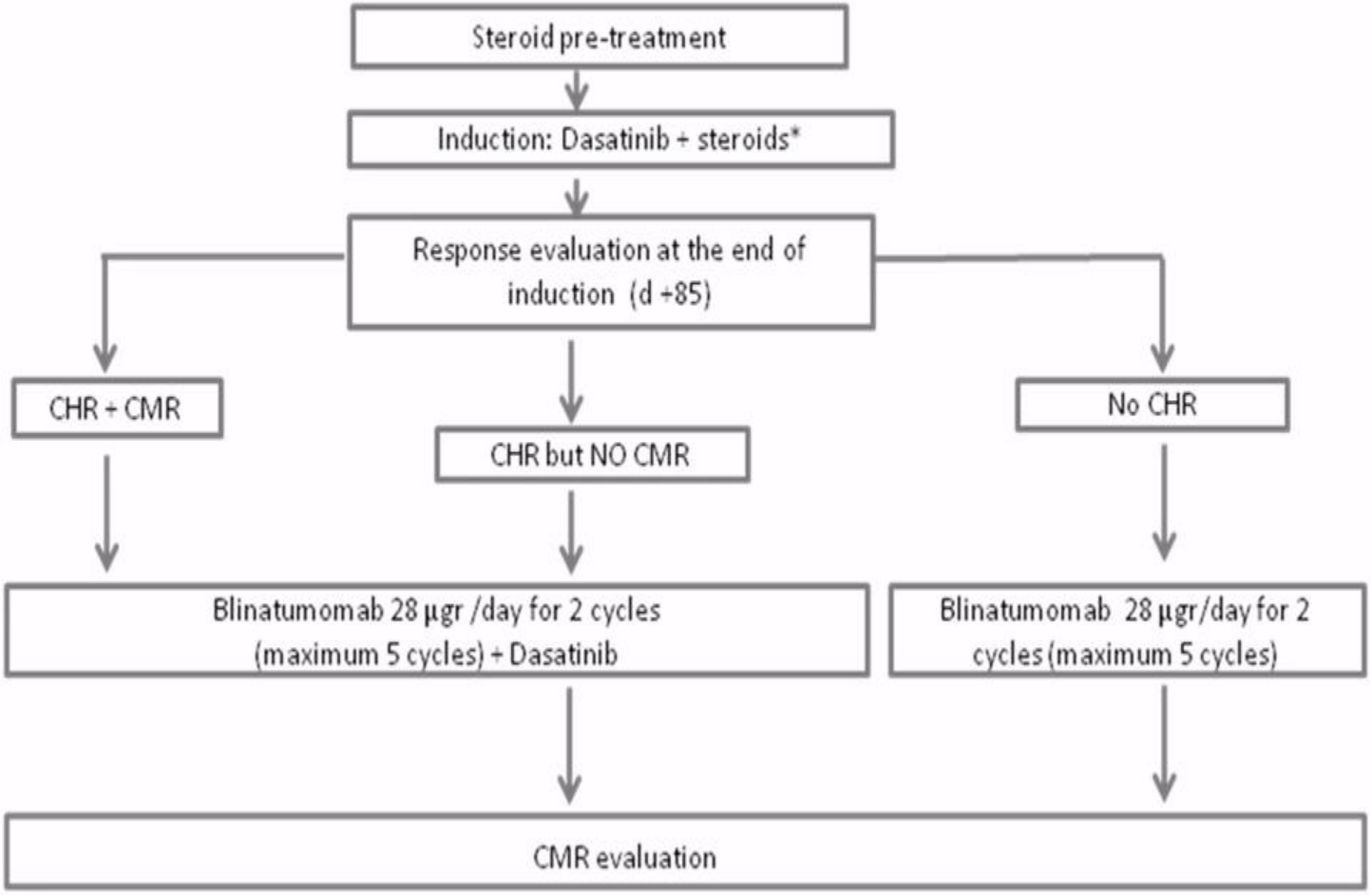
Ph+ ALL: the present

GIMEMA LAL2116



*up to day +31

Patients will be subsequently enrolled in an ancillary study for follow-up

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

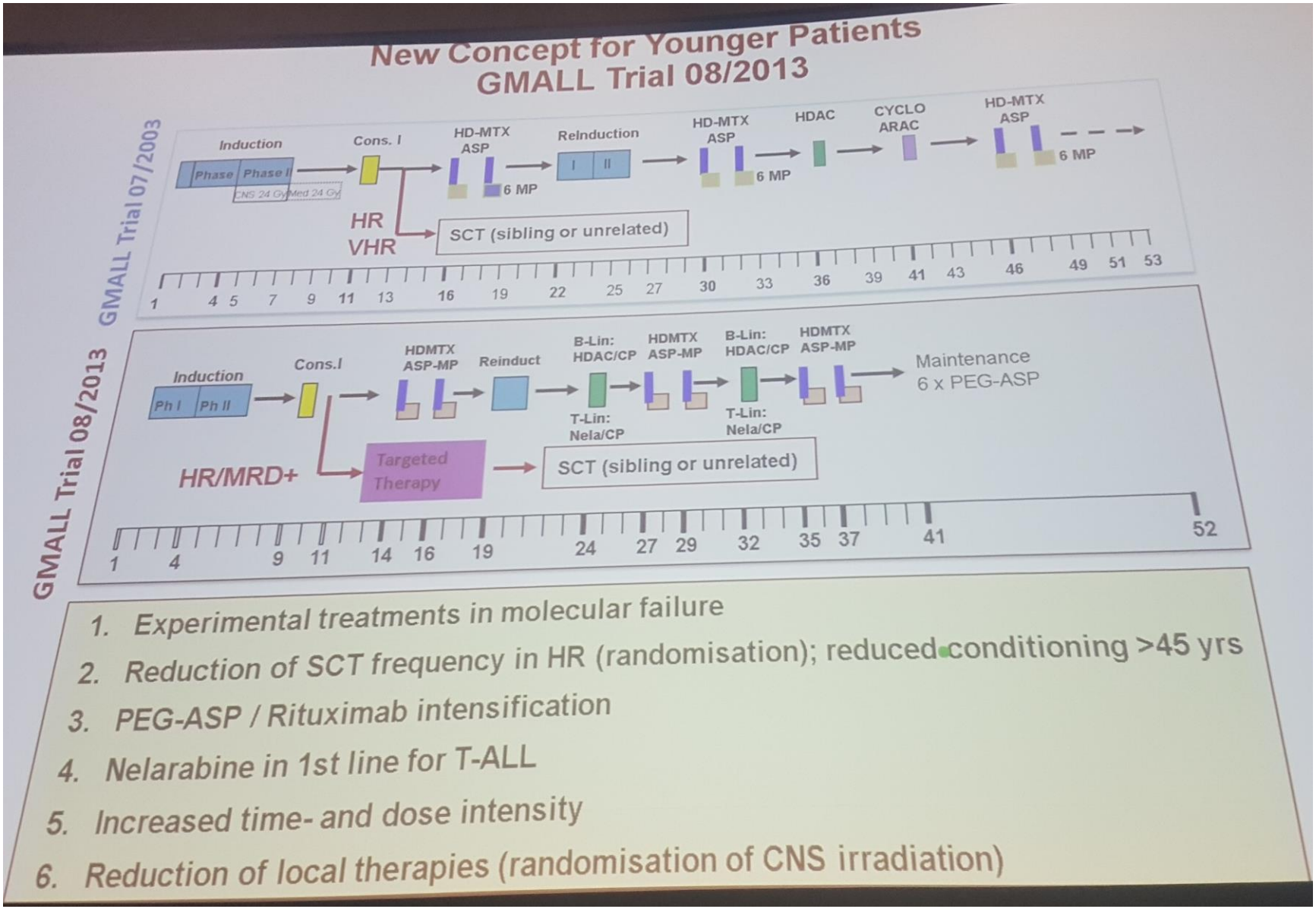
To determine whether risk-adapted introduction of unrelated donor HSCT (myeloablative conditioning in patients <40 years old and non-myeloablative conditioning in patients >40 years old) improves EFS in patients at highest risk of relapse.

NCRI National Cancer Research Institute

UCL

Fielding A

GMALL: moving forward



Goekbuget N

Conclusions for EWALL scientific workshop

- Concordance on prognostic factors:

-Age still counts !!

-MRD is strongly predictive of outcome

-Novel biologic factors

- Incorporation of novel drugs (e.g. blina, inotuzumab, nelarabine) all over Europe
- Guidelines for management of toxicity (mostly ASP) are taken into account

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- Novel treatments:

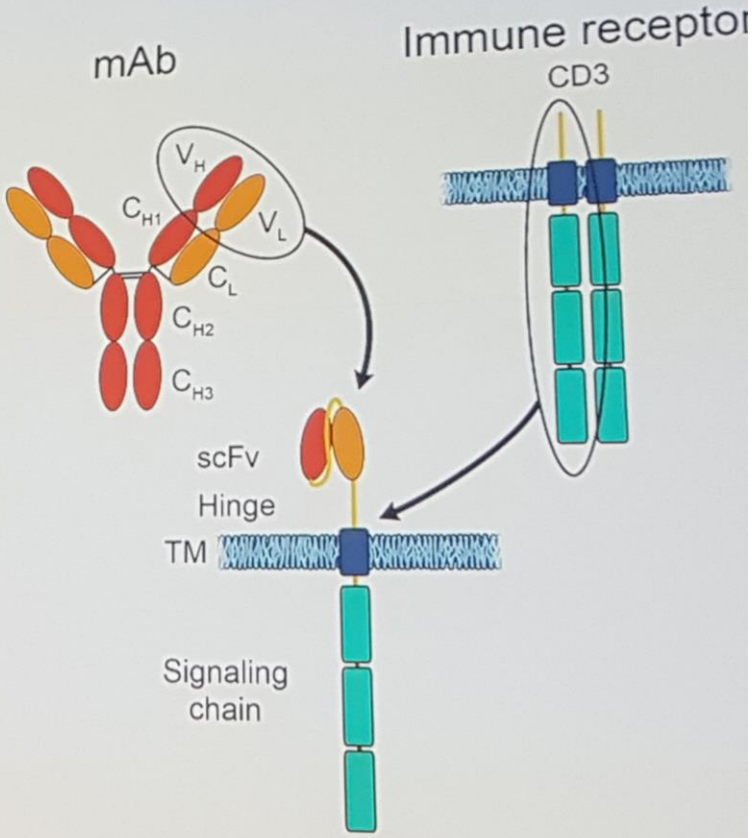
  -**focus on CAR-T**

  -updates on blinatumomab and inotuzumab treatment

CAR T cells

Chimeric Antigen Receptor (CAR) T Cells

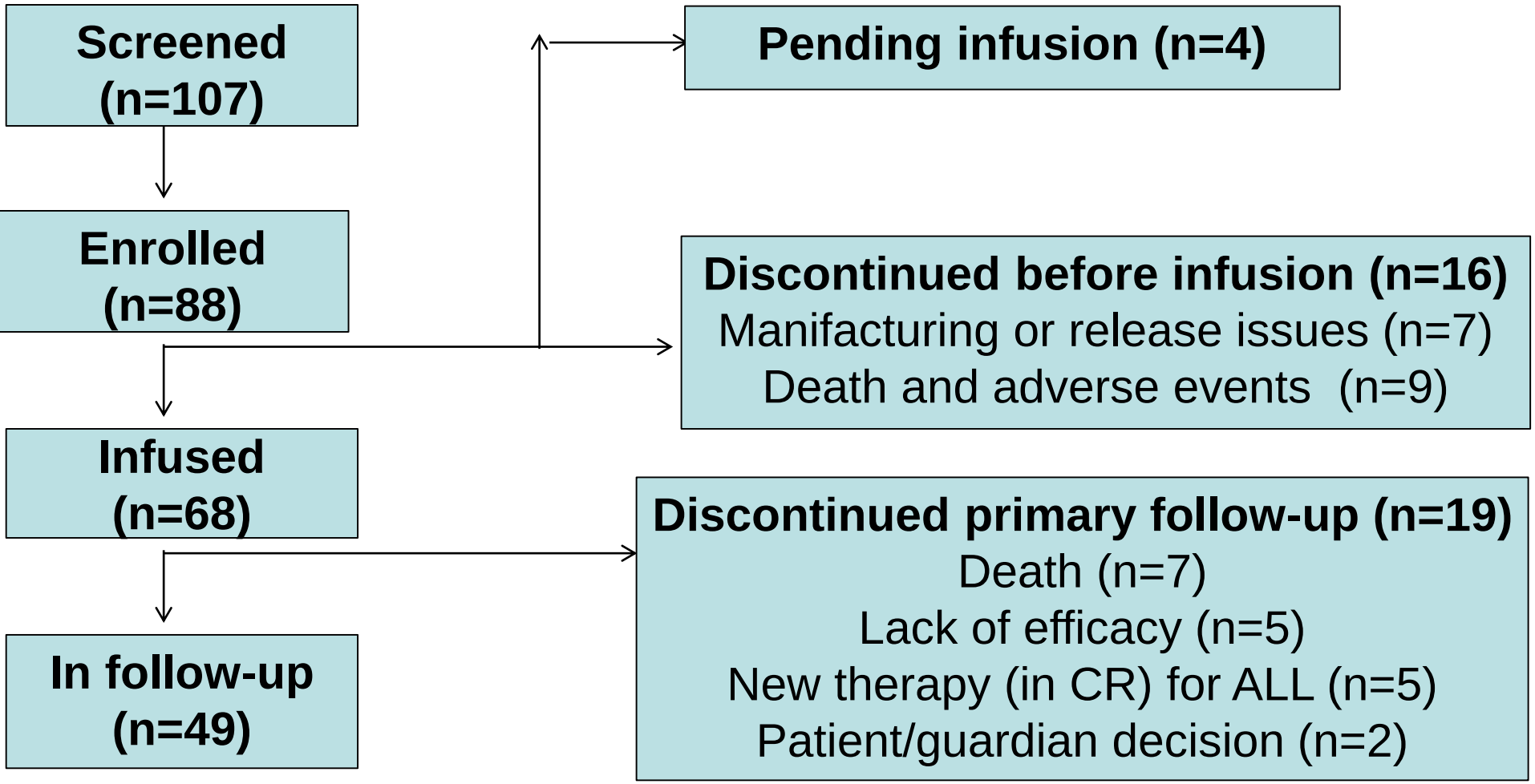
- **Combine the scFv from a monoclonal antibody with an intracellular signalling domain[1]**
- **Signalling domains differ, eg:**
  - *41BB (CTL019 – CHOP/UPenn)*
  - *CD28 (KTE-C19 – NCI; 19-28z – MSKCC)*
- **Modified CAR-T cells**
  - *Redirect T-cell antigen specificity*
  - *Stimulate T-cell activation*
  - *Further enhance T-cell function via costimulation domains in the cytoplasmic tail[1,2]*



rtellieri M, et al. *J Biomed Biotechnol.* 2010;2010:956304. 2. Davila ML, et al. *Sci Trans Med.* 2014;6(224):224ra25

FDA approved on August 31, 2017

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

Key patients characteristics

Baseline characteristics	Patients (n= 68)
Age, median (range), years	12(3-23)
Male sex, %	56
Prior SCT, %	59
Previous lines of therapy, median (range) %	3 (1-8)
Morphologic blast count in bone marrow, median (range), %	73 (5-99)
Disease status, %	
Refractory	21
Relapsed	79
High-risk genetic lesions, %	29
Down syndrome, %	9

Buechner et al, abs#S476

Primary assessment of efficacy

Parameter	Efficacy analysis set (n=63)¥		
Primary endpoint	*% (n/N)*	*95% CI*	*P value*
Overall remission rate (CR+CRi)	83 (52/63)	(71-91)	<0.01
Best overall response			
CR	63		
CRi	19		
Secondary endpoint			
Best overall response of CR-Cri within 3 months with MRD-negative BM*	83	(71-91)	<0.001

¥ Patients infused ≥ 3 months prior to data cut-off; MRD<0.01%

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)

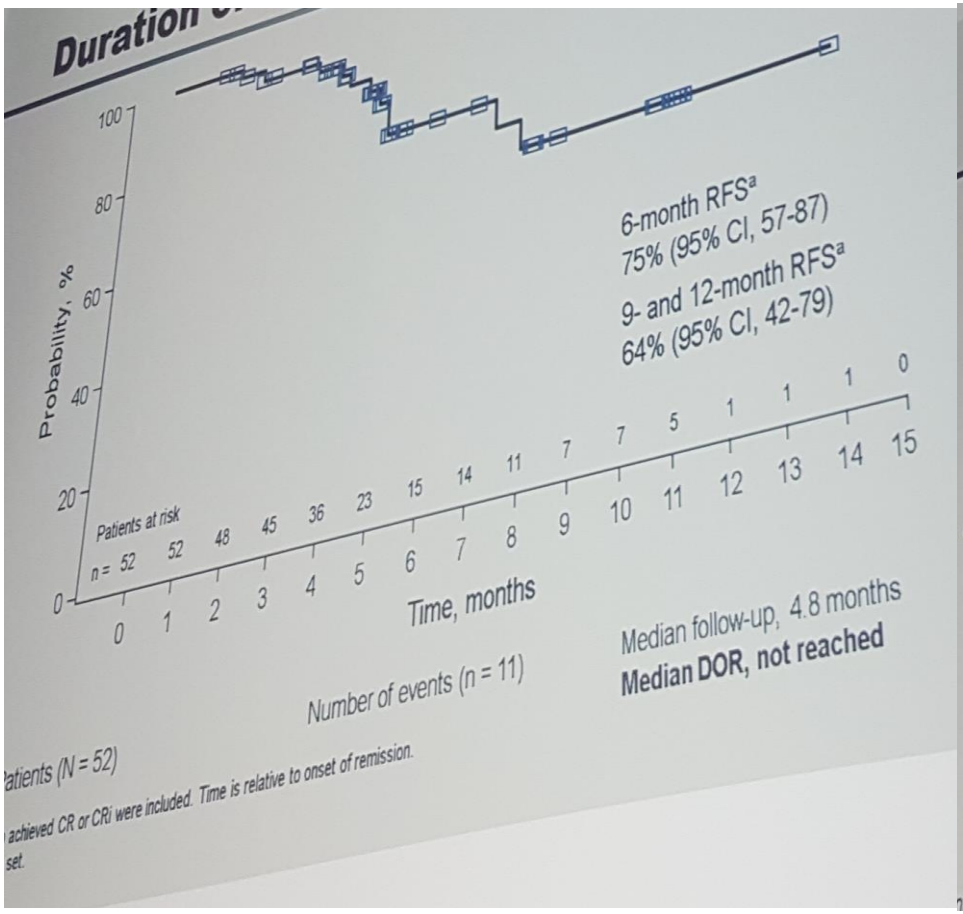
	CRS
Days of duration	8 (1-36)
ICU admission,%	46
Anticytokine therapy,%	38
Hypotension requiring intervention,%	51
HD vasosuppressors,%	25
Intubation,%	15
Dialysis,%	10

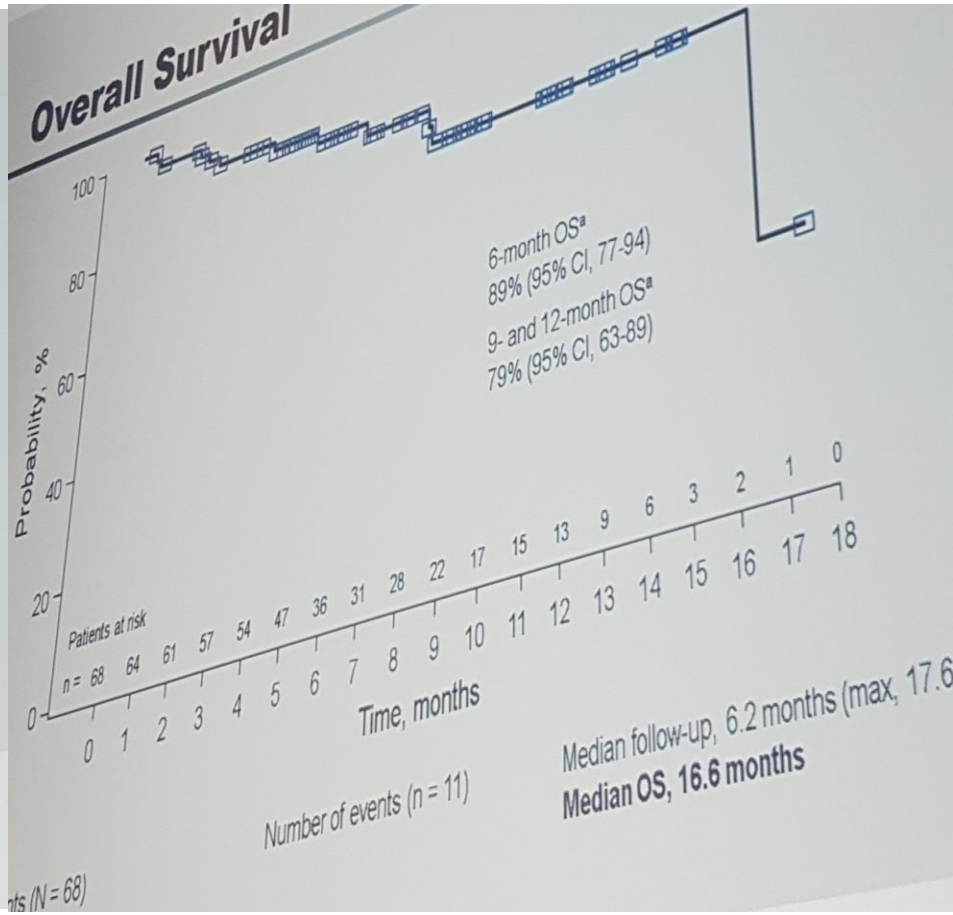
CRS	Any neurologic event,%	G3 neurologic event,%
No CRS (n=15)	27	7
G1/2 (n=21)	33	5
G3 (n=14)	50	14
G4 (n=18)	67	33

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

RFS and OS



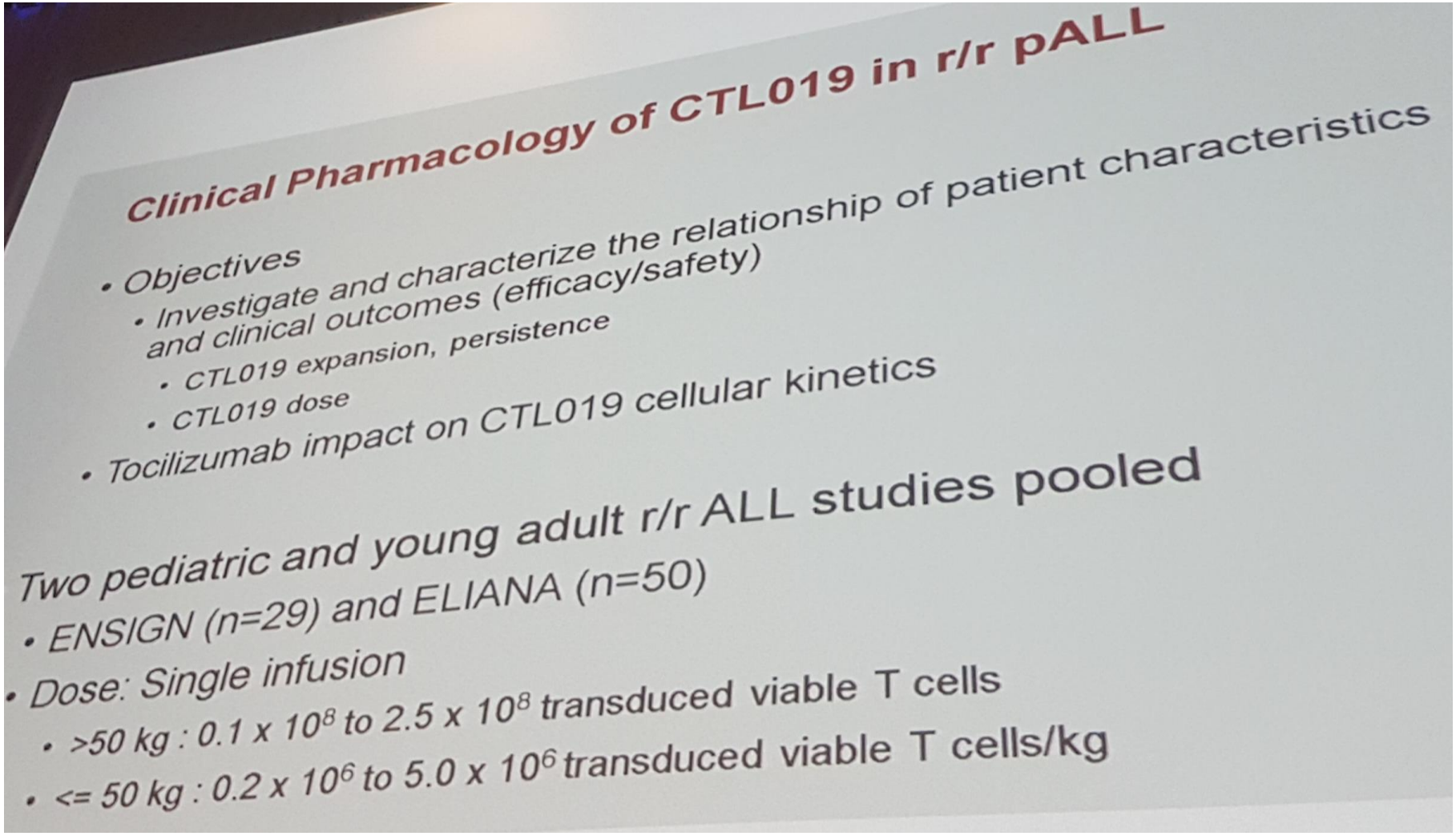


6 months RFS: 75%

6 months OS: 89%

Buechner et al, abs#S476

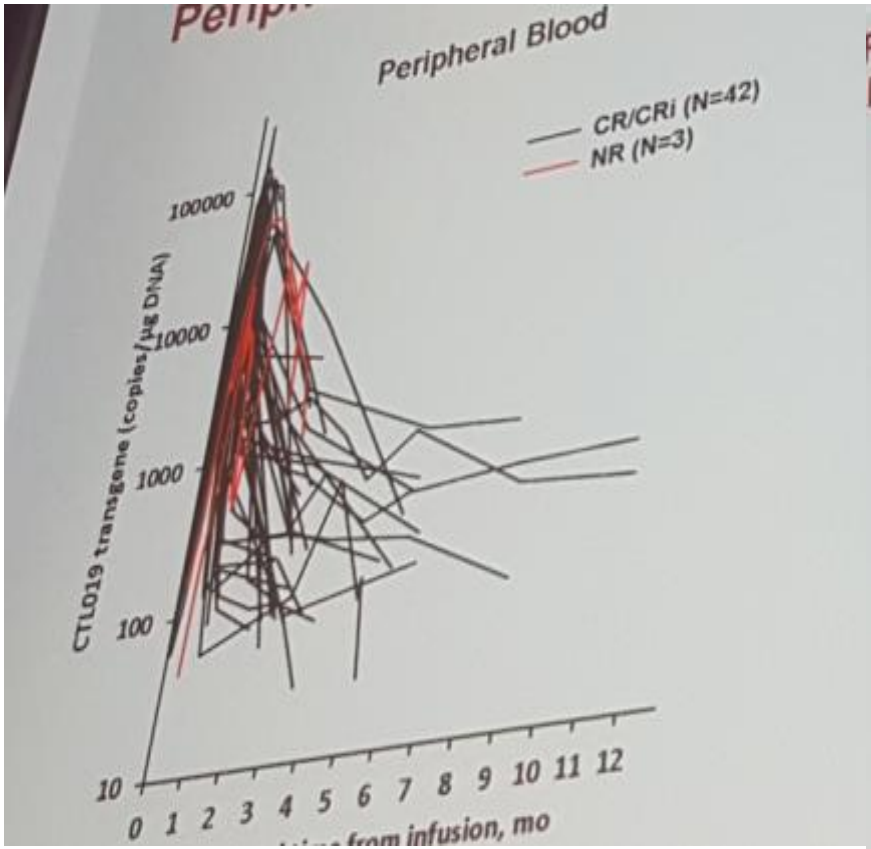
CTL019 clinical pharmacology and biopharmaceutics in pediatric patients (pts) with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL)



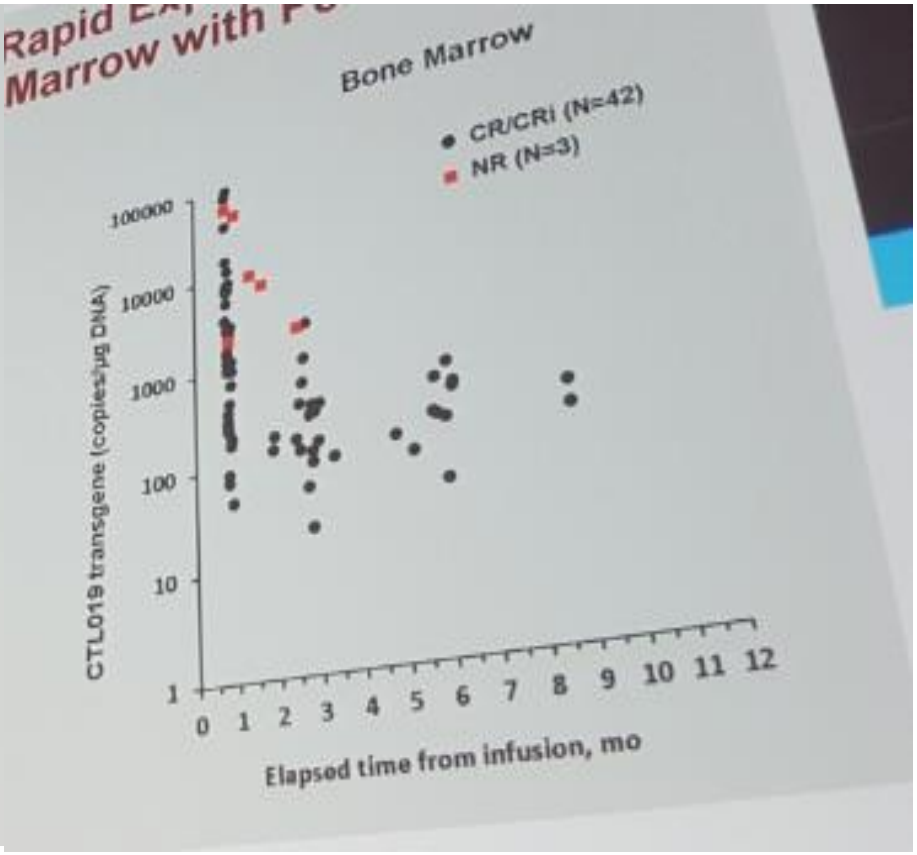
Mueller et al, abs#S477

Responding pts have rapid expansion in peripheral blood and bone marrow and persistence

Peripheral blood

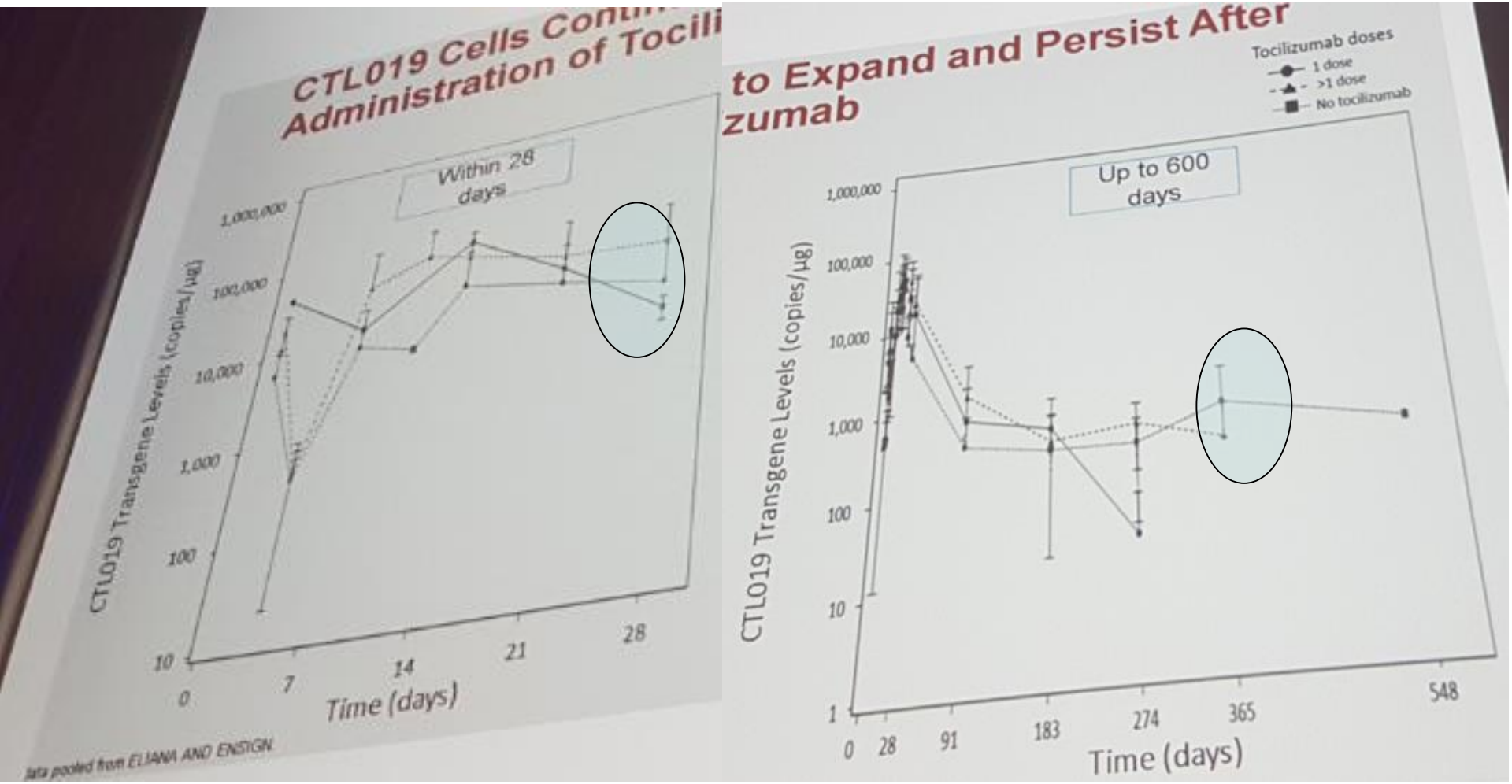


Bone marrow



Mueller et al, abs#S477

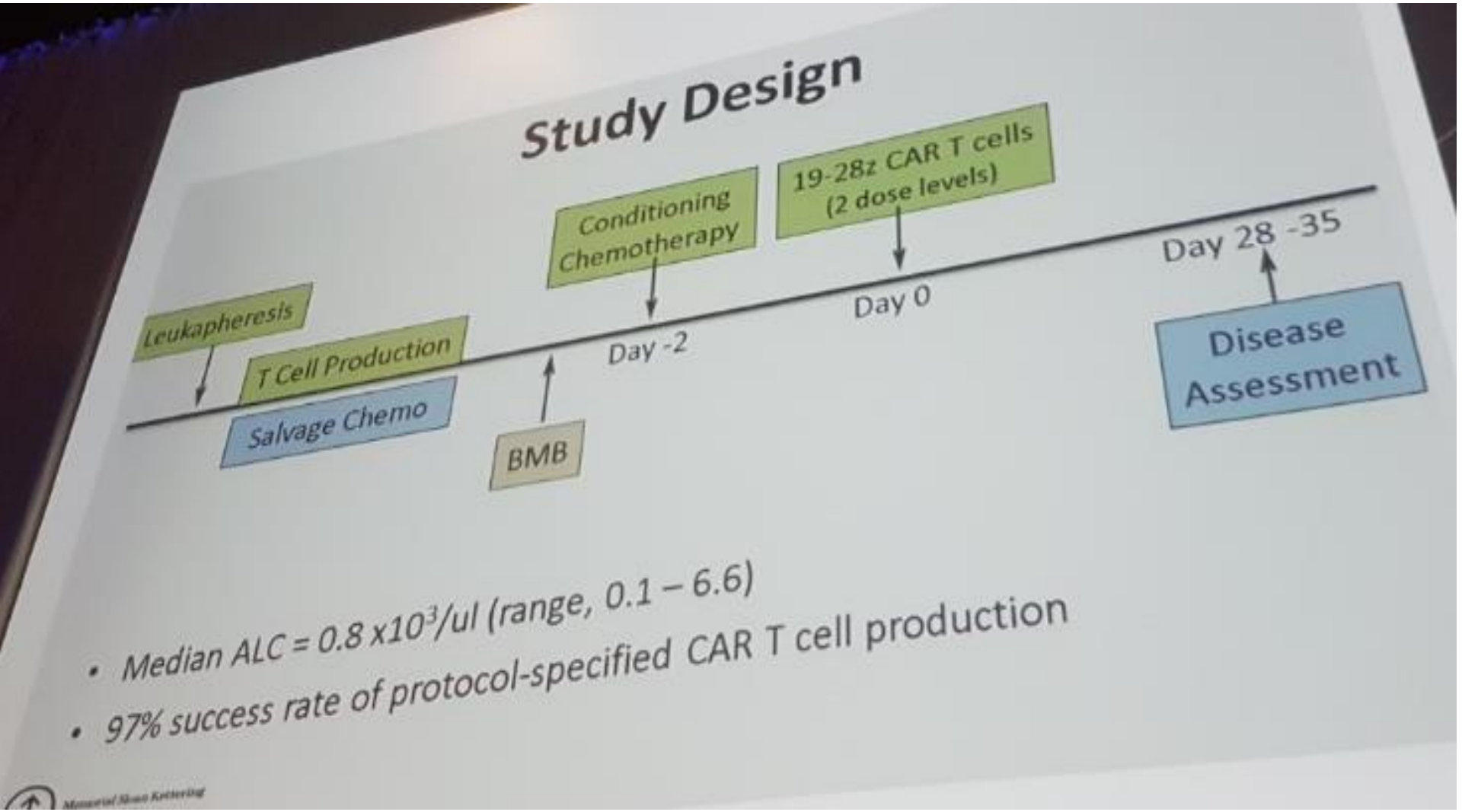
Tocilizumab does not affect expansion



Mueller et al, abs#S477

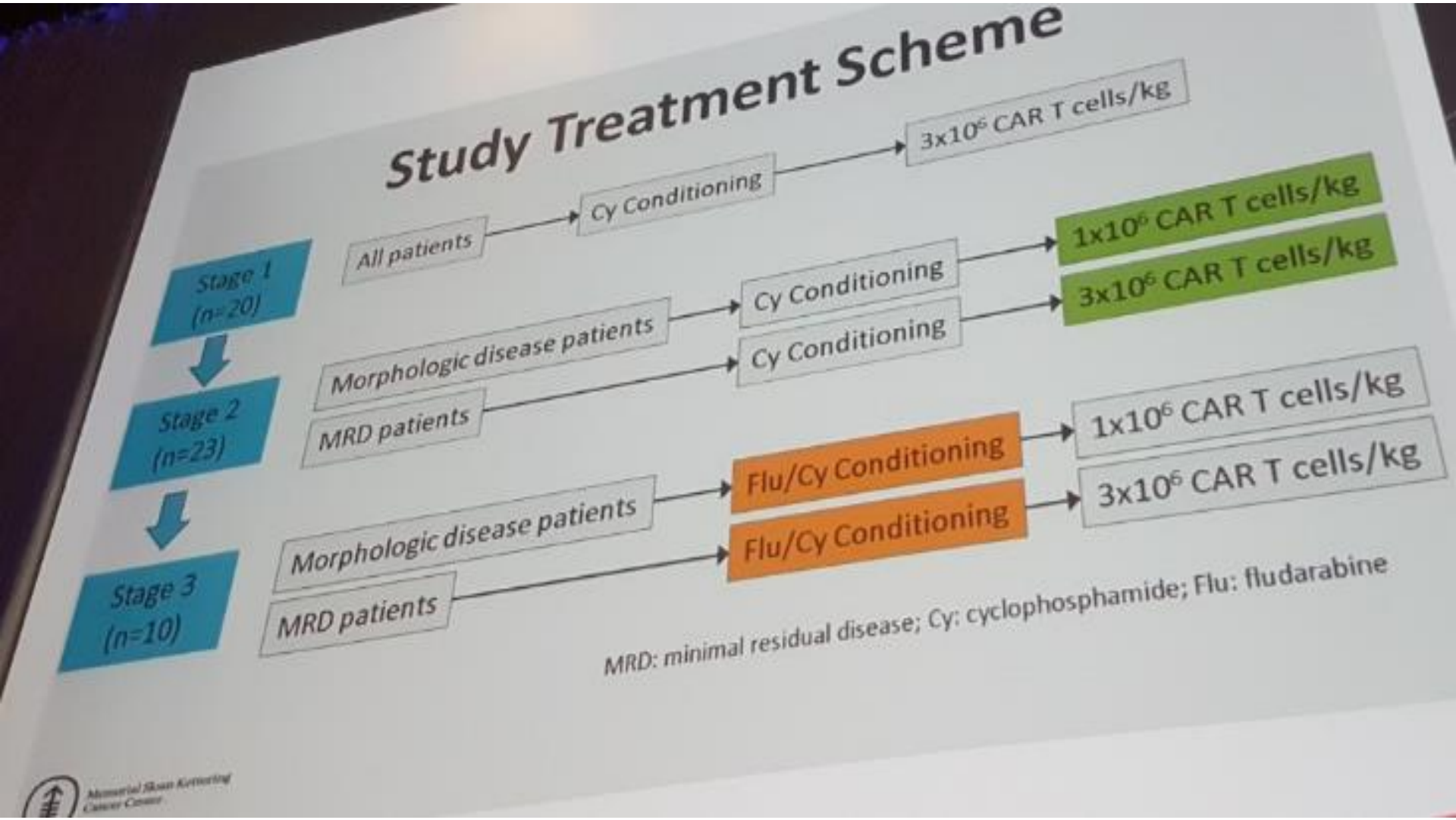
Tocilizumab treatment can be safely administered, if required, and does not impact on short and long term CTL functionality

Durable long-term survival of adult patients with B-ALL after CD19 CAR(19-28z) T cell therapy



Smith E et al, abs#S479

Treatment scheme: 3 stages



NCT01044069

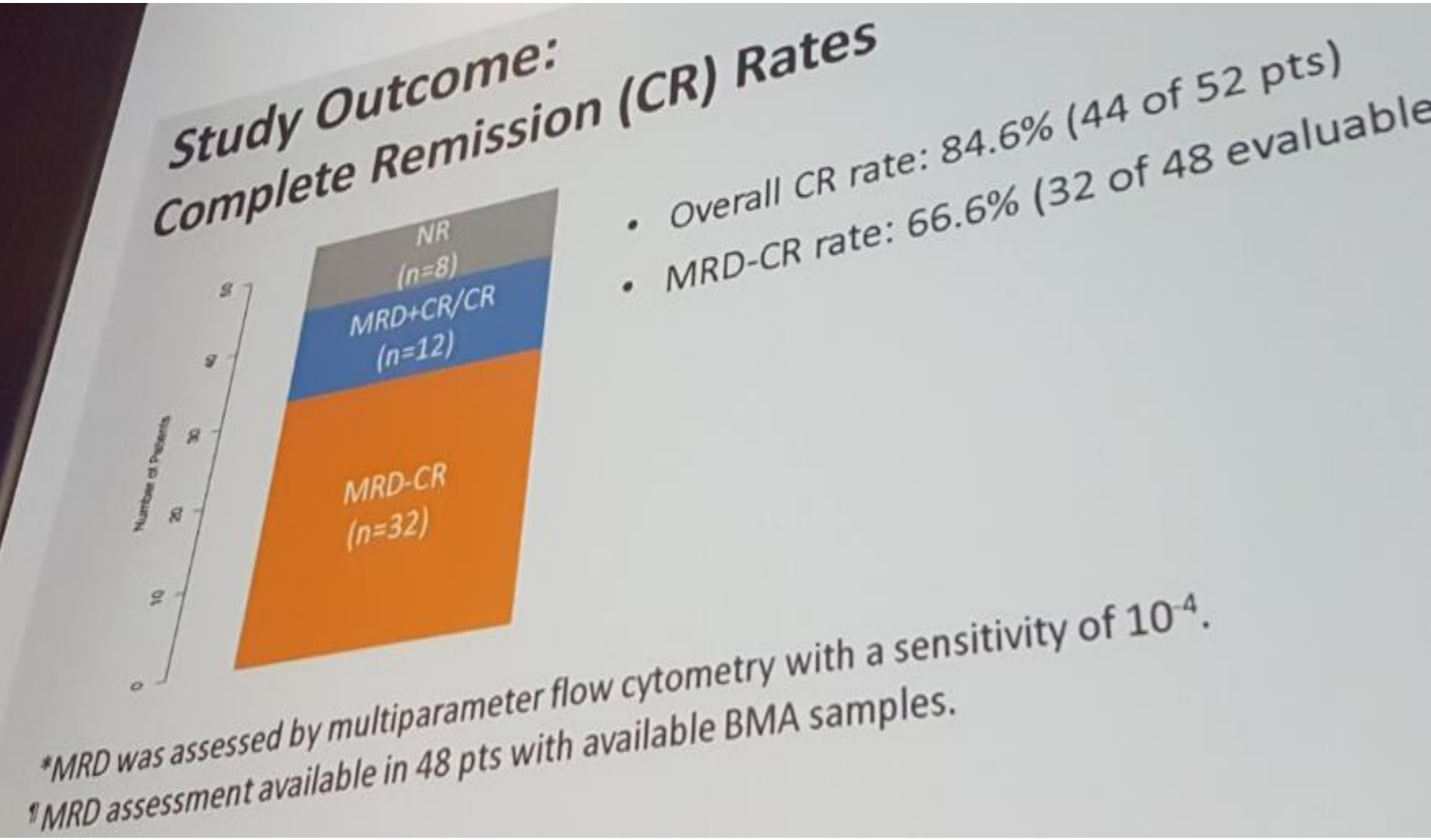
Smith E et al, abs#S479

Baseline characteristics

Characteristic	Patients (n=53)
Age, median (range)- yr	44 (23-74)
Salvage-treatment phase – no. (%) 1 2 3 4 ≥5	 1 (2) 16 (30) 17 (32) 9 17) 10 (19)
Primary refractory disease – no. (%) Yes No	 12 (23) 41 (77)
Prior allogeneic HSCT – no. (%) Yes No	 19 (36) 34 (64)
Bone marrow blasts, median % (range) ≥5% <5% <5% with extramedullary disease	63 (5 - 97) 27 (51) 21 (40) 5 (9)
Philadelphia chromosome (Ph)-positive – no. (%) Yes No	 16 (30) 37 (70)

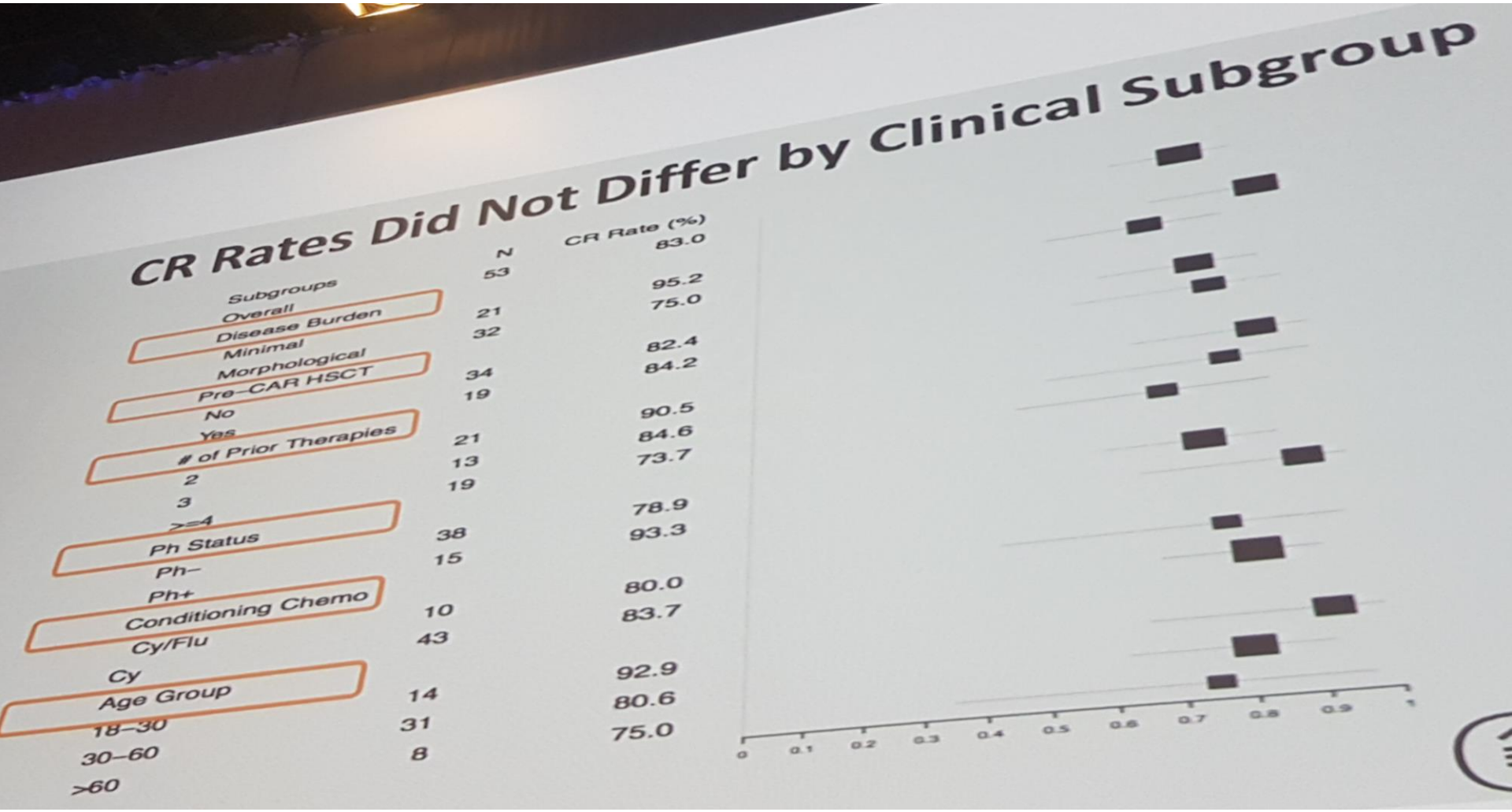
Smith E et al, abs#S479

CR rates



Smith E et al, abs#S479

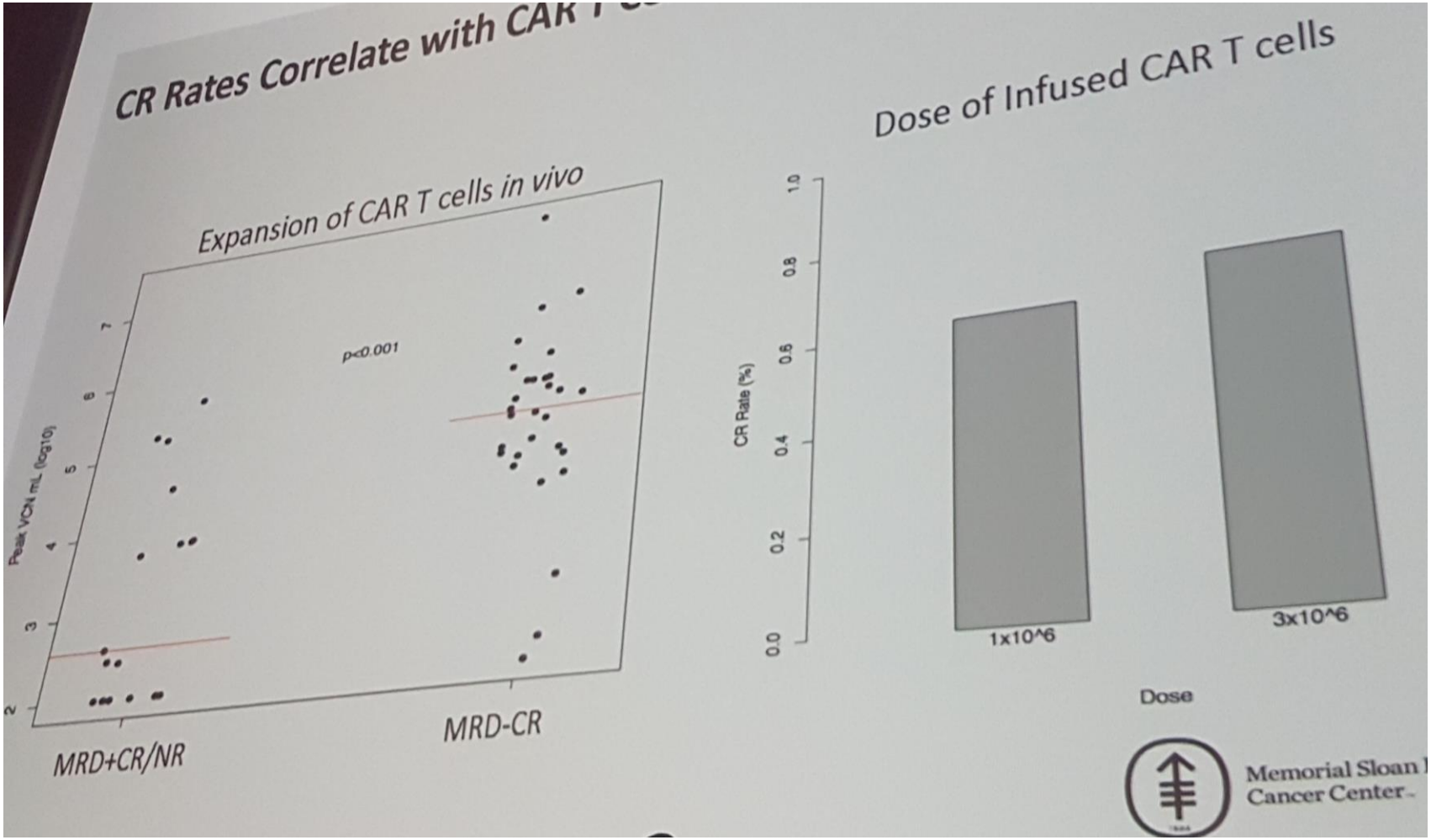
Response among subgroups



Better (p=ns) responses in MRD+ vs morphological, < lines of therapy, Ph+ and younger patients

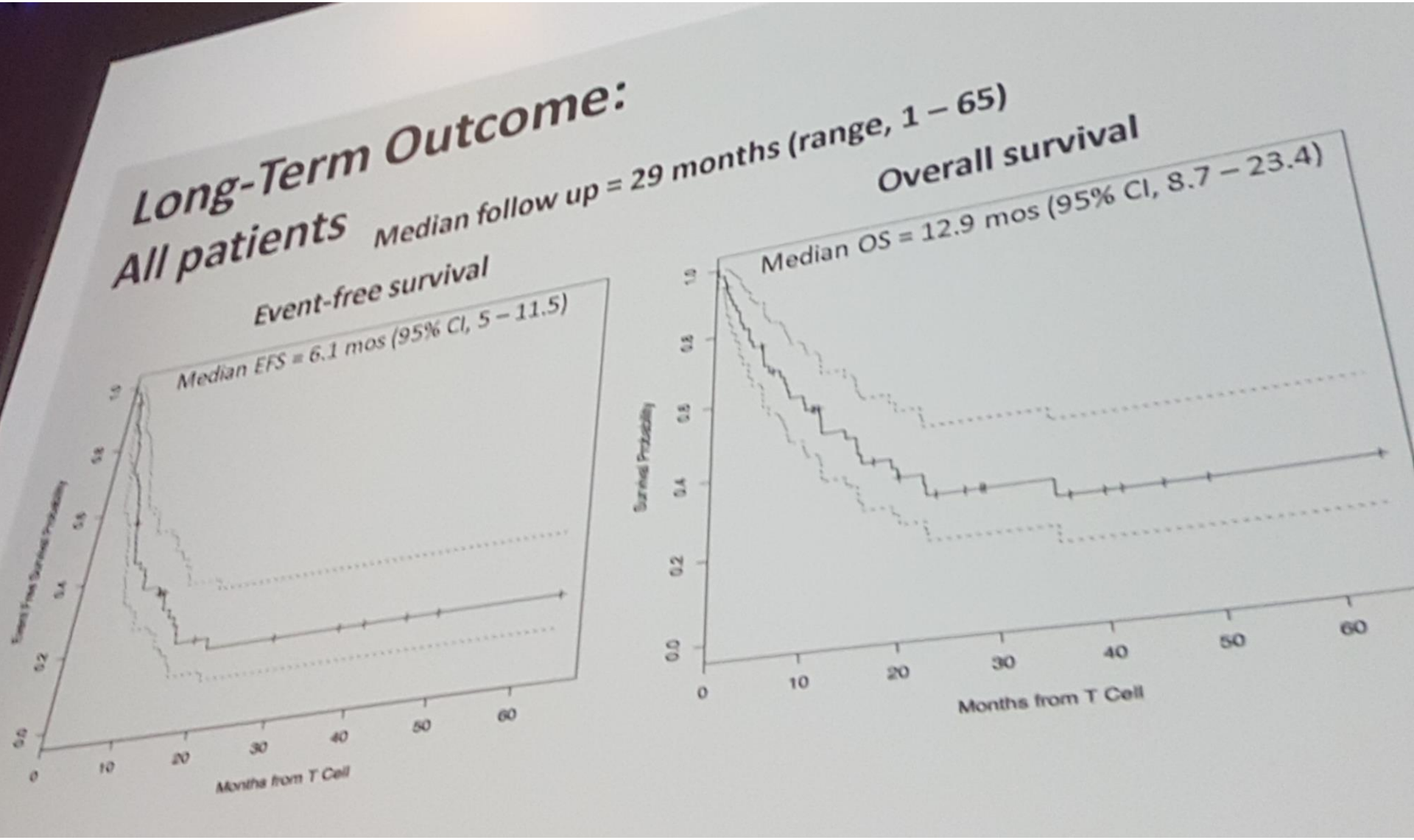
Smith E et al, abs#S479

CR correlates with CAR T expansion but not infused dose



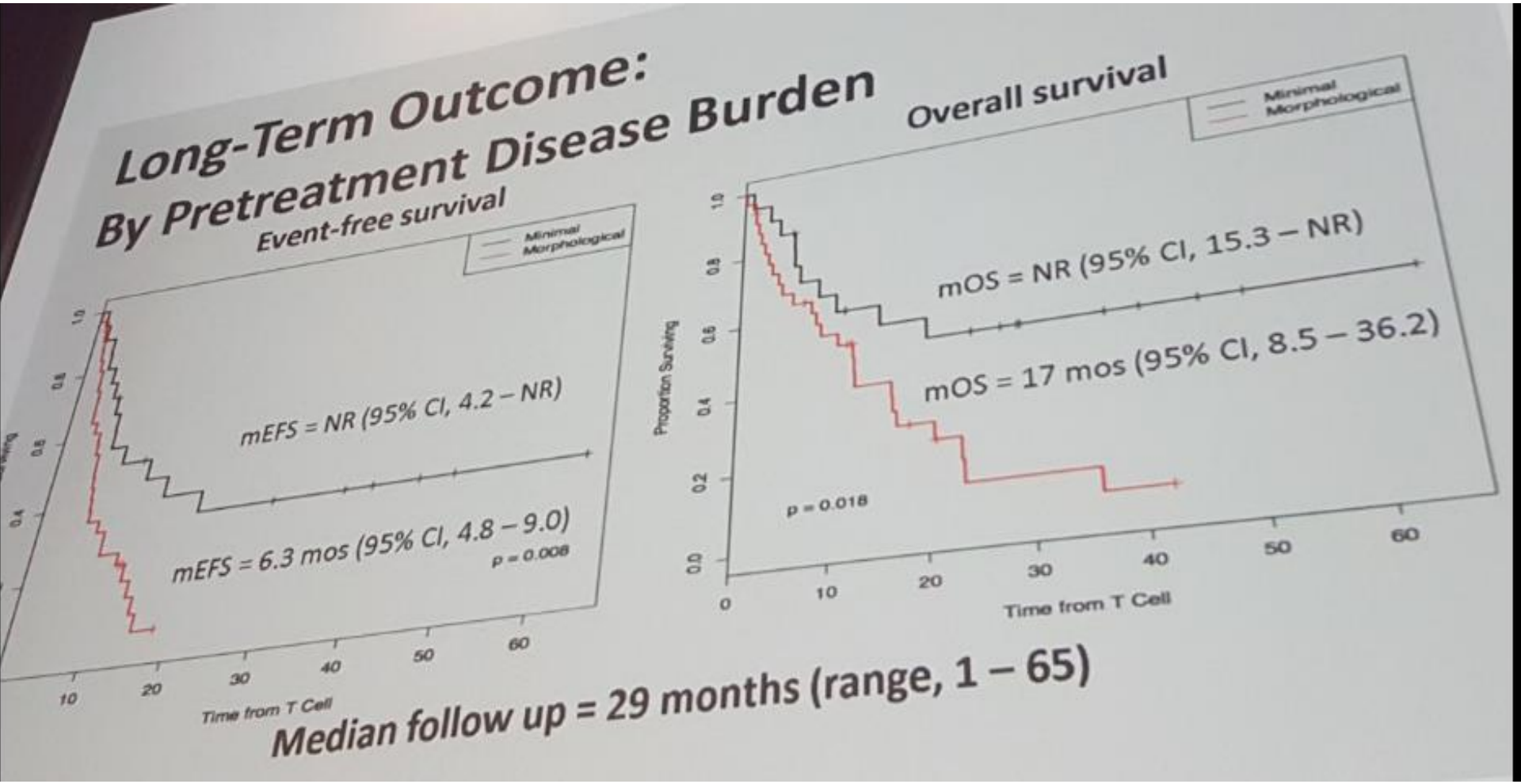
Smith E et al, abs#S479

Overall long-term outcome



Smith E et al, abs#S479

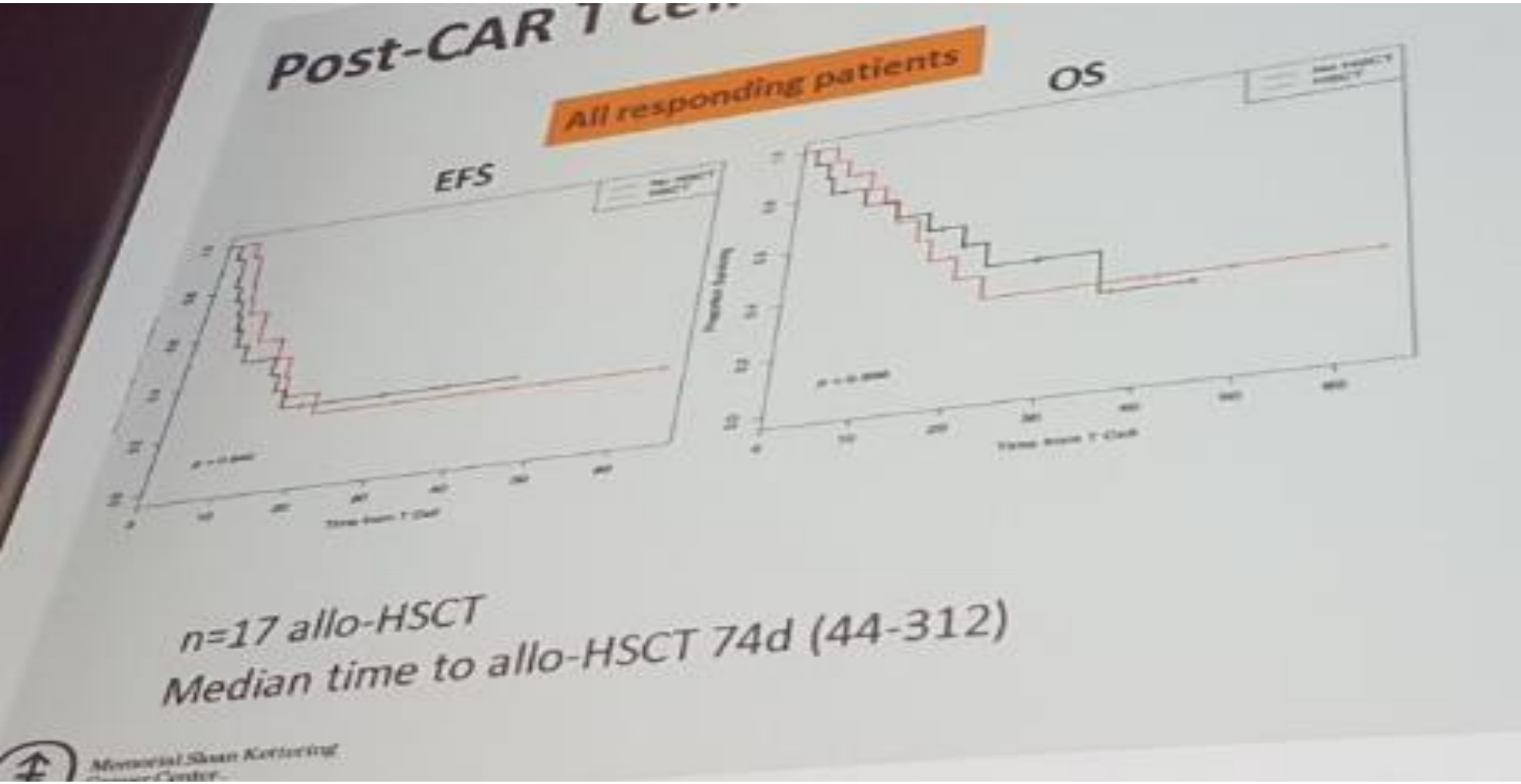
Long-term outcome by disease burden



Better outcomes in MRD+ vs morphological

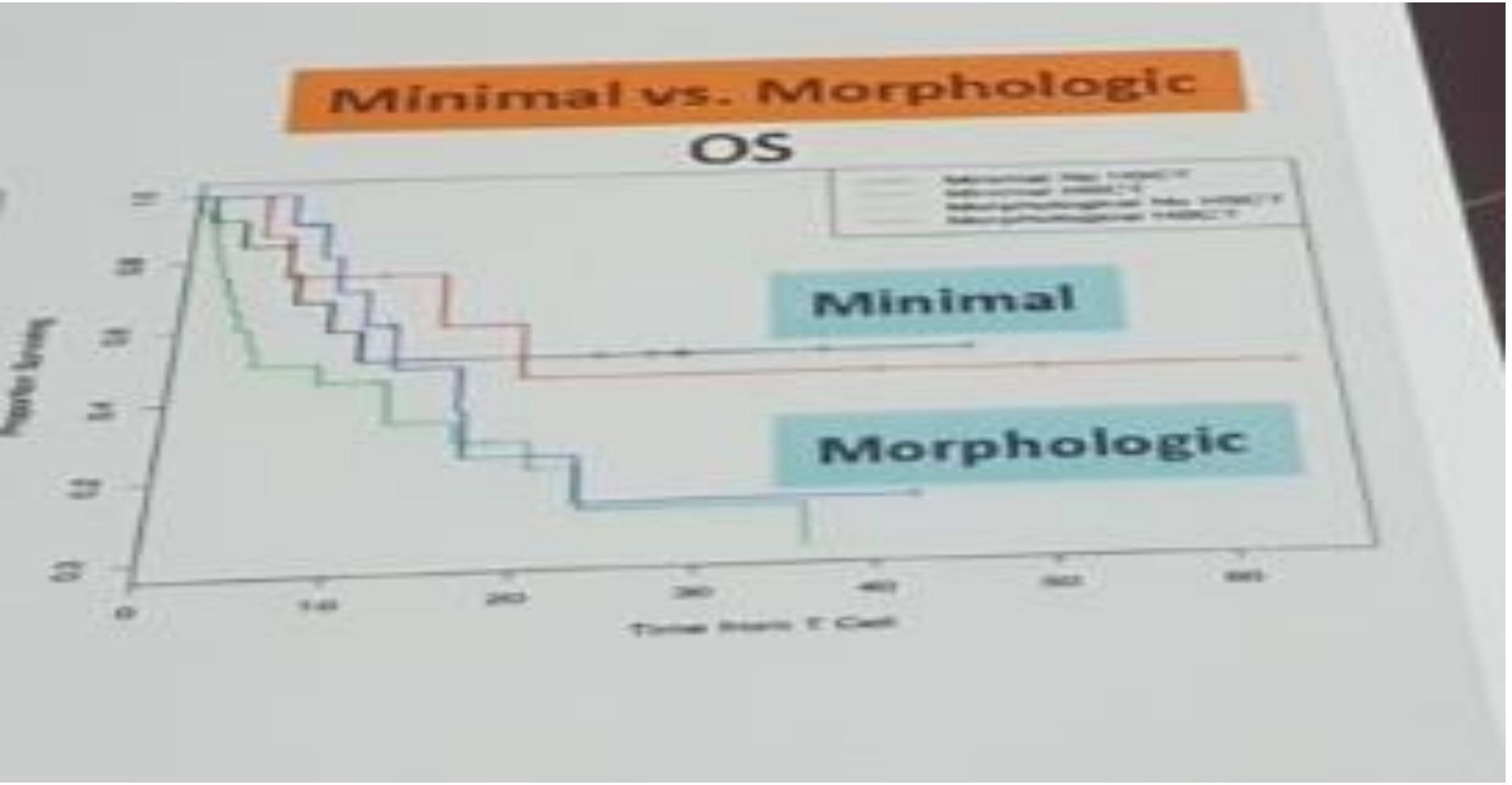
Smith E et al, abs#S479

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

Adverse events

- Cytokine release syndrome (CRS):
  - Fever
  - Hypotension
  - Respiratory insufficiency

- Neurological changes: **NO Grade 5 NTX**
  - Delirium
  - Aphasia
  - Global encephalopathy
  - Seizure-like activities/seizure

Smith E et al, abs#S479

Baseline and early post-treatment clinical and laboratory factors associated with severe neurotoxicity following 19-28z CAR T cells in adult patients with relapsed B-ALL

- **Aims**

To identify predictive parameters of neurotoxicity (NTX)

- **Population**

51 R/R patients treated with 19-28z CAR T

- **Results**

Clinical parameters:

-Correlation with disease burden (≥50% blasts)at the time of infusion

-Post-treatment ≥Gr3 CRS

-Fever

Blood parameters at day +3:

Low Plts (<60x10^9/l)

High ferritin levels

MCHC

Results

Cytokine profile at day +3:

GM-CSF

IFN

IL-2*

IL-5*

IL-10

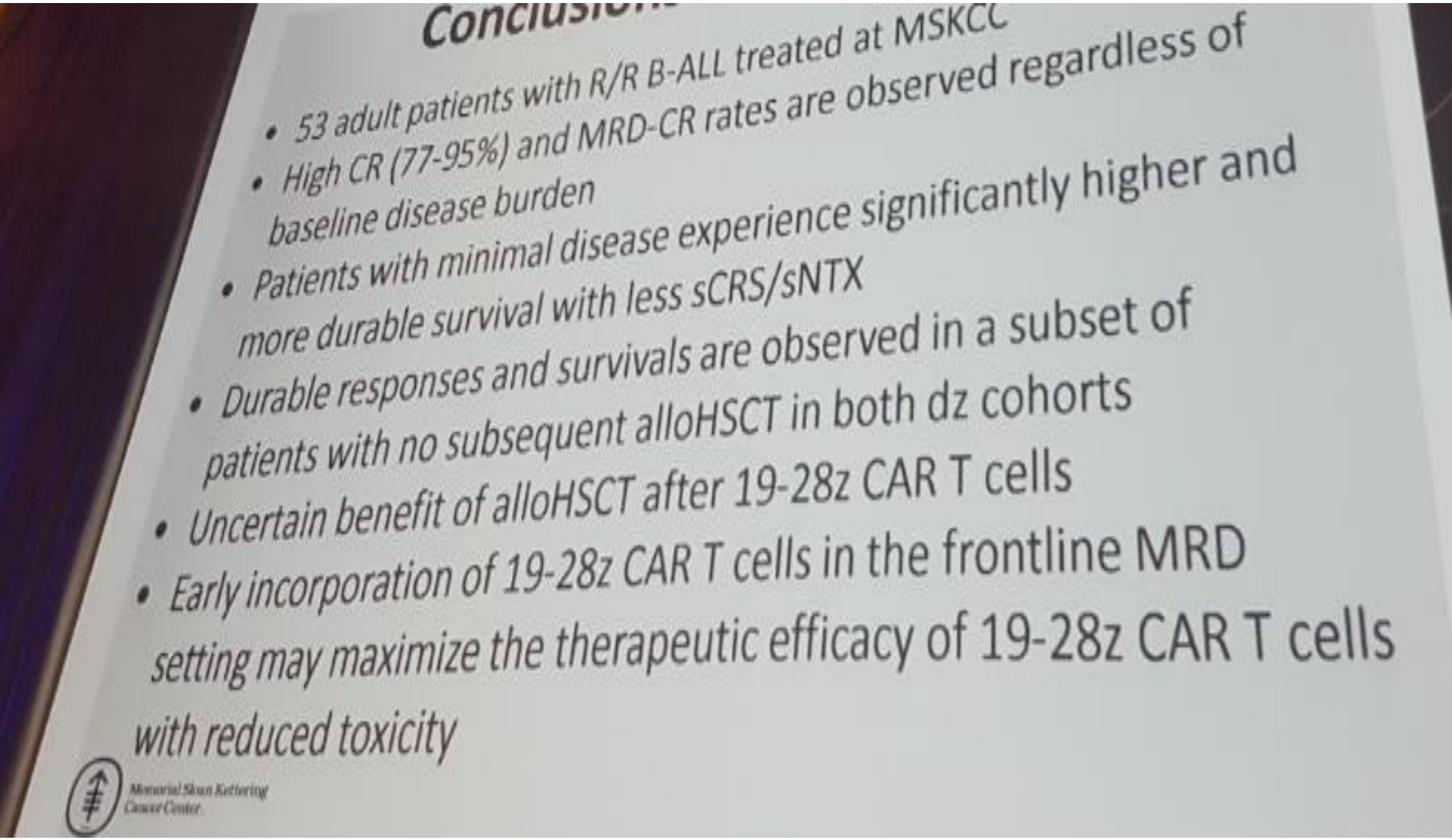
IL-15

In vivo peak CAR T expansion at day +7

Multivariate analysis revelead that baseline Plts <60 x10^9/l or MCHC>33.2% and morphologic disease (>5% blasts) has 95% sensitivity and 70% specificity of identifying NTX patients.

Park et al, abs# S143

Conclusions and perspectives



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????

Topics

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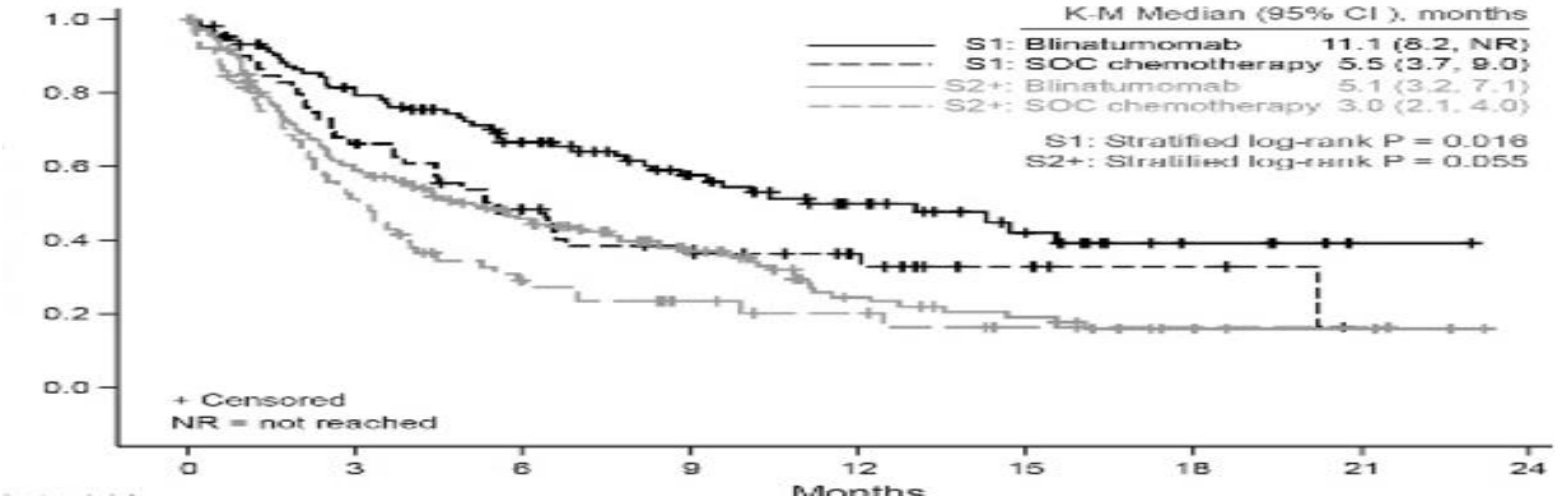
- Novel treatments:

  -focus on CAR-T

  -updates on **blinatumomab** and inotuzumab treatment

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	



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

Dombret H et al, abst#S478

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 the repertoire expansion during Blin treatment is sharper in responders.

Kotrova M et al, abs# S803

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

Inotuzumab ozogamicin in combination with low-intensity chemotherapy (mini-hyper-CVD) as frontline therapy for older patients with acute lymphoblastic leukemia: updated results from a phase I/II trial

Aims and methods

Update of previous findings in elderly.

Inotuzumab upfront + mini hyper-CVD (and rituximab).

Pts in CR after 8 cycles received POMP maintenance for 3 years.

Patients:

47, median age 68 yrs (range, 60-81), 4 already in CR at the time of enrollment.

Evaluable for response: 43.

Results

Response:

ORR: 42/43 (98%), CR: 36 (84%), CRp: 5 (12%), CRi: 1 (2%)

MRD- (6-colours FCM):

day +21: 31/41 (76%); week 12: 44/4 (96%)

Follow-up (median, range): 24, 1-55 months:

21 pts still on treatment, 3 underwent allo-SCT, 6 relapsed (13%), 16 died.

3-year CCR and OS: 72% and 54%.

Complications:

Grade ≥3 transaminase elevation: 9 pts (19%)

Hyperbilirubinemia: 8 pts (17%).

VOD: 4 pts (9%, 1 after ASCT).

Short N, et al, abst#P170

Inotuzumab and allo-SCT (I)

Aim: to identify factors associated with outcomes after allo-SCT in prev treated R/R ALL pt with InO.

Background and population: Phase 3 INO-VATE trial; InO n=77; SOC n=31

Results:

-More InO pts achieved MRD^{neg} (71%) vs control group(26%)

-Less InO group received add therapy before HSCT(14% vs 55%)

-NRM rates were higher in InO group at 1yr (36% vs 20%) and at 2yrs (39% vs 31%) but relapse rate were lower both at 1yr (23% vs 29%) and 2yrs (33% vs 46%)

-No significant difference in post allo-SCT survival observed among groups.

VOD observed in 5 pts (all during the first 100 days after allo-SCT) InO and 0 in SOC group.

Conclusions:

- Compared with the SOC, InO permitted more pts with R/R ALL to proceed to allo-SCT in CR/Cri with MRDneg
- In order to reduce NRM and improve OS avoid dual alkylator conditionings regimens, especially those containing Thiotepa.

Stellijesn et al, abs#P525

Inotuzumab and allo-SCT (II)

- **Aim**: to Investigate transplant outcomes for pts with or without InO exposure.
- **Method**: Nested control comparison of pts transplanted during the year in which they recived InO.
- **Population**: 251 pts with B-ALL(median age 35yr;range 4-70) who received allo-SCT
- **Results**:
  - VOD: 21 pts (8%); median onset 19 days following allo-SCT;
  - Fatal VOD :in 5 overall pts (2%),

Factors contributing to VOD

- Prior exposure to InO(HR 3.05, 95% C.I. 1.3-7.2, p=0.01)
- Receiving a busulfan-based transplant preparative regimen(HR 3.4, 95% C.I. 1.02-12, p=0.05).

Protective factors to VOD

- Not receiving a prior SCT(HR 0.3, 95% C.I. 0.1-0.8, p=0.02).

Classification and regression tree analysis show that the combination of InO and a double alkylator preparative regimen was significantly associated with VOD(HR 5.9, 95% C.I. 1.9-18, p=0.002).

Kebriaei et al, abs #P739

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?