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

Abstract 676

Kyriakos P. Papadopoulos[1], Justin C Moser[2], Jordi Rodon[3], Yaara Ofir-Rosenfeld[4], Hendrik Weisser[4], Melinda Snyder[4], Tess Schmalbach[4], Tess Barker[4], Deepa Deshpande[4], Ben Skead[4], Doug Hester[2], Nidhi Sheth[2], Pamela Saldana Leon[3], Edwin Blanco-Cepeda[1], Oliver Rausch[4], Josefin-Beate Holz[4]

[1]START San Antonio, San Antonio, TX, US; [2]HonorHealth Research Institute, Scottsdale, AZ, US; [3]Department of Investigational Cancer Therapeutics (Phase 1 Clinical Trials Program), The University of Texas MD Anderson Cancer Center, Houston, TX, US; [4]Storm Therapeutics Ltd, Cambridge, Cambridgeshire, UK

Background

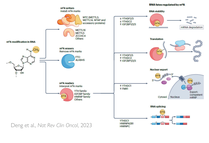
METTL3 is the RNA methyltransferase responsible for depositing N-6-methyladenosine modification (m6A) on mRNA. m6A is the most abundant modification on mRNA, regulating mRNA stability, splicing and protein translation. STORM Therapeutics developed STC-15, a potent and selective METTL3 inhibitor currently 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. 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 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 leads to enhanced expression of interferon-stimulated genes and secretion of cytokines and chemokines in tissue culture. These processes may remodulate the tumour microenvironment (TME) to support a shift from an immunosuppressive to an immunostimulatory state.

Mechanisms of Action

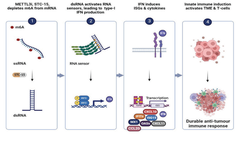
- METTL3 inhibition interrupts the deposition of m6A on mRNA, leading to the formation of dsRNA
- Pattern Recognition Receptors activate a type-1 IFN innate immune response
- STC-15 enhances the secretion of cytokines and chemokines such as IFNβ and CXCL10, that attract T-cells and other immune cell populations into the tumour
- STC-15 activates and primes dendritic cells and macrophages, indirectly aiding the activation of cytotoxic T-cells
- STC-15 induces immunogenic cell death *in vitro*

METTL3 Determines RNA Biology



Deng et al., Nat Rev Cin Oncol, 2023

METTL3 Inhibition Activates Innate Immunity



Phase 1 Study Endpoints

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

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.

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	73.0	62.5	49.5	48.0	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%)

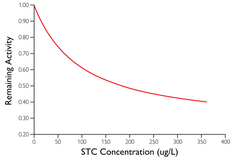
Safety

AE >1 Event/ 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 (%)
Thrombo-cytopenia	G1/2 (G3+)	6 (2)	1 (17) (2(33))	2	2 (67)	3	3 (21)	17	5 (42)	8	5 (71)	38	18 (43)
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 (G3+)	0 (1)	0 (1 (17))	0	0	0	0	3	1 (8)	1	1 (14)	6	4 (9)
Metabolic Changes	G1/2 (G3+)	0	0	1	1 (33)	2	1 (7)	8 (2)	3 (25) (2 (17))	1	1 (14)	15	9 (21)
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.

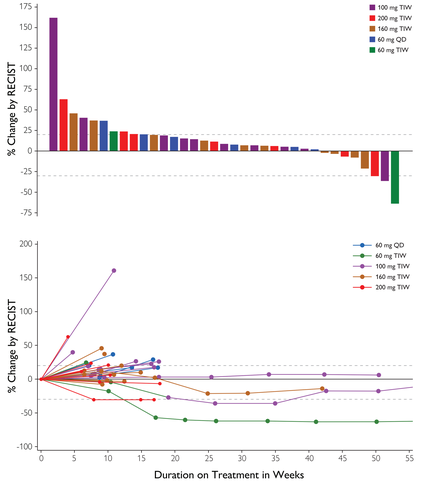
- 60 mg to 200 mg TIW (3x per week) dosing tolerated without DLTs; no MTD established
- One DLT observed at 60 mg QD (pneumonitis) resulted in modification of dose schedule to TIW dosing due to drug accumulation
- Majority of AEs are METTL3-related: hematologic (thrombocytopenia) and immune-related (diarrhea, rash, pruritis)
- STC-15 related TEAEs were mostly mild to moderate, manageable, transient, and did not result in discontinuation of study treatment
- A total of 28 subjects (67%) experienced 33 SAEs

STC-15 Effect on Platelet Formation
(indirect response model)



- Inhibition of platelets formation, resulting in platelet count reduction, is considered a METTL3 on-target event, in line with preclinical toxicity studies and with the literature (Sturgess 2023)
- The graph depicts a model correlating the percentage of platelet formation with STC-15 concentration measured in blood
- The E_{max} is approximately 75%, and no further inhibition is expected with increased dose/exposure
- STC-15 concentration at IC_{50} is 95 µg/L

Clinical Activity

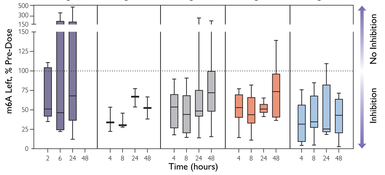


Overall Response Assessment

- CR: 0/33 = 0%
- PR: 3/33 = 9%
- SD: 19/33 = 58%
- PD: 11/33 = 33%
- ORR (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 Overall Response Rate (ORR)
- Of 42 patients enrolled, 33 had at least one (1) on-treatment scan

Target Engagement

m6A Target Engagement Assay – Cycle 1

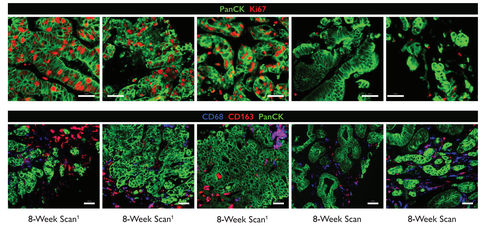


- Reduction in the PD biomarker m6A demonstrates target engagement at all dose levels
- Cohort 5 displays a trend toward stronger and longer inhibition
- m6A level tends to normalize back to pre-dose levels at 48 hours post dose, but the median value stays below 100%

Tumor Biopsy Analysis

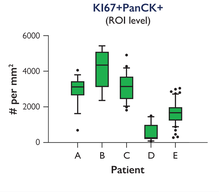
Assessment of Tumor Proliferation and Macrophage Infiltration in GI Cancer Biopsies

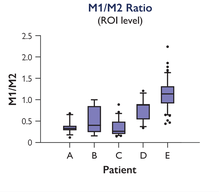
- All biopsies were collected in Week 4 on treatment (C2D1), after 9 doses of STC-15



[1]Discontinued treatment prior to 16-week scan.
PanCK: Tumor cells; Ki67: Proliferation marker; CD68+CD163-: M1 macrophages; CD68+CD163+: M2 macrophages.

Tumor Cell Proliferation and M1/M2 Ratio in Tumor Biopsies

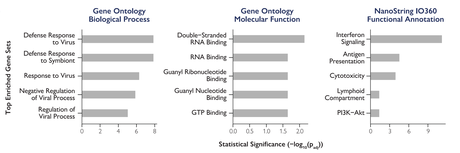




Gene Expression

STC-15 Activates Innate Immunity Pathways in Blood

A



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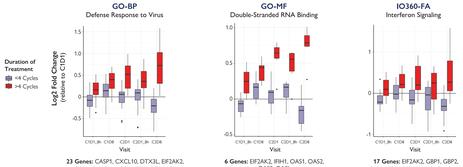

- Peripheral blood samples were collected from all 36 patients treated with TIW dosing at each study visit, from baseline to C2D8
- Gene expression was analyzed using the Nanostring IO360 platform
- Samples were divided into two groups split by total duration of treatment, of greater than or less than 84 days (C4D1):
  - DOT > C4D1 was enriched with patients with disease control (PR and SD) (n=14)
  - DOT < C4D1 was enriched with patients with progressive disease (n=22)
- Unbiased pathway enrichment analysis was performed, comparing differential gene expression against baseline in each group (A)
- Box plots were generated for the highest scoring terms in (A), comparing the fold changes in each visit against the pre-treatment baseline of the relevant genes (B)
- Upregulation of genes related to IFN signaling, response to virus and dsRNA binding in the first weeks of treatment correlated with patients remaining on trial >4 cycles

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
- Platelet suppression increases with STC-15 exposure in the serum
- TIW dosing effectively manages platelet inhibition, with safety events limited to Gr1/2

Clinical Activity

- Tumor regressions were achieved at all dose levels, 60 mg - 200 mg TIW, with three (3) sustained Partial Responses (PRs) at 60 mg, 100 mg, and 200 mg TIW
- Clinical activity was observed in multiple tumor types

Target Engagement

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

Tumour Biopsy Analysis

- Cancer proliferation markers and M1/M2 macrophages observed in on-treatment tumor biopsies

Gene Expression Changes in Blood

- Pathways related to IFN signalling, response to virus and dsRNA binding were enriched in patients experiencing longer DoT on STC-15 treatment

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.

Contact: Yaara Ofir-Rosenfeld
Email: yaara.ofir-rosenfeld@stormtherapeutics.com

Clinicaltrials.gov ID# NCT05584111

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