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

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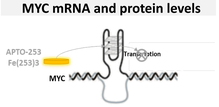
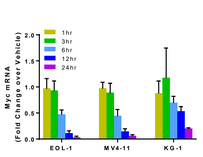
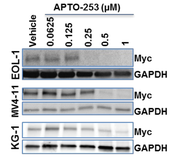
INTRODUCTION

APTO-253 represses expression of the *MYC* oncogene by targeting a conserved G-quadruplex structure in its promoter, down-regulates *MYC* mRNA and protein levels and induces apoptosis in AML cell lines and primary samples from patients with AML, MDS, and MPN. Following infusion into patients, a fraction of APTO-253 binds iron and transforms to the $Fe(253)_3$ conjugate which retains full activity. APTO-253 has been granted orphan drug designation for AML by the US FDA.

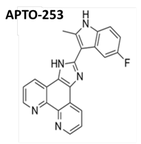
- **APTO-253 targets a conserved G4 structure in the promoter of the *MYC* oncogene*; reduces MYC mRNA and protein levels**

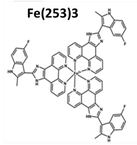






- **APTO-253 binds Fe^{2+} and forms an iron conjugate $Fe(253)_3$ – an active drug species with similar *in vitro* anti-tumor potency as its monomeric form****





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

OBJECTIVES & STUDY DESIGN

Ongoing Phase 1a/b, open-label, single arm, multicenter, 3 + 3 dose-escalation clinical study of APTO-253 in patients with relapsed or refractory AML, higher-risk MDS, or MYC-rearranged B-cell malignancies (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

Key Inclusion Criteria:

- Histologically or cytologically proven relapsed or refractory AML, higher-risk MDS, or MYC-rearranged B-cell malignancies for whom all standard therapy options have failed or which are considered inappropriate by the primary treating physician and/or Principal Investigator

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

Patient Demographics

Patient Demographics	Cohorts 1 to 6 (N=21)*
Median Age (Range), Years	**66.1 (36, 85)**
Sex, N (%)	
Male	**10 (47.6%)**
Female	**11 (52.4%)**
Ethnicity, N (%)	
Hispanic or Latino	**1 (4.8%)**
Not Hispanic or Latino	**19 (90.5%)**
Not Reported	**1 (4.8%)**
Race, N (%)	
White	**17 (81.0%)**
Black or African American	**2 (9.5%)**
Not Reported	**2 (9.5%)**
ECOG Score, N (%)	
0 -Normal activity	**1 (4.8%)**
1 -Symptoms, but ambulatory	**12 (57.1%)**
2 -In bed <50% of the time	**8 (38.1%)**
Disease Type / Subtype, N (%)	
MDS	**2 (9.5%)**
MDS Type, N (%) **	
Primary	**2 (100%)**
AML	**19 (90.5%)**
AML Type, N (%) **	
Relapsed	**7 (36.8%)**
Refractory	**7 (36.8%)**
Associated with treatment from prior malignancy	**1 (5.3%)**
Evolved from antecedent hematologic malignancy	**4 (21.1%)**
Median Number (Range) of Prior Therapy	**2.7 (1, 9)**
Chemotherapy, N(%)	**10 (47.6%)**
Stem Cells	**1 (4.8%)**
Targeted and Immunotherapy, N (%)	
Hypomethylating Agent	**18 (85.7%)**
BCL-2 Inhibitor	**13 (61.9%)**
Kinase Inhibitor***	**6 (28.6%)**
Other Experimental Agent	**4 (19.0%)**
Anti-CD33 Antibody Drug Conjugate	**2 (9.5%)**
Immune Cell Therapy	**1 (4.8%)**
Anti-CD123 Antibody Drug Conjugate	**1 (4.8%)**
Anti-CD123 Targeted Toxin	**1 (4.8%)**
Anti-PD-1 Antibody	**1 (4.8%)**
Antibody	**1 (4.8%)**
IDH1 Inhibitor	**1 (4.8%)**
mTOR Inhibitor	**1 (4.8%)**
RBC Transfusion Dependent, N(%)	
Yes	**18 (85.7%)**
Platelet Transfusion Dependent, N(%)	
Yes	**16 (76.2%)**

* Data-cut date: Sep. 22, 2021; ** % of MDS or AML patients

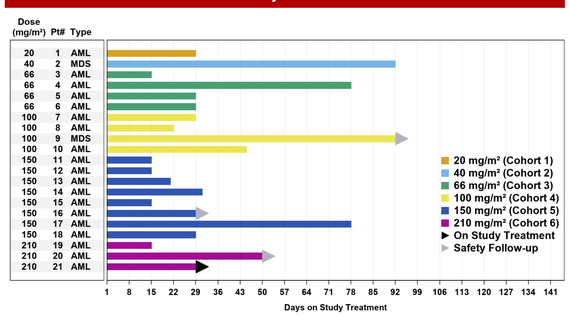
*** Including FLT3i midostaurin, HM43239 and gilteritinib, JAKi ruxolitinib

ACKNOWLEDGEMENTS

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

ASH2021 Abstract# 3411

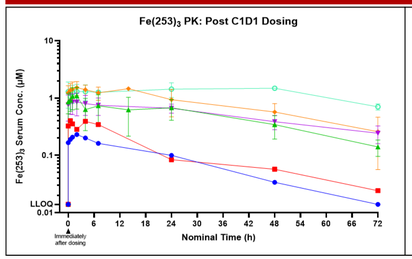
Treatment Cohort, Dose and Duration

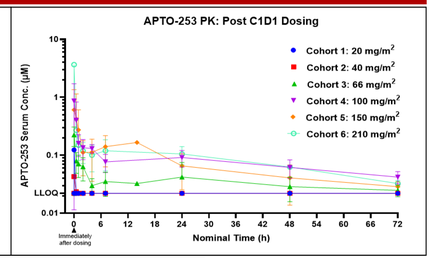


As of September 22, 2021

- **21 patients have been enrolled and treated in 6 cohorts;**
- **1 patient remains on study treatment;**
- **3 out of 8 patients treated in Cohort 5 were evaluable.**

Patient Serum PK Profiles for Cohorts 1 to 6





Cohort	APTO-253				Fe(253)3			
	$AUC_{0\text{-}72h}$ (μM*h)		C_{max} (μM)		$AUC_{0\text{-}72h}$ (μM*h)		C_{max} (μM)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cohort 1 (n=1): 20mg/m^2	1.60	-	0.07	-	5.78	-	0.23	-
Cohort 2 (n=1): 40mg/m^2	1.59	-	0.03	-	8.76	-	0.40	-
Cohort 3 (n=4): 66mg/m^2	2.70	1.37	0.12	0.04	38.70	15.91	1.10	0.45
Cohort 4 (n=4): 100mg/m^2	5.57	0.57	0.45	0.42	38.20	6.49	0.91	0.33
Cohort 5 (n=2[†]): 150mg/m^2	3.87	2.32	0.74	0.71	51.57	28.23	1.51	0.41
Cohort 6 (n=2[†]): 210mg/m^2	4.46	0.63	1.85	0.14	66.46	55.32	1.56	0.49

† As of September 22, 2021, PK samples collected from 8 and 3 patients in Cohort 5 and 6, respectively, were analyzed by LC-MS/MS. One patient of each Cohort 5 and 6 had samples collected on one or two timepoints and so data were excluded from statistical analysis.

- **Serum levels of APTO-253 and the $Fe(253)_3$ conjugate were dose proportional.**
- **$Fe(253)_3$ was detected in patient serum at significantly higher concentrations than the APTO-253 monomer.**

APTO-253 Safety and Tolerability Profile

As of September 22, 2021

- **2 of 21 patients experienced 3 related TEAEs of grade 3 or greater.**
- **Only 1 SAE was deemed related to APTO-253 (Grade 1 cellulitis, probably related) for a patient treated at 210 mg/m² (Cohort 6).**
- **There were no DLTs in patients treated at dose levels 1 to 5.**

APTO-253 Related Treatment Emergent Adverse Events

Preferred Term	Cohorts 1 to 6 (N=21)*	
	Any Grade, N (%)	Grade ≥ 3, N (%)
Patients with Any Event	7 (33.3%)	2 (9.5%)
Fatigue	2 (9.5%)	1 (4.8%)
Hyperuricaemia	2 (9.5%)	0
Phlebitis	2 (9.5%)	0
Alanine aminotransferase increased	1 (4.8%)	0
Aspartate aminotransferase increased	1 (4.8%)	0
Blood alkaline phosphatase increased	1 (4.8%)	0
Blood creatinine increased	1 (4.8%)	0
Cellulitis	1 (4.8%)	0
Decreased appetite	1 (4.8%)	0
Dizziness	1 (4.8%)	0
Haematoma	1 (4.8%)	0
Hypoalbuminaemia	1 (4.8%)	0
Hypocalcaemia	1 (4.8%)	0
Hypokalaemia	1 (4.8%)	0
Infusion related reaction	1 (4.8%)	0
Lymphocyte count decreased	1 (4.8%)	1 (4.8%)
Muscle spasms	1 (4.8%)	0
Neutrophil count decreased	1 (4.8%)	0
Pyrexia	1 (4.8%)	0
Thrombophlebitis	1 (4.8%)	0
Upper respiratory tract infection	1 (4.8%)	0
White blood cell count decreased	1 (4.8%)	1 (4.8%)

* Data-cut date: Sept. 22, 2021

Events	Cohorts 1 to 6 (N=21)
Any Treatment Emergent Adverse Events (TEAEs)	21 (100%)
Any TEAEs ≥ Grade 3	16 (76.2%)
Any APTO-253 Related TEAEs ≥ Grade 3	3 (14.3%)
TEAE Leading to Treatment Discontinuation	3 (14.3%)*
TEAE Leading to Death	11 (52.4%)*
Any Serious Adverse Events (SAE)	18 (85.7%)**

*Unrelated to APTO-253; **One SAE - Grade 1 cellulitis was deemed probably related to APTO-253.

CONCLUSIONS

- **In a Phase 1a/b trial, APTO-253 has been well-tolerated in the patients treated at 20, 40, 66, 100 and 150 mg/m^2 over multiple cycles, supporting continued dose escalation.**
- **APTO-253 monomer rapidly transformed to and co-existed with the $Fe(253)_3$ conjugate in peripheral blood.**
- **Serum levels of APTO-253 and the $Fe(253)_3$ conjugate were dose proportional with significantly higher concentrations of $Fe(253)_3$ conjugate compared to monomer.**
- **Collectively, these findings support continued dose escalation of APTO-253 in patients with relapsed / refractory AML and higher-risk MDS.**

Disclosures: Current clinical study is sponsored by Aptose Biosciences Inc. The following authors are employees of Aptose Biosciences Inc.: H Zhang, N Rastgoo, G Su, D Haney, Y Jin, J Marango, W Rice and R Bejar