SELECT-AML-1 Trial in Progress: A Phase 2 Study of Tamibarotene in Combination with Venetoclax and Azacitidine in Previously Untreated Adult Patients Selected for RARA-positive AML who are Ineligible for Standard Induction Therapy

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Study Overview

SELECT-AML-1 is a randomized, Phase 2 trial which will evaluate the safety and efficacy of tamibarotene and azacitidine in combination with venetoclax compared to venetoclax and azacitidine in RARA-positive newly diagnosed unfit AML patients

Background

- RARA-positive AML is a novel patient subset with an actionable target for treatment with tamibarotene, an oral, selective RARα agonist
- Targeting the biology of *RARA* overexpression with tamibarotene plus azacitidine provides a novel therapeutic approach in AML
- Despite recent advancements, there remains an unmet need for newly diagnosed unfit AML patients
  - Approximately one-third of these patients do not response to upfront treatment with venetoclax/azacitidine, and nearly all patients eventually relapse[1]
  - Translational data suggest RARA positivity enriches for monocytic features reported to be associated with venetoclax resistance[2,3]
  - Venetoclax resistance is associated with monocytic phenotype[3-5]; most RARA+ patients, including those who achieved CR/CRi in SY-1425-201 tamibarotene trial, have this monocytic phenotype[2]
  - This data suggest RARA biomarker selects for AML patients who may respond to tamibarotene and may be less likely to respond to venetoclax/azacitidine[2]
- In a Phase 2 study (NCT02807558) tamibarotene/azacitidine induces high CR rates, rapid onset of action and meaningful durability in RARA+ ND unfit AML[6,7]

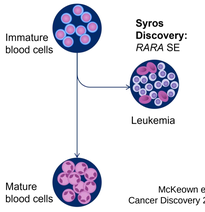


- Combination of tamibarotene with azacitidine has been generally well-tolerated with no increase in neutropenia, anemia and thrombocytopenia compared to single-agent azacitidine[6]
  - Majority of non-hematologic AEs are low grade and reversible

[1]Dinardo, NEJM 2020; [2]Fiore, ASH 2020; [3]Zhang, Nature 2018; [4]Kuusanmäki, Haematologica 2019; [5]Pei, Cancer Discovery 2020; [6]de Botton, ASH 2020; [7]Data is from 18 response evaluable RARA-positive patients

RARA-positive AML is a Novel Patient Subset with an Actionable Target for Treatment with Tamibarotene

Super-enhancer mapping identifies novel patient subset



RARA biomarker in AML

Subset of non-APL AML patients characterized by overexpression of the *RARA* gene

- Actionable target for treatment with tamibarotene, an oral, selective RARα agonist
- Approximately 30% of AML patients are RARA-positive[1]
- Novel blood-based biomarker test identifies patients for treatment[1,2]
- Most known AML mutations are unassociated with RARA pathway activation[2]

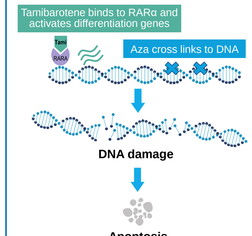
[1]Vigil, ESH 2017; [2]McKeown et al., Cancer Discovery 201

Tamibarotene

- Tamibarotene is an orally available, synthetic retinoid designed to be a more potent and selective RARα agonist than ATRA
- Tamibarotene is a first-in-class selective RARα agonist approved in Japan for R/R APL, with >1000 patients treated
- Preclinical synergy of tamibarotene with azacitidine supported development of the combination in RARA-positive myeloid malignancies[1]
- Tamibarotene provides a next generation differentiation agent that, in combination with azacitidine, leads to tumor cell death via enhanced apoptosis
- Tamibarotene is orally delivered and convenient to administer

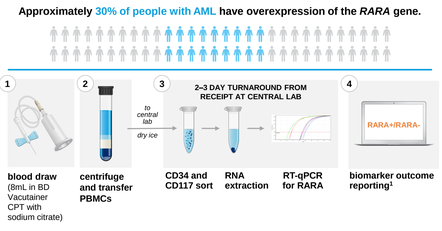
[1]McKeown, Haematologica 2018

Tamibarotene enhances azacitidine apoptosis preclinically



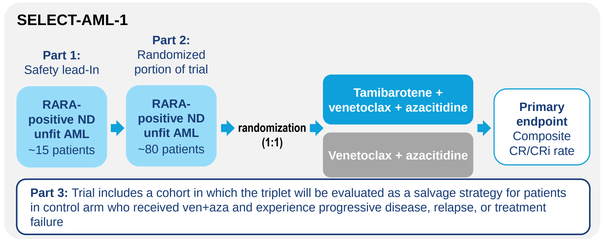
RARA Biomarker

- A peripheral blood sample is used to identify patients with RARA-positive AML using an investigational assay at a central laboratory
- The RARA biomarker is assessed at a pre-screening visit for study eligibility

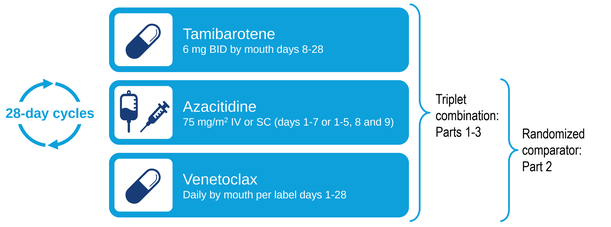


[1]Vigil, ESH 2017

Study Schema



Study Treatment



Key Eligibility Criteria

INCLUSIONS:

- RARA-positive
- ND AML, at least 18 years old
- Ineligible for intensive chemotherapy 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 treatment with hypomethylating agent, venetoclax, chemotherapy, or hematopoietic stem cell transplant (with the exception of hydroxyurea)

Overview of Study Objectives

PRIMARY OBJECTIVE:

Part 1:
- Characterize the safety and tolerability of the tamibarotene/venetoclax/azacitidine combination

Part 2:
- Characterize and compare CR/CRi rate of tamibarotene/venetoclax/azacitidine combination versus venetoclax/azacitidine by ELN criteria

SECONDARY OBJECTIVES:

Part 1:
- Characterize the overall response rate of the tamibarotene/venetoclax/azacitidine combination
- Characterize PK of tamibarotene when administered as part of tamibarotene/venetoclax/azacitidine

Part 2:
- Characterize the safety and tolerability of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine
- Characterize and compare CR rate and CR/CRh rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine
- Characterize duration of CR, duration of CR/CRi, and duration of CR/CRh Characterize time to CR, time to CR/CRi, and time to CR/CRh

Part 3:
- Characterize overall response rate after treatment with tamibarotene/venetoclax/azacitidine for patients who have experienced progressive disease, relapse, or treatment failure on venetoclax/azacitidine

EXPLORATORY OBJECTIVE:
- Characterize and compare MRD-negative response rate of tamibarotene/venetoclax/azacitidine versus venetoclax/azacitidine

Endpoints

Efficacy:
- CR/CRi response assessed per ELN AML criteria[1] based on local bone marrow evaluation

Safety:
- AEs, PE, VS, ECG, hematology and chemistry parameters assessed throughout the study
- Adverse event severity graded using NCI CTCAE v5.0

Pharmacokinetics:
- Sparse PK sampling for plasma concentrations of tamibarotene

Biomarkers:
- Blood and marrow samples to evaluate AML molecular features including genetic mutations and/or gene expression markers associated with response and loss of response

[1]Dohner 2017 and Bloomfield 2018

Conclusions

- Unmet need in newly diagnosed unfit AML remains high despite recent advancements
  - ~1/3 of patients do not respond to standard of care; most patients who respond relapse or do not have long term benefit
  - Targeting RARA overexpression with tamibarotene has the potential to improve outcomes in a biomarker selected patient subset
- SELECT-AML-1 is an ongoing Phase 2 study evaluating the safety and efficacy of tamibarotene and azacitidine in combination with venetoclax compared to venetoclax and azacitidine in RARA-positive newly diagnosed unfit AML patients
- Study initiated in 2021 with ongoing enrollment in the U.S. and France (NCT04905407)

Contact Information

We would like to acknowledge all the SELECT-AML-1 study centers and all the patients and their caregivers for their participation.

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