Development of a Derived Induction Failure and Relapse (dIFR) Variable for Acute Myeloid Leukemia (AML) Using Real-World (RW) Data from an Electronic Health Record (EHR)-Derived Database

RWD158

Christina Fullerton, PharmD, BCOP[1]; Qianyi Zhang, MS[1]; Kelly Magee, FNP-BC[1]; Madeline Richey, MPH[1]; Tori Williams, BA[1]; Doug Donnelly, CMPP[1]; Niquelle Brown Wadé, PhD[1]; Aaron Dolor, PhD[1]; Ahmed Sawas, MD[1]

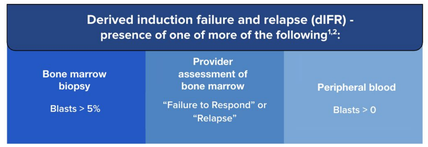
[1] Flatiron Health, New York, NY

Background

- Progression in AML is defined by induction failure and relapse events, as described in consensus guidelines.[1,2] These events are anchored to hematologic parameters, namely percentage of blasts in bone marrow biopsies and peripheral blood.
- We developed a novel approach using both structured and abstracted data to derive induction failure and relapse events. Capturing induction failure and relapse enables common analyses utilized in AML, including real-world event-free survival (rwEFS).
- This approach aligns with the industry guidance published in October 2022 by the FDA for assessing AML endpoints in that it incorporates the necessary components (e.g., bone marrow results, peripheral blood blasts) to derive clinically accepted endpoints using real-world data.[3]

Methods

- Patients (pts) with AML diagnosed between 1/1/2014 and 3/31/2022 from the nationwide Flatiron Health EHR-derived de-identified database were included in the study. During the study period, the de-identified data originated from approximately 280 US cancer clinics (~800 sites of care). Data sources include both patient-level de-identified structured and unstructured data curated via technology-enabled abstraction.[4,5]
- dIFR events were anchored to results of bone marrow biopsy reports (unstructured data) and peripheral blood lab tests (combination of structured and unstructured data). The algorithm below was applied to the entire cohort and across each patient journey to capture dIFR events from initial diagnosis to end of chart activity.



Performance of the dIFR variable was assessed via:

- Descriptive statistics to summarize pt demographic and clinical characteristics.
- Inter-rater agreement via duplicate abstraction, indexed to diagnosis date, first and second oncologist-defined, rule-based line of therapy (LoT: 1L, 2L) start date:
  - Event agreement: agreement between two abstractors on whether at least one dIFR event has occurred.
  - Date agreement: conditional on agreement for the presence of at least one dIFR event, agreement between two abstractors on the date of the first dIFR event, as well as within 15-day and 30-day window.
- Distribution of source evidence of initial dIFR event following 1L + 14 days
- Association of dIFR with clinically meaningful downstream events: 1) new therapy start, 2) therapy stop, 3) within LoT treatment change, 4) death
  - Among pts with a dIFR event after 1L + 14 days, the number (N) and % of pts for whom we observe a clinically relevant downstream event within a window of 15 days prior to 30 days after the initial dIFR event
- Endpoint analyses
  - Kaplan-Meier (KM) curves and median estimates were generated for real-world overall survival (rwOS), rwEFS and real-world time-to-next treatment (rwTTNT) in overall and clinically distinct (e.g., age, cytogenetic risk, therapy class) cohorts.
    - Exclusion windows were applied in rwEFS to account for recommended timing of response assessment as defined by AML consensus guidelines (i.e., eligible dIFR events beginning 42-days after the start of intensive induction chemotherapy).
  - Correlation of rwEFS and rwTTNT to rwOS in the overall cohort

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Results

Table 1. Patient characteristics

	Study cohort (N=6845)
Age (years) at diagnosis, Median [IQR]	69.0 [58.0;77.0]
Received 2L+: Yes	3309 (48.3%)
Sex:	
Female	2926 (42.7%)
Male	3919 (57.3%)
Race/Ethnicity:	
Non-Hispanic White	4624 (67.6%)
Non-Hispanic Black or African American	470 (6.9%)
Non-Hispanic Asian	145 (2.1%)
Other Race/Ethnicity (including Hispanic or Latinx)	932 (13.6%)
Unknown	674 (9.8%)
Practice type:	
Academic	1628 (23.8%)
Community	5111 (74.7%)
Both	106 (1.5%)
1L Therapy class*:	
Antibody-drug conjugate + chemotherapy	139 (2.0%)
Acute promyelocytic leukemia therapies	560 (8.2%)
BCL-2 inhibitor + chemotherapy	1159 (16.9%)
Chemotherapy	3944 (57.6%)
Clinical study drug-based therapies	434 (6.3%)
FLT3 inhibitor + chemotherapy	267 (3.9%)
Cytogenetic risk:**	
Favorable/low risk	647 (20.5%)
Intermediate risk	567 (18.0%)
Poor/adverse/high risk	1936 (61.5%)
Treatment related AML: Yes	540 (7.9%)
Ever had an allogeneic transplant: Yes	1248 (18.2%)
Follow-up time from diagnosis date to last confirmed activity (months), Median [IQR]	8.6 [3.1;21.3]

*Therapy classes containing <25 patients were not reported, **Cytogenetic risk unknown for 3695 patients (54%)*

Inter-rater agreement via duplicate abstraction (Table 2)

- Event agreement: ≥97% for dIFR events after diagnosis date, and 1L/2L start dates + 14 days.
- Conditional on the event agreement, the exact date agreement for the first dIFR event after diagnosis date, and 1L/2L start + 14 days were 68% - 79%, and all increased to ≥ 84% within a 15-day or 30-day window (≥ 90%).

Table 2. Inter-rater agreement of the event, date (with exact, 15- and 30-day window)

Index date	Event Agreement (proportion (95% CI))		Date Agreement * (proportion (95% CI))			
	N	Exact	N	Exact	15-day window	30-day window
Diagnosis date	100	0.97 (0.91, 0.99)	62	0.77 (0.65, 0.87)	0.89 (0.78, 0.95)	0.90 (0.80, 0.96)
1L start + 14 days	92	0.97 (0.91, 0.99)	53	0.79 (0.66, 0.89)	0.92 (0.82, 0.98)	0.94 (0.84, 0.99)
2L start + 14 days	49	0.98 (0.89, 1.00)	31	0.68 (0.49, 0.83)	0.84 (0.66, 0.95)	0.9 (0.74, 0.98)

Among patients with an agreed upon event

Distribution of source evidence for initial dIFR event

- There were 4358 (64%) of patients with an initial dIFR event following 1L + 14 days, of those events:
  - ~35% and 36% had bone marrow biopsy (BMBx) blast result, BMBx provider assessment as one of the components of dIFR events, respectively
  - ~33% had peripheral blasts (PB) structured lab as one of the components
  - PB lab document and clinician document were less common components (~17%, ~18%)
  - All component combinations were observed, with the most common combination being BMBx blast results and BMBx provider assessment (~26%)

Distribution of downstream events

- Of patients with dIFR event after 1L + 14 days (n=4358), 53% (n=2328) had at least one downstream event: new therapy start (68%), therapy stop (45%), death (18%), within LoT treatment change (12%) (Table 3).
  - Investigation into dIFR events occurring without a corresponding downstream event identified the following reasons: 1) downstream event occurred outside of a 30-day window in relation to dIFR, 2) clinician judgment (i.e., significant decrease in BMBx blasts from baseline or low levels of BMBx or PB not considered clinically significant), 3) downstream event was outside of our definition (i.e., hospice).

Table 3. Distribution of downstream events amongst patients with a dIFR event

Time window and method	N of pts with a dIFR event	Pts with any downstream event (N, % (95% CI))		Breakdown of Downstream events (N, % with 95% CI among downstream events)							
				therapy stop		new therapy start		death event		within LoT change	
Index to 1L											
Within -15 to 30 days of first dIFR	4358	2328	53%^ (52%, 55%)	1044	45% (43%, 47%)	1577	68% (66%, 70%)	415	18% (16%, 19%)	267	12% (10%, 13%)

^ Percent of patients with downstream events changed by ≤1% when analyses were restricted to patients with at least 30 days of follow-up time

Endpoint analyses

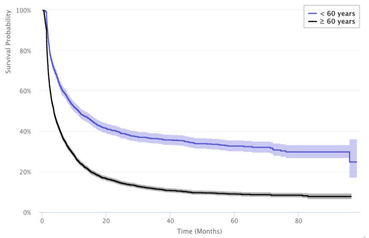
- In alignment with expectations, patients in poor prognostic subgroups (e.g., age ≥ 60 years, poor/adverse/high cytogenetic risk) had shorter median rwOS, rwEFS and rwTTNT vs patients in better prognostic subgroups. (Table 4, Figures 1 and 2).
- The Spearman's rank correlation were both similarly strong between median rwOS and rwEFS, ρ = 0.70 (0.68, 0.72), and rwTTNT ρ = 0.68 (0.67, 0.7), respectively.

Table 4. Median estimates and 95% CI of the endpoint analyses

	N	Median rwOS (months, (95% CI))	Median rwEFS (months, (95% CI))	Median rwTTNT (months, (95% CI))
Overall^^	6769	14.0 (13.5, 14.6)	4.7 (4.5, 5.0)	4.4 (4.2, 4.6)
Age at diagnosis				
< 60 years	1825	87.2 (72.3, -)	11.3 (9.8, 13.1)	5.9 (5.2, 6.5)
>= 60 years	4944	10.3 (9.8, 10.7)	3.7 (3.5, 3.8)	4.1 (3.9, 4.3)
Cytogenetic risk				
Favorable/low risk	646	NR	32.4 (24.1, 47.7)	16.2 (12.7, 22.7)
Intermediate risk	561	29.9 (23.6, 35.7)	8.4 (7.1, 10.2)	5.2 (4.5, 6.0)
Poor/adverse/high risk	1925	10.5 (9.8, 11.1)	3.7 (3.5, 4.1)	3.7 (3.4, 4.0)

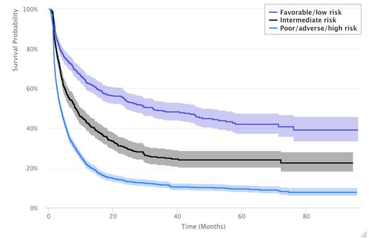
^^ Cohort size was dependent on patient eligibility at time of analysis

Figure 1. KM-plot for rwEFS stratified by age < vs ≥ 60 years old at 1L start date



Age	0 mos	10 mos	20 mos	30 mos	40 mos	50 mos	60 mos	70 mos	80 mos	90 mos	100 mos
< 60 years	1826	769	519	377	278	193	127	79	46	21	0
≥ 60 years	4955	1154	559	345	225	159	103	65	32	11	0

Figure 2. KM-plot for rwEFS stratified by cytogenetic risk



Cytogenetic risk	0 mos	10 mos	20 mos	30 mos	40 mos	50 mos	60 mos	70 mos	80 mos	90 mos	100 mos
Favorable/low	646	353	240	176	130	93	55	37	18	7	0
Intermediate	561	219	137	84	57	39	24	17	12	3	0
Poor/adverse/high	1928	419	199	127	82	65	44	26	13	4	0

Discussion

Strengths

- Derivation approach employed multiple methods of assessing disease, including objective criteria from AML consensus definitions and provider assessment. At event level, the approach can also distinguish which criteria determined the event.
- Combination of structured and unstructured data sources were utilized to improve completeness of data elements.
- By applying exclusion windows for endpoint analyses, we restricted assessment timepoints to those that were clinically meaningful for assessing treatment response.

Limitations

- As with all real-world data sources, there is the potential for data missingness which can include information related to patient characteristics, treatment, and outcomes.
- dIFR variable does not currently distinguish between induction failure and relapse, however future work, such as incorporating treatment sequence information, can help to disaggregate the two event types.

Conclusions

- Performance of the novel dIFR variable was strong, as evidenced by the following:
  - dIFR event and associated dates were highly reliable based on inter-rater agreement via duplicate abstraction.
  - Association between dIFR events and downstream events aligned with clinical expectations.
  - Endpoints analyses results aligned with clinical expectations, with rwEFS and rwOS demonstrating trends similar to a large retrospective study of newly diagnosed patients with AML.[6] Stratified rwOS, rwEFS and rwTTNT demonstrated construct validity of dIFR events by showing differences in clinically-distinct groups.
- This study demonstrates the feasibility of using EHR data to derive rw progression in AML, which unlocks the ability to conduct rw outcome studies across large AML cohorts.

References

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Authors would like to acknowledge Erica Yim for her contributions to statistical analyses and Lawrence Bellomo, Sarah Brake, Martha Griffin and Dana Panzer for their contributions to variable development and performance assessment.

Presented at ISPOR 2023: For additional information, contact Christina Fullerton at christina.fullerton@flatiron.com.

Disclosures: At the time of the study, all authors report employment at Flatiron Health, Inc., which is an independent subsidiary of the Roche Group, and stock ownership in Roche. This study was sponsored by Flatiron Health, Inc., which is an independent member of the Roche Group.