Acute Myeloid Leukemia

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DICHIARAZIONE

Relatore: SERGIO AMADORI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(Amgen, Celgene, Daiichi-Sankyo, Janssen, Novartis, Pfizer)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Clinical trials

- Risk-adapted/MRD-directed therapy in adult AML (GIMEMA AML-1310)

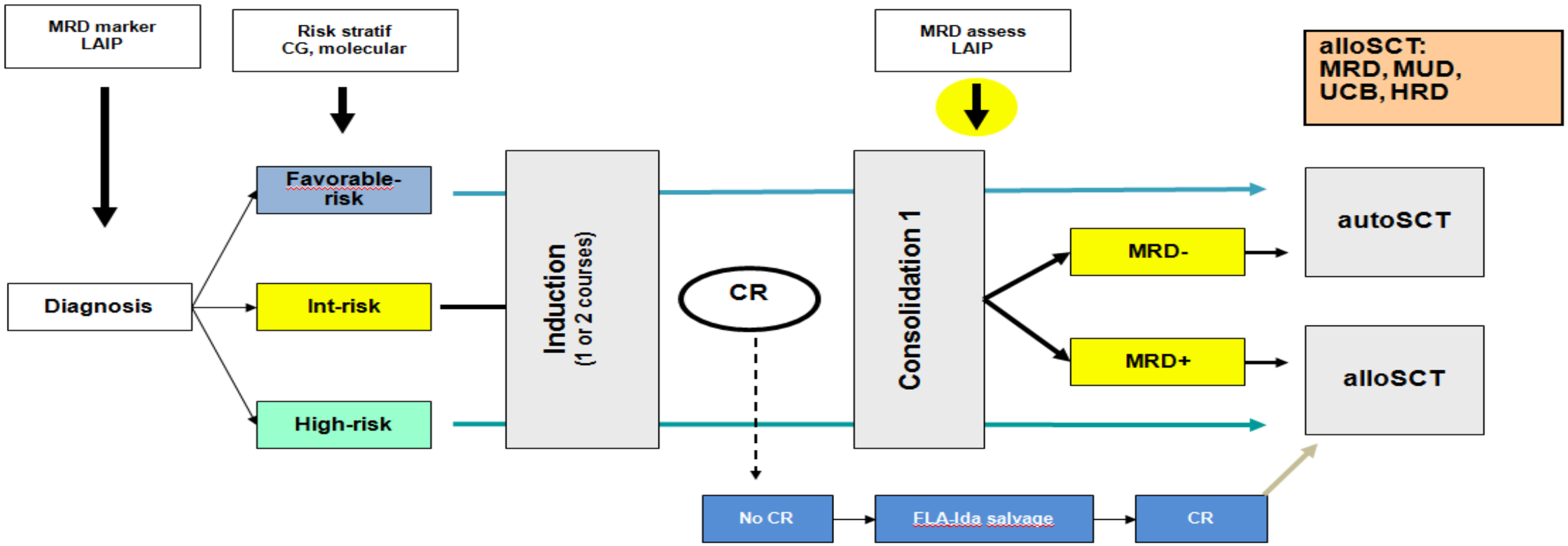
Novel targeted agents to watch….

- Venetoclax + LDAC in older unfit patients with ND-AML (update)
- Venetoclax + HMAs in older patients with ND-AML (update)
- Enasidenib in mut-IDH2 R/R AML (update)
- Nivolumab + AZA in R/R AML (update)

Risk-adapted, MRD-directed therapy for young adults with newly diagnosed AML: Results of the AML-1310 trial od the GIMEMA group

Venditti A et al, abstract S111

AML-1310 study design



Low-risk: CBF/Kit^{wt}; NPM1+/FLT3-
Int-risk: all others
High-risk: Adverse K; FLT3-ITD

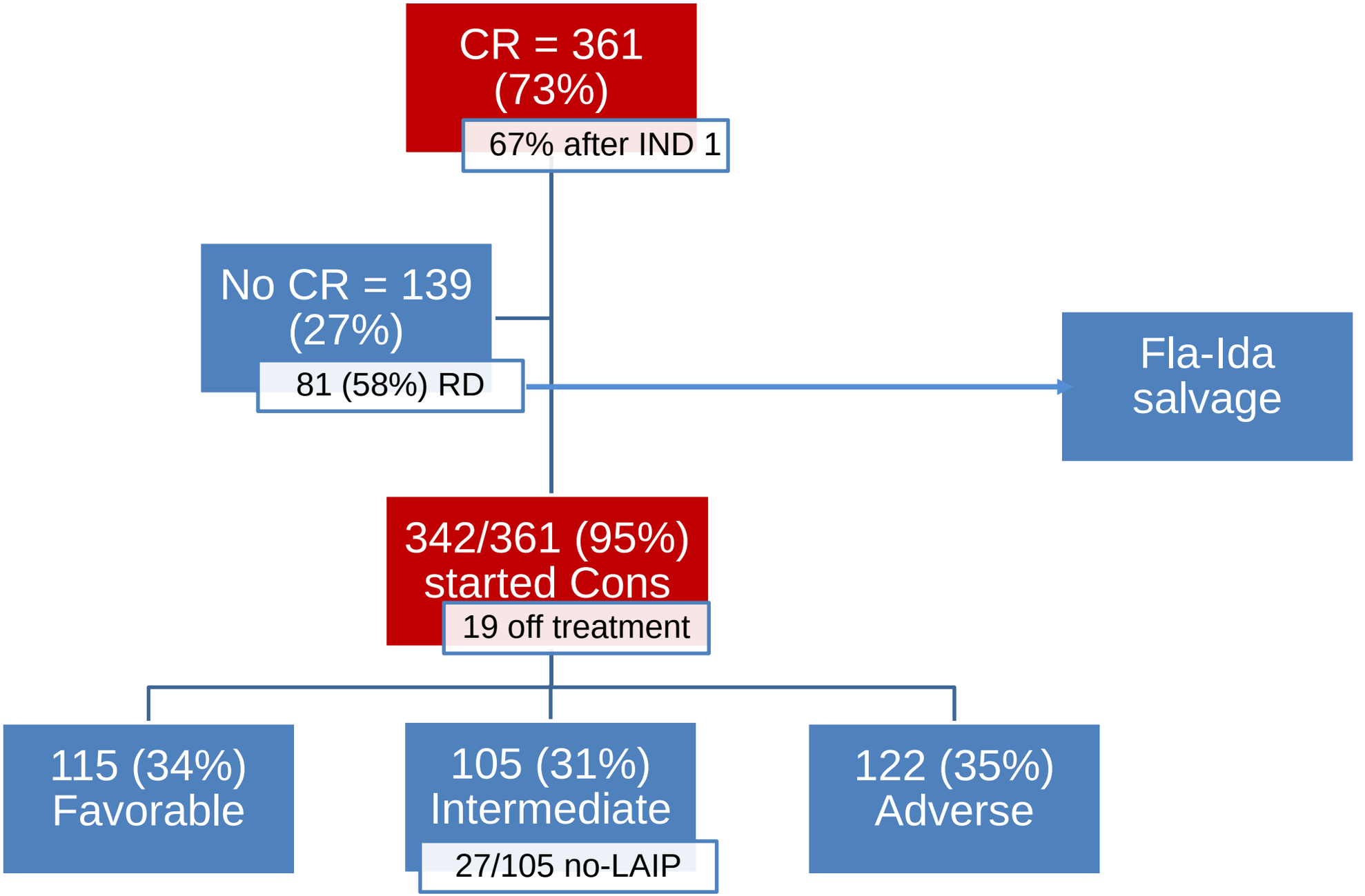
- *INDUCTION*
  - *Daunorubicin : 50 mg/m2 iv D 1,3,5*
  - *SD-Ara-C: (100 mg/m2 c.i. D 1-10)*
  - *Etoposide: 100 mg/m2 iv D 1-5*
- *CONSOLIDATION*
  - *Daunorubicin : 50 mg/m2 iv D 4-6*
  - *ID-Ara-C : 500 mg/m2/q12 hrs, over 2 hrs, D 1-6*

AML1310: Patient characteristics (n=500; 01/12-05/15)

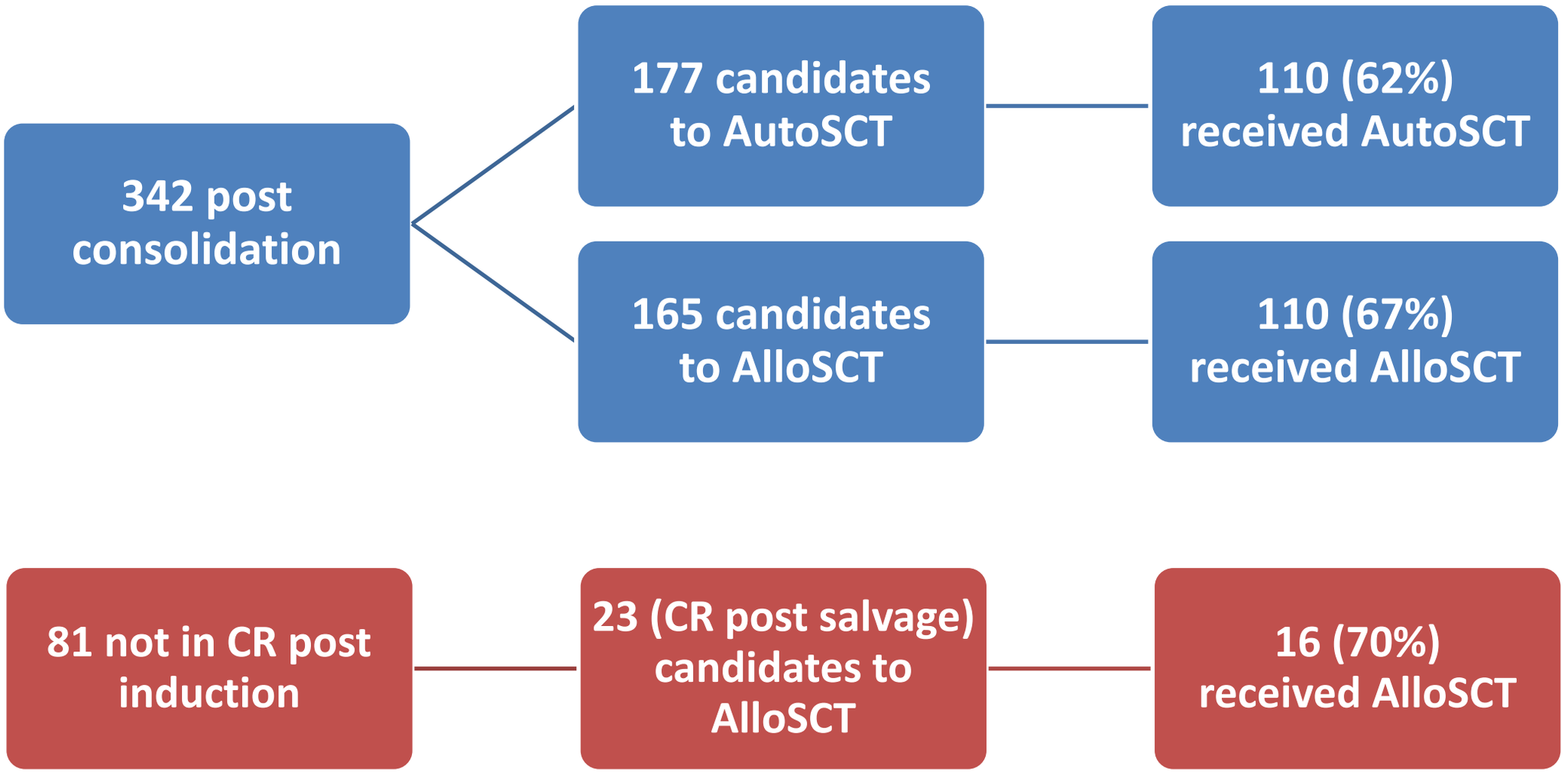
fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

Age, yrs		
median	49	
range	18-61	
Gender		
M/F	260/240	
WBCcx10^9/L		
median	13.9	
range	0.16-352	
ELN category		
Favorable	138 (28%)	→ AutoSCT
Intermediate	174 (35%)	→ Wait for MRD after Cons
Adverse	188 (38%)	→ AlloSCT
LAIP not detected		
Favorable	4	→ AutoSCT
Intermediate	43	→ AutoSCT
Adverse	0	
Total	47 (9%)	

AML1310: results (n=500)

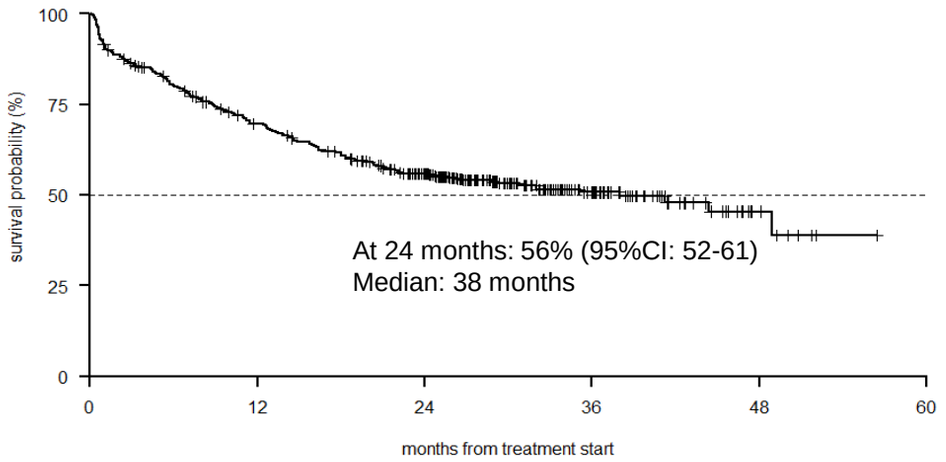


AML1310: results

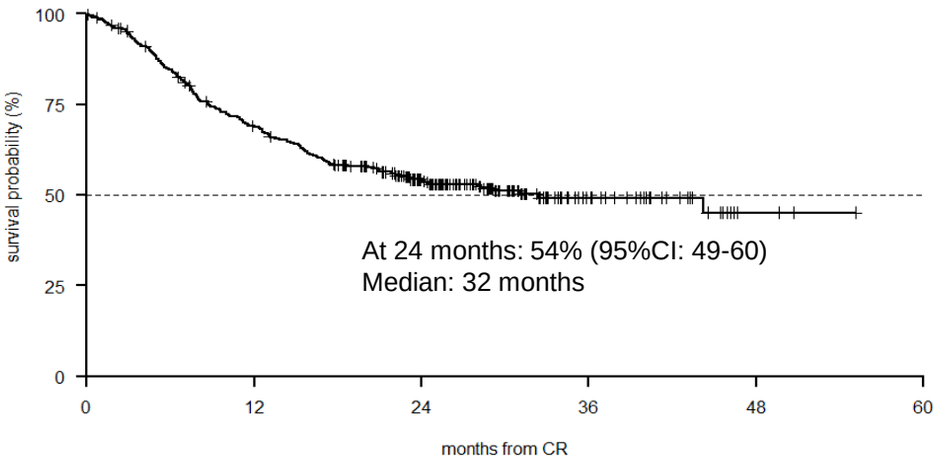


AML1310: results (median follow-up: 27.8 months)

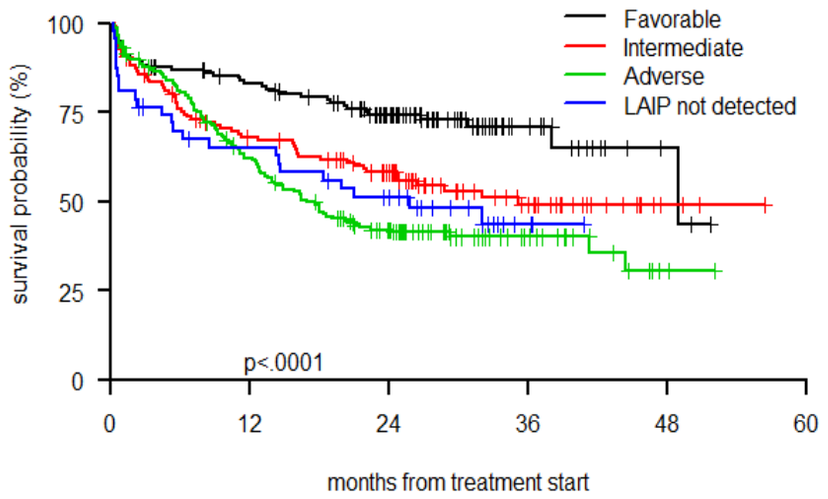
Overall Survival



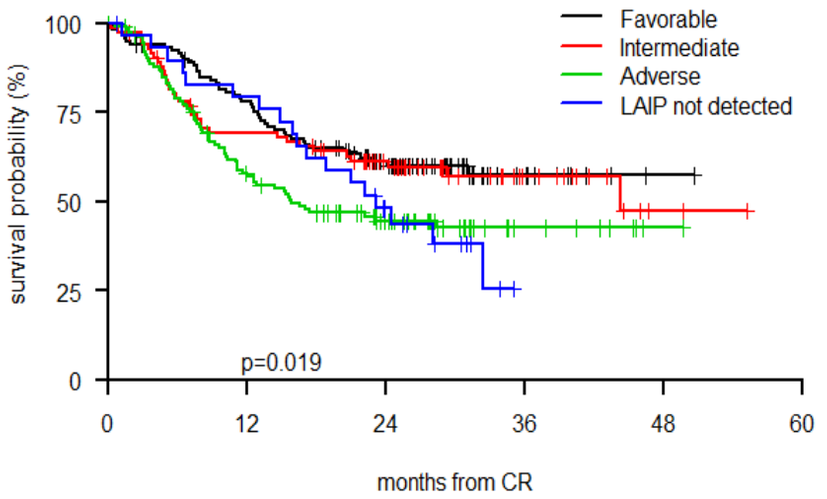
Disease Free Survival



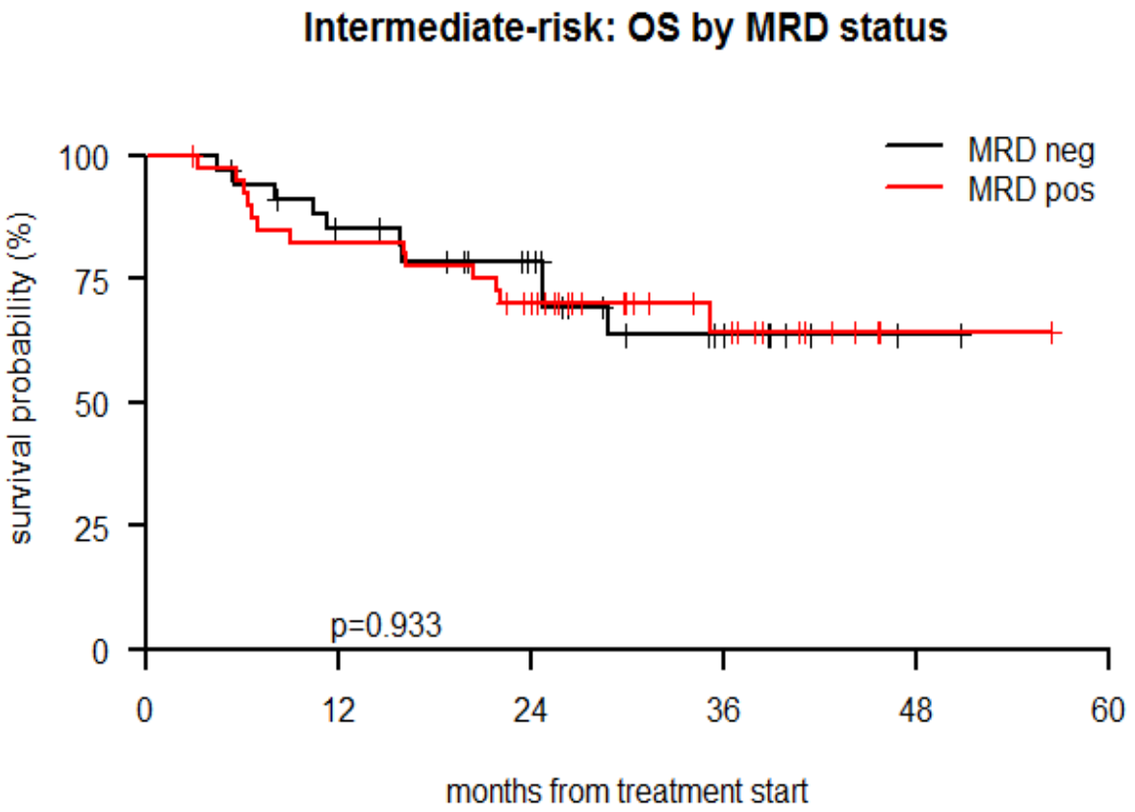
OS by ELN category

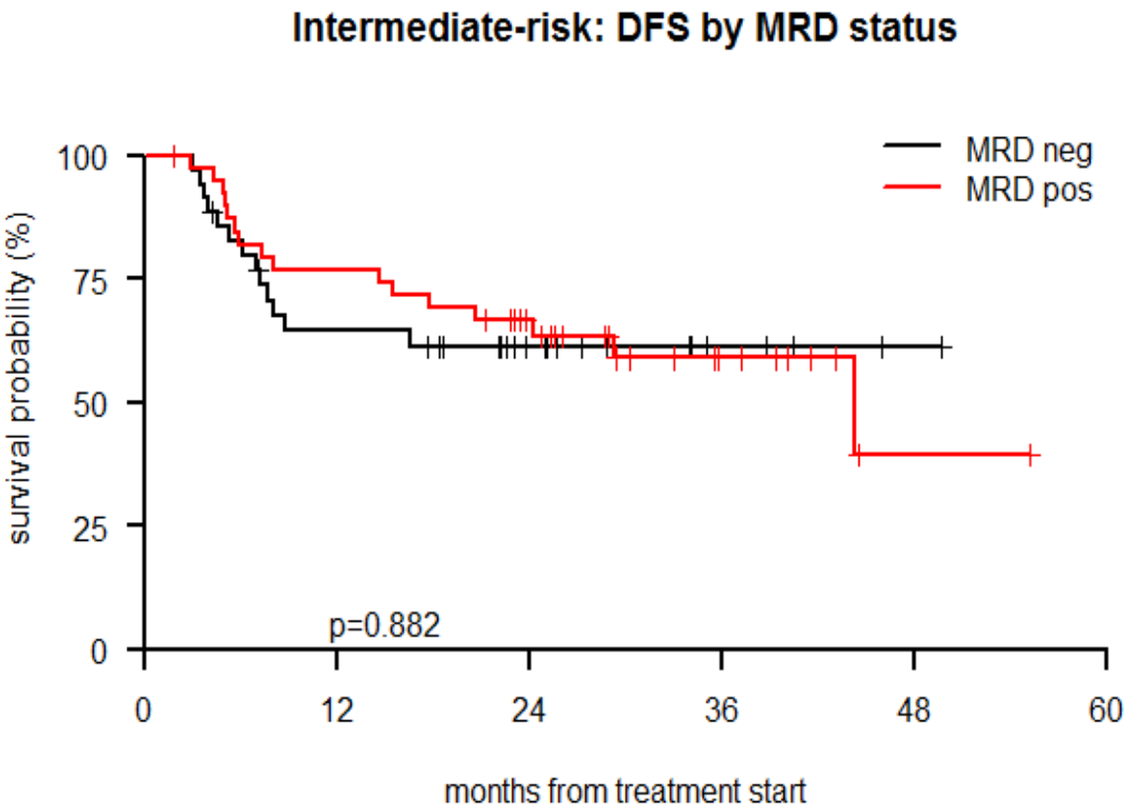


DFS by ELN category



AML1310: intermediate-risk OS and DFS by MRD status





AML1310: Conclusions

- **A risk-stratified therapeutic approach integrating upfront genetics and post-consolidation MRD status is feasible in a multicenter setting**
  - **centralized genetic and MRD studies**

- **AutoSCT might still have a role in the post-remission treatment of patients with AML (fav-risk + interm-risk^{MRDneg})**

- **Using all the available sources of stem cells, alloSCT was delivered to 67% of patients (adv-risk + interm-risk^{MRDpos})**

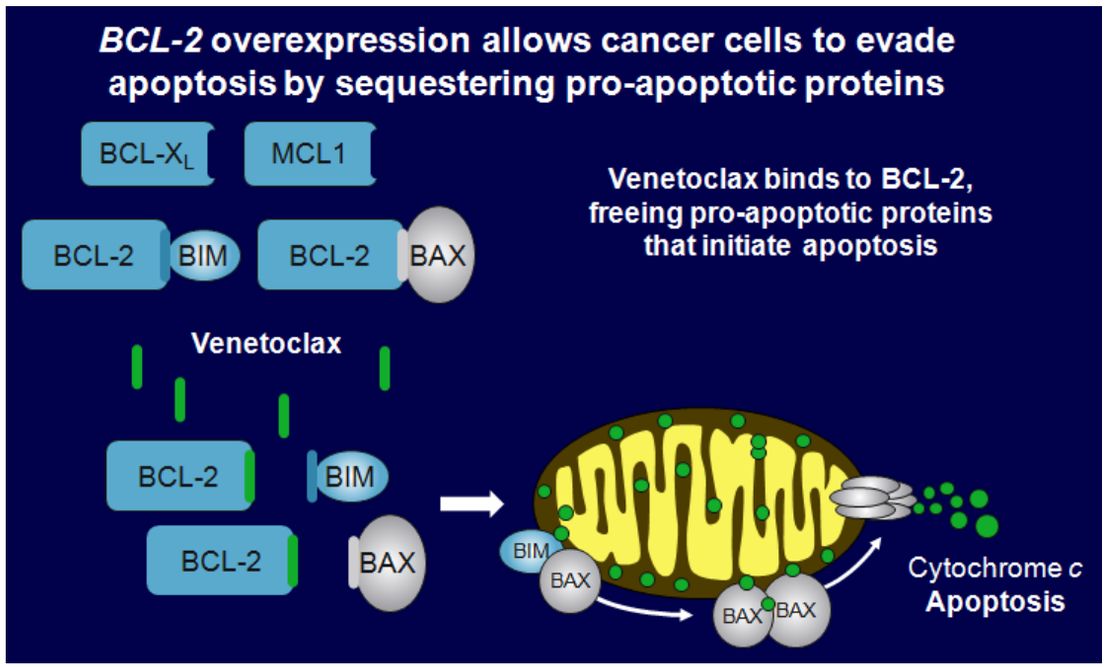
Updated safety and efficacy of a phase 1/2 study of Venetoclax + LDAC in treatment-naive patients with AML ≥65 years and unfit for standard induction therapy

Wei AH et al, abstract S473

Safety and efficacy of Venetoclax in combination with Decitabine or Azacitidine in treatment-naive, elderly patients ≥65 years with AML

Pratz K et al, abstract S472

VEN: mechanism of action



Bcl-2: a promising therapeutic target in AML

- Overexpression enhances survival of AML blasts
- Associates with chemoresistance and poor survival

Venetoclax: selective, oral Bcl-2 inhibitor

- Active in AML cell lines and primary patient samples

Venetoclax monotherapy in AML

- Phase 2 study in R/R AML: CR/CRi rate 19%

Souers A et al, Nat Med 2013; Konopleva M et al, Cancer Discov 2016

VEN + LDAC trial

Phase 1 (3+3)
(600-800 mg)

→

RP2D
600 mg/day (28-day cycles)

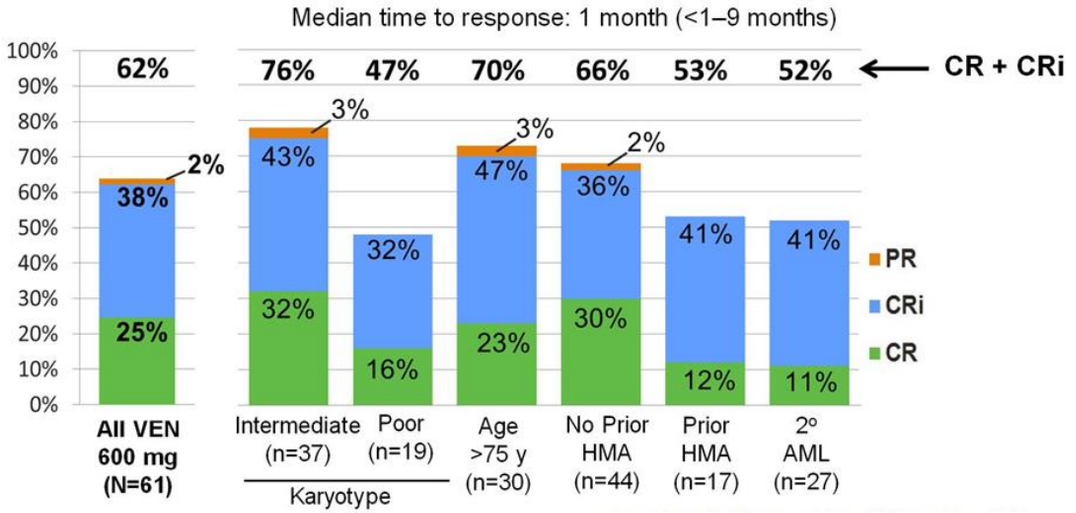
→

Phase 2
VEN 600 mg, days 1-28
LDAC 20 mg/m2 sc, days 1-10

Inclusion criteria	Objectives	Patients treated at RP2D (600 mg/day)
• Adults ≥65y with untreated AML, ineligible for standard induction therapy, ECOG PS 0-2	• Primary: safety and efficacy at the RP2D • Secondary: response rates, DOR and OS	• Patients: n=61 • phase 1: n=8 • phase 2, n=53

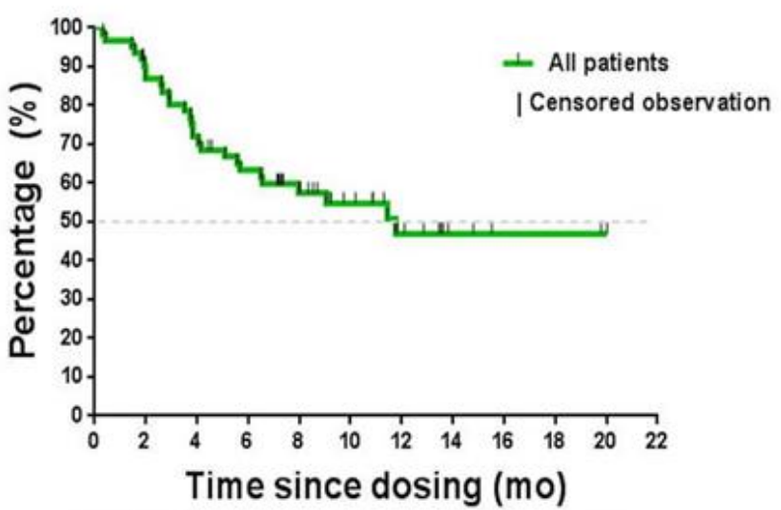
Wei AH et al, EHA 2017

Outcomes (N=61)

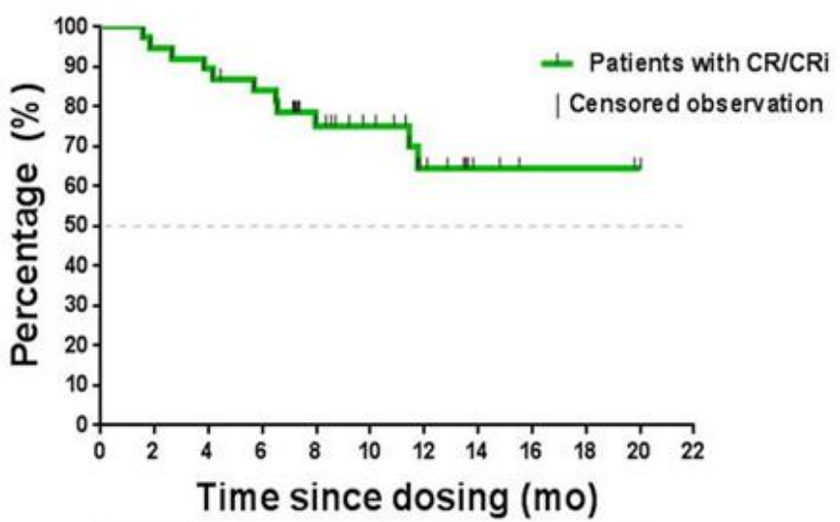


Grade 3 or 4 (≥10% of Patients)	VEN 600 mg N=61
Hematologic, n (%)	
Thrombocytopenia	27 (44)
Febrile neutropenia	22 (36)
Neutropenia	20 (33)
Anemia	17 (28)
Nonhematologic, n (%)	
Hypokalemia	10 (16)
Hypophosphatemia	8 (13)
Hypertension	7 (12)

OS for All Patients



OS for Patients with CR/CRi

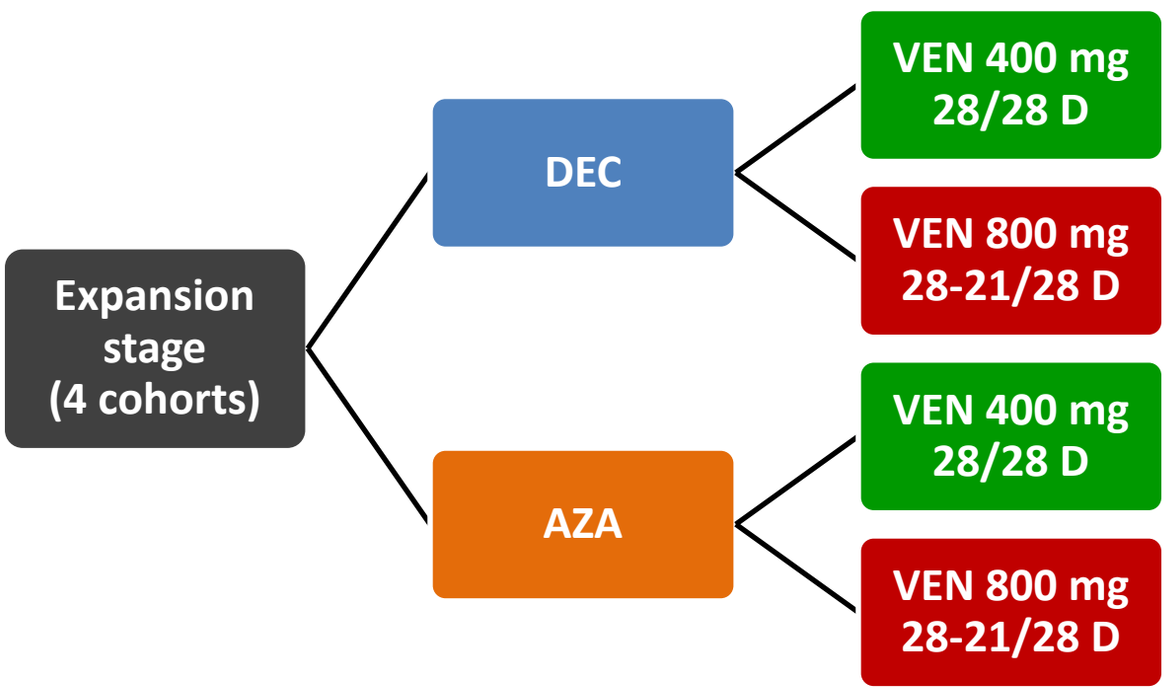


30d mortality 3%

Phase 3 ongoing

VEN + HMAs trial

- **Phase 1b, open-label, multicenter study with dose-escalation and expansion stages**
  - **VEN + DEC (20 mg/m2 iv, D1-5, 28D cycles) or VEN + AZA (75 mg/m2 iv/sc, D1-7, 28D cycles)**
  - **Dose escalation stage: CR/CRi rate 60%** (Pollyea D et al, ASCO 2016)



Eligibility criteria

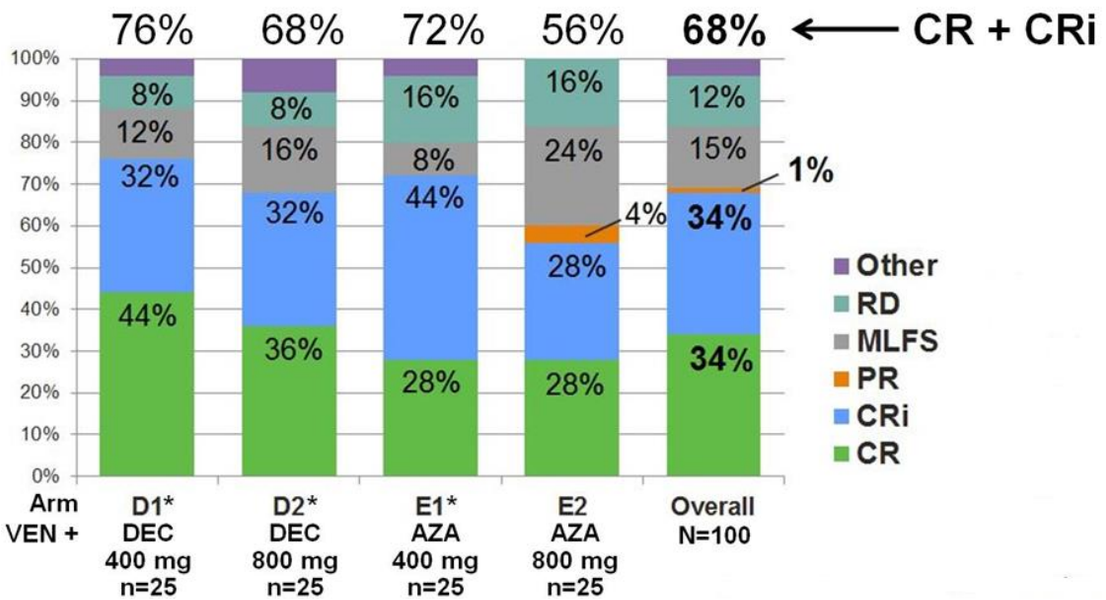
- Patients ≥65y with untreated AML; Int/Adv CG; ECOG ≤2; ineligible for standard induction therapy

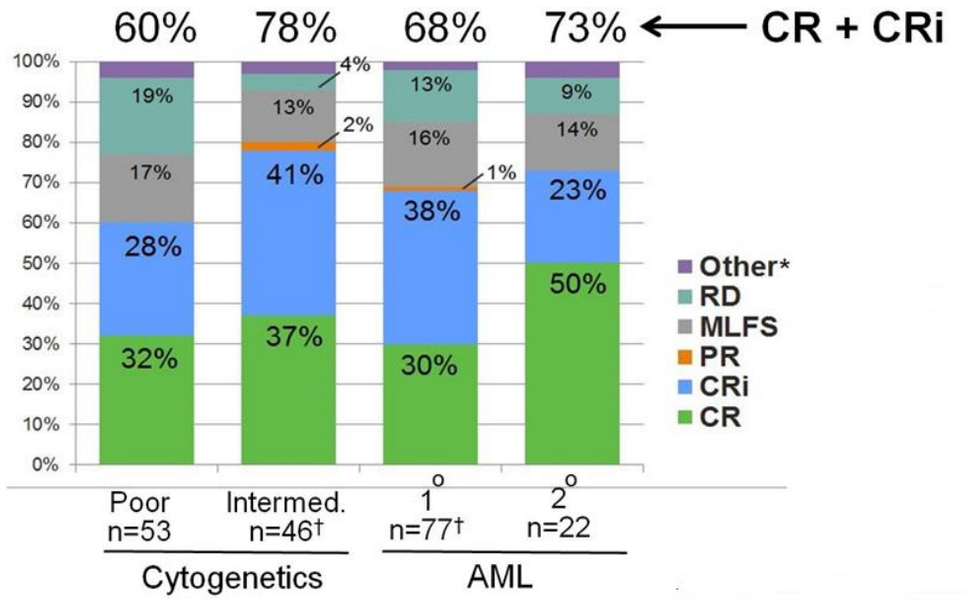
Objectives

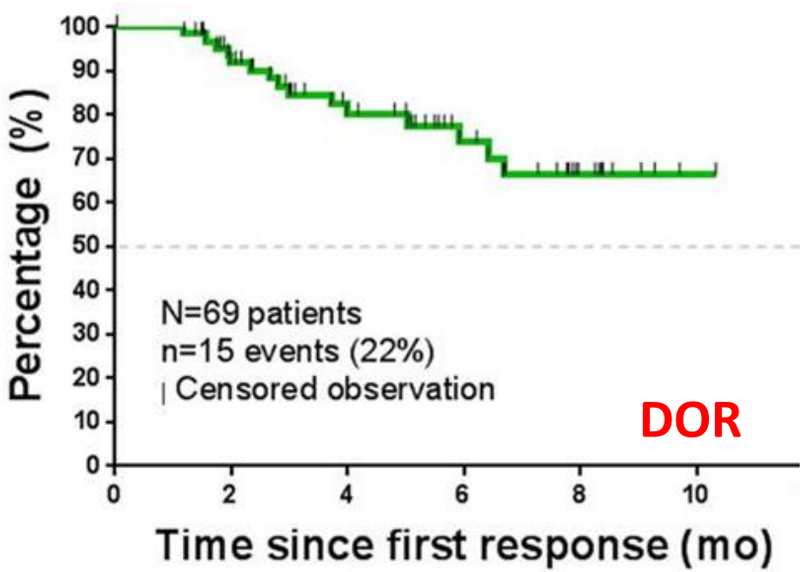
- Primary: efficacy and safety
- Secondary: CR, CRi, DOR, OS

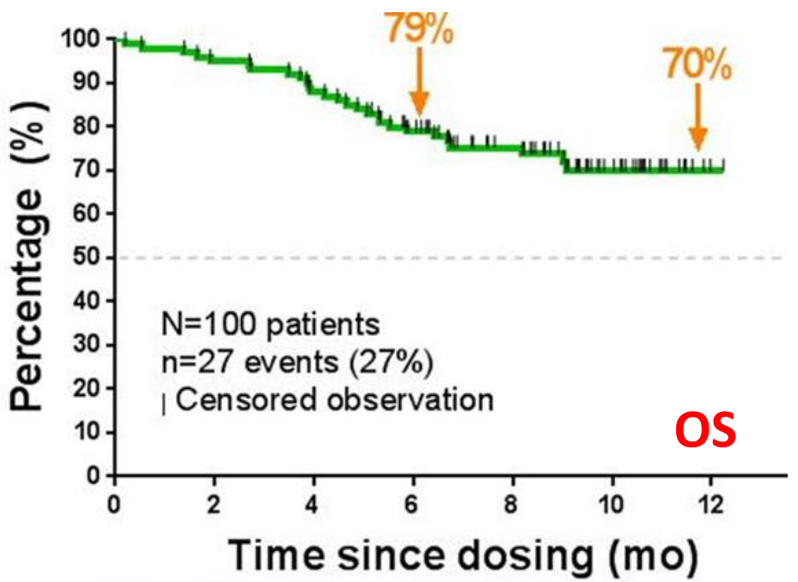
Pratz K et al, EHA 2017

Outcomes (N=100)









30/60d mortality 3%/15%

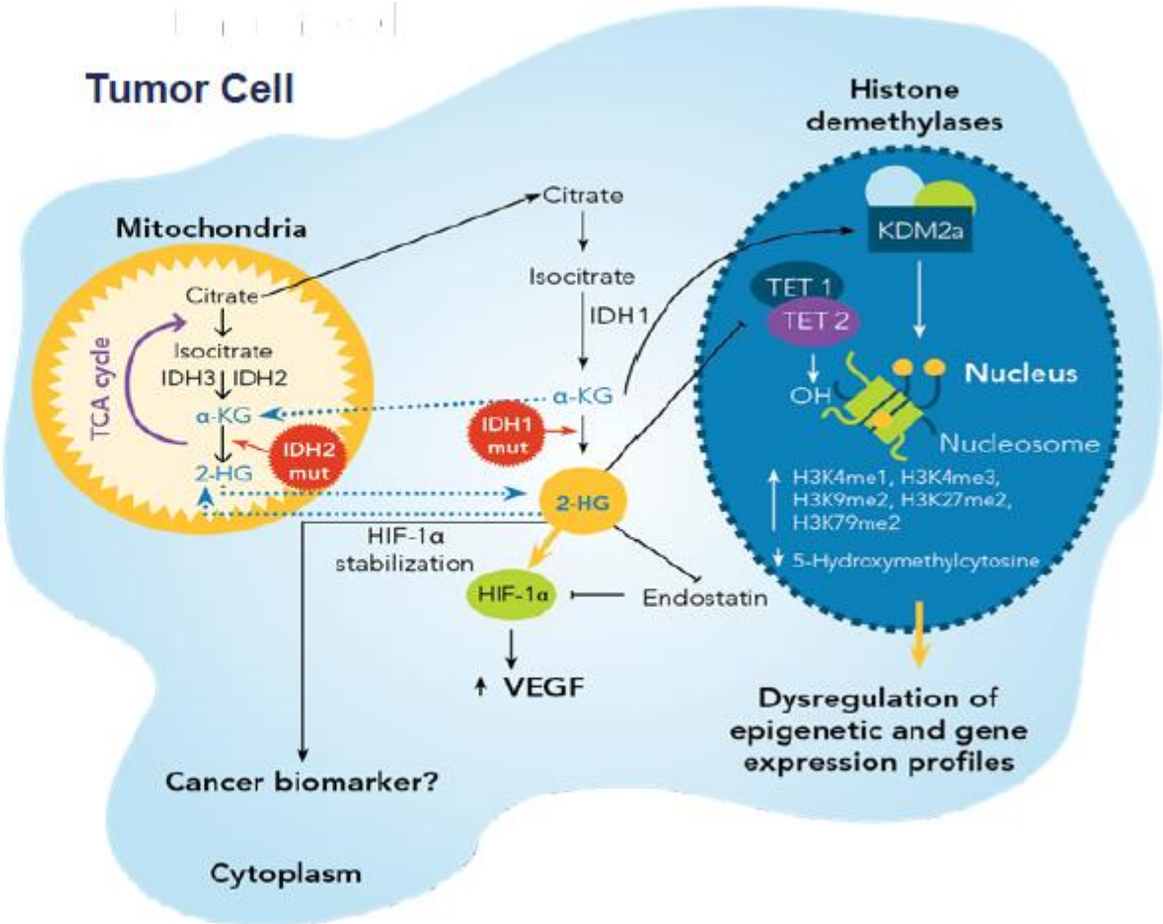
Phase 3 (VEN+AZA) ongoing

Enasidenib (AG-221) in mutant-IDH2 relapsed or refractory AML: results of a phase 1 dose-escalation and expansion study

Stein EM et al, abstract S471

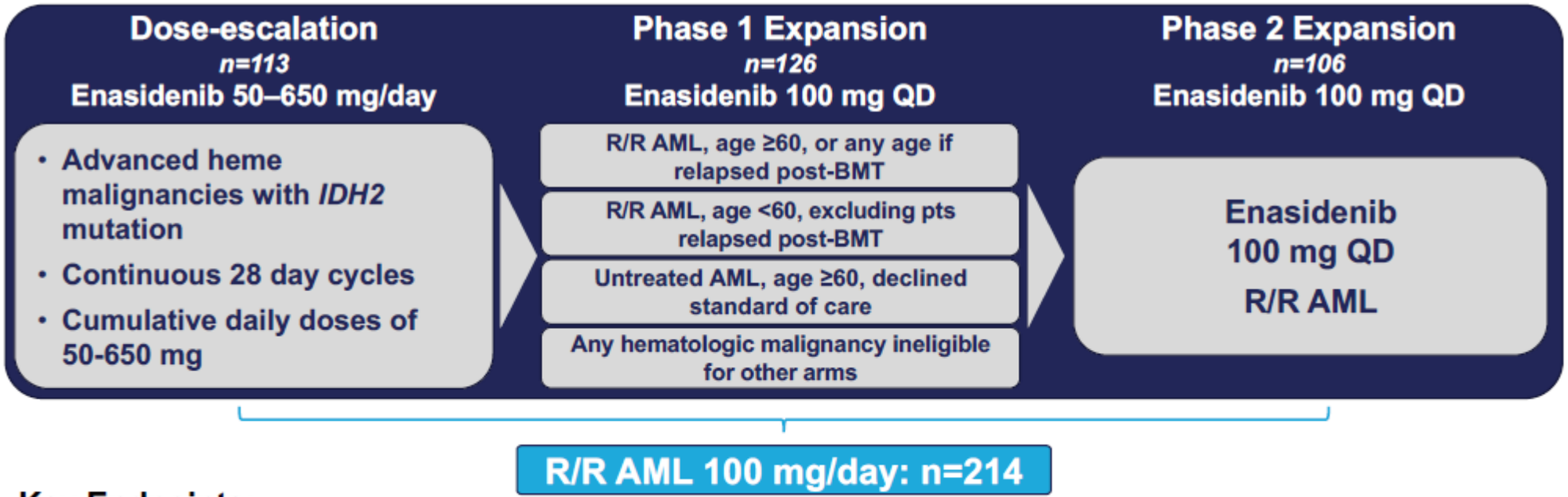
Enasidenib: mechanism of action

- IDH2 is an enzyme of the citric acid cycle
- Mutant *IDH2* (m*IDH2*) occurs in ~12% of patients with AML[1]
- m*IDH2* produces 2-HG, which alters DNA methylation and leads to a block in cellular differentiation
- Enasidenib (AG-221) is a selective, oral, potent inhibitor of mIDH2 enzyme
- Enasidenib induces differentiation of leukemic cells



[1]*DiNardo CD et al, Am J Hematol 2015*

Phase 1/2 study design



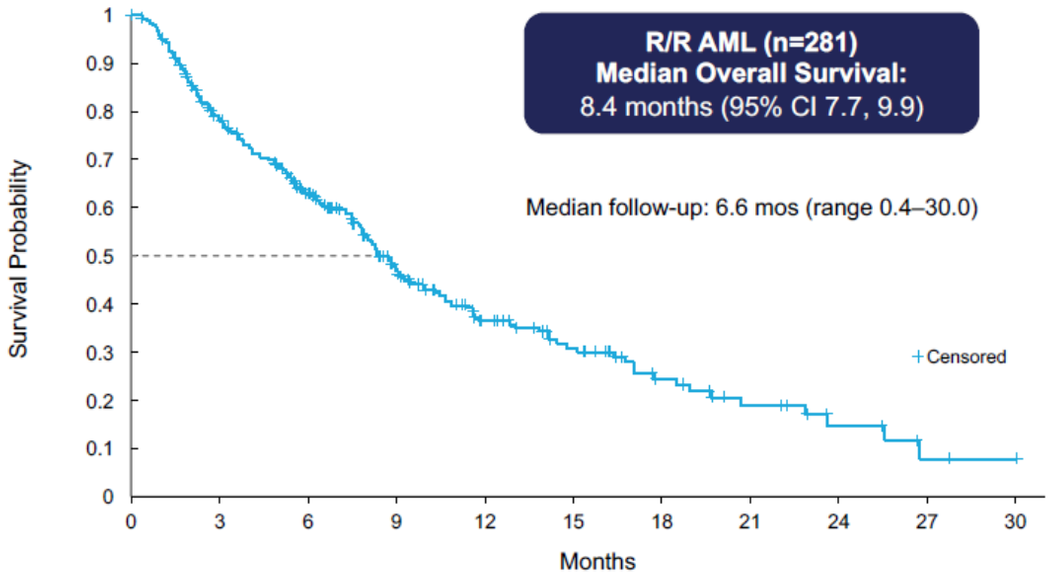
Key Endpoints:

- Safety, tolerability, MTD, DLTs
  - MTD not reached at doses up to 650 mg/day
- Responses assessed by local investigator per IWG criteria[1]
- Assessment of clinical activity, with focus on 100-mg daily dose in patients with R/R AML

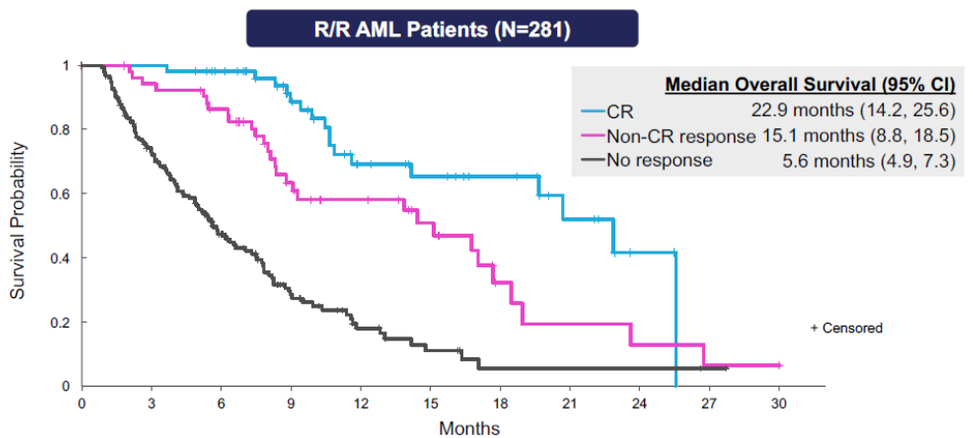
Outcomes

	Relapsed/Refractory AML	
	Enasidenib 100 mg/day (n=214)	All doses (N=281)
Overall response rate, % [n/N] [95% CI]	**37% (79/214)** [30.4, 43.8]	**38% (108/281)** [32.7, 44.4]
Best response		
CR, n (%) [95% CI]		**55 (19.6)** [5.1, 24.7]
CRi or CRp, n (%)		22 (7.8)
PR, n (%)		16 (5.7)
MLFS, n (%)		15 (5.3)
SD, n (%)		137 (48.8)
PD, n (%)		15 (5.3)
NE, n (%)	2 (0.9)	3 (1.1)
Time to first respo (mos), median (range)	1.9 (0.5–11.1)	1.9 (0.5-11.1)
Duration of response (mos), median [95%CI]	5.6 [4.6, 7.4]	5.6 [4.6, 6.5]
Time to CR (mos), median (range)	3.7 (0.7–11.2)	3.8 (0.5-11.2)
Duration of response in pts with CR (mos), median [95%CI]	8.8 [5.6, NR]	7.4 [6.4, 14.7]

FDA-approved August 1, 2017 (R/R mIDH2 AML)



OVERALL SURVIVAL BY BEST RESPONSE



Most common Tx-related G3-4 AEs: hyperbilirub 11%, DS 7%

Differentiation of AML blasts drives clinical efficacy

Phase 3 (ENA vs CCR) in older pts with late-stage AML

Phase 1/2 (ENA + chemo) in ND-AML

Phase 1b/2 study of nivolumab in combination with azacytidine in patients with relapsed AML

Daver N et al, abstract S474

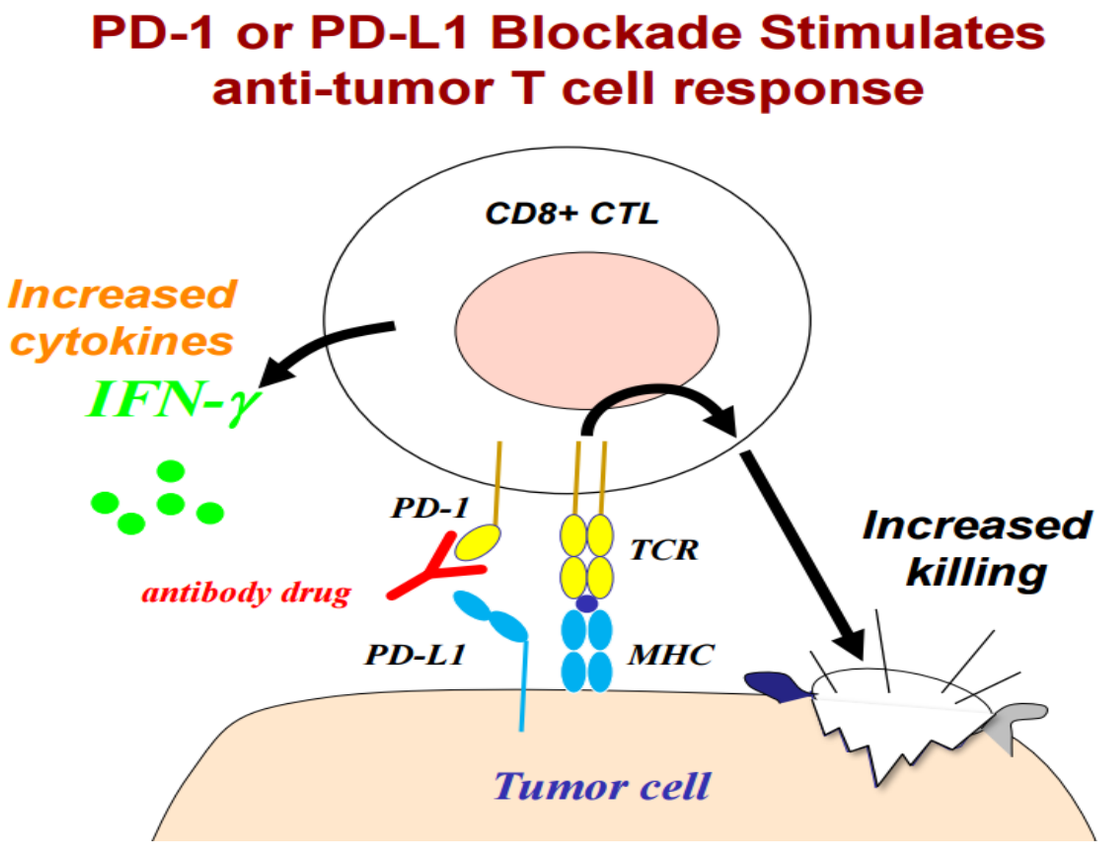
Nivolumab: an anti-PD-1 MoAb

The PD-1/PD-L1 pathway plays a major role in immune evasion and CTL exhaustion in AML and MDS[1,2]

HMAs upregulate PD-1 and PD-L1 genes promoting resistance to epigenetic therapy[3]

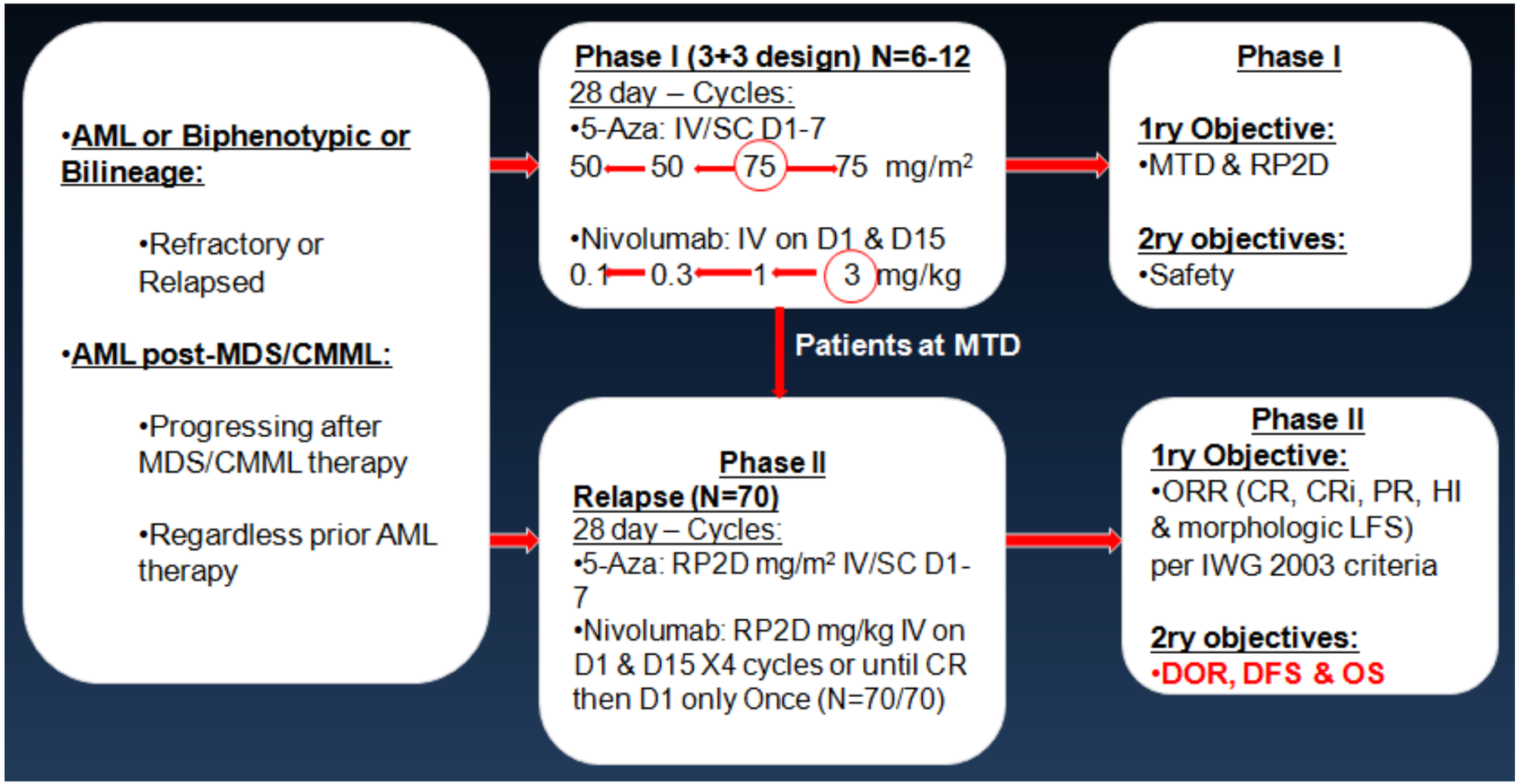
PD-1/PD-L1 blockade may improve response and abrogate resistance to HMAs

Nivolumab (OPDIVO) is a fully human MoAb that binds PD-1



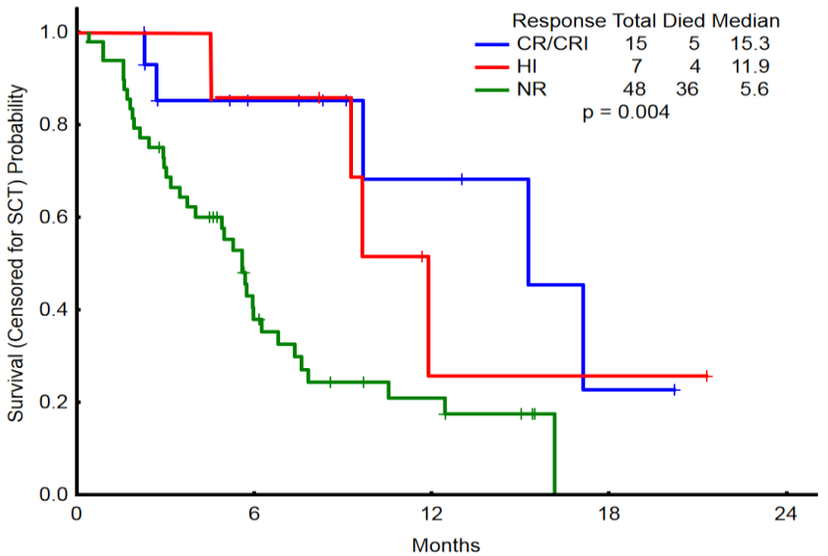
[1]Zhang L et al, Blood 2009; [2]Yang H et al, Leukemia 2013; [3]Orskov AD et al, Oncotarget 2015

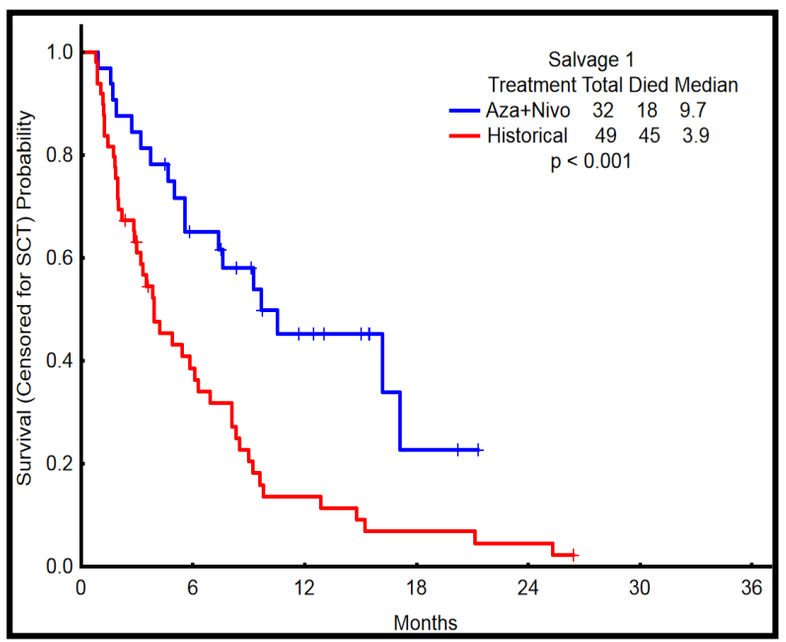
AZA + NIVO (phase 1b/2)



Outcomes (N=70)

Best response / Outcome	N (%) / Med [Range]
Evaluable	70
ORR	22 (32)
CR/CRi	15 (22)
HI + 50% blast reduction (6mo+)	7 (10)
50% reduction in blast	17 (24)
Progression/Stable dis (6 mo+)	26 (37) [21/5]
8-week mortality	5 (7)
Median cycles to response	2 [1 - 13]
Median follow-up	8.6 mo [2.8 – 21.3]





G2-4 immune tox → **26% (< 6 wks)** → **Respond to steroids**

Plans: 1) AZA+NIVO frontline in AML > 65y;
2) AZA + NIVO + IPI (anti-CTLA-4)

Temi per il gruppo di lavoro AML

- **MRD: nuovo endpoint surrogato (OS, EFS) nella AML?**
  - Quali tecnologie?; quali time-points?
- **L'era della chemio intensiva di prima linea ("AML Dogma") è ormai prossima alla fine?**
  - *Eccellenti risultati (CR/CRi, tossicità) con nuovi farmaci mirati (Venetoclax in primis) in combinazione con HMAs o chemio a bassa intensità (LDAC) in pazienti anziani poor-risk (età/fitness, biologia)*
    - **Tutti gli anziani?**
    - **Anche nei giovani?**
    - **Chi dovrebbe continuare ad essere trattato con chemio intensiva?**