Nivolumab Plus Ipilimumab (PX0371) FMEC Responses to Questions from the Drug Programs

Responses Summary

Drug program implementation questions	Clinical expert response	FMEC response
Relevant comparators		
The NADINA trial compared 2 cycles of neoadjuvant nivolumab-ipilimumab followed by either surveillance if major pathologic response, or if partial or no pathologic response, 11 cycles of adjuvant nivolumab, or if *BRAF* V600E/K, 46 weeks of adjuvant dabrafenib-trametinib against 12 cycles of adjuvant nivolumab for patients with resectable Stage III melanoma. How does the NADINA regimen compare against the SWOG S1801 (neoadjuvant to adjuvant pembrolizumab) or adjuvant pembrolizumab, or if *BRAF* mutation, adjuvant dabrafenib-trametinib?	The clinical experts commented that the SWOG S1801 study used single agent pembrolizumab for 3 cycles up followed by surgery and then adjuvant pembrolizumab for 15 additional treatments; all patients received adjuvant treatment, which was not dependent on pathologic response. For patients with a *BRAF* mutation, *BRAF*/MEK targeted therapy may be best suited for those with intolerance to immunotherapy toxicity, acknowledging that there is evidence (per International Neoadjuvant Melanoma Consortium updated pooled analysis) demonstrating reduced efficacy with neoadjuvant treatment with BRAF/MEK inhibitors among patients with a *BRAF* mutation. Nivolumab and pembrolizumab are both PD-1 drugs and are considered equivalent as they have similar efficacy and toxicity profiles. Hence, even though nivo/ipi neoadjuvant was not compared to pembrolizumab, nivo/ipi showed improved EFS over nivo and hence most likely more efficacious than pembro.	FMEC agree with the clinical experts
Considerations for initiation of therapy		
The jurisdictions would like to inform FMEC that they have implemented weight-based dosing up to a cap for nivolumab policies (i.e., nivolumab 3mg/kg up to 240mg every 2 weeks or 6mg/kg up (up to 480mg) every 4 weeks).	The experts indicated that the dosage that was used in the NADINA trial should be implemented, since patients would receive a total of 2 doses only (with a lower dose of ipilimumab) and highlighted the risk of under-dosing. However, the clinical experts indicated that weight-based dosing is reasonable for the adjuvant setting.	FMEC agrees with the clinical experts FMEC is aware that jurisdictions implement weight-based dosing to a cap. However, no data were reviewed regarding this particular issue as part of this project
Special implementation issues		

Drug program implementation questions	Clinical expert response	FMEC response
The following patients were excluded in the trial. Should neoadjuvant nivolumab-ipilimumab be considered in patients with: • ECOG >1 • Mucosal melanoma? • Uveal melanoma? • Melanoma with more than 3 in-transit metastases?	The clinical experts considered patients with mucosal melanoma to be eligible for treatment with neoadjuvant nivolumab-ipilimumab based on known efficacy of neoadjuvant ipilimumab in the metastatic setting as well as adjuvant immunotherapy for mucosal melanoma. The experts considered patients with in-transit metastases to be eligible for treatment with neoadjuvant nivolumab-ipilimumab if the in-transit metastases were resectable, regardless of the number of in-transit metastases. However, patients with ECOG > 1 or with uveal melanoma (a distinct form of disease and poor response to nivolumab-ipilimumab in the metastatic setting) would not be considered for treatment with neoadjuvant nivolumab-ipilimumab.	FMEC agrees with the clinical experts Please refer to the Initiation condition as outlined in Table 2 of the Recommendation Report.
Under what clinical circumstances would neoadjuvant nivolumab-ipilimumab+/- adjuvant therapy be preferred over neoadjuvant-adjuvant pembrolizumab and vice-versa?	Given the risk of increased toxicity with neoadjuvant nivolumab-Ipilimumab, the experts noted that patients with reduced tolerance for combined immunotherapy toxicity may be treated with a single agent immunotherapy (e.g., neoadjuvant-adjuvant pembrolizumab).	FMEC defers to the clinical experts
For patients with partial pathologic response or non-response to 2 cycles of nivolumab-ipilimumab, can adjuvant pembrolizumab be given in place of adjuvant nivolumab?	Since pembrolizumab and nivolumab are considered equivalent in terms of treatment response, the clinical experts were not aware of any reason to prefer one over the other to warrant switching patients from adjuvant nivolumab; the choice of adjuvant pembrolizumab or adjuvant nivolumab may be based on known or observed adverse events (e.g., infusion reactions).	FMEC agrees with the clinical experts. Refer to the implementation guidance under discontinuation and renewal condition as outlined in Table 2 of the recommendation report.
Can the committee confirm the downstream sequencing for patients treated with the following, but whose disease either progress during or recurs within 6 months: • Only 2 cycles of neoadjuvant nivolumab-ipilimumab due to major pathologic response? • 2 cycles of neoadjuvant nivolumab-ipilimumab followed by either adjuvant nivolumab or adjuvant dabrafenib-trametinib?	The clinical experts emphasized that treatment with neoadjuvant nivolumab-ipilimumab should not alter access to any of the treatment options in the metastatic setting. Sequencing of treatment in the following scenarios are as follows, according to the clinical experts: If a patient progresses after 2 cycles of neoadjuvant nivolumab-ipilimumab, there are limited options unless they have BRAF-mutated melanoma. Patients should have the option for	This question is outside the scope of this review and addresses a different population of patients with metastatic melanoma. Sequencing of treatment options may be addressed via a provisional funding algorithm.

Drug program implementation questions	Clinical expert response	FMEC response
	metastatic treatment with nivolumab-ipilimumab as a different dosing regimen is used in the metastatic setting, as well as the option to continue receiving adjuvant nivolumab after achieving major pathologic response (until further evidence is available for longer follow-up). If a patient progresses after 2 cycles of neoadjuvant nivolumab-ipilimumab followed by either adjuvant nivolumab or adjuvant dabrafenib-trametinib, they could be switched to the other treatments (e.g., a patient who had 2 cycles of neoadjuvant nivolumab-ipilimumab followed by adjuvant nivolumab, but then experiences disease progression, could subsequently be offered treatment with adjuvant dabrafenib-trametinib).	
Can the committee comment on downstream eligibility for first line and later line ipilimumab-nivolumab for patients whose disease progress while on or within 6 months of a prior PD-1 inhibitor?	The clinical experts reiterated that treatment with nivolumab-ipilimumab in the neoadjuvant setting should not alter any subsequent lines of therapy in the metastatic setting, noting that the dosing of nivolumab-ipilimumab is different for metastatic disease.	This is also outside the scope of this review. Sequencing of treatment options may be addressed via a provisional funding algorithm.
System and economic issues		
There is uncertainty in the uptake for neoadjuvant nivolumab-ipilimumab given neoadjuvant to adjuvant pembrolizumab is also under review. Clinicians may also want to wait for more data to support not giving adjuvant treatment for patients with major pathologic response.	The clinical experts stated that there are patients for whom treatment with pembrolizumab may be appropriate (e.g., among patients with intolerability to toxicity of combined immunotherapy (nivolumab-ipilimumab) and the decision of which to use (either neoadjuvant nivolumab plus ipilimumab or neoadjuvant-adjuvant pembrolizumab) should be left to the treating clinician.	Shared decision making would be required to support people with this condition to make an informed decision, particularly given uncertainty around long-term outcomes (e.g., overall survival).

BRAF = proto-oncogene B-Raf; ECOG = Eastern Cooperative Oncology Group; FMEC = Formulary Management Expert committee; PD-1 = program cell death protein 1;