Other Novel Agents and Promising Strategies Under Evaluation for Patients with AML

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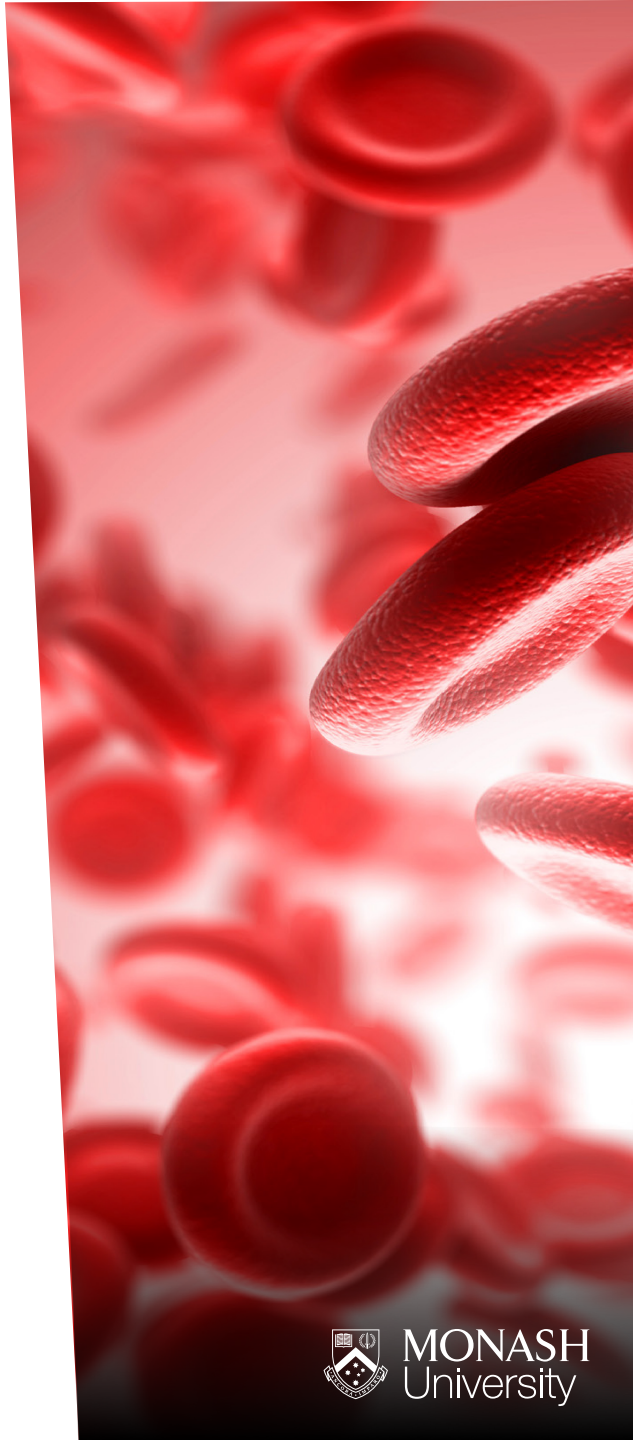
TheAlfred

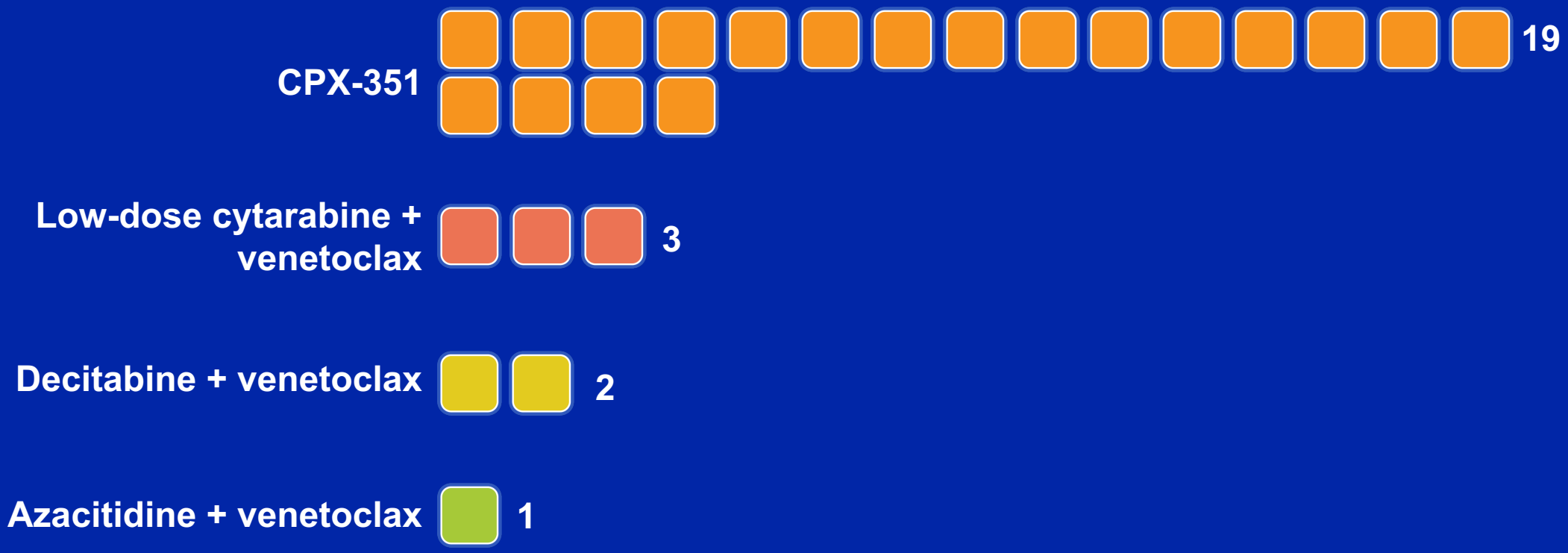


MONASH University

Disclosures

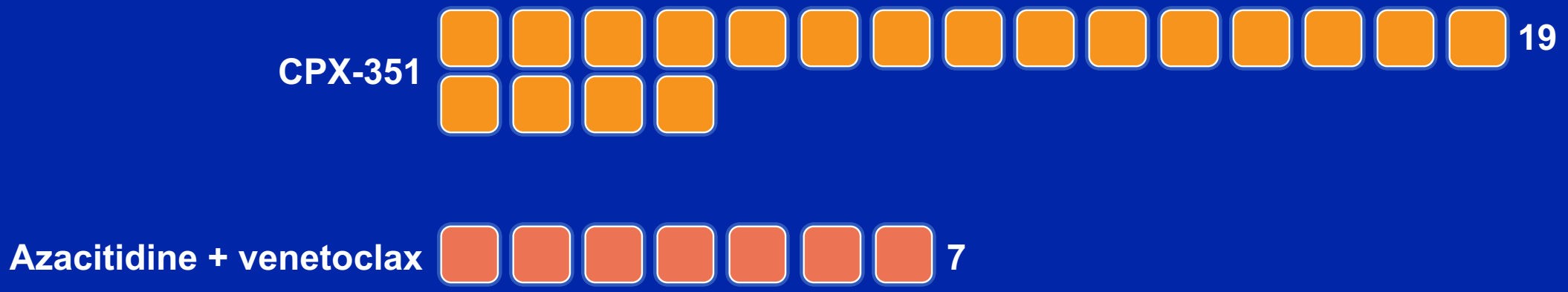
Advisory Committee	AbbVie Inc, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Celgene Corporation, Genentech, Janssen Biotech Inc, MacroGenics Inc, Novartis, Pfizer Inc, Servier
Consulting Agreement	Servier
Contracted Research	AbbVie Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, Celgene Corporation, Novartis, Servier
Speakers Bureau	AbbVie Inc, Novartis
Other	Royalty payments related to venetoclax research from Walter and Eliza Hall Institute of Medical Research

A 69-year-old woman with a history of myelodysplastic syndrome (MDS) treated with azacitidine for 10 months presents 1 year later with AML with 35% marrow blasts, trisomy 8 and ASXL1, NRAS and U2AF1 mutations (VAFs 45, 20 and 45, respectively). What would you recommend?



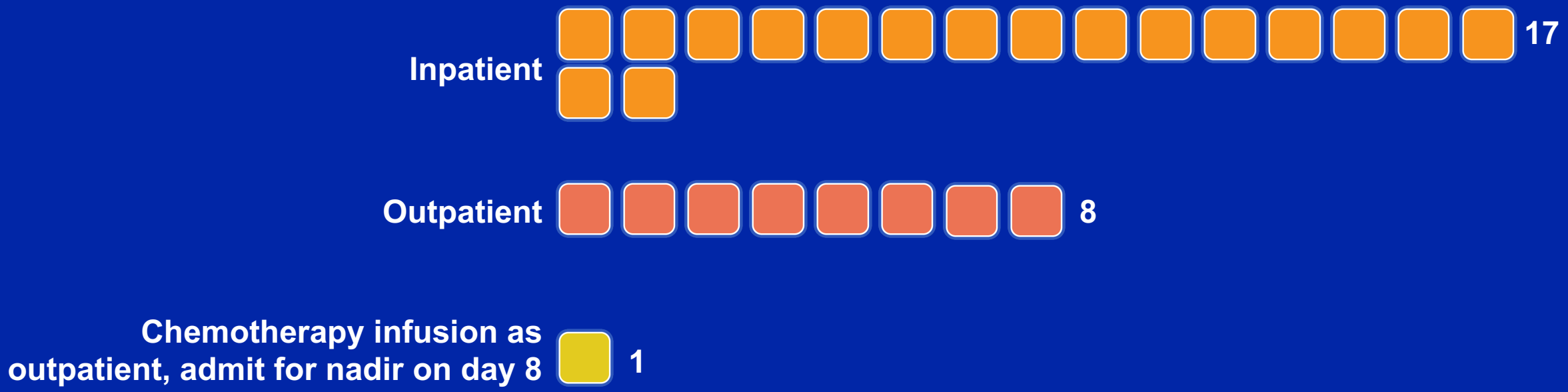
N = 25

What initial treatment would you recommend for a 68-year-old woman with a history of breast cancer, for which she received adjuvant chemotherapy, who now presents with bone marrow findings consistent with therapy-related AML with MDS-related changes, del(20q) cytogenetics and a PS of 1?



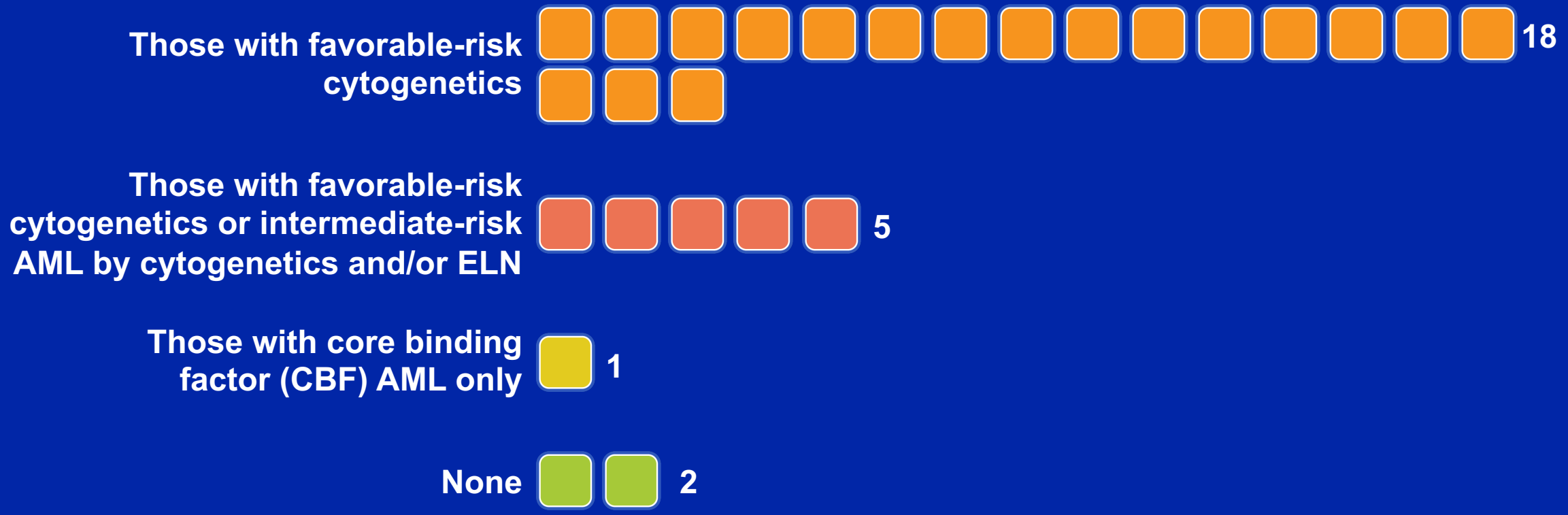
N = 26

In general, how do you or would you administer CPX-351 to medically stable patients with AML?



N = 26

For which patients with AML do you routinely administer gemtuzumab ozogamicin?



N = 26

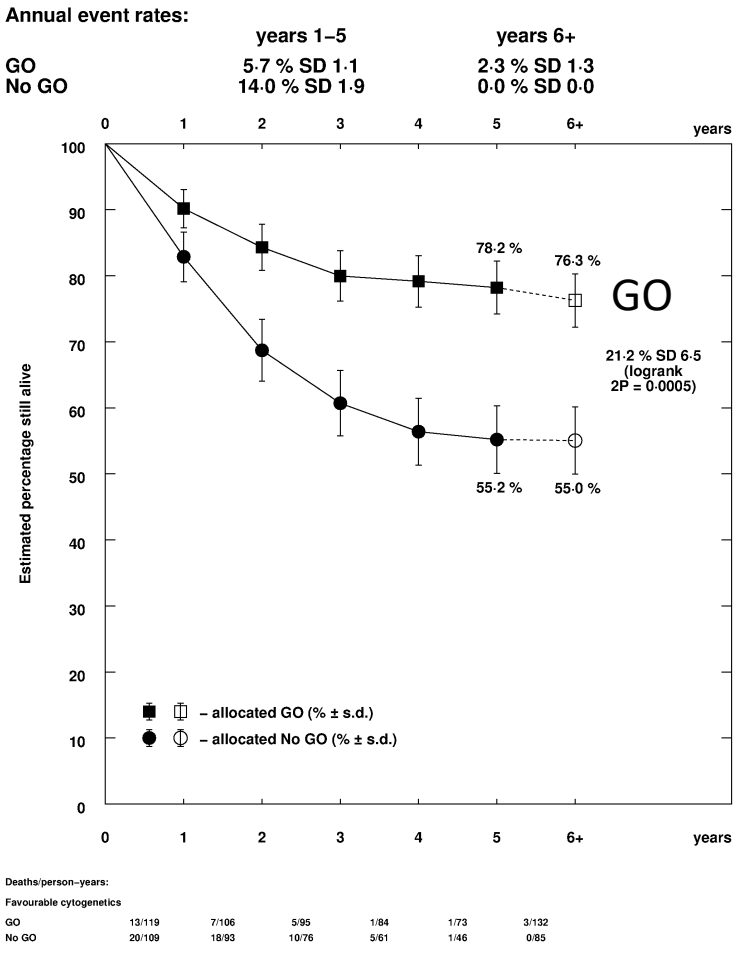
Gemtuzumab ozogamicin

- FDA approved Sept 1st, 2017
- Pivotal phase 3 ALFA-0701 trial in *de novo* AML 50-70yo
  - Induction: GO 3 mg/m^2 D1,4,7 with daunorubicin 60 mg/m^2 D1-3 and cytarabine 200 mg/m^2 D1-7

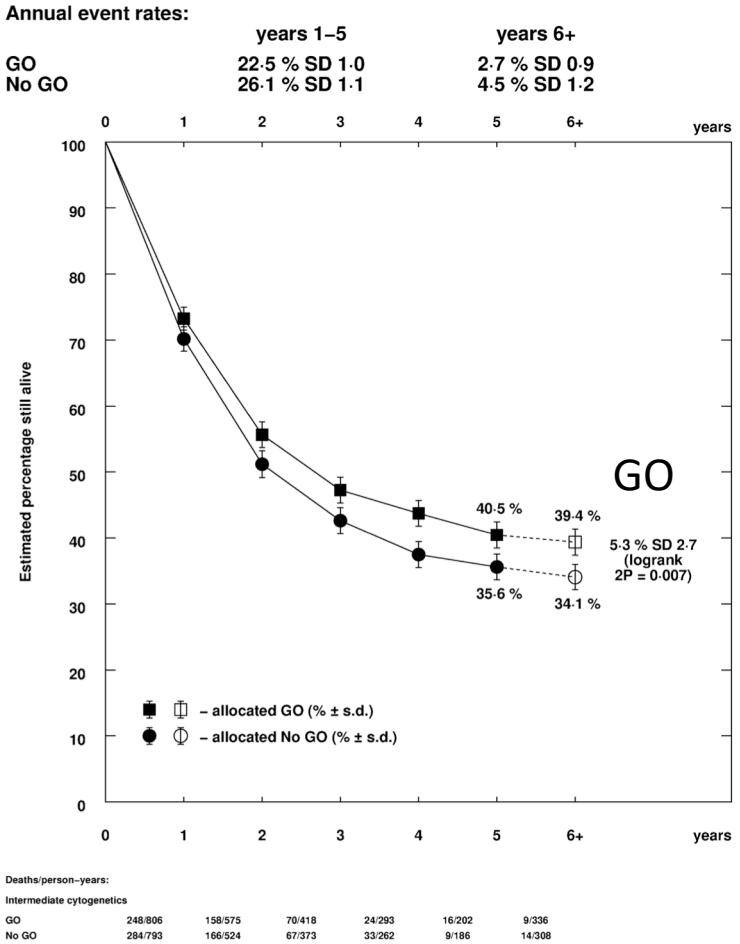
Sylvie Castaigne, Lancet, Vol 379 April 21, 2012

GO beneficial in favorable and intermediate risk AML

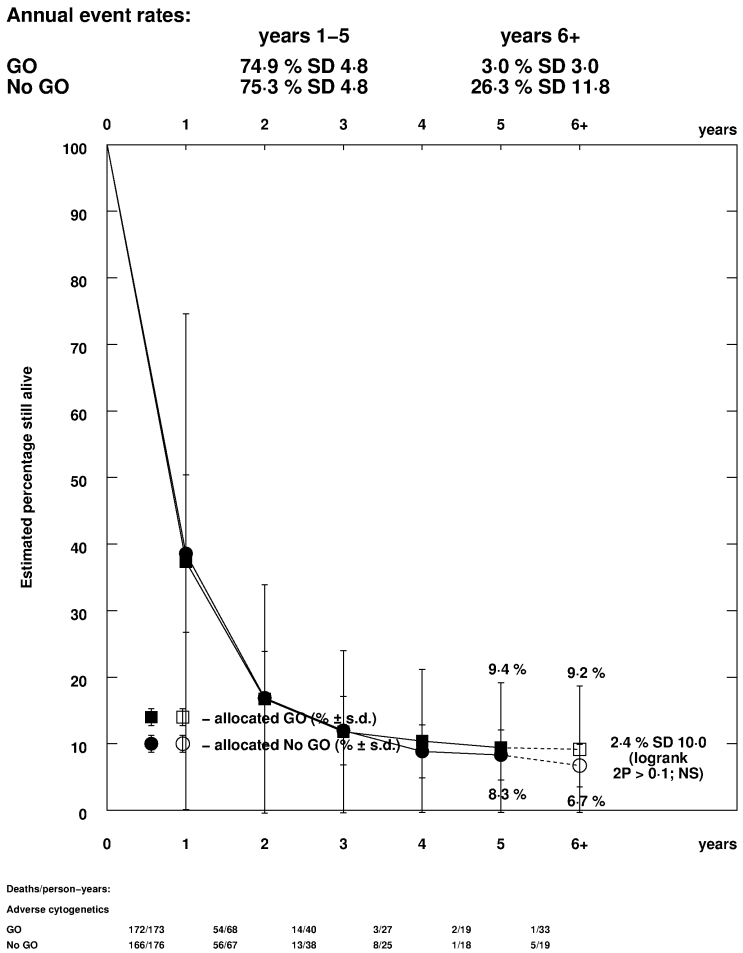
Favorable



Intermediate

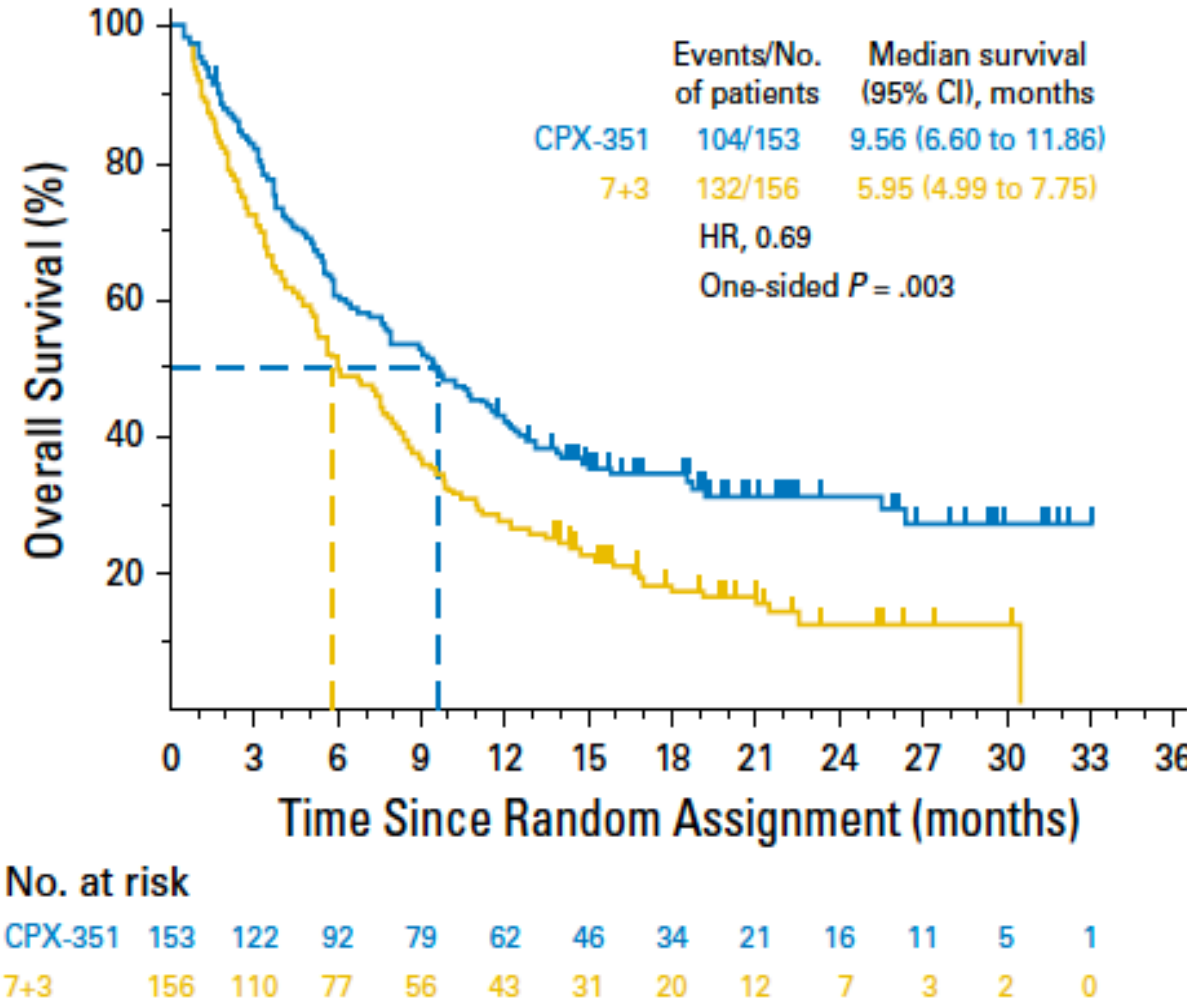


Adverse

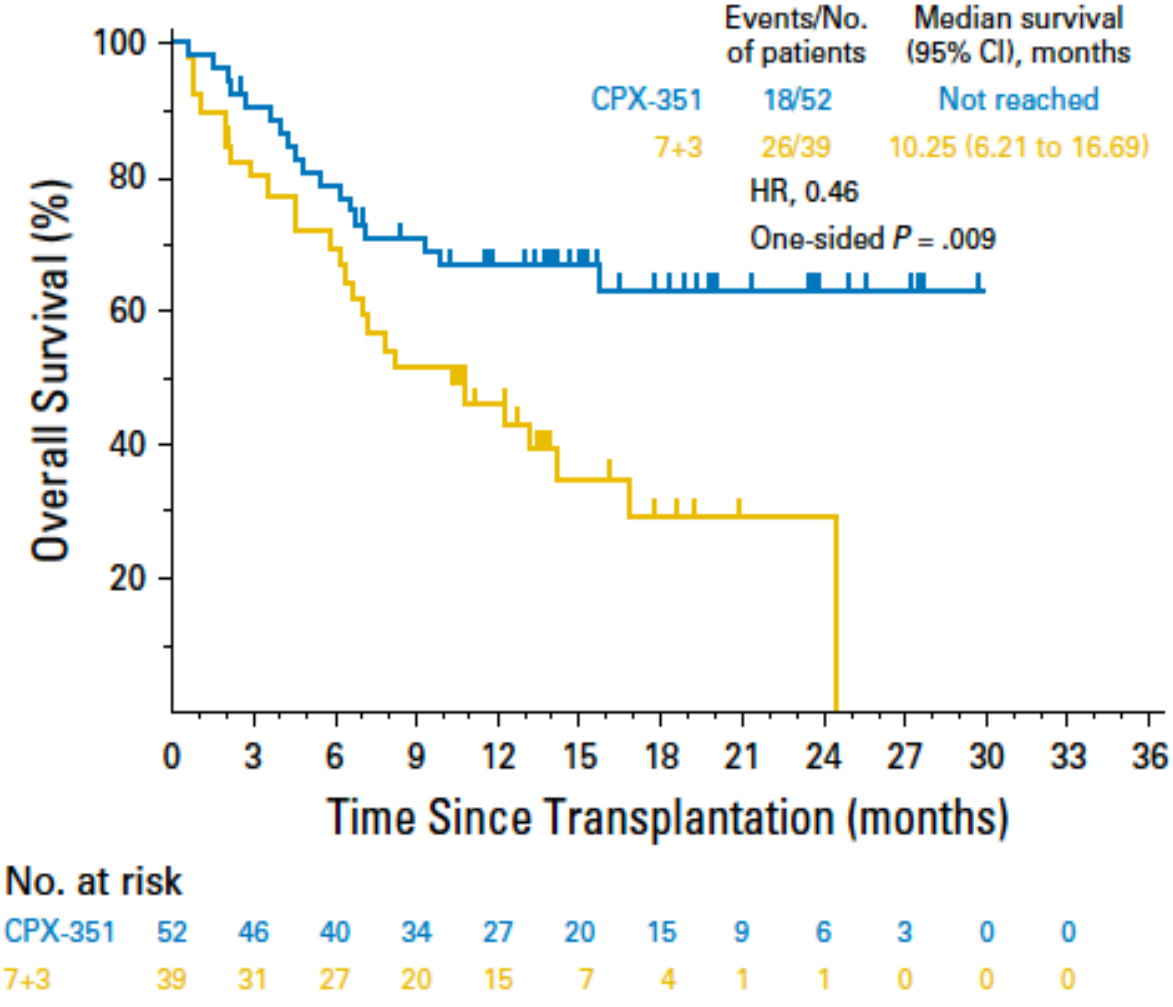


Robert Hills, Lancet Oncol 2014; 986

CPX-351 improves OS vs 7+3 in secondary/therapy related AML



Post HSCT outcomes



Lancet et al, JCO 2018, 2684

Liposomal Cytarabine and Daunorubicin (CPX-351) in Combination with Gemtuzumab Ozogamicin (GO) in Relapsed/Refractory (R/R) Patients with Acute Myeloid Leukemia (AML) and Post-Hypomethylating Agent (Post-HMA) Failure High-Risk Myelodysplastic Syndrome (HR-MDS)

Background: Both agents approved. Hypothesized that combination of CPX-351 and GO would be superior to either agent alone

Objectives: To determine the safety and efficacy of CPX-351 in combination with GO in R/R AML and post-HMA failure HR-MDS

Regimen: CPX-351 (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) IV D1, 3 and 5. GO 3 mg/m^2 (always capped at one 4.5 mg vial) IV on day 1

Population:
CD33 positive R/R AML, post-HMA failure.
High-Risk MDS (>10% blasts), and pts with newly diagnosed secondary AML after receiving HMA therapy.

	N	Grade	Percent
Neutropenic Fever	10	3	83%
Bacteremia	7	3	58%
Mucositis	4	2	33%
Lung Infection	2	3	17%
ALT	1	1	8%
Sinusitis	1	3	8%
Creatinine	1	2	8%
Pruritus	1	1	8%
Diarrhea	1	3	8%
Polyneuropathy	1	2	8%
GI Bleed	1	2	8%
Severe Sepsis	1	5	8%
Syncope	1	3	8%

- 12 enrolled
- 10 evaluable patients
- CR/CRi 5/10
- Median time to ANC >0.5 x 10^9/L was 33 days (range 30-45) and
- Plt >50 x 10^9/L was 38 days (range 33-45).
- TRM = 1/12

Multi-Center Retrospective Evaluation of High-Dose Cytarabine Based Induction Versus CPX-351 Induction in Patients with Secondary AML

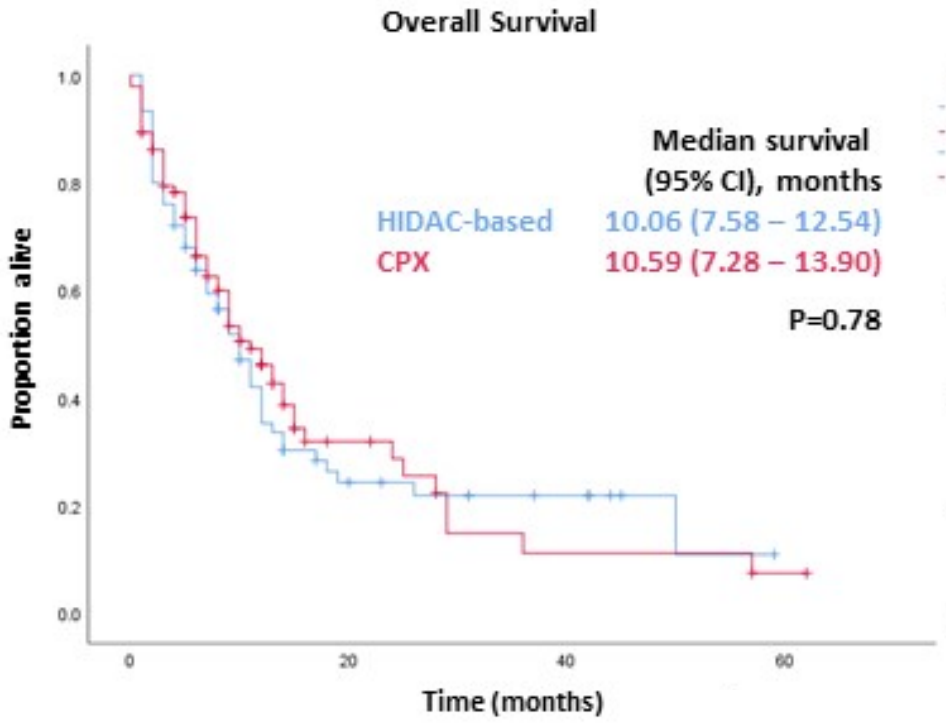
Background: CPX-351 recently approved for sAML based on a randomized trial against 7+3. Superiority to more intensified induction regimens unknown.

Objectives: To compare outcomes of CPX-351 with HIDAC based regimens in a retrospective multi-institutional comparison in secondary AML

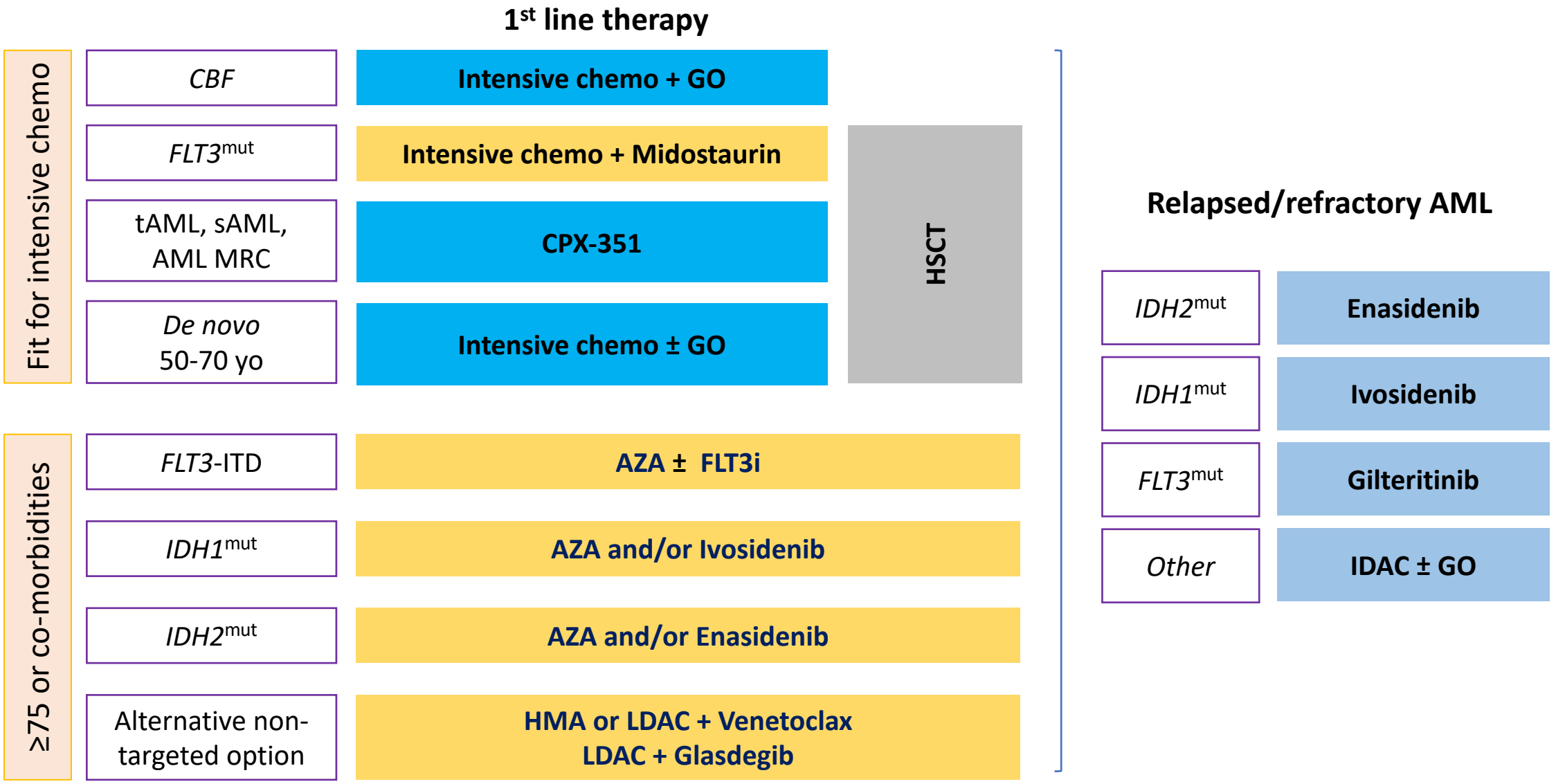
Regimen: HIDAC-based regimen distribution was as follows: fludarabine/cytarabine ± G-CSF (n=73) and clofarabine/cytarabine ± G-CSF (n=2)

University of Michigan n=73, MD Anderson Cancer Center n=27, Barnes Jewish Hospital n=22, University of North Carolina n=21, Huntsman Cancer Institute n=9, University of Rochester n=9, Indiana University n=8

	HIDAC-based (n= 75)	CPX-351 (n = 94)	P-value
CR/CRi	**47 (62.7)**	45 (47.9)	0.002 (one-sided for non-inferiority)
CR	37 (49.3)	39 (41.5)	0.352
CRi	10 (13.3)	6 (6.4)	0.125
MLFS	1 (1.3)	14 (14.9)	0.002
No response	27 (36)	35 (37.2)	0.869
AlloHCT	30 (40)	29 (30.9)	0.215
AlloHCT in CR/CRi	23/30 (76.7)	27/29 (93.1)	0.079



Changing clinical landscape in AML



A 61 yo woman with *de novo* AML

Diagnosis:

- FBE: Hb 86, WCC 3.5, Neut 0.3 , Plt 24
- Bone marrow: 91% blasts
- Flow cytometry: MPO+, CD34+, DR+, CD33+, CD7+

Prognosis and fitness:

Trisomy 4

FLT3, NPM1, IDH1/2 negative for mutations

Obese

Treatment history:

(1L) 2016: 7+3 → Resistant (57% blasts)

(2L) FLAG-Ida → CRi (4% blasts)

Severe peripheral neuropathy → walking frame, incontinent, ECOG 2

Not fit for further intensive chemotherapy or transplant

Is there a role for maintenance therapy?

Objectives of maintenance therapy

- Suppress MRD
- Prolong remission
- Increase overall survival

When would maintenance be considered?

- Not eligible for allogeneic SCT
- Unable to tolerate repeated rounds of consolidation therapy
- Higher risk of relapse
  - Elderly
  - Adverse CG or molecular risk
  - CRi
  - MRD positive

Selected maintenance trials in CR1

Population	Intervention	Control	N	Prior therapy	DFS	OS	Ref
CR1 >60y	Azacitidine 9 cycles	Observation	530	2 cycles of chemo		Not significant	UK MRC Burnett
CR1 ≥60y	Azacitidine 5 cycles	Observation	116	2 cycles of chemo	3-year DFS↑	Not significant	HOVON97 Gerwin Huls Blood 2019, 1457-1464
CR1 ≥60y	Norethandrolone 2 years post induction	Observation	330	Induction with ida (5d), ara-C (7d), lomustine re-induction (5+1) x6 + MTX/6MP	5-year DFS ↑	5-year OS ↑ (OS curve crossed at 2.5y)	Arnaud Pigneux, JCO 35:387-393, 2016
CR1/CR>1: <6 mo ≥18y	Histamine dichloride +IL-2 10 cycles	IL-2	320	Induction/ consolidation	3-year DFS↑	Not significant	Mats Brune Blood 2006;108: 88-96
CR1 <6 mo 60-80y	Lirilumab 1mg/kg or 0.1 mg/kg	Placebo	151	1-2 induction and 1-2 consolidation cycles	Not significant		FILO/ALFA Norbert Vey ASH 2018

A 61 yo woman with *de novo* AML

Diagnosis:

- FBE: Hb 112, WCC 3.5, Neut 0.7 , Plt 56
- Bone marrow: 91% blasts
- Flow cytometry: CD34+, DR+, CD33+, CD7+

Prognosis and fitness:

Trisomy 4

FLT3, NPM, IDH WT

Treatment history:

(1L) 2016: 7+3 → Resistant (57% blasts)

(2L) IDAC → CRi (4% blasts)

Severe peripheral neuropathy → walking frame, incontinent, obese, ECOG 2

Not fit for further intensive chemotherapy or transplant

Aug 2016: QUAZAR maintenance trial, randomized to oral azacitidine (CC-486) or placebo (14d schedule)

July 2017 (C12): Relapsed with 8% blasts. Treatment changed to 21 day schedule

July 2019 (C36): 12% blasts. Sudden onset of non-neutropenic sepsis

Treatment unblinded in September 2019: patient was randomized to CC-486 arm

The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 (Oral Formulation of Azacitidine) in Patients with Acute Myeloid Leukemia (AML) in First Remission

Background: RP2D of oral CC-486 is 300 mg 14-21 days. Prolonged exposure and longer duration of therapy than inkectable AZA

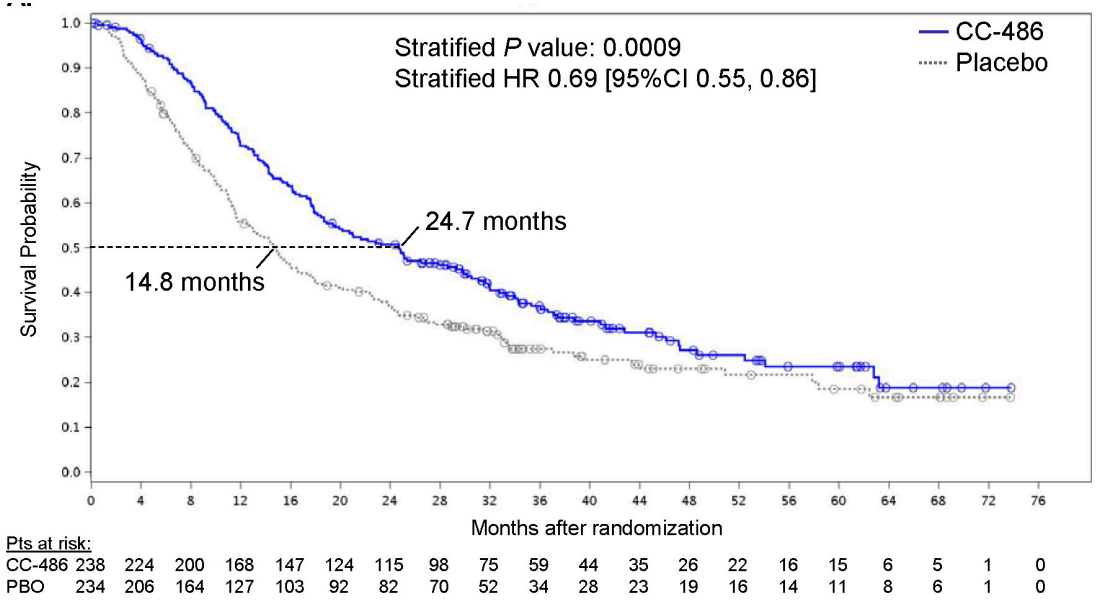
Objectives: Report results of 472 pts with AML ≥55 yrs randomized within 4 months of first CR or CRi after intensive induction +/- consolidation therapy

Regimen: CC-486 300 mg D1-14 q 28 days

Median F/U 41 mo	CC-486	Placebo
N	238	234
Prior induction, CR/CRi	81%/19%	
Median cycles (range)	12 (1-80)	6 (1-73)
Median OS (mo)	24.7	14.8
Median RFS (mo)	9.7	4.8
Notable AEs	N+V Diarrhea	

CC-486 improved OS and RFS regardless of baseline CG risk, # of prior consolidations, CR/CRi status

Overall survival



Presentation: LBA-3 Tuesday, December 10, 2019, 7:30 AM-9:00 AM

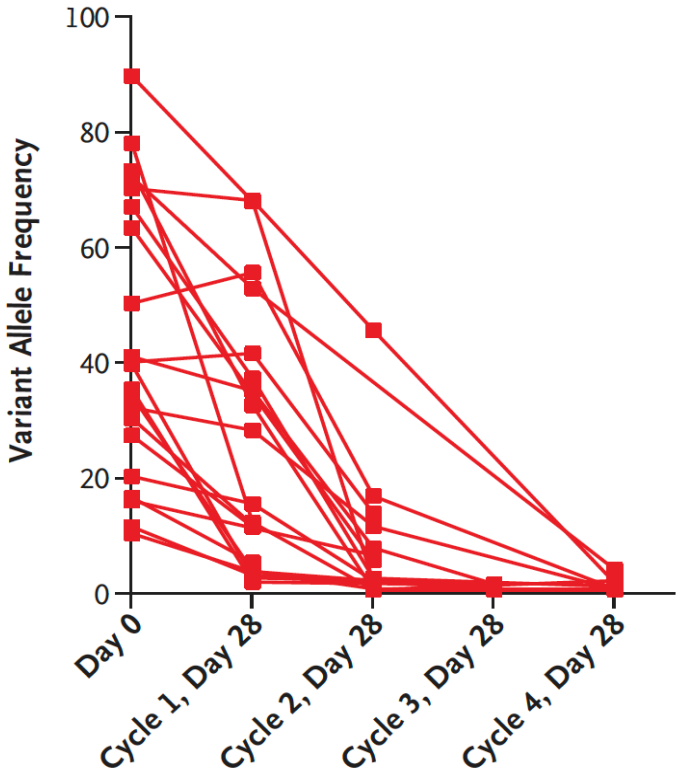
A 69 yo woman with *de novo* AML

Diagnosis:
March 2016 FBE 36/4.5/38
ECOG 2
BMAT: 28% blasts with dysplastic changes.

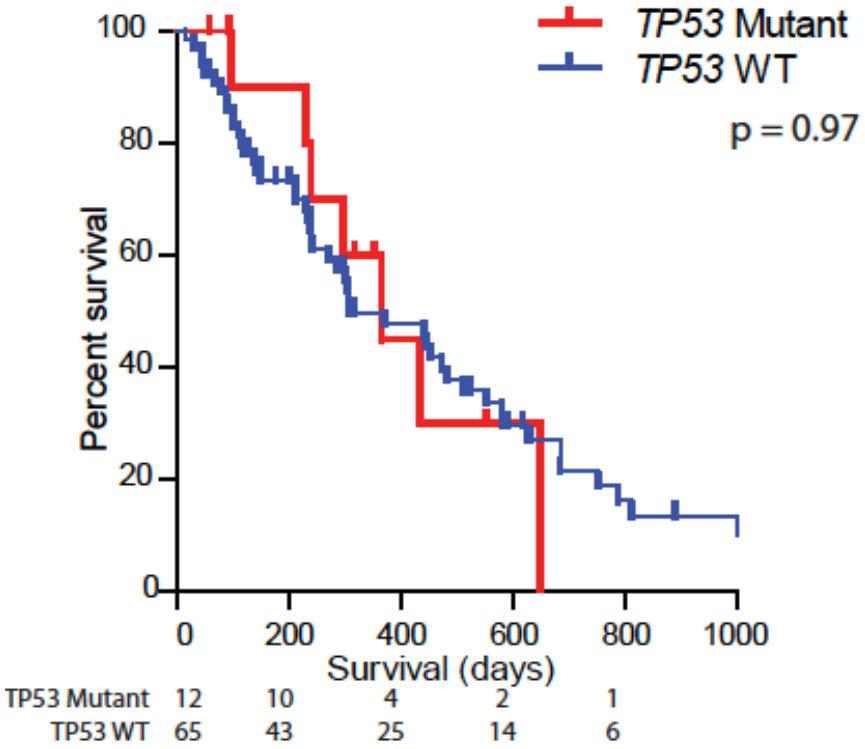
Prognosis:
Karyotype: complex and monosomal
AML panel: TP53 V272M

10-day decitabine

TP53 VAF



AML



Welch, NEJM 2016

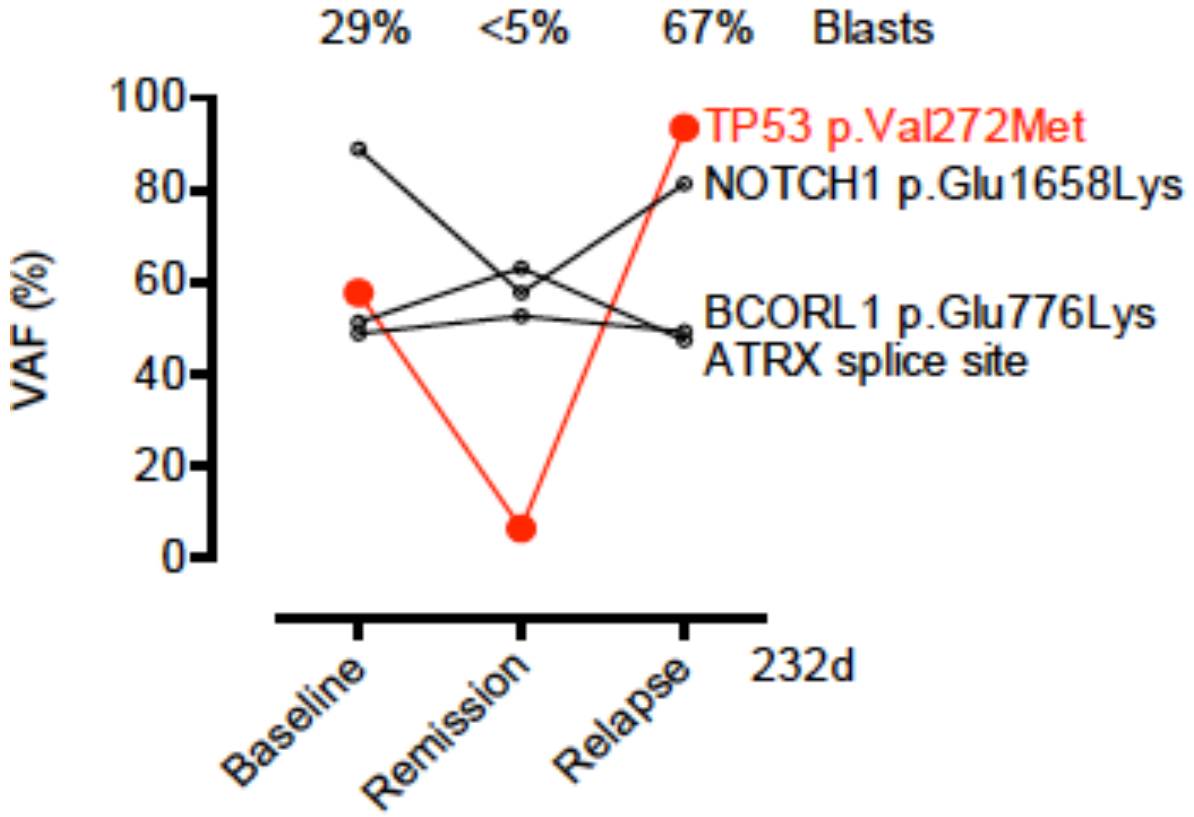
A 69 yo woman with *de novo* AML

Diagnosis:
March 2016 FBE Hb 36, WBC 4.5, Neut 0.3, Platelets 38;
BMAT: 29% blasts with dysplastic changes

Prognosis:
Karyotype: complex and monosomal
AML panel: TP53 V272M

Treatment

- Decitabine + venetoclax→ MLFS
- Cycle 4→ CRi with CG remission
- Cycle 7 → PD with 67% blasts



Emerging therapies for TP53 mutant AML

Therapy	N	CR/CRi	OS	Ref
5d DAC	7	29%	5.5m	Short, et al. *Lancet Haematol* 2019
10d DAC	17	47%	4.9m	Short, et al. *Lancet Haematol* 2019
CPX-351	24	29%	4.5m	Lindsley, et al. *Blood* 2018
AZA	21	NA	7.2m	Tang, et al. *Blood* 2016
HMA + VEN	36	47%	7.2m	DiNardo, et al. *Blood* 2019
AZA + APR-246	11	80%	NA	Sallman, et al. *ASH 2019*
AZA + Hu5F9-G4	5	83%	NR	Sallman, et al. *ASCO 2019*

AML, acute myeloid leukaemia; **CR**, complete remission; **CRi**, incomplete blood count recovery; **DAC**, decitabine; **HMA**, hypomethylating agent; **LDAC**, low-dose AraC; **m**, months; **MUT**, mutated; **OS**, overall survival; **TP53**, tumour protein 53; **VEN**, venetoclax.

DiNardo CD, et al. *Blood* 2019;133(1):7–17; Sallman DA, et al. *Blood* 2018;132:3091; Short NJ, et al. *Lancet Haematol* 2019; 6(1):e29–e37; Tang L, et al. *Blood* 2016; 128:2859; Wei AH, et al. *J Clin Oncol.* 2019;37(15):1277–1284.

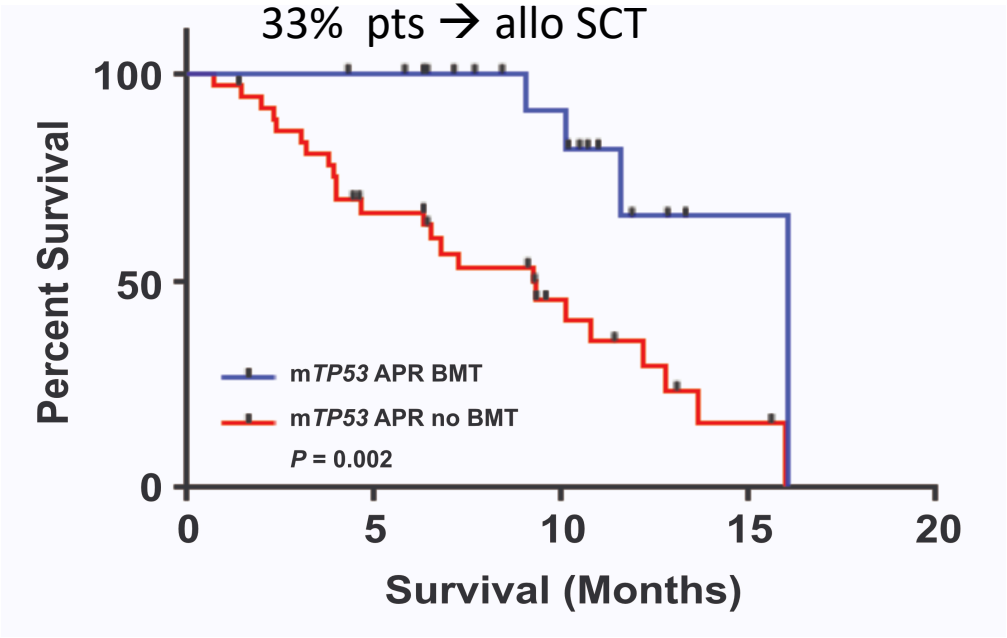
Phase 2 Results of APR-246 and Azacitidine (AZA) in Patients with *TP53* mutant Myelodysplastic Syndromes (MDS) and Oligoblastic Acute Myeloid Leukemia (AML)

Background: TP53 mut poor outcomes in MDS and AML. Preliminary results for APR-246 in combination with AZA promising (Sallman ASH 2018)

Objectives: Report results of completed phase 2 results in 55pts with treatment naïve MDS and oligoblastic AML (<30%)

Regimen: APR-246 RP2D 4500 mg d1-4 + AZA 75 mg/m2 D4-10 or 4-5 and 8-12

Median F/U 10.5 mo	MDS	AML	MDS/MPN
N	40	11	4
Evaluable	33	8	4
CR	61%	50%	0%
ORR	88%		75%
Median DoR	6.5 mo		
Median OS	11.6 mo		
Notable AEs	Dizziness 33%, Neuropathy 22%		



Next step: Randomized phase 3 study of APR-246+AZA versus AZA alone in m*TP53* MDS (NCT03745716)

APR-246 Combined with Azacitidine (AZA) in TP53 Mutated Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML). a Phase 2 Study By the Groupe Francophone Des Myélodysplasies (GFM)

Background: TP53 mut poor outcomes in MDS and AML. Preliminary results for APR-246 in combination with AZA promising (Sallman ASH 2018)

Objectives: Report results of completed phase 2 results in 53pts with treatment naïve MDS and oligoblastic AML

Regimen: APR-246 RP2D 4500 mg d1-4 + AZA 75 mg/m2 D4-10

	MDS	AML
N	34	19
Evaluable	16	
CR	56%	
ORR	75%	
Notable AEs	Neurological 40%* Mainly ataxia	

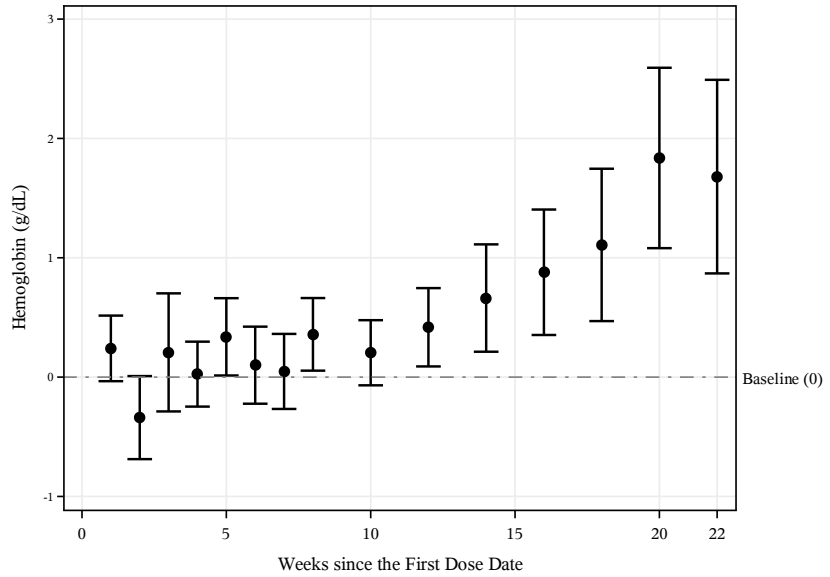
* correlated with lower GFR at treatment onset. Spontaneously regressed within 5 days of drug discontinuation. Did not recur in subsequent cycles after APR 246 dose reductions

The First-in-Class Anti-CD47 Antibody Hu5F9-G4 is Well Tolerated and Active Alone or with Azacitidine in AML and MDS Patients: Initial Phase 1b Results

Background: CD47 is a "do not eat me" signal on cancers enabling macrophage immune evasion. 5F9 is a Macrophage Immune Checkpoint Inhibitor Targeting CD47

Objectives: Report results of 5F9 Alone or in Combination with Azacitidine in AML and MDS (5F9005 Study)

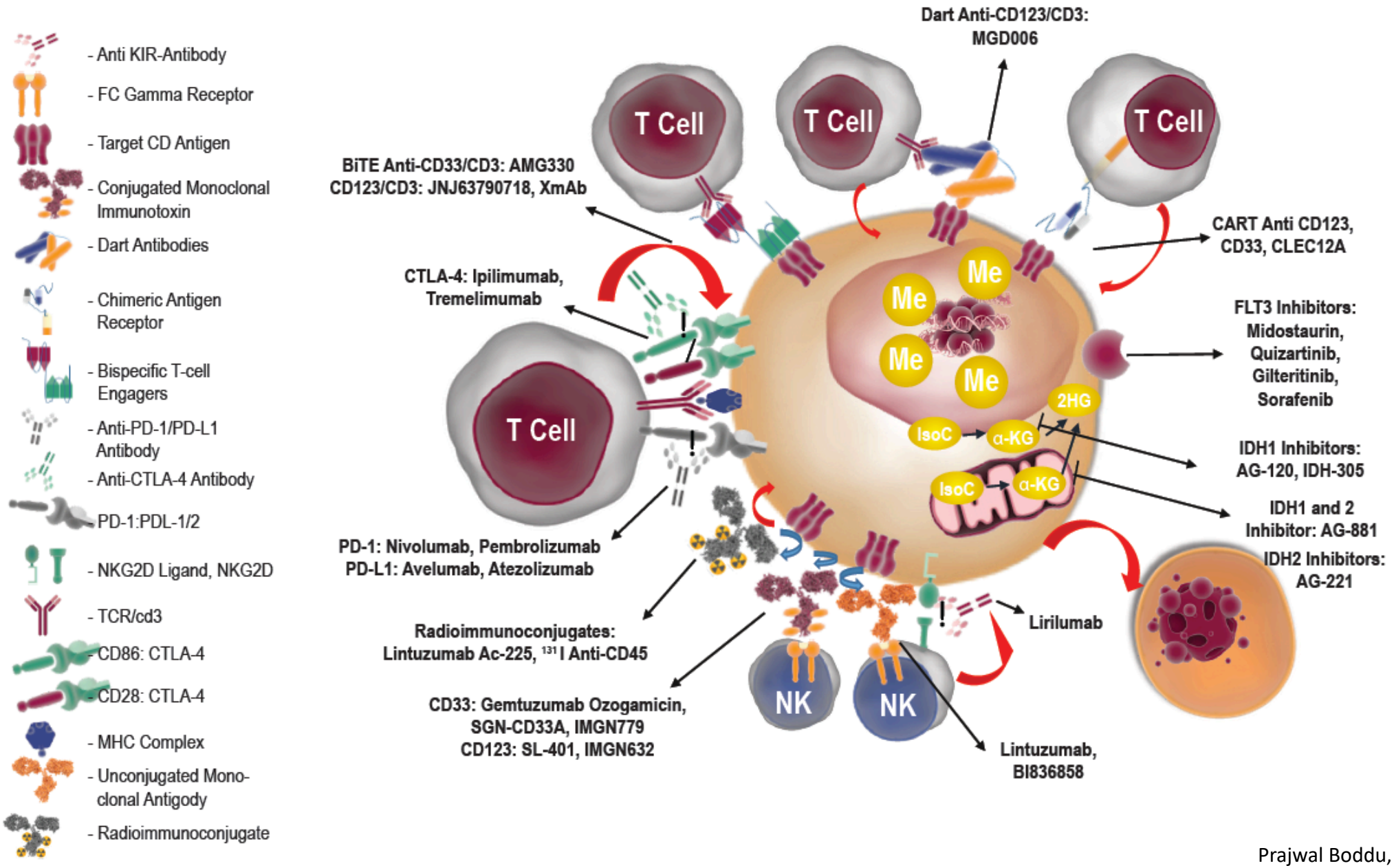
5F9: 1, 30 mg/kg* weekly and AZA: 75 mg/m^2 D1-7. * Dose ramp up from 1 to 30 mg/kg by week 2,



TP53 mutant cases	1L AML (N=6)	1L MDS (N=2)	Total (N=8)
ORR	5/6 (83%)	2/2 (100%)	7/8 (88%)
Median duration of response	NR	NR	NR
Median overall survival	NR	NR	NR
Median follow-up*	5.8 months	4.9 months	

Updated data: presented at ASH Abstract 569: December 9th at 8am

Immunotherapeutic strategies targeting AML at ASH



Prajwal Boddu, AJHO. 2017;13(4):4-15

Selected immunotherapy papers at ASH 2019

Treatment	N	CR/CRi	Presentation
Unfit older AML (checkpoint inhibitors)			
AZA + Durvalumab (PD-L1) vs AZA in unfit older AML	64 65	31% 35%	*829- Zeidan, Monday, 4:30 PM*
Relapsed/refractory AML (checkpoint inhibitors)			
HiDAC + Pembrolizumab (PD-1)	37	38%	*831- Zeidner, Monday, 5:00 PM*
AZA + Nivolumab (PD-1) AZA + Nivo + Ipilimumab (CTLA4)	70 25	22% 36%	*830- Daver, Monday, 4:45 PM*
DAC + MBG453 (TIM3)	17	29%	*570- Borate, Monday, 8:15 AM*
Relapsed/refractory AML (BiTES)			
Anti-CD33 x CD3 (AMG673)	30	1	*833- Subklewe, Monday, 5:30 PM*
Anti-CD33 x CD3 (AMV564)	36	2	*834- Cortes, Monday, 5:45 PM*
Anti-CD123 x CD3 (Flotetuzumab)	30 1º Ref	32%	*733- Uy, Monday, 2:45 PM*

Concluding statements

- Maintenance therapy newly defined role in AML
- New treatment options for TP53 mutant AML emerging
- Immunotherapy options still evolving