Improving Outcomes With Current Therapies in Acute Myeloid Leukemia and Acute Promyelocytic Leukemia: What We Recommend in 2023

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- Research Funding
  - Abbvie
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- Royalties
  - UpToDate
- Off label use
  - Gileritinib, quizartinib
  - Enasidenib, ivosidenib
  - Venetoclax
  - Magrolimab
  - Pevonedistat
  - Uproleselan
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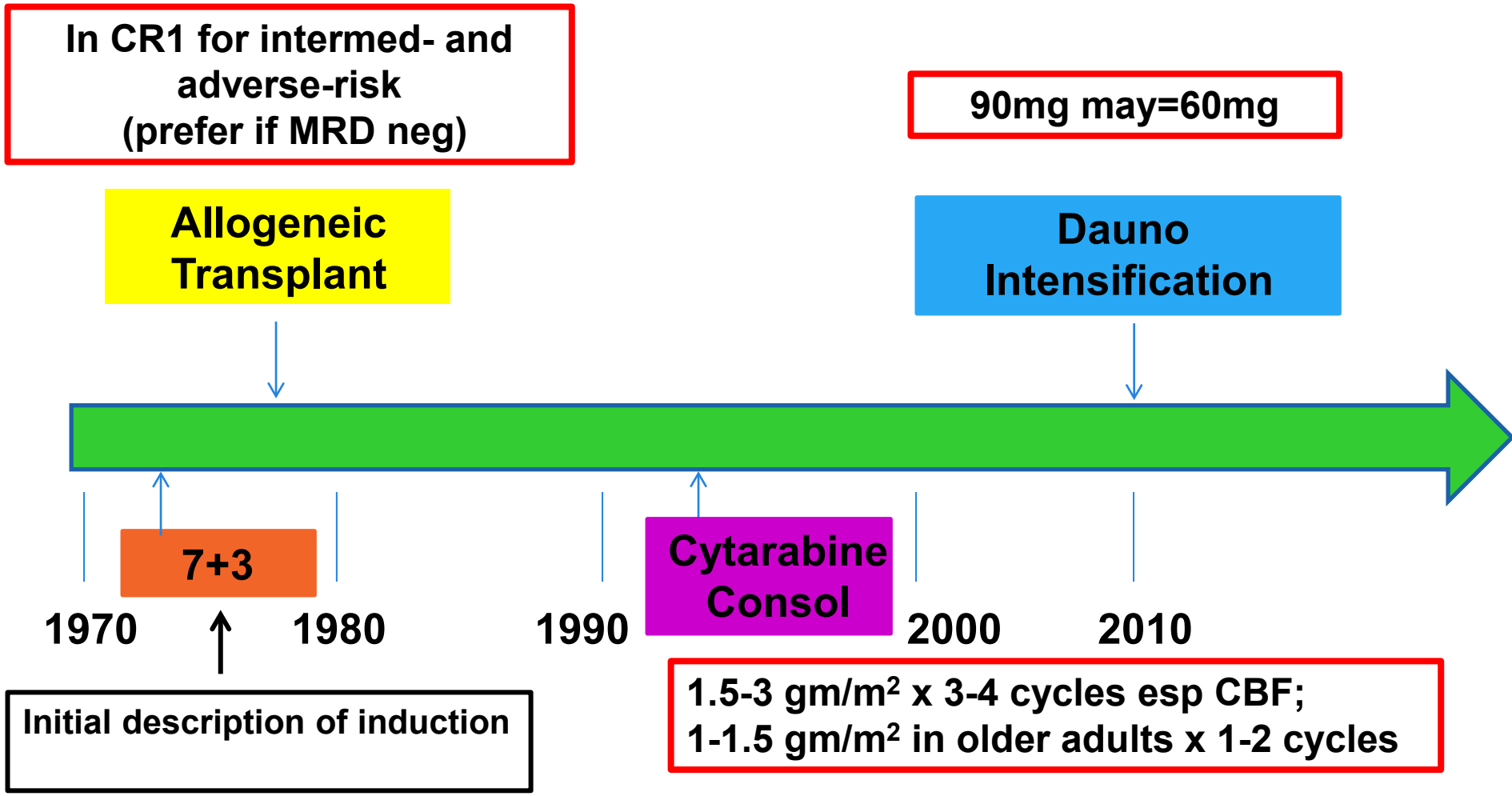
Objectives

- Describe the prevailing therapeutic paradigm in AML and outcomes before 2017
- Discuss selective novel agents for AML, new treatment strategies and changing therapeutic paradigms
- Define the evolving landscape in AML

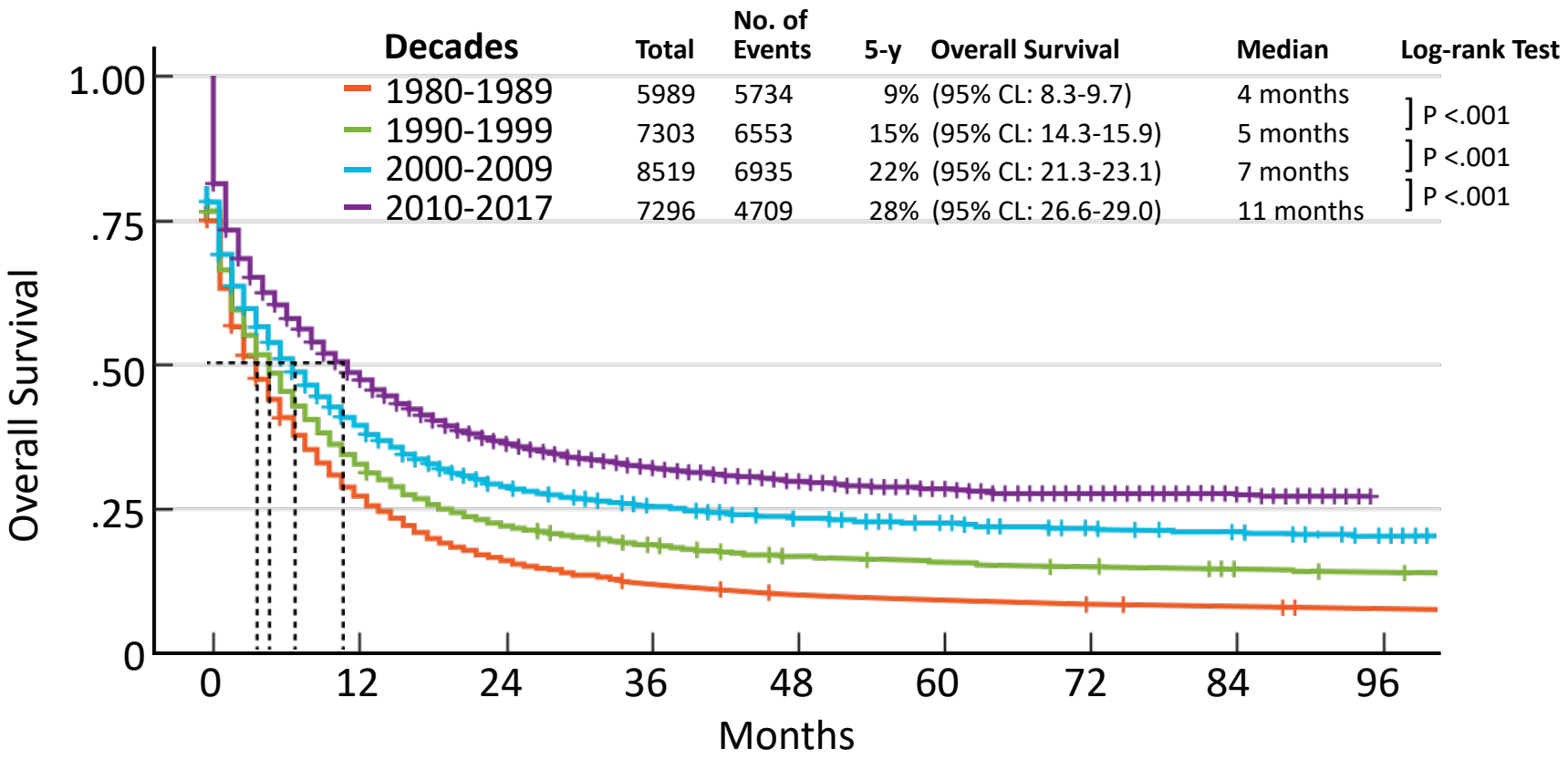
Prevailing Therapeutic Paradigm in AML 1973-2017



Fernandez et al. New Engl J Med, 2009; Luskin et al. Blood, 2016; Begna et al. ASH, 2021 (abstr 1267); Rollig et al. ASH, 2022 (abstr 217); Burnett et al. J Clin Oncol, 2013

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

SEER All AML: All Ages



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 measurable residual disease

Gene Mutations Important in Everyday Practice

Gene	Incidence	Association	Impact
FLT3-ITD/TKD	25%	*NPM1*	Unfavorable
NPM1	13%	*FLT3*	Favorable
bZIP *CEBPα*	11%	*FLT3*	Favorable[1]
C-KIT	15%	*CBF*	Unfavorable[2]
IDH1/2	22%	*NPM1*	Favorable
TP53	7%	t-AML, complex karyotype	Unfavorable
RUNX1	10%	Mutually exclusive with recurrent genetic abn	Unfavorable
ASXL1	7-30%	Secondary AML	Unfavorable
TET2	27%	*NPM1*, *FLT3*, *JAK2*, *RUNX1*, *CEBPα, KRAS,* but not *IDH*	Unfavorable

[2]in t(8;21), and maybe inv(16), but less clear

[1]Wakita et al. Blood Adv, 2022; [2]Hyak et al. ASH, 2022 (abstr 536)

ELN 2022 Changes to Risk Classification

- All recurrent genetic abn (ex *BCR*::*ABL1*) define AML if >/=10% blasts including *NPM1*, bZIP *CEBPα*
- *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 *CEBPα* is favorable-risk (either monoallelic or biallelic)

Dohner et al. Blood, 2022

Recently Approved Agents for AML 2017-2023

Agent	Target	Population
Midostaurin	*FLT3*	Induction, consol, (maint)
Gilteritinib	*FLT3*	Rel/Refr
Ivosidenib/Enasidenib	*IDH1/2*	Rel/Refr or de novo (Ivo)
Venetoclax (w HMA or LoDAC)	*BCL-2*	De novo, >/=75, comorbidities
Glasdegib (w HMA or LoDAC)	Smoothened receptor	De novo, >/=75, comorbidities
Gemtuzumab ozogamicin	CD33	Fav/intermed, rel/refr
CPX-351	Cytotoxic	t-AML, AML-MRC, age 60-75
CC-486	DNA methyltransferase	CR/CRi1, ineligible for curative therapy
Olutasidenib	*IDH1*	Rel/Refr

Evolving Use of Novel Agents in AML

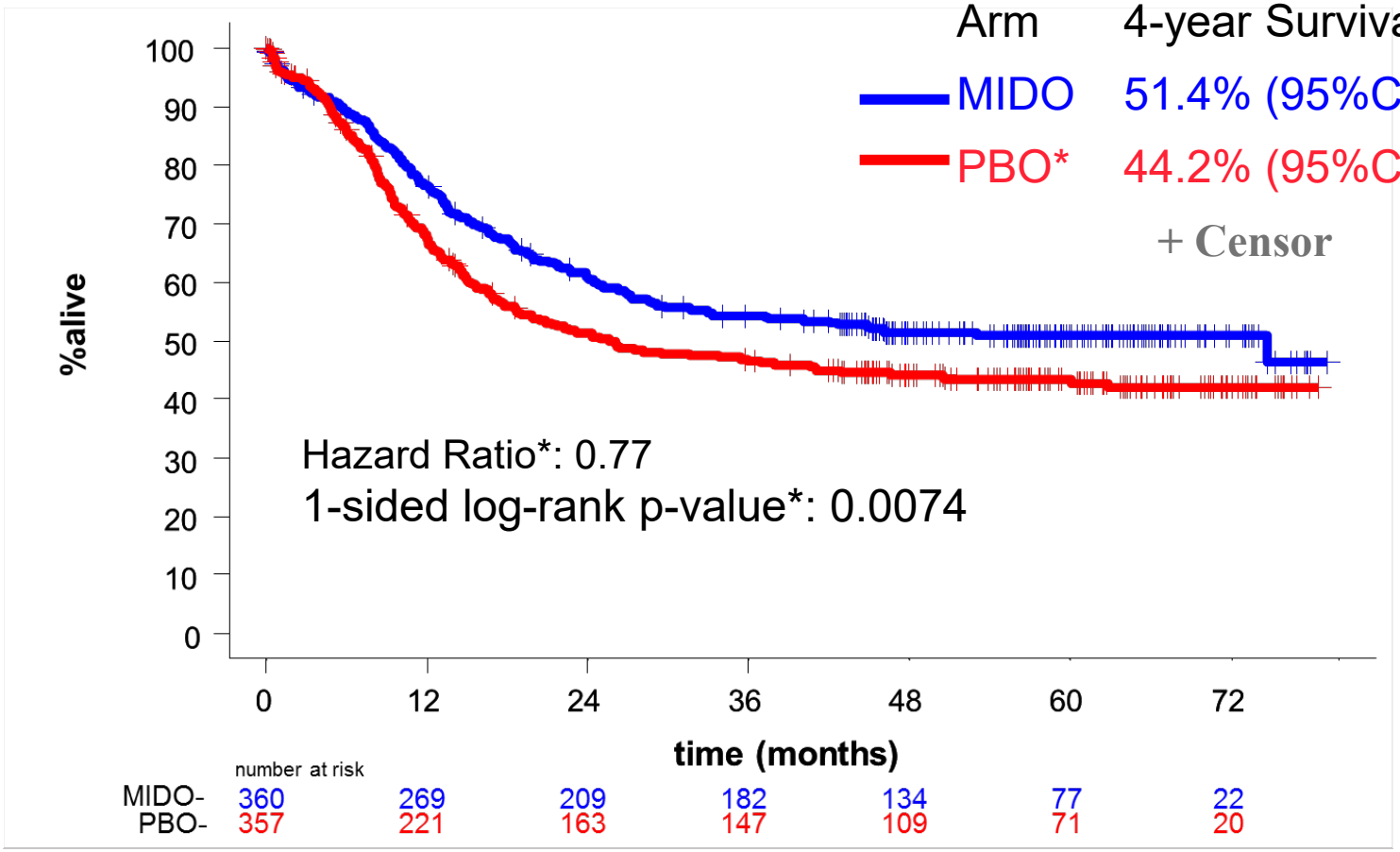
Single agent (CPX-351, CC-486)

Novel agent combined with chemo (*FLT3*i, *IDH1,* Venetoclax, GO)

Novel-novel combination doublets (Venetoclax + Gilteritinib)

Novel-novel-chemo triplet (*FLT3*i or Gilt+ Venetoclax + HMA)

Overall Survival
Chemo + Midostaurin or Placebo
Ratify Trial



***PBO=Placebo**

Stone et al. N Engl J Med, 2017

Midostaurin in AML

- First agent with (sustained) regulatory approval in ~50 years
- It changed practice and therapeutic paradigm, but full potential *FLT3*i not realized
  - OS increase only 7%
  - Benefit more in *FLT3*-TKD than ITD
  - Which phase of treatment important if not all 3?
  - Among least potent *FLT3* inhibitors
  - Role in maintenance unclear[1]
  - Beneficial effect of Midostaurin most pronounced in *NPM1*^{wt}/*FLT3*^{high} group, but also beneficial in *NPM1*^{pos}[2]

[1]*Larson et al. Leukemia, 2021;* [2]*Dohner et al. Blood, 2020*

Midostaurin in AML

- All *FLT3*^{mut} pts get 7 + 3 + Midostaurin in induction, consol then allo or maintenance

- Second gen *FLT3*i: Quizartinib + chemo vs placebo + chemo and maint Quiz or placebo and/or allo followed by 3 yr Quiz or placebo
  - n=539, new dx, *FLT3*-ITD^{mut}
  - med OS quiz 32 mo vs 15 placebo (p=0.0324)
  - CRc 72% vs 65%.
  - But ? Control arm

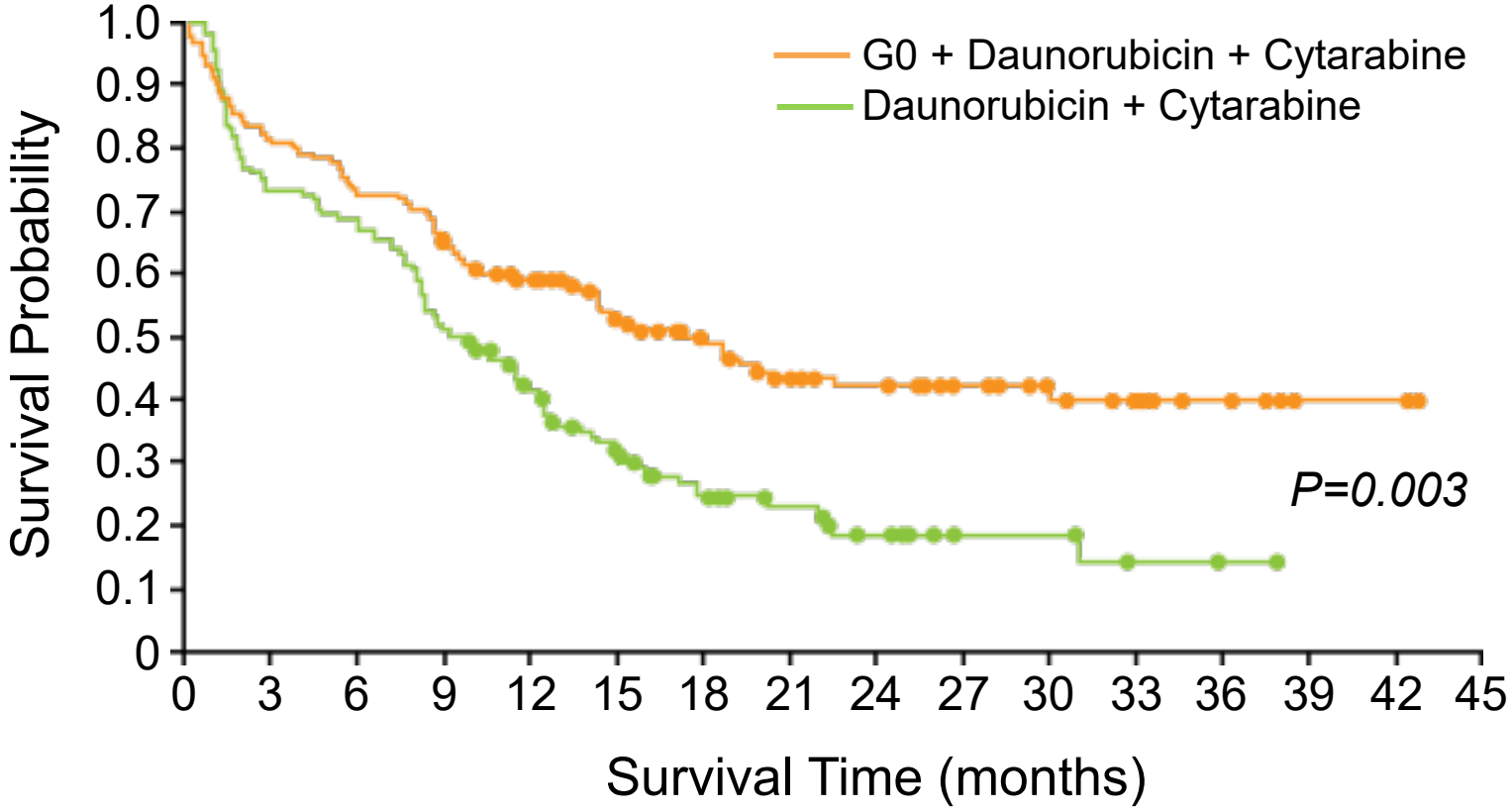
Erba et al. EHA, 2022 (abstr S100)

Gemtuzumab Ozogamicin (Fractionated)

Newly Diagnosed AML Ages 50-70

Kaplan-Meier Plot of Event-Free Survival

ALFA-0701 Trial



Castaigne et al. Lancet, 2012 and update

Gemtuzumab Ozogamicin

- Reduced and fractionated schedule reduces toxicity (4.6% SOS in ALFA 0701) but no benefit in OS[1]
- OS benefit in fav-risk and trend in intermed-risk, but not adverse-risk[2]
- OS no benefit in younger pts[3]
- OS benefit in older adults (25% vs 20%, P=0.05)[4]
- Risk of SOS/VOD 8% after allograft; higher if allo <3 mo from GO exposure[5]

[1]Lambert et al. Haematologica, 2019; [2]Burnett et al. J Clin Oncol, 2011; [3]Petersdorf et al. Blood, 2013; [4]Burnett et al. J Clin Oncol, 2012; [5]Battipaglia et al. BMT, 2017

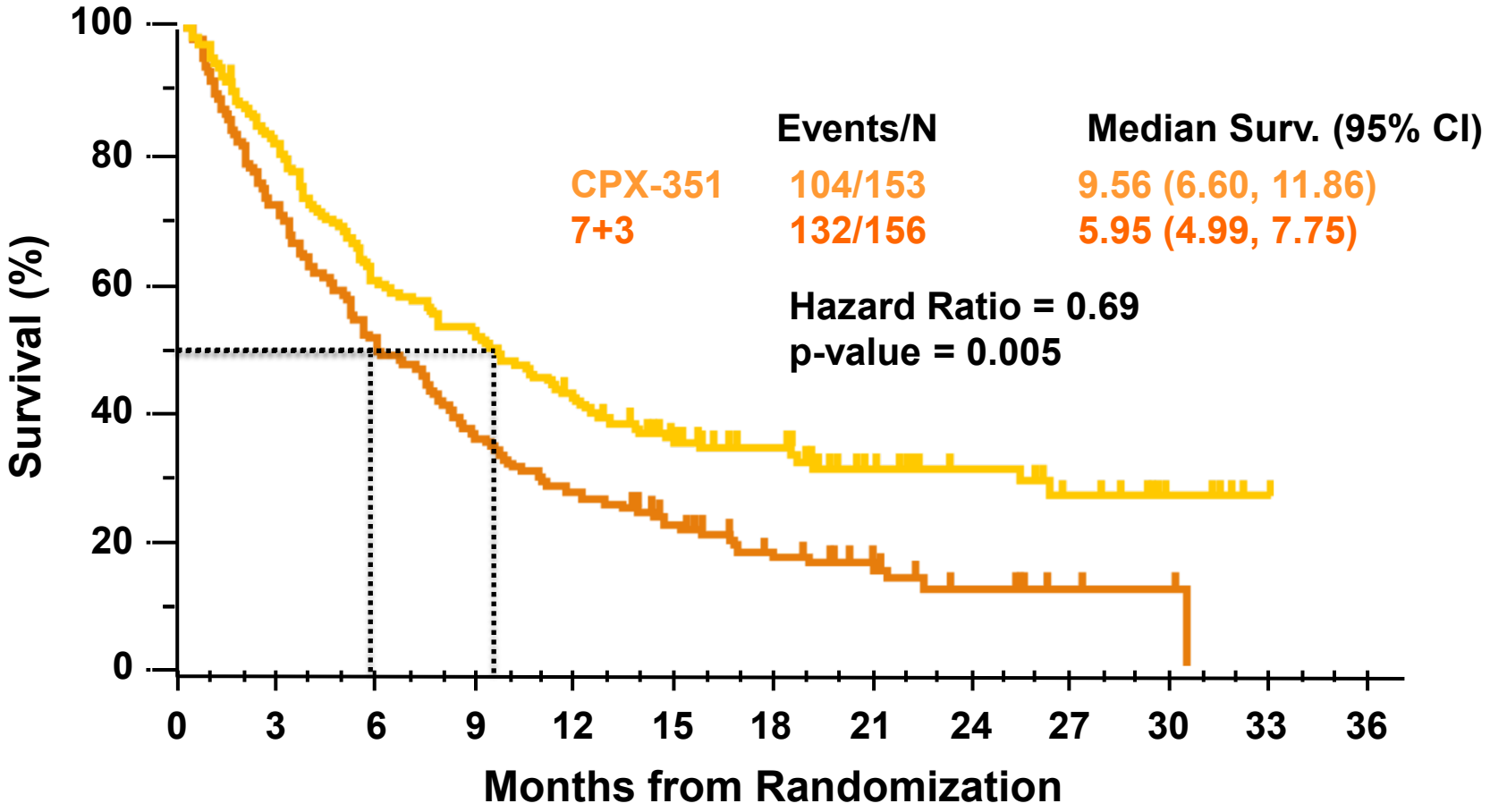
Gemtuzumab Ozogamicin

- 5 Randomized trials in AML (UK MRC AML15, UK NCRI AML 16, SWOG 0106, GOELAMS AML 2006IR, ALFA 0107)
- CR not improved
- OS benefit in 2 of the 5 (marginal in 1)
- UK studies complicated with multiple randomizations
- Has role in 2 small subsets of AML: high-risk APL and CBF, but not clearly otherwise

Hills et al. Lancet Oncology, 2014

Overall Survival Greater in the CPX-351 Arm Compared to the 7+3 Arm

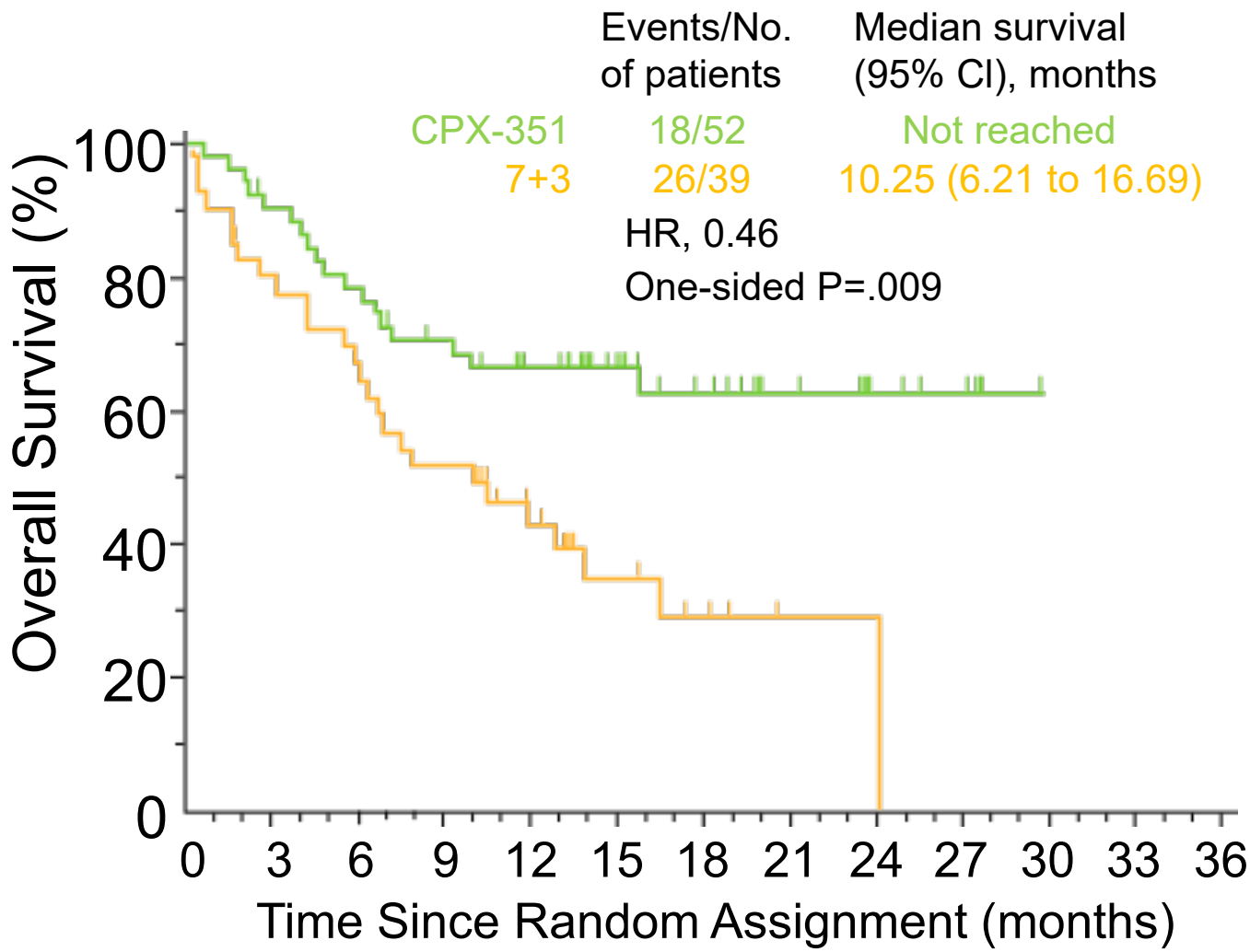
High-risk and Secondary AML



Lancet et al. J Clin Oncol, 2018;
Lancet et al. Lancet Haematol, 2021

Impact of CPX-351 on Transplant Outcome

Overall Survival



Lancet et al. J Clin Oncol, 2018

CPX-351

- Why is CPX-351 more effective in t-AML and AML with MRC?
- Not better in pts with hx prior MDS and HMA exposure
- Why is outcome after allo-HCT better with CPX-351 than with with 7 + 3?
  - Deeper remission?
  - Less toxicity pre-transplant?
- Will CPX-351 be effective either alone or when combined with other agents in adverse subtypes?[1-3] *TP53* → poor outcome with chemo and CPX-35[2]
- Approved for t-AML and AML –MRC and has changed SOC

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[1]Chiche et al. ASH, 2019 (abstr 1355); [2]Lindsley et al. ASH, 2019 (abstr 15); [3]Goldberg et al. ASH, 2018 (abstr 1433)

Ivosidenib or Enasidenib Plus Chemotherapy Phase I Trial

Best Overall Response Summary

	Ivosidenib + CT			Enasidenib + CT		
Response, (%)	All (n=60)	De novo (n=42)	sAML (n=18)	All (n=91)	De novo (n=56)	sAML (n=35)
CR+CRi/CRp	77	88	50	74	80	63
CR	68	76	50	55	64	40
CRi/CRp	8	12	-	19	16	23
MLFS	7	7	6	11	9	14
PR	3	-	11	2	2	3
Treatment failure	13	5	33	13	9	20

Need randomized trials of chemo w or wo Ivo or Ena

Stein et al. Blood, 2020

Ivosidenib and Enasidenib In AML

- Approved and readily used in relapsed/refractory *IDH1/2*-mutated AML
- In de novo *IDH1*-mut AML prefer Azacitidine + Venetoclax since *IDH*-mut AML responds well[1] or possibly Aza + Ivo[2]
- I don't add Ivo or Ena to HMA + Ven outside a clinical trial
- I don't combine Ivo or Ena with induction chemo outside a trial

[1]DiNardo et al. Blood, 2017; [2]Montesinos et al. N Engl J Med, 2022

Venetoclax + HMA in Newly Dx "Unfit" AML

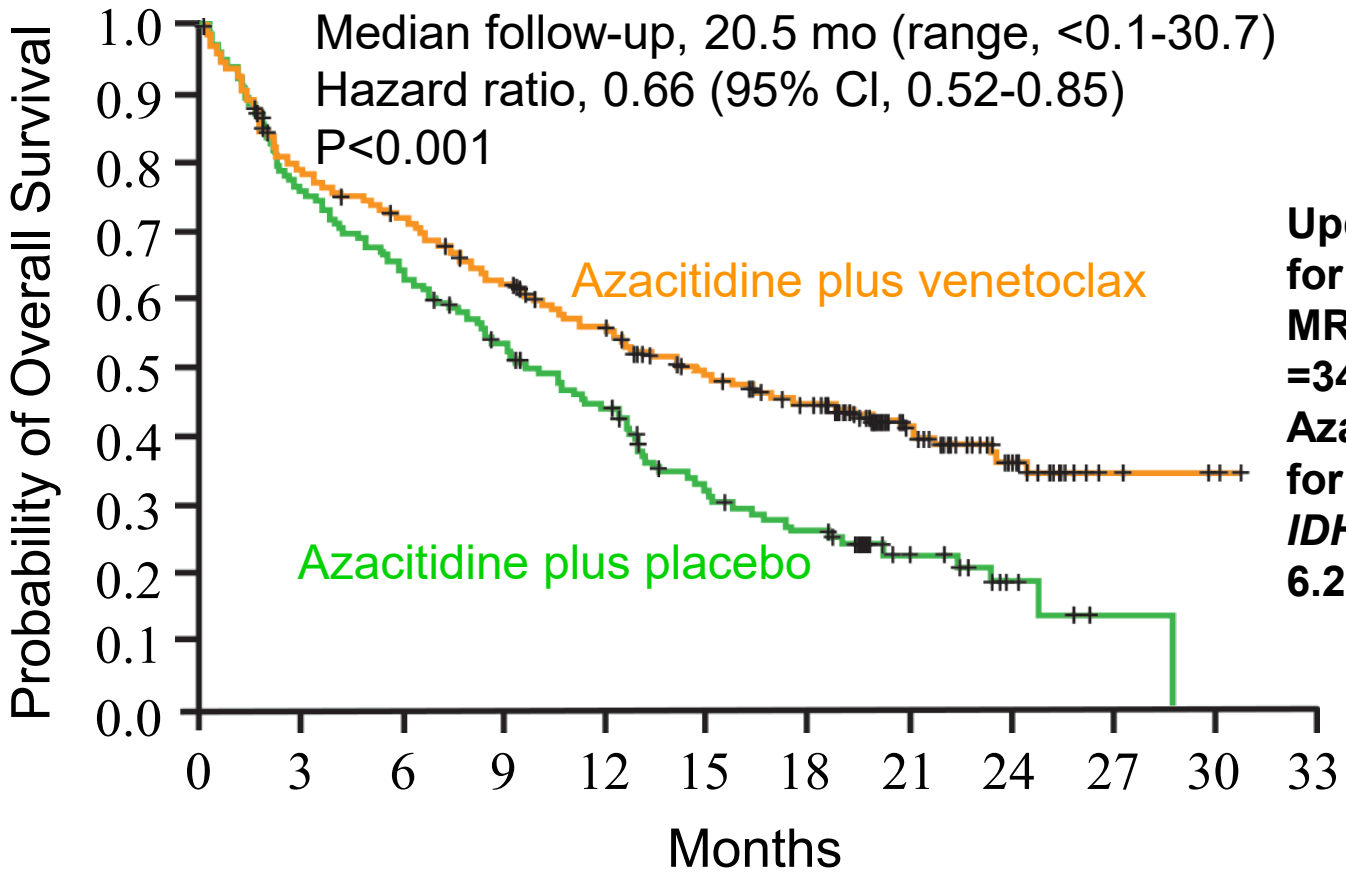
Table 5. Efficacy outcomes by subgroups

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



Update: Med OS for MRD- in CR/CRi =34mo for Aza/Ven vs 25 mo for Aza and for *IDH*+=19.9mo vs 6.2 mo

DiNardo et al. N Engl J Med, 2020; Pratz et al. ASH, 2022 (abstr 219)

HMA + Venetoclax 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 7 or 14 days of subsequent 28-day cycles to avoid prolonged cytopenias
- Consider GCSF if CR and ANC <500/uL for >42 days
- If no CR after 1-2 cycles, consider abandoning

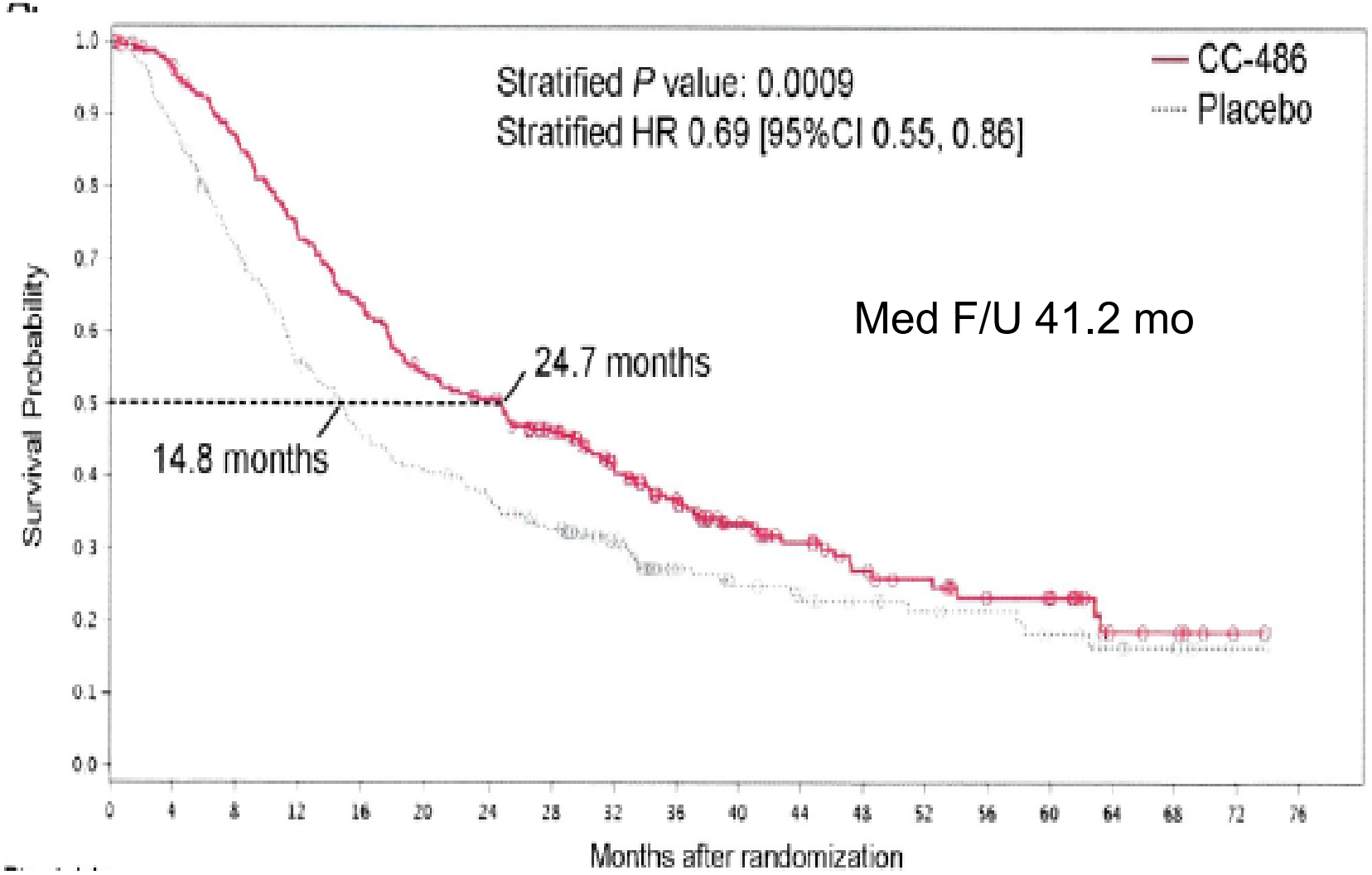
HMA + Venetoclax
Research Directions at ASH2022

- Aza/Ven + novel agents
  - Gilteritinib (FLT3 inhibitor)
  - Pevonedistat (NEDD8 inhibitor)
  - Magrolimab (Anti-CD47 ab)
  - Uproleselan (E-selectin antagonist)
  - SNDX-5613 (Menin-MLL binding inhibitor)
- Aza/Ven + or vs or as maintenance after induction chemotherapy
- Aza/Ven in high-risk younger pts
- Aza/Ven as a bridge to allo for molecular persistence of *NPM1*
- Aza/Ven as maintenance after allo

Short abstr 831; Ong #2161; Daver #61; Jonas #2764; Zeidner #4085; Wang #1450; Matthews #426; Basinet #4059; Xie #601; Sartor #4071; Ionescu #538; Oran # 4738

QUAZAR AML-001 Maintenance Trial of CC-486

Oral Azacitidine For AML in CR1



Wei et. al. N Engl J Med, 2020

QUAZAR AML-001 Maintenance Trial
Oral Aza CC-486

- Phase III placebo controlled trial, age >/=55
- AML in CR1, intermediate- or high-risk, not candidates for allograft
- Prolonged OS and RFS, indep of *NPM1* and *FLT3* status and MRD
- It's oral
- But, pretreatment not prescribed and varied (~20% no consol)
- Pts in relapse with 5-15% blasts could continue CC-486 until >15% blasts or HSCT
- Myelosuppression and other toxicities
- I generally do not use it

Wei al. N Engl J Med, 2020; Dohner et al. Blood, 2022; Roboz et al. Blood, 2022

MRD in AML

- FC, PCR (for *NPM1* and CBF), NGS
- Measure after 2 cycles of intensive treatment
- Sensitivity increased with combined FC and NGS
- 30% MRD- relapse and 30% MRD+ (esp *NPM1* and CBF) do not re
- When is optimal time to measure? After 2 cycles of intensive therapy
- MRD eval must be integrated with other parameters

Getta et al. BBMT, 2017Jongen-Lavrencic et al. N Engl J Med, 2018; Willekens et al. Haematologica, 2016

The Transplant Conundrum

- Poor responders to induction or relapsed pts, (N=272)
- Randomized to remission induction with HAM (N=143) or **W**atch and **W**ait (N=138), then HCT
- To HCT: W and W 98% HAM 96%
- CR@d56 after HCT: W and W 84.1%, HAM 81.3%
- OS by IIT: 3-yr W and W 51%, HAM 54.2%
- Concl: Intensive reinduction did not confer an OS advantage

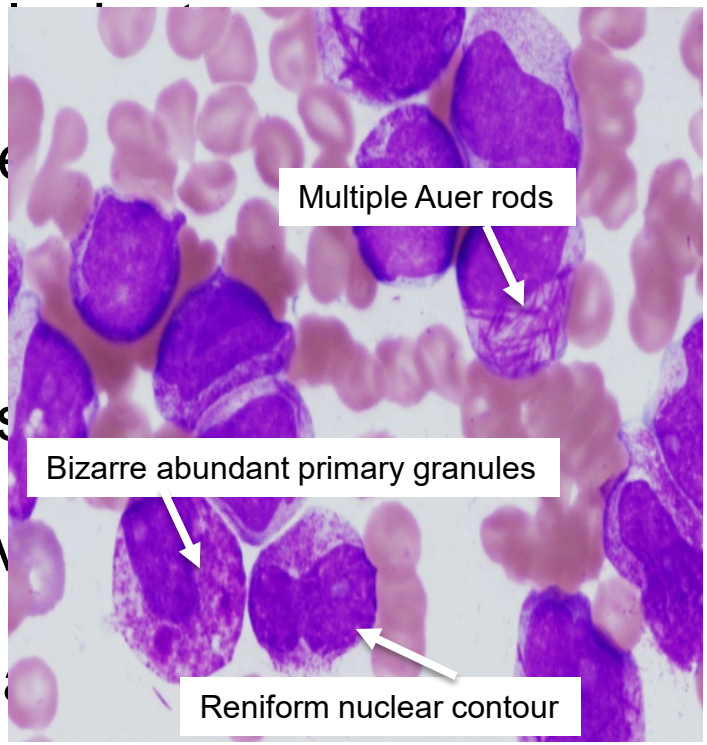
  Data support HCT wo prior remission induction when a donor is readily available
- **Likelihood of achieving MRD$^-$ is mutation dependent, rely less on intensive chemo beyond C1 consolidation, need MRD "erasers"**

Stelljes et al. ASH, 2022 (abstr 4)

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 s
- 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 or Burnett), optimize electrolytes
- 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 (no data, NCCN notes “consider”)
- Prophylactic steroids for DS (no rando data, but commonly given for all, if not, maintain suspicion and give dex at first sign or sx)
- ATRA 45 mg/m^2, 25 mg/m^2 for peds pts or toxicity (oral ATO coming)
- High-risk: give 12-24 hrs of ATRA first to stabilize coagulopathy

Lo Coco et al. New Engl J Med, 2013; Burnett et al. Lancet Oncol, 2015; Abaza et al. Blood, 2017; NCCN AML Guidelines 2023; Castaigne et al. Blood, 1993

Consolidation in APL

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

  OR (if unable or ATO not available)

- 3 cycles anthracycline-based chemo (leads to molec 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

Conclusions

- 10 new drugs recently approved for AML
- Mido new SOC, second gen more potent *FLT3*i avail, 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 and maybe even younger adults with poor-risk disease (await studies)
  - Serves as a backbone for combinations with novel agents
- Therapeutic paradigms are changing
- Just how large the pot of gold at the end of the rainbow is requires more study

Changing Landscape in AML 2023

- Move towards less chemo and in fact, away from chemo with targeted strategies
- New-found ability to effectively treat older adults, poor-risk pts and those with comorbidities
- Revisiting maintenance
- Shift to oral therapies, future may be doublets, triplets and beyond
- Increased burden on outpatient care delivery