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

17.05.2023

Kerstin Rauwolf & Charlotte Niemeyer

Secondary malignancy after B-NHL

Moderation: Andishe Attarbaschi

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COI declaration

- CN: Employment / Leadership Position: none; Advisory Role: BMS, Novartis, Apriligen; Stock Ownership: none; Honoraria: BMS, Apriligen; Financing of Scientific Research: none; Expert Testimony: BMS, Apriligen; Other Financial Relationships: none

- KR: none

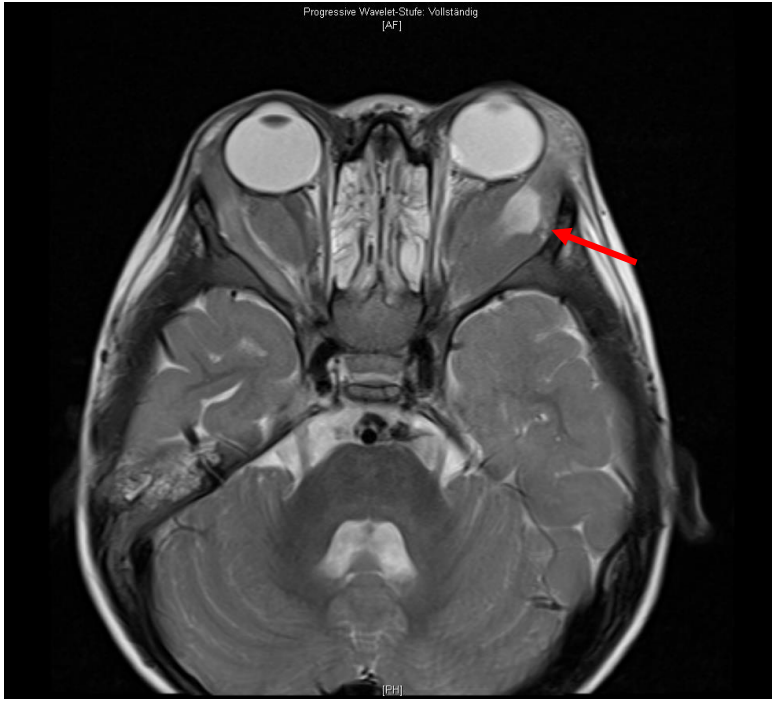
Medical history

- Boy, 2 years old, no underlying disease, development according to age
- Family history: cousin testicular carcinoma, aunt breast cancer

Medical history

- Strabismus of the left eye, injection of the conjunctiva, outpatient treatment for infection
- No improvement, increasing injection of the conjunctiva (in both eyes), proptosis of both eyes, presentation in hospital

Diagnostic

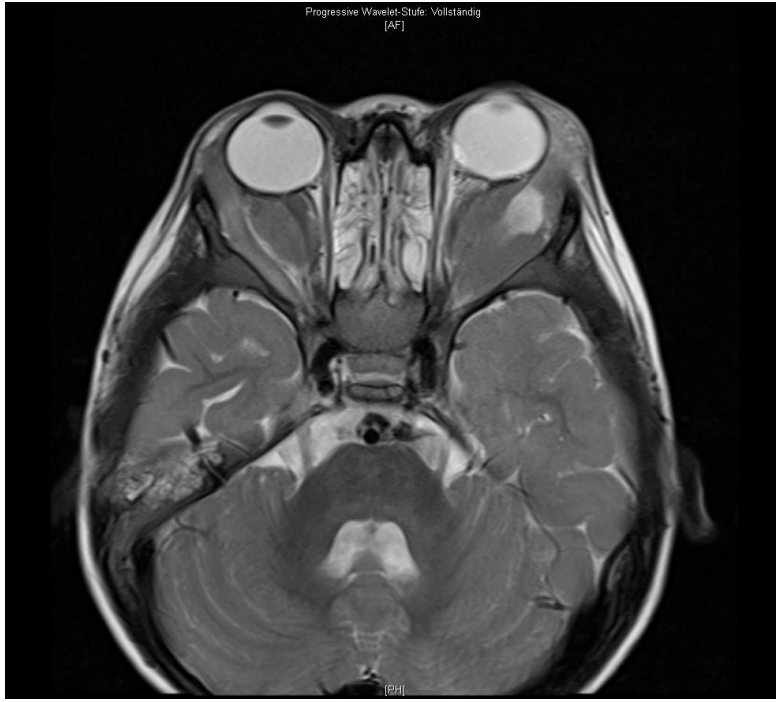


MRI, T1, with contrast media

Question 1

- What is your suspected diagnosis?
  a) Retinoblastoma
  b) Non-Hodgkin Lymphoma
  c) Lymphangioma
  d) Infection
  e) Opticusglioma

Diagnostic



MRI, T1, with contrast media

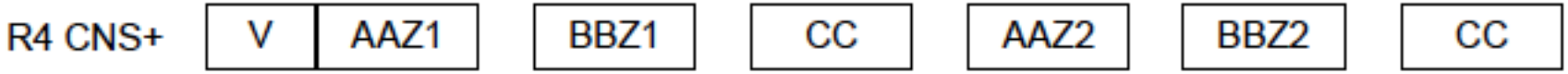
biopsy -> lymphoblastic B-cell NHL, CD79a +, partial CD20 +, but c-Myc translocation
CNS positiv, no BM-involvement

Risk stratification

risk group	resection status	stage and initial serum LDH level
R1	complete	
R2	incomplete	stage I + II stage III and LDH < 500 U/L
R3	incomplete	stage III and LDH ≥ 500 U/L but < 1.000 U/L stage IV/B-AL and LDH < 1.000 U/L and CNS negative
R4	incomplete	stage III and LDH ≥ 1.000 U/L stage IV/B-AL and LDH ≥ 1.000 U/L and CNS negative
R4 CNS+	incomplete	stage IV/B-AL and CNS positive

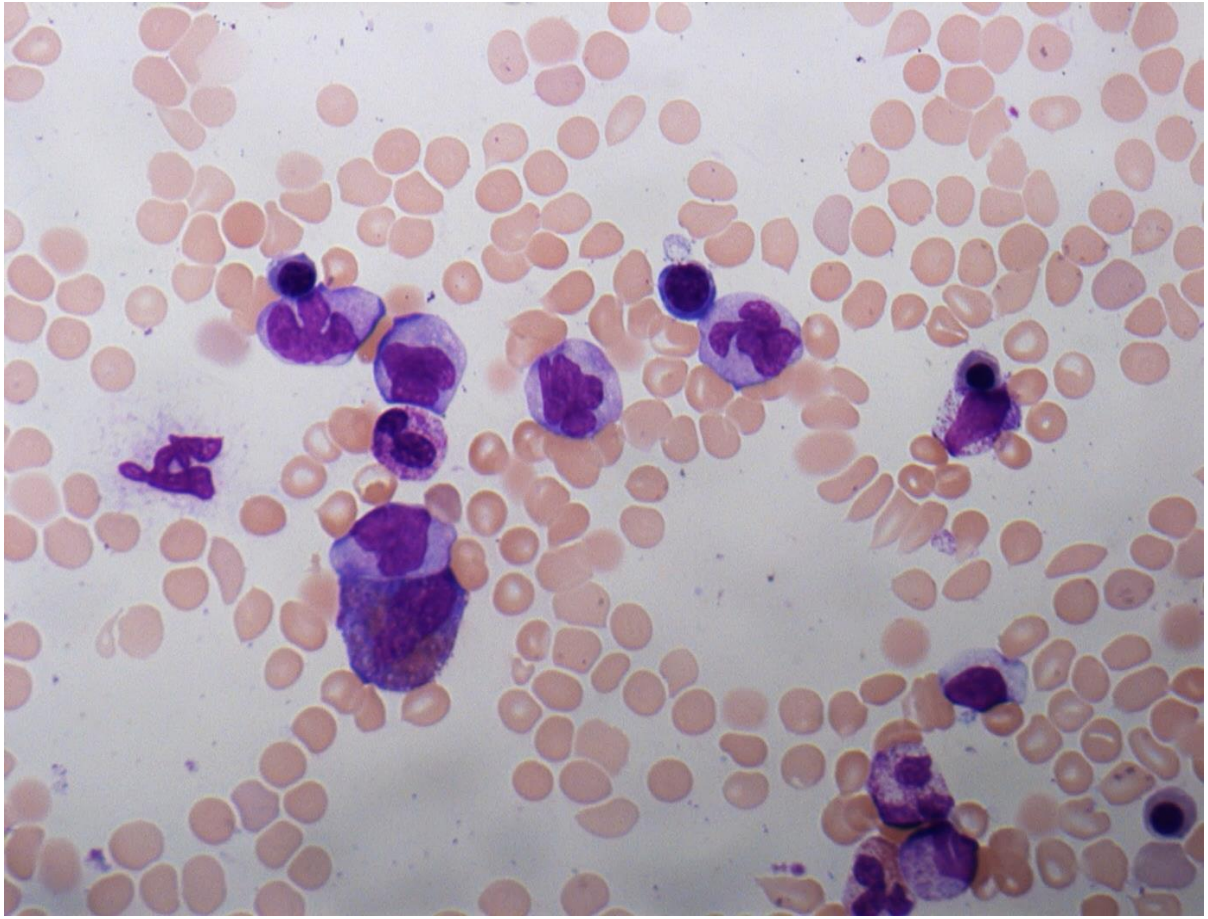
Treatment

- Treatment according to consensus of NHL expert panel, registered in the NHL-BFM Registry 2012



Treatment

- severe complications:
  - line infection, sepsis with S. pneumoniae
  - line infection, sepsis with Staph. haemolyticus and coronavirus SARS-CoV-2 in respiratory secretion
  - secondary ARDS with septic cardiomyopathy -> ECMO (in total 4d)
  - relapsing pleural effusions
- during maintenance treatment -> prolonged recovery of the blood count, monocytosis

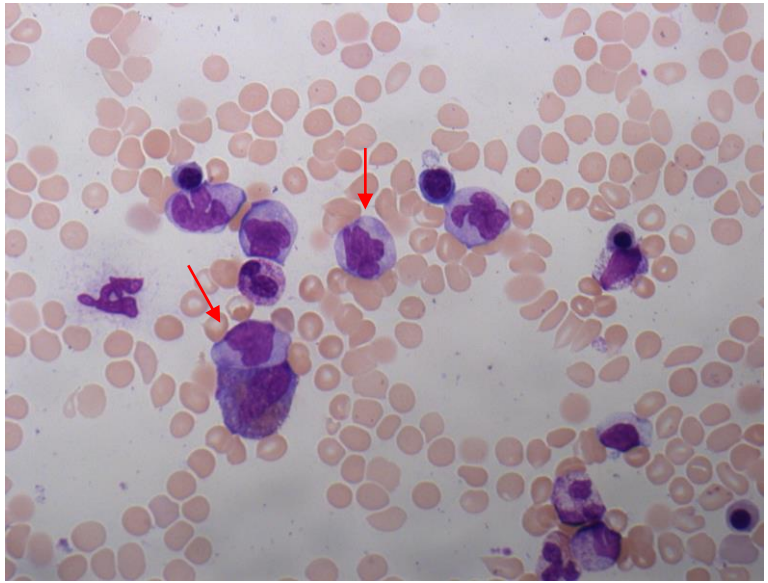


HE stain of smear from bone marrow aspirate

Question 2

- How would you proceed?
  a) Bone marrow examination (aspirate, biopsy)
  b) Watch and wait
  c) HSCT
  d) Chemotherapy

Bone marrow aspirate



Bone marrow biopsy:
Megakaryopoesis absent, hypoplasia and leftshift of erythropoesis and granulopoesis
approx. 10% CD34 – blasts
mild bone marrow fibrosis
-> MDS with excess blasts, therapy-related

Therapy-related MDS

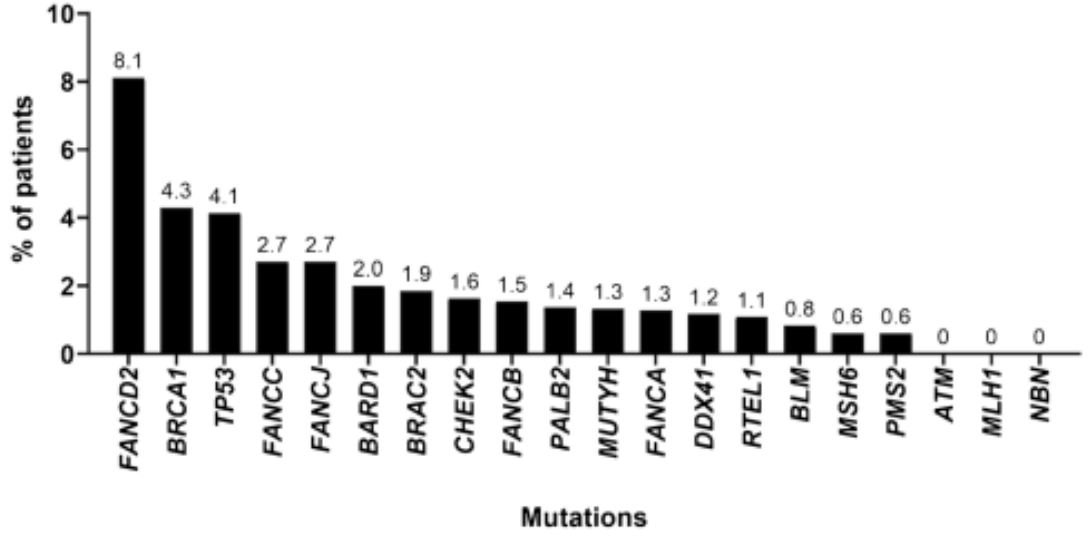
- Normal karyotype, FISH: no -7, del(7q) or +8; NGS: no *TP53* mutation or any other oncogenic mutation.

  (later performed on research basis WES: *KRAS* mutation c.351A>T, p.Lys117Asn)
- HSCT, myeloablative conditioning regime with thiotepa, treosulfan, fludarabine, ATG (according to expert consensus from EWOG-MDS)
- HSCT without severe complications, engraftment on day +30
- currently in good general condition (over 2 years after HSCT)

Question 3

- Whould you send the family to a human geneticist?
  a) Yes
  b) No

Current estimate of the relative contribution of the most commonly observed pathogenic germline variants in therapy-related myeloid neoplasms (t-MNs) - adult and pediatric -



Baranwal et al. Curr Hematol Malig Rep. 2022.

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DISCUSSION

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ARTICLE

Ferrata Storti Foundation

Haematologica 2021
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Second malignancies after treatment of childhood non-Hodgkin lymphoma – a report of the Berlin-Frankfurt-Muenster study group

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Table 3. Characteristics and outcome of patients with second malignant neoplasms after non-Hodgkin lymphoma in children.

		Second malignant neoplasm			Primary NHL				
No. of pts	Sex M/F	SMN type [no. of patients]	Latency years median (range)	Outcome: alive/death/3rd malignancy/LFU	Type of NHL [no. of patients]	Age at Dx years median (range)	Stage of disease I/II/III/IV	Therapy type ALL/B-NHL	Radio-therapy Yes/no/ unknown
21	12/9	MDS and AML MDS-AML del(5),del(7) and/or complex karyotype [6] AML t(11q23) [4] AML normal karyotype [5] AML other [3] AML no cytogenetics [3]	3.1 (0.3 – 8.7)	5/14/1/2	T-LBL [9] pB-LBL [5] BL/B-AL [5] B-NHL [1] NHL nfc [1]	3.4 (0.7-14.6)	1/0/8/12	15/6	4/15/2

ARTICLE

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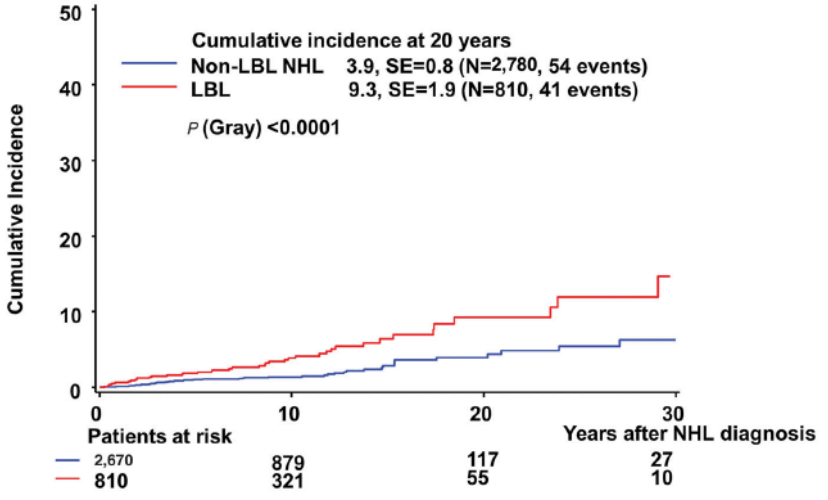
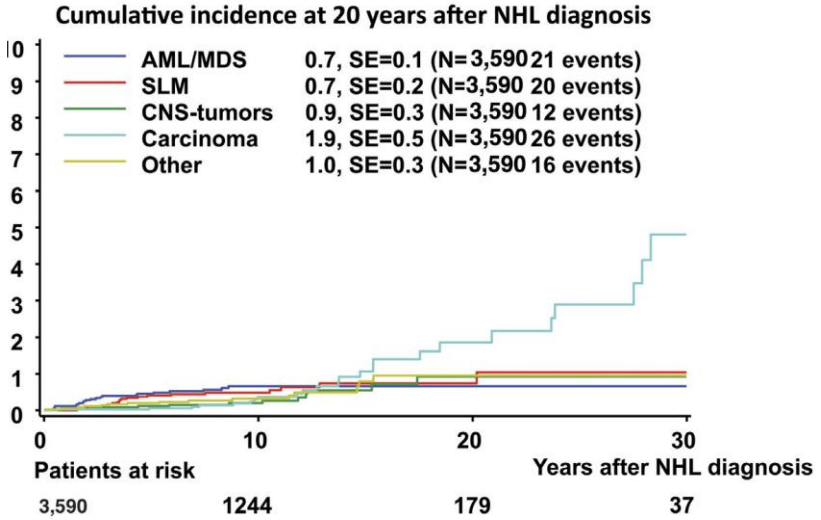
Non-Hodgkin Lymphoma

Ferrata Storti Foundation

Second malignancies after treatment of childhood non-Hodgkin lymphoma – a report of the Berlin-Frankfurt-Muenster study group





Retrospective analysis of therapy-related MDS

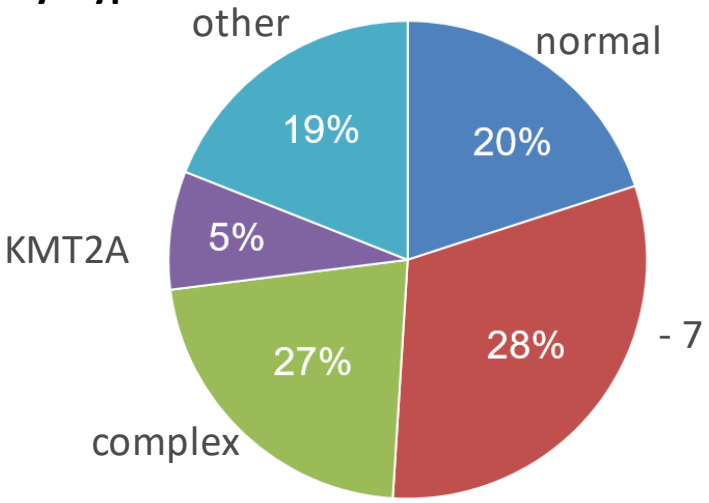
EWOG-MDS

N=145

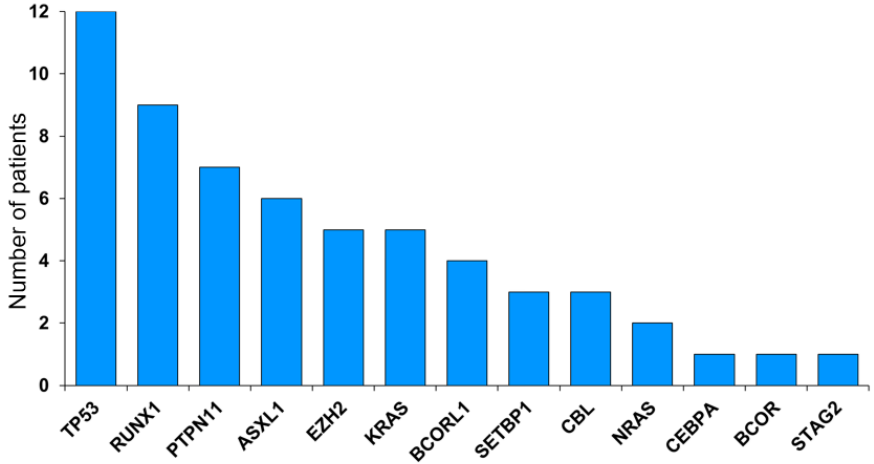
First malignancy:

hematological N=74
solid tumor N=48
brain tumor N=13

Karyotype



Mutations



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Landscape of somatic mutations in therapy-related MDS

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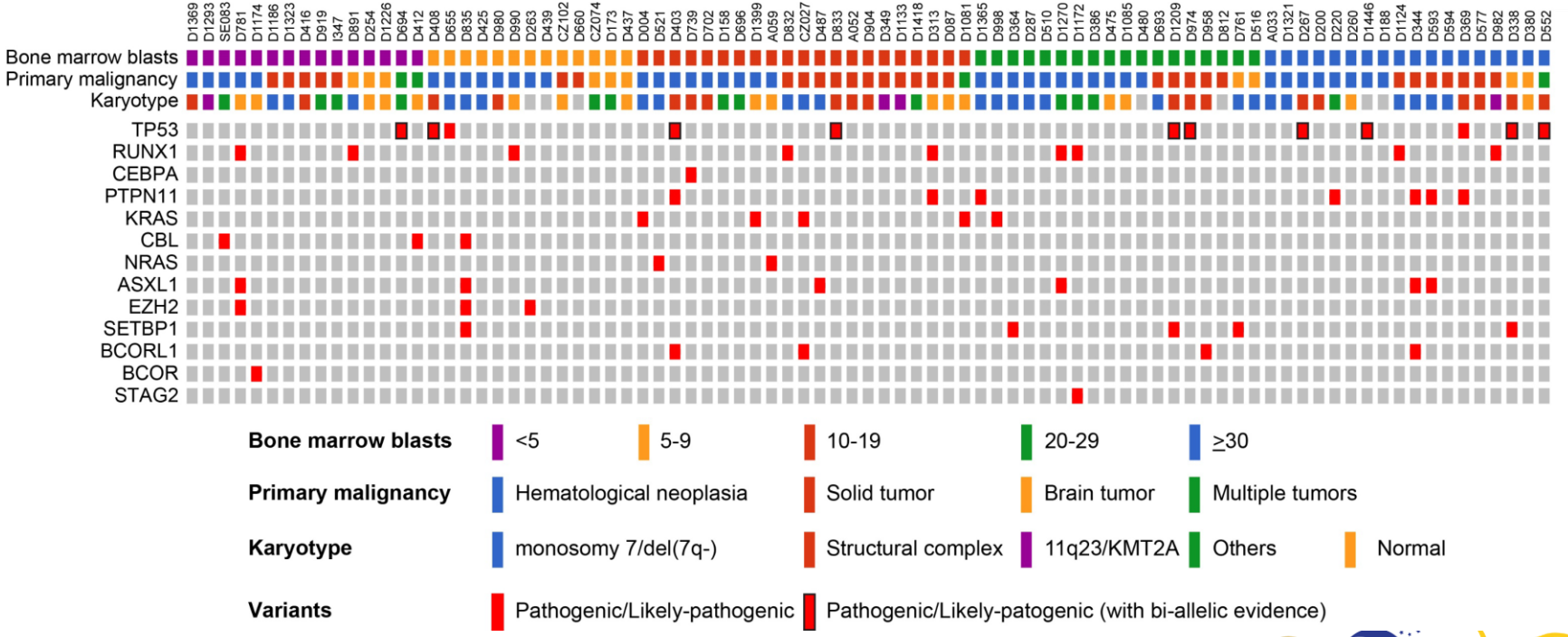
EWOG-MDS



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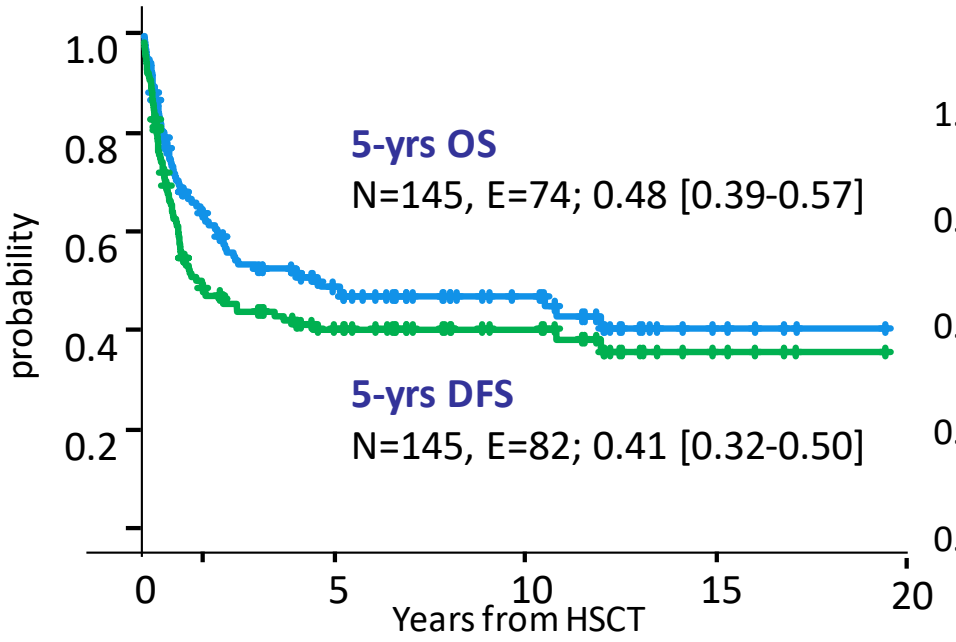
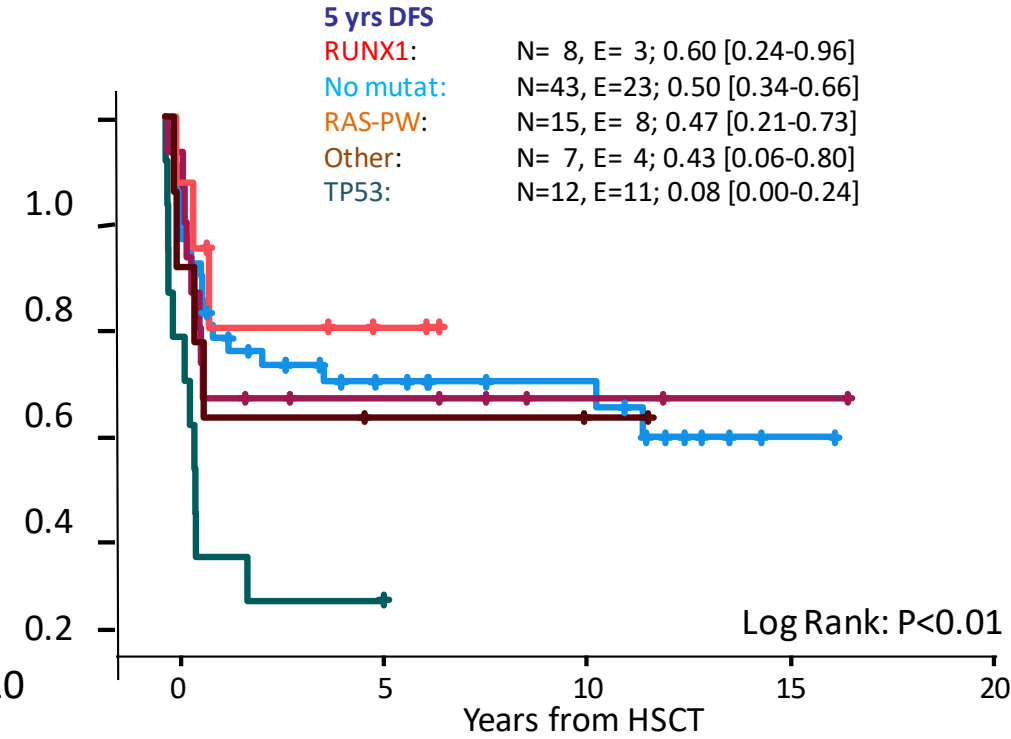
EBMT Kornemann et al. ePoster 49th Annual Meeting, 23-26 April 2023, Paris

Retrospective analysis on therapy-related MDS

EWOG-MDS





Take home messages

- be aware of secondary malignancies after childhood cancer treatment
  - Early: therapy-related MDS, leukemia
  - Late: brain tumors, solid tumors
- initiate work-up for an underlying tumor predisposition syndrome

Literature

- Rudelius M, Weinberg OK, Niemeyer CM, Shimamura A, Calvo KR. The International Consensus Classification (ICC) of hematologic neoplasms with germline predisposition, pediatric myelodysplastic syndrome, and juvenile myelomonocytic leukemia. Virchows Arch. 2023 Jan;482(1):113-130. doi: 10.1007/s00428-022-03447-9.
- Moser O, Zimmermann M, Meyer U, Klapper W, Oschlies I, Schrappe M, Attarbaschi A, Mann G, Niggli F, Spix C, Kontny U, Klingebiel T, Reiter A, Burkhardt B, Woessmann W. Second malignancies after treatment of childhood non-Hodgkin lymphoma: a report of the Berlin-Frankfurt-Muenster study group. Haematologica. 2021 May 1;106(5):1390-1400. doi: 10.3324/haematol.2019.244780.