

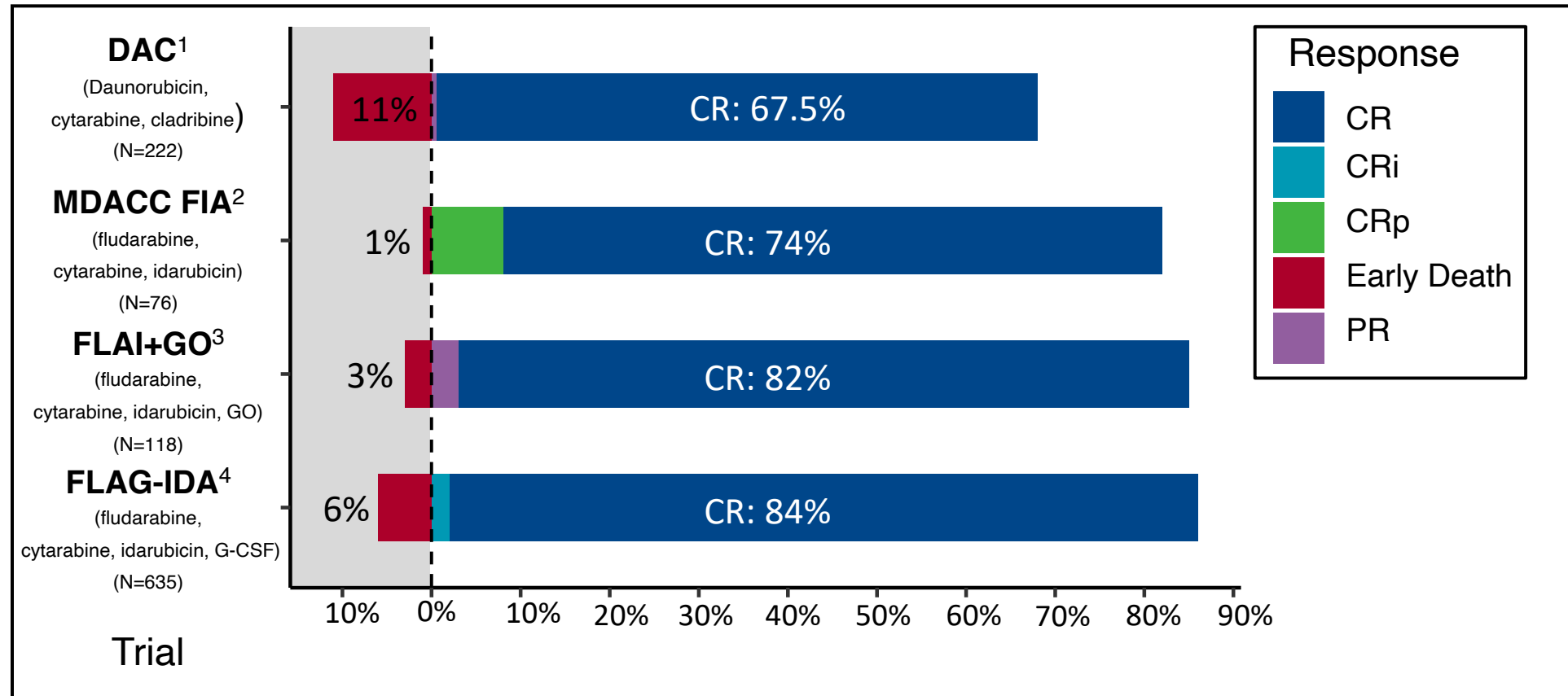
# Venetoclax combined with FLAG-IDA induction and consolidation in newly diagnosed acute myeloid leukemia

Curtis A. Lachowicz, M.D.<sup>1</sup>, Koichi Takahashi, M.D.<sup>2</sup>, Sanam Loghavi, M.D.<sup>3</sup>, Lianchun Xiao, M.S.<sup>4</sup> Tapan Kadia, M.D.<sup>2</sup>, Naval Daver, M.D.<sup>2</sup>, Maria Adeoti, R.N.<sup>2</sup>, Nicholas J. Short, M.D.<sup>2</sup>, Koji Sasaki, M.D.<sup>2</sup>, Sa Wang, M.D.<sup>3</sup>, Gautam Borthakur, M.D.<sup>2</sup>, Ghayas Issa, M.D.<sup>2</sup>, Abhishek Maiti, M.B.B.S.<sup>2</sup>, Yesid Alvarado, M.D.<sup>2</sup>, Naveen Pemmaraju, M.D.<sup>2</sup>, Guillermo Montalbán Bravo, M.D.<sup>2</sup>, Lucia Masarova, M.D.<sup>2</sup>, Musa Yilmaz, M.D.<sup>2</sup>, Nitin Jain, M.D.<sup>2</sup>, Michael Andreeff, M.D., Ph.D.<sup>2</sup>, Elias Jabbour, M.D.<sup>2</sup>, Guillermo Garcia-Manero, M.D.<sup>2</sup>, Steven Kornblau, M.D.<sup>2</sup>, Farhad Ravandi, M.D.<sup>2</sup>, Marina Y. Konopleva, M.D., PhD<sup>2</sup>, Hagop M. Kantarjian, M.D.<sup>2</sup>, Courtney D. DiNardo, M.D., M.S.C.E.<sup>2</sup>

<sup>1</sup>Division of Cancer Medicine, <sup>2</sup>Department of Leukemia, <sup>3</sup>Department of Hematopathology, <sup>4</sup>Department of Biostatistics, The University of Texas M.D. Anderson Cancer Center, Houston, TX

## Background

Multiagent induction chemotherapy consisting of fludarabine, cytarabine, G-CSF, and idarubicin (FLAG-IDA) results in complete remission in approximately 85% of newly diagnosed patients with acute myeloid leukemia (ND-AML), however 30-40% experience relapse (**Figure and Table**). Combining the BCL-2 inhibitor venetoclax (VEN) with chemotherapy results in synergistic leukemic cell death, inferring FLAG-IDA+VEN may improve response rates and outcomes in ND-AML.



|              | DAC (N=222)  | MDACC FIA (N=76) | FLAI+GO (N=118)      | FLAG-IDA (N=635) |
|--------------|--------------|------------------|----------------------|------------------|
| EFS          | 45% (5-year) | 44% (2-year)     | 52% (5-year)         | 45% (8-year)     |
| OS           | 45% (3-year) | 57% (2-year)     | 63% (2-year)         | 44% (8-year)     |
| alloHSCT     | 22%          | 37%              | 46%                  | Not reported     |
| MRD Negative | Not reported | 65% (MFC)        | 51% (WT1 transcript) | Not reported     |

## Objectives and inclusion criteria

| Primary Objectives (Phase 2)               | Inclusion Criteria           | Exclusion Criteria          |
|--------------------------------------------|------------------------------|-----------------------------|
| Overall activity of FLAG-IDA+VEN in ND-AML | ND or R/R-AML                | APL                         |
| Secondary Objectives                       | High-risk MDS (≥ 10% blasts) | Prior BCL-2 inhibitor       |
| Response by revised IWG criteria           | CrCl ≥ 30 mL/min             | Known CNS disease           |
| Duration of response                       | Total bilirubin < 1.5x ULN   | NYHA Class III/IV (EF <40%) |
| Overall and event-free survival            | AST and/or ALT < 3x ULN      | GI/malabsorption disorders  |
| Biomarkers predictive of VEN sensitivity   |                              |                             |

## FLAG-IDA+VEN: Regimen

| Course                                     | Drug                                  | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Days 8-14 |
|--------------------------------------------|---------------------------------------|-------|-------|-------|-------|-------|-------|-------|-----------|
| FLAG-IDA+VEN Induction (28-day cycles)     | Venetoclax 400 mg                     |       |       |       |       |       |       |       |           |
|                                            | G-CSF                                 |       |       |       |       |       |       |       |           |
|                                            | Fludarabine (30 mg/m <sup>2</sup> )   |       |       |       |       |       |       |       |           |
|                                            | Cytarabine (1.5 gram/m <sup>2</sup> ) |       |       |       |       |       |       |       |           |
|                                            | Idarubicin (8mg/m <sup>2</sup> )      |       |       |       |       |       |       |       |           |
| FLAG-IDA+VEN Consolidation (28-day cycles) | Venetoclax 400 mg                     |       |       |       |       |       |       |       |           |
|                                            | G-CSF                                 |       |       |       |       |       |       |       |           |
|                                            | Fludarabine (30 mg/m <sup>2</sup> )   |       |       |       |       |       |       |       |           |
|                                            | Cytarabine (1.5 gram/m <sup>2</sup> ) |       |       |       |       |       |       |       |           |
|                                            | Idarubicin (8mg/m <sup>2</sup> )      |       |       |       |       |       |       |       |           |

**G-CSF:** 5 mcg/kg the day prior to and days of IV chemotherapy followed by 1 dose of pegfilgrastim or biosimilar the day following chemotherapy each 28 D cycle

**Consolidation:** Idarubicin permitted on days 3 and 4 in 2 post-remission cycles (ie. C2 or C3 and C5 or C6) at physician discretion

## Patient Demographics

| Demographic                  | N=41       |
|------------------------------|------------|
| Age, years median (range)    | 44 (20-65) |
| Sex, male N(%)               | 19 (46)    |
| Median blast % at enrollment | 46 (4-85)* |
| AML Type                     |            |
| De Novo AML                  | 29 (71)    |
| Secondary AML (sAML)         | 7 (17)     |
| Treated-secondary AML        | 3 (7)      |
| Therapy-related AML (tAML)   | 5 (12)     |
| ELN Risk Group               |            |
| Favorable                    | 8 (20)     |
| Intermediate                 | 15 (37)    |
| Adverse                      | 18 (44)    |
| Cytogenetics                 |            |
| Favorable                    | -          |
| Diploid                      | 19         |
| Other intermediate risk      | 9          |
| Adverse risk/Complex         | 7          |
| Complex                      | 5          |
| del(7)                       | 1          |
| inv(3)                       | 1          |
| KMT2A-rearranged             | 5          |
| Insufficient                 | 1          |

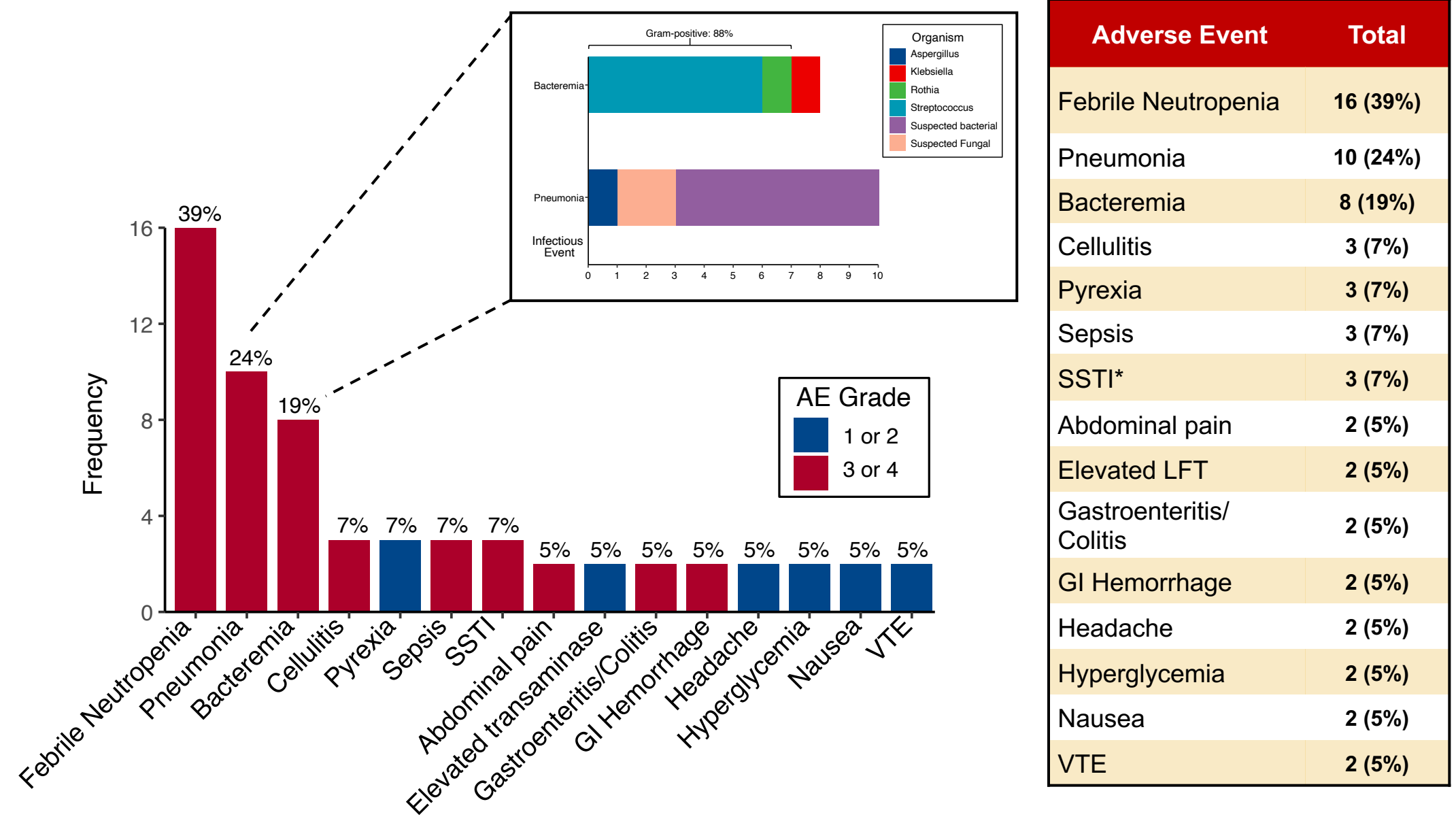
**Mutation**

NRAS 3, IDH2 3, RUNX1 3, NPM1 3, CEBPA 3, No Mutation 1, GATAD2 1, DNMT3A 1, PTPN11 1, KRAS 1, FLT3 D835 1, TP53 2, IDH1 1, BCOR 1, ASXL1 1, U2AF1 1, TET2 1, WT1 1, SF3B1 1, PHF6 1, FLT3 ITD 1, DDX41 1, ZRSR2 1, U2AF2 1, STAT5A 1, STAG2 1, SRSF2 1, SMC3 1, SETBP1 1, RAD21 1, KIT 1, KZF1 1, FLT3 M578T 1, ETV6 1, CREBBP 1, CBL 1, BRINP3 1

Legend: De Novo AML (blue), sAML/tAML (red)

## FLAG-IDA+VEN: Safety

Common adverse events were predominantly infectious, and within the anticipated range for a patient population undergoing intensive induction therapy. **30- or 60-day mortality is 0%.**



## FLAG-IDA+VEN: Response

FLAG-IDA+VEN was associated with an ORR of 98%, including a **Composite CR rate of 88%, with 92% attaining MRD negative CRc.**

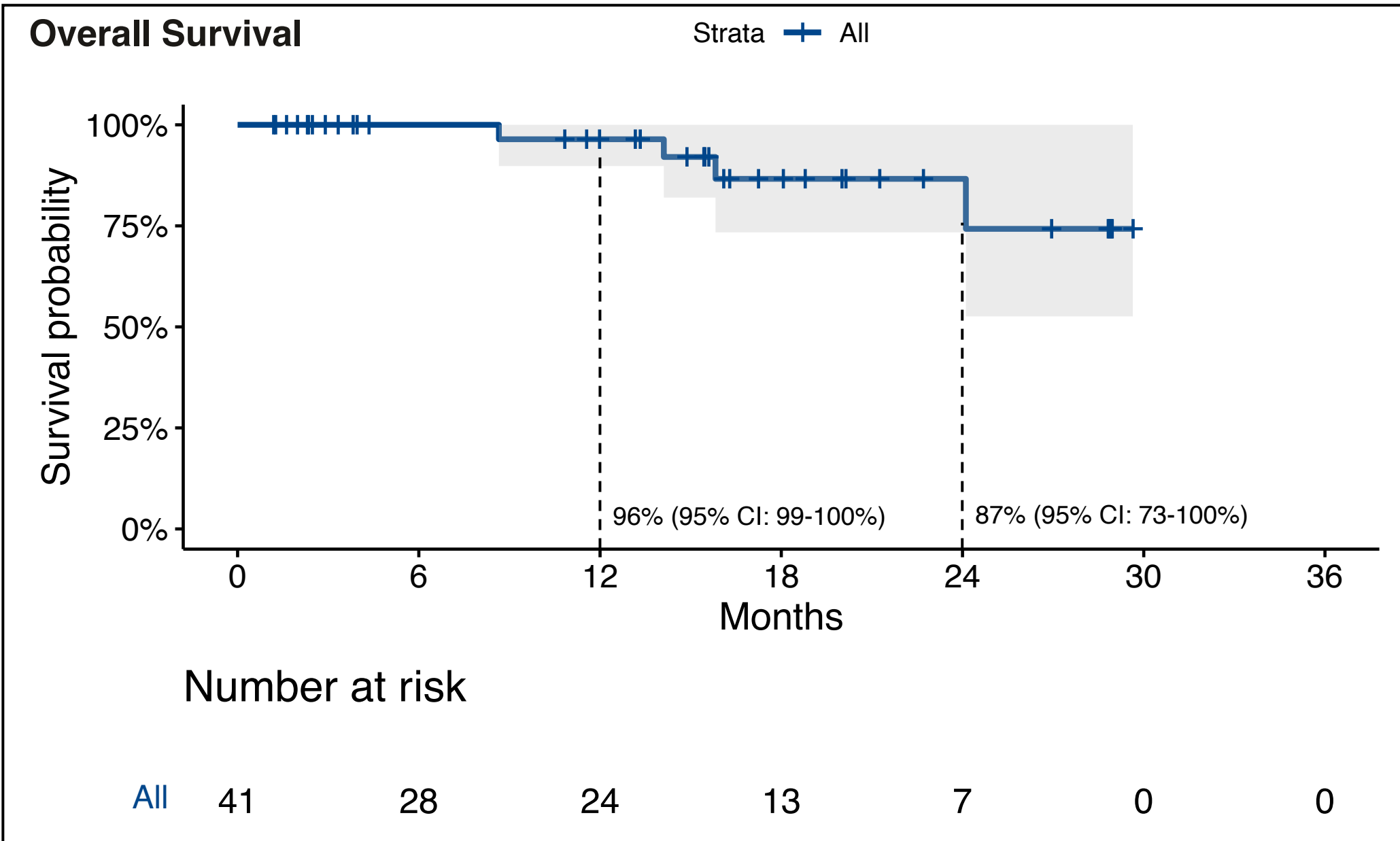
| Demographic Median (range)/ N (%) | All patients (N=41) | De Novo AML (n=29) | sAML/tAML (n=12) | P-value |
|-----------------------------------|---------------------|--------------------|------------------|---------|
| Overall Response Rate             | 40 (98%)            | 29 (100%)          | 11 (92%)         | -       |
| Composite CR                      | 36 (88%)            | 26 (90%)           | 10 (83%)         | -       |
| CR                                | 30 (73%)            | 24 (83%)           | 6 (50%)          | 0.052   |
| CRh                               | 5 (12%)             | 2 (7%)             | 3 (25%)          | -       |
| CRi                               | 1 (2%)              | -                  | 1 (8%)           | -       |
| MRD-Negative CRc*                 | 33 (92%)            | 24 (92%)           | 9 (100%)         | -       |
| MLFS                              | 4                   | 3 (10%)            | 1 (8%)           | -       |
| NR/PD                             | 1                   | -                  | 1 (8%)           | -       |

**Percent**

Legend: CR (blue), CRc (green), CRh (purple), CRi (orange), MLFS (grey), MRD-negative (red), NR/PD (dark red)

## FLAG-IDA+VEN: Survival

After median follow up of 16 months, Median overall survival was not reached. **12- and 24-month overall survival was 96% and 87%, respectively. 12- and 24-month EFS was 70% and 60%, respectively.**



## FLAG-IDA+VEN: HSCT Outcomes

FLAG-IDA+VEN permitted transition to HSCT in **66% (n=27)** patients. Median overall survival was not reached in patients undergoing HSCT. **12-month and 24-month survival was 95% and 82% respectively. No 30- or 60-day mortality post-HSCT has been observed to date.**

## FLAG-IDA+VEN: Conclusions

- Results in high CRc rates in both de novo AML and sAML/tAML
- MRD-negative composite CR attained in > 90% of patients
- Demonstrates an acceptable safety profile with infectious complications most common
- Enables a high rate of transition to consolidative allogeneic transplantation

<sup>1</sup>Holowiecki, J et. al. *J Clin Oncol*, 30(20), pp.2441-2448; <sup>2</sup>Jabbour E et. al. *Cancer*. 2017 Nov 15;123(22):4430-9. <sup>3</sup>Candoni A et. al. *American journal of hematology*. 2018 May;93(5):655-63. <sup>4</sup>Burnett AK et. al. *Journal of clinical oncology*. 2011 Feb 1;29(4):369-77.