

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213176Orig1Orig2s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 116762
Request Receipt Date	28NOV2018
Product	TGR-1202 (umbralisib)
Indication	Relapsed or refractory marginal zone lymphoma after receipt of at least one anti-CD20 based regimen
Drug Class/Mechanism of Action	PI3K delta inhibitor
Sponsor	TG Therapeutics
ODE/Division	OHOP/DHP
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	28JAN2019

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the **MPC meeting minutes**, and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

As monotherapy for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen

- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

☐ YES ☒ NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

- Consideration of Breakthrough Therapy Criteria:**

- Is the condition serious/life-threatening¹?

☒ YES ☐ NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

- Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

- i. Only animal/nonclinical data submitted as evidence ☐
- ii. Insufficient clinical data provided to evaluate the BTDR
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Umbralisib is an orally administered PI3K delta and casin Kinase 1 episilon inhibitor

Indication/Disease: Treatment of patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen. MZL is a serious and life-threatening disease, and comprises approximately 10% of all cases of non-Hodgkin lymphoma. Although median overall survival is about 10 years, the clinical course is characterized by multiple relapses, and more therapies are needed.

Available therapies: There are currently no therapies which have been granted regular approval for second line therapy in this patient population. Ibrutinib has been granted accelerated approval for the indication.

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

7. Information related to endpoints used in the available clinical data:

Overall response rate with umbralisib in this preliminary analysis was 55%, the complete response rate was 11% and the median duration of response (DOR) was not reached with 86% of responders achieving DOR of at least 6 months duration.

The most common adverse reactions were diarrhea (45%), fatigue (26%), headache (26%), nausea (26%), cough (24%), decreased appetite (21%), ALT increased (18%), AST increased (18%), and peripheral edema (18%). The most common Grade 3-4 adverse reactions were diarrhea (5%), fatigue (3%), headache (3%), ALT increased (3%), and AST increased (3%).

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

Ibrutinib received accelerated approval in August 2017 for the treatment of adults with marginal zone lymphoma after at least one line of anti-CD20 based therapy, based on overall response rate of 46% and a complete response rate of 3%.

Off-label, second line and subsequent treatment regimens include; lenalidomide single agent, bendamustine + rituximab, R-CHOP, R-CVP, rituximab single agent, lenalidomide + rituximab, bendamustine + obinutuzumab, ibritumomab tiuxetan, and the three marketed PI3K inhibitors (idelalisib, copanlisib and duvelisib). Hematopoietic stem cell transplantation may be appropriate for a select sub-population of patients with relapsed MZL.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

None known

10. Information related to the preliminary clinical evidence:

Preliminary clinical evidence of efficacy and safety was presented from the first 38 patients on the monotherapy arm of study UTX-TCR-205 that had been followed for at least 6 months.

As for granting breakthrough designation, the Agency feels that:

The magnitude and durability of responses achieved with umbralisib represents preliminary evidence of substantial improvement over available therapy. There are no therapies with regular approval for the proposed indication. The Division has considered ORR and DOR results as acceptable endpoints for BTDR requests.

In addition, patients may be able to remain on therapy with umbralisib for longer periods of time due to the different toxicity profile of this PI3K delta inhibitor. Ibrutinib is associated with bleeding and arrhythmias.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Preliminary efficacy and safety for this agent in a serious disease with an unmet need for second line therapy.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

Sponsor plans to submit an application based on data from the entire cohort of 72 patients who received monotherapy umbralisib for MZL.

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):
- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

NCCN v 1 2019

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Revised 10/17/17/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CANDIS MORRISON
01/16/2019 03:00:22 PM

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01/16/2019 04:38:00 PM

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