Acute leukemia & agressive lymphoma in children

BHS training course, 16/12/2023

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Age specific incidence of pediatric cancer

- Cancer incidence in children (<16y): **~150 per million/year**
- 1/600 children is diagnosed with cancer before 16 y
- <1% of cancer burden in Belgium

2004-2020 **Annually in Belgium**:

340 children (until 15y)

180 adolescents (15-18y)

https://kankerregister.org/publications

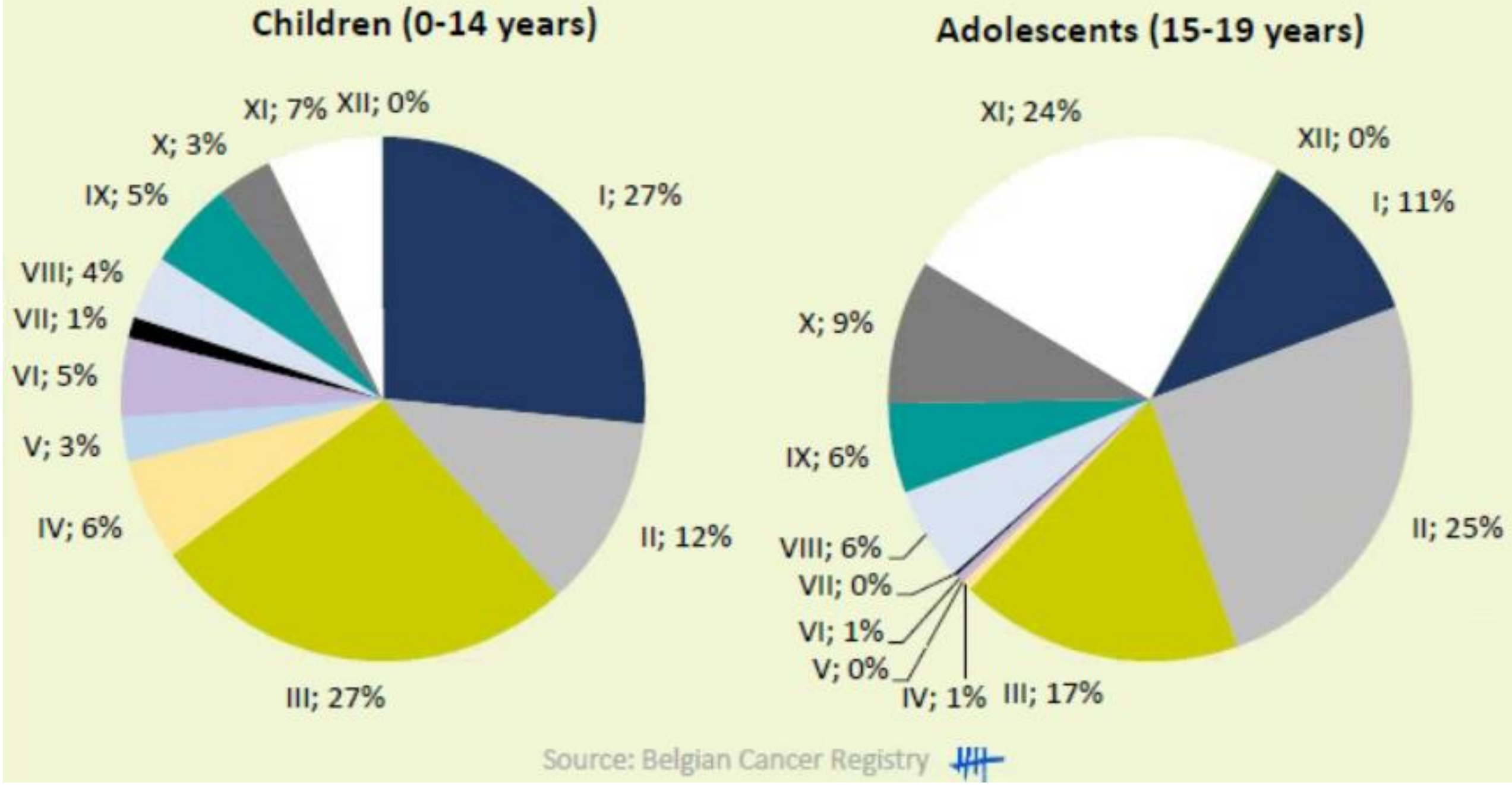
Belgian Cancer Registry

Pediatric cancer types

Code	Description
I	Leukaemia
II	Lymphoma
III	Brain tumours
IV	Neuroblastoma
V	Retinoblastoma
VI	Renal tumours
VII	Hepatic cancer
VIII	Bone tumours
IX	Soft tissue tumours
X	Germ cell tumours
XI	Epithelial tumours
XII	Other and unspecified

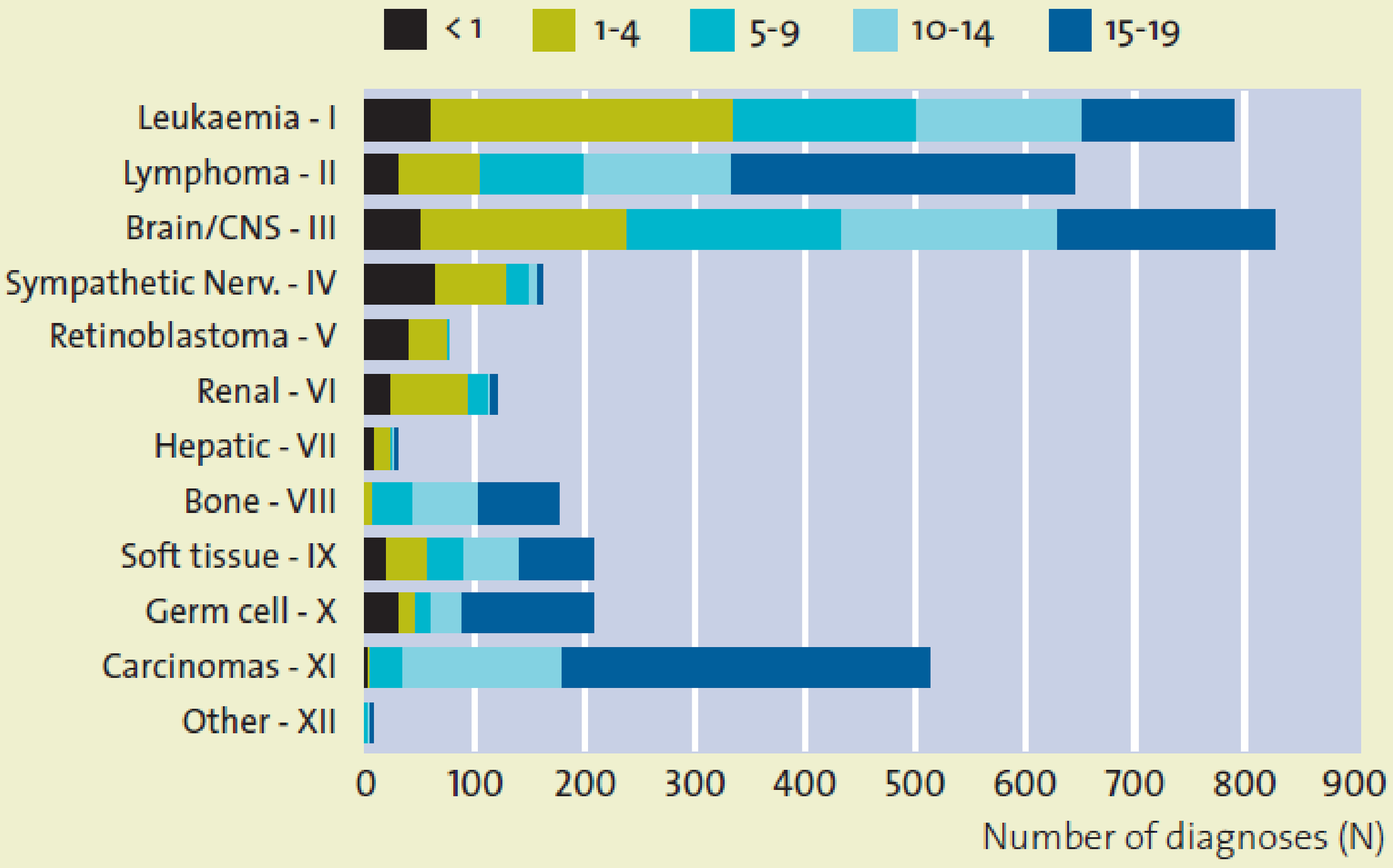
- ALL, AML, CML, JMML, MDS
- Hodgkin, Non-Hodgkin Lymphoblastic Lymphoma
- Medulloblastoma, ependymoma, …
- Nephroblastoma, …
- Hepatoblastoma, …
- Osteosarcoma, Ewing sarcoma
- Rhabdomyosarcoma, …
- Carcinoma, melanoma

Figure 6: Cancer in children and adolescents: incidence by tumour type, Belgium 2011-2020



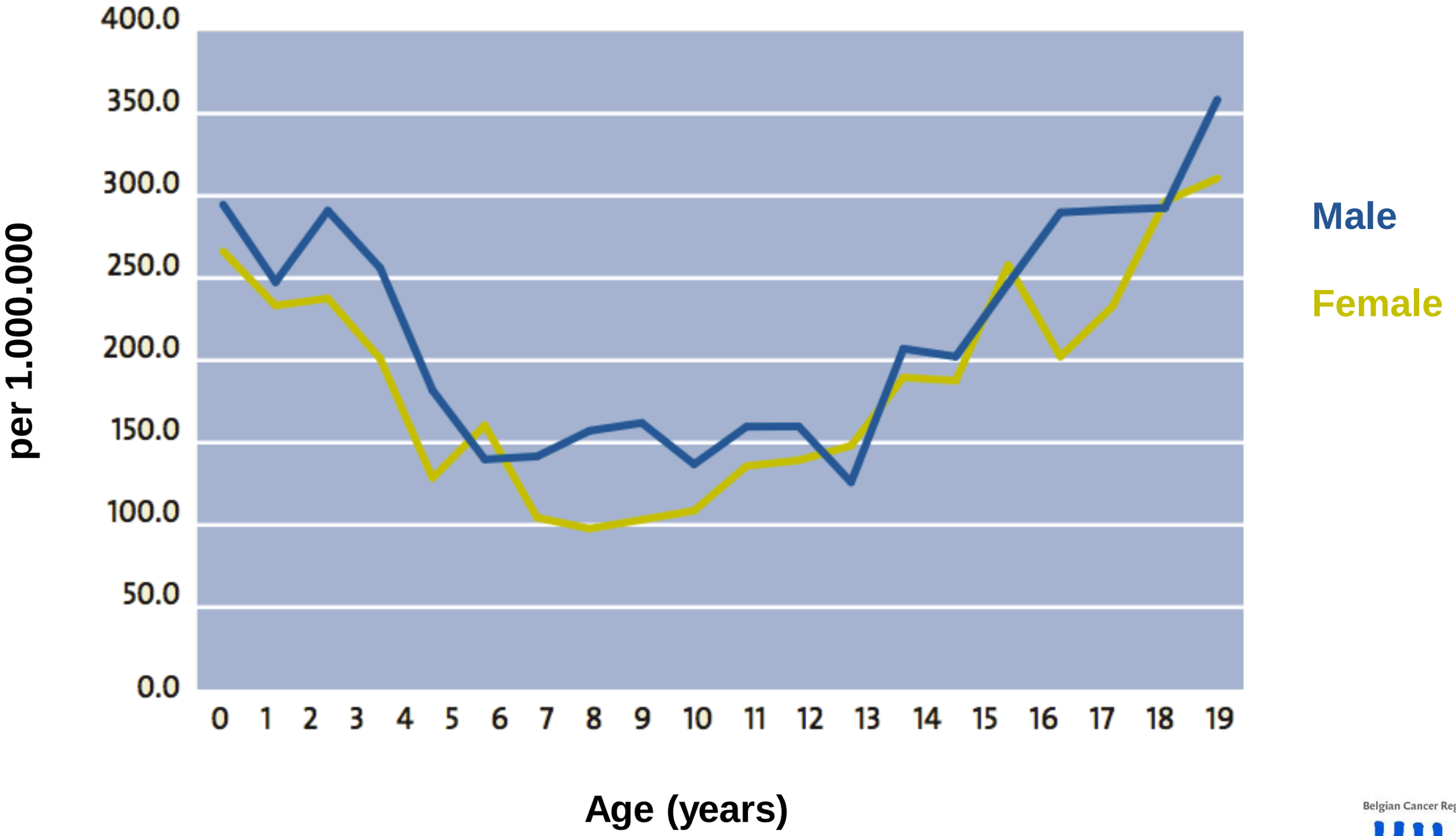
I : Leukemia
II: Lymphoma

Figure 5 Cancer in children and adolescents: New diagnoses by tumour type and age group, Belgium 2010-2016



Source: Belgian Cancer Registry

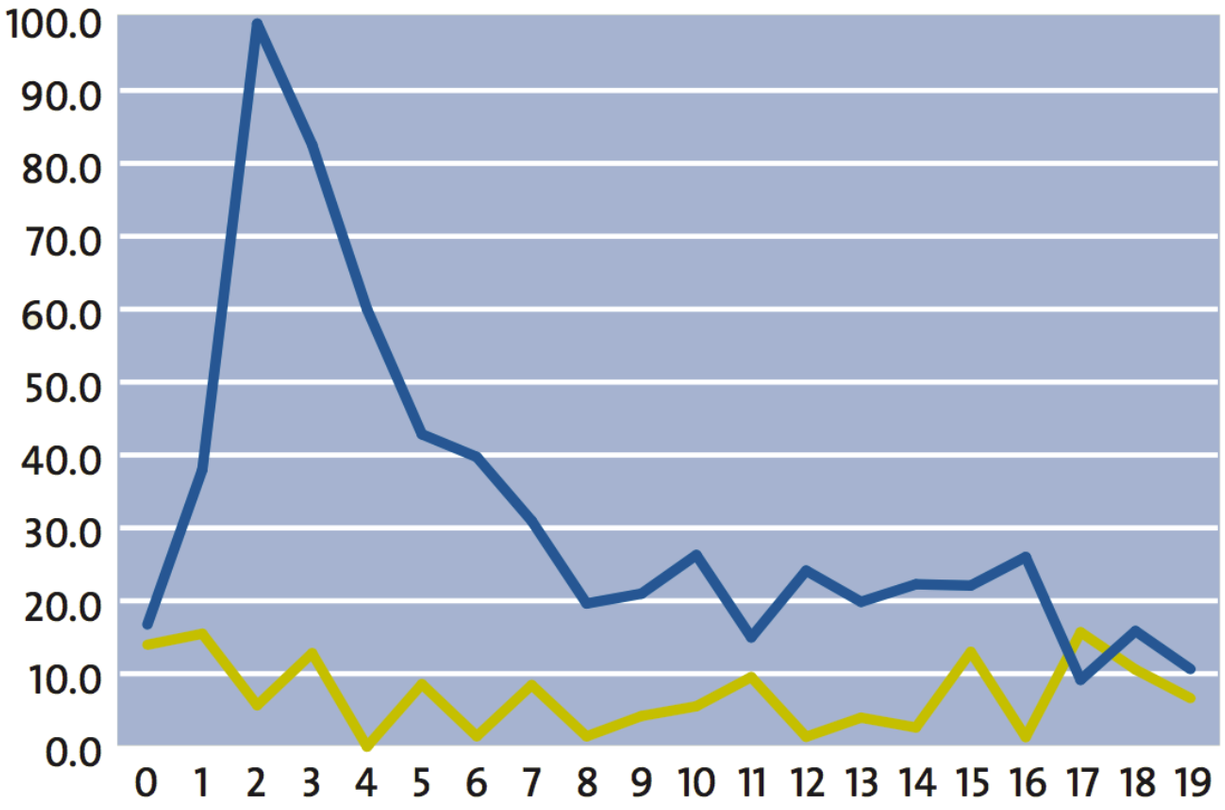
Age specific incidence of pediatric cancer

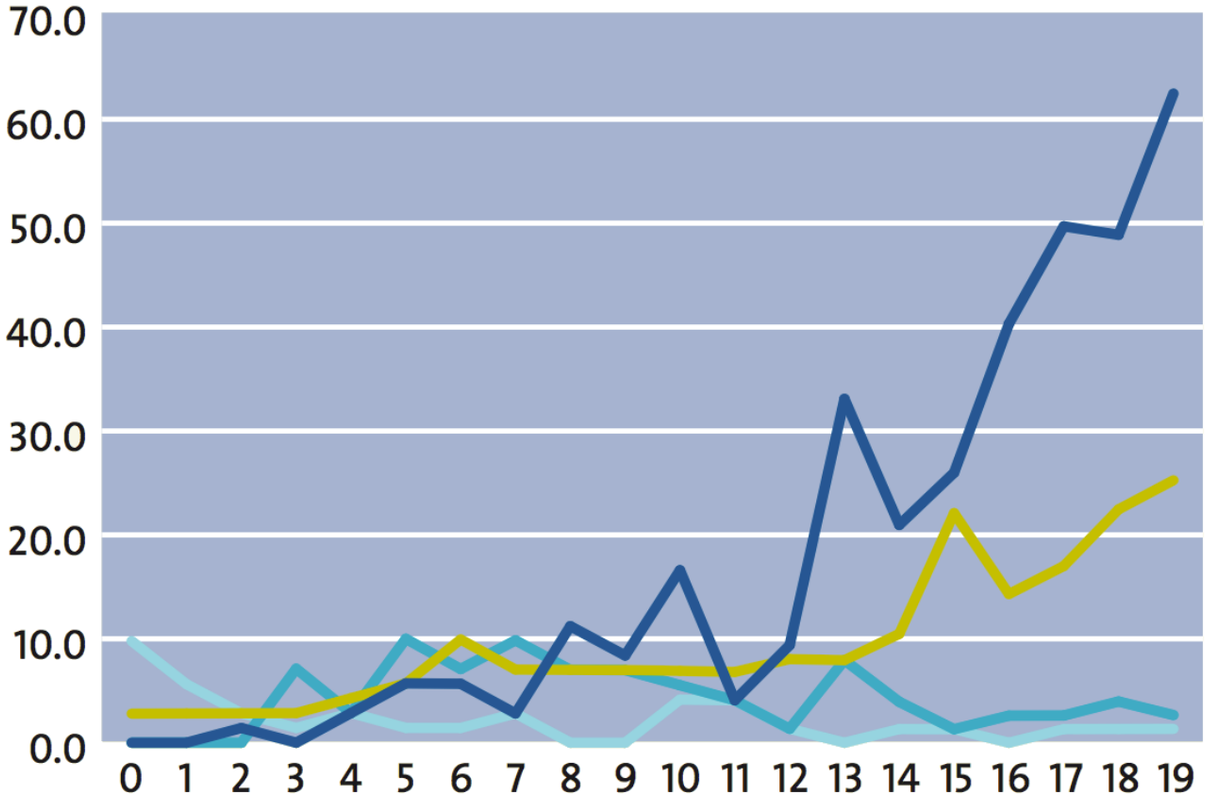


Belgian Cancer Registry

Acute lymphoblastic leukemia

Acute myeloid leukemia



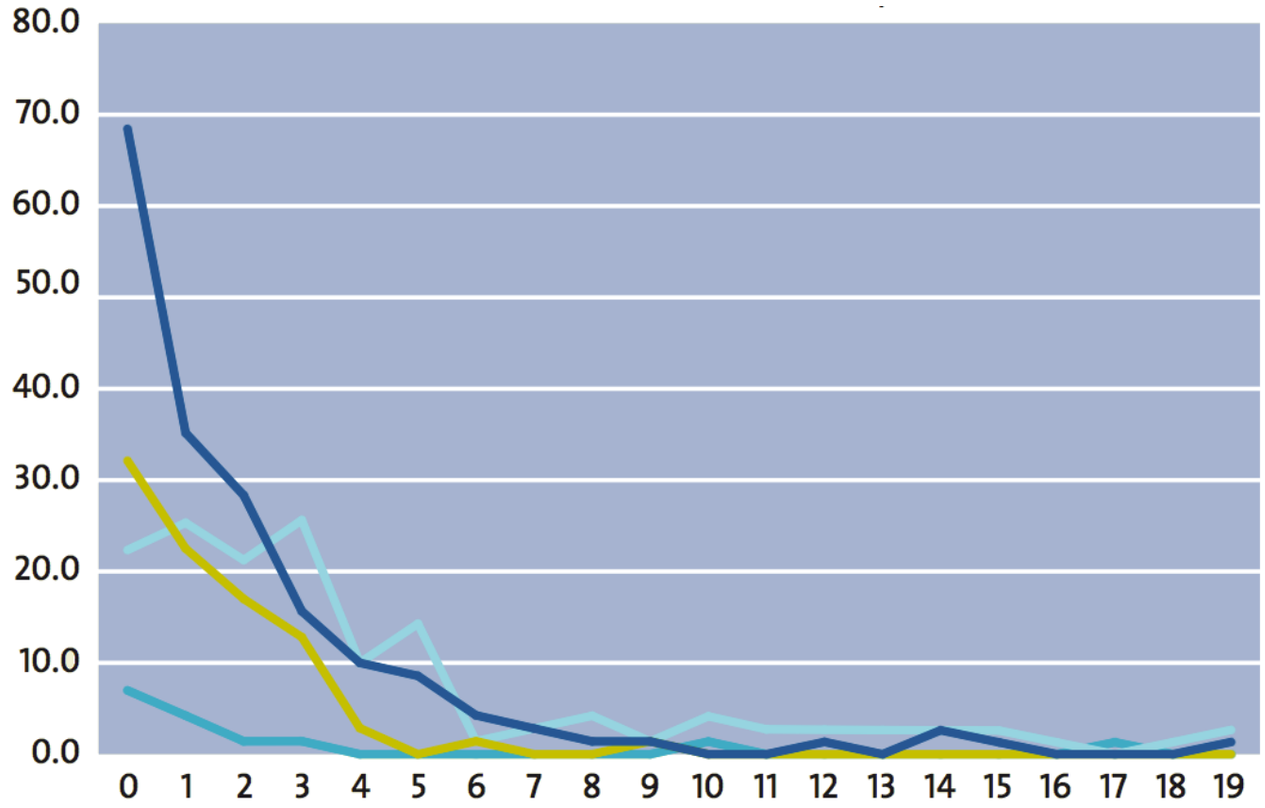


Neuroblastoma

Retinoblastoma

Nephroblastoma

Hepatoblastoma



Age specific incidence rate (/1.000.000)

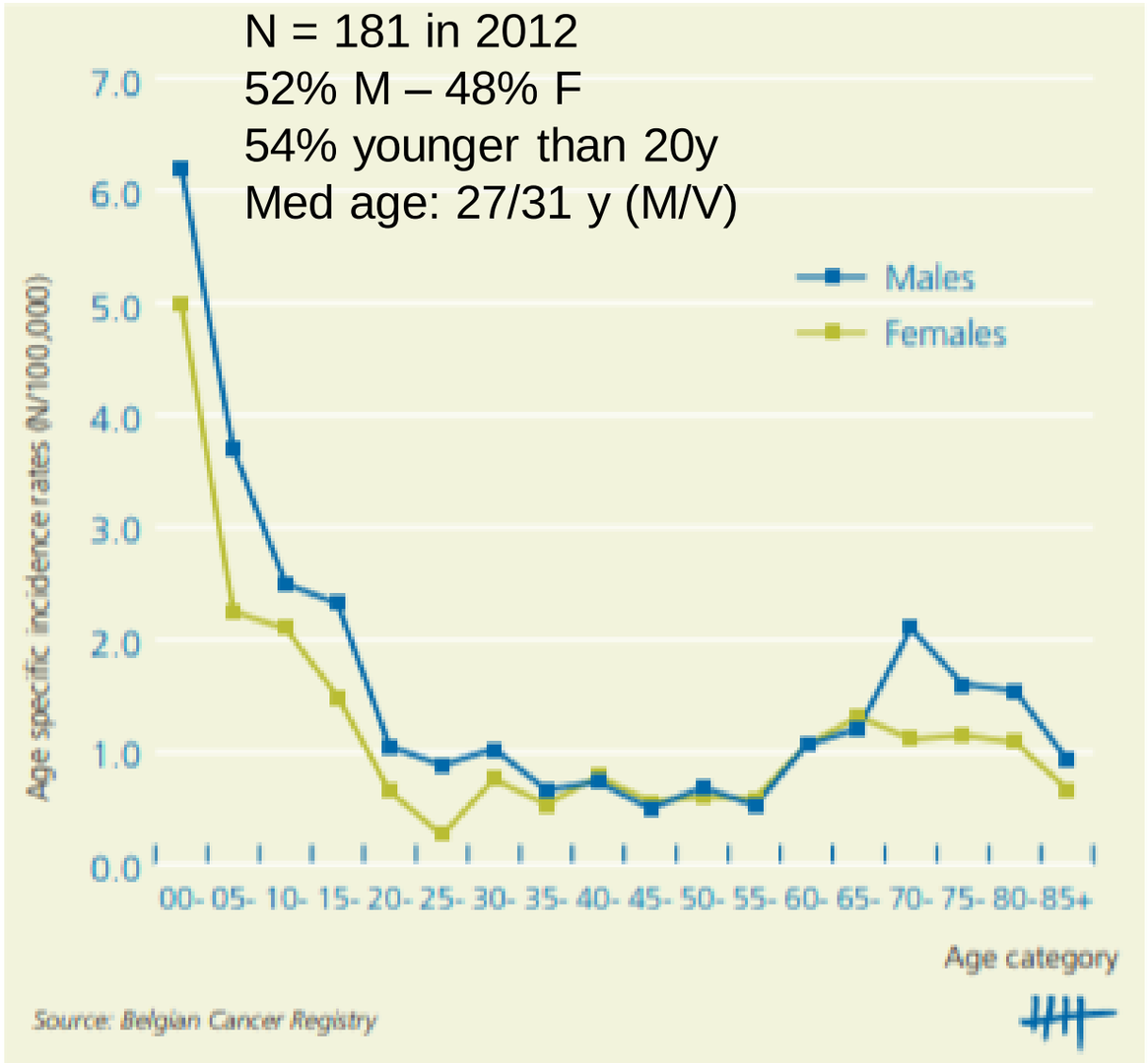
Hodgkin lymphoma

Non Hodgkin lymphoma

Burkitt lymphoma

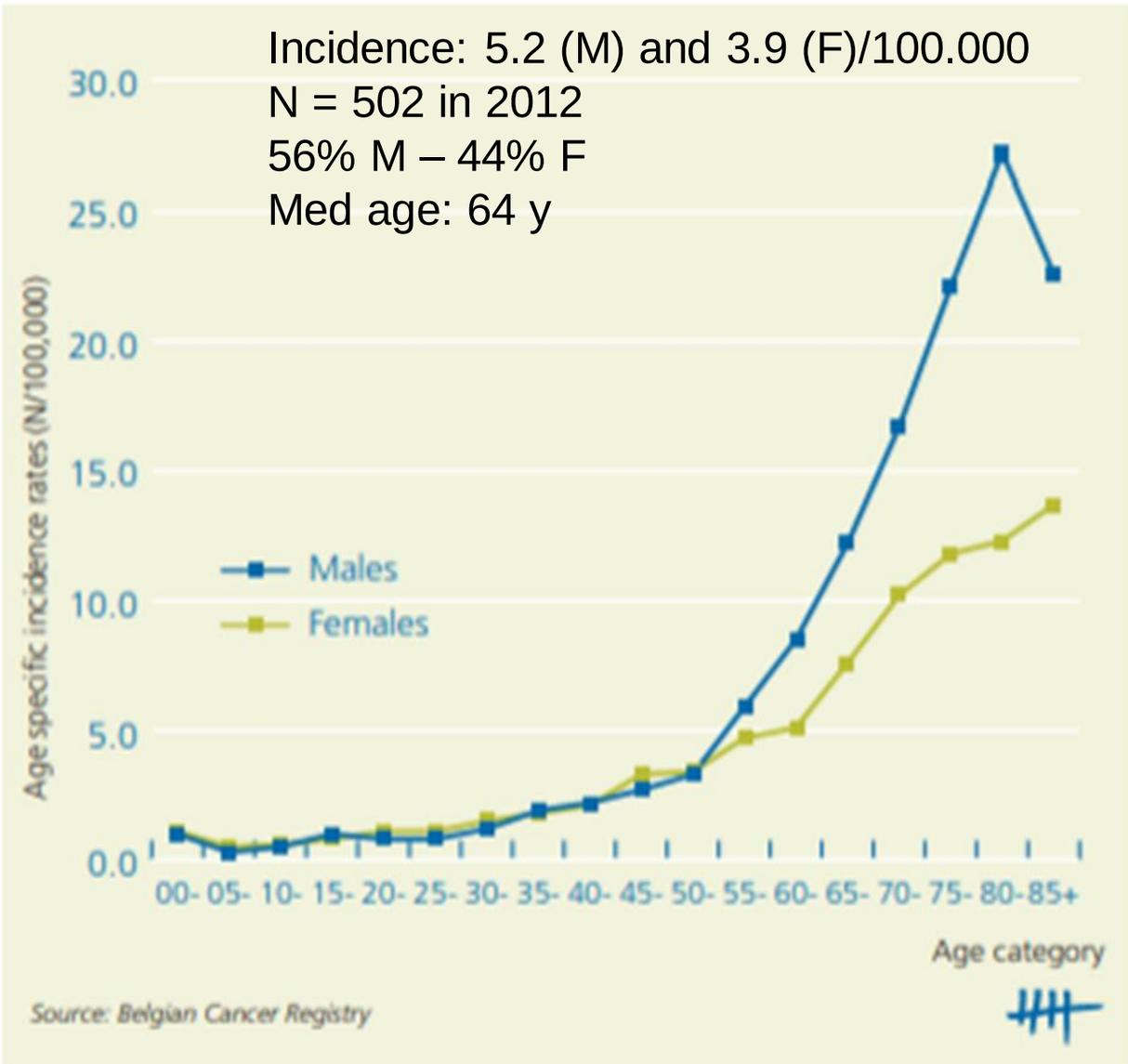
Other lymphoma

FIGURE 97 LYMPHOBLASTIC LYMPHOMA/ACUTE (PRECURSOR CELL) LYMPHOBLASTIC LEUKAEMIA: AGE-SPECIFIC INCIDENCE RATES (N/100,000) BY SEX, BELGIUM 2004-2012



Source: Belgian Cancer Registry

FIGURE 111 ACUTE MYELOID LEUKAEMIA: AGE-SPECIFIC INCIDENCE RATES (N/100,000) BY SEX, BELGIUM 2004-2012



Source: Belgian Cancer Registry

Ped leukemia and lymphoma types (0-14y) (Belgian Cancer Registry, 2004-2013)

- **Leukemia** — **25%**
- **Lymphoma** — **13%**
  - Hodgkin lymphoma — 4%
  - Non Hodgkin lymphoma — 9%
    - Burkitt lymphoma (50-60%) — 3%
    - Diffuse large B-cell lymphoma (DLBCL)
    - Lymphoblastic lymphoma (25-30%)
      - T-cell (~4/5)
      - Precursor B-cell (~1/5)
    - Anaplastic large cell lymphoma (ALCL) (10-15%)

Agressive lymphoma in children

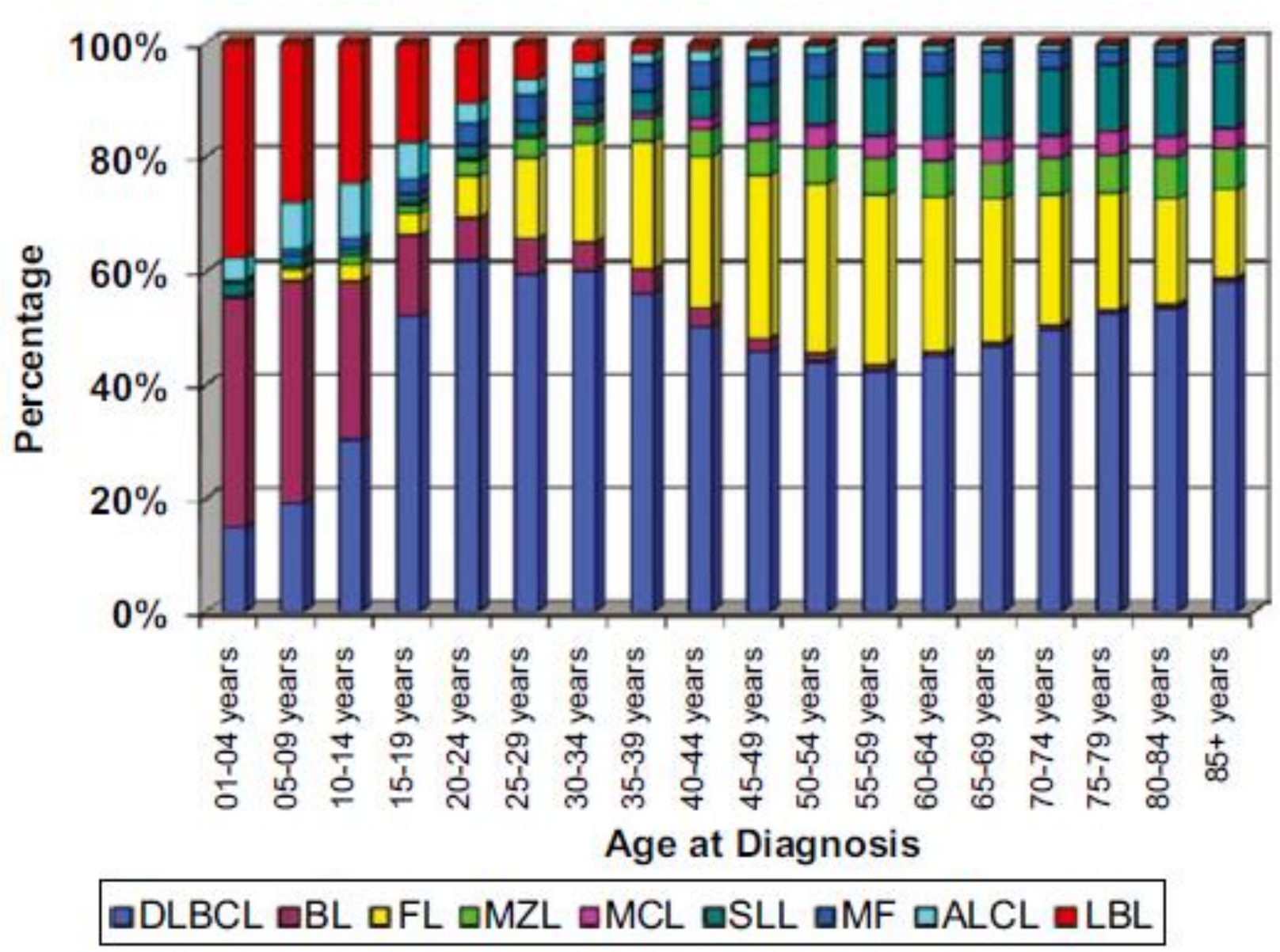
Non Hodgkin lymphoma:

Burkitt lymphoma

Lymphoblastic lymphoma

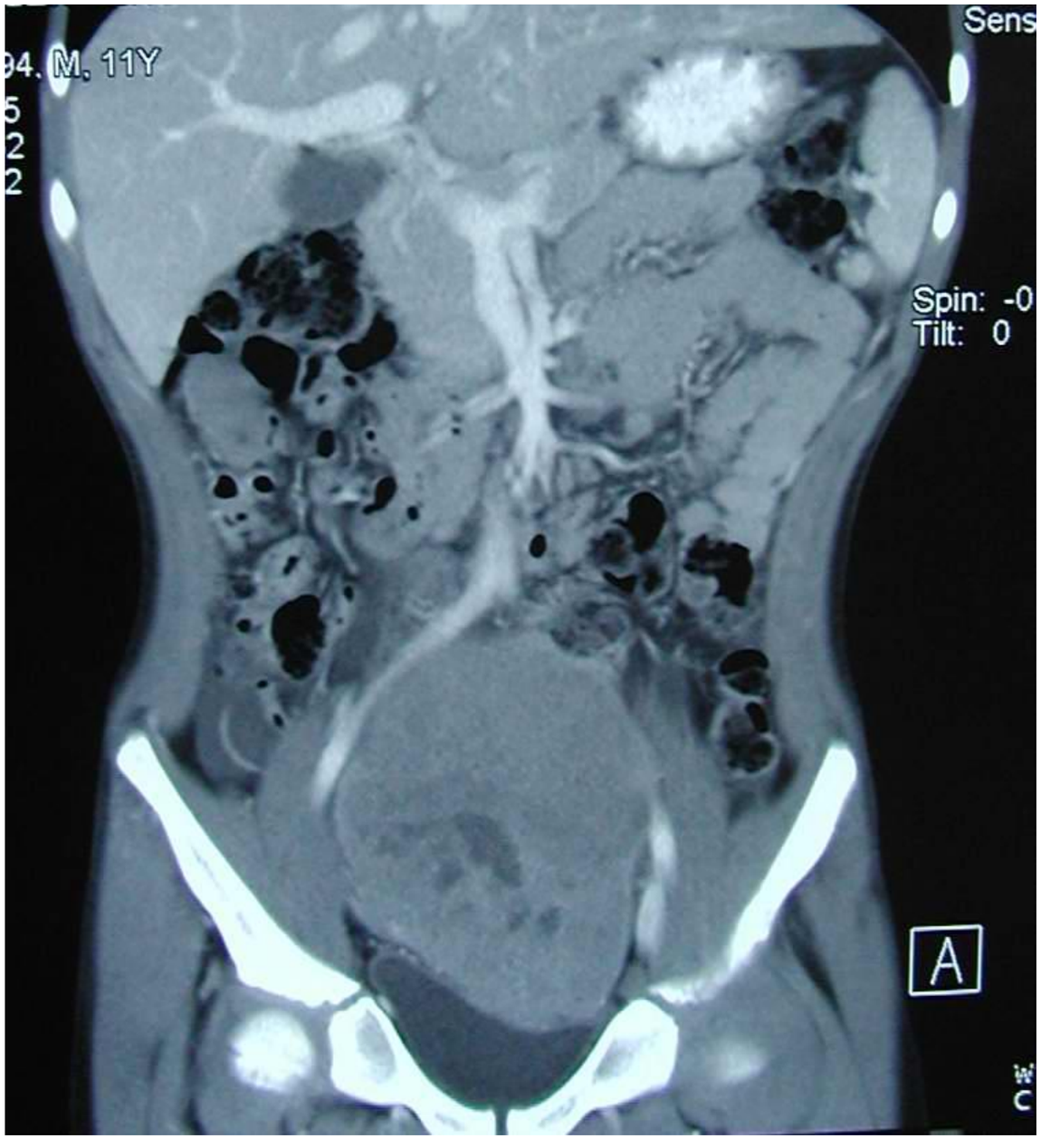
DLBCL

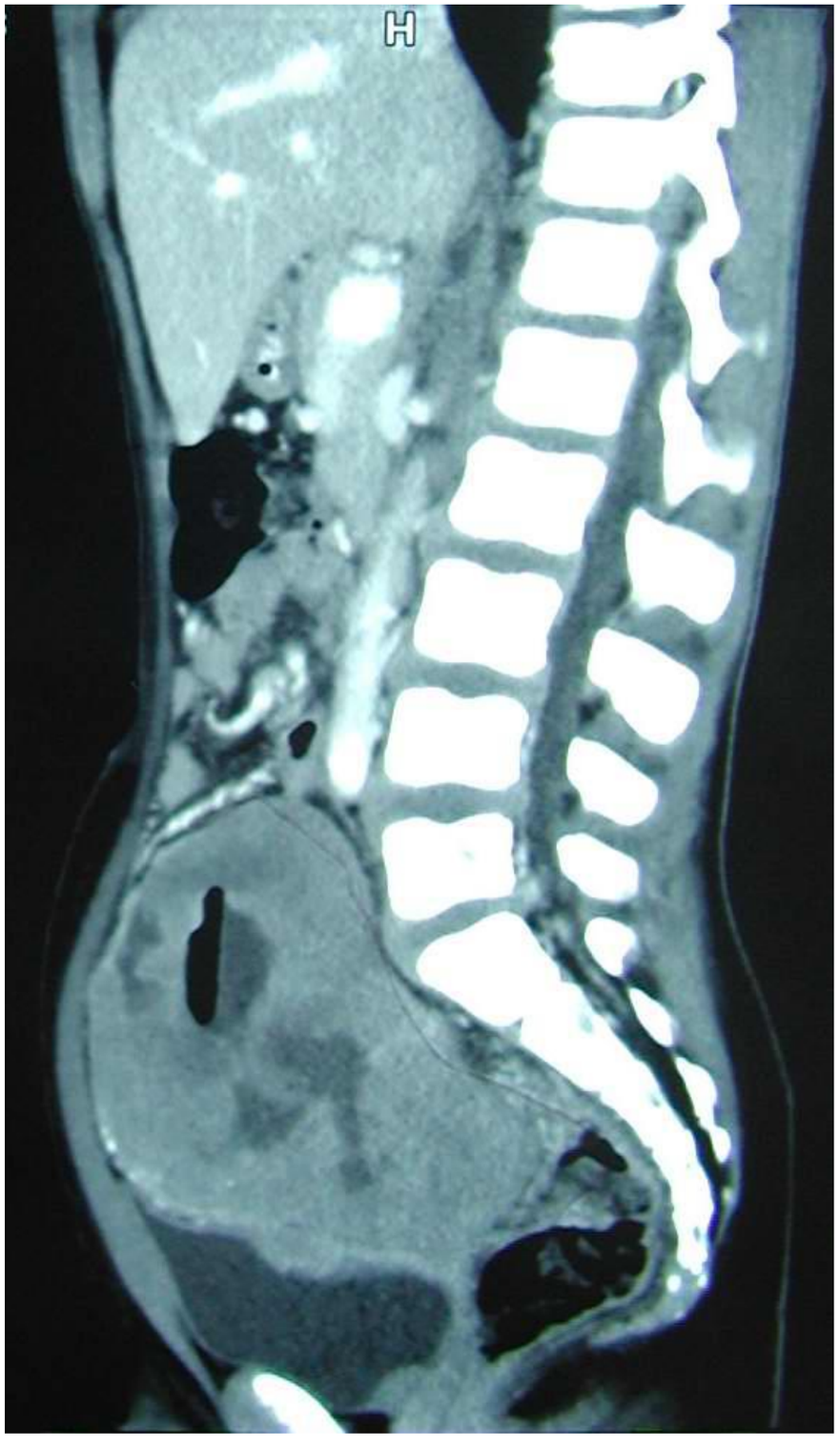
ALCL



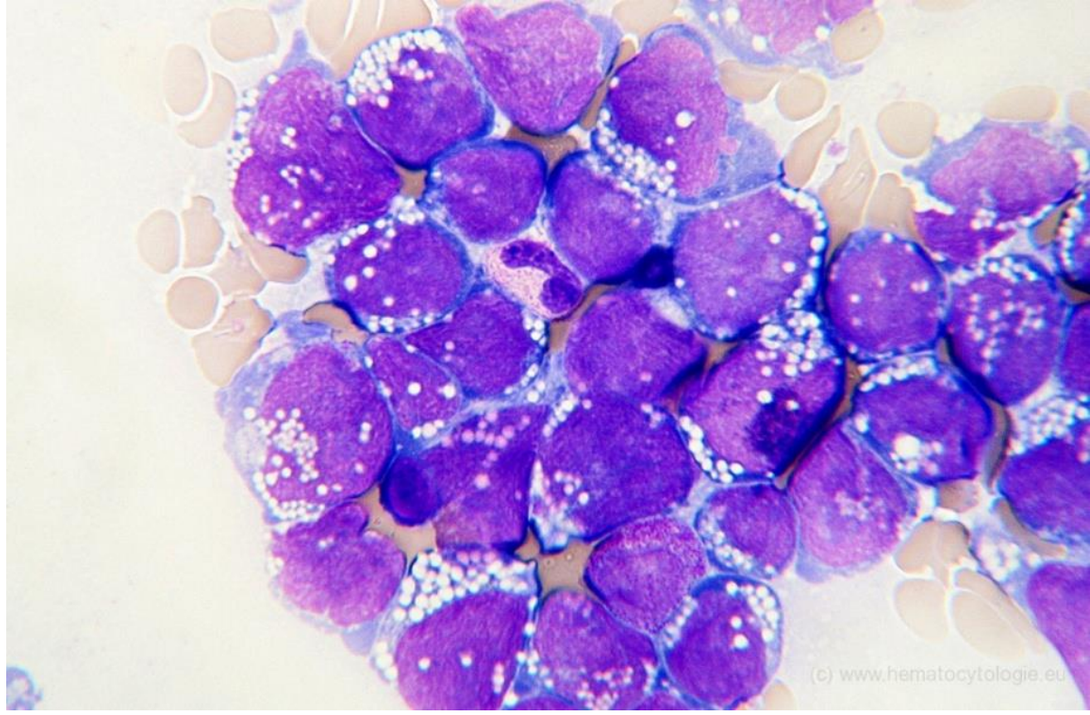
Sandlund and Martin, Hematology 2016

Burkitt lymphoma





Burkitt lymphoma



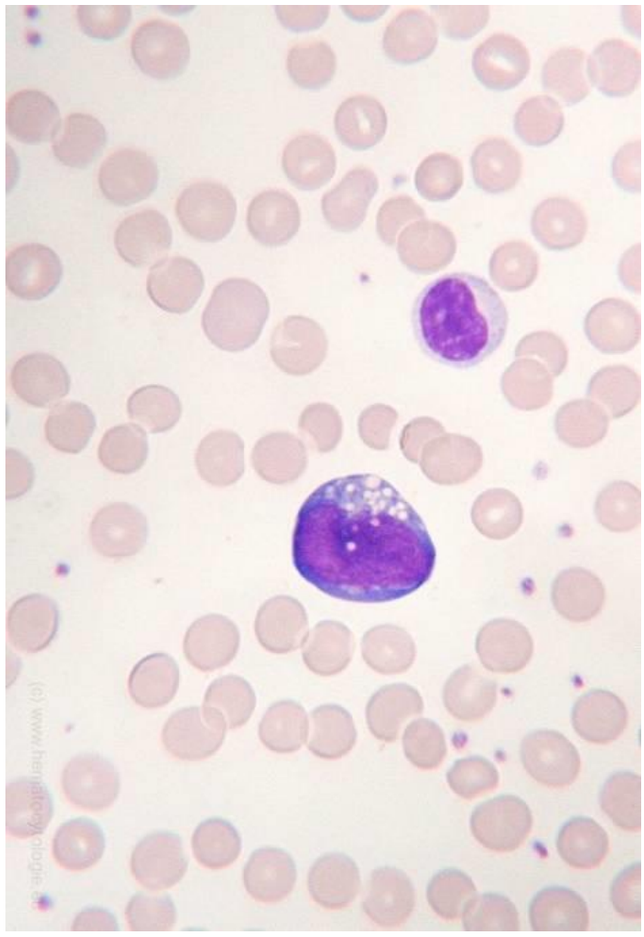
- 50-60% of pediatric NHL
- > abdominal localisation
- Murphy stage I to IV – Burkitt leukemia
- Typical morphologic features: FAB L3 cells
- Immunophenotyping:

  mature B: sIg, CD19-20-22-10
- Cytogenetic – molecular:

  c-myc (chrom 8) translocation

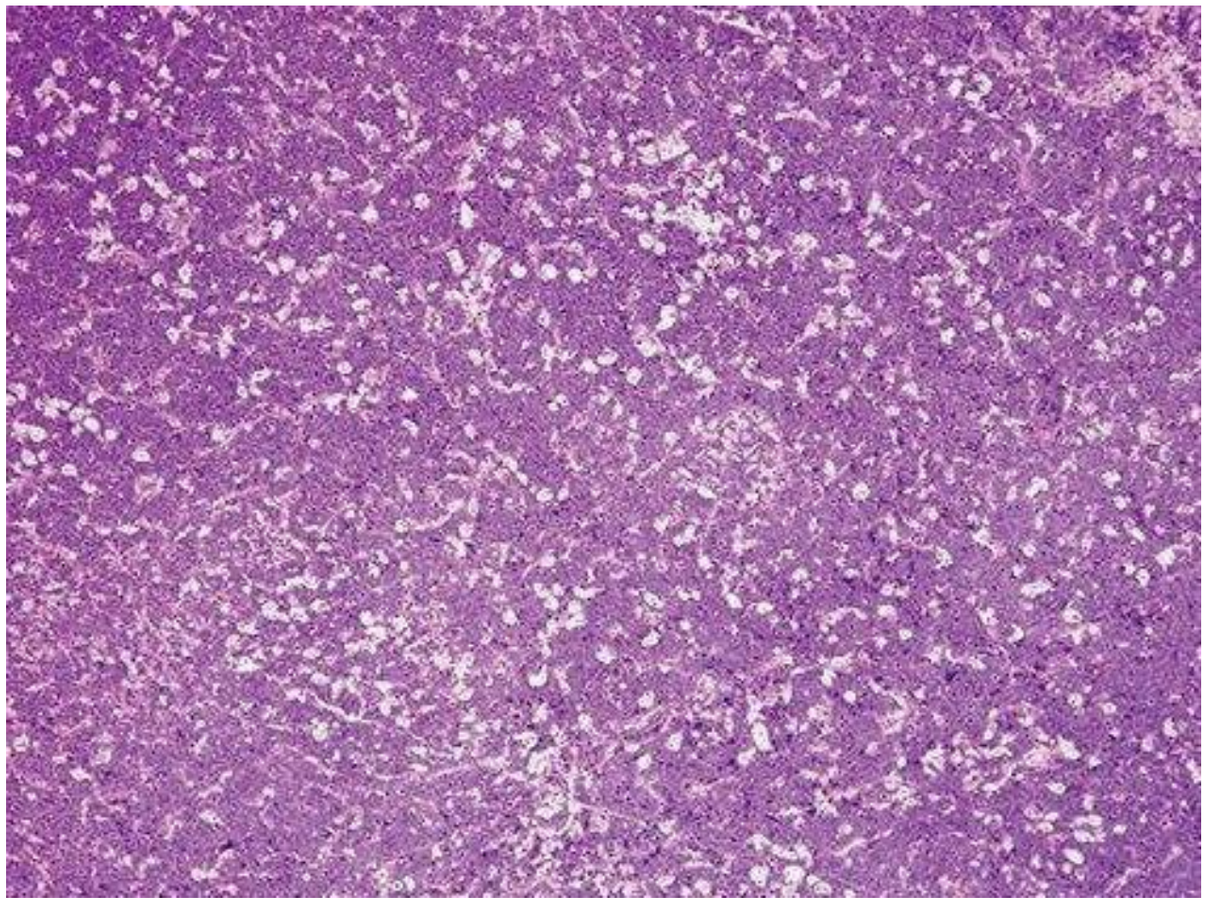
  t(8;14), t(8;22), t(2;8)

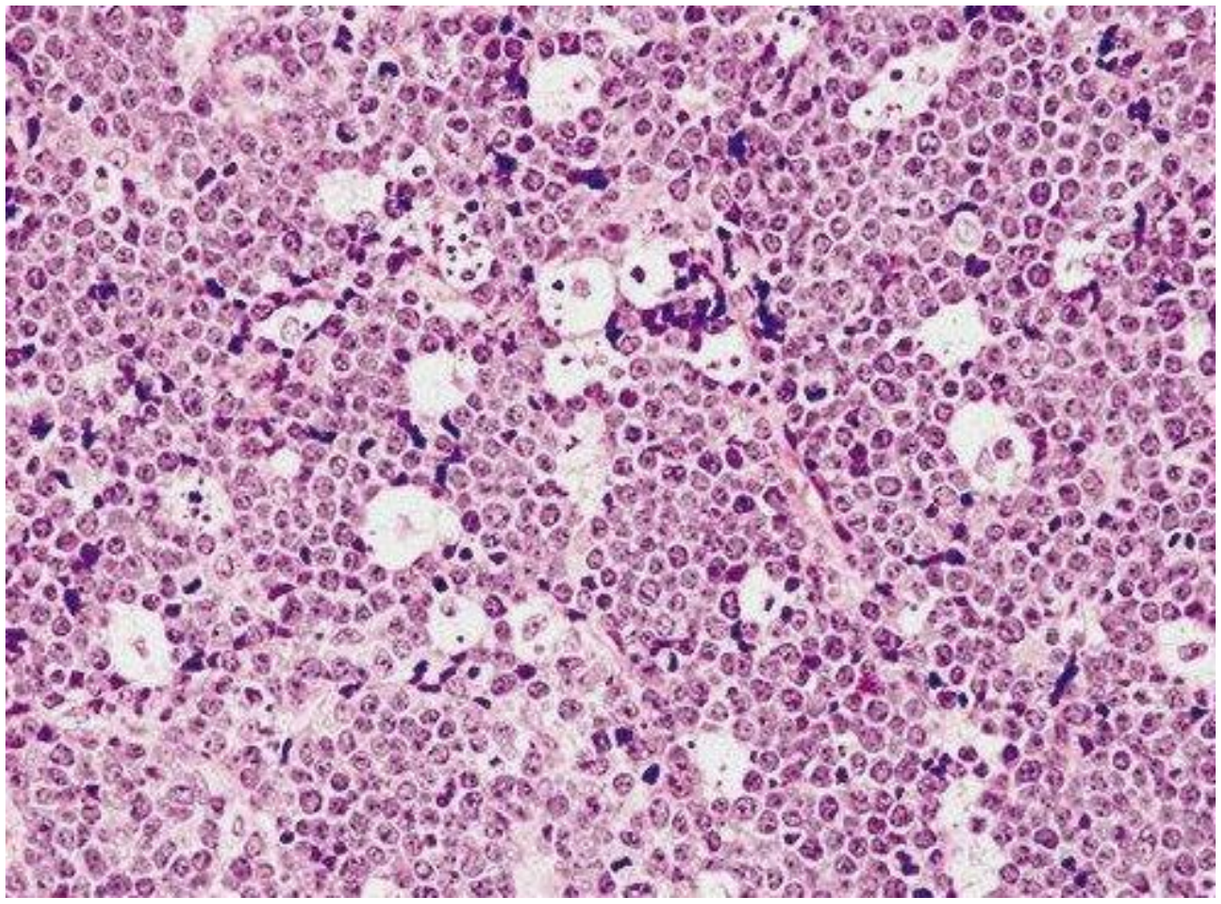
Heavy-chain Ig gene Light-chain Ig gene



Burkitt lymphoma

- Histology: “small round blue cell” tumor
- = diagnostic dilemma
- “starry sky” pattern





Burkitt lymphoma

- Treatment: intensive polychemotherapy
- Survival : ’70: 10 % → ’90: 90 %
- **Inter-B NHL 2010 Low/Intermediate risk**
  - No immunodeficiency, Stage I-III, LDH <2xULN
- **Inter-B NHL Ritux 2010 High risk**
  - Stage III + LDH ≥ 2xULN, Stage IV, B-leukemia

High proliferation rate
High tumor burden
⇒ Risk of tumor lysis syndrome

Inter-B NHL 2010 Low/Intermediate risk

<u>Group A</u>: resected stage I and resected abdominal stage II

COPAD	COPAD

No IT

<u>Group B low/intermediate</u>: B-low: non resected stage I and II
B-intermediate: stage III with LDH<u>≤</u> Nx2

Prephase	*Induction*		*Consolidation*	
COP*	COPADM	COPADM	CYM#	CYM

HD MTX 3g/m² infused over 3h, one TIT per course ("modified" COPADM and CYM)
**Non responder at D7 assigned to C1*
 # If residual mass with documented viable cells, « slow responders » assigned to C1 starting at 1st CYVE

Inter-B NHL Ritux 2010 (high risk B-cell NHL or B-AL)

GROUP B – high risk

- stage III with high LDH level (>N x2)
- Stage IV CNS negative

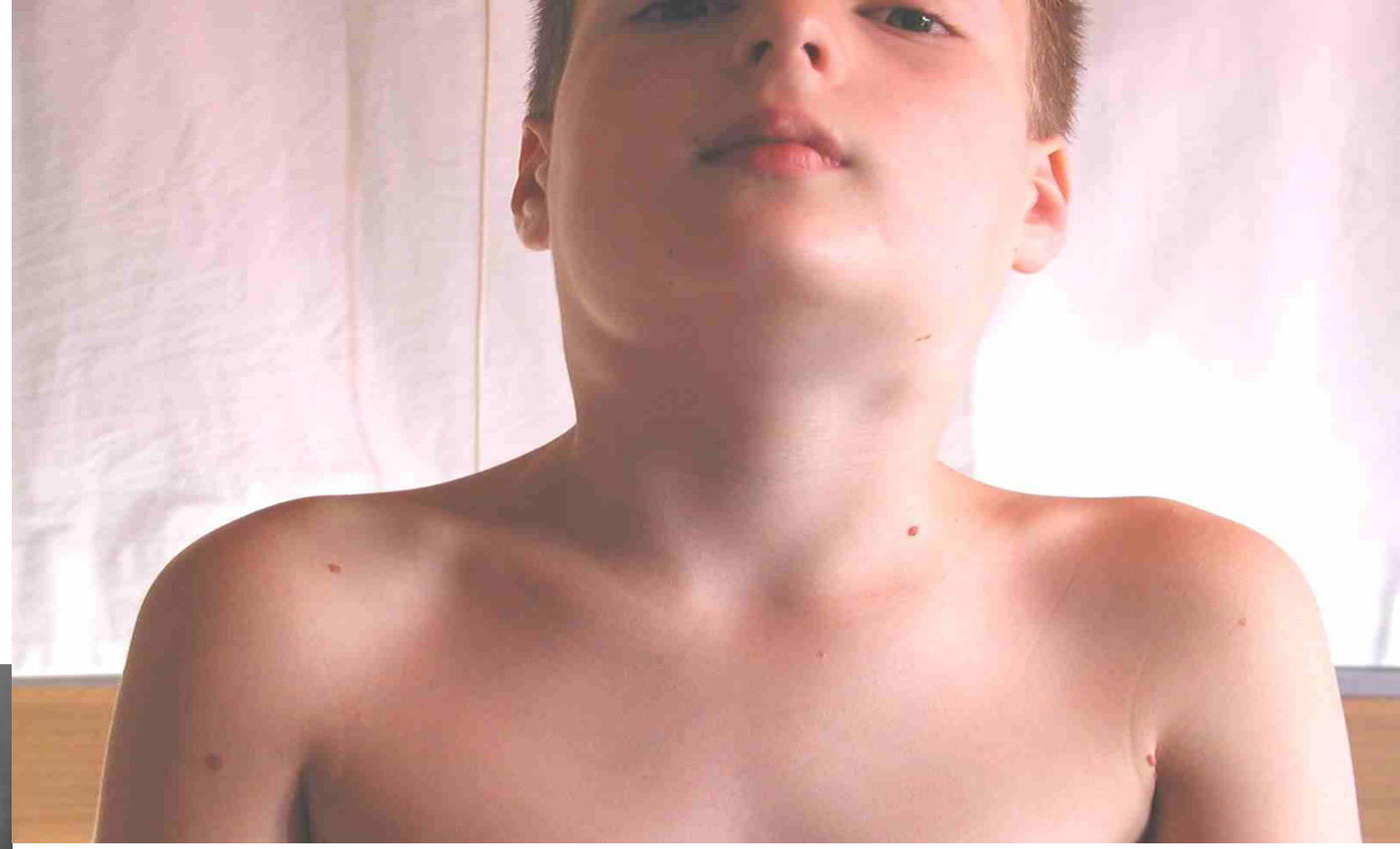
GROUP C1

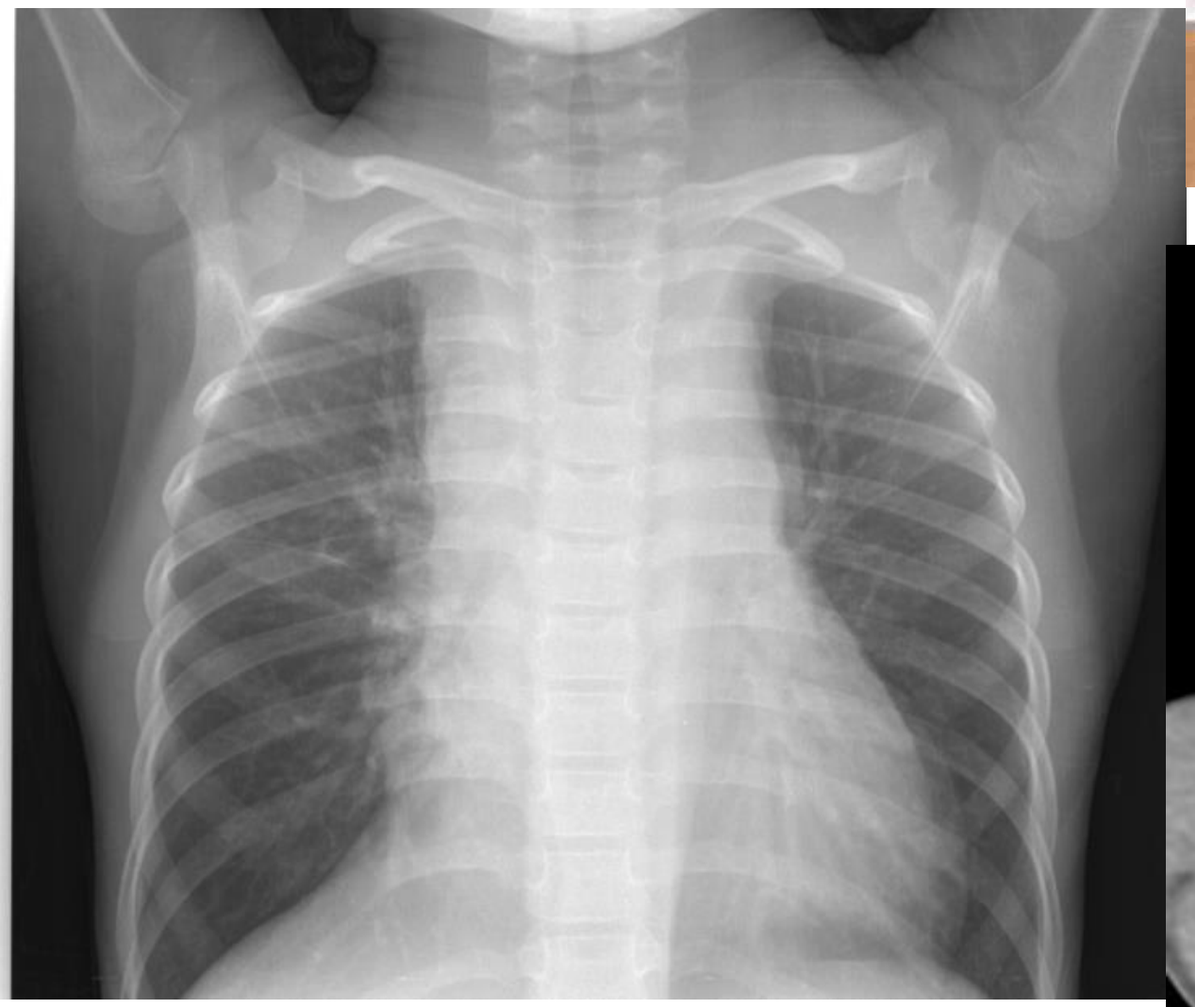
- B-AL CNS negative
- Stage IV & B-AL CNS positive and CSF negative

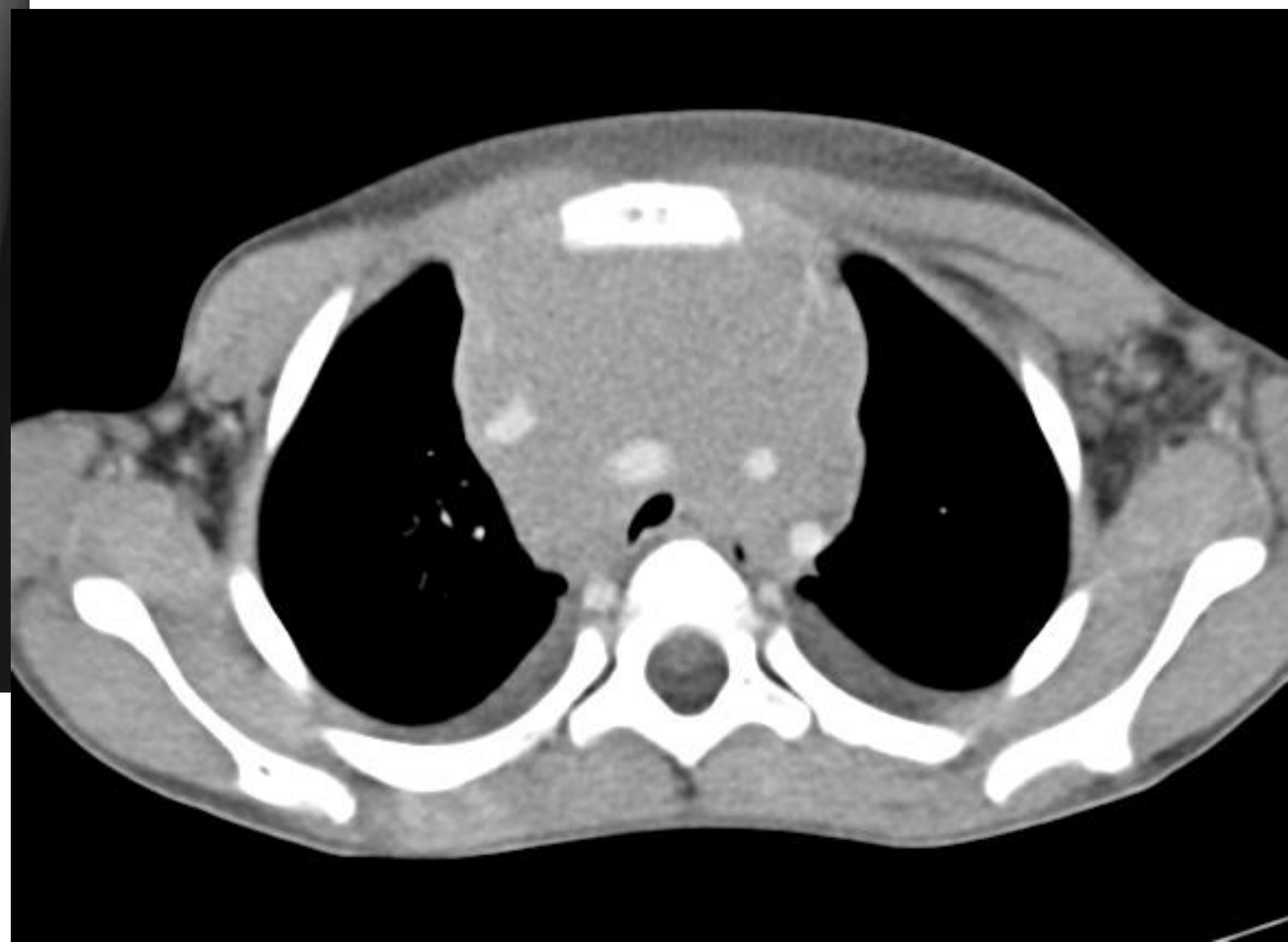
GROUP C3

- B-AL CSF positive
- Stage IV CSF positive

Lymphoblastic lymphoma







Lymphoblastic lymphoma

- 25-30% of pediatric NHL
- 80% T-cell and 20% precursor B-cell
  - T→ mediastinal involvement
  - pB → skin, subcutaneous tissue, bone

Main localization		
Bone	13	26·4
Skin or sub cutaneous	12	22·6
Chest	6	11·3
Bone marrow	7	13·2
Lymph nodes alone	7	13·2
Gonad	4	5·7
Head and neck	2	3·8
Kidney	1	1·9
Digestive	1	1·9

53 pts, LMT96 & EORTC 88-95
Ducassou et al, Br J Haematol 2011

- Overall survival 85% (LBL2018 protocol)

LBL 2018 – Treatment plan

Standard arm

Standard risk group I/II
pB-LBL stage I/II

protocol Ib → protocol M → maintenance

Standard risk group
T-LBL N/F^{mut}
NOTCH1 or FBXW7 mut

protocol Ib → protocol M → protocol II → maintenance

R1

protocol Ia-Pred
protocol Ia-Dexa

High risk group
T-LBL N/F^{WT}
pB-LBL stage III/IV
all CNS positive patients

Standard arm

R2

protocol Ib → protocol M
protocol Ib* → intensified protocol M

→ protocol II → maintenance

Intensified arm

Mediastinal Non Hodgkin lymphoma

- Urgency !
- Morphologic (Immunoflow) evaluation of blood and BM
- Imaging: diameter of the trachea

TD<50% **TD>50%**

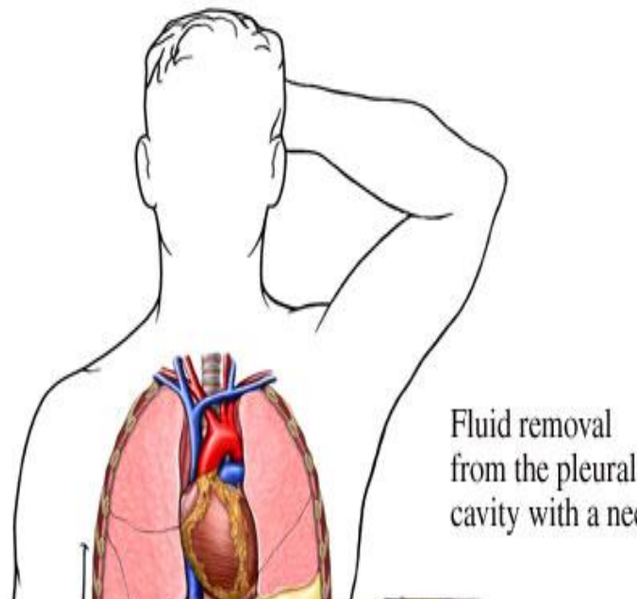
High anesthesia risk **Low anesthesia risk**

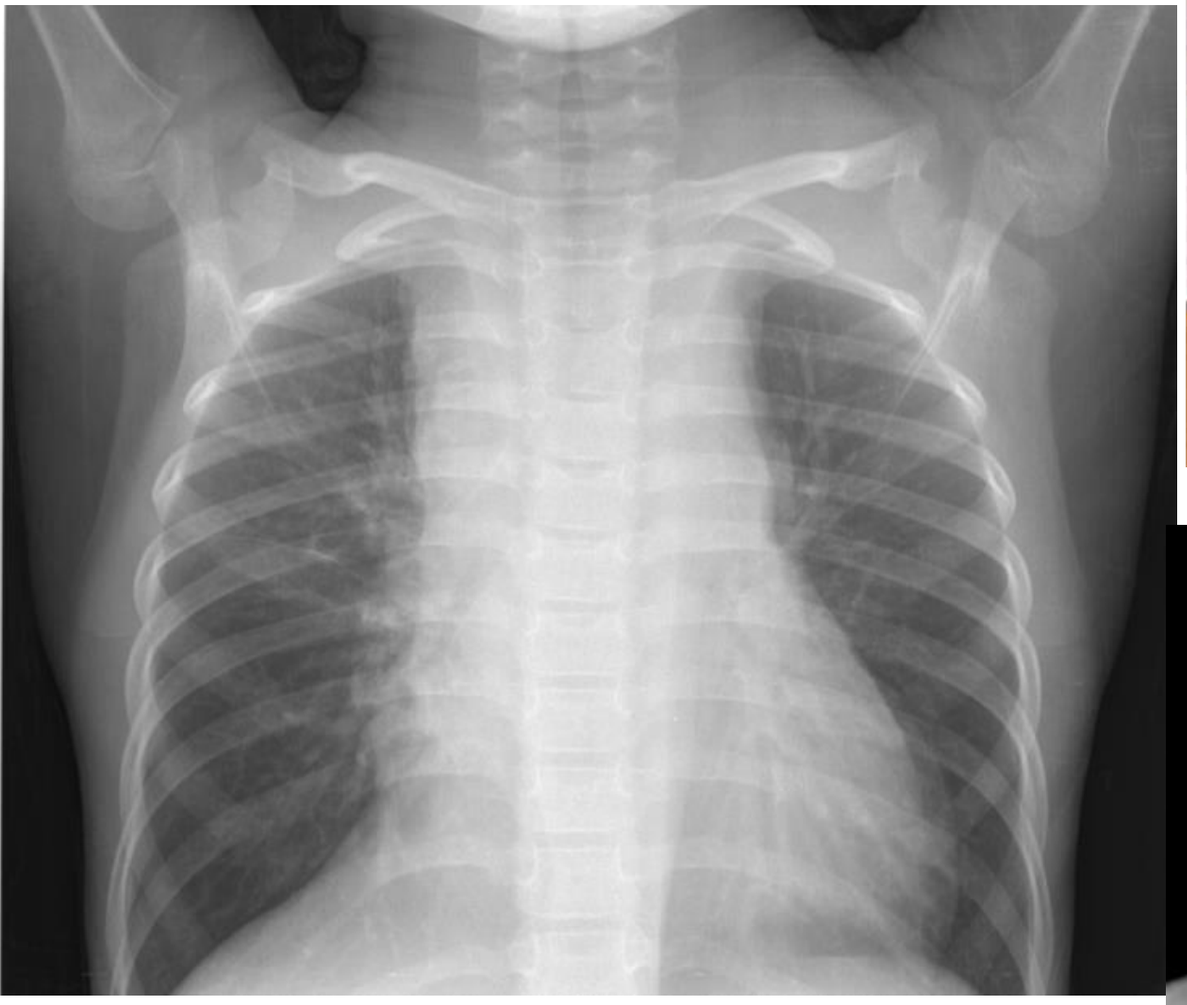
Minimal touch !

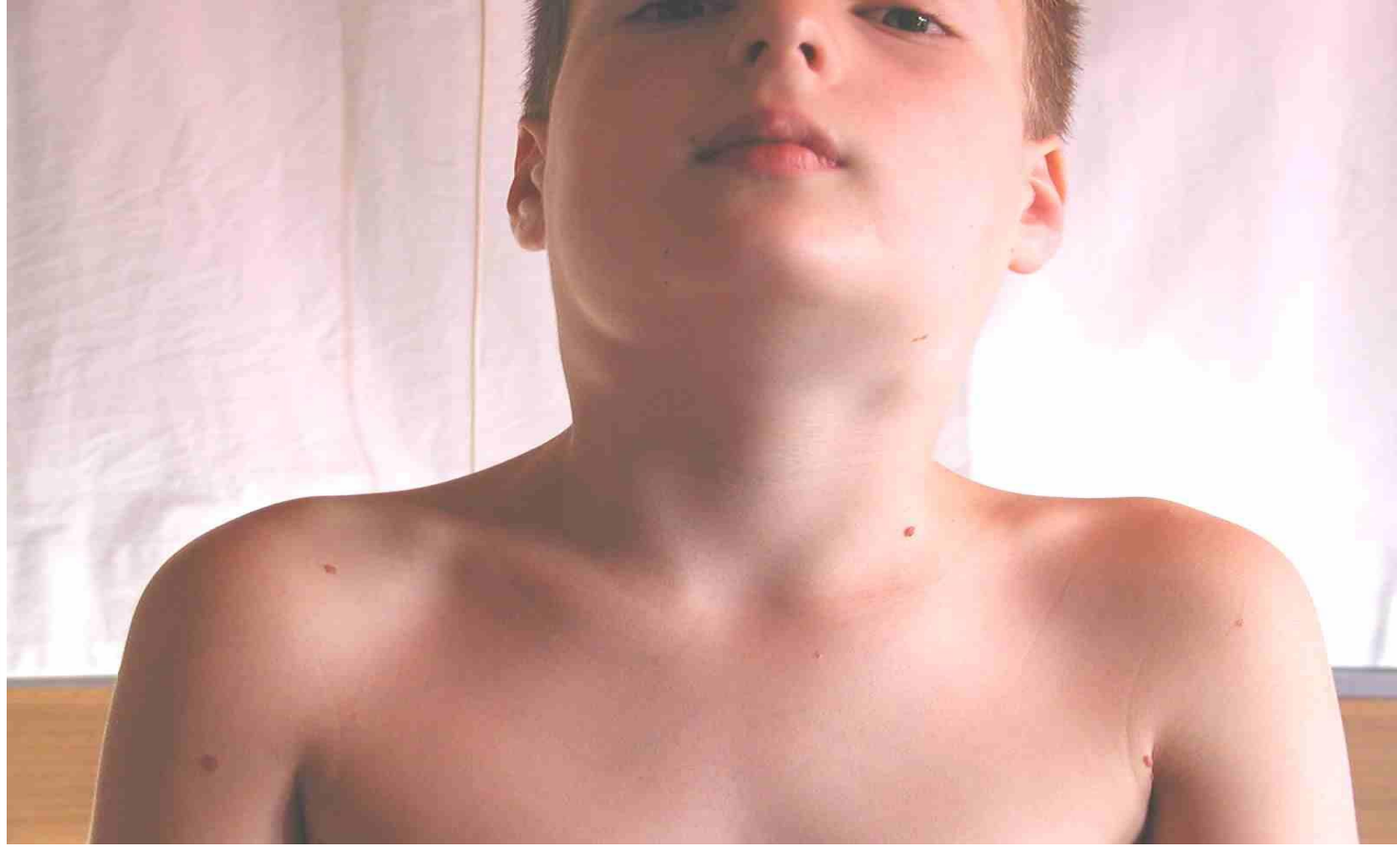
Pleural fluid removal (local anesthesia/upright position)

Biopsy of a lesion outside the thorax (lymph node) under local anesthesia

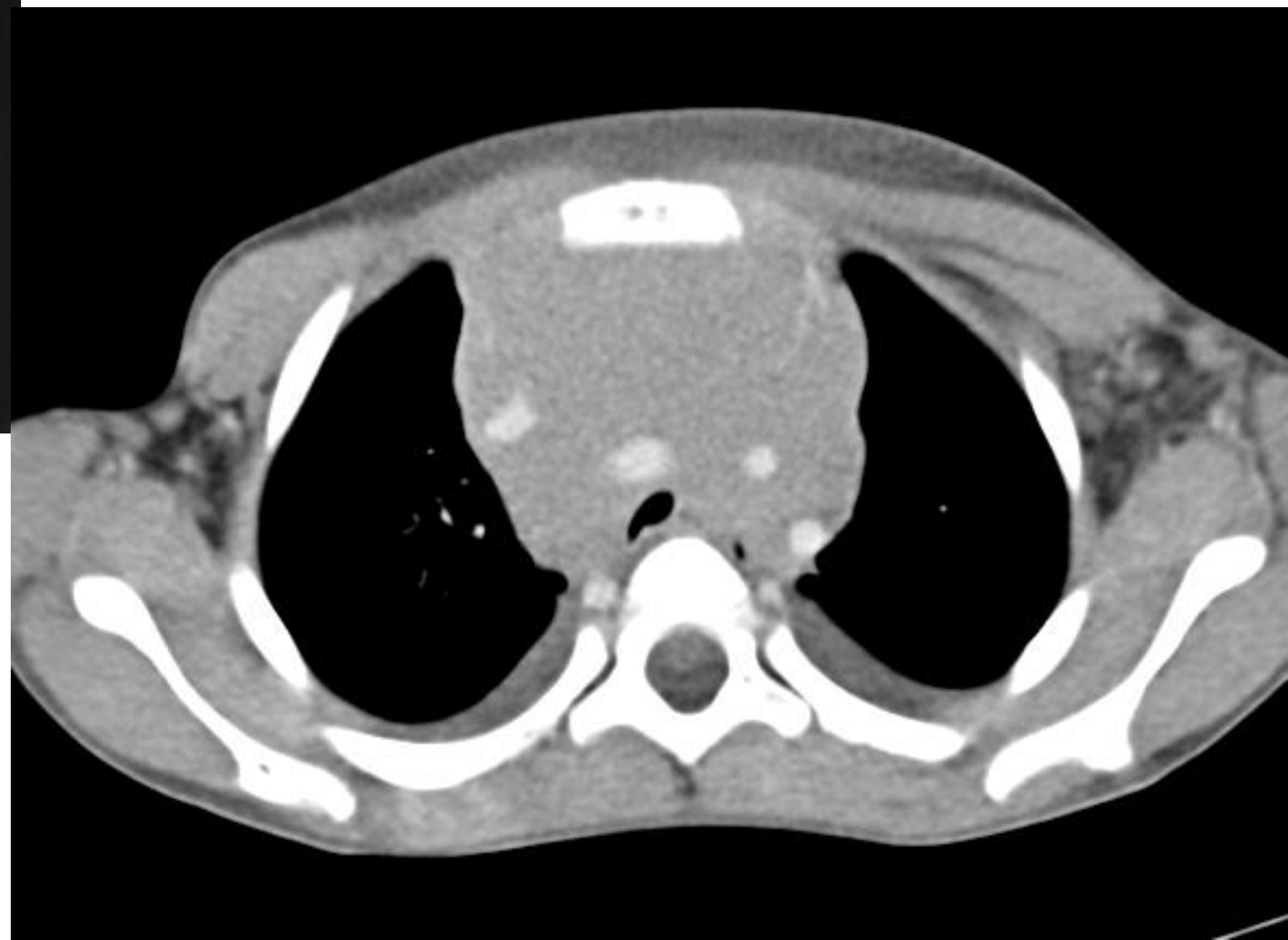
If unpossible or too risky: start empirical treatment



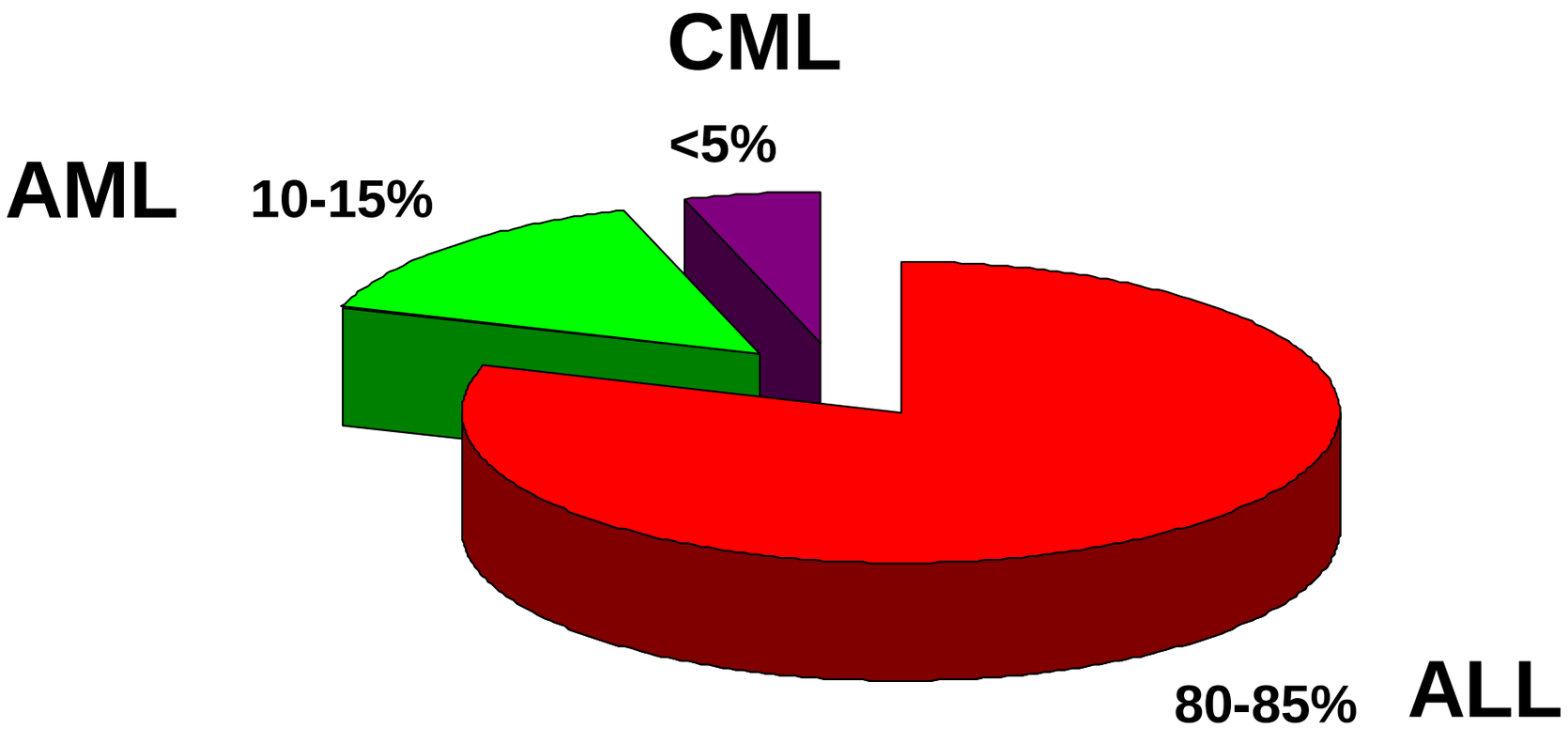




WBC 21 580/µL
40% blasts (T-cells)
LDH 1657 U/L

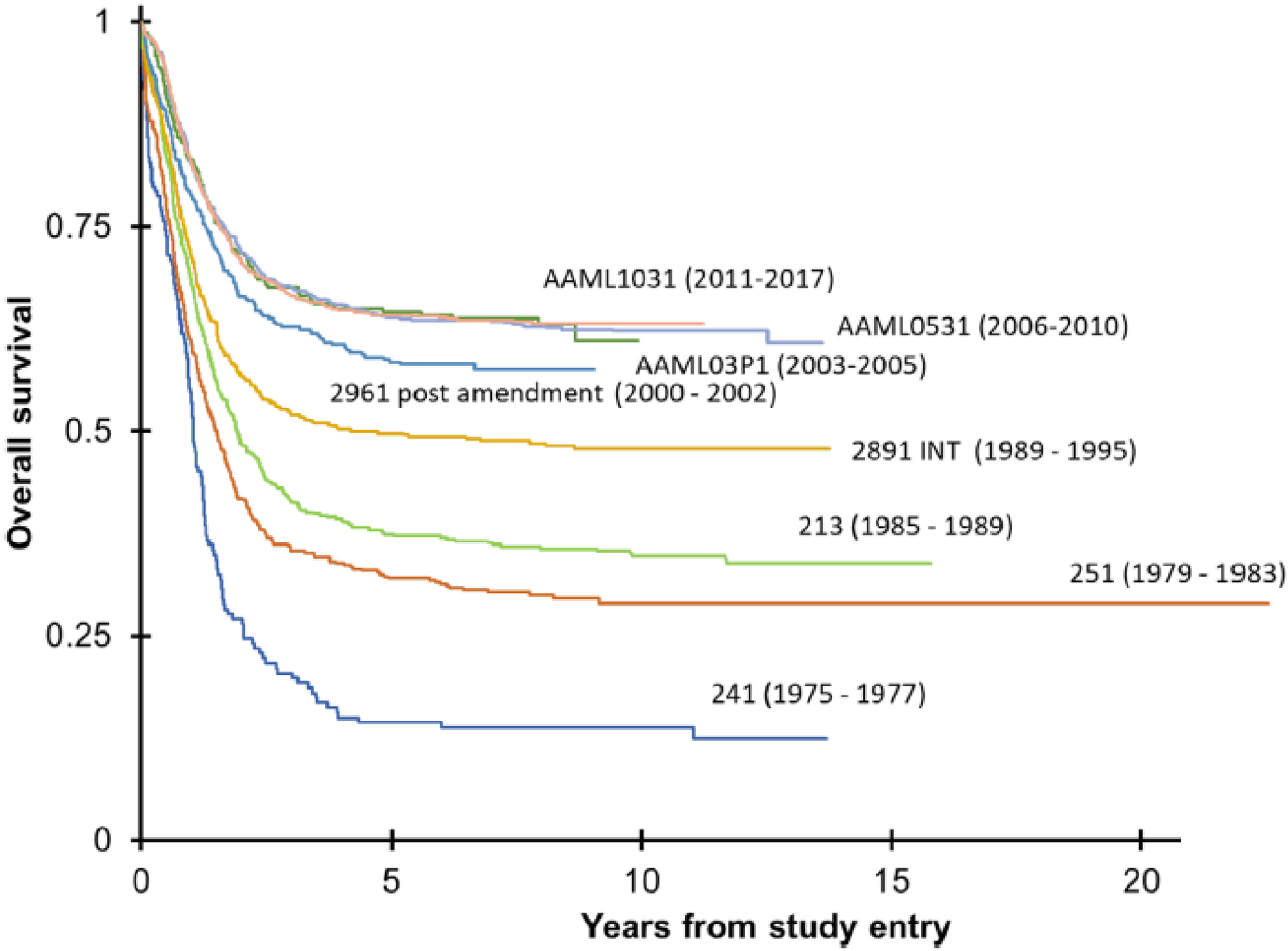


Leukemia in children (0-14y)



ALL = acute lymphoblastic leukemia → 70 children/year in Belgium
AML = acute myeloïd leukemia → 10 children/year in Belgium
CML = chronic myeloïd leukemia → 1-2 children/year in Belgium

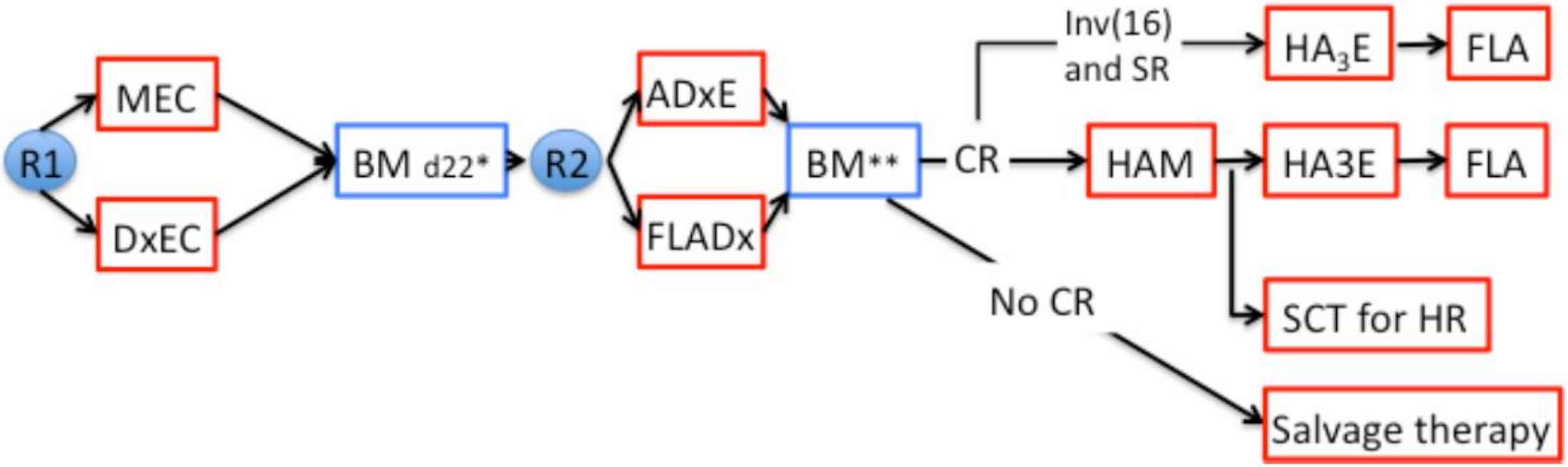
Leukemia in children: AML



Cooper et al, Pediatr Blood Cancer 2023

AML treatment by the NOPHO-DB SHIP consortium

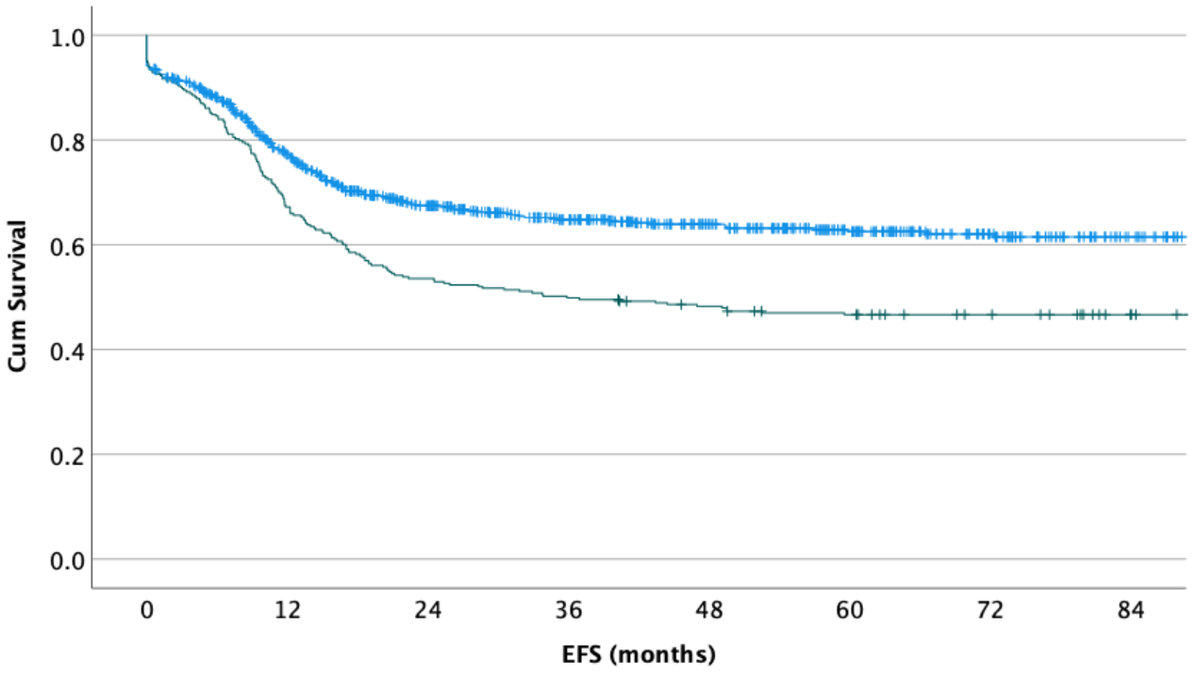
NOPHO-DBH AML 2012



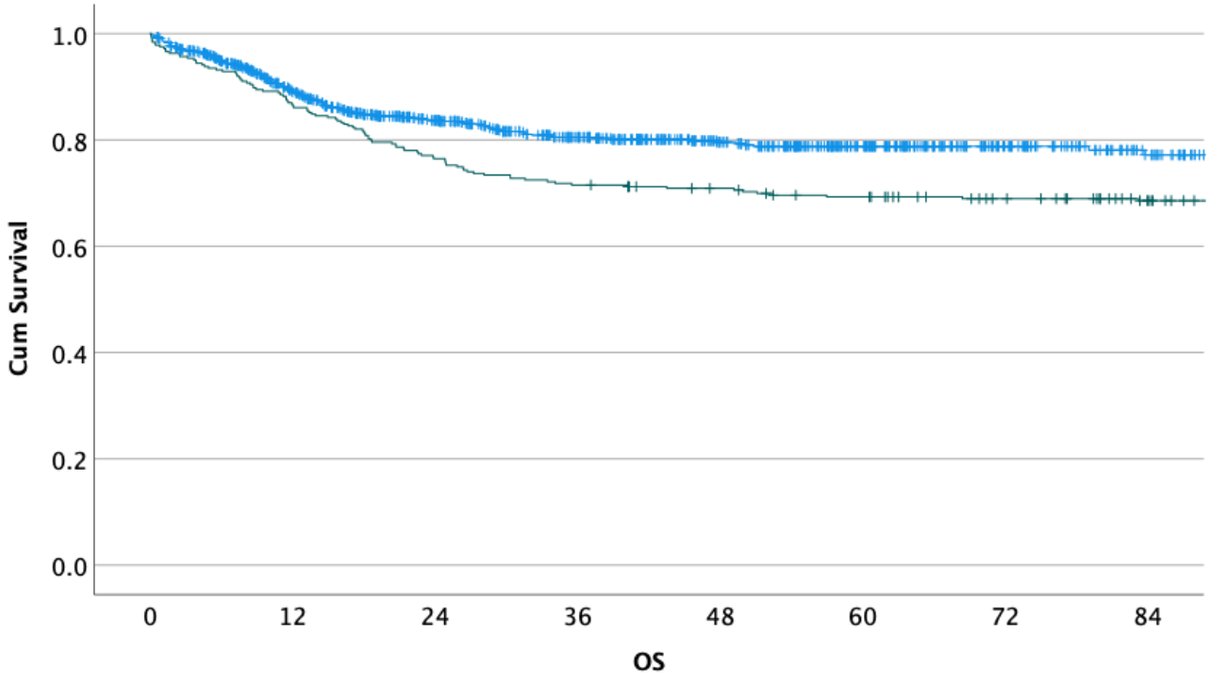
High risk definition: **(<20%)**
MRD ≥15% at any time after course 1
MRD ≥0.1% before consolidation
FLT3-ITD without NPM1

Overall outcome NOPHO-DBH AML 2012

EFS



OS

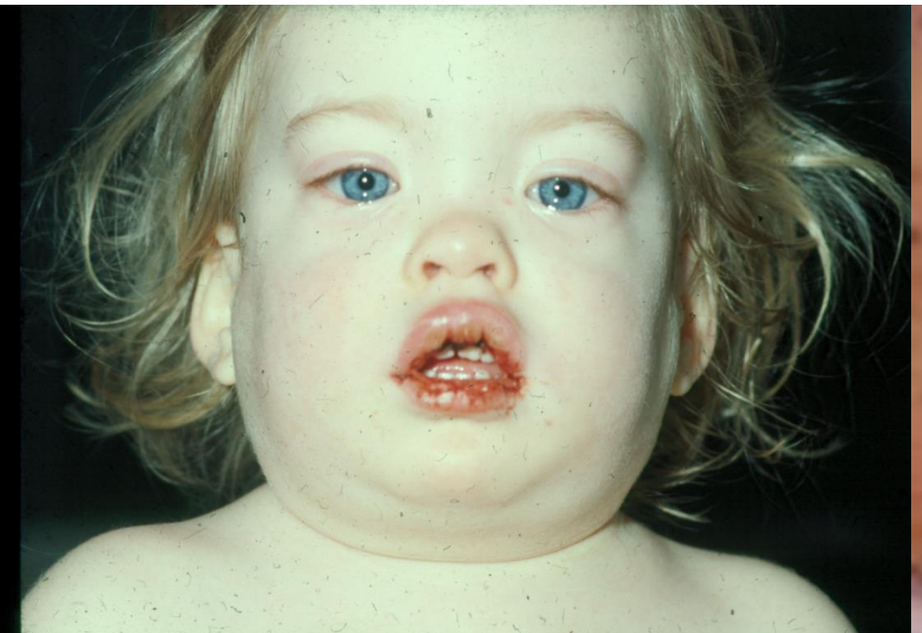


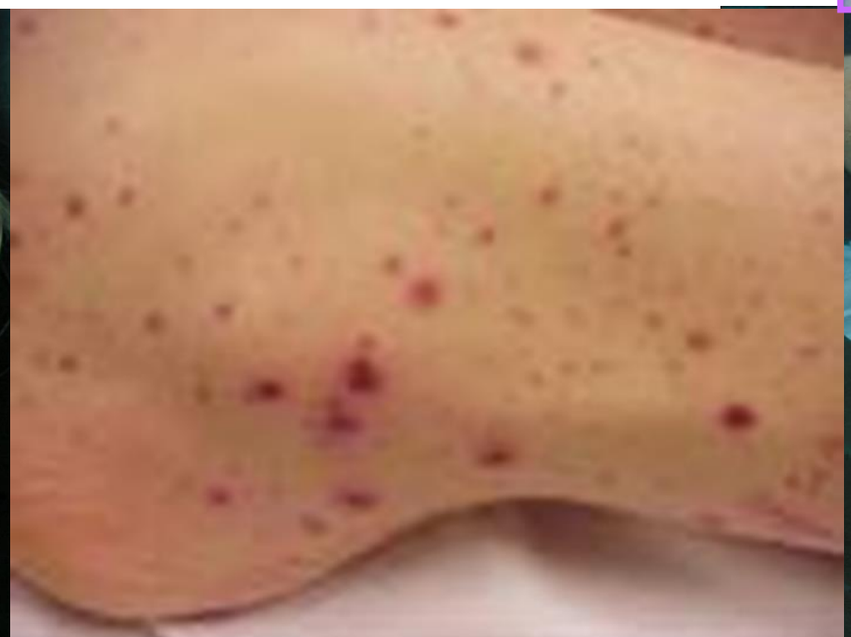
	N	EFS_{5y}	OS_{5y}
AML 2012	858	62.5 ± 1.9	78.8 ± 1.6
AML 2004	323	46.7 ± 2.8	69.3 ± 2.6

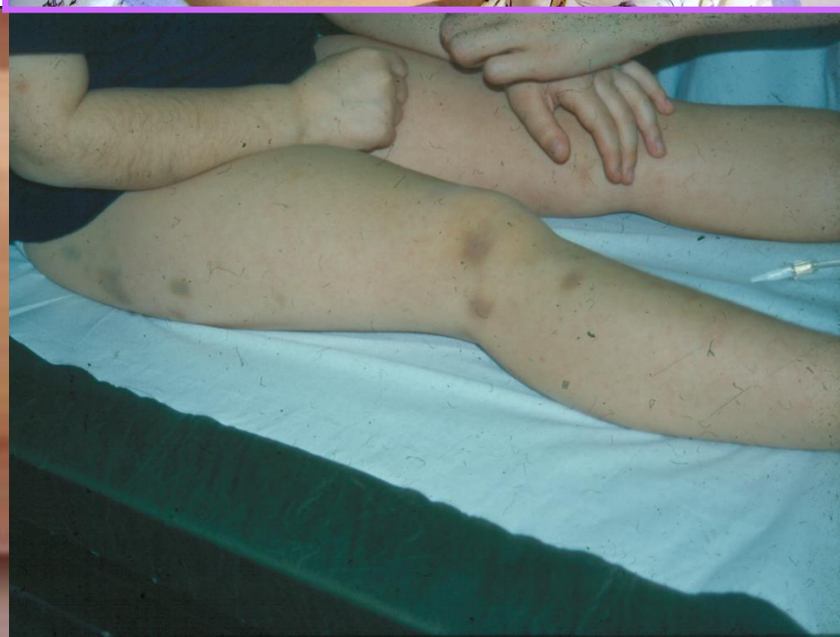
De Moerloose B et al, ASH 2023, #831

ALL: symptoms and clinical presentation

- Pallor, fatigue
- Petechiae, purpura, bleeding tendency
- Fever, infections
- Bone pain, limping
- Enlarged lymph nodes
- Hepatosplenomegaly
- …





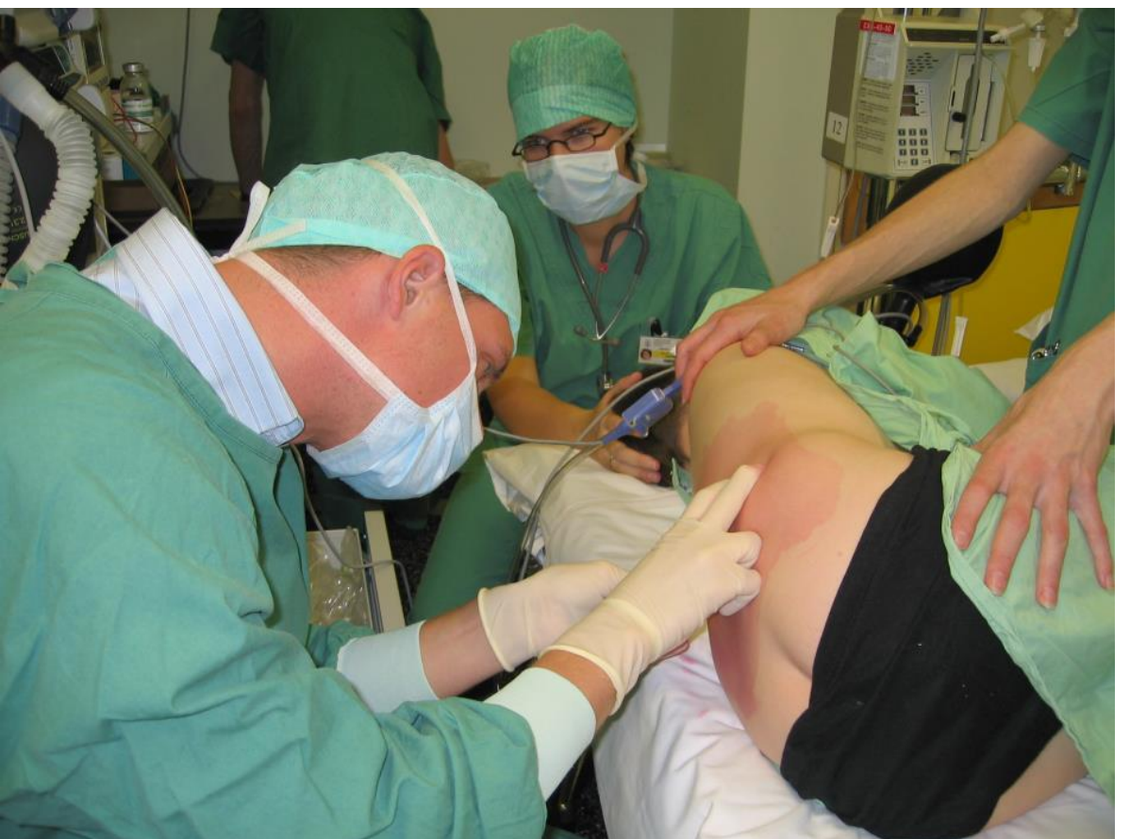


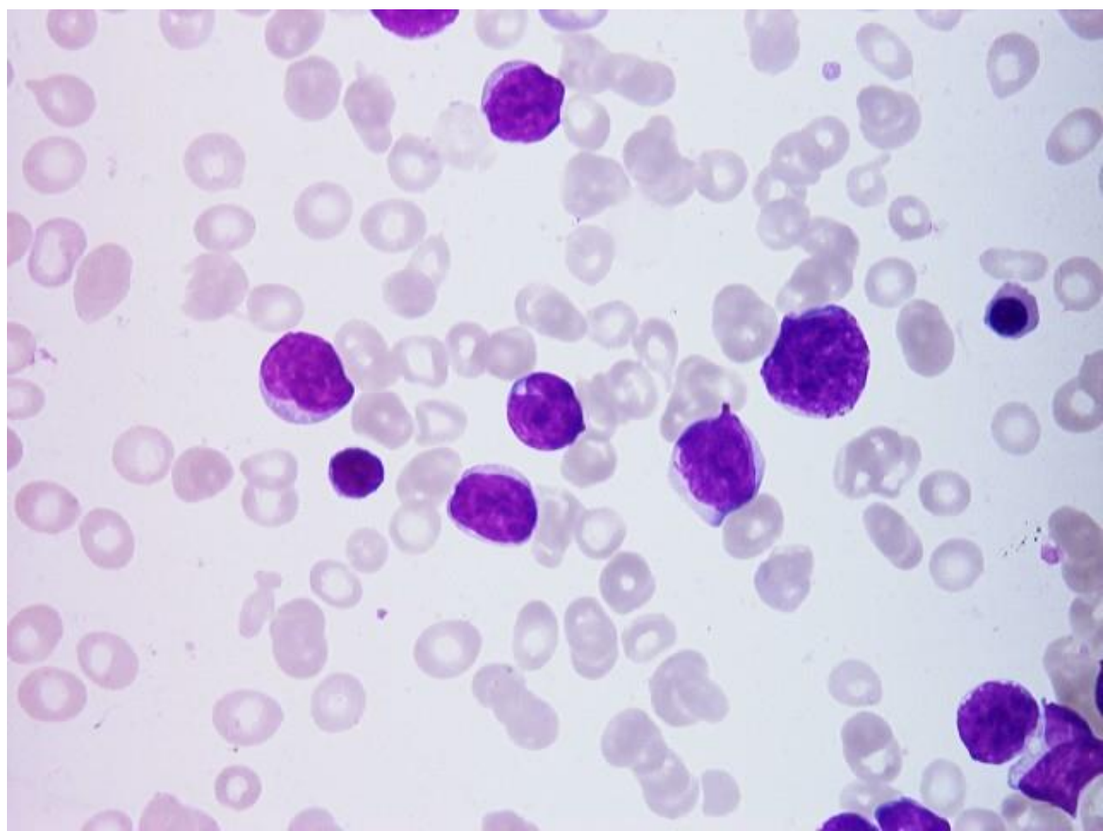
Diagnostic examinations

- Blood:

  WBC with microscopy, hemoglobin, platelets

  LDH, tumorlysis parameters (K, P, Ca, uric acid), renal function
- Bone marrow aspirate (<< biopsy)
- Lumbar puncture (with injection of chemo!)
- Imaging: RX thorax - abdominal ultrasound

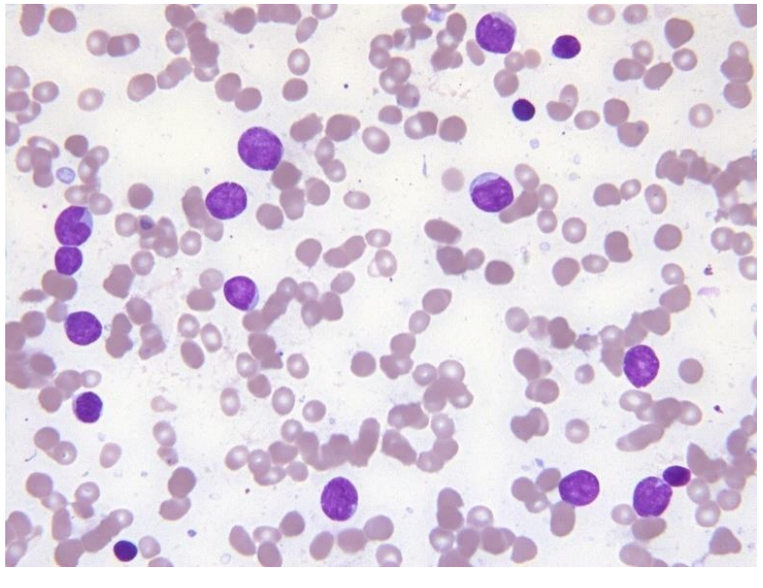




Bone marrow analysis in pediatric ALL:

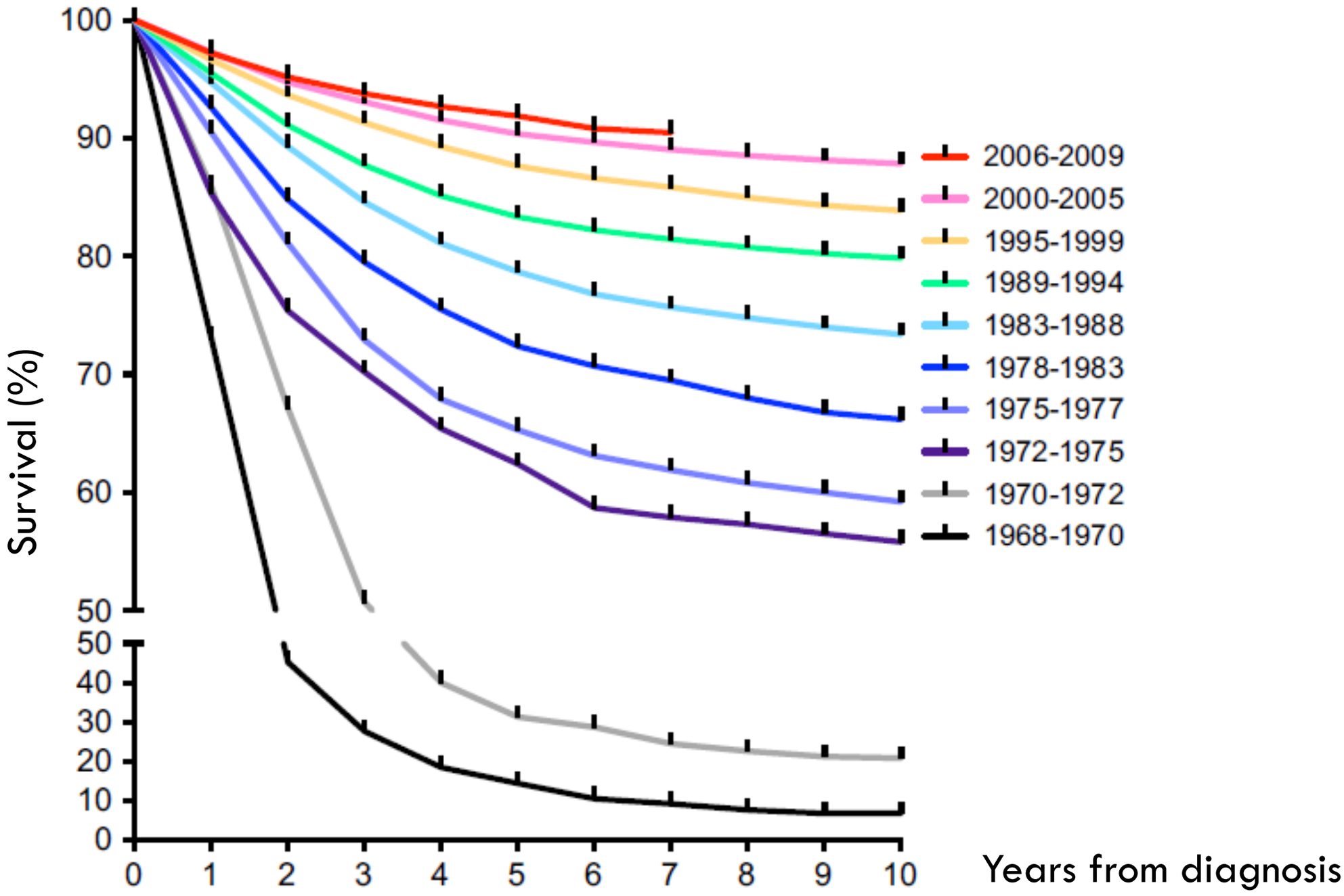
- Cytomorphology: % blasts, FAB L1-L2
- Immunophenotyping (flow cytometry): T or pB

- Conventional cytogenetics (karyotyping, FISH)
- Array CGH
- Molecular analysis



Prognostic markers
used in risk stratification

Outcome of pediatric ALL



Tasian & Hunger, Br J Haematol 2016

BFM treatment for pediatric ALL

General design

Induction Consolidation	**Interval**	**Reinduction**	**Maintenance**
Prephase | **Protocol I a + b**	**HD MTX**	**Protocol II**	
10 wks	**2 w**	**8 wks**	**2 w**	**6 wks**	**2 w**	**total 2 years**

BFM = Berlin-Frankfurt-Münster

BFM treatment for pediatric ALL

Prephase	Prednisone; IT	1 week
Induction (IA)	Prednisone; VCR; asparaginase; Daunorubicine; IT	4 weeks
Consolidation (IB)	6-MP; AraC; Cyclofosfamide; IT	4 weeks
Interval	6-MP; HD-MTX; IT	8 weeks
Reinduction (IIA)	Dexa; VCR; asparaginase; Doxo	4 weeks
Reconsolidation (IIB)	6-TG; AraC; Cyclofosfamide; IT	2 weeks
Maintenance	6-MP; MTX	74 weeks

Hallmarks: 4-drug induction, high cumulative asparaginase dose, delayed intensifications, prophylactic CNS treatment

Risk factors in pediatric ALL

- Age
- WBC count at diagnosis
- Extramedullary disease
- Immunophenotype
- Cytogenetic/molecular characteristics
- Response to pred prephase
- Response to induction
- Minimal residual disease
- New characteristics

Unfavorable:

- < 1 year or ≥ 10 years
- ≥ (50 or) 100x10^9/L
- CNS or gonadal involvement
- T-cell
- Low hypodiploidy, near-haploidy, t(9;22), t(4;11), 11q23, t(17;19), iamp21
- ≥ 1x10^9/L blasts in PB
- ≥ 5% blasts in BM at D35
- ≥ 10^{-2} D35 or ≥ 10^{-3} D90
- IKZF1 deletion

ALL frontline treatment according to EORTC 58081

Risk Group	Induction	Consolid	Interval	Reinduct	Maintenance
VLR	I A Reduc	I B Reduc	4x HDMTX	II A Reduc II B Reduc	Maintenance - no pulses
AR1	I A	I B	4x HDMTX	II A /II B	Maintenance - pulses
AR2-B ALL	I A Augment	I B	4x HDMTX	II A / II B	Maintenance with HDMTX/aspa and pulses
AR2 – T ALL	I A	I B	4x HDMTX	II A / II B	Maintenance with HDMTX - no pulses

		1° Consol.	2° Consol.	Interval	Reinductions & Interval			Mainten
VHR	I A + **cyclo**	I B Lyon	Vanda	3x HD MTX	IIA mod IIB	3x HDMTX	IIA mod IIB	MT No pulses

Allo-HSCT if indicated

Ped ALL treatment protocols in Belgium

Frontline

- VLR = low risk (20%)
- AR1 = average low (48%)
- AR2 = average high (12-15%)

  AR2-B & AR2-T
- VHR = high risk (10-15%)

- Mature B-ALL (3%)

  Inter-B Ritux 2010
- Infant ALL (4%)

  Interfant-06 (+ Blina)
- Phi+ ALL (4%)

  EsphALL protocol (imatinib)

Relapse

- IntReALL SR 2010 protocol: closed
- IntReALL HR 2010 protocol: still open for T
- IntReALL BCP 2020 protocol: Q4 2024
- Tisagenlecleucel (Kymriah)

Future protocols

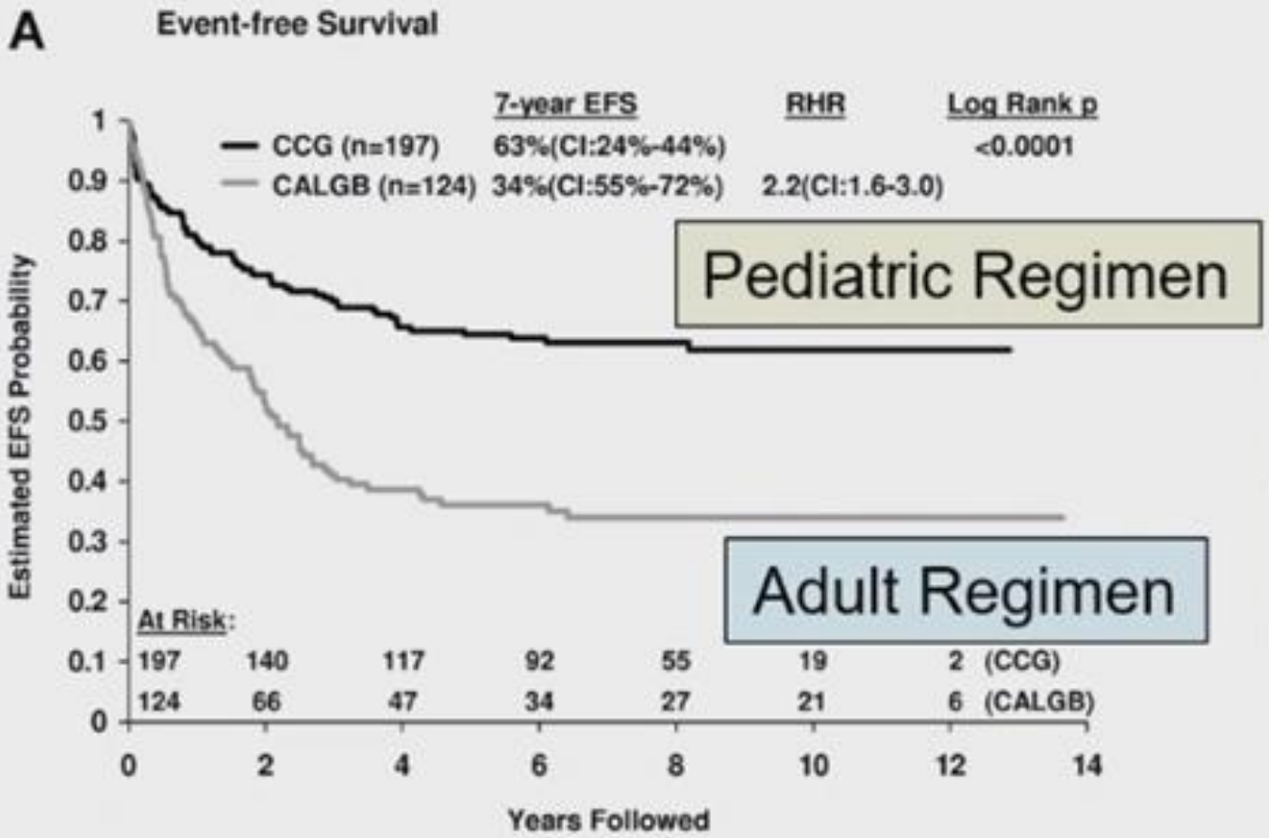
- AYA (adolescents and young adults)?
- Resistant ALL?

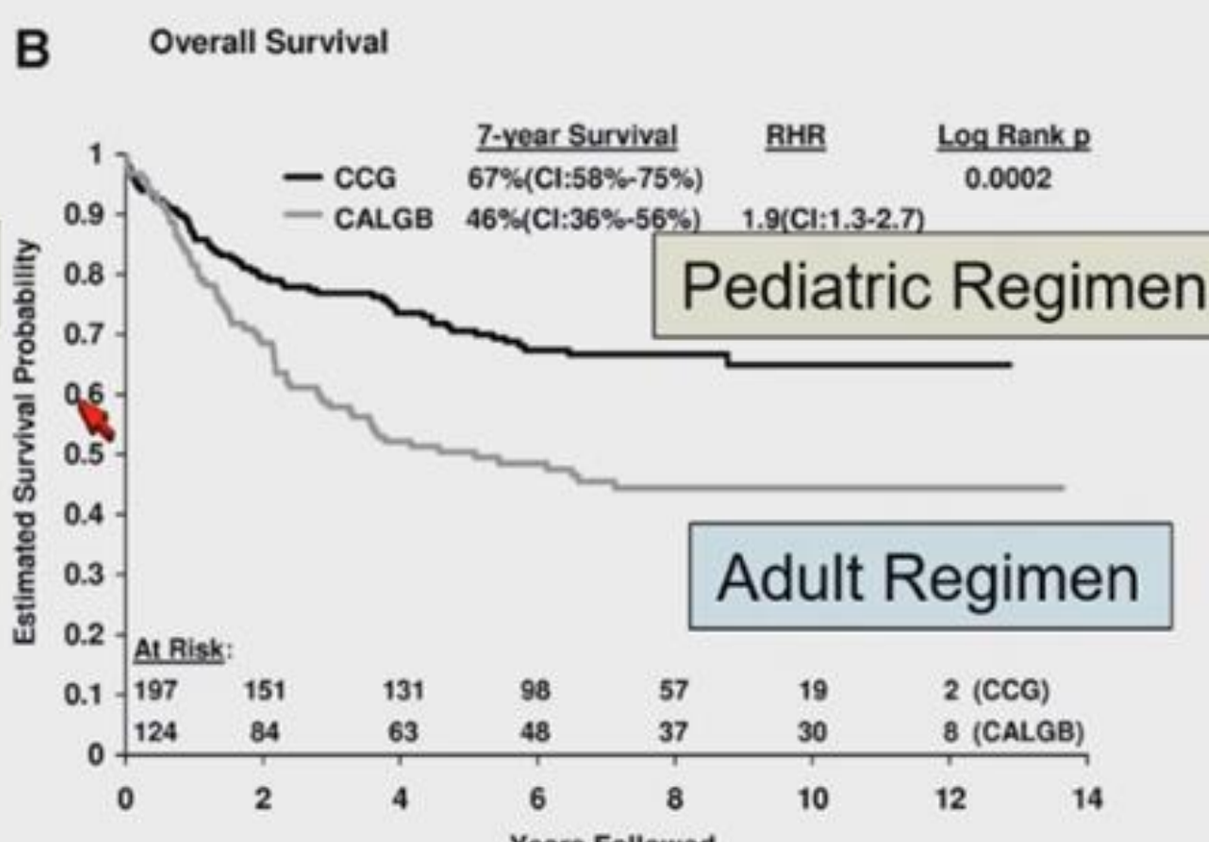
New frontline protocol (Q4 2020)

“ALLTogether”: 1 -> 45y

Pediatric-Inspired Regimens: Upfront Treatment in AYA ALL

Outcomes historically depended on which door you walked into:





Adolescent and Young Adults, Ages 16-20 years

American Society *of* Hematology

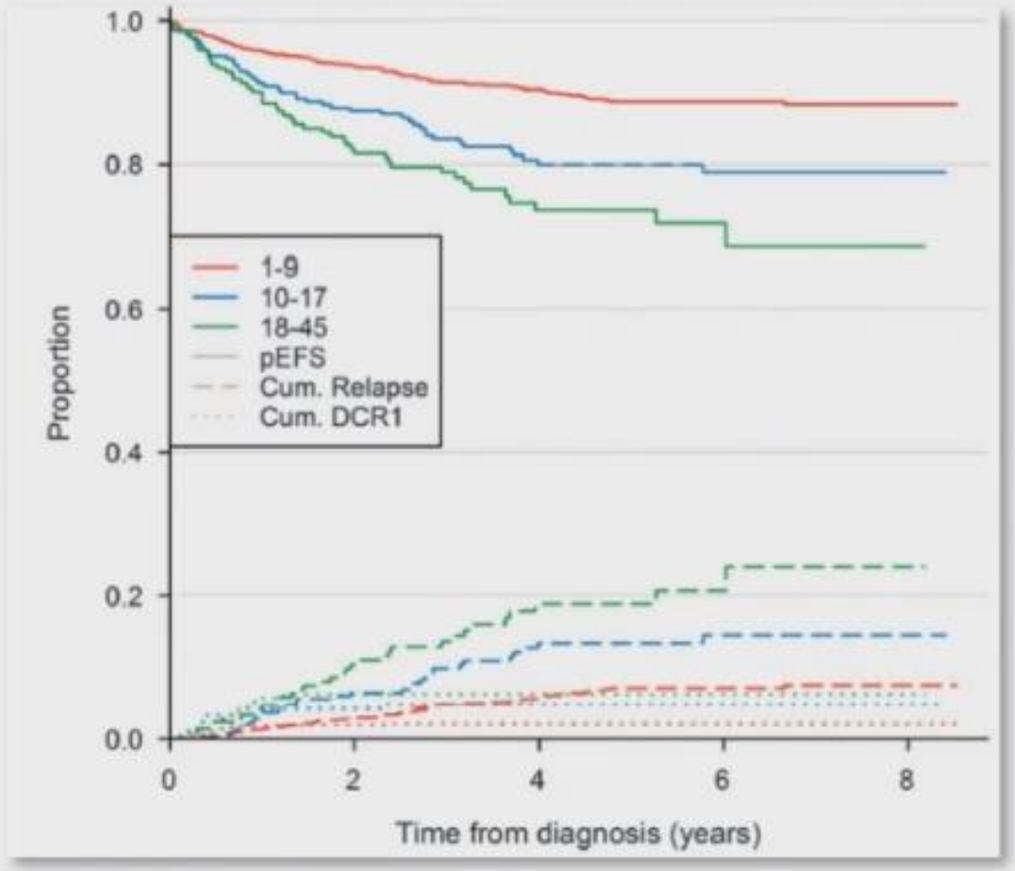
Stock W, et al. Blood. 2008 Sep 1;112(5):1646-54

Janardan and Miller, ASH Educational Program 2023
Molina and Rotz, ASH Educational Program 2023

Pediatric-Inspired Regimens: Upfront Treatment in AYA ALL

ORIGINAL ARTICLE

Results of NOPHO ALL2008 treatment for patients aged 1–45 years with acute lymphoblastic leukemia



Nordic/Baltic NOPHO ALL 2008 (N=1509)

221 patients = 18-45 years

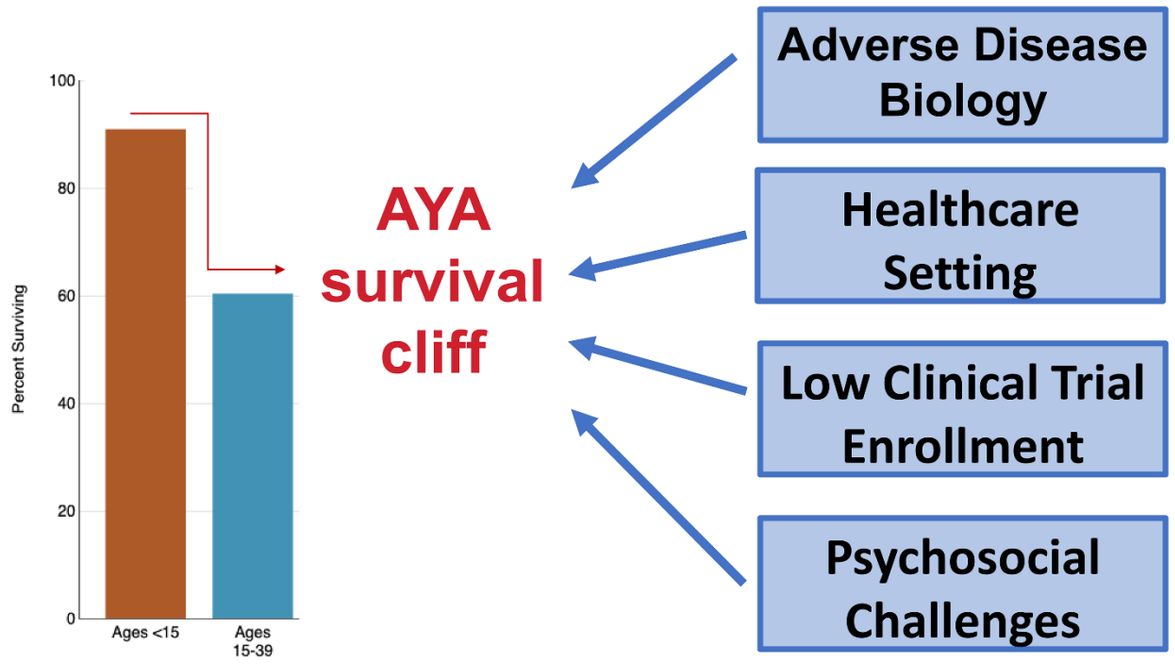
5 year EFS young adults 74%

5 year OS young adults 78%

Toft N. et al. Leukemia 2018 Mar;32(3):606-615

SURVIVAL GAP

Janardan and Miller, ASH Educational Program 2023
Molina and Rotz, ASH Educational Program 2023



Annabelle Anandappa, Emily Curran
Acute lymphoblastic leukemia in young adults: which treatment?
Hematology Am Soc Hematol Educ Program, 2023,

Moorman et al, Haematol 2016

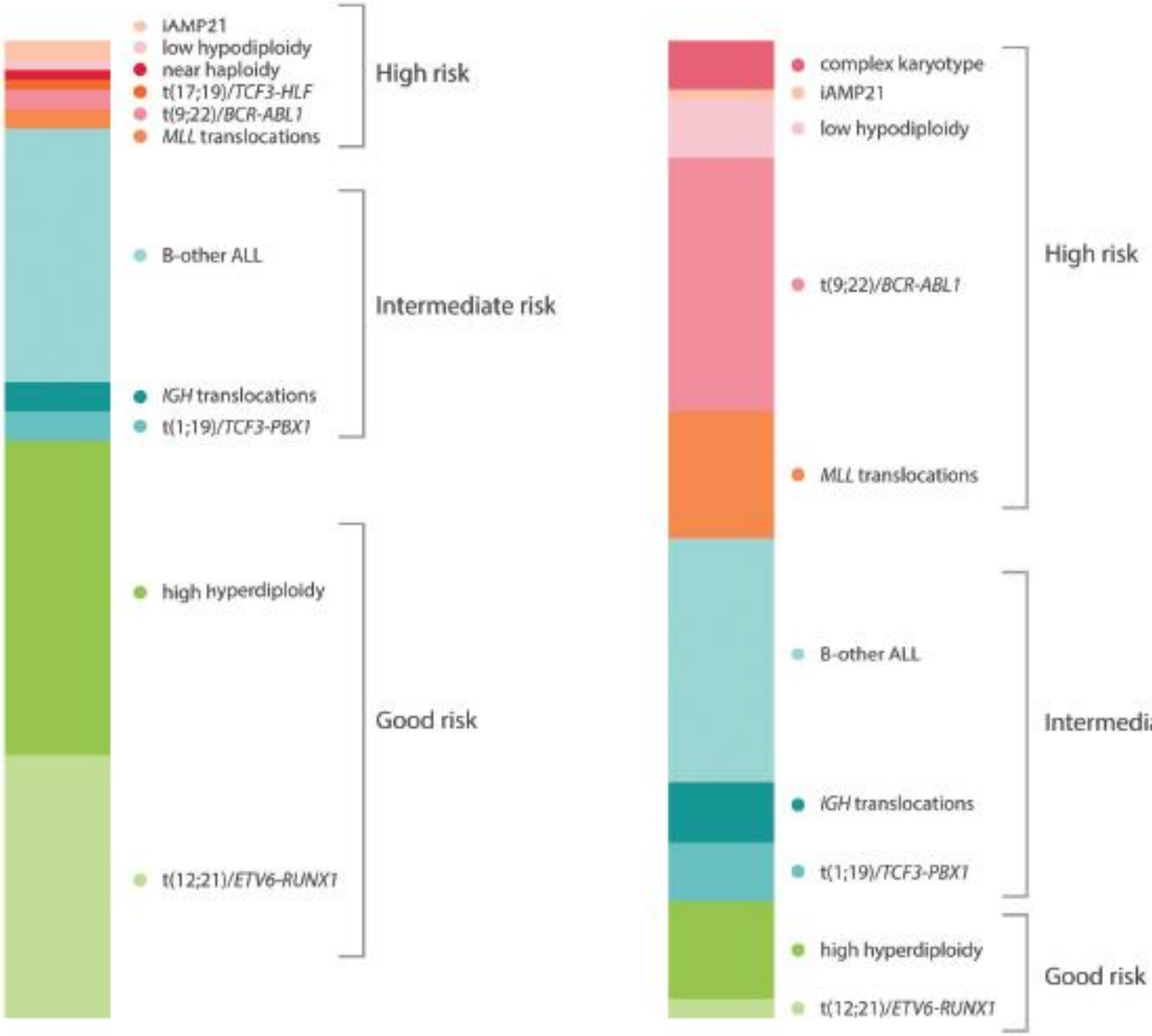


Figure 2. Frequency of primary chromosomal abnormalities in children and adults with B-cell precursor acute lymphoblastic leukemia.

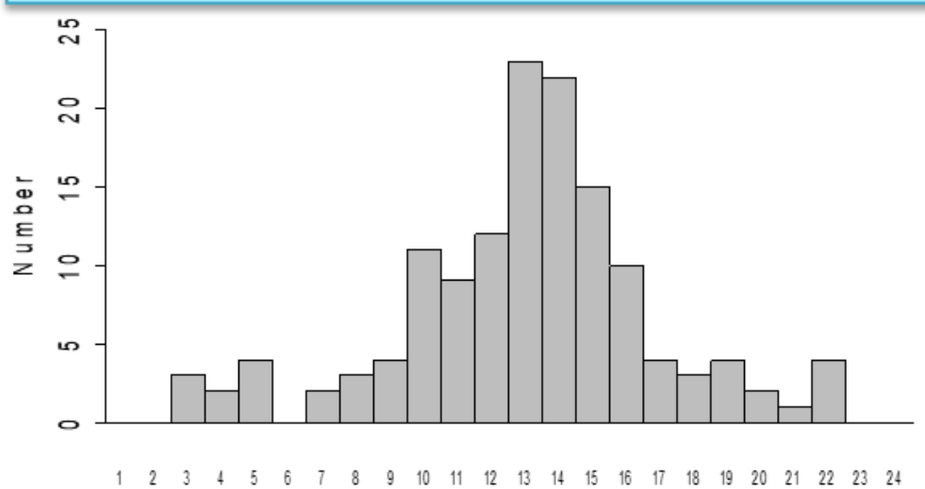
Impact of age on toxicity

A - More common in >10 years

- Methotrexate neurotoxicity
- Pancreatitis
- Hyperglycaemia

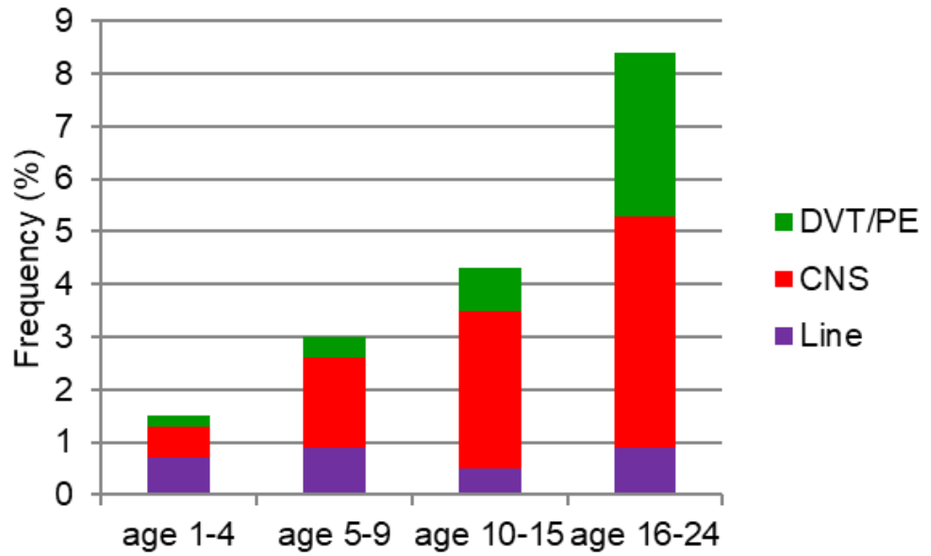
B - Primarily seen in adolescents

- AVN



C - Increasing risk with increasing age

- Thrombosis
- Psychosis
- Infection

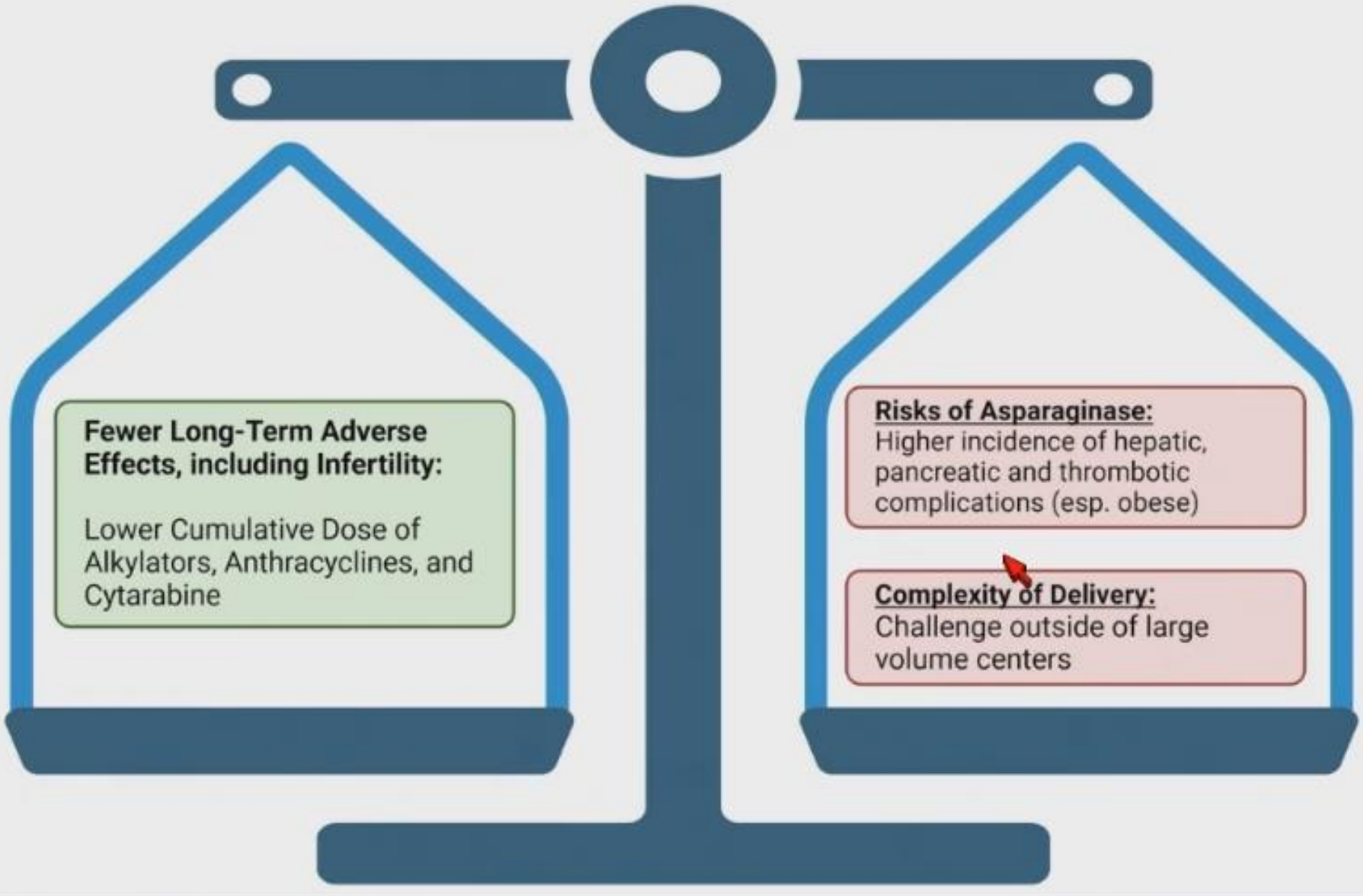


D - No Impact

- Vincristine neurotoxicity
- Line related thrombosis/infection

Hough et al. Br J Haematol, 2016;172: 439-51

Pediatric-Inspired Regimens: Upfront Treatment in AYA ALL



Newman H, Hunger SP. J Clin Oncol. 2023 Oct 27:JCO2301351.

Janardan and Miller, ASH Educational Program 2023
Molina and Rotz, ASH Educational Program 2023

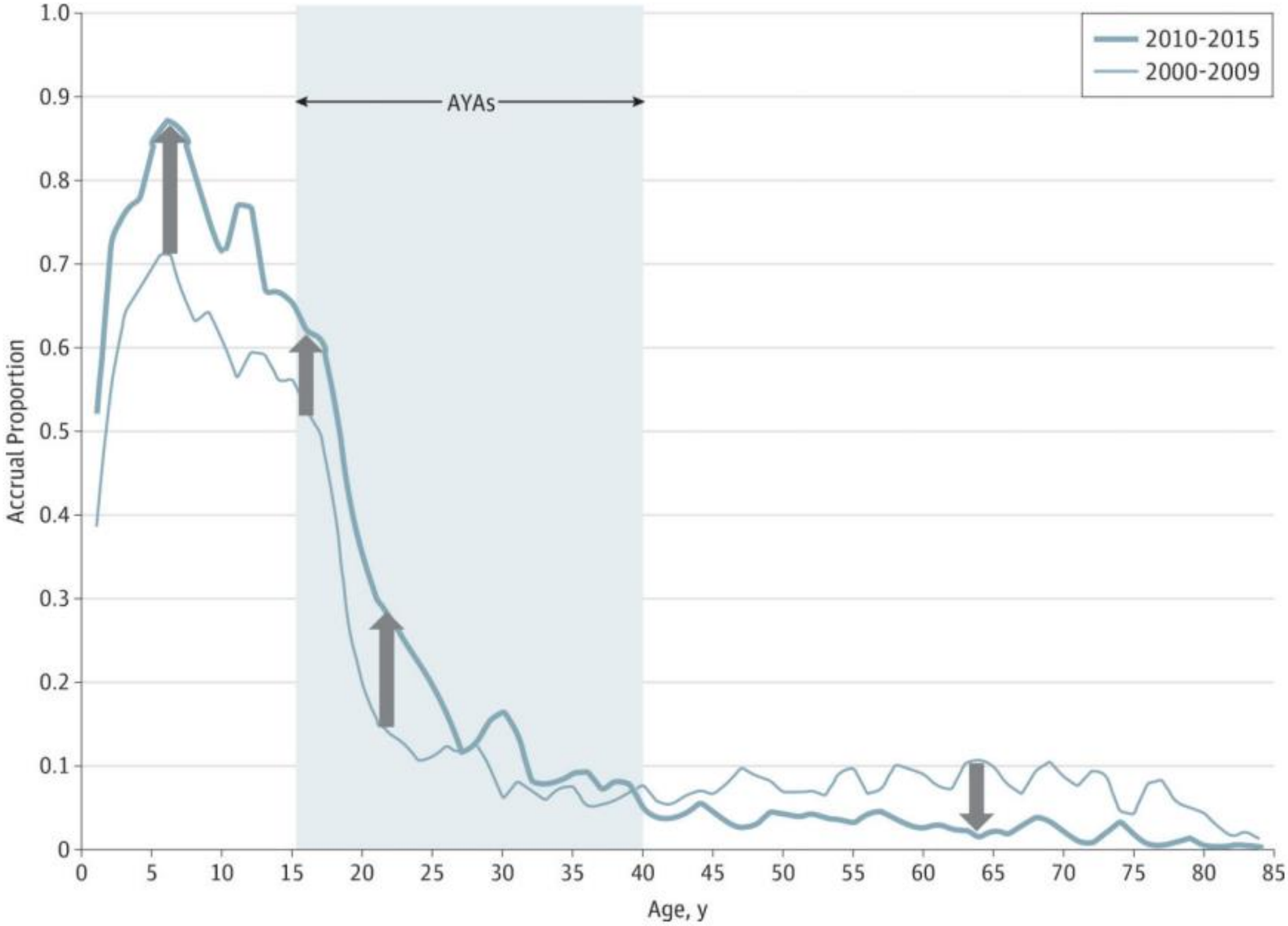


Figure 4. Estimated Accrual Proportion From 2000 to 2009 and 2010 to 2015 Onto National Cancer Institute–Sponsored National Treatment Acute Lymphoblastic Leukemia Trials

ACCRUAL GAP

Siegel S et al, JAMA Oncol. 2018

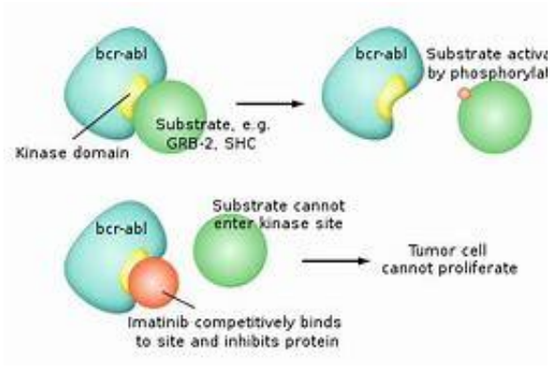
ALL Together protocol: Aims?

Low risk ALL	**Further de-escalation of therapy, substitution of elements of chemotherapy with new agents**
Intermediate risk ALL	**Add new agents to conventional chemotherapy regimens**
High risk ALL	**Ongoing role of HSCT, possible role of CAR T cell therapy**

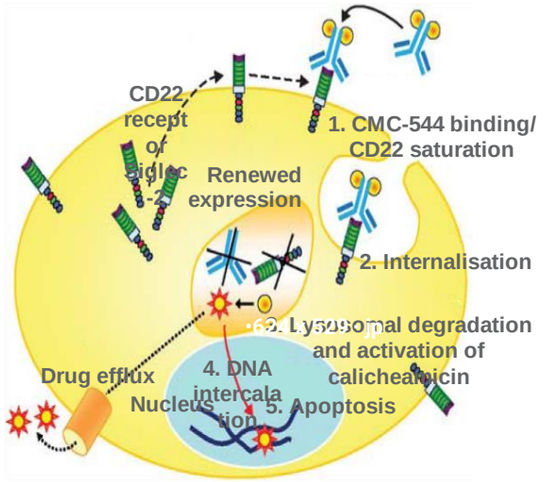
Improved risk stratification essential

New agents present new possibilities

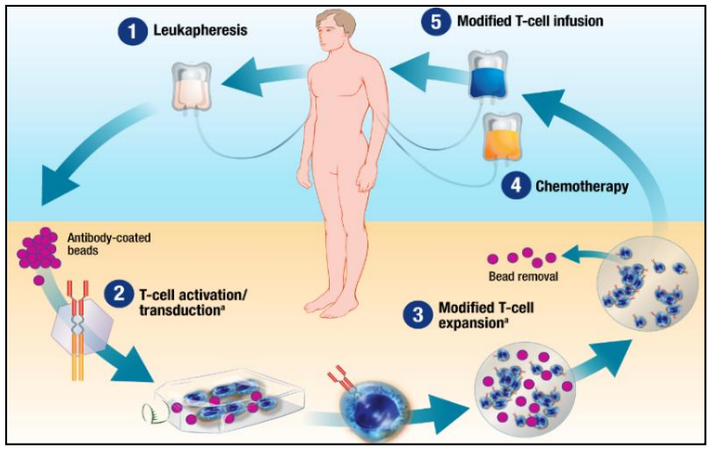
TKI



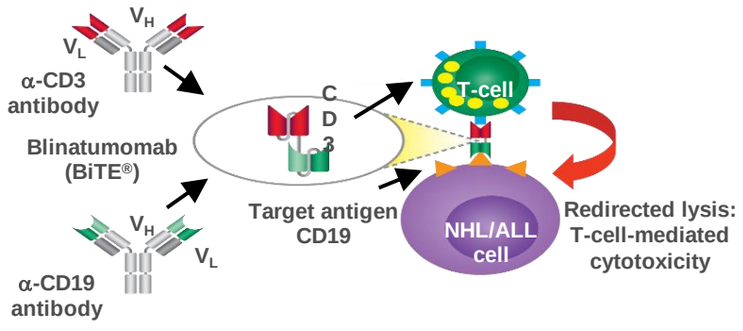
Inotuzumab

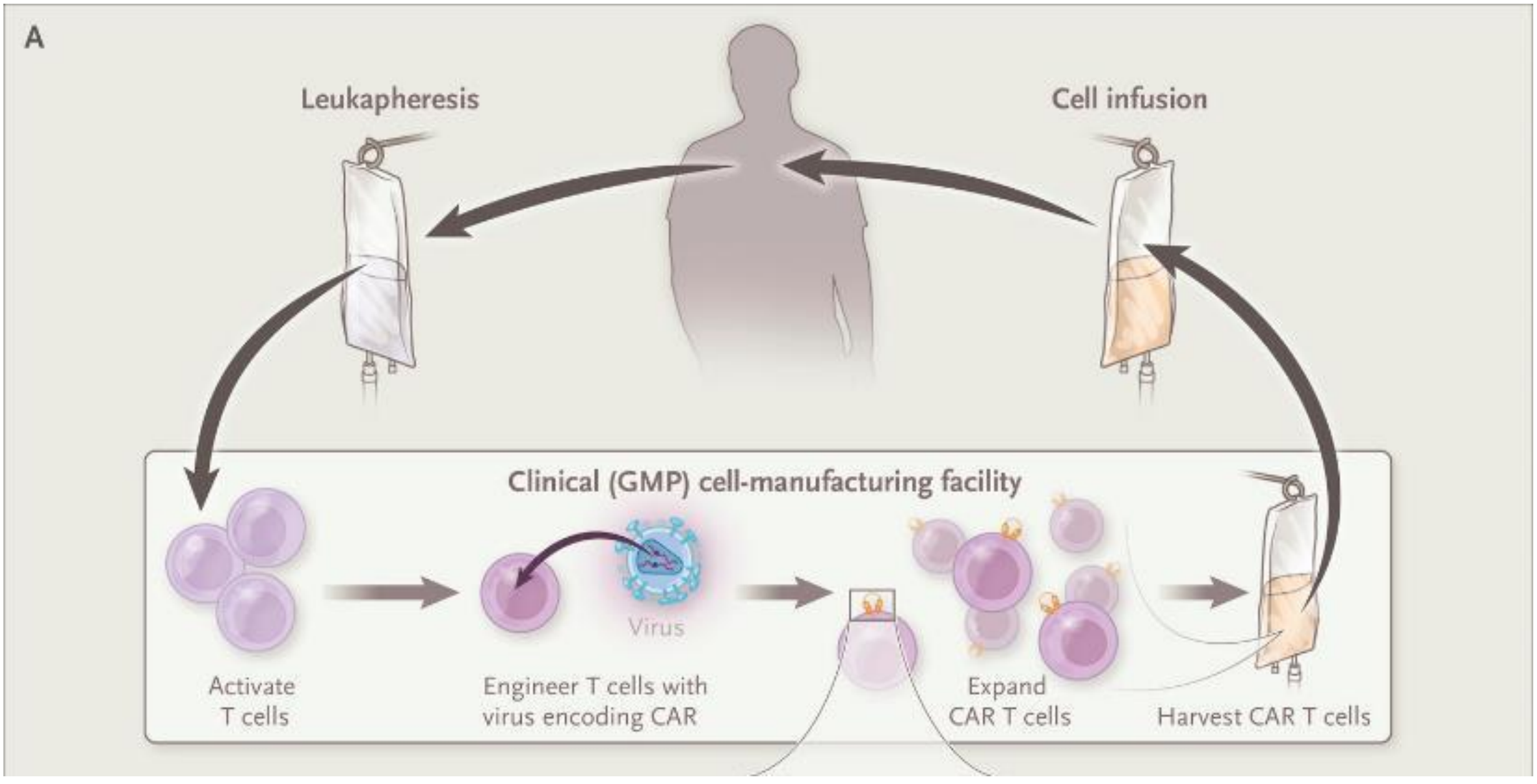


CAR T cells



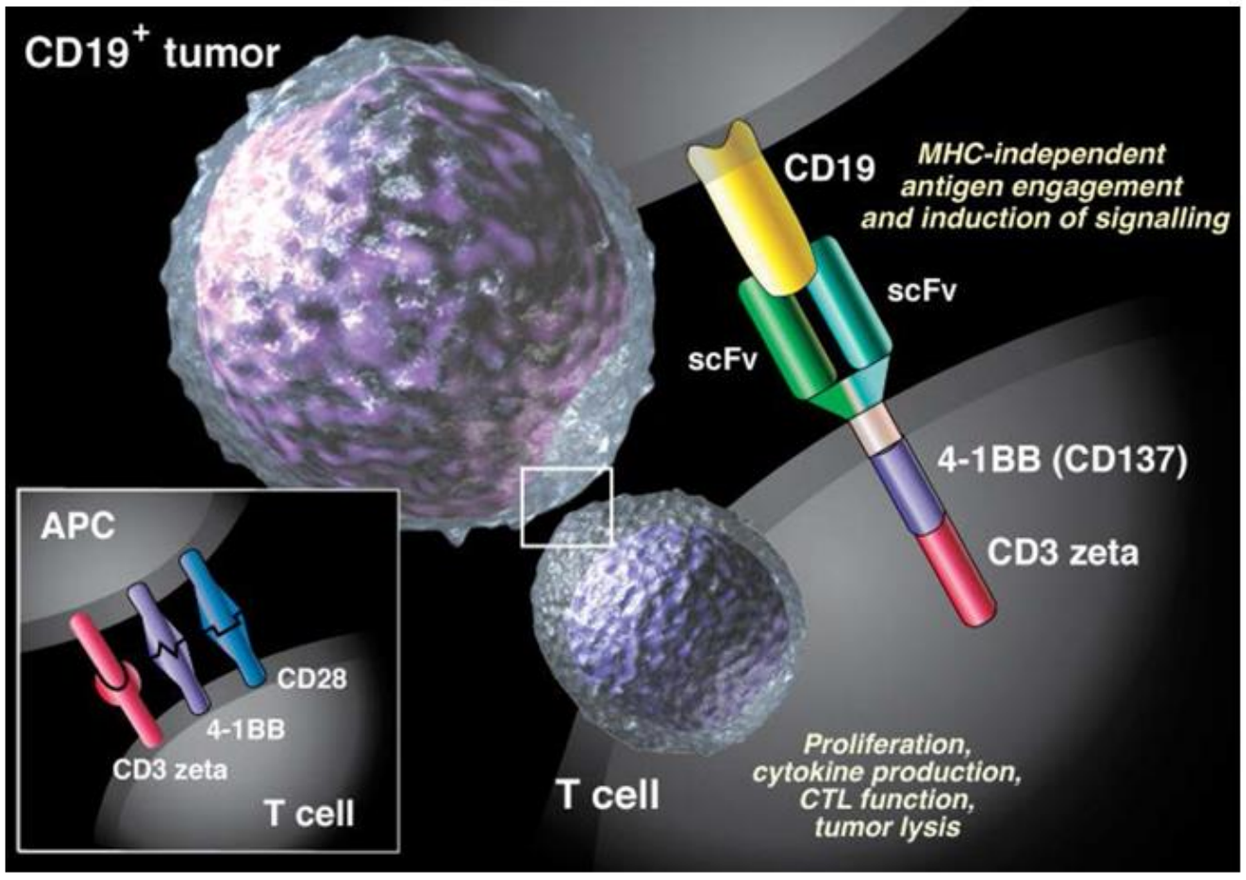
Blinatumomab





Tran E et al. N Engl J Med 2017;377:2593-2596.

Tisagenlecleucel in R/R B-ALL



The NEW ENGLAND JOURNAL of MEDICINE 2014

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

Therapy overview

SR
- MRD TP1 true neg
- No HR gen
- No CNS3

24 %

CONS I: 6MP (60mg) asp x2 AraC 75x8

Total 4 x asp

Cons II HD-MTX 5g x2 q3w+ 6MP (25mg)

R 1

DI part 1

DI part 1 w/o Dox

Maintenance: no pulses 2yrs from EOI

Eligibility randomisations 1-4 + CAR-T window

R1: all VLR
R2 : IR-low
R3 (InO): IR-high BCP
R3 (TEAM): all IR-high
CAR-T window: BCP HR

NCI-LR

INDUCTION VADex

INDUCTION VADexDNR

NCI-HR
T-cell

MRD TP1

IR
- MRD pos but <5%
- MRD 0% but HR genetics
- MRD unknown

72-73 %

MRD TP2

CONS I: Std BFM +asp x3

IR-low
- MRD-algorithm low:
- T-cell: MRD TP2 0%
- BCP: by genetic subgroup & MRD TP1
- no HR genetics
- Patients <16
- No CNS3

36%

IR-high
- MRD-algorithm high:
- T-cell: MRD TP2 pos
- BCP: by genetic subgroup & MRD TP1
- Patients >16
- HR-genetics
- CNS3

36%

Cons II – IR-low: HD-MTX 5g x2 q3w +6MP (25mg) No asp (total 5 doses)

Cons II – IR-high HD-MTX 5g x2 q3w +6MP (25mg) Asp x3 (total 8 doses)

R 2

DI: ALLTogether type with Dox

DI: ALLTogether type w/o Dox

DI: ALLTogether type with Dox

Cons III: HD-MTX 5g x2 q3w

Cons III: HD-MTX 5g x2 q3w

R 2

R 3

Maintenance: with pulses VCR/Dexa 2yrs from EOI

Maintenance: no pulses VCR/dexa 2yrs from EOI

Maintenance: with pulses VCR/dexapulses 2yrs from EOI

+/-

Maintenance: with pulses 2yrs from EOI + TEAM

Novel agent INOTUZUMAB

Maintenance: with pulses 2 yrs from EOI

Targetable lesions: TKI from D15, then IR-high or HR (MRD-dep)

HR

MRD >5% TP1 or t(17;19)

3-4 %

MRD TP2

CONS I: Std BFM +asp x3

HR (chemo)
- MRD >5% TP1 and $\leq 5 \times 10^{-4}$ TP2

1-2%?

HR (SCT)
- MRD $> 5 \times 10^{-4}$ TP2
- t(17;19)

3-4%?

CAR-T window (BCP)

CAR-T window (BCP)

Back-up:

A1 B1 C1 A2 B2 C2 MT1 DI MT2

2yrs from EOI

HR-blocks x 6 + Nelarabine (T-cell)?

If successful: End of therapy

Back-up:

HR-blocks x ≥ 3 + Nelarabine (T-cell)?

SOC= Allo-HSCT

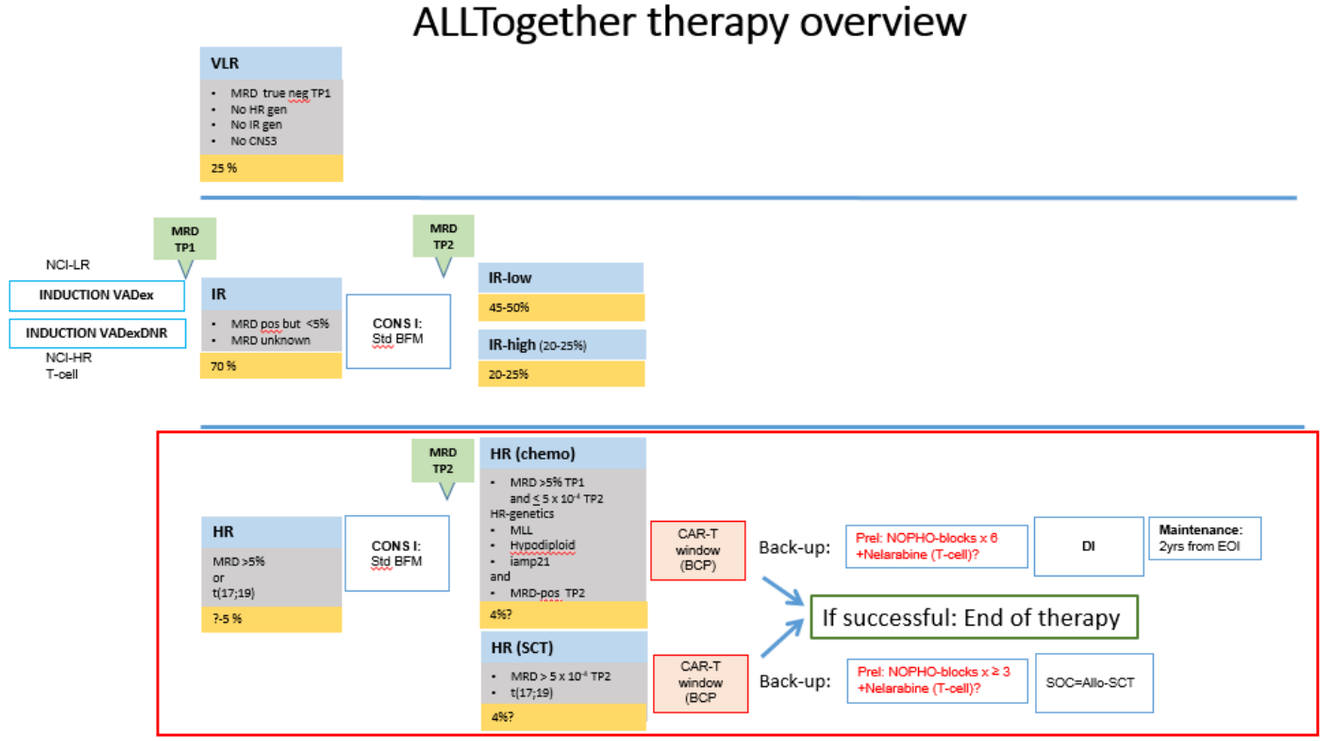
A1 B1 C1

Cassiopeia

Protocol CCTL019G2201J - Novartis (A single arm phase II trial to assess the efficacy and safety of tisagenlecleucel in **first-line high-risk** (HR) pediatric and young adult patients with B-cell acute lymohoblastic leukemia (B-ALL) who are minimal residual disease (MRD) positive at the end of consolidation (EOC) therapy)

- Open in COG and in EU. **Open in UZGent**
- Compared to historical COG control
- Integrated in ALLTogether protocol

NCI HR B-ALL
CR1
MRD EOC ≥ 0,01%
Central flow lab!



Therapy overview for AYA (>16y)

SR
- No T-cell
- MRD true neg TP1
- No HR gen
- No CNS3/TLP+

22%

CONS I: 6MP asp 2x AraC 75x8

Total 4 x asp

Cons II HD-MTX 5g x2 q3w

R 1

DI part 1 with Dox

Maintenance: no pulses 2yrs from EOI

MRD TP1

INDUCTION VADexDNR

NCI-HR
T-cell

IR
- MRD pos but <5%
- MRD unknown

75 %

MRD TP2

CONS I: Mod std BFM

IR-high
- MRD-algorithm high
- MRD < 0.05% TP2
- MRD unknown
- All age-groups
- HR-genetics

38.9 %

Cons II – IR-high HD-MTX 5g x2 q3w asp x3 (total 8 doses)

DI: ALLTogether type with Dox

Cons III: HD-MTX 5g x2 q3w

R 3

Novel agent (InO) 6 weeks

Maintenance: VCR-Dex pulses 2yrs + 6 wks from EOI

Maintenance: VCR-Dex pulses 2yrs from EOI

Maintenance: VCR-Dex pulses +6TG-addition (TEAM) 2yrs from EOI

TKI for Abl-class fusions from d15. If response – strat & Tx as IR-high + TKI throughout – estimated to be 0.5% of all patients, 1.2% are estimated to be HR-patients

---

MRD TP2

HR
- MRD >5%
- t(17 19)

3.%

CONS I: Mod std BFM

HR-HSCT
- MRD ≥ 0.05% TP2

<3%

CAR-T Window* (BCP) Both arms

If successful: End of therapy

Back-up if CAR-T not available/T-cell NOPHO-blocks x 3 in total

Allo-SCT

*Separate study

ALL Together

Ped ALL treatment protocols in Belgium

Frontline

- VLR = low risk (20%)
- AR1 = average low (48%)
- AR2 = average high (12-15%)
  AR2-B & AR2-T
- VHR = high risk (10-15%)

- Mature B-ALL (3%)
  Inter-B Ritux 2010
- Infant ALL (4%)
  Interfant-06 (+ Blina)
- Phi+ ALL (4%)
  EsphALL protocol (imatinib)

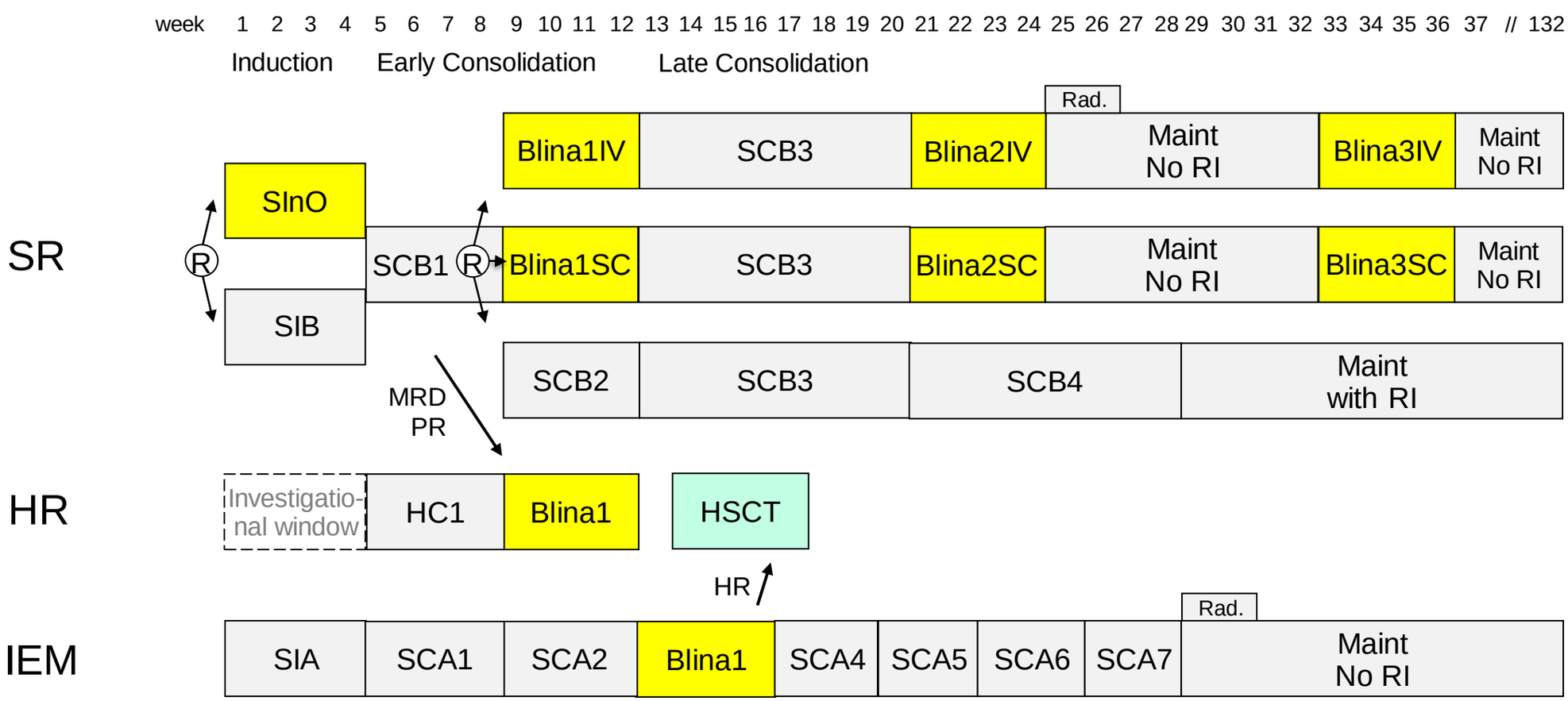
Relapse

- IntReALL SR 2010 protocol: closed
- IntReALL HR 2010 protocol: open for T-ALL
- IntReALL BCP 2020 protocol: Q4 2024
- Hem-iSmart
- Tisagenlecleucel (Kymriah)

Future protocols

- AYA (adolescents and young adults)?
- Resistant ALL?

Design IntReALL-BCP 2020



VHR ITCC-059 Ino study → Hem-iSMART→ CD19 CAR

Pediatric AL and agressive lymphoma: Conclusions (1)

- Rare diseases
- National and international collaboration

BSPHO

http://www.bspho.be/

- Registration in academic clinical trials
- >> conventional chemotherapy
- < allo-HSCT
- < targeted therapy or immunotherapy

Frontline treatment !

Pediatric AL and agressive lymphoma: Conclusions (2)

- Progress in outcome for ALL patients
  - Treatment intensification (BFM- schedule)
  - CNS prophylactic treatment
  - Better supportive care (for ex. chicken pox prevention…)
  - Risk stratification
- MRD and genetics are used in risk stratification
- Using ALL current protocols, OS = 75-95%
- A2G: ↑ individualized treatment

  monitoring (asparaginase), farmacogenomics, …

  ↑ targeted treatment & immunotherapy