Acute Myelogenous Leukemia: New Therapies after 40 Years!

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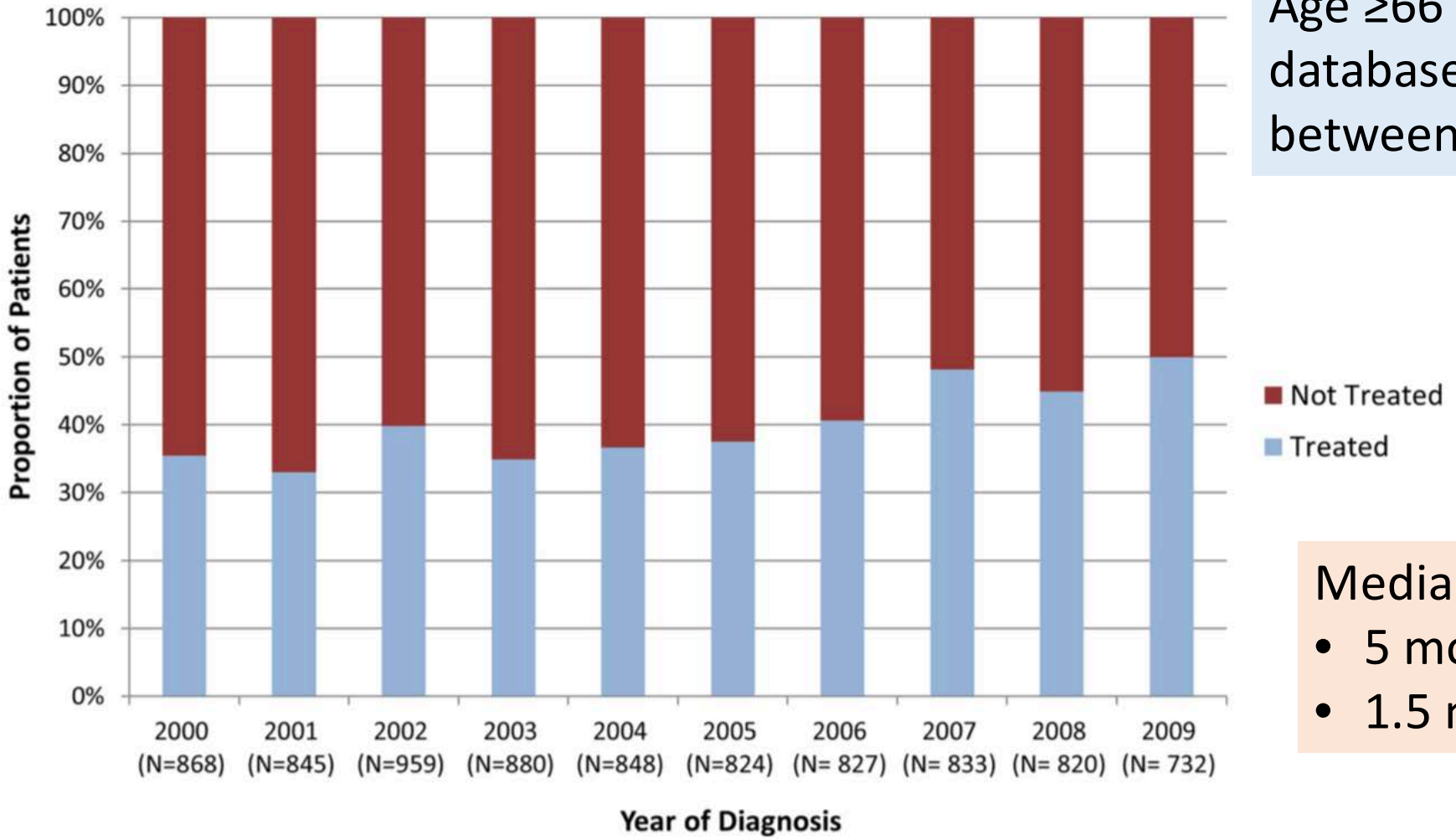
Outline

- Recent Advances for the Treatment of AML

- New agents approved for AML
  - Venetoclax
  - Glasdegib
  - Ivosidenib
  - Vyxeos

- Biomarkers in AML
  - Molecular Mutations as Biomarker of Response to Therapies
  - Minimal Residual Disease

AML Treatment Patterns over Time



Age ≥66 SEER and Medicare database with DX AML between 2000-2009 (n=8336)

60% of elderly AML patients are untreated!!

Median OS (all) 2.5 mo

- 5 mo for treated pts
- 1.5 mo for untreated pts

Madeiros et al., Ann Hematol, 2015

Recent Advances in AML Therapy

Mutation	Treatment	Indications	FDA Approval
FLT3	Midostaurin Gilterinib	Upfront treatment Relapsed	April 2018 Dec 2018
IDH1	**Ivosidenib**	Relapsed	Oct 2018
IDH2	Enasidenib	Relapsed	Aug 2017

Mechanism	Drug	Indications	Approval
BCL-2 inhibitor	**Venetoclax**	Frontline (elderly, unfit) Relapsed (off-label)	Nov 2018
Smoothen Hedgehog pathway	**Glasdegib**	Frontline (elderly, unfit)	Nov 2018
CD33 antibody-drug conjugate	Gemtuzumab Ogazomicin	Upfront treatment (good risk), Relapsed	Sept 2017
1:5 fixed molar ratio of 7+3 (Dauno/Cyt)	**Liposomal 7+3 (Vyxeos)**	Upfront Secondary AML or AML-MRC	Aug 2018

Glasdegib

- FDA-approved in combination with low-dose Ara-C in newly diagnosed AML or high-risk MDS age 75 or older ineligible for intensive chemotherapy (BRIGHT AML 1003)

- Mechanism: Small molecule Smoothened Hedgehog signaling pathway inhibitor

- Administration: Glasdegib PO 100 mg daily (28 day cycles) + LDAC 20 mg SC bid x 10 days (28 day cycles)

Pharmacology

- Metabolism: CYP3A4
  - Drug interactions: Strong CYP3A inhibitors increase Glasdegib concentrations , Strong CYP4A Inducers decrease Glasdegib concentrations, QTc prolonging drugs may increase risk of QTc prolongation (intermittent use likely OK)
- Steady state plasma levels at 8 days of daily dosing
- Half life 17 hours

Phase II randomized trial of Glasdegib + LDAC vs LDAC alone in newly DX AML/high grade MDS

	Glasdegib + LDAC (n = 88)	LDAC (n = 44)
Age (median)	77 (63-92)	75 (58-83)
AML / MDS (%)	89 / 11	86 / 14
BM blasts (med) (AML)	41 (16-100)	46 (13-95)
ECOG 0 / 1 / 2	12/ 33/ 53	7 / 41/ 52
ELN Risk Group (AML) (%) Favorable Int I/II Adverse	 6 35 / 27 32	 8 28 / 21 42
Duration since DX (month) (median) AML MDS	 0.6 (0.03-3.52) 1 (0.2 – 13.6)	 0.5 (0.07-3.84) 2.2 (0.43 – 14.98)

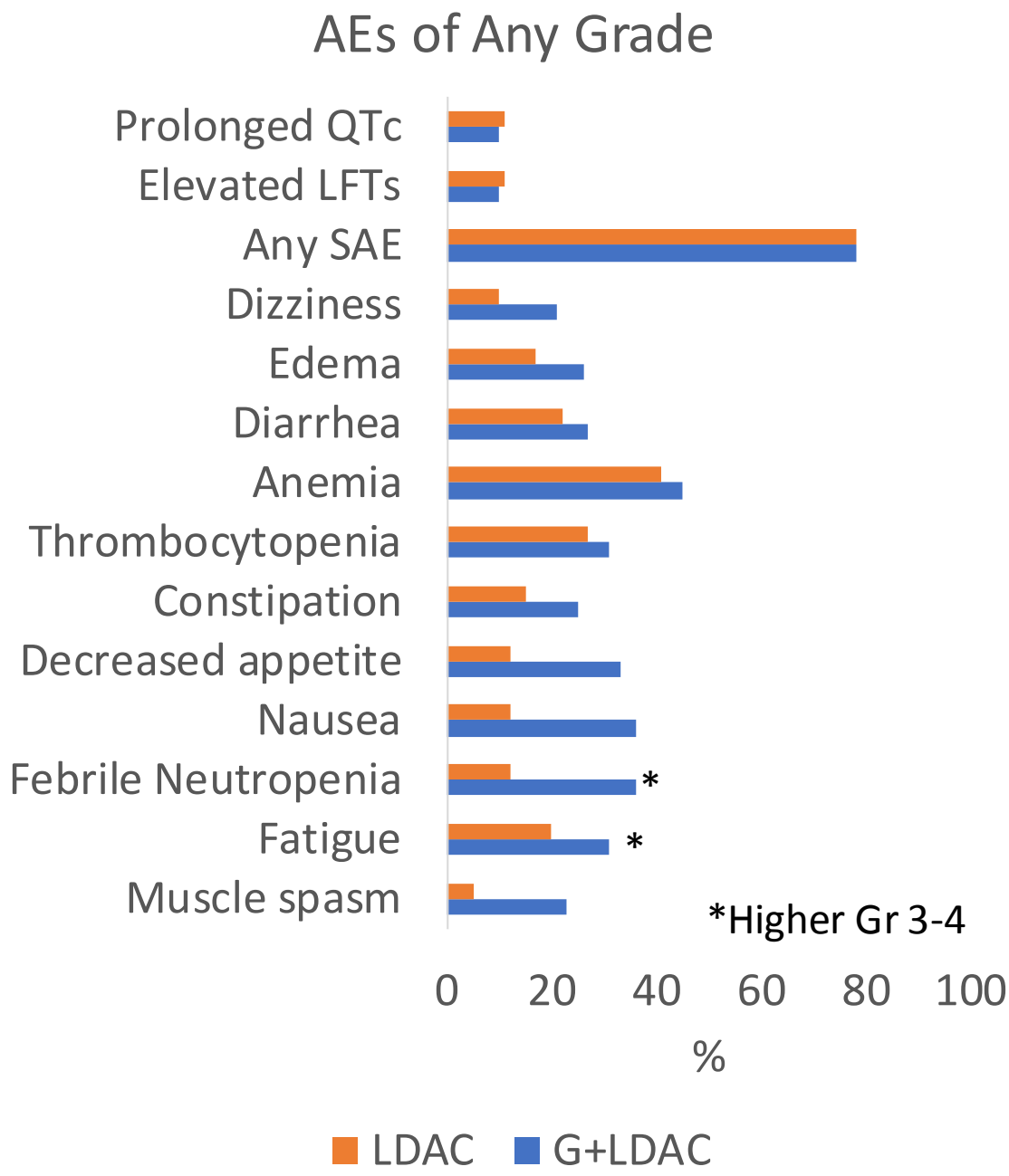
Eligibility Criteria:

- Age ≥55
- Prevously untreated AML or high-risk MDS
- Not suitable for intensive chemotherapy
  - Age ≥75
  - SCr > 1.3 mg/dL
  - EF < 45%
  - ECOG 2
- Exclusions- APML, t(9;22), active CNS leukemia

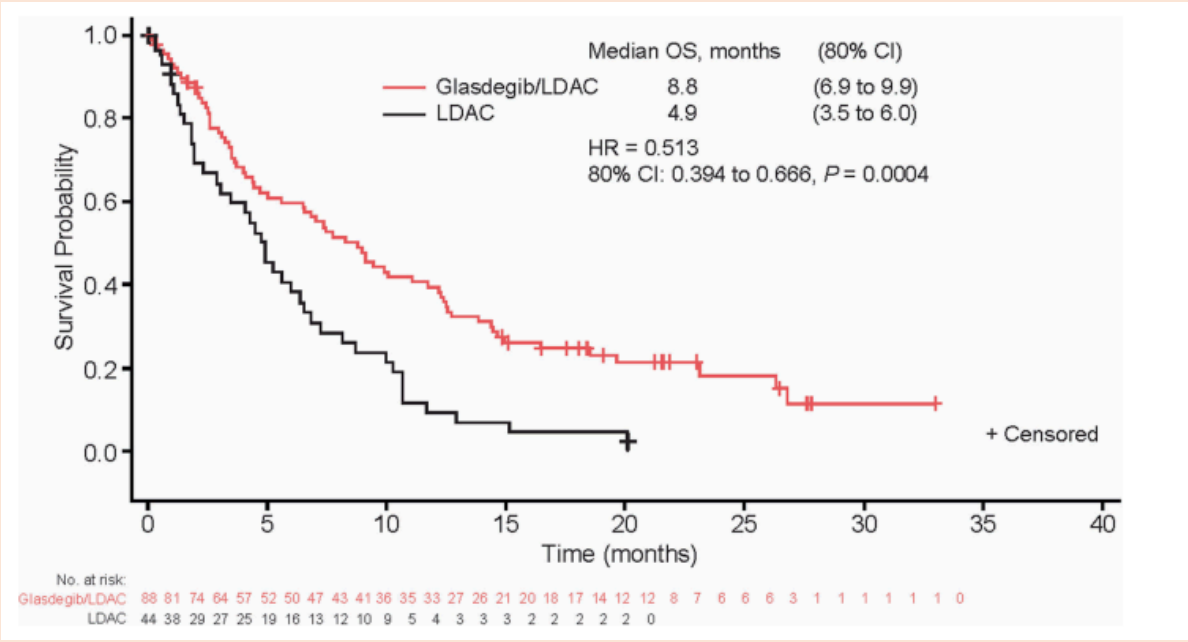
Cortes et al., Leukemia, Feb 2019

	Glasdegib + LDAC (n = 88)	LDAC (n = 44)	Pearson Chi square
ORR, n (%) AML MDS	 27% 20%	 5% 0%	
CR, n (%)	15 (17%)	1 (2.3%)	P = 0.01
Median DoR CR CR/CRi/MLFS	 9.9 mo. 6.5 mo.		
CG risk Good/Int Adverse	 10/52 (19.2%) 5/36 (13.9%)	 0/25 (0%) 1/19 (5.3%)	
Median Duration of TX	2.7 mo.	1.5 mo.	

Dose reductions in 1 of 4 patients in combination arm

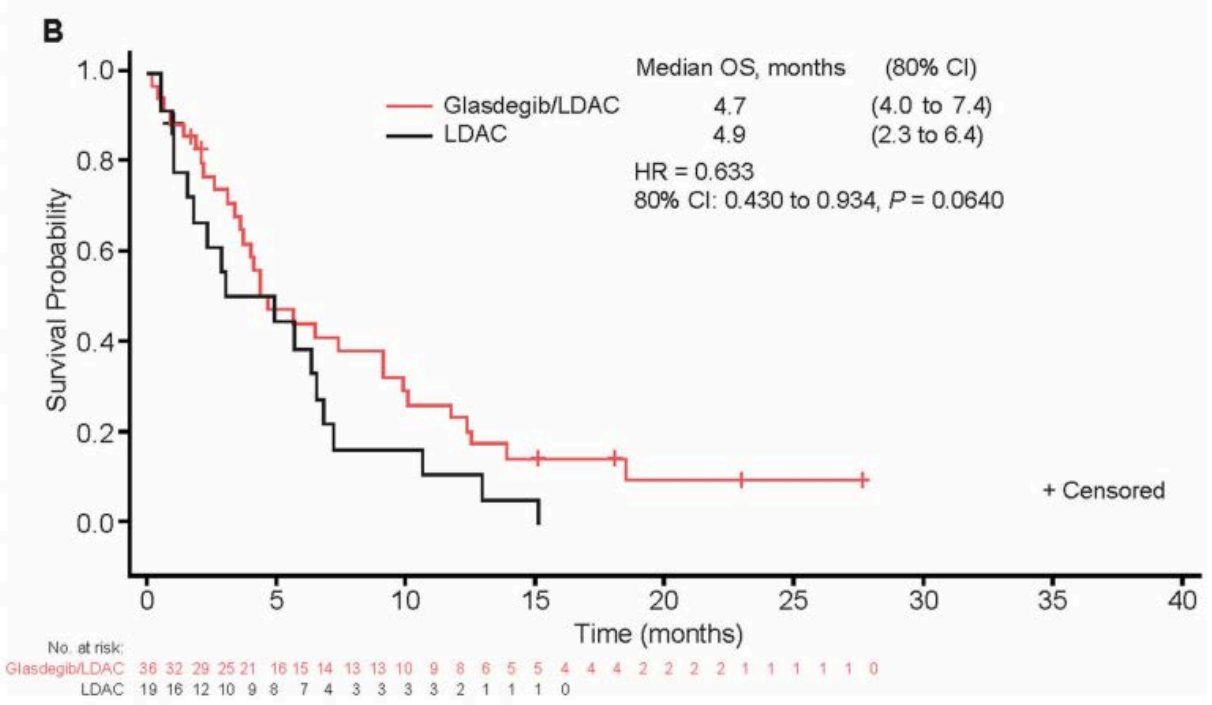


Good/Int Cytogenetic Risk



mOS 12.2 vs 4.8 mo with Glasdegib/LDAC vs LDAC alone (p = 0.0008), 80% CI 0.3 to 0.609

Adverse Cytogenetic RIsk



mOS 4.7 vs. 4.9 mo with Glasdegib/LDAC vs LDAC alone (p = 0.0640), 80% CI 0.43 to 0.934)

Glasdegib Monitoring

- Monitoring:
  - Baseline CK (muscle spasms)
  - Baseline, post-1 week, then monthly EKG x 2 months for QTc
  - Renal function and Electrolytes monthly
  - Pregnancy test in WOCB potential
- Grade 3 nonhematologic toxicity → may decrease Glasdegib to 50 mg qd OR reduce dose of cytarabine to 10-15 mg SC bid
- QTc 480-500 ms → Adjust other QT prolonging medications, monitor EKGs, QTc > 500 ms → HOLD Glasdegib and resume at 50 mg qd when Qtc < 480 ms
- ANC < 0.5 or Plt < 10 x 42 days in absence of disease → Discontinue Glasdegib and LDAC permanently

Venetoclax

- FDA-approved in combination with Azacitidine or Decitabine or low-dose Ara-C for treatment of adult patients with newly diagnosed AML ≥75 years old or with comorbidities precluding use of intensive chemotherapy

- Mechanism: Small molecule BCL-2 inhibitor

- Administration: 400 mg in combination with Azacitidine/Decitabine, 600 mg in combination with LDAC

Venetoclax Frontline Prospective Combination trials in AML

- Venetoclax + Azacitidine/Decitabine (Phase 1b dose escalation/expansion) (n=145)
- Pts ≥65 yo., previously untreated AML, ineligible for intensive induction
- ORR (CR + CRi + PR) = 68%

DiNardo et al., Blood, Jan. 2019

- Venetoclax + LDAC Phase I/II study) (n=82)
- Previously untreated AML, ineligible for intensive induction
- ORR (CR + Cri) = 54%

Wei et al, ASH 2018, Abstract #615

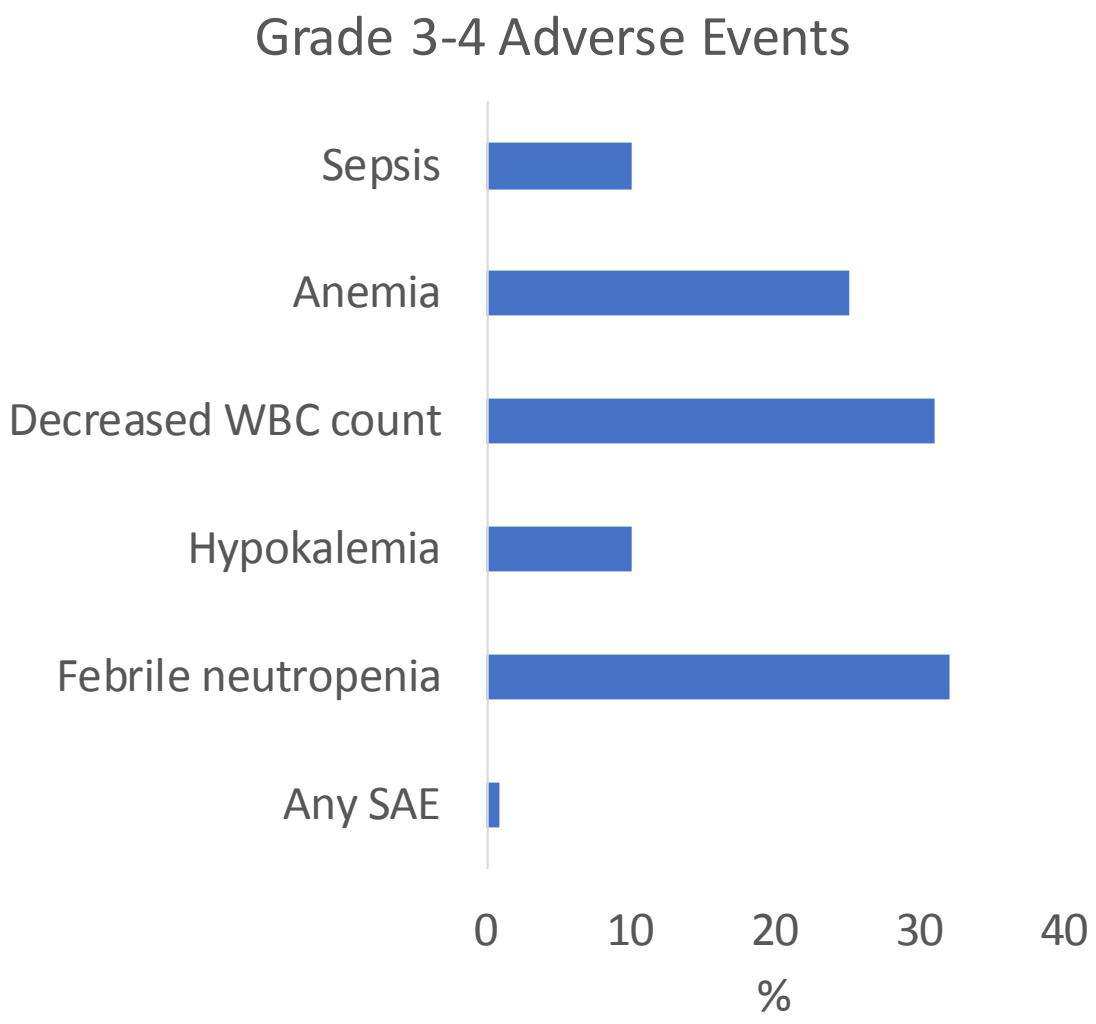
Venetoclax + Azacitidine/Decitabine

	Dose escalation + Expansion phase (n=145)
Median age	74 (65-86); 36% > age 75
ECOG PS 0 / 1/ 2	22% / 62% / 16%
CG (n,%)	Intermediate 51% Poor 49%
De Novo Secondary	75% 25%
Mutation (no., %) FLT3 IDH1/ IDH2 NPM1 TP53	 18 (12%) 35 (24%) 23 (16%) 36 (25%)
Baseline BM blast count <30% / 30-50% / ≥50%	 24% / 38% / 38%
Median time on study (range), months	8.9 (0.2 to 31.7)

DiNardo et al., Blood, Jan. 2019

Safety

- 3 x 3 dose escalation (400 mg Venetoclax, n= 60; 800 mg Venetoclax, n = 74; 1200 mg venetoclax (n = 11) with Aza/Decitabine (~50% each)
- Mainly Grade I/II Gastrointestinal Aes
- 1200 mg qd Venetoclax cohort trended towards higher rate of hematologic and GI AEs compared to 400 mg and 800 mg cohorts, requiring dose reduction in 5 of 12 pts
- 400 mg Venetoclax cohort had fewer GI symptoms
- Similar AE rate between AZA/DEC



DiNardo et al., Blood, Jan. 2019

Efficacy

	CR + CRi	ORR (CR + Cri + PR)	Leukemia Response rate (CR + CRi + PR + MLFS)	Median DoR (mo.)	Median OS (95% CI)
Ven 400 mg + HMA (n=60)	73%	73%	82%	12.5 (7.8 – NR)	NR (11.0 – NR)
Ven 800 mg + HMA (n = 74)	65%	68%	85%	11.0 (6.5 to 12.9)	17.5 (10.3 – NR)
Ven 1200 mg + HMA (n=11)	45%	45%	73%	9.4 (3.1 – NR)	11.4 (0.9 – NR)
ALL	**67% (37% CR)**	**68%**	**83%**	**11.3 (8.9 – NR)**	**17.5 (12.3 – NR)**

DoR = Duration of Response, OS = Overall Survival

MRD negativity by flow ($<10^{-3}$)

- **29%;** Median DoR not reached in this group

Median time to first response 1.2 months (range 0.8 – 13.5)

Median time to CR 2.1 months (range 0.9 to 13.5)

DiNardo et al., Blood, Jan. 2019

Subgroups

	CR/CRi (%)	Median DoR (mo.)	Median OS (mo.)
CG risk Poor Intermediate	 60 74	 6.7 12.9	 9.6 NR
TP53	47	5.6	7.2
FLT3 (n = 10 ITD, n = 5 TKD, n = 3 other)	72	11	NR
IDH1/IDH2	71	NR	24.4
NPM1*	92	NR	NR

DoR = Duration of Response, OS = Overall Survival

*NPM1 significant predictor of response in multivariate analysis

DiNardo et al., Blood, Jan. 2019

Venetoclax combinations for Relapsed AML (off-label)

Regimen	Study Design	Population	Response Rates	Median OS	Ref
Venetoclax + HMA	Prospective	N = 22, Adults with AML relapsed after HMA	41% CR	5.5 mo	Ram et al., ASH abstract 4046, 2018
Venetoclax with HMA	Retrospective	N = 33, Adults with relapsed AML (failed 1 prior therapy), 39% prior alloHCT	64% ORR (30% CR, 21% Cri, 12% MLFS)	1 yr	Aldoss et al., Haematologica, 2017
Venetoclax with HMA or LDAC	Retrospective	N = 39, Adults with relapsed AML	21% ORR (5% CR)	3 mo.	DiNardo et al., Am J Hematol, 2017

HMA = hypomethylating agent, LDAC = low dose Ara-C

Pharmacology

- Ramp-up of 100 mg on D1, 200 mg on D2, 400 mg on D3 recommended
- Concurrent CYP3A inhibitors (azoles)
  - Posaconazole- Ramp up to 70 mg, Voriconazole- ramp up to 100 mg. Moderate CYP3A inhibitors- reduce dose by 50%.
- Dose modifications: For Grade 4 neutropenia, it is not recommended to interrupt doses prior to achieving remission. After remission > 7 days, subsequent cycles may be delayed.
- Laboratory monitoring: ≥10% pts have new or worsening hyponatremia, hypocalcemia, hypokalemia, hypophosphatemia
- Half life 26 hours

Venetoclax in AML

- Data suggests that Venetoclax more effective in up front setting and in combination with HMAs
- Tumor Lysis Syndrome has only been observed rarely in AML at initiation of Venetoclax in contrast to CLL
  - 3% incidence of laboratory TLS with Venetoclax+LDAC
  - CrCl < 80 mL/min at higher risk
  - Hydration and Allopurinol initiation prior to first Venetoclax dose
- Venetoclax appears effective across multiple molecular and cytogenetic risk groups
  - NPM1 mutation may confer higher sensitivity to Venetoclax

Ivosidenib

- FDA approved for treatment of adult patients with relapsed or refractory AML with IDH1 mutation
- IDH1 mutations occur in 6-10% of AML
- Mechanism: Small molecule inhibitor of mutant IDH1 enzyme
  - Susceptible mutations lead to increased 2-hydroxyglutarate (2-HG) in leukemic cells, most commonly R132H and R132C substitutions
- Administration: 500 mg PO daily

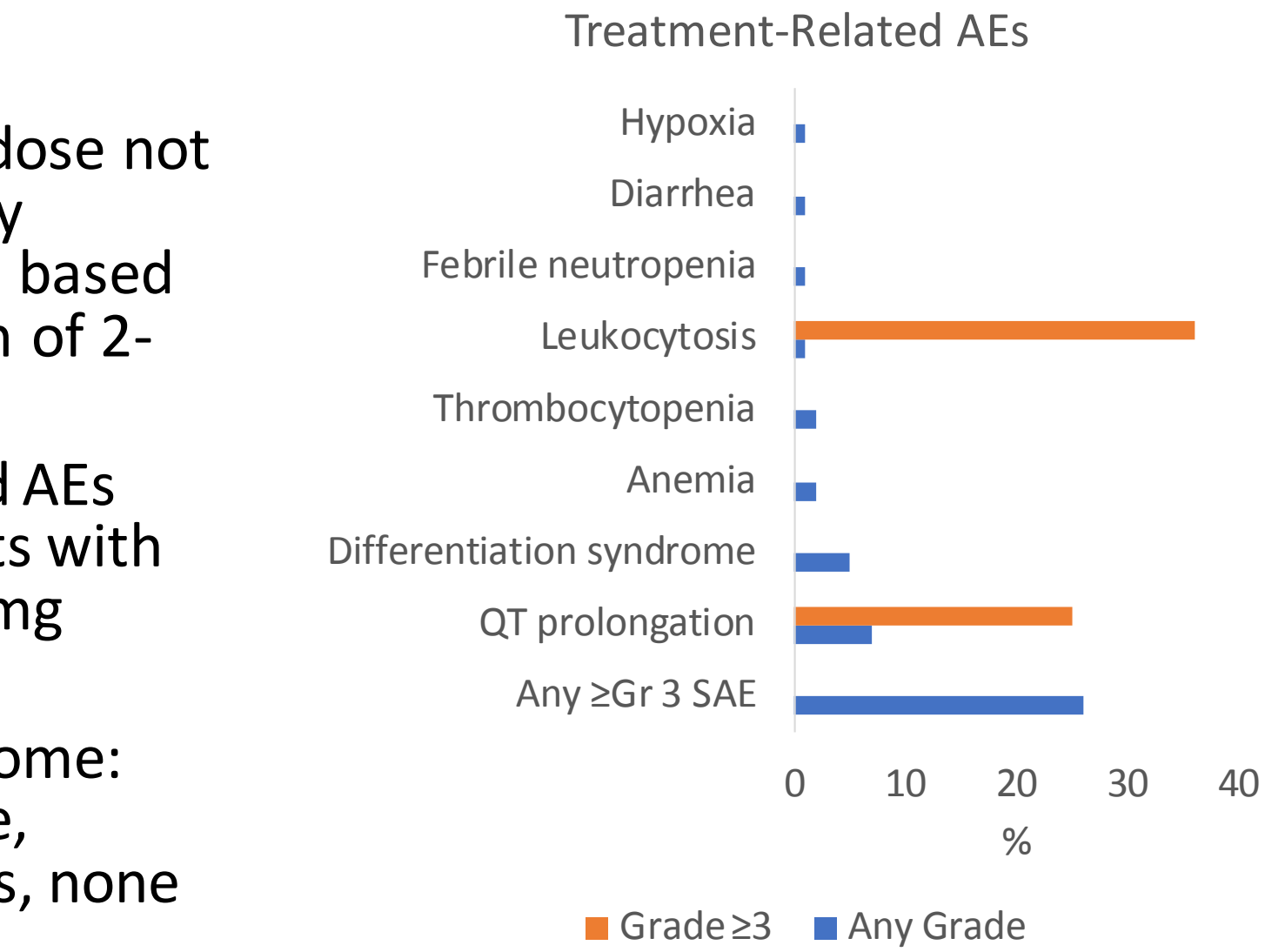
Phase 1 study of Ivosidenib for IDH-1 mutated R/R AML

	Primary Efficacy Population (n=125)	R/R AML (n=179)
Median age (yr)	67 (18-87)	67 (18-87)
AML subtype		
De novo	66%	67%
Secondary	34%	33%
Prior therapies (median)	2 (1-6)	2 (1-6)
Prior AlloHCT	29%	24%
Cytogenetic Risk		
Intermediate	53%	59%
Adverse	30%	28%
Unknown	17%	13%
FLT3 mutation	8%	6%
NPM1 mutation	20%	26%
R132C mutation	60%	56%
R132H mutation	24%	24%
R132G/L/S mutation	16%	17%

DiNardo et al, NEJM, June 2018

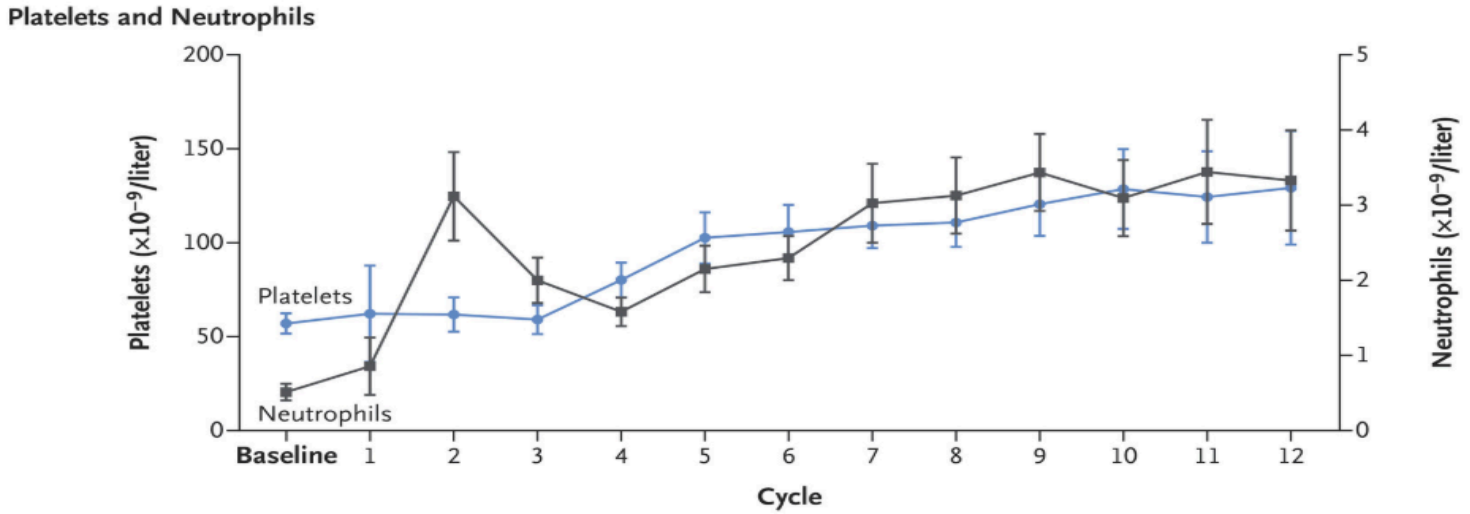
Safety

- Maximum tolerated dose not reached; 500 mg daily chosen for expansion based on maximal inhibition of 2-HG at this dose
- No treatment-related AEs leading to death in pts with starting dose of 500 mg Ivosidenib
- Differentiation Syndrome: 11% rate of any grade, median onset 29 days, none fatal



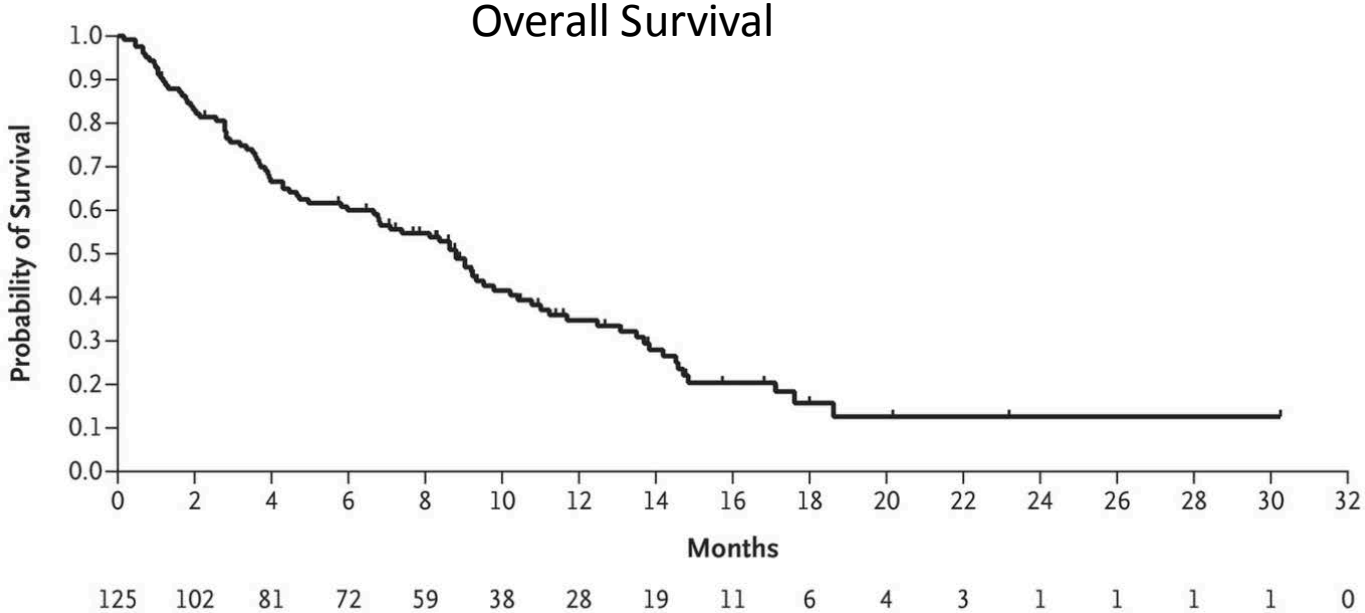
Efficacy

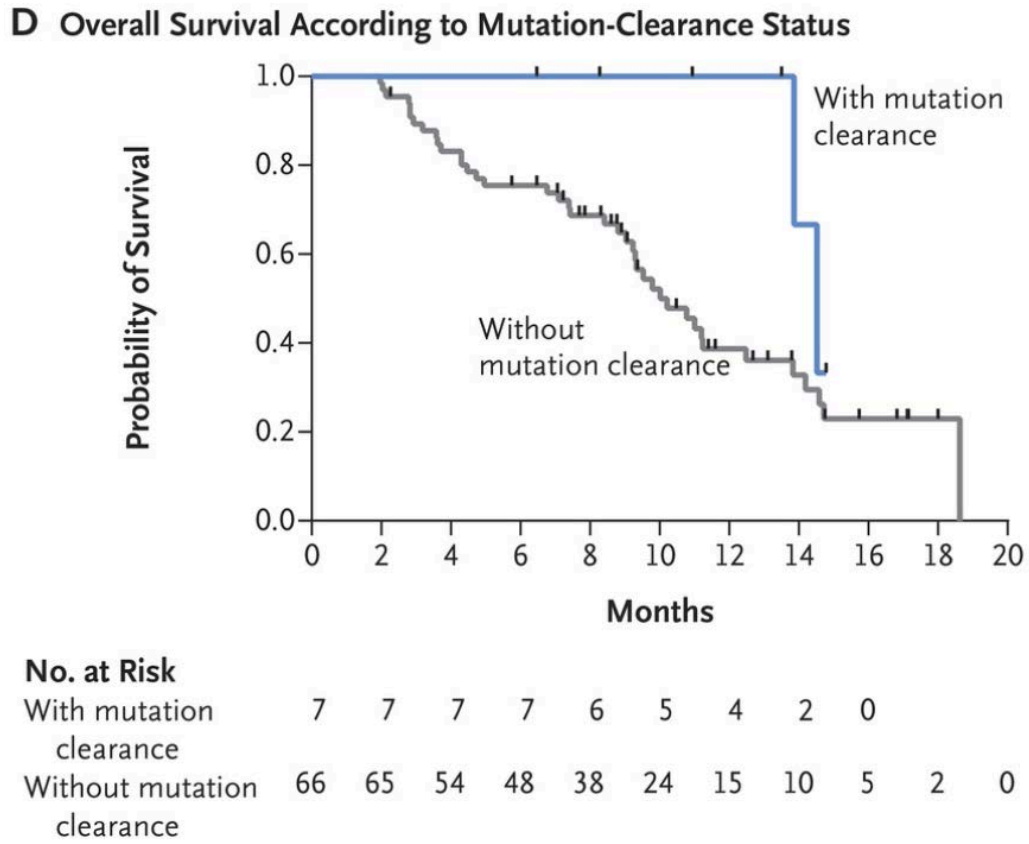
	Primary efficacy population (n=125)
CR/CRh	30%
CR	22%
Median time to CR	2.8 months (0.9-8.3)
Mediation duration of CR	9.3 months (5.6-18.3)
ORR (CR/CRh/PR/MLFS)	42%



35% of RBC-transfusion dependent patients became transfusion-independent

Overall Survival





Among CR/CRh pts, 7 of 34 (21%) cleared mutation (dPCR)

- Associated with prolonged duration of remission and OS

Differentiation Syndrome

- 12-19% rate in clinical trials, with ~80% rate of resolution
  - Similar rates as IDH2 inhibitors for IDH2 mutant AML
- Timing: Earliest 1 day from Ivosidenib initiation, latest up to 3 months
- SX: Dyspnea, leukocytosis, edema, fever, pleural effusion, fluid overload, elevated creatinine
- **Treatment: Dexamethasone 10 mg IV q24 hours with taper after resolution of symptoms, minimum 3 days of steroids; hydroxyurea (2-3g BID or TID) or leukapheresis as clinically indicated for hyperleukocytosis**
- Hold Ivosidenib for severe differentiation syndrome or persistence of symptoms > 48 hours after initiation of steroids

Monitoring

- CBC and Chemistries once weekly x 1 month, then every other week x 1 month, then once monthly for duration of therapy
- CK level weekly x 1 month
- EKG weekly x 3 weeks, then monthly
- Dose Modifications/Interruptions
  - **Severe persistent differentiation syndrome >48 hrs despite steroids - HOLD**
  - **Noninfectious leukocytosis > 25 x 10^9/L not improving with hydroxyurea - HOLD**
  - QTc > 480 ms – resume at 500 mg qd after QTc <480 ms
  - QTc > 500 ms – resume at 250 mg qd after QTc < 480 ms or within 30 ms of baseline
  - Life threatening QTc prolongation – discontinue permanently
  - Guillain Barre syndrome- discontinue permanently
  - Grade ≥3 toxicity- HOLD until toxicity resolves, resume at 250 mg daily

Pharmacology

- Metabolized by CYP3A3
  - Strong CYP4A4 inhibitors- reduce dose to 250 mg daily
- Long half life of 93 hours, steady state plasma levels in 14 days
- No PK data on GFR < 30 mL/min, moderate or severe hepatic impairment (Bilirubin >1.5 ULN)

Ivosidenib

- Activity in relapsed setting in IDH-1 mutated AML, CR rates and OS compares favorably to historical treatments for R/R AML
- Well tolerated, with manageable AEs of leukocytosis, differentiation syndrome, and QTc prolongation
- Efficacy correlated with reduction of plasma 2-HG concentrations to levels of healthy controls
- MRD negative status likely confers longer duration of response and longer OS, but larger studies are needed to confirm this

CPX-351 (Liposomal Daunorubicin and Cytarabine)

- FDA approved for adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)

- Mechanism: Liposomal combination of Daunorubicin (Topoisomerase inhibitor) and Cytarabine (nucleoside antimetabolite)
  - Greater uptake in leukemic cells with more persistent 5:1 ratio C:D, may bypass drug efflux pumps

- Administration: IV infusion on D1, 3, 5 induction (44 mg/m^2 Dauno/100 mg/m^2 Ara-C) and D1 and D3 for consolidation (Dauno 29 mg/m^2 and Ara-C 65 mg/m^2)

Phase II study of CPX-351 vs 7+3 in frontline AML

- Non-significant trend towards higher response rates (CR/CRi) compared to 7+3 (67% vs 52%, p=0.07) and similar OS (14.7 vs 12.9 mo)
- Trend towards lower 60 day mortality in CPX-351 arm (4.7 vs 14.6%, p=0.053)
- Subgroup analysis showed higher CR rates in adverse cytogenetics (77% vs 38%,p=0.03), sAML (58% vs 32%, p=0.06)

Cortes et al., Cancer, 2015

Phase III RCT of CPX-351 vs 7+3 frontline treatment of AML

	CPX-351 (N=153)	7+3 (N=156)
Age (mean)	67	67
Male (%)	61	61
ECOG 0/ 1/ 2	24% / 66% / 10%	29% / 57% / 14%
AML subtype T-AML AML with prior MDS AML with prior CMML AML with MDS CG karyotype	 20% 46% 7% 27%	 21% 47% 8% 24%
Prior HMA exposure	40%	45%
CG risk Favorable / Int / Adverse	 5% / 45% / 50%	 3% / 40% / 57%

Eligibility

- Age 60-75, newly diagnosed therapy-related AML, AML with antecedent MDS or CMML, or de-novo AML with MDS-related cytogenetic abnormalities
- Exclusions: APL, CBF AML, active CNS leukemia, prior anthracycline exposure >368 m/m2

Lancet, JCO, 2018

	CPX-351	7+3	Odds Ratio (95% CI)
CR	37%	26%	1.77 (1.11 to 2.81)
CR+CRi	48%	33%	1.69 (1.03 to 2.78)
DoR (median)	6.9	6.1	
Consolidation with alloHCT in CR/CRi	34%	25%	

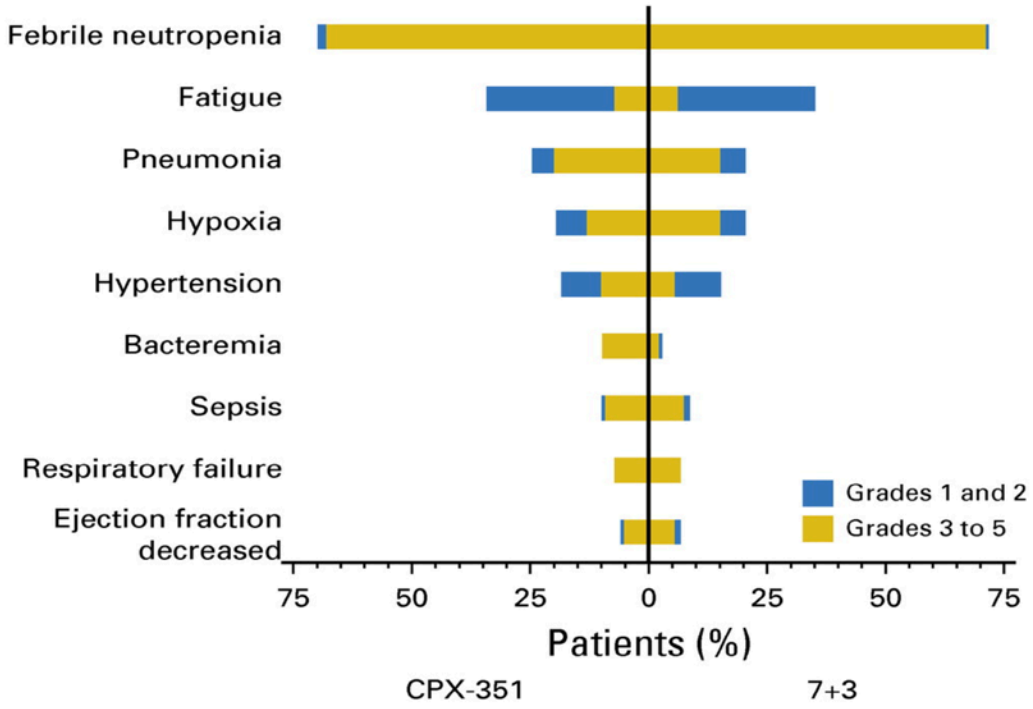
Similar benefit of CPX-351 similar across age (60-69 vs 70-75), disease subgroups, cytogenetic risk groups

Adverse Events: Similar among cohorts, but higher rates of bleeding of any grade with CPX-351 (7% vs 2.6%)

CPX-351 Longer time to recovery of neutrophils and platelets in CR/CRi

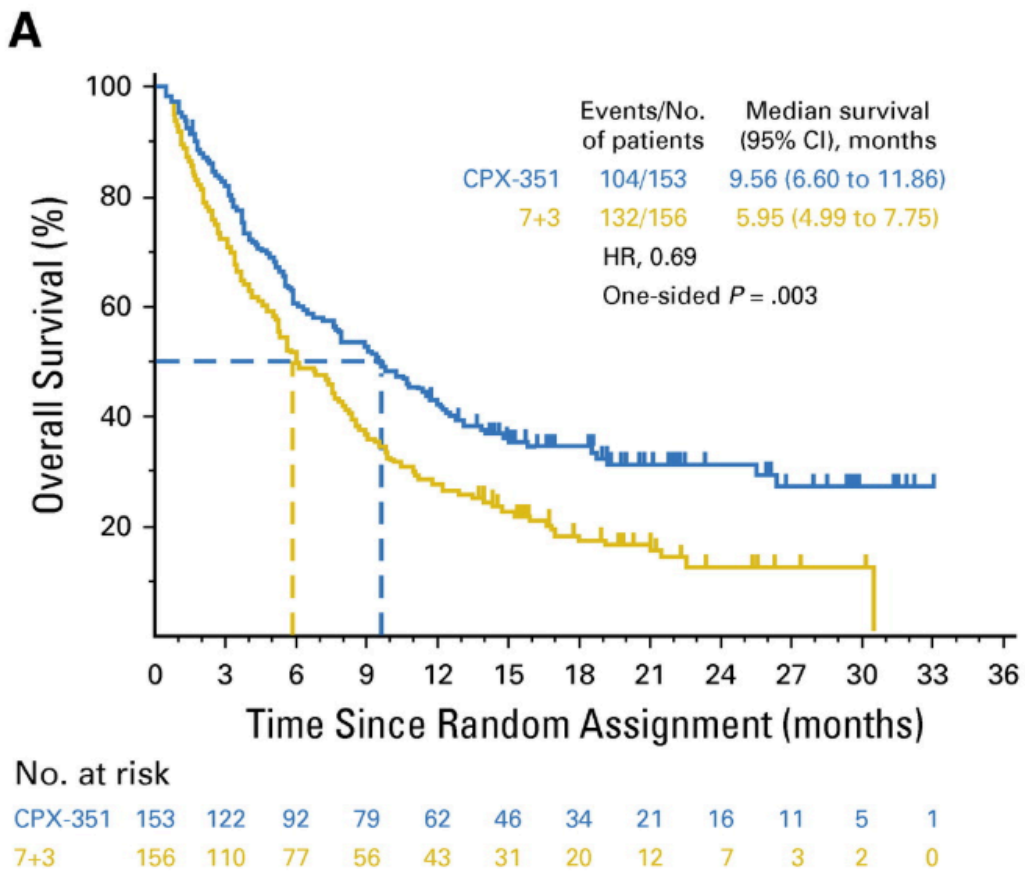
- 35 vs 29 days ANC≥500/uL
- 36 vs 29 days Plt ≥50/uL

30 Day Early mortality rate 5.9 vs 10.6% (p=0.149)

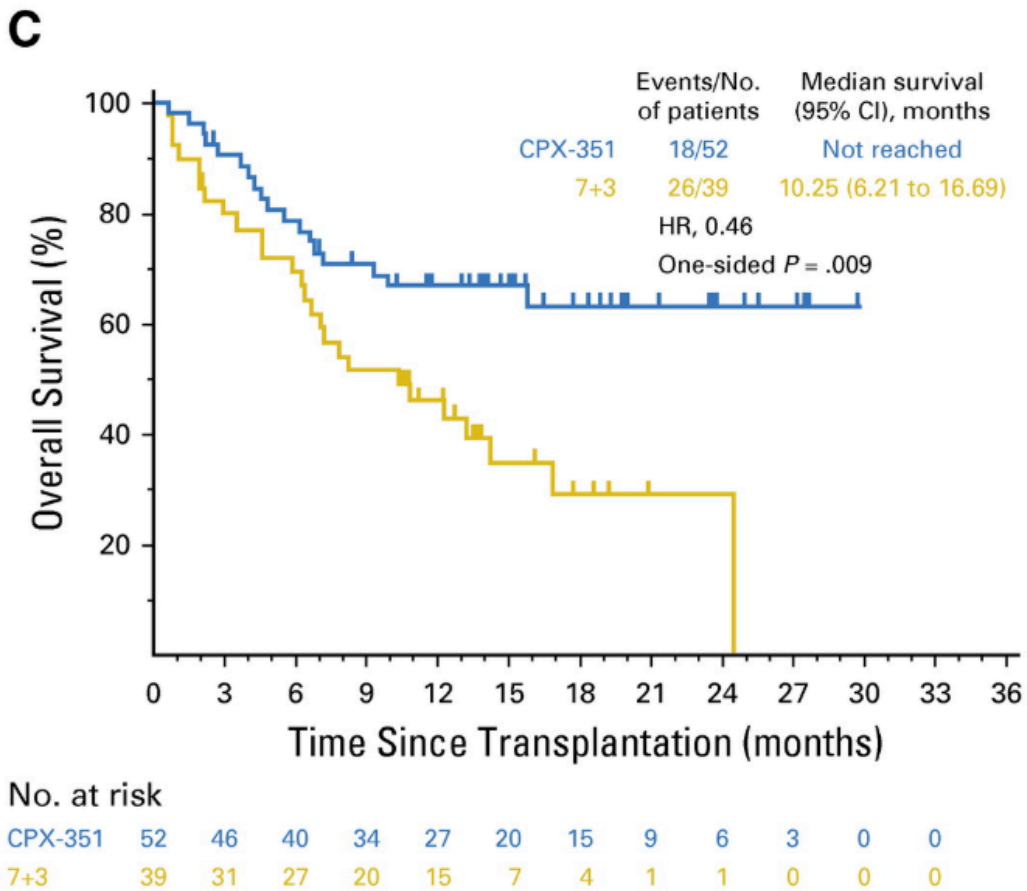


Lancet, JCO, 2018

OS



OS landmarked at Transplant



?Deeper Remissions at time of transplant

Lancet, JCO, 2018

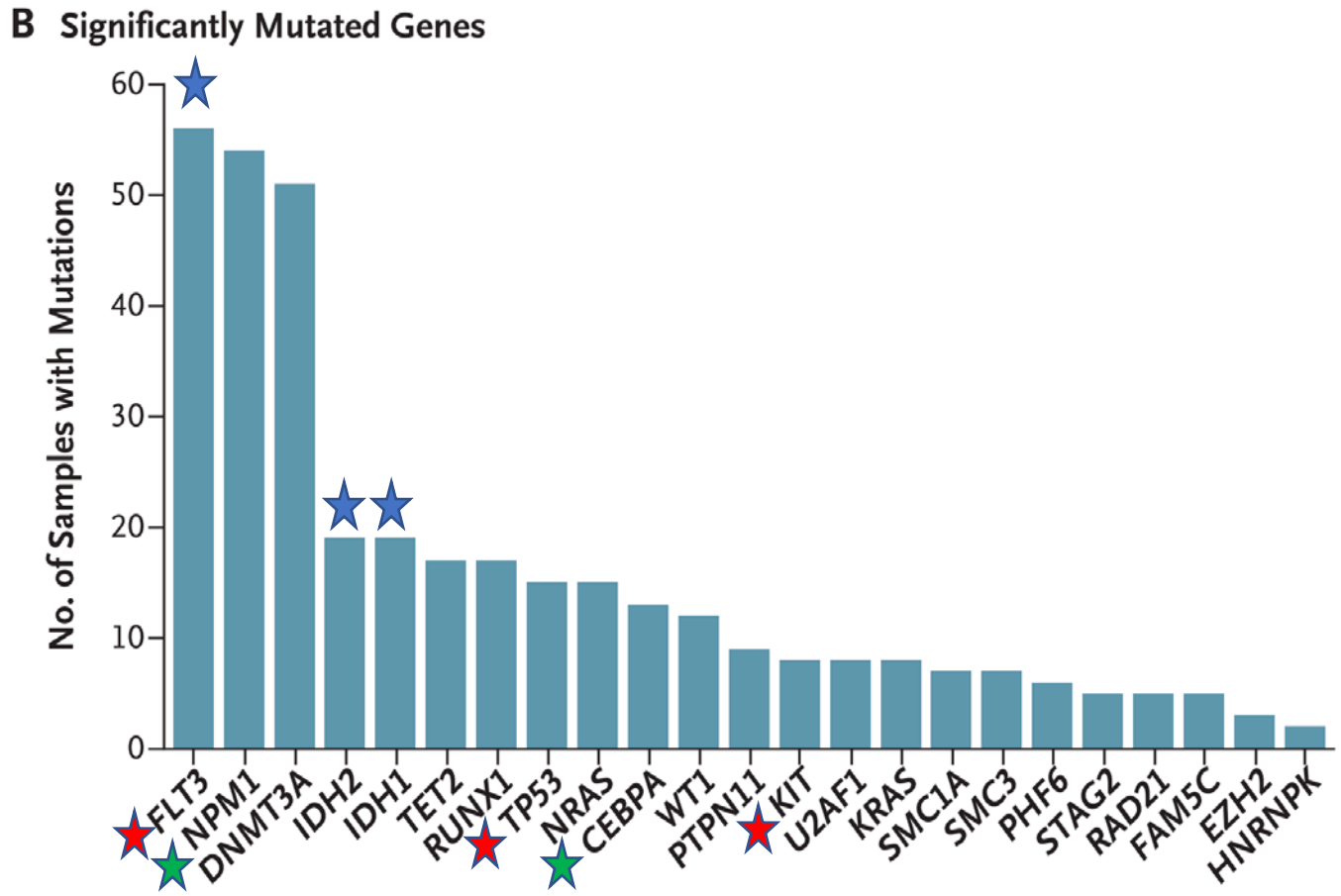
CPX-351

- New standard of care for frontline treatment for adults with T-AML, AML with antecedent MDS or CMML, AML with MRC
  - Other groups that may benefit: adverse CG, FLT3 mutated
- Trend towards lower early mortality, but expect prolonged count recovery by about 1 week compared to 7+3
  - Less hair loss, higher rates of cytarabine rash
- 90 minute infusion → potential for outpatient infusion in select patients and care settings
- Cost:Benefit analysis remains ongoing topic of debate
  - $40,000 vs $4300 for 7+3

Biomarkers in AML

- Molecular Mutations
- Minimal Residual Disease

Molecular Targeting of AML



N = 200 cases of de novo adult AML from The Cancer Genome Atlas

Drug Targets

Good Prognostic

Poor Prognostic

Voigt, NEJM, 2013.

BEAT AML Master Trial

- Multicenter Umbrella Trial enrolling newly diagnosed AML patients ≥60 years old to personalized frontline treatment based on mutations on next-generation sequencing (11 TX arms)
- N = 268 patients enrolled thus far (target 500), median age 72
- 95% of patients assigned to a treatment arm based on NGS results within 7 days (met feasibility goal)
- 51% pts had identified mutation, assigned to targeted therapy arm
- 48% pts marker-negative, treated with SOC, palliative care, or other

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Burd, A., et al. (2018). Initial Report of the Beat AML Umbrella Study for Previously Untreated AML: Evidence of Feasibility and Early Success in Molecularly Driven Phase 1 and 2 Studies. *Blood,* 132(Suppl 1), 559.

AML Subtype	Drug
CBF	Samalizumab (CD200 Ab) + induction
NPM1 + FLT3-ITD	Entospletinib (Syk inhibitor) + induction (fit) Entospletinib (Syk inhibitor) monotherapy (unfit)
MLL rearranged	Entospletinib (Syk inhibitor)
IDH2 +	Enasidenib
IDH1 +	Ivosidenib + Aza
TP53+	Entospletinib (Syk inhibitor) + Decitabine
TP53 - Complex Karotype (≥ 3 abn)	Entospletinib (Syk inhibitor) + Decitabine
TP53+	Pevonedistat (Nedd8 inhibitor) + Aza
FLT3-ITD+ or FLT3-TKD +	Gilteritinib monotherapy or + Decitabine
Tet2/WTI	BI 836858 (CD33 Ab) + Aza
Marker Negative	BI 836858 (CD33 Ab) + Aza

FLT3 mutation

- Transmembrane ligand-activated tyrosine kinase → mutation confers constitutive activity and proliferation
- ITD, TKD mutations (30% of AML)
  - ITD (25%) confers worse prognosis
  - TKD neutral prognosis
  - FLT3 mutation associated with lower survival, higher relapse rate2 approved FLT3 inhibitors
  - Midostaurin (Combination with 7+3 in FLT3 mutated previously untx AML)
  - Gilterinib (single agent for relapsed/refractory FLT3 mutated AML)
- **FLT3 testing should be done in all patients with newly diagnosed AML, Midostaurin should be added to induction therapy at Day 8 in age <60**
- FLT3 mutation can develop during clonal evolution
  - Re-test relapsed patients for FLT3 mutation

FLT3 mutations

	ELN 2017	NCCN
Good Risk	Mutated NPM1 with FLT—ITD^{low}	
Poor Risk	Wild type NPM1 and FLT3-ITD^{high}	Mutated *FLT3*-ITD

FLT3-ITD high = allelic ratio ≥0.5
FLT3-ITD low = alleleic ratio <0.5

How to detect FLT3 mutation?

- PCR (highly specific, detects only amplified region)
- Sequencing
  - Targeted NGS
  - Whole genome sequencing (detects other FLT3 mutations)

Molecular Biomarkers of Prognosis

Good	Intermediate	Adverse
NPM1 mutated	NPM1 mutated and FLT3-high mutated	RUNX1 mutated
Biallelic CEBPA mutated	NPM1 WT and FLT-3 WT or FLT-3 low mutated	ASXL1 mutated
IDH2 mutated	KRAS mutated	TP53 mutated
	NRAS mutated	FLT3-high mutated
		GATA2 mutated
		WT1 mutated
		IDH1 mutated
		MLL mutated

Minimal Residual Disease in AML

- Flow cytometry MRD – 10^{-3} sensitivity
- Molecular MRD
  - NPM1- RQ PCR based testing, sensitivity of 10^{-5}, highly sensitive and specific for disease relapse
  - RUNX1-RUNX1T1, CBFB-MYH11, PML-RARa

- Not validated for MRD (Use flow cytometry in these groups)
  - FLT3- most useful in combination with second MRD marker
  - DTA mutations (DNMT3A, TET2, ASXL1) – persistence does not correlate with increased relapse rate, likely related to age-related clonal hematopoiesis[1]

- NGS sequencing (non-DTA mutations) and Flow Cytometry for MRD during complete morphologic remission have added prognostic value to predict relapse and survival [1]

- Send "1st Pull" from bone marrow biopsy for MRD testing

1. Jongen-Lacrencic et al., NEJM, 2018

PML-RARa in APL

- Most important MRD end point is PCR-negativity for PML-RARa at **end of consolidation**
- For low/intermediate risk APL treated with ATO and ATRA, can discontinue MRD testing after morphologic and molecular CR in bone marrow is attained
- MRD+ during APL induction should not change management
- MRD- to MRD+ indicates impending relapse

New Approaches for AML

Stable

<72 hrs

<24 hrs

4-24 hrs

BM BX → AML → Treat

Morphology,
Flow cytometry

Prelim Cytogenetics,
NGS (FLT3)

Acutely Sick

<24 hrs

4-24 hrs

BM BX → AML → Treat

Summary

- Multiple new approved agents for AML
  - Newly diagnosed
    - CPX-351 for tAML, AML with MRC
    - Venetoclax/Azacitidine for age≥75 or ineligible for intensive chemotherapy
    - 7+3 + Midostaurin for FLT3 mutated AML
    - Glasdegib + LDAC for age≥75 or ineligible for intensive chemotherapy
  - Relapsed
    - Ivosidinib for IDH1 mutated AML
    - Gilterinib for FLT3 mutated AML
    - Enasidenib for IDH2 mutated AML

Thank you!