pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Sorafenib (Nexavar) for Differentiated Thyroid Cancer

July 16, 2015

INQUIRIES

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Name of the Drug and Indication(s):	Sorafenib (Nexavar®) for Differentiated Thyroid Cancer
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	Bayer

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part x disagree

Differentiated Thyroid Carcinoma (DTC) refractory to radioactive iodine (RAI-R DTC) is a rare disease with a global incidence rate of 4 per million. A lack of effective approved therapies for the treatment of locally advanced/metastatic RAI-R DTC constitutes a significant unmet need. NEXAVAR is the first and only therapy specifically approved for these patients. It provides a statistically significant and clinically meaningful improvement in progression free survival (PFS), and has a tolerable safety profile in this setting. Hence, Bayer disagrees with pERC's interpretation of the clinical benefit in the initial recommendation, and agrees with the Endocrine Clinical Guidance panel's position that "*there is a net overall clinical benefit of sorafenib"* (CGR, 1.3 Conclusions p.3 par 1).

Moreover, given that no other approved therapies exist, NEXAVAR represents an important advancement in the treatment of these patients and supporting access is an appropriate use of public health care dollars. Withholding NEXAVAR from RAI-R DTC patients means that the only treatment options available for them will be *"repeated surgery to manage recurrent disease in the neck, and external beam radiation therapy to deal with symptoms from metastatic bone and lung disease such as pain and hemolysis"* (CGR, 3.2 Accepted Clinical Practice, p.9, par 1). These options will incur extra costs to the health system while negatively impacting quality of life and increasing morbidity to patients.

The main concerns highlighted by pERC which inform their recommendation were *"the decline in quality of life, the rates of high grade toxicity, and uncertainty in overall survival benefit of sorafenib versus placebo"* (pERC Initial Recommendation, pERC Recommendation p.1 par 1). **Bayer disagrees with pERC's interpretation of the clinical data and urges pERC to reconsider it for the following reasons:**

1. NEXAVAR's changes in quality of life

- "Patients living with this type of thyroid cancer are aware that their advanced disease will progress with worsening symptoms until death" (pERC Initial Recommendation, Patient-Based Values p.5 par 1).
- In the DECISION trial, the quality of life (QoL) changes were individually heterogeneous; while some patients showed a minimal decrease others showed an improvement (EPAR p.43 par 1).
- Bayer encourages interpreting the DECISION trial QoL data with caution. When evaluating the QoL results it should be noted that the FACT-G scale barely reached the minimum clinically important difference threshold while the EQ-5D scale was determined not clinically meaningful.
- The patient advocacy input provides an important perspective to assist in the interpretation of QoL results from the trial. Rather than being *"contradictory"* (pERC Initial Recommendation, Summary of pERC Deliberations p.2 par 3), it emphasizes the heterogeneity of QoL changes and that patients are "*willing to tolerate the adverse events"* (pERC Initial Recommendation, Patient-Based Values p.5 par 2) *"given the stage of disease and time-limited treatment options"* (CGR, 2.1.6 Other Considerations p.6 par 1).

2. NEXAVAR's benefit-risk profile

- The adverse event (AE) profile of NEXAVAR is well-characterized, tolerable and manageable. The observed safety profile of NEXAVAR in DTC has been documented in other indications, and clinicians have been prescribing NEXAVAR since 2006, when it was first approved for marketing in Canada, and are familiar with the management of NEXAVAR-related AEs.
- Medically serious identified risks of NEXAVAR, such as myocardial infarction/ischemia, gastrointestinal perforation, drug induced hepatitis and hemorrhage do not occur more frequently in DTC patients than observed in other tumor types.
- As noted by pERC, *"treatment with sorafenib for patients with DTC is a relatively new strategy… with more experience with DTC and sorafenib there might be potential to manage the dosing and toxicity of sorafenib more effectively"* (pERC Initial Recommendation, Overall Clinical Benefit p.5 par 1).
- Furthermore, in the DECISION trial *"grade 4 toxicities were uncommon and only 1 toxic death was observed in the sorafenib arm. This compares favourably with commonly used cytotoxic agents"* (CGR, 2.2 Interpretation and Guidance p.7 par 3).

3. NEXAVAR's overall survival benefit

- In previous assessments of other clinical trials pERC has recognized and accepted the crossover adjustment methods used in the DECISION trial to correct for patient switching despite "the absence of national or international guidelines on the validity of methodologies for crossover adjustment" (pERC Initial Recommendation, Overall Clinical Benefit p.5 par 2).

- Furthermore, while evidence for a relationship between OS and PFS has not been published for this setting, the reason is not a lack of relationship but rather a reflection of the rarity of the condition and the paucity of major published trials and natural history data. In this case, the absence of evidence is not necessarily the evidence of absence.
- The DECISION trial met its primary endpoint and demonstrated the efficacy of NEXAVAR in locally advanced or metastatic RAI-R DTC by showing a statistically significant, clinically meaningful prolongation of PFS. All predefined sensitivity analyses of PFS were consistent and supportive of the overall primary analysis results of PFS. Therefore, the observed PFS benefit is of great clinical significance and "the value of extending the time that their cancer is progression-free is also important to patients" (CGR, 2.1.6 Other Considerations p.6 par 1).

In conclusion, Bayer does not agree with pERC's interpretation of the clinical benefit in the initial recommendation.

Additionally, as supported by the Provincial Advisory Group (PAG), "the incremental budget impact would be small due to the small number of patients who would be candidates for sorafenib" (pERC Initial Recommendation, Overall Clinical Benefit p.6 par 6).

Furthermore, Bayer would be supportive of PAG considering limiting NEXAVAR's public funding *"to patients who are symptomatic from their cancer or whose cancer is progressing rapidly and who are likely to become symptomatic"* as stated in the Clinical Guidance Report (CGR, Evidence-Based Considerations for a Funding Population p.10 par 2).

Based on the above considerations, Bayer requests that pERC reconsiders its initial recommendation and in its final assessment recommends funding NEXAVAR for those few Canadian Patients who have DTC refractory to radioactive iodine.

References:

1. pERC Initial Recommendation for Sorafenib (Nexavar) for Differentiated Thyroid Carcinoma, pERC Meeting: April 16, 2015.
2. pCODR Initial Clinical Guidance Report (CGR) – Sorafenib (Nexavar) for Differentiated Thyroid Carcinoma, pERC Meeting: April 16, 2015.
3. European Public Assessment Report (EPAR): Nexavar (sorafenib) [Internet]. London: European Medicines Agency; 2015. [cited 2015 May 12]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000690/human_med_000929.jsp

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

_____	Support conversion to final recommendation. Recommendation does not require reconsideration by pERC.	___x___	Do not support conversion to final recommendation. Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

1 About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

2 Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer

of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½″ by 11″ paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.