

8 minutes of LLA in AYA

Young to be adults, but no longer children: how to treat the young adult (AYA) with ALL?

Fábio Kerbauy

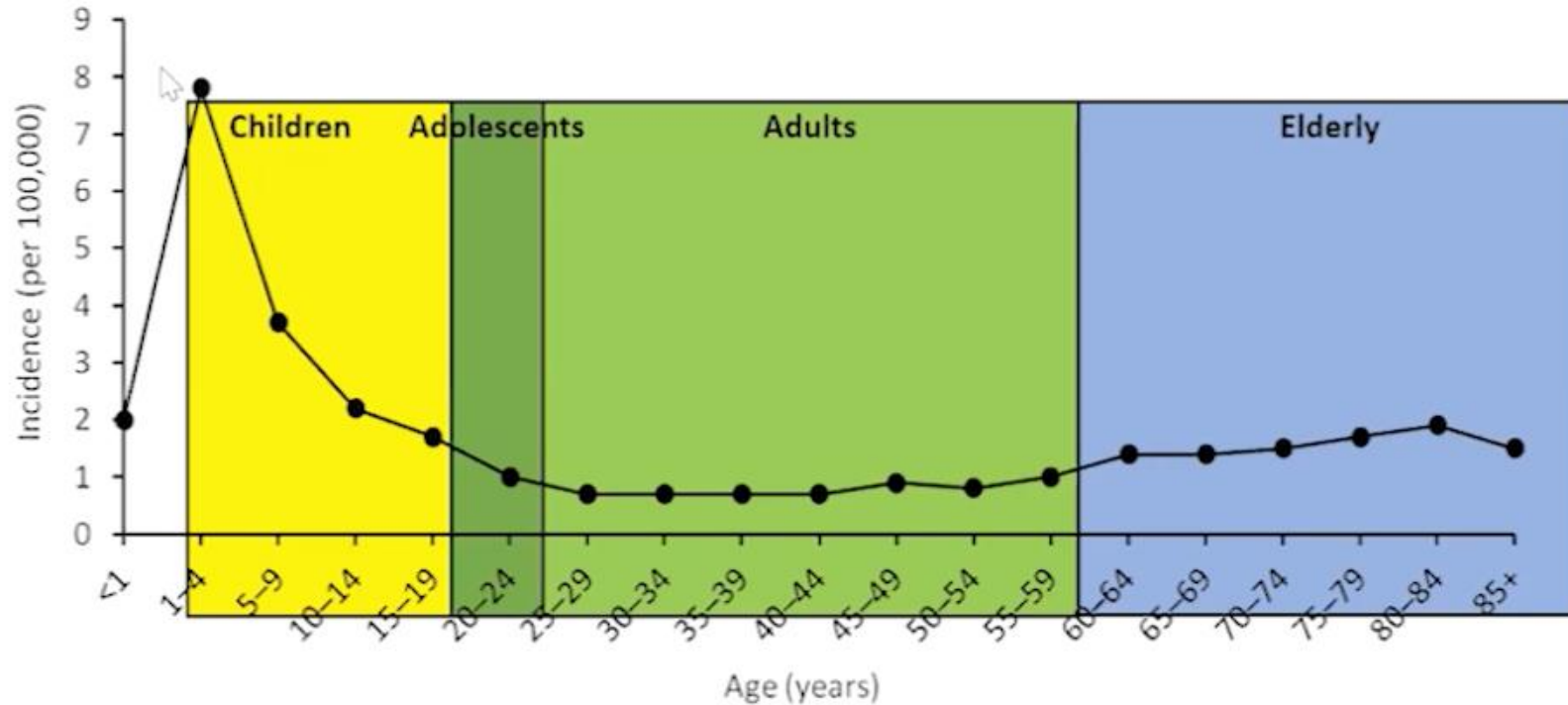
Beneficência Portuguesa de SP - TMO
Prof Adjunto UNIFESP/EPM – Leucemias



APOIO
INSTITUCIONAL



Acute lymphoblastic leukemia

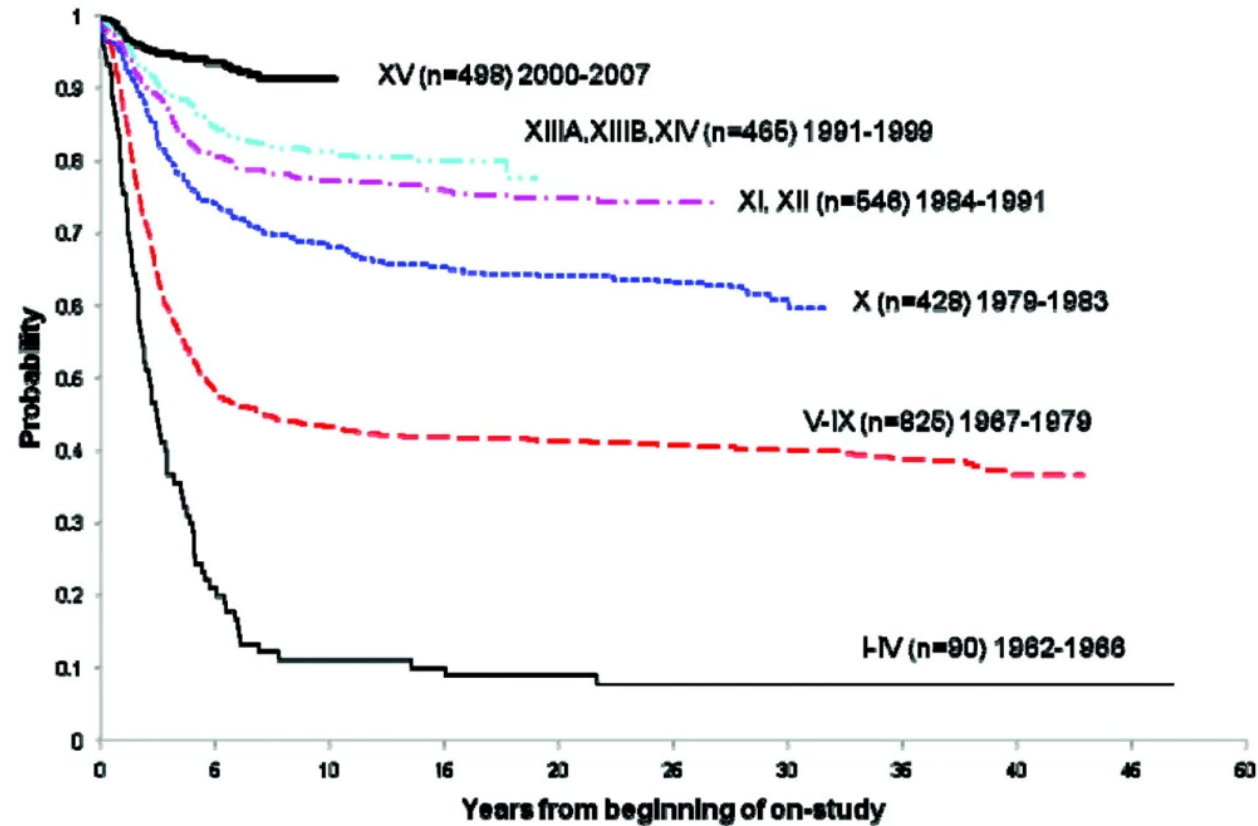


Acute lymphocytic leukemia is most frequently diagnosed among people aged <20.

Median Age
At Diagnosis

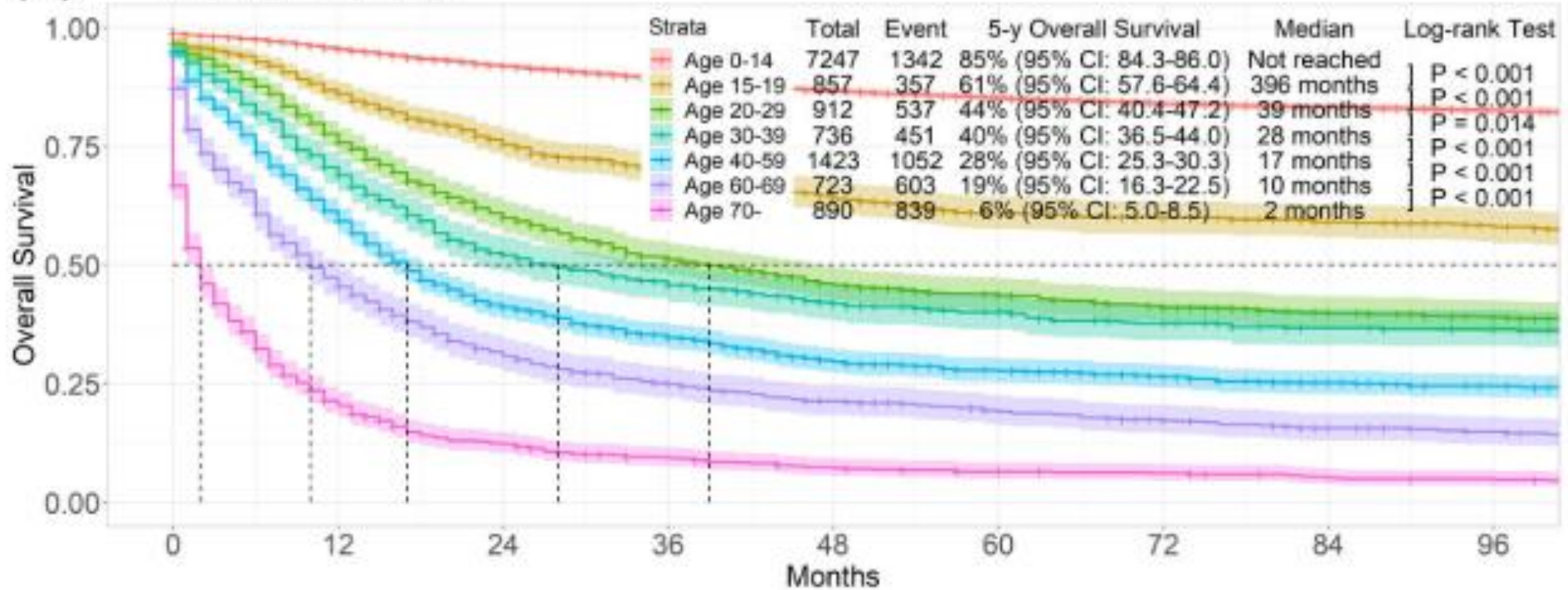
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ALL in children: OS evolution

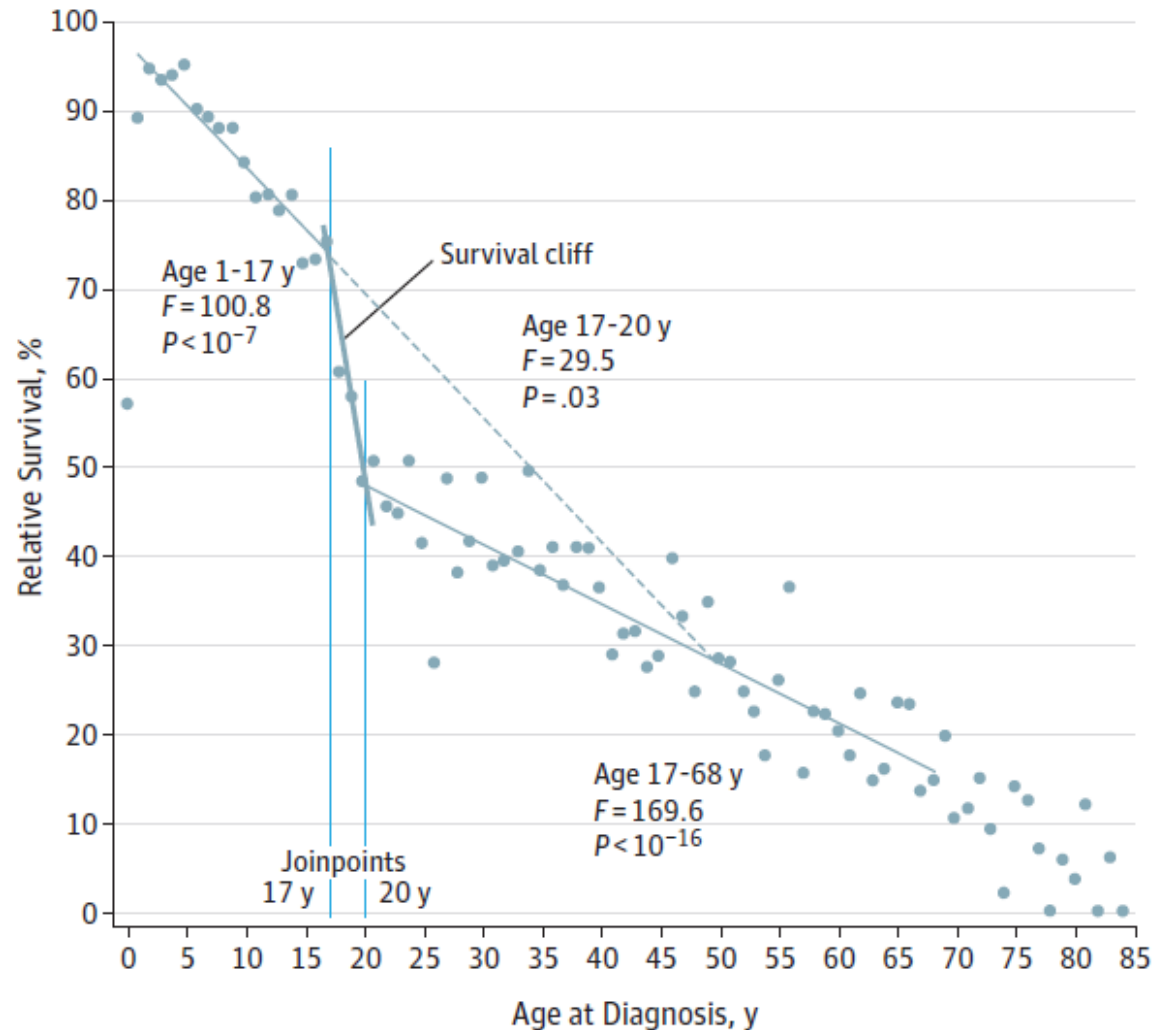


Acute lymphoblastic leukemia: A population-based study of outcome in the United States based on the surveillance, epidemiology, and end results (SEER) database, 1980–2017

(B) All ALL by Age

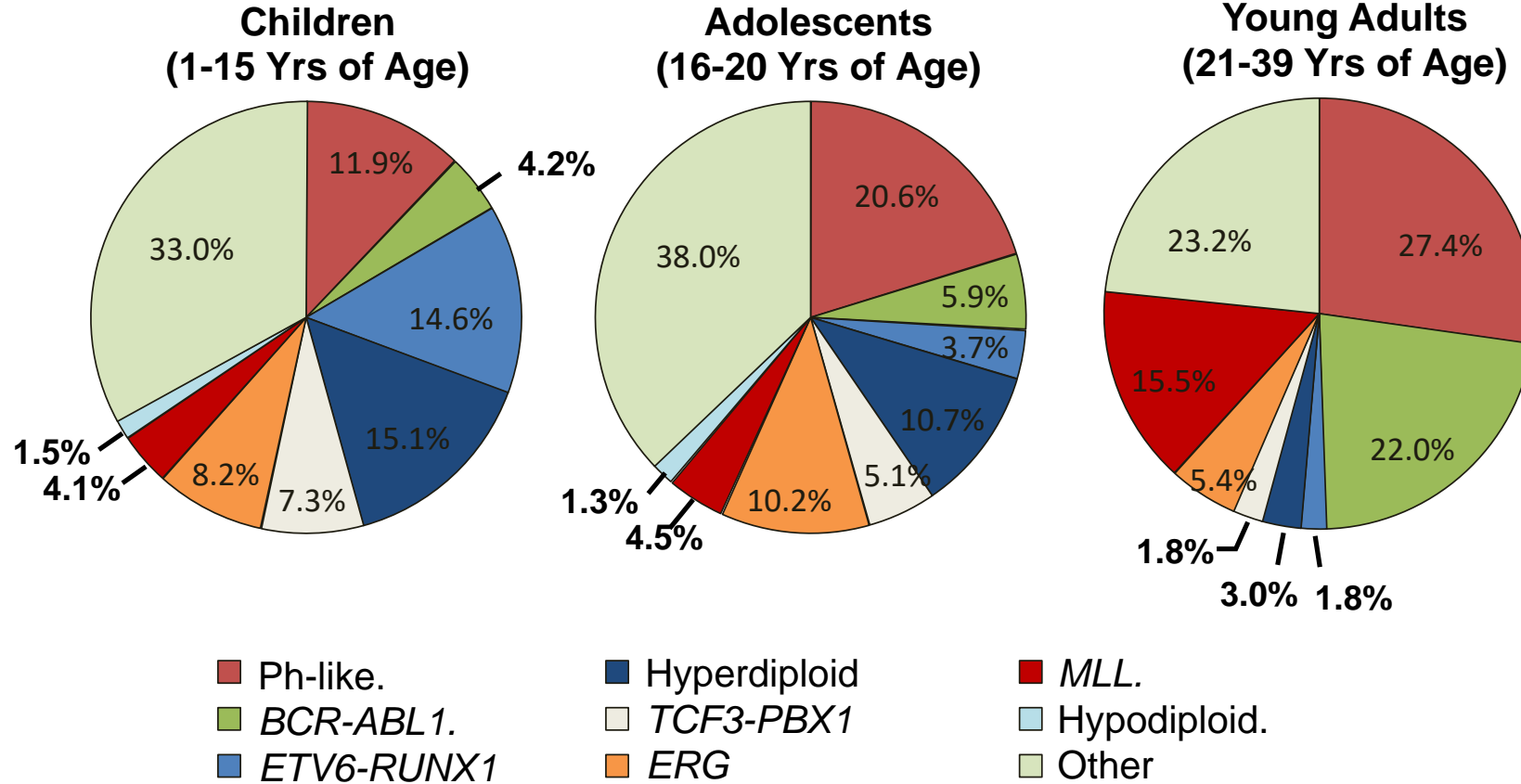


ALL Survival Cliff



- Adverse disease biology
- differences in treatment setting
- psychosocial factors
- access to clinical trials

ALL Classification



Roberts KG, et al. N Engl J Med. 2014;371:1005-1015.

Clinical Trials

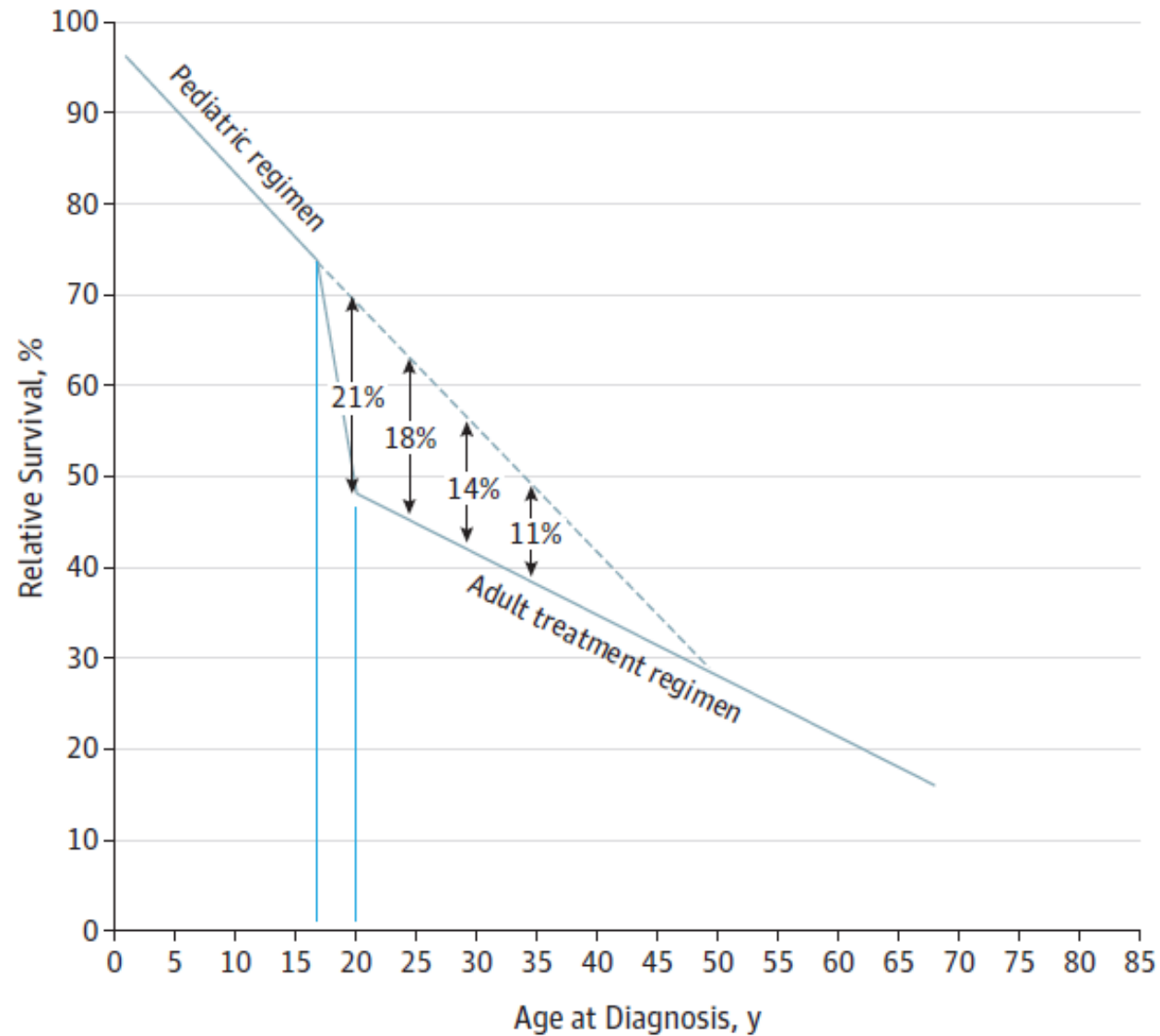
- **Ph-like:** Ruxolitinib +/- dasatinib, Blinatumomab, CAR-T
- **KMT2Ar:** Menin inhibitor (revumenib)
- **LLA-T:** Venetoclax/ponatinib, nelarabine, daratumumab
- **Up-front:** inotuzumab, blinatumomab

CR rate x OS

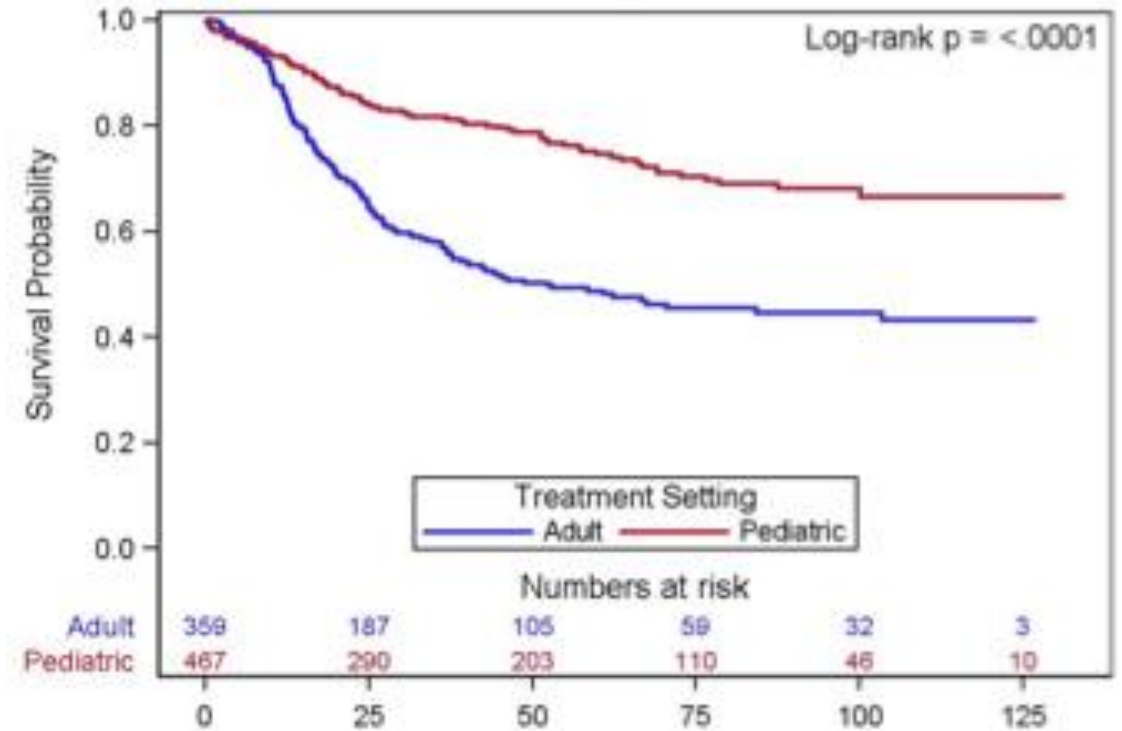
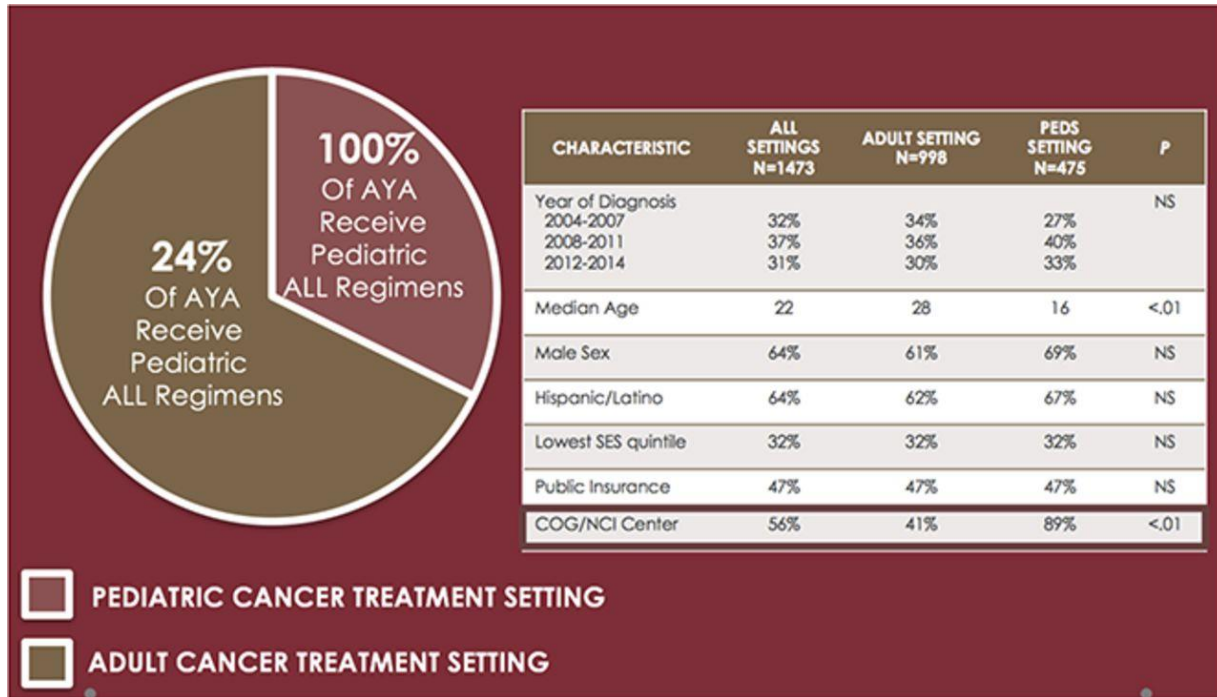
(Era pré DRM, pré blina, pré ino)

Study	Year	N	Median Age (Range)	SCT	CR Rate	Early Death	Survival
CALGB 9111, USA ⁵	1998	198	35 (16–83)	Ph+	85%	8%	40% (3 y)
LALA 87, France ¹	2000	572	33 (15–60)	PO	76%	9%	27% (10 y)
NILG 08/96, Italy ⁷	2001	121	35 (15–74)	PR	84%	8%	48% (5 y)
GMALL 05/93, Germany ⁸	2001	1163	35 (15–65)	PR	83%	n.r.	35% (5 y)
JALSG-ALL93, Japan ²	2002	263	31 (15–59)	PO	78%	6%	30% (6 y)
UCLA, USA ⁹	2002	84	27 (16–59)	PR	93%	1%	47% (5 y)
Sweden ¹⁰	2002	153	42 (16–82)	PR	75%	n.r.	28% (5 y)
GIMEMA 0288, Italy ¹²	2002	767	28 (12–60)	—	82%	11%	27% (9 y)
MD Anderson, USA ⁶	2004	288	40 (15–92)	Ph+	92%	5%	38% (5 y)
EORTC ALL-3, Europe ³	2004	340	33 (14–79)	PO	74%	n.r.	36%*(6 y)
LALA 94, France ¹¹	2004	922	33 (15–55)	PR	84%	5%	36% (5 y)
GOELAL02, France ¹³	2004	198	33 (15–59)	HR	86%	2%	41% (6 y)
MRC XII/ECOG, UK-USA ⁴	2005	1521	15–59	PO	91%	n.r.	38% (5 y)
GIMEMA 0496, Italy ¹⁴	2005	450	16–60	n.r.	80%	n.r.	33% (5 y)
Pethema ALL-93, Spain ¹⁵	2005	222	27 (15–50)	HR	82%	6%	34% (5 y)

How to overcome ALL Survival Cliff?



Patterns of care and outcomes in AYA ALL patients



AYA pediatric x adult regimen

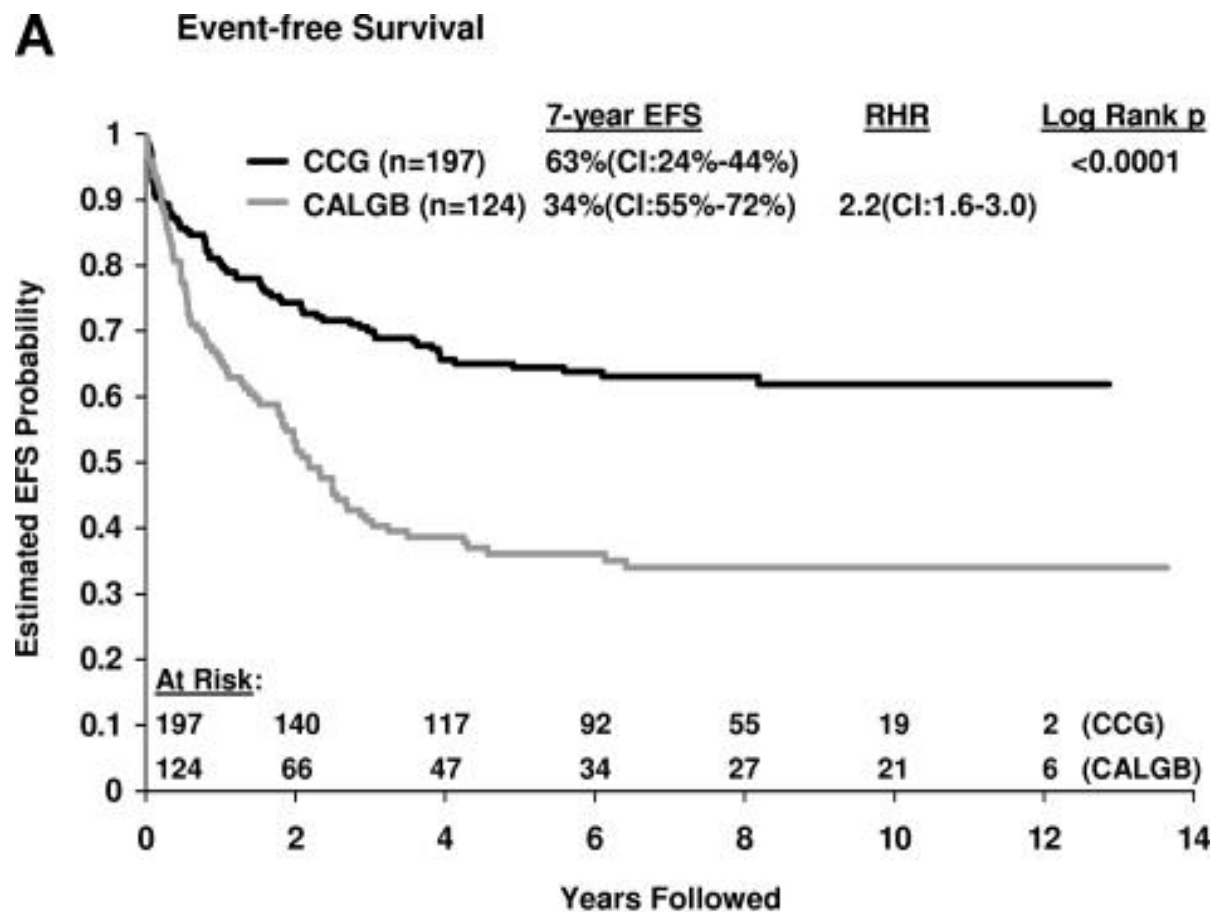
1988 to 2001

n= 321 ages 16 to 20 years

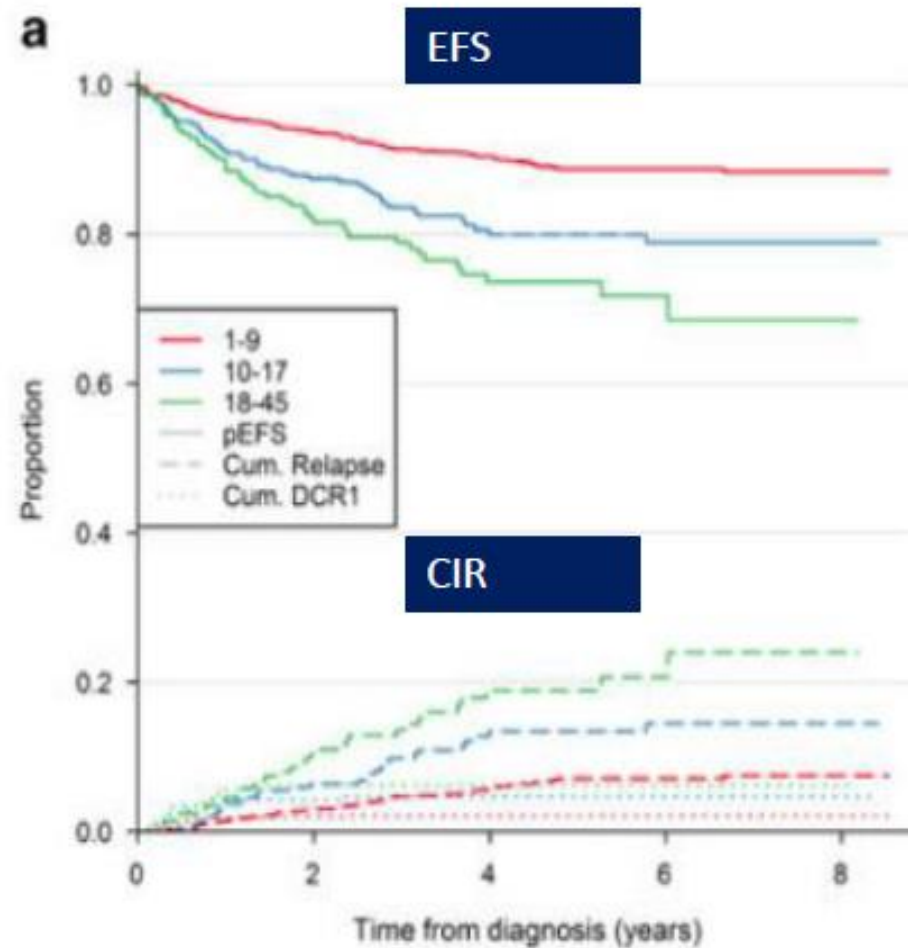
Children's Cancer Group (CCG)

Cancer and Leukemia Group B (CALGB)

No HCT consolidation in 1st CR



NOPHO protocol (n=1509)



1-9 yrs EFS: 89%



10-17 yrs EFS: 80%



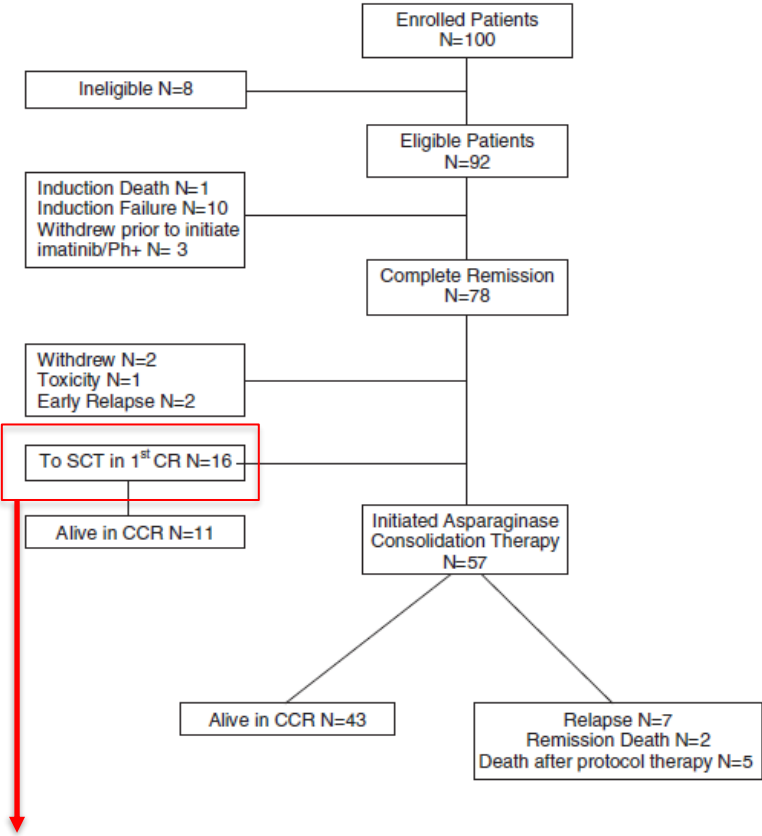
18-45 yrs EFS: 74%

Median f/u = 4.6

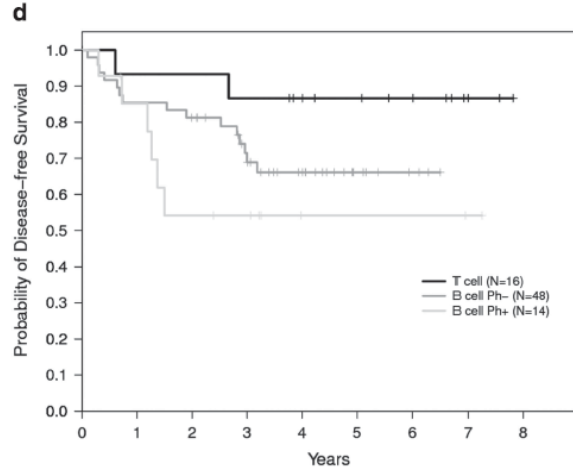
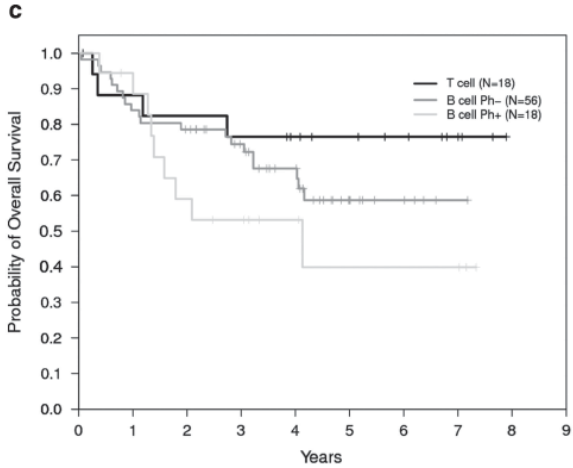
**years; Includes B and T
ALL**

100 patients were eligible for hSCT in first remission based on MRD levels measured on day 29/post A1 (n=61) or day 79/post-B1 (n=39). Of these 100 patients, 18 were not transplanted

Possível e efetivo até 50 anos (DFCI)

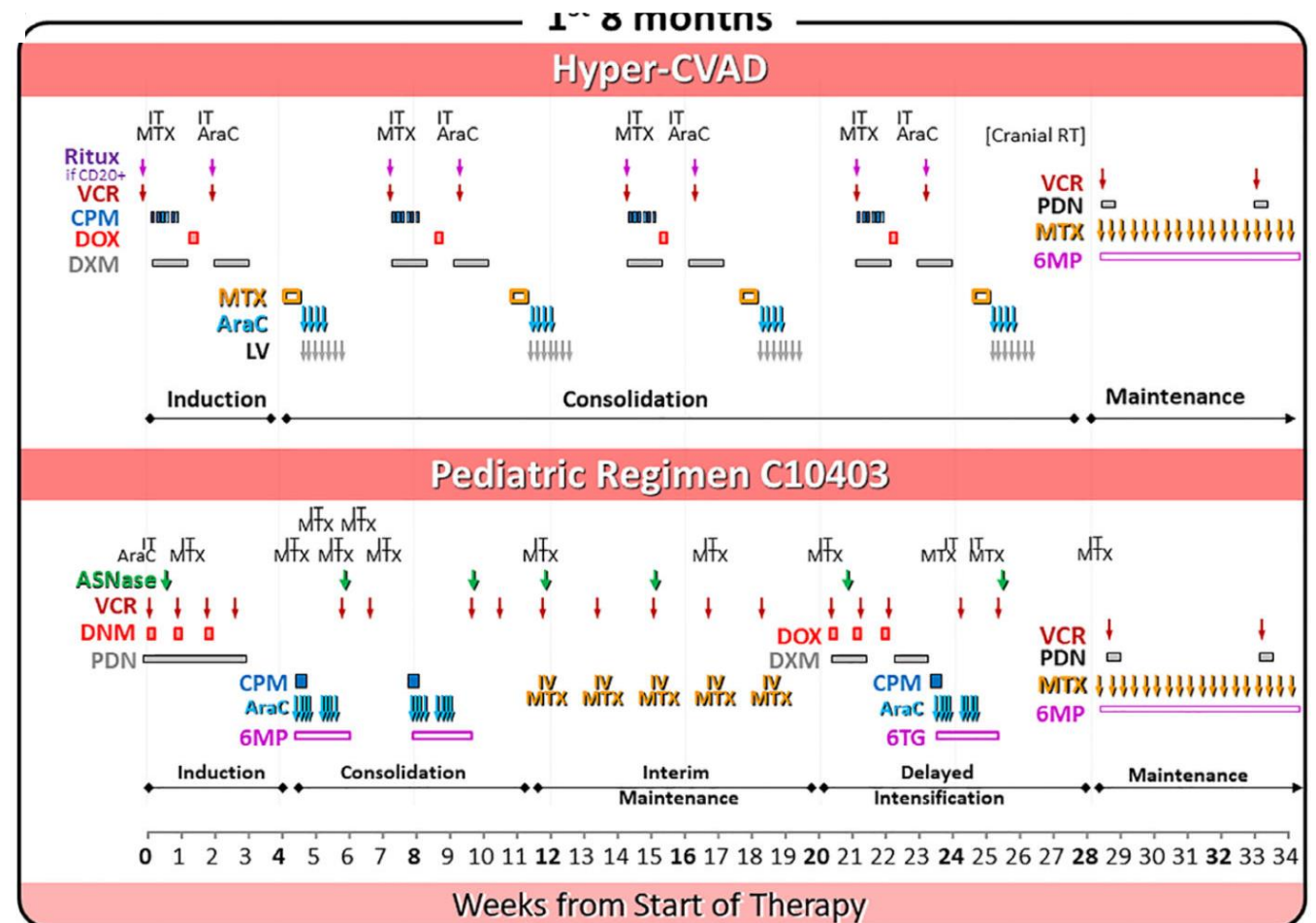


Allogeneic stem cell transplantation was not mandated but encouraged for all patients with high-risk cytogenetic features, such as the Philadelphia chromosome or translocations involving the MLL gene on 11q23



Pediatric x adult regimen

- Mais esteróides, vincristina, asparaginase
- 7-8 drogas com menor mielossupressão
- Profilaxia SNC: Precoce e mais intensa
- DRM
- TCH em risco muito alto (ex, t[4:11])
- Nelarabina em LLA-T



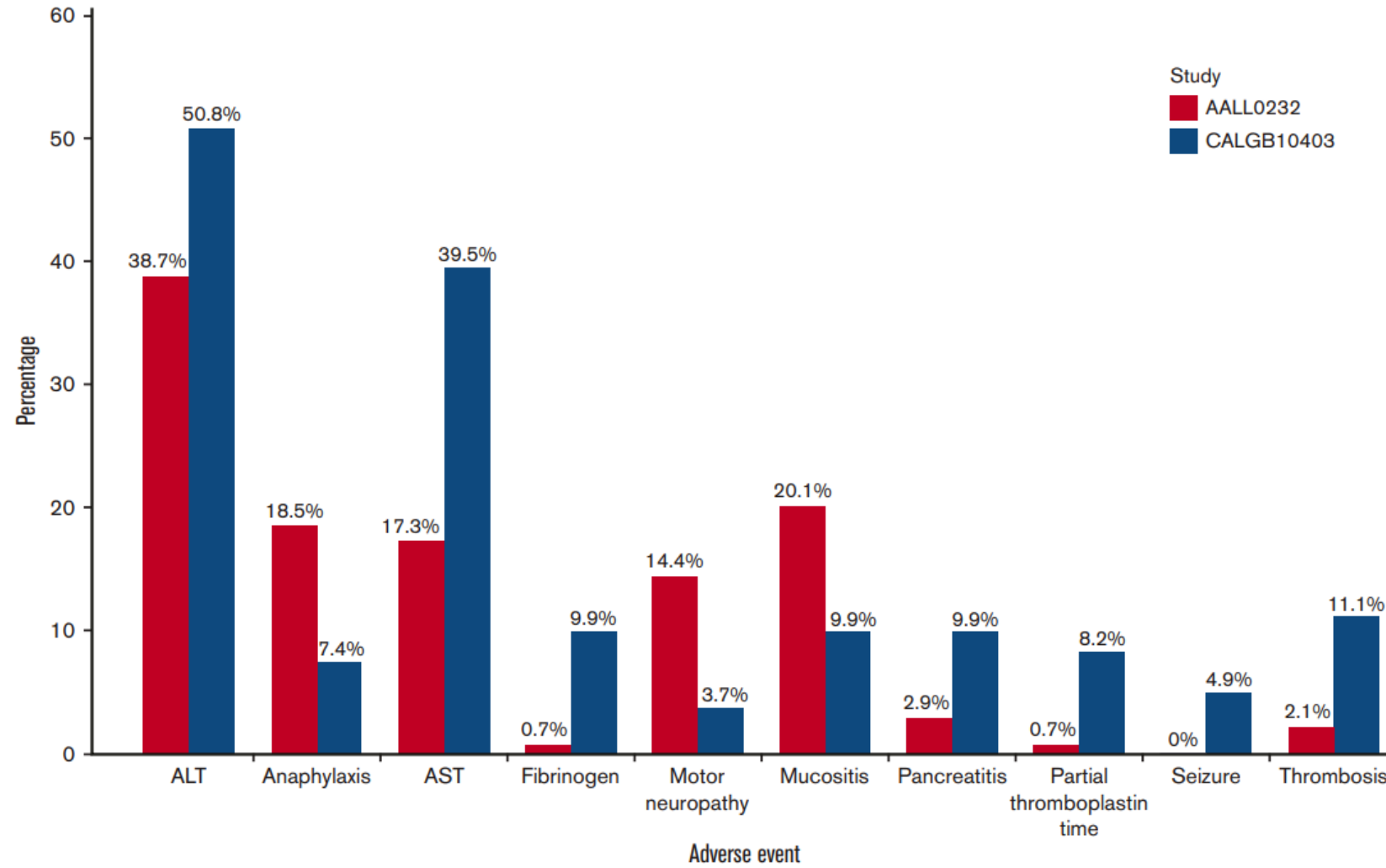
“Pediatric-inspired” B-ALL trials

Trial	No. of patients	Age (years), median (range)	CR (%)	OS (%)	EFS (%)	DFS (%)	Duration of follow-up	AlloHSCT
JALSG 202-U	139	19 (16–24)	97	74	-	71	4 year	t(4;11)
DFCI 01-1756	92	28 (18–50)	86	70	-	71	4 year	t(4;11), +8, Ph+
DFCI 06-254	110	32 (18–50)	89	75	-	73	3 year	t(4;11), +8, Ph+
UKALL 2003	229	16–24	97	76.4	72.3	-	5 year	
MDACC aBFM	106	22 (13–39)	93	53	-	60	5 year	t(4;11) or MRD+
NOPHO ALL 2008	221	26 (18–45)	-	78	74	-	5 year	D29 MRD >5% or D79>0.1%
GRAALL 2005	787	36 (18–60)	92	58.5	52	-	5 year	High risk or MRD+
CALGB10403	295	24 (17–39)	89	73	59	66	3 year	
ALLRE08 PETHEMA	89	20 (15–29)	95	74	62	65	5 year	MRD+
ALL06	86	22 (15–39)	90.2	74.9	-	72.8	3 year	t(4;11), MRD+, poor steroid response or WBC >100
GIMEMA LAL-1308	76	23 (18–35)	92	60.3	-	60.4	4 year	No CR at D33, pro-B ALL or WBC >100, t(4;11), MRD+

Intensidade de quimioterapia

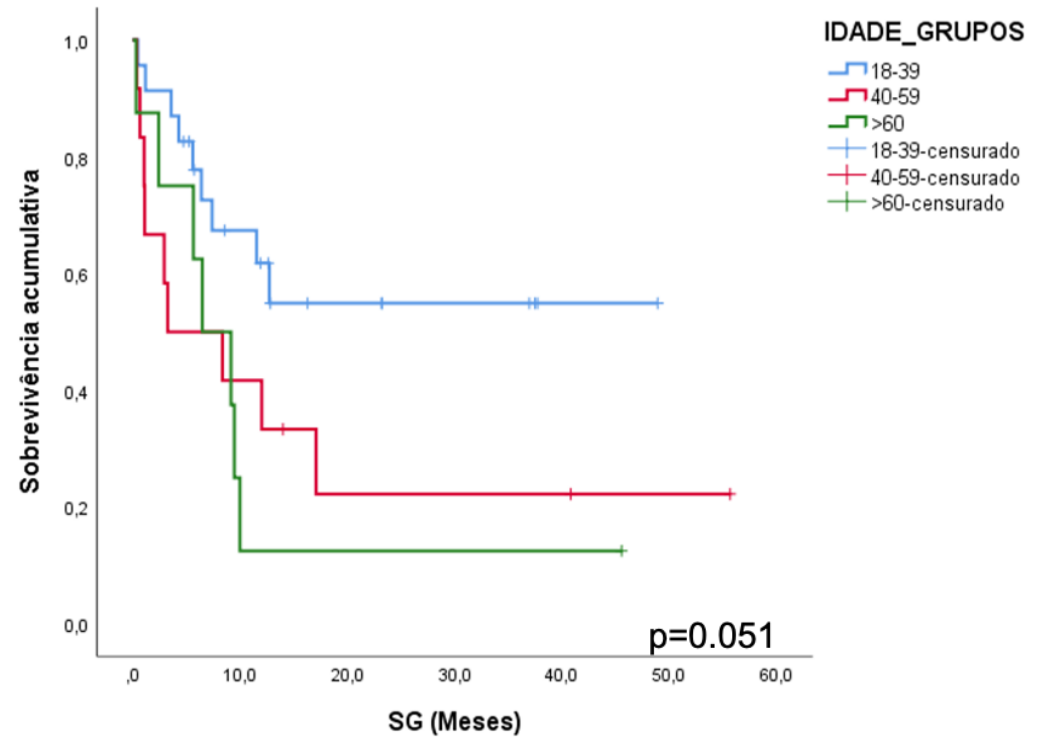
	GRAALL 05	CALGB 10403	A-BFM	DFCI 01-175	HyperCVAD
Idade	<i>18-59</i>	<i>15-39</i>	<i>15-40</i>	<i>18-50</i>	<i>15-40</i>
Prednisona	5040	1680	1680	1120	24000
Vincristina	16	72	80	86	80
Dexametasona	0	656	940	1590	1280
Asparaginase	96000	0	0	150000	0
Onco-Aspar	0	17500	17500	0	4000
Ara-C	64000	1800	1200	0	48000
Ciclofosfamida	7500	1000	3000	0	7200
Methotrexate VO	2600	3210	1920	1000	2080
Methotrexate IV	18000	1000	1000	4000	4000
Daunorrubicina	360	100	100	0	0
Doxorrubicina	0	75	75	300	200
Etoposideo	0	0	0	0	0
Tioguanida	0	840	840	0	0
Mercaptopurina	43800	77280	54840	7000	100800
Radioterapia SNC	18	0	0	18	0
QT IT	6	23	15	25	16
Rituximab	16	0	0	0	10

Pediatric protocol toxicity



ALL patients

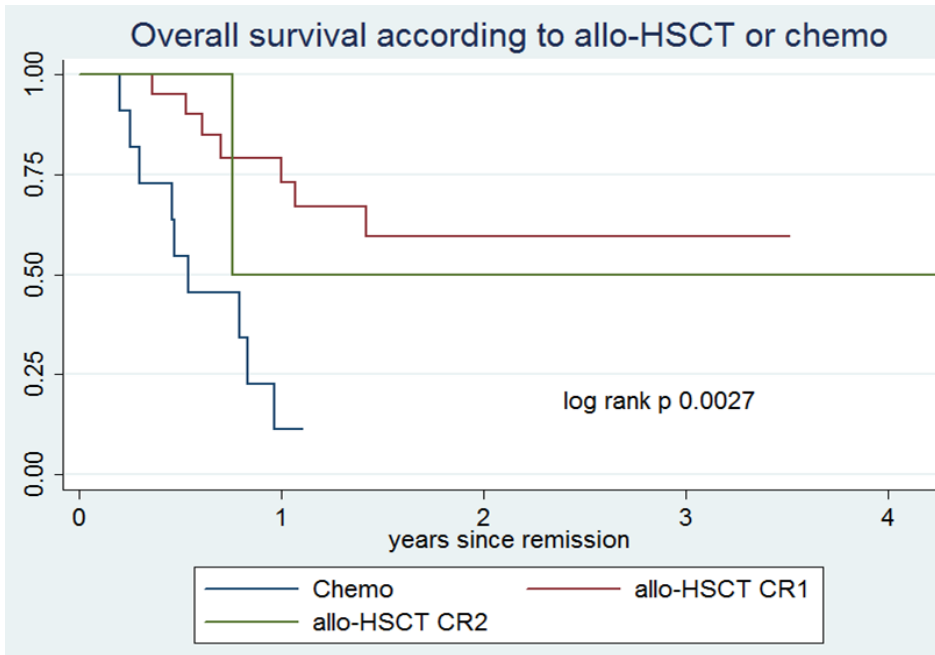
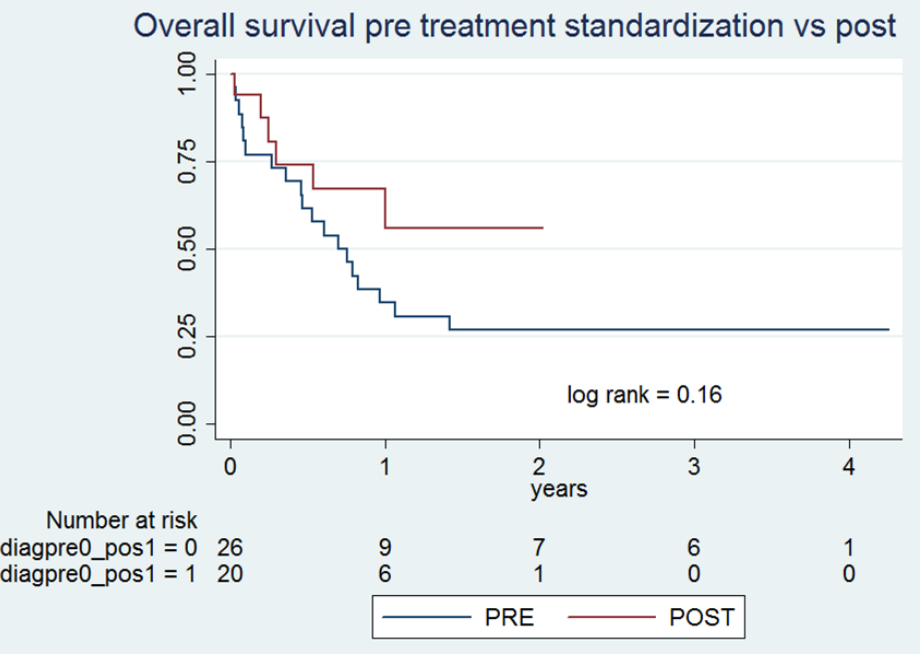
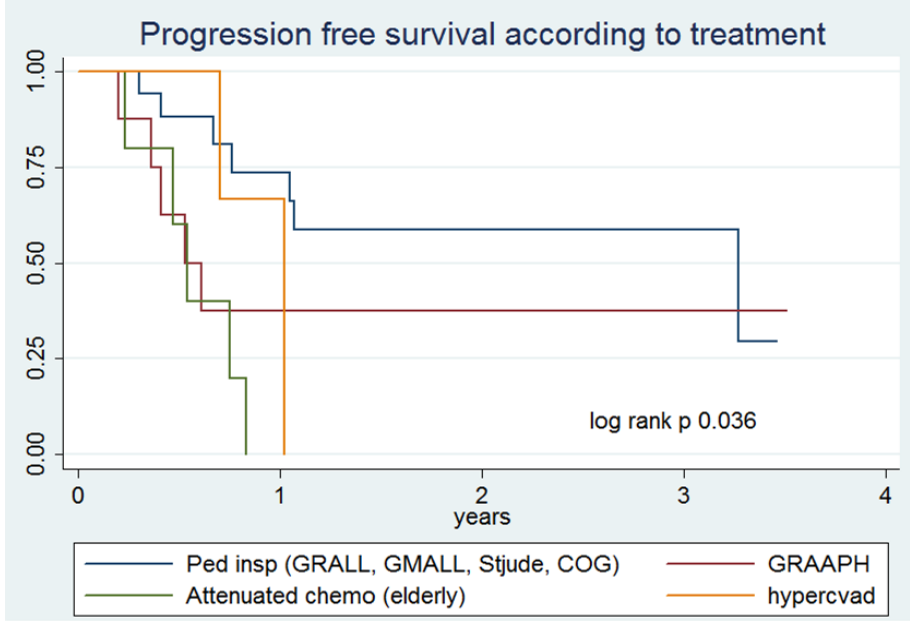
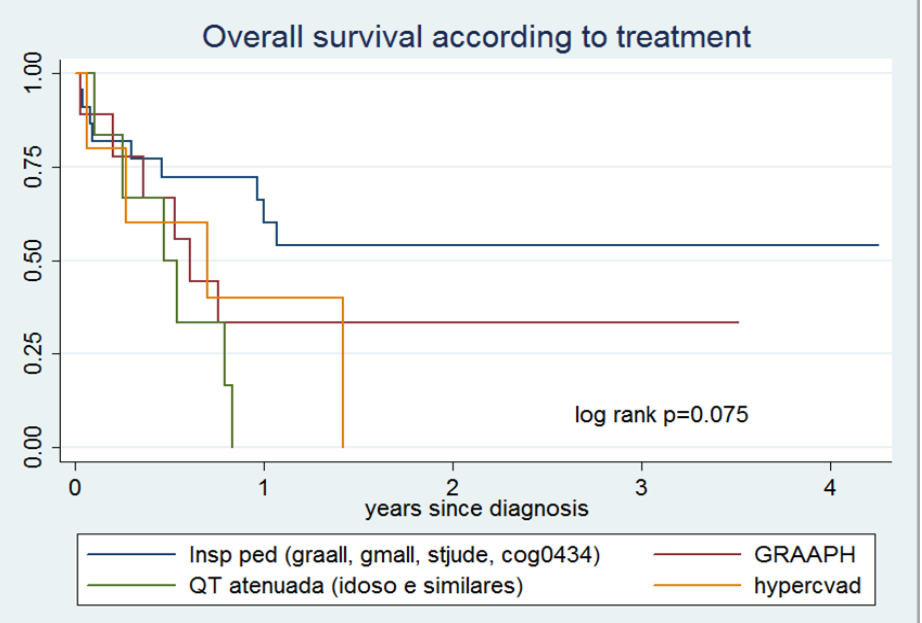
n=46 (2018-22)



- BFM (3,4%)**
- COG ALL (6,89%)**
- FLAG-Dauno + ITK (3,4%)**
- GMALL (1,72%)**
- GRAAL (32,7%)**
- GRAAPH (20,6%)**
- HYPERCVAD (8,6%)**
- PETHEMA (3,4%)**
- ST JUDE (17,24%)**



ALL patients n=46 (2018-22)



Indicações de TCH em RC1

GRAALL 05

GB > 30,000/mcL
Acometimento do SNC (LCR+ ou Sintomas)
CD10- LLA imatura
t(v;11) e KMT2A-
t(1;19) e E2A/PBX1+
Cariótipo Complexo
Diploidia baixa (< 40)
Triploidia (60-78)
Corticorresistência (pré-fase)
Persistência de blastos D8
Ausência de CR após indução

PETHEMA HR 11

Idade 30-60 anos
GB > 30,000/mcL (LLA B)
GB > 100,000 mcL (LLA T)
LLA Early T
LLA T Madura (CD1a+, sCD3+,
CD4+ ou CD8+)
LLA pró B (CD34+/CD10-)
t(v;11) ou KMT2A-
Hipodiploidia
Cariótipo Complexo
E a presença de DRM +

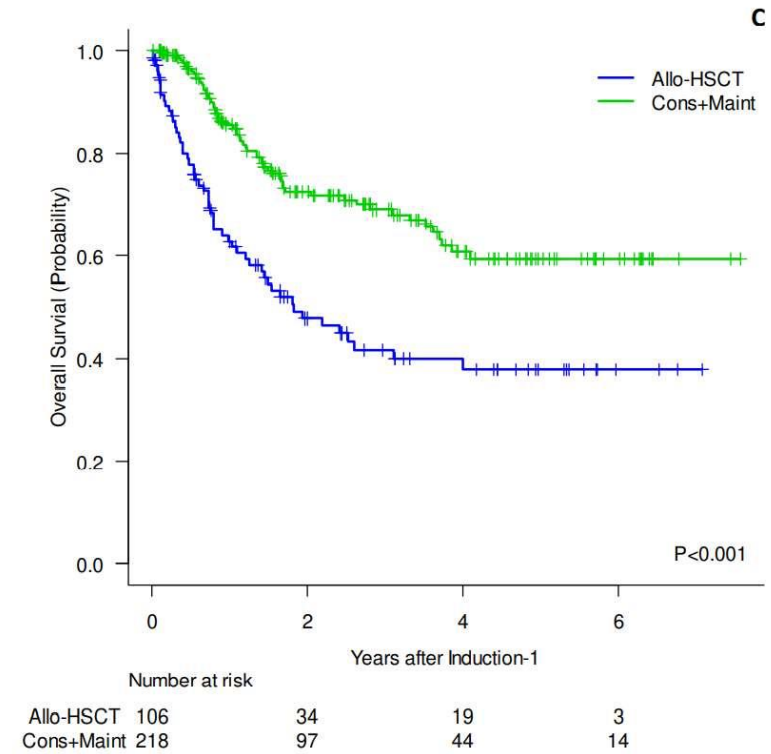
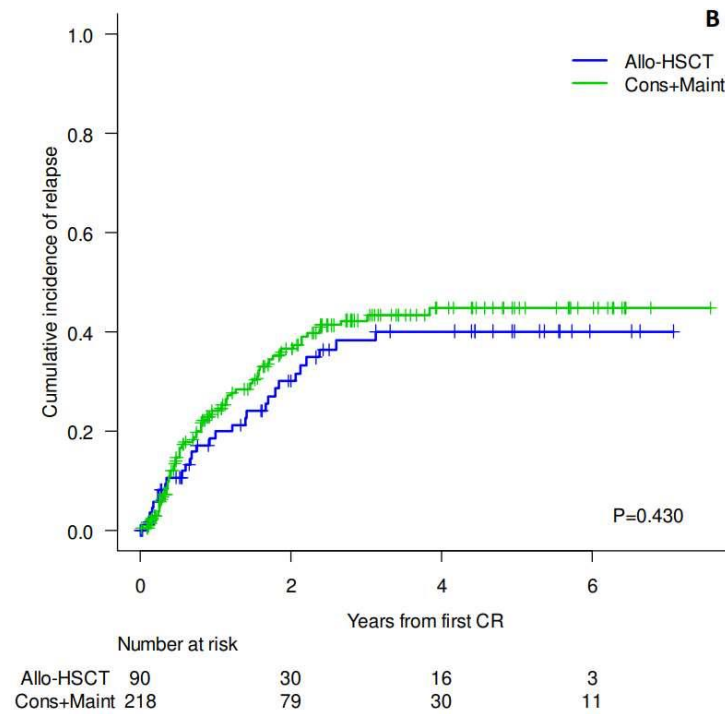
CALGB 10403

Falha de Indução (BI > 25%)
Hipodiploidia (< 44)
t(9;22) ou BCR-ABL1
DRM d29 > 1%
DRM d84 > 0,01%
t(v;11) ou KMT2A- e Slow Resp.

LLA Early T?
Ph1-like?

PETHEMA HR11

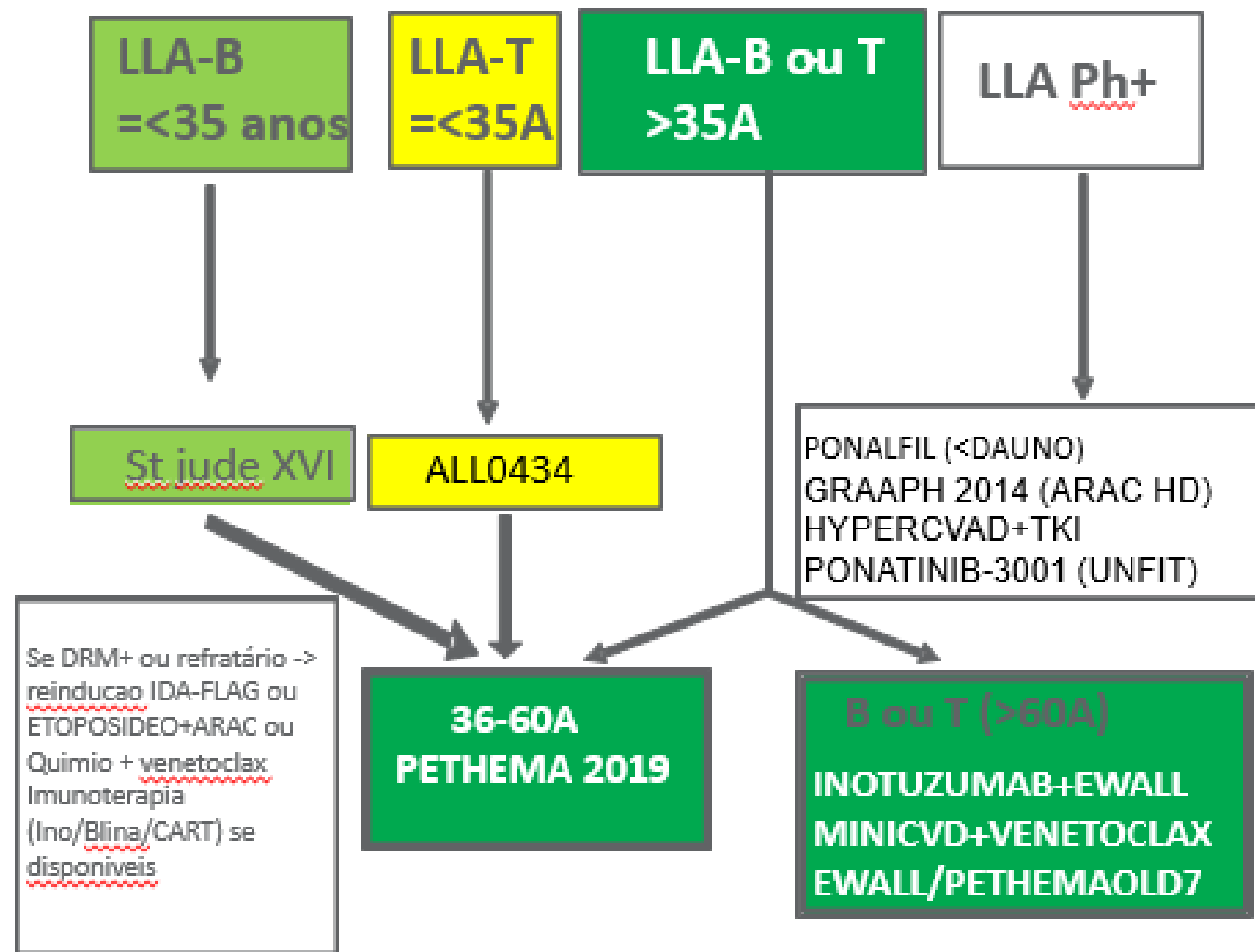
DRM-/consolidação vs DRM+/HSCT



“Melhor” protocolo de indução com QT/DRM

- Protocolo baseado em ped (CALGB, PETHEMA, etc)
- DRM de acordo com protocolo
- Tentativa de eliminar TMO em 1ª RC em baixo risco e DRM-
- Blinatumomab para DRM+ (pré TMO)

Antecipação do uso de blinatumomab (ECOG, ASH 2022)?





LLA-B Ph- <55: CALGB 10403

LLA-B Ph- 55+: mini-Hyper-CVD + Blina +/-TMO

LLA-B Ph+ <55:GRAAPH

LLA-B Ph+ 55+: ALBA modificado

LLA-T <55: CALGB 10403

LLA-T 55+: mini-Hyper-CVD

Lucia Lee
Andre Dias Américo
Fabio Pires



Eduardo Chap Chap

obrigado!
fkerbauy@gmail.com