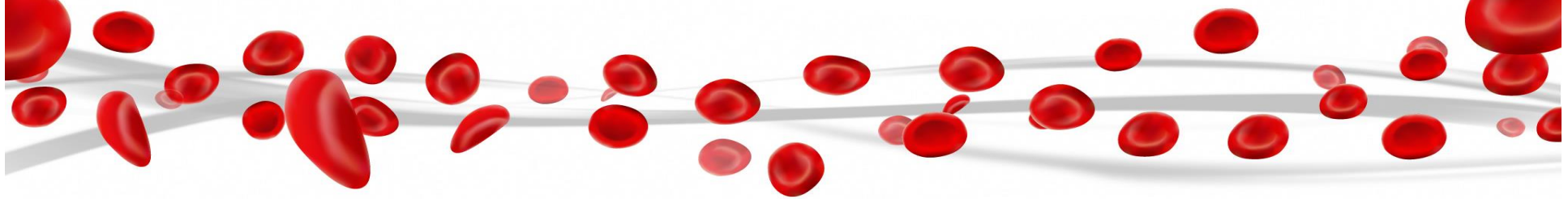


Thursdays Webinars

EuroBloodNet

Treatment of AML in the elderly: intensive or not?

Gert Ossenkoppele
Emeritus Prof. Hematology
Amsterdam UMC, location VUmc
ERN-EuroBloodNet subnetwork
Amsterdam– The Netherlands
3 `Dec 2020

Co-funded by
the Health Programme
of the European Union

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

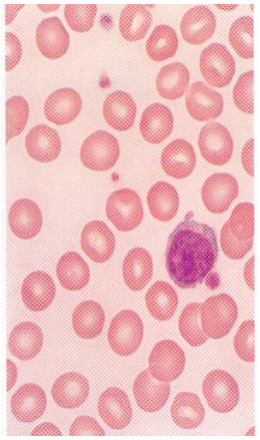
Conflicts of interest

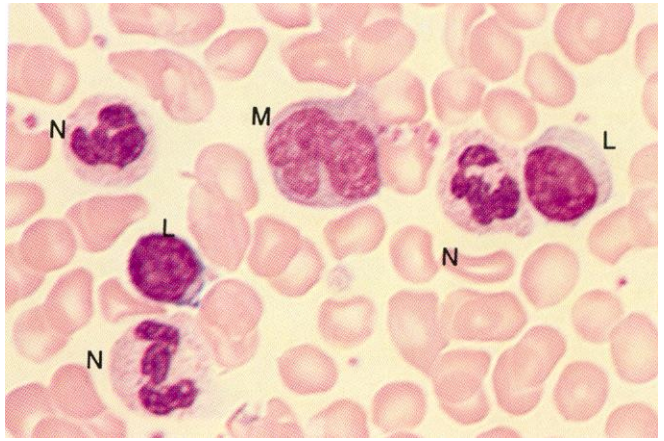
Company name	Research support	Consultant	Advisory board
Novartis	x		x
Pfizer			X
BMS			x
J&J	x	x	x
Sunesis		x	x
Celgene	x	x	x
AGIOS			x
Amgen			x
BD	x		
Astellas			x
Roche		x	x
JAZZ Pharmaceuticals			X
MERUS			x

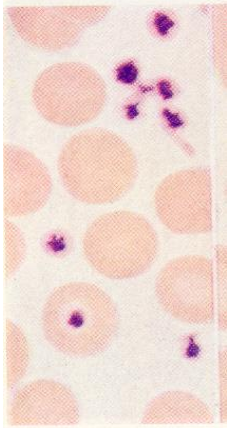
Oxygen transport

Resistance

hemostasis



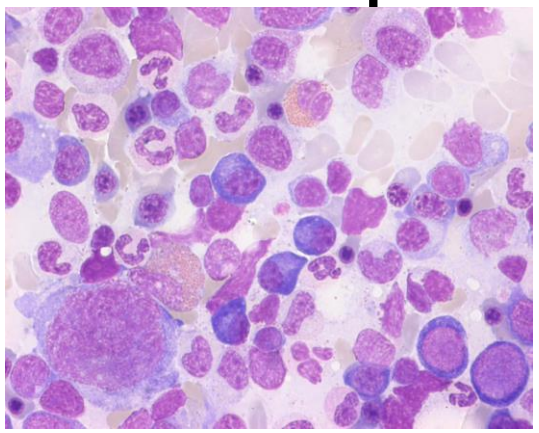




Erythrocytes

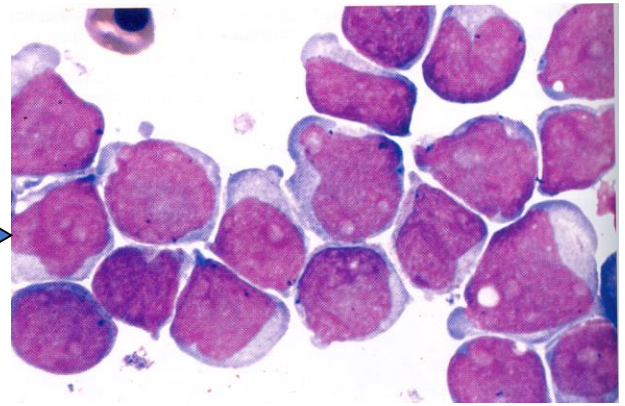
Leukocytes

Platelets



Normal bonemarrow

Maturation disturbance



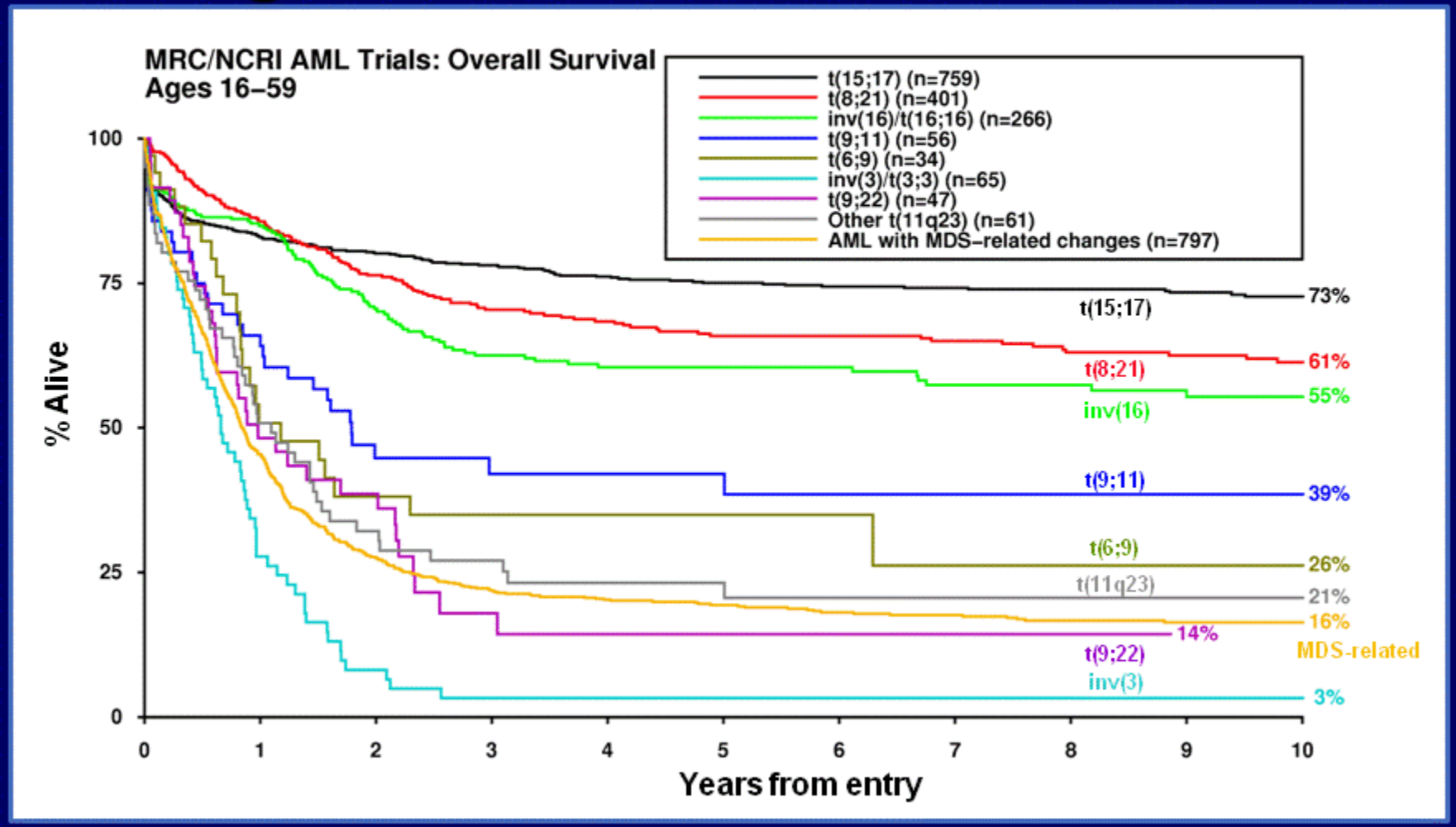
Acute leukemia

Anemia

Bleeding

Infections

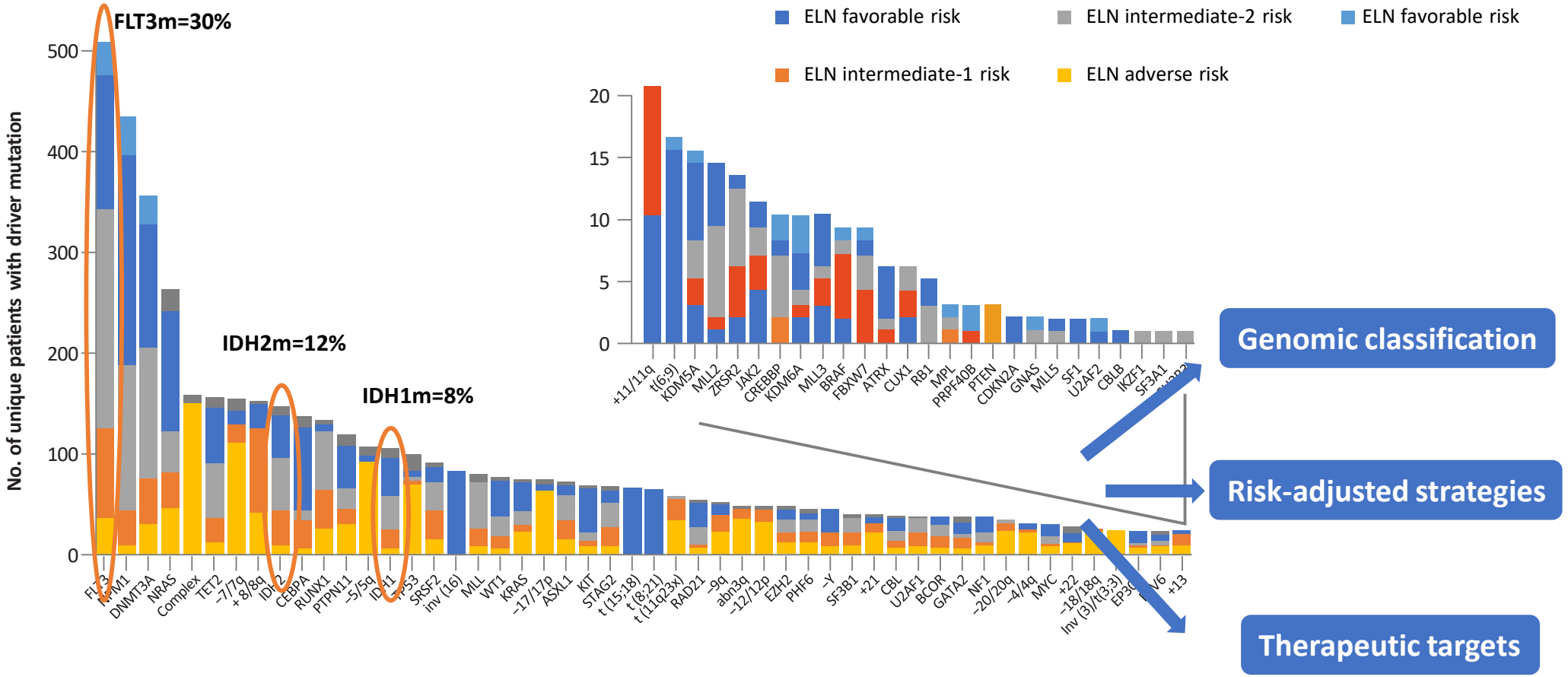
Outcome of cytogenetic entities recognised in 2008 WHO classification



Analysis of 5,876 cases entered in MRC AML10, 12 & 15 trials

Grimwade *et al. Blood*. 2010;116: 354-365.

Genomic landscape of adult AML



- Targeted resequencing of 111 myeloid cancer genes (combined with cytogenetic profiles) in 1540 AML
- 5236 driver mutations (i.e., fusion genes, copy number alterations, gene mutations) involving 77 loci
- 6 genes mutated in >10% pts; 13 genes 5-10% pts; 24 genes 2-5% pts; 37 genes <2% pts

Papaemmanuil, Gerstung, Bullinger et al. N Engl J Med 2016

2017 ELN Prognostic Stratification of AML

Favourable

- t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- **Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}**
- Biallelic mutated *CEBPA*

Intermediate

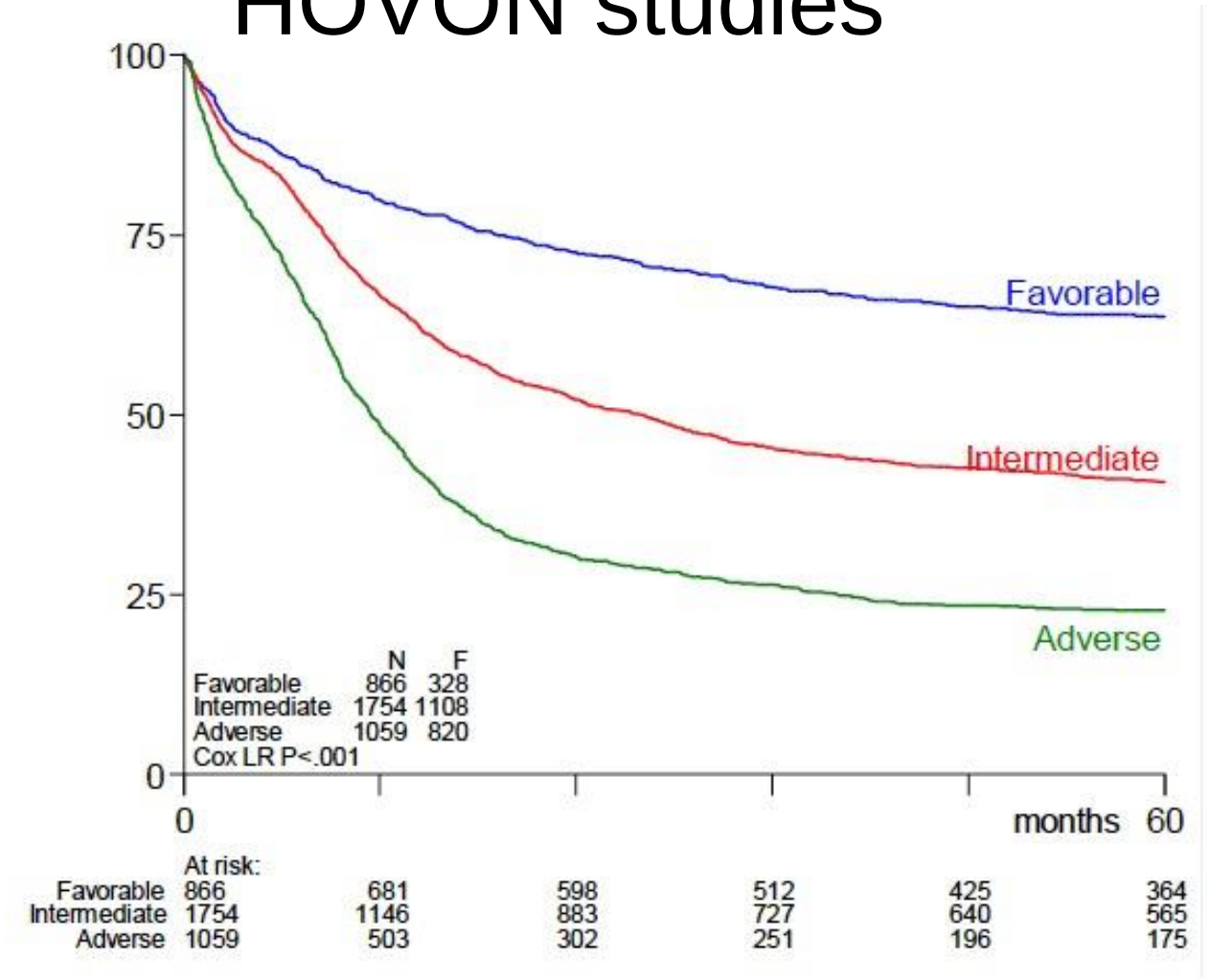
- **Mutated *NPM1* and *FLT3*-ITD^{high}**
- **Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}** (without adverse-risk genetic lesions)
- t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
- Cytogenetic abnormalities not classified as favourable or adverse

Adverse

- t(6;9)(p23;q34.1); *DEK-NUP214*
- t(v;11q23.3); *KMT2A* rearranged
- t(9;22)(q34.1;q11.2); *BCR-ABL1*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
- −5 or del(5q); −7; −17/abn(17p)
- Complex karyotype, monosomal karyotype
- **Wild-type *NPM1* and *FLT3*-ITD^{high}**
- **Mutated *RUNX1*¶**
- **Mutated *ASXL1*¶**
- **Mutated *TP53***

FLT3-ITD allelic ratio defined as: low, <0.5; high, ≥0.5. ¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes. Döhner H *et al. Blood* 2017;129:424–447.

Overall survival according to ELN 2017 in 3679 newly diagnosed AML patients treated in HOVON studies



Patient data derived from AML29, AML42, AML92 and AML102 HOVON-SAKK studies.

“I Am Older, Not Elderly,” Said the Patient With Acute Myeloid Leukemia

Charles A. Schiffer, *Division of Hematology/Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI*

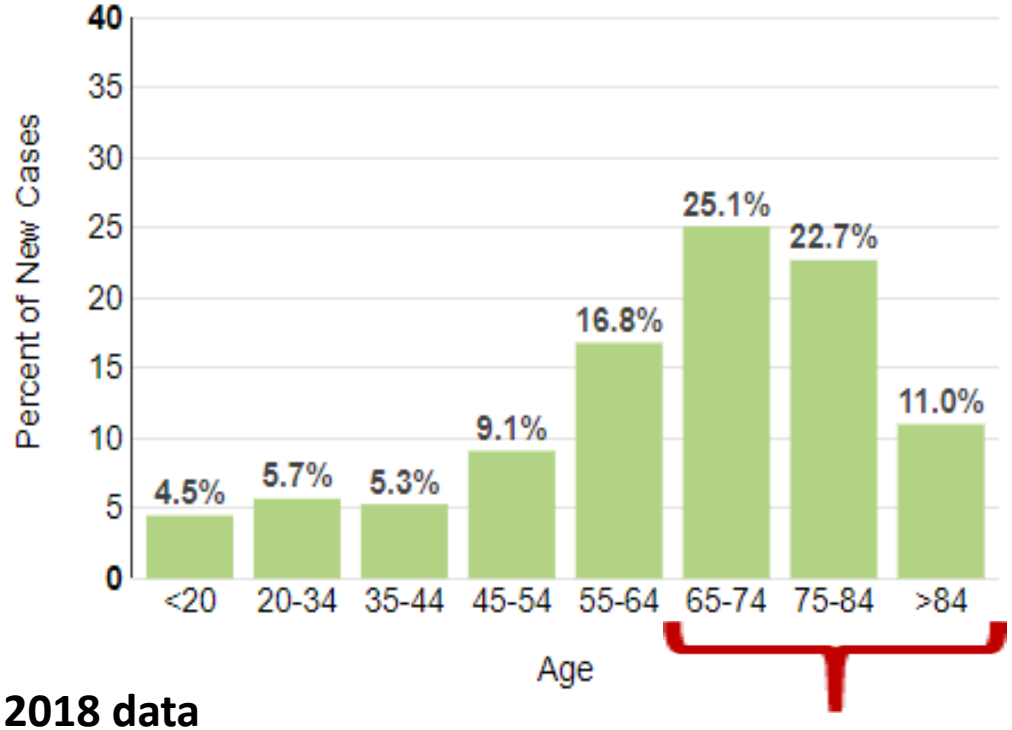
Charles Schiffer JCO 2009; juli 1:521

Median age at diagnosis:

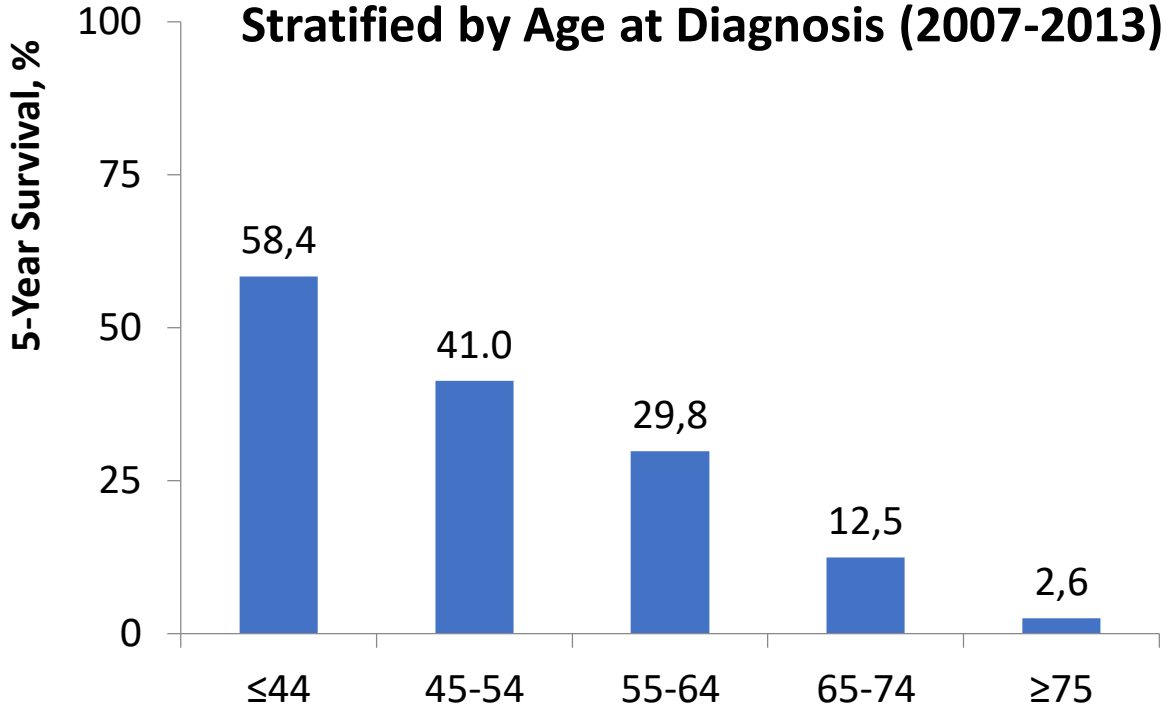
68-70+ years

5-yr survival is 28.3%

Incidence of AML by Age Group



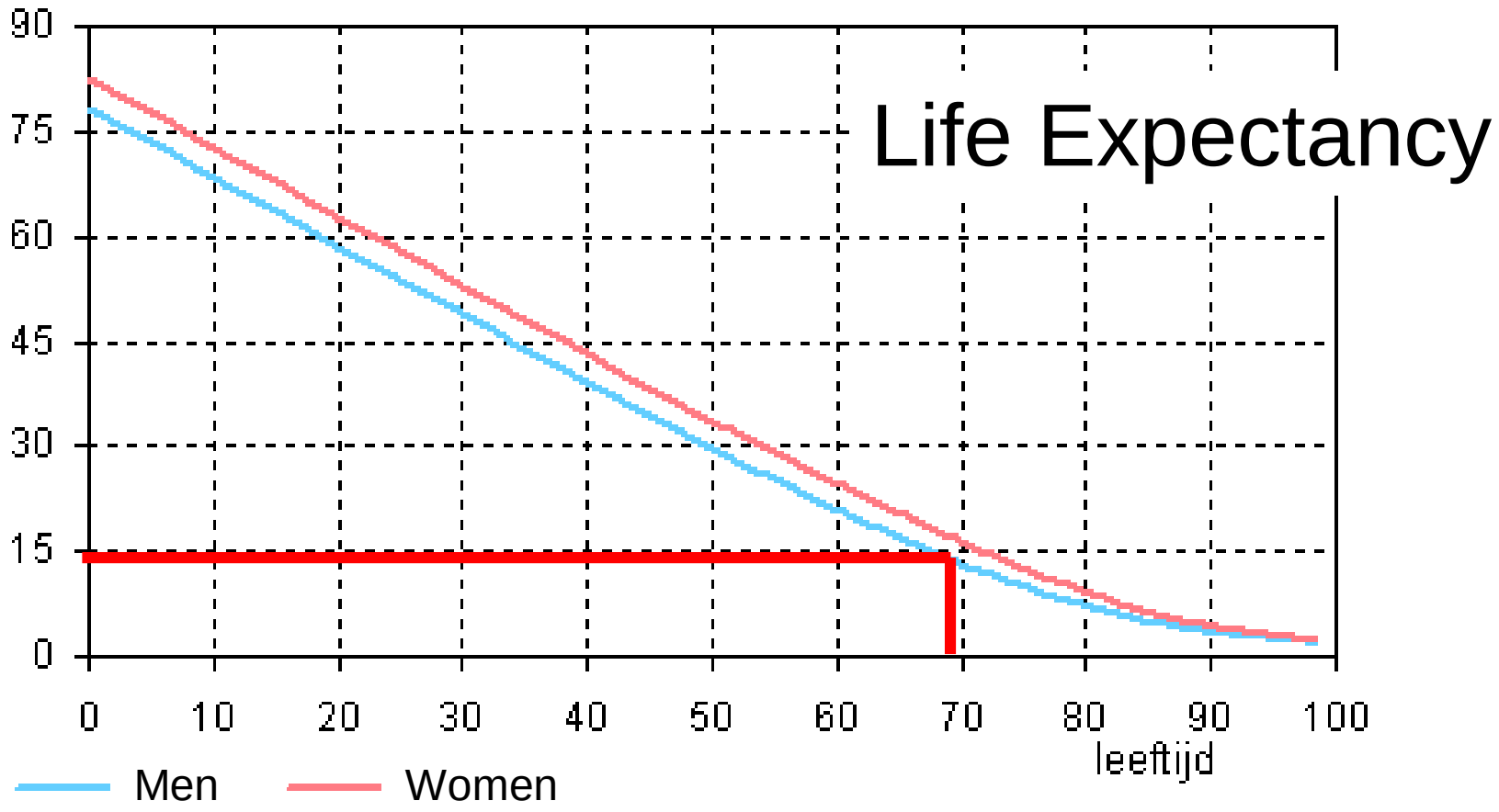
5-Year Survival of Newly Dx AML, Stratified by Age at Diagnosis (2007-2013)



SEER 2018 data

https://seer.cancer.gov/statfacts/html

Ageing is a biological dynamic process beyond human control and there is no general prognosis of the age at which a person becomes old



VU Hematologie

http://www.rivm.nl/vtv/object_document/o2309n18838.html

Characteristics AML in Elderly

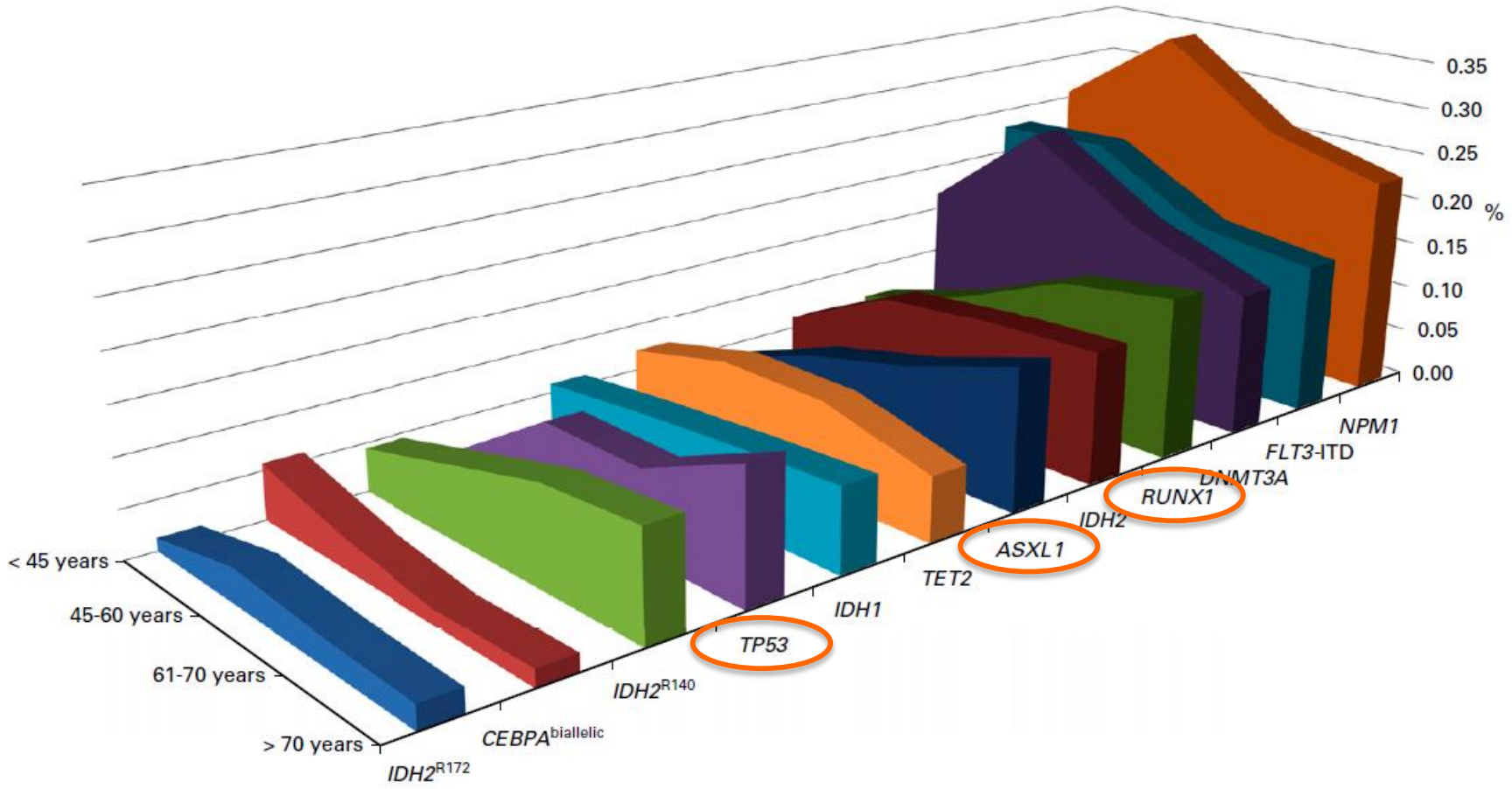
- **Disease related factors**
  - Antecedent Hematological Disorder
  - Adverse Prognostic Cytogenetic Profile
  - Overexpression MDR1 gene
  - Gene Expression Profile differences

  → **Chemotherapy less effective**

- **Host related factors**
  - Worse performance status
  - More co-morbidity
  - PK and PD changes

  → **Increased Toxicity of Chemotherapy**

Age-related frequency of gene mutations



Analysis based on 10,622 AML patients from the AMLSG data base

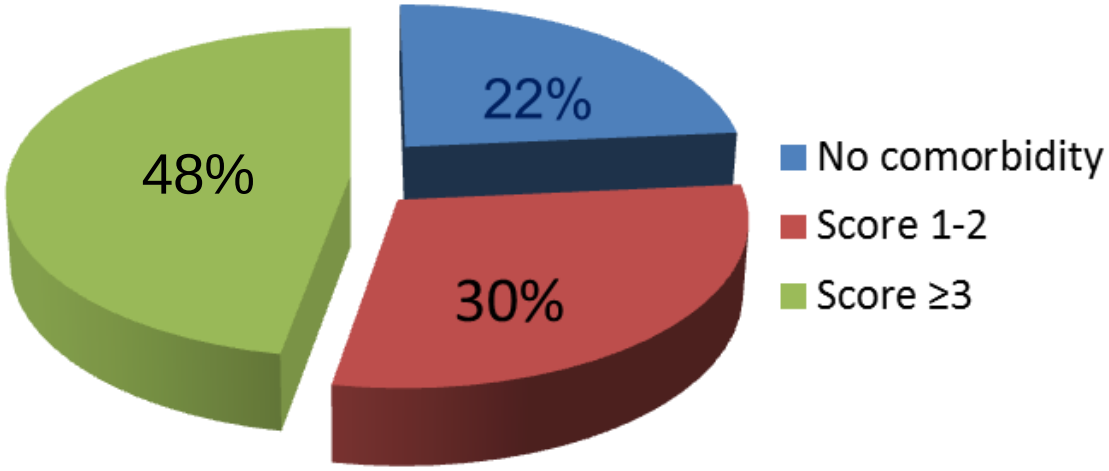
Age distribution: <45 yrs, n=2,228; 45-60 yrs, n=3,392; 61-70 yrs, 2,517; **>70 yrs, n=2,485**

Bullinger et al. J Clin Oncol 2017

Fit or Unfit Elderly

HCT-CI predicts early mortality and survival

- Prospective study n=177
- AML pts ≥ 60 years who received induction chemotherapy

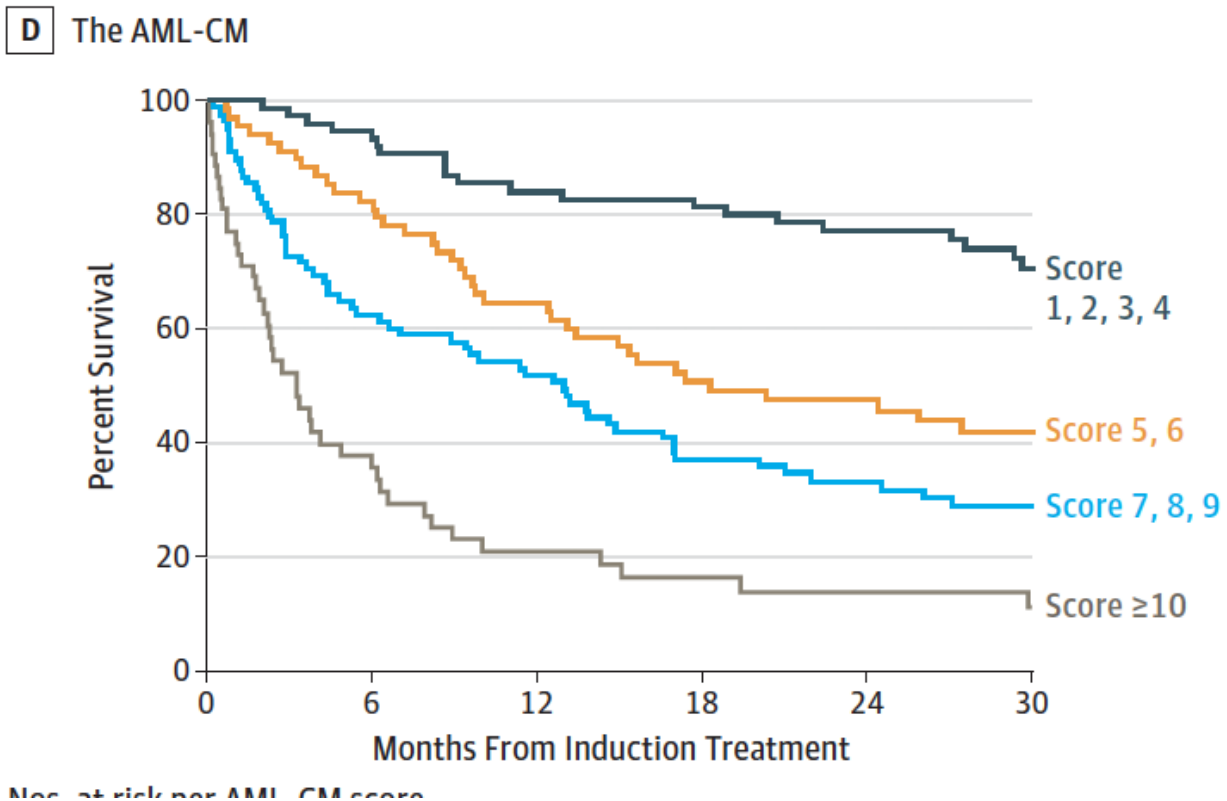


HCT-CI score	30-day mortality %	Median survival (weeks)
0	3	45
1-2	11	31
≥ 3	29	19
P-value	P<0.001	p-=0.04

Giles et al. BJH 2006

AML-CM	Augmented HCT-CI + age + cytogenetic/ molecular risks

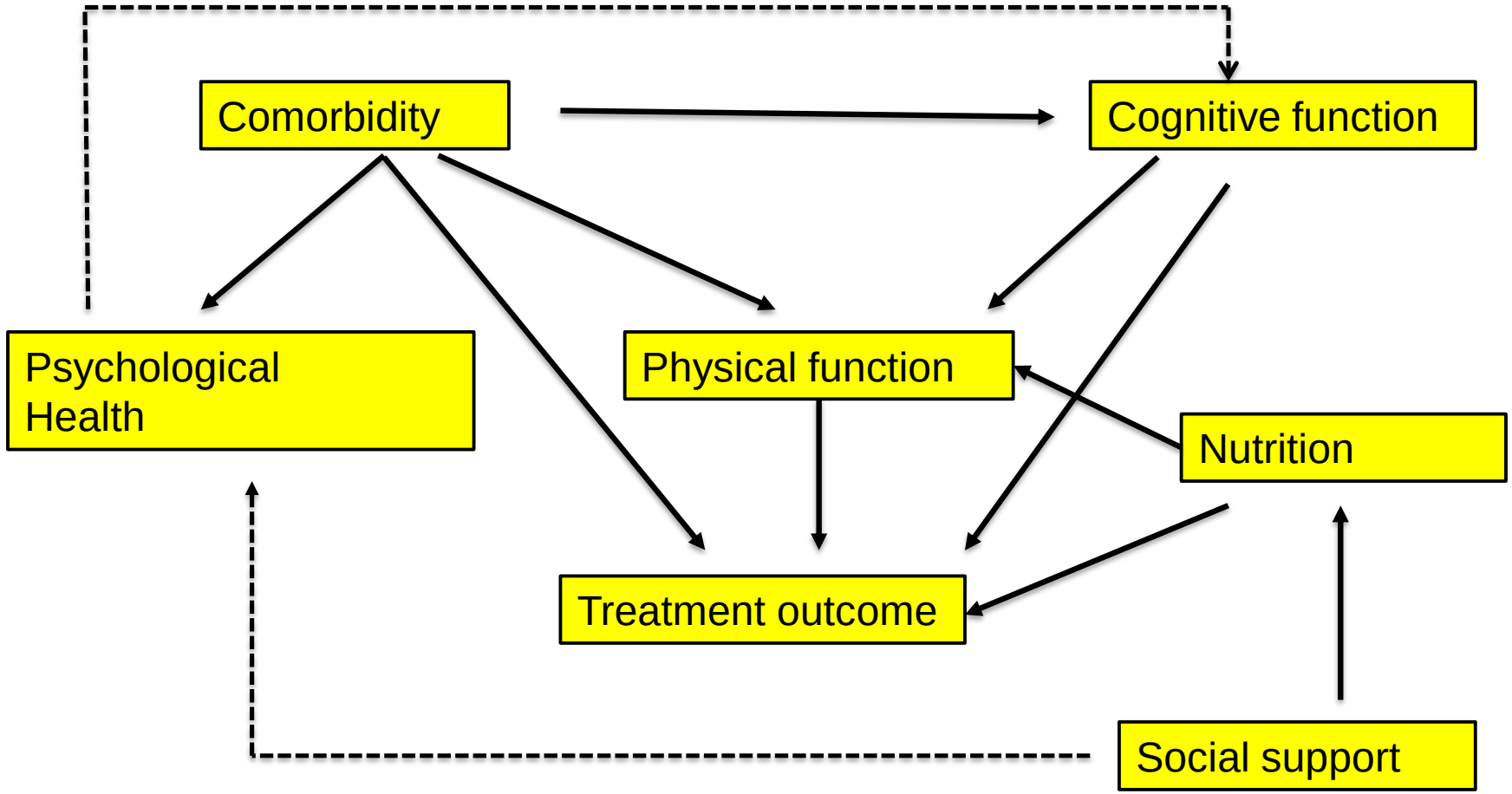
Sorror et al JAMA Oncol. 2017;3(12):1675-1682.



Augmented HCT-CI	Original HCT-CI + albumin level <3.5 g/dL, platelet count <20 × 10^3 cells/μL, LDH level 200-1000 U/L, and LDH level >1000 U/L

http://www.amlcompositemodel.org/

Differentiating fit from unfit requires a comprehensive approach



H. Klepin ASH 2014

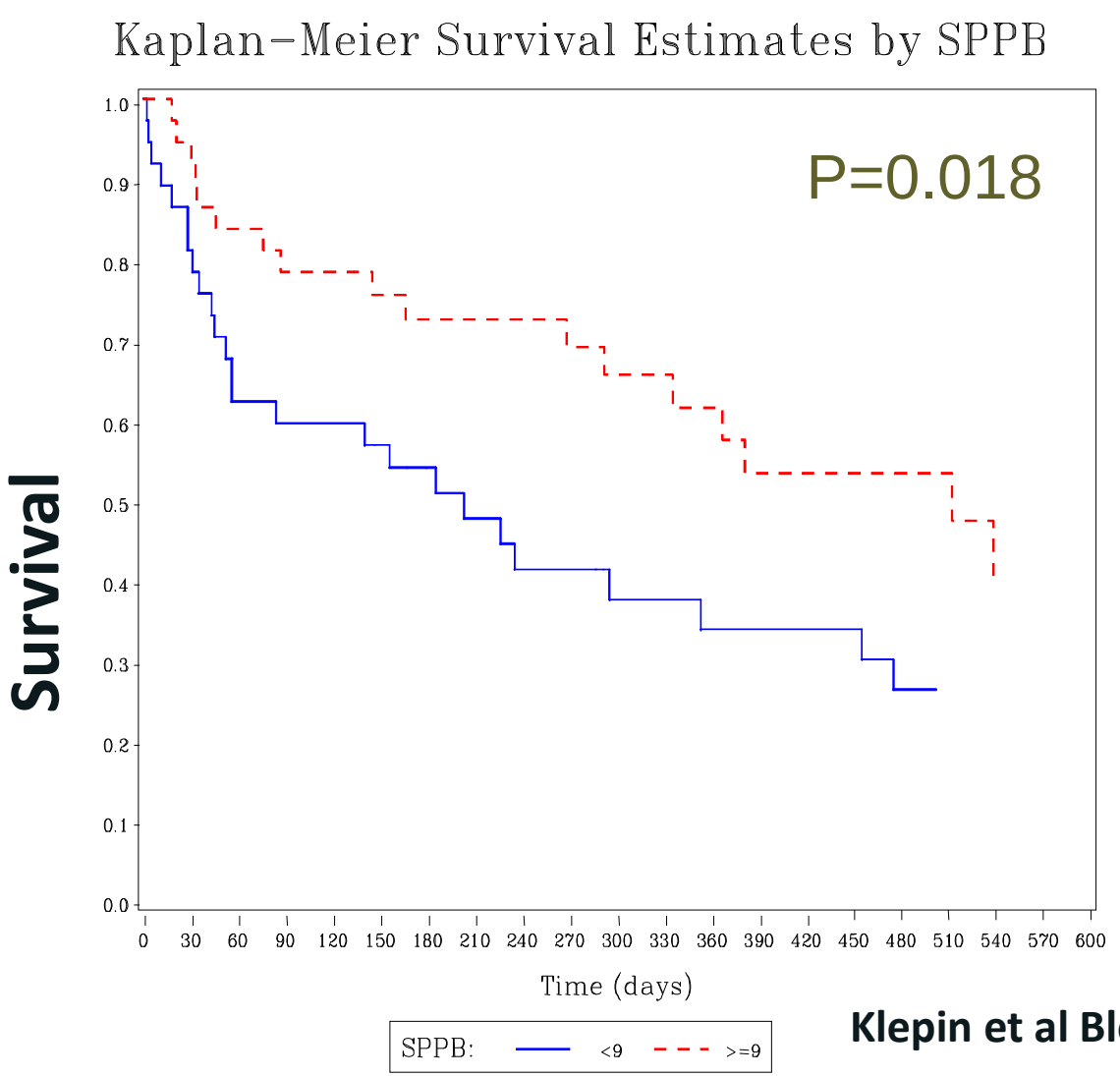
Geriatric assessment predicts survival in older AML patients receiving induction therapy

- N=74, prospective single institution study, median age 68.8 years
- GA done within 5 days of admission for induction chemotherapy
- Cognitive function was assessed using the 100-point Modified Mini-Mental State (3MS)
- SPPB assessed using a short walk (4 m), repeated chair stands, grip strength and balance test

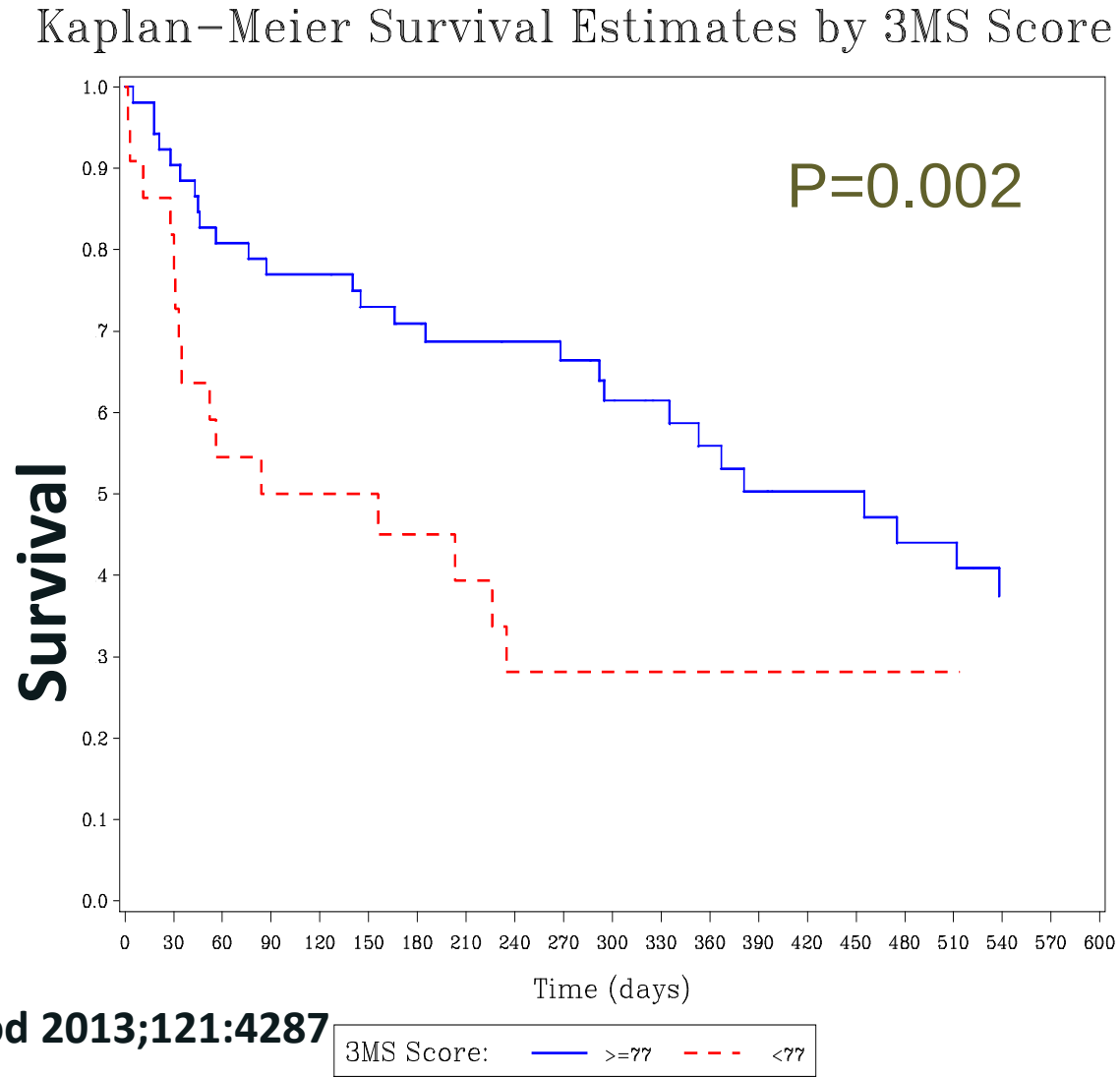
Klepin et al Blood 2013;121:4287

Objectively measured physical and cognitive function were more important than chronologic age in predicting survival

Objective physical function

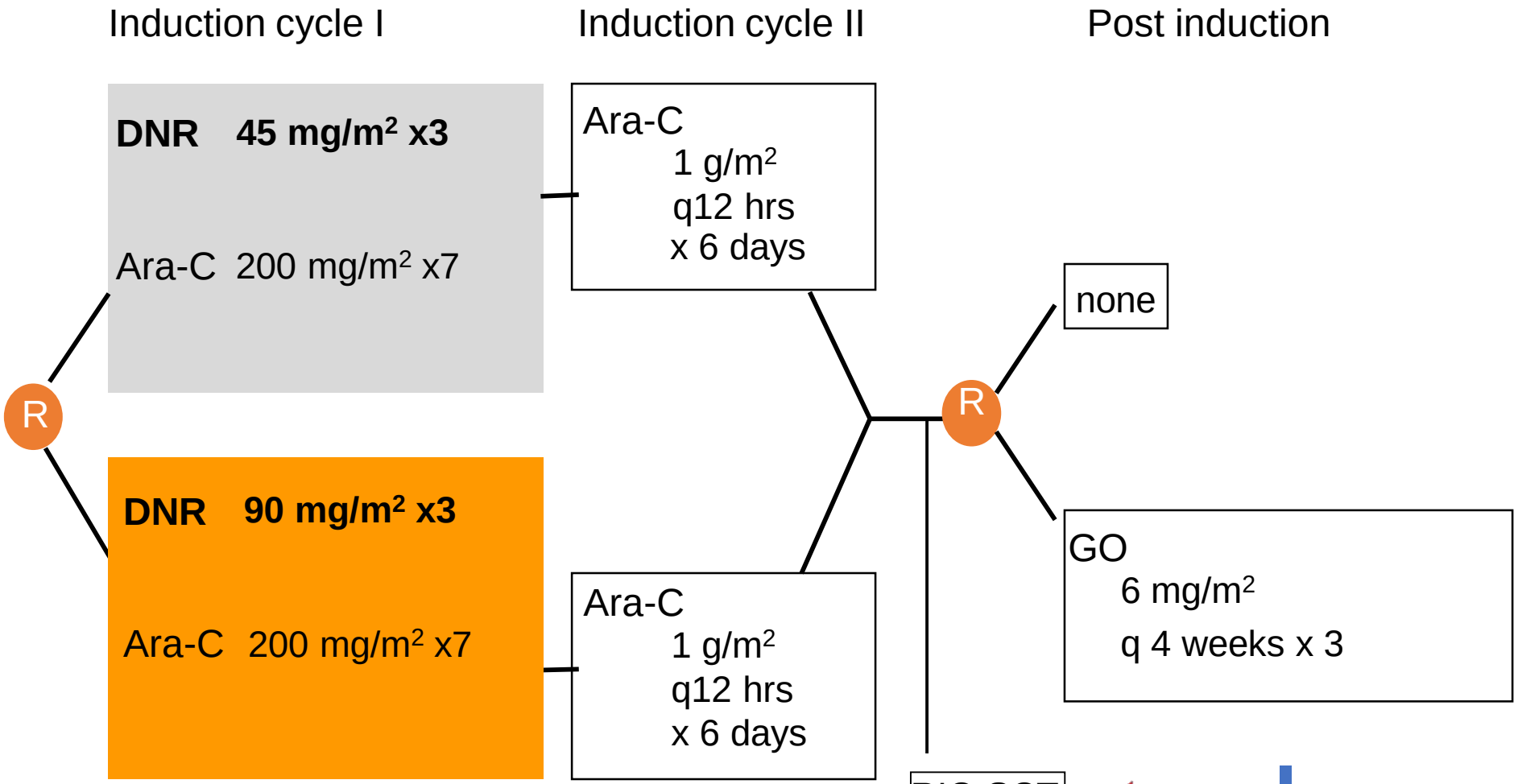


Cognitive function



Klepin et al Blood 2013;121:4287

HOVON 43: Daunorubicin Dose Intensification in elderly AML



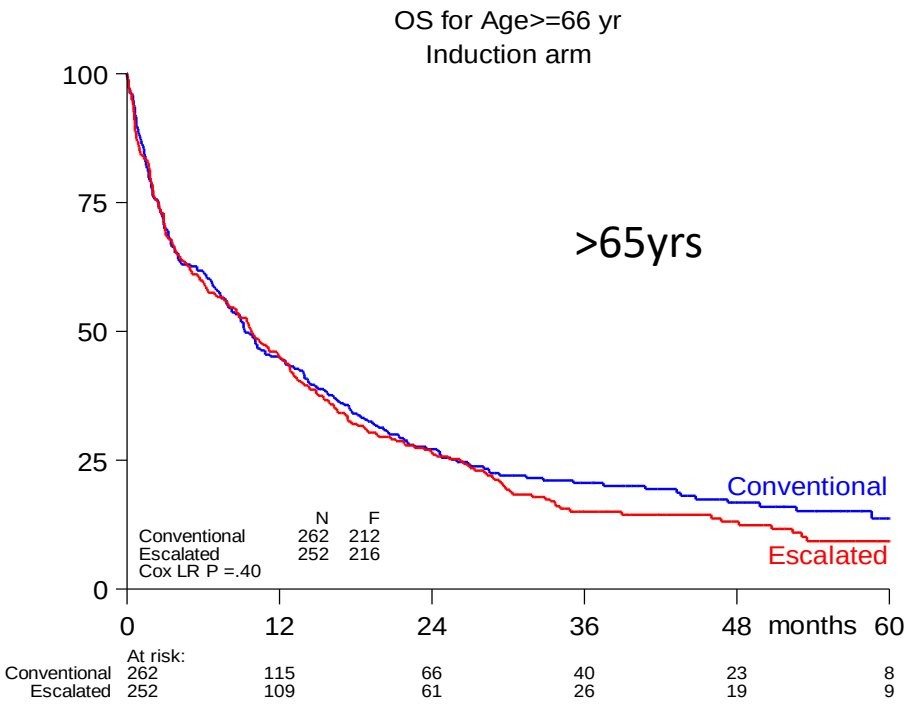
Lowenberg, Ossenkoppele et al, NEJM 2009:361:1235

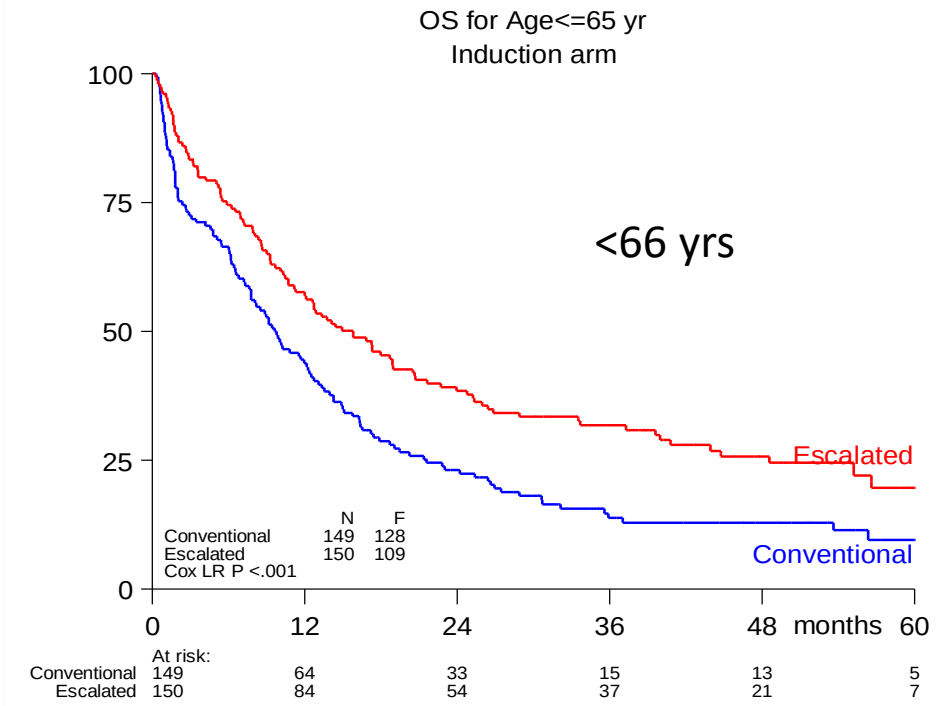
HOVON

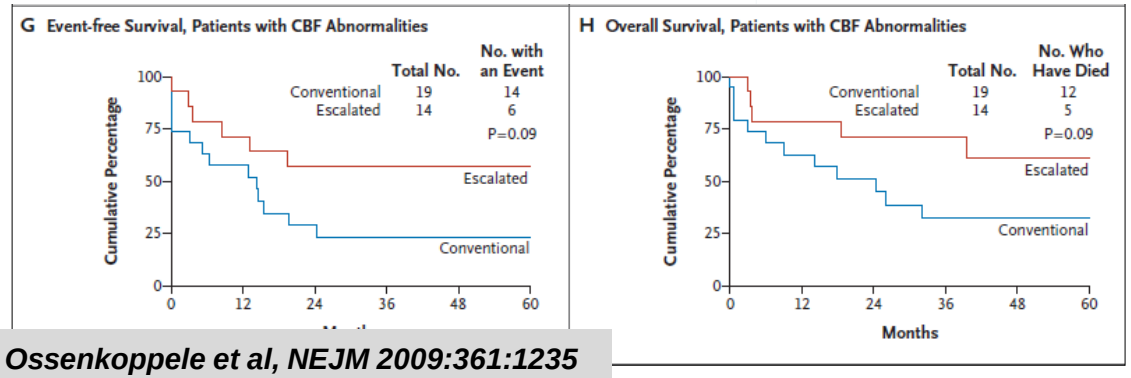
SAKK

Schweizerische Arbeitsgemeinschaft für Kli
Groupe Suisse de Recherche Clinique sur
Swiss Group for Clinical Cancer Research
Gruppo Svizzero di Ricerca Clinica sul Can

HOVON 43: Daunorubicin Dose Intensification in elderly AML:OS







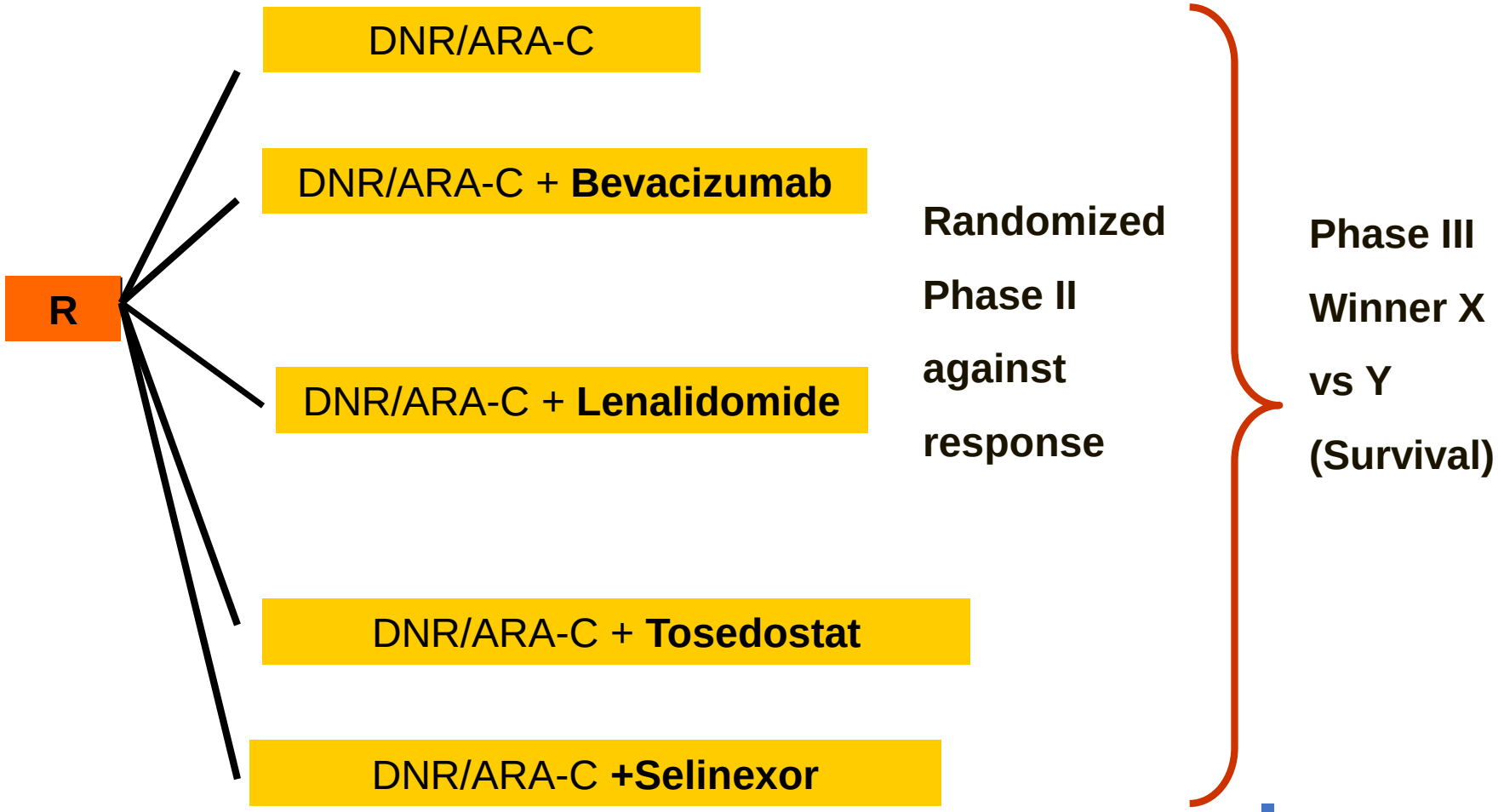
Lowenberg, Ossenkoppele et al, NEJM 2009:361:1235

HOVON SAKK

Schweizerische Arbeitsgemeinschaft f
Groupe Suisse de Recherche Clinique
Swiss Group for Clinical Cancer Rese
Gruppo Svizzero di Ricerca Clinica su

New Trial Design in Elderly AML

Octopus design: HOVON 103

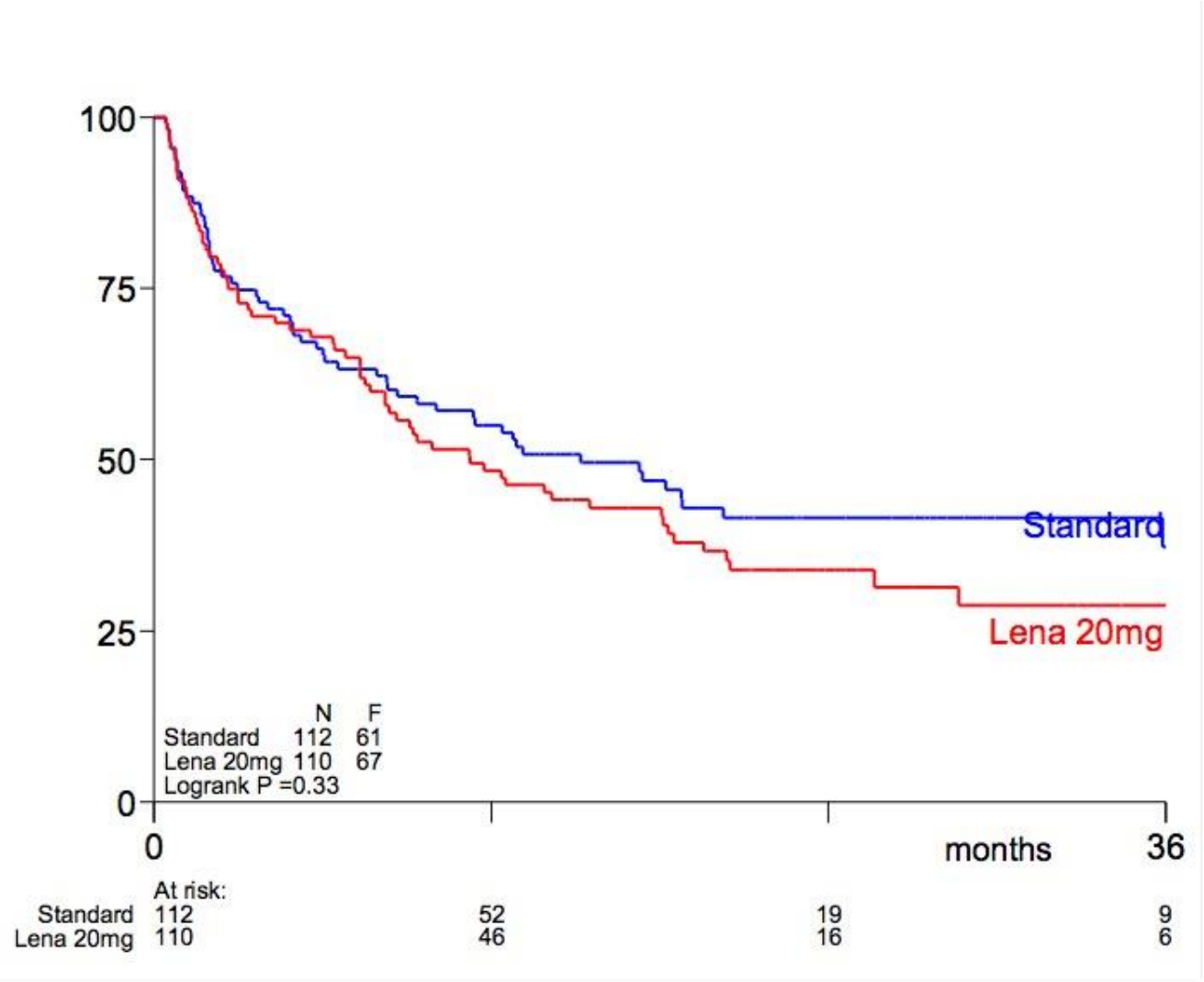


VU Hematologie

HOVON SAKK

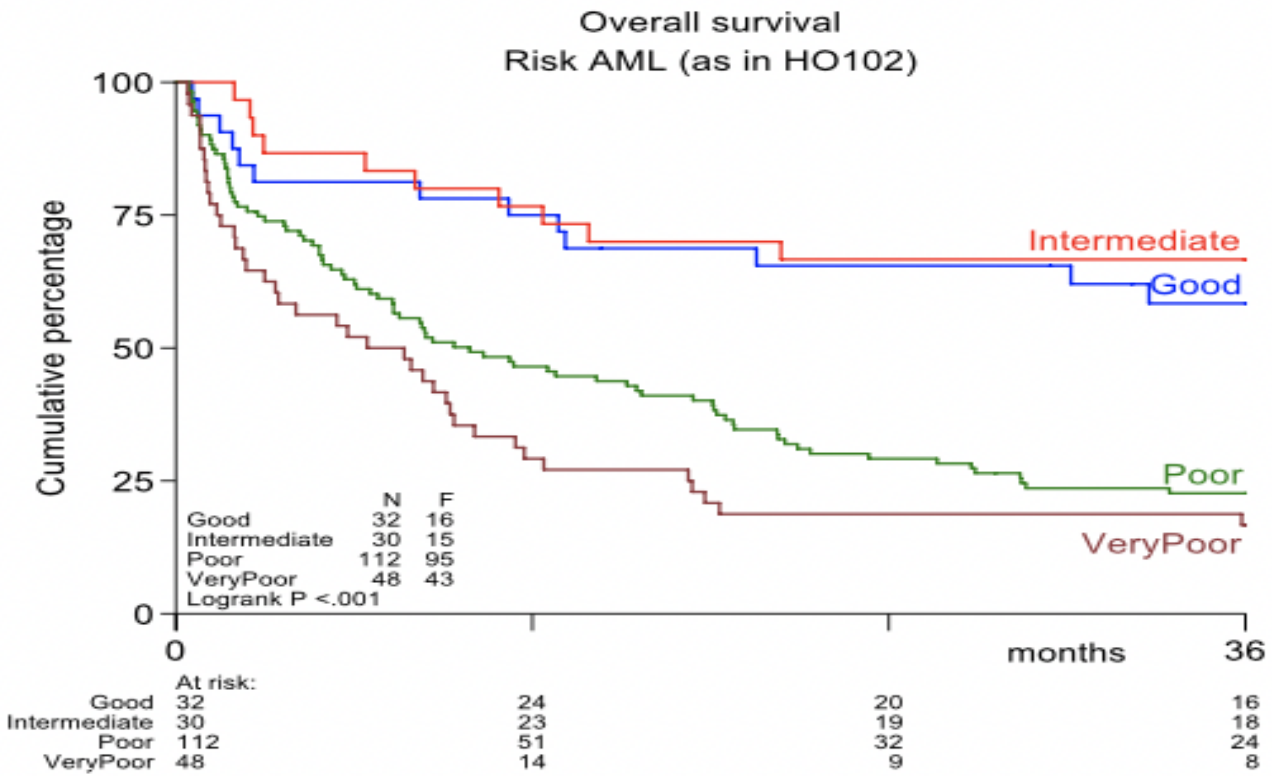
Schweizerische Arbeitsgemeinschaft für Kli
Groupe Suisse de Recherche Clinique sur
Swiss Group for Clinical Cancer Research
Gruppo Svizzero di Ricerca Clinica sul Can

HOVON 103 Lenalidomide Overall Survival



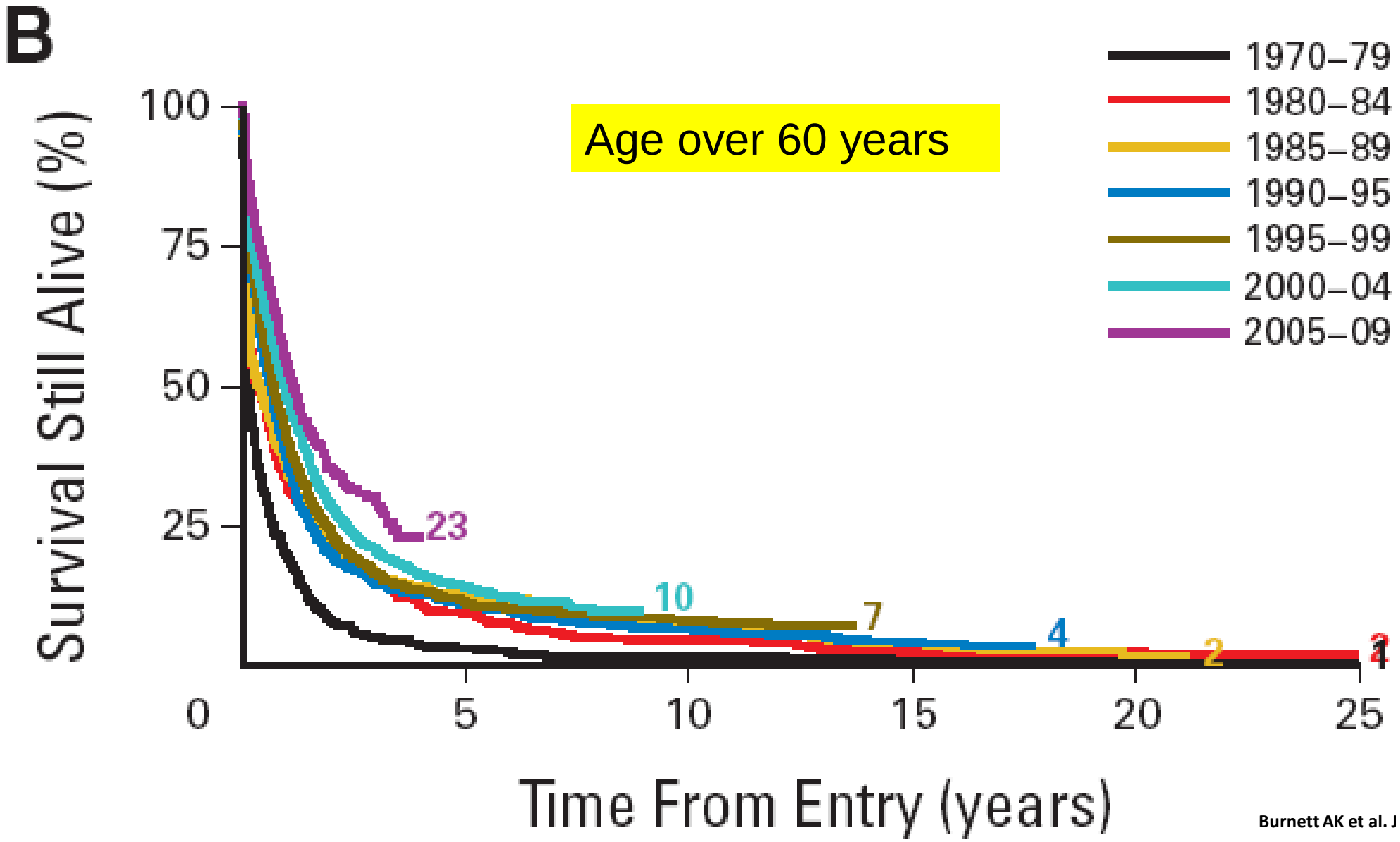
Ossenkoppele Leukemia 2020

HOVON 103 Lenalidomide
Overall Survival



Ossenkoppele Leukemia 2020

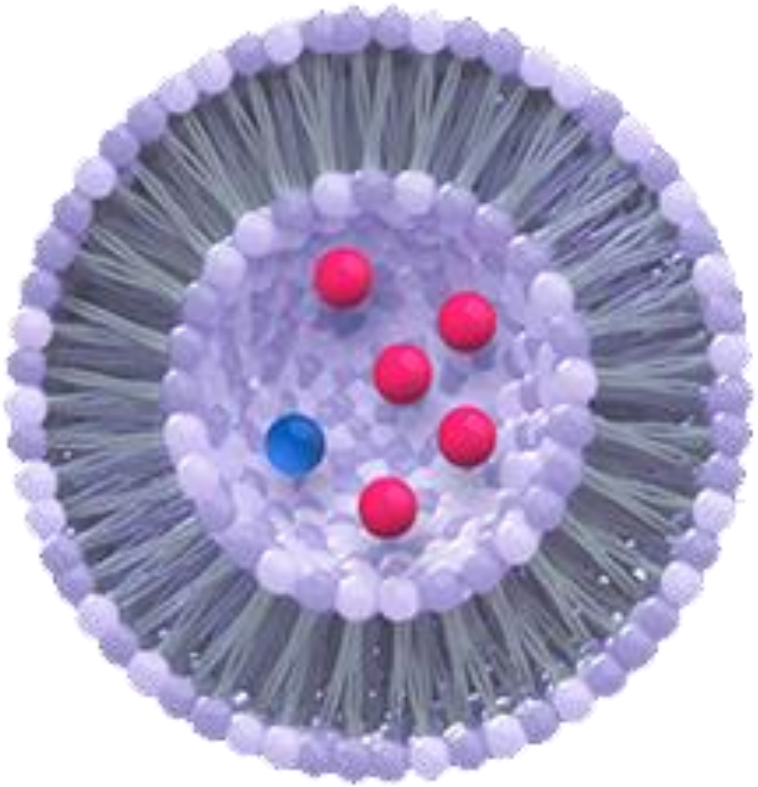
Change in overall survival in time age 15-59 yrs



Burnett AK et al. J Clin Oncol (2011

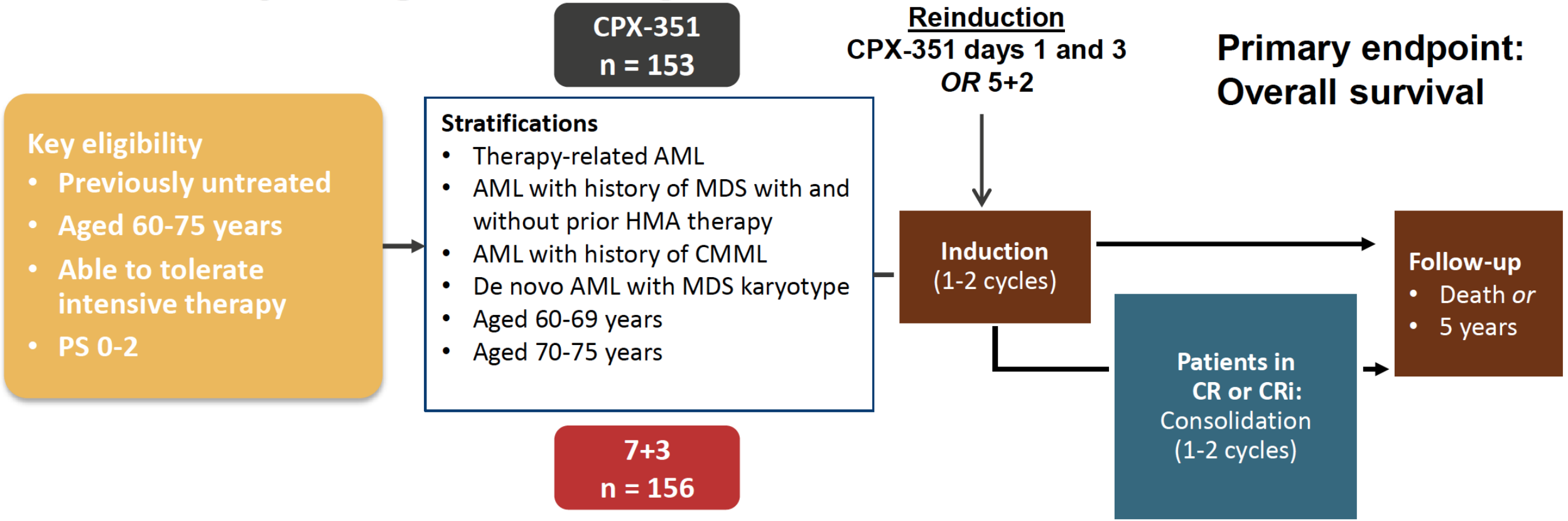
New Treatment Modalities!!!

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 unit = 0.44 mg daunorubicin plus 1.0 mg cytarabine (1:5 molar ratio) complexed with copper
- Targets bone marrow and preferentially targets leukemic compared with normal marrow progenitors

Phase 3 Study of CPX-351 Versus 7+3 in Older Patients With Newly Diagnosed High-Risk AML

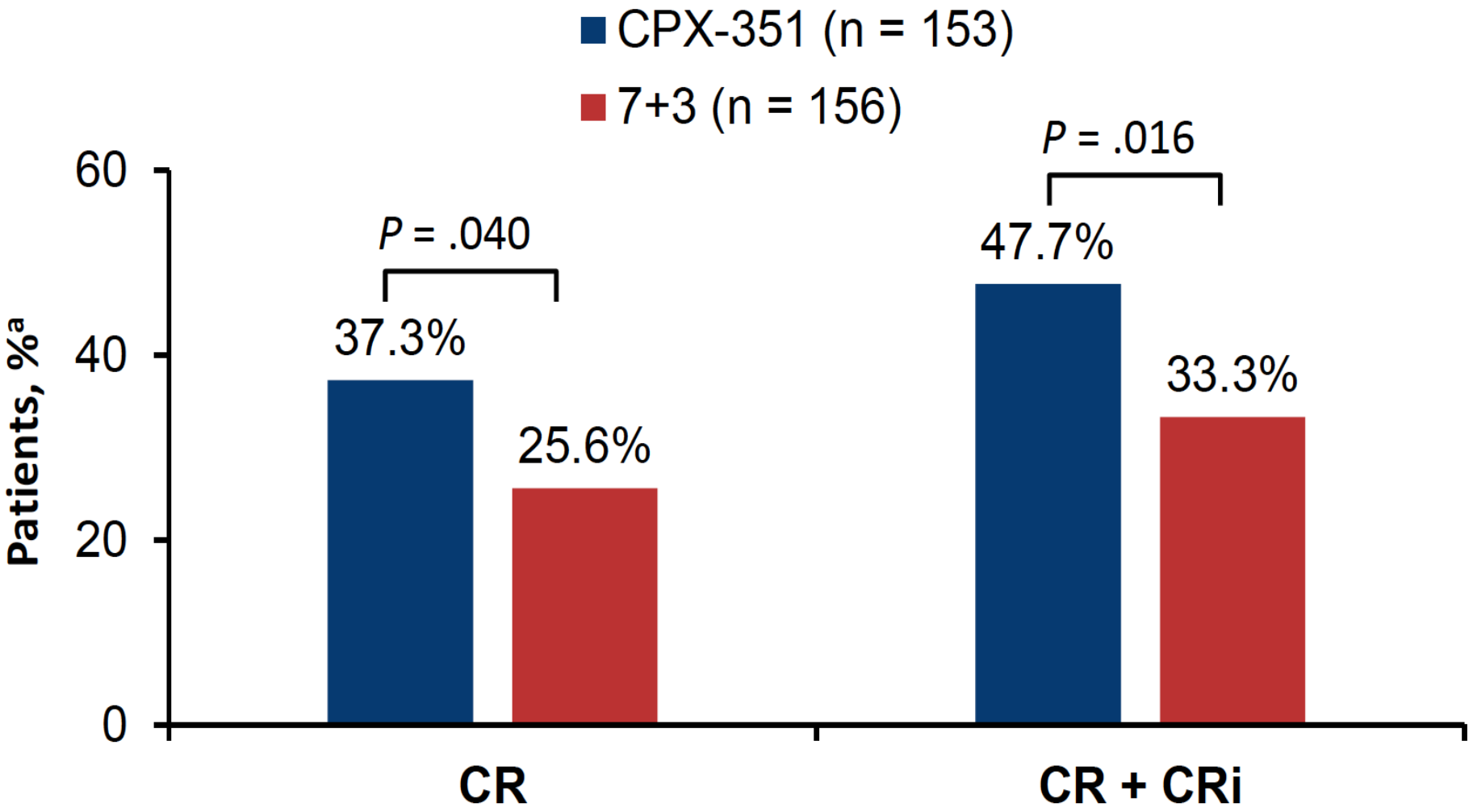


Induction
- CPX-351 44 mg/100 mg per m^2 IV days 1, 3, 5
- Cytarabine 100 mg/m^2/day x 7 plus daunorubicin 60 mg/m^2/day x 3

Consolidation
- CPX-351 29 mg/65 mg per m^2 IV days 1, 3
- Cytarabine 100 mg/m^2/day x 5 plus daunorubicin 60 mg/m^2/day x 2

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

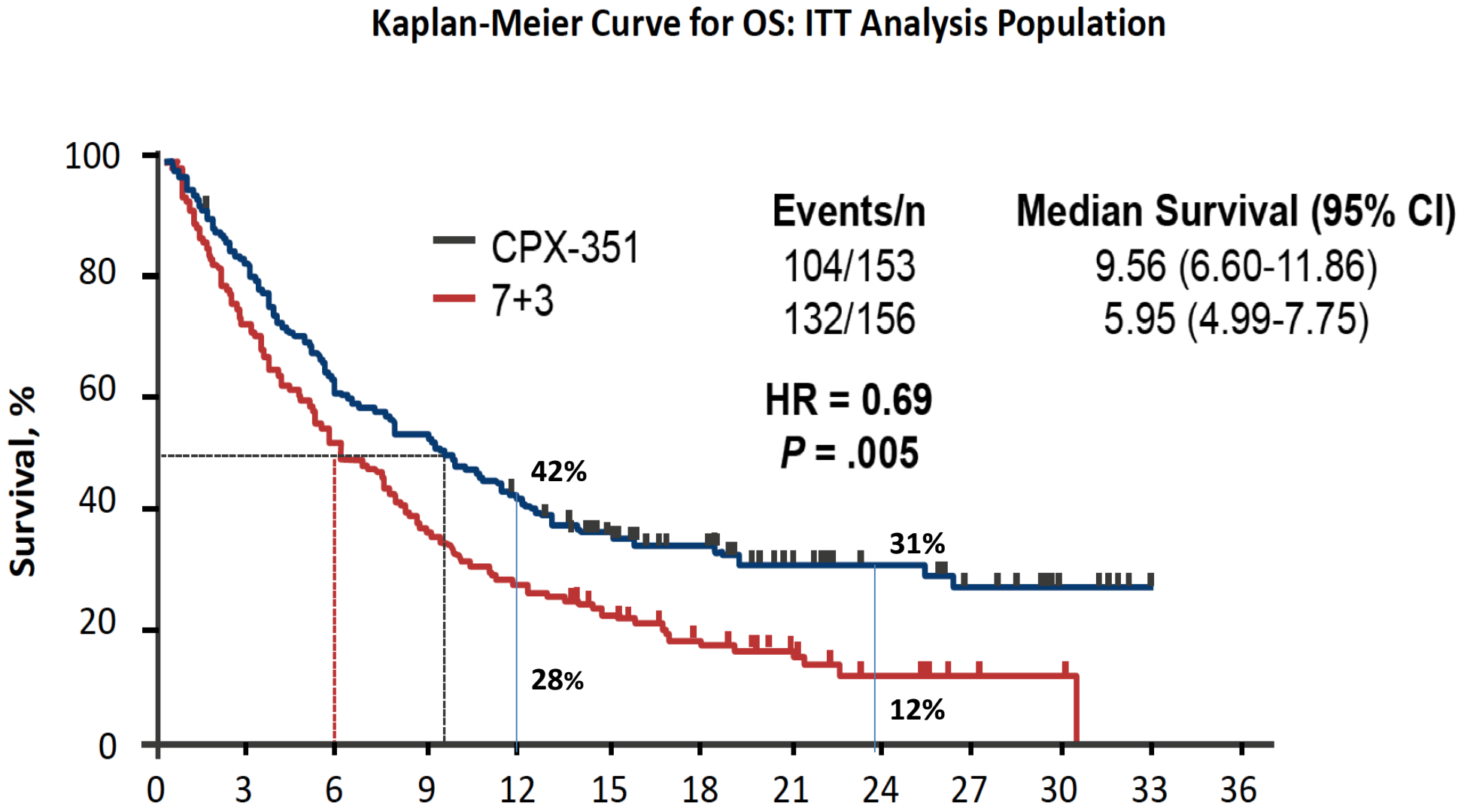
Phase 3 Study of CPX-351 Vs 7+3 in High-Risk AML: Response Rate



	CR	CR + CRi
Odds ratio (95% CI)	1.69 (1.03, 2.78)	1.77 (1.11, 2.81)

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

CPX-351 Improves Survival Among Older, High-Risk AML



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

“Current” standard for unfit elderly

- Prospective randomized trials in unfit AML:

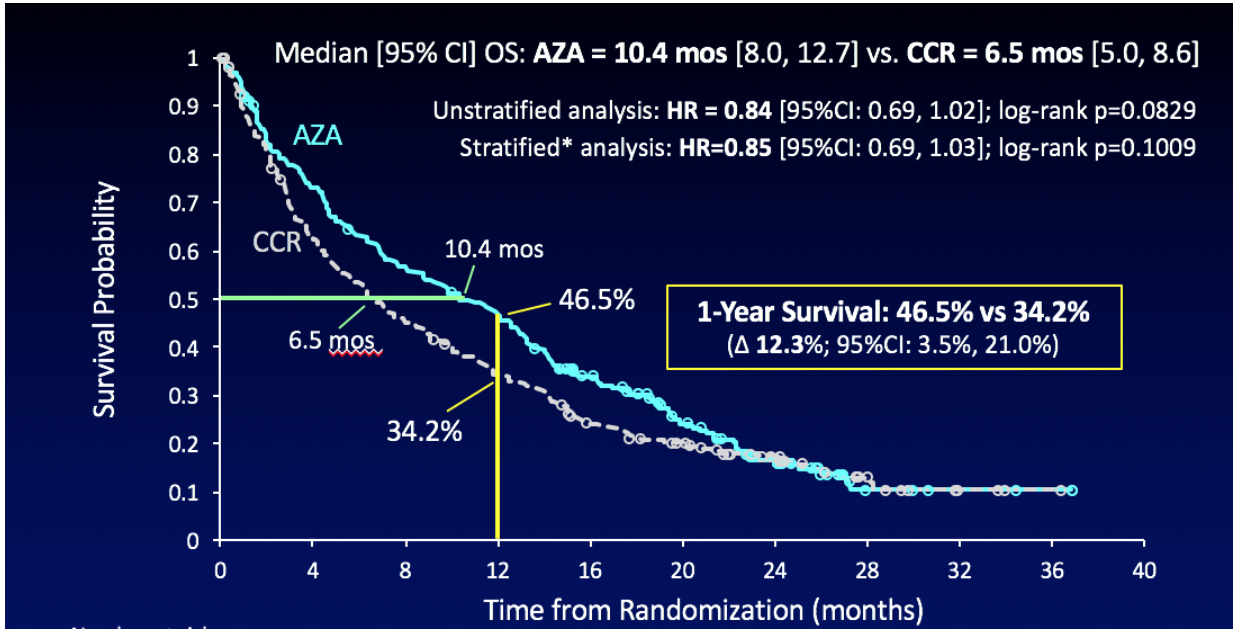
  - ◆Low dose Ara-C superior to BSC
    (Burnett et al. Cancer. 2007)

  - ◆Decitabine 5-days 20 mg/m^2 superior to CC
    (Kantarjian et al. JCO. 2012)

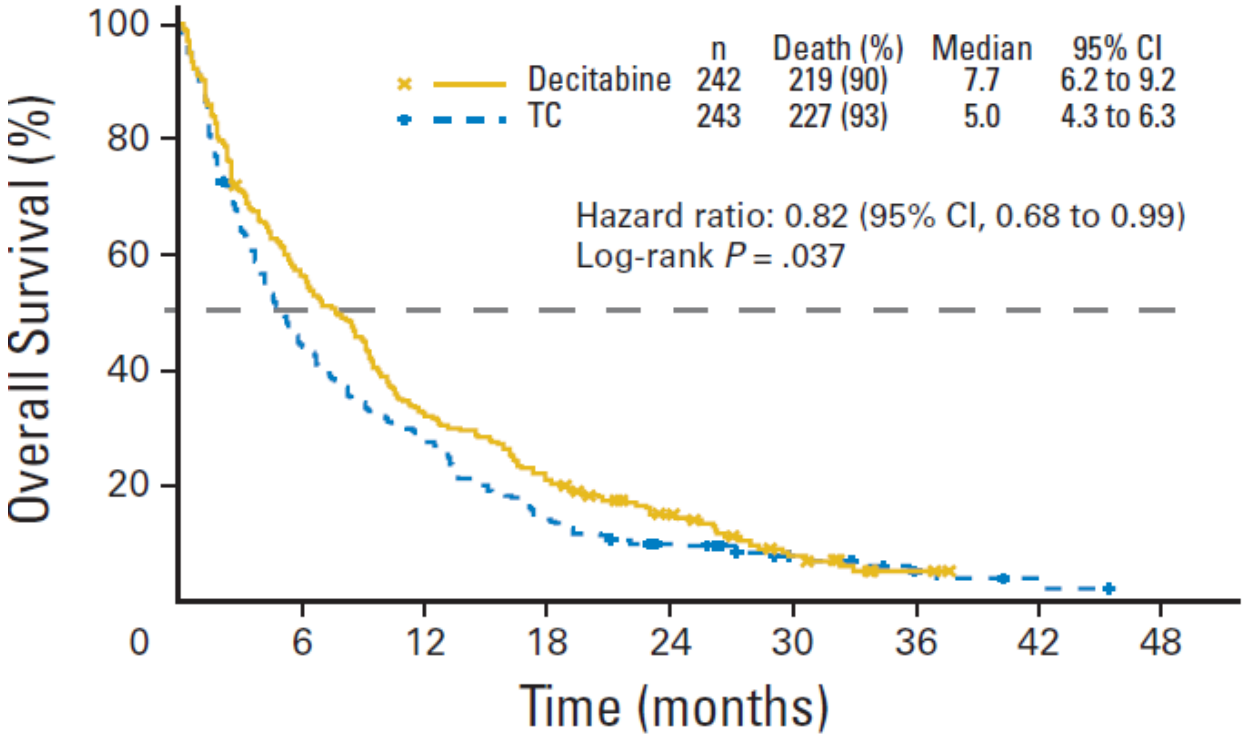
  - ◆Azacytidine 7-days 75mg/m2 superior to CC
    (Dombret et al. Blood 2015)

Frontline treatment for elderly patients with AML unfit for Intensive Chemotherapy

Azacytidine vs CCR[2]



Decitabine vs TC[1]



1. Kantarjian et al. J Clin Oncol 2012;30:2670-7. 2. Dombret et al. Blood 2015;126:291-9.

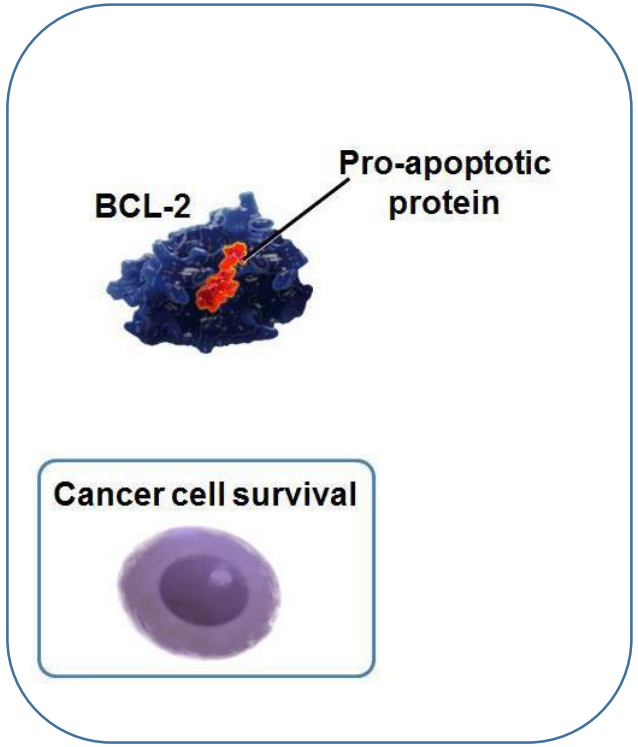
Recent approvals in AML

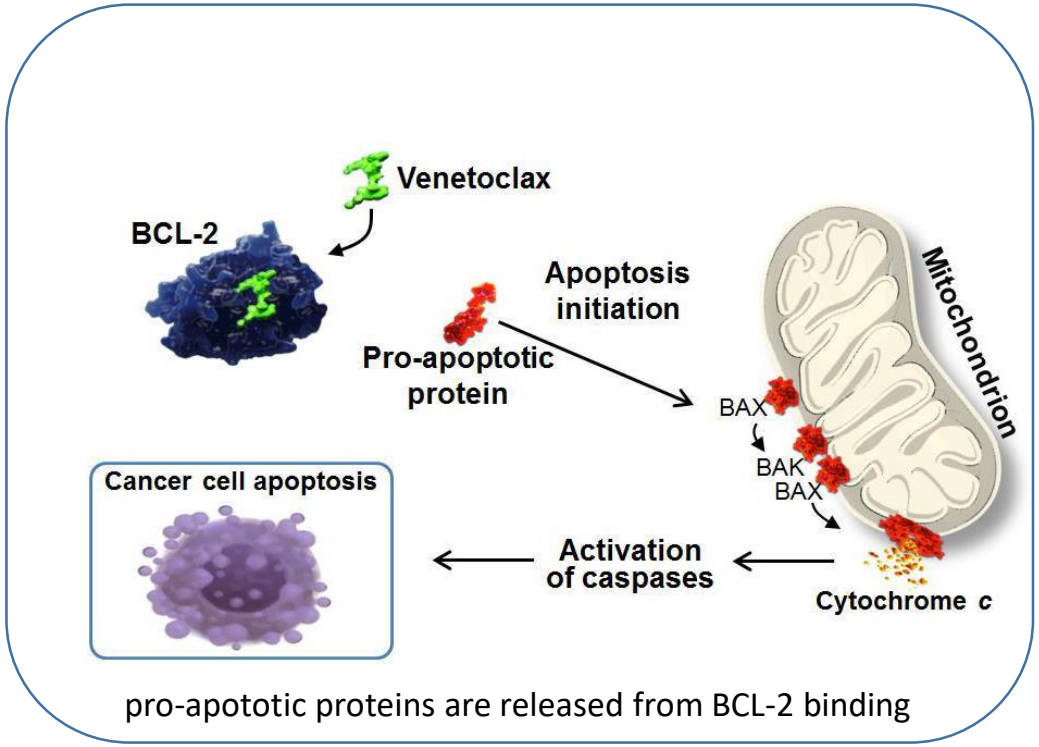
Drug	Indication	Approval
Midostaurin[1,2]	*De novo* AML with FLT3 mutation	FDA: 2017 EMA: 2017
Gemtuzumab ozogamicin[3,4]	*De novo* CD33^{+} AML (also R/R AML in the US)	FDA: 2017 EMA: 2018
CPX-351[5,6]	*De novo* t-AML or MRC-AML	FDA: 2017 EMA: 2018
Ivosidenib[7]	*De novo* R/R AML with IDH1 mutation	FDA: 2018
Enasidenib[8]	R/R AML with IDH2 mutation	FDA: 2017
Gilteritinib[9]	R/R AML with FLT3 mutation	FDA: 2018
Glasdegib[10]	(+LDAC) *De novo* AML in patients ≥75 years old or who have comorbidities precluding use of intensive chemotherapy	FDA: 2018
Venetoclax[11]	(+LDAC/HMA) *De novo* AML in patients ≥75 years old or who have comorbidities precluding use of intensive chemotherapy	FDA: 2018
Tagraxofusp: fusion protein of IL-3 and diphtheria toxin	Blastic Plasmacytoid Dendritic Cell Neoplasm	FDA: 2018

1. Novartis Pharmaceuticals. RYDAPT® (midostaurin) Prescribing Information. 2017; 2. Novartis Pharmaceuticals. RYDAPT® (midostaurin) summary of product characteristics. 2018; 3. Pfizer. MYLOTARG™ (gemtuzumab ozogamicin) Prescribing Information. 2017; 4. Pfizer. MYLOTARG™ (gemtuzumab ozogamicin) summary of product characteristics. 2018; 5. Jazz Pharmaceuticals. VYXEOS™ (daunorubicin and cytarabine) Prescribing Information. 2017; 6. Jazz Pharmaceuticals. VYXEOS™ (daunorubicin and cytarabine) summary of product characteristics. 2018; 7. Agios Pharmaceuticals, Inc. TIBSOVO® (ivosidenib) Prescribing Information. 2018; 8. Agios Pharmaceuticals, Inc. IDHIFA ® (enasidenib) Prescribing information. 2017; 9. Astellas. XOSPATA® (gilteritinib) Prescribing Information. 2018; 10. Pfizer. Daurismo™ (glasdegib) Prescribing information. 2018;

Venetoclax: selective bcl-2 inhibitor

Many tumors overexpress bcl-2





pro-apototic proteins are released from BCL-2 binding

Konopleva M Cancer Discovery 2016

A Randomized, Double-blind, Placebo-controlled Study of Venetoclax with Azacitidine vs Azacitidine in Treatment-naïve Patients with Acute Myeloid Leukemia Ineligible for Intensive Therapy: VIALE-A

Eligibility

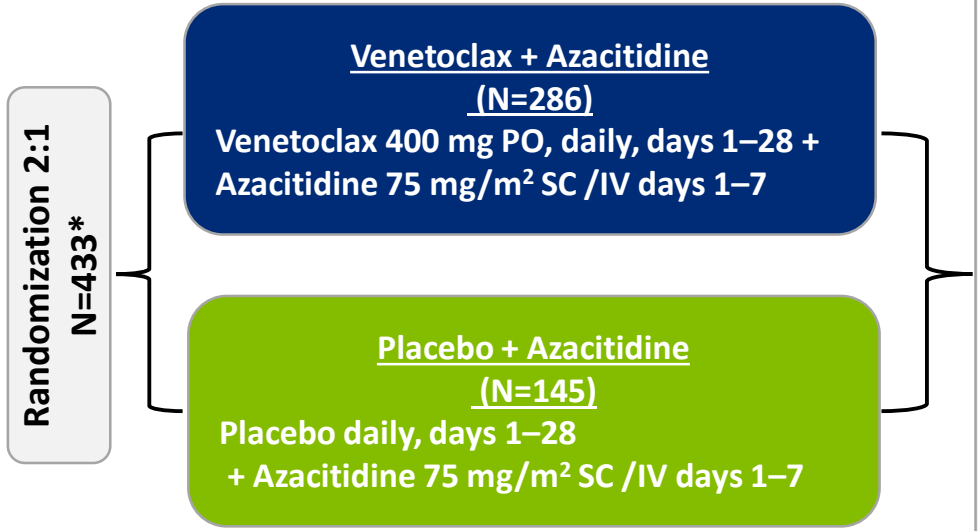
Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment



Endpoints

Primary

- Overall survival

Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

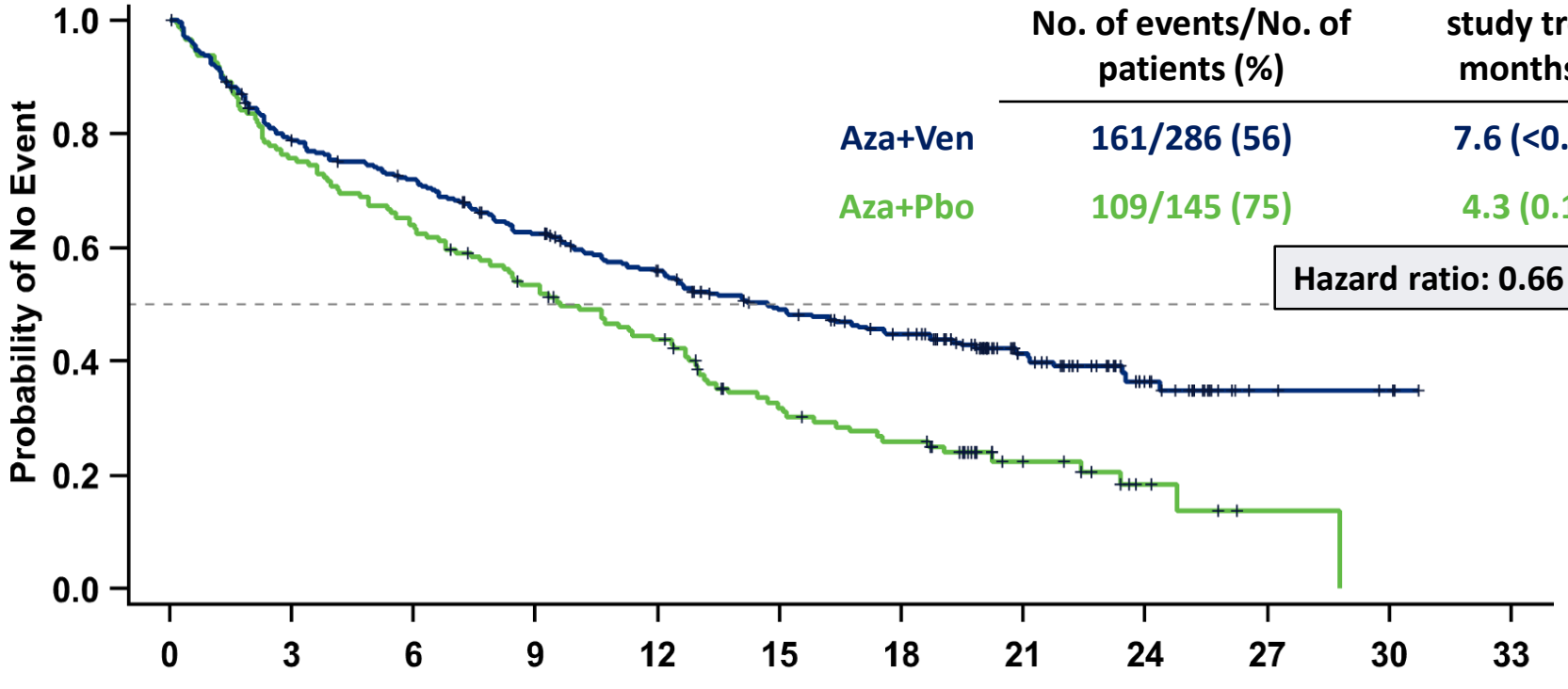
Randomization Stratification Factors Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up **Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg
Cycle 2 → Day 1-28: 400 mg

Courtesy C.Dinardo

N Engl J Med. 2020 Aug 13;383(7):617-629

Overall Survival



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001

35

Patients at Risk

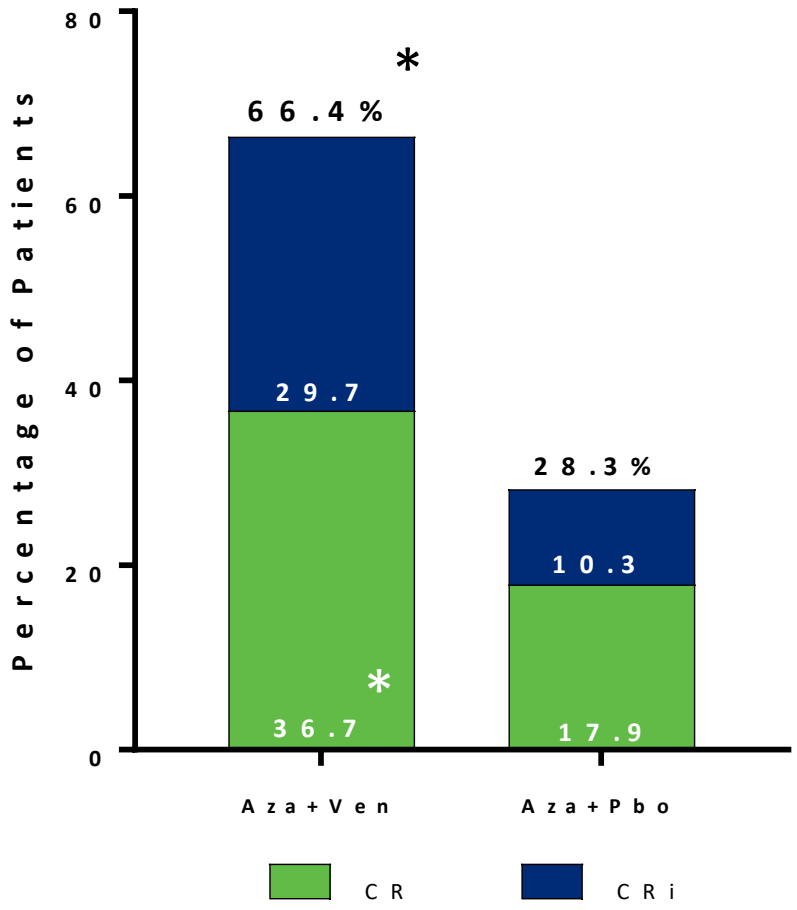
Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

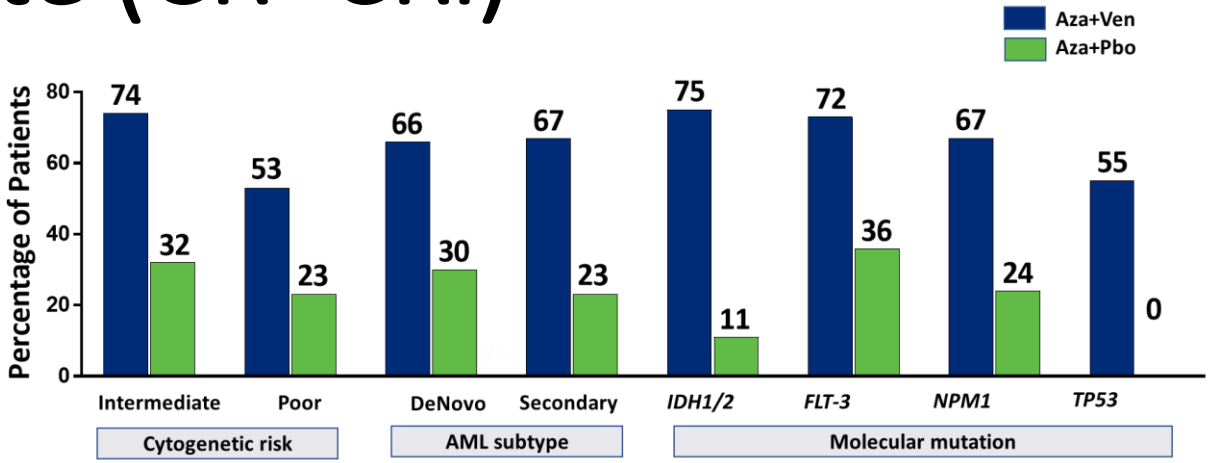
Median follow-up time: 20.5 months (range: <0.1 – 30.7)

Courtesy C.Dinardo

N Engl J Med. 2020 Aug 13;383(7):617-6

Composite Response Rate (CR+CRi)





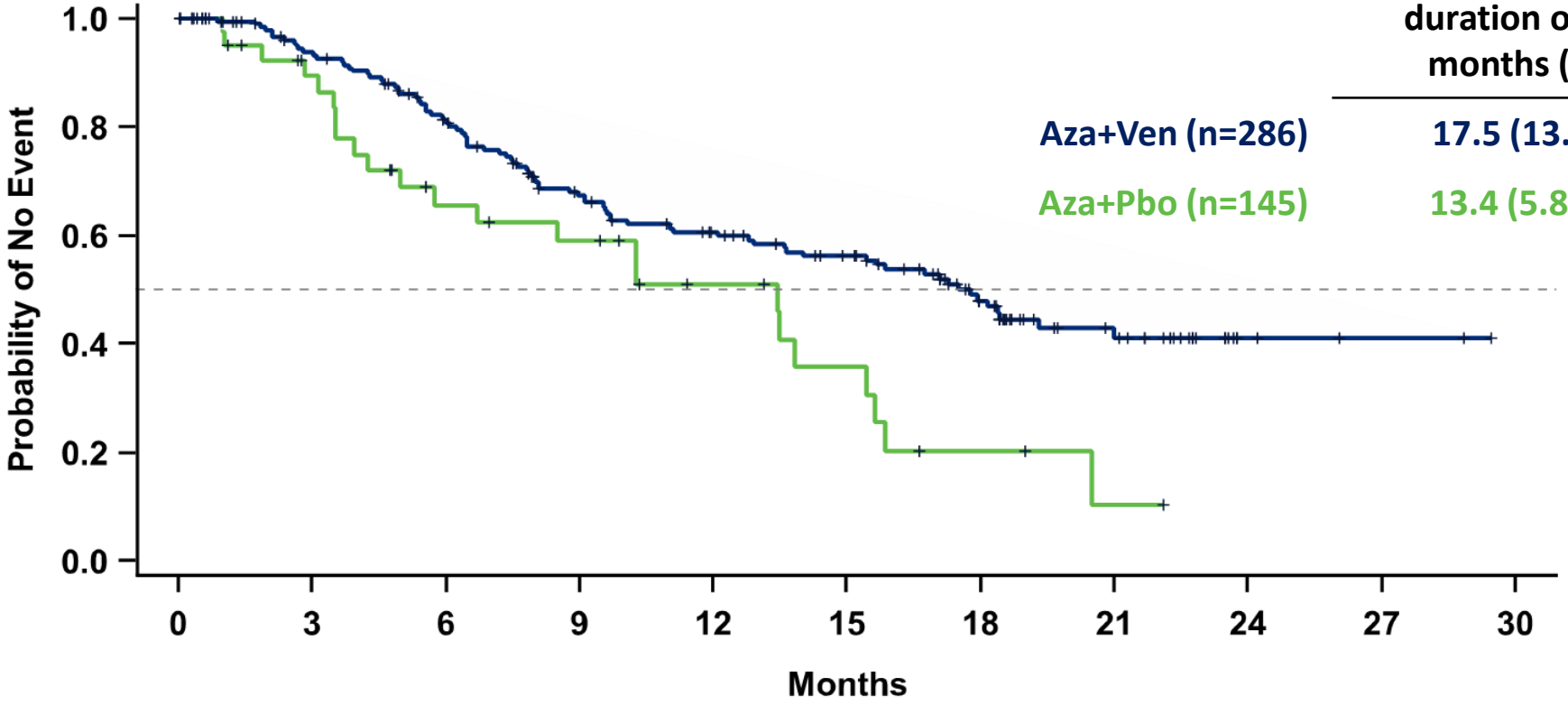
	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza+Ven (n=286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza+Pbo (n=145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 by CMH test

Courtesy C.Dinardo

N Engl J Med. 2020 Aug 13;383(7):617-62

Duration of Response After Achieving CR/CRi



	Median duration of CR/CRi, months (95% CI)	Median duration of CR, months (95% CI)
Aza+Ven (n=286)	17.5 (13.6 – NE)	17.5 (15.3 – NE)
Aza+Pbo (n=145)	13.4 (5.8 – 15.5)	13.3 (8.5 – 17.6)

Patients at Risk

Aza+Ven	190	161	133	101	85	72	44	23	4	2	0
Aza+Pbo	41	31	20	17	11	7	3	1	0	0	0

Courtesy C.Dinardo

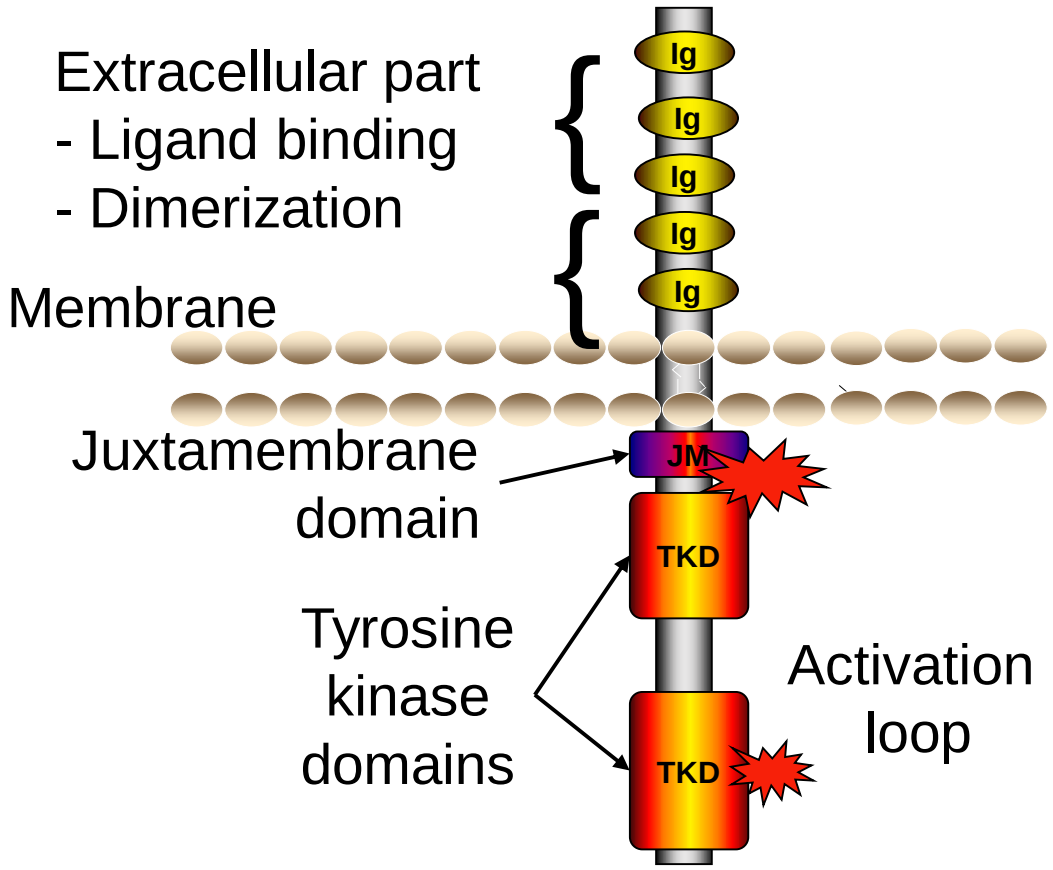
Aza: Azacitidine; CR: Complete remission; CRi: CR with incomplete count recovery ; NE: Not estimable; Pbo: Placebo; Ven: Venetoclax

N Engl J Med. 2020 Aug 13;383(7):617-62

Combination of venetoclax plus an HMA is the new gold standard for unfit AML

- **Azacitidine and venetoclax combination significantly extended survival in treatment-naïve patients with AML ineligible for standard induction therapy compared to azacitidine and placebo**
- **Patients treated with azacitidine and venetoclax combination had significantly higher remission rates and transfusion independence**
- **The adverse events with azacitidine and venetoclax combination were similar to previously reported experiences**

FLT3-ITD Mutations in AML



- *FLT3* internal tandem duplication (ITD) occurs in ≈ 25% of younger adult patients with AML (28%-34% CN-AML)
- FLT3 TKD mutations (5-10%)

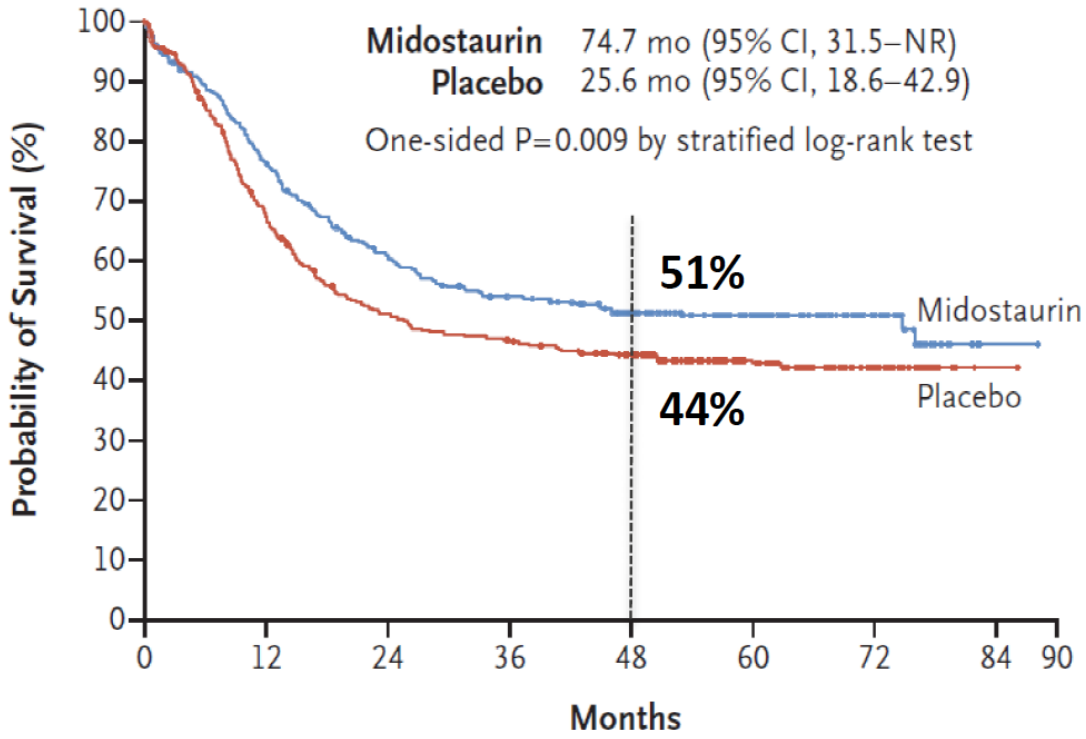
- ligand-independent dimerization and constitutive activation of the tyrosine kinase domain
  - ⇨ factor-independent growth
  - ⇨ block in myeloid differentiation

- Associated with adverse prognosis

Whitman SP, et al. *Cancer Res*. 2001;61:7233-7239; Thiede C, et al. *Blood*. 2002;99:4326-4335; Kottaridis PD, et al. *Blood*. 2002;100:2393-2398; Gale R, et al. *Blood*. 2008;111:2776-2784; Breitenbuecher F, et al. *Blood*. 2009;113:4074-4047; Kayser S, et al. *Blood*. 2009;114:2386-2392; Breitenbuecher F, et al. *Blood*. 2009;113:4063-4073; Schlenk RF, et al. *Blood*. 2014;124:3441-3449; Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

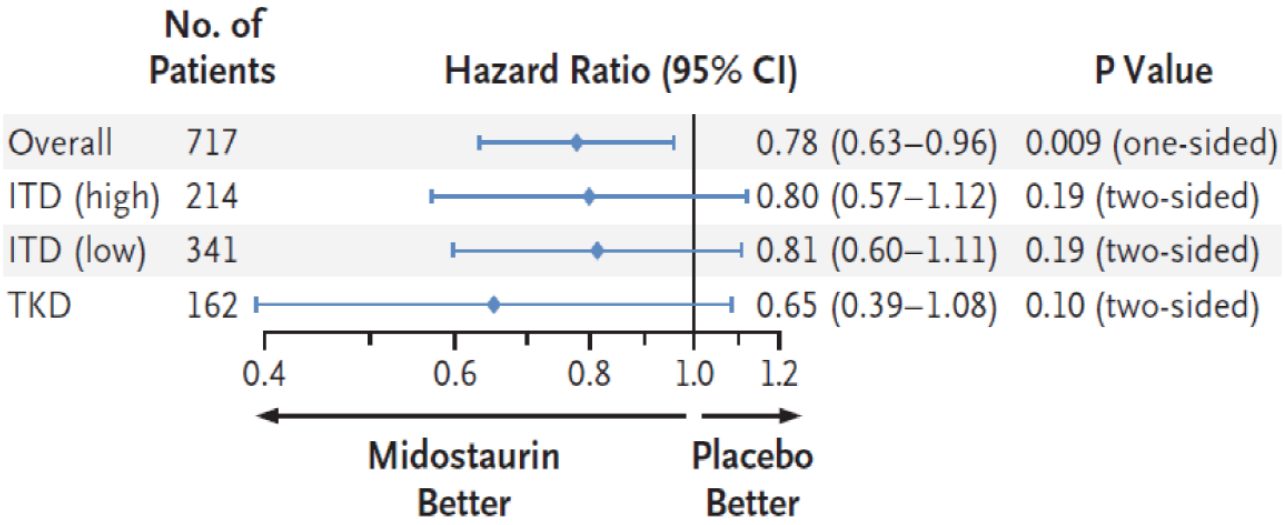
RATIFY (CALGB 10603): Overall Survival

Median OS



22% reduced risk of death in the midostaurin arm)

OS Subgroup Analysis



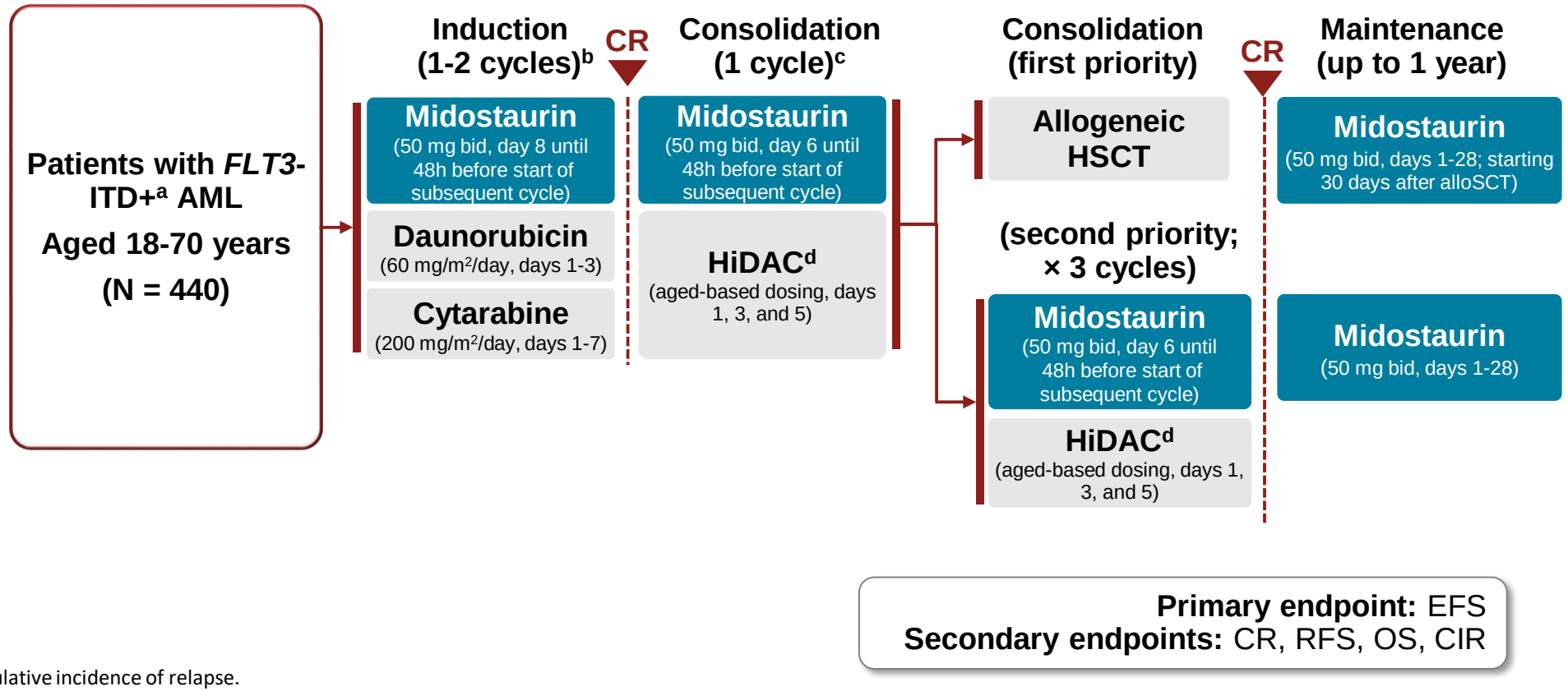
Toxicity

No difference in early mortality

Higher rate of rash and GI toxicity with mido

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

Midostaurin Plus Chemotherapy for *FLT3*-ITD+ AML *AMLSG 16-10 Trial*



CIR, cumulative incidence of relapse.

[a] *FLT3* screening results within 48 hours; *FLT3*-ITD/-WT ratio > 0.05 by GeneScan-based fragment length analysis required to be *FLT3*-ITD+.

[b] During induction, patients achieving PR after cycle 1 can receive an optional cycle 2.

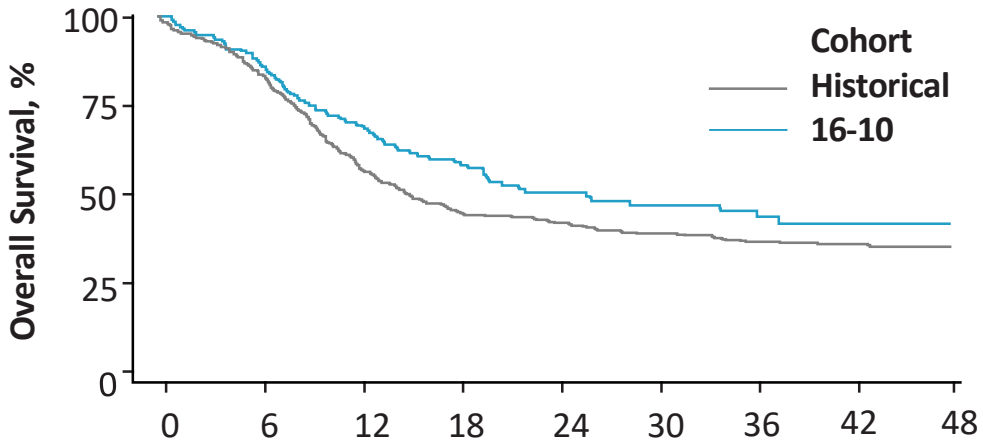
[c] For patients eligible for alloSCT, 1 course of HiDAC is optional before alloSCT.

[d] Age-appropriate cytarabine dose on days 1, 3, and 5: 18-65 years, 3 g/m^2 q12h (total dose 18 g/m^2); > 65 years ,1 g/m^2 q12h (total dose 6 g/m^2).

1. Schlenk RF, et al. *Blood*. 2016;128(22) [abstract 449]. 2. https://clinicaltrials.gov/ct2/show/NCT01477606. Accessed Oct 23, 2017.

Comparison AMLSG 16-10 vs Historical Control Propensity Score Weighting Analysis*

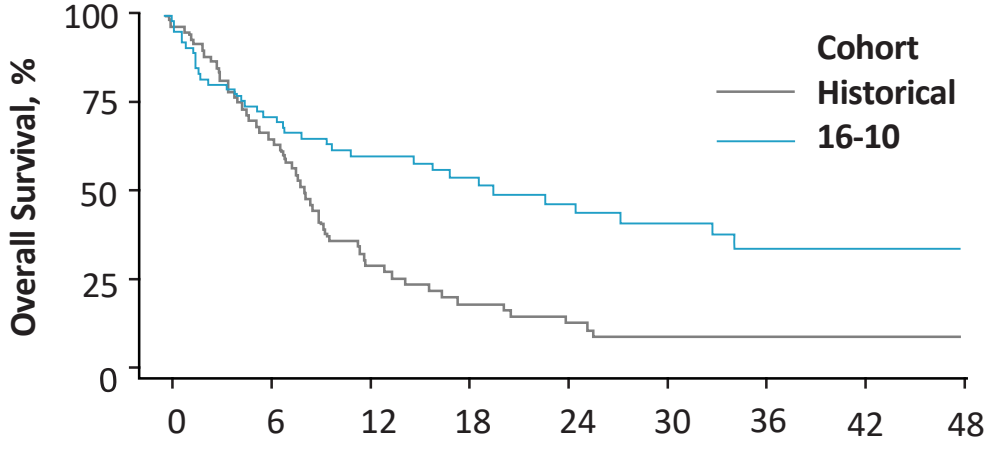
Age 18-60 years



Cohort									
Historical	353	296	203	155	141	131	121	111	97
16-10	155	131	92	67	46	36	28	12	4

HR = 0.70 (95 CI, 0.535-0.920)

Age 60-70 years



Cohort									
Historical	62	41	19	11	9	5	5	5	5
16-10	62	48	34	27	18	14	8	6	4

HR = 0.49 (95% CI, 0.316-0.753)

*Propensity score weighting on age, gender, WBC, marrow blasts, *NPM1* mutations

Unpublished data.
ClinicalTrials.gov: NCT01477606 (active)

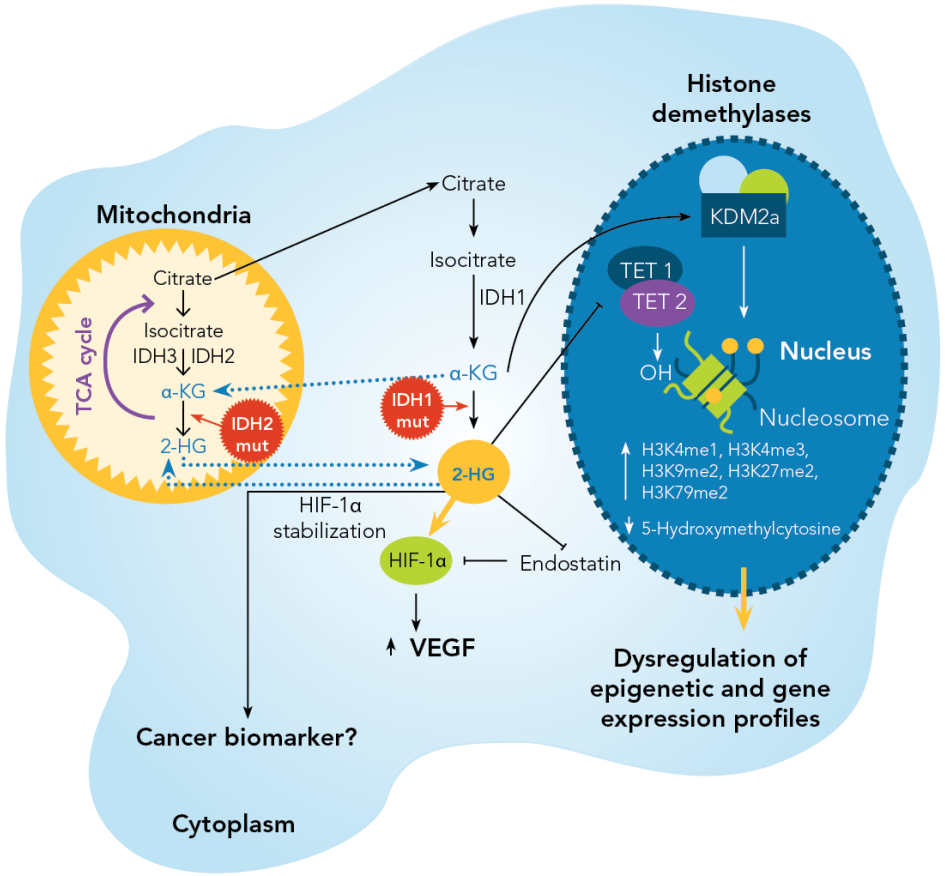
Older pts with Newly Diagnosed *FLT3*^{mut} AML Frontline FLT3i + Lower Intensity Therapy

Regimen	Age	CR/CRi (%)	Median OS, mo	N
SORAFINIB + AZA	64 (24-87)	43	6.2	43 (6 were ND)
MIDOSTAURIN + AZA	65 (21-85)	26	5.1	54 (14 were ND)
GILTERITINIB + AZA (LACEWING)	76 (65-86)	67	8.7	15
QUIZARTINIB + AZA/LDAC	68 (>60)	83	21.1	12
AZA/DAC + VEN	>65	53-65	12-13	30
TKI + DEC10-VEN	70 (64-80)	100	NR	10

Courtesy Dr Dinardo

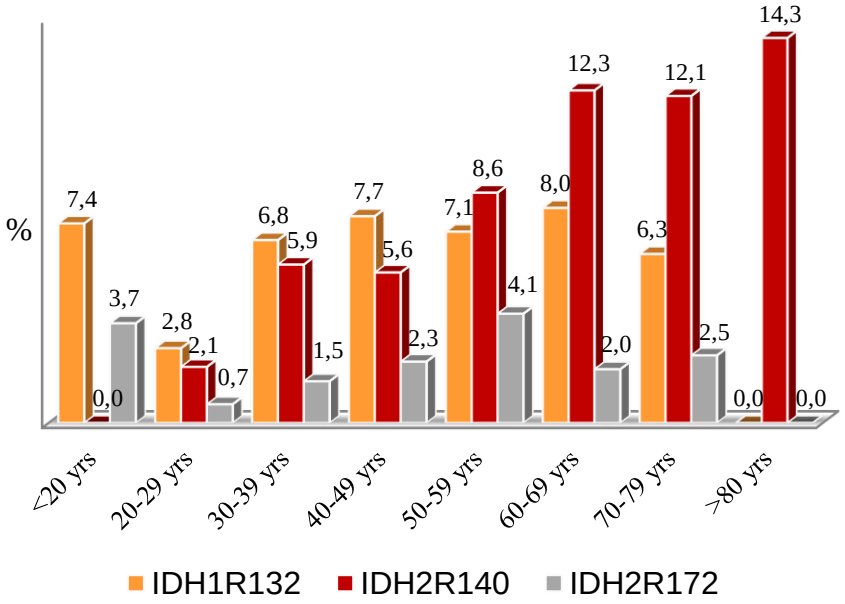
Strati P et al, AJH 2015., Esteve J et al, EMJ Hematol. 2019
Esteve J et al, ASH 2018, Swaminathan et al. Blood. 2017,
DiNardo CD et al, Blood 2019. Maiti A et al, ASCO poster #7519

Role of IDH in Cancer



- **IDH is a critical metabolic enzyme in the citric acid cycle**
- **IDH1 in cytoplasm and IDH2 in mitochondria**
- **Cancer-associated IDHm produces 2-hydroxyglutarate (2-HG) and blocks normal cellular** differentiation

Mutation frequency in AML (n=2,464 pts)[2]



Mutation frequency: *IDH1*: 7.5%; *IDH2*: 11.5%

Dohner unpublished

Prensner and Chinnaiyan Nature, 2011

nature ARTICLES

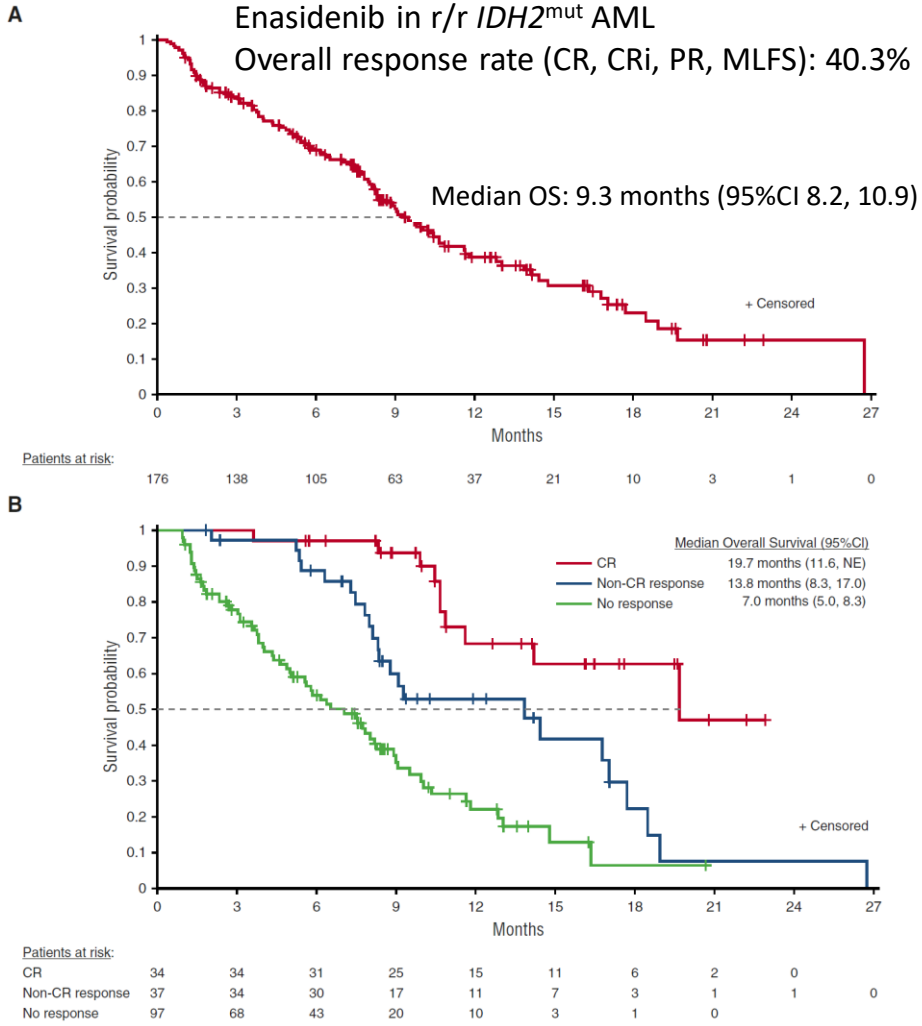
Cancer-associated IDH1 mutations produce 2-hydroxyglutarate

Enasidenib and ivosidenib in R/R AML

	Enasidenib 100 mg (n=214) (Stein et al, Blood 2017/2019)	**Ivosidenib 500 mg** (n=125) (DiNardo et al, NEJM 2018)
Overall response (number, %)	83 (38.8%)	52 (41.6%)
CR (number, %)	42 (19.6%)	27 (21.6%)
CRi or CRp (number, %)	20 (9.3%)	16 (12.8%)
Time to first response, median (months, range)	1.9 (0.5 – 9.4)	1.9 (0.8 – 4.7)
Duration of response, median (months, 95% CI)	5.6 (3.8 – 7.4)	6.5 (4.6 – 9.3)
Duration of response in patients with CR (months, 95% CI)	8.8 (5.6 – NR)	9.3 (5.6 – 18.3)
Median overall survival (months, 95% CI)	8.8 (7.7 – 9.6)	8.8 (6.7 – 10.2)

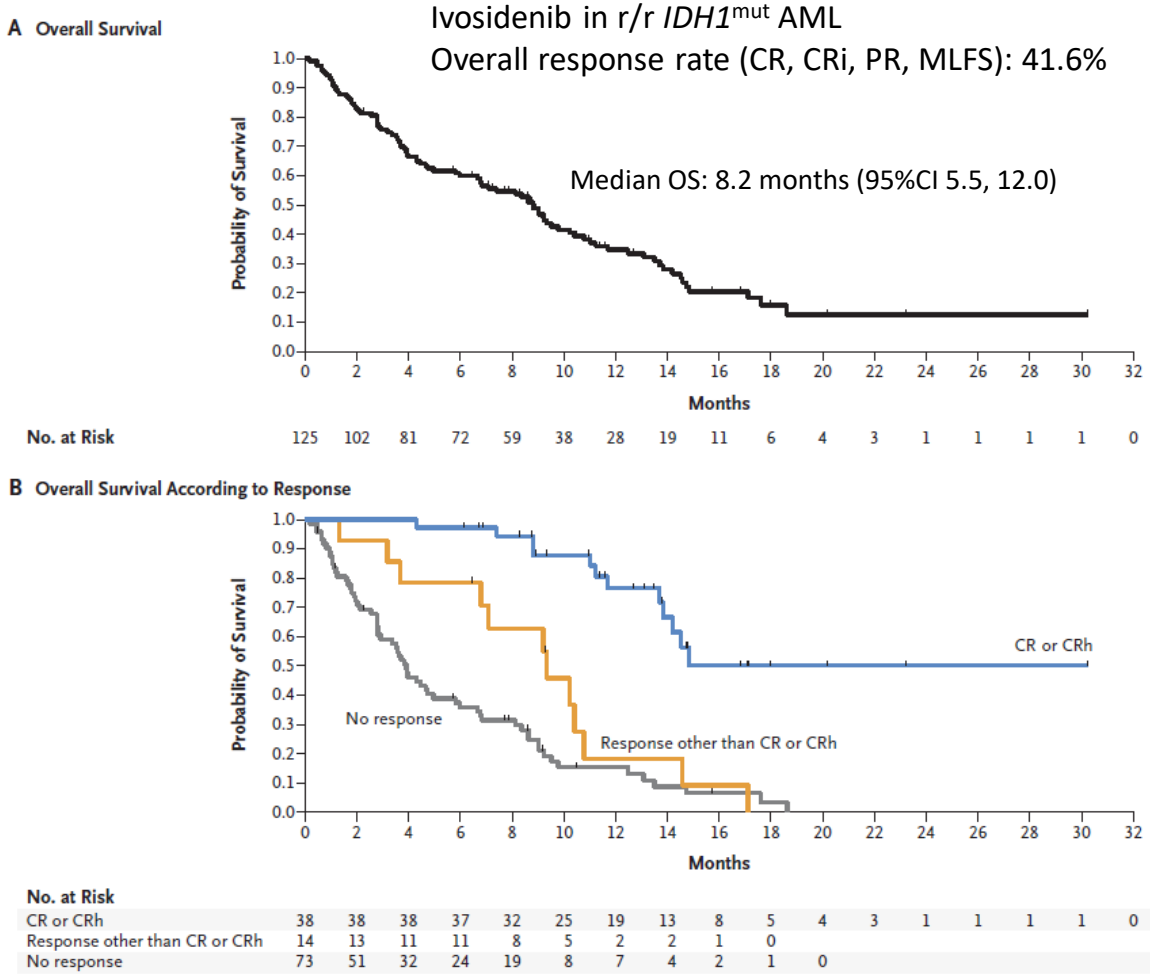
Enasidenib (AG-221) and Ivosidenib (AG-120) in mutant *IDH2* and *IDH1* relapsed or refractory AML

Enasidenib in r/r *IDH2*^{mut} AML
Overall response rate (CR, CRi, PR, MLFS): 40.3%



Stein E, et al. Blood. 2017;130(6):722-31.

Ivosidenib in r/r *IDH1*^{mut} AML
Overall response rate (CR, CRi, PR, MLFS): 41.6%



DiNardo CD, et al. N Engl J Med. 2018;378(25):2386-2398.

Ivosidinib in untreated AML

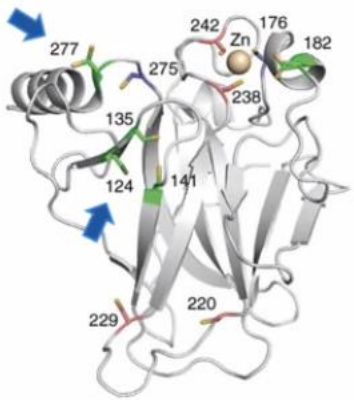
Ivosidinib	N=34
Median age	76.5 yrs (range 64-87)
sec AML	76%
prior MDS	53%
Overall response rate, n (%)	**55%**
CR	**30%**
CR+CRh	**42%**
Duration of CR, months	NE
12-months duration of response,	78%
mIDH1 clearance in CR+CRh patiens	9/14

G.Roboz EHA 2019 PS1025

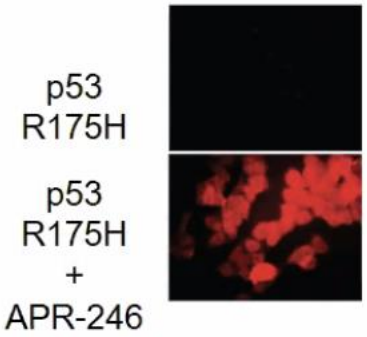
Ivosidinib plus AZA	N=23
Median age	76 yrs (range 61-88)
Overall response rate, n (%)	**78%**
CR	**57%**
CR+CRh	**70%**
Median time to response	1.8 months
Median time to CR	3.5 months
Median duration of response	NE
mIDH1 clearance	10/16(63%)

C.Dinardo EHA 2019 PS 1023

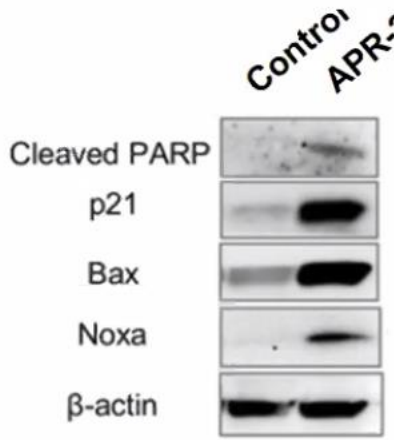
Targeting *TP53* mutations in MDS/AML via APR-246



APR-246 binds covalently to p53…



…restores wt p53 conformation & activity…



…and triggers cell cycle arrest and apoptosis

Courtesy: Dr. D. Sallman

MOFFITT CANCER CENTER

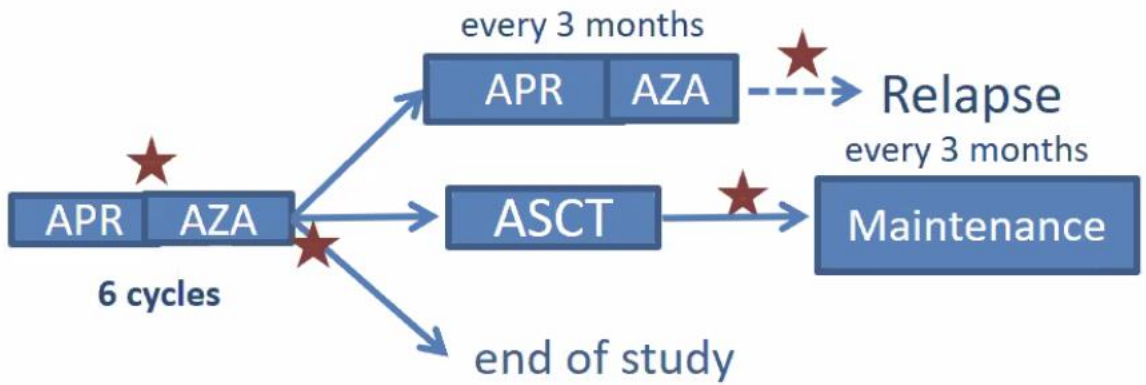
A. Fersht et al. (2010) Prot. Sci; Q. Zhang et al, (2018) Cell Death Disease; H. Furukawa et al, (2018) Cancer Sci.

APR-246 Combined with Azacitidine (AZA) in *TP53* Mutated Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML). A Phase 2 Study By the Groupe Francophone Des Myélodysplasies (GFM)

Thomas Cluzeau, Marie Sebert, Ramy Rahmé, Stefania Cuzzubbo, Anouk Walter-Petrich, Jacqueline Lehmann-Che, Isabelle Madelaine, Pierre Peterlin, Blandine Bève, Habiba Attalah, Fatiha Chermat, Elsa Miekoutima, Odile Beyne Rauzy, Christian Recher, Aspasia Stamatoullas, Lise Willems, Emmanuel Raffoux, Céline Berthon, Bruno Quesnel, Antoine F. Carpentier, David A. Sallman, Sylvie Chevret, Lionel Ades, Pierre Fenaux

Université Côte d'Azur; CHU of Nice, Hematology department; Mediterranean center of molecular medicine, INSERM U1065; Groupe Francophone des Myélodysplasies (GFM)

GFM-APR phase 2 study design

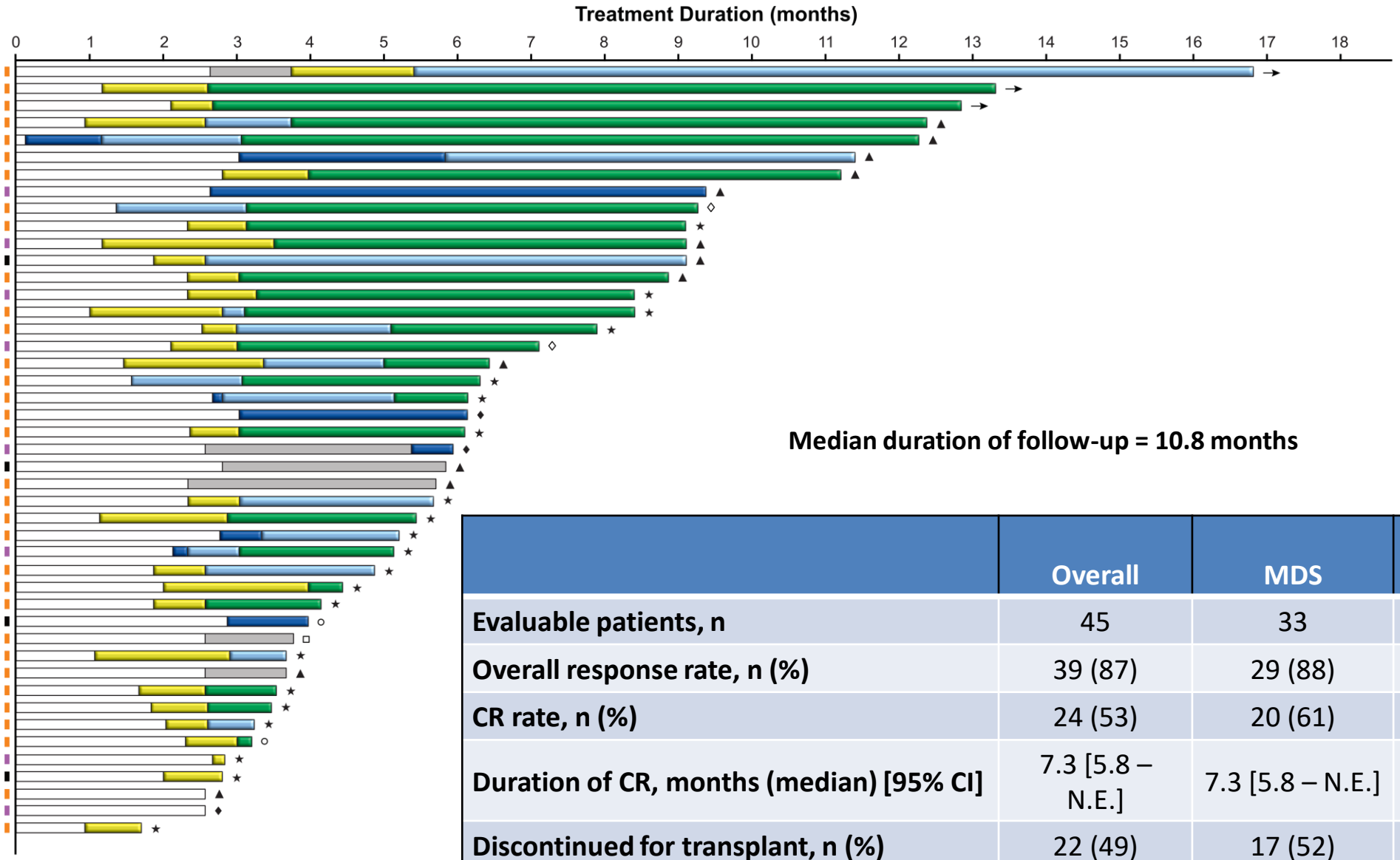


- APR-246 4500mg/d IV over 6 hours days 1-4
- AZA 75mg/m² SC daily days 4-10
- 28 day cycles
- Maintenance treatment after Allogeneic SCT for 12 months:
  - Azacitidine 36mg/m² SC daily days 1-5
  - APR-246 3700mg/d IV over 6 hours days 1-4

➢ MDS intermediate, high and very high IPSS-R and AML (including with > 30% marrow blasts) with *TP53* mutation

★ Bone marrow evaluation

Response to Treatment in Evaluable Patients (n=45) receiving AZA + APR-246



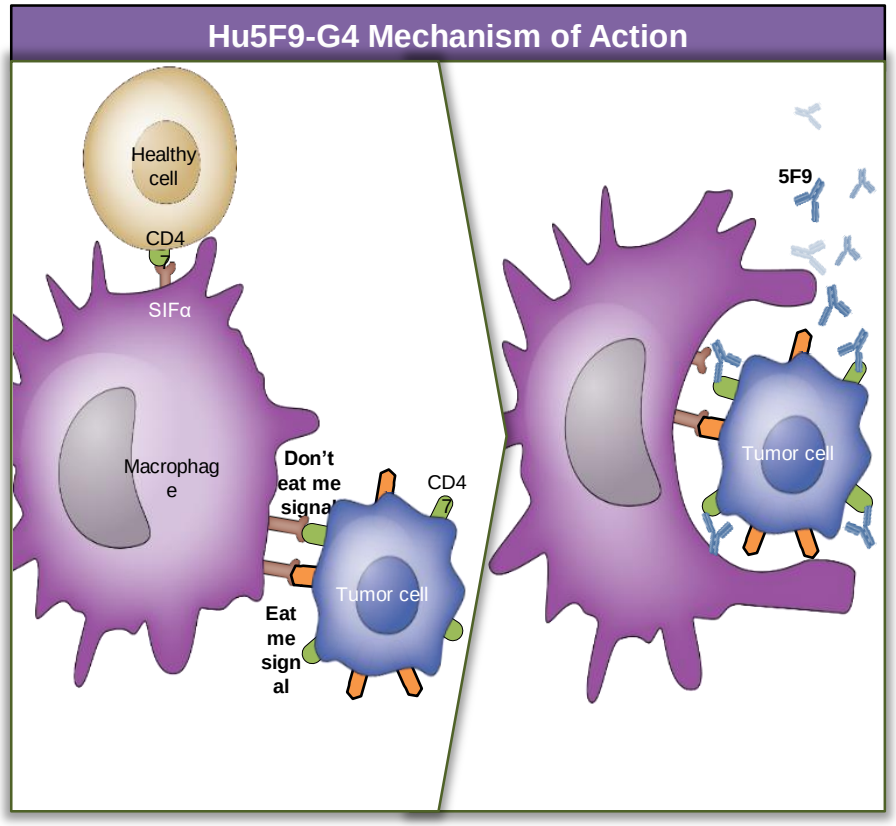
MDS
AML
CMML/MDS-MPN
CR
mCR + HI
mCR / MLFS
HI
SD
NR / NE
Ongoing
Discontinued: Transplant
Discontinued: AE
Discontinued: Withdrawal / Refusal
Discontinued: Other
Progressive Disease
Death

Median duration of follow-up = 10.8 months

	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	**8**	4
Overall response rate, n (%)	39 (87)	29 (88)	**7 (88)**	3 (75)
CR rate, n (%)	24 (53)	20 (61)	**4 (50)**	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	**7.0 [3.3 – N.E.]**	N.E.
Discontinued for transplant, n (%)	22 (49)	17 (52)	**4 (50)**	1 (25)

Sallman D et al, ASH 2019

Azacitidine + CD47 Antibody Magrolimab for MDS/AML



- **CD47 is a "don't eat me" signal on cancer cells that enables macrophage evasion**
- **Magrolimub (Hu5F9-G4) targets CD47 on tumor cells, inducing macrophage phagocytosis**

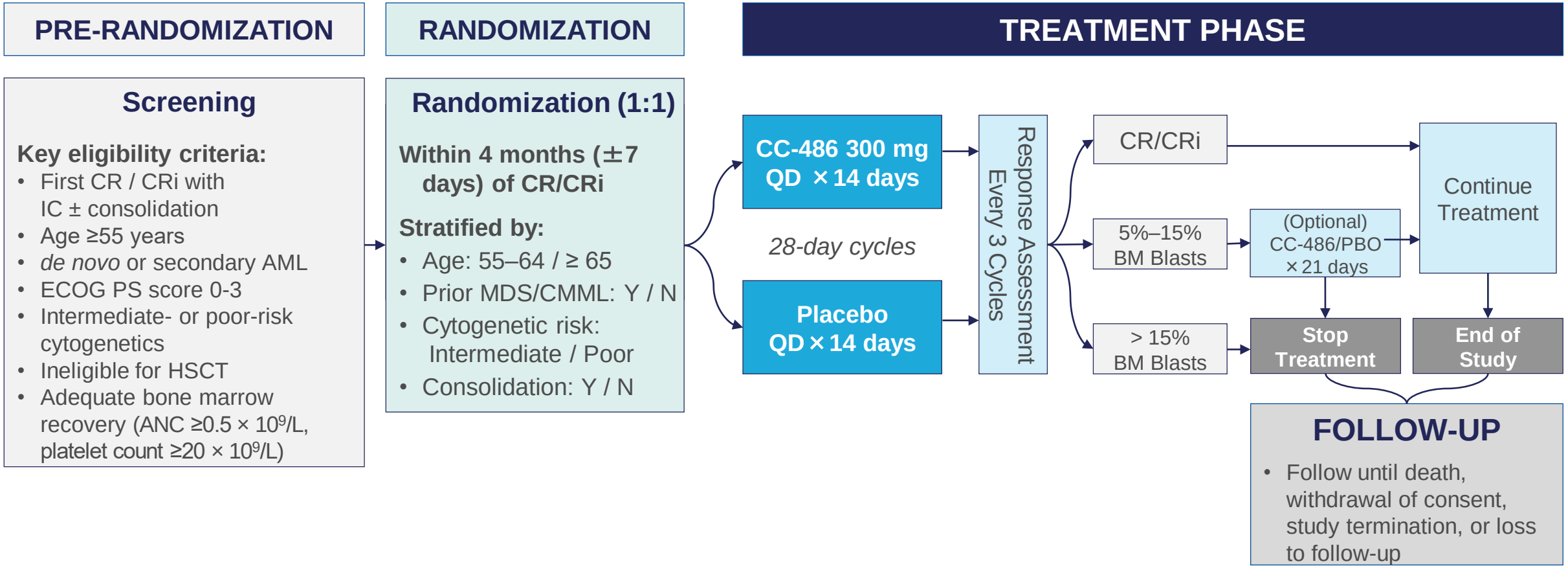
Efficacy	MDS (n=33)	AML (n=25)
ORR, n (%)	**30 (91%)**	**16 (64%)**
CR	**14 (42%)**	**10 (40%)**
CRi	-	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%)	1 (%)
Median time to first response (range), months	1.9 mo	
MRD-neg in responders, n/N (%)	6/30 (20%)	8/16 (50)
Median follow-up (range), months	5.8 (2.0-15)	9.4 (1.9-16.9)
Median DOR (range), months	**NR (0.03-10.4+)**	**NR (0.03-15.1+)**
Median OS, months	NR	NR

- **In patients with *TP53*-mutated AML (n=12), the ORR was 75% and the median DOR and OS were not reached**
- **6- mo OS 91% in TP53-mutated AML**
- CD34+CD38− LSC were eliminated in 40% of patients overall

Sallman D, et al. ASH 2019 Abstract #569
Sallman D, et al. ASCO 2020 Abstract #7507

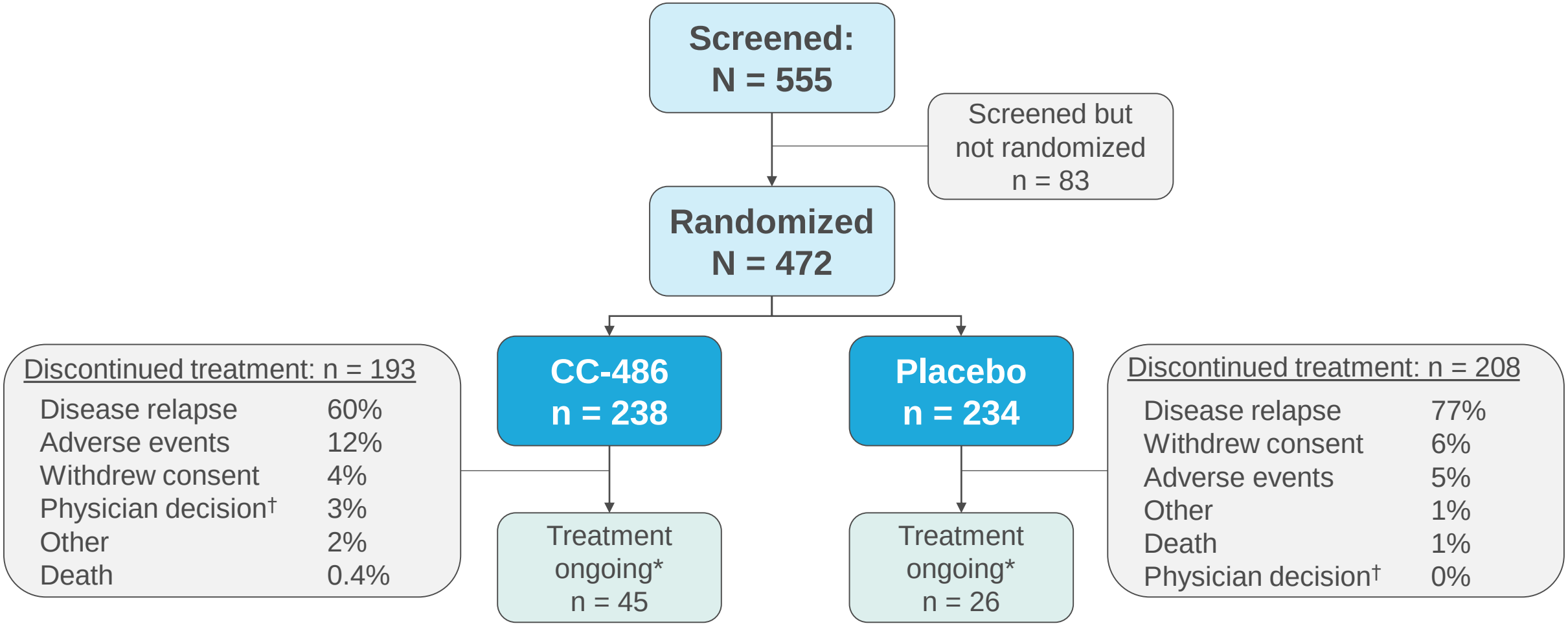
QUAZAR AML-001: STUDY DESIGN

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



AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; BSC, best supportive care; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PBO, placebo.

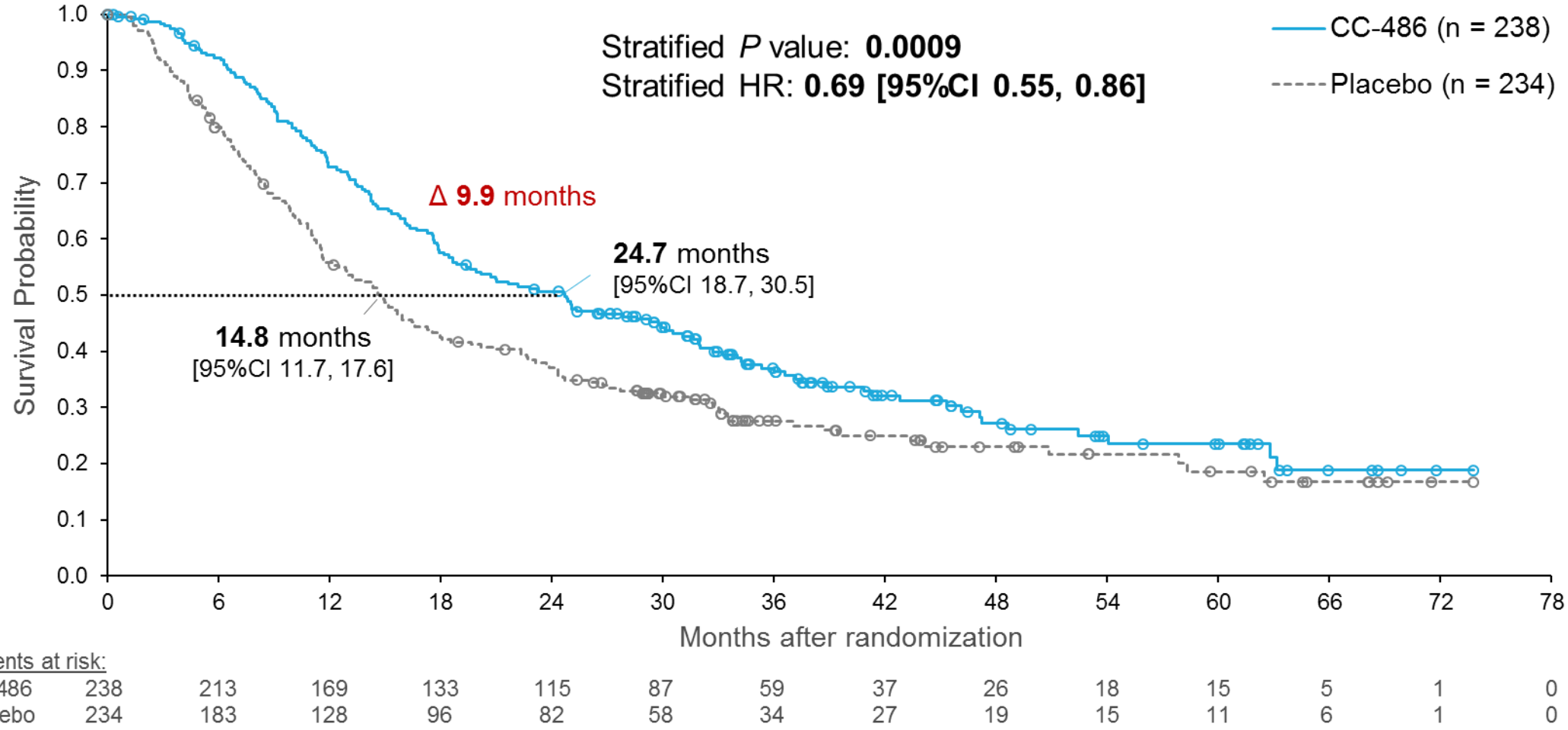
PATIENT DISPOSITION



*Still receiving study drug at data cutoff (July 15, 2019).
†Became eligible for hematopoietic stem cell transplant during treatment.

PRIMARY ENDPOINT: OVERALL SURVIVAL FROM RANDOMIZATION

- Median follow-up: 41.2 months



Patients at risk:

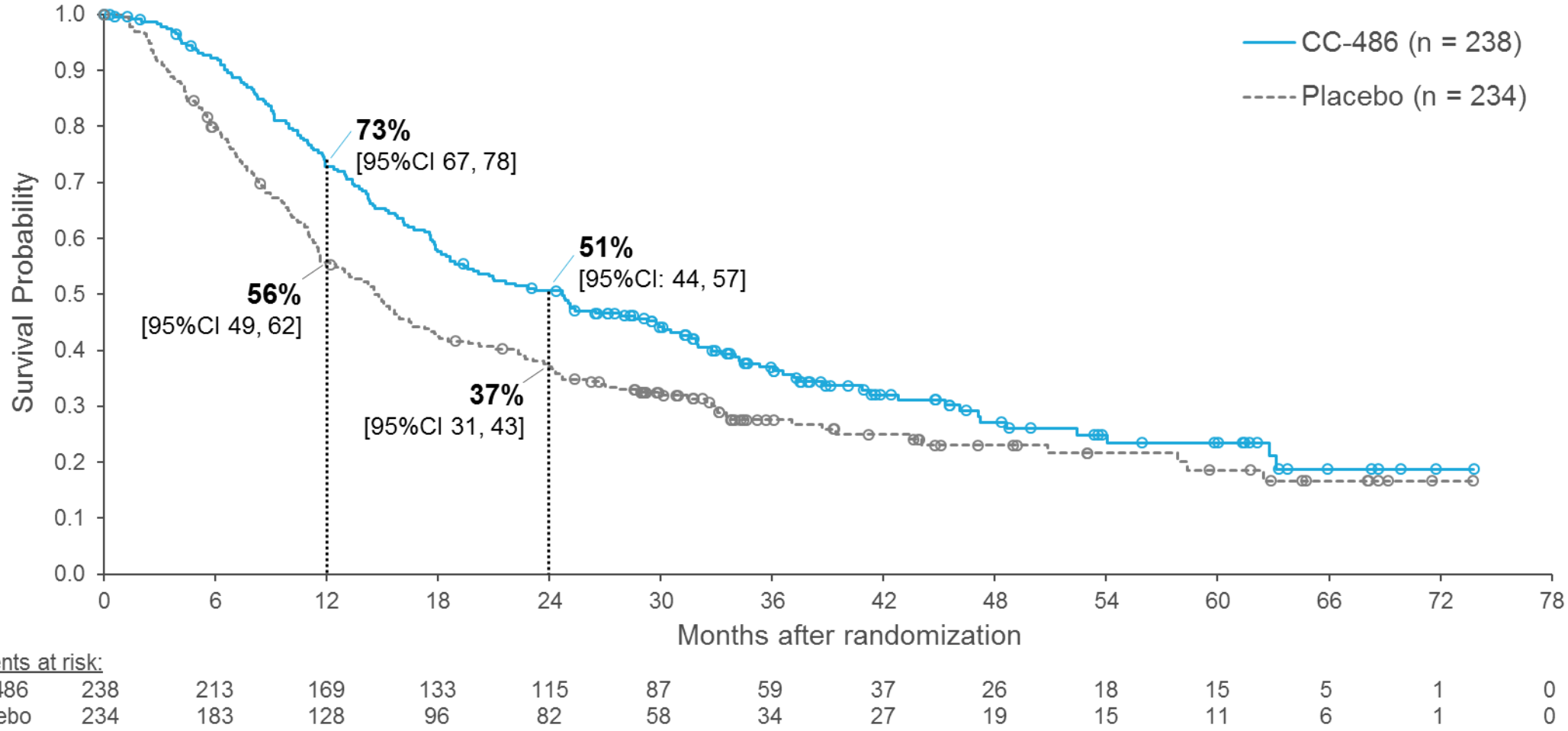
CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Data cutoff: July 15, 2019

OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 *vs.* placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.

95%CI, 95% confidence interval; HR, hazard ratio.

1-YEAR AND 2-YEAR SURVIVAL RATES



Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Data cutoff: July 15, 2019

OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 *vs.* placebo by stratified log-rank test. 95%CIs were generated using a stratified Cox proportional hazards model.

95%CI, 95% confidence interval.

Maintenance therapy with CC-486 represents a new potential therapeutic standard for patients aged ≥55 years with AML in first remission

- **CC-486 is the first maintenance therapy to provide statistically significant and clinically meaningful improvements in both OS and RFS in a broad range of patients with AML in remission following intensive chemotherapy, with or without consolidation**
  - ***OS and RFS benefits with CC-486 were observed across key patient subgroups***
- **The safety and tolerability of CC-486 was manageable, with no unexpected adverse events**
- **CC-486 preserved overall HRQoL *vs.* placebo**

Take Home messages

- **Fully characterize AML also in the elderly**

- **Intensive or non-intensive approaches for older pts?**
  - How to determine fitness?
  - Intensive chemotherapy no longer required prior to SCT?

- **What is the preferred regimen for *FLT3* and *IDH* mutant AML?**
  - Targeted Tx with intensive chemo for the fit?
  - AZA + targeted tx & AZA + venetoclax both effective
  - Triplet combinations?

- **Can we change the natural history of *TP53* mutant AML?**
  - APR-286 and Magrolimab are potential candidates

– **How do we best incorporate maintenance therapy, immunotherapy**


thank you
merci
hvala
obrigado
arigatô
terima kasih
dakujem
grazie
mahalo
diolch
barka
misaotra
kia ora
maururu
krap
sulpáy