Abstract 451

First Results of a Phase 1 Study Evaluating Safety, PK, PD and Clinical Activity of STC-15, a METTL3 Inhibitor, in Patients with Advanced Malignancies

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Background

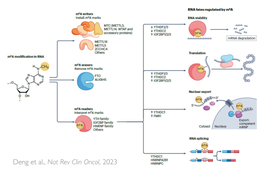
METTL3 is the RNA methyltransferase responsible for the deposition of N-6-methyladenosine modification (m6A) on mRNA. m6A is the most abundant modification on mRNA, regulating mRNA's stability, splicing and protein translation. STORM Therapeutics developed STC-15, a potent and selective METTL3 inhibitor currently under evaluation for the treatment of advanced malignancies.

In solid and hematologic cancers, multiple publications suggest that m6A modification plays a key role in cancer progression, in acquired drug resistance and in the maintenance of leukemic stem cells. Moreover, m6A modifications play a role in the cells' ability to recognize foreign RNA. Removal of m6A by genetic means or pharmacological inhibition activates innate immunity. In the absence of m6A, a subset of transcripts adopt dsRNA formation that leads to the activation of Pattern Recognition Receptors (PRRs) such as retinoic acid-inducible gene I (RIG-I) and melanoma differentiation associated protein 5 (MDA-5), which in turn induce the type-I interferon (IFN) and nuclear factor kappa B (NF-kB) pathways. The activation of type-I IFN signaling in cancer cells by METTL3i led to enhanced expression of interferon-stimulated genes (ISGs) and secretion of cytokines and chemokines. These processes remodulate the tumour microenvironment (TME) to support a shift from an immunosuppressive to an immunostimulatory state.

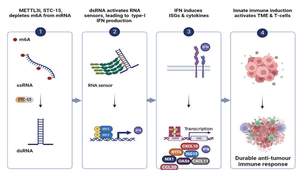
Mechanisms of Action

- METTL3 inhibition creates an anti-tumour immune response that is orthogonal to anti-PD1 and drives a cancer-intrinsic type-1 IFN program
- STC-15 enhances the secretion of cytokines and chemokines that attract T-cells and other immune cell populations into the tumour (IFNβ, CXCL10…)
- STC-15 releases Damage-Associated Molecular Patterns that activate and prime dendritic cells and macrophages, indirectly aiding the activation of cytotoxic T-cells
- STC-15 induces Immunogenic Cell Death

METTL3 Determines RNA Biology



METTL3 Inhibition Activates Innate Immunity



Study Design

DE – Dose escalation; **DLT** – Dose limiting toxicity; **MTD** – Maximum tolerated dose

Cohort Schedule	Dose Level	# Enrolled	# On Treatment	# Off Treatment
Cohort 1	60 mg/dose QD	6	0	6
Cohort 2	60 mg/dose TIW	3	1	2
Cohort 3	100 mg/dose TIW	14	1	13
Cohort 4	160 mg/dose TIW	12	4	8
Cohort 5	200 mg/dose TIW	7	2*	5
	TOTAL	42	8	34

*2 active patients have dose reduced to 160 mg

Objectives

Primary

- Assess safety of STC-15
- Determine maximum tolerated dose
- Determine PK parameters

Secondary

- Assess preliminary anti-cancer activity of STC-15 per RECIST 1.1
- Determine Recommended Phase 2 Dose of STC-15

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Vendors: Acumen Medical Communications, Almac Clinical Services, Clinical Research Strategies, Veramed, Universal Regulatory Inc., MVG Consulting Services, Medpace Bioanalytical and Reference Labs, NeoGenomics, Projections Research, Evotec.

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Clinicaltrials.gov ID# NCT05584111

Key Inclusion Criteria

- Histologically proven, relapsed or refractory, unresectable, locally advanced metastatic malignancies who have failed at least 1 prior line of therapy
- Adequate end organ function (hematological, hepatic and renal function)
- ECOG performance status 0 or 1
- Prior (immune related) AEs resolved or improved to Grade 1
- Prior immune-related AE's did NOT cause permanent discontinuation of therapy
- Absence of treatment related pleural effusions and/or ir-pneumonitis
- Absence of active CNS disease or ≥Grade 3 drug-related CNS toxicity

Demographics and Baseline Characteristics

Characteristics	Cohort 1 60 mg QD (N=6)	Cohort 2 60 mg Q3 W (N=3)	Cohort 3 100 mg Q3 W (N=14)	Cohort 4 160 mg Q3 W (N=12)	Cohort 5 200 mg Q3 W (N=7)	Total (N=42)
Age (Years)						
n	6	3	14	12	7	42
Mean (SD)	64.0 (19.3)	67.0 (12.2)	59.3 (7.5)	49.5 (15.2)	54.6 (17.4)	56.9 (14.5)
Median	68.5	73	62.5	49.5	48	59.5
Min,Max	38.0, 85.0	53.0, 75.0	43.0, 67.0	24.0, 79.0	36.0, 77.0	24.0, 85.0
Sex [n (%)]						
Male	4 (66.7%)	1 (33.3%)	7 (50.0%)	7 (58.3%)	5 (71.4%)	24 (57.1%)
Female	2 (33.3%)	2 (66.7%)	7 (50.0%)	5 (41.7%)	2 (28.6%)	18 (42.9%)
Cancer Type	CRC (2) Esophagus H&N Hepatic Sarcoma	CRC Lung Skin	Bone Breast CRC (5) Kidney Pancreas (2) Sarcoma (2) Skin	Breast Lung Neuroblastoma Pancreas Sarcoma (6) Skin	Breast CRC (2) H&N Kidney Sarcoma (2)	
Number of Lines of Prior Therapy						
n	6	3	14	12	7	42
Mean (SD)	4.0 (3.5)	5.0 (2.6)	4.1 (2.4)	4.2 (2.3)	3.9 (1.3)	4.1 (2.3)
Median	3	4	4	4	4	4
Min,Max	1.0, 10.0	3.0, 8.0	0.0, 9.0	2.0, 11.0	2.0, 6.0	0.0, 11.0
IO Pre-Treated						
Yes	3 (50.0%)	1 (33.3%)	3 (21.4%)	2 (16.7%)	3 (42.9%)	12 (28.6%)
No	3 (50.0%)	2 (66.7%)	10 (71.4%)	8 (66.7%)	4 (57.1%)	27 (64.3%)
No Response Recorded	0 (0.0%)	0 (0.0%)	1 (7.1%)	2 (16.7%)	0 (0.0%)	3 (7.1%)

Safety

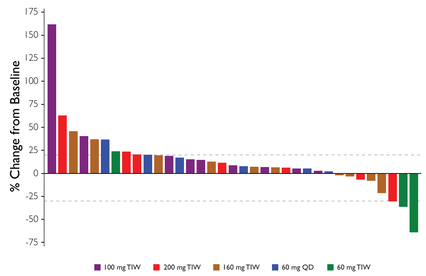
AE >1 Event per Cohort	Severity	Cohort 1 # Events	Cohort 1 Subj (%)	Cohort 2 # Events	Cohort 2 Subj (%)	Cohort 3 # Events	Cohort 3 Subj (%)	Cohort 4 # Events	Cohort 4 Subj (%)	Cohort 5 # Events	Cohort 5 Subj (%)	Total # Events	Total Subj (%)
Hematology		8	3 (50)	5	3 (100)	6	5 (36)	20	5 (42)	8	5 (71)	47	21 (50)
Thrombocytopenia	G1&2	6	1 (17)	2	2 (67)	3	3 (21)	17	5 (42)	8	5 (71)	36	16 (38)
	G3 +	2	2 (33)	0	0	0	0	0	0	0	0	2	2 (5)
GI disorders		0	0	0	0	1	1 (7)	11	5 (42)	11	3 (43)	23	9 (21)
Diarrhea	G1&2	0	0	0	0	0	0	2	2 (17)	5	1 (14)	7	3 (7)
N&V	G1&2	0	0	0	0	1	1 (7)	7	5 (42)	2	2 (28)	10	8 (19)
Infections	G1&2	0	0	0	0	0	0	3	1 (8)	1	1 (14)	5	3 (7)
	G3+	1	1 (17)	0	0	0	0	0	0	0	0	1	1 (2)
Laboratory Changes		0	0	0	0	0	0	2	1 (8)	1	1 (14)	3	2 (5)
Metabolic Changes	G1&2	0	0	1	1 (33)	2	1 (7)	8	3 (25)	1	1 (14)	12	6 (14)
	G3+	0	0	0	0	0	0	2	2 (17)	0	0	3	3 (7)
Skin		2	2 (33)	6	2 (67)	10	4 (29)	15	6 (50)	8	4 (57)	41	18 (43)
Rash	G1&2	1	1 (17)	3	2 (67)	6	4 (29)	8	6 (50)	5	3 (43)	23	16 (38)
Pruritus	G1&2	1	1 (17)	1	1 (33)	4	3 (21)	7	4 (33)	2	2 (29)	15	11 (26)

Patients may have multiple events

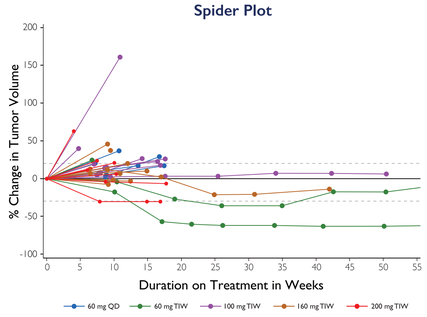
- No MTD established up to 200 mg TIW
- 1 DLT observed at 60 mg QD resulting in modification of schedule to TIW dosing due to accumulation
- Thrice weekly dosing of 60 mg to 200 mg tolerated without dose limiting toxicity
- Dose modifications due to AEs observed mainly in 200 mg cohort
- Main AEs are hematological (thrombocytopenia), and immune related (diarrhea, rash, pruritus) and indicative of pharmacology (METLL3 inhibition)
- STC-15 related TEAEs were in mostly mild to moderate, manageable, transient and did not result in discontinuation of study treatment
- A total of 28 subjects (67%) experienced 33 serious adverse events. One event was deemed related to study drug/treatment (pneumonitis) and resulted in a DLT and discontinuation of study treatment.
- A total of 18 deaths occurred on study, all deemed unrelated to study treatment and the majority were disease related (PD)

Clinical Activity

Waterfall Plot



Spider Plot



Overall Response Assessment

- CR: 0/33 = 0%
- PR: 3/33 = 9%
- SD: 19/33 = 58%
- PD: 11/33 = 33%
- BOR (CR+PR) = 3/33 = 9%
- DCR (CR + PR + SD) = 22/33 = 67%
- 1 confirmed PR *ongoing* for 11 months
- 1 confirmed PR *ongoing* for 4 months
- 1 confirmed PR duration 4 months

- Disease Control Rate (DCR) and Best Overall Response (BOR)
- 33 of 42 patients with at least 1 on-treatment scan
- 9 patients discontinued before first scan and are considered non-evaluable for RECIST

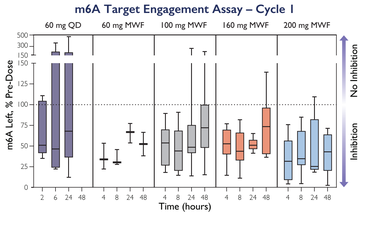
Treatment Duration

Characteristics	Cohort 1 60 mg QD (N=6)	Cohort 2 60 mg Q3 W (N=3)	Cohort 3 100 mg Q3 W (N=14)	Cohort 4 160 mg Q3 W (N=12)	Cohort 5 200 mg Q3 W (N=7)	Total (N=42)
Treatment Duration[1]						
n	6	3	14	12	7	42
Mean (SD)	51.0 (38.61)	323.7 (249.99)	77.1 (94.03)	79.3 (75.43)	72.4 (49.96)	90.8 (110.84)
Median	34.5	467	44	57	58	55
Min, Max	25, 124	35, 469	12, 375	4, 291	19, 145	4, 469

[1]Treatment duration is calculated as (Last Dose Date - First Dose Date) + 1

Target Engagement

m6A Target Engagement Assay – Cycle 1



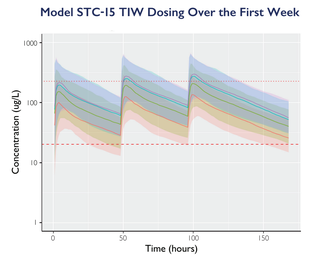
- Reduction in the PD biomarker m6A demonstrates target engagement at all dose levels
- Cohort 5 displays a trend toward stronger and longer inhibition
- m6A level tends to normalize back to pre-dose levels at 48 hours post dose, but the median value stays below 100%

PK Parameters

TIW Dose		C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-48h} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	V/F (L)	CL/F (L/h)
60 mg	N	3	3	1	2	1	1	1
	Mean (SD)	125 (23.3)	2.00 (0.00)	–	2930 (408)	–	–	–
100 mg	N	14	14	6	14	6	6	6
	Mean (SD)	229 (149)	4.29 (2.67)	17.8 (3.13)	4080 (1980)	5340 (1730)	569 (338)	21.7 (11.4)
160 mg	N	10	10	8	10	8	8	8
	Mean (SD)	394 (149)	4.40 (2.07)	19.4 (2.47)	8940 (3060)	12400 (2360)	369 (72.1)	13.3 (2.50)
200 mg	N	7	7	5	7	5	5	5
	Mean (SD)	294 (176)	3.00 (2.38)	21.4 (4.25)	6390 (3270)	8350 (4450)	1550 (2070)	49.0 (64.0)

PK Model

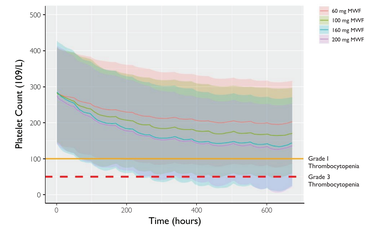
Model STC-15 TIW Dosing Over the First Week



- Red lines represent IC50 and IC90 of m6A inhibition in blood treated with STC-15 *ex-vivo* (20.2 ug/L and 226.2 ug/L, respectively)
- PK model suggests TIW dosing between 60 mg and 200 mg is sufficient to achieve pharmacologically active exposure

PK-PD Model of Platelet Reductions

STC-15 PD Model Over First Four Weeks



- Thrombocytopenia emerged as an on-target biomarker. Platelet reduction was correlated with STC-15 plasma level and can be used as a PD biomarker.
- Model predicts the reduction of platelets over time with STC-15 TIW dosing
- Platelet inhibition plateaus at ~75% and no further inhibition is expected with increased exposure. The IC50 for platelets inhibition is 95 ug/L.

STC-15 Phase 1 Conclusions

Safety

- MTD not established
- TEAEs were mainly mild, transient and well managed with supportive care and treatment modifications if indicated
- TE immune-related AEs (e.g. platelet reductions, rash, pruritis, GI toxicity) were not treatment limiting
- TIW dosing effectively manages platelet inhibition, with safety events limited to Gr1/2

Clinical Activity

- Disease control was achieved at all dose levels, with sustainable partial response achieved at 60 mg, 100 mg and 200 mg
- Clinical activity was observed in multiple tumor types without correlation to exposure or duration of treatment.

Target Engagement

- m6A data indicates rapid METTL3 modulation with maximum inhibition observed at 6-8 hours, but does not increase with dose

PK

- Dose dependent increase of exposure up to 160 mg TIW, with high variability and low bioavailability at 200 mg TIW