Nivolumab Plus Ipilimumab

Formulary Management Expert Committee Responses to Questions From the Drug Programs

Table 1: Responses Summary

Drug program implementation questions	Clinical expert response	FMEC response
Relevant comparators		
The NADINA trial compared 2 cycles of neoadjuvant nivolumab plus ipilimumab followed by either surveillance (if there was major pathologic response), 11 cycles of adjuvant nivolumab (if there was partial or no pathologic response), or 46 weeks of adjuvant dabrafenib plus trametinib (if *BRAF* V600E/K) against 12 cycles of adjuvant nivolumab for patients with resectable stage III melanoma. How does the NADINA trial regimen compare to the SWOG S1801 trial regimen (neoadjuvant to adjuvant pembrolizumab) or adjuvant pembrolizumab, or (if there is a *BRAF* mutation) adjuvant dabrafenib plus trametinib?	The clinical experts commented that the SWOG S1801 study used single-agent pembrolizumab for 3 cycles 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 the 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, although neoadjuvant nivolumab plus ipilimumab was not compared to pembrolizumab, nivolumab plus ipilimumab showed improved EFS over nivolumab alone, and therefore is likely to be more efficacious than pembrolizumab.	FMEC agrees with the clinical experts.

Drug program implementation questions	Clinical expert response	FMEC response
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 3 mg/kg up to 240 mg every 2 weeks, or 6 mg/kg up to 480 mg every 4 weeks).	The experts indicated that the dosage used in the NADINA trial should be implemented, given that patients would receive a total of 2 doses only (with a lower dose of ipilimumab), and highlighted the risk of underdosing. 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		
The following patients were excluded in the trial. Should neoadjuvant nivolumab plus ipilimumab be considered in patients with the following? • ECOG score >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 plus 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 plus ipilimumab if the in-transit metastases were resectable, regardless of the number of in-transit metastases. However, patients with uveal melanoma (a distinct form of disease with a poor response to nivolumab plus ipilimumab in the metastatic setting) would not be considered for treatment with neoadjuvant nivolumab plus ipilimumab. Patients with good performance status (ECOG score ≤ 2) may be considered for neoadjuvant treatment with nivolumab plus ipilimumab.	FMEC agrees with the clinical experts. Refer to the *Initiation* condition, as outlined in Table 2 of the recommendation report.

Drug program implementation questions	Clinical expert response	FMEC response
Under what clinical circumstances would neoadjuvant nivolumab plus ipilimumab (with or without adjuvant therapy) be preferred over neoadjuvant and adjuvant pembrolizumab, and vice versa?	Given the risk of increased toxicity with neoadjuvant nivolumab plus ipilimumab, the experts noted that patients with reduced tolerance for combined immunotherapy toxicity may be treated with a single-agent immunotherapy (e.g., neoadjuvant and adjuvant pembrolizumab).	FMEC defers to the clinical experts.
For patients with partial pathologic response or nonresponse to 2 cycles of nivolumab plus ipilimumab, can adjuvant pembrolizumab be given in place of adjuvant nivolumab?	Given that 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 the *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 progresses or recurs within 6 months? • Only 2 cycles of neoadjuvant nivolumab plus ipilimumab due to major pathologic response • 2 cycles of neoadjuvant nivolumab plus ipilimumab followed by either adjuvant nivolumab or adjuvant dabrafenib plus trametinib	The clinical experts emphasized that treatment with neoadjuvant nivolumab plus ipilimumab should not alter access to any of the treatment options in the metastatic setting. Sequencing of treatment in the following scenarios is as follows, according to the clinical experts: If a patient progresses after 2 cycles of neoadjuvant nivolumab plus ipilimumab, there are limited options unless they have *BRAF*-mutated melanoma. Patients should have the option for metastatic treatment with nivolumab plus ipilimumab (as a different dosing regimen is used in the metastatic setting), as well as the option to continue receiving adjuvant nivolumab after experiencing major pathologic response (until further evidence is available for longer follow-up).	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
	If a patient progresses after 2 cycles of neoadjuvant nivolumab plus ipilimumab followed by either adjuvant nivolumab or adjuvant dabrafenib plus trametinib, they could be switched to the other treatments (e.g., a patient who had 2 cycles of neoadjuvant nivolumab plus ipilimumab followed by adjuvant nivolumab but then experienced disease progression could subsequently be offered treatment with adjuvant dabrafenib plus trametinib).	
Can the committee comment on downstream eligibility for first-line and later-line ipilimumab plus nivolumab for patients whose disease progresses during treatment with, or within 6 months of, a prior PD-1 inhibitor?	The clinical experts reiterated that treatment with nivolumab plus ipilimumab in the neoadjuvant setting should not alter any subsequent lines of therapy in the metastatic setting, noting that the dosing of nivolumab plus 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 plus ipilimumab, given that neoadjuvant to adjuvant pembrolizumab is also under review. Clinicians may also wish to wait for more data to support not offering adjuvant treatment to 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 plus ipilimumab]), and the decision of which treatment to use (either neoadjuvant nivolumab plus ipilimumab, or neoadjuvant and 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 the uncertainty around long-term outcomes (e.g., overall survival).

ECOG = Eastern Cooperative Oncology Group; FMEC = Formulary Management Expert Committee.