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Date of request: June 29, 2017

NCCN Guidelines Panel: Melanoma

#### Change requests for Melanoma

On behalf of Amgen, I respectfully submit for consideration of the panel, that the NCCN Clinical Practice Guidelines for Melanoma, Stage III-IV be updated to reflect the publication of phase 2 study data<sup>1</sup> that demonstrated immunotherapy products talimogene laherparepvec in combination with ipilimumab improved overall response rate (ORR) in adult patients with unresected stage IIIB-IV melanoma, compared to ipilimumab alone.

#### Clinical Data

The Phase 2 study was a prospective, randomized, open-label study that investigated the effect of talimogene laherparepvec and ipilimumab in combination (T+I) versus ipilimumab alone (I) in unresected stage IIIB-IV melanoma. The primary endpoint was ORR. Adult patients were randomized in a 1:1 ratio to receive T+I or I alone.

Talimogene laherparepvec was given at approved doses and intervals until there were no tumors left to inject, disease progression (PD) had occurred, or intolerance had developed. Ipilimumab was started at week 6 in the T+I arm and at week 1 in the I arm at 3 mg/kg IV Q3W x 4. The primary endpoint was ORR by immune-related response criteria and secondary endpoints included duration of response, disease control rate (DCR), progression free survival (PFS), overall survival (OS) and safety.

In the Phase 2 study, 198 patients were randomized to T+I (n = 98) or I (n = 100) and analyzed for efficacy. Patients randomized to T+I demonstrated a significantly higher ORR (38.8%) compared to those that received I (18%), P=0.002, odds ratio (OR) 2.9. Eighty-nine percent (89%) of the T+I and 83% of the I patients remained in response at the time of primary analysis. Unconfirmed visceral lesion response rate (defined as ≥ 50% reduction in total tumor area) was 35.5% T+I vs 13.6% I. OS is immature. Of 190 patients (safety set: 95 T+I, 95 I), the most common adverse events (AEs) for T+I, I (%) were fatigue (59, 42), chills (53, 3), and diarrhea (42, 35). Twenty-eight percent (28%) of the patients in the T+I arm and 18% of the patients in the I arm had grade ≥ 3 treatment-related adverse events. There were 3 deaths in the T+I arm, all considered unrelated to the investigational products: 1 due to myocardial infarction and 2 due to progression of disease.

Note: the combination use of talimogene laherparepvec and ipilimumab is not approved by the FDA.

#### Supporting Documentation

Please find attached the relevant abstract and accompanying poster in support of this request.



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1. Chesney J, Andtbacka R, *et al.* Primary results from a randomized (1:1), open-label phase 2 study of talimogene laherparepvec (T) and ipilimumab (I) vs I alone in unresected stage IIIB-IV melanoma. *J Clin Oncol* 35, 2017 (15 Suppl; Abstr 9509) and presented at ASCO 2017 as poster discussion.

Sincerely,

A handwritten signature in black ink, appearing to read "David Cohan", is written over the printed name and title.

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