Tailoring Induction and Maintenance Therapy for Younger Patients with AML without Targetable Tumor Mutations

Mark Levis MD PhD
Director, Adult Leukemia Service
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University

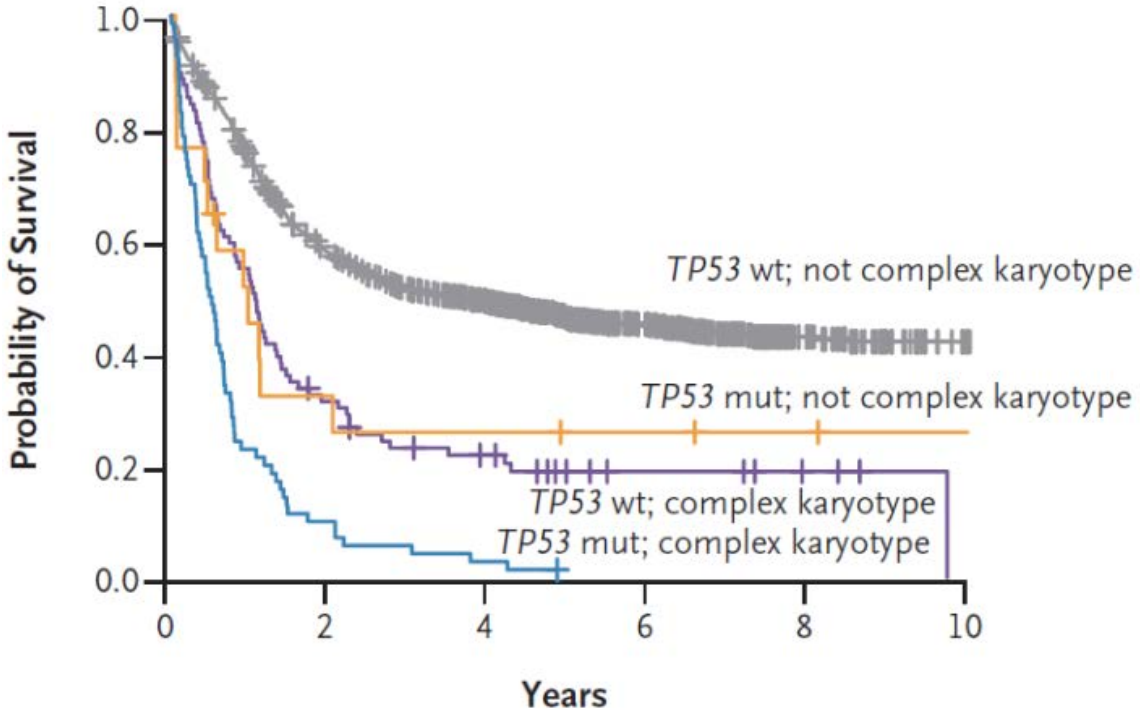
Case 1

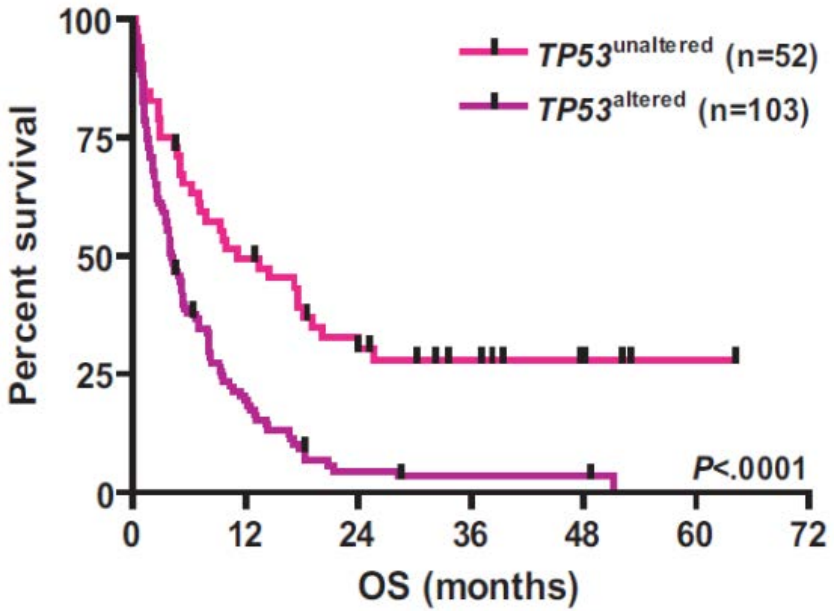
- 70 yo man, recently retired
  - Travelling around country with spouse
- Notices unusual fatigue while hiking...
  - …and an infected tooth not responding to antibiotics.
- Sees internist on return from trip
  - Blood work ordered:
    - WBC 2.2, ANC 670, Hgb 9.1, platelets 143
- Referred to a hematologist
- Bone marrow biopsy:
  - AML with dysplastic granulocytes
  - 60% blasts
- Molecular analysis:
  - Monosomal/complex karyotype
    - 45XY, -3; del5q22q33; t(3;6)(q26;p25); t(9;15)(p24;q22); -14; 15; add (17)(p11.2);-22
  - NGS:
    - TP53 H179Q VAF 36.8%

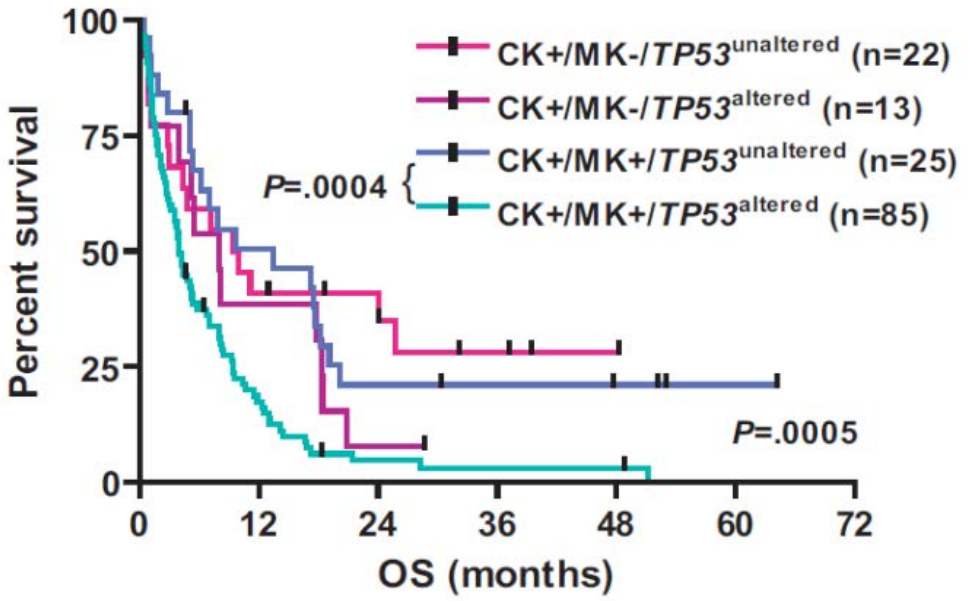
Courtesy of Mark Levis, MD, PhD

AML with complex karyotype and TP53 mutations treated with intensive chemotherapy:

Very short median survival…







Courtesy of Mark Levis, MD, PhD

N Engl J Med 2016;374:2209-21

Blood. 2012;119:2114-2121

Treatment options (Case 1 cont.)

- Supportive care
- Clinical trial
- Decitabine 20 mg/m^2/day x 10 days
- Azacitidine 75 mg/m^2/day x 7 days
- Azacitidine or decitabine + Venetoclax 400 mg/day

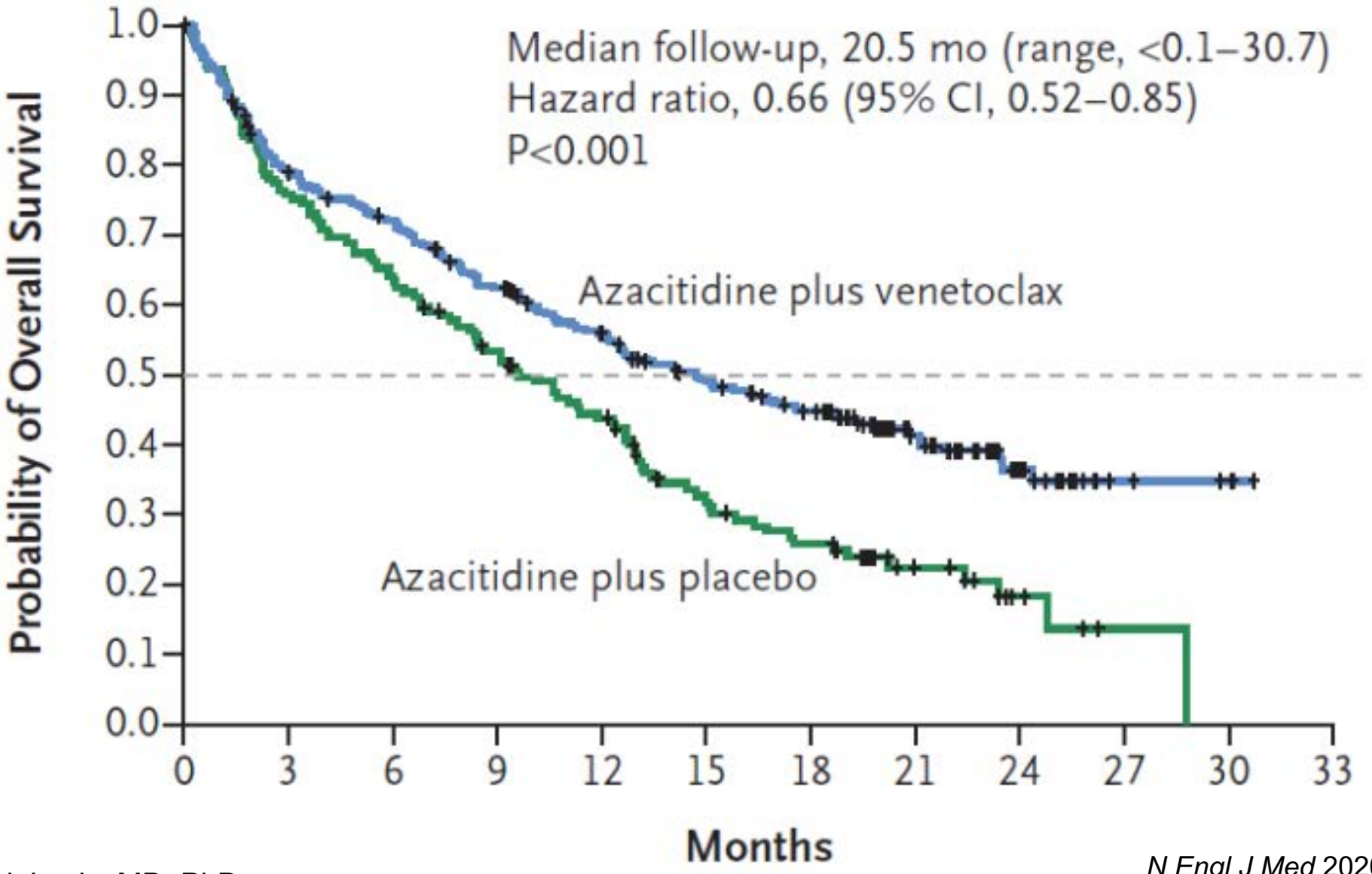
Courtesy of Mark Levis, MD, PhD

Phase III VIALE-A Trial

- Patients with newly-diagnosed AML
  - Age 75 or older…or…
  - ..”unfit” for intensive chemotherapy
- Randomization (2:1):
  - Azacitidine + venetoclax
  - Azacitidine + placebo
- Primary endpoint: Overall Survival
- 431 patients enrolled from Feb 2017 to May 2019
  - Median age 76
  - Poor-risk cytogenetics in 36%

Courtesy of Mark Levis, MD, PhD

VIALE-A Trial



N Engl J Med 2020;383:617-29

Courtesy of Mark Levis, MD, PhD

Case 1 (cont.)

Patient admitted, started on “aza/ven”

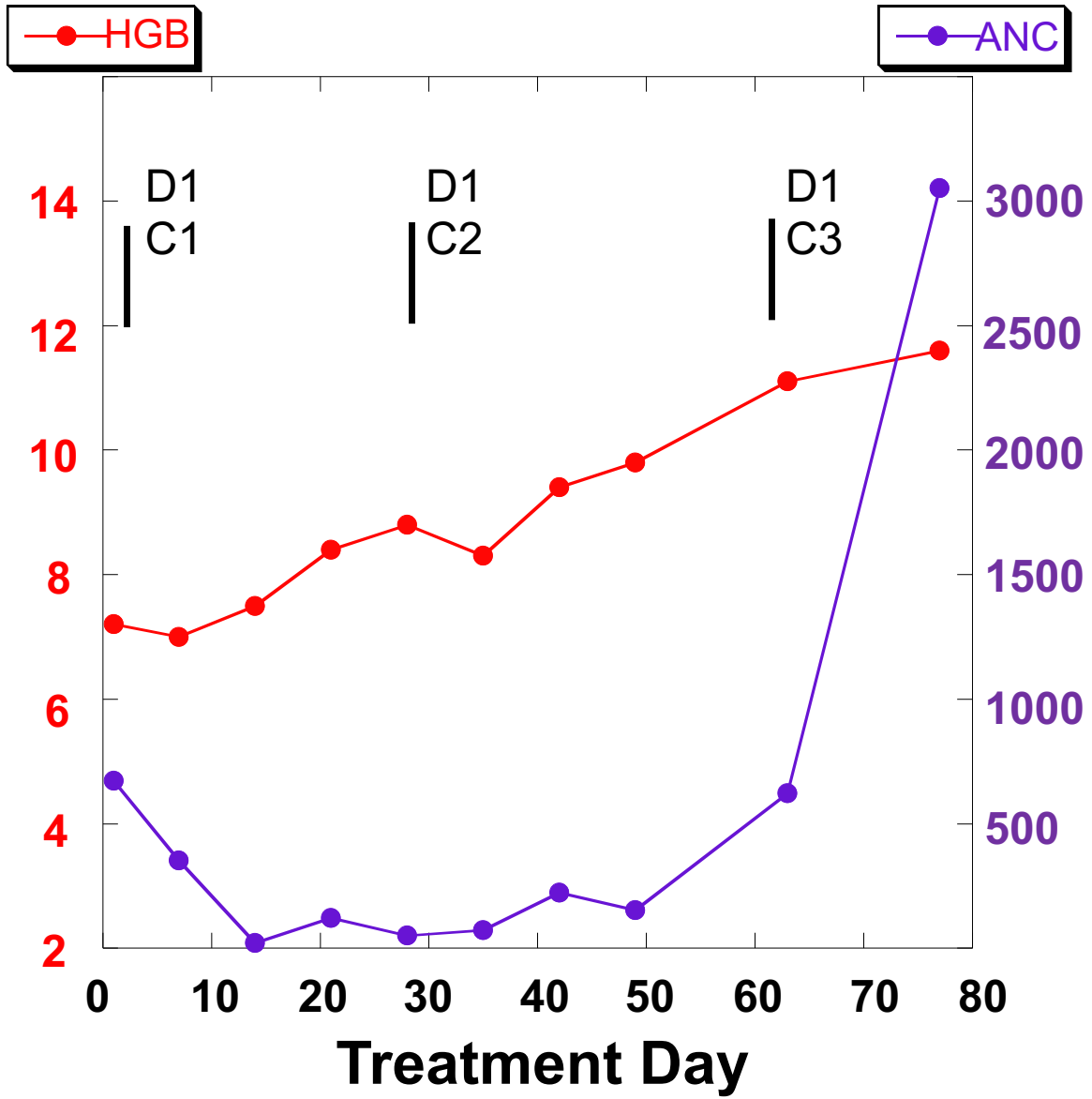
Azacitidine:
75 mg/m^2 IV daily x 7 days

Venetoclax:
100 mg Day 1
200 mg Day 2
400 mg Day 3-28

Courtesy of Mark Levis, MD, PhD

Case 1 (cont.)

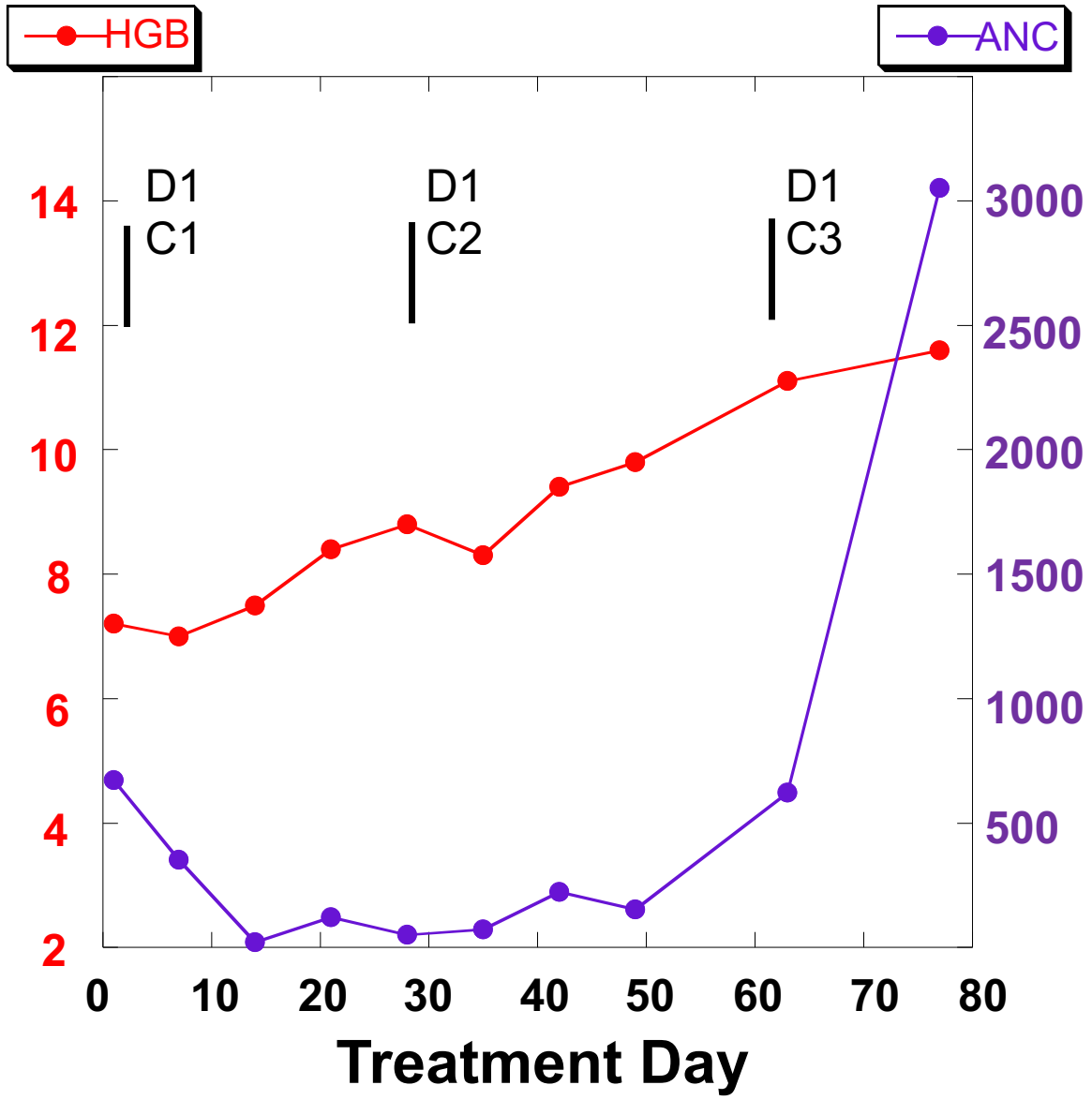
- Marrow blasts fall to 5% after cycle 1
- Marrow blasts fall to 1% after cycle 2
- Other than protocol-mandated admission on Day 1 Cycle 1, no further admissions.
  - After cycle 3, resumes active lifestyle, including travel



Courtesy of Mark Levis, MD, PhD

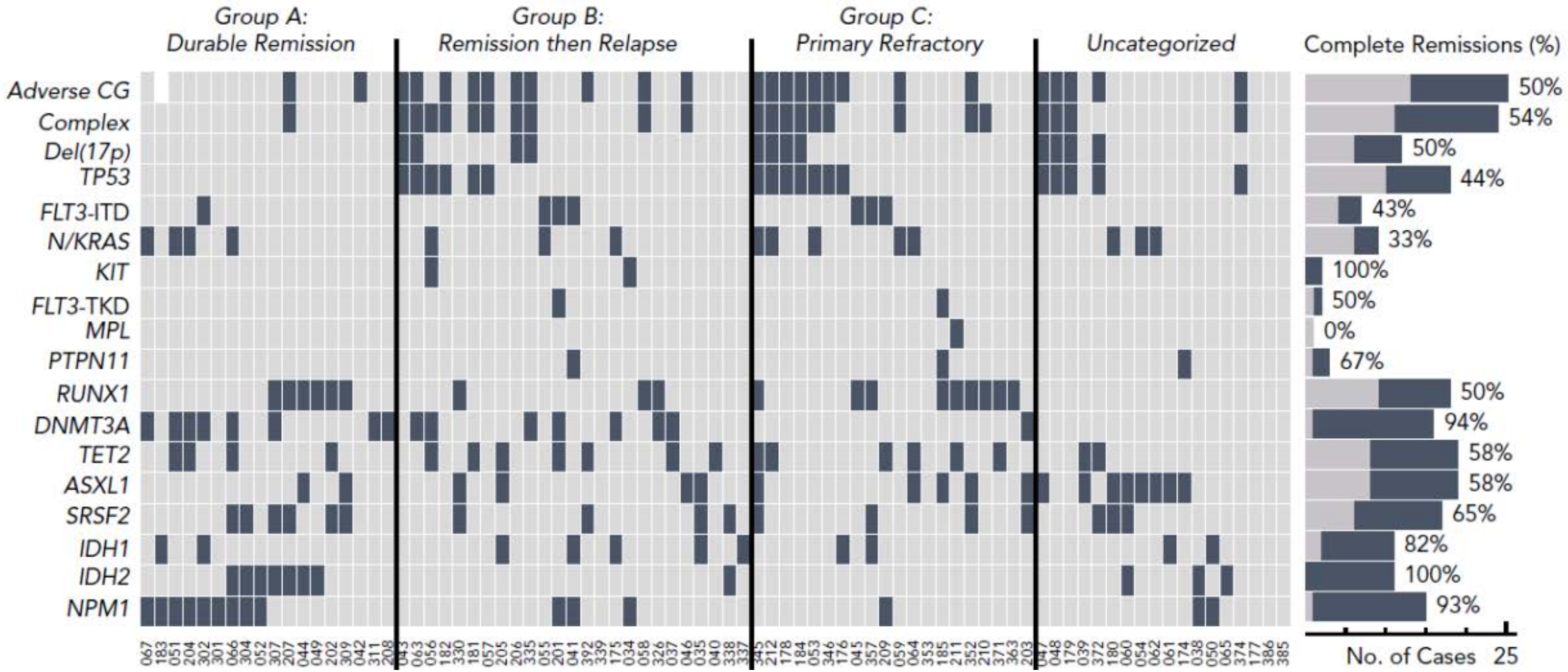
Case 1 (cont.)

- Marrow blasts fall to 5% after cycle 1
- Marrow blasts fall to 1% after cycle 2
- Other than protocol-mandated admission on Day 1 Cycle 1, no further admissions.
  - After cycle 3, resumes active lifestyle, including travel
- Completes 12 cycles, then progresses.
- Dies of progressive AML 18 months after diagnosis.



Courtesy of Mark Levis, MD, PhD

TP53 and FLT3-ITD mutations: Decreased response rate and shorter duration of response to HMA/ven



Blood. 2020;135:791-803

Courtesy of Mark Levis, MD, PhD

Case 2

- 73 yo man, still working
  - MDS (mild anemia) diagnosed three years previously, no treatment required so far
- Develops dyspnea on exertion
  - CBC shows Hgb 8.3, platelets 56K, white blood cells 26K, 40% blasts
- Diagnosed with AML
  - Normal karyotype
  - NGS: STAG2, TET2, NRAS mutations
- Initiated on azacitidine and venetoclax
- Achieves a prompt remission after 1 cycle, normalization of counts
  - Bone marrow biopsy normal, no mutations detected
- Bone marrow biopsy after 10 cycles (~14 months):
  - Mutations re-emerging, dysplasia evident
- Allogeneic transplant is offered:
  - Non-myeloablative
  - Successful engraftment

Courtesy of Mark Levis, MD, PhD

Case 2 (cont.)

- Post-transplant
  - Counts normal
  - Resumes work
- Early 2020 (2.5 years after transplant - now age 78)
  - CBC shows platelet count of 70K, 5% circulating blasts
  - Bone marrow shows 5% blasts, recurrence of STAG2 and TET2 mutations
  - Donor chimerism now 52%
- Treatment with SQ azacitidine initiated
- Counts normalize after 2 cycles
- Patient inquires:
  - “Do I have to keep coming into clinic? Are there any pills I can take…?”

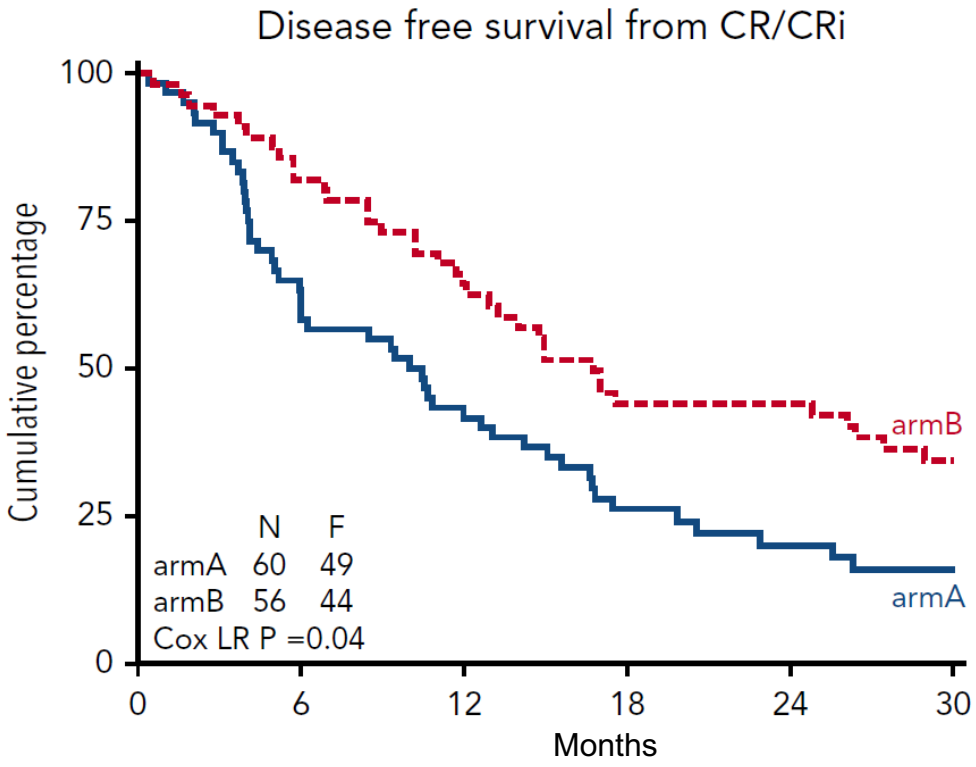
Courtesy of Mark Levis, MD, PhD

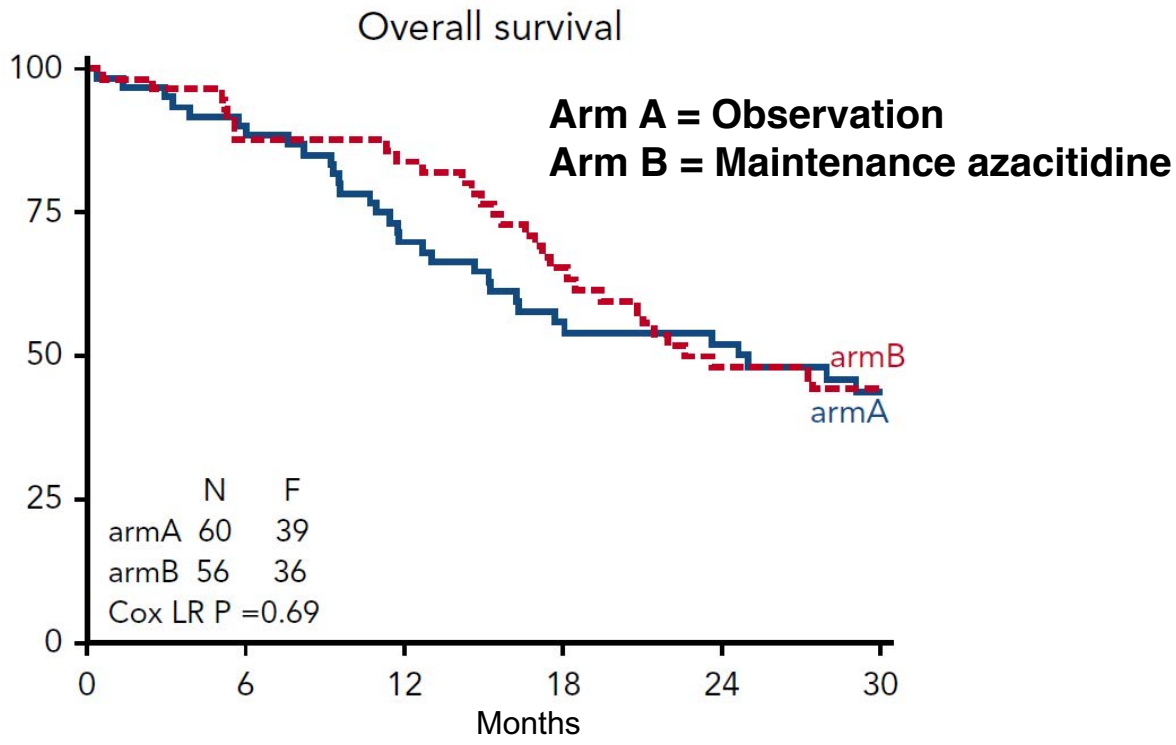
What do we know about maintenance therapy for AML?

Courtesy of Mark Levis, MD, PhD

Phase III HOVON97 Trial

- Patients with newly-diagnosed AML age 60+
- In CR1 after 2 courses of intensive chemotherapy
- Randomized to either observation or 12 cycles of azacitidine
  - Azacitidine 50 mg/m^2/day x 5 days q4 weeks



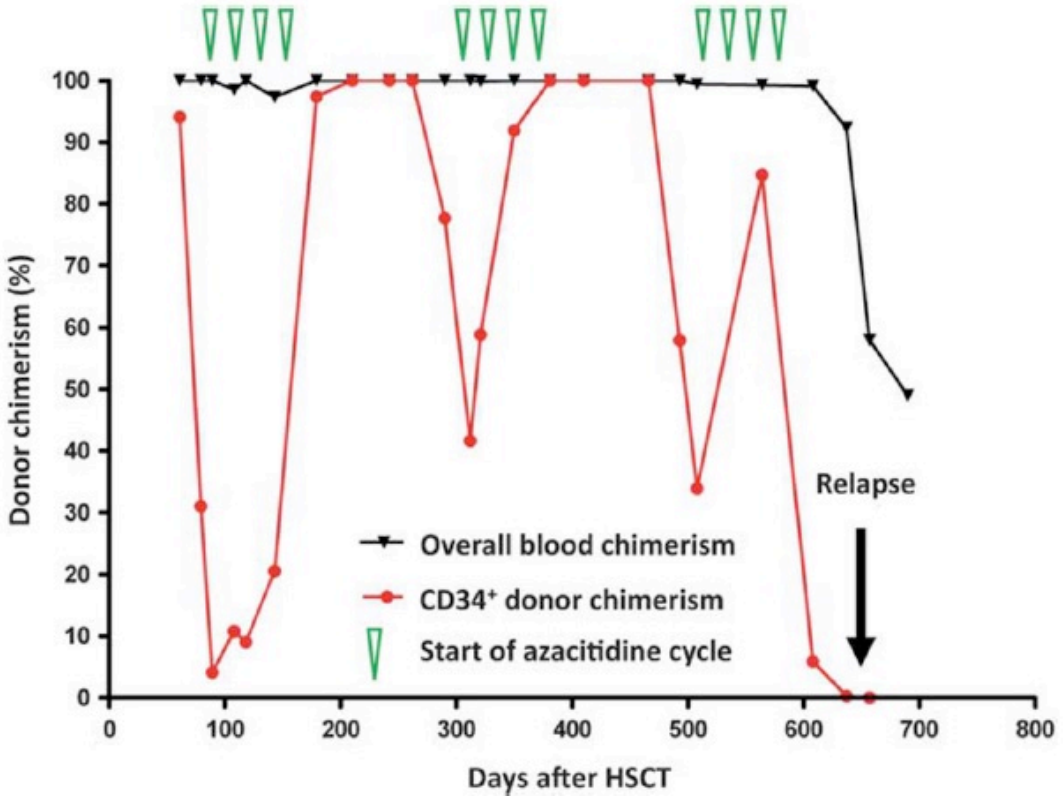


Courtesy of Mark Levis, MD, PhD

Huis G et al. Blood. 2019; 133:1457-1464

RELAZA Trial

- Patients with AML post-allogeneic transplant in early relapse
  - Not in hematologic relapse- blasts < 5%, decreasing donor chimerism
- 4 cycles of azacitidine, 75 mg/m^2/day x 7 days, q4 weeks
  - If response, could repeat at disease progression



Courtesy of Mark Levis, MD, PhD

Leukemia. 2012; 26:381-389

Evidence-Based Focused Review

blood

Maintenance therapy in acute myeloid leukemia: an evidence-based review of randomized trials

Armin Rashidi,[1] Roland B. Walter,[2-4] Martin S. Tallman,[5] Frederick R. Appelbaum,[2,6] and John F. DiPersio[1]

"…the benefit of maintenance seems more apparent after suboptimal induction and consolidation. This may be relevant to patients who cannot tolerate consolidation (e.g., some elderly patients or those who develop serious complications during induction)."

Courtesy of Mark Levis, MD, PhD

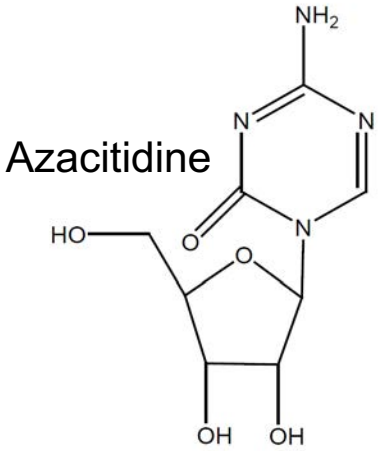
Blood. 2016; 128:763-773

Case 2 continued: Treatment options

- No further therapy until counts change again
- Continue azacitidine indefinitely, until disease progression

Any other options…?

Courtesy of Mark Levis, MD, PhD



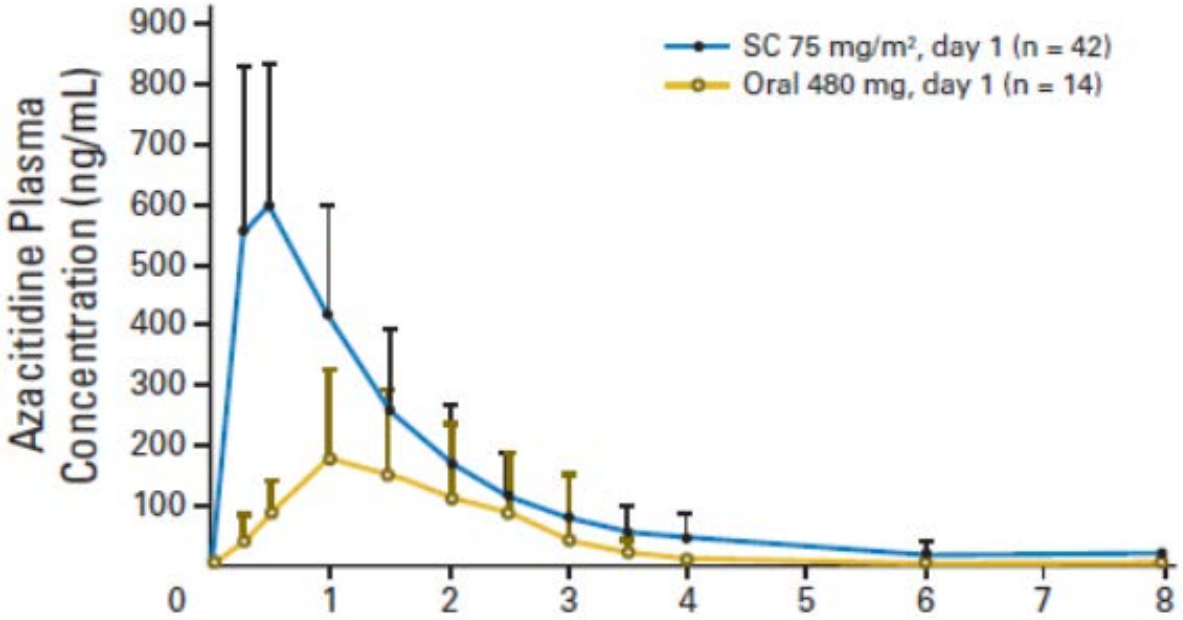
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase I Study of Oral Azacitidine in Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, and Acute Myeloid Leukemia

Guillermo Garcia-Manero, Steven D. Gore, Christopher Cogle, Renee Ward, Tao Shi, Kyle J. MacBeth, Eric Laille, Heidi Giordano, Sarah Sakoian, Elias Jabbour, Hagop Kantarjian, and Barry Skikne

J Clin Oncol. 2011; 29:2521-2527

- 45 patients with MDS or AML
- First cycle treated with SQ aza
- Second cycle and beyond:
  - Oral azacitidine (CC-486)
- Overall response rate in untreated patients:
  - 73%



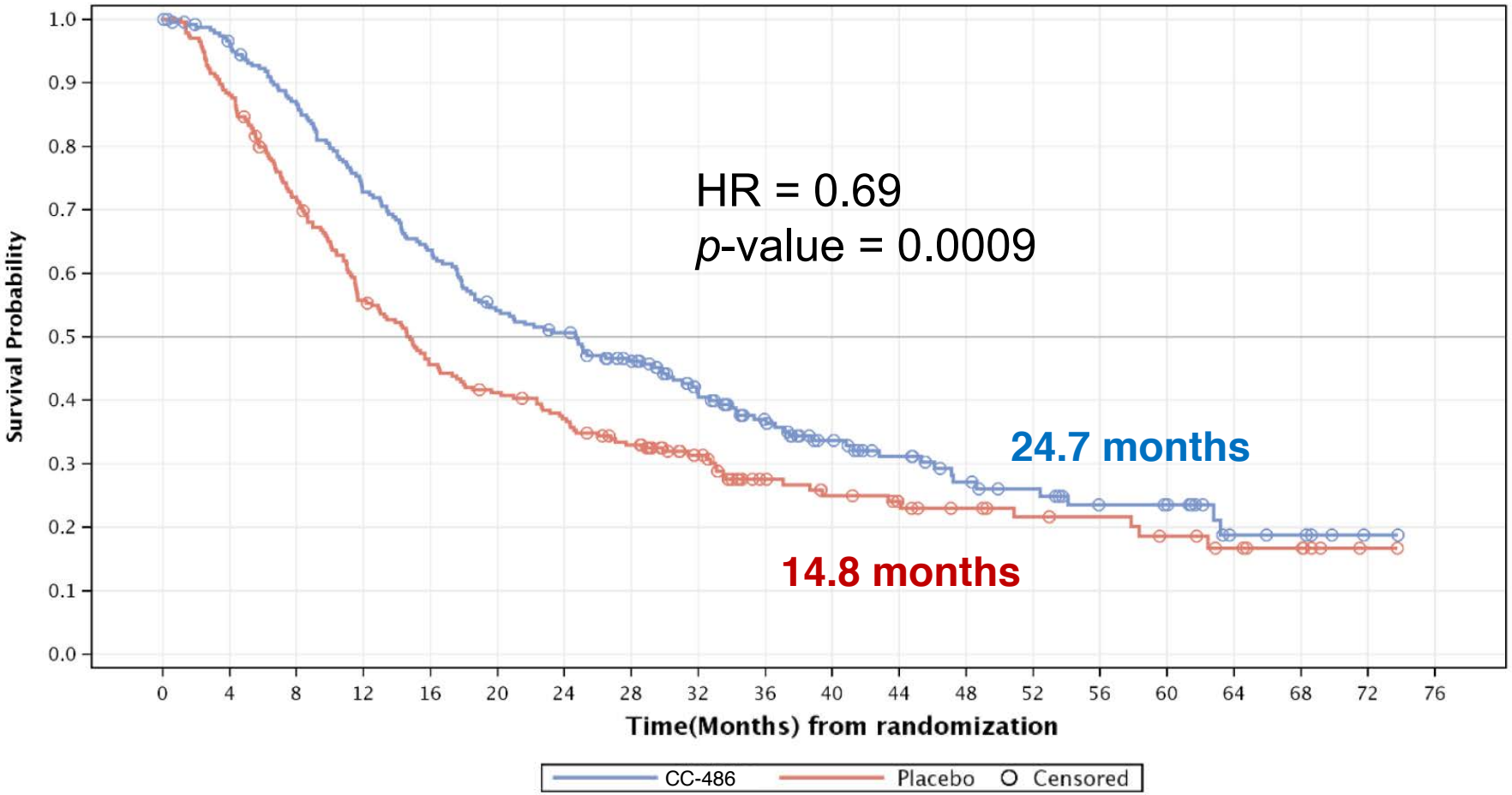
Courtesy of Mark Levis, MD, PhD

The Phase III QUAZAR AML-001 Study

- Multi-center, randomized, double-blinded, placebo-controlled
- Patients age 55+ with AML
  - Within 4 months of achieving CR or CRi after intensive induction
- 472 randomized
  - Median age 68
  - Most (65%) had received 0 or 1 cycle consolidation
- Primary endpoint:
  - Overall survival

Courtesy of Mark Levis, MD, PhD

Maintenance therapy with oral azacitidine after partially-completed intensive therapy for AML prolongs survival



On September 1, 2020, the FDA approved oral azacitidine (CC-486) for the continued treatment of AML in patients who attain first complete remission (CR) or CR with incomplete blood count recovery (CRi) after intensive induction chemotherapy and who are not able to complete intensive curative therapy.

Approval was based on the results of the QUAZAR AML-001 trial.

Courtesy of Mark Levis, MD, PhD

Case 2 (cont.)

- At age 78, in early relapse 2.5 years post-transplant
- Counts normalized after 2 cycles of SQ azacitidine
- Begins therapy with oral azacitidine (CC-486)

Courtesy of Mark Levis, MD, PhD

Conclusions

- AML patients without obvious targetable mutations can still clearly benefit from newer induction regimens with targeted drugs.
  - Venetoclax with azacitidine/decitabine is a “targeted” regimen with broad applicability.
- Maintenance therapy with a hypomethylating agent seems to be most effective in AML patients who have been unable to complete a standardized course of intensive chemotherapy
- Oral azacitidine appears to offer a more patient-friendly version of this type of maintenance.
- Question going forward:
  - Can oral azacitidine (or oral decitabine) be substituted for the SQ/IV versions in a venetoclax-based induction?

Courtesy of Mark Levis, MD, PhD