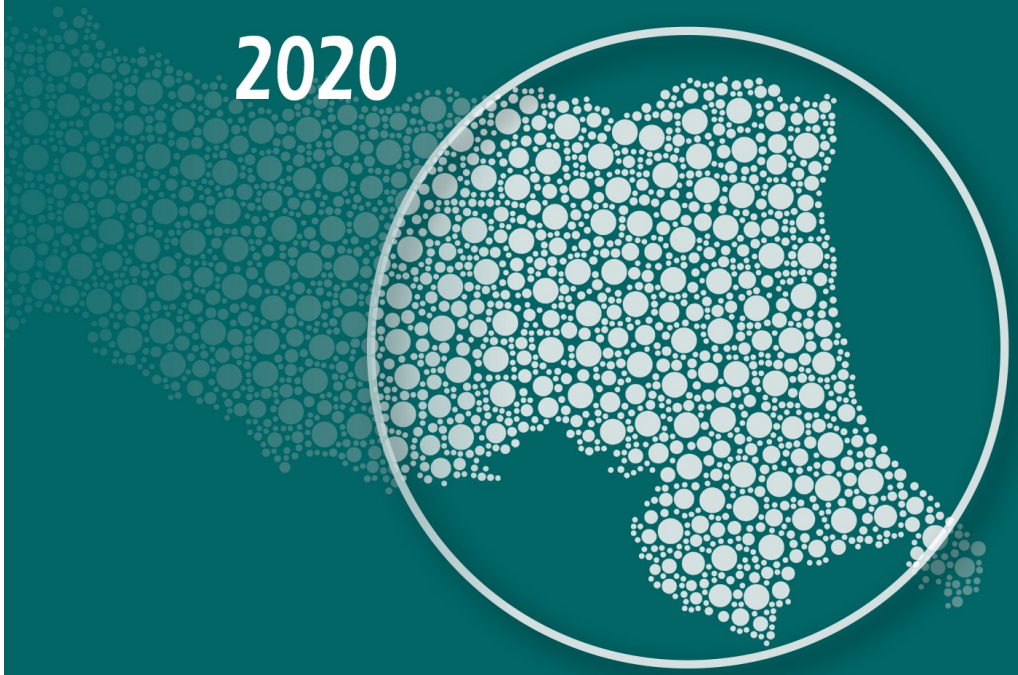


Progetto Ematologia Romagna

La terapia di prima linea nella LMA introduzione

Antonio Curti

Istituto di Ematologia «Seràgnoli», Azienda ospedaliero-universitaria Policlinico S.Orsola-Malpighi di Bologna

CONFLITTO DI INTERESSI

Partecipazione ad Advisory Board e Congressi:

- AbbVie
- Pfizer
- Novartis

AML front-line therapy for fit patients

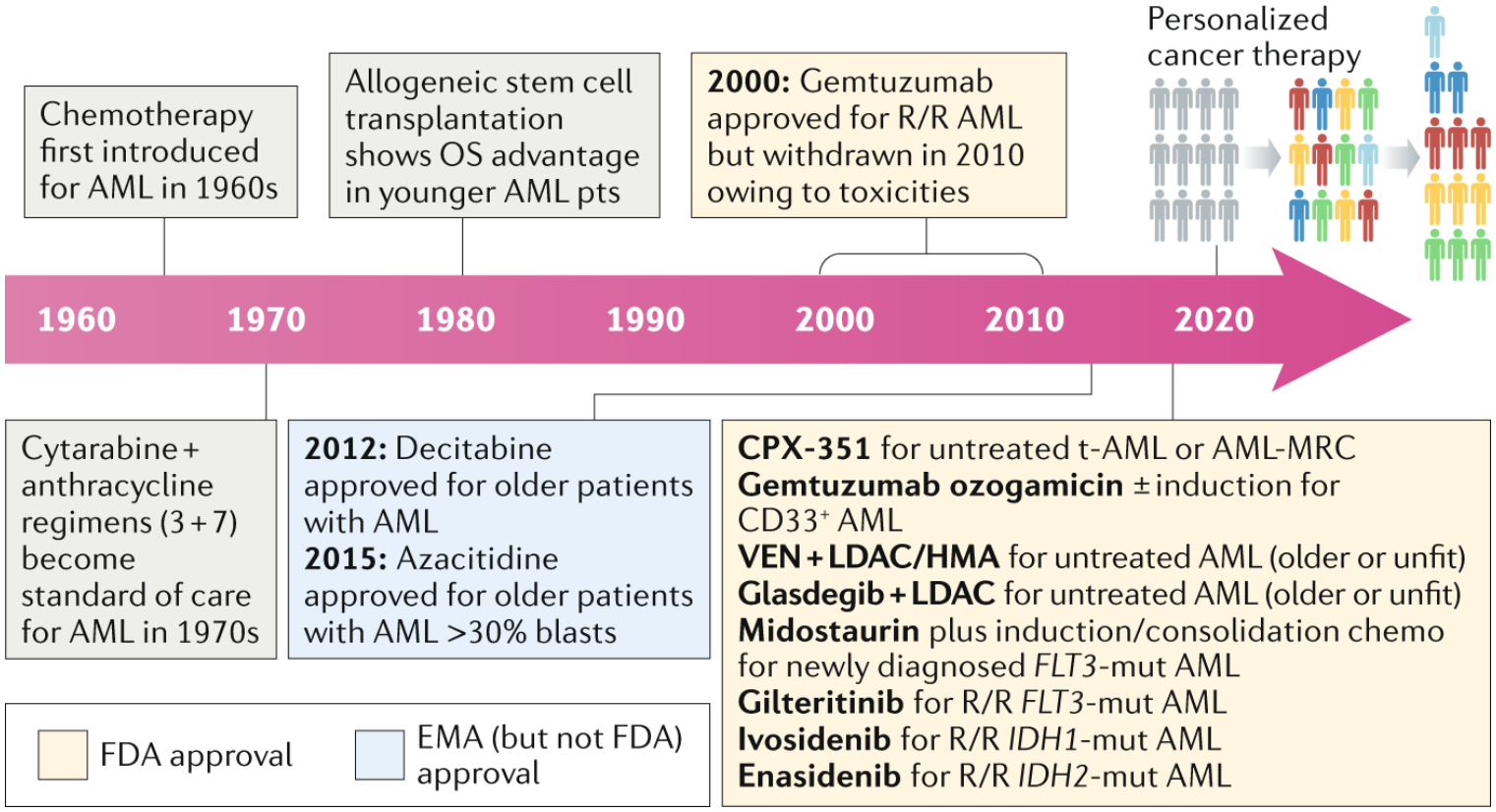
- **"3+7" induction** first introduced in 1973, still represents mainstay of induction therapy
  - ✓ CR achieved in 60-80% of patients < 60 years
  - ✓ CR achieved in 20-60% of patients > 60 years

- **Consolidation therapy:** single agent cytarabine at high dose (HiDARAC) or intermediate dose cytarabine (IDARAC) 2-4 cycles

- **Allogeneic HCT:** depends on assessment risk-benefit ratio; recommend if risk of relapse without the procedure > 35-40% → intermediate/high risk patients

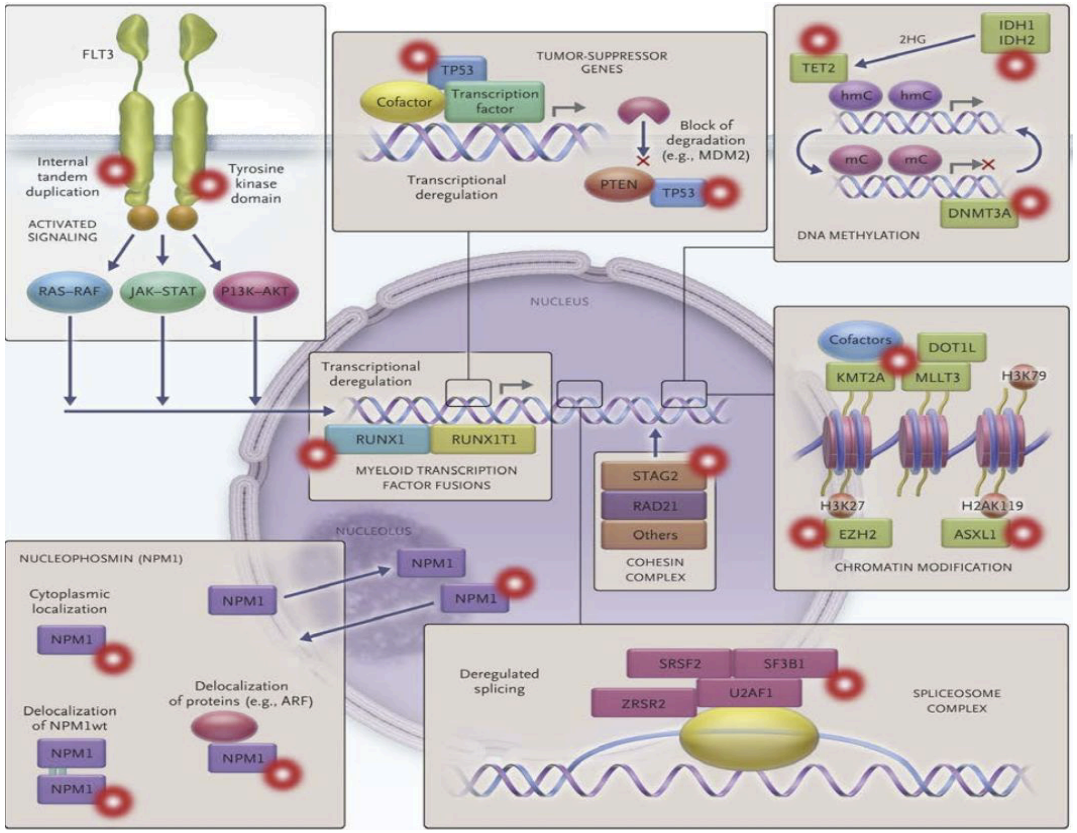
Dohner H et al Blood. 2017 Jan 26;129(4):424-447

Advances in patient care through increasingly individualized therapy



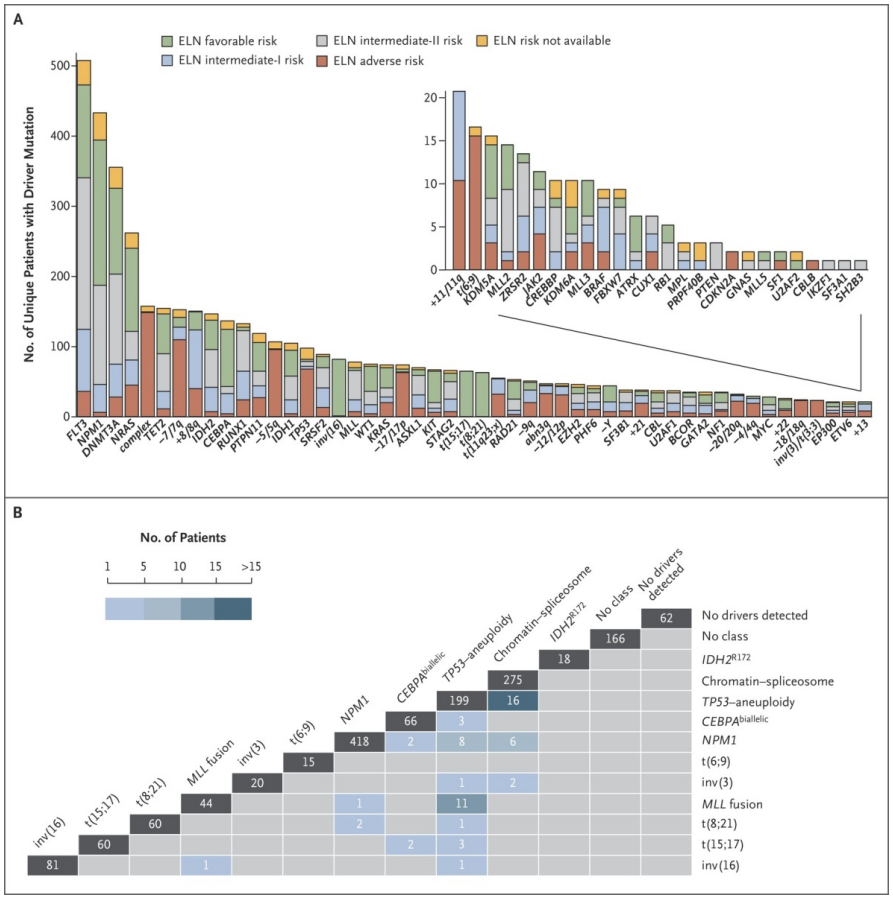
Courtney D. DiNardo & Alexander E. Perl *Nature Reviews Clinical Oncology* volume 16, pages73–74 (2019)

Pathobiology of AML



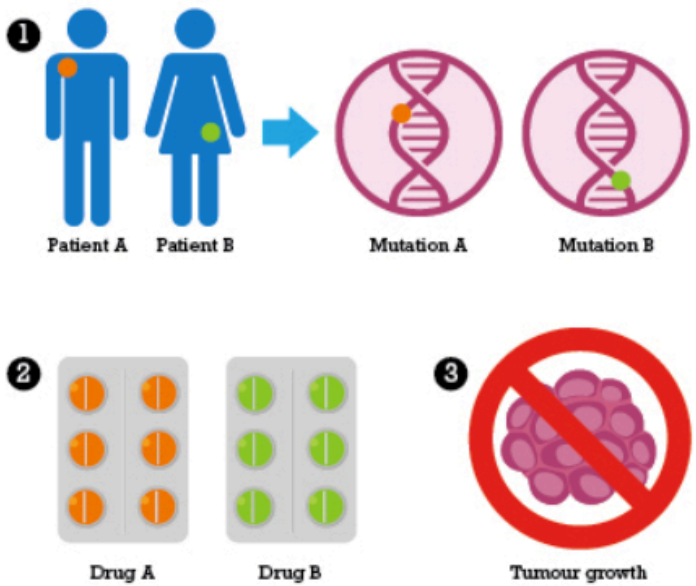
Dohner et al N Engl J Med 2015

Landscape of Driver Mutations in Acute Myeloid Leukemia



Papaemmanuil E et al. N Engl J Med 2016;374:2209-2221

Personalized cancer therapy



Personalized medicine:

1. The genetic changes in a person's cancer are discovered.
2. Drugs that target these genetic changes are identified.
3. The patient is treated and their response to therapy is monitored.

ELN-AML Classification

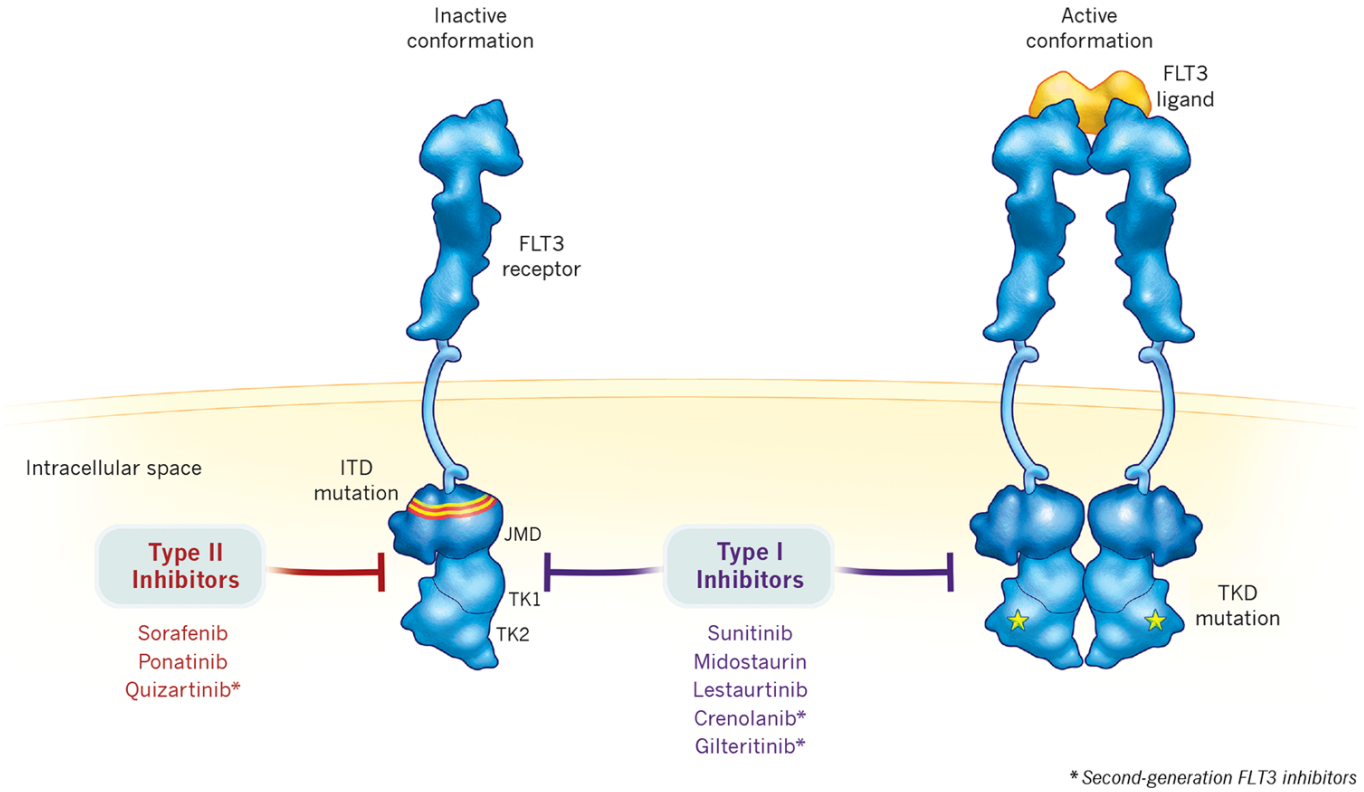
Risk category*	ELN criteria[10]	NCCN criteria[6]
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	Core binding factor: inv(16)†,‡ or t(16;16)†,‡ or t(8;21)†,‡ or t(15;17)‡
	inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Normal cytogenetics: *NPM1* mutation in absence of *FLT3*-ITD or isolated biallelic (double) *CEBPA* mutation
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}§	
	Biallelic mutated *CEBPA*	
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}§	Normal cytogenetics
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}§ (without adverse-risk genetic lesions)	+8 alone
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‖	t(9;11)
	Cytogenetic abnormalities not classified as favorable or adverse	Other nondefined
		Core binding factor with *KIT* mutation
Poor/adverse	t(6;9)(p23;q34.1); *DEK-NUP214*	Complex (≥3 clonal chromosomal abnormalities)
	t(v;11q23.3); *KMT2A* rearranged	Monosomal karyotype
	t(9;22)(q34.1;q11.2); *BCR-ABL1*	−5, 5q−, −7, 7q−
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*	11q23 – non t(9;11)
	−5 or del(5q); −7; −17/abn(17p)	inv(3), t(3;3)
	Complex karyotype,¶ monosomal karyotype#	t(6;9)
	Wild-type *NPM1* and *FLT3*-ITDhigh	t(9;22)
	Mutated *RUNX1***	Normal cytogenetics: with *FLT3*-ITD mutation††
	Mutated *ASXL1***	*TP53* mutation
	Mutated *TP53*‡‡	

Dohner Blood 2017 129:424-447;; NCCN Guidelines for Acute Myeloid Leukemia V1.2017

How to improve induction therapy for fit patients?

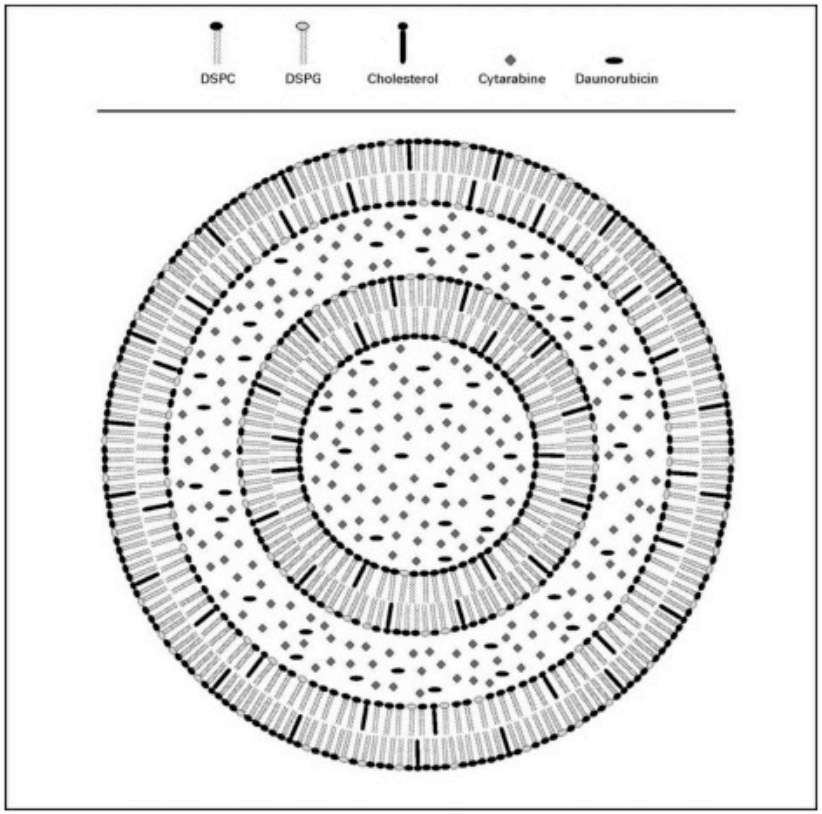
- ✓ Adding a FLT3 inhibitor in *FLT3* mutated AML
- ✓ Adding Gemtuzumab ozagamicin in CD33 positive AML
- ✓ Optimizing standard chemotherapy by using innovative formulations, i.e CPX-351
- ✓ Adding a third chemotherapic agent, i.e purine analogs, including cladribine, fludarabine

Targeting *FLT3* mutations in AML



Leukemia volume 33, pages299–312(2019)

CPX-351(cytarabine:daunorubicin) liposome injection

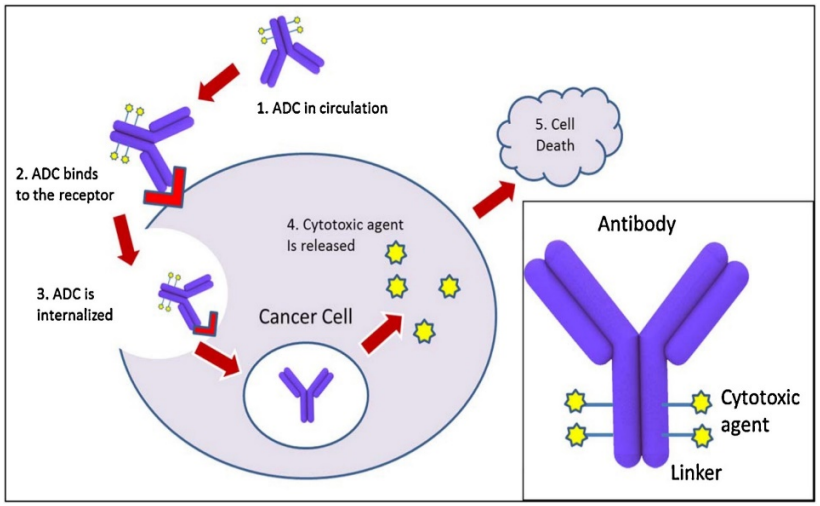


The active agents, cytarabine and daunorubicin, are encapsulated in the aqueous space of both vesicles at a 5:1 molar ratio. The strength of CPX-351 is 5 units/mL, where 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin (base).

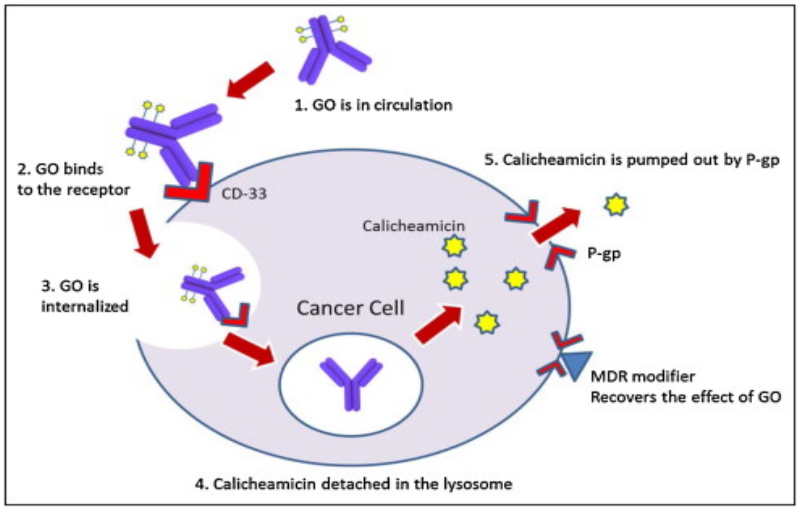
Feldman JE et al. *Journal of Clinical Oncology* 2011 29979-985.

Antibody-targeted drugs and drug resistance
Challenges and solutions

Scheme of ADC structure and mechanism of action



Gentuzumab ozogamicin mechanism of action, P-gp-mediated drug resistance and overcoming resistance by MDR modifier



Fludarabine-based induction chemotherapy: background

VOLUME 31 · NUMBER 27 · SEPTEMBER 20 2013

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Optimization of Chemotherapy for Younger Patients With Acute Myeloid Leukemia: Results of the Medical Research Council AML15 Trial

Alan K. Burnett, Nigel H. Russell, Robert K. Hills, Ann E. Hunter, Lars Kjeldsen, John Yin, Brenda E.S. Gibson, Keith Wheatley, and Donald Milligan

Pts n° 635
ORR (CR + CRi) 86%
ORR post C1 77%

RESEARCH ARTICLE | Full Access

Flai (fludarabine, cytarabine, idarubicin) plus low-dose Gemtuzumab Ozogamicin as induction therapy in CD33-positive AML: Final results and long term outcome of a phase II multicenter clinical trial

Anna Candoni, Cristina Papayannidis, Giovanni Martinelli, Erica Simeone, Michele Gottardi, Ilaria Iacobucci, Filippo Gherlinzoni, Giuseppe Visani, Michele Baccarani, Renato Fanin

First published: 02 February 2018 | https://doi.org/10.1002/ajh.25057

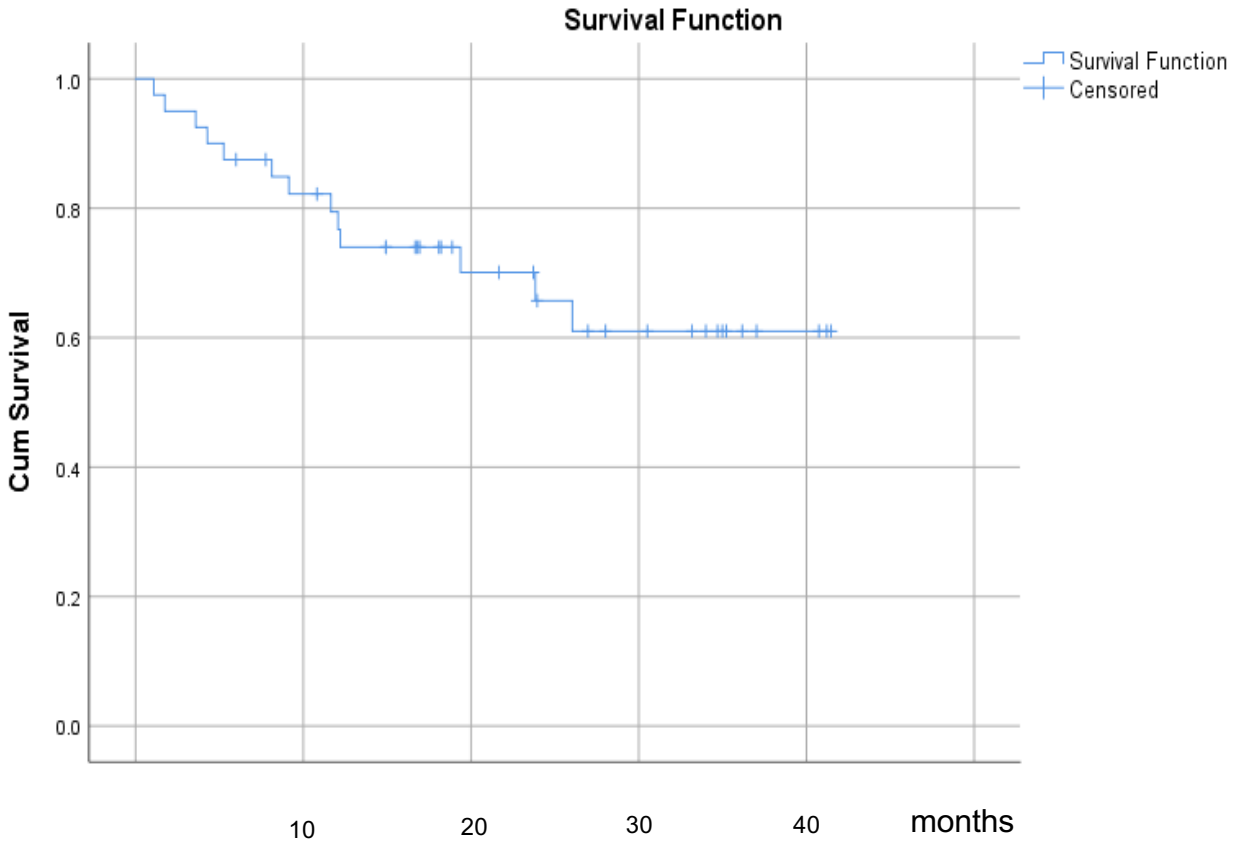
Pts n° 130
ORR 85%

FLAI-5: results after induction

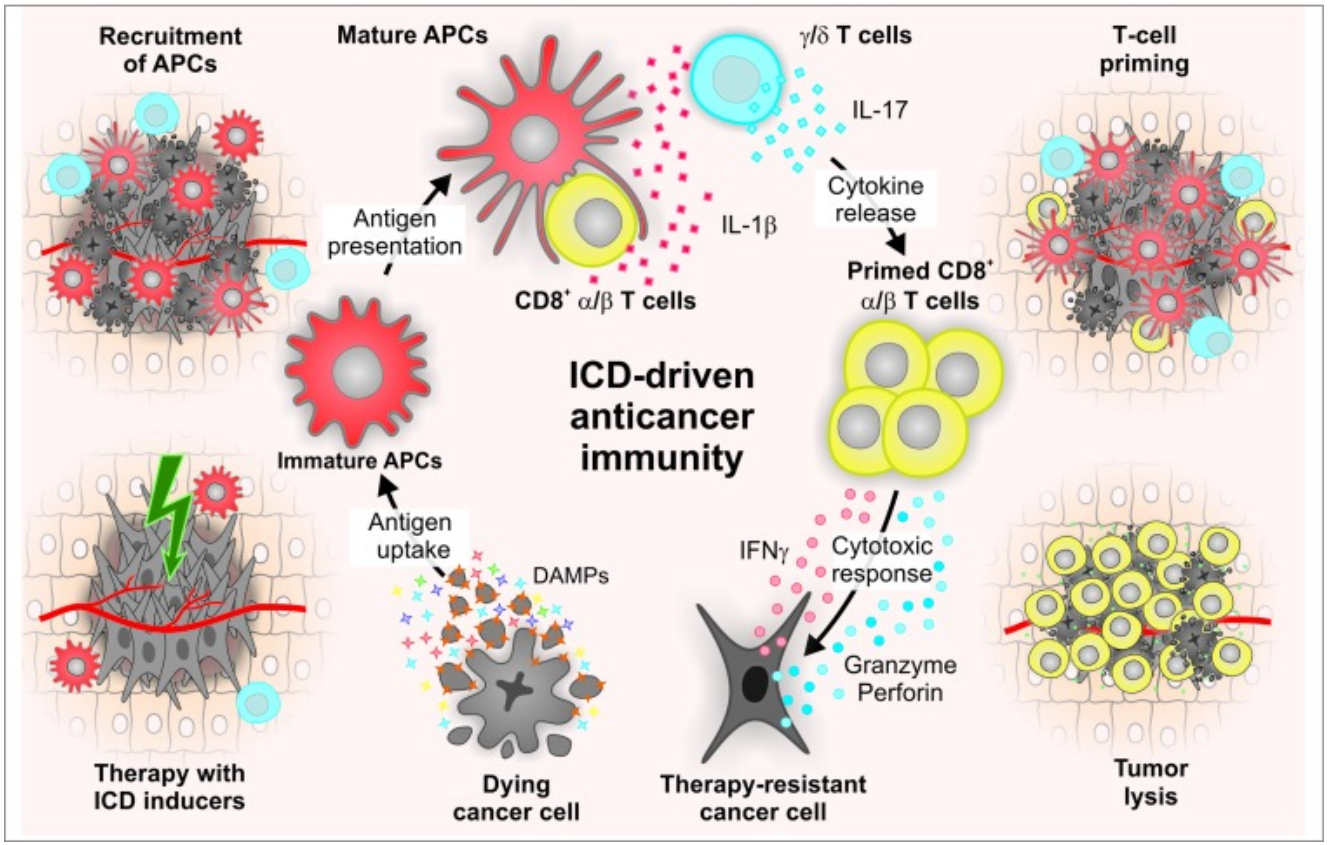
Depth of CR	
CR	35/40 (87.5%)
NCCN 2016 favorable	12/12 (100%)
Intermediate	9/10 (90%)
High	15/17 (88%)
Unknown	1/1
CR MRD^-	15/29 (52%)*
CR MRD^+	14/29 (48%)**
Morphologic CR	5/34
Cytogenetic CR	1/34

*29 pts entering CR evaluable for MRD marker (WT1/NPM/CBF-MYH11)
** 22/29 (76%) if analyzed with WT1

FLAI-5: Overall Survival



Immunogenic cell death (ICD): clinical relevance

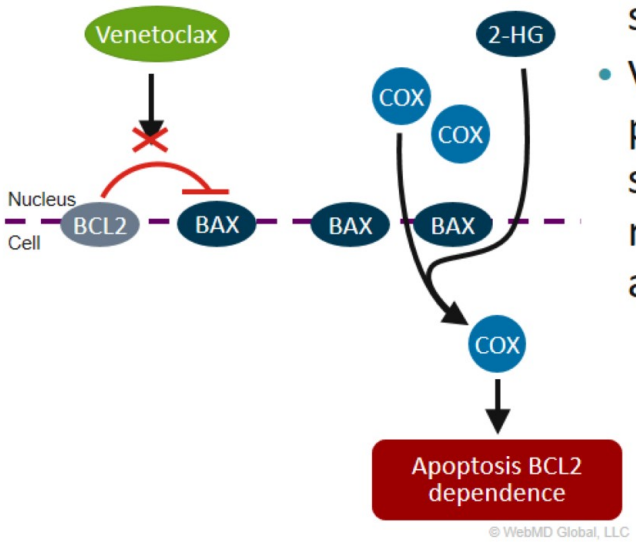


Kepp et al, Oncoimmunology 2014

New emerging and promising options

- Optimizing intensive chemotherapy
  - GO instead of anthracyclines
  - Liposomal formulation (CPX-351)
- Different strategies
- New agents +/- HMAs
  - Ivosidenib/Enasidenib
  - Glasdegib
  - Venetoclax

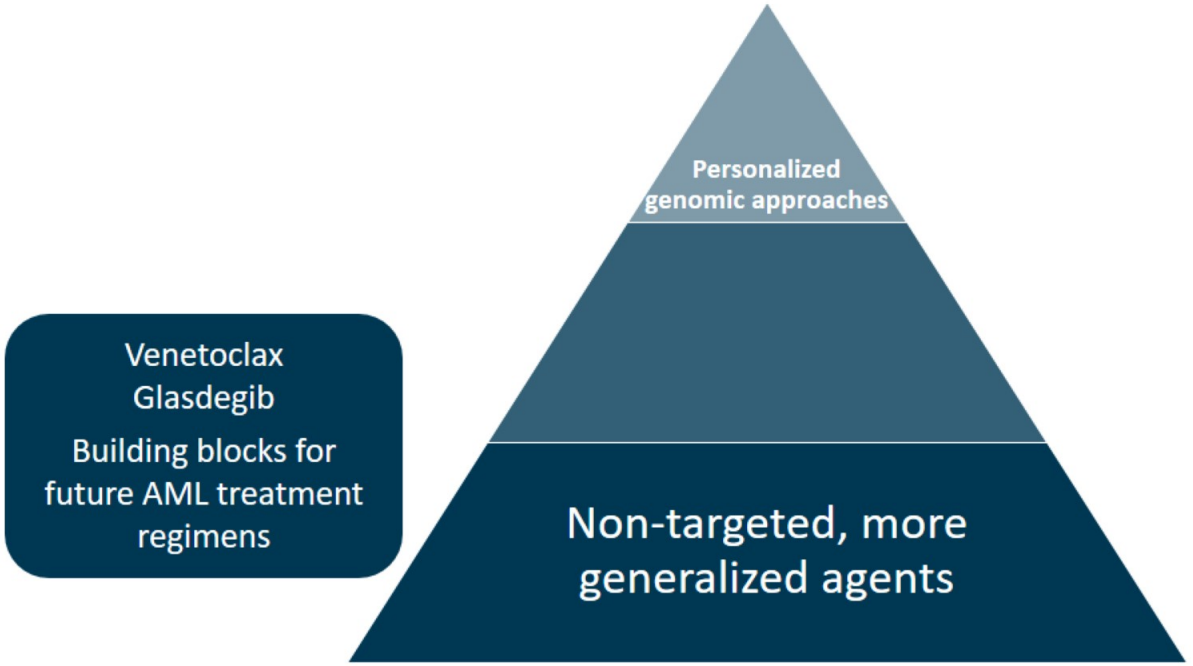
Venetoclax Mechanism of Action



- Venetoclax is a highly selective, BCL2 inhibitor.
- Venetoclax binds to BCL2, proapoptotic proteins such as BIM and BAX are released, and induction of apoptosis is facilitated

Buege MJ, et al. *Cancers (Basel)*. 2018;10. pii: E187.

Resurgence of Nontargeted Therapy for AML Treatment



LAM E ALLO-TMO: INDICAZIONI

FASE DI MALATTIA	CATEGORIA PAZ
CR1	ALTO RISCHIO RISCHIO INT MRD-POS
CR2	TUTTI I RISCHI
MALATTIA ATTIVA	PAZ REL/REF

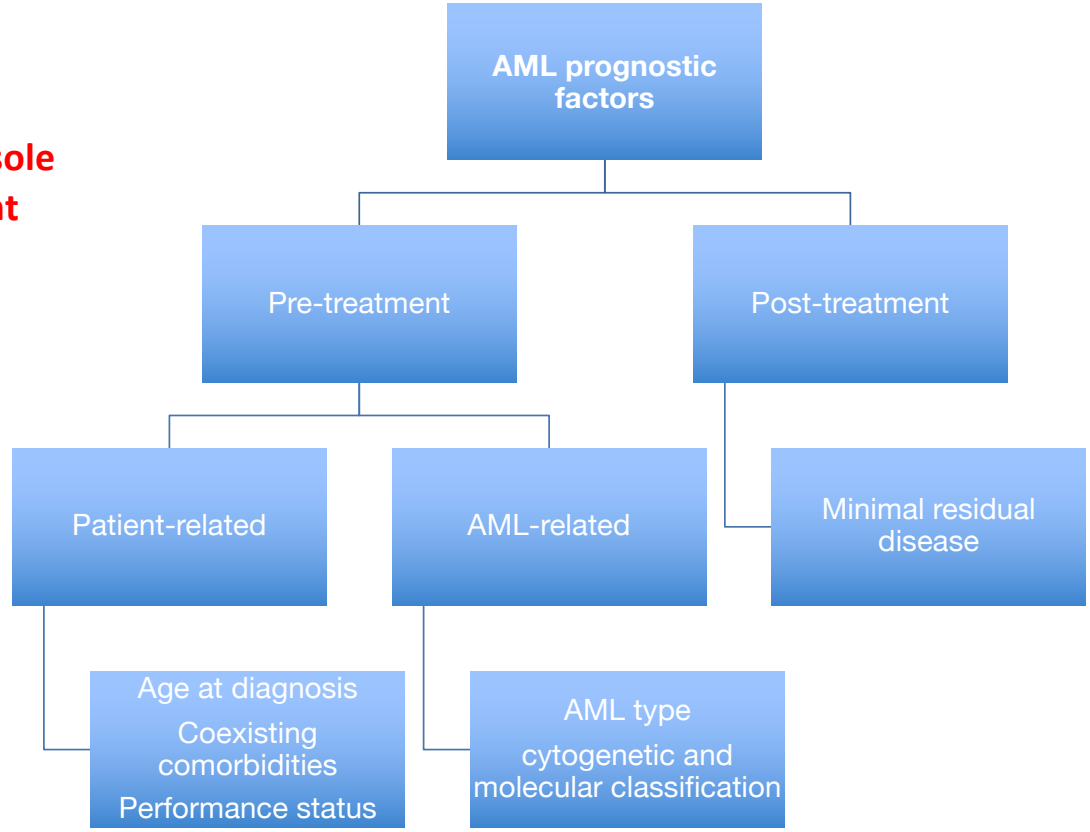
OPEN ISSUES:

- PAZ A BASSO RISCHIO IN CR2
- PAZ A RISCHIO INTERMEDIO, MRD-NEG, IN CR1

Cornelissen JJ, Nat Rev Clin Oncol 2012

Verso un trattamento MRD-oriented

Age alone should not be sole determinant for treatment decision!



Dohner Blood 2017 129:424-447