SUPPLEMENTAL MATERIAL

Talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone for advanced melanoma: 5-year final analysis of a multicenter, randomized, open-label, phase II trial

End points and assessments

Responses were assessed by investigators per immune-related response criteria (irRC) every 12 weeks until disease progression. Objective response rate was defined as the incidence rate of patients with a complete response (CR) or partial response (PR) in patients with stage IIIB–IV melanoma. The disease control rate was defined as the incidence rate of patients with a CR/PR or stable disease (SD). Durable response rate (DRR) was defined as the incidence rate of patients with a duration of response per modified irRC of ≥6 months. SD was defined as being no earlier than 77 days after the date of enrollment/randomization. Time to response was measured from the date of randomization to the date of the first confirmed CR or PR per modified irRC. Patients who did not have a confirmed CR/PR were censored at their last evaluable tumor assessment date. Duration of response (calculated only for patients with an objective response per modified irRC) was defined as the time from the first confirmed objective response to confirmed disease progression per modified irRC or death, whichever occurred earlier. Responses were censored at the last assessment not confirming disease progression. Progression-free survival (PFS) was measured from the date of randomization to the date of disease progression (as measured by modified irRC) or death, whichever occurred first. Patients with no documented disease progression or death while on study were censored at the last disease assessment date. Treatment-emergent adverse events (AEs) were defined as AEs that occurred after the first dose through 30 days after the last administration of talimogene laherparepvec or 60 days after the last administration of ipilimumab, whichever occurred later. The Medical Dictionary for Regulatory Activities v23.1 was used to code AEs to a system organ class (SOC) and a preferred term within the SOC.

Statistical analysis

Best overall response categories (response evaluation by investigator using modified irRC) were summarized (number and percentage) by treatment arm as randomized. Disease control rate and DRR were summarized with exact binomial two-sided 95% CI reported by treatment. Wilson score method with continuity correction was used to calculate an approximate 95% CI for the between-arm difference in binary rates. The HR for overall survival (OS) and two-sided 95% CI were estimated using an unstratified Cox proportional hazards model.

Kaplan-Meier curves for OS were generated by treatment arm. Kaplan-Meier estimates and the 95% CIs for within each treatment and between treatment differences of annual OS rates were provided. The CI for treatment annual rate differences was based on variance estimates using Greenwood's formula. The CIs for the Kaplan-Meier quartiles were provided by treatment arm. OS was compared with an unstratified log-rank test using a two-sided significance level of 0.05.

Analyses of time to response, duration of response, and PFS by investigator using modified irRC were the same as those described for OS, except that all p values were descriptive. Time to response and duration of response were analyzed for responders without treatment arm comparisons.

Baseline demographics

Sixty-two (63.3%) patients in the combination arm and 55 (55.0%) patients in the ipilimumab arm were men, and most patients (99.0% and 92.0%, respectively) were White. The mean (standard deviation) age was 63.6 (14.0) years in the combination arm and 64.2 (13.3) years in the ipilimumab arm. Most patients (70.4%, combination arm; 73.0%, ipilimumab arm) had an Eastern Cooperative Oncology Group performance status of 0. Overall, 54.0% of patients had earlier stages of disease (stage IIIB to IVM1a) and 46.0% of patients had more advanced disease (stage IVM1b/c), with similar percentages between treatment arms.

Baseline lactate dehydrogenase (LDH) levels were ≤upper limit of normal (ULN) in 80.6% of patients in the combination arm and 74.0% of patients in the ipilimumab arm. Elevated LDH levels of >1 and up to 2 times the ULN were reported in a lower percentage of patients in the combination arm (10.2%) than in the ipilimumab arm (20.0%); LDH levels >2 times the ULN were reported in 7.1% of patients in the combination arm and 5.0% of patients in the ipilimumab arm. Approximately one-third of patients in each treatment arm had tumors that tested positive for the *BRAF* V600E or V600K mutation. The mean (standard deviation) baseline sum of the products of the two largest perpendicular diameters of all index lesions was 2163.79 (4317.12) mm^2 in the combination arm and 1731.77 (2644.60) mm^2 in the ipilimumab arm. In the combination arm, 64.3% of patients were seropositive for herpes simplex virus 1 at baseline. Twenty-five (25.5%) patients in the combination arm and 29 (29.0%) patients in the ipilimumab arm reported prior anticancer therapies. The most frequently reported prior anticancer therapies in the combination arm and the ipilimumab arm were immunotherapy (29.4% and 41.3%, respectively), radiotherapy (25.5% and 32.6%), and chemotherapy (13.7% and 10.9%). Overall, most patients (96.5%) had no prior line of systemic therapy.