UCI 趙 Chao Family Comprehensive Cancer Center

Adding pitavastatin to venetoclax-based therapies for leukemias:
An experience in drug re-purposing

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Heme Malignancies: Major Concepts

- Aggressive = chance of cure
  - Indolent = incurable (but manageable!)

- Staging is different than solid tumors
  - Prognosis is typically driven by cytogenetics
    - -17p (p53 deletion) = bad

How to Categorize Lymphomas/Leukemias

- Myeloid vs lymphoid
  - Lymphoid: B vs T
- Indolent (slow growing) vs aggressive (fast growing)

- Mostly in blood (high white blood cell count) = leukemia
- Mostly in lymph nodes (or other places you might find white blood cells): lymphoma

A phase 1 study of adding PIT to VEN-based therapies in AML and CLL/SLL

Eligibility Criteria

- Patients with diagnosed AML otherwise eligible for induction therapy with azacitidine (AZA) and venetoclax (VEN) per SOC
- Patients with CLL/SLL could receive VEN with either obinatuzumab or rituximab
- Patients already on a statin were eligible if their other statin was stopped for 72 hours before starting PIT
- For DL1 (2mg) — CrCl > 30ml/min
  - For DL2 (4mg) cohort — CrCl > 60ml/min

Study Design

- Phase 1
- Single center
- 3+3 design
- 2 dose levels: 2mg, 4mg
  - DL -1 if needed: 1mg
  - Planned sample size 6-12
- Primary endpoint: safety, RP2D

Patient Enrollment

- 14 patients signed informed consent
  - 6 were ineligible
  - 2 withdrew consent before starting PIT
- 6 patients were treated
  - 2 had AML
  - 2 CLL, 2 SLL — all 4 received ven + obinatuzumab
- 1 subject was on rosuvastatin prior to enrollment
  - The other 5 were statin-naive

All pts achieved CR!

Clinical characteristics and outcomes of treated patients

Treated patient	PIT dose	Disease with relevant mutations	Best response	Outcome	Grade 3-5 adverse events•
1	2 mg	AML (+9; ASXL1, TET2, ETV6; progression from MDS)	CR	Achieved CR after 1 cycle but was MRD-positive on flow cytometry. Passed away shortly thereafter due to infection.	Leukopenia (grade 3), neutropenia (4), thrombocytopenia (4), lung infection (5)
2	2 mg	CLL (11q-, 13q-, unmutated IgVH)	CR	Treatment discontinued early due to neutropenia but was MRD-negative by clonoSEQ negative at the end of therapy. Had a history of cirrhosis and passed away during admission for acute encephalopathy; CLL was in remission when passed.†	Neutropenia (grade 4), pancreatitis (3)
3	2 mg	SLL (11q-; IgVH unknown)	CR	Was in remission at the last follow-up.†	
4	4 mg	AML (del 20q, +8; progression from MDS)	CR	Treatment discontinued due to recurrent pericardial effusion, unclear if related. Resumed AZA for treatment of MDS, but AML remained in remission at the last follow-up.	Febrile neutropenia (grade 3), vasovagal reaction (3)
5	4 mg	CLL (IgVH-negative, FISH unable to be done)	CR	Clinically remains in remission. MRD positive by peripheral blood flow (0.01%).†	Leukopenia (grade 3), neutropenia (4), thrombocytopenia (4), anemia (3)
6	4 mg	SLL (trisomy 12; IgVH status unknown)	CR	In CR based on CT scans. MRD-negative by peripheral blood flow.	

Brem et al, Blood Neoplasia, 2024

In Vivo response to VEN and PIT via flow

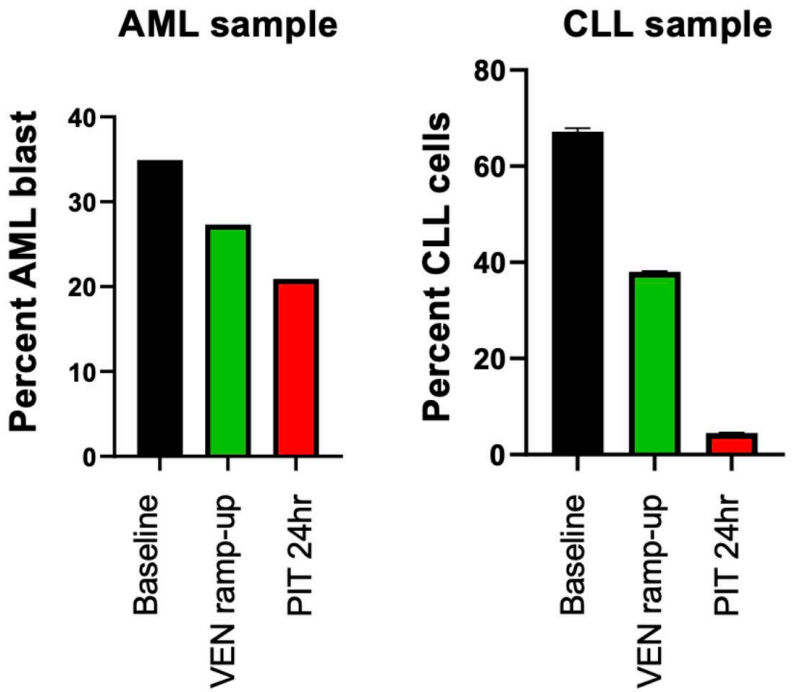


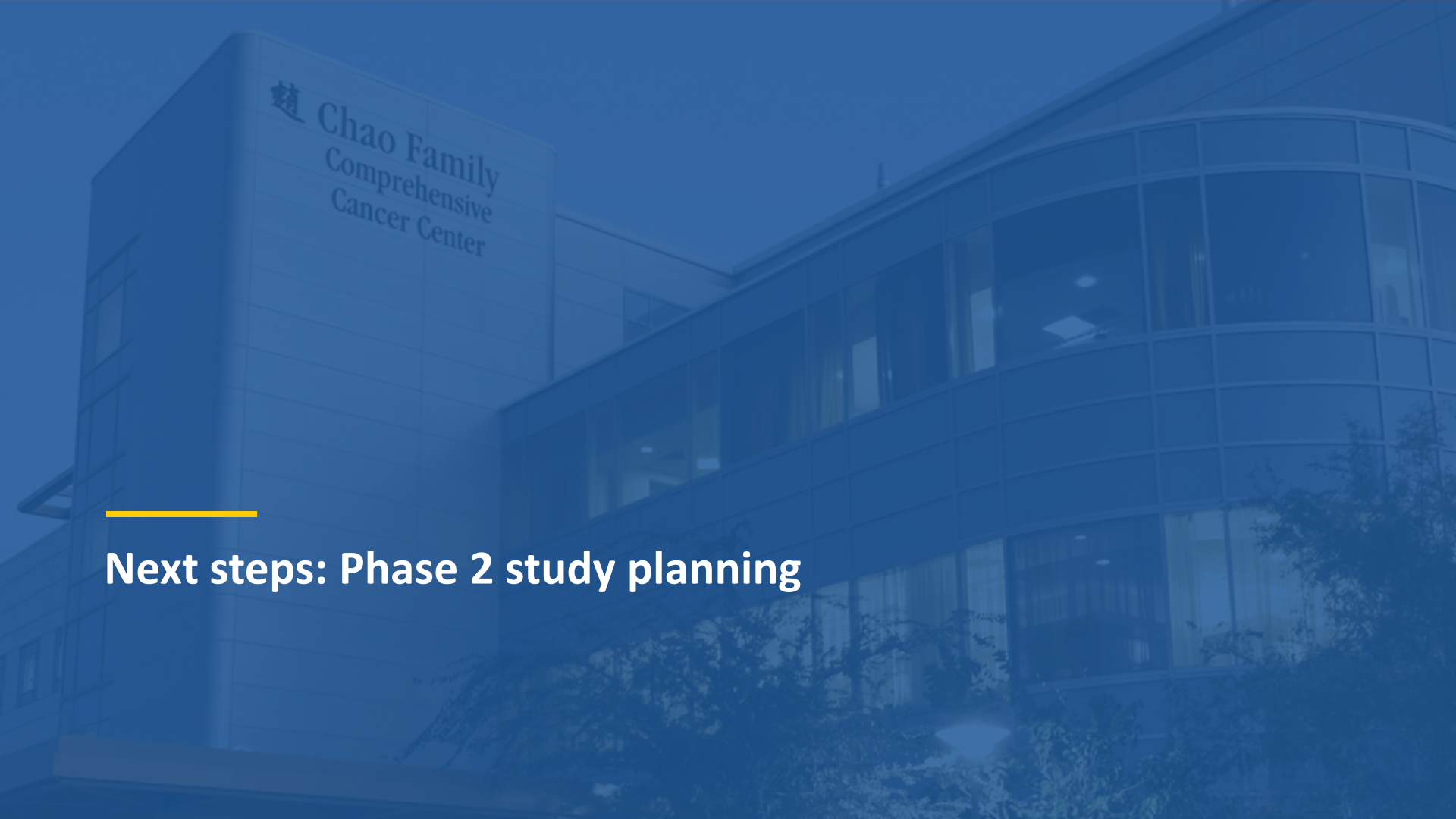
Figure 4: % AML blasts ($CD45^{lo}CD33+$) or CLL cells (CD19+CD5+) was assessed by flow cytometry using PBMCs from trial subjects. Blood samples were collected at **diagnosis** (baseline), after **venetoclax** ramp-up, and 24hr after the first dose of **pitavastatin** at dose level 1 (2 mg).

Study Take Aways

- RP2D: 2mg
- Toxicities were not worse or different than what would be expected with SOC therapies alone

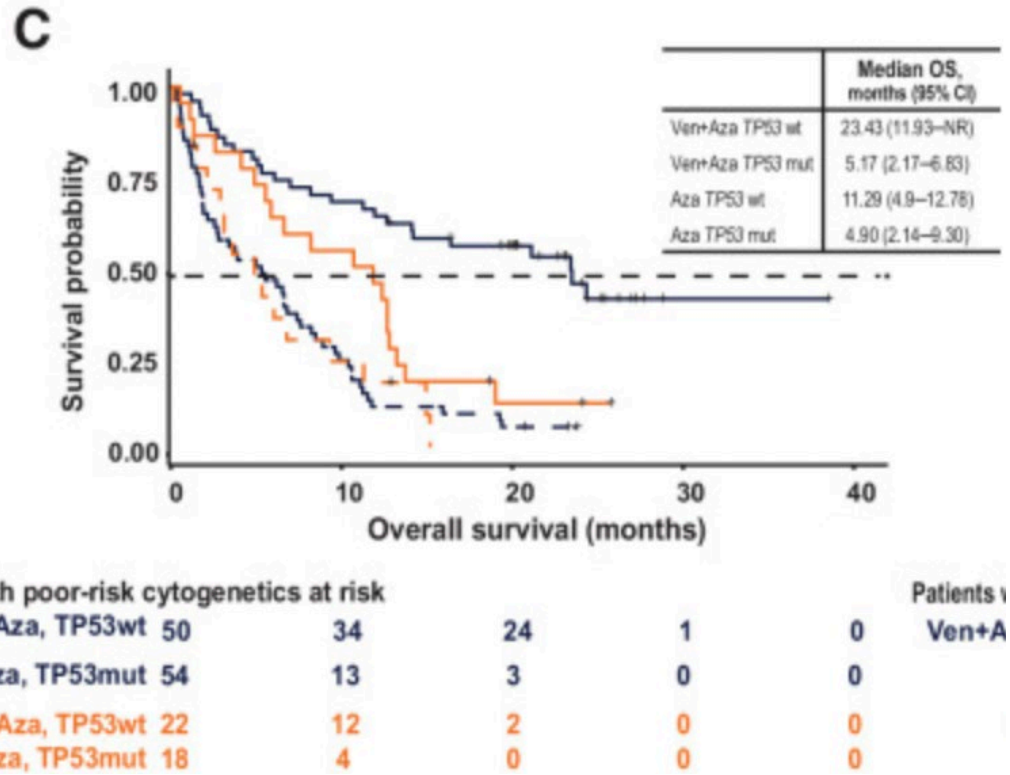
What have we learned?

- Most patients with AML receiving aza/ven do not have a CrCl of > 60
- There's a lot of room for improvement for our AML therapies
  - Patients with CLL/SLL on ven-based therapies do very well, and it's hard to make this better with out a very big or very long study
- Funding studies like this is hard!



Next steps: Phase 2 study planning

AML with TP53 aberrations have worse outcomes



Pollyea DA et al, 2022

AML with TP53 aberrations may particularly benefit from statins

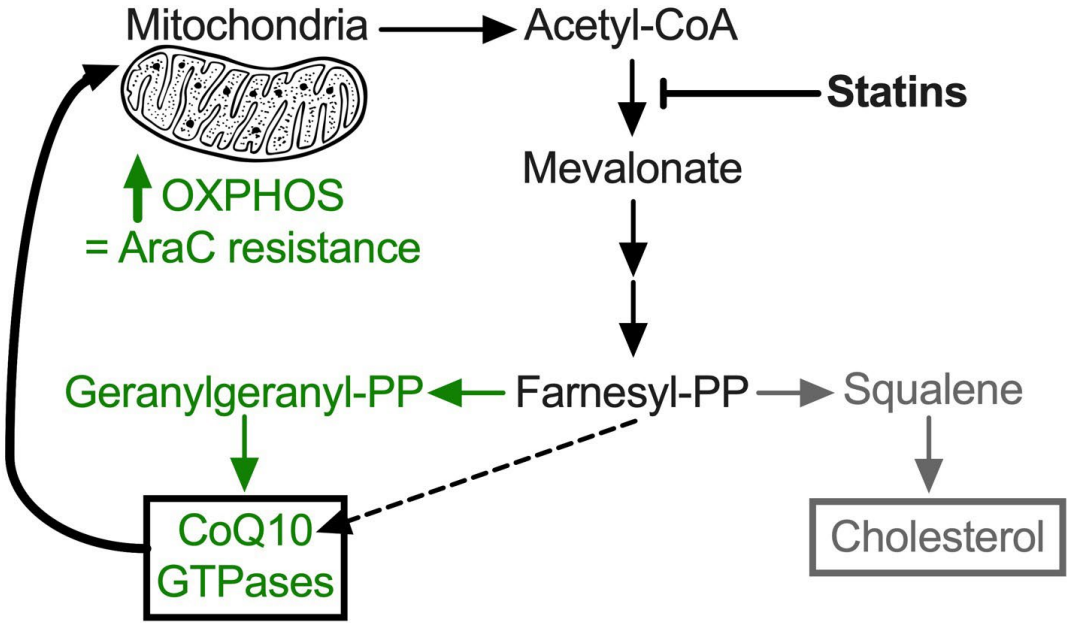


Figure 1. Proposed mevalonate pathway dependencies in chemoresistant *TP53* MT AML.

Next steps: Phase 2

- AML patients whose disease has a 17p deletion or other TP53 aberration
- Primary endpoint: OS
  - Secondary endpoints: rates of MRD undetectability, CR/CRi rate
  - Correlative endpoints — both looking at both modulation of the BCL2 pathway and cardiac outcomes
- N = 70
- Multiple sites: UC Heme Consortium (Davis and SF), U Penn, Roswell Park
- DoD grant submitted 

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Questions?

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