Brentuximab Vedotin

Abstract

Brentuximab vedotin (cAC10-vcMMAE; SGN 35; SGN-35) is an anticancer antibody-drug conjugate under development by Seattle Genetics Inc. and its licensee Millennium: The Takeda Oncology Company. It comprises the anti-CD30 monoclonal antibody cAC10 conjugated to the cytotoxic agent monomethyl auristatin E, a synthetic analog of the tubulin polymerization inhibitor dolastatin 10. It is under investigation for use in Hodgkin lymphoma and non-Hodgkin lymphoma (specifically anaplastic large cell lymphoma) in North America and Europe. This review discusses the key development milestones and therapeutic trials of this drug.

1. Introduction

Brentuximab vedotin is an anticancer antibody-drug conjugate (ADC) product under development by Seattle Genetics Inc. (Bothell, WA, USA) and its licensee Millennium: The Takeda Oncology Company. The ADC comprises the anti-CD30 monoclonal antibody cAC10 conjugated to the cytotoxic agent monomethyl auristatin E (MMAE), a synthetic analog of the tubulin polymerization inhibitor dolastatin 10. The chimeric antibody is covalently coupled to MMAE through a valine-citrulline peptide linker. Brentuximab vedotin is designed to be stable in the bloodstream, but to release MMAE upon internalization into CD30-expressing tumor cells, resulting in a targeted cell-killing effect. The CD30 antigen is highly expressed by a variety of hematologic malignancies, including Hodgkin lymphoma and some T-cell non-Hodgkin lymphomas. Clinical development for the treatment of Hodgkin lymphoma and non-Hodgkin lymphoma (specifically anaplastic large cell lymphoma [ALCL]) is being conducted in North America and Europe.

1.1 Company Agreements

In December 2009, Seattle Genetics Inc. and Millennium: The Takeda Oncology Company, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, entered into a collaboration agreement to globally develop and commercialize brentuximab vedotin. Under the collaboration, Seattle Genetics Inc. will receive an upfront payment of $US60 million and retains full commercialization rights for brentuximab vedotin in the US and Canada. The Takeda Group will have exclusive rights to commercialize the product candidate in all countries other than the US and Canada. Seattle Genetics Inc. is entitled to receive progress and sales-dependent milestone payments in addition to tiered double-digit royalties based on net sales of brentuximab vedotin within the Takeda Group’s licensed

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territories. Milestone payments to Seattle Genetics Inc. could total more than $US230 million. Seattle Genetics Inc. and the Takeda Group will jointly fund worldwide development costs on a 50:50 basis. Development funding by the Takeda Group over the first 3 years of the collaboration is expected to be at least $US75 million. In Japan, the Takeda Group will be solely responsible for development costs.\[1\]

An agreement between Seattle Genetics Inc. and Albany Molecular Research for the current good manufacturing practice (cGMP) of its proprietary drug-linker system was established in May 2005. The arrangement also secures rights for ADC licensees of Seattle Genetics Inc. to work directly with Albany Molecular Research to obtain cGMP clinical trial supplies of drug-linker units.\[2,3\]

1.2 Key Development Milestones

Seattle Genetics Inc. plans to submit a biologics license application (BLA) to the US FDA in the first quarter of 2011. The BLA will aim to seek approval for both relapsed or refractory Hodgkin lymphoma and relapsed or refractory systemic ALCL. In Europe, Millennium: The Takeda Oncology Company has initiated discussions with regulators to support the submission of a marketing authorization application (MAA) to the European Medicines Agency (EMA) in the first half of 2011.\[4\]

The US FDA and the EMA have granted orphan drug designation to brentuximab vedotin for the treatment of Hodgkin lymphoma and ALCL (a type of non-Hodgkin lymphoma).\[5,6\] In March 2009, the FDA granted fast-track designation to brentuximab vedotin for the treatment of Hodgkin lymphoma.\[7\]

1.2.1 Hodgkin Lymphoma

Seattle Genetics Inc. and Millennium: The Takeda Oncology Company have initiated a phase III study (NCT0196208) of brentuximab vedotin in patients with Hodgkin lymphoma who received placebo in the phase III AETHERA trial (NCT01100502). The trial expects to enroll up to 80 patients by invitation only and aims to be completed by December 2011.

In February 2009, Seattle Genetics Inc. initiated a single-arm pivotal phase II trial (NCT00848926) to assess the efficacy and safety of single-agent brentuximab vedotin (1.8 mg/kg every 3 weeks) in 102 patients with relapsed or refractory Hodgkin lymphoma under a special protocol assessment agreement. The primary endpoint of the study will be objective response rate and secondary endpoints to include duration of response, PFS, overall survival, and tolerability. The company completed enrollment of patients at more than 30 sites in the US, Canada, and Europe in August 2009. Top-line data were
reported by Seattle Genetics Inc. and Millennium: The Takeda Oncology Company in September 2010.[10]

In July 2009, Seattle Genetics Inc. initiated a multicenter, phase II trial (NCT00947856) investigating the efficacy and tolerability of retreatment with brentuximab vedotin (1.8 mg/kg every 3 weeks) in patients with relapsed or refractory Hodgkin lymphoma or systemic ALCL who had previously responded to brentuximab vedotin. The trial is expected to enroll 125 patients and is taking place in the US and Europe.[11,12]

In January 2010, Seattle Genetics Inc. and Millennium: The Takeda Oncology Company initiated an open-label, single-arm phase I trial (SGN35-009; NCT01060904) of brentuximab vedotin in combination with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) in the treatment of patients with newly diagnosed Hodgkin’s lymphoma. The dose-escalation trial will enroll 40 patients in the US and Canada.[13]

1.2.2 Non-Hodgkin Lymphoma (including Anaplastic Large Cell Lymphoma)

In June 2009, Seattle Genetics Inc. initiated a pivotal phase II study (NCT00866047) of single-agent brentuximab vedotin (1.8 mg/kg every 3 weeks) in patients with relapsed or refractory systemic ALCL. Recruitment of 58 patients from centers in the US, Canada, and the EU was completed in May 2010. Preliminary, top-line results have been reported.[14-17]

In July 2009, Seattle Genetics Inc. initiated a multicenter, phase II trial (NCT00947856) investigating the efficacy and tolerability of retreatment with brentuximab vedotin (1.8 mg/kg every 3 weeks) in patients with systemic ALCL or relapsed or refractory Hodgkin lymphoma who had previously responded to brentuximab vedotin. The trial is expected to enroll 125 patients and is taking place in the US and Europe.[11,12]

1.2.3 General Hematologic Malignancies

Seattle Genetics Inc. has conducted a phase I trial (NCT00430846) of brentuximab vedotin (given every 21 days) in 44 refractory patients with Hodgkin lymphoma or CD30-positive hematologic malignancies. The trial evaluated the safety and pharmacokinetics of brentuximab vedotin among patients enrolled at multiple centers throughout the US. Data presented in December 2008 demonstrated multiple complete and partial responses at well tolerated doses.[18-20]

Seattle Genetics Inc. and Millennium: The Takeda Oncology Company are also conducting a phase I study to assess the cardiac safety of brentuximab vedotin in patients with CD30-positive hematologic cancers (NCT01026233).[21]

The study was expected to be completed in August 2010 but as of February 2011, the companies have completed enrollment of 40 patients and the trial is ongoing.

A phase I trial (NCT00649584) was initiated in the US in March 2008, to evaluate brentuximab vedotin in 72 patients with refractory or relapsed CD30-positive hematologic malignancies (Hodgkin lymphoma or systemic ALCL). The study was expected to be completed in December 2010. However, this trial was terminated as Seattle Genetics Inc. decided not to enroll cohorts of combined brentuximab vedotin and gemcitabine therapy.[17,22-24]

1.3 Patent Information

The US Patent and Trademark Office has issued Seattle Genetics Inc. with a patent related to its ADC technology. US Patent No. 7 659 241, covers cleavable linkers and potent auristatin drug payloads used in certain Seattle Genetics Inc. ADC programs, including brentuximab vedotin.[25]

Seattle Genetics Inc. was issued a US patent covering the cell-killing component of brentuximab vedotin in May 2005.[3]

2. Scientific Summary

2.1 Pharmacokinetics

Phase 1: Area under the concentration-time curve (AUC) increased relative to dose level of brentuximab vedotin in this phase I trial. The trial enrolled patients with relapsed or refractory CD30-positive lymphomas (n = 37) and brentuximab vedotin was administered weekly for 3 weeks in 28-day treatment cycles at doses of 0.4–1.4 mg/kg (30 minute or 2 hour intravenous infusions).[26]
AUC increased relative to dosage and did not accumulate with repeated dosing in a phase I dose-escalation trial in patients with hematologic malignancies.\[27\]

**Preclinical:** The elimination half-life of brentuximab vedotin in mice was approximately 5 days and the maximum tolerated dose was >30 mg/kg.\[28\]

### 2.2 Adverse Events

**Phase III:** In the interim results from the ATHERA trial of brentuximab vedotin in patients at high risk of residual Hodgkin lymphoma following ASCT, the most common adverse events were peripheral sensory neuropathy (47%), fatigue (46%), nausea (42%), upper respiratory tract infection (37%), and diarrhea (36%). The most common grade 3 or 4 adverse events were neutropenia (20%), peripheral sensory neuropathy (8%), thrombocytopenia (8%), and anemia (6%).\[9\]

**Phase II:** Brentuximab vedotin demonstrated a similar safety and tolerability profile to prior clinical studies in a phase II trial of 102 patients with relapsed or refractory Hodgkin lymphoma. In this open-label trial, patients received brentuximab vedotin (1.8 mg/kg) every 3 weeks for a maximum of 16 doses.\[10\]

Brentuximab vedotin was associated with manageable adverse events in a phase II clinical trial in 58 patients with relapsed or refractory systemic ALCL. The most common adverse events were nausea (38%), peripheral neuropathy (38%), fatigue (34%), fever (33%), and diarrhea (29%). The most common grade 3 or higher adverse events were neutropenia (21%), peripheral neuropathy (10%), thrombocytopenia (14%), and anemia (7%).\[4\]

**Phase I:** In a phase I trial, brentuximab vedotin exceeded a maximum tolerated dose at 1.4 mg/kg and exhibited grade 3 dose-limiting toxicities of diarrhea and vomiting, and hyperglycemia grade 4. The most common drug-associated adverse events were peripheral neuropathy, nausea, fatigue, diarrhea, dizziness, and neutropenia; most were grade 1 or 2 in severity. The trial enrolled patients with relapsed or refractory CD30-positive lymphomas (n = 37) and brentuximab vedotin was administered weekly for 3 weeks in 28-day treatment cycles at doses of 0.4–1.4 mg/kg (30 minute or 2 hour intravenous infusions).\[26\]

Brentuximab vedotin was generally well tolerated in a phase I trial among 44 evaluable

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Table I. Features and properties

| Feature                  | cAC10-vcMMAE; SGN 35; SGN-35 |
|--------------------------|-------------------------------|
| Originator               | Seattle Genetics Inc.         |
| Licensee(s)              | Millennium: The Takeda Oncology Company |
| Highest development phase| Hodgkin lymphoma, Non-Hodgkin lymphoma |
| Active development indications | Auristatins, drug conjugates, monoclonal antibodies |
| Mechanism of action      | Tubulin polymerization inhibitors |
| CAS Registry number      | 914088-09-8                   |
| Route of administration  | IV                            |
| Pharmacodynamics         | Potent cytotoxic activity against CD30-expressing cells *in vitro*; associated with disease-free survival mouse Hodgkin lymphoma model; dose-dependent antitumor activity in preclinical models of anaplastic large cell lymphoma; has superior antitumor efficacy compared with non-targeted drugs, in preclinical models of Hodgkin lymphoma |
| ATC codes                | WHO ATC code L01 (Antineoplastic Agents), L01X-C (Monoclonal antibodies) |
|                          | EphMRA ATC code L1 (Antineoplasics), L1X3 (Antineoplastic monoclonal antibodies) |
| Adverse events           | Occasional | Alopecia, diarrhea, fatigue, fever, injection-site reactions, musculoskeletal pain, nausea, neutropenia, peripheral nervous system diseases, thrombocytopenia |

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Drugs R D 2011; 11 (1)
| Event Date       | Update type       | Comment                                                                                                                                                                                                 | Update date  |
|------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 7 December 2010  | Scientific Update | Efficacy and adverse events data from a phase II trial in anaplastic large cell lymphoma presented at the 52nd Annual Meeting and Exposition of the American Society of Hematology (ASH-2010)[4] | 11 December 2010 |
| 6 December 2010  | Scientific Update | Interim efficacy and adverse events data from the phase III AETHERA trial in Hodgkin lymphoma presented at the 52nd Annual Meeting and Exposition of the American Society of Hematology (ASH-2010)[9] | 9 December 2010 |
| 5 December 2010  | Scientific Update | Additional efficacy data from a phase II trial in Hodgkin lymphoma presented at the 52nd Annual Meeting and Exposition of the American Society of Hematology (ASH-2010)[37] | 7 December 2010 |
| 11 October 2010  | Scientific Update | Efficacy data from a phase II trial (NCT00866047) in relapsed and refractory non-Hodgkin lymphoma (anaplastic large cell lymphoma) released by Seattle Genetics Inc. and Millennium: The Takeda Oncology Company[14] | 12 October 2010 |
| 27 September 2010 | Scientific Update | Efficacy data from a pivotal phase II trial in relapsed and refractory Hodgkin lymphoma released by Seattle Genetics Inc. and Millennium: The Takeda Oncology Company[10] | 1 October 2010 |
| 8 June 2010      | Scientific Update | Interim efficacy and adverse events data from a clinical trial in Hodgkin lymphoma and systemic anaplastic large cell lymphoma (non-Hodgkin lymphoma) presented at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO-2010)[31] | 15 June 2010 |
| 24 May 2010      | Trial Update      | Seattle Genetics Inc. completes enrollment in its phase II trial for relapsed/refractory anaplastic large cell lymphoma in the US, EU, and Canada | 26 May 2010 |
| 30 April 2010    | Trial Update      | Seattle Genetics Inc. terminates the phase I trial of brentuximab alone and in combination with gemcitabine for CD30-positive hematologic malignancies | 19 May 2010 |
| 10 April 2010    | InThought Forecasts| inThought Analysis for Hodgkin lymphoma updated | 10 April 2010 |
| 30 March 2010    | Phase Change      | Phase III clinical trials in Hodgkin lymphoma (patients at high risk of residual Hodgkin lymphoma following autologous stem cell transplant) in Europe (IV) | 15 February 2011 |
| 30 March 2010    | Phase Change      | Phase III clinical trials in Hodgkin lymphoma (patients at high risk of residual Hodgkin lymphoma following autologous stem cell transplant) in the US (IV) | 30 March 2010 |
| 29 January 2010  | Phase Change      | Phase I clinical trials (combination therapy) in Hodgkin lymphoma in Canada (IV) | 5 February 2010 |
| 29 January 2010  | Phase Change      | Phase I clinical trials (combination therapy) in Hodgkin lymphoma in the US (IV) | 5 February 2010 |
| 16 December 2009 | Licensing Status  | Seattle Genetics Inc. enters into a licensing agreement with Millennium: The Takeda Oncology Company[11] | 17 December 2009 |
| 8 December 2009  | Scientific Update | Efficacy, pharmacokinetic, and adverse events data from a phase I trial in Hodgkin lymphoma and non-Hodgkin lymphoma presented at the 51st Annual Meeting and Exposition of the American Society of Hematology (ASH-2009)[26] | 9 December 2009 |
| 5 December 2009  | Scientific Update | Updated interim efficacy and adverse events data from a phase I trial in Hodgkin lymphoma and CD30-positive lymphoma presented at the 51st Annual Meeting and Exposition of the American Society of Hematology (ASH-2009) | 31 December 2009 |

Continued next page
| Event Date      | Update type | Comment                                                                                                                                                                                                 | Update date       |
|-----------------|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| 8 September 2009| Scientific Update | Further updated efficacy data from a phase I trial in Hodgkin lymphoma and CD30-positive hematologic malignancies released by Seattle Genetics Inc.⁹⁰    | 16 September 2009 |
| 25 August 2009  | Trial Update | Seattle Genetics Inc. completes enrollment in its phase II trial for brentuximab vedotin in Hodgkin lymphoma in the US, Canada, and Europe                                                              | 31 August 2009    |
| 25 July 2009    | Trial Update | Seattle Genetics Inc. initiates a phase II trial of retreatment in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma in the US⁹¹† | 28 July 2009      |
| 23 July 2009    | Scientific Update | Pharmacodynamics data from a preclinical trial in Hodgkin lymphoma presented at the 100th Annual Meeting of the American Association for Cancer Research (AACR-2009)⁹² | 23 July 2009      |
| 19 June 2009    | Phase Change | Phase II clinical trials in non-Hodgkin lymphoma in Canada (IV)                                                                                                                                 | 23 June 2009      |
| 2 June 2009     | Scientific Update | Interim efficacy and adverse events data from a phase I trial in hematologic malignancies presented at the 45th Annual Meeting of the American Society of Clinical Oncology (ASCO-2009)²³ | 8 June 2009       |
| 31 March 2009   | Regulatory Status | Brentuximab vedotin receives fast-track designation for Hodgkin lymphoma (IV, infusion) in the US                                                                                                           | 1 April 2009      |
| 19 March 2009   | Phase Change | Phase II clinical trials in non-Hodgkin lymphoma in the EU (IV)                                                                                                                                 | 19 June 2009      |
| 19 March 2009   | Phase Change | Phase II clinical trials in non-Hodgkin lymphoma in the US (IV)                                                                                                                                 | 19 June 2009      |
| 20 February 2009| Phase Change | Phase II clinical trials in Hodgkin lymphoma in Canada (IV)                                                                                                                                              | 23 February 2009  |
| 20 February 2009| Phase Change | Phase II clinical trials in Hodgkin lymphoma in Europe (IV)                                                                                                                                              | 23 February 2009  |
| 20 February 2009| Phase Change | Phase II clinical trials in Hodgkin lymphoma in the US (IV)                                                                                                                                              | 23 February 2009  |
| 20 February 2009| Trial Update | Seattle Genetics Inc. initiates enrollment in a phase II trial for Hodgkin lymphoma in Canada, Europe, and the US                                                                                         | 23 February 2009  |
| 27 January 2009 | Regulatory Status | Brentuximab vedotin receives orphan drug status for non-Hodgkin lymphoma in the EU                                                                                                                     | 28 January 2009   |
| 27 January 2009 | Regulatory Status | Brentuximab vedotin receives orphan drug status for Hodgkin lymphoma in the EU                                                                                                                           | 28 January 2009   |
| 27 January 2009 | Regulatory Status | Brentuximab vedotin receives orphan drug status for non-Hodgkin’s lymphoma in the US                                                                                                                    | 28 January 2009   |
| 8 December 2008 | Scientific Update | Updated efficacy data from a phase I trial in hematologic malignancies presented at the 50th Annual Meeting and Exposition of the American Society of Hematology (ASH-2008)¹⁸ | 10 December 2008  |
| 25 October 2008 | Scientific Update | Interim efficacy data from a phase I trial in hematologic malignancies presented at the 20th-EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR-2008)¹⁹ | 28 October 2008   |
| 24 October 2008 | Scientific Update | Pharmacodynamic data from a preclinical trial in hematologic malignancies presented at the 20th-EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR-2008)³⁵ | 12 November 2008  |
| 4 June 2008     | Scientific Update | Interim efficacy and adverse events data from a phase I trial in Hodgkin lymphoma presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008)³⁰ | 11 June 2008      |
| 3 June 2008     | Scientific Update | Pharmacokinetics data from a phase I trial in Hodgkin lymphoma presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008)²⁷ | 18 June 2008      |

*Continued next page*
patients with Hodgkin lymphoma and CD30-positive hematologic malignancies. The majority of adverse events were grade 1 and 2, with the most common being fatigue, fever, diarrhea, nausea, and peripheral neuropathy. The maximum tolerated dose was defined as 1.8 mg/kg. Patients received doses of brentuximab vedotin every 3 weeks, escalating from 0.1 mg/kg to 3.6 mg/kg. Dose-limiting toxicities of hyperglycemia, prostatitis, and neutropenic fever were observed at 2.7 mg/kg. One patient treated at 3.6 mg/kg experienced fever, neutropenia, and sepsis, and died 14 days after the first dose of brentuximab vedotin. An additional two patients developed a positive anti-therapeutic antibody response to brentuximab vedotin in preliminary analyses. Less than 10% of brentuximab vedotin doses were delayed due to toxicity, primarily neutropenia, at higher doses.\cite{18,20,29,30}

In an open-label, uncontrolled, phase I trial evaluating weekly dosing for refractory or relapsed lymphoma (Hodgkin or systemic ALCL), interim results for 35 evaluable patients showed that brentuximab vedotin was generally well tolerated. The majority of adverse events were grade 1 and 2, with the most common being fatigue, nausea, neutropenia, and peripheral neuropathy. Patients received weekly doses of 0.4–1.4 mg/kg, for 3 of 4 weeks, for a minimum of two cycles.\cite{22,23}

Preliminary data from 11 patients with Hodgkin lymphoma (n = 9) and systemic ALCL (non-Hodgkin lymphoma; n = 2) who received retreatment with brentuximab vedotin monotherapy have shown that the drug was well tolerated in this setting. All drug-related adverse events were grade 1 or 2, with the most common events being peripheral neuropathy, hair loss (alopecia), joint pain (musculoskeletal pain), and injection-site irritation. Patients were heavily pretreated with a range of 2–11 prior therapies. Five patients had received a prior ASCT. Patients had achieved

### Table II. Contd

| Event Date       | Update type       | Comment                                                                                     | Update date       |
|------------------|-------------------|--------------------------------------------------------------------------------------------|-------------------|
| 31 March 2008    | Trial Update      | Seattle Genetics Inc. initiates enrollment in a second phase I trial for refractory or relapsed CD30-positive hematologic malignancies in the US | 2 April 2008      |
| 8 November 2007  | Scientific Update | Interim results from a phase I clinical trial in patients with hematologic malignancies added to the adverse events and cancer therapeutic trials sections\cite{20} | 8 November 2007   |
| 15 February 2007 | Regulatory Status | Brentuximab vedotin receives orphan drug status for Hodgkin lymphoma in the US              | 15 February 2007  |
| 22 November 2006 | Phase Change      | Phase I clinical trials in hematologic malignancies in US (IV)                              | 22 November 2006  |
| 8 August 2006    | Regulatory Status | Seattle Genetic Inc. has filed an IND with the US FDA for the treatment of Hodgkin lymphoma and other CD-positive hematologic malignancies | 8 August 2006     |
| 13 September 2005| Scientific Update | Data presented at the 9th International Conference on Malignant Lymphoma (ICML-2005) have been added to the cancer pharmacodynamics section\cite{34} | 13 September 2005 |
| 15 June 2005     | Scientific Update | Preclinical data from a media release have been added to the cancer pharmacodynamics section\cite{33} | 15 June 2005      |
| 15 July 2004     | Licensing Status  | Seattle Genetics Inc. enters preferred provider agreement with Albany Molecular Research for antibody-drug conjugate manufacturing\cite{2} | 15 July 2004      |
| 12 September 2003| Scientific Update | A preclinical study has been added to the adverse events section\cite{32} | 12 September 2003 |
| 22 July 2003     | Scientific Update | Data presented at the 94th Annual Meeting of the American Association for Cancer Research (AACR-20-03) have been added to the cancer pharmacodynamics and pharmacokinetics section\cite{28} | 22 July 2003      |
| 28 May 2003      | Phase Change      | Preclinical trials in hematologic malignancies in the US (IV)                              | 28 May 2003       |
stable disease with decreasing tumor volume or better during prior treatment with brentuximab vedotin, discontinued treatment, and subsequently experienced disease progression.\textsuperscript{[31]}

**Animal Toxicology:** In severe combined immunodeficiency (SCID) mouse xenograft models of ALCL or Hodgkin lymphoma, mice treated with brentuximab vedotin 30 mg/kg showed no signs of toxicity.\textsuperscript{[32]}

### 2.3 Pharmacodynamics

#### 2.3.1 Cancer

**Preclinical:** *In vitro* studies showed that the peptide linkage in brentuximab vedotin was efficiently cleaved by lysosomal proteases following CD30 binding and internalization, releasing the fully active drug compound, MMAE into the cell cytosols. This resulted in growth arrest in G2/M phase, apoptosis, and death. Brentuximab vedotin had potent cytotoxic activity against CD30+ expressing cells (50% inhibitory concentration [IC\textsubscript{50}] <10 ng/mL) but was 300-fold less potent against antigen-negative cells. *In vivo* studies showed that 80% of Hodgkin lymphoma and ALCL xenografted mice treated with brentuximab vedotin survived disease-free at doses as low as 1 mg/kg.\textsuperscript{[28,32]}

In preclinical models of ALCL, brentuximab vedotin displayed IC\textsubscript{50} values ranging from 3.9 to 15.8 ng/mL against CD30+ cell lines, and an IC\textsubscript{50} >1000 ng/mL against the CD30 line WSU-NHL. In a SCID mouse model of ALCL, brentuximab vedotin exhibited dose-dependent antitumor activity, with complete regressions achieved using doses ≥0.5 mg/kg (with repeat dosing) and ≥1 mg/kg (with single dosing).\textsuperscript{[33,34]}

Preclinical studies in animal models of Hodgkin lymphoma indicated that brentuximab vedotin localized in tumor tissue and had potent antitumor activity whether administered alone or in combination with chemotherapy. When combined with doxorubicin, bleomycin, vinblastine, and dacarbazine, or gemcitabine, the antitumor activity was markedly better than with brentuximab vedotin alone or chemotherapy alone. Combination therapy was not associated with alterations in CD30 expression in tumors.\textsuperscript{[35]}

Preclinical data have demonstrated the superior antitumor activity of brentuximab vedotin in Hodgkin lymphoma, compared with that of several non-targeted drugs, including vinorelbine, vinblastine, and unconjugated MMAE. Due to the targeting ability of brentuximab vedotin, concentrations of MMAE within tumors were up to 30-fold higher than the non-targeted drugs. Also, MMAE concentrations in tumors were 1000-fold greater than MMAE blood concentrations following brentuximab vedotin administration.\textsuperscript{[36]}

### 2.4 Therapeutic Trials

#### 2.4.1 Cancer

**Phase III:** In interim results from the AETHERA trial of brentuximab vedotin in patients at high risk of residual Hodgkin lymphoma following ASCT, 75% of patients achieved an objective response, including 34% complete remissions,
and 40% partial remissions. The median duration of response was 29 weeks by independent central review and 47 weeks by investigator assessment. Stable disease was observed in 22% of patients, of which 3% had progressive disease and one patient was not evaluable for response. Tumor reductions were achieved in 94% of patients. PFS among all patients was 25 weeks by independent review and 39 weeks by investigator assessment. PFS among patients achieving a complete remission and median overall survival had not yet been reached at a median follow-up of approximately 1 year.[9]

**Phase II:** Treatment with brentuximab vedotin caused tumor reductions in 94% of patients with relapsed or refractory Hodgkin lymphoma in a pivotal, open-label phase II trial (n = 102). Furthermore, 75% of patients had an objective response that lasted for 6 months. Brentuximab vedotin (1.8 mg/kg) was administered every 3 weeks for up to a total of 16 doses.[10,14,37]

Results from a phase II single-arm clinical trial with brentuximab vedotin (1.8 mg/kg every 3 weeks for up to 16 total doses) in 58 patients with relapsed or refractory systemic ALCL showed an objective response in 86% of patients. Complete remission was achieved in 53% of patients. The rate of partial remissions was 33%, 3% of patients had stable disease, and 5% had progressive disease.[14]

**Phase I:** In a phase I study, brentuximab vedotin lead to an objective response rate in evaluable patients of 46%, with 29% achieving complete remission. Median duration of response to date was at least 16 weeks with 15 patients continuing treatment. The trial enrolled patients with relapsed or refractory CD30+ lymphomas (n = 37) and brentuximab vedotin was administered weekly for 3 weeks in 28-day treatment cycles at doses of 0.4–1.4 mg/kg (30 minute or 2 hour intravenous infusions).[26]

In a phase I trial of brentuximab vedotin among 44 evaluable patients with Hodgkin lymphoma and CD30+ hematologic malignancies, 17 patients achieved objective responses, including nine complete responses and eight partial responses. A total of 18 additional patients had stable disease and nine patients progressed. The median duration of response was 22 weeks, with 11 responses ongoing at the time results were published. Across all dose levels, 86% of the 42 patients who had at least one post-baseline assessment achieved reductions in tumor volume. Among 28 evaluable patients treated at doses of 1.2 mg/kg and higher, 54% achieved an objective response, including 32% with complete responses. Additionally, 93% of these patients achieved tumor reductions, and their mean PFS was greater than 6 months. Patients received doses of brentuximab vedotin every 3 weeks, escalating from 0.1 mg/kg to 3.6 mg/kg.[18,19,20,30] A further update showed that the objective response rate (combining all dose levels) was 39% (based on investigator assessment) and 41% (based on independent review). In patients who received brentuximab vedotin at doses of ≥1.2 mg/kg, the overall response rate was 54% (based on investigator assessment) and 57% (based on independent review). The median duration of response was ≥7.3 months and eight patients remained in ongoing response.[29]

In an open-label, uncontrolled, phase I trial evaluating weekly brentuximab vedotin dosing for refractory or relapsed CD30+ lymphoma (Hodgkin or systemic ALCL), interim results showed that 16 of 35 evaluable patients achieved objective responses (ten complete responses). Eleven patients had stable disease and three had progressive disease. The median duration of response is ≥16 weeks, with 15 patients still receiving treatment. Patients received weekly doses of 0.4–1.4 mg/kg, for 3 of 4 weeks, for a minimum of two cycles.[22,23]

Preliminary data from 11 patients with Hodgkin lymphoma (n = 9) and systemic ALCL (non-Hodgkin lymphoma; n = 2) who were retreated with brentuximab vedotin monotherapy have shown that objective responses were achieved in seven retreated patients (64% of patients, including two complete remissions and five partial remissions). Tumor reductions were observed in 10 of 11 retreated patients. All patients were heavily pretreated (i.e. 2–11 prior therapies). Five patients had received a prior ASCT. Patients had achieved stable disease with decreasing tumor volume or better during prior treatment with brentuximab vedotin, discontinued treatment,
and subsequently experienced disease progression. The time to objective response ranged from 5 to 15 weeks. Three patients showed stable disease and one had progressive disease. The duration of retreatment objective responses ranged from <1 week (retreatment ongoing), to >58 weeks. Based on the small sample size, no difference in duration of retreatment response between patients with Hodgkin lymphoma and non-Hodgkin lymphoma (ALCL) was observed. Retreatment is ongoing in three patients.[31]

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2. Seattle Genetics, Inc. Seattle Genetics Establishes Preferred Antibody-Drug Conjugate Manufacturing Relationship with Albany Molecular Research, Inc. www.seattlegenetics.com, 13 Jul 2004 Media Release

3. Seattle Genetics, Inc. Seattle Genetics Launches Manufacturing Campaign with Albany Molecular Research. www.seattlegenetics.com, 05 May 2005 Media Release

4. Seattle Genetics, Inc. Millennium: The Takeda Oncology Company. Seattle Genetics and Millennium Report Positive Data from Phase II Trial of Brentuximab Vedotin (SGN-35) in Relapsed or Refractory ALCL at ASH Annual Meeting. www.takeda.co.jp, 07 Dec 2010 Media Release

5. Seattle Genetics, Inc. Seattle Genetics Receives Orphan Drug Designations for SGN-35 in the United States and Europe. www.seattlegenetics.com, 27 Jan 2009 Media Release

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