SELECT-AML-1
Investor Event

December 10, 2022

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, SY-2101 and SY-5609, Syros' ability to deliver benefit to patients and value to stockholders, the timing and impact of upcoming clinical data readouts, the timing for submitting a new drug application to the Food and Drug Administration, and the sufficiency of Syros' capital resources to fund its operating expenses and capital expenditure requirements into 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, SY-2101 and SY-5609, 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 and maintain collaboration agreements 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, 2021 and Syros' Quarterly Report on Form 10-Q for the quarter ended September 30, 2022, each of which is on file with the Securities and Exchange Commission (SEC). In addition, the extent to which the COVID-19 pandemic continues to impact our workforce and our discovery research, supply chain and clinical trial operations activities, and the operations of the third parties on which we rely, will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration and severity of the pandemic, additional or modified government actions, and the actions that may be required to contain the virus or treat its impact. 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.

Today’s agenda

Opening remarks and corporate overview
Nancy Simonian, M.D., Chief Executive Officer of Syros

Safety lead-in results from the SELECT-AML-1 Phase 2 trial and next steps
David A. Roth, M.D., Chief Medical Officer of Syros

Current and emerging treatment landscape in newly diagnosed unfit AML and perspectives on tamibarotene opportunity
Daniel Pollyea, M.D., M.S., Professor of Medicine, Clinical Director of Leukemia Services and Robert H. Allen MD Chair in Hematology Research, University of Colorado School of Medicine

Q&A

Here's what you will take away from today

- Encouraging safety lead-in data from SELECT-AML-1 suggest tamibarotene can augment standard-of-care to improve outcomes for newly diagnosed, unfit AML patients with *RARA* overexpression
- Results support initiation of randomized portion of SELECT-AML-1 trial in 1Q 2023; data expected 2023/2024
- Significant opportunity in frontline unfit AML, with approximately 30% of patients positive for *RARA* overexpression
- Tamibarotene offers optimal product profile to address unmet need in AML and HR-MDS: biologically targeted, oral drug, favorable tolerability and novel mechanism of action important for combination

Company Overview

Nancy Simonian, MD
CEO

Developing new standards-of-care for the frontline treatment of hematologic malignancies

TARGETED HEMATOLOGY PORTFOLIO

Advancing clinical trials in frontline MDS, AML and APL with the potential to set new standards-of-care, supported by a growing body of data

MULTIPLE NEAR-TERM CATALYSTS

Upcoming opportunities to build momentum and create value, which include pivotal SELECT-MDS-1 data, randomized SELECT-AML-1 data and initiation of Phase 3 trial in APL

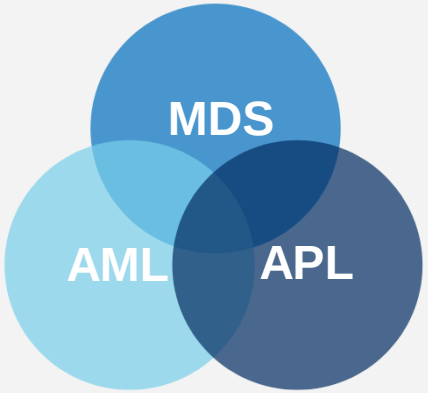
SIGNIFICANT MARKET OPPORTUNITIES IN FRONTLINE

Targeting patient populations underserved by existing options, which are commercially synergistic

STRONG CORPORATE POSITION

Cash runway to fund operations into 2025

3 clinical programs
from our **hematology portfolio**



Clinical development strategy reinforced by encouraging, consistent data from multiple trials

Growing body of clinical evidence for tamibarotene

- ✓ Single-agent tamibarotene in R/R HR-MDS patients with *RARA* overexpression showed 60% hematologic response, including one marrow CR[1]
- ✓ Phase 2 data evaluating tamibarotene with azacitidine in ND unfit AML patients with *RARA* overexpression showed:
  - **61% CR/CRi rate**[2]
  - **67% CR rate** in low blast count subset
- ✓ Data from SELECT-AML-1 safety lead-in evaluating tamibarotene with venetoclax and azacitidine in ND unfit AML patients with *RARA* overexpression showed:
  - **83% CR/CRi rate**[3]
- ✓ Safety profile supports ability to use full doses of tamibarotene in combinations with azacitidine in MDS and with venetoclax/azacitidine in AML

Tamibarotene in **HR-MDS**

Pivotal data from
SELECT-MDS-1 Phase 3 trial
expected late 2023 / early 2024

Tamibarotene in **AML**

Data from randomized portion of
SELECT-AML-1 trial Phase 2 trial
expected 2023 / 2024

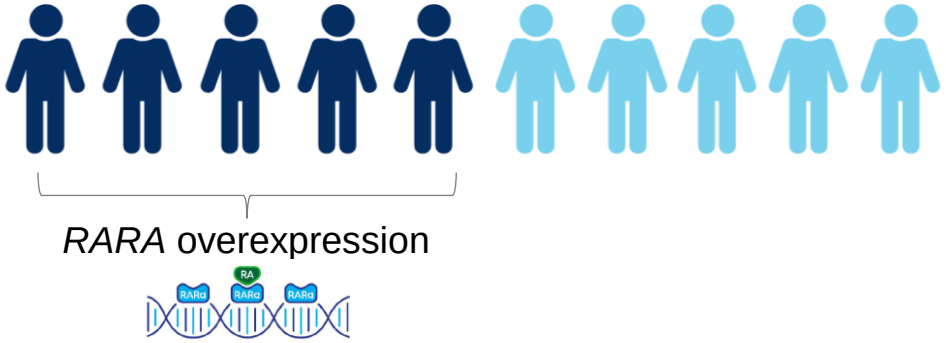
SYROS

[1] Data presented at ASH 2017; [2] Data presented at ASH 2020; [3] Data presented at ASH 2022

Large targeted populations and frontline settings provide attractive market opportunities for tamibarotene

~21,000[1] newly diagnosed HR-MDS patients in US and EU estimated annually

MDS represents a
~$3.3B* market by 2026



50% of patients with HR-MDS are positive for *RARA* overexpression[3]

~ 25,000[2] newly diagnosed Unfit AML patients in US and EU estimated annually

Newly diagnosed AML represents a
~$6.6B** market by 2025

30% of patients with AML are positive for *RARA* overexpression[4]

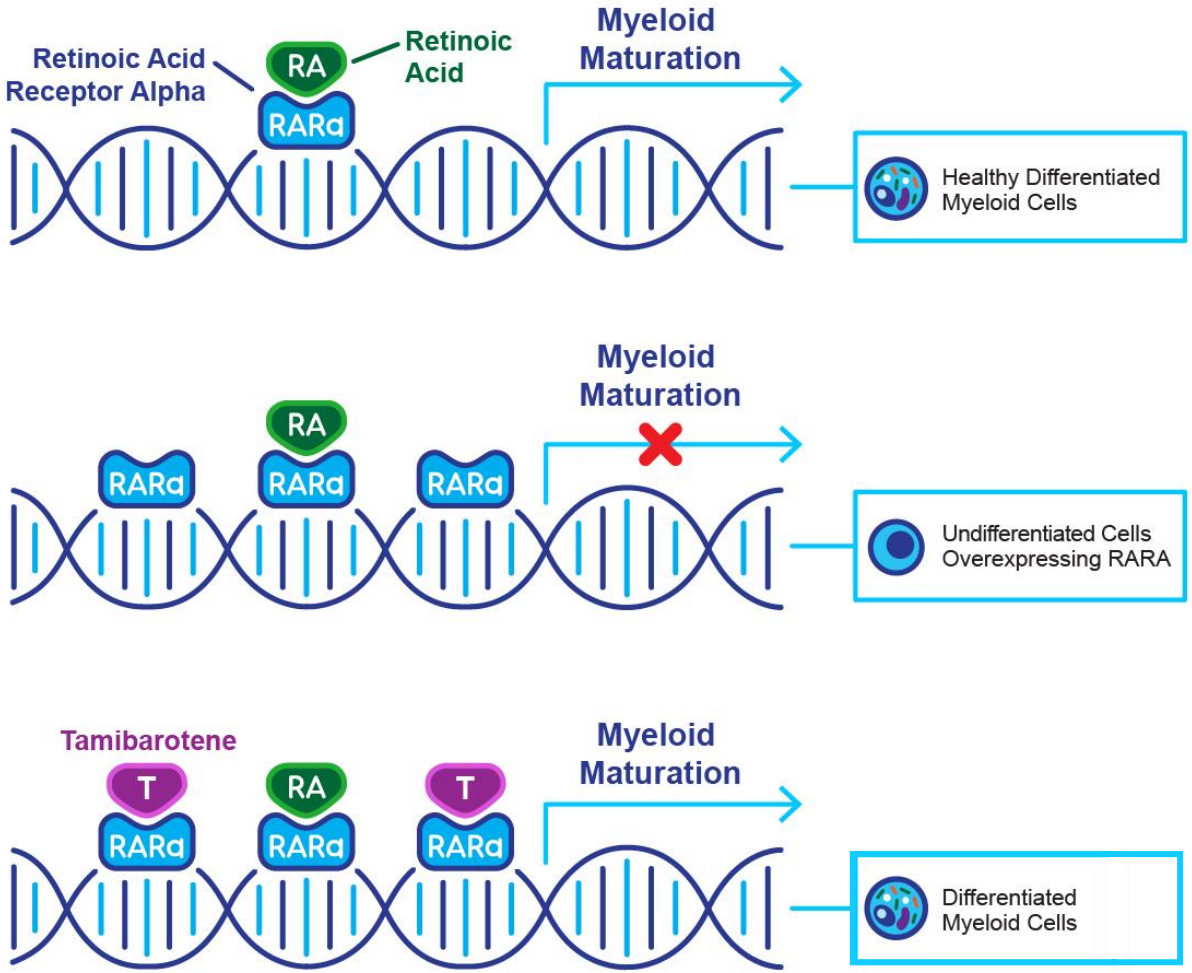
[1]Sources: Decision Resources Group, NCCN guidelines NOTE*:Evaluate Pharma market estimate includes all risk groups for MDS;
[2]Sources: Evaluate Pharma NOTE**: market estimate includes all AML (fit and unfit);
[3]Patients with MDS: RARA-positivity based on Syros data on file from Study SY-1425-201 and the SELECT-MDS-1 Study (27May2022) from over 175 patients with MDS;
[4]Patients with AML: Prevalence of RARA-positive patients based on data presented at ESH 2017 and ESH 2019

SELECT-AML-1

David A. Roth, MD
CMO

AML and MDS with *RARA* overexpression: a novel patient subset with an actionable target for treatment with tamibarotene

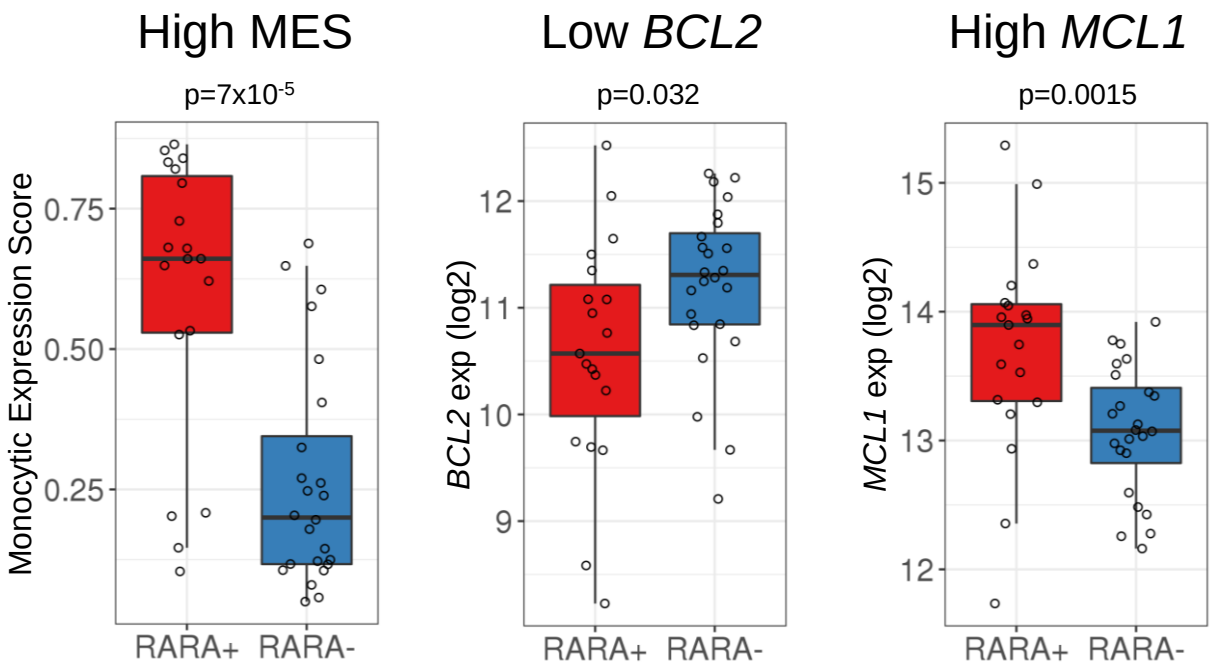
- Tamibarotene, a next generation **synthetic retinoid**, is an **oral, highly selective and potent RARα agonist**
  - 0.26 nM binding on RARα
  - Greater than 100x selectivity over RARβ and RARγ
- ***RARA* gene overexpression** inhibits downstream transcription of the myeloid differentiation gene program and **sensitizes cells to tamibarotene**



References: McKeown, Cancer Discovery 2017; Sanford et al: Br J Heamatol 2015; 171 (4): 471

AML with *RARA* overexpression is enriched for features associated with venetoclax resistance and clinical response to tamibarotene plus azacitidine

Patient Sample Analysis from Clinical Trial



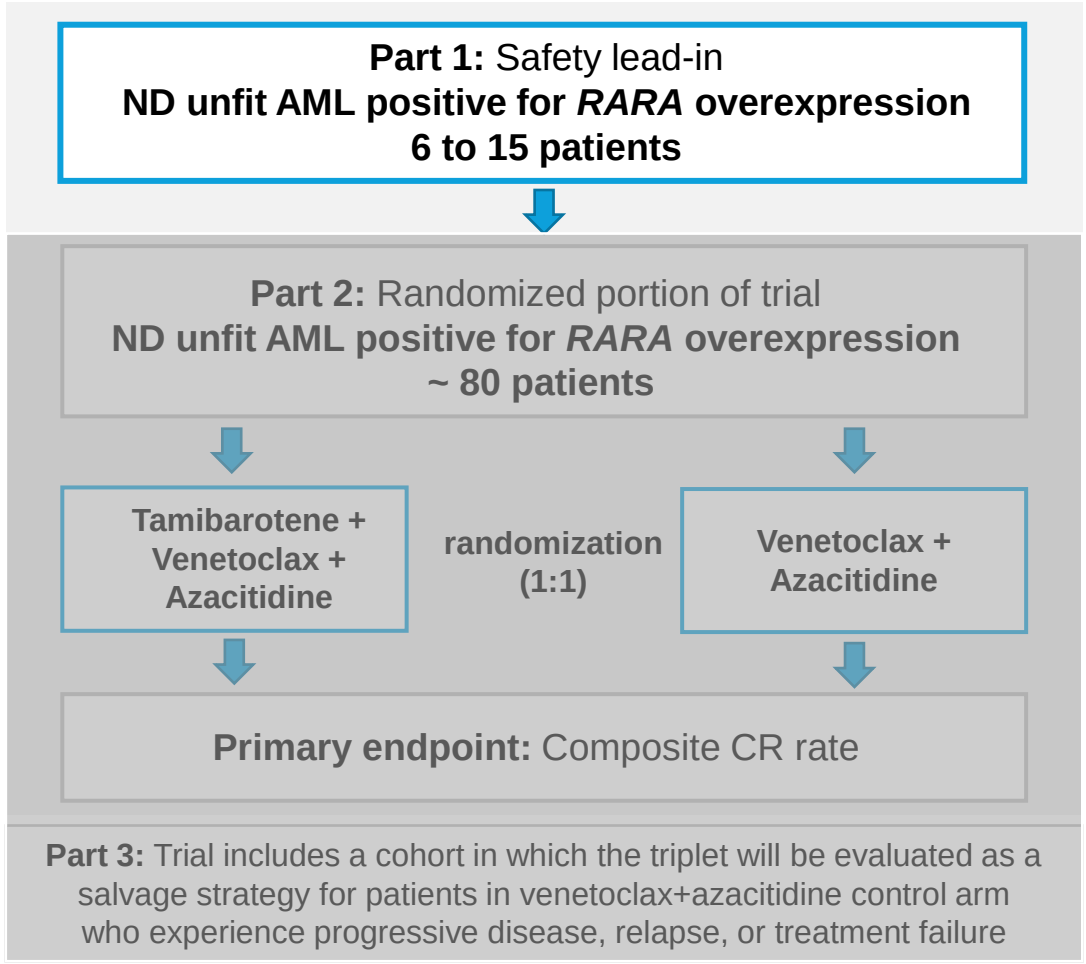
- Multiple recent studies report venetoclax resistance is associated with a monocytic phenotype[1-3]
- Majority (~80%) of newly diagnosed unfit AML trial patients with *RARA* overexpression have a monocytic phenotype based on a positive monocytic expression signature score (>0.5), with additional gene expression patterns associated with features of venetoclax resistance, including[4]:
  - Low *BCL2* expression
  - High *MCL1* expression
- ND unfit AML patients with *RARA* overexpression who achieved CR/CRi with tamibarotene/aza also have gene expression patterns associated with venetoclax resistance[4]

SYROS

[1]Zhang, Nature 2018; [2]Kuusanmäki, Haematologica 2019; [3]Pei, Cancer Discovery 2020; [4]Fiore, ASH 2020

SELECT-AML-1 study design

- Newly diagnosed adult AML patients with *RARA* gene overexpression, ineligible for standard intensive induction therapy based on age, performance status or comorbidities, WBC <25K at study drug initiation



Dosing Regimen

Tamibarotene
6 mg BID by mouth days 8-28

Azacitidine
75 mg/m^2 IV or SC (days 1-7 or 1-5, 8 and 9)

Venetoclax
Daily by mouth per label Days 1-28

Triplet combination: Parts 1-3

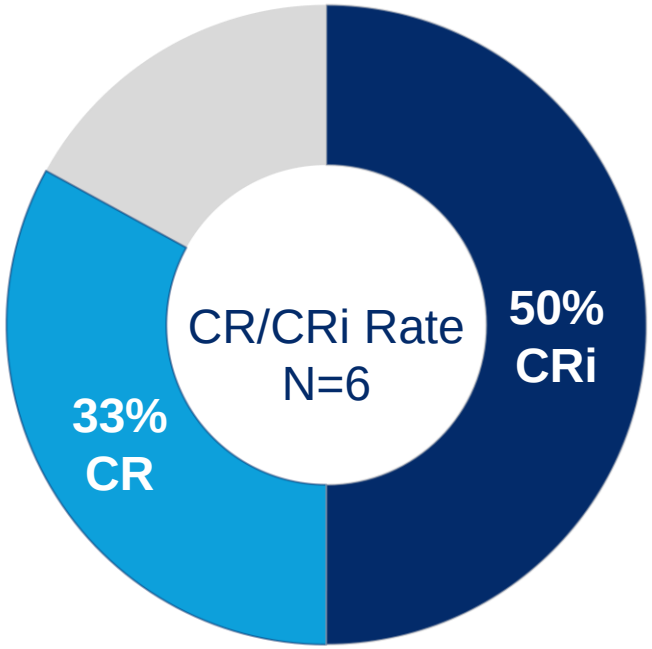
Randomized comparator: Part 2

Demographics and baseline AML characteristics

Response Evaluable[1] 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	
M1	2 (33)
M4	1 (17)
Unknown	3 (50)
Cytogenetics	
Normal	3 (50)
Inversion 16	1 (17)
Del 5q and -7	1 (17)
-7	1 (17)
Molecular Abnormalities	
Normal	4 (67)
Complex mutations including: IDH2, BCOR, SRSF2, CSF3R	1 (17)
FLT-3 ITD low	1 (17)
MES (Monocytic Expression Score)	
High	4 (67)
Low	1 (17)
Undetermined	1 (17)

[1] 8 patients enrolled, 6 response evaluable, Response evaluable defined as completed at least one cycle of therapy with available data or progressed prior to first assessment; 2 non-evaluable, had no data available at time of data cut-off 13OCT 22.

Response summary



CR/CRi Rate

83%

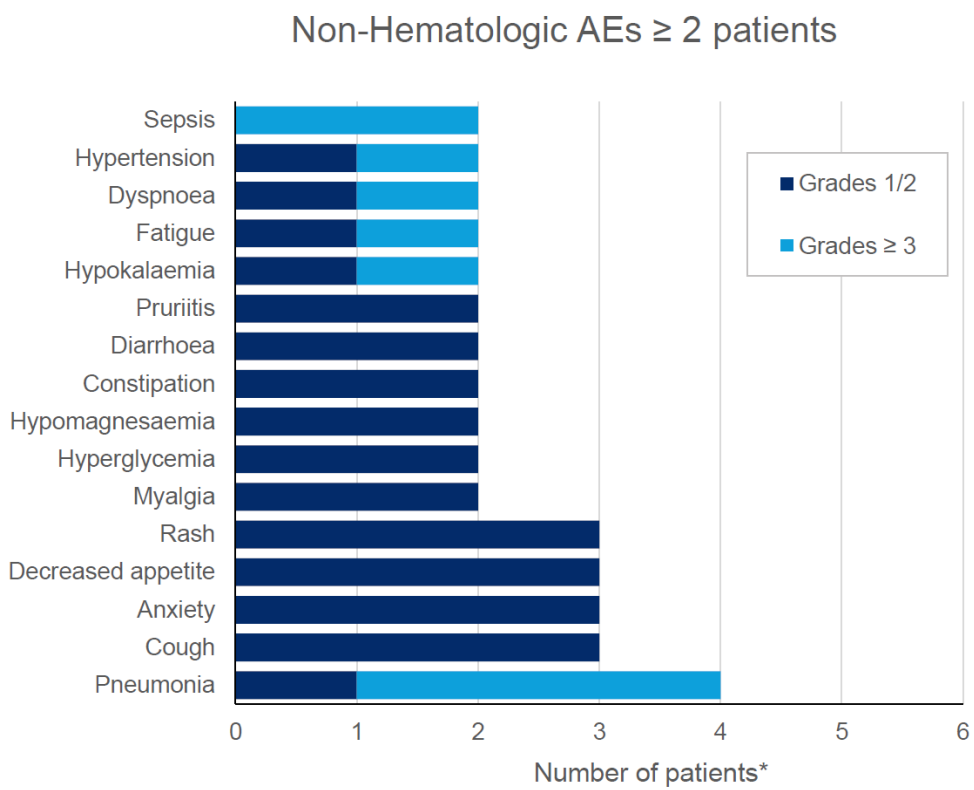
Median Time to CR/CRi

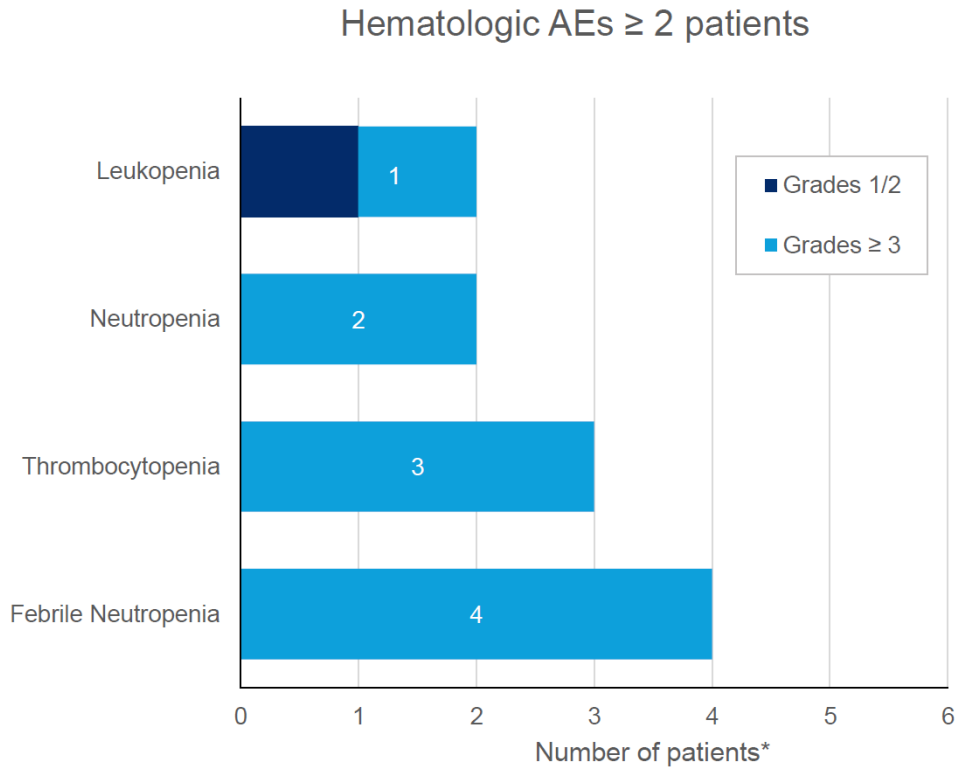
33 days (range 25–88 days)

CR = complete response; CRi = CR with incomplete hematologic recovery;

4/5 patients with CR/CRi had high monocytic expression score (MES) associated with venetoclax resistance

Safety summary





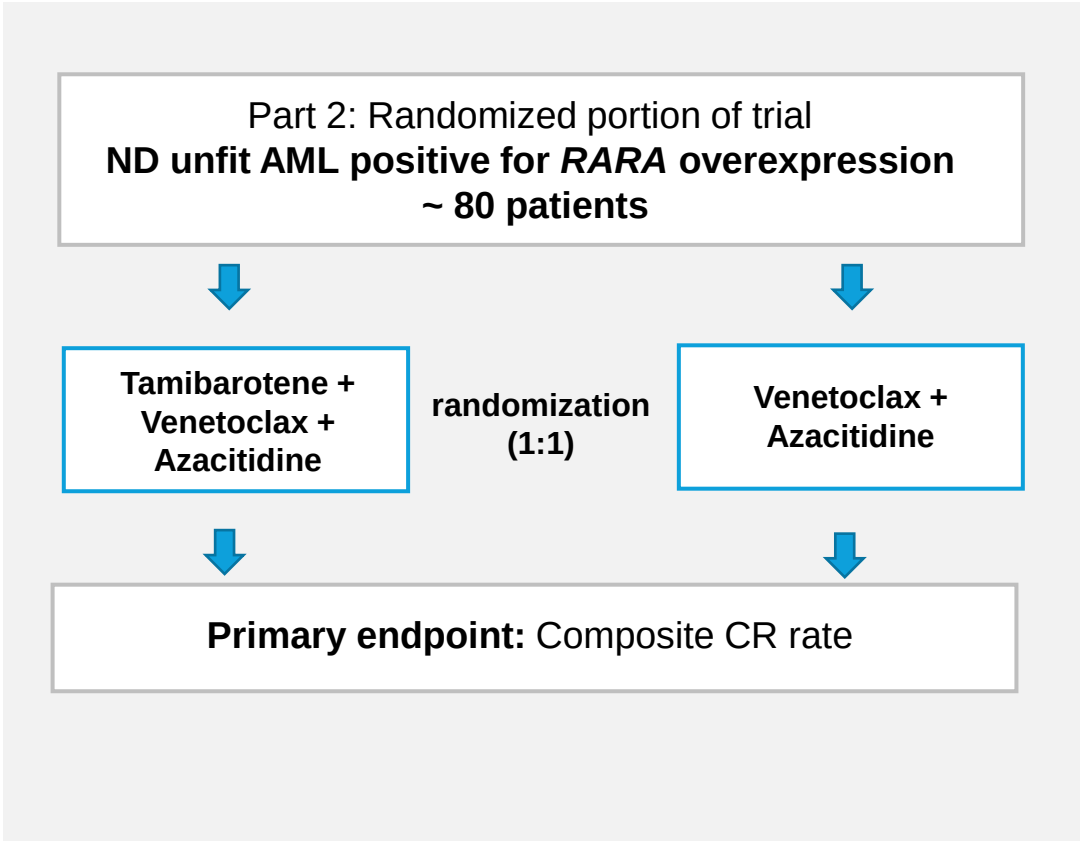
- Myelosuppression is comparable to reports of venetoclax + azacitidine in this population
- The majority of non-hematologic AEs are low grade and reversible
- SAEs were reported in 6 patients; the most frequent (occurring in ≥ 2 pts) included febrile neutropenia (4 pts) and pneumonia (3 pts)
- Median duration of therapy was 76.5 days (20-104); Median duration of follow-up was 107 days (56-314)

*6 patients with AE data available at time of data cut off 13OCT 22

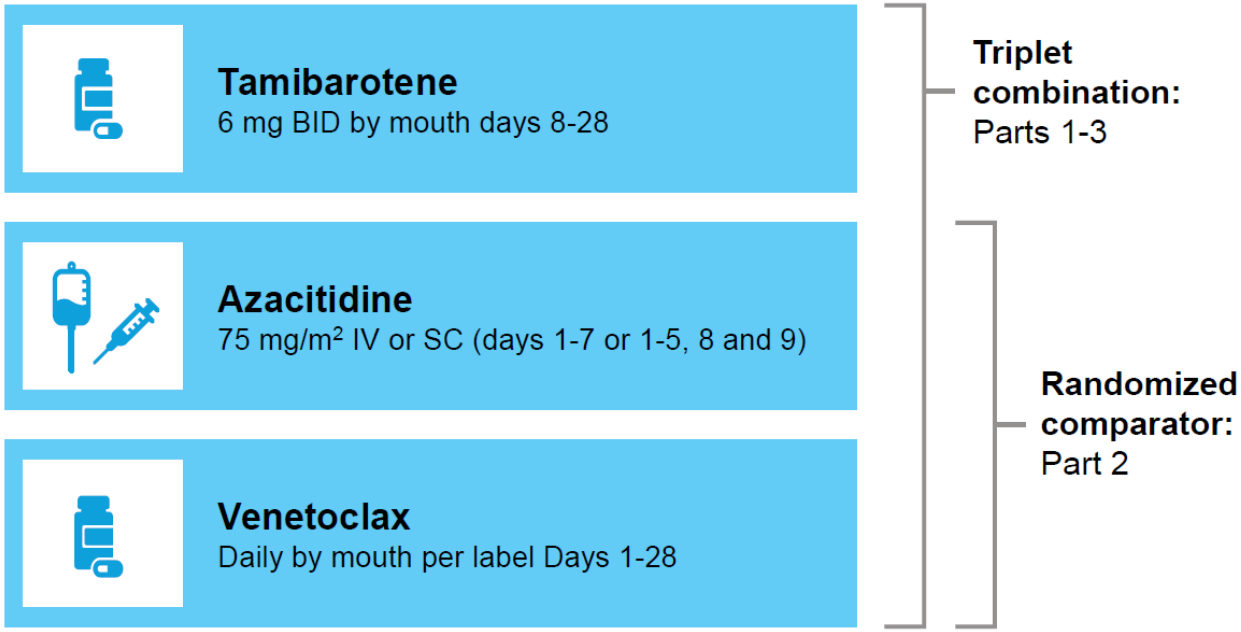
Safety lead-in data conclusions

- Early results of tamibarotene/ven/aza in newly diagnosed unfit AML patients with *RARA* overexpression demonstrate 83% (5/6) CR/CRi rate with rapid onset of action
- No new safety signal identified with triplet tami/ven/aza compared to ven/aza
- Data support initiation of the randomized portion of SELECT-AML-1 comparing tami/ven/aza to ven/aza in patients with *RARA* overexpression

Plan to initiate randomized portion of the SELECT-AML-1 trial



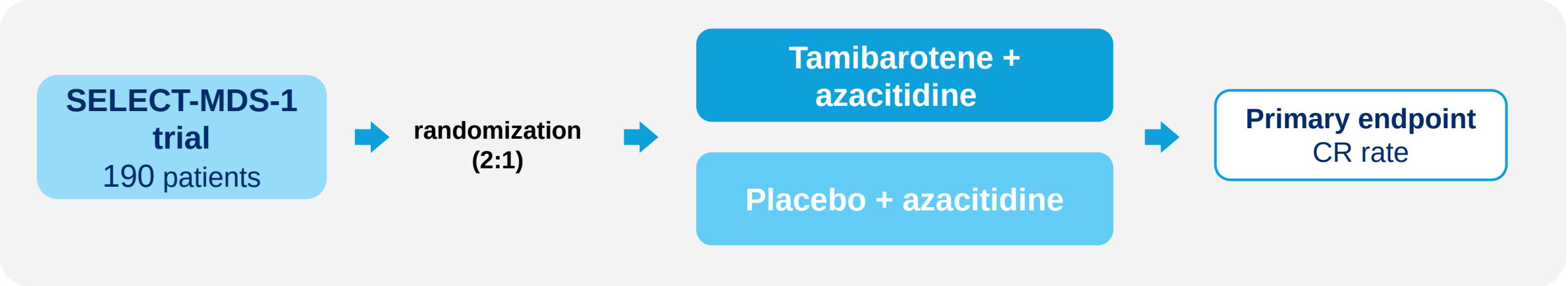
Dosing Regimen



Recently published guidance on venetoclax dose modifications (ELN 2022) will be incorporated into both arms of the randomized portion of the trial.

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

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



- Robustly designed, double-blind, placebo-controlled study
- 90% power to detect a difference in CR rates between experimental and control arms
- 2:1 randomization with one-sided alpha of 0.025
- FDA feedback supports:
  - Focus on population with *RARA* overexpression
  - CR as primary endpoint for approval
  - Azacitidine as appropriate comparator

Key Milestones

Phase 3 data	4Q23/1Q24
Potential NDA filing	2024

SYROS

Treatment landscape in newly diagnosed unfit AML

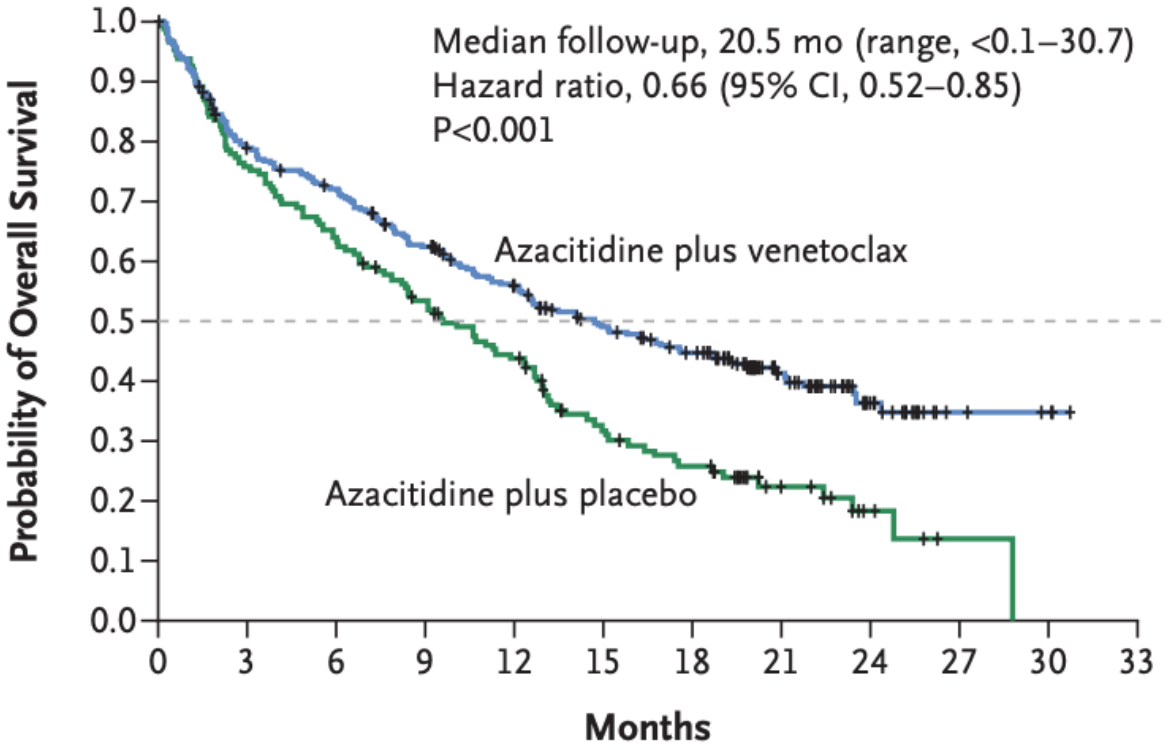
DAN POLLYEA, M.D., M.S

Acute Myeloid Leukemia

- Most common acute leukemia in adults; ~20,000 cases/year in US[1]
- Impacts elderly with median age 68[1]
- Historically only relevant treatment was intensive induction chemotherapy which was not appropriate for older/comorbid patients
- Questions of ”fitness” for intensive induction were important
- Disconnect between a standard of care treatment and the reality of the disease, plus improved understanding of its molecular basis, led to approvals for multiple therapies starting in 2017

[1]Shallis et al. Blood Reviews, 2019

Venetoclax: Most Impactful New Therapy



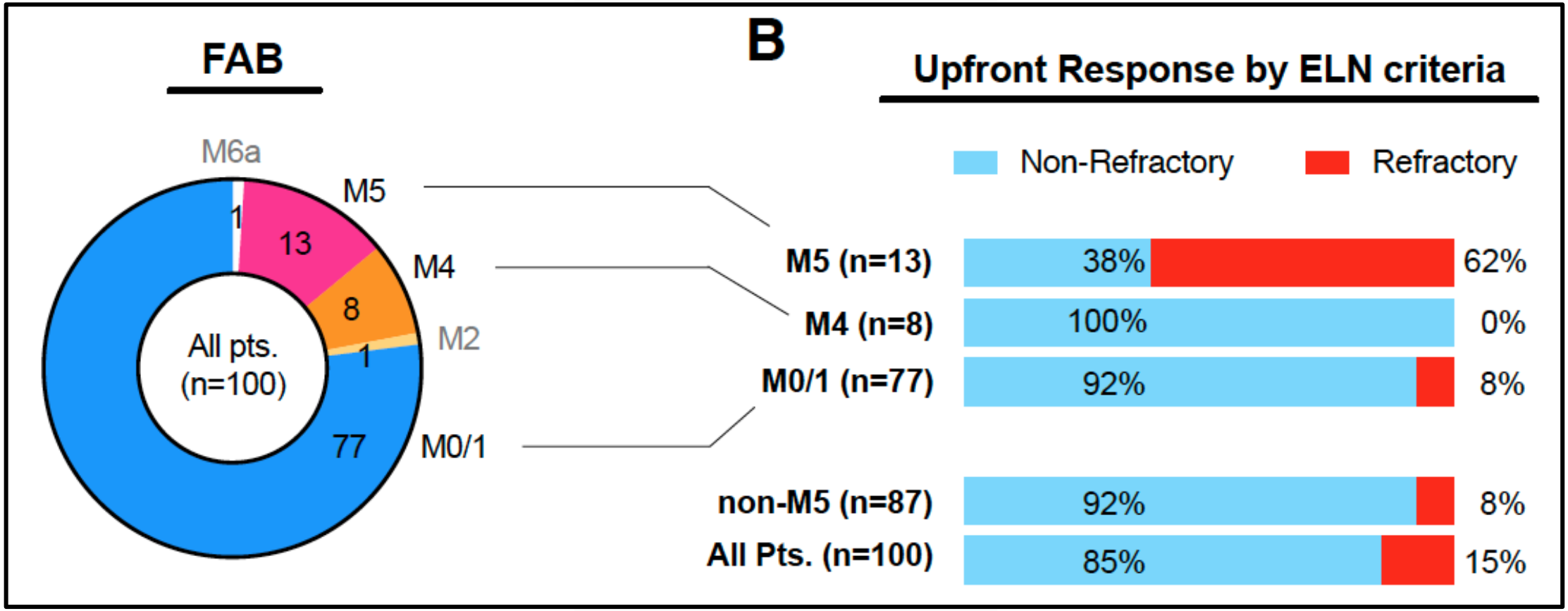
- Clinically (and statistically) meaningful improvement in outcomes for “unfit” newly diagnosed AML
- Widespread use
- Makes “fitness” discussions less relevant
- But not a panacea

DiNardo et al, NEJM 2020

Venetoclax Resistance

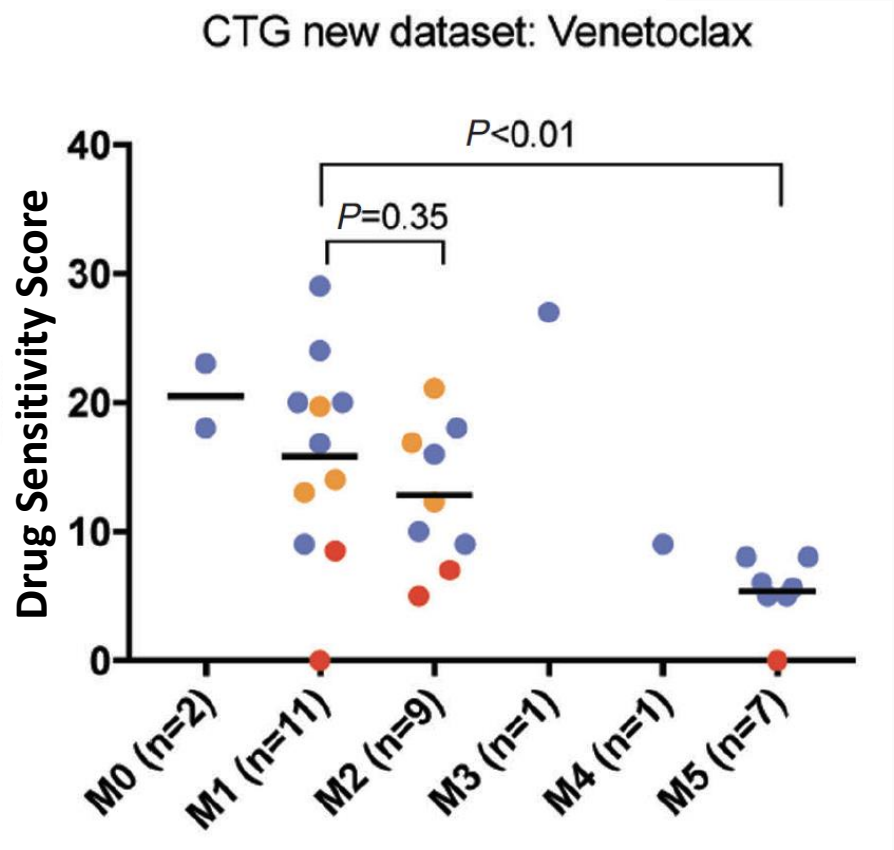
- ~30% do not respond
- Almost all responders will relapse
- “Traditional” risk factors do not always seem to apply
- What factors predict venetoclax resistance?

FAB-M5: The Ven/Aza Soft Spot



Pei et al, Cancer Discovery 2020

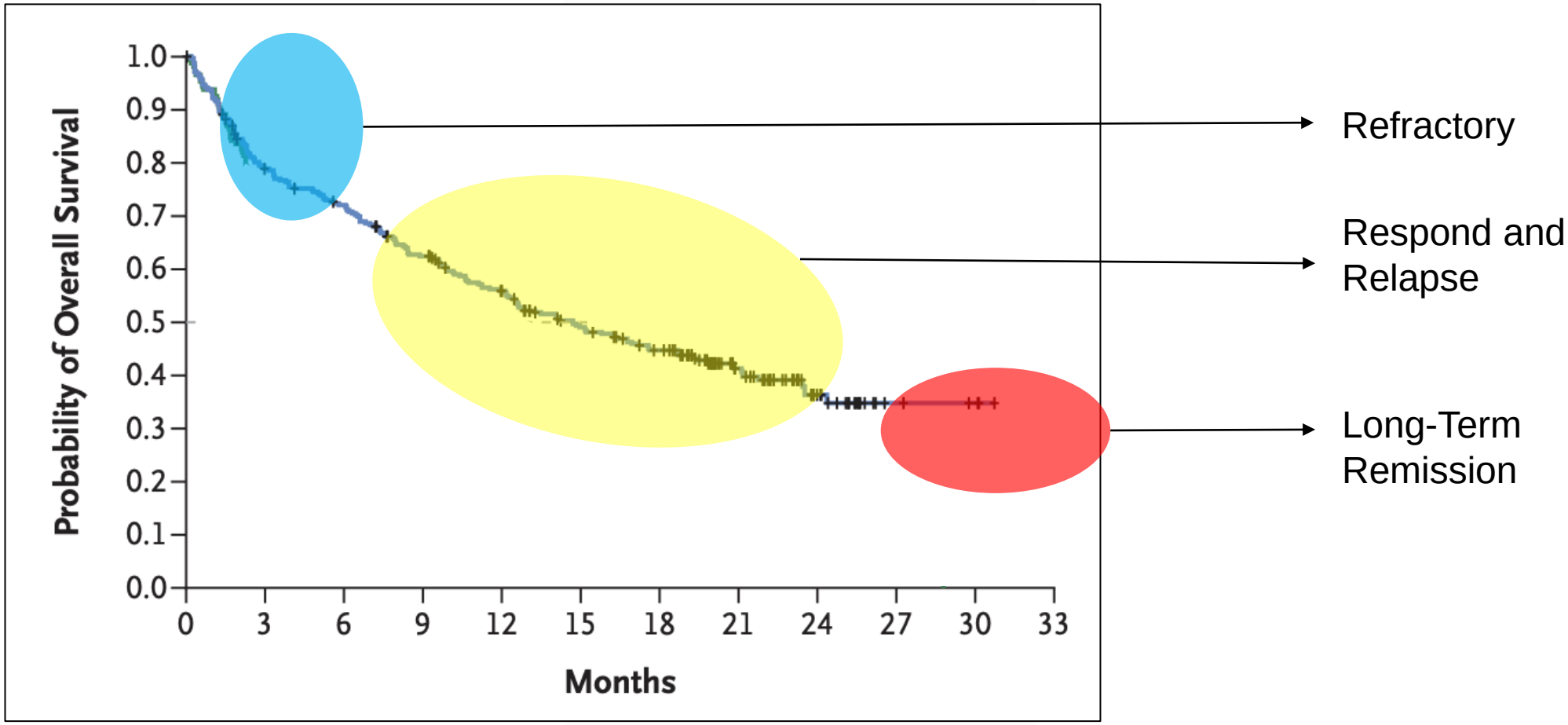
Similar Observations Published



Kuusanmaki et al, Haematologica 2020

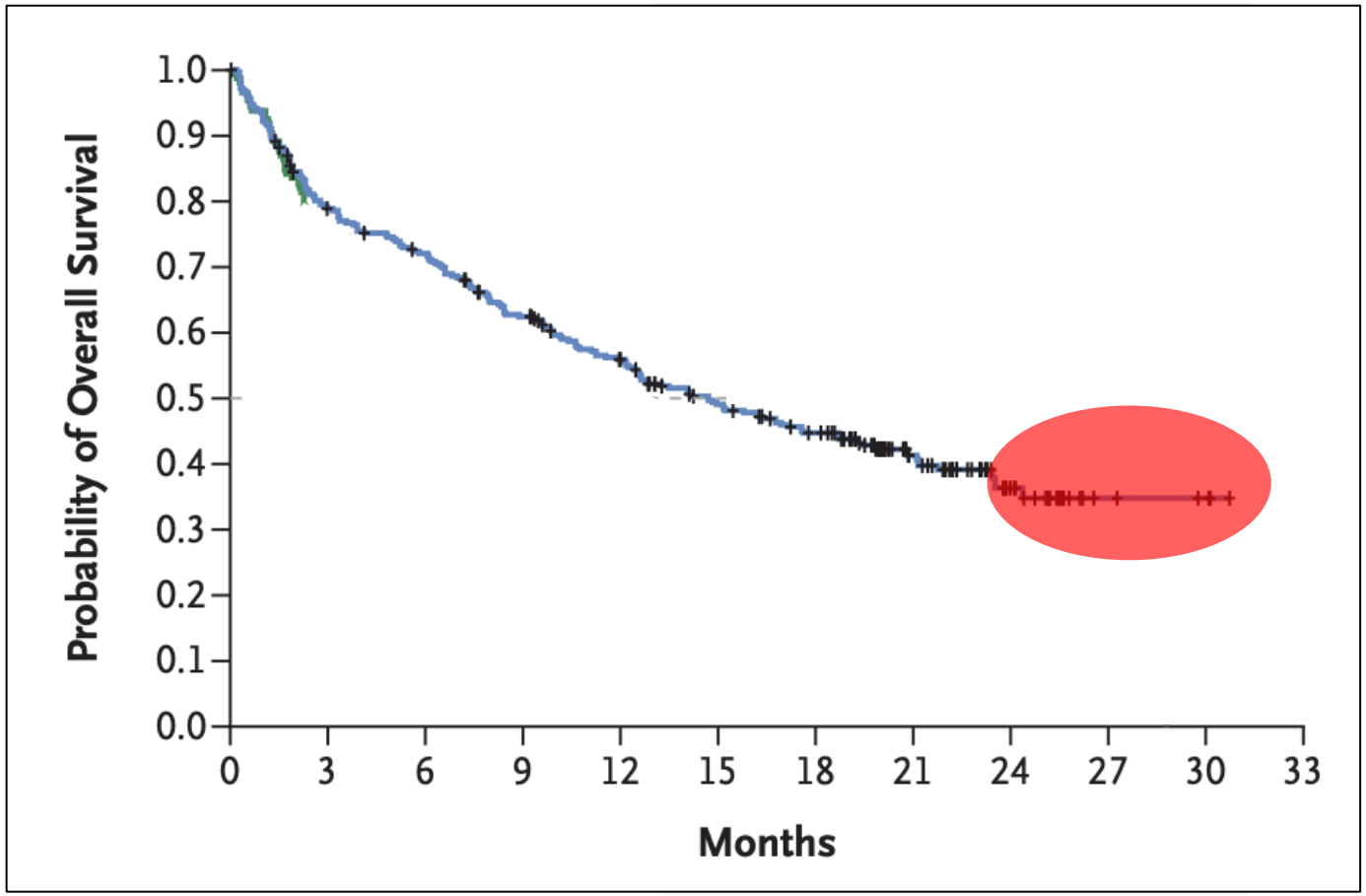
- Bottomly et al, Cancer Cell 2022
- White et al, NPJ Precis Oncol 2021
- Zhang et al, Nat Cancer 2020

My Vision for a Post-Ven/Aza Future



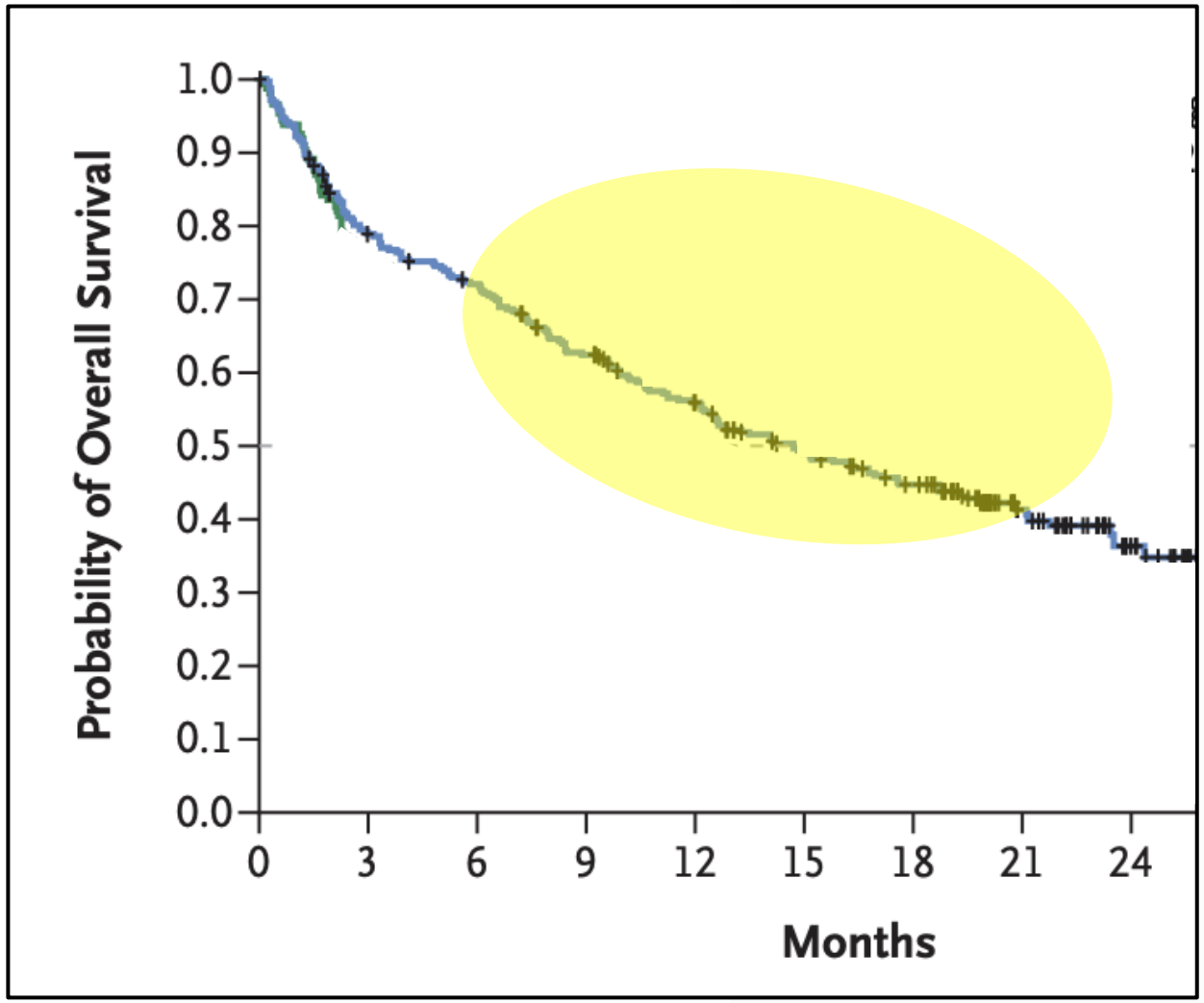
DiNardo et al, NEJM 2020

Long Term Responders



- Identify who these patients are and leave them alone
- Primary effort should be to determine how to minimize therapy

What To Do For the Majority of Patients Who Will Respond and Then Relapse?



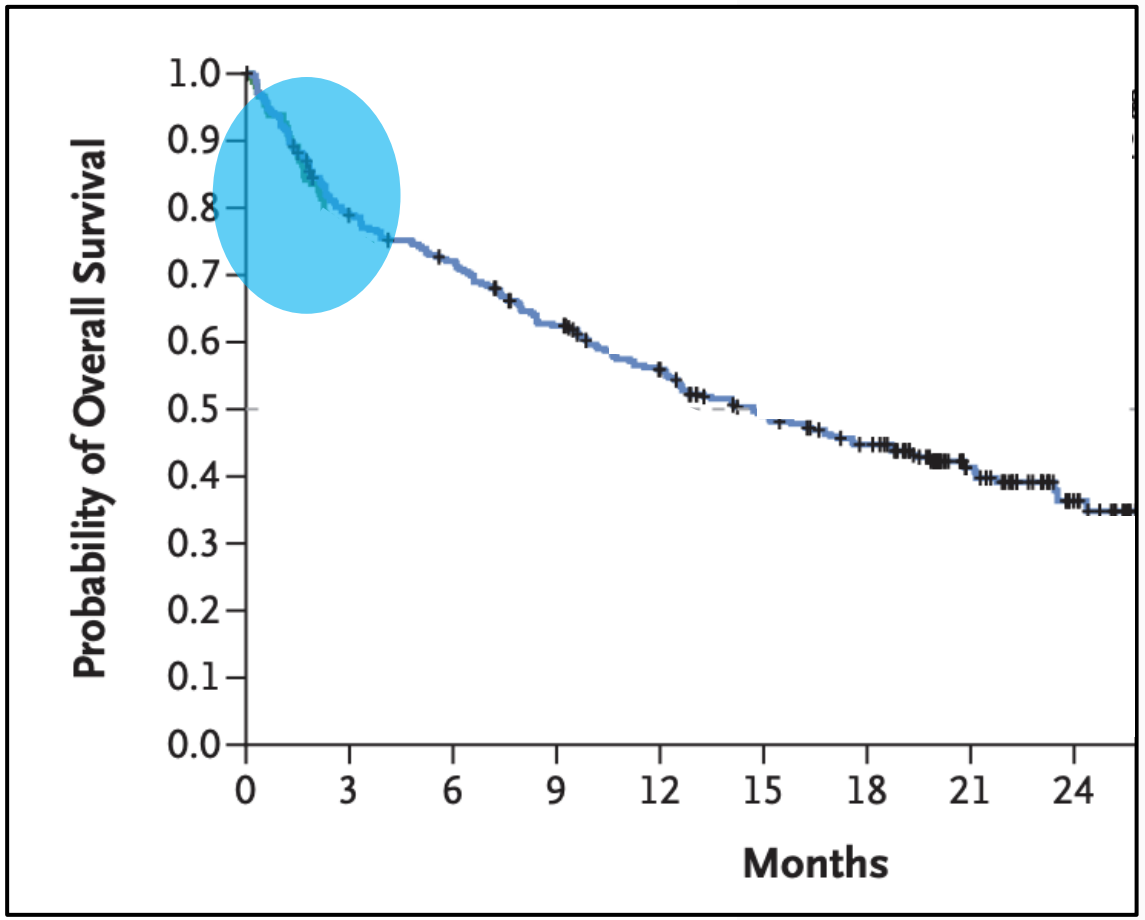
- Relapse after frontline ven/aza associated with very poor outcomes[1,2,3]

Until we have more effective treatments the only logical strategy:

<u>Prevent Relapse</u>

[1]Maiti et al, Haematologica 2021
[2]Zainaldin et al, Leukemia Lymphoma 2022
[3]Bewersdorf et al, Leuk Res 2022

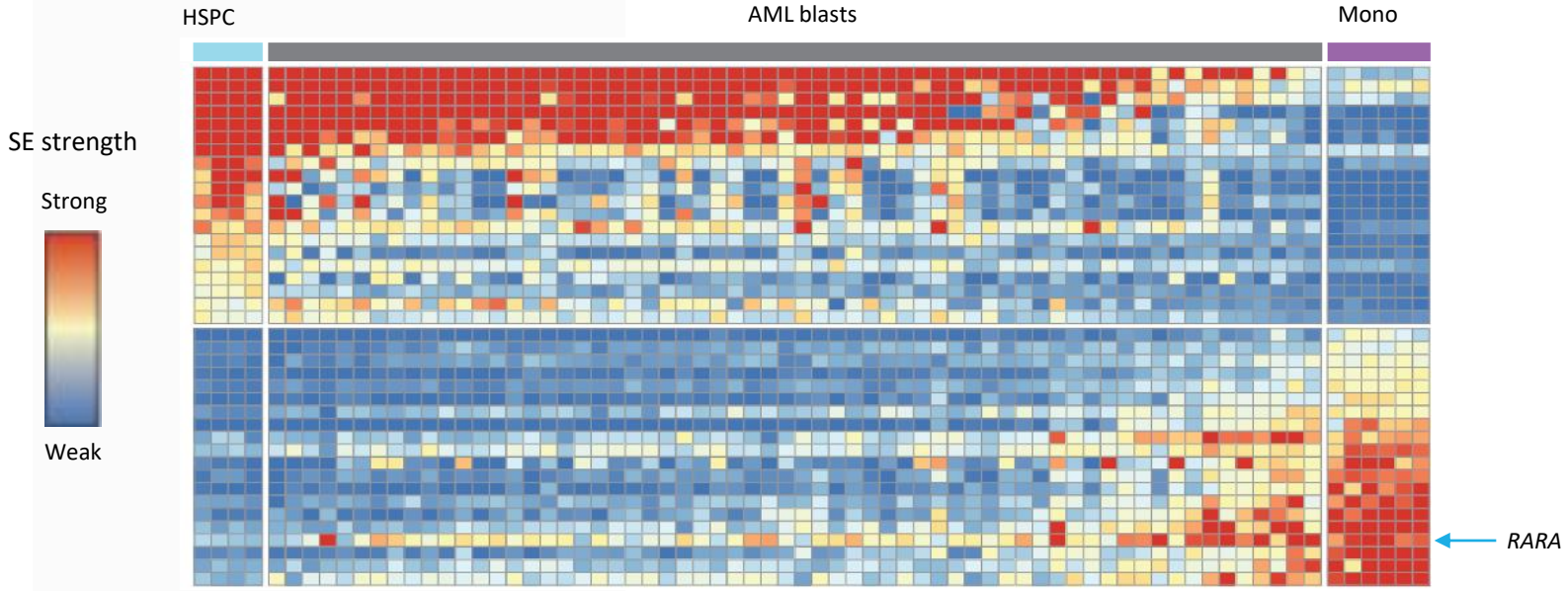
Refractory Patients: Can We Overcome Resistance to Ven/Aza (or Replace it)?



- No indiscriminate triple combinations
- Understand this biology, recognize and try to target it

Overcoming Resistance with RARα Agonist Tamibarotene

- ~1/3 non-APL AML overexpresses *RARA*
- These are associated with features of monocytic AML
- Monocytic AML responds poorly to ven/aza alone
- Phase 2 study of ven/aza vs tamibarotene + ven/aza (NCT04905407)



McKeown et al, Cancer Discovery 2017

Where the Field is Going vs Where the Field Should go

CONVENTIONAL WISDOM

- AML drug development will proceed like multiple myeloma
- Develop potent therapies and use them all up-front

MY BET

- Continue to develop drugs for specific niches based on biological observations (biologically targeted therapies)
- Ven/aza is the framework but be selective of the drug and situation in which combinations to this backbone will occur
- Focus on oral well-tolerated therapies that could combine with ven/aza based on non-overlapping MoA

Closing Remarks

Nancy Simonian, MD
CEO

Key takeaways from today’s event

- Encouraging safety lead-in data from SELECT-AML-1 suggest tamibarotene can augment standard-of-care to improve outcomes for newly diagnosed, unfit AML patients with *RARA* overexpression
- Today's results add to growing body of evidence demonstrating encouraging, consistent data across multiple trials and reinforces our clinical development strategy
- Planning to initiate randomized portion of SELECT-AML-1 trial in 1Q 2023; data expected 2023/2024
- Large targeted populations and frontline settings with sizeable market opportunities
- Tamibarotene offers an optimal product profile to address unmet needs: biologically targeted, oral drug, favorable tolerability, novel mechanism of action


SYROS