Phase 3 Study Evaluating Ipilimumab for Melanoma in an Adjuvant Setting Meets Primary Endpoint of Recurrence-Free Survival

- Results demonstrate a significant improvement in recurrence-free survival for an unlicensed investigational dose of ipilimumab vs. placebo for adult patients with stage 3 melanoma at high risk of recurrence following surgical resection.

- Types of adverse event were generally consistent with those observed using ipilimumab in advanced melanoma, although a higher incidence of endocrinopathies was observed.

- Third positive Phase 3 trial of ipilimumab in melanoma, now with a study demonstrating efficacy in an earlier stage of the disease.

(Uxbridge, Middlesex, June 10, 2014) – Bristol-Myers Squibb Company has announced results from a Phase 3 randomised, double blind study demonstrating that ipilimumab 10 mg/kg (n=475) significantly improved recurrence-free survival (RFS, the length of time before recurrence or death) vs. placebo (n=476) for patients with stage 3 melanoma who are at high risk of recurrence following complete surgical resection, an adjuvant setting. A twenty-five percent reduction in the risk of recurrence or death was observed (HR = 0.75; 95% CI = 0.64–0.90; p = 0.0013). At three years, an estimated 46.5% of patients treated with ipilimumab were free of disease recurrence compared to an estimated 34.8% of patients on placebo. The median RFS was 26.1 months for ipilimumab vs. 17.1 months for placebo, with a median follow-up of 2.7 years.

Treatment-related adverse events were common, with most being immune-related, and were managed using standard ipilimumab adverse event (AE) management protocols. These Grade ≥3 AEs in the ipilimumab and placebo arms, respectively, were gastrointestinal (15.9% vs. 0.8%), liver (10.6% vs. 0.2%), endocrine (8.5% vs. 0%) and dermatologic (4.5% vs. 0%). Most were managed and resolved using established algorithms. Per investigator assessment, the incidence of drug-related death in the ipilimumab arm was 1.1% (n=5) and no drug-related deaths were observed in the placebo arm. Of the patients who began treatment with ipilimumab (n=471), 48.8% (n=230) discontinued treatment due to drug-related AEs versus 1.7% (n=8) in the placebo arm.

“Despite the strong likelihood of disease recurrence among stage 3 melanoma patients, there are very limited treatment options available to help reduce the risk of metastatic disease after surgery. There is only one class of therapies available to patients and this standard of care has remained largely unchanged over the last 20 years,” said Alexander Eggerton, Director General,
Cancer Institute Gustave Roussy, Villejuif, France, presenter of the results and lead author of the abstract. “These findings are significant not only because ipilimumab is the first immune-checkpoint inhibitor to demonstrate an improvement in recurrence-free survival in this earlier treatment setting, but also because this benefit was observed across all patient sub-groups, including those who were at highest risk of recurrence. These findings add to the growing body of data demonstrating the efficacy of ipilimumab, which is currently approved at 3 mg/kg for metastatic melanoma.”

“This is the third positive Phase 3 trial of ipilimumab in melanoma, reflecting our commitment to seeking options to address unmet medical needs across stages of disease and lines of therapy for melanoma,” said Michael Giordano, Senior Vice President, Head of Development, Oncology & Immunosciences, Bristol-Myers Squibb. “These findings demonstrate, for the first time, that ipilimumab has the potential to reduce the risk of cancer recurrence at an earlier stage of melanoma and support our belief that immuno-oncology may have broad applicability across lines of therapy and stages of the disease.”

Additional trials of ipilimumab as an adjuvant therapy for melanoma are ongoing, including a Phase 3 study sponsored by the U.S. National Cancer Institute and conducted by ECOG-ACRIN investigating ipilimumab at doses of 3 mg/kg and 10 mg/kg, or high-dose interferon alfa-2b in patients with high-risk stage 3 and resectable stage 4 melanoma.

**About Study -029**

CA184-029 (EORTC 18071) is a randomised, double-blind Phase 3 trial sponsored by Bristol-Myers Squibb and conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), assessing the efficacy of ipilimumab at the investigational dose of 10 mg/kg in preventing or delaying recurrence after complete resection of high-risk Stage 3 melanoma. The trial enrolled adult patients in the United States, Canada, Europe, Russia and Australia who underwent complete resection of stage 3 cutaneous melanoma, excluding lymph node metastasis ≤1 millimeter or in-transit metastasis. Patients had stage 3A (21%), 3B (45%) or 3C (35%) melanoma; 41% percent had ulcerated primary melanoma and 56% had macroscopic lymph node involvement. Patients were stratified by stage and region and were randomized 1:1 to receive ipilimumab 10 mg/kg (n=475) or placebo (n=476) every 3 weeks for 4 doses, then every 3 months for up to 3 years until completion, disease recurrence, or unacceptable toxicity. The primary endpoint was recurrence-free survival, analysed on the intent-to-treat population.
Adjuvant Therapy in Melanoma

Melanoma is separated into five staging categories (stages 0-4) based on the thickness and ulceration of the tumour, whether the cancer has spread to the lymph nodes, and how far the cancer has spread to other parts of the body.\(^2\)

Stage 3 melanoma has spread to one or more lymph nodes but has not yet spread to distant lymph nodes or to other parts of the body (metastasised), and requires surgical resection of the primary tumour as well as the involved lymph nodes.\(^2,3\) Some patients may also be treated with adjuvant therapy, although adjuvant treatment options are very limited.\(^3,4\) Despite surgical intervention and possible adjuvant treatment, there is a high risk of relapse and mortality.\(^5\)

About ipilimumab

Ipilimumab is a fully human monoclonal antibody that works by stimulating the body’s own immune system to fight cancer. Its mechanism of action in patients with melanoma is indirect, possibly through T-cell mediated anti-tumour immune responses.\(^6\)

In July 2011, ipilimumab received a European licence for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.\(^7\) Ipilimumab is now licensed in more than 40 countries in this setting. In November 2013, ipilimumab was granted an extension to its licence to include its use as a treatment for advanced (unresectable or metastatic) melanoma in adults who have not yet received prior therapy.\(^6\)

There is a broad, ongoing development programme in place for ipilimumab spanning multiple tumour types. This includes Phase 3 trials in prostate and lung cancers.

Safety information on ipilimumab as monotherapy in melanoma\(^2\)

The safety profile of ipilimumab is considered to be related to its mechanism of action as an immunotherapy. In a pivotal Phase III clinical trial, drug-related adverse events related to the study drug were mostly immune-related adverse events (irAEs). Immune-related adverse events described to date have included gastrointestinal, skin, liver, endocrine or nervous systems. The most frequently reported adverse events (≥ 10% of patients) included diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, and abdominal pain. The majority were mild to moderate. The safety profile of ipilimumab in previously-untreated (first line) patients is comparable to that seen in those who have been previously-treated (second line). Early diagnosis and appropriate management of adverse events using established product-specific guidelines are essential to minimise complications.
The full Summary of Product Characteristics for ipilimumab can be found online at:
http://www.medicines.org.uk/emc/medicine/24779/SPC/YERVOY+5+mg+ml+concentrate+for+solution+for+infusion/

**Immuno-Oncology at Bristol-Myers Squibb**

Surgery, radiation, cytotoxic or targeted therapies have represented the mainstay of cancer treatment over the last several decades, but long-term survival and a positive quality of life have remained elusive for many patients with advanced/metastatic disease. To address this unmet medical need, Bristol-Myers Squibb is leading advances in a rapidly evolving field of cancer research and treatment known as immuno-oncology, which involves agents whose primary mechanism is to work directly with the body’s immune system to fight cancer. This includes conducting research on the potential of combining immuno-oncology agents that target different and complementary pathways in the treatment of cancer.

Bristol-Myers Squibb is committed to advancing the science of immuno-oncology, with the goal of changing survival expectations and the way patients live with cancer.

**About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit www.b-ms.co.uk

**Bristol-Myers Squibb Forward-Looking Statement**

*This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that the clinical trials of Yervoy for the investigational uses described in this release will support regulatory filings, or that the investigational uses of Yervoy described in this release will lead to additional approved indications, or, if approved, that they will become commercially successful. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb’s business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2013 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.*
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References

1. Eggermont et al. Ipilimumab versus placebo after complete resection of stage III melanoma: initial efficacy and safety results from the EORTC 18071 phase III trial. Data presented at the 50th Annual Meeting of the American Society of Clinical Oncology press briefing (LBA9008).