Acute Myeloid Leukemia in 2024

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Disclosures - JMF

- **Research Support**  Astellas, Astex, Celgene, Chordia, Novartis, Actinium, Gilead, H3Biosciences (Roivant/Hemavant), Kura, Sellas, and Takeda

- **Advisory Board**  Intrinsiq (AmeriSource Bergen), Lava Therapeutics, Targeted Oncology, Treadwell, National Cancer Institute & NHLBI

- **Off-Label Use**  $^{131}$I-Apamistamab & AlloHCT for rel/ref AML; Magrolimab for TP53$_{\text{mut}}$ AML
Happy Groundhog Day!

Feliz Día de la Marmota!

Alas, 6 more weeks of winter…
AML Updates in 2024

- Evolving Treatment Landscape
- Advances with Lower Intensity Therapy
- High quality remission & *Measurable Residual Disease*
- New Targeted Strategies
  - Mutation-based: Menin inhibitors for KMT2A & NPM1
  - Radioimmunotherapy: I$^{131}$-Apamistamab
  - Targeting TP53: Magrolimab, Allogeneic Transplantation
# 2024 AML Estimates in United States

## Cases: n=20,800
- **Male**: 11,600
- **Female**: 9,200

## Deaths: n=11,220
- **Male**: 6,290
- **Female**: 4,930

### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>299,010</td>
<td>222,900</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,310</td>
<td>110,900</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>61,540</td>
<td>54,800</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>63,070</td>
<td>56,800</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>59,170</td>
<td>54,800</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>52,380</td>
<td>48,900</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>44,590</td>
<td>42,900</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>41,510</td>
<td>39,800</td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td>36,450</td>
<td>26,320</td>
</tr>
<tr>
<td>Pancreas</td>
<td>34,530</td>
<td>26,320</td>
</tr>
<tr>
<td><strong>All sites</strong></td>
<td>1,029,080</td>
<td>797,060</td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>65,790</td>
<td>59,280</td>
</tr>
<tr>
<td>Prostate</td>
<td>35,250</td>
<td>27,900</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>28,700</td>
<td>24,480</td>
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<tr>
<td>Pancreas</td>
<td>27,270</td>
<td>24,310</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>19,120</td>
<td>17,240</td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td>13,640</td>
<td>10,030</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,880</td>
<td>12,740</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,290</td>
<td>10,030</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,780</td>
<td>8,360</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>10,690</td>
<td>8,070</td>
</tr>
<tr>
<td><strong>All sites</strong></td>
<td>322,800</td>
<td>288,920</td>
</tr>
</tbody>
</table>

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

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*Siegel et al, CA Cancer J Clin 74:12-49, 2024*
Myeloid Classification: from 2016 to 2023

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia


The 5th edition of the World Health Organization Classification of Haematological Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

Khoury JD et al. Leukemia 2022;36(7):1703-1719

In its final version

• ICC – MDS/AML (10-19% blasts, replaces RAEB-2)

To be published as WHO Blue Book 5th edition by end of 2023 (current Beta version on IARC website)
Despite a Wealth of Innovative Options, More Work Needs to Be Done to Expose Patients to Effective Therapy

RW analysis of 629 newly diagnosed AML patients from a comprehensive health system in the Midwest United States, including metropolitan and rural populations (2011-2018)

- 66% of patients aged ≥75 years did not receive any chemotherapy or alternative treatment
- Only 13% of patients had evidence of a genomic report, although it has been used for prognostication for at least the last decade

EMR data from 2,133 AML patients to determine the effect of COVID-19 on AML care

- Compared with the pre-COVID-19 cohort, post-COVID-19 patients were significantly less likely to receive HCT
- Longer HCT waiting times suggest the pandemic affected access to timely transplantation

Twenty five years of UK trials in acute myeloid leukaemia: what have we learned?
Burnett AK, British Journal of Haematology, 188:86-100, 2020

- More intensive chemotherapy combinations have been facilitated by better supportive care, including support from other medical disciplines, and nursing expertise.
Randomized 1:1 to Intensive therapy ("7&3", HiDAC x2 consolidation), vs. single agent Clofarabine

* Superior OS with 7&3

Advantage in achieving CR vs. CR/CRi
- Diminished Benefit CRi after 12 months
- MLFS survival is similar to treatment failure
Prospective MRD Evaluation in E2906 using Multiparameter Flow Cytometry

- CR/CRI 50%
- MRD-negative remission in 41% (n=161 evaluable)

Foran et al, ASH 2018 (m/s under review)
From: Association of Measurable Residual Disease With Survival Outcomes in Patients With Acute Myeloid Leukemia: A Systematic Review and Meta-analysis
Short et al, JAMA Oncol. 2020;6(12):1890-1899.

• N=11,151 from 81 publications
• MRD by PCR, MFC, NGS, cytogenetics and/or FISH, or others
• Average Hazard Ratio for achieving MRD negativity:
  • OS  HR 0.36 (95% Bayesian credible interval [CrI], 0.33-0.39)
  • DFS  HR 0.37 (95% CrI, 0.34-0.40)
Mechanism of action of Venetoclax

- Highly selective oral BCL2 inhibitor
- Overexpressed in AML & in Leukemia Stem Cells
- Promising single agent activity
• Patients age >75 years, or **ineligible** for standard induction therapy
  • CHF or chronic stable angina
  • Pulmonary Disease (DLCO or FEV1 <65%)
  • ECOG performance-status score >1

• n=431, 2:1 randomization

Viale A: Phase 3 randomized study
AZA-Venetoclax vs. AZA-Placebo

- Improved OS overall
- Higher CR rates across all subgroups
- Some able to proceed to ‘curative’ AlloHCT

* Venetoclax Dosing recommendations: DiNardo & Wei, Blood 135:85, 2020
“How I treat AML in the era of new drugs”
### Viale-A SubGroup Analysis

- Significantly higher CR rates in all subgroups
- Some subgroups **not** significant for OS (post hoc)

- Age <75 years
- Poor Risk cytogenetics
- Some mutation groups (e.g. TP53, NPM1, FLT3)
Original Study

Induction Therapy and Survival for Acute Myeloid Leukemia in Hispanic Adults from Puerto Rico

Maira A. Castaneda-Avila,1,8 Tonatiuh Suárez Ramos,2,9 Carlos R. Torres-Cintrón,2,9 Luis A. Corto-Santana,3 Guillermo Tortolero-Luna,2,4,9 Karen J. Ortiz-Ortiz2,4,5,9

Abstract

We described the first-line therapy and survival of Hispanics from Puerto Rico with acute myeloid leukemia. Age, risk, and comorbidities were associated with induction therapy type. Among patients who received intensive therapy, those ≥60 years had a higher risk of death. The low survival and the disparities observed highlighted the need to examine further new treatment options for older and comorbid patients.

Background: Acute myeloid leukemia (AML) is the most common type of leukemia in adults. There are no previous studies evaluating AML treatment patients in Puerto Rico. We describe the first-line therapy patterns and survival of patients diagnosed with AML in Puerto Rico using the Puerto Rico Central Cancer Registry Health Insurance Linkage Database (2011-2015).

Methods: We describe patient characteristics according to intensive, non-intensive, and non-treatment status. We used Cox proportional hazard models to evaluate the factors associated with the risk of death stratified by intensive and non-intensive therapy. For this study, 385 patients with AML were included.

Results: The median age was 67 years old and 50.1% were female. Nearly half of AML patients (46.9%) received intensive treatment, 23.6% received non-intensive treatment, and 28.2% did not receive treatment. The overall 3-year survival rate was 179%. Among those who received intensive therapy, the risk of death among females was lower than males (hazard ratio [HR]: 0.64, 95% confidence interval [CI]: 0.44-0.83). Patients 60 years or older who received intensive treatment had a higher risk of death than younger patients (HR: 1.67, 95% CI: 1.08-2.55). Patients with poor/prognostic risk receiving intensive (HR: 3.43, 95% CI: 1.79-6.69) or non-intensive (HR: 4.32, 95% CI: 1.68-11.28) treatment had a higher risk of death than patients with a favorable risk category.

Conclusion: Our findings are the first step to monitor the quality of care of patients with AML in Puerto Rico, particularly related to the administration of appropriate induction therapies, which is one of the most important predictors of AML survival.

Clinical Lymphoma, Myeloma and Leukemia, Vol. 22, No. 10, e922-e930 © 2022 Published by Elsevier Inc.

Keywords: AML, Hazard ratio, Prognostic markers, Leukemia treatment, Risk of death

Castaneda-Avila et al, Clinical Lymphoma, Myeloma & Leukemia. 22:e922-930, 2022
• Prospective central (LabCorp) MRD testing by MFC
  • 86% of CRc patients evaluable
  • Threshold $10^{-3}$ (i.e. <0.1%) residual leukemia blasts
  • 41% MRD-neg CR/CRi

Pratz et al, JCO 40:855, 2022
Multivariate analysis showed CRc with MRD $<10^{-3}$ was a strong predictor of OS [HR 0.285 (95% CI, 0.159 - 0.510), $p<0.001$]
Pre-MEASURE Observational Study of FLT3\textsubscript{m} and NPM1\textsubscript{m} in Remission Prior to Allogeneic Transplantation

- Variants in FLT3 \& NPM1 from Blood from AML patients
- 111 CIBMTR sites from 2013 through 2019. Clinical data were collected through May 2022
- Targeted error-corrected DNA sequencing at a variant allele fraction (VAF) of 0.01%

- 17.3% with residual NPM1 and/or FLT3-ITD variants
- Higher rates of relapse at 3 years 68% vs 21%
- HR 4.32 [95% CI, 2.98-6.26]; \( P < .001 \)
- Decreased survival at 3 years 39% vs 63%
- HR, 2.43 [95% CI, 1.71 - 3.45]; \( P < .001 \).
### Evaluating MRD in AML

<table>
<thead>
<tr>
<th>Timing</th>
<th>Platform</th>
</tr>
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<tbody>
<tr>
<td>CR/CRi; Later if low intensity…</td>
<td>MFC (LAIP, DFN, both)</td>
</tr>
<tr>
<td>Prior to Transplant</td>
<td>PCR (NPM1, FLT3, CBF), or NGS</td>
</tr>
<tr>
<td>Surveillance</td>
<td>PCR (NPM1, CBF), or NGS</td>
</tr>
</tbody>
</table>

**Goals & Challenges:**

- *Increase MRD-negative CR rate*
  - Addition targeted inhibitors, immunotherapy (clinical trials)
- *Improve outcomes in MRD-positive remission*
  - e.g. intensify HiDAC consolidation (older adults); maintenance with oral azacitidine (e.g. NPM1\textsubscript{m}); addition of targeted agents (Gilteritinib in MRD+ AML with FLT3-ITD after AlloHCT), etc.
Emerging advances center on:

- Integrating novel targeted doublets and triplets
- Development novel targeted agents, and strategies for challenging subgroups (e.g. TP53-mutated AML)
- Determining role for immunotherapy in AML and increasing benefit of allogeneic transplantation

Since 2017, we have seen FDA approval of:

- CPX-351 (sAML, AML-MRC)
- Midostaurin, Gilteritinib & Quizartinib
- Ivosidenib, Olutasidenib, and Enasidenib
- Ivosidenib + azacitidine combo
- Re-emergence of gemtuzumab-ozogamicin
- Venetoclax
- Oral azacitidine as maintenance
- Glasdegib
Enasidenib

Ivosidenib

*2022 Olutasidenib
• Median survival 24.0 vs. 7.9 months
  • HR 0.44 (95% CI, 0.27-o 0.73; p=0.001)
• CR/CRh 53% vs.18% (p<0.001)
• DS 14 %
• FDA Approval 1st line Aza combination 12/22

Differentiation Syndrome

- Dexamethasone 10mg IV BID
- Hydroxyurea
- Continue Agent if possible

Norsworthy, Clin Cancer Res 26:4280, 2020
Zeidner, Clin Cancer Res 26:4174, 2020
New Oral agents in AML

Menin Inhibitors - NPM1\textsubscript{mut} & MLL rearrangement

- Target HOXA9/Meis1 overexpression in AML, which leads to AML proliferation/renewal
- AML with NPM1\textsubscript{mut} or MLLr
- Promising agents in clinical development (KO-539, SNDX-5613, BMF-219, others...)
- DS as a clinical toxicity/concern

**FIGURE.** Targeting Menin-MLL Interactions

- **KMT2A(MLL) rearrangement**
  - ON
  - Menin interacts with KMT2A(MLL) to promote leukemogenesis.
  - OFF
  - Menin-KMT2A(MLL) interaction is targeted to reverse epigenetic dysregulation in MLL-rearranged AML.

- **NPM1-mutant AML**
  - ON
  - Menin interacts with NPM1 to promote leukemogenesis.
  - OFF
  - Menin-NPM1 interaction is targeted to reverse epigenetic dysregulation in NPM1-mutant AML.

5%-10% KMT2A Translocation 25-30% NPM1 mutation
Ziftomenib Monotherapy Drives Durable Responses

- **Median DoR 8.2 months** (med. follow up 8.8 months)
- **35% CR rate** (7/20) at 600mg dose (RP2D)
  - 33% (2/6) with FLT3 co-mutations, and 50% (4/8) with IDH co-mutations achieved CR
- **DS:** 15% (grade 1/2) and 5% (grade 3)
- Ziftomenib less likely to induce Menin resistance mutations

Fathi et al, EHA 2023, LB
AML with TP53 Mutation

- Despite surge in use of venetoclax-based therapy, no improvement in duration response or overall survival in “Real World” dataset (Badar, ASH 2023)

- Impact of Allogeneic Transplantation, esp. in 1st line (Med. OS 30.5 mos. vs. 20.2 mos.), again demonstrated in RWD analysis (Badar, ASH 2023)

  HR: 0.15 (95% CI 0.04-0.40), p=0.002
Mechanism of Action of CD47-Blocking Antibodies as Novel Checkpoint Inhibitors

Chao MP et al. Front Oncol 9:1380, 2019
Magrolimab + Azacitidine Appeared “Efficacious” Against TP53 AML in Early Phase Trial

- No significant cytopenias, infections, or immune-related AEs observed
- **On-target hemolytic anemia**
- Median OS - 10.8 months

### Outcome

<table>
<thead>
<tr>
<th>Patients With TP53 AML (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
</tr>
<tr>
<td><strong>CR, % (95% CI)</strong></td>
</tr>
<tr>
<td>MRD- CRa, % (95% CI)</td>
</tr>
<tr>
<td><strong>CRi/CRh, n (%)</strong></td>
</tr>
<tr>
<td><strong>PR, n (%)</strong></td>
</tr>
<tr>
<td><strong>MLFS, n (%)</strong></td>
</tr>
<tr>
<td><strong>DOR, median (95% CI), mo</strong></td>
</tr>
</tbody>
</table>

Frontline TP53-mutated AML in the Phase 3 ENHANCE-2 trial (currently recruiting; NCT04778397)

Daver N. EHA2022 Hybrid Congress. Abstract S132.
Gilead Statement on the Discontinuation of Magrolimab Study in AML with TP53 Mutations

Foster City, Calif., September 26, 2023 – Gilead Sciences has stopped its ENHANCE-2 study in acute myeloid leukemia (AML) with TP53 mutations. Based on an ad hoc analysis, and following review by an independent data monitoring committee, Gilead concluded that magrolimab is unlikely to demonstrate a survival benefit in AML with TP53 mutations compared to standard of care. There were no new safety signals identified and the safety profile was comparable between treatment arms. ENHANCE-2 is a randomized, open-label, Phase 3 trial to determine if magrolimab plus azacitidine improves overall survival, compared to physician’s choice of venetoclax plus azacitidine or intensive chemotherapy in previously untreated AML with TP53 mutations. Gilead is working with study investigators on appropriate next steps for patients enrolled in this study. This decision follows the previously announced partial clinical hold placed on the ENHANCE-2 study.
Iomab-B ($^{131}$I-Apamistamab) & CD45: Mechanisms and Biodistribution

- CD45 antigen expressed on virtually all lymphocytes, and 85%-90% of acute leukemias
- Iomab-B ($^{131}$I apamistamab): anti-CD45 mAb targeting lymphohematopoietic cells with β-particle-emitting radionuclide $^{131}$I
- Offers target-specific ablation as HCT conditioning regimen
- Does not bind other normal tissues; directs radiation to leukemic and immune cells

Phase 3 SIERRA Trial: Iomab-B Prior to HCT vs Chemotherapy in R/R AML

Inclusion Criteria
- Aged ≥55 years, KPS ≥70 with active, R/R AML
  - Primary induction fail ≥2 cycles Chemo
  - 1st early relapse <6m
  - Refractory to salvage chemotherapy with high-dose cytarabine
  - ≥ 2nd Relapse
- 8/8 HCT donor match

Study arm: Iomab-B and HCT
1:1 central randomization

Control arm: chemotherapy

No CR
Follow-up

CR
Observation

Crossover

NMA/RIC and HCT followed by observation

Other modalities or observation

Primary endpoint: durable CR
Secondary endpoint: 1-year OS

a Control arm patients with no CR offered crossover for ethical reasons.
b Physician choice of best salvage chemotherapy using approved products.
SIERRA: Iomab-B Treatment Schedule

Iomab-B Specific

Dosimetry
Iomab-B (~10-20 mCi)

Therapy Dose
Iomab-B (24 Gy to liver, mean ~600 mCi)

~7 days

Imaging
-12 days to HCT

Standard Transplant Procedure

Dosimetry
NMA

Therapy Dose
HCT

~12 days

Immunosuppression

-4 -3 -2 -1 0

FLU 30 mg/m²/day
TBI 200 cGy

Therapy dose individualized and calculated based on upper limit of 24 Gy liver exposure

Gyurkocza B et al. ASTCT/CIBMTR (Tandem) 2023 and EHA 2023
**131-Apamistamab vs. Conventional Care**

<table>
<thead>
<tr>
<th></th>
<th>131-Apamistamab (n=76)</th>
<th>Conventional Care (n=77)</th>
<th>Crossover (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRp</td>
<td>60.5%</td>
<td>6.5%</td>
<td>52.3%</td>
</tr>
<tr>
<td>*Durable CR</td>
<td>17.1%</td>
<td>0%</td>
<td>(*p&lt;0.0001)</td>
</tr>
</tbody>
</table>

**Iomab-B conditioning**

- Well-tolerated
  - Low NRM rates <10%
  - Lower incidence of sepsis compared to the CC group (p=0.002)
### Table 2: CR and dCR rates by TP53 mutation status and treatment received

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Iomab-B + Crossover</th>
<th>Conventional Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 27</td>
<td>N = 10</td>
</tr>
<tr>
<td>TP53 Positive</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>55.56 (35.33, 74.52)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Durable CR</td>
<td></td>
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<tr>
<td></td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>14.81 (4.19, 33.73)</td>
<td>0</td>
</tr>
<tr>
<td>Wildtype</td>
<td>CR</td>
<td></td>
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<tr>
<td></td>
<td>54</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>58.06 (47.38, 68.22)</td>
<td>17.39 (4.95, 38.78)</td>
</tr>
<tr>
<td></td>
<td>Durable CR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>16.13 (9.32, 25.20)</td>
<td>0</td>
</tr>
</tbody>
</table>

- 24.2% with TP53 mutation in trial
  - Similar CR and dCR with TP53$_{\text{mut}}$ vs. TP53$_{\text{wt}}$
- Excluding CO, Median OS 5.49 mos. vs. 1.66 mos.in pts who did not receive Iomab-B (Figure)
  - HR=0.23; 95% CI [0.10, 0.52]; (p=0.0002)
Conclusions

• Goal - Achievement high quality (MRD-negative) remission

• Novel targeted agents, novel toxicities (DS, AIHA)

• Targeting TP53 remains a pressing clinical need

  • Allogeneic transplantation improves OS for eligible patients, although long-term DFS rates remain poor

• Advances in relapsed & refractory AML, including matched donor AlloHCT for high-risk populations

• Importance of supporting clinical trials in diverse clinical populations
"The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, a union of forces is necessary."

1910: Dr. William J. Mayo  Rush Medical College, commencement address