European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

17.02.2026

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Successful combined anti- CD19 immunotherapy of relapsed acute lymphoblastic leukaemia in a child with Nijmegen breakage syndrome

Moderation: Fiona Poyer

Funded by the European Union's EU4Health Programme

SIOPE YOUNG

St. Anna Kinderkrebs Forschung

COI declaration

Novartis, ALSAC at St. Jude – support for attending meetings and travel

A 4-year-old boy with Nijmegen Breakage Syndrome

Symptoms at the time of diagnosis of acute lymphoblastic leukemia:

- Fever
- swelling of the wrist and ankle joints
- generalized lymphadenopathy
- Hepatosplenomegaly
- blood count: Hb 11.6 g/dL; WBC 14.4 × 10^3/µL; PLT 43 × 10^3/µL
- peripheral blood smear: 38% blasts
- bone marrow immunophenotype: (95% blast cells, expression of $CD19^+$, $CD10^+$, $CD22^+$, $CD34^+$, $HLA\text{-}DR^+$; co-expression of CD33 and CD15)
- karyotype: **high hyperdiploidy**, no KMT2A or BCR::ABL1 rearrangements

What is the most likely diagnosis?

A. Juvenile myelomonocytic leukemia (JMML)
B. B-cell Acute lymphoblastic leukemia (B-ALL)
C. Acute myeloid leukemia (AML)
D. Epstein–Barr virus (EBV)–associated lymphoproliferative disease
E. T-cell acute lymphoblastic leukemia (T-ALL)

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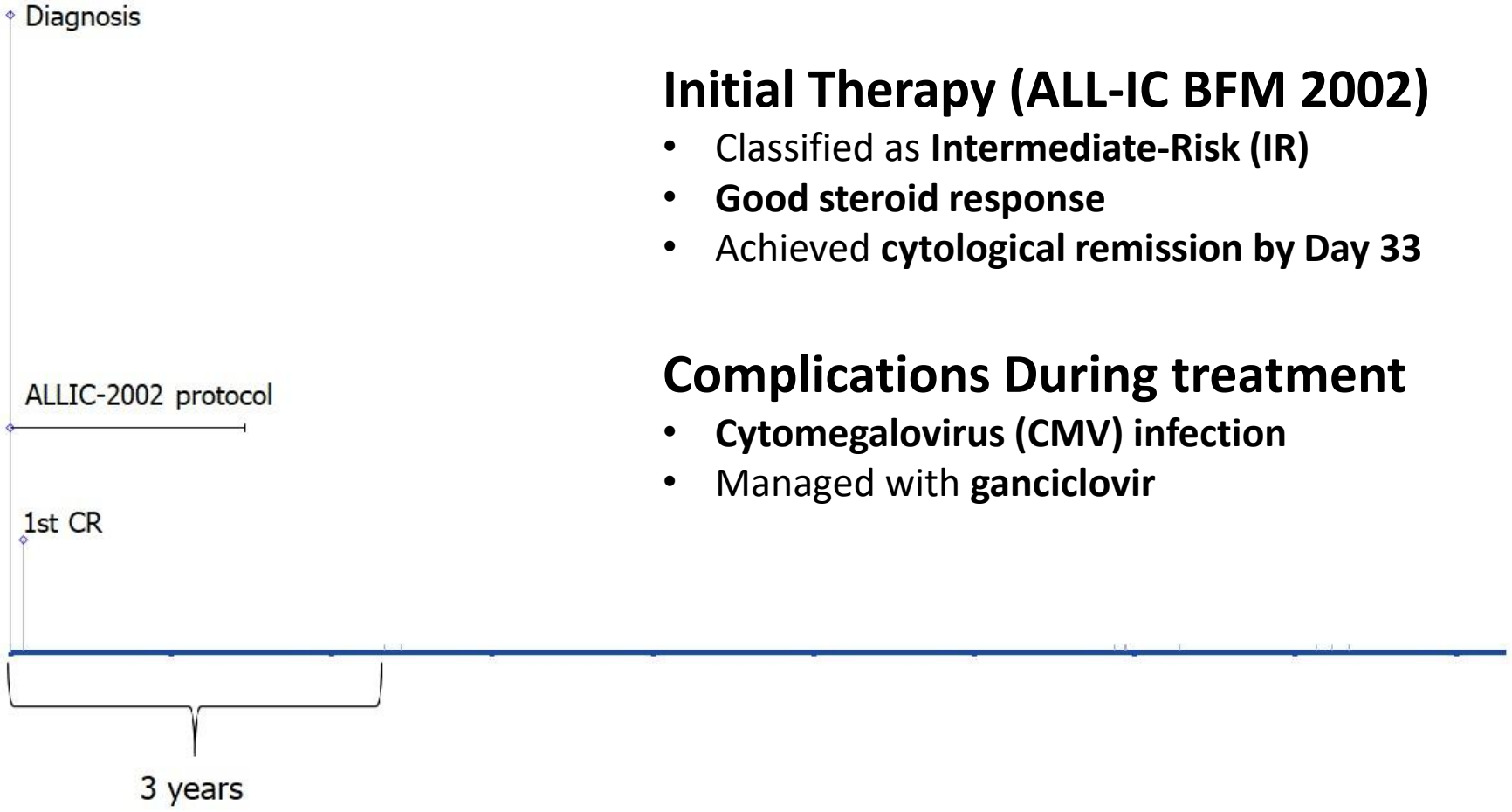
Nijmegen Breakage Syndrome (NBS)

- A rare autosomal recessive disease from the group of **chromosomal instability syndromes** (CIS).
- A disorder of double-strand DNA break repair (**DNARD**).
- Characteristic clinical features: congenital **microcephaly**, growth retardation**, immunodeficiency, hypersensitivity to ionizing radiation**.
- High risk of hematologic malignancies (**DLBCL**, T-lymphoblastic lymphoma, T-ALL)

Nijmegen Breakage Syndrome (NBS)

- Immunological mechanisms: defect in V(D)J recombination and Ig class-switch recombination, limited clonal diversity of Ig and TCR receptors, reduced or absent IgA and IgG2, **low T-cell count and impaired T-cell maturation**.

- Clinical consequences: recurrent infections, prolonged pancytopenia after chemotherapy, the need to modify standard oncologic treatment protocols, frequent therapy interruptions and dose reductions → **poorer prognosis**.

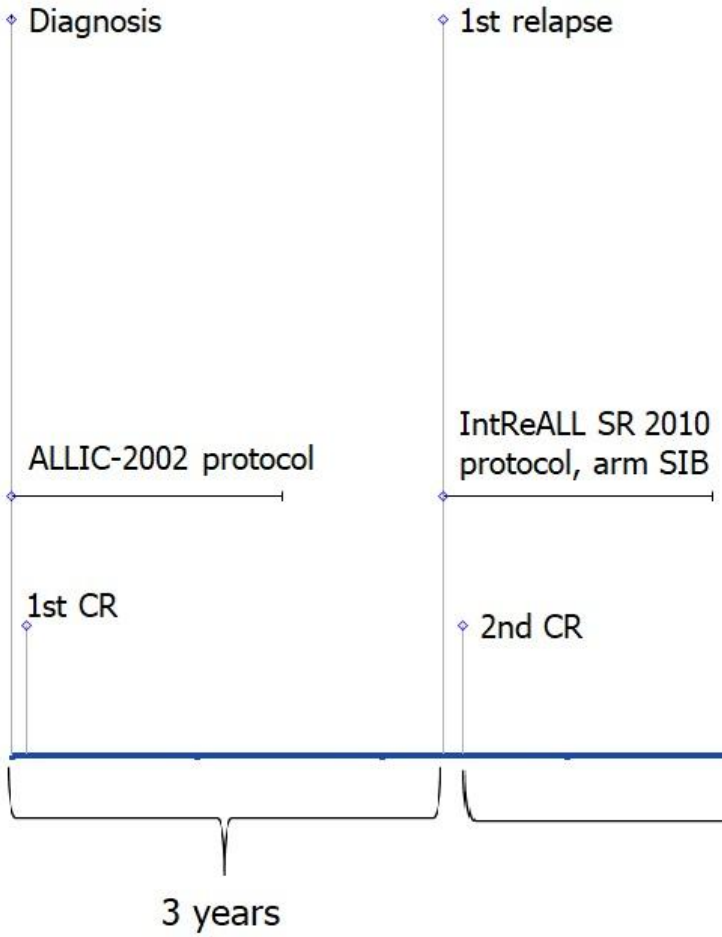


Initial Therapy (ALL-IC BFM 2002)

- Classified as **Intermediate-Risk (IR)**
- **Good steroid response**
- Achieved **cytological remission by Day 33**

Complications During treatment

- **Cytomegalovirus (CMV) infection**
- Managed with **ganciclovir**



Late Relapse (3 Years After Diagnosis)

- **Testicular relapse** with consistent BCP-ALL immunophenotype
- Treated with:
- **Orchidectomy**
- **IntReALL SR 2010 protocol**, Arm **SIB**
- Achieved **complete remission**

Complications During Remission (likely NBS-related)

- **Intestinal polyposis**
- **Severe hemorrhagic colitis**
- **Recurrent CMV infection**
- Treated with **valganciclovir**
- **Recurrent otitis media** (*Pseudomonas aeruginosa*)
- **Respiratory tract colonization** with *Pseudomonas aeruginosa*

Second Mixed Relapse (BM + CNS)

- Presented with **bone pain** and **fever**
- CBC: **49% blasts** in peripheral blood
- Bone marrow: **94% blasts** (BCP-ALL immunophenotype)
- CSF: **11% blasts → BM + CNS relapse**

Treatment

- **IntReALL HR 2010 protocol**, Arm **B**
- **Bortezomib** added
- Achieved **molecular and cytological remission**

Complications

- **Prolonged pancytopenia**
- **Aspergillus fungal infection**

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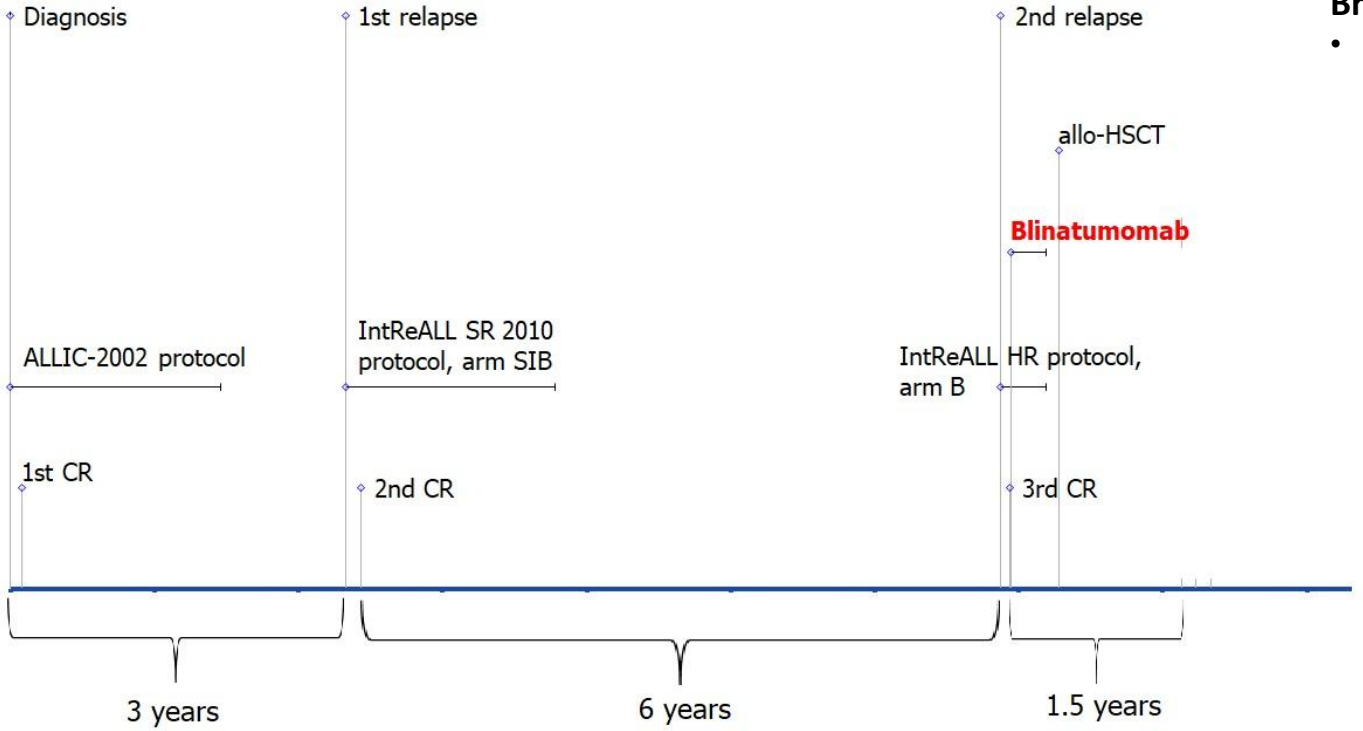
Bridging to HSCT

- No family donor



What bridging therapy would you give while awaiting an unrelated donor for HSCT?

A. No treatment — observation only
B. High-dose methotrexate
C. Re-induction chemotherapy (IntReALL HR re-induction)
D. Blinatumomab
E. Intrathecal chemotherapy alone

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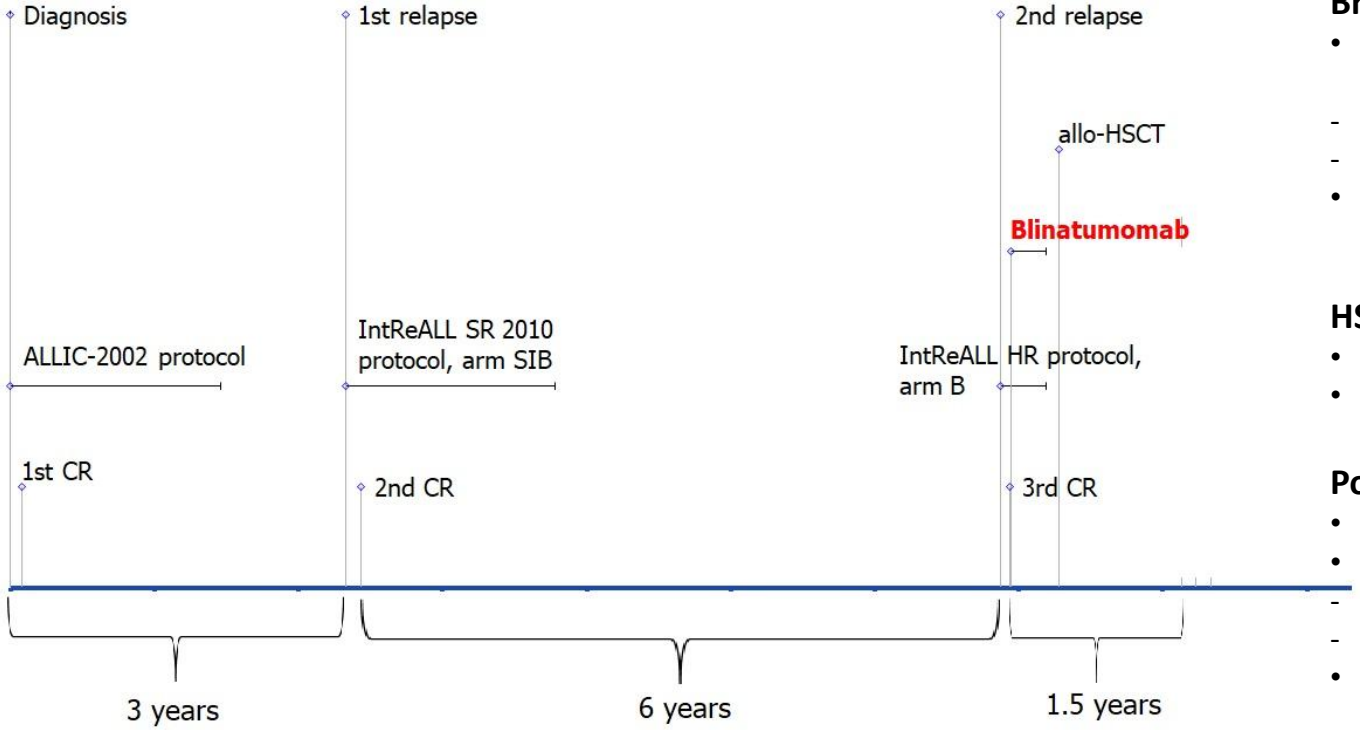


Bridging to HSCT

- No family donor → **3 cycles of blinatumomab**
  - Well-tolerated
  - Used to deepen remission
- Proceeded to **allogeneic HSCT** from **HLA-matched unrelated donor**

HSCT Details

- **Conditioning (modified GEFA03)**
- **GvHD Prophylaxis**

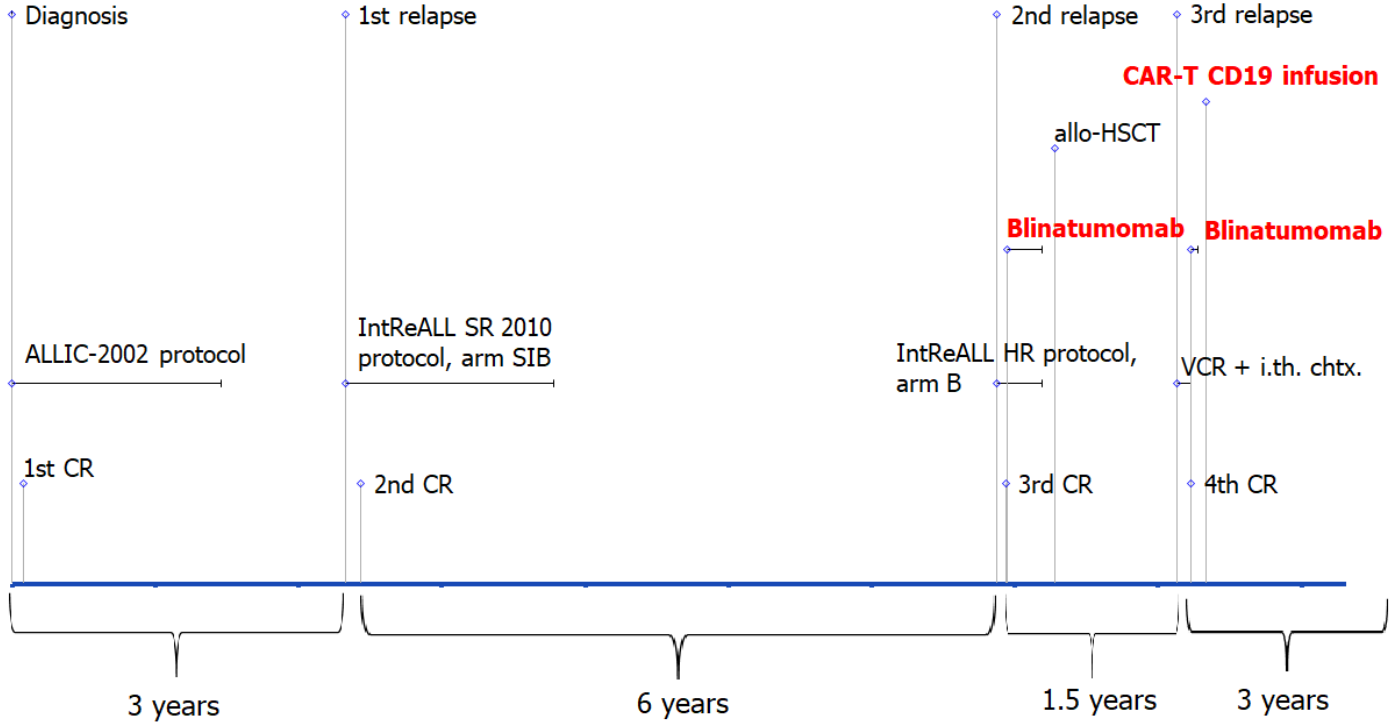
Post-Transplant Complications

- **Hemolytic anemia**
- **Opportunistic infections**
  - CMV reactivation
  - Adenovirus reactivation
- **Acute skin GvHD, Stage 3**

Third Isolated Relapse (Post-HSCT)

- Rising **autologous chimerism (17%)**
- **1 year post-HSCT**: evaluation for bone pain → **blasts in CBC**
- Bone marrow: **BCP-ALL relapse**
- **Phenotypic change** vs. initial disease:

- Loss of CD20 expression



What next-line therapy would you give to this patient with isolated post-HSCT relapse?

A. Donor lymphocyte infusion (DLI)
B. High-intensity re-induction chemotherapy
C. Blinatumomab prior to CAR-T CD19
D. Rituximab monotherapy
E. Proceed to a second HSCT

Third Isolated Relapse (Post-HSCT)

- Rising **autologous chimerism (17%)**
- **1 year post-HSCT**: evaluation for bone pain → **blasts in CBC**
- Bone marrow: **BCP-ALL relapse**
- **Phenotypic change** vs. initial disease:

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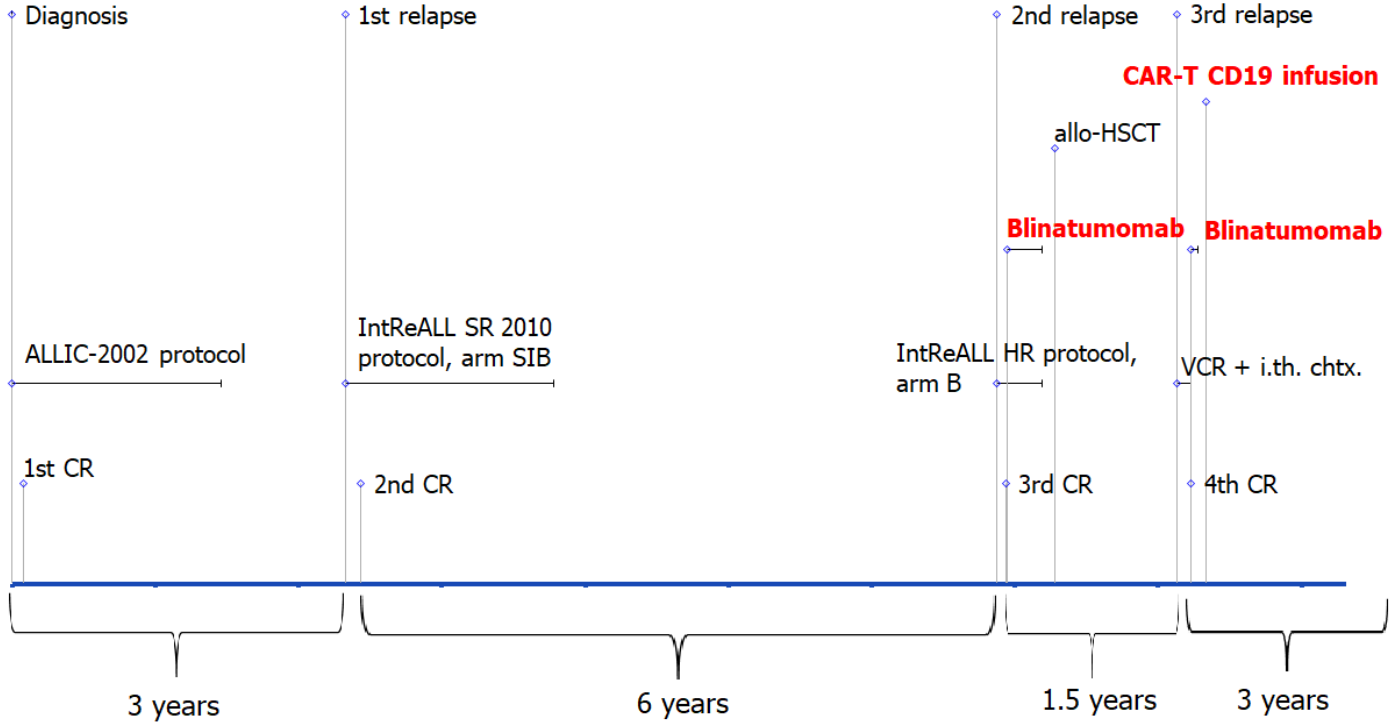
Bridging Therapy Before CAR-T

- Vincristine (VCR), Intrathecal therapy
- **1 cycle blinatumomab →**

- **Hematological remission**
- **PCR-MRD negative**



CAR-T CD19 Therapy

- Lymphodepletion: **cyclophosphamide + fludarabine**

Early Post-Infusion Course

- **CRS Grade 1** (fever, edema)
- **Complications:**

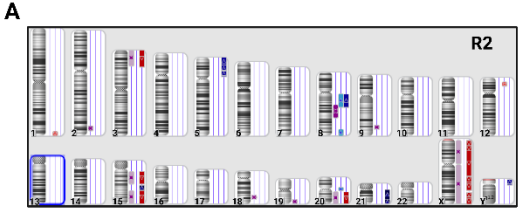
- *Clostridium difficile* infection
- **BK virus** reactivation

Outcome

- **CAR-T cells detectable in BM for up to 2 years**
- **3 years post-CAR-T:**

- **Complete remission**
- **PCR-MRD negative (10^{-5} sensitivity)**

Genetic profile



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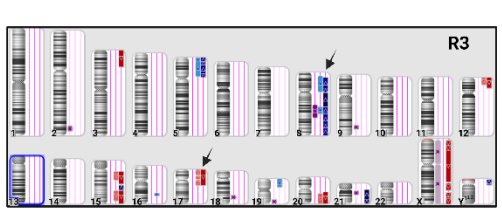

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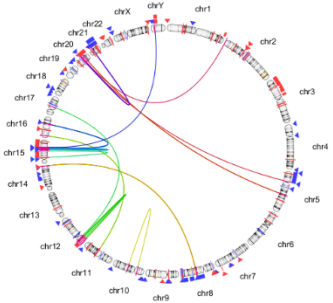

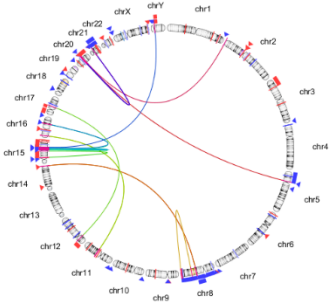

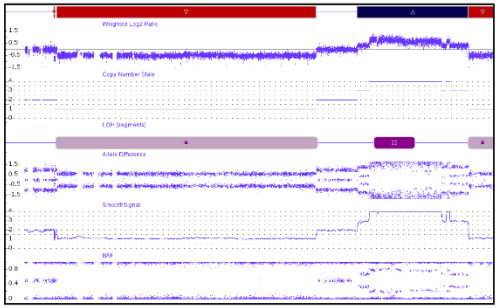

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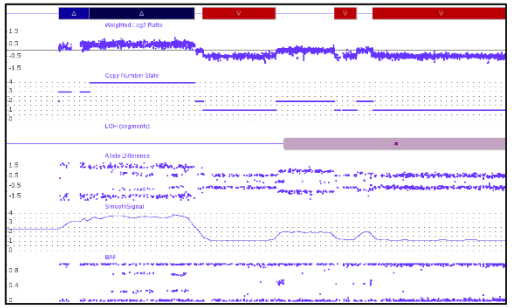


20q11.21q11.23(29421118_35534860) cth

Genetic analysis of relapses R2 and R3: RNA-seq, SNP array, optical genome mapping

- **Structural aberrations >5 Mbp** and **evidence of chromothripsis**:

- 15q12–q23
- 20q11.21–q11.23

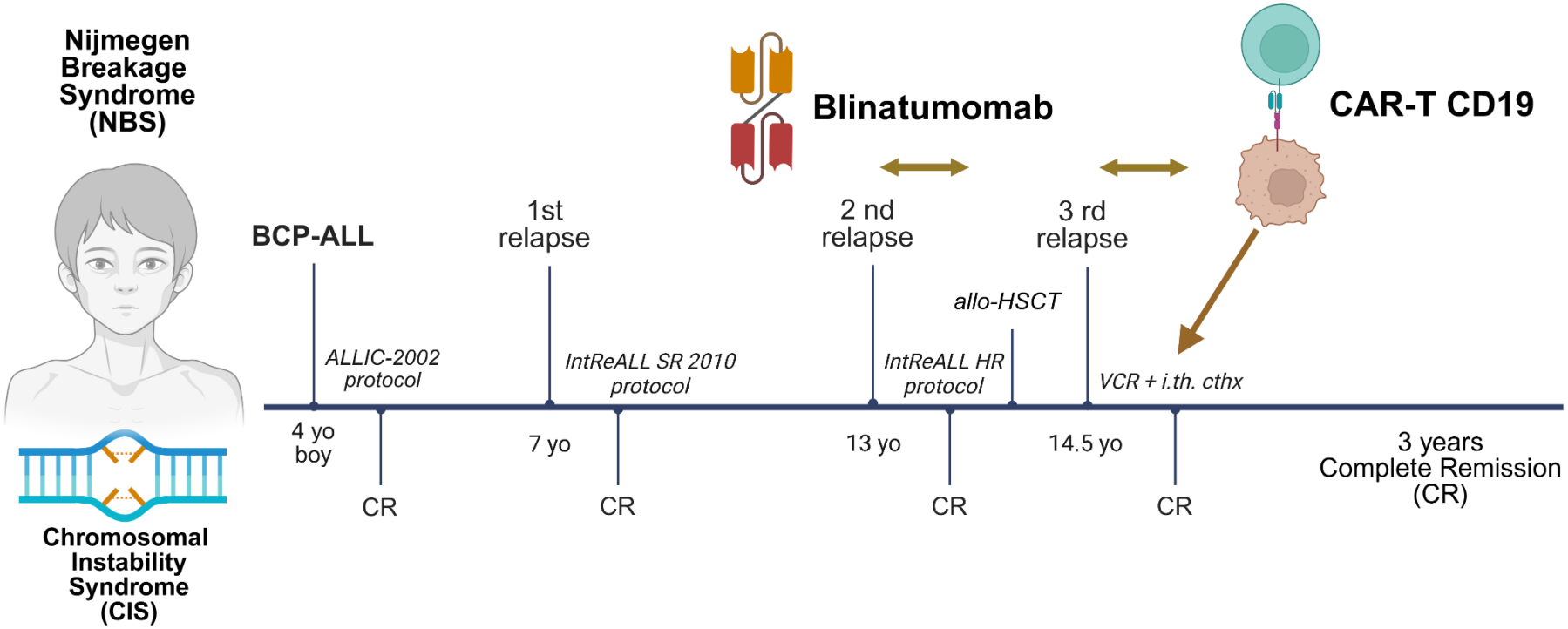
→ indicates **high genomic instability**, characteristic of aggressive, relapsed B-ALL in NBS

- **Gene fusions**: *IL7::IGH, NOX5::SMAD6, CBFA2T2*

- **Clonal evolution from R2 → R3**:

- 17p deletion involving **TP53**
- 8p and 8q deletions

Oszer et al., *British Journal of Haematology*, 2025



Oszer et al., *British Journal of Haematology*, 2025

Results of literature search for clinical reports utilizing immunotherapy to treat B-cell lymphoid malignancies among patients with chromosomal instability syndrome (CIS).

Age at lymphoid diagnosis, years	Sex	Chromosomal instability syndrome (CIS)	Gene mutated	Type of immunotherapy	Type of lymphoid malignancy	Outcome	References
7	F	Ataxia telangiectasia	ATM	Rituximab	LBCL	7 months in remission	Czarny et al.[8]
15	F	Ataxia telangiectasia	ATM	Rituximab	DLBCL	18 months in remission	Kropshofer et al.[9]
17	F	Ataxia telangiectasia	ATM	Rituximab	DLBCL	2 years in remission	Rossi et al.[10]
3.5	M	Ataxia telangiectasia	ATM	Rituximab	LBCL	4 years in remission	Shabbat et al.[11]
11	M	Bloom syndrome	BLM	Rituximab	Mature B-cell lymphoma	After 4 years remission, develop second malignancy, acute myeloid leukemia	Jastaniah et al.[12]
17	M	Nijmegen breakage syndrome	NBN	Rituximab	DLBCL	3 years in remission	Dumic et al.[13]

Oszer et al., *British Journal of Haematology*, 2025

Question 1

- How should anti-CD19 therapies be incorporated into treatment strategies for patients with chromosomal instability syndromes, given their limited tolerance for standard-intensity chemotherapy?

Question 2

- Does the presence of donor-derived immune reconstitution after allo-HSCT influence the safety or effectiveness of subsequent CAR-T CD19 therapy in patients with primary immunodeficiencies such as NBS?

Question 3

- What is the impact of chromothripsis and ongoing clonal evolution (e.g., acquisition of TP53 loss) on treatment decisions and timing of immunotherapy in NBS-associated leukemias?

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DISCUSSION

Funded by the European Union's Health Programme

Take home messages

Anti-CD19 immunotherapies (blinatumomab and CAR-T) can achieve deep molecular remission in NBS patients with multiply relapsed BCP-ALL, despite underlying immunodeficiency and genomic instability.

Reduced-intensity regimens and high infectious toxicity often limit standard approaches in CIS patients, making targeted immunotherapies an important therapeutic option.

Long-term remission after CAR-T therapy demonstrates that sustained CAR-T persistence and disease control can be achieve after allo-HSCT in the context of NBS-related immune dysfunction.