# A Phase 1a/b Dose Escalation Study of the MYC Repressor APTO-253 in Patients with Relapsed or Refractory AML or Higher-risk MDS

**Presented by:** Rafael Bejar[1,2]

**Authors:**

Rafael Bejar[1,2] Hongying Zhang[1] Nasrin Rastgoo[1] Khalid Benbatoul[1]
Yuying Jin[1] Mathew Thayer[1] Susan Sheng[1] Victor Montalvo-Lugo[1]
Gregory Chow[1] Jotin Marango[1] Stephen Howell[2] William Rice[1]

[1] Aptose Biosciences, San Diego, CA
[2] UC San Diego, Moores Cancer Center, La Jolla, CA

**ASH 2020**

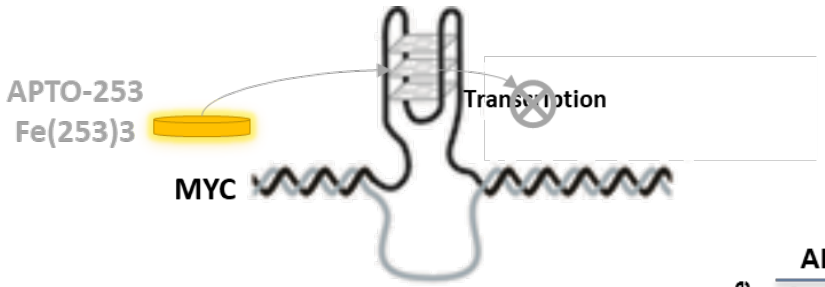
**ASH Virtual Abstract Presentation #1042**

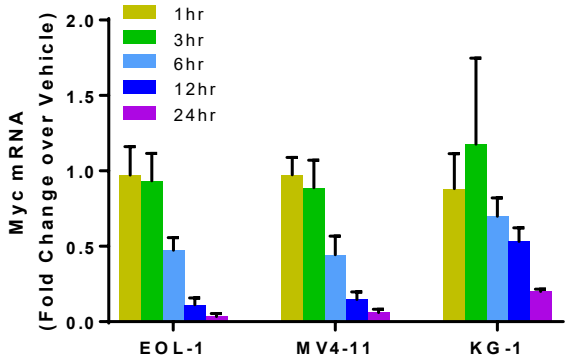
Dec 5th, 2020

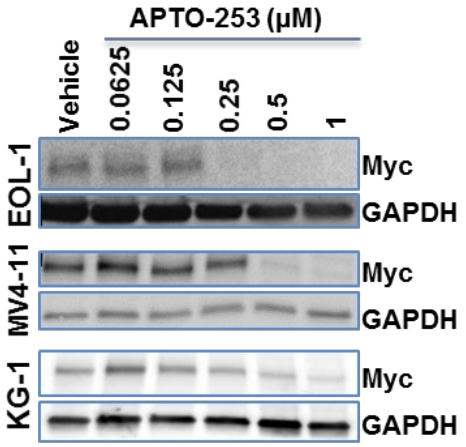
## **Presenter Disclosures**:

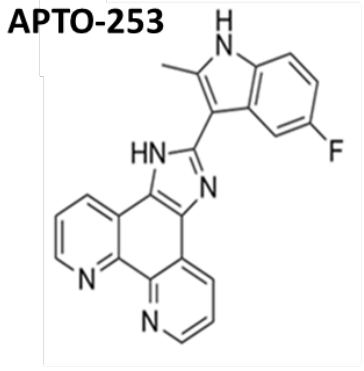
- Aptose Biosciences – Chief Medical Officer and Senior Vice-President
- Bristol Myers Squibb – Consultant, DSMB Chair, Research Funding
- Gilead – Consultant, Data Monitoring Committee
- Takeda – Consultant, Research Funding
- Daichi-Sankyo – Consultant
- AbbVie – Consultant
- Astex – Consultant, Data Review Committee

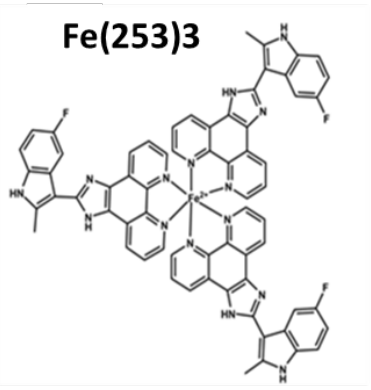
# APTO-253, a Unique Small Molecule Repressor of MYC in Clinical Development




- **The MYC oncogene is dysregulated in > 50% all human cancers and generally considered "undruggable"**
- **APTO-253 targets a conserved G4 structure in the promoter of the MYC oncogene***
  - Reduces MYC mRNA and protein levels, causes induction of p21
  - Triggers cell cycle arrest at G0-G1 phase and induces apoptosis
  - Broad killing of primary mononuclear cells isolated from bone marrow of patients with AML, MDS, or MPN**
- **APTO-253 binds $Fe^{2+}$ intracellularly and forms iron adduct $Fe(253)_3$ – an active drug species with similar *in vitro* anti-tumor potency as its monomeric form*****
- **APTO-253 was granted orphan drug designation for the treatment of AML by the US FDA**

*Local et al., 2018; **Kurtz, et al., 2017; Tsai, et al., 2018

# APTO-253 Phase 1a/b Dose Escalating Clinical Trial Ongoing and Now in Dose Level 5

## Objectives

Ongoing Phase 1 a/b, open-label, single arm, multicenter, 3 + 3 dose-escalation clinical study of APTO-253 in patients with relapsed or refractory AML or high-risk MDS (NCT02267863).

**Primary objectives:**

- Assess safety and tolerability of APTO-253
- Determine MTD and DLT of APTO-253 given on days 1, 8, 15 and 22 of each 28-day cycle
- Determine recommended Phase 2 dose (RP2D)

**Key secondary objectives:**

- Assess PK profile and PD activity
- Obtain preliminary evidence of antitumor activity

## Dose Escalation Phase

- Patients administered **IV infusion**
- **Weekly on days 1, 8, 15, and 22** on a **28-day cycle**
- Planned 9 dose levels
- Planned expansion cohorts

## PATIENT POPULATION

**Relapsed or refractory AML or high-risk MDS** (with > 10% bone marrow blasts) who have **been failed by or be intolerant** to all standard therapies

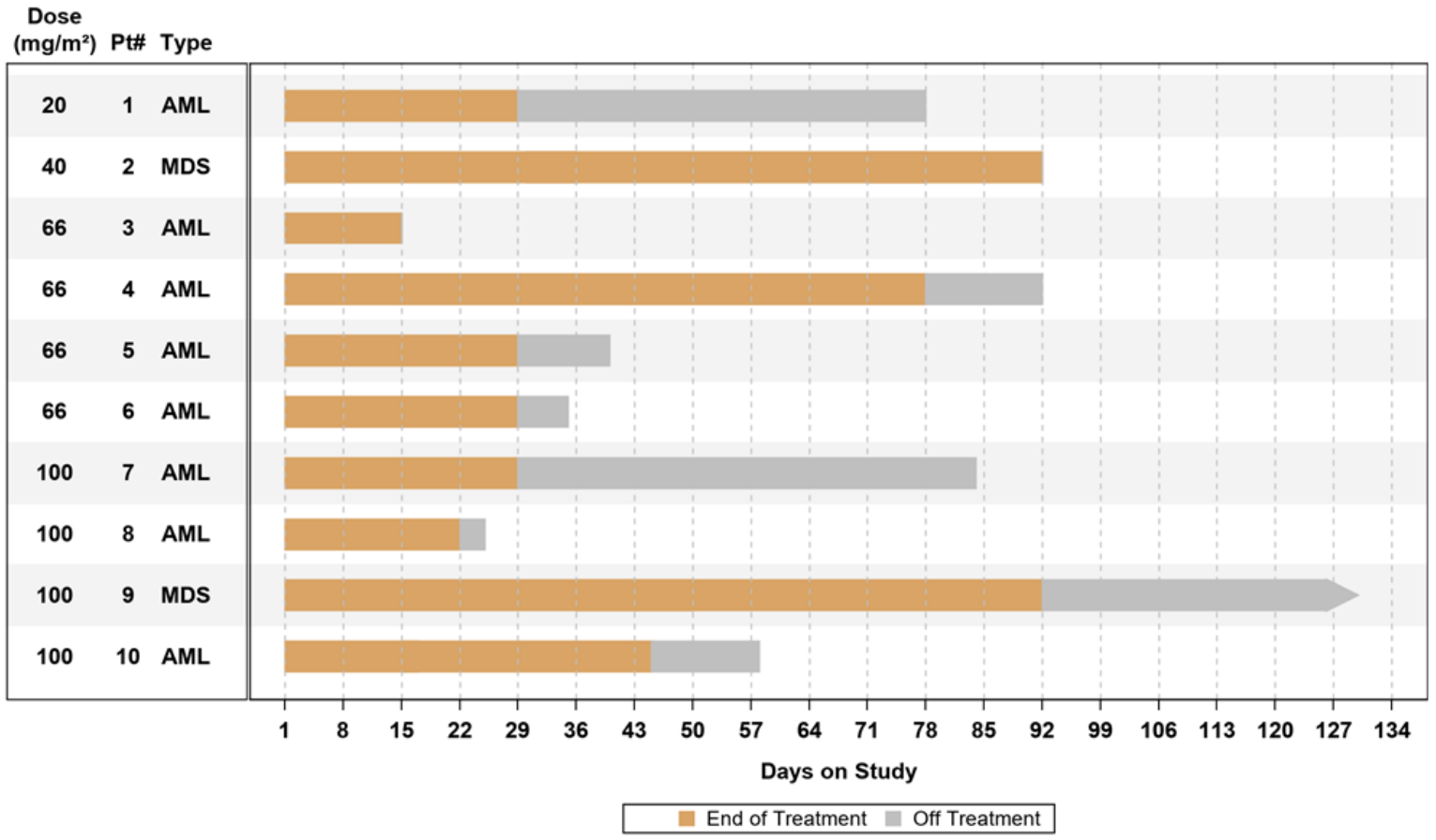
| Dose Level | Dose | Status | Patients |
|---|---|---|---|
| 1 | 20 mg/m2 | Completed | AML |
| 2 | 40 mg/m2 | Completed | MDS |
| 3 | 66 mg/m2 | Completed | AML |
| 4 | 100 mg/m2 | Completed | AML & MDS |
| 5 | 150 mg/m2 | Ongoing | |
| 6 | 210 mg/m2 | Planned | |
| 7 | 280 mg/m2 | Planned | |
| 8 | 350 mg/m2 | Planned | |
| 9 | 403 mg/m2 | Planned | |

# APTO-253 has been Administrated to Patients at 20, 40, 66, and 100 mg/m$^2$ Over Multiple Cycles

| Patient Demographics | Cohorts 1 to 4 (N=10)* |
|---|---|
| **Median Age (Range), Years** | **66.0 (41, 85)** |
| **Sex, N (%)** | |
| Male | **5 (50.0%)** |
| Female | **5 (50.0%)** |
| **Ethnicity, N (%)** | |
| Not Hispanic or Latino | **9 (90.0%)** |
| Not Reported | **1 (10.0%)** |
| **Race, N (%)** | |
| White | **8 (80.0%)** |
| Black or African American | **1 (10.0%)** |
| Not Reported | **1 (10.0%)** |
| **ECOG Score, N (%)** | |
| 0 -Normal activity | **1 (10.0%)** |
| 1 -Symptoms, but ambulatory | **4 (40.0%)** |
| 2 -In bed <50% of the time | **5 (50.0%)** |
| **Disease Type / Subtype, N (%)** | |
| MDS | **2 (20.0%)** |
| MDS Type, N (%)** | |
| Primary | **2 (100%)** |
| AML | **8 (80.0%)** |
| AML Type, N (%)** | |
| Relapsed | **5 (62.5%)** |
| Refractory | **1 (12.5%)** |
| Associated with treatment from prior malignancy | **1 (12.5%)** |
| Evolved from MDS | **1 (12.5%)** |
| **RBC Transfusion Dependent, N(%)** | |
| Yes | **10 (100%)** |
| **Platelet Transfusion Dependent, N(%)** | |
| Yes | **9 (90.0%)** |
| **Median Number (Range) of Prior Therapy** | **2.5 (1, 9)** |
| Chemotherapy, N(%) | **6 (60.0%)** |
| Stem Cells | **1 (10.0%)** |
| Targeted and Immunotherapy, N (%) | |
| Hypomethylating Agent | **9 (90.0%)** |
| BCL-2 Inhibitor | **6 (60.0%)** |
| Kinase Inhibitor*** | **2 (20.0%)** |
| Immune Cell Therapy | **1 (10.0%)** |
| Anti-CD123 Antibody Drug Conjugate | **1 (10.0%)** |
| Anti-CD123 Targeted Toxin | **1 (10.0%)** |
| Anti-CD33 Antibody Drug Conjugate | **1 (10.0%)** |
| Anti-PD-1 Antibody | **1 (10.0%)** |

* Data-cut date: Oct. 5, 2020; ** % of MDS or AML patients

*** One patient was on FLT3i Midostaurin; another patient on JAKi Ruxolitinib



# APTO-253 Safety and Tolerability Profile

## APTO-253 Well Tolerated

- **Only 1 TEAE of grade 3 or greater (fatigue, considered possibly drug-related) has occurred as of Oct 5, 2020**
- **No DLT or APTO-253 related SAEs in patients treated at dose levels 1 to 4**

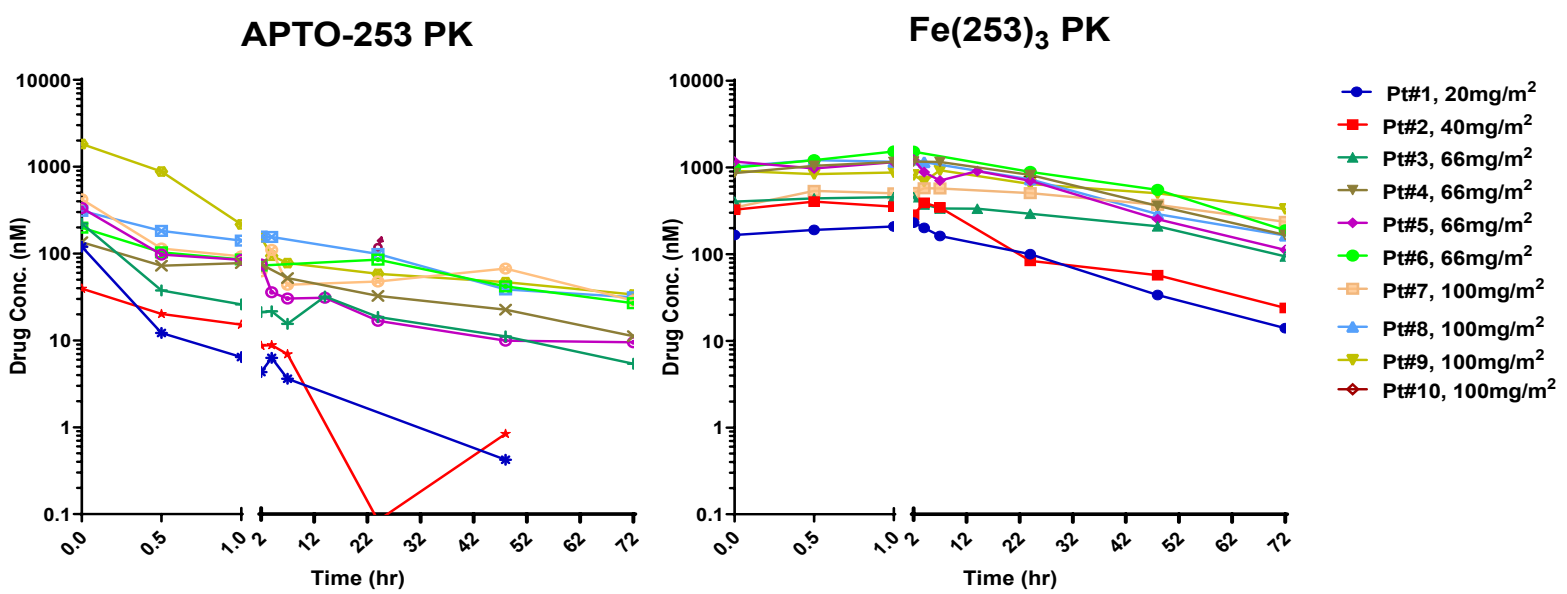
| Events | Cohorts 1 to 4 (N=10) |
|---|---|
| Any Treatment Emergent Adverse Events (TEAEs) | 10 (100%) |
| Any TEAEs ≥ Grade 3 | 8 (80.0%) |
| Any APTO-253 Related TEAEs ≥ Grade 3 | 1 (10.0%) |
| TEAE Leading to Treatment Discontinuation | 0 (0.0%) |
| TEAE Leading to Death | 5 (50.0%)* |
| Any Serious Adverse Events | 9 (90.0%)* |

*Unrelated to APTO-253

| APTO-253 Related Treatment Emergent Adverse Events | | |
|---|---|---|
| Preferred Term | Cohorts 1 to 4 (N=10) | |
| | Any Grade, N (%) | Grade 3, N (%)* |
| Fatigue | 2 (20.0%) | 1 (10.0%) |
| Hyperuricaemia | 2 (20.0%) | 0 |
| Alanine aminotransferase increased | 1 (10.0%) | 0 |
| Aspartate aminotransferase increased | 1 (10.0%) | 0 |
| Blood alkaline phosphatase increased | 1 (10.0%) | 0 |
| Blood creatinine increased | 1 (10.0%) | 0 |
| Decreased appetite | 1 (10.0%) | 0 |
| Dizziness | 1 (10.0%) | 0 |
| Haematoma | 1 (10.0%) | 0 |
| Hypoalbuminaemia | 1 (10.0%) | 0 |
| Hypocalcaemia | 1 (10.0%) | 0 |
| Hypokalaemia | 1 (10.0%) | 0 |
| Muscle spasms | 1 (10.0%) | 0 |
| Pyrexia | 1 (10.0%) | 0 |
| Thrombophlebitis | 1 (10.0%) | 0 |
| Upper respiratory tract infection | 1 (10.0%) | 0 |

* No APTO-253 Related TEAEs ≥ Grade 4 as of Oct. 5, 2020

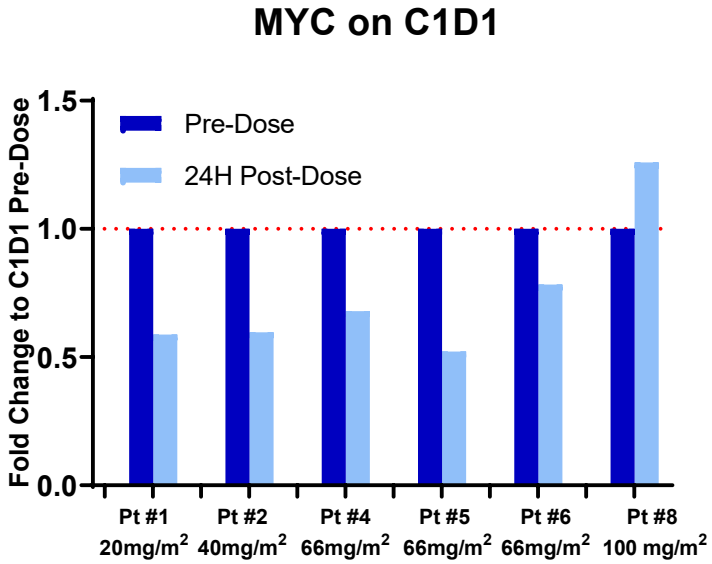
# APTO-253 and $Fe(253)_3$ Pharmacokinetics and MYC Target Engagement










| | APTO-253 | | | | | | Fe(253)3 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $AUC_{0\text{-}72h}$ (nM*h) | | $C_{max}$ (nM) | | $T_{max}$ (h) | | $AUC_{0\text{-}72h}$ (nM*h) | | $C_{max}$ (nM) | | $T_{max}$ (h) | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Cohort 1 (n=1): 20mg/m$^2$ | 108.7 | | 60.0 | | 0.0 | | 5777.0 | | 231.2 | | 2.0 | |
| Cohort 2 (n=1): 40mg/m$^2$ | 151.8 | | 20.2 | | 0.5 | | 8745.0 | | 403.9 | | 0.5 | |
| Cohort 3 (n=4): 66mg/m$^2$ | 2270.5 | 1410.2 | 114.8 | 37.9 | 0.4 | 0.5 | 38677.0 | 15901.9 | 1096.6 | 455.2 | 1.5 | 0.6 |
| Cohort 4 (n=4): 100mg/m$^2$ | 4794.3 | 871.0 | 435.6 | 414.7 | 0.2 | 0.3 | 38196.0 | 6494.6 | 913.2 | 330.8 | 4.3 | 2.5 |

- *qRT-PCR using mRNA isolated from the whole blood cells*
- *Data cut on Oct 5, 2020*
- *Samples of 6 out 10 patients were tested since mRNA extract of the other 4 patients' samples failed to pass assay QC.*

- Plasma levels of APTO-253 and the $Fe(253)_3$ iron adduct were dose proportional
- $Fe(253)_3$ detected in patient plasma at significantly higher concentrations than the APTO-253 monomer
- MYC reduction in 5 out 6 patients 24h after dosing on C1D1 → Proof-of-concept: APTO-253 is a MYC repressor

# APTO-253 Clinical Summary and Acknowledgements

- **Phase 1a/b Ongoing in R/R AML and higher-risk MDS**
  - Targeting MYC to treat patients failing standard therapies
  - Observed safety: well-tolerated, no DLTs or APTO-253 related SAEs occurred as of data-cut on October 5, 2020
  - APTO-253 monomer rapidly transformed to and co-existed with the $Fe(253)_3$ complex in peripheral blood


## Acknowledgements:

- **We thank our study principal investigators, clinical site staff, and most importantly, our patients and their families for their participation in this clinical trial.**


- **To learn more, please go to: http://aptose.com/news-media/presentations**