European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

15.11.2023

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The unknown diagnostic tool of MRD in pediatric AML

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Funded by the European Union's EU4Health Programme

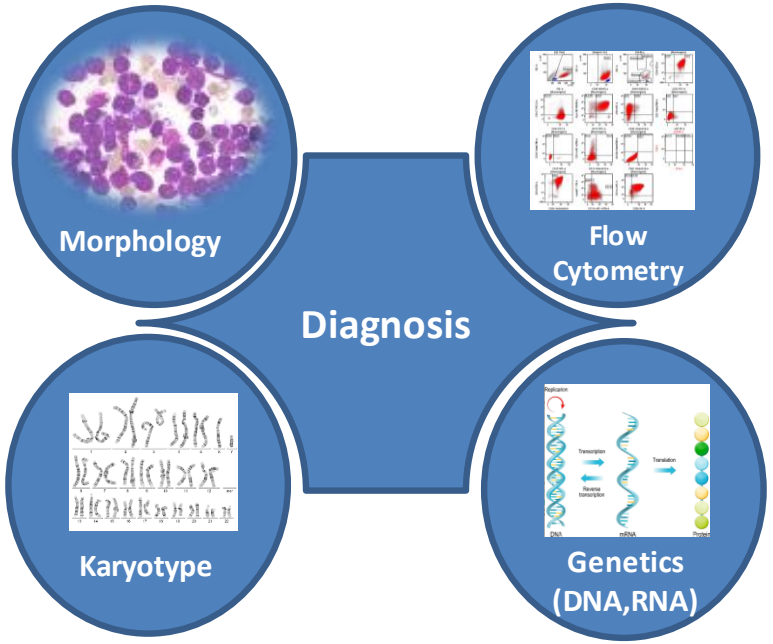
COI declaration

- No conflincts

Case -previous history

- 15 y.o. male
- First diagnosis: June 2021
  de novo AML M5, CNS positive
  - genetics: t(11;19), normal karyotype

- No other comorbidities
- Family history: negative



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Standard-risk group	
Definition	All patients with the following evidence: • Inv(16)(p13.1q22) • t(16;16)(p13;q22) • t(8;21)(q22;q22) • t(1;11) (q21;q23) • *Normal karyotype and NPM1-mutation* • *Normal karyotype and CEBPA* (double mutation)

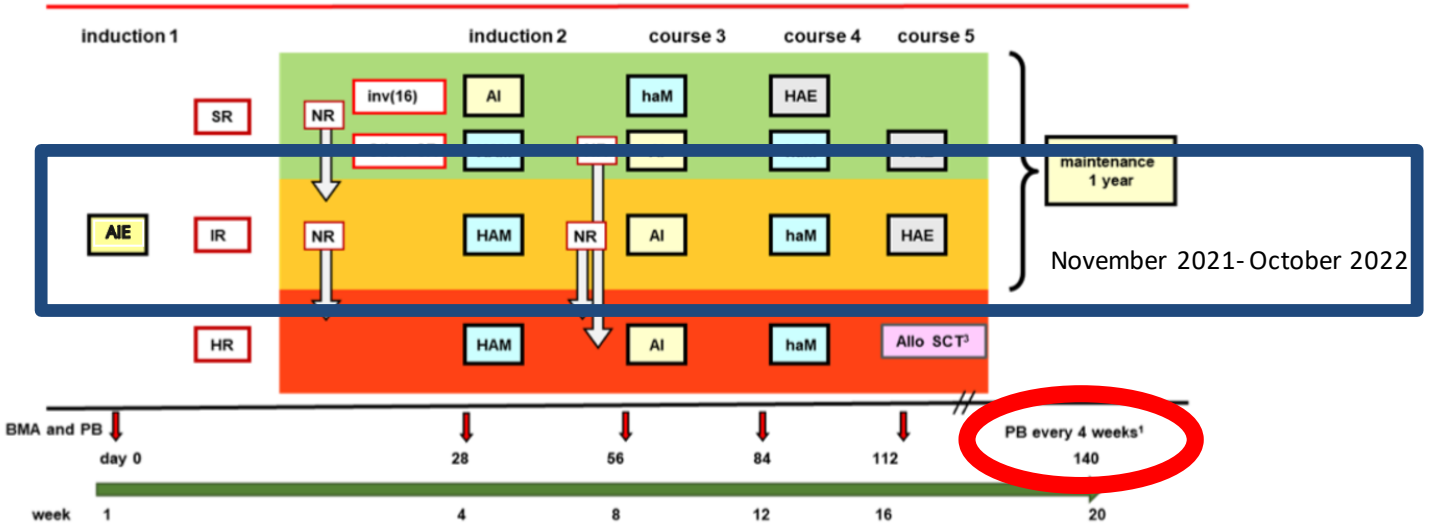
Intermediate-risk group	
Definition	All patients with de-novo AML, who do not belong to the standard-risk group (favorable prognosis) or to the high-risk group (unfavorable prognosis).

High-risk group	
Definition	All patients with the following genetic evidence: • abnormalities in chromosome 12p/ t(2;12) • monosomy 5/5q- • WT1mut and FLT3-ITD • monosomy 7 (not in combination with favorable/MLL- aberrations) • t(4;11)(q21;q23); MLL/AF4 • t(5;11)(q35.3;p15); NUP98/NSD1 • t(6;11)(q27;q23)); MLL/AF6 • t(10;11)(p12;q23); MLL/AF10 • t(6;9)(p23;q34) • t(7;12)(q36;p13) • t(9;22)(q34;q11) • complex karyotype (three or more aberrations, including at least one structural aberration, without favorable genetics and without MLL-rearrangement.) • inv(3)(q21q26.2)/t(3;3)(q21;q26.2) • t(16;21)(p11;q22); FUS/ERG • Inv(16)(p13.3q24.3) CBFA2T3-GLIS2

Case-therapy

- Therapy: June 2021-April 2022

  CNS positive ⟶ Cranial Irradiation 23.12.2021-06.01.2022



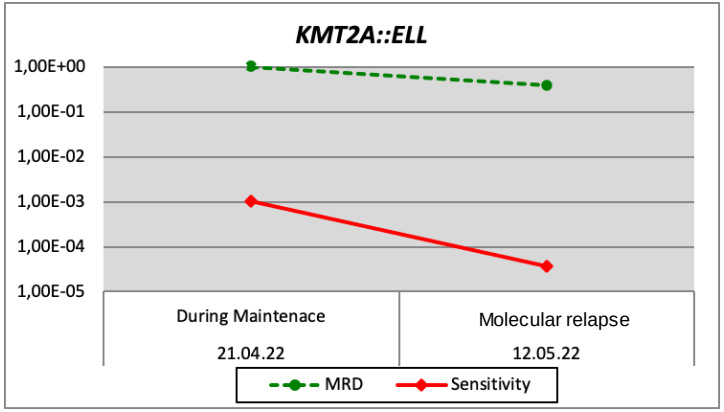
Question 1

Which methods are part of diagnosis of AML?

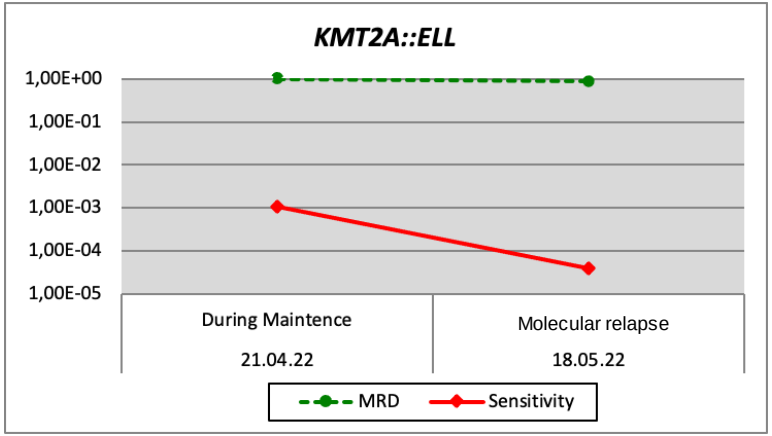
1. Morphology and Karyotype
2. Morphology, Genetics(RNA, NGS) and Karyotype
3. Morphology, Flow cytometry and Genetics (RNA,NGS) and Karyotype

Case - MRD marker

- Examination in our outpatient clinic in April 2022
- detection of t(11;19) (Fusion: KMT2A::ELL)



peripheral blood



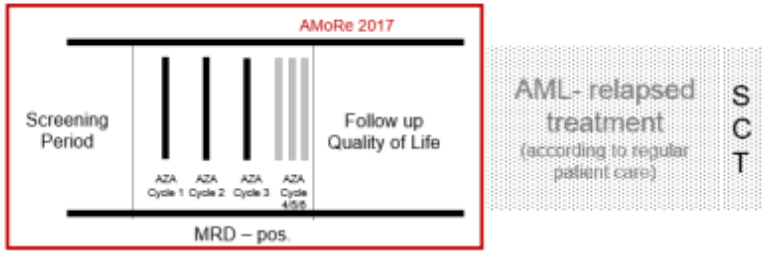
bone marrow

Case-Therapy

molecular relapse

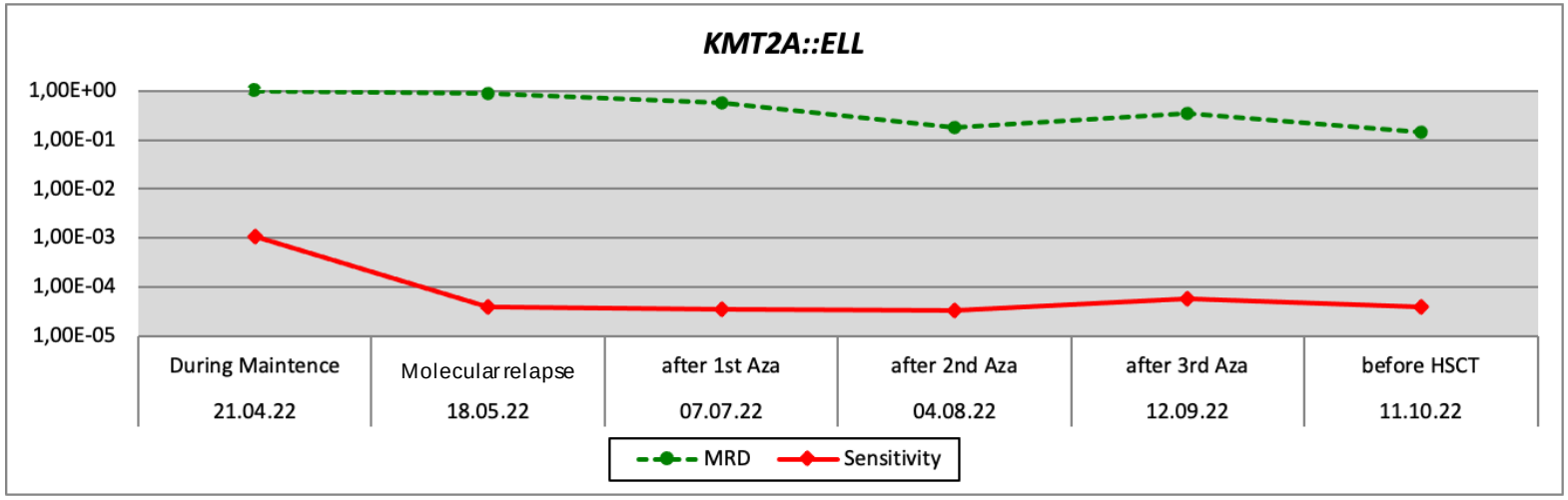
inclusion in AMoRe 2017

INTERNATIONAL MULTICENTER, OPEN-LABEL, PHASE 2 STUDY TO TREAT MOLECULAR RELAPSE OF PEDIATRIC ACUTE MYELOID LEUKEMIA WITH AZACITIDINE

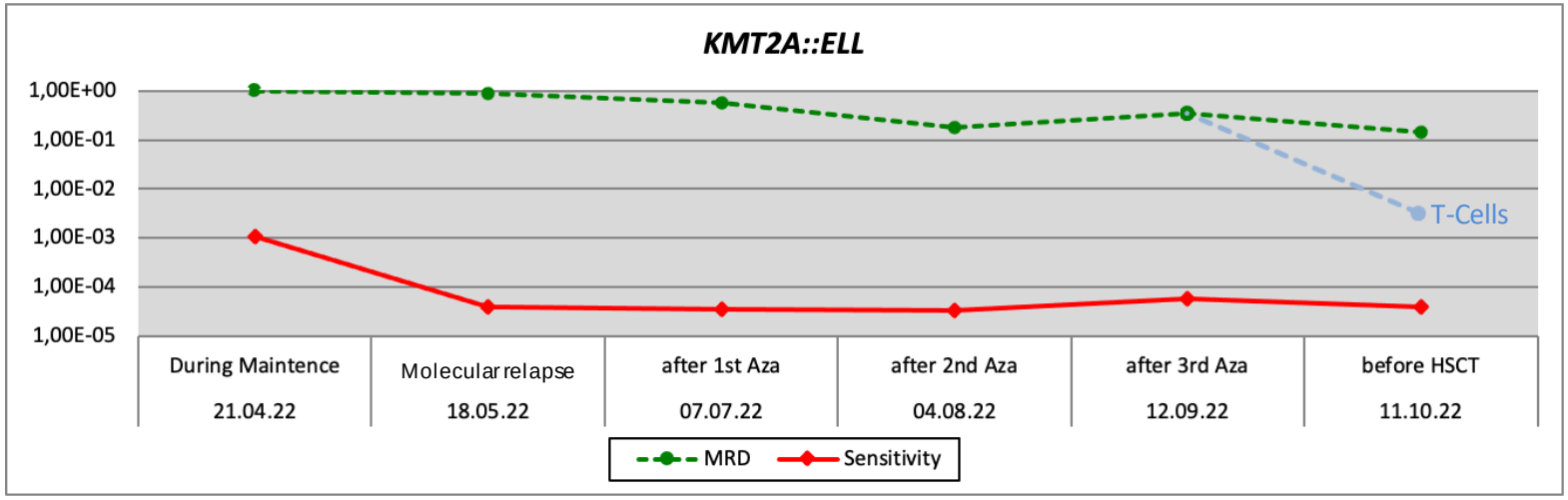


DNA-methylation inhibitor

Case-Therapy



Case-Therapy

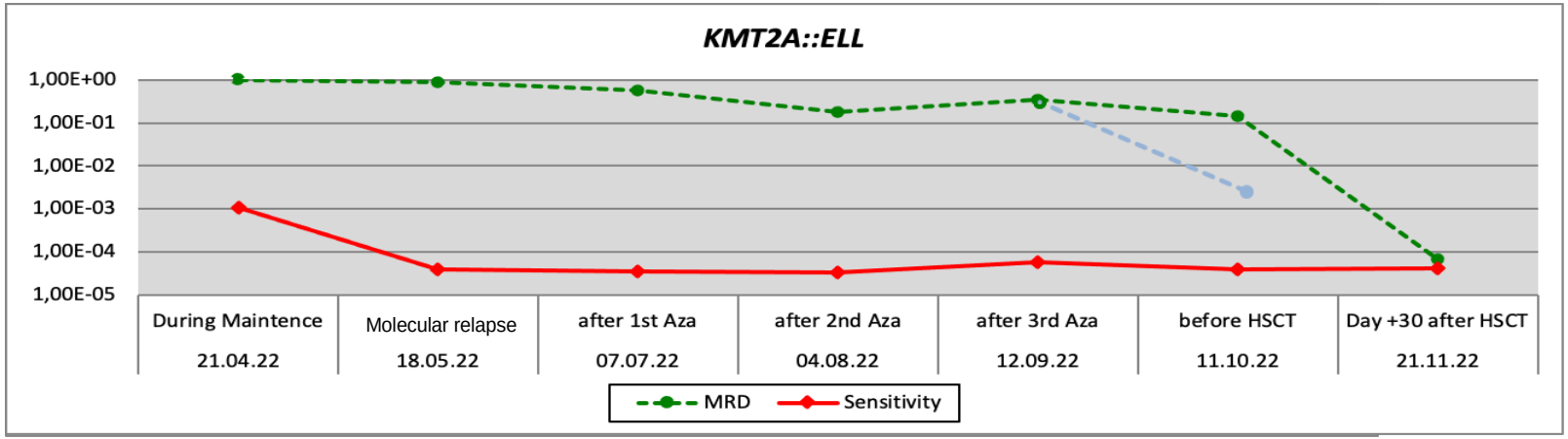


Question 2

How should be MRD evaluated?

1. MRD positivity is equal to relapse
2. Importance of MRD kinetics for diagnosis of relapse
3. MRD signals are detected only in leukemic blasts

Case-Therapy



HSCT, MUD

- **Conditioning:**
  Fludarabin,
  Treosulfan, Thiotepa
- **GvHD-Prophylaxis:**

ATG, CSA, MTX

Case report- HSCT complications

Day + 31:
Katheter Infection: Staphylococcus epidermidis (Tazobac resistant)
- Antibiotics change to Meropenem/Vancomycin

Day +36:
Fever, tachycardia
Pulmonary distress
Anurie -> Renalfailure
Multiorgan failure: renal and pulmonary failure

Toxoplasma gondii	PCR	**positiv**

Staphylococcus aureus	PCR	negativ
Streptococcus pneumoniae	PCR	negativ
Enterococcus faecium	PCR	negativ
Enterococcus faecalis	PCR	negativ
Escherichia coli	PCR	negativ
Klebsiella pneumoniae	PCR	negativ
Klebsiella oxytoca	PCR	negativ
Klebsiella aerogenes	PCR	negativ
E. cloacae Komplex	PCR	negativ
Serratia marcescens	PCR	negativ
Pseudomonas aeruginosa	PCR	negativ
Stenotrophomonas maltophilia	PCR	negativ
Candida albicans	PCR	negativ
Candida glabrata	PCR	negativ

Question 3

How to prevent transplant related mortality (TRM)?

1. Reduce toxicity by detection of molecular relapse and early intervention
2. Standartise screening for microbiology and virology in order to start with antibiotics/antiviral therapy early
3. Prompt antibiotics and antimycotic prophylaxis
4. Treatment by experienced intensive care staff
5. All of the above

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DISCUSSION

Co-funded by the European Union's Health Programme

Take home messages

- Different relapse kinetics of MRD
  - MRD persistence after therapy for CBF
  - rapid relapses in subgroups of MLL

- No standard therapy for molecular relapse yet defined but in order to avoid TRM at HSCT: **early diagnosis and lower intensity treatment**

  Avoid HSCT if not indicated! Consider the complications!

- Refine stratification and response assessment

- Optimisation of viral and microbiological screening/prophylaxis during HSCT

Literature

- Karlsson et al., Fusion transcript analysis reveals slower response kinetics than multiparameter flow cytometry in childhood acute myeloid leukaemia. Int J Lab Hematol. 2022
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- Sockel et al. Minimal residual disease-directed preemptive treatment with azacitidine in patients with NPM1-mutant acute myeloid leukemia and molecular relapse. Haematologica. 2011
- Viehmann et al. Monitoring of minimal residual disease (MRD) by real-time quantitative reverse transcription PCR (RQ-RT-PCR) in childhood acute myeloid leukemia with AML1/ETO rearrangement. Leukemia. 2003
- Maurer-Granofszky et al. Genomic breakpoint specific monitoring of measurable residual disease in pediatric non-standard risk acute myeloid leukemia. Haematologica. 2023