Trend-02 study - a phase ii exploratory de-escalation trial of neoadjuvant sacituzumab govitecan plus tislelizumab (sg/i) in early triple-negative breast cancer

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Abstract

- Refining neoadjuvant chemoimmunotherapy and establishing predictive biomarkers remain pivotal challenges in early TNBC. Although SG/P (sacituzumab govitecan/PD-1 inhibitor) shows clinical promise, validation of responder identification tools is warranted.
- This phase II trial aims to identify a precision TNBC population suitable for de-escalated neoadjuvant therapy with sacituzumab govitecan plus tislelizumab, based on differential Trop-2 expression (±) and PD-L1 status (CPS >10% vs. <10%). Primary endpoints include pCR rate and safety; exploratory biomarker analyses will assess mechanisms of response/resistance.

Introduction

- **Sacituzumab Govitecan (SG)** is a TROP-2-directed antibody-drug conjugate (ADC) approved for the treatment of metastatic triple-negative breast cancer (TNBC) and hormone receptor-positive (HR+), HER2-negative metastatic breast cancer.
- **Tislelizumab (I)** is a humanized IgG4 variant monoclonal antibody targeting programmed cell death protein 1 (PD-1). Characterized by high specificity, high affinity for PD-1, and slow dissociation kinetics, it theoretically enables more durable blockade of immunosuppressive signals and enhances anti-tumor immune responses. Currently, tislelizumab combined with chemotherapy has demonstrated survival benefits in the first-line treatment of multiple tumor types, including esophageal squamous cell carcinoma (ESCC) and metastatic nasopharyngeal carcinoma (NPC) . Recently, the European Medicines Agency (EMA) granted an additional approval for its use in first-line NPC treatment. In China, tislelizumab has received National Medical Products Administration (NMPA) approval for 14 indications, with 11 indications already included in the National Reimbursement Drug List (NRDL). This makes it the domestically developed PD-1 inhibitor with the highest number of approved and NRDL-listed indications in China. Given the favorable efficacy and well-tolerated safety profile demonstrated by tislelizumab across various tumor types, its potential application in the neoadjuvant setting for TNBC warrants further investigation, aiming to provide additional clinical benefits for TNBC patients.

Methods and Materials

Primary Objective

- To evaluate the pathological complete response (pCR) rate (ypT0/Tis ypN0) following neoadjuvant sacituzumab govitecan plus immunotherapy (SG/I) in biomarker-selected TNBC.

Secondary Objectives

- Proportion requiring protocol-permitted additional NACT at investigator's discretion
- Radiographic response rate (RR)
- Safety and tolerability
- 24-month event-free survival (EFS)

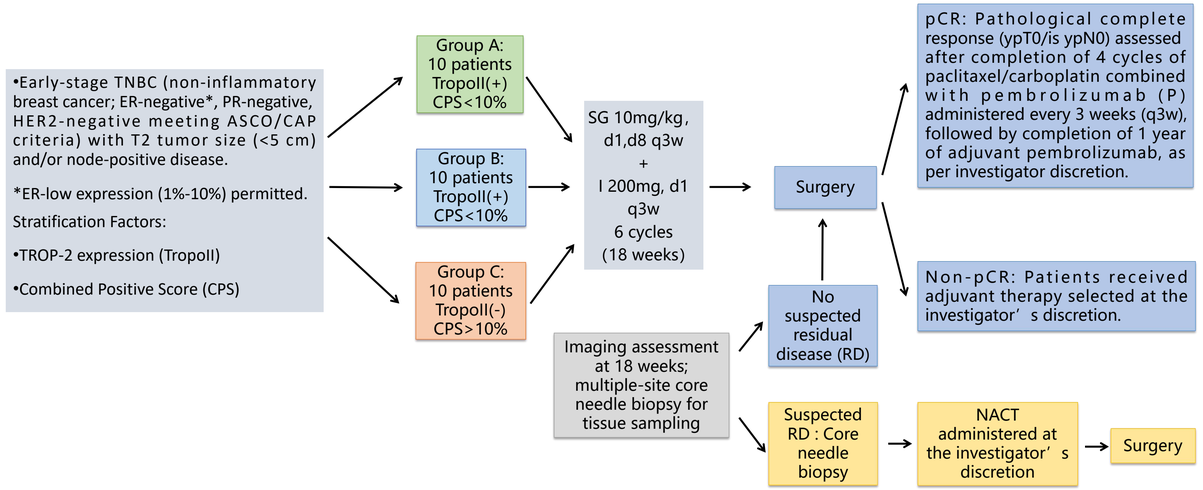


Figure 1. Study design of TREND-02.

Discussion

- Although the KEYNOTE-522 study[1] demonstrated that adding an immune checkpoint inhibitor (ICI) to neoadjuvant TCb-AC chemotherapy significantly improved pathological complete response (pCR) rates, translating into enhanced event-free survival (EFS) and overall survival (OS) benefits, optimization of the chemotherapy backbone and identification of patients most likely to benefit remain critical areas for exploration. Currently, while platinum-based agents are the predominant chemotherapy partners in neoadjuvant immunotherapy regimens, their associated severe myelosuppression may compromise immune efficacy by impairing innate immune cell function. Furthermore, the pronounced heterogeneity of TNBC in clinical characteristics and treatment responses significantly complicates the selection of therapeutic targets and the development of precise treatment strategies.
- Consequently, defining the molecular features dictating TNBC response to immunotherapy and identifying novel biomarkers are crucial for selecting patients who will derive benefit.
- The single-center, prospective, single-arm phase II TREND trial[2] (ChiCTR2000035262) aims to evaluate the efficacy and safety of tislelizumab combined with a low-dose, platinum-free chemotherapy regimen (Nab-P-AC: nab-paclitaxel 100mg/m² followed by epirubicin 75mg/m² + cyclophosphamide 600mg/m²) as neoadjuvant therapy for TNBC. It further employs multi-omics analyses to identify predictive biomarkers and characterize dynamic features of the tumor microenvironment (TME). This study is the first in the neoadjuvant TNBC setting to demonstrate that this synergistic combination of a platinum-free, reduced-dose chemotherapy regimen (nab-paclitaxel reduced from 125mg/m² to 100mg/m²; epirubicin reduced from 90mg/m² to 75mg/m²) with tislelizumab achieved a pCR rate of 68.2% (15/22), comparable to platinum-containing regimens, while significantly reducing the incidence of grade ≥3 hematological toxicities to 11.32%.
- The NeoSTAR study (NCT04230109) [3]is a response-guided phase II trial investigating neoadjuvant sacituzumab govitecan and pembrolizumab (SG/P) in early-stage TNBC. This cohort evaluated 4 cycles of neoadjuvant SG + P: 16 out of 50 patients (32%) achieved pCR after 4 cycles of SG/P. This regimen demonstrated a more favorable toxicity profile compared to the standard KEYNOTE-522 regimen. These results indicate that SG/P is a promising combination strategy for early-stage TNBC; however, further work is needed to identify the patients most likely to achieve a response with this regimen.

Conclusions

- This phase II trial aims to identify a precision TNBC population suitable for de-escalated neoadjuvant therapy with sacituzumab govitecan plus tislelizumab, based on differential Trop-2 expression (±) and PD-L1 status (CPS >10% vs. <10%). Primary endpoints include pCR rate and safety; exploratory biomarker analyses will assess mechanisms of response/resistance.

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