Abstract #587

A Phase 1b/2 Dose Escalation and Expansion Study of STC-15, a METTL3 Inhibitor, in Combination with Toripalimab, an Anti-PD-1 Antibody, in Patients with Advanced Solid Tumors

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Background

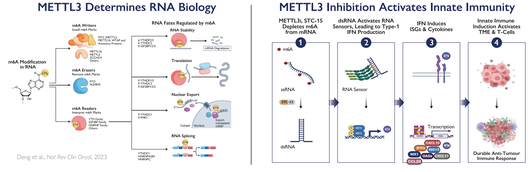
RNA modifications profoundly impact RNA fate and have emerged as key post-transcriptional regulators in cancer. N6-Methyladenosine (m6A), the most prevalent internal mRNA modification, is installed by the RNA methyltransferase METTL3. METTL3 drives oncogenesis, tumor persistence, and tumor immune evasion by downregulating tumor suppressor pathways, including immune checkpoints. Conversely, METTL3 inhibition has been shown to enhance antitumor immunity by upregulating PD-L1 expression on tumor cells, promoting CD8+ T and NK cell tumor infiltration, reducing immunosuppressive myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), and coordinating immuno-stimulatory changes in the tumor microenvironment. Targeting METTL3 offers a promising strategy to induce anti-tumor responses and overcome immune resistance.

STC-15 is a potent, first-in-class small molecule inhibitor of METTL3. Initial Phase 1 trial data demonstrated that STC-15 monotherapy induced durable, well-tolerated clinical responses in patients with advanced solid tumors. Preclinical findings demonstrate that STC-15 sensitizes the tumor microenvironment to checkpoint blockade, suggesting that combination therapy of STC-15 and toripalimab, an anti-PD-1 antibody, will provide a synergistic therapeutic benefit to enhance clinical activity.

Mechanisms of Action

- Dysregulation of m6A modification frequently occurs in many types of cancer, influencing malignant phenotypes and behaviors by controlling the expression of oncogenes and tumor suppressor genes and the regulation of different biological processes, including innate immunity, DNA repair and differentiation
- Previously, we have shown that METTL3 inhibition or m6A removal activates innate immunity through the interferon and nuclear factor kappa B (NF-kB) pathways. This activation leads to interferon signaling, signal transducer and activator of transcription 1 (STAT-1) phosphorylation, increased expression of Interferon-stimulated genes (ISGs), and secretion of cytokines and chemokines, enhancing the response of cytotoxic T-cells and a shifting towards an inhospitable tumor microenvironment
- More recently, we have demonstrated in immunocompetent preclinical models the ability of STC-15 to potentiate the effects of the checkpoint inhibitor aPD-1 that is consistent with activation of the innate immune response and remodeling of an immunosuppressive tumor microenvironment into an immunostimulatory, anti-tumor state resulting in T-cell mediated tumor growth inhibition
- Collectively, this provides the early rationale for the combination of our METTL3 inhibitor, STC-15, with the anti-PD1 checkpoint inhibitor Toripalimab

Figure 3. STC-15 Mechanism of Action



Trial Design

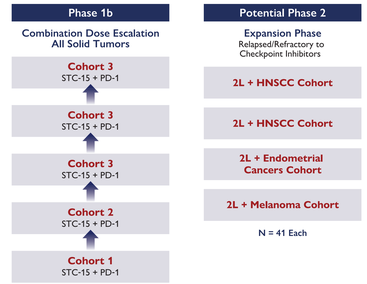
This is an open-label, non-randomized, multi-cohort, multicenter Phase 1b/2 dose-escalation and expansion study to investigate the efficacy, safety, tolerability, and pharmacokinetics/pharmacodynamics (PK/PD) of STC-15 in combination with toripalimab in patients with advanced solid tumors.

Phase 1b Dose Escalation evaluates multiple ascending doses of STC-15 in combination with toripalimab (240 mg Q3W) using a modified Fibonacci 3+3 design to evaluate dose-limiting toxicities (DLTs) during Cycle 1 and determine the recommended Phase 2 dose (RP2D). A fixed dose of toripalimab will be administered via intravenous (IV) infusion on Day 1 of each 21-day cycle. Approximately 24 to 36 participants with unresectable, locally advanced, or metastatic cancers will be treated and evaluated in the Phase 1b combination dose escalation part to evaluate the rate of DLTs.

The Phase 2 dose-expansion will use a Simon 2 Stage design to evaluate the combination of STC-15 at RP2D with toripalimab in 164 participants (up to 41 per cohort) with recurrent or metastatic non-small cell lung cancer (NSCLC), melanoma, endometrial cancers, or head and neck squamous cell carcinoma (HNSCC) that have progressed following anti-PD-1/L1 therapy.

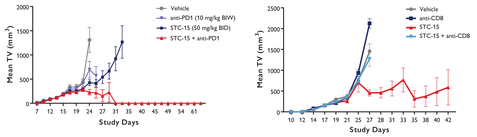
Whole blood will be collected to analyze PD via m6A quantification and ctDNA. Plasma, serum, and optional biopsies will be collected to determine treatment PK, transcriptional changes, and profile immune activation.

Figure 7. STC-15 Phase 1b/2 Study Schema



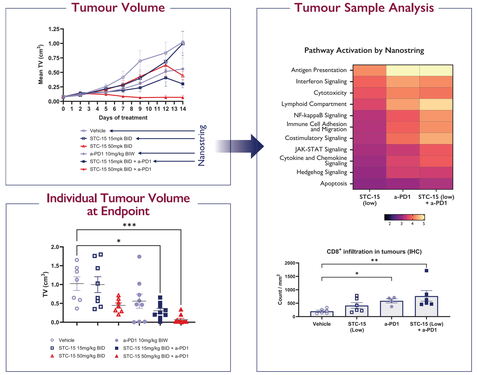
STC-15 Efficacy is T-Cell Mediated

Figure 1. A20 Lymphoma Model – STC-15 + PD1



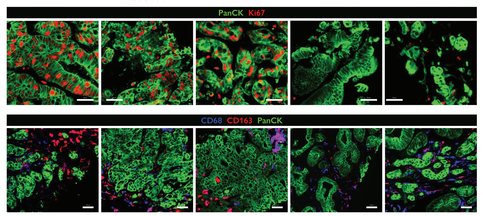
STC-15 + PD1 in MC38 Colorectal Cancer Model

Figure 2. STC-15 + PD1 in MC38 Colorectal Cancer Model



Tumor Biopsy Analysis

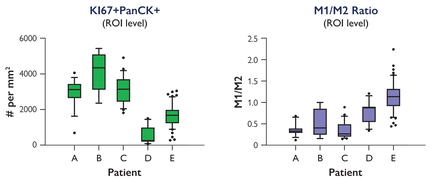
Figure 4. Assessment of Tumor Proliferation and Macrophage Infiltration in GI Cancer Biopsies



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

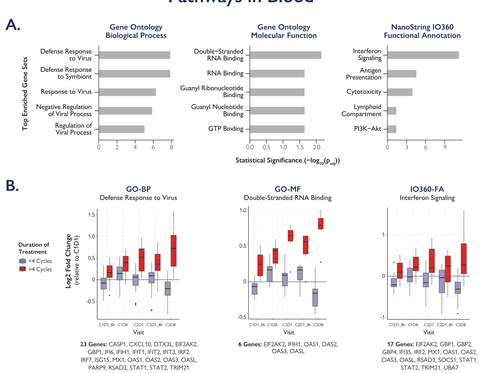
¹Discontinued treatment prior to 16-week scan.
PanCK: Tumor cells; Ki67: Proliferation marker; CD68+CD163-: M1 macrophages; CD68+CD163+: M2 macrophages.

Figure 5. Tumor Cell Proliferation and M1/M2 Ratio in Tumor Biopsies



Gene Expression

Figure 6. STC-15 Activates Innate Immunity Pathways in Blood



- 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 (Figure 6A)
- Box plots were generated for the highest scoring terms in (Figure 6A), comparing the fold changes in each visit against the pre-treatment baseline of the relevant genes (Figure 6B)
- 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

Objectives

Phase 1b

Primary

- To evaluate the safety and tolerability of the combination (STC-15 and toripalimab) and to determine the recommended Phase 2 dose (RP2D) of STC-15 to be administered in combination with toripalimab

Secondary

- To evaluate the antitumor activity of the combination of STC-15 combined with toripalimab as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and immune RECIST (iRECIST) criteria
- To characterize the PK profile of STC-15 in combination with toripalimab
- To evaluate the RP2D of STC-15 in combination with toripalimab

Phase 2

Primary

- To evaluate the antitumor activity of STC-15, administered at RP2D, combined with toripalimab
- To evaluate the safety and tolerability profile of the combinations

Secondary

- To further assess the antitumor activity of STC-15 with defined combination therapy through duration of responses, survival, clinical benefit
- To characterize the PK profile of STC-15 in combination with toripalimab

Key Inclusion Criteria

- Male or Female patients ≥18 years of age with locally advanced or metastatic or unresectable solid tumors in both Part 1 & 2 with additional tumor specific criteria for Part 2 Expansion Cohorts of Melanoma, endometrial, NSCLC and HNSCC
- ECOG Performance status ≤1
- Estimated life expectancy ≥3 months
- Measurable disease according to RECIST 1.1 criteria
- Intact Hematologic and Organ Function: ANC ≥1,500 mm³, Platelets ≥100,000/mm³, Hemoglobin ≥9 g/dL, Serum creatinine ≤1.5 mg/dL, ALT and AST ≤3.0 times the upper limit of normal

Key Exclusion Criteria

- Women who are pregnant or lactating
- Active autoimmune disease
- Ongoing infection requiring systemic antibiotic therapy or with active EB, Hep B/C virus or HIV
- Clinically significant pulmonary disease, chronic or recurrent renal or urinary tract disease, liver disease, endocrine disorder
- Participants with a clinically significant cardiovascular disease or condition
- Major surgery within the last 4 weeks
- Prior systemic anticancer therapy, including investigational agents or devices, within 4 weeks prior to the first IMP administration

Current Status

The study is currently in Phase 1b dose escalation

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