Acute Myeloid Leukemia and Acute Promyelocytic Leukemia

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Disclosures

- Research Funding
  - Abbvie
  - Rafael
  - Biosight
  - Glycomimetics
  - Orsenix
- Royalties
  - UpToDate
- Off label use
  - Gilteritinib, quizartinib
  - Enasidenib
  - Venetoclax
  - Magrolimab
  - SNDX-5613

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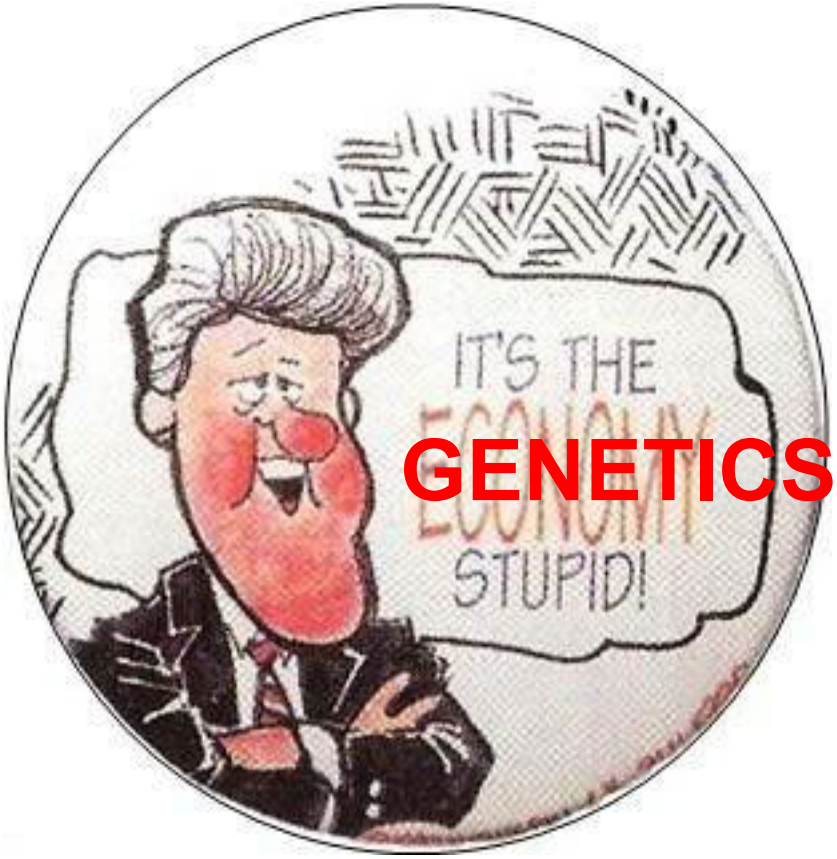
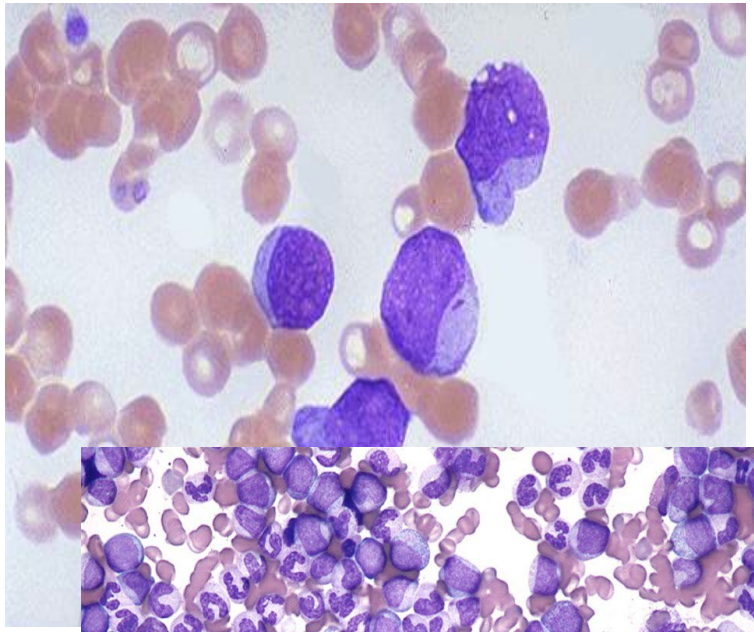
  - Innate Pharma
  - Ipsen Biopharma
  - Jazz Pharma
  - KAHR
  - Novartis
  - Orsenix
  - Roche
  - Syros

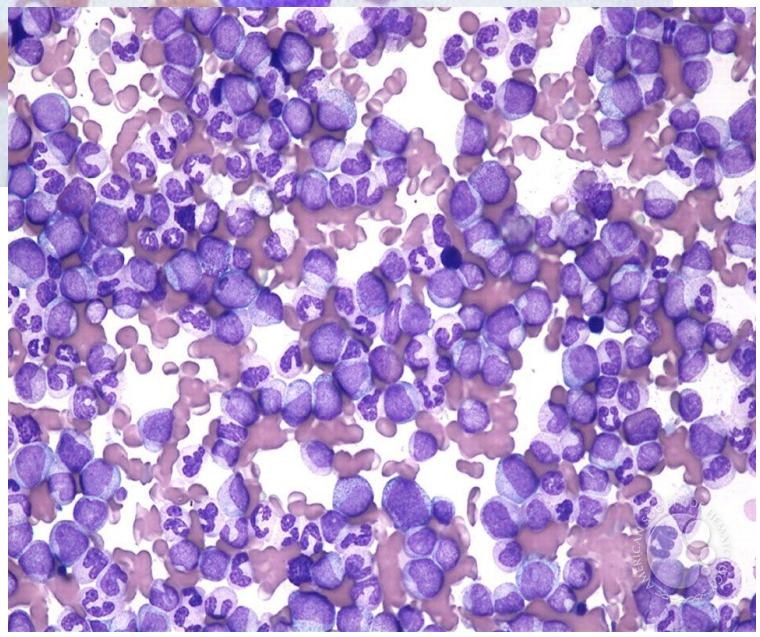


This is my single most important overriding message

Objectives

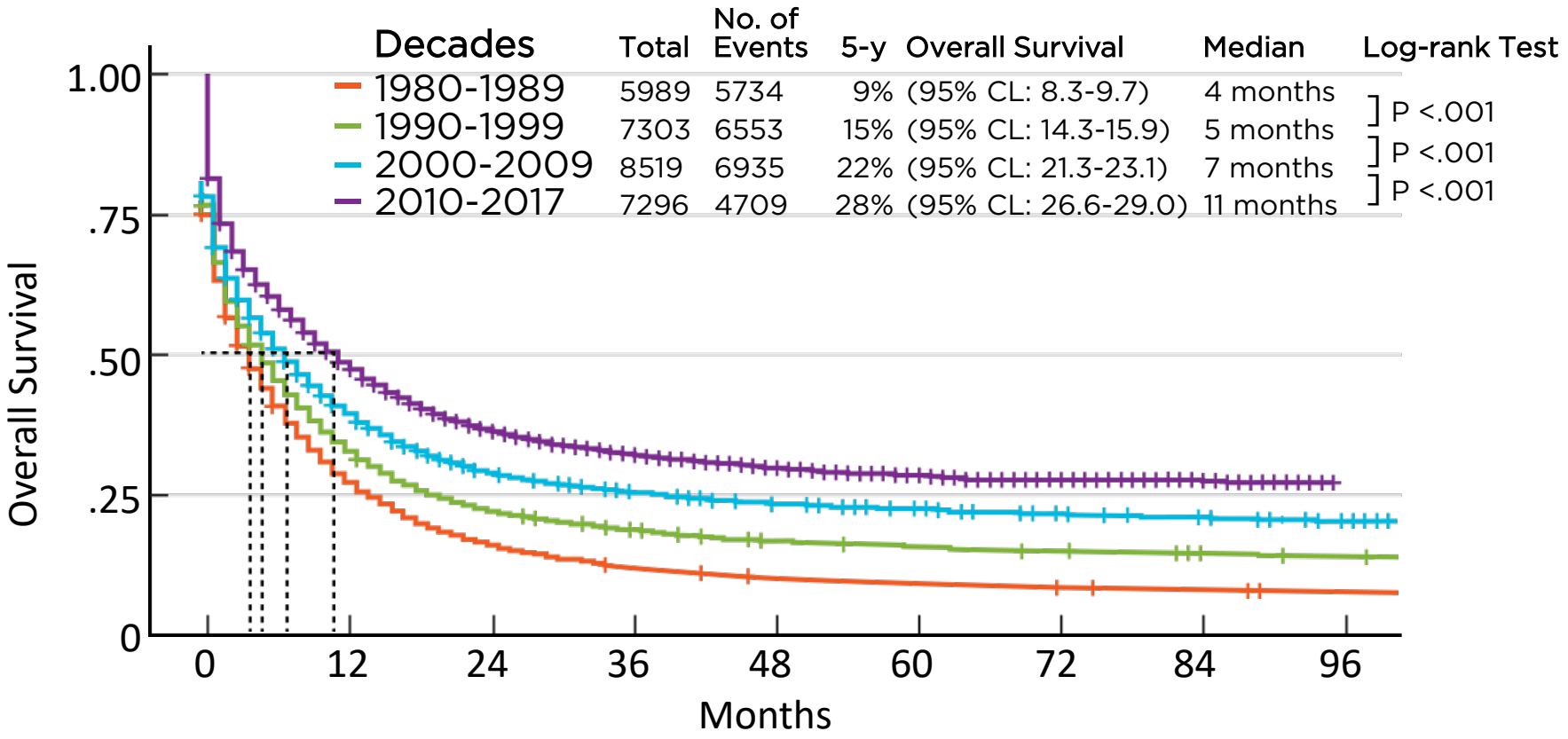
- Describe major advances in AML over ~5 decades and current outcomes including APL
- Demonstrate importance of genetic profiling for prognosis and therapy
- Discuss new agents, approved and nonapproved, for AML and new treatment strategies
- Define changing landscape for AML





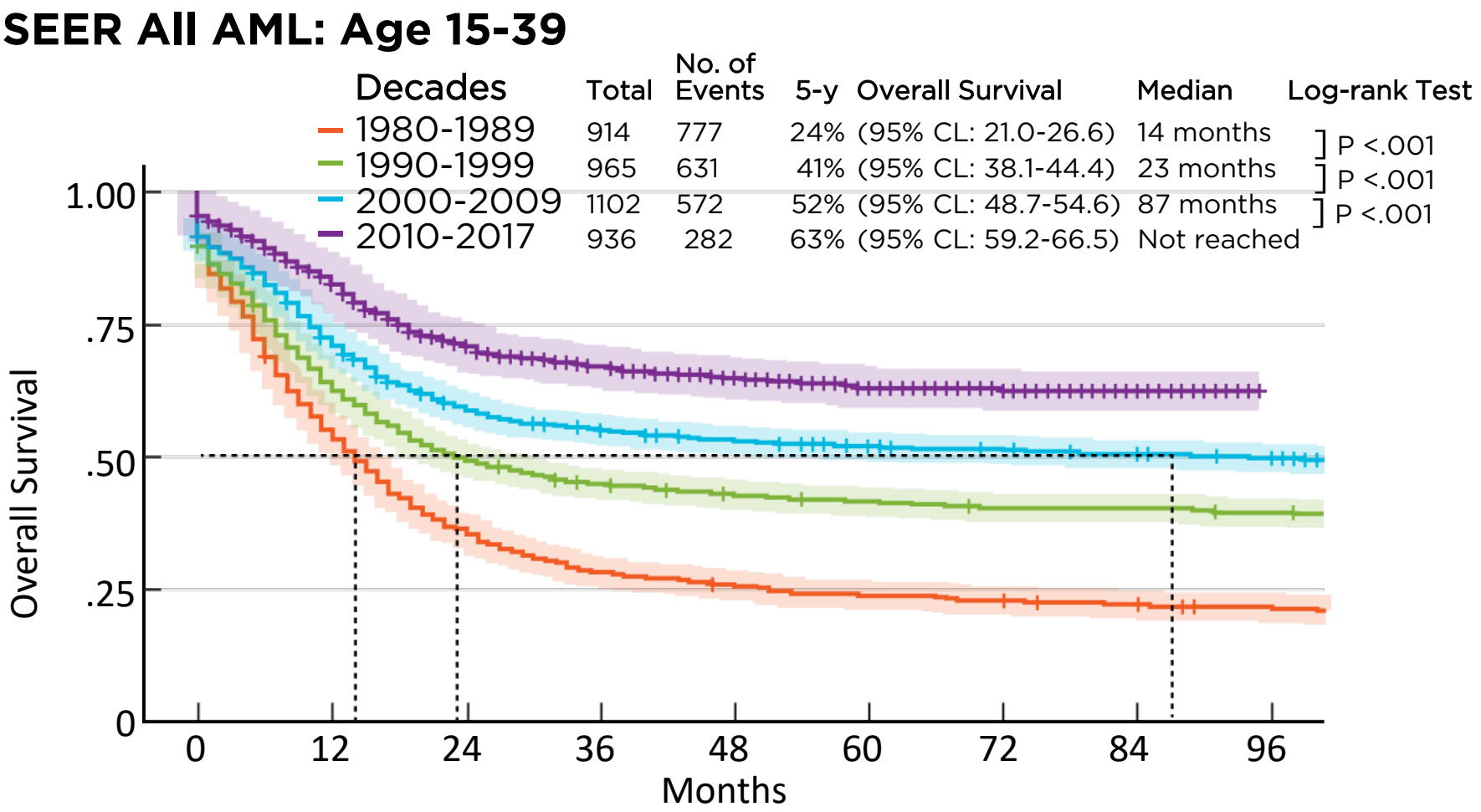
Kaplan-Meier Estimates for all Types of Acute Myeloid Leukemia by Decade of Diagnosis

SEER All AML: All Ages



Sasaki et al. Cancer, 2021

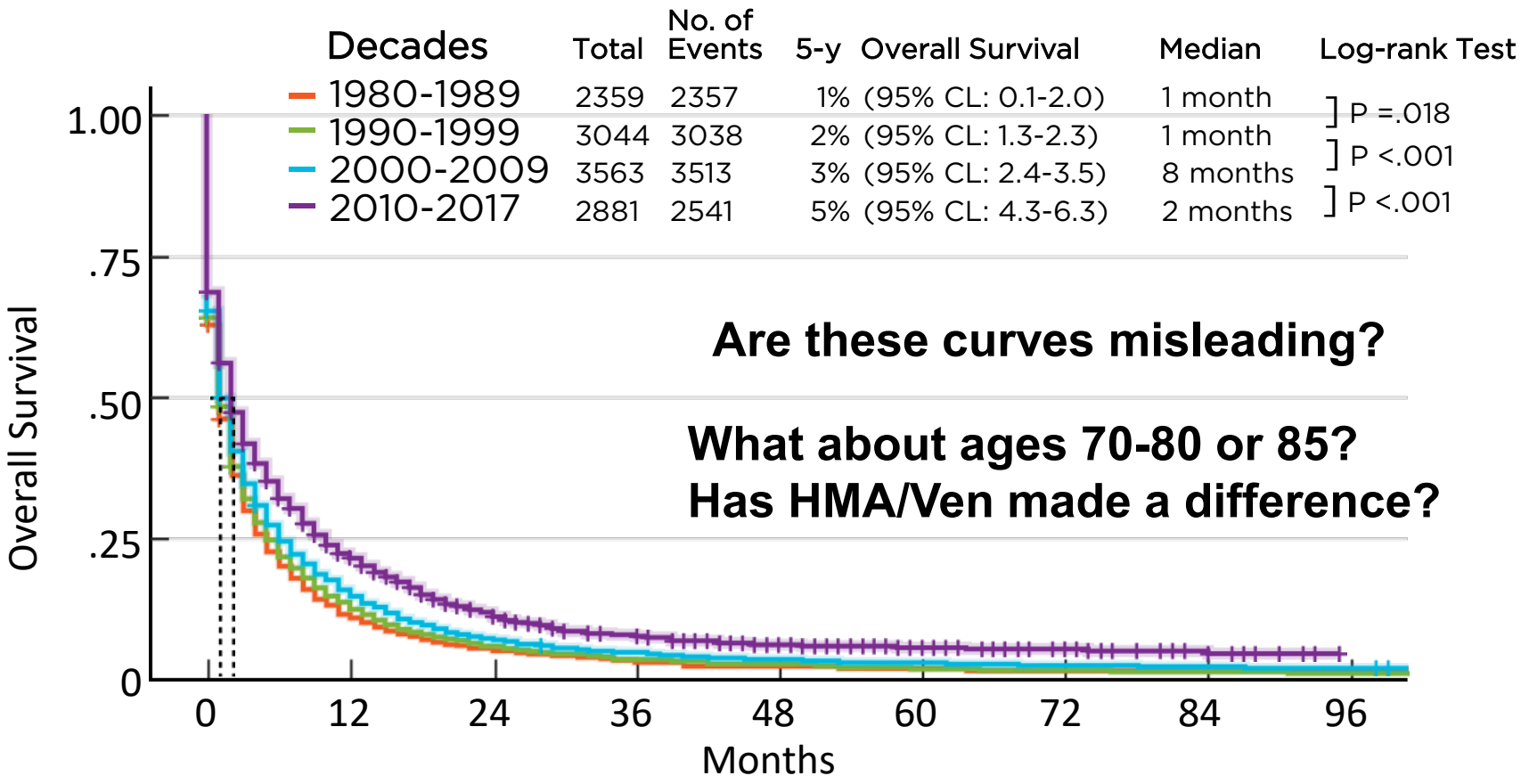
Kaplan-Meier Estimates for all Types of Acute Myeloid Leukemia by Decade of Diagnosis



Sasaki et al. Cancer, 2021

Kaplan-Meier Estimates for all Types of Acute Myeloid Leukemia by Decade of Diagnosis

SEER All AML: Age ≥70

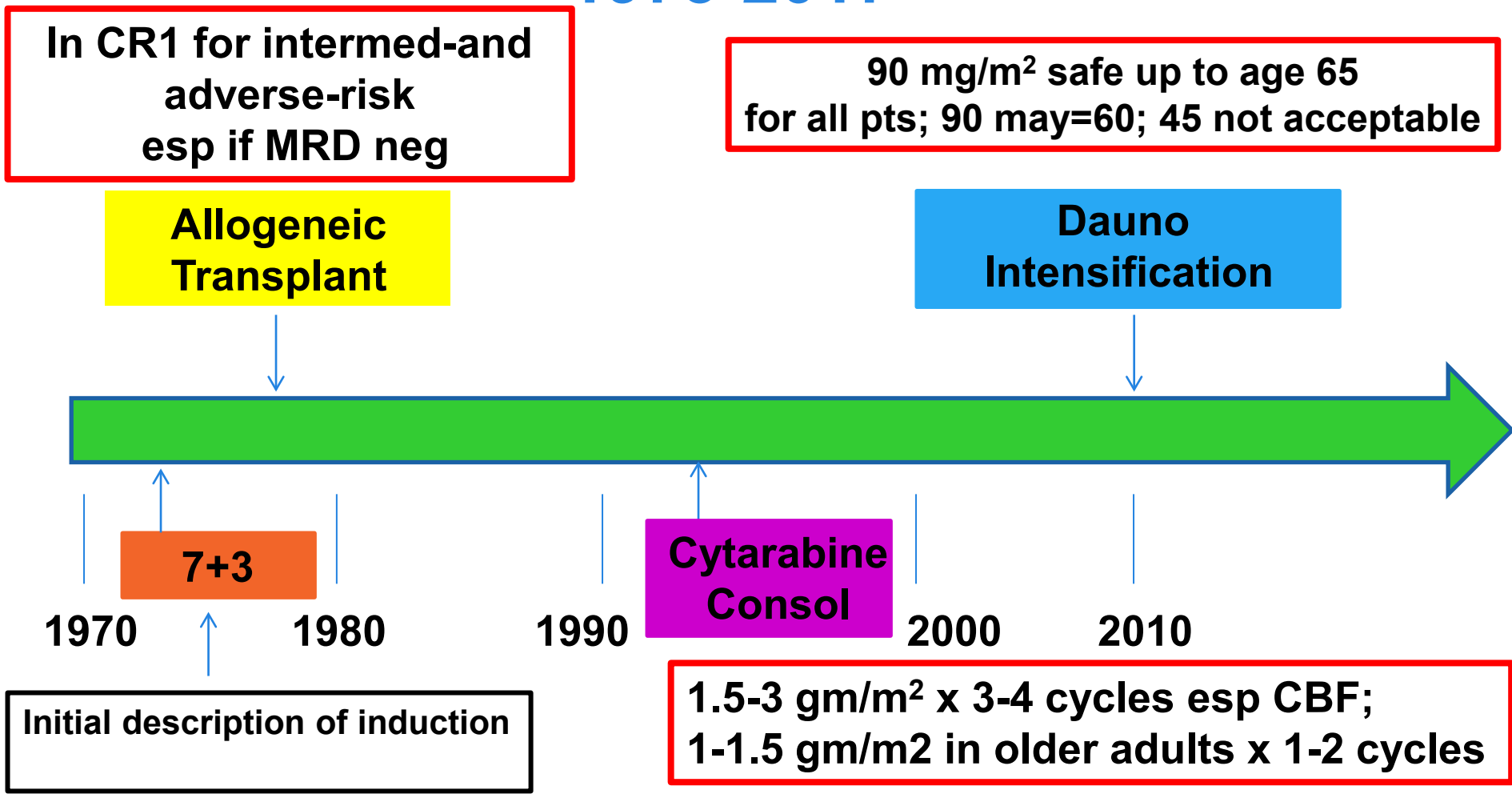


Sasaki et al. Cancer, 2021

Recent Progress in AML

- Insights into genetic pathogenesis/integrated genetic profiling
- Recognition of inherited familial predisposition syndromes
- Drug discovery/targeted therapy
- Expanded availability and advances in transplantation
- Paradigm shift in approach to older adults
- Increased importance of minimal (measurable) residual disease

Practice Changing Treatments in AML 1973-2017



Yates et al. Cancer Chemother Rep, 1973; Thomas et al. New Engl J Med, 1979; Mayer et al. New Engl J Med, 1994; Fernandez et al. New Engl J Med, 2009; Burnett et al. J Clin Oncol, 2013; Luskin et al. Blood, 2016; Begna et al. ASH, 2021 (abstr 1267)

Recently Approved Agents for AML 2017-2022

Agent	Target	Population
Midostaurin	*FLT3*	Induction, consol, (maint)
Gemtuzumab ozogamicin	CD33	CBF, de novo (fav/intermed), relapsed
CPX-351	Cytotoxic	t-AML, AML-MRC, age 60-75
Ivosidenib/enasidenib	*IDH1/2*	Rel/ref or de novo (Ivo)
Venetoclax	*Bcl-2*	De novo, >/=75, comorbidities
Gilteritinib	*FLT3*	Rel/ref
Glasdegib	Smoothened receptor	De novo, >/=75, comorbidities
CC-486	DNA methyltransferase	CR/CRi1, inelig for curative therapy

ELN 2022 Classification Changes

- **Changes to blast thresholds defining AML**
  - All recurrent genetic abn (ex *BCR*::*ABL1*) define AML if >/=10% blasts including *NPM1*, bZIP *CEBPα*
  - New category: Designated AML if >/=20% blasts and MDS/AML with defined genetic abn if 10-19% blasts:
    - Mutated *TP53*
    - AML with MDS-related mutations *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*
    - AML with MDS-related cytogenetic changes

Dohner et al. Blood, 2022

ELN 2022 Changes to Risk Classification

- *FLT3*-ITD ratio not relevant, all *FLT3*-ITD are intermediate risk (+/- *NPM1)*
- AML with myelodysplasia-related gene mutations is adverse-risk
- Adverse cytogenetics in *NPM1*-mutated AML is adverse
- bZIP *CEBP*α is favorable-risk (either monoallelic or biallelic)
- Additional adverse disease-defining cyto include t(3q26.2;v) involving *MECOM*, t(8;16)(p11;p13) with *KAT6A::CREBBP*

Dohner et al. Blood, 2022

Gene Mutations/Rearrangements to Establish Diagnosis or Identify Actionable Therapeutic Targets

- Gene mutations
  - ***FLT3, IDH1/IDH2, NPM1***
  - ***CEBP*α*, DDX41, ***TP53***, ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2***
  - ***C-KIT*** in CBF AML
  - For *NPM1* and CBF perform baseline qPCR or dPCR for MRD in CR

- Gene rearrangements
  - ***PML::RARA***, ***CBF::MYH11***, ***RUNX1::RUNX1T1***, *KMT2A rearrangements, BCR::ABL1*

Dohner et al. Blood, 2022

Identification of Significant Co-mutational Pattern in *NPM1* Mutant AML

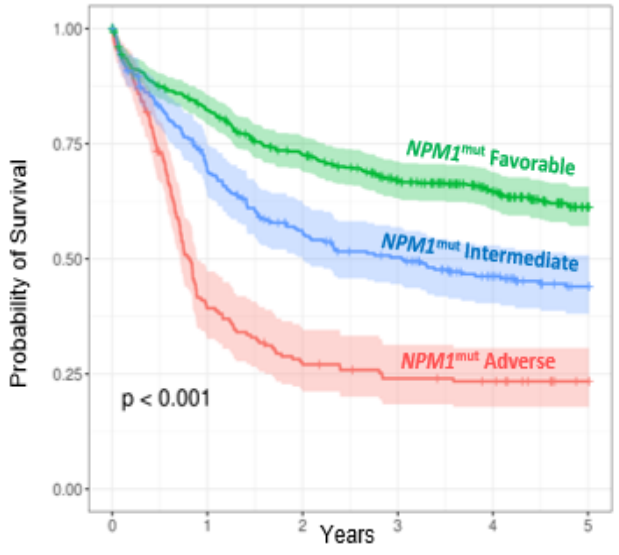
- N=1,001
- Med age 53 yrs
- ELN Classification
  68% favorable, 29% intermed, 3% adverse
- Common mutations
  DNMT3A 54%, *FLT3-ITD* 38%, *RAS* 21%

Figure 1. Classification criteria for $NPM1^{mut}$ AML (A) and Kaplan-Meier OS analysis in each group (B)

A

Proposed risk group in $NPM1^{mut}$ AML	Criteria
Adverse (18%)	• *FLT3*-ITD^{high} + *DNMT3A*^{mut} • *TP53*^{mut}
Intermediate (26%)	• *FLT3*-ITD^{high} + *DNMT3A*^{wt} • *FLT3*-ITD^{low} + *DNMT3A*^{mut} • Absence *FLT3*-ITD + *DNMT3A*^{mut} without any favorable (*PTPN11*^{wt}+*NRAS*^{wt}+*RAD21*^{wt}+*KRAS*^{wt})
Favorable (56%)	• Not meeting Adverse or Intermediate criteria

B



Hernandez-Sanchez et al. EHA, 2022 (abstr S130)

Venetoclax + HMA in Newly Dx "Unfit" AML

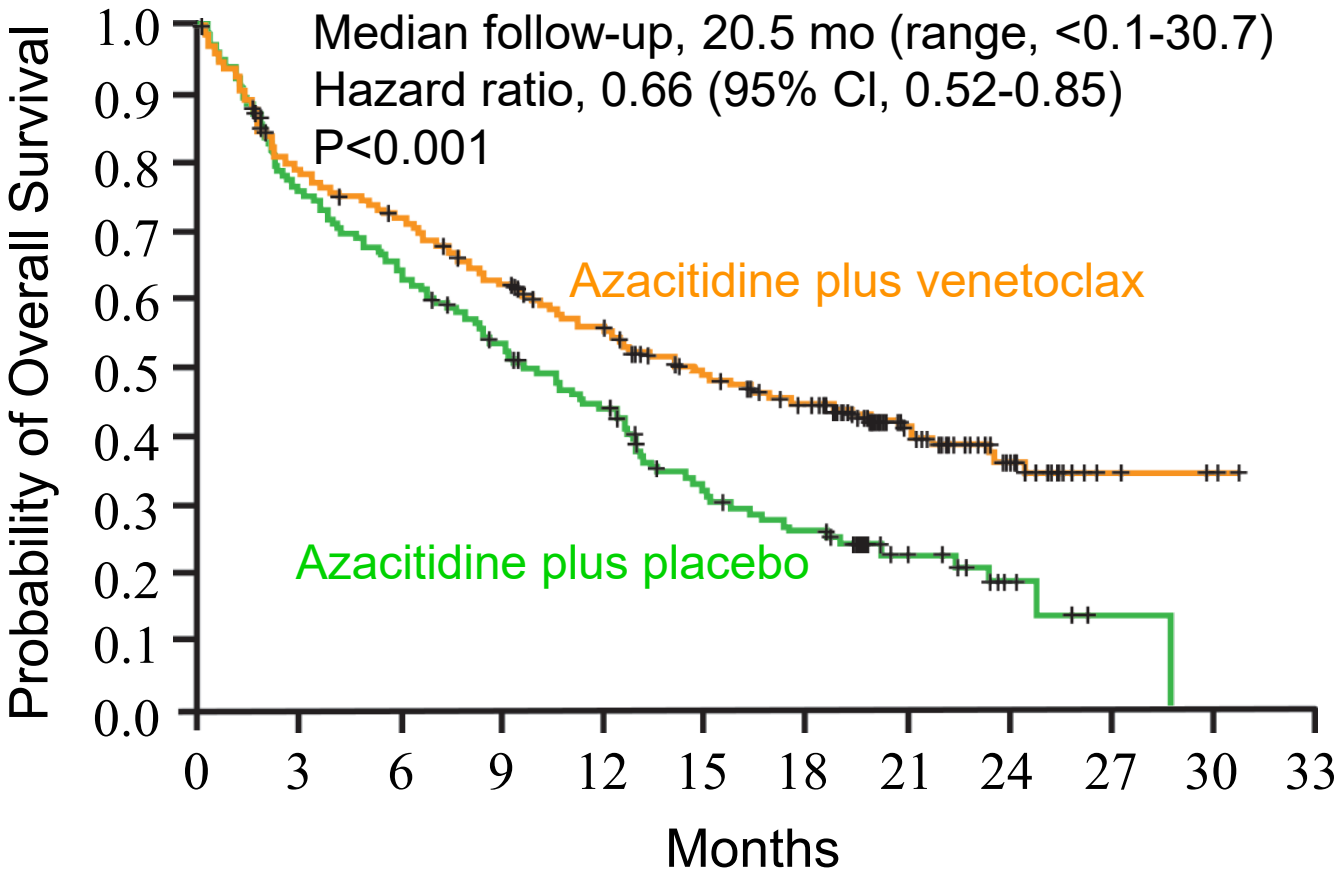
Table 5. Efficacy outcomes by subgroups

Subgroup	Evaluable for response/OS, n (%)	CR + CRi, n (%)	n for Median duration of CR + CRi	Median duration of CR + CRi, mo (95%CI)	Median OS, mo (95%CI)
All patients	145	97 (67)	97	11.3 (8.9, NR)	17.5 (12.3-NR)
Cytogenetic risk					
Intermediate	74 (51)	55 (74)	55	12.9 (11, NR)	NR (17.5-NR)
Poor	71 (49)	42 (60)	42	6.7 (4.1, 9.4)	9.6 (7.2-12.4)
Age					
≥75 y	62 (43)	40 (65)	40	9.2 (6.4, 12.5)	11 (9.3-NR)
<75 y	83 (57)	57 (69)	57	12.9 (9.2, NR)	17.7 (14.2-NR)
AML					
De novo	109 (75)	73 (67)	73	9.4 (7.2, 11.7)	12.5 (10.3-24.4)
Secondary	36 (25)	24 (67)	24	NR (12.5, NR)	NR (14.6-NR)
Mutations*					
FLT3†	18 (12)	13 (72)	13	11 (6.5, NR)	NR (8-NR)
IDH1 or 2‡	35 (24)	25 (71)	25	NR (6.8, NR)	24.4 (12.3-NR)
NPM1	23 (16)	21 (91)	21	NR (6.8, NR)	NR (11-NR)
TP53	36 (25)	17 (47)	17	5.6 (1.2, 9.4)	7.2 (3.7-NR)

DiNardo et al. Blood, 2019

Overall Survival

Aza + Venetoclax vs Aza + Placebo



DiNardo et al. N Engl J Med, 2020

Venetoclax + HMA in AML

Tricks of the Trade

- Tumor lysis very uncommon in AML, but some admit to initiate C1
- With concomitant azoles Ven dose reduced from 400mg qd
  - Per FDA 100mg for vori and 70mg for posa
- Continue Ven for 28 days in C1 without interruption for cytopenias
- Bone marrow biopsy day 14-21 C1. If no decrease in blasts, consider alternative therapy; if marrow aplasia hold C2 until recovery
- Once in remission, Ven often decreased to 21 days or 14 days of subsequent 28-day cycles to avoid prolonged cytopenias
- Consider GCSF if in CR and ANC <500/uL for >42 days
- If no CR after 1-2 cycles, consider abandoning

What's New In Induction Therapy?
Intensified Induction, Adverse-risk AML

- **FLAG-ida + Venetoclax[1]**: n=45, newly diagnosed (ND), CRc 89%, MRD^{-} in 93%, 60% to allo, 24-month EFS 64%, OS 76%

- **Aza + Ven + Gilteritinib[2]**: n=26, *FLT3*^{mut}, relapsed/refractory: ORR 67%, CR 7% and CRi 20%, med OS 10.5 mo; ND: all in marrow CR by D14, CR 73% and CRi 9%

- **Quizartinib vs placebo + chemo and maint quiz[2]**: n=539, *FLT3*-ITD^{mut}, ND, med age 51, med OS quiz 32 mo vs 15 placebo, CRc 72% vs 65%. **But ? Control arm**

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[1]DiNardo et al. Am J Hematol, 2022; [2]Short et al. ASH, 2021 (abstr 696); [3]Erba et al. EHA, 2022 (abstr S100)

What's New In Induction Therapy?
Adverse-risk AML

- **HMA + Ven in adverse-risk AML w or wo *TP53* mutation[1]:** ND, age >/=75, adverse-risk cyto with *TP53*^{wt} CR/CRi with Aza/Ven vs Aza 70% vs 23%, OS 23.4 vs 11.3 mo; with *TP53*^{mut} CR/CRi 41% vs 17%, OS 5.2 vs 4.9 mo.

- **Aza + Ven + Magrolimab[2]**: n=38, ND and R/R, med age 70 in ND, CR/CRi in ND 94% and CR 81% (82% adverse risk), CRcyto 75%, MRD$^-$ 55%

- **Menin inhibitor SNDX-5613[3]**: n=45 with *MLL*r, CRc 49% and in *NPM1* 30% with MRD$^-$ in 70%

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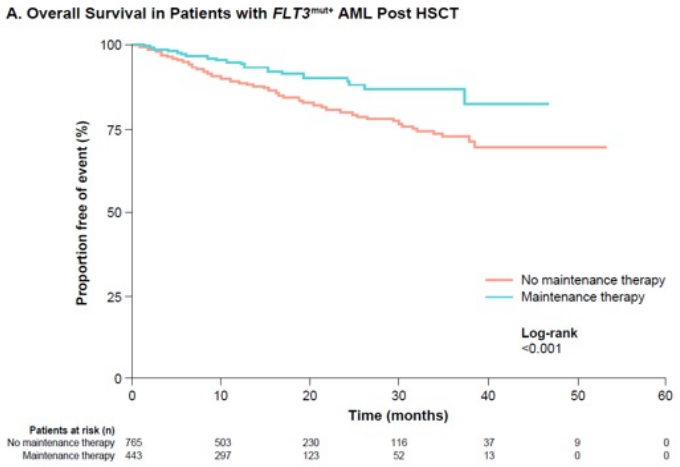
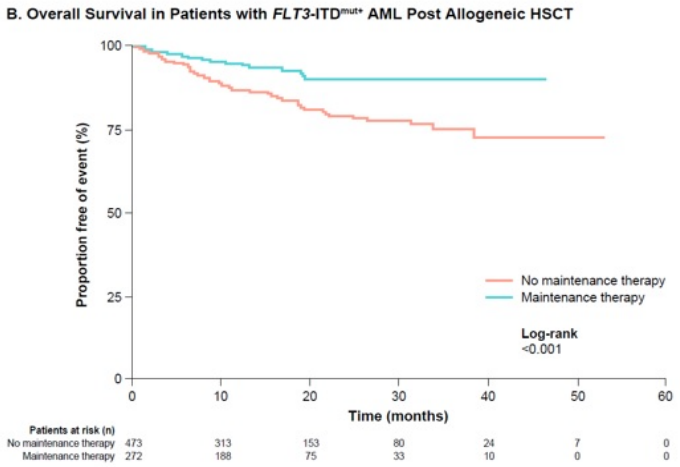
[1]Pollyea et al. ASH, 2021 (abstr 224); [2]Daver et al. ASH, 2021 (abstr 371); [3]Stein et al. ASH, 2021 (abstr 699)

Any Progress In Maintenance Therapy?

- **Maintenance after HSCT for *FLT3-ITD*^{mut} AML**
- Retrospective
- n=1,208 (756 no maint, 443 maint)
- OS longer for and maint *FLT3*i, HMA, chemo, targeted agents) (p<0.001)





Yang et al. ASH, 2021 (abstr 693)

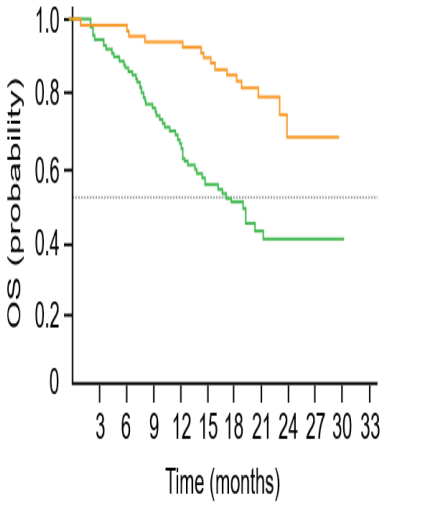
Measurable Residual Disease and Clinical Decisions

- Not all MRD$^-$ pts are in CR; not all MRD$^+$ pts will relapse
- CBF and *NPM1,* most reliably studied, may show persistent low level of MRD without prognostic significance[1,2]
- Detectable MRD pre-transplant independent predictor of posttransplant outcome[3]
- Pts with *RUNX1, SF3B1,TP53* unlikely to achieve MRD$^-$ CR/CRi while *NPM1, IDH1, KRAS* predict high rates of MRD$^-$ prior to transplant; post-transplant OS better if MRD- pre-transplant regardless if pts require additional therapy beyond induction.

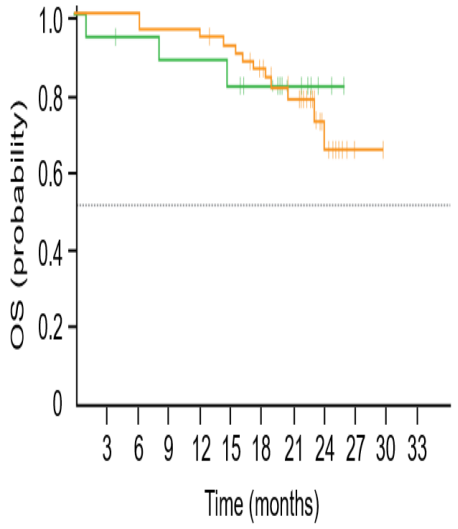
[1]Rucker et al. Blood, 2019; [2]Tiong et al. Blood Adv, 2021;
[3]Hourigan et al. ASCO, 2022 (abstr 7006); Stahl et al. ASH, 2020 (abstr 273)

Measurable Residual Disease in AML Treated With Low-Intensity Therapy

- n=164 with CRc evaluable for MRD
- Treated with Aza/Ven
- MRD assessment by MFC
- MRD <10^{-3}: 41%, MRD >/=10^{-3}: 59%
- Multivariable analysis: CRc and MRD 10^{-3} predicted OS (p<0.001)
- **MRD important for patients treated with low-intensity therapy**



OS	No. of Events	12 Months, % (95% CI)	18 Months, % (95% CI)	Median OS, Months (95% CI)
CR + CRi + MRD < 10^{-3}	15	94.0 (84.7 to 97.7)	84.8 (73.3 to 91.4)	NR (24.4 to NR)
CR + CRi + MRD ≥ 10^{-3}	52	67.9 (57.6 to 76.2)	50.1(39.6 to 59.8)	18.7 (12.9 to NR)



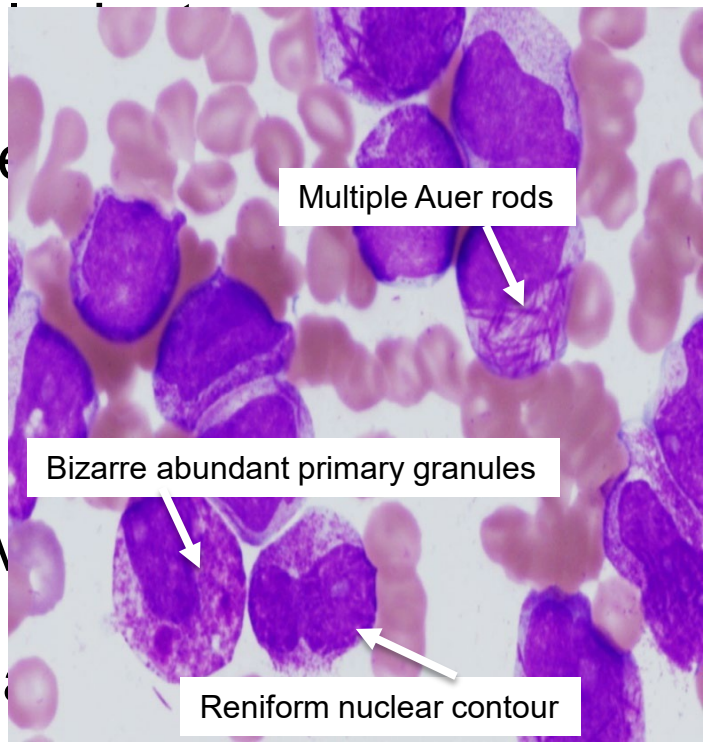
OS	No. of Events	12 Months, % (95% CI)	18 Months, % (95% CI)	Median OS, Months (95% CI)
CR + CRi + MRD < 10^{-3} by the end of cycle 1	3	87.8 (59.5 to 96.8)	81.8 (53.0 to 93.7)	NR (NR to NR)
CR + CRi + MRD ≥ 10^{-3} thereafter	12	96.0 (84.9 to 99.0)	85.8 (72.5 to 93.0)	NR (24.4 to NR)

Pratz et al. J Clin Oncol, 2022

Why Talk About APL Separately from Other AMLs?

- Cells are attractive and intriguing to
- Molecular pathogenesis has been de
- Clinical manifestations are unique
- Treatment is different from all other
- Disease is highly curable (almost ev
- This is the one AML that every hema

(such pts are notoriously admitted on Friday nights)



Important Concepts in Induction in APL

- No modification based on additional cyto abn (? if complex[1]), therapy-related, *FLT3* mutations (treated with ATO[2]), *PML* isoform, morphology (M3V), or $CD56^{pos}$
- Bone marrow not needed on day 14 and not at CR
  - **No primary resistance**
  - **No prognostic importance of cyto/molecular genetics in CR1 at end of induction**
  - **EVERY pt achieves CR (if no early death)**
- Maybe no marrow needed at presentation for some pts if diagnosis unequivocal (provocative concept)

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[1]*Epstein-Peterson et al. Blood Adv, 2022;*
[2]*Poire et al. Leuk Lymph, 2014*

Induction in APL

- ATRA + ATO for low-risk (Lo Coco regimen)
- ATRA + ATO + ida (or GO) for high-risk (Iland or Estey/Ravandi/Abaza regimen)

  OR (if ATO unavailable)

- ATRA + ida
- CNS prophylaxis for high-risk (IT x 4-6-no data, but I do it)
- Prophylactic steroids for all

Lo Coco et al. New Engl J Med, 2013; Abaza et al. Blood, 2017

Consolidation in APL

- ATRA + ATO
  - Low-risk: 4 courses (Lo Coco)
  - High-risk: 2 courses with ida in induction (Iland)

  OR (if ATO not available)

- 3 cycles anthracycline-based chemo (leads to molecular CR in 95%)
  - ATRA for 2 weeks with each cycle, based on historical comparisons of consecutive series

- High-risk patients require either
  - ATO in induction or consolidation
  - IDAC in consolidation

Lo Coco et al. New Engl J Med, 2013; Iland et al. Blood, 2012; Mandelli et al. Blood, 1997; Diverio et al. Blood, 1999; Sanz et al. Blood, 2009; Powell et al. Blood, 2010

The 3 Big Questions in AML in 2022

- Is patient a candidate for intensive chemotherapy?
- Do patient's leukemia cells have a targetable mutation or antigen?
- Is patient a transplant candidate?

AML Treatment Strategies in 2022

AML subgroup	Candidate for intensive chemo	Not candidate for intensive chemo
All patients	Clinical trial preferred	Clinical trial preferred
CBF	GO + chemo, ? If pretrans	HMA + Venetoclax
CD33 pos	?GO + chemo,? If pretransplant	GO d1,8 or HMA + Venetoclax
t-AML or AML with MRC (incl complex cyto)	CPX-351 induc/consol, transplant	HMA + Venetoclax
TP53 mutant	Chemo or ?decitabine x 5-10d +/- Venetoclax[1]	?Decitabine x 5-10d +/- Venetoclax[1]
FLT3+	Mido + chemo induc/consol/?maint, transplant	HMA + Venetoclax
*IDH*1/2+	Chemo (on trial with *IDH*i)	HMA + Venetoclax or Ivo
Marker -	Chemo	HMA + Venetoclax

[1]*Maiti et al. ASH, 2021 (abstr 694)*

AML Treatment Strategies in 2022: Rel/Ref

AML subgroup	Candidate for intensive chemo	Not a candidate for intensive chemo
All patients	Clinical trial preferred	Clinical trial preferred
IDH2+	Enasidenib	Enasidenib
IDH1+	Ivosidenib	Ivosidenib
FLT3+	Gilteritinib or Gilteritinib + Venetoclax[2] or HMA + Venetoclax	Gilteritinib or Gilteritinib + Venetoclax[2] or HMA + Venetoclax
TP53 mutant	Chemo vs decitabine x 5-10d +/- Venetoclax	Decitabine x 5-10d +/- Venetoclax
CD33+	Chemo or GO	HMA + Venetoclax[1] or GO
marker -	Chemo vs HMA vs HMA + Venetoclax[*1]	HMA vs HMA + Venetoclax[*1]

[*]Lower RR for HMA + Venetoclax in R/R setting.[1]*DiNardo et al. Am J Hematol 2018*; [1]*Goldberg et al. ASH 2017, (abstr 1353)*; [2]*Daver et al. J Clin Oncol, 2022*

Conclusions

- 9 new drugs recently approved for AML
- Second gen more potent *FLT3*i available, in randomized trials
- CPX-351 new SOC for t-AML, AML-MRC, prior MDS/CMML
- Venetoclax + HMA
  - highly effective new SOC for older adults, unfit adults or maybe even younger adults with poor-risk disease (await studies)
  - Serves as a backbone for combinations with novel agents
- MRD incorporated into clinical decisions (but pre-transplant conundrum persists)
- Therapeutic paradigms are changing

Changing Landscape in AML 2022

Final Thoughts

- Move towards less chemotherapy and in fact, away from chemotherapy with targeted strategies
- New-found ability to effectively treat older adults, poor-risk pts and those with comorbidities (major areas of unmet need)
- Shift to oral therapies, future may be doublets, triplets and beyond
- Increased burden on outpatient care delivery


Northwestern Medical Center