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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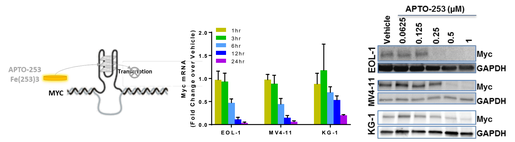
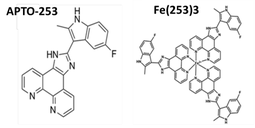
INTRODUCTION

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 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

Key Inclusion Criteria:

- Histologically or cytologically proven relapsed or refractory AML or high-risk MDS for whom all standard therapy options have failed or which are considered inappropriate by the primary treating physician and/or Principal Investigator

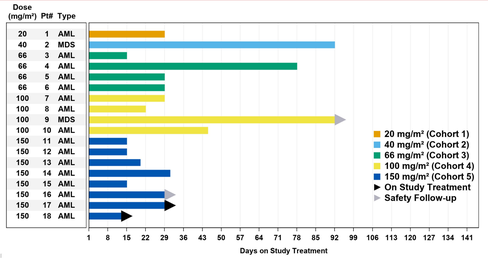
Dose Level	Dose	Status	Patients
1	20 mg/m^2	Completed	AML
2	40 mg/m^2	Completed	MDS
3	66 mg/m^2	Completed	AML
4	100 mg/m^2	Completed	AML & MDS
5	150 mg/m^2	Completed	AML
6	210 mg/m^2	Ongoing	
7	280 mg/m^2	Planned	
8	350 mg/m^2	Planned	
9	403 mg/m^2	Planned	

Patient Demographics

Patient Demographics	Cohorts 1 to 5 (N=18)*
Median Age (Range), Years	**64.0 (36, 85)**
Sex, N (%)	
Male	8 (44.4%)
Female	10 (55.6%)
Ethnicity, N (%)	
Hispanic or Latino	1 (5.6%)
Not Hispanic or Latino	16 (88.9%)
Not Reported	1 (5.6%)
Race, N (%)	
White	14 (77.8%)
Black or African American	2 (11.1%)
Not Reported	2 (11.1%)
ECOG Score, N (%)	
0 -Normal activity	1 (5.6%)
1 -Symptoms, but ambulatory	8 (44.4%)
2 -In bed <50% of the time	8 (44.4%)
3 -In bed >50% of the time	1 (5.6%)
Disease Type / Subtype, N (%)	
MDS	2 (11.1%)
MDS Type, N (%)**	
Primary	2 (100%)
AML	16 (88.9%)
AML Type, N (%)**	
Relapsed	7 (43.8%)
Refractory	4 (25.0%)
Associated with treatment from prior malignancy	1 (6.3%)
Chemotherapy	1 (6.3%)
Radiation	1 (6.3%)
Evolved from antecedent hematologic malignancy	4 (25.0%)
MDS	3 (18.8%)
Myelofibrosis	1 (6.3%)
AML RBC Transfusion Dependent, N (%)	
Yes	14 (87.5%)
No	2 (12.5%)
AML Platelet Transfusion Dependent, N (%)	
Yes	12 (75.0%)
No	4 (25.0%)
MDS RBC Transfusion Dependent, N (%)	
Yes	2 (100%)
No	0
MDS Platelet Transfusion Dependent, N (%)	
Yes	1 (50.0%)
No	1 (50.0%)
Median Number (Range) of Prior Therapy	**3 (1, 9)**
Chemotherapy, N (%)	9 (50.0%)
Stem Cells	1 (5.6%)
Targeted and Immunotherapy, N (%)	
Hypomethylating Agent	15 (83.3%)
BCL-2 Inhibitor	11 (61.1%)
Kinase Inhibitor***	5 (27.8%)
Immune Cell Therapy	1 (5.6%)
Anti-CD123 Antibody Drug Conjugate	1 (5.6%)
Anti-CD123 Targeted Toxin	1 (5.6%)
Anti-CD33 Antibody Drug Conjugate	2 (11.1%)
Anti-PD-1 Antibody	1 (5.6%)
Antibody	1 (5.6%)
Other Experimental Agent	3 (16.7%)
IDH1 Inhibitor	1 (5.6%)
mTOR Inhibitor	1 (5.6%)

* Data-cut date: Apr 14, 2021; ** % of MDS or AML patients
*** Including FLT3i Midostaurin and HM43239, JAKi Ruxolitinib

Treatment Cohort, Dose and Duration



As of April 14, 2021

- **18 patients have been enrolled and treated in 5 cohorts; 2 patients remain on study treatment.**
- **3 out of 8 patients treated in Cohort 5 were evaluable, 5 out of 8 were non-evaluable (Cohort 5 was completed on May 5, 2021).**

APTO-253 Safety and Tolerability Profile

As of April 14, 2021

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

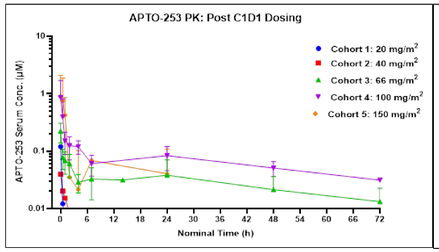
Events	Cohorts 1 to 5 (N=18)
Any Treatment Emergent Adverse Events (TEAEs)	17 (94.4%)
Any TEAEs ≥ Grade 3	13 (72.2%)
Any APTO-253 Related TEAEs ≥ Grade 3	1 (5.6%)
TEAE Leading to Treatment Discontinuation	1 (5.6%)
TEAE Leading to Death	9 (50.0%)*
Any Serious Adverse Events	14 (77.8%)*

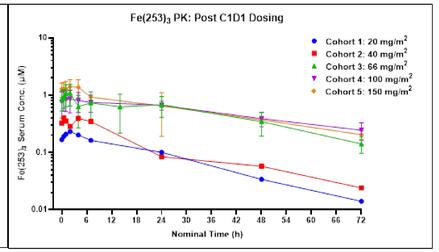
*Unrelated to APTO-253

APTO-253 Related Treatment Emergent Adverse Events		
Preferred Term	Cohorts 1 to 5 (N=18)	
	Any Grade, N (%)	Grade 3, N (%)*
Patients with Any Event	4 (22.2%)	1 (5.6%)
Fatigue	2 (11.1%)	1 (5.6%)
Hyperuricaemia	2 (11.1%)	0
Alanine aminotransferase increased	1 (5.6%)	0
Aspartate aminotransferase increased	1 (5.6%)	0
Blood alkaline phosphatase increased	1 (5.6%)	0
Blood creatinine increased	1 (5.6%)	0
Decreased appetite	1 (5.6%)	0
Dizziness	1 (5.6%)	0
Haematoma	1 (5.6%)	0
Hypoalbuminaemia	1 (5.6%)	0
Hypocalcaemia	1 (5.6%)	0
Hypokalaemia	1 (5.6%)	0
Muscle spasms	1 (5.6%)	0
Phlebitis	1 (5.6%)	0
Pyrexia	1 (5.6%)	0
Thrombophlebitis	1 (5.6%)	0
Upper respiratory tract infection	1 (5.6%)	0

* No APTO-253 Related TEAEs ≥ Grade 4 as of April 14, 2021

Patient Serum PK Profiles for Cohorts 1 to 5





Treatment	APTO-253						$Fe(253)_3$					
	$AUC_{0\text{-}72h}$ (μM*h)		C_{max} (μM)		T_{max} (h)		$AUC_{0\text{-}72h}$ (μM*h)		C_{max} (μM)		T_{max} (h)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cohort 1 (n=1): 20 mg/m^2	0.11		0.06		0.0		5.78		0.23		2.0	
Cohort 2 (n=1): 40 mg/m^2	0.15		0.02		0.5		8.75		0.40		0.5	
Cohort 3 (n=4): 66 mg/m^2	2.27	1.41	0.11	0.04	0.4	0.5	38.68	15.90	1.10	0.46	1.5	0.6
Cohort 4 (n=4): 100 mg/m^2	4.79	0.87	0.44	0.41	0.2	0.3	38.20	6.49	0.91	0.33	4.3	2.5
Cohort 5 (n=4[†]): 150 mg/m^2	1.91	0.72	1.36	0.60	0.5	0.5	33.52	28.46	1.33	0.42	0.7	0.3

† As of April 14, 2021, PK samples collected from 4 out of 8 patients in Cohort 5 were analyzed. Analysis of the rest of samples 5 is currently in process.

- **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.**

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 high-risk MDS.**

ACKNOWLEDGEMENTS

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