Mitoxantrone and Leukemogenesis

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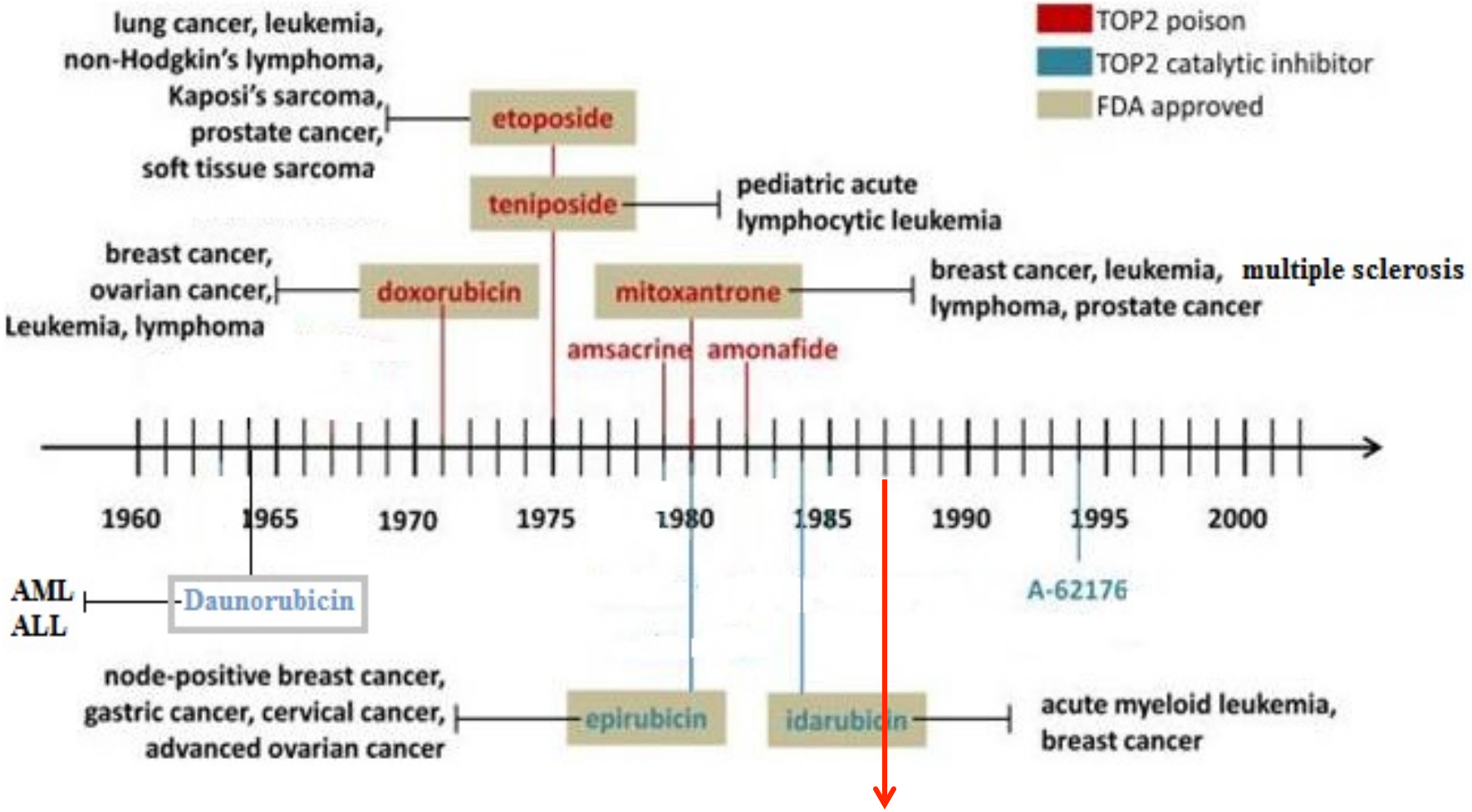
Outline

- Mitoxantrone (an overview)
- Mechanism of action
- Mitoxantrone in multiple sclerosis
- Mitoxantrone induced acute promyelocytic leukemia
- Genetic predisposition?

Mitoxantrone (MTZ)

- Mitoxantrone is a synthetic anthracenedione originally developed to improve the therapeutic/safety profile of anthracyclines
- Commonly used in treatment of breast & prostate cancer, lymphoma, leukemia and multiple sclerosis (MS)
- Mitoxantrone is an established DNA topo-II poison & also functions an immunosuppressive agent

Topoisomerase II catalytic inhibitors and poisons



Modified with permission from Chen et al, *Oncogene* 2015

Daunorubicin as anticancer drug

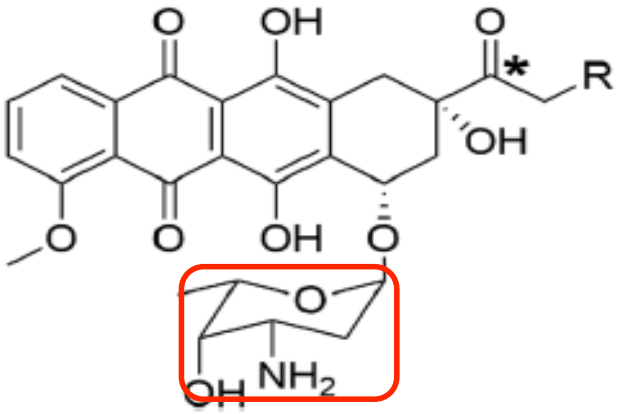
- In 1964 Farmitalia Labs in search of anticancer compound discovered a red color compound from southeast Italian soil microbes*
- At the same time a French group identified identical compound (Rubidomycin)**
- *Dauni* was the pre Roman tribe that occupied the area where compound was isolated in Italy (Puglia region)
- The two groups agreed on naming the compound Daunorubicin
- By 1967, Fatal cardiac toxicity of Daunorubicin recognized

*Dimarco et al, *Nature* 1964 ** Dubost et al, *Cancer Chemother Rep* 1964

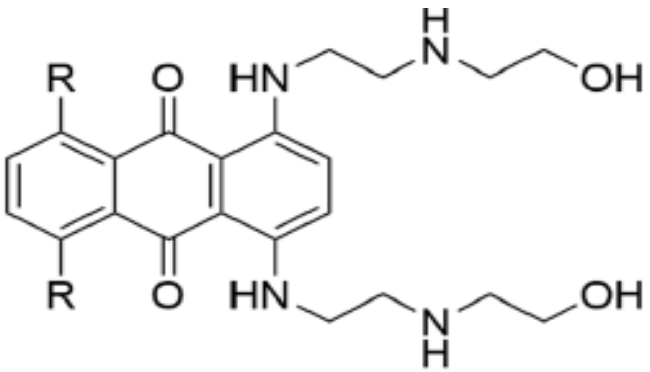
Development of Mitoxantrone

- American Cynamide company, with the idea to overcome the cardiotoxicity, discovered mitoxantrone*

- Daunosamine sugar portion of anthracyclines, considered responsible for the cardiotoxicity was replaced



Anthracyclines



Mitoxantrone

*Murdock et al, *J Med Chem* 1979

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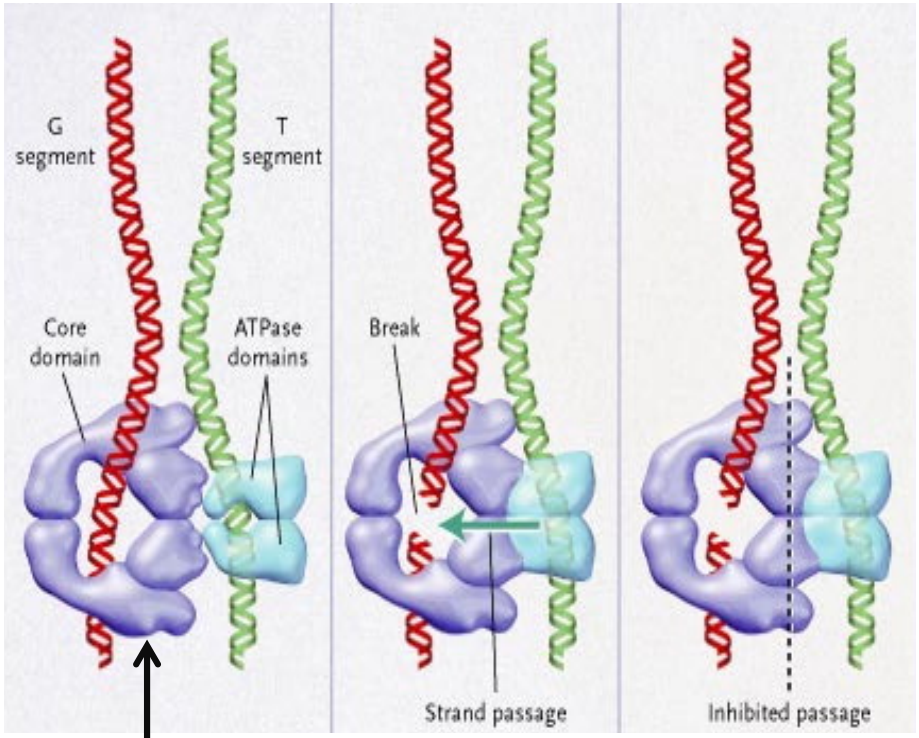
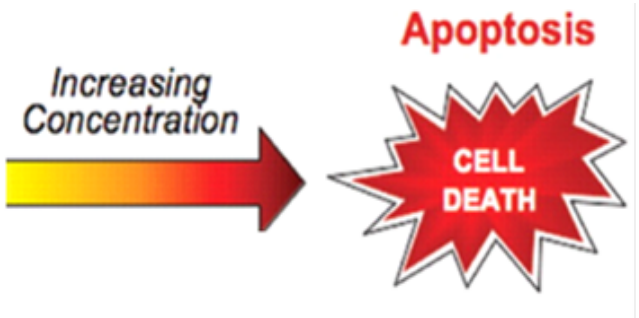
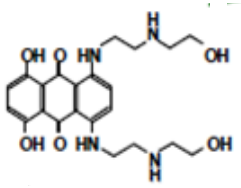
Mitoxantrone: Mechanism of action

- Topoisomerase II alpha is a molecular target of mitoxantrone





Topoisomerase II alpha

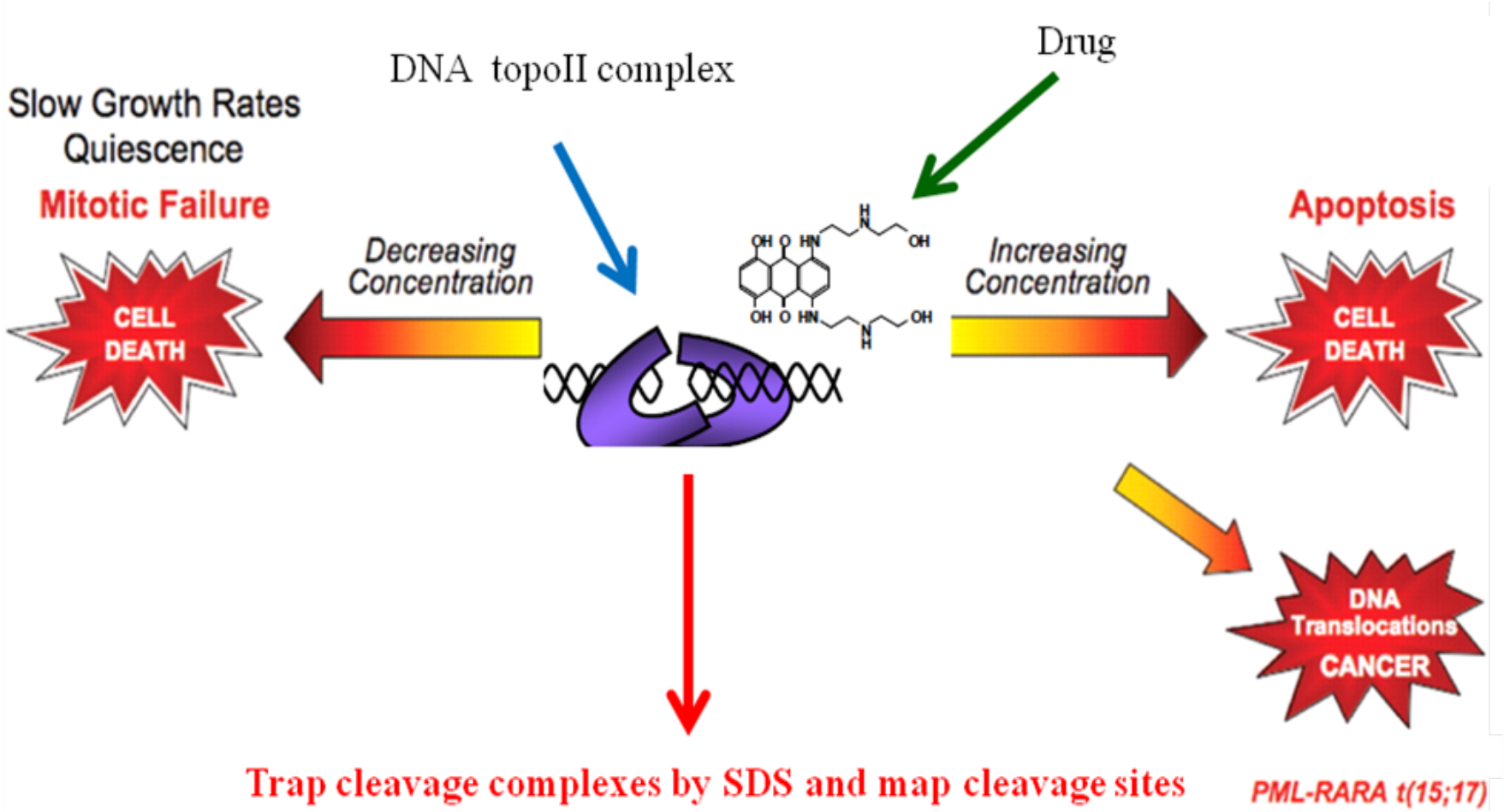


Mitoxantrone

Modified from Pedersen *N Engl J of Med* 2005

DNA-topoII cleavage complexes

- The ability of topoII poisons to ‘cause’ rather than ‘cure’ cancer may be related to cellular levels of cleavage complexes



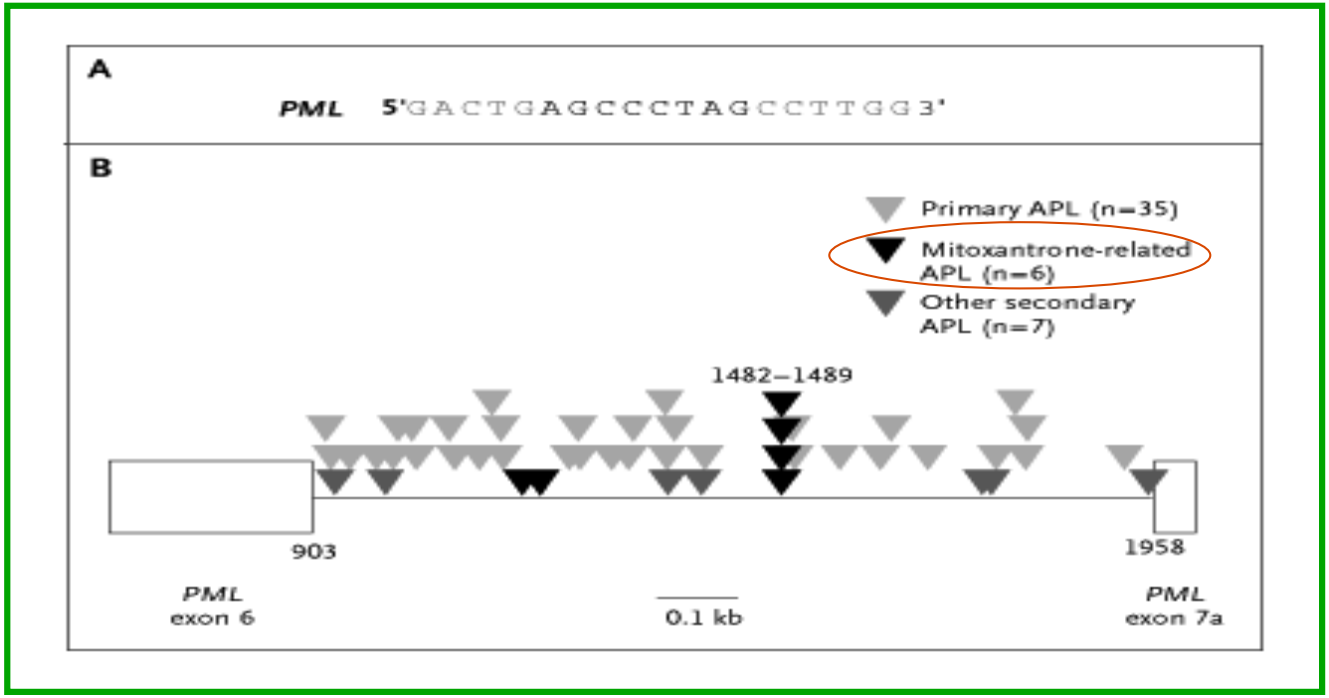
Deweese and Osheroff , *Nucleic acid Res* 2009

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

DNA Topoisomerase II in Therapy-Related Acute Promyelocytic Leukemia

Anita R. Mistry, Ph.D., Carolyn A. Felix, M.D., Ryan J. Whitmarsh, B.A., Annabel Mason, B.Sc., Andreas Reiter, M.D., Bruno Cassinat, Pharm.D., Anne Parry, Ph.D., Christoph Walz, Joseph L. Wiemels, Ph.D., Mark R. Segal, Ph.D., Lionel Adès, M.D., Ian A. Blair, Ph.D., Neil Osheroff, Ph.D., Andrew J. Peniket, B.A., Marina Lafage-Pochitaloff, Ph.D., Nicholas C.P. Cross, Ph.D., Christine Chomienne, Ph.D., Ellen Solomon, Ph.D., Pierre Fenaux, Ph.D., and David Grimwade, Ph.D.



Mistry et al, *N Engl J Med* 2005

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Use of MTZ in multiple sclerosis

- Used as a monotherapy in MS, whereas it is commonly given in combination in cancer
- Approved for secondary progressive MS
- MTZ associated malignancies in MS
- t-APL seems over-represented in MS setting
- MTZ still used in countries with limited resources

Malignancies after mitoxantrone for multiple sclerosis
Single Center Retrospective Analysis

Number of MTZ treated MS pts (n)	677
Median age at MTZ initiation, yrs	41
Median cumulative dose, mg/m^2	79
Pts with other immunosuppressive agents	239
Median time of follow-up, yrs	8.7
Therapy related malignancies a) Breast carcinoma (n=9) b) Colorectal cancer (n=7) c) AML (n=4) d) Glioblastoma, Lung, Pancreatic, Prostate cancer (n=2 each) e) Other malignancies (n=9)	37

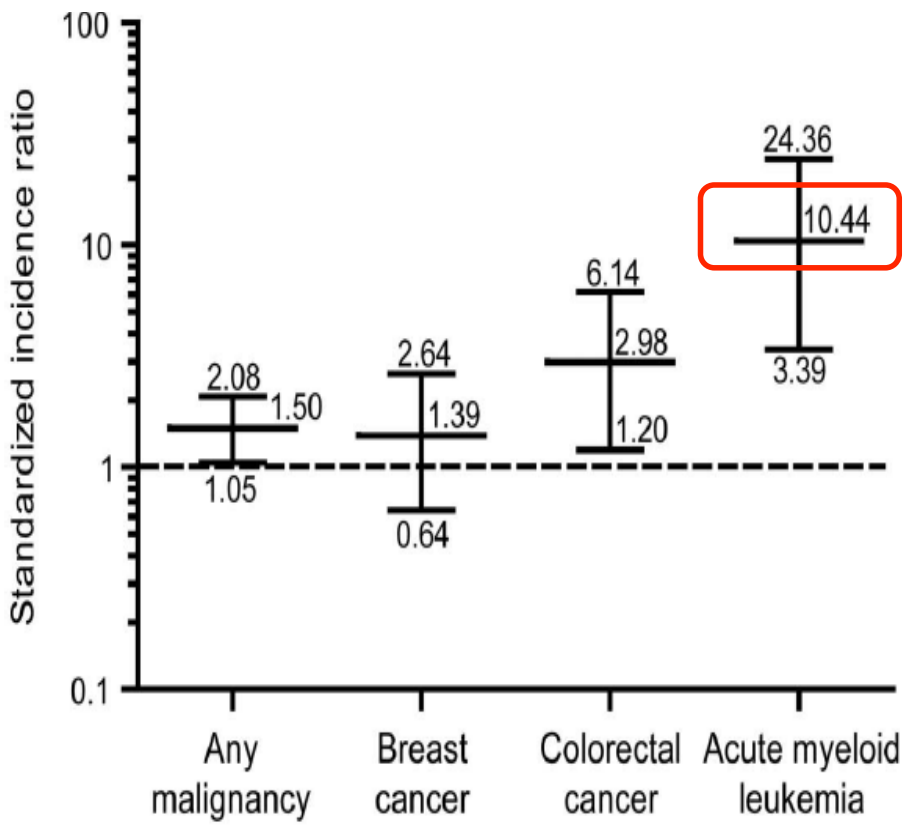
Buttmann et al, *Neurology* 2016

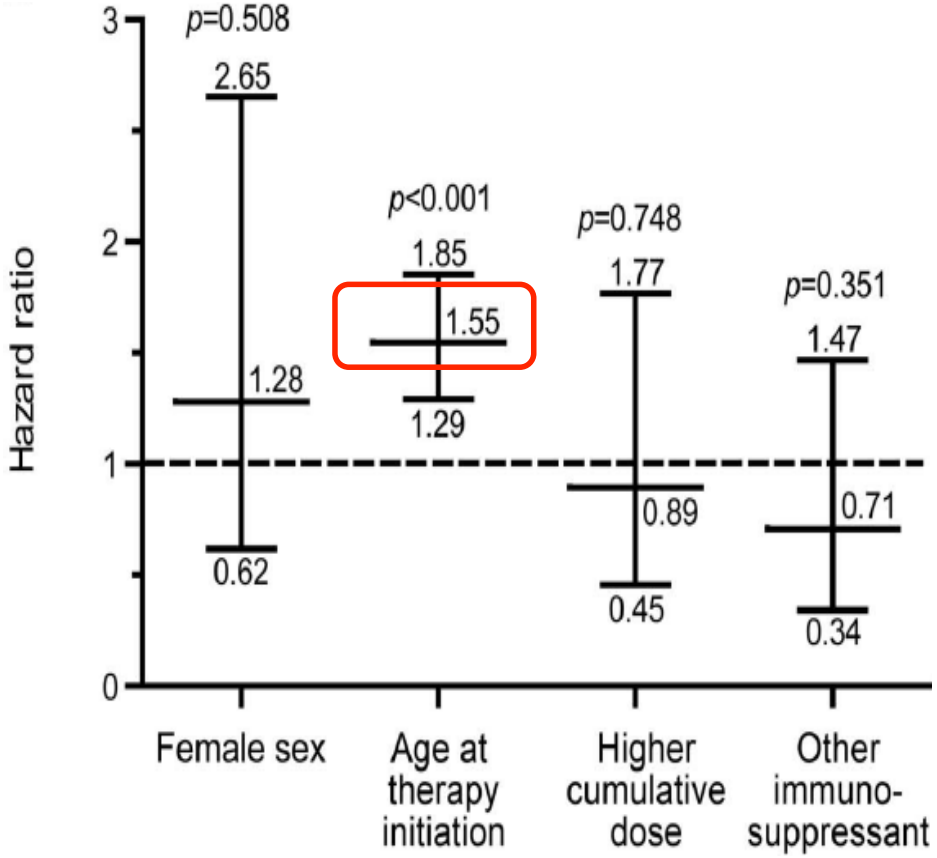
Malignancies after mitoxantrone for multiple sclerosis Single Center Retrospective Analysis

	t-AML	Colorectal cancer
Median age	38	58
Cumulative dose mg/m^2	98	61
Latency b/w MTZ and malignancy (months)	35	74

Buttmann et al, *Neurology* 2016

Incidence of cancers & risk factors in MS after MTZ compared to German national cancer registry





Dashed line: data from Robert Koch Institute, Berlin

Buttmann et al, *Neurology* 2016

Therapy related-AL (TRAL) after MTZ in MS

Parameters	Ellis et al	
	2009	2015
Number of case series	15	27
MS patients treated with MTZ	5472	12896
Median age	39.5	42.2
Median follow up	3 yrs	4 yrs
Cumulative MTZ dose	76.1 mg/m^2	89 mg/m^2
Therapy related acute leukemia (TRAL)	34	150
TRAL in pts receiving MTZ > 60 mg/m^2	28	122
TRAL in pts receiving MTZ < 60 mg/m^2	6	28
Median latency between MTZ and TRAL	18.5 months	22 months
Incidence of TRAL in MS	0.4%	0.8%

Risk of TRAL 0.8% compared with 0.003% for developing AML in general population

Ellis et al, *Multiple sclerosis* 2009 & 2015

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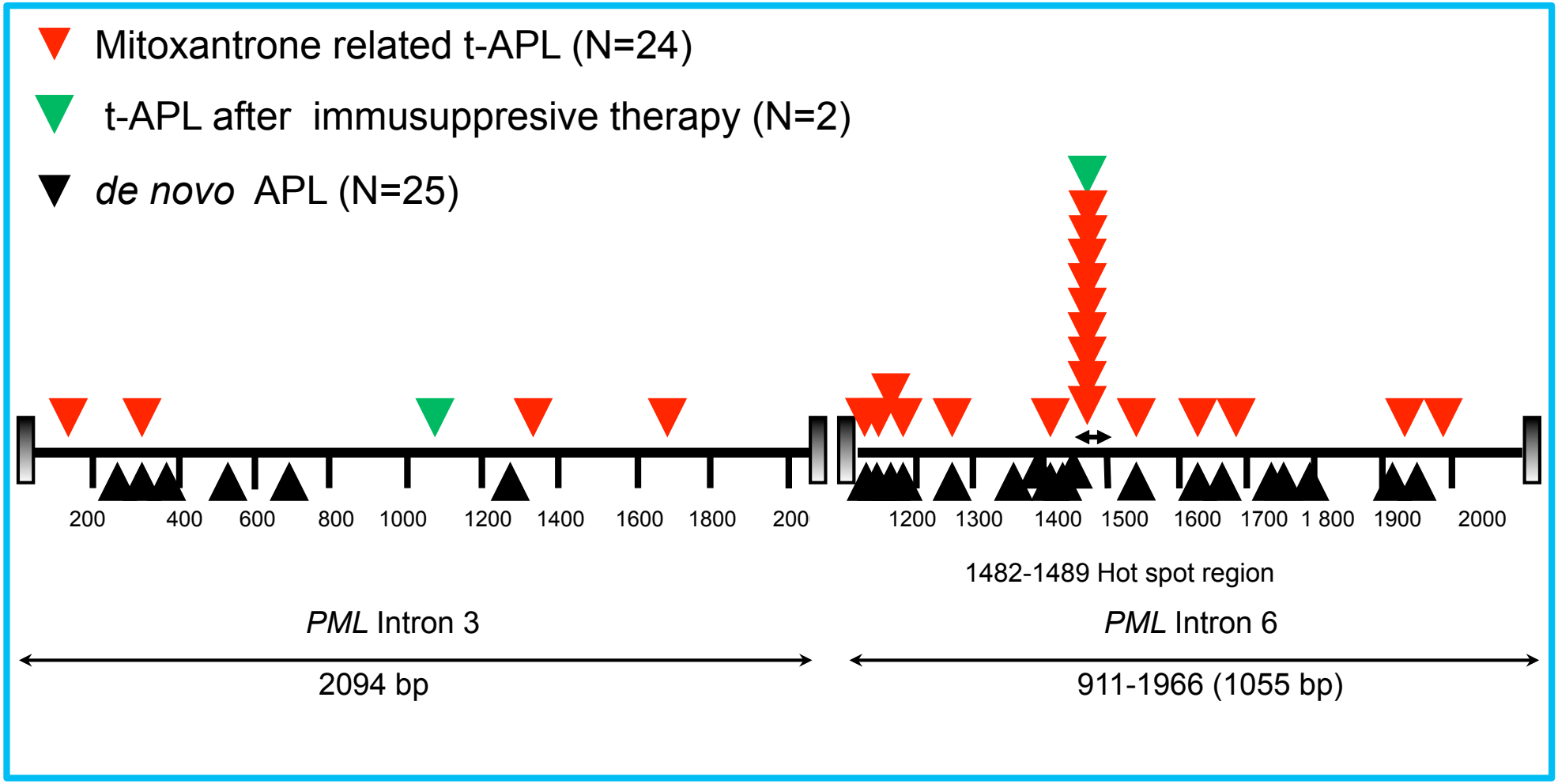
t-APL cases (ELN collaboration = 41 cases)

Patient	Primary disorder	Treatment	Mean Latency	*PML-RARA* isoform
UPN 1 to 26	Multiple Sclerosis	Interferon and Mitoxantrone	28 mos.	bcr1- 21 bcr3 - 5
UPN 27	LS syndrome	Azathioprine	120 mos	bcr1
UPN 28-37	Breast Carcinoma	Epirubicin, cyclophosphamide, radiation and Tamoxifen	24 mos.	bcr 1
UPN 38	Hodgkin lymphoma	Adriamycin, Bleomycin Vinblastine, Dacarbazine and Radiation	33 mos.	bcr 1
UPN 39	Corpus uteri Caricinoma	5 adjuvant after loading radiation	69 mos.	bcr 1
UPN 40	Non Hodgkin Lymphoma	Cyclophosphamide, Hydroxydaunurubicin, Oncovin and Presdnisone	24 mos.	bcr 1
UPN 41	Histiocytoma	Surgery and radiotherapy	29 mos	bcr3

Characterization of *PML* breakpoints



8 bp Hotspot region **A G C C C T A G**

t-APL cases N= 10/26

de novo APL N= 0/25

P = 0.003

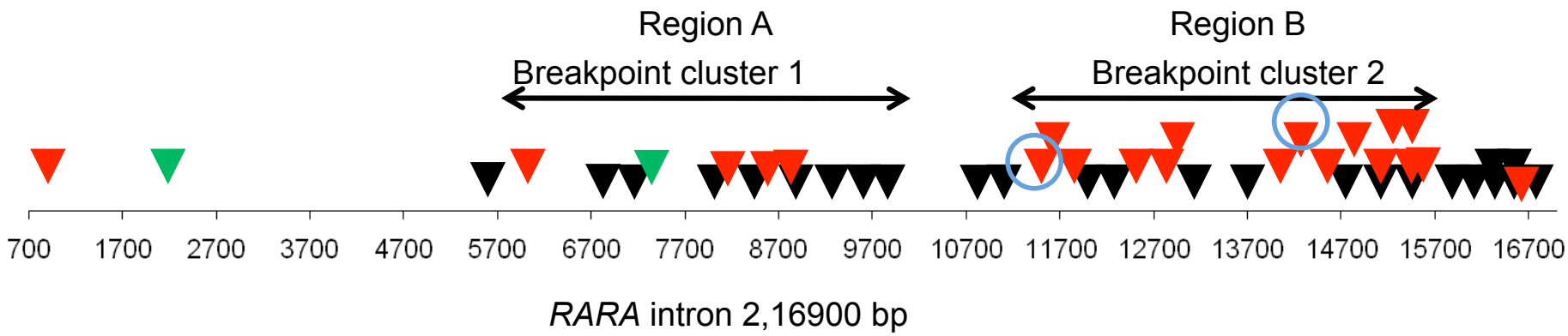
Hasan, Mays et al, *Blood* 2008

Characterization of *RARA* breakpoints

Mitoxantrone related t-APL

t-APL after immunosuppressive therapy

de novo APL



*Identical mapping at nucleotide 11569-71 & 14446-49 as reported by Mistry *et al,*NEJM 2005

Hasan et al, *Genes chromosomes and cancer* 2010

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SNP analysis*: DSB repair and drug metabolism genes

MS patients divided in 3 groups:

Multiple Sclerosis: 253

MS treated with mitoxatrone: 41

MS who developed APL (t-APL): 20 (18 out 20 treated with MTZ)

210 SNPs	22 genes	314 cases, 310 controls

*Sequenom-iPLEX Genotyping

Hasan et al, *Neurology* 2011

Clinical characteristics of t-APL & MS

Characteristics	t-APL	Multiple sclerosis
No. of cases	20	294
Treatment with MTZ	18	41
Median age, years (range)	34.5 (21-59)	32 (13-63)
Gender (M/F)	9/11	86/208
Cumulative MTZ dose in mg, median (range)	97 (14-234)	78 (24-150)
Time elapsed from MTZ treatment (mos)	26.5 (4-56)	57 (27-113)

Hasan et al, *Neurology* 2011

Results

Risk of t-APL development in Multiple Sclerosis:

- Carriers of *XRCC5* (rs207906) + *BRCA2* (rs1801406)

  t-APL vs MS (p=0.001) and t-APL vs MS+MTZ (p=0.04)

- Variant form *BRCA1* & *CYP3A4* more frequent in t-APL

  rs16940 (*BRCA1*): t-APL vs MS+MTZ (p=0.01)

  rs2740574 (*CYP3A4*): t-APL vs MS+MTZ (p=0.03)

Hasan et al, *Neurology* 2011

Hematologic monitoring of pts at higher risk of MTZ-TRAL

Routine Lab test	Time points	RED FLAGS		Suggested action
		Lab	**Clinical**	
			B-symptoms	
			Coagulopathy, Anemia, Infection, Splenomegaly	consult hematologist, blood smear
Complete blood counts	Prior of each MTZ infusion	Persistant cytopenia		
	Every 3 mons Upto 5 yrs after cessation	Increase leukocytes		consult hematologist
Coagulation studies	Only if prolonged thrombocytopenia	Platelet <100,000/mm^3 for > 3 weeks of MTZ		Discontinue MTZ
		Dysplasia, bone marrow blasts		Discontinue MTZ, Cytogenetics

Chan & Lo-Coco, *Neurology* 2013

Thank you