ONTARGET: CROFELEMER OR PLACEBO FOR THE PROPHYLAXIS OF DIARRHEA IN ADULTS WITH SOLID TUMORS INITIATING TARGETED THERAPY ± CHEMOTHERAPY

Pablo C. Okhuysen, MD[1], Lee Schwartzberg, MD[2], Eric Roeland, MD[3], Gregory Vidal, MD, PhD[4], Sandra M. Swain MD[5], Hope Rugo, MD[6], Enoch Bortey, PhD[7], James Bolognese, MS[8], Stacey Tinianov, MPH[9], Kelly Shanahan, MD[10], Darlene Horton, MD[11], and Pravin Chaturvedi, PhD[11] on behalf of OnTarget Investigators

1. The University of Texas MD Anderson Cancer Center, Houston, TX. 2. Renown Health, Reno, NV. 3. Oregon Health & Science University, Portland, OR. 4. West Clinic, Germantown, TN. 5. Georgetown University Medical Center, Washington, DC, 6. University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA. 7. Pharmaceutical Development Strategies, Chapel Hill, NC. 8. Cytel Inc., Cambridge, MA. 9. Advocates for Collaborative Education, CA. 10. METAvivor, CA. 11. Napo Pharmaceuticals Inc., San Francisco, CA

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Introduction

Cancer therapy-related diarrhea is common in patients with cancer that are treated with targeted therapy ± chemotherapy.

Cancer therapy-related diarrhea impacts quality of life, results in treatment modifications and poor clinical outcomes.

Crofelemer, an antisecretory agent that modulates the cystic fibrosis transmembrane conductance regulator, is minimally absorbed, and FDA-approved for relief of HIV-associated, noninfectious diarrhea.

Methods

OnTarget (NCT04538625), a phase 3, randomized, multicenter, double-blind, placebo-controlled prophylactic trial evaluated crofelemer or placebo in 287 adults with solid tumors initiating targeted therapy ± chemotherapy.

Patients were randomized 1:1 to crofelemer 125 mg BID or placebo for 12 weeks concurrently with targeted therapy ± chemotherapy for diarrhea prophylaxis.

Patient reported outcomes, collected via electronic diaries, including loose/watery stools, were used for efficacy endpoints including durable response.

The primary endpoint was average weekly number of liquid, watery stools over 12 weeks.

Time to onset of durable response was evaluated using Kaplan-Meier analysis.

To assess sustainability of response, patient global impression of severity scores that included GI quality of life domains, were obtained from weekly diaries and using anchor-based methods, established cutoff values for liquid watery stools passed per week. This was then used to define monthly responders.

Results: OnTarget did not meet the primary efficacy endpoint. However, in a pre-specified subgroup analysis of 183 patients with breast cancer (Table 1), the time to onset of durable response was earlier for crofelemer than placebo (Figure 1, HR=1.76, [95%CI 1.01-3.06]; p=0.045). There were more patients with breast cancer declared as monthly responders on crofelemer than placebo by month 2 (Figure 2, OR=2.24 [95%CI 1.17-4.29]; p=0.015); and for all 3 months (OR=2.46 [95%CI 1.22-4.97]; p=0.012). The adverse event profiles for crofelemer and placebo were similar.

Table 1. Demographic Characteristics for Patients with Breast Cancer in the OnTarget study

	Placebo N=94	Crofelemer N=89	All N=183
Age (years)			
n	94	89	183
Mean (SD)	56.5 (11.7)	57.3 (12.7)	56.9 (12.2)
Median (Range)	58.0 (35 - 81)	57.0 (28 - 86)	57.0 (28 - 66)
Sex			
Female	93 (98.9%)	88 (98.9%)	181 (98.9%)
Race			
Asian	4 (4.3%)	3 (3.4%)	7 (3.8%)
Black or African American	10 (10.6%)	12 (13.5%)	22 (12.0%)
White	64 (68.1%)	63 (70.8%)	127 (69.4%)
Race Category			
White	64 (68.1%)	63 (70.8%)	127 (69.4%)
Non-White	16 (17.0%)	18 (20.2%)	34 (18.6%)
Ethnicity			
Hispanic or Latino	19 (20.2%)	16 (18.0%)	35 (19.1%)
Not Hispanic or Latino	71 (75.5%)	69 (77.5%)	140 (76.5%)
Baseline ECOG Score			
0	76 (80.9%)	73 (82.0%)	149 (81.4%)
1	16 (17.0%)	12 (13.5%)	28 (15.3%)
2	2 (2.1%)	4 (4.5%)	6 (3.3%)
Metastatic			
Yes	39 (41.5%)	38 (42.7%)	77 (42.1%)
Targeted Therapies			
Abemaciclib	49 (52.1%)	48 (53.9%)	97 (53.0%)
Pertuzumab in any combination	32 (34.0%)	36 (40.4%)	68 (37.2%)
Kinase inhibitors	9 (9.6%)	4 (4.5%)	13 (7.1%)

Figure 1. Kaplan Meier estimates to the time to meeting durable response (prevention of diarrhea) in the subgroup of patients with breast cancer participating in the clinical trial.

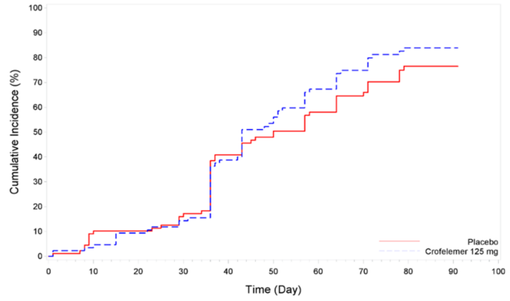
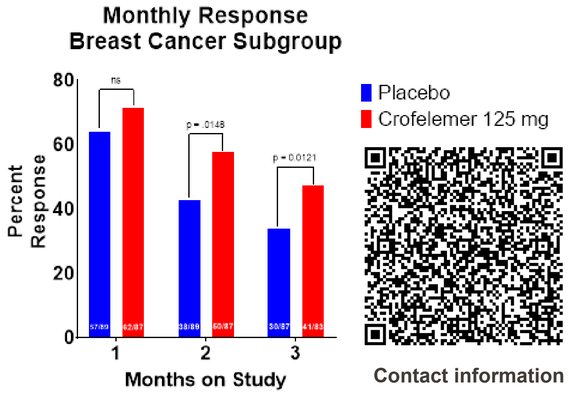


Figure 2. Proportion of monthly responders at the end of month 1, end of month 2, and end of month 3.



Contact information

Conclusions

In this double blind, placebo-controlled, multicenter study done in patients at risk of developing diarrhea due to the use of targeted therapy ± chemotherapy, crofelemer was safe and effective in preventing cancer treatment-related diarrhea in a subgroup of patients with breast cancer.

When compared to placebo, the prophylactic, anti-diarrheal effect of crofelemer was seen earlier and was more likely to be sustained during the 3-month study.

The sustained efficacy and favorable safety profile of crofelemer supports its use for CTD prophylaxis in PBCs receiving targeted therapy ± chemotherapy

Lay Summary:

Cancer therapy-related diarrhea is a common and frequently disruptive side effect of targeted cancer therapies. The OnTarget study was a large clinical trial that tested crofelemer, an FDA-approved drug for HIV-related diarrhea, in 287 adults with various solid tumors starting targeted therapies. Participants were randomly assigned to take either crofelemer or a placebo twice a day for 12 weeks. The primary objective was to see if crofelemer could reduce the number of days patients experienced loose or watery stools for the 12-week treatment period. While the primary objective was not met, crofelemer showed promising results within the planned subgroup analysis of the 183 breast cancer patients receiving targeted therapies, including abemaciclib and pertuzumab.

Breast cancer patients used electronic diaries to report on their bowel movements, GI symptoms, and how these affected their daily life. Based on this data, researchers looked at how many patients achieved "adequate relief" from diarrhea—defined as having no more than nine loose stools per week for at least half the weeks in a month. More breast cancer patients in the crofelemer group met this goal compared to those on placebo, especially by the second month and throughout the three-month treatment period. Crofelemer was also well tolerated, with a safety profile similar to placebo.

In summary, while crofelemer did not show a benefit for all cancer patients in the study, it may be a helpful option for preventing diarrhea in breast cancer patients receiving targeted therapies. These results suggest that crofelemer could improve comfort and help maintain uninterrupted treatment in this specific group.