Feasibility Assessment of an Indirect Treatment Comparison of Sacituzumab Govitecan vs. Trastuzumab Deruxtecan in HR+/HER2– Metastatic Breast Cancer

Poster #SA21

Scan for more information

Anuj Shah[1], Ryan Thaliffdeen[1], David Proudman[2], Wendy Verret[1], Nikoleta Sjekloca[3], Mario Campone[4]

[1]Gilead Sciences, Inc., Foster City, CA, USA; [2]Analysis Group, Inc., Menlo Park, CA, USA; [3]Gilead Sciences Europe Ltd., Uxbridge, UK; [4]Institut de Cancérologie de l'Ouest, France

Key Findings

- In this targeted literature review, four trials were found eligible for inclusion that matched the specific indications for HR+; two trials being identified for each of T-DxD (DAISY and DB04) and SG (IMMU-132-01 and TROPiCS-02).
- Most efficacy outcomes were generally available by histology for all trials, except IMMU-132-01, for which published efficacy outcomes stratified by HER2 expression levels are not available.
- Safety outcomes were only fully available for TROPiCS-02 and DB04, but not for DAISY (no safety data).
- The differences in design and population characteristics, as well as variable levels of available information on relevant population characteristics, efficacy and safety parameters demonstrate that an unbiased ITC (adjusted or unadjusted) for SG vs. T-DxD is not currently feasible in the directly overlapping population.

Conclusions

Heterogeneity in patient population, their baseline characteristics, prior treatment history, performance status, and lack of uniformity in reporting of efficacy outcomes and prognostic factors may result in residual differences between the SG and T-DxD population that cannot be adjusted for. This heterogeneity results in minimal effective comparability between trials and demonstrated only a modest overlap between the two populations, yielding a low effective sample size.

Therefore, an ITC to compare the relative efficacy and safety of SG and T-DxD among HR+/HER2- mBC patients is not currently feasible and no comparative conclusions can be made without risk of significant bias.

Introduction

- Single agent chemotherapy is the Standard of Care (SoC) among patients with metastatic breast cancer (mBC) despite low response rates, short progression-free survival, and poor survival rates associated with their use.
- In the hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) (IHC 0, 1+, 2+/ISH-) metastatic breast cancer trial (TROPiCS-02) among patients who received at least 2 lines of chemotherapy, Sacituzumab Govitecan (SG), an antibody–drug conjugate directed to human trophoblast cell-surface antigen 2 (Trop-2) demonstrated statistically significant improvements vs. chemotherapy in progression-free survival and overall survival[1,2]. Overall survival difference was found to be clinically meaningful.
- Separately, Trastuzumab Deruxtecan (T-DxD) also demonstrated clinical benefits in patients with HR+/HER2-low (IHC 1+, 2+/ISH-) mBC in the Destiny Breast-04 (DB04) trial of patients who received at least one prior line of chemotherapy[3].
- While SG and T-DxD have both demonstrated efficacy and safety benefits in HER2- and HER2-low mBC patients, respectively, no head-to-head trials have examined their comparative efficacy.
- Therefore, an indirect treatment comparison (ITC) feasibility assessment was needed to assess if SG and T-DxD clinical benefits may be compared indirectly.

Objective

- To conduct an ITC feasibility assessment for SG and T-DxD in HR+/HER2- mBC post-endocrine-based therapy and at least two chemotherapies.

Methods

- A targeted literature review of PubMed and Google Scholar was conducted in September 2022 to find clinical trials with SG and T-DxD in HR+/HER2- mBC.
- A feasibility assessment was performed to determine if an ITC of SG vs T-DxD using either unadjusted (anchored) methods (e.g., Bucher's method) or population-adjusted indirect methods (PAIC) was possible.
- During feasibility assessment, heterogeneity was examined with regards to the population due to differences in trial design, patient characteristics, efficacy and prognostic data. Availability of safety outcomes was also evaluated.

Results

- In total, four (two comparator-control and two single-arm) clinical trials were considered eligible for feasibility evaluation of ITC among HR+/HER2- patients on SG vs T-DxD. Data from HR+/HER2- cohorts or sub-groups from these 4 trials were included in the feasibility evaluation, the details of which are presented in **Table 1.** List of trials identified in the literature search are as follows:
  - Two trials for SG (TROPiCS-02-NCT03901339, and IMMU-132-01-NCT01631552)
  - Two trials for T-DxD (DESTINY-Breast-04 (DB04)-NCT03734029, and DAISY-NCT04132960)
- Study population in these trials had different patient eligibility criteria, number of prior therapy use, and disease characteristics, as well as variable reporting of efficacy and safety parameters.

Description of Eligible Studies

- Specifically, in the TROPiCS-02 trial, patients must have been previously treated with a taxane, whereas DB04 or DAISY did not have this requirement; and the proportion of patients with prior history with taxane in these trials has not been published **(Table 1).**
- Additionally, comparator arm therapy composition was different in both the controlled trials (TROPiCS-02 did not include taxane vs. DB04 did not include vinorelbine).
- Furthermore, prior treatment history were not comparable across the trials, thus precluding unadjusted ITC methods **(Table 1).**

Table 1. Study Design of Identified Studies

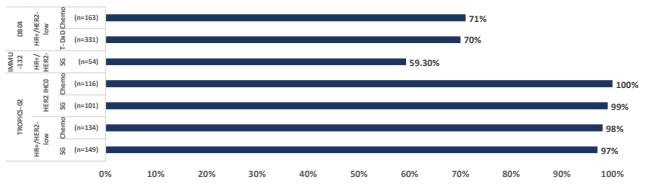
Intervention	SG		T-DxD	
Trials	**TROPiCS-02 (NCT03901339)**	**IMMU-132-01 (NCT01631552)**	**DB04 (NCT03734029)**	**DAISY (NCT04132960)**
Comparator	Chemo (eribulin, capecitabine, gemcitabine, vinorelbine)	None	Chemo (eribulin, capecitabine, gemcitabine, paclitaxel, nab-paclitaxel)	None
Study design	Randomized, open-label, Ph 3 trial	Single-arm, open-label, Ph 1/2 trial	Randomized, open-label, Ph 3 trial	Single-arm, open-label, Ph 2 trial
Histology	HR+/HER2- mBC, with HR+/HER2-low subgroup	mTNBC* and HR+/HER2- mBC cohorts	HER2-low mBC, with HR+ and HR- cohorts	HER2+, HER2-low, and HER2-0 mBC cohorts
Treatment history*	• Received 2-4 prior systemic chemotherapy regimens for metastatic disease • Previously received ≥1 taxane in any setting, ≥1 anticancer hormonal treatment in any setting, and ≥1 CDK4/6i in metastatic setting • (Neo) adjuvant therapy for early-stage disease qualified as one of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within 12 months of therapy (early relapse)	**HR+/HER2- mBC cohort*:** • Received ≥1L endocrine therapy in metastatic setting • Received ≥1L chemotherapy in metastatic setting	• Primarily received 1-2 lines of chemotherapy in metastatic setting • Received ≥1L endocrine therapy in any setting for patients with HR+ disease • No history of anti-HER2 therapy	• Received ≥1L chemotherapy in metastatic setting

*Only HR+/HER2- cohort in IMMU-132-01 was considered for inclusion in the feasibility analysis

Prior Therapy Use and ECOG Performance Status

- Higher number of patients in TROPiCS-02 were pretreated compared to patients in DB04 (median number of prior chemotherapies: 3 vs 1) and had severe disease (liver metastases: 86% vs 70%).
- Patients in TROPiCS-02 had an ECOG 1 ranging from 59-61%. On the other hand, patients in DB04 and DAISY had ECOG 1 ranging from 40-55%.
- In TROPiCS-02, ~97-99% patients had prior CDK4/6i use in the SG groups, and only ~70% patients had prior CDK4/6i use in DB04 **(Figure 1).**

Figure 1. Prior CDK4/6i Use*



*Prior CDK4/6i use was not reported in DAISY

Baseline Characteristics

- Baseline characteristics and comorbidity profile also had distinct differences in some of the eligible trials such as TROPiCS-02 population vs. HER2- subgroups in other trials **(Table 2).**
- The median age at study entry among four trials ranged from 54-58 years. Other baseline characteristics are reported in **Table 2**.
- Data on prognostic factors for the directly overlapping population from both trials (TROPiCS-02 and DAISY) was not available from DAISY, precluding an unbiased adjusted ITC.
  - Population-adjusted ITC using data from single arm trials (IMMU-132-01 and DAISY) was assessed as not feasible due to insufficient data on prognostic factors.

Table 2. Baseline Population Characteristics in Eligible Studies

Variables	Description of HER2 Sub-Groups
Age	• The median age at study entry among four trials ranged from 54-58 years.
Race	• Asian population for HR+ T-DxD arm was 40% in DB04, compared to 4% and 3% in HR+ SG arm in TROPiCS-02 and IMMU-132-01, respectively. Race information was not reported for DAISY.
Chemotherapies in the Metastatic Setting	• In TROPiCS-02, ~60% of the patients received 3 or more prior chemotherapies • In DB04, only a negligible amount (1%) of patients received 3 or more prior chemotherapies • In DAISY, ~80% of the patients received 3 or more previous lines of treatment in the metastatic setting. Number of prior chemotherapy lines received was not reported. • Information on prior therapies were not reported for IMMU-132-01
Liver Metastasis	• Almost ~74% patients for HR+ T-DxD arm in DB04 had liver metastasis. In TROPiCS-02, 84% of SG arm (ITT population) had liver metastasis.

Efficacy & Safety

- Finally, information on efficacy outcomes was not uniformly reported in all 4 trials **(Table 3).**
- In the HR+/HER2-low subgroup, efficacy outcomes of interest were available for SG in the TROPiCS-02 trial (with the notable exception of OS) and for T-DxD in the DB04 trial.
- Safety outcomes were only available for TROPiCS-02 and DB04, but not for DAISY (no safety data).

Table 3. Description of efficacy outcomes in HER2 subgroups

	TROPiCS-02[2]		DB04[3,4,a]		DAISY[5]	TROPiCS-02[2]		DAISY[5]
	HR+/HER2-low[b]					HR+/HER2 IHC0		
Outcomes	**SG (n=149)**	**Chemo (n=134)**	**T-DxD (n=331)**	**Chemo (n=163)**	**T-DxD (n=58)**	**SG (n=101)**	**Chemo (n=116)**	**T-DxD (n=26)**
mPFS, months (95% CI)	6.4	4.2	10.1 (9.5-11.5)	5.4 (4.4-7.1)	6.9 (5.5-8.7)	5.0	3.4	4.5 (1.5-6.9)
Hazard risk for mPFS (95% CI)	0.58 (0.42-0.79), P<0.001		0.51 (0.40-0.64), P<0.001		NR	0.72 (0.52-1.00), P=0.05		NR
mOS, months (95% CI)	NR	NR	23.9 (20.8-24.8)	17.5 (15.2-22.4)	NR	NR	NR	NR
Hazard risk for mOS (95% CI)	NR		0.64 (0.48-0.86), P=0.0028		NR	NR		NR
ORR, % (95% CI)	26	12	52.6 (47-58)	16.3 (11-22.8)	36	16	15	23
Overall Response, n (%)								
CR	2 (1)	0	12 (3.6)	1 (0.6)	1 (1.7)	0	0	0 (0)
PR	36 (24)	16 (12)	164 (49.2)	26 (15.7)	20 (34.5)	16 (16)	17 (15)	6 (23)
CBR, n (%)[c]	56 (38)	26 (19)	237 (71.2)	57 (34.3)	NR	31 (31)	25 (22)	NR
mDoR, months (range)	7.4 (5.8-8.9)	4.1 (2.8-6.1)	10.7	6.8	NR	8.1 (4.1-NE)	6.1 (2.8-8.3)	NR

Notes: a) HER2-low is defined as IHC1+, or IHC2+ and ISH-negative/unverified. **b)** For DB04, clinical benefit was a composite of complete response, partial response, and more than 6 months of stable disease, according to blinded independent central review. **Abbreviations:** CBR, clinical benefit rate; CI, confidence interval; CR, complete response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ISH, in situ hybridization; mDoR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; NR, not reported; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SG, sacituzumab govitecan-hziy; T-DXd, fam-trastuzumab deruxtecan-nxki.

References: 1. Rugo HS, Bardia A, Marmé F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2022:40(29):3365-3376. **2.** Schmid P, Cortés J, Marmé F, et al. 214MO Sacituzumab govitecan (SG) efficacy in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (MBC) by HER2 immunohistochemistry (IHC) status in the phase III TROPiCS-02 study. ESMO Congress. September 9-13, 2022; Paris, France. **3.** Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Results of DESTINY-Breast04, a randomized, phase 3 study. ASCO Annual Meeting. June 3-7, 2022; Chicago, IL. **4.** Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med. 2022;387(1):9-20. **5.** Sharma P. Optimizing use of HER2 therapies in metastatic breast cancer. San Antonio Breast Cancer Symposium. December 7-10, 2021; San Antonio, TX.

Correspondence: Ryan Thaliffdeen, ryan.thaliffdeen@gilead.com

Acknowledgements: We would like to acknowledge Ankita Kaushik and Yumi Asukai, who are employees of Gilead Sciences, Inc. for their support of this work.

Disclosures: This study was funded by Gilead Sciences, Inc., Foster City, CA, USA. Editorial and design support were provided by Antiliks, Inc. and MAO Graphics, and funded by Gilead Sciences, Inc. **RT** is an employee of Gilead Sciences, Inc. and may own Gilead stock or stock options. **WV** and **NS** are employees of Gilead Sciences Europe Ltd. and may own Gilead stock or stock options. **DP** is an employee of Analysis Group, Inc., who received research funding for this study from Gilead Sciences, Inc. **MC** is affiliated with Institut de Cancérologie de l'Ouest, France. **AS** was an employee of Gilead Sciences, Inc., at the time of the study.