Initial Results from SELECT-AML-1, a Phase 2 study of Tamibarotene in Combination with Venetoclax and Azacitidine in *RARA*-positive Newly Diagnosed AML Patients Ineligible for Standard Induction Chemotherapy

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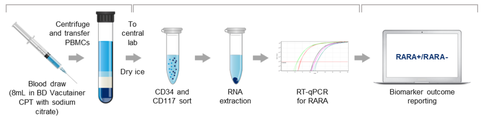
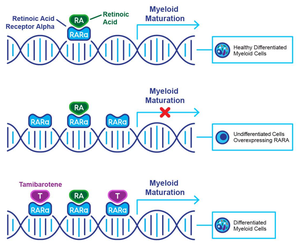
Introduction

AML patients with *RARA* gene overexpression represent a novel patient subset with an actionable target for treatment with tamibarotene, an oral, selective RARα agonist

- Tamibarotene, a next generation synthetic retinoid, is a highly selective, oral RARα agonist initially developed for ATRA-resistant APL
- Approximately 30% of AML patients are positive for *RARA* overexpression, as measured by a blood-based biomarker assay[1]
- *RARA* overexpression assay identifies patients for treatment with tamibarotene[1,2]



Functionally, *RARA* overexpression leads to impaired differentiation and maturation arrest



Background

- In a Phase 2 study (NCT02807558) tamibarotene + azacitidine induced high CR/CRi rates, rapid onset of action and meaningful durability in newly diagnosed AML patients with *RARA* overexpression ineligible for standard intensive induction therapy[3]

- Combination of tamibarotene with azacitidine was generally well-tolerated with no increase in neutropenia, anemia and thrombocytopenia compared to single-agent azacitidine[3]
- Majority of non-hematologic AEs were low grade and reversible

SELECT-1-AML

- Venetoclax + azacitidine has demonstrated an improvement in response rates and survival in patients ineligible for standard intensive induction therapy but challenges remain with approximately 1/3 not responding and nearly all eventually relapsing[4]
- *RARA* overexpression was identified in approximately 30% of patients with AML and defined a novel subset[1]. Approximately 80% of these *RARA*-positive patients were also enriched for monocytic features reported to be associated with possible venetoclax resistance[5,6]
- These data suggested that the *RARA* overexpression assay identified patients who were likely to respond to tamibarotene but may also predict which patients are less likely to respond to venetoclax + azacitidine alone and is the basis for the SELECT-AML-1 trial

Study Design

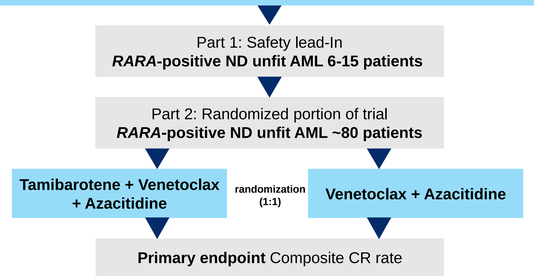
Key Entry Criteria:

Inclusions:

- *RARA*-positive as determined by a blood test for *RARA* gene overexpression
- Adult ND AML, ineligible for standard intensive induction therapy based on age, performance status or comorbidities
- WBC count <25,000 at the time of initiation of study drug

Exclusions:

- APL
- CNS involvement with AML
- Prior AML/MDS treatment with hypomethylating agent, venetoclax, chemotherapy, or hematopoietic stem cell transplant (with the exception of hydroxyurea)



Part 3: Trial includes a cohort in which the triplet, tamibarotene + venetoclax + azacitidine, will be evaluated as a salvage strategy for patients in venetoclax + azacitidine control arm who experience progressive disease, relapse, or treatment failure

Objectives:

Part 1 Safety Lead-In: Safety and tolerability and pharmacokinetics of tamibarotene + venetoclax + azacitidine

Part 2 Randomized Comparison: Clinical activity, safety, and tolerability comparison between tamibarotene + venetoclax + azacitidine and venetoclax + azacitidine

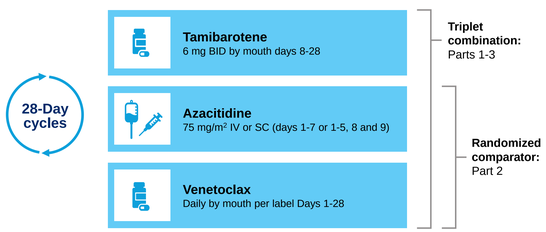
Part 3 Salvage Strategy: Clinical activity of tamibarotene rescue in those with progression in venetoclax + azacitidine control arm

Exploratory: Characterize monocytic expression score (MES) across patients

Assessments:

Response Assessments per ELN with bone marrow aspirations, safety assessments, pharmacokinetics

SELECT-AML-1 Study Treatment



Results

Enrollment

Patients with *RARA* overexpression assay results available as of 13 October 2022:

- *RARA*-positive: N = 29

Patients enrolled: 8

- Common reasons for screen fails:
  - Insufficient organ function, incorrect diagnosis (MDS), elected for alternative therapy, death prior to treatment initiation

Response evaluable: N = 6

- Completed at least 1 cycle of therapy with available data or progressed prior to first assessment

Demographics and Baseline AML Characteristics of Response Evaluable Patients

Response Evaluable Enrolled Patients	N= 6
Gender n (%)	
Male	3 (50)
Female	3 (50)
Median age, years (range)	61 (55-82)
Median blasts, % (range)	63 (39-100)
FAB Classification n (%)	
M1	2 (33)
M4	1 (17)
Unknown	3 (50)
Cytogenetics n (%)	
Normal	3 (50)
Inversion 16	1 (17)
Del 5q and -7	1 (17)
-7	1 (17)
Molecular Abnormalities n (%)	
Normal	4 (67)
Complex mutations including: IDH2, BCOR, SRSF2, CSF3R	1 (17)
FLT-3 ITD low	1 (17)
MES (Monocytic Expression Score) n (%)	
High	4 (67)
Low	1 (17)
Undetermined	1 (17)

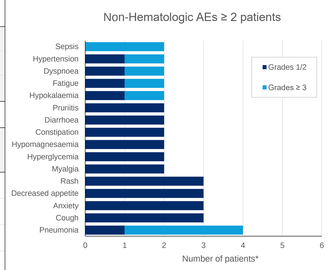
Response Summary

Best Overall Response	N=6 n (%)
CR/CRi*	5 (83)
CR	2 (33)
CRi	3 (50)
PD	1 (17)

CR = complete response; CRi = CR with incomplete hematologic recovery; PD = progressive disease
* 4/5 patients with CR/CRi had high MES predictive of venetoclax resistance

- Median Time to CR/CRi: 33 days (range 25–88 days); median 1 cycle (range 1-2 cycles)
- Median Duration of Treatment: 76.5 days (range 20 - 104 days)
- Median Duration of Follow-Up: 107 days (range 56 – 314 days)

Safety Summary



- Myelosuppression is comparable to reports of venetoclax + azacitidine in this population
- The majority of non-hematologic AEs are low grade and reversible
- SAEs were reported in 6; the most frequent (occurring in ≥ 2 pts) included febrile neutropenia (4 pts) and pneumonia (3 pts)

* 6 of 8 patients with data at 13OCT22 datacut

Conclusions

- Early results of tamibarotene + venetoclax + azacitidine in newly diagnosed AML patients positive for *RARA* overexpression and ineligible for standard intensive induction therapy demonstrate a high CR/CRi rate with rapid onset of response
- No new safety signal identified with triplet tamibarotene + venetoclax + azacitidine compared to venetoclax + azacitidine
- Data from the safety lead-in supports initiation of the randomized portion of the trial in which tamibarotene + venetoclax + azacitidine will be compared to venetoclax + azacitidine in AML patients with *RARA* overexpression
- Recent ELN 2022[7] AML venetoclax adaptive dosing will be incorporated into both arms of the randomized portion of the trial

Acknowledgements and Contact Information

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Trial Information:
Tamibarotene Plus Venetoclax/Azacitidine in Participants With Newly Diagnosed AML

ClinicalTrials.gov Identifier: NCT04905407

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