

Sacituzumab govitecan in patients with advanced or metastatic radioactive-iodine refractory thyroid carcinoma: The phase 2 SETHY, GETNE-T2318 trial

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INTRODUCTION

Thyroid cancer is the most common endocrine neoplasm with high prevalence worldwide. Based on histology, thyroid cancers are classified into differentiated thyroid cancers (DTC) that include papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), and undifferentiated, the anaplastic thyroid carcinoma (ATC) ¹⁻³. Recent studies revealed that the transmembrane glycoprotein and calcium signal transducer trophoblast cell-surface antigen 2 (TROP2) is a key tumor development factor ⁴ and highly expressed among patients with thyroid cancer, in up to 82,5% ⁵. Elevated TROP2 expression closely correlates with tumor aggressiveness and poor prognosis ⁶. Therefore, TROP2 constitutes a potential target for treatment ⁷. Sacituzumab govitecan (SG) is a TROP2-directed antibody-drug conjugated (ADC) enclosing a payload of SN-38, a topoisomerase I inhibitor (Fig.1) ⁸. By targeting TROP2 expressing tumor cells, SG can deliver cytotoxic chemotherapy to tumors, including adjacent cancer cells, in concentrations that are higher than those with standard chemotherapy, and reduce toxic effects in normal tissues that do not express the target ⁹. Based on these evidences the SETHY trial aims to seek for the effectiveness and safety of treatment with sacituzumab govitecan in DTC and ATC patients.

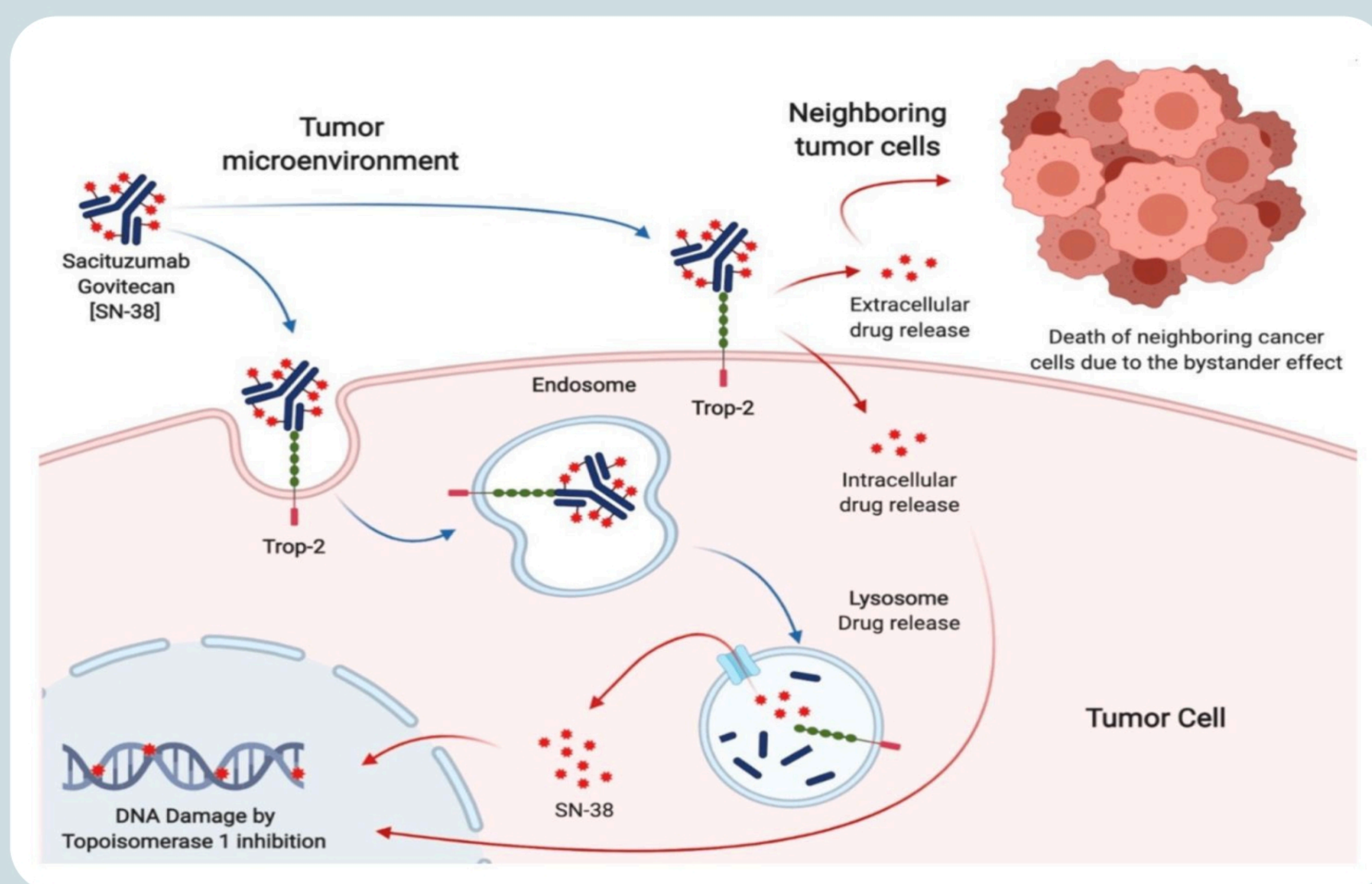


Figure 1. Sacituzumab govitecan mechanism of action (extracted from Pavone G et al. Molecules 2021)

TRIAL DESIGN

The SETHY trial is a multicenter, open label, two-cohort, single arm, phase II study to evaluate the efficacy and the safety of sacituzumab govitecan in patients with advanced DTC and ATC (Fig.2 & 3). Sacituzumab govitecan (10 mg/kg intravenously) will be administered on Days 1 and 8 of a 21-day cycle (Fig.4). Patients will be treated until progression, death, study withdrawal, or unacceptable toxicity.

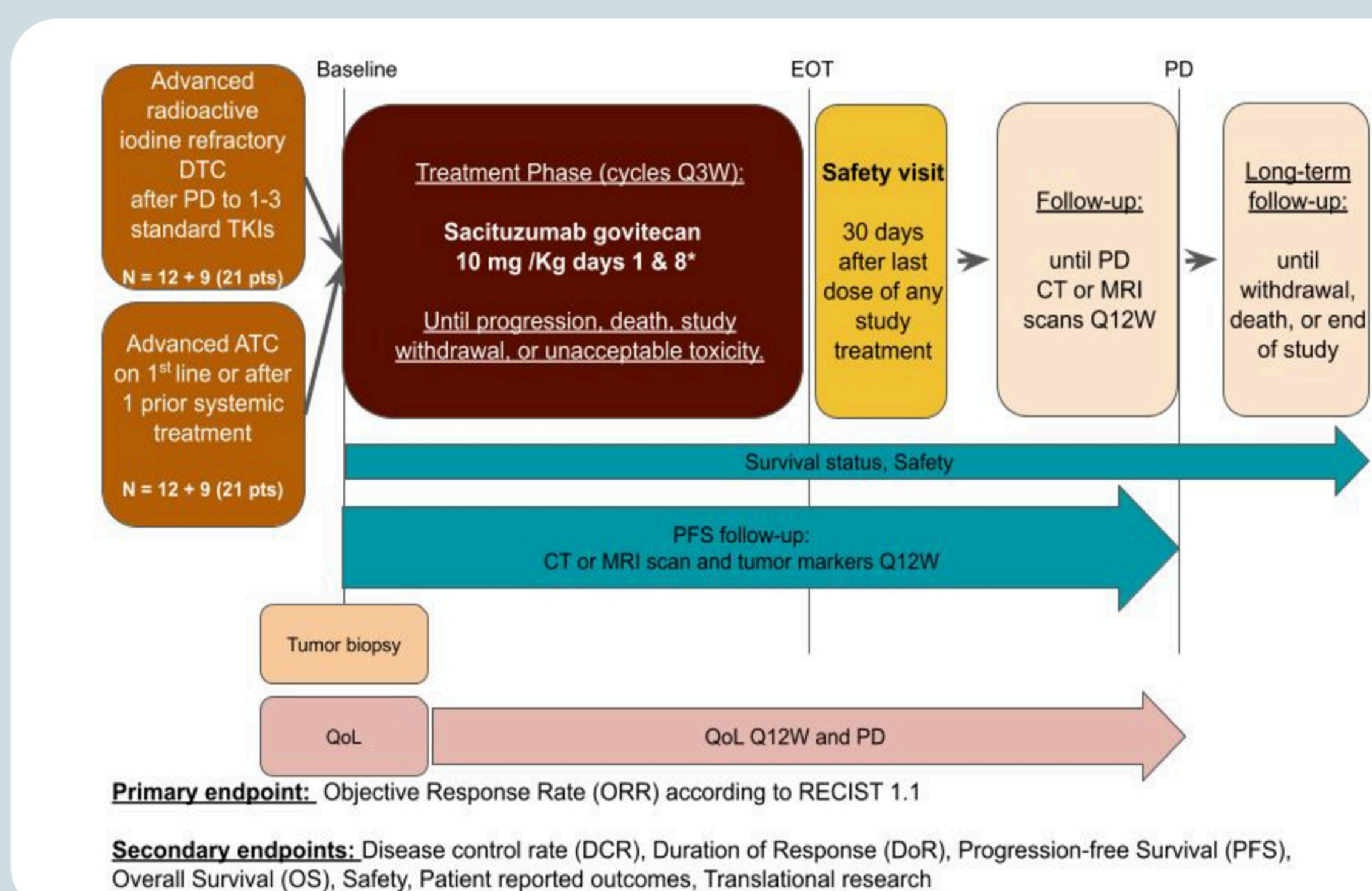


Figure 2. Study scheme.

OBJECTIVES

Primary:

- ❖ To assess the efficacy and safety of sacituzumab govitecan for differentiated and anaplastic thyroid neoplasms using objective response rate (ORR) according to RECIST V1.1.

Secondary:

- ❖ To determine clinical outcomes such as disease control rate (DCR), duration of response (DoR), progression free survival (PFS) and overall survival (OS) of sacituzumab govitecan.
- ❖ To determine the correlation of risk factors in the efficacy of sacituzumab govitecan for differentiated and anaplastic thyroid neoplasms.
- ❖ To determine the correlation between TROP2 expression levels at baseline and the efficacy of sacituzumab govitecan for differentiated and anaplastic thyroid neoplasms.
- ❖ To determine the correlation between pathology-specific genetic alterations (i.e. TP53, TERT, BRAF or RAS mutations; NTRK and ALK rearrangements; RET fusions) at baseline, and the levels of TROP2 and the efficacy of sacituzumab govitecan.

SAMPLE SIZE

A total of 21 patients per cohort will be included using a Simon II stage design, establishing that ORR = 5% (null hypothesis) versus an alternative of ORR = 20%, with $\alpha=0.1$ and $\beta=80\%$. The Stage I will include 12 patients per cohort. If there is one or more confirmed responses reported, the cohort will be expanded with 9 additional patients to the expected 21 patients.

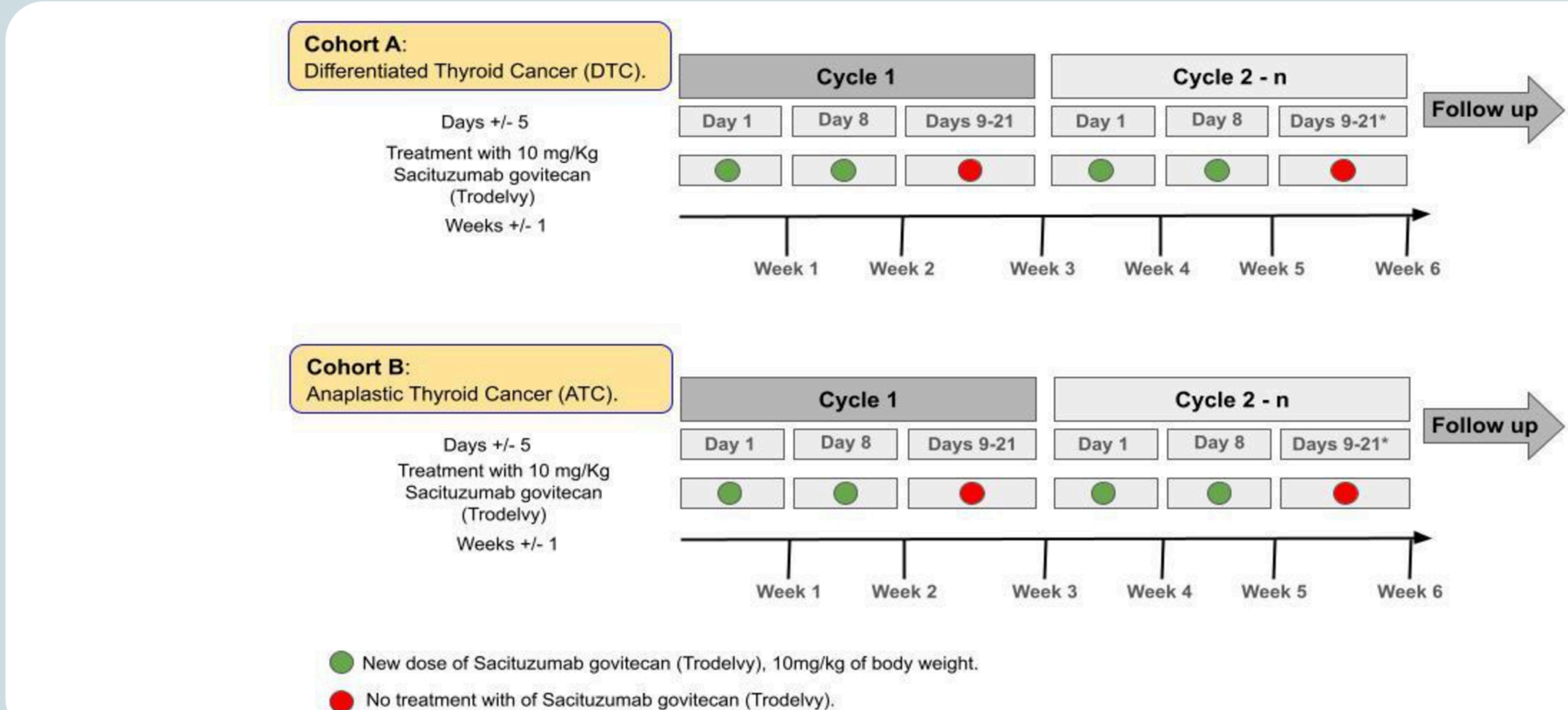


Figure 4. Schema of Study Treatment.

PATIENT ELIGIBILITY

Inclusion

- ≥ 18 years old (male or female).
- Histologically confirmed metastatic or locally advanced unresectable radioactive-iodine refractory DTC (Cohort A) or ATC (Cohort B).
- Patients with DTC must have progressed to 1 -3 previous systemic therapies with approved drugs (Sorafenib, Lenvatinib or Cabozantinib).
- Patients with ATC must be included in first-line setting or after progression to 1 systemic therapy.
- ECOG-PS of 0-1.
- Available archival tissue sample (if not a new biopsy tissue sample should be provided).
- Adequate organ function without transfusional support.

Exclusion

- Patients with central nervous system metastasis.
- History of another malignancy within 3 years.
- Active infections.
- Uncontrolled hypertension or diabetes.
- Cardiac diseases.
- Active chronic obstructive pulmonary disease or inflammatory bowel disease are excluded.
- Previous local therapies should be finished 4 weeks before the first dose of study treatment.

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- **Accrual started in May 2024 and is expected to last until January 2026.**
- **Recruitment for Stage I (9 patients) expected to be completed by May 2025.**

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