TRILACICLIB COMBINED WITH SACITUZUMAB GOVITECAN (SG) IN METASTATIC TRIPLE-NEGATIVE BREAST CANCER (mTNBC): PRELIMINARY PHASE 2 RESULTS

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INTRODUCTION

- Trilaciclib is a highly potent, highly selective, reversible cyclin-dependent kinase 4/6 inhibitor that enhances antitumor immunity (anticancer efficacy) and preserves hematopoietic stem and progenitor cells, as well as immune system function (myeloprotection), when administered intravenously prior to chemotherapy[1–7]
- Results from a phase 2 study in patients with mTNBC showed that administering trilaciclib prior to gemcitabine plus carboplatin provided long-term benefit by prolonging overall survival (OS) compared with administering gemcitabine plus carboplatin alone (median, 19.8 vs 12.6 months; hazard ratio, 0.37; $P < 0.0001$)[8]
  - Enriched T-cell diversity and decreased clonality in peripheral blood were observed in trilaciclib-treated patients[8]
- SG, an antibody–drug conjugate comprising a trophoblast cell surface antigen 2–directed antibody linked to the topoisomerase I inhibitor SN-38, is indicated for the treatment of adult patients with mTNBC who have received ≥ 2 prior systemic therapies, ≥ 1 of which for metastatic disease[9]
  - When internalized by tumor cells, SG induces DNA damage, leading to cell death
- In the phase 3 ASCENT study in 468 patients with previously treated mTNBC without brain metastases, SG significantly extended survival versus single-agent chemotherapy, with median progression-free survival (mPFS) of 5.6 versus 1.7 months and median OS of 12.1 versus 6.7 months, respectively[10]
  - A numerical difference in mPFS was observed between patients in the SG cohort with prior treatment with programmed death protein-1 (PD-1) or programmed death-ligand 1 (PD-L1) immunotherapy versus without: 4.2 (95% CI, 3.2–5.6) versus 6.2 (95% CI, 4.9–7.1) months[10]
  - Compared with single-agent chemotherapy, SG was associated with increased neutropenia, anemia, alopecia, and gastrointestinal adverse events (AEs) (**Table 1**)[10]
  - Dose reductions due to AEs occurred with similar frequency in the 2 groups (22% with SG vs 26% with chemotherapy), and AEs leading to treatment discontinuation occurred in 12 patients (5%) in each group[10]

Table 1. Any-Grade Treatment-Related AEs (TRAEs) of Interest for Which There was a ≥ 10% Increase With SG vs Chemotherapy, in the ASCENT Study[10]

Any-Grade TRAE,[a] n (%)	SG (n = 258)	Chemotherapy (n = 224)
Neutropenia[b]	163 (63)	96 (43)
Diarrhea	153 (59)	27 (12)
Nausea	147 (57)	59 (26)
Alopecia	119 (46)	35 (16)
Fatigue	115 (45)	68 (30)
Anemia[c]	89 (34)	54 (24)
Vomiting	75 (29)	23 (10)

[a] TRAEs related to any study drug occurring in ≥ 10% of patients.
[b] Category includes neutropenia and decreased neutrophil count.
[c] Category includes anemia, decreased red blood cell count, and decreased hemoglobin.
SG, sacituzumab govitecan; TRAE, treatment-related adverse event.

- The mechanism of action of SG may complement the observed positive impact of trilaciclib on antitumor immune modulation in this patient population
- This study was designed to determine whether administration of trilaciclib prior to SG improves antitumor efficacy and reduces myelotoxicity in patients with mTNBC

METHODS

- The aim of this phase 2, single-arm, open-label study was to evaluate the safety and efficacy of trilaciclib plus SG in patients with unresectable, locally advanced TNBC or mTNBC who had received ≥ 2 prior systemic treatments, ≥ 1 of which in the metastatic setting (NCT05113966)
- Key eligibility criteria included:
  - Age ≥ 18 years
  - Unresectable, locally advanced TNBC or mTNBC
  - Hormone (estrogen and progesterone) receptor–negative and human epidermal growth factor receptor 2–negative status
  - ≥ 2 prior systemic therapies, ≥ 1 of which in the metastatic setting
  - Measurable disease per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1)
  - Eastern Cooperative Oncology Group performance status of 0 or 1
  - Absence of brain metastases at enrollment
- Enrolled patients received intravenous trilaciclib 240 mg/m^2 prior to SG 10 mg/kg on days 1 and 8 of each 21-day cycle until disease progression or toxicity
- Tumor assessments occurred at screening, every 6 weeks until week 36, then every 9 weeks until disease progression or subsequent anticancer therapy
- **Primary endpoint:** PFS per RECIST v1.1
- **Secondary endpoints:** objective response rate (ORR), clinical benefit rate, duration of response, OS, myeloprotection, and safety/tolerability

RESULTS

Patient Disposition and Characteristics

- As of April 3, 2023, enrollment was complete and all patients (N = 30) had received ≥ 1 dose of any study drug
- Baseline patient demographics and clinical characteristics are summarized in **Table 2**
  - 73.3% (22/30) of patients had received prior PD-(L)1 immunotherapy
- 11 patients remain on study treatment and 22 patients remain in the study (**Table 3**)
  - The primary reason for treatment discontinuation was disease progression (n = 17)
- Patients received a median (range) of 5.5 (1–20) cycles of treatment, and median follow-up was 5.5 (1–13) months

Table 2. Demographic and Clinical Characteristics at Baseline

Characteristic	Patients With mTNBC (N = 30)
Median age, years (range)	56.0 (30–75)
Female, n (%)	30 (100)
Race, n (%)	
White	26 (86.7)
Black or African American	3 (10.0)
Asian	1 (3.3)
ECOG PS, n (%)	
0	20 (66.7)
1	10 (33.3)
Stage at screening, n (%)	
Locally advanced	2 (6.7)
Metastatic	28 (93.3)
TNBC at diagnosis, n (%)	25 (83.3)
PD-L1 status,[a] n (%)	
Positive	19 (63.3)
Negative	8 (26.7)
No data	3 (10.0)
*BRCA*1/2 mutation status,[a] n (%)	
Negative	17 (56.7)
Positive	6 (20.0)
No data	7 (23.3)
Prior systemic anticancer regimens, n (%)	
2 or 3	22 (73.3)
> 3	8 (26.7)
Prior PD-(L)1 treatment, n (%)	22 (73.3)

[a] PD-L1 and *BRCA* mutation statuses were not required per protocol.
BRCA, breast cancer gene; ECOG PS, Eastern Cooperative Oncology Group performance status; mTNBC, metastatic triple-negative breast cancer; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; TNBC, triple-negative breast cancer.

Table 3. Patient Disposition

Study Drug Disposition, n (%)	Overall (N = 30)
Ongoing	11 (36.7)
Discontinued (all study drugs)	19 (63.3)
Primary reason for discontinuation[a]	
Progressive disease	17 (89.5)
AE	1 (5.3)
Physician decision	0 (0)
Withdrawal by patient	1 (5.3)

[a] Calculated as a percentage of the patients who discontinued (n = 19).
AE, adverse event.

Efficacy

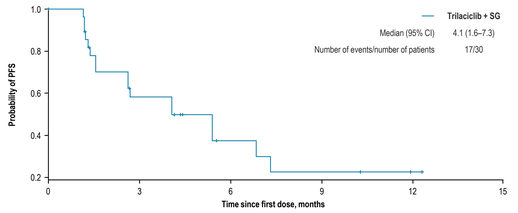
- Preliminary antitumor activity is summarized in **Table 4**
  - In the response-evaluable population (n = 28), the confirmed ORR was 25.0% (n = 7)
  - In patients with PD-L1–positive (PD-L1+) mTNBC (n = 17), the confirmed ORR was 35.3% (n = 6)
- In the overall population (N = 30), mPFS (95% CI) with trilaciclib plus SG was 4.1 (1.6–7.3) months (**Figure 1**)
- Treatment duration and response, and best change from baseline in tumor size for target lesions in the overall population, are presented in **Figures 2** and **3**, respectively

Table 4. Current Antitumor Activity in Patients Receiving Trilaciclib Plus SG

	Response-Evaluable Population (n = 28)	Patients With PD-L1+ mTNBC (n = 17)
BOR, n (%)		
CR	0	0
PR	7 (25.0)[a]	6 (35.3)
SD	13 (46.4)	6 (35.3)
PD	7 (25.0)	5 (29.4)
NE	1 (3.6)	0
ORR,[b] n (%)	7 (25.0)	6 (35.3)
CBR,[c] n (%)	9 (32.1)	8 (47.1)
Median DOR, months (95% CI)	5.7 (4.0–NE)	NR (4.0–NE)

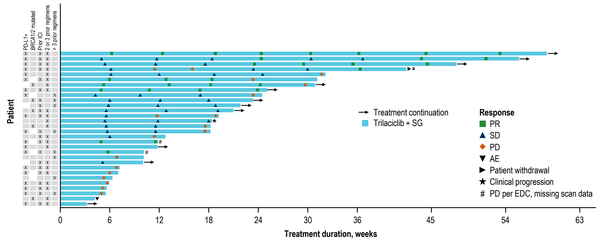
[a] 9 (32.1%) patients achieved a PR; 7 patients had a confirmed PR, 1 patient had an unconfirmed PR, and 1 patient achieved a PR (59% reduction in SLD) after initial PD (21% increase in SLD) with continuation of therapy.
[b] Confirmed CR + PR.
[c] Confirmed CR + PR + SD lasting longer than 24 weeks.
BOR, best overall response; CBR, clinical benefit rate; CR, complete response; DOR, duration of response; mTNBC, metastatic triple-negative breast cancer; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PD-L1+, programmed death-ligand 1–positive; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; SLD, sum of longest diameters.

Figure 1. Current PFS in the Overall Population (N = 30)



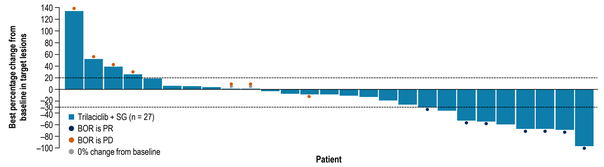
PFS, progression-free survival; mPFS, median progression-free survival; SG, sacituzumab govitecan.

Figure 2. Current Treatment Duration and Response in the Overall Population (N = 30)



[a] Patient achieved a PR (59% reduction in SLD) after initial PD (21% increase in SLD) with continuation of therapy.
AE, adverse event; BRCA, breast cancer gene; EDC, electronic data capture; ICI, immune checkpoint inhibitor; PD, progressive disease; PD-L1+, programmed death-ligand 1–positive; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; SLD, sum of longest diameters.

Figure 3. Best Change From Baseline in Tumor Size for Target Lesions



BOR, best overall response; PD, progressive disease; PR, partial response; SG, sacituzumab govitecan.

Safety and Tolerability

- Safety data are summarized in **Table 5**
- TRAEs of any grade were reported in 76.7% of patients
  - The most common TRAEs were fatigue (46.7%), alopecia (33.3%), nausea (30.0%), and diarrhea (26.7%)
- Serious AEs related to any study treatment occurred in 3 (10.0%) patients
  - 1 patient had febrile neutropenia, diarrhea, nausea, and vomiting related to SG
  - 1 patient had acute respiratory failure related to SG
  - 1 patient had a gait disturbance related to trilaciclib + SG
- Growth factors were administered to 5 (16.7%) patients
- SG dose reductions occurred in 3 (10.0%) patients and treatment cycles were delayed in 14 (46.7%) patients
- AEs leading to treatment discontinuation of study drug (trilaciclib and SG) occurred in 1 (3.3%) patient, and included oropharyngeal candidiasis, acute respiratory failure, dyspnea, pneumonitis, and pulmonary embolism

Table 5. Summary of TRAEs and Hematologic AEs

	Any Grade (N = 30)	Grade 3/4 (N = 30)
Patients with TRAE,[a] n (%)	23 (76.7)	7 (23.3)
Fatigue	14 (46.7)	0
Alopecia	10 (33.3)	0
Nausea	9 (30.0)	1 (3.3)
Diarrhea	8 (26.7)	1 (3.3)
Decreased appetite	5 (16.7)	0
Headache	5 (16.7)	0
Vomiting	5 (16.7)	1 (3.3)
Constipation	4 (13.3)	0
Abdominal pain	3 (10.0)	1 (3.3)
Patients with hematologic AE,[b] n (%)	13 (43.3)	5 (16.7)
Neutropenia[c]	9 (30.0)	4 (13.3)
Leukopenia[d]	7 (23.3)	4 (13.3)
Anemia[e]	3 (10.0)	0

[a] TRAEs related to any study drug occurring in ≥ 10% of patients.
[b] Regardless of causality.
[c] Category includes neutropenia and decreased neutrophil count.
[d] Category includes leukopenia and decreased white blood cell count.
[e] Category includes anemia, macrocytic anemia, decreased red blood cell count, and decreased hemoglobin.
AE, adverse event; TRAE, treatment-related adverse event.

CONCLUSIONS

- Preliminary data suggest administration of trilaciclib prior to SG has the potential to reduce AEs in heavily pretreated patients with mTNBC
- Although cross-trial comparisons should be made with caution, lower frequencies of neutropenia, anemia, nausea, and diarrhea were observed with trilaciclib plus SG in this study compared with historical data for SG alone
- With a median follow-up of 5.5 months, it is too early to fully determine the efficacy of trilaciclib prior to SG in this patient population
  - Current data show that ORR is higher in patients with PD-L1+ mTNBC, relative to the overall study population
- Monitoring of efficacy is continuing to assess the potential of trilaciclib to improve OS when combined with additional regimens beyond gemcitabine/carboplatin in mTNBC

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