# A Subset Analysis of Clinical Activity and Pharmacodynamic Biomarkers in Patients with Sarcomas in the Phase 1 Dose Escalation Study of STC-15, a METTL3 Inhibitor

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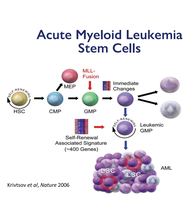
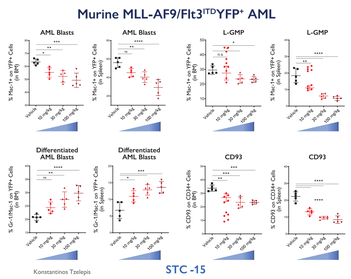
## METTL3 is a Novel Target for Cancers Arising from Transformed Stem Cells

- The RNA methyltransferase METTL3 is responsible for the generation of N6-methyladenosine ($m^6A$), the most abundant modification on mRNA. Accumulating evidence suggests numerous roles of METTL3 in cancer initiation and progression highlighting the rationale for targeting this enzyme in oncology.
- STC-15, a first in class small molecule inhibitor of METTL3 developed by Storm Therapeutics, demonstrated efficacy in pre-clinical models of cancer characterized by their dependence on $m^6A$-mediated mRNA metabolism, including leukemias that derive from a transformed myeloid progenitor.
- We report the clinical activity and exploratory biomarkers observed in a subset analysis of sarcomas from a first-in-human trial in patients with advanced malignancies. Full results of the study have been previously presented at the annual meeting of the Society for Immunotherapy in Cancer in 2024.

### METTL3 Identified as a Key Driver of Cancer Stem Cell Renewal via Differentiation



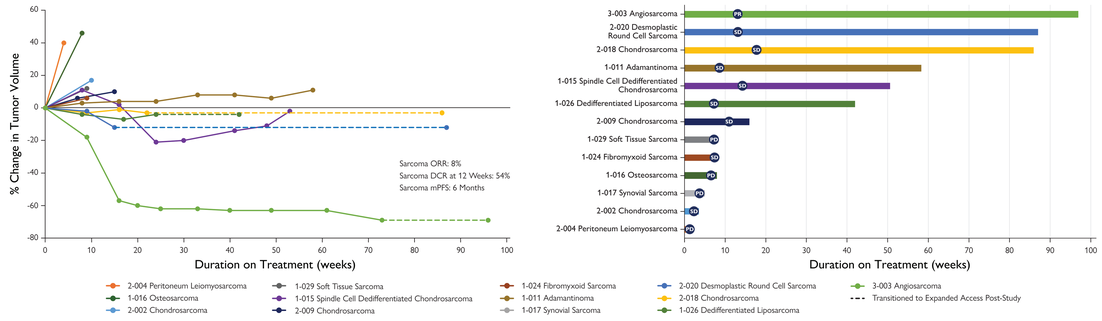

## First-in-Human Study of STC-15 as a Monotherapy in Solid Tumors – Sarcoma Subset

### STC-15 is Well-Tolerated, MTD Not Reached

| # of Events | 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=12 | Cohort 5 200 mg TIW N=7 |
|---|---|---|---|---|---|
| Most Freq TEAEs | | | | | |
| Thrombocytopenia | 3 (50%) | 2 (67%) | 4 (28.6%) | 8 (67%) | 5 (52.4%) |
| Pruritus | 2 (33%) | 1(33%) | 3 (21.4%) | 4 (33%) | 2 (28.6%) |
| Rash | 1 (16.7%) | 2 (67%) | 5 (35.7%) | 6 (50%) | 3 (42.9%) |
| Grade 3 TEAEs | 5 | 2 | 8 | 6 | 4 |
| Related SAEs | 1 | 0 | 0 | 0 | 0 |
| Dose Limiting Toxicity | 1 | 0 | 0 | 0 | 0 |

- Of 42 solid tumor patients treated with STC-15, 13 patients had sarcomas.
- All sarcoma patients were Stage 4 metastatic, with an average of 3 prior lines of therapy.
- Thrombocytopenia onsets in C1/C2 and stabilizes/recovers under continuous TIW dosing in C3; managed (if necessary) with dose interruptions. METTL3 inhibition has been shown to inhibit the differentiation of hematopoietic cells in preclinical models (Sturgess et al., 2023).
- No grade 4 or 5 treatment-related TEAEs reported.
- Pruritus and rash were treated with antihistamine and topical therapy with good results.
- At 200 mg TIW, 1 patient discontinued during Cycle 1, was replaced; 4 patients who started on 200 mg were dose reduced to 160 mg TIW after Cycle 1.
- 160 mg TIW was selected as the RP2D after a 30-hour half-life was observed.

### Durable Tumor Regressions and Disease Control in Sarcoma Patients





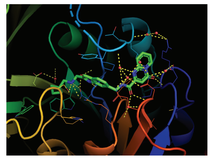


- Three (3) Partial Responses were observed during the Phase 1 study: angiosarcoma, NSCLC, and thymoma.
- One (1) patient remains on treatment after 23 months on treatment: neuroblastoma.

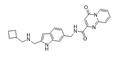
## STC-15 Mechanism of Action and Clinical Benefit in Sarcoma Patients

### STC-15: First RNA Modifying Enzyme Inhibitor in Clinic

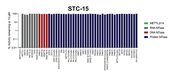
**Structurally Enabled First-in-Class Inhibitor Design**



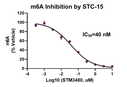
**Novel and Proprietary, First-in-Class**



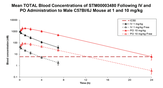
**Exquisite Selectivity vs Other Methyltransferases**



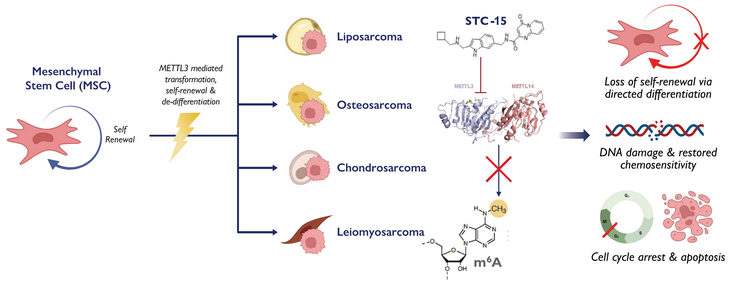

**Potent Inhibition of Cellular $m^6A$**




**Excellent PK Profile**

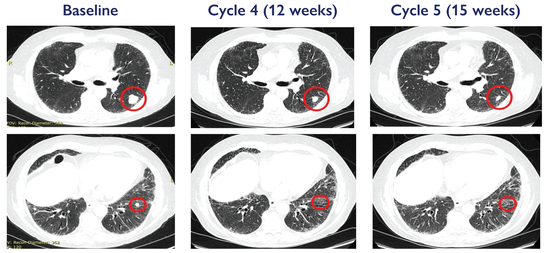



### Exploiting Vulnerabilities in Sarcomagenesis




- Clinical proof of METTL3 mechanism observed in sarcoma patients, consistent with pre-clinical results in leukemia, and suggesting that sarcoma differentiation from common mesenchymal progenitors is similarly dependent on $m^6A$-mediated mRNA metabolism.
- Sarcoma patients experienced anecdotal benefits not observable by RECIST:
  - Patient 1-026 dedifferentiated liposarcoma mass "deflated" or "pancaked" registering as only a 5% reduction by RECIST. This patient was able to leave his wheelchair and returned to his work and fitness routine.
  - Patient 2-009 chondrosarcoma patient appeared to have disease progression by RECIST. At surgery, his tumor was necrotic.

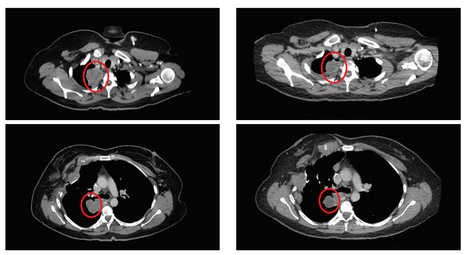
### Lung Lesions in Patient 3-003 Angiosarcoma




- Angiosarcoma – UV-induced originating on scalp, metastatic Stage 4, poorly-differentiated.
- 73 year-old male
- High (>16) bTMB score
- Dosing at 60 mg TIW

- Confirmed PR of target lesion (-70% in target lesion in lungs).
  - Non-target lesions regressed as well
  - PI reports that remaining lesions appear to be necrotic/scar tissue
- 3 prior lines of treatment:
  - Bev/Doc/Gem/Paclitaxel (CR)
  - Paclitaxel (PD)
  - WEE1 inhibitor (PD)

### Lung Lesions in Patient 1-015 Chondrosarcoma

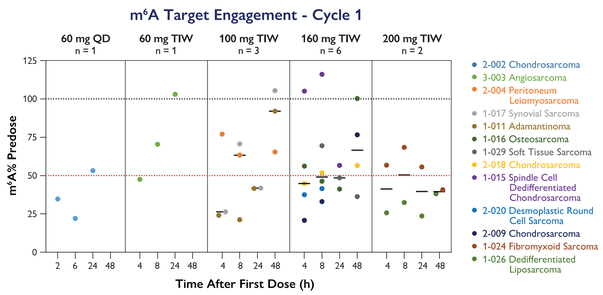



- Spindle cell dedifferentiated chondrosarcoma – metastatic, Stage 4, moderately differentiated
- 39 year-old female
- PHF1-TFE3 gene fusion positive and Caspase-8 deleterious mutation
- Dosing at 160 mg MWF

- Best overall response in target lesion -21% (SD)
- 4 prior lines of treatment:
  - Cistplatin/Doxo (CR)
  - Ifofsamide (SD)
  - Votrient (SD)
  - Fascin inhibitor (SD)

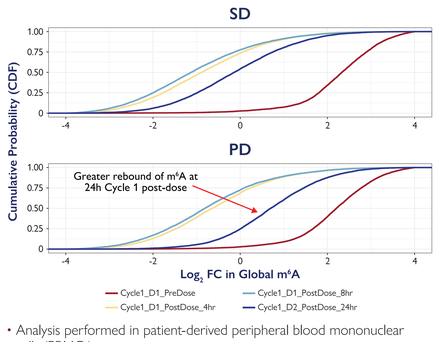
## STC-15 Impact on $m^6A$ and Gene Expression in Clinical Samples

### STC-15 Inhibits $m^6A$ in Sarcoma Patients




- METTL3 is the catalytic subunit of a methyltransferase complex that adds a methyl group to mRNA creating $N^6$-methyladenosine ($m^6A$) – the most abundant mRNA modification.
- $m^6A$ MSD assay demonstrates a >50% reduction in $m^6A$ (methylated adenosine) marks on mRNA within 24 hours of dosing across dose cohorts.

### Alida Bio EpiPlex™ RNA Modification Profiling – METTL3 Inhibition and Target Engagement

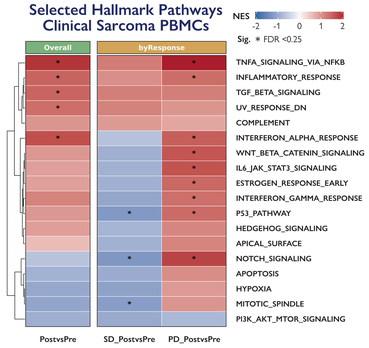



- Analysis performed in patient-derived peripheral blood mononuclear cells (PBMCs).

- The EpiPlex™ platform allows for the detection, localization, and quantification of multiple RNA modifications, including $m^6A$, in parallel with measuring RNA expression.
- Cumulative density function (CDF) plot shows the median $\log_2$ fold change (FC) (x-axis) in global $m^6A$ vs. control when 25%, 50%,75% of the cumulative data are observed (y-axis).
- During Cycle 1, a time-dependent decrease in global $m^6A$ was achieved with a greater recovery observed in the progressive disease cohort (PD) relative to stable disease (SD).
- Collectively, this data suggest that a more durable reduction in $m^6A$ may result in an improved clinical response.

### Alida EpiPlex Gene Expression Analysis

**Selected Hallmark Pathways Clinical Sarcoma PBMCs**




**Confirmed METTL3 Target Engagement:**

- Inflammatory pathways positively enriched with treatment.

**By Response: Stable (SD) vs. Progressive Disease (PD)**

- NOTCH, WNT and HEDGEHOG pathways showed the greatest differences in enrichment between the PD and SD groups.
- Switch from positive enrichment in PD to negative enrichment in SD indicates that these pathways are down-regulated by STC-15.

## Conclusions

- STC-15 is well-tolerated and showed preliminary clinical benefit in a broad cohort of sarcoma patients.
- Sarcomas are vulnerable to METTL3 inhibition by disrupting the transformation and self-renewal of mesenchymal stem cells differentiating into sarcoma cells.
- Early biomarker analysis reveals that the duration of $m^6A$ target engagement may be correlated with clinical benefit.
- Better clinical outcomes may be associated with down-regulation of METTL3-dependent pathways involved in cancer stem cell maintenance and de-differentiation, including WNT and NOTCH.

### Next Steps

- Phase 2 Study in Selected Sarcomas is enrolling patients at US sites (NCT06975293).
- STC-15 is available to patients with sarcomas and other tumors deriving from a mesenchymal origin via Expanded Access.