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Prevention of sacituzumab govitecan-related neutropenia and diarrhea in patients with triple-negative or HR[+]/HER2[-] advanced breast cancer (PRIMED): a phase 2 trial

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BACKGROUND

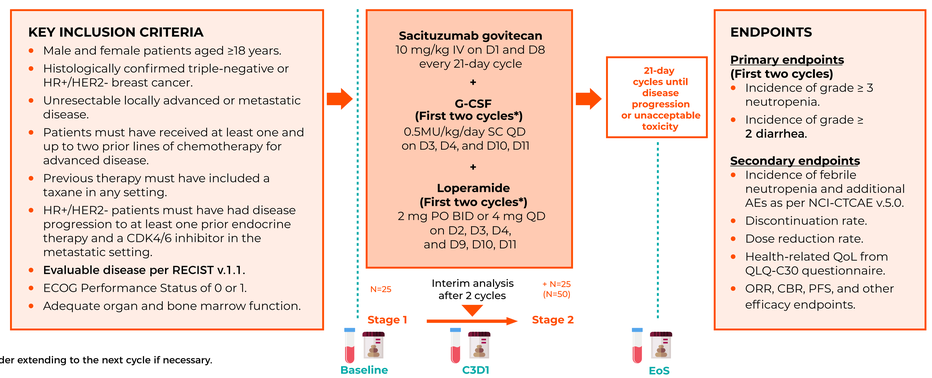
- Trophoblast cell surface antigen 2 (Trop-2) is a calcium signal transducer that plays a role in cell growth, migration, and invasion and is highly expressed in breast cancer (approximately 80-90%).[1-3]
- Sacituzumab govitecan is a Trop-2 directed antibody-drug conjugate that has demonstrated a significant improvement in progression-free survival and overall survival in patients with pretreated, triple-negative and HR+/HER2- advanced breast cancer in ASCENT and TROPiCS-02 phase III trials, respectively.[4-7]
- The most common treatment-emergent adverse events (AEs) observed in these phase III trials were neutropenia and diarrhea, leading to dose reductions and treatment interruptions/discontinuations.[5-6]
- Granulocyte colony-stimulating factors (G-CSF) and loperamide are commonly used to treat and prevent drug-associated neutropenia and diarrhea in cancer patients, respectively.[8,9]
- PRIMED is a phase II clinical trial assessing the feasibility of primary prophylaxis with G-CSF and loperamide to improve the tolerability of sacituzumab govitecan and ultimately decrease treatment modifications.

PRIMARY OBJECTIVE

PRIMED (NCT05520723) is evaluating the incidence of neutropenia and diarrhea in patients with unresectable locally advanced or metastatic triple-negative or HR+/HER2- breast cancer treated with sacituzumab govitecan in combination with G-CSF and loperamide.

STUDY DESIGN

Figure 1. PRIMED clinical trial design



*Consider extending to the next cycle if necessary.

STATISTICS

Final analysis (N=50): The study will be declared positive if any of the following outcomes are achieved after the first two cycles of treatment.

1. If there are ≤14 (28.0%) patients with grade (G) ≥ 3 neutropenia (expected rate as null hypothesis 40.0%).
2. If there are ≤7 (14.0%) patients with G ≥ 2 diarrhea (expected rate as the null hypothesis 25.0%).

Abbreviations: **AEs:** adverse events; **BID:** twice a day; **CBR:** clinical benefit rate; **D:** days; **ECOG:** Eastern Cooperative Oncology Group; **EoS:** end of study; **G:** grade; **G-CSF:** granulocyte-colony stimulating factor; **IV:** Intravenous; **n(%):** number of patients (percentage of patients); **NA:** not available; **NCI-CTCAE:** National Cancer Institute-Common Terminology Criteria for Adverse Events; **ORR:** objective response rate; **PO:** orally; **PFS:** progression-free survival; **QD:** daily; **QoL:** quality of life; **RECIST V.1.1:** Response Evaluation Criteria In Solid Tumors 1.1; **SC:** subcutaneous; **TEAEs:** Treatment emergent adverse events; **TNBC:** Triple-negative breast cancer

PATIENT DISPOSITION

- Between February 2023 and September 2023, 50 patients were enrolled in the PRIMED study **(Table 1).**
- At data cut-off (October 18, 2023), with a median follow-up time of 4.3 (range; 0.2-8.6) months, 31 patients (62.0%) remained on treatment.
- The main reason for treatment discontinuation was progressive disease, which occurred in 16 patients (32.0%).

Table 1. Patient baseline characteristics

Patient characteristics, n (%)	TNBC (N = 32)	HR+/HER2- (N = 18)	Overall (N = 50)
Age in years, Median (Min; Max)	51.0 (31; 74)	53.5 (37; 72)	52.0 (31; 74)
ECOG			
0	18 (56.3%)	12 (66.7%)	30 (60.0%)
1	14 (43.8%)	6 (33.3%)	20 (40.0%)
Visceral disease			
Yes	20 (62.5%)	15 (83.3%)	35 (70.0%)
No	12 (37.5%)	3 (16.7%)	15 (30.0%)
Prior chemotherapy in the (neo)adjuvant setting			
Yes	19 (59.4%)	5 (27.8%)	24 (48.0%)
No	13 (40.6%)	13 (72.2%)	26 (52.0%)
Prior chemotherapy regimens for advanced disease			
0*	8 (25.0%)	2 (11.1%)	10 (20.0%)
1	18 (56.3%)	11 (61.1%)	29 (58.0%)
2	6 (18.8%)	5 (27.8%)	11 (22.0%)

* Earlier systemic treatment in the curative setting was considered as one line **of therapy if the development of unresectable locally advanced or metastatic disease occurred within a 12-month period after completion of chemotherapy or** immunotherapy.

RESULTS

- During the first two cycles, the incidence of any G neutropenia and diarrhea were 28.0% and 34.0%, respectively **(Table 2).**
- Eight patients (16.0%) experienced G ≥ 3 neutropenia, meeting this primary endpoint (p<0.001). No patients developed febrile neutropenia. Eight patients (16.0%) experienced G ≥ 2 diarrhea (p=0.084) **(Table 2).**
- TEAEs were similar to the known safety profile of sacituzumab govitecan except for constipation. Twenty-three patients (46.0%) had constipation of any grade and no patients experienced G ≥ 3 constipation in the first two cycles **(Table 3).**
- During the first two cycles, there were seven patients (14.0%) that had an adverse event (AE) that led to a dose reduction and 15 patients (30.0%) required treatment interruptions; however, no patients experienced an AE that led to permanent discontinuation **(Figure 3).**
- The rates of neutropenia and diarrhea **(Figure 2)**, as well dose reductions and permanent discontinuations **(Figure 3)** were lower in PRIMED (first two cycles only) than those reported in ASCENT[5,10] and TROPiCS02[6].

RESULTS

Table 2. Primary endpoints: Rates of neutropenia and diarrhea during the first two cycles

Neutropenia			
Any grade n(%)	**Grade 2**	**Grade 3**	**Grade 4**
14 (28.0%)	4 (8.0%)	6 (12.0%)	2 (4.0%)

Diarrhea			
Any grade n(%)	**Grade 2**	**Grade 3**	**Grade 4**
17 (34.0%)	6 (12.0%)	2 (4.0%)	0 (0.0%)

Figure 2. Treatment-related rates of neutropenia and diarrhea in ASCENT[5] and TROPiCS02[6] and PRIMED (first two cycles)

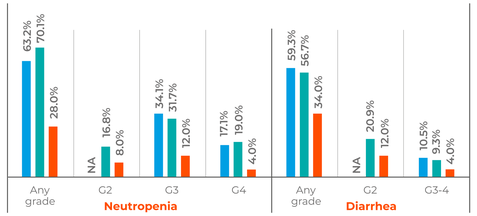


Figure 3. AEs leading to dose reductions, treatment interruptions, and permanent discontinuations in ASCENT[5,10], TROPiCS02[6], and PRIMED (first two cycles)

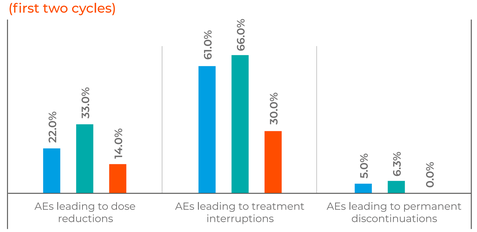


Table 3. TEAEs during the first two cycles (any G ≥ 20% in the overall population or that includes at least one G ≥ 3)

	Any Grade	Any Grade 3	Any Grade 4
All TEAEs, n (%)	**49 (98.0)**	**15 (30.0)**	**2 (4.0)**
Gastrointestinal Disorders	39 (78.0)	4 (8.0)	0 (0.0)
Constipation	23 (46.0)	0 (0.0)	0 (0.0)
Nausea	21 (42.0)	0 (0.0)	0 (0.0)
Diarrhea	17 (34.0)	2 (4.0)	0 (0.0)
Abdominal Upper Pain	5 (10.0)	1 (2.0)	0 (0.0)
Intestinal Obstruction	1 (2.0)	1 (2.0)	0 (0.0)
Blood and Lymphatic System Disorders	19 (38.0)	8 (16.0)	2 (4.0)
Neutropenia	14 (28.0)	6 (12.0)	2 (4.0)
Anemia	9 (18.0)	2 (4.0)	0 (0.0)
Other	45 (90.0)	7 (14.0)	0 (0.0)
Asthenia	28 (56.0)	4 (8.0)	0 (0.0)
Alopecia	11 (22.0)	0 (0.0)	0 (0.0)
Gamma-Glutamyltransferase Increased	3 (6.0)	2 (4.0)	0 (0.0)
Acute Pyelonephritis	1 (2.0)	1 (2.0)	0 (0.0)

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CONCLUSIONS

- **Prophylactic administration of G-CSF and loperamide resulted in a clinically relevant reduction in the incidence and severity of sacituzumab govitecan-related neutropenia and diarrhea.**
- **This combination could help mitigate dose reductions and treatment interruptions, as well as permanent discontinuations due to these treatment-related AEs.**
- **The study is ongoing with global safety and efficacy expected at the end of 2024.**

Scan here to view a plain language summary of this study