Year in Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Saturday, February 8, 2020, 8:00 AM – 4:00 PM
Charlotte, North Carolina

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Moderator

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Research To Practice®

Agenda

Module 1 — Lung Cancer: *Drs Langer and Riely*

Module 2 — Acute Leukemias: *Drs DiNardo and Stone*

Module 3 — Lymphomas and Chronic Lymphocytic Leukemia: *Drs Abramson, LaCasce and Smith*

Module 4 — Gastrointestinal Cancers: *Drs Bendell, Marshall and Wainberg*

Module 5 — Genitourinary Cancers: *Drs Oh and Petrylak*

Module 6 — Gynecologic Cancers: *Drs Armstrong and Liu*

Module 7 — Breast Cancer: *Drs Geyer and Krop*

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Disclosures

Advisory Committee	Jazz Pharmaceuticals Inc
Consulting Agreements	AbbVie Inc, Agios Pharmaceuticals Inc, Celgene Corporation, Daiichi Sankyo Inc, Notable

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Disclosures

Advisory Committee	Actinium Pharmaceuticals Inc, Amgen Inc, Astellas, BioLineRx, GEMoaB, Janssen Biotech Inc, MacroGenics Inc, Novartis, Takeda Oncology, Trovagene
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Contracted Research	Arog Pharmaceuticals Inc, Novartis
Data and Safety Monitoring Board/Committee	Celgene Corporation

Acute Leukemias — Drs DiNardo and Stone

Acute Myeloid Leukemia

Acute Lymphoblastic Leukemia

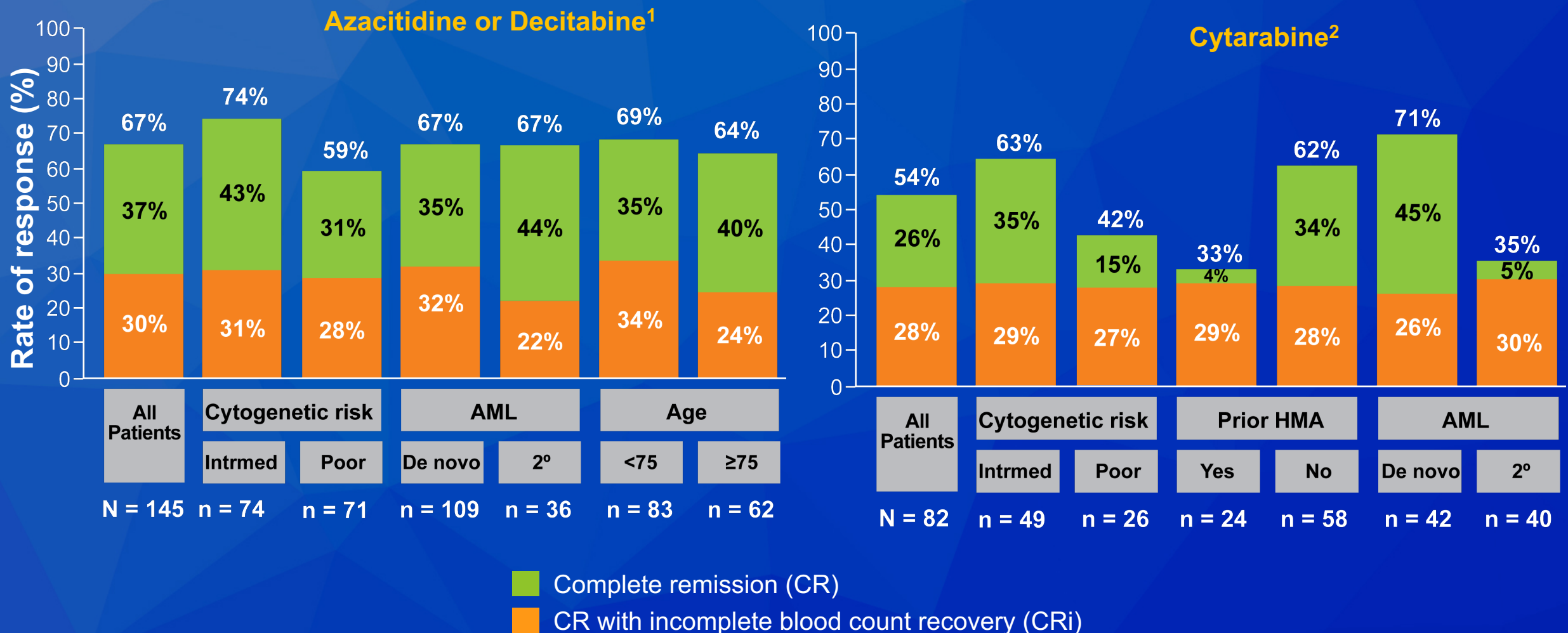
Venetoclax Combined with Decitabine or Azacitidine in Treatment-Naive, Elderly Patients with Acute Myeloid Leukemia[1]

Venetoclax Combined with Low-Dose Cytarabine for Previously Untreated Patients with Acute Myeloid Leukemia: Results from a Phase Ib/II Study[2]

[1] DiNardo CD et al.
Blood 2019;133(1):7-17.

[2] Wei AH et al.
J Clin Oncol 2019;37(15):1277-84.

Venetoclax with either Azacitidine or Decitabine[1] versus Low-Dose Cytarabine[2]: Response Rates by Subgroup



[1] DiNardo CD et al. *Blood* 2019;133(1):7-17; [2] Wei AH et al. *J Clin Oncol* 2019;37(15):1277-84.

Venetoclax (VEN) with Either Azacitidine (AZA) or Decitabine (DEC)[1] versus Low-Dose Cytarabine (LDAC)[2]: Select Adverse Events

Grade 3/4 AEs	VEN 400 mg		VEN 800 mg		VEN 1,200 mg	
	DEC (n = 31)	AZA (n = 29)	DEC (n = 37)	AZA (n = 37)	DEC (n = 5)	AZA (n = 6)
Febrile neutropenia	19 (61%)	11 (38%)	15 (41%)	13 (35%)	2 (40%)	3 (50%)
Decreased WBC count	13 (42%)	7 (24%)	10 (27%)	12 (32%)	2 (40%)	1 (17%)
Diarrhea	2 (6%)	1 (3%)	2 (5%)	2 (5%)	0	0

Grade ≥3 AEs	VEN 600 mg + LDAC (n = 82)
Febrile neutropenia	34 (42%)
Thrombocytopenia	31 (28%)
Decreased WBC count	28 (34%)

[1] DiNardo CD et al. *Blood* 2019;133(1):7-17; [2] Wei AH et al. *J Clin Oncol* 2019;37(15):1277-84.

Select Ongoing Phase III Trials of Venetoclax-Based Therapies for Treatment-Naïve AML Ineligible for Intensive Chemotherapy

Trial	N	Randomization	Estimated primary completion
M15-656 (NCT02993523)	443	Venetoclax → azacitidine Placebo → azacitidine	February 2020
M16-043 (NCT03069352)	211	Venetoclax + low-dose cytarabine Placebo + low-dose cytarabine	July 2020
M19-072 (NCT03941964)	60	Venetoclax + azacitidine Venetoclax + decitabine	November 2020

www.clinicaltrials.gov. Accessed September 2019.

Editorial — Dr Erba

Venetoclax is an orally bioavailable small molecule inhibitor of Bcl-2. In a phase I/II study in relapsed/refractory AML patients, single-agent venetoclax demonstrated minimal evidence of activity (less than 20% response rate). However, even as a single agent, 4 of 6 subjects with an IDH mutation had a response. In phase Ib studies leading to FDA approval, venetoclax was combined with less-intensive therapies for treatment-naïve older or unfit AML patients, including azacitidine, decitabine and low dose cytarabine (LoDAC). The rationale was not based on preclinical data, but instead the combinations were studied in an effort to improve the poor outcomes seen with the less intensive standard-of-care therapies. Although the optimal dose of venetoclax was evaluated in these phase Ib studies, the optimal dosing schedule (concurrent, sequential, or both as well as duration of venetoclax therapy) was not evaluated. The overall response rate with hypomethylating agents (HMA) plus venetoclax is remarkable, 71% CR/CRi.

Editorial — Dr Erba (continued)

The median time to response was short, 1-2 months. The responses also appeared durable, and the median overall survival was 16 months with HMA plus venetoclax. Although response rates greater than 50% were observed in the phase Ib study across mutational subsets, including TP53, the response rates were highest among patients with IDH1, IDH2 and NPM1 mutations. The 30-day mortality in the azacitidine plus venetoclax arm was less than 5%. AML patients previously treated with HMA for myelodysplastic syndrome were excluded from the HMA plus venetoclax phase Ib study. However, such patients were treated with LoDAC plus venetoclax; the overall response rate in these patients was only 33%, with only 1 of 24 subjects achieving CR. Single-institution data supports the use of HMA plus venetoclax in patients with relapsed/refractory AML or in AML patients previously treated with an HMA.

Editorial — Dr Erba (continued)

Two potential toxicities should be considered with these combinations: tumor lysis syndrome (TLS) and myelosuppression. Tumor lysis syndrome was not observed in the HMA plus venetoclax phase Ib study. However, the study required subjects to have a WBC count less than 25,000/microliter. Although hydroxyurea was allowed prior to treatment, only 10% of the subjects received hydroxyurea. In fact, 25%-30% subjects had only 20%-30% marrow blasts, and less than 50% of subjects in both phase Ib studies had over 50% marrow blasts. Patients receiving venetoclax with HMA or LoDAC should be monitored closely for TLS. Great caution should be exercised if using venetoclax with HMA or LoDAC in the setting of uncontrolled leukocytosis or renal insufficiency.

Venetoclax will contribute to myelosuppression, especially neutropenia. The risk of hematologic toxicity appeared higher in the decitabine/venetoclax arm compared with the azacitidine/venetoclax arm of the phase Ib study.

Editorial — Dr Erba (continued)

Two thirds of subjects in the HMA/venetoclax phase Ib study required dose interruption. There are no formal guidelines on the management of cytopenias during maintenance therapy with venetoclax plus HMA or LoDAC. The prescribing information suggests the use of myeloid growth factors, but dose reductions may also be considered. Since myelosuppression is uncommon with single-agent HMA once a remission has been achieved, and the optimal number of days of venetoclax was not studied, I prefer to limit the number of days of venetoclax therapy during subsequent cycles. CYP3A4 inhibitors will increase exposure to, and toxicity from, venetoclax. The dose of venetoclax should be reduced to 50-100 mg daily with concomitant use of a strong CYP3A4 inhibitor. Two international phase III studies of azacitidine with venetoclax/placebo and LoDAC with venetoclax/placebo have completed enrollment. The primary endpoint of these two studies includes overall survival.

Editorial — Dr Erba (continued)

Since the median survival of AML patients in the phase Ib studies exceeded 12 months, it is anticipated that these two studies will be positive. However, a phase III study of standard therapy with venetoclax vs placebo in relapsed myeloma was halted due to worse survival in the experimental arm, despite a higher response rate. If the phase III studies of these venetoclax combinations in treatment-naïve, older and/or unfit AML patients are negative and do not confirm a survival benefit, these combinations may still provide benefit based on the rapid achievement of remission in a high percentage of patients without early induction mortality.

Venetoclax inhibits the anti-apoptotic protein Bcl-2. Therefore, this agent may act synergistically with other cytotoxic or targeted agents in AML. Phase I studies combining venetoclax with FLT3 inhibitors, IDH inhibitors and standard cytotoxic chemotherapy such as 7+3 are under way.

Response to Venetoclax in Combination with Low Intensity Therapy (LDAC or HMA) in Untreated Patients with Acute Myeloid Leukemia with IDH, FLT3 and Other Mutations and Correlations with BCL2 Family Expression

Chyla BJ et al.
ASH 2019;Abstract 546.

Phase Ib/II Trial: Molecular Marker-Defined Subgroup Analysis of Clinical Outcomes with Venetoclax + HMA or LDAC

Molecular marker*	CR/CRi	Median OS	Median TTFR	DoR
Molecular marker cohort (n = 167)	109 (65.3%)	12.5 mo	1.2 mo	15.0 mo
IDH1/IDH2 mutation (n = 43)	36 (83.7%)	NR	1.1 mo	NR
NPM1 mutation (n = 26)	22 (84.6%)	NR	1.3 mo	NR
TP53 mutation (n = 37)	22 (59.5%)	8.9 mo	1.5 mo	5.6 mo
FLT3 mutation (n = 30)	16 (53.3%)	12.4 mo	1.8 mo	19.9 mo

NR = Not reached; CRi = incomplete complete remission; TTFR = time to first response; DoR = duration of response.

* Pts with co-expressing mutations are represented more than once.

- VEN + HMA or LDAC has efficacy across multiple molecular markers in AML.
- Activity with VEN + HMA or LDAC is rapid and durable, and is observed across different levels of *BCL2* expression in AML blasts.

Chyla BJ et al. ASH 2019;Abstract 546.

Editorial — Dr Stone

Based on high response rates in phase II studies, the FDA approved the combinations of either low-dose ara-C or a hypomethylating agent plus venetoclax in previously untreated patients with AML deemed unfit for standard chemotherapy due to age greater than 75 or significant co-morbidities. Phase III trials comparing the aforementioned low dose chemotherapy alone plus or minus venetoclax with survival as the primary endpoint have been completed; results are expected in 2020. Nonetheless, these venetoclax-containing combinations have become the “go-to” therapy for many newly diagnosed older adults with AML, even some beyond the approved indication. Thus, it is very important to understand any clinical and/or biological characteristics that might predict for response. In this pharma-written abstract, 209 patients who received venetoclax (400-600 milligrams per day) plus a hypomethylating agent or low dose ara-C were analyzed for response according to mutations (IDH1/2, NPM1, TP53 and FLT3).

Editorial — Dr Stone (continued)

As has been previously published, patients with IDH1/2 or NPM1 mutations were more likely to respond and responded durably compared to those with a FLT3 or particularly a TP53 mutation. The authors also could not show that intracellular Bcl-2 levels independently correlated with response to the chemotherapy/venetoclax combination; however, a multivariate analysis displayed a trend toward IDH1 and IDH2 mutant patients having higher Bcl-2 expression levels and those with TP53 mutations having lower expression levels.

While the data in this abstract are interesting, the key question of whether venetoclax plus chemotherapy is superior to chemotherapy alone in the individual subgroups will not be answered until the phase III results are available. Moreover, we are given no information about the response according to variant allele frequency nor in those with more than one mutation. This data is of insufficient utility to warrant a change in clinical practice when treating patients with specific mutations.

American Journal of Hematology AJH

Glasdegib in combination with cytarabine and daunorubicin in patients with AML or high-risk MDS: phase 2 study results

Jorge E. Cortes, MD,[1] B. Douglas Smith, MD,[2] Eunice S. Wang, MD,[3] Akil Merchant, MD,[4] Vivian G. Oehler, MD,[5] Martha Arellano, MD,[6] Daniel J. DeAngelo, MD,[7] Daniel A. Pollyea, MD,[8] Mikkael A. Sekeres, MD,[9] Tadeusz Robak, MD,[10] Weidong Wendy Ma, PhD,[11] Mirjana Zeremski, MD,[11] M. Naveed Shaik, PhD, [11] A. Douglas Laird, PhD[11] Ashleigh O'Connell, BSc,[11] Geoffrey Chan, MD,[11] and Mark A. Schroeder, MD[12]

2018;93(11):1301-10.

BRIGHT AML 1003: Glasdegib with Chemotherapy for Untreated AML or High-Risk MDS

	Glasdegib + chemotherapy (n = 69)
Median OS (n = 69)	14.9 mo
CR (n = 69)	46.4%
CR in patients ≥55 years old (n = 60)	40.0%

Select adverse events	Glasdegib + chemotherapy (n = 69)	
	Any grade	Grade ≥3
Any adverse event	100%	98.6%
Diarrhea	71.0%	1.4%
Febrile neutropenia	63.8%	63.8%
Hypokalemia	53.6%	13.0%
Anemia	40.6%	37.7%
Thrombocytopenia	33.3%	31.9%

Cortes JE et al. *Am J Hematol* 2018;93(11):1301-10.

BRIGHT AML1019: Ongoing Phase III Trial Design

Target accrual (N = 720)

- Previously untreated AML
- Adequate organ function
- No APL
- No AML with BCR ABL1 or t(9;22)(q34;q11.2) as sole abnormality
- No active CNS leukemia

R

1:1

Glasdegib + 7+3 induction (intensive study) or Glasdegib + azacitidine (non-intensive study)

Placebo + 7+3 induction (intensive study) or Placebo + azacitidine (non-intensive study)

Primary endpoint: Overall survival

www.clinicaltrials.gov (NCT03416179). Accessed January 2020.

Editorial — Dr Erba

Glasdegib is an orally bioavailable inhibitor of Smoothened, a component of the Hedgehog pathway. Preclinical studies of this agent do not show convincing evidence of a direct effect on the AML leukemic cell or even normal hematopoiesis. On the other hand, it has been postulated that glasdegib may interfere with the interaction between the leukemic stem cells and the bone marrow microenvironment. Glasdegib has been FDA approved based on the results of a randomized, phase II study in treatment-naïve, older, unfit AML patients. Patients were randomly assigned in a 2:1 fashion to receive either low dose cytarabine (LoDAC) with glasdegib 100 mg once daily continuously or low dose cytarabine alone, respectively. There was no placebo control; patients and their physicians were not blinded to the treatment assignment. The primary endpoint of the study was met with improvement in median survival from 4 months to 8.3 months with the addition of glasdegib.

Editorial — Dr Erba (continued)

However, the complete remission rate in the control arm was less than 5%, lower than that observed in several other studies with low dose cytarabine alone. This suggests that subjects assigned to single-agent LoDAC may have been removed from the study before a response could be achieved. Glasdegib was associated with GI toxicity including dysgeusia, nausea and diarrhea, as well as alopecia and muscle cramps. Cortes and colleagues have published the results of a phase II study of glasdegib in combination with daunorubicin and cytarabine induction therapy followed by intermediate-dose cytarabine consolidation (2-4 cycles). Subjects in CR not proceeding to allogeneic hematopoietic stem cell transplant (allo HSCT) then received six 28-day cycles of glasdegib maintenance. The primary endpoint of the study was improvement in the CR rate to greater than 54% for the 60 evaluable patients aged 55 years and older.

Editorial — Dr Erba (continued)

The primary endpoint was not achieved; only 40% of the patients achieved a CR. Although the authors report that the CR rate was not affected by the identified mutations in these patients, the CR rate in patients with poor-risk karyotype was only 18% (3 of 17 patients). On the other hand, the authors were encouraged by a median survival of 14.7 months in patients aged 55 years and older. They suggest that glasdegib may exert a benefit by affecting the survival of the leukemic stem cell through an effect on paracrine signaling in the marrow microenvironment. In this way, glasdegib may affect risk of relapse and overall survival more than CR rate. However, median duration of CR was short (100 days), potentially due to methodologic issues. The protocol-defined pharmacodynamics studies on peripheral blood samples could not demonstrate an effect of glasdegib on Hedgehog signaling due to low baseline expression of GLI proteins.

Editorial — Dr Erba (continued)

Other than the expected hematologic toxicity of intensive chemotherapy, there was expected GI toxicity (dysgeusia, nausea, anorexia). The authors conclude that the addition of glasdegib was well tolerated, since these toxicities were generally grade 1-2. The true benefit of glasdegib in AML has not yet been established. We eagerly await the results of the BRIGHT AML randomized trials to assess the benefit of Hedgehog inhibition in AML.

FDA Approves Addition of Survival Data to Gilteritinib Label for Relapsed or Refractory AML with a FLT3 Mutation

Press Release – May 29, 2019

"On May 29, 2019, the Food and Drug Administration approved the addition of overall survival data in labeling for gilteritinib, indicated for adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test.

Approval was based on the ADMIRAL trial (NCT02421939), which included 371 adult patients with relapsed or refractory AML having a FLT3 ITD, D835, or I836 mutation by the LeukoStrat CDx FLT3 Mutation Assay. Patients were randomized (2:1) to receive gilteritinib 120 mg once daily (n = 247) over continuous 28-day cycles or prespecified salvage chemotherapy (n = 124). Salvage chemotherapy included either intensive cytotoxic chemotherapy or a low-intensity regimen. For the analysis, overall survival (OS) was measured from the randomization date until death by any cause. After a median follow-up of 17.8 months, median OS was 9.3 months for patients receiving gilteritinib and 5.6 months for those on the chemotherapy arm (HR 0.64; $p = 0.0004$)."

Gilteritinib was initially approved on November 28, 2018 based on an interim analysis of response rates from ADMIRAL. After a median follow-up of 4.6 months, 29 patients achieved complete remission (CR) or CR with partial hematologic recovery (CRh) (21%).

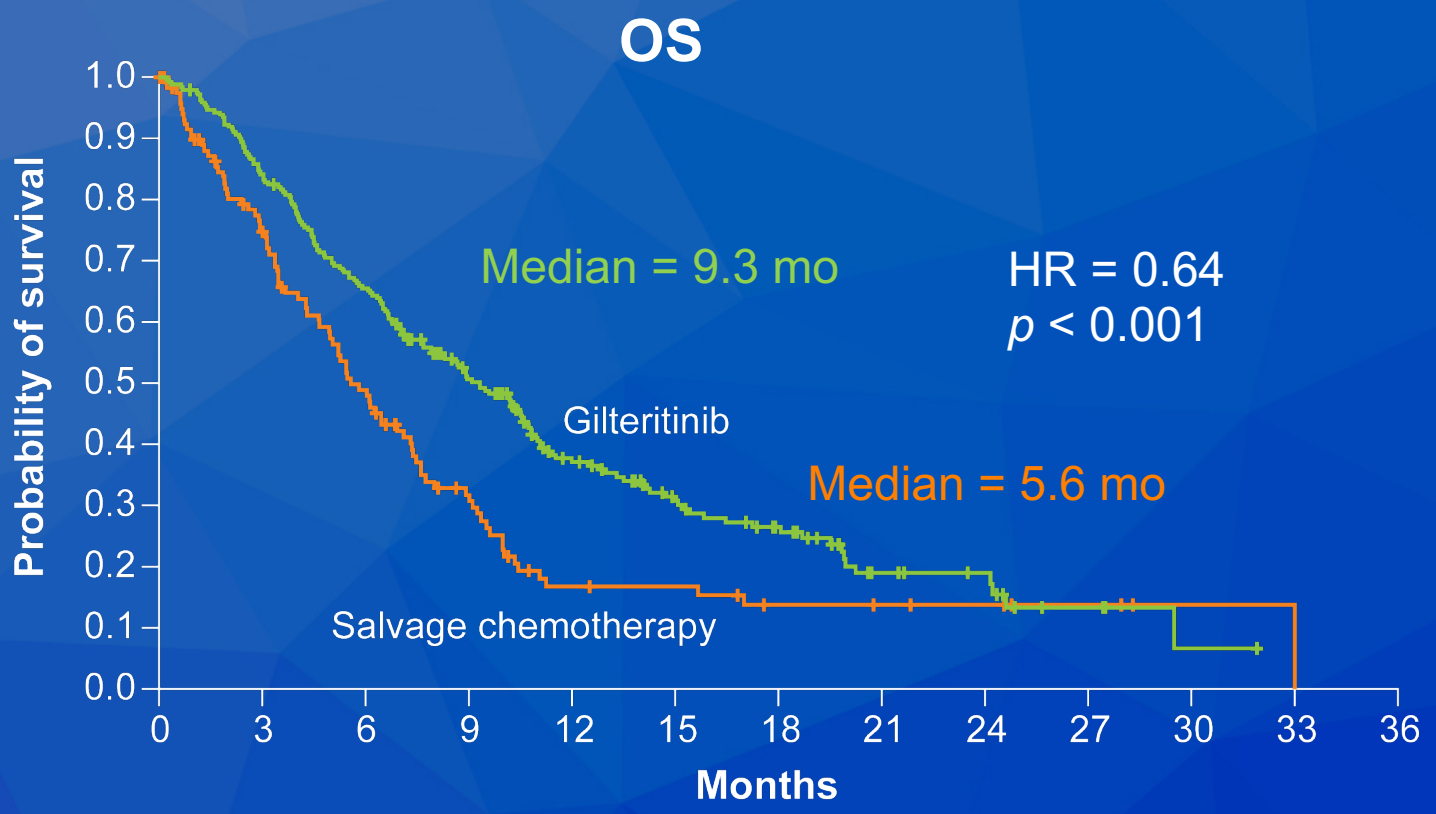
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-addition-survival-data-gilteritinib-label-refractory-aml-flt3-mutation; https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm627045.htm

https://www.fda.gov/drugs/fda-approves-gilteritinib-relapsed-or-refractory-acute-myeloid-leukemia-aml-flt3-mutatation

Gilteritinib or Chemotherapy for Relapsed or Refractory *FLT3*-Mutated AML

Perl AE et al.
N Engl J Med 2019;381(18):1728-40.

ADMIRAL: Phase III Trial Efficacy Results



Outcome	Gilteritinib (n = 247)	Chemo (n = 124)	HR* or RD+
Median EFS	2.8 mo	0.7 mo	0.79*
Median LFS	4.4 mo	6.7 mo	NE
ORR	67.6%	25.8%	—
CR	21.1%	10.5%	10.6+
CRi	25.5%	11.3%	ND
CRp	7.7%	0	ND
CRc	54.3%	21.8%	32.5+
PR	13.4%	4.0%	ND
Median DoR	11.0 mo	NE	NE

HR = hazard ratio; RD = risk difference; EFS = event-free survival; LFS = leukemia-free survival; NE = not estimable; ORR = overall response rate; CRp = CR with incomplete platelet recovery; CRc = composite CR; CRi = CR with incomplete hematologic recovery; ND = not determined; DoR = duration of remission

Perl AE et al. *N Engl J Med* 2019;381(18):1728-40.

ADMIRAL: Safety

	Gilteritinib (n = 246)		Salvage Chemotherapy (n = 109)	
Select AEs	All grades	Grade ≥3	All grades	Grade ≥3
Febrile neutropenia	46.7%	45.9%	36.7%	36.7%
Anemia	47.2%	40.7%	34.9%	30.3%
Pyrexia	42.7%	3.3%	29.4%	3.7%
Increased ALT	41.9%	13.8%	9.2%	4.6%
Increased AST	40.2%	14.6%	11.9%	1.8%
Thrombocytopenia	25.6%	22.8%	16.5%	16.5%
Peripheral edema	24.0%	0.4%	11.9%	0
Dyspnea	23.6%	4.1%	6.4%	2.8%

Perl AE et al. *N Engl J Med* 2019;381(18):1728-40.

Select Ongoing Phase III Trials of Gilteritinib-Based Therapies for AML with FLT3 Mutation

Trial	N	Setting	Randomization	Estimated primary completion
2215-CL-0303 (NCT03182244)	318	Refractory to first-line tx with or without HSCT	Gilteritinib Salvage chemotherapy	March 2020
2215-CL-0304 (NCT02997202)	346	Maintenance tx following allogeneic transplant	Gilteritinib Placebo	April 2025
2215-CL-0201 (NCT02752035)	323	Newly diagnosed Intensive chemo ineligible	Gilteritinib Gilteritinib + azacitidine Azacitidine	April 2021
HOVON 156 AML (NCT04027309)	768	Newly diagnosed Intensive chemo eligible	Gilteritinib* + chemotherapy Midostaurin* + chemotherapy	May 2023

* Administered sequentially to standard induction and consolidation chemotherapy; patients who achieve CR/CRi/MLFS will receive maintenance gilteritinib or midostaurin

www.clinicaltrials.gov. Accessed September 2019.

Editorial — Dr Erba

Activating mutations of FLT3 occur in about one third of AML patients. The more common mutation is an internal tandem duplication (ITD) in the juxtamembrane region, encoded by exons 14 and 15. FLT3 tyrosine kinase domain (TKD) mutations are identified in 5%-10% of AML patients. The presence of the FLT3 ITD mutation has been associated with a worse overall survival due to higher risk of relapse. Midostaurin was FDA approved in April 2017 for treatment-naïve AML patients with either a FLT3 ITD or TKD mutation in combination with standard daunorubicin and cytarabine induction therapy and cytarabine consolidation, based on the results of the RATIFY trial. Although the CR rate was not improved by the addition of midostaurin to standard induction therapy, the survival of patients at 4 years was superior with midostaurin compared with placebo (51% vs 44%). The survival benefit was most apparent for patients receiving midostaurin-containing therapy who proceeded to allo HSCT in first CR.

Editorial — Dr Erba (continued)

Midostaurin is a first-generation type I inhibitor. First-generation FLT3 inhibitors are less selective. In fact, some have speculated that the survival benefit observed with midostaurin in the RATIFY trial may be due to its activity against a broad range of both tyrosine and serine-threonine kinases. Type I inhibitors interfere with the ATP binding site and are active against both ITD- and TKD-mutant enzymes. Gilteritinib is an orally bioavailable, type I, second-generation FLT3 inhibitor with greater specificity for FLT3 than midostaurin. Gilteritinib was compared with either intensive (MEC, IdaFLAG) or less intensive (azacitidine, low dose cytarabine) salvage therapy for FLT3-mutated AML patients with refractory or first relapse disease in a 2:1 randomization, respectively. Gilteritinib was superior to salvage chemotherapy in terms of efficacy: higher CR rate (21% vs 11%), higher CR + CRh rate (34% vs 15%), improvement in median overall survival (9.3 vs 5.6 months), improvement in one-year survival (37% vs 17%) and higher number of patients able to proceed to allo HSCT (26% vs 15%), the only potentially curative option.

Editorial — Dr Erba (continued)

Patients who continued gilteritinib after allo HSCT had a better overall survival compared to those who did not, but the true benefit of gilteritinib maintenance post allo HSCT is difficult to discern given the selection bias inherent in this type of comparison. The BMT CTN trial is evaluating gilteritinib post allo HSCT in a placebo-controlled randomized phase III trial. The benefit of gilteritinib over salvage chemotherapy was observed regardless of co-mutations (NPM1, DNMT3A, WT1) and high vs low FLT3 allelic ratio. There was no significant safety signal, although gilteritinib has been associated with differentiation syndrome. I believe this data strongly supports the use of gilteritinib (over chemotherapy alone) in this population. However, the survival of patients with FLT3-mutated AML who received either gilteritinib or salvage chemotherapy was dismal at 2 years (approximately 10%). Since FLT3 mutation appears to be a late event in leukemogenesis, it is not surprising that targeting a single mutation will not result in long-term benefit. Clearly, other interventions are required. Gilteritinib is being studied in combination with chemotherapy as well as MDM2 and Bcl-2 inhibitors.

Editorial — Dr Erba (continued)

Other FLT3 inhibitors are in development, including quizartinib and crenolanib. Quizartinib is arguably the most potent of the selective FLT3 inhibitors. As a type II inhibitor, it is only active against the FLT3 ITD mutation. Nonetheless, in the initial phase I studies of quizartinib, AML patients with a FLT3 ITD variant allelic frequency less than 10% also responded. The QuANTUM-R study compared quizartinib to salvage chemotherapy in a design nearly identical to the ADMIRAL trial. The primary endpoint of the study was achieved, with improvement in median overall survival (27 weeks vs 20 weeks). The response rate was also higher with quizartinib than chemotherapy (48% vs 27%), and more patients were able to proceed to allo HSCT after quizartinib therapy (32% vs 12%). The magnitude of the survival benefit seemed less than that observed with gilteritinib. However, the survival of patients in the QuANTUM-R study may have been affected by 23% of subjects assigned to the chemotherapy arm not accepting their treatment assignment. In terms of toxicity, quizartinib has been associated with QT prolongation, especially at higher doses explored in the initial phase I studies.

Editorial — Dr Erba (continued)

In QuANTUM-R only 3% of subjects experienced asymptomatic prolongation of the QTc interval to greater than 500 milliseconds. Although ODAC advised against approval of quizartinib based on uncertain benefit-to-risk ratio, the drug has been approved in Japan.

FDA Approval of Ivosidenib as First-Line Treatment for AML with IDH1 Mutation

Press Release – May 2, 2019

“On May 2, 2019, the Food and Drug Administration approved ivosidenib for newly-diagnosed AML with a susceptible IDH1 mutation, as detected by an FDA-approved test, in patients who are at least 75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy. Approval was based on an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) of single-agent ivosidenib for newly-diagnosed AML with an IDH1 mutation.

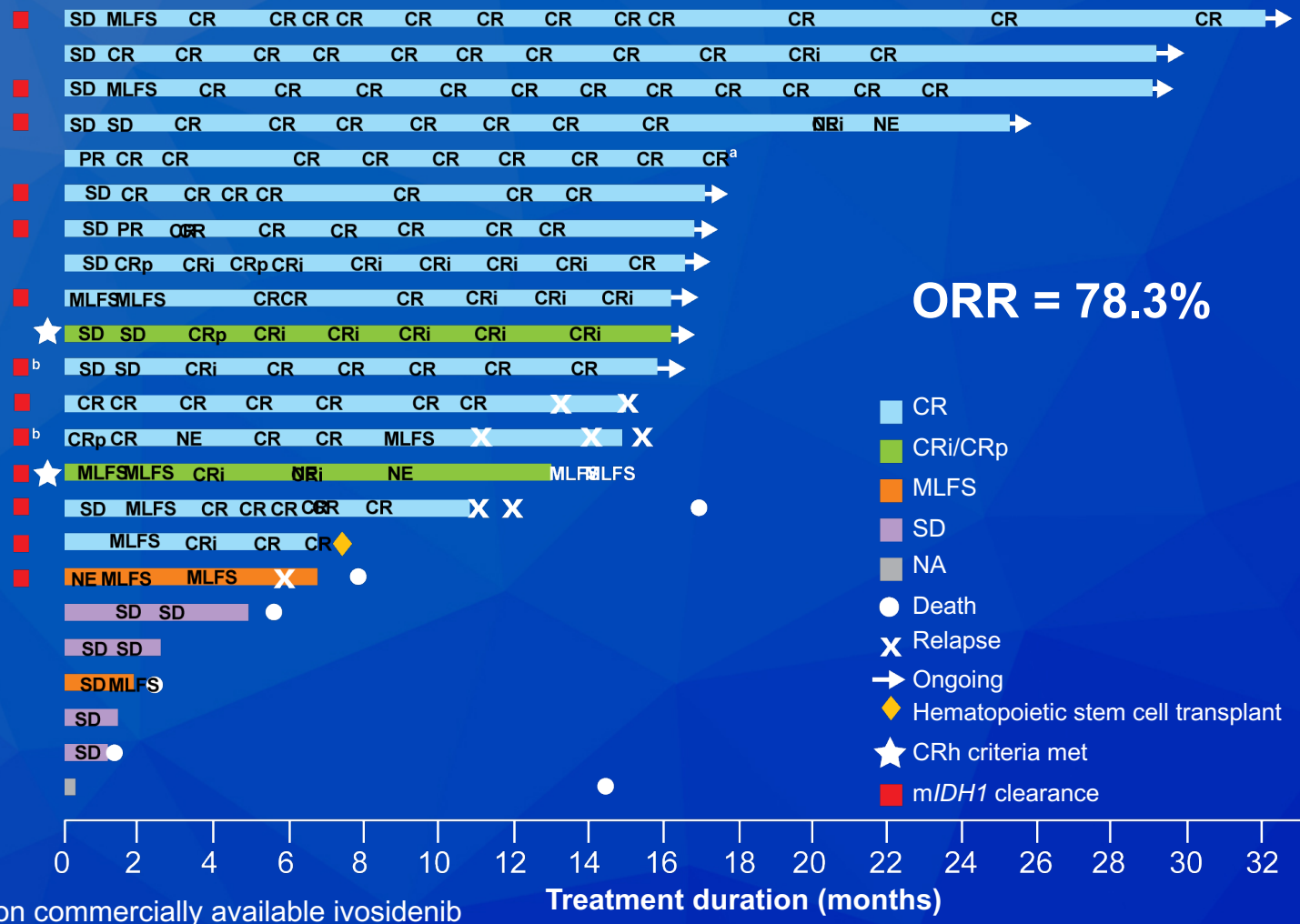
The adverse reactions that occurred in at least 25% of patients were diarrhea, fatigue, edema, decreased appetite, leukocytosis, nausea, arthralgia, abdominal pain, dyspnea, differentiation syndrome and myalgia. Prescribing information contains a Boxed Warning alerting health care professionals and patients about the risk of differentiation syndrome which may be life-threatening or fatal.”

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-first-line-treatment-aml-idh1-mutation

Mutant IDH1 Inhibitor Ivosidenib (IVO; AG-120) in Combination with Azacitidine (AZA) for Newly Diagnosed Acute Myeloid Leukemia (ND AML)

Dinardo CD et al.
Proc ASCO 2019;Abstract 7011.

Ivosidenib and Azacitidine in Newly Diagnosed AML with IDH1 Mutation: Treatment Duration and Best Overall Response



[a] Patient continued on commercially available ivosidenib

[b] Patient had m*IDH1* clearance in PBMCs only (BMMCs not available); all other patients had m*IDH1* clearance in both BMMCs and PBMCs

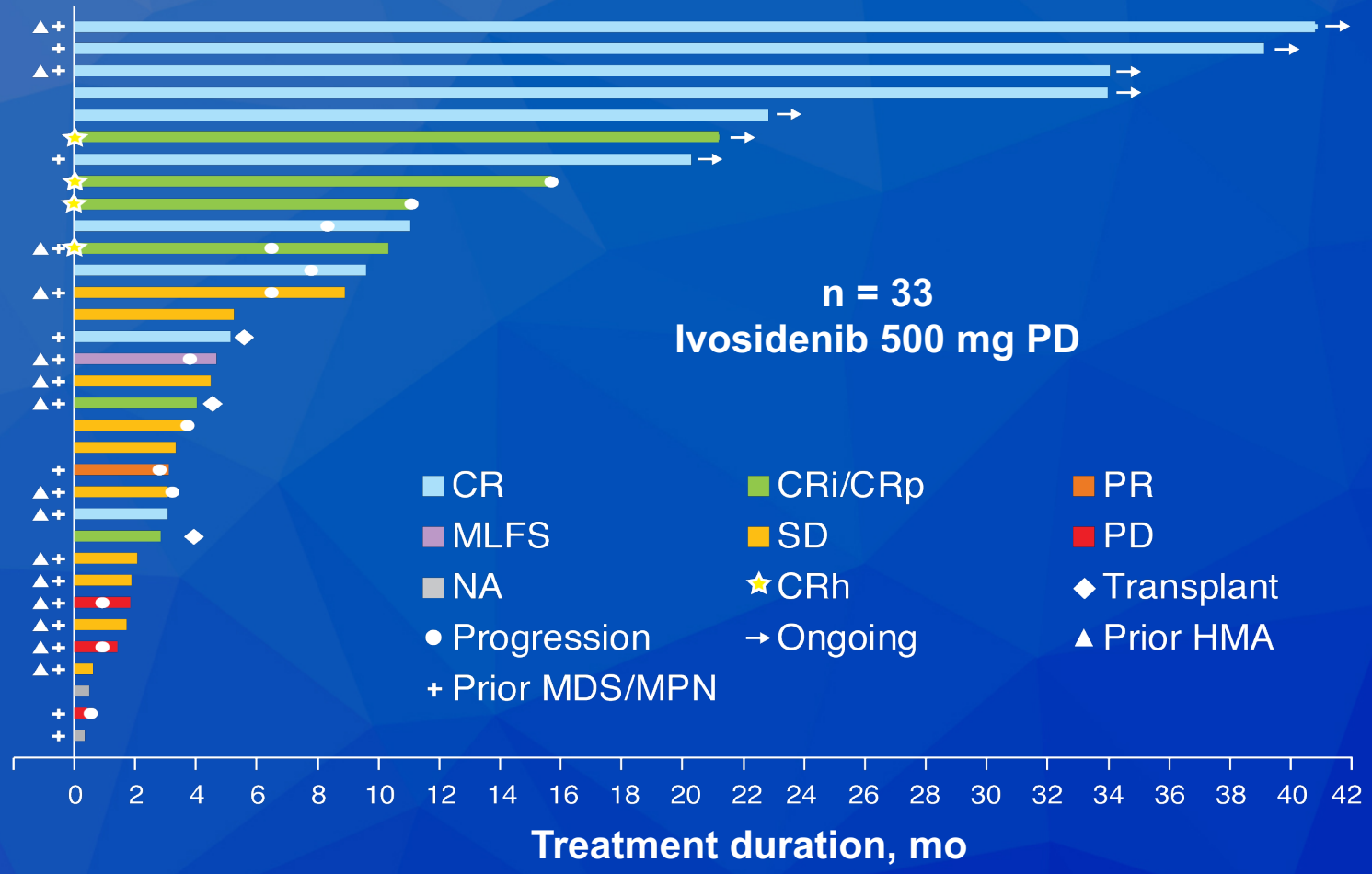
NA = not assessed; NE = not evaluable

Dinardo CD et al. *Proc ASCO* 2019;Abstract 7011.

Ivosidenib Induces Deep Durable Remissions in Patients with Newly Diagnosed IDH1-Mutant Acute Myeloid Leukemia

Roboz GJ et al.
Blood 2019;[Epub ahead of print].

Ivosidenib in Newly Diagnosed AML with IDH1 Mutation: Best Response, Overall Survival and Tolerability



Best response	Ivosidenib (n = 33)
ORR	18 (54.5%)
CR	10 (30.3%)
CRi/CRp	6 (18.2%)
PR	1 (3.0%)
MLFS	1 (3.0%)

CRi = CR with hematologic recovery

CRp = CR with incomplete platelet recovery

MLFS = morphologic leukemia-free state

- Median OS = 12.6 mo
- Ivosidenib monotherapy was well tolerated.

Roboz GJ et al. *Blood* 2019;[Epub ahead of print].

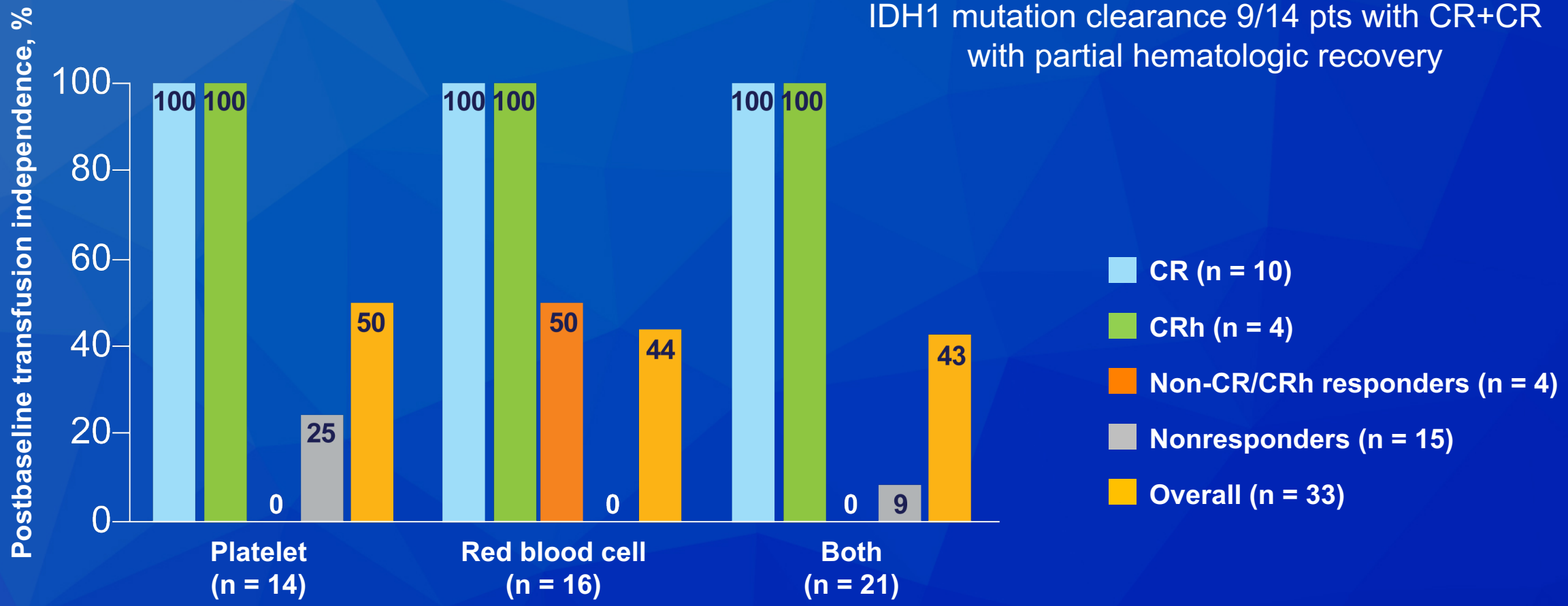
Ivosidenib in Newly Diagnosed AML with IDH1 Mutation: Transfusion Independence

Transfusion Independence

Patients Dependent at Baseline (n = 21)

Achieved transfusion independence (n = 9)

IDH1 mutation clearance 9/14 pts with CR+CR with partial hematologic recovery



Roboz GJ et al. *Blood* 2019;[Epub ahead of print].

Editorial — Dr Erba

Both ivosidenib and enasidenib have been listed in NCCN AML practice guidelines for the treatment of treatment naïve, older, IDH mutated AML patients unable to tolerate intensive chemotherapy. Roboz et al report the efficacy and safety of single-agent ivosidenib in treatment naïve IDH1m AML patients. The rate of CR/CRh with single-agent ivosidenib is 42% with 30% CR. The median time to CR/CRh response was almost 3 months. Two thirds of IDH1m AML patients achieving a CR or CRh were still in a response at 12 months. Mutational clearance was achieved in 64% of the CR/CRh patients. The adverse event profile is similar to that observed in R/R IDH1m AML. However, the combination of HMA with venetoclax has been associated with a very high response rate (over 90% CR/CRi) in treatment-naïve IDHm AML patients. Responses with HMA/venetoclax are often seen after only one cycle of therapy.

Editorial — Dr Erba (continued)

Since AML patients previously treated with an HMA for MDS were excluded from the phase I/II study of HMA/venetoclax, this data supports the use of ivosidenib for initial therapy of AML patients who have already progressed from myelodysplastic syndrome after having received an HMA. IDH mutations are not infrequently discovered at the time of progression of MDS to AML. Ivosidenib is now FDA approved for initial treatment of IDH1m AML patients based on this single-agent data. The combinations of azacitidine with full doses of the IDHm inhibitors appear safe based on the results of a phase Ib study. DiNardo et al have presented the results of an expanded cohort (N = 23) of treatment-naïve, older/unfit IDH1m AML patients treated with azacitidine and ivosidenib. The response rates are higher than expected with either agent alone (70% CR/CRh and 78% ORR). Furthermore, 63% of CR/CRh patients achieved MRD-negative remissions as judged by clearance of the IDH1 mutant allele by digital PCR assay.

Editorial — Dr Erba (continued)

Median duration of response has not been reached, with seven of the CR/CRi patients with ongoing responses for more than 12 months. Importantly, neutrophil counts improved during the first cycle of therapy and remained above 500/mm^3 in the responders with subsequent cycles of therapy. Rapid and sustained blood count recovery may be a point of distinction between azacitidine with ivosidenib versus HMA with venetoclax. The toxicity profile was similar to that expected with either drug alone. Differentiation syndrome occurred in 17% of subjects and grade 3/4 QT prolongation in 13%. Ideally, we would want to compare the outcomes of patients given azacitidine with either placebo or an IDHm inhibitor. The AGILE trial is attempting to address this question with ivosidenib in treatment-naïve, IDH1 mutated, older AML patients unfit for intensive chemotherapy. However, there are significant challenges affecting accrual to the study. First, less than 10% of AML patients will have an IDH1 R132 mutation necessary for treatment on the study.

Editorial — Dr Erba (continued)

Second, other agents are being combined with HMA, such as the Bcl-2 inhibitor venetoclax and the Smoothen inhibitor glasdegib. Based on very encouraging response rates and median survival in phase Ib studies, some clinicians are treating older unfit patients, regardless of mutational status, with the combination of azacitidine with venetoclax. Third, if a patient is not responding on study, then ethically the subject needs to be told if he/she has been randomized to ivosidenib or placebo, since ivosidenib would be an available option for the patient randomized to receive placebo. Therefore, the blind would need to be broken. How long would an investigator allow their patient to remain on such a blinded study without a response, knowing the subject may have been randomized to placebo? One cycle, two cycles? Finally, overall survival is the primary endpoint of the AGILE trial. An OS benefit may be obscured by available salvage therapies following treatment on the AGILE trial, such as ivosidenib itself, Bcl-2 inhibitors, and immunotherapeutic approaches with BiTE, DART and antibody-drug conjugates.

Editorial — Dr Erba (continued)

Event-free survival could circumvent this problem and decrease the sample size. However, complete response rate already appears to be lower with azacitidine alone (20%) compared with azacitidine with ivosidenib. Therefore, EFS would likely show a benefit of the combination but predominantly due to difference in CR. Ultimately, these obstacles may be insurmountable, indicating the need for alternative approaches to FDA approval and/or clinical adoption of novel therapeutic options for AML patients. Finally, assuming that the phase III studies of HMA or LoDAC with venetoclax show a survival benefit over single-agent HMA or LoDAC alone, the phase III study would ideally compare azacitidine plus ivosidenib to azacitidine plus venetoclax. A phase Ib study has shown that both ivosidenib and enasidenib can also be safely combined with 7+3 induction and high dose cytarabine consolidation therapies in treatment-naïve IDH1m and IDH2m AML patients, respectively.

Editorial — Dr Erba (continued)

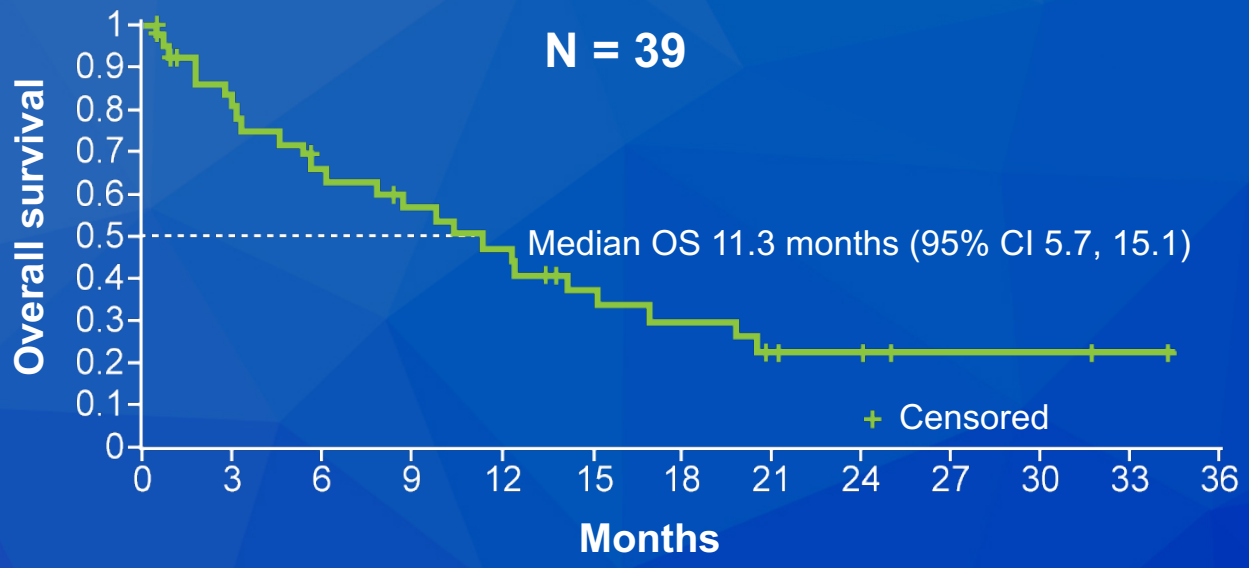
The investigators reported the rates of response, including MRD-negative responses (using both flow cytometry and digital PCR assays) and survival at one year (over 75% in both groups of patients). However, the benefit of adding IDHm inhibitors to standard AML therapy can only be truly discerned from placebo-controlled, double-blind, randomized phase III trials. The HOVON has launched such a trial. These trials will exclude subjects with a concomitant FLT3 mutation, since midostaurin is approved in Europe for these patients.

Enasidenib, an Inhibitor of Mutant IDH2 Proteins, Induces Durable Remissions in Older Patients with Newly Diagnosed Acute Myeloid Leukemia

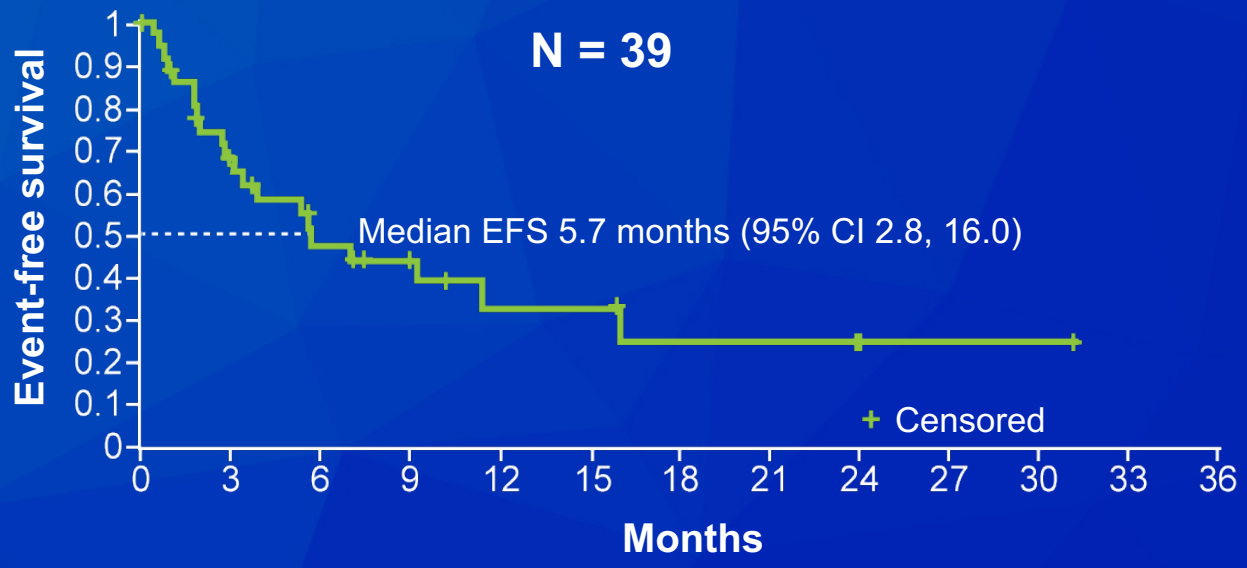
Pollyea DA et al.
Leukemia 2019;33(11):2575-84.

Enasidenib for Older Patients Newly Diagnosed with AML with IDH2 Mutation: Survival Outcomes

Overall Survival



Event-Free Survival



Pollyea DA et al. *Leukemia* 2019;33(11):2575-84.

Editorial — Dr Erba

The Phase I studies of ivosidenib and enasidenib in the respectively IDH1 and IDH2 mutated, relapsed and refractory (R/R) AML patients have produced very similar results. 33% of IDH1m+ R/R AML patients and 25% of IDH2m+ R/R AML patients achieve a complete remission or complete remission with partial hematologic recovery (CRh, ANC over 500/mm^3 **AND** platelets over 50,000/mm^3). The median time to CR + CRh is 2 months with ivosidenib and almost 4 months with enasidenib. The majority, if not all, of the responses will be seen by 6 months. Furthermore, transfusion dependent AML patients may become transfusion independent, even without achieving CR or CRh. The median duration of response has been approximately 6-9 months; however, some patients have been in remission for over 1.5 years. The major toxicity to consider with both ivosidenib and enasidenib is differentiation syndrome (DS), occurring in 10% to 20% of patients, depending on grade, often associated with hyperleukocytosis.

Editorial — Dr Erba (continued)

DS may occur as early as the first week of therapy and as late as several months into therapy. The signs of DS include fluid retention with pulmonary edema, pleural/pericardial effusions, fever, dyspnea, hypoxia, hypotension and renal insufficiency. When DS is suspected, the patient should be monitored closely and started on dexamethasone 10 mg IV twice daily. If the WBC count is increasing, hydroxyurea should be started. Unlike APL, only half of the patients experiencing DS will actually achieve remission. There are several potential explanations for this observation. There may be multiple subclones of the disease at the time of relapse, some of which may not respond to the IDHm inhibitors due to the presence of other drivers, while the IDHm-driven disease does respond. It is also possible that the signs of disease progression may be mistaken for those of DS. There is no laboratory evaluation that allows us to definitively diagnose DS.

Editorial — Dr Erba (continued)

The diagnosis of DS (as opposed to AML progression) may be favored if there are signs of granulocytic differentiation in the blood smear. Also, DS tends to respond within the first few days of steroid therapy, whereas AML progression will not respond.Stein et al have updated results from the phase I/II study of enasidenib in R/R AML patients. The response rates did not change (20% CR, 40% ORR). There were a few important observations. A significant minority of patients (38%) only maintained stable disease during the first 90 days on study. However, 30% of these patients (N = 25) achieved an IWG-defined response in the next 90 days, including CR in 16 of these 25 patients. Subjects with three or fewer mutations were more likely to have a response (29% CR, 55% ORR) compared with those with six or more mutations (16% CR, 31% ORR). FLT3 ITD or TKD co-mutation was associated with lower chance of remission.

Editorial — Dr Erba (continued)

Mutations in the genes for spliceosome enzymes and receptor kinase signaling pathways were associated with lower chance of response. Subjects achieving a molecular remission by PCR had a better survival than those who did not. These patients were also likely to have achieved a CR. However, there was no difference in the survival of morphologic CR patients either achieving a molecular remission or not. This analysis did show that lower VAF was associated with greater chance of achieving a response (statistically significant only for the R140 mutation). However, the significant overlap in the range of VAF among responders and non-responders make this observation of limited clinical value. High baseline 2HG levels were associated with a greater chance of remission for the IDH2 R172 population only. Rapid, significant suppression of 2-HG levels was observed regardless of response in IDH2 R140-mutant AML patients. However, suppression of the 2-HG levels correlated with response in the R172 group.

Editorial — Dr Erba (continued)

Although this observation suggests a different mechanism of action of enasidenib in these two subgroups, the authors make no comment about this difference between the R140 and R172 groups. The response rate was nominally higher in the R172 group, but this was likely due to a lower number of co-mutations. Although these correlative studies are interesting and may provide insight into mechanism of action, these features do not allow us to select patients who should or should not receive enasidenib. Both ivosidenib and enasidenib have been listed in NCCN AML practice guidelines for the initial treatment of older, IDH-mutated AML patients unable to tolerate intensive chemotherapy. Pollyea et al report the efficacy and safety of single-agent enasidenib in treatment-naïve IDH2m AML patients. The overall response rate (31% CR, CRi, PR and MLFS) is similar to that observed in the cohort of the phase I study of R/R AML patients; only 18% achieved a CR.

Editorial — Dr Erba (continued)

The time to first response was just under 2 months and time to best response almost 4 months. The BEAT AML study has demonstrated similar efficacy of enasidenib in this patient population. If no response after four cycles, azacitidine would be added to enasidenib in the BEAT AML study. The adverse event profile is similar that observed in R/R IDH2m AML. However, the combination of HMA with venetoclax has been associated with a very high response rate (CR/CRi) in treatment-naïve AML patients with IDH mutations. Responses with HMA/venetoclax are often seen after only one cycle of therapy. On the other hand, since AML patients previously treated with an HMA for MDS were excluded from the phase I/II study of HMA/venetoclax, this data supports the use of enasidenib in AML patients who have already progressed from myelodysplastic syndrome and have received hypomethylating agents (HMA). Not infrequently, IDH mutations are discovered at the time of progression of MDS to AML.

Editorial — Dr Erba (continued)

A phase Ib study has shown that both ivosidenib and enasidenib can be safely combined with 7+3 induction and high dose cytarabine consolidation therapies in treatment-naïve IDH1m and IDH2m AML patients, respectively. The investigators reported the rates of response, including MRD-negative responses (using both flow cytometry and digital PCR assays) and survival at one year (over 75% in both groups of patients). However, the benefit of adding IDHm inhibitors to standard AML therapy can be truly discerned only from placebo-controlled, double-blind, randomized phase III trials. The HOVON has launched such a trial. These trials will exclude subjects with a concomitant FLT3 mutation, since midostaurin is approved in Europe for these patients.

Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Compared with Azacitidine Alone in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) with Isocitrate Dehydrogenase 2 (*IDH2*) Mutations: Interim Phase II Results from an Ongoing, Randomized Study

DiNardo CD et al.

Proc ASH 2019;Abstract 643.

Results from an Ongoing Phase II Trial of Enasidenib/Azacitidine versus Azacitidine Alone for Newly Diagnosed AML with IDH2 Mutation

Response	Enasidenib+AZA (n = 68)	AZA (n = 33)	*p*-value
Overall response rate	46 (68%)	14 (42%)	0.0155
Best response			
CR	34 (50%)	4 (12%)	0.0002
CRi/CRp	6 (9%)	4 (12%)	—
PR	3 (4%)	4 (12%)	—
Morphologic leukemia-free state	3 (4%)	2 (6%)	—

CRi/CRp = CR with incomplete recovery

- Median time to CR = 5.0 mo (Enasidenib/AZA) vs 3.7 mo (AZA)
- Median TTFR = 1.9 mo (Enasidenib/AZA) vs 2.0 mo (AZA)
- Median DoR = NR (Enasidenib/AZA) vs 10.2 mo (AZA)
- Combination therapy was generally well tolerated, with a safety profile similar to that reported for either monotherapy.

DiNardo CD et al. *Proc ASH* 2019;Abstract 643.

Editorial — Dr Stone

What is the optimal treatment for newly diagnosed older adults deemed unfit for chemotherapy with an IDH2 mutation, given the availability of enasidenib, an oral agent approved for relapsed/refractory mutant-IDH2 AML? The standard of care for such patients a couple of years ago would have been a hypomethylating agent alone. Results of a trial that randomized such patients on a 2-to-1 basis to enasidenib plus azacitidine vs azacitidine alone indicated that the response rate in those who were randomized to the doublet was significantly higher (68%) than in the single-agent arm (42%). The durability of response and the ability to reduce the mutant IDH2 burden was greater in the combination than in the single-agent arm. The doublet was fairly well tolerated, though 18% in this arm experienced differentiation syndrome. However, at the ASH meeting, data was presented showing that the survival in both arms was similar, in part due to the use of enasidenib as a salvage in those who were randomized to the single agent (though only a minority in the control arm eventually received enasidenib).

Editorial — Dr Stone (continued)

While one might well choose the combination over the single agent, notably absent from consideration in this study was enasidenib alone or the most commonly used regimen for such patients today, azacitidine plus enasidenib. Moreover, in the future, it is likely that the triplet of enasidenib plus azacitidine plus venetoclax will be tested in this patient population.

Genetic Characteristics and Outcomes by Mutation Status in a Phase 3 Study of CPX-351 versus 7+3 in Older Adults with Newly Diagnosed, High-Risk/Secondary Acute Myeloid Leukemia (AML)

Lindsley RC et al.
Proc ASH 2019;Abstract 15.

Outcomes with CPX-351 versus 7+3 in Older Patients with Newly Diagnosed High-Risk/Secondary AML: By Most Frequently Occurring Mutation

Outcome	ASXL1		DNMT3A		RUNX1		TET2		TP53	
	CPX-351 (n = 30)	7+3 (n = 20)	CPX-351 (n = 20)	7+3 (n = 21)	CPX-351 (n = 21)	7+3 (n = 22)	CPX-351 (n = 26)	7+3 (n = 17)	CPX-351 (n = 24)	7+3 (n = 35)
CR	17%	20%	35%	52%	24%	27%	19%	41%	29%	34%
Odds ratio	0.80		0.49		0.83		0.34		0.79	
CR+CRi	37%	35%	60%	57%	33%	32%	35%	47%	29%	40%
Odds ratio	1.08		1.13		1.07		0.60		0.62	
Transplant	27%	30%	55%	38%	29%	18%	23%	18%	13%	31%
Odds ratio	0.85		1.99		1.80		1.40		0.31	
Median OS	9.1 mo	6.3 mo	12.6 mo	5.5 mo	8.9 mo	4.1 mo	9.1 mo	3.7 mo	4.5 mo	5.1 mo
HR	0.67		0.41		0.58		0.47		1.19	
Median EFS	1.6 mo	1.4 mo	6.0 mo	3.6 mo	2.0 mo	1.2 mo	1.6 mo	1.6 mo	1.0 mo	1.6 mo
HR	0.79		0.45		0.57		0.93		1.13	
Median remission duration	6.4 mo	4.1 mo	9.9 mo	4.3 mo	8.1 mo	3.5 mo	6.4 mo	3.5 mo	8.1 mo	3.5 mo

Lindsley RC et al. *Proc ASH* 2019;Abstract 15.

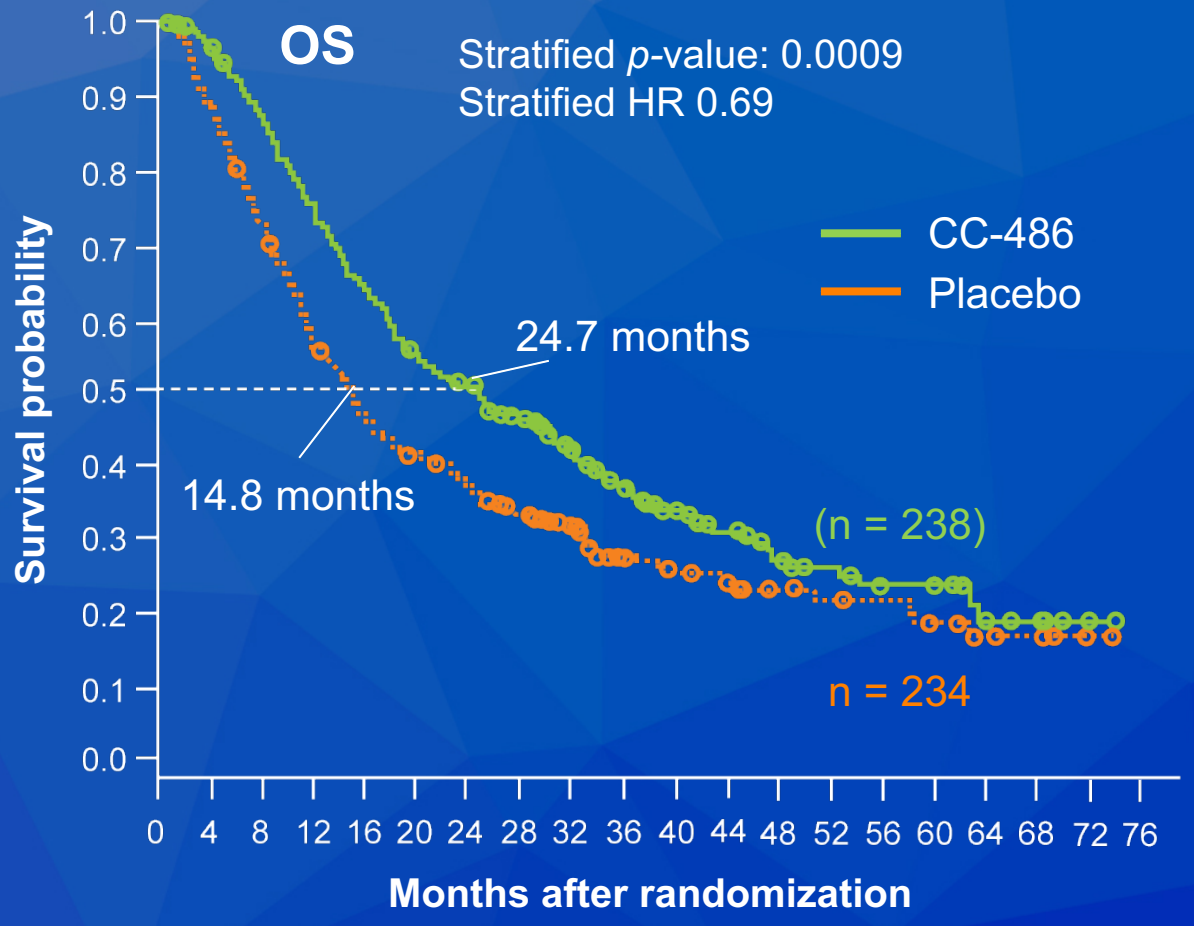
Editorial — Dr DiNardo

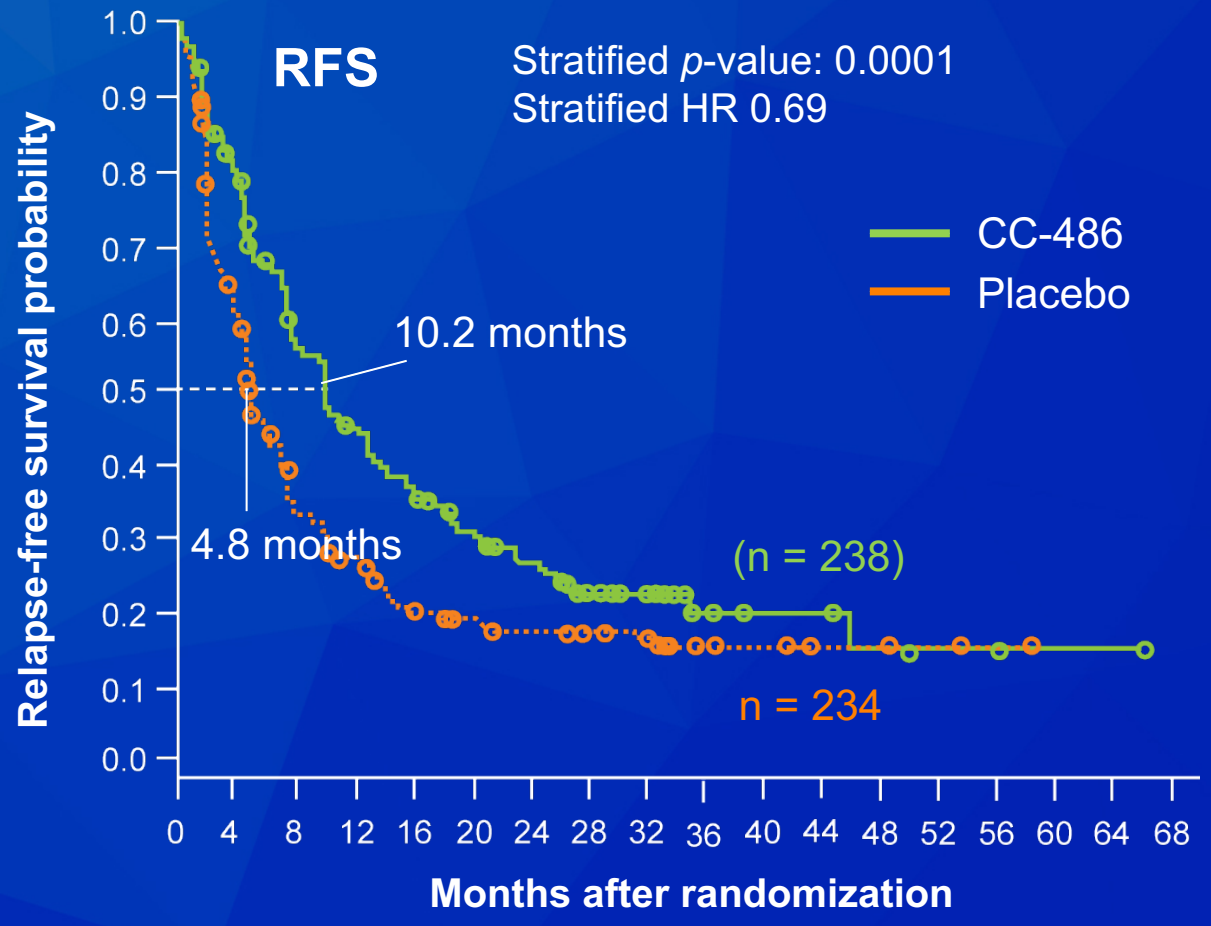
Older patients make up the majority of all patients with AML, with a median age of 68 years. In older adults, and for patients with secondary AML (i.e., AML evolving from an antecedent hematologic disorder or developing as a complication of previous chemotherapy or radiotherapy), standard 7+3 chemotherapy is associated with poor outcomes related to both increased toxicities and lower response and overall survival. Results of the Phase III trial of 7+3 versus CPX-351, a liposomal encapsulation of cytarabine plus daunorubicin at a fixed 5:1 molar ratio, demonstrated improved response (CR/CRi 48% versus 33%) and survival (median OS 9.56 versus 5.95 months; P = 0.003) in fit patients 60-75 years of age with secondary AML or AML with MDS-related cytogenetic abnormalities. Notably, while CPX-351 was identified to be effective in nearly all subpopulations evaluated, patients who had previously received hypomethylating agents had no obvious survival benefits from CPX-351 compared with 7+3 chemotherapy, thus confirming an unfortunately high unmet clinical need for these patients.

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

Wei AH et al.
Proc ASH 2019;Abstract LBA-3.

QUAZAR AML-001: Survival Outcomes at a Median Follow-Up of 41.2 Months





RFS = Relapse-free survival

Wei AH et al. *Proc ASH* 2019;Abstract LBA-3.

QUAZAR AML-001: Safety

Select Grade 1/2 AEs	CC-486 (n = 238)	Placebo (n = 234)
Nausea	64%	23%
Vomiting	59%	10%
Diarrhea	49%	21%
Select Grade 3/4 AEs	**n = 238**	**n = 234**
Neutropenia	41%	24%
Thrombocytopenia	23%	22%
Anemia	14%	13%
Serious AEs	**n = 238**	**n = 234**
Infections	17%	8%

- Few AEs led to treatment discontinuation, most often GI events (CC-486, 5%; PBO, 0.4%).

Wei AH et al. *Proc ASH* 2019;Abstract LBA-3.

Editorial — Dr Stone

Maintenance therapy is universally used in patients with acute lymphoblastic leukemia, but its role in AML has been questionable. Not only have very few studies shown any value for low dose chemotherapy after the completion of intensive induction and consolidation therapy, but patients are generally reluctant to receive any additional therapy after an arduous course. Oral azacitidine, which has a multiplicity of potential effects beyond hypomethylation, was evaluated in an important phase III trial in patients greater than 55 years old with AML in first remission, presented as a late-breaking abstract at ASH. Patients received intensive remission induction therapy alone and up to several cycles of consolidation chemotherapy followed by either placebo or oral azacitidine (300 milligrams daily for 14 days during 28-day cycles).

Editorial — Dr Stone (continued)

This study met its primary endpoint of improved overall survival in the oral azacitidine arm. Those receiving the study drug had a median survival of 25 months compared to 15 months for those on the placebo arm (HR 0.69; $p = 0.0009$). Benefits were seen across baseline characteristics, including cytogenetics, number of consolidation cycles and CR vs CRi status at the time of enrollment. Oral azacitidine did not adversely affect quality of life given that the safety profile was quite manageable with serious adverse events seen in 17% on the oral azacitidine vs 8% on the placebo arm. The results of this study will presumably lead to the approval of oral azacitidine as maintenance therapy in patients who would have been eligible for this trial. However, many of these patients, especially those age 55 to 75, would be considered to be transplant candidates. Thus, a key unanswered question is whether or not the benefit of oral azacitidine maintenance will extend to those who have had stem cell transplants as consolidation therapy in first remission.

Acute Leukemias — Drs DiNardo and Stone

Acute Myeloid Leukemia

Acute Lymphoblastic Leukemia

FDA Authorizes First Next-Generation Sequencing (NGS)-Based Test for Very Low Levels of Remaining Cells in ALL or Multiple Myeloma (MM)

Press Release – September 28, 2018

"The Food and Drug Administration permitted marketing of ClonoSEQ assay, an NGS-based test for minimal residual disease (MRD) in patients with acute lymphoblastic leukemia (ALL) or MM. MRD is a measure of the amount of cancer cells remaining in a person's bone marrow.

[The] approval is an important step forward for patients with ALL and MM.

Determining whether a patient has residual cancer cells remaining after treatment provides information on how well a patient has responded to therapy and how long remission may last. Having a highly sensitive test available to measure MRD in ALL or MM patients can help providers manage their patients' care."

https://www.fda.gov/news-events/press-announcements/fda-authorizes-first-next-generation-sequencing-based-test-detect-very-low-levels-remaining-cancer

ClonoSEQ Assay for the Detection of Lymphoid Malignancies

Monter A, Nomdedéu JF.
Expert Rev Mol Diagn 2019;19(7):571-8.

Editorial — Dr Levis

The use of MRD to assess response and guide therapeutic decisions can now be considered a standard of care in the management of patients with ALL. While no single assay platform or method has been established as definitively better than any other, worldwide, most centers use flow cytometry for MRD in ALL. The unique features of this disease lend itself to identification of a leukemia-associated phenotype that can be detected at a level of 1 cell in 10,000 and can be followed throughout treatment. The ClonoSEQ® platform authorized by the FDA is DNA-based, in that it uses a combination of multiplex PCR (meaning PCR with multiple sets of primers) and NGS to detect unique immunoglobulin sequences within the malignant lymphocyte clone. Those unique sequences are then tracked (with a sensitivity of up to 1 cell in a million) over time. There are other, similar commercially available platforms. We know that the presence/persistence of MRD in patients who have otherwise achieved a morphologic (ie, microscopic) response predicts for a much worse outcome.

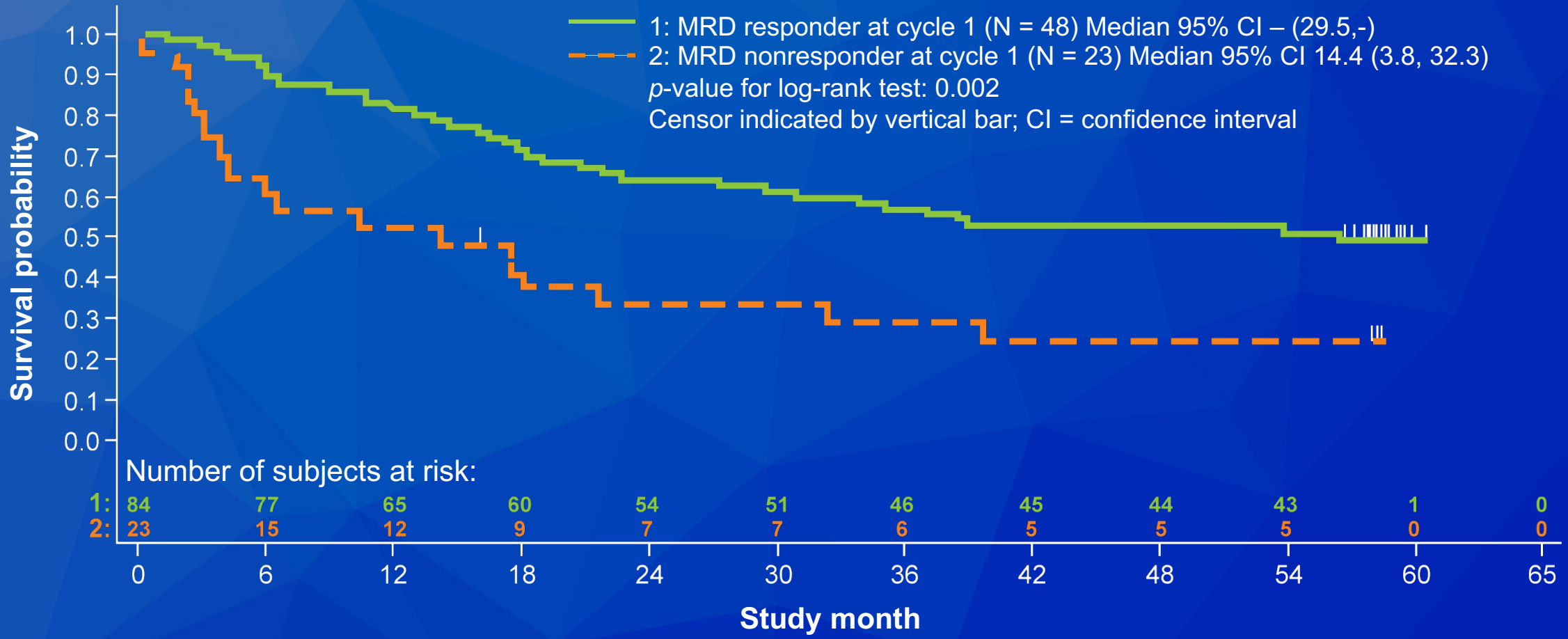
Editorial — Dr Levis (continued)

While virtually all major academic centers treating this disease use MRD in management of ALL, the exact use varies widely. At our center, we use flow-based MRD. A typical scenario might be as follows. A 31-year-old patient with Ph- B-ALL is treated according to a pediatric regimen. After induction and consolidation, a bone marrow biopsy reveals MRD at a level of 0.06%. Planning for an allogeneic transplant gets under way, and a cycle (or two) of blinatumomab is administered. The bone marrow is now MRD-negative, and the patient undergoes transplant. It is assumed that having a blinatumomab-induced MRD-negative marrow will improve outcomes from the transplant — but that is only an assumption, and really requires prospective clinical data for validation.

Blinatumomab for Minimal Residual Disease (MRD) in Adults with B-Cell Precursor Acute Lymphoblastic Leukemia (BCPALL): Median Overall Survival (OS) Not Reached at 5 Years for Complete MRD Responders

Goekbuget N et al.
Proc EHA 2019;Abstract S1619.

Blinatumomab in B-Cell ALL: Survival According to MRD Response



Goekbuget N et al. *Proc EHA* 2019;Abstract S1619.

ECOG-E1910: Ongoing Phase III Trial Design

Eligibility (N = 488)

- Newly diagnosed B-lineage ALL
- BCR-ABL-negative disease
- No concurrent active cancer
- No history of recent myocardial infarction (within 3 months)
- ECOG PS 0-3

R

- **Chemotherapy**
- **Blinatumomab + chemotherapy**

Primary endpoint: Overall survival

www.clinicaltrials.gov (NCT02003222). Accessed September 2019.

Editorial — Dr Levis

This abstract provides follow-up data from the BLAST study, in which patients with B-ALL in morphologic remission but with MRD were treated with blinatumomab. Previously this group reported that 78% of these patients achieved MRD negativity with blinatumomab treatment. The issue is whether or not that results in an improvement in survival. The median survival of the 84 MRD-negative patients wasn’t reached, whereas it was 14.4 months for those failing to become MRD negative after blinatumomab. This result implies that “scrubbing” a marrow clean of MRD with blinatumomab is a good thing. However, everyone received blinatumomab, and the persistent MRD in the “non-responders” may have just been a marker of worse disease. The simplest explanation, however, is that the elimination of MRD by blinatumomab is what resulted in the improved outcome.

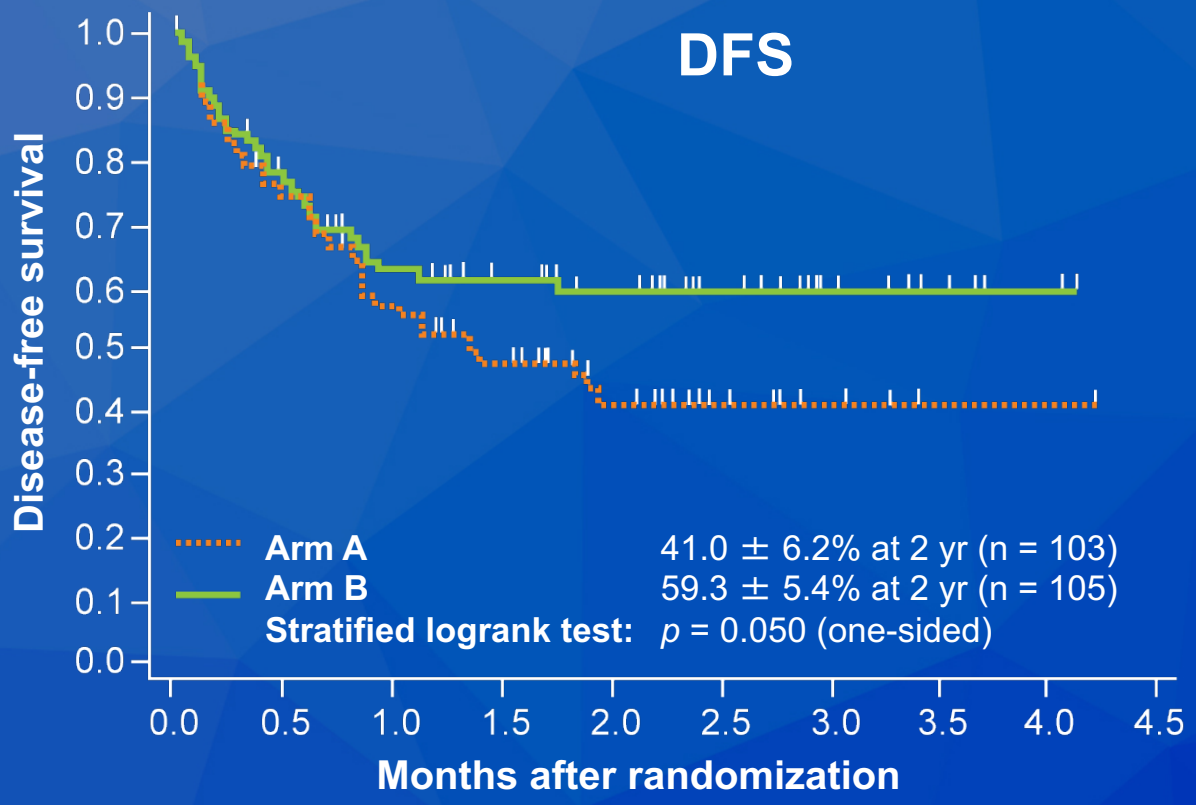
Editorial — Dr Levis (continued)

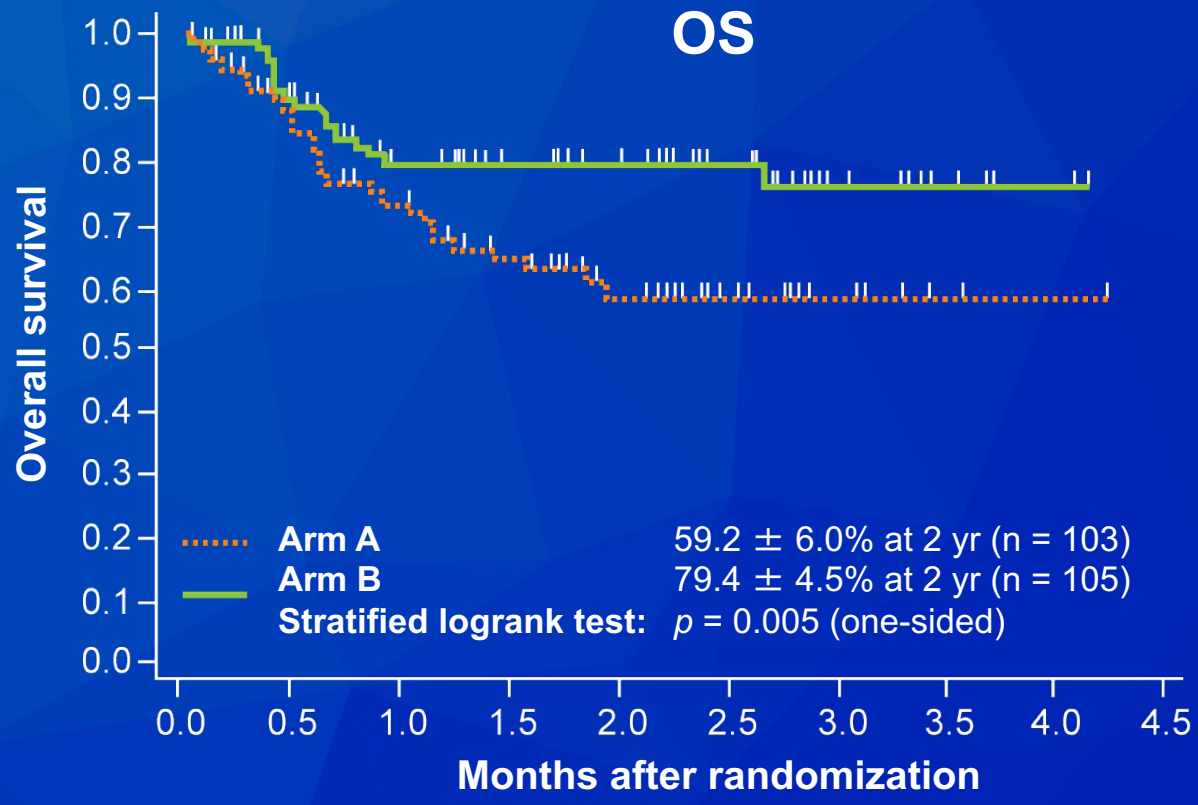
Randomized data is really what is needed here, and the results of the ECOG-E1910 trial, which has just finished accrual in the US, may provide that data. While blinatumomab is often very well tolerated, there is still likely some underlying toxicity — 74 patients in the BLAST study went to transplant after blinatumomab, with a 36.5% rate of treatment-related mortality. This is quite a high rate, and one wonders if depletion of immunoglobulin (an effect of blinatumomab) increases transplant risk.

A Randomized Phase 3 Trial of Blinatumomab vs. Chemotherapy as Post-Reinduction Therapy in High and Intermediate Risk (HR/IR) First Relapse of B-Acute Lymphoblastic Leukemia (B-ALL) in Children and Adolescents/Young Adults (AYAs) Demonstrates Superior Efficacy and Tolerability of Blinatumomab: A Report from Children's Oncology Group Study AALL1331

Brown PA et al.
ASH 2019;Abstract LBA-1.

AALL1331: Survival Outcomes at a Median Follow-Up of 1.4 Years





Arm A = pts received 2 intensive chemotherapy blocks of UKALLR3; Arm B = pts received two 4-week blocks of blinatumomab, each followed by 1 week of rest

- Among patients with detectable MRD (≥0.01%) at the completion of Block 1 chemo, the proportion with undetectable MRD (<0.01%) after Block 2 (Arm A) vs. Blina cycle 1 (Arm B) was 21% vs. 79% ($p < 0.0001$).
- The rates of MRD response were similar with Block 3 or Blina cycle 2.

Brown PA et al. ASH 2019;Abstract LBA-1.

AALL1331: Safety

Select Grade ≥3 AEs	Arm A (UKALLR3 Chemo)		Arm B (Blinatumomab)	
	Block 2	Block 3	Cycle 1	Cycle 2
Febrile neutropenia*	44%	46%	4%	0
Infections*	41%	61%	10%	11%
Sepsis*	14%	21%	1%	2%
Mucositis	25%	7%	0	1%
CRS	NR	NR	1%	0
Seizure	NR	NR	1%	0
Other neurotoxicity⁺	NR	NR	2%	2%

* $p < 0.001$; ⁺Including cognitive disturbance, tremor, ataxia and dysarthria

- All blinatumomab-related AEs fully resolved
- The rate of patients successfully proceeding from randomization to HSCT (data cut-off 9/30/19) was strikingly different between arms.
- On Arm A, only 45% (44 of 98 who received randomized therapy) proceeded to HSCT.
- On Arm B, 73% (75 of 103 who received randomized therapy) proceeded to HSCT ($p < 0.0001$).

Brown PA et al. ASH 2019;Abstract LBA-1.

Editorial — Dr Stone

Allogeneic transplant is generally considered the treatment of choice for patients with pre-B-cell ALL who relapse, except perhaps in younger patients who achieve MRD negativity after reinduction chemotherapy. However, allogeneic stem cell transplantation is not possible in all patients and carries risks of mortality and significant long-term morbidities. Could the use of the CD3-CD19 bispecific antibody blinatumomab be better salvage induction chemotherapy, leading to better post-transplant outcomes? This study compared disease-free survival of those aged 1-30 with pre-B-cell ALL with early relapse or later relapse with MRD after reinduction receiving either two intensive chemotherapy blocks or two four-week blocks of blinatumomab. After receipt of randomized therapy, patients on both arms were to proceed to stem cell transplant. The trial was stopped early because there was improved disease-free survival, superior overall survival, lower toxicity and superior MRD clearance rates in those randomized to blinatumomab.

Editorial — Dr Stone (continued)

Specifically, the two-year disease-free survival was 59% for those on blinatumomab and 41% on those who received chemotherapy. Moreover, blinatumomab was much better in achieving undetectable MRD (0.1% and sensitivity) compared to salvage chemotherapy. There were four deaths on the chemo arm and no deaths with blinatumomab. A few patients on blinatumomab did experience short-lived cytokine release or neurological side effects. The rate of proceeding to stem cell transplant was significantly greater in those randomized to blinatumomab (73% vs 45%).

The results of this study are not surprising given the fact that blinatumomab “beat” chemotherapy in relapsed adults with ALL. Nonetheless, this represents a practice-changing trial for patients up to age 30 with B-ALL. The standard of care for many relapsed pediatric and adolescent/young adults with B-ALL should be blinatumomab (rather than chemotherapy) followed by stem cell transplant.

End of Phase I Results of ZUMA-3, A Phase 1/2 Study of KTE-X19, Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Adult Patients (Pts) with Relapsed/Refractory (R/R) Acute Lymphoblastic Leukemia (ALL)[1]

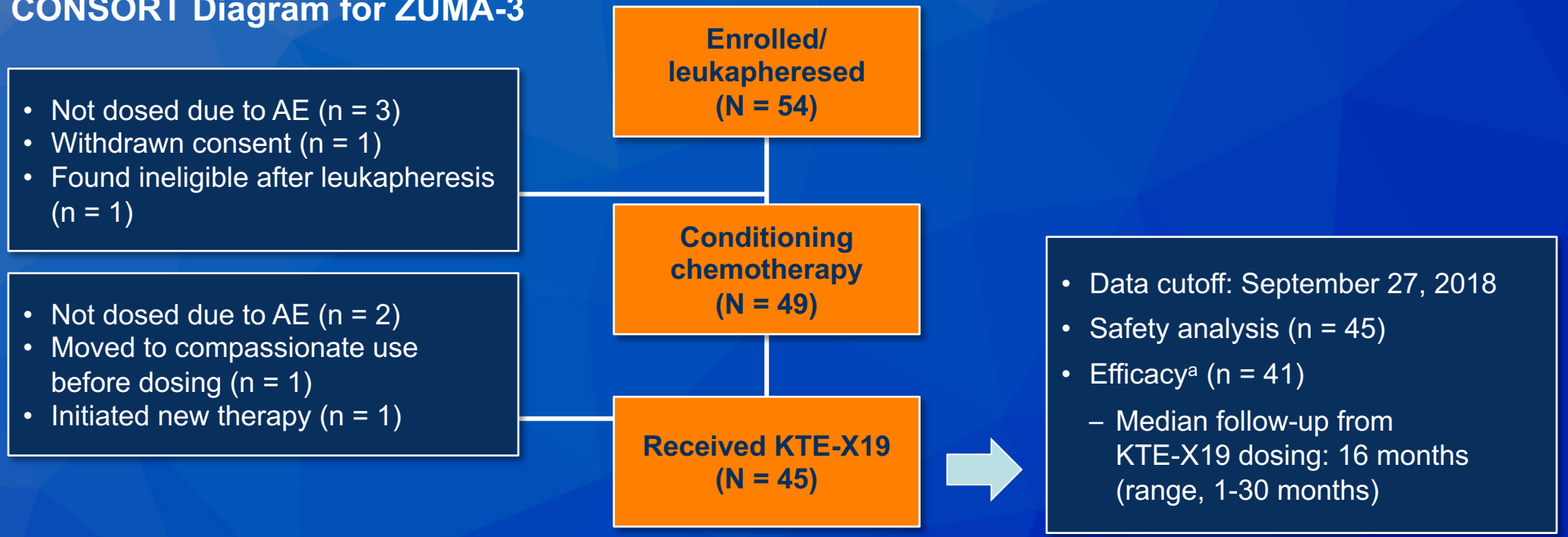
KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T Cell Therapy, in Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia: End of Phase 1 Results of ZUMA-3[2]

[1] Shah BD et al.
Proc ASCO 2019;Abstract 7006.

[2] Shah BD et al.
Proc EHA 2019;Abstract PS945.

ZUMA-3: A Phase I/II Trial Design

CONSORT Diagram for ZUMA-3



- 100% manufacturing success for all enrolled/leukapheresed patients
  - Only 2 patients required additional leukapheresis for product manufacturing
- Overall, 83% of patients received KTE-X19
- The primary reason for not receiving KTE-X19 was AEs (n = 5)

[a] Patients were eligible for efficacy analysis after 8 weeks of follow-up; the efficacy-evaluable population includes all patients with a minimum of 2 months of follow-up.
AE = adverse event

Shah BD et al. *Proc ASCO* 2019;Abstract 7006.

ZUMA-3: Incidence of Treatment-Emergent Cytokine Release Syndrome (CRS)- and Neurologic Event (NE)-Specific Symptoms

	2 x 10^6 (n = 6)		1 x 10^6 (n = 23)		0.5 x 10^6 (n = 16)		Overall (N = 45)	
Event, %	**Any**	**Grade ≥3**	**Any**	**Grade ≥3**	**Any**	**Grade ≥3**	**Any**	**Grade ≥3**
Any CRS[a,b]	**100**	**50**	**100**	**26**	**81**	**25**	**93**	**29**
Pryrexia	100	50	87	39	63	31	80	38
Hypotension	67	50	74	39	50	19	64	33
Sinus tachycardia	33	0	43	4	13	0	31	2
Chills	17	0	39	0	13	0	27	0
Any NE[b]	**83**	**50**	**87**	**43**	**63**	**25**	**78**	**38**
Encephalopathy	67	33	48	26	13	13	38	22
Confusional state	33	17	39	4	31	13	36	9
Tremor	17	0	35	0	25	0	29	0

- Of 41 patients with ≥2 months of follow-up, 68% had CR/CRi and 73% had undetectable MRD.

[a] CRS was graded per a modified grading system proposed by Lee DW, et al. *Blood* 2014;124:188-95; [b] Individual symptoms of CRS and NEs were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03.
CRS = cytokine release syndrome; NE = neurologic event

Shah BD et al. *Proc ASCO* 2019;Abstract 7006; Shah BD et al. *Proc EHA* 2019;Abstract PS945.

Tisagenlecleucel Appears Effective and Safe in Pediatric and Young Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia with High-Risk Cytogenetic Abnormalities

Grupp S et al.
Proc EHA 2019;Abstract S1618.

ELIANA and ENSIGN Phase II Studies of Tisagenlecleucel in Relapsed/Refractory ALL: Pooled Efficacy Data in Patients with High-Risk (HR) Cytogenetic Abnormalities

Clinical variable	N = 29 With HR cytogenetics	N = 108 Without HR cytogenetics
Confirmed remission per IRC assessment MRD-negative	19 (65.5%) 18	— —
Median duration of response 12-mo relapse-free probability 24-mo relapse-free probability	Not reached 74.6% 74.6%	— 61.7% 58.5%
Median overall survival 12-mo survival probability 24-mo survival probability	Not reached 74.9% 66.6%	— 70.7% 58.8%

Grupp S et al. *Proc EHA* 2019;Abstract S1618.

OBERON: Ongoing Phase III Trial Design

Target accrual (N = 220)

- Patients with CD19-expressing B-cell precursor ALL ***AND***
  - Untreated first or second relapse **or**
  - Refractory disease to primary induction therapy ***or***
  - Refractory disease to first salvage therapy ***or***
  - Relapse after allogeneic stem cell transplant
- No untreated first relapse of ALL more than 24 months after initial diagnosis

R

- **Tisagenlecleucel**
- **Blinatumomab or inotuzumab**

Primary endpoint: Overall survival

www.clinicaltrials.gov (NCT03628053). Accessed September 2019.

Editorial — Dr Levis

This abstract reports the results of a post-hoc subgroup analysis of outcomes from two CAR T-cell (tisagenlecleucel) trials enrolling pediatric and young adult relapsed/refractory B-ALL patients. The subgroup of interest was defined as having high-risk cytogenetics/mutations (BCR-ABL, MLL, CRLF2, TP53, etc). They identified 29 such patients and reported that 19 of these achieved a CR, 18 of whom were MRD negative. The 24-month survival for the patients in this high-risk group ended up actually being higher than for those patients lacking high-risk features. This data highlights the remarkable efficacy of this therapeutic approach — provided patients can actually make it through the long process of getting to a CAR T-cell infusion.