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A Multicenter, Multi-Cohort, Phase II Study of Sacituzumab Tirumotecan with or Without Tislelizumab in Patients with Advanced Thyroid Cancer

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Background

Anaplastic thyroid carcinoma (ATC) is one of the most aggressive solid malignancies, characterized by rapid local invasion, early metastasis, and a median overall survival of less than one year despite multimodal therapy. Poorly differentiated thyroid carcinoma (PDTC) represents an intermediate biological entity between differentiated thyroid carcinoma (DTC) and ATC and is associated with significantly worse outcomes compared to well-differentiated disease.

Radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) develops resistance to radioactive iodine (RAI) therapy and carries a markedly reduced survival compared with RAI-sensitive DTC. Although multi-target tyrosine kinase inhibitors (TKIs) provide modest progression-free survival benefit, durable responses remain limited, and treatment resistance frequently occurs.

ATC is characterized by high tumor mutational burden, frequent PD-L1 expression, and substantial immune cell infiltration, suggesting potential sensitivity to immune checkpoint blockade. However, single-agent PD-1/PD-L1 inhibitors have demonstrated limited efficacy in this setting.

Sacituzumab tirumotecan is a humanized anti-TROP2 antibody-drug conjugate (ADC) linked to a topoisomerase I inhibitor payload. TROP2 is overexpressed

in multiple epithelial malignancies, including aggressive thyroid cancers. Preclinical studies have demonstrated significant antitumor activity of sacituzumab tirumotecan in ATC xenograft models. Combination with PD-1 blockade may further enhance anti-tumor immunity by promoting immunogenic cell death and tumor antigen release.

Given the unmet clinical need and strong biological rationale, this study aims to explore the efficacy and safety of sacituzumab tirumotecan with or without tislelizumab in patients with advanced thyroid cancer.

Study Objectives

Primary Objectives

- To evaluate overall survival (OS) in patients with unresectable or metastatic ATC treated with sacituzumab tirumotecan in combination with tislelizumab.
- To evaluate progression-free survival (PFS) in patients with unresectable or metastatic PDTC and RAIR-DTC treated with sacituzumab tirumotecan monotherapy.

Secondary Objectives

- To evaluate PFS in the ATC cohort.
- To evaluate OS in the PDTC and RAIR-DTC cohorts.
- To evaluate objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) according to RECIST v1.1.
- To evaluate R0/R1 resection rate in PDTC patients who become surgically resectable during treatment.
- To evaluate safety and tolerability according to NCI CTCAE v5.0.

Exploratory Objectives

- To assess correlations between TROP2 expression and clinical outcomes.
- To evaluate tumor genomic and immune profiling, including next-generation sequencing (NGS), circulating tumor DNA (cfDNA), and immune-related biomarkers.
- To evaluate longitudinal changes in tumor microenvironment and systemic immune parameters.

Study Design

This is a multicenter, open-label, multi-cohort, Phase II exploratory study.

Approximately 94 patients will be enrolled across three parallel cohorts:

- ATC cohort (n=40)
- PDTC cohort (n=30)
- RAIR-DTC cohort (n=24)

Study Population

Inclusion Criteria

Participants must meet **all** of the following criteria:

1. Age ≥ 18 years at the time of informed consent.
2. Histologically confirmed unresectable, locally advanced, or metastatic:
    - Anaplastic thyroid carcinoma (ATC), or
    - Poorly differentiated thyroid carcinoma (PDTC), or
    - Radioactive iodine-refractory differentiated thyroid carcinoma (RAIR-DTC), including papillary thyroid carcinoma or follicular thyroid carcinoma and variants.
3. For ATC or PDTC:
    - No BRAF V600E mutation, RET fusion, NTRK fusion, or ALK fusion;
    - Or harboring such alterations but have failed prior standard first-line targeted therapy.

4. For RAIR-DTC:

   Disease must be refractory to radioactive iodine (RAI), defined as at least one of the following:

   - No RAI uptake in measurable lesions;
   - Radiographic progression within 12 months after RAI therapy;
   - Cumulative RAI dose >600 mCi (or iodine-equivalent);
   - Fluorodeoxyglucose (FDG)-avid measurable disease;
   - Failure of prior multi-target tyrosine kinase inhibitor (TKI) therapy.

5. At least one measurable lesion per RECIST version 1.1.
6. ECOG performance status 0–2.
7. Life expectancy ≥ 12 weeks.
8. Adequate hematologic function:
   - Absolute neutrophil count ≥ 1.2×10^9/L
   - Platelet count ≥ 100×10^9/L
   - Hemoglobin ≥ 90 g/L
9. Adequate hepatic function:
   - AST and ALT ≤ 2.5 × upper limit of normal (ULN)
   - ≤ 5 × ULN if liver metastases present
   - Total bilirubin ≤ 1.5 × ULN
10. Adequate renal function:

- Creatinine clearance ≥ 60 mL/min (Cockcroft–Gault formula)

11. No active autoimmune disease requiring systemic therapy.
12. No concurrent active malignancy requiring treatment.
13. Willing and able to provide written informed consent.

Exclusion Criteria

Participants meeting **any** of the following criteria will be excluded:

1. Prior therapy targeting TROP2.
2. Prior treatment with any topoisomerase I inhibitor antibody-drug conjugate.
3. Prior immune checkpoint agonists (e.g., ICOS, CD40, CD137, GITR, OX40) or immune cell therapy.
4. Another malignancy within 3 years prior to first dose, except adequately treated localized cancers (e.g., basal cell carcinoma, squamous cell carcinoma of the skin, carcinoma in situ of the cervix).
5. Uncontrolled or symptomatic central nervous system metastases.
    - Patients with treated and stable CNS disease for ≥4 weeks and off corticosteroids for ≥2 weeks may be eligible.
6. Significant uncontrolled comorbidities including, but not limited to:
    - Uncontrolled hypertension
    - Severe diabetes mellitus
    - Active infection

7. History of interstitial lung disease (ILD) or non-infectious pneumonitis requiring steroids, or current suspected ILD.
8. Unresolved toxicities from prior anti-cancer therapy greater than Grade 1 (CTCAE v5.0), except alopecia or other clinically insignificant toxicities.
9. Active autoimmune disease requiring systemic treatment within the past 2 years (excluding hormone replacement therapy such as levothyroxine or physiologic corticosteroids).
10. Systemic corticosteroid use >10 mg/day prednisone equivalent within 10 days prior to first dose (except inhaled, topical, or physiologic replacement doses).
11. Known HIV infection or AIDS.

    Active syphilis infection.
12. History of allogeneic organ transplantation or hematopoietic stem cell transplantation.
13. Known severe hypersensitivity to study drugs or components.
14. Chemotherapy, radiotherapy, immunotherapy, biologic therapy, TKI, or systemic immune stimulation within protocol-defined washout period prior to first dose.
15. Pregnant or breastfeeding women.
16. Severe ocular disorders that may interfere with corneal healing (e.g., severe dry eye syndrome, severe meibomian gland disease).

Treatment Regimens

ATC cohort:

Sacituzumab tirumotecan 5 mg/kg intravenously plus tislelizumab 200 mg intravenously on Day 1, Day 15, and Day 29 of each 6-week cycle.

PDTC and RAIR-DTC cohorts:

Sacituzumab tirumotecan 5 mg/kg intravenously on Day 1, Day 15, and Day 29 of each 6-week cycle.

Treatment will continue until radiographic disease progression, unacceptable toxicity, withdrawal of consent, death, or investigator decision.

Tumor Assessments

Radiographic tumor assessments will be performed:

- Every 6 weeks (±7 days) during the first year
- Every 12 weeks (±7 days) thereafter

Tumor response will be evaluated by investigators according to RECIST version 1.1.

For patients who achieve resectability (R0 or R1 resection) during treatment:

- Surgery will not be considered a PFS event.
- PFS will be calculated from the date of first dose.
- ORR and DCR will be based on the best preoperative imaging response.

Patients who discontinue treatment for reasons other than disease progression will continue radiographic assessments until documented progression or initiation of new anticancer therapy.

Statistical Considerations

This is an exploratory Phase II study with fixed sample sizes per cohort.

Time-to-event endpoints (OS and PFS) will be estimated using the Kaplan-Meier method with corresponding 95% confidence intervals. ORR and DCR will be summarized with exact (Clopper–Pearson) confidence intervals. Safety analyses will include incidence and severity of adverse events.

The study is designed to generate preliminary efficacy signals and biomarker hypotheses to support future confirmatory trials.