Evolving Practice in AML:
A Case-based Guide to New and Emerging Treatment Options

Evolving Practices in AML: A Case-based Guide to New and Emerging Treatment Options

Wednesday, September 11, 2019
Houston, Texas

This is not an official event of the SOHO 2019 Annual Meeting.
Not sponsored or endorsed by the Society of Hematologic Malignancies.

Supported by educational grants from Agios Pharmaceuticals, Inc., Astex Pharmaceuticals, Jazz Pharmaceuticals, Inc., and Pfizer, Inc.

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1

The Impact of Cytogenetic and Molecular Abnormalities on Patient Management: Diagnostic, Prognostic, and Therapeutic Importance

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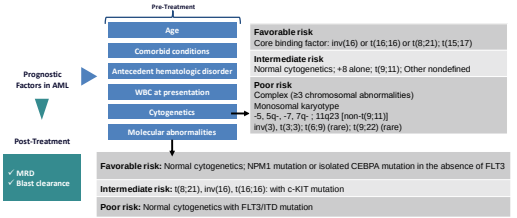
6

Traditional and New Prognostic Factors in AML[1,2]



AML=acute myeloid leukemia; CEBPA=CCAAT/enhancer binding protein α; FLT3=FMS-like tyrosine kinase 3; ITD=internal tandem duplications; MRD=minimal residual disease; NPM1=nucleophosmin; WBC=white blood cell

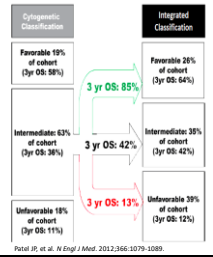
[1]Grimwade D, Hills RK. *Hematology Am Soc Hematol Educ Program.* 2009:385-395; [2]NCCN Clinical Practice Guidelines in Oncology. Acute myeloid leukemia. Version 1. 2016.

16

AML Genomic Profiling: FLT3 Mutations Are Common.

How Does Mutational Profiling in AML Impact Clinical Practice?

Gene	Overall Frequency, %
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPα	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

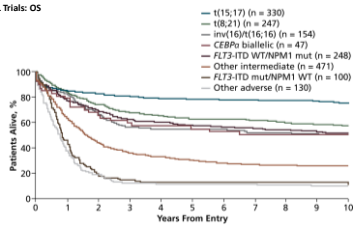


Patel JP, et al. *N Engl J Med*. 2012;366:1079-1089.

17

Cytogenetic and Molecular Abnormalities: Survival

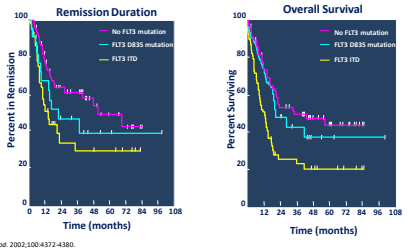
MRC/NCRI AML Trials: OS



MRC=Medical Research Council; NCRI=National Cancer Research Institute; OS=overall survival; WT=wild type
Smith ML, et al. *Blood Rev*. 2011;25:39-51.

18

Prognostic Impact of FLT3 Mutations in Frontline AML: Five-year OS <20% in 2002

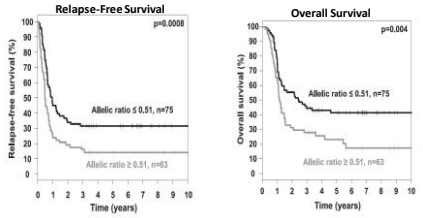


Frohling S, et al. *Blood*. 2002;100:4372-4380.

19

All FLT3 Are Not the Same: Allelic Ratio, Comutations, Karyotype May Impact Outcome

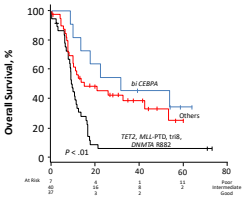
Prognostic Impact of FLT3 Allelic Ratio



Schlenk R, et al. *Blood*. 2014;124(23):3441-3449.

20

Further Molecular Stratification of FLT3-ITD^{POS} Intermediate Risk AML



- Group 1 (favorable): biallelic *CEBPA*
- Group 3 (poor-risk): *TET2*, trisomy 8, *DNMT3A R882*, or *MLL-PTD (KMT2A)*
- Group 2: all others
- Can discriminate patients with *FLT3*-mutant disease with much poorer outcome than others

Patel J, et al. *N Engl J Med*. 2012;366(12):1079-1089.

21

Genetic Risk Group	Frequency	Survival	ELN 2017 Subset
Favorable	15%	65-75%	• t(8;21)(q22;q22); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* • Mutated *NPM1* without *FLT3*-ITD or *FLT3*-ITD ^{low} • Biallelic mutated *CEBPA*
Intermediate	55%	50-55%	• Mutated *NPM1* and *FLT3*-ITD ^{high} • Wild-type *NPM1* without *FLT3*-ITD or *FLT3*-ITD ^{low} (without adverse-risk genetic lesions) • t(9;11)(p22;q23); *MLLT3-MLL* • Any cytogenetics not classified as favorable or adverse
Adverse	30%	20-25%	• t(6;9)(p23;q34); *DEK-NUP214* • t(v;11)(v;q23); *MLL (KMT2A)* rearranged • Inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1 (GATA2, MECOM (EVI1)* • t(9;22)(q34.1;q11.2) *BCR-ABL1* • Monosomy 5 or del(5q); monosomy 7; monosomy 17; abnormal 17p • Complex karyotype(≥ 3 abnormalities) or monosomal karyotype • Wild-type *NPM1* and *FLT3*-ITD ^{high} • Mutated *RUNX1* • Mutated *ASXL1* • Mutated *TP53*

Döhner H, et al. *Blood*. 2017;129(4):424-447.

22

Major Targets of Past and Future Therapeutic Development

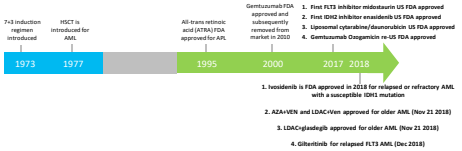
AML with *FLT3* internal tandem duplication	▪ Impact on both therapy and prognosis ▪ Many *FLT3* kinase inhibitors explored in recent years…now several next-generation agents in development
***KIT* mutations in CBF AML**	▪ *KIT* mutations found in 30%-35% of CBF AML cases, but rare in other AML subgroups ▪ In CBF AML, mutations cluster mainly in exons 8 and 17
IDH mutations in AML	▪ *IDH1/2* mutations confer a gain-of-function, including increased histone and DNA methylation and impaired cellular differentiation
***Bcl-2* as a therapeutic target in AML**	▪ *Bcl-2* binds and sequesters pro-apoptotic molecules; inhibition of *Bcl-2* primes cancer cells for death
Epigenetic targets (EZH2, LSD1, BRD, PRMT5, others)	▪ Novel agents on the horizon that target specific epigenetic pathways ▪ These are in early clinical trial development
TP53, C-CBL, MLL-Menin	▪ Phase 1 clinical trials

23

Treatment of AML (Accelerated Progress 2017-2019): History

Since its introduction in the early 1970s, 7+3 therapy (Cytarabine for 7 days + Anthracycline for 3 days) has been the standard of care for AML

US FDA approvals



Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

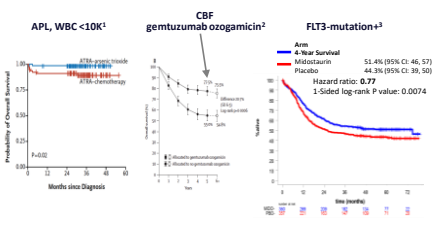
24

Data-driven Therapy for Molecular Subtypes

APL, WBC <10K[1]

CBF gemtuzumab ozogamicin[2]

FLT3-mutation+[3]

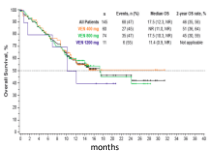


[1]Lo Coco F, et al. *N Engl J Med.* 2013;369:111–121. [2]Hills RK, et al. *Lancet Oncol.* 2014;15:986–996. [3]Stone RM, et al. *N Engl J Med.* 2017;377:454–464.

25

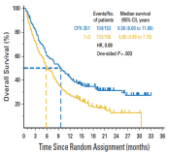
Hope for Even High-risk AML

Unfit, age >65[1]



Venetoclax + hypomethylating agent

Fit, age 60–75 with t-AML or AML-MRC[2]

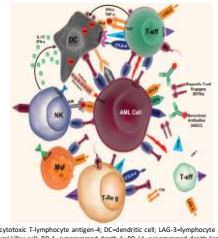


CPX-351 versus 7+3

[1]DiNardo CD, et al. *Blood*. 2017;130:2628. [2]Lancet JE, et al. *J Clin Oncol*. 2018;36:2684–2692.

26

Major Approaches to Immune Therapies in AML



Two major approaches:

1. Antibody drug conjugates
2. T-cell based therapies
   a. Bi-specific antibodies (CD3 x AML antigen)
   b. Immune checkpoint-based approaches
   c. CAR T (CAR NK)

CTLA-4=cytotoxic T-lymphocyte antigen-4; DC=dendritic cell; LAG-3=lymphocyte activation gene-3; MΨ=macrophages; MHC=major histocompatibility complex; NK=natural killer cell; PD-1=programmed death-1; PD-L1=programmed death-ligand 1; TCR=T-cell receptor; T-eff=T-effector cells; TIM-3=T-cell immunoglobulin and mucin domain-containing protein; T-reg=T-regulatory cells
Asgi R [Daver N], et al. *Curr Opin Hematol*. 2018;25:136–145.

27

Current and Emerging Therapies in Newly Diagnosed AML:
Adapting Treatment to Meet Needs of the Individual Patient

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28

Case 1: Presentation

- 68-year-old woman with prior history of polycythemia vera diagnosed 5 to 6 years ago and treated with intermittent phlebotomy only. Over time, her hemoglobin has normalized; however her WBC has started to rise. Also has atrial fibrillation s/p CVA on coumadin therapy, Graves disease, HTN
  - June 2019: CBC showed WBC of 30K, normal hgb and platelet count
  - Early August 2019: WBC 108K with 50% blasts
  - Mid-August 2019: Referred to academic center for new leukemia diagnosis
- Complains of increased shortness of breath for weeks prior to admission, intermittent blurry vision, morning nausea, and blood-stained stools

34

Case 1 (continued)

- Exam: ECOG 1, BP 164/69, 92% oxygen saturation on room air, unremarkable exam except decreased breath sounds in both lungs, no organomegaly
  - CBC: WBC 139K, hgb 11.7, plts 208, 66% peripheral blasts, INR 2.46
  - Chemistry: BUN 35, Cr 1.65, uric acid 12.9, LDH 1361, Ph 4.9
  - Cardiac echo: Normal LVEF 65-70%
  - Peripheral blasts: MPO+
  - Flow cytometry: 100% of blasts are CD33+ bright
  - Cytogenetics: Normal female karyotype
  - Molecular: $FLT3^{wt}$, $IDH1/2^{wt}$, $DNMT3A^{mut}$, $TET2^{mut}$, $JAK2V617F^{mut}$, $TP53^{mut}$

35

Case 2: Presentation

- 87-year-old woman with PMHx COPD, HTN, PMR presents for second opinion for AML
  - March 2018: Counts noted to be slowly dropping
  - Dec 2018: Pancytopenic, referred to hematologist
    - BMBx: Hypercellular BM with 10% blasts, normal karyotype -> Dx MDS
    - Started darbepoetin alfa growth factor therapy -> no response
  - April 2019: azacitidine SQ 5 days every 28 days (now cycle 4 day 13)
  - July 2019: Neutropenic fever, RLL pneumonia treated with IV antibiotics
- Repeat BMBx: AML with 20% blasts, MDS related changes

38

Case 2 (continued)

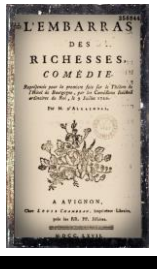
- Complains of chronic fatigue improved after transfusions, mouth sore, easy bruising but remains very active and mobile with family support present
  - Exam: ECOG 1, one oral ulcer, scattered bruises, independent ambulation
  - CBC: WBC 0.87, hgb 6.6 gm/dl, plts 16K, 1% blasts, 37% neutrophils, 55% lymphs
- Repeat BMBx: AML with 21% blasts, MDS related changes
- Flow cytometry: 86% of blasts are CD33+
- Cytogenetics: normal karyotype
- Molecular panel: NPM^{wt}, $FLT3^{wt}$ (full NGS panel is pending)

39

Please Pick up Your Key Pad to Answer the Following Question

40

AML Therapy: An Embarrassment of Riches



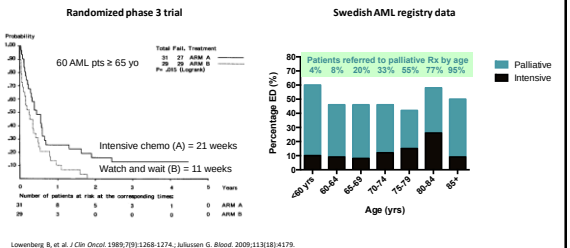
Nine Drugs FDA approved for AML since 2017

1. Midostaurin (April 2017)
2. Liposomal cytarabine/daunorubicin (Aug 2017)
3. Enasidenib (Aug 2017)
4. Gemtuzumab ozogamicin (Sept 2017)
5. Ivosidenib (July 2018)
6. Gilteritinib (Nov 2018)
7. Glasdegib (Nov 2018)
8. Venetoclax (Nov 2018)
9. Tagraxofusp-erzs* (Dec 2018)

*Tagraxofusp-erzs FDA approved for the treatment of BPDCN

42

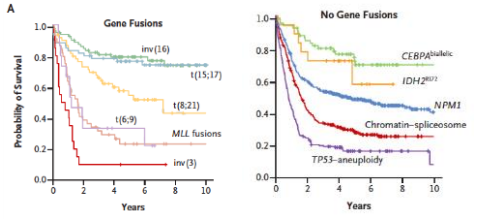
Benefit of Chemotherapy in Older Newly Diagnosed AML Patients



Lowenberg B, et al. *J Clin Oncol*. 1989;7(9):1268-1274.; Juliussen G. *Blood*. 2009;113(18):4179.

45

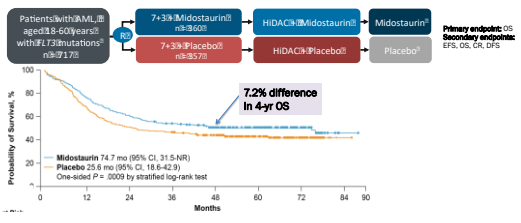
Outcomes of 7+3 by AML Disease Biology



Papaemmanuil E, et al. *N Engl J Med*. 2016;74(23):2209-2221.

46

Midostaurin Plus 7+3 vs 7+3 in De Novo *FLT3* Mutant AML



Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

47

Evolving Practice in AML:
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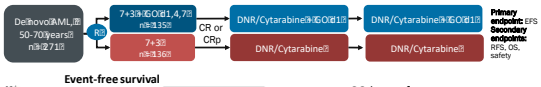
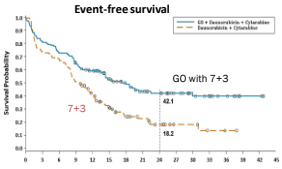
ALFA-0701: Phase 3 Trial of GO Plus 7+3 vs 7+3



Event-free survival

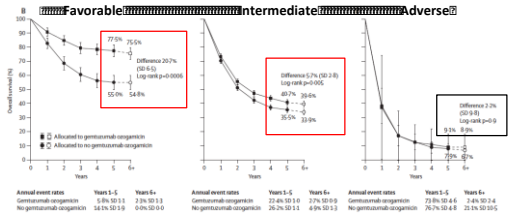


- GO better for favorable/intermediate risk
- Increased Gr3 hemorrhage
- Prolonged thrombocytopenia
- No increase in early mortality (3.8% vs 2.2%) with GO
- VOD 4.6% (GO/7+3) vs 1.5% (7+3)

Lambert J, et al. *Haematologica*. 2018. [Epub ahead of print]

48

Meta-analysis of Gemtuzumab Ozogamicin Plus 7+3



Meta-analysis of overall survival of 3325 AML patients stratified by cytogenetic risk

Hills RK, et al. *Lancet Oncol*. 2014;15:986-996.

49

AML with Myelodysplasia-related Changes (AML-MRC)

Definition: AML with a history of MDS or MDS-related cytogenetic findings

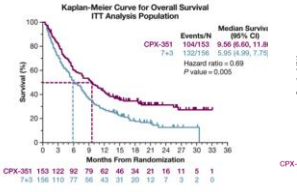
- **20% or more blasts in the peripheral blood or marrow AND**
- **Any of the following:**
  - Previously documented MDS or MDS/MPN
  - Myelodysplasia-related cytogenetic abnormalities[a]
  - Morphologic detection of multilineage dysplasia[b]

a. Complex karyotype, chromosome 5 and 7 aberrations, multiple others
b. In the absence of CEBPalpha mutations
Arber DA, et al. *Blood*. 2016;127(20):2391-2405.; Vardiman JW, et al. *Blood*. 2009;114(5):937-951.

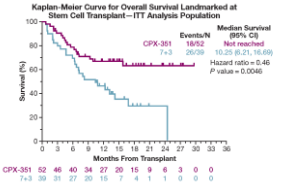
50

Liposomal 7+3 in Older AML Patients with AML-MRC/t-AML

Overall survival



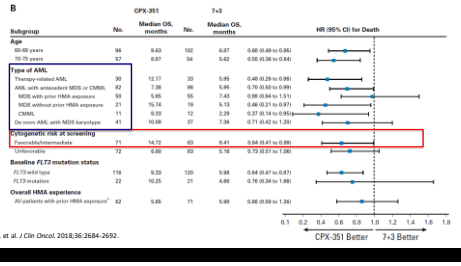
Outcomes following transplant



Lancet JE, et al. *J Clin Oncol.* 2018;36:2684-2692.

51

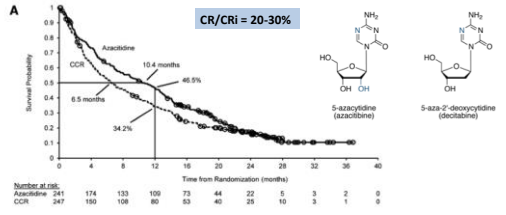
Liposomal 7+3 in Older AML Patients with AML-MRC/t-AML



Lancet JE, et al. *J Clin Oncol.* 2018;36:2684-2692.

52

Hypomethylating Agents Are Well Tolerated and Results in Similar Survival as 7+3 in Older Patients but Lower Response Rates

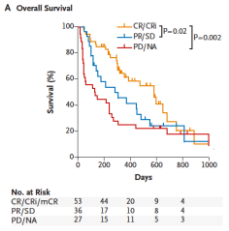


Dombret H, et al. *Blood.* 2015;36126(3):291-299.

53

Decitabine Monotherapy in *TP53 M*utant AML Patients

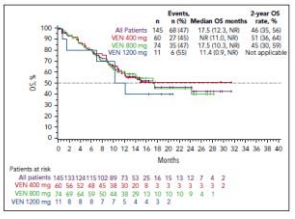
- 116 patients with AML or MDS
- Decitabine 20 mg/m^2 qd x 10d
- 46% (53/116) responses
- High responses in unfavorable (67%) vs favorable/intermediate (34%) cytogenetics
- 100% response in TP53 mutant (21/21) vs wild-type (32/78, 41%) patients



Welch JS, et al. *N Engl J Med*. 2016;375 (21):2027-2036.

54

Venetoclax + Hypomethylating Agents - Phase 1b



Baseline Characteristics	N = 145
Median age, y	74
Age ?75 years, %	36
Baseline BM blasts > 50%, %	38
Poor-risk cytogenetics, %	49
Baseline hydroxyurea use, %	12

- CR + CRi = 97 (67%)
- Median duration of response = 11.3 mos (8.9 – not reached)
- Median overall survival = 17.5 mos (12.3 – not reached)

DiNardo CD, et al. *Blood*. 2019;133:7-17.

55

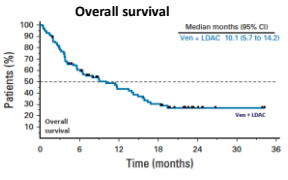
Venetoclax + Azacitidine/Decitabine: Phase 1b Subgroup Results

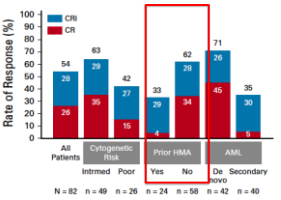
Subgroup	Evaluable for responses/OS, n (%)	CR + CRi, n (%)	n for Median duration of CR + CRi	Median duration of CR + CRi, (95% CI)	Median OS, mo (95% CI)
All patients	145	97 (67)	97	11.3 (8.9, NR)	17.5 (12.3-NR)
Cytogenetic risk					
Intermediate	74 (51)	55 (74)	55	12.9 (11, NR)	NR (17.5-NR)
Poor	71 (49)	42 (60)	42	6.7 (4.1, 9.4)	9.6 (7.2-12.4)
Age					
≥75 y	62 (43)	40 (65)	40	9.2 (6.4, 12.5)	11 (9.3-NR)
<75 y	83 (57)	57 (69)	57	12.9 (9.2, NR)	17.7 (14.2-NR)
AML					
De novo	109 (75)	73 (67)	73	9.4 (7.2, 11.7)	12.5 (10.3-24.4)
Secondary	36 (25)	24 (67)	24	NR (12.5, NR)	NR (14.6-NR)

DiNardo CD, et al. *Blood*. 2019;133:7-17.

56

Phase 1/2 Study of Venetoclax + LDAC in Older AML Patients



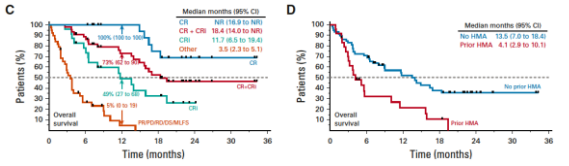


TP53mut: 30% IDHmut: 72%
NPM1mut: 89% FLT3 mut: 44%

Wei A, et al. *J Clin Oncol.* 2019;37(15):1277-1284.

57

Phase 1/2 Study of Venetoclax + LDAC in Older AML Patients



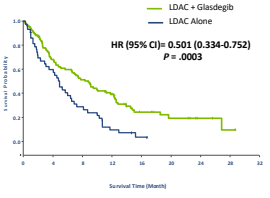
Wei A, et al. *J Clin Oncol.* 2019;37(15):1277-1284.

58

Glasdegib + LDAC vs LDAC in Unfit Older AML Patients

Phase II study in pts with AML and high-risk myelodysplastic syndrome (N = 132)

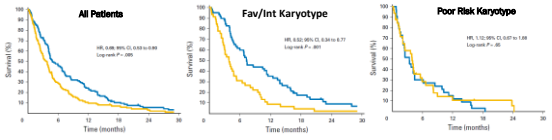
	LDAC + Glasdegib (n = 88)	LDAC Alone (n = 44)
Median age, yrs (range)	77 (63-92)	75 (58-83)
Good/Int CG, n (%)	52 (60)	25 (57)
CR/CRi (n, %)	**20 (23)**	**2 (4.5)**
Median OS (mos)	**8.8 mos**	**4.9 mos**



Cortes J, et al. *Am J Hematol.* 2018;93:1301-1310.

59

GO vs Best Supportive Care in Older AML Patients



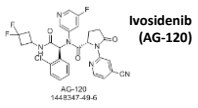
- GO 6 mg/m^2 day 1, 3 mg/m^2 day 8, patients who did not progress after GO induction could receive up to eight monthly infusions of the immunoconjugate at 2 mg/m^2
- GO results in CR + CRi rate = 27%
- Median overall survival: GO 4.9 months, BSC 3.6 months
- Decreased survival benefit with lower CD33 expression, PS 2, and poor risk karyotype

GO, n = 118
BSC, n = 119

Amadori S, et al. *J Clin Oncol.* 2016;34:972-979.

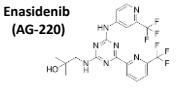
60

First-in-Class Inhibitors of *IDH1/2* Mutant AML



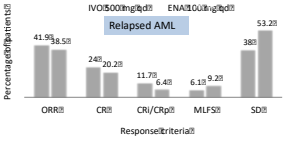
Ivosidenib (AG-120)

AG-120
1448347-49-6



Enasidenib (AG-220)

Patients	De novo AML
Fit patient	Ivosidenib + 7+3 Enasidenib + 7+3
Unfit patient	Ivosidenib* Enasidenib



61

Ivosidenib/Enasidenib for Newly Diagnosed *IDH1/2* Mutant AML

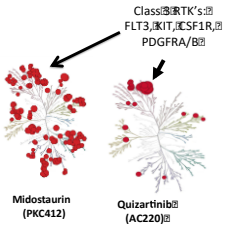
Single agent	IVO 500 mg qd (N=33)	ENA 100 mg qd (N=27)
CR/CRh	14 (42.4%)	12 (44.4%)
Median OS	12.6 mos	--

Combo therapy	IVO plus 7+3 (n=41)	ENA plus 7+3 (n=77)
CR/CRi/CRp (All)	32/41 (78%)	53/77 (69%)
CR/CRi/CRp (De novo)	26/28 (93%)	33/45 (73%)
CR/CRi/CRp (Secondary AML)	6/13 (46%)	20/32 (63%)

Roboz GJ, et al. ASH 2018. Abstract 561.; Stein E, et al. ASH 2018. Abstract 287.; Stein E, et al. ASH 2018. Abstract 560.

62

Second-generation FLT3 Inhibitors vs Midostaurin



	Other Kinases	IC_{50} (plasma)
Lestaurtinib	JAK2, TrkA	700 nM
Midostaurin	cKIT, PKC, PDGFR, VEGFR	1000 nM
Sorafenib	cKIT, PDGFR, RAF, VEGFR	265 nM
Quizartinib	cKIT, PDGFR, RET	18 nM
Crenolanib	PDGFR	48 nM
Gilteritinib	AXL	43 nM

Pratz KW, et al. *Blood*. 2010;115(7):1425-1432.; Zarrinkar P, et al. *Blood*. 2009;114(14):2984-2992.; Galanis A, et al. *Blood*. 2014;123(1):94-100.; Levis MJ, et al. ASCO 2015. Abstract 7003.

63

FLT3 TKI Plus 7+3 for Younger FLT3 Mutant AML Patients

FLT3 TKI	No. patients	CR/CRi/CRh	2-year OS	Ongoing
Midostaurin + 7+3	717 (ph 3)	59%	60%	AraC/DNR vs AraC/Ida
Quizartinib + 7+3	16 (ph 1)	**84%**	Ph 3 ongoing	Phase 3 (7+3) ongoing
Crenolanib + 7+3	38 (ph 2)	**88%**	79% Ph 3 ongoing	Phase 3 (mido) ongoing
Gilteritinib + 7+3	30 (ph 1)	**93%**	Not known Ph 3 planned	Phase 3 (mido) planned

Stone RM, et al. *N Engl J Med*. 2017;377:454-464.; Wang E, et al. ASH 2017.; Altman J, et al. *Am J Hematol*. 2018;93(2):213-221.; Pratz K, et al. ASH 2018.

64

AML: Take Home Points

- Timely knowledge of cytogenetics, mutations (*FLT3, IDH1/2*), and antigen expression (CD33) is required to select best therapy in this new era
- Choice of therapy should be individualized based on:
  - Patient age, fitness, and goals of care
  - Disease biology
  - Transplant eligibility
- Novel regimens offer survival benefits in older individuals without the need for intensive chemotherapy. Future combination regimens promise to further improve outcomes

70

Optimizing Outcomes in Relapsed/Refractory AML: Incorporating New Treatment into Practice

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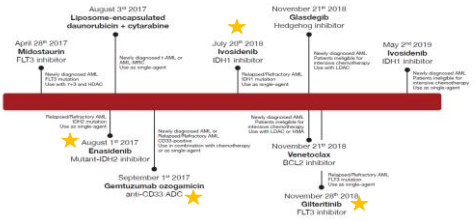
Associate Professor of Medicine
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

71

How Do We Best Incorporate Novel Therapies?



72

Case #1

- 58-year-old male with gingival swelling, myalgias, fevers and epistaxis. WBC 44K, Hgb 6.8 g/dl, Plts 22K. Bone marrow with 72% MPO+, CD33+ and CD123+ blasts. Diploid cytogenetics. ECOG PS 0. NPM1, IDH1, and FLT3-ITD (AR 0.49) mutations
- Started 7+3 + midostaurin, attained CR. Received 4 consolidation courses. No maintenance midostaurin
- Noted to have WBC 27K with 37% circulating blasts 5 months after last consolidation

- How would you treat this patient?...

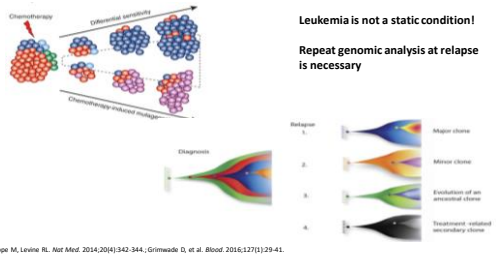
73

Case #2

- 68-year-old female with history of coronary artery disease and CHF. Noted to have pancytopenia on pre-op labs for knee repair. WBC 2.8K, Hgb 8.7g/dl, Plts 128K. Bone marrow with 27% MPO+ CD33+ CD123+ blasts with MDS-related changes. Trisomy 8 cytogenetics. Received azacitidine for 8 cycles with transfusion independence and CR documented after 3 cycles, however progressive anemia noted and repeat marrow with 32% blasts. +8 and new del(20q) detected on cytogenetics. NGS panel with DNMT3A, IDH2 and SRSF2 mutations
- How would you treat this patient?

76

Individualizing Therapy at Relapse



Leukemia is not a static condition!

Repeat genomic analysis at relapse is necessary

Kleppe M, Levine RL. *Nat Med*. 2014;20(4):342-344.; Grimwade D, *et al. Blood*. 2016;127(1):29-41.

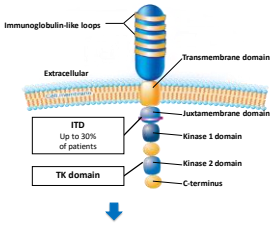
79

Targeting FLT3 Mutations

80

Characteristics of FLT3 Mutations in AML

- *FLT3-ITD* in ~25% and *FLT3-TKD* in ~10% AML
- More frequent in younger patients, *de novo* AML and diploid cytogenetics
- Leads to constitutive activation of FLT-3 receptor
- *FLT3-ITD* independent predictor of poor prognosis

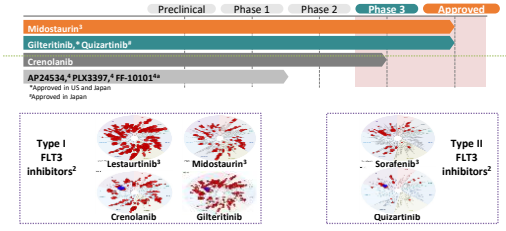


Activated proliferation and pro-survival pathways

Litzow MR, et al. *Blood.* 2015;126(7):833-841.

81

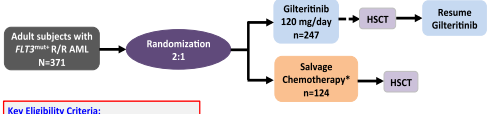
FLT3 Inhibitors in Development[1-5]



[1]Daver N, et al. *Expert Rev Hematol.* 2016;9:433-445. [2]Cortes J, et al. ASH 2018. [3]Adapted from Zarrinkar PP, et al. *Blood.* 2009;114:2984-2992. [4]Perl AE, et al. *Lancet Oncol.* 2017;18:1061-1075. [5]Galanis A, et al. *Blood.* 2012;120:1341.

82

Gilteritinib: ADMIRAL Phase III Trial in RR *FLT3*^{mut} AML



Key Eligibility Criteria:
- Refractory to initial induction or untreated first relapse after prior CRc (defined as CR plus CRi plus CRp)
  - Prior frontline midostaurin or sorafenib allowed
  - Prior gilteritinib or other FLT3 inhibitors excluded
- Central laboratory-confirmed *FLT3*-ITD or *FLT3*-TKD (D835/I836) by PCR
- ECOG performance status ≤2
- Normal liver, renal function
- QTcF ≤450 msec by central ECG reading

Co-Primary Endpoints: OS, CR/CRh rate
Key Secondary Endpoints: EFS, CR rate

***Salvage chemotherapy regimen was selected prior to randomization**
MEC (mitoxantrone, etoposide, and cytarabine) } High intensity (1–2 cycles)
FLAG-IDA (fludarabine, cytarabine, idarubicin, and G-CSF)
Low-dose cytarabine } Low intensity (given until disease progression or intolerance)
Azacitidine

Perl A, et al. AACR 2019.

84

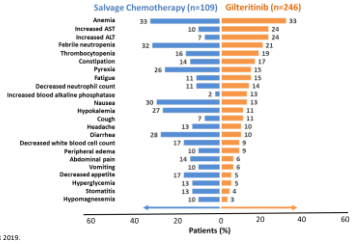
Response Outcomes (ITT Population: N=371)

Parameter*	Gilteritinib (n=247)	Salvage Chemotherapy (n=124)
CR, n (%)	52 (21)	13 (11)
CRh, n (%)	32 (13)	6 (5)
CRi, n (%)	63 (26)	14 (11)
CRp, n (%)	19 (8)	0 (0)
CRc, n (%)	134 (54)	27 (22)
CR/CRh, n (%)	84 (34)	19 (15)
PR, n (%)	33 (13)	5 (4)
ORR, n (%)	167 (68)	32 (26)
NR, n (%)	66 (27)	43 (35)
Median duration of drug exposure (range), months	4.1 (0.1–29.1)	0.9 (0.2–7.1)
Median time to achieve CRc (95% CI), months	1.8 (0.9, 9.5)	1.1 (0.8, 2.9)
Median DoR† (95% CI), months	11.0 (4.6, NE)	1.8 (NE, NE)
Allogeneic HSCT, n (%)	63 (26)	19 (15)

*Response was not evaluable in 14 patients (6%) in the gilteritinib arm and in 49 patients (40%) in the salvage chemotherapy arm
†Duration of remission was defined as the duration of CR/CRh

85

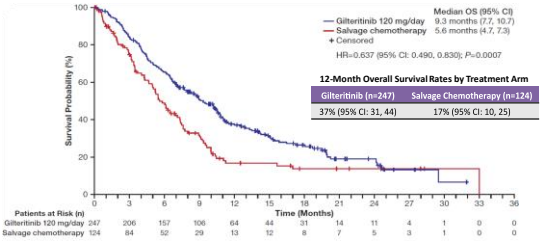
All-grade TEAEs During the First 30 Days of Treatment in ≥10% of Patients in Any Treatment Arm



Perl A, et al. AACR 2019.

86

ADMIRAL Trial: Overall Survival (n=371)



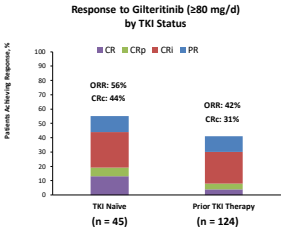
12-Month Overall Survival Rates by Treatment Arm

Gilteritinib (n=247)	Salvage Chemotherapy (n=124)
37% (95% CI: 31, 44)	17% (95% CI: 10, 25)

Perl A, et al. AACR 2019.

87

CHRYSALIS: Response by TKI Status



Perl AE, et al. *Lancet Oncol.* 2017;18:1061-1075.

88

Molecular Response: Chrysalis

Response Outcomes in All FLT3-ITD^{mut+} Patients	N=80
Patients who had a molecular response (ITD signal ratio ≤10^{-2}), n (%)	20 (25)
Patients who had MMR (ITD signal ratio ≤10^{-3}), n (%)	18 (23)
Patients who had MRD negative status (ITD signal ratio ≤10^{-4}), n (%)	13 (16)
Median time to achieve minimum ITD signal ratio, weeks (range)	8.2 (3.7–64)
Median OS, weeks (95% CI)	32.6 (25.1–42.4)

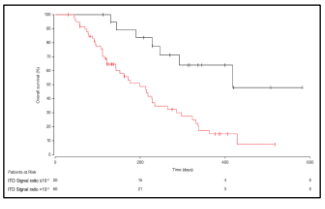
- Three patients with a molecular response underwent allogeneic HSCT

CI=confidence interval; FLT3=fms-like tyrosine kinase 3; ITD=internal tandem duplication; MRD=minimum residual disease; MMR=major molecular response; OS=overall survival

Presented by Jessica K. Altman, MD ASCO 2017

89

Overall Survival and Clinical Response Stratified by Molecular Response: ITD Signal Ratio ≤10−2



Molecular response	Median OS, Weeks (95% CI)		P-value*
	Achieved a molecular response (n=20)	Did not achieve a molecular response (n=60)	
ITD signal ratio ≤10^{-2}	59.6 (35.1–NA)	28.4 (20.3–33.4)	.001

Molecular Response in Patients Who Achieved CRc† n, (%)	
CR (n=10)	CRp/CRi (n=34)
8 (80)	7 (21)

*Log rank test
†CRc was defined as CR plus CRp plus CRi
All percentages were rounded to the nearest whole number

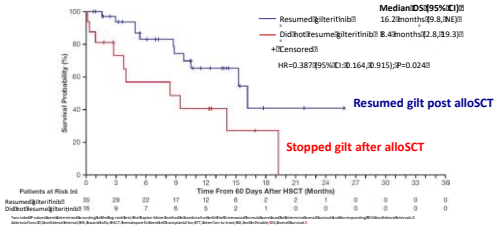
CR=complete remission; CRp=complete remission with incomplete platelet recovery; CRi=complete remission with incomplete hematologic recovery; ITD=internal tandem duplication; NA=not available; NR=no response; PR=partial remission

Presented by Jessica K. Altman, MD ASCO 2017

90

ADMIRAL Trial: Post-HSCT Survival in the Gilteritinib Arm

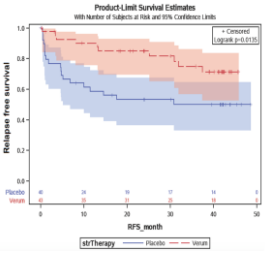
Effect of Maintenance Therapy (Landmark Analysis Day 60 Post-HSCT; n=51)



91

AML FLT3-ITD: Sorafenib After Allo-SCT

- 83 patients, median age 54 years, after allo-SCT
- Randomization to sorafenib 200-400 mg BID vs placebo
- Two-year RFS 85% with sorafenib vs 53% with placebo
- Also significant survival benefit



Burchert A, et al. ASH 2018. Abstract 661.

92

Targeted Therapy: FLT3 Inhibitors

- FLT3-inhibitors are safe and effective targeted therapeutics
  - Well tolerated
  - Improved outcomes
  - Responses short-lived as single agents
  - Resistance is common with single agents and depends on the unique FLT3i
- FLT3 inhibitors improve outcomes in newly diagnosed and R/R patients, rational combinations to prevent resistance will further improve upon FLT3 outcomes

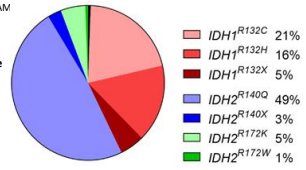
93

Targeting IDH1 and IDH2 Mutations

96

Characteristics of mIDH AML

- **IDH mutations occur in ~20% of AML**
  - Most (~85%) occur in *de novo* diploid or +8 AML
  - IDH1 in ~8% AML, IDH2 in ~12% AML
  - ↑ prevalence with ↑ patient age
- **Hot-spot mutations in enzymatic active site**
  - **IDH1-R132**, **IDH2-R140** or **IDH2-R172**
- **Often early mutational events**
  - Ancestral in **20% IDH1** and **35% IDH2** cases
- **Can be acquired at progression**
  - **~10-15% of AML from MDS**
  - **~20-25% of AML from MPN**

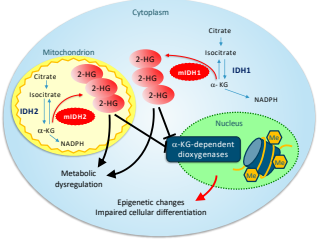


Dang L, et al. *Trends Mol Med.* 2010;16(9):387-397.; Chou WC, et al. *Leukemia.* 2011;25(2):246-253.; Molenaar RJ, et al. *Leukemia.* 2015;29(11):2134-2142.

97

Pathophysiology of IDH Mutations

- mIDH results in accumulation of the oncometabolite 2-HG which competitively inhibits aKG-dependent reactions
- 2HG leads to DNA and histone hypermethylation, and a resultant block in differentiation

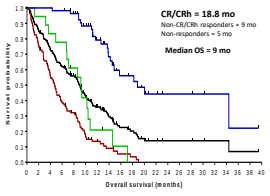


98

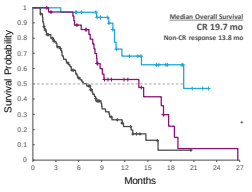
IDH1- or IDH2-inhibitor Monotherapy in R/R AML

CR rate ~20%
CR/CRh rate ~30%
ORR ~40%

Ivosidenib (IDH1 inhibitor)



Enasidenib (IDH2 inhibitor)

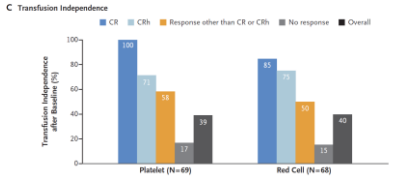


DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398.; Stein EM, et al. *Blood*. 2017;130(6):722-731.

99

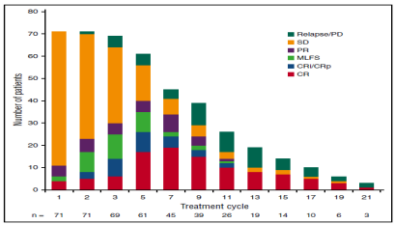
Ivosidenib in Relapsed/Refractory AML

- Transfusion independence was observed across all response categories in R/R AML 500 mg patients who were dependent at baseline



100

Evolution of Response With Enasidenib



Stein EM, et al. *Blood*. 2017;130(6):722-731.

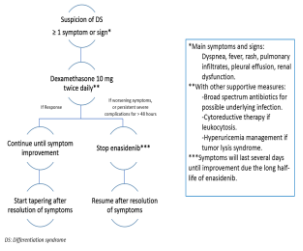
101

Identification and Treatment of Clinical IDH-DS

Table 1. Frequency of Signs and Symptoms Consistent With IDH-DS[a]

Sign or Symptom	Patients With IDH-DS, No. (%) (n = 33)[b]
Dyspnea	28 (85)
Unexplained fever (body temperature of 38.0°C for 2 d)	26 (79)
Pulmonary infiltrates	24 (73)
Hypoxia	19 (58)
Acute kidney injury (CTCAE grade ≥2)	14 (42)
Pleural effusion	14 (42)
Bone pain or arthralgia	9 (27)
Lymphadenopathy	8 (24)
Rash	8 (24)
Disseminated intravascular coagulopathy	7 (21)
Edema or weight gain of >5 kg from screening	7 (21)
Pericardial effusion	5 (15)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events[16]; IDH-DS, isocitrate dehydrogenase differentiation syndrome.
[a] Signs and symptoms included in this table are based on retrospective differentiation syndrome review committee review of clinical records.
[b] Patients may have had multiple symptoms.

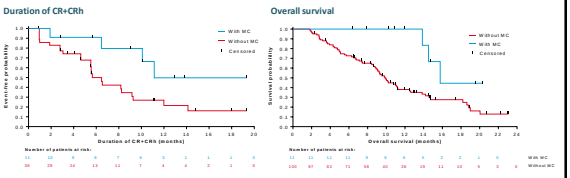


*Main symptoms and signs: Dyspnea, fever, rash, pulmonary infiltrates, pleural effusion, renal dysfunction.
**With other supportive measures: -Broad spectrum antibiotics for possible underlying infection. -Cytoreductive therapy if leukocytosis. -Hyperuricemia management if tumor lysis syndrome.
***Symptoms will last several days until improvement due the long half-life of enasidenib.

Fathi A, et al. *JAMA Oncol*. 2018;4(8):1106-1110.; Abou Dalle I, et al. *Ther Adv Hematol*. 2018;9(7):163-173.

102

Impact of IDH1 Mutation-clearance Status with AG120

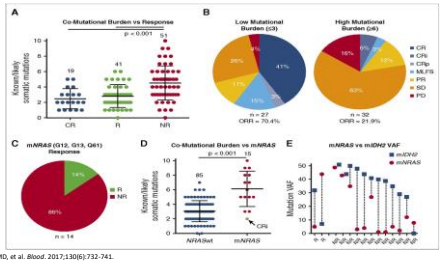


- Patients with "deep IDH mutational clearance" had improved DOR and OS vs those in CR/CRh with persistent IDH1 mutation detected
- Defined as a reduction in mIDH1 VAF to below the limit of detection by digital PCR (0.02-0.04%)

Pollyea D, et al. EHA 2018.

103

Impact of Co-occurring Mutations at Start of Enasidenib



Amatangelo MD, et al. *Blood*. 2017;130(6):732-741.

104

IDH Inhibitor Therapy Take-Aways

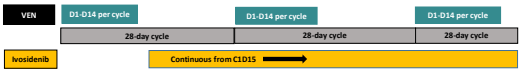
- Ivosidenib and enasidenib are safe and effective oral targeted therapies for patients with IDH1 or IDH2 mutant AML
  - Well-tolerated oral therapies
  - Durable responses
  - Improved outcomes
- Ivosidenib and enasidenib in combination therapies will further enhance responses
  - In combination with standard agents; ie, 7+3 and azacitidine
  - With other small molecule and targeted therapies (FLT3i, MEKi, VEN, others)

105

Phase Ib/II Open-label Study of Ivosidenib in Combination with Venetoclax

Phase 1b: To determine the safety and tolerability, maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of the combination of ivosidenib and venetoclax +/- azacitidine

DLT Period *= 2 cycles to ensure adequate safety evaluation of the combination*



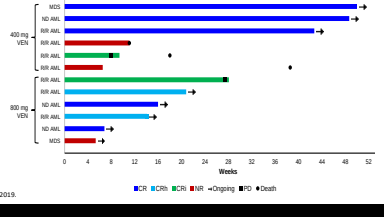
Phase 1 Cohorts	Venetoclax	Ivosidenib	Azacitidine
+2 (Target dose)	400 mg once daily	500 mg once daily	75 mg/m² days 1–7
+1 (Target dose)	800 mg once daily	500 mg once daily	
0 (Starting dose)	400 mg once daily	500 mg once daily	

DiNardo CD, et al. EHA 2019.

106

Response and Duration

- ORR was 75%, which included CR (42%), CRh (17%), and CRi (17%)
- Median time to first response was one month (range 1-3 months)



DiNardo CD, et al. EHA 2019.

108

Case #1

- 58-year-old male with gingival swelling, myalgias, fevers and epistaxis. WBC 44K, Hgb 6.8 g/dl, Plts 22K. Bone marrow with 72% MPO+, CD33+ and CD123+ blasts. Diploid cytogenetics. ECOG PS 0. NPM1, IDH1, and FLT3-ITD (AR 0.49) mutations
- Started 7+3 + midostaurin, attained CR. Received 4 consolidation courses. No maintenance midostaurin
- Noted to have WBC 27K with 37% circulating blasts 5 months after last consolidation
- How would you treat this patient?...

109

Case #2

- 68-year-old female with history of coronary artery disease and CHF. Noted to have pancytopenia on pre-op labs for knee repair. WBC 2.8K, Hgb 8.7g/dl, Plts 128K. Bone marrow with 27% MPO+ CD33+ CD123+ blasts with MDS-related changes. Trisomy 8 cytogenetics. Received azacitidine for 8 cycles with transfusion independence and CR documented after 3 cycles, however progressive anemia noted and repeat marrow with 32% blasts. +8 and new del(20q) detected on cytogenetics. NGS panel with DNMT3A, IDH2 and SRSF2 mutations
- How would you treat this patient?

112

Conclusions

- **Targeted therapy and precision medicine**: transitioning from population-based → individual "genotype-phenotype" based treatment
- Important for disease classification and prognostication
- Can now be used to guide and inform clinical practice
  - Optimal treatment strategies (at diagnosis and relapse)
  - Addition of target-specific drugs
  - *Improved treatment options for poor-risk patients still needed*
- NGS-panel testing for prognostic and therapeutically informative mutations should be performed at diagnosis and relapse time-points to optimize informed decision-making

115

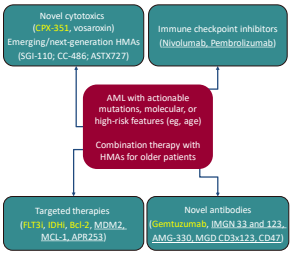
Evolving Treatment Paradigms in AML:
New Data and Clinical Trials That Could Change Clinical Practice

Naval Daver, MD
Associate Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

121

New Therapies for AML…and Novel Combinations

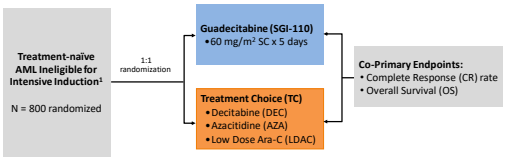
…for many populations, including those at high risk or defined by molecular abnormalities



HMA=hypomethylating agent

122

ASTRAL-1: Phase 3 Study Design



[1]Age 75 years or older, or major organ comorbidities, and poor Eastern Cooperative Oncology Group (ECOG) Performance Status 2-3
Fenaux P, et al. EHA 2019.

123

ASTRAL-1

Co-primary Efficacy Endpoints (ITT analysis)

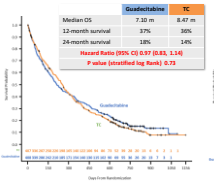
	Guadecitabine	TC
Median OS	7.10 m	8.47 m
12-month survival	37%	36%
24-month survival	18%	14%
Hazard Ratio (95% CI) 0.97 (0.83, 1.14)		
P value (stratified log Rank) 0.73		

Complete Response (CR)

Guadecitabine	TC
79 (19.4%)	71 (17.4%)
Stratified *P* value	0.48

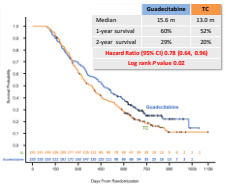
Median Time to CR (min, max): months

Guadecitabine	TC
4.5 (1.9, 19.1)	4.4 (1.9, 15.1)



Survival Analysis in Patients Treated for Minimum of 4 Cycles (n=476)

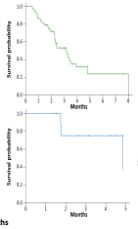
	Guadecitabine	TC
Median	15.6 m	13.0 m
1-year survival	60%	52%
2-year survival	29%	20%
Hazard Ratio (95% CI) 0.79 (0.64, 0.96)		
Log rank P value 0.02		



124

Venetoclax in Salvage: Multiple Ongoing Combinations -HMA + Venetoclax in R/R AML: Modest Efficacy

[1]Characteristic	N=43 (%)[1]
VEN combination cycles received	
1	17 (40)
2	18 (42)
≥3	8 (19)
VEN maintenance dose, median (range)	200 mg (100–800)
Response: no. (%)	
ORR	**9 (21)**
CR	2 (5)
CRi	3 (7)
MLFS	4 (9)
NR	34 (79)
Early death (within 30 days)	5 (12)
Overall survival, median (range)	3 months (0.5–8.0)
Estimated 6-month survival	24%



Total = 43; died = 27
Median: 3.0 months
6-month: 24%

Total = 9; fail = 3
Median: 4.8 months

[1]On protocol DAC10+VEN: maybe slightly better: CR/CRi 30%, med OS: 6 months

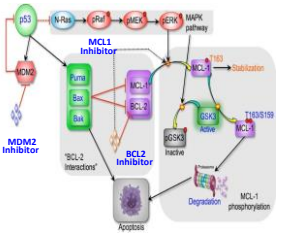
*Venetoclax is not approved for use in AML; †All patients treated off-protocol

DiNardo CD, et al. *Am J Hematol.* 2018;93:401-407.; Maiithi A, et al. ASH 2018. Oral abstract.

125

Synthetic Lethality of BCL-2 Inhibition with MCL-1 and/or MDM2 Inhibition and/or CDK9 Inhibitors

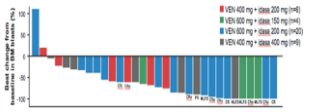
- **MCL1 inhibitors may prevent resistance to BCL2i therapy**
  - S6345
  - AMG176
  - AZD5991
  - VU661013
- **MDM2 inhibition can reactivate wild-type p53;**
- MDM2 inhibition promotes degradation of MCL-1, via p53 activation
  - Idasanutlin
  - Milademetan
  - AMG-232



Adapted from Pan R, et al. *Cancer Cell.* 2017;32(6):748-760.e6.

126

Encouraging Response Observed in VEN 600 mg + Idasa 150/200 mg Dose Cohorts



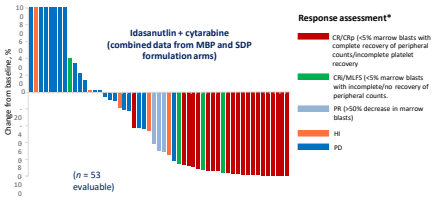
n (%)	VEN 400 mg + idasa 200 mg (n=6)	VEN 600 mg + idasa 150 mg (n=4)	VEN 600 mg + idasa 200 mg (n=20)	VEN 400 mg + idasa 400 mg (n=9)	Total Arm B (N=39)
Anti-leukemic response	1 (17)	3 (75)	8 (40)	2 (22)	14 (36)
CR	-	-	2 (10)	-	2 (5)
CRi + CRp	1 (17)	1 (25)	5 (25)	-	7 (18)
PR	-	-	-	1 (11)	1 (3)
MLFS	-	2 (50)	1 (5)	1 (11)	4 (10)
Time to best response	1.4 months (range: 1-3)				
Duration of response	3.0 months (range: 0.6-9.7)				

Daver N, et al. ASH 2018. Oral Abstract 767.

127

Phase Ib: Idasanutlin + IDAC (1 g/m^2 Cytarabine)

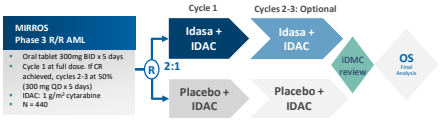
20/53 (38%) evaluable patients had CR with full count recovery
Median duration of response for patients with CR/CRp/CRi was >8 months



MBP=microprecipitated bulk powder; SDP=spray-dried powder
Martinelli G, et al. EHA 2016. Abstract S504.

128

Idasanutlin Registrational Ph III Randomized MIRROS Study – R/R AML, Fit Patients



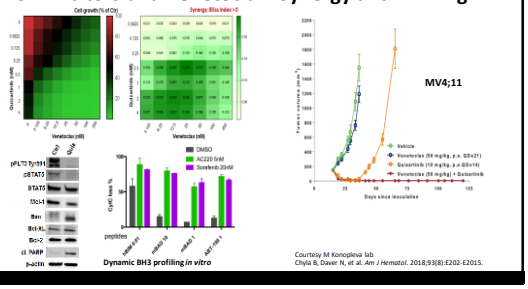
Study-specific key inclusion criteria

- Documented/confirmed 1st/2nd refractory/relapsed AML using WHO classification, except APL (AML patients with CR1 duration of >1 year AND age <60 years are excluded)
- No more than two prior induction regimens (excl. prior HSCT) and one must have included cytarabine with an anthracycline (or anthracenedione)
- ECOG performance status of 0 to 1 and patient should be a potential candidate for allogeneic HSCT

ECOG=Eastern Cooperative Oncology Group; IDAC=intermediate-dose cytarabine
ClinicalTrials.gov Identifier: NCT02545283

129

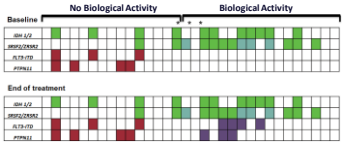
FLT3 Inhibitors and Venetoclax: Synergy and Priming



Courtesy M Konopleva lab
Chyla B, Daver N, et al. *Am J Hematol*. 2018;93(8):E202-E2015.

130

Comparison of Pre-treatment and Relapse Genetic Abnormalities (Single-agent VEN Phase 1)



- FLT3i also down regulate MCL1 (a major pathway of resistance to BCL2i)
- FLT3-ITD selected at relapse in LDAC+VEN and HMA+VEN combinations
- DOUBLET COMBINATIONS OF VEN WITH GILTERITINIB AND VEN with QUIZARTINIB ONGOING

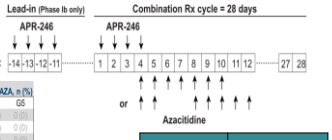
Group	N	Median time (days)
Resistant	6	25
Secondary resistance	5	87
Sensitive	8	131

Chyla B, Daver N, et al. *Am J Hematol*. 2018;93(8):E202-E2015.

131

APR-246 + Azacitidine in TP53MUT MDS/AML

- MDS or oligoblastic AML (<30% blasts)
- RP2D 4500mg IV



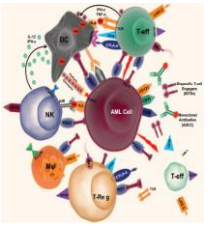
Most common TEAEs with any relation to APR-246 or AZA, n (%)	G1	G2	G3	G4	G5
Nausea	9 (42)	3 (14)	0 (0)	0 (0)	0 (0)
Peripheral neuropathy	8 (38)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	6 (29)	2 (10)	0 (0)	0 (0)	0 (0)
Dizziness	4 (19)	2 (10)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	0 (0)	1 (5)	0 (0)	5 (24)	0 (0)
Neutropenia	0 (0)	0 (0)	0 (0)	6 (29)	0 (0)
Pruritus	4 (19)	1 (5)	0 (0)	0 (0)	0 (0)
Tremor	4 (19)	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	3 (14)	1 (5)	0 (0)	0 (0)	0 (0)
Headache	4 (19)	0 (0)	0 (0)	0 (0)	0 (0)
Leukopenia	0 (0)	0 (0)	1 (5)	3 (14)	0 (0)

	APR-246 + AZA
N	20
MDS:AML	15:5
CR (MDS)	67%
CR (AML)	80%

Sallman D, et al. ASH 2018.

132

Major Approaches to Immune Therapies in AML



Two major approaches:

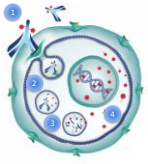
1. Antibody drug conjugates
2. T-cell based therapies
   a. Bi-specific antibodies (CD3 x AML antigen)
   b. Immune checkpoint-based approaches
   c. CAR T (CAR NK)

CTLA-4=cytotoxic T-lymphocyte antigen-4; DC=dendritic cell; LAG-3=lymphocyte activation gene-3; MΦ=macrophages; MHC=major histocompatibility complex; NK=natural killer cell; PD-1=programmed death-1; PD-L1=programmed death-ligand 1; TCR=T-cell receptor; T-eff=T-effector cells; TIM-3=T-cell immunoglobulin and mucin domain-containing protein; T-reg=T-regulatory cells

Assi R (Daver N), et al. *Curr Opin Hematol.* 2018;25:136-145.

133

IMGN632: A Novel CD123-Targeting ADC



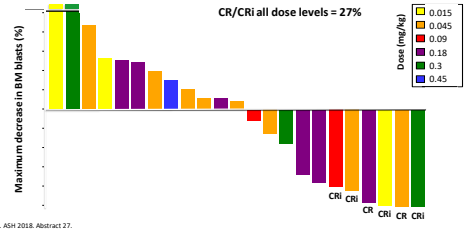
1 - ADC binds target
2 - ADC internalized
3 - Payload released
4 - Payload alkylates DNA

- Novel anti-CD123 antibody
  - Higher affinity binding to CD123
  - Unique epitope in extracellular domain
- Novel IGN payload (DGN549)
  - DNA-alkylating activity, single strand DNA breaks (vs. double strand)
  - 10-20x more potent than the IGN in IMGN779
  - Uniform loading of 2 IGN molecules per antibody
- Stable peptide linker
  - Protease cleavable
  - Confers stability in circulation, and controlled intracellular payload release

Kovtun Y, et al. *Blood Adv.* 2018;2:848-858.; Daver N, et al. ASH 2018. Abstract 27.

134

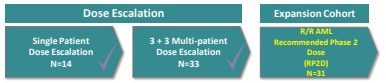
IMGN632 (CD123 ADC): Anti-leukemia Activity
BM-evaluable AML Patients (N=23)
Best Decrease from Baseline in Bone Marrow Blasts (%)



Daver N, et al. ASH 2018. Abstract 27.

135

Flotetuzumab (CD3 x CD123) Phase 1 Study Design



Key entry criteria

- Relapsed/refractory AML unlikely to benefit from cytotoxic chemotherapy
  - Refractory to ≥2 induction attempts
  - First relapse with initial CR duration of <6 months or any prior unsuccessful salvage
  - Second relapse or higher
  - HMA failure
- No prior allogeneic hematopoietic cell transplant

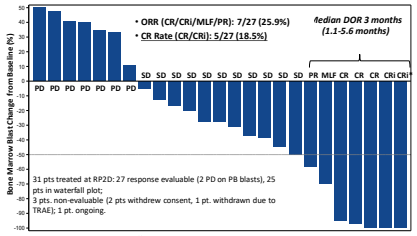
Study objectives

- Safety and preliminary clinical activity
- Optimize delivery and supportive care (manage CRS while minimizing corticosteroid use)
- Define PK, PD and PK/PD relationships

CRS=cytokine release syndrome
Uy G, et al. ASH 2018.

136

Flotetuzumab (CD3 x CD123) Activity in Overall RP2D Cohort



Patient subsequently underwent HSCT in remission; Data cut-off Nov 1, 2018.
MLF=morphologic leukemia-free state; PR=partial response; RP2D=recommended phase 2 dose; SD=stable disease; PD=treatment failure
Uy G, et al. ASH 2018.

137

AZA + Nivo in Relapsed AML: Response (N = 70)[1]

Best response	N (%); Median [Range]	
	Azacitidine/Nivolumab	Control
Overall Response Rate	23 (33)	35 (20)
CR	4 (6)	17 (10)
CRi/CRp	11 (16)	15 (9)
PR	1 (1)	1 (1)
HI* (6 months+)	7 (10)	2 (1)
Stable disease (6 months+)[@]	6 (9)	NA
Non responders	41 (58)	131 (76)
Median cycles to response	2 [1 – 13]	2 [1 – 6]
Median follow up, in months	13.3 [8.2 – 25.5]	51 [0.1 – 64.8]
ORR in prior HMA-Naïve (N=25)	52%	19% (P<0.001)
CR/CRi in prior HMA-naïve	28%	16% (P=0.18)
ORR in prior HMA-exposed (N=45)	22%	23%
CR/CRi in prior HMA-exposed	16%	23%

*-@ Response maintained >6 months

[1]Daver N, et al. *Cancer Discov.* 2018;9(3):370-383. [2]Stahl M, et al. *Blood Advances.* 2018 [Epub]; [3]DiNardo C, et al. *Am J Hematol.* 2018;93(3):401-407. [4]Goldberg A, et al. ASH 2018. Abstract 1353.

How does this compare to other HMA Rx in R/R AML??

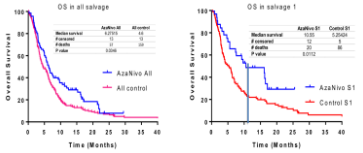
[2]Single-agent AZA/DAC (n = 670) in prior HMA-naïve retro analysis, ORR = 23%
CR/CRi rate = 16%

[3,4]AZA/DAC + VEN in prior HMA- naïve:
CR/CRi: 30-35%

138

OS AZA + NIVO vs Historical HMA Combos at MDACC R/R AML; Censored for SCT

- 70 patients with R/R AML (median age 70 years)
- [1]Median OS better than historical with AZA/DAC matched R/R AML clinical trial controls, particularly in salvage 1 (10.5 months vs 5.4 months, *P*<.011); 1-year OS = 50%



Expected survival in salvage 1 with HMA (n=670): 6.0 mos, 12-mo OS: 16%[2]

Improved efficacy in early salvage: Blina and CART in ALL, MGD006 in prim ref AML

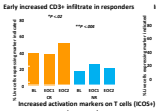
[1]Daver N, et al. *Cancer Discov.* 2018;9(3):370-383. [2]Stahl M, et al. *Blood Advances.* 2018. Abstract 148.

139

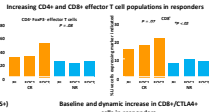
Azacitidine + Nivolumab in R/R AML: Biomarkers of Response and Effects on T Cells

BM optimal cutoff CD3 >13.2%
25/47 (55%) of all patients were above optimal cutoff
ORR was 56% versus 23% (*P*=.03), based on cutoff

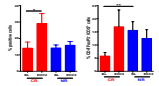
Early increased CD3+ infiltrate in responders



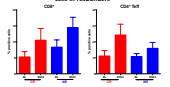
Increasing CD4+ and CD8+ effector T cell populations in responders



Increased activation markers on T cells (ICOS+) in responders



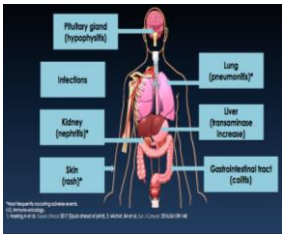
Baseline and dynamic increase in CD8+/CTLA4+ cells in responders



Daver N, et al. *Cancer Discover.* Oct 2018 [Epub ahead of print].

140

Overview of Toxicities with I-O Therapy[1,2]



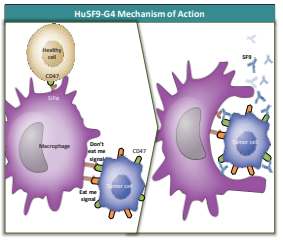
- Immune toxicity management
  - Occur in 20-25%
  - Easily missed
  - May mimic infections
  - 95% reversible if steroids started within 24 hours
  - Must initiate steroid (with or without antibiotics, if on CPI)
  - Establish and follow IO guidelines for randomized trials
  - Like bispecifics and CART the CPIs should be in leukemia centers of excellence

[1]Sang K, et al. ASH 2017. Abstract 3588. [2]Daver N, Kontoyiannis D, et al. *Lancet Oncol.* 2017;18(12):1571-1573.

141

Background on CD47 in AML

- Macrophages are a key part of the innate immune system
  - Engulf cancer cells
  - Recruit, activate, and present cancer cell antigens to T cells
- CD47 is a "do not eat me" signal on cancer cells that enables them to evade macrophages
- Increased CD47 expression predicts worse outcomes for AML patients
- Hu5F9-G4 (5F9) targets CD47 on tumor cells, inducing macrophage phagocytosis

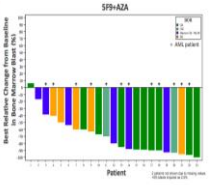


AML=acute myeloid leukemia; CD47=integrin-associated protein
Sallman DA, et al. 2019 ASCO. Abstract 7009.

142

Anti-leukemic Activity is Observed with 5F9 Monotherapy and in Combination with AZA in AML and MDS

Best Overall Response	R/R AML/MDS 5F9 mono N=10	1L AML 5F9+AZA N=14	1L MDS 5F9+AZA N=11
ORR	1 (10%)	9 (64%)	11 (100%)
CR	0	5 (36%)	6 (55%)
CRi	0	2 (14%)	–
PR	0	0	0
MLFS/ marrow CR	1 (10%)	2 (14%)	4 (36%) 2 with marrow CR+i
Hematologic improvement (HI)	–	–	1 (9%)
SD	7 (70%)	5 (36%)	0
PD	2 (20%)	0	0



- 5F9 monotherapy has an ORR of 10% in r/r AML/MDS
- 5F9+AZA has an ORR of 100% in MDS, 64% in AML which compares favorably to AZA monotherapy
  ORR Median time to response is more rapid (1.9 months) than AZA alone

143

Conclusions

- HMA+VEN outstanding in frontline unfit AML but response and OS in R/R AML modest. Novel combinations VEN+MDM2, VEN+MCL1i, VEN+FLT/IDH appear encouraging. Triplets ongoing/planned
- MDM2i (Idasanutlin) and E-selectin-I (GMI-1271) in phase 3, registrational trials
- Immune therapies (novel and safer ADCs, bispecific Ab, CPI based) may be next major wave of development in AML, multiple trials ongoing
- AML may be following MM paradigm, effective and safe doublets/triplets to improve PFS/OS with lower toxicity/mortality

145