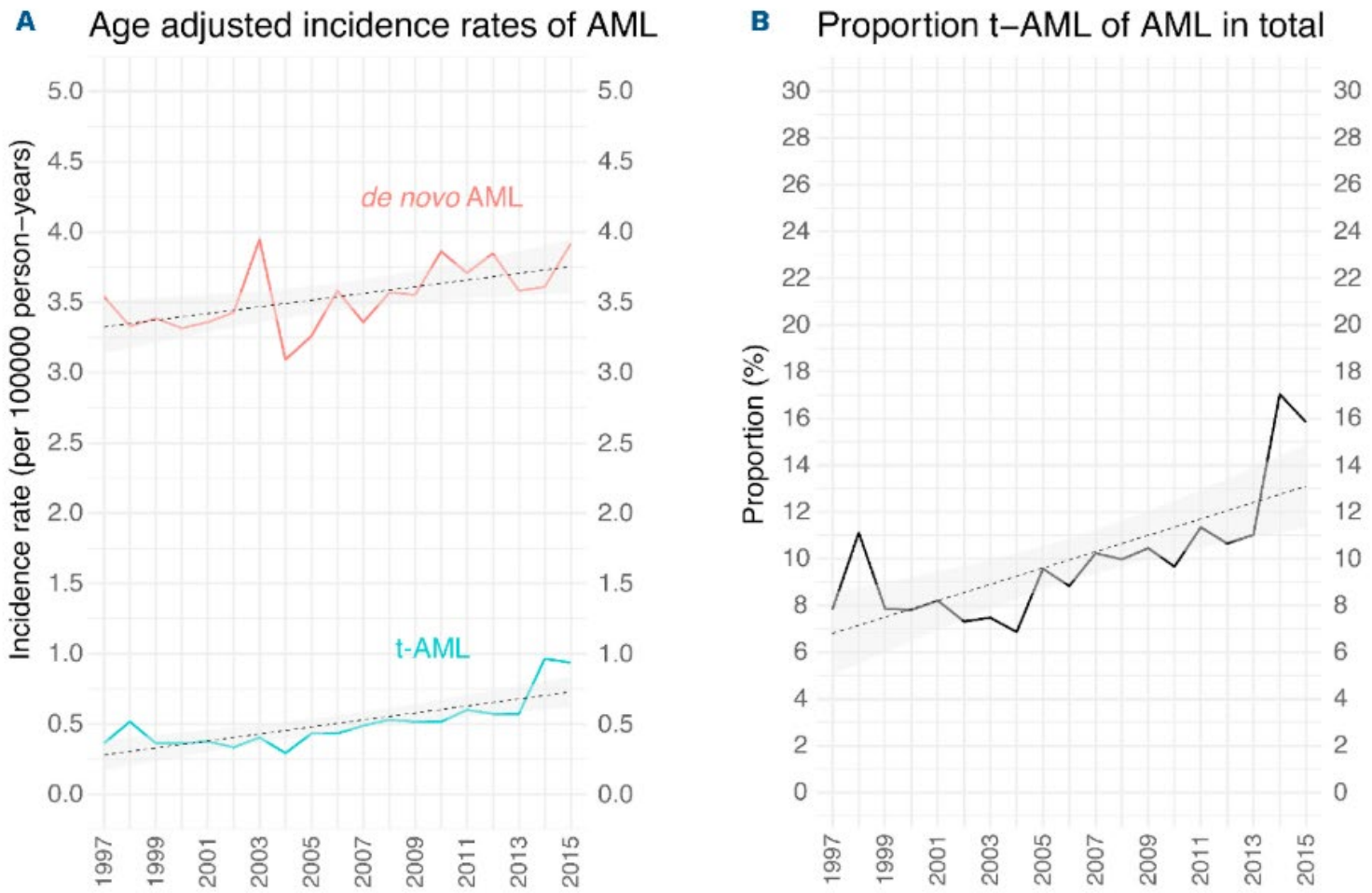
AML secondary to Hematologic malignancies (topo-II inhibitors, lenalidomide, autologous transplantation)

Sylvain Garciaz, MD-PhD

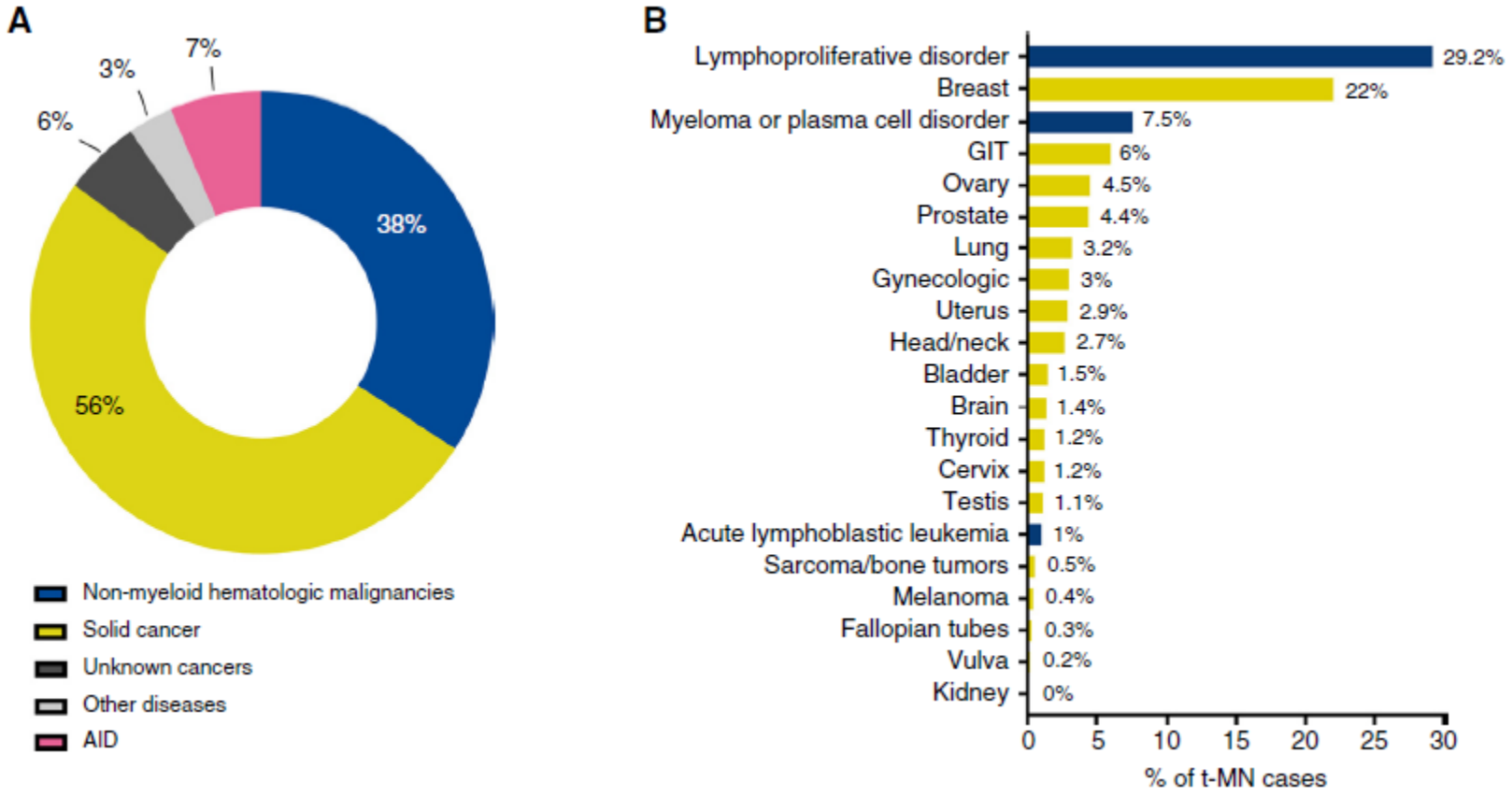
Institut Paoli-Calmettes, Marseille, France

Incidence of t-AML is increasing



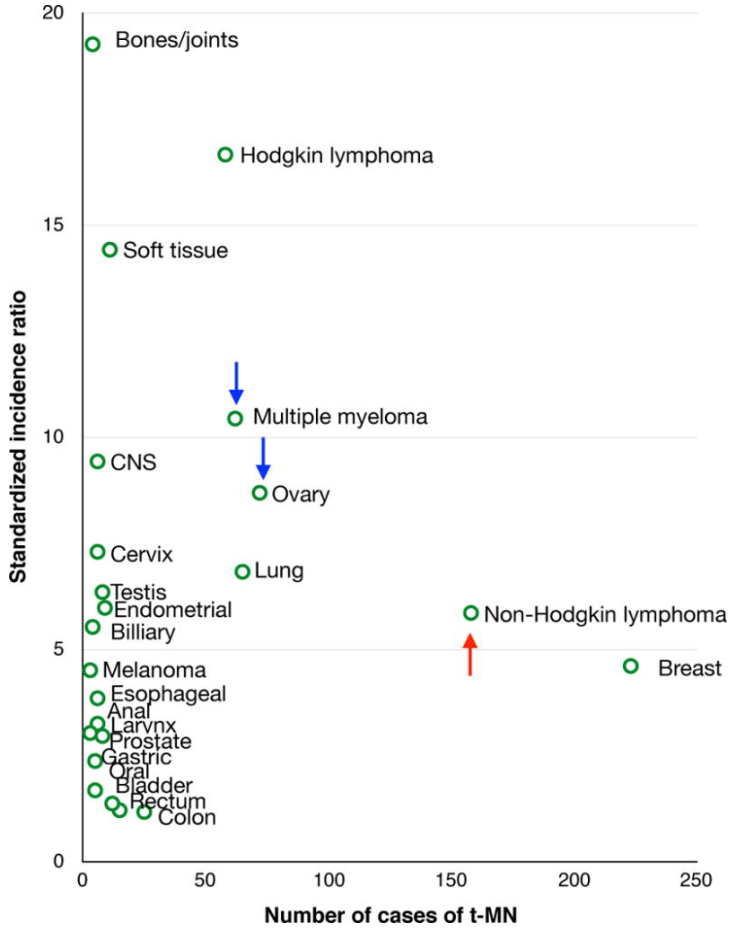
Nillson K, Haematologica 2023

40% of the t-AML are secondary to lymphoid malignancies



Singhal D. Blood Cancer Discov. 2024

Less AML secondary to myeloma and Hodgkin lymphoma



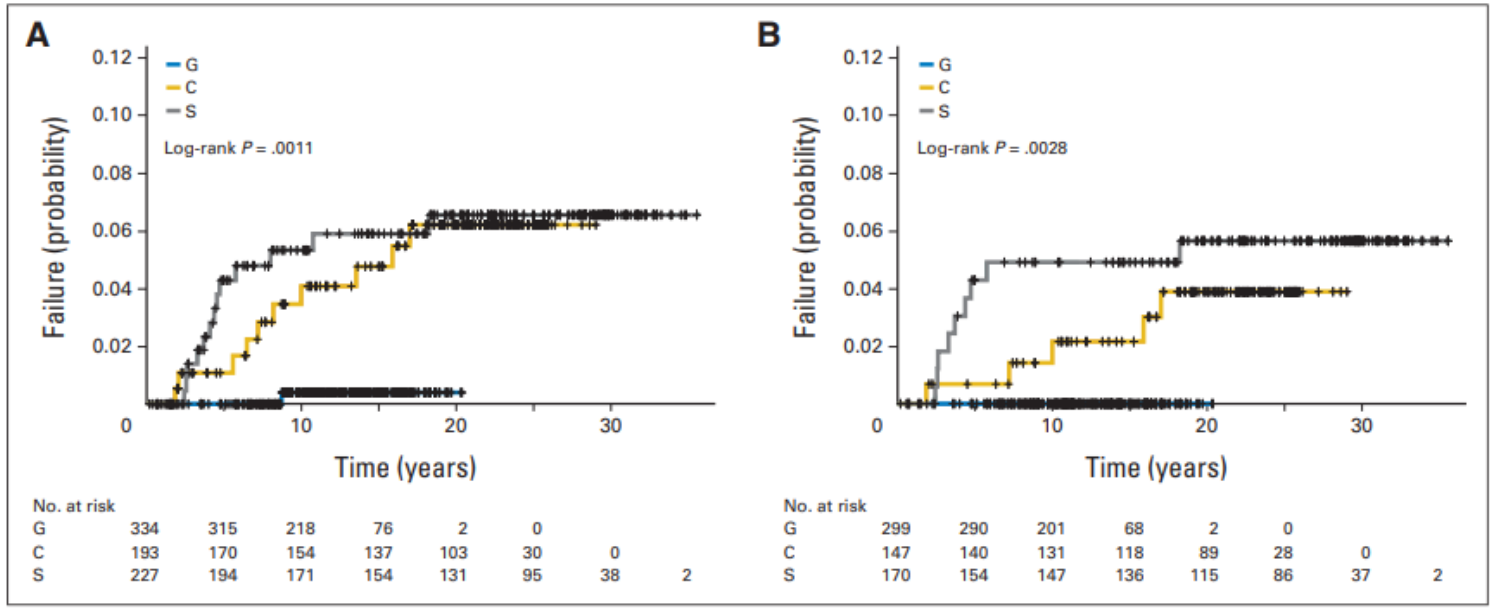
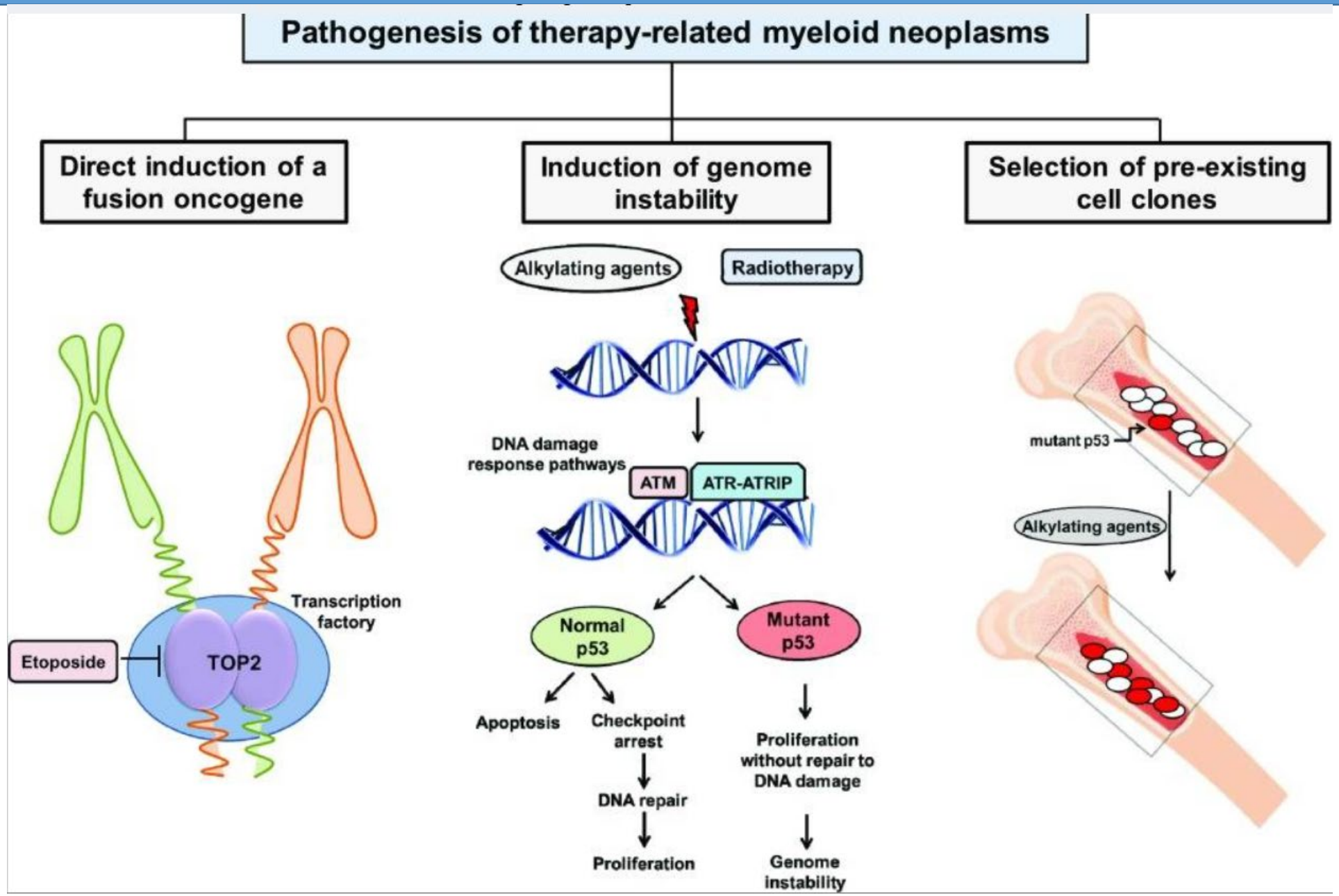


Fig 3. (A) Incidence of therapy-related acute myeloid leukemia/myelodysplastic syndrome (t-AML/MDS) in the G, C, and S studies. (B) Incidence of t-AML/MDS after primary therapy in the G, C, and S studies.

McNerney ME et al. Nat Rev Cancer 2017
Morton L et al., Blood 2013
Koontz, JCO 2013



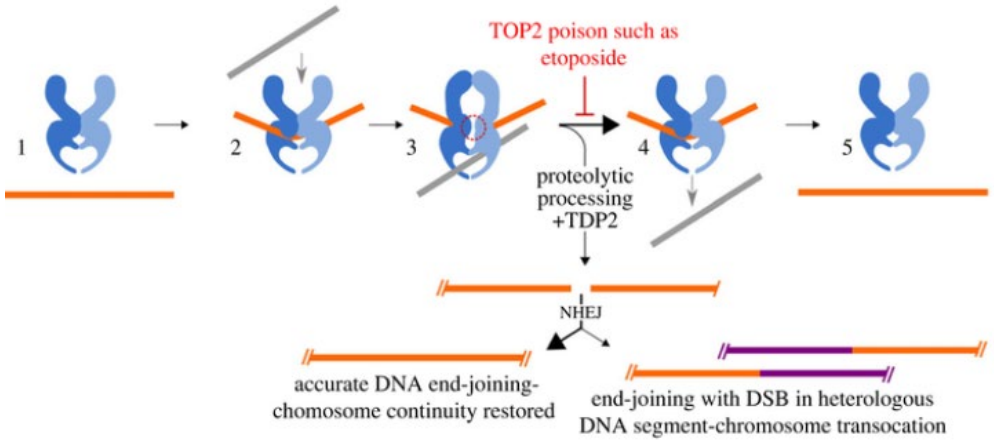
Heuser et al. 2016

Two types of t-AML

Fréquence	75%	25%
Prior exposition	Alkylating agents	Topo II inh.
Prior MDS	+++	-
Latency	5-10 yrs	2-3 yrs
Karyotype	Adverse complex, 5/7 Abn	KMT2A-r t(15;17), t(8;21), inv16
Prognosis	Adverse	favorable
Mechanism	Clonal selections TP53, spliceosome mut… (Wong, *Nature* 2015)	Recurrent translocations (ex. anthracyclins & t-APL, Grimwade, *Blood* 2010)

Adapted from Deschler & Lübbert, Cancer 2006

Mechanism



- TOP2 induces a double-strand break during DNA replication and can link 2 DNA strands together after replication.
- TOP2 inhibitors stabilize the double-strand break and delay the ligation of the free DNA ends.
- The free DNA end can thus more easily recombine with DNA from another chromosome.

Gene	Translocation	Partner	References
	t(8;21)(q22;q22)	*ETO* (***RUNX1T1***)	[13,14,19,20,21]
AML1 (***RUNX1***)	t(3;21)(q26.2;q22)	*MDS1-EVI1* (***MECOM***, *PRDM3*)	[22,23]
	t(1;21)(p36;q21)	***PRDM16***	[24,25]
	t(9;11)(p22;q23)	*AF9* (***MLLT3***)	[14,20]
	t(4;11)(q21;q23)	*AF4* (***AFF1***, *MLLT2*)	[26,27]
MLL (***KMT2A***)	t(19;11)(q13;q23)	***ELL***	[20,28]
	t(11;19)(q23;p13.3)	*ENL* (***MLLT1***)	[20,28,29]
	t(11;16)(q23;p13)	***CREBBP***	[30,31,32]

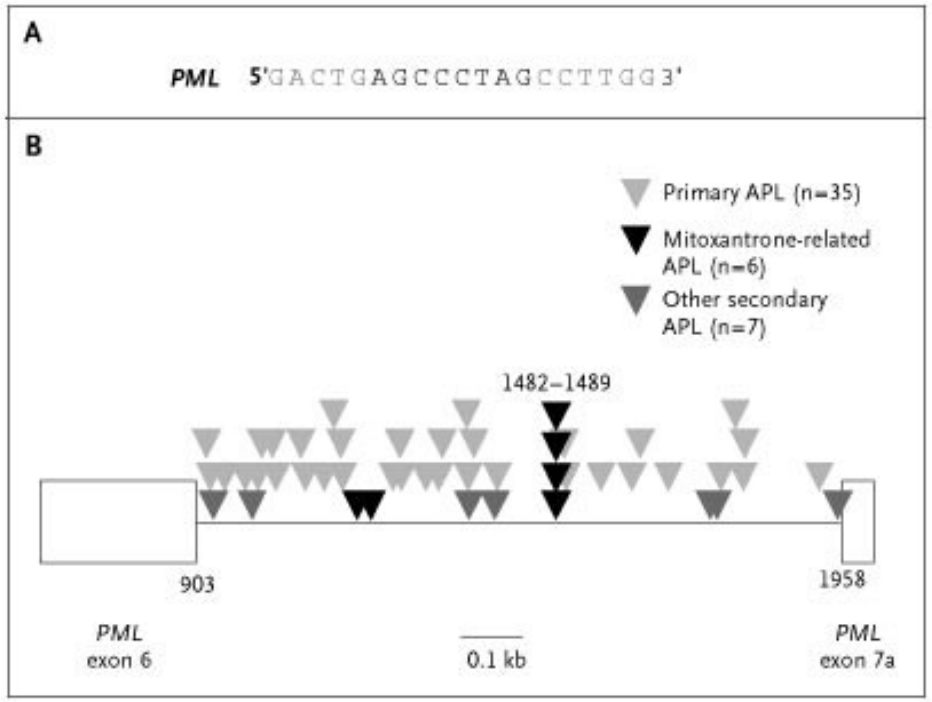
→**balanced aberrations** with a rearrangement, but no gain or loss, of chromosomal material.

Lomov et al. Int. J. Mol Science 2022

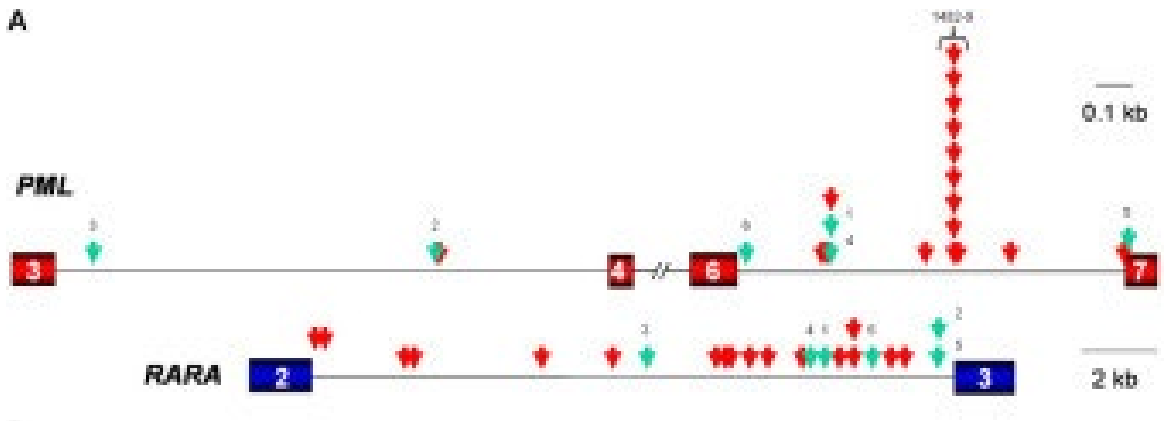
Anthracyclin and APL

- Breakpoints fall within previously identified breakpoint clusters
- Distribution are skewed compared to the distribution of *de novo* AML breakpoints.

Mitoxanthrone



Epirubicine



Mistry et al., NEJM 2005
Mays AN et al. Blood 2010
Hasan et al. Bood 2008

Outcomes of t-APL

Reference	Patient #	Age yrs median (range)	Male: female	Primary disease	Rx for primary	Rx for APL
Pulsoni[3]	51	57 (27-76)	17:34	Breast 15 Lymphoma 12 Female reproductive 9 Others 15	Surgery 14 Chemo 10 RT 17 Chemo + RT 10	AIDA 31; ATRA alone 8; Other chemo 12
Beaumont[5]	106	55 (12-82)	28:78	Breast 60 Lymphoma 15 Other cancers 29 MS 1 Other disease 1	Chemo 30 RT 27 Chemo + RT 49	ATRA + chemo 83 Chemo alone 16
Hasan[4]	14	40 (27-67)	6:8	MS 12	Mitoxantrone 12 Other 2	ATRA + chemo 13 NA 1
Dayyani[6]	29	54 (35-81)	15:14	Breast 9 Prostate 5 Lymphoma 4	Chemo 6 RT 10 Chemo + RT 13	ATRA + chemo 10 ATRA + ATO 19

ATRA: all trans retinoic acid; RT: radiation therapy; AIDA: ATRA plus idarubicin; NA: not available; ATO: arsenic trioxide

- CR rate = 89% with ATO (vs 85% in de novo APL) and 3-year OS = 65%
- ATRA and arsenic trioxide should be considered the standard of care in low- and intermediate-risk APL patients, independent of the etiology

Ravandi F. et al Haematologica 2010
Dayyani F. Cancer 2010

CBF t-AML

Study	Number of patients	CR rate	Overall survival
Gustafson et al	13 t(8;21) t-AML	91% vs 95%	Median OS= 19 mo vs >37 mo
Krauth et al	16 t(8;21) t-AML	-	2-y OS=46.8% vs 76.4%
Kayser et al	18 t(8;21) t-AML 15 with inv(16)	equivalent	Equivalent for t(8;21) Lower for inv(16)
Borthakur et al	13 with inv(16), 4 with t(8;21)	92%	1.9 y vs > 5y

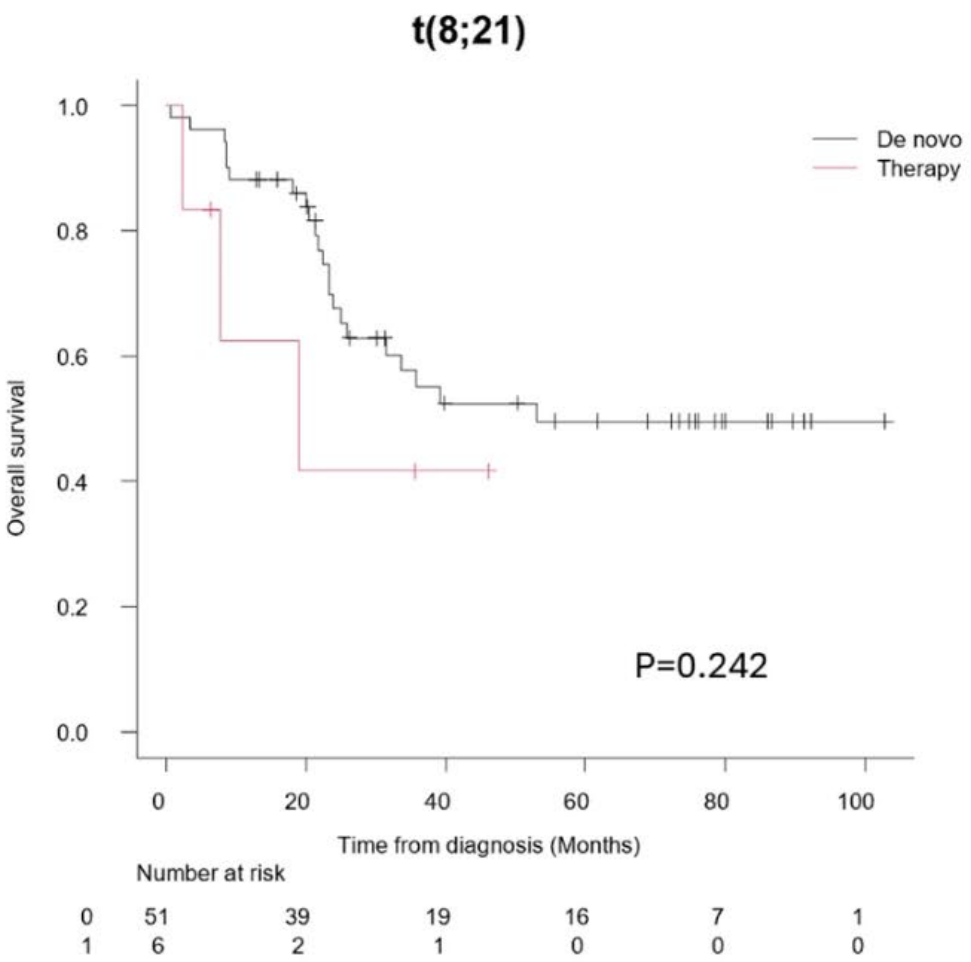
Chiu M. et al. Blood Cancer Journal 2023

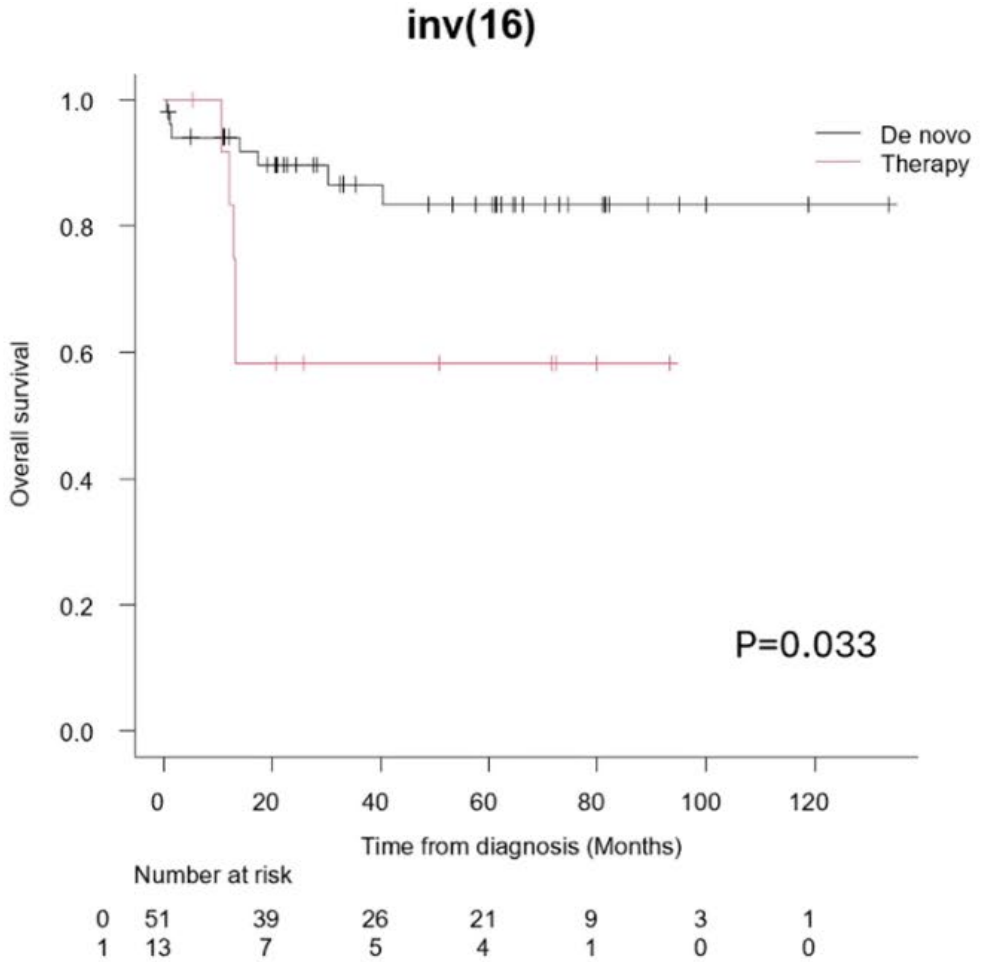
CBF t-AML in the MRD era

- 136 CBF-AML → 25 (18.4%) had t-CBF-AML.
- 20% had prior history of cancers
  - Lymphoma (*n* = 8, 29.6%)
  - breast (*n* = 7, 25.9%)
- Therapy-related patients were older (median age of 64 vs. 48 years in dn-CBF-AML, *p* = 0.001) and predominantly female (68% vs. 36%, *p* = 0.03)
- Mutations frequently associated with therapy-related AML, including TP53, PTPN11 and PPM1D, were not found in our t-CBF-AML cohort.
- 80% achieved MRD ≥ 3LR at EOT (no ≠ between t-AML and de novo)

Chiu M. et al. Blood Cancer Journal 2023

CBF t-AML in the MRD era





Chiu M. et al. Blood Cancer Journal 2023

t-AML with t(9;11); KMT2A-MLLT3

- 180 AML patients with 11q23 translocations →16% were therapy related
- Secondary AML (including t-AML and AML after MDS) was an independent negative risk factor for OS
- Favorable impact of allogeneic HCT
- Allogeneic HCT in first CR should be recommended for eligible t-AML patients with t(9;11).

Krauter J, JCO 2009

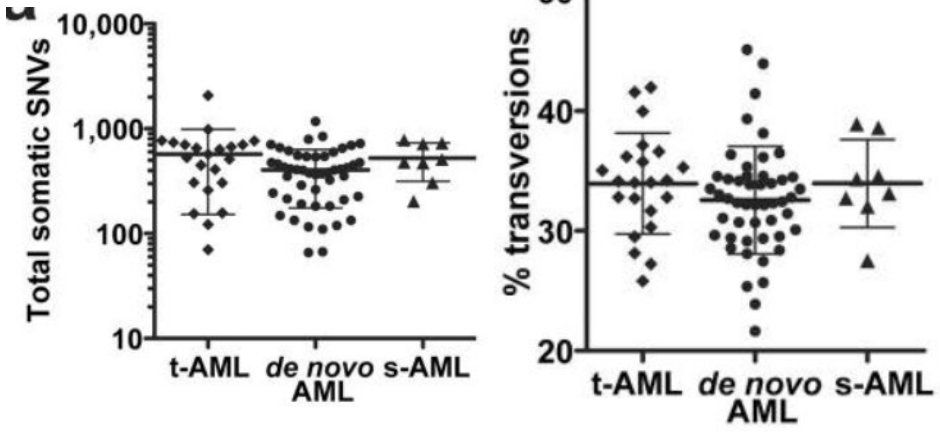
Two types of t-AML

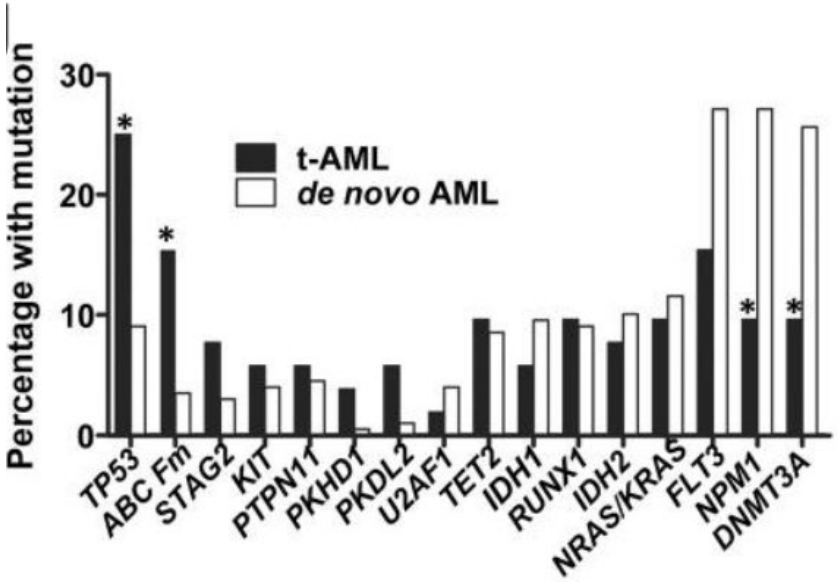
Fréquence	75%	25%
Prior exposition	Alkylating agents	Topo II inh.
Prior MDS	+++	-
Latency	5-10 yrs	2-3 yrs
Karyotype	Adverse complex, 5/7 Abn	Favorable t(15;17), t(8;21), inv16
Prognosis	Adverse	favorable
Mechanism	Clonal selections TP53, spliceosome mut… (Wong, *Nature* 2015)	Recurrent translocations (ex. anthracyclins & t-APL, Grimwade, *Blood* 2010)

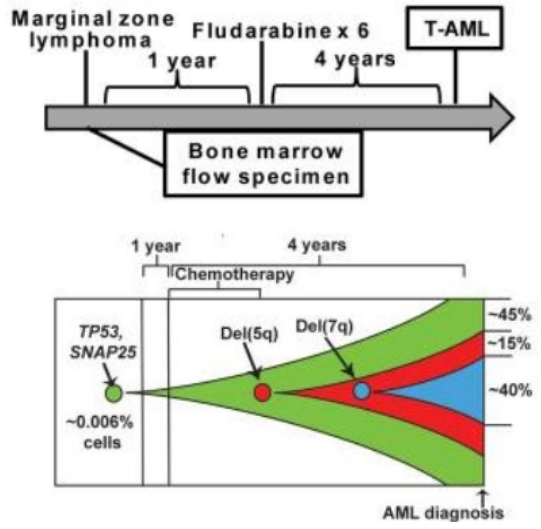
Adapted from Deschler & Lübbert, Cancer 2006

Genetic instability or clonal selection?

- Complex caryotype + 5q and/or 7q abn → 70% of t-AML vs 20% of de novo AML
- 3.46 copy number alterations (CNAs) in *t*-AML compared with 1.9 CNAs in de novo AML (Ithzar N. PLoS One 2011)



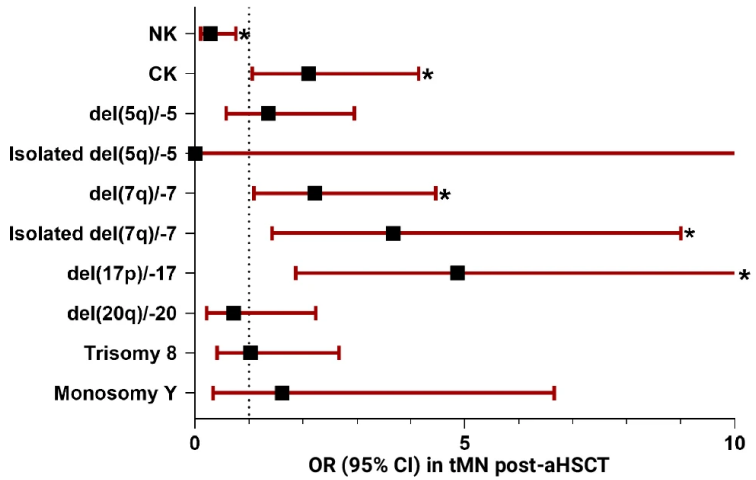


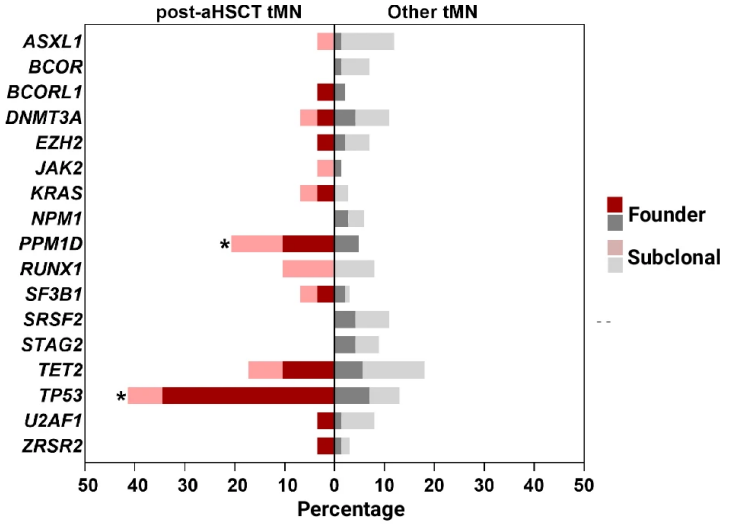


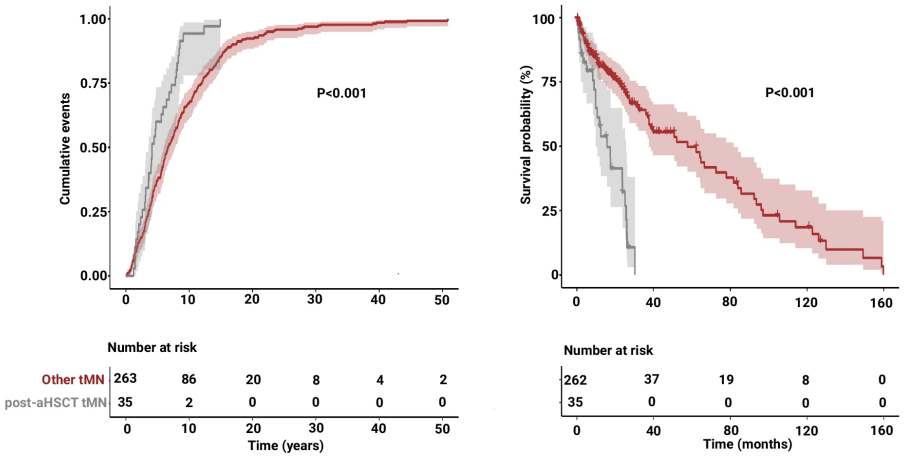
Wong et al. Nat 2015

Post-ASCT myeloid neoplasms (MN)

- Cohort of 1507 patients who underwent aHSCT. With a median follow-up of 4.4 years (IQR 2.3–7.5), 35 patients (2.3%) developed a tMN at a median time of 2.6 years (IQR 1.4–4.3) after transplant.



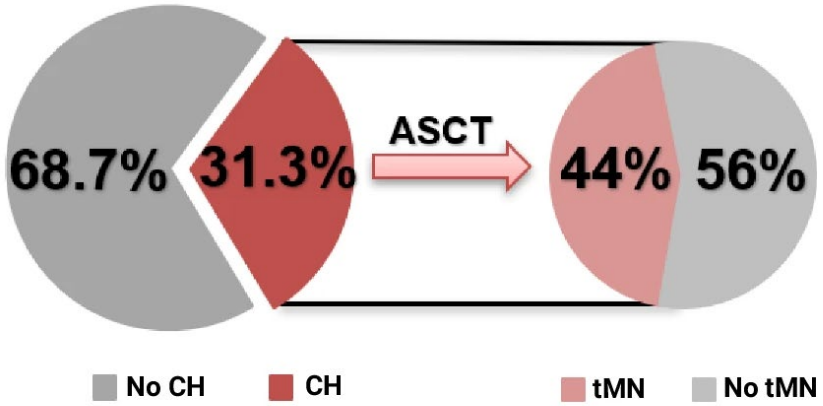


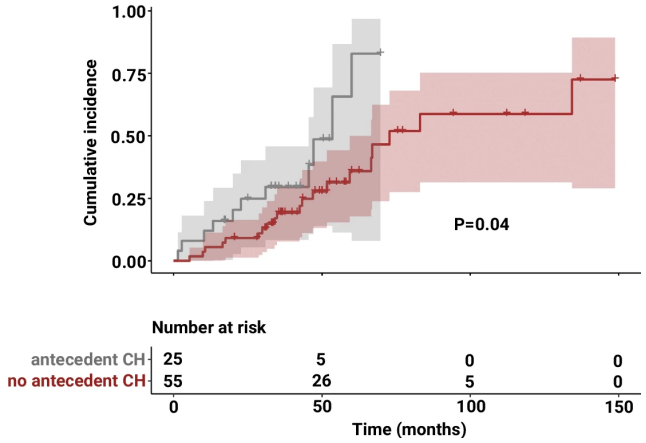


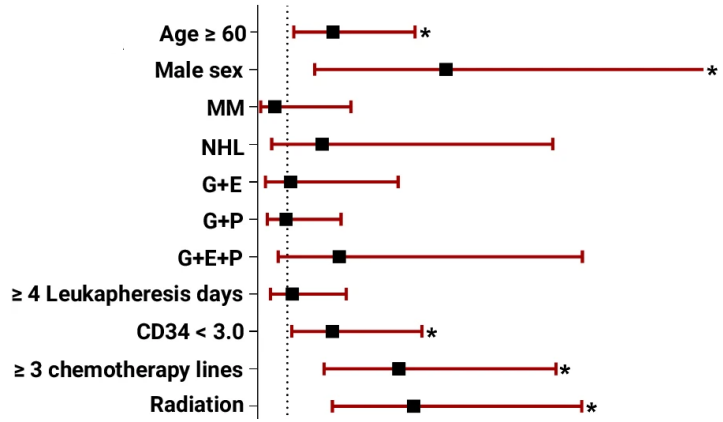
Post ASCT AML are associated with adverse risk and poor outcomes

Awada, H., et al *Leukemia*, 2024

Clonal hematopoiesis (CH) before ASCT



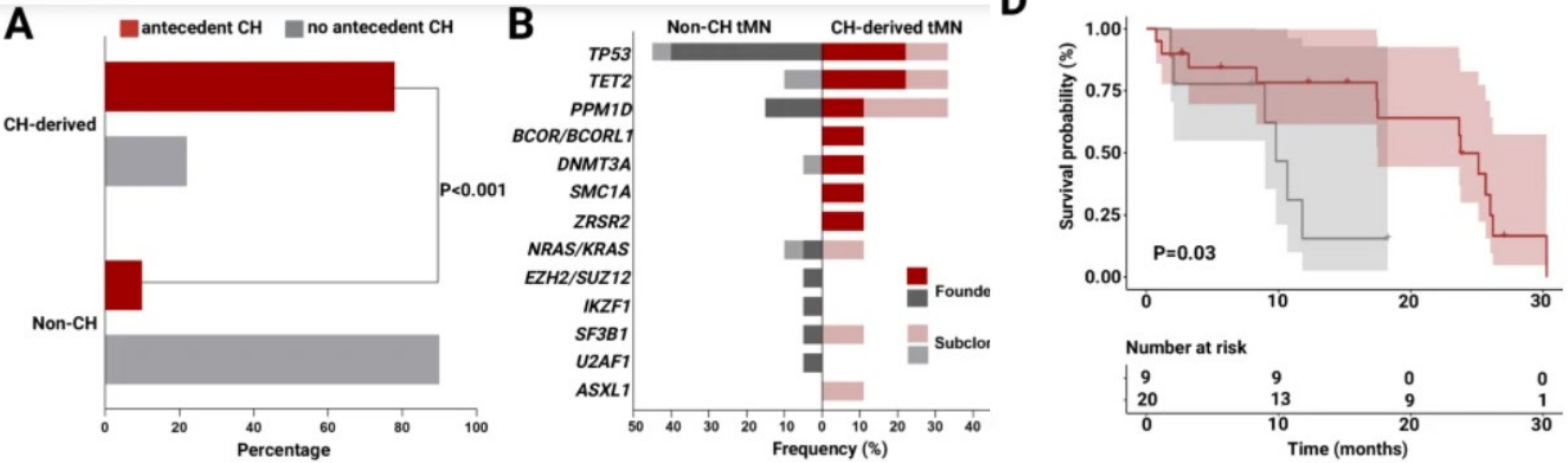




CHIP is often present pre ASCT and associated with severe post ASCT AML

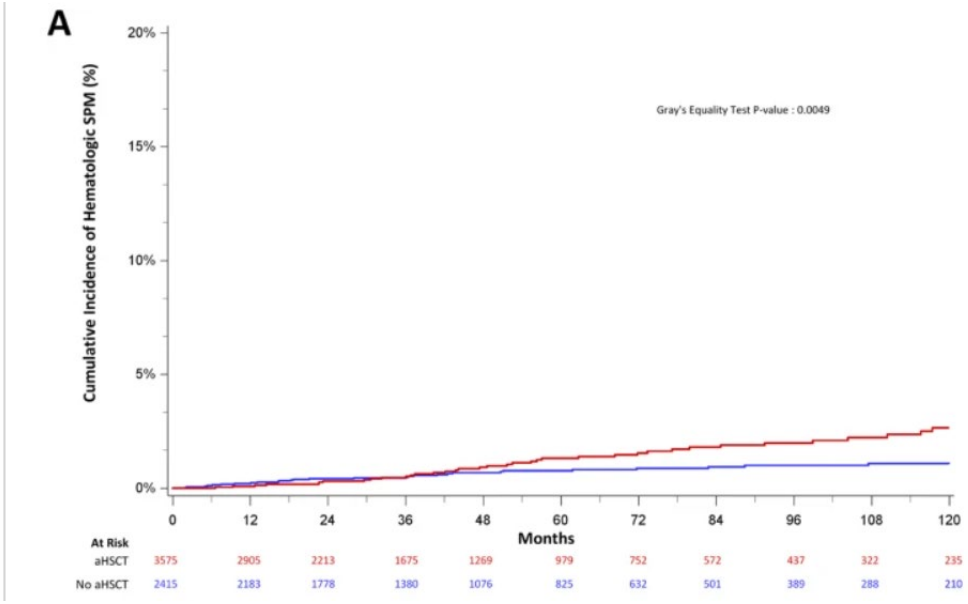
Awada, H., et al *Leukemia*, 2024

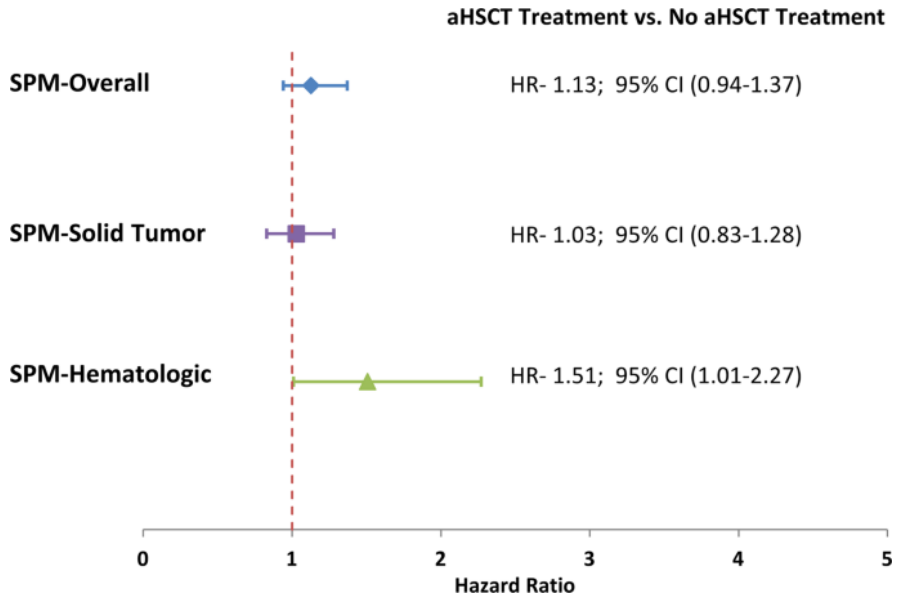
Characteristics of CH-derived t-MN



Awada, H., et al *Leukemia*, 2024

Incidence of t-AML secondary to ASCT in the myeloma treatment

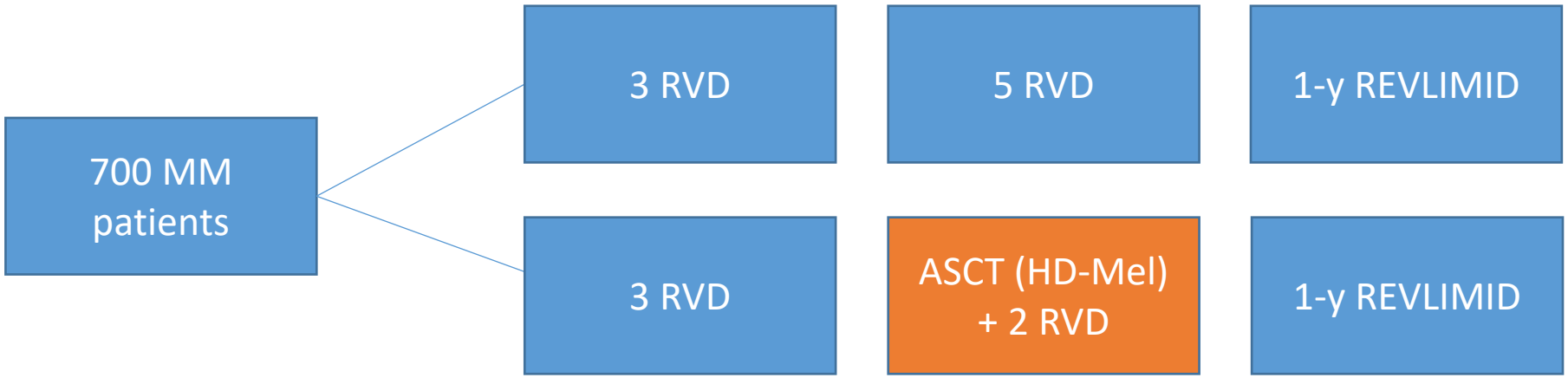




- Second primary malignancy rates 5 years after ASCT were very similar between the Mel140 (4.8%; 95% CI: 1.1–8.5) and Mel200 groups (4.8%; 95% CI: 3.6–6.0) (*P*=0.61).

Rosenberg AS. Blood Cancer Journal 2021
Auner HW. Et al. Haematologica 2018

Phase III study randomizing ASCT



- No significant difference in the incidence of invasive second primary cancers (P=0.36). Five cases of acute myeloid leukemia occurred: 1 in the RVD-alone group, and 4 in the transplantation group (P=0.21).

Attal M et al. NEJM 2016

Impact of ASCT in lymphoma

- Risk between 5-15%
- Risk factors Impact of TBI +++
  - Older age
  - Prior RT
- Less impact of BEAM regimen compared with TBI

Stone RM, JCO 1994, Darrington JCO 1994, Pedersen-Bjergaard J Blood 1997, Friedberg JCO 1999, Milligan DW BJH 2001, Pedersen-Bjergaard, Blood 2000, Harrison CN, BJC 1999, Pedersen-Bjergaard, Leukemia 1997

Lenalidomide and t-AML

- Mechanism of action

→Lenalidomide's **immunosuppressive activity**, and its effects on the tumor microenvironment, may favor the escape/ growth of abnormal clones that could result in t-AML/MDS development

→Inhibition of cereblon/DDB1 complex by lenalidomide impairs repair mechanisms after melphalan-induced **DNA damage**, and could therefore facilitate the development of t-AML/MDS

Lenalidomide consolidation after ASCT

- Large, phase III, randomized trials (IFM 2005-002, CALGB 100104, MM-015),
- Significantly increased incidence of secondary malignancies in newly diagnosed patients with MM who received lenalidomide maintenance versus similar patients who did not receive lenalidomide maintenance after either ASCT
- 3.1 per 100 patient-years in the lenalidomide group versus 1.2 per 100 patient-years in the placebo group (P=0.002) Attal et al NEJM 2012

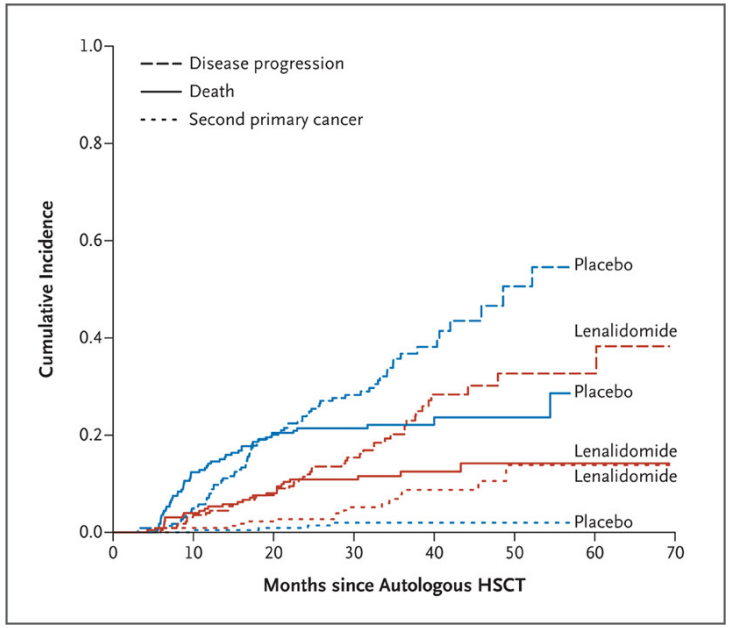
Lenalidomide consolidation after ASCT

Table 4. Types of Lesions in Patients with at Least One Second Primary Cancer.*

Type of Lesion	Lenalidomide Group (N=306)	Placebo Group (N=302)	Total (N=608)
	number of patients (percent)		
Hematologic cancers	13 (4)	5 (2)	18 (3)
AML or MDS	5	4	
ALL	3	0	
Hodgkin's lymphoma	4	0	
Non-Hodgkin's lymphoma	1	1	
Solid tumors	10 (3)	4 (1)	14 (2)
Esophageal	1	0	
Colon	3	0	
Prostate	2	1	
Breast	2	0	
Lung	0	1	
Sinus	1	0	
Kidney	1	1	
Melanoma	0	1	
Nonmelanoma skin cancers	5 (2)	3 (1)	8 (1)
Total	26 (8)	11 (4)	37 (6)

Table 3. Second Primary Cancers from Randomization to February 2012.

Second Cancer	Lenalidomide (N=231)	Placebo (N=229)
	number of patients	
Hematologic cancers*		
Acute lymphoblastic leukemia	1	0
Acute myeloid leukemia	5	0
Hodgkin's lymphoma	1	0
Myelodysplastic syndrome	1	0
Non-Hodgkin's lymphoma	0	1
Total	8	1
Solid-tumor cancers		
Breast cancer	3	0
Carcinoid tumor	0	1
Central nervous system cancer	1	0
Gastrointestinal cancer	2	1
Gynecologic cancer	1	1
Malignant melanoma	1	2
Prostate cancer	1	0
Thyroid cancer	1	0
Total	10	5
Basal-cell carcinoma	2	1
Squamous-cell carcinoma	2	2

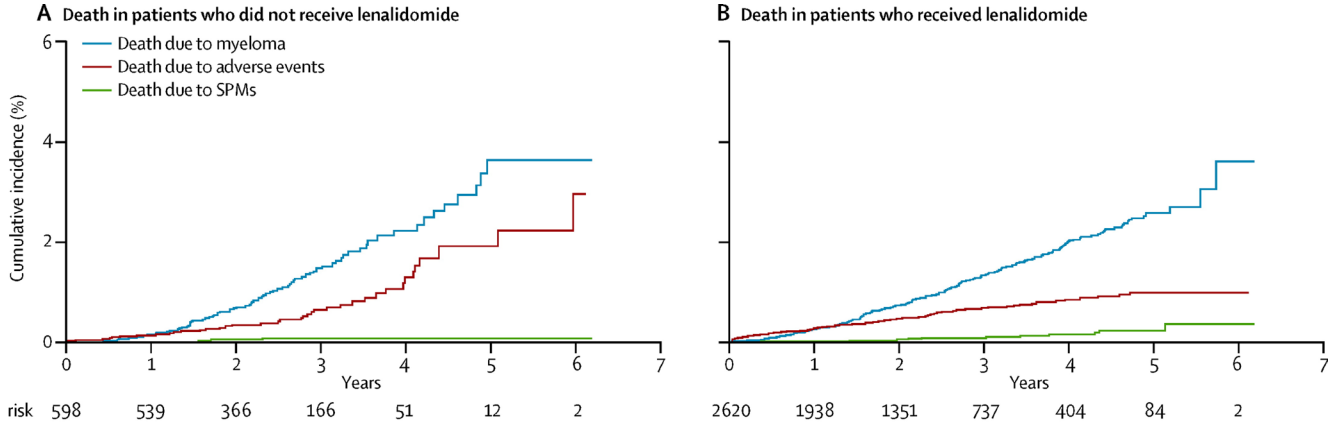


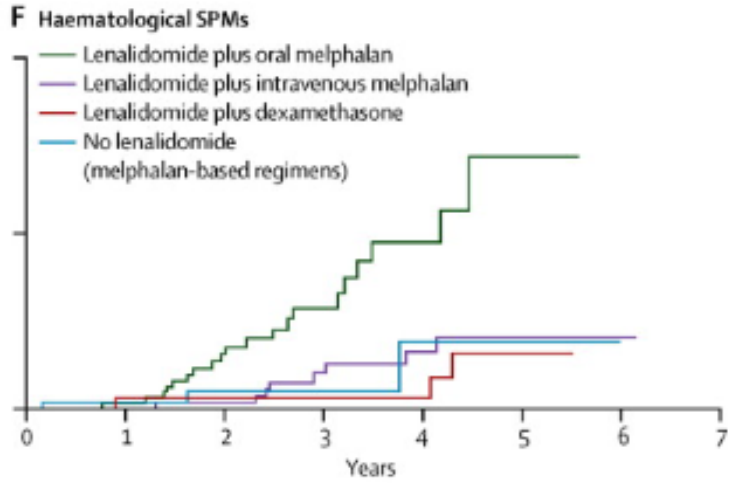
Attal et al NEJM 2012
McCarthy et al. NEJM 2012
Hlostein SA. Lancet Haematol 2018

Metanalysis

	3-year cumulative incidence		5-year cumulative incidence	
	Lenalidomide	**No lenalidomide**	**Lenalidomide**	**No lenalidomide**
SPMs				
Overall	3·9% (3·0–4·9)	3·3% (1·7–4·9)	6·9% (5·3–8·5)	4·8% (2·0–7·6)
Solid	2·6% (1·8–3·3)	2·9% (1·4–4·4)	3·8% (2·7–4·9)	3·4% (1·6–5·2)
Haematological	1·4% (0·8–2·0)	0·4% (0·0–0·9)	3·1% (1·9–4·3)	1·4% (0·0–3·6)
Death				
All causes	23·5% (21·4–25·7)	24·8% (20·6–29·6)	47·0% (43·1–51·1)	68·2% (56·9–78·9)
Myeloma	13·3% (11·6–15·1)	14·6% (11·0–18·3)	25·6% (22·4–28·8)	36·3% (25·9–46·6)
Adverse events	6·7% (5·5–7·9)	6·4% (3·8–8·9)	9·8% (8·0–11·6)	19·2% (12·1–26·3)
SPMs	1·0% (0·5–1·5)	0·7% (0·0–1·5)	2·4% (1·3–3·5)	0·7% (0·0–1·5)

Data are % (95% CI). SPM=second primary malignancy.

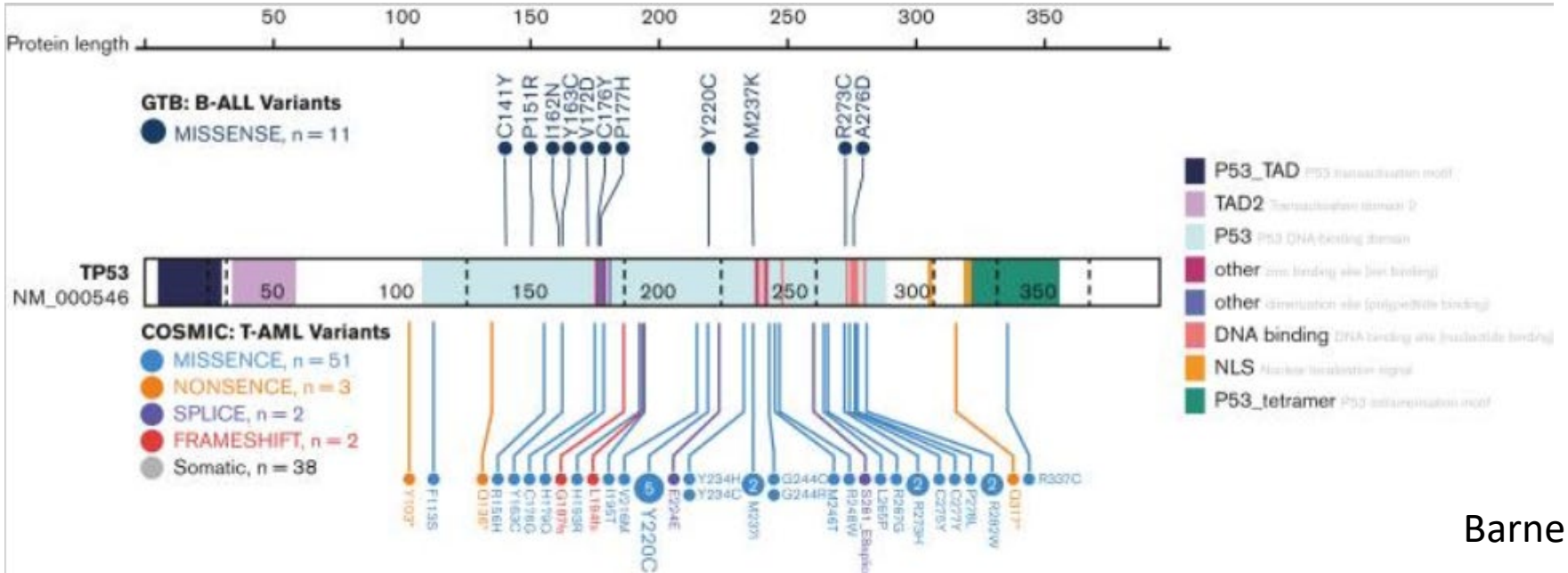




Palumbo et al. 2014

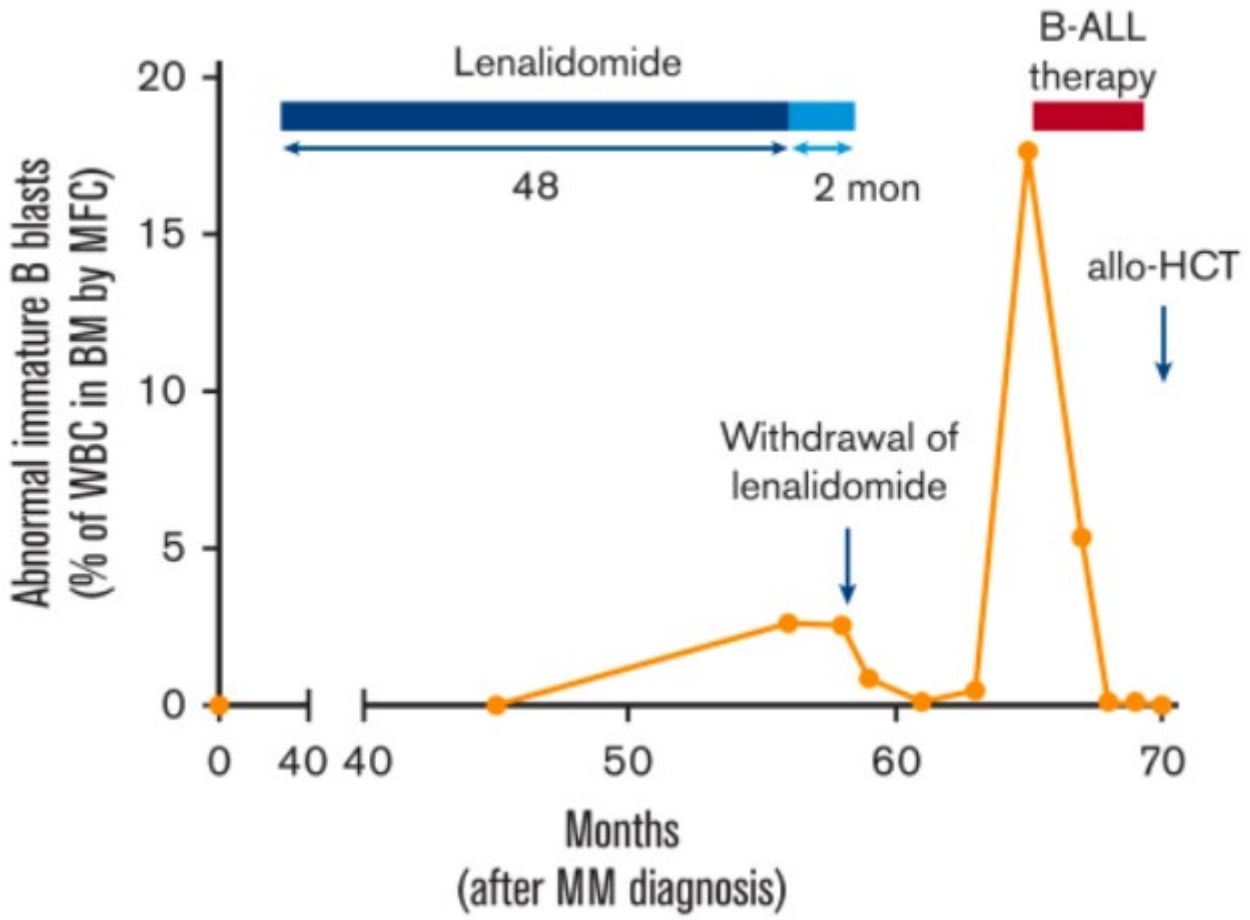
Lenalidomide and B-ALL

- Clonal selection of TP53mut clones
- 14 of the 17 patients (82%) harbored at least 1 somatic *TP53* mutation
- The incidence of *TP53* variants in de novo adult B-ALL varies between 2% and 15%.



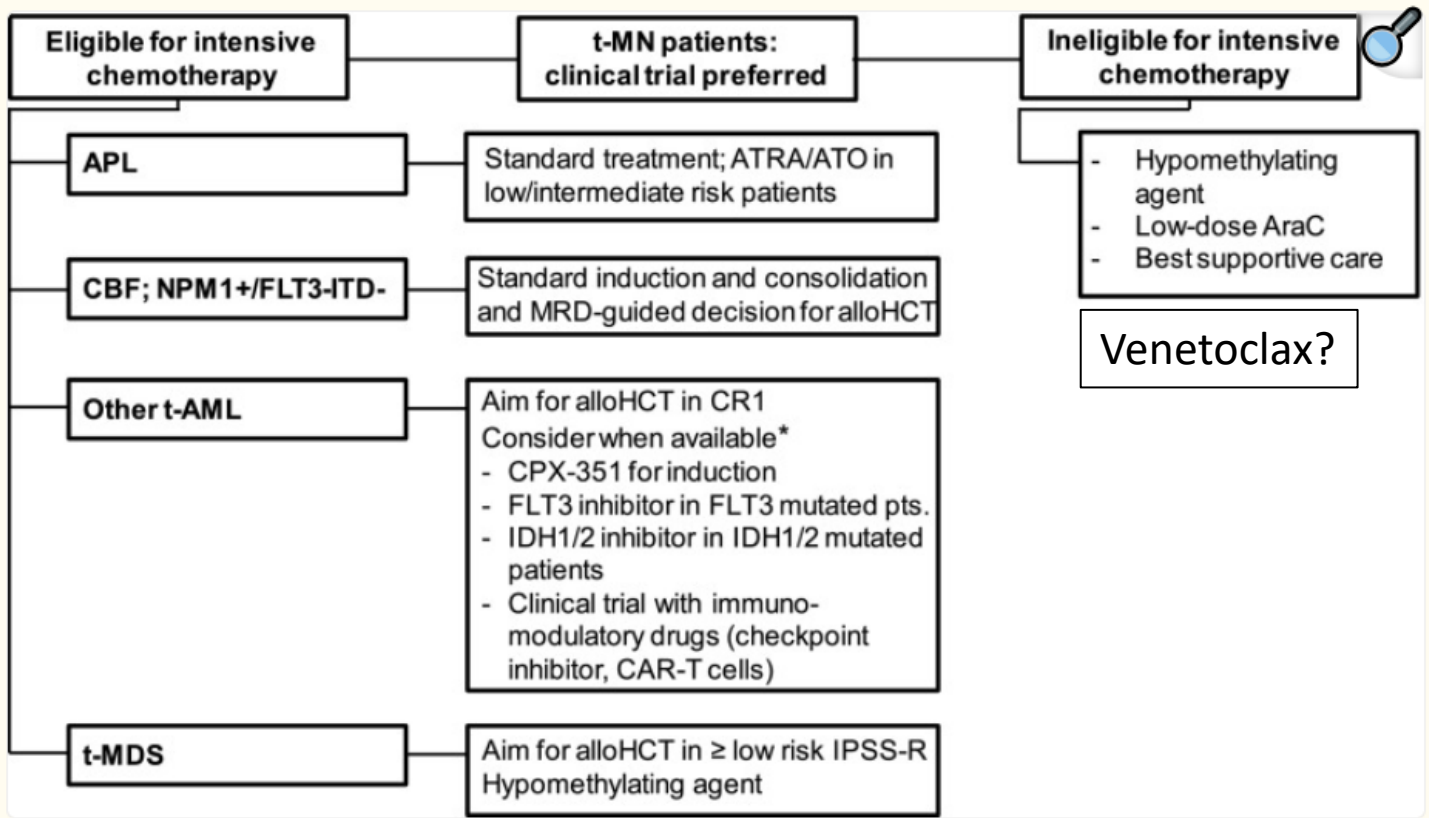
Barnell EK. Blood Advances 2022

Spontaneous remission of B-ALL after lenalidomide withdrawal



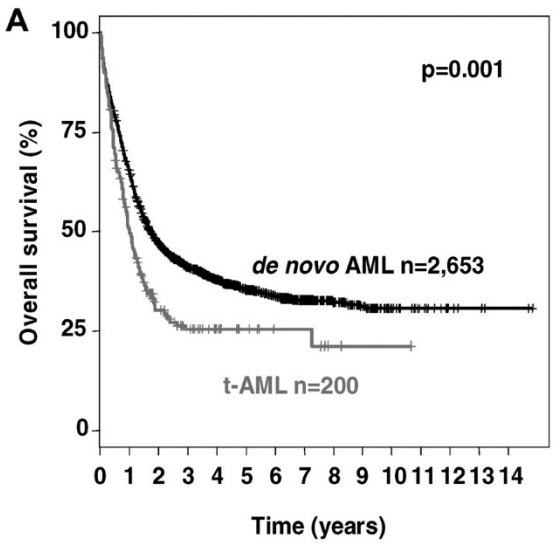
Geyer BG. Blood Advances 2023

Treatment of t-AML secondary to hematological malignancies



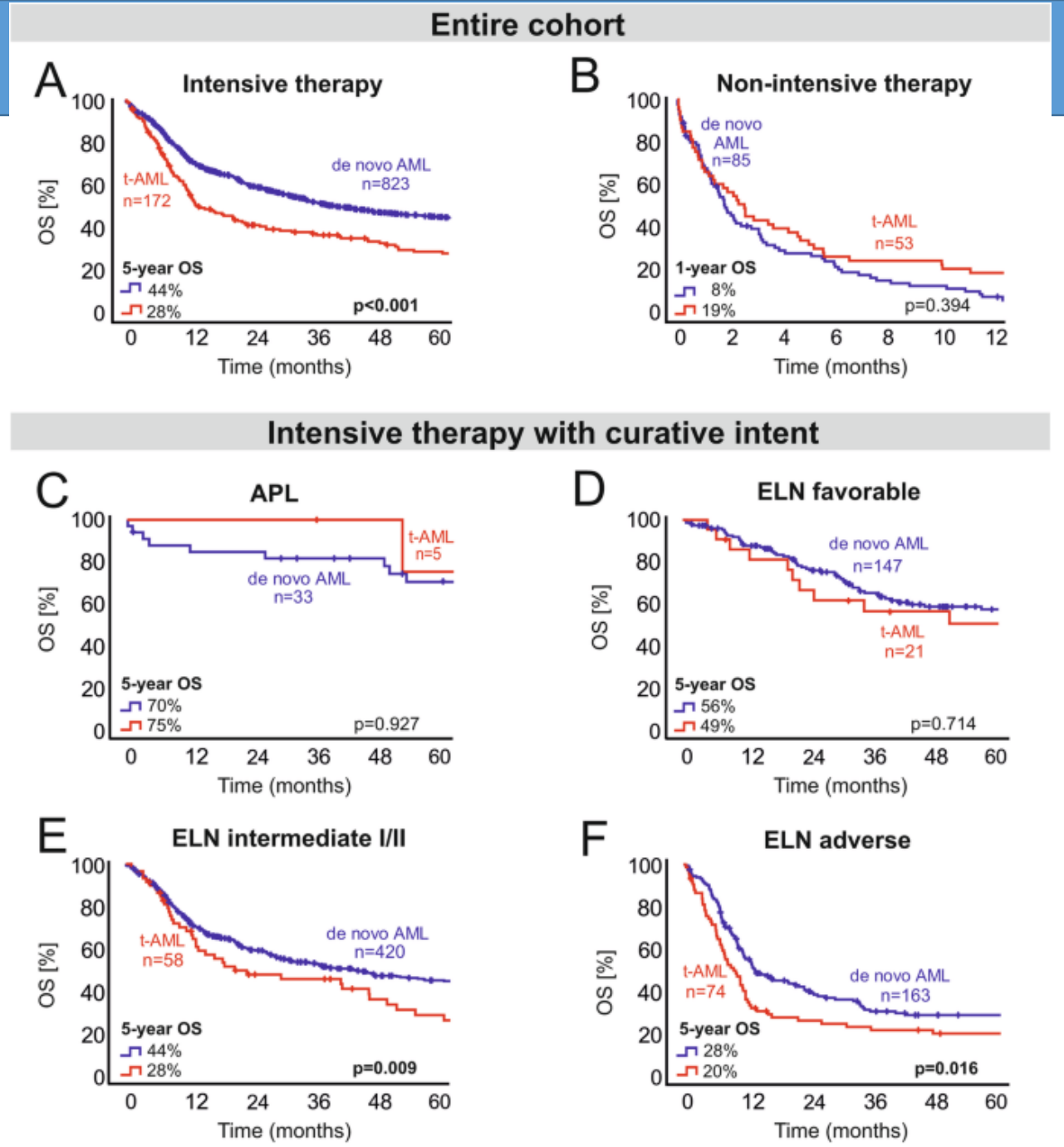
Adpated from Heuser et al. 2016

Outcomes



Karyotype	No. of patients (%)		Median survival (months)		
	t-AML (n=121)	*de novo* AML (n=1511)	t -AML	*de novo* AML	p
Favorable	29 (24)	306 (20)	27	>60	0.02
Intermediate	34 (28)	903 (60)	12	16	0.19
Unfavorable	58 (48)	302 (20)	6	7	0.006

Kayser et al, Blood 2011
Kern JCO 2004



Gross S. et al. Blood Cancer Journal 2024

Take-home messages

- Global incidence if t-AML is increasing
- A slightly higher risk of t-AML with ASCT and Lenalidomide
- Clinical impact of ASCT and lenalidomide is far higher than the risk of developing t-AML
- A lower survival in t-AML compared with de novo AML
- To be rediscussed with new therapeutics

Thank you for your attention!

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Questions?

- AML secondary to topoisomerase II inhibitors are characterized by
  - An adverse caryotypes (False)
  - A Frequent preexisting MDS (False)
  - A short latency (1-2 yrs) (Right)
  - Frequent MLL tranlsocations (Right)
  - Frequent TP53 mutated clonal selection (False)
- AML secondary to myeloma treatment
  - Are frequent after ASCT (>10%) (False)
  - Are frequent after lenalidomide (>10%) (False)
  - Are related to the clonal selection of prexesting mutated clones (Right)
  - Are often associated with adverse cytogenetics and molecular risk (Right)
- How do you treat t-AML secondary to hematological malignancies? (open question)