

Treatment Free Remission (TFR) After Ceasing Venetoclax-based Therapy in Responding Patients with Acute Myeloid Leukemia

C.C. Chua^{1, 2}, D. Hammond³, A. Kent⁴, I.S. Tiong^{1, 2}, D.M. Ong^{1, 2}, M. Konopleva³, D.A. Pollyea⁴, C.D. DiNardo³, A.H. Wei^{1,2}

1.Department of Haematology, The Alfred Hospital, 2.Australian Centre for Blood Diseases, Monash University, Melbourne, Australia, 3.Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas, 4.Division of Hematology, University of Colorado School of Medicine, Aurora, United States

Introduction

- Two phase 3 trials (VIALE-A and VIALE-C) have recently confirmed the clinical benefit of the BCL-2 inhibitor venetoclax (VEN) in combination with azacitidine (AZA) or low dose cytarabine (LDAC) in older/unfit patients with newly diagnosed (ND) acute myeloid leukemia (AML).^{1,2}
- For patients (pts) responding to VEN-AZA (66%) or VEN-LDAC (48%), the median duration of response was 18 and 12 months, respectively. Therefore, remission duration will exceed 12 months in majority of responding pts.
- It is unknown whether pts responding to VEN-based combinations should continue therapy until progression and whether elective cessation of therapy could detrimentally impact long-term outcomes.

Objective

To compare the natural history of pts with ND AML receiving ≥ 12 months of VEN-based therapy in first remission after either:

- electively ceasing therapy and undergoing monitoring, or
- continuing treatment until disease progression.

Methods

- Retrospective review of 3 centres:
 - Alfred Health, MD Anderson Cancer Center and University of Colorado
- Eligibility for review:
 - Elderly/unfit patients with newly diagnosed AML
 - Received VEN combined with either a hypomethylating agents (HMA) or LDAC as frontline therapy for ≥ 12 months and in sustained first CR/CRi
- Two treatment approaches were compared:
 - Elective cessation of therapy whilst in remission (**STOP cohort**)
 - Continuation of therapy until relapse (**CONT cohort**)
- Landmark analysis was performed to compare OS and PFS between the STOP and CONT cohorts
- Data cut-off 31 January 2021

Results

Table 1. Patient Characteristics

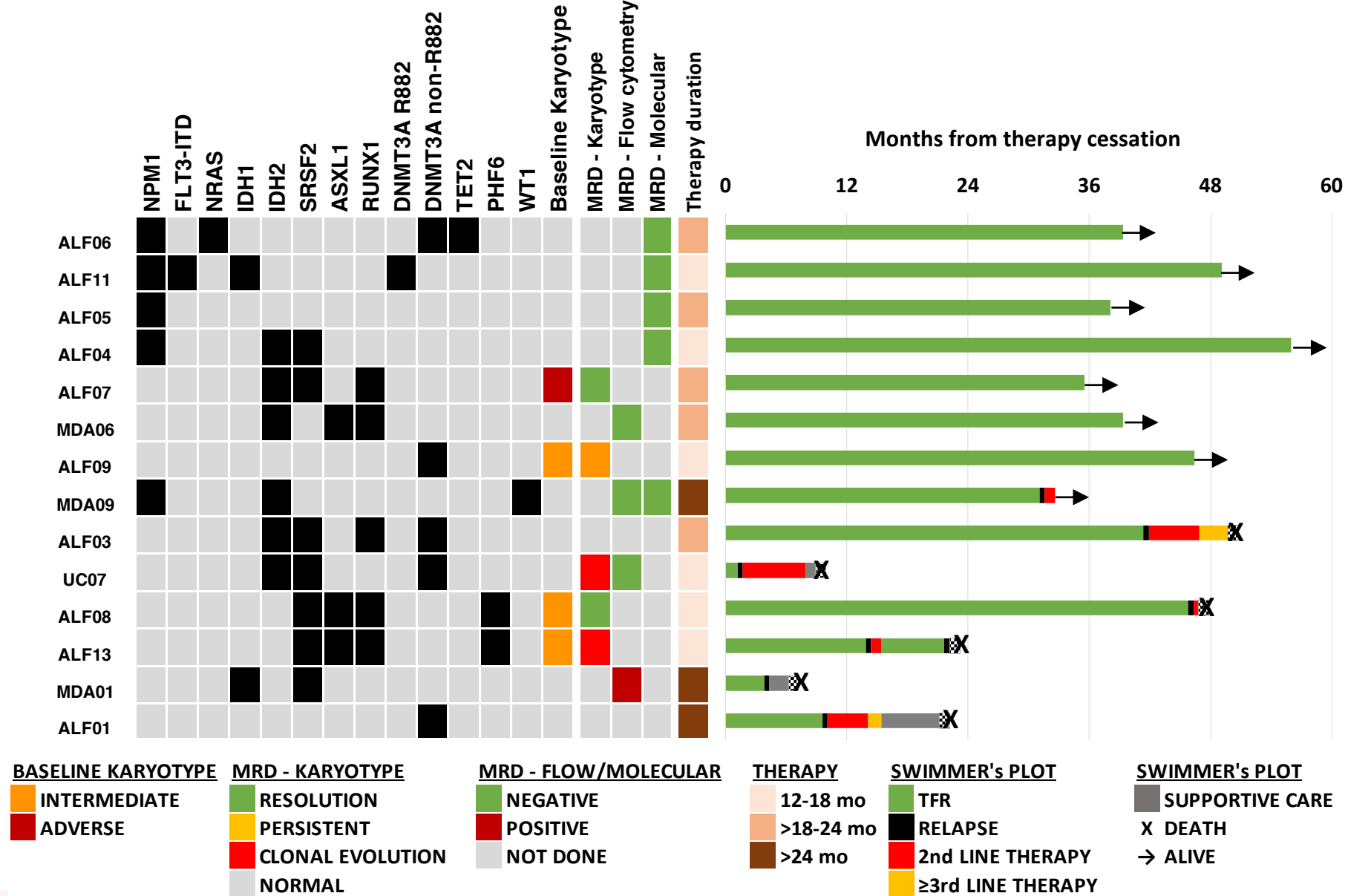
- N=28
- Median follow up: 60.9 months
 - 58.0 months for CONT
 - 61.4 months for STOP
- Median OS for entire cohort:
 - 71.3 months
- Reasons for elective cessation
 - Patient request (N=6, 43%)
 - Medical decision (N=8, 57%)

	STOP cohort	CONT cohort	P-value
N	14	14	
Age at AML diagnosis	74 y (65-80)	72.5 y (66-80)	0.83
ELN2017 risk			
Favorable	5 (36%)	6 (43%)	0.86
Intermediate	3 (21%)	2 (14%)	
Adverse	6 (43%)	6 (43%)	
VEN LDAC	7 (50%)	2 (14%)	0.06
VEN HMA	7 (50%)	12 (86%)	
Median no. of cycles received	17 (11-29)	30 (13-64)	0.004
Median months on therapy	19.0 (14.4-35.8)	32.7 (14.0-61.3)	0.008

Durable treatment free remission (TFR) observed in the STOP cohort

- Median TFR was 45.8 months (95% CI 9.6-not reached)
- 7/14 (50%) patients have relapsed
 - Late relapses were observed with 3 pts relapsing at 31, 41 and 46 months after ceasing therapy, respectively.
 - 1 pt (MDA09) with *NPM1*-mutant patient relapsed after 31 months of TFR with isolated extramedullary disease
- 7/14 (50%) pts have not relapsed, with a minimum TFR of 35.5 months.
 - 6/7 (86%) pts had *NPM1*- and/or *IDH2* mutant disease, all with undetectable measurable residual disease (MRD) at time of therapy cessation

Figure 1. Characteristics and outcomes of patients in the STOP cohort



Results

CONT cohort outcomes

- 9/14 (64%) pts relapsed: 3 relapsed after receiving >41 months of therapy
- 5/14 pts remain in remission and receiving ongoing therapy: 4/5 (80%) patients had *NPM1* and/or *IDH2* mutant disease, all achieved undetectable MRD

Comparable overall survival (OS) and progression free survival (PFS) in STOP and CONT cohorts

- A landmark analysis was performed with the landmark taken from the median time on treatment TOT in the STOP group (19 months), to exclude lead-time bias in pts relapsing early in the CONT group
- This revealed no significant difference in PFS (P=0.14, Figure 4) or OS (P=0.24, Figure 5)

Figure 2. Landmark PFS analysis

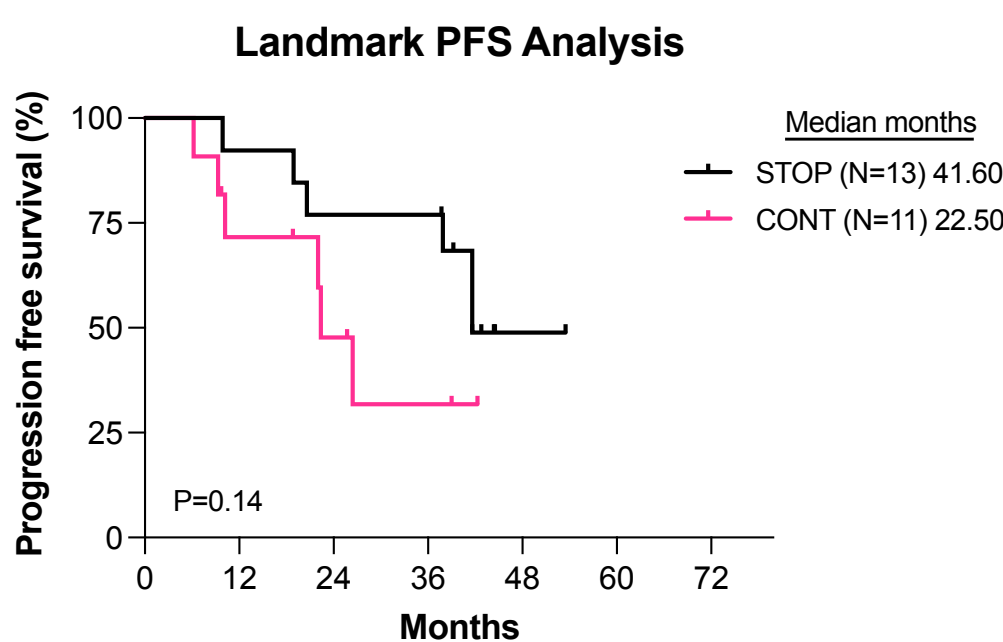
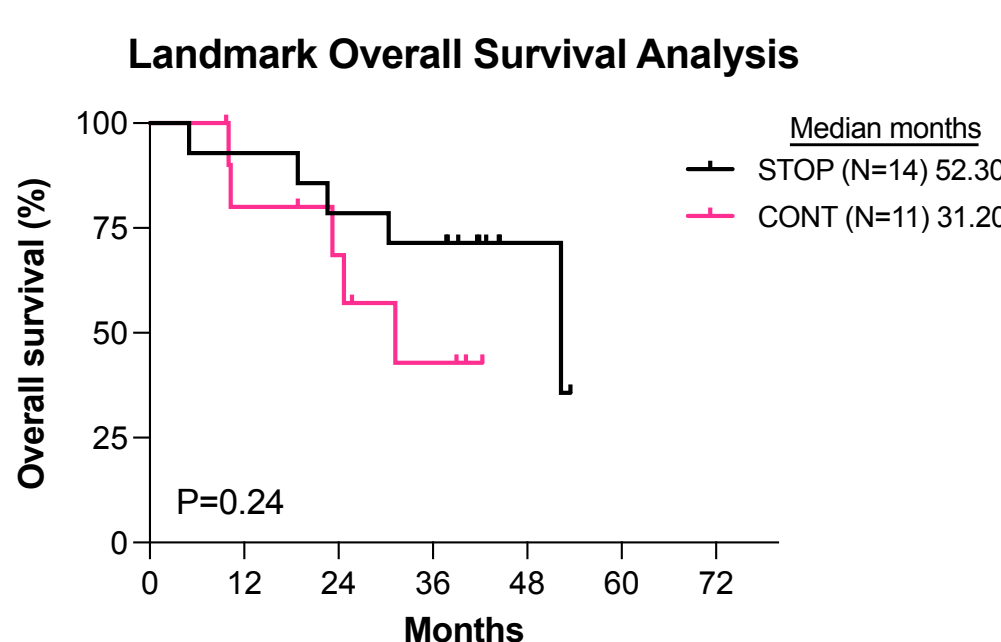


Figure 3. Landmark OS analysis



MRD negativity is a pre-requisite for durable remission

- 19/28 patients had serial MRD assessment by either molecular (n=8) and/or flow cytometry (n=15). 2/19 (11%) had persistent MRD and both relapsed.
- 17/19 (89%) achieved MRD negativity, with a median time to MRD negativity of 1.5 cycles (range 1 to 4 cycles). To date, 10/17 (59%) have not relapsed with a median RFS of 51.1 month
- 2/8 (25%) patients who achieved molecular *NPM1* MRD negativity relapsed; 7/13 (54%) patients who achieved flow MRD negativity relapsed (two had MRD assessment by both modalities)

Outcomes following relapse

- Cytogenetic evolution is dominant at relapse (9/16, 56%) and more frequent in the CONT cohort (6/9, 67%)
- Salvage therapy was delivered in 5/7 (71%) STOP pts and 4/9 (44%) CONT pts who relapsed
- Median time from relapse to death were 3.8 vs. 8.9 months in CONT vs. STOP cohorts, respectively (p=0.96)

Conclusion

- In elderly/unfit pts with AML receiving frontline VEN-based treatment with a sustained CR/CRi after receiving at least 12 months of therapy, the likelihood of a durable TFR is highest among pts with an *NPM1*- and/or *IDH2* mutant disease and MRD negativity at the time of therapy cessation.
- A prospective, randomised, discontinuation study in pts in sustained CR_{MRDneg} after 12 months of therapy warrants exploration.

Acknowledgements

We would like to thank all the patients, families and staff members.

References

- Wei AH, Montesinos P, Ivanov V, DiNardo CD, Novak J, Laribi K, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. **Blood**. 2020;135(24):2137-45.
- DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. **New England Journal of Medicine**. 2020;383(7):617-29.

Contact information

Dr. Chong Chyn Chua (Chyn)
Department of Haematology, Alfred Hospital, Melbourne, Australia.
c.chua@alfred.org.au