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<thead>
<tr>
<th>Name of Sponsor/Company:</th>
<th>Individual Study Table Referring to the Dossier</th>
<th>(For National Authority Use Only)</th>
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<td>Ipilimumab</td>
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**SYNOPSIS**

Addendum 01 Final Clinical Study Report for Study CA184029

**TITLE OF STUDY:** Adjuvant immunotherapy with anti-CTLA-4 monoclonal antibody (ipilimumab) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group

**INVESTIGATORS/STUDY CENTERS:** A total of 1211 subjects were enrolled and screened for study participation. Of these subjects, 951 were randomly assigned to blinded study drug at a total of 92 sites in Australia (7 sites), Europe (Austria [2 sites], Belgium [2 sites], Czech Republic [2 sites], Denmark [3 sites], Finland [2 sites], France [8 sites], Germany [10 sites], Italy [6 sites], Netherlands [5 sites], Norway [1 site], Poland [1 site], Russian Federation [13 sites], Spain [2 sites], Sweden [1 site], Switzerland [1 site], United Kingdom [5 sites]), and North America (United States [18 sites], Canada [3 sites]).

**PUBLICATIONS:**


**STUDY PERIOD:**

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**CLINICAL PHASE:** 3

**OBJECTIVES:** This is a clinical study report (CSR) addendum 01 for the Phase 3 study, CA184029 (also known as European Organization for Research and Treatment of Cancer [EORTC] 18071), which was designed to determine the efficacy and toxicity of post-operative adjuvant treatment with ipilimumab compared to placebo in subjects with resected stage IIIA (>1 mm metastases), IIIB, and IIIC (with no in-transit metastases) cutaneous melanoma.

The purpose of this CSR addendum is to report results from additional subgroup analysis of recurrence-free survival as well as sensitivity analyses for the health-related quality of life using the EORTC QLQ C-30 Health-related quality of life (HRQoL) questionnaire. The results of neutralizing antibody activity in those samples that were confirmed as positive for anti-drug antibodies (ADA) using either one of two validated electrochemiluminescent (ECL) homogeneous bridging immunoassays (the original ADA screening assay and the more drug tolerant [enabling better detection of anti-ipilimumab antibodies] screening assay) are also presented in this addendum. The safety narratives were updated based on new criteria for AEs leading to discontinuation and for minor corrections. Medical review of select unresolved gastrointestinal, liver and dermatitis imAR events for the overall study period are also included.
NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 950 subjects randomized (475 to each treatment group). Enrolled: 1211 (signed study-specific informed consent); Randomized: 951 (475 ipilimumab; 476 placebo); Randomized and treated: 945 (471 ipilimumab; 474 placebo).

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS: Subject disposition and a summary of demographic and baseline characteristics of the study population are presented in the final CSR.

TESTING METHODOLOGY FOR THE PRESENCE OF NEUTRALIZING ANTIBODY: Anti-drug antibodies samples collected in the study were analyzed by either the original assay or the drug tolerant assay. Samples that confirmed positive by either the most recent validated, drug tolerant or by the original ADA screening assay were analyzed at Bristol-Myers Squibb (Lawrenceville, New Jersey) for neutralizing ADA activity using a validated cell-based functional assay. The sample analysis was conducted in accordance with the applicable regulations, standard operating procedures (SOPs), and study design.

STATISTICAL CONSIDERATIONS:

Analysis Populations:
Secondary Analysis - Quality of Life and Recurrence-Free Survival (RFS); Intention-to-treat (ITT) Population: All subjects randomized to a treatment group. This population can also be referred to as “randomized subjects”. Subjects were analyzed in the treatment group to which they were allocated by randomization (i.e., “as randomized”).
Neutralizing Antibody; Immunogenicity Population: All randomized subjects with a baseline ADA measurement and at least one post-baseline ADA measurement. The neutralizing antibody status was assessed in samples with an ADA positive status.

Statistical Analyses
Secondary Analysis - Quality of Life
The following sensitivity analyses were performed.

Logistic regression modeling was used to investigate whether HRQoL compliance was related to any of the following covariates: treatment group, assessment timepoint, disease stage at study entry case report form (CRF), region, age, Eastern Cooperative Oncology Group (ECOG) performance status, and gender.

In order to assess the robustness of the results with respect to missing data, the following sensitivity analyses were performed. Missing HRQoL global health status values were imputed via a general linear regression model fitted to the observed HRQoL global health status data with explanatory covariates: treatment group, assessment timepoint, disease stage at study entry (CRF), region, age, ECOG performance status, and gender. The imputed dataset was analyzed according to the primary analysis strategy. Global health status scores were summarized by treatment group and assessment timepoint. The mean scores during and after induction were summarized and compared between the two treatments groups similar to the primary analysis.

RFS
An additional RFS subgroup analysis was performed that combined Stages IIIC with 1-3 positive lymph nodes and IIIC with 4 or more positive lymph nodes.

Neutralizing Antibody
In the final CSR, the frequency of baseline ADA positive subjects, post-baseline ADA negative subjects and post-baseline ADA positive subjects were tabulated by treatment group and by assay type for the immunogenicity population. In this addendum, the frequency of baseline neutralizing ADA positive subjects and post-baseline neutralizing ADA positive subjects are tabulated by treatment group and by assay type for the samples from the immunogenicity population that were tested and were confirmed positive and specific to anti-ipilimumab antibody.
SUMMARY OF RESULTS:

Efficacy

- **Additional subgroup analysis of recurrence-free survival:** In the original analysis, results from the prespecified subgroup analyses show RFS hazard ratios < 1 for ipilimumab compared with placebo in all but 1 small subgroup (ulceration unknown, 50 subjects), and thus support similar efficacy across subgroups, consistent with the overall study population. An additional analysis was performed that combined Stages IIIC with 1-3 positive lymph nodes and IIIC with 4 or more positive lymph nodes; results from this additional subgroup analysis show RFS hazard ratios < 1 for ipilimumab compared with placebo, demonstrating consistent benefit from ipilimumab in this high risk subgroup compared to the overall population. Based on this new analysis and previously conducted prespecified subgroup analyses, the benefit from ipilimumab appears to be consistent or even pronounced in subjects with poor prognostic factors, such as Stage IIIC (HR = 0.73 [95% CI 0.56 - 0.94], ipilimumab: 101 events/164 subjects; placebo: 137 events/181 subjects), whose primary lesion is ulcerated (HR = 0.67 [95% CI 0.52 - 0.86]), and whose disease has spread to 4 or more lymph nodes (HR = 0.65 [95% CI 0.46 - 0.91]). These data support similar efficacy across subgroups, consistent with the overall study population.

Safety

- **Medical review of imARs** for the overall study period:
  - **GI/Liver:** There were 5 subjects who had unresolved worst grade 2 GI imARs and 11 subjects who had unresolved worst grade 3-5 GI imARs. In addition, there were 2 subjects who had unresolved worst grade 2 liver imARs and 3 subjects who had unresolved worst grade 3-4 liver imARs.
  - **Dermatitis:** There were 9 subjects who had unresolved last grade >1 dermatitis imARs.

- **Safety narratives:** The safety narratives were updated based on new criteria for AEs leading to discontinuation. In addition, the narratives were corrected to denote all “other significant medical events” that met the criteria for narrative preparation and narrative event fields were updated to remove all Grade 1 imAR events.

Other Study Results

- **Quality of Life - EORTC QLQ-C30 Questionnaire:** HRQoL compliance analyses indicated lower compliance in the ipilimumab arm, at later assessment time points and at higher disease stages.
  - The overall health status/QoL responses are seven-point Likert scales ranging from 1 (Very Poor) to 7 (Excellent). Scale items are scored using recommended EORTC procedures. Raw scores are transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher global health status/QoL. A score difference of 10 is used as an estimate of the minimally important difference (MID) for the subscales of the EORTC QLQ-C30.
  - The results of the sensitivity analyses after imputing missing global health status scores were similar to the primary analysis thereby confirming the robustness of the primary findings. No clinically meaningful changes from baseline were seen in global health status scores in either treatment arm, according to pre-specified criteria at the assessment time point level, nor during the entire induction, nor after induction.

- **Neutralizing Antibody:** Ipilimumab treatment was not associated with neutralizing antibody activity. No subject treated with ipilimumab that screened positive in the original or drug tolerant ADA assay was identified as neutralizing ADA positive. One placebo subject that tested positive at Day 43 with the more sensitive drug tolerant assay was identified as neutralizing ADA positive. Subsequent samples from this subject out to Day 848 were ADA negative, suggesting a false positive result at Day 43.

CONCLUSIONS:

Based on the scores averaged separately over the induction period and after induction, none of the observed differences for the primary global health status scale between treatment groups were considered clinically meaningful.

All ipilimumab treated subjects that screened positive by either the original or the more sensitive drug ADA tolerant assay were neutralizing antibody-negative.

DATE OF REPORT: 26-Nov-2014