Abstract: S136

Title: FLAG-IDA + VENETOCLAX (VEN) IN NEWLY DIAGNOSED (ND) OR RELAPSED / REFRACTORY (RR) AML

Abstract Type: Oral Presentation

Session Title: Acute myeloid leukemia - Clinical 2 - Ven/Aza

Background:

Intensive chemotherapy (IC) with cytarabine and an anthracycline is the standard for fit AML pts. Intensification with FLAG-IDA+VEN may improve efficacy with reasonable tolerability.

Aims:

We report the outcomes of a phase 2 study to investigate the activity of FLAG-IDA+VEN in ND and RR AML.

Methods:

Pts age ≥18 with ND or RR AML / MDS-EB2, with adequate cardiac, renal and hepatic function, were eligible if they had no prior VEN exposure. Pts with CNS involvement were excluded. Induction comprised fludarabine 30mg/m2 D2–6, cytarabine 1.5g/m2 D2–6, idarubicin 8mg/m2 (6mg/m2 if RR) D4–6 and filgrastim 5mcg/kg D1–7. Consolidation comprised fludarabine and cytarabine D2–4, and idarubicin D3–4 at physician discretion. VEN 400mg was administered D1–14 with dose adjustments for concomitant CYP3A inhibitors until Jul 2023; following a protocol modification, VEN is now administered D1–7 only.

The primary outcome was ORR (CR + CRh + CRi + MLFS + PR, as defined by the European LeukaemiaNet [ELN]). Secondary outcomes were CRc (CR + CRh + CRi), overall survival (OS), event-free survival (EFS) and duration of response (DOR). Measurable residual disease (MRD) was assessed via flow cytometry with a sensitivity 10-4.

Results:

As of Jan 2024, 134 pts have enrolled, 127 (68 ND and 59 RR) evaluable at data cut. Median age was 45 (range, 18 – 73); 19 (15%) age ≥60. 13 (19%), 22 (32%) and 33 (49%) ND pts were ELN 2022 favorable, intermediate, and adverse risk, respectively. There were seven (10%) secondary (s) AML, including four hypomethylating agent failure, and seven (10%) therapy-related (t) AML. In RR pts, 40 (68%) were in first salvage (S1), of whom 32 (54%) were *TP53*WT. 20 (34%) RR pts had relapsed after prior stem cell transplant (SCT).

In ND pts, ORR was 99%, (96% CRc, of whom 89% MRD negative [**Table**]). No significant differences were seen across ELN risk groups or in s/tAML. At median follow-up (mFU) of 30 months (mo), the mOS, mEFS and mDOR were not reached (NR). The 2yr OS, EFS and DOR were 75% (95%CI, 64 – 88), 68% (95%CI, 56 – 81) and 71% (95%CI, 59 – 85) respectively, with no differences among ELN groups or age ≥60. 39 (57%) proceeded to SCT in CR1. Landmark analysis demonstrated the benefit of SCT in CR1 (mOS NR with SCT vs 23.4mo without, $p = 0.03$). 4/4 pts with *TP53*mut achieved CRc MRD negative, but mDOR was only 8.2mo (95%CI, 2.2 – NE), resulting in poor mOS (13.5mo, 95%CI, 8.6 – not estimable [NE]).

In RR pts, ORR was 70% (66% CRc, of whom 79% MRD negative [**Table**]). At mFU 27mo, the mOS, mEFS and mDOR were 12 (95%CI, 7 – 33), 7 (95%CI, 4 – 23) and 21 (95%CI, 8 – NE) mo respectively. The 2yr OS, EFS and DOR were 40% (95%CI, 28 – 55), 34% (95%CI, 23 – 49) and 49% (95%CI, 35 – 68) respectively. 58% proceeded to SCT upon remission attainment. S1+ *TP53*WT pts had mOS of 34mo (95%CI, 12 – NE), with 72% going to SCT in CR2.

Pts received a median of two cycles of FLAG-IDA+VEN. 30d and 60d mortality were 0% and 3%, respectively. Of the four deaths within 60d, one was sepsis-related in a ND pt in CR1, while three were disease-related in non-responding RR pts. The most frequent adverse event was infection. Grade ≥3 infections, gastrointestinal

toxicities and bleeding occurred in 102 (80%), 20 (16%) and 9 (7%) pts respectively. The median time to neutrophils >1x109/L and platelets >50x109/L were 27d and 28d for C1, 39d and 67d for C2 and 35d and 50d for C3 respectively.

Summary/Conclusion:

FLAG-IDA+VEN results in high MRD negative response rates, leading to impressive survival outcomes across ELN risk groups in ND AML. It is an effective salvage regimen for RR AML, especially for *TP53*WT pts in first salvage.

	ND All n = 68 *n* (%)	**Favorable n = 13 *n* (%)**	**Intermediate n = 22 *n* (%)**	**Adverse n = 33 *n* (%)**	**RR All n = 59 *n* (%)**	**S1 + TP53^{WT} n = 32 *n* (%)**
ORR	67 (99)	13 (100)	21 (96)	33 (100)	41 (70)	26 (81)
CRc	65 (96)	13 (100)	20 (91)	32 (97)	39 (66)	24 (75)
CR	56 (82)	13 (100)	19 (86)	24 (73)	24 (41)	18 (56)
CRh	3 (4)	0 (0)	1 (4)	2 (6)	8 (14)	4 (13)
CRi	6 (9)	0 (0)	0 (0)	6 (18)	7 (12)	2 (6)
MLFS	2 (3)	0 (0)	1 (4)	1 (3)	2 (3)	2 (6)
NR	1 (2)	0 (0)	1 (4)	0 (0)	18 (31)	6 (19)
MRD Negative	58 (89)	12 (92)	18 (90)	28 (88)	31 (79)	20 (83)

Keywords: Acute myeloid leukemia, AML, Venetoclax, Chemotherapy