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Acute leukemias

December 13, 2025

BHS course

Pediatric aggressive hemopathies

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BHS course Acute leukemias: 13-12-2025

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Pediatric aggressive hemopathies

PART 1

- Introduction
- Aggressive lymphomas
- Acute lymphoblastic leukemia (ALL)

PART 2

- Myeloid malignancies in children:
  - Acute myeloid leukemia (AML)
  - Myelodysplasia (MDS)
  - Juvenile myelomonocytic leukemia (JMML)
  - Myeloid disorders associated with Down syndrome (TAM/TMD, ML-DS)

2004-2020 **Annually in Belgium:**

340 children (0-15y)

180 ado's (15-19y)

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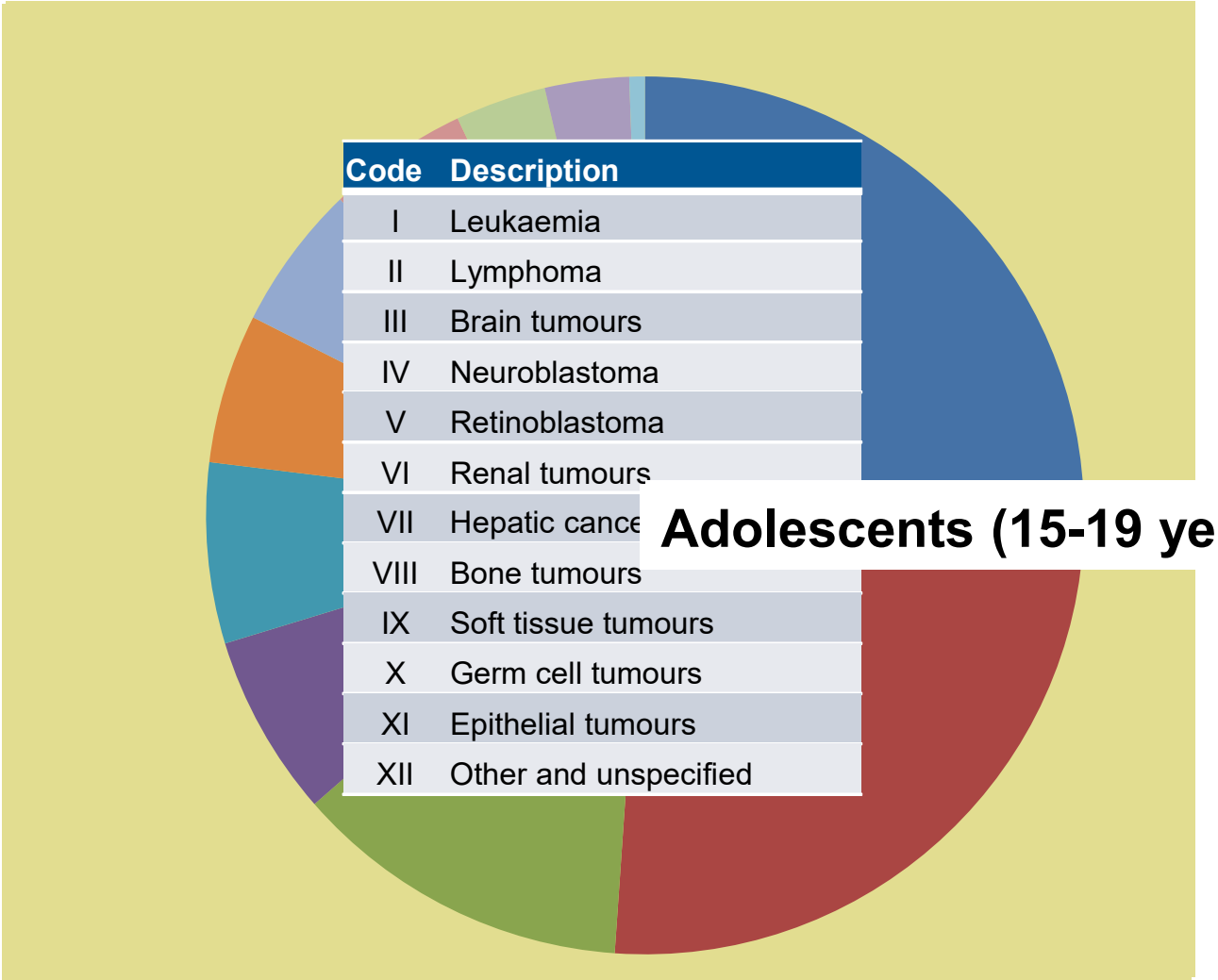
Types of cancer in pediatrics



Adolescents (15-19 years)

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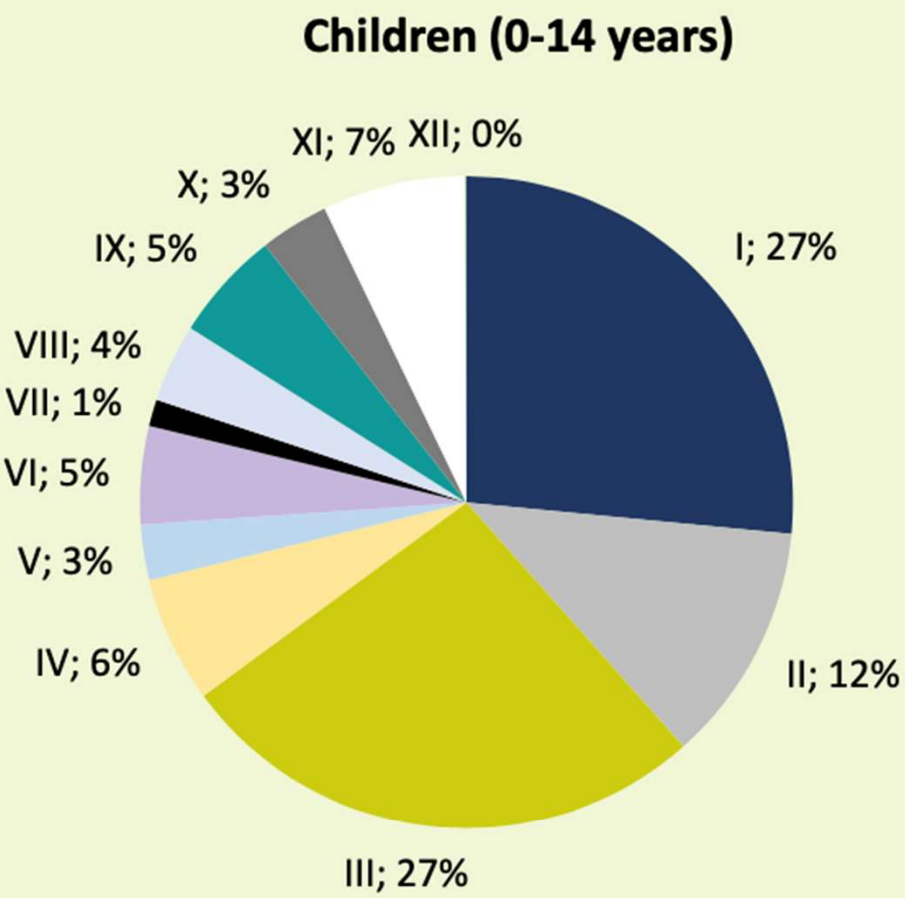
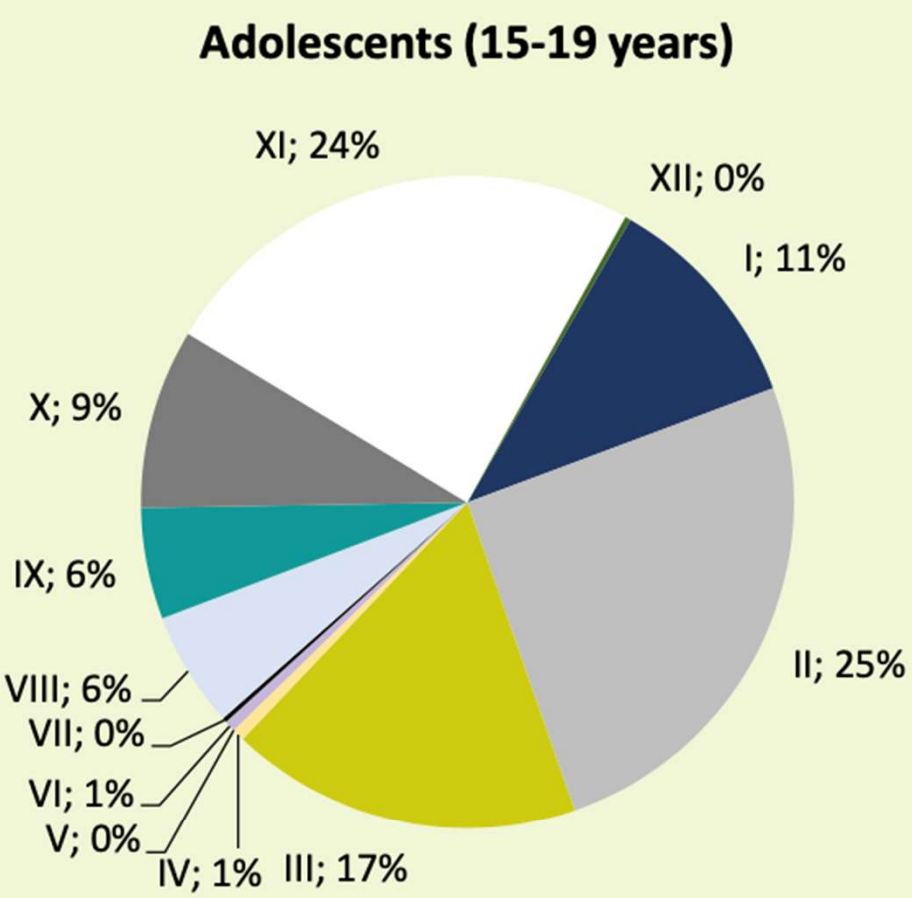
Figure 6: Cancer in children and adolescents: incidence by tumour type, Belgium 2011-2020





Source: Belgian Cancer Registry

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

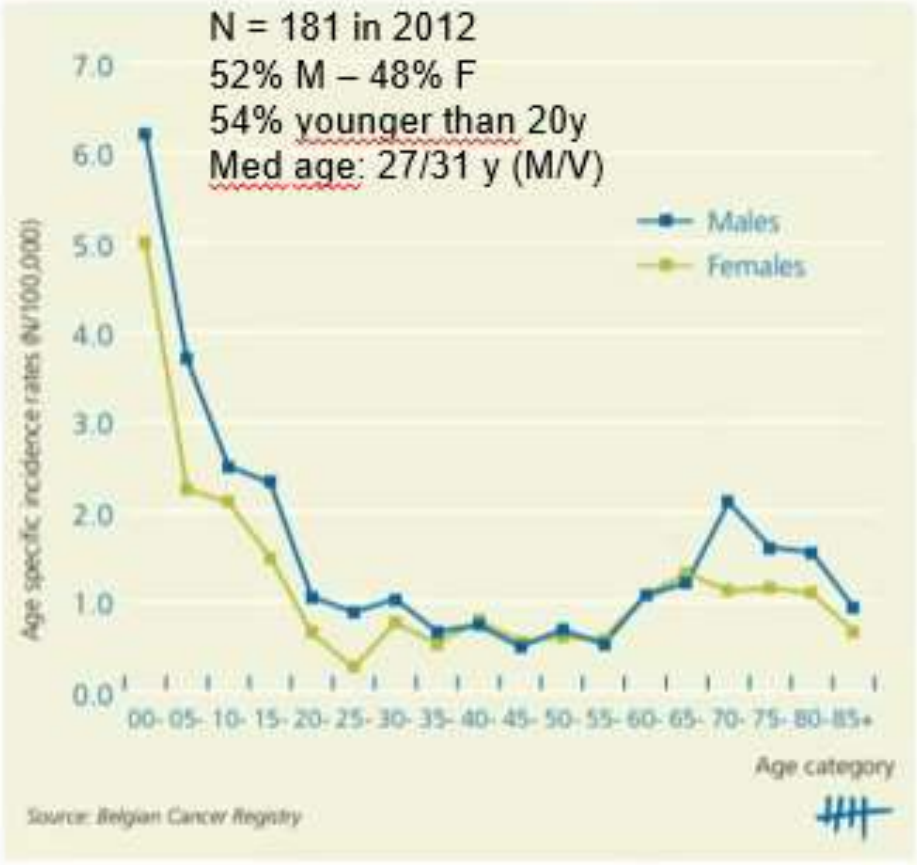
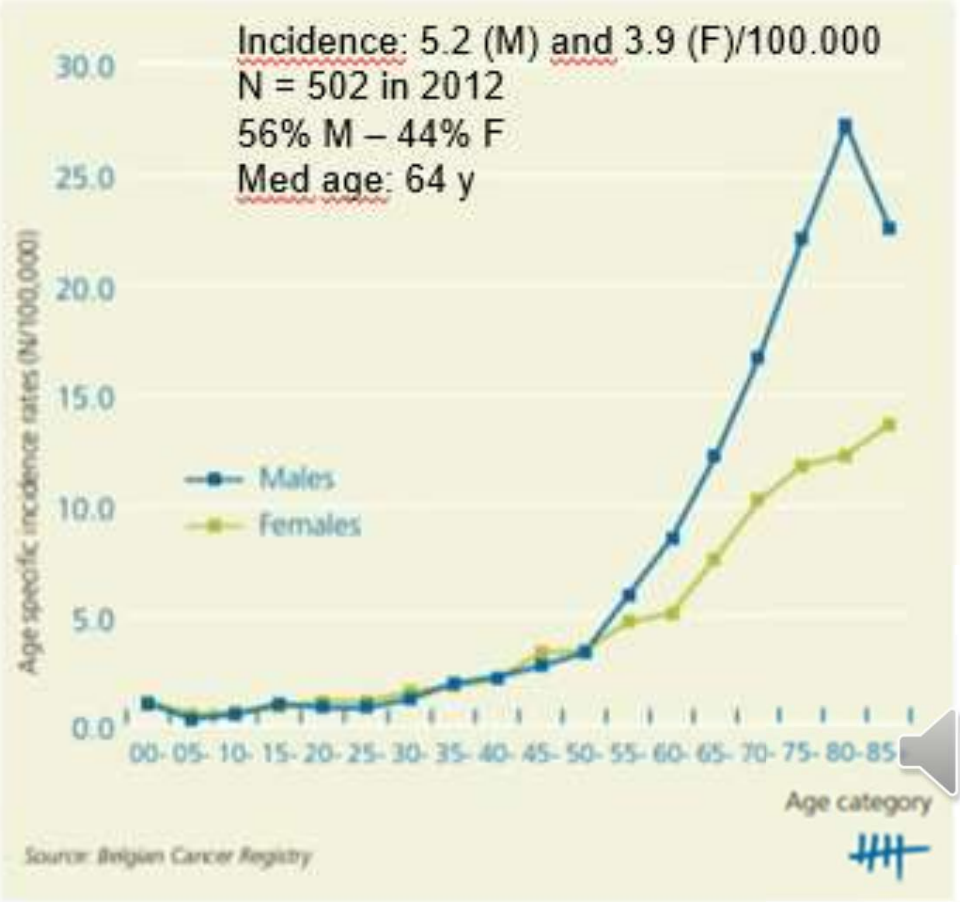


FIGURE 111 ACUTE MYELOID LEUKAEMIA: AGE-SPECIFIC INCIDENCE RATES (N/100,000) BY SEX, BELGIUM 2004-2012



Pediatric leukemia and lymphoma types
(Belgian Cancer Registry, 2004-2013)

- Leukemia — 25%
- Lymphoma — 13%
  - Hodgkin lymphoma — 4%
  - Non Hodgkin lymphoma — 9%
    - Burkitt lymphoma (50-60%)
    - 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%)

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Agressive lymphoma in children

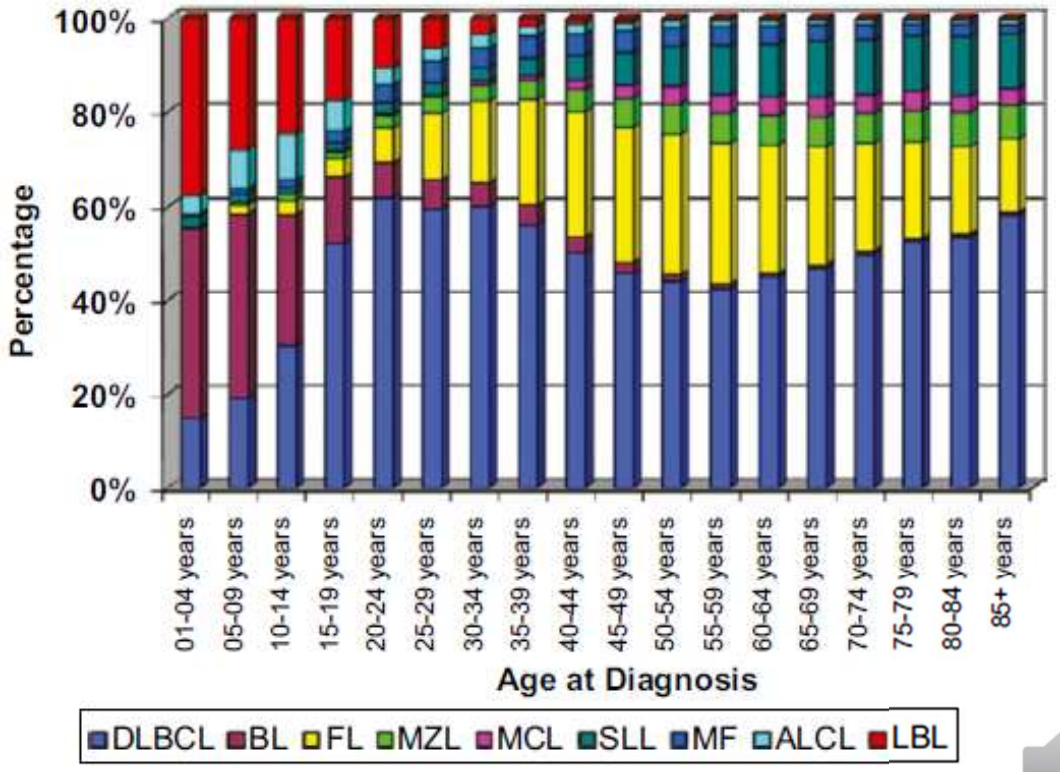
Non Hodgkin lymphoma:

Burkitt lymphoma

Lymphoblastic lymphoma

DLBCL

ALCL



Sandlund and Martin, Hematology 2016

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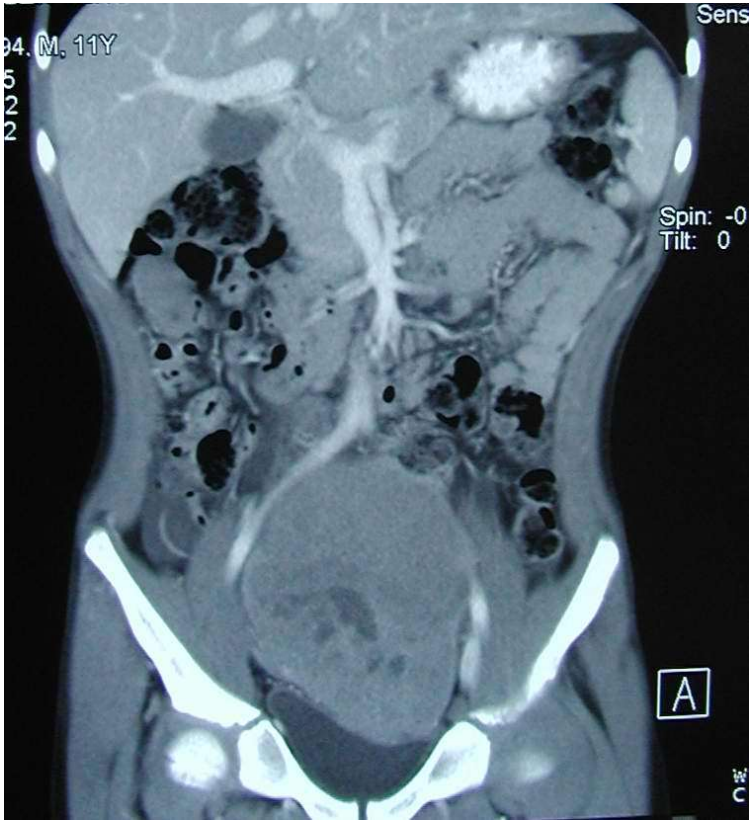
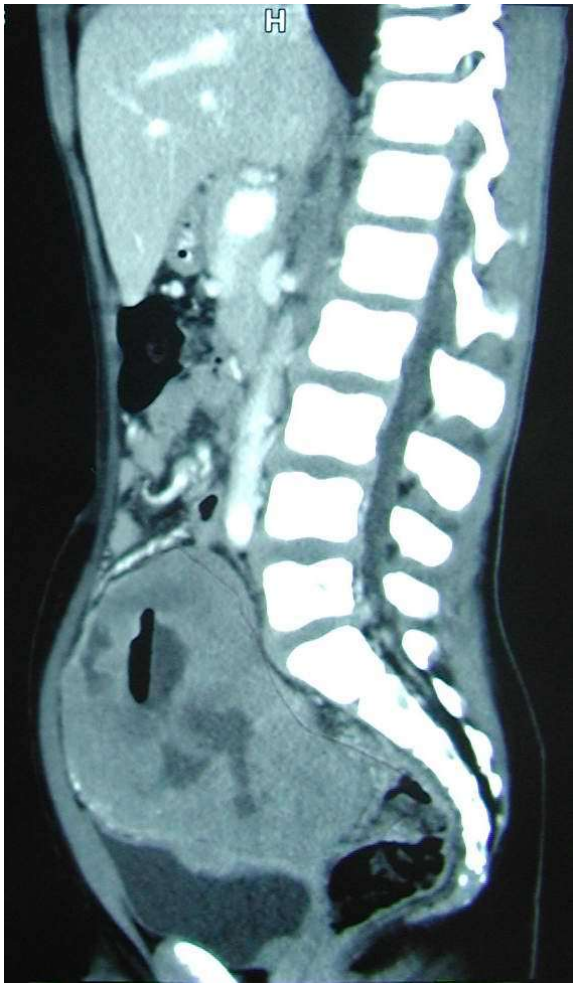
Burkitt lymphoma





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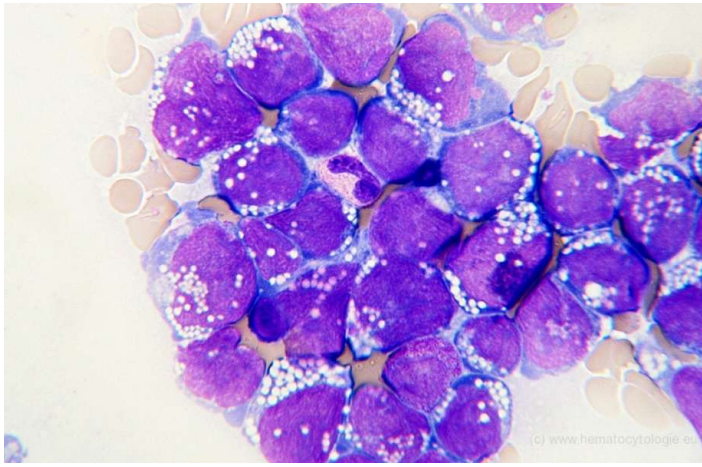
Burkitt lymphoma



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

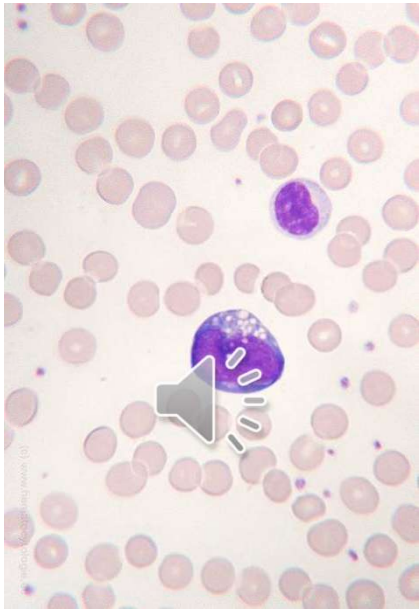
  mature B: sIg (λ or κ), CD19,20,22,10
- Cytogenetic – molecular:

  c-myc (chrom 8) translocation

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

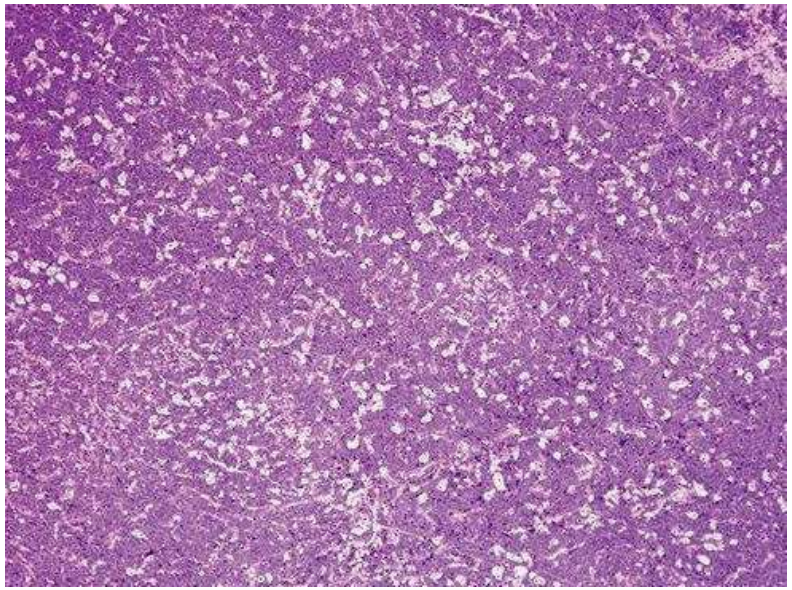
Heavy-chain Ig gene

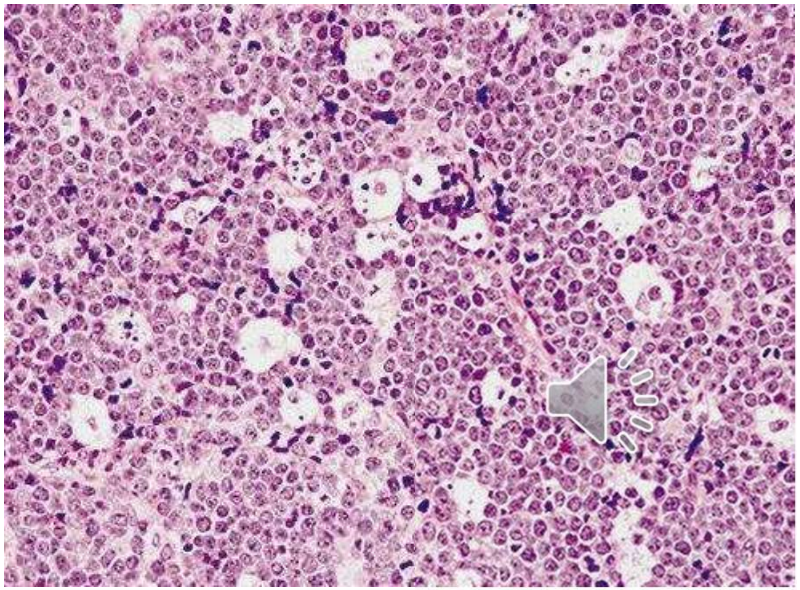
Light-chain Ig gene



Burkitt lymphoma

- Histology: “small round blue cell” tumor
  = diagnostic dilemma in pediatric oncology
- “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 !!!

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Inter-B NHL 2010 Low/Intermediate risk

Group A: resected stage I and resected abdominal stage II

COPAD	COPAD

No IT

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

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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

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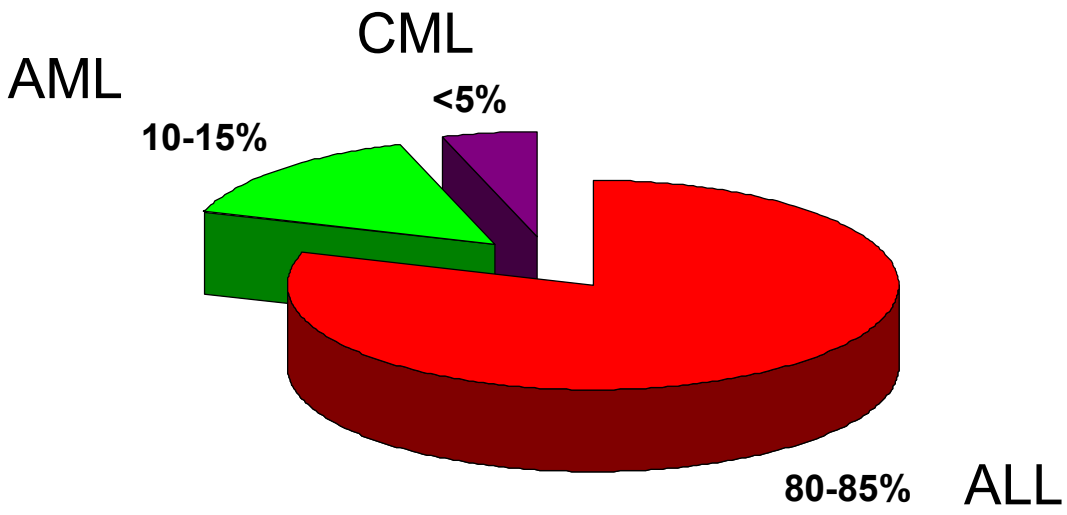
Leukemia in children (<15y)



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

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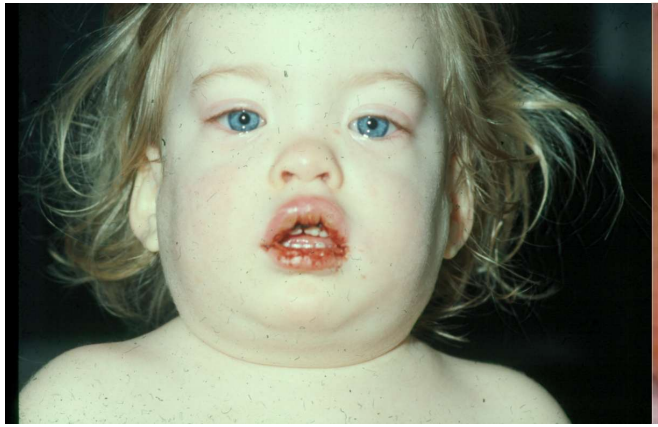
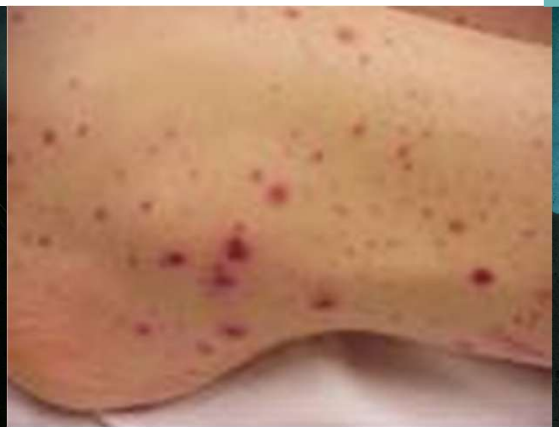
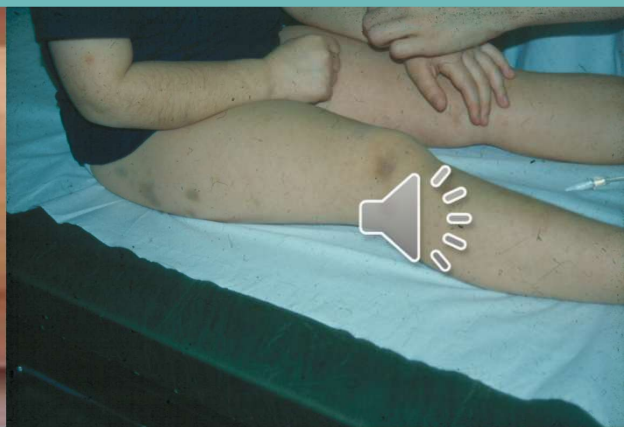
ALL: symptoms and clinical presentation

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





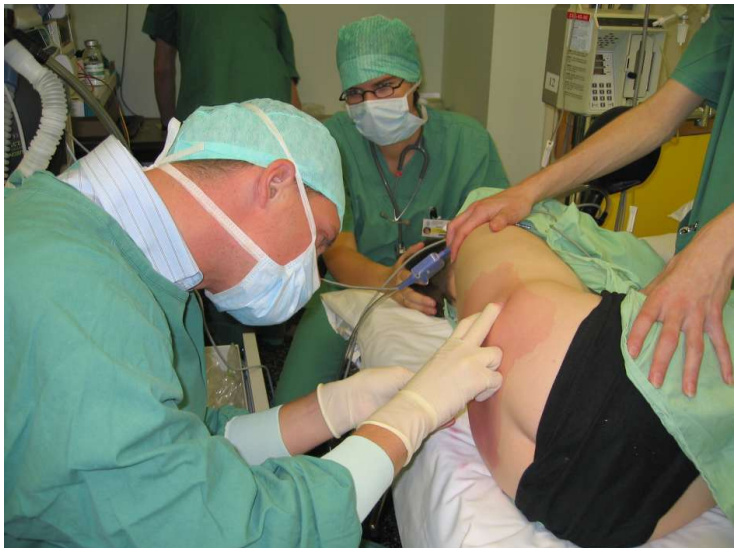


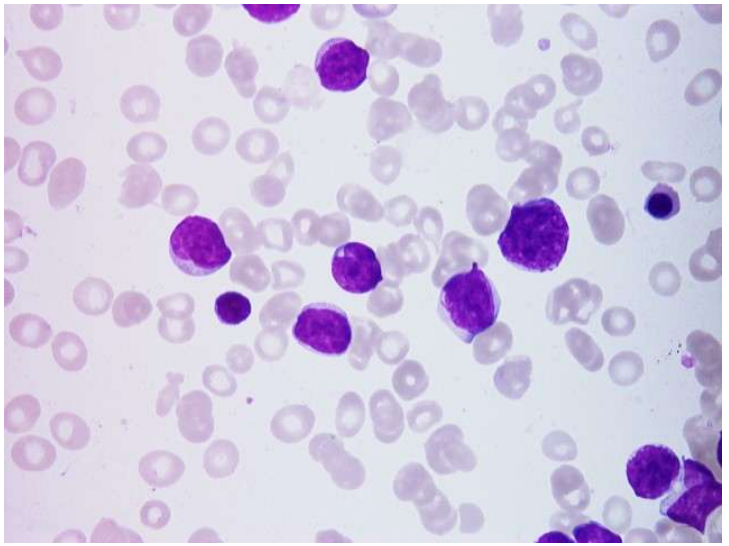
Diagnostic examinations

- 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





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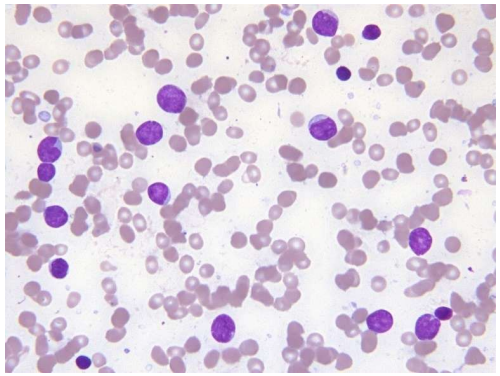
Bone marrow analysis in pediatric ALL:

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

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



Prognostic markers
used in risk stratification

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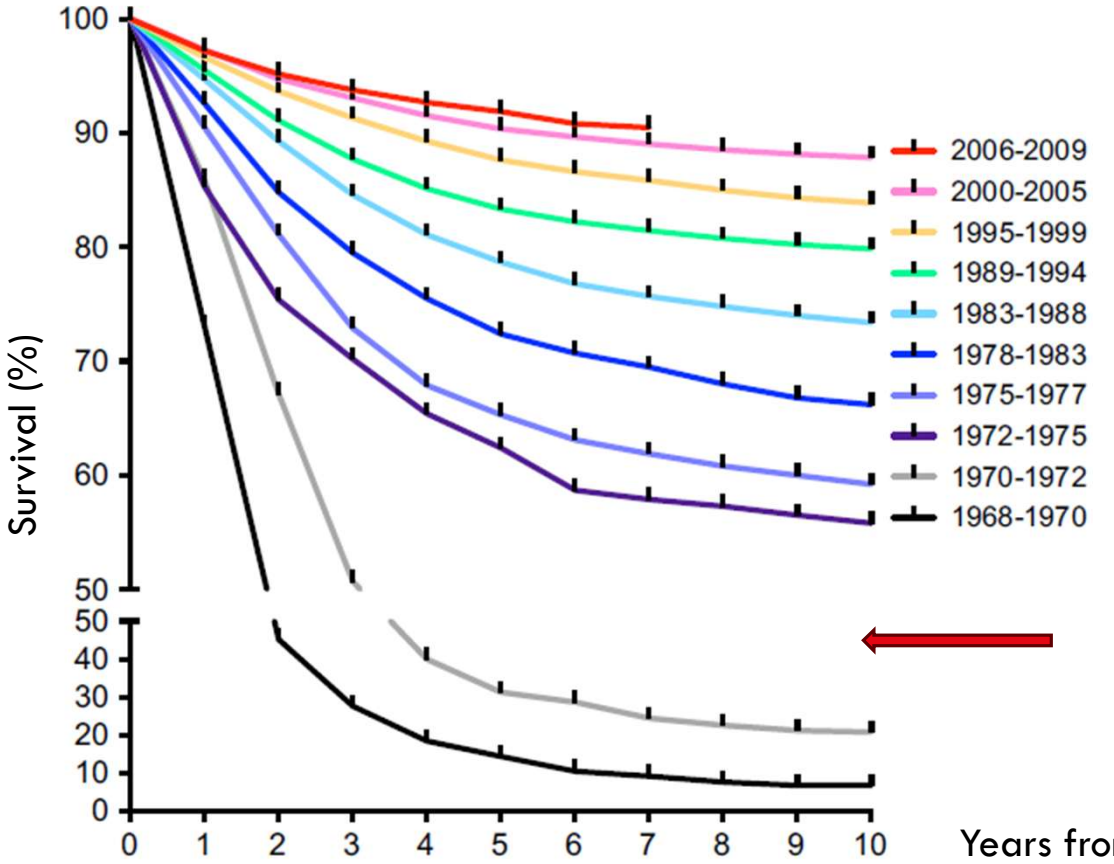
Outcome of pediatric ALL



BFM schedule
CNS treatment & prophylaxis

Years from diagnosis

Tasian & Hunger, Br J Haematol 2016

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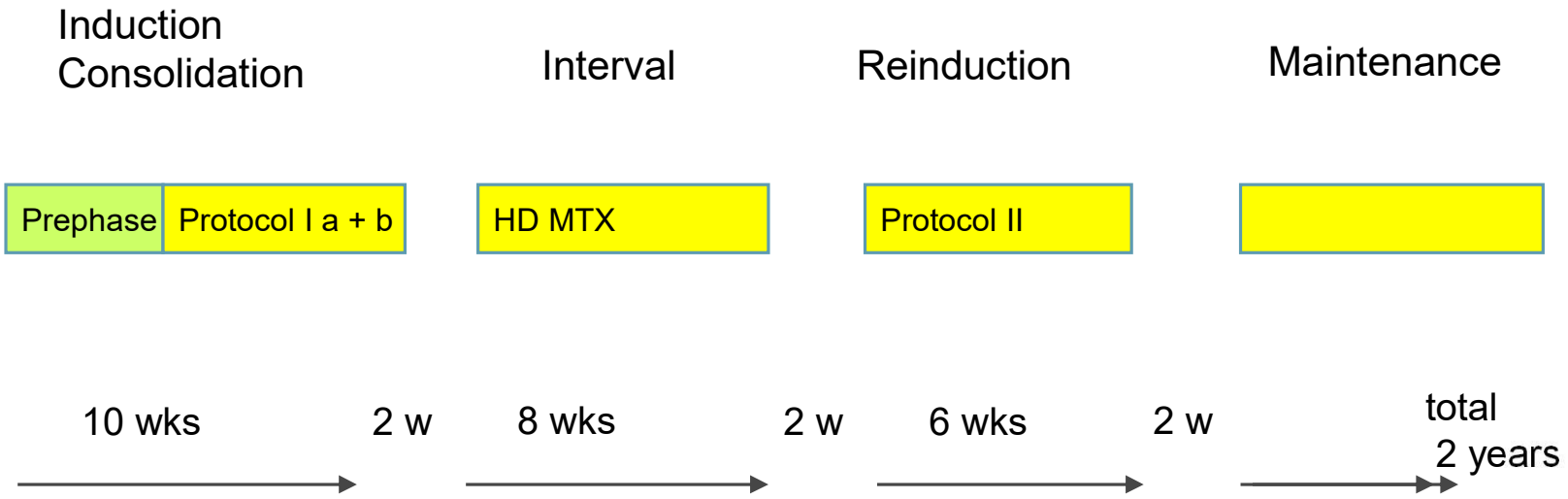
BFM treatment for pediatric ALL

General design



BFM = Berlin-Frankfurt-Münster

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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

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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

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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

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

  EsphALL protocol (imatinib-dasatinib)

Relapse

- IntReALL SR 2010 protocol → IntReALL 2020 B (T)
- IntReALL HR 2010 protocol
- Tisagenlecleucel (Kymriah)
- ARI-chALL
- Early phase trials (ITCC, Hem-iSMART)

Current frontline protocol (since Q4 2020)

"ALLTogether01": 1 -> 45y

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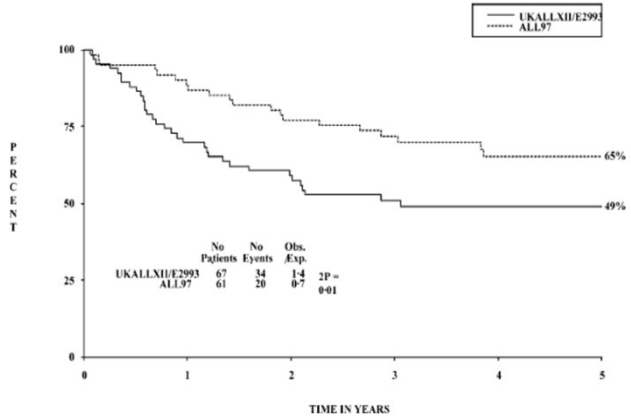
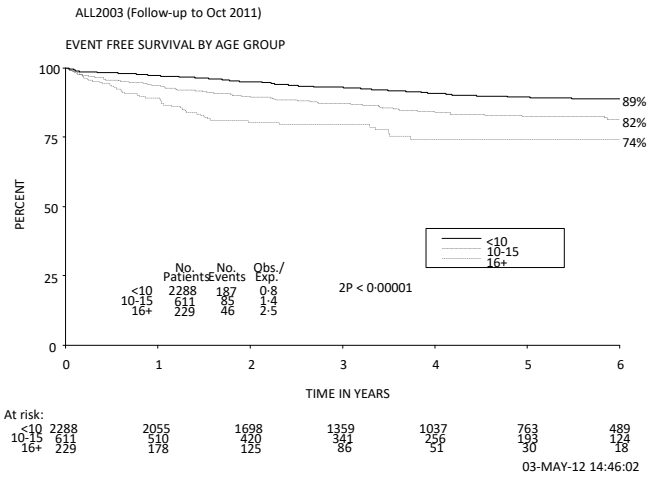
TYA ALL patients (16-24y) have a better EFS if treated on pediatric or ‘pediatric inspired’ protocols



Ramanujachar, Pediatr Blood Cancer 2006



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

BUT TYA patients have an inferior survival compared to younger children

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Moorman et al, Haematol 2016

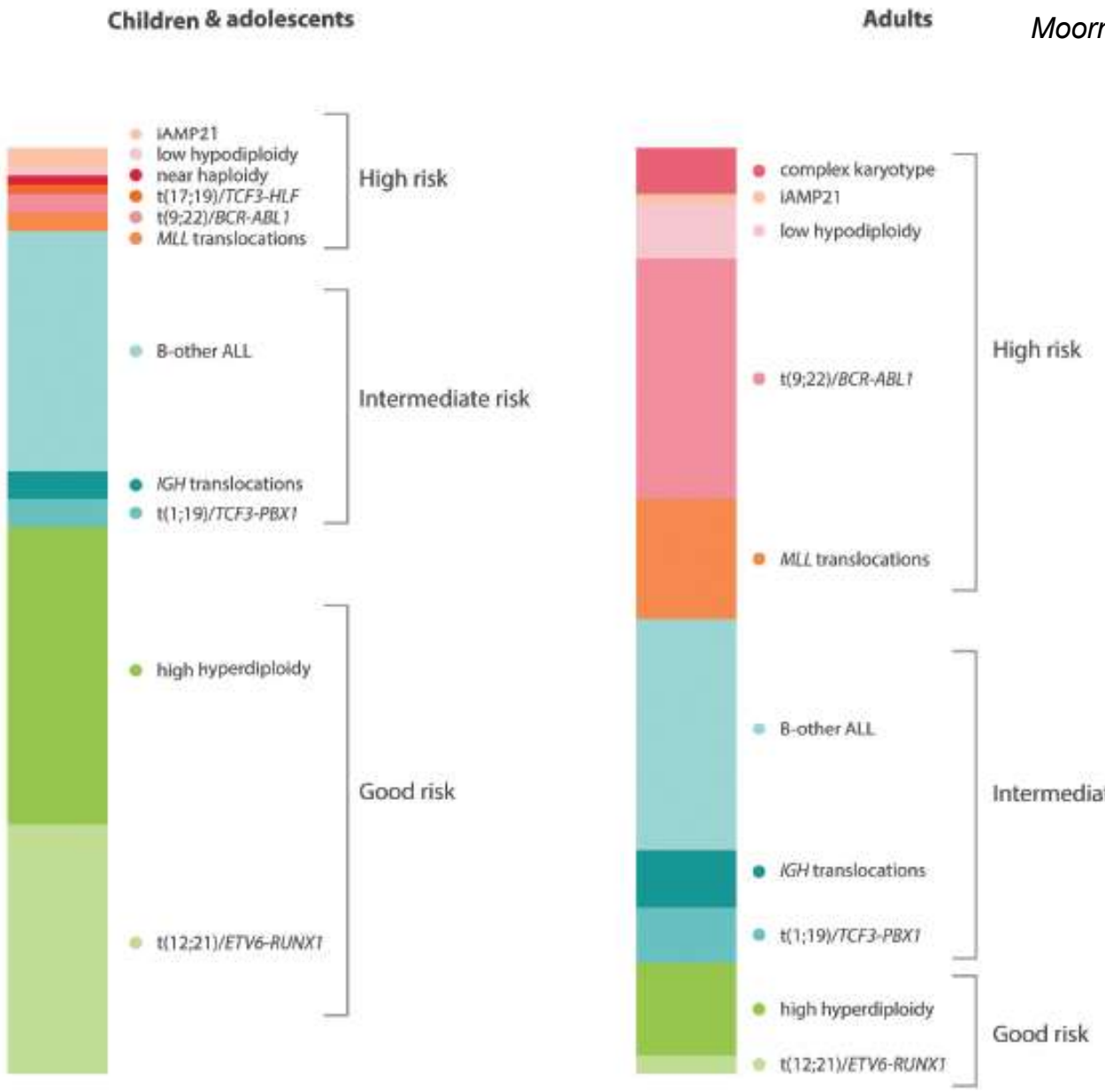

Figure 2. Frequency of primary chromosomal abnormalities in children and adults with B-cell precursor acute lymphoblastic leukemia.

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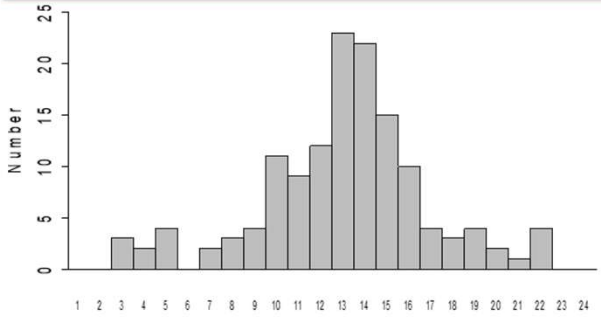
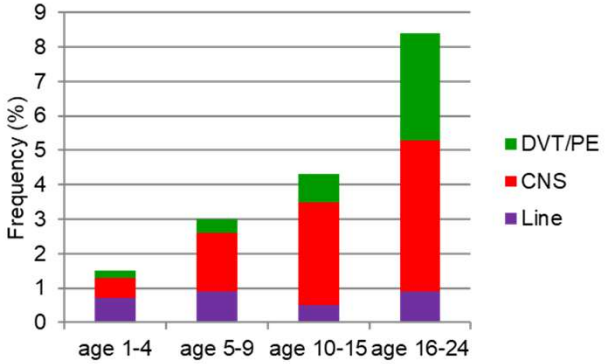
Impact of age on toxicity

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

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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

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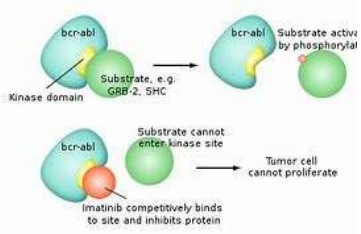
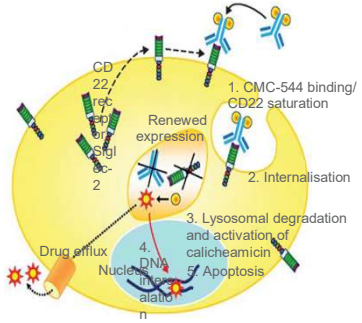
New agents present new possibilities

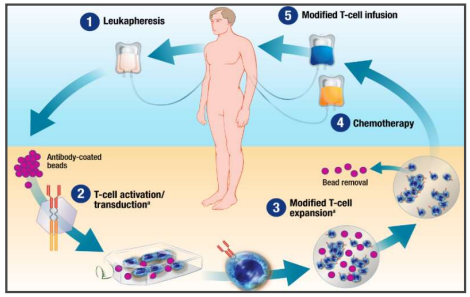
TKI



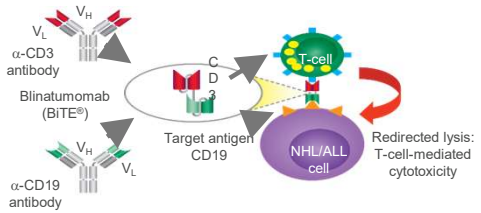
Inotuzumab



CAR T cells



Blinatumomab



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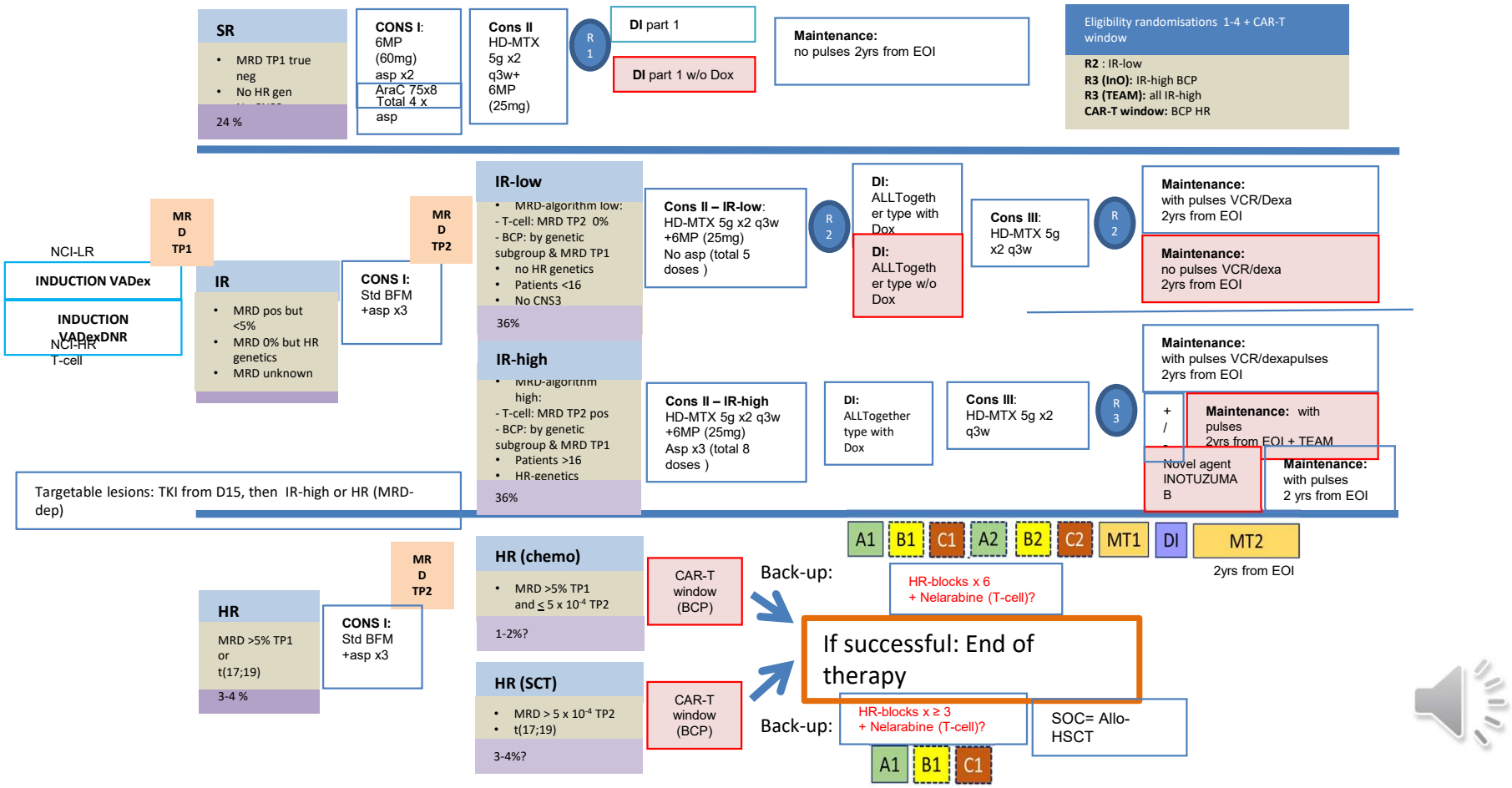
Therapy overview



Randomisation 1: de-escalation for SR-patients

Induction

SR

- MRD neg TP1
- No HR gen
- No CNS3/TLP+

25 %

Cons I:
6MP (60mg)
AraC 75x8

Cons II "(protocol M/2)"
HD-MTX 5g x2 q3w+
6MP (25mg)
asp x2

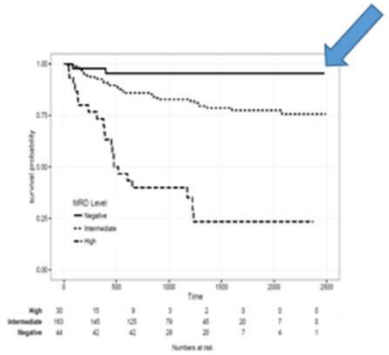
Total 4 x asp

R 1

DI with Dox

DI without Dox

Maintenance:
no pulses 2yrs from EOI



- EFS 95% in this group (children: 97%)
- SR backbone represents signification dose reduction compared to UKALL2003 protocol

TYA patients will be treated on SR backbone but not be entered into the R1 randomisation

ALL Together

Randomisation 2: de-escalation for IR-low patients

Induction
Cons 1

IR-low
- MRD-algorithm (low)
- no HR genetics
- Patients <16
- No CNS3

35%

Cons II "(protocol M/2)"
HD-MTX 5g x2 q3w+
6MP (25mg)

Total 5 x asp (TDM

R 2

DI with Dox

DI without Dox

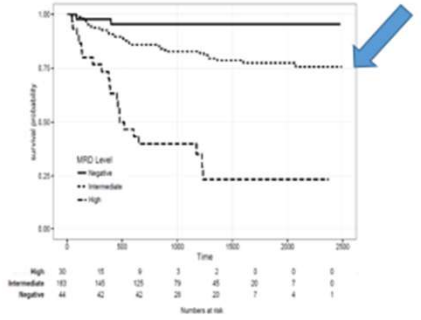
Cons III "(protocol M/2)"
HD-MTX 5g x2 q3w+
6MP (25mg)

Maintenance: with pulses
2yrs from EOI

Maintenance: no pulses
2yrs from EOI

3-way randomisation
Control: +Dox + Pulses
Exp 1: +Dox - Pulses
Exp 2: -Dox + Pulses

- EFS is approximately 80% in this group (children 95%)
- De-escalation of therapy is not appropriate



TYA patients will not be treated in the IR-low arm

Randomisation 3: Experimental intensification for IR-high patients

Ind
Cons 1

IR-high
- MRD-algorithm (high)
- Patients >16
- HR-genetics
- CNS3/TLP+ >5

37%

Cons II "(protocol M/2)"
HD-MTX 5g x2 q3w+
6MP (25mg) + asp x 3

Total 8 x asp (TDM

Long DI:
DFCI/DCOG-type with DOX

Cons III "(protocol M/2)"
HD-MTX 5g x2 q3w+
6MP (25mg)

R 3

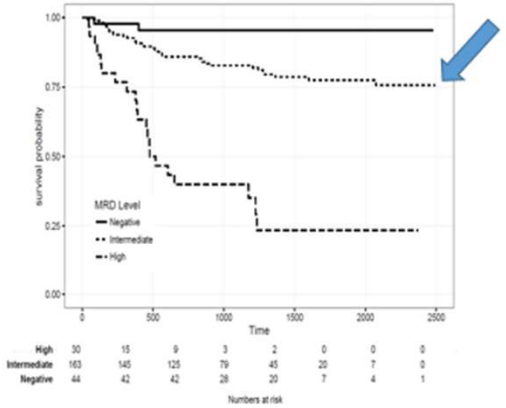
Maintenance: with pulses
2yrs from EOI

Maintenance:with pulses
2yrs from EOI + TEAM

Novel agent (InO)

Maintenance: with pulses
2yrs from EOI+ 6w

EFS approx 80% in this group
De-escalation of therapy not priority
Addition of novel approach to conventional chemotherapy very attractive



All IR TYA patients will be treated on IR-high arm and be eligible for both randomisation arms

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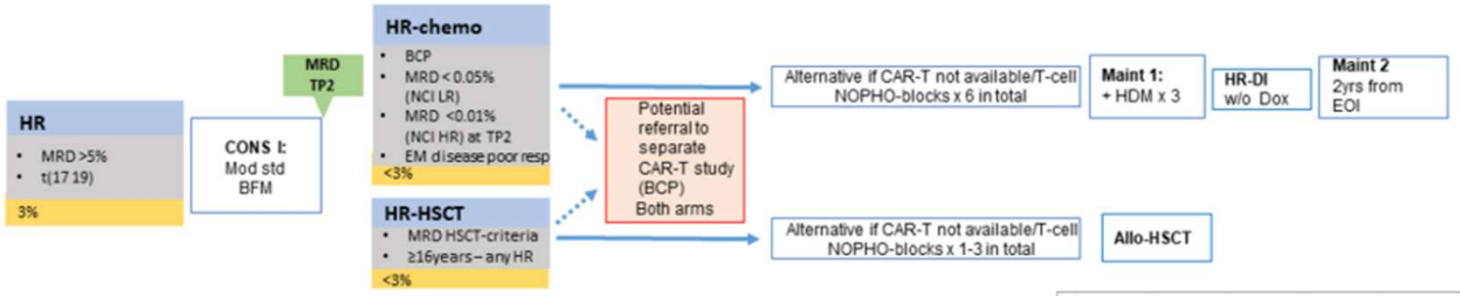
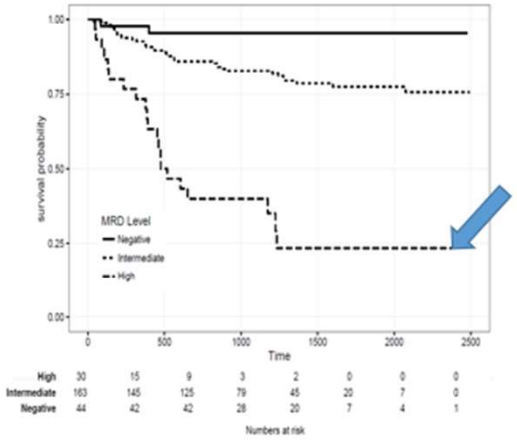
HR patients

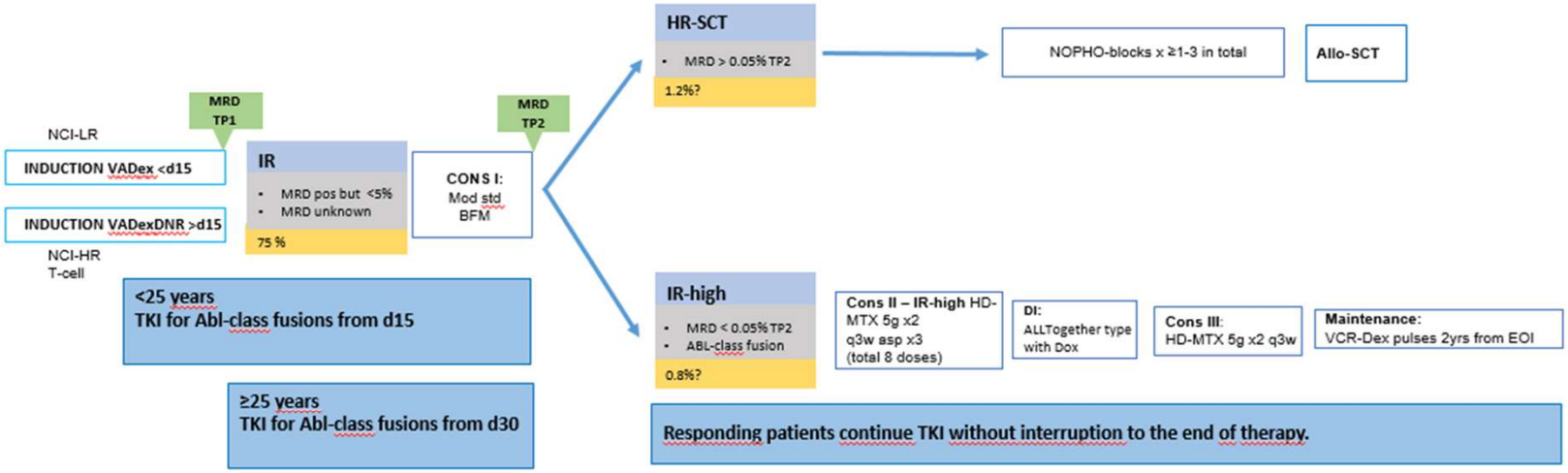


- EFS is 23% in this group!!
- All patients go to transplant or CAR-T (Cassiopeia – max 24 years)
- Additional MRD at D50
- Patients on chemo should go to transplant as soon as MRD and donor available



Non-randomised intervention – ABL-class fusions

- Addition of TKI from day 15 in induction (if <25 years)
- Addition of TKI from day 30 (if ≥25 years)



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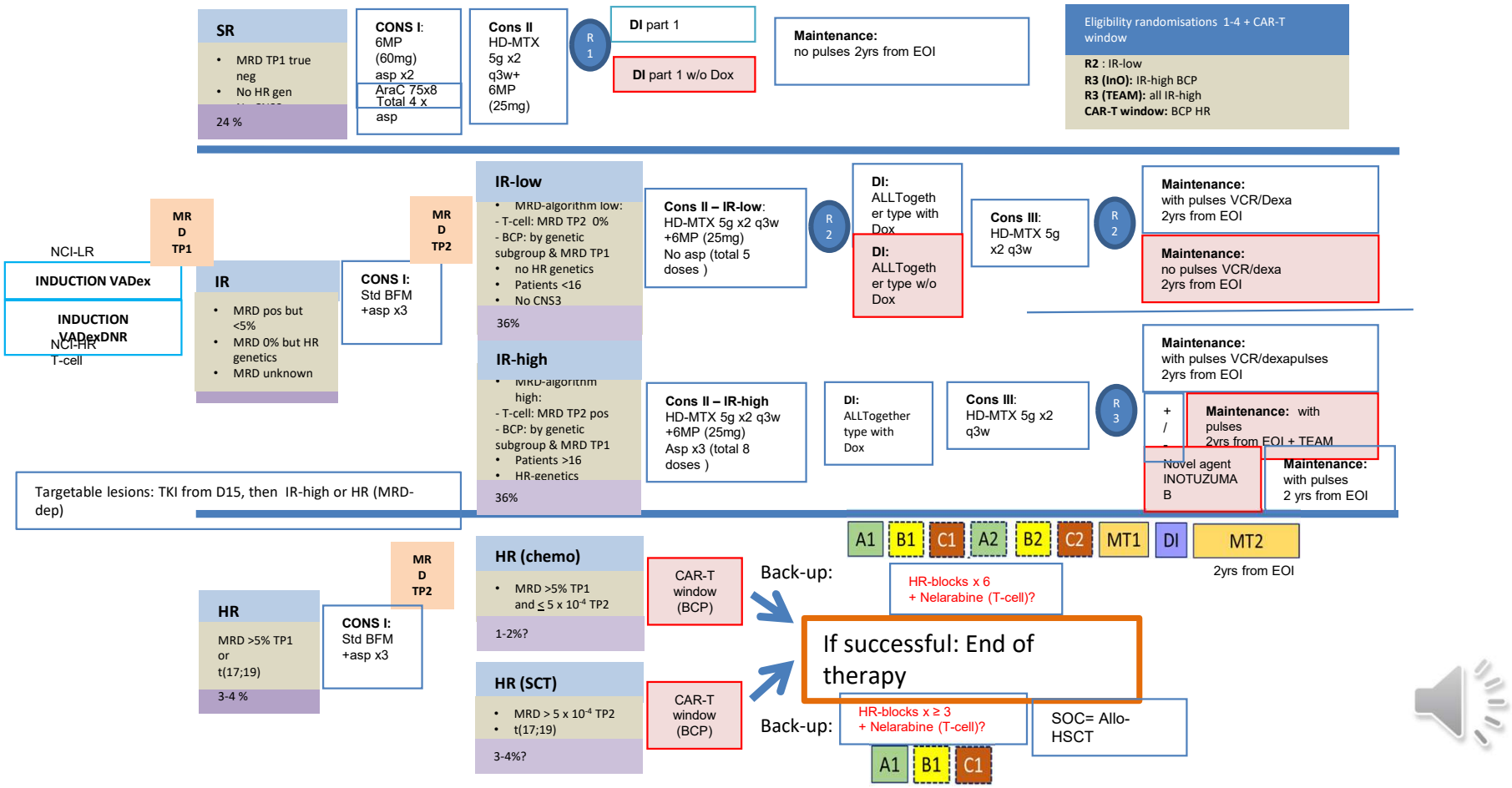
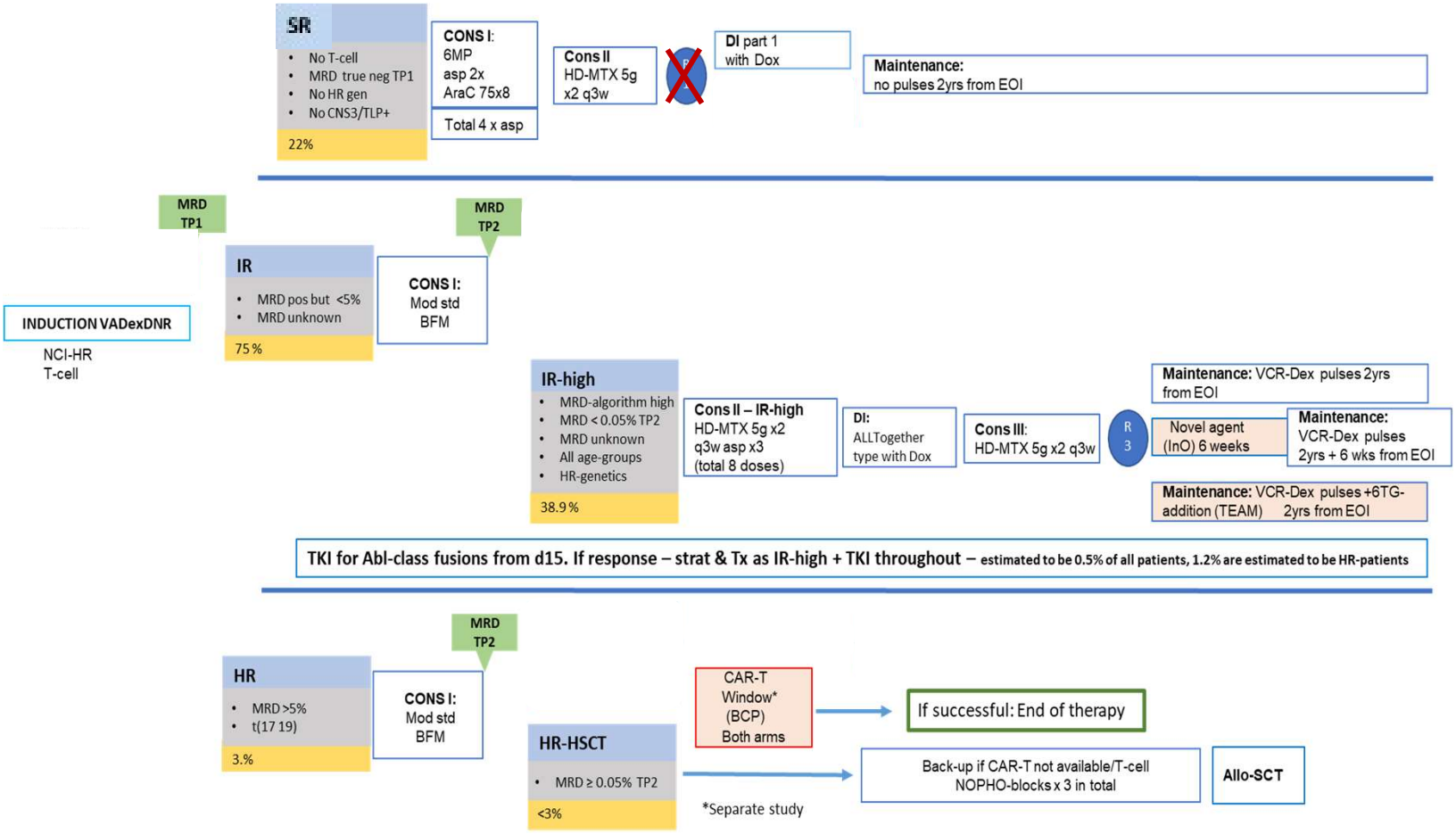
ABL-class fusions = Fusion genes involving ABL1, ABL2, PDGFRB and CSF1R except t(9;22)/BCR-ABL1

Therapy overview



Therapy overview for TYA



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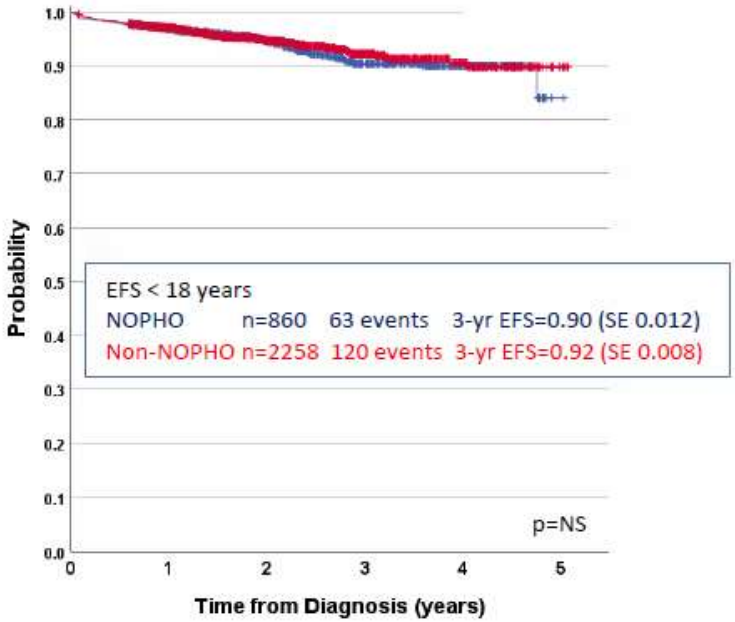
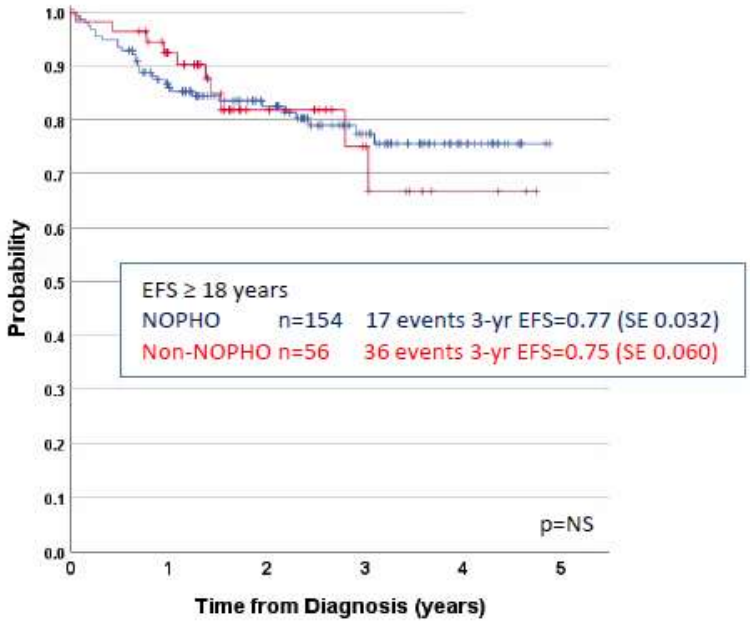
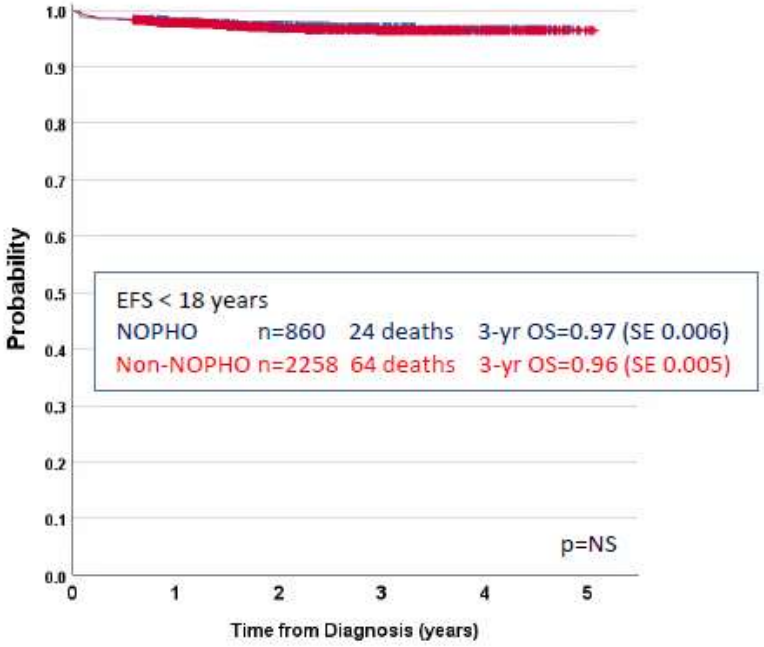
EFS-comparison NOPHO vs non-NOPHO by age-group

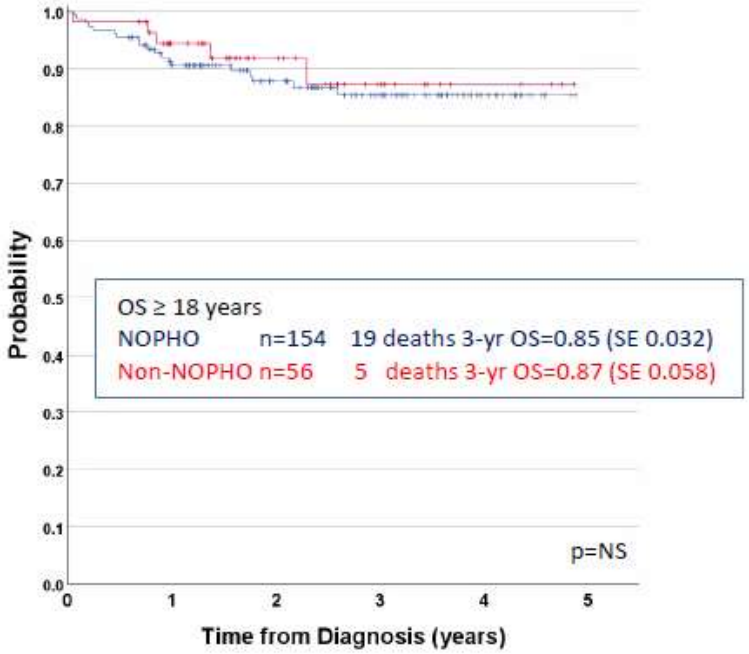




Preliminary outcome data (September 2025), unpublished.

OS-comparison NOPHO vs non-NOPHO by age-group

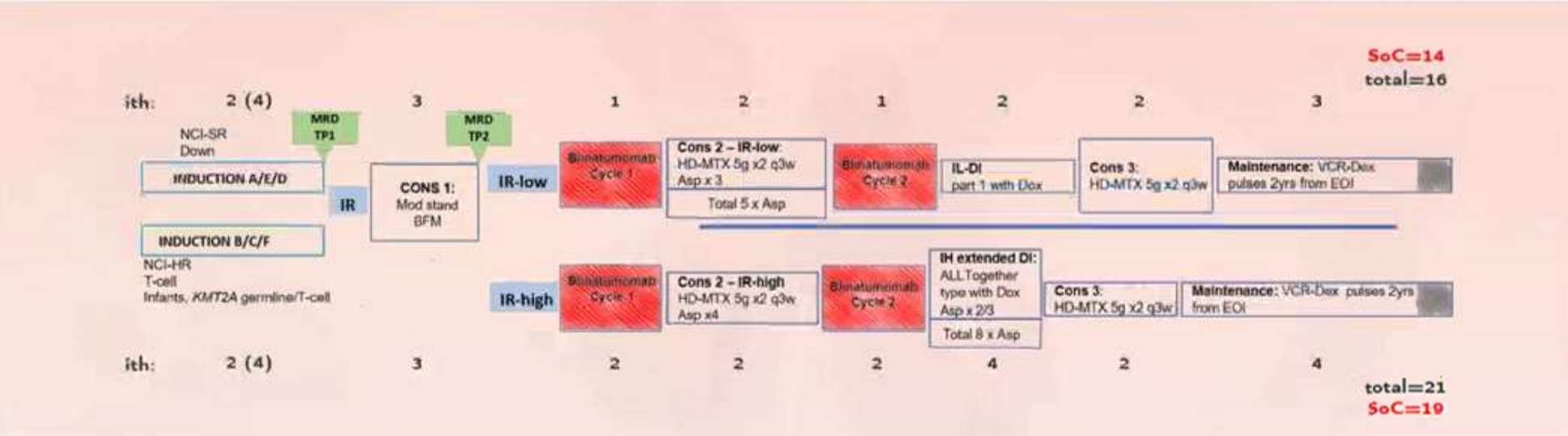




Preliminary outcome data (September 2025), unpublished.

VOETTEKST

ALLTogether01: optional treatment recommendation for IR patients <18y (under discussion)



Addition of 2 courses of Blinatumomab ?

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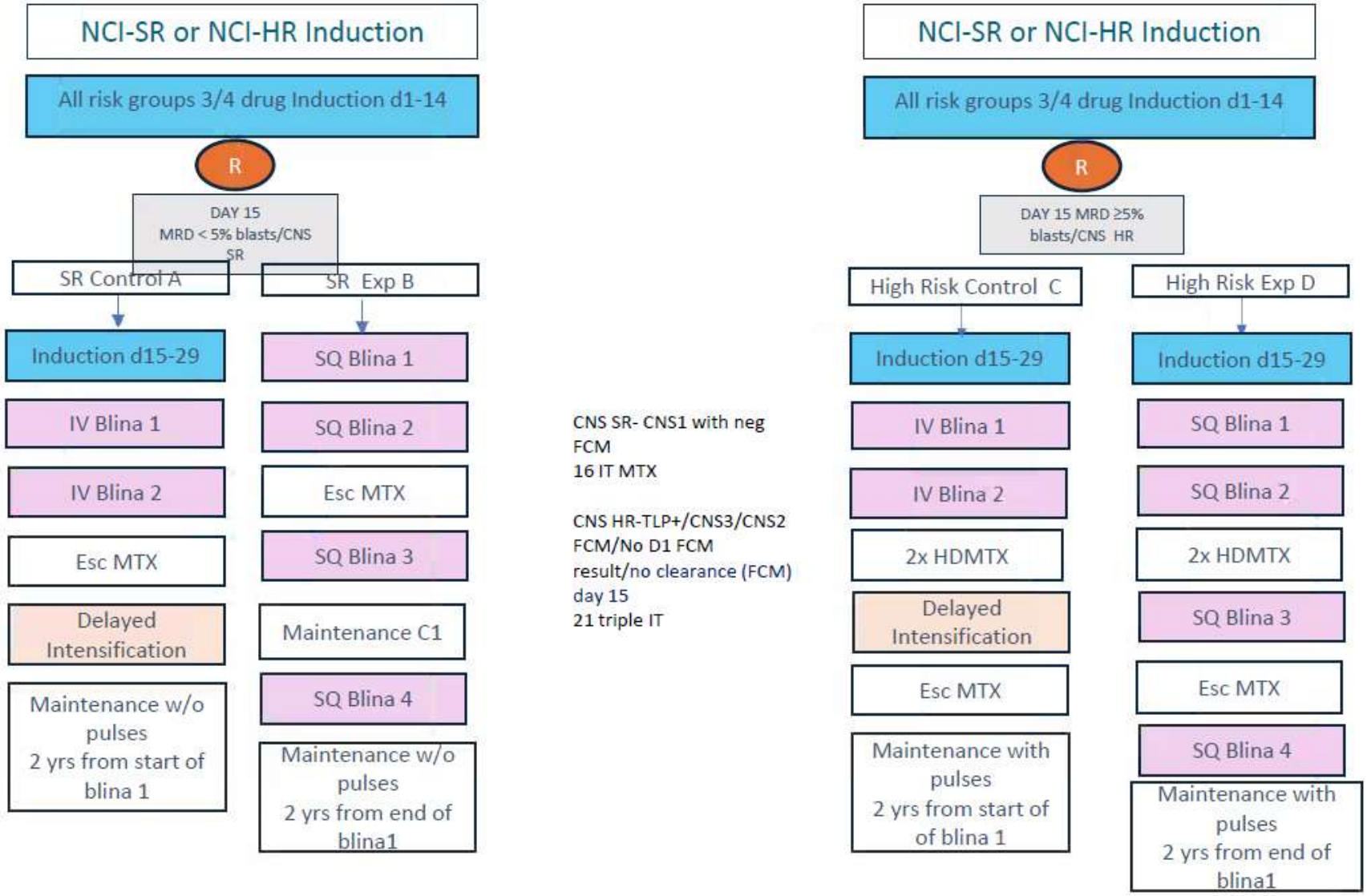
ALLTogether2: BCP: under discussion



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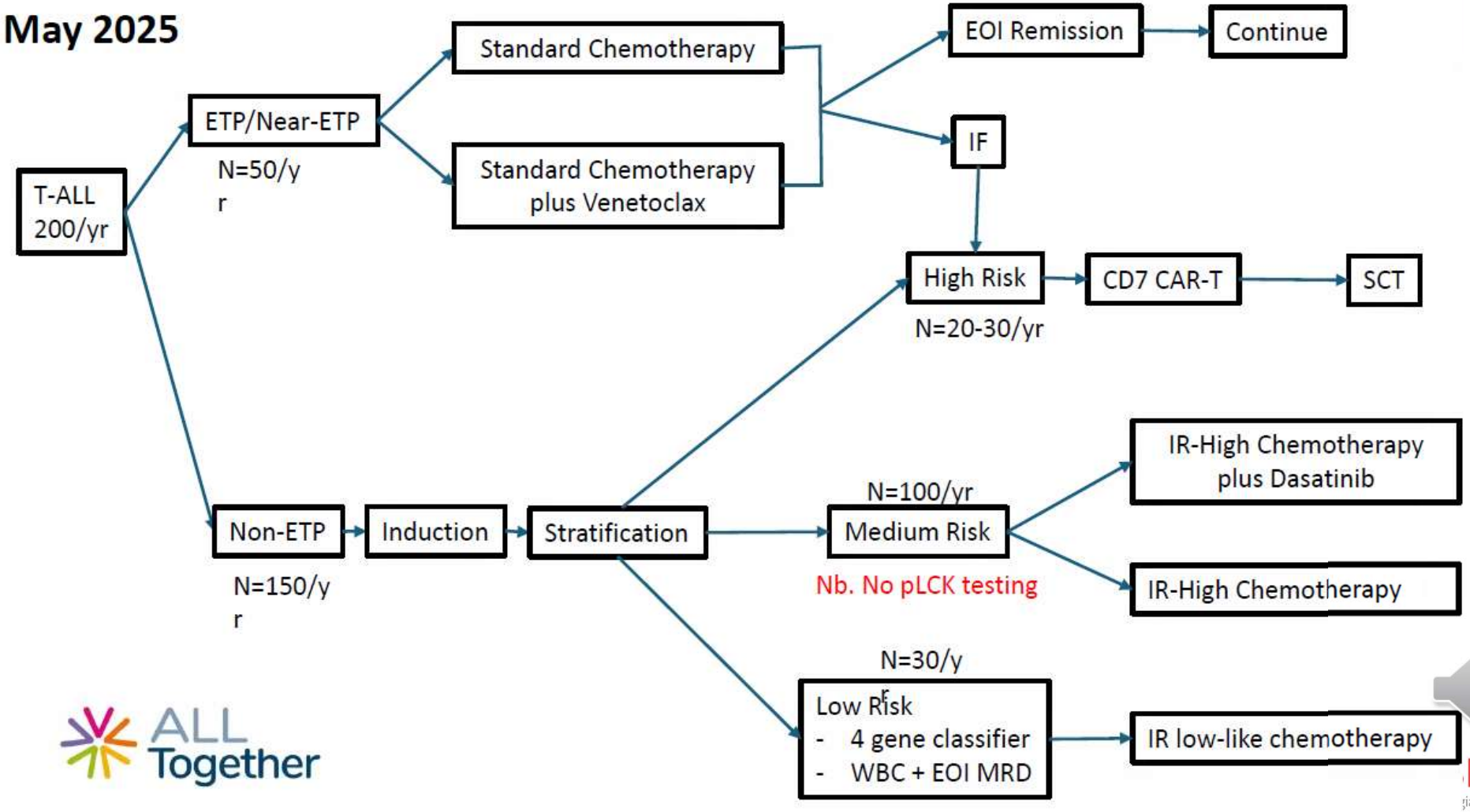
ALLTogether2: T : under discussion



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

  EsphALL protocol (imatinib-dasatinib)

Relapse

- IntReALL SR 2010 protocol → IntReALL 2020 B (T)
- IntReALL HR 2010 protocol
- Tisagenlecleucel (Kymriah)
- ARI-chALL
- Early phase trials (ITCC, Hem-iSMART)

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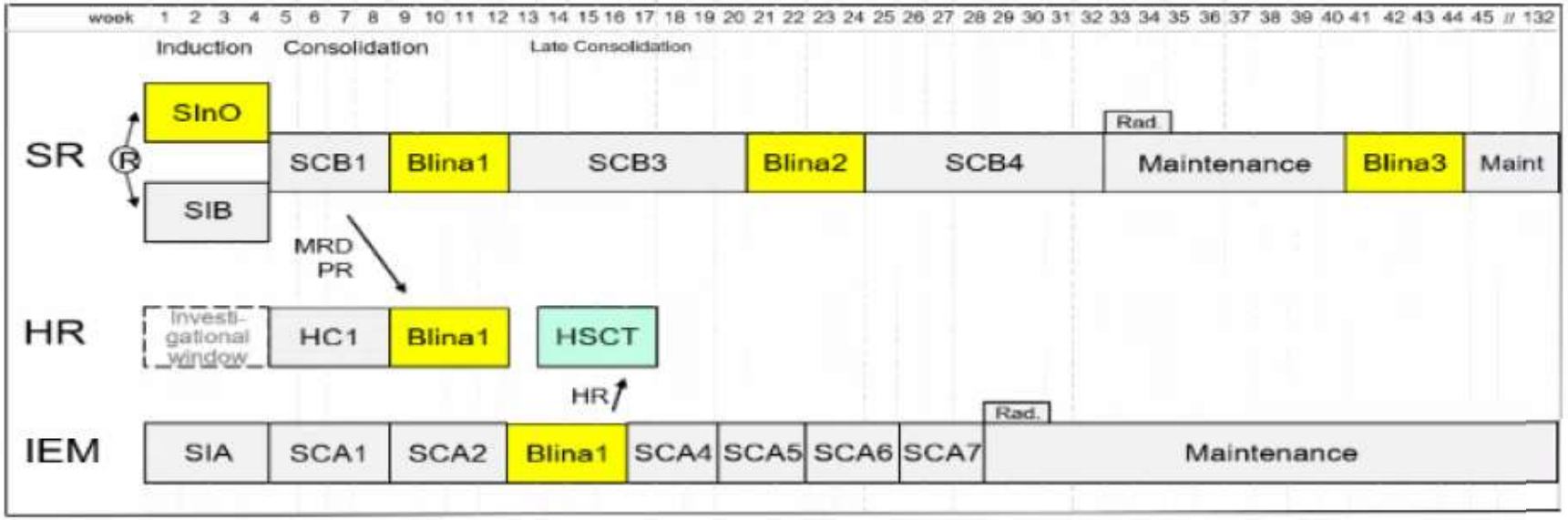
IntReALL BCP 2020, 1st relapse



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Pediatric ALL: Conclusions (1)

- Rare disease
- National and international collaboration

http://www.bspho.be/

BSPHO

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

Frontline treatment !

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Pediatric ALL : 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

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