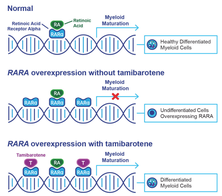
SELECT-AML-1: Phase 2 Randomized Trial of Tamibarotene in Combination With Venetoclax and Azacitidine in Adult Patients With Previously Untreated AML With *RARA* Overexpression, Who Are Ineligible for Standard Induction Therapy

Uma Borate MD[1], Christine McMahon MD[2], Pierre Fenaux MD[3], Pierre Peterlin MD[4], Brian Ball MD[5], Sylvain Chantepie MD[6], Alireza Eghtedar MD[7], Suman Kambhampati MD[8], Sylvain Thepot MD[9], Melhem Solh MD[10], Jose Torregrosa-Diaz MD[11], Thorsten Braun MD[12], Stephan de Botton MD, PhD[13], James Dugan MD[14], Jonathan Feld MD[15], Marie-Pierre Gourin MD[16], Arnaud Pigneux MD[17], Jean-Baptiste Robin MD[18], Gary Schiller MD[19], David A Roth MD[20], Kristen Baker MSN[20], Sofia Paul PhD[20], Michael Kelly MD[20], Daniel Pollyea MD[2], Thomas Cluzeau MD, PhD[21]

[1]Ohio State University Cancer Center, Columbus, OH, USA. [2]University of Colorado, Aurora, CO, USA. [3]Hôpital Saint-Louis, Paris, France. [4]Centre Hospitalier Universitaire de Nantes, Nantes, France. [5]City of Hope, Duarte, CA, USA. [6]Centre Hospitalier Universitaire de Caen, Normandie, France. [7]Colorado Blood Cancer Institute, Sarah Cannon Research Institution, Denver, CO, USA. [8]HCA Midwest Research Medical Center, Sarah Cannon Research Institution, Kansas City, MO, USA. [9]Centre Hospitalier Universitaire Angers, Angers, France. [10]Northside Hospital, Atlanta, GA, USA. [11]Centre Hospitalier Universitaire de Poitiers, Poitiers, France. [12]Centre Hospitalier Universitaire Hôpital Avicenne, Bobigny, France. [13]Institut Gustave Roussy, Paris, France. [14]Novant Health Cancer Institute, Winston-Salem, NC, USA. [15]Icahn School of Medicine at Mount Sinai, New York, NY, USA. [16]Centre Hospitalier Universitaire Limoges, Limoges, France. [17]Centre Hospitalier Universitaire de Bordeaux Hopital Haut-Leveque, Bordeaux, France. [18]Centre Hospitalier de la Côte Basque, Bayonne, France. [19]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA. [20]Syros Pharmaceuticals, Inc., Cambridge, MA, USA. [21]Centre Hospitalier Universitaire de Nice, Nice, France.

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 (McKeown 2017)
- Tamibarotene is in clinical development for frontline treatment of patients with acute myeloid leukemia with *RARA* gene overexpression (SELECT-AML-1, NCT04905407)



Background

- A high CR/CRi rate with rapid onset of response, meaningful durability, and generally well-tolerated safety profile were observed in newly diagnosed unfit AML patients with *RARA* overexpression treated with tamibarotene plus azacitidine (de Botton 2023)
- While venetoclax/azacitidine has emerged as standard of care, approximately one-third of patients do not achieve CR/CRi (DiNardo 2020) and nearly all relapse with a very poor prognosis, including a median overall survival of 2.4 months (Maiti 2021), supporting an opportunity for a biomarker-based therapeutic approach to improve clinical outcomes by adding tamibarotene
- The SELECT-AML-1 study completed a safety lead-in which supported initiation of the randomized portion of the study, in which tamibarotene/venetoclax/azacitidine will be compared to venetoclax/azacitidine in AML patients with *RARA* overexpression (Kambhampati 2022). Since that time, enrollment has been ongoing in the randomized portion of the study at 28 sites in the U.S. and France

Key Entry Criteria

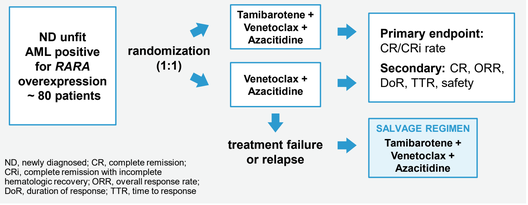
INCLUSION:

- Positive for *RARA* gene overexpression as determined by a blood-based biomarker test
- Adult newly diagnosed 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

EXCLUSION:

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

Study Design



ND, newly diagnosed; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; ORR, overall response rate; DoR, duration of response; TTR, time to response

Enrollment

- 51 participants were randomized by the date of the data cutoff (06 June 2024) in support of a prespecified interim analysis that was triggered when the 40th enrolled participant had received approximately 3 months of study drug (or discontinued earlier)
- In addition to the analyses on all 51 enrolled participants (25 randomized to tami/ven/aza and 26 randomized to ven/aza), a prespecified efficacy data analysis for futility was performed on the first 40 randomized participants

Baseline Characteristics

Characteristic	Tami/Ven/Aza N=25	Ven/Aza N=26
Age		
Median (range), years	76 (62, 85)	76 (69, 84)
≥75 years, n (%)	13 (57)	16 (62)
Male sex, n (%)	12 (48)	14 (54)
AML type, n (%)		
De novo AML	20 (80)	19 (73)
AML evolved from antecedent hematologic malignancy	5 (20)	6 (23)
AML associated with treatment from prior malignancy	0 (0)	1 (4)
ECOG, n (%)		
0	4 (16)	7 (27)
1	15 (60)	12 (46)
2	5 (20)	7 (27)
3	1 (4)	0 (0)
Baseline bone marrow blasts ≤30%	12 (48)	10 (38)
ELN risk status, n (%)		
Favorable	5 (20)	2 (8)
Intermediate	8 (32)	7 (27)
Adverse	11 (44)	17 (65)
Missing	1 (4)	0 (0)
Molecular abnormalities, n (%)		
NPM1	7 (28)	1 (4)
FLT3	3 (12)	4 (15)
TP53	3 (12)	5 (19)
IDH1	1 (4)	0 (0)
IDH2	2 (8)	2 (8)

Safety Summary

- Median duration of exposure of 2.2 (0.3-10.7) months for tami/ven/aza and 2.4 (0.2-13.2) months for ven/aza as of data cutoff (06 June 2024)
- The majority of non-hematologic AEs were low grade
- No additive myelosuppression when combining tamibarotene with venetoclax/azacitidine

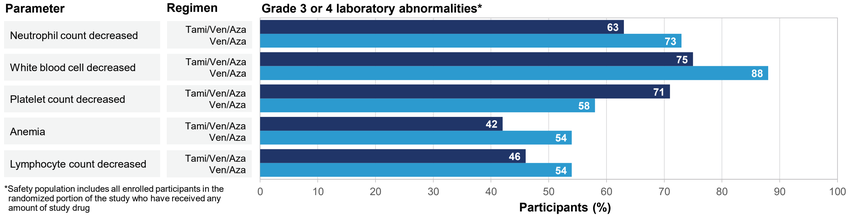
All terms	Tami/Ven/Aza N=24*	Ven/Aza N=27*^
Any grade TEAE, n (%)	24 (100)	24 (89)
Any grade non-hematologic TEAE in ≥25% participants, n (%)		
Constipation	10 (42)	5 (19)
Diarrhoea	9 (38)	6 (22)
Nausea	8 (33)	9 (33)
Oedema peripheral	7 (29)	3 (11)
Pruritis	7 (29)	0 (0)
Weight decreased	6 (25)	3 (11)
Decreased appetite	5 (21)	7 (26)
Dyspnoea	5 (21)	7 (26)
Grade 3/4 TEAE, n (%)	19 (79)	23 (85)
Grade 3/4 TEAE in ≥10% participants, n (%)		
Neutropenia/neutrophil count decreased	10 (42)	12 (44)
Thrombocytopenia/platelet count decreased	8 (33)	3 (11)
Leukopenia/white blood cell count decreased	7 (29)	5 (19)
Febrile neutropenia	6 (25)	7 (26)
Anemia	6 (25)	5 (19)
Sepsis	5 (21)	4 (15)
Asthenia	3 (13)	1 (4)
Pneumonia	3 (13)	1 (4)
Hypokalemia	3 (13)	2 (7)
Lymphocyte count decreased	1 (4)	3 (11)
Decreased appetite	0 (0)	3 (11)
Serious TEAE, n (%)	15 (63)	13 (48)
Serious AE in ≥10% of participants, n (%)		
Febrile neutropenia	5 (21)	6 (22)
TEAE leading to death, n (%)		
Sepsis	1 (4)	0 (0)
Septic shock	0 (0)	1 (4)
Lung disorder	0 (0)	1 (4)

*Safety population includes all enrolled participants in the randomized portion of the study who have received any amount of study drug. Treatment groups for this population were assigned according to the actual treatment the participants received

^Includes 1 participant randomized to tami/ven/aza who received ven/aza and discontinued treatment prior to receiving tami

TEAE, treatment emergent adverse event

Summary of Hematology Abnormalities



*Safety population includes all enrolled participants in the randomized portion of the study who have received any amount of study drug

Response Summary

	Tami/Ven/Aza N=25*	Ven/Aza N=26*
Primary Endpoint		
CR/CRi, n (%)	15 (60)	18 (69)
95% CI of CR/CRi rate	(39, 79)	(48, 86)
CR	12 (48)	15 (58)
CRi	3 (12)	3 (12)
Secondary Endpoints		
ORR†, n (%)	20 (80)	19 (73)
95% CI of ORR	(59, 93)	(52, 88)
CRh	0 (0)	0 (0)
MLFS	4 (16)	1 (4)
PR	1 (4)	0 (0)
Other		
SD	3 (12)	2 (8)
PD	0 (0)	1 (4)
No response evaluation performed	2 (8)	4 (15)
Duration of CR/CRi, median (range), mo	293 (66, NE)	253 (56, 263)
Time to CR/CRi, median (range), mo	21 (15, 63)	25 (14, 57)

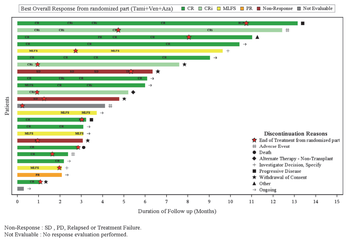
*mITT population includes all participants who were randomized, started dosing, and were RARA-positive at enrollment

†ORR includes CR, CRi, CRh, MLFS, or PR, as determined by the investigator. Responses are in alignment with ELN AML criteria (Döhner 2017 and Bloomfield 2018). Hematology evaluations performed prior to commencement of the next treatment cycle may be used to reflect the best AML response achieved (Döhner 2022)

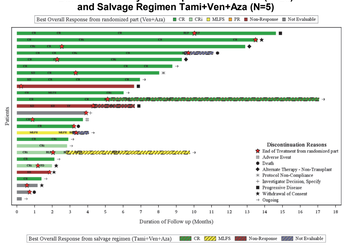
Post data-cut in the tami/ven/aza arm, 1 participant with MLFS achieved a CRi response and 1 participant with PR achieved a CRi response (data from Electronic Data Capture)

CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; mITT, modified intent-to-treat; MLFS, morphologic leukemia free state; mo, months; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

Duration on Study and Responses: Tami+Ven+Aza (N=25)



Duration on Study and Responses: Ven+Aza (N=26) and Salvage Regimen Tami+Ven+Aza (N=5)



Non-Response : SD , PD, Relapsed or Treatment Failure.
Not Evaluable : No response evaluation performed.

Interim Futility Analysis

	Interim Analysis Set	
	Tami/Ven/Aza N=20	Ven/Aza N=20
CR/CRi, n (%)	**13 (65)**	**14 (70)**
95% CI of CR/CRi rate	(41, 85)	(46, 88)
ORR, n (%)	**17 (85)**	**15 (75)**
Best Response, n (%)		
CR	10 (50)	12 (60)
CRi	3 (15)	2 (10)
CRh	0 (0)	0 (0)
MLFS	4 (20)	1 (5)
PR	0 (0)	0 (0)
SD	2 (10)	2 (10)
PD	0 (0)	1 (5)
No response evaluation performed	1 (5)	2 (10)

- A prespecified interim analysis was performed for the first 40 randomized participants who had received approximately 3 months of treatment or had discontinued treatment
- Futility analysis results provide a low probability of success of the SELECT-AML-1 study to demonstrate superior response rates with tami/ven/aza compared to ven/aza at the final analysis in 80 randomized participants

CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; MLFS, morphologic leukemia free state; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

Salvage Regimen

- 5 participants initially randomized to ven/aza who relapsed or had treatment failure received salvage treatment with tami/ven/aza; 3 participants remain on treatment
- Of the 3 participants with a response evaluation performed:
  - 1 participant in CR lost response during cycle 4 of ven/aza with 8% bone marrow blasts at relapse, regained CR after 1 cycle with salvage therapy, and is ongoing in cycle 6 of salvage treatment
  - 1 participant in CRi lost response after 2 cycles of ven/aza with 21% bone marrow blasts at relapse, achieved MLFS after 1 cycle of salvage therapy and remains on treatment
  - 1 participant with treatment failure after 3 cycles of ven/aza had progressive disease after cycle 1 of salvage therapy and discontinued treatment

Response Summary	N=3†
Best Response	
CR	1
MLFS	1
PD	1

CR, complete remission; MLFS, morphologic leukemia free state; PD, progressive disease

Note: Treatment failure is defined as failure to achieve a bone marrow blast count of <5% following at least 2 cycles of therapy, as determined by the investigator

†Response evaluable population includes participants who have either completed at least 1 response assessment or have discontinued treatment due to clinical progression/progressive disease prior to any response assessments; there were 2 participants without a response evaluation: 1 did not reach the initial response assessment at the time of the data cutoff and 1 patient died prior to the initial response assessment

Conclusions

- Tamibarotene in combination with ven/aza was well tolerated with no new safety signals or evidence of increased myelosuppression compared with ven/aza alone
- Similar overall response rates and CR/CRi rates were observed between treatment arms at this interim data analysis suggesting no added benefit of increasing the response rates with the tami/ven/aza triplet vs the ven/aza doublet in AML with *RARA* overexpression
  - Prespecified efficacy futility analysis on the initially enrolled 40 participant subgroup supports a low likelihood of demonstrating superiority of CR/CRi responses at the time of a final analysis in 80 enrolled participants
- A similar CR/CRi rate of 61% was observed in a prior Phase 2 study in newly diagnosed AML with *RARA* overexpression treated with the tami/aza doublet, compared to the tami/ven/aza triplet in this study, suggesting lack of mechanistic synergy with the addition of ven to tami/aza, thus contributing to a lack of increased response rate with the triplet regimen
- Encouraging preliminary clinical activity was observed in the salvage arm of this study in which 2 participants who relapsed on treatment with ven/aza achieved a response with the addition of tamibarotene
- SELECT-AML-1, while now closed to further enrollment, provides the opportunity to evaluate the longer-term impact of tamibarotene on duration of response, survival, and salvage therapy in participants continuing in follow-up

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