

Tremelimumab

Abstract

Tremelimumab (CP 675206; CP-675; CP-675,206; CP-675206; Ticilimumab) is a fully human IgG2 antibody, which is directed against human cytotoxic T lymphocyte-associated antigen 4 (CTLA4). It is being developed by Pfizer for the treatment of various cancers. It is currently in worldwide phase III development for malignant melanoma, phase II development for colorectal cancer, gastrointestinal cancer, gynecological cancer, and non-small cell lung cancer in the US and other countries, and is also being investigated for prostate, breast, and pancreatic cancer in various countries. This review discusses the key development milestones and therapeutic trials of this drug.

1. Introduction

Tremelimumab (formerly ticilimumab) is a fully human IgG2 monoclonal antibody, which is directed against human cytotoxic T lymphocyte-associated antigen 4 (CTLA4), it is also an interleukin-2 (IL-2) stimulant. The antibody is being developed by Pfizer as an anticancer agent, which was generated using XenoMouse™ technology provided by Abgenix (now Amgen). Tremelimumab is in clinical development for the treatment of various cancers.

CTLA4 (CD152) is a cell surface receptor expressed on activated T cells. In mice, T cell-mediated killing of tumors is enhanced by blocking the binding to CTLA4 of its natural ligands, such as B7.1 (CD80) and B7.2 (CD86), which are expressed on antigen-presenting cells.

1.1 Company Agreements

In January 2010, Pfizer and Debiopharm Group entered into a co-development agreement

to conduct a phase III trial of tremelimumab for the treatment of patients with unresectable, stage IV melanoma. A biomarker will be used to select patients considered likely to respond to tremelimumab. Under the terms of the agreement, Debiopharm will assume responsibility for conducting the phase III trial of tremelimumab and Pfizer will retain responsibility for worldwide commercialization of the compound. Financial terms of the agreement were not disclosed.^[1]

In September 2004, Medarex and Pfizer signed a strategic alliance, and exchanged non-exclusive licenses to patents relating to antibodies to CTLA4. Pursuant to this license agreement, Medarex has the potential to receive milestone and royalty payments based upon commercial sales of any Pfizer anti-CTLA4 antibody product, including tremelimumab.^[2]

1.2 Key Development Milestones

A rollover protocol, phase II study (NCT00378482) intended to provide access to

tremelimumab for patients who have previously received this drug in a clinical trial is taking place in the US and UK. This open-label study will enroll approximately 200 patients at locations in the US, Italy, and the UK, and will monitor long-term efficacy, safety, and tolerability.

1.2.1 Bladder Cancer

In June 2009, Pfizer initiated an open-label phase I trial (NCT00880854) of tremelimumab in combination with Bacillus Calmette-Guérin (BCG) in patients with BCG-resistant, recurrent bladder cancer. This study will investigate the safety, efficacy, and immunogenicity of the therapy in approximately 24 patients in the US.

1.2.2 Breast Cancer

According to the September 2008 Pfizer pipeline, a phase I trial was initiated in this indication. However, as of June 2010, no development has been reported.

1.2.3 Colorectal Cancer

Pfizer has completed a phase II trial (NCT00313794) evaluating tremelimumab as a monotherapy in 49 patients with refractory metastatic adenocarcinoma of the colon or rectum who failed standard chemotherapy. The single-arm study was conducted at sites in the US and Canada. Patients received 15 mg/kg every 90 days via intravenous infusion until disease progression. The primary objective was response rate by RECIST (Response Evaluation Criteria In Solid Tumours) criteria. Secondary objectives included safety, duration of response, progression-free survival, and overall survival. A single patient, who had a stable ovarian mass and a substantial regression in an adrenal mass, received a second dose. The remaining 46 patients had disease progression or disease-related death before reaching the planned second dose at 3 months.^[3] Following the completion of this trial in July 2008, no further development was reported and as the indication does not appear on the January 2010 Pfizer pipeline, development is presumed to have been discontinued.

1.2.4 Gastrointestinal Cancer

According to Pfizer's pipeline dated March 2009, tremelimumab is in phase II clinical development for gastrointestinal cancers.

1.2.5 Liver Cancer

In December 2008, Pfizer initiated a phase II trial (NCT01008358) of tremelimumab in patients with late-stage unresectable liver cancer who also have hepatitis C infections. This primary endpoint of this single-armed study is the tumor response following therapy. The study will also evaluate changes in hepatitis C viral load. Approximately 20 patients will be enrolled in Spain.

1.2.6 Malignant Melanoma

Based on a co-development agreement with Pfizer, Debiopharm Group began planning a phase III trial of tremelimumab for the treatment of unresectable late-stage malignant melanoma using a biomarker to select individuals that might respond to the therapy.^[1] According to the Debiopharm pipeline (accessed in June 2010), phase III development has begun.

A phase III trial of tremelimumab in combination with either dacarbazine or temozolomide in treatment-naïve patients with surgically incurable metastatic melanoma was discontinued by Pfizer due to interim results not demonstrating superiority over standard chemotherapy. Overall survival was the primary endpoint. Debiopharm has used data from this trial to identify a biomarker within the responding population, which is being used to select patients for their phase III trial.^[4-6]

Pfizer, in collaboration with the University of Pittsburgh, is conducting a phase II trial (NCT00610857) of tremelimumab in combination with high-dose interferon- α -2b in patients with recurrent inoperable stage III or IV melanoma. This open-label study has completed enrollment of 37 patients in the US. Promising interim results were reported at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008).^[7]

A phase II study (NCT00254579) of tremelimumab (15 mg/kg every 90 days) in 215 patients with advanced refractory and/or relapsed melanoma is ongoing in the US, Argentina, Australia, Canada, France, Germany, Italy, Spain, and the UK. Objective response rate is the primary endpoint and enrollment was completed in June 2009.

Pfizer is conducting a phase II trial (NCT00471887) of tremelimumab in patients with late-stage or metastatic melanoma to investigate its mechanism of action. This open-label study has reached its target enrollment of 34 patients and is being carried out in the US.

In August 2003, Pfizer initiated a phase I/II study (NCT00086489) evaluating the efficacy and safety of 2 dose levels (10 and 15 mg/kg) of tremelimumab in 125 patients with advanced melanoma in the US. The endpoints are assessed every 2–3 months up to 2 years from the first dose of tremelimumab. Recruitment was completed in October 2007.

A phase I/II trial of tremelimumab has been conducted in the US in patients with advanced melanoma. It was an open-label, non-randomized, dose-escalation study sponsored by the M.D. Anderson Cancer Center. Results have been reported.^[8]

1.2.7 Non-Small Cell Lung Cancer (NSCLC)

In June 2010, Pfizer completed a phase II study (NCT00312975) involving 87 patients with late-stage NSCLC who had stable disease following first-line platinum based therapy. This randomized, open-label trial was conducted to assess the efficacy of tremelimumab compared with best supportive care and was conducted at sites across the US, Canada, the UK, Czech Republic, and South Korea. Interim results were presented at ASCO-2009.^[9]

1.2.8 Pancreatic Cancer

An open-label phase I trial (NCT00556023) is underway in Canada and Italy to determine the dose-limiting toxicities of tremelimumab in combination with gemcitabine in approximately 48 patients with chemotherapy-naïve, inoperable, metastatic pancreatic cancer.

1.2.9 Prostate Cancer

A phase II, open-label, randomized study (NCT00075192) of tremelimumab in 30 patients with high-risk prostate cancer has been completed in the US in June 2006. The trial compared the efficacy of tremelimumab in combination with neoadjuvant androgen ablation, with androgen ablation alone.

A phase I, dose-escalation trial (NCT00702923) is underway in the US to determine the safety of tremelimumab in combination with bicalutamide (a short-term androgen deprivation drug) in approximately 24 patients with prostate-specific antigen-recurrent non-metastatic (stage D0) prostate cancer.

1.2.10 Renal Cancer

A phase I trial (NCT00372853) is underway to determine the highest tolerable dose of tremelimumab when given in combination with sunitinib in patients with previously untreated metastatic renal cell carcinoma. Enrollment of 28 patients was completed in January 2010.

1.2.11 Urogenital Cancer

According to Pfizer's pipeline dated March 2009, tremelimumab is in phase II development for urogenital cancer.

2. Scientific Summary

2.1 Pharmacokinetics

A phase I study evaluated the pharmacokinetics and clinical activity of tremelimumab in 39 patients with advanced solid malignancies. As per ELISA results, peak plasma concentrations and systemic exposure of tremelimumab were dose dependent. After doses of ≥ 6 mg/kg, the plasma concentrations of tremelimumab were >10 $\mu\text{g/mL}$ (target efficacious concentration) and remained at this level for >4 weeks. Tremelimumab had an elimination half-life of 25.6 days.^[10]

2.2 Adverse Events

2.2.1 Colorectal Cancer

Phase II: Tremelimumab (15 mg/kg, intravenous infusion) was well tolerated without any

Table I. Features and properties

Alternate names	CP 675206; CP-675; CP-675, 206; CP-675206; Ticiilimumab
Originator	Pfizer
Highest development phase	III (US)
Active development-indications	Bladder cancer, gastrointestinal cancer, liver cancer, malignant melanoma, non-small cell lung cancer, pancreatic cancer, prostate cancer, renal cancer, urogenital cancer
Class	Monoclonal antibodies
Mechanism of action	Cytotoxic T-lymphocyte antigen 4 inhibitors, interleukin-2 stimulants
Chemical name	Immunoglobulin G2, anti-(human cytotoxic T-lymphocyte protein 4 [CD 152 antigen]) [human monoclonal CP-675206 clone 11.2.1 heavy chain] disulphide with human monoclonal CP-675206 clone 11.2.1 light chain, dimer
Molecular formula	C6500 H9974 N1726 O2026 S52
CAS registry number	745013-59-6
Route of administration	IV
Pharmacodynamics	Enhances production of interleukin-2 in T cells of cancer patients
ATC codes	
WHO ATC code	L01X-C (monoclonal antibodies)
EphMRA ATC code	L1X3 (antineoplastic monoclonal antibodies)
Pharmacokinetics	
$t_{1/2\beta}$ (h):	614.4 (unspecified)
Adverse events	
Occasional	Colitis, dermatitis, diarrhea, fatigue, pruritus, skin eruptions, vitiligo
Rare	Gastrointestinal perforations, idiopathic thrombocytopenic purpura, sudden death

unexpected and manageable adverse events in patients with relapsed/refractory colorectal cancer despite standard chemotherapy in a phase II study. Treatment-emergent grade 3/4 adverse events were diarrhea (6.4%) and idiopathic thrombocytopenia purpura (2.1%). The frequency of grade 2 diarrhea was 8.5%.^[3]

2.2.2 Malignant Melanoma

Phase III: The most common adverse events in a phase III study in 655 patients with advanced melanoma were diarrhea (43% overall, 14% grade 3/4), pruritus (25%), and rash (23%). Of the 655 patients, 328 were randomized to receive oral tremelimumab 200 mg/m² on days 1–5 of a 28-day cycle (324 treated) and 327 to intravenous dacarbazine 1000 mg/m² every 21 days (319 treated). Pituitary or adrenal gland toxicities were observed in 3% of patients, and thyroid toxicities in 4%. There were three treatment-related deaths in the active arm, compared with none in the control arm.^[11]

Phase II: Intravenous tremelimumab (15 mg/kg, every 12 weeks) appeared to be well tolerated in patients with advanced (incurable stage III or IV) malignant melanoma in a phase II, open-label, single-arm study (n=251). The majority of treatment-related adverse events were mild to moderate. Grade 3 or 4 AEs included diarrhea (n=28, 11.4%), fatigue (n=6, 2.4%), and colitis (n=6, 2.4%). There were two (0.8%) treatment-related deaths (one sudden death and one diverticular perforation).^[12]

Interim results of a phase II trial showed acceptable tolerability for the combination of tremelimumab with high-dose interferon- α -2b in a phase II trial in patients with stage IV melanoma. Sixteen such patients received intravenous tremelimumab 15 mg/kg per 12-week treatment course. Concurrently, interferon- α -2b was administered, beginning with an intravenous induction regimen of 20 MU/m² for 5 days per week for 4 weeks, followed by a subcutaneous maintenance regimen of 10 MU/m² three times per week for 8 weeks per treatment course. Beginning

with the second treatment course, interferon- α -2b was administered only subcutaneously as 10 MU/m² three times per week. The rate of adverse events of grade 3/4 severity with the combination was not more than that observed with high-dose interferon- α -2b only. Grade 3/4 adverse events included neutropenia (n=3); elevations of hepatic enzymes to more than 5 times the upper limit of normal (n=2); fatigue (n=6); and anxiety (n=2). Grade 4 autoimmune colitis was observed in one patient and resulted in withdrawal from the study; the patient subsequently recovered completely.^[7]

In a phase II study involving 28 patients with advanced melanoma, two patients at the monthly dose (10 mg/kg) and five patients at the quarterly dose (15 mg/kg) continued on the study beyond 1 year. Currently, six patients at the monthly dose and two patients at the quarterly dose have discontinued due to toxicity. There have been no drug-related deaths in the study.^[8]

Phase I: In a phase I study in melanoma patients treated with tremelimumab, no grade 4 toxicities were observed. Grade 3 diarrhea occurred in one patient at 3 mg/kg and two patients at 10 mg/kg. Grade 2 treatment-related toxicities included dermatitis (n=4), and one case each of diarrhea, pruritus, hypothyroidism, urticaria, and myalgias. Toxicity in one patient who had received ten doses at 10 mg/kg, has been restricted to autoimmune thyroiditis requiring hormonal replacement, *de novo* vitiligo, and chronic pruritus.^[13]

2.2.3 NSCLC

According to interim results from a phase II trial (NCT00312975; n=87), the incidence of treatment-emergent adverse events was 61% and 7% following first-line maintenance therapy with tremelimumab plus best supportive care (BSC) and BSC alone in patients with advanced NSCLC. Grade 3/4 adverse events were reported in 21% and 0% of patients receiving tremelimumab plus BSC and BSC alone, respectively. The most frequently reported tremelimumab-related grade 3/4 adverse events were diarrhea and colitis.^[9]

2.2.4 Solid Tumors

Phase I: In a phase I study in 39 patients with advanced solid malignancies, tremelimumab was safe and well tolerated. The most frequently reported adverse events included dermatitis (39%), fatigue (39%), pruritus (25%), and diarrhea (25%). Dose-limiting toxicities were grade 3 diarrhea at 6 mg/kg (n=1) and 15 mg/kg (3), and grade 3 dermatitis at 15 mg/kg (1). The single MTD was 10 mg/kg. All autoimmune adverse events except vitiligo were manageable and reversible.^[10]

2.3 Pharmacodynamics

2.3.1 Cancer

Preclinical Studies

Tremelimumab showed affinities of 0.28 and 0.98 nmol/L for binding to human and monkey CTLA4 immunoglobulin, respectively. The antibody was >500-fold more selective for human CTLA4 immunoglobulin than for human CD28 immunoglobulin, B7.2 immunoglobulin, or IgG1. Tremelimumab inhibited binding of human CTLA4 immunoglobulin to immobilized B7.1 and B7.2 with respective concentrations that inhibit 50% (IC₅₀) values of 0.65 and 0.50 nmol/L. In human T-cell blasts stimulated with B7-positive Raji cells, tremelimumab enhanced production of IL-2 and interferon- γ .

In human and cynomolgus monkey whole blood and peripheral blood mononuclear cells stimulated with staphylococcal enterotoxin A superantigen, tremelimumab dose-dependently enhanced IL-2 production.^[14]

In vitro, whole blood and peripheral blood mononuclear cells from both normal donors and patients with cancer at different stages were stimulated with staphylococcal enterotoxin A superantigen and incubated with tremelimumab (0.1–100 μ g/mL) or an isotype-matched control monoclonal antibody, for 72 hours at 37°C. Tremelimumab 30 μ g/mL enhanced production of IL-2 in both normal samples and those from cancer patients, irrespective of tumor stage. Soluble CTLA4 levels were <9 ng/mL in both normal and cancer patient samples; staphylococcal enterotoxin A superantigen stimulation did not significantly affect levels of CTLA4 expression.^[15]

Table II. History

Date	Comment
2 July 2010	inThought analysis for breast cancer updated
2 July 2010	inThought analysis for non-small cell lung cancer updated
30 June 2010	inThought analysis for colorectal cancer updated
28 June 2010	Debiopharm initiates enrollment in a phase III trial for unresectable metastatic malignant melanoma in the US before June 2010
28 June 2010	No development reported – phase I for breast cancer in the US (IV)
14 June 2010	Pfizer completes a phase II trial (NCT00312975) in late-stage non-small cell lung cancer (in treatment experienced patients) in the US, Canada, Czech Republic, South Korea, and the UK
19 April 2010	Phase II clinical trial (NCT00312975) in non-small cell lung cancer is ongoing but no longer recruiting patients
16 April 2010	inThought analysis for malignant melanoma updated
8 April 2010	Suspended – phase II for late-stage non-small cell lung cancer (in treatment experienced patients) in Canada (IV)
8 April 2010	Suspended – phase II for late-stage non-small cell lung cancer (in treatment experienced patients) in Czech Republic (IV)
8 April 2010	Suspended – phase II for late-stage non-small cell lung cancer (in treatment experienced patients) in South Korea (IV)
8 April 2010	Suspended – phase II for late-stage non-small cell lung cancer (in treatment experienced patients) in the UK (IV)
19 March 2010	Suspended – phase II for late-stage non-small cell lung cancer (in treatment experienced patients) in the US (IV)
19 February 2010	Pfizer completes enrolment in its Phase-II trial (NCT00312975) for non-small cell lung cancer in USA, Canada, the UK, Czech Republic, and South Korea
19 January 2010	Pfizer completes enrollment in its phase I trial (NCT00372853) for metastatic renal cancer (in combination with sunitinib) in the US
8 January 2010	Pfizer enters into a co-development agreement with Debiopharm for phase III development of tremelimumab in patients with advanced malignant melanoma ^[1]
31 December 2009	Development discontinued for refractory metastatic colorectal cancer (second-line monotherapy in treatment experienced patients) in the US and Canada after 2008
16 November 2009	Pfizer completes enrollment in its phase II trial (NCT00610857) for late-stage inoperable recurrent malignant melanoma (in combination with high-dose interferon- α -2b) in the US
30 June 2009	Phase I clinical trials in BCG resistant, recurrent bladder cancer (in combination with BCG) in the US (IV)
13 June 2009	Pfizer completes enrollment in its phase II trial (NCT00254579) for late-stage refractory and/or relapsed melanoma in the US, Argentina, Australia, Canada, France, Germany, Italy, Spain, and the UK
2 June 2009	Interim efficacy and adverse events data from a phase II trial in non-small cell lung cancer were presented at the 45th Annual Meeting of the American Society of Clinical Oncology (ASCO-2009) ^[9]
7 May 2009	Pfizer completes enrollment in its phase II trial (NCT00471887) for late-stage or metastatic malignant melanoma in the US
31 March 2009	Phase II clinical trials in gastrointestinal cancer in the US (IV)
31 March 2009	Phase II clinical trials in urogenital cancer in the US (IV)
1 December 2008	Phase II clinical trials in late-stage unresectable liver cancer in Spain (IV)
30 September 2008	Phase I clinical trials in breast cancer in the US (IV)
16 September 2008	Safety and efficacy data from a phase II trial in patients with advanced malignant melanoma presented at the 33rd Congress of the European Society for Medical Oncology (ESMO-2008) ^[12]
31 July 2008	Phase I clinical trials of tremelimumab in combination with bicalutamide in prostate cancer in the US (IV)
14 July 2008	Pfizer completes a phase II trial (NCT00313794) in refractory metastatic colorectal cancer (second-line monotherapy in treatment experienced patients) in the US and Canada
30 June 2008	Phase I clinical trials in inoperable, metastatic pancreatic cancer (in combination with gemcitabine in treatment-naive patients) in Italy (IV)
30 June 2008	Phase I clinical trials in inoperable, metastatic pancreatic cancer (in combination with gemcitabine in treatment naive patients) in Canada (IV)

Continued next page

Table II. Contd

Date	Comment
3 June 2008	Efficacy data from a phase I/II trial in malignant melanoma presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008) ^[16]
3 June 2008	Final efficacy data from a phase III trial in malignant melanoma presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008) ^[11]
3 June 2008	Interim efficacy data from a phase II trial of tremelimumab in combination with high-dose interferon- α -2b presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008) ^[7]
30 May 2008	Phase II clinical trials of tremelimumab in combination with interferon- α -2b in malignant melanoma in the US (IV)
2 April 2008	Discontinued – phase III for malignant melanoma in the world (IV)
7 February 2008	Phase II clinical trials in late-stage inoperable recurrent malignant melanoma (in combination with high-dose interferon- α -2b) in the US (IV)
22 October 2007	Pfizer completes enrollment in its phase I/II trial (NCT00086489) for late-stage melanoma in the US
19 June 2007	Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO-2007) added to the adverse events and cancer therapeutic trials sections ^[3,8]
31 December 2006	Phase I clinical trials in metastatic renal cancer (in combination with sunitinib) in the US (IV)
8 June 2006	Pfizer completes a phase II trial (NCT00075192) for prostate cancer (in combination with neoadjuvant androgen ablation therapy) in the US
31 May 2006	Phase II clinical trials in late-stage non-small cell lung cancer (in treatment-experienced patients) in Canada (IV)
31 May 2006	Phase II clinical trials in late-stage non-small cell lung cancer (in treatment-experienced patients) in South Korea (IV)
31 May 2006	Phase II clinical trials in late-stage non-small cell lung cancer (in treatment-experienced patients) in the UK (IV)
31 May 2006	Phase II clinical trials in late-stage non-small cell lung cancer (in treatment-experienced patients) in the US (IV)
31 May 2006	Phase II clinical trials in late-stage non-small cell lung cancer (in treatment experienced patients) in the Czech Republic (IV)
31 May 2006	Phase II clinical trials in refractory metastatic Colorectal cancer (second-line monotherapy in treatment experienced patients) in USA (IV)
31 May 2006	Phase II clinical trials in refractory metastatic colorectal cancer (second-line monotherapy in treatment experienced patients) in Canada (IV)
31 December 2005	Phase II clinical trials in late-stage refractory and/or relapsed malignant melanoma in Argentina (IV)
31 December 2005	Phase II clinical trials in late-stage refractory and/or relapsed malignant melanoma in Canada (IV)
31 December 2005	Phase II clinical trials in late-stage refractory and/or relapsed malignant melanoma in the EU (IV)
31 December 2005	Phase II clinical trials in late-stage refractory and/or relapsed malignant melanoma in the US (IV)
31 December 2005	Phase II clinical trials in late-stage refractory and/or relapsed malignant melanoma in Australia (IV)
30 December 2005	Phase III clinical trials in malignant melanoma in the US (IV)
18 May 2005	Data presented at the 41st Annual Meeting of the American Society of Clinical Oncology have been added to the adverse events and cancer therapeutic trials sections ^[13]
6 July 2004	Data presented at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO-2004) have been added to the adverse events, pharmacokinetics and cancer therapeutic trials sections ^[10]
20 April 2004	Phase I/II clinical trials in malignant melanoma in the US (IV)
20 April 2004	Phase II clinical trials in prostate cancer in the US (IV)
20 April 2004	Profile created from data presented at the 95th Annual Meeting of the American Association for Cancer Research (AACR-2004)

2.4 Therapeutic Trials

2.4.1 Cancer

Colorectal Cancer

Phase II: Tremelimumab (15 mg/kg, intravenous infusion) did not demonstrate substantial

single-agent activity in patients with relapsed/refractory, metastatic, colorectal cancer despite standard chemotherapy in a phase II study (n = 47). Only one patient had a stable ovarian mass and a substantial regression in an adrenal mass; this patient has progressed to the second dose. The

Table III. Forecasts

InThought Probability of Approval^a			
Indication	Approval Date Estimate	inThought Approvability Index	Last Update
Gastrointestinal cancer	NE	31% (NYR)	27 Jul 2009
Malignant melanoma	NE	63% (NYR)	16 Apr 2010
Non-small cell lung cancer	NE	31% (NYR)	2 Jul 2010
Pancreatic cancer	NE	25% (NYR)	27 Jul 2009
Prostate cancer	NE	31% (NYR)	27 Jul 2009
Renal cancer	NE	25% (NYR)	27 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.

other 46 patients experienced disease progression or disease-related death before reaching the planned second dose at 3 months.^[3]

Malignant Melanoma

Phase III: Tremelimumab as a single-agent, first-line therapy failed to demonstrate an improvement in overall survival compared with chemotherapy in a phase III study in 655 patients with advanced melanoma. Of the 655 patients, 328 were randomized to receive oral tremelimumab 200 mg/m² on days 1–5 of a 28-day cycle (324 treated) and 327 to intravenous dacarbazine 1000 mg/m² every 21 days (319 treated). The primary endpoint of improved overall survival was not met; it was 11.8 months and 10.7 months in the tremelimumab and dacarbazine groups, respectively. Based on a protocol specified second interim analysis with 340 deaths, the independent DSMC (Direct Simulation Monte Carlo) advised to stop the study as the log-rank test statistic crossed the O'Brien-Flemming futility boundary.^[11]

Phase II: Patients with advanced (incurable stage III or IV) malignant melanoma in a phase II, open-label, single-arm study (n = 251) experienced potentially beneficial tumor responses when treated with tremelimumab (15 mg/kg, intravenous infusion every 12 weeks). Among

242-response evaluable participants, there were 11 cases of ongoing partial responses, which ranged from 6.0+ to 17.7+ months. The majority of partial responses involved target lesions in lung, lymph nodes, and/or liver. An additional 36 patients had stable disease; thus, the clinical benefit rate was 22% (partial responses plus stable diseases). Six patients (2.5%) had a partial response in target lesions while having overall progressive disease, and these patients remain alive on study with censored overall survival, which ranged from 14.82+ to 18.23+ months. Median overall survival for all patients was 10.1 months, and Kaplan-Meier estimate of 12-month survival was 41%. While the findings did not show a second-line response rate exceeding 10%, the duration of response to this regimen indicated that tremelimumab could be beneficial in this population.^[12]

Interim results of a phase II trial showed promising efficacy for the combination of tremelimumab with high-dose interferon- α -2b in a phase II trial in patients with stage IV melanoma. Sixteen such patients received intravenous tremelimumab 15 mg/kg per 12-week treatment course. Concurrently, interferon- α -2b was administered, beginning with an intravenous induction regimen of 20 MU/m² for 5 days per week for 4 weeks, followed by a subcutaneous maintenance regimen of 10 MU/m² three times per week

for 8 weeks per treatment course. Beginning with the second treatment course, interferon- α -2b was administered only subcutaneously as 10 MU/m² three times per week. There were partial responses in 3 of 16 (19%) patients after administration of a total of 24 treatment courses (median of one course per patient); these responses lasted for ≥ 2 months. Six patients had stable disease lasting ≤ 4.5 months and disease progression was observed in three patients.^[7]

In the phase II portion of a phase I/II trial involving 28 patients with histologically confirmed stage IIIc (unresectable) or stage IV recurrent metastatic melanoma, tremelimumab doses of 10 mg/kg monthly and 15 mg/kg quarterly showed a median overall survival rate of 10.3 months and 11.2 months, respectively. In the phase I portion, an estimated 21.7-month median overall survival rate was observed across several dose groups of tremelimumab (3, 6, and 10 mg/kg).^[8]

Phase I/II: Data derived from a phase I/II, randomized, open-label trial in 119 adult patients with stage III/IV melanoma suggested that those patients receiving previous therapy with IL-2 derived less benefit from tremelimumab than patients not treated with IL-2. The researchers noted that a number of confounding factors may, however, have introduced bias into the data, and further larger studies are planned.^[16]

Phase I: In a phase I trial in 14 stage IIIc/IV melanoma patients, one patient receiving tremelimumab at 10 mg/kg had an ongoing response at the time of reporting, and continues on therapy after ten doses. Four biopsies of residual lesions revealed no melanoma in most areas with a dermo-epidermal CD3/CD8 lymphocytic infiltrate. An area with viable melanoma cells had a prominent intratumoral CD3/CD8 lymphocytic infiltrate. Another patient receiving tremelimumab 10 mg/kg developed a new brain metastasis at 2 months. After external radiation therapy, no new metastases were noted for 7 months with stable lymph node metastasis.^[13]

NSCLC

According to interim results from a phase II trial (NCT0031297; n=87), first-line mainten-

ance tremelimumab plus BSC did not significantly increase the progression-free survival rate at 3 months (primary endpoint), compared with best supportive care alone, in patients with advanced non-small cell cancer (21% vs 14% of patients). The partial response rate was 5% in the tremelimumab plus BSC group and 0% in the BSC group; the stable disease rate was 17.5% and 14% in the respective groups.^[9]

Solid Tumors

Phase I: There were two complete responders (18+, 8+ months), one partial responder and six cases of stable disease (3+ to 16 months) among 34 patients with measurable disease in a phase I trials (n = 39). Patients were administered a single intravenous infusion of tremelimumab at seven dose levels (0.01, 0.1, 1.0, 3.0, 6.0, 10.0, and 15 mg/kg). Five patients in the lowest dose cohort were also re-enrolled and received treatment at a higher dose level.^[10]

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