Advancing Novel Treatments for Hematologic Malignancies

March 2024

Forward-looking statements

This presentation contains forward-looking statements (including within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, and Section 27A of the Securities Act of 1933, as amended) concerning Syros and other matters, such as Syros' clinical development plans, including with respect to tamibarotene, Syros' ability to deliver benefit to patients and value to stockholders, the timing and impact of upcoming enrollment milestones and clinical data readouts, and the sufficiency of Syros' capital resources to fund its operating expenses and capital expenditure requirements into the second quarter of 2025. These statements may discuss goals, intentions and expectations as to future plans, trends, events, results of operations or financial condition, or otherwise, based on management's current beliefs, as well as assumptions made by, and information currently available to, management. Forward-looking statements generally include statements that are predictive in nature and depend upon or refer to future events or conditions, and include words such as "may," "will," "should," "would," "expect," "anticipate," "plan," "likely," "believe," "estimate," "project," "intend," and other similar expressions. Statements that are not historical facts are forward-looking statements. Forward-looking statements are based on current beliefs and assumptions that are subject to risks and uncertainties and are not guarantees of future performance. Actual results could differ materially from those contained in any forward-looking statement as a result of various factors, including, without limitation, Syros' ability to: advance the development of its programs, including tamibarotene, under the timelines it projects in current and future clinical trials; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of its drug candidates; sustain the response rates and durability of response seen to date with its drug candidates; successfully develop a companion diagnostic test to identify patients with the RARA biomarker; obtain and maintain patent protection for its drug candidates and the freedom to operate under third party intellectual property; obtain and maintain necessary regulatory approvals; identify, enter into out-licensing arrangements with third parties; manage competition; manage expenses; raise the substantial additional capital needed to achieve its business objectives; attract and retain qualified personnel; and successfully execute on its business strategies. The foregoing review of important factors that could cause actual events to differ from expectations should not be construed as exhaustive and should be read in conjunction with statements that are included herein and elsewhere, including the risk factors included in Syros' Annual Report on Form 10-K for the year ended December 31, 2023, which is on file with the Securities and Exchange Commission (SEC). Except as required by applicable law, Syros undertakes no obligation to revise or update any forward-looking statement, or to make any other forward-looking statements, whether as a result of new information, future events or otherwise.

Advancing our vision to deliver on the value of tamibarotene

Now

Advancing tamibarotene as a potential new standard of care for HR-MDS and AML patients with *RARA* gene overexpression

Preparing for product launch and commercialization

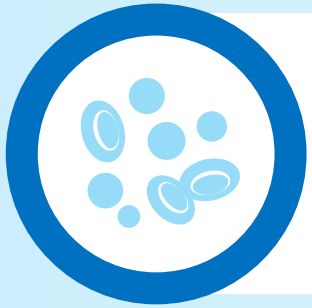
Cash runway to fund planned operations into Q2 of 2025

Vision

Commercial company delivering new standard of care for frontline treatment of hematologic malignancies

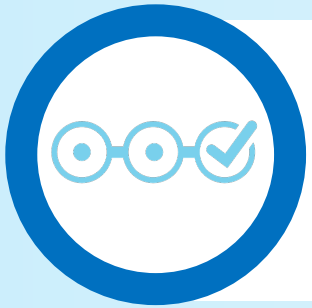
Advancing Tamibarotene:

Potential to establish new standard of care for the frontline treatment of hematologic malignancies



ENCOURAGING, CONSISTENT DATA FROM MULTIPLE CLINICAL TRIALS SUPPORT DEVELOPMENT STRATEGY

Growing body of evidence in MDS and AML patients with *RARA* overexpression



MEANINGFUL NEAR-TERM CATALYSTS

Upcoming opportunities to build momentum and create value:
pivotal SELECT-MDS-1 data and additional randomized SELECT-AML-1 data, both expected in 2024

LARGE MARKET OPPORTUNITIES IN FRONTLINE SETTINGS

Building a focused infrastructure to support targeted patient populations underserved by existing options

$45M FINANCING ADDS TO STRONG CORPORATE POSITION:
CASH RUNWAY TO FUND OPERATIONS INTO Q2 OF 2025

Multiple near-term value-driving milestones and pre-launch activities underway

Tamibarotene
in newly diagnosed HR-MDS

Last patient enrolled for the pivotal CR data from SELECT-MDS-1 Phase 3 trial	✓
Pivotal data from SELECT-MDS-1 Phase 3 trial	**By mid-4Q 24**

Tamibarotene
in newly diagnosed unfit AML

Initial data from randomized SELECT-AML-1 trial	✓
Additional data from randomized SELECT-AML-1 trial	**2024**

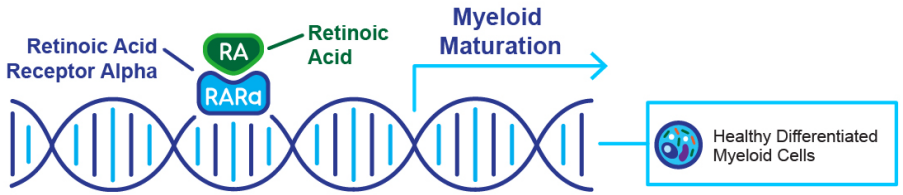
Pre-launch
activities

- Educating and preparing the treatment community for tamibarotene and *RARA* overexpression
- Planning distribution and sales infrastructure
- Partnered with Qiagen to ensure *RARA* testing availability at launch

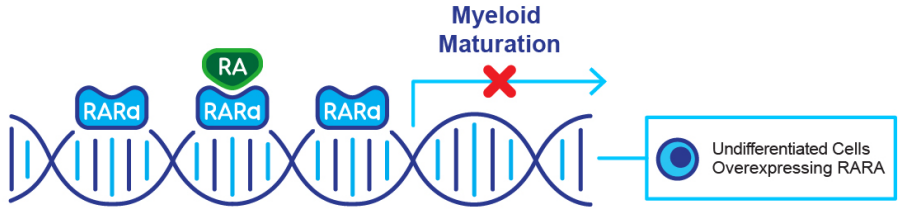
Tamibarotene: Compelling profile that addresses large targeted populations

Tamibarotene is a **selective and potent** RARα agonist[1]

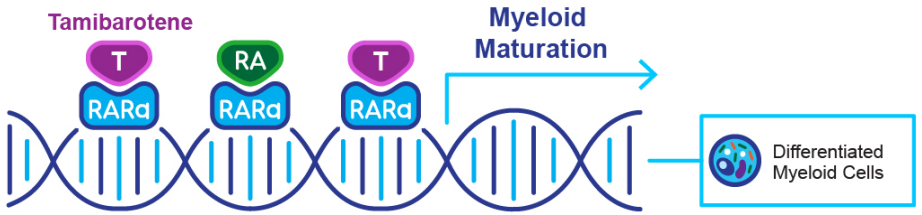
Normal



***RARA* overexpression without tamibarotene**



***RARA* overexpression with tamibarotene**



~50% of patients with HR-MDS are positive for *RARA* overexpression[2]

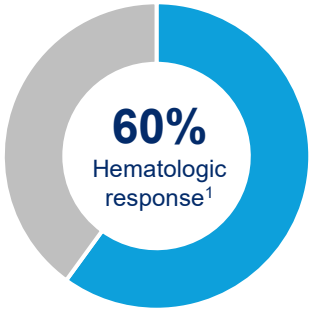
~30% of patients with AML are positive for *RARA* overexpression[2]

[1]McKeown, Cancer Discovery 2017; [2]de Botton S., et al. Blood Advances 2022

Growing body of clinical evidence for tamibarotene in HR-MDS and AML patients with *RARA* overexpression supports development strategy

2017

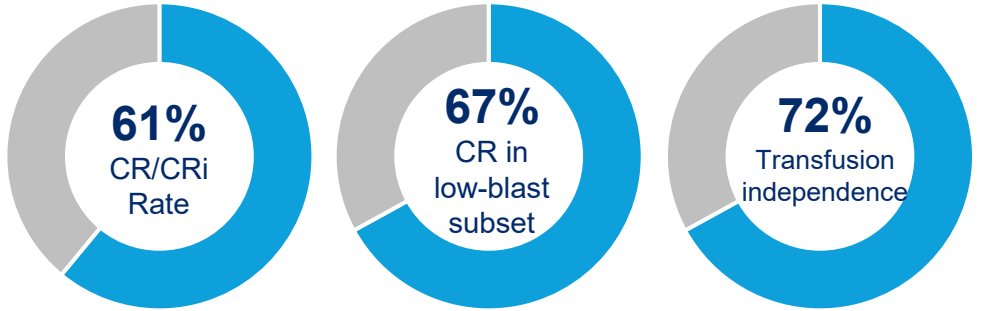
Single-agent tamibarotene in R/R HR-MDS patients[1]



including one marrow CR

2020

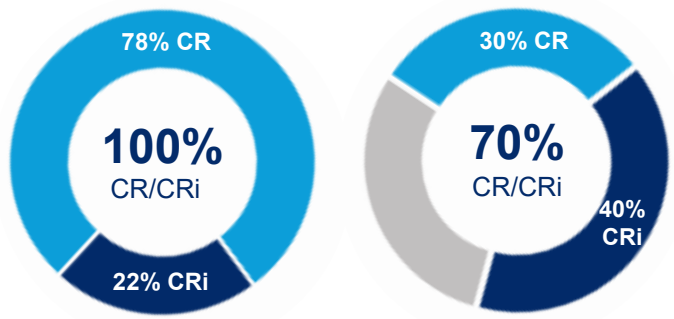
Phase 2 data evaluating Tami/Aza in ND unfit AML patients[2]



Median time to response[3]: **1.2 months**
Median duration of response: **10.8 months**
Overall survival for complete responders: **18 months**

2023

Phase 2 initial **randomized** data evaluating Tami/Ven/Aza vs. Ven/Aza in ND unfit AML patients[4]



Tami/Ven/Aza Median time to response:
21 days

Tamibarotene in HR-MDS

Tamibarotene in AML

[1]Data presented at ASH 2017, and Syros Data on File; [2]de Botton S., et al. Blood Advances 2022; [3]Response includes CR, CRi or CRh; [4]Data presented by Syros 06Dec2023

Tamibarotene has demonstrated a well-tolerated safety profile

Safety profile supports use of tamibarotene in combination with azacitidine in MDS and with venetoclax/azacitidine in AML

Well-characterized in over 1,000 acute promyelocytic leukemia ("APL") patients treated with tamibarotene[1]

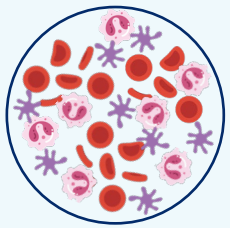
Single agent in AML and MDS patients and doublet (Tami/Aza) in AML patients[2,3]

Triplet (Tami/Ven/Aza) in AML patients[4,5]

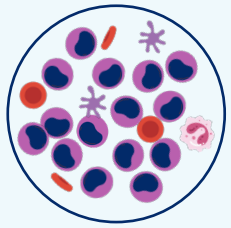
- Daily dosing of tamibarotene as a single-agent and in combination with azacitidine has been generally well-tolerated.[2-5]
  - No evidence of increased toxicity in combination, with rates of myelosuppression comparable to single-agent azacitidine.[2-5]
- As a triplet, myelosuppression has been comparable to venetoclax + azacitidine[4,5]
- The majority of non-hematologic AEs have been low grade and reversible[2-5]

[1]Amnolake® post-marketing surveillance data on file; [2]Data presented at ASH 2017; [3]de Botton S., et al. Blood Advances 2022; [4]Data presented at ASH 2022; [5]Data presented by Syros 06Dec2023

Significant unmet need in newly diagnosed unfit AML



Normal



AML

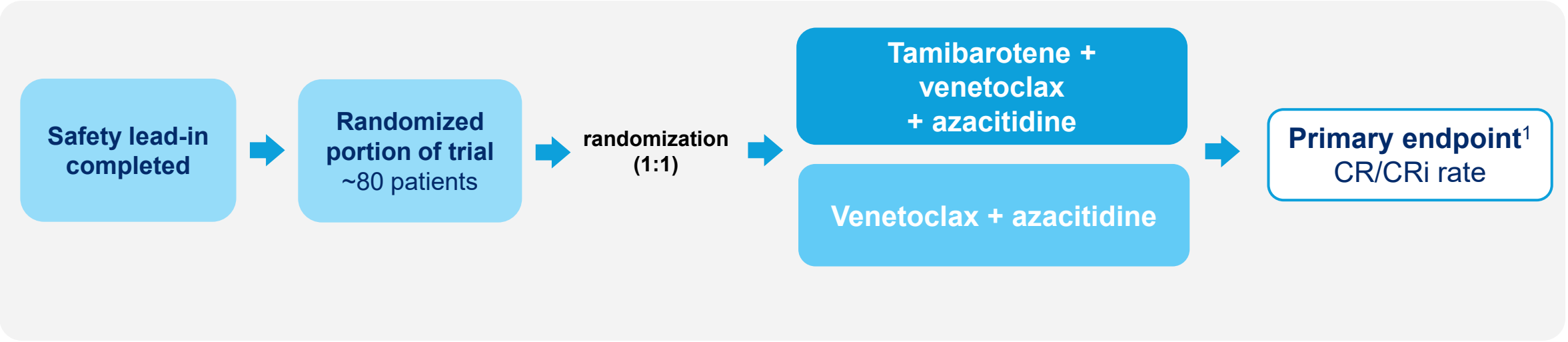
- Acute myeloid leukemia (AML) is a cancer of the blood forming cells in the bone marrow
- ~50% of the patients are not eligible for intensive treatment and are considered “unfit”[1]

The standard of care falls short, underscoring the critical demand for improved treatments for newly diagnosed unfit AML patients

- Venetoclax with azacitidine is standard of care, with a **66%** CR/CRi, **37%** CR rate and median OS of **14.7** months[2]
- Approximately **1/3** of patients do not respond, and nearly all relapse with a very poor prognosis, median OS of **2.4** months[3]

[1] Ferrara F., Clin Lymphoma Myeloma Leuk. 2011; [2]DiNardo CD, et al., New England Journal of Medicine, 2020; [3]Maiti A., et al., Haematologica, 2021.

Ongoing SELECT-AML-1 Phase 2 trial of triplet regimen (Tami/Ven/Aza) in newly diagnosed unfit AML patients with *RARA* overexpression



Key Milestones

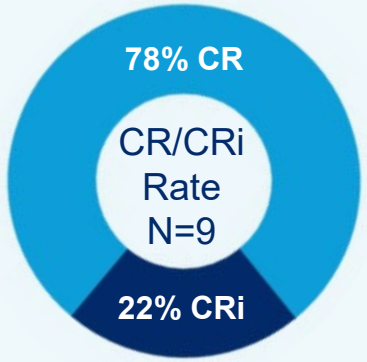
Initial randomized SELECT-AML-1 clinical data from 23 enrolled patients^	✓
Additional data from randomized SELECT-AML-1 trial	**2024**

[1] The study is 80% powered to detect a difference between the CR/CRi rates in the experimental and control arms
^ Data presented by Syros 06Dec2023; Data cut-off was November 13, 2023

Initial randomized SELECT-AML-1 Phase 2 data in newly diagnosed unfit AML patients with *RARA* overexpression demonstrate 100% CR/CRi rate

Initial randomized data builds on previous reported data from the safety lead-in:

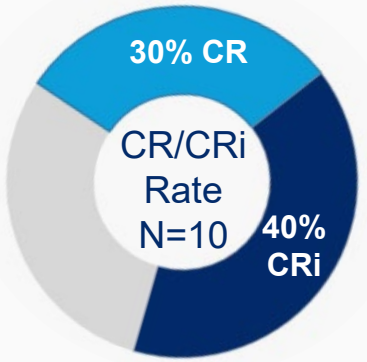
TREATMENT ARM: Tami/Ven/Aza



CR/CRi Rate
100%

CR Rate
78%

CONTROL ARM: Ven/Aza



CR/CRi Rate
70%

CR Rate
30%

Tamibarotene in combination with venetoclax and azacitidine was **well tolerated with no new safety signals identified**

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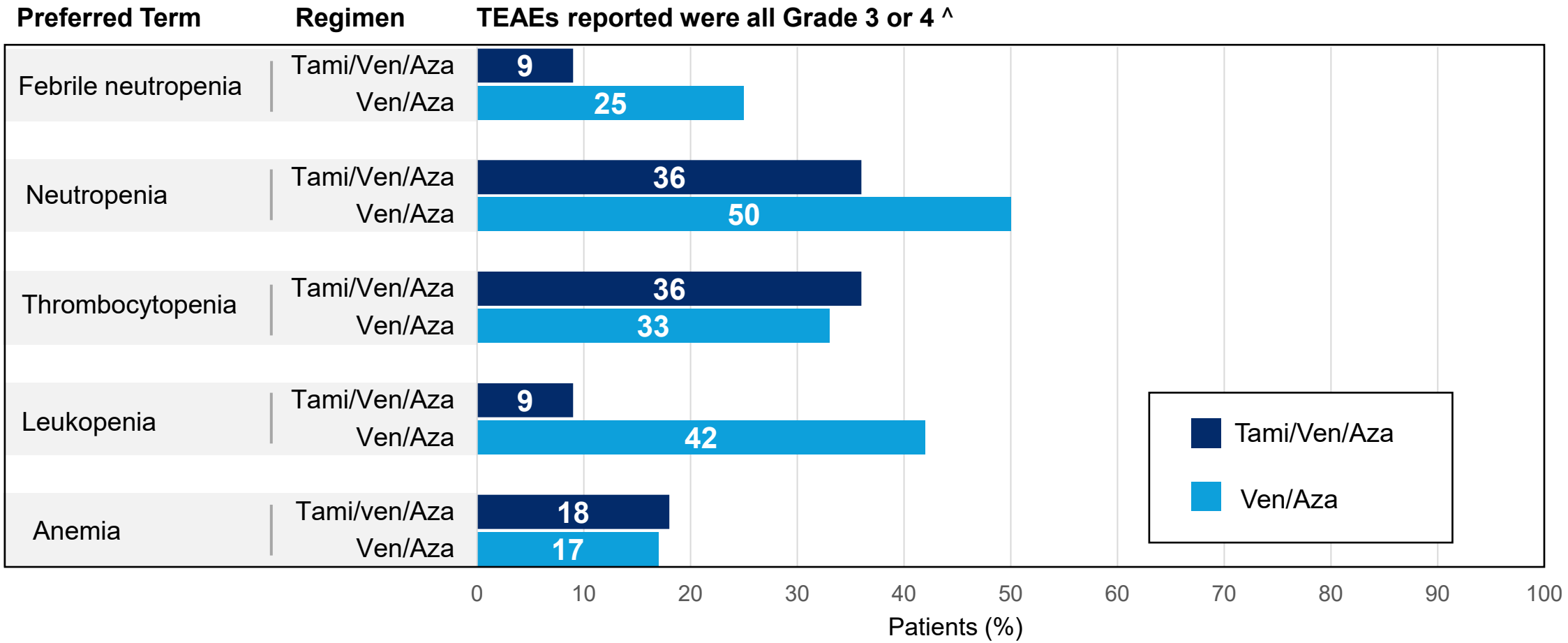
Data presented by Syros 06Dec2023; Data cut-off was November 13, 2023

Initial randomized SELECT-AML-1 Phase 2 data: Hematologic safety profile shows no additive myelosuppression when combining tamibarotene with Ven/Aza

Hematologic AEs - All Causality



Tami/Ven/Aza Safety Population, N=11; Ven/Aza Safety Population, N=12*

* Includes 1 patient randomized to Tami/Ven/Aza who received Ven/Aza and discontinued treatment prior to receiving tamibarotene.
^ No low-grade (Grade 1/Grade 2) Hematology AEs were reported for patients in either arm of the study.

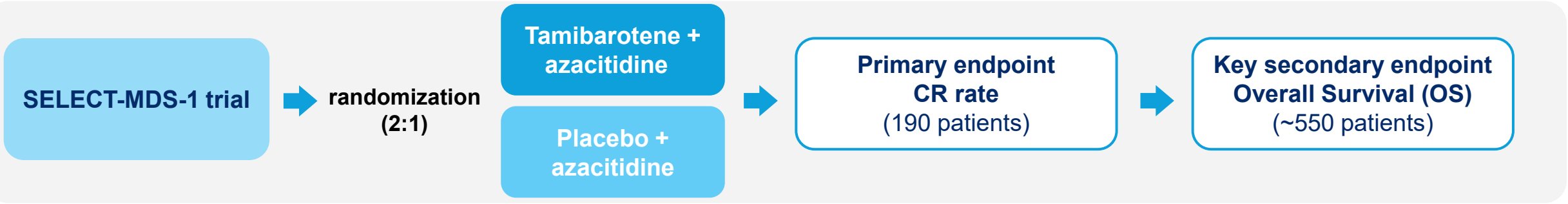
Higher-Risk MDS (HR-MDS) is closely related to AML

- Myelodysplastic syndrome (MDS) is also a cancer of the blood forming cells in the bone marrow
- HR-MDS often is a precursor to AML. More than half of HR-MDS patients progress to AML[1]
- Azacitidine, a hypomethylating agent (HMA), is SOC with a **17% CR rate** and a median OS of **18.6 months**[2]
- There is a **significant need for new therapies** - no new therapies beyond HMAs approved since 2006

"MDS-excess blasts" and "AML" essentially form a continuum…Rather than blast percentage, disease categorization may be more accurate if based on biologic features." – Estey et al., 2022[3]

[1] Greenberg, Blood, 2012; [2]Garcia, J et al., Leukemia Research, 2021; [3]Elihu Estey, et al., Blood 2022

Ongoing SELECT-MDS-1 Phase 3 trial in newly diagnosed HR-MDS patients with *RARA* overexpression



- Robustly designed, double-blind, placebo-controlled study
- 2:1 randomization
- Global study with over 120 sites recruiting in 13 countries
- FDA feedback supports:
  - Focus on population with *RARA* overexpression
  - CR as primary endpoint for approval (full or accelerated) with supporting data on durability of remission
  - Azacitidine as appropriate comparator
- Primary endpoint of CR rate is over 90% powered to detect a difference between experimental and control arms with a one-sided alpha of 0.025
- Inclusion of OS key secondary endpoint will allow this single trial to efficiently serve as a confirmatory study if needed for full approval
- Fast Track Designation by the FDA

Key Milestones

Last patient enrolled for the pivotal CR data from SELECT-MDS-1 Phase 3 trial	✓
Pivotal data from SELECT-MDS-1 Phase 3 trial	**by mid-4Q 24**

SYROS

Planning our commercial launch in the United States

- Experienced leadership team with proven capabilities and expertise in launching targeted oncology medicines
- Planning our distribution and sales infrastructure strategy for a launch in the U.S.
- Targeted patient populations will allow for a focused, specialized sales force
- Partnered with Qiagen to ensure *RARA* testing availability

Large market opportunities in frontline settings

Building infrastructure to target synergistic patient populations underserved by existing options

MYELODYSPLASTIC SYNDROME (MDS)

~18,500 Newly Diagnosed HR-MDS patients in the US and EU annually[1]

PROJECTED MDS GLOBAL MARKET BY 2028:

~$4.7B[3]

ACUTE MYELOID LEUKEMIA (AML)

~25,000 Newly Diagnosed Unfit AML patients in US and EU annually[2]

PROJECTED AML GLOBAL MARKET BY 2028:

~$7.5B[4]

[1]Epidemiology projections from DRG Myelodysplastic Syndromes-Landscape & Forecast-Report 2020 and from Syros Data on File; [2]Epidemiology projections from DRG Acute Myelogenous Leukemia-Landscape & Forecast-Report 2020; [3]Evaluate Pharma global market estimate includes all risk groups for MDS; [4]Global market estimate includes all AML (fit and unfit)

Multiple near-term value-driving milestones and pre-launch activities underway

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in newly diagnosed HR-MDS

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