Treatment of Adult AML Patients Appropriate for Intensive Therapy: It isn't just 7+3 anymore!

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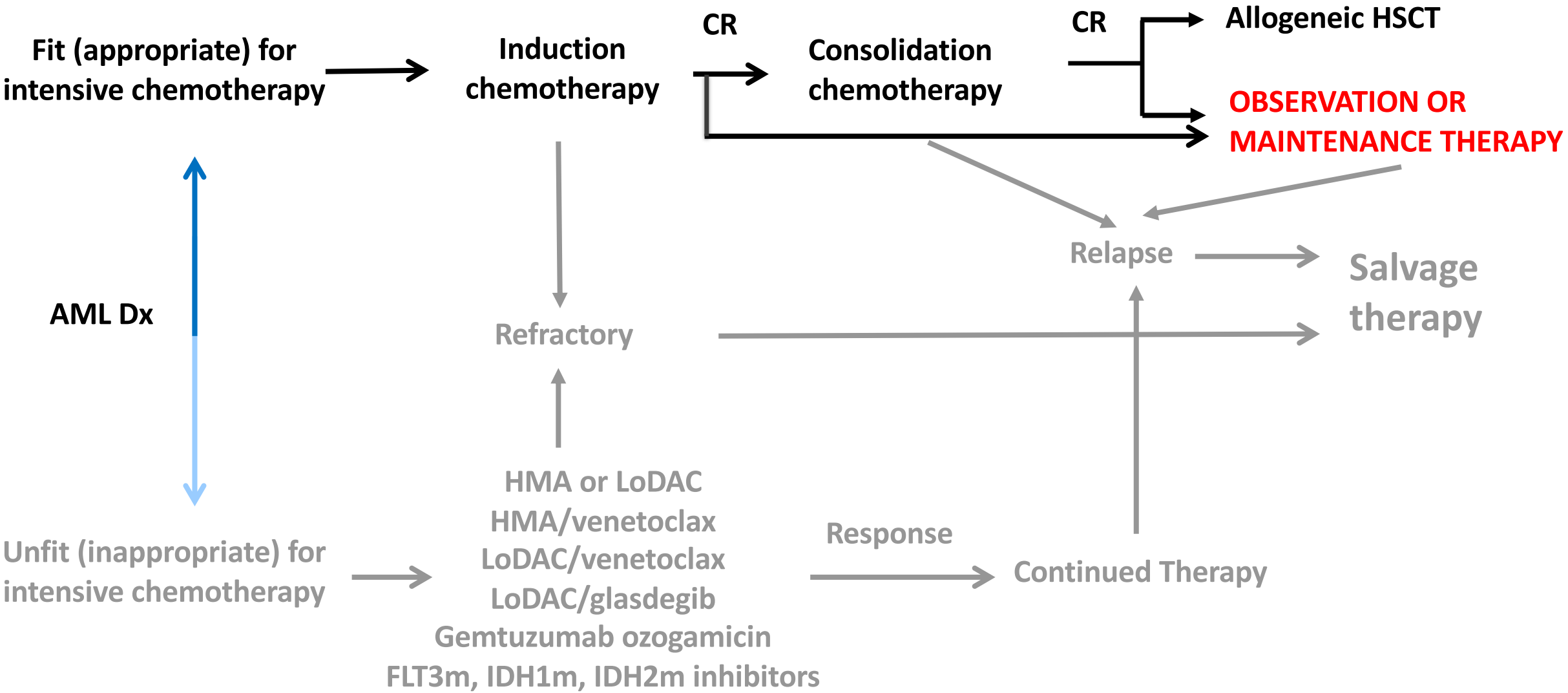
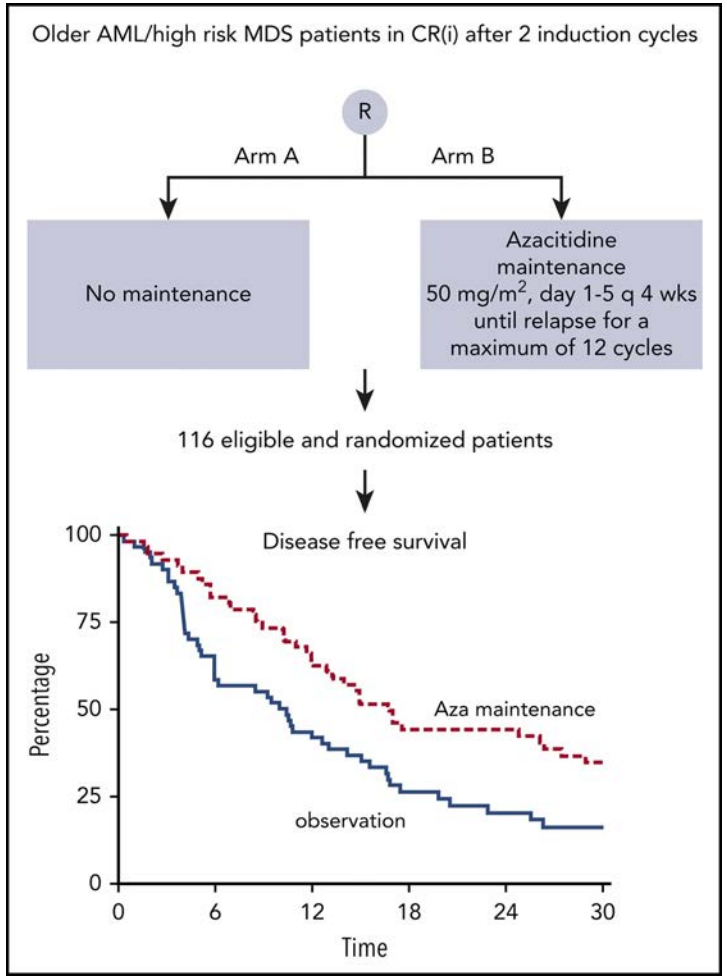
The Current AML Treatment Algorithm



Case #1: Maintenance therapy for AML

- 73-year-old man without any significant medical history presented with pancytopenia and peripheral blood myeloblasts.
- Bone marrow biopsy: acute myeloid leukemia with normal karyotype
- Myeloid gene panel detects six pathogenic mutations: NPM1, FLT3 ITD (AR 0.08), IDH2 R140Q, JAK2 V617F, SRSF2 P95R, and TET2 A1863V
- He received cytarabine and daunorubicin (7+3) with midostaurin.
- He achieved first complete remission following one cycle induction therapy.
- He then received two cycles of cytarabine 1.5 gram/m^2/dose x 6 doses
- End-of-consolidation bone marrow biopsy: 10-20% cellularity, trilineage hematopoiesis, focal reticulin fibrosis
  - Flow cytometry negative for leukemic blast population
  - SRSF2 (VAF 41.5%), JAK2 (VAF 5.6%) , and TET2 (VAF 27.4%) variants still present.

Randomized Maintenance Therapy with Azacitidine (Vidaza) in Older Patients (≥ 60 years of age) with Acute Myeloid Leukemia (AML) and Refractory Anemia with Excess of Blasts (RAEB, RAEB-t). Results of the HOVON97 Phase III Randomized Multicentre Study (EudraCT 2008-001290-15)

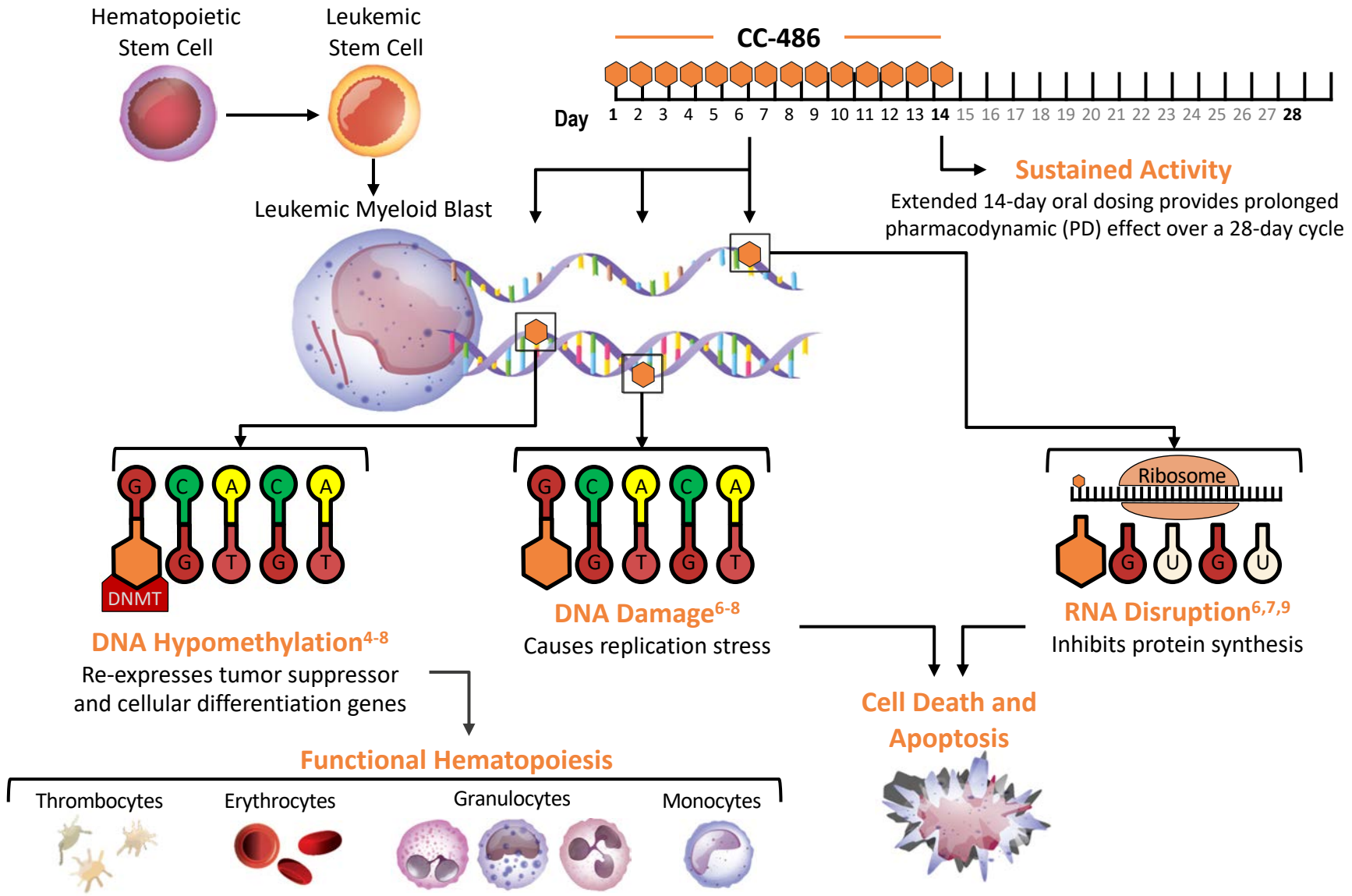


No improvement in overall survival, even if censored at time of allo HSCT

Huls G et al. *Blood* 2019; 133 (13): 1457–1464.

CC-486

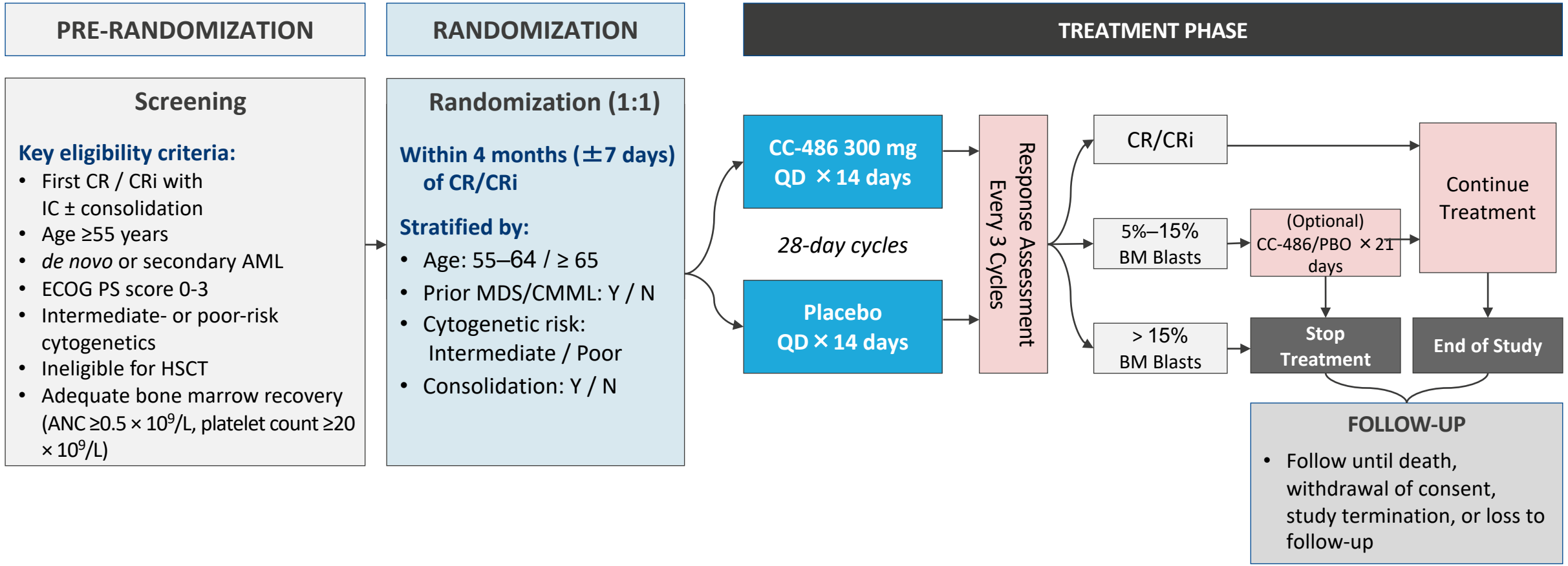
- CC-486 is an oral hypomethylating agent with a distinct PK/PD profile from injectable azacitidine[1,2]
- CC-486 has demonstrated clinical activity in patients with hematologic malignancies[1–4]
- Oral dosing of CC-486 allows for extended drug exposure during each treatment cycle to prolong therapeutic activity[1,2]
- We hypothesized that prolonged treatment with CC-486 could be effective as post-remission maintenance in AML



1. Garcia-Manero et al. *J Clin Oncol.* 2011;29(18):2521–7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. Garcia-Manero et al. *Leukemia*. 2016;30(4):889–96. 4. Savona et al. *Am J Hematol.* 2018;93(10):1199–206. 5. Streseman et al. *Mol Cancer Ther*. 2008;7:2998–3005. 6. Hollenbach et al. *PLoS One*. 2010;5(2):e9001. 7. Scott LJ. *Drugs*. 2016;76(8):889–900. 8. Stresemann C, Lyko F. *Int J Cancer*. 2008;123(1):8–13. 9. Aimiuwu et al. *Blood*. 2012;119(22):5229–38.
AML, acute myeloid leukemia; DNMT, DNA methyltransferase; PD, pharmacodynamic; PK, pharmacokinetic.

QUAZAR AML-001: Study design

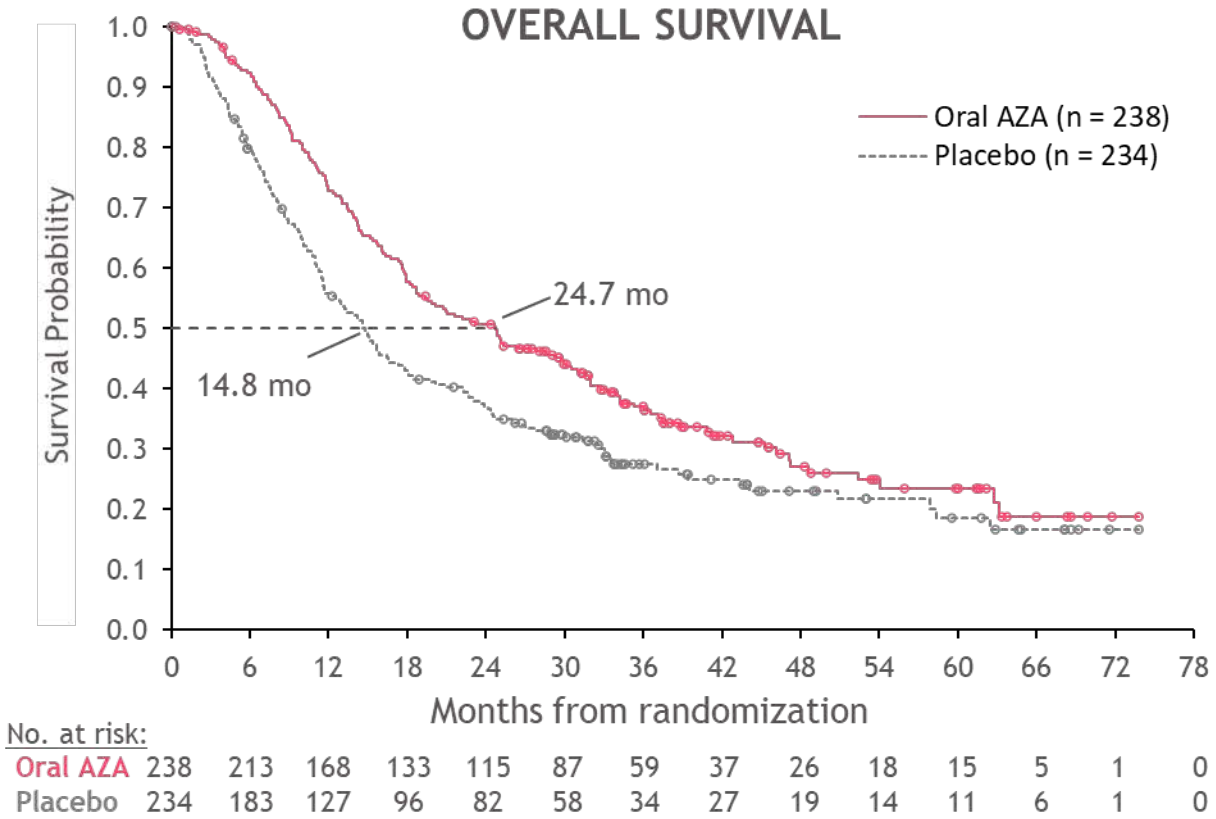
International, multicenter, placebo-controlled, double-blind, randomized, phase III study that enrolled patients from 148 sites in 23 countries (NCT01757535)

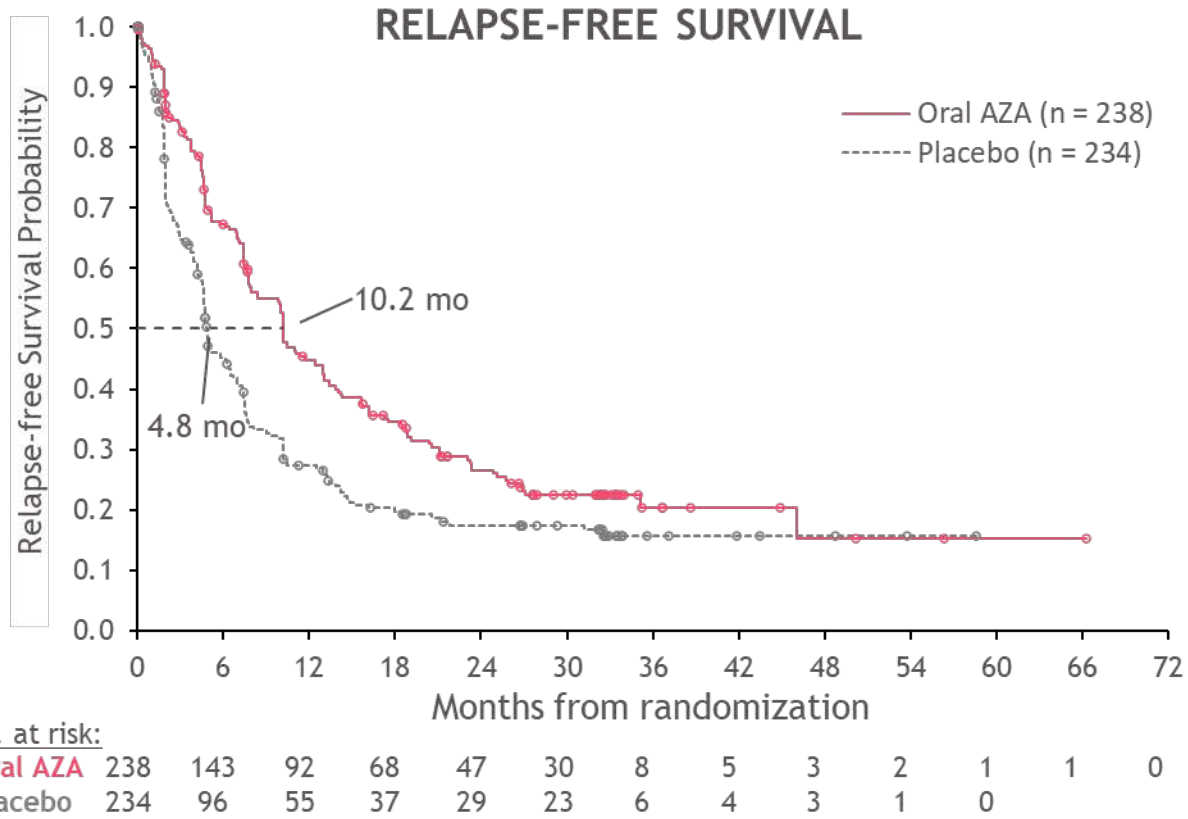


Wei A et al. *N Engl J Med* 2020; 383: 2526-37. Wei A et al. *Blood* 2019;134(Supplement2):LBA-3.

QUAZAR AML-001: Overall and Relapse-free Survival

Oral AZA 300 mg QD was associated with significantly improved overall survival (OS) (*P* = 0.0009) and relapse-free survival (RFS) (*P* = 0.0001) vs. PBO

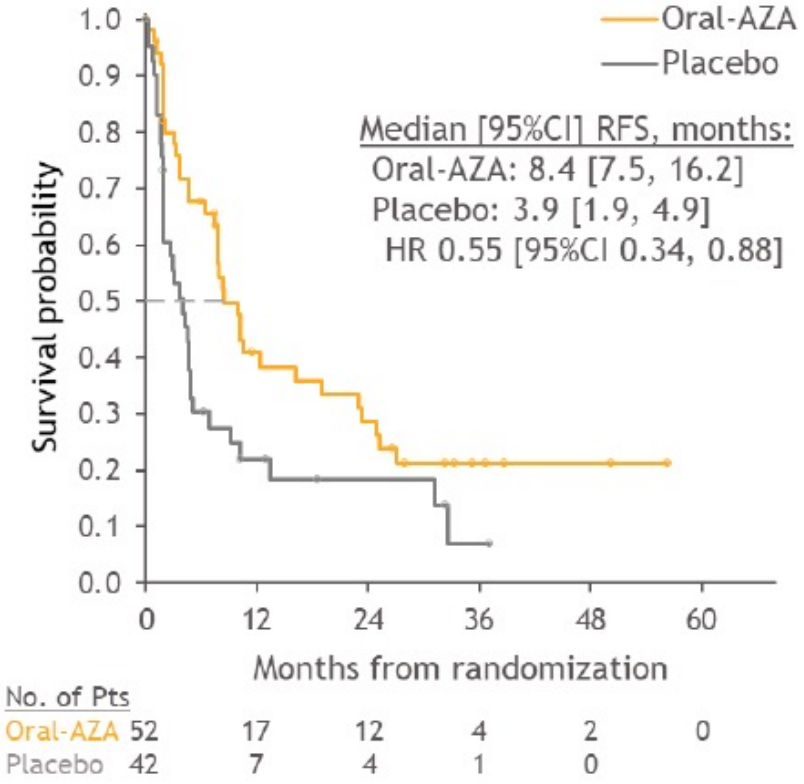




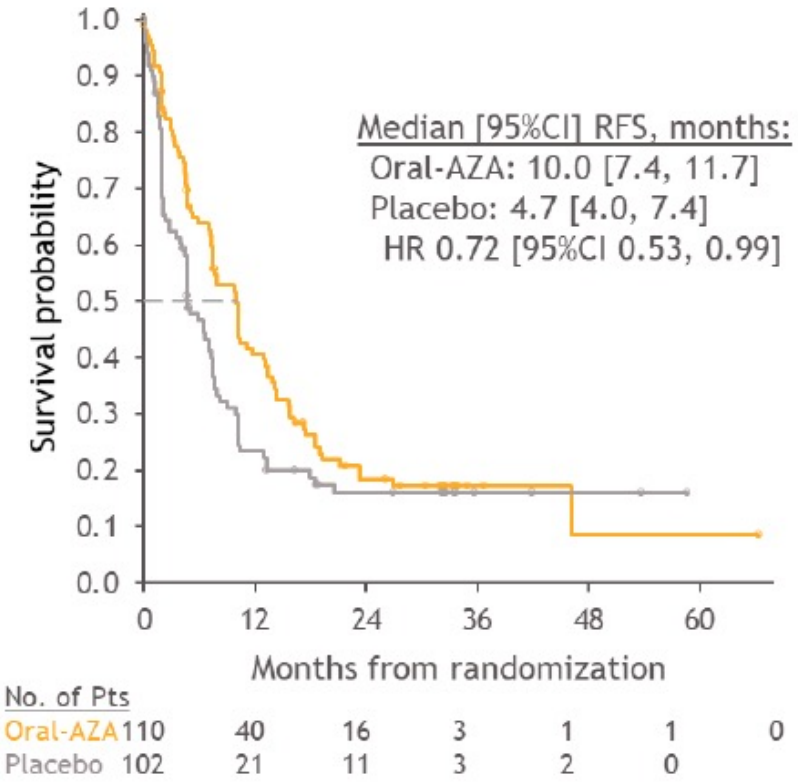
Wei A et al. *N Engl J Med* 2020; 383: 2526-37.

QUAZAR AML-001: RFS by Number of Consolidation Cycles

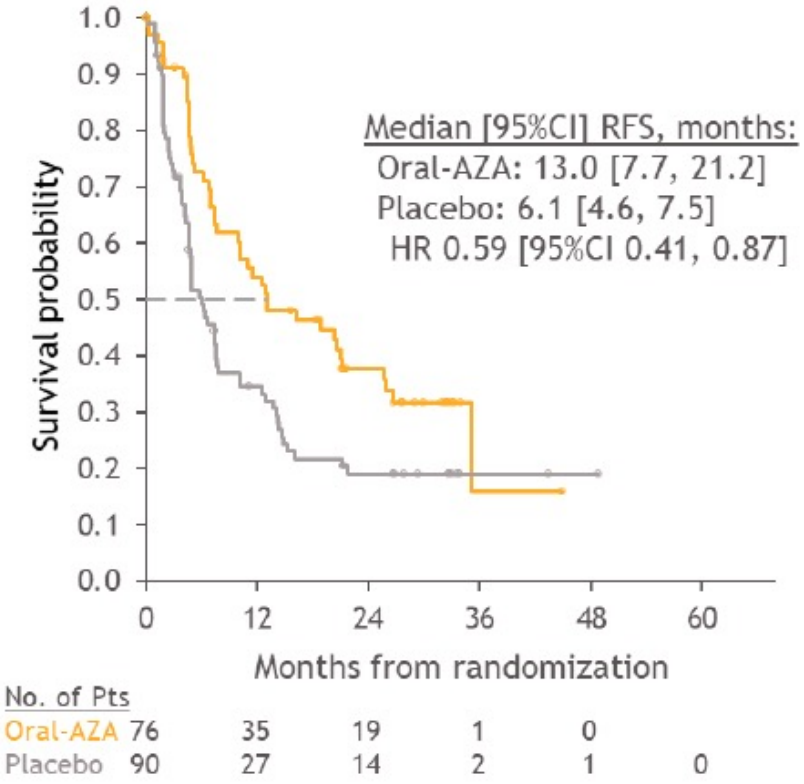
No Consolidation



1 Consolidation



≥2 Consolidations

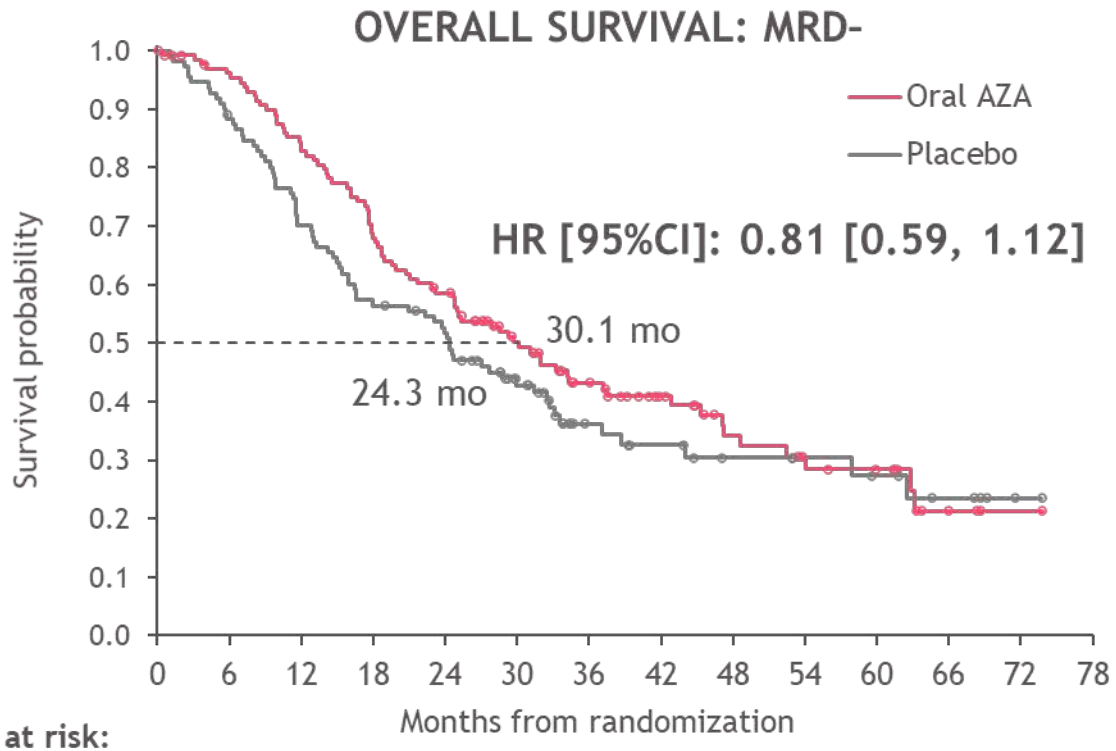


*RFS estimates were derived using Kaplan–Meier methods and compared for Oral-AZA vs. placebo using log-rank test. Hazard ratios (HRs) and 95% CIs were generated using a stratified Cox proportional hazards model.

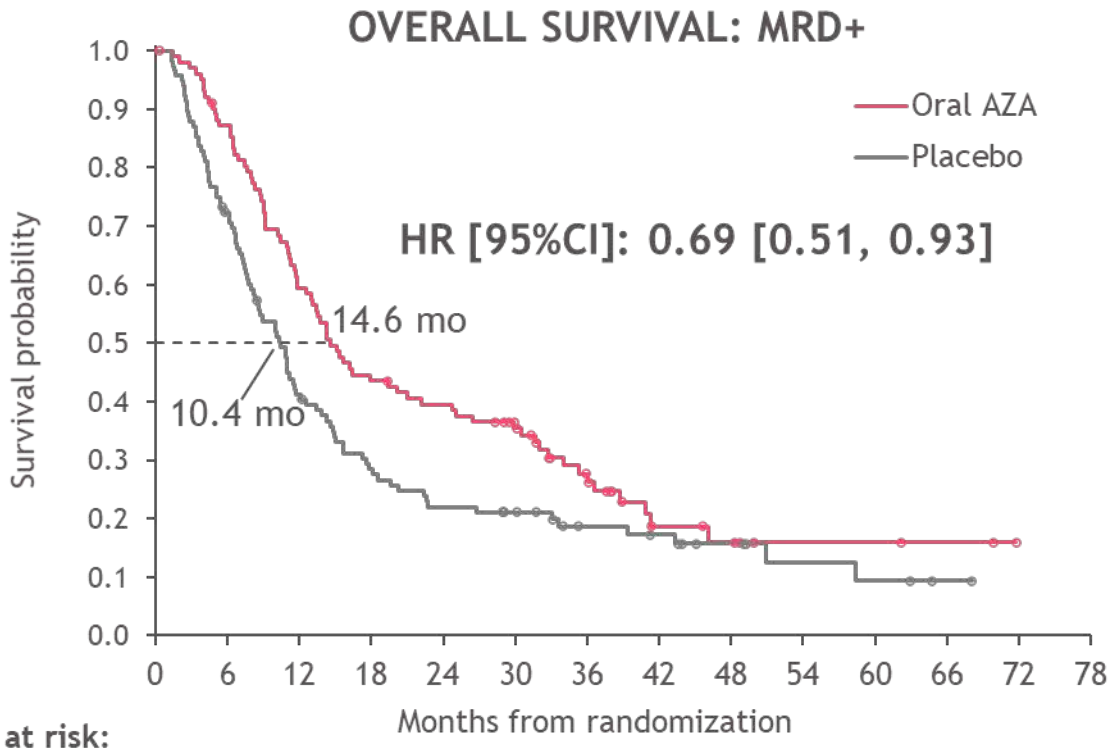
Wei A, et al. ASH 2020. Abstract 1036

QUAZAR AML-001: Overall survival by baseline MRD status and treatment arm

– **Treatment with Oral AZA (CC-486) resulted in improved OS from time of randomization compared with PBO in pts who were MRD+ or MRD– at study entry**



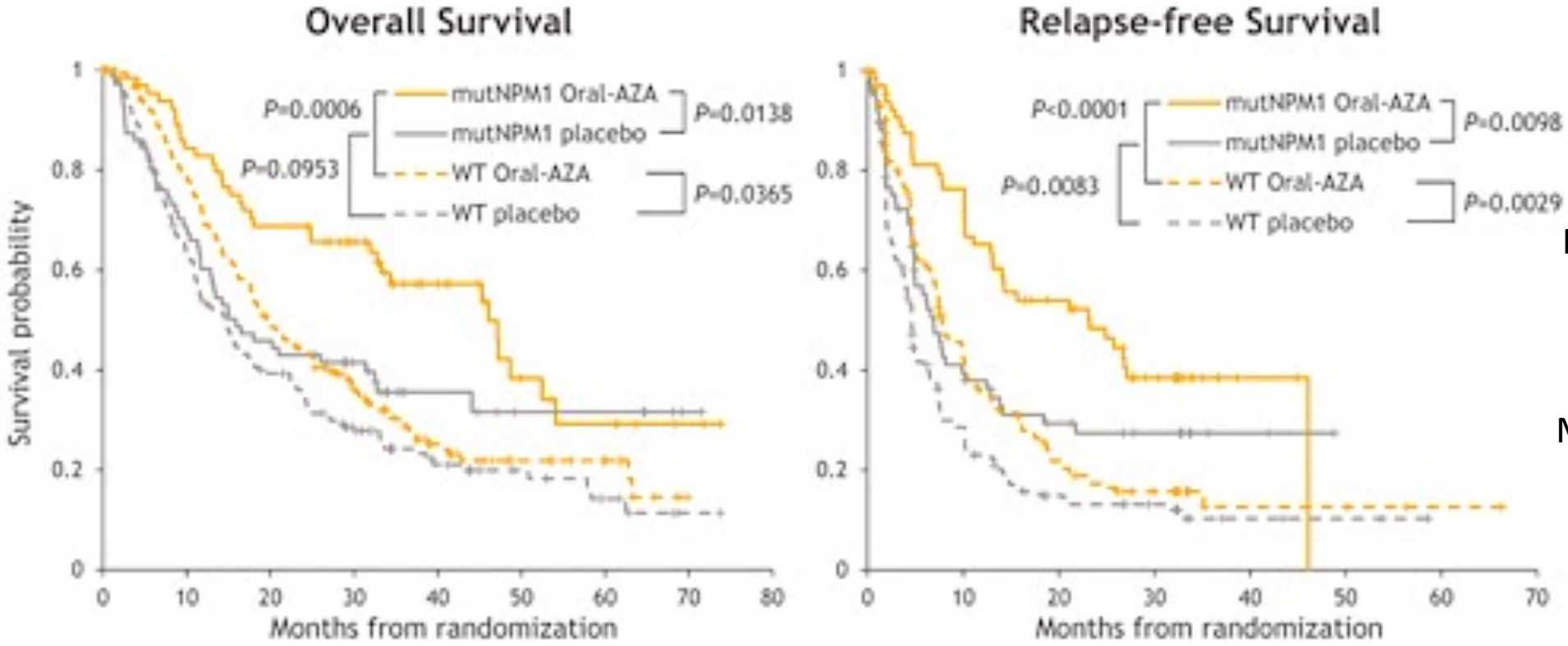
No. at risk:														
Oral AZA	133	123	106	87	74	54	39	28	19	14	11	3	1	0
Placebo	111	97	77	62	55	37	20	16	12	10	8	5	1	0



No. at risk:														
Oral AZA	103	88	60	44	39	31	19	8	6	3	3	2	0	
Placebo	116	82	46	31	24	20	13	11	7	4	3	1	0	

Roboz GR et al. ASH 2020; abstract 692

QUAZAR AML-001: Effect of AZA/PBO on OS and RFS based on NPM1 mutations status



AZA, azacitidine; mut, mutated; NPM1, Nucleophosmin 1.

Median OS (months, oral Aza)

NPM1 Mut	46.1
NPM1 WT	15.9

Median RFS (months, oral Aza)

NPM1 Mut	23.2
NPM1 WT	16.9

Dohner H, et al. EHA 2021, abstract S131

QUAZAR AML-001 Study: Safety

- Gastrointestinal adverse events (AEs) in the CC-486 arm were most common during the first 2 treatment cycles
- Serious AEs were reported for 34% and 25% of patients in the CC-486 and placebo arms, respectively
- No treatment-related deaths

Preferred term	CC-486 n = 236		Placebo n = 233	
	All Grades	Grade 3–4	All Grades	Grade 3–4
	n (%)			
Patients with ≥1 AE	**231 (98)**	**169 (72)**	**225 (97)**	**147 (63)**
Gastrointestinal				
Nausea	153 (65)	6 (3)	55 (24)	1 (0.4)
Vomiting	141 (60)	7 (3)	23 (10)	0
Diarrhea	119 (50)	12 (5)	50 (22)	3 (1)
Constipation	91 (39)	3 (1)	56 (24)	0
Hematologic				
Neutropenia	105 (45)	97 (41)	61 (26)	55 (24)
Thrombocytopenia	79 (34)	53 (23)	63 (27)	50 (22)
Anemia	48 (20)	33 (14)	42 (18)	30 (13)
Other				
Fatigue	70 (30)	7 (3)	45 (19)	2 (1)
Asthenia	44 (19)	2 (1)	13 (6)	1 (0.4)
Pyrexia	36 (15)	4 (2)	44 (19)	1 (0.4)
Cough	29 (12)	0	39 (17)	0

Adverse events reported in ≥15% of patients in either arm

Wei AH, et al. *N Engl J Med* 2020; 383: 617-29

Case #1: Maintenance therapy for AML

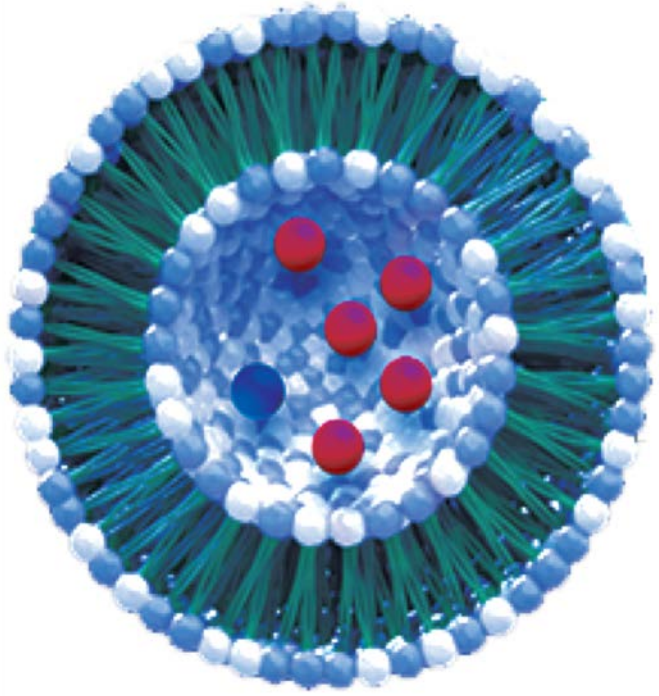
- A 73-year-old man with acute myeloid leukemia with normal karyotype and NPM1, FLT3 ITD (AR 0.08), IDH2 R140Q, JAK2 V617F, SRSF2 P95R, and TET2 A1863V
- 7+3 with midostaurin followed by 2 cycles of high dose cytarabine
- End-of-consolidation bone marrow biopsy: 10-20% cellularity, trilineage hematopoiesis, focal reticulin fibrosis
  - Flow cytometry negative for leukemic blast population
  - SRSF2 (VAF 41.5%), JAK2 (VAF 5.6%) , and TET2 (VAF 27.4%) variants still present.
- Maintenance therapy with oral azacitidine
  - Cycle 1 complicated by nausea, constipation
  - Cycle 2 complicated by prolonged cytopenias
  - Now cycle 6 after dose adjustment and tolerating well

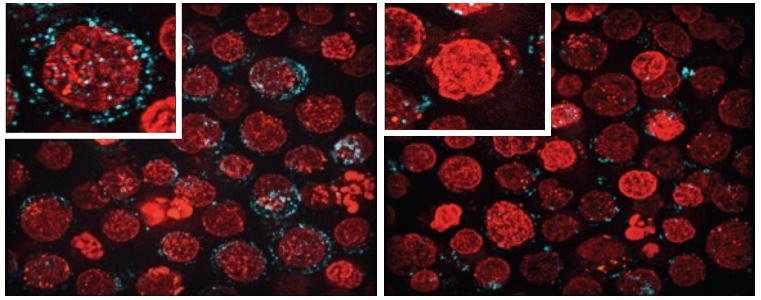
Case #2: Secondary AML

- A 74-year-old man without any medical comorbid illness
- Absolute monocytosis for 2 years, mild thrombocytopenia for 6 years
- He develops fatigue (PS 1), night sweats, unintentional weight loss, and myalgias
- **CBC:** leukocytosis (WBC 30,000 with 45% monocytes atypical)
- **BM biopsy:** AML with severe fibrosis
- **Cytogenetics:** 46, XY [20]
- **NGS:** *ASXL1, SRSF2, TET2,* and *CBL*

Liposomal Daunorubicin and Cytarabine (CPX-351)

- 1:5 molar ratio of daunorubicin to cytarabine
- Synergistic activity in both in vitro and animal models
- 100-nm bilamellar liposomes
- 1 vial = 44 mg daunorubicin plus 100 mg cytarabine (1:5 molar ratio) complexed with copper
- Targets bone marrow and preferentially targets leukemic compared with normal marrow progenitors

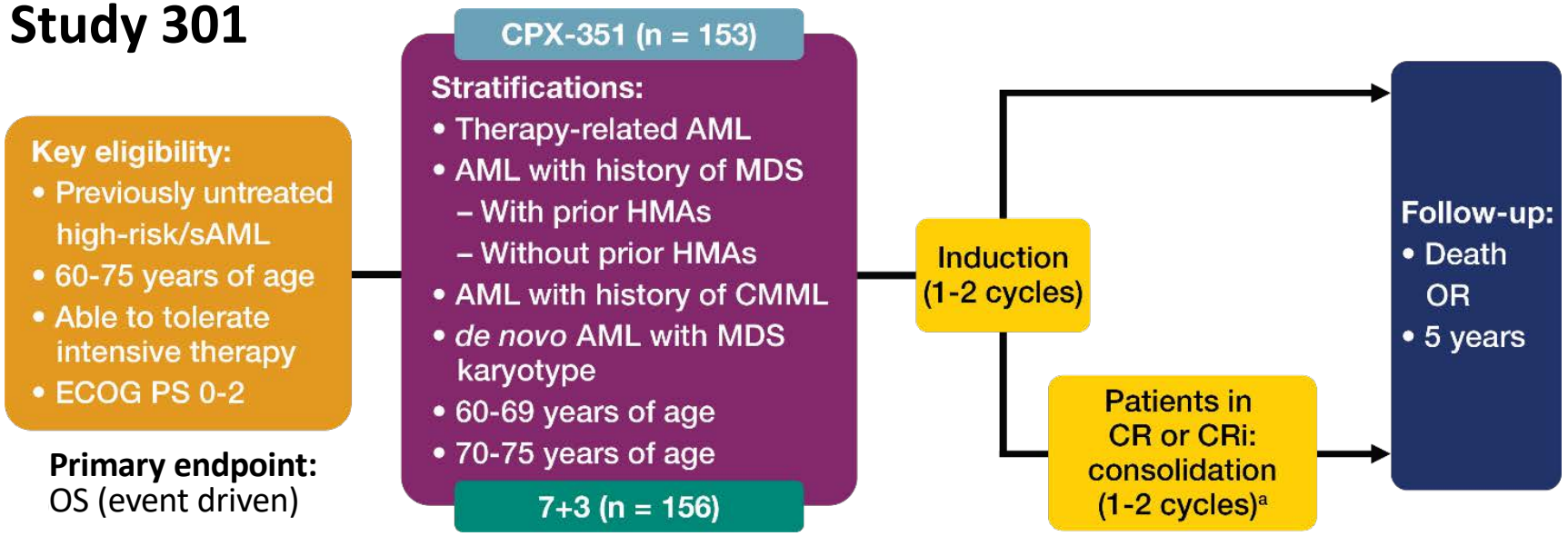




Lancet JE et al. *Blood*. 2014;123:3239-3246.

Randomized, Phase 3 Study of CPX-351 vs 7+3: Design

Study 301



This analysis reports the prospectively planned final 5-year follow-up results

Subgroup analyses were conducted in patients who achieved remission, those aged 60 to 69 years and 70 to 75 years, and those who proceeded to HCT

[a]Patients with documented complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CRi) were eligible for consolidation if they had left ventricular ejection fraction of ≥50%, ECOG PS of 0-2, absolute neutrophil count recovered to >500/μL, and platelet count recovered to >50,000/μL. CR was defined as having bone marrow blasts <5%, absence of blasts with Auer rods, absence of extramedullary disease, absolute neutrophil count ≥1.0 × 10^9/L, platelet count ≥100 × 10^9/L, and independence from red cell transfusions; CRi was defined as having all CR criteria except residual neutropenia (<1.0 × 10^9/L) or thrombocytopenia (<100 × 10^9/L).

CPX-351[b]
Administered as a 90-minute infusion

Induction: 100 units/m^2 on Days 1, 3, and 5 (Days 1 and 3 for 2nd induction)
Consolidation: 65 units/m^2 on Days 1 and 3

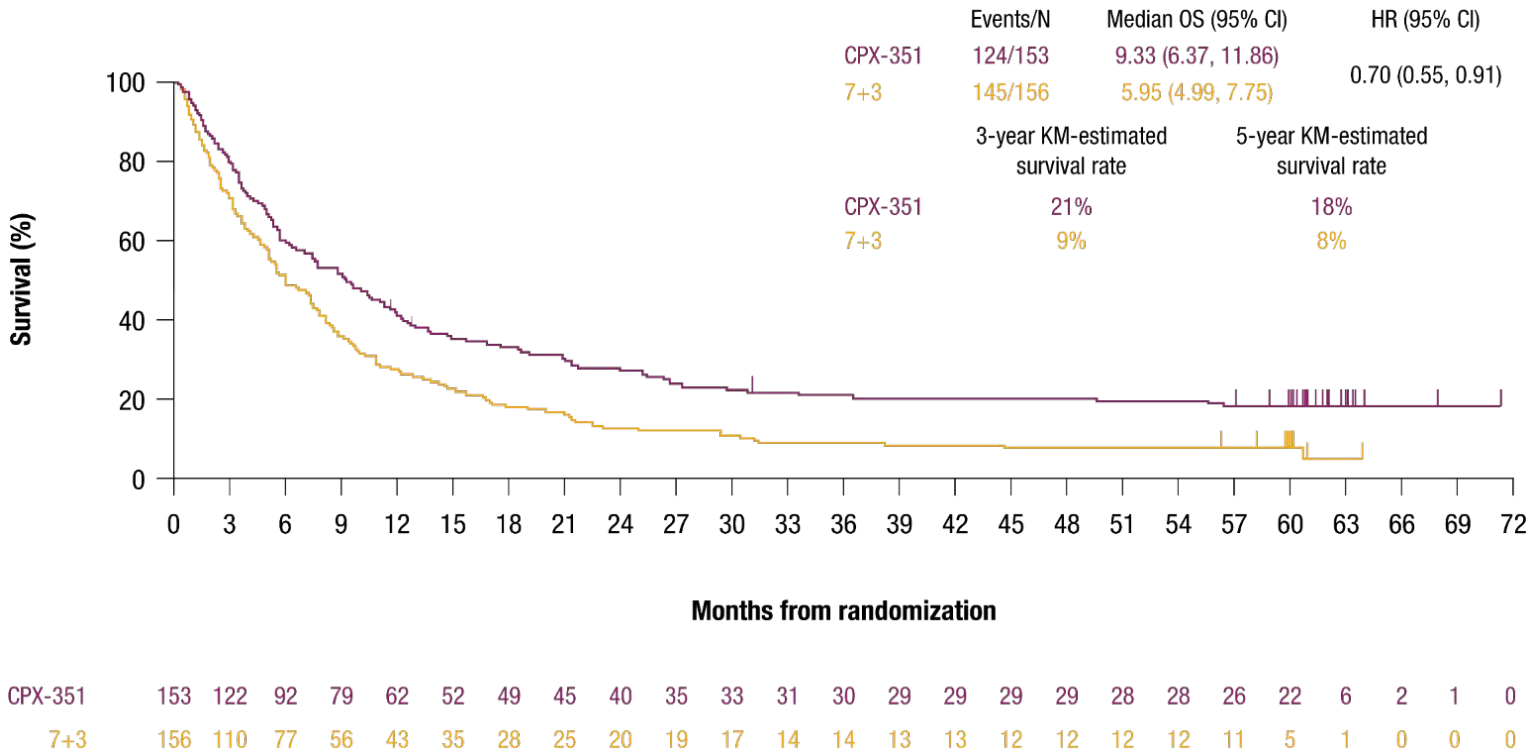
7+3
Cytarabine + daunorubicin

Cytarabine 100 mg/m^2/day continuous infusion + daunorubicin 60 mg/m^2/day
Induction: 7+3 schedule (5+2 for 2nd induction)
Consolidation: 5+2 schedule

[b]1 unit = 0.44 mg daunorubicin + 1 mg cytarabine.

Lancet JF et al. *J Clin Oncol.* 2018; 36: 2684-92.

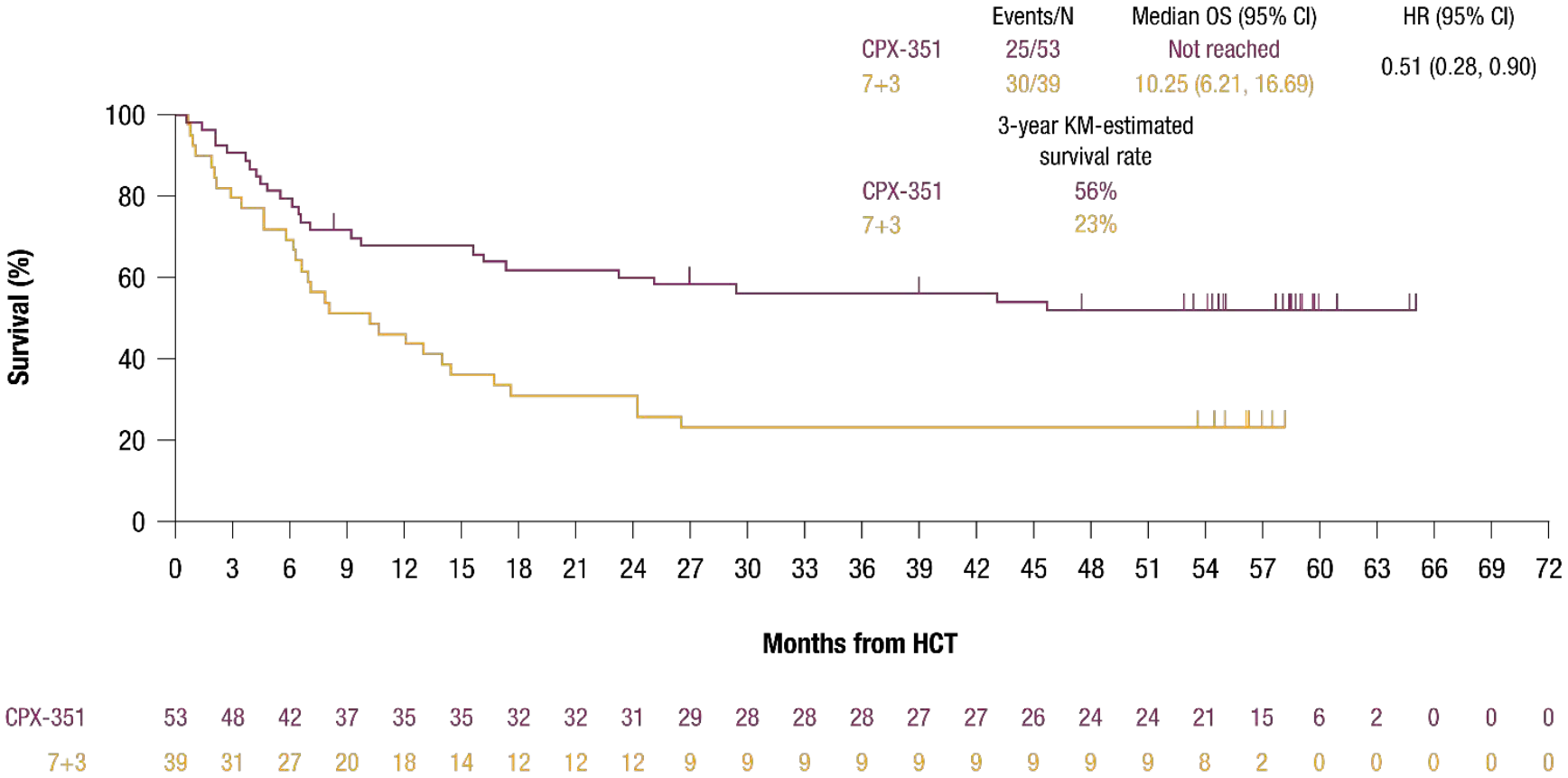
5 Year Update of the Phase 3 Study of CPX-351 vs 7+3: Overall Survival

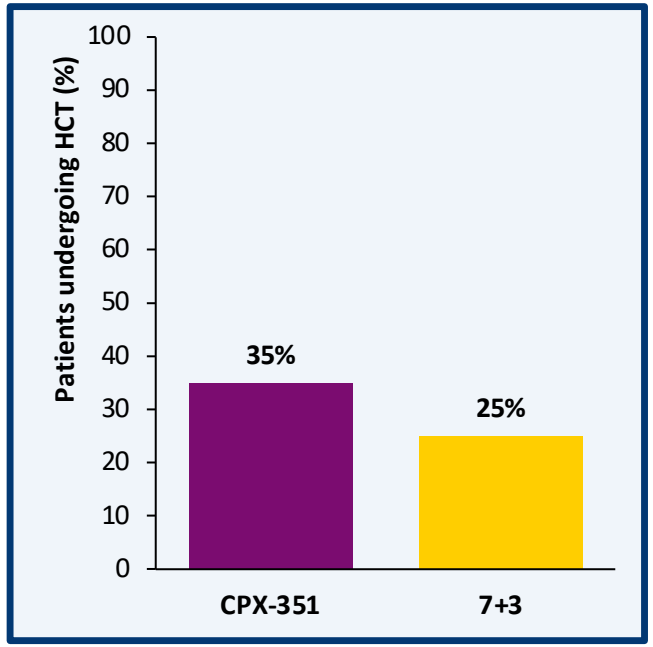


Overall remission rate was also significantly higher with CPX-351 vs 7+3: 47.7% vs 33.3%

Lancet JE et al. *Lancet Haematol*. 2020; 8(7): E481-E491.

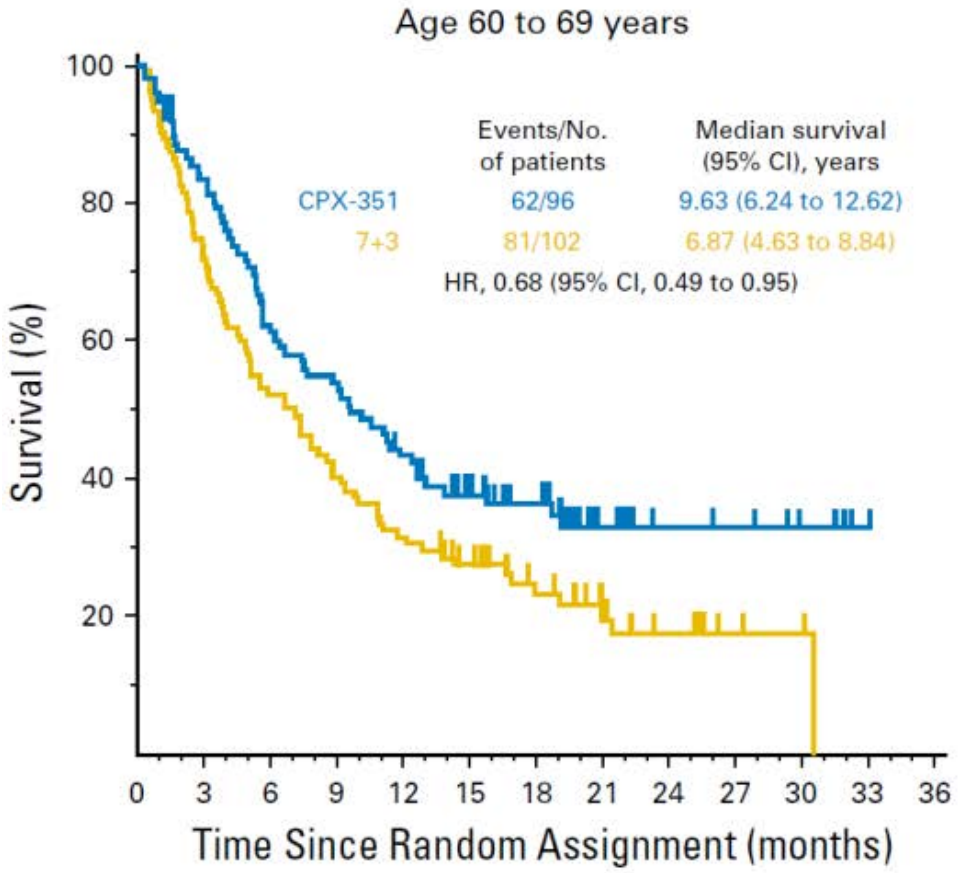
Phase 3 Study of CPX-351 vs 7+3: Overall Survival Landmark from HSCT

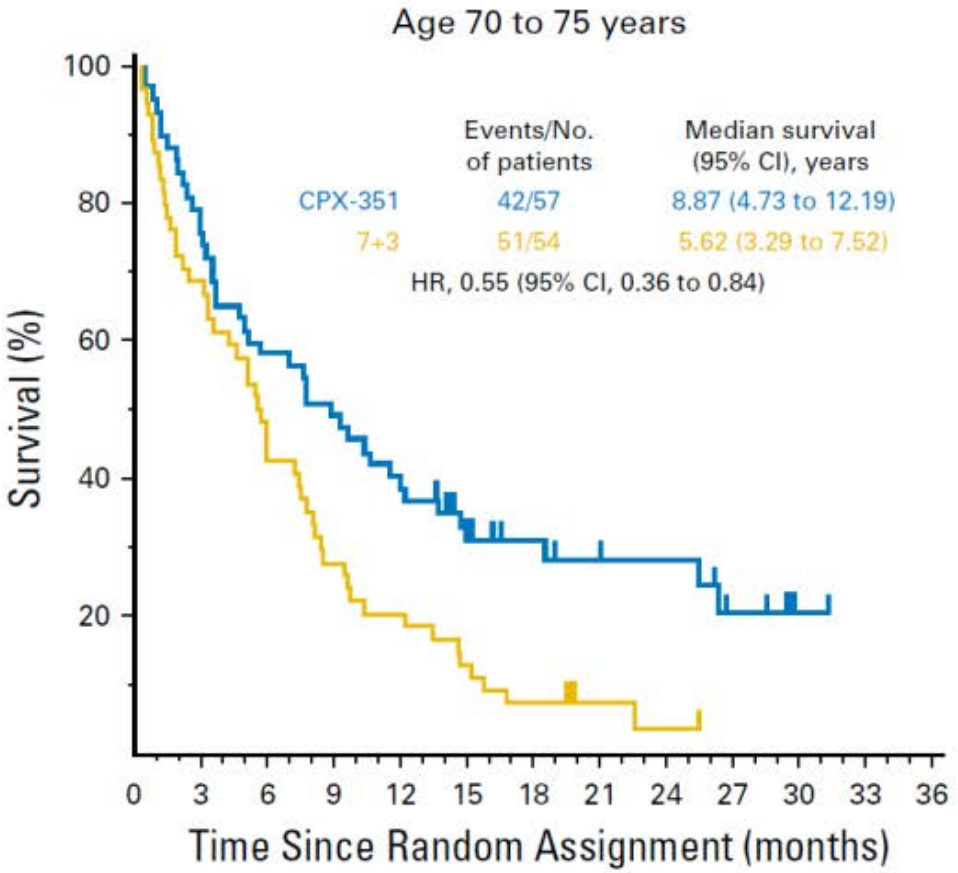




Lancet JE et al. *Lancet Haematol*. 2020; 8(7): E481-E491.

Phase 3 Study of CPX-351 Versus 7+3 in Older Patients With Newly Diagnosed Secondary AML: OS by Age





Lancet JF et al. *J Clin Oncol.* 2018; 36: 2684-92

Case #2: Secondary AML (Continued)

- A 74-year-old man without medical comorbid illness
- Absolute monocytosis for 2 years, mild thrombocytopenia for 6 years
- He develops fatigue (PS 1), night sweats, unintentional weight loss, and myalgias
- **CBC:** leukocytosis (WBC 30,000 with 45% monocytes atypical)
- **BM biopsy:** AML with severe fibrosis
- **Cytogenetics: 46, XY [20]**
- **NGS:** *ASXL1, SRSF2, TET2,* and *CBL*

Receives CPX-351 on 5/20/19 as outpatient

- ✓ Culture negative for febrile neutropenia
- ✓ 06/28/19: BM CRp by 07/16/19
- ✓ 07/24/19: CPX-351 consolidation as outpatient
- ✓ 08/28/19: BM CR (NGS panel is negative)

→

Proceeds to allogeneic HCT

- ✓ 10/18/19: preparative regimen fludarabine/melphalan
- ✓ 10/23/19: haplo (son) alloHCT
- ✓ Cyclophosphamide post cells
- ✓ Last visit, 02/10/20: doing well