Acute Myeloid Leukemia: Targets and Curability, so Close But a Journey So Far

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Disclosure

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Consultant	None
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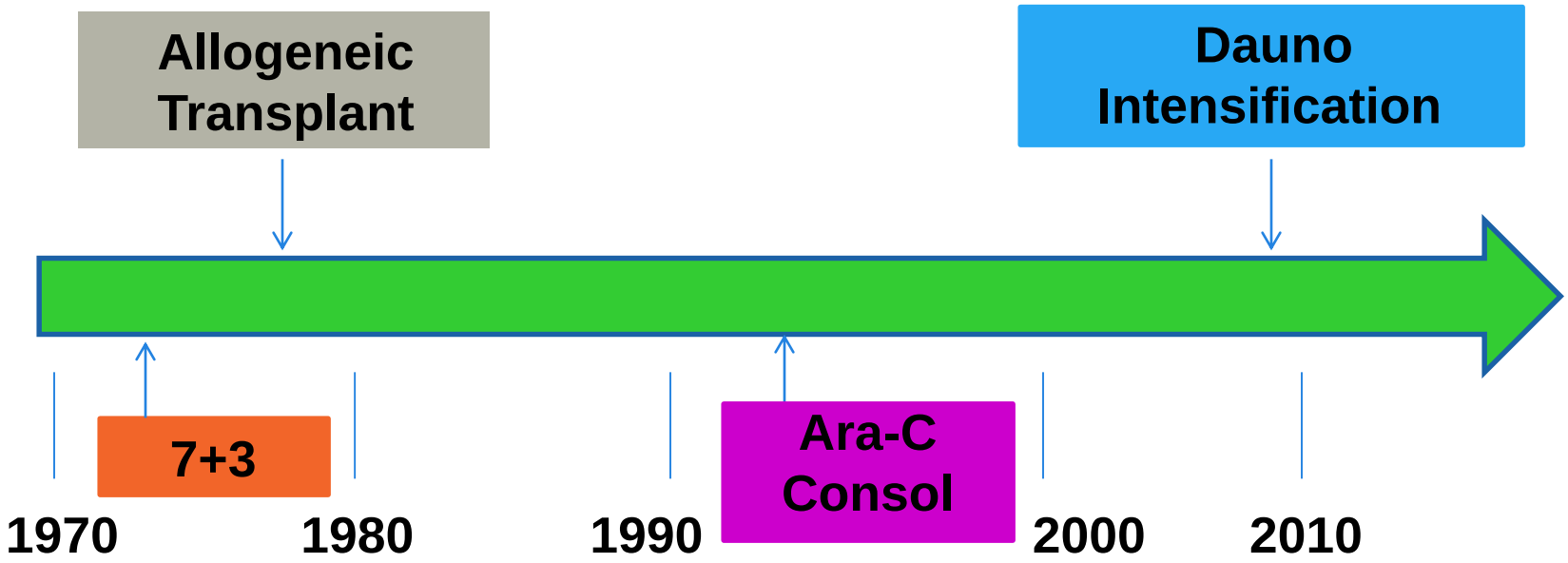
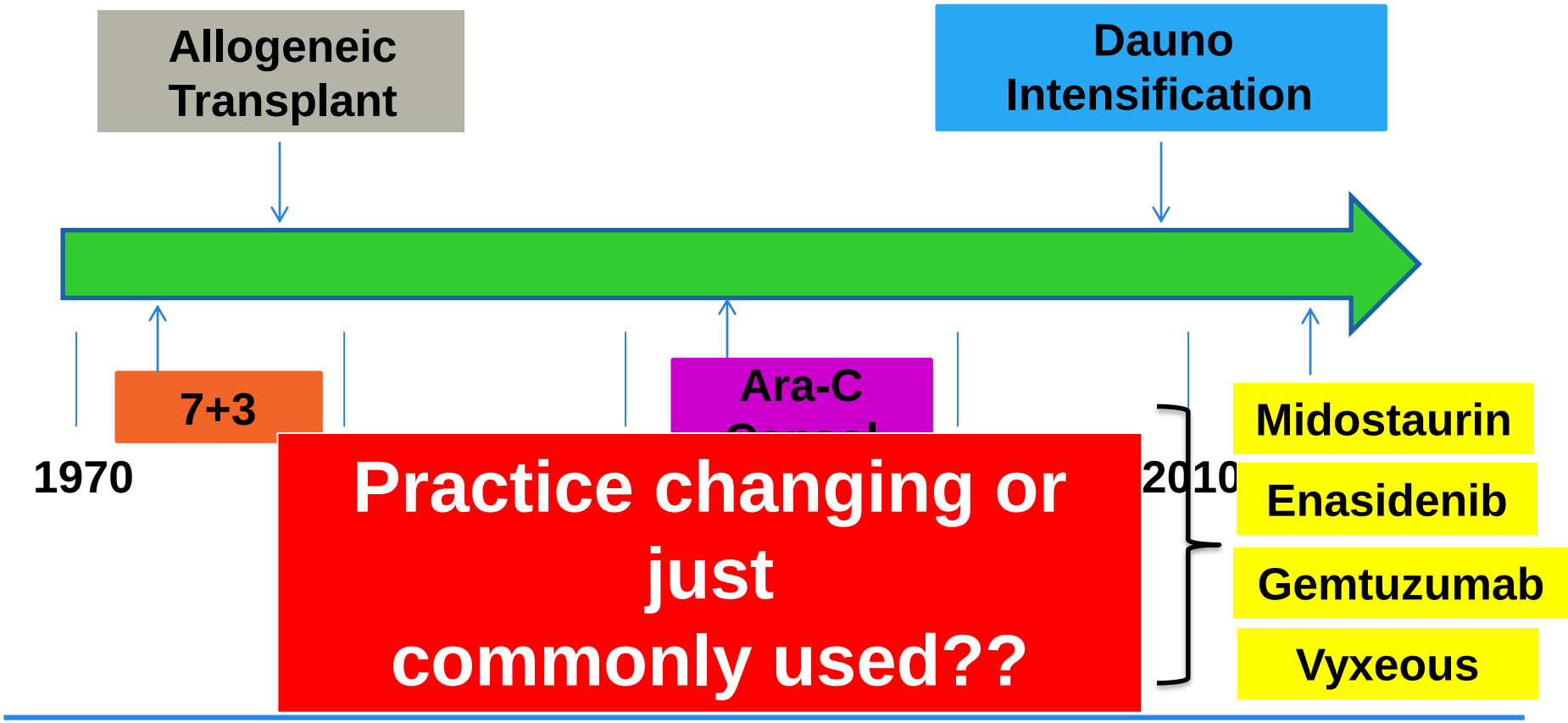
Presentation includes the following off-label drug use:
Gilteritinib, Quizartinib, Crenolanib, Venetoclax, Selinexor, Tamobarotene, Entospletinib, Palbociclib, Cobimetinib, Pevonedistat, H3B-8800

Practice Changing Treatments in AML



Thomas et al. NEJM, 1979; Mayer et al. NEJM, 1994; Fernandez et al. NEJM, 2009; Stone et al. NEJM, 2017

Practice Changing Treatments in AML



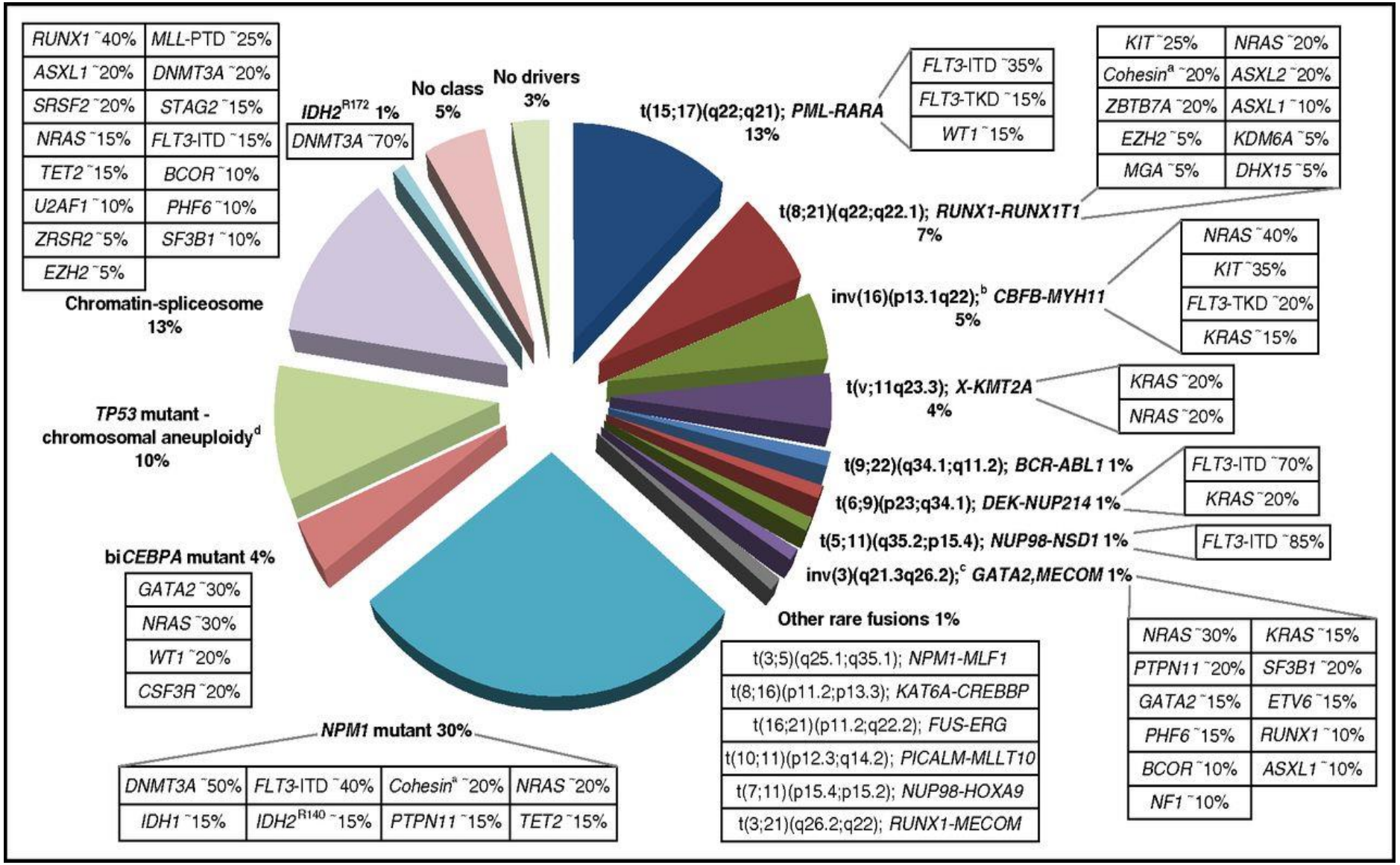
Thomas et al. NEJM, 1979; Mayer et al. NEJM, 1994; Fernandez et al. NEJM, 2009; Stone et al. NEJM, 2017

Acute Myeloid Leukemia

State-of-the-Art 2018

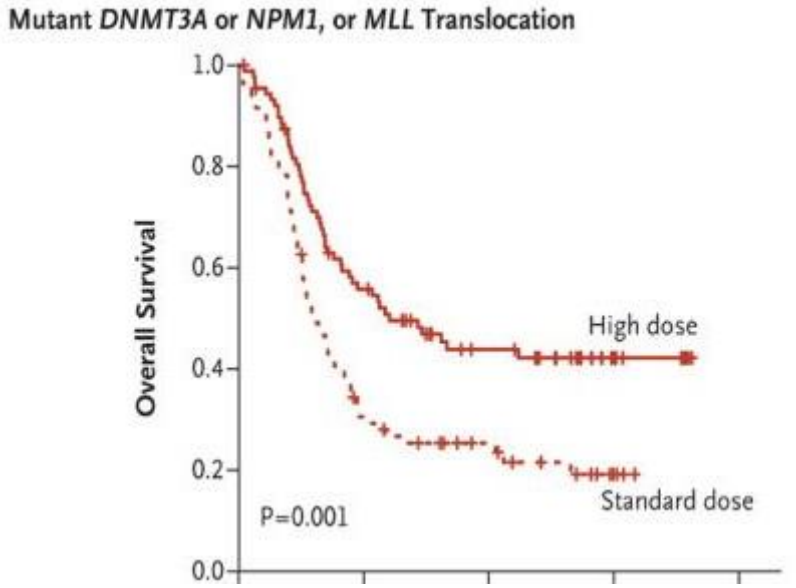
- **Defined by cytogenetic and molecular interactions**
- Intensified induction/less intensive consolidation
- Increased importance of minimal residual disease
- Expanded availability of allogeneic transplantation
- Paradigm shift in older patients
- Incorporation of novel agents

Molecular Classes of AML and Recurrent Gene Mutations

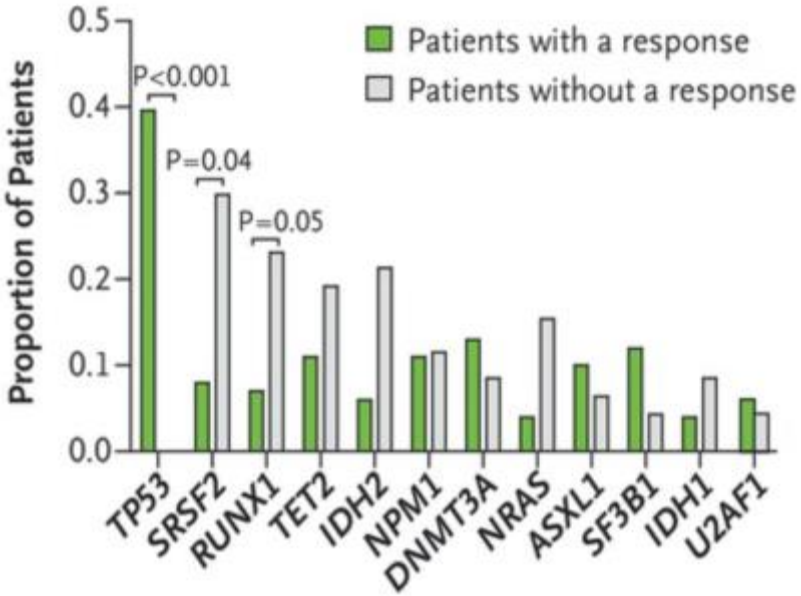


Döhner et al. Blood, 2017

Risk-Stratification and Prognostication of AML Informed by Mutational Profile



Patel et al. NEJM, 2012



Welch et al. NEJM, 2016

Mutation Patterns in Older Adults Predict Response to Chemotherapy

Good Risk	Poor Risk
• CR 81%: *NPM1* plus	CR 32%
– Chromatin mutations	U2AF1
– Cohesin mutations	WT1
– *FLT3-TKD*	Complex karyotype
– Spliceosome mutations	
– *RAS* pathway mutations	
– *FLT3-ITD*^{wt}	
• DFS 46%: *NPM1* plus	DFS 2%
– *ASXL1*	*FLT3*
– *SF 1*	*RUNX1*
– *SMC1A*	*TP53, U2AF1*
– *SRSF2*	
• OS 45%: *NPM1* plus	OS 4%
– Chromatin mutations	*BCOR*
– *IDH2* mutation	*FLT3-ITD*
– *SF 1*	*U2AF1, WT1*
– *SRSF2*	t(9;11), complex karyotype

Eisfeld et al. ASH abstr 103, 2017

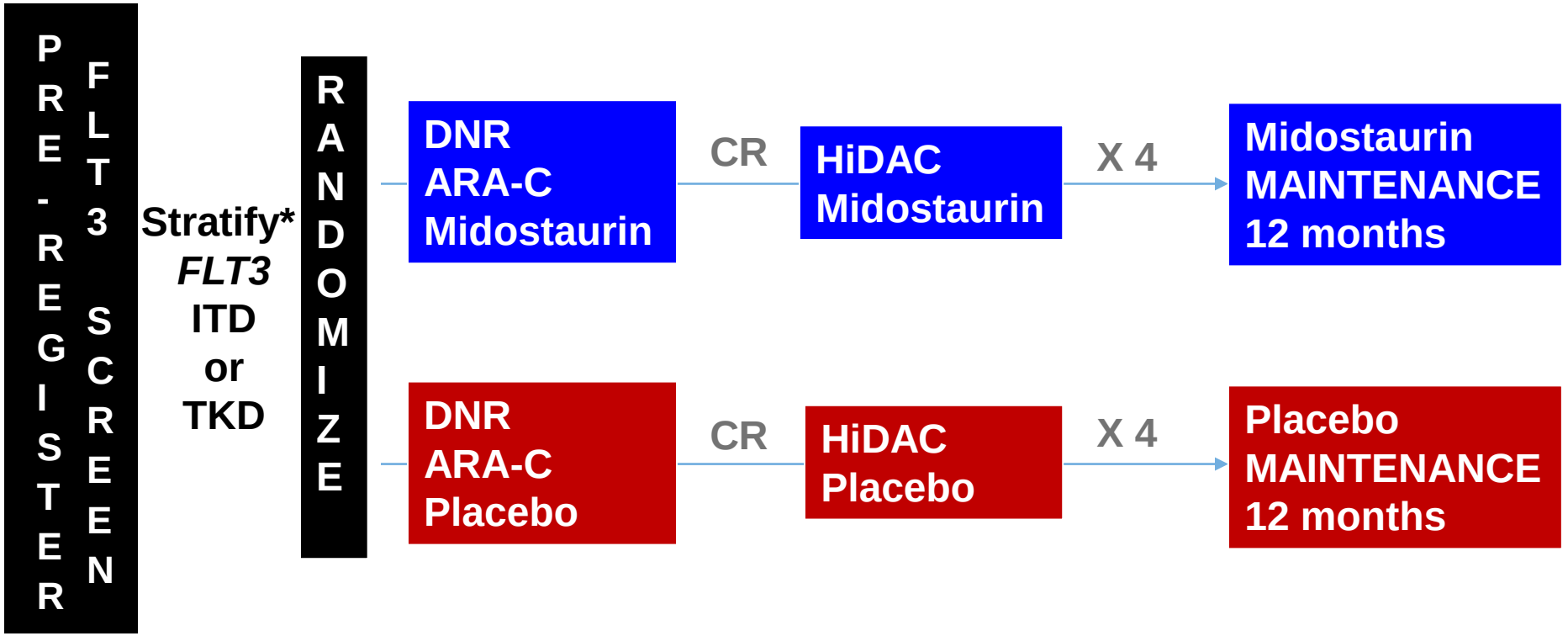
Gene Mutations Important in Everyday Practice

"Clinically Actionable"

Gene	Incidence	Associations	Impact
FLT3-ITD/(TKD)	25%	*NPM1*	Unfavorable
NPM1	33%	*FLT3*	Favorable
dCEBPα	8%	*FLT3*	Favorable
C-KIT	15%	*CBF*	Unfavorable [in t(8;21), but less clear in inv(16)]; [1]D816 worse than others
IDH1 and 2	22%	*NPM1*	Favorable
P53	7%	t-AML, Complex karyotype (60%)	Unfavorable

[1]*Yui et al. ASH abstr 2785, 2016*

RATIFY (C10603) Trial Schema

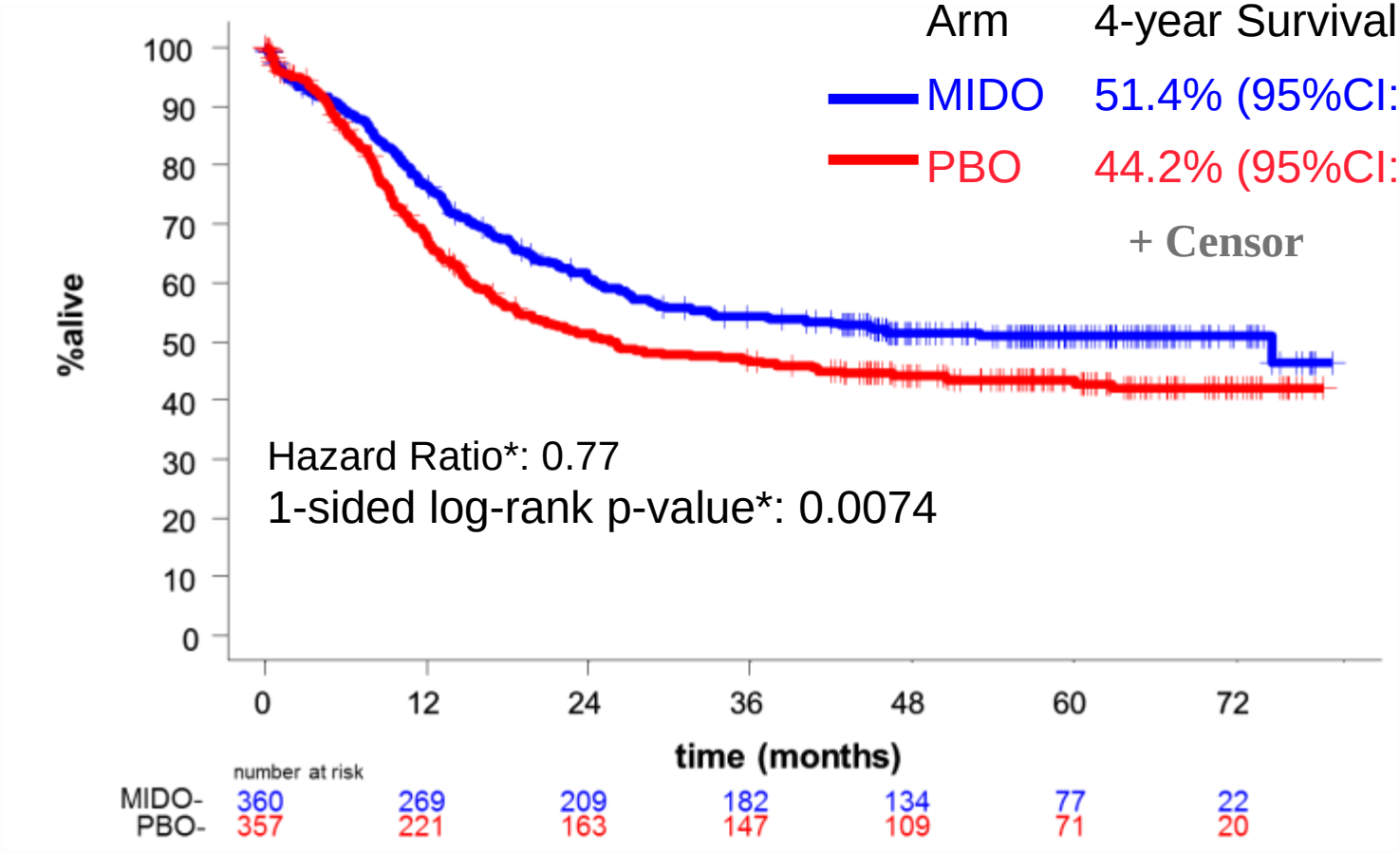


Stratification: TKD; ITD with allelic ratio <0.7 ‘vs’ ≥0.7

Stone et al. NEJM, 2017

Overall Survival

23% reduced risk of death in the Mido arm



Stone et al. NEJM, 2017

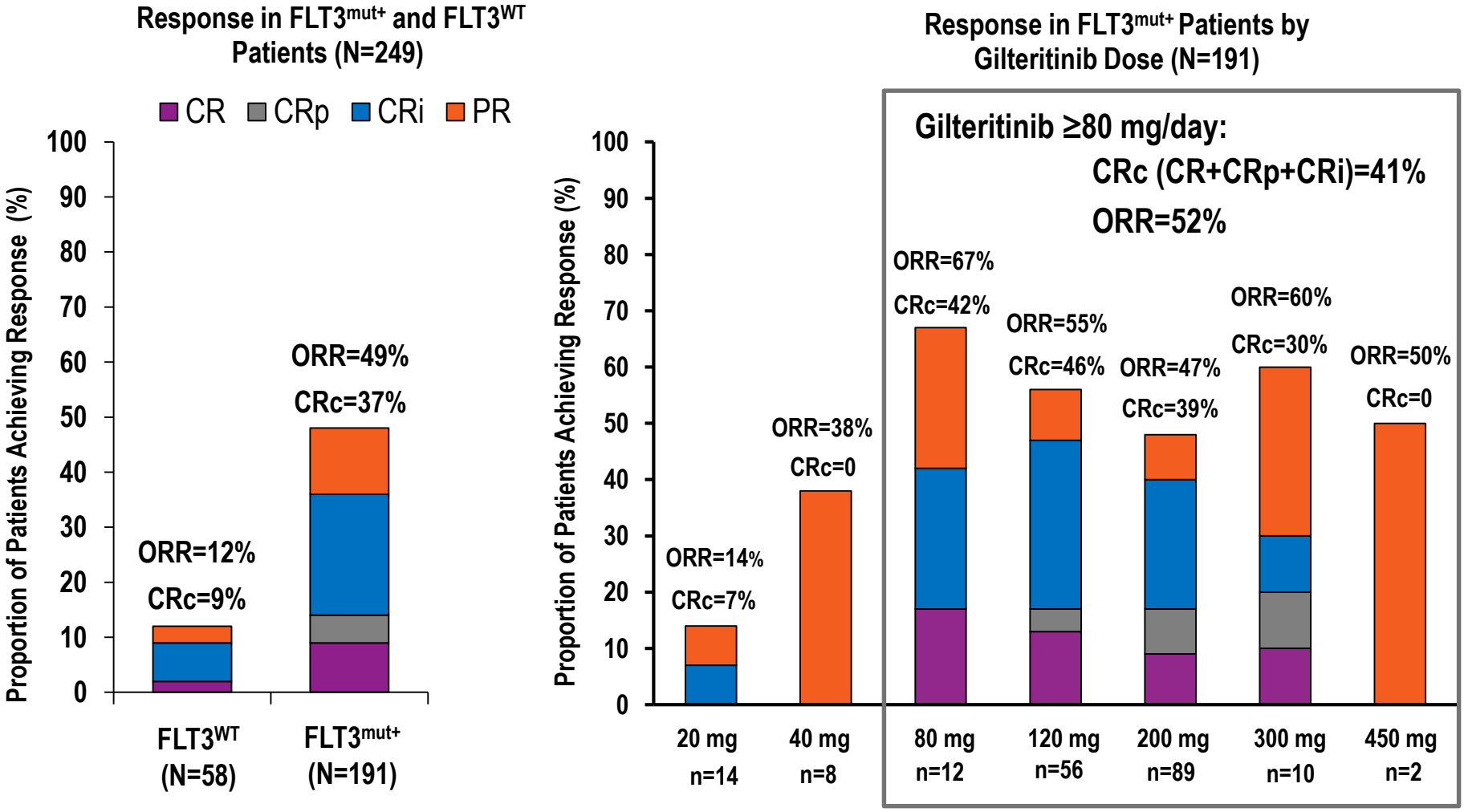
Midostaurin in AML

- First agent with (sustained) regulatory approval in 40 years

- BUT, will it be practice changing? Will it have a true (clinically meaningful) impact?
  - OS increase only 7%
  - Benefit more in *FLT3*-TKD than ITD
  - Which phase of treatment important?
  - Among least potent *FLT3* inhibitors
  - Role in maintenance unclear[1]
  - Beneficial effect of Midostaurin most pronounced in *NPM1*^{wt}/*FLT3*^{high} *group*[2]

[1]*Larson et al. ASH abstr 145, 2017;*
[2]*Dohner et al. ASH abstr 467, 2017*

Antileukemic Activity of Gilteritinib



Perl et al. Lancet Oncol, 2017

Second Generation *FLT3* Inhibitors

- **Gilteritinib: inhibits *FLT3-ITD* and *D835***
  - rando trial vs Midostaurin + induction chemo
  - vs placebo as maint posttransplant (MORPHO)
  - vs chemo in rel/refr (registration)
  - with 7+3 and HiDAC, CRc 90% in *FLT3* pos[1]
- **Quizartinib: most potent *FLT3* inhibitor**
  - rando trial vs placebo + induction chemo (QuANTUM-First)
  - vs salvage chemo in R/R (QuANTUM-R)
  - with AZA or LoDAC in R/R, high ORR[2]
- **Crenolanib: inhibits *FLT3-ITD,* D835, *PDGFa* and *b***
  - with induction chemo CR 83%, 72% with 1 cycle[3]

[1]Pratz et al. ASH, 2017 (abstr 722); [2]Swaminathan et al. ASH, 2017 (abstr 723); [3]Wang et al. ASH, 2017 (abstr 566)

FLT3 Mutations in AML

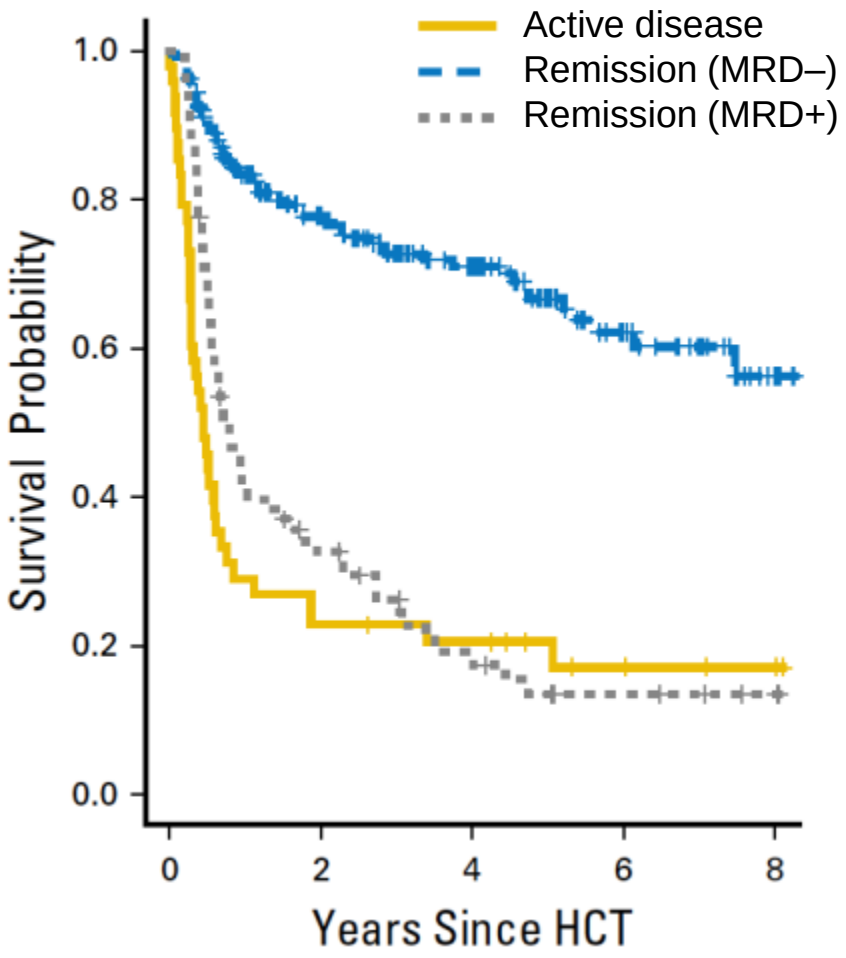
- Frequent in normal cytogenetic AML
- Associated with high WBC, packed marrow
- ITD associated with high relapse rate, poor OS; TKD less so
- Most common in APL, but appears not prognostic
- Resistance mechanisms include point mutations, high levels of *FLT3* ligand

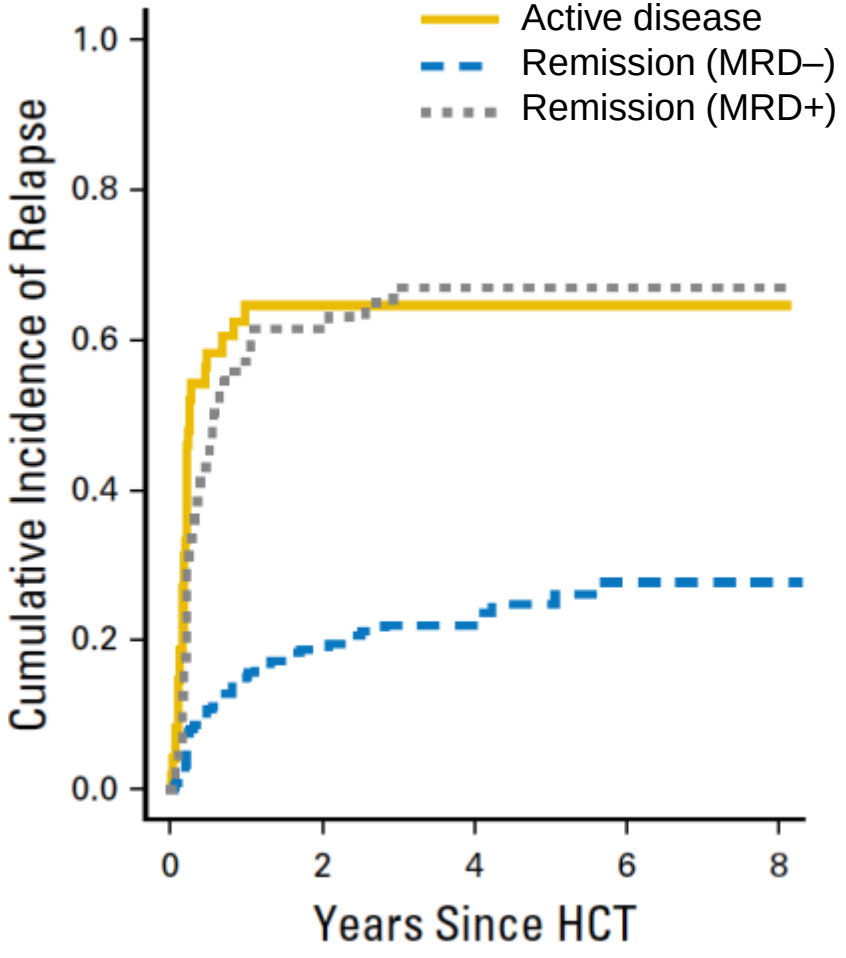
Minimal Residual Disease

- Detected by increasingly sensitive techniques (immunophenotyping, PCR, sequencing)
- Most studied in patients with *NPM1* mutation and CBF AMLs[1,2]
- Persistence of somatic mutations with VAF>1% in CR assoc. with increased risk of death and relapse[3]
- Complex due to genetic heterogeneity and multiple subclones
- Has prognostic implications following chemotherapy and before allogeneic transplantation
- Will rapidly become incorporated in routine clinical practice

[1]Ivey et al. NEJM, 2016; [2]Kapp-Schwoerer.et al. ASH abstr 183, 2017; [3]Morita et al. ASH abstr 2667, 2017

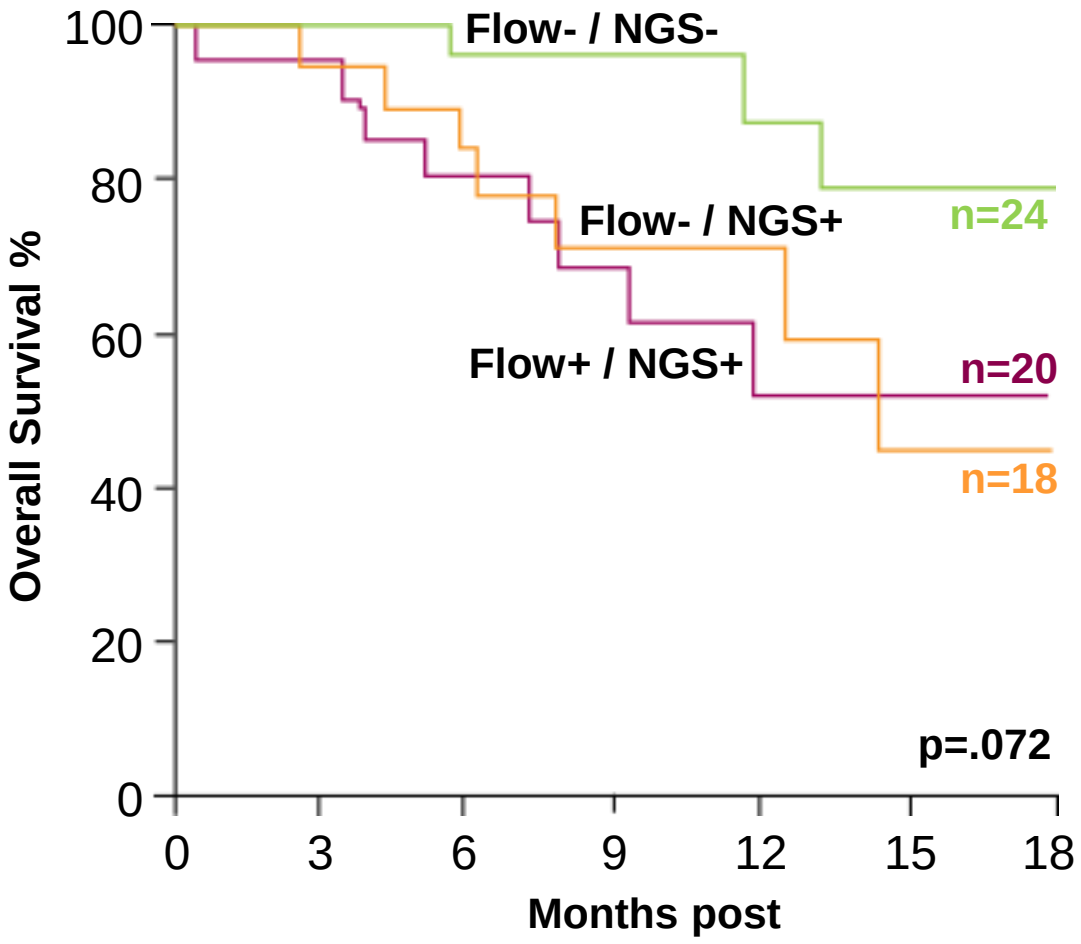
Equivalent Post-Transplant Outcomes for Pre-transplant AML MRD (by FC) and Active AML





Araki et al. J Clin Oncol, 2016

Flow Cytometry and NGS in AML Assessment Pre-allogeneic Transplant



Getta et al. BBMT, 2017

Limitations of MRD Detection in AML

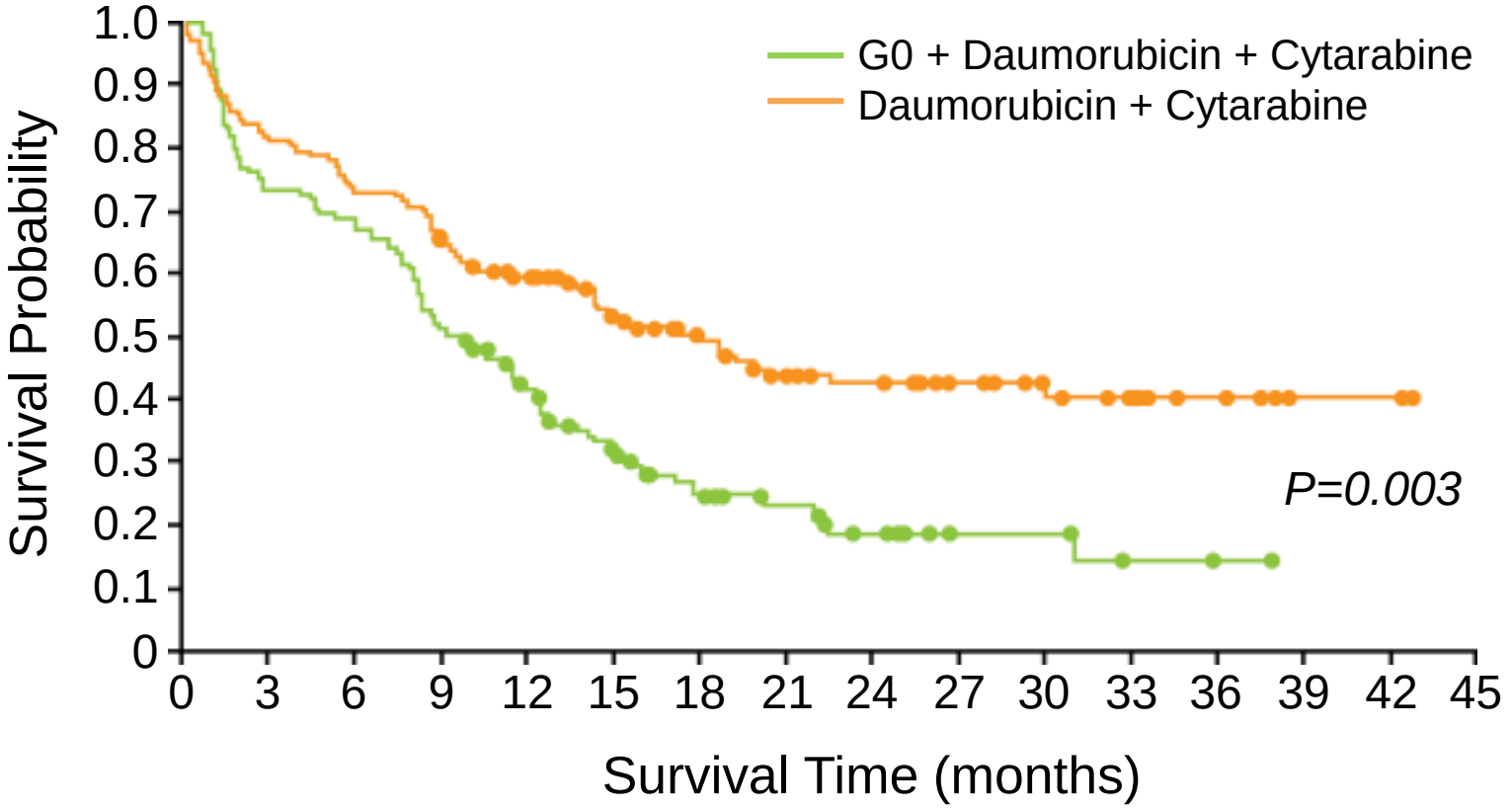
- Methodologies not standardized
- Thresholds for defining MRD vary
- Heterogeneity of the disease
- Clonal hematopoiesis
- Variable distribution of leukemia cells after treatment
- Lack of effective agents to target MRD
- Randomized trials needed to show benefit of intervention

Agents With Regulatory Approval (or Breakthrough Designation)

Agent	Target	Population	Setting
Midostaurin	*FLT3*	*FLT3-ITD* or *TKD*	Treatment naïve w chemo in induc and consol
Gemtuzumab ozogamicin	*CD33*	CBF and possibly intermed-risk	Treatment naïve CD33+ adults w chemo or single agent or Rel/refr adults and peds
CPX-351	Cytotoxic	t-AML or AML with MRC	Treatment naïve with t-AML or AML with MRC
Enasidenib	*IDH2*	IDH mutated	Rel/refr AML w m*IDH2*
Venetoxlax	*BCL-2*	Elderly adults	Treatment naïve (with LoDAC)

Gemtuzumab Ozogamicin (Fractionated) in Newly Diagnosed AML Ages 50-70

Kaplan-Meier Plot of Event-Free Survival (mITT Population) ALFA-0701 Trial



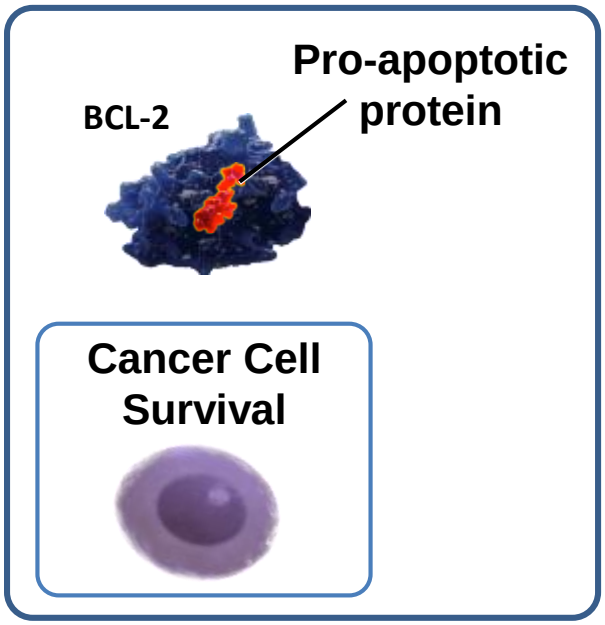
Castaigne. et al. Lancet, 2012 and update

Gemtuzumab Ozogamicin: Reapproved

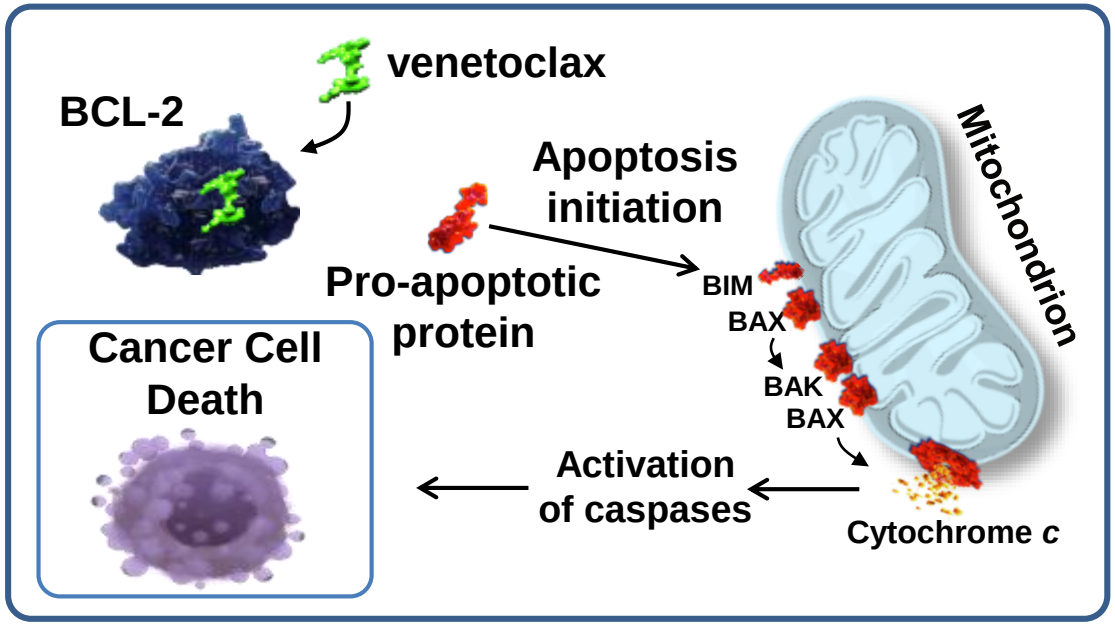
- First ab-drug conjugate approved for human use-2000
- Withdrawn, lack of OS benefit and toxicity-2010
- Reapproved for adults with new AML and pts > age 2 with R/R disease-2017
- CD33 single nucleotide polymorphism rs121459419 C⟹T may be biomarker for response
- OS benefit in fav-risk and trend in intermed-risk
- Risk of SOS/VOD 8% in 146 pts (69 with prophylaxis: heparin or ursodiol or defibrotide) after allograft
- Expression of CD33 blast expression impacts outcome

Lamba et al. JCO, 2017; Burnett et al. JCO, 2011; Battipaglia et al. BBMT, 2017; Olombel et al. Blood, 2016; Lamba et al. ASH abstr 3826, 2017

Venetoclax: Promotes Apoptosis Through Selective Inhibition of BCL-2



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]

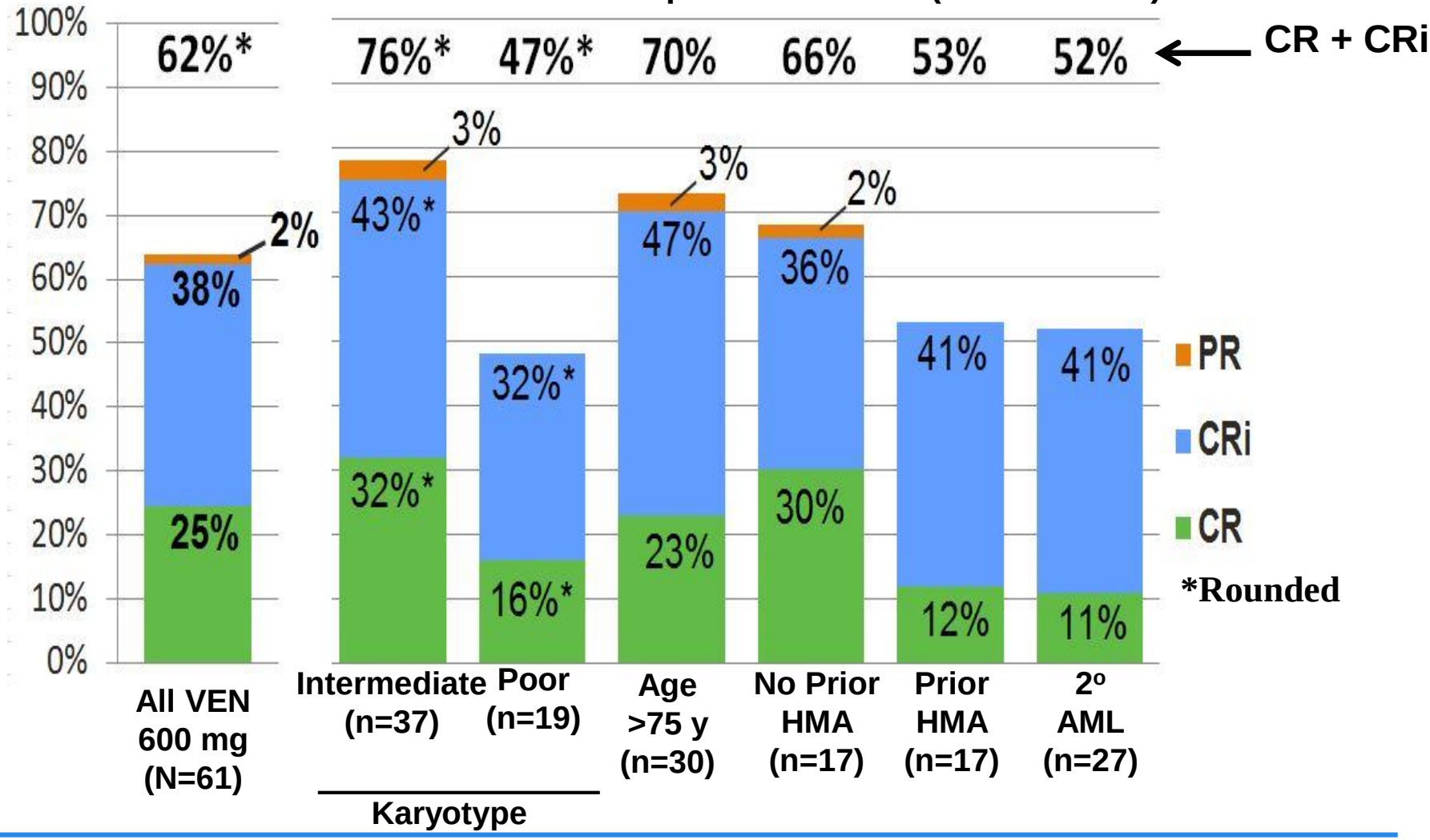


Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]

1. *Leverson et al. Sci Transl Med 2015; 2. Czabotar, et al. Nature Reviews 2014; 3. Plati et al. Integr Biol (Camb) 2011; 4. Certo et al. Cancer Cell. 2006; 5. Souers et al. Nat Med. 2013; 6. Del Gaizo Moore V et al. J Clin Invest. 2007*

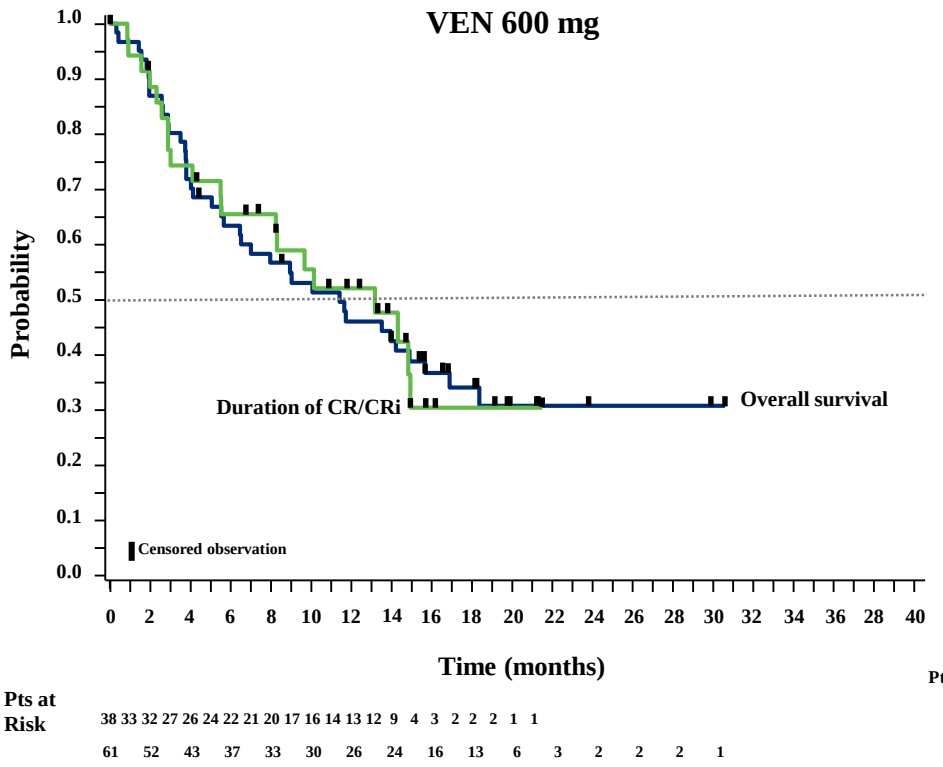
CR/CRi Rates
LoDAC + Venetoclax

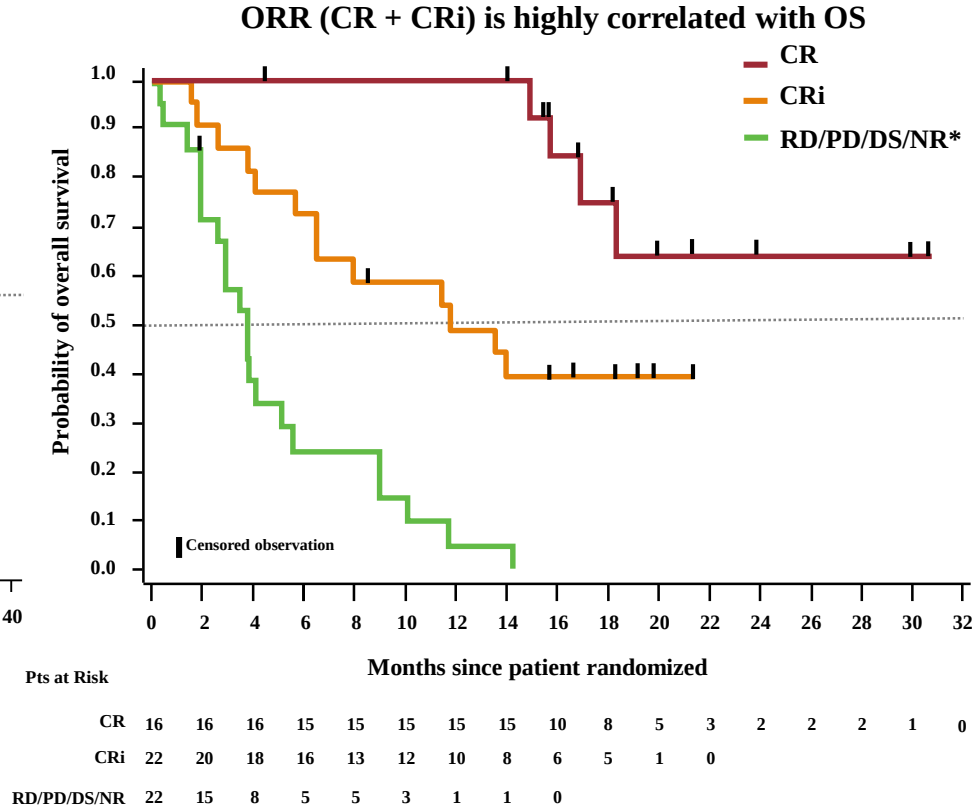
Median time to response: 1 month (<1–9 months)



Wei et al. EHA, 2017 and ASH abstr 890, 2017

DOR, Survival, and Survival by Response



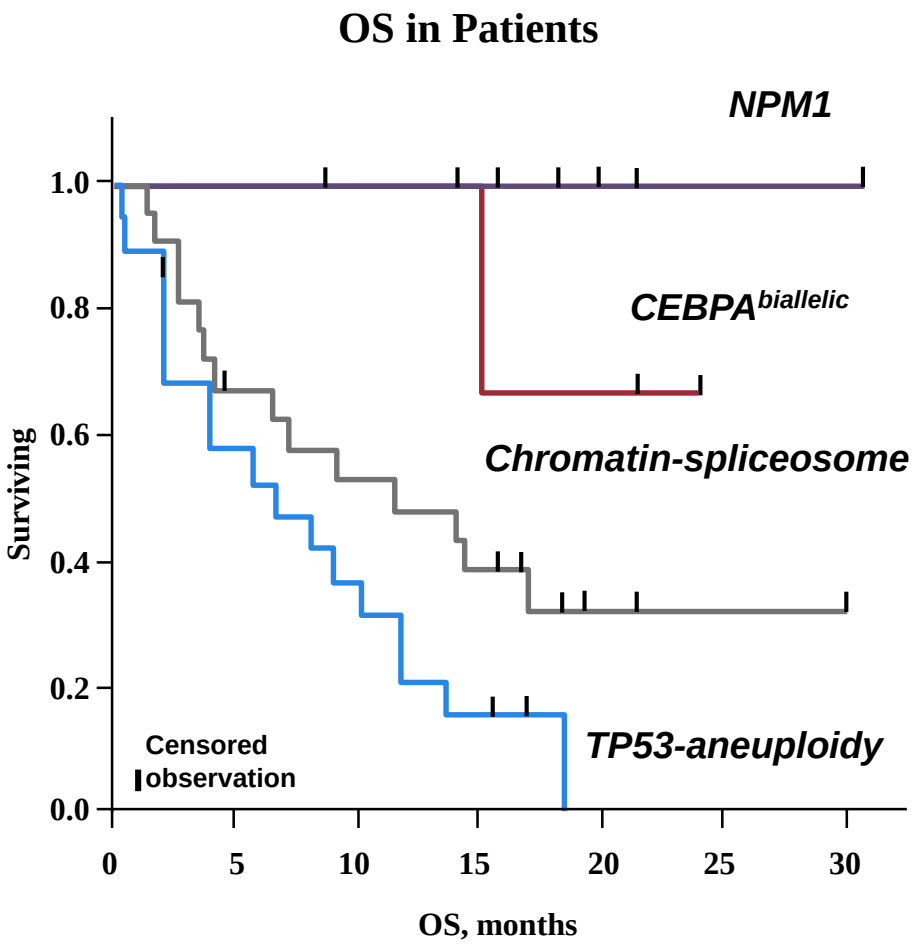


Wei et al. ASH abstr 890, 2017

Outcomes According to Molecular Drivers of AML

Cytogenetics	ORR (CR + CRi)	Median OS, mo
Intermediate risk n = 37	28 (76%)	15.7
Adverse risk n = 19	9 (47%)	5.7

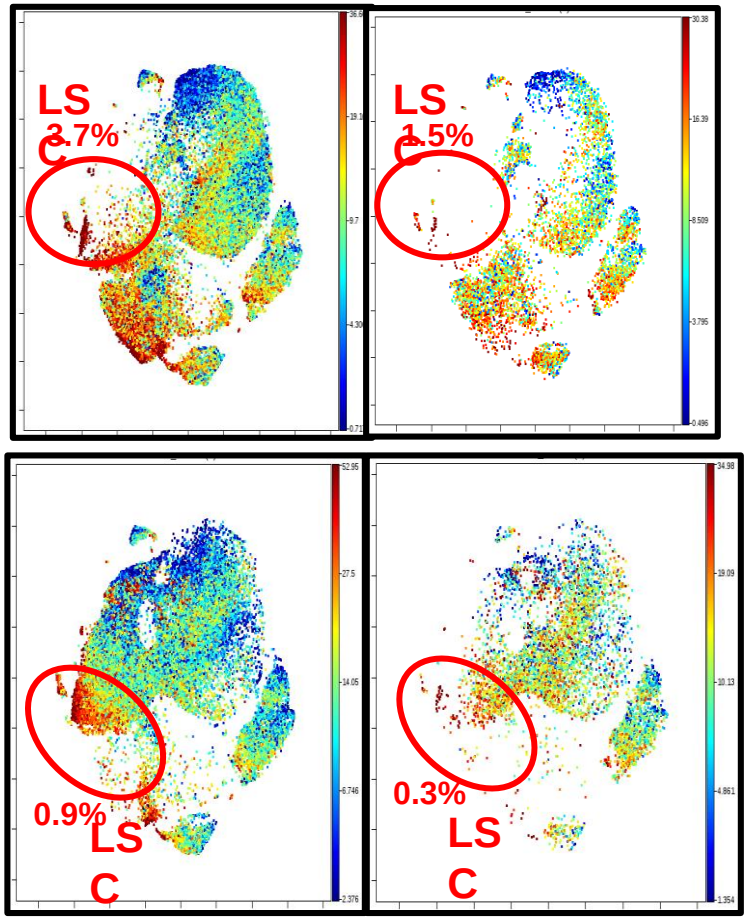
Molecular Subgroups		
NPM1 n = 7*	7 (100%)	NR
CEBPA^{biallelic} n = 3	3 (100%)	NR
Chromatin-spliceosome n = 22	15 (68%)	11.4
TP53-aneuploidy n = 20	10 (50%)	6.5



Wei et al. ASH abstr 890, 2017

Venetoclax and Azacitidine Results in Rapid Eradication of Blasts and LSCs

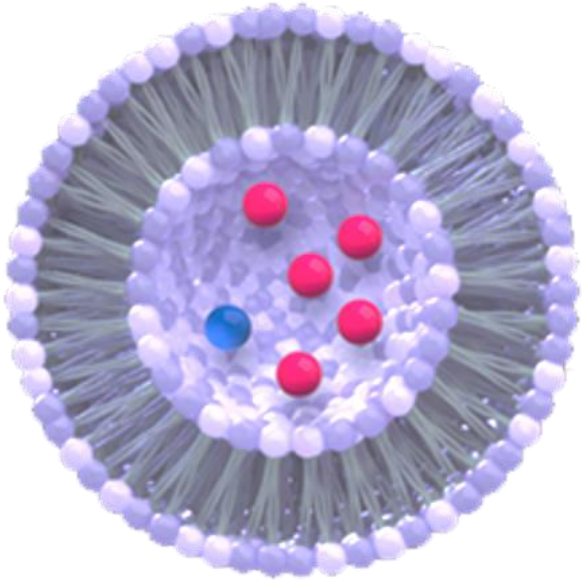
Peripheral Blood Blasts (%)			
	Pre- Treatment	24 Hours Post-Treatment	72 Hours Post-Treatment
Pt 1	71%	50%	16%
Pt 2	81%	72%	34%



LSCs defined as Lin-/CD34+/CD123+/HLA-DR+/CD117+/CD33

Pollyea et al. ASH abstr 181, 2017

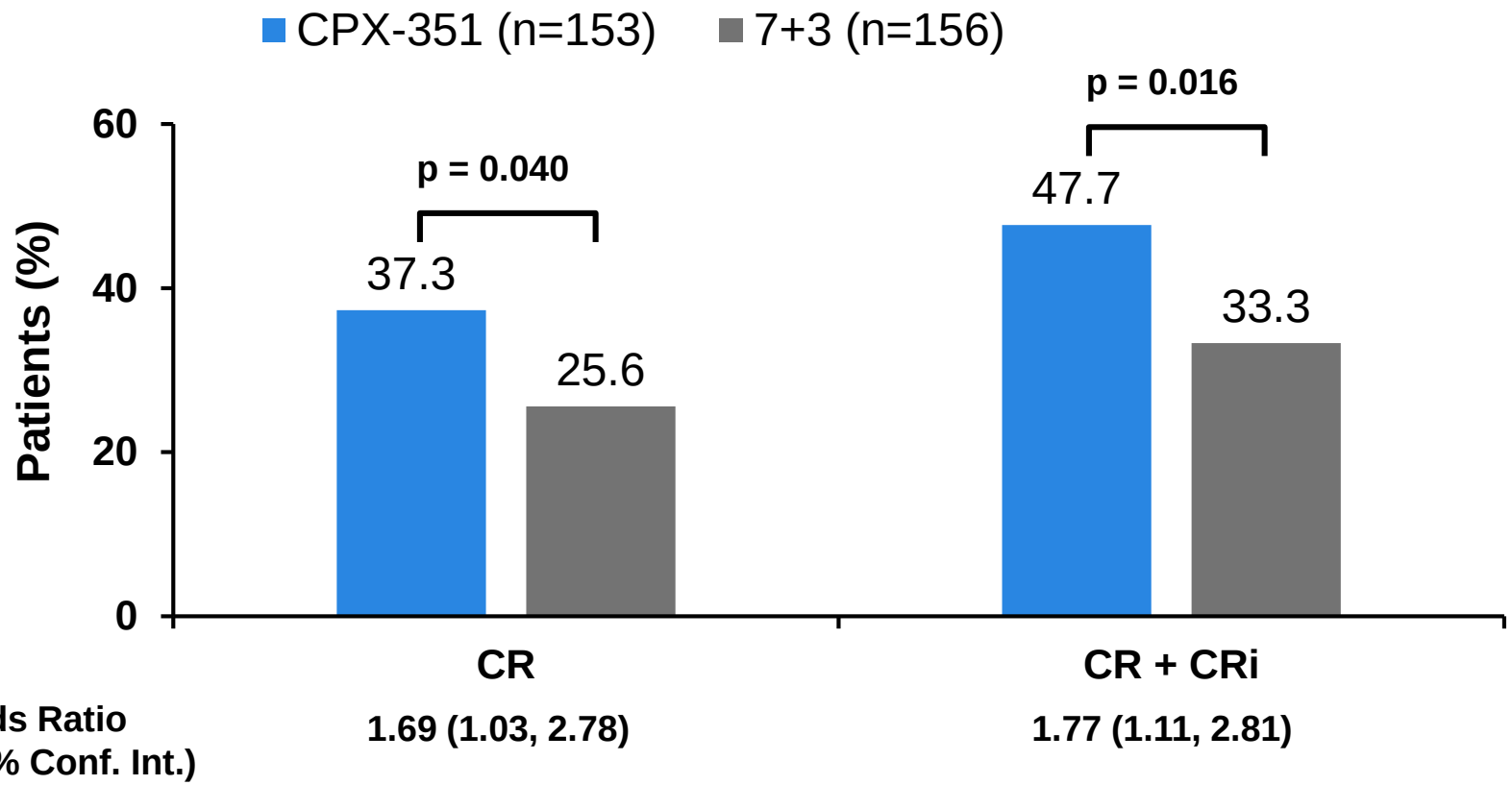
CPX-351 Uses a Nano-Scale Delivery Complex



- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

US FDA Approved August 2017 for t-AML and AML with MRC

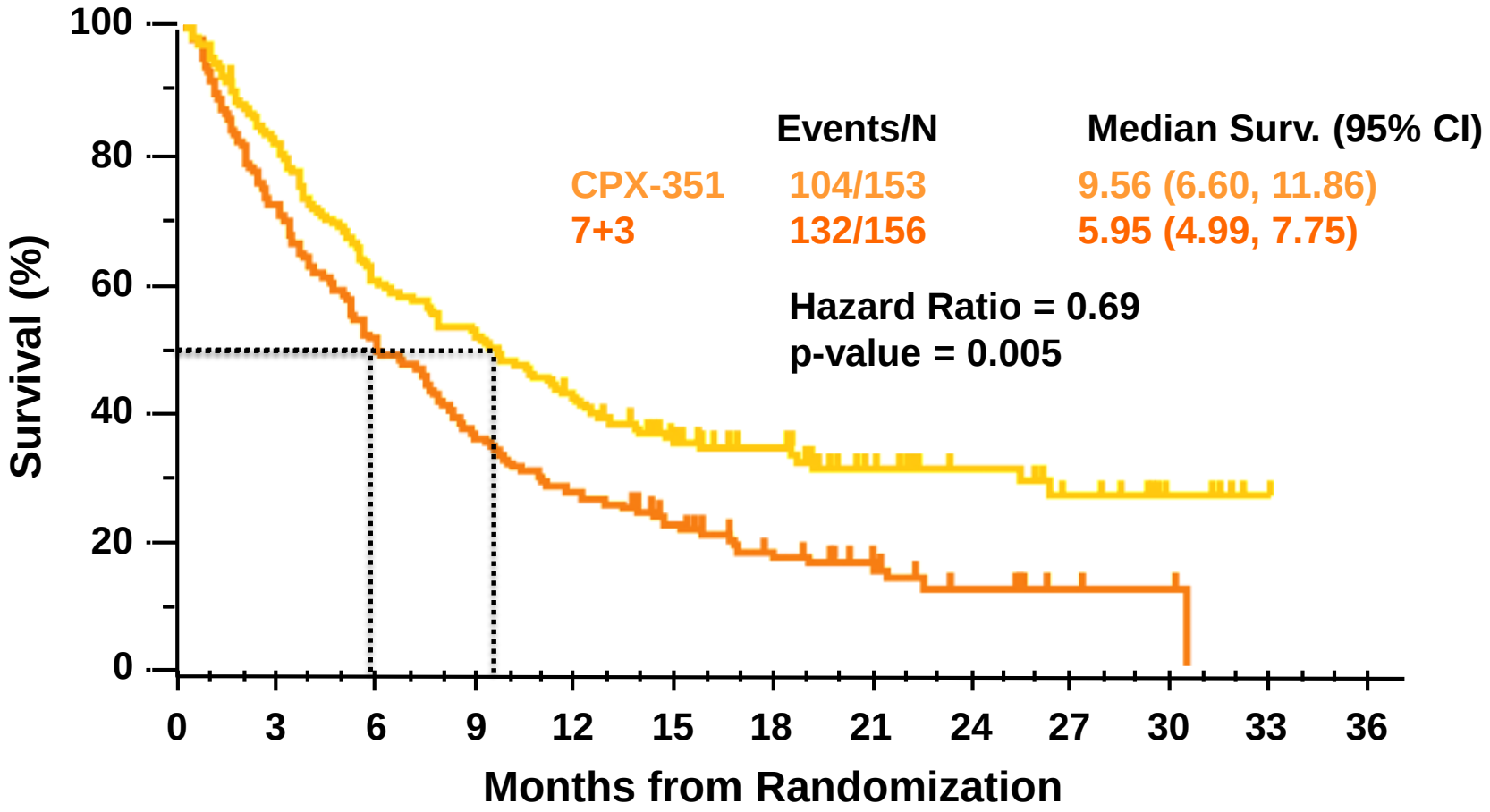
Patients Treated With CPX-351 Exhibited Statistically Significant Improvements in Response Rate



Lancet et al. ASCO abstr 7000, 2016

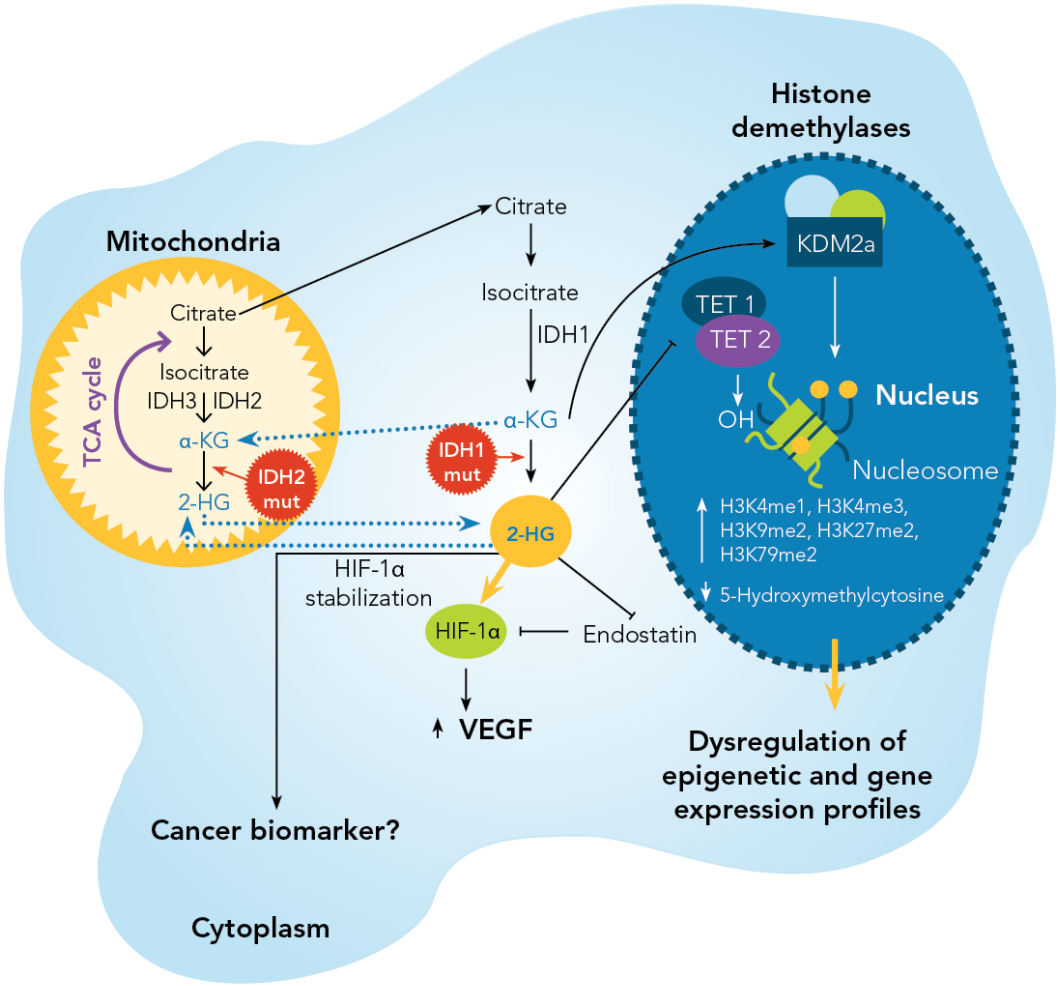
Overall Survival Was Greater in the CPX-351 Arm Compared to the 7+3 Arm

Kaplan-Meier Curve for Overall Survival ITT Analysis Population



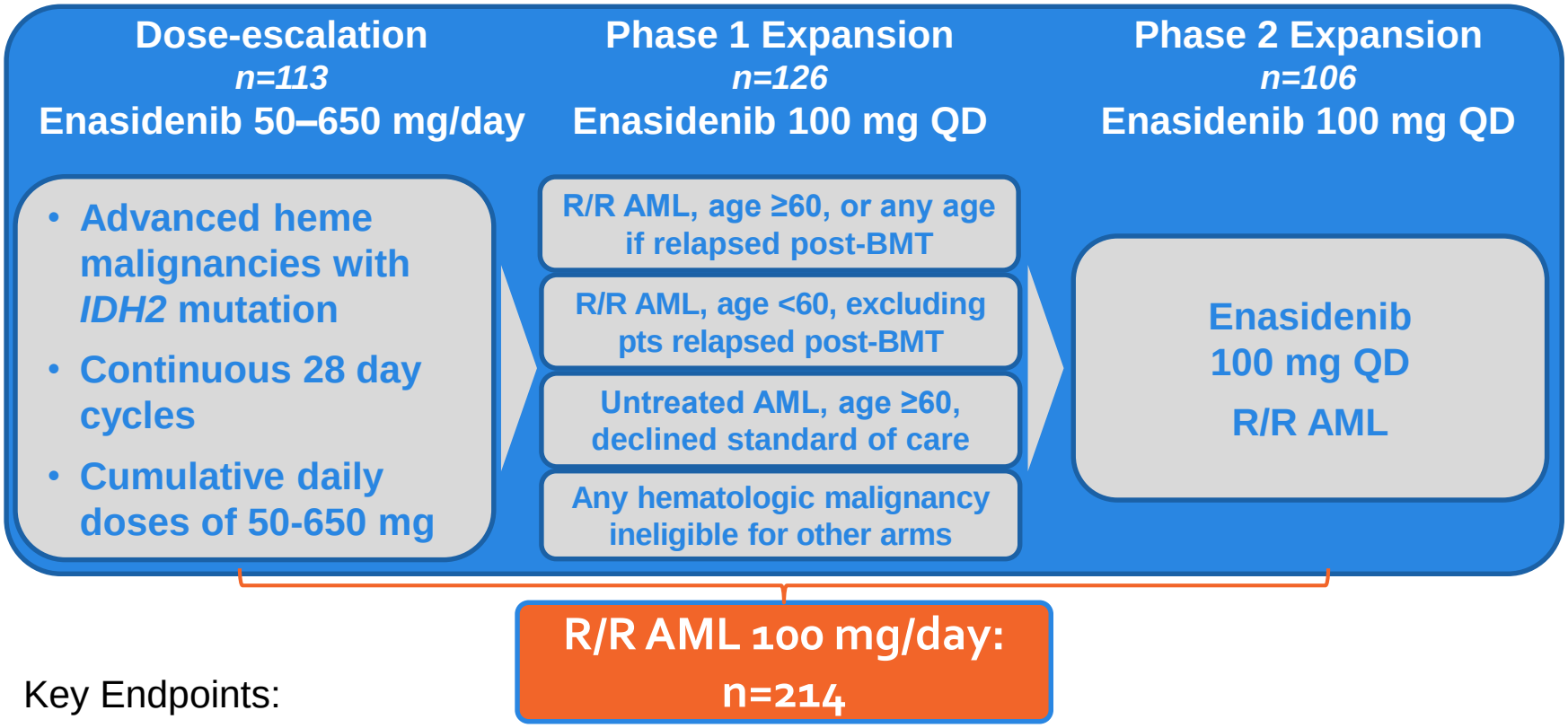
Lancet et al. ASCO abstr 7000, 2016

Role of *IDH* in Malignancy



- IDH is critical metabolic enzyme in the citric acid cycle
- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (2-HG) and blocks normal cellular differentiation

Phase 1/2 Study Design



Key Endpoints:

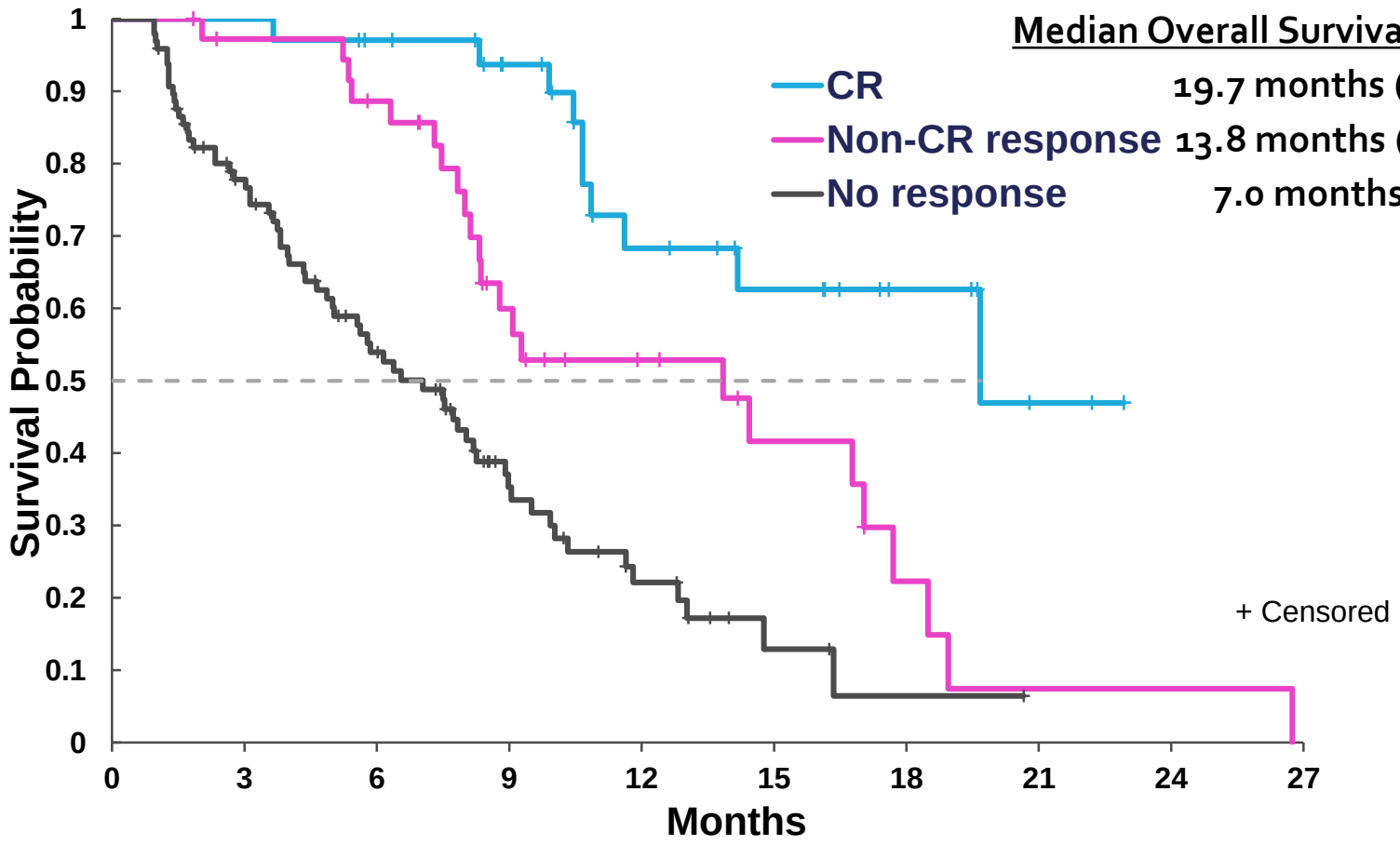
- Safety, tolerability, MTD, DLTs
  - MTD not reached at doses up to 650 mg/day
- Responses assessed by local investigator per IWG criteria[1]
- Assessment of clinical activity, with focus on 100-mg daily dose in patients with R/R AML

Response in R/R AML

	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]	**43 (20.1)** [14.9, 26.1]	**55 (19.6)** [15.1, 24.7]
CRi or CRp, n (%)	17 (7.9)	22 (7.8)
PR, n (%)	8 (3.7)	16 (5.7)
MLFS, n (%)	11 (5.1)	15 (5.3)
SD, n (%)	110 (51.4)	137 (48.8)
PD, n (%)	11 (5.1)	15 (5.3)
NE, n (%)	2 (0.9)	3 (1.1)
Time to first response (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]

Stein et al. ASCO, 2017 and Blood, 2017

Overall Survival by Best Response

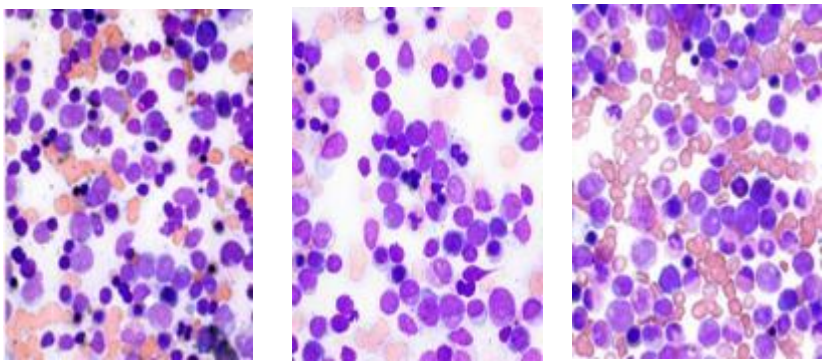


Stein et al. ASCO abstr 7004, 2017 and Blood, 2017

Morphological evidence of myeloid differentiation

Patient 1

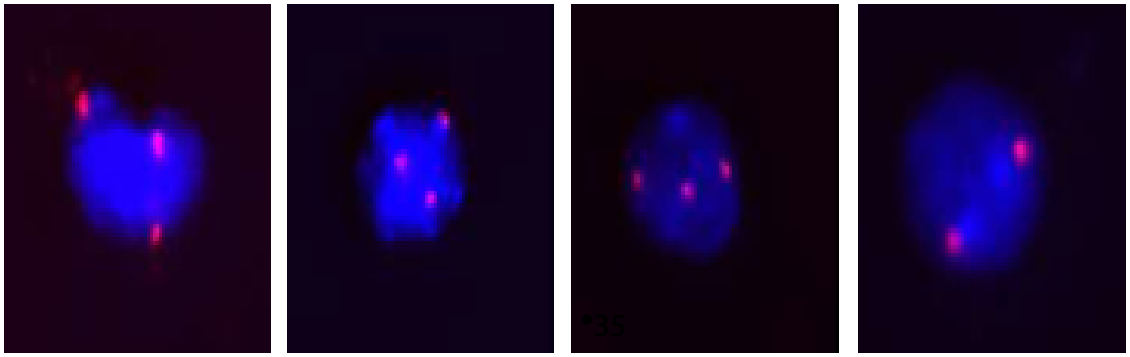
Screening	Cycle 1 Day 15	Cycle 3 Day 1
37% blasts	Evidence of cellular differentiation	4% blasts



FISH evidence of myeloid differentiation

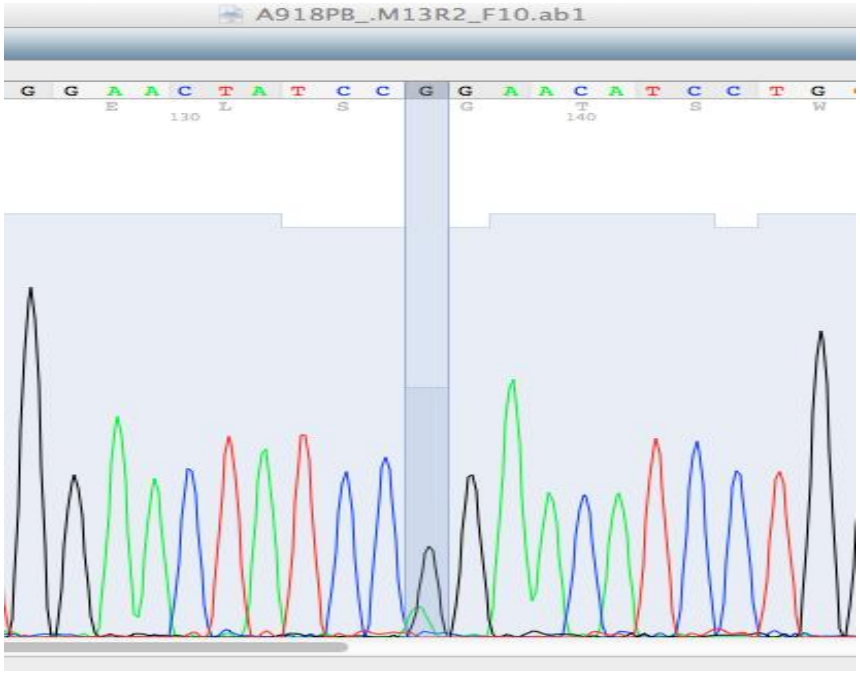
Patient 2 C2D1, trisomy 8

Blasts	Promyelocytes	Mature Granulocyte	Lymphocytes

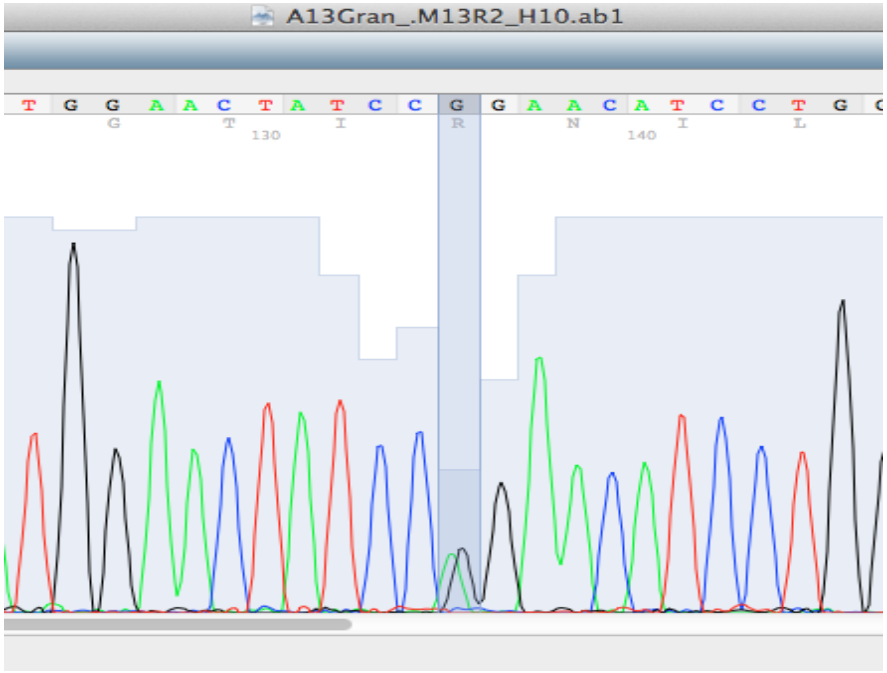


Molecular Evidence of Differentiation

Screening – PBMC

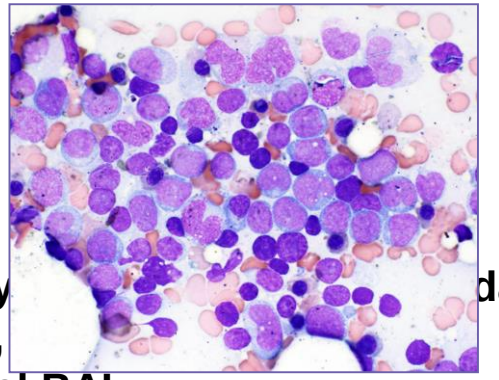


Cycle 3 day 1 – Remission - Granulocytes

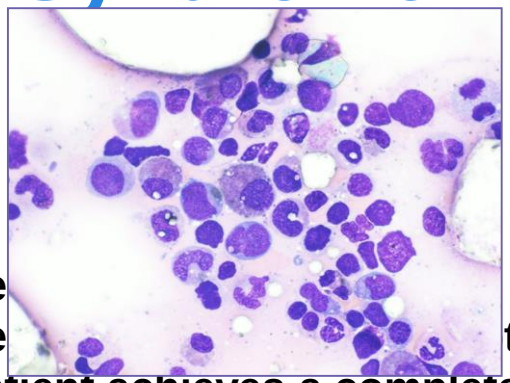


Alan Shih and Ross Levine, MSKCC

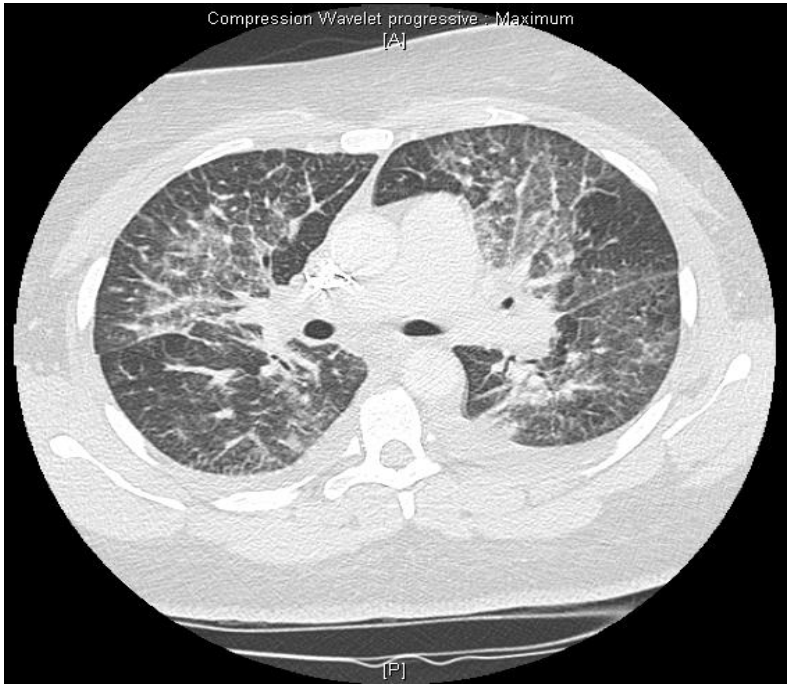
Differentiation Syndrome

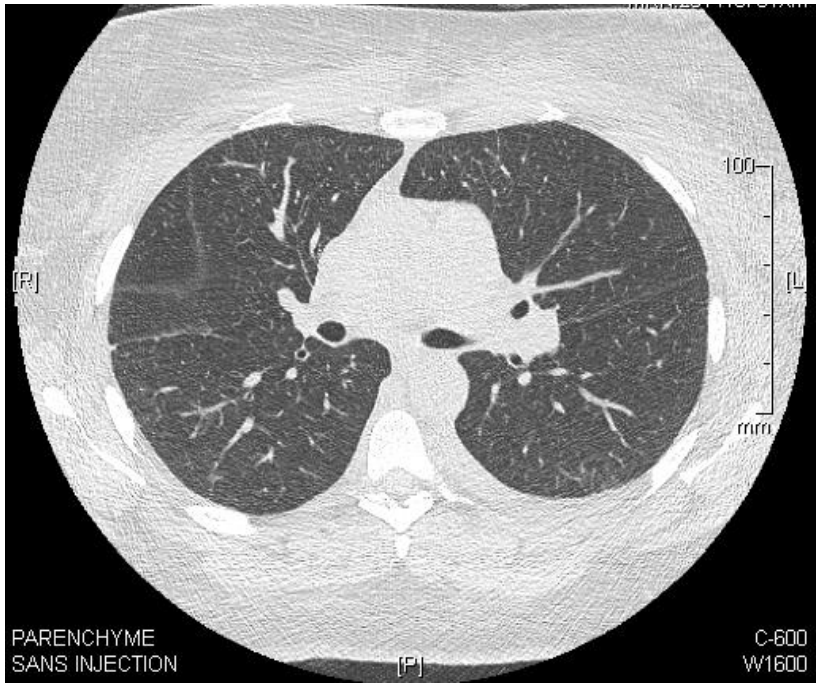


- 21 day … daily
- Fever, …
- Normal BAL



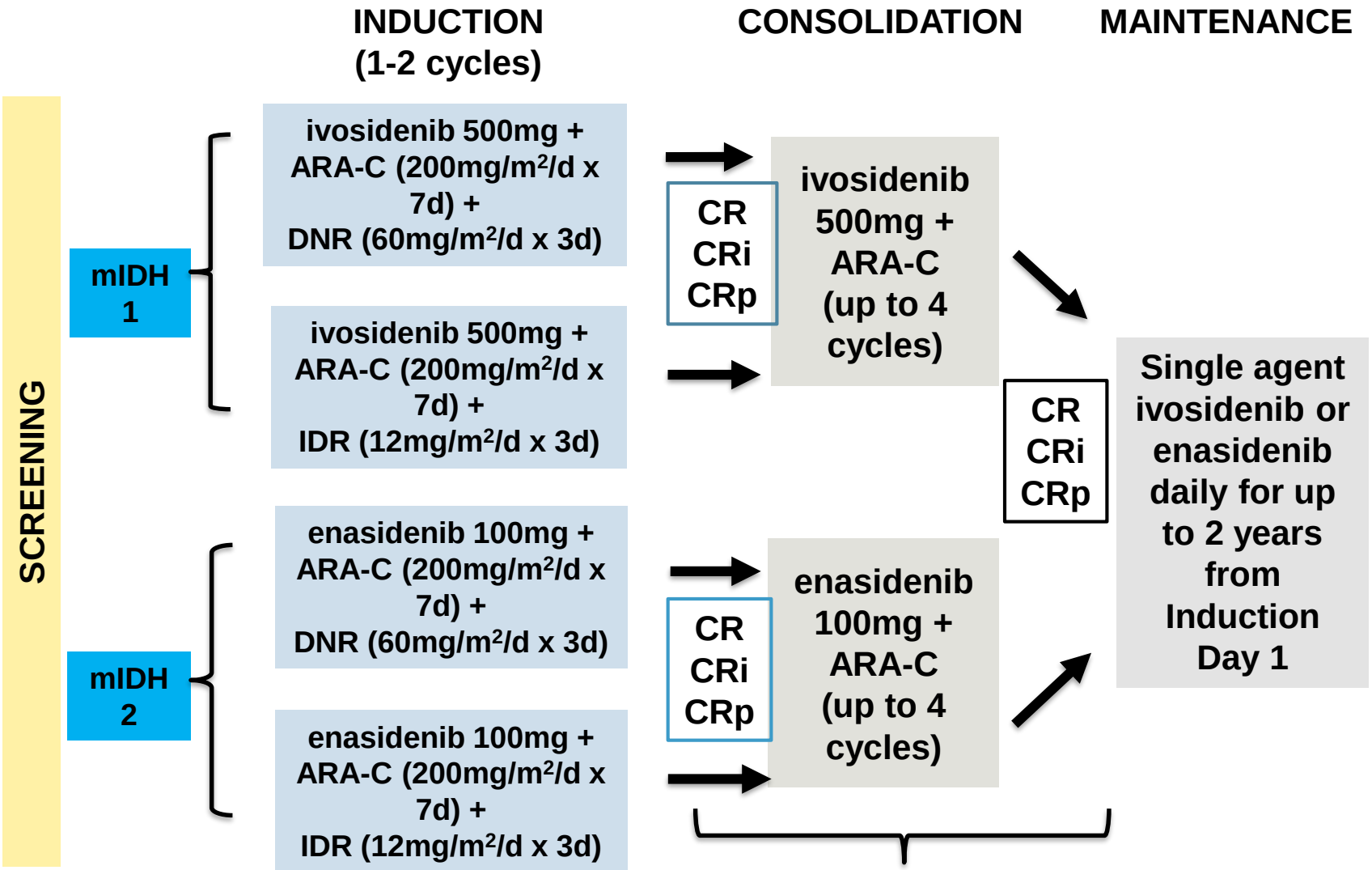
- De… for 15 days
- Re… toms
- Patient achieves a complete remission





Courtesy Dr. Stephane De Botton

Ivosidenib or Enasidenib Plus Chemotherapy Phase I Trial



Stein et al. ASH abstr 726, 2017

Patients who discontinue to go to transplant may not re-start study treatment

Best Overall Response Summary

	Ivosidenib (AG-120) + CT			Enasidenib (AG-221) + CT		
Response, n (%)	All (n=30)	De novo (n=21)	sAML (n=9)	All (n=50)	De novo (n=27)	sAML (n=23)
CR+CRi/CRp	77	91	44	62	67	57
CR	63	71	44	50	59	39
CRi/CRp	13	19	-	12	7	17
MLFS	3	-	11	20	15	26
PR	7	5	11	-	-	-
Persistent disease	7	5	11	10	7	13
NE	7	-	22	8	11	4

Stein et al. ASH abstr 726, 2017

Novel Agents in AML

Agent	Target
Selinexor	XPO1
Tamibarotene	*RAR*-alpha
Entospletinib	*SYK*
Palbociclib	CDK6
Cobimetinib	*MAPK*
Pevonedistat	NEDD8-activating enzyme
H3B-8800/E7070, E7820 (Spliceosome inhibitors)	SF3B1/RBM39

Daver et al. ASH abstr 1344, 2017; Drusbosky et al. ASH abstr 3909, 2017; Daver et al. ASH abstr 813, 2017; Guo et al. ASH abstr 3820, 2017; Yoshimi et al. ASH abstr 473, 2017

Questions Generated From New Drug Approvals

- Should Gemtuzumab be given to all CBF AMLs and older adults with fav- and intermed-risk?
- How should transplant strategies be affected by Gemtuzumab in induction?
- Must Gemtuzumab be given as in ALFA trial with specific induction and chemotherapy regimens (dauno in consol)? For Midostaurin?
- When a pt has AML with MRC and an *IDH2* mutation, should pt be treated with CPX-351 or on trial with chemotherapy and Enasidenib? If AML-MRC and FLT3 pos: CPX-351 or Mido?

AML Treatment Strategies in 2018

AML subgroup	Candidate for intensive chemo	Not a candidate for intensive chemo
All patients	Clinical trial preferred	Clinical trial preferred
CBF	GO + chemo	HMA/LoDAC + Venetoclax*
CD33 pos	GO + chemo, ? If pretransplant	GO or HMA/LoDAC + Venetoclax
t-AML or AML w/MRC (incl complex cyto)	CPX-351 ind/consol, transplant	HMA/LoDAC + Venetoclax*
TP53 mutant	Chemo vs decitabine x 10d	Decitabine x5d or x10d
FLT3+	Mido + chemo ind/consol/maint, transplant	?AZA + sorafenib or HMA alone
*IDH*1/2+	Chemo	HMA/LoDAC + Venetoclax*
Marker -	Chemo	HMA/LoDAC + Venetoclax*

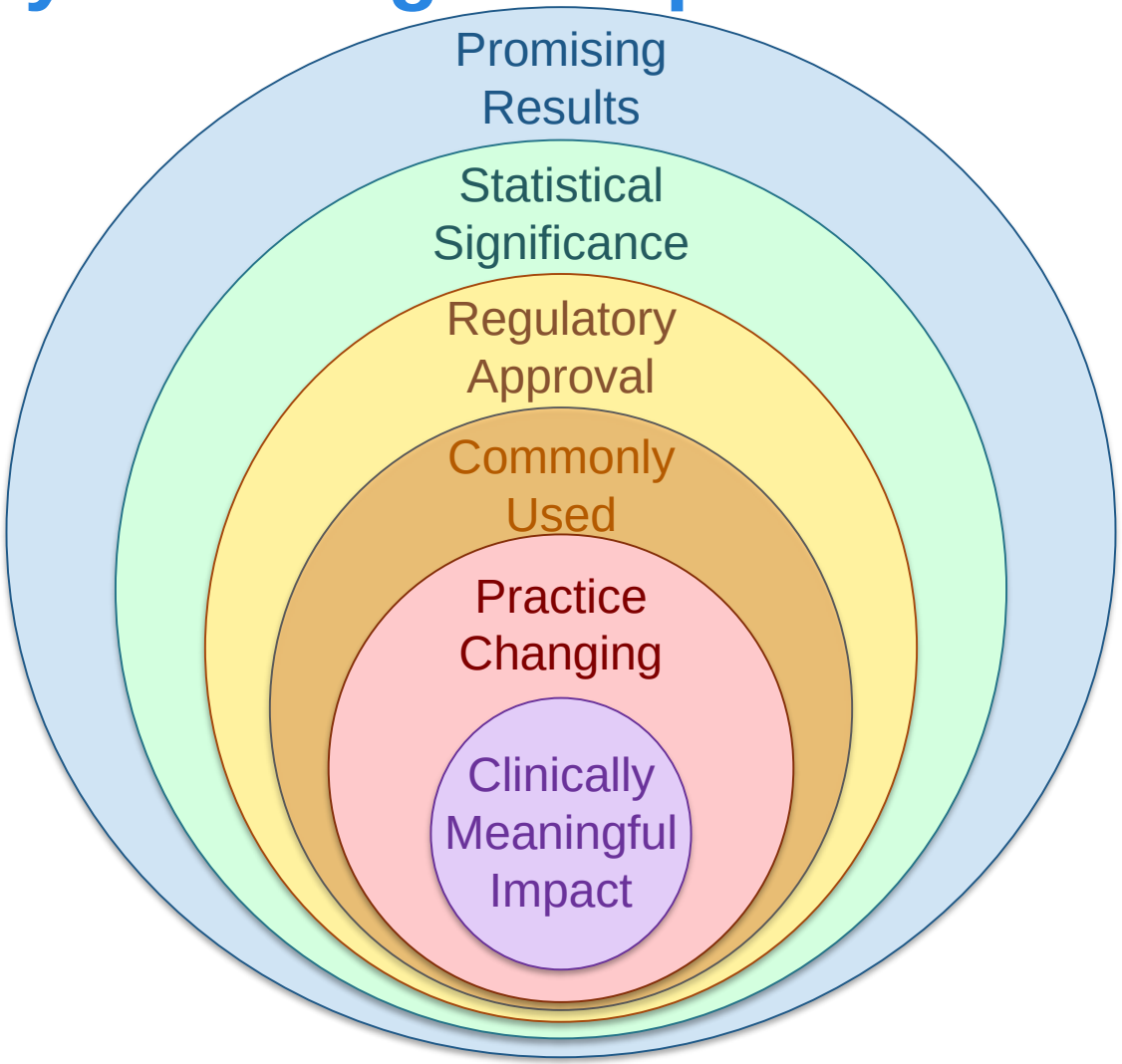
*HMA/LoDAC + Venetoclax awaiting phase III data

AML Treatment Strategies in 2018: R/R

AML subgroup	Candidate for intensive chemo	Not a candidate for intensive chemo
All patients	Clinical trial preferred	Clinical trial preferred
R/R *IDH2*+	Enasidenib	Enasidenib
R/R *IDH1*+	Clinical trial with ivosidenib preferred	Clinical trial with ivosidenib preferred
R/R *FLT3*+	Strongly favor clinical trial	Strongly favor clinical trial
R/R *TP53* mutant	Chemo vs decitabine x 10d	Decitabine x5d or x10d
R/R CD33+	Chemo or GO	HMA/LoDAC + Venetoclax* or GO
R/R post-allo transplant w extramedullary AML	Chemo vs HMA vs ipilimumab	HMA vs ipilimumab
R/R marker -	Chemo vs HMA vs HMA/LoDAC + Venetoclax*	HMA vs HMA/LoDAC + Venetoclax*

*Lower RR for HMA/LoDAC + Venetoclax in R/R setting
(*Dinardo et al. Am J Hematol 2018*; *Goldberg et al. ASH 2017, abstr 1353*)

The Circuitous Road To A Clinically Meaningful Impact Of A New Drug



Summary and Conclusions

- AML is a heterogeneous disease of diverse somatic genetic mutations
- Molecular genetics inform classification, prognosis, therapy and depth of remission
- Era of precision medicine is here
- Many novel agents with unique mechanisms of action available
- MRD has emerged an important prognostic factor
- Therapeutic paradigms are shifting

Acknowledgments

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