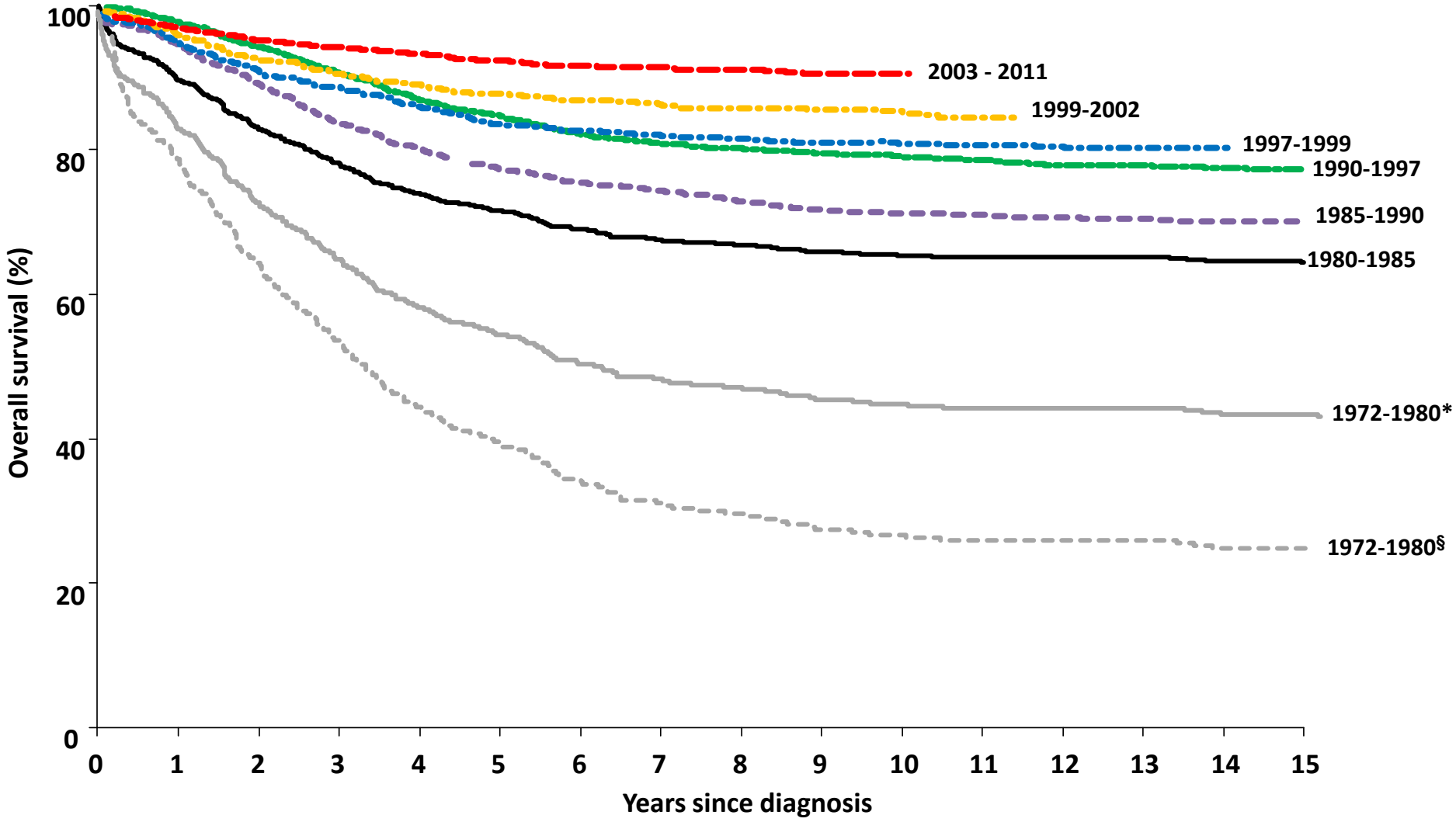
De-escalation of chemotherapy for children and young persons with ALL

Ajay Vora

Great Ormond Street Hospital

London

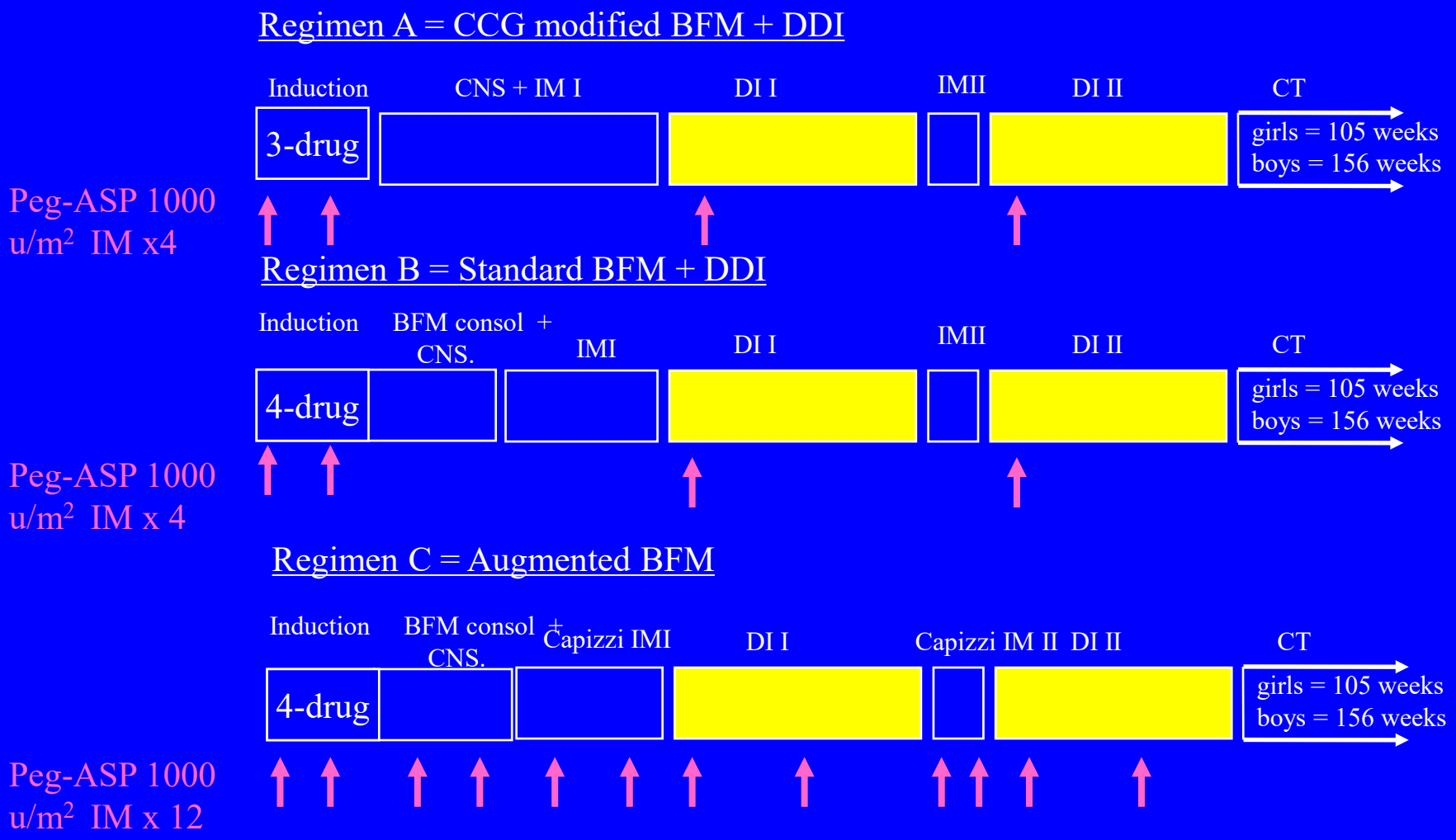
Improvements in overall survival for successive UK childhood ALL trials



BJH 2020

UKALL 2003 treatment regimens

Dex 6 mg/m^2



UKALL 2003 treatment regimens

Dex 6 mg/m^2

De-escalation – Why?

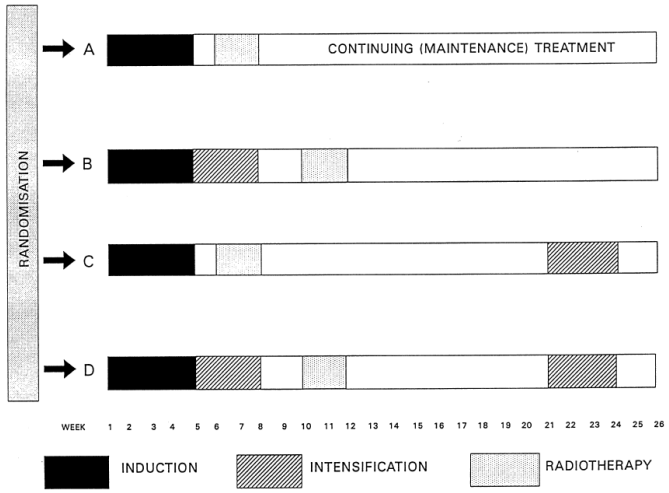
Over-treatment

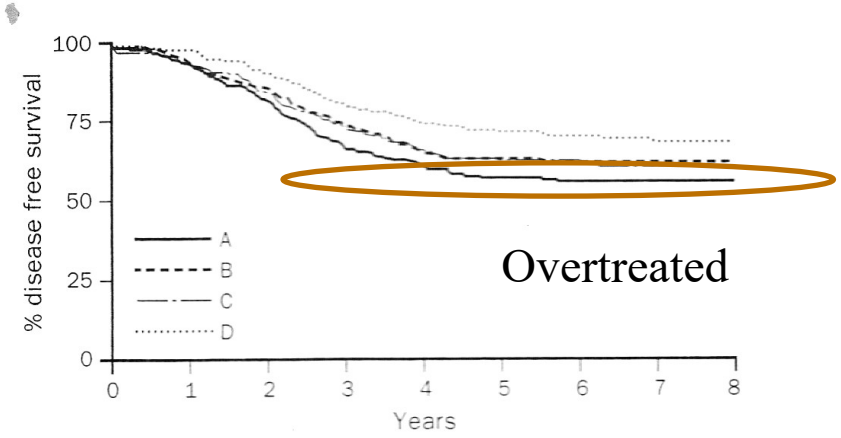
Mortality, morbidity and QOL

Burden of care

Overtreatment
UKALL X (1982 – 86)

Chessells et al, Lancet. 1995;345:143-148

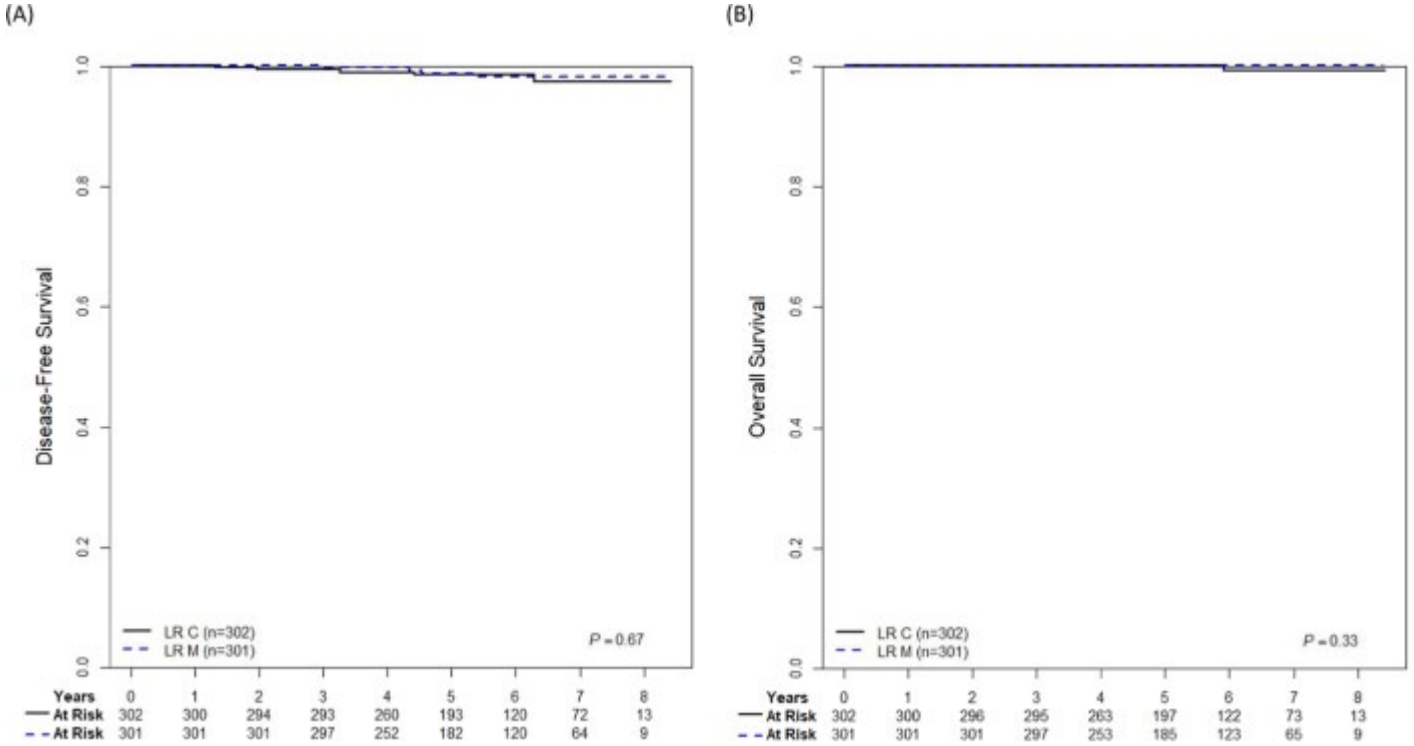




Group	N	O	O/E	5 yr disease-free survival (%)
A	291	124	1.3	57% (50.9–62.7)
B	293	109	1.0	62% (56.6–68.0)
C	294	111	1.0	61% (55.7–67.1)
D	293	86	0.8	71% (65.5–76.1)

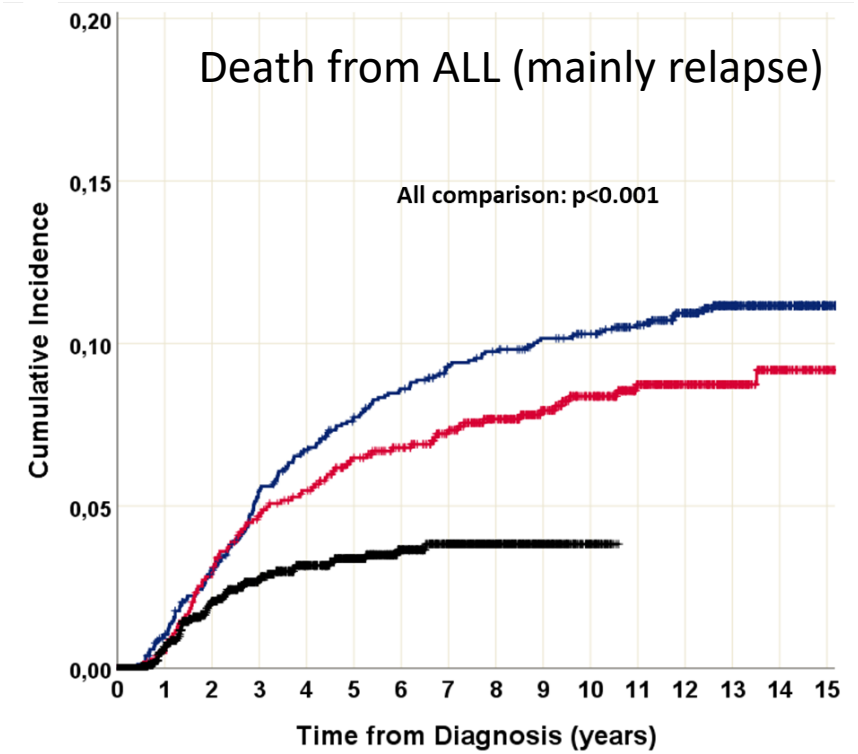
Figure 4: **Comparison of disease-free survival in four randomised treatment arms**

Schore, R.J., Angiolillo, A.L., Kairalla, J.A. *et al.* Correction: Outstanding outcomes with two low intensity regimens in children with low-risk B-ALL: a report from COG AALL0932. *Leukemia* **37**, 1406 (2023).

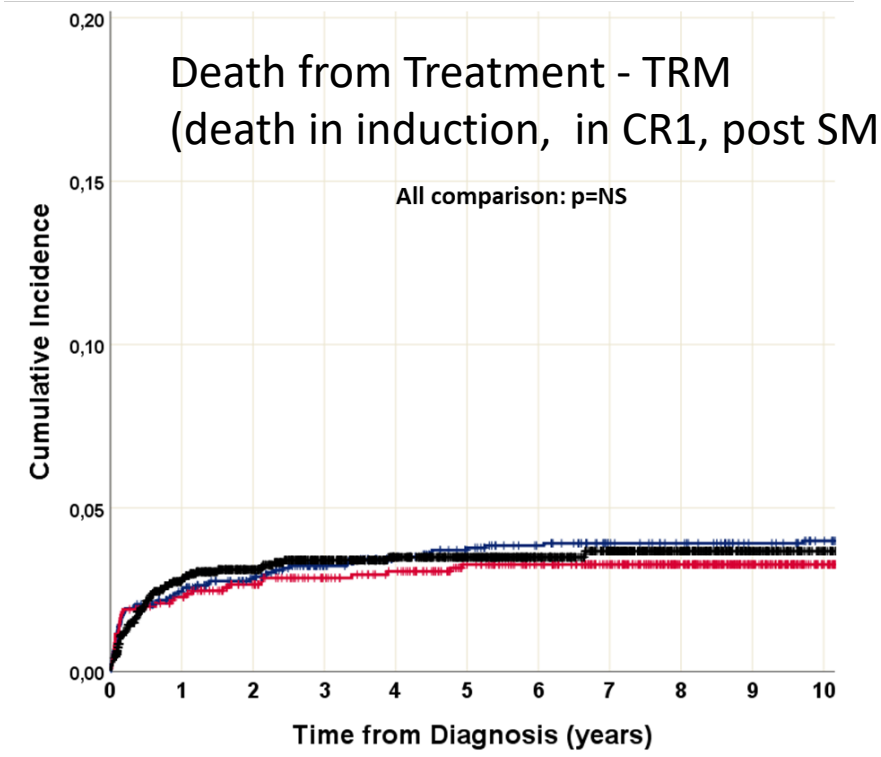


Death Due to disease is now similar to TRM

NOPHO ALL-2008 patients vs 92- and 2000-, 1-15 years at Dx



Cohort	Total n	DoD	noDoD	pDoD (5yr)	pDoD (10 yr)
92	1561	169	1392	0.077	0.103
2000	1056	85	971	0.065	0.084
2008	1936	51	1885	0.032	0.038



Cohort	Total n	TRM	noTRM	pTRM (5yr)	pTRM (10 yr)
92	1561	65	1496	0.038	0.040
2000	1056	35	1021	0.033	0.033
2008	1936	62	1874	0.035	0.037

Death from disease has decreased over time – TRM has changed little

ALL is (nowadays) an unusual diagnosis in paediatric oncology: death from disease ≈ death from therapy ≈ 4%

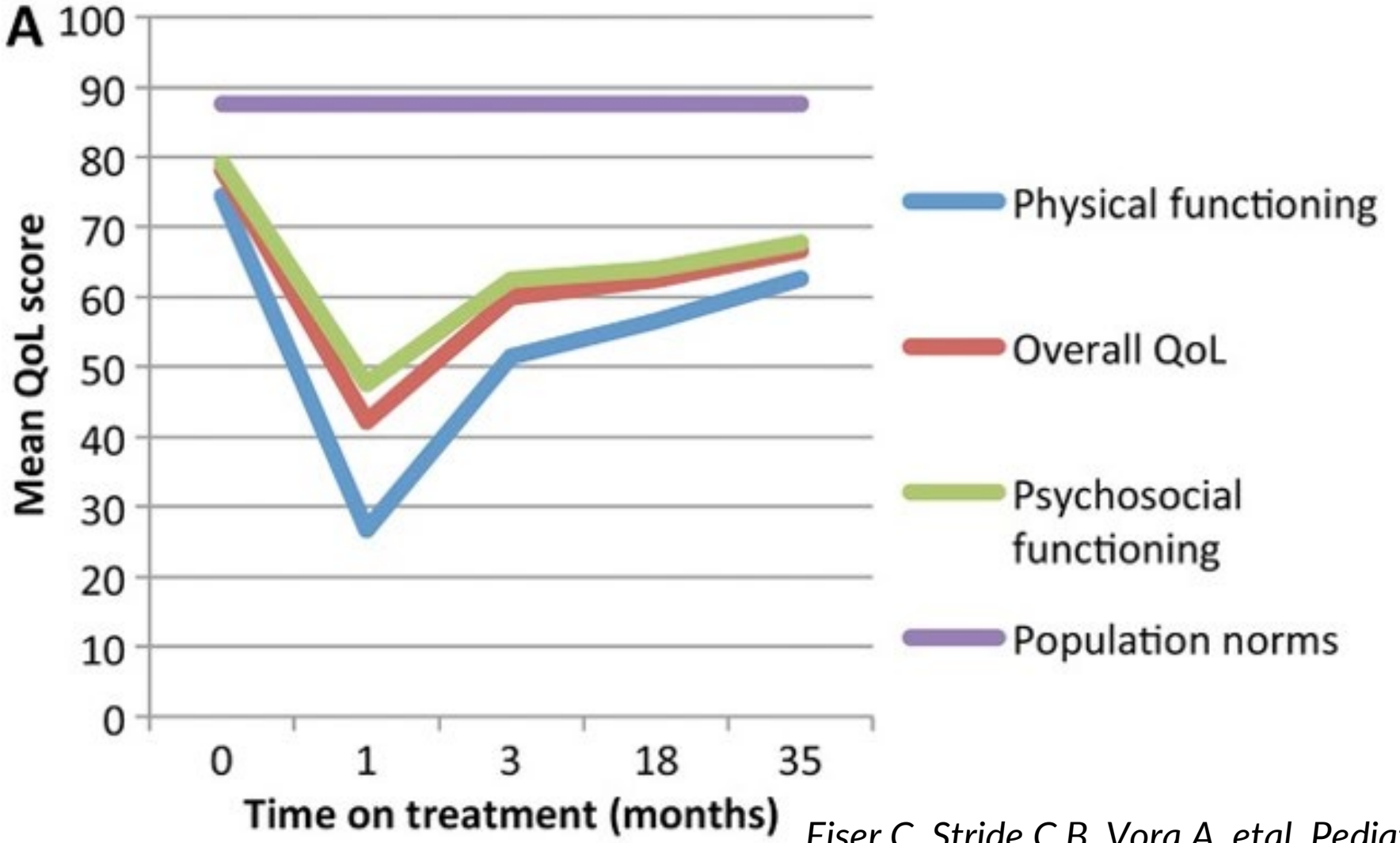
Patients ≥15-45 years ≈ 20%

Patients ≥15-45 years ≈ 8%

UKALL 2003
Serious Adverse Events

Risk Group	All patients (%)	Reg A (%)	Reg B (%)	Reg C (%)	p-value (Reg C vs A/B)
Any infection	307 (13.3)	134 (11.1)	98 (17.5)	75 (14.0)	0.63
Fungal infection	81 (3.5)	25 (2.1)	35 (6.2)	21 (3.9)	0.58
Encephalopathy (excluding seizure)	164 (7.1)	43 (3.6)	58 (10.4)	63 (11.7)	**<0.0001**
Asparaginase Hypersensitivity	47 (2.0)	4 (0.3)	3 (0.5)	40 (7.4)	**<0.0001**
Pancreatitis	33 (1.4)	9 (0.7)	8 (1.4)	16 (3.0)	**0.0006**
Osteonecrosis	88 (3.8)	9 (0.7)	52 (9.3)	27 (5.0)	**0.097**
Thrombosis	51 (2.2)	20 (1.7)	15 (2.7)	16 (3.0)	0.17
CNS Thrombosis	31 (1.3)	12 (1.0)	10 (1.8)	9 (1.67)	0.45
Number in risk groups	2300	1203	560	537	

UKALL 2003 QOL



Eiser C, Stride C B, Vora A, etal. Pediatr Blood Cancer. 2017;64:e26615.

De-escalation:How?

Better risk stratification

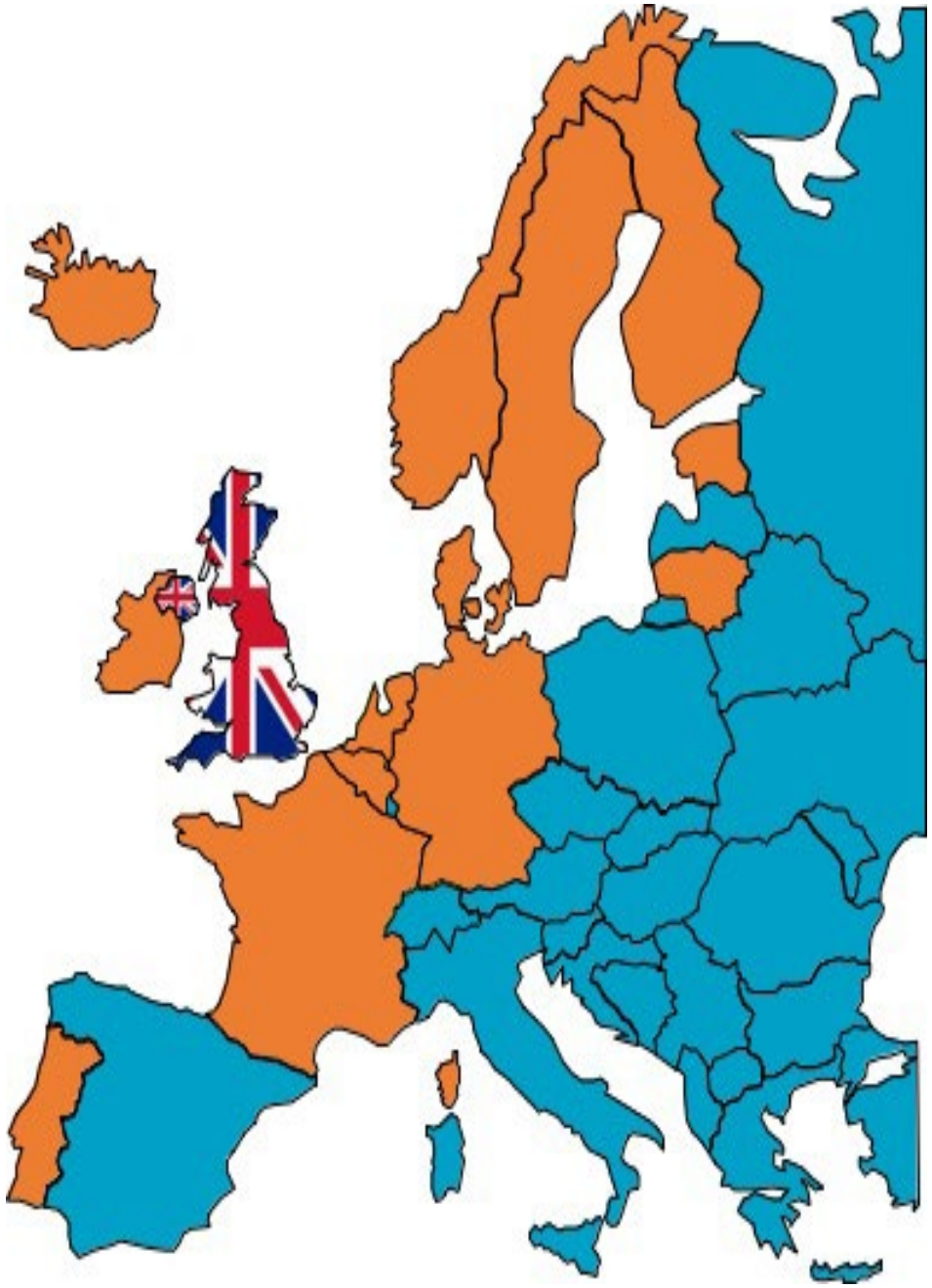
New agents

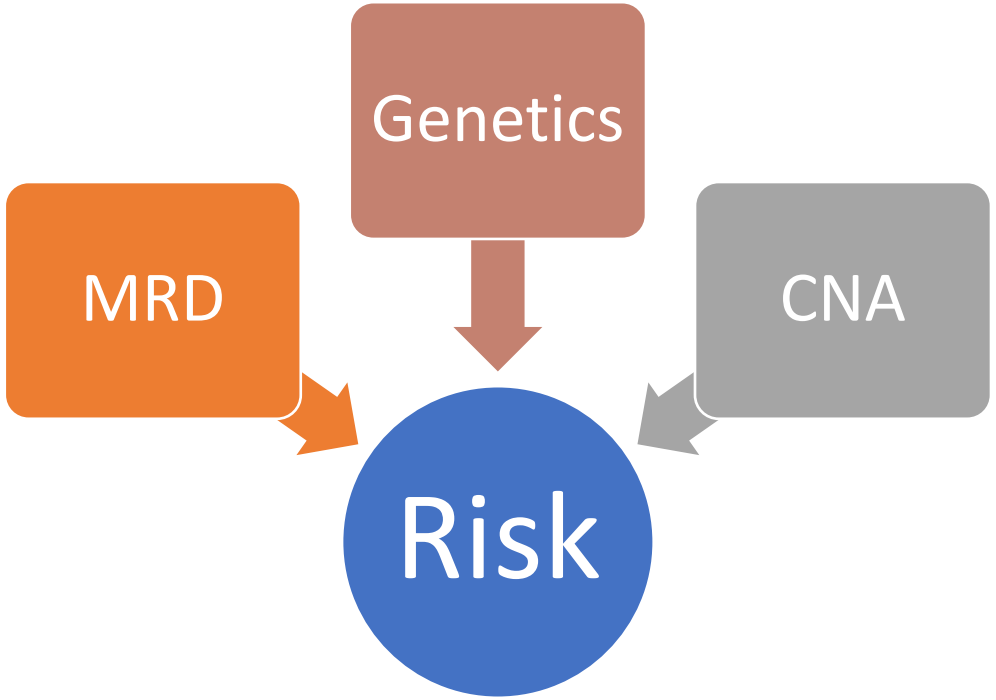
End-point Overall survival >EFS

The ALLTogether Consortium

More than 1400 patients per year from 14 countries

Age 1-45 (1-24 in the UK)





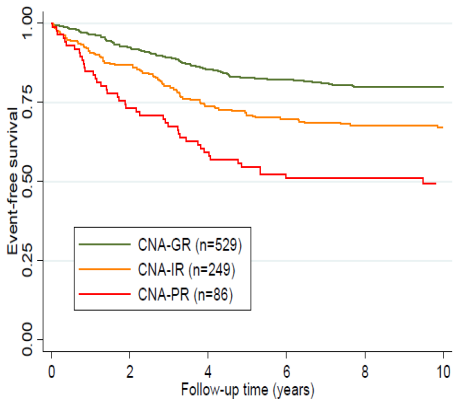
ALLTogether
Risk
Stratification

Copy number alteration (CNA) classifier

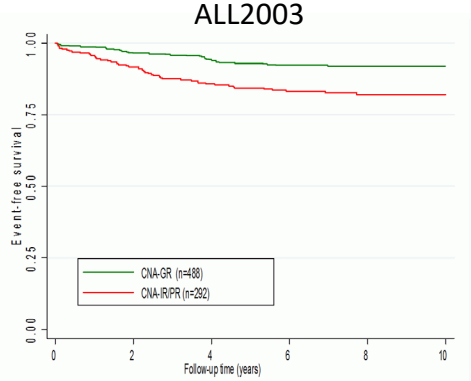
Integrating CNA + cytogenetics

CNA profile defines risk groups

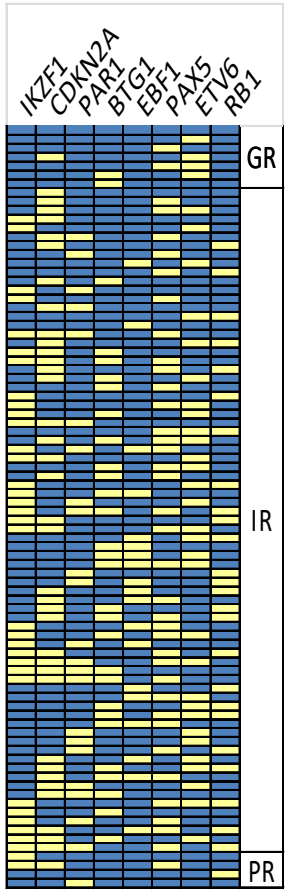
ALL97/99



ALL2003



CNA profiles defined by MLPA P335 kit



Good risk
- No deletion
- Isolated deletion of *ETV6, PAX5*, or *BTG1*
- *ETV6* deletion + *BTG1, CDKN2A/B* or *PAX5 deletion*

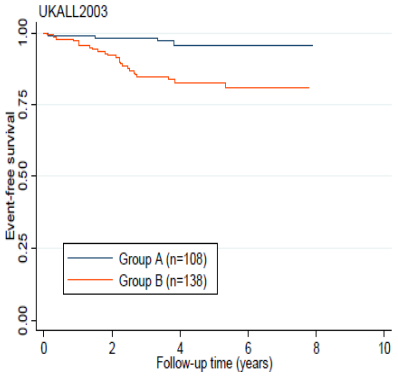
Intermediate risk
- All other CNA profiles

Poor risk
- Isolated *IKZF1, PAR1* or *RB1* deletion
- Deletion of *IKZF1/PAX5/CDKN2A/B*

Defines genetic risk group

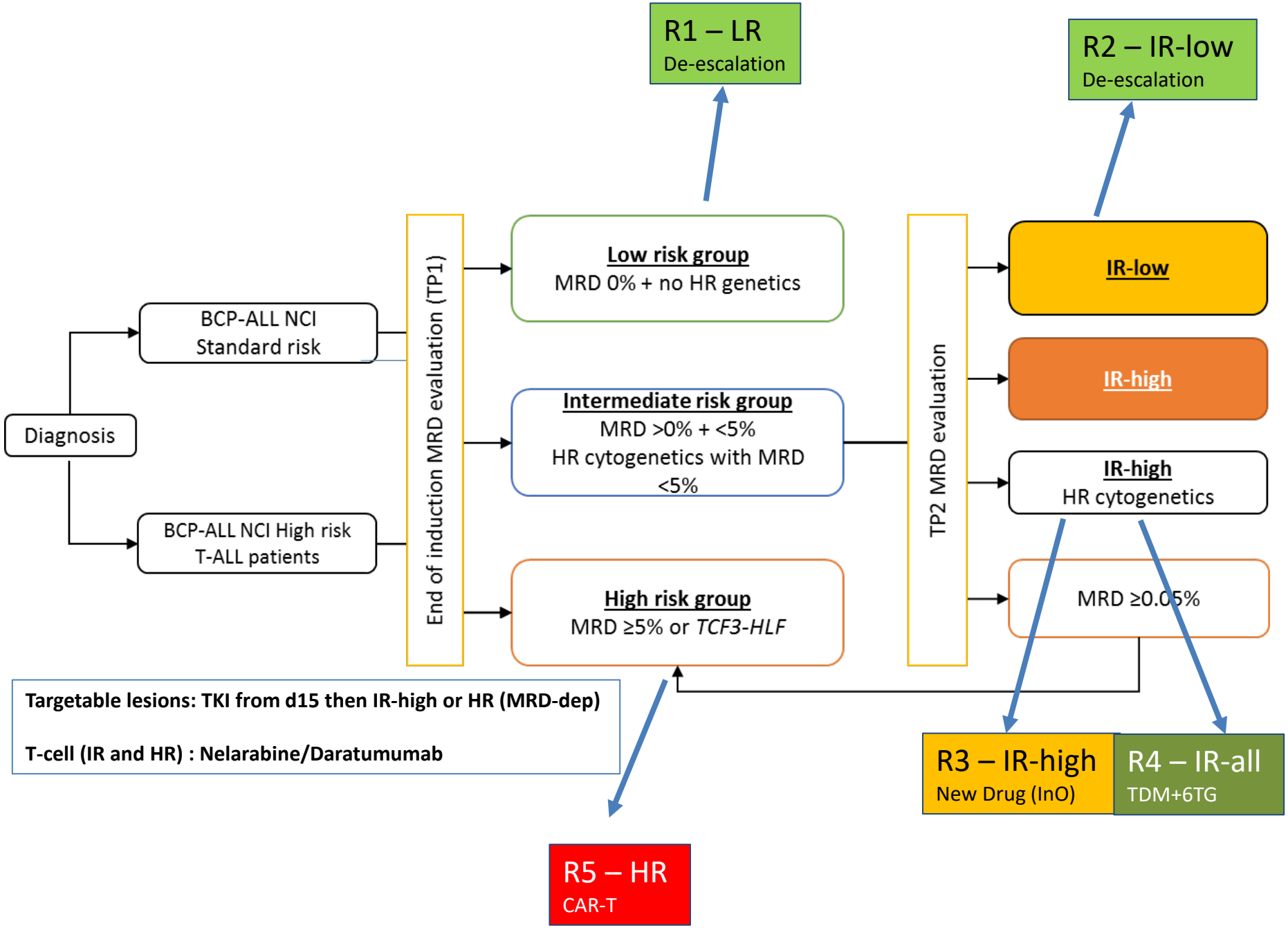
Risk	Cytogenetic: Good	Cytogenetic: Inter	Cytogenetic: High
CNA: Good			
CNA: Inter			
CNA: Poor			

Segregates B-other ALL



Moorman et al (2014) Blood 124:1434

Risk group	% patients	EFS%	OS%	RR%	% of relapses	% of all events
VLR	21.9	95	99	3.7	10	10
IR-L	36.2	94	98	2.8	12.5	20
IR-H	38.9	82	89	15	72	64
VHR	3.0	78	78	14	5	6


R1 – LR
De-escalation
R2 – IR-low
De-escalation
Diagnosis
BCP-ALL NCI
Standard risk
BCP-ALL NCI High risk
T-ALL patients
End of induction MRD evaluation (TP1)
Low risk group
MRD 0% + no HR genetics
Intermediate risk group
MRD >0% + <5%
HR cytogenetics with MRD <5%
High risk group
MRD ≥5% or TCF3-HLF
TP2 MRD evaluation
IR-low
IR-high
IR-high
HR cytogenetics
MRD ≥0.05%
Targetable lesions: TKI from d15 then IR-high or HR (MRD-dep)
T-cell (IR and HR) : Nelarabine/Daratumumab
R3 – IR-high
New Drug (InO)
R4 – IR-all
TDM+6TG
R5 – HR
CAR-T

Drugs Active in Lymphoid Malignancies

- Aminopterin (Methotrexate)1948
- Cortisone 1952
- Mercaptopurine 1953
- Cyclophosphamide 1959
- Vincristine 1963
- Asparaginase 1967
- Daunorubicin 1968
- Cytarabine 1968
- Etoposide/Teniposide 1970

Paediatrics and Child Health, 26 (2), 51-56.

New agents

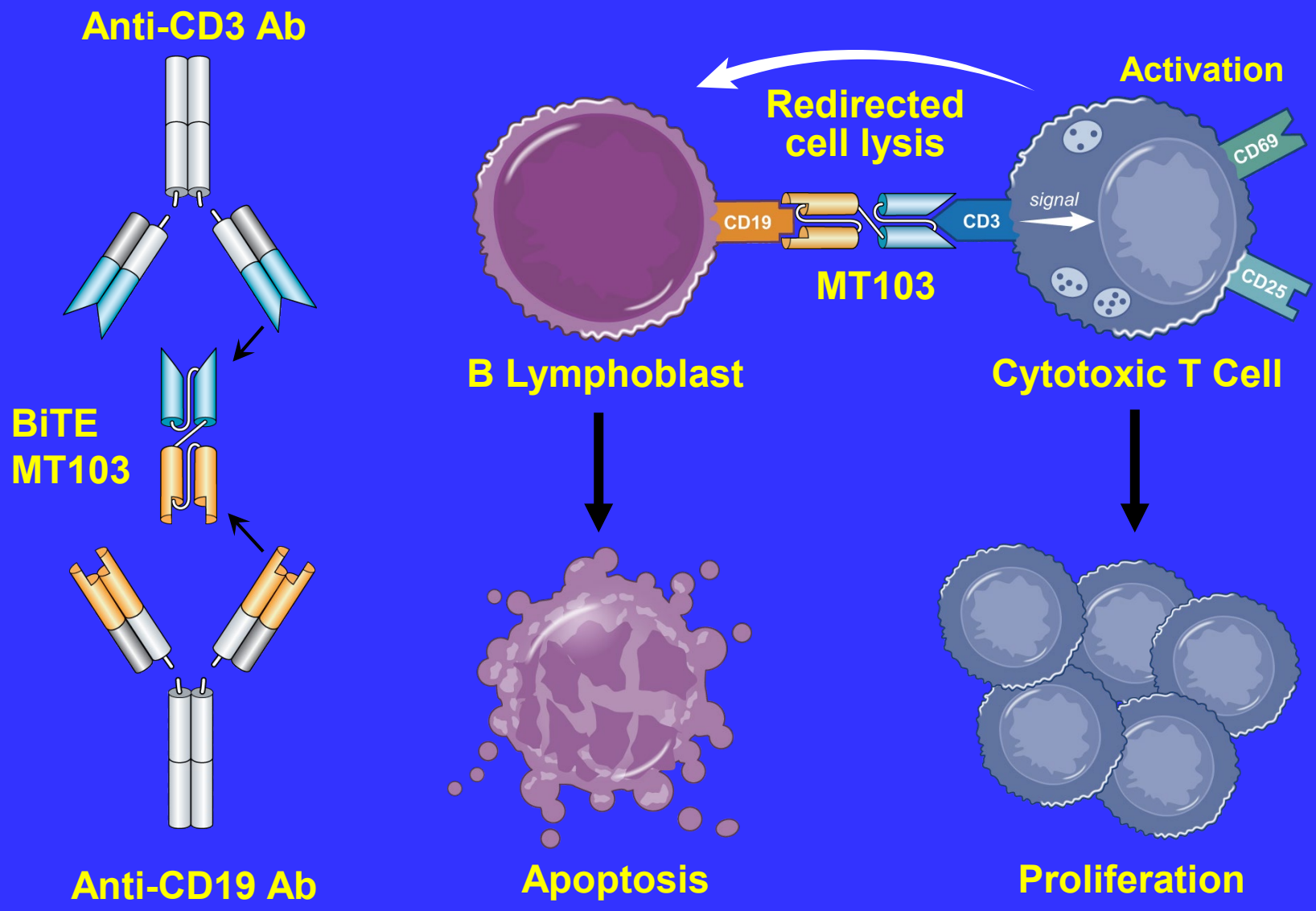
TKIs

Targeted chemotherapy - Inotuzumab

Immune therapy – Blinatumomab, CART

Potential: Daratumumab, JAK/STAT/Menin inhibitors

Blinatumomab- A bispecific T Cell-Engaging BiTE Antibody



Half-life < 2 hours

Licence indications

- Relapse (Ph-neg)
- Primary refractory/resistant disease – MRD ≥ 0.1% (Ph – pos and neg)

Children's Cancer and Leukaemia Group | the EXPERTS in CHILDHOOD CANCER

Guidelines for Blinatumomab in Upfront Acute Lymphoblastic Leukaemia

Authors: Sujith Samarasinghe, Lamia Samin, Caroline Osborne, Danny Cheng, John Moppett and Ajay Vora

Serious toxicity during induction/consolidation which in a clinical significant manner precludes timely delivery of further chemotherapy or requires a global reduction in chemotherapy dosage. Alternatively consider in patients who are at high risk of chemotherapy toxicity due to co-morbidities.

Hodder et al JCO 2023

Blinatumomab for chemotherapy intolerance or resistance

Chemotherapy group: 85 patients	
Indication	Detail
Severe toxicity (n=53)	18 sepsis (6=G3, 12=G4), the majority (n=11) of whom required intensive care
	13 invasive fungal infection (6=G3, 7=G4), including CNS (n=2), pulmonary mucormycosis (n=1) and biopsy proven disseminated aspergillus (n=4)
	7 severe pancreatitis (5=G3, 2=G4), associated with typhlitis (n=4).
	7 severe typhlitis (3=G3, 4=G4) requiring ileostomy (n=2) or TPN (n=2)
	3 Grade 3/4 encephalopathy)
	2 G3 CNS thrombosis
	2 G4 Liver failure requiring intensive care
	1 G4 CNS haemorrhage
Comorbidities (n=16)	8 Down Syndrome
	2 Li-Fraumeni
	6 others* (Bloom syndrome, Overgrowth syndrome with PIK3CA mutation, Rett syndrome, Schimke immuno-osseous dysplasia, 7q11.21-23 duplication, 11q duplication)
EOC MRD>0.05% (n=10)	Not suitable for HSCT due to poor patient performance status, co-morbidities or lack of suitable donor
Persistent MRD + HR cyto (n=5)	2 PH+
	2 KMT2A
	1 Near haploid
Jehovah's witness (n=1)	Refused blood products

HSCT group: 20 patients	
Indication	Detail
Refractory post-consolidation (n=17)	6 MRD >5%,
	4 MRD 1-5%
	7 MRD 0.05-1%
Refractory post-induction (n=2)	1 Ph+ ALL and 1 Ph-like ALL with MRD>5%
Pre-existing condition (n=1)	Immunodeficiency syndrome (Omenn syndrome) requiring further HSCT[28]

Hodder et al JCO 2023

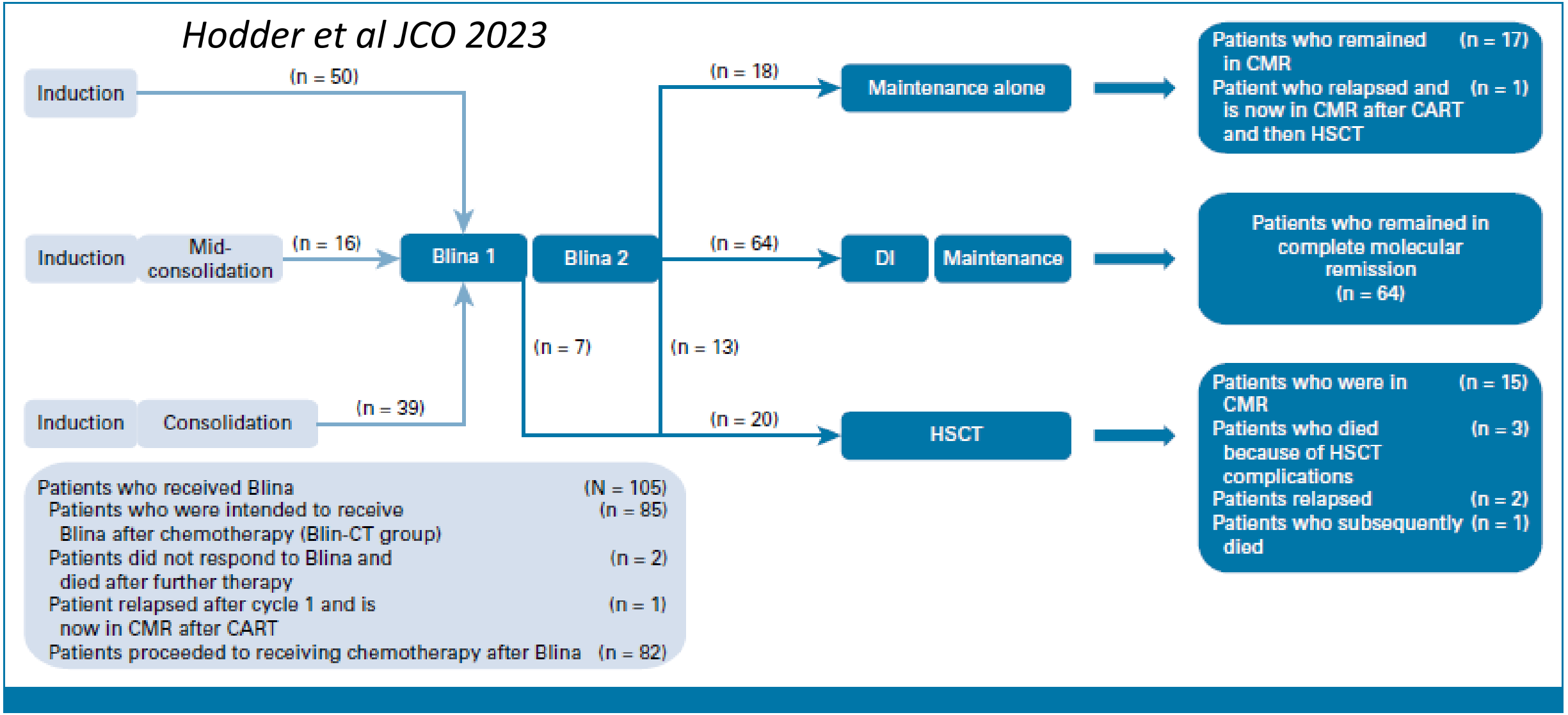
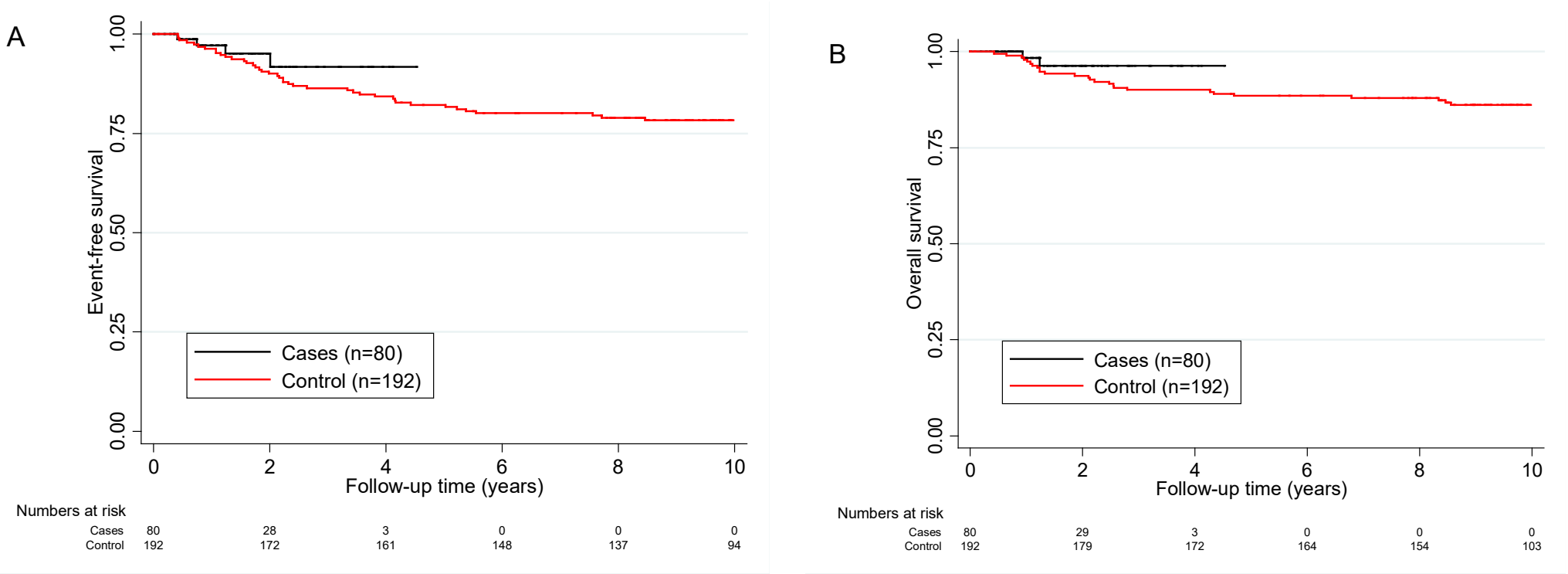


FIG 1. CONSORT diagram: patients started Blina at the end of induction, mid-consolidation, or the end of consolidation and as bridge to HSCT or continuing chemotherapy. Blina, blinatumomab; Blin-CT, blinatumomab chemotherapy; CART, chimeric antigen receptor T-cell therapy; CMR, complete molecular remission; DI, delayed intensification; HSCT, hematopoietic stem-cell transplant.

Hodder et al JCO 2023

Figure 2 – Event-free (A) and overall (B) survival of Blin-CT matched cohort compared to UKALL 2003 controls



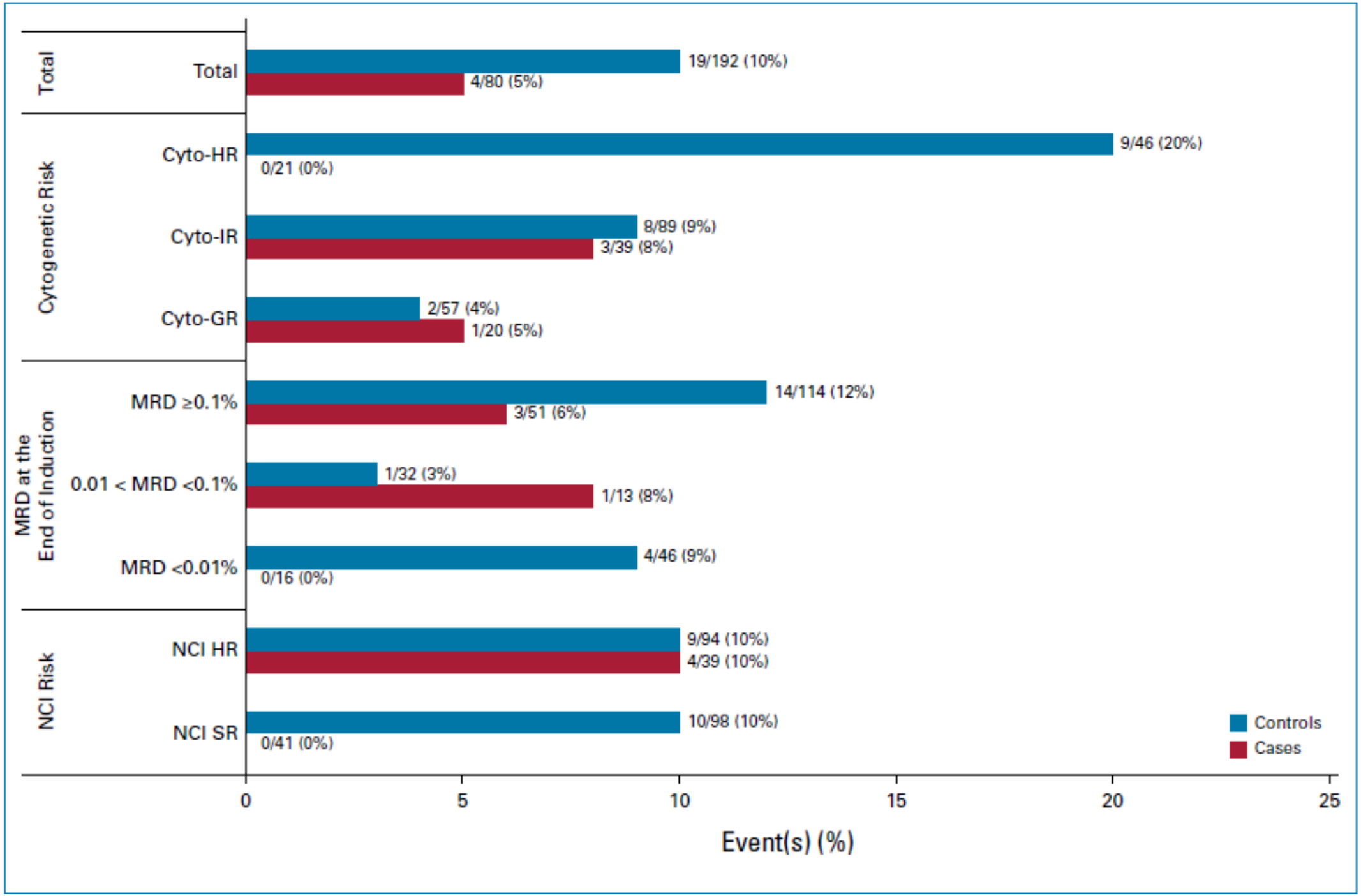

Total
Total
19/192 (10%)
4/80 (5%)
Cytogenetic Risk
Cyto-HR
9/46 (20%)
0/21 (0%)
Cyto-IR
8/89 (9%)
3/39 (8%)
Cyto-GR
2/57 (4%)
1/20 (5%)
MRD at the End of Induction
MRD ≥0.1%
14/114 (12%)
3/51 (6%)
0.01 < MRD <0.1%
1/32 (3%)
1/13 (8%)
MRD <0.01%
4/46 (9%)
0/16 (0%)
NCI Risk
NCI HR
9/94 (10%)
4/39 (10%)
NCI SR
10/98 (10%)
0/41 (0%)
Controls
Cases
0
5
10
15
20
25
Event(s) (%)

Table 3 – Outcome of patients with an indication for HSCT by intervention

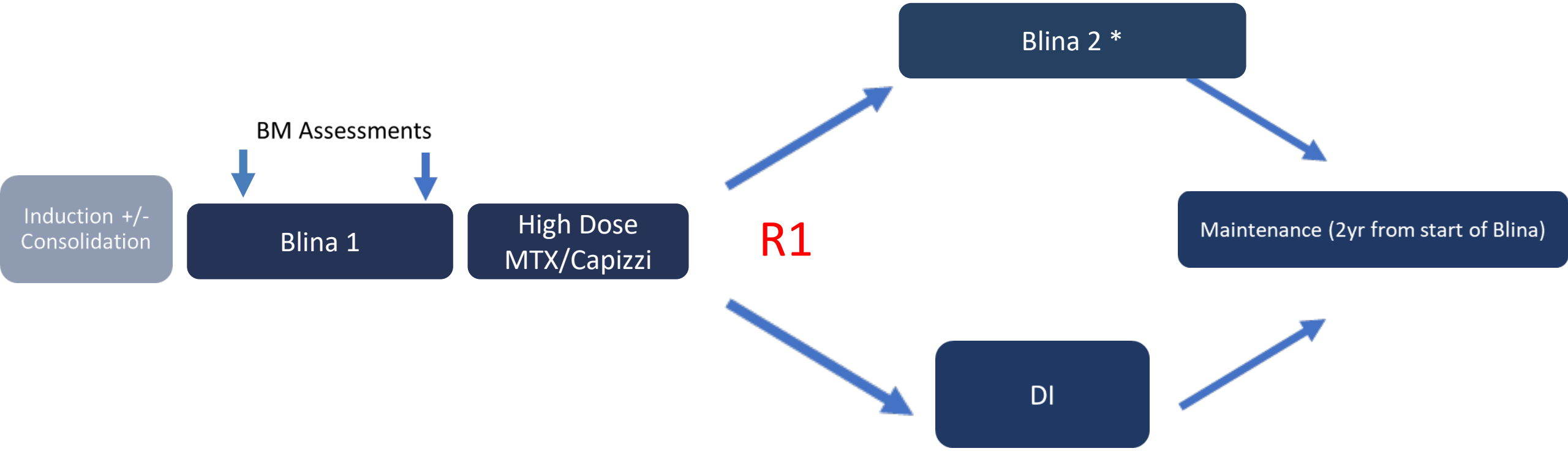
Hodder et al JCO 2023

	HSCT	Chemotherapy
Number of patients	20	12 (EOC MRD >0.05%)
Events	5 (3 died due to TRM, 2 relapsed of whom 1 died)	0
Median follow up	26 months	26 months

HSCT = haematopoietic stem cell transplant; EOC= end of consolidation; TRM = treatment related mortality.

Randomise Blinatumomab vs Delayed Intensificatior

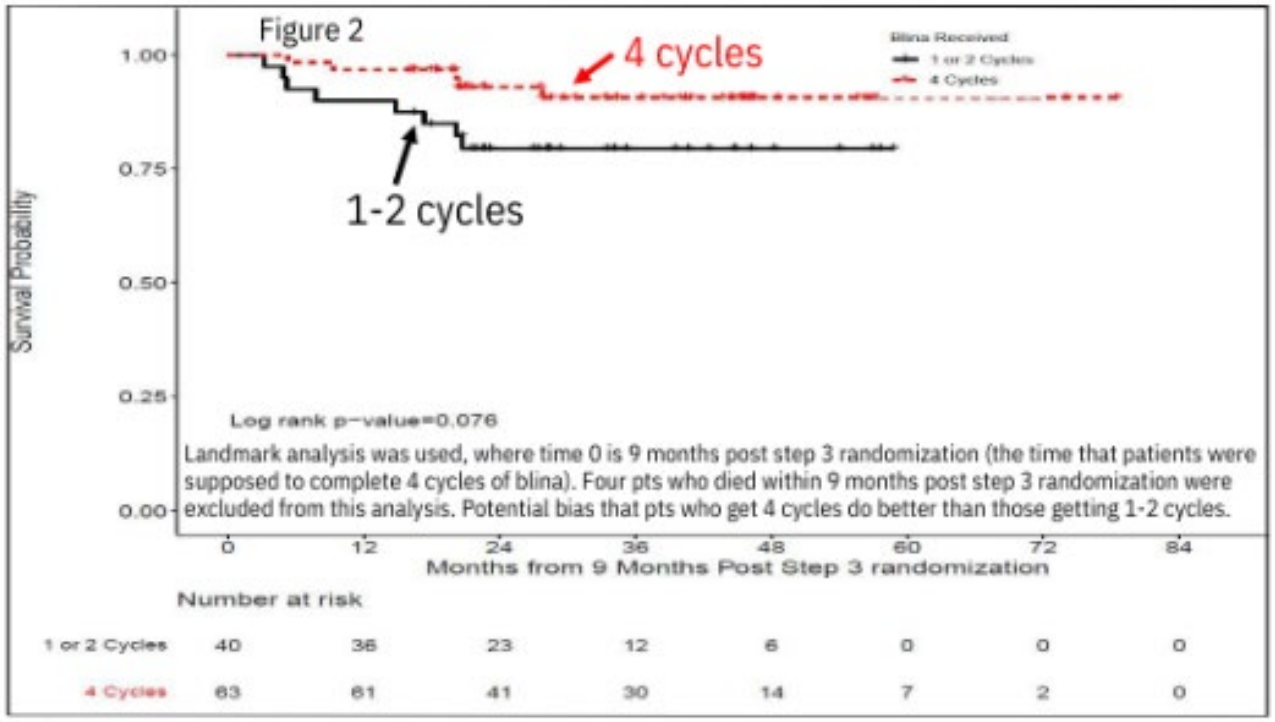
ALL patients to Get 1 Blina Consolidation Cycle



*SR/IR low (2/3 of patients) - 1 Blina Cycles Randomise 1 x 2 Cycles

*IR High Risk (1/3 of patients) -3 Blina Cycles Randomise 1 x 4 Cycles

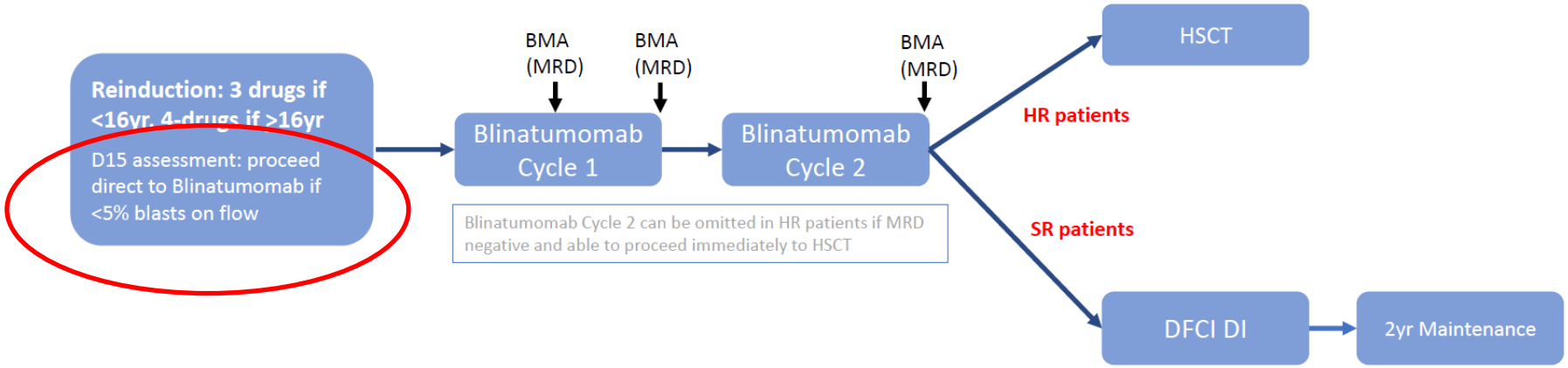
ECOG ARCIN: 4 Cycles of Blina potentially better than 1-2



Luger et al ASH Abstracts 2023

2877 Assessment of Outcomes of Consolidation Therapy By Number of Cycles of Blinatumomab Received in Newly Diagnosed Measurable Residual Disease Negative Patients with B-Lineage Acute Lymphoblastic Leukemia: In the ECOG-ACRIN E1910 Randomized Phase III National Clinical Trials Network Trial

UK Relapse Strategy



- High risk defined as all very early/early relapses and/or high risk cytogenetics.
- Standard risk defined as all late relapses without high risk cytogenetics.
- Early CART was available if failed reinduction (disease >25%) or if they were HR without a suitable donor.

UK Reduced Intensity Induction compared to COG AALL1331: Reduced Intensity Induction leads to Reduced TRM and improved MRD responses

Strict Definition ie. Death within first 28 days

- COG 16 (2.4%) vs. UK 0, p=0.09

Wider Definition ie. Death within 2 weeks of completing induction

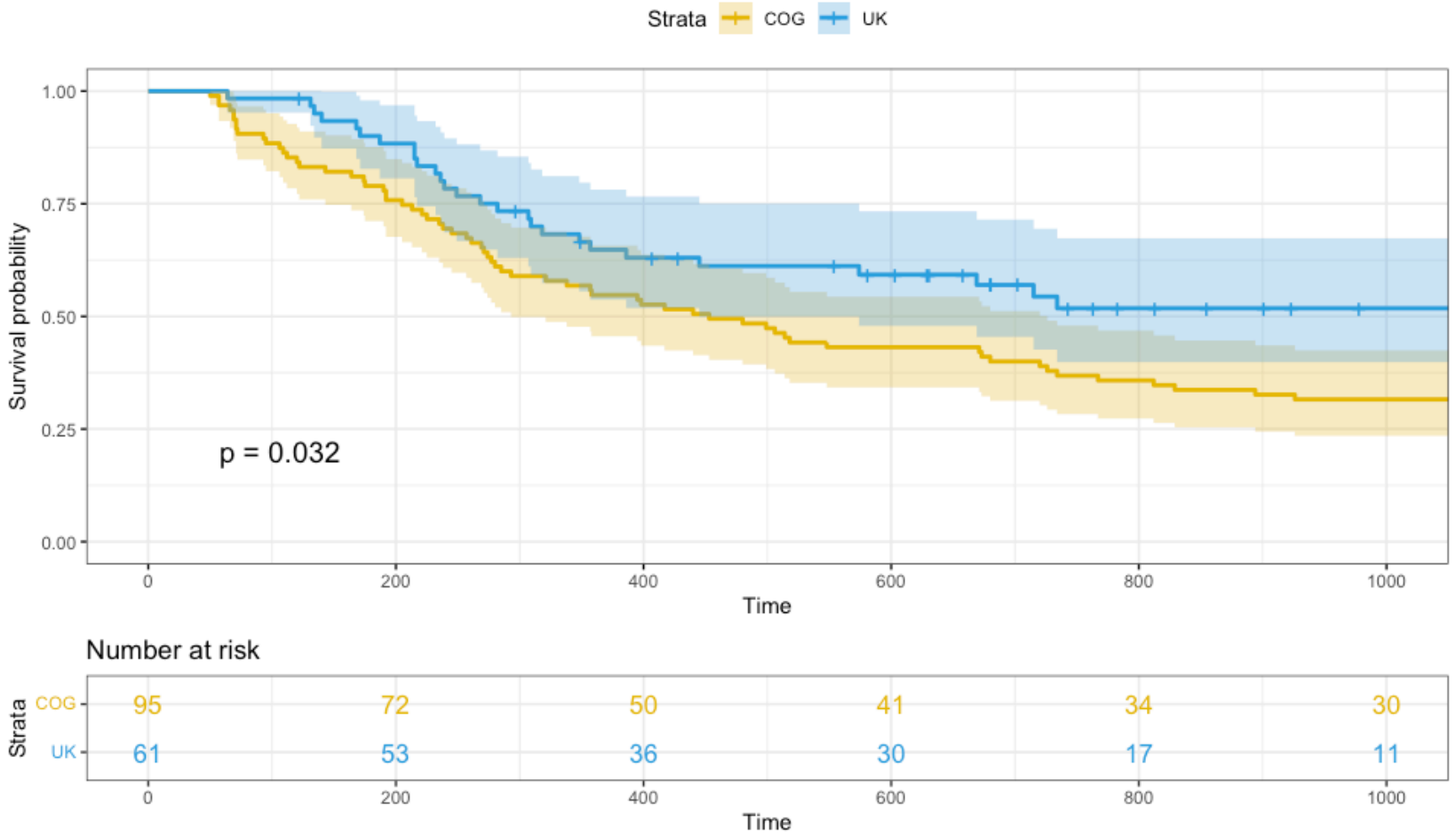
- COG 21 (3.1%) vs. UK 0, p=0.035

Significantly more UK patients were MRD negative after Blina Course 2:

- 88 vs. 69%, p<0.0001

COG plan to adopt reduced intensity induction prior to blina in relapsed HR ALL (Dave Teachey comms)

Superior UK Results compared to Matched COG AALL1331 VE/Early Relapses- Early introduction of Blina Beneficial

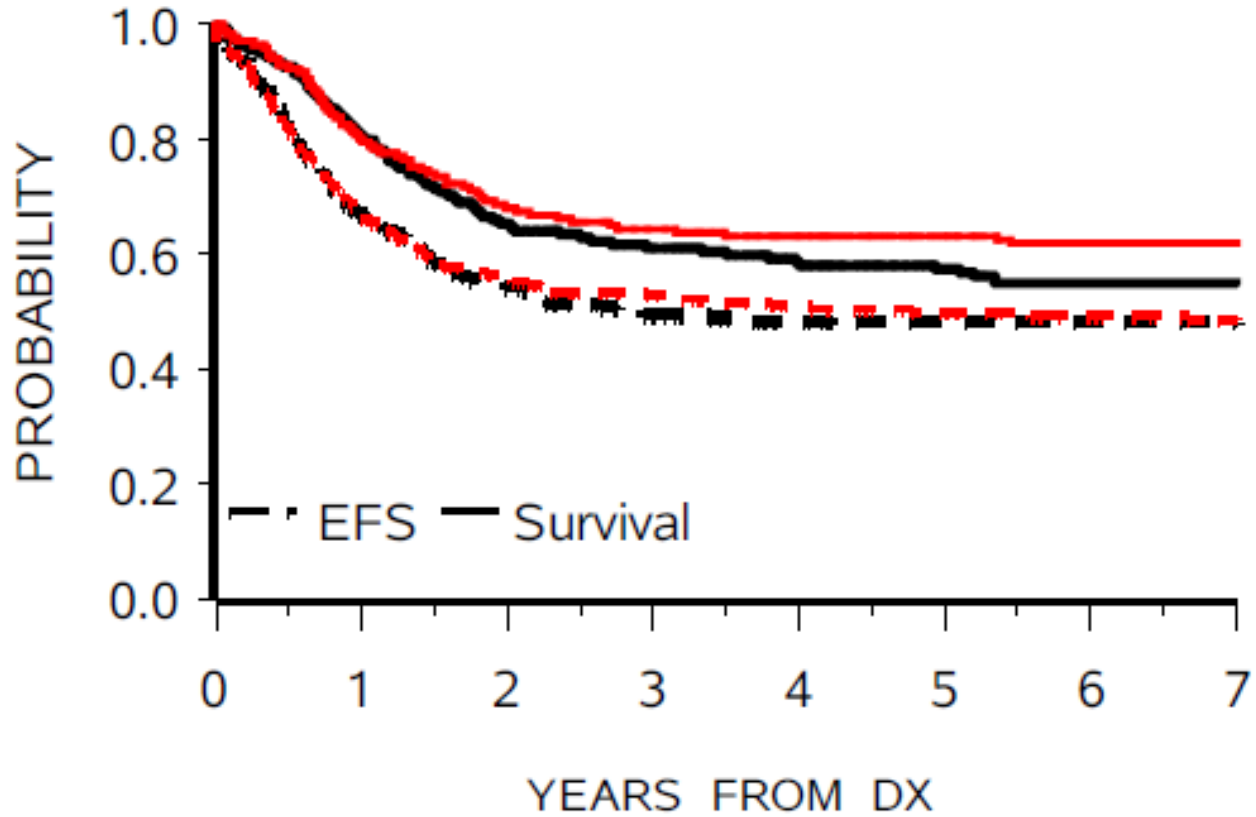


COG 2 year EFS 37.9 % vs 54.4 % UK

O'Connor et al – not published

Infant

ORIGINAL GROUPS



in red, Interfant06 curves

N. pts. (%)		6-year EFS (SE)		6-year Survival (SE)	
Int99	*Int06*	Int99	*Int06*	Int99	*Int06*
388	*447*	48.0 (2.6)	*49.4 (2.5)*	55.5 (2.6)	*62.1 (2.4)*
81%	*69%*	*p=0.73*		*p=0.20*	

Blinatumomab for infant acute lymphoblastic leukemia

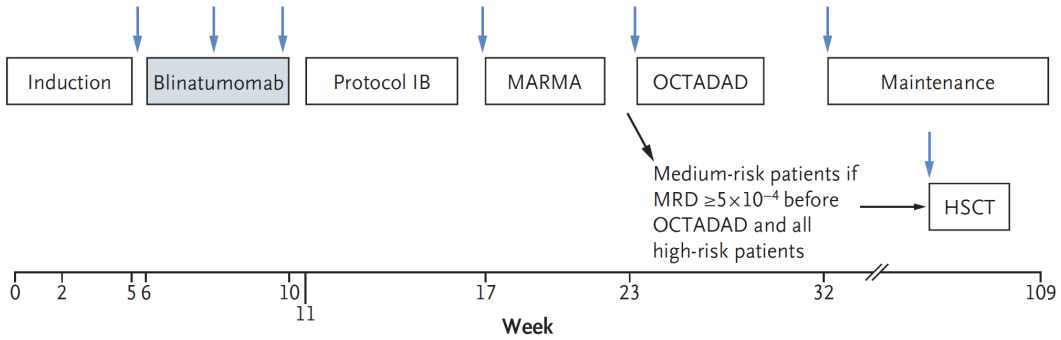
blood® 23 APRIL 2020 | VOLUME 135, NUMBER 17 **1501**

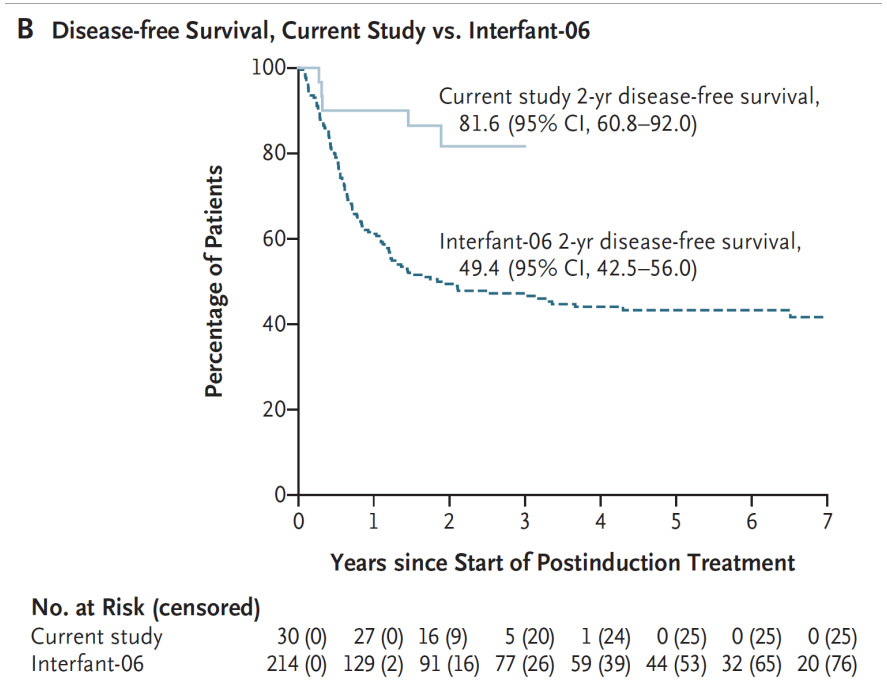
[1]Great Ormond Street Hospital for Children, London, United Kingdom

Patient/disease characteristics		Blinatumomab treatments							Outcomes		
Age at blinatumomab administration, y/sex	Disease status	Pre-CNS status	Pre-MRD, %	Lymphocyte count pre-blinatumomab (×10⁹/mL)	Cycles, n	CRS	Neurotoxicity	Post-MRD, %	HSCT conditioning	Donor source	Status
0.75/M	CR2	CNS 1	0.1	0.94	1	No	No	<0.005	FBT	MUD	CR
0.75/F	CR2	CNS 3	0.6	0.22	1	No	No	<0.005	FTT	MSD	CR
0.5/M	CR2	CNS 1	1	0.55	1	Grade 1	No	<0.005	FTT + ATG	MMUD	CR
0.41/F	CR2	CNS 1	1	N/A	1	No	No	<0.005	FTT	MSD	Relapse→died*
0.5/M	Primary refractory	CNS 1	9	0.28	1	No	No	0.06	FTT + ATG	MUD	CR
0.5/M	CR2	CNS 1	0.3	0.35	1	No	No	0.05	N/A		Relapse→CR†
0.5/F	CR1	CNS 1	0.06	0.41	1	Grade 2	Yes	<0.005	FTT + ATG	MMSD	CR
0.2/F	CR1	CNS 1	0.06	2.43	1	No	No	<0.005	FTT	MSD	Relapse‡
0.2/M	First relapse	CNS 3	40	N/A	1	Grade 1	No	<0.005	FTT + ATG	MUD	Died§
2.9/M	CR2	CNS 1	0.01	0.95	2	No	No	<0.005¶	CY/TBI/Alem	MSD	CR
0.2/F	Primary refractory	CNS 1	9	N/A	2	No	No	<0.005¶	FTT/ATG	MUD	Relapse→CR‖

Blinatumomab Added to Chemotherapy in Infant Lymphoblastic Leukemia

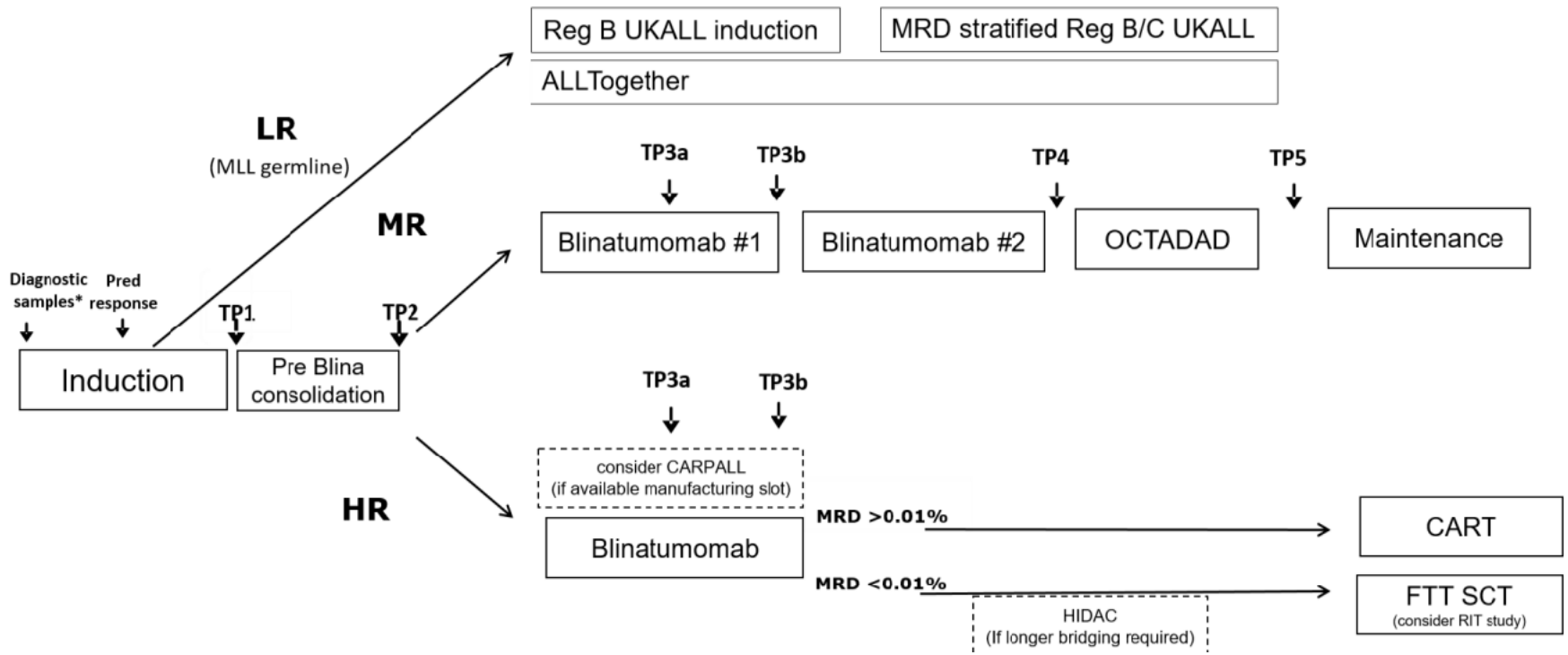
N Engl J Med 2023;388:1572-81.





No. at Risk (censored)

Current study	30 (0)	27 (0)	16 (9)	5 (20)	1 (24)	0 (25)	0 (25)	0 (25)
Interfant-06	214 (0)	129 (2)	91 (16)	77 (26)	59 (39)	44 (53)	32 (65)	20 (76)


Reg B UKALL induction
MRD stratified Reg B/C UKALL
ALLTogether
LR
(MLL germline)
MR
HR
Diagnostic samples*
Pred response
TP1
TP2
Induction
Pre Blina consolidation
TP3a
TP3b
TP4
TP5
Blinatumomab #1
Blinatumomab #2
OCTADAD
Maintenance
consider CARPALL
(if available manufacturing slot)
Blinatumomab
MRD >0.01%
MRD <0.01%
CART
FTT SCT
(consider RIT study)
HIDAC
(If longer bridging required)

Conclusion

Blinatumomab is effective as replacement for intensive chemotherapy in chemo-intolerant, resistant and relapse patients

Test as replacement in all BCP-ALL patients

Aim for chemotherapy-free treatment in 5-10 years

Acknowledgements

Clinicians:
Sujith Samarasinghe
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Persis Amrolia
Waseem Qasim

Statisticians:
Sue Richards
Rachel Wade
Amy Kirkwood

Scientists:
Lynne Lennard
Anthony Moorman
Christine Harrison
Jerry Hancock
MRD network lab staff

Patients and families

CART UK experience - Autologous

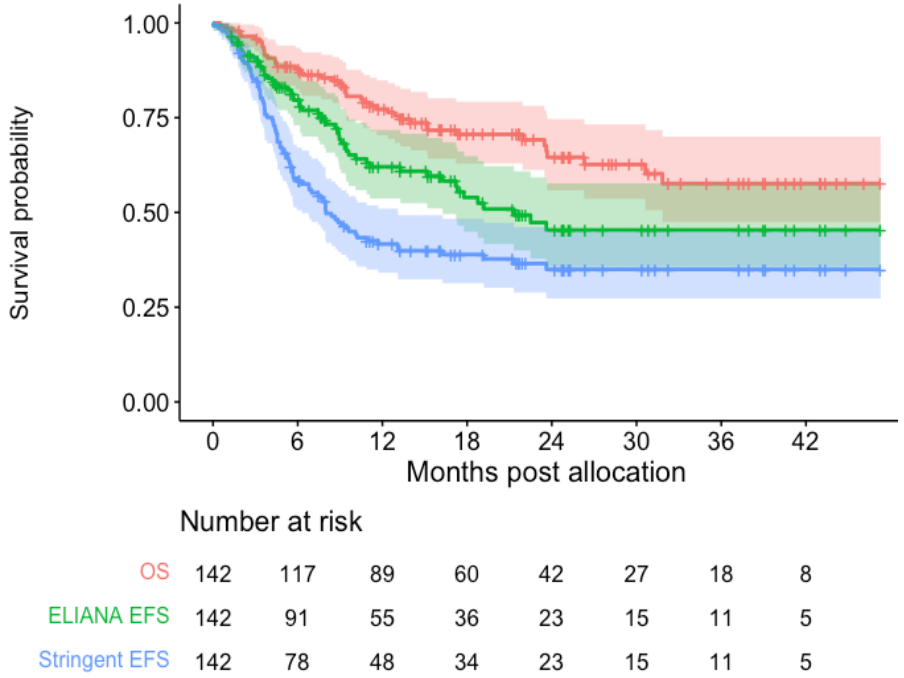
Persis Amrolia

Stringent EFS
Infant
Maintenance

Sara Ghorashian

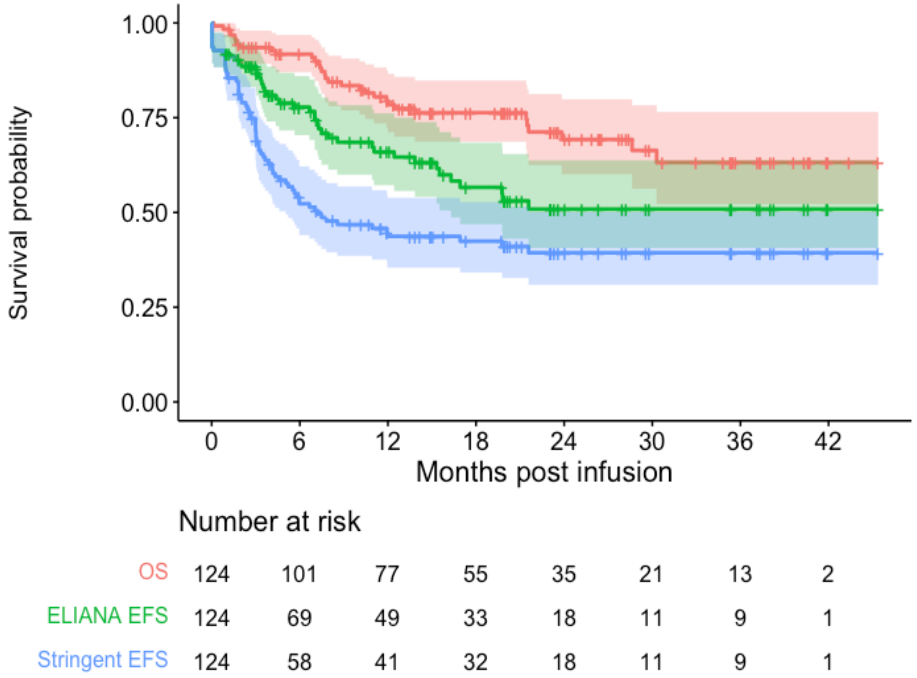
Stringent EFS: Failure to respond, Relapse, Loss of BCA requiring intervention, Recurrent MRD, Second cancer, Death Ghorashian et al In Press

Intention to treat



	2-y	(95% CI)	Median survival (95% CI)
OS	64.5%	(56 - 75)	not reached
ELIANA EFS	45.4%	(36 - 58)	21.3mo (16 -)
Stringent EFS	35%	(27 - 45)	8 mo (6.3-13.1)

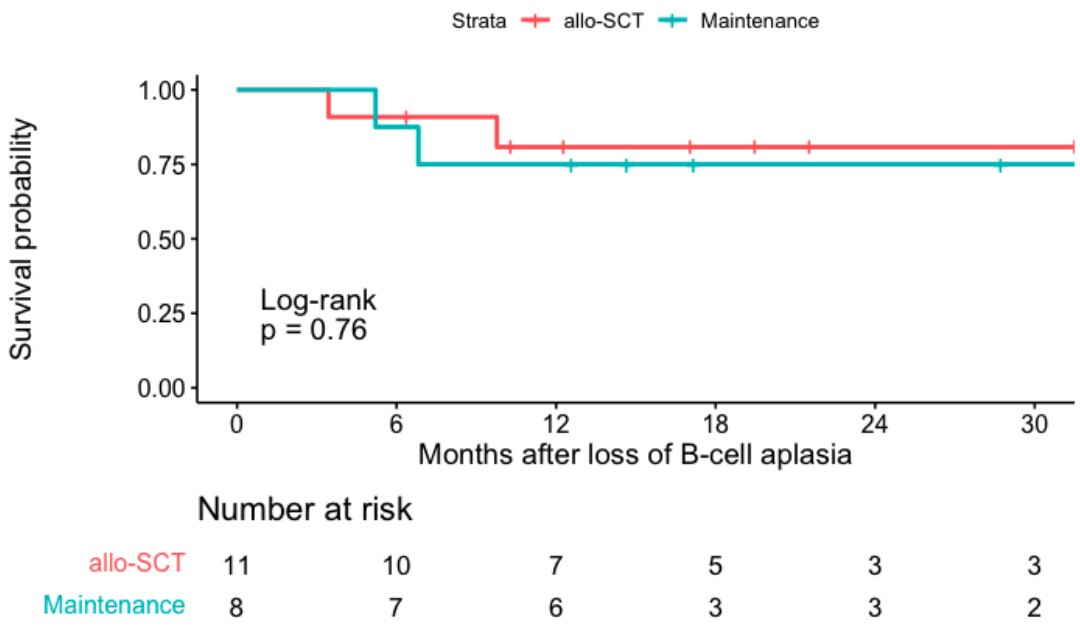
Infused



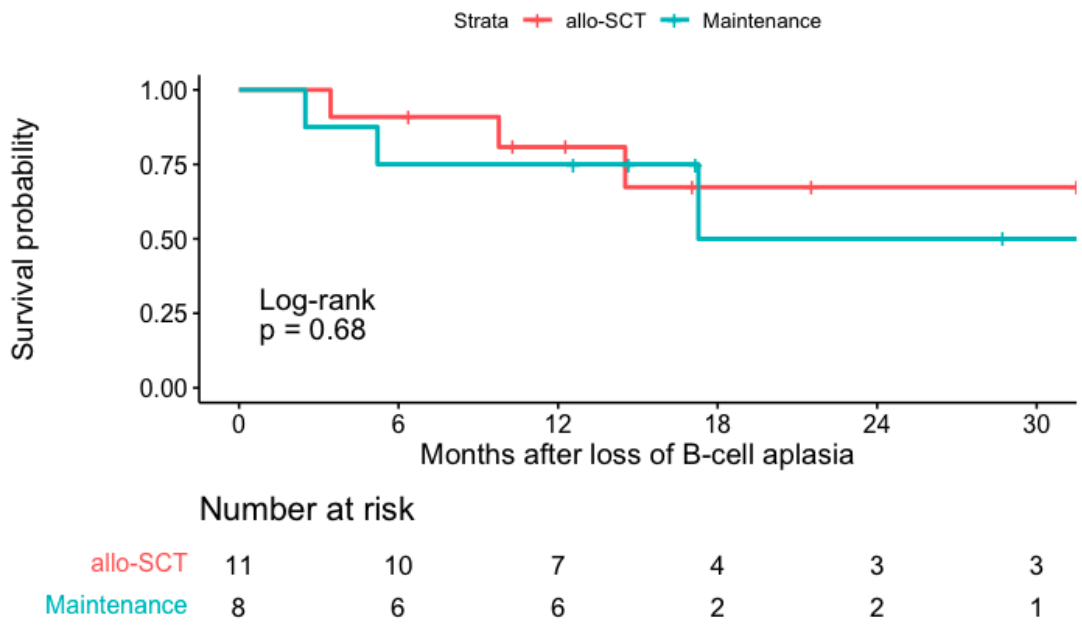
	2-y	(95% CI)	Median survival (95% CI)
OS	69.2%	(60 - 80)	not reached
ELIANA EFS	50.9%	(41 - 64)	not reached
Stringent EFS	39.3%	(31 - 50)	7.2 mo (5.1-)

Maintenance for early loss of B cell aplasia

Overall survival

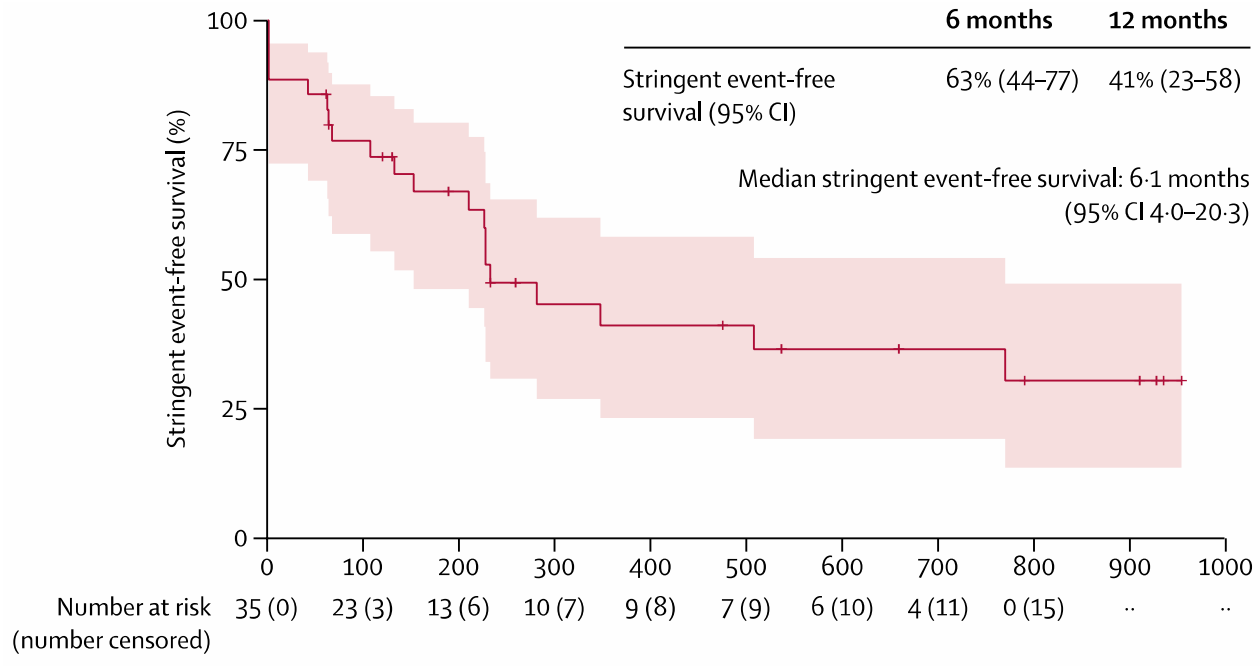


Event-free survival

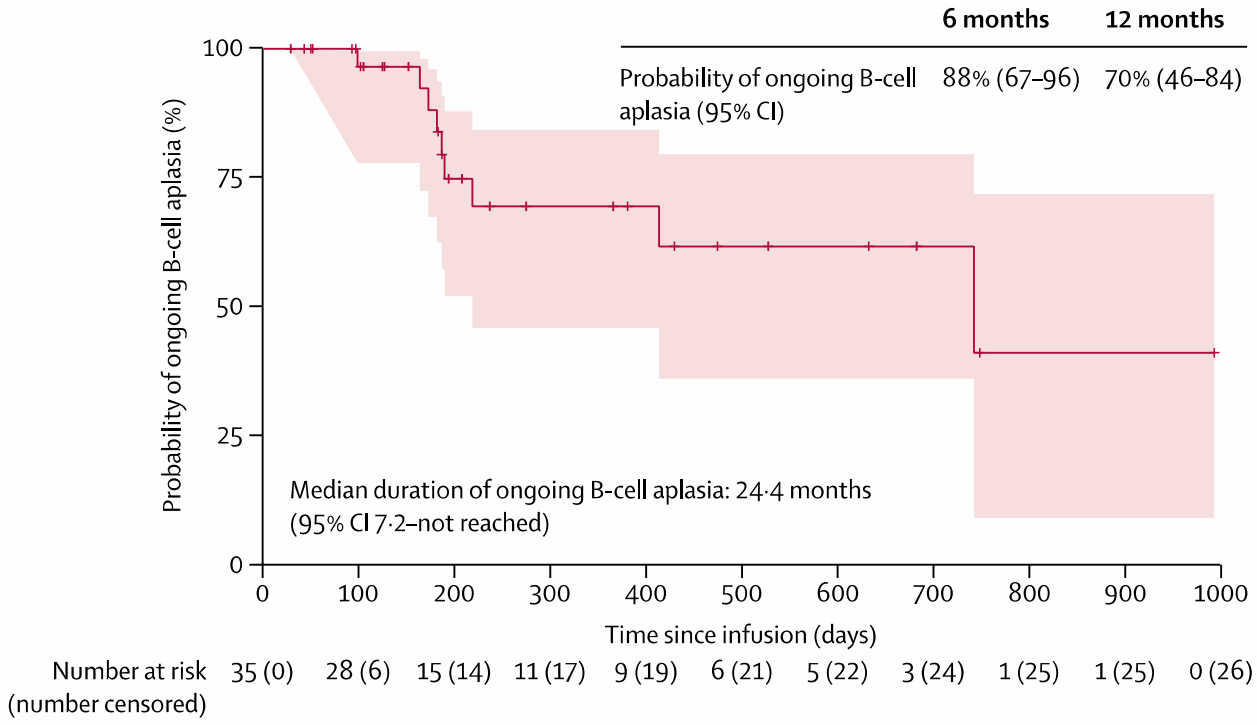


Tisagenlecleucel for infant ALL – equivalent EFS and no excess of lineage switch relapse

Stringent survival



Probability of B cell aplasia

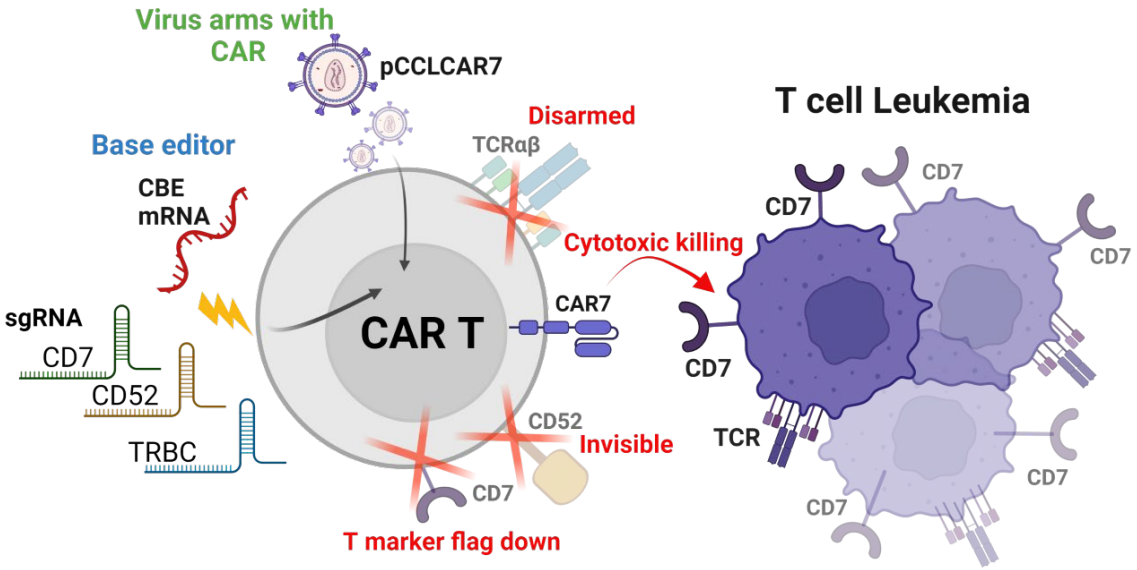


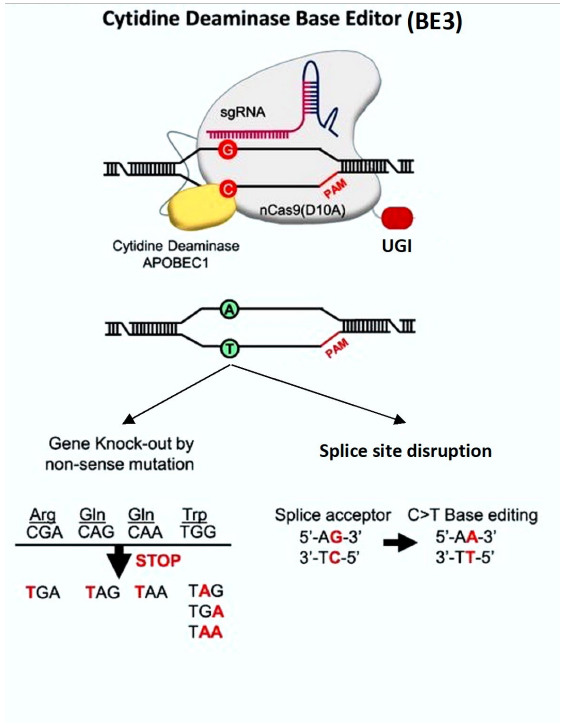
- 2 additional cases of MRD emergence
  - 1 CD19neg, 1 CD19 pos, both went onto further therapy

Ghorashian et al. Lancet Haematology 2022

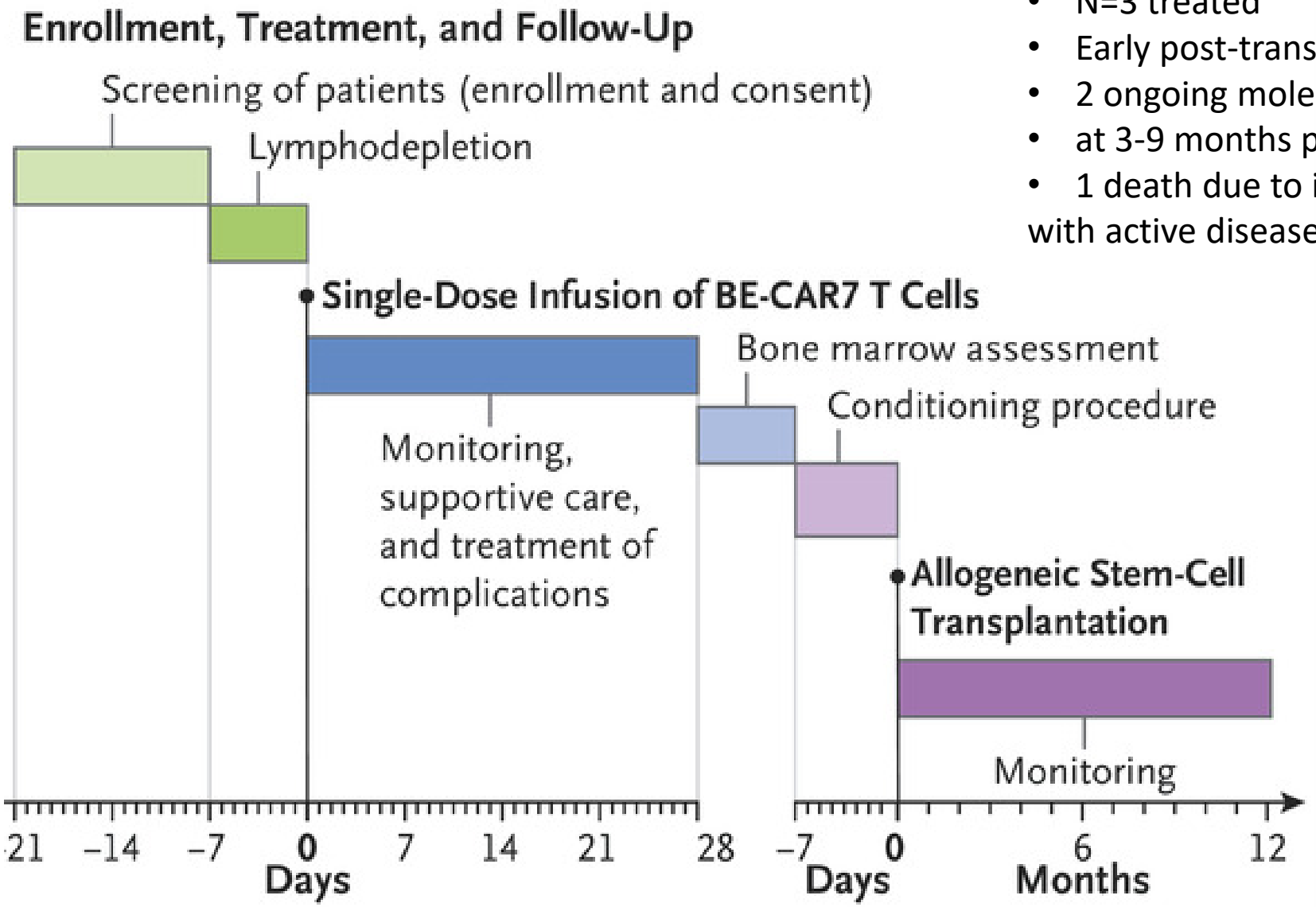
Base-edited CD7 CART cells to target T cell cancers

Waseem Qasim



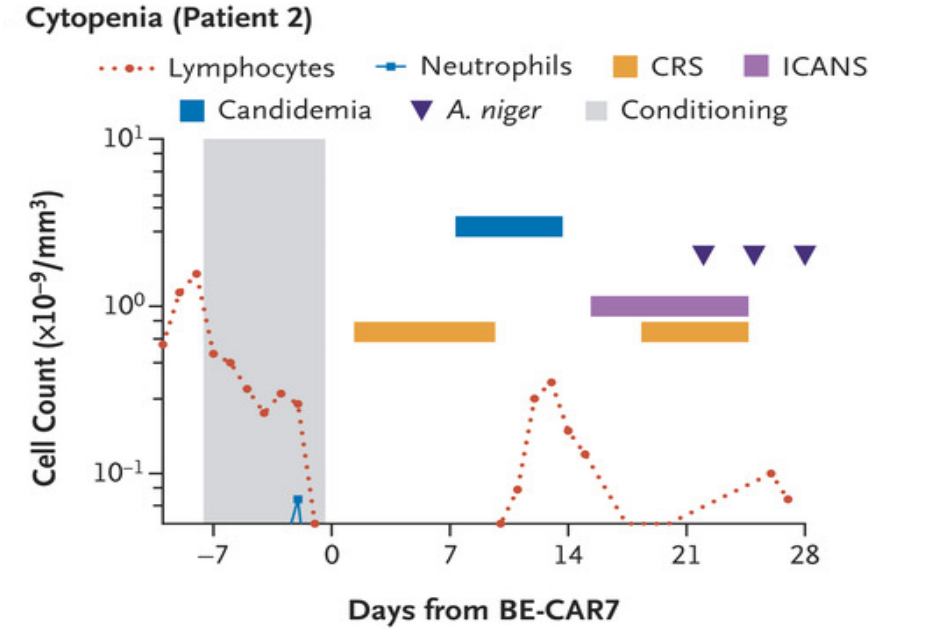


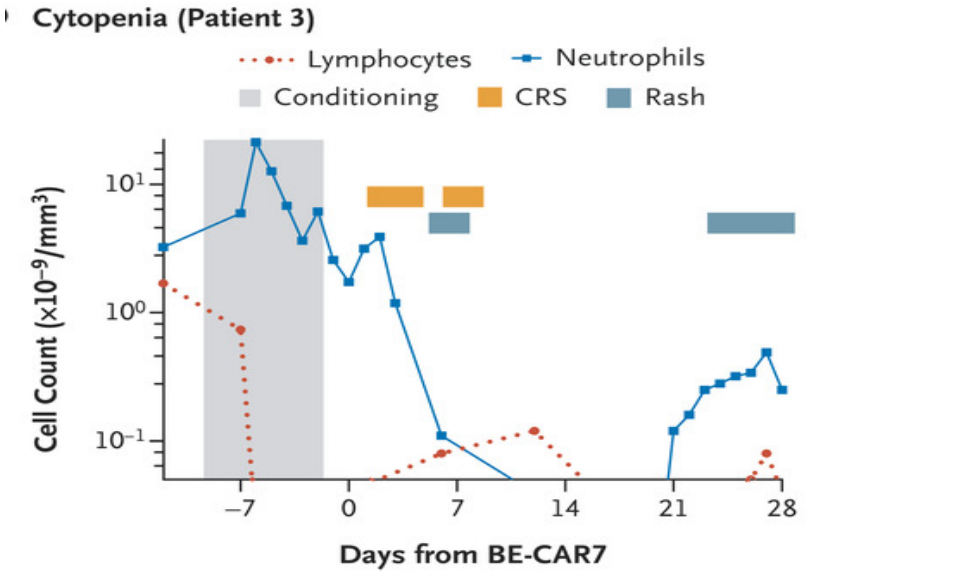
Open Phase 1 study of base-edited CD7 CART for paediatric T-ALL

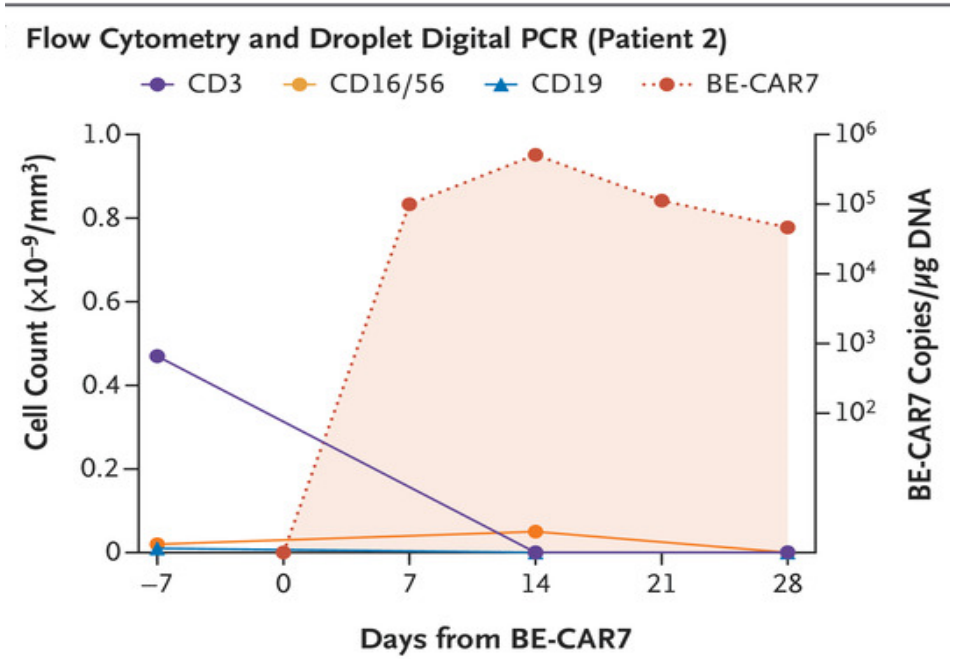


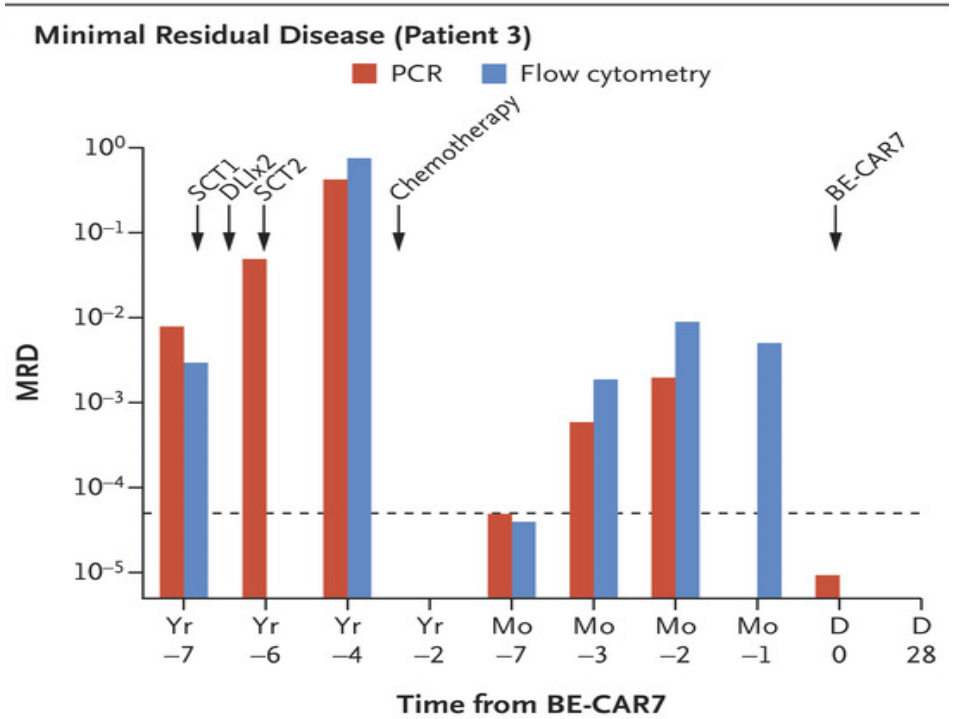
- N=3 treated
- Early post-transplant relapse
- 2 ongoing molecular CR
- at 3-9 months post SCT
- 1 death due to infection with active disease

NEJM 2023


Cytopenia (Patient 2)
Lymphocytes
Neutrophils
CRS
ICANS
Candidemia
A. niger
Conditioning
Cell Count (×10⁻⁹/mm³)
Days from BE-CAR7


Cytopenia (Patient 3)
Lymphocytes
Neutrophils
Conditioning
CRS
Rash
Cell Count (×10⁻⁹/mm³)
Days from BE-CAR7


Flow Cytometry and Droplet Digital PCR (Patient 2)
CD3
CD16/56
CD19
BE-CAR7
Cell Count (×10⁻⁹/mm³)
BE-CAR7 Copies/μg DNA
Days from BE-CAR7


Minimal Residual Disease (Patient 3)
PCR
Flow cytometry
SCT1
DLIx2
SCT2
Chemotherapy
BE-CAR7
MRD
Yr −7
Yr −6
Yr −4
Yr −2
Mo −7
Mo −3
Mo −2
Mo −1
D 0
D 28
Time from BE-CAR7

CD33 allo-CAR

- Base edited
- Bridge to transplant
- Flu/Cy/Campath LD
- First patient – CRS with HLH, in flow negative CR at one month
- Plan is to combine with CD7/123 CAR