Abstract 443280

Phase 1 Dose Escalation and Cohort Expansion Study Evaluating Safety, PK, PD and Clinical Activity of STC-15, a METTL3 Inhibitor in Patients with Advanced Malignancies

Justin C Moser[1], Kyriakos P Papadopoulos[2], Jordi Rodon Ahnert[3], Yaara Ofir-Rosenfeld[4], Josefin-Beate Holz[4], STC15-22101 Study Team

[1]HonorHealth Research Institute; [2]START San Antonio; [3]The University of Texas MD Anderson Cancer Center; [4]Storm Therapeutics LTD

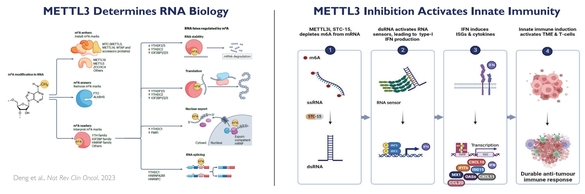
Background

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

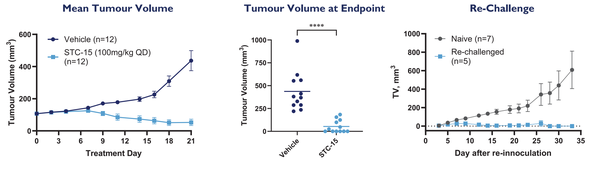
- METTL3 inhibition creates an anti-tumour immune response that is orthogonal to anti-PD1 and drives a cancer-intrinsic type-1 IFN program
- STC-15 enhances the secretion of cytokines and chemokines that attract T-cells and other immune cell populations into the tumour (IFNβ, CXCL10, CCL5)
- STC-15 releases 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



Deng et al., *Nat Rev Clin Oncol*, 2023

Preclinical Data

GL261 Syngeneic Model

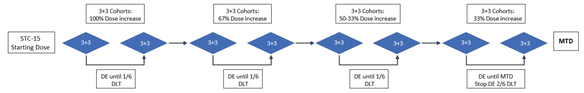


- GL261 is a syngeneic glioma model highly sensitive to STC-15 as a single agent
- 8 of 12 of tumour bearing mice had tumour regression following STC-15 treatment
  - 6 of 12 had complete regression
- Mice with complete regression did not regrow tumours upon re-implantation, suggesting that a durable immune memory was established

Scan to view poster

STC-15 Study Team: Storm Therapeutics – Melinda Snyder, Tess Schmalbach, Tess Barker, Deepa Deshpande, Ben Skead, Claire Sadler, Hendrik Weisser, Oliver Rausch **Sites:** Doug Hester[1], Nidhi Sheth[1], Pamela Saldana Leon[1], Edwin Blanco-Cepeda[1] **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

Study Design



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

Cohort Schedule	Dose Level	# Enrolled
Cohort 1	60 mg/dose QD	6
Cohort 2	60 mg/dose TIW	3
Cohort 3	100 mg/dose TIW	14
Cohort 4	160 mg/dose TIW	6
Cohort 5	200 mg/dose TIW	4
	TOTAL	33

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

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

Patient Demographics

	Cohort 1 60 mg N=6	Cohort 2 60 mg N=3	Cohort 3 100 mg N=14	Cohort 4 160 mg N=6	Cohort 5 200 mg N=4
Schedule	QD	TIW	TIW	TIW	TIW
Age (mean, yrs)	64	67	59.3	54.2	50.3
Sex (male)	4 (67.5%)	1 (33%)	7 (50%)	3 (50%)	2 (50%)
Prior Lines of Therapy (mean)	4	5.3	4.2	3.3	4.3
Cancer Type	CRC (2) Esophagus H&N Hepatic Sarcoma	CRC Lung Sarcoma	CRC (5) Bone Breast Melanoma (2) Pancreas (2) Pheochromocytoma Sarcoma (2)	CRC Lung Melanoma Sarcoma (3)	CRC Breast Renal Thymoma

Safety Data

	Cohort 1 60 mg QD N=6	Cohort 2 60 mg TIW N=3	Cohort 3 100 mg TIW N=14	Cohort 4 160 mg TIW N=6	Cohort 5 200 mg TIW N=4
Related TEAEs	9	5	11	17	3
Most Freq TEAEs					
Platelet # Decr	2 (33%)	0	2 (14%)	5 (83%)	1 (25%)
Pruritus	2 (33%)	1 (33%)	2 (14.3%)	2 (33%)	0
Rash	1 (17%)	2 (67%)	4 (29%)	2 (33%)	1 (25%)
Grade 3 TEAEs	2	0	0	1	0
Related SAEs	1	0	0	0	0
Dose Limiting Toxicity	1	0	0	0	0

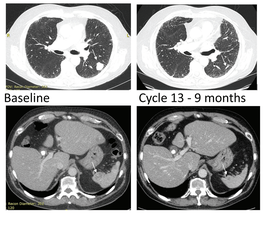
- No Grade 4 or 5 TEAEs have been reported; one DLT & related SAE pneumonitis (Grade 3), occurred in a 44 yo male after 7 doses of STC-15 60 mg QD
- IrAEs (pruritus and rash) were treated with antihistamine and topical therapy with good result
- Thrombocytopenia, onset C1/C2 and max. C3 stabilizes/recovers under continuous TIW dosing; managed (if necessary) with dosing interruption

Clinical Activity

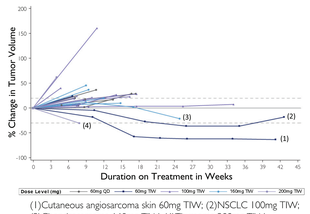
27 patients with at least 1 on-study scan

- 73 yo m Stage 4 cutaneous angiosarcoma and 3 lines of prior therapy; 60 mg TIW. PR at Week 16 (contd. at week 33). Grade 2 rash
- 75 yo f Stage 4 NSCLC with 4 lines of prior therapy (incl. IO); dose escalated 60 to 100 mg TIW. PR at Week 24 (contd. at week 30); up-dosing to 200 mg TIW
- 36 yo m Stage 4 thymoma and 3 lines of prior therapy; 200 mg TIW – reduced to 160 mg. PR at Week 8 (contd. Week 12)

(1) Patient with cutaneous angiosarcoma



Clinical Activity



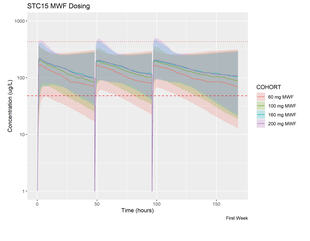
(1)Cutaneous angiosarcoma skin 60mg TIW; (2)NSCLC 100mg TIW; (3)Chondrosarcoma 160mg TIW; (4)Thymoma 200mg TIW

DCR of 63% (3 PR, 14 SD); ORR is 3/27 (11%) all doses; all tumor types

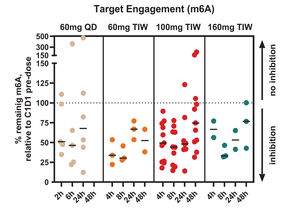
PK

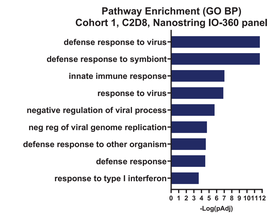
Dose (mg)	t1/2α (h)	t1/2β (h)	AUC (μg*h/L)	CL (L/h)
60	18.8	600	10	6.6
100	18.8	1400	19	7
160	17.6	750	40	4.5
200	18.3	400	31	10

PK Model suggests TIW dosing between 60 mg and 200 mg is sufficient to achieve pharmacologic active exposure (>IC50/90 & >EC50/90 inhibition of platelet formation)



Biomarker Data

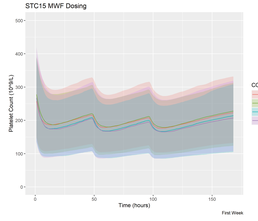




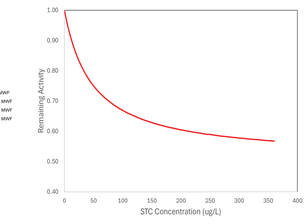
- Similar level of m6A reduction achieved in all doses at early timepoints following dosing
- A trend for later m6A level recovery in the higher dose cohorts
- Pathway enrichment analysis on Cohorts 1-4 revealed activation of innate immunity and IFN signaling
- Recapitulates pre-clinical MoA

STC-15 Inhibition of Platelet Formation

STC-15 PD Model



STC-15 Effect on Platelet Formation



- PK/PD model describes STC-15 pharmacology well
- STC-15 dosing resulted in target engagement at all dose levels tested
- STC-15 target modulation and PD (inhibition of platelet formation) increased with dose with maximum pharmacology effect suggested at 200 mg TIW dosing

Conclusions

- STC-15 well tolerated across pharmacologically active dose range
  - TEAEs manageable & most common related AE's were thrombocytopenia, rash, pruritus
- Clinical activity observed with 63% DCR and 11% ORR
- PK simulations and safety data support dosing ≥60 mg TIW
- Early PD marker analysis:
  - Activation of innate immune response and POC
  - Indirect Response (PD) Model: Max PAD established at 200 mg
- Recommended Phase 2 dose between 60 mg and 200 mg TIW
- Study is ongoing with expansion cohorts to further evaluate safety, food effect, PK/PD, clinical activity, with goal to determine optimized active doses
- Protocol amendment for CPI combination in progress

Contact: Josefin-Beate Holz, MD **Email:** josi.holz@stormtherapeutics.com

Clinicaltrials.gov ID# NCT05584111