SELECT-MDS-1 Trial in Progress: A Phase 3 Randomized, Double-blind, Placebo-controlled Study of Tamibarotene/Azacitidine vs Placebo/Azacitidine in Newly Diagnosed (ND) Adult Patients Selected for RARA-positive HR-MDS

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soho22 TENTH ANNUAL MEETING

Objectives

SELECT-MDS-1 is a randomized, double-blind, placebo-controlled trial which will evaluate the safety and efficacy of tamibarotene with azacitidine compared to placebo with azacitidine in newly diagnosed higher-risk MDS (HR-MDS) patients

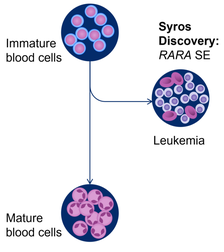
Background

- For patients with HR-MDS the unmet need is significant as the existing standard of care treatment options with hypomethylating agents only moderately improve patient prognosis
- RARA-positive HR-MDS 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 HR-MDS
- In a Phase 2 study (NCT02807558) single agent tamibarotene demonstrated clinical activity in RARA-positive R/R HR-MDS[1] and tamibarotene/aza led to a CR/CRi rate of 61% and a rapid onset of response (1.2 months) in RARA-positive newly diagnosed unfit AML, including those with low blast count (≤ 30%) AML[2]
- Combination of tamibarotene + azacitidine is generally well-tolerated with no increase in neutropenia, anemia or thrombocytopenia compared to single-agent aza[2]
  - Majority of non-hematologic AEs are low grade and reversible

[1]Jurcic, ASH 2017 [2]de Botton, ASH 2020

RARA-positive AML/HR-MDS are Novel Patient Subsets with an Actionable Target for Treatment with Tamibarotene

Super-enhancer mapping identifies novel patient subset



McKeown et al., Cancer Discovery 2017

RARA biomarker in AML/MDS

- Subset of non-APL AML and HR-MDS patients characterized by overexpression of the *RARA* gene
- Approximately 50% of HR-MDS patients are RARA-positive[1]
- Novel blood-based biomarker test identifies patients for treatment[1,2]
- Most known AML/MDS mutations are unassociated with RARA pathway activation[2]
- Independent analyses of BeatAML[3] and TCGA[4] show that prognosis is similar regardless of levels of *RARA* expression

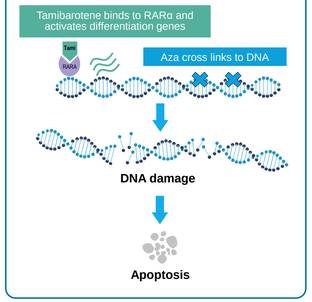
[1]Syros data on file from study SY-1425-201 and the SELECT-MDS-1 Study (27May2022) from over 175 patients with MDS; [2]McKeown et al., Cancer Discovery 2017; [3]Tyner et al., Nature 2018; [4]TCGA Research Network, Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia, NEJM 2013

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 plus azacitidine supported development of the combination in RARA-positive myeloid malignancies[1]
- Tamibarotene is orally delivered and convenient to administer

[1]McKeown, Haematologica 2018

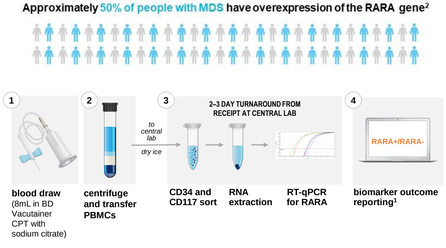
Tamibarotene enhances azacitidine apoptosis preclinically



RARA Biomarker

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

Approximately 50% of people with MDS have overexpression of the RARA gene[2]



[1]Vigil, ESH, 2017 [2]Syros data on file from study SY-1425-201 and the SELECT-MDS-1 Study (27May2022) from over 175 patients with MDS

Study Schema



*Stratification by IPSS-R risk and geographic region

Eligibility Criteria

Key Inclusions:

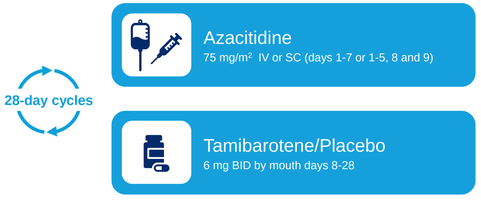
- Patients must be RARA-positive
- Patients must be newly diagnosed with HR-MDS as follows:
  - Diagnosis of MDS according to WHO[1] and classified by the IPSS-R risk category[2] as:
    - Very high (risk score > 6 points)
    - High (risk score > 4.5 to 6 points), OR
    - Intermediate (risk score > 3 to 4.5 points)
- Patients must have measurable disease with bone marrow blasts > 5% at the screening visit

Key Exclusions:

- Patients who are suitable for allogeneic hematopoietic stem cell transplantation (HSCT) at the time of screening
- Patients who received prior treatment for MDS with any HMA, chemotherapy or allogeneic HSCT

[1]Arber, Blood 2016; [2]Greenberg, Blood 2012

Study Treatment



Study Endpoints

Primary Endpoint:

- Complete Remission Rate

Secondary Endpoints:

- Overall Survival
- Overall Response Rate (CR, Partial Response, Marrow CR and Hematologic Improvement, all per modified IWG for MDS[1])
- Event Free Survival (time to AML transformation or death)
- Transfusion Independence
- Duration of CR, Duration of Response
- Time to CR, Time to initial response
- Safety

[1]Cheson, Blood 2006

Study Design

Efficacy:

- Response assessed per the modified IWG MDS criteria
- Response determined based on local BMA with central review
- Study provides 90% power to detect a difference in CR rates between experimental and control arms (1-sided α = 0.025)

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:

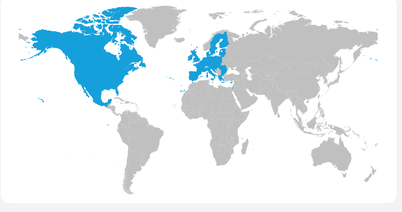
- MDS associated genetic mutations at screening, variant allele frequency change over time

PROs:

- Patient-reported health related quality of life will be evaluated using European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 and EuroQol 5 dimensions

Conclusions

- Patients with HR-MDS have a poor prognosis and a need for more effective and tolerable treatment options
- SELECT MDS-1 is an ongoing Phase 3 study evaluating the safety and efficacy of tamibarotene + azacitidine compared to placebo with azacitidine in newly diagnosed RARA-positive HR-MDS patients
- Study initiated in February 2021 and is actively enrolling with sites planned in USA, EU, UK, Canada, Israel, Mexico (NCT04797780)



Contact Information

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

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