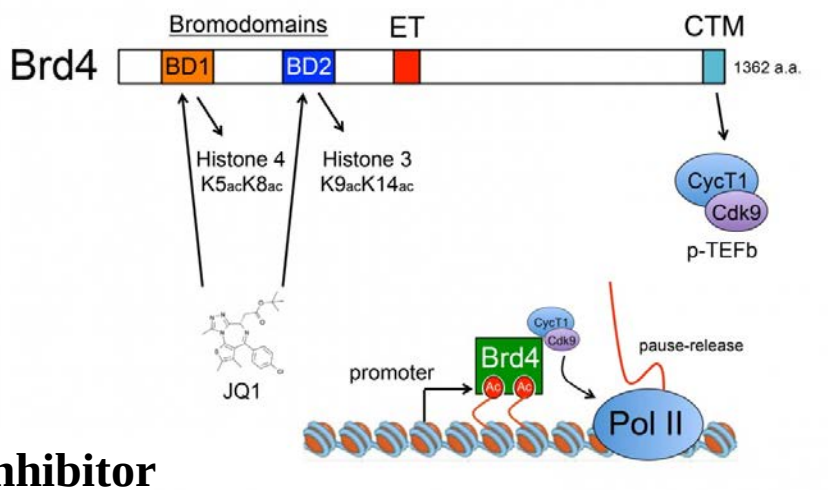
Update on AML at ASH San Francisco

Dec 5-8th 2014

- Novel drugs: BET-BRD inhibitor, IDH2 inhibitor
- Azacitidine AML-001 trial data
- Dasatinib in KIT-mutated CBF AML
- Molecular markers and MRD: DNMT3A

BET family of Bromodomain-containing proteins (BRD2,3,4)

'Read' acetylated histone tails and direct the assembly of transcriptional machinery (pTEF-b complex).
Implicated in several cancers including MLL leukaemia
Small molecule inhibitors available: JQ1 and OTX015.



117 A Phase 1 Study of the BET-Bromodomain Inhibitor OTX015 in Patients with Advanced Acute Leukemia

Hervé Dombret, MD, PhD[1], Claude Preudhomme, MD, PhD[2], Céline Berthon, MD[2*], Emmanuel Raffoux, MD, PhD[3*], Xavier Thomas, MD, PhD[4], Norbert Vey, MD PhD[5*], Carlos Gomez-Roca, MD[6*], Mark Ethell, MD[7*], Karen Yee, MD[8], Fabrice Bourdel, MSc[9*], Patrice Herait, MD, PhD[10*], Mauricette Michallet, MD, PhD[11], Christian Recher, MD-Ph.D.[6], Christophe Roumier[2*] and Bruno Quesnel, MD[12*]

OXT015 : inhibitor of BRD2,3,4: showed some promise in triggering apoptosis in acute leukaemia cells in vitro.
Phase I study: 5/36 previously treated, refractory AML patients showed some response (1CR, 1CRp, 2 had >50% BM blast reduction', 1 resolved gum hypertrophy)

8 Adding *KIT* Inhibitor Dasatinib (DAS) to Chemotherapy Overcomes the Negative Impact of KIT Mutation/over-Expression in Core Binding Factor (CBF) Acute Myeloid Leukemia (AML): Results from CALGB 10801 (Alliance)

Guido Marcucci, MD[1], Susan Geyer, PhD[2*], Weiqiang Zhao, MD, PhD[3], Andrew J Caroll, PhD[4*], Donna Bucci[3*], Geoffrey L. Uy, MD[5], William Blum, MD[3], Timothy Pardee, MD, PhD[6], Meir Wetzler, MD[7], Wendy Stock, M.D.[8], Jonathan E. Kolitz, M.D.[9], Ann-Kathrin Eisfeld, MD[3*], Clara D. Bloomfield, MD[3], Richard M. Stone, MD[10] and Richard A. Larson[11]

Dasatinib in KIT-mut CBF AML

- CBF AML: 25% have mutated or overexpression of KIT.

- 40-50% patients with CBF AML relapse
- KIT mutations and high expression levels associated with higher relapse risk.
- KIT/ c-kit/ CD117 = receptor for Stem Cell Factor (SCF) is a tyrosine kinase, Dasatinib inhibits KIT

- Patients receive induction with DA (3+7) + Dasatinib 100mg/d D8-28.
- Consolidated with HD AraC + Dasatinib
- Those in CR -> Dasatinib for 12 months

- Primary outcome was non-inferiority of CR rate compared with historical controls
- 59 patients: 65% had Inv16, 25% had t(8;21). 18% (10 pts) also had mutated KIT.

- Data so far suggests that patients with KIT mutations do as well as patients with wt KIT (but small numbers of patients).

621 Overall Survival in Older Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) with >30% Bone Marrow Blasts Treated with Azacitidine By Cytogenetic Risk Status: Results of the AZA-AML-001 Study

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AML001 trial results
Phase III RCT
n=488

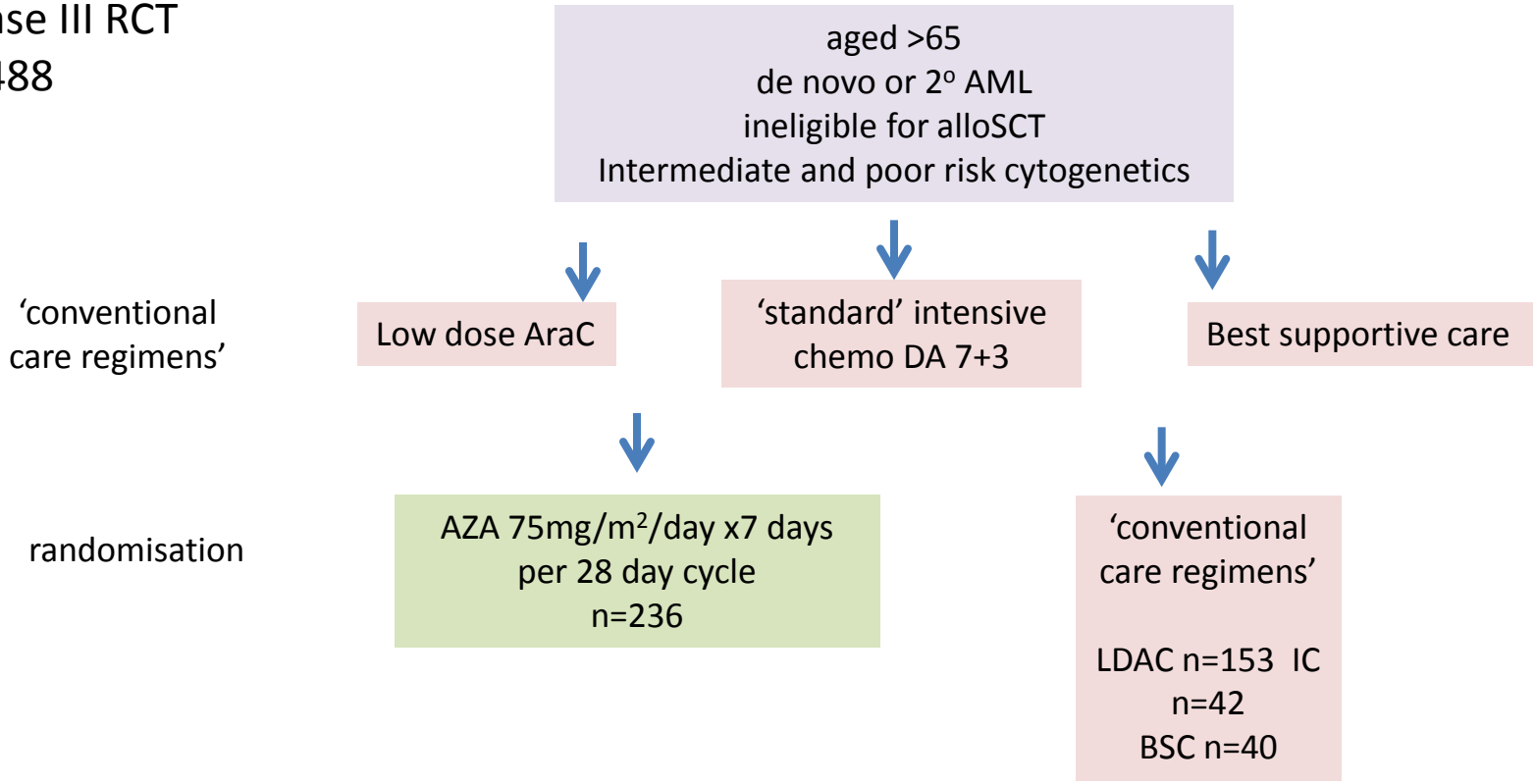


Table. Demographic and Disease Characteristics at Baseline and Study Drug Exposure

Baseline Characteristics	AZA*			CCR*		
	Intermediate (n=155)	CN (n=113)	Poor[‡] (n=85)	Intermediate (n=160)	CN (n=105)	Poor[‡] (n=85)
Age (years), median (range)	75 (65, 91)	75 (67, 89)	76 (64, 90)	76 (65, 89)	76 (65, 89)	74 (65, 87)
Age ≥75 years	56.8%	53.1%	57.6%	53.8%	53.3%	47.1%
Gender male, n (%)	84 (54.2)	59 (52.2)	55 (64.7)	105 (65.6)	66 (62.9)	43 (50.6)
AML classification, n (%)						
AML not otherwise specified	107 (69.0)	75 (66.4)	45 (52.9)	108 (67.5)	74 (70.5)	34 (40.0)
AML with myelodysplasia-related changes	43 (27.7)	34 (30.1)	32 (37.6)	44 (27.5)	28 (26.7)	39 (45.9)
Therapy-related myeloid neoplasms	5 (3.2)	4 (3.5)	3 (3.5)	7 (4.4)	3 (2.9)	5 (5.9)
AML with recurrent genetic abnormalities	0	0	5 (5.9)	1 (0.6)	0	7 (8.2)
Prior MDS, n (%)	31 (20.0)	25 (22.1)	18 (21.2)	22 (13.8)	12 (11.4)	16 (18.8)
% BM blasts,[†] % median (range)	72.5 (3, 100)	75.5 (5, 99)	68 (2, 100)	75 (4, 100)	76 (6, 100)	70.5 (8, 100)
ECOG PS, n (%)						
Grade 0-1	125 (80.6)	96 (85.0)	61 (71.8)	125 (78.1)	81 (77.1)	63 (74.1)
Grade 2	30 (19.4)	17 (15.0)	24 (28.2)	35 (21.9)	24 (22.9)	22 (25.9)

Duration of Treatment Exposure

Cytogenetics	Median (Range) Treatment Cycles[§]			
	AZA (n=236)	LDAC (n=153)	IC (n=42)	BSC (n=40)
CN	9 (1-28)	5 (1-25)	2 (1-3)	47 (8-245)
Intermediate	8 (1-28)	4 (1-25)	3 (1-3)	72 (8-535)
Poor	5 (1-26)	2 (1-21)	2 (1-3)	60 (6-127)

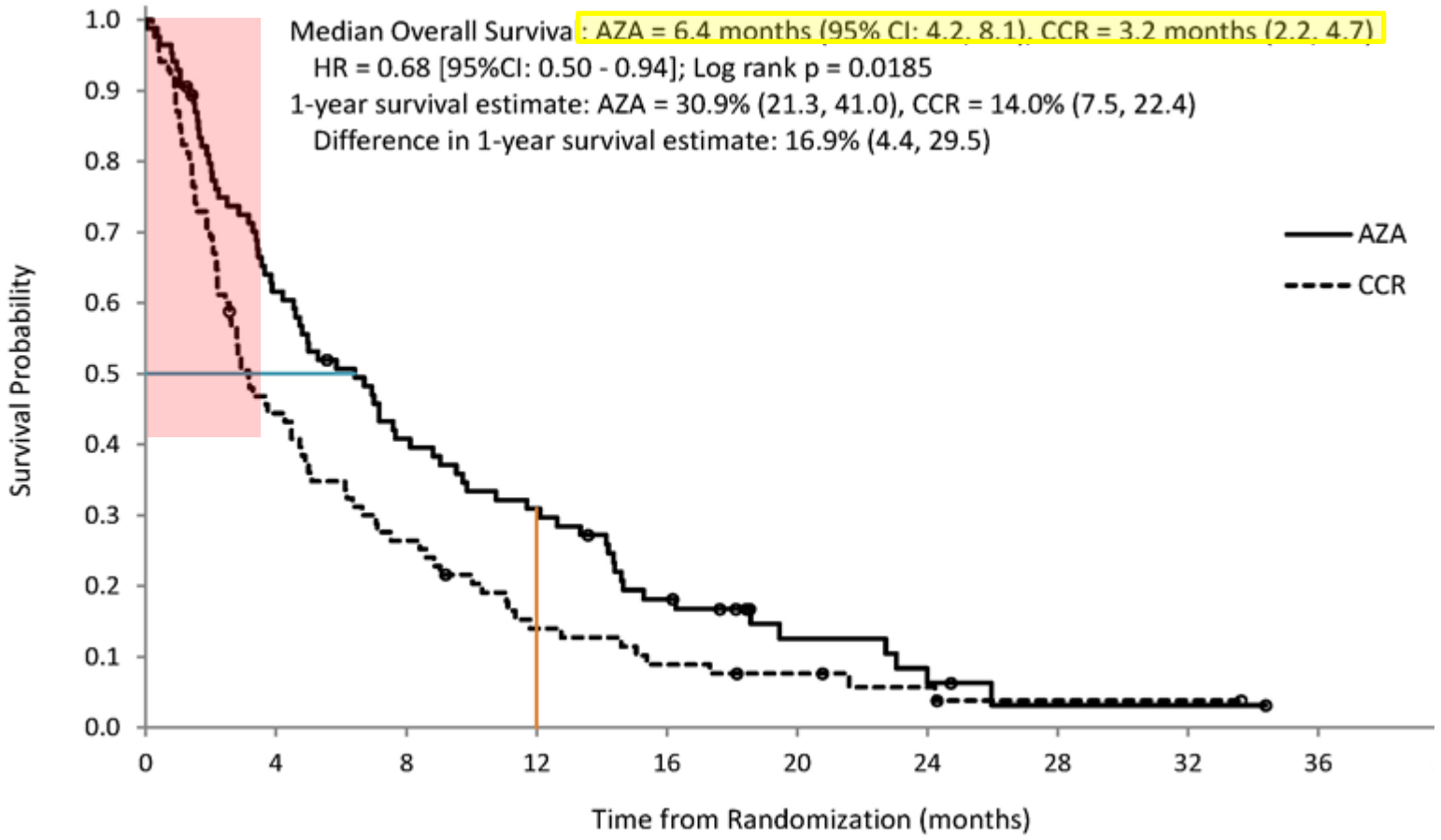
AZA = azacitidine; CCR = conventional care regimens; CN=cytogenetic normal; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; BM = bone marrow; ECOG PS = Eastern Cooperative Oncology Group performance status; Hgb = hemoglobin; WBC = white blood cell

*Cytogenetic data missing for 1 AZA pt and 2 CCR pts.

[†]Centrally adjudicated

[‡]Poor-risk abnormalities included: Complex (≥3 abnormalities); -5; 5q-; -7; 7q-; 11q23 – non t(9;11); inv(3); t(3;3); t(6;9)

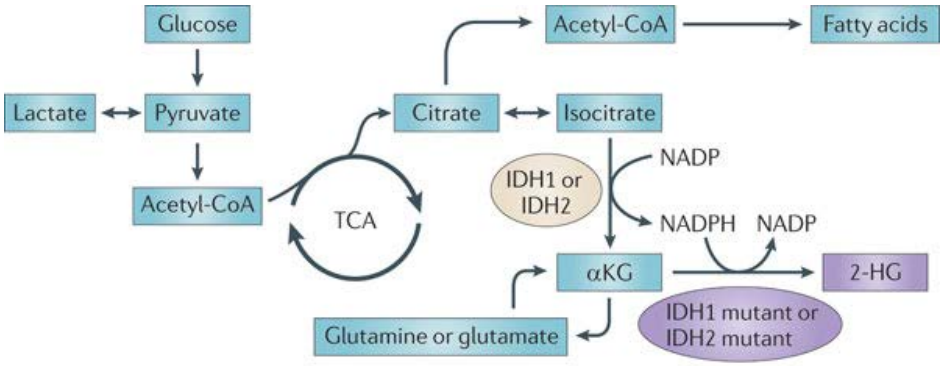
[§]AZA, LDAC, IC duration in cycles; BSC duration in days



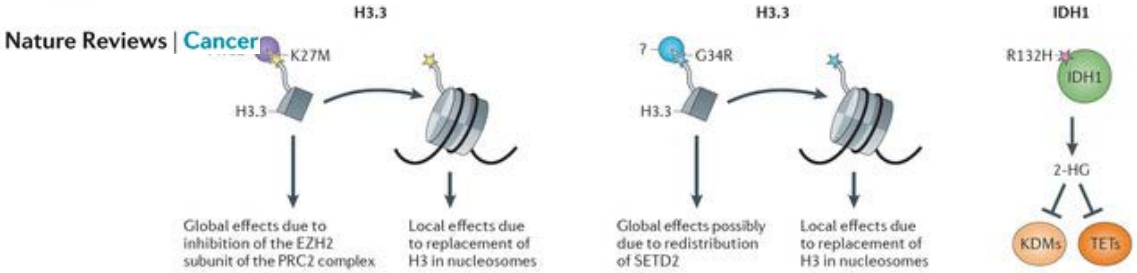
Patients receiving AZA twice as likely to be alive at 1 year as those treated with CCR.

IDH mutations in AML: 8% AML, mainly cytogenetically normal

- Concurrent mutations in NPM1, DNMT3A, FLT3, NRAS and CEBPA are common
- Mutations result neomorphic enzymatic activity which leads to accumulation of an oncometabolite: 2-hydroxyglurate (2-HG).
- Elevated 2-HG is associated with widespread epigenetic change and differentiation block.



From Cairns et al. 2011



	H3.3-K27M mutation	H3.3-G34R mutation	IDH1-R132H mutation
Targeted enzyme	EZH2 in PRC2	SETD2?	KDMs and TETs
5mC	Hypomethylation	Hypomethylation	Hypermethylation
Histone modifications	H3K27me3 decreased and redistributed	H3K36me3 redistributed	H3K9me3 increased, H3K27me3 increased, H3K4me3 increased and H3K36me3 increased
Developmental gene-expression pattern	Neurogenic and mid-to-late cortical development	Neurogenic and early-to-late neocortical development	Neurogenic and neural progenitor cell bias
Gene expression owing to 5mC changes	PRC2-target genes upregulated, *FOXG1* downregulated and *OLIG2* upregulated	*MYCN* upregulated, *FOXG1* upregulated and *OLIG2* downregulated	Genes involved in differentiation downregulated
ALT	Yes	Yes	Not known
Prevalence in childhood glioblastoma	19%	15%	<10%
Prevalence in adult glioblastoma	0%	0%	77%

From Plass et al. Nat Rev Genetics 2013

115 AG-221, an Oral, Selective, First-in-Class, Potent Inhibitor of the IDH2 Mutant Metabolic Enzyme, Induces Durable Remissions in a Phase I Study in Patients with IDH2 Mutation Positive Advanced Hematologic Malignancies

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AG-221: IDH2 inhibitor

Preliminary data from phase 1 open-label trial of AG-221: oral agent given od/ bd
48 patients with 'advanced IDH2-mutated haematological malignancy'
Drug is well tolerated and MTD not yet reached.
9 deaths: 8 occurred within 28 days; one possibly related to the drug

Detected large reduction in 2-HG levels after multiple doses of AG-221

32/48 patients were evaluable for response:
20 responders: 8CR, 1CRp, 3CRi , 8PR.
5 have stable disease
7 had disease progression
5 who attained CR went on to have alloSCT

Data from mouse models suggest that AG-221 causes differentiation of AML (monocytic maturation), with reversal of the epigenetic changes cause by mutated IDH2 and elevated 2-HG.
But IDH mutations often co-occur with others including FLT3 ITD and in mouse models: AG-221 alone is insufficient to reduce leukaemic burden.

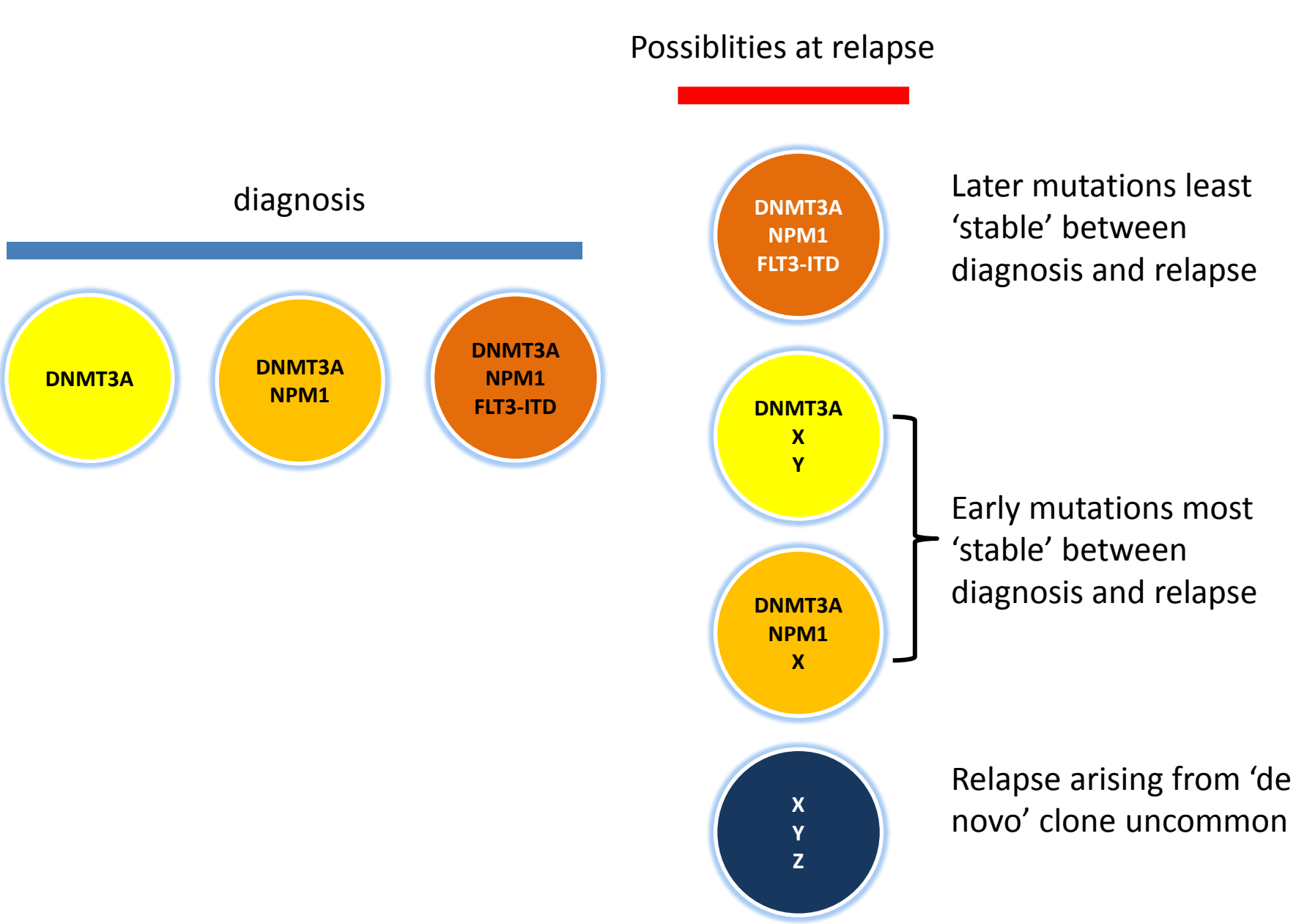
Mutations in AML:

- Which came first?
- Does it matter?
- Impact on MRD monitoring:
- Does detection of mutations at follow up = ‘minimal’ residual disease?

Increasing amounts of data from NGS data in AML
We know that there is a lot of heterogeneity: but patterns are emerging.
Key questions surrounding the common mutations in AML: NPM1, FLT3, DNMT3A

Founder vs. driver?
Which (if any) should we monitor?
Prognostic information

DNMT3A – early; probably founder, present in haematologically normal elderly
NPM1- early or late, can be a founder or driver
FLT3- late, most likely driver


Possiblities at relapse
diagnosis
DNMT3A
DNMT3A
NPM1
DNMT3A
NPM1
FLT3-ITD
DNMT3A
NPM1
FLT3-ITD
Later mutations least 'stable' between diagnosis and relapse
DNMT3A
X
Y
DNMT3A
NPM1
X
Early mutations most 'stable' between diagnosis and relapse
X
Y
Z
Relapse arising from 'de novo' clone uncommon

MRD monitoring in AML:
PML-RARA monitoring works well and informs clinical decision making
APL is a relatively uniform disease with well defined pathogenic-molecular aberrations

NPM1: David Grimwade's data suggests that detection of NPM1 MRD is a good predictor of relapse, and most relapses in NPM1-mutated AML will have NPM1-mutation. NPM1 mutations are stable between diagnosis and relapse in >90% of patients.

(However this does not necessarily mean that detection of NPM1-mutation must mean imminent relapse)

FLT3-ITD is not stable (70% of patients)

DNMT3A: frequency co-occurrence with NPM1- mutations
Current data suggests that it's a founder mutation in many of these cases (Shlush et al. Nature 2014)
Stable between diagnosis and relapse (Kronke et al. Blood 2013)
Presence of DNMT3A worsens prognosis (regardless of NPM1-mutation status) (Rosemary Gale).

However: DNMT3A R882 mutations have been detected in people who are haematologically normal (mainly at low allele frequencies 1-10%) (Xie et al. Nat Med 2014)

122 *DNMT3A* is a Powerful Follow-up Marker in *NPM1* mutated AML

Susanne Schnittger, PhD[1], Claudia Haferlach, MD[1], Tamara Alpermann[1*], Niroshan Nadarajah, M.Sc.[1*], Manja Meggendorfer, PhD[1*], Karolina Perglerová[2*], Wolfgang Kern, MD[1] and Torsten Haferlach[1]

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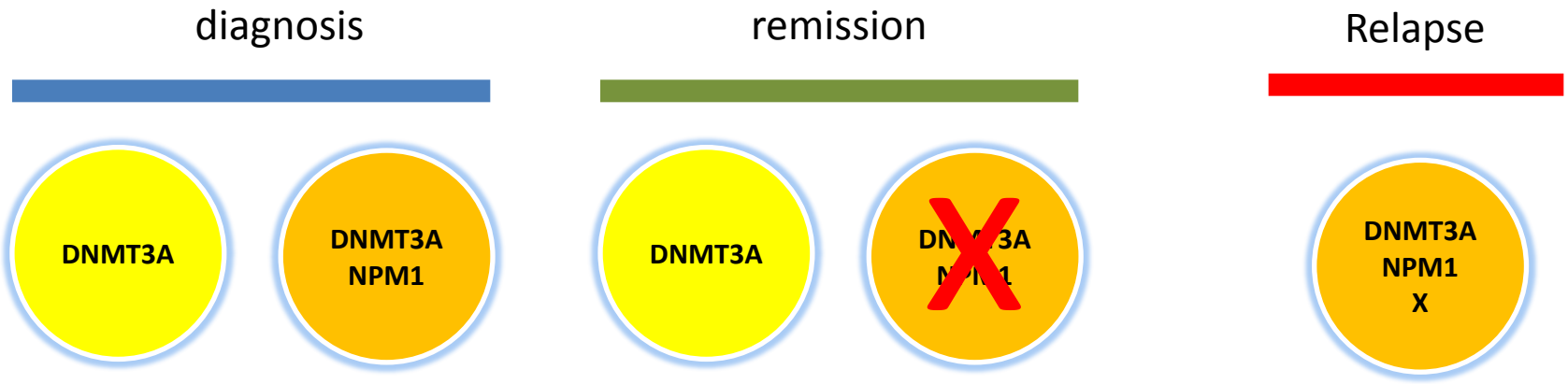
- 103 patients with AML: paired diagnostic and relapse samples
- 59% had DNMT3A mutation
- In 93% DNMT3A was stable

- 54 paired NPM1- and DNMT3A-mutated where there was at least one follow-up sample with NPM1 mut level <0.01%.

- 2/54 cases had morphological relapse but was NPM1-mut negative (so NPM1 is stable in 96%), but DNMT3A was present
- 1/54 lost DNMT3A but retained NPM1

- 32/54 (59%) cases: DNMT3A persisted at quite high levels (2-59% allele frequency) in morphological CR and **NPM1-MRD negativity**.

- Patients with persistent DNMT3A mutation relapsed sooner and had lower OS (69 vs. 96 months p=0.053m n=22) **[Note 10 patients with persistent DNMT3A have yet to relapse]**
- However: when these patients relapsed: the majority did so with disease that had both DNMT3A and NPM1 mutations.



Detection of DNMT3A MRD in the absence of NPM1 mut MRD could mean:

- Imminent relapse
- Pre-leukaemic, but functionally normal haematopoiesis (latency?)
- Cure

Predictions for the future?

- More trials of novel small molecule inhibitors + chemo in selected patients
- Bridging strategies for high risk patients (with appropriate mutations)to alloSCT
- Multi-gene MRD