Advancing ARGX-110 to clinical proof-of-concept in AML and CTCL

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ASH workshop, December 11, 2017, Atlanta

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Agenda

12:00 **Welcome & Introduction**

12:05 **ARGX-110 in acute myeloid leukemia**

- **AML: High unmet medical need**
  Gail Roboz, MD, Weill Cornell Medical College

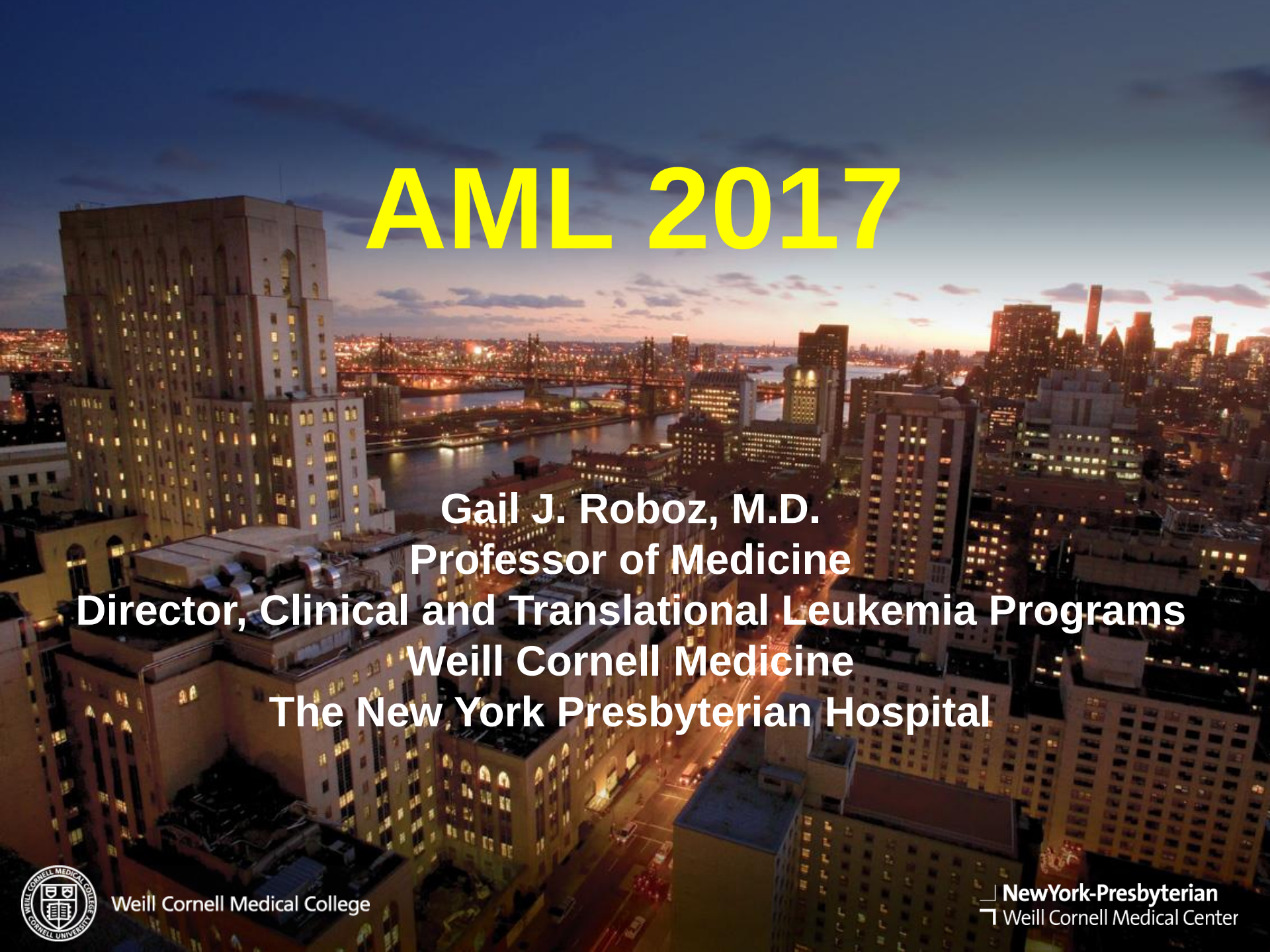
- **CD70: Novel AML target**
  Hans de Haard, PhD, CSO

- **Phase 1/2 trial in newly diagnosed AML: Proof-of-Biology**
  Nicolas Leupin, MD, CMO

13:00 **ARGX-110 in cutaneous T-cell lymphoma**

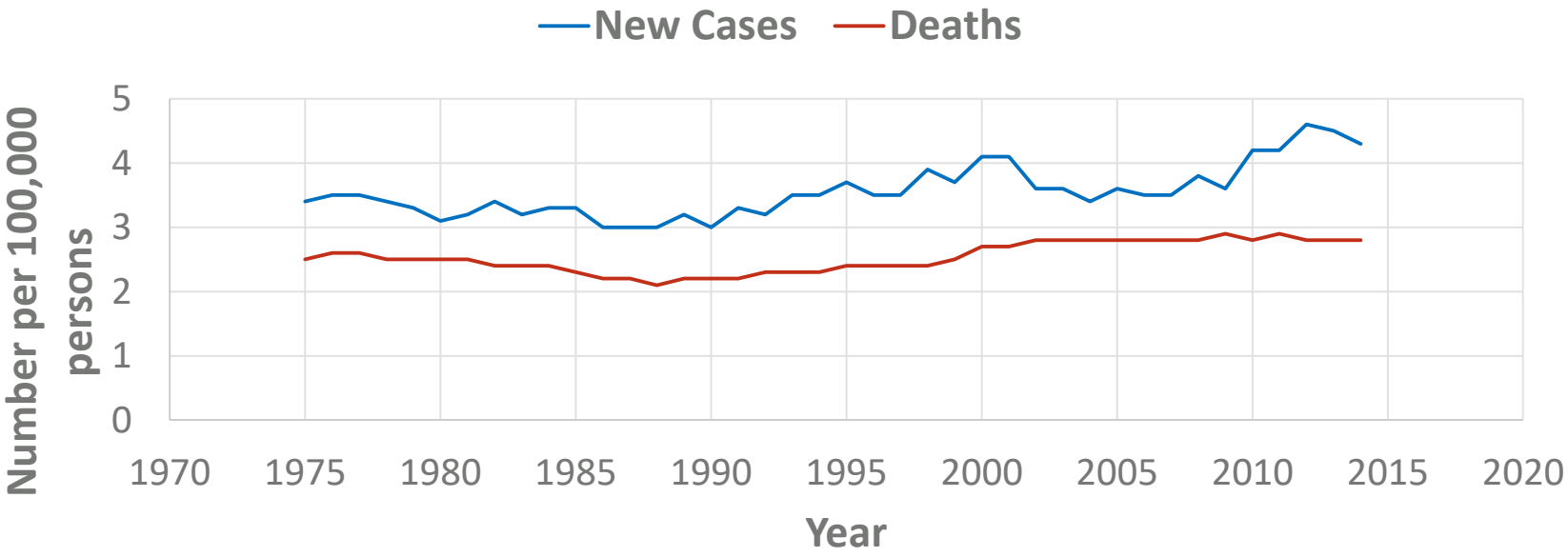
- **Phase 1/2 clinical trial: Status update**
  Nicolas Leupin, MD, CMO

13:10 **Q&A**

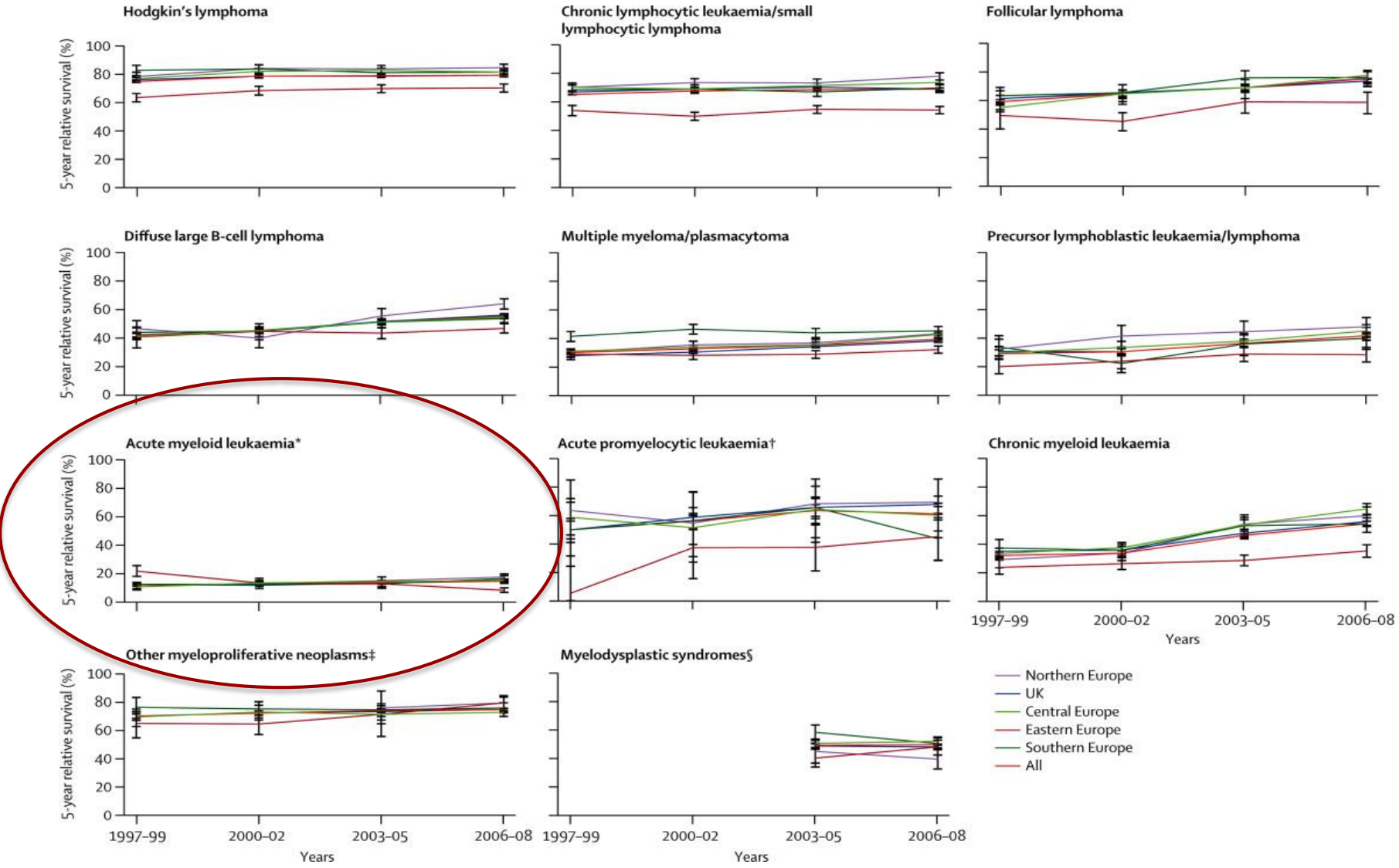

AML 2017
Gail J. Roboz, M.D.
Professor of Medicine
Director, Clinical and Translational Leukemia Programs
Weill Cornell Medicine
The New York Presbyterian Hospital
Weill Cornell Medical College
NewYork-Presbyterian
Weill Cornell Medical Center

Epidemiology

- Most common acute leukemia in adults
- Lifetime risk: ~0.5% of population
- Estimated incidence in 2017: ~21,400 new cases (1.3% of new cancer cases)
- Estimated mortality in 2017: ~10,600 deaths



National Cancer Institute Surveillance, Epidemiology, and End Results Program (2017). Cancer Stat Facts: Acute Myeloid Leukemia. Retrieved from https://seer.cancer.gov/statfacts/html/amyl.html



Milena Sant , Pamela Minicozzi , Morgane Mounier , Lesley A Anderson , Hermann Brenner , Bernd Holleczek , Rafael ... Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. The Lancet Oncology, Volume 15, Issue 9, 2014, 931 – 942. http://dx.doi.org/10.1016/S1470-2045(14)70282-7

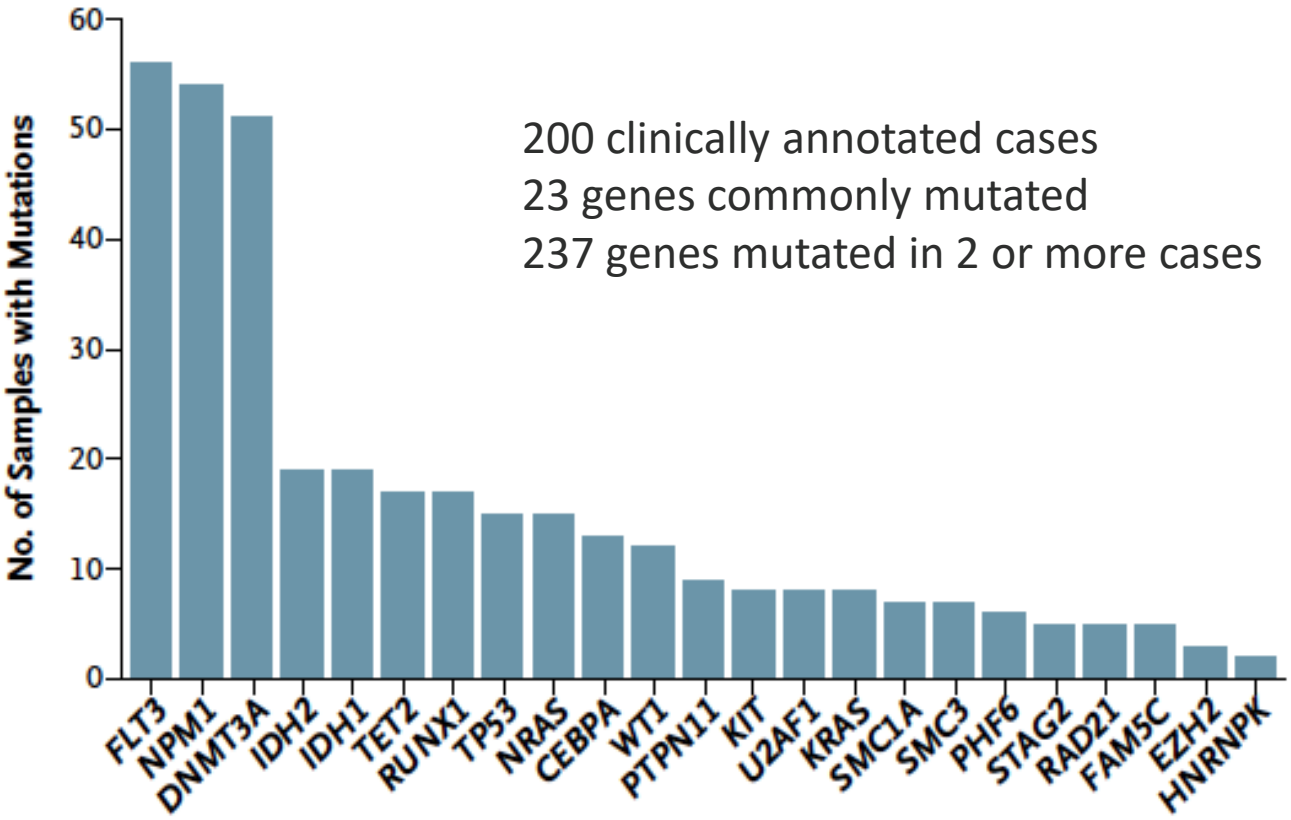
Risk Factors & Etiologies

- **Genetic disorders**
  - Down syndrome
  - Klinefelter syndrome
  - Patau syndrome
  - Ataxia telangiectasia
  - Shwachman syndrome
  - Kostman syndrome
  - Neurofibromatosis
  - Fanconi anemia
  - Li-Fraumeni syndrome
  - Noonan syndrome
- **Physical and Chemical Exposures**
  - Benzene
  - Organic solvents
  - Pesticides
  - Cigarette smoking
  - ? Herbicides/Agent Orange
  - ?WTC/911 exposure
- **Nontherapeutic, therapeutic radiation**
- **Chemotherapy**
  - Alkylating agents
  - Topoisomerase-II inhibitors
  - Anthracyclines
  - Taxanes
- **Bone marrow failure syndromes**
  - Dyskeratosis congenita
  - Fanconi anemia
- **Myeloid neoplasms with germ line predisposition**
  - germ line mutations in CEBPA, DDX41, RUNX1, ANKRD26, ETV6, GATA2, SRP72, 14q32.2 genomic duplication (ATG2B/GSKIP)

Deschler, B., & Lübbert, M. (2006). Acute myeloid leukemia: epidemiology and etiology. *Cancer*, *107*(9), 2099-2107.
Leonard JP, Martin P, Roboz GJ. JCO 2017; Epub ahead of print.

Pathogenesis and Biology of AML

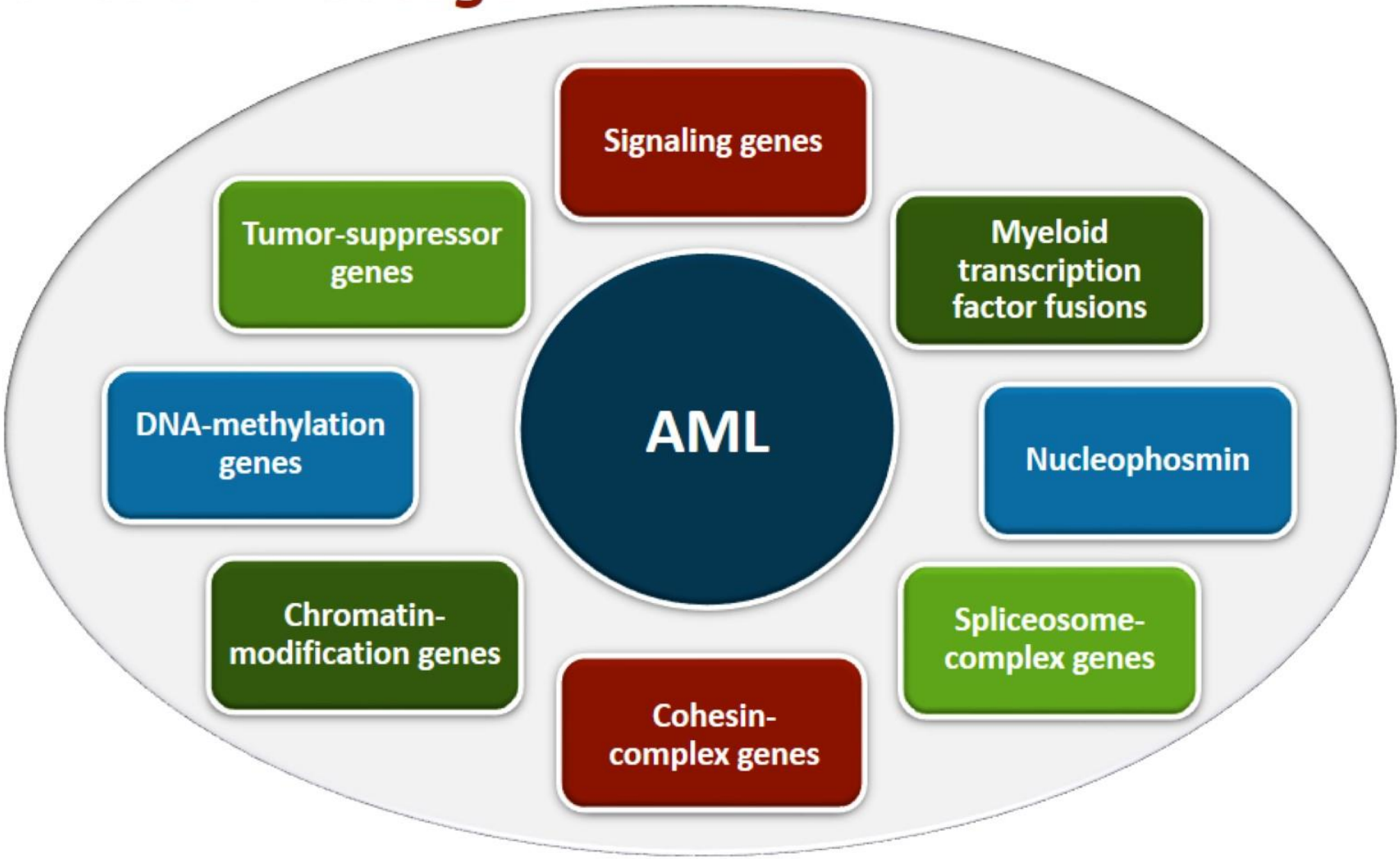
Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2



200 clinically annotated cases
23 genes commonly mutated
237 genes mutated in 2 or more cases

Patel, et al., NEJM 2012; TCGA NEJM 2013.

Genetic Mutations in AML
Functional Categories



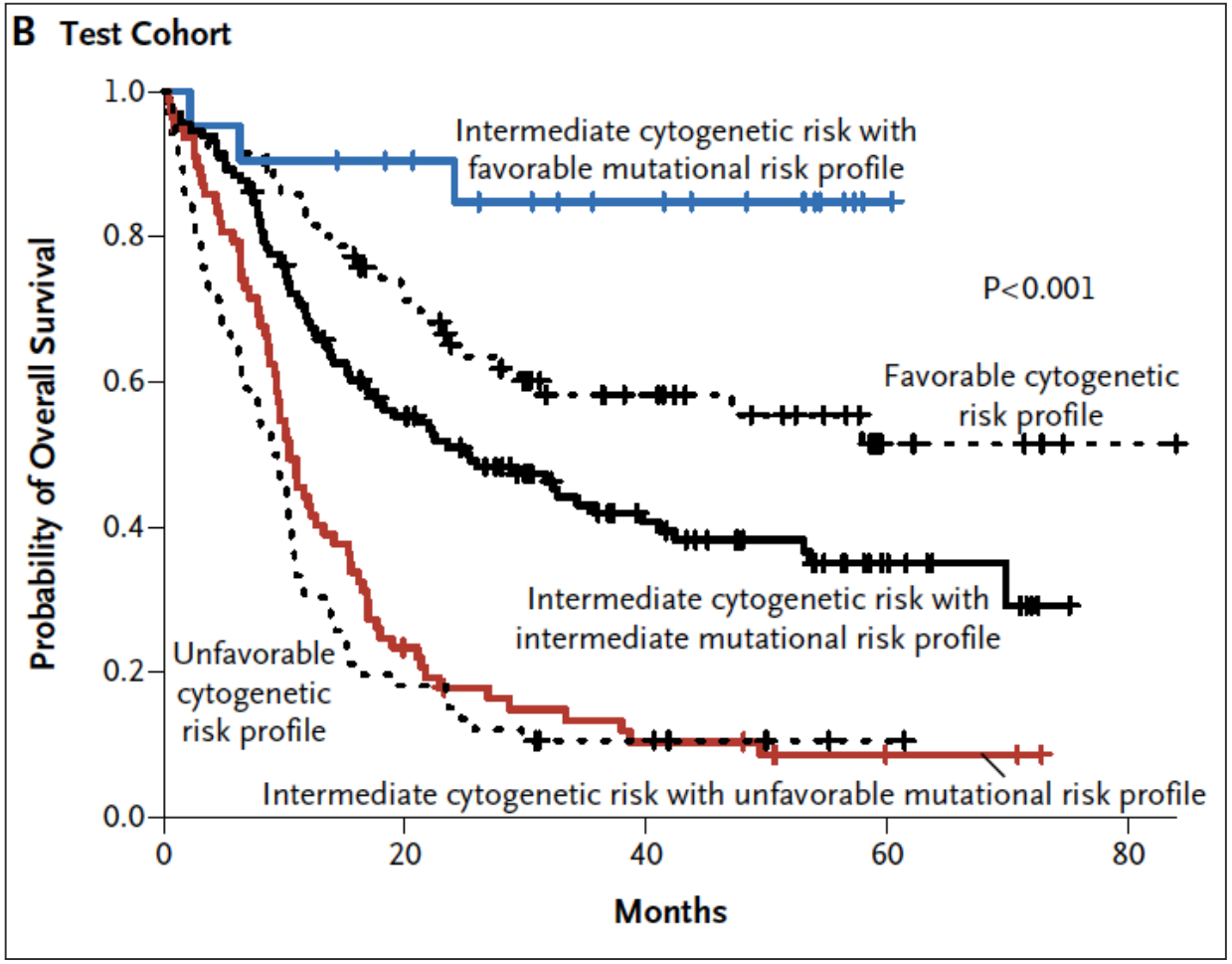
Döhner H, et al. *N Engl J Med* 2015;373:1136-1152.

2017 European LeukemiaNet Stratification by Genetics

Genetic Risk Group	Subset
Favorable	• t(8;21)(q22;q22); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* • Mutated *NPM1* without *FLT3*-ITD (normal karyotype) • Biallelic mutated *CEBPA* (normal karyotype)
Intermediate	• Mutated *NPM1* and *FLT3*-ITD^{high} (normal karyotype) • Wild-type *NPM1* without *FLT3*-ITD or *FLT3-ITD*^{low} (normal karyotype) • t(9;11)(p22;q23); *MLLT3-MLL* • Any cytogenetics not classified as favorable or adverse
Adverse	• inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *GATA2.MECOM(EVI1)* • t(6;9)(p23;q34); *DEK-NUP214* • t(v;11)(v;q23); *KMT2A*rearranged • Monosomy 5 or del(5q); monosomy 7; -17p; complex karyotype (≥3 abnormalities) • Mutated *RUNX1* • Mutated *ASXL1* • Mutated *TP53*

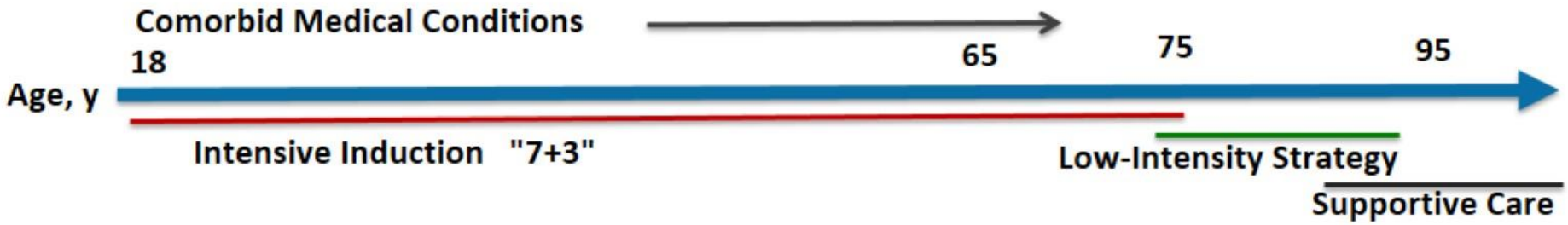
Döhner et al. Blood 2017;129:424-447.

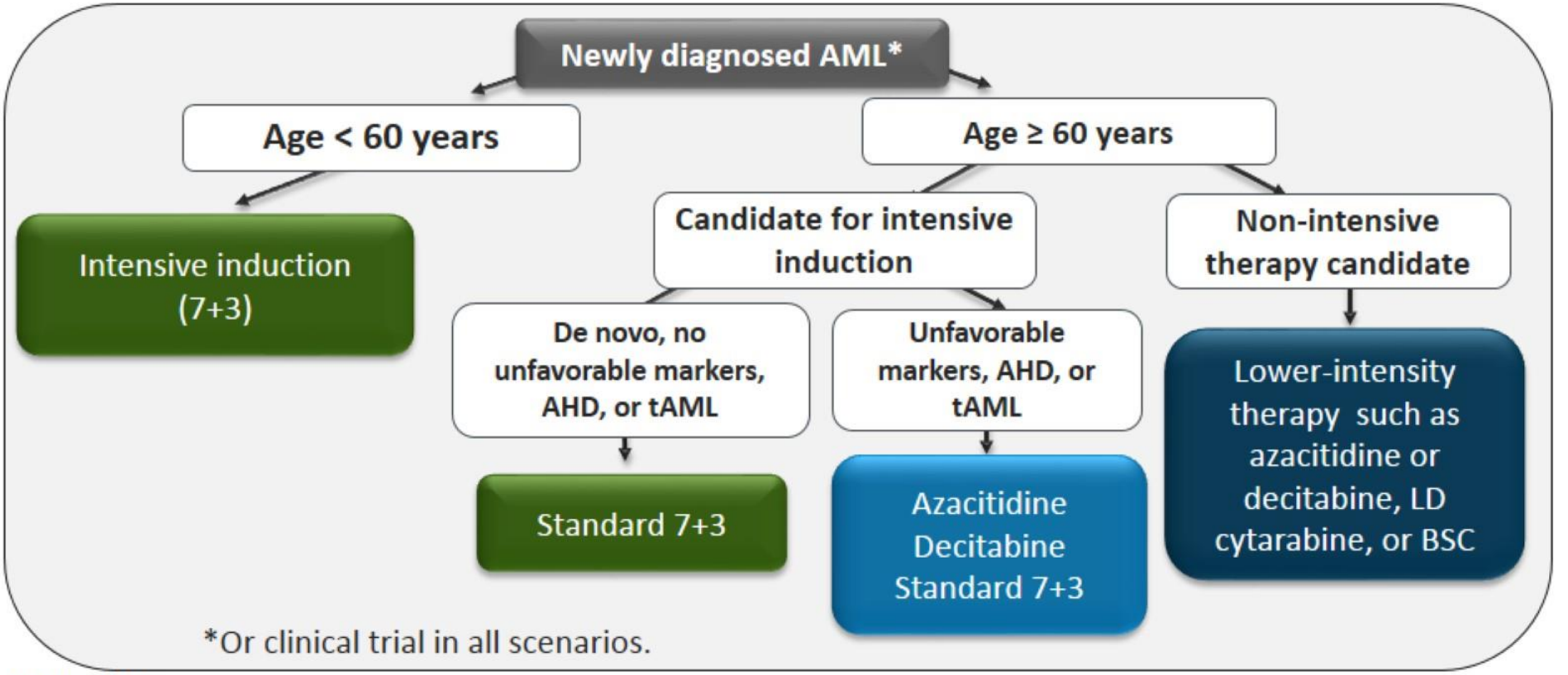
Revised Risk Stratification of Patients with AML on the Basis of Integrated Genetic Analysis



Patel et al. NEJM 2012 March 22; 366(12):1079-89.

Treating Newly Diagnosed AML
Current Paradigms





NCCN website.

Results of Selected Trials of Intensive Induction Therapy For Adult AML

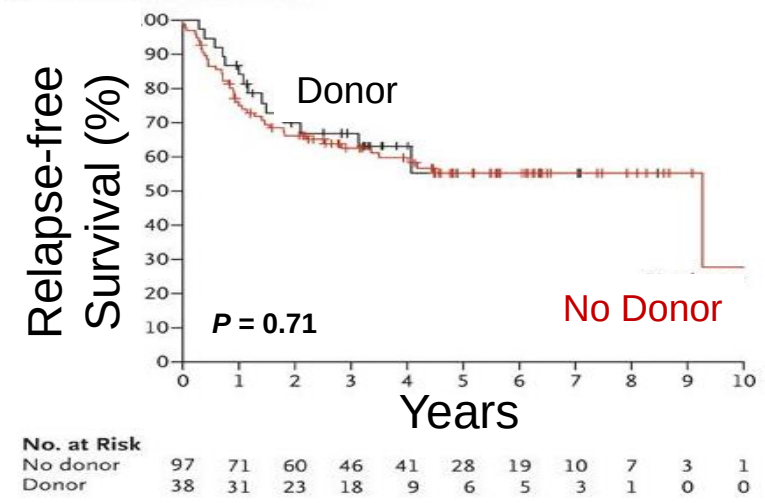
Trial	Regimen	*n*	CR total (%)	CR cycle 1 (%)	Early death (%)	Resistant disease (%)	OS 3-year (%)
PALG[3]	DA	211	56	51	10	34	33
	DAF	219	59	55	9	32	35
	DAC	222	67.5	62	11	21	45
SWOG[6]	DA	300	69	50	1	29	55
JALSG[7]	DA	525	77.5	61.1	2	20	48
	IA	532	78.2	64.1	5	17	48
ECOG[5]	D45A	293	57.3	41.1	4.5	39	33
	D90A	289	70.6	58.8	5.5	25	40
MRC[2]	DA	240	83	NA	6	11	41*

*5-year overall survival. Abbreviations: CR, complete remission; D45A, DA 45 mg/m² per day; D90A, DA 90 mg/m² per day; DA, daunorubicin and cytarabine; DAC, daunorubicin, cytarabine and cladribine; DAF, daunorubicin, cytarabine and fludarabine; IA, idarubicin; NA, not applicable; OS, overall survival.

Appelbaum F. Nat Rev Clin Oncol 2012;9:376.

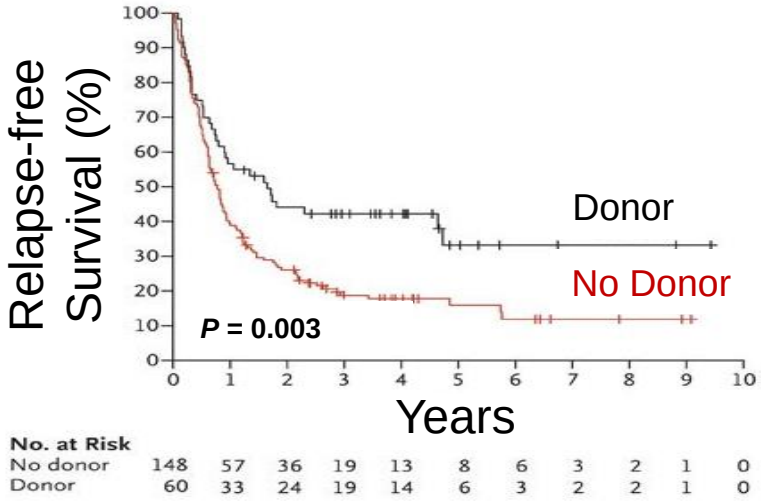
Allogeneic stem cell transplantation for AML patients in first remission

Mutant *NPM1*, No *FLT3*-ITD



No benefit from allo SCT in patients with: mutated *NPM1 and* wild-type *FLT3*

Other Genotypes



In cases other than ELN favorable:
allo SCT may be superior:
DON'T transplant ELN favorable in CR1

Schlenk RF et al. *N Engl J Med*. 2008;358:1909-1918.

CR, Early Death, and Survival Rates in Older (≥ 55 years) AML

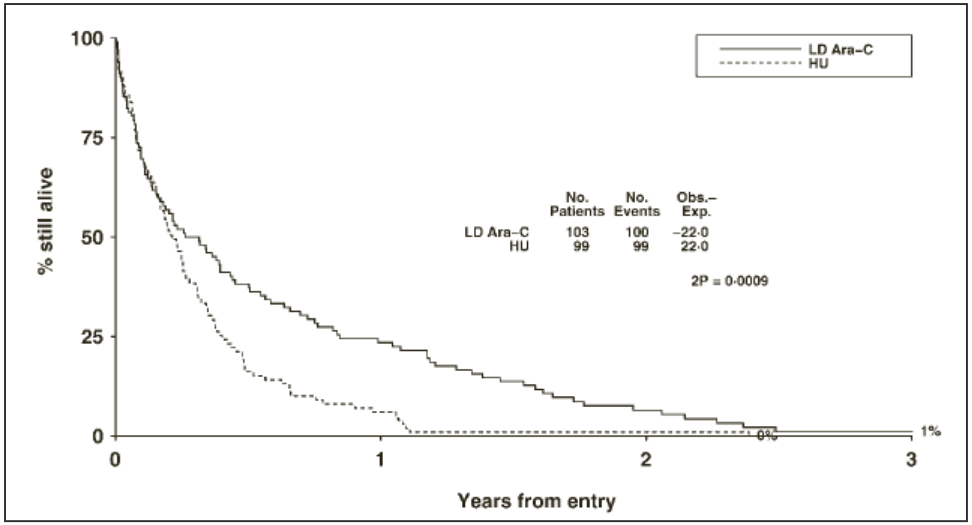
STUDY	N	Induction / Consolidation	CR	ED	OS(3-5 year)
CALGB	388	DA/A or MA	52%	25%	15%
ECOG	348	D or I or M (each) + A/A	42%	17%	10%
SWOG	328	DA or ME/DA	43%	7%	19%
MRC	1,314	DAT or ADE or MAC/DAT Or COAP, DAT, COAP	55%	19%	10%
Kantarjian H, et al.*	466	Various cytarabine-based intensive chemotherapy regimens	45%	-	4 weeks = 26% 8 weeks = 36% 1 year = 28%

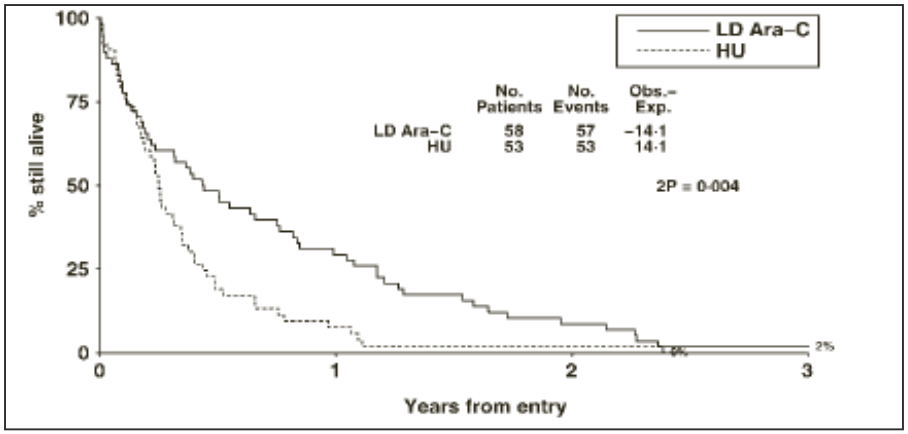
***Age 70 years or older.**

Tallman MS, et al. *Hematology.* 2005;143-150; Kantarjian H, et al. *Blood* July 28, 2010.

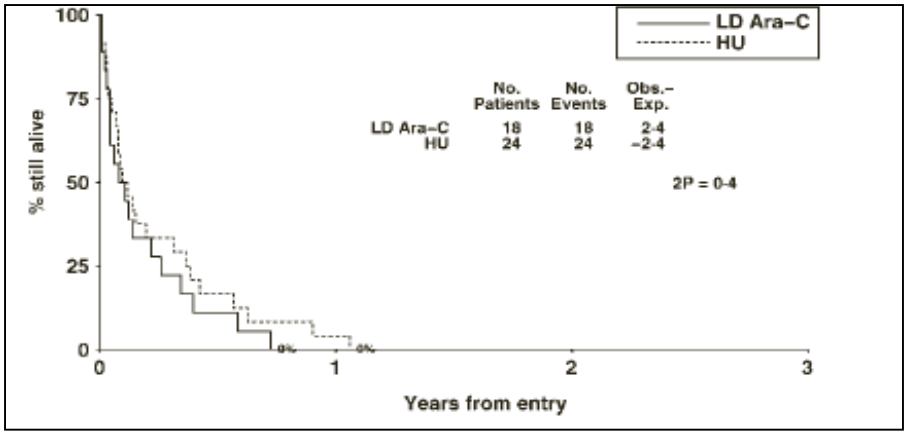
UK NCRI AML 14 Trial (Non-Intensive)

Response	Ara-C (N=102)	HU (N=99)
Induction Death	26%	26%
CR	18%	1%





Favorable/intermediate-risk karyotype



Poor-risk karyotype

Burnett et al. *Cancer*, 2007; 109: 1114-1124.

AML therapies: Inhibition of DNA methyltransferase

Azacitidine

- FDA-approved for MDS[1]
- EMA-approved for AML with 20–30% blasts and multilineage dysplasia and for AML with >30% marrow blasts[2]
- Incorporates into DNA and RNA[2]

Decitabine

- FDA-approved for MDS[3]
- EMA-approved for *de novo* or secondary AML[4]
- Incorporates into DNA[3]

Both azacitidine and decitabine inhibit DNMT at low doses[1–4]

Mechanism of action NOT fully understood

1. Vidaza USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050794s011lbl.pdf. Accessed June 2017;
2. Vidaza SmPC. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000978/WC500050239.pdf. Accessed June 2017;
3. Dacogen USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021790s006lbl.pdf. Accessed June 2017;
4. Dacogen EMA SmPC. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002221/WC500133569.pdf. Accessed June 2017.

MDS, myelodysplastic syndromes.

What we know about decitabine in AML

Decitabine clinical trials
1L AML in patients >60 years, unfit for chemotherapy[1,3–5] or with intermediate/poor risk cytogenetics[2,6,7]

Study	n	Dose	Response	Median OS, months
German multicenter, phase 2[1]	227	135 mg/m^2 over 72 hours, every 6 weeks	CR + PR 26%	5.5
US multicenter, phase 2[2]	55	20 mg/m^2 daily for 5 days, every 4 weeks	CR 24%	7.7
3 single-center US[3–5]	53[3] 52[4] 45[5]	20 mg/m^2 daily for 10 days, every 4 weeks	CR 47%[3] CR 40%[4] CR 31%[5]	~13[3] ~11[4] 9[5]
Multinational, phase 3[6,7]	242	20 mg/m^2 daily for 5 days, every 4 weeks	CR + CRp 17.8%	7.7

LDAC, low-dose cytarabine;
CRp, CR with incomplete platelet recovery.

1. Lübbert M, *et al. Haematologica* 2012; **97:**393–401; 2. Cashen AF, *et al. J Clin Oncol* 2010; **28:**556–561; 3. Blum W, *et al. Proc Natl Acad Sci U S A* 2010; **107:**7473–7478; 4. Ritchie EK, *et al. Leuk Lymphoma* 2013; **54:**2003–2007; 5. Bhatnagar B, *et al. Leuk Lymphoma* 2014; **55:**1533–1537; 6. Mayer J, *et al.* BMC Cancer 2014; **14:**69; 7. Kantarjian HM; *et al. J Clin Oncol* 2012; **30:**2670–2677.

What we know about azacitidine in AML

Azacitidine clinical trials				
Study	**n**	**Dose**	**Response**	**Median OS, months**
Austrian multicenter, 1L and R/R AML[1]	302	75 mg/m^2 SC for 7 days (reached in 33% of applied cycles)	ORR 48% CR/mCR 17%	9.6
French multicenter, 1L AML in patients ineligible for intensive chemotherapy[2]	149	75 mg/m^2 SC for 7 days, every 4 weeks	ORR 33% CR/CRi 23%	9.4
International, phase 3, 1L AML with >30% blasts[3]	241	75 mg/m^2 SC for 7 days, every 4 weeks	CR/CRi 27.8%	12.1

SC, subcutaneous.

1. Pleyer L, *et al. Ann Hematol* 2014; **93:**1825–1838;
2. Thépot S, *et al. Am J Hematol* 2014; **89:**410–416; 3. Dombret H, *et al. Blood* 2015; **126:**291–299.

What we know about decitabine and azacitidine in AML

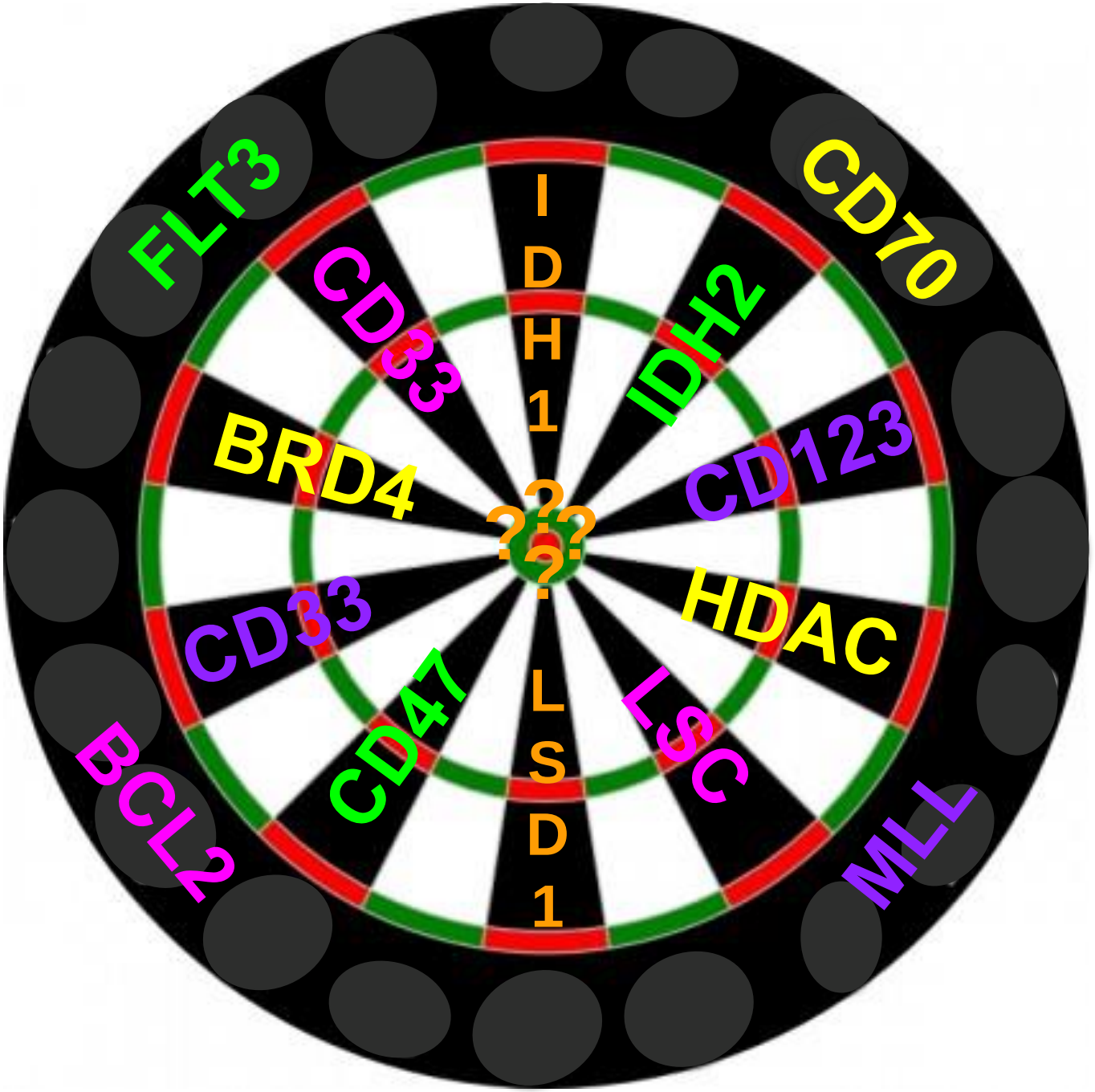
- Older patients[1–10]
- Responses despite unfavorable karyotype/poor prognostic features[1–10]
- Proliferative patients included[3,4,8,9]
- Low 30-day[2–7] and 60-day mortality[4,6,7,9]
  - Most common toxicities with both decitabine and azacitidine are hematological[1,2,4,5]
  - Extramedullary toxicity generally mild[1,2,4,7,8,10]
- Can take several cycles for response[1–10]
- ARE THEY BETTER THAN LDAC?

1. Lübbert M, *et al. Haematologica* 2012; **97:**393–401; 2. Cashen AF, *et al. J Clin Oncol* 2010; **28:**556–561;
3. Blum W, *et al. Proc Natl Acad Sci U S A* 2010; **107:**7473–7478; 4. Ritchie EK, *et al. Leuk Lymphoma* 2013; **54:**2003–2007;
5. Bhatnagar B, *et al. Leuk Lymphoma* 2014; **55:**1533–1537; 6. Mayer J, *et al.* BMC Cancer 2014; **14:**69;
7. Kantarjian HM; *et al. J Clin Oncol* 2012; **30:**2670–2677; 8. Pleyer L, *et al. Ann Hematol* 2014; **93:**1825–1838;
9. Thépot S, *et al. Am J Hematol* 2014; **89:**410–416; 10. Dombret H, *et al. Blood* 2015; **126:**291–299.

Open questions with DNA methyltransferase inhibitors

- Dose?
- Schedule?
- Ongoing therapy beyond response? Forever?
- Priming post-remission therapy?
- Biomarkers?
- Molecular prognostic factors?
- Combination partners?

TARGET



PRACTICE

Novel/Newly Approved Therapies

- Cytotoxic chemotherapy (eg. CPX-351, Vosaroxin)
- BCL-2 inhibitors (venetoclax)
- Hypomethylating agents (guadecitabine, oral azacitidine)
- Immunotherapies (bispecific and other antibodies, CAR-T)
- Immunoconjugates (eg. Gemtuzumab ozogamicin)
- FLT3 inhibitors
- IDH1 and IDH2 inhibitors
- And many others at ASH 2017

ELN 2017 New Response Category in AML: CR without minimal residual disease

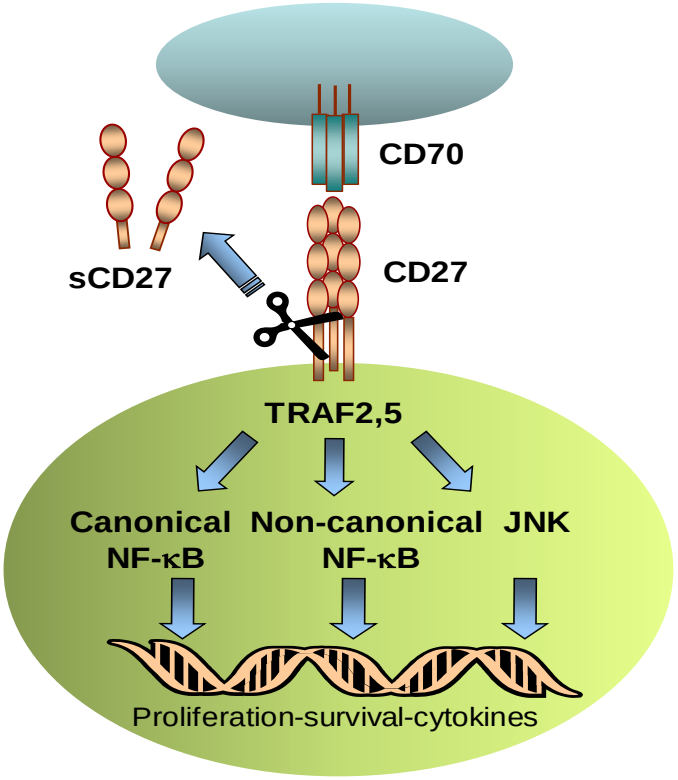
Standard morphologic CR: Bone marrow blasts <5%;
absence of circulating blasts and blasts with Auer rods;
absence of extramedullary disease;
ANC ≥1.0X10^9/L;
platelet count ≥100 x 10^9/L

Standard morphologic CR is not good enough in AML.
THE HOLY GRAIL in AML Therapy: Eradication of MRD

Döhner et al. Blood 2017;129:424-447.

CD70: Novel AML target

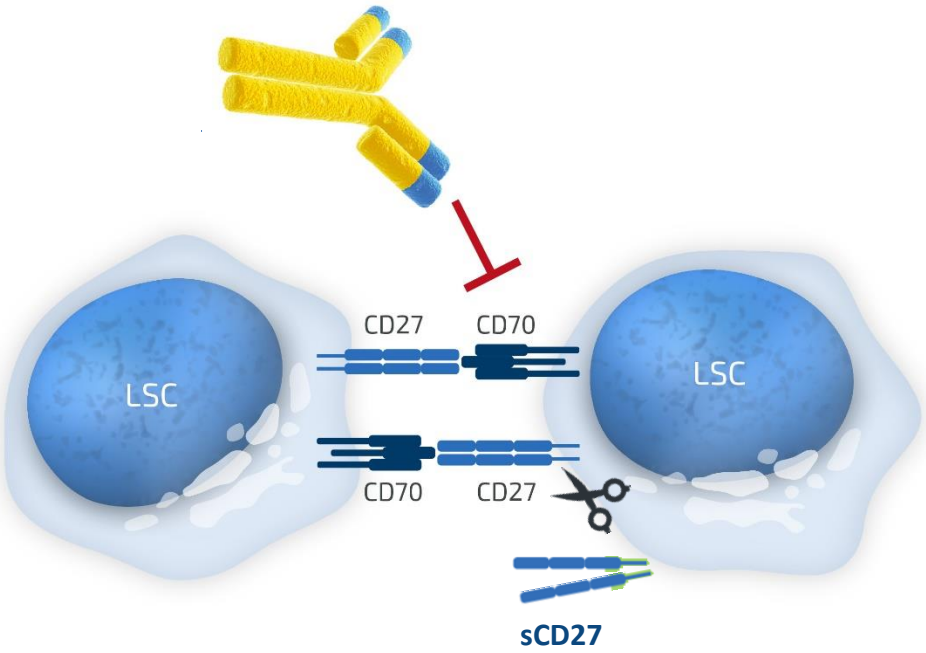
CD70/CD27 axis involved in lymphoma and leukemia pathogenesis



- Signaling via CD27, NF-κB/ JNK: proliferation, survival
- Shedding of soluble CD27 (sCD27): biomarker of CD70 activity

Wajant et al. 2016, Exp Opin Therap Targets; Silence et al. 2014, mAbs; Reviews: Croft 2009 & 2014; Nolte, 2009; Talabian, 2009

ARGX-110: Highly differentiated antibody targeting CD70



- SIMPLE Antibody™ with multiple modes of action addressing leukemic stem cells (LSCs) in AML
  - Blocking of CD70/CD27 axis
  - Killing of CD70+ cells through enhanced ADCC and ADCP (POTELLIGENT®) and CDC

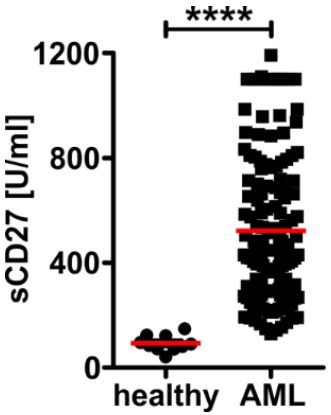
ADCC: antibody-dependent cellular cytotoxicity, ADCP: antibody-dependent cellular phagocytosis, CDC: complement-dependent cytotoxicity

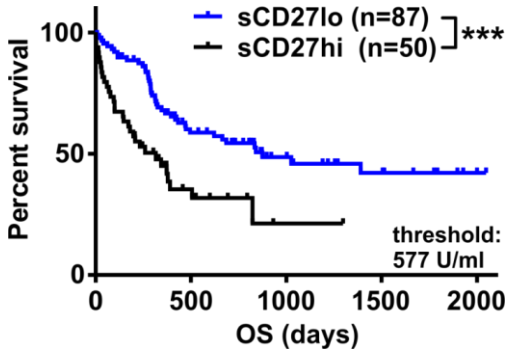
Silence et al. 2014, mAbs.

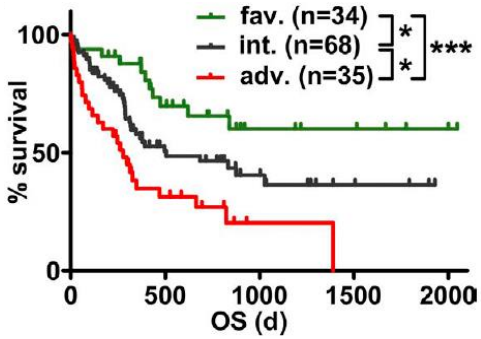
CD70 provides unifying rationale across risk & age classes in AML

Potential to selectively target leukemic stem cells in AML patients

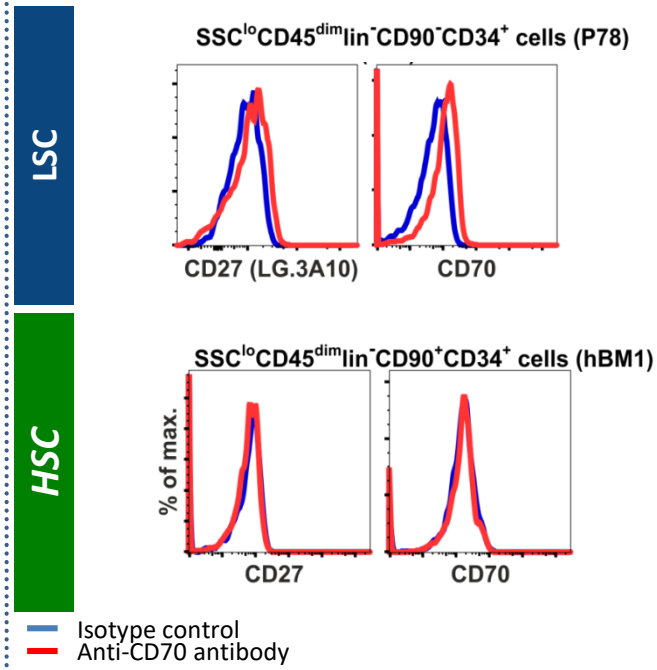
Elevated sCD27 serum levels correlate with poor prognosis







CD70 is a selective LSC marker



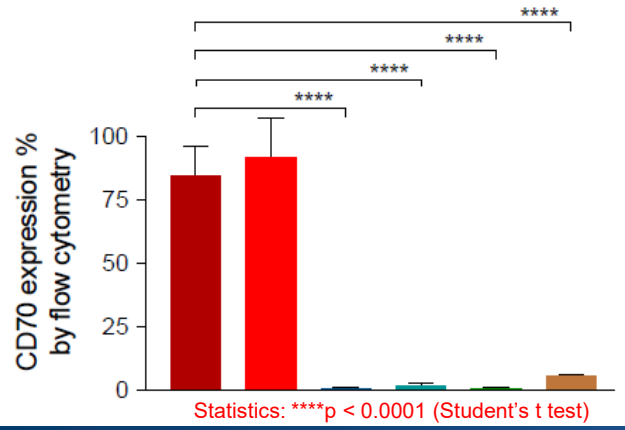
Legend: adv., adverse; CI, confidence interval; fav., favorable; int., intermediate; OS, overall survival. Statistics: left: one-way ANOVA; middle: log-rank test. *, P < 0.05; **, P < 0.01; ***, P < 0.001.

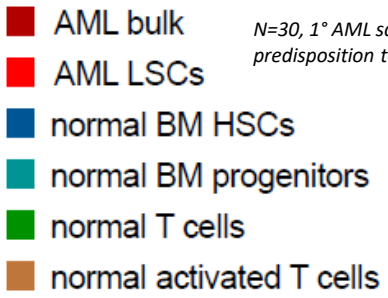
- Elevated sCD27 serum levels in all newly diagnosed AML patients, regardless of risk or age categories
- sCD27 levels are an independent negative prognostic marker in all newly diagnosed AML patients
- CD70 expressed on ~86-100% of AML blasts, majority of malignant cells are CD70/CD27 double-positive
- CD70/CD27 selectively overexpressed on leukemic stem cells (LSCs), not on hematopoietic stem cells (HSCs)

Riether et al. 2017, J Exp Med.

CD70 is a highly selective marker of primary AML cells

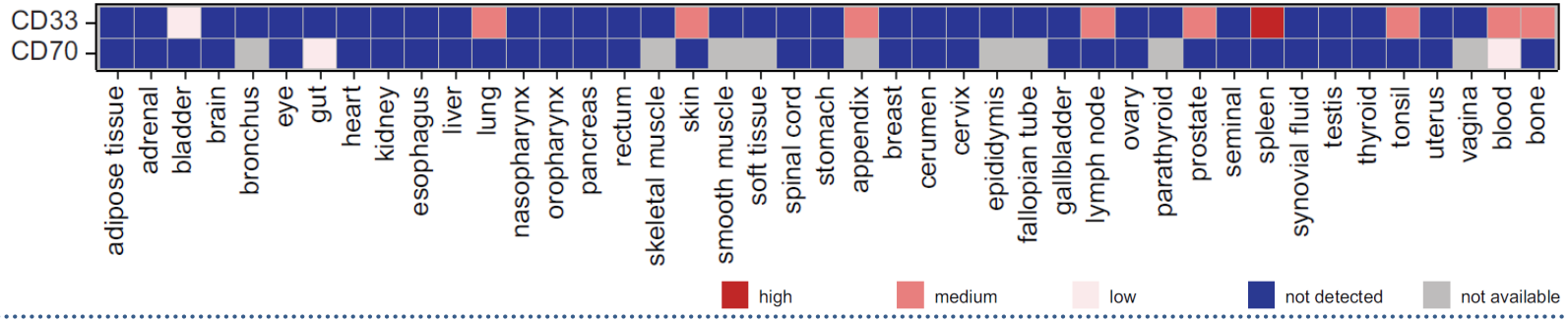
Selective CD70 expression on AML cells vs. healthy hematopoietic cells





N=30, 1° AML samples; genetic predisposition to clinical relapse

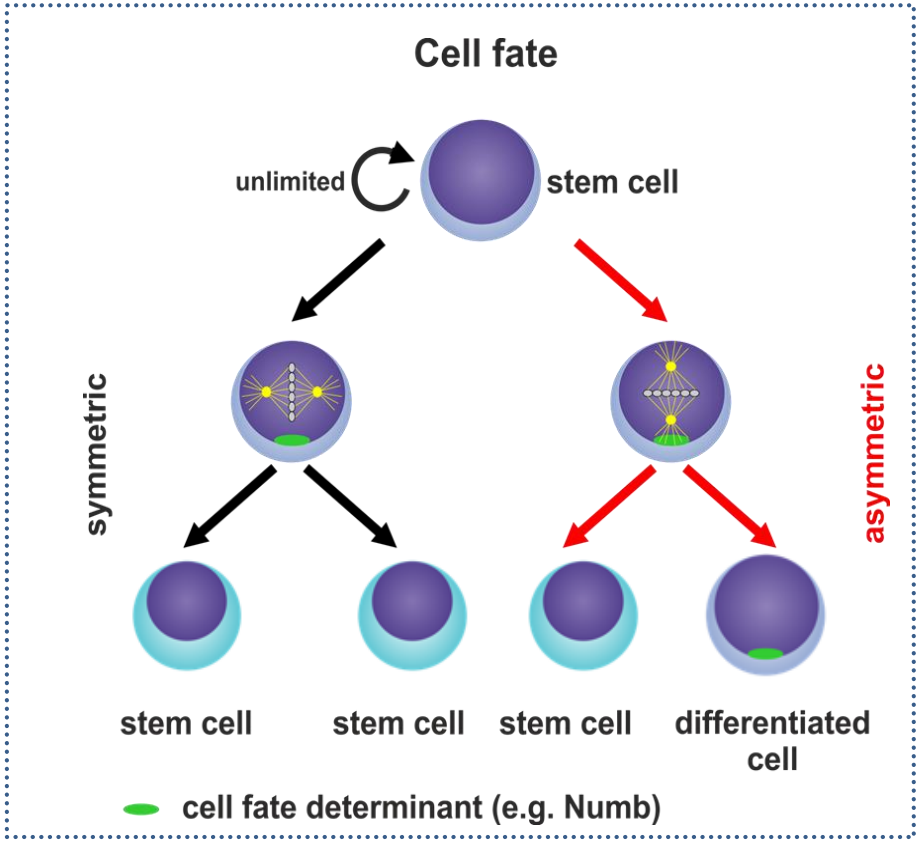
Very low expression throughout organism



- Extensive transcriptome and proteome analysis independently revealed CD70 as 1 of only 4 targets of interest for selective targeting of AML blasts and LSCs

Perna et al. 2017, Cancer cell

Leukemic stem cells responsible for disease relapse in AML

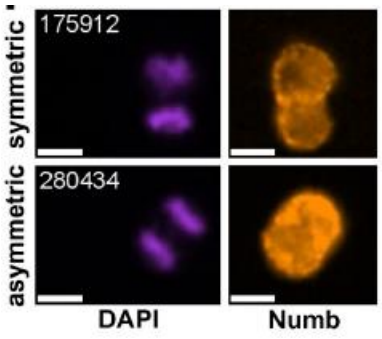


- Accumulation of blasts in bone marrow and blood results in reduction in red blood cells, platelets and normal white blood cells
- Symmetric division increases disease aggressiveness

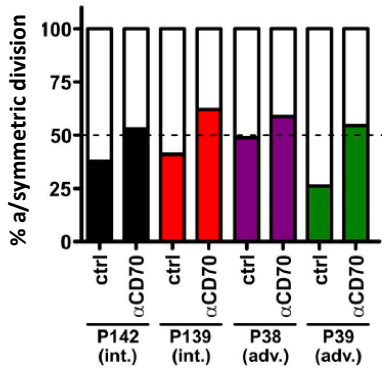
Blocking CD70 drives AML cells into myeloid differentiation

Proteome level

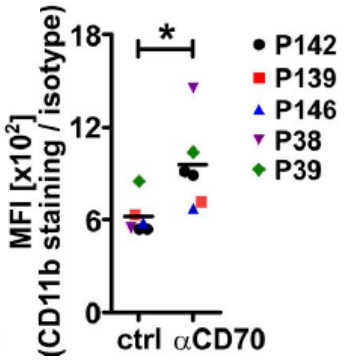
Numb distribution *(dividing U937)*



A/symmetric division *(1° blasts)*



Myeloid differentiation CD11b FACS



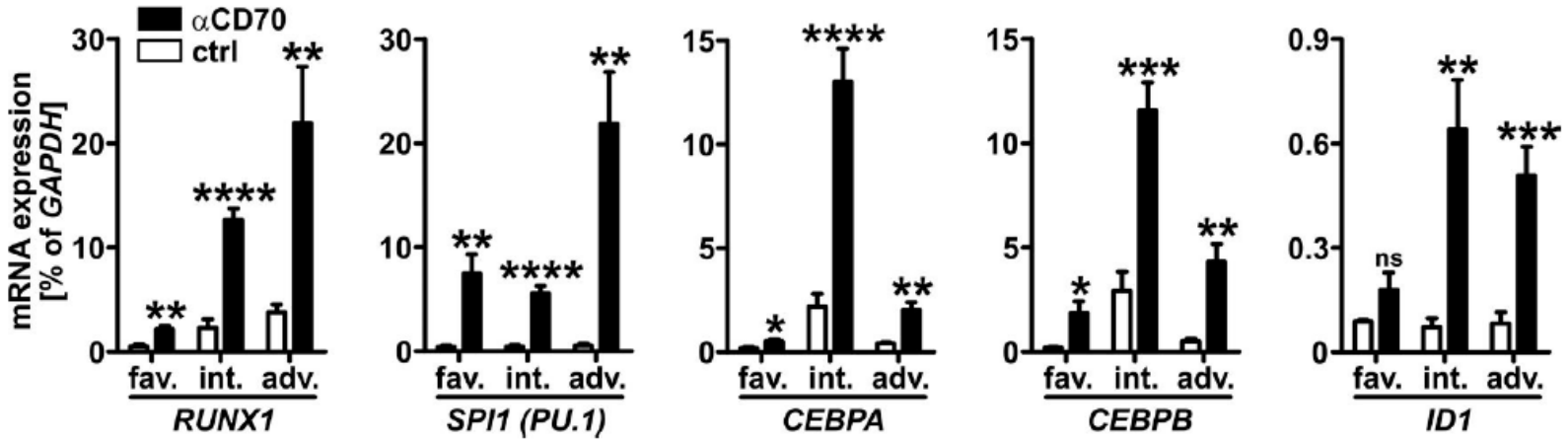
Legend: adv., adverse; ctrl, control; int., intermediate; MFI, mean fluorescence intensity. Statistics: t test. *, P < 0.05

- Increased asymmetric division results in decreased stemness and disease aggressiveness
- Increased myeloid differentiation demonstrated on proteome levels

Riether et al. 2017, J Exp Med.

Blocking CD70 induces myeloid differentiation factors

Transcriptome level



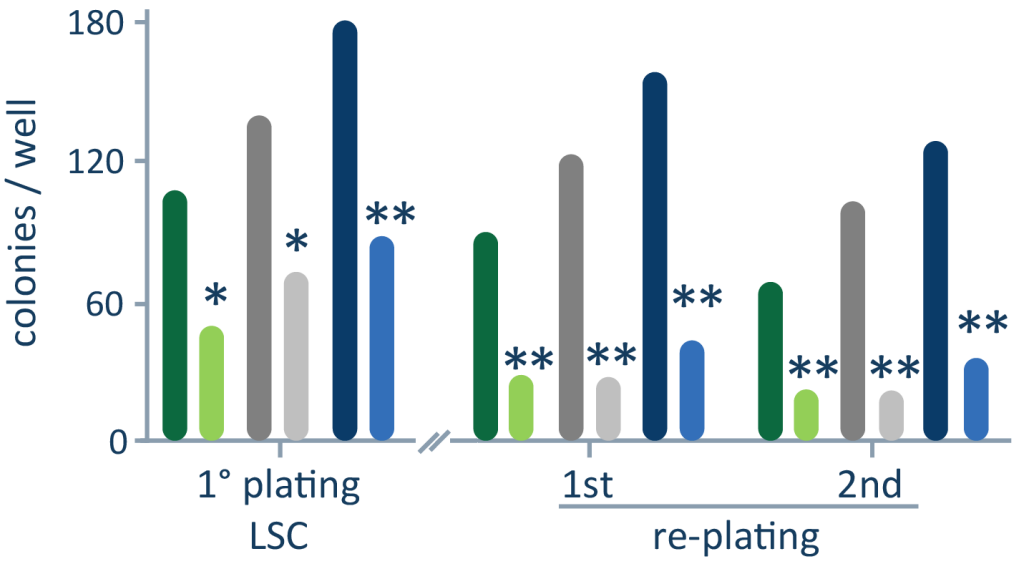
Legend: adv., adverse; ctrl, control; fav., favorable; int., intermediate. Statistics: Student's t test; *, P < 0.05; **, P < 0.01; ***, P < 0.001; ****, P < 0.0001.

- Increased myeloid differentiation demonstrated at transcriptional and translational levels
- Expression differentiation-inducing genes RUNX1, SPI1 (PU.1), CEBPα, CEBPβ, and ID1 significantly increased in AML leukemic stem cells cultured overnight in the presence of blocking ARGX-110 compared with control mAb

Riether et al. 2017, J Exp Med.

ARGX-110 inhibits leukemic stem cell proliferation

Long-term effects *ex vivo*



ctrl
ARGX-110 variant
Favorable risk patient (p1)

ctrl
ARGX-110 variant
Intermediate risk patient (p2)

ctrl
ARGX-110 variant
Adverse risk patient (p2)

ARGX-110 variant = ARGX-110 without Fc effector functions

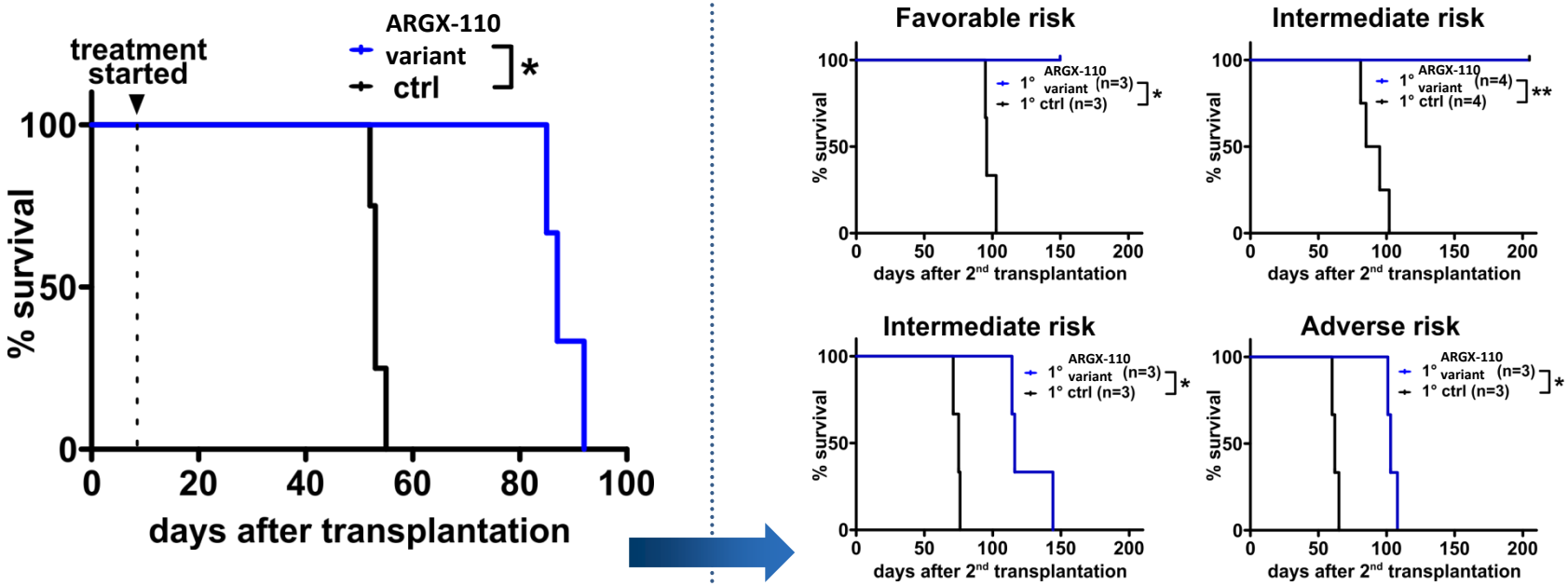
Statistics: Student's t test; *, $P < 0.05$; **, $P < 0.01$

- Reduces LSC colony formation across patient risk categories (favorable/intermediate/adverse risk)
- Reduces LSC numbers as determined in serial re-plating experiments
- Blocking CD70 results in: (1) lasting down-regulation of stem cell genes (2) increasing myeloid differentiation

Riether et al. 2017, J Exp Med.

Curative potential of ARGX-110 monotherapy in mouse model

Shown to reduce leukemic stem cells, increasing survival in AML model



Initial in vivo treatment
+ARGX-110 variant

Grafting Whole Bone Marrow cells from treated into new mice (14d after start of treatment)

Transplant, evaluation
-ARGX-110 variant

Statistics: log-rank test; *, $P < 0.05$; **, $P < 0.01$.

- Increased survival after secondary transplantation of AML bone marrow cells from primary recipients transiently treated with ARGX-110 variant
- Increased survival observed for AML blasts taken from all 3 AML risk categories (fav/int/adv)

Riether et al. 2017, J Exp Med.

Blocking CD70/CD27 signaling in combination with hypomethylating agents eradicates human CD34$^+$ AML stem and progenitor cells in vitro and in vivo

Poster 2652 (Sun Dec 10, 6-8pm)

Leukemia stem cells (LSCs) are the origin of acute myeloid leukemia (AML) and are resistant to standard therapeutic regimens resulting in relapse of the disease and poor prognosis. Consequently, LSCs represent a major obstacle for AML therapy. We recently identified the interaction of the TNF ligand CD70 and its receptor CD27 on LSCs as a promising therapeutic strategy to target LSCs. In this study, we demonstrate for the first time that treatment with hypomethylating agents (HMA) up-regulates CD70 expression on human AML cell lines and on primary CD34$^+$ AML stem/progenitor cells from newly diagnosed AML patients in vitro and in vivo. Co-treatment of CD34$^+$ AML stem/progenitor cells with the HMA and a blocking αCD70 monoclonal antibody reduced colony-forming and re-plating capacity in vitro compared to single agent treatment. Furthermore, combining HMA treatment with CD70 blockade effectively eliminated human CD34$^+$CD38$^-$CD45RA$^-$ LSCs in limiting dilution patient-derived xenograft experiments. Consequently, combining HMAs with blocking CD70/CD27 signaling may represent a novel strategy to eradicate human LSCs.

Author(s): Hinterbrandner M[1], Kallen NM[1], Lüthi U[1], Pabst T[3], Van Rompaey L[2], Leupin N[2], De Haard H[2], Ochsenbein A[1, 3] and Riether C[1, 3*]

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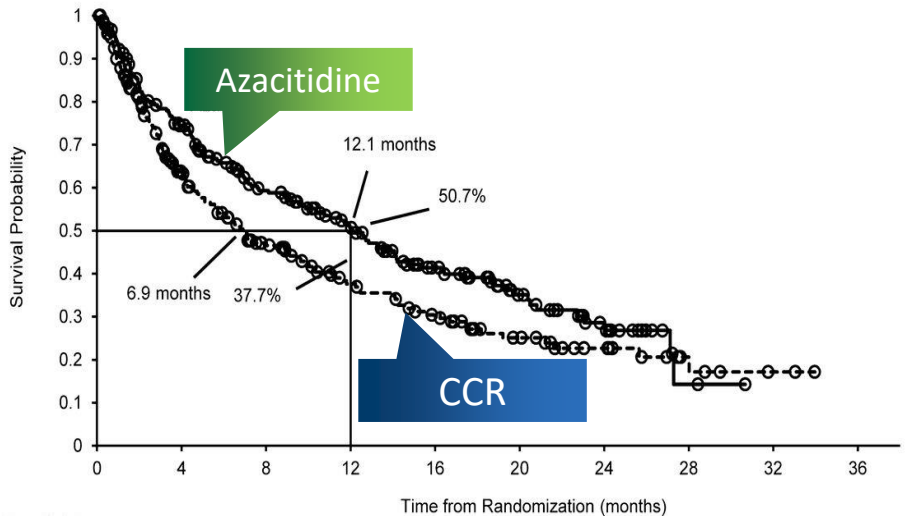
* Presenting and corresponding author

Phase 1/2 trial in newly diagnosed AML: Proof-of-Biology

High unmet need in newly diagnosed, elderly AML patients

Standard of care provides limited survival benefit

Phase 3 study of azacitidine vs. conventional care regimens in older patients with newly diagnosed AML with >30% blasts (1)



- 60% of newly diagnosed AML patients are more than 60 years old
- Hypomethylating agents are standard of care in newly diagnosed AML patients unfit for intensive chemotherapy
- Hypomethylating agents have limited effect on leukemic stem cells responsible for relapse

(1) Dombret et al. 2015, Blood
(2) American Cancer Society: http://www.cancer.org/cancer/leukemia-acutemyeloidaml/detailedguide/leukemia-acute-myeloid-myelogenous-key-statistics .

High unmet need in newly diagnosed, elderly AML patients

Azacitidine provides limited response rate and comes with some side effects

Study	Patients (N=)	Adverse events (G3-G4)	%	ORR (%)
Falantes *et al.* 2017	710	Pancytopenia Febrile neutropenia Infections	8 – 75 11 – 50 6 – 30	**35.5**
Dombret *et al.* 2015	231	Febrile neutropenia Neutropenia Thrombocytopenia Pneumonia Anemia Leukopenia Hypokalemia Infections	28 26 24 24 19 16 7 5	**31.1**

Dombret et al. 2015, Blood; Falantes et al. 2017, Leukemia & Lymphoma

Open label, non-controlled, non-randomized Phase I study

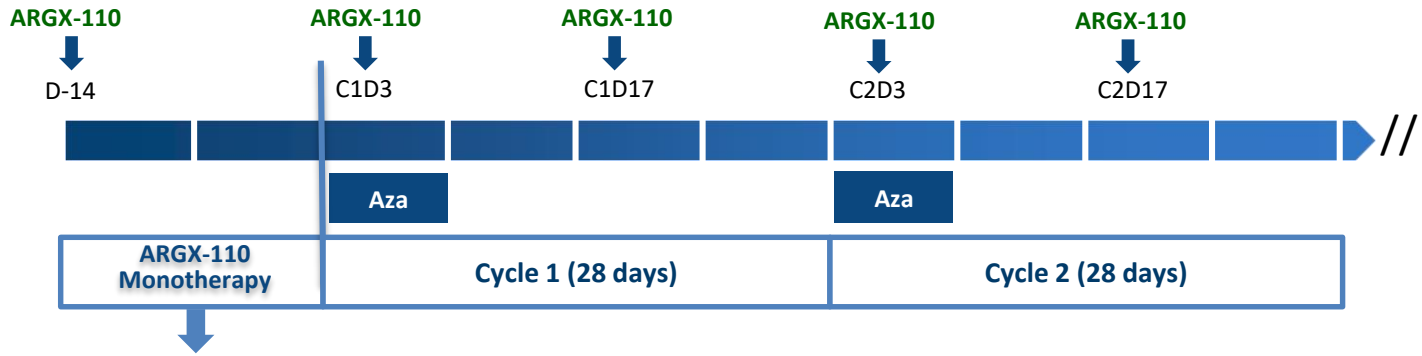
In newly diagnosed AML patients unfit for intensive chemotherapy

Study design

Treatment schedule

ARGX-110
1, 3, 10 mg/kg q2wk IV

Azacitidine
75 mg/m² 7d/month sc



Allows unique insight into CD70 pathology via translational program

Patient characteristics and preliminary data

Non-transplantable patients with intermediate & adverse risk and high blast count in bone marrow

9 newly diagnosed AML patients

Baseline characteristics (N=9)	ARGX-110 + Azacitidine			
	1 mg/kg	3 mg/kg	10 mg/kg	Total
Age				
Median	71	75	71	**72**
	71-80	71-84	64-75	**64-84**
Gender: Male/Female	2/1	1/2	2/1	**5/4**
Risk (ELN 2017)				
Intermediate	1	2	2	**5**
Adverse	2	1	1	**4**
Blasts in the bone marrow				
Median %	51.3	40	70	**53.6**
	24-90	20-60	50-80	**20-90**
AML classification (WHO 2016)				
Not other specified		1	3	**4**
With Myelodysplasia- related changes	2	2		**4**
Therapy-related myeloid neoplasm	1			**1**
French-American-British subtypes	M4,M1,M2	M4,M5,M2	M1,M2,M5a	

ELN: European Leukemia Net, Dohner et al. 2017, Blood

Source: argenx data – patient anecdotes – uncleaned data

Limited number of grade 3-4 toxicities

6/9 newly diagnosed AML patients

Grade 3-4 Adverse Events in 6 patients	1 mg/kg Events (Patients)	3 mg/kg Events (Patients)
Anemia	2 (1)	7* (2)
Thrombocytopenia	9* (2)	2 (1)
Neutropenia	1 (1)	
Leucopenia	1 (1)	
Febrile neutropenia	2 (2)	
Pleuropericartidits	1 (1)	
Lung infection	1 (1)	
Constipation		1 (1)
Proctitis		1 (1)
Hypertension		2 (1)
Hypokalemia		1 (1)

*Intermittent toxicities for the same patient

Cut-off date: 15 November 2017

- G3-G4 hematological toxicity reflecting the azacitidine safety profile is observed for 1 and 3 mg/kg
- Evaluation for 10 mg/kg is ongoing; so far safety data in line with 1 and 3 mg/kg doses

Source: argenx data – patient anecdotes – uncleaned data

Favorable safety and tolerability profile in 94 patients

Monotherapy ARGX-110 in heavily pre-treated CD70+ patients

Adverse events ≥ 2 patients

Adverse Events	Grade 3 Events (Patients)	Grade 4 Events (Patients)	Grade 5 Events (Patients)	Total % of Patients**
General health deterioration due to progressive disease	4 (4)		6 (6)	**10.6**
Anemia	11 (9)			**9.5**
Fatigue	8 (8)			**8.5**
Pneumonia	4 (4)			**4.2**
Asthenia	3 (3)			**3.1**
Decreased appetite	3 (3)			**3.1**
Febrile neutropenia	3 (3)			**3.1**
Leukocytosis	3 (3)			**3.1**
Abdominal pain	3 (2)			**2.1**
Haemolytic anemia	3 (2)			**2.1**
Hypokalemia	3 (2)			**2.1**
Neutropenia	2 (2)	1 (1*)		**3.1**
Edema peripheral	2 (2)			**2.1**
Pulmonary embolism	2 (2)	1 (1)		**3.1**

94 patients= ARGX-110-1201 clinicaltrials.gov NCT 01813539

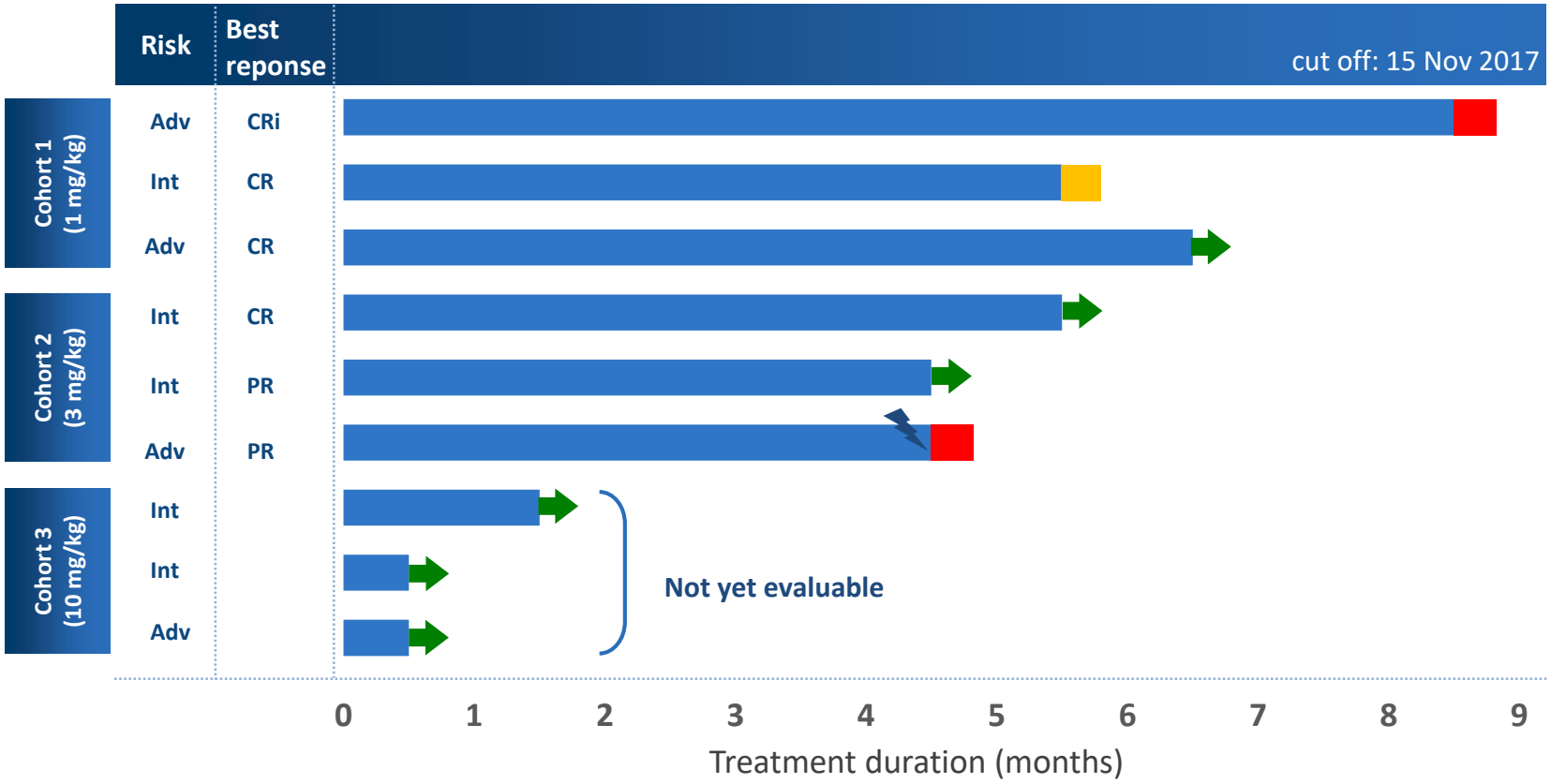
cut off: 15 Nov 2017

- Anemia and fatigue are the most frequent G3-G4 toxicities in this heavily pre-treated population

Source: argenx data – patient anecdotes – uncleaned data

Response in 6/6 evaluable newly diagnosed AML patients

ARGX-110/Aza treatment



- So far, all patients responded (3 CR, 1 CRi, 2 PR) , MRD negativity reached in 2 patients so far (exploratory)
- 1 patient reached CR and bridged to allogeneic stem cell transplant after 5 cycles
- 6/9 patients are currently still on treatment

Study ended

Patient successfully transplanted

Adverse event leading to discontinuation

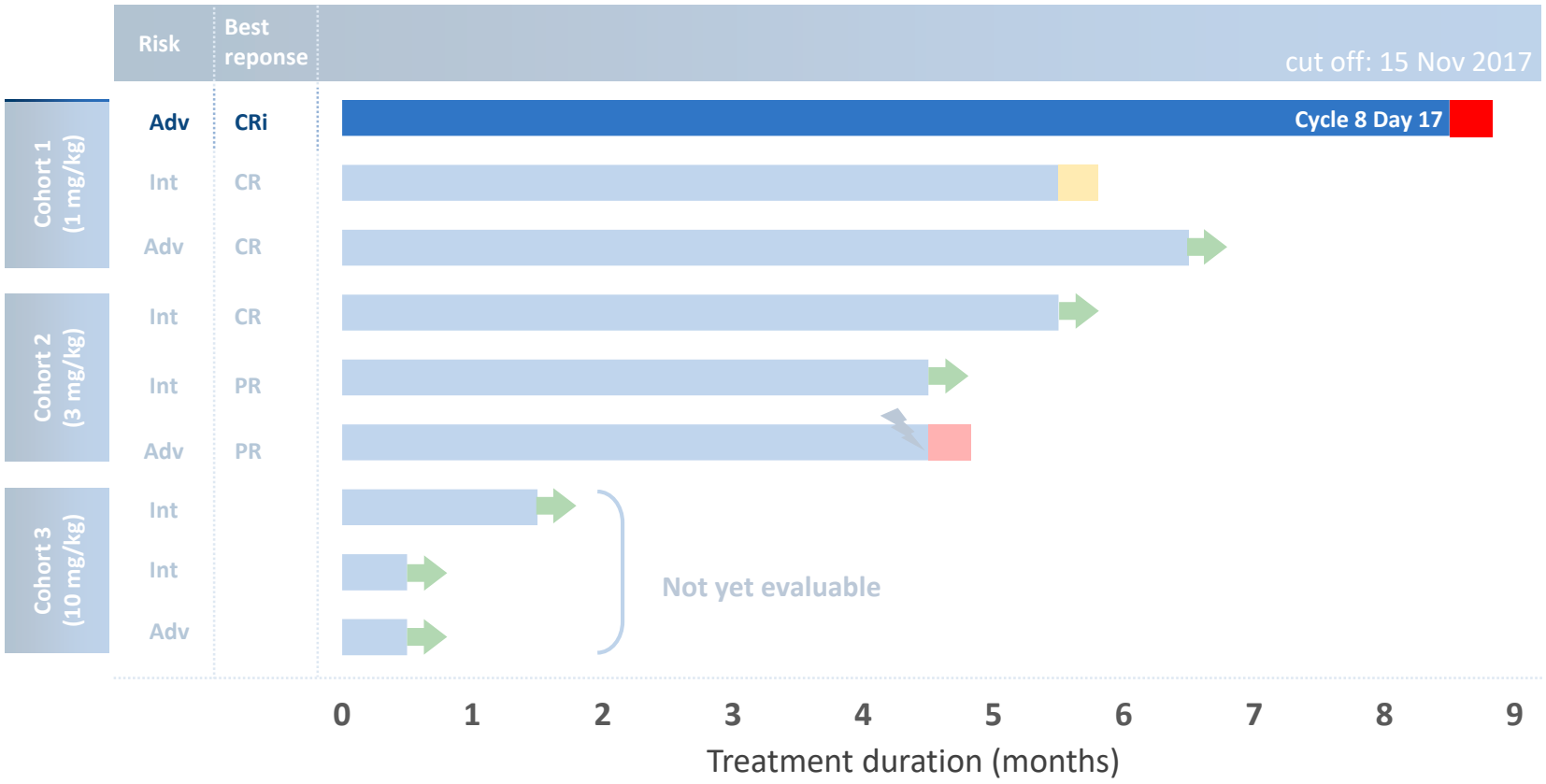
Ongoing study

Source: argenx data – patient anecdotes – uncleaned data

Case studies

Case 1: Patient cohort 1 – 1 mg/kg – 8 cycles on study

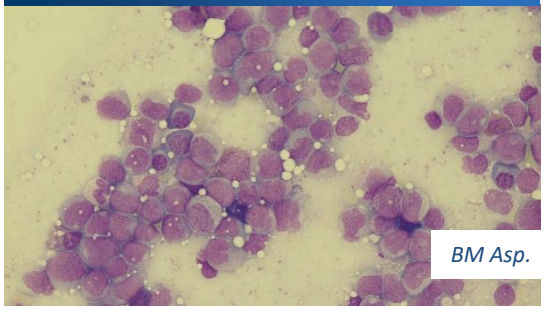
- 80 year old female
- Therapy-related AML, M4; BM ~65% blasts
- Molecular genetics: FLT3-ITD; DNMT3Amut; RUNX1mut; WT1mut; cytogenetics: normal



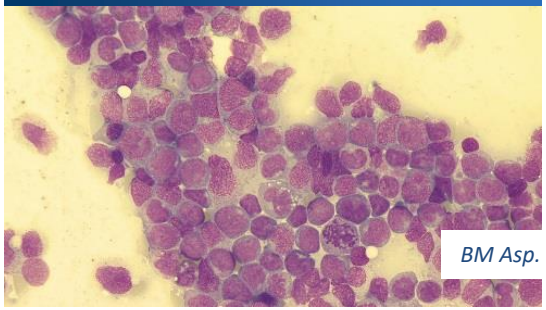
Source: argenx data – patient anecdotes – uncleaned data

Case 1: Complete remission with incomplete hematological recovery

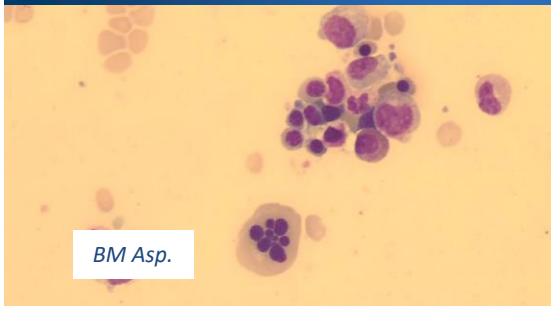
Screening



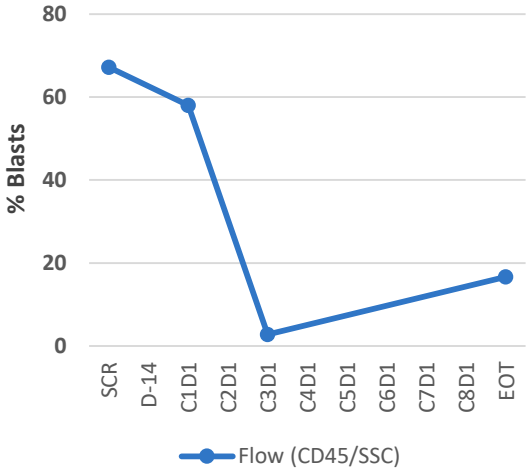
Leukemic blast persistence – (C1D1)



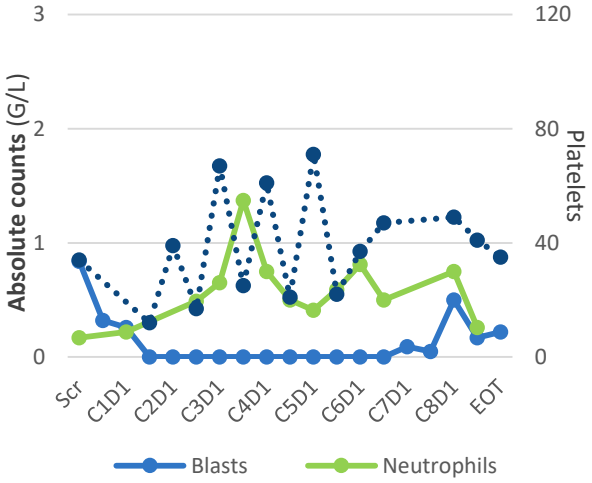
Leukemic clearance – (EOT)



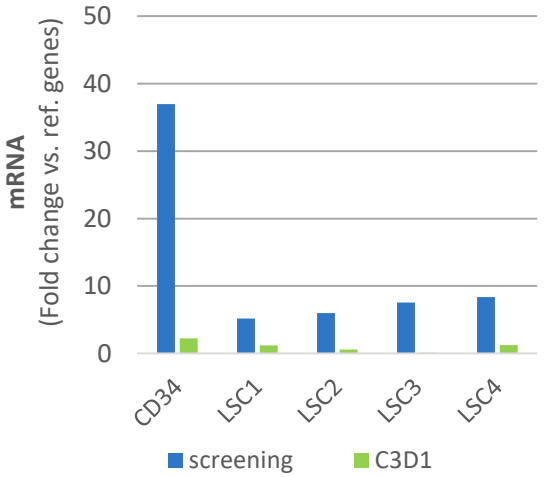
Bone marrow: % Blasts, flow cytometry



Blood analysis: Absolute counts (G/L)



ARGX-110/Aza reduces experimental LSC gene signature

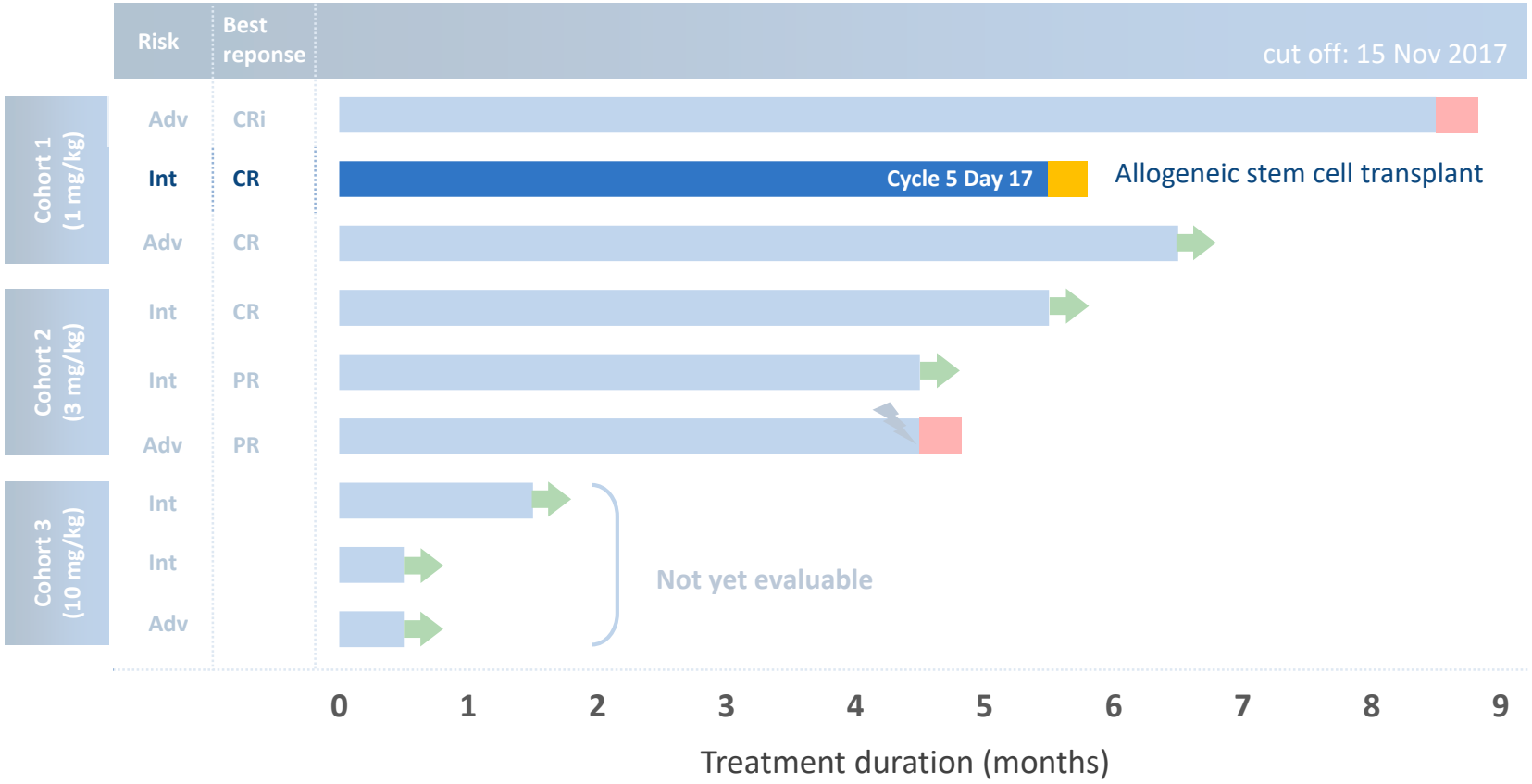


Ng. et al. 2016, Nature

Source: argenx data – patient anecdotes – uncleaned data

Case 2: Patient cohort 1 – 1 mg/kg – 5 cycles on study

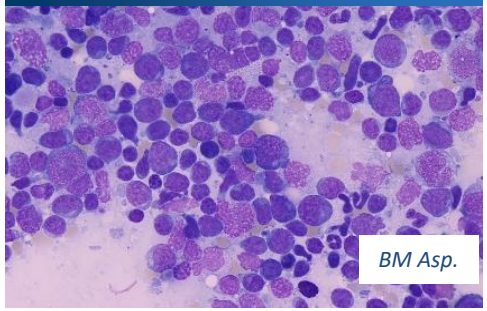
- 75 year old male
- AML with myelodysplasia-related changes, M1/M2; BM ~40% blasts
- Molecular genetics: U2AF1mut; DNMT3Amut; cytogenetics: normal



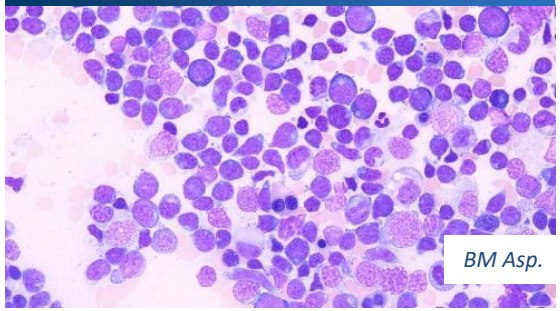
Source: argenx data – patient anecdotes – uncleaned data

Case 2: ARGX-110/Aza induces complete remission & bridges to transplant

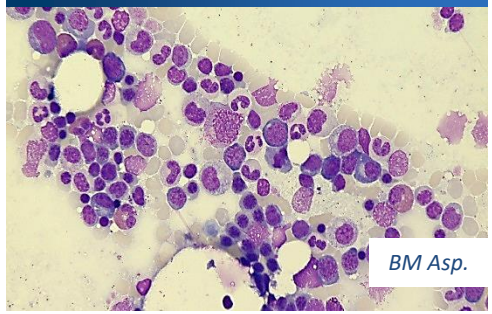
Screening



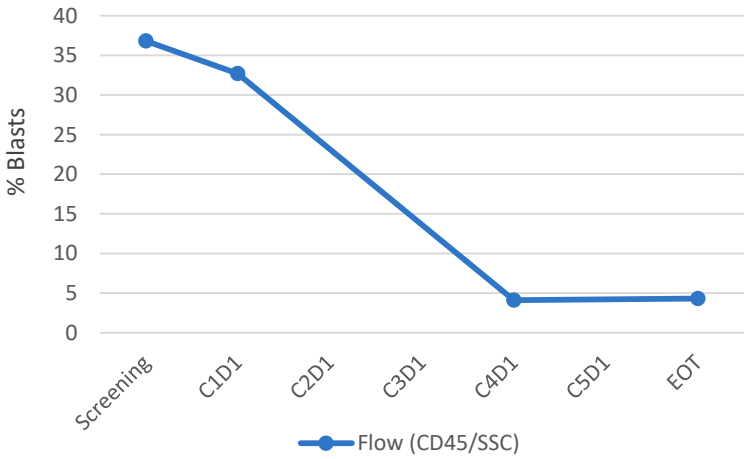
Leukemic blast persistence – (C1D1)



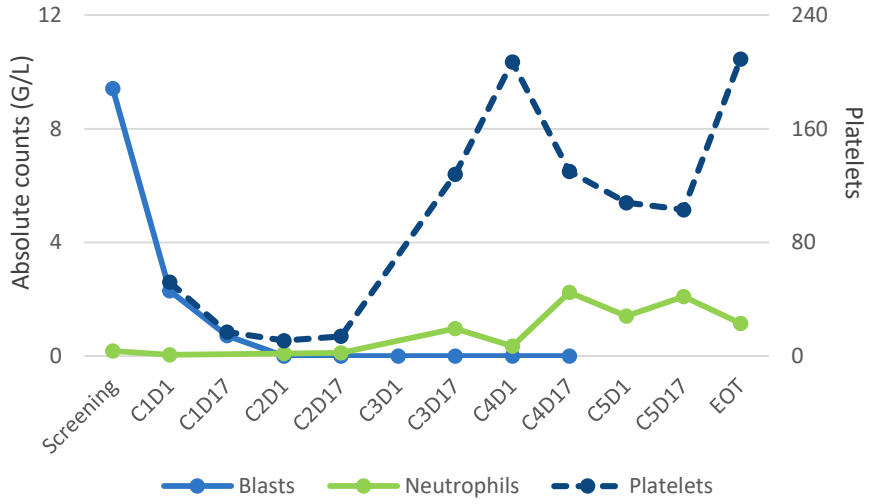
Leukemic clearance – (EOT)



Bone marrow: % Blasts, flow cytometry



Blood analysis: Absolute counts (G/L)



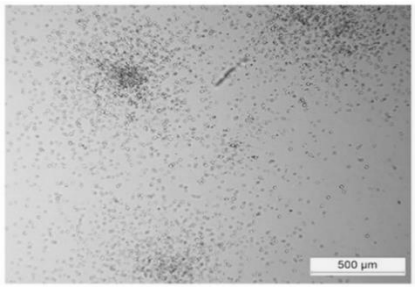
Source: argenx data – patient anecdotes – uncleaned data

Case 2: ARGX-110/Aza combo reduces AML stemness

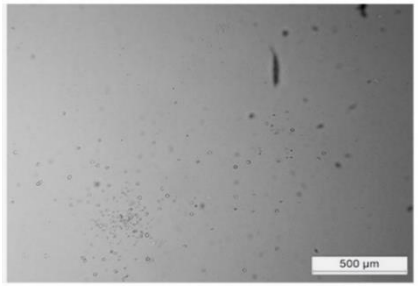
ARGX-110 monotherapy reduces LSCs outgrowth

White light microscopy (5,000 cells)

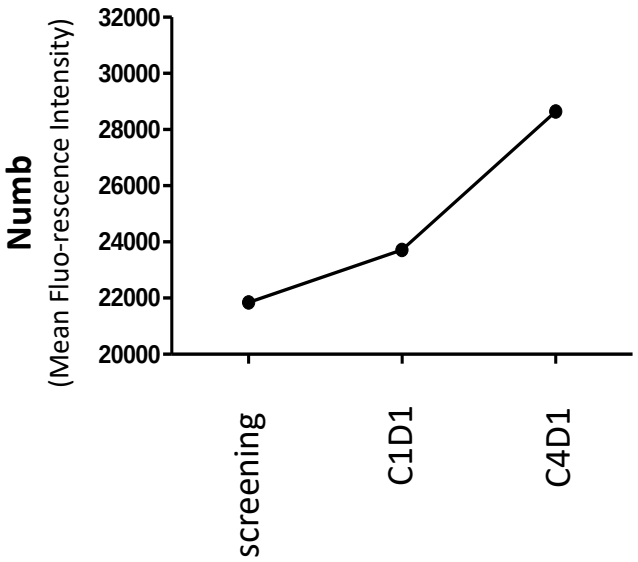
Screening



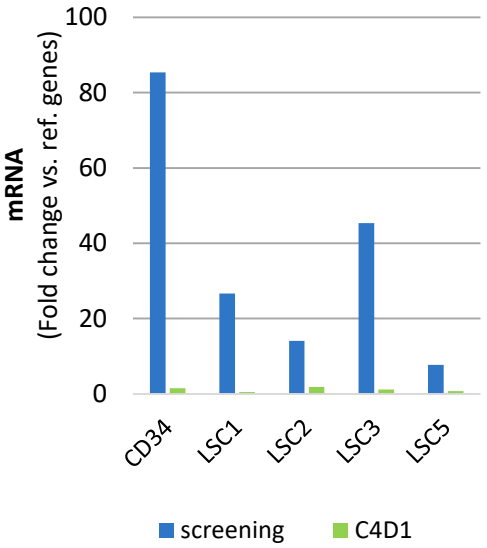
ARGX-110: Cycle 1 Day 1



ARGX-110/Aza increases asymmetric LSC division



ARGX-110/Aza reduces experimental LSC gene signature



- Significantly reduced leukemic stem cell colony formation
- Increased myeloid differentiation (asymmetric division) of leukemic stem cells
- Reduction of LSC gene signature

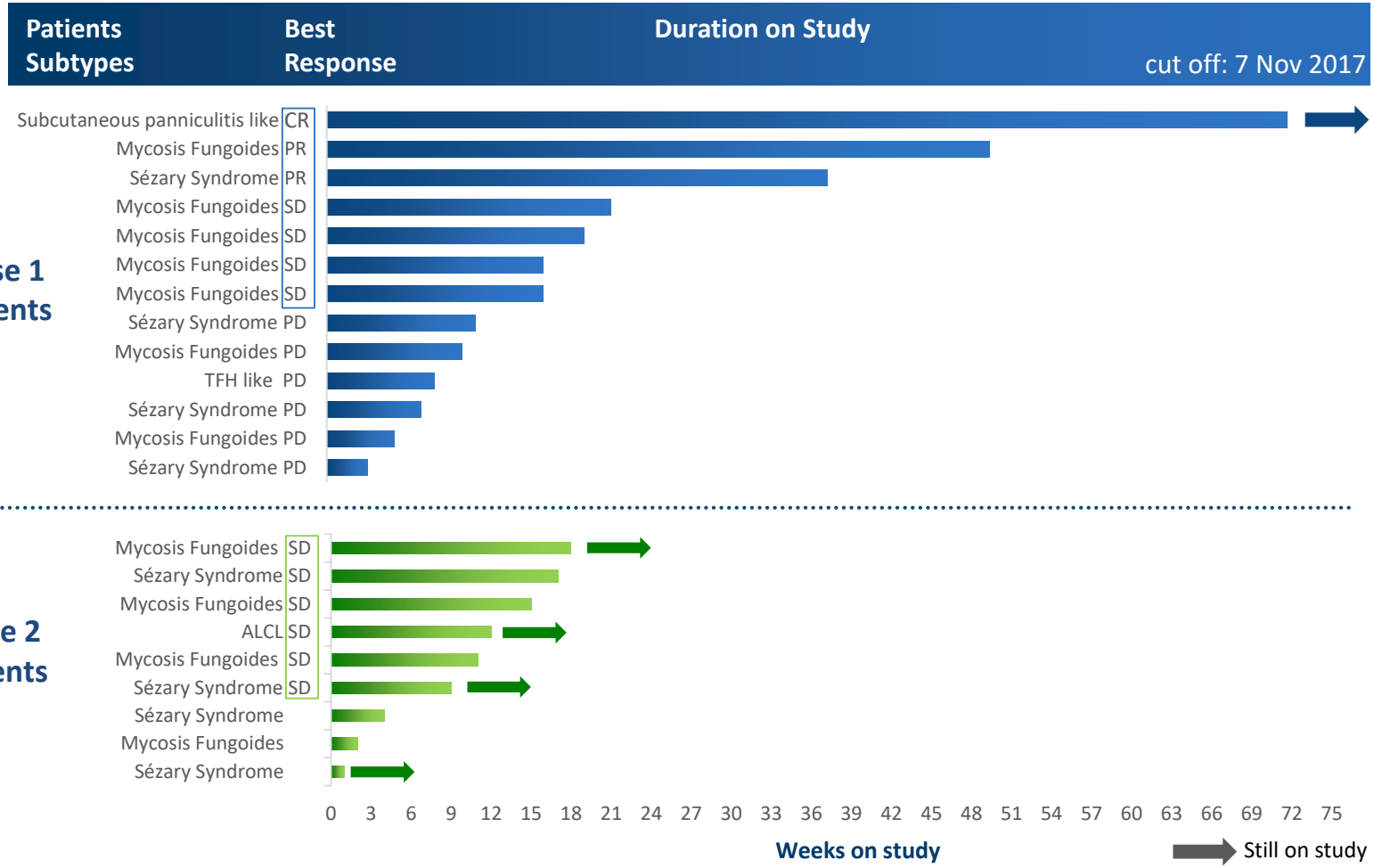
Ng. et al. 2016, Nature

Source: argenx data – patient anecdotes – uncleaned data

Phase 1 / 2 CTCL clinical trial: Data update

Disease control in 59% (13/22) of RR-CTCL patients

Duration on study



- Encouraging signs of clinical activity
- 5 patients still on study at 5 mg/kg

Source: argenx data – patient anecdotes – uncleaned data

Favorable safety and tolerability profile in CTCL patients

Monotherapy ARGX-110 (1 and 5mg/kg)

All grade adverse events : >2 events in 22 CTCL patients

Adverse Event	G1	G2	G3	G4	G5	Total
Pruritus	2	6	1			**9**
Astenia	4	1				**5**
Fever	3	2	1			**6**
Dyspnea	1	3				**4**
Peripheral edema	2	2				**4**
Diffuse rash		3				**3**
Flush	3					**3**
Back pain	1	1				**2**
Chill	2					**2**
Cystitis	2					**2**
Diarrhoea	1	1				**2**
Fatigue	2					**2**
Headache	2					**2**
Infusion related Reaction	1	1				**2**
Hyperaemia of the larynx		2				**2**
Sepsis Staphylococcus		2				**2**
Vomiting	1	1				**2**

cut off: 7 Nov 2017

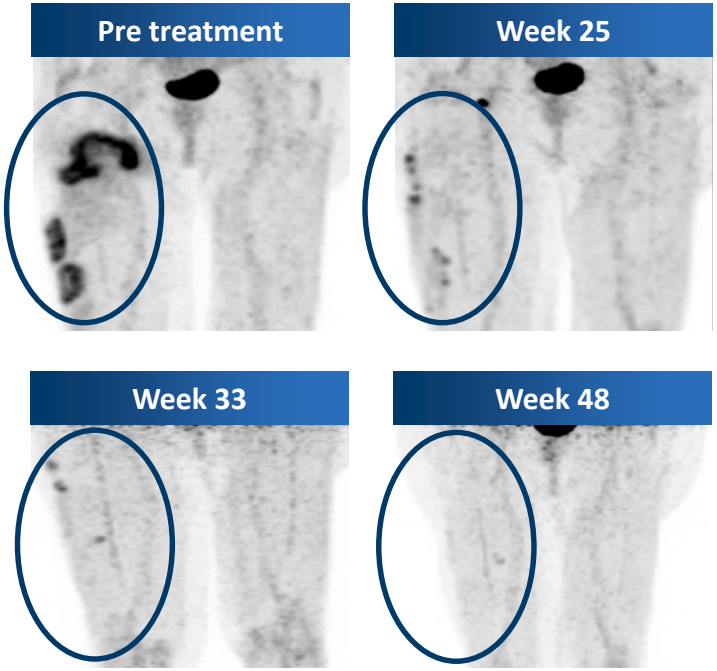
- Pruritus is the most frequent adverse event - 9 events on 6/22 patients (27%)
- Astenia and fever occurred in 5/22 patients (22.7%)
- No hematological toxicity of any grade detected
- Favorable safety profile observed for 1 and 5 mg/kg

Source: argenx data – patient anecdotes – uncleaned data

ARGX-110 induces complete response

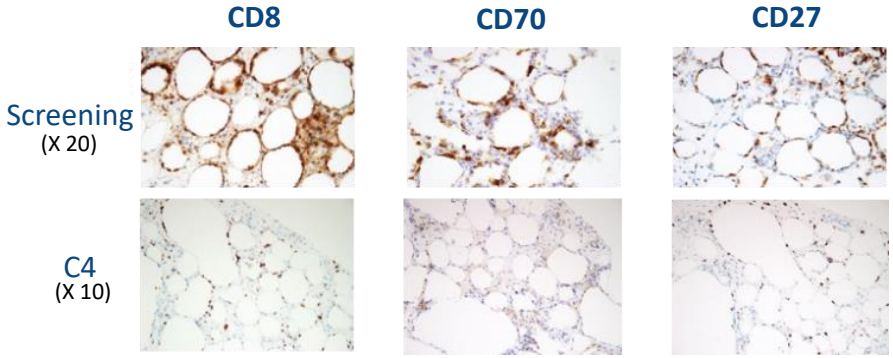
Update on panniculitis patient

- 84 year old female, diagnosed June 2015
- Tumor: Skin T3, nodal NO, visceral MO, blood BO
- Doses: 10 (1 mg/kg q3w) + 8 (5 mg/kg q6w)



Pictures kindly provided by investigator

Pat 2203	PreC1 29/jun/16	C4 1/sep/16	C6 13Oct16	C9 15/dec/16	C11 mC1 26/jan/17	mC4 29/mei/17	mC6 23/aug/17
FDG-PET/CT global response in skin (SUV max)	10.3	14.8	7.2 PR	5.1 PR	4.3 PR	2.8 PR	1.8 PR



- Partial response after 6 doses (dose 1 mg/kg) in maintenance (5 mg/kg /6 weeks) since January 2017
- Complete response after 17 doses (dose 5mg/kg)
- The patient is still on a maintenance dose of 5 mg/kg q6wk

Source: argenx data – patient anecdotes – uncleaned data

ARGX-110 in newly diagnosed AML patients – summary

Preliminary data from first 6 patients – additional data needed

Preliminary clinical data confirm preclinical observations

Promising preliminary activity obtained in first set of patients

- 6/6 responders
- 1 patient bridged to transplantation

Encouraging safety and tolerability profile

- No exacerbation of azacitidine toxicity

Highly differentiated drug profile

- CD70 uniformly & selectively expressed
- Driving LSCs into myeloid differentiation

Source: argenx data – patient anecdotes – uncleaned data

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