ASCENT-05/OptimICE-RD (AFT-65): Phase 3, Randomized, Open-label Study of Adjuvant Sacituzumab Govitecan + Pembrolizumab vs Pembrolizumab ± Capecitabine in Patients With Triple-Negative Breast Cancer and Residual Disease After Neoadjuvant Therapy and Surgery

Poster TPS619

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Background

- Triple-negative breast cancer (TNBC) has an aggressive disease course with poor prognosis for patients with residual disease (RD) after neoadjuvant therapy (NAT)[1] and there is a high unmet need for new treatment options
- In the phase 3 KEYNOTE-522 study, patients with TNBC treated with neoadjuvant chemotherapy + the immune checkpoint inhibitor pembrolizumab (pembro) then adjuvant pembro ± radiotherapy for a total of ~1 year had a 3-year event-free survival of 85%[2]
- Sacituzumab govitecan (SG) is a Trop-2–directed antibody-drug conjugate (Figure 1) approved for pretreated metastatic TNBC (mTNBC) in multiple countries and for pretreated HR+/HER2– metastatic breast cancer in the United States[3-7]
- In the phase 3 ASCENT study, SG significantly improved both progression-free survival and overall survival (OS) compared with standard chemotherapy in patients with mTNBC who received ≥ 2 lines of systemic therapy, with a manageable safety profile[8]
- Preclinical data suggest that the SN-38 payload of SG potentiates the activity of immune checkpoint inhibitors by enhancing antitumor immunity and increasing lymphocyte recruitment to the tumor via the activation of the stimulator of interferon genes (STING) pathway[9-11]
  - Thus, the combination of SG plus pembro has the potential to improve clinical outcomes in patients with mTNBC

Objective

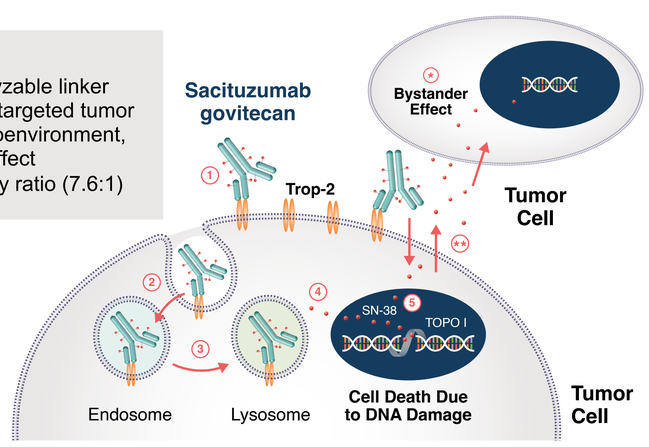
- The ASCENT-05/OptimICE-RD (AFT-65) study, conducted in collaboration with the Alliance Foundation Trials (AFT), will assess the impact of adjuvant therapy with the combination of SG plus pembro in patients with TNBC and RD after NAT

Figure 1. Sacituzumab govitecan: a novel antibody-drug conjugate[3-5]

SN-38 payload
- SN-38 more potent than parent compound, irinotecan (TOPO I inhibitor)
- SN-38 rapidly internalized and efficiently released to the tumor with minimized effect on healthy tissues

Linker for SN-38
- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)

Humanized anti–Trop-2 antibody
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

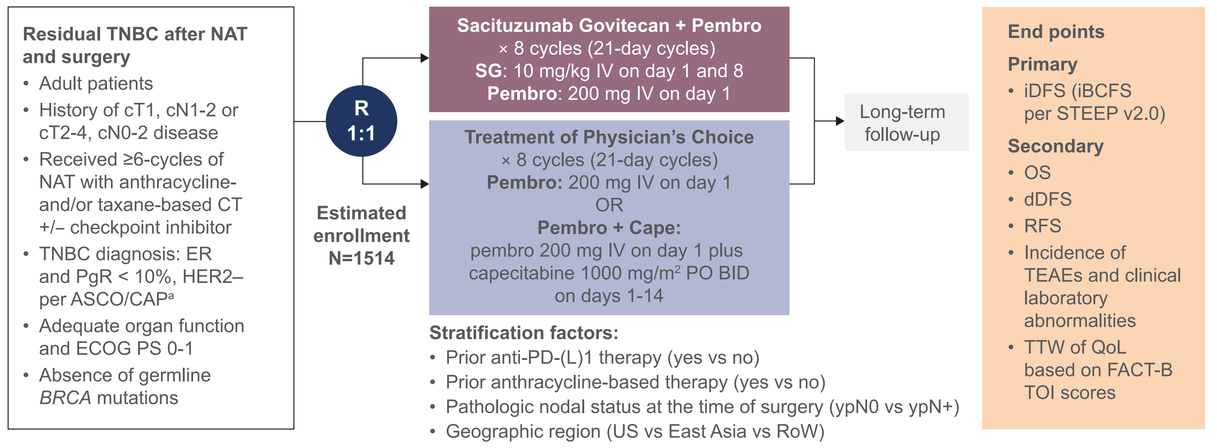


Adapted from Rugo HS, et al. TROPiCS-02: A phase III study investigating sacituzumab govitecan in the treatment of HR+/HER2- metastatic breast cancer. *Future Oncol*. 2020; 16:705-715. Complete licensing info can be found here: http://creativecommons.org/licenses/by-nc-nd/4.0/.

TOPO I, topoisomerase I; Trop-2, trophoblast cell surface antigen 2.

Methods

Figure 2. An open-label, global, multicenter, randomized phase 3 study of adjuvant SG combined with pembro versus TPC in patients with TNBC and RD after neoadjuvant therapy and surgery (NCT05633654)

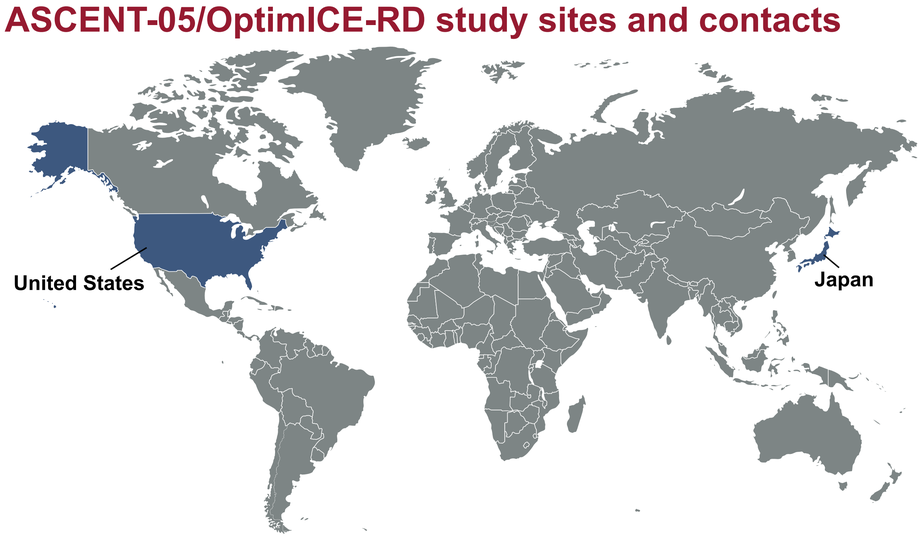


[a]IHC0, IHC1+, or IHC2+/ISH–.

ASCO, American Society of Clinical Oncology; BID, twice daily; CAP, College of American Pathologists; Cape, capecitabine; dDFS, distant disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; FACT-B, functional assessment of cancer therapy for breast cancer; *BRCA*, breast cancer gene; HER2, human epidermal growth factor receptor 2; iBCFS, invasive breast cancer-free survival; iDFS, invasive disease-free survival; IHC, immunohistochemistry; ISH, in-situ hybridization; IV, intravenous; NAT, neoadjuvant therapy; OS, overall survival; Pembro, pembrolizumab; PO, orally; PgR, progesterone receptor; QoL, quality of life; R, randomized; RFS, recurrence-free survival; RoW, rest of the world; SG, sacituzumab govitecan; STEEP, standardized definitions for efficacy end points; TEAEs, treatment-emergent adverse events; TNBC, triple-negative breast cancer; TOI, trial outcome index; TPC, treatment of physician's choice; TTW, time to worsening; US, United States.

Study Sites/Enrollment

Figure 3. ASCENT-05/OptimICE-RD study sites and contacts



Study enrollment for ASCENT-05/OptimICE-RD study (NCT05633654) began in January 2023 and is currently ongoing. Overall, enrollment will occur at approximately 300 sites initially in the United States and Japan. For more information, please visit https://clinicaltrials.gov/ct2/show/NCT05633654

Contact email: GileadClinicalTrials@gilead.com

Table 1. Key eligibility criteria

Inclusion	Exclusion
Aged ≥ 18 years, with a history of cT1, cN1-2 or cT2-4, cN0-2 TNBC with RD in the breast or lymph node(s) after NAT and surgery — TNBC diagnosis per local assessment is based on ER and PgR < 10%, HER2– per ASCO/CAP guidelines (IHC0, IHC1+, or IHC2+/ISH–) — TNBC confirmation from posttreatment surgical tissue is preferred if possible	Stage IV breast cancer as well as history of any prior ipsilateral or contralateral invasive breast cancer
	Prior NAT with anti-HER2 agents
	Prior treatment with another stimulatory or coinhibitory T-cell receptor agent
Adequate excision and surgical removal of all clinically evident disease in the breast and/or lymph nodes and adequate recovery from surgery[a]	Prior treatment with topoisomerase 1 inhibitors or ADCs containing a topoisomerase inhibitor
Must have received ≥ 6 cycles of neoadjuvant chemotherapy (taxane and/or anthracycline-based) with or without a checkpoint inhibitor	Evidence of recurrent or distant metastatic disease following preoperative therapy and surgery
Submission of both pre-neoadjuvant treatment diagnostic biopsy and resected residual invasive disease tissue	Germline *BRCA* mutations
Must have received appropriate radiotherapy and have recovered prior to starting study treatment	Myocardial infarction within 6 months of enrollment or history of serious ventricular arrhythmia or LVEF <50%
Adequate organ function and ECOG performance status 0-1	Active serious infection requiring treatment

[a]No more than 16 weeks should elapse between the completion date of surgery and the date of randomization.

ADCs, antibody-drug conjugates; ASCO, American Society of Clinical Oncology; *BRCA*, breast cancer gene; CAP, College of American Pathologists; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epithelial growth factor 2; IHC, immunohistochemistry; ISH, in-situ hybridization; LVEF, left ventricular ejection fraction; NAT, neoadjuvant therapy; PgR, progesterone receptor; RD, residual disease; TNBC, triple-negative breast cancer.

References: **1.** Gupta GK, et al. *Cancers (Basel)*. 2020;12:2392. **2.** Schmid P, et al. *N Engl J Med*. 2022;386:556-567. **3.** Rugo HS, et al. *Future Oncol*. 2020;16:705-715. **4.** Cardillo TM, et al. *Bioconjugate Chem*. 2015;26:919-931. **5.** Goldenberg DM, et al. *Oncotarget*. 2015;6:22496-22512. **6.** TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Gilead Sciences, Inc., Foster City, CA; February 2023. **7.** Trodelvy [summary of product characteristics]. The European Medicine Agency. (https://www.ema.europa.eu/en/medicines/human/EPAR/trodelvy); February 2023. **8.** Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541. **9.** Iwai T, et al. *Oncotarget*. 2018;9:31411-31421. **10.** McKenzie JA, et al. *J Natl Cancer Inst*. 2018;110:777-786. **11.** Parkes EE, et al. *J Natl Cancer Inst*. 2016;109:djw199.

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