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Date of request: October 28, 2015
NCCN Guidelines Panel: Melanoma Panel

On behalf of Amgen, I respectfully request the NCCN Melanoma panel members to review the enclosed clinical data for inclusion of IMLYGIC™ (talimogene laherparepvec) in the NCCN Clinical Practice Guidelines for Melanoma.

Change requests

I respectfully request that talimogene laherparepvec be added to sections ME-8, ME-9 and ME-10 of the NCCN Melanoma Guideline Version 1.2016.

FDA Clearance received on October 27, 2015

IMLYGIC (talimogene laherparepvec) was approved by FDA for the following indication: IMLYGIC is a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases[1].

Clinical Data

The safety and efficacy of talimogene laherparepvec was based on a randomized, multicenter, open-label phase 3 clinical study of patients with unresectable stage IIIB/C, and IV melanoma[1] that was informed by a prior phase 2 trial[3]. Talimogene laherparepvec was injected into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. Injection in visceral lesions was not allowed.[1] The primary endpoint was durable response rate (DRR), defined as the percent of patients with complete response (CR) or partial response (PR) maintained continuously for a minimum of 6 months.[1] Key secondary endpoints included Overall Response Rate (ORR), Time to Response and Overall Survival (powered for HR = 0.67).[2] Responses were assessed by an independent blinded endpoint assessment committee (EAC).[2]

Between May 2009 and July 2011, a total of 436 patients were randomized (2:1) to receive either intralesional talimogene laherparepvec (n=295) or subcutaneous GM-CSF (n = 141).[1] Durable response rate was 16.3% (48/295) in the talimogene laherparepvec arm and 2.1% (3/141) in the GM-CSF arm.[1] ORR was also higher in the T-VEC arm (26.4% vs 5.7%) in the GM-CSF arm (p = 0.001).[2] Overall a complete response was noted in 10.8% (32/295) with talimogene laherparepvec compared with <1% (1/141) in the GM-CSF arm.[2] There was no statistically significant difference in Overall Survival (OS) between the talimogene laherparepvec and the GM-CSF arm.[1] At the primary analysis of OS, 290 deaths had occurred.[2] Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) in the T-VEC arm and 18.9 months (95% CI, 16.0 to 23.7

months) in the GM-CSF arm (HR 0.79; 95% CI, 0.62 to 1.00; p= 0.051).[2] The median OS in the overall study population based on a sensitivity analysis that included updated survival data from 5 subjects (obtained after data cutoff date) was 22.9 months in the IMLYGIC arm and 19.0 months in the GM-CSF arm (p = 0.116).[1]

Exploratory subgroup analyses were performed to investigate the treatment effect across key covariates for DRR, ORR and OS.[2] Differences in DRR between the talimogene laherparepvec and GM-CSF arms were more pronounced in patients with stage IIIB/C (33% vs 0%) and IVM1a (16% vs 2%) than in patients with stageIVM1b (3% vs 4%) and IVM1c (7.5% vs 3%).[2] Differences in DRR were also more pronounced in patients with treatment-naive metastatic melanoma (24% vs 0%) than in those receiving treatment as ≥second line therapy (10% vs 4%).[2] A similar pattern was seen for ORR in these subgroups.[2] Treatment effects of talimogene laherparepvec on OS were more pronounced among patients with stage IIIB/C and IVM1a (HR = 0.57; 95% CI, 0.40 to 0.80) compared with patients with IVM1b/c (HR = 1.07; 95% CI, 0.75 to 1.52) and previously untreated patients (HR 0.50; 95% CI, 0.35 to 0.73) compared with those receiving talimogene laherparepvec second-line or greater (HR = 1.13; 95% CI, 0.82 to 1.57).[2]

The most common adverse drug reactions occurring in greater than or equal to 25% talimogene laherparepvec -treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain.[1] Most adverse reactions reported were mild or moderate in severity and generally resolved within 72 hours.[1] The most common grade 3 or higher adverse reaction was cellulitis.[1]

Supporting Documentation

The following data have been submitted in support of this request. In addition we would like to acknowledge the contributions of the NCCN panel members who co-authored and contributed to the publications and participated in the clinical trials of talimogene laherparepvec.

1. IMLYGIC™(talimogene laherparepvec) prescribing information, Amgen
2. Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. *J Clin Oncol.* 2015;33:2780-2788
3. Senzer NN, Kaufman HL, Amatruda T, et al. Phase II Clinical Trial of a Granulocyte-Macrophage Colony-Stimulating Factor–Encoding, Second-Generation Oncolytic Herpesvirus in Patients With Unresectable Metastatic Melanoma. *J Clin Oncol.* 2009;27:5763-5771

Sincerely,

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