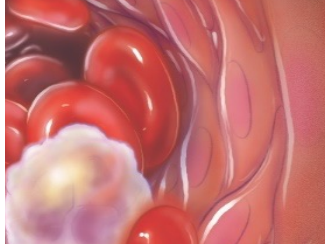

Induction and Maintenance Options for Younger Patients with AML and No Targetable mutations

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AML: Induction and Maintenance Options in patients without targeted agent

- GOALS
- DISEASE HETEROGENEITY
- INDUCTION RESULTS
  - INDUCTION with VENETOCLAX
- POST-REMISSION THERAPY
  - CHEMOTHERAPY CONSOLIDATION
  - ALLOGENEIC TRANSPLANT
  - MAINTENANCE

AML: General Treatment Principles

- **Goal 1: Induction therapy to reduce gross leukemia to undetectable levels (2-3 log cell kill); to achieve CR (no AML, nl CBC)**

- **Goal 2: Reduce 10^9 - 10^{10} cells, undetectable by standard means, present at CR, to a level low enough to achieve prolonged disease-free survival ('cure')**

AML: Key Endpoints

- Overall survival (OS)
- Event-free survival (event= no CR, relapse, death)
  - Somewhat correlated with OS
  - Has intrinsic value to pts: when no event they are in CR with acceptable counts
- Complete remission (CR)
  - CR with incomplete plt (or ANC) recovery has value
  - CR at MRD negative level has most value !

New European Leukemia Net (ELN) 2017:Genetic-Cytogenetic Prognostic Subgroups

Genetic Risk Group	Frequency	CR	OS	ELN 2017 Subset
Favorable	15%	80-90%	65%	• t(8;21)(q22;q22); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* • Mutated *NPM1* without *FLT3*-ITD or *FLT3*-ITD ^{low} • Biallelic Mutated *CEBPA*
Intermed	55%	60-75%	50%	• Mutated *NPM1* and *FLT3*-ITD ^{high} • Wild-type *NPM1* without *FLT3*-ITD or *FLT3*-ITD ^{low} (without adverse-risk genetic lesions) • Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) • t(9;11)(p22;q23); *MLLT3-MLL* • Any cytogenetics not classified as favorable or adverse
Adverse	30%	40-50%	20% (7% in MK)	• t(6;9)(p23;q34); *DEK-NUP214* • t(v;11)(v;q23); *MLL (KMT2A)* rearranged • Inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1 (GATA2, MECOM (EVI1)* • t(9;22)(q34.1;q11.2) *BCR-ABL1* • Monosomy 5 or del(5q); monosomy 7; monosomy 17; abnormal 17p • Complex karyotype(≥ 3 abnormalities) or monosomal karyotype • Wild-type *NPM1* and *FLT3*-ITD ^{high} • Mutated *RUNX1* • Mutated *ASXL1* • Mutated *TP53*

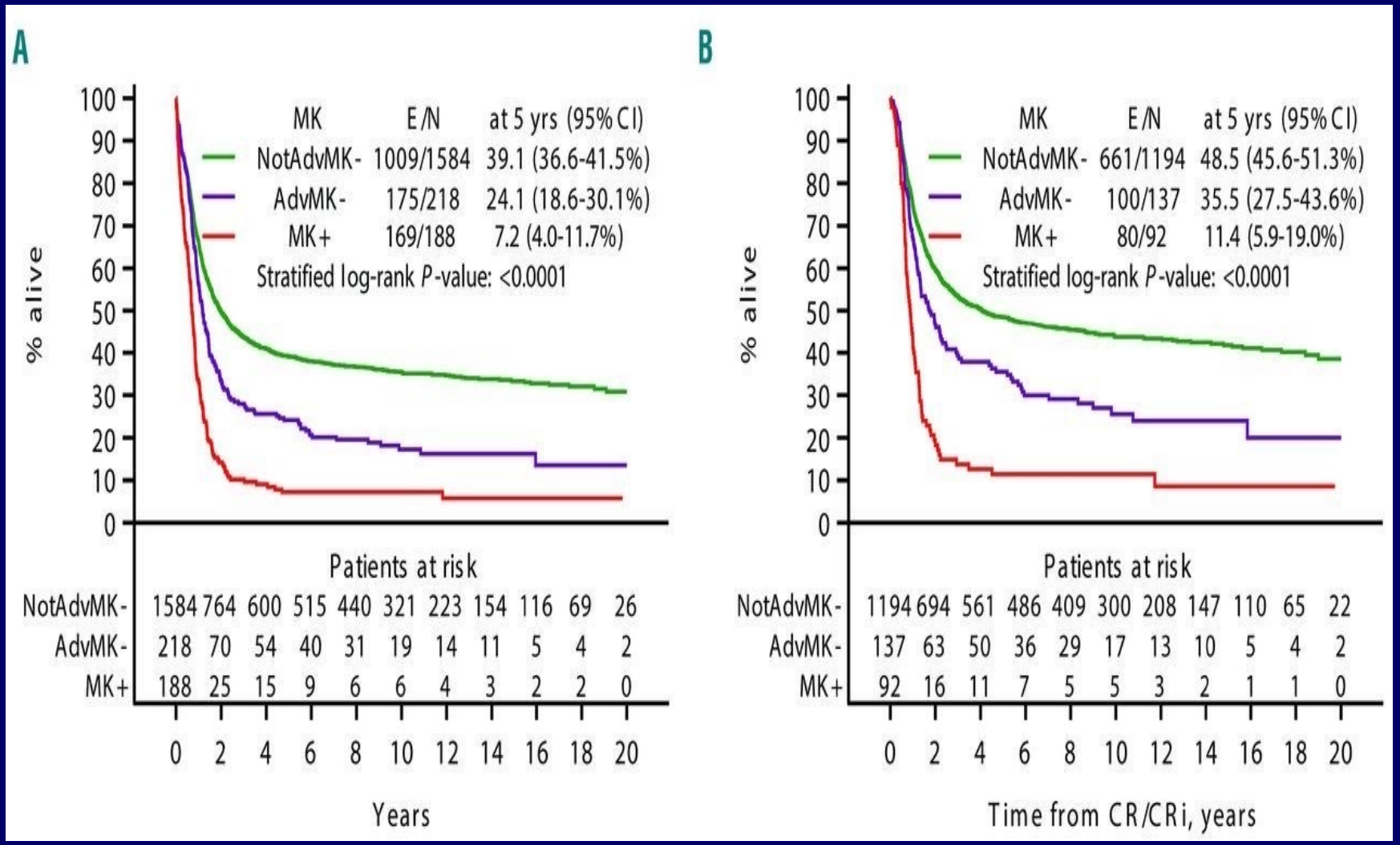
Döhner H et al, *Blood* 2017. Bothakur G et al, *Am J Hematol*, 2014. Baron F et al, *Haematologica*, 2019

AML Therapy for Patients Age <60 Years:

- INDUCTION
  - Daunorubicin 60-90 mg/m^2/d x 3 (or ida 12 mg/m2/d x3)
    Cytarabine 100-200 mg/m^2/d x 7 continuous infusion*
  - Add Midostaurin 50 mg bid day 8-21 for mut FLT3
  - Add GO 3 mg/m2 d 1, 4, and 7, esp in CBF
  - CPX-351, d 1, 3, and 5 for h/o MDS, MDS-type cytogenetics
  - ??Substitute HMA-VEN based regimens in adverse risk

*FLAG-IDA may have a role in the very fit

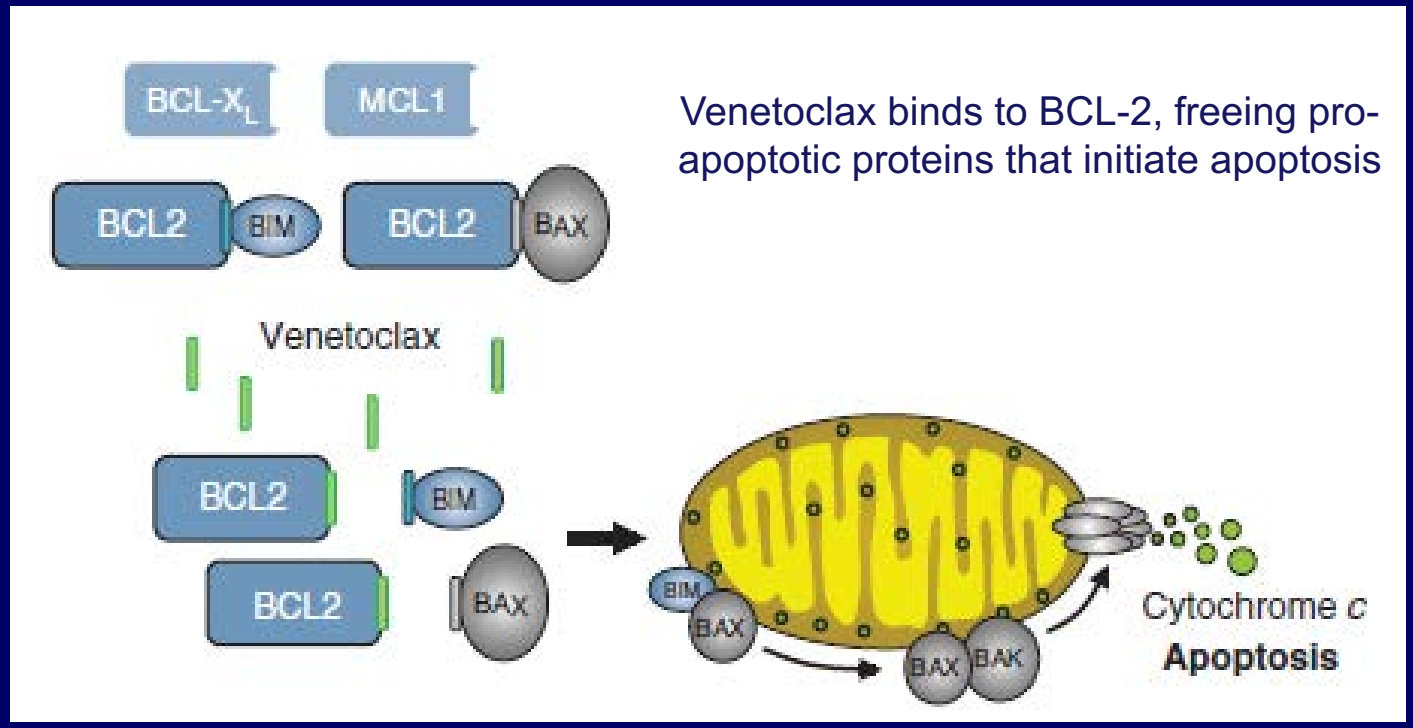
Long term Outcome in Adverse risk pts is poor



Baron F et al, *Haematologica*, 2019

Venetoclax: BCL-2 Selective Inhibitor

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins



Venetoclax binds to BCL-2, freeing pro-apoptotic proteins that initiate apoptosis

Konopleva M, et al. *Cancer Discov*. 2016. Epub ahead of print. Lin T, et al. ASCO 2016. Abstract 7007.

FLAG-IDA-VEN: Study Cohorts and Treatment Schedule, Dinardo C, et al, JCO 2021

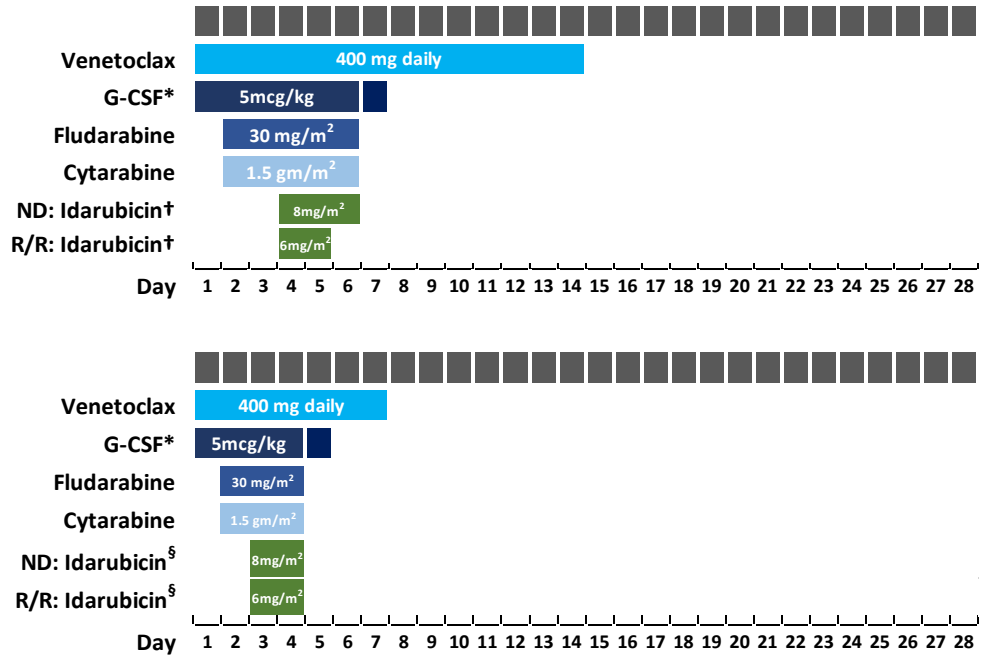
Phase 1b	Phase 2A	Phase 2B
R/R-AML	ND-AML	R/R-AML
N=16	N=29	N=23

Induction	Consolidation
Venetoclax 400 mg D1-14	Venetoclax 400 D1-7
G-CSF D1-6	G-CSF D1-4
Pegfilgrastim or biosimilar D7	Pegfilgrastim or biosimilar D5
Fludarabine 30 mg/m^2 D2-6	Fludarabine 30 mg/m^2 D2-4
Cytarabine 1.5 gm/m^2 D2-6	Cytarabine 1.5 gm/m^2 D2-4
ND: Idarubicin 8 mg/m^2 D4-6	ND: Idarubicin 8 mg/m^2 D3-4
R/R: Idarubicin 6 mg/m^2 D4-5	R/R: Idarubicin 6 mg/m^2 D3-4

Phase 1b		Phase 2
Cytarabine 2 gm/m^2	RP2D *	**Cytarabine 1.5 gm/m^2**
Venetoclax D1-21		**Venetoclax D1-14**

* 5/6 initially enrolled P1b patients developed bacteremia/sepsis with P1b dosing

Phase 2 Induction/Consolidation Schedule



*G-CSF: 5 mcg/kg the day prior to and days of IV chemotherapy followed by 1 dose of pegfilgrastim or biosimilar each 28 D cycle
† Induction: ND-AML: Idarubicin 8 mg/m^2 days 4-6, R/R-AML Idarubicin 6 mg/m^2 days 4 and 5
§ Consolidation: Idarubicin permitted on days 3 and 4 in 2 post-remission cycles (ie. C2 or C3 and C5 or C6) at physician discretion

FLAG-IDA-VEN: Treatment Response

Parameter	All (N=68)	Phase 2A ND-AML (N=29)	R/R-AML (N=39)	Phase Ib R/R-AML (N=16)	Phase 2B R/R-AML (N=23)
Overall Response	56 (82%)	28 (97%)	28 (72%)	12 (75%)	16 (70%)
Composite CR	52 (76%)	26 (90%)	26 (67%)	12 (75%)	14 (61%)
CR	37	20	17	6	11
CRh	10	5	5	2	3
CRi	5	1	4	4	-
MRD negative (FC)	43 (83%)	25 (96%)	18 (69%)	7 (58%)	11 (79%)
MLFS	4	2	2	-	2
No response	12	1	11	4	7

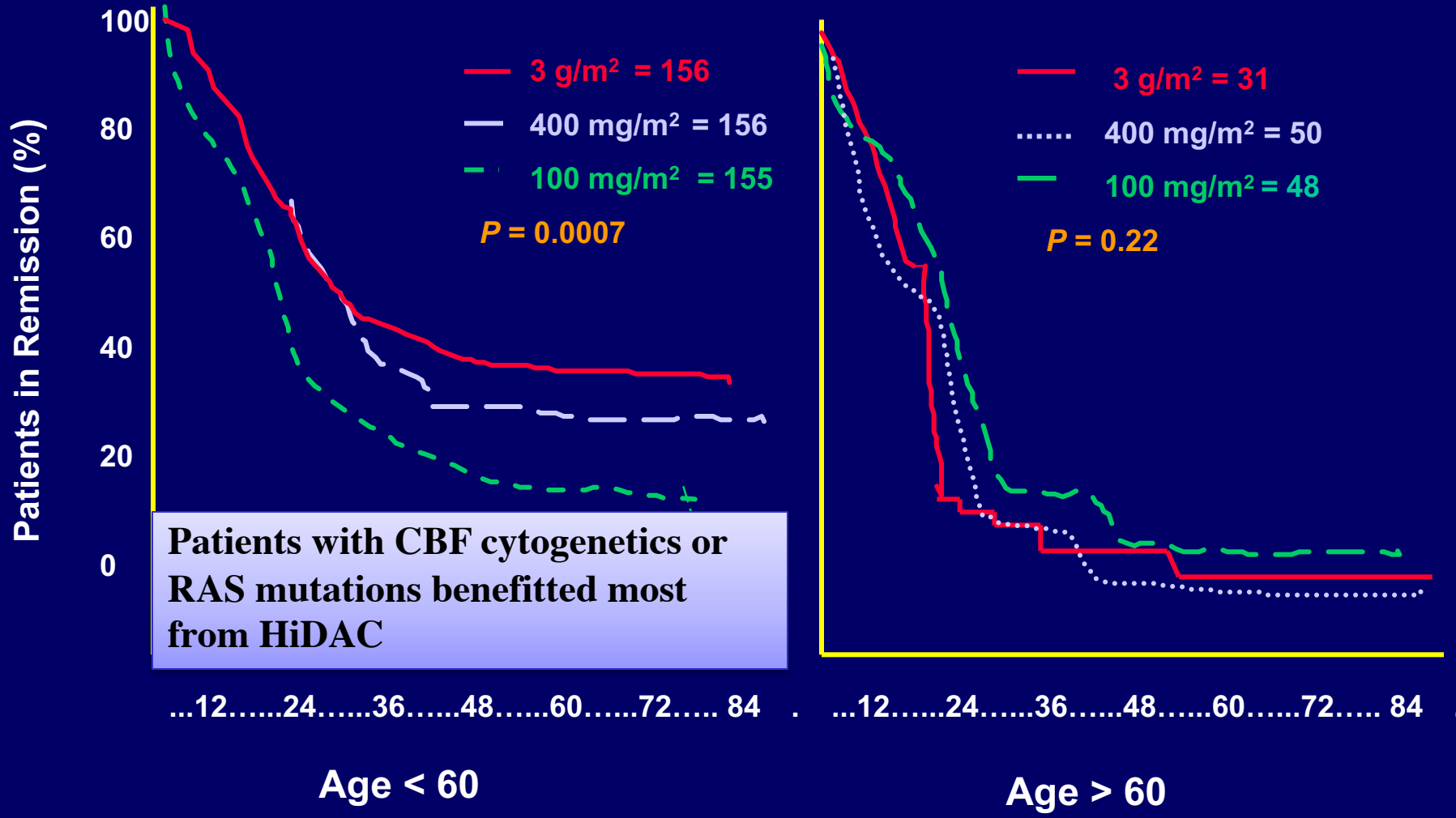
INTENSIVE CHEMO + VEN: Other Trials

Venetoclax Combination	Pts	Ph	N	Median age (range)	Response definition Response rates	Median OS/ 12m OS	Side effects FN bacteremia, sepsis ED (30d & 60d)	Time to count recovery (days)
"5+2" +Ven (CAVEAT) (Chua JCO 2020)	ND-AMD >65 y.o (or > 60 y.o with MK)	Ib	51	72 (63-80)	CR/CRi – 72% de-novo AML: 97%; CR 68% sAML: 43%; CR 9%	Median OS 11.2 months (31.3 in de-novo AML vs. 6.1 in sAML)	FN 55% sepsis 35% ED 30d 6%	ANC 26 (19-36) PLT 25 (20-NR), longer in consolidations (39-47)
"7+3" +Ven (Stone ASH 2020)	ND AML	I	13	54.5 (22-73)	CR/CRi 100% among evaluated patients (90% CR 75% MRD^-)	-	50% FN and sepsis ED 30d 15% & ED 60d 15% (2 ED in day 9 and 14)	33 (24-38)
Clad+ARA-C+IDA+Vern (Kadia , ASH 2020)	AML MPAL HR-MDS 18-65 y.o	II	50	48 (18-65)	cCR = CR+CRi cCR 94%; CR 84%, MRD^- 82%	At 12 months 85%	FN 84% ED 30d 2%, ED 60d 2%	27 (IQR 25-37) In responding patients

AML Therapy for Patients Age <60 Years:

- POST-REMISSION
  - CBF: High dose ara-C 3 g/m2/3h q12h d1, 3, and 5 x 4 cycles
  - *NPM1* mut/*FLT3* WT: as above, ex ? 1.5 g/m2
  - Adverse risk: Allo SCT w best available donor
  - Intermediate risk: AlloSCT
  - ?? What to do with MRD results
  - Oral aza maintenance in age >55 non-tx

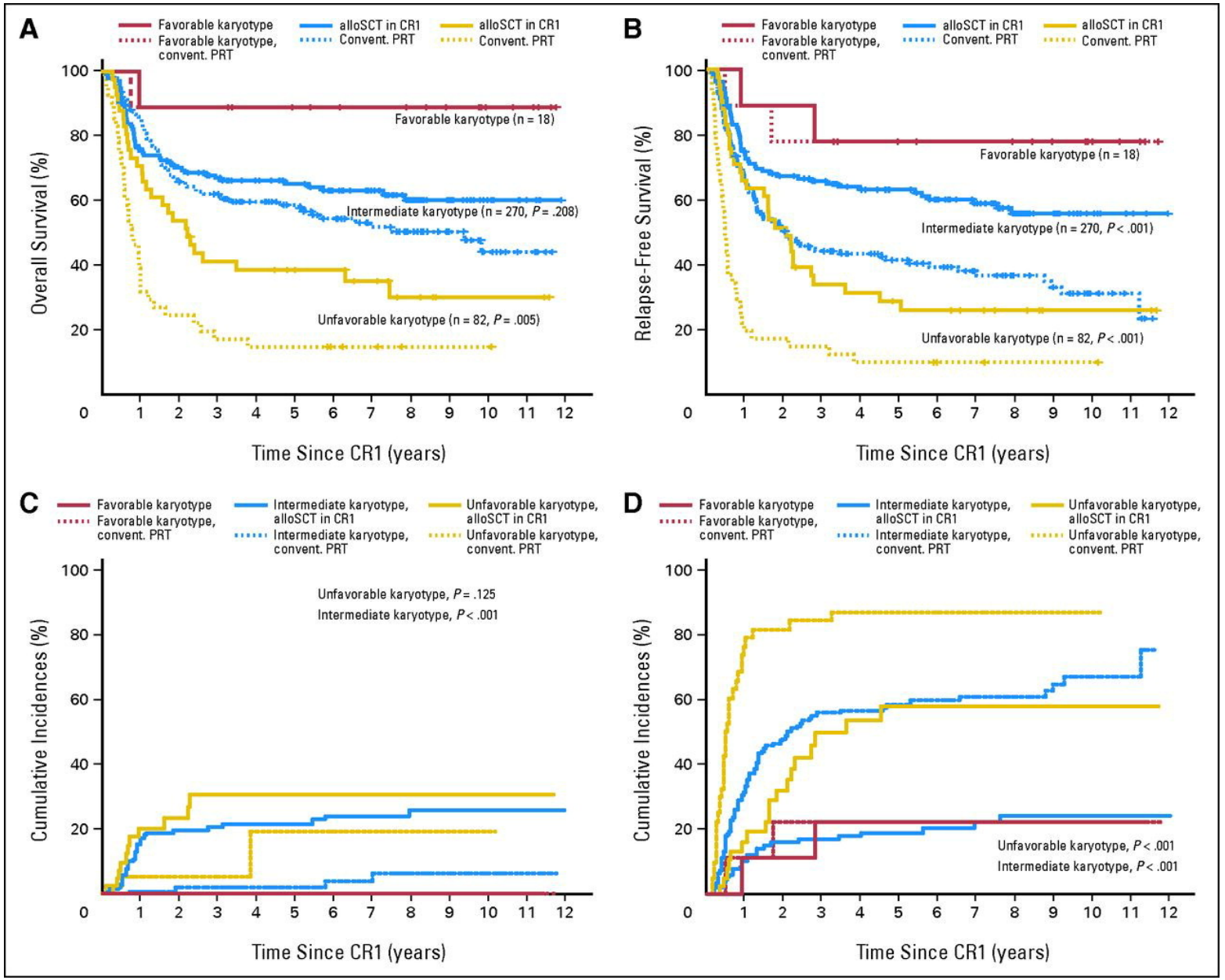
Consolidation: DFS (and OS) Benefit Only in Patients < 60 Years Receiving High-Dose Ara-C



Bloomfield CD, et al. *Cancer Res.*1998;58(18):4173-4179; Neubauer A, et al. *J Clin Oncol.* 2008; 26(28):4603-4609;

Mayer RJ, et al. *N Engl J Med*. 1994;33(1):896-903.

Allo SCT better than chemo in AML for non-fav KT



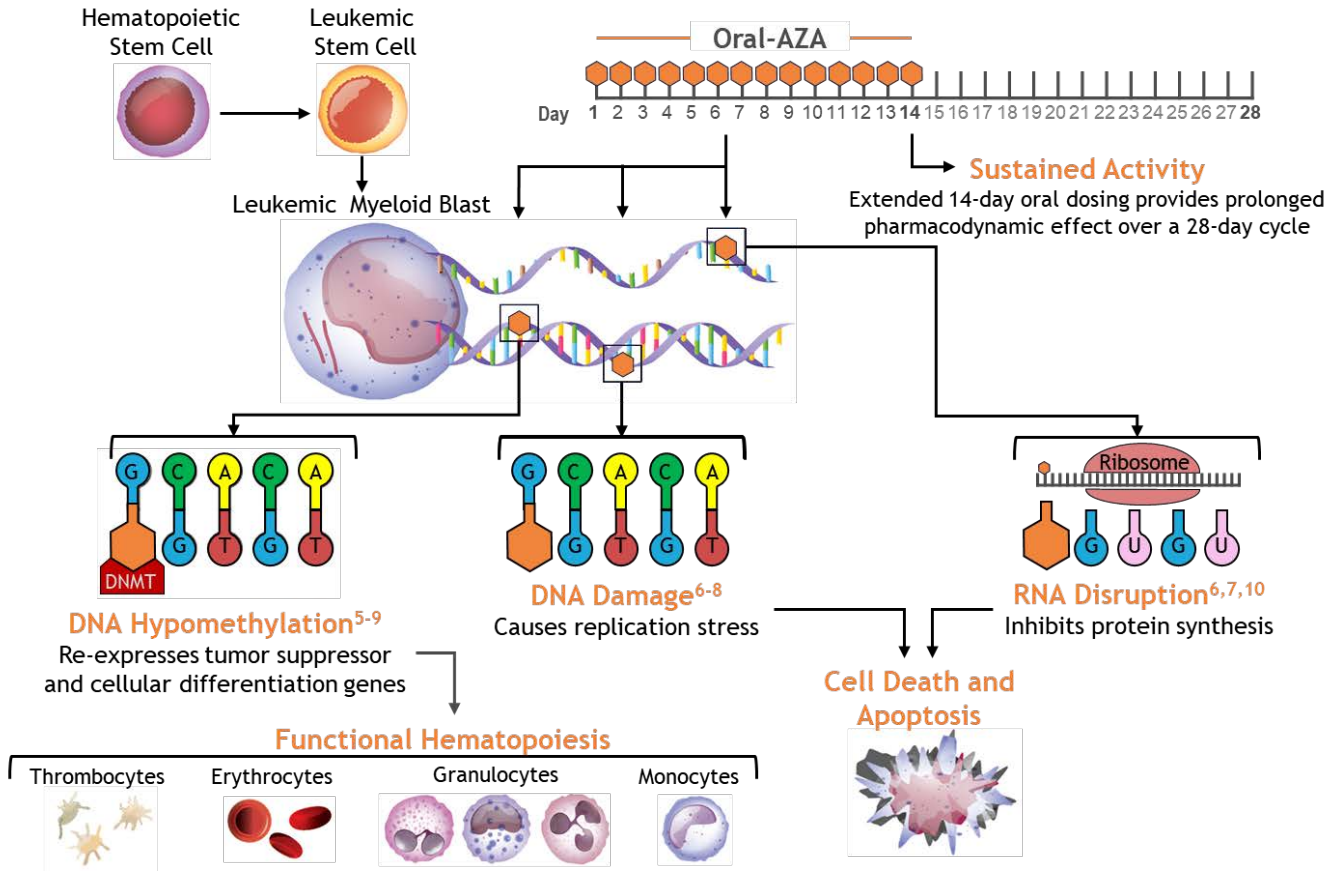
Stelljes M et al; *Journal of Clinical Oncology, 2014*

VIALE-T: Is there a useful post alloCT maintenance rx?

- Randomized, 2-Arm, Multicenter, Phase 3 Study of Venetoclax and Azacitidine Versus Best Supportive Care as Maintenance Therapy for Patients Undergoing alloSCT (VIALE-M)
- Part 1 will be the Dose Confirmation portion to determine recommended Phase 3 dose (RPTD) of venetoclax (d1-28) in combination with AZA (d1-5) in post alloSCT setting.
- Part 3 will be conducted in 2 phases - Dose Finding portion to determine RPTD of venetoclax in combination with aza and Randomization portion to evaluate if venetoclax in combination with aza as maintenance therapy improves relapse-free survival (RFS) compared to BSC. N=424, any age >17

Oral azacitidine

- Oral azacitidine (Oral-AZA [CC-486]):
  - Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent[1,2]
  - Approved in the United States for continued Tx of adult pts with AML in first CR/CRi post-IC and not able to complete intensive curative therapy (eg, HSCT)[3]
- Oral dosing allows for extended drug exposure during each Tx cycle to prolong AZA activity[1,2]

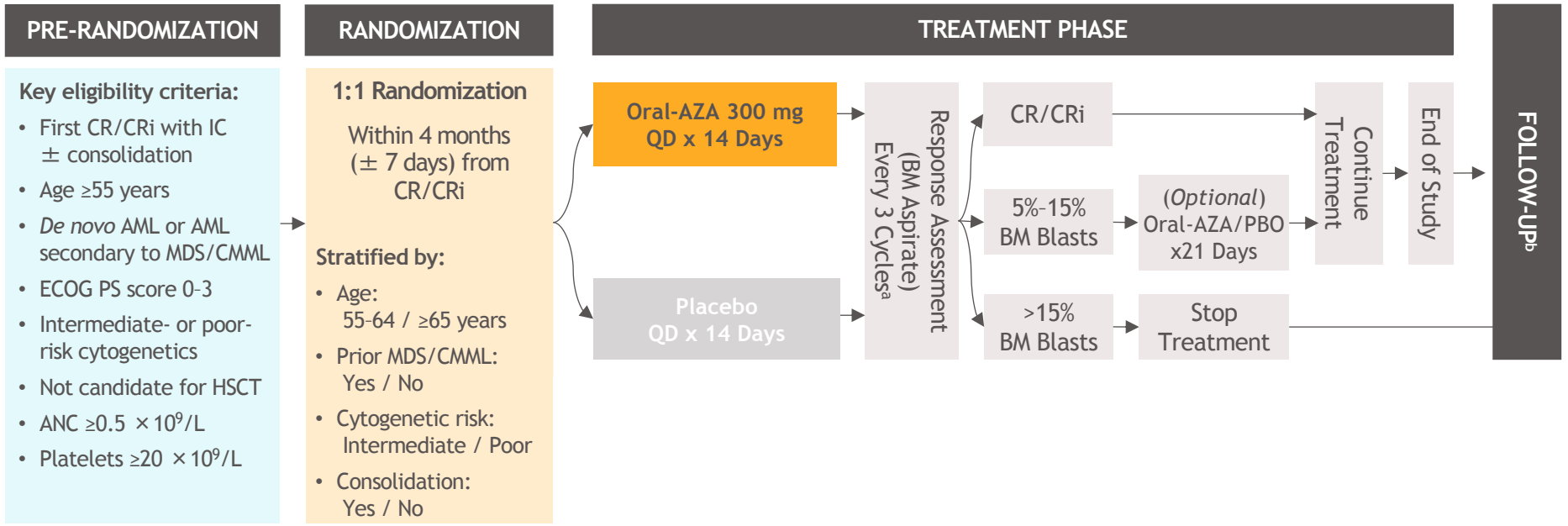


Garcia-Manero et al. *J Clin Oncol*. 2011;29(18):2521–7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. ONUREG® (azacitidine) tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Rev. 9/2020. 4. Savona et al. *Am J Hematol*. 2018;93(10):1199–206. 5. Stresemann et al. *Mol Cancer 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; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; Tx, treatment.

QUAZAR AML-001: Study design and eligibility criteria, Wei et al NEJM, 2020.

International, multicenter, placebo (PBO)-controlled, double-blind, randomized, phase III study of Oral-AZA as maintenance Tx in pts with AML in first remission post-IC

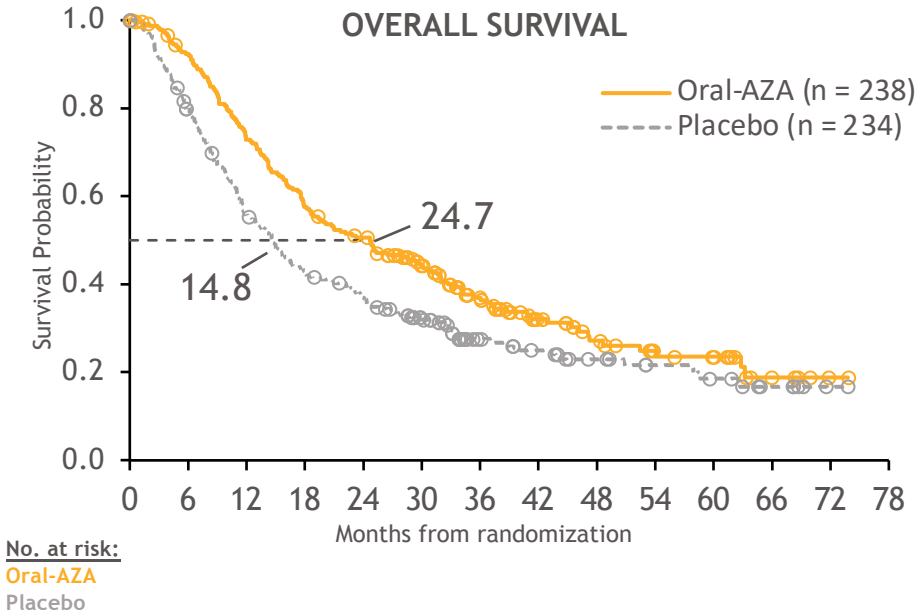


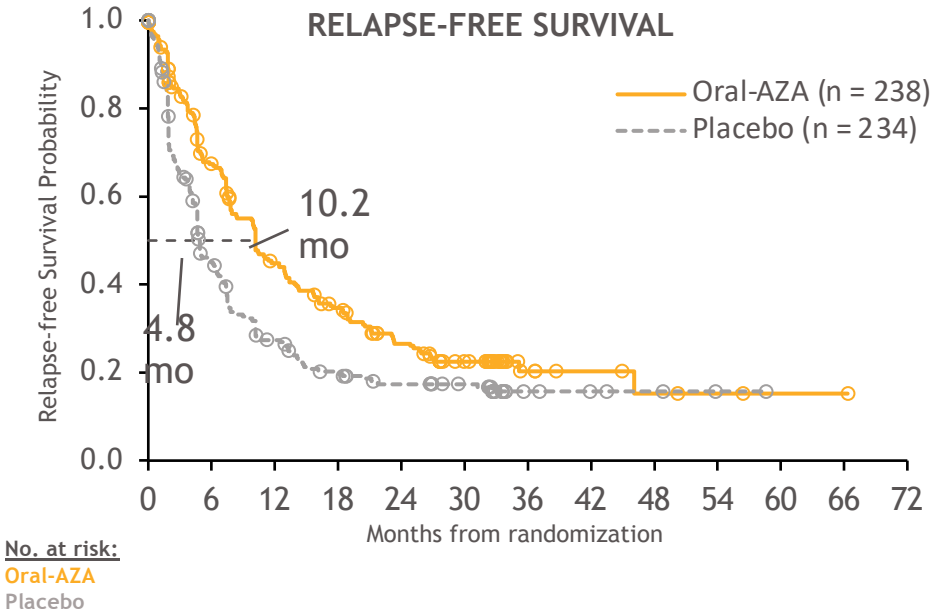
[a]BM aspirates were collected every 3 cycles through cycle 24, at cycle 30 and cycle 36, and as clinically indicated thereafter. BM assessments were also performed as clinically indicated. [b]Patients were followed until death, withdrawal of consent, study termination, or loss to follow-up.

AML, acute myeloid leukemia; ANC, absolute neutrophil count; AZA, azacitidine; BM, bone marrow; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PBO, placebo.

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[1]





1. Wei et al. *NEJM 2021*.
OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for Oral-AZA *vs.* placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.
AZA, azacitidine; mo, months; No., number; OS, overall survival; PBO, placebo; RFS, relapse-free survival.

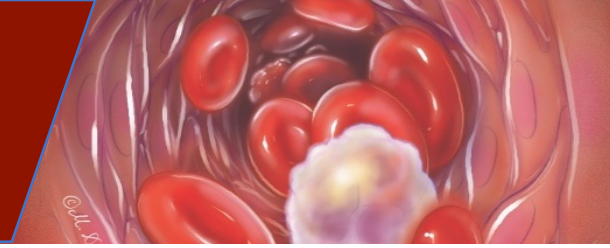
Wei et al NEJM, 2020

VIALE-M: Is there a better maintenance rx?

- Randomized, Double-Blind, 2-Arm, Multicenter, Phase 3 Study of Venetoclax and Oral Azacitidine Versus Oral Azacitidine (CC-486) as Maintenance Therapy for Patients With Acute Myeloid Leukemia in First Remission After Conventional Chemotherapy (VIALE-M)
- Part 1 will be the Dose Confirmation portion to determine recommended Phase 3 dose (RPTD) of venetoclax in combination with CC-486.
- Part 3 will be conducted in 2 phases - Dose Finding portion to determine RPTD of venetoclax in combination with CC-486 and Randomization portion to evaluate if venetoclax in combination with CC-486 as maintenance therapy improves relapse-free survival (RFS) compared to CC-486. N=482, any age>17 yo

AML: Induction and Maintenance Options in patients without targeted agent: CONCLUSIONS

- ONE INDUCTION SIZE DOES NOT FIT ALL
- INDUCTION GOAL: Safe achievement of minimal disease state
  - Addition of VEN may help
- POST-REMISSION Goal: Eradicate all ds
  - ALLOGENEIC TRANSPLANT helps most
  - Addition of HMA maint +/- VEN may help



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Dana-Farber Cancer Institute