Penn Medicine

AML: Where are we now? Where are we going?

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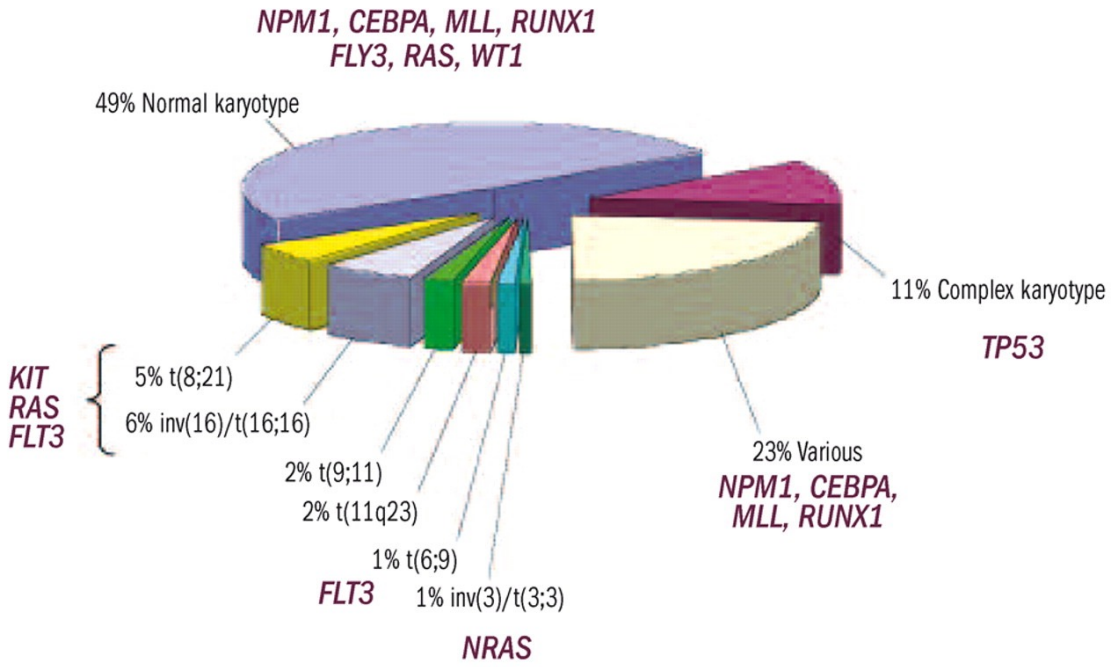
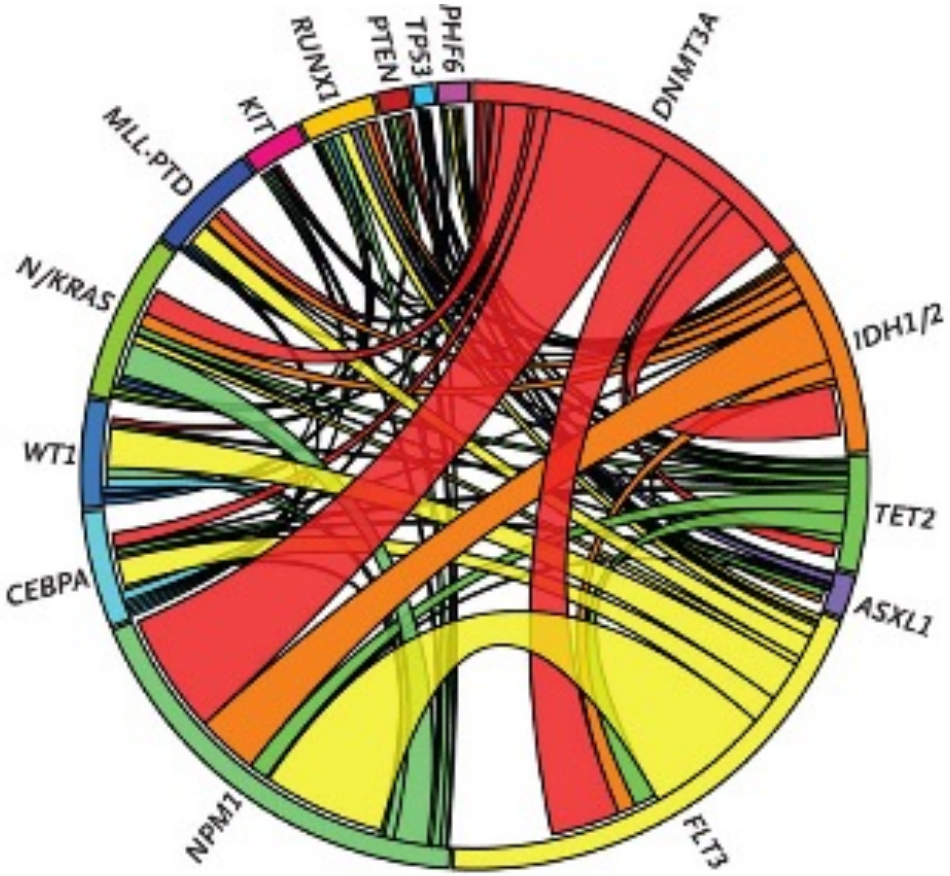
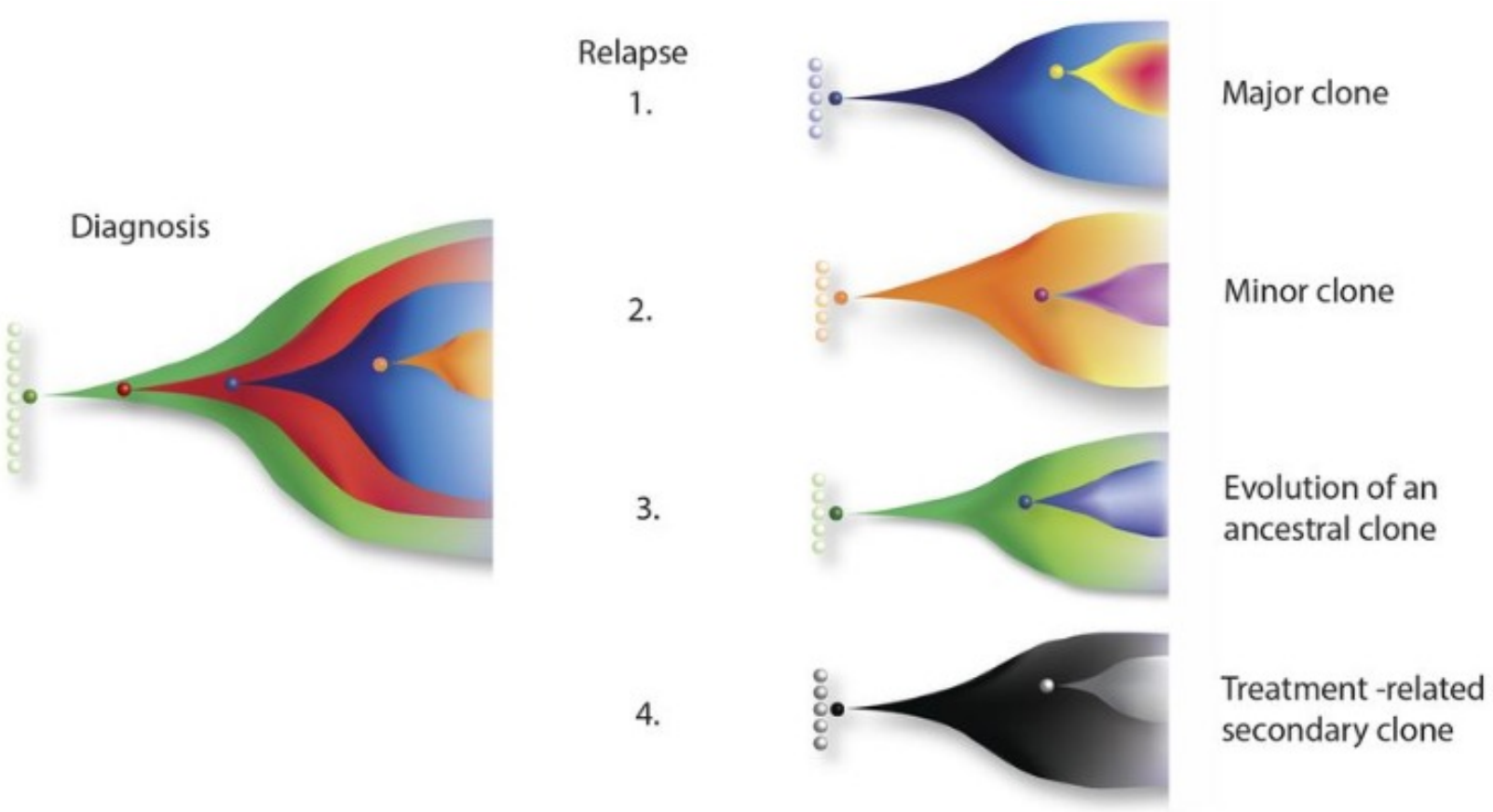
AML is Not One Disease





Patel et al. N Engl J Med 2012
Papaemmanuil et al. NEJM 2016

Clonal Evolution Makes Treatment Challenging



Grimwade et al. Blood 2016 127:29-41

World Health Organization (WHO) and International Consensus Classification Guidelines 2022

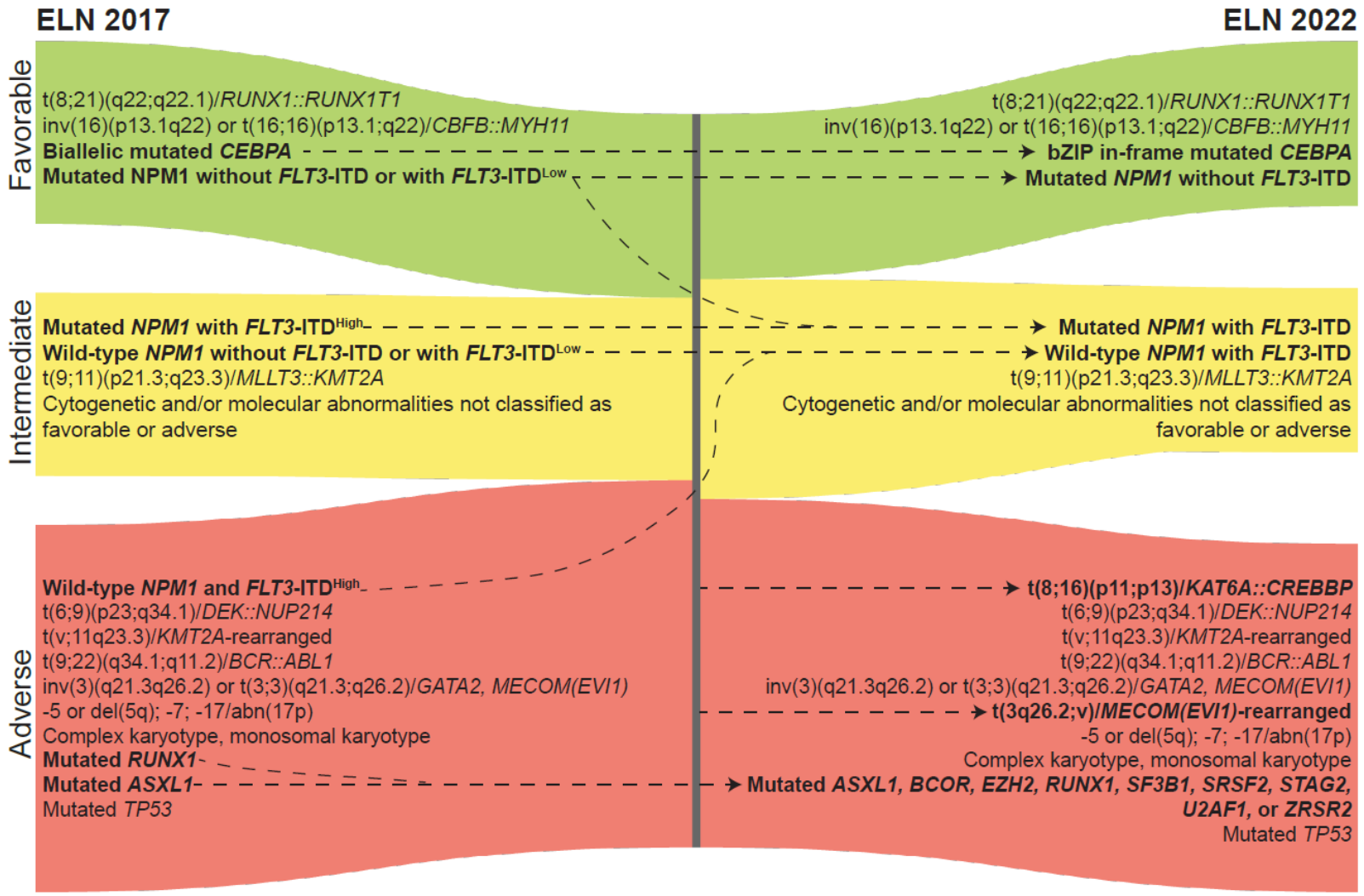
	WHO 2022	ICC 2022*
AML with defining genetic abnormalities**	APL with *PML::RARA* fusion	APL with t(15;17)(q24.1;q21.2)/*PML::RARA*§
		APL with other *RARA* rearrangements§
	AML with *RUNX1::RUNX1T1* fusion	AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*§
	AML with *CBFB::MYH11* fusion	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*§
	AML with *DEK::NUP214* fusion	AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214*§
	AML with *RBM15::MRTFA* fusion	*Not recognized*
	AML with *BCR::ABL1* fusion	AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1*#
	AML with *KMT2A* rearrangement	AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*§
		AML with other *KMT2A* rearrangements§
	AML with *MECOM* rearrangement	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2; MECOM(EVI1)*§
		AML with other *MECOM* rearrangements§
	AML with *NUP98* rearrangement	*Not recognized*
	AML with *NPM1* mutation	AML with mutated *NPM1*§
	AML with *CEBPA* mutation	AML with in-frame bZIP *CEBPA* mutations§
	AML, myelodysplasia-related†	AML# and MDS/AML§ with mutated *TP53*
		AML# and MDS/AML§ with myelodysplasia-related gene mutations
		AML# and MDS/AML§ with myelodysplasia-related cytogenetic abnormalities
		MDS/AML NOS§
	AML with other defined genetic alterations	AML with other rare recurring translocations#
		Myeloid proliferations associated with Down syndrome
AML, defined by differentiation	AML with minimal differentiation	AML NOS#
	AML without maturation	
	AML with maturation	
	Acute basophilic leukemia	
	Acute myelomonocytic leukemia	
	Acute monocytic leukemia	
	Acute erythroid leukemia	
	Acute megakaryoblastic leukemia	
	Myeloid sarcoma	Myeloid sarcoma
	Blastic plasmacytoid dendritic cell neoplasm	Blastic plasmacytoid dendritic cell neoplasm

*Requires mention of qualifiers (Therapy-related, Progressing from MDS, Progressing from MDS/MPN, and/or Germline predisposition)
**≥20% blast cutoff is no longer required for AML with defining genetic abnormalities except for *BCR::ABL* fusion and *CEBPA* mutation
† AML, myelodysplasia-related encompasses AML transformation from MDS and MDS/MPN
§Blast cutoff ≥10%
#Blast cutoff ≥20%

	WHO 2022	ICC 2022
MDS-defining cytogenetics	Complex karyotype (≥3 abnormalities)	Complex karyotype (≥3 abnormalities)
	5q deletion or loss of 5q due to unbalanced translocation	5q deletion, 5q addition, or loss of 5q due to unbalanced translocation
	Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation	Monosomy 7 or 7q deletion
	11q deletion	Trisomy 8
	12p deletion or loss of 12p due to unbalanced translocation	12p deletion, 12p addition, or loss of 12p due to unbalanced translocation
	Monosomy 13 or 13q deletion	Isochromosome 17q
	17p deletion or loss of 17p due to unbalanced translocation	17p deletion, 17p addition, or monosomy 17
	Isochromosome 17q	20q deletion
	Idic(X)(q13)	Idic(X)(q13)
MDS-defining somatic mutations	*ASXL1*	*ASXL1*
	BCOR	*BCOR*
	EZH2	*EZH2*
	RUNX1	*RUNX1*
	SF3B1	*SF3B1*
	SRSF2	*SRSF2*
	STAG2	*STAG2*
	U2AF1	*U2AF1*
	ZRSR2	*ZRSR2*

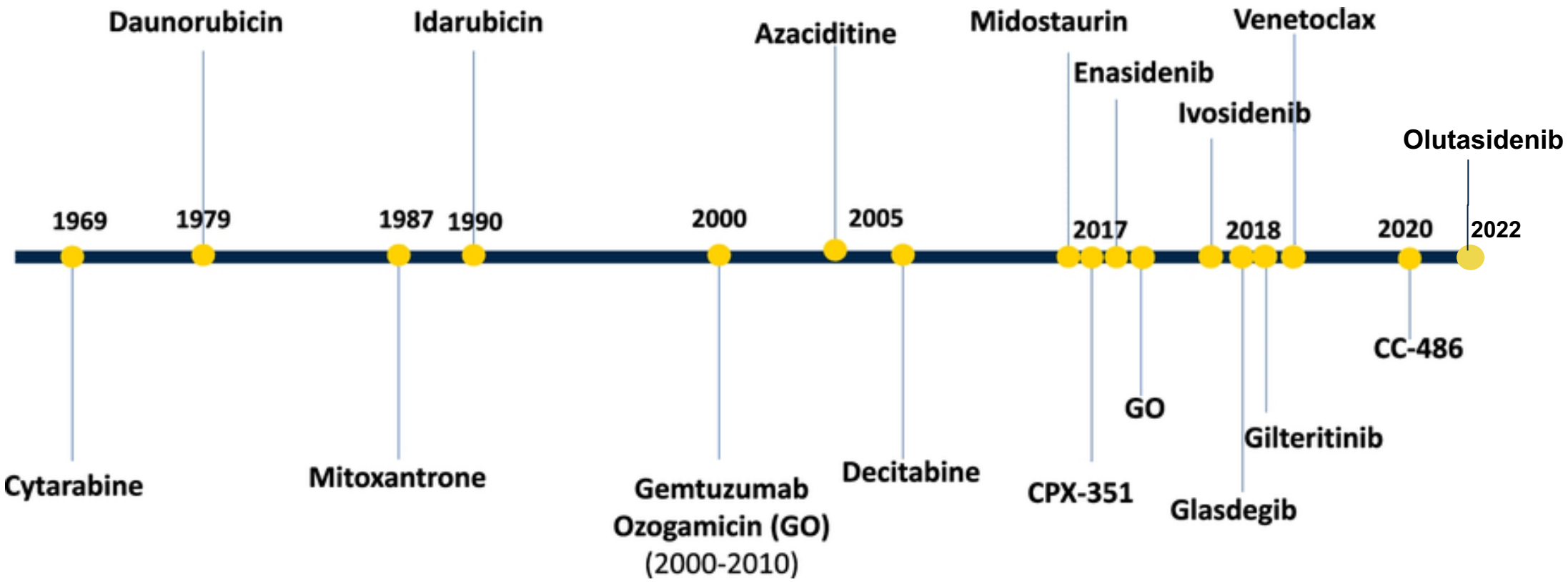
Bhansali, Lai et al. unpublished

European Leukemia Network Updated in 2022



Bhansali, Lai et al. unpublished

What has been accomplished in AML treatment?



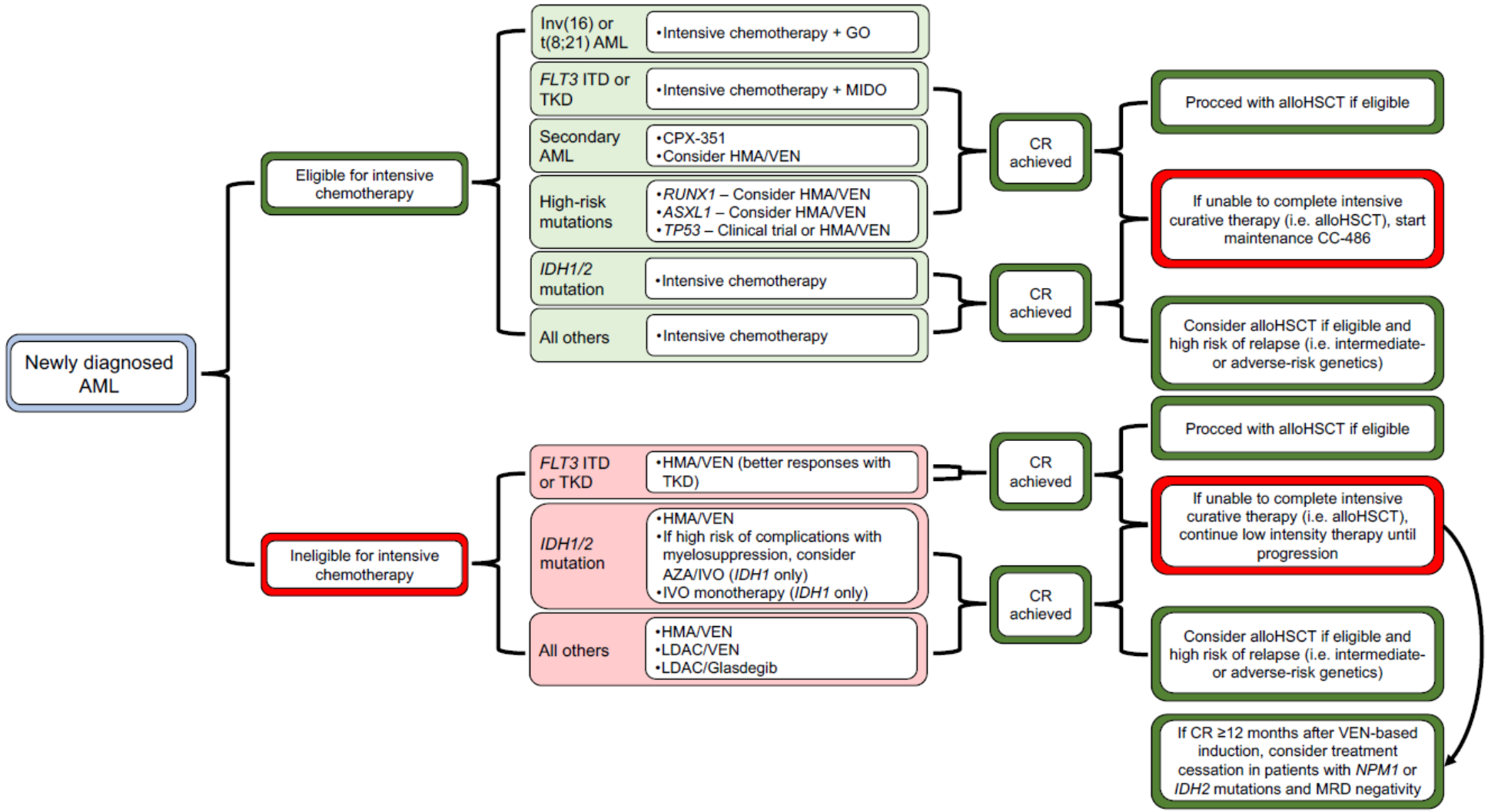
Ochs et al. Annals of Hematology 2022

FDA Approved Drugs Since 2017

- **Newly diagnosed**
  - Midostaurin – April 2017
  - CPX-351 – August 2017
  - Venetoclax – November 2018
  - Glasdegib – November 2018
- **Relapsed/refractory**
  - Enasidenib – August 2017
  - Gilteritinib – November 2018
  - Olutasidenib – December 2022
- **Newly diagnosed and Relapsed/Refractory**
  - Gemtuzumab ozogamicin – September 2017
  - Ivosidenib – July 2018, May 2019
- **Maintenance**
  - CC-486 – September 2020

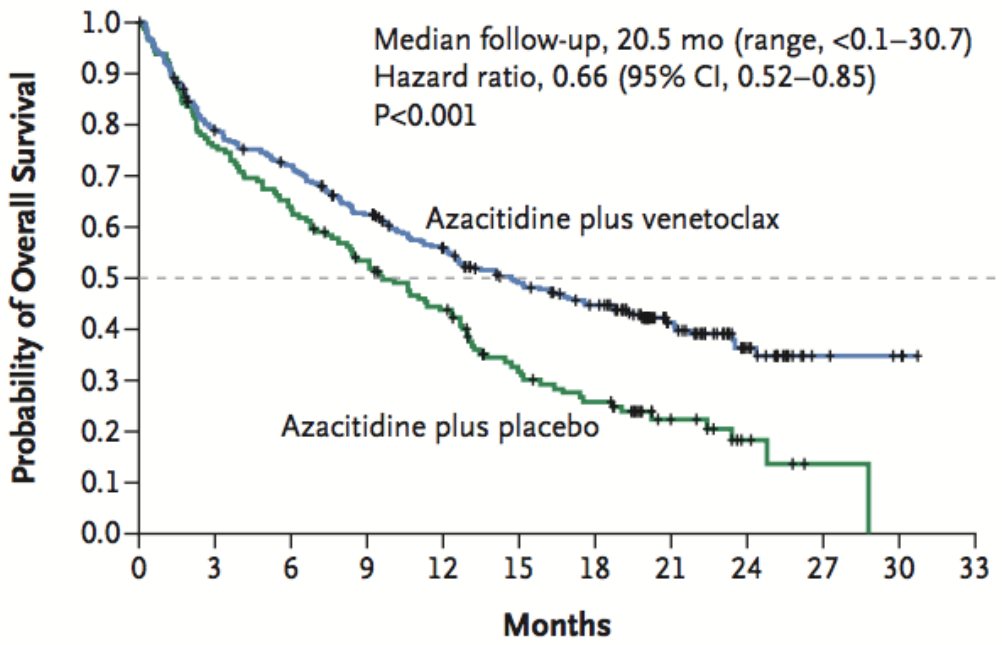
Historical Standard Approach To Induction Chemotherapy

New Standard Approach to Newly Diagnosed AML



Bhansali, Lai et al. unpublished

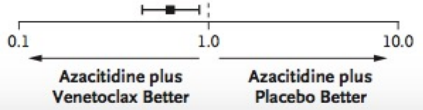
VIALE-A: AZA + Venetoclax Superior to AZA alone



No. at Risk

Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0

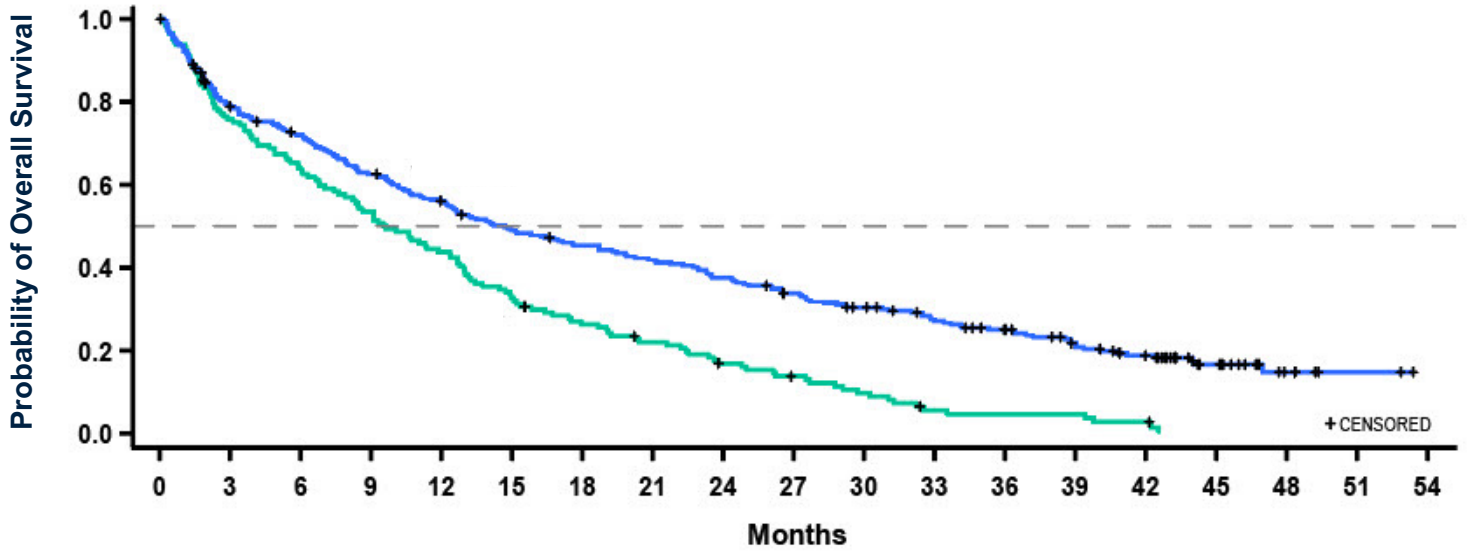
Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
All patients	161/286 (56.3)	109/145 (75.2)	0.64 (0.50–0.82)
Sex			
Male	61/114 (53.5)	41/58 (70.7)	0.68 (0.46–1.02)
Female	100/172 (58.1)	68/87 (78.2)	0.62 (0.46–0.85)
Age			
<75 yr	66/112 (58.9)	36/58 (62.1)	0.89 (0.59–1.33)
≥75 yr	95/174 (54.6)	73/87 (83.9)	0.54 (0.39–0.73)
Geographic region			
United States	27/50 (54.0)	21/24 (87.5)	0.47 (0.26–0.83)
Europe	70/116 (60.3)	46/59 (78.0)	0.67 (0.46–0.97)
China	9/24 (37.5)	5/13 (38.5)	1.05 (0.35–3.13)
Japan	10/24 (41.7)	9/13 (69.2)	0.52 (0.20–1.33)
Rest of world	45/72 (62.5)	28/36 (77.8)	0.73 (0.45–1.17)
Baseline ECOG score			
Grade <2	89/157 (56.7)	65/81 (80.2)	0.61 (0.44–0.84)
Grade ≥2	72/129 (55.8)	44/64 (68.8)	0.70 (0.48–1.03)
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)
Bone marrow blast count			
<30%	46/85 (54.1)	28/41 (68.3)	0.72 (0.45–1.15)
30 to <50%	36/61 (59.0)	26/33 (78.8)	0.57 (0.34–0.95)
≥50%	79/140 (56.4)	55/71 (77.5)	0.63 (0.45–0.89)



Dinardo et al. NEJM 2020

Sustained OS benefit to Azacitidine/Venetoclax Over Azacitidine/Placebo with Long-term Follow Up of VIALE-A

Median follow-up time: 43.2 months (range: < 0.1 - 53.4)



Patients at Risk																			
Ven+Aza	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0
Pbo+Aza	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0	0	0	0

	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza	222/286 (77.6)	14.7 (12.1 - 18.7)
Pbo+Aza	138/145 (95.2)	9.6 (7.4 - 12.7)

Hazard ratio: 0.58 (95% CI, 0.465 - 0.723), P < 0.001

HR reduction from 0.66 (95% CI, 0.52 - 0.85) at 75% OS analysis

Pratz KW et al, ASH 2022, abstract #219

Doublets versus Triplets : Is More Better?

vs.

Doublets

vs.

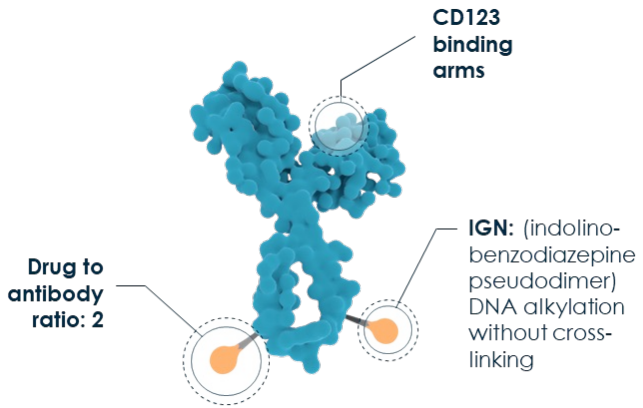
Triplets

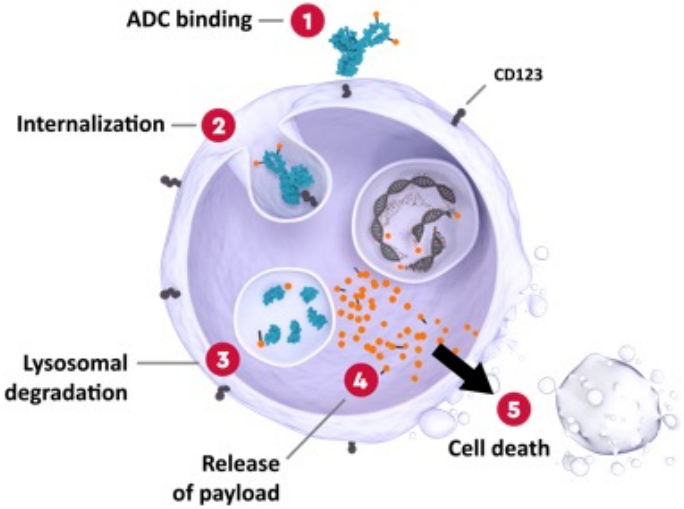
- 7+3
- Venetoclax + HMA (azacitidine or decitabine)
- Ivosidenib + azacitidine
- CPX-351
- FLAG-IDA

- 7+3+midostaurin
- Venetoclax + HMA + novel target (e.g.- gilteritinib, ivosidenib, enasidenib, magrolimab, PVEK) – not FDA approved
- FLAG-IDA + venetoclax – not FDA approved

Pivekimab sunirine (PVEK)

- CD123 is expressed on the majority of AML blasts and leukemic stem cells, while minimally expressed on normal hematopoietic stem cells[4]
- Pivekimab sunirine (PVEK) is a novel CD123-targeted antibody drug conjugate with single agent activity in BPDCN[4] and single agent CR/CRi rates of 22-40% in R/R AML[5]
- Preclinical data demonstrated synergy between PVEK and AZA and/or VEN, including overcoming AZA/VEN resistance in murine AML models[6]
- Here we report safety and anti-leukemic activity of PVEK+AZA+VEN from the dose-escalation and expansion cohort in patients with:
  - R/R AML
  - Ongoing expansion cohort in frontline AML

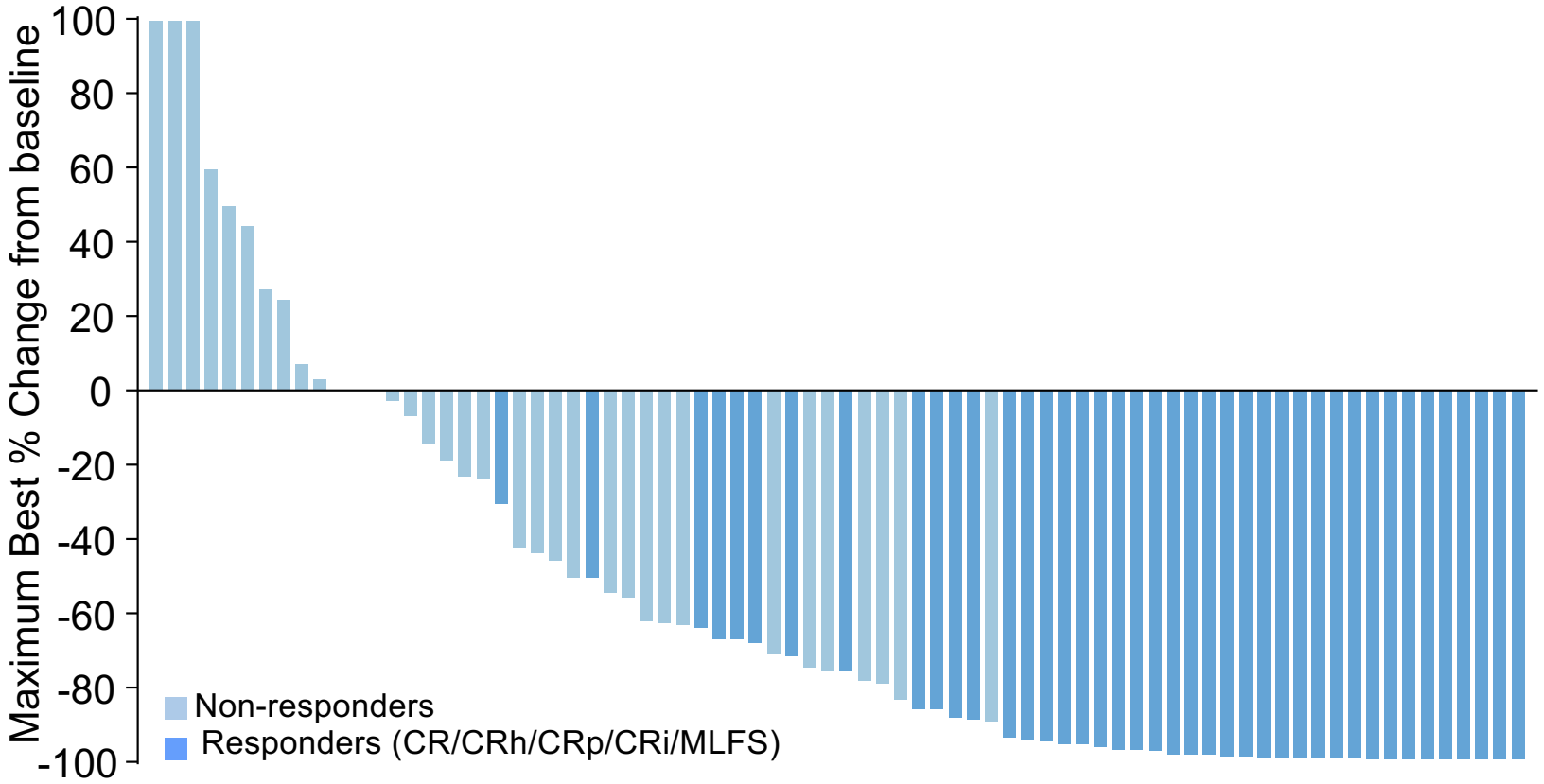




Slide courtesy of Naval Daver, presented at ASH 2022

4. Gill S, et al. *Blood.* 2014; 123(15):2343-2354. 4. Daver N et al. *Blood.* 2019;134 (supp 1):2601. 5. Daver N et al. *Blood*. 2019; 134 (supp 1):734. 6. Kuruvilla VM et al. *Blood.* 2020; 136 (supp 1):32-33.

Phase IB/II PVEK + Azacitidine + Venetoclax: Anti-Leukemic Activity in R/R AML



- Median time to CCR was 1.1 months (range 0.5-6.5)
- Median duration of CCR was 7.7 months (range 0.3-15.6 months)
- Of MRD-evaluable responders, 8 (32%) achieved MRD-negativity*
- 24% of responders (10/41) proceeded to SCT

Note: 15 patients are not represented on the plot due to missing bone marrow data: 10 had clinical disease progression; 3 died without an assessment; 2 were otherwise unevaluable

*MRD assessed centrally by multiparameter flow cytometry with threshold of <0.1% by Hematologics, Inc.

Slide courtesy of Naval Daver, presented at ASH 2022

BM, bone marrow; CCR, composite complete remission; CR, complete remission; ITT, intention-to-treat; MRD, minimal residual disease; R/R, relapsed/refractory; SCT, stem cell transplant.

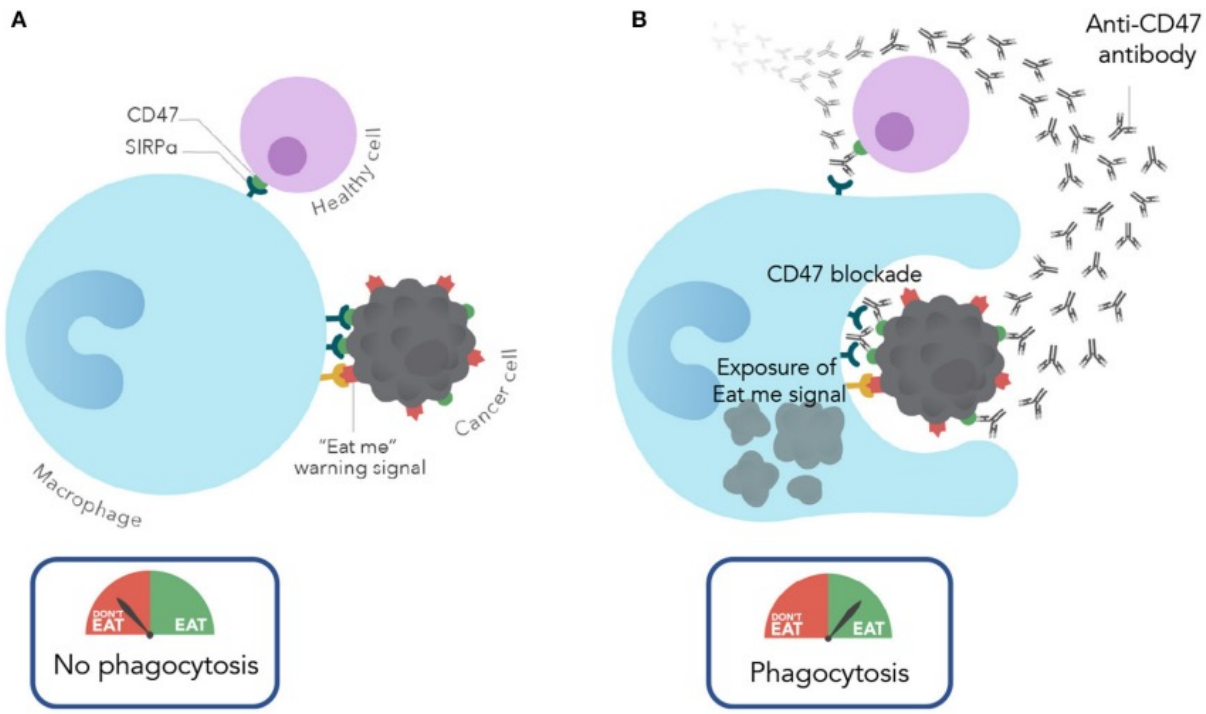
Responses in R/R AML Subsets

ITT Population (all doses and schedules), n=91					
Previous Treatments	**N**	**ORR**	**CCR**	**CR**	**CR/CRh**
VEN naïve	47	53%	38%	26%	34%
Prior VEN	44	36%	11%	0%	9%
First Relapse	32	56%	44%	22%	41%
First Relapse & VEN Naïve	17	65%	59%	41%	53%
Prior Stem Cell Transplant	23	43%	26%	13%	22%
Cytogenetics	**N**	**ORR**	**CCR**	**CR**	**CR/CRh**
ELN Adverse Risk	48	42%	21%	10%	16%
IDH2 Mutant	12	67%	50%	33%	50%
FLT3-ITD	11	82%	64%	18%	54%

Slide courtesy of Naval Daver, presented at ASH 2022

CCR, composite complete remission; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission/response with incomplete recovery; ELN, European LeukemiaNet; ITD, internal tandem duplication; ITT, intention-to-treat; ORR, overall response rate; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; VEN, venetoclax.

Magrolimab

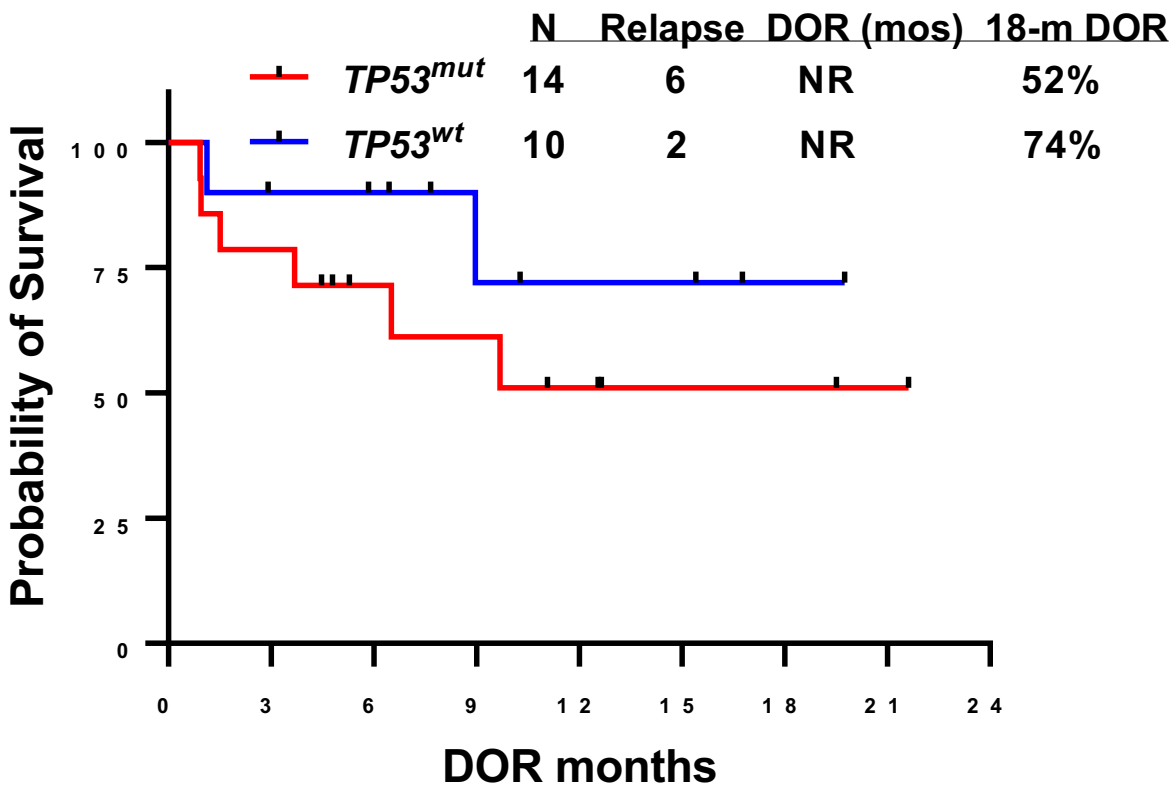


- Mechanism: Anti CD47 monoclonal antibody
- Despite CR/CRi rates of 65-70% in frontline older/unfit AML with AZA-VEN, only 35-40% remain alive beyond 2 yrs
- HMA + CD47 blockade with encouraging safety and activity in single-arm studies in frontline *TP53*^{mut} (CR 33%, mOS 10m) and *TP53*^{WT} AML (CR 42%, mOS 18m)
- Frontline *TP53*^{mut} AML have dismal outcomes with CR/CRi 30-45% (CR 20-30%) and median OS of 5-7 months with intensive or HMA-VEN based approach.

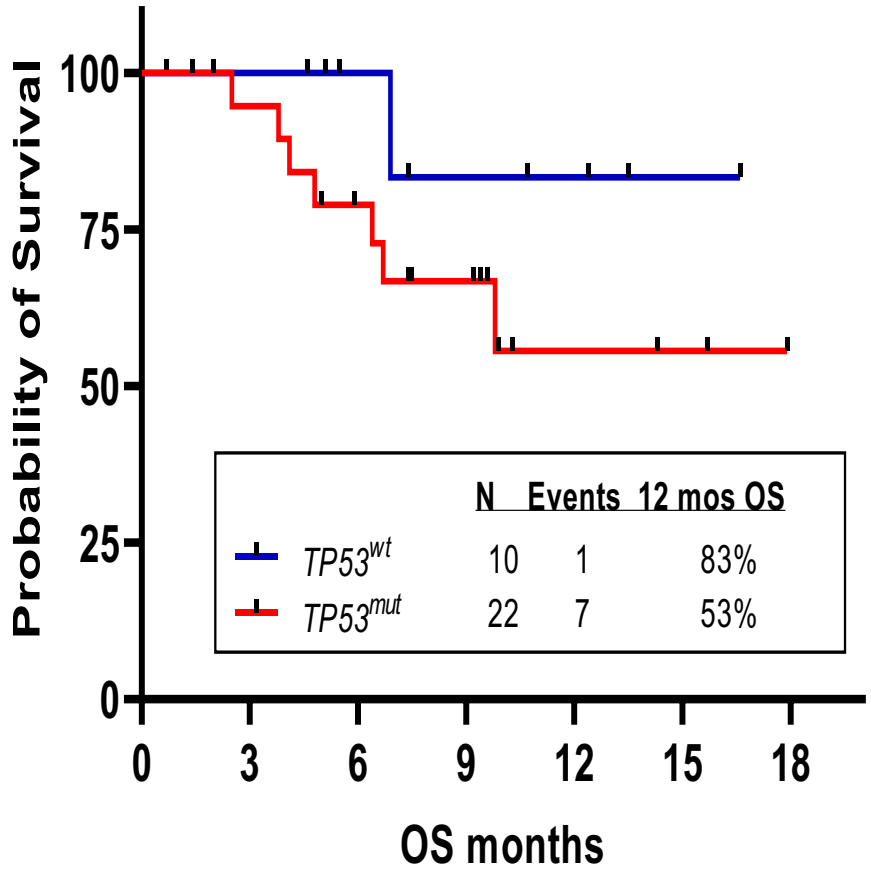
Chao et al. Frontiers 2020

Phase I/II of Azacitidine + Venetoclax + Magrolimab : Duration of Response and Overall Survival in Newly Diagnosed AML with a Median Follow up of 14.5months

DOR (De Novo patients, N=33)



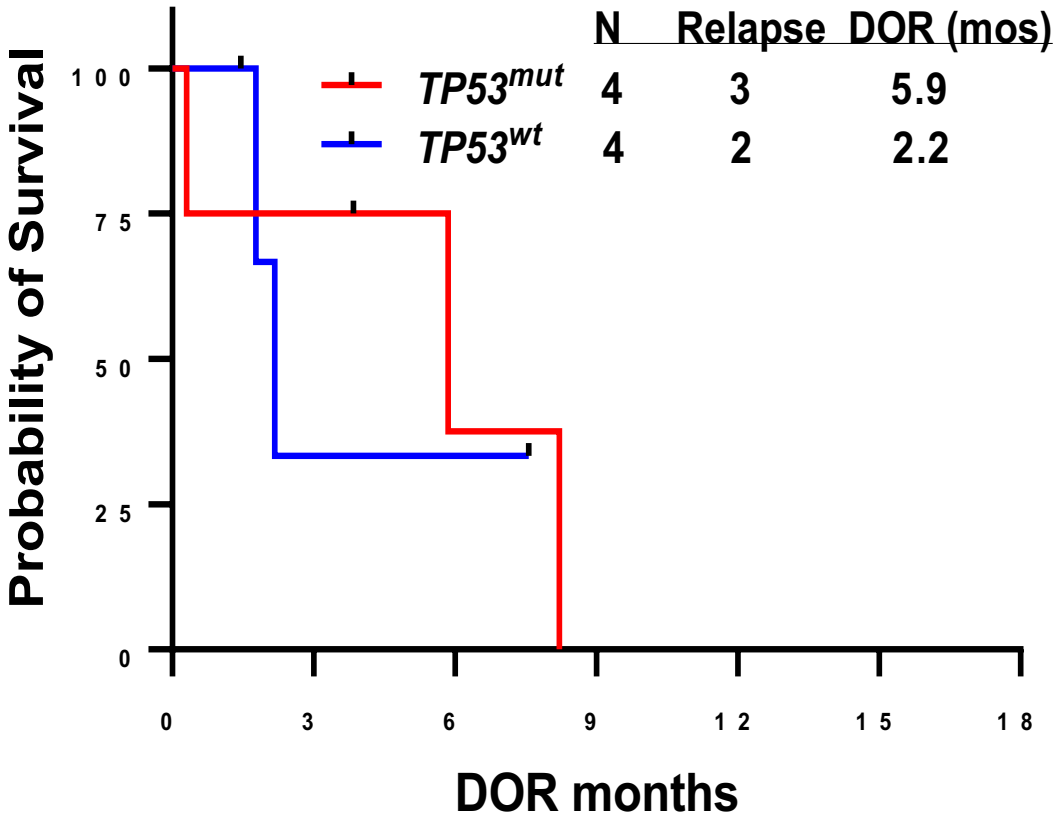
Overall Survival (De Novo patients, n=33)



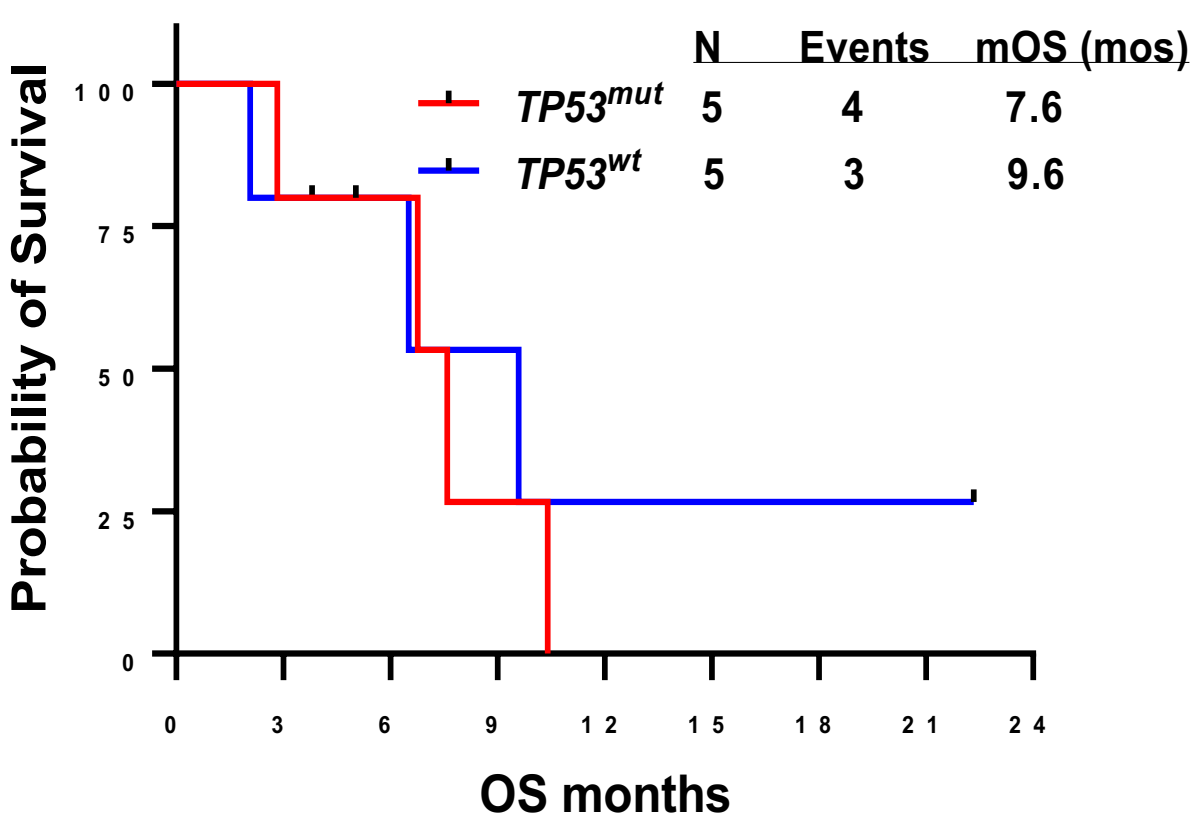
Images courtesy of Naval Daver, presented at ASH 2022

DOR and OS is Not Better for All Subtypes of AML

DOR (Secondary AML, N=10)

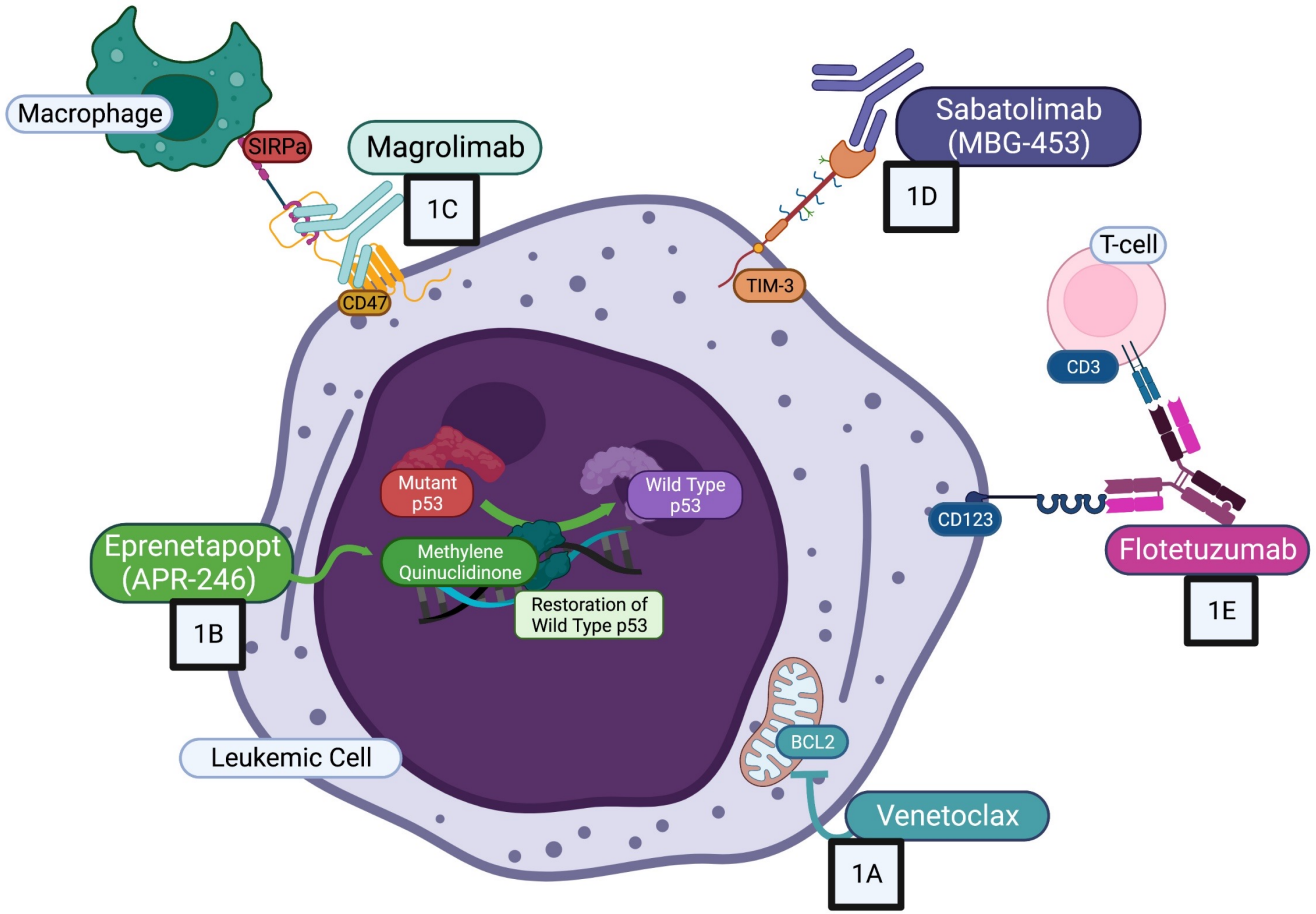


Overall survival (Secondary AML, n=10)



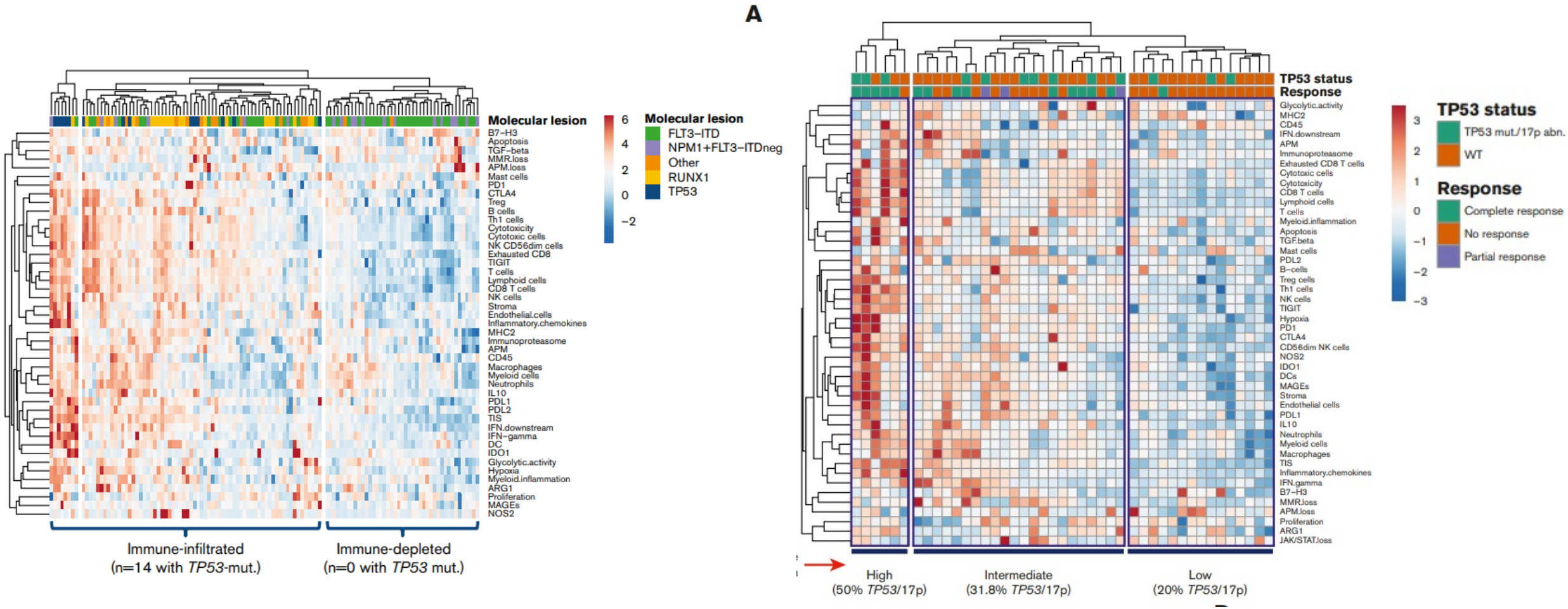
Images courtesy of Naval Daver, presented at ASH 2022

TP53 Remains the Most Challenging to Treat



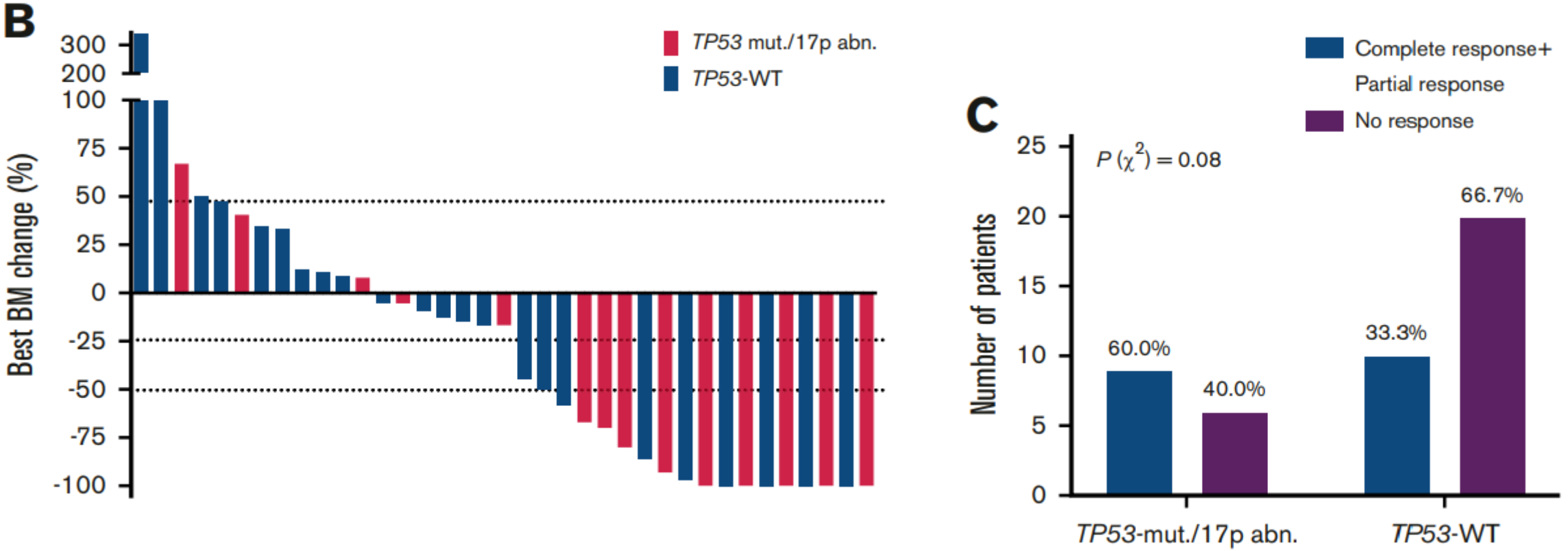
Marks, Lai et al. unpublished

TP53 Mutations Correlate with an Immune-infiltrated Tumor Microenvironment and Response to Flotetuzumab



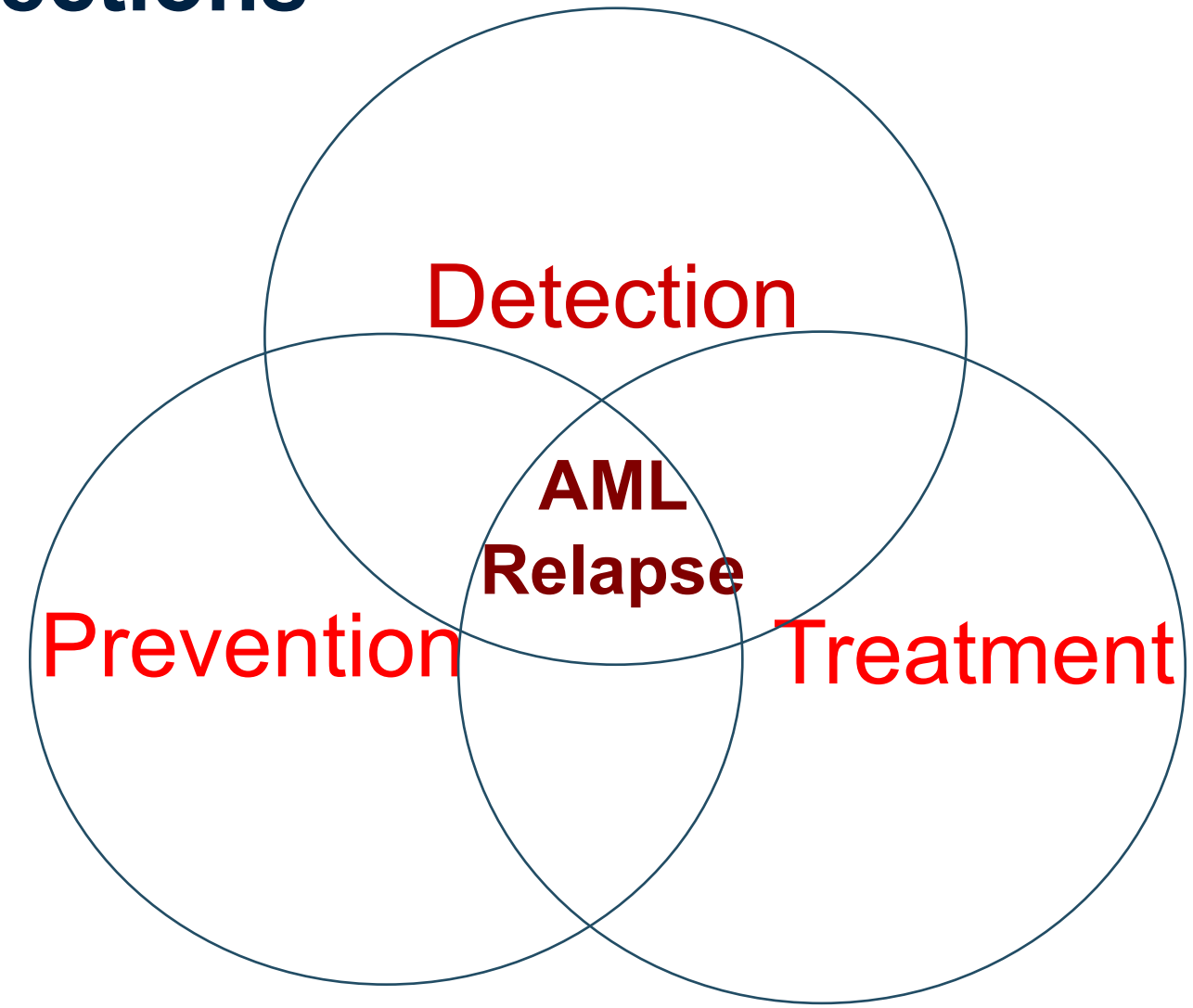
Vadakekolathu J, Lai C et al. Blood Adv, 2020

Response to Flotetuzumab in Patients with *TP53* Mutations and/or 17p deletion

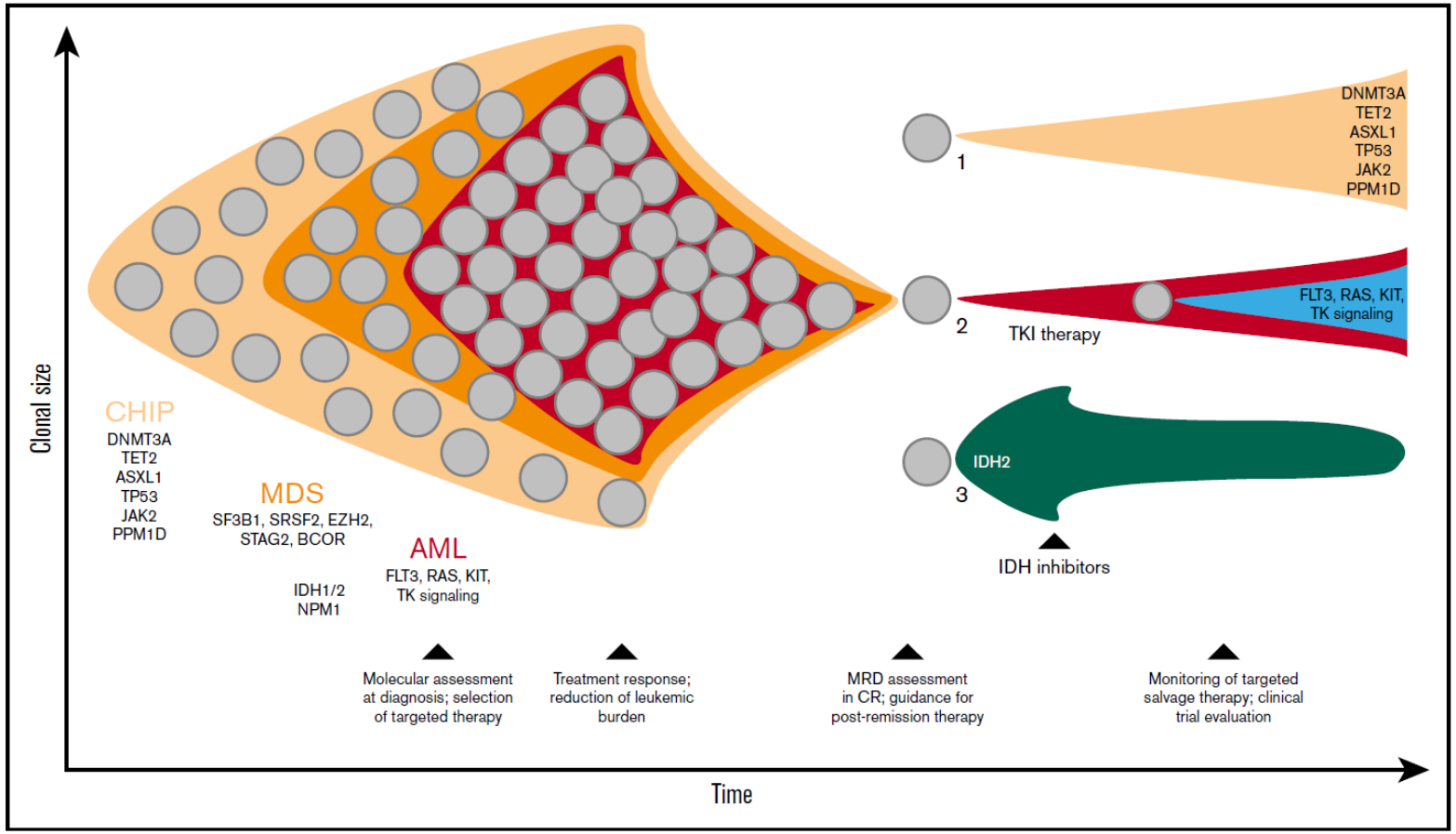


Vadakekolathu J, Lai C et al. Blood Adv, 2020

Future Directions



Molecular Profiling Plays a Role at Diagnosis and Response to Treatment



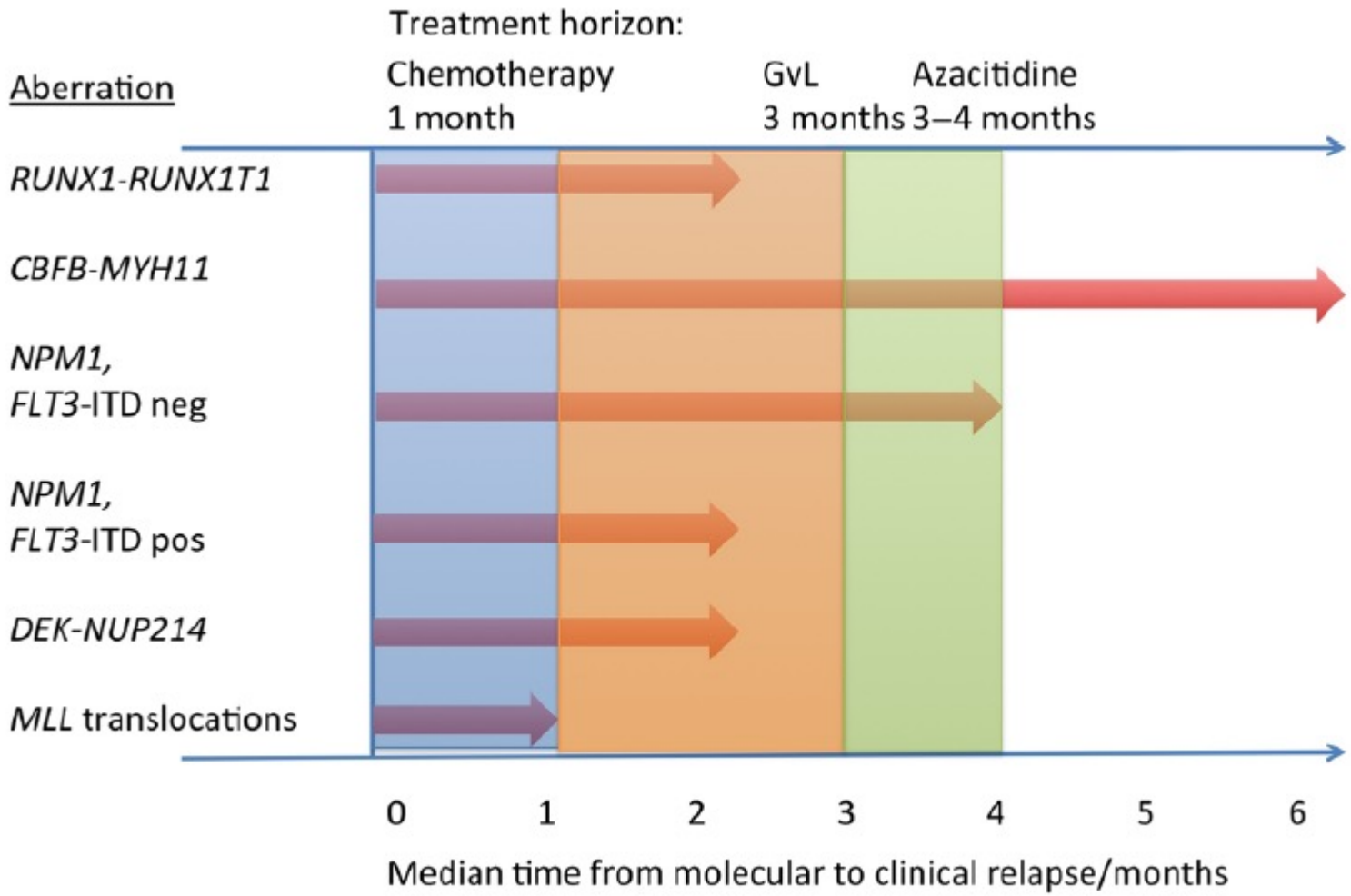
CR

Relapse

MRD

Roloff et al. Blood Advances 2018

Understand Relapse Kinetics of AML



Ommen Ther Adv Hematol 2016

Target Pathways

Functional class	Specific example mutations
Signaling and kinase pathway	*FLT3*, *KRAS*, *NRAS*, *KIT*, *PTPN11*, and *NF1*
Epigenetic modifiers (DNA methylation and chromatin modification)	*DNMT3A*, *IDH1*, *IDH2*, *TET2*, *ASXL1*, *EZH2*, and *MLL/KMT2A*
Nucleophosmin	*NPM1*
Transcription factors	*CEBPA*, *RUNX1*, and *GATA2*
Tumor suppressors	*TP53*
Spliceosome complex	*SRSF2*, *U2AF1*, *SF3B1*, and *ZRSR2*
Cohesin complex*	*RAD21*, *STAG1*, *STAG2*, *SMC1A*, and *SMC3*

DiNardo et al. ASH Educ 2016

Take home message

Normal bone marrow

Bone marrow with AML

- Know the types of flowers in your garden = What molecular abnormalities are present? What mutations are driving the disease burden?
- Understand the optimal conditions for growth = Modify how we approach standard therapy in older AML
- Use the appropriate weed killer = Tailor treatment to individual genetic profiles and physiologic function to change survival outcomes

“The greater our knowledge increases, the greater our ignorance unfolds.”

- John F. Kennedy

Questions?

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Thank you!