Evolving Paradigms in Up-Front Treatment for Older Patients or Those Ineligible for Intensive Chemotherapy

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Research To Practice
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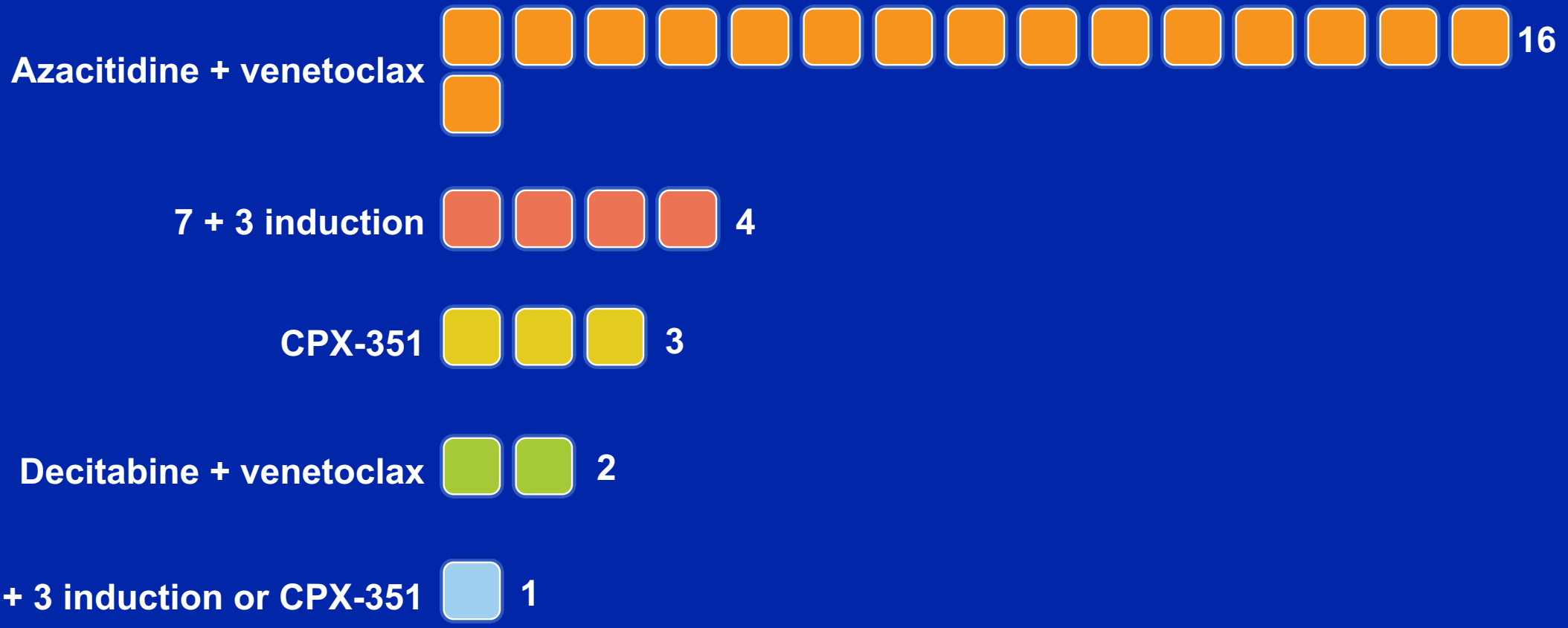
Disclosures

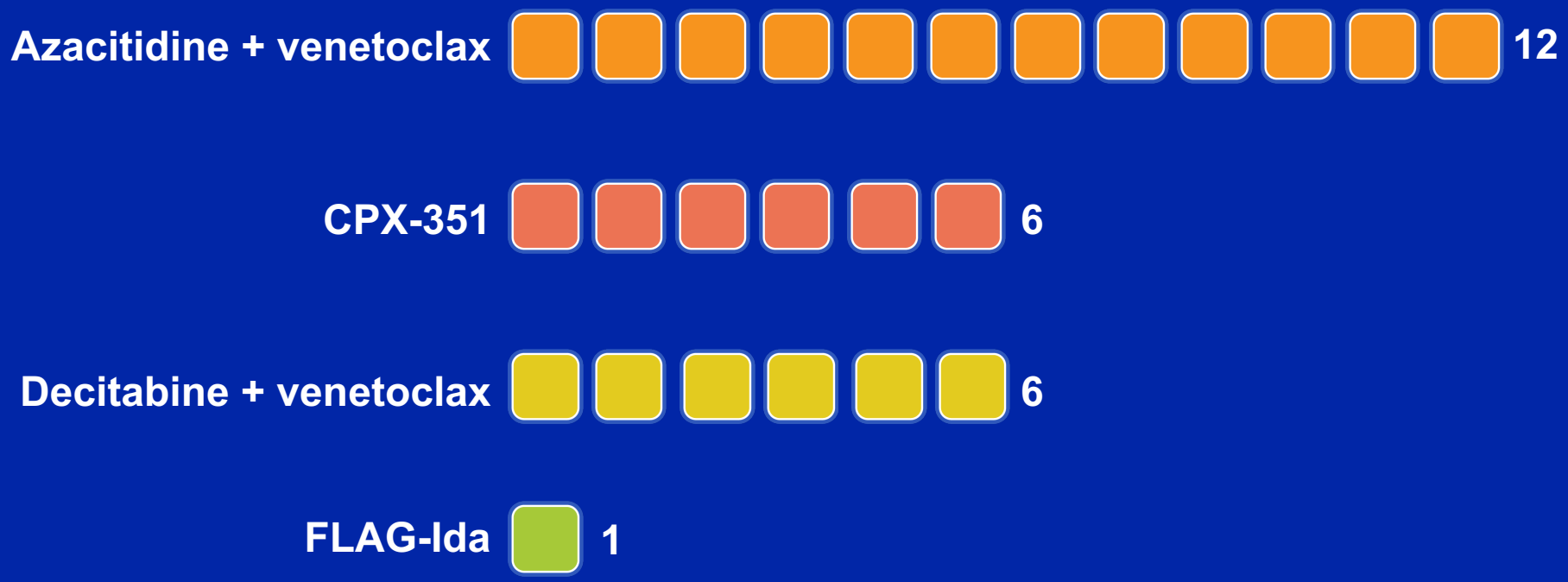
Advisory Committee	AbbVie Inc, Agios Pharmaceuticals Inc, argenx, Celgene Corporation, Celyad, Forty Seven Inc, Gilead Sciences Inc, Janssen Biotech Inc, Pfizer Inc
Consulting Agreements	AbbVie Inc, Astellas, Daiichi Sankyo Inc, Genentech, Takeda Oncology
Contracted Research	AbbVie Inc, Agios Pharmaceuticals Inc
Data and Safety Monitoring Board/Committee	GlycoMimetics Inc, Tolero Pharmaceuticals

What initial treatment would you recommend for a 68-year-old woman with AML with a performance status (PS) of 2 and a history of hypertension, coronary artery disease, anemia for 2 years with unclear etiology and diabetes mellitus, assuming organ function is normal?



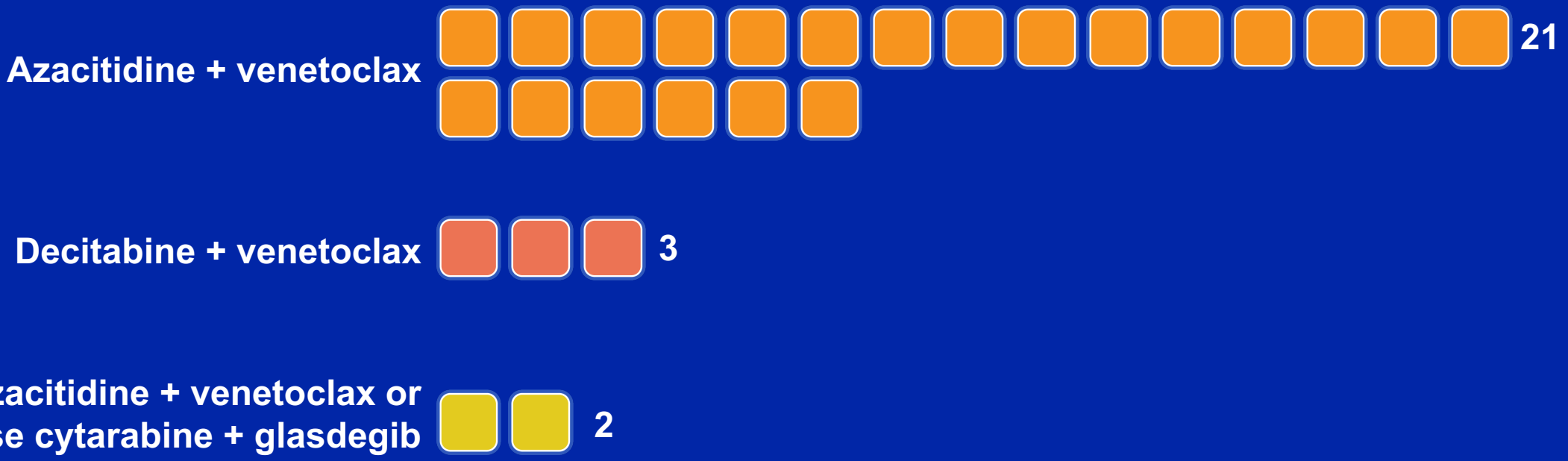
N = 26

What initial treatment would you recommend for a 65-year-old man with AML with a PS of 1 and pancytopenia, 35% marrow myeloblasts, a complex karyotype and a TP53 mutation?



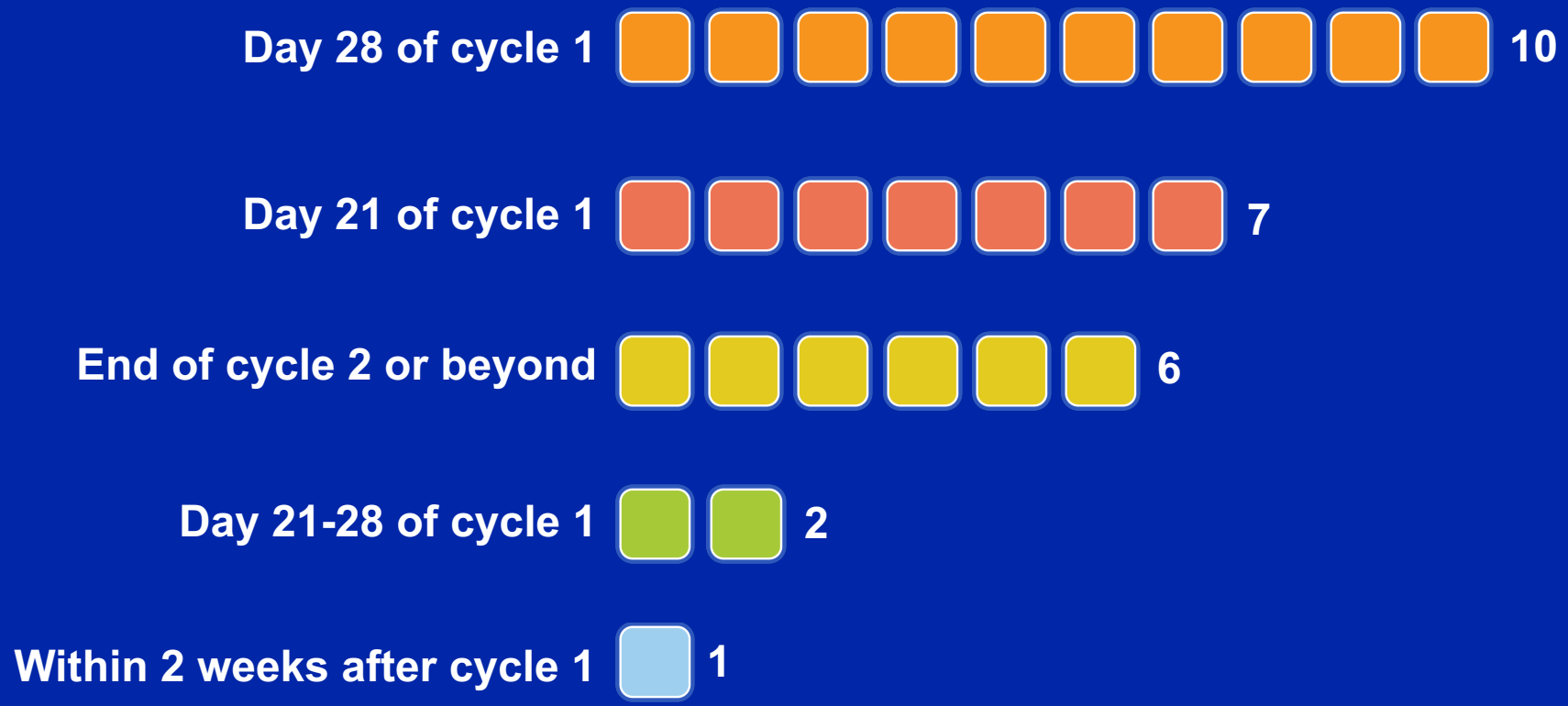
N = 25

What initial treatment would you generally recommend for an 80-year-old woman with AML with intermediate-risk cytogenetics?



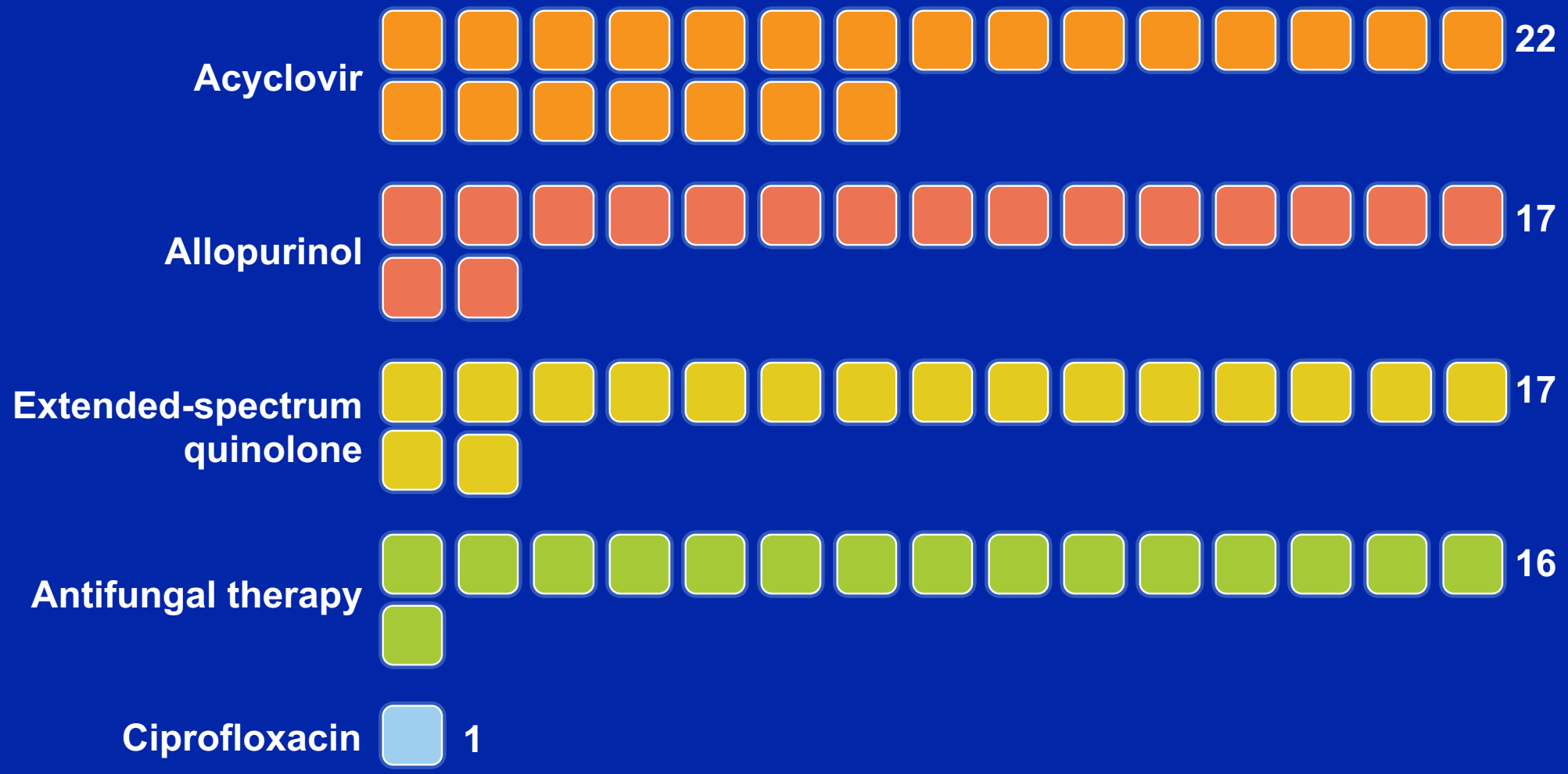
N = 26

When do you perform the first bone marrow evaluation in a patient to whom you are administering venetoclax in combination with a hypomethylating agent (HMA) or low-dose cytarabine?



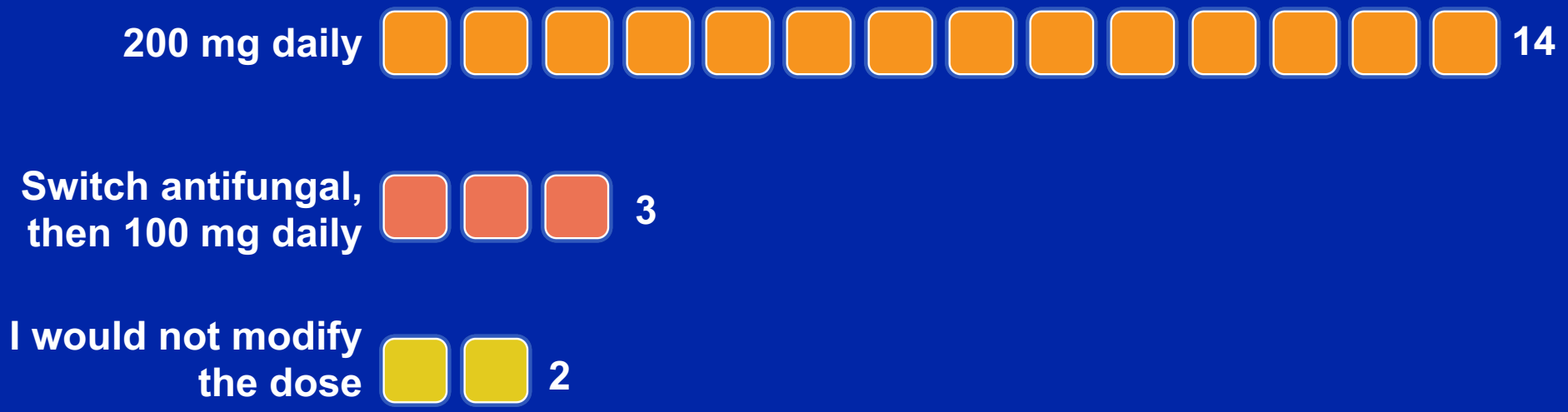
N = 26

Which of the following do you generally administer as prophylaxis to patients receiving venetoclax in combination with azacitidine? (Select all that apply.)



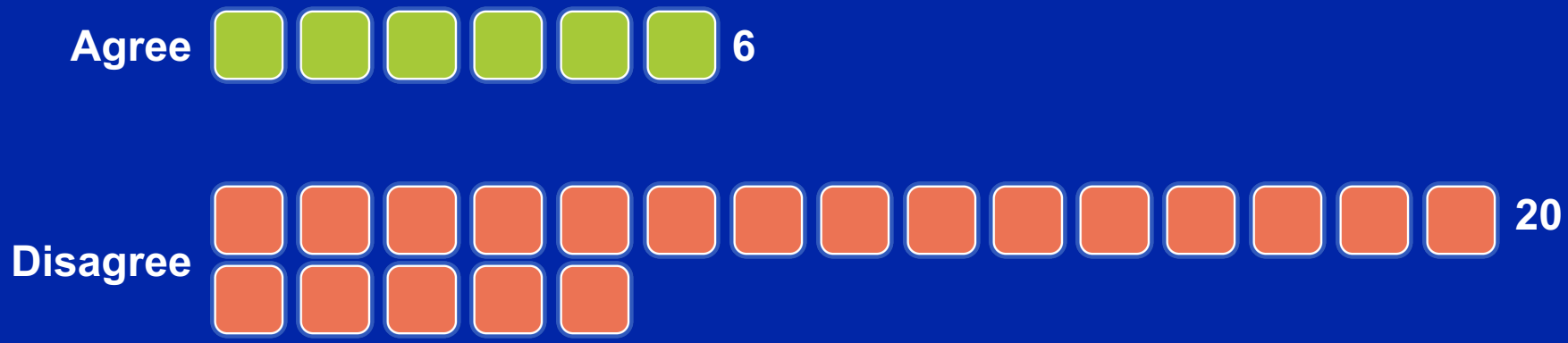
N = 26

How, if at all, would you modify your approach to venetoclax dosing for a patient who is receiving fluconazole?



N = 19

All patients with AML who are receiving venetoclax in combination with an HMA should be admitted to the hospital regardless of disease burden or performance status.



N = 26

A Younger Patient with AML and High-Risk Factors who Received Venetoclax+HMA

- 35 year old woman with ulcerative colitis and prior thyroid cancer s/p thyroidectomy develops fatigue and weakness over 3 month period.
- Noted to have pancytopenia and bone marrow biopsy confirms AML with 35% blasts and an inv(3;3) cytogenetic abnormality with an SF3B1 mutation on next generation sequencing.
- Patient is a fit candidate for induction chemotherapy but is a Jehovah's witness and refuses to accept blood product transfusions, making her ineligible for induction chemotherapy.
- Venetoclax is acquired and initiated with azacitidine, at 50% dose for 5 instead of 7 days.

A Younger Patient with AML and High-Risk Factors who Received Venetoclax+HMA

- During cycle 1 the patient's lowest hemoglobin is 7.2 g/dL and lowest platelet count is 35. No bleeding complications. The course is complicated by a DVT, treated with a DOAC.
- After cycle 1 the patient has achieved a CRi. She continues subsequent cycles, with no opportunity for an allogeneic stem cell transplantation, and is currently 18 months into therapy in an ongoing CR with bone marrow biopsies every 6 months.

An Older Patient with AML Who Is Not Eligible for Intensive Chemotherapy and Received Venetoclax/HMA

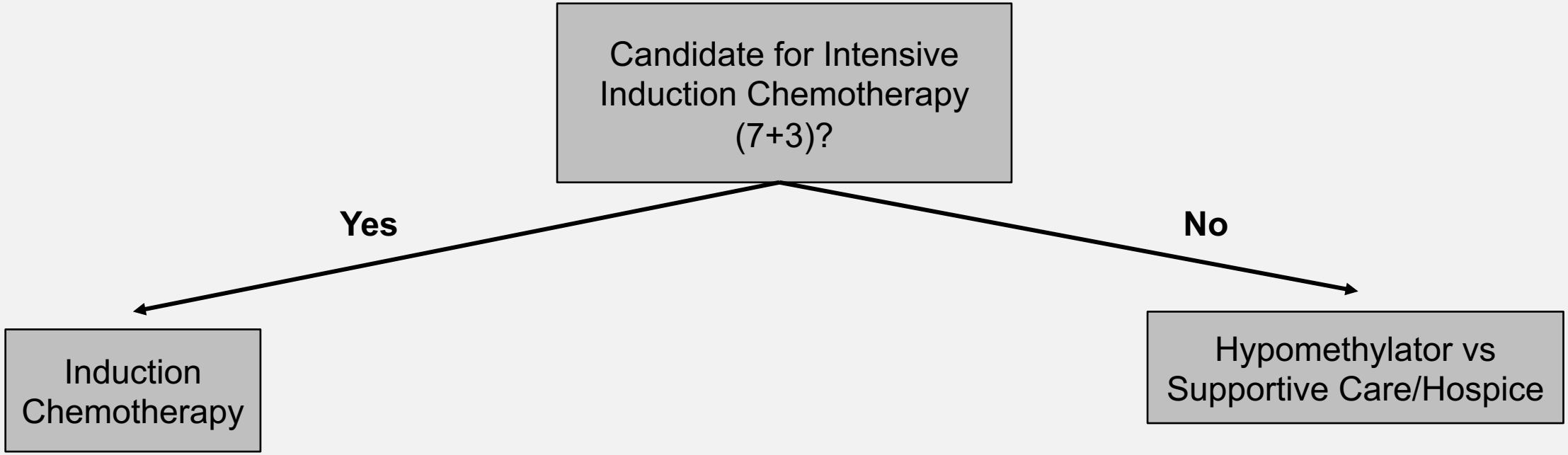
- 69 YO F who lives independently in an assisted facility for significant developmental delay since birth, etiology unknown, IQ commensurate with an 8-10 year old, found down in her room and later noted to have a WBC>100K.
- Stabilized, bone marrow biopsy confirms AML with 70% blasts, normal femal karyotype, later noted to have mutations in FLT3 (ITD), NPM1, DNMT3A.
- Hydroxyurea initiated then leukapheresis for respiratory concerns; after extensive discussion with patient and family decide to initiate therapy with venetoclax + azacitidine.
- On day 2 WBC 22,000 and treatment initiated.
- Uncomplicated treatment initiation with rapid clearance of circulating blasts and no evidence of TLS with aggressive mitigation.

An Older Patient with AML Who Is Not Eligible for Intensive Chemotherapy and Received Venetoclax/HMA

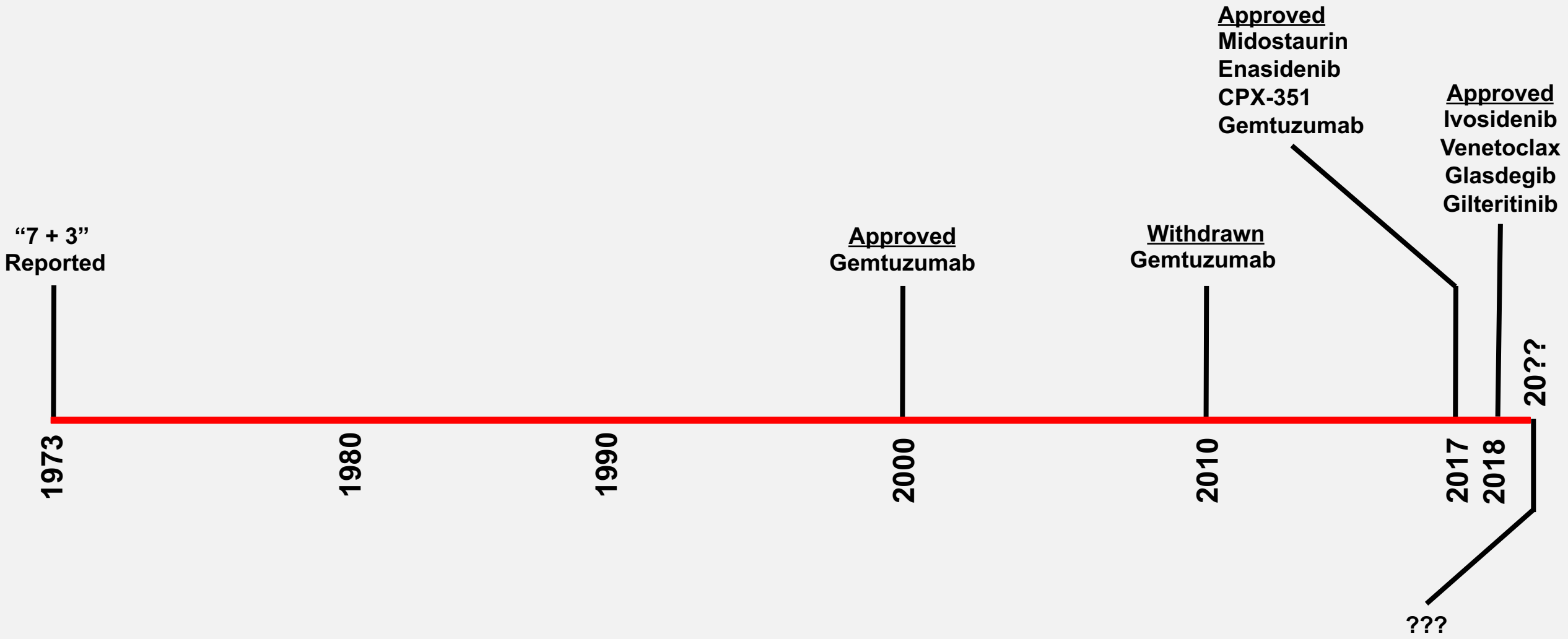
- Day 28 bone marrow biopsy shows morphologic remission without recovery of platelets or ANC. After 2 week delay, with use of 3 doses of filgrastim, platelets are 125 and ANC 2.4. Cycle 2 recommended, as outpatient.
- Patient receives 6 cycles with continued logistical challenges receiving the azacitidine each month; recommended to transition to venetoclax alone.
- Eight months after this decision the patient relapses and no treatment is recommended; the patient expires in hospice two months later.

The Treatment of AML
Flashback: March 2017

Binary treatment approach to newly-diagnosed older AML patient

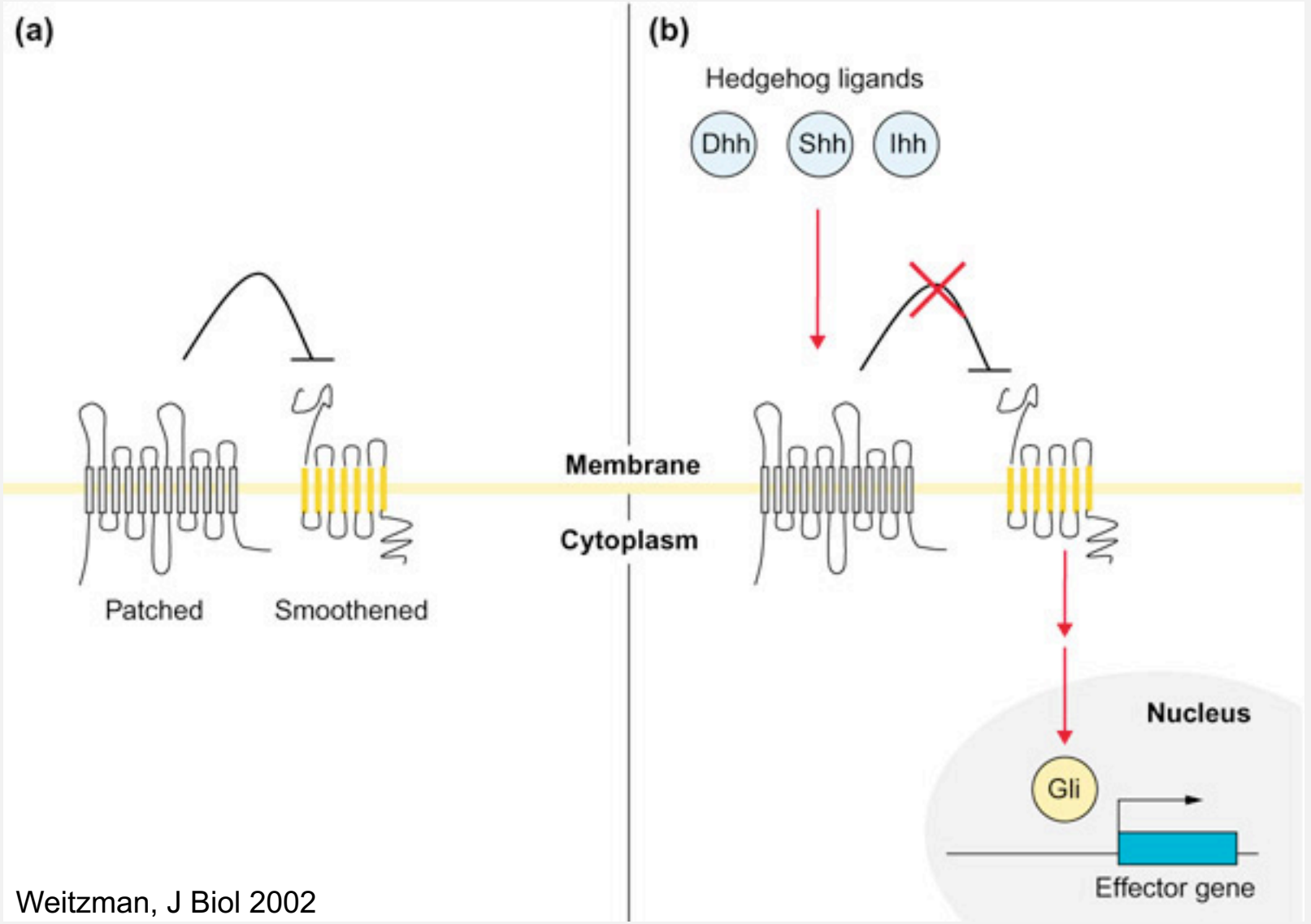


Recent Explosion of AML Drugs Approved



Glasdegib: Inhibitor of Smoothened

- Glasdegib is a Hedgehog pathway inhibitor
- Aberrant Hedgehog signaling implicated in hematologic malignancies and is critical for leukemia stem-cell survival and expansion



Weitzman, J Biol 2002

Glasdegib in Newly Diagnosed AML

- BRIGHT 1003: Phase II, randomized, open-label trial
- Patients had AML or high-risk MDS and were unfit for intensive chemotherapy (N = 132)
- Glasdegib 100 mg (oral, QD) + LDAC 20 mg (subQ, BID) vs LDAC
- Patients stratified by cytogenetic risk, randomized 2:1
- >50% of enrolled patients older than 75 years of age

Cortes et al, Leukemia 2019.

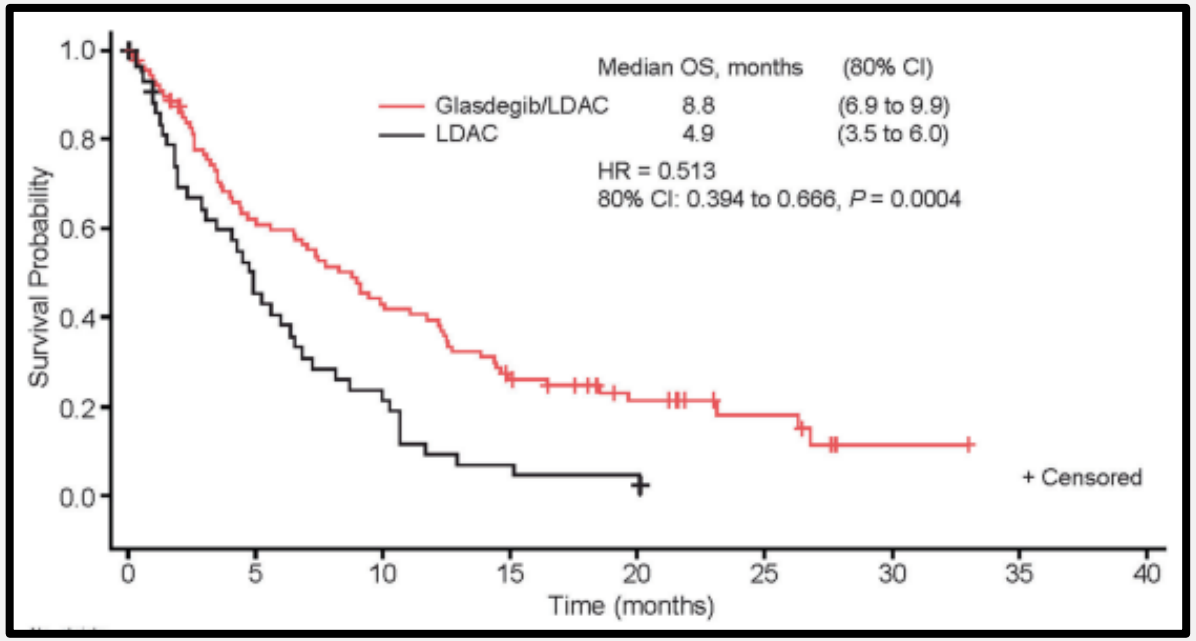
Glasdegib Study Results: Toxicity and Efficacy

MedDRA preferred term[a], *n* (%)	Glasdegib 100 mg+LDAC, *N* = 84			
	Grade 1–2	Grade 3–4	Grade 5	Total
Any AEs	6 (7.1)	54 (64.3)	24 (28.6)	84 (100.0)
Anemia	3 (3.6)	35 (41.7)	0	38 (45.2)
Febrile neutropenia	0	30 (35.7)	0	30 (35.7)
Nausea	28 (33.3)	2 (2.4)	0	30 (35.7)
Decreased appetite	25 (29.8)	3 (3.6)	0	28 (33.3)
Fatigue	14 (16.7)	12 (14.3)	0	26 (31.0)
Thrombocytopenia	0	26 (31.0)	0	26 (31.0)
Pneumonia	4 (4.8)	14 (16.7)	6 (7.1)	24 (28.6)
Diarrhea	19 (22.6)	4 (4.8)	0	23 (27.4)
Pyrexia	21 (25.0)	2 (2.4)	0	23 (27.4)
Edema peripheral	22 (26.2)	0	0	22 (26.2)
Constipation	20 (23.8)	1 (1.2)	0	21 (25.0)
Dysgeusia	21 (25.0)	0	0	21 (25.0)
Dyspnea	15 (17.9)	6 (7.1)	0	21 (25.0)
Muscle spasms	15 (17.9)	4 (4.8)	0	19 (22.6)
Cough	18 (21.4)	0	0	18 (21.4)
Dizziness	17 (20.2)	1 (1.2)	0	18 (21.4)
Vomiting	16 (19.0)	2 (2.4)	0	18 (21.4)

[a] MedDRA (version 19.1) coding dictionary applied

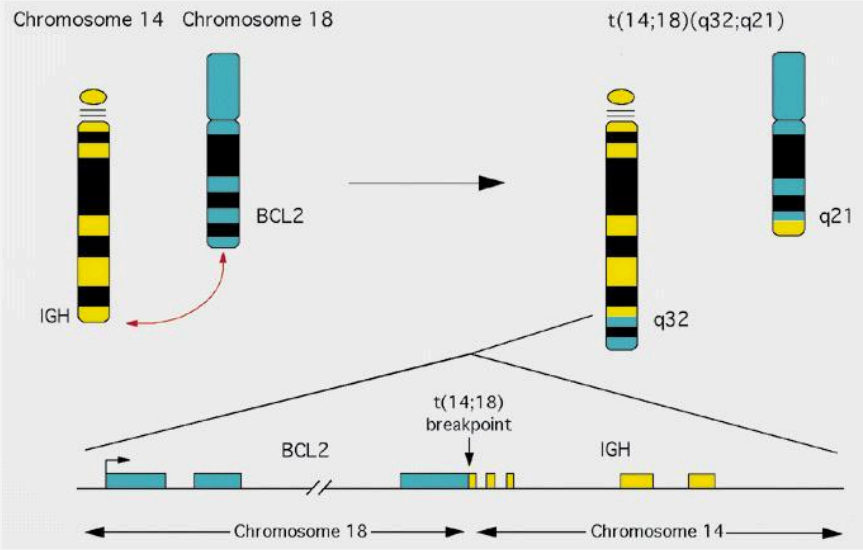
Cortes et al, Leukemia 2019.

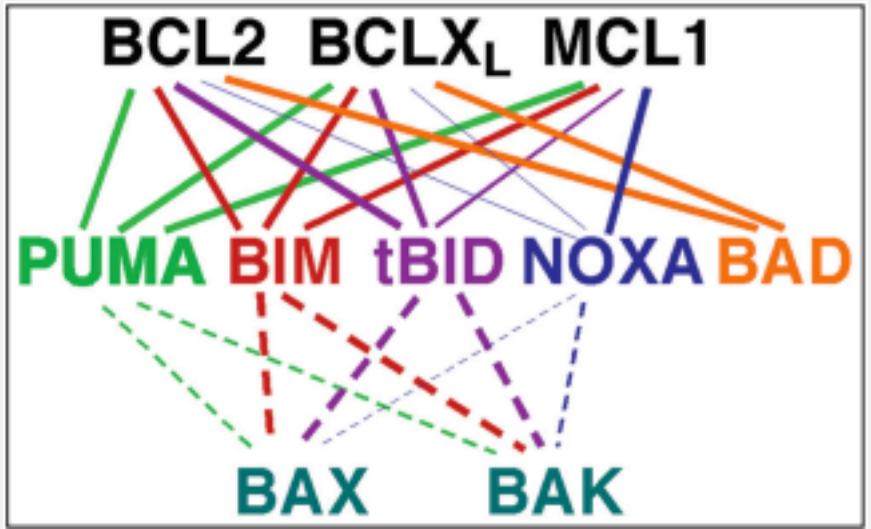
Response	LDAC + Glasdegib	LDAC
AML	n = 78	n = 38
CR, n (%)	14 (18)	1 (3)
CR/CRi, n (%)	19 (24)	2 (5)



BCL-2 Family of Proteins Mediate Apoptosis

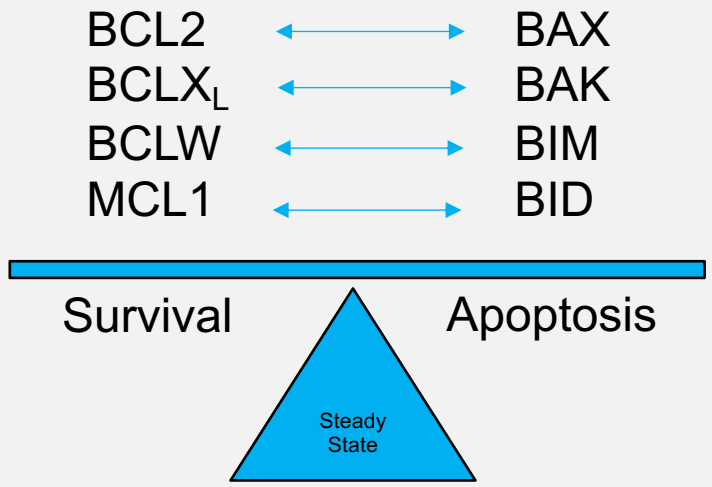
- BCL-2 gene discovered at the t(14;18) breakpoint in follicular lymphoma
  - Results in overexpression
- BCL-2 overexpression did not cause proliferation; it impaired cell death
  - Nearly universally overexpressed in many B-cell lymphomas
- Multiple BCL-2 family of proteins, of which BCL-2 is a member
  - Critical function to control apoptosis

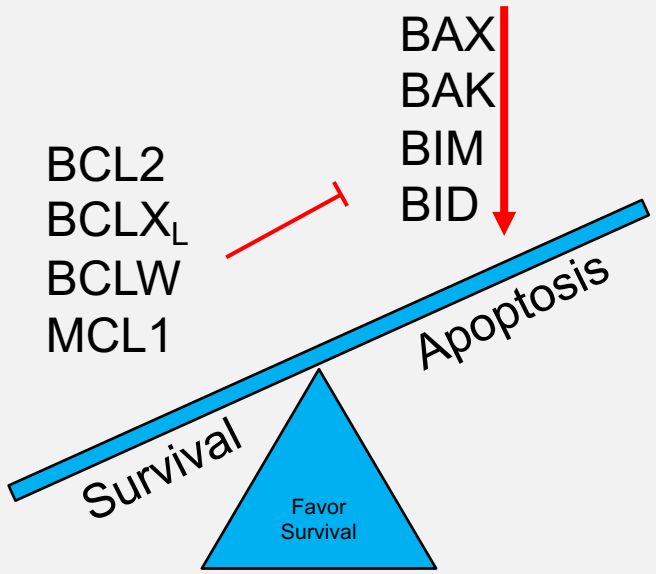




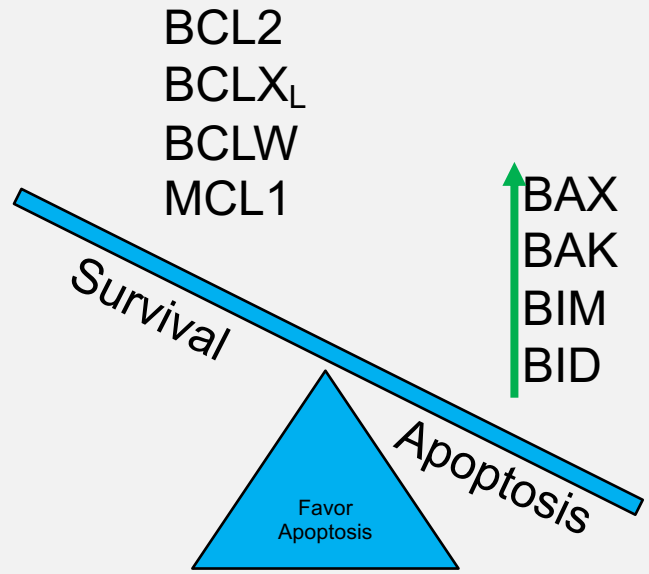
Tsujimoto et al. Science 1985
Cleary et al. Cell 1986
Dai et al. Cancer Transl Med 2016.

Cells Use the BCL-2 Family of Proteins to Decide Whether to Die or to Survive





Anti-apoptotic proteins bind and sequester pro-apoptotic proteins



BH3 proteins bind anti-apoptotic proteins, resulting in the release and activation of pro-apoptotic proteins

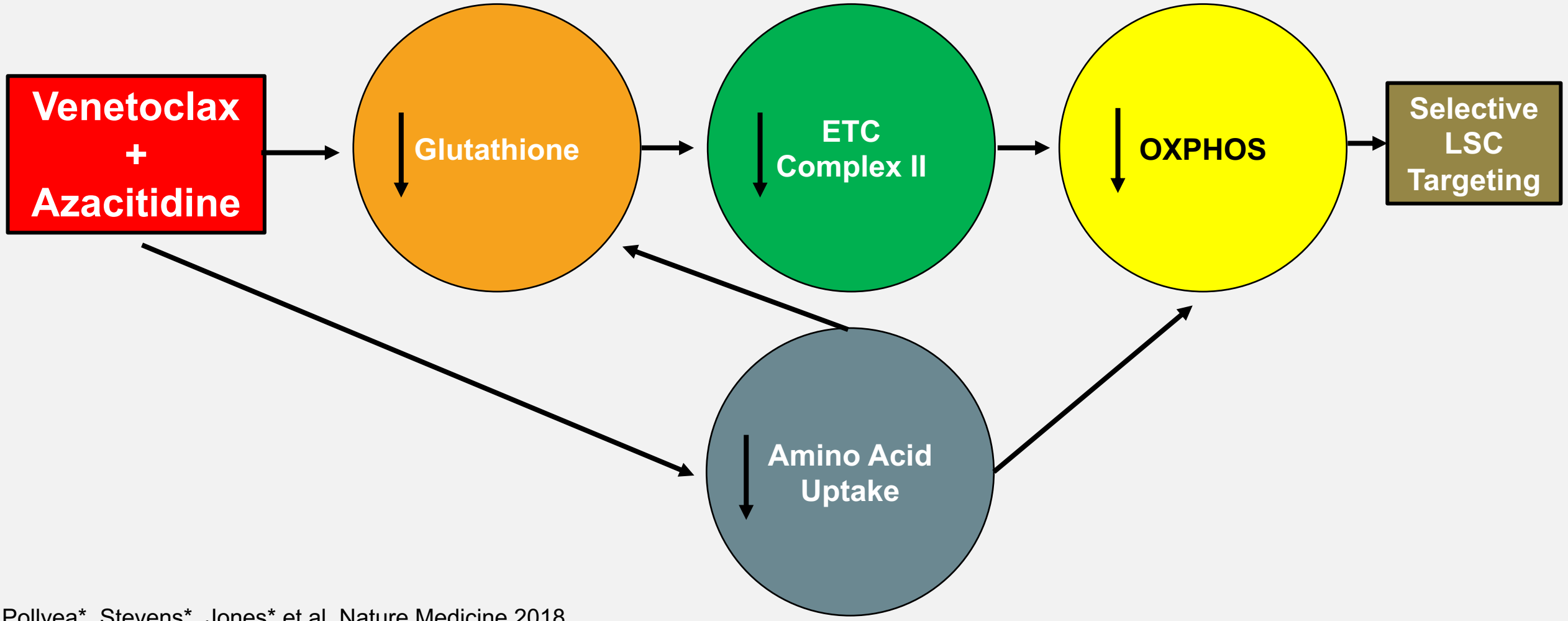
Rationale for BCL-2 Inhibition in AML

- Targeting BCL-2 may allow for apoptosis to be restored
- BCL-2 overexpression associated with worse outcomes in AML, and higher resistance to conventional therapy
- But BCL-2 overexpression not universal in AML

Additional rationale for targeting BCL-2 in AML?

Karakas et al. Annals of Oncology 1998
Lauria et al. Leukemia 1997
Campos et al. Blood 1993
Certo, Letai et al. Cancer Cell 2006

Venetoclax + Azacitidine Specifically Targets Untreated LSCs by Altering Metabolism

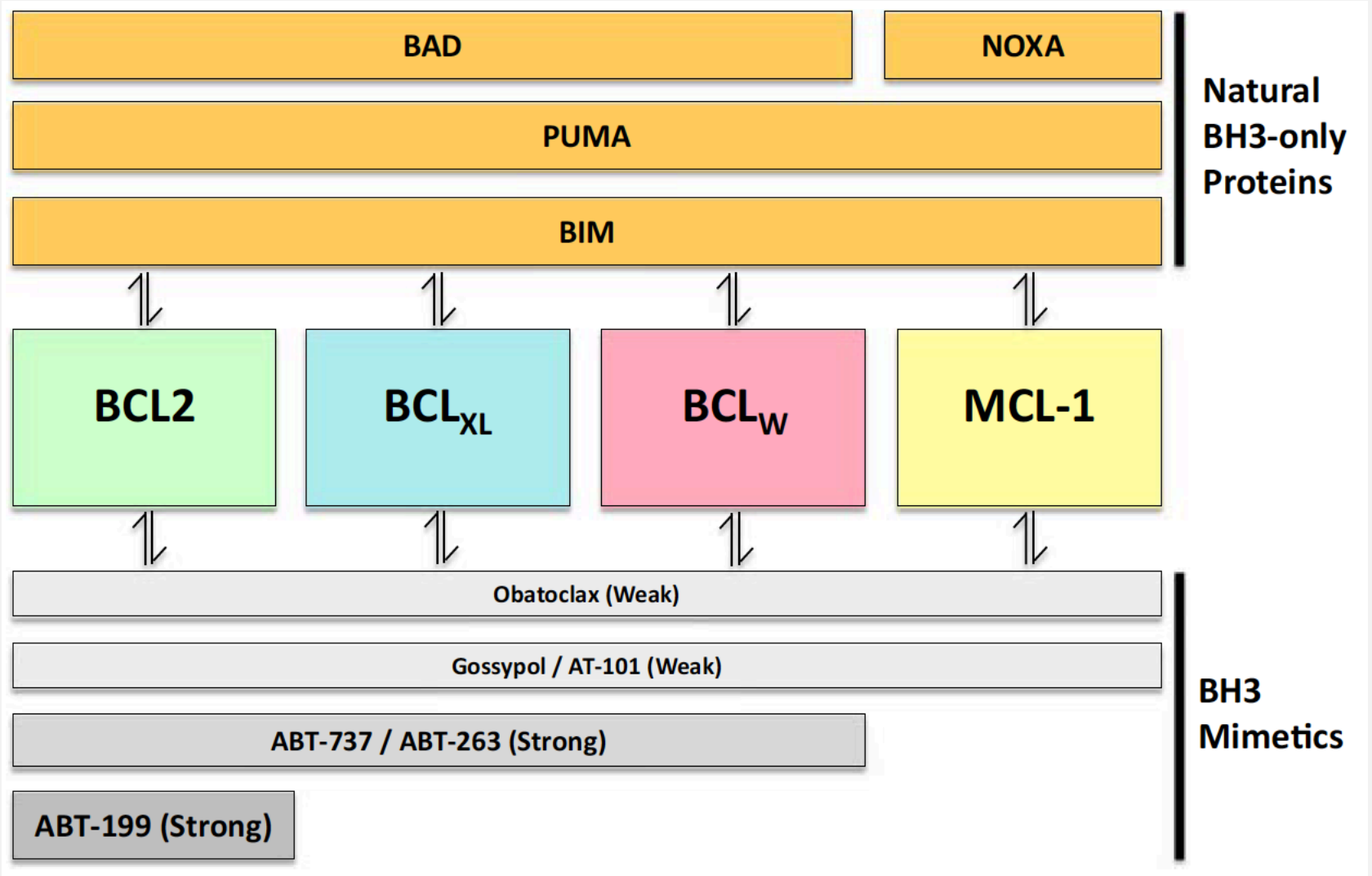


Pollyea*, Stevens*, Jones* et al. Nature Medicine 2018.
Jones et al. Cancer Cell 2018.

Pre-Venetoclax BCL-2 Inhibitor Clinical Trials in AML

Drug	Mechanism	Clinical Setting	Response	Reference
Oblimersen	Antisense oligonucleotide	Phase 1: Relapsed/refractory AML combined with FLAG	7/17 CR+CRi+MLFS	Marcucci et al, Blood 2003
		Phase 1: Older untreated AML combined with 7+3	14/29 CR	Marcucci et al, JCO 2005
		Phase 2: Older relapsed AML combined with gemtuzumab	12/48 CR+CRp	Moore et al, Leukemia Research 2006
		Phase 3: Randomized study of chemotherapy +/- oblimersen for untreated elderly AML	No difference in CR or OS for experimental arm	Marcucci et al, ASCO presentation, 2007
Obatoclax	BH3 mimetic; pan BCL-2 inhibitor	Phase 1: Single agent; refractory AML/MDS	1/25 AML (CR) 3/14 MDS (HI)	Schimmer et al. Clin Cancer Res 2008
		Phase 2: Single agent; untreated MDS	2/24 (HI)	Arellano et al. Clin Lymph Myel Leuk 2014
		Phase 1/2: Single agent; older untreated AML	0/18 responses	Schimmer et al. PLOS ONE 2014

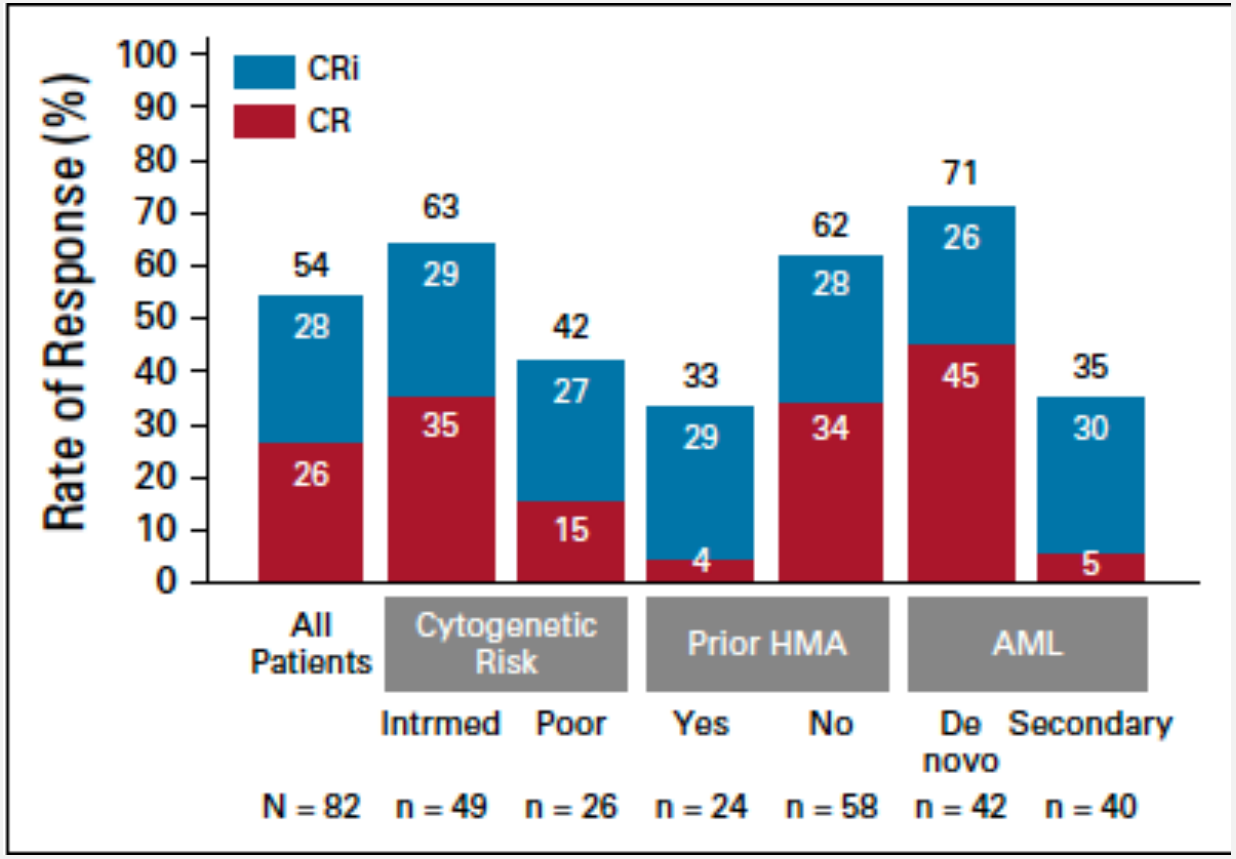
Venetoclax (ABT-199) is a Potent, Selective Inhibitor of BCL-2

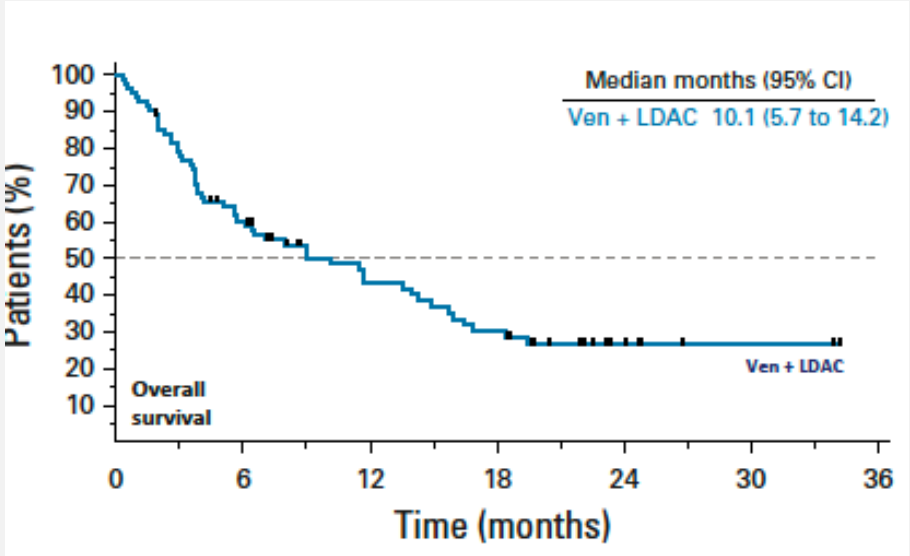


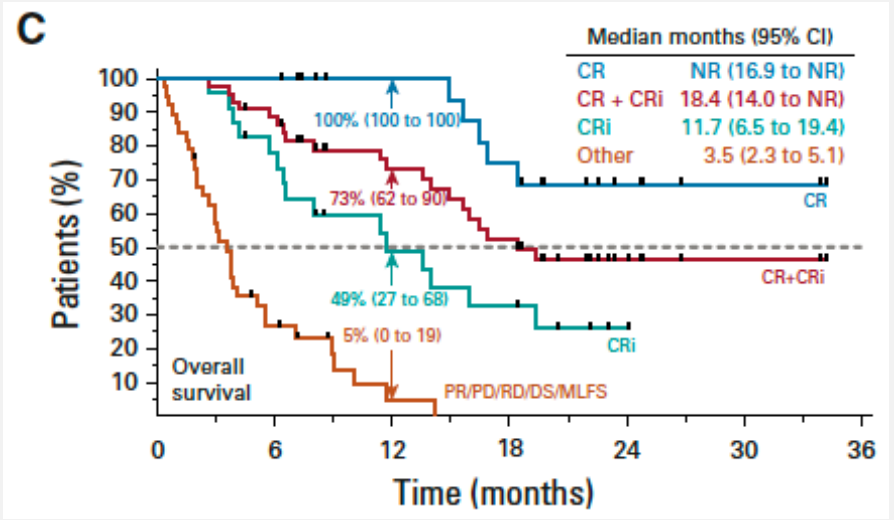
Tam et al. Seminars in Oncology 2016

Venetoclax Plus LDAC in Newly Diagnosed Elderly AML Patients

- Venetoclax dose escalated to maximum dose of 600 mg/daily
- LDAC given 20 mg/m^2 SC daily on days 1-10

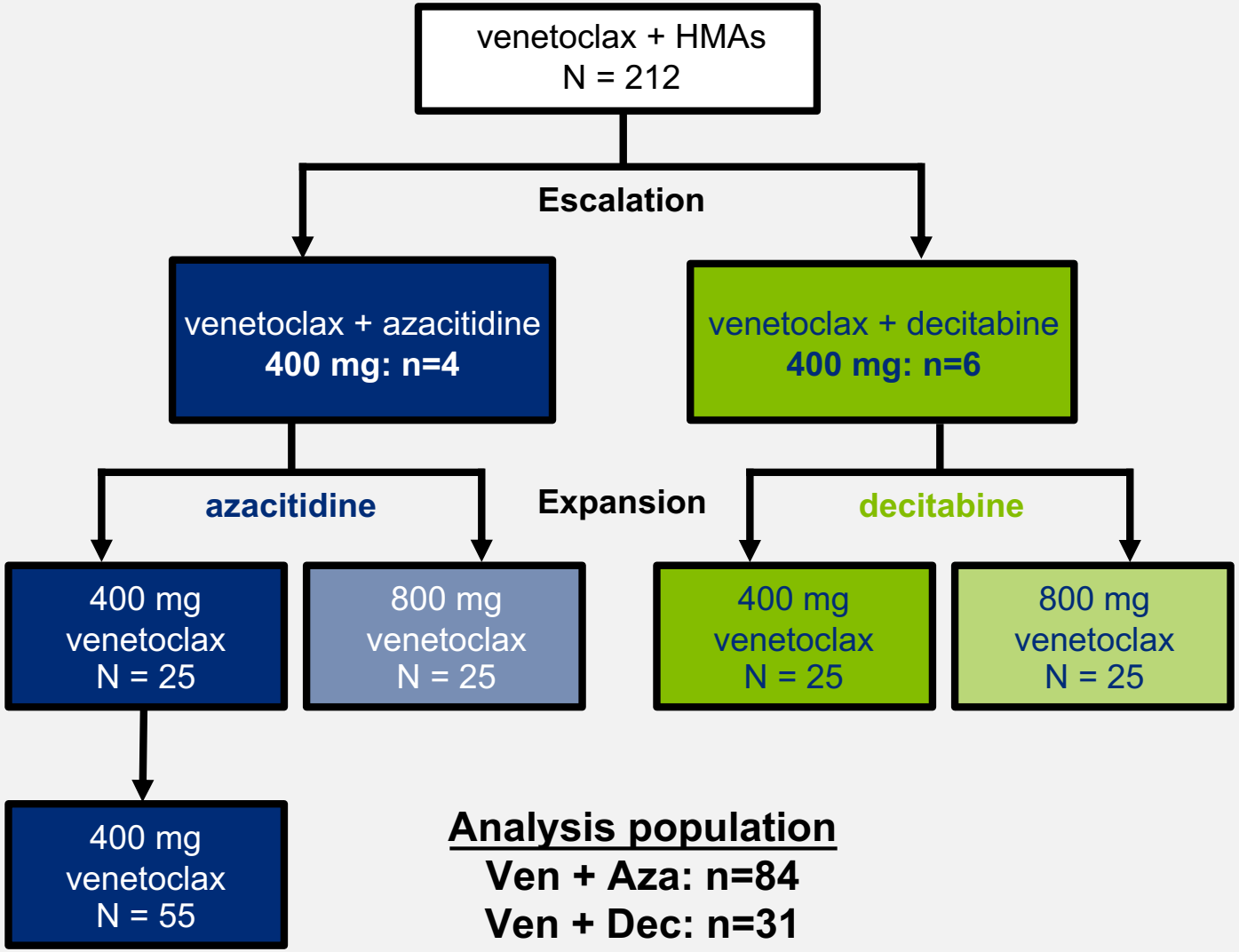






Wei et al, JCO 2019

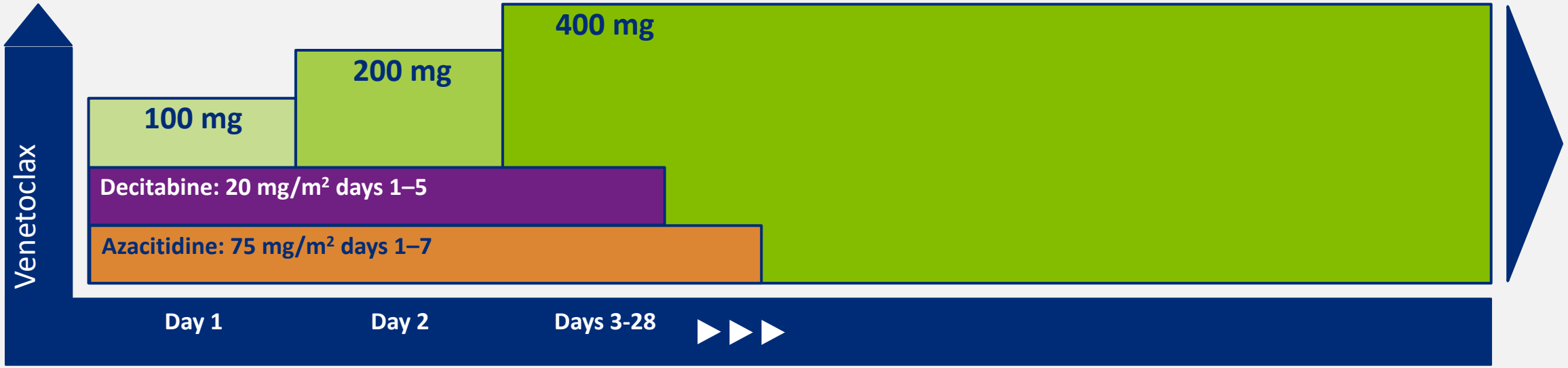
Venetoclax Plus a Hypomethylator in Newly Diagnosed Elderly AML Patients



Analysis population
Ven + Aza: n=84
Ven + Dec: n=31

Pollyea et al, ASH 2018
DiNardo et al, Blood 2019

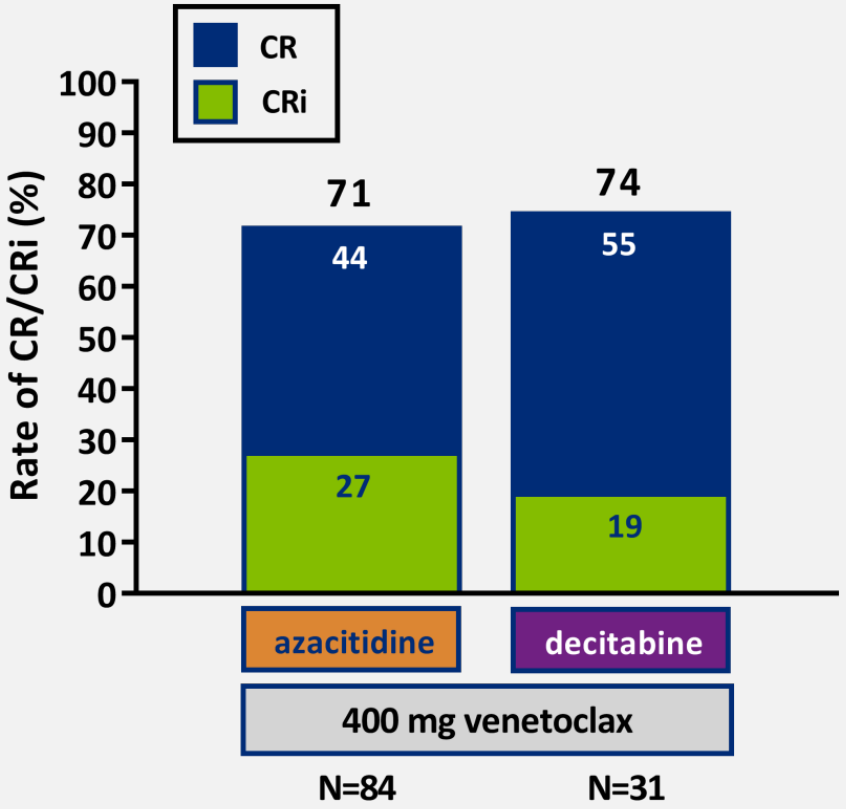
Dose Escalation of Venetoclax with HMA



Patients received venetoclax plus decitabine or azacitidine

Pollyea et al, ASH 2018

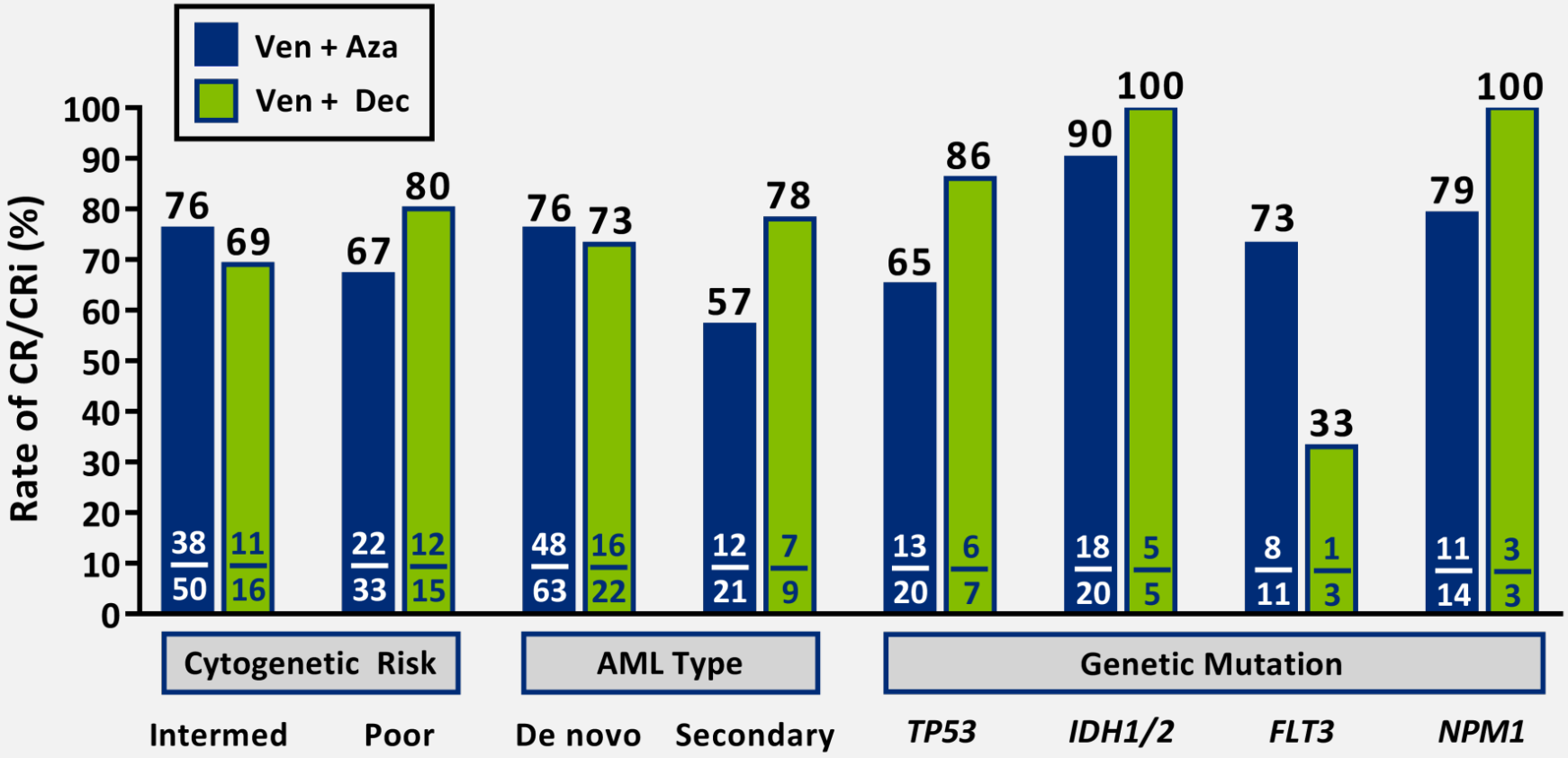
High Response Rates that Occur Rapidly



	Ven + Aza	Ven + Dec
Time to CR		
median (range)	1.2 (0.7–5.5)	1.9 (0.9–4.6)
No. of treatment cycles for these patients		
median (range)	6.0 (1–32)	6.0 (1–29)

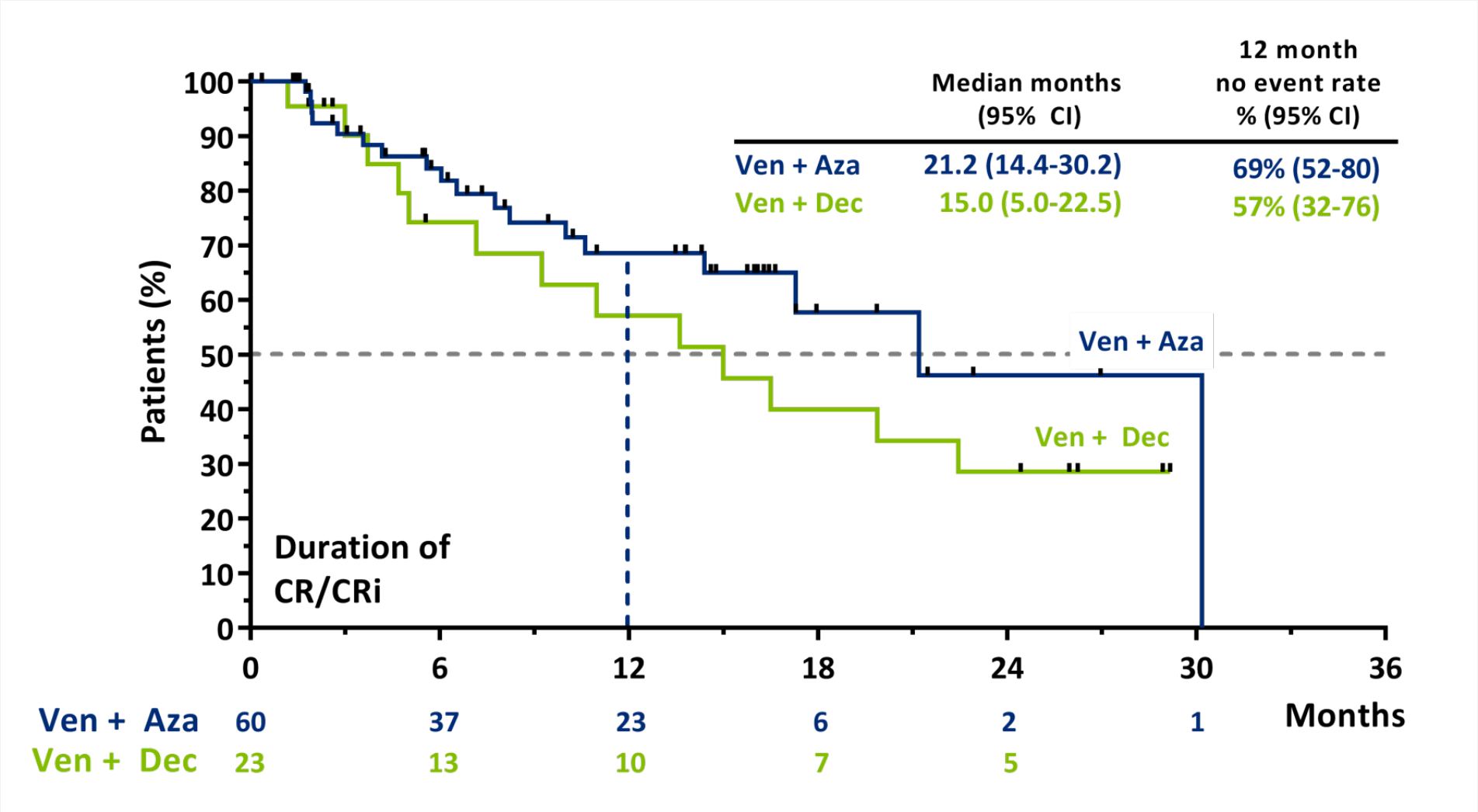
Pollyea et al, ASH 2018

Responses Occur Across the AML Landscape



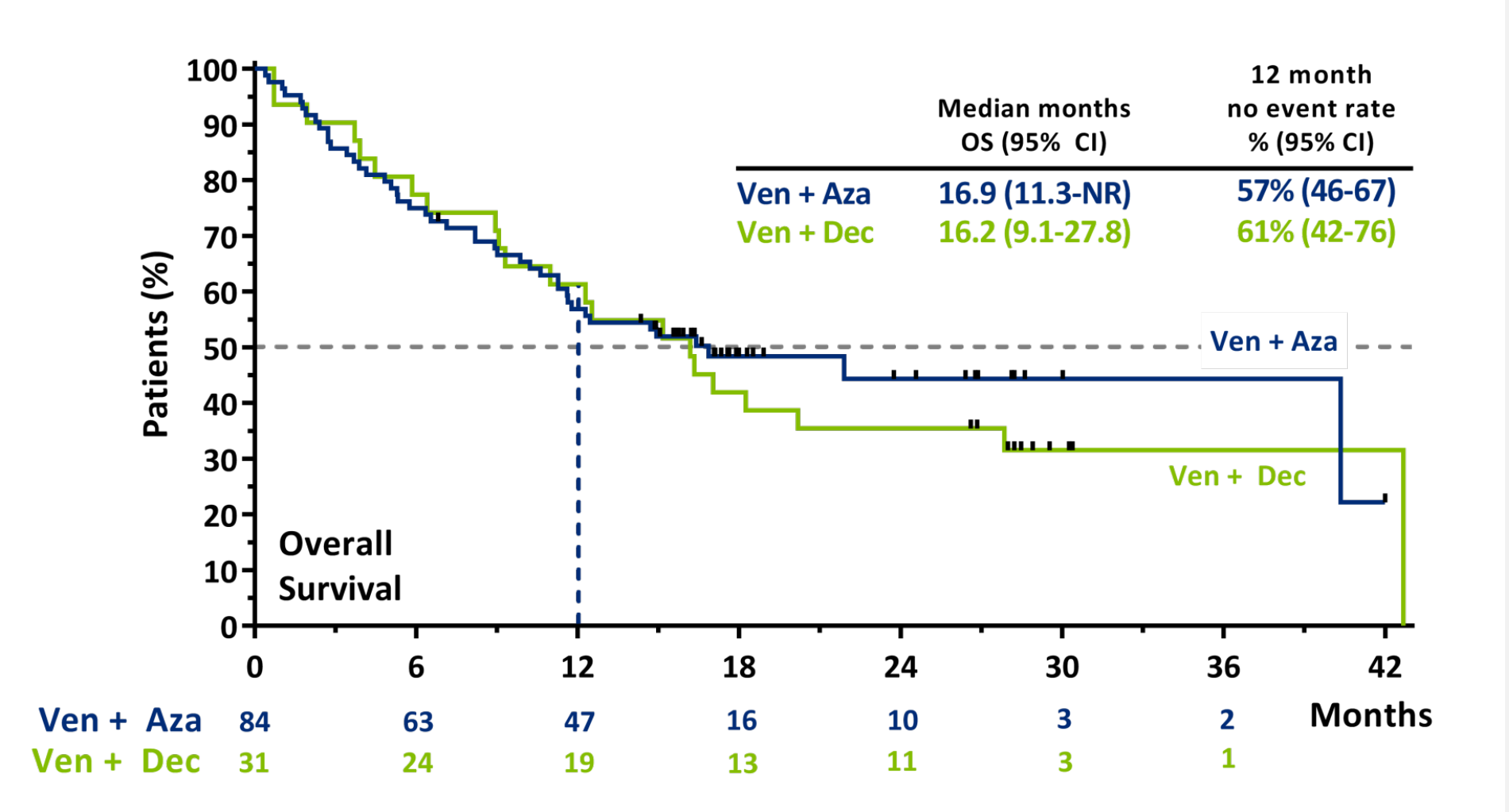
Pollyea et al, ASH 2018

Venetoclax + HMA: Duration of Response



Pollyea et al, ASH 2018;Abstract 285

Venetoclax + HMA: Overall Survival



Pollyea et al, ASH 2018;Abstract 285

Venetoclax + LDAC: Select Toxicities and Tumor Lysis Syndrome

AE	Venetoclax 600 mg + LDAC (n = 82)
Any AE	82 (100)
AE with grade ≥ 3	
Febrile neutropenia	34 (42)
Thrombocytopenia	31 (38)
WBC count decreased	28 (34)
Anemia	22 (27)
Neutropenia	22 (27)
Platelet count decreased	20 (24)
Lymphocyte count decreased	15 (18)
Neutrophil count decreased	14 (17)
Serious AE	
Anemia	25 (31)
Febrile neutropenia	22 (27)
Pneumonia	8 (10)
AML progression	7 (9)
Sepsis	6 (7)

Wei J et al. JCO 2019;37:1277-1284.

All patients hospitalized with aggressive TLS mitigation strategies

- 2 episodes of laboratory TLS with venetoclax + LDAC (no clinical TLS)

Venetoclax 400 mg + HMA: Select Toxicities and Tumor Lysis Syndrome

Adverse event (N = 145)	Venetoclax 400 mg (n = 60)			
	DEC (n = 31)		AZA (n = 29)	
	Any grade	Gr3/4	Any grade	Gr3/4
Any event, n (%)	31 (100)	24 (77)	29 (100)	25 (86)
Nausea	17 (55)	0	18 (62)	1 (3)
Diarrhea	13 (42)	2 (6)	15 (52)	1 (3)
Constipation	14 (45)	0	17 (59)	2 (7)
Febrile neutropenia	19 (61)	19 (61)	11 (38)	11 (38)
Fatigue	12 (39)	3 (10)	10 (34)	0
Hypokalemia	10 (32)	4 (13)	5 (17)	2 (7)
Decreased appetite	8 (26)	0	8 (28)	1 (3)
Decreased WBC count	13 (42)	13 (42)	7 (24)	7 (24)
Vomiting	10 (32)	0	9 (31)	0
Anemia	7 (23)	7 (23)	9 (31)	9 (31)

DiNardo CD et al, Blood 2019;133(1):7-17.

All patients hospitalized with aggressive TLS mitigation strategies

- No TLS seen with venetoclax+HMA