# Outcomes of relapsed or refractory acute myeloid leukemia after front-line hypomethylating agent and venetoclax regimens

*Abhishek Maiti,[1] Caitlin R. Rausch,[2] Jorge E. Cortes,[3] Naveen Pemmaraju,[3] Naval G. Daver,[3] Farhad Ravandi,[3] Guillermo Garcia-Manero,[3] Gautam Borthakur,[3] Kiran Naqvi,[3] Maro Ohanian,[3] Nicholas J. Short,[3] Yesid Alvarado,[3] Tapan M. Kadia,[3] Koichi Takahashi,[3] Musa Yilmaz,[3] Nitin Jain,[3] Steven Kornblau,[3] Guillermo Montalban-Bravo,[1] Koji Sasaki,[3] Michael Andreeff,[3] Prithviraj Bose,[3] Alessandra Ferrajoli,[3] Ghayas C. Issa,[3] Elias J. Jabbour,[3] Lucia Masarova,[3] Philip A. Thompson,[3] Sa Wang,[4] Sergej Konoplev,[4] Sherry A. Pierce,[3] Jing Ning,[5] Wei Qiao,[5] John S. Welch,[6] Hagop M. Kantarjian,[3] Courtney D. DiNardo[3] and Marina Y. Konopleva[3]*

*[1]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston,TX; [5]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX and [6]Divisions of Hematology and Oncology, Washington University School of Medicine in St. Louis, MO, USA*

*Correspondence: COURTNEY D. DINARDO - CDiNardo@mdanderson.org*

*MARINA Y. KONOPLEVA - mkonople@mdanderson.org*

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## Supplemental Appendix

**Table S1**. Intensive chemotherapy regimens in historical cohort of 278 patients matched for age and European LeukemiaNet cytogenetic risk status

| **Intensive Chemotherapy Regimens** | |
|---|---|
| BID FA – based (n=34)<br>With or without gemtuzumab ozogamicin, sorafenib, or rituximab | Fludarabine 15 mg/m$^2$ IV every 12 hours on days 1 to 5 and<br>Cytarabine 500 mg/m$^2$ IV over 2 hours every 12 hours on days 1 to 5 |
| CLIA – based (n=7)<br>With or without sorafenib | Cladribine 5 mg/m$^2$ IV daily on days 1-5,<br>Cytarabine 1000-2000 mg/m$^2$ IV daily on days 1-5, and<br>Idarubicin 10 mg/m$^2$ IV daily days 1-3.<br>Consolidation consisted of up to 5 more cycles of cladribine 5 mg/m$^2$ IV over 30 minutes on days 1-3 with cytarabine 750-1500 mg/m$^2$ IV on days 1-3 and idarubicin 8 mg/m$^2$ IV on days 1-2. |
| CLOFA+HiDAC (n=21) | Clofarabine 40 mg/m$^2$ IV daily on days 2 to 6<br>Cytarabine 1000 mg/m$^2$/d daily on days 1 to 5 |
| FAI (n=8) | Fludarabine 30 mg/m2 IV daily on days 1 to 5<br>Cytarabine 1000 mg/m$^2$ IV daily on days 1 to 5<br>Idarubicin 10 mg/m$^2$ IV daily on days 1-3 |
| FLAG+IDA (n=3) | Fludarabine 30 mg/m$^2$ IV daily on days 2 to 6<br>Cytarabine 2000 mg/m$^2$ IV daily on days 2 to 6<br>Idarubicin 8 mg/m$^2$ IV daily on days 4 to 6<br>Filgrastim 263 mcg SC daily on days 1 to 7 |
| IA–based (n=187)<br>With or without Sorafenib or Interleukin-11 or Nivolumab or Pravastatin or Vorinostat or Tipifarnib | Idarubicin 12 mg/m$^2$ IV daily on days 1-3<br>Cytarabine 1000-2000 mg/m$^2$ IV daily on days 1-4 |
| Liposomal daunorubicin + HiDAC (n=18)<br>With or without thalidomide | Daunorubicin 100 mg/m$^2$/day IV daily on days 1–3<br>Cytarabine 1000 mg/m$^2$/day IV daily on Days 1–4. |

**Table S2**. Salvage therapies and responses in 24 patients with refractory disease or relapse after frontline venetoclax and hypomethylating agent therapy

| Regimens | n (%) | Responses (n/N) |
|---|---|---|
| **Subsequent venetoclax** | **1 (4)** | **0/1** |
| **Intensive chemotherapy-based** | **8 (32)** | **2/8** |
| CLIA (± GO or Venetoclax) | 3 (13) | CR (n=1), CRi (n=1) |
| BID FA (± Prexasertib) | 3 (13) | |
| CPX-351 + GO | 1 (4) | |
| Clofarabine + HiDAC | 1 (4) | |
| **Non-intensive chemotherapy-based** | **9 (38)** | **3/9** |
| FLT3i combination | 4 (16) | |
| AZA + Quizartinib or Crenolanib | 2 (8) | CRi (n=1) |
| LDAC + Quizartinib | 2 (8) | MLFS (n=1) |
| Checkpoint inhibitor | 4 (16) | |
| AZA + Nivolumab + Ipilimumab | 2 (8) | MLFS (n=1) |
| AZA+ Nivolumab or Lirilumab | 2 (8) | |
| AZA+ IDHi (Enasidenib) | 1 (4) | |
| **Single agent targeted therapy** | **4 (16)** | **0/4** |
| IDHi (IDH305, FT-2102) | 2 (8) | |
| OxPhos inhibitor (IACS-010759) | 1 (4) | |
| Peg-arginine deiminase (ADI-PEG 20) | 1 (4) | |
| **Immunotherapy** | **3 (14)** | **0/3** |
| BiTE (AMV564), ADC (IMGN632) | 3 (13) | |
| **Allo-SCT** | **1/5** | |

CLIA = cladribine idarubicin cytarabine, BID FA = twice daily fludarabine and cytarabine, GO = gemtuzumab ozogamicin, HiDAC = high dose cytarabine, FLT3i = FLT3 inhibitor, AZA = azacitidine, LDAC = low-dose cytarabine, IDHi = IDH inhibitor, BiTE = bispecific T-cell engager, allo-SCT = allogeneic stem cell transplantation.

**Table S3**. Outcomes with salvage therapy in mutational subgroups after frontline venetoclax and hypomethylating agent failure

| Mutational subgroups (n) | Received salvage therapy | TKI used in salvage regimen | CR/CRi/ MLFS | Comment |
|---|---|---|---|---|
| ***FLT3*-ITD (5)** | 4 | 3 | 2/4 | Both responding patients received quizartinib |
| ***IDH1/2* (6)** | 4 | 3 | 0/4 | All patients had concomitant mutations in either *N/KRAS, TP53, FLT3, or ASXL1* |
| ***TP53* (6)** | 5 | – | 1/5 | The responding patient received azacitidine, nivolumab, ipilimumab |
| ***N/KRAS* (11)** | 10 | – | 3/10 | Intensive chemotherapy (2), hypomethylating agent (1) |

TKI = tyrosine kinase inhibitor

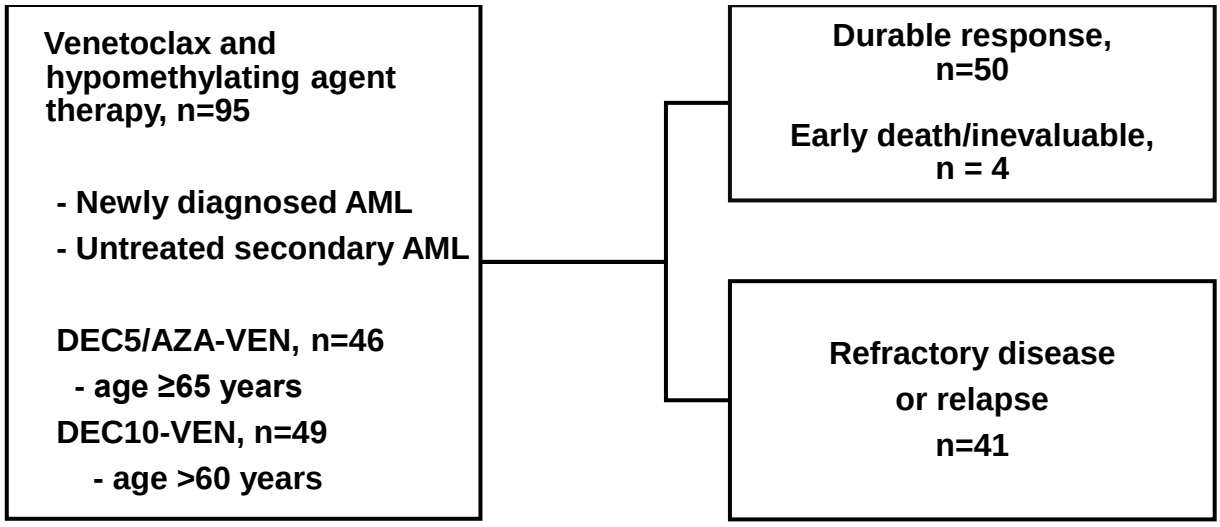


**Fig S1**. Flow diagram of patients treated with frontline venetoclax and hypomethylating agent-based therapy

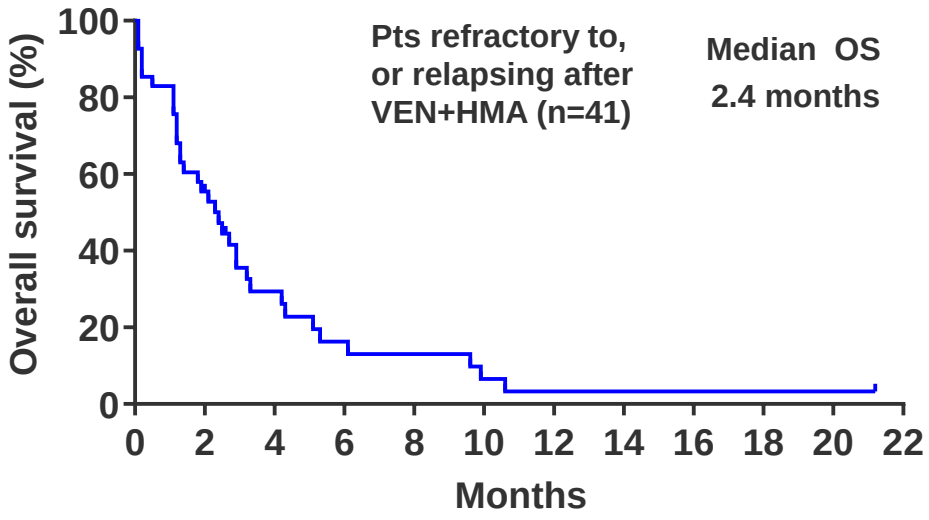


**Fig S2**. Overall survival of 41 patients with refractory disease or relapse after frontline venetoclax and hypomethylating agent-based therapy

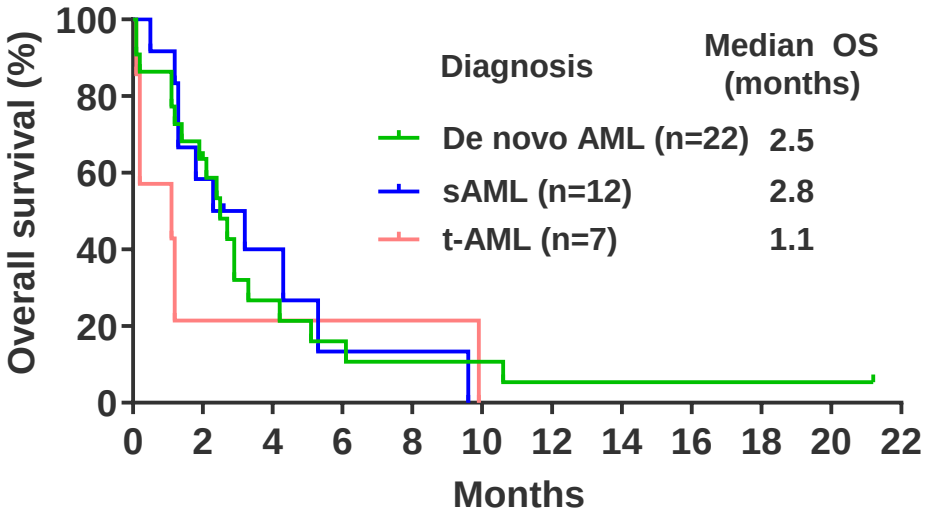


**Fig S3**. Overall survival of patients with refractory disease or relapse after frontline venetoclax and hypomethylating agent-based therapy according to diagnosis

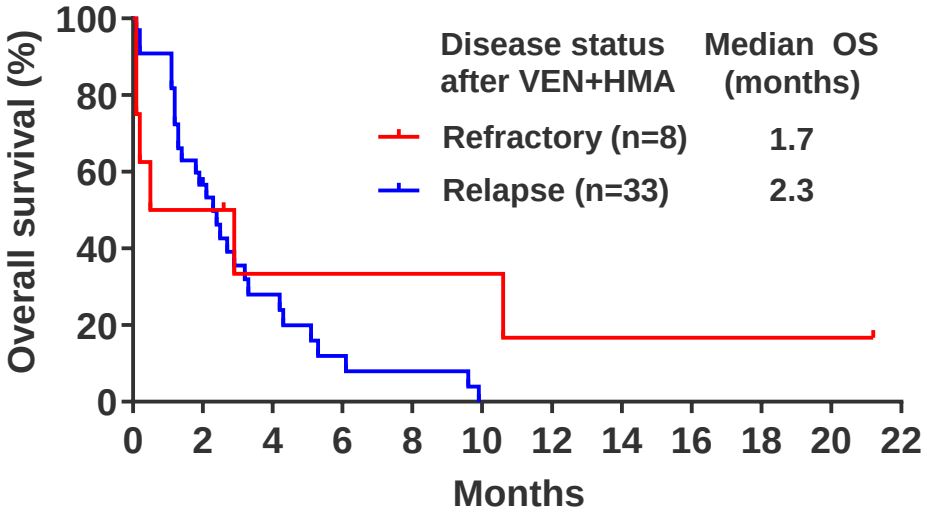


**Fig S4**. Overall survival of patients with refractory disease versus relapse after frontline venetoclax and hypomethylating agent-based therapy