Acute Leukemia: new agents

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36a Diada Internacional
Therapeutic advances in Hematology
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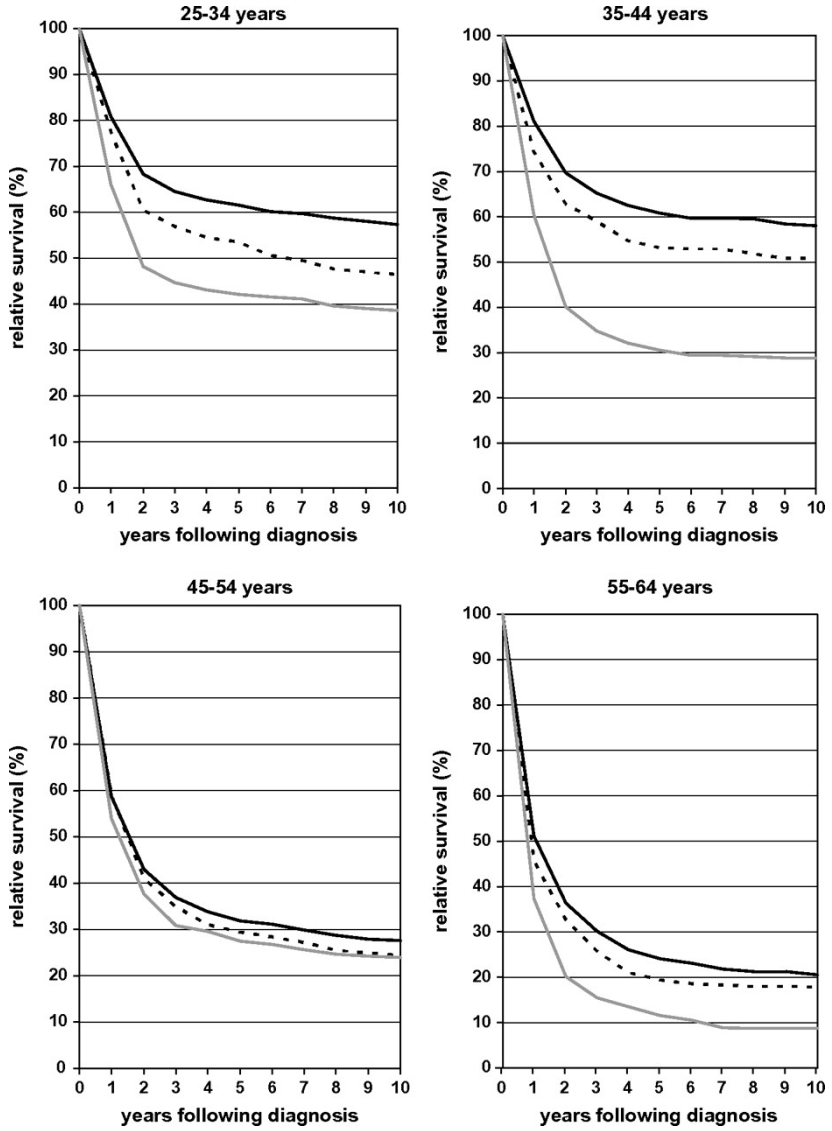
Outcome of AML in adult patients: a real need for new agents

- Curation of of only a fraction of patients (<50%) – insufficient antileukemic potential
- Remission is based on highly myelotoxic agents – toxicity
- Limited target population of hematopoietic stem-cell transplant
- “High-risk” presentation forms – need of a different/“more gentle APL-like approach”

Outcome for patients with AML: any improvement for the last two decades?



2006-2010

2001-2005

1991-1995

Pulte D et al. Ann Oncol 2009

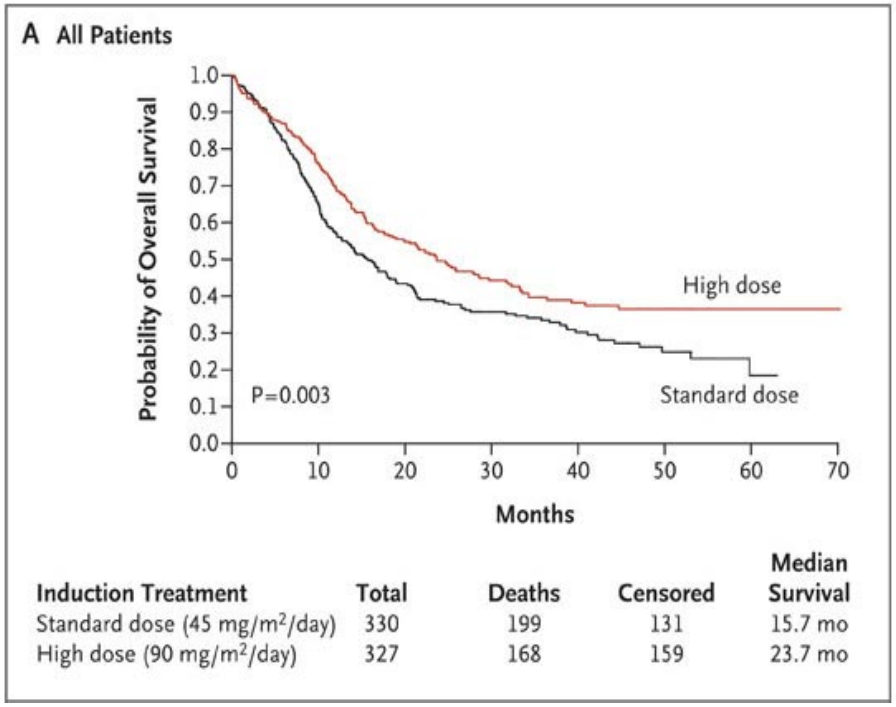
Acute Myeloid Leukemia (AML): temptative definition

- Genetically heterogeneous clonal disorder
- Origin in hematopoietic progenitor cells
- Due to accumulation of somatic acquired genetic & epigenetic alterations
- Altered mechanisms of self-renewal, proliferation & differentiation
- Resulting in an impaired *leukemic* hematopoietic hierarchy: the leukemia stem-cell model

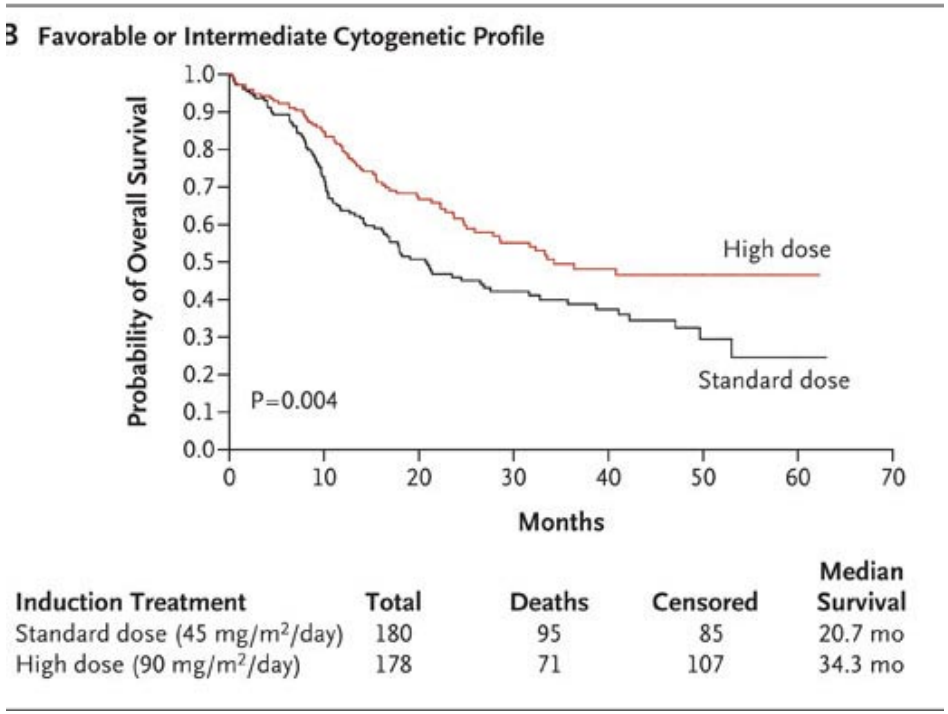
Novel therapeutic strategies introduced in AML in recent years

- Intensified anthracyclines in induction therapy
- Addition of GO to CT (gemtuzumab ozogamycin, antiCD33+calicheamicin)
- Targeted therapy: TKIs (FLT3 inhibitors,…)
- Demethylating agents in AML
- Histone deacetylase inhibitors
- Priming with G-CSF: chemosensitizing or blocking *stromal* protection (CXCR4 antagonists)
- …

High-dose daunorubicin in AML: benefit for good & intermediate-risk cytogenetics



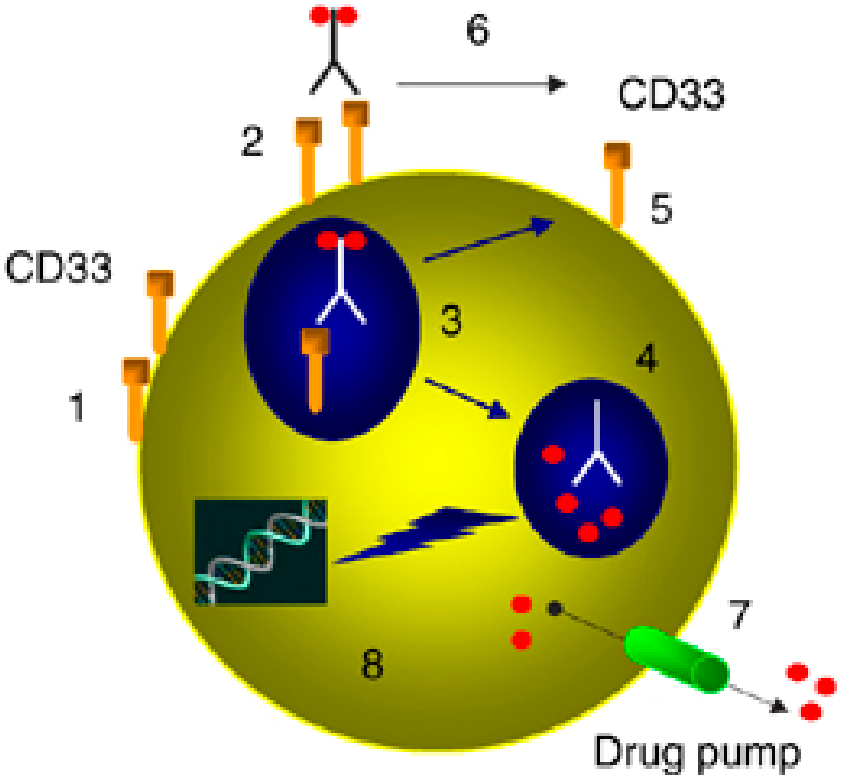
Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m²/day)	330	199	131	15.7 mo
High dose (90 mg/m²/day)	327	168	159	23.7 mo



Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m²/day)	180	95	85	20.7 mo
High dose (90 mg/m²/day)	178	71	107	34.3 mo

Fernández HF (ECOG), NEJM 2009

MoAbs in AML: Humanized antiCD33 Ab Gemtuzumab + calicheamicin (Mylotarg)



1-2. Binding to CD33 Ag
3-4. Internalization & calicheamicin activation
8. Antitumoral effect: induction of DNA breaks
7. Mechanisms of resistance: drug efflux
5. Rapid CD33 re-expression

Mylotarg in relapsed AML: the old concept

✓ Significant activity but transient duration of response - monotherapy (9 mg/m^2 x 2 doses) for relapsed AML

- 26% CR
- Median response duration: 7 mos

✓ Significant hepatotoxicity (SOS)

✓ Uncertain synergy with chemotherapy

✓ Role in APL: *chemo-free* front-line, molecular relapses

Sievers E, JCO 2001
Larson R, Cancer 2005
Estey E, Blood 2002
Lo Coco F, Blood 2004

Mylotarg revisited: from early withdrawal to *resurrection* – a dose issue?

✓ Addition of a 6 mg/m^2 at day +4 of DA induction – excess of induction death in the GO arm (5.4 vs. <2%) - (SWOG S0106)

✓ Addition of low-dose GO (3 mg/m^2) to induction & course 3: survival benefit in pts with favorable cytogenetics - MRC AML15 Trial

✓Addition of multiple doses of GO (3 mg/m^2) to standard AML chemotherapy: days 1, 4 & 7 during induction, day 1 of consolidation (x 2 courses) – ALFA-0701

Petersdorf S, ASH 2009
Burnett A, JCO 2011
Castaigne S, Lancet 2012

Mylotarg revisited (II): from early withdrawal to *resurrection* – a dose issue?

✓ Improved EFS, but not OS, in IR-AML pts receiving GO at a dose of 6 mg/m^2 at induction & consolidation who did not undergo alloHSCT– (GOELAMS AML 2006 IR Study)

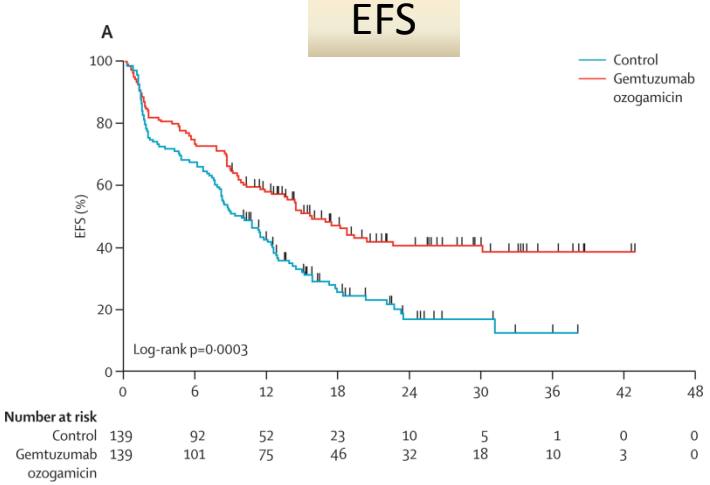
✓ Toxicity related to GO:

- Delayed plated recovery
- Increased hepatic toxicity (6 mg/m^2)

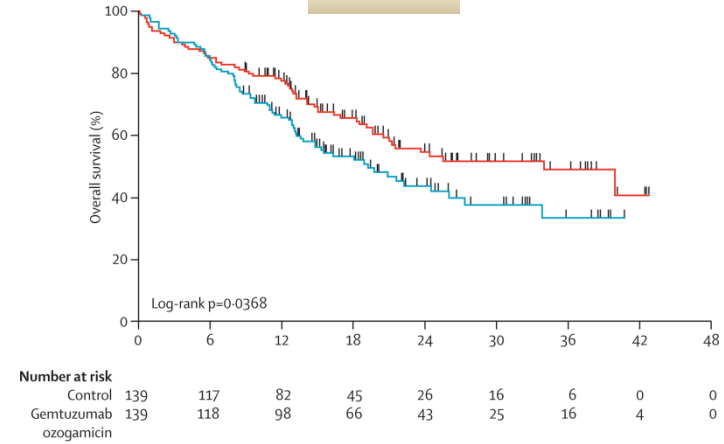
Delaunay J, ASH 2011
Castaigne S, Lancet 2012

Mylotarg revisited: benefit in frontline therapy

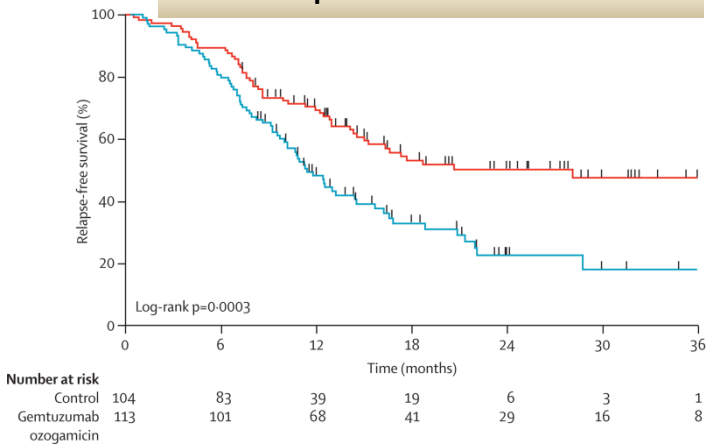
EFS



OS



Relapse-free survival

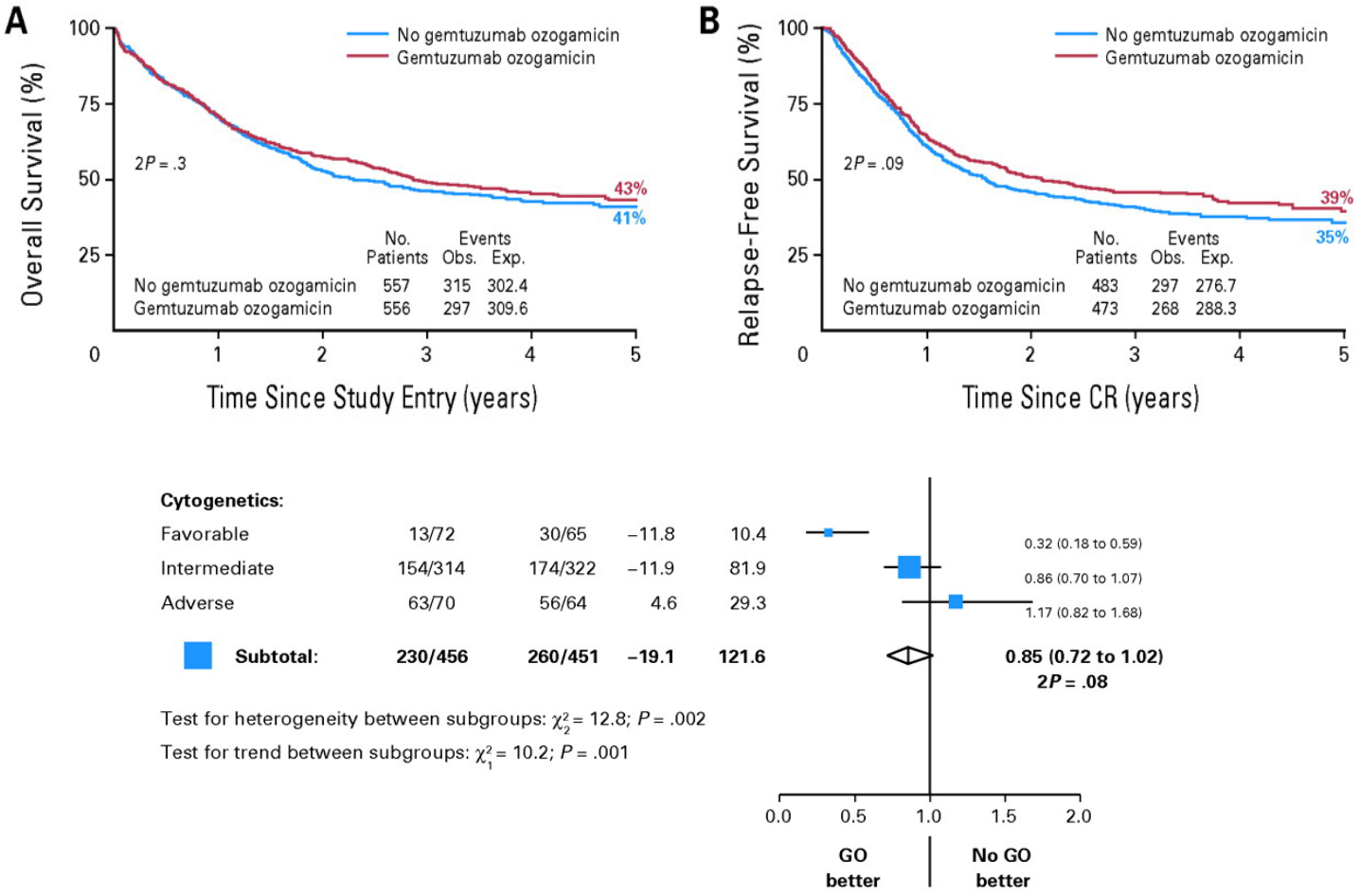


2-yr RFS: 50 (+GO) vs. 22.7%

De novo AML
50-70 year-old
280 randomized pts.

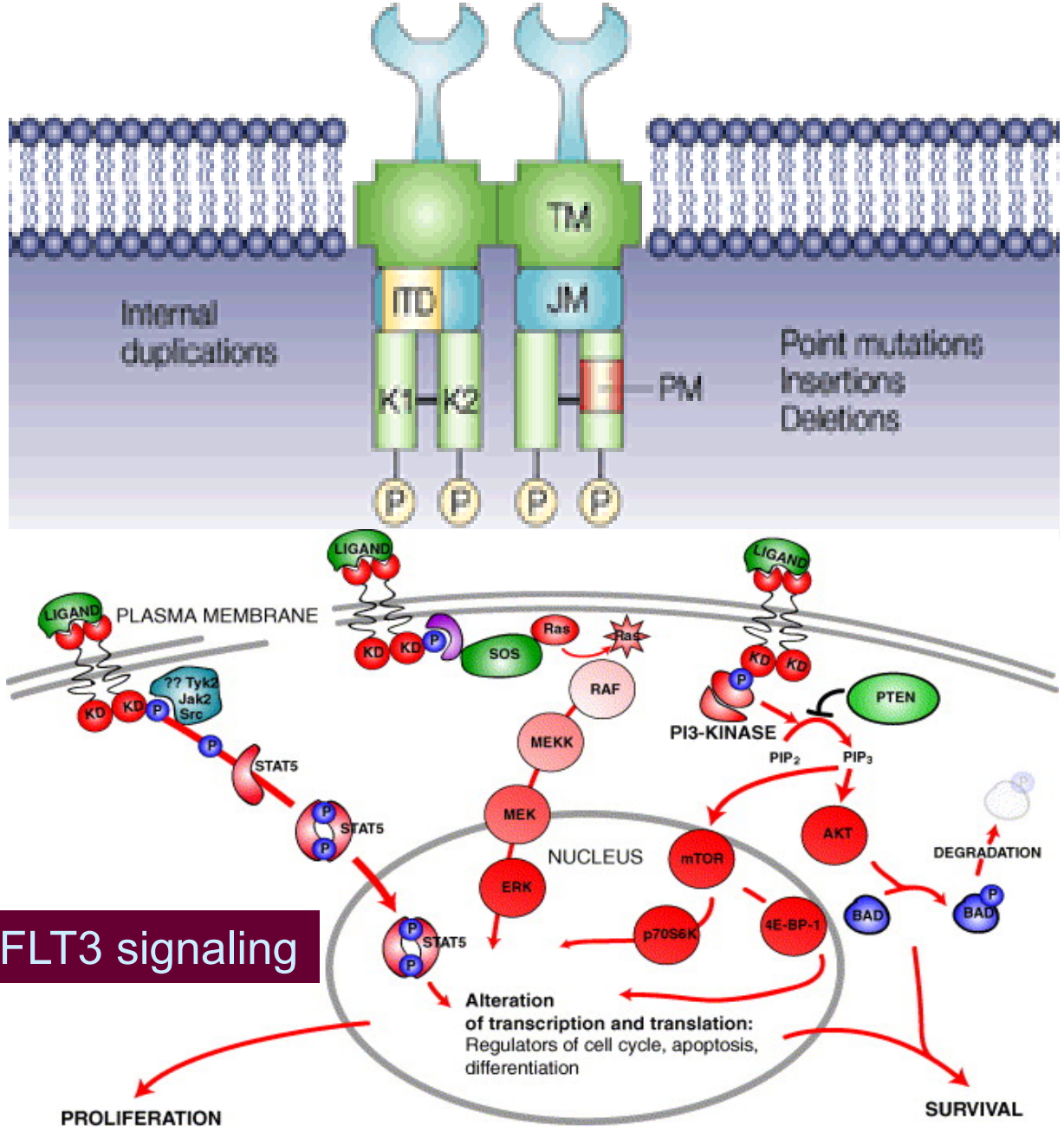
Castaigne S, Lancet 2012

Good-risk patients benefit from the addition of Mylotarg: MRC AML15 Trial



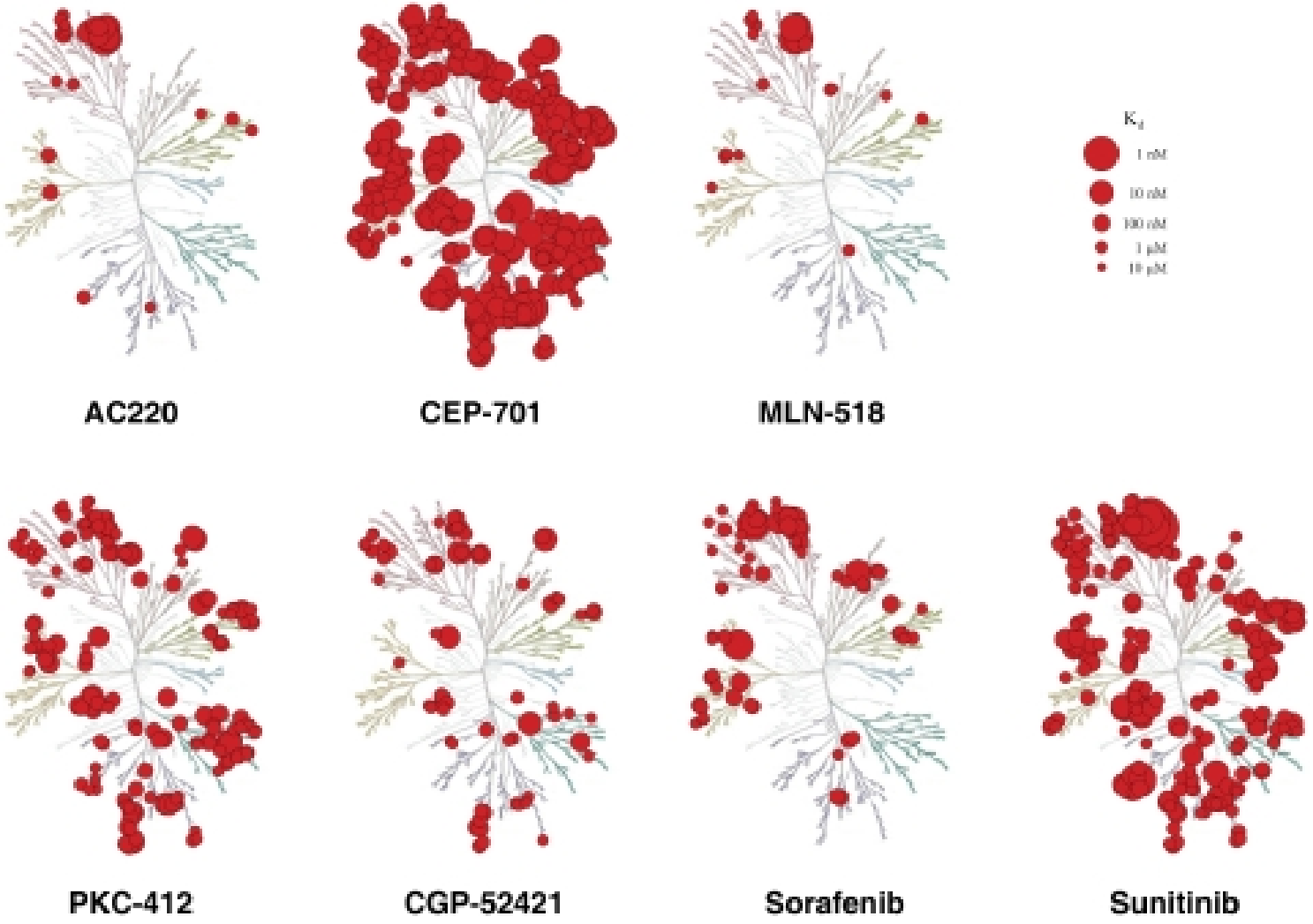
Burnett A, JCO 2011

FLT3 (fms-like TK) Internal Tandem Duplication (ITD)



Downstream FLT3 signaling

FLT3 inhibitors: diverse specificity against multiple targets



FLT3 inhibitors: currently existing experience

✓Limited activity in monotherapy (sorafenib, midostaurin,…)

✓Possible synergy in combination with chemotherapy

- Lestaurtinib: no benefit in relapsed AML
- Midostaurin/PKC-412: on-going trial (front-line tx)

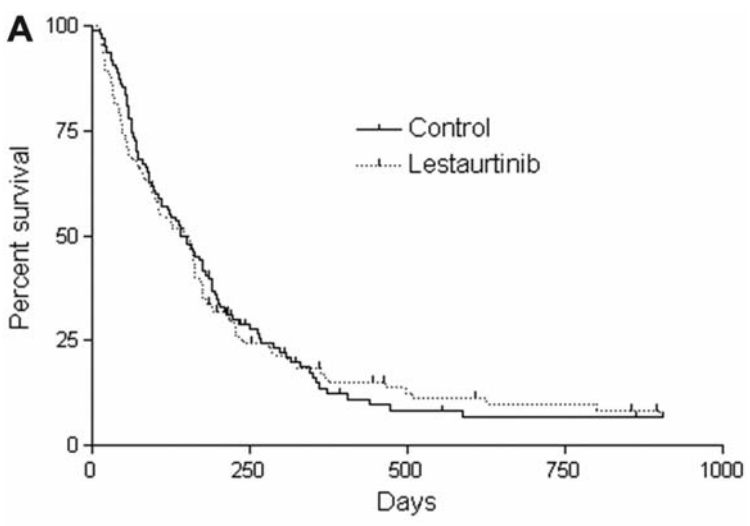
✓Role in the alloHSCT setting: anecdotal reports of responding patients

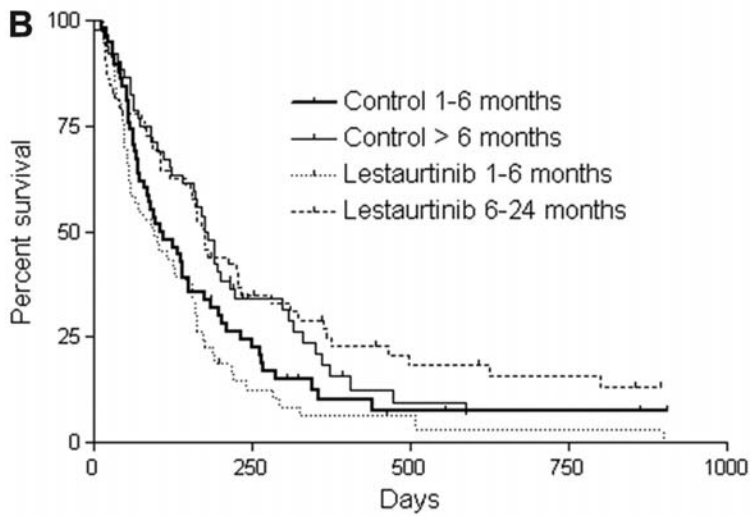
✓AC220 (quizartinib): remarkable activity in monotherapy

- Composite response rate (CR+CRp+CRi) of ≈45%
- Differentiating potential in AML blasts

Fischer T, JCO 2010
Levis M, Blood 2011
Cortes J, Haematologica 2011

Lestaurtinib added to CT failed to improved outcome in relapsed AML





Control arm: CT (MEC or HiDAC)

Experimental arm: CT + lestaurtinib

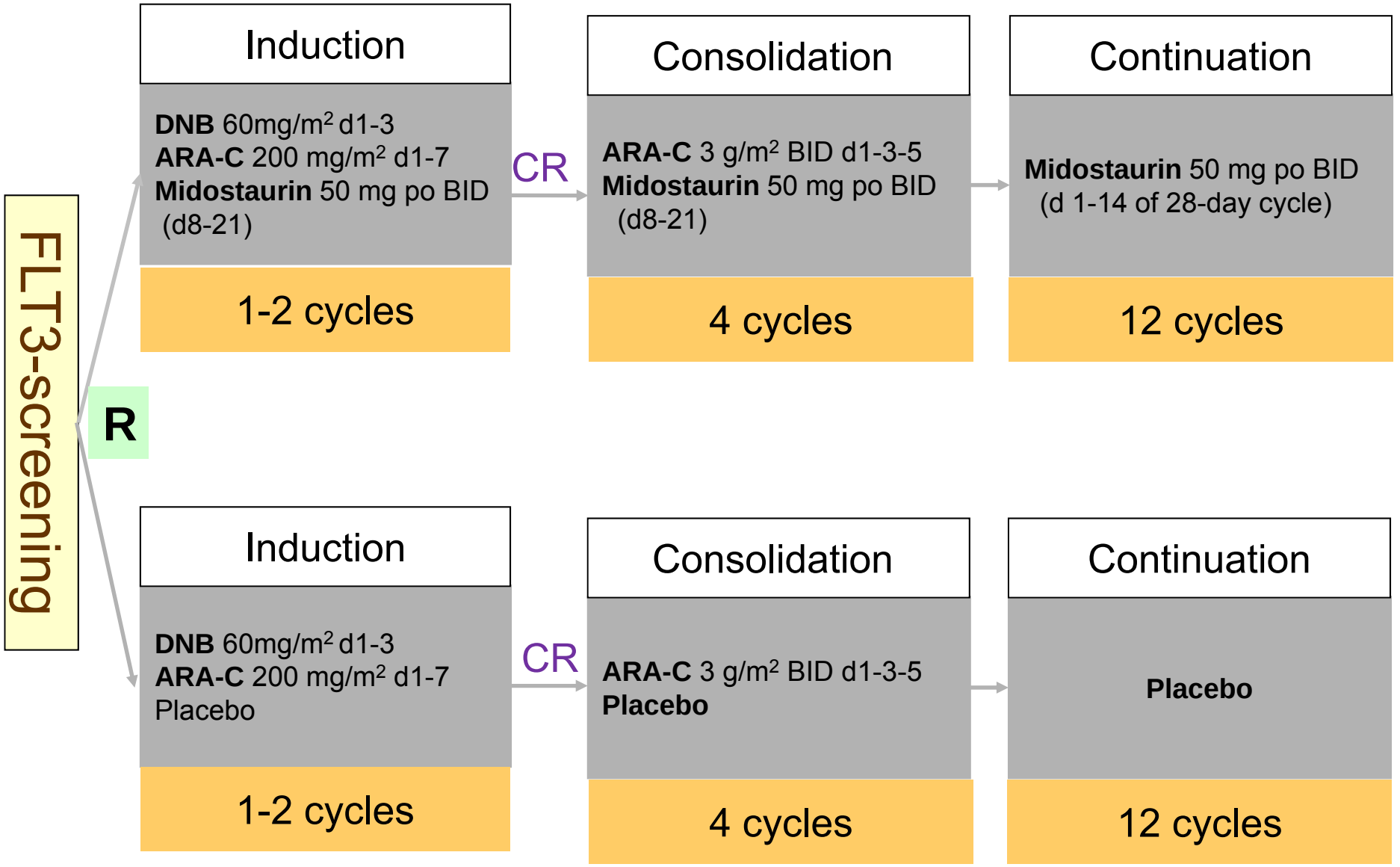
Levis M et al. Blood 2011

Midostaurin (PKC412): experience combined to CT

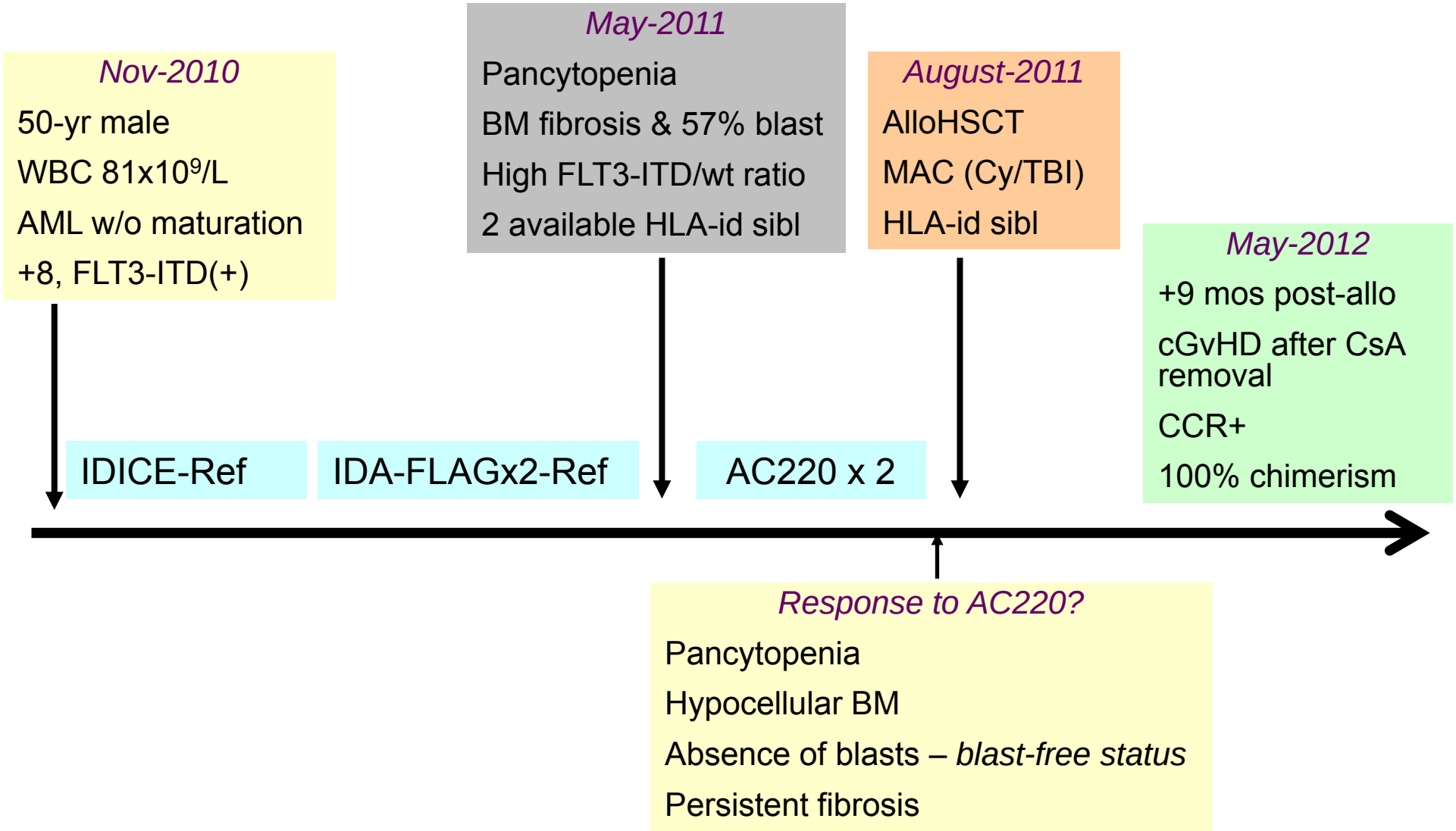
- ✓ Sequential (day 8→21) or simultaneous (1 →21)
- ✓ administration with CT (daunorubicin/SD ara-C)
- ✓ Reduced dose (50 mg BID) was better tolerated
- ✓ Results in 40 pts:
  - CR in 12/13 (92%) FLT3mut AML
  - CR in 20/26 (77%) FLT3wt
- ✓ Sequential regimen were better tolerated

Stone R, Blood 2005

RATIFY trial: exploring the effect of adding midostaurin (PKC412) to frontline CT in FLT3-ITD AML



AC220 as a *bridge strategy* to alloHSCT in a patient wirth a primary chemorefractory FLT3-ITD(+) patient



FLT3 inhibitors: an adequate target?

✓ FLT3-ITD: a frequent mutation (≈20%) & frequent FLT3 overexpression in unmutated FLT3 AML cases

✓ Driver or passenger mutation?

Passenger mutation

Evolutive mutation

Insufficient to induce AML in preclinical models

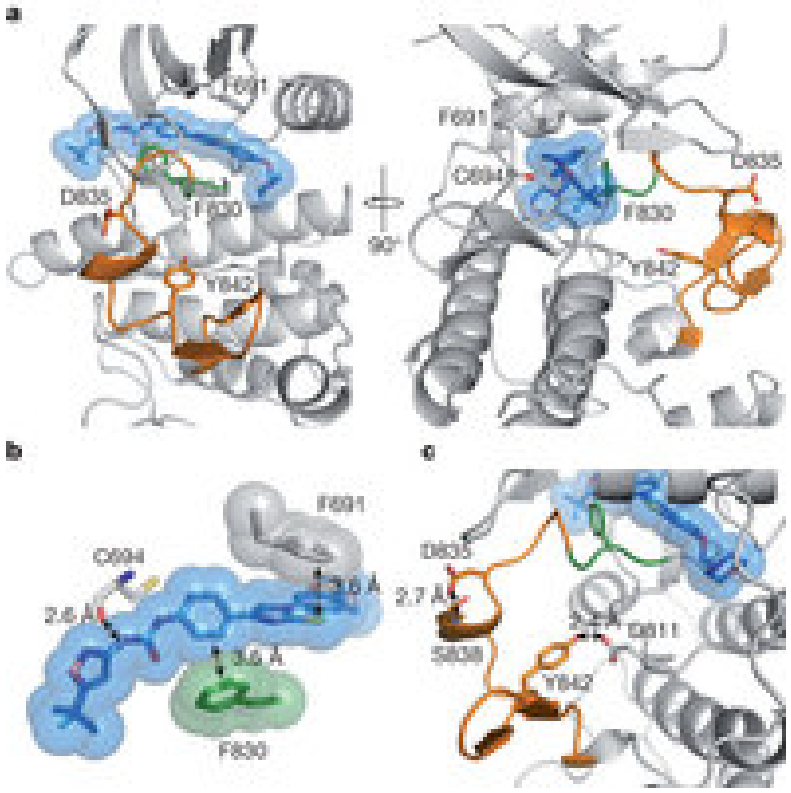
Not present in all paired relapsed samples

Highly variable allelic burden

Driver mutation

Identification of TK domain mutations confering resistance in relapsed patients

FLT3 mutations arising in relapsed pts under quizartinib involve critical residues for drug-target interaction – a mechanism of selected pressure



Mutations in 8/8 relapsed pts

Critical residues

“Polyclonal” resistance

Cross-resistance with sorafenib

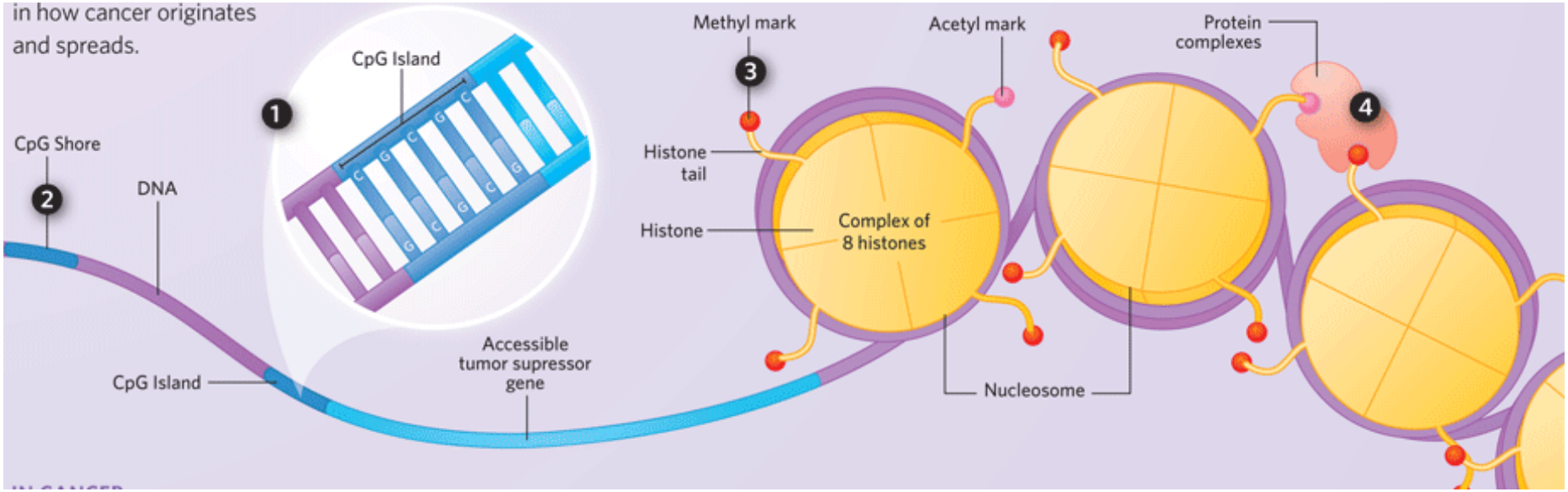
FLT3-ITD as a driver mutation

FLT3-ITD involves LICs?

Confers oncogene addiction

Smith CC, Nature 2012

AML is a disease with deregulated epigenetic program: role for *epigenetic* therapy



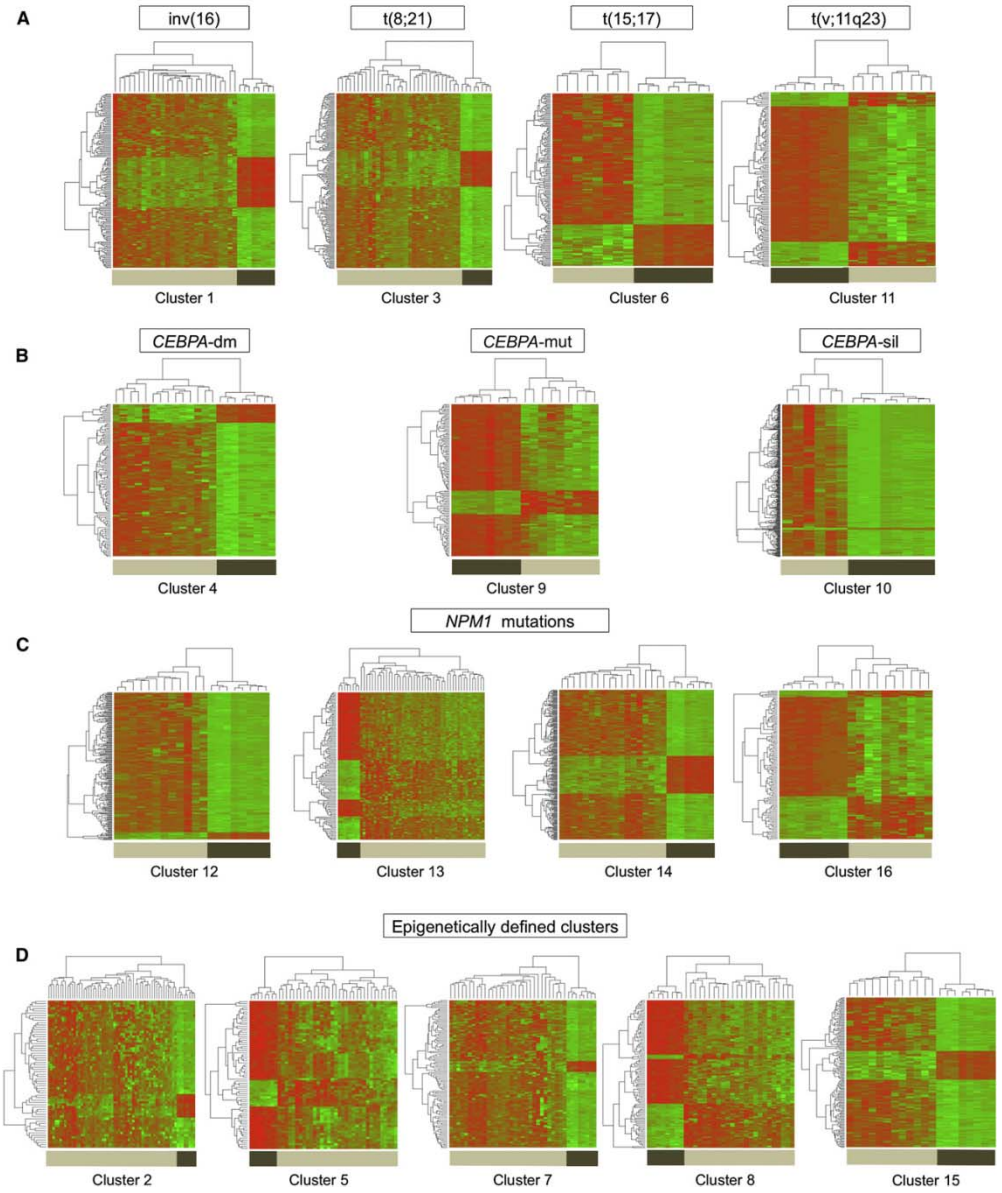
DNA methylation (CpG islands) – demethylating agents

Histone deacetylation – HDAC inhibitors

Histone methylation

miRNA gene methylation

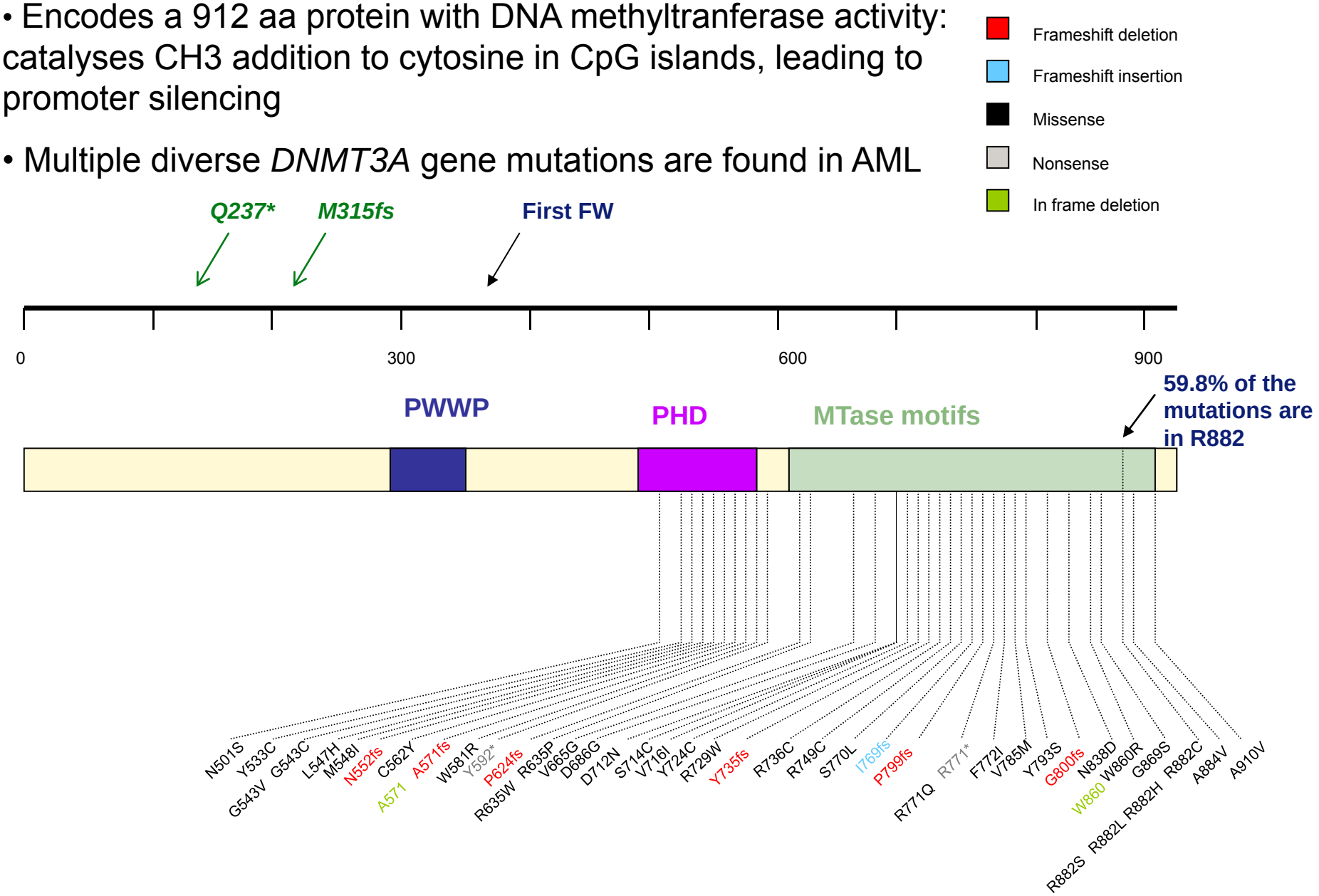
Epigenetic signatures in AML



Figueroa ME, Cancer Cell 2010

DNMT3A gene

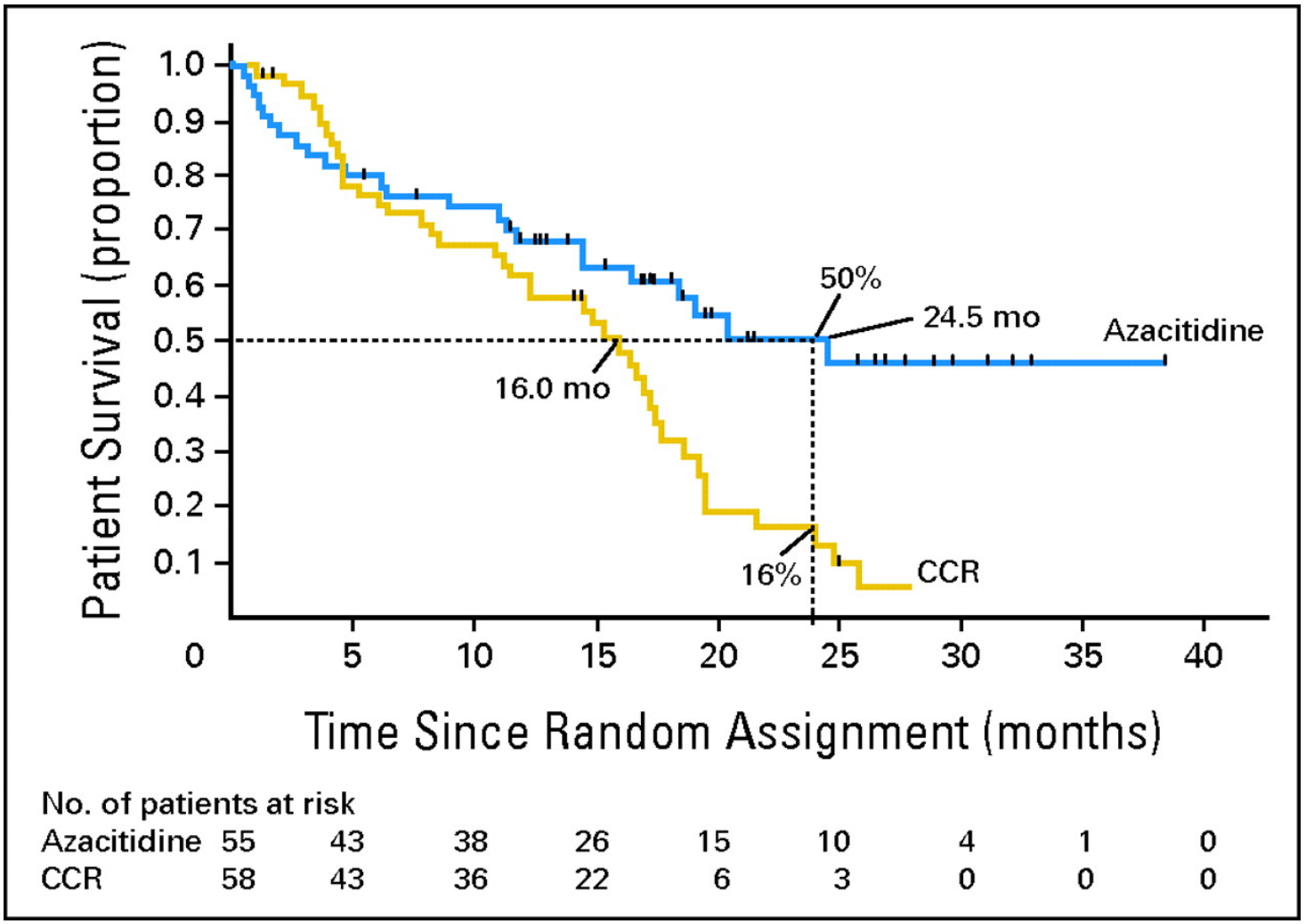
- Encodes a 912 aa protein with DNA methyltranferase activity: catalyses CH3 addition to cytosine in CpG islands, leading to promoter silencing
- Multiple diverse *DNMT3A* gene mutations are found in AML



Demethylating agents in AML – possible development

- Monotherapy in pts unfit for intensive CT – benefit in "low-count" (20 – 30%) blast AML
- Role in higher blast %?
- Maintenance after CT-induced response – looking for a post-remission strategy in high-risk disease
- Combination with HDAC inhibitors – the *García-Manero's way*
- In combination with frontline chemotherapy - Synergistic potential? Best time sequence? AMLSG 12-09 trial
- Aza after transplant – pre-emptive/therapy for relapse

Azacitidine Prolongs Survival (vs. Conventional Care Regimens) in Elderly Patients With Low Bone Marrow Blast Count AML

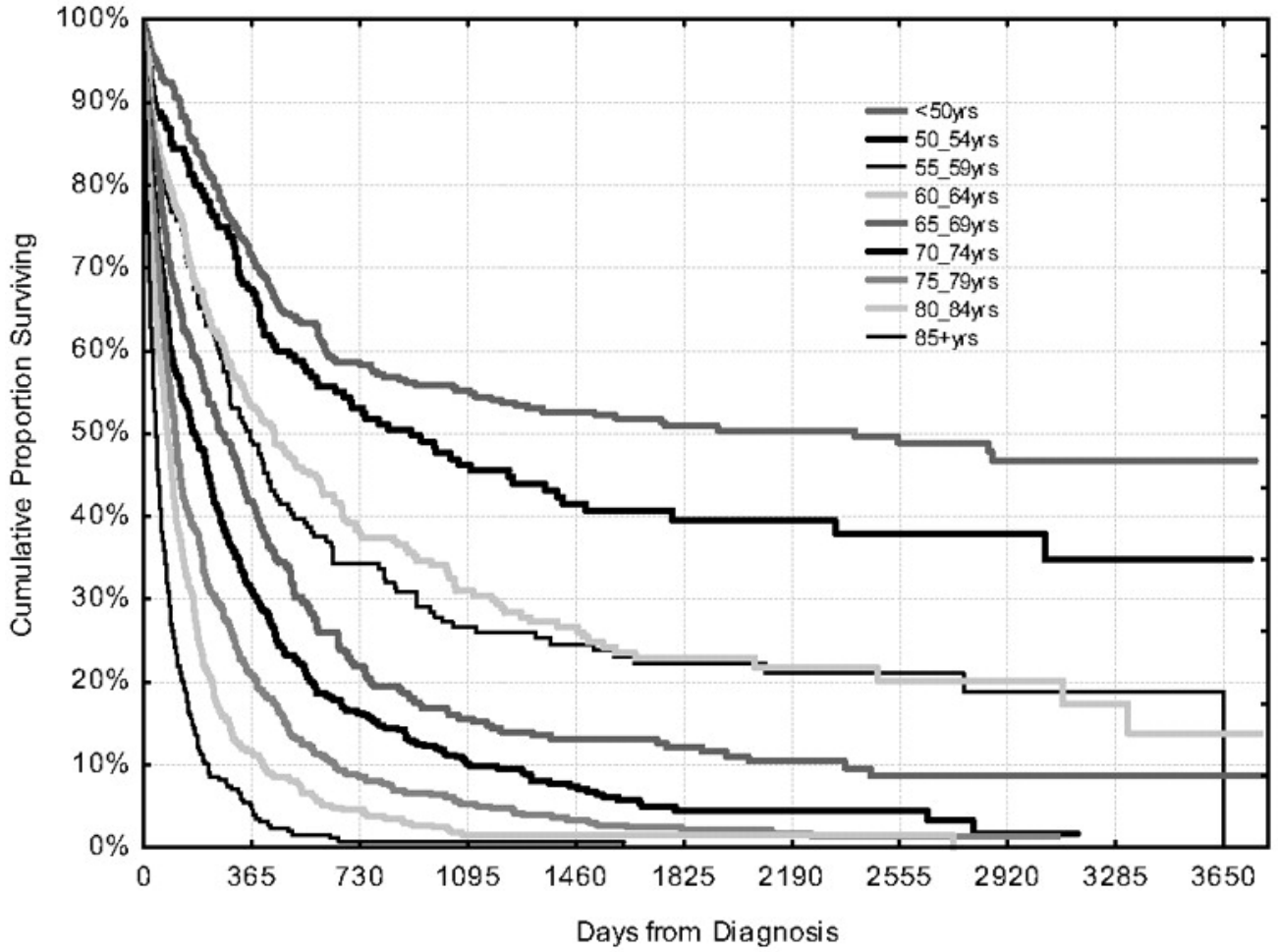


Fenaux P et al. JCO 2010

Demethylating agents in AML – possible development

- Benefit (prolonged response) for a subgroup of pts – tools for identifying predictors
- No eradicative potential – need to associate to other strategies
- Reasons for non-eradicative nature - evasion of LSCs?
- True mechanism of action of demethylating agents: more than CpG demethylation
- Optimal dose – regimen are still unknown

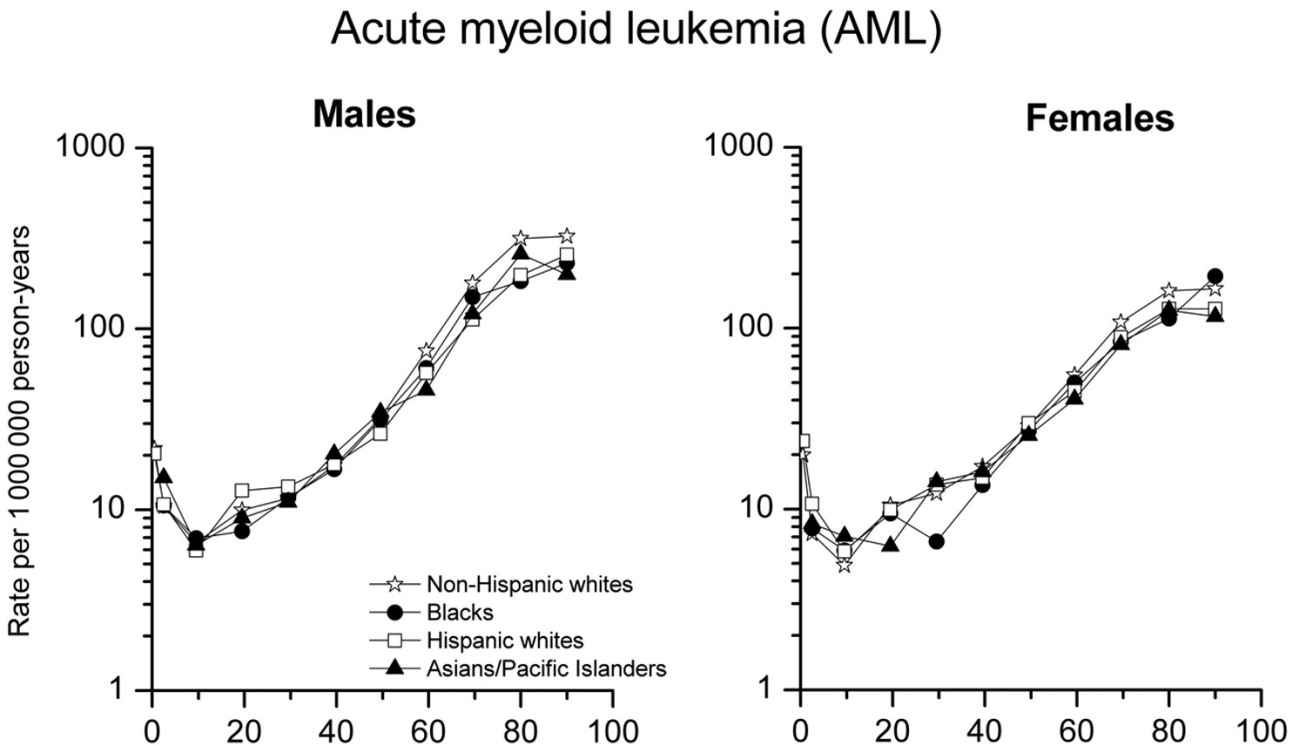
Survival according to age: Swedish Acute Leukemia Registry (1997-2005)



Overall survival according to age irrespective of management (top, n = 2767)

Juliusson G, et al. Blood 2009

Increasing incidence of AML with age: a work of years



Dores GM, et al. Blood 2012

New agents for elderly AML patients – urgent progress needed!

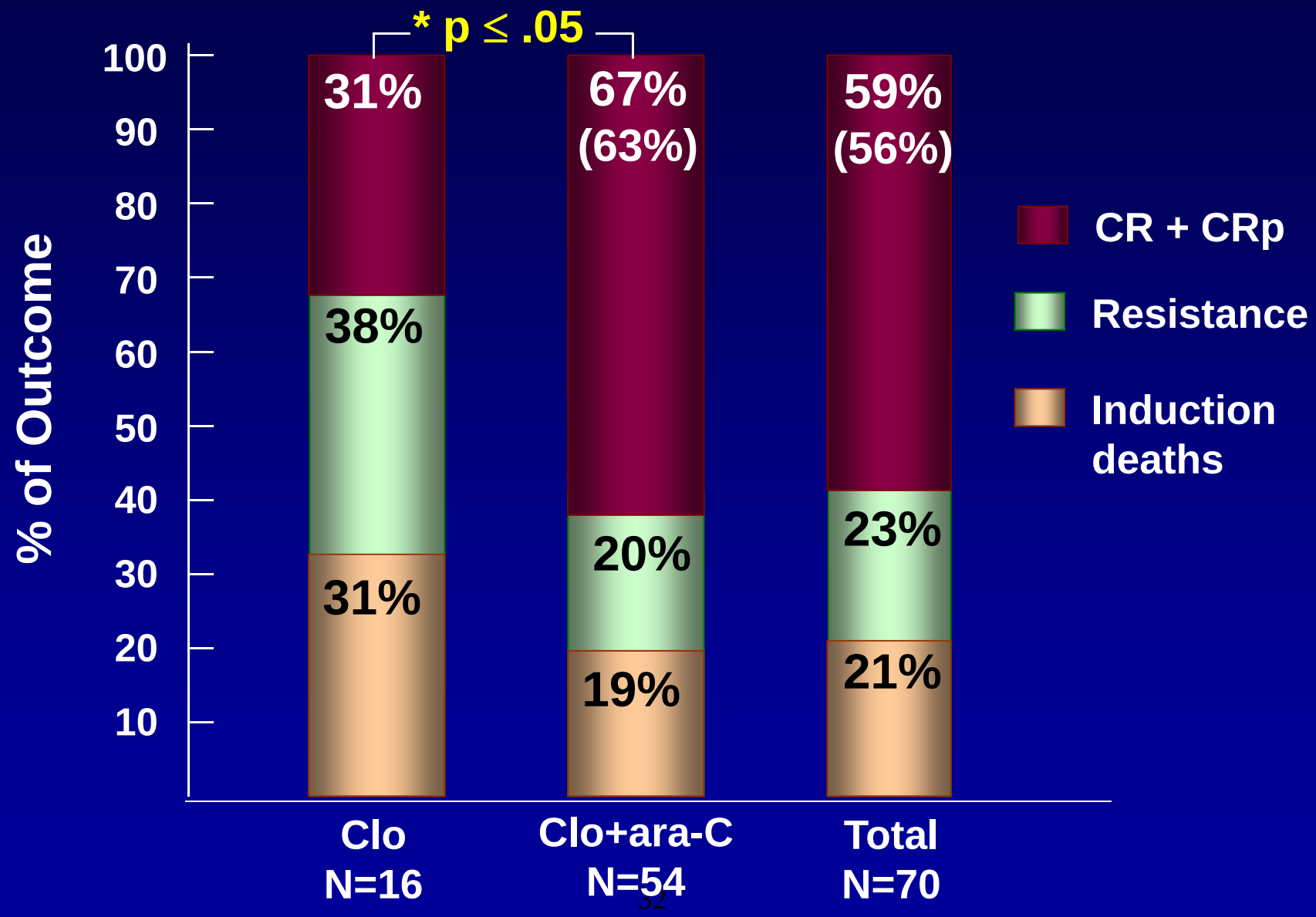
- Absence of benefit with intensive CT – selected pts with highly chemosensitive AML

- How to be more efficient in the search of new agents? The “pick-a-winner” MRC approach
  - Multitesting several with “control arm”
  - Interim assessment to avoid useless recruitment
  - Response rate is a valid surrogate?

Constant search of new agents for AML

Evaluated	*Under evaluation*
MDR inhibitors	Newer nucleoside analogs (clofarabine, troxacytabine, elacytarabine,…)
Farnesyl-transferase inhibitors (tipifarnib,…)	FLT3 inhibitors
Lestaurtinib (FLT3 inh)	Demethylating agents
Laromustine (cloretazine)	Histone modificators (HDACs)
Amonafide	Aminopeptidase inhibitors
Arsenic Trioxide	Hedgehog inhibitors
ATRA+CT in non-APL	NEDD8-Activating Enzyme (NAE) inhibitors
…	mTOR inhibitors
	…

Clofarabine + LDAC: Outcome (N=70)



Faderl S. Blood 2008;112:1638

Analyzing causes of failure - challenges for developing a curative therapy in AML

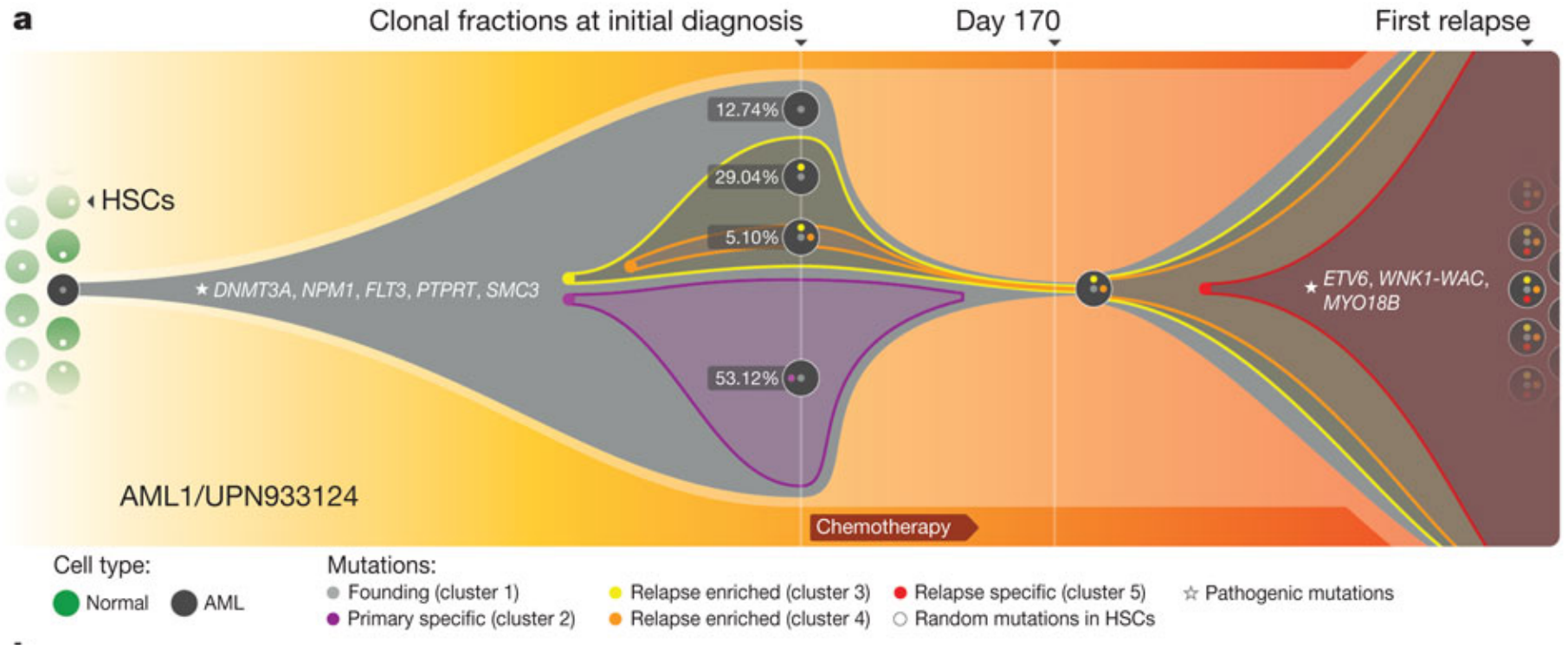
- Biological heterogeneity – not a unique target
- Multi-step process – lessons from whole-genome sequencing
- Quiescence of leukemia-stem cells confers chemoresistance – need to target LSCs
- AML: a family of different subclones – preleukemic & evolutive clones
- BM microenvironment – a protective *milieu*

Lessons from complete sequencing of AML

- Concurrence of multiple mutations per patient (>8):
  - A set of recurrent mutated genes (>50)
  - Most commonly mutated genes: *FLT3* (36%), *NPM1* (25%), *DNMT3A* (21%), *IDH1* (18%), *IDH2* (10%), *TET2* (10%), *ASXL1* (6%), *NRAS* (6%), *TTN* (6%) & *WT1* (6%)
  - Mutation in genes previously unknown
  - New leukemic pathways unraveled: the cohesin complex (STAG2, SMC1A/3, RAD21)
  - Subtype-specific mutations & other *transversal* mutations

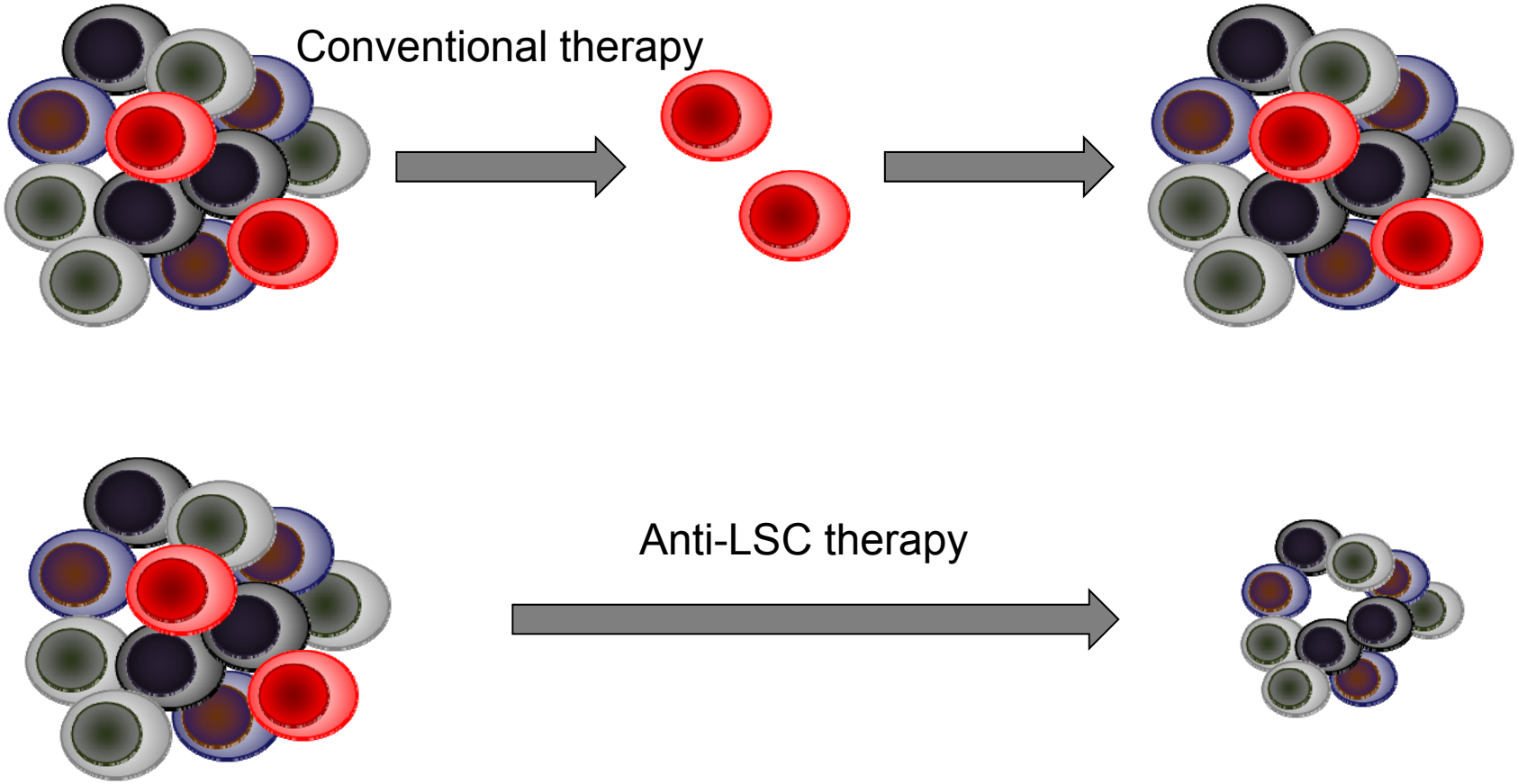
John Welch/T Ley (University of Washington), ASH 2011

Origin of relapse in AML: evolution from founding clone / subclone / ancestral clone?



L Ding *et al*. *Nature 2011*

Why are LSCs important?

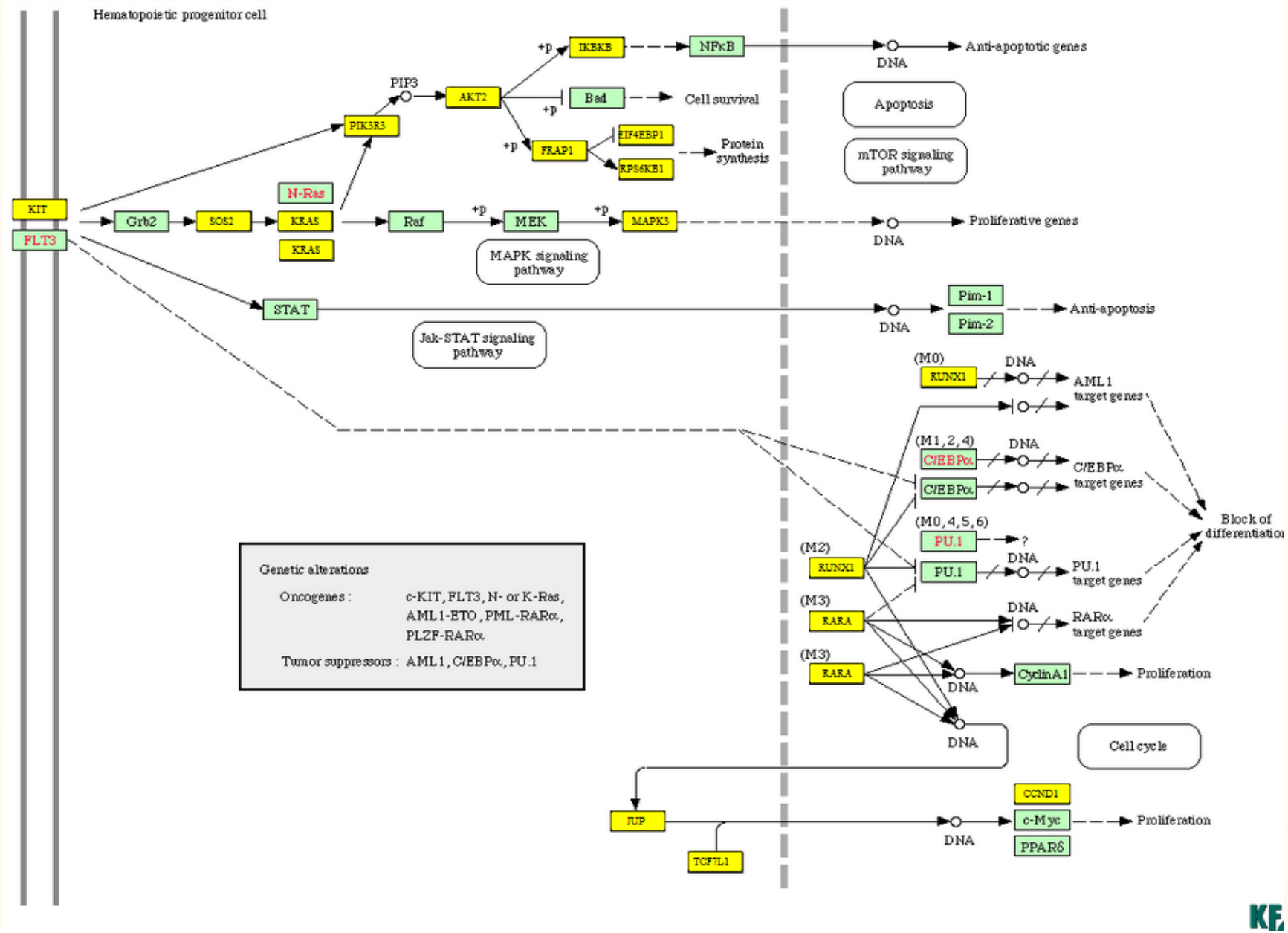


Cortesía de Ruth M. Risueño

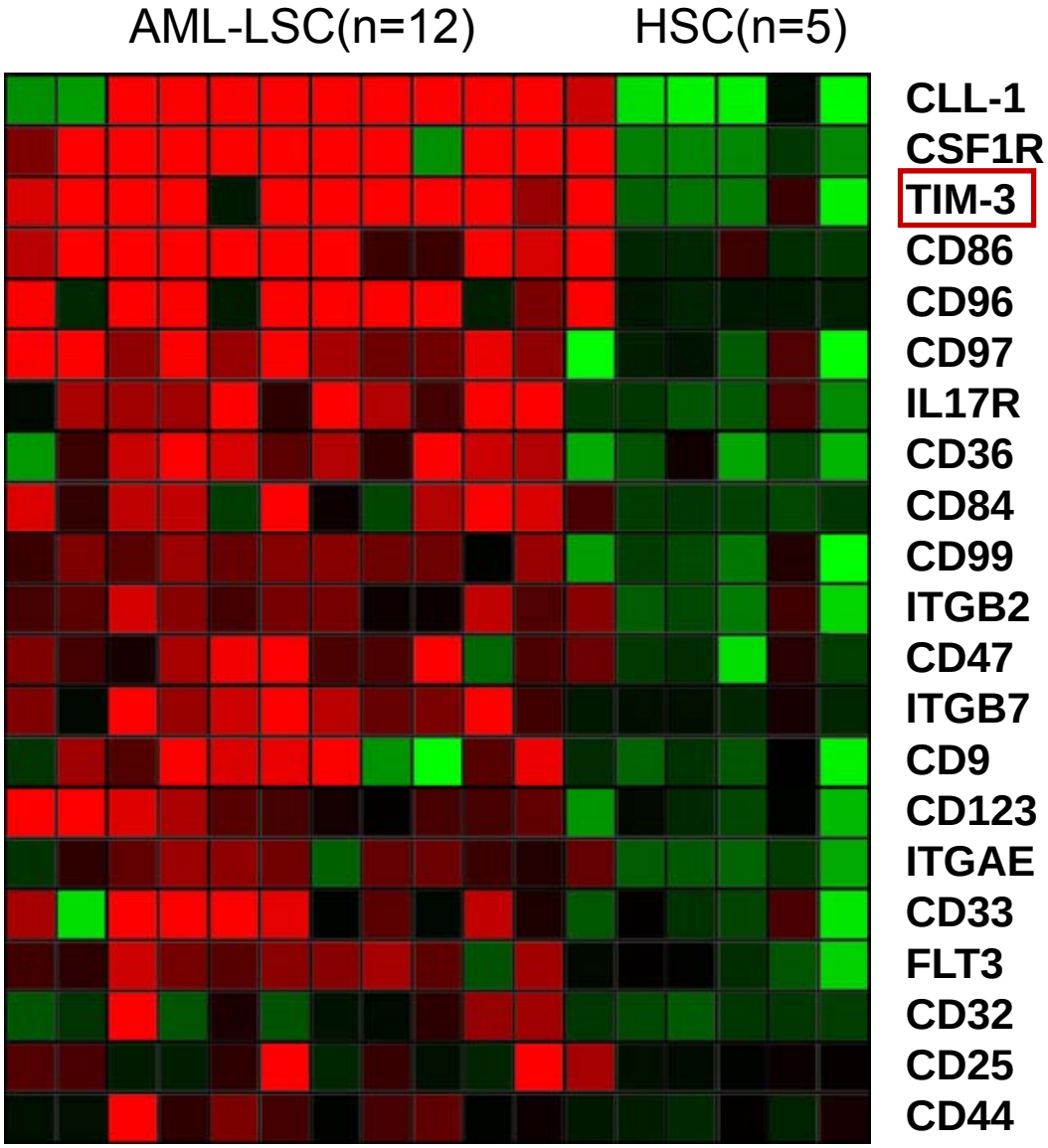
Potential mechanisms for targeting Leukemia Stem Cells

- Targeting fusion proteins
  - High diversity in AML
- Signaling pathways (JAK/STAT, Wnt, Hedghog,…)
  - Diversity
  - Redundancy-overlapping
- Self-renewal mechanisms
  - Similarity HSCs - LSCs
- Inducing differentiation – the ATRA model
- MoAbs against specific LSC Ags

AML biology: putative involved pathways

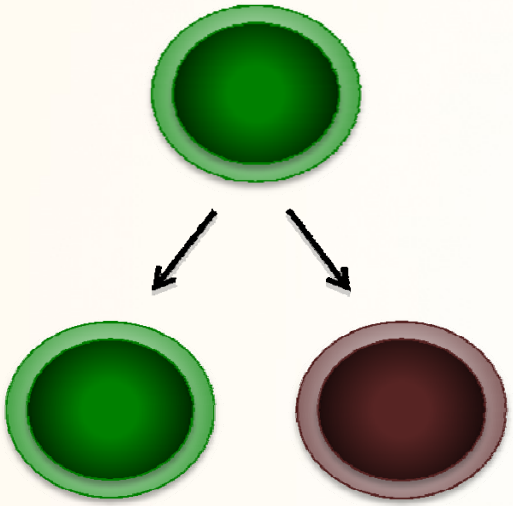


Selective targeting of Leukemia-Stem Cells: still an utopy?



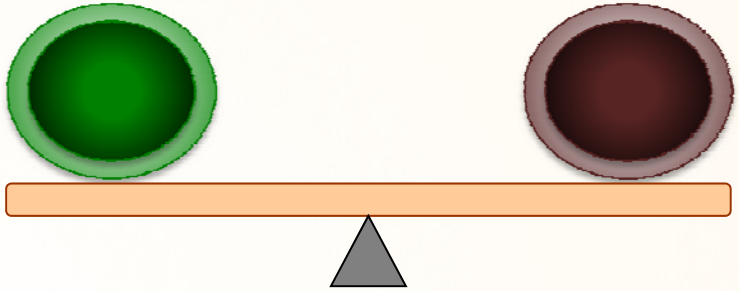
Kikushige Y, Cell Stem Cell 2010

Self-renewal/Differentiation balance in HSCs/LSCs: promoting differentiation induces LSC apoptosis

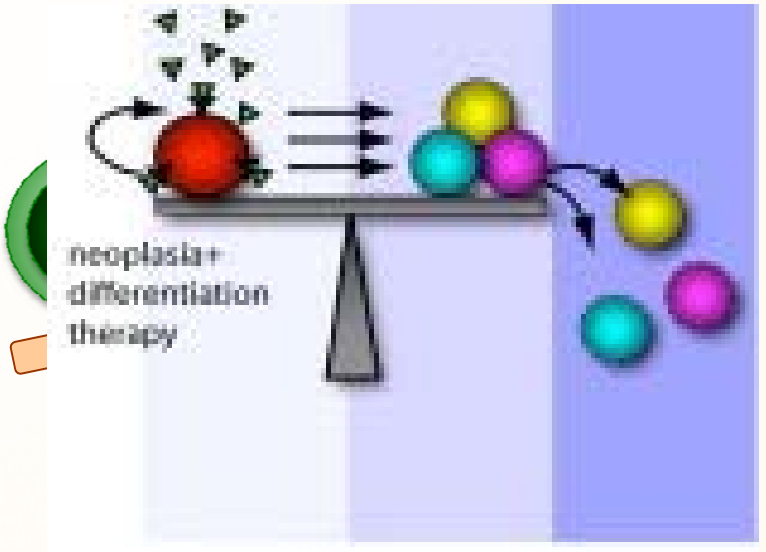


Asimétrica

HSCs



LSCs

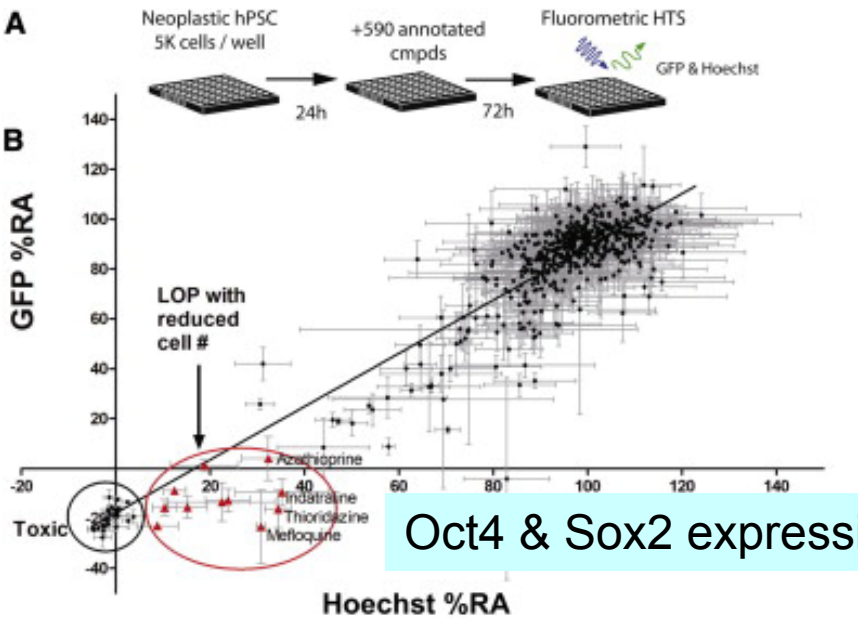


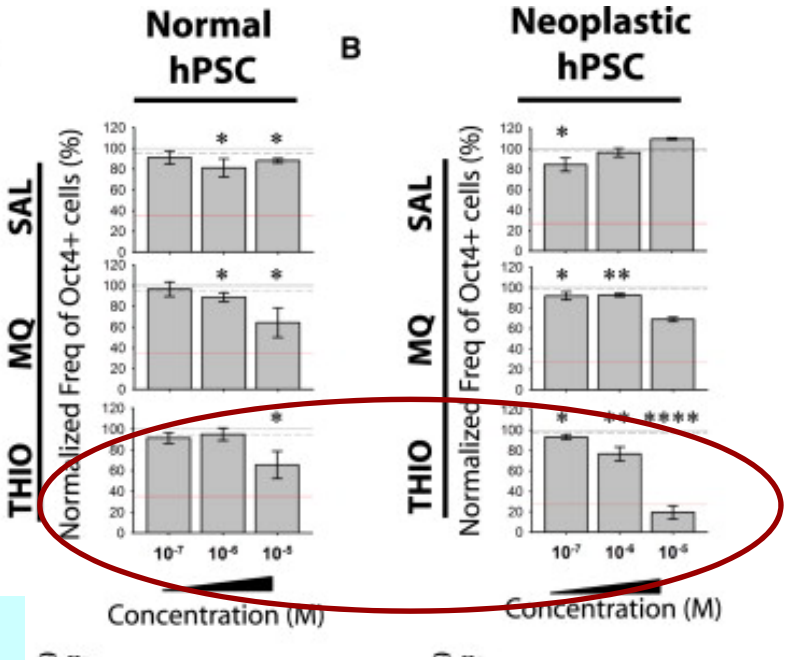
Sachlos E, Risueño RM, Cell 2012

Chemical screening of compounds leading to **loss of pluripotency (LOP)**

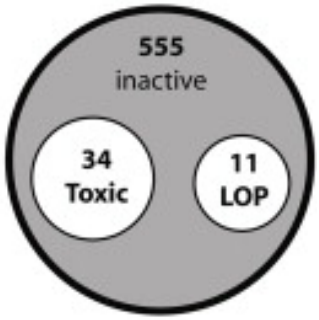
Selection of selective compounds against LSCs

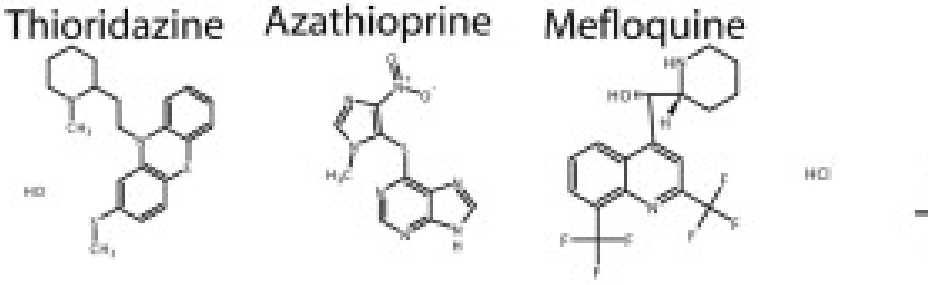
Differentiation / Self-renewal





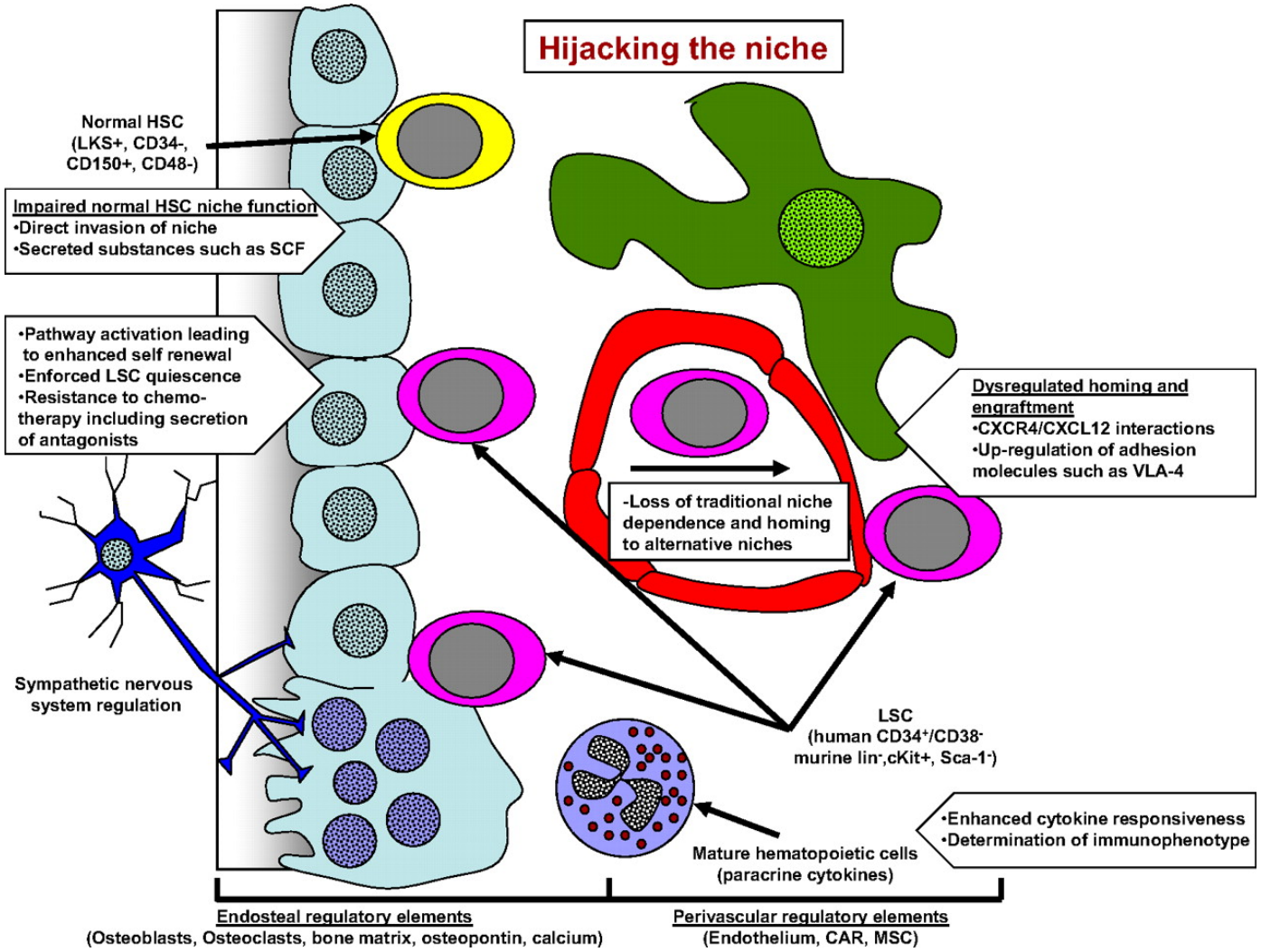
Oct4 & Sox2 expression





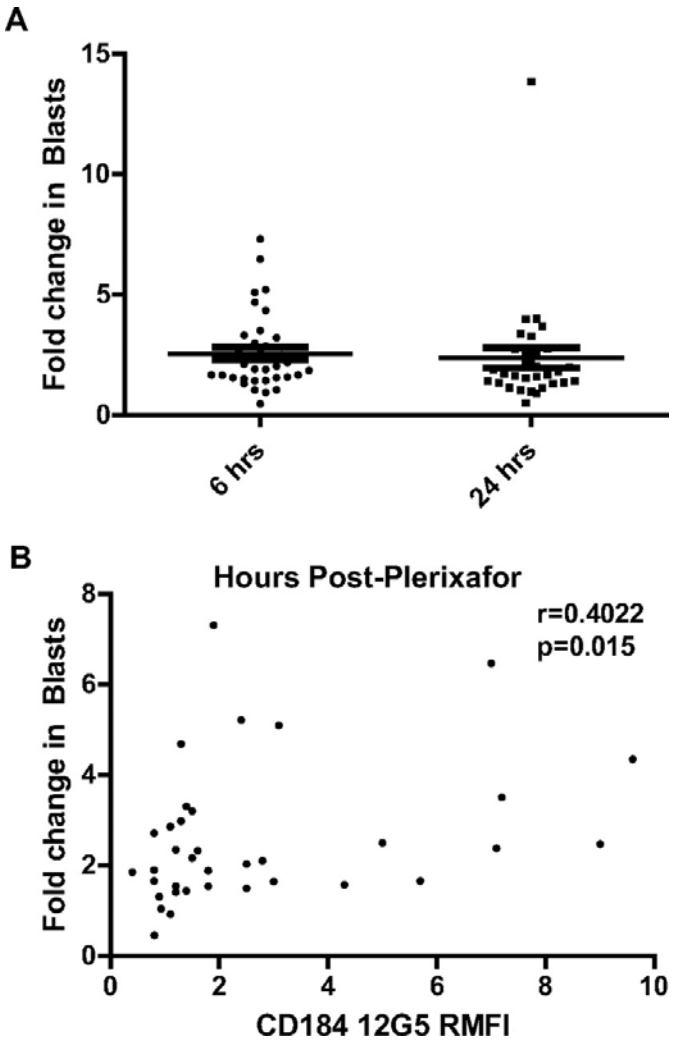
Sachlos E, Risueño RM, Cell 2012

AML & hematopoietic niche: protection, disruption



Lane SW et al, Blood 2009

Mobilization of AML blasts after CXCR4 antagonist plerixafor: a true chemosensitization method?

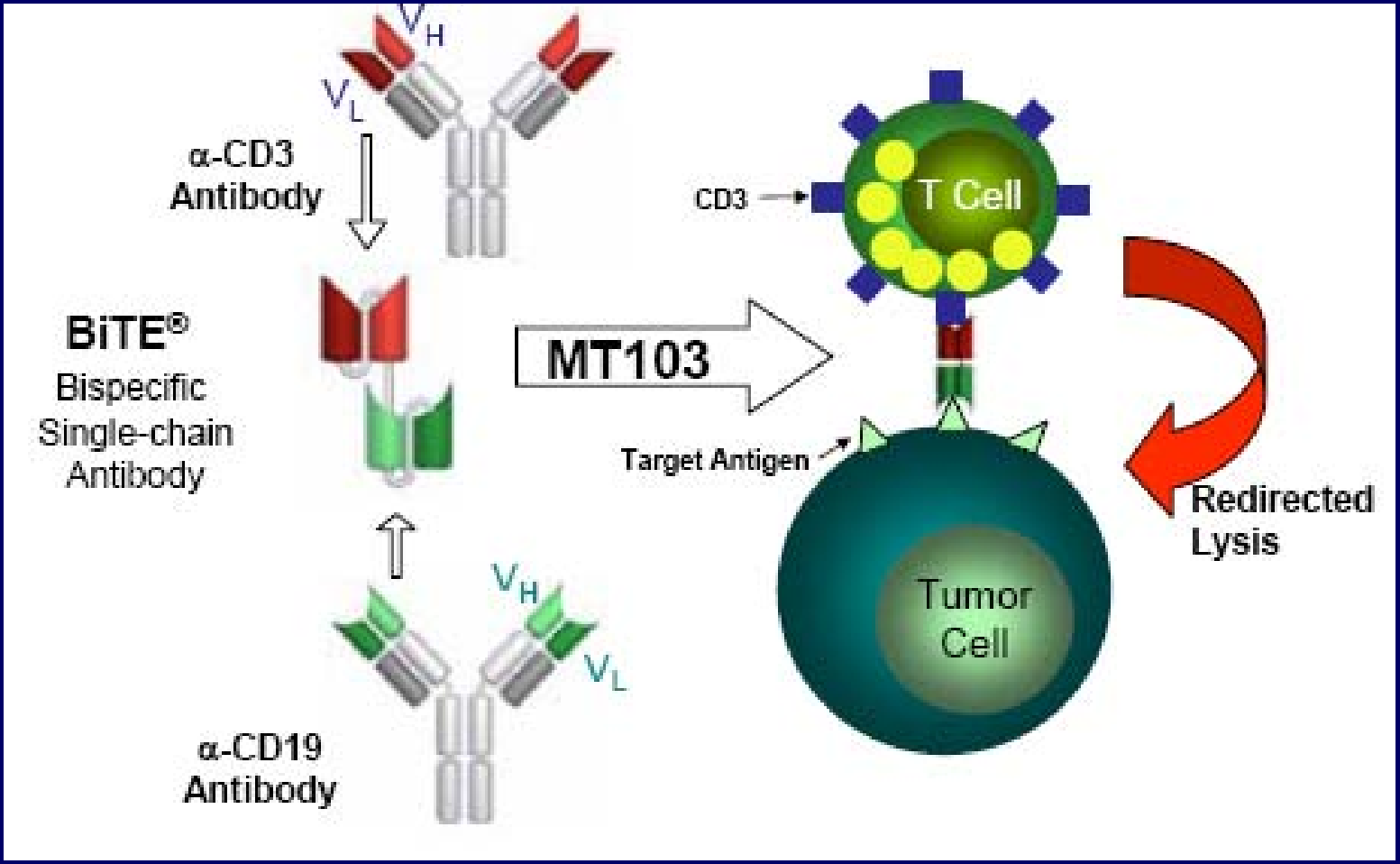


Uy G L et al. Blood 2012

Adult ALL – state-of the art

- Despite high initial response, less than 50% of pts are cured – insufficient antileukemic potential of current agents
- Dense-intense regimens used in adult B-ALL cause significant toxicity
- AlloHSCT arises as the only curative option for very high-risk subsets
- Need to identify future relapsers:
  - Sensitive assessment of MRD (the era of MRD-based protocols)
  - High-risk molecular markers (del IKAROS, MLL-r,…)

Blinatumomab: bispecific (CD19-CD3) recombinant antibody

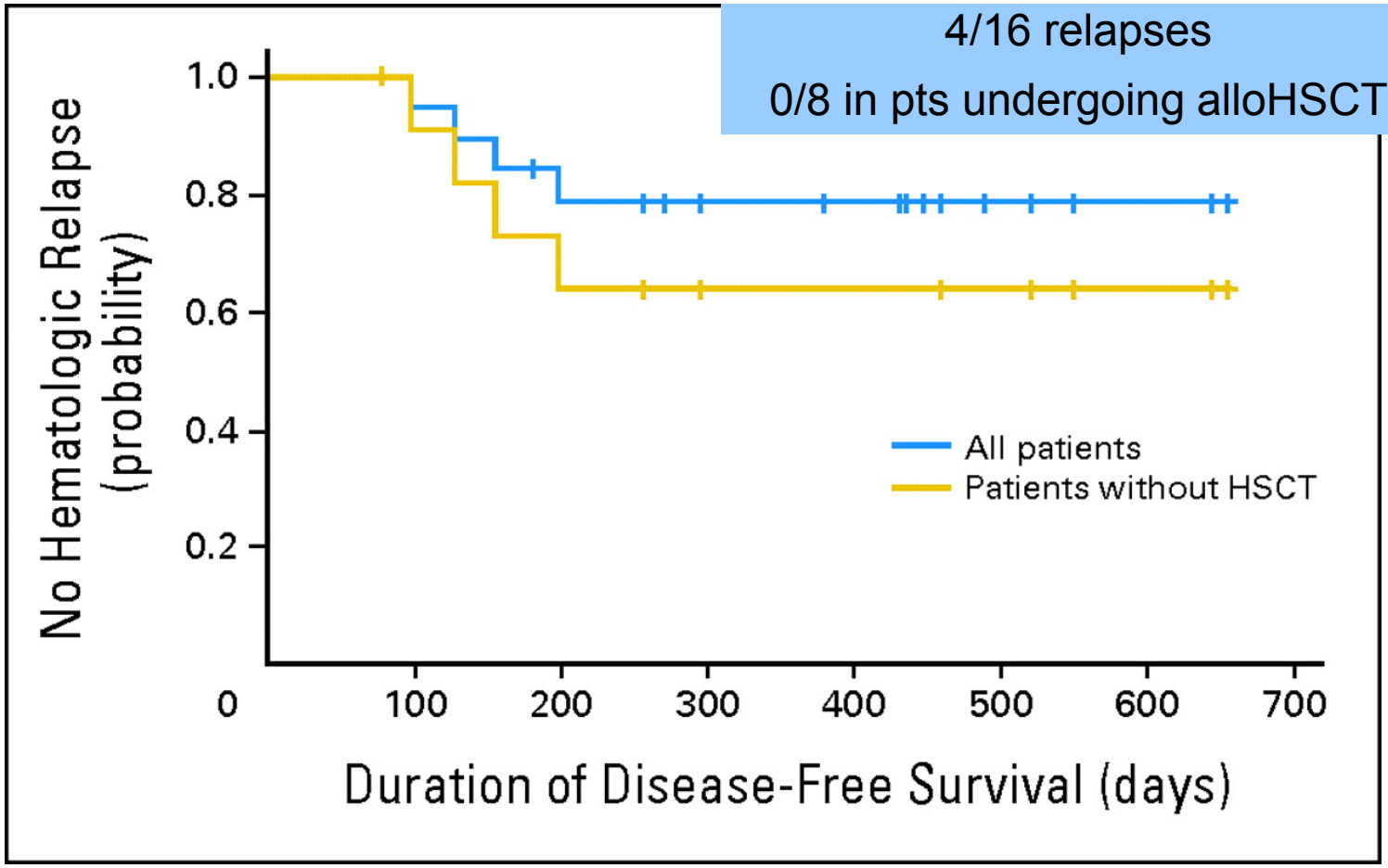


Blinatumomab for eradication of MRD in B-ALL: experience in a Phase-II trial

- Adult B-ALL in morphological CR with detectable MRD at molecular level (≥1 x 10^{-4}) after induction/consolidation – molecularly refractory or molecular relapse
- Blinatumomab at 15μg/m^2 as continuous infusion x 4 weeks (1 – 4 cycles). AlloHSCT was proposed in responders
- 20 pts evaluable:
  - Obtention of molCR in 16 (80%) after 1st cycle
  - Active in molecularly refractory and high burden MRD

Topp MS (GMALL), JCO 2011

Sustained response after Blinatumomab in MRD(+) B-ALL



Topp MS (GMALL), JCO 2011

Blinatumomab: *unexpected* adverse events

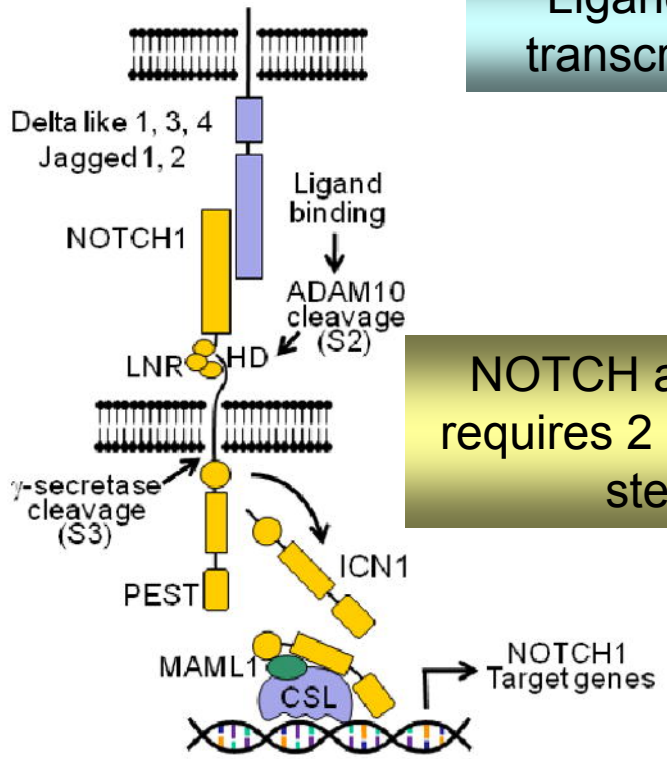
- High frequency of serious CNS events (ataxia-apraxia, aphasia, seizures, cognitive disturbance,…) with first doses
- Cytokine release syndrome (CRS) with DIC in pts with high-burden disease
- Lowering initial dose & pre-phase with dexamethasone ±cyclophosphamide to prevent CRS

Blinatumomab: considerations & future development

- Role in overt-morphological refractory/relapsed B-ALL
- Role in other B-cell malignancies
- Mechanisms of disease *escape*:
  - Body sanctuaries (CNS, testis)
  - Loss of CD19 expression
- Future development of new targets for bispecific moAbs:
  - Anti CD33-CD3 (AML)

Role of NOTCH mutations in T-ALL pathogenesis: an opportunity for targeted therapy

Ligand-activated transcription factor



NOTCH activation requires 2 proteolytic steps

-Anabolic glycolysis

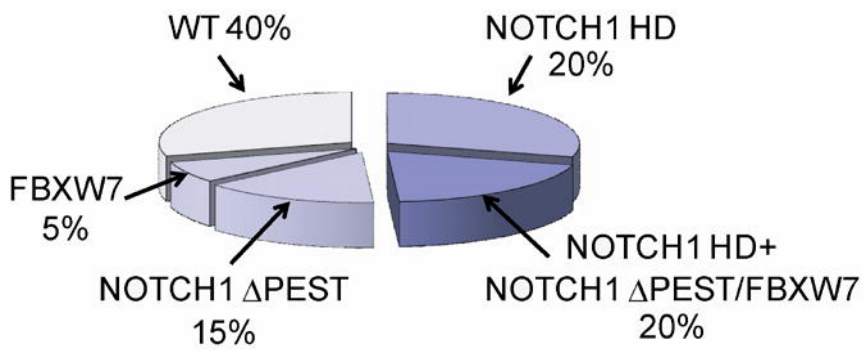
- Cell growth (PI3K-AKT-mTOR)

Activation of target genes

Ferrando A, ASH 2009

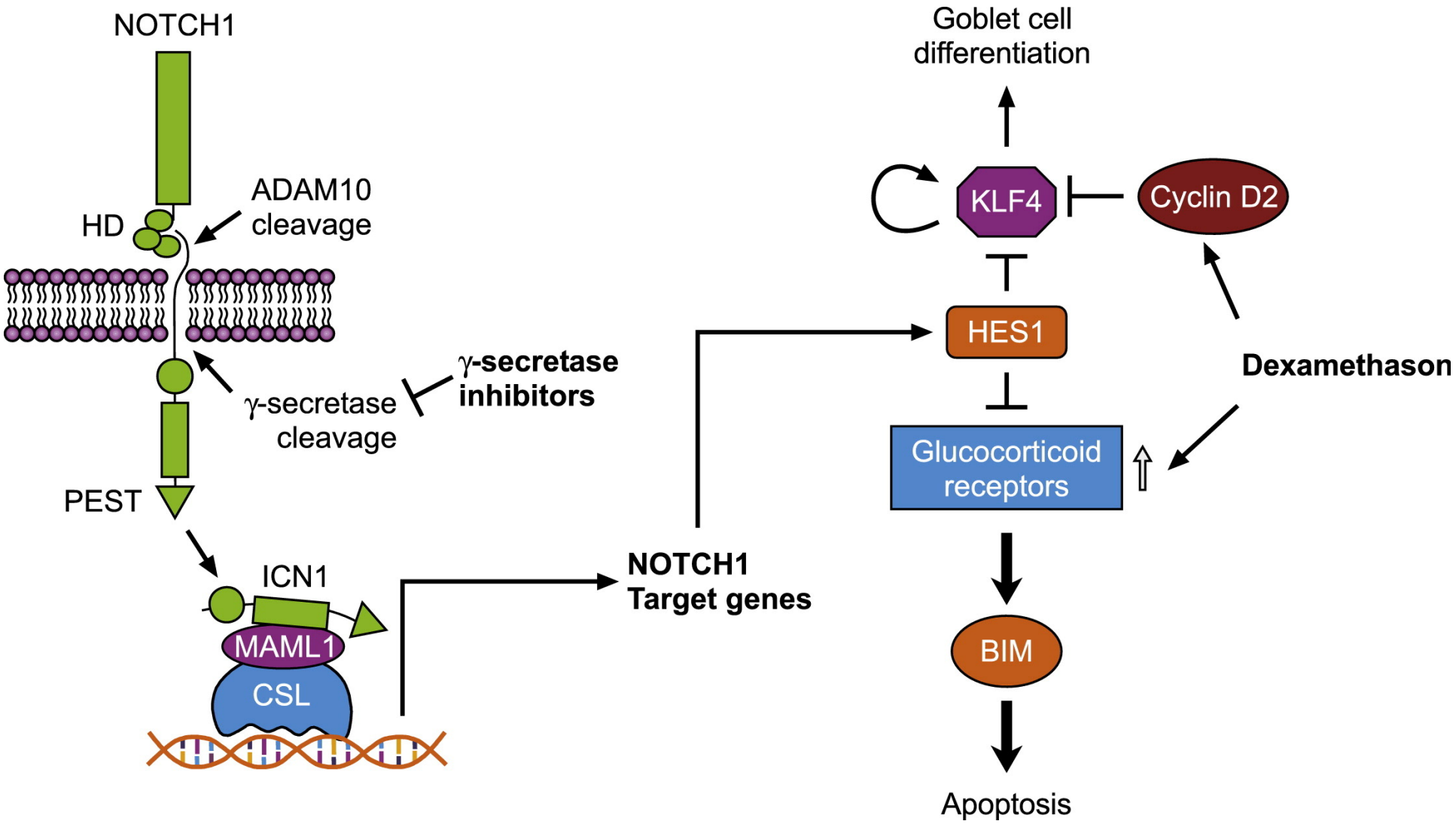
Aberrant NOTCH1 signaling in T-ALL

- Constitutive activation of NOTCH1 is found in ≈60% of T-ALL



- Gamma-secretase (GS) cleavage is essential for NOTCH1 activation:
  - GS inhibitors (GSIs) are a potential targeted therapy (GSI PF-03084014, MK-0752)

Benefits of combined GSIs + dexamethasone: ↓less GI toxicity, ↑ anti-leukemic effect



Real PJ et al , Nature Medicine 2009

New agents for acute leukemia – remarks (I)

- Progress in AML/ALL biology knowledge is essential for developing new therapies
- Heterogeneity of disease – analysis of benefit in specific populations
- Multistep disease – need of combining agents against diverse targets
- Targeting LSCs: hope for cure

New agents for AL – remarks (II)

- Interfering with microenvironment protection might increase antileukemic efficacy
- Need to develop more rapid strategies for identifying active compounds
- Relevant role of clinical trials to improve outcome: company vs. non-benefit groups sponsored trials

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