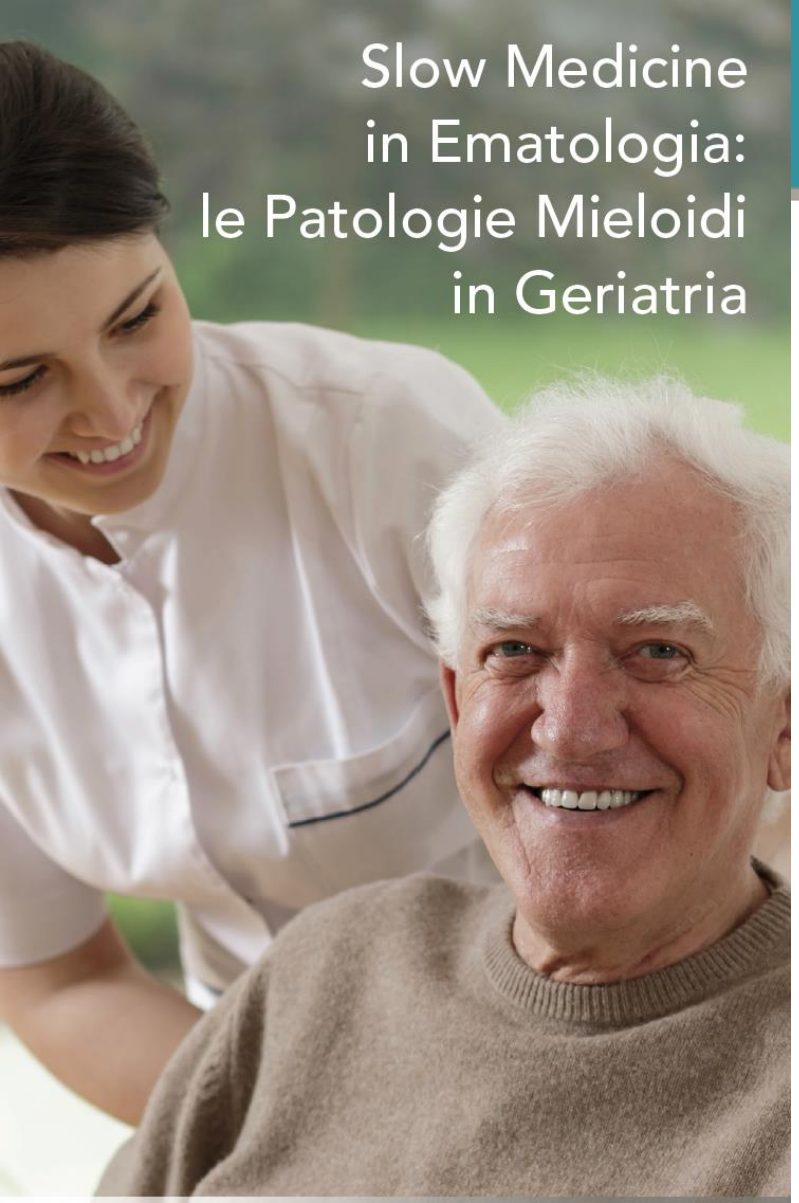


Giovanni Martinelli

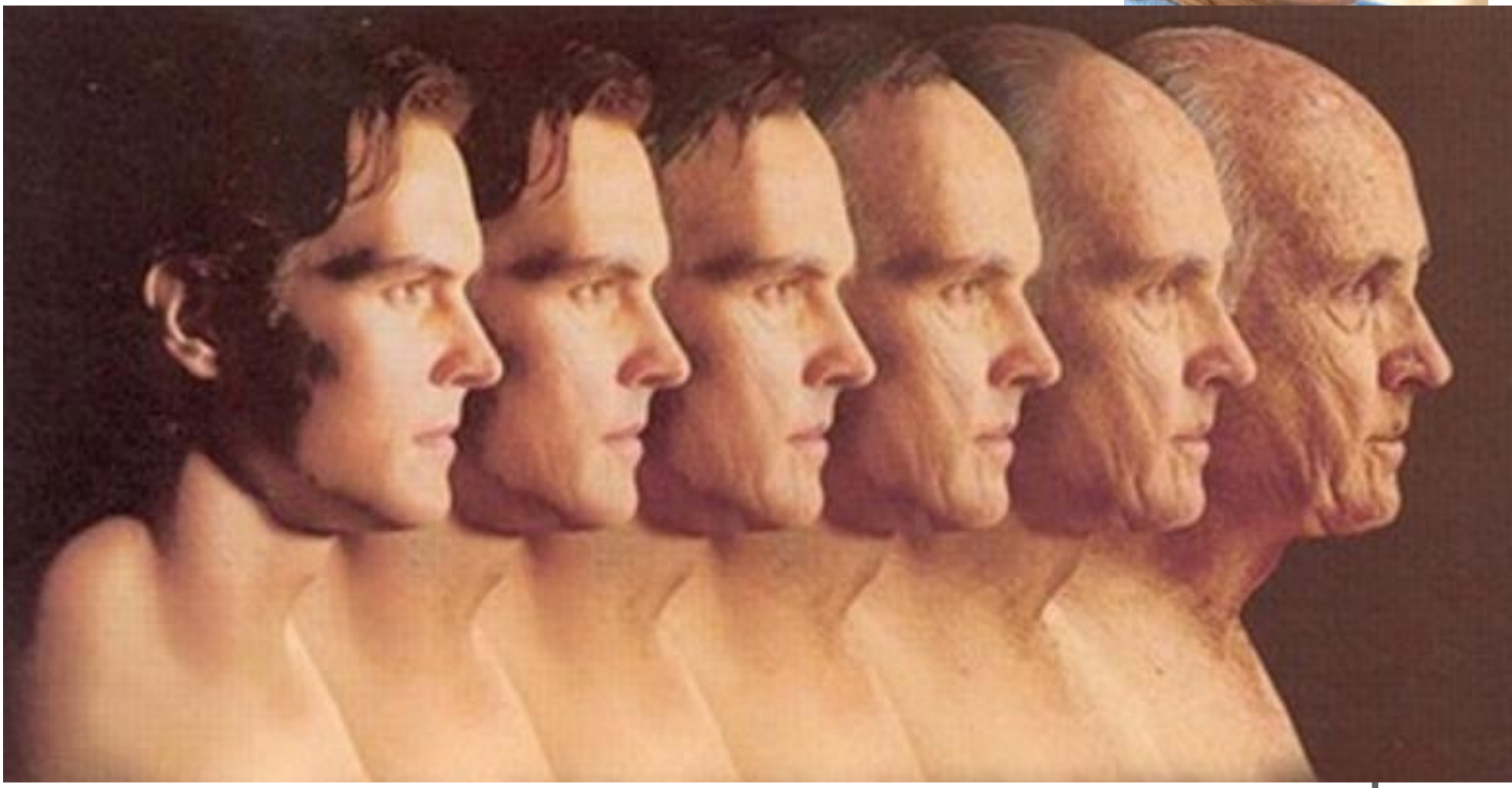
Institute of Hematology "L. e A. Seragnoli"
University of Bologna, Bologna, Italy

Slow Medicine in Ematologia: le Patologie Mieloidi in Geriatria

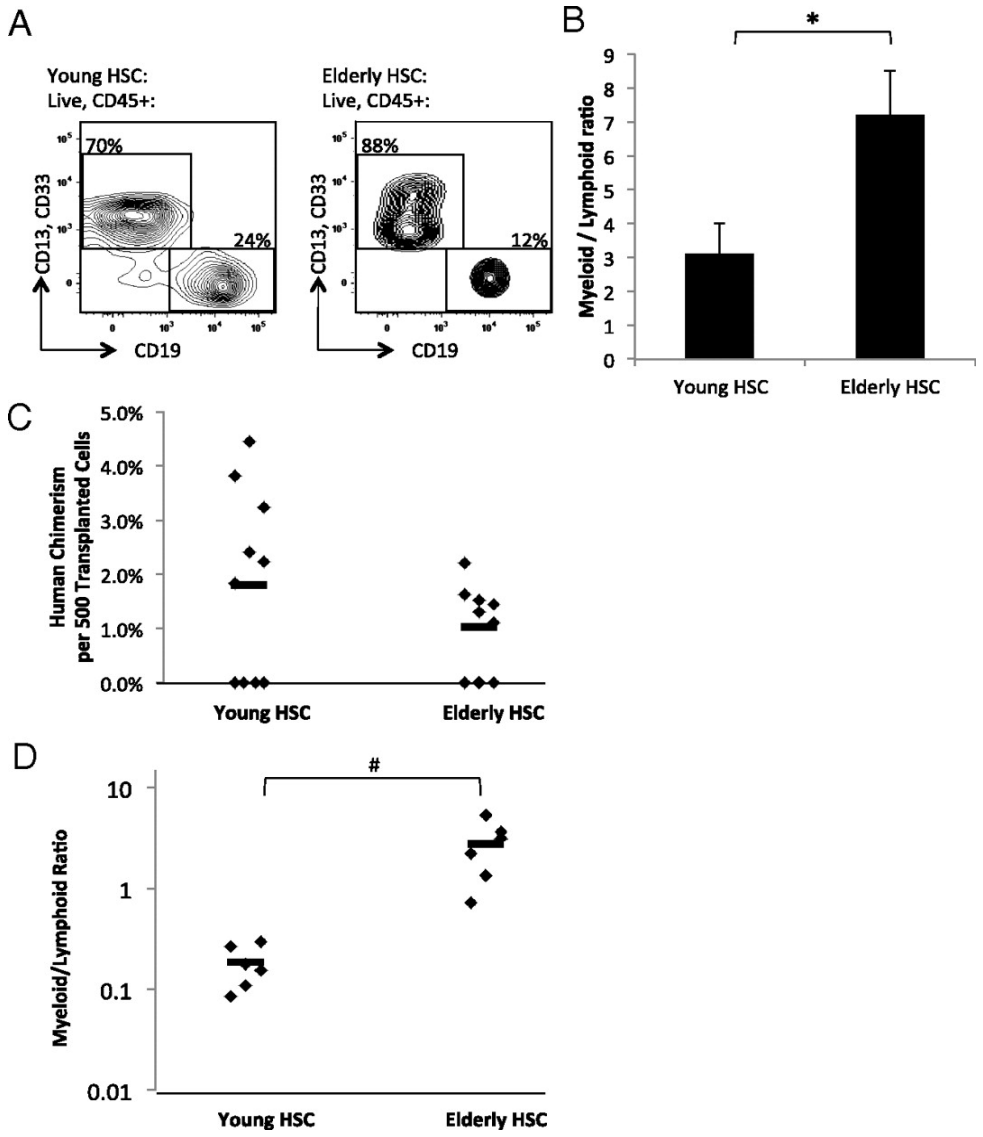
SEVENTH FRAMEWORK PROGRAMME

NEXT GENERATION SEQUENCING for Targeted Personalized Therapy of Leukemia

Senescenza biologica



Diminished lymphoid versus myeloid differentiation capacity of HSC from normal elderly bone marrow compared to young bone marrow.



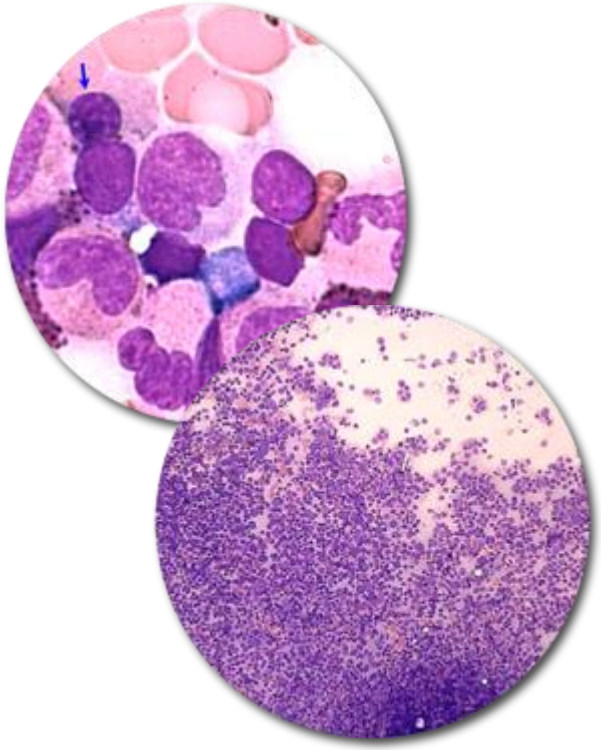
©2011 by National Academy of Sciences

Tipo di leucemia
LEUCEMIA ACUTE MIELOIDE: L'INCIDENZA

- La leucemia acuta **mieloide** è **+frequente nell'anziano**
- Età **mediana d'insorgenza: 67 anni**
- **Incidenza** nell'**adulto**: **2,7/100000** per anno
- Incidenza **sopra i 65 anni**: **14/100000** per anno

LEUCEMIA ACUTA MIELOIDE NELL' ANZIANO

LA MALATTIA E' DIVERSA BIOLOGICAMENTE



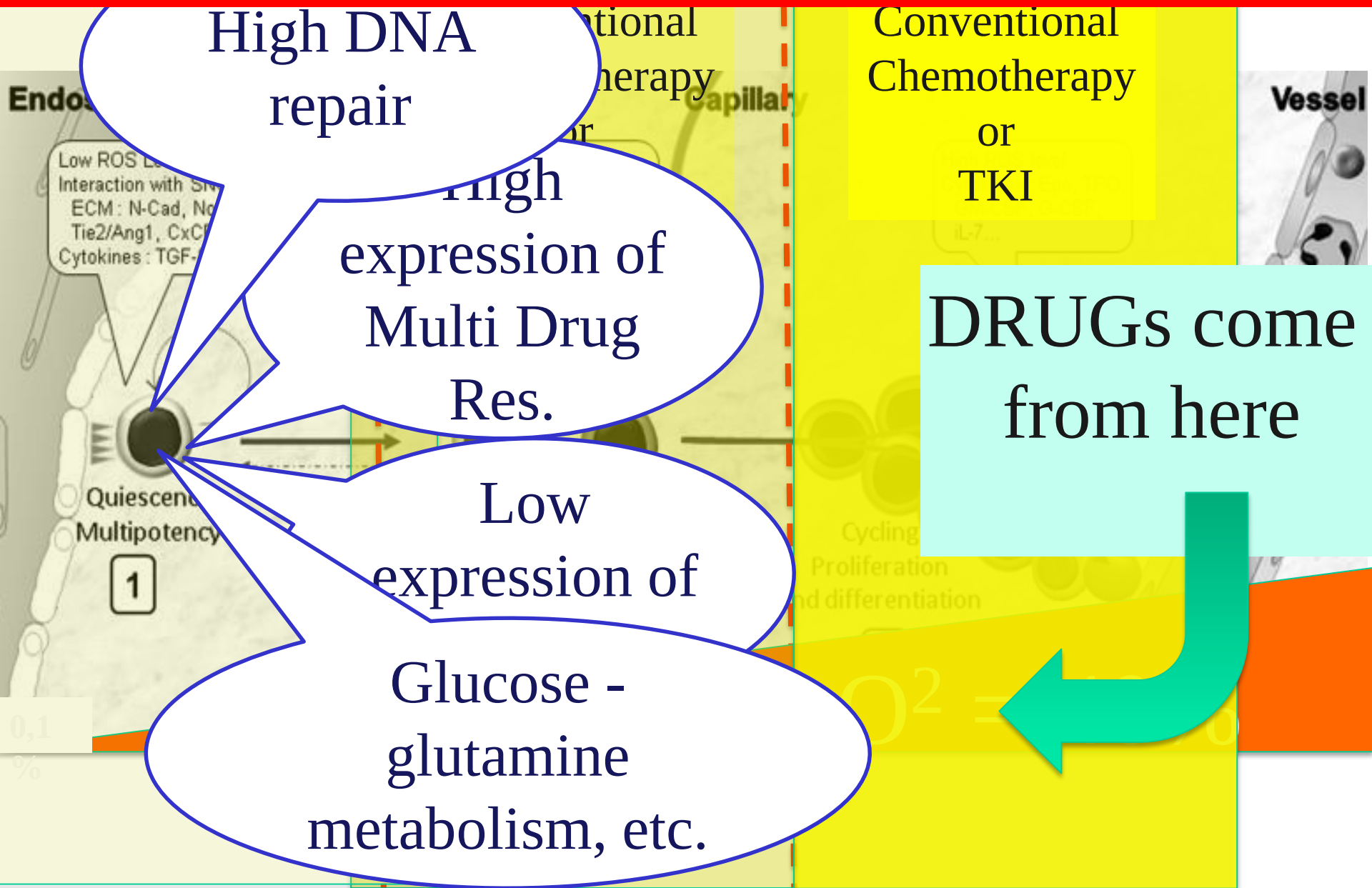
Più spesso nell'anziano

- **preceduta da SMD** o segue **radio/chemio**

citogenetica sfavorevole

- **spesso refrattaria alla chemio** (geni di resistenza)

Is this relevant for therapy? Yes
Hypoxia, stiffness, and polarity conditioned LSC Self-renewal



blood
2009 113: 4179-4187
Prepublished online November 13, 2008;
doi:10.1182/blood-2008-07-172007

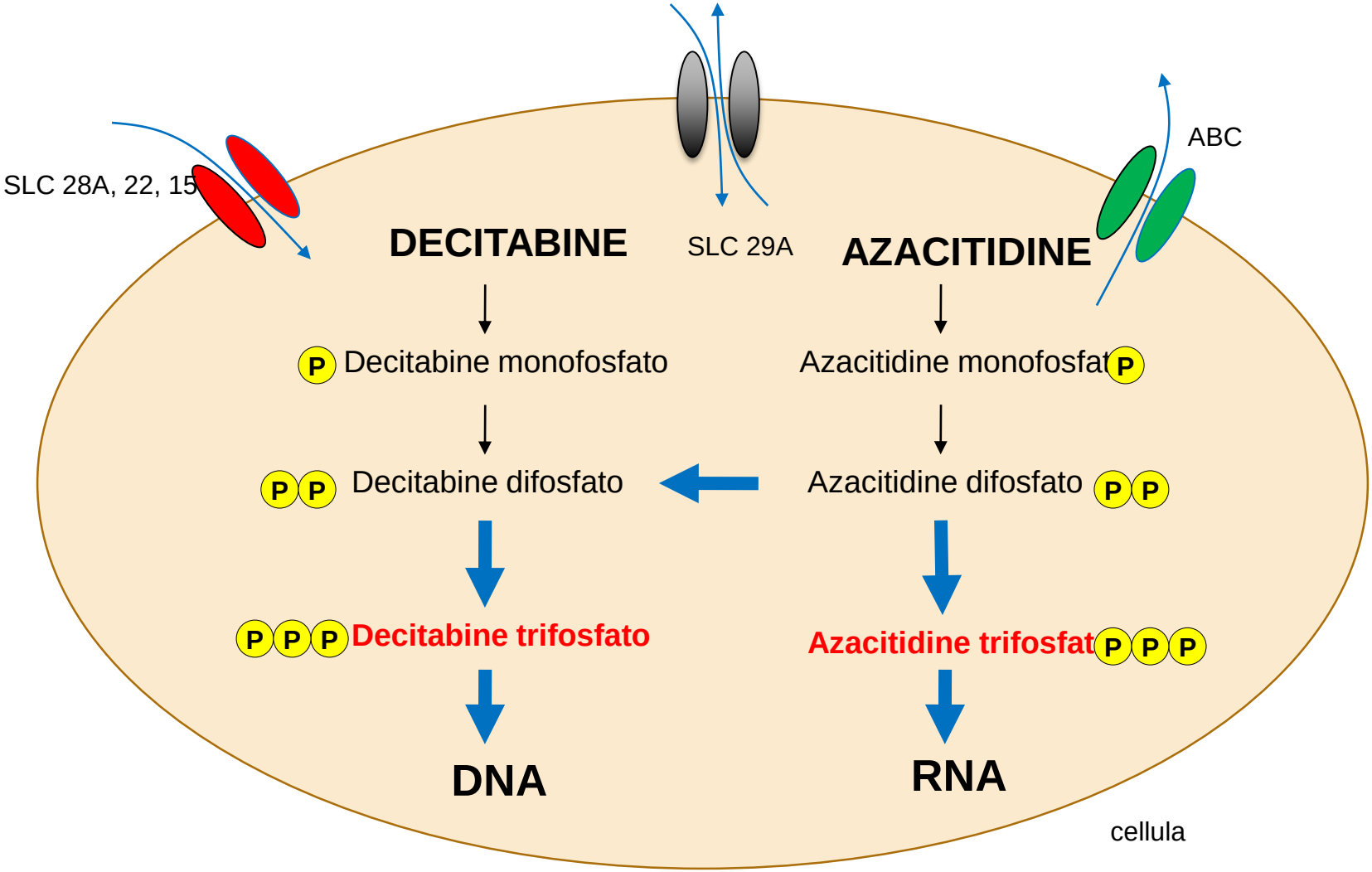
Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry

Gunnar Juliusson, Petar Antunovic, Åsa Derolf, Sören Lehmann, Lars Möllgård, Dick Stockelberg, Ulf Tidefelt, Anders Wahlin and Martin Höglund

Age	% Eligible for intensive therapy
60-64	92%
65-69	80%
70-74	67%
75-79	45%
80-84	23%
85+	4%

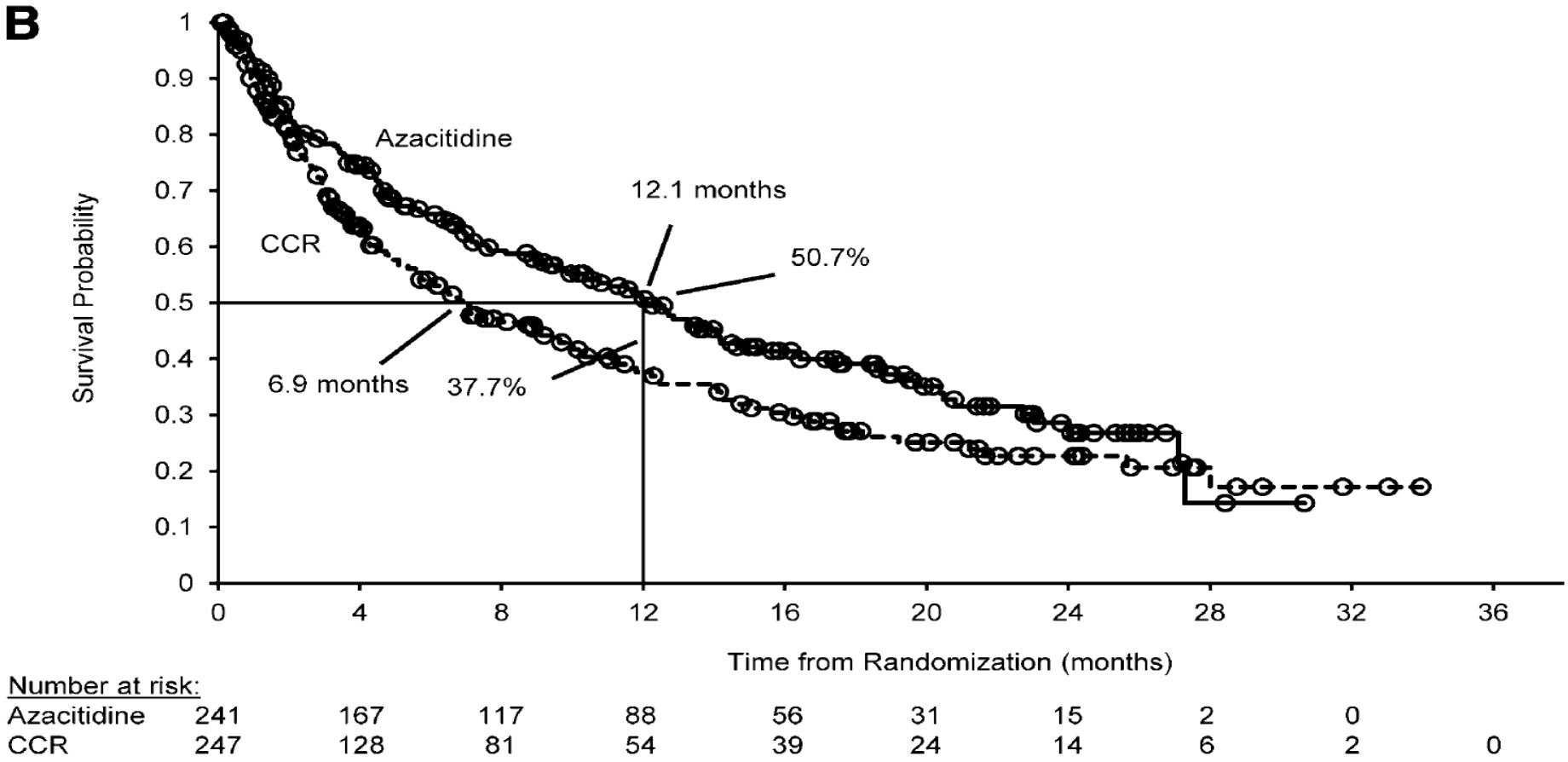
5-Azacitidina e' particolarmente attiva nelle AML

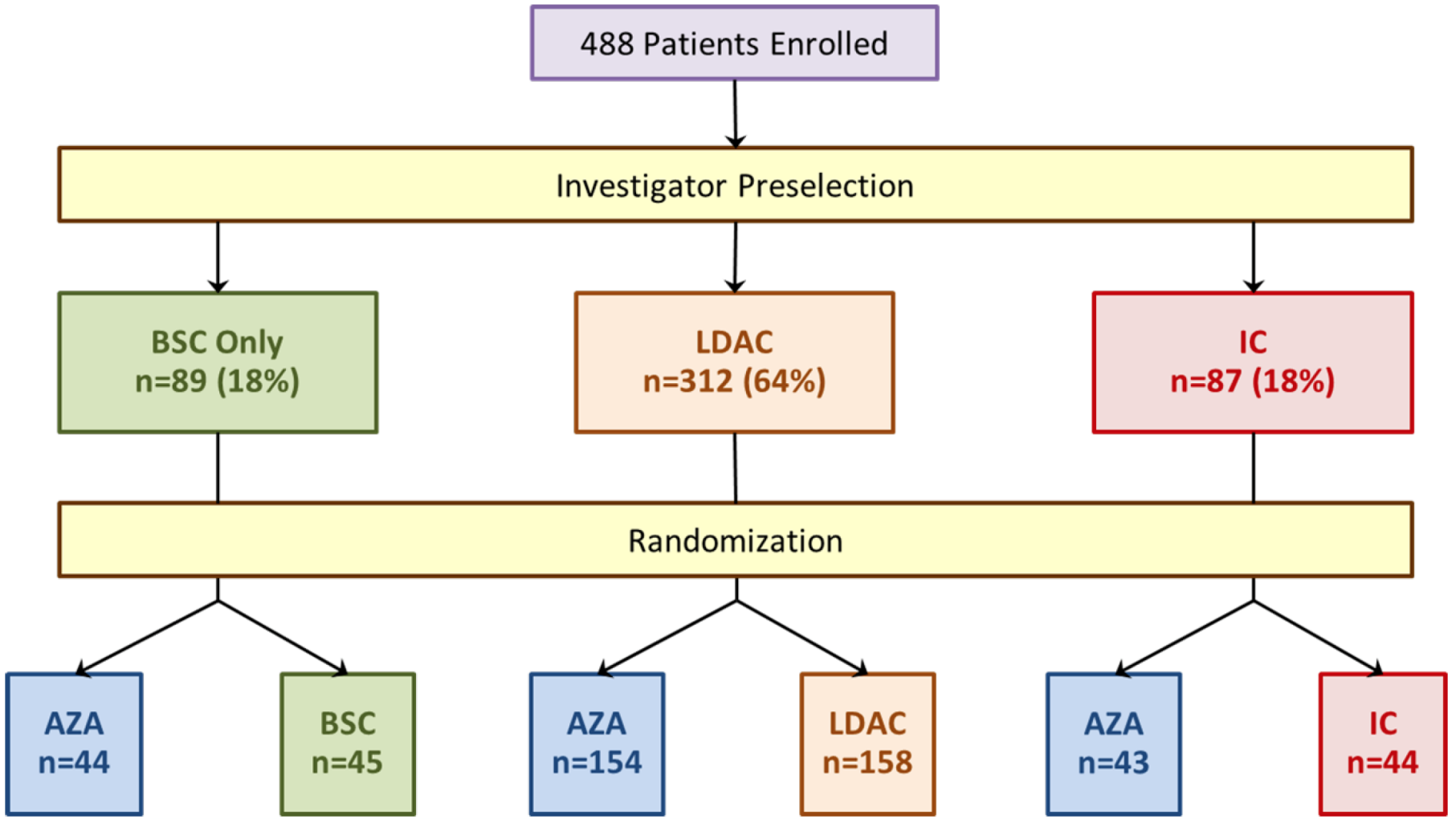
L'incorporazione nel DNA della decitabine e nell'RNA della azacitidine avviene solo in seguito alla loro fosforilazione.



International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

Hervé Dombret,[1] John F. Seymour,[2] Aleksandra Butrym,[3] Agnieszka Wierzbowska,[4] Dominik Selleslag,[5] Jun Ho Jang,[6] Rajat Kumar,[7] James Cavenagh,[8] Andre C. Schuh,[9] Anna Candoni,[10] Christian Récher,[11] Irwindeep Sandhu,[12] Teresa Bernal del Castillo,[13] Haifa Kathrin Al-Ali,[14] Giovanni Martinelli,[15] Jose Falantes,[16] Richard Noppeney,[17] Richard M. Stone,[18] Mark D. Minden,[9] Heidi McIntyre,[19] Steve Songer,[19] Lela M. Lucy,[19] C. L. Beach,[19] and Hartmut Döhner[20]




488 Patients Enrolled
Investigator Preselection
BSC Only
n=89 (18%)
LDAC
n=312 (64%)
IC
n=87 (18%)
Randomization
AZA
n=44
BSC
n=45
AZA
n=154
LDAC
n=158
AZA
n=43
IC
n=44

Supplementary Table 1. Mean (SD) Changes from Baseline QLQ-C30 Domain Scores*: Primary and Secondary Endpoints

Cycle #	Cycle 3		Cycle 5		Cycle 7		Cycle 9	
	AZA	CCR	AZA	CCR	AZA	CCR	AZA	CCR
N	**135**	**101**	**112**	**66**	**94**	**53**	**80**	**36**
Fatigue	-1.5 (24.7)	-1.9 (23.5)	-2.8 (27.4)	-7.1 (27.6)	-6.1 (26.9)	−12.2† (30.5)	−9.0 (27.9)	−10.2† (33.9)
N	**136**	**101**	**112**	**66**	**94**	**53**	**81**	**36**
Dyspnea	5.1 (26.9)	−1.7 (30.7)	3.9 (27.5)	−6.6 (28.2)	0.4 (29.9)	−8.8 (28.6)	−4.9 (26.9)	−2.8 (26.9)
N	**136**	**102**	**112**	**67**	**94**	**54**	**81**	**36**
Physical Function	−4.2 (18.0)	−0.3 (18.9)	−4.4 (19.3)	−1.3 (20.4)	1.6 (18.8)	1.5 (23.1)	3.5 (18.3)	−0.4 (22.8)
N	**134**	**101**	**112**	**66**	**94**	**52**	**80**	**36**
Global QoL	0.9 (21.0)	3.8 (26.4)	1.6 (22.5)	9.0 (24.8)	5.1 (25.8)	8.7 (27.9)	7.8 (27.3)	10.4† (23.1)

NEXT GENERATION SEQUENCING
for Targeted Personalized
Therapy of Leukemia

2013
2015

NEXT GENERATION SEQUENCING
for Targeted Personalized
Therapy of Leukemia

Insert text

SEVENTH FRAMEWORK PROGRAMME

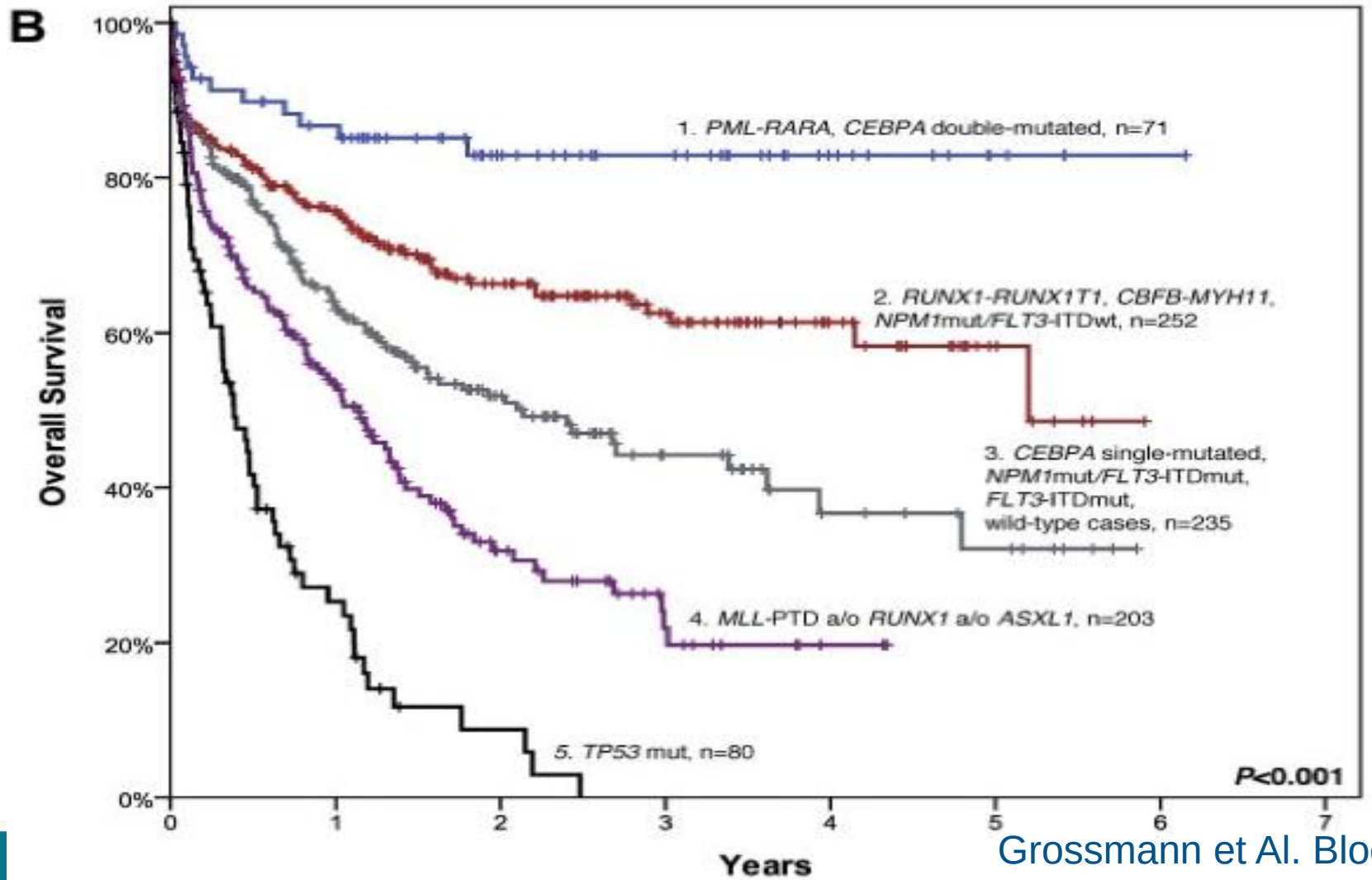
TOGETHER TO IMPROVE MEDICAL CARE.
TOGETHER TO SAVE HUMAN LIVES.

10 international partners are joining their efforts to build up a highly innovative and ambitious research project: the outstanding mission of sequencing the genome of Leukemia patients to develop personalized and more effective therapies.

FIGHT AND WIN
~~LEUKEMIA~~
BY SEQUENCING
THE GENOME

now we really can.

Caratterizzazione Molecolare delle Leucemie



Grossmann et Al. Blood 2013

The personalized druggable genome in myeloid malignancies

ABL1		***HRAS***	***MYD88***	*SF3B1*
ASXL1	*CSF3R*	***IDH1***	***NOTCH1***	*SMC1A*
ATRX	*CUX1*	***IDH2***	*NPM1*	
BCOR	***DNMT3A***	***IKZF1***	***NRAS***	*SRFS2*
BCORL1	*ETV6*	***JAK2***	***PDGFRA***	*STAG2*
BRAF		*JAK3*	*PHF6*	*TET2*
CALR		*KDM6A*	*PTEN*	***TP53***
CBL	***FLT3***	***KIT***	*PTPN11*	*U2AF1*
CBLB	*GATA1*	***KRAS***	*RAD21*	*WT1*
CBLC	*GATA2*	*MLL*	*RUNX1*	*ZRSR2*
CEBPA	*HRAS*	*MPL*	*SF3B1*	

AG120

AG221

Cobimetinib

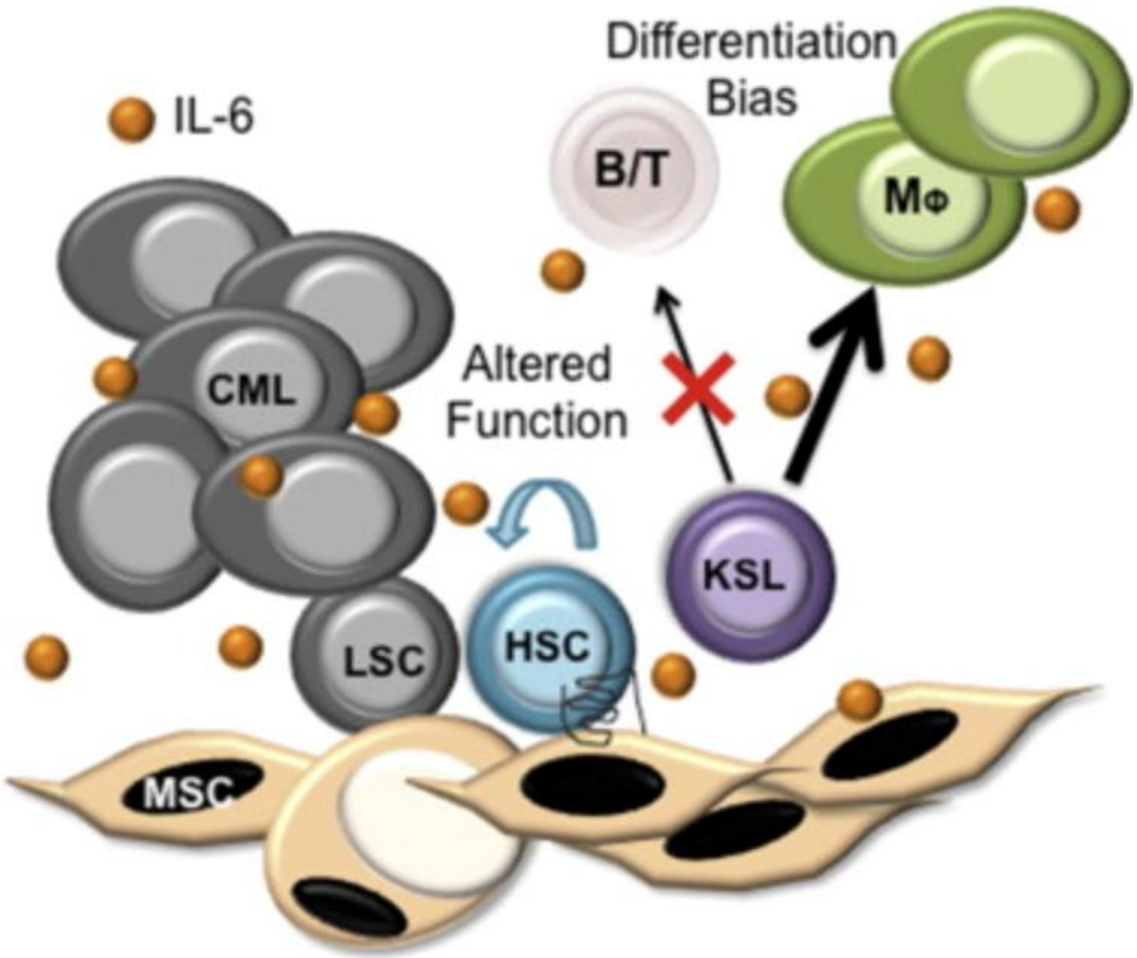
Vemurafenib

Azacitidine
Decitabine

Idasanutlin

Sorafenib
Midstaurin
Quizartinib

Cobimetinib



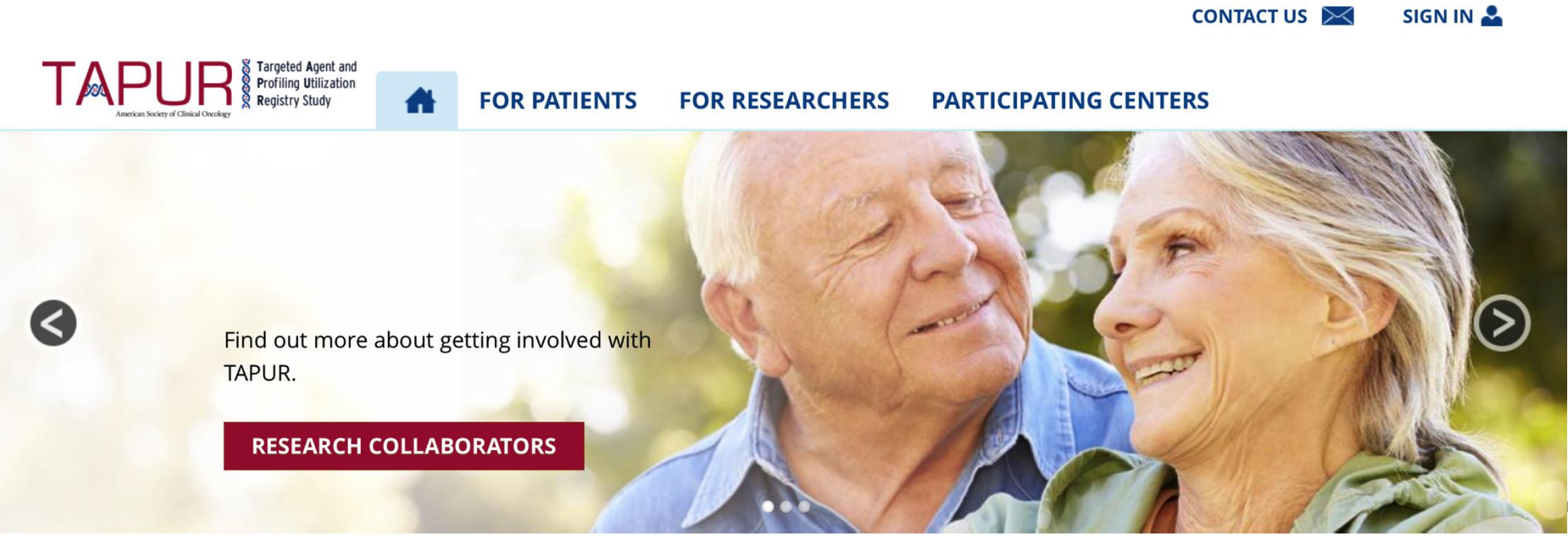
Targeting the micro-enviromental?

Cancer Cell 2015

Targeted Agent and Profiling Utilization Registry (TAPUR)

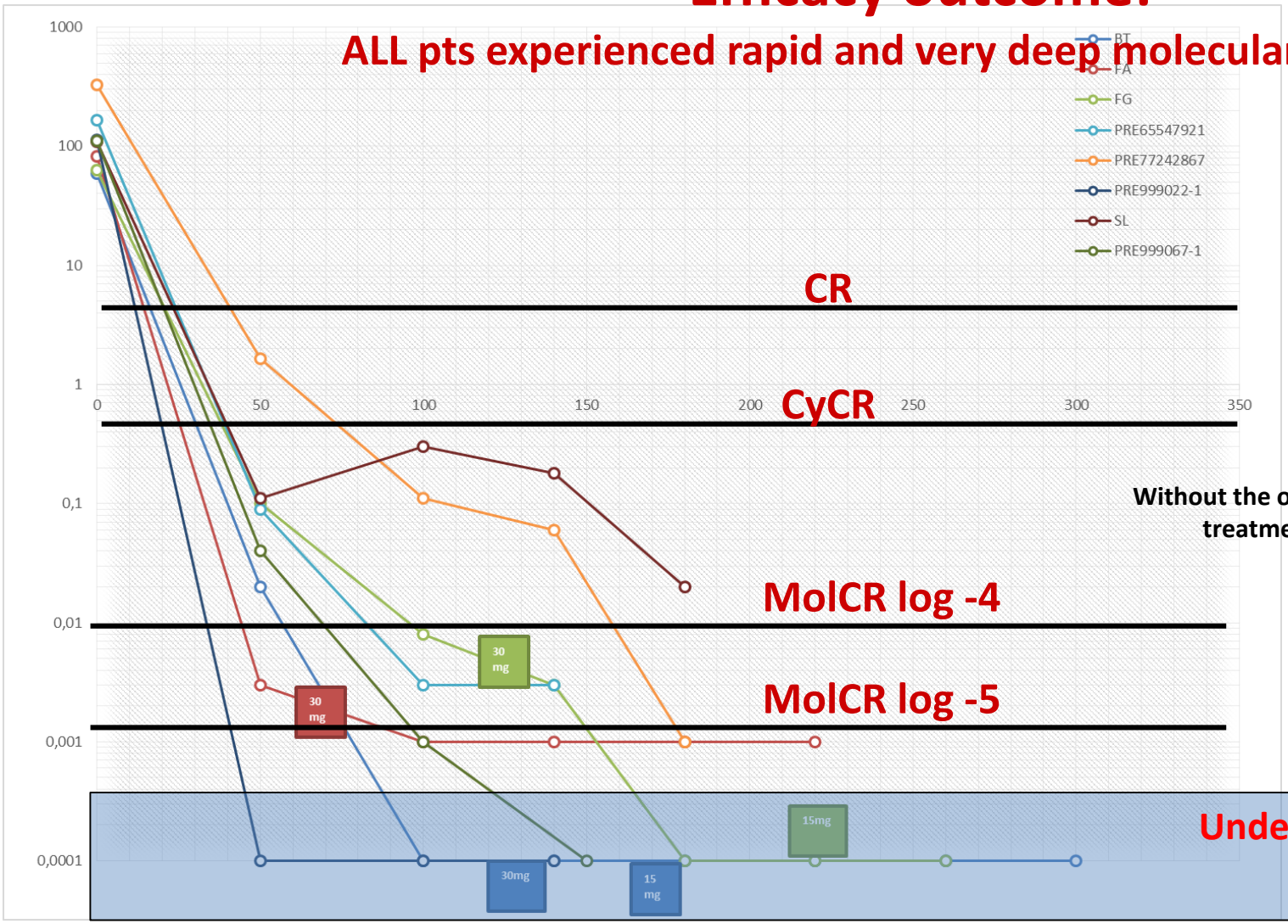
AIM

To define safety and efficacy of commercially available, targeted anticancer drugs for treatment of patients with advanced cancer that having a potentially actionable genomic variant



Efficacy outcome:

ALL pts experienced rapid and very deep molecular responses



Without the only patient with no treatment adherence

GIMEMA
Gruppo Italiano Malattie EMatologiche dell'Adulto

Acknowledgments

Supported by: FP7, European LeukemiaNet, AIL, AIRC, FIRB 2006, Fondazione del Monte di Bologna e Ravenna