Acute Myeloid Leukemias: Treatment Options in 2019

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Disclosures

- Research Funding
  - Cellerant
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  - Orsenix
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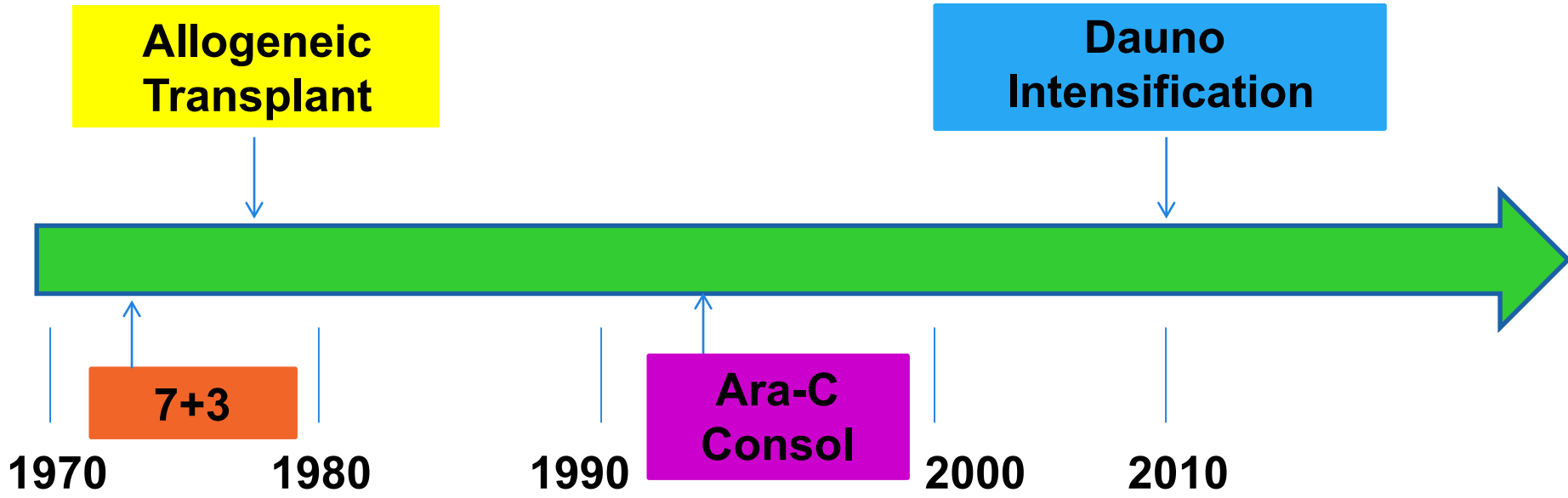
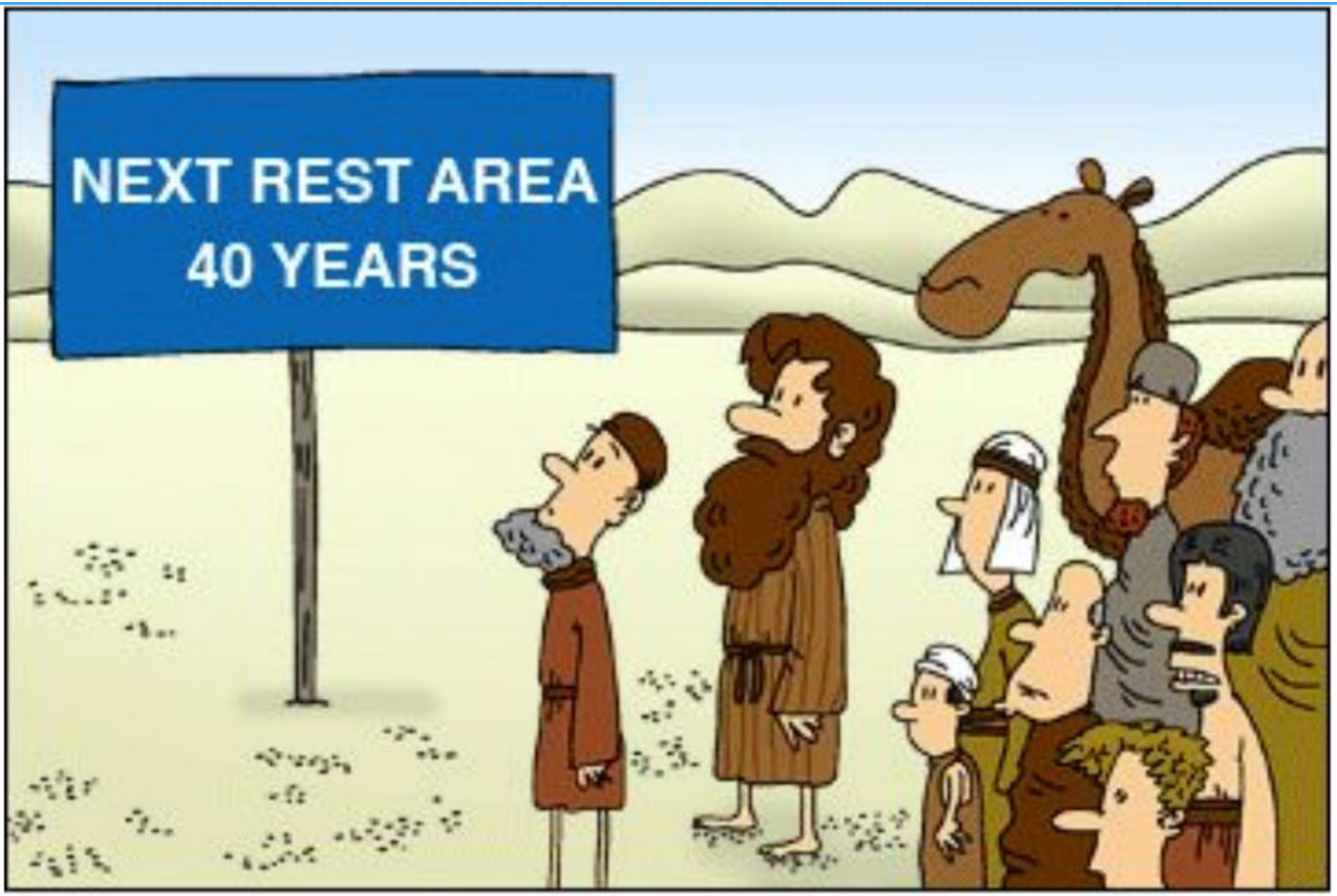
  - Rigel
  - Abbvie
  - Bioline
  - Biosight
  - KAHR
  - Delta Fly Pharma
- Off label use
  - Venetoclax
  - Gilteritinib
  - Quizartinib
  - Crenolanib
  - Ipilumumab
  - Azacitidine, decitabine

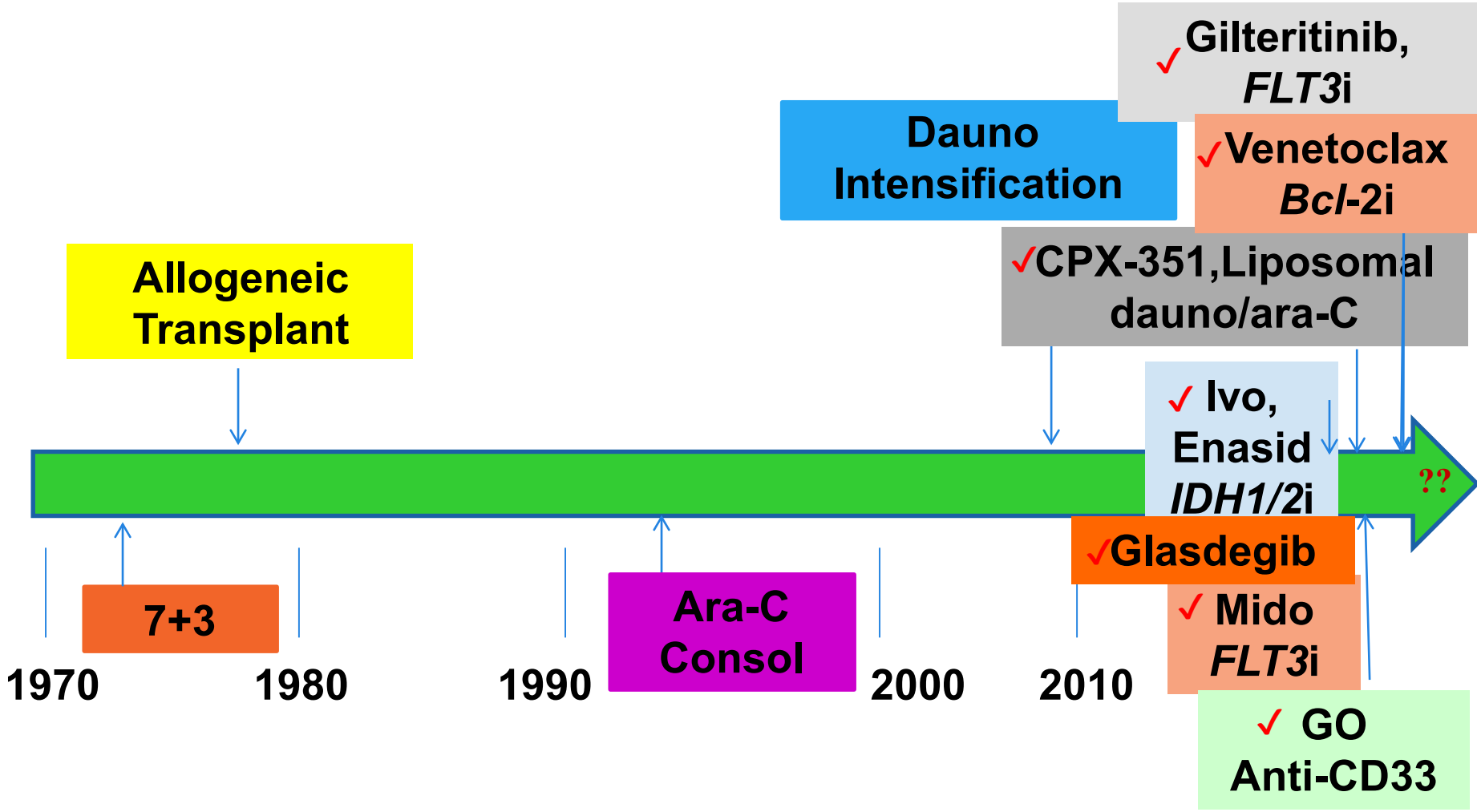
Practice Changing Treatments in AML
Established Standard of Care



Yates et al. Cancer Chemother Rep, 1973;
Thomas et al. NEJM, 1979; Mayer et al. NEJM, 1994; Fernandez et al. NEJM, 2009


NEXT REST AREA
40 YEARS

Practice Changing Treatments in AML

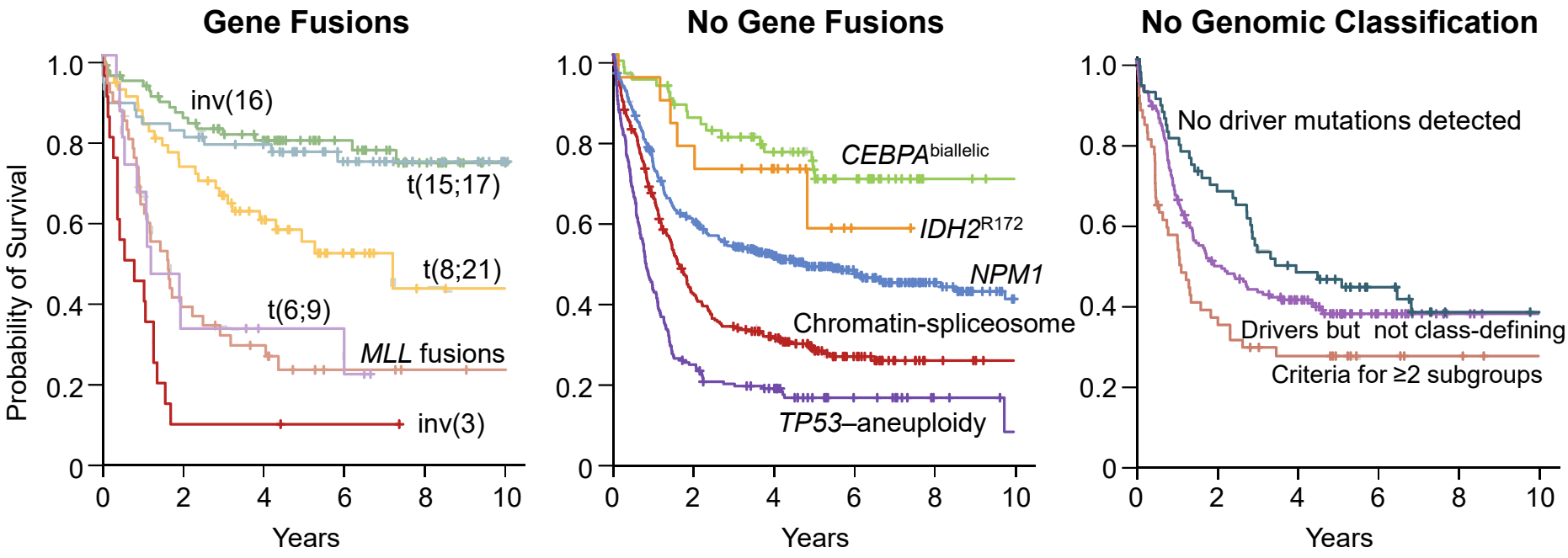


Yates et al. Cancer Chemother Rep, 1973; Thomas et al. NEJM, 1979; Mayer et al. NEJM, 1994; Fernandez et al. NEJM, 2009; Stone et al NEJM 2017; Stein et al Blood 2017 Lancet et al ASCO 2017; Castaigne et al. Lancet 2012; Cortes et al. Blood, 2016

Progress in AML in the Last 40 Years

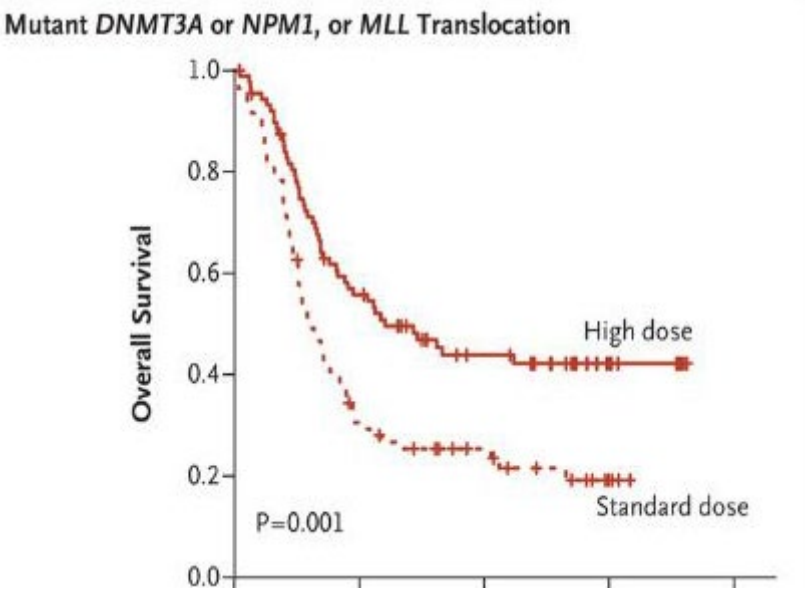
- Insights into genetic pathogenesis/integrated genetic profiling
- Intensified induction and less intensive postremission strategies
- **Drug Discovery**
- Expanded availability of hematopoietic cell transplantation
- Change in approach to older adults
- Increased importance of MRD

Kaplan-Meier Curves for Overall Survival

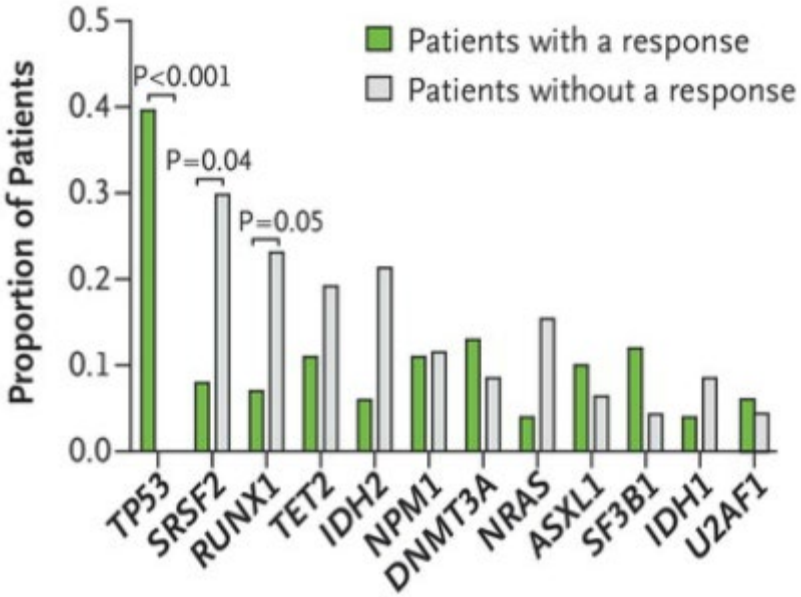


Papaemmanuil et al. N Engl J Med, 2016

Risk-Stratification and Prognostication of AML Informed by Mutational Profile



Patel et al. NEJM, 2012



Welch et al. NEJM, 2016

Gene Mutations Important in 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 not in inv(16)]; D816 worse than others[1], MRD poor prog factor in inv(16)[2]
IDH1 and 2	22%	*NPM1*	Favorable
TP53	7%	t-AML, Complex karyotype (60%)	Unfavorable

[1]*Yui et al. Ann Hematol, 2017;*
[2]*Kawashima et al. ASH, 2018 (abstr 438)*

New Agents With Regulatory Approval

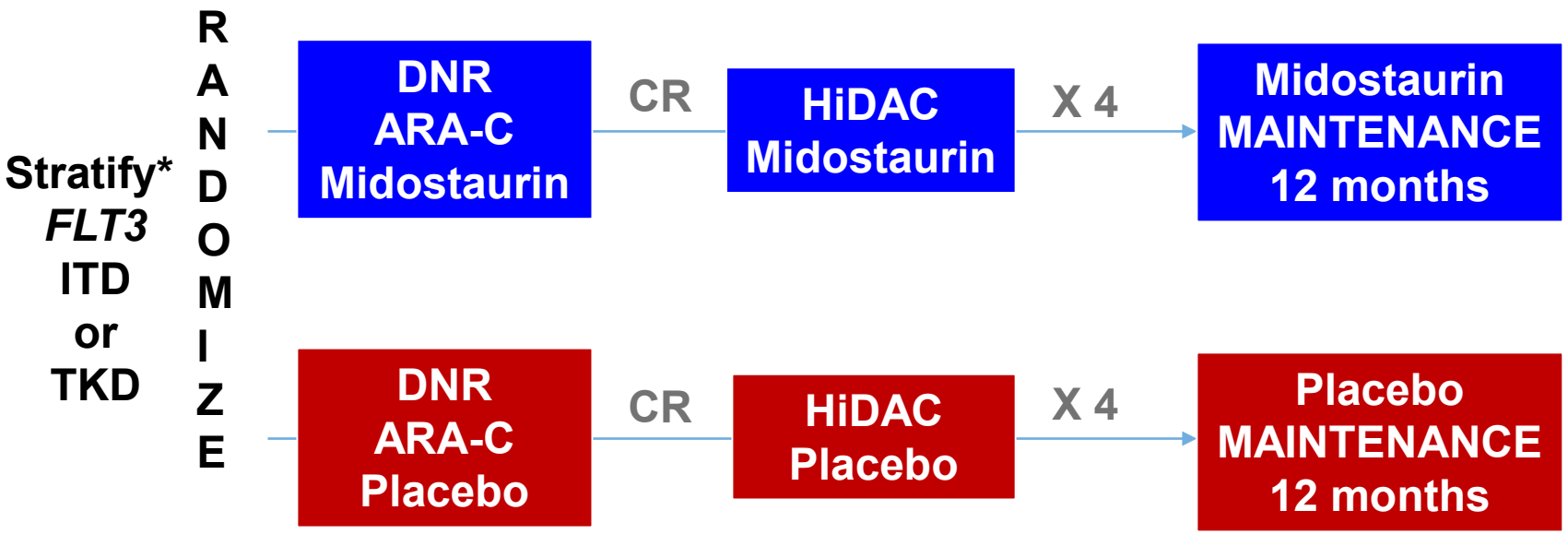
Agent	Target	Population	Setting
Midostaurin	*FLT3*	*FLT3-ITD* or *TKD*	Treatment naïve w chemo in induc and consol
Gemtuzumab ozogamicin	CD33	CBF and possibly intermed-risk	Treatment naïve CD33+ adults w chemo or single agent or Rel/refr adults and peds
CPX-351	Cytotoxic	t-AML or AML with MRC	Treatment naïve with t-AML or AML with MRC
Enasidenib/Ivosidenib	*IDH2/1*	IDH mutated	Rel/refr AML w m*IDH2/1*
Venetoclax	*BCL-2*	Age >/=75 or comormidities	Treatment naïve w HMA or LoDAC
Gilteritinib	*FLT3*	*FLT3-ITD or TKD*	Rel/refr AML
Glasdegib	Smoothened Receptor in Hedgehog pathway	Age >/=75 or comorbidities	Treatment naïve w LoDAC

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

RATIFY (C10603) Trial

Schema

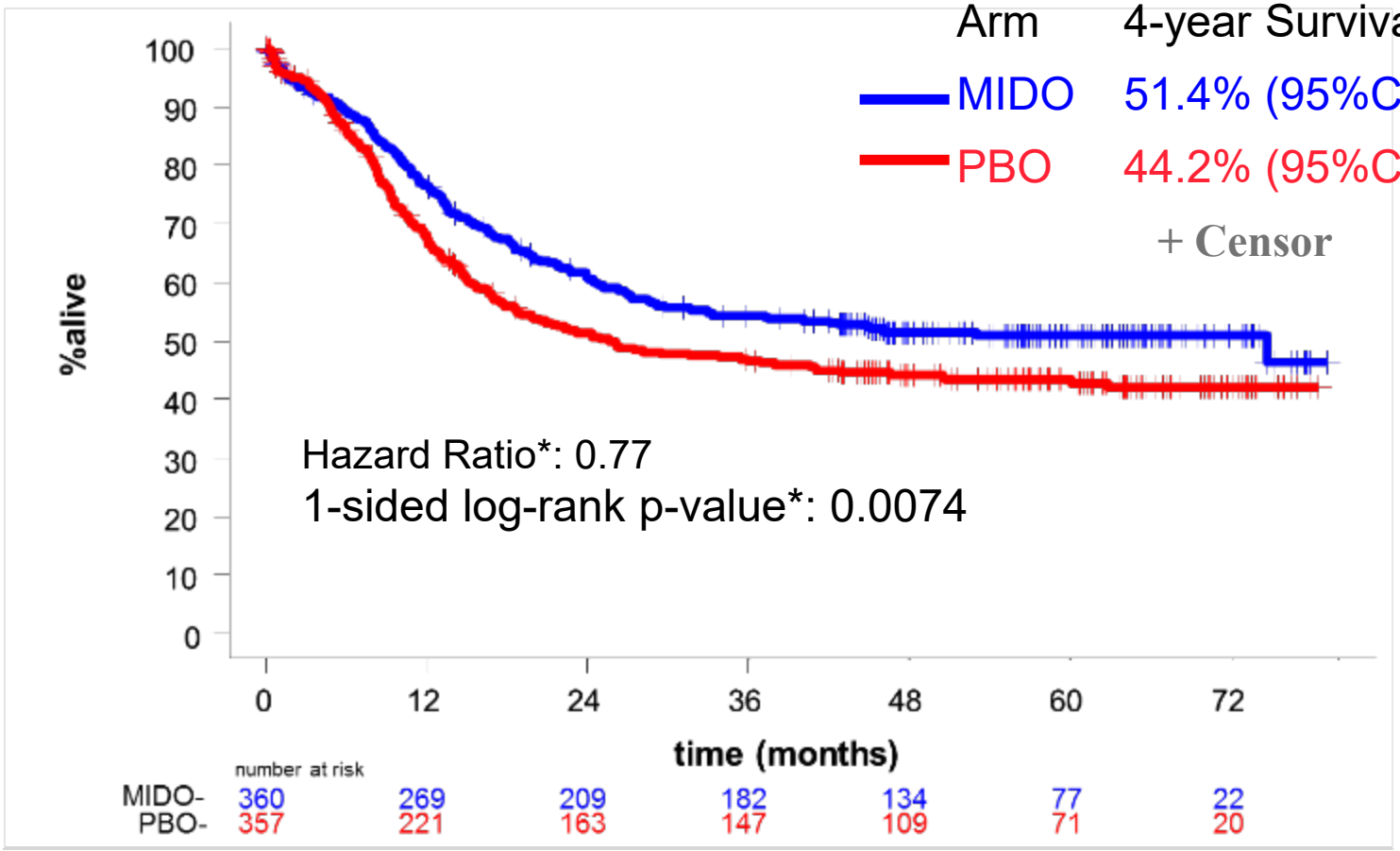


***Stratification: TKD; ITD with allelic ratio <0.7 'vs' ≥0.7**

Stone et al. N Engl J Med, 2017

Overall Survival

23% reduced risk of death in the Mido arm



Stone et al. N Engl J Med, 2017

Midostaurin in AML

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

- It has changed practice, but some caution warranted
  - OS increase 7%
  - Benefit more in *FLT3*-TKD than ITD
  - Men OS benefit ITD not TKD; woman trend for benefit OS TKD not ITD
  - Which phase of treatment important? Induction? Consol? Both?
  - Among least potent *FLT3* inhibitors
  - Role in maintenance unclear[1]
  - Beneficial effect of Midostaurin most pronounced in *NPM1*^{wt}/*FLT3*^{high} group, but some benefit among pts *NPM1*^{mut2}

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

Second Generation *FLT3* Inhibitors

- **Gilteritinib**
  - **Inhibits *FLT3-ITD and TKD***, in newly diagnosed pts w chemo and single agent maint CRc 89%[1]; Ph3 randomized trial in de novo disease underway;
- **Quizartinib**
  - Most potent *FLT3*i, **inhibits *FLT3-ITD*** and *PDGFa*, in R/R AML OS benefit vs std care[2]; Ph3 randomized trial in de novo disease underway
- **Crenolanib**
  - **Inhibits *FLT3-ITD, TKD,*** *PDGFa and b*, in trial with induction chemo CR 88% w 1 cycle[3]; randomized trial in newly diagnosed pts of chemo w crenolanib vs midostaurin underway

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[1]Pratz et al. ASH, 2018 (abstr 564); [2]Cortes et al. ASH, 2018 (abstr 563); [3]Wang et al ASH, 2016 (abstr 1071);

Gemtuzumab Ozogamicin: Reapproved

New Insights

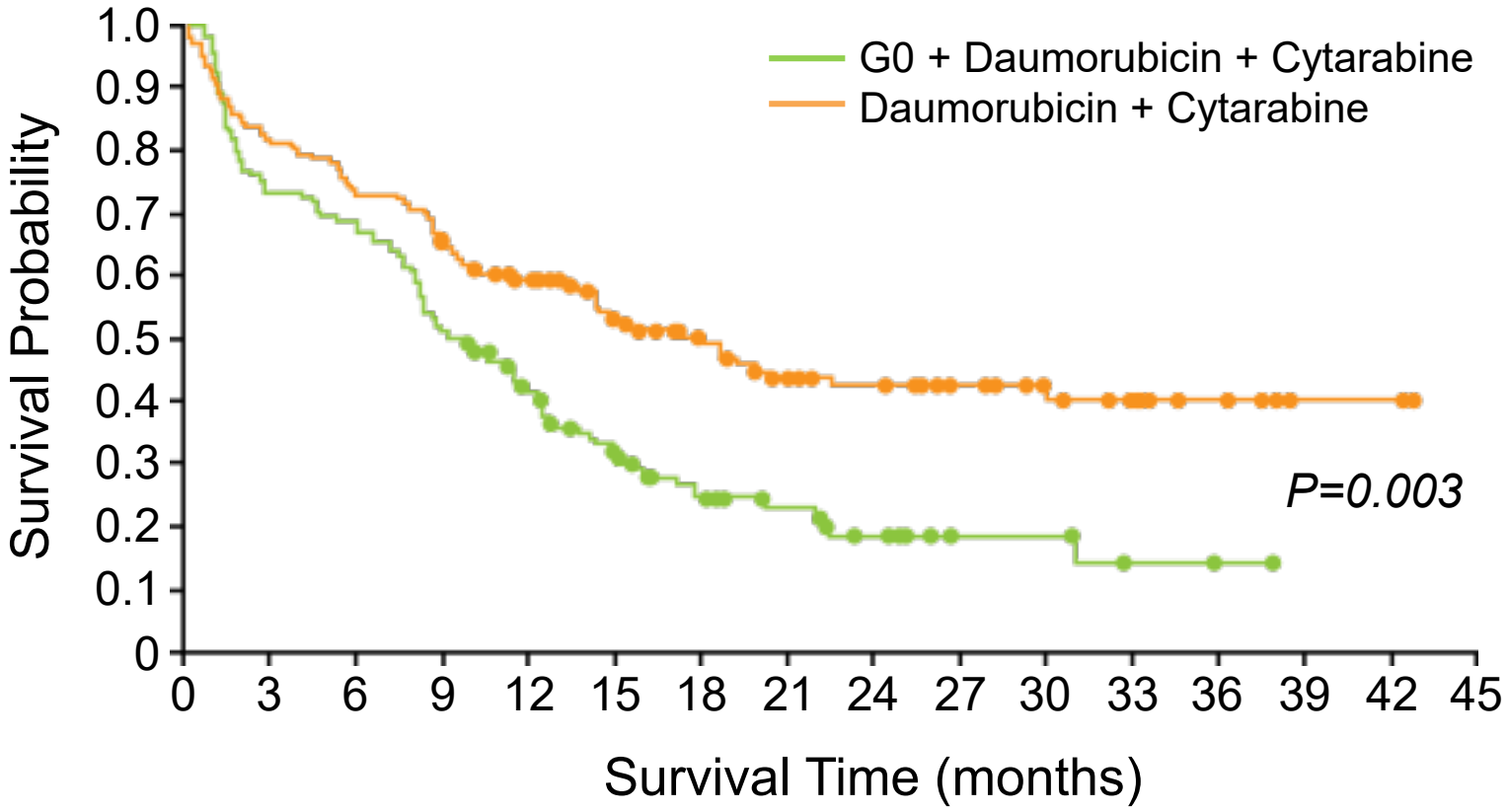
- CD33 single nucleotide polymorph rs121459419 C⟶T may be biomarker for response
- Fractionated schedule reduces toxicity
- OS benefit in favorable-risk and trend in intermediate-risk
- Risk of SOS/VOD 8% after allograft; higher if allo <3 mo of GO
- CD33 blast expression impacts outcome

Reapproved for: treatment naïve CD33+ adults w chemo or single agent or R/R adults and peds

Lamba et al. J Clin Oncol, 2017; Burnett et al. J Clin Oncol, 2011; Battipaglia et al. BBMT, 2017; Olombel et al. Blood, 2016; Lamba et al. ASH, 2017 (abstr 3826)

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

Kaplan-Meier Plot of Event-Free Survival
ALFA-0701 Trial

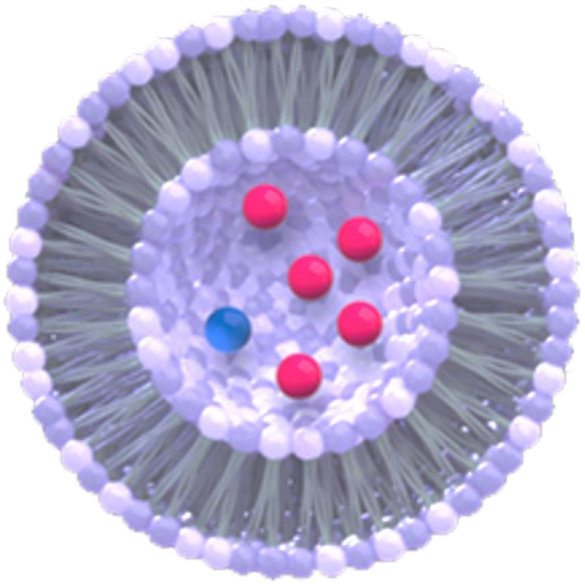


Castaigne. et al. Lancet, 2012 and update

Gemtuzumab Ozogamicin
Questions Emerge

- How does GO compare to other regimens for rel/ref disease?
- How should transplant be affected by GO in induction?
- What is the role in *NPM1*+ AML (high CD33 expression)?
- What is the role in APL (high CD33 expression) in ATRA/ATO era?

CPX-351 Uses a Nano-Scale Delivery Complex



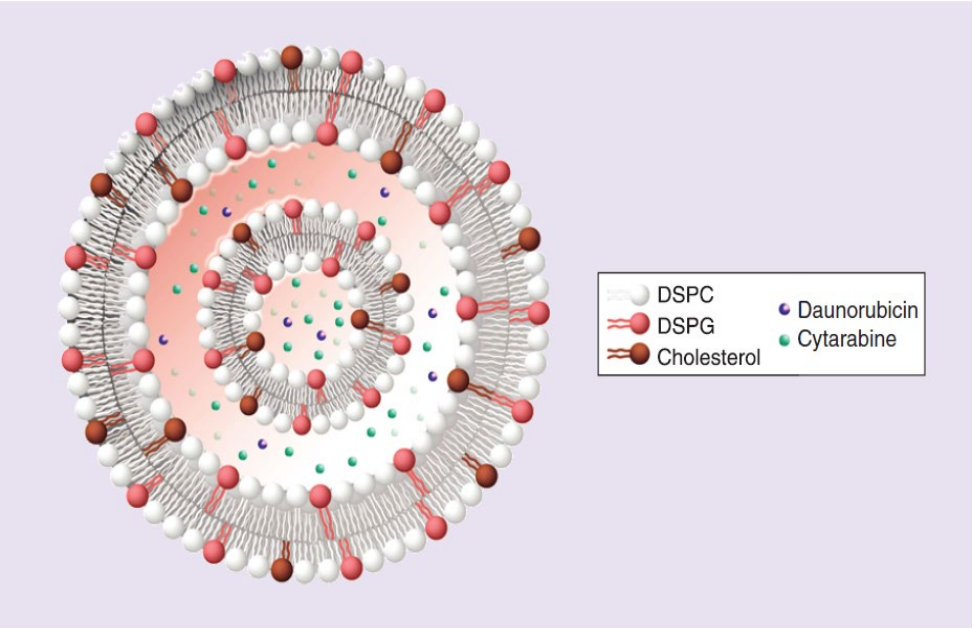
- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

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

CPX-351

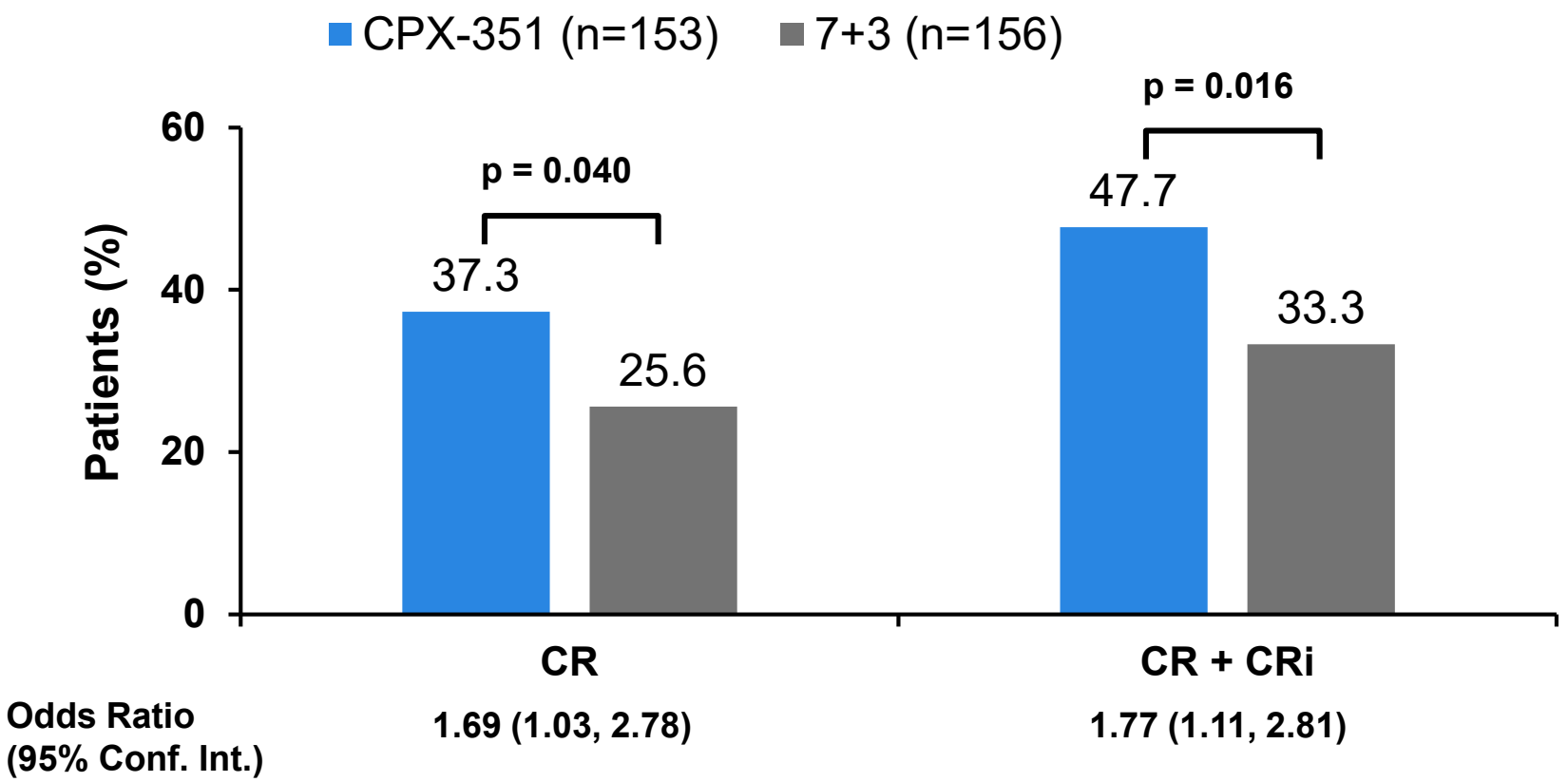
- A fixed 5:1 **synergistic** molar ratio of cytarabine to daunorubicin is maintained for a **prolonged** period of time[1]
- CPX-351 accumulates and persists in the bone marrow in **high concentrations**[1]
- CPX-351 is **preferentially taken up** by leukaemic cells vs normal bone marrow cells[1]

Schematic representation of CPX-351[2]



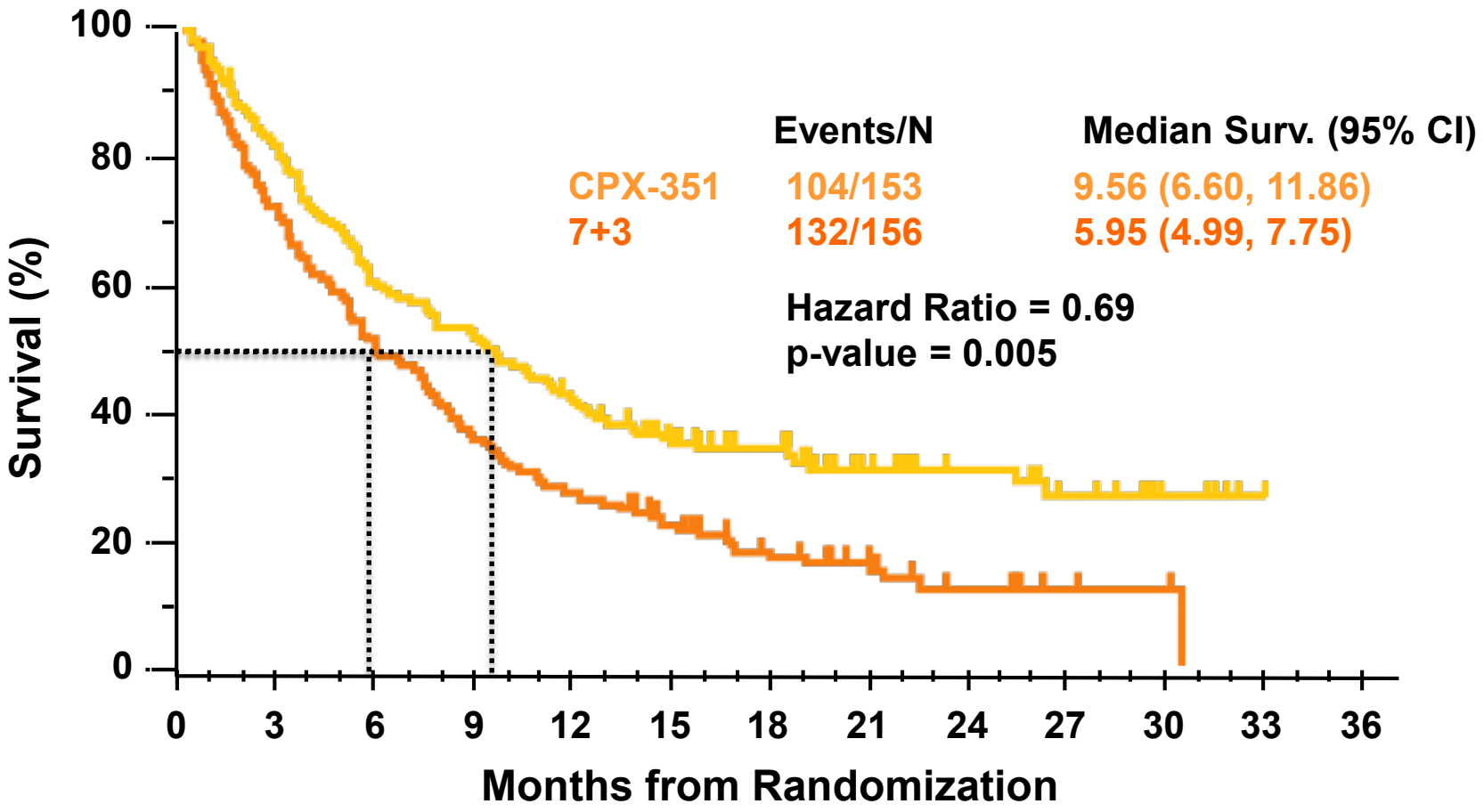
1. Jazz Pharmaceuticals. Vyxeos® 44mg/100mg (danorubicin/cytarabine) Summary of Product Characteristics 2018;
2. Tolcher AW, Mayer LD. Future Oncol, 2018

Patients Treated With CPX-351 Exhibited Statistically Significant Improvements in Response Rate in sAML Ages 60-75



Lancet et al. J Clin Oncol, 2018

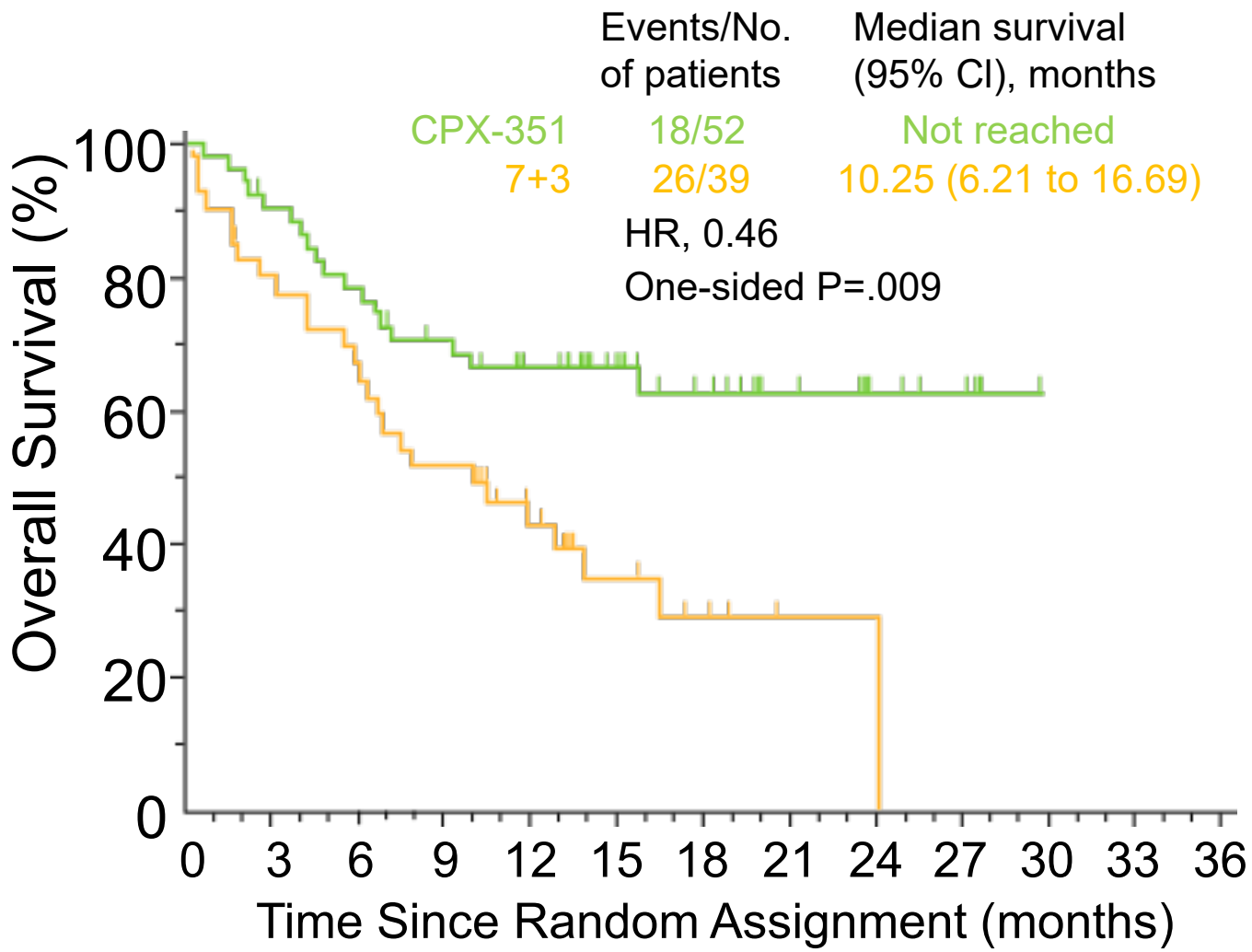
Overall Survival Was Greater in the CPX-351 Arm Compared to the 7+3 Arm



Lancet et al. J Clin Oncol, 2018

Impact of CPX-351 on Transplant Outcome

Overall Survival

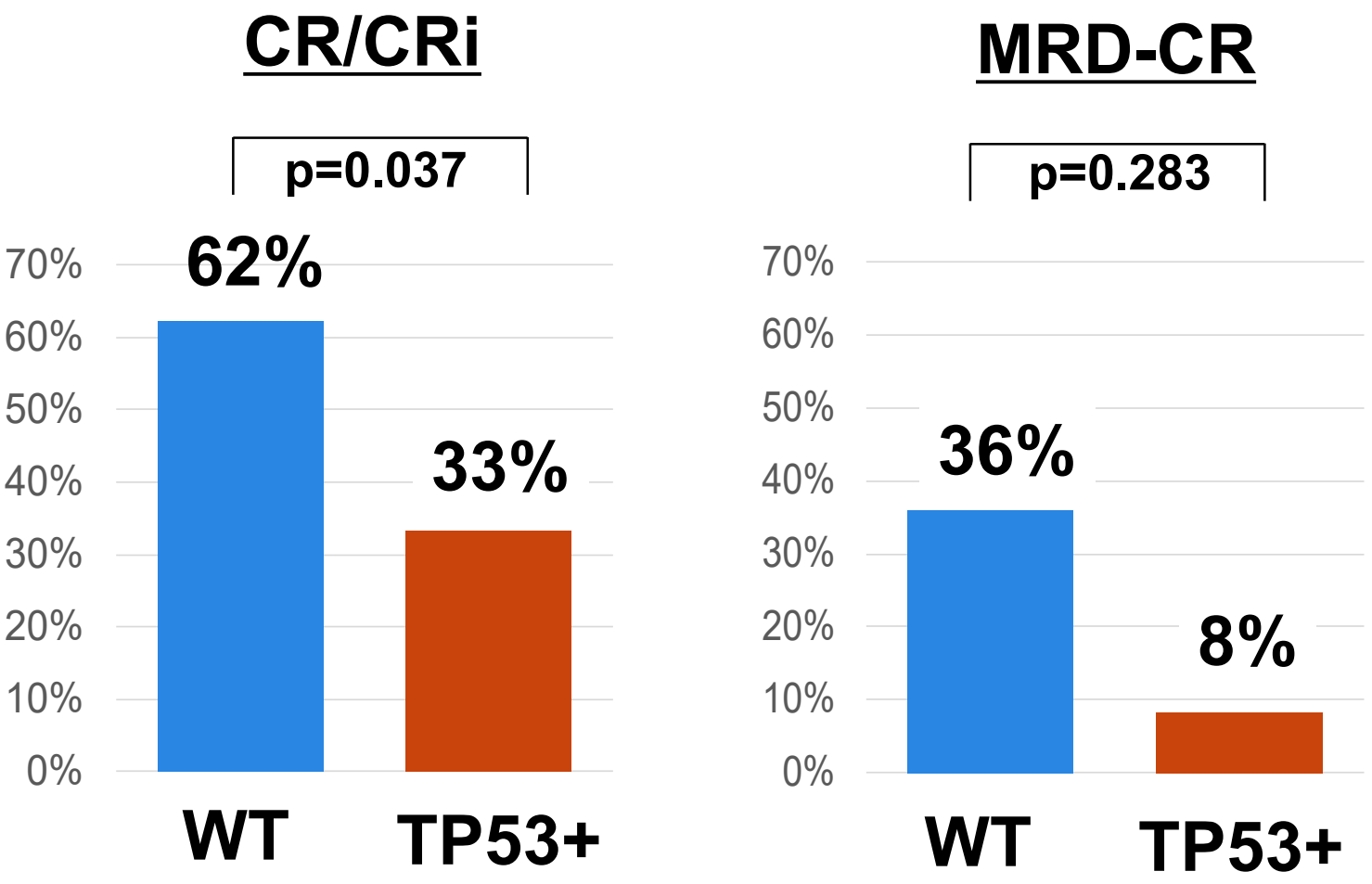


Lancet et al. J Clin Oncol, 2018

CPX-351
Questions Emerge

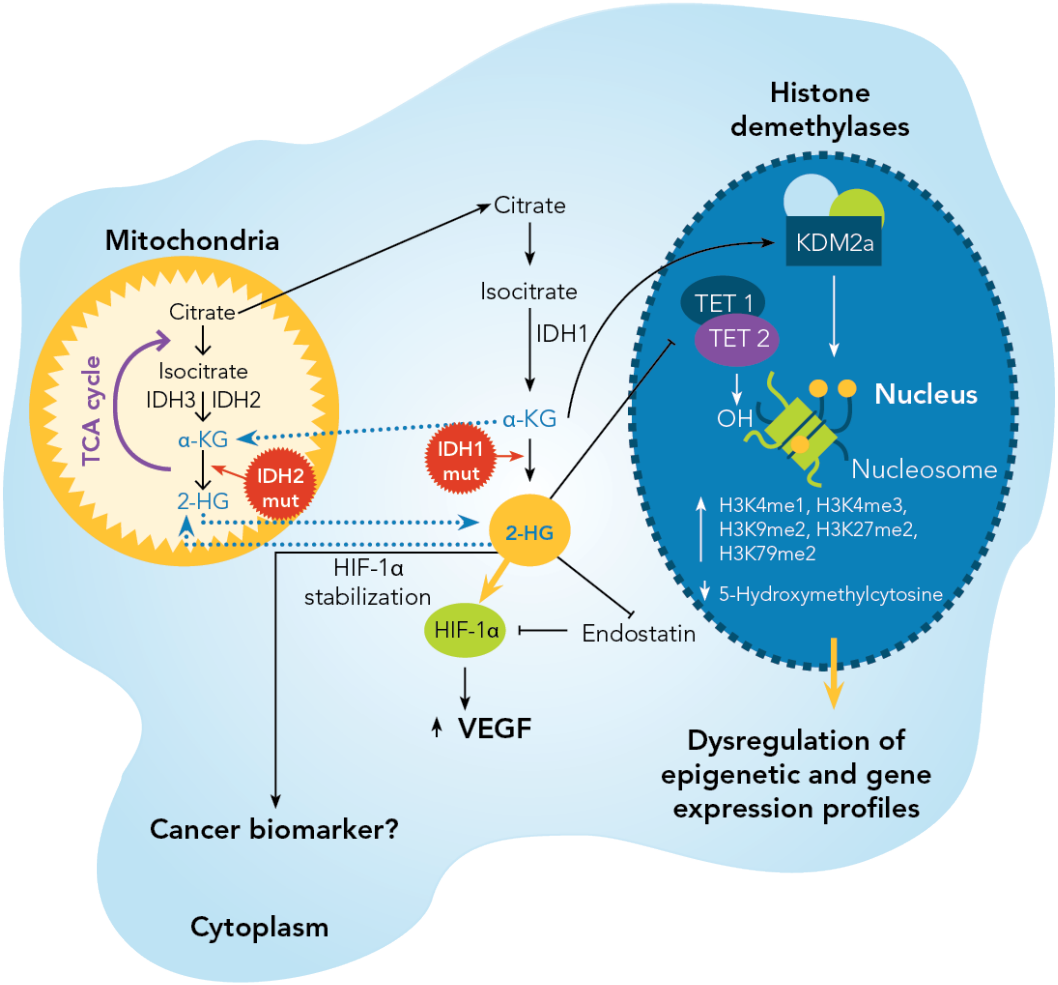
- Why is CPX-351 more effective in t-AML and AML with MRC?
- Why is outcome after allograft better with CPX-351 than with with 7 + 3? (less toxicity? less MRD?)
- Will CPX-351 be effective alone or when combined with other agents in adverse subtypes?

TP53 Mutations Predict Lower Rates of CR/CRi Following CPX-351



Goldberg et al. ASH, 2019 (abstr 1433)

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

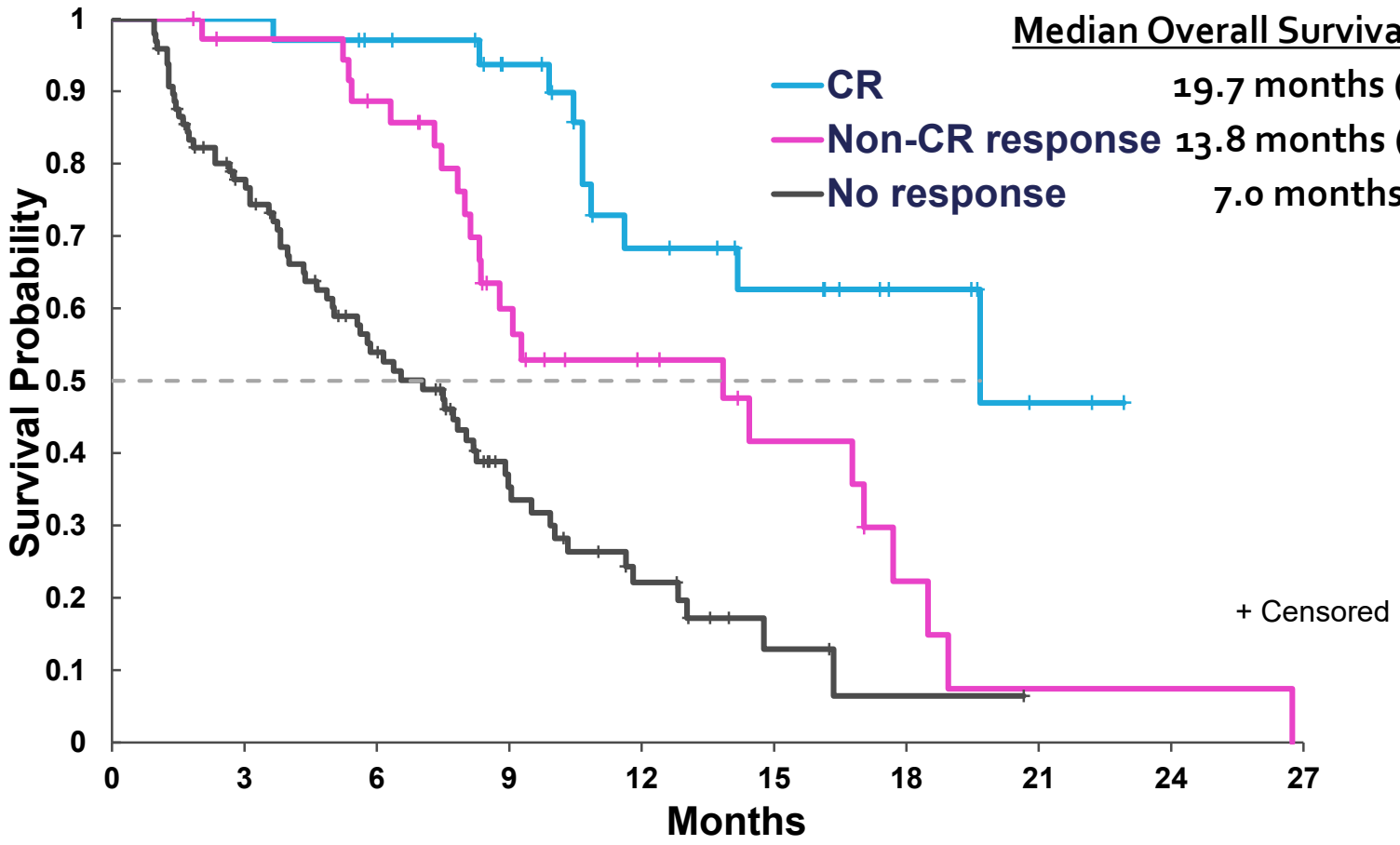
Prensner et al. Nature Med, 2011

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] INDY.03.08.19	**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. Blood, 2017

Overall Survival by Best Response



Stein et al. Blood, 2017

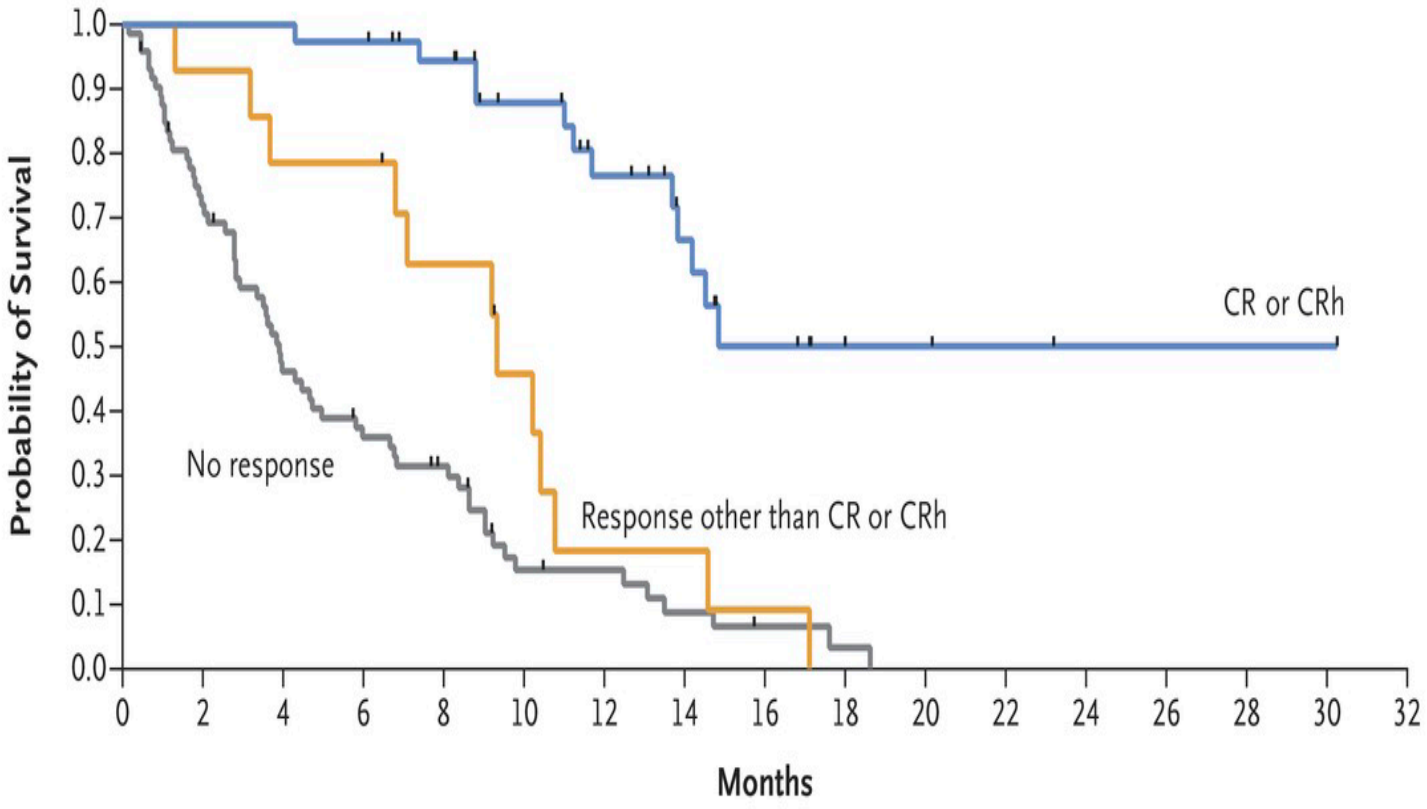
Ivosidenib or Enasidenib Plus Chemotherapy Phase I Trial

Best Overall Response Summary

	Ivosidenib (AG-120) + CT			Enasidenib (AG-221) + CT		
Response, (%)	All (n=41)	De novo (n=28)	sAML (n=13)	All (n=77)	De novo (n=45)	sAML (n=32)
CR+CRi/CRp	78	93	46	69	73	63
CR	66	79	39	55	62	44
CRi/CRp	12	14	8	14	11	19
MLFS	5	-	15	13	9	19
PR	2	0	8	1	-	3
Persistent disease	5	4	8	12	13	9
NE	10	4	23	5	4	6

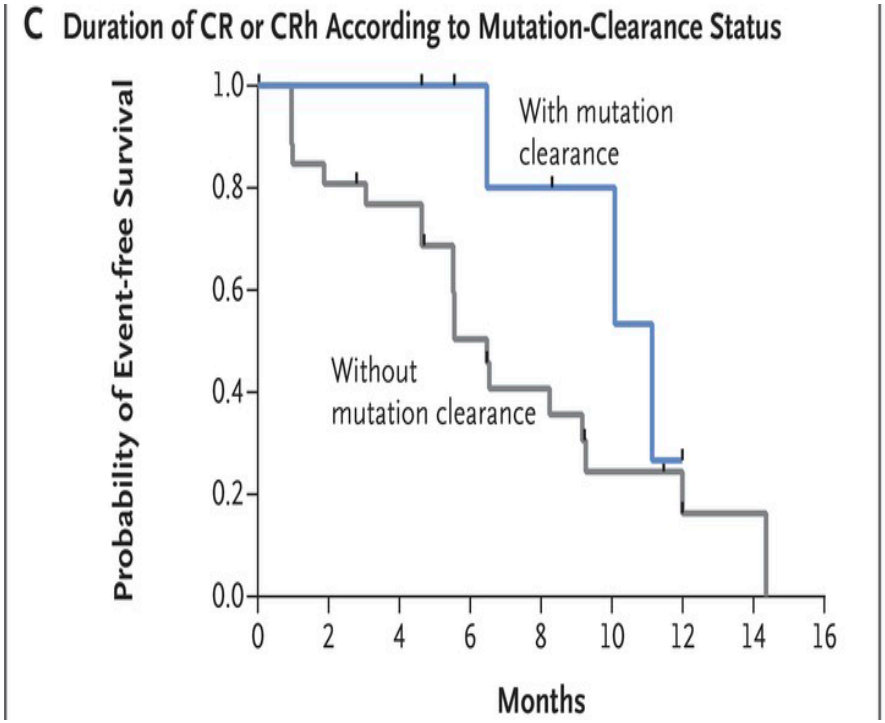
Stein et al. ASH, 2018 (abstr 560)

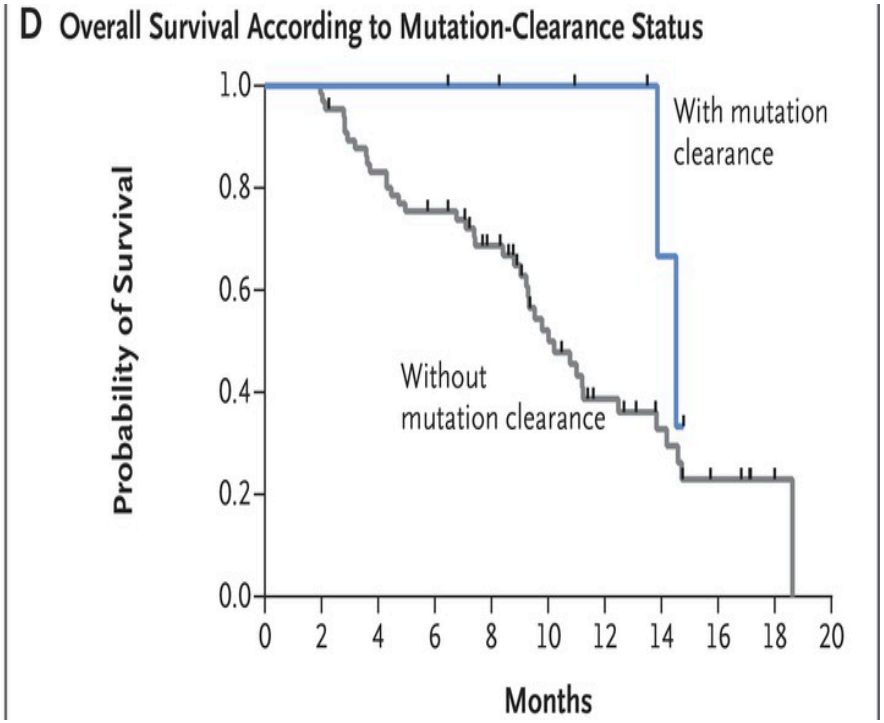
Overall Survival According to Response to Ivosidenib in *IDH1* Mutated Relapsed or Refractory AML



DiNardo et al. N Engl J Med, 2018

Duration of CR or CRh and OS According to Mutation Clearance Status in IDH-1 Mutated AML





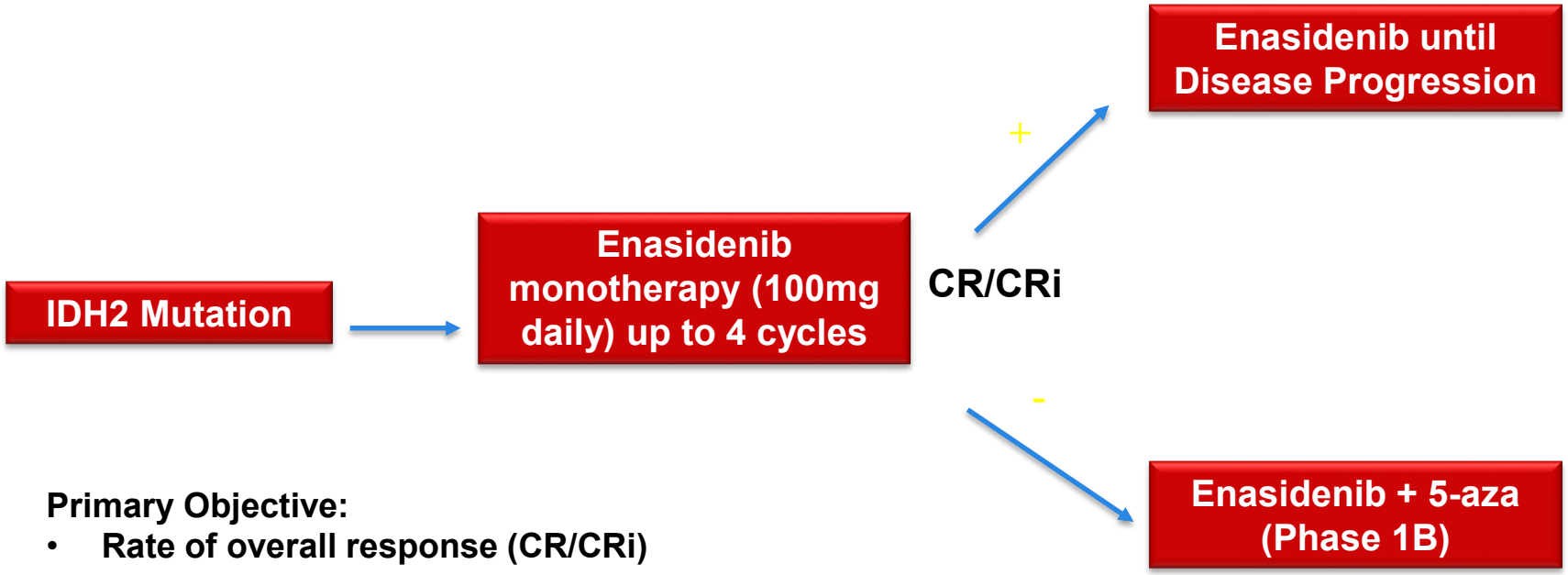
DiNardo et al. N Engl J Med, 2018

Frequently Asked Questions Re: *IDH2*

- Does molecular CR occur? Yes, about 30%
- Does differentiation syndrome occur? Yes (12-19%), and can occur late (d48,10-340)
- How long does it take to achieve CR? 21% by C3, 68% by C5, 82% by C7
- Are molecular signatures predictive of response or nonresponse? RAS mutations assoc with NR
- What is the longest duration of CR? >36 months

Norsworthy et al. ASH, 2018 (abstr 288)

BEAT AML
Substudy 3 – Study Design and Objectives



Primary Objective:

- **Rate of overall response (CR/CRi)**

Key Secondary Objectives:

- **To explore the toxicity profile of combining Enasidenib with azacytidine**
- **Estimate progression free and overall survival in patients treated with Enasidenib**

Response in Newly Diagnosed *IDH2* Mut AML

	N=27*
Overall response (CR, CRi), n (%)	**12 (44.4)**
Best response, n (%)	
CR	10 (37)
CRi	2 (7.4)
MLFS	0 (0)
No response (PR, SD, TF/PD) n (%)	15** (55.6)
Early Death (death within 30 days)	0

Median number of enasidenib treatment cycles: 5 (range 1-14+)

Stein et al. ASH, 2018 (abstr 287)

IDH Inhibitors

Fundamental Questions for Future Research

- Do co-mutations (beyond *RAS* and *MAPK*) influence response?
- Will combinations with other targeted therapies be more effective?
- What are other mechanisms of resistance? Second site mutation in trans position[1]

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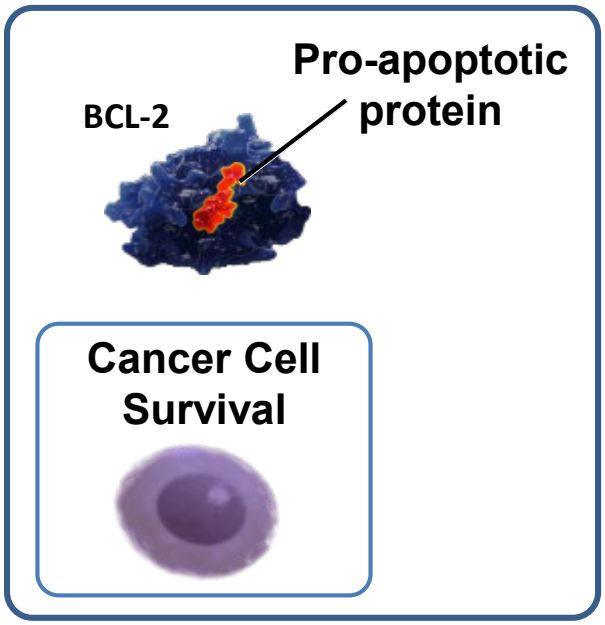
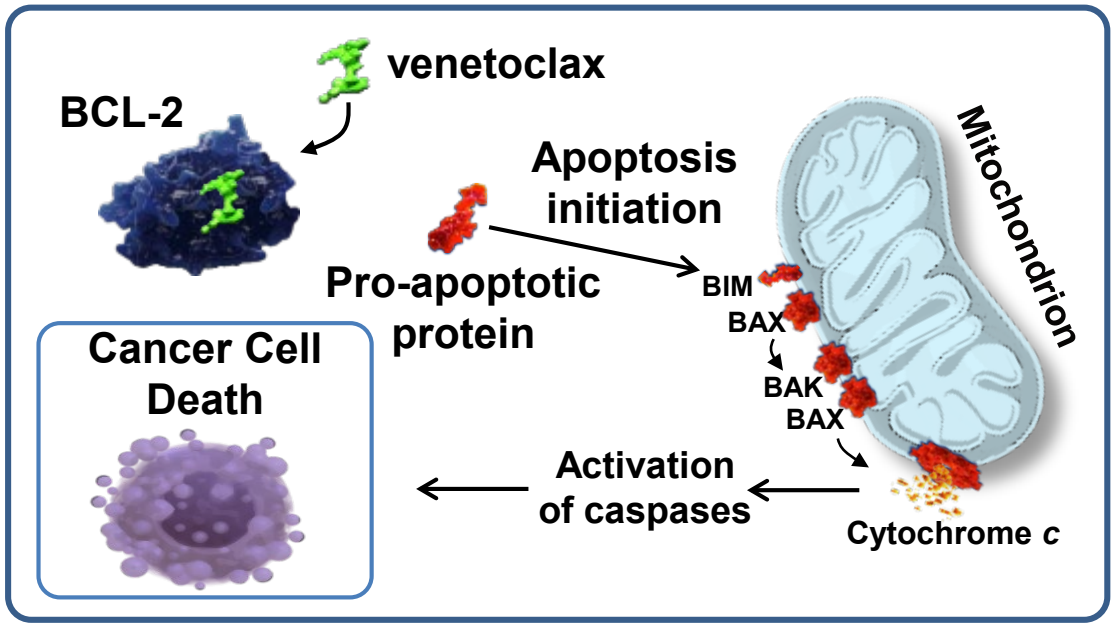
[1]*Intlekofer et al. Nature, 2018*

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]

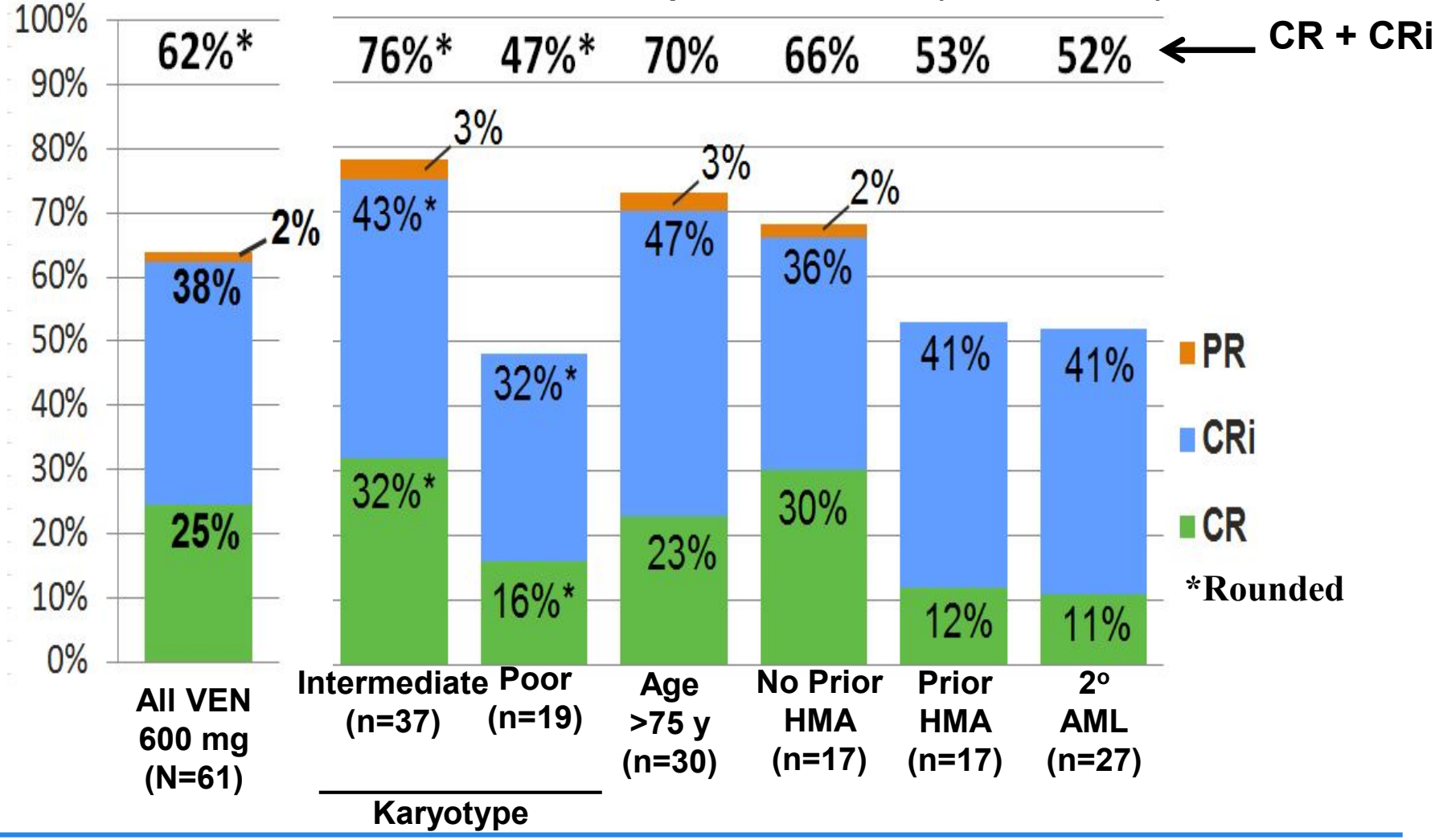


Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]

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, 2017 (abstr 890)

Venetoclax + LoDAC in Previously Untreated Older Adults with AML Not Eligible for Intensive Chemotherapy

- N=82
- CR 26%, CR/CRi 54%
- Med dur of response for CRs 14.8 mo
- CR/CRi in specific mutations
  - *TP53* 30%
  - *IDH1/2* 72%
  - *FLT3* 44%
  - *NPM1* 89%
- OS med 10.1 mo, estimate at 24 mo 27%
- MRD neg 32%
- Transfusions indep RBC 49%, plts 65%

Wei et al. ASH, 2018 (abstr 284)

Venetoclax + HMA in Older Newly Diagnosed Pts Ineligible for Intensive Chemotherapy

• N=115	Aza 84, DAC 31
• Med age:	75, 72, respectively
• Secondary AML:	25% and 29%
• Poor risk cyto:	39% and 48%
• CR/CRi:	70% and 75%
• Med time to first response:	1.2 mo and 1.9 mo
• Med OS:	14.9 mo and 16.2 mo
• Among CR/CRi's	MRD neg 45%

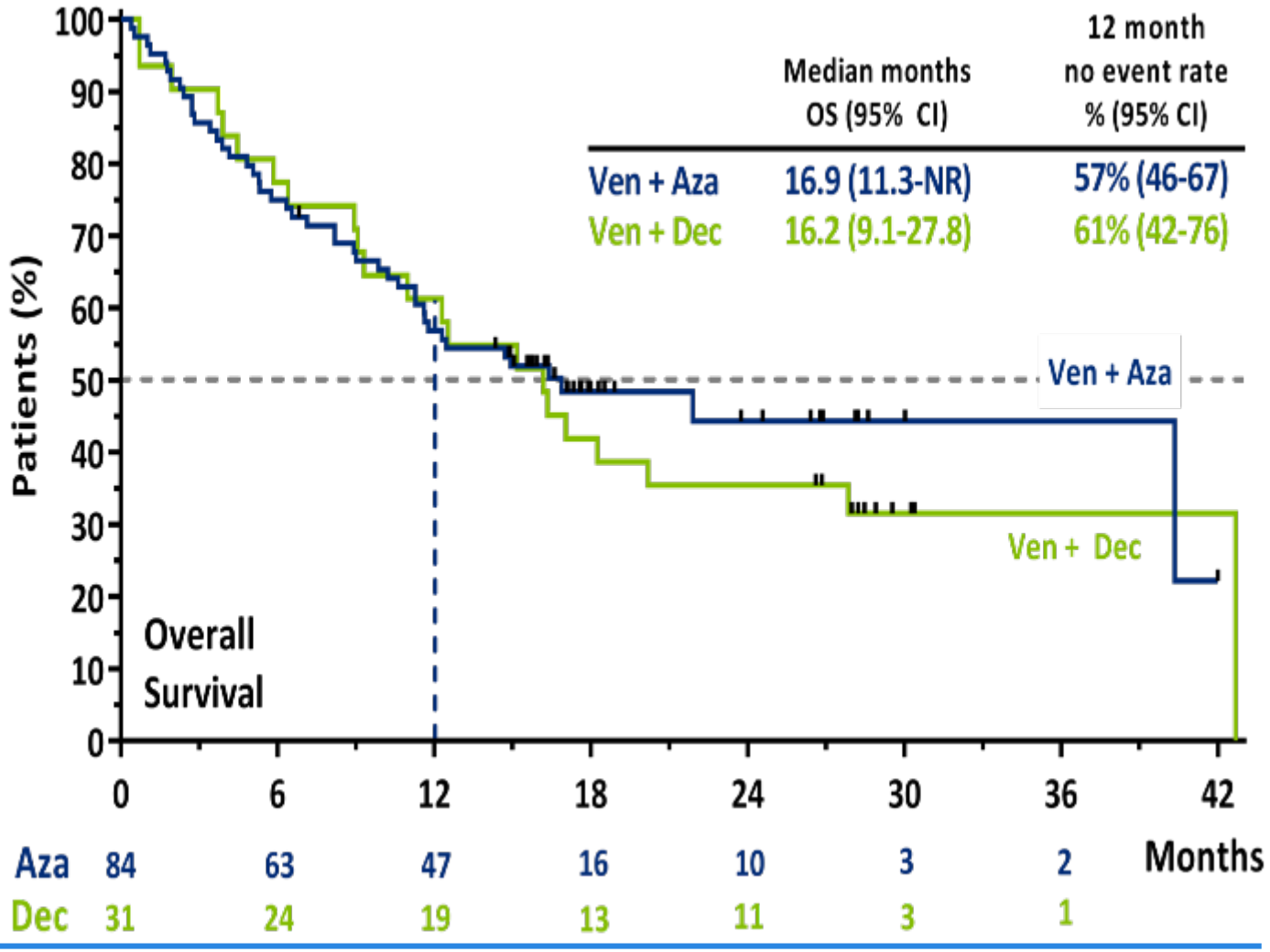
Pollyea et al. ASH, 2018 (abstr 285)

Overall Survival in Untreated Older AML

Median Follow-up

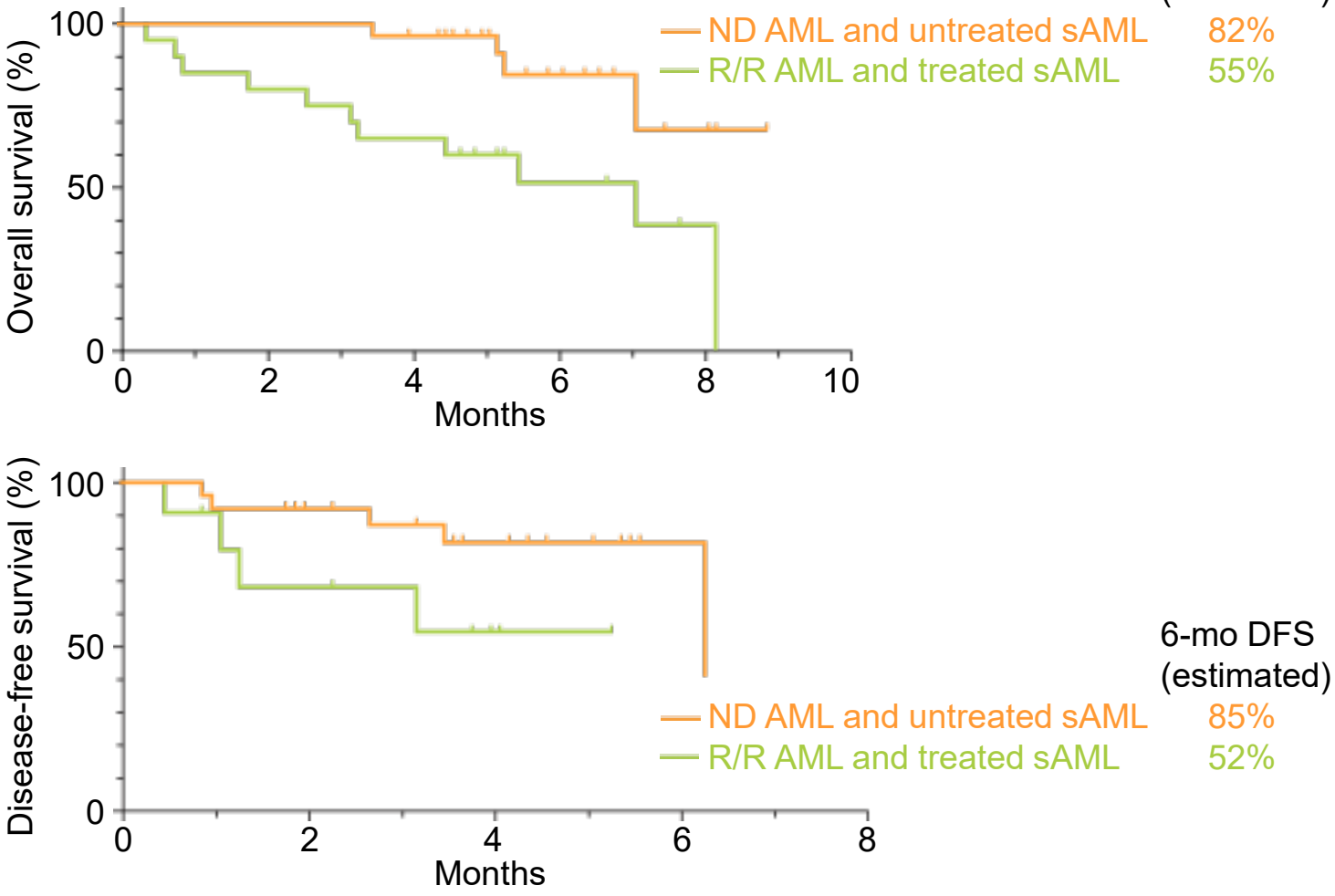
Venetoclax + azacitidine
14.9 months (range 0.4–42.0)

Venetoclax + decitabine
16.2 months (range 0.7–42.7)



Pollyea et al. ASH, 2018 (abstr 285)

DEC10-VEN in AML/MDS
Disease-free Survival



Maiti et al. ASH, 2018 (abstr 286)

AML Treatment Strategies in 2019

AML subgroup	Candidate for intensive chemo	Not candidate for intensive chemo
CBF	GO + chemo	HMA/LoDAC + Venetoclax*
CD33 pos	GO + chemo, ? If pretransplant	GO d1,8 or HMA/LoDAC + Venetoclax
t-AML or AML w/MRC (incl complex cyto)	CPX-351 ind/consol, transplant	HMA/LoDAC + Venetoclax*
***TP53* mutant**	Chemo or decitabine x 5 or 10d +/- Venetoclax	Decitabine x 5 or 10d +/- Venetoclax
***FLT3*+**	Mido + chemo ind/consol/maint, transplant	?Aza + sorafenib or HMA/LoDAC + Venetoclax
***IDH*1/2+**	Chemo (on trial with IDHi)	HMA/LoDAC + Venetoclax*
Marker -	Chemo	HMA/LoDAC + Venetoclax*

*HMA/LoDAC + Venetoclax awaiting phase III data

AML Treatment Strategies in 2019: Rel/Ref

AML subgroup	Candidate for intensive chemo	Not a candidate for intensive chemo
R/R *IDH2*+	Enasidenib	Enasidenib
R/R *IDH1*+	Ivosidenib	Ivosidenib
R/R *FLT3*+	Gilteritinib	Gilteritinib
R/R *TP53* mutant	Chemo vs decitabine x 5 or 10d +/- Venetoclax	Decitabine x 5 or 10d +/-
R/R CD33+	Chemo or GO	HMA/LoDAC + Venetoclax* or GO
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*)

Summary and Conclusions

- AML is a heterogeneous disease of diverse somatic genetic mutations
- Molecular genetics inform classification, prognosis, and therapy
- Era of precision medicine is here
- Many novel agents with unique mechanisms of action now available with more to come
- Treatment options are (finally) expanding

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