Novel Therapeutic Strategies in Acute Myeloid Leukemia:
Our Cup Runneth Over

Martin S.Tallman, M.D.
Chief, Leukemia Service
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, NY

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- Research Funding
  - Cellerant
  - AROG
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  - Orsenix
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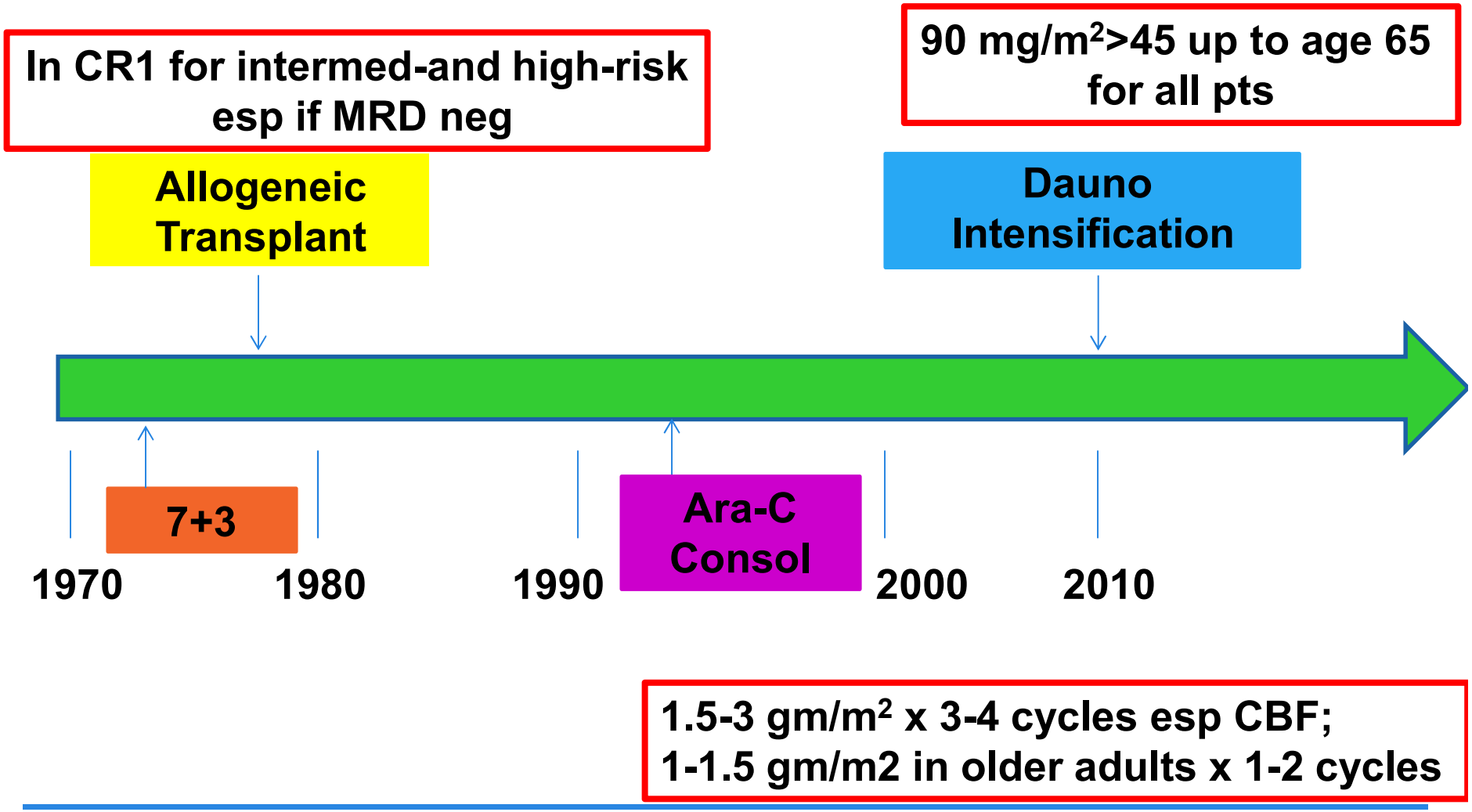
  - Abbvie
  - Bioline
  - Biosight
  - KAHR
  - Delta Fly Pharma
  - Jazz
  - Oncolyze
- Off label use
  - Venetoclax
  - Gilteritinib
  - Quizartinib
  - Crenolanib
  - GMI-1271
  - Idasanutlin

Objectives

- Describe the major advances in AML over the past 4 decades
- Demonstrate the importance of genetic profiling for prognosis and therapy
- Discuss the 8 newly approved agents for AML
- Provide treatment strategies in the era of targeted therapy

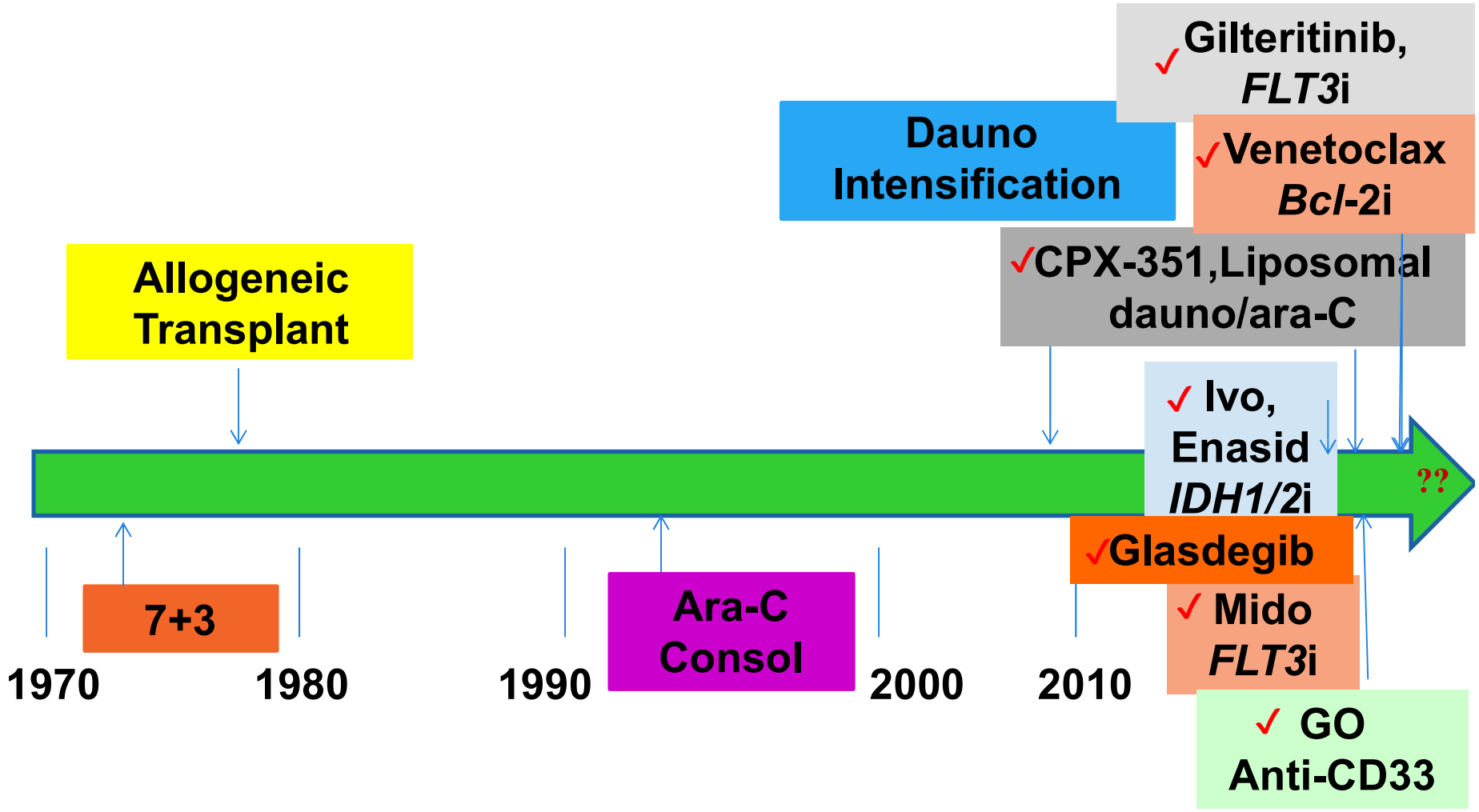
Practice Changing Treatments in AML 1973-2017



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



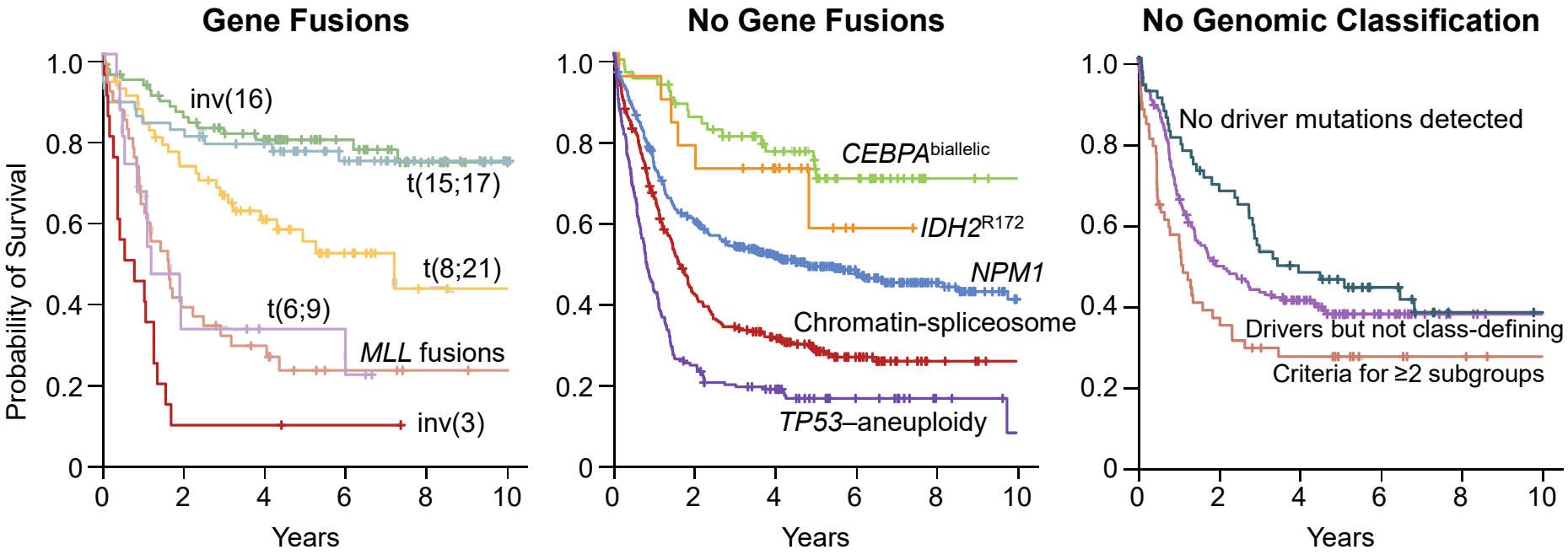
Will They Have a Clinically Meaningful Impact?

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. J Clin Oncol, 2018; Castaigne et al. Lancet 2012; Cortes et al. Leukemia, 2019; Dinardo et al. Blood, 20129

Recent Progress in AML

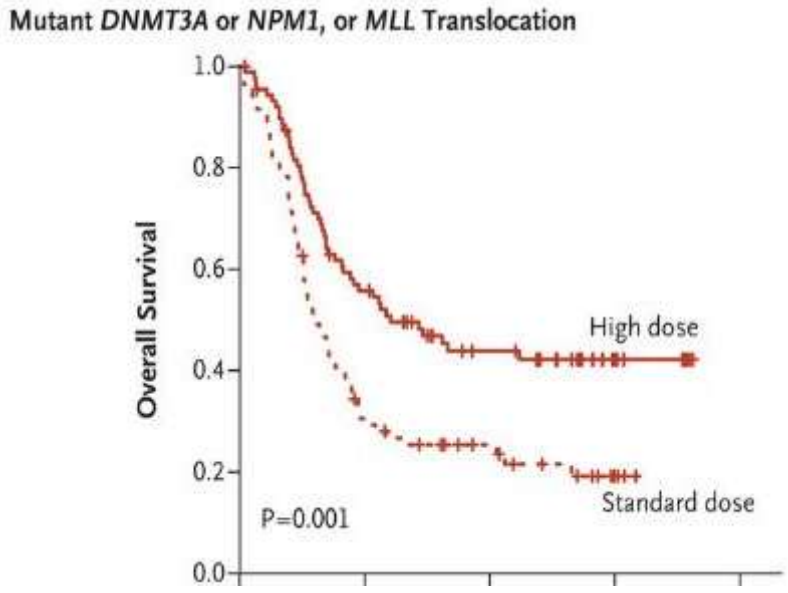
- Insights into genetic pathogenesis/integrated genetic profiling
- Intensified induction and less intensive postremission strategies
- **Drug Discovery**
- Expanded availability of hematopoietic cell transplantation
- Change in approach to older adults
- Increased importance of MRD

Kaplan-Meier Curves for Overall Survival

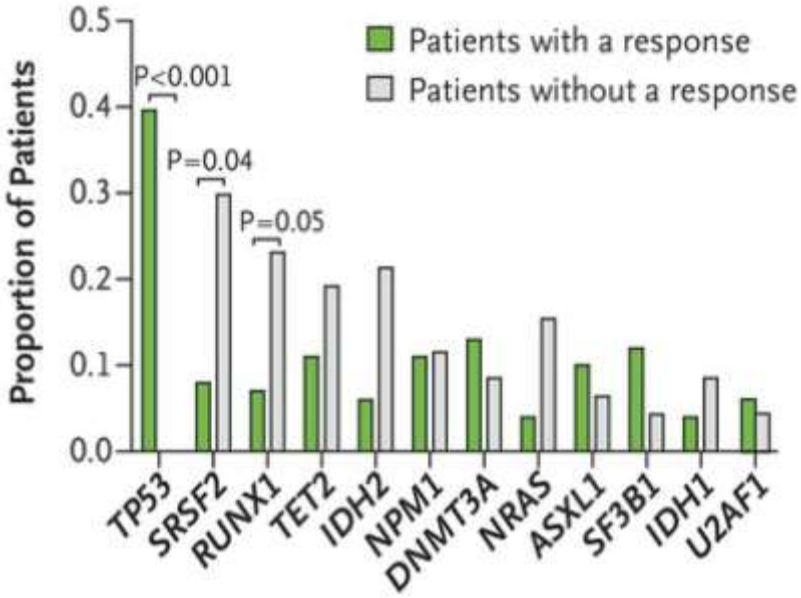


Papaemmanuil et al. N Engl J Med, 2016

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 prognostic 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 w t-AML or AML with MRC
Ivosidenib/Enasidenib	*IDH1/2*	*IDH1/2+* Ivo in age >/=75 or comorbidities	Rel/refr AML Ivo in treatment naive
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	Age >/=75 or comorbidities	Treatment naïve w LoDAC

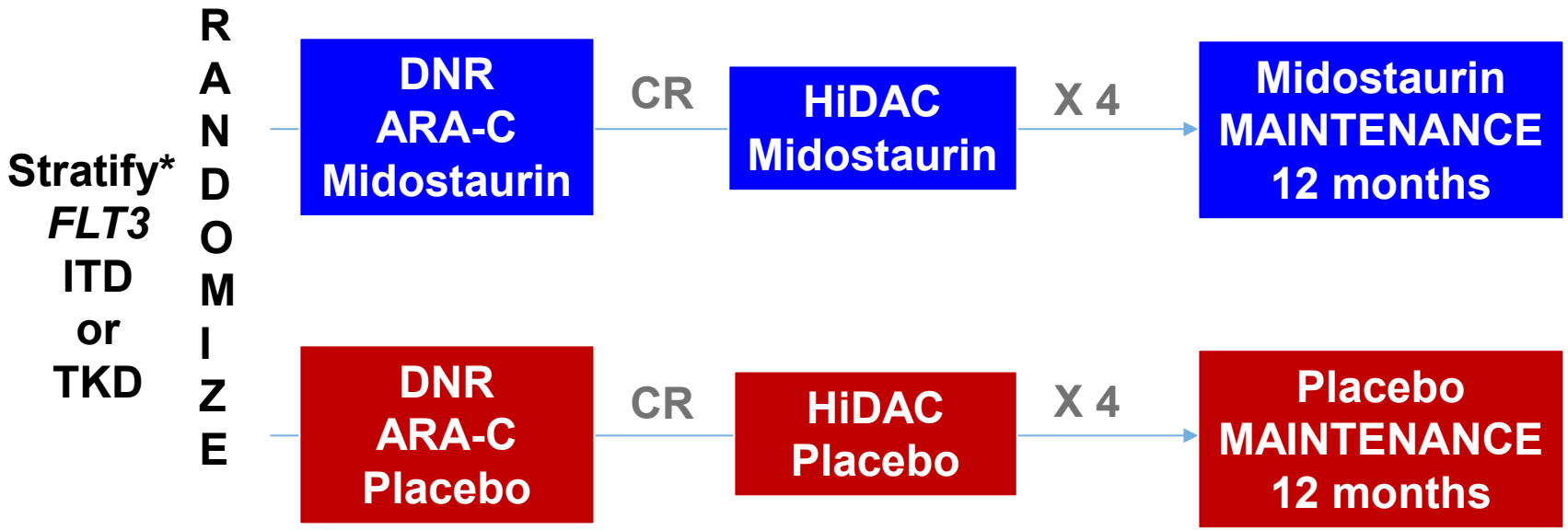
FLT3 Mutations in AML

Background

- 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

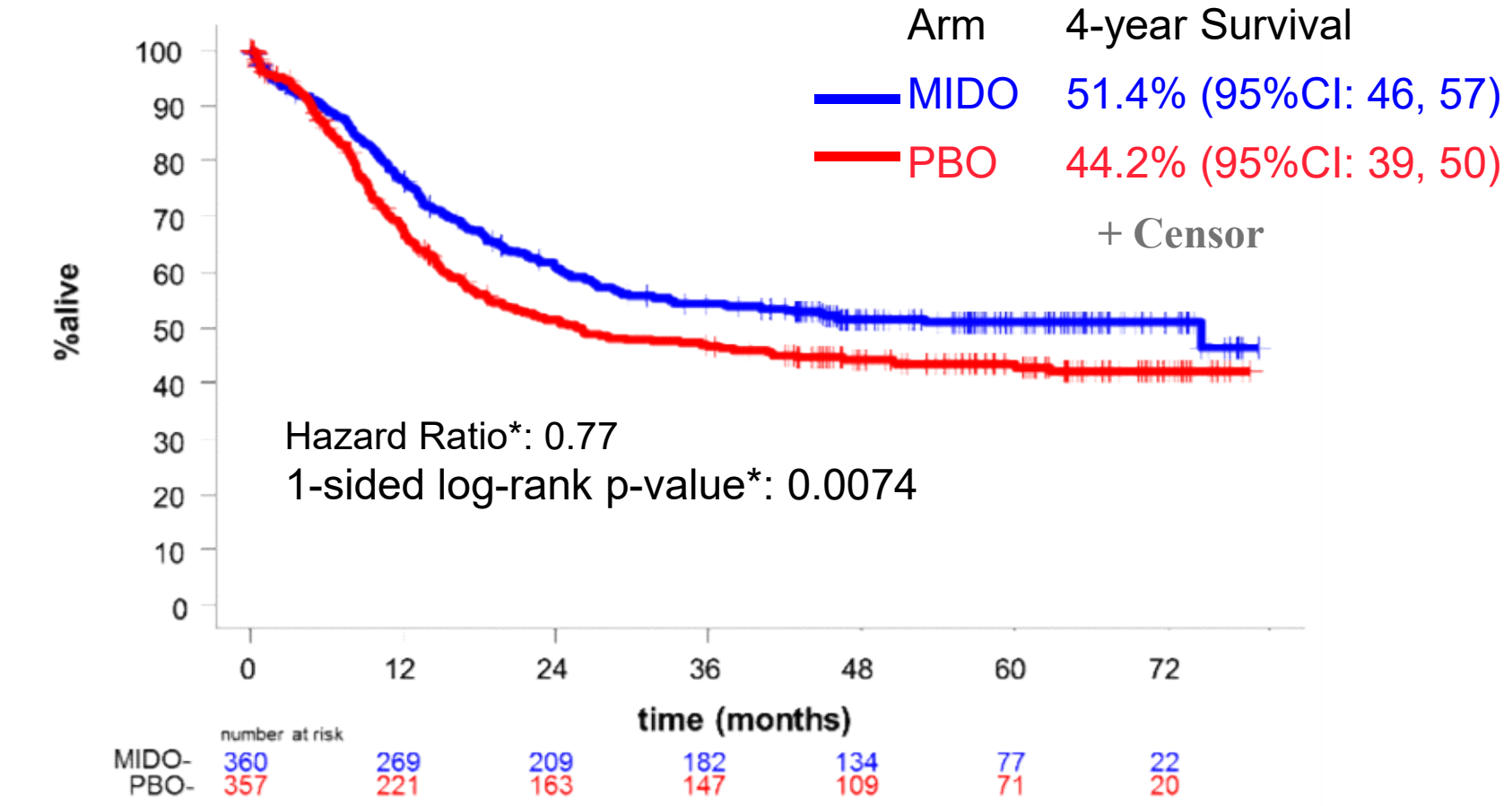


***Stratification: TKD; ITD with allelic ratio <0.7 'vs' ≥0.7**

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
Limitations

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

- It has changed practice, but will it have a clinically meaningful impact?
  - 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?
  - Among least potent *FLT3* inhibitors
  - Role in maintenance unclear[1]
  - Beneficial effect of Midostaurin most pronounced in *NPM1*^{wt}/*FLT3*^{high} group but benefit also in *NPM1*pos[2]

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**

– Inhibits *FLT3-ITD* and *PDGFa*, most potent FTLT3i, 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 ether crenolanib vs midostaurin underway[4]

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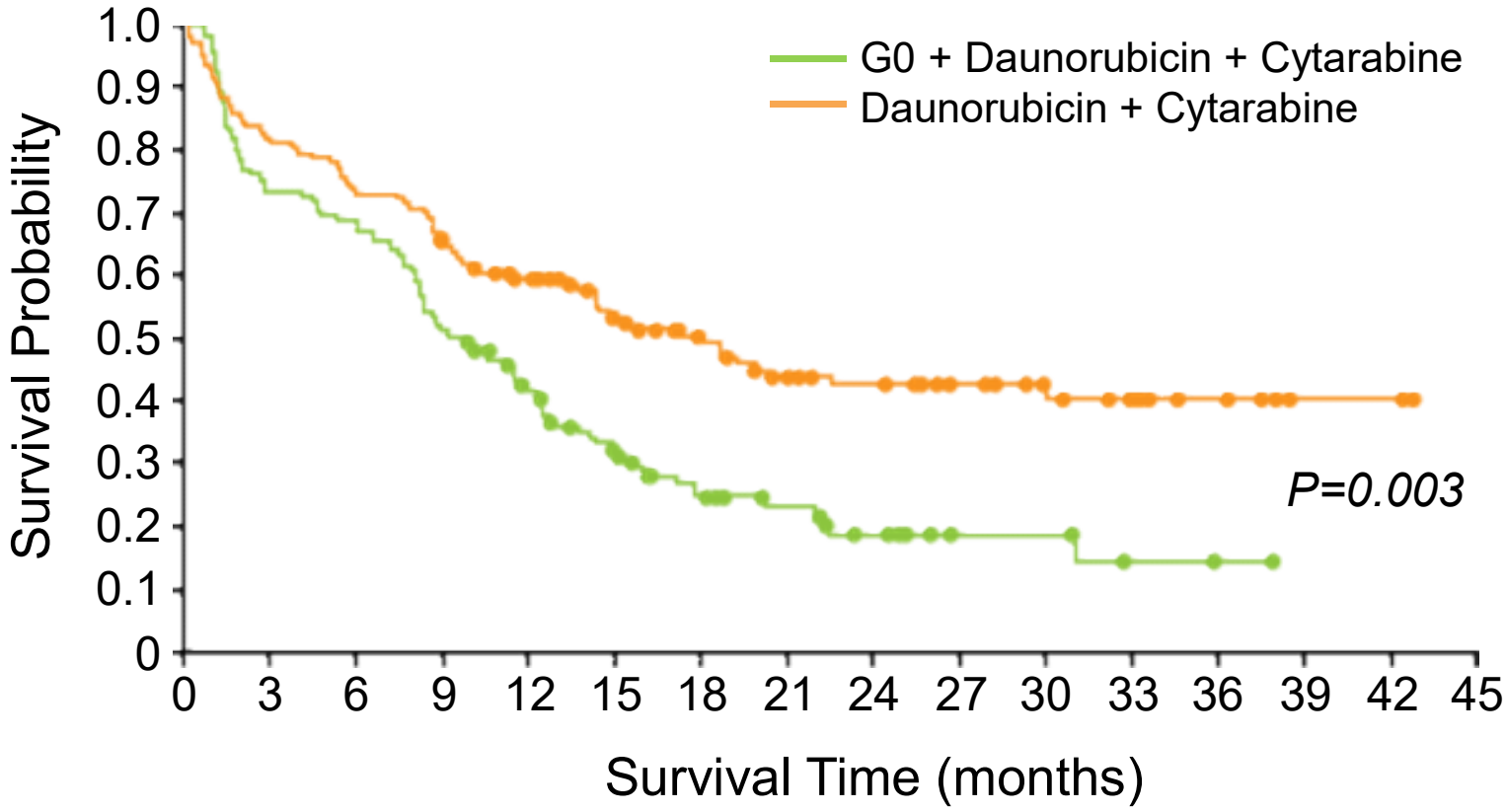
[1]Pratz et al. ASH, 2018 (abstr 564); [2]Cortes et al. Lancet Oncol, 2019;
[3]Wang et al ASH, 2016 (abstr 1071); Stone et al. ASCO, 2019 (abstr 7068)

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: Reapproved

New Insights

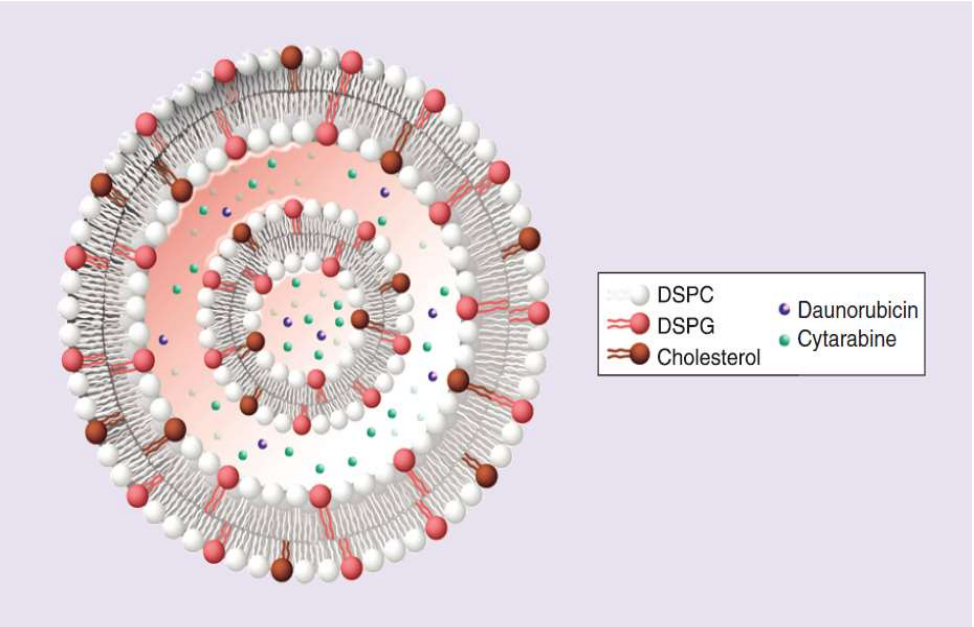
- CD33 single nucleotide polymorph rs121459419 C⟶T may be biomarker for response
- Fractionated schedule reduces toxicity
- OS benefit in fav-risk and trend in intermed-risk
- Risk of SOS/VOD 8% after allograft; higher if allo <3 mo of GO
- CD33 blast expression impacts outcome

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)

CPX-351

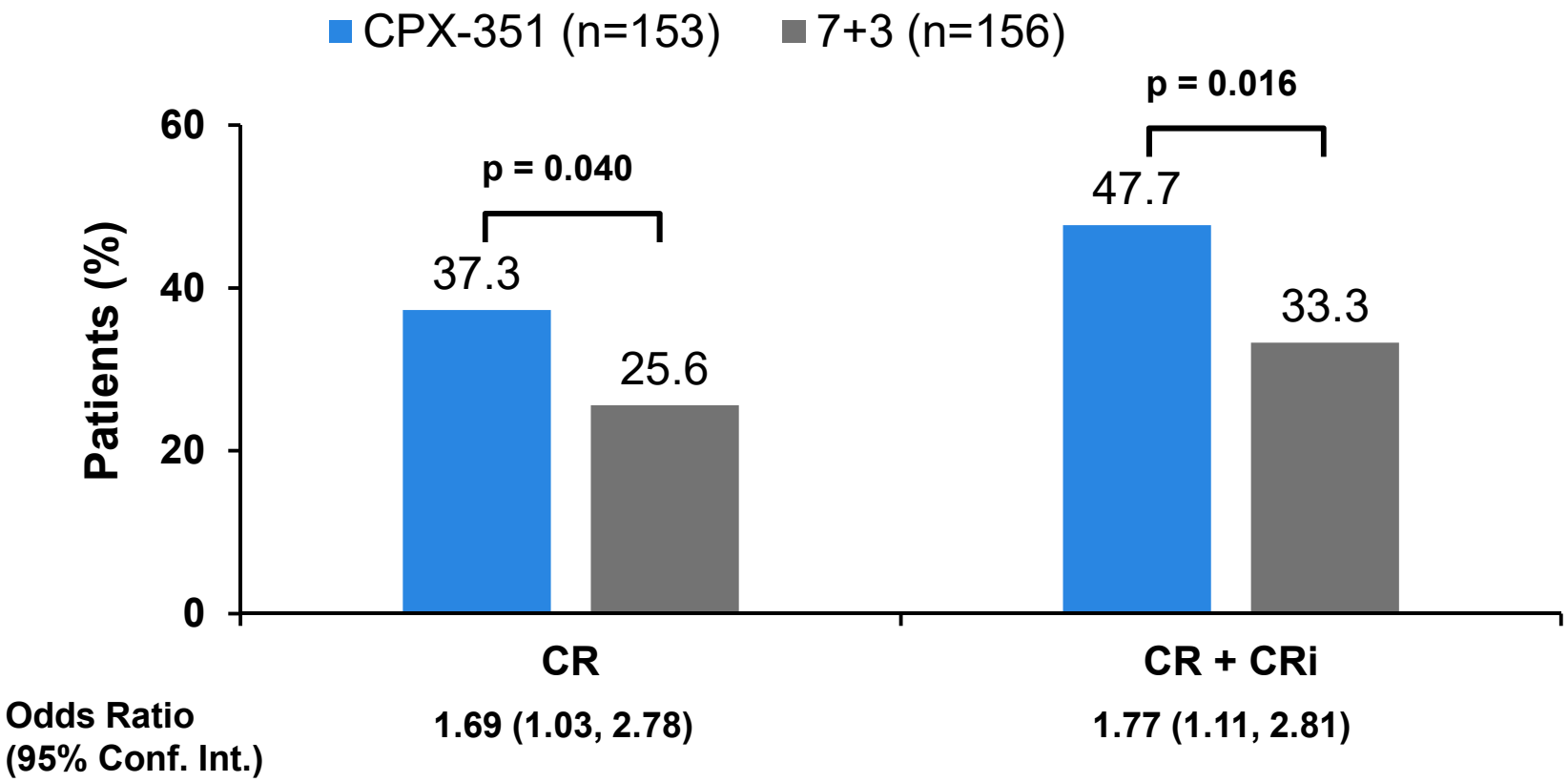
- A fixed 5:1 **synergistic** molar ratio of cytarabine to daunorubicin is maintained for a **prolonged** period of time[1]
- CPX-351 accumulates and persists in the bone marrow in **high concentrations**[1]
- CPX-351 is **preferentially taken up** by leukemic cells vs normal bone marrow cells[1]

Schematic representation of CPX-351[2]



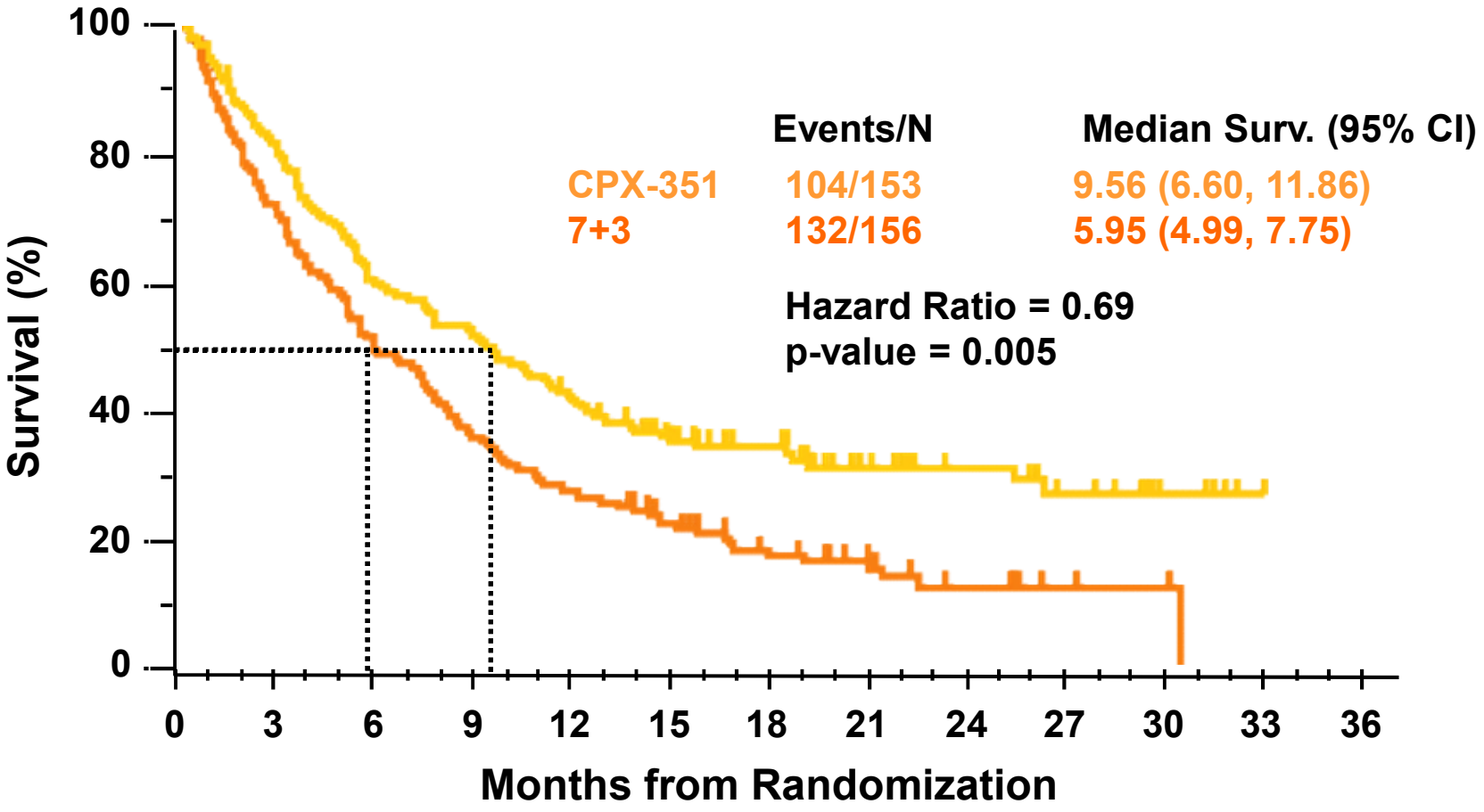
[1]Jazz Pharmaceuticals. Vyxeos® 44mg/100mg (danorubicin/cytarabine) Summary of Product Characteristics 2018; [2]Tolcher AW, Mayer LD. Future Oncol, 2018

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



Lancet et al. J Clin Oncol, 2018

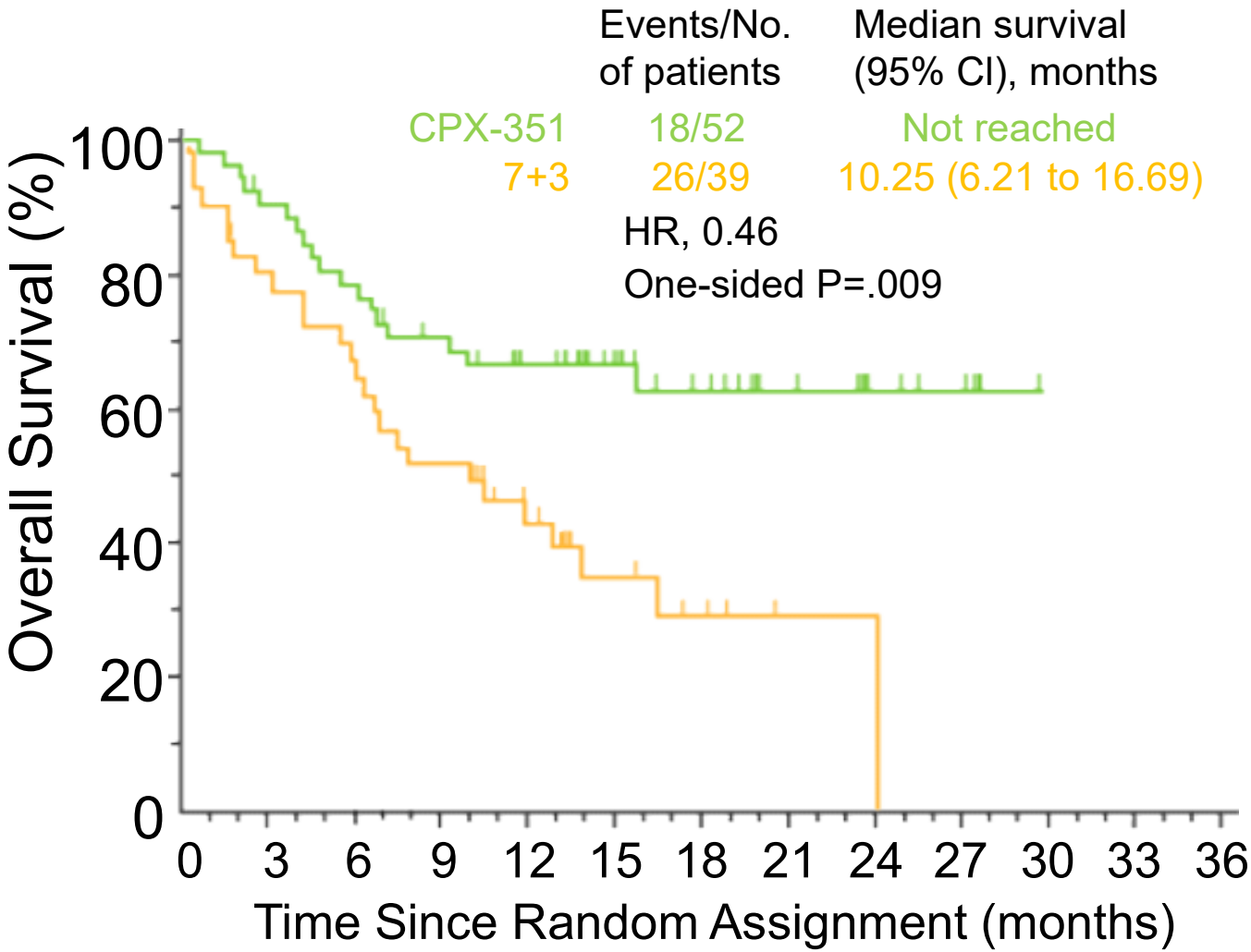
Overall Survival Was Greater in the CPX-351 Arm Compared to the 7+3 Arm



Lancet et al. J Clin Oncol, 2018

Impact of CPX-351 on Transplant Outcome

Overall Survival



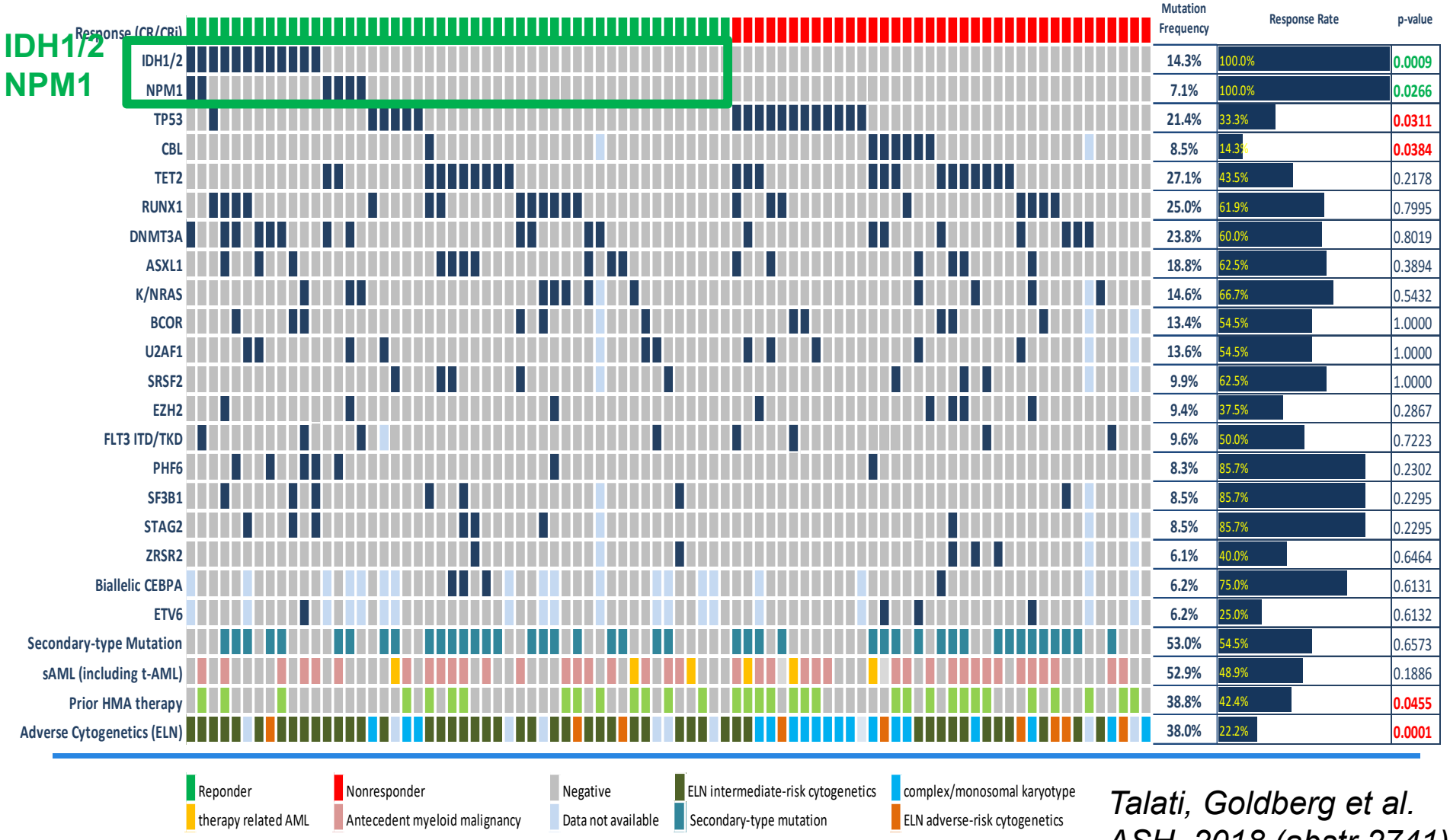
Lancet et al. J Clin Oncol, 2018

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?
- Will CPX-351 be effective alone or when combined with other agents in adverse subtypes?
  - 11q23/*MLL*?
  - *P53* predicts poorer response: CR + CRi 62% vs 33%, CR 45% vs 28%, MRD CR 36% vs 8%[1]

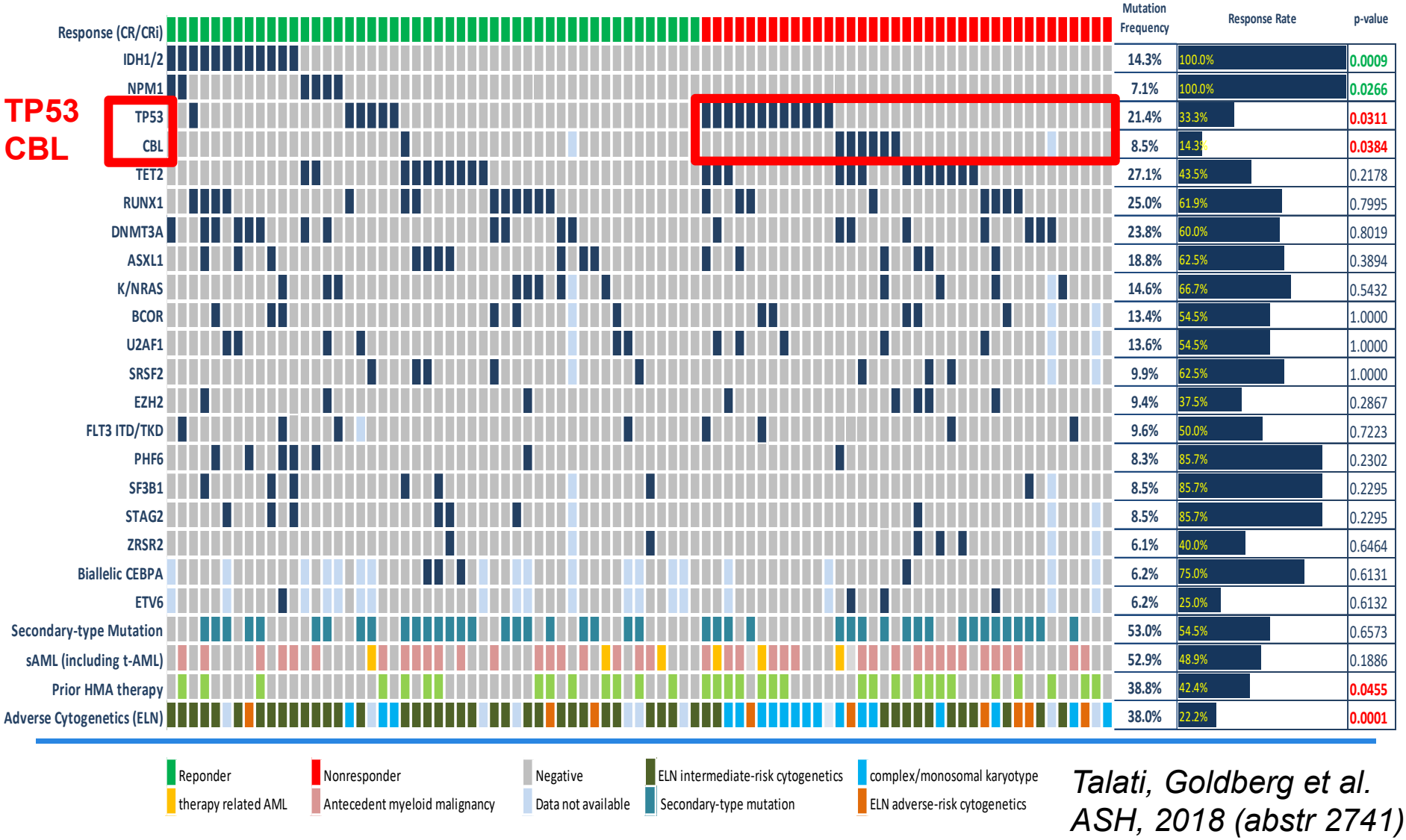
[1]*Goldberg et al. ASH, 2018 (abstr)*

Genomic Landscape Impacts Induction Outcome With CPX-351



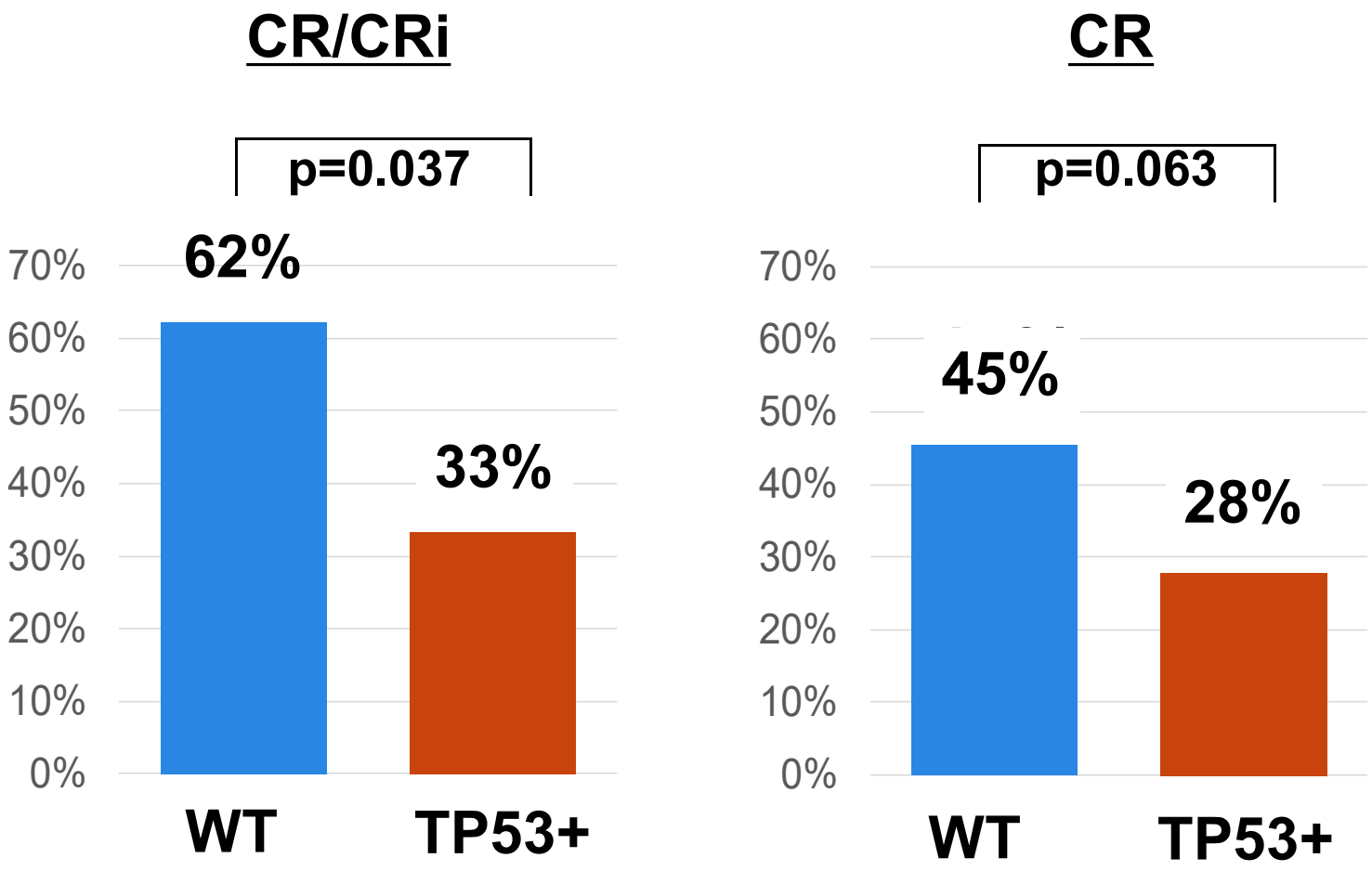
Talati, Goldberg et al. ASH, 2018 (abstr 2741)

Genomic Landscape Impacts Induction Outcome With CPX-351



Talati, Goldberg et al. ASH, 2018 (abstr 2741)

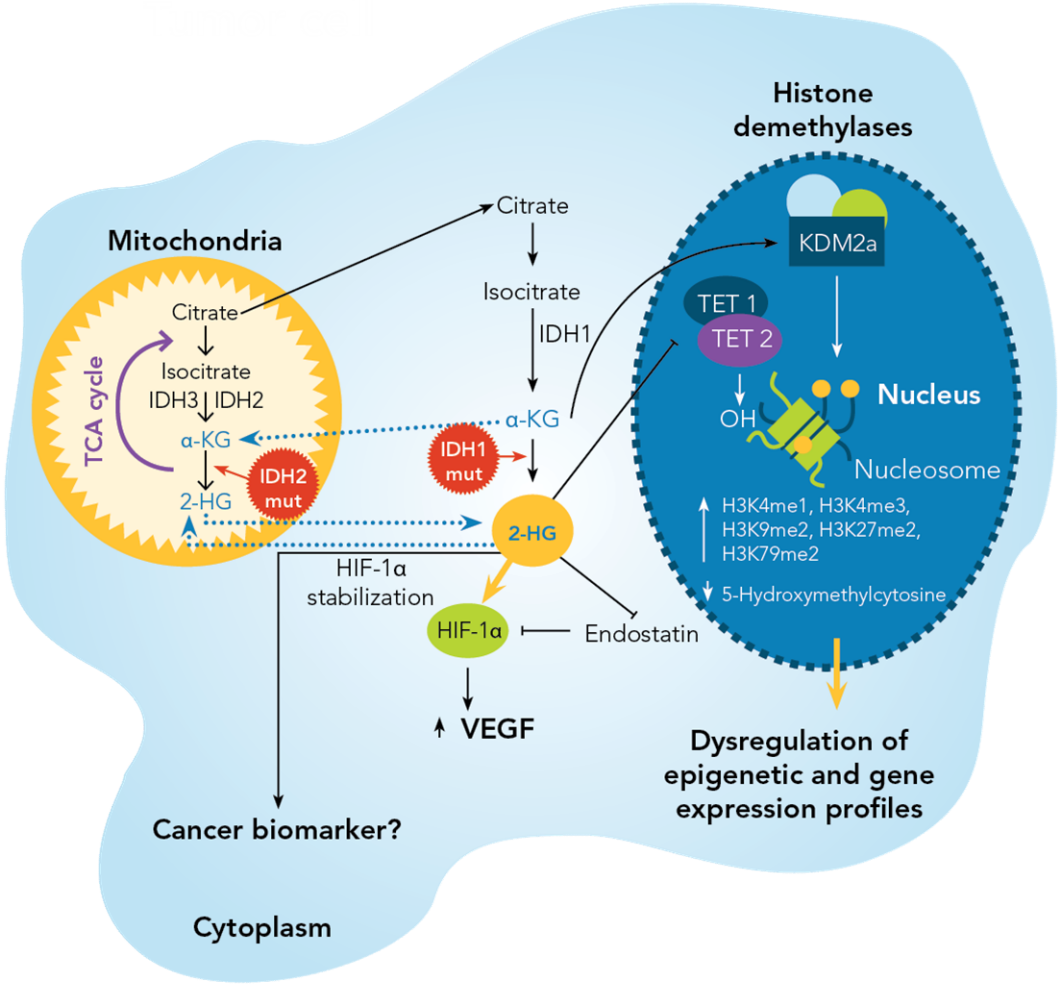
TP53 Mutations Predict Lower Rates of CR/CRi following CPX-351



Goldberg, Talati et al. ASH, 2018 (abstr 1433)

Role of *IDH* in Malignancy

Background



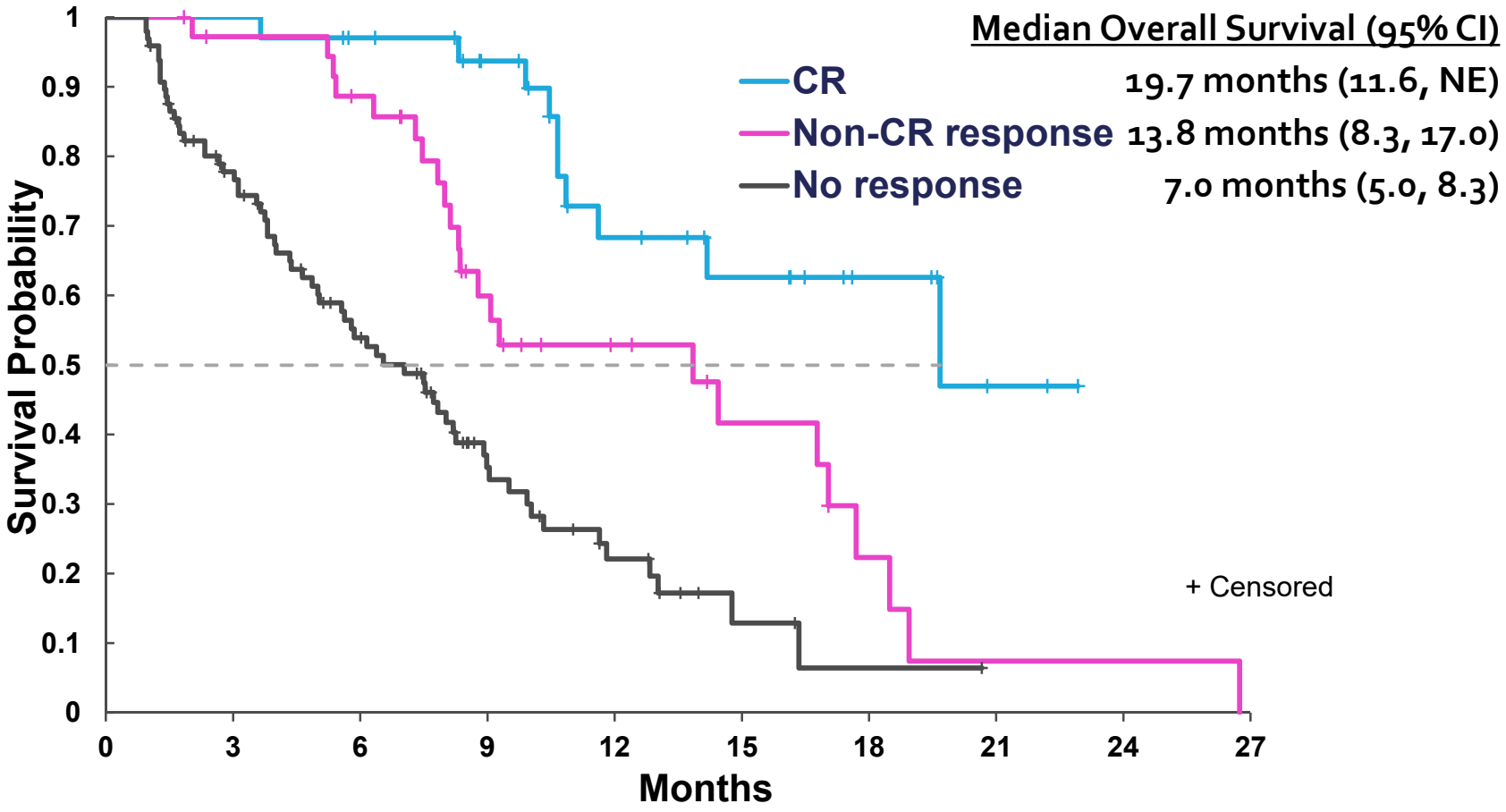
- IDH is critical metabolic enzyme in the citric acid cycle
- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (2-HG) and blocks normal cellular differentiation

Response With Enadisenib 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. Blood, 2017

Overall Survival With Enasidenib by Best Response

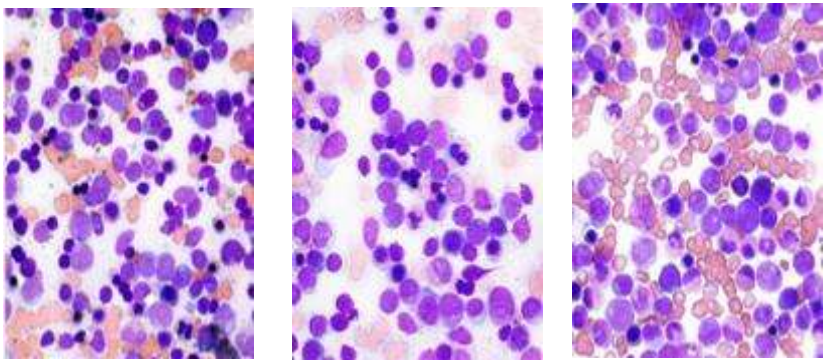


Stein et al. Blood, 2017

Morphological evidence of myeloid differentiation

Patient 1

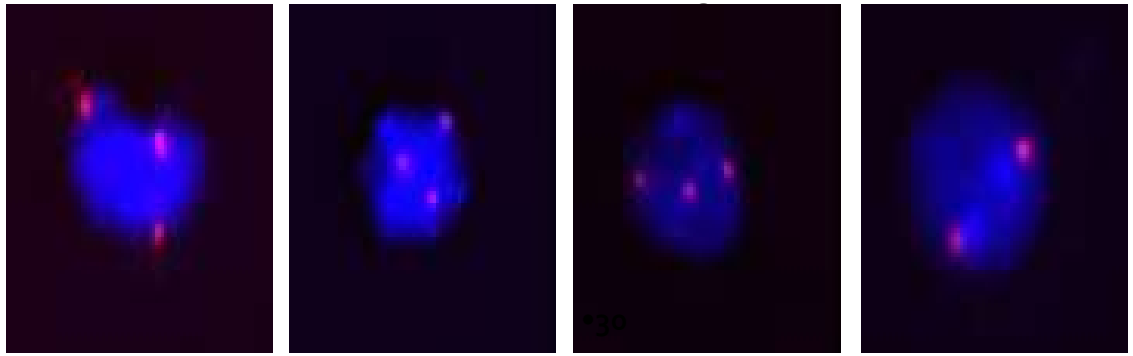
Screening	Cycle 1 Day 15	Cycle 3 Day 1
37% blasts	Evidence of cellular differentiation	4% blasts



FISH evidence of myeloid differentiation

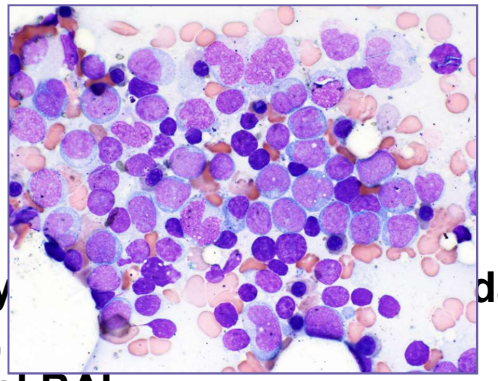
Patient 2 C2D1, trisomy 8

Blasts	Promyelocytes	Mature Granulocyte	Lymphocytes

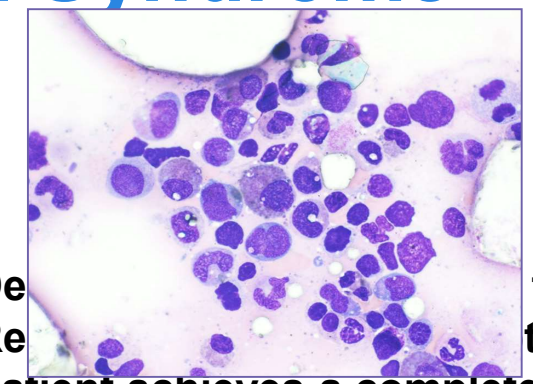


Stein et al. Blood, 2017

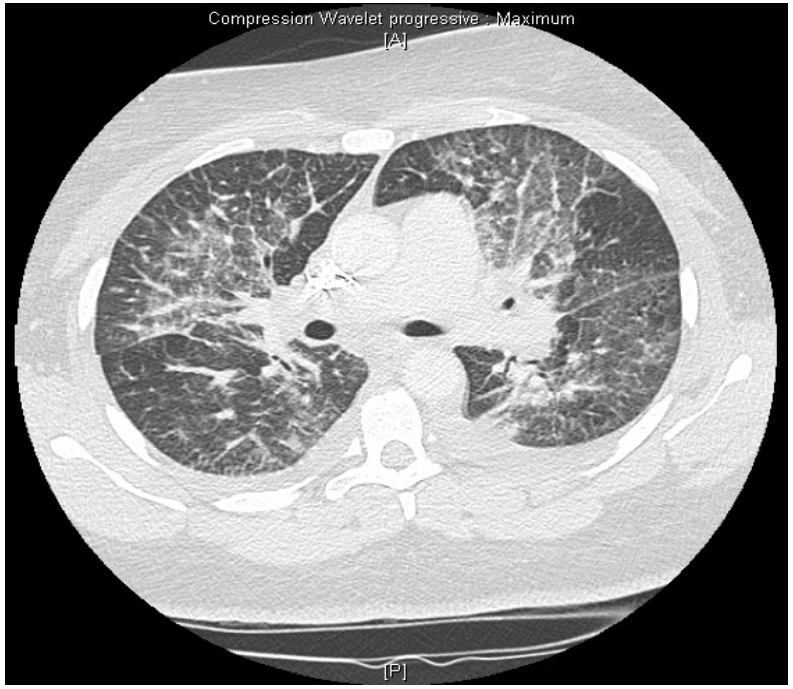
Differentiation Syndrome

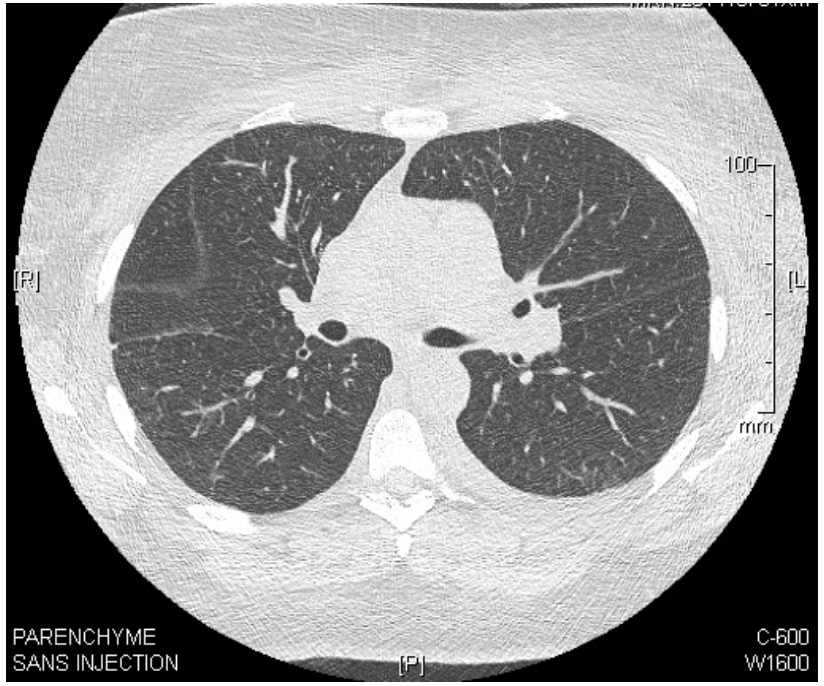


- 21 day … daily
- Fever, …
- Normal BAL



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





Courtesy Dr. Stephane De Botton

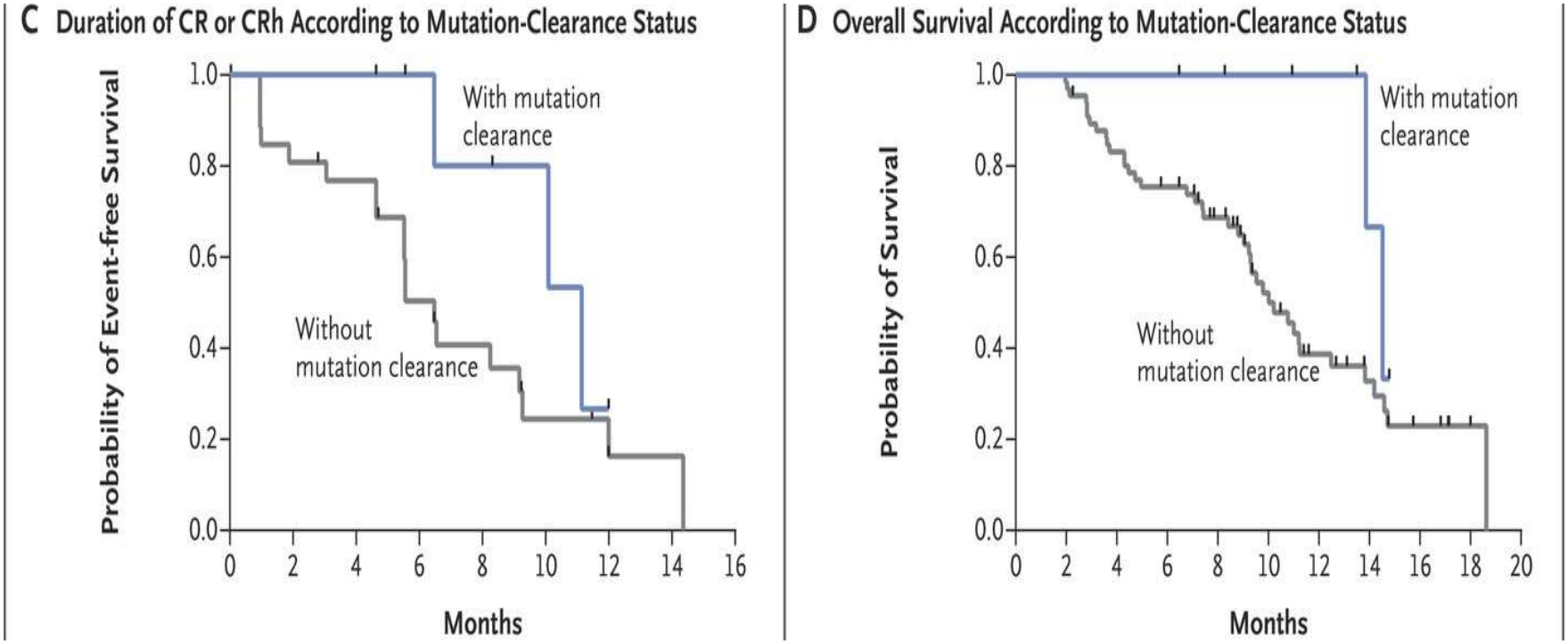
Ivosidenib or Enasidenib Plus Chemotherapy Phase I Trial

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)

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



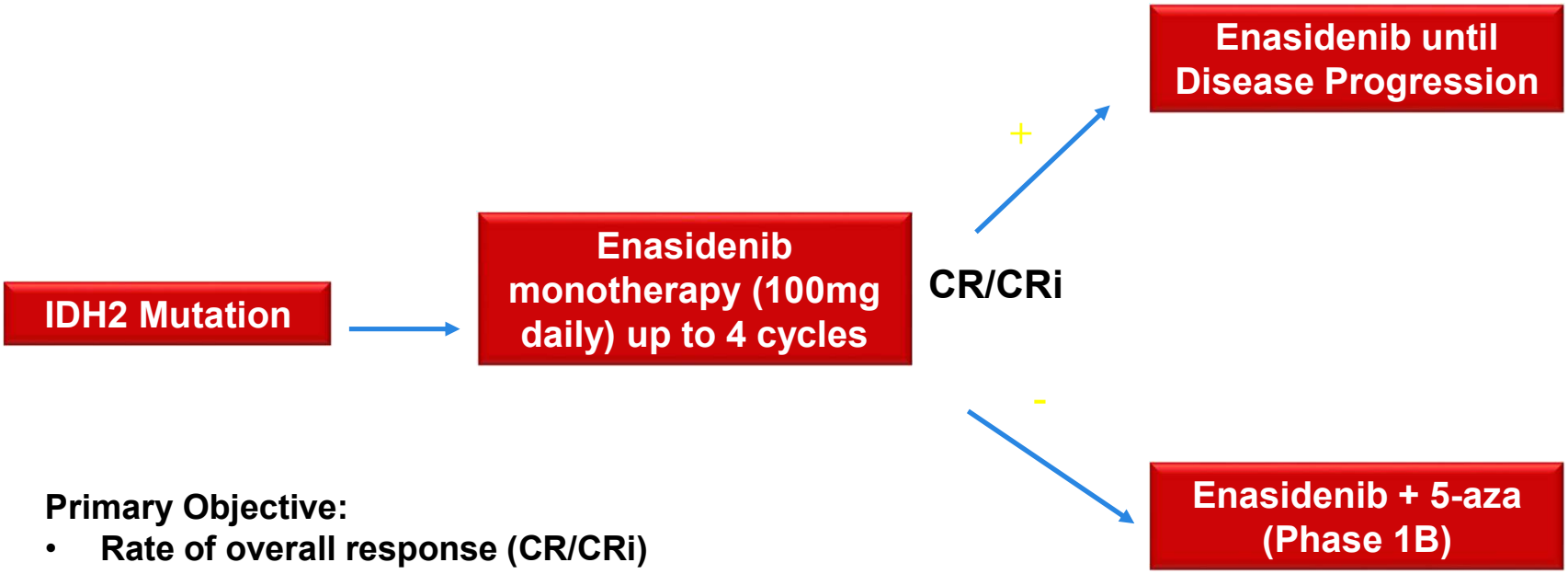
DiNardo et al. N Engl J Med, 2018

Mutant *IDH1* Inhibitor Ivosidenib In Combination With Azacitidine For Newly Diagnosed AML

- Ivo in *IDH1*mut newly diagnosed AML[1]
  - N=34
  - Med age 77, 56% >/=75
  - Secondary AML 76%, prior MDS 53%, prior HMA for AHD 47%
  - CR 30%, CR + CRh 42%, ORR 55%, transf indep 43%
- Ivo + Aza in *IDH1*mut newly diagnosed AML[2]
  - N=23
  - CR 57%, CRi/CRp 13%, MLFS 9%, ORR 78% (exceeding Aza alone *Dombret Blood, 2015*)
  - Med time to response 1.8 mo and to CR 3.5 mo
  - IDHmut clearance 63%

[1]*Roboz et al. ASCO, 2019 (abstr 7028);*
[2]*Dinardo et al. ASCO, 2019 (abstr 7011)*

Beat AML
s3 – 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**

Stein et al. ASH, 2018 (abstr 287)

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

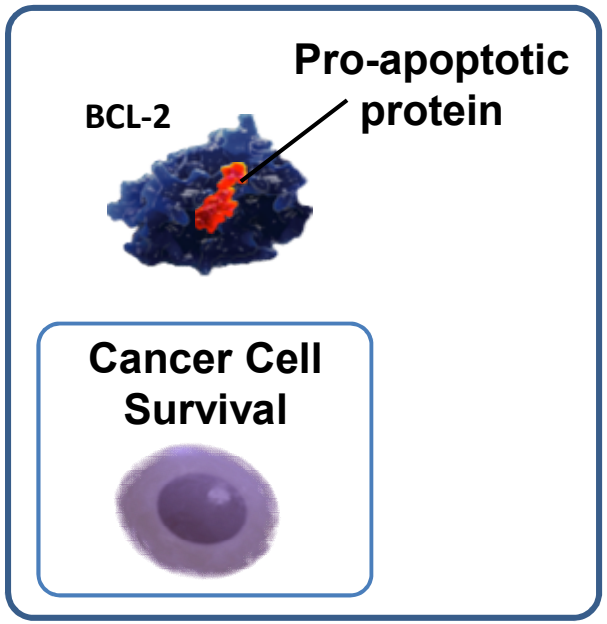
Median number of enasidenib treatment cycles: 5 (range 1-14+)

Stein et al. ASH, 2018 (abstr 287)

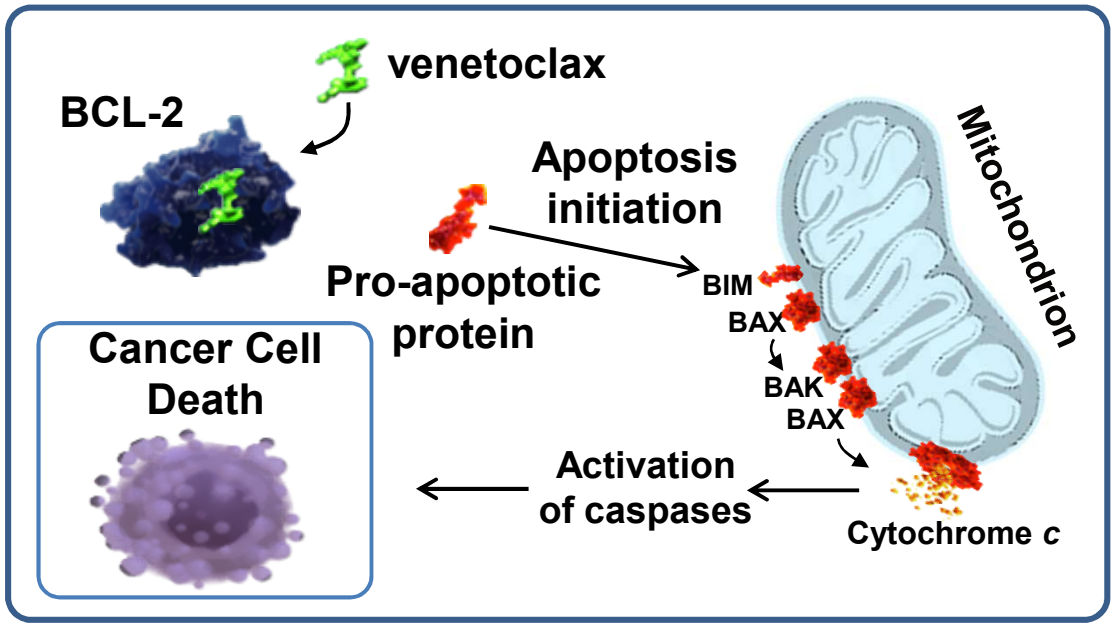
Frequently Asked Questions Re: *IDH2*

- Does molecular CR occur? Yes, about 30%
- Does differentiation syndrome occur? Yes, and can occur late (med 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

Venetoclax: Promotes Apoptosis Through Selective Inhibition of *BCL-2*



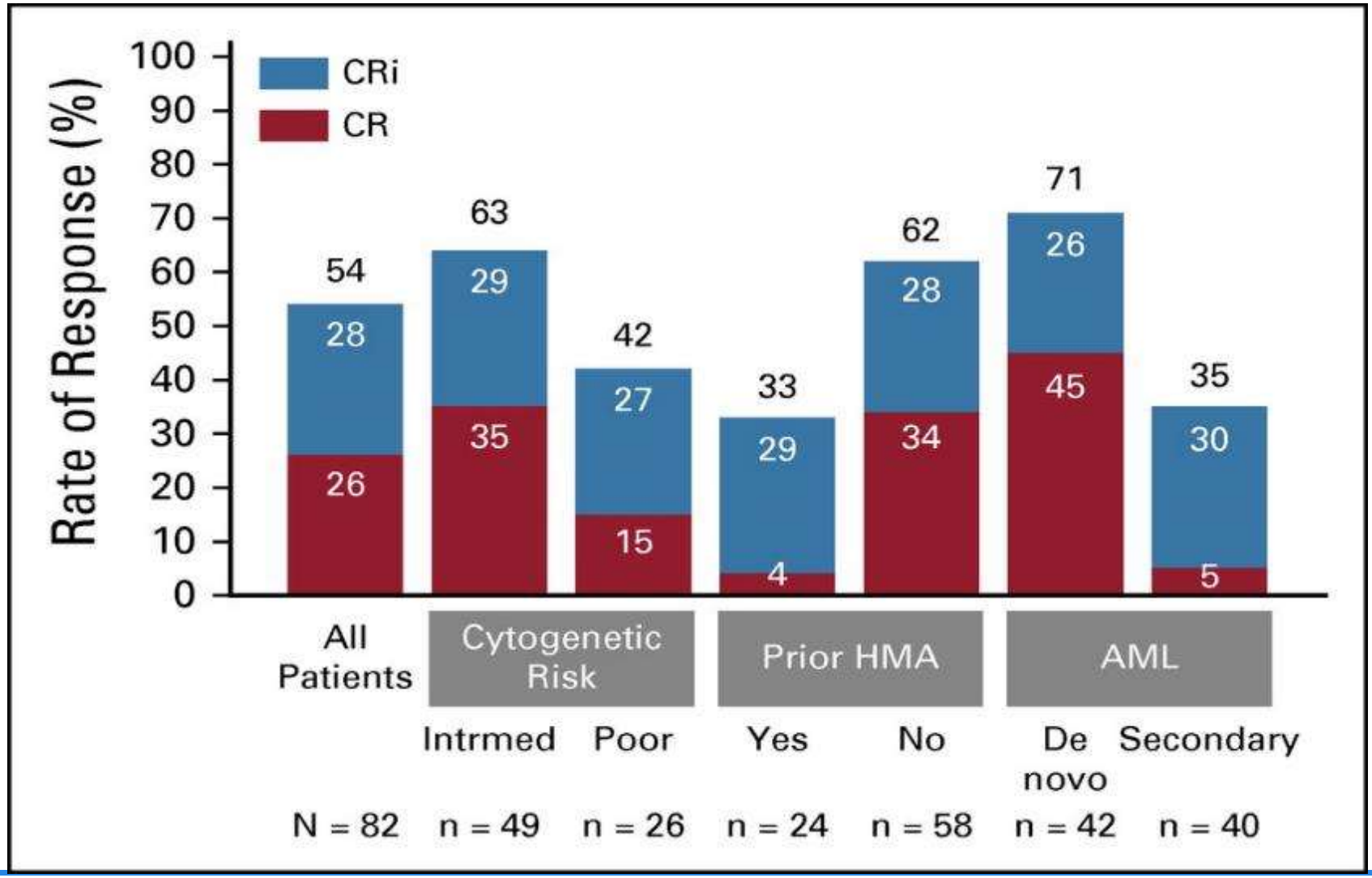
BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins[1-3]



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 By Patient Subgroups Treated With LoDAC + Venetoclax



Wei et al. J Clin Oncol, 2019

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

- N=115 **Aza 84, DAC 31**
- Med age**:** **75 and 72**, respectively
- Secondary AML: **25% and 29%**
- Poor risk cyto: **39% and 48%**
- CR/CRi: **70% and 75%**
- Med time to CR: **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)

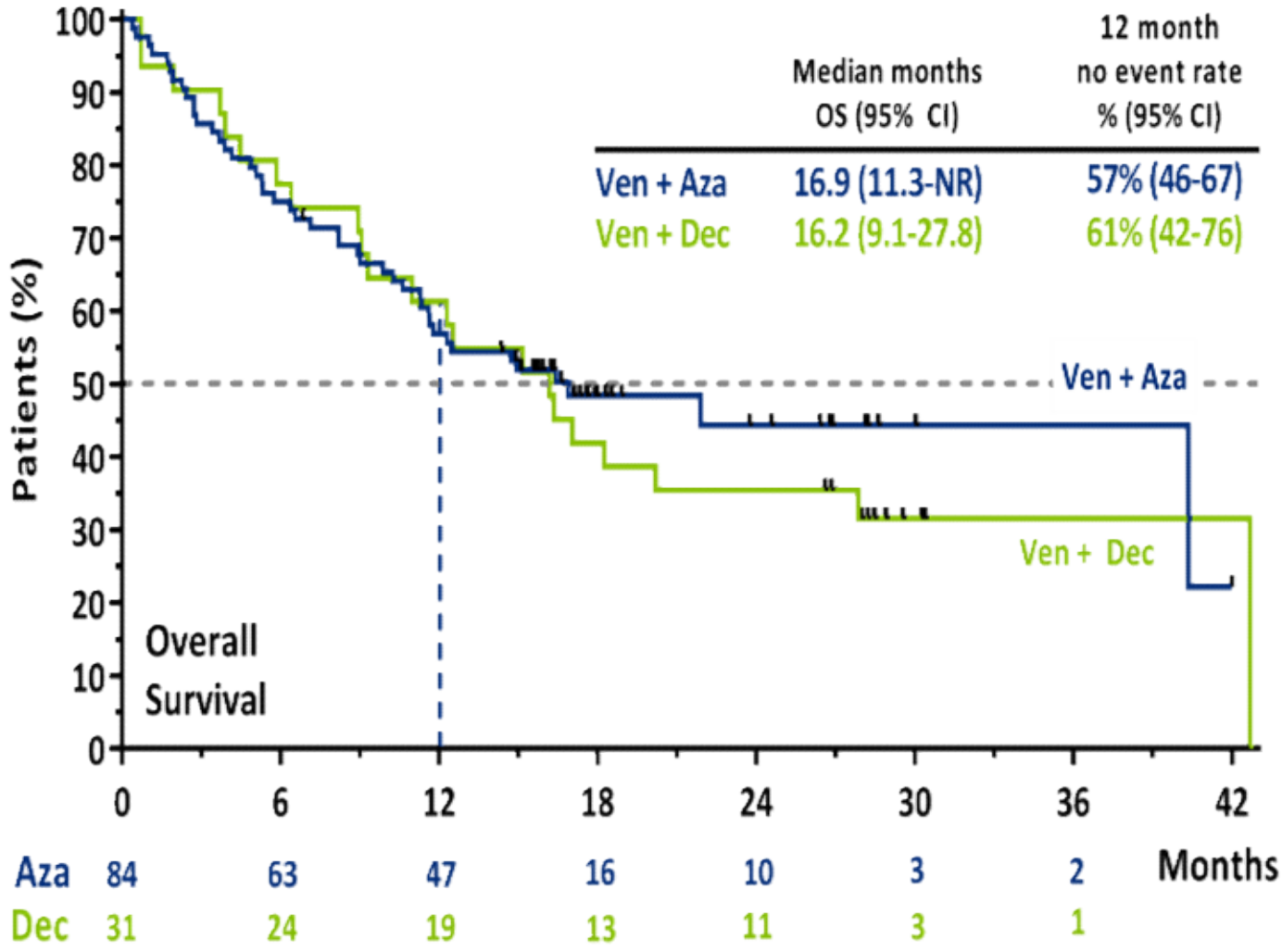
Overall Survival in Untreated Older AML

HMA + Venetoclax

Median Follow-up

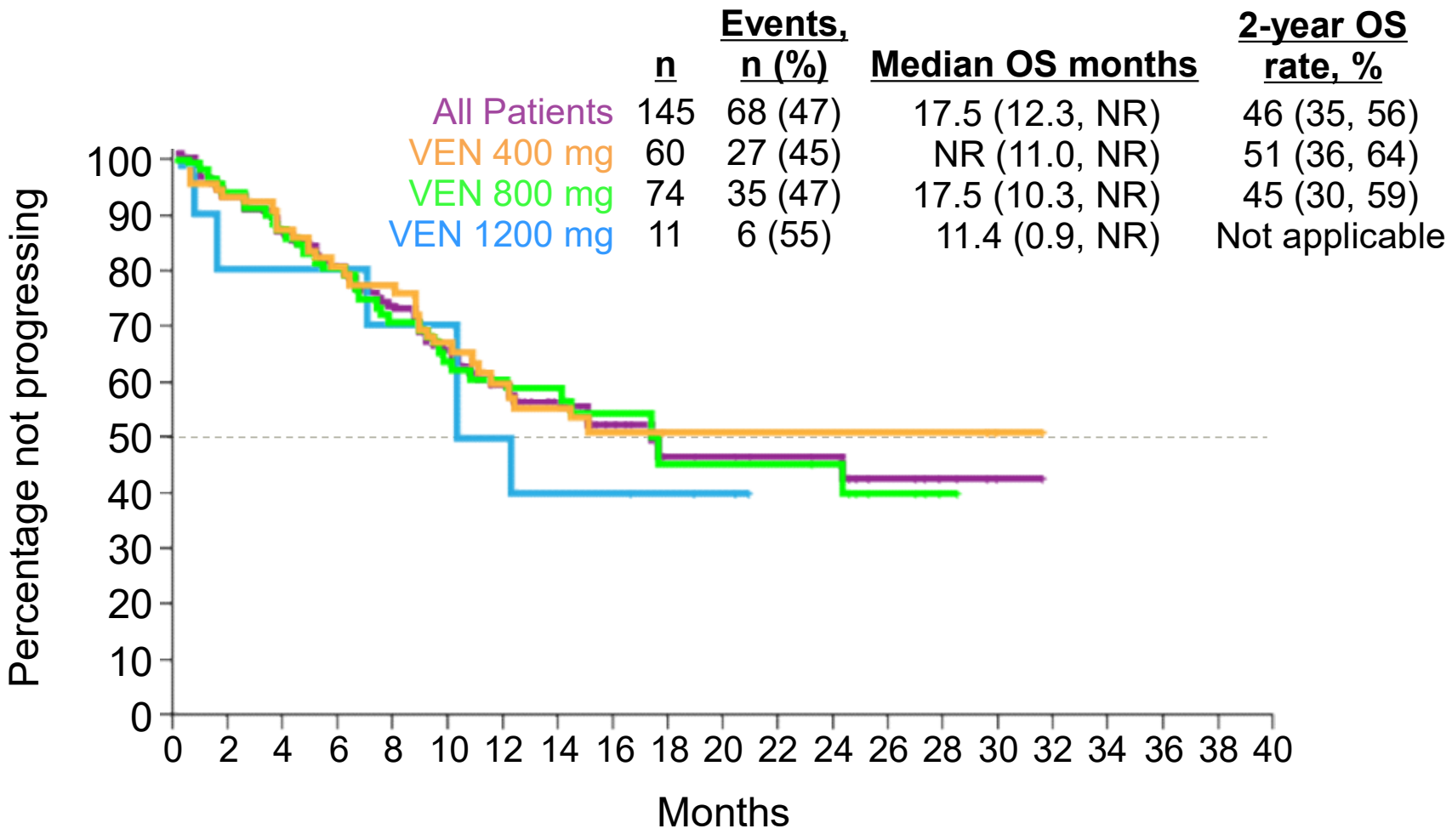
Venetoclax + azacitidine
14.9 months (range 0.4–42.0)

Venetoclax + decitabine
16.2 months (range 0.7–42.7)



Pollyea et al. ASH, 2018 (abstr 285)

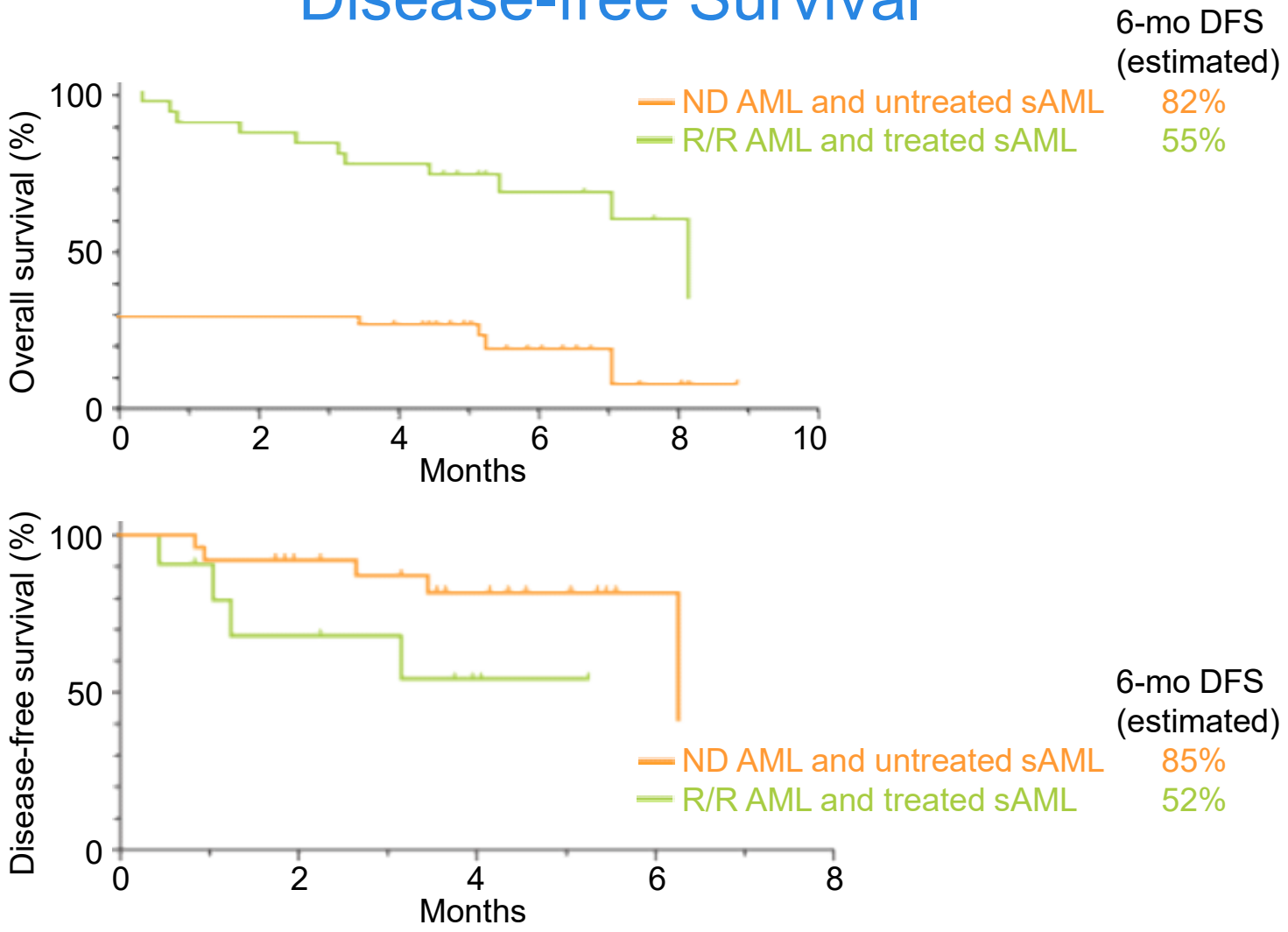
OS by Venetoclax Dose Levels in Treatment Naïve Elderly AML



Dinardo et al, Blood, 2019

DEC10-VEN in AML/MDS

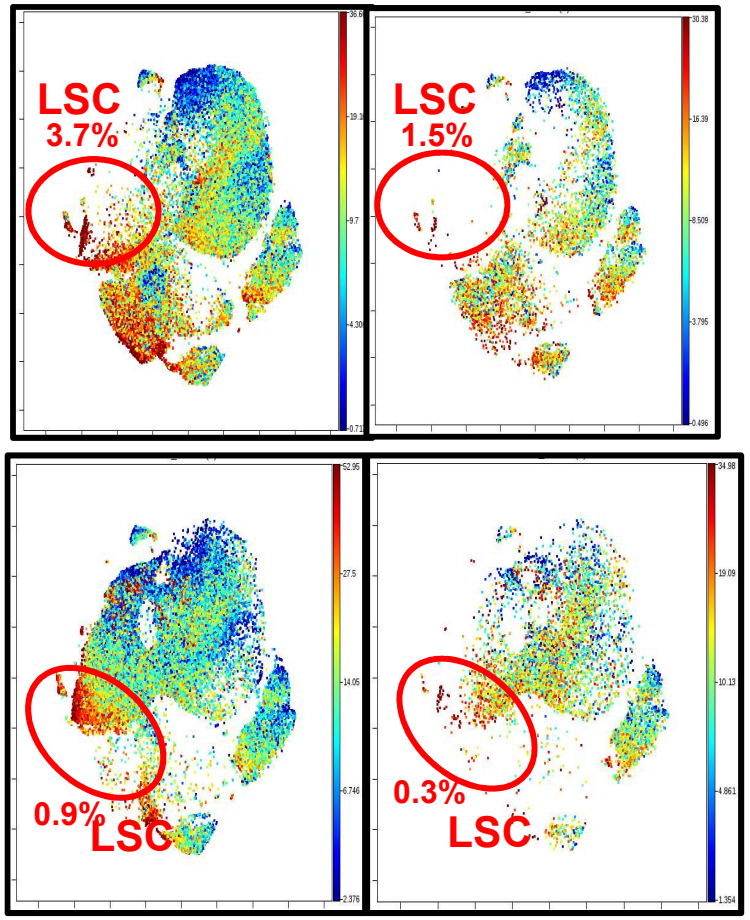
Disease-free Survival



Maiti et al. ASH, 2018 (abstr 286)

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. Nature Med, 2018

AML Treatment Strategies in 2019

AML subgroup	Candidate for intensive chemo	Not candidate for intensive chemo
All patients	Clinical trial preferred	Clinical trial preferred
CBF	GO + chemo, ? If pretrans	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 5-10d +/- Venetoclax	Decitabine x 5-10d +/- Venetoclax
FLT3+	Mido + chemo ind/consol/maint, transplant	?AZA + sorafenib or HMA alone
*IDH*1/2+	Chemo (on trial with IDHi)	HMA/LoDAC + Venetoclax* or Ivo
Marker -	Chemo	HMA/LoDAC + Venetoclax*

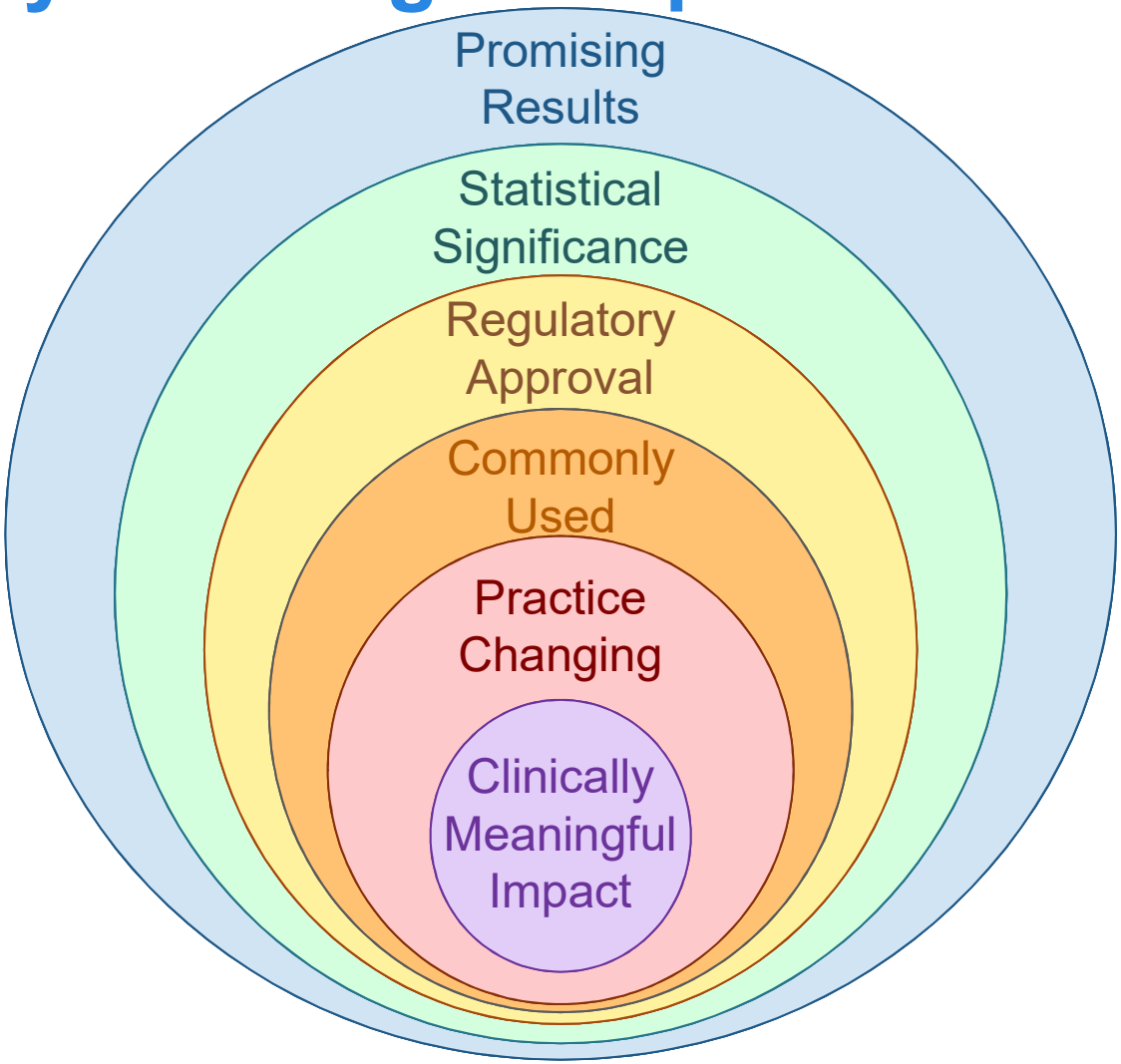
*HMA/LoDAC + Venetoclax awaiting phase III data

AML Treatment Strategies in 2019: Rel/Ref

AML subgroup	Candidate for intensive chemo	Not a candidate for intensive chemo
All patients	Clinical trial preferred	Clinical trial preferred
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 x10d +/- Venetoclax
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*)

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



Summary and Conclusions

- 8 new drugs are recently approved for AML, era of precision medicine in AML
- Second gen more potent FLT3i available, in randomized trials
- CPX-351 new SOC for t-AML and AML-MRC
- Venetoclax + HMA or LoDAC highly effective even in high risk pts (P53), may emerge as a new SOC for older adults
- Many novel agents in AML with unique mechanisms of action available
- Therapeutic paradigms are (finally) shifting, more care now delivered as outpt potentially placing strain on outpt services

Acknowledgments

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