Secondary leukemias and primary malignancies: Lymphoproliferative Disorders

FIFTH
INTERNATIONAL SYMPOSIUM ON
SECONDARY LEUKEMIA
AND LEUKEMOGENESIS

HONORARY PRESIDENT: GIUSEPPE LEONE
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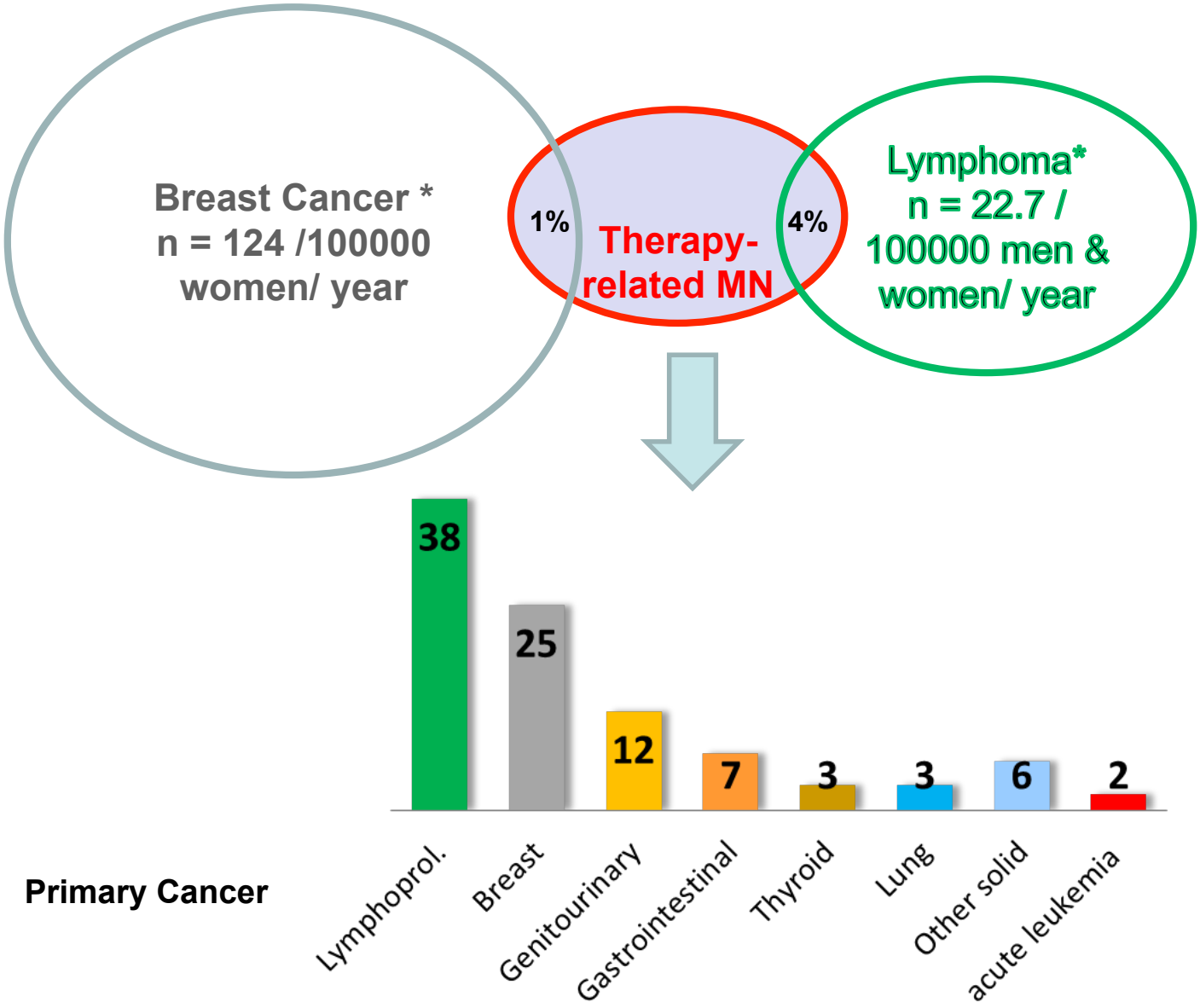
Incidence of t-MN:

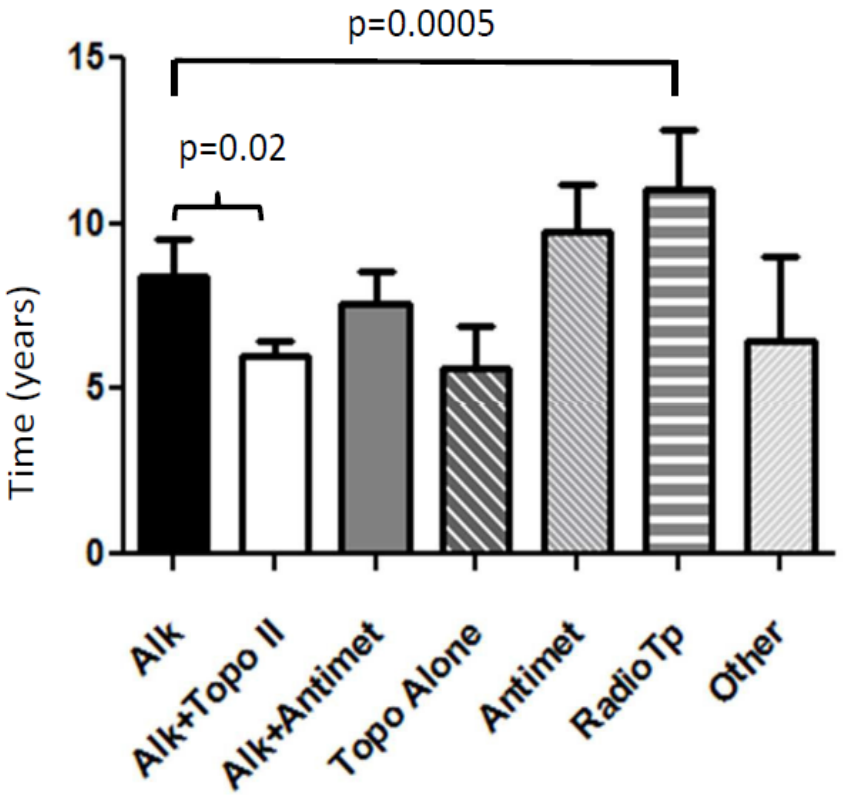
35-40% of patients had a previous lymphoproliferative disorder



Adapted from Fianchi et al, Am J Hematol 2015; 90:E80 (Italian t-MN registry)

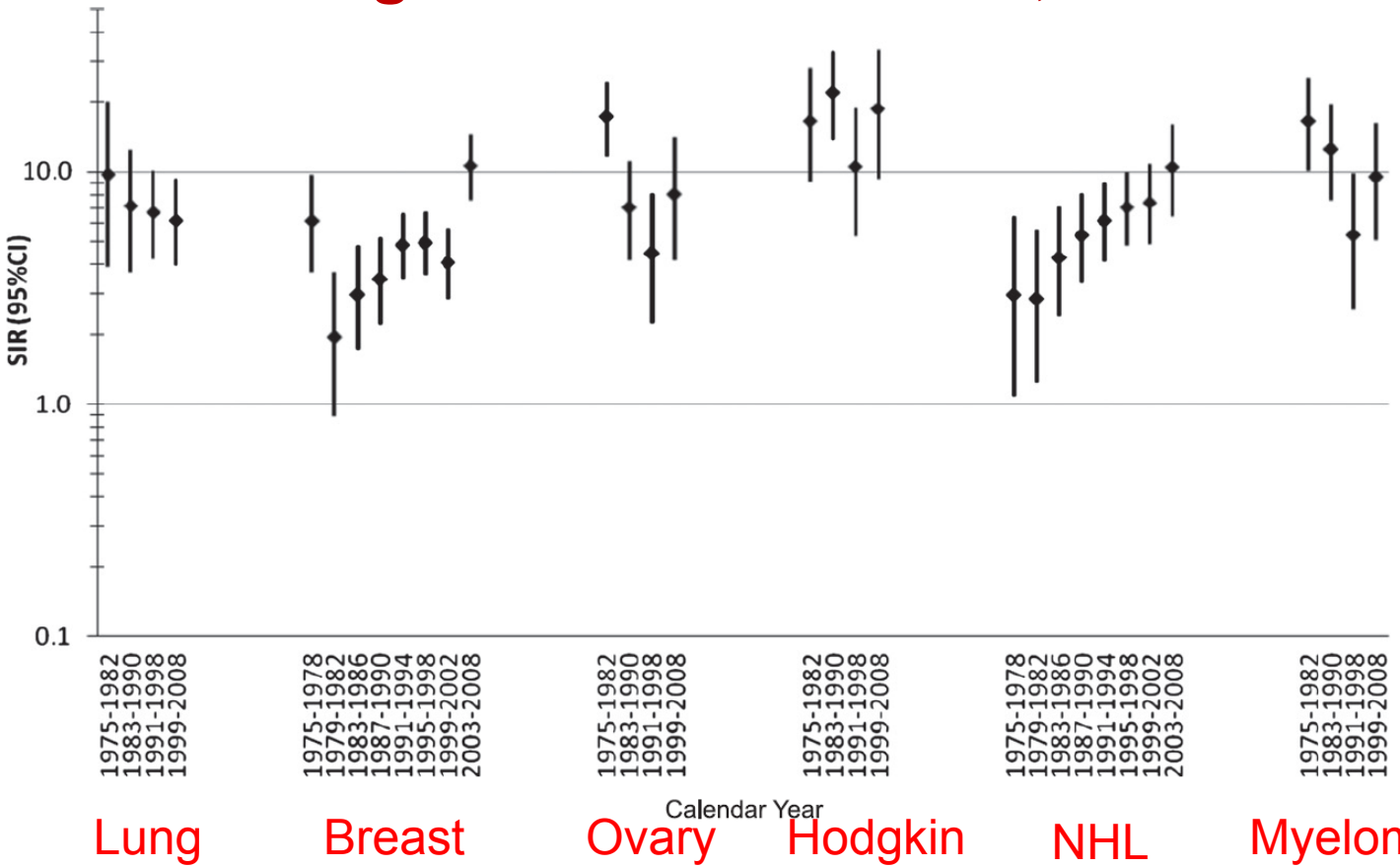
Latency between Primary Disease and t-MN

Alkylating agents	Topo II inhibitors	Anti-metabolites
Busulfan	Bimolane	Azathioprine
Carmustine	Dactinomycin	**Fludarabine**
Chlorambucil	Daunorubicin	Mercaptopurine
CTX	Doxorubicin	Methotrexate
Dacarbazine	**Epidoxorubicin**	
Dihydroxybusulfan	**Etoposide**	
Lomustine	**Mitoxantrone**	
Mechlorethamin	Razoxane	
Melphalan	Teniposide	
Procarbazine		
Thiotepa		



Fianchi et al, Am J Hematol 2015; 90:E80 (Italian t-MN Multicenter registry)

Evolving Risk of t-AML in US, 1975-2008



801 t-AML in 426,068 adults treated with chemotherapy for first primary malignancy (9 US population-based cancer registries, 1975-2008, 4.70 times more than expected in the general population, P < .001).

Morton et al, Blood 2013; 121, 2996

Secondary leukemias and primary malignancies: Lymphoproliferative Disorders

Epidemiological data

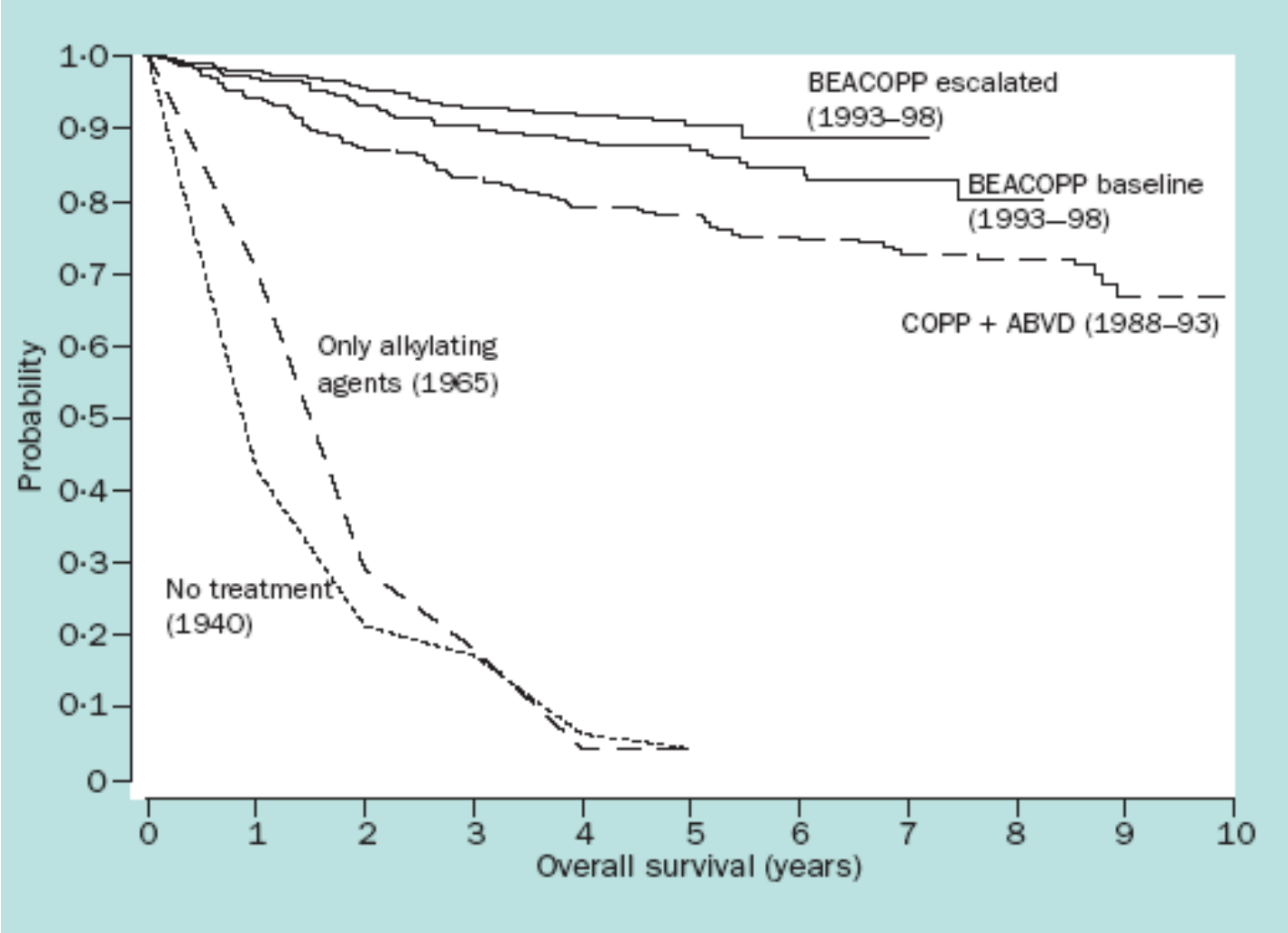
Hodgkin's lymphoma

Non-Hodgkin's lymphoma

Risk factors

Model of secondary leukemogenesis in lymphomas

«The treatment of Hodgkin lymphoma is the greatest success story in medical oncology»



The Dilemma of Treatment Choices in Hodgkin's Lymphoma

Survival

QoL

organ toxicity
- Gonadal
- Thyroid
- Pulmonary
- Cardiac
- **Secondary** cancer, **AML**

Efficacy **Tollerability**

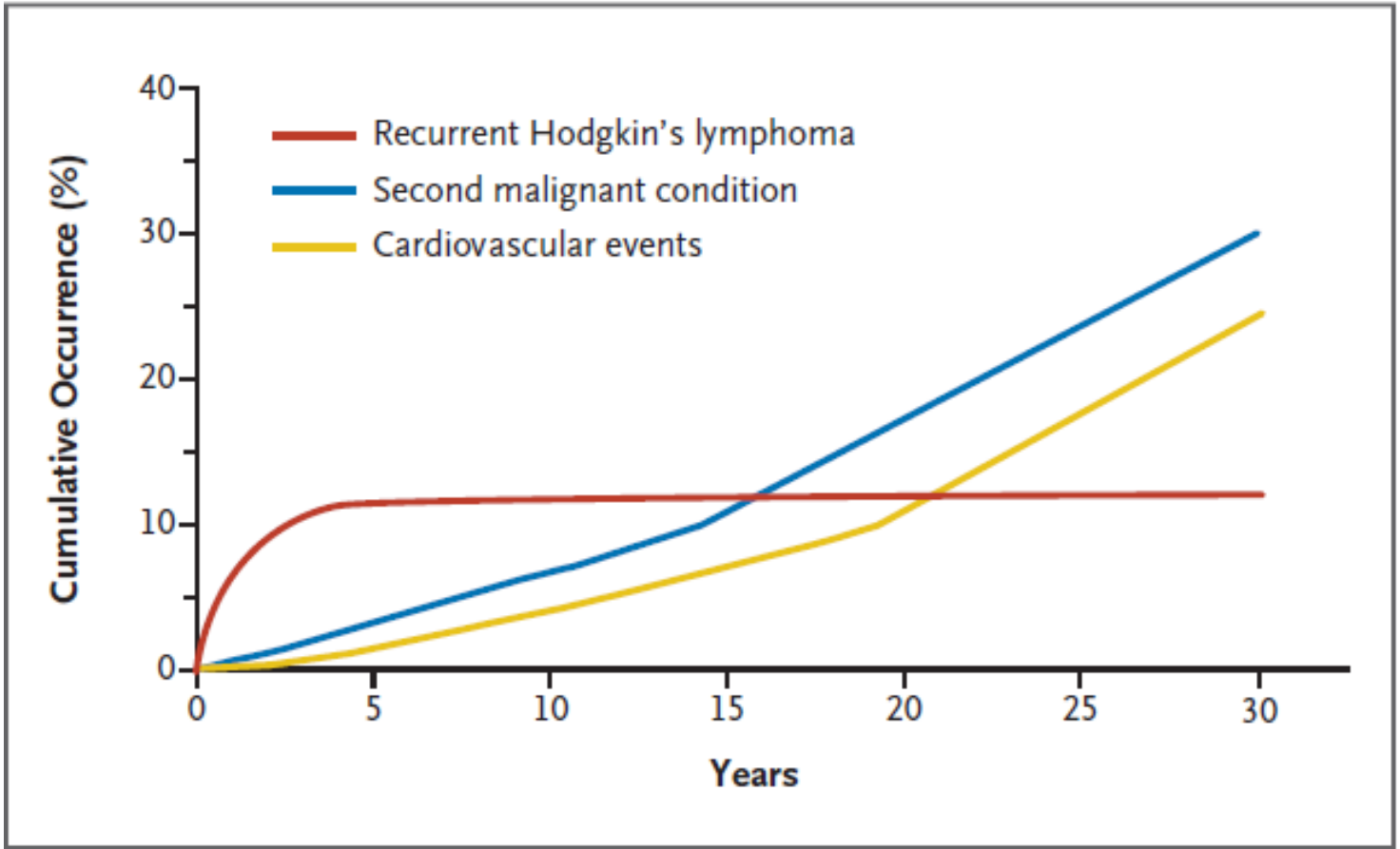
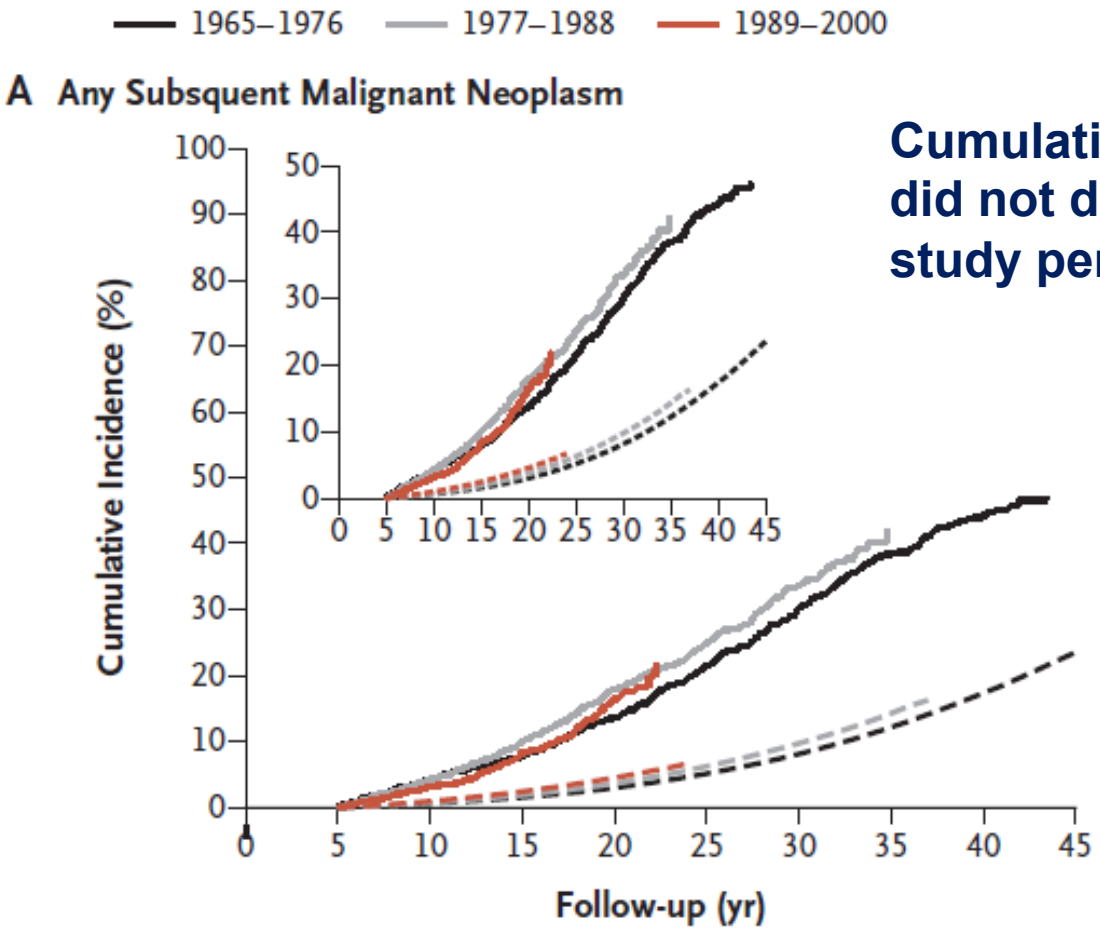


Figure 1. Approximate Cumulative Risk of Recurrent Hodgkin's Lymphoma, Second Malignant Conditions, and Cardiovascular Events among Patients Receiving Both Radiotherapy and Chemotherapy for Early-Stage Hodgkin's Lymphoma.

Armitage, N Engl J Med 2010; 363:653

Second Cancer Risk in Hodgkin's Lymphphoma

3905 pts treated between 1965 and 2000



Cumulative incidence did not differ according to study period

Risk of breast cancer:

Lower in patients treated
- without mantle field irradiation
- procarbazine doses of >4.3 g/m2 (associated with premature ovarian failure)

Schaapveld et al, N Engl J Med 2015; 373:26

Second Cancer Risk in Hodgkin's Lymphoma

3905 pts treated between 1965 and 2000

Second Cancer or Cancer Site	No. of Patients	Standardized Incidence Ratio (95% CI)	Absolute Excess Risk	30-Yr Cumulative Incidence (95% CI)
			no./10,000 person-yr (95% CI)	
Any cancer, excluding MDS†	884	4.6 (4.3 to 4.9)	121.8 (111.8 to 132.4)	32.5 (30.4 to 34.6)
Any solid cancer	757	4.2 (3.9 to 4.5)	100.5 (91.3 to 110.2)	28.5 (26.4 to 30.5)
Leukemia	41	9.5 (6.8 to 12.9)	6.1 (4.2 to 8.5)	1.3 (0.9 to 1.7)

Schaapveld et al, N Engl J Med 2015; 373:26

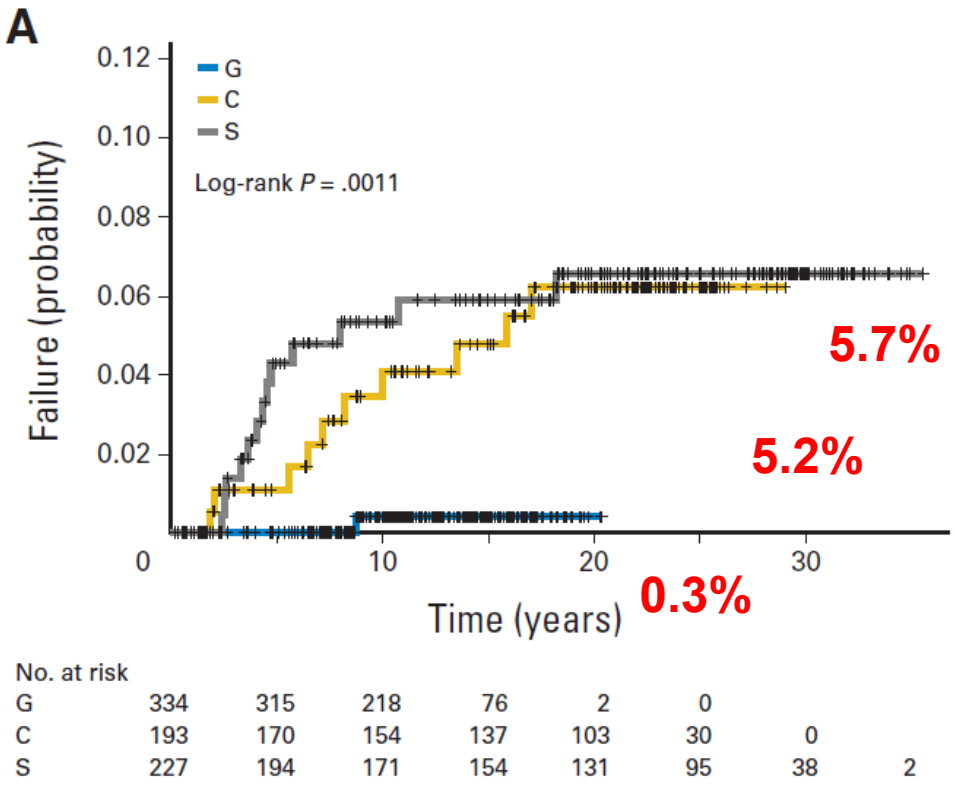
Hodgkin's Lymphoma

Reference	n	Therapy	t- AML	Cumul. Risk (%)	Time to AML	Median Foll-up
Delwail et al. BJH, 2002	373 374 36	ABVD + RT MOPP +RT IF MOPP + RT EF	4 5 4	1.3 2.4 13.9%	-	15 yrs
Brusamolino et al Clin Can Res, 2006	120	ABVD (4-6 cy) + RT IF	0	0	-	10 yrs
Schwartz et al Blood 2009	209	ABVE-PC	3	1.4%	-	5.2 yrs
Josting et al. JCO, 2003	677 1775 304 550 460	RT COPP+ABVD ABVD BEACOPP-B BEACOPP-E	4 15 1 2 8	0.6 0.8 0.3 0.4 1.7	12.5 mths (0-128)	4.5 yrs
Engert et al JCO, 2009	261 469 466	COPP/ABVD BEACOPP-B BEACOPP-E	1 7 14	0.4 2.2 3.2	Most < 7 yrs	9.2 yrs

Adapted from Leone et al, Haematologica 2007; 92:1389

Therapy-related AML/MDS in Hodgkin's Lymphoma: Stanford Studies

Demographic or Characteristic	Study S	C	G
Years of study	1974-1980	1981-1989	1989-2003
Patients, No.	227	193	334
Median age, years	27	26	29
Male			
No.	129	113	179
%	57	59	54
Median follow-up, years	22	20	11
Stage			
I-II			
No.	96	97	226
%	42	50	68
III-IV			
No.	131	96	108
%	58	50	32
Splenectomy			
No.	200	122	34
%	88	63	10
Cumulative doses of chemotherapy agents, mg/m^2			
Mechlorethamine*	72	72	12-18
Procarbazine†	8,400	8,400	—
Melphalan‡	180	180	—
Etoposide	—	—	240-360
RT dose in S, Gy			
Stage I-II, IF	44		
Stage III, STLI/TLI	44		
Stage IV, IF or STLI/TLI	44		
RT dose in C, Gy			
Stage I-II, IF		40-44	
Stage IIX, mantle		44	
Stage III-IV, IF or STLI/TLI		30-44	
RT dose in G, Gy			
Stage I-II, modified IF			30-36
Stage IIX, III-IV, modified IF, sites > 5 cm, spleen			36



Koontz et al, J Clin Oncol 2013, 31:592

Escalated-Dose BEACOPP in the Treatment of Patients With Advanced-Stage Hodgkin's Lymphoma: 10 Years of Follow-Up of the GHSG HD9 Study

		FFTF	OS
BEACOPPesc	C:	82%	86%
BEACOPPbase	B:	70%	80%
COPP/ABVD	A:	64%	75%

at 10 years

Table 3. Causes of Death

Condition	Arm (% of all patients)		
	A	B	C
No. of patients	261	469	466
Hodgkin's lymphoma	11.5	8.1	2.8
Acute toxicity (first line)	1.9	1.5	1.7
Acute toxicity (salvage)	1.9	1.5	0.6
Second malignancy	3.1	3.6	3.2
Cardiorespiratory	1.2	0.9	0.9
Pulmonary	0.4	0.4	0.2
Other	3.8	3.0	2.1

Engert et al, J Clin Oncol 2009; 27:4548

Therapy-related AML/MDS in Hodgkin's Lymphoma:

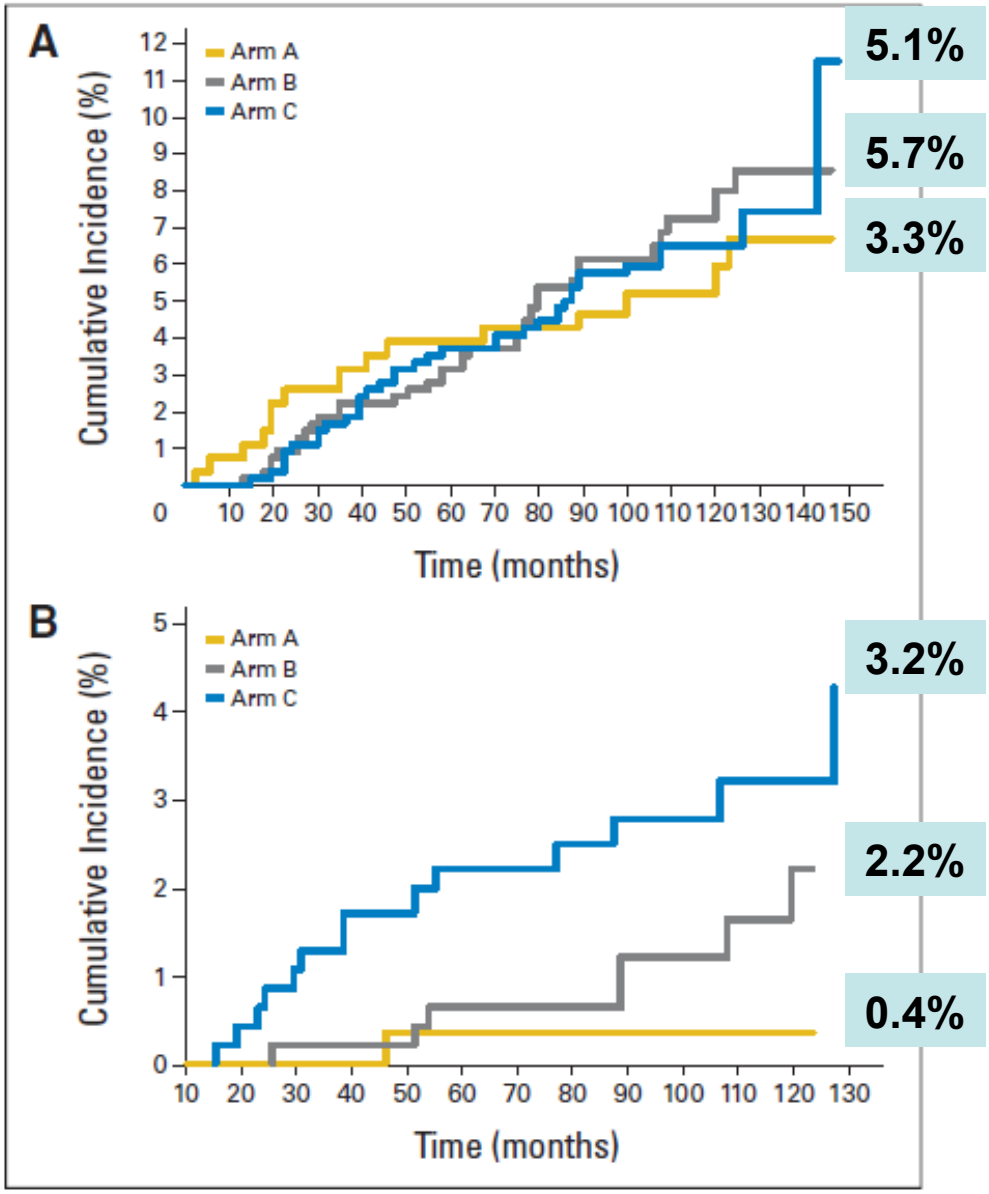


Fig 1. (A) Cumulative incidence plots for second malignancies and (B) secondary acute myeloid leukemia and myelodysplastic syndrome accounting for other deaths as a competing risk.

GSHG HD9 Study

9.2 years Follow-up

Cumulative incidence of second malignancies

- BEACOPPesc
- BEACOPPbase
- COPP/ABVD

Cumulative incidence of secondary AML/MDS

Engert et al, J Clin Oncol 2009; 27:4548

Therapy-related AML/MDS in GSHG Studies

	Patients with t-AML/MDS (n = 106)	All patients (n = 11 952)	
Sex			0.9%
Male	53%	56%	
Age			
Median (range)	43 (16-71)	34 (16-75)	
HL risk group			
Early favorable	5%	25%	
Early unfavorable	20%	34%	
Advanced	75%	41%	
First-line chemotherapy for HL			
No BEACOPP	23%	49%	0.3%
<4 cycles $BEACOPP_{escalated}$	19%	23%	0.7%
≥4 cycles $BEACOPP_{escalated}$	58%	28%	1.7%
Radiotherapy for HL			
No RT	45%	27%	
<EF	41%	63%	
EF	14%	10%	

Median time from HL to t-MN: 31 months

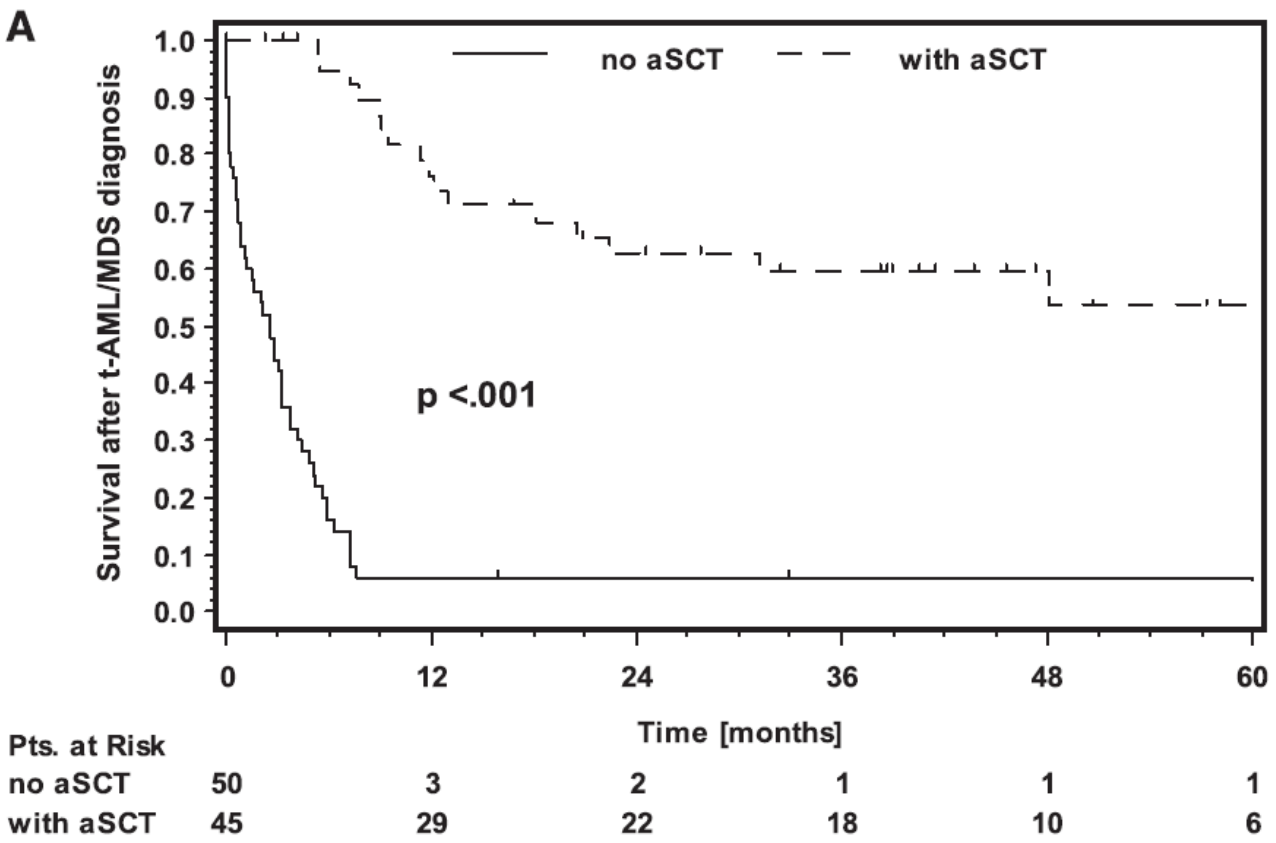
Eichenauer et al, Blood 2014; 123:1658

Therapy-related AML/MDS in GSHG Studies

61 pts with cytogenetic data:

- 19 MLL rearrangements
- 8 chromosome 5/and or 7 aberrations
- 14 complex karyotypes
- 7 normal
- 13 other

AlloSCT



Eichenauer et al, Blood 2014; 123:1658

Advanced-Stage Hodgkin Lymphoma: Treatment

	Cure Rate	t-MN
• ABVD	60-70%	<1%
• Stanford V	60-70%	<1%
• BEACOPP dose-escalated	80-85%	~2%
• PET-guided ABVD	75-80%	?
• A-AVD (Brentuximab)	?	?

Non Hodgkin Lymphoma: CHOP / R-CHOP

Reference	n	Histology	Therapy	t- AML	Time to AML	Median Follow-up	Solid tumor (n)
Andre' Blood 2004	2837	DLBCL (55%)	CHOP-like	12 (0.4%)	40 mths	6.2 yrs	64
Coiffier Blood 2010	197 202	DLBCL elderly	CHOP R-CHOP	2 (1%) 2 (1%)	N.A.	10 yrs	22 21

High-dose therapy and t-MDS/AML

Reference	n	Histology	Therapy	t- MDS/ AML	Time to AML	Median Follow-up	Solid tumor (n)
Montoto Leukemia 2007	401 289	Follicular	HDT (TBI) HDT	34(8.5%) 3 (1%)	5 yrs	10.3 yrs	27
Gyan Blood 2009	80 86	Follicular	CHOP HDT (TBI)	1(1.2%) 6 (7%)		9 yrs	6
Tarella JCO 2011	1024 234 89	B cell Hodgkin T cell	Mitox/Melp BEAM	53(4.5%) (10 yrs)	3.3 yrs	7 yrs	65 (6.8%)
El-Najjar Ann Oncol 2014	2233	Follicular	HDT(TBI) HDT (BEAM)	3.4% 2.8%	4.2 yrs	5.6 yrs	6.3% 5.1%
Waterman, BMT 2012	171	Follicular	BU-CY	7.3% (10 yrs)		4.8 yrs	

Risk factors for secondary AML/MDS after ASCT in NHL:

advanced age
male sex
use of second PBSC harvest

number of chemotherapy cycles (per 1 increase)	**1.7**
> 5 leukaphereses	**18.1**
fludarabine (per 50 mg/m^2 increase)	**1.27**

Tarella et al, J Clin Onocl 2011; 29: 814

Waterman et al, Bone Marrow Transpl 2012; 47: 488

Risk factors for secondary AML/MDS in NHL: G-CSF

SEER- Medicare database:

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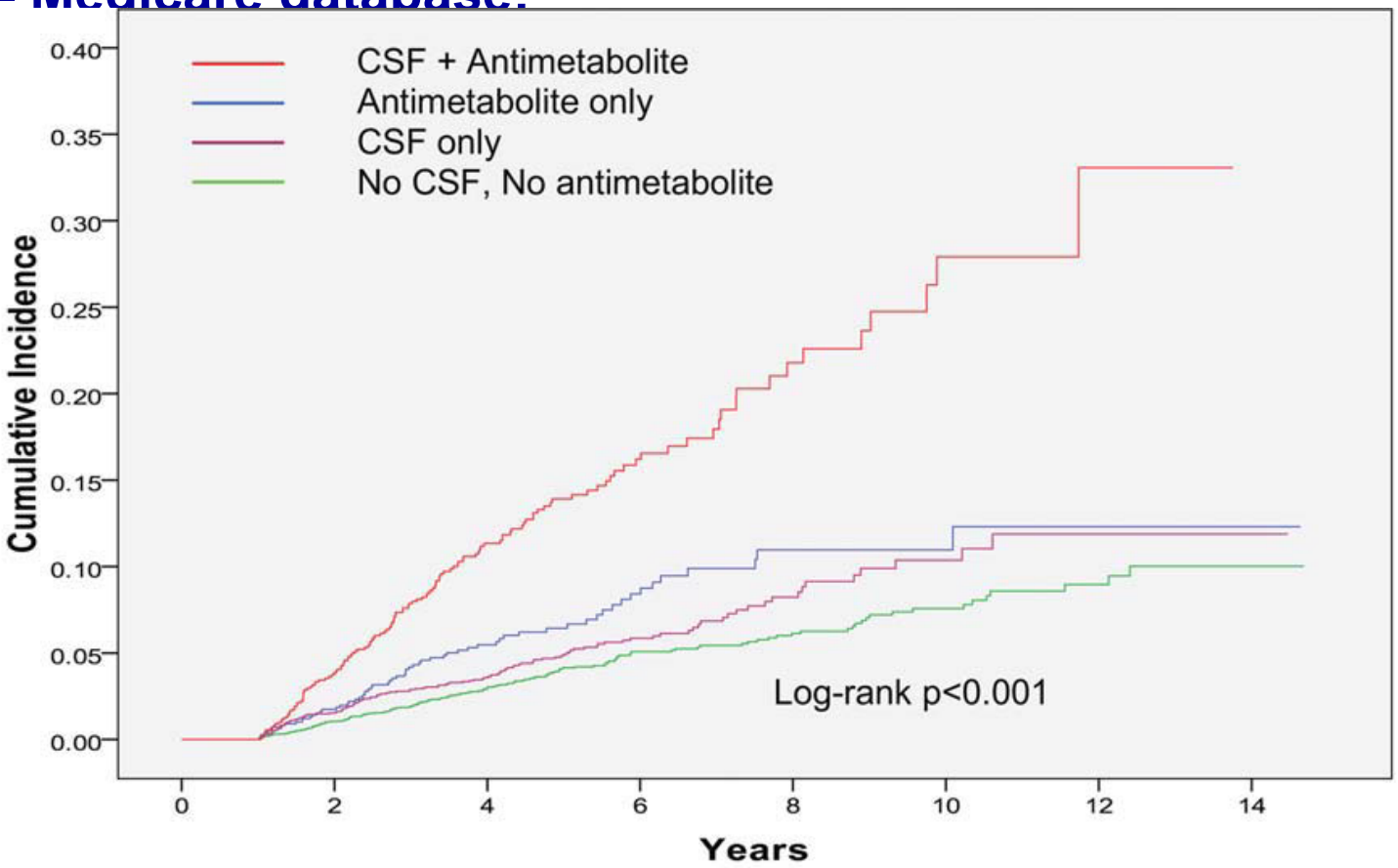

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20(years

G-CSF: HR: 1.71 (1.17 – 2.51)

Lam et al, Leukemia 2016; 30: 1187

Risk factors for secondary AML/MDS in NHL: Fludarabine

Reference (year)	n	Histology	Therapy	t- MDS/ AML	Median Follow-up
McLaughlin et al Blood 2005	202	Indolent	R-FND (6) +CHOP (2)	8 (4%) at 36 mths	4.6 yrs
Leleu et al, JCO 2009	193 136 110	WM	Fludara/ 2-CDA Non- NA No Treat.	3 (1.6%) 0 0	5 yrs
Morrison et al, JCO 2002	191 142 188	CLL	Chlorambucil Chlor.+Fludara Fludarabine	0 5 (3.5%) 1 (0.5%)	4.2 yrs
Tam et al, Blood 2008	300	CLL	FCR	8 (2.8%)	6 yrs

Risk factors for secondary AML/MDS in NHL: Fludarabine

Reference	n	Histology	Therapy	t- MDS/ AML	Median Follow-up
Federico et al JCO 2013	168 165 171	FL	R-CVP R-CHOP R-FM	0 0 4 (2.3%)	2.8 yrs
Benjamini et al Leuk&Lymph 2015	234	CLL	FCR	12 (5.1%)	4.4 yrs
Lam et al 2016	33922	Elderly NHL	Any Fludarabine	150 at 3.2 yrs HR 4.48	

Risk factors for secondary AML/MDS in NHL: Bendamustine

161 patients with low-grade lymphoma and median of 2 previous chemotherapy regimens: 5 MDS, 2 AML, 1 CMML (5%)

Cheson et al, Clin Lymphoma Myeloma Leuk. 2010; 10:452

Still few data despite wide-spread use!

Risk factors for secondary AML/MDS in NHL: Radioimmunotherapy

Y^{90}

Sample	Mass (g)	Disintegrations per minute	Measured activity concentration at the time of biopsy (μCi/g)	Percentage of injected dose/g
Lymph Node	0.011	9633	1.140	0.013
Bone Marrow	0.036	4840	0.175	0.002
Whole Blood	0.108	16,452	0.198	0.002
Buffy Coat	0.093	1325	0.019	0.000
Serum	0.108	30,791	0.371	0.004

Jacobs et al, Mol Imaging Biol 2009

Reference	Disease	Treatment	T-AML	Latency from RIT
Magni et al, Leuk Res 2009 (Y^{90})	DLBCL, M, 48 yo, 2001	6xR-CHOP: CR 2xR-DHAP Z-HDT	Inv(16) (present in PBSC)	5 mths
Focosi et al, Hemat Oncol 2008 (Y^{90})	FL, F, 61yo, 2000	6x ProM-Cytab ESHAP-HDT (2002) R-VABEC /Zevalin	-5,+8, -11, -17, -21	15 mths
Gopal et al, Blood 2003 (I^{131})	27 FL 98 FL	RI-HDT HDT	2 (7.4%) 6 (6.1%)	ca 5 yrs ca 2-3 yrs

Risk factors for secondary AML/MDS in NHL: Radioimmunotherapy (90Y-ibritumomab tiuxetan)

Reference	n	Histology	Therapy	t- MDS/ AML	Time to AML	Median Follow-up
Morschhauser JCO 2013	207 202	FL 1°rem.	CHOP +IT CHOP	7 (4.2%) 1 (0.6%)	4.8 yrs	7.3 yrs
Scholz JCO 2013	59	FL 1°line	IT	0		2.5 yrs
Andrade-Campos EJH 2016	96 144	FL relapsed	IT No IT	2 (2%) 0	4 & 8 yrs	5 yrs
Devizzi JCO 2013	60	Poor-risk NHL	IT +ASCT	9.4% (8 yrs)		5.9 yrs
Reiss Leuk Lymph 2015	25 35	FL 1°line	CVP +IT Flu +IT	2 (8%) 5 (14%)		11 yrs
Casadei Cancer Med 2016	55	FL	FMR +IT	4 (7.3%)	3.5 yrs	7 yrs

Non Hodgkin Lymphoma:
Addition of Biologic Agents to standard R-CHOP?

R-CHOP

+Lenalidomide?

+Bortezomib?

+Ibrutinib?

Will this have an impact on sAML risk ??

Risk factors for secondary AML/MDS in NHL: Autoimmune Diseases /Infections

SEER-Medicare database:

33,922 patients aged 66-83 years with NHL diagnosis between 2000 -2009
150 pts with second AML/MDS, median interval 3.2 years

Increased sAML/MDS risk

Autoimmune diseases prior to NHL: 1.5-2 fold

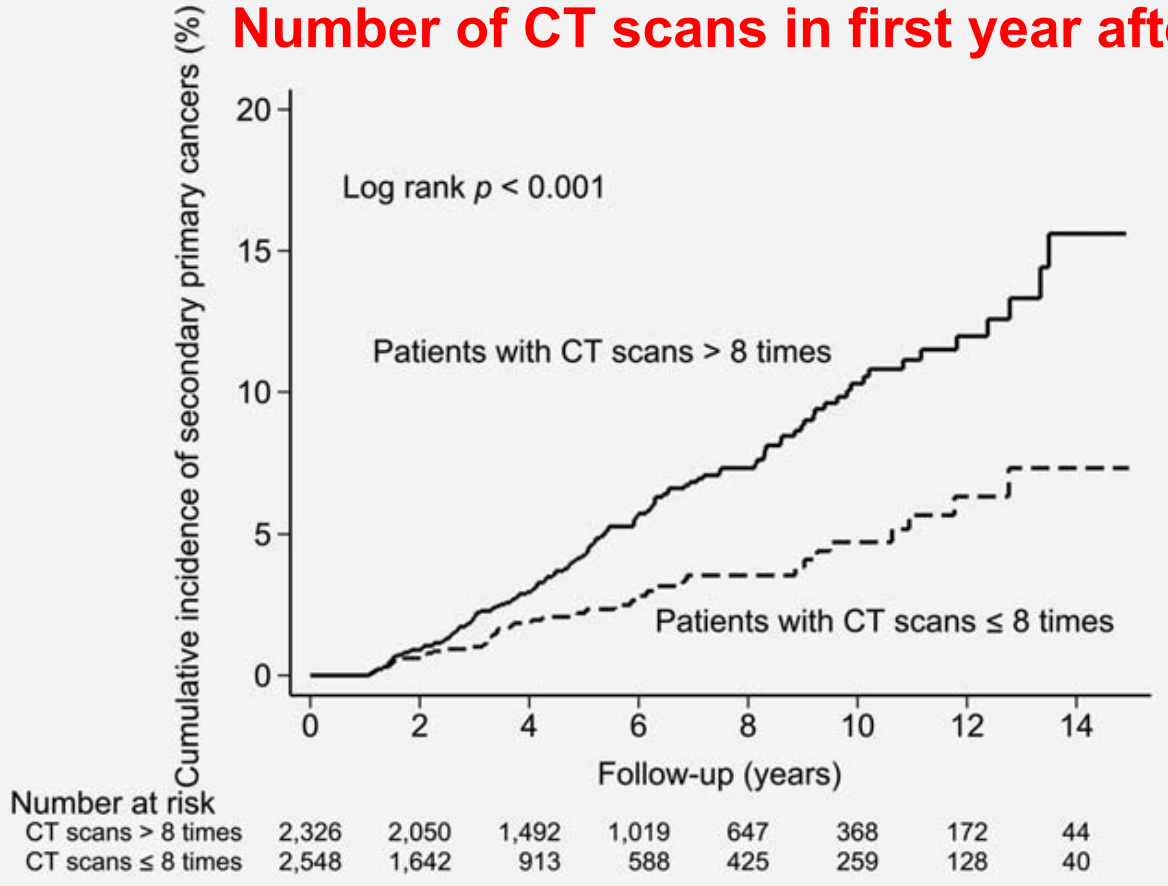
Infections

prior to NHL: Herpes zoster	**1.9 fold**
after NHL: respiratory	**1.5-2 fold**
urinary tract	**1.8-fold**
gastrointestinal	**1.8**
prostatitis	**2.6**

Lam et al, Leukemia 2016; 30: 1187

Risk factors for secondary cancers in NHL: Frequency of Surveillance CT scans

Number of CT scans in first year after diagnosis



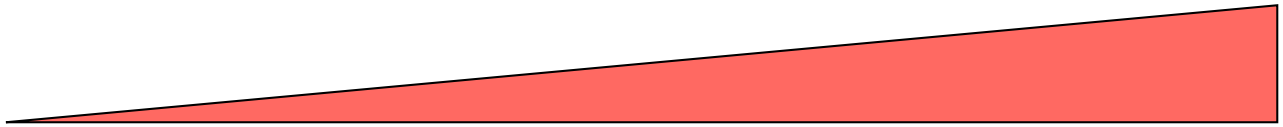
HR 2.25
(95% C.I. 1.61-31-13)

HR:
Breast: 11.22
Stomach 5.22
Liver/Biliary: 2.18

Leukemia: not significant

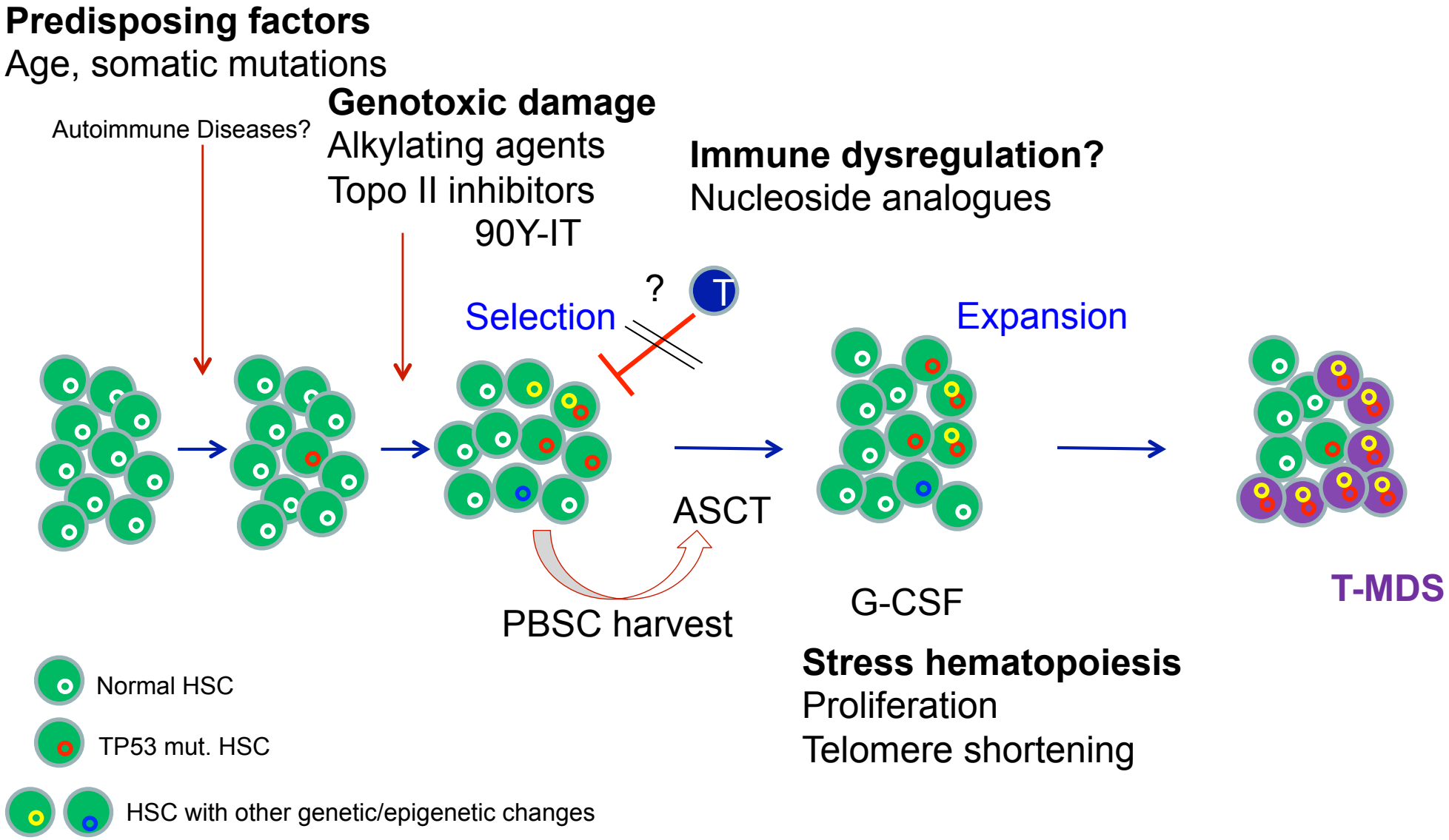
Chien et al, Int J Cancer 2015; 137: 658

Risk of Therapy-related MDS AML in Hematological Malignancies



Disease	Low <2%	Intermediate 2-5%	High 5-10%	Very high >10%
Hodgkin	ABVD	MOPP-RT IF BEACOPP		MOPP-RT EF
CLL/WM		Alkyl. Agents Bendamustine Fludarabine	Nucl. Analog. +Alkyl. Agents	
LNH	CHOP	90Y-IT	Nucl. Analog. +90Y-IT HDT-TBI	

Integrating Epidemiological Data on t-MN in Lymphoproliferative Diseases into a Model of Secondary Leukemogenesis



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