REFERRING PHYSICIANS TO BECOME OnTarget INVESTIGATORS

Healthcare Professional Referral Kit Overview

The HCP referral kit was developed to support your efforts and provide IRB-approved template materials to recruit additional investigators to participate in the OnTarget clinical study.

Do not hesitate to keep us posted on your results!

All materials found by clicking here

Referral Kit Materials:

- **ABOUT THE STUDY**
- **BACKGROUNDER**
- **DOCTOR REFERRAL LETTER**
- **INCLUSION AND EXCLUSION CRITERIA**

MATERIAL DETAILS

About the Study

This document relays topline and important information about the study and primary eligibility criteria. This document can be shared with other physicians to see if any of their patients would qualify and be quality candidates for the study.

Backgrounder

The fact sheets can be useful background materials to provide to other physicians who may be interested in the study, with additional information on cancer treatment-related diarrhea (CTD), the clinical study, and the importance of supportive trials.

Doctor Referral Letter

This letter is an outreach note to share with other physicians who may be interested in participating in the study.

Inclusion and Exclusion Criteria Card

This card will be used as a reminder card for physicians to easily reference the primary inclusion and exclusion criteria.

ABOUT THE STUDY

OnTarget (NP303-102) is a Phase 3, multicenter, randomized clinical trial evaluating whether crofelemer is effective in reducing cancer treatment-related diarrhea (CTD) in adult patients who are receiving targeted therapies for treatment of solid tumors, with or without chemotherapy. These include patients with gastrointestinal, respiratory, or other types of cancers, such as breast and endocrine.

It is important that patients not only receive their appropriate cancer treatment, but also receive supportive care treatment to conquer the side effects of their cancer treatments. Doing so will help patients adhere to their cancer regimen improving clinical outcomes and their quality of life.

The OnTarget study is a supportive care trial designed to examine how to improve the quality of life for cancer patients by reducing CTD. Specifically, this trial evaluates the ability of a first-in-class study drug to prevent, or substantially reduce, the highly prevalent side effect of diarrhea associated with targeted therapies. Recent data shows that as many as 82% of patients experience diarrhea, with up to one-third of patients experiencing severe (grade 3 or 4) diarrhea.

The OnTarget study will assess the frequency of diarrhea as measured by daily patient reported loose and/or watery stools (Bristol Stool Form Scale 6 and 7) for the 12- week double-blind placebo-controlled treatment period (Stage 1). The primary endpoint is the average number of weekly watery stools over the 12-week double-blind placebo-controlled treatment period (Stage I). The 12-week period accommodates approximately 3 chemotherapy cancer treatment dosing-cycles for those patients who are also receiving chemotherapy. After 12 weeks, subjects will have the option to re-consent for an additional blinded, placebo-controlled 12-week extension period.

ABOUT CROFELEMER:

- Crofelemer is a novel drug antisecretory, antidiarrheal drug that reduces intestinal chloride ion and fluid secretion by modulating the cystic fibrosis transmembrane conductance regulator (CFTR) chloride ion channel. It is already approved to treat non-infectious HIV-related diarrhea in patients receiving antiretroviral therapy (ART) therapy. Its efficacy was shown in various clinical studies (such as in cholera and Traveler's diarrhea) when compared to placebo.

- In the pivotal phase 3 ADVENT clinical trial in HIV+ individuals with diarrhea, crofelemer was well-tolerated. The safety profile for crofelemer was comparable to placebo in each dose group; there was no apparent dose-response relationship for the most common adverse events reported.[ii] The most common side effects of crofelemer include upper respiratory tract infections, bronchitis, cough, flatulence (gas), and increased bilirubin (a waste product of the breakdown of red blood cells measured by a blood test) (Mytesi package insert).

WHO IS ELIGIBLE TO PARTICIPATE IN THE OnTarget STUDY?

- Adult, non-pregnant patients newly diagnosed with solid tumors who are scheduled to receive targeted cancer therapy drugs that have reported an all-grade diarrhea incidence of 50% or higher. Patients can be receiving standard chemotherapy but cannot be receiving any type of immunotherapy.

- Patients must be enrolled in the study before they begin a targeted therapy, with or without cycle chemotherapy, so that their study participation coincides with the start of their targeted therapy treatment.

TO LEARN MORE VISIT: www.ontargetstudyinvestigator.com

[i]Maroun, J. A., Anthony, L. B., Blais, N., Burkes, R., Dowden, S. D., Dranitsaris, G., Samson, B., Shah, A., Thirlwell, M. P., Vincent, M. D., & Wong, R. (2007). Prevention andmanagement of chemotherapy-induced diarrhea in patients with colorectal cancer: A consensus statement by the Canadian Working Group on chemotherapy-induced diarrhea. Current Oncology, 14(1), 13–20. https://doi.org/10.3747/co.2007.96

[ii] MacArthur et al. Advent Trial Results – HIV Clin Trials 2013

OnTarget BACKGROUNDER

Cancer Therapy-Related Diarrhea (CTD) can be debilitating and, in some cases, life threatening.[i]

- Findings in such patients include volume depletion, renal failure, and electrolyte disorders such as metabolic acidosis and, depending upon water intake, hyponatremia or hypernatremia.[i]

- Diarrhea is a common side effect of cancer therapy and the incidence of all grades of diarrhea during chemotherapy.[ii]
  - It has been reported to be as high as 82%, with up to one third of patients experiencing severe (grade 3 or 4) diarrhea.[ii]

Need for Treatments:

- Current CTD treatments are limited, and none target the underlying physiological mechanism of diarrhea. Because aggressive daily orally administered targeted therapies play an ever-increasing role in cancer treatment, the need to prevent and mitigate diarrhea is critical for ensuring treatment adherence and better patient quality of life.

OnTarget Trial: Seeking Solutions for Cancer Treatment-Related Diarrhea:

- **OnTarget (NP303-102)** is a Phase 3 multicenter, randomized, double-blind, placebo-controlled trial evaluating crofelemer for the prophylaxis of diarrhea in adult patients with solid tumors receiving targeted-cancer therapies, with or without standard chemotherapy regimens.

- **OnTarget** is a supportive care trial designed to examine how to improve quality of life for cancer patients by reducing CTD and/or improving their adherence to their prescribed targeted therapy.

- The 24-week **OnTarget** Clinical Trial (Protocol NP303-102) will:
  - Evaluate the safety and efficacy of orally administered crofelemer for the prophylaxis of diarrhea in adult patients with solid tumors receiving targeted cancer therapies with or without standard chemotherapy regimens.
  - Assess the frequency of diarrhea as measured by loose and/or watery stools per week.
  - Monitor the mean number of loose and/or watery bowel movements during the 12-week period.
  - Evaluate the difference in durable responders in the crofelemer versus placebo groups.

After completing the Stage 1, 12-week treatment phase, patients will have the option of remaining in their treatment arm for the Stage II, 12-week extension period.

About Crofelemer:

- Crofelemer is a novel, botanical antidiarrheal drug

- Modulates the cystic fibrosis transmembrane receptor (CFTR) channel and reduces intestinal chloride ion and fluid secretion. It is already approved for treating non-infectious HIV-related diarrhea in patients receiving antiretroviral (ART) therapy. Its efficacy was shown in various clinical studies (such as cholera and traveler's diarrhea) when compared to placebo.

- In the pivotal phase 3 ADVENT clinical trial, crofelemer was well-tolerated in HIV+ individuals with diarrhea.

Who is Eligible?

- Adult, non-pregnant patients newly diagnosed with solid tumors who are scheduled to receive targeted cancer therapy drugs that, have reported an all-grade diarrhea incidence of 50% or higher. Patients can be receiving standard chemotherapy but cannot be receiving any type of immunotherapy.

- To ensure adequate inclusion of diverse solid tumors, no more than 50% of participants will represent either a respiratory, gastrointestinal, or other (breast, endocrine, etc.) specific solid tumor type.

- Patients must be enrolled when they are first diagnosed and before they begin cancer treatment. Patients can be receiving standard chemotherapy but cannot be receiving any type of immunotherapy.

Importance of Conducting Supportive Care Trials:

Treatment adherence is crucial to obtain optimal outcomes such as cure or improvement in quality of life. Poor adherence decreases clinical benefits and overall effectiveness of the healthcare system.

- Although targeted therapies show much promise in treating solid tumors, many patients discontinue treatment upon experiencing the debilitating side effect of diarrhea.

- Severe CTD also can necessitate reduced doses or interrupted cancer therapies, affecting treatment outcomes.

    - Results showed patients with cancer-related diarrhea more frequently discontinued index therapy (82.4% vs. 64.6%; P < .0001). The trend persisted regardless of treatment type (chemotherapy, 81.5% vs. 62.3%; targeted therapy, 69.2% vs. 64.3%; both, 96% vs. 85.5%; P < .0001). [iv]

- For over 30% of CTD sufferers, it interferes with their daily activities (Stein et al., 2010), with detrimental effects on the mental and social health of cancer survivors.

TO LEARN MORE VISIT: www.ontargetstudyinvestigator.com

[i]Stein, A., Voigt, W., & Jordan, K. (2010, January). Chemotherapy-induced diarrhea: Pathophysiology, frequency and guideline-based management. Therapeutic advances in medical oncology. Retrieved September 23, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3126005/#bibr3-1758834009355164.

[ii] Maroun, J. A., Anthony, L. B., Blais, N., Burkes, R., Dowden, S. D., Dranitsaris, G., Samson, B., Shah, A., Thirlwell, M. P., Vincent, M. D., & Wong, R. (2007). Prevention and management of chemotherapy-induced diarrhea in patients with colorectal cancer: A consensus statement by the Canadian Working Group on chemotherapy-induced diarrhea. Current Oncology, 14(1), 13–20. https://doi.org/10.3747/co.2007.96

[iii]Puts, M. T. E., Tu, H. A., Tourangeau, A., Howell, D., Fitch, M., Springall, E., & Alibhai, S. M. H. (2014). Factors influencing adherence to cancer treatment in older adults with cancer: A systematic review. Annals of Oncology, 25(3), 564–577. https://doi.org/10.1093/annonc/mdt433

[iv]NCI. Gastrointestinal complications (PDQ)-Health Professional Version. Available at: www.cancer.gov/about-cancer/treatment/side-effects/constipation/gi-complications-hp-pdq#section/all. Accessed June 2, 2021. Okhuysen PC, et al. Abstract 12111. Presented at: ASCO Annual Meeting (virtual meeting); June 4-8, 2021.

[v]McQuade, R. M., Stojanovska, V., Abalo, R., Bornstein, J. C., & Nurgali, K. (2016). Chemotherapy-Induced Constipation and Diarrhea: Pathophysiology, Current and Emerging Treatments. Frontiers in pharmacology, 7, 414. https://doi.org/10.3389/fphar.2016.00414

[Date]
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Re: Clinical research study for people with Cancer Treatment-Related Diarrhea Associated with Targeted Therapies

Dear [doctor]:

I am reaching out to you as we are looking to identify patients for participation in the OnTarget (NP303-102), supportive care trial, a clinical study for people with Cancer Treatment-Related Diarrhea (CTD) associated with targeted therapies. As you know, as many as 82% of patients on targeted therapies experience diarrhea, with up to one-third of patients experiencing severe (grade 3 or 4) diarrhea. Therefore, it is important that patients not only receive proper care and treatment but also supportive care treatment, to help them adhere to their cancer regimens improving clinical outcomes and their quality of life.

OnTarget is a Phase 3, multicenter, randomized clinical trial evaluating whether crofelemer is effective in reducing CTD in adult patients who are receiving targeted therapies for treatment of solid tumors, with or without chemotherapy. These include patients with gastrointestinal, respiratory, and other types of cancers, including, breast and endocrine.

Crofelemer is a novel, antidiarrheal drug that reduces intestinal chloride ion and fluid secretion, and is already approved for the symptomatic relief of non-infectious HIV-related diarrhea in patients receiving antiretroviral (ART) therapy.

KEY INCLUSION CRITERIA

- Adult, non-pregnant patients newly diagnosed with solid tumors who are scheduled to receive targeted cancer therapy drugs that have reported an all-grade diarrhea incidence of 50 percent or higher. Patients can receive standard chemotherapy but cannot receive any type of immunotherapy.

- Patients must be enrolled before they begin their targeted therapy treatment so that their study participation coincides with the first dose of their targeted therapy treatment.

YOUR PATIENT'S PARTICIPATION

Patients will be enrolled in a 24-week OnTarget Clinical Trial that will:

- Evaluate the safety and efficacy of orally administered crofelemer for the prophylaxis of diarrhea in adult patients with solid tumors receiving targeted cancer therapies with or without standard chemotherapy regimens.

- Assess the frequency of diarrhea as measured by loose and/or watery stools per week.

- Monitor the mean number of loose and/or watery bowel movements during the 12-week period.
- Evaluate the difference in durable responders in the crofelemer versus placebo groups.

After completing the Stage 1, 12-week treatment phase, patients will have the option to reconsent and remain in their treatment arm for the Stage II, 12-week extension period.

REFERRING PATIENTS

I would greatly appreciate any referrals that you may have for this important clinical study. I am available to consult with you further regarding the eligibility of any of your patients and to provide additional information regarding this study. If you have or know of potentially eligible patients that would benefit from participating in this study, please refer them to our study coordinator, [name] at [phone number], for further evaluation. Any patients you refer will be seen by me and my staff for study purposes only, and we will continue to provide you with any progress updates you request.

I greatly appreciate your assistance with this clinical research study and thank you for your consideration.

Sincerely,
[Investigator]

OnTarget CLINICAL STUDY

Quick Screening Reference

KEY INCLUSION CRITERIA:

1. Adult consenting patients to receive at least one targeted cancer therapy drug that has reported an all grade diarrhea incidence of 50% or higher (e.g., TKIs, CDK 4/6 inhibitors, anti-EGFR, etc.) for treatment of pathologically and/or radiologically confirmed diagnosis of solid tumors.
2. Eligible to receive targeted cancer therapy per NCCN (National Comprehensive Cancer Network) guidelines and/or standard-of-care practice.
3. Patient can receive concomitant cycle [standard] chemotherapy agents together with their targeted cancer therapy treatment regimens.
4. ECOG (Eastern Cooperative Oncology Group) performance status 0-2 and expected to survive for 12-weeks.
5. Patients of childbearing potential must use an adequate method of contraception and women must obtain a negative urine pregnancy test.
6. Patient must be willing and able to access an electronic app via a smartphone, tablet, or computer to complete their bowel movement diaries.

KEY EXCLUSION CRITERIA:

1. Patients receiving any type of immunotherapy.
2. Patients receiving any cancer therapy for which antidiarrheal (antimotility) medications are mandatory, such as neratinib and irinotecan.
3. Ongoing irritable bowel syndrome (IBS) or colitis.
4. Ongoing diarrhea and/or diarrheal episodes within the previous 7 days.
5. Laxative use within 7 days or a history of constipation requiring the use of laxatives for more than 30 consecutive days.
6. Inadequate organ function within 28 days prior to signing consent.
7. Use of other investigational drugs within 4 weeks of signed informed consent.
8. Use of antibiotics within the past 7 days (up to 2 prophylactic doses of antibiotic for procedures is acceptable) prior to randomization.
9. Total colectomy and/or any type of gastrointestinal ostomy, major abdominal or pelvic surgery within the past 3 months.
10. Previous (within 1 month) or planned abdominal and/or pelvic radiation.
11. Fecal incontinence from ongoing radiation-induced diarrhea or constipation.
12. Active systemic infection requiring ongoing intervention, including but not limited to oral and intravenous antibiotics, anti-fungals, anti-parasitics, and anti-viral drugs.
13. Inability to document bowel movements using an electronic app via a smartphone, tablet, or computer.
14. Pregnant and/or breastfeeding.

PLEASE REFER TO THE COMPLETE PROTOCOL FOR ALL INCLUSION AND EXCLUSION CRITERIA.