PATIENTS WITH METASTATIC TRIPLE-NEGATIVE BREAST CANCER WHO RECEIVE TRILACICLIB PRIOR TO CYTOTOXIC CHEMOTHERAPY EXHIBIT IMPROVED SURVIVAL AFTER RECEIVING SUBSEQUENT ANTICANCER THERAPY

Shom Goel[1]; Joyce O'Shaughnessy[2]; Kun-Hui Lu[1]; Andrew Beelen[3]; Symantha Melemed[3]; John S. Yi[3]; Michael Danso[4]; and Antoinette R. Tan[5]

[1] The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia; [2] Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [3] G1 Therapeutics, Inc., Research Triangle Park, NC, USA; [4] Virginia Oncology Associates, Norfolk and Virginia Beach, VA, USA; [5] Levine Cancer Institute, Atrium Health, Charlotte, NC, USA

INTRODUCTION

- Administering trilaciclib (COSELA®; G1 Therapeutics, Inc.), an intravenous myeloprotection therapy, prior to chemotherapy results in the transient arrest of cyclin-dependent kinase (CDK)4/6-dependent hematopoietic stem and progenitor cells (HSPCs) and immune cells in the G_1 phase of the cell cycle, thus protecting these cells from chemotherapy-induced damage and modulating antitumor immunity[1–3]
- Data from murine models suggest that trilaciclib-induced inhibition of CDK4/6 may preserve the long-term function of HSPCs and improve T-cell memory[2,4–6]
- In an open-label phase 2 trial in 102 patients with metastatic triple-negative breast cancer (mTNBC; NCT02978716), administering trilaciclib prior to gemcitabine plus carboplatin (GCb) significantly prolonged overall survival (OS; a secondary endpoint) compared with administering GCb alone (median 19.8 vs 12.6 months; hazard ratio 0.37; $P < 0.0001$), with a nonsignificant trend toward improved progression-free survival (PFS; median 9.0 vs 5.7 months; hazard ratio 0.62; $P = 0.13$)[7,8]
  - Administering trilaciclib prior to GCb resulted in significantly fewer peripheral CD8+ T cells and myeloid-derived suppressor cells after 2 cycles compared with baseline, and enhanced T-cell effector function compared with administering GCb alone[9]
- Here, we report results from a post hoc analysis that aimed to examine survival outcomes in patients with mTNBC who received subsequent anticancer therapy (SACT) after receiving GCb with or without trilaciclib in the phase 2 trial
  - We also evaluate memory T-cell responses in preclinical models

METHODS

- In the phase 2 trial, patients with ≤ 2 prior chemotherapy regimens for locally recurrent or mTNBC were randomized 1:1:1 to receive GCb on days 1 and 8 (n = 34), trilaciclib prior to GCb on days 1 and 8 (n = 33), or trilaciclib alone on days 1 and 8 and prior to GCb on days 2 and 9 (n = 35)[7]
- To determine if trilaciclib improved outcomes in patients who received additional therapy after GCb, a post hoc exploratory survival analysis was performed using data from patients who received any SACT; the 2 trilaciclib groups were combined for this analysis
  - OS, defined as the time to death (event), was plotted for each treatment group using Kaplan-Meier product limit survival curves
- Murine models of colorectal cancer (CT26) and breast cancer (MMTV-rtTA/tetO-HER2) were utilized to quantify the infiltration of central memory T cells in the tumor microenvironment 7 days after a single dose of trilaciclib or immediately after 7 consecutive daily doses of trilaciclib
- Memory T-cell recall responses were also evaluated in the CT26 model
  - Tumor-bearing mice were treated once weekly with combined anti–programmed cell death protein-1 (α-PD-1; 5 mg/kg; clone RMP1-14) and anti–lymphocyte-activation gene-3 (α-LAG3; 10 mg/kg; clone C9B7W) antibodies, with or without concomitant trilaciclib (100 mg/kg), followed by a second dose of α-PD-1 and α-LAG3 after 3 days
  - Surviving mice (ie, those with complete tumor regression) were rechallenged 150 days later with CT26 cells injected into the opposite flank, and tumor volume and weight were measured 2–3 times per week

RESULTS

Patient Disposition and Characteristics

- Demographic and clinical characteristics, including time from end of study treatment to first SACT, and type of SACT, were balanced between the prior trilaciclib plus GCb (n = 43) and GCb-only (n = 20) groups (**Table 1**)
  - Overall, 61.7% of patients received SACT, most commonly gemcitabine, capecitabine, eribulin, taxanes, checkpoint inhibitors, carboplatin, and anthracyclines

Table 1. Demographic and Clinical Characteristics

Characteristic		Prior Trilaciclib Plus GCb (n = 43)	Prior GCb Only (n = 20)
Age	Median (range), years	61 (39–78)	56 (37–86)
Race, n (%)	White	32 (74.4)	16 (80.0)
	Black or African American	6 (14.0)	3 (15.0)
	Asian	4 (9.3)	0
	Other	1 (2.3)	1 (5.0)
ECOG PS, n (%)	0	27 (62.8)	9 (45.0)
	1	16 (37.2)	11 (55.0)
Time from end of study treatment to first SACT	Median (range), months	0.95 (0.07–6.41)	1.20 (0.72–4.90)

ECOG PS, Eastern Cooperative Oncology Group performance status; GCb, gemcitabine plus carboplatin; SACT, subsequent anticancer therapy.

Survival Outcomes

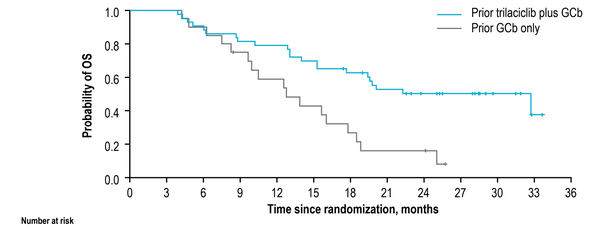
- After a median follow-up time of 12.7 months, deaths were observed in 22/43 patients in the prior trilaciclib plus GCb group and 17/20 patients in the prior GCb-only group
  - Median time on treatment was 5.5 months in the trilaciclib plus GCb group and 3.3 months in the GCb-only group
- Median (95% CI) OS in patients who received SACT following trilaciclib plus GCb was 32.7 (15.3–not estimable) months compared with 12.8 (8.3–17.8) months in those who had received prior GCb only ($P = 0.001$), with increasing separation of survival curves over time (**Table 2**; **Figure 1**)
  - Median OS and PFS were higher in the prior trilaciclib plus GCb group compared with the prior GCb-only group, regardless of the type of SACT received
  - Improved OS and sustained separation of curves were also observed in patients unable to receive SACT (trilaciclib, n = 25; placebo, n = 14), although the magnitude of benefit was smaller (median 9.4 vs 5.4 months)

Table 2. PFS and OS by SACT in the Phase 2 Intention-to-Treat Population

	Prior Trilaciclib Plus GCb (n = 68)			Prior GCb Only (n = 34)		
	Patients, n (%)	PFS, Median (95% CI)	OS, Median (95% CI)	Patients, n (%)	PFS, Median (95% CI)	OS, Median (95% CI)
Any SACT	43 (63.2)	11.3 (8.8–13.9)	32.7 (15.3–NE)	20 (58.8)	8.3 (4.8–NE)	12.8 (8.3–17.8)
Gemcitabine	16 (23.5)	13.9 (7.3–14.6)	NR (15.3–NE)	6 (17.6)	13.5 (8.3–NE)	15.8 (7.5–NE)
Capecitabine	12 (17.6)	10.9 (7.3–NE)	32.7 (5.1–NE)	4 (11.8)	9.2 (9.2–NE)	15.8 (9.7–NE)
Eribulin	11 (16.2)	10.9 (6.4–NE)	NR (15.3–NE)	7 (20.6)	4.8 (1.4–NE)	10.5 (4.8–16.0)
Taxane	12 (17.6)	11.9 (1.3–NE)	32.7 (10.2–NE)	7 (20.6)	9.2 (1.9–NE)	18.5 (4.2–NE)
Carboplatin	13 (19.1)	13.9 (7.3–NE)	NR (15.3–NE)	5 (14.7)	8.8 (8.3–NE)	13.9 (7.5–NE)
PD-L1 inhibitor	9 (13.2)	10.9 (1.2–NE)	32.7 (3.9–NE)	5 (14.7)	4.8 (1.4–NE)	7.5 (4.8–NE)
No SACT	25 (36.8)	6.2 (4.3–9.0)	9.4 (7.1–NE)	14 (41.2)	3.3 (0.1–9.9)	5.4 (0.3–NE)

GCb, gemcitabine plus carboplatin; NE, not estimable; NR, not reached; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SACT, subsequent anticancer therapy.

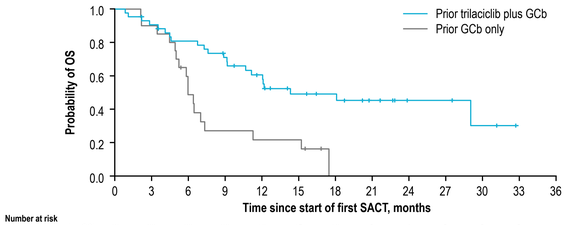
Figure 1. OS in Patients Who Received SACT



GCb, gemcitabine plus carboplatin; OS, overall survival; SACT, subsequent anticancer therapy.

- Among patients who received SACT, median (95% CI) OS relative to time since start of first SACT was 14.0 (9.0–not estimable) months in the prior trilaciclib plus GCb group versus 5.8 (4.8–7.2) months in the prior GCb-only group ($P = 0.001$; **Figure 2**)

Figure 2. OS Relative to Time Since Start of First SACT

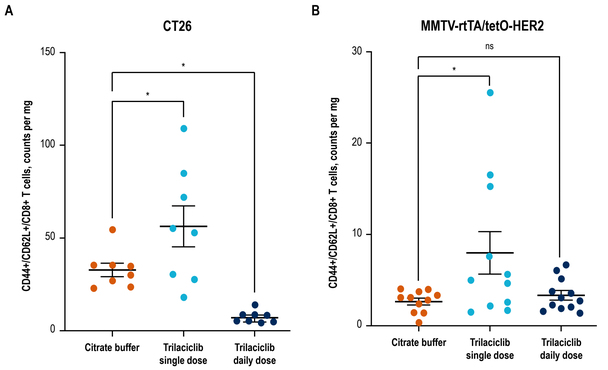


GCb, gemcitabine plus carboplatin; OS, overall survival; SACT, subsequent anticancer therapy.

Single-Dose Trilaciclib Increases Tumor-Infiltrating CD8+ Central Memory T Cells Compared With Daily Dosing

- Compared with daily dosing, single-dose trilaciclib increased the number of tumor-infiltrating CD8+ central memory T cells in the tumor microenvironment on day 7 in both the CT26 and MMTV-rtTA/tetO-HER2 models (**Figure 3A** and **3B**)

Figure 3. Effect of Single vs Daily Dosing of Trilaciclib on Tumor-Infiltrating CD8+ Central Memory T Cells on Day 7 in (A) the CT26 Model and (B) the MMTV-rtTA/tetO-HER2 Model

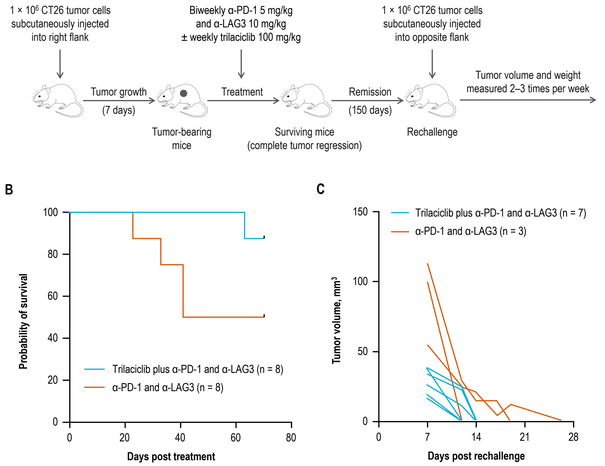


* $P \leq 0.05$.
ns, not significant.

Addition of Trilaciclib to α-PD-1 and α-LAG3 Results in Smaller Tumors Following Rechallenge in Surviving Mice

- Administering trilaciclib enhanced the efficacy of combination immunotherapy with α-PD-1 plus α-LAG3
  - Seven of eight mice that received trilaciclib plus α-PD-1 and α-LAG3 survived treatment (complete response)
  - Three of eight mice survived following treatment with α-PD-1 plus α-LAG3
- Following rechallenge in the opposite flank of the surviving mice, tumors implanted in those previously treated with trilaciclib grew to a smaller volume and regressed faster than in the controls (**Figure 4**)

Figure 4. (A) Combining Trilaciclib With α-PD-1 and α-LAG3 in the CT26 Model: Effects on (B) Survival and (C) Tumor Volume Following Rechallenge in Surviving Mice



LAG3, lymphocyte-activation gene-3; PD-1, programmed cell death protein-1.

CONCLUSIONS

- Data from the randomized phase 2 trial suggest that patients with mTNBC who received trilaciclib prior to cytotoxic chemotherapy have prolonged survival, which is notably improved for patients who receive any SACT following discontinuation of trilaciclib
  - Improved OS in patients receiving trilaciclib may be associated with preservation of the lymphoid lineage and expanded memory T-cell pool, which is critical for long-term immune surveillance and in eliciting rapid recall responses
- Data from murine models suggest that trilaciclib-mediated transient CDK4/6 inhibition may enhance tumor infiltration of CD8+ central memory T cells and augment memory T-cell recall responses
- OS is being evaluated in patients with mTNBC in the phase 3 trial of trilaciclib prior to GCb (PRESERVE 2; NCT04799249) and the phase 2 trial of trilaciclib prior to sacituzumab govitecan (NCT05113966)

San Antonio Breast Cancer Symposium (SABCS) | December 5–9, 2023 | San Antonio, TX, USA

REFERENCES:
1. COSELA® (trilaciclib). Prescribing Information. https://www.g1therapeutics.com/cosela/pi/. Accessed November 10, 2023.
2. He S, et al. *Sci Transl Med*. 2017;9:eaal3986.
3. Lai AY, et al. *J Immunother Cancer*. 2020;8:e000847.
4. Goel S, et al. *Nature*. 2017;548:471–5.
5. Heckler M, et al. *Cancer Discov*. 2021;11:2564–81.
6. Lelliott EJ, et al. *Cancer Discov*. 2021;11:2582–601.
7. Tan AR, et al. *Lancet Oncol*. 2019;20:1587–601.
8. Tan AR, et al. *Clin Cancer Res*. 2022;28:629–36.
9. Tan AR, et al. *Breast Cancer Res Treat*. 2023;201:307–16.

ACKNOWLEDGMENTS:
- Study sponsored by G1 Therapeutics, Inc. Medical writing assistance was provided by Farhana Burnett, PhD, of Envision Pharma Group, funded by G1 Therapeutics.