



# **BRISTOL-MYERS SQUIBB COMPANY**

## **IPILIMUMAB**

**Final Clinical Study Report for Study CA184095**

### **ABBREVIATED REPORT**

#### **A RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL TO COMPARE THE EFFICACY OF IPILIMUMAB VS. PLACEBO IN ASYMPTOMATIC OR MINIMALLY SYMPTOMATIC PATIENTS WITH METASTATIC CHEMOTHERAPY-NAIVE CASTRATION RESISTANT PROSTATE CANCER**

|                                            |                                                                    |
|--------------------------------------------|--------------------------------------------------------------------|
| <b>Indication:</b>                         | Metastatic Chemotherapy-Naive Castration Resistant Prostate Cancer |
| <b>Phase:</b>                              | 3                                                                  |
| <b>Study Initiation Date:</b>              | 28-Jul-2010                                                        |
| <b>Study Completion Date:</b>              | 17-Jul-2015                                                        |
| <b>Report Date:</b>                        | 25-Jan-2016                                                        |
| <b>Document Control Number:</b>            | 930097582                                                          |
| <b>Previous Version(s) of this Report:</b> | None                                                               |

**THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE**

**Sponsor's Responsible Medical Officer:**



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|                                                  |                                                    |                                      |
|--------------------------------------------------|----------------------------------------------------|--------------------------------------|
| Name of Sponsor/Company:<br>Bristol-Myers Squibb | Individual Study Table Referring<br>to the Dossier | (For National Authority Use<br>Only) |
| Name of Finished Product:<br>YERVOY              |                                                    |                                      |
| Name of Active Ingredient:<br>Ipilimumab         |                                                    |                                      |

## SYNOPSIS

### Final Clinical Study Report for Study CA184095

#### ABBREVIATED REPORT

**TITLE OF STUDY:** A randomized, double blind, phase 3 trial to compare the efficacy of ipilimumab vs. placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naïve castration resistant prostate cancer

**INVESTIGATORS/STUDY CENTERS:** A total of 602 subjects were randomized to receive blinded study medication treatment across multiple global sites.

**PUBLICATIONS:** None

**STUDY PERIOD:** Study Initiation Date: 28-Jul-2010

**CLINICAL PHASE:** 3

Study Completion Date: 17-Jul-2015

**INTRODUCTION:** Results of study CA184095 are being reported in an abbreviated Clinical Study Report because this study did not meet its primary endpoint of demonstrating a statistically significant prolongation of OS for the ipilimumab group over the placebo group, and because further development of ipilimumab treatment in patients with metastatic prostate cancer will not be pursued.

**OBJECTIVES:** Those protocol-specified objectives analyzed in this abbreviated report include the following: The primary objective was to compare overall survival of subjects with chemotherapy-naïve castration resistant prostate cancer (CRPC) who were randomized to ipilimumab vs placebo

The secondary objectives of this study were:

- To compare Progression Free Survival (PFS)
- To compare time to subsequent non-hormonal cytotoxic therapy
- To compare time to pain progression
- To characterize the safety profile

Exploratory and descriptive objectives presented in this report include:

- Estimate time to subsequent docetaxel therapy
- Estimate radiologic PFS (rPFS)
- Estimate time to pain increase by the BPI-SF
- Estimate time to opioid analgesic use
- Estimate time to subsequent therapy (hormonal, non-hormonal, immunotherapy)
- Estimate Prostate-Specific Antigen (PSA) response rate
- Characterize PSA kinetics

- Determine the presence of human anti-human antibodies (HAHA/ADA)
- Characterize ipilimumab trough concentrations

One remaining exploratory objective of this study was not analyzed (changes in pain as measured by the BPI-SF), and is not presented in this abbreviated report.

**METHODOLOGY:** This was a double-blind, randomized, 2-arm, multi-center, Phase 3 study in subjects with asymptomatic or minimally symptomatic, chemotherapy-naïve, CRPC who had progressed despite receiving hormonal therapies, and who had no known visceral metastases.

Eligible CRPC subjects were randomized in a 2:1 ratio to ipilimumab or placebo, stratified by the following factors:

- Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs 1)
- Lactase dehydrogenase (LDH) ( $< 200$  vs  $\geq 200$  IU/L)
- Pain (none vs minimal)
- Region (US/Canada vs non-US/Canada)

This study was divided into 4 phases:

- Screening (determination of eligibility)
- Induction (eligible subjects were randomized and treated with blinded study drug every 3 weeks for up to 4 doses)
- Maintenance (continued dosing with blinded study drug at 12 week intervals)
- Follow-up (Toxicity/Progression Follow-up and Survival Follow-up)

Subjects who did not meet the Treatment Stopping Criteria specified in Section 5.3.5 of the protocol could continue in the Maintenance Phase until Treatment Stopping Criteria were met or until other reasons for discontinuing study treatment occurred, as specified in Section 4.2.3 of the protocol. Subjects who met the Treatment Stopping Criteria or who did not wish to continue treatment phase study assessments in the Induction Phase or Maintenance Phase entered the Toxicity/Progression Follow-up Phase. Subjects in this Follow-up Phase continued to have adverse event (AE) evaluations, Tumor Assessments (TAs), and PSA tests performed at 12 week intervals until all AEs resolved, and until either Progressive Disease (PD) was documented or until the initiation of alternative systemic anti-cancer therapy.

**NUMBER OF SUBJECTS (Planned and Analyzed):** Approximately 600 eligible CRPC subjects were planned to be randomized in a 2:1 ratio to ipilimumab or placebo. The study actually randomized and analyzed 602 subjects, 400 to the ipilimumab arm and 202 to the placebo arm. Of those randomized, 399 ipilimumab and 199 placebo subjects were treated.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** Male subjects at least 18 years of age with histologic or cytologic confirmation of adenocarcinoma of the prostate that had been treated by orchiectomy or LH-RH analog, with a testosterone level  $\leq 50$  ng/dL, asymptomatic or minimally symptomatic, chemotherapy-naïve, metastatic disease by CT, MRI, or bone scan, and had progressed during hormonal treatment, were eligible.

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT:** Ipilimumab 10 mg/kg was administered intravenously (IV) over 90 minutes with a normal saline flush at the end. Induction dosing occurred on Days 1, 22, 43, and 64 during the Induction phase and every 12 weeks starting at Week 24 during the Maintenance phase, until treatment stopping criteria or other reasons for permanent discontinuation as described in the protocol were met.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT:**

Placebo solution (0.9% Sodium Chloride or 5% Dextrose) was administered intravenously (IV) over 90 minutes with a normal saline flush at the end. Induction dosing occurred on Days 1, 22, 43, and 64 during the Induction phase and every 12 weeks starting at Week 24 during the Maintenance phase, until treatment stopping criteria or other reasons for permanent discontinuation as described in the protocol were met.

## CRITERIA FOR EVALUATION:

**Safety:** The assessment of safety was based on adverse events (AEs), serious adverse events (SAEs), immune-related adverse events (irAEs), immune-mediated adverse reactions (imARs), deaths, and clinical laboratory data. Events were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The presence of anti-drug antibodies (ADA) was analyzed in blood samples obtained prior to study drug dosing and at specified time points.

**Other:** Efficacy endpoints included overall survival (OS), progression free survival by investigator assessment (PFS), time to pain progression, time to subsequent non-hormonal cytotoxic therapy, time to subsequent treatment, time to docetaxel therapy, time to pain increase by the BPI-SF, time to opioid analgesic use, and PSA response rate. PK concentration was analyzed in blood samples obtained prior to study drug dosing and at specified time points.

**STATISTICAL CONSIDERATIONS:** The study was powered for analysis of the primary endpoint, OS. Safety and exposure analyses were performed on the treated population (those subjects who received at least one dose of ipilimumab or placebo) as treated, meaning analyzed in the arm of the treatment actually received, even if different from the randomized arm. Analyses of baseline characteristics and efficacy endpoints were based on all randomized subjects. All PFS events were based on investigator assessments. Two analyses of the primary endpoint were conducted, an interim at 324 deaths and a final at 379 deaths. Lan-DeMets group sequential method with O'Brien Fleming alpha spending function was used to control the overall type I error rate at 0.05 for superiority testing.

## SUMMARY OF RESULTS:

**Disposition and Baseline/Demographic Characteristics:** Subject disposition is presented in Table 1. Of the 837 subjects who were enrolled and screened for study participation, 602 (71.9%) were randomized, including 400 to ipilimumab and 202 to placebo. The primary reason for discontinuing treatment was disease progression, followed by study drug toxicity.

**Table 1: Subject Disposition**

|                                                      | Not Randomized<br>N (%) | Placebo<br>N (%) | 10 mg/kg<br>Ipilimumab<br>N (%) | Total<br>N (%) |
|------------------------------------------------------|-------------------------|------------------|---------------------------------|----------------|
| No. of Subjects Enrolled <sup>a</sup>                | 235                     | 202              | 400                             | 837            |
| No. of Subjects Randomized                           |                         | 202 (100.0)      | 400 (100.0)                     | 602 (71.9)     |
| No. of Subjects Not Randomized                       | 235                     |                  |                                 | 235 (28.1)     |
| No. of Subjects Treated                              |                         | 199 (98.5)       | 399 (99.8)                      | 598 (71.4)     |
| Not Treated                                          | 235 (100.0)             | 3 (1.5)          | 1 (0.3)                         | 239 (28.6)     |
| Treated Subjects - Reason Off Treatment <sup>b</sup> |                         | 199              | 399                             | 598            |
| Disease Progression                                  |                         | 156 (78.4)       | 197 (49.4)                      | 353 (59.0)     |
| Study Drug Toxicity                                  |                         | 5 (2.5)          | 114 (28.6)                      | 119 (19.9)     |
| Adverse Event Unrelated to Study Drug                |                         | 13 (6.5)         | 29 (7.3)                        | 42 (7.0)       |
| Subject Withdrew Consent                             |                         | 7 (3.5)          | 11 (2.8)                        | 18 (3.0)       |
| Subject Request to Discontinue Study Treatment       |                         | 3 (1.5)          | 14 (3.5)                        | 17 (2.8)       |
| Death                                                |                         | 2 (1.0)          | 12 (3.0)                        | 14 (2.3)       |
| Maximum Clinical Benefit                             |                         | 5 (2.5)          | 5 (1.3)                         | 10 (1.7)       |
| Poor/Non-Compliance                                  |                         | 0                | 1 (0.3)                         | 1 (0.2)        |

**Table 1: Subject Disposition**

|                                           | Not Randomized<br>N (%) | Placebo<br>N (%) | 10 mg/kg<br>Ipilimumab<br>N (%) | Total<br>N (%) |
|-------------------------------------------|-------------------------|------------------|---------------------------------|----------------|
| Subject No Longer Meets<br>Study Criteria |                         | 0                | 1 (0.3)                         | 1 (0.2)        |
| Administrative Reason by<br>Sponsor       |                         | 0                | 0                               | 0              |
| Completed the Induction<br>Phase          |                         | 0                | 0                               | 0              |
| Completed the Maintenance<br>Phase        |                         | 0                | 0                               | 0              |
| Lost to Follow Up                         |                         | 0                | 0                               | 0              |
| Pregnancy                                 |                         | 0                | 0                               | 0              |
| Other                                     |                         | 6 (3.0)          | 13 (3.3)                        | 19 (3.2)       |
| Not Reported                              |                         | 1 (0.5)          | 1 (0.3)                         | 2 (0.3)        |

<sup>a</sup> The denominator to calculate each percentage is the number of enrolled subjects.

<sup>b</sup> Percentages based on the number of subjects treated

The demographic and key baseline characteristics, including stratification factors, of randomized subjects were generally comparable between the 2 treatment groups, as shown in Table 2.

**Table 2: Baseline and Demographic Characteristics**

|                         | Placebo<br>N=202 | 10 mg/kg<br>Ipilimumab<br>N=400 | Total<br>N=602 |
|-------------------------|------------------|---------------------------------|----------------|
| Race                    |                  |                                 |                |
| White                   | 185 (91.6)       | 361 (90.3)                      | 546 (90.7)     |
| Black                   | 11 (5.4)         | 20 (5.0)                        | 31 (5.1)       |
| Asian                   | 2 (1.0)          | 4 (1.0)                         | 6 (1.0)        |
| American Indian/Alaskan | 1 (0.5)          | 2 (0.5)                         | 3 (0.5)        |
| Native Hawaiian/Pacific | 0                | 1 (0.3)                         | 1 (0.2)        |
| Other                   | 3 (1.5)          | 12 (3.0)                        | 15 (2.5)       |
| Age (Years)             |                  |                                 |                |
| Median                  | 69.0             | 69.5                            | 69.0           |
| Min-Max                 | 42 - 92          | 44 - 91                         | 42 - 92        |
| Region                  |                  |                                 |                |
| US/Canada               | 70 (34.7)        | 136 (34.0)                      | 206 (34.2)     |
| Non-US/Canada           | 132 (65.3)       | 264 (66.0)                      | 396 (65.8)     |
| ECOG Performance Status |                  |                                 |                |
| 0                       | 151 (74.8)       | 299 (74.8)                      | 450 (74.8)     |
| 1                       | 51 (25.2)        | 100 (25.0)                      | 151 (25.1)     |
| 2                       | 0                | 1 (0.3)                         | 1 (0.2)        |
| LDH                     |                  |                                 |                |

**Table 2: Baseline and Demographic Characteristics**

|               | Placebo<br>N=202 | 10 mg/kg<br>Ipilimumab<br>N=400 | Total<br>N=602 |
|---------------|------------------|---------------------------------|----------------|
| < 200 IU/L    | 130 (64.4)       | 250 (62.5)                      | 380 (63.1)     |
| ≥ 200 IU/L    | 72 (35.6)        | 149 (37.3)                      | 221 (36.7)     |
| Not Reported  | 0                | 1 (0.3)                         | 1 (0.2)        |
| Pain          |                  |                                 |                |
| None          | 109 (54.0)       | 215 (53.8)                      | 324 (53.8)     |
| Minimal       | 90 (44.6)        | 179 (44.8)                      | 269 (44.7)     |
| Not Reported  | 3 (1.5)          | 6 (1.5)                         | 9 (1.5)        |
| Gleason Score |                  |                                 |                |
| ≤ 7           | 103 (51.0)       | 189 (47.3)                      | 292 (48.5)     |
| ≥ 8           | 91 (45.0)        | 192 (48.0)                      | 283 (47.0)     |
| Not Reported  | 8 (4.0)          | 19 (4.8)                        | 27 (4.5)       |
| PSA           |                  |                                 |                |
| Mean          | 179.4            | 155.3                           | 163.4          |
| Median        | 49.5             | 41.2                            | 45.1           |
| Min-Max       | 0.01 - 9297.00   | 0.05 - 4956.00                  | 0.01 - 9297.00 |

**Safety Results:** An overall safety summary is presented in [Table 3](#). At least one AE was reported in nearly all subjects in both treatment arms. Among treated subjects, Grade 3/4 AEs, SAEs, drug-related AEs, and AEs leading to drug discontinuation were more frequently reported in the ipilimumab group than in the placebo group. On-study irAEs (all grades and Grade 3-5) were reported more frequently in the ipilimumab group than in the placebo group. The most frequently reported (≥ 10% of subjects) on-study irAEs in the ipilimumab group were diarrhea, rash, and pruritus. Worst grade of Grade 2 and Grade 3-5 imARs were reported more frequently in the ipilimumab group than in the placebo group. The most frequently reported imAR classes were dermatitis, enterocolitis and endocrinopathies for subjects with worst grade of Grade 2 events, and enterocolitis, endocrinopathies, and hepatitis for those with worst grade of Grade 3-5. Similar percentages of deaths occurred in the two treatment groups, 259 (64.9%) subjects in the ipilimumab group and 130 (65.3%) subjects in the placebo group died as of final database lock. Most of the deaths occurred > 70 days after the last dose of study drug.

**Table 3: Overall Safety Summary - All Treated Subjects**

|                                                    | Number (%) of Subjects |                                   |
|----------------------------------------------------|------------------------|-----------------------------------|
|                                                    | Placebo<br>N =199      | 10 mg/kg<br>Ipilimumab<br>N = 399 |
| Any on-study AE (Any grade)                        | 182 (91.5)             | 381 (95.5)                        |
| Grade 3 - 4                                        | 59 (29.6)              | 223 (55.9)                        |
| Grade 5                                            | 6 (3.0)                | 34 (8.5)                          |
| Drug-related on-study AE (Any grade)               | 98 (49.2)              | 325 (81.5)                        |
| Grade 3 - 4                                        | 11 (5.5)               | 158 (39.6)                        |
| Grade 5                                            | 0                      | 7 (1.8)                           |
| Any on-study SAE                                   | 53 (26.6)              | 213 (53.4)                        |
| Grade 3-4                                          | 39 (19.6)              | 153 (38.3)                        |
| Grade 5                                            | 6 (3.0)                | 34 (8.5)                          |
| On-study AE leading to discontinuation (Any grade) | 20 (10.1)              | 139 (34.8)                        |
| Grade 3-4                                          | 14 (7.0)               | 103 (25.8)                        |
| Grade 5                                            | 1 (0.5)                | 10 (2.5)                          |
| Any on-study irAE (Any grade)                      | 57 (28.6)              | 309 (77.4)                        |
| Grade 3-4                                          | 3 (1.5)                | 125 (31.3)                        |
| Grade 5                                            | 0                      | 3 (0.8)                           |
| Any on-study imAR (Grade $\geq$ 2)                 | 14 (7.0)               | 273 (68.4)                        |
| Any death                                          | 130 (65.3)             | 259 (64.9)                        |
| Death within 30 days of last dose of study drug    | 2 (1.0)                | 13 (3.3)                          |
| Death within 70 days of last dose of study drug    | 5 (2.5)                | 35 (8.8)                          |

**Other Results:** The study did not meet its primary endpoint of demonstrating a statistically significant prolongation of survival for the ipilimumab group compared with the placebo group. The HR of 1.11 (95% CI: 0.88-1.39) for survival did not favor ipilimumab, with a p-value of 0.3667. The median survival was numerically longer for placebo than for ipilimumab (29.7 vs. 28.7 months). Observationally, the median PFS interval by investigator was longer for the ipilimumab group (5.59 months) than for the placebo group (3.81 months), and treatment with ipilimumab resulted in a 33% reduction in the risk of progression relative to placebo (HR = 0.67; 95% CI: 0.55, 0.80). The median time to non-hormonal cytotoxic therapy use was 18.0 months in the ipilimumab group and 10.9 months in the placebo group (HR = 0.65; 95% CI: 0.52-0.83). The number of subjects meeting the pre-specified criteria for a pain response (time to pain progression) was too small to allow meaningful assessment of a treatment effect (HR = 0.98; 95% CI: 0.71-1.35).

**CONCLUSIONS:** The study did not meet its primary endpoint based on intent-to-treat analysis. The HR 1.11 (95.87% CI: 0.88-1.39), p-value = 0.3667 for overall survival did not favor ipilimumab. Results from sensitivity and subgroup analyses demonstrated consistency with that seen in the overall study population. There was an

observationally longer median PFS interval for the ipilimumab group (5.36 months) than for the placebo group (2.99 months) (HR = 0.65; 95% CI: 0.54, 0.79), which may be indicative of activity of ipilimumab in delaying disease progression. The median time to non-hormonal cytotoxic therapy use was 18.04 months in the ipilimumab group and 10.91 in the placebo group (HR = 0.65; 95% CI: 0.52-0.83) may also be an indication of activity of ipilimumab. The number of subjects with a pain response was too small to allow meaningful determination of a treatment related differences (HR = 0.98; 95% CI: 0.71-1.35). The safety profile of ipilimumab in this study was generally consistent with the experience in other studies using 10 mg/kg ipilimumab. No new safety signals were identified in this patient population. Common toxicities of ipilimumab (e.g. inflammatory events reflecting immune based mechanism of action of ipilimumab) most frequently affected the gastrointestinal (GI) tract and skin. Most of the on-study irAEs (or imARs) were reversible using the standard ipilimumab management algorithm. Nine deaths (2.3%) in the ipilimumab group occurred due to study drug toxicities, including two deaths due to post-study events (i.e., onset after 70 days from last dose) of pneumonia and hepatotoxicity. One death occurred due to intestinal perforation, two due to cardiac arrest, one due to renal failure, one due to hepatitis, one due to pneumonitis, and one due to multi-organic lymphatic infiltration that resulted in cardiac arrest. There were no deaths due to drug-related adverse events in the placebo arm. The PSA response rate was higher in the ipilimumab arm (23.0, 95% CI: 18.96-27.44) than in the placebo arm (7.9, 95% CI: 4.60-12.54) and may be another indication of activity of ipilimumab.

**DATE OF REPORT:**25-Jan-2016