

Safety and efficacy of casein kinase 1 α and cyclin dependent kinase 7/9 inhibition in patients with relapsed or refractory AML: A first-in-human study of BTX-A51

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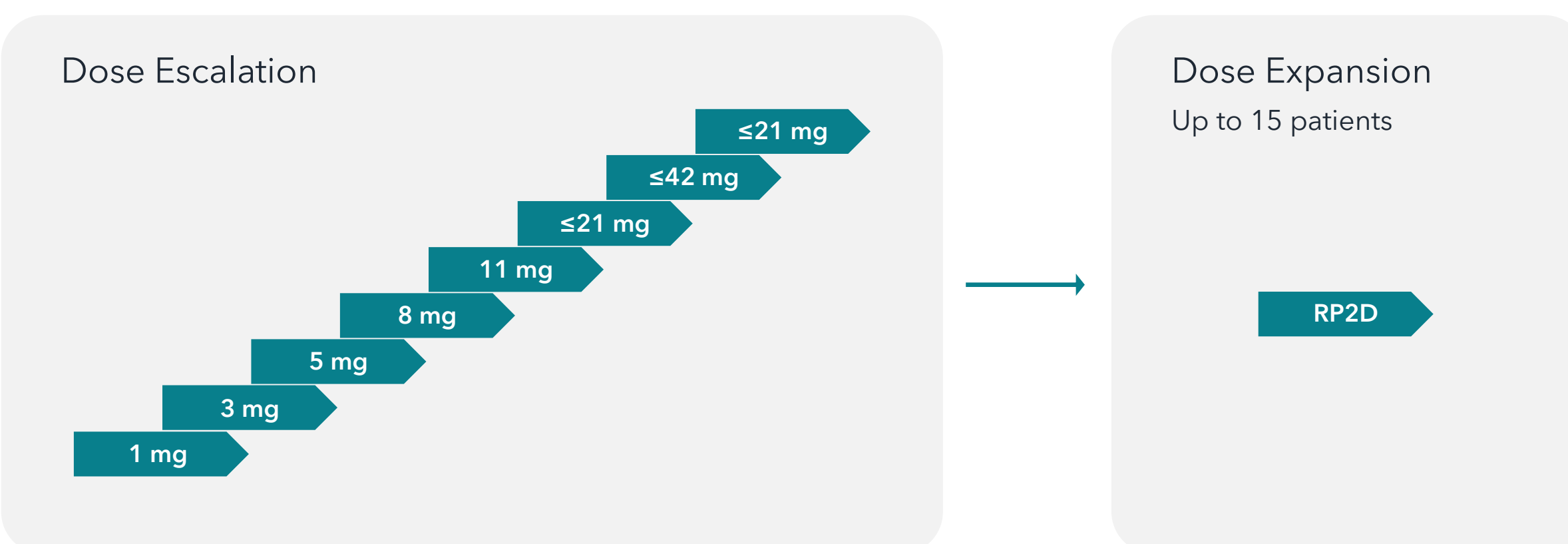
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BACKGROUND

- Inactivation of p53 and overexpression of Mcl1 are common mechanisms that cancer cells use to evade apoptosis
- Inhibition of CK1 α increases p53 protein levels while inhibition of cyclin dependent kinase 7 (CDK7) and 9 decreases super-enhancer transcription of *Myc* and *Mcl1*, enabling selective apoptosis of leukemia cells
- BTX-A51 is a novel, oral, direct inhibitor of CK1 α , CDK7, and CDK9¹
- We report the interim results of the first-in-human (FIH) study of BTX-A51 in patients with R/R AML and HR-MDS

STUDY DESIGN AND OBJECTIVES

BTX-A51-001 is a Phase 1, open label, multicenter dose-escalation with expansion study in patients with relapse or refractory AML/HR-MDS for which no recognized standard therapy exists. This study is registered at ClinicalTrials.gov (NCT04243785).



Bayesian Optimal Interval Design:

The maximum tolerated dose (MTD) will be the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate of 0.3.

Primary Objectives

- To characterize BTX-A51 safety and tolerability
- To determine the MTD and recommended Phase 2 dose (RP2D) of BTX-A51

Secondary Objectives

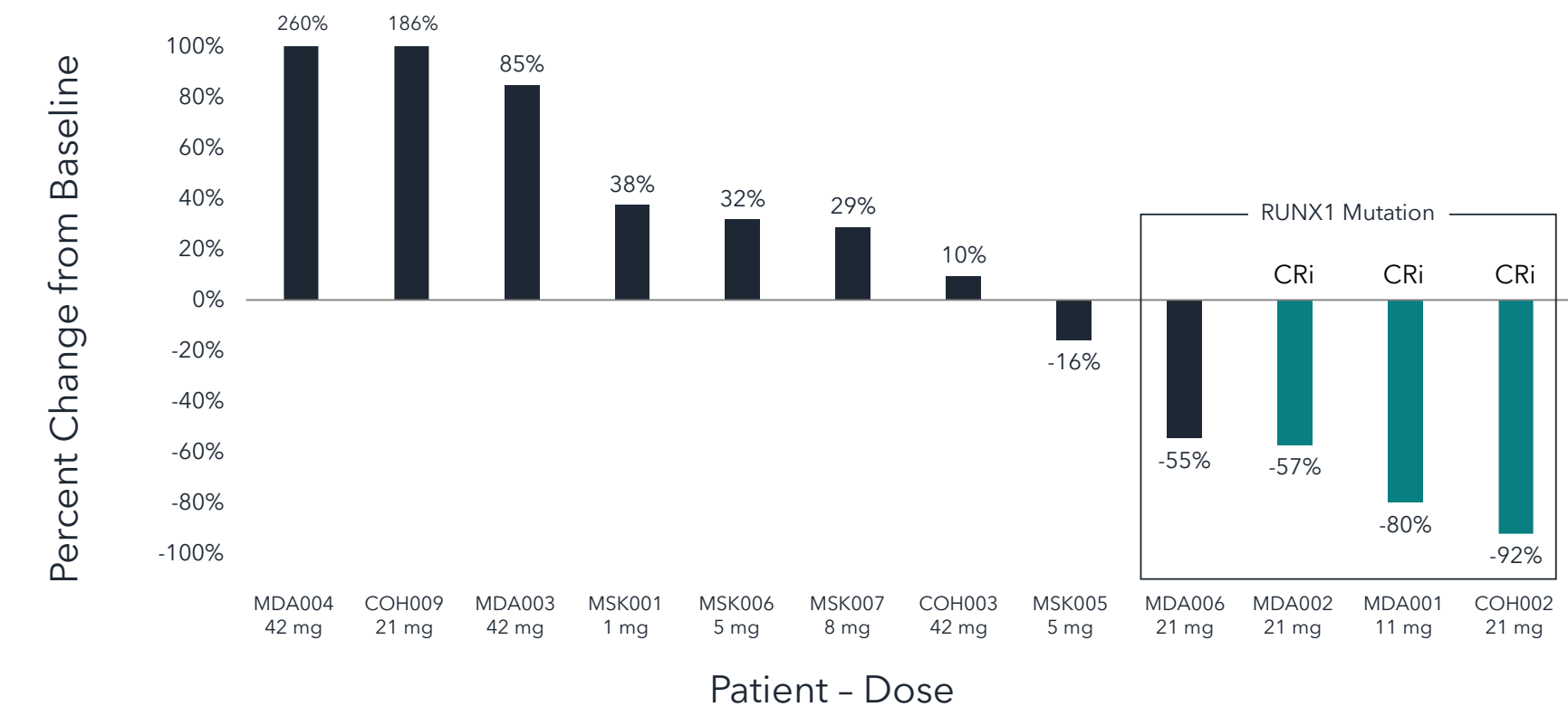
- To determine PK of BTX-A51
- To evaluate preliminary efficacy (ORR, EFS, OS)
- To evaluate pharmacodynamic biomarkers

REFERENCES

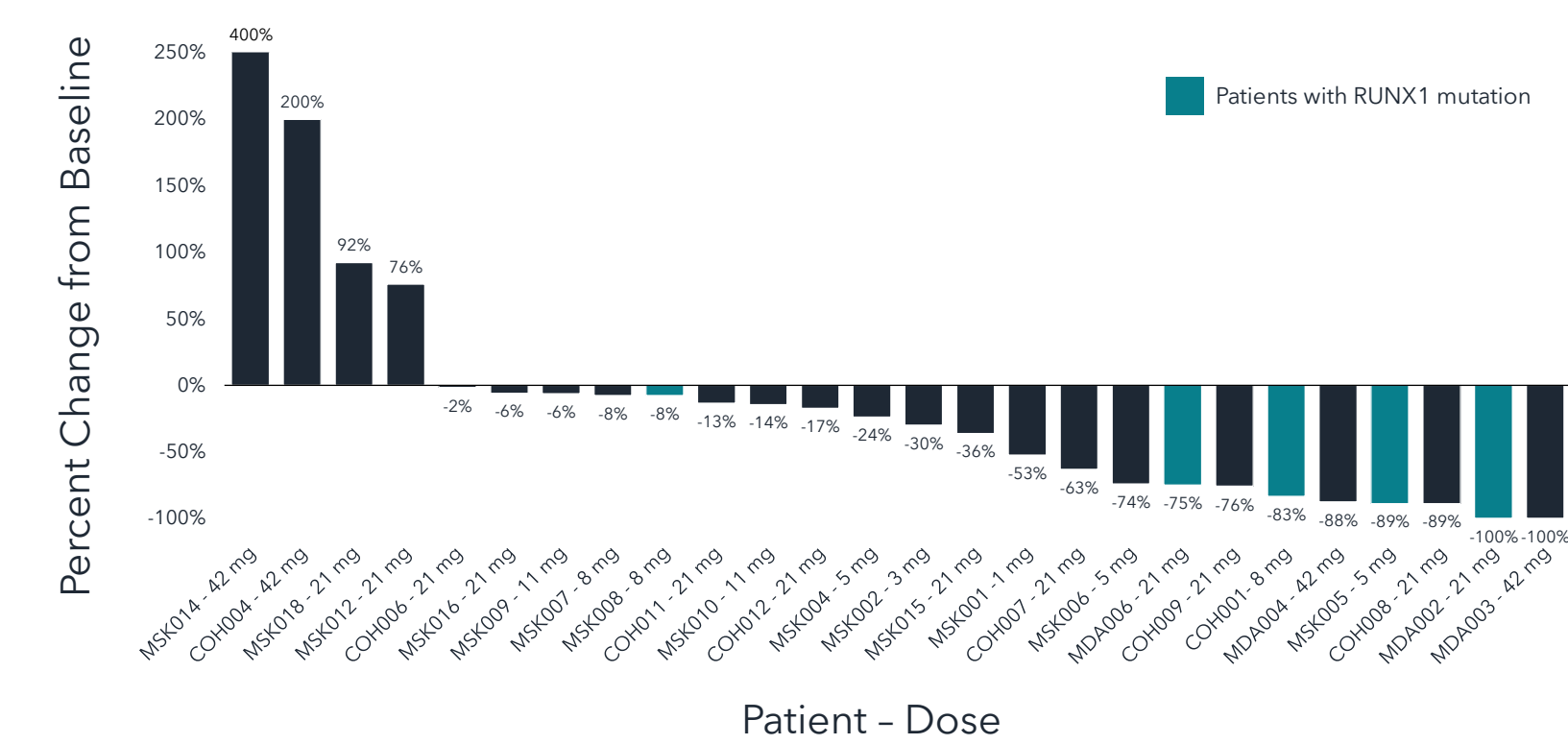
1. Minzel, W., A. Venkatachalam, A. Cell **175**(1): 171-185 e125.

RESULTS

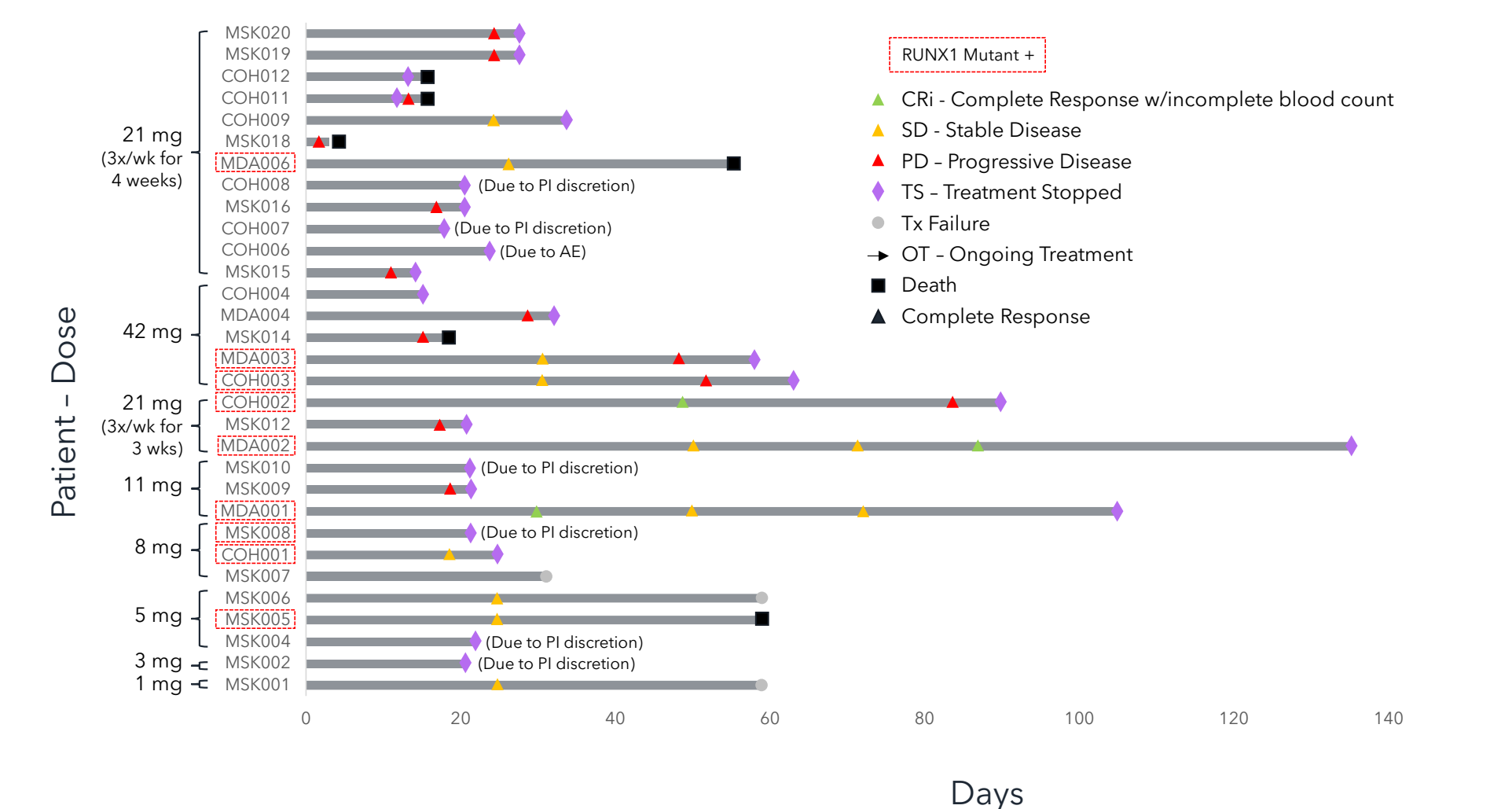
Best Percent Change in Bone Marrow Blasts



Best Percent Change in Peripheral Blasts



Time on Study



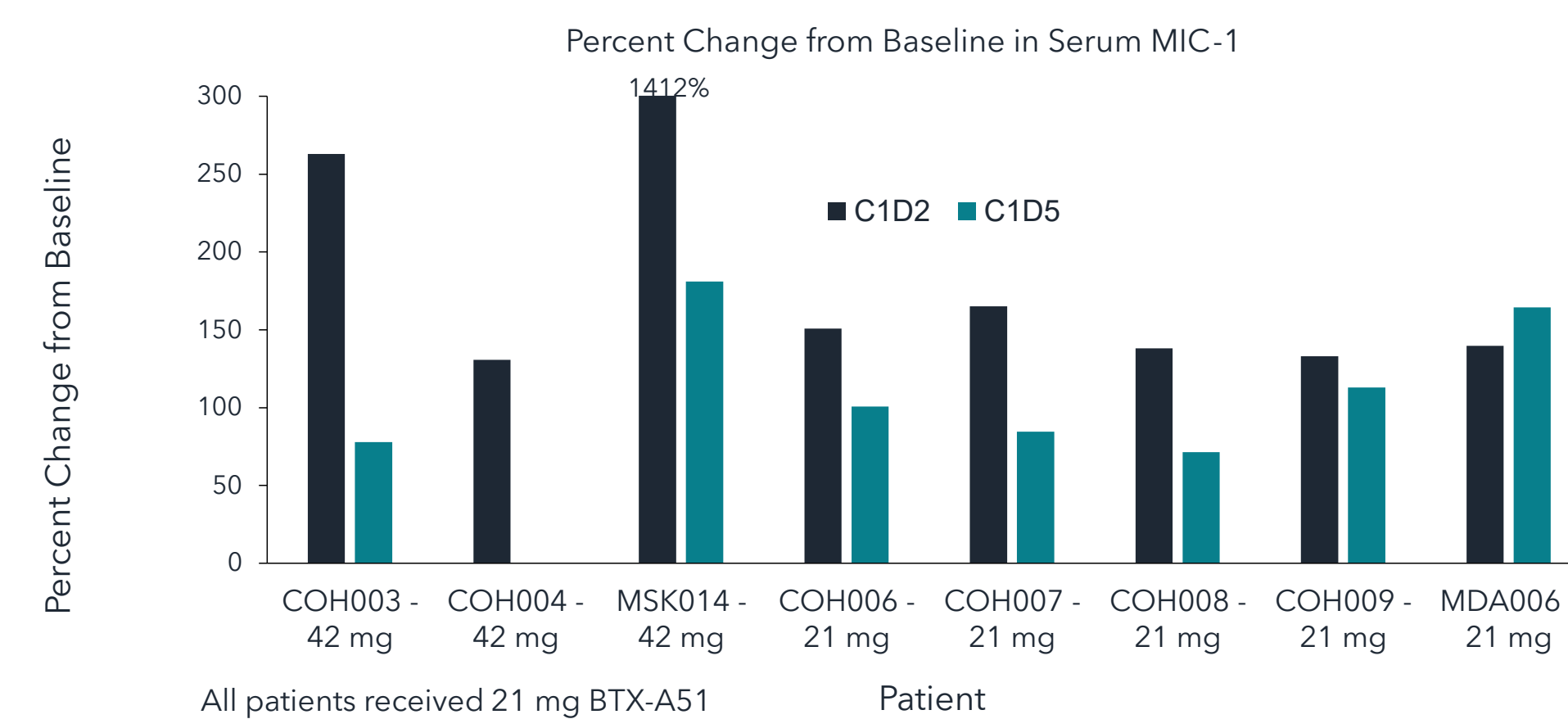
CR/CRI (n) % [95%CI]	Population	
	ITT (n=32)	RUNX1 Mutant (n=13)
	3 (9%) [2-25]	3 (23%) [5-54]

Pharmacokinetics of BTX-A51

Dose (mg)	N	Cmax (ng/mL)		AUC (ng*hr/mL)		Half-life (hrs)
		Day 1	Day 5	Day 1	Day 5	
1	1	1.14	1.86	36.1	43.0	17.7
3	1	4.72	20.5	125	600	24.8
5	3	10.7 (45)	25.7 (22)	233 (58)	702 (69)	18.3
8	3	18 (6.4)	37.1 (51)	573 (15)	937 (4.1)	45
11	3	27.8 (26)	52.3 (79)	828 (26)	1820 (77)	30.8
21	8	120 (64)	130 (46)	2137 (50)	3773 (48)	38
42	5	99 (79)	155 (22)	4773 (30)	4773 (30)	21

Mean (%CV)

Macrophage Inhibitor Cytokine 1



Treatment Related Adverse Events

Treatment Emergent AEs Related to BTX-A51	Total Patients (n=27)	
	All Grades > 10% patients	Grade 3/4
Preferred Term	n (%)	n (%)
Any Treatment Related AEs	20 (74.1%)	5 (18.5%)
Nausea	13 (48.1%)	-
Vomiting	9 (33.3%)	-
Hypokalaemia	5 (18.5%)	-
Fatigue	4 (14.8%)	-
Alanine aminotransferase increased	4 (14.8%)	1 (3.7%)
Aspartate aminotransferase increased	3 (11.1%)	1 (3.7%)
Diarrhoea	3 (11.1%)	-
Hypoalbuminaemia	3 (11.1%)	-
Hypocalcaemia	3 (11.1%)	-
Anaemia	3 (11.1%)	2 (7.4%)
Blood alkaline phosphatase increased	3 (11.1%)	-
Dry mouth	3 (11.1%)	-
Hypomagnesaemia	3 (11.1%)	-
Hypophosphataemia	3 (11.1%)	-
Oedema peripheral	3 (11.1%)	-
Oral pain	3 (11.1%)	-
Thrombocytopenia	-	1 (3.7%)
Acute hepatic failure	-	1 (3.7%)
Blood bilirubin increased	-	1 (3.7%)
Gamma-glutamyl transferase increased	-	1 (3.7%)
Platelet count decreased	-	1 (3.7%)

- Dose limiting toxicity of acute hepatic failure associated with increases in ALT, AST, total bilirubin, and INR and meeting Hy's Law was observed in one patient dosed in Cohort 7 at 42 mg. Patient recovered after discontinuation of BTX-A51.

CONCLUSIONS

- BTX-A51 demonstrated an acceptable safety profile and promising monotherapy antileukemic activity in pts with heavily pretreated R/R AML and HR-MDS
- MIC-1, a marker of p53 activation, was increased in patients dosed at 21 mg
- The 21 mg dose administered 3x/week for 4 weeks of a 28-day cycle was identified as the RP2D
- RUNX1 mutations were enriched among responders and pts attaining > 50% BM blast reduction

KEY ELIGIBILITY CRITERIA

Inclusion Criteria

- ≥ 18 years of age
- Documented diagnosis of refractory or relapsed AML or HR-MDS that is ineligible for or has exhausted standard therapeutic options
- ECOG performance status of ≤2
- Adequate organ function
- White blood cell count ≤ 25,000/mL

Exclusion Criteria

- Diagnosis of acute promyelocytic leukemia
- Autologous or allogeneic stem cell transplantation within 3 months prior to screening
- Treatment with systemic immunosuppressive medications for at least 1 week prior to Screening
- Left ventricular ejection fraction <40%

STUDY TREATMENT

- BTX-A51 is administered every other day (3x/week) orally
- Each treatment cycle consists of 28 days

Cohort	Planned Daily Dose (mg)	Number of patients	Maximum Weekly Dose (mg)		Cycle Dosing Regimen ^a
			5 Days/Week	3 Days/Week	
1	1	1	5	-	3 wk on/1wk off
2	3	1	-	9	3 wk on/1wk off
3	5	3	-	15	3 wk on/1wk off
4	8	3	-	24	3 wk on/1wk off
5	11	3	-	33	3 wk on/1wk off
6	≤21	3	-	≤63	3 wk on/1wk off
7	≤42	5	-	≤126	3 wk on/1wk off
8	≤21	12	-	≤63	4 wk on

^a One cycle consists of 28 days.

ENROLLMENT

Baseline Characteristics	N = 32
Median age (range)	75 (22-84)
Sex, n (%) Male	18 (56%)
AML, n (%)	29 (91%)
MDS, n (%)	3 (9%)
IPSS-R High risk, n (%)	3 (9%)
Prior Venetoclax, n (%)	31 (97%)
Prior HMA, n (%)	31 (97%)
Primary induction failure, n (%)	13 (41%)
RUNX1-mutated, n (%)	13 (41%)
# Prior lines of therapy, median	3

ACKNOWLEDGEMENTS

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