Cytogenetic and Molecular Drivers of Outcome with Venetoclax-Based Combination Therapies in Treatment-Naïve Elderly Patients with AML   AML-181

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BACKGROUND

- Approximately half of patients diagnosed with Acute myeloid leukemia (AML) are age 65 or older[1]
- Elderly patients (≥65 years) and patients with significant comorbidities may not be eligible for intensive chemotherapy, though may be able to receive low intensity therapies
- Regardless of therapeutic intensity, older patients with AML generally have a worse prognosis than younger patients[2,3]
- Tumor-related genetic abnormalities in AML have been shown to be key prognostic factors affecting outcomes to standard treatments[4]
- Combinations of venetoclax, an oral BCL-2 inhibitor, and hypomethylating agents[5] or low-dose cytarabine[6] have demonstrated promising rates of response in elderly patients with AML unfit for standard induction chemotherapy
- It is important to gain a better understanding of the genetic milieu of AML and to identify genetic and molecular predictors of response to venetoclax combinations in that setting

OBJECTIVE

- To evaluate the impact of molecular profiles in elderly, previously untreated patients with AML, who are ineligible for standard induction chemotherapy and receiving venetoclax combination therapies

METHODS

- This analysis includes combined data from two open-label multicenter trials assessing the safety and efficacy of venetoclax combination therapies
  – Venetoclax in combination with azacitidine or decitabine (NCT02203773; phase 1b; data cutoff July 7, 2017)
  – Venetoclax in combination with low-dose cytarabine (NCT02287233; phase 1/2; data cutoff August 15, 2017)
- Key study enrollment criteria are shown in **Table 1**
- Patients were classified into ten molecular subgroups based on cytogenetic (site-reported) and molecular mutations identified using next-generation sequencing in baseline bone marrow or blood samples (**Table 2**)
- Response to venetoclax combination therapies was evaluated in patients with intermediate and poor cytogenetic risk, as well as in patients within molecular subgroups
- Determination of minimal residual disease (MRD; 10⁻³ cutoff) used uniform multicolor flow cytometry analyzed at a central laboratory; assessments were any time after initiation of therapy, but prior to study drug discontinuation (plus 7 days) or disease progression, whichever occurred first

Table 1. Key Patient Enrollment Criteria

M14-358: Venetoclax plus Azacitidine or Decitabine

Inclusion	Exclusion
Age 65 or older	Favorable risk cytogenetics*
AML by WHO criteria	White blood cell count >25 x10⁹ cells per liter
Ineligible for standard induction chemotherapy with cytarabine and anthracycline	History of prior hypomethylating agents or has acute promyelocytic leukemia
No prior treatment for AML	Active CNS involvement
ECOG performance score of 0 – 2	Patient is candidate for stem cell transplant within 12 weeks after enrollment

M14-387: Venetoclax plus Low-dose Cytarabine

Inclusion	Exclusion
Age 65 or older	Favorable risk cytogenetics*
Histological confirmation of AML	Patient is candidate for bone marrow or stem cell transplant within 12 weeks after enrollment
Ineligible for standard induction chemotherapy with cytarabine and anthracycline	History of myeloproliferative neoplasm or has acute promyelocytic leukemia
No prior treatment for AML	Active CNS involvement
ECOG performance score of 0 – 2	White blood cell count >25 x10⁹ cells per liter
Moderate hepatic impairment with total bilirubin >1.5 – ≤3.0x ULN	Prior treatment with cytarabine
Creatinine clearance >30 mL/min – <45 mL/min	

* As defined by the National Comprehensive Cancer Network Guidelines v2.0, 2014 for AML.
AML, acute myeloid leukemia; WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group; CNS, central nervous system; ULN, upper limit of normal.

DISCLOSURES & ACKNOLEDGEMENTS

METHODS (CONTINUED)

Table 2. Molecular Classification Subgroups for AML

Genomic Subgroup*	Abbreviation
Mutated chromatin, RNA-splicing genes, or both†	Spliceosome
TP53 mutations, chromosomal aneuploidy, or both‖	TP53 / Aneuploidy
NPM1 mutation	NPM1
MLL fusion genes; t(x;11)(x;q23)	
Biallelic CEBPA mutations	
Inv(3)(q21q26.2) or t(3;3)(q21;q26.2); GATA2, MECOM (EVI1)	
IDH2^R172 mutation and no other class-defining lesions	Other
t(6;9)(p23;q34); DEK-NUP214	
Inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11	
Driver mutations but no detected class defining lesions	

*Subgroups based on Papaemmanuil et al. N Engl J Med. 2016 Jun 9;374(23):2209-2221. † Requires mutation in RUNX1, ASXL1, BCOR, STAG2, EZH2, SRSF2, SRSF2, SF3B1, U2AF1, ZRSR2, or MLL^PTD; at least two such mutations required if other class defining lesions are present. ‖ Requires TP53 mutation, complex karyotype, or in the absence of other class-defining lesions, one or more of the following: −7/7q, −5/5q, −4/4q, −9q, −12/12p, −17/−17p, −18/18q, −20/20q, +11/11q, +13, +21, or +22.
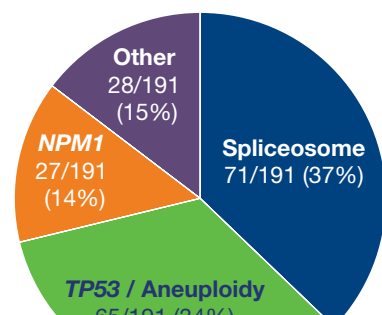
RESULTS

Table 3. Patient Demographics*

Characteristic		N=191
Median age (range), years		74 (65–87)
Age >65 years, n (%)		112 (59)
Male, n (%)		
ECOG Performance Score, n (%)	0	35 (18)
	1	123 (64)
	2	32 (17)
Cytogenetics†, n (%)	Intermediate risk	102 (53)
	Poor risk	84 (44)
	Not available	5 (3)
Secondary AML, n (%)		58 (30)
Baseline bone marrow blasts, n (%)	≤30%	61 (32)
	31 – 50%	55 (29)
	>50%	75 (39)

* One patient had an ECOG score of 3 at baseline † Cytogenetic risk groups defined in 2014 NCCN guidelines, version 2, based on site-reported cytogenetics.

Figure 1. Patients Within Key Molecular Subgroups for AML

Spliceosome 71/191 (37%); TP53 / Aneuploidy 65/191 (34%); NPM1 27/191 (14%); Other 28/191 (15%)

RESULTS (CONTINUED)

Table 4. Frequency of Molecular Drivers Mutations

Molecular Subgroup	Patients, n (%)
Mutated chromatin, RNA-splicing genes, or both*	71 (37)
RUNX1	32 (45)
SRSF2	28 (39)
STAG2	19 (27)
ASXL1	15 (21)
BCOR	11 (15)
SF3B1	11 (15)
U2AF1	9 (13)
EZH2	8 (11)
MLLPTD	7 (10)
ZRSR2	3 (4)
TP53 mutations, chromosomal aneuploidy, or both*	65 (34)
3 or more abnormalities	50 (77)
TP53 mutation	44 (68)
Other	11 (17)
NPM1 mutation	27 (14)
MLL fusion genes; t(x;11)(x;q23)	6 (3)
Biallelic CEBPA mutations	5 (3)
Inv(3)(q21q26.2) or t(3;3)(q21;q26.2); GATA2, MECOM (EVI1)	4 (2)
IDH2^R172 mutation and no other class-defining lesions	1 (1)
t(6;9)(p23;q34); DEK-NUP214	1 (1)
Inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11	0
Driver mutations but no detected class defining lesions	8 (4)
No detected driver mutations	3 (2)

* Patients listed below with individual mutations may have more than one mutation and thus be counted in multiple groups.

- 26/32 (81%) patients with RUNX1 mutations and 20/28 (71%) patients with SRSF2 mutations achieved CR/CRi
- Of the 50 patients with 3 or more chromosomal abnormalities, 35 (70%) patients had a mutation in TP53
- Across both studies, 26/50 (52%) patients with 3 or more abnormalities (as defined in the TP53 / Aneuploidy molecular subgroup in **Table 2**) achieved CR/CRi
  – 17/44 (39%) patients with TP53 mutations achieved CR/CRi

Figure 2. Response Rate by Subgroups*
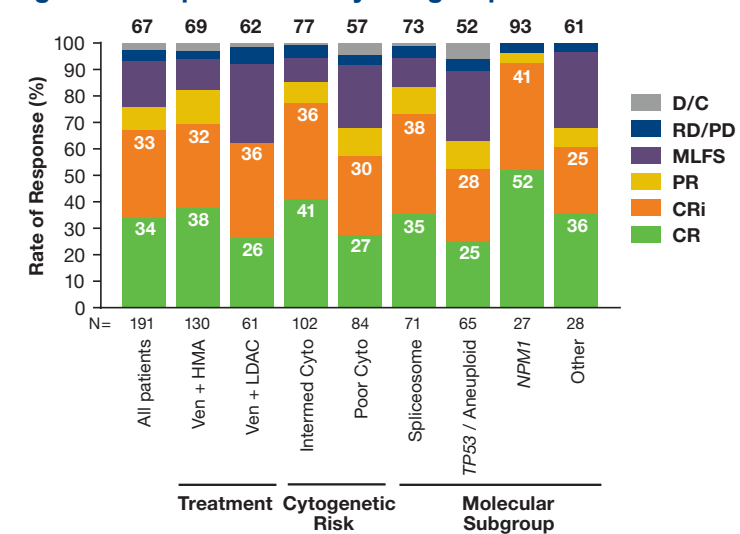
* Numbers on top of bars represent the total percentage of patients that achieved CR/CRi in a given subgroup. HMA, hypomethylating agent (decitabine or azacitidine); LDAC, low dose cytarabine; Cyto, cytogenetic risk group; CR, complete remission; CRi, CR with incomplete blood count recovery; PR, partial remission; MLFS, morphologic leukemia free state; RD/PS, resistant or progressive disease; D/C, discontinued prior to assessment.

- Patients with Intermediate cytogenetic risk had higher rates of CR/CRi than those with Poor risk
- Patients with Spliceosome or NPM1 mutations had relatively higher rates of CR/CRi (>70%), while those with TP53 mutations or aneuploidy had a lower rate (52%)
- 20/30 (67%) of patients with mutated FLT3 achieved CR/CRi

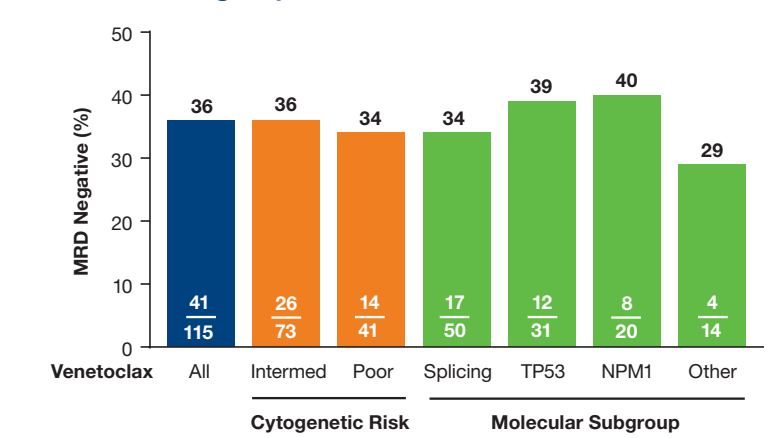### Figure 3. MRD Negativity (<10⁻³) by Cytogenetic Risk and Molecular Subgroups
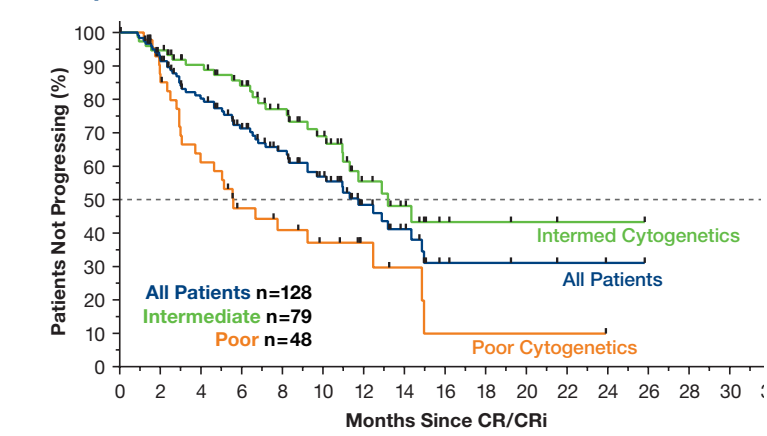

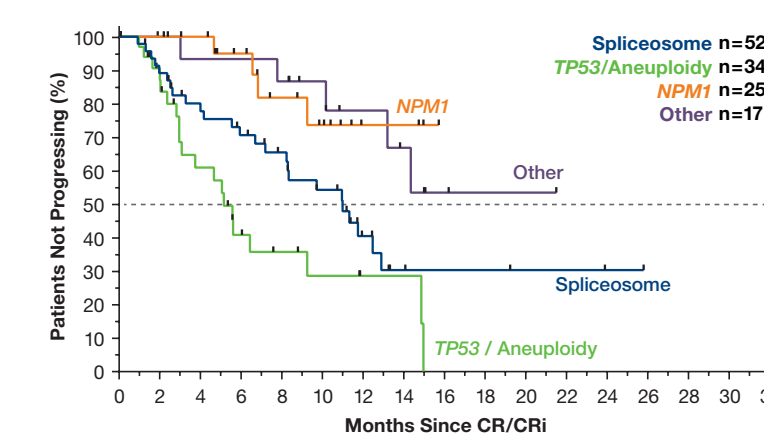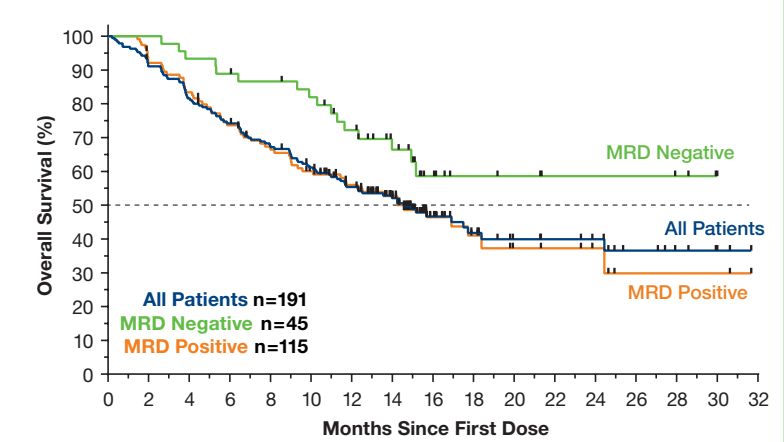### Figure 4. Duration of Response by Cytogenetic Risk Group

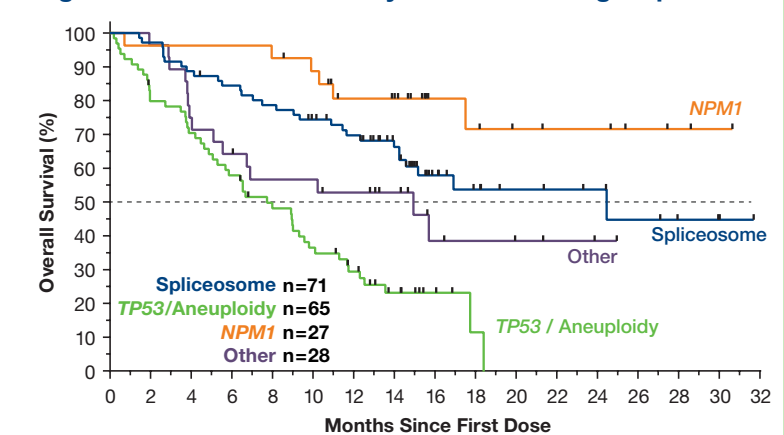### Figure 5. Duration of Response by Molecular Subgroup

See Table 2 for definitions and defining mutations of each molecular subgroup.

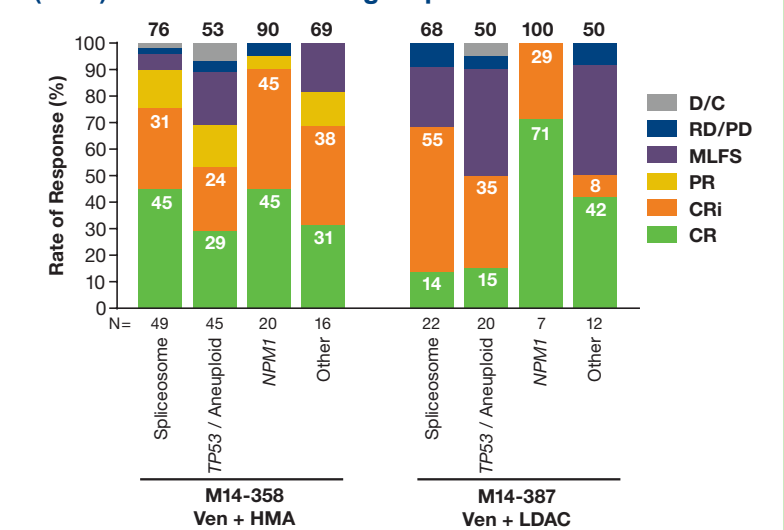### Figure 6. Overall Survival by Whether a Patient Achieved MRD Negativity (<10⁻³)

All Patients n=191; MRD Negative n=45; MRD Positive n=115

MRD negativity was defined as 10-3 leukemic cells at any measurement during treatment.

Figure 7. Overall Survival by Molecular Subgroup

Spliceosome n=71; TP53/Aneuploidy n=65; NPM1 n=27; Other n=28

See Table 2 for definitions and defining mutations of each molecular subgroup.

Figure 8. Response Rate by Combination Treatment (Trial) and Molecular Subgroup

* Numbers on top of bars represent the total percentage of patients that achieved CR/CRi in a given subgroup. HMA, hypomethylating agent (decitabine or azacitidine); LDAC, low dose cytarabine; Cyto, cytogenetic risk group; CR, complete remission; CRi, CR with incomplete blood count recovery; PR, partial remission; MLFS, morphogenic leukemia free state; RD/PD, resistant or progressive disease; D/C, discontinued prior to assessment.

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5. DiNardo CD, Pratz KW, Letai A, et al: Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol 19:216-228, 2018.
6. Wei AH, Strickland SA, Roboz GJ, et al: Phase 1/2 Study of Venetoclax with Low-Dose Cytarabine in Treatment-Naive, Elderly Patients with Acute Myeloid Leukemia Unfit for Intensive Chemotherapy: 1-Year Outcomes. Blood 130:890, 2017.

CONCLUSIONS

- Mutations in spliceosome-related genes, followed closely by TP53, and then NPM1 were the most frequently observed in these trials
- Patients with NPM1 mutations tended to have longer duration of response and better median survival time than patients in other molecular subgroups
  – Patients with NPM1 mutations had the highest relative rate of CR/CRi (93%) and MRD negativity (40%)
- Patients in the molecular subgroup defined with TP53 mutations and/or aneuploidy had the lowest rate of CR/CRi (52%), shortest duration of response, and shorter median duration of survival
- Patients who achieved MRD negativity had better median survival time than those who did not

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