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Strategies to minimize the occurrence of t-MN: the paradigm of childhood ALL

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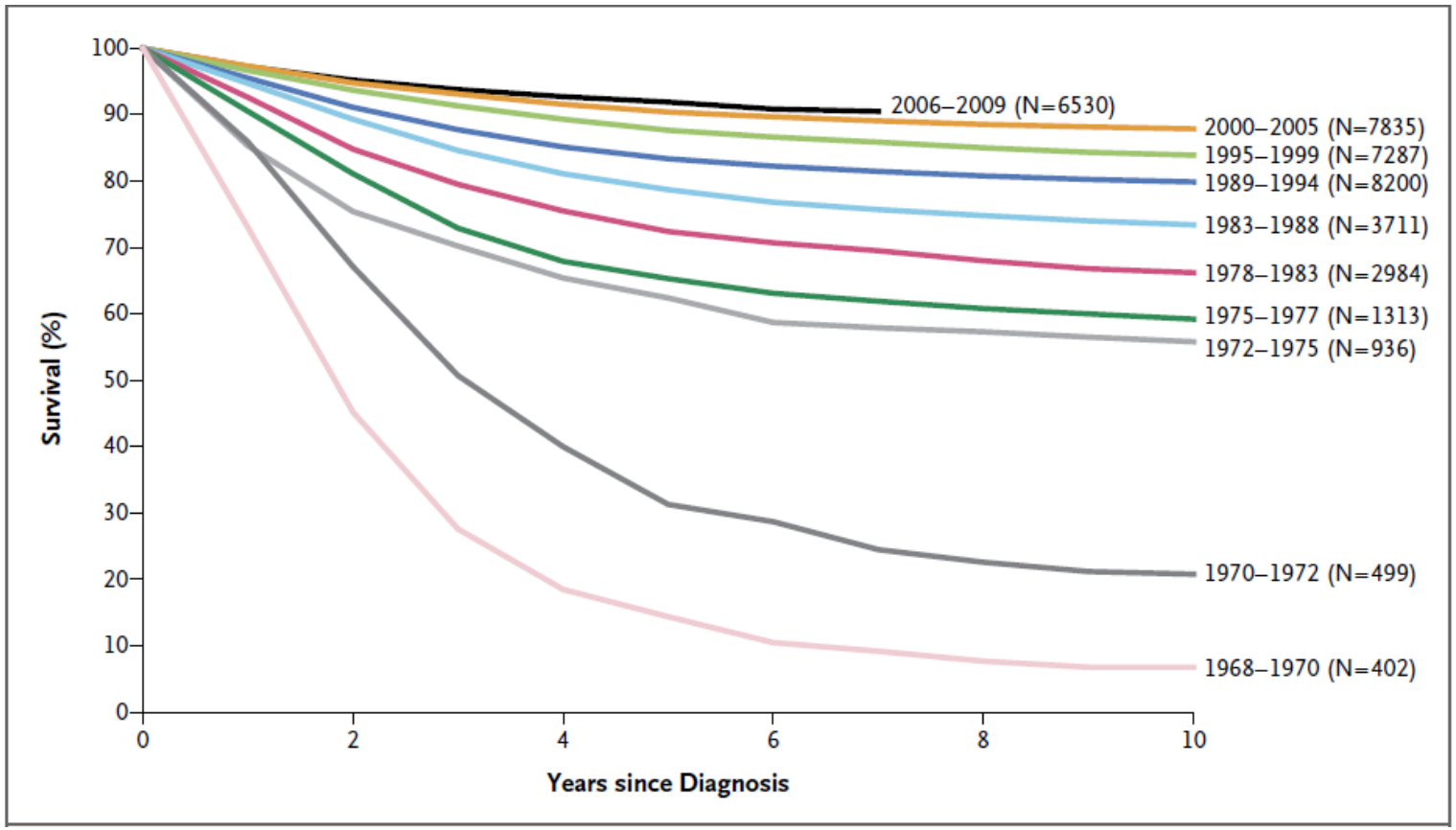
Contents

- ✓ ALL in childhood ad adolescents : the context and the current challenges;
- ✓ t-MN in the context of the Italian experience;
- ✓ The results of the “Ponte di Legno” consortium;
- ✓ Could we further reduce the risk of t-MN?

  “Be less hard and more smart”

Overall survival among children with ALL (1968-2009)



CCG and COG Clinical Trials - Hunger SP and Mullighan CG N Engl J Med 2015;373: 1541-52

Outcome of contemporary trials involving children and adolescents with ALL

Research Group	Trial	Reference	Region	Years	Subgroup	No. of Patients	Event-free Survival††	Overall Survival††
							percent	
COG	Many trials	Hunger et al.[37]	United States, Canada, Australia, New Zealand	2000–2005	All patients B-cell ALL T-cell ALL	6994 5845 457	N/A N/A N/A	91.3 92.0 81.5
SJCRH	Total Therapy Study XV	Pui et al.[56]	United States	2000–2007	All patients B-cell ALL T-cell ALL	498 422 76	85.6 86.9 78.4	93.5 94.6 87.6
DFCI	DFCI ALL Consortium Protocol 00–01	Vrooman et al.[57]	United States, Canada	2000–2004	All patients B-cell ALL T-cell ALL	492 443 49	80.0 82.0 69.0	91.0 N/A N/A
AIEOP-BFM	AIEOP-BFM ALL 2000	Conter et al.,[49] Schrappe et al.[50]	Western Europe	2000–2006	All patients B-cell ALL T-cell ALL	4480 4016 464	80.3 80.4 75.9	91.1 91.8 80.7
MRC-NCRI	UKALL 2003	Vora et al.[58]	United Kingdom	2003–2011	All patients B-cell ALL T-cell ALL	3126 2731 388	87.2 N/A N/A	91.5 N/A N/A
DCOG	DCOG Protocol ALL-9	Veerman et al.[59]	The Netherlands	1997–2004	All patients B-cell ALL T-cell ALL	859 701 90	81 82 72	86 N/A N/A
EORTC CLG	EORTC CLG 58591	Domenech et al.[60]	Belgium, France	1998–2008	All patients	1940	82.6	89.7
NOPHO	ALL-2000	Schmiegelow et al.[61]	Denmark, Finland, Iceland, Norway, Sweden	2000–2007	All patients B-cell ALL T-cell ALL	1023 906 115	79 81 64	89 91 72

* Infants younger than 1 year of age were excluded from these studies when possible. AIEOP denotes Italian Association of Pediatric Hematology and Oncology, BFM Berlin–Frankfurt–Münster, DCOG Dutch Childhood Oncology Group, DFCI Dana–Farber Cancer Institute, EORTC CLG European Organization for Research and Treatment of Cancer–Children's Leukemia Group, MRC-NCRI Medical Research Council–National Cancer Research Institute, N/A not available, NOPHO Nordic Society of Paediatric Haematology and Oncology, SJCRH St. Jude Children's Research Hospital, and UKALL Medical Research Council Working Party on Leukaemia in Children UK National Acute Lymphoblastic Leukaemia Trial.
† Survival percentages shown are the rates at 5 years except for the rates for the AIEOP-BFM trial, which were reported at 7 years.

Hunger SP and Mullighan CG N Engl J Med 2015;373: 1541-52

How many childhood cancer survivors are in Europe?

- 1 subject over 750 young adults in the US general population is a survivor of childhood cancer (Meadows, 2003)
- 1 subject over 1,000 (0.1%) of the Nordic countries population is a childhood cancer survivor (Olsen, 2009)

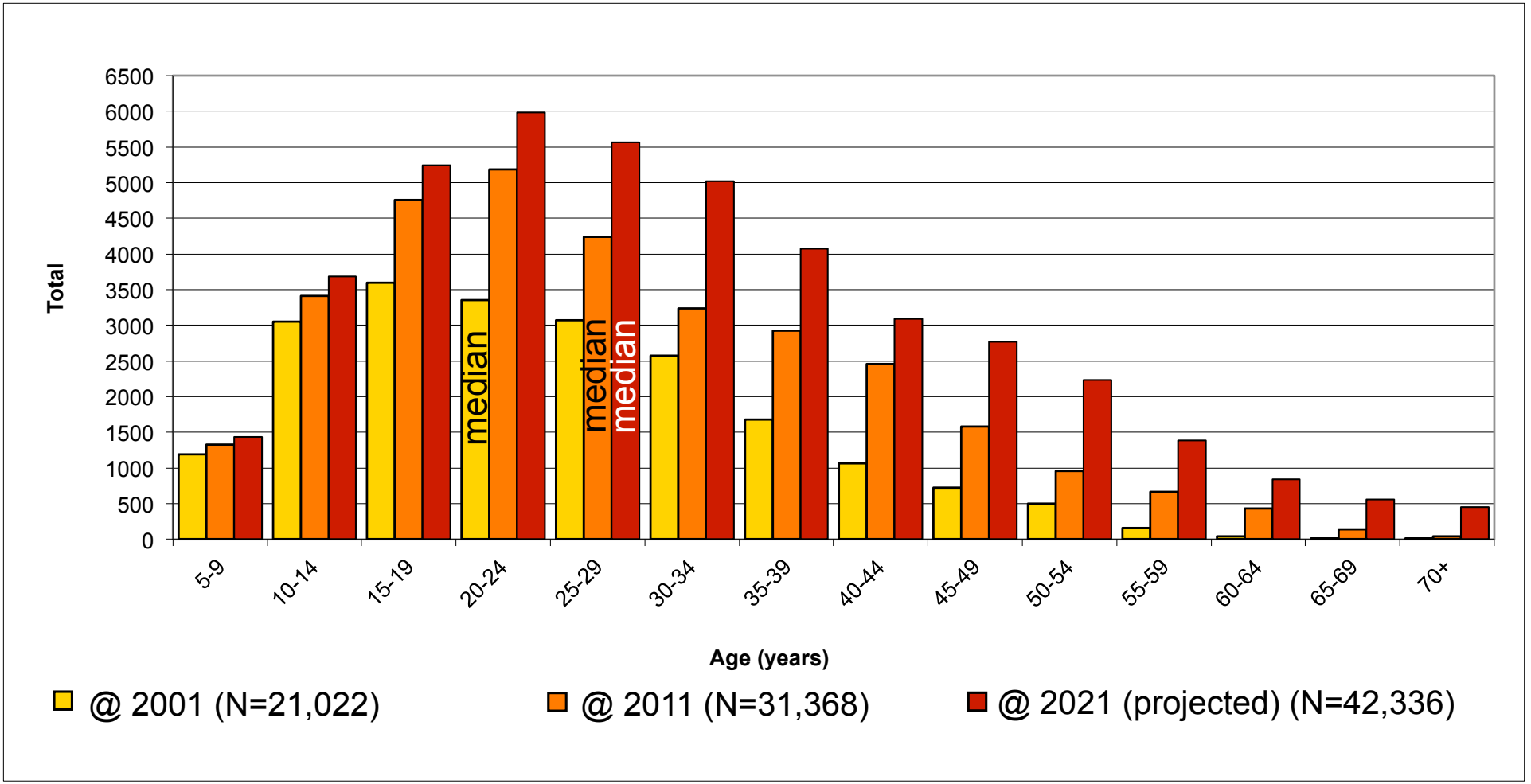
	Population	Survivors
U.S. *	250 M	328,000
E.U.	488 M	~300 – 500,000?

* Mariotto AB. et al. Cancer Epidemiol Biomarkers Prev, 2009

Average statistics on childhood cancer survivors in Europe

Total population of the 27 EU countries	~ 488,5 million
Percentage of the population 0-14 years	~ 16%
Population aged 0-14 years	~ 78,2 million
New cases of cancer aged 0-14 years	~ 11,000/year
Overall conservative 5-year survival	75%

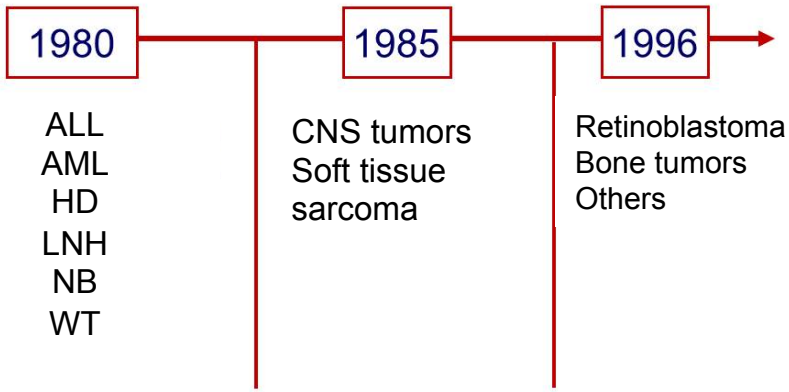
Age distribution of 5 year childhood cancer survivors in Great Britain in 2001-2021 (projected)

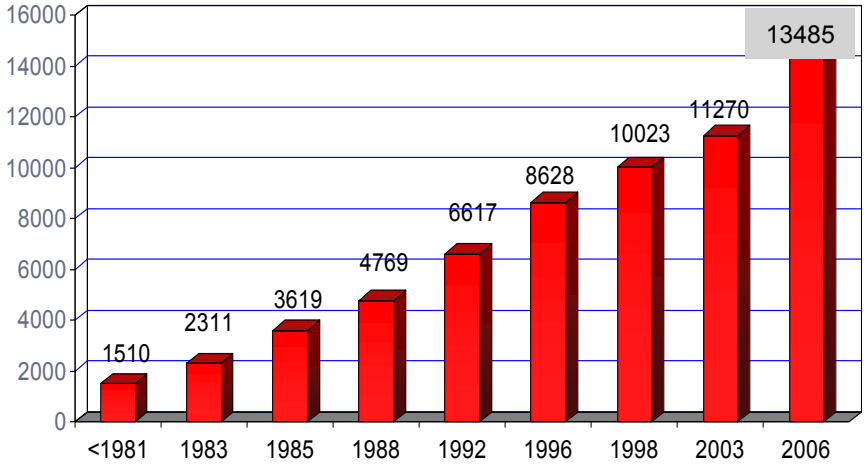


Courtesy of Stiller CA, GB National Registry of Childhood Tumours

AIEOP Registry of Patients Off-Therapy

- Funded in 1980 with the aim to collect long-term health information of patients surviving from childhood cancer . According to the current bylaws in 2012 it was established as “Observational Retrospective and Prospective ROT study”.





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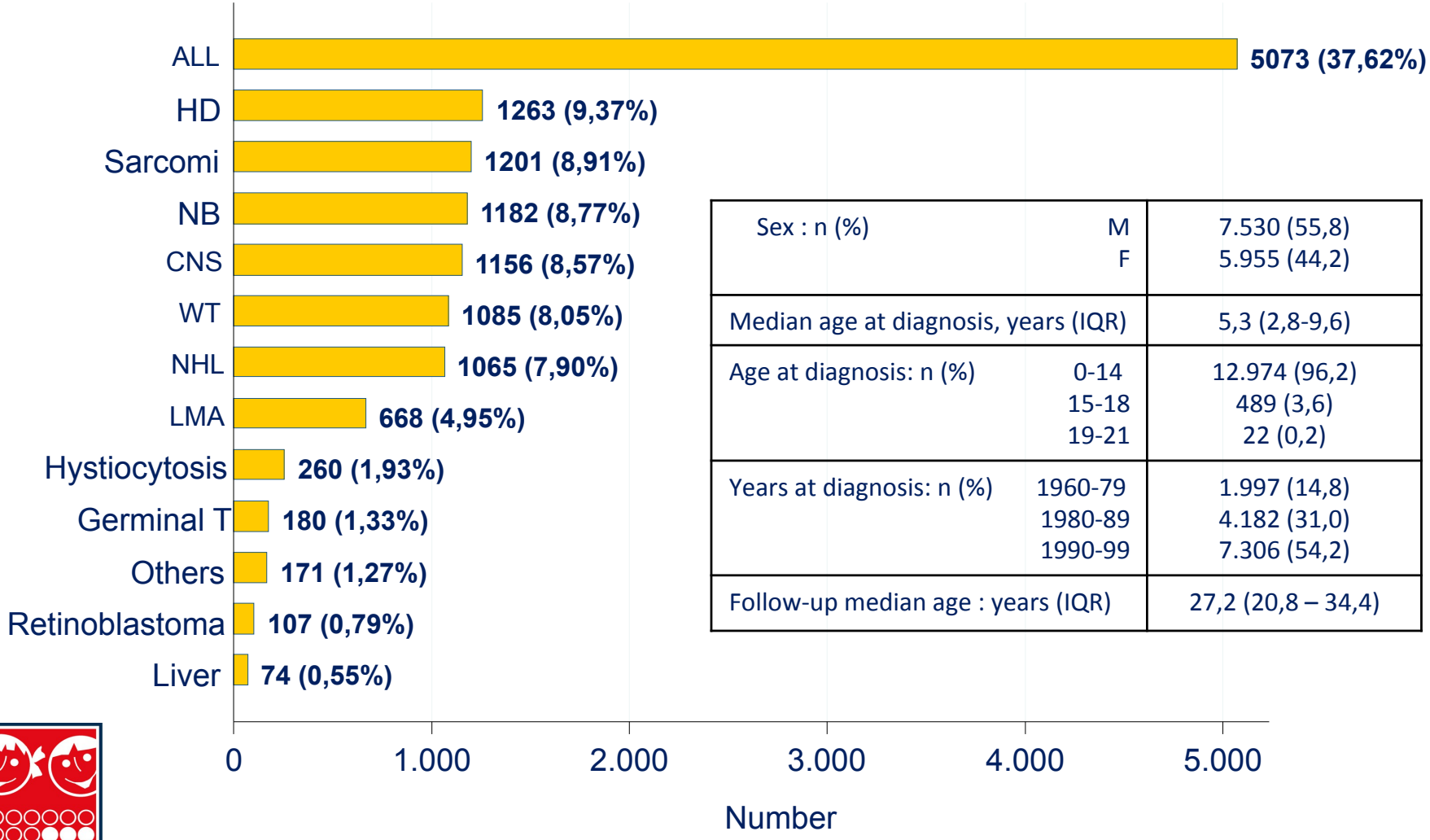
Clinical features of the 13.485 off-therapy patients OTR



Sex : n (%)	M F	7.530 (55,8) 5.955 (44,2)
Median age at diagnosis, years (IQR)		5,3 (2,8-9,6)
Age at diagnosis: n (%)	0-14 15-18 19-21	12.974 (96,2) 489 (3,6) 22 (0,2)
Years at diagnosis: n (%)	1960-79 1980-89 1990-99	1.997 (14,8) 4.182 (31,0) 7.306 (54,2)
Follow-up median age : years (IQR)		27,2 (20,8 – 34,4)

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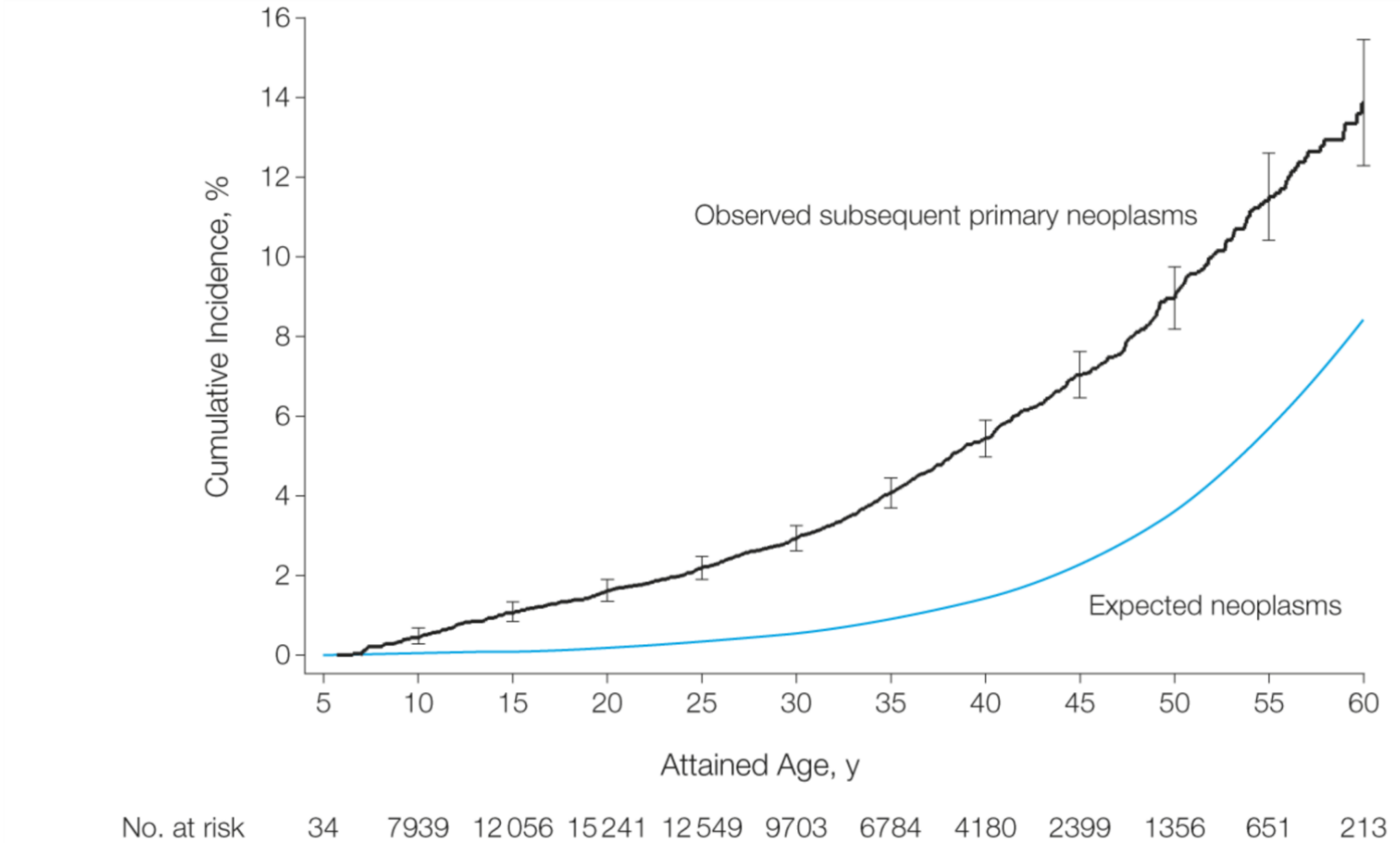
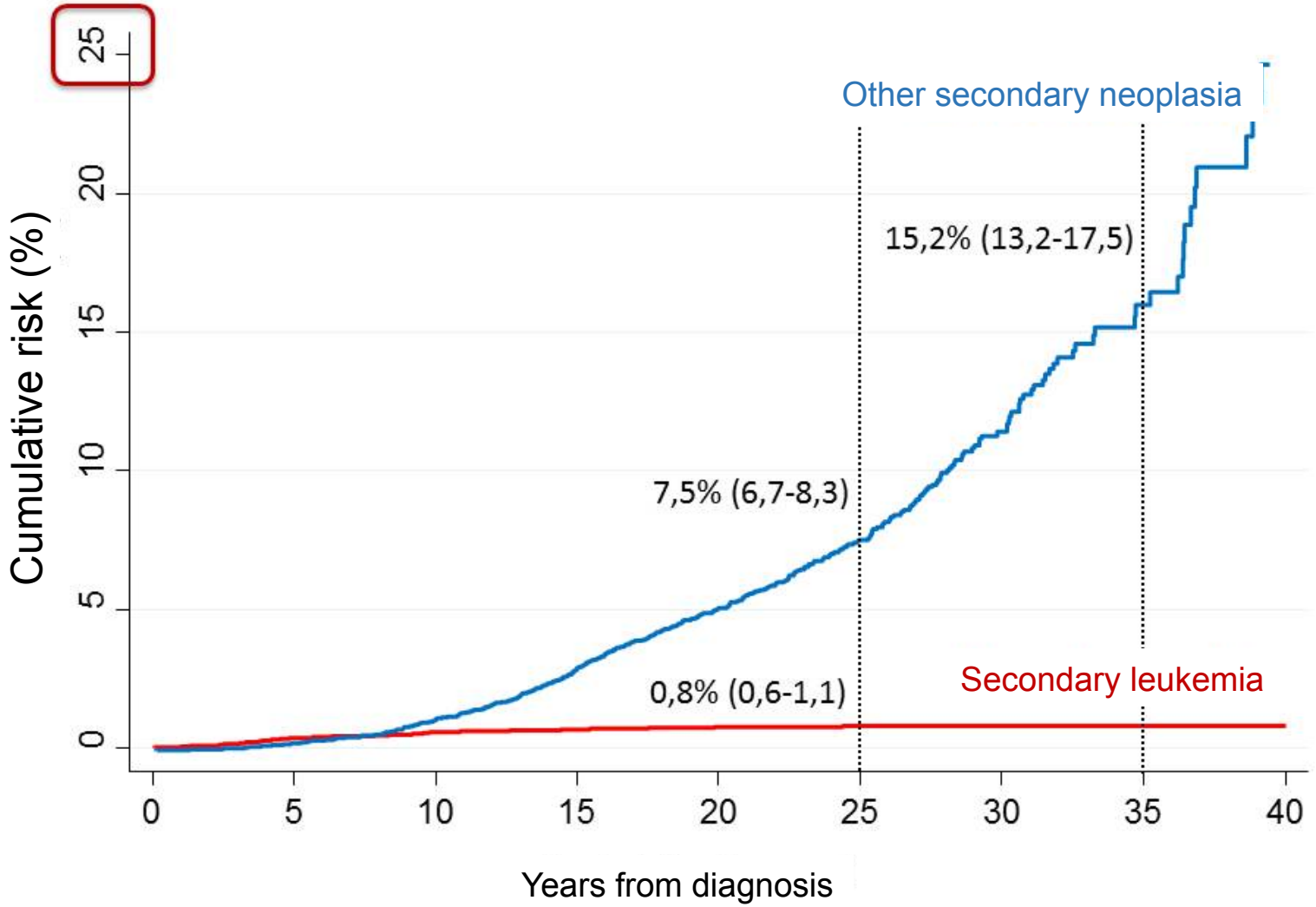
Cumulative incidence of SMN in CCS as compared to the general population (UK)



Roulen, JAMA 2011

Cumulative risk of leukemia and other SN in OTR patients



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t-MDS/AML after childhood cancer

	Exposure	
	Alkylants agents	Topoisomerasi II Inhibitors
Latency (years)	4-7	0.5-5
Clinical features	Cytopenia 2/3 myelodisplasia 1/3 AML with MDS features	Acute leukemia
Chromosomal abnormalities	-5(-5/del[5q]); -7 (-7/del[7q])	Balanced translocations 11q23 21q22
Drug exposure	Dose related	Schedule related

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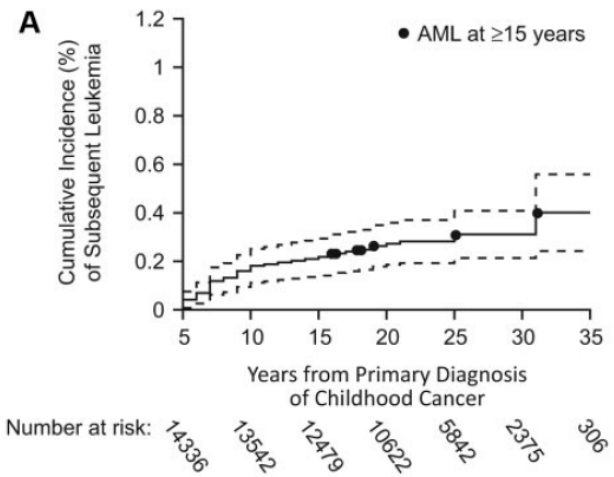
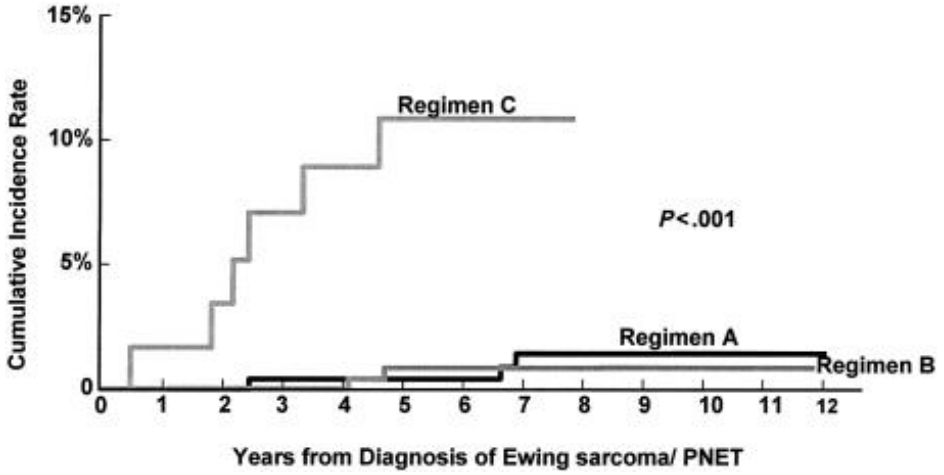
Hijiya N, Ness KK, Ribeiro RC, Hudson MM. Cancer. 2009 Jan 1;115(1):23-35. Review.

t-MDS/AML risk after childhood cancer

	Cumulative risk% (95% CI)	Follow-up (years)
All solid tumors	0,3 (0.21-0.41)	35
HD	2.1 (1.3-2.9)	14
LLA treated with epipodophyllotoxin	3.8 (2.3-6.1)	6
Ewing (AA high dose + topoisomerasi inhibitors)	11	6



Nottage , Blood 2015



Bathia , Blood 2007

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t-MDS/AML risk in children with leukemia treated with epipodophyllotoxin

Cumulative dose (mg/ m^2)	Administration	Treated/AML	Cumulative risk at a 8 years % (95%CI)
0	-	154/1	1 (0.8-5,3)
2.700	Every 2 weeks	155/1	1.1 (0,1-7,1)
19.200	Every 2 weeks	217/2	<1
9.240	Twice/ week	85/8	12,3 (5,7-25,4)
19.200	Once / week	84/4	12,4 (6,1-24,4)

Pui et al. NEJM, 1991

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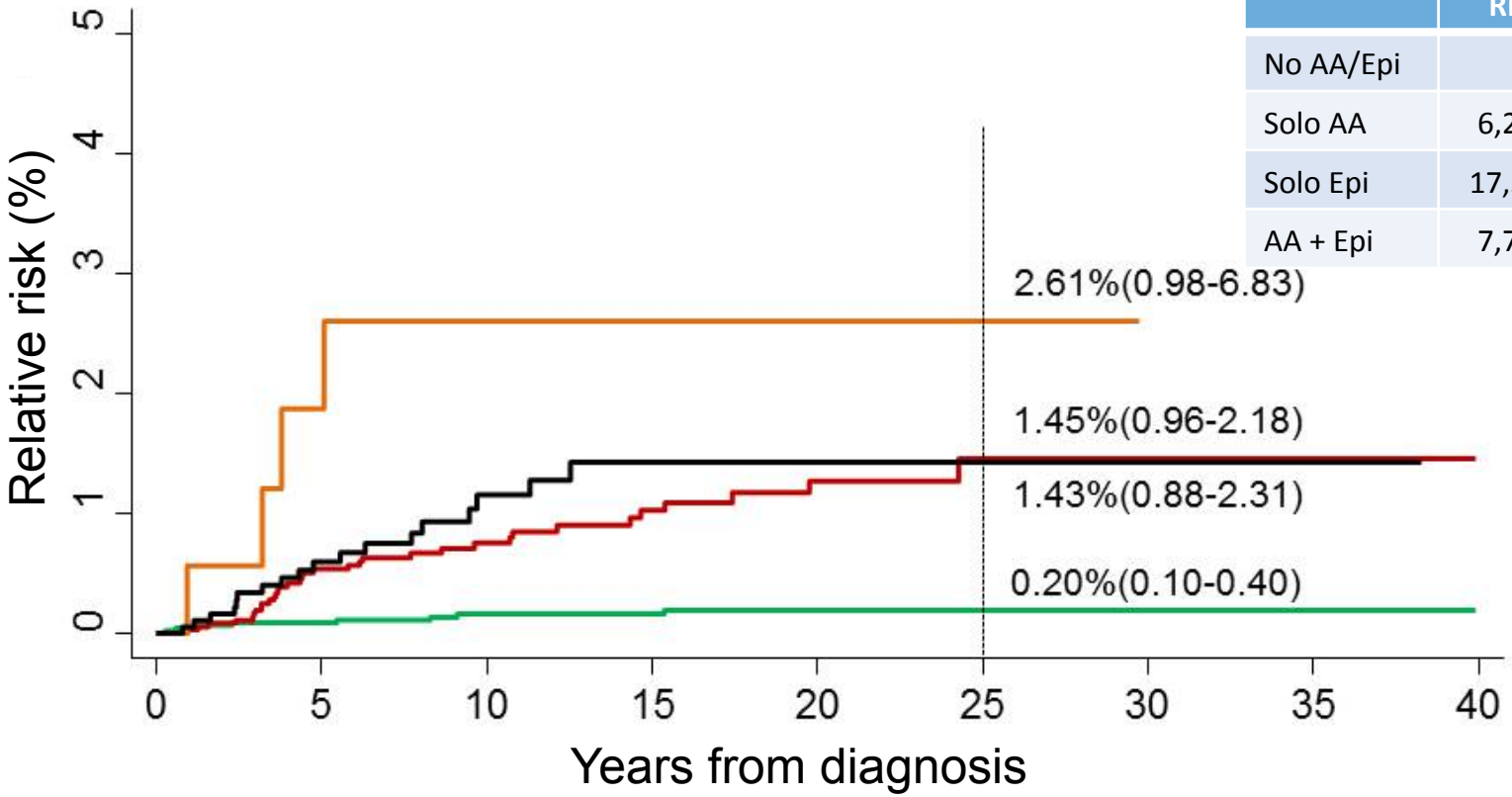
OTR-AIEOP: Relative risk of secondary leukemia according to drug exposure during therapy

	RR (95% CI)
No AA/Epi	Ref.
Solo AA	6,2 (2,8-13,4)
Solo Epi	17,3 (5,2-57,8)
AA + Epi	7,7 (3,3-17,9)



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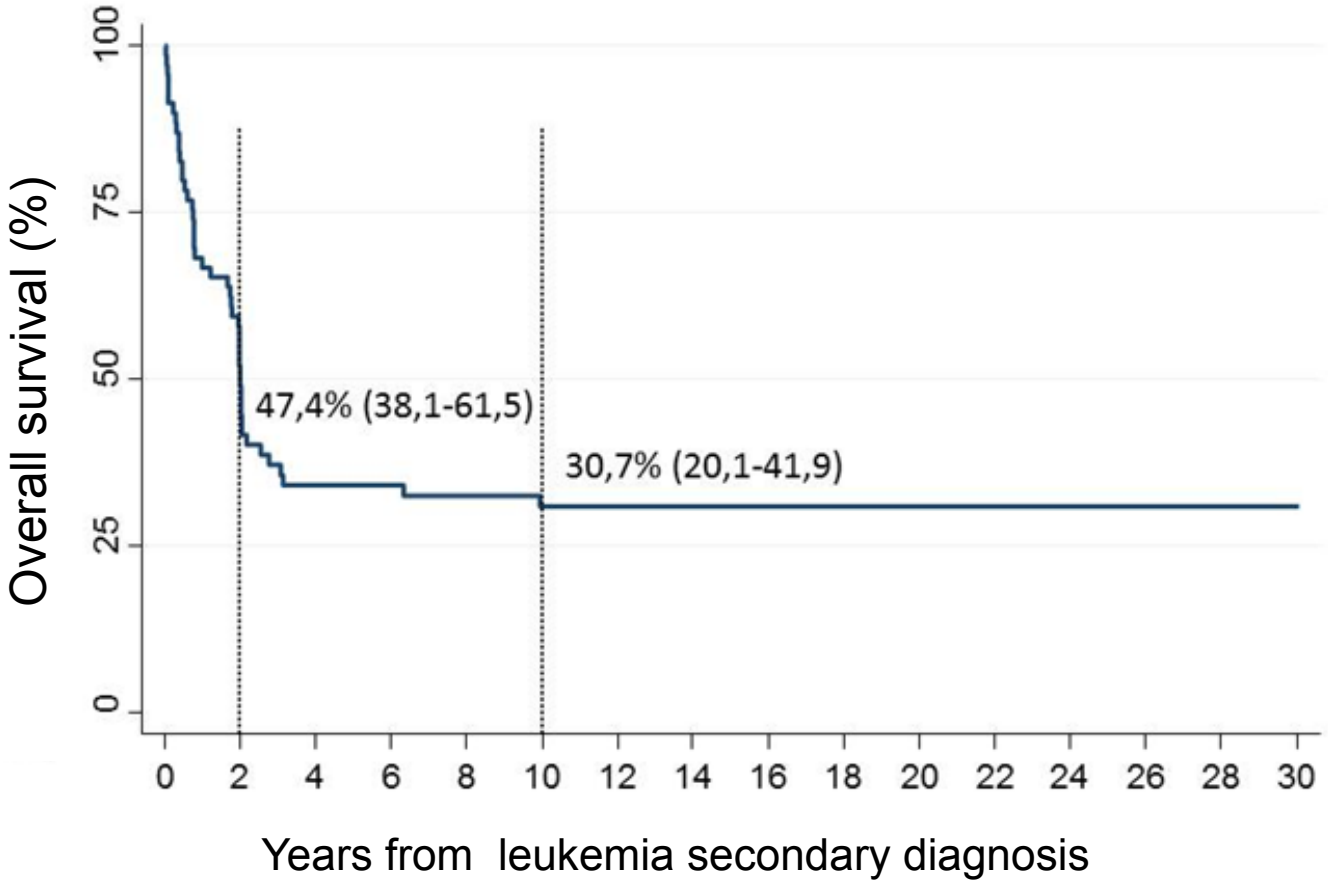
OTR: Overall survival in 69 patients with t-MDS/AML diagnosis



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Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration*

- The **Ponte di Legno (PDL) group**, formed in 1995:

  15 national study groups or major institutions; 14 working group meetings.

- The participants agreed to use the same or similar criteria for the stratification:
- To study rare subsets of ALL
- To compare results of clinical trials ;
- To identify effective treatment strategies for specific subsets of childhood ALL (Ph+ALL an infant ALL)

* Pui CH..Biondi A *et al* JCO 2015

Second malignant neoplasms (SMN) after treatment of Childhood ALL

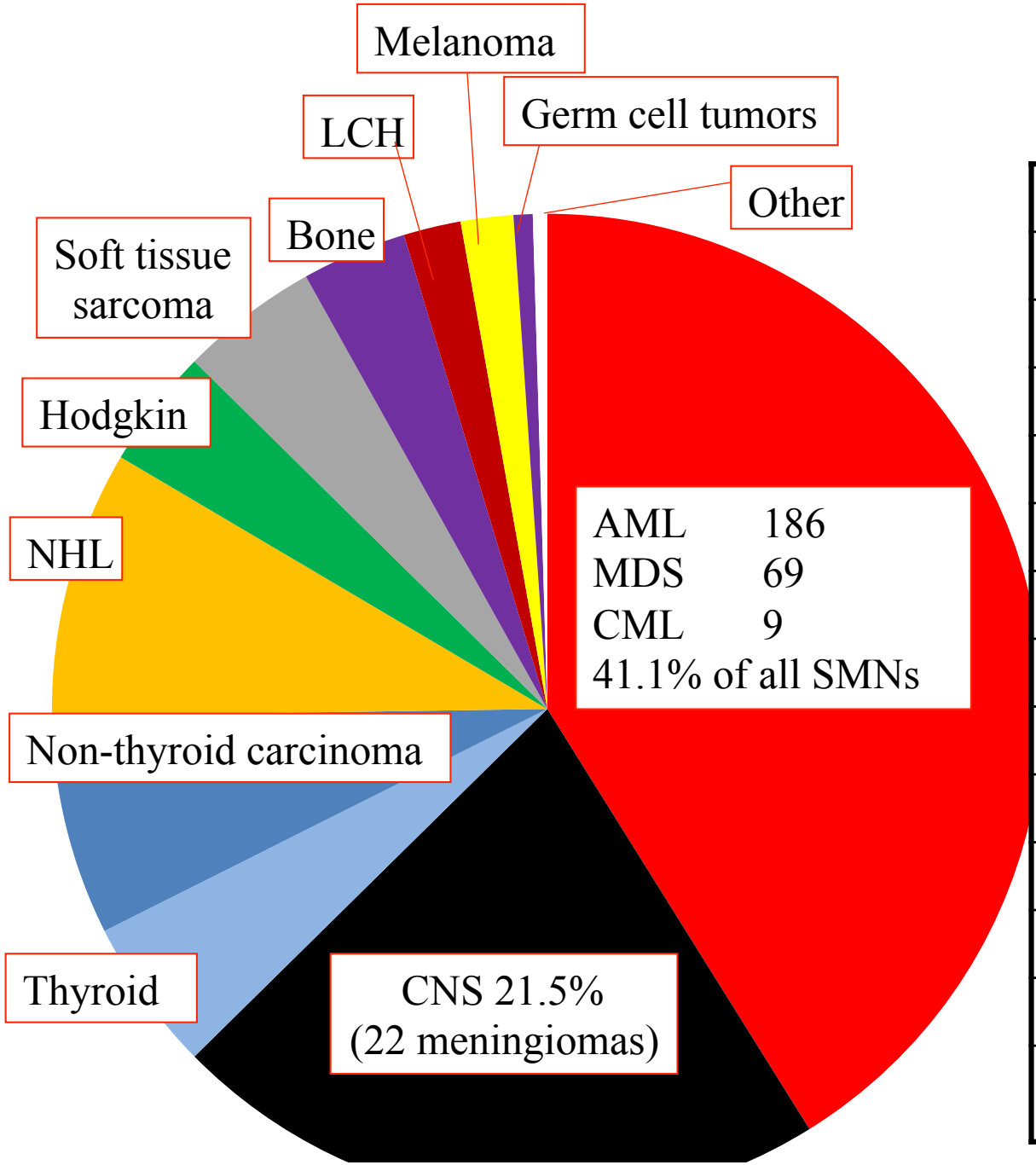
- SMNs from **54,068** children and adolescents up to 21 years of age with newly diagnosed ALL enrolled onto controlled clinical trials between 1980 and 2007;

- Data on individuals with SMNs to form a common data base with predefined clinical and biological data (including cytogenetic characteristics for myeloid neoplasia);

- **642** were registered with a malignant neoplasms or a CNS tumor as the first event after diagnosis of **ALL**;

Schmiegelow K *et al* JCO 2013

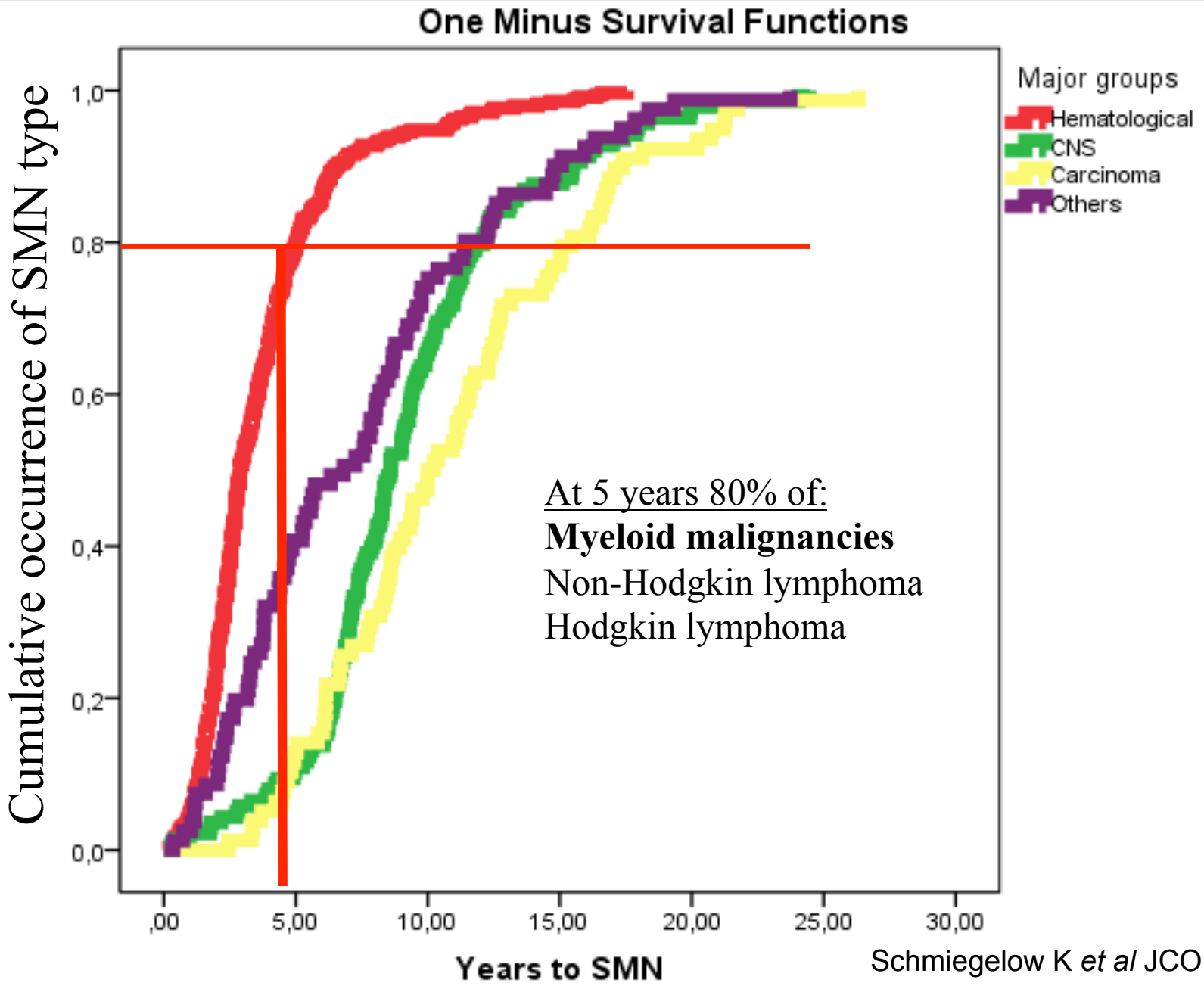
sMN after treatment of childhood ALL



Schmiegelow K *et al* JCO 2013

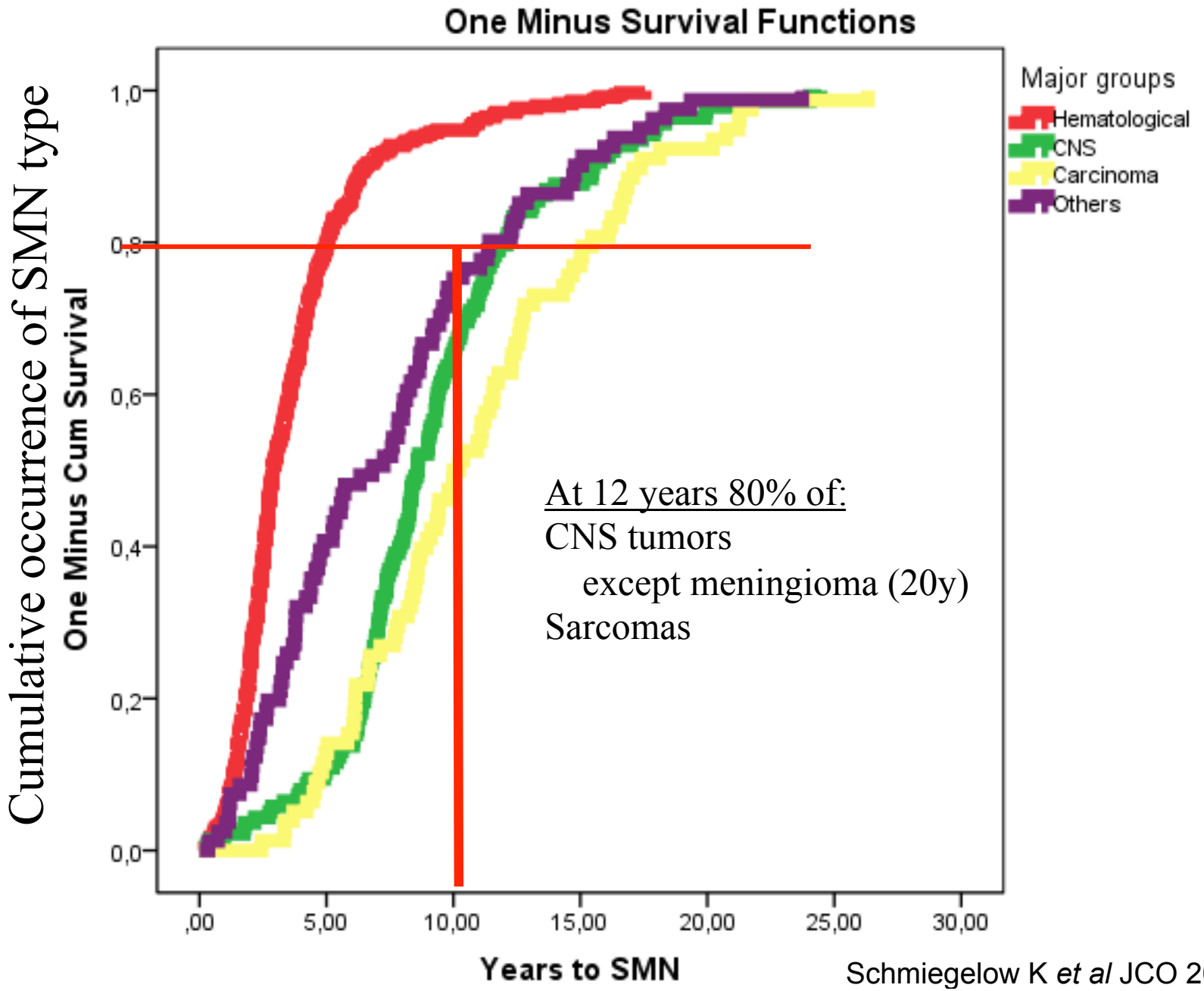
SMN type	N
AML/MDS/CML	264
CNS	138
Thyroid	32
Other carcinomas	46
Non-Hodgkin	56
Hodgkin	25
Soft tissue sarcoma	29
Bone tumors	22
Histiocytosis	12
Melanoma	11
Germ cell tumor	4
Other	3
Total	**642**

Interval from diagnosis of ALL to diagnosis of SMN



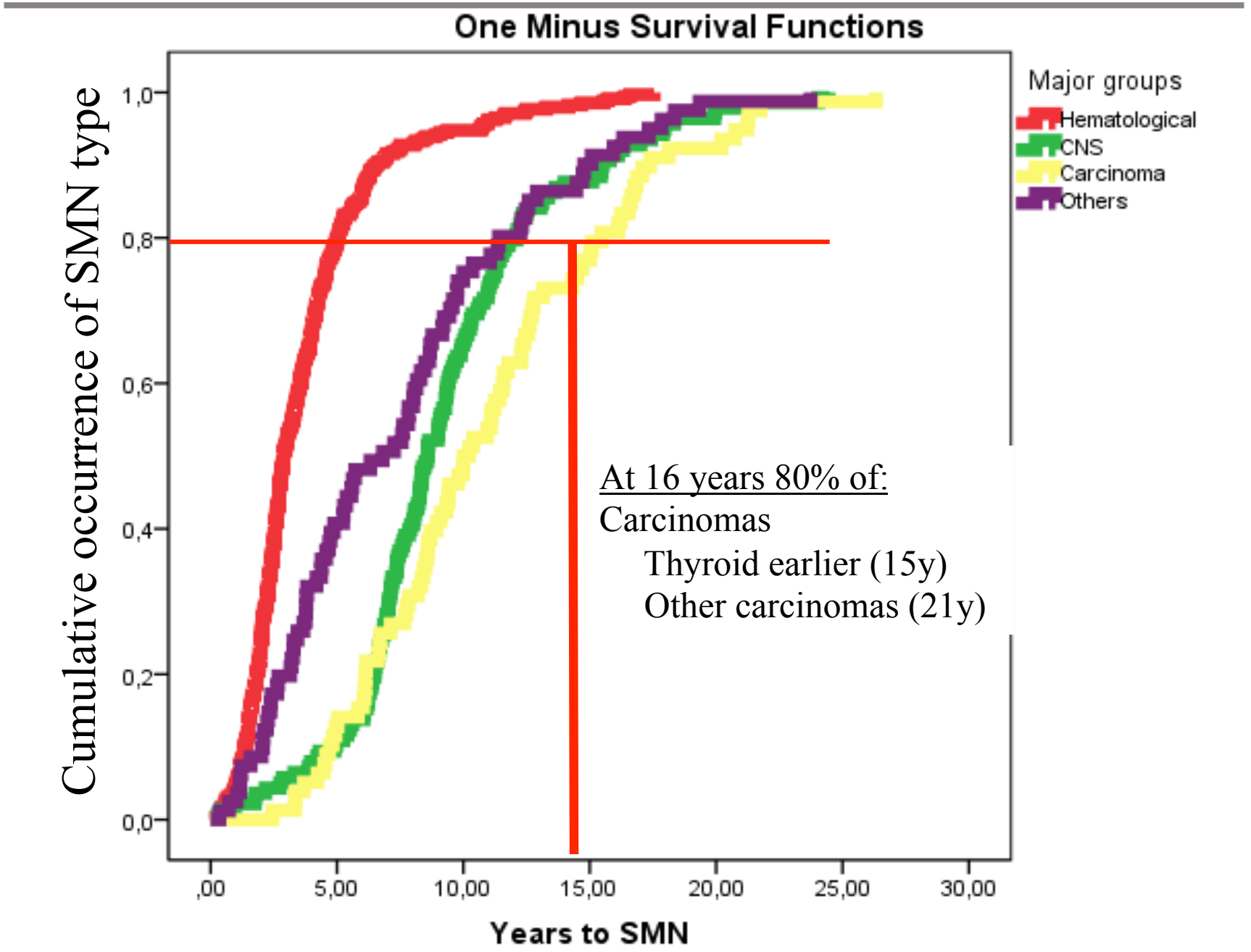
Schmiegelow K *et al* JCO 2013

Interval from diagnosis of ALL to diagnosis of SMN

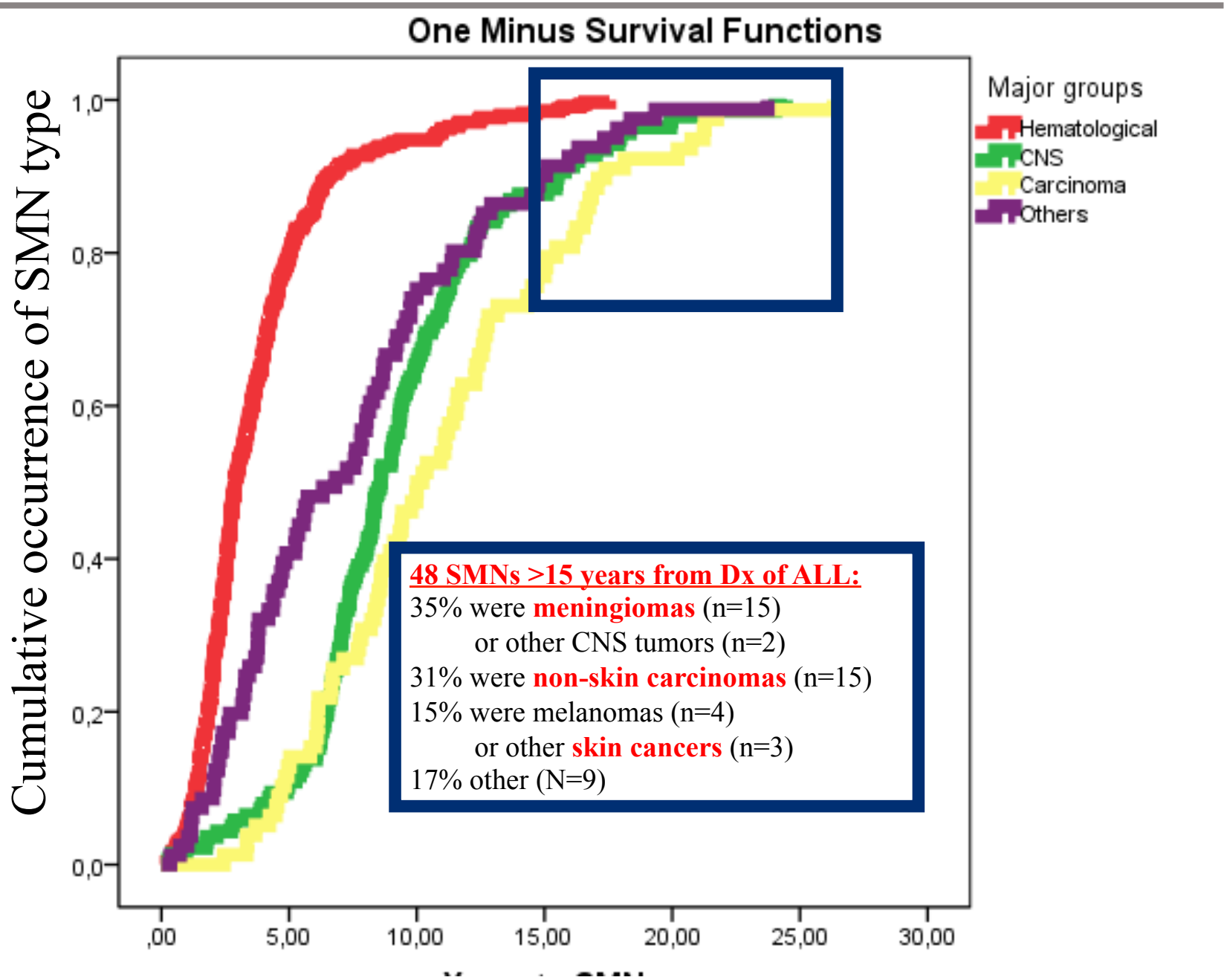


Schmiegelow K *et al* JCO 2013

Interval from diagnosis of ALL to diagnosis of SMN



Interval from diagnosis of ALL to diagnosis of SMN



Associations of 1st and 2nd cancer

- 10 out of 11 sLCH had T-ALL
  - vs 20% of other SMNs (p<0.001) Trebo, Leuk Lymphoma 2005
  - Generally young at diagnosis of T-ALL (4.2 years)
- Primary ALL vs AML/MDS karyotypes:

Karyotype t-MN\ALL	Total	HeH*	Translocations t(1;19), t(12;21), t(9;22), MLL	Other aberrations
MLL/11q23	25	6	13 (52%)	6
5q-/-7	20	11 (55%)	3	6

P=0.03

*HeH: High Hyperdiploid (chromosome modal numer above 50)

Conclusion:

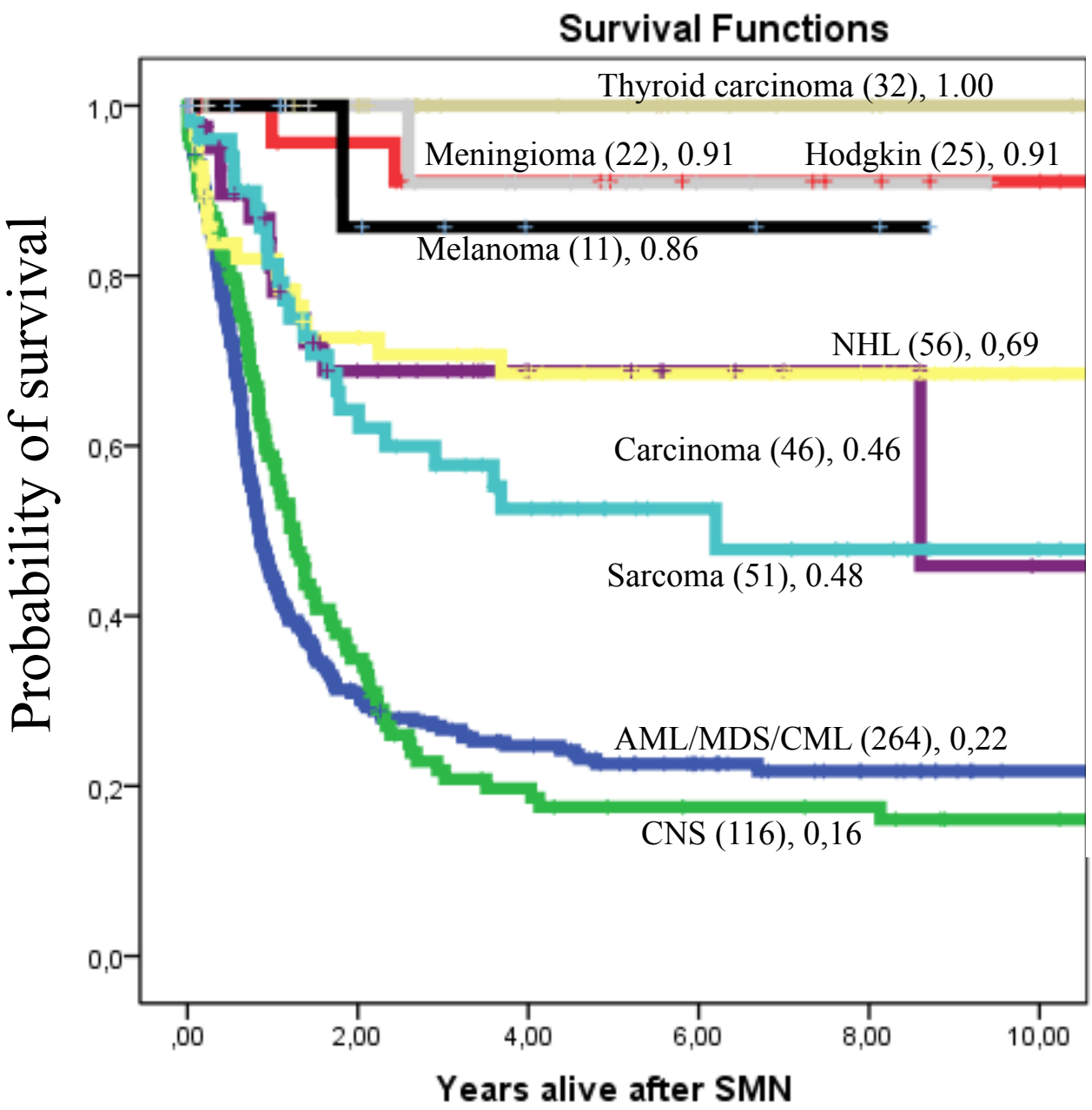
ALL/t-MN pts seem predisposed to either non-disjunctions or numerical aberrations

Associations of ALL Tx and t-MN

- 76% (38/50) of t-MN with aberrant karyotype and exposure to epipodophyllotoxins had MLL-rearr.
  - vs 28% of t-MN not exposed to epipodophyllotoxins ($p<0.001$)
  - Not found for antracycline exposure;

- t-AML/MDS had received (compared to other SMN)
  - **longer maintenance** (31% vs 18% received 2.5yrs+, $p=0.001$)
  - **higher maintenance** MTX and 6MP **doses**
    - Most pronounced for CNS-irradiated pts ($p<0.001$)
    - May explain why *TPMT* status is related to SMN risk in SJCRH (Relling, Lancet 1999) and Nordic studies (Schmiegelow, Blood 2009); but not in BFM study (Stanulla, Blood 2009)

Survival after SMN



t-AML/MDS:

Prognosis improved; 2000+
AML 34% , MDS 48%
Death hazard by lag time
-10%/year ALL-MN interval
No effect of hSCT
when adj. by waiting time
2000+: 42% vs 47% OS

CNS tumors:

No improvement over time

B-cell NHL (N=27):

5yrs OS 77%
Median yrs to SMN: 2.3

Basal cell and parotid c.:

10yrs OS 100% (N=16)

Other inner organ carcinoma.:

5yrs OS 40% (N=18)

Potential genetic factors influencing the risk of t-MDS/AML

Gene(s) involved in drug metabolism

GSTP1-105Val more expressed in in t-AML

- as compared to *de novo* AML : **OR 1.8** (95% CI 1.1-2.9)
- t-AML secondary to chemiotherapy : **OR 2.7** (95% CI 1.4-5.1)
- In the case of GSTP1 substrate exposure (ifo, busulfan, clorambucil): **OR 4.3** (95% CI 1.4-13-2)

DNA repair mechanism(s)

- Mismatch repair: 50% of t-AML show microsatellite instability associated to MLH1 gene methylation or MSH2 polymorphisms ;
- Double strand breaks:

  Homologous recombination : *RAD51-G-135C:* OR 2.7*;*

  RAD51-G-135C + XRCC3-241Met: **OR 8.1**

  Non homologous terminal joining : MLL translocations
- Base excision repair: *XRCC1-399Gln*: protective per t-AML
- Nucleotide excision repair: ERC*C2 Lys751Gln*

The new genetic landscape of predisposing gene in childhood ALL

- Common low-penetrance susceptibility alleles contribute to the risk of developing childhood ALL (Papaemmanuil I *et al* Nat Genet 2009; Trevino LR et al Nat Genetic 2009);
- High frequency of *TP53* alterations in both pediatric and adult low-hypodiploid ALL (91.2% and 90.9%, respectively). Inherited origin of the *TP53* mutation identified in one pediatric low-hypodiploid case (Holmfeldt L et al Nature 2013)
- Germline mutations in cancer-predisposing genes were identified in 8.5% of the children and adolescents with cancer (Zhang J et al al N Engl J Med 2015);

Conclusions

- The cumulative incidence is 1-2% but varies widely between groups and protocols ;
- Overall survival of t-MDS and AML after ALL low as compared to other SMN;
- Current strategies for ALL treatment have reduced reduced the use of CNS RTx and epipodophyllotoxins;
- International collaboration is needed for exploration of predisposing individual genetic factors and the optimal therapy for t-MDS and AML.

Stop treating hard start treating smart ?

Courtesy of M.Stanulla, 2015