LEUKEMIA2020-2021

April 26-27, 2021

Coordinator: A.M. Carella
AIL President: S. Amadori

ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

Novel approaches to targeted epigenetic therapy

Simona Sica
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per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO

SIE - Società Italiana di Ematologia

- disclosures
- Advisory board: Jazz Pharma, Alexion, Amgen

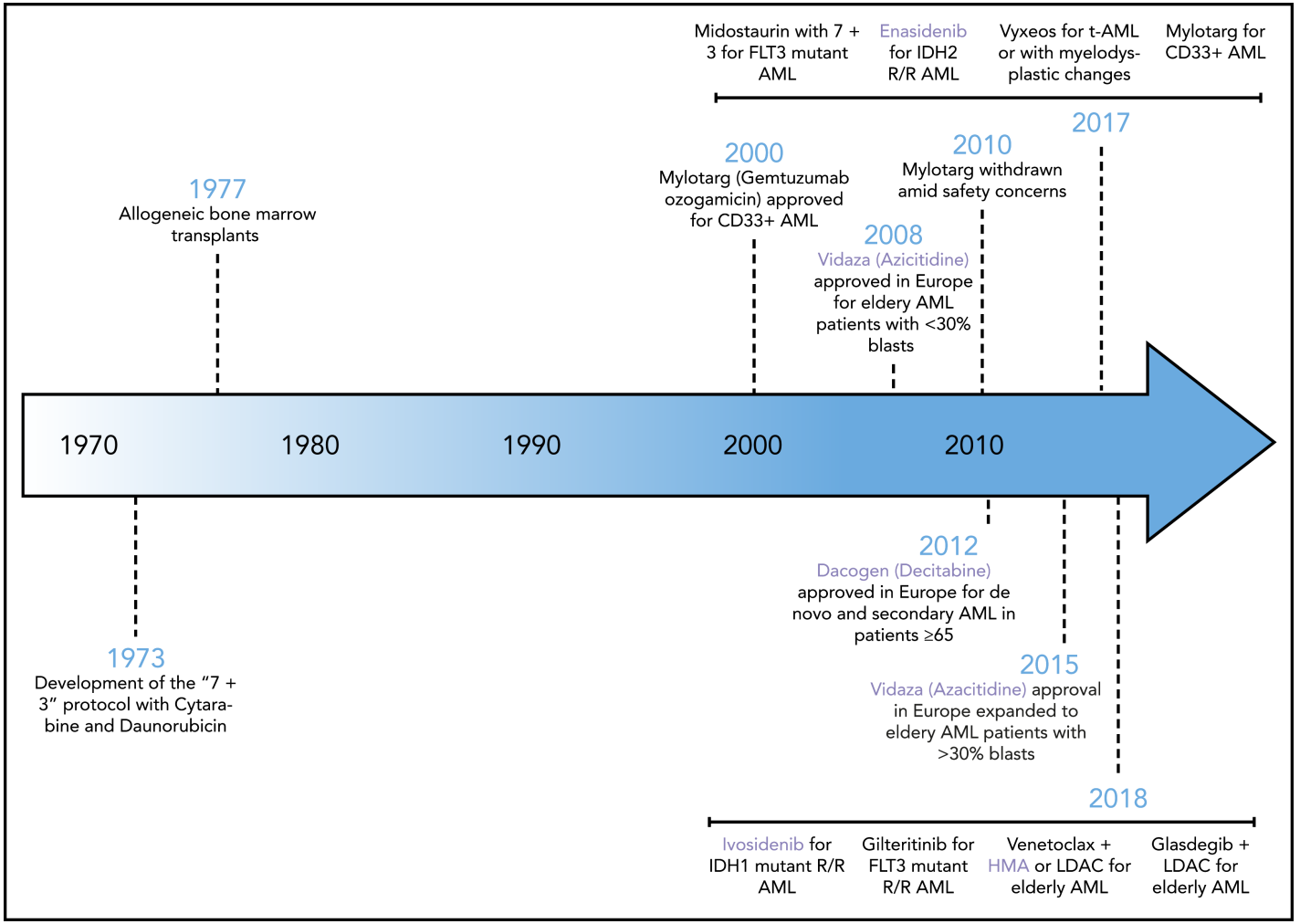
Epigenetics

- Study of the events that regulates access to DNA template to facilitate transcription, DNA repair and DNA replication

- Many of the mutations found in AML are located in epigenetic regulators

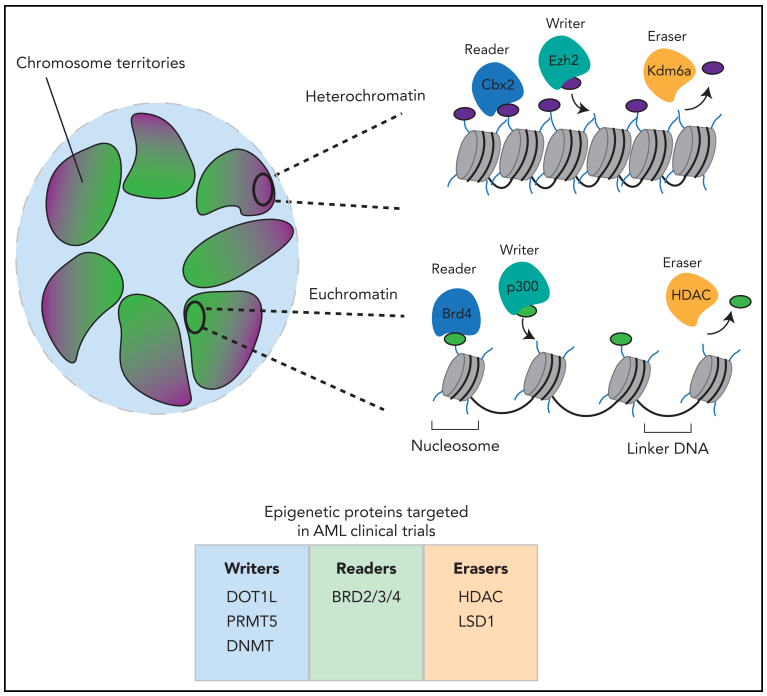
Katie A. Fennell,Charles C. Bell,Mark A. Dawson, Epigenetic therapies in acute myeloid leukemia: where to from here?, Blood, 2019,

Epigenetic therapies in acute myeloid leukemia: where to from here?



American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Katie A. Fennell,Charles C. Bell,Mark A. Dawson, Epigenetic therapies in acute myeloid leukemia: where to from here?, Blood, 2019,

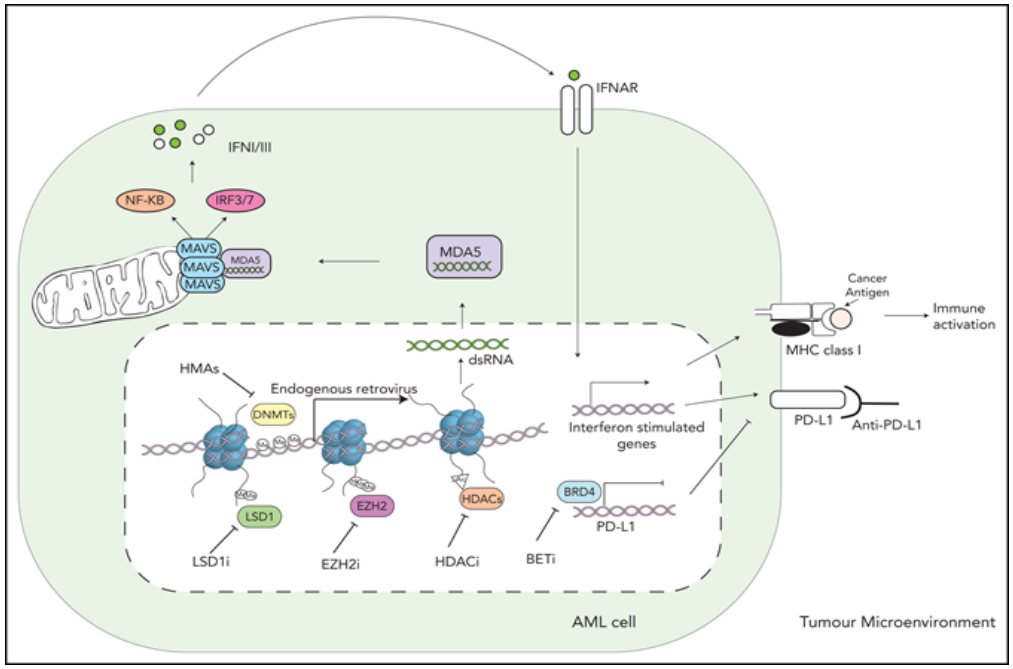


Epigenetic proteins targeted in AML clinical trials

Writers	Readers	Erasers
DOT1L	BRD2/3/4	HDAC
PRMT5		LSD1
DNMT		

Both active and repressive histone modifications are regulated by writers, readers or erasers proteins

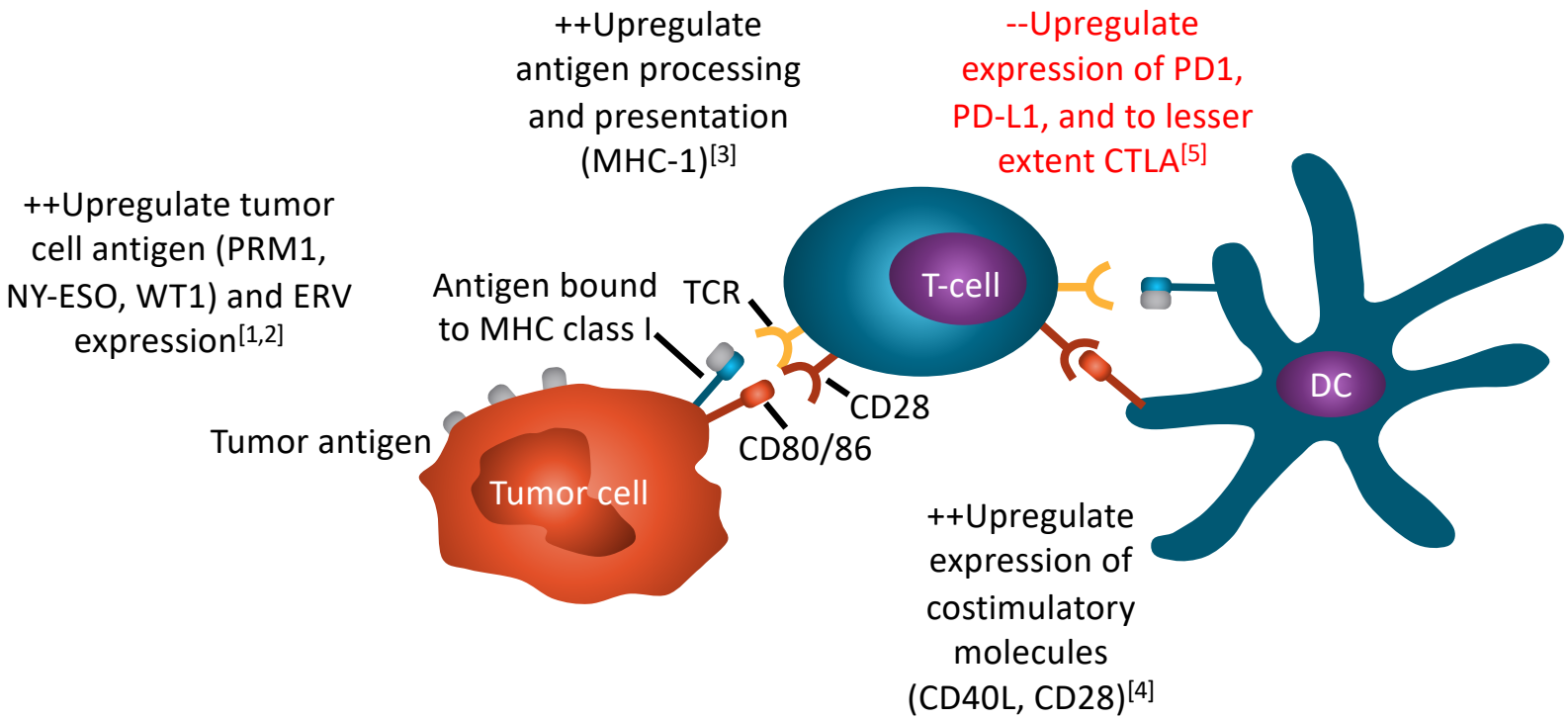
Katie A. Fennell,Charles C. Bell,Mark A. Dawson, Epigenetic therapies in acute myeloid leukemia: where to from here?, Blood, 2019,



A large body of emerging evidence suggests that DNA hypometilating agents can have direct or indirect effect on immuno-modulatory effect on malignant cells through derepression of immune-related genes signaling IFN, ERV with upregulation of apoptotic and IFN response genes

Katie A. Fennell,Charles C. Bell,Mark A. Dawson, Epigenetic therapies in acute myeloid leukemia: where to from here?, Blood, 2019,

Hypomethylating Agents and Immune Regulation

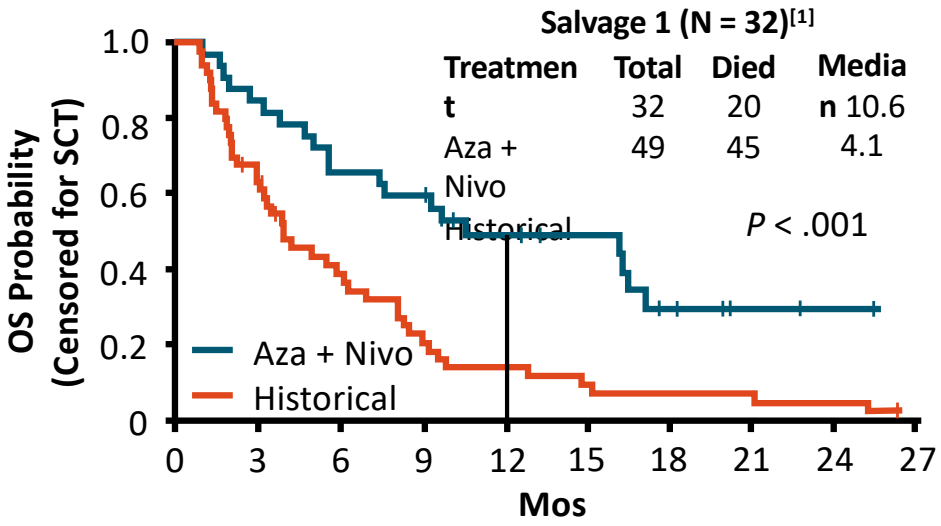


1. Sato. Cold Spring Harb Perspect Med. 2017;7. 2. Goodyear. Blood. 2010;116:1908.
3. Li. Oncotarget. 2014;5:587. 4. Wang. PLoS One. 2013;8:e62924. 5. Yang. Leukemia. 2014;28:1280.

Combinations with immunotherapies

Epigenetic therapies in combination with immunotherapies				
Azacitidine + nivolumab (MDX-1106) +/or ipilimumab (MDX-010)	DNMT + PD-1 + CTLA-4	2	2015	NCT02397720
Azacitidine + pembrolizumab (MK-3475)	DNMT + PD-1	2	2016	NCT02845297
Decitabine + ipilimumab (MDX-010)	DNMT + CTLA-4	1	2016	NCT02890329
Guadecitabine + atezolizumab (MPDL 3280A)	DNMT + PD-L1	1/2	2016	NCT02935361
Decitabine + PDR001 +/or MBG453	DNMT + PD-1 + TIM-3	1	2017	NCT03066648
Azacitidine + Hu5F9-G4	DNMT + CD47	1	2017	NCT03248479
Decitabine + CDX-1401 + poly ICLC + nivolumab (MDX-1106)	DNMT + DEC-205 + TLR-3 + PD-1	1	2017	NCT03358719
Decitabine + avelumab	DNMT + PD-L1	1	2018	NCT03395873
Azacitidine + nivolumab (ADVL1412)	DNMT + PD-1	1/2	2019	NCT03825367

OS of Azacitidine + Nivolumab vs Historical HMA Combinations at MDACC; Censored for SCT



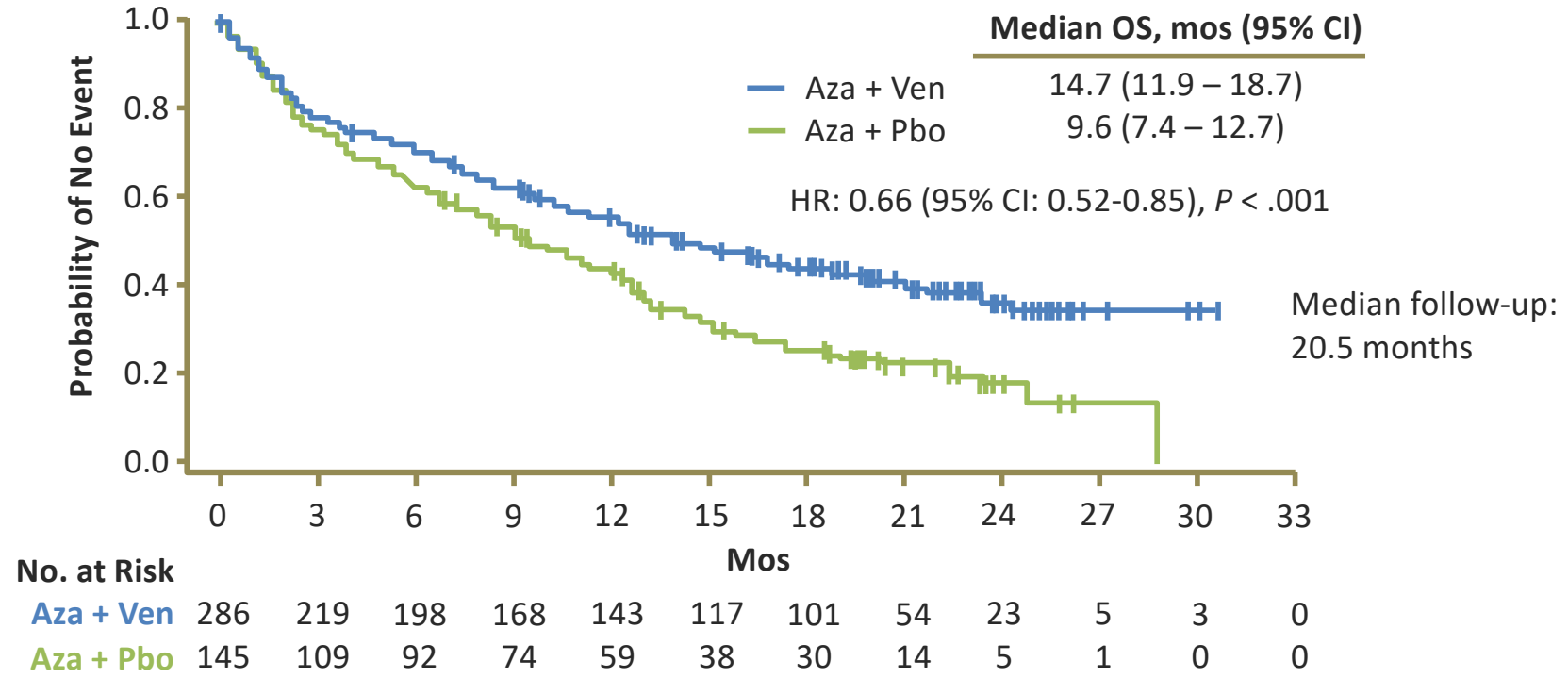
- Salvage 1[1]
  - Median age: 72 yrs
  - Secondary AML: 42%
  - Adverse cytogenetics: 35%
- Expected survival in salvage 1/2: 5-7 mos, 12-mo OS (N = 655): 16%[2]
- Survival with HMA + venetoclax in salvage (off protocol): 3-4 mos[3]

1. Daver. EHA 2017. Abstr S474. 2. Stahl. Blood Adv. 2018;2:923. 3. DiNardo. Am J Hematol. 2018;93:401.

Drug	Targets	Phase	Date	Clinical trial
Combinations of epigenetic therapies				
Azacitidine + entinostat (MS275)	DNMT + HDAC	2	2011	NCT01305499
Azacitidine + FT-2102	DNMT1 + IDH1	1/2	2016	NCT02719574
Azacitidine + LSD1 inhibitor (NCB059872)	DNMT1 + LSD1	1/2	2016	NCT02712905
Azacitidine + ivosidenib (AG-120)	DNMT + IDH1	3	2017	NCT03173248
Azacitidine + pracinostat (SB939)	DNMT + HDAC	3	2017	NCT03151408
Decitabine + vorinostat before or during FLAG	DNMT + HDAC	1	2017	NCT03263936
Azacitidine + PRMT5 inhibitor (GSK3326595)	DNMT + PRMT5	1	2018	NCT03614728
Low-dose azacitidine + vorinostat after alloHSCT	DNMT + HDAC	1	2019	NCT03843528

Epigenetic therapies in combination with targeted therapies				
Azacitidine + milademetan	DNMT + MDM2	1	2014	NCT02319369
Decitabine + rapamycin or ribavirin	DNMT + mTOR	1/2	2014	NCT02109744
Decitabine + BI836858	DNMT + CD33	2	2015	NCT02632721
Decitabine + BP1001	DNMT + Grb-2	2	2016	NCT02781883
Azacitidine + gilteritinib (ASP2215)	DNMT + FLT3	2/3	2016	NCT02752035
Decitabine + talazoparib	DNMT + PARP	1/2	2016	NCT02878785
Decitabine + onvansertib	DNMT + PLK1	1b/2	2017	NCT03303339
Azacitidine + AZD2811 nanoparticles	DNMT + AURKB	2	2017	NCT03217838
Azacitidine + SL-401	DNMT + IL3	1	2017	NCT03113643
Decitabine + AMG-232	DNMT + MDM2	1	2017	NCT03041688
Decitabine + pevonedistat (MLN4924)	DNMT + NEDD8	1	2017	NCT03009240
Azacitidine + pevonedistat	DNMT + NEDD8	3	2017	NCT03268954
Decitabine + venetoclax (ABT-199)	DNMT + BCL-2	2	2018	NCT03404193
Azacitidine + pevonedistat	DNMT + NEDD8	2	2018	NCT03709576
Azacitidine + HMPL-523	DNMT + SYK	1	2018	NCT03483948
Decitabine + quizartanib (AC-220)	DNMT + FLT3	1/2	2018	NCT03661307
Azacitidine + enasidenib mesylate (AG-221 mesylate)	DNMT + IDH2	2	2018	NCT03683433
Azacitidine + nintedanib (BIBF-1120)	DNMT + VEGF + FGFR + PDGFR	1	2018	NCT03513484
Belinostat (PCD-101) + pevonedistat (MLN4924)	HDAC + NEDD8	1	2018	NCT03772925
Azacitidine + glasdegib (PF-04449913)	DNMT + SHH	3	2018	NCT03416179
Pracinostat + gemtuzumab ozogamicin	HDAC + CD33	1	2019	NCT03848754
Azacitidine or decitabine + venetoclax (ABT-199)	DNMT + BCL-2	3	2019	NCT03941964
Azacitidine + APR-246	DNMT + P53	2	2019	NCT03931291

VIALE-A: Venetoclax + Azacitidine vs Azacitidine—OS



DiNardo. N Engl J Med. 2020;383:617.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Acute Myeloid Leukemia (Age ≥18 years)

NCCN Guidelines Index
Table of Contents
Discussion

THERAPY FOR RELAPSED/REFRACTORY DISEASE[1]

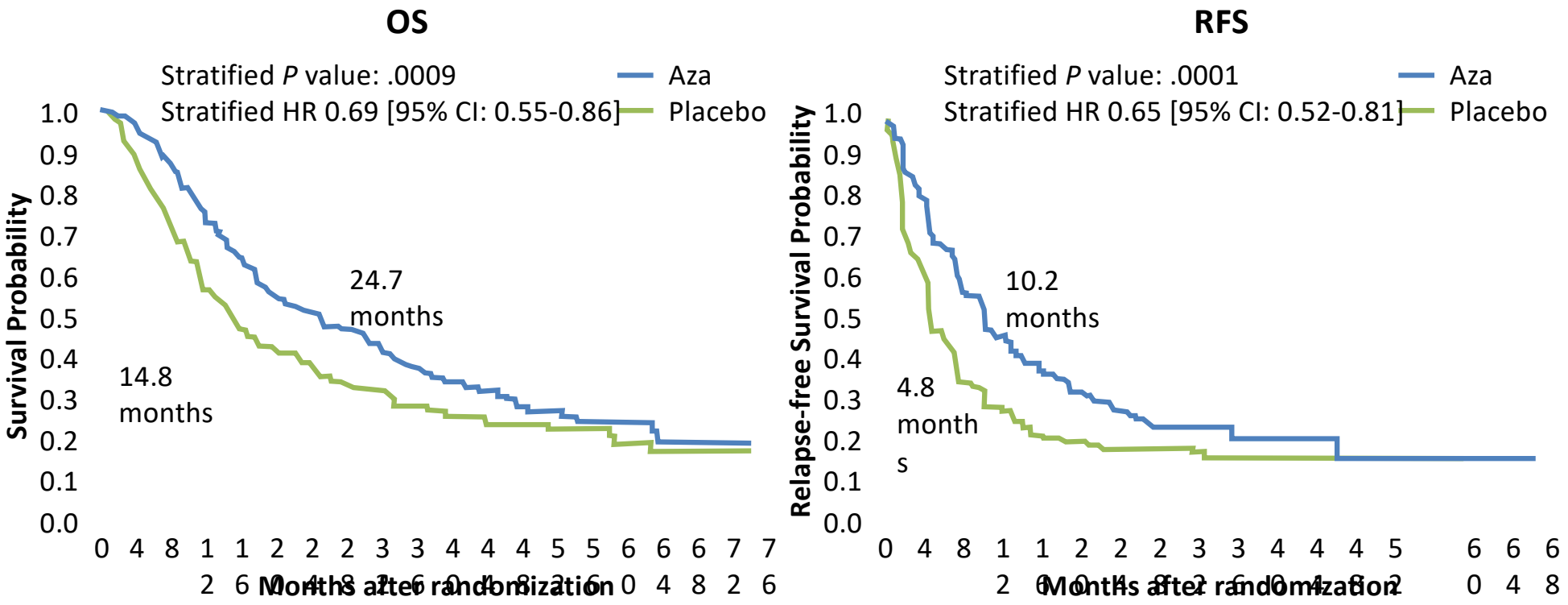
Clinical trial[1]

Targeted therapy:
- Therapy for AML with *FLT3*-ITD mutation
  - Gilteritinib[2] (category 1)
  - Hypomethylating agents (azacitidine or decitabine) + sorafenib[3,4]
- Therapy for AML with *FLT3*-TKD mutation
  - Gilteritinib[2] (category 1)
- Therapy for AML with *IDH2* mutation
  - Enasidenib[5]
- Therapy for AML with *IDH1* mutation
  - Ivosidenib[6]
- Therapy for CD33-positive AML
  - Gemtuzumab ozogamicin[7]

Aggressive therapy for appropriate patients:
- Cladribine + cytarabine + G-CSF ± mitoxantrone or idarubicin[8,9]
- HiDAC (if not received previously in treatment) ± (idarubicin or daunorubicin or mitoxantrone)[10]
- Fludarabine + cytarabine + G-CSF ± idarubicin[11,12]
- Etoposide + cytarabine ± mitoxantrone[13]
- Clofarabine ± cytarabine ± idarubicin[14,15]

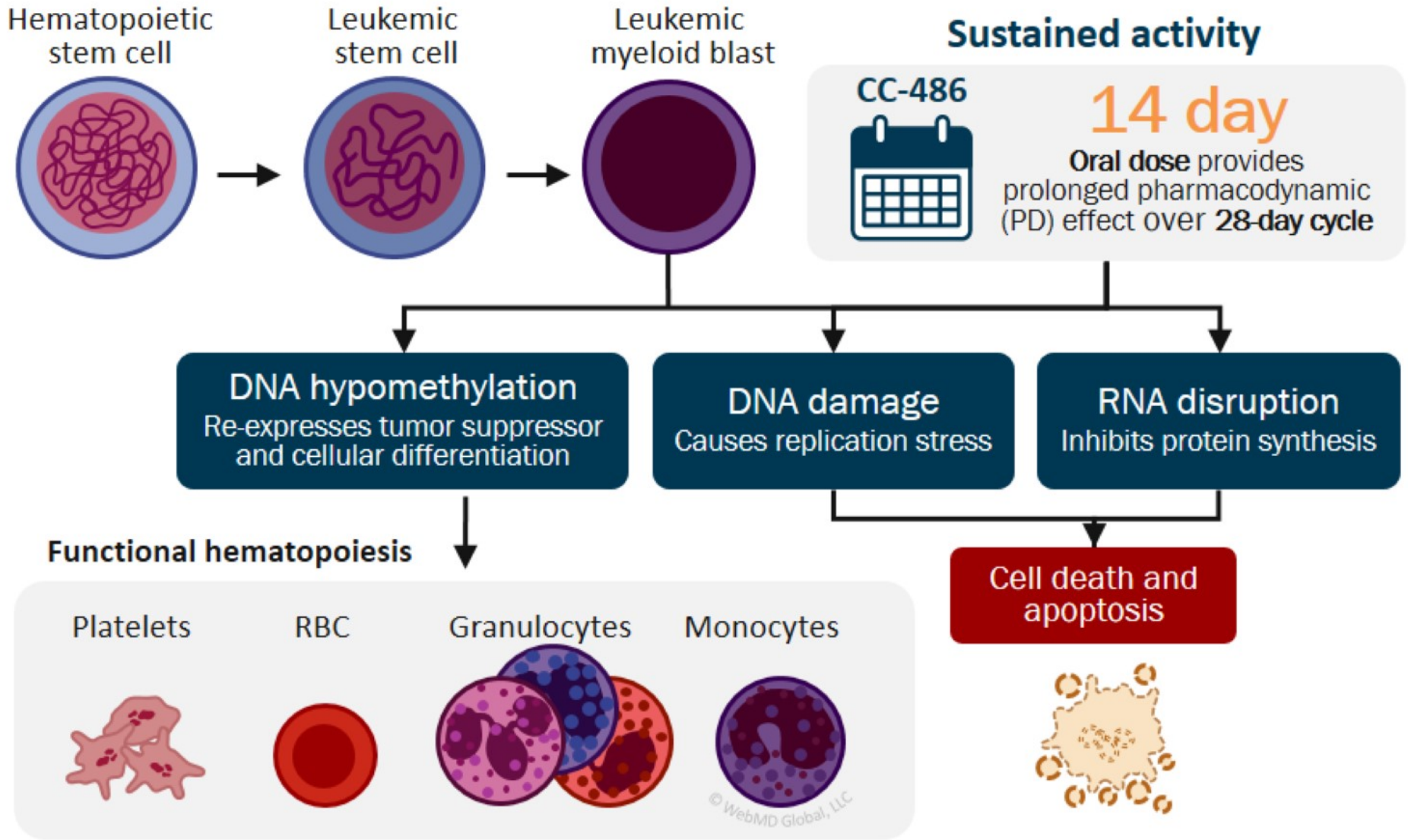
Less aggressive therapy:
- Hypomethylating agents (azacitidine or decitabine)
- LDAC (category 2B)
- Venetoclax[16] + HMA/LDAC[17,18]

QUAZAR AML-001: Survival and RFS



Wei. ASH 2019. Abstr LBA_3.

Biologic Consequences of CC-486 vs Azacitidine



Wei A, et al. ASH 2019. Abstract LBA-3.

Open-Label Phase 1b Trial of Ivosidenib + Azacitidine for Newly Diagnosed *IDH1*-Mutant AML

Patients

- N = 23
  - Dose-finding phase: n = 7
  - Dose expansion phase: n = 16
- Confirmed *IDH1* mutation
- Unfit for intensive chemotherapy
- No prior treatment with azacitidine or decitabine
- ECOG PS 0-2
- Adequate renal and hepatic function
- Median age (range): 76 y (61 - 88)

Treatment

- Continuous 28-day cycles
  - Oral ivosidenib 500 mg once daily
  - SC azacitidine 75 mg/m^2 on days 1-7 of each cycle
- Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or investigator judgment
- Key objectives: safety and clinical activity
- Median treatment duration (range): 15.1 mo (0.3 - 32.2)
- Median follow-up: 16 mo

DiNardo CD, et al. *J Clin Oncol*. 2020. [Epub ahead of print.]

Open-Label Phase 1b Trial of Ivosidenib + Azacitidine

Hematologic Responses and TEAEs

Hematologic Response Category	Response
CR + CRh, n (%) [95% CI]	16 (69.6) [47.1, 86.8]
Median time to CR/CRh, mo (range)	2.8 (0.8-11.5)
Median DOR, mo (95% CI)	NE (12.2, NE)
CR, n (%) [95% CI]	14 (60.9) [38.5, 80.3]
Median time to CR, mo (range)	3.7 (0.8-15.7)
Median DOR, mo (95% CI)	NE (9.3, NE)
ORR*, n (%) [95% CI]	18 (78.3) [56.3, 92.5]
Median time to response, mo (range)	1.8 (0.7-3.8)
Median DOR, mo (95% CI)	NE (10.3, NE)

Grade ≥ 3 TEAEs Occurring in ≥ 3 Pts	Pts, n (%)
Any cause	23 (100)
Thrombocytopenia	14 (60.9)
Anemia	10 (43.5)
Febrile neutropenia	10 (43.5)
Neutropenia	7 (30.4)
Sepsis	5 (21.7)
ECG QT Prolonged	3 (13.0)

12-month survival estimate (95% CI): 82% (58.8%, 92.8%)

*ORR = CR + CRi + CRp + PR + MLFS

DiNardo CD, et al. *J Clin Oncol*. 2020. [Epub ahead of print.]

AG221-AML-005: Addition of Enasidenib to Azacitidine in Newly Diagnosed AML with Mutated *IDH2*

- Dose-finding (3+3) phase Ib study followed by randomized phase II study

Adult patients with mutant *IDH2* ND AML, ineligible for intensive CT and no history of treatment with hypomethylating agents (N = 101)

2:1

Enasidenib 100 mg QD +
Azacitidine 75 mg/m^2/day SQ x 7 days/28-day cycle
(n = 68)

Azacitidine Monotherapy
75 mg/m^2/day SQ x 7 days/28-day cycle
(n = 33)

- Primary endpoint: ORR
- Key secondary endpoints: CR, safety, OS, EFS

DiNardo. ASCO 2020. Abstract 7501.

AG221-AML-005: Response Rates

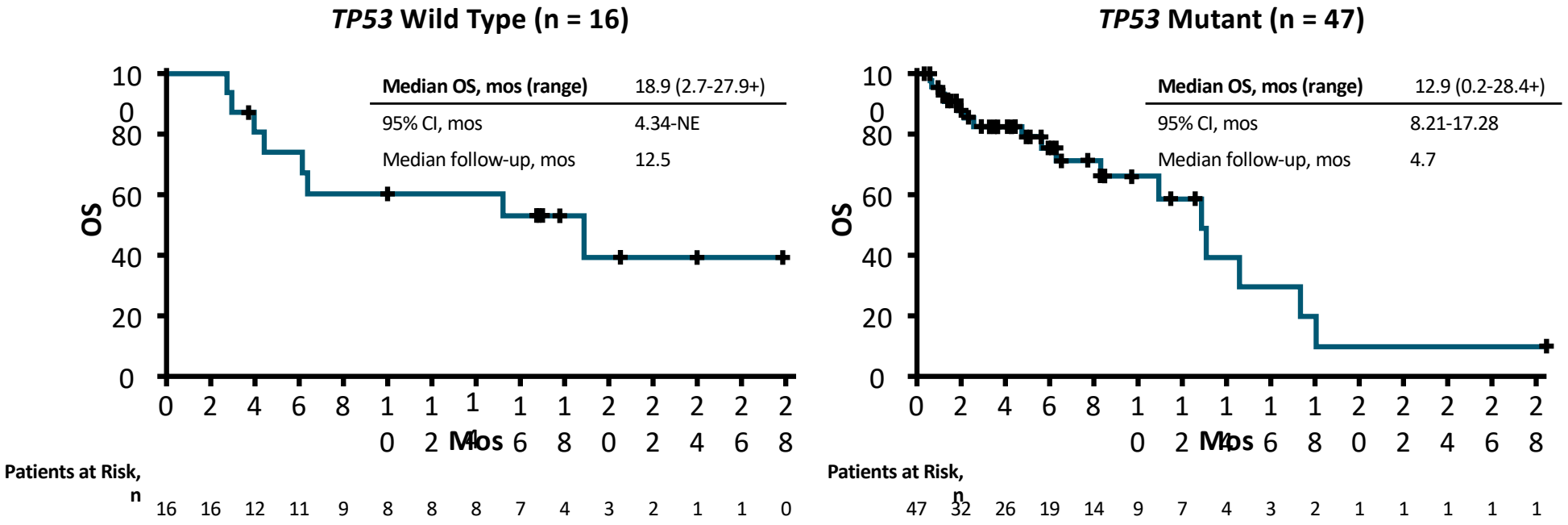
- ORR and CR rates significantly higher with enasidenib + azacitidine vs azacitidine alone

Endpoint	Enasidenib + Azacitidine (n = 68)	Azacitidine Monotherapy (n = 33)	*P* Value
ORR, % (95% CI)	71 (58-81)	42 (26-61)	.0064
CR, % (95% CI)	53 (41-65)	12 (3-28)	.0001
CRi/CRp, n (%)	7 (10)	4 (12)	--
PR, n (%)	3 (4)	4 (12)	--
MLFS	2 (3)	2 (6)	--
SD, n (%)	13 (19)	13 (39)	--
Disease progression, n (%)	2 (3)	1 (3)	--
Missing data or not evaluable, n (%)	5 (7)	5 (15)	--

Endpoint	Enasidenib + Azacitidine (n = 68)	Azacitidine Monotherapy (n = 33)	*P* Value
Median time to first response, mos (range)	1.9 (0.7-9.0)	2.0 (0.8-5.8)	--
Median time to CR, mos (range)	5.5 (0.7-19.5)	3.7 (3.0-4.1)	--
Median duration of response, mos (95% CI)	24.1 (11.1-NR)	12.1 (2.8-14.6)	.0548

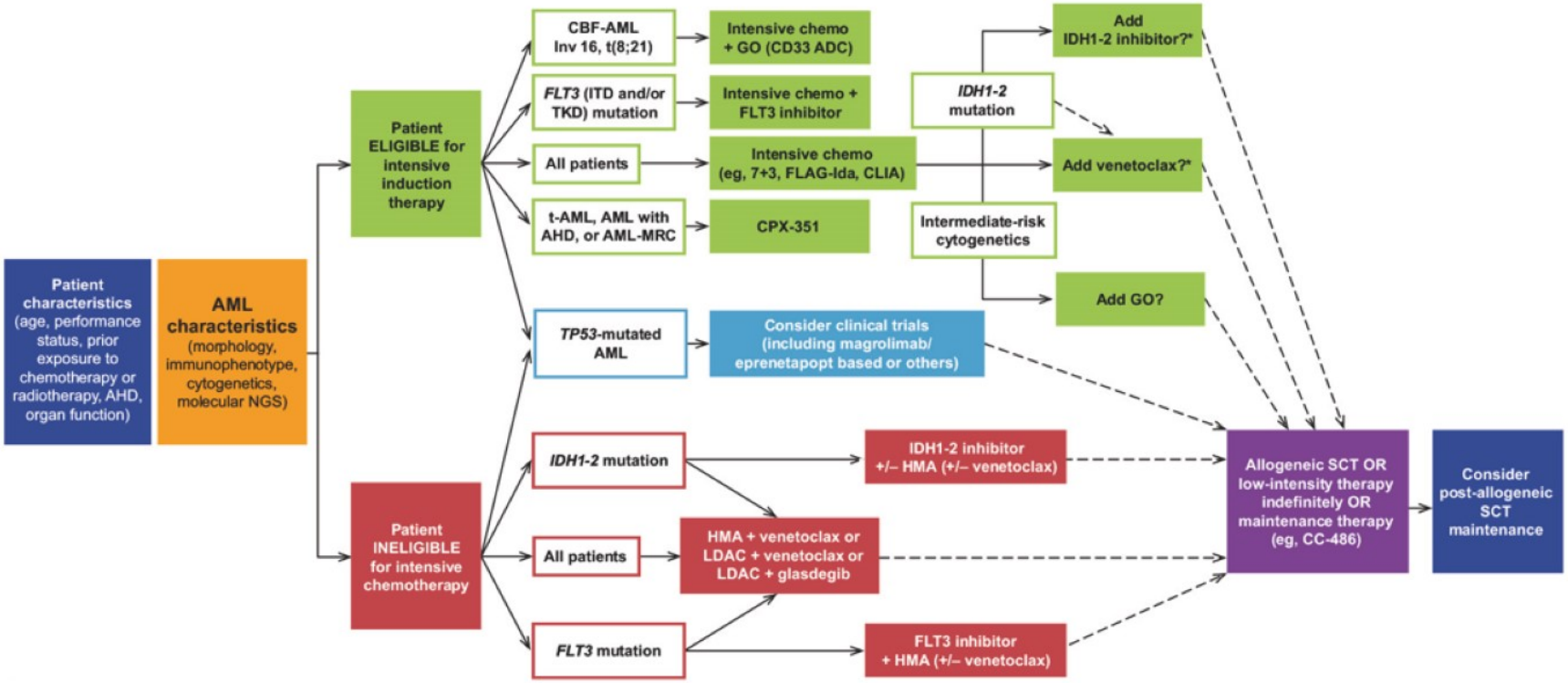
DiNardo. ASCO 2020. Abstract 7501.

Magrolimab + Azacitidine in Untreated AML: Preliminary OS

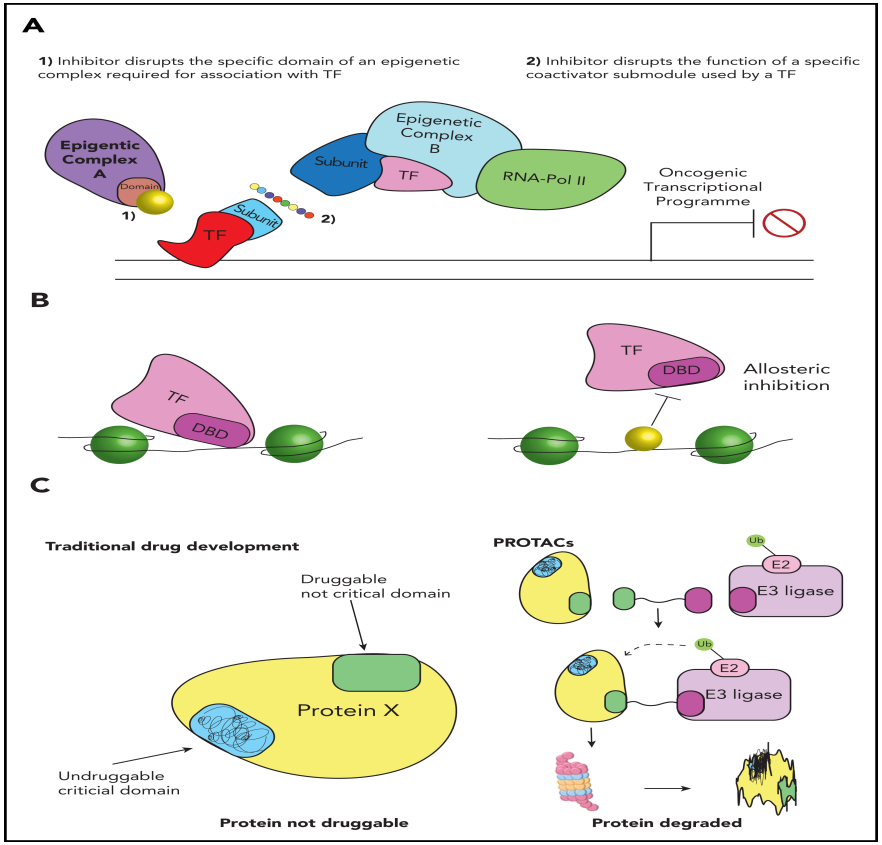


Sallman. ASH 2020. Abstr 330. Reproduced with permission.

Diagnostic and Treatment Paradigm for Newly Diagnosed AML



Daver N, et al. *Blood Cancer J*. 2020;10:107.



Disrupting specific epigenetic programs

Katie A. Fennell,Charles C. Bell,Mark A. Dawson, Epigenetic therapies in acute myeloid leukemia: where to from here?, Blood, 2019.

Conclusions

- Epigenetics therapies are not cytotoxic drugs
- Many of these drugs take months to exert their maximum effect
- Immune system may play a critical role in their clinical activity
- Appropriate combination therapies required

Grazie