Nivolumab Plus Ipilimumab

Formulary Management Expert Committee Responses to Questions from the Drug Programs

Table 1: Response Summary

Drug program implementation questions	Clinical expert response	FMEC response
Considerations for initiation of therapy		
While the reimbursement request is currently only for first line, should patients who have progressed during or within 6 months of anti-PD-1 adjuvant therapy be eligible for ipilimumab plus nivolumab in both the first- and second-line unresectable or metastatic settings (for example, if the patient has a *BRAF* mutation and receives targeted therapy first line in the unresectable or metastatic setting)?	Per the clinical experts, any patient who progresses on anti-PD-1 therapy, whether in the adjuvant setting or in the first-line metastatic setting, should be eligible for combination nivolumab plus ipilimumab therapy. These are similar populations of patients, and hence, they were grouped together in the clinical trials and retrospective studies. There is no scientific reason to treat these groups separately or to think that they would respond any differently.	FMEC noted that the reimbursement request for a combination of nivolumab and ipilimumab was for patients who progressed on adjuvant anti-PD-1 therapy. Second-line treatment was deemed out of the scope of this review.
Should patients who have progressed during or within 6 months of anti-PD-1 adjuvant therapy and are *BRAF* mutation-positive be eligible for ipilimumab plus nivolumab in the unresectable or metastatic setting?	According to the clinical experts, patients who have progressed during or within 6 months of anti-PD-1 adjuvant therapy and are *BRAF* mutation-positive should be eligible for ipilimumab plus nivolumab in the unresectable or metastatic setting. The experts noted that studies assessing sequencing *BRAF/MEK* versus ipilimumab plus nivolumab have shown that the combination upfront is better than starting patients with *BRAF/MEK*.	FMEC agrees with the clinical experts.
In what clinical scenario would patients be treated with anti-PD1 in a metastatic setting and then switched to a combination?	According to the clinical experts, in the current funding scenario, most patients are given the combination upfront (approximately more than 90%), as patients will not have access to the combination should they progress on a single drug anti-PD1. Only certain patients (e.g., with low volume disease, skin metastases only, without brain metastasis, or who are	FMEC agrees with the clinical experts.

	older or have other medical comorbidities or autoimmune disease) are given single drug anti-PD1. However, if there was an option for a combination after progression on anti-PD1 treatment, then it is expected that fewer patients would be started on the combination.	
Special implementation issues		
Nivolumab and relatlimab combination (that is, PD-1 and LAG-3 inhibitor) is currently under review as a first-line treatment for advanced melanoma. Would approving ipilimumab plus nivolumab for fast progressors set a precedent for other combination immunotherapies used for unresectable or metastatic melanoma?	According to the clinical experts, given that the trials for new agents are still in the early stage, it is not possible to estimate the benefit of other combinations and, hence, their impact on the treatment landscape for melanoma.	FMEC did not review any data for relatlimab. The trial and evidence review of relatlimab and nivolumab would inform the reimbursement population for this regimen.
The study by VanderWalde et al. (2023). included patients who had received anti-PD-1 monotherapy as first-line treatment for unresectable or metastatic melanoma and progressed during or within 6 months of completing treatment (81% in the ipilimumab plus nivolumab arm and 95% in the ipilimumab monotherapy arm). Would this population be considered eligible for treatment with ipilimumab plus nivolumab in the second-line setting, provided they are able to tolerate the drug?	—	This population is out of scope for this review.
Will patients who have relapsed during or within 6 months of anti-PD-1 adjuvant therapy and are either on ipilimumab monotherapy or recently finished ipilimumab monotherapy have a time-limited opportunity to add nivolumab for 4 cycles, then move to nivolumab maintenance therapy?	According to the clinical experts, virtually all patients should start with combination treatment unless there are contraindications.	Given that these patients would not have access to nivolumab plus ipilimumab at any future time, it would be reasonable to allow the addition of nivolumab both with ipilimumab and as maintenance.

FMEC = Formulary Management Expert Committee; PD-1 = Programmed Cell Death Protein 1; MEK = Mitogen-activated Extracellular signal-regulated Kinase.