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Ipilimumab

Abstract

Ipilimumab (BMS734016; MDX 101; MDX-010; MDX-CTLA-4; MDX-CTLA4) is an anti-CTLA-4 monoclonal antibody, which is in development by Medarex Inc. and Bristol-Myers Squibb as treatment for malignant melanoma, prostate cancer, lymphoma, and lung cancer. It is currently in phase III development for the melanoma and prostate cancer indications, and phase II for lymphoma and non-small cell lung cancer in the US and other areas of the world. This review discusses the key development milestones and therapeutic trials on this drug to date.

1. Introduction

Bristol-Myers Squibb (BMS) is developing an anti-CTLA-4 monoclonal antibody, ipilimumab, as a treatment for malignant melanoma, prostate cancer and non-small cell lung cancer. Ipilimumab blocks the effects of the negative T-cell regulator CTLA-4, which may, in turn, augment T-cell responses to tumor cells. Preclinical studies have indicated that blocking CTLA-4 with an antibody can lead to potent immune responses. Ipilimumab is awaiting approval as second-line therapy for metastatic melanoma in the EU. The compound is also in phase III development as first-line therapy for melanoma and prostate cancer worldwide, and is in phase II development for non-small cell lung cancer.

Ipilimumab was originated by the University of California in the US. The compound was subsequently licensed to Medarex, which was later acquired by BMS.

Data from a survey of US and European oncologists in 2009 have indicated that ipilimumab would earn a higher patient share in the US (60%) than in Europe (40%) for treating stage IV malignant melanoma.[1]

1.1 Company Agreements

In September 2009, Medarex became a wholly owned subsidiary of BMS.[2]

In January 2005, Medarex and BMS entered into a worldwide collaboration to develop and commercialize ipilimumab and MDX 1379. BMS and Medarex were to share profits and the costs of developing the compounds in the US and EU based on a pre-agreed percentage allocation. BMS was to receive an exclusive licence to territories outside the US and pay royalties to Medarex. Medarex will receive an initial cash payment of $US50 million and up to $US480 million in regulatory and sales-related milestone payments.[3]

In May 2003, Cell Genesys and Medarex entered into a research and development collaboration to evaluate combination therapy with Cell Genesys' GVAX® prostate cancer vaccine and ipilimumab. A phase I trial was completed for this combination therapy and under terms of the

agreement, both companies shared the cost of the trial equally. However, Cell Genesys discontinued all clinical development activities in June 2009 as part of its restructuring plan.[4]

In June 2002, Medarex entered into a joint development and supply agreement with IDM (later IDM Pharma). Under the agreement, ipilimumab and various Cell Drug™ combinations were be investigated. The first combination to undergo investigation was expected to be ipilimumab and IDD 1.

However, the development of IDD 1 was later discontinued. Earlier, in December 1999, IDM became Medarex's first partner in a program investigating the use of CTLA-4 blockade technology to increase the efficacy of cancer vaccines.

In August 1999, Medarex obtained an exclusive sublicense from Gilead Sciences. The sublicense gave Medarex access to the CTLA-4 blockade intellectual property rights owned by the University of California, Berkeley (UC Berkeley), CA, USA, which held a number of patents relating to blockade of CTLA-4. Gilead Sciences had previously acquired a sublicensable licence from UC Berkeley, through its merger with NeXstar Pharmaceuticals. The sublicense allowed Medarex to further develop fully human antibodies that inhibit CTLA-4, including ipilimumab, which was created using Medarex's proprietary HuMAb-Mouse™ technology. Under the terms of the sublicensing agreement, Medarex also had an option to develop non-antibody agents that block CTLA-4. Both Gilead Sciences and UC Berkeley were to receive a royalty split based on future product sales and UC Berkeley was also to receive milestone payments.

1.2 Key Development Milestones

1.2.1 Malignant Melanoma (Second-Line Therapy)

BMS filed a MAA with the European Medicines Agency in the first half of 2010, for ipilimumab as second-line therapy in patients with metastatic melanoma. The company expects to file a BLA submission with the US FDA for the same indication in 2010.

Overall survival was significantly extended in patients with previously treated metastatic melanoma who received ipilimumab compared with patients who received therapy with a gp100 peptide vaccine, thus meeting the primary endpoint of a phase III trial (NCT00094653; Study 020) of the agent. In this double-blind trial, patients were randomized to receive ipilimumab alone, ipilimumab in combination with a gp100 peptide vaccine, or the control therapy of gp100 alone. The study enrolled approximately 676 patients with unresectable stage III or IV metastatic melanoma who had received prior therapies and who were HLA-A2-positive, at sites in the US, EU, Canada, Argentina, Brazil, Chile, South Africa, Switzerland, and the UK. Fast track status has been granted to this combination therapy by the US FDA. The gp100 vaccine, also called MDX 1379, consists of two gp100 melanoma peptides that Medarex in-licensed from the US NCI. The study was designed under the SPA process.[5-9]

Medarex and BMS conducted a registrational monotherapy program to evaluate ipilimumab for the treatment of metastatic melanoma. The program consisted of three phase III trials (008, 022, and 007) which enrolled a total of 487 patients with advanced stage III or stage IV metastatic melanoma from centres across the US, EU, South America, and Africa. Study 008 was an open-label, single-arm trial evaluating overall response rate in 155 patients who progressed on or following standard treatment. Study 002 was a randomized, double-blind trial that evaluated the efficacy of three dose levels of ipilimumab in 216 patients who were previously treated, relapsed or failed to respond to experimental treatment or who were unable to tolerate currently approved therapies. Finally, study 007 was a randomized, double-blind, placebo-controlled trial in 116 patients, comparing the safety of ipilimumab, with or without prophylactic oral budesonide. The ipilimumab monotherapy program was reviewed under a SPA in March 2006. In December 2006, ipilimumab received fast track designation from the FDA for use as a monotherapy in previously treated patients with metastatic melanoma.[10] Top-line results from studies 008, 022, and 007 have been announced. The results from study 008 did not meet the primary endpoint,

which was to rule out a best objective response rate of less than 10%. However, the totality of data from the registrational program included a clear dose response effect observed in study 022 and best objective response rates across the three studies as determined by independent radiology review.[10,11]

BMS, in collaboration with the MD Anderson Cancer Center, have initiated a phase II trial evaluating the combination of ipilimumab and temozolomide in metastatic melanoma (NCT01119508). In the induction phase of the trial, patients will receive open-label treatment with intravenous ipilimumab 10 mg/kg over 90 minutes on day 1, plus oral temozolomide 200 mg/m^2 on days 1–4; both drug regimens will continue to be administered every 3 weeks for four courses over 3 months. In the maintenance phase of the study, ipilimumab treatment will continue as above every 12 weeks, whilst temozolomide will be administered on day 1–5, and repeated every 4 weeks. Approximately 64 patients will be enrolled.

1.2.2 Malignant Melanoma (First-Line Therapy)

A phase III registrational trial (NCT00324155) of ipilimumab in combination with chemotherapy (dacarbazine) as a first-line treatment for patients with unresectable stage III or IV metastatic melanoma began in June 2006, and was cleared to continue by a data monitoring committee in 2008. The trial is being conducted in the US, Europe, Canada, Australia, Israel, South Africa, and South America. The double-blind, two-arm study has approximately 500 patients with previously untreated stage III or IV metastatic melanoma who have been randomized to receive dacarbazine with or without ipilimumab (10 mg/kg). Treatments will be administered once every 3 weeks for up to four doses and patients who have no experienced disease progression at week 24 will continue in a maintenance phase where a single dose of ipilimumab will be administered once every 12 weeks until disease progression. The primary endpoint is overall survival. The trial is expected to be completed in late 2011. Fast-track status was granted for this indication in the US.[12-15]

1.2.3 Non-Small Cell Lung Cancer

BMS has completed a double-blind, phase II trial (NCT00527735, 041) of ipilimumab in patients with previously untreated advanced non-small cell lung cancer. Approximately 330 patients were randomized to receive ipilimumab in combination with paclitaxel/carboplatin or paclitaxel/carboplatin alone. The trial was conducted at sites in the US, EU, Russia, and India. Positive data were reported in May 2010. The study met its primary endpoint (defined as significant improvement in immune-related progression-free survival).[16] BMS intends to commence a phase III study of ipilimumab for the treatment of non-small cell lung cancer in 2010.[16]

1.2.4 Prostate Cancer

BMS is recruiting patients in a phase III clinical trial (NCT00861614) to assess ipilimumab in combination with radiotherapy, compared to radiotherapy alone, in patients with castration-resistant prostate cancer who have received prior treatment with docetaxel. This trial is expected to recruit approximately 800 patients and is taking place in the US, Canada, Europe, Australia, and Latin America. BMS plans to commence a second phase III trial (NCT01057810) in August 2010 in patients with metastatic castration-resistant prostate cancer. Approximately 600 patients will be enrolled at sites in US, Canada, Europe, Australia, India, and Latin America.

BMS has completed a phase I/II trial (NCT00323882) of ipilimumab in patients with metastatic hormone-refractory prostate cancer in the US. The trial recruited 66 patients who had not previously received chemotherapy or immunotherapy. Four dose levels were investigated.

Interim results from a phase I trial of ipilimumab in combination with Cell Genesys' GVAX® vaccine in patients with metastatic hormone-refractory prostate cancer were presented in June 2007. The multi-dose, dose-escalation trial was conducted in the Netherlands and evaluated the safety and efficacy of the combination therapy. Additional results from this trial were released in April 2008. This trial arose from a collaboration entered into by Medarex and Cell Genesis in 2003.[17-19] However, in June 2009, Cell Genesys

discontinued all clinical development activities including the development of GVAX® immunotherapy for prostate cancer.[4]

1.2.5 Other Cancers

In October 2009, BMS completed a phase I study (NCT00362713) of ipilimumab as neoadjuvant therapy in patients with urothelial cancer. Twelve patients were enrolled in the US. The tolerability and anticancer immunological activity of ipilimumab monotherapy was investigated.

Results from a phase I trial in patients with various cancers including lymphomas (Hodgkin and non-Hodgkin) and treated with ipilimumab after relapse of their tumor following allogeneic hematopoietic stem cell transplantation have been presented. Results have also been presented from a phase I/II trial with ipilimumab in patients with relapsed or refractory follicular lymphoma.[20] Additional trials were planned. However, no recent development has been reported.

Another phase I trial of the agent in combination with the GVAX® vaccine was conducted in patients with a range of tumors, including metastatic melanoma, non-small cell lung cancer, ovarian cancer, acute myeloid leukemia and myelodysplastic syndromes.[21]

1.3 Patent Information

BMS owns a composition of matter patent covering ipilimumab, which expires in the US in 2016. The company also has rights to method of use patents owned by Medarex that expire in the US in 2015. BMS has rights to a Medarex composition of matter patent that expires in 2020 (extended to 2022 by a patent term adjustment) and also has pending Medarex patent applications covering composition of matter and method of use of ipilimumab.

2. Scientific Summary

2.1 Adverse Events

2.1.1 Lymphoma

***Phase I*:** In a phase I trial in 17 patients with lymphomas (Hodgkin, non-Hodgkin), myeloma,

Table I. Features and properties

Alternate names	BMS734016; MDX 101; MDX-010; MDX-CTLA-4; MDX-CTLA4
Originator	University of California at Berkeley
Highest development phase	Preregistration (EU)
Active development-indications	Malignant melanoma, non-small cell lung cancer, prostate cancer, urogenital cancer
Class	Monoclonal antibodies
Mechanism of action	Cytotoxic T-lymphocyte antigen 4 inhibitors, immunostimulants, T-lymphocyte stimulants
Chemical name	Immunoglobulin G1, anti-(human CTLA-4 (antigen)) (human γ1-chain), disulphide with human κ-chain, dimer
Molecular formula	C6472 H9972 N1732 O2004 S40
CAS registry number	477202-00-9
Route of administration	IV
Pharmacodynamics	Inhibition of tumor growth in mice; eradication of primary and metastatic murine melanomas with anti-CTLA-4 + sargramostim-producing vaccines; dose-dependent increase in T-cell activation and decreases in serum prostate specific antigen levels in prostate cancer patients;
Immunogenicity	Combination therapy with GVAX® and ipilimumab enhances T-cell and dendritic cell activity; increases T-cell activation with a concurrent reduction in naive T cells
ATC codes	
WHO ATC code	L01X-C (monoclonal antibodies), L03A (immunostimulants)
EphMRA ATC code	L1X3 (antineoplastic monoclonal antibodies), L3A (immunostimulating agents excluding interferons)
Adverse events	
Occasional	Adrenal insufficiency, arthritis, colitis, dermatitis, diarrhea, fatigue, hepatitis, hypopituitarism, laryngospasm, neutropenia, pancreatitis, skin eruptions, uveitis

leukemia (chronic myeloid, chronic lymphocytic, acute myeloid), renal, and breast cancers, who were treated with ipilimumab (0.1–3.0 mg/kg) after relapse of their tumor following allogeneic hematopoietic stem cell transplantation showed that the drug was generally tolerable and without dose-limiting toxicities or clinically important graft-versus-host disease. Two possible immune-related adverse events included one grade 2 (thyroid function test abnormalities without clinical symptoms) and one grade 3 polyarthropathy.[20]

Preliminary results from an ongoing phase I/II clinical trial in 12 patients with relapsed or refractory follicular lymphoma showed that ipilimumab was generally tolerable. There were six grade 3 adverse events, including diarrhea (4), fatigue (1), and neutropenia (1).[20]

2.1.2 Melanoma

***Phase III*:** The most common side effects (SEs) were immune-related in a phase III trial of ipilimumab, alone and in combination with a gp100 peptide vaccine, in patients with unresectable stage III or IV metastatic melanoma who had received prior therapies and who were HLA-A2-positive. In this double-blind trial, patients were randomized to receive ipilimumab plus gp100 (3 mg/kg and 1 mg/kg every 3 weeks for four doses; n = 403), ipilimumab plus placebo (3 mg/kg every 3 weeks for four doses; n = 137) or gp100 plus placebo (n = 136). Grade 3/4 drug-related adverse events (AEs) were observed in 17%, 23% and 11% of the ipilimumab plus gp100, ipilimumab and gp100 arms, respectively. Grade 3/4 immune-related AEs (irAEs) were observed in 10–15% of the ipilimumab treatment arms, and 3% in the gp100 alone arm. The irAEs were sometimes severe and life-threatening and most often affected the gastrointestinal, skin, liver, or endocrine systems. A total of 14 drug-related deaths (2.1%, 3.1%, and 1.5% of each of the respective groups) occurred in the study, with seven (1.3%, 1.5%, and 0% of the respective groups) attributed to an irAE. All irAEs were treated with the use of supportive care and systemic steroids using established protocol-specific treatment guidelines.[5,6]

***Phase II*:** In data for three phase I studies (008, 022, and 007), the most common immune-related adverse events were rash, diarrhea, and hepatitis. Grade 3 and 4 immune-related adverse event rates were approximately 20–28% and 0–12%, respectively.[22]

Ipilimumab plus budesonide and ipilimumab plus placebo in 115 patients were associated with a similar incidence of diarrhea in patients with malignant melanoma (33% and 35%, respectively) in a phase II trial. Prophylactic budesonide did not appear to have a clinically meaningful effect on diarrhea. Most patients had at least one immune-related adverse event. However, no bowel perforations were reported and ipilimumab was generally well tolerated. Adverse events involving the CNS were reported in 5 of 16 patients, and considered drug-related in two (grade 2 headache and grade 1 dizziness). There was an increase irAEs from 0.3 to 3 to 10 mg/kg.[23-26]

In a phase II study of ipilimumab in combination with MDX 1379 at 3 or 1 mg/kg/day, grade 3/4 adverse events were observed in 31% and 26%, respectively, of patients with metastatic malignant melanoma. The most frequent events were colitis and dermatitis. Grade 3/4 events were reported in all patients with an extended complete or partial response duration.[27]

Interim results from 12 months extended dosing with ipilimumab (3.0 mg/kg) and MDX 1379 in 25 patients with resected stage IIIc or stage IV melanoma showed that the regimen was generally well tolerated. Twelve patients experienced grade II or III colitis, rash, or hypopituitarism (immune breakthrough events).[28]

***Phase I*:** In a phase I/II trial of metastatic melanoma patients receiving ipilimumab in combination with IL-2, five patients reported grade 3/4 adverse events, including colitis, and uveitis, which were consistent with the immune-based mechanism of action, as well as pancreatitis, arthritis, and laryngospasm. All patients recovered without sequelae.[29]

In a study in melanoma patients treated with ipilimumab at 9 mg/kg and presenting with dermatitis, skin manifestations consisted of pruritic, localized erythematous papules and thin plaques. Histologically, CD4-predominant T-cell infiltrates with rare dyskeratotic cells, mild to moderate spongiosis, occasional exocytosis of

Table II. History

Date	Comment
1 July 2010	No development reported – phase II for Lymphoma in USA (IV)
9 June 2010	inThought Analysis for malignant melanoma updated
8 June 2010	Interim efficacy and adverse event data from a phase III trial in metastatic melanoma presented at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO-2010)[5,6]
1 June 2010	Preregistration for malignant melanoma in EU (IV)
27 May 2010	Bristol-Myers Squibb initiates enrollment in a phase II trial for malignant melanoma in the US
25 May 2010	Safety and efficacy data from a phase II study in non-small cell lung cancer released by Bristol-Myers Squibb[16]
2 September 2009	Medarex has been acquired by Bristol-Myers Squibb
1 June 2009	Interim efficacy data from a pooled analysis of phase II trials in malignant melanoma presented at the 45th Annual Meeting of the American Society of Clinical Oncology (ASCO-2009)[37]
31 May 2009	Phase III clinical trials in prostate cancer in Australia (IV)
31 May 2009	Phase III clinical trials in prostate cancer in Canada (IV)
31 May 2009	Phase III clinical trials in prostate cancer in Europe (IV)
31 May 2009	Phase III clinical trials in prostate cancer in Latin America (IV)
31 May 2009	Phase III clinical trials in prostate cancer in USA (IV)
16 September 2008	Efficacy and adverse events data from three phase II trials in malignant melanoma released by Bristol-Myers Squibb and Medarex[22]
16 September 2008	Efficacy, adverse events, and immunogenicity data from a phase II trial in malignant melanoma presented at the 33rd Congress of the European Society for Medical Oncology (ESMO-2008)[23-25,35,40,41]
1 July 2008	Phase II clinical trials in malignant melanoma and brain metastases in the US (IV)
3 June 2008	Efficacy and adverse events data from a phase II trial of ipilimumab plus budesonide in malignant melanoma presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008)[26]
3 June 2008	Interim adverse events data from a phase I trial in prostate cancer presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008)[34]
2 June 2008	Efficacy data from phase III, phase II, and phase I/II trials in malignant melanoma presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008)[38,42-44]
25 April 2008	Phase II clinical trials in non-small cell lung cancer in the US (IV)
25 April 2008	Phase II clinical trials in non-small cell lung cancer in EU (IV)
16 April 2008	Interim efficacy data and pharmacodynamic data from phase I trials in prostate cancer presented at the 99th Annual Meeting of the American Association for Cancer Research (AACR-2008)[17,36,49]
3 April 2008	Data Monitoring Committee recommends the phase III study of ipilimumab study 024 should continue[13]
1 October 2007	Phase I clinical trials in urogenital cancer in the US (IV)
11 June 2007	Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO-2007) added to the adverse events, cancer therapeutic trials, and cancer immunogenicity sections[19,45]
9 January 2007	Medarex completes enrollment in its single-arm, monotherapy phase III trial for metastatic melanoma
11 December 2006	Data presented at the 48th Annual Meeting and Exposition of the American Society of Hematology (ASH-2006) added to the adverse events and cancer therapeutic trials sections[20]
7 December 2006	Ipilimumab receives fast-track status for use as a monotherapy in the second-line treatment of malignant melanoma in the US
7 December 2006	Ipilimumab receives fast-track status for use in combination with dacarbazine as a first-line treatment for malignant melanoma in the US
19 June 2006	Data presented at the 42nd Annual Meeting of the American Society of Clinical Oncology (ASCO-2006) have been added to the adverse events and cancer pharmacodynamics and therapeutic trials sections[28,31,33]
31 March 2006	Medarex has initiated enrollment in a registrational phase III trial of ipilimumab monotherapy for metastatic melanoma worldwide
23 March 2006	Data presented at the Prostate Cancer Symposium 2006 (PCS-2006) have been added to the cancer pharmacodynamics and adverse events sections[32]

Continued next page

Table II. Contd

Date	Comment
29 August 2005	A study has been added to the cancer therapeutic trials section[50]
22 July 2005	Data presented at the 66th Annual Meeting of the Society of Investigative Dermatology (SID-2005) have been added to the adverse events section[30]
5 May 2005	Data presented at the 96th Annual Meeting of the American Association for Cancer Research (AACR-2005) have been added to the adverse events and cancer therapeutic trials sections[27]
31 March 2005	Phase III clinical trials in breast cancer in the world (IV)
31 March 2005	Phase III clinical trials in malignant melanoma in the world (IV)
9 March 2005	Data from a media release have been added to the adverse events and cancer therapeutic trials sections[29]
10 November 2004	Ipilimumab has been licensed to Bristol-Myers Squibb worldwide excluding the US
7 October 2004	MDX 010 in combination with MDX 1379 has received fast track status for malignant melanoma in the US
29 September 2004	Phase III clinical trials in malignant melanoma in the US (IV)
13 September 2004	Phase I clinical trials in prostate cancer in the Netherlands in combination with GVAX® (IV)
25 August 2004	Medarex has received US FDA agreement on its SPA for a phase III study of MDX 010 in melanoma
6 July 2004	Data presented at the 40th Annual Meeting of the American Society of Clinical Oncology (ASCO-2004) have been added to the cancer therapeutic trials section[21]
14 June 2004	Ipilimumab has received Orphan Drug Status for malignant melanoma in the US
23 April 2004	Phase I clinical trials in solid tumors and hematological malignancies in combination with GVAX® in the US (IV)
23 April 2004	Phase II clinical trials in renal cancer in the US (IV)
23 February 2004	Data presented at the JP Morgan 22nd Annual Healthcare Conference held in January 2004 have been added to the cancer therapeutic trials section[47]
9 September 2003	Phase II clinical trials in breast cancer in the US (IV)
13 June 2003	Phase I/II clinical trials in HIV infections treatment in the US (IV)
31 May 2003	Cell Genesys and Medarex have entered into an agreement to develop a combination therapy using GVAX® and ipilimumab
30 September 2002	Phase II clinical trials in lymphoma in the US (IV)
8 November 2001	A phase I/II study has been added to the cancer therapeutic trials section[51]
8 November 2001	Phase II clinical trials for malignant melanoma in the US (IV)
8 November 2001	Phase II clinical trials for prostate cancer in the US (IV)
18 January 2000	Anti-CTLA-4 monoclonal antibodies are available for licensing from Medarex (http://www.medarex.com)
1 December 1999	A preclinical study has been added to the pharmacodynamics section
3 November 1998	A preclinical study has been added to the pharmacodynamics section
16 May 1996	New profile
16 May 1996	Preclinical development for cancer in the US (IV)

T cells and eosinophils in the dermis were observed. Five patients also presented with an increase in the peripheral blood eosinophil count. Ipilimumab-treated patients who developed skin manifestations also tended to develop a more focal cutaneous reaction with a predominance of CD+4 T cells in the dermis.[30]

2.1.3 Non-Small Cell Lung Cancer

***Phase II*:** In a double-blind, phase II trial (041) in patients with previously untreated advanced non-small cell lung cancer receiving treatment with ipilimumab in combination with paclitaxel/carboplatin, grade 3/4 adverse events were observed in 58%, 52%, and 42% of patients in the concurrent, phased and paclitaxel/carboplatin alone groups, respectively. The incidences of grade 3/4 irAEs were 20% and 15% for the concurrent and phased groups, respectively. These events were treated with supportive care and systemic steroids based on established protocol treatment guidelines.[16]

2.1.4 Prostate Cancer

***Phase II*:** Ipilimumab (either alone or in combination with docetaxel) was generally well tolerated

Table III. Forecasts

InThought Probability of Approval[a]			
Indication	Approval Date Estimate	inThought Approvability Index	Last Update
Lymphoma	NE	30% (NYR)	21 Jul 2009
Malignant melanoma	5 Jan 2013	51% (C)	9 Jun 2010
Non-small cell lung cancer	NE	30% (NYR)	21 Jul 2009
Prostate cancer	NE	30% (NYR)	21 Jul 2009

a The Wolters Kluwer Health Approvability Index is a dynamic tool that assesses the progress of a drug candidate through clinical development, evaluating strength of clinical data and trial design, benchmarked against historical parameters and likelihood to maintain forward momentum. Points are assigned for specific line items relating to safety, efficacy, and other factors in each phase of clinical development. Possible points total 100 upon drug approval, and are allocated in each phase according to the historical approval rate of similar drugs, such that the current points of a drug relate to its probability of approval. In addition, a letter grade is assigned and reflects the momentum of a drug candidate in its current phase, with "A" indicating significantly above average/likely to progress, "C" indicating average, and "F" indicating significantly below average/unlikely to progress. 'NYR' stands for 'Not Yet Rated,' indicating that the probability of approval is based on historical approval rates for similar drugs according to indication, molecule type, novelty, and phase, but without analyses of clinical data, trial design, and other factors specific to the individual agent.

NE = no estimate; **NYR** = not yet rated.

in a phase II trial in 44 patients with hormone refractory prostate cancer. Four patients experienced an immune breakthrough event, with the most common events being diarrhea, colitis, and adrenal or pituitary insufficiency.[31]

***Phase I*:** Results from a phase I clinical trial in 18 patients with hormone refractory prostate cancer showed that ipilimumab (0.5–3.0 mg/kg) in combination with subcutaneous sargramostim (250 mg/m^2/day) was generally well tolerated. The two patients who responded to treatment both experienced an immune breakthrough event (recognized AE), one of rash and one of hypopituitarism.[31,32]

Combination therapy with ipilimumab and GVAX® did not result in any dose-limiting toxicities in 12 patients with metastatic hormone-refractory prostate cancer. In the five patients who experienced a prostate specific antigen (PSA) response, all experienced grade 2/3 immune-mediated endocrine deficiencies, which were successfully treated with standard hormone replacement. Importantly, the PSA declines could not be consistently correlated with declines in adrenal androgens and there was no induction of the alpha-21-hydroxylase auto-antibody that is seen in 90% of cases of auto-immune adrenal insufficiency. Two patients requiring thyroid replacement therapy were successfully tapered off after recovery of thyroid function, with one patient subsequently maintaining a PSA response. One patient who received the highest dose of ipilimumab tested in the trial developed a grade 3 dose-limiting pulmonary alveolitis that responded to steroid treatment.[19,33]

Preliminary data from a phase I study of ipilimumab alone and in combination with radiotherapy in patients with metastatic castration-resistant prostate cancer showed irAEs. Nineteen patients experienced 29 irAEs, including diarrhea/colitis (14), rash (9), hepatitis (4), and endocrinopathy (2). Nine patients had grade ≥3 irAEs, including gastrointestinal (6), hepatitis (2), and rash (1), which were generally responsive to immunosuppressants.[34]

2.2 Immunogenicity

2.2.1 Cancer

In a phase II trial involving 115 patients with advanced melanoma, an overall mean increase of approximately 10% in activated CD4+ and CD8+ T cells, and a decrease in naive CD4+ and CD8+ T cells was observed by week 4. By week 4, 96% of evaluable patients had an increase in activated T cells and 82% of evaluable patients had a decrease in naive T cells. In more than 50% of patients, these changes continued to evolve between weeks 4 and 12.[35]

Combination therapy with GVAX® and ipilimumab in a phase I trial of patients with meta-

static hormone-refractory prostate cancer, enhanced T cell and dendritic cell activity, and this was more pronounced at the higher dose levels. Evaluation of antibody responses showed that the combination therapy induced antibody responses to a broad array of previously identified cancer-associated antigens including PSMA, NY-ESO-1, and filamin-B, and that these responses were patient-specific with respect to the pattern of antibodies detected in different patients.[19]

2.3 Pharmacodynamics

2.3.1 Cancer

Preliminary results from a phase I trial in which patients with metastatic, hormone-refractory prostate cancer were treated with subcutaneous GM-CSF (250 mg/m^2/day) and escalating doses of ipilimumab showed that two of three patients treated with ipilimumab (3.0 mg/kg) in combination with sargramostim experienced >50% decreases in PSA serum levels. Seven patients out of a total of 18 evaluable patients had a <50% reduction in their PSA levels. A dose-response relationship was seen between the ipilimumab dose and CD8 T-cell activation. Interferon-γ production and lytic activity were enhanced in antigen-specific CD8+ T cells following treatment.[31,32]

Decreases in serum PSA levels of >50% were seen in 3 of 24 hormone-refractory prostate cancer patients treated with ipilimumab in a phase II trial. Ipilimumab in combination with docetaxel resulted in decreases in serum PSA levels of >50% in 3 of 20 patients.[31]

Twelve patients with advanced prostate cancer have completed treatment in an ongoing phase I combination trial of GVAX® and ipilimumab. An association was observed between the dose-dependent increase in T-cell activation and decreases in PSA levels. According to this trial, patients receiving the three highest doses of ipilimumab in combination with GVAX® immunotherapy showed an increase in the percentage of memory T cells, as measured through peripheral blood T-cell monitoring. Patients receiving the two highest doses of ipilimumab in combination with GVAX® immunotherapy had an increase in HLA-DR on T cells, indicating T-cell activation.[36]

2.4 Therapeutic Trials

2.4.1 Cancer

Melanoma

***Phase III*:** Overall survival was significantly extended in patients with previously-treated metastatic melanoma who received ipilimumab therapy in a phase III trial (study 020, NCT00094653) of the agent alone and in combination with a gp100 peptide vaccine. In this double-blind trial, patients were randomized to receive ipilimumab plus gp100 (3 mg/kg and 1 mg/kg every 3 weeks for four doses; n = 403), ipilimumab plus placebo (3 mg/kg every 3 weeks for four doses; n = 137) or gp100 plus placebo (n = 136). Re-induction was allowed within 28 days of documented progression, provided the patient had no experienced any dose-limiting toxicities or response to the initial cycle of therapy was stable disease lasting ≥3 months from the first tumor assessment at week 12, or complete or partial response. Patients were re-induced with 1–3 additional courses of the originally assigned regimen in 7.2%, 6.5%, and 1% of ipilimumab plus gp100, ipilimumab and gp100 arms, respectively. Median overall survival was 10, 10.1, and 6.4 months for patients treated with ipilimumab plus gp100, ipilimumab alone and gp100 alone, respectively (hazard ratio [HR] 0.68 and 0.66, p = 0.0004 and 0.0026; for the comparisons between the ipilimumab plus gp100 and gp100 groups, and ipilimumab and gp100 groups, respectively). At 1 year, 44–46% of patients treated with ipilimumab were alive compared with 25% of patients treated with gp100 alone. At 2 years, 22–24% of patients treated with ipilimumab were alive compared with 14% of patients treated with gp100 alone.[5,6]

***Phase II*:** Two-year survival rates in three phase II trials of ipilimumab 10 mg/kg in patients with advanced metastatic melanoma (stage III or IV) were 33%, 30%, and 41% (for trials 008, 022, and 007, respectively) based on follow-up of up to 37.5 months. One-year survival rates reported previously in the three studies were 47%, 48%, and 51%, respectively, based on median follow-up periods of 24.8 months, 21.88 months, and 26.32 months, respectively. Study 008 included 155 patients who had progressed while on, or

after, receiving standard treatment. Study 022 included 217 patients who were previously treated, relapsed or failed to respond to experimental treatment, or were unable to tolerate currently approved therapies. Study 007 included 115 treatment-naive patients and patients previously treated with therapy other than ipilimumab.[22,37]

A 2-year projected survival rate of 30% and a median overall survival of 13.4 months was seen in heavily pre-treated melanoma patients in a phase I/II study (MDX010-15) in 23 patients. The median follow-up for survival was 15.5 months.[38,39]

There was no significant difference between ipilimumab plus budesonide and ipilimumab plus placebo in the disease control rate (31% vs 35%) or in the best overall clinical response rate (12% vs 16%) in a phase II trial in patients with malignant melanoma. 115 patients with unresectable stage III or IV malignant melanoma (who were either treatment naive or had received previous treatment with systemic therapy for advanced melanoma) were treated with ipilimumab 10 mg/kg/day every 3 weeks for four courses, plus placebo or budesonide at a dosage of 9 mg/day to week 12, 6 mg/day to week 14, and 3 mg/day to week 16. Eligible patients could enter maintenance treatment with ipilimumab 10 mg/kg/day every 12 weeks, at week 24. The modified WHO best overall response rate (primary endpoint) was 5.8%. Late responses or stable disease with a decline in tumor volume of more than 25% were also observed. Median follow-up for survival was 9.5 months, with a median overall survival of 10.22 months. Based on the initial survival analysis at 6 months in 12 patients with brain metastases, one patient survived less than 6 months, and three survived between 6 and 9 months. The remaining eight patients were alive at 2.56+, 5.32+, 6.05+, 6.11+, 6.74+, 8.51+, 10.81+, and 14.06+ months. One patient experienced a partial response, and three experienced stable disease. In the only patient with a brain lesion as an index lesion, the lesion decreased by week 12. The survival rate at 1 year was 46.67%. There was a significant dose effect based on best overall response with highest activity in the 10 mg/kg group.[23,25,26,40,41]

In a follow-up study to determine overall survival in patients with metastatic melanoma previously enrolled in three phase I and II studies performed between 2000 and 2005, the median overall survival for responders had not been reached with a 25th percentile of 21.7 months. The median overall survival for patients in Medarex studies –02, –08, and –015 were 19.4, 12.9, and 10.0 months, respectively. In contrast, the median overall survival for non-responders was 10.9 months, with 25th and 75th percentile overall survival of 5.7 and 19.4 months.[42]

In a phase II study of previously treated patients with unresectable stage III/IV melanoma, an Independent Review Committee concluded that the best overall response rates were similar when ipilimumab was used either as a first or second-line monotherapy.[43]

Long-term follow-up data and overall survival results from the phase II study, MDX010-08, of ipilimumab in combination with dacarbazine demonstrated that 11.4% (4 of 35 patients) were alive at ≥4 years of follow-up. The median overall survival time for patients treated with the combination therapy was 15 months compared with the median overall survival data from the literature of 6–9 months for patients with advanced melanoma receiving standard chemotherapy.[44]

Overall disease control was achieved in 19% of patients in a phase II dose-escalation trial of ipilimumab in patients with unresectable stage III or stage IV malignant melanoma. The study enrolled 88 patients in three cohorts. In the cohort of 23 patients who were treated at 10 mg/kg, disease control was achieved in 39% (9 of 23), which lasted 6 months or longer in nearly all patients (8 of 9). Duration of disease stabilization or response exceeded 6 months in 15% (13 of 88) of patients. The longest effect observed (stable disease) is ongoing for more than 1 year.[45]

Results from the initial cohort of this phase II study showed an objective response rate of 21% which included two complete responses and one partial response. There also appeared to be an apparent correlation between the development of an autoimmunity and durable clinical responses. Six patients reported drug-related autoimmune adverse events, which were resolvable with medication, and of these, 50% also experienced an

anti-tumor response. The results suggest that these 'autoimmune break through events' may be associated with the induction of anticancer immune responses. Patients received a regimen of 3.0 mg/kg of MDX 010 once every 3 weeks in combination with two peptides from the gp100 melanoma-associated antigen gp100.[46]

In preliminary results from a phase II study of 30 melanoma patients treated with MDX 010 in combination with dacarbazine, there were two partial responses, three unconfirmed partial responses and five reports of stable disease compared to one partial response and four stable disease reports in patients receiving dacarbazine monotherapy.[47]

In a phase II study, MDX 010 in combination with MDX 1379 at doses of 3 or 1 mg/kg/day was associated with complete responses in 7% and 0%, respectively, and partial responses in 7% and 11%, respectively, of 56 patients with metastatic malignant melanoma. The complete response duration was >30 and >31 months, while the partial response duration was 4 to >34 months.[27]

Interim results from 12 months' extended dosing with ipilimumab (3.0 mg/kg) and MDX 1379 in 25 patients with resected stage IIIc or stage IV melanoma showed that six patients had relapsed but all 25 were still alive at the time of follow-up.[28]

In results from a phase I/II trial in 36 metastatic melanoma patients receiving MDX 010 in combination with IL-2, eight patients experienced objective tumor regression. Patients received MDX 010 every 3 weeks, with three patients per dose level at 0.1, 0.3, 1.0, and 2.0 mg/kg. Two patients in the 3.0 mg/kg cohort experienced complete responses that are ongoing at over 13 months, and one patient in the 2.0 mg/kg cohort experienced a complete response that was ongoing at over 16 months. Five patients experienced partial responses, with responses ranging from 7 months to the longest duration ongoing at over 19 months.[29]

Non-Small Cell Lung Cancer

***Phase II*:** In a double-blind, phase II trial (041) in patients with previously untreated advanced non-small cell lung cancer, treatment with ipilimumab in combination with paclitaxel/carboplatin resulted in immune-related progression-free survival rate of 5.52 months ($p = 0.094$), 5.68 months ($p = 0.026$) and 4.63 months for the concurrent, phased and paclitaxel/carboplatin alone groups, respectively. Progression-free survival, as assessed by modified WHO criteria, was 4.11 months ($p = 0.250$), 5.13 months ($p = 0.024$) and 4.21 months for the concurrent, phases and paclitaxel/carboplatin alone groups, respectively. Interim data for overall survival were 11.01 months, 11.56 months, and 9.99 months for the concurrent, phased and paclitaxel/carboplatin alone groups, respectively.[16]

Prostate Cancer

***Phase II*:** A confirmed response of 246 days in duration and a confirmed response of ≥79 days in duration were seen in 2 of 24 hormone refractory prostate cancer patients treated with ipilimumab in a phase II trial. There was also a third unconfirmed response. Ipilimumab in combination with docetaxel resulted in one confirmed response (280 days) and two unconfirmed responses.[31]

***Phase I*:** Twelve patients with advanced prostate cancer have completed treatment in an ongoing phase I combination trial of GVAX® and ipilimumab. Of the six patients treated in the two highest dose groups, antitumor activity has been observed in five patients. PSA declines of greater than 50% were maintained in four of these patients for at least 6 months, with the longest response ongoing at more than 16 months. Clinical evidence of antitumor activity has been observed in four of five PSA responders, including complete resolution of multiple lesions on bone scan in two patients, and resolution of abdominal lymph node disease by CT scan and improvement in bone pain in one patient each. Additional data showed that in the 16 patients from the expansion cohort, an ipilimumab dose-related association with increased T-cell activation was seen. Associated anti-tumor activity was seen from the initial 12 patients.[17,19,33,48]

Preliminary data from an ongoing phase I study of ipilimumab in combination with sargramostim showed that of the six patients treated at 3 mg/kg ipilimumab, three patients experienced decreases in prostate-specific antigen serum

levels of over 50% and one patient experienced a partial response in hepatic metastases.[17,49]

Lymphoma

***Phase I*:** Preliminary results from a phase I/II clinical trial in patients with relapsed or refractory follicular lymphoma showed that one of six patients who had been previously treated with a lymphoma vaccine experienced a partial response that was ongoing at >10 months duration.[20]

Renal Cancer

***Phase I*:** MDX 010 had moderate efficacy in a phase II study in patients with metastatic renal cancer. Partial clinical response rates were 5% and 13% for patients in the 1 and 3 mg/kg/day treatment groups, respectively. Significantly more patients who experienced a major immune-mediated event achieved an objective clinical response compared with those who did not.[50]

Solid Tumors

***Phase I*:** Treatment with a single dose of ipilimumab 3 mg/kg via infusion resulted in stable disease and marked reduction in CA 125 (from 3478 to 145) with tumor regression in two ovarian cancer patients, respectively. The patients had previously received treatment with GVAX® and are part of a phase I trial, which will accrue 48 patients with a range of solid tumors. Results from a pilot study, in which all patients had previously received treatment with GVAX®, also showed a reduction in CA 125 levels following treatment with ipilimumab in two ovarian cancer patients. In addition, ipilimumab induced extensive tumor destruction with lymphocyte and granulocyte infiltrates in all three melanoma patients in the pilot study.[21]

Among 18 patients with metastatic melanoma and 14 patients with hormone-refractory prostate cancer receiving a single dose of ipilimumab 3 mg/kg, two prostate cancer patients experienced a >50% reduction in serum PSA levels that lasted for 3–6 months.[51]

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