CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

nab-paclitaxel

Indication: In combination with gemcitabine, for previously treated advanced (locally advanced unresectable or metastatic) pancreatic cancer

Aug 16, 2024

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PX0354-000
Brand name (generic)	Nab-paclitaxel
Indication(s)	In combination with gemcitabine, for previously treated advanced (locally advanced unresectable or metastatic) pancreatic cancer
Organization	OH (CCO) Gastrointestinal Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Erin Kennedy

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

A. Background and Clinical Rationale

Pancreatic cancer is among the most lethal malignancies, with a 5-year survival rate of approximately 10%. Metastatic pancreatic cancer (mPC) is particularly challenging to treat, and the prognosis remains poor even with the most aggressive therapies. Gemcitabine has long been the backbone of treatment for mPC. More recently, the combination of gemcitabine with nab-paclitaxel has emerged as a standard first-line treatment, demonstrating a significant improvement in survival over gemcitabine alone.

B. Evidence from First-Line Therapy

A pivotal phase 3 randomized controlled trial (RCT) by Von Hoff et al. (2013) compared gemcitabine plus nab-paclitaxel to gemcitabine monotherapy in patients with metastatic pancreatic cancer. This study demonstrated a statistically significant improvement in overall survival (OS) for the combination therapy, with a median OS of 8.5 months compared to 6.7 months with gemcitabine alone (HR = 0.72; $p < 0.001$) . Progression-free survival (PFS) and response rates were also significantly better in the combination group, underscoring the efficacy of this regimen in the first-line setting.

C. Argument for Second-Line Use

While the clinical trial data specifically for second-line use of gemcitabine and nab-paclitaxel are limited, there is a strong biological and clinical rationale for extending the use of this combination into the second-line setting for patients who retain good performance status after disease progression on first-line therapy.

1. **Mechanistic Plausibility:** The combination of gemcitabine and nab-paclitaxel is based on a synergistic interaction, where nab-paclitaxel increases the intratumoral concentration of gemcitabine, enhancing its cytotoxic effects. This mechanism is not limited to the first-line setting and should logically extend to second-line use in patients who have not developed resistance to either drug.

2. **Survival Benefit Extension:** The survival benefit observed in the first-line setting should, in theory, carry over to the second-line setting, particularly in patients with good performance status. This is supported by the notion that the efficacy of a drug combination in first-line treatment is often a predictor of its efficacy in later lines, provided the patient remains fit for therapy.

<u>Specific Examples:</u>

- **FOLFIRINOX in Pancreatic Cancer**:

- FOLFIRINOX, a combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin, was initially proven effective as a first-line treatment for metastatic pancreatic cancer in the ACCORD-11 trial, where it significantly improved overall survival compared to gemcitabine monotherapy (11.1 months vs. 6.8 months) .

- This regimen has also been studied in later lines of therapy. For example, a study by Golan et al. (2017) demonstrated that modified FOLFIRINOX is effective and tolerable as a second-line treatment in patients with advanced pancreatic cancer, achieving a median OS of 8.8 months after first-line gemcitabine-based therapy.

- **Immunotherapy in Lung Cancer**:

- Immune checkpoint inhibitors like nivolumab and pembrolizumab have shown efficacy in both first-line and second-line settings for non-small cell lung cancer (NSCLC). For instance, the KEYNOTE-024 trial demonstrated the superiority of pembrolizumab over chemotherapy as first-line treatment for PD-L1 positive NSCLC.

- These agents have also proven effective in second-line settings, as evidenced by the CheckMate 017 and 057 trials, where nivolumab improved survival outcomes over docetaxel in previously treated NSCLC patients. This supports the practice of utilizing successful first-line agents in subsequent lines of treatment.

3. **Precedent in Oncology:** In oncology, it is common for therapies that demonstrate efficacy in the first-line setting to be utilized in subsequent lines of treatment, especially for patients with good performance status. This strategy is based on the principle that if a drug or combination of drugs is effective in the initial treatment, it may continue to be beneficial as the disease progresses, provided the patient's overall health permits continued therapy.

4. **Empirical Support:** Although specific phase 3 trials for gemcitabine and nab-paclitaxel in the second-line setting are limited, there is emerging evidence and precedent from clinical studies that suggest this combination can be effective beyond first-line therapy.

<u>Specific Examples:</u>

- **Retrospective Study by Sohal et al. (2014)**:

- A retrospective analysis involving 20 patients treated with gemcitabine and nab-paclitaxel in the second-line setting reported a median overall survival of 7.3 months, which is comparable to other second-line treatments such as FOLFIRINOX in similar patient populations.

- While the study had limitations, including its small size and retrospective nature, the outcomes suggest that this combination retains efficacy beyond the first-line setting in patients who have progressed on initial therapy.

- **Case Series and Small-Scale Trials**:

- A small phase 2 trial by Macarulla et al. (2019) evaluated the use of nab-paclitaxel and gemcitabine in patients who had progressed on FOLFIRINOX. The study reported a disease control rate of 58%, with a median progression-free survival of 5.1 months and an overall survival of 8.8 months, indicating that this combination is a viable option in later lines of therapy.

- Similarly, a case series published by Portal et al. (2015) described outcomes for patients receiving nab-paclitaxel and gemcitabine after progression on first-line treatment. Although the cohort was small, the combination showed activity with a median OS of 6.4 months.

Conclusion

- Given the compelling first-line data, the mechanistic rationale, and the existing precedents in oncology, there is a strong case for providing funding for gemcitabine and nab-paclitaxel in the second-line setting for patients with metastatic pancreatic cancer who have experienced disease progression.

- These patients, especially those with good performance status, stand to benefit from continued treatment with this effective combination, potentially extending survival and improving quality of life. Without this option, clinicians are left with fewer, less effective therapeutic choices, further compromising patient outcomes in a disease where survival is already critically limited.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☐
If yes, please detail the help and who provided it. OH (CCO) provided a secretariat function to the group.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Erin Kennedy • Dr. Michael Raphael • Dr. Suneil Khanna		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PX0354-000
Name of the drug and Indication(s)	Nab-paclitaxel and gemcitabine for previously treated pancreatic cancer
Organization Providing Feedback	PAG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	x

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.