Horizon Scanning in Oncology

Brentuximab (Adcetris®) for the treatment of relapsed Hodgkin's lymphoma (HL) or relapsed systemic anaplastic large cell lymphoma (sALCL)

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1 Drug description

Generic/Brand name/ATC code:

brentuximab vedotin (Adcetris®)

Brentuximab vedotin (SGN-35) / Adcetris® / L01XC12

Developer/Company:

Seattle Genetics and Takeda Group

Seattle Genetics: commercialisation rights in the US and Canada; *Takeda Group:* commercialisation rights in the rest of the world

Description:

an antibody-drug conjugate directed against CD30 receptor

Brentuximab vedotin is an antibody-drug conjugate (ADC) directed against the tumour necrosis factor (TNF) receptor CD30 which is expressed on the surface of tumour cells in haematological malignancies including Hodgkin's lymphoma (HL) and anaplastic large cell lymphoma (ALCL) [1]. Brentuximab vedotin has potential antineoplastic activity and consists of three components: the chimeric immunoglobulin G1 mAb cAC10, which is specific for human CD30; the microtubule-disrupting agent monomethyl auristatin E (MMAE – a synthetic analogue of the marine natural product doastatin 10 that inhibits tubulin polymerization); and a protease-cleavable covalent linker that attaches cAC10 to MMAE [1, 2]. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex. Within the cell, MMAW is released via proteolytic cleavage. Binding of MMAW to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cells [3].

3 core components

apoptotic death of CD30 cells by cell cycle arrest

The recommended dose of brentuximab vedotin is 1.8mg/kg administered as an intravenous (i.v.) infusion over 30 minutes once every 3 weeks (= one cycle). Duration of treatment is recommended for up to 16 cycles, disease progression or unacceptable toxicities [4].

recommended dose: 1.8 mg/kg iv once every 3 weeks
max: 16 cycles

2 Indication

Brentuximab vedotin is indicated

indication:
- relapsed or refractory HL
- relapsed sALCL

- for the treatment of relapsed or refractory Hodgkin's lymphoma (HL) after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for stem cell transplantation
- and for the treatment of relapsed systemic anaplastic large cell lymphoma (sALCL) after at least one prior multi-agent chemotherapy.

3 Current regulatory status

not yet approved in Europe

In June 2011, Takeda announced that the European Medicines Agency (EMA) has accepted the marketing authorisation application of Adcetris™ for the treatment of relapsed or refractory HL and relapsed or refractory sALCL for review [5]. Brentuximab vedotin has received orphan drug designation for the treatment of cutaneous T-cell lymphoma in January 2011 [6].

08/2011: accelerated FDA approval for relapsed or refractory HL and relapsed sALCL ...

In August 2011, the US Food and Drug Administration (FDA) approved brentuximab vedotin (Adcetris®) for the following two indications:

- for the treatment of patients suffering from HL after failure of autologous stem cell transplantation (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates;
- for the treatment of patients with sALCL after failure of at least one multi-agent chemotherapy regimen.

... based on response rates in 2 single-arm phase II studies

Brentuximab vedotin was approved for both indications based on response rates assessed in two phase II single-arm trials [7]. Data presenting improvements in patient reported outcomes or survival with brentuximab vedotin are not yet available [4, 7]. In January 2007, the FDA granted orphan drug designation for brentuximab vedotin for the treatment of patients with HL [8] and in March 2009, fast track designation for the same indication was given [9].

4 Burden of disease

lymphomas are a heterogeneous type of malignant haematological disorders

Lymphomas are a type of malignant haematological disorders characterised by malignant cells generally originating from the lymph nodes. Depending on the histology, type and stage of the disease, lymphomas can be curable. Overall lymphomas are divided in Hodgkin's lymphoma (HL; or Morbus Hodgkin) and Non-Hodgkin's lymphoma (NHL) based on the presence or absence of the Reed-Sternberg-Cells (RS cells) [10]. HL is characterised by the presence of RS cells which carry the antigen CD30 acting as an integral membrane glycoprotein at their surface in 98.4% of all HL cases [11].

Hodgkin's Lymphoma

HL accounts for ~30% of all lymphomas

bimodal age-specific incidence pattern

HL accounts for approximately 30% of all lymphomas and presents with a bimodal age-specific incidence pattern: patients between 15-35 years and patients aged >55 years [7]. The incidence of HL is 3 per 100,000 inhabitants annually, with men generally more often affected than women [10].

widely unknown aetiology

The aetiology of HL is generally unknown. Because of presence of the Epstein-Barr-Virus (EBV) DNA in the RS cells (40% in industrialised countries and 90% in developing countries), infections with the EBV are associated to play an important role for the development of HL [10]. At time of diagnosis >90% of patients present with a painless enlargement of lymph nodes, spleen or other immune tissues and with B-symptoms (fever >38°C, unexplained weight loss >10% of body weight within 6 months and night sweat). Other symptoms that might be present at diagnosis in 2-10% of HL cases are pruritus, fatigue, appetite loss and painful lymph nodes induced by alcohol [7, 10].

symptoms: painless enlargement of lymph nodes, spleen, B symptoms

median 5-year survival: >90%

Overall, HL is considered to be a highly curable disease with a median 5-year survival rate of >90% [12]. Despite good initial responses to therapy about 10-15% of patients with early stage disease and about 40% of patients with advanced-stage disease will relapse [11, 13].

high cure rate

About >85% of HL patients achieve long-term remissions (>90% in the localized and 70 - 80% in the advanced stages of the disease [12, 14]). Patients not achieving a remission or relapsing after initial therapy are eligible for high-dose chemotherapy with subsequent autologous hematopoietic stem cell transplantation (ASCT). About 30% of these patients then achieve long term remission [10] and up to 40% of patients that received ASCT will relapse [7]. Patients in late relapse which are re-treated with chemotherapy achieve long-term disease-free survival in 50% of cases [14, 15].

40% will relapse after HSCT

Ann Arbor classification for the staging of HL

Based on the Ann Arbor staging classification for Hodgkin and non-Hodgkin lymphomas, four disease stages (stage I, II, III and IV) can be distinguished. Additionally, different sub-classifications are added to describe the characteristics of the disease in more detail. For example the letters A and B are added to the stage for the absence (A) or presence (B) of B symptoms [16, 17], the letter X is added when the bulk is >10 cm and E indicating extra-nodal disease [18]. Patients suffering from HL are usually classified in the following three groups: early stage favourable disease (stage I and II with no unfavourable factors), early stage unfavourable disease (stage I and II with any unfavourable factor such as large mediastinal adenopathy, B symptoms, numerous sites of disease, or significantly elevated erythrocyte sedimentation rate (ESR)), and advanced stage disease (stage III and IV) [7, 19].

unfavourable factors that reduce survival rates

Unfavourable prognostic factors in early stage HL are mediastinal bulk, presence of B symptoms, >3 nodal sites of disease or an ESR of 50 or more [19]. In addition to that, seven unfavourable factors that reduce survival rates by 7% to 8% per year have been identified for advanced stage of HL: age ≥45 years, male gender, stage IV disease, albumin level below 4 g/dL, leucocytosis (white blood cell count more than 15,000/mm^3), lymphocytopenia (lymphocyte count less than 8% of the white blood count and/or lymphocyte count less than 600/mm^3) [19].

~15HL pts require third-line chemotherapy in Austria per year

In 2009, 161 patients (79 men and 82 women) were newly diagnosed with HL in Austria [20]. Applying the above mentioned estimates, about 15 HL patients will require third-line therapy in Austria per year.

Systemic Anaplastic Large Cell Lymphoma (sALCL)

ALCL is a rare and aggressive type of NHL

3 sub-types: primary cutaneous; ALK-positive and ALK-negative

ALK status of prognostic relevance

40-65% will require 2nd-line therapy

Anaplastic large cell lymphomas (ALCL) are a rare, aggressive and heterogeneous type of non-Hodgkin's Lymphoma (NHL). ALCL account for approximately 2-3% of all NHLs and for about 12% of all peripheral T-cell lymphomas (PTCL) [11, 21, 22]. The World Health Organisation's (WHO) classification of haematopoietic tumours and lymphoid tissues breaks down ALCL into three sub-types: primary cutaneous (localized) ALCL and primary systemic (widespread) anaplastic lymphoma kinase (ALK-)positive ALCL and ALK-negative ALCL [21, 23, 24]. About 60% of ALCL patients present ALK-positive disease [24, 25]. Overall, ALCL has a considerable superior survival compared to other PTCLs which is mainly driven by the improved prognosis of ALK-positive patients compared to ALK-negative disease (5-year failure-free survival (FFS), 60% vs. 36%, p=0.015; and 5-year overall survival (OS), 70% vs. 49%, p=0.016, respectively) [23]. Response to initial ALCL therapy is usually of short duration and approximately 40-65% of patients will develop recurrent disease. A complete remission based on second-line therapy is achieved by approximately 25-30% of initially recurrent patients [26]. In ALK-positive ALCL median age at diagnosis is 35 years and men are more often affected than women; the median age of patients at diagnosis in ALK-negative disease is 61 years with no gender predominance [21].

B symptoms and advanced stage of disease

The majority (75%) of ALK-positive ALCL patients present with B symptoms and advanced stage of disease (stage III or IV) at time of diagnosis [21, 24]. ALCL frequently involves both lymph nodes and extranodal sites (50-80%). The most common extranodal site is skin (21-35%), followed by bone (17%), soft tissue (17%), lung (11%), bone marrow (10%) and liver (8%) [24].

ALK positivity and IPI of prognostic relevance

Ann Arbor staging

In ALCL, the most important prognostic indicator is ALK positivity. Also the International Prognostic Index (IPI) is of prognostic relevance in ALCL, despite it is validated in patients with diffuse-large B-cell lymphoma and not an appropriate prognostic tool for T-cell lymphomas overall [24]. The IPI provides a prognostic score based on clinical and laboratory factors taking age, elevated serum LDH, performance status, stage of the disease (Ann Arbor staging) and extranodal involvement into account [25]. Depending on the amount of presenting risk factors four risk groups (low, low intermediate, high intermediate and high) are distinguished [27].

~15 patients in Austria per year

In Austria, 1,125 patients (577 men and 548 women) were diagnosed with NHL in 2009 [28]. Applying the above mentioned estimates, there are about 15 ALCL patients eligible for second-line therapy in Austria per year.

5 Current treatment

Hodgkin's lymphoma

HL is a highly curable disease

Overall, HL is considered to be a highly curable haematological malignancy due to a significant progress in the management of HL patients in the past few decades. As a result of the development major treatment considerations in newly diagnosed HL patients nowadays often relate to the long-term toxicity, especially for patients with early- or intermediate-stage disease [29]. Despite these advances, about 30-40% of patients with advanced stage of the disease will relapse or are refractory to primary treatment [9].

long-term toxicities of major importance in treatment management

monitoring of potential secondary malignancies

Initial therapy of HL typically consists of chemotherapy and/ or radiation therapy depending on the stage of the disease, patient's age and presence of risk factors [14, 29]. After completion of initial therapy follow-up is essential in order to monitor late effects such as secondary malignancies (e.g. lung cancer, breast cancer), cardiovascular disease, hypothyroidism and fertility issues [19].

second-line therapy:

- high-dose chemotherapy followed by ASCT

Patients who relapse on or who are refractory to first-line therapy will then receive multi-agent chemotherapy with subsequent ASCT [30].

In order to reduce the tumour burden and to mobilize stem cells prior to high-dose chemotherapy and ASCT, the following salvage regimens are given:

salvage treatment

- DHAP – dexamethasone / high-dose ara-C / cisplatin
- IGEV – ifosfamide / gemcitabine / vinorelbine / dexamethasone
- ICE – ifosfamide / carboplatin / etoposide [30].

Subsets of patients e.g. low-risk patients relapsing after primary treatment with two cycles of chemotherapy followed by radiotherapy or patients with localized late relapse, can be successfully salvaged with a second more intensive conventional therapy (i.e. BEACOPPescalated) or radiotherapy alone, respectively [30].

However, about 40-50% of these patients will relapse again and have a poor prognosis with a median survival of 2 years from time of relapse to post-ASCT [9, 14, 31].

Patients who are resistant to chemotherapy are not considered candidates for ASCT [32]. For patients not being eligible for ASCT or who relapse following an ASCT, no EMA or FDA approved agent exists. In the absence of randomized controlled trials (RCTs) investigating the efficacy of therapeutic options in that setting, no specific recommendations for the care of these patients can be made and therefore, enrolment in a clinical trial is recommended [9, 14, 19]. Novel agents such as small molecule inhibitors, antibodies or immunotoxins as single agents or in combination with conventional chemotherapy play an increasingly important role in the palliative setting of HL treatment [30].

treatment goals vary from palliation to durable remission

For now, the major goals for the treatment of patients who are refractory or relapse after ASCT range from palliation of symptoms in relatively young patients to near-complete eradication of lymphoma cells to enable durable remission [9].

Systemic anaplastic large cell lymphoma

currently no FDA approved drugs for the treatment of ALCL

ALK+: CHOP

ALK-: no recommended 1st-line regimen

Besides brentuximab vedotin, there are currently no FDA approved drugs specifically for systemic ALCL. The current standard of care for first-line treatment of ALK-positive ALCL is CHOP, a combination regimen of the four chemotherapeutic drugs cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone [26]. Generally, the prognosis in this group of patients is so good that transplants should only be considered at relapse [24, 33]. ALK-negative ALCL is less well characterized than ALK-positive ALCL. Currently the management is the same as for ALK-positive ALCL but as outcomes are less favourable it is recommended that the standard management should become the same as that for PTCL not otherwise specified (PTCL-NOS) a subgroup of PTCLs [24]. Despite disappointing results with conventional chemotherapy including CHOP in these subgroups of PTCL patients, CHOP remains besides enrolment onto a clinical trial the most commonly used first-line treatment as to date no preferred or most effective treatment for non-ALK-positive PTCLs has been established [24].

enrolment onto a clinical trial recommended

Patients relapsing after first-line therapy should be treated with a platinum-based therapy or enrolled onto a clinical trial. Further second-line therapy options are dependent on whether patients are eligible for stem cell transplantation or not. Generally, only PTCL patients that relapse or are primary refractory and have chemo-sensitive disease are considered to be transplant candidates [24, 34].

several treatment options available (category 2A recommendation)

Second-line therapy options for chemo-resistant patients and thus being non-candidates for stem cell transplantation are alemtuzumab, bortezomib, brentuximab vedotin for nodal ALCL only (excluding cutaneous ALCL), denileukin diftitox, gemcitabine, pralatrexate, radiation therapy or romidepsin [27]. At this point it has to be mentioned that, whereas pralatrexate was approved for the treatment of relapsed or refractory PTCL by the US FDA in 2009, the EMA refused approval in 2012 for this indication due to concerns whether the benefits of pralatrexate could outweigh its risks [35] and is thus not available in Europe. Romidepsin for the treatment of relapsed or refractory PTCL is currently under approval review by the EMA and was approved for this indication by the US FDA in June 2011 based on response rates investigated in two single-arm phase II studies [36-38].

pralatrexate and romidepsin not available in Europe

treatment goal is palliative

superiority of one agent over another is not known yet

Treatment of patients who are not transplant candidates, who fail to respond to second-line chemotherapy regimens, or who relapse after transplant has a palliative intent. Data supporting the use of most agents are limited [17]. At present, no single chemotherapy regimen is clearly superior to any other in the setting of relapsed disease. Outside the context of a clinical trial, the selection of treatment should be based upon expected toxicities, patient comorbidities and convenience. For most patients with relapsed or refractory PTCL, the administration of a traditional chemotherapy regimen rather than the use of a novel agent is suggested. This preference is based upon the higher response rates seen with traditional agents and the knowledge that patients who achieve a complete response have a chance of long-term survival with transplantation. Novel agents are typically reserved for subsequent relapses [17].

traditional agents preferred over novel agents

6 Evidence

A literature search was conducted on January 3rd, 2012 in four databases (The Cochrane Library, EMBASE, Ovid, and CRD Database) yielding 28 references overall. In addition a hand search was performed including web-sites of the EMA and the FDA.

literature search in 4 databases

Considered were only those studies which had enrolled patients with relapsed or refractory HL or relapsed sALCL, resulting in two phase II single-arm trials presented in the FDA approval documents [7, 26]. While compiling this report the pivotal trial SG035-0003 for HL has been fully published by Younes et al. [14].

2 single-arm phase II studies included

6.1 Efficacy and safety – pivotal studies

Hodgkin's lymphoma

Table 6.1-1: Efficacy of the SG035-0003 trial (Hodgkin's lymphoma)

Study title A pivotal study of SGN-35 in treatment of patients with relapsed or refractory Hodgkin lymphoma (HL) [7, 9, 14, 39]		
Study identifier	SG035-0003 trial – single arm, phase 2 trial; NCT00848926	
Design	Single-arm, open-label, multicenter, pivotal phase II	
	Duration	Enrolment: February 2009 – August 2009 Median follow-up: 23.5 months [39] Cut-off date: primary analysis August 2010, subsequent cut-off date: March 2011 [7, 14]
Hypothesis	Single-arm study With a sample size of 100, a 29% ORR (CR +PR) would allow the Sponsor to state with 95% confidence (2-sided) that the true ORR is greater than 20%. Assuming the true ORR is 35%, the study would have approximately 90% power.	
Funding	Seattle Genetics	
Treatment groups	Intervention	Brentuximab vedotin 1.8 mg/kg administered as a single IV infusion over 30 minutes on day 1 of each 21-day cycle. Patients (pts) were allowed to continue on study treatment until disease progression or unacceptable toxicity. Pts who achieved a stable disease or better were allowed to receive a minimum of 8, but no more than 16 cycles of study treatment
	Control	- (no control group)

Endpoints and definitions*	Overall objective response rate per an independent review facility (IRF) *(primary outcome)*	ORR	Sum of the complete and partial remission rates (CR and PR)
	Complete remission	CR	Complete disappearance of all detectable clinical evidence of disease. This includes lymphadenopathy, splenomegaly, hepatomegaly, bone marrow involvement and disease-related symptoms if present before therapy.
	Partial remission	PR	Greater than 50% decrease in the size of the index lesions. Per imaging charter, index lesions are typically the largest dominant nodes or nodal masses, and are most representative of the patient's disease. Up to 6 index lesions were quantitatively identified per patient.
	Stable disease	SD	Failure to attain CR/PR or PD, no new sites of lesions.
	Relapsed disease or progressive disease	PD	Any new lesion or increase by ≥50% of previously involved sites from nadir
	Duration of Response	DOR	DOR is defined as the time from start of the first documentation of ORR to the first documentation of objective tumour progression or to death due to any cause, whichever comes first.
	Progression-free survival per IRF	PFS	Time from start of study treatment to disease progression per independent review group or death due to any cause.
	Overall survival	OS	Time from start of study treatment to date of death due to any cause.
<u>Results and analysis</u>			
Analysis description	Intent-to-treat analysis The complete remission was derived and its two-sided 95% exact confidence interval was calculated using the F distribution method (Collet 1991). Time-to-Event outcomes were estimated using the Kaplan-Meier methodology. The median duration of response, duration of response in the subset of patients achieving CR, PFS, OS and their two-sided 95% CI by Brookmeyer and Crowley were calculated.		
Analysis population	Characteristics	*Demographic parameters* 102 patients from 25 sites Mean age, years (SD): 34 (12); 75% of patients were aged between 18-39 years, 3 % were aged ≥65 years Male vs. female, n (%): 48 (47) vs. 54 (53) Caucasian vs. non-caucasian, n (%): 89 (87) vs. 13 (13) ECOG PS 0 (no symptoms) vs. 1 (symptomatic but fully ambulatory), n (%): 42 (41) vs. 60 (59) *Baseline disease characteristics* Stage I/II/III/IV (%): 4/46/26/20 Disease stage relative to most recent prior therapy (%): Relapse: 58; Refractory: 42 Prior cancer-related therapies Number of systemic chemotherapy regimens (excluding ASCT), median (range): 3.5 (1 to 13) 1 / ≥2 ASCT, n (%): 91 (89) / 11 (11) Time from initial diagnosis to first dose, months (range): 39.9 (11.8 to 219.7) Time to relapse from ASCT, n(%) ≤1 year: 72 (71) >1 year: 30 (29) Bone marrow involvement, n (%): 8 (8) B symptoms present, n (%): 35 (34)	

		Prior radiation therapy, n (%): 67 (66) Histology subtype, n (%): Nodular sclerosing: 63 (62) Mixed cellularity: 5 (5) Lymphocyte-rich: 3 (3) Lymphocyte-depleted: 3 (3) Not otherwise specified (NOS): 28 (27)	
	Inclusion	- Pts with relapsed or refractory HL who have received ASCT at least 12 weeks (3 months) before first dose of brentuximab and completed any prior treatment with radiation, chemotherapy, biologics and/or other investigational agents at least 4 weeks prior to first dose of SGN-35; must have completed any prior immunotherapy (e.g., rituximab) or radioisotopic therapy at least 12 weeks prior first dose of SGN-35 in the absence of clear disease progression - Histologically-documented CD30-positive disease - Age ≥18 years OR ≥12 years enrolled at US sites - ECOG performance status 0 or 1	
	Exclusion	- Previous treatment with SGN-35 - Previously received allogeneic HSCT - Congestive heart failure, Class III or IV, by the NYHA criteria - History of another malignancy that has not been in remission for at least 3 years (except: nonmelanoma skin cancer, curatively treated localized prostate cancer, and cervical carcinoma in situ) - Known cerebral/meningeal disease - Any active viral, bacterial, or fungal infection requiring treatment with antimicrobial therapy within two week prior to first dose of SGN-35 - Current therapy with any other systemic anti-neoplastic or investigational agents; - Therapy with corticosteroids at greater than or equal to 10mg/day prednisone equivalent within 1 week prior to the first dose of SGN-35	
Descriptive statistics and estimated variability		*Applicant's endpoint results (ITT population) [7]*	*FDA endpoint results (ITT population) [7]*
	Number of subjects	n=102	n=102
	ORR, n (%; 95% CI) CR, n (%; 95% CI) PR, n (%; 95% CI) SD , n (%; 95% CI)	76 (74.5; 64.9 to 82.6) 35 (34.3; 25.2 to 44.4) 41 (40.2; 31.5 to 49.4) 22 (22; NA) [14]	74 (72.5; 63.9 to 80.1) 33 (32.4; 23.3 to 42.3) 41 (40.2; 31.5 to 49.4) NA
	Median DOR, months (95% CI) ORR (n=74) CR (n=33) PR (n=40)	NA	 6.7 (4 to 14.8) 20.5 (12 to NE) 3.5 (2.2 to 4.1)
	Median PFS per IRF, months (95% CI)	5.6 (5 to 9)	NA
	Median duration of OS, months (95% CI)	22.4 (21.7 to NE)	NA

**responses were assessed using the 2007 Cheson response criteria [40] for malignant lymphoma. The applicant defined "refractory" disease as a response of stable disease (SD) or progressive disease (PD) to the most recent prior therapy and "primary refractory" disease as failure to achieve CR or disease progression within 3 months of first-line therapy. Thus, the applicant's definition of refractory in SG035-0003 trial should not be interpreted as not responding to all lines of therapy [7].*

Abbreviations: 95% CI – 95% confidence interval; SD – standard deviation; NE – not evaluable, NA – not available

Table 6.1-2: Incidence of most frequent (>10%) treatment-emergent adverse events of the SG035-0003 trial [7]

		SG035-0003 (n=102)	
Grade (according to CTC version 3.0)	**Outcome (%)**	**Any Grade**	**Grade 3-4**
	Neutropenia	54	21
	Peripheral sensory neuropathy	52	8
	Fatigue	49	3
	Upper respiratory tract infection	47	0
	Nausea	42	0
	Diarrhoea	36	1
	Anaemia	33	10
	Fever	29	2
	Thrombocytopenia	28	9
	Rash	27	0
	Abdominal pain	25	3
	Cough	25	0
	Vomiting	22	0
	Headache	19	0
	Arthralgia	19	0
	Pruritus	17	0
	Myalgia	17	0
	Peripheral motor neuropathy	16	4
	Constipation	16	0
	Insomnia	14	0
	Back pain	14	0
	Dyspnoea	13	1
	Alopecia	13	0
	Chills	13	0
	Night sweats	12	0
	Anxiety	11	2
	Dizziness	11	0
	Decreased appetite	11	0
	Lymphadenopathy	11	0
	Oropharyngeal pain	11	0
Other Outcomes (%)			
	Serious AE	25	
	Treatment discontinuation due to: Completion of 16 cycles Progressive disease AEs Stem cell transplant Other	 18 49 21 9 5	
	Grade 3/4 treatment-emergent AEs	55	

The SG035-0003 trial was the pivotal trial leading to accelerated FDA approval of brentuximab vedotin for the treatment of HL patients after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens. Overall, 102 patients from 25 different sites with a mean age of 34.1 (SD 12) years were included. The majority (75%) of patients was aged 18-39 years. 71% of patients relapsed less than one year from the time of transplant. 66% of patients received prior radiation therapy, 35% had B symptoms at baseline and all patients were confirmed to have CD30-positive disease [7].

102 HL pts from 25 sites

Approval is based on response rates observed in this single-arm phase II clinical trial. The median duration of brentuximab treatment was 27 weeks (range 3 to 56 weeks) with a median number of 9 (range 1 to 16) cycles administered per patient. 75% of patients had an objective response (complete or partial remission) with a median duration of 6.7 months. Notably, 34% of patients achieved complete remission with a median duration of 20.5 months.

OOR: 75%

median duration of ORR: 6.7 months (mths)

No deaths occurred within 30 days of the last dose of brentuximab vedotin; 25 (25%) patients experienced serious adverse events (SAE); 21 (21%) patients discontinued treatment due to AEs; 56 (55%) patients had a grade 3 or 4 treatment-emergent adverse event. The most common adverse event leading to treatment discontinuation (12 patients) and dose reduction (10 patients) was peripheral neuropathy; overall 56 patients in the SG035-0003 trial developed neuropathy. Other SAEs included hyperglycaemia, gastrointestinal haemorrhage, grade 3-4 pneumonitis and pulmonary embolism [31]. 47 protocol violations (e.g. therapy with tipifarnib 27 days prior brentuximab vedotin therapy, lower/higher dose of brentuximab vedotin, concomitant medication, study conduct (e.g. missing neck CT), informed consent, SAE reporting) were reported in the FDA medical review.

25% of patients suffered from SAEs

peripheral neuropathy of major concern

47 protocol violations

Sub-group analyses for ORR and CR were conducted but should be interpreted with caution due to the small number of patients overall which further limits the subgroup analysis. It was shown that the treatment effects of brentuximab vedotin on ORR an CR were consistent for gender, age group, US sites, B symptoms and time to relapse post-transplant [7].

subgroup analyses have to be interpreted with caution

Systemic Anaplastic Large Cell Lymphoma

Table 6.1-3: Efficacy of the SG035-0004 trial (systemic anaplastic large cell lymphoma)

Study title A phase II study of SGN-35 in treatment of patients with relapsed or refractory systematic anaplastic large cell lymphoma (ALCL) [26, 41]		
Study identifier	SG035-0004 trial – single arm, phase 2 trial; NCT00866047	
Design	Single-arm, open-label, multicenter (22 sites in 5 countries: Belgium, Canada, France, UK, US)	
	Duration	Enrolment: June 2009 to May 2010 Maximum duration of follow-up: 17.5 months [41] Cut-off date for final analysis: January 14, 2011 [26]
Hypothesis	Single-arm study	
Funding	Seattle Genetics	

Treatment groups	Intervention	Brentuximab vedotin, 1.8 mg/kg administered as a single IV infusion over 30 minutes on day 1 of each 21-day cycle. Patients (pts) were allowed to continue on study treatment until disease progression or unacceptable toxicity. Pts who achieved a stable disease or better were allowed to receive a minimum of 8, but no more than 16 cycles of study treatment.	
	Control	- (no control group)	
Endpoints and definitions	Overall objective response rate per an independent review facility (IRF) *(primary outcome)*	ORR	Percentage of participants who achieved a best response of complete remission (CR, disappearance of all evidence of disease) or partial remission (PR, regression of greater than or equal to 50% of measurable disease and no new sites) per Cheson 2007 Revised Response Criteria for Malignant Lymphoma [40].
	Complete remission	CR	Percentage of participants who achieved a best response of CR (disappearance of all evidence of disease) per Cheson 2007 Revised Response Criteria for Malignant Lymphoma. This includes lymphadenopathy, splenomegaly, hepatomegaly, bone marrow involvement and disease-related symptoms if present before therapy.
	Partial remission	PR	Greater than 50% decrease in the size of the index lesions. Per imaging charter, index lesions are typically the largest dominant nodes or nodal masses, and are most representative of the patient's disease. Up to 6 index lesions were quantitatively identified per patient.
	Stable disease	SD	Failure to attain CR/PR or PD.
	Relapsed disease or progressive disease	PD	Any new lesion or increase by ≥50% of previously involved sites from nadir.
	Duration of Response	DOR	DOR is defined as the time from start of the first documentation of ORR to the first documentation of objective tumour progression or to death due to any cause, whichever comes first.
	Progression-free survival per IRF	PFS	Time from start of study treatment to disease progression per independent review group or death due to any cause.
	Overall survival	OS	Time from start of study treatment to date of death due to any cause.
<u>Results and analysis</u>			
Analysis description	**Intention-to-treat (ITT) analysis**		
Analysis population	Characteristics	- Median age, years (range): 52 (14 to 76) - Males vs. females, n (%): 33 (57) vs. 25 (43) - Caucasians, n (%): 48 (83) - ECOG PS 0 / 1 / 2, n (%): 19 (33) / 38 (66) / 1 (2) - Relapsed / refractory* disease, n (%): 29 (50) / 29 (50) - ALK-negative disease, n (%): 42 (72) - Median number of prior therapies, n (range): 2 (1 to 6) - Prior ASCT, n (%): 15 (26) - Baseline B symptoms, n (%): 17 (29) - Baseline bone marrow involvement, n (%): 8 (14)	
	Inclusion	- Patients with relapsed or refractory ALCL who had previously received front-line chemotherapy (CHOP or multi-agent chemotherapy regimens with curative intent) - Documented ALK-status - Histologically-confirmed CD-30 disease - Age ≥18 years; except in the US and Canada where patients ≥12 years of age were enrolled	

		- previous ASCT at least 12 weeks prior to the first study dose; completed any treatment with radiation, chemotherapy, biologics and/or other investigational agents at least 4 weeks prior to the first dose of SGN-35, unless progressing on therapy; completed any prior immunotherapy (e.g., monoclonal antibody) or radioisotopic - ECOG PS 0 or 1
	Exclusion	- Previous treatment with SGN-35 - Previous allogeneic transplant - Current diagnosis of primary cutaneous ALCL unless transformed to systemic ALCL - Congestive heart failure, class III or IV, by the NYHA criteria - History of another primary malignancy that has not been in remission for at least 3 years; except for non-melanoma skin cancer, curatively localized prostate cancer, cervical carcinoma in situ - Known cerebral/meningeal disease - Any active Grade 3 or higher viral, bacterial or fungal infection within 2 weeks prior to the first dose of SGN-35 - Women who are pregnant or lactating - Patients with a known hypersensitivity to any excipient contained in the drug formulation - Patients with dementia or an altered mental state that would preclude the understanding and rendering of informed consent
Descriptive statistics and estimated variability		
	Number of subjects	n=58
	ORR, n (%; 95% CI) CR n (%; 95% CI) PR n (%; 95% CI)	50 (86; 77 to 95) 33 (57; 44 to 70) 17 (29; 18 to 41)
	Median DOR, months (95% CI) ORR (n=50) CR (n=33) PR (n=17)	 12.6 (5.7 to NE) 13.2 (10.8 to NE) 2.1 (1.3 to 5.7)
	Median PFS per IRF, months (95% CI) [41]	13.3 (6.9 to NA)
	Median duration of OS, months (95% CI) [41]	NA (14.6 to NA)

**Patients were defined to have refractory disease if they had a best response of PR, SD or PD if a patient had only one prior therapy, or best response of SD or PD to the most recent prior therapy if a patient had more than one prior therapy. According the applicant, patients were considered to have primary refractory disease if they had no CR or if they relapsed within 3 months of front-line therapy. As this is not a commonly accepted definition of refractory disease the FDA medical reviewer sought to adjudicate the patient's disease status based upon more commonly accepted definitions of refractory and primary refractory, yielding 11 patients with primary refractory disease; 2 with refractory to last line of treatment; 15 had relapsed disease and the status of 1 is unknown. Factors leading to these discrepancies were that the applicant assigned response after extremely short periods of exposure to prior treatment regimens (e.g.: in 9 cases exposure to prior lines of therapy were one cycle only), that the response of PR to prior therapy was not considered as a response in 5 subjects although the overall response rate in the applicant's trial SG035-004 counted PR in the primary endpoint of ORR and that the response to prior therapies was unknown in one patient [26].*

Table 6.1-4: Incidence of most frequent (>10%) adverse events of the SG035-0004 trial [26]

Grade (according to CTC version 3.0)	Outcome (%)	Any Grade	Grade 3-4
	Treatment emergent adverse events	100	
	Blood and lymphatic system disorders		
	Neutropenia	55	12
	Anaemia	52	2
	Thrombocytopenia	16	10
	Lymphadenopathy	10	-
	Nervous system disorders		
	Peripheral sensory neuropathy	53	10
	Headache	16	2
	Peripheral motor neuropathy	7	3
	Dizziness	16	-
	General disorders and administrative site disorders		
	Fatigue	41	4
	Pyrexia	38	2
	Chills	12	-
	Night sweats	9	-
	Pain	28	5
	Infections and infestations		
	Upper respiratory tract infection	12	-
	Gastrointestinal disorders		
	Nausea	38	2
	Diarrhoea	29	3
	Abdominal pain	9	2
	Vomiting	17	3
	Constipation	19	2
	Oropharyngeal pain	9	-
	Skin and subcutaneous tissue disorders		
	Rash	31	-
	Pruritus	19	-
	Alopecia	14	-
	Dry skin	10	-
	Respiratory, Thoracic and Mediastinal Disorders		
	Cough	17	-
	Dyspnoea	19	2
	Musculoskeletal and Connective Tissue Disorders		
	Arthralgia	9	-
	Myalgia	16	2
	Back pain	10	2
	Pain in extremity	10	4
	Muscle spasms	10	2
	Edema peripheral	16	-

	Psychiatric Disorders		
	Insomnia	16	-
	Anxiety	7	-
	Metabolism and Nutrition Disorders		
	Decreased appetite	16	2
	Investigations		
	Weight decreased	12	3
Other Outcomes, n (%)			
	Serious AE	23 (40)	
	Treatment discontinuation due to: Completed 16 cycles Disease progression Adverse events Investigator decision Patient decision	49 (84) 3 (5) 13 (22) 14 (24) 14 (24) 5 (9)	
	Grade 3/4 AEs	36 (62)	
	Deaths within 30 days	6 (12)	

Overall 58 patients with CD30-positive disease and a median age of 52 (range 14 to 76) years were included in the ITT analysis; 72% of patients had ALK-negative disease 57% of included patients were male. 33%, 66% and 2% of patients had ECOG performance status 0, 1 and 2, respectively. All of the patients have received previous therapy.

72% of pts had ALK-negative ALCL

Though, 2 patients had CD30-positive disease but not ALCL (1 HL and 1 lymphoproliferative disorder) and one patient was considered un-evaluable because of eligibility criteria violation and dose violation they were not included in the ITT analysis. 3 patients completed the maximum allowable number of cycles of therapy (=16); 9 (16%) patients were continuing therapy with brentuximab vedotin at time of data cut-off and 49 patients had discontinued therapy.

protocol violations

The overall response rate was 86% with a median duration of 12.6 months and CR was achieved by 57% of patients with a median duration of CR of 13.2 months. Having in mind, that median duration of response of PR was 2.1 months, the duration of response appears to be driven by the patients who achieved complete remissions. At time of data cut-off the median PFS was 13.3 months (95% CI 6.9 to not available). The upper bound of the PFS analysis and median OS could not be estimated due to insufficient number of events at the time of data cut-off [41].

ORR: 86%

median duration of ORR: 12.6 months …

… mainly driven by those who achieved CR

All of the subjects of the SG035-0004 trial had systemic ALCL although a majority (72%) had ALK-negative disease. Generally, ALK-negative disease is associated with a worse prognosis than ALK-positive disease. In this trial, a subgroup analysis showed similar response rates between the two groups (88% vs. 81%) [26].

similar response rates of ALK-negative and ALK-positive ALCL

most frequent grade 3/4 AEs: neutropenia, thrombocytopenia and peripheral sensory neuropathy

The most common grade 3/4 AEs were neutropenia, thrombocytopenia and peripheral sensory neuropathy was observed in almost half of the patients. Peripheral sensory neuropathy had not completely resolved by the end of treatment and/or long-term follow-up visits in 23 of 28 patients [26]. 40% of patients suffered from serious adverse events and 84% of patients discontinued treatment due to several reasons. More than half of these patients discontinued therapy due to disease progression or adverse events. Overall the limitations inherent to a single-arm trial do not allow the concise attribution of adverse reactions to the therapy without a randomized controlled trial and therefore, the safety profile has not been fully characterized.

84% of pts discontinued therapy

applicant's definition of "refractory disease" does not correlate with the commonly used and accepted definition

Another issue raised in the medical review of the FDA approval documents is, that the applicant applied a definition of "refractory" disease that does not correlate with the commonly used definition. For details about the discrepancy of the definition please refer to the explanation right after Table 6.1-3. Due to these reasons each patient was "re-labelled" by the FDA based on the available data. Of the 29 (50%) patients having refractory disease according to the applicant, 3 were considered to suffer from refractory disease by FDA's medical reviewer; the remaining were rated as relapsed (n=15), primary refractory (n=11; =refractory to first-line therapy which not necessarily was the previous therapy) and unknown (n=1).

6.2 Efficacy and safety - further studies

no further studies included

No further studies meeting our inclusion criteria were identified.

7 Estimated costs

one 3-week cycle of brentuximab treatment is estimated to cost around EUR 10,000.-

Brentuximab vedotin is approved at a dose of 1.8mg/kg administered once every three weeks (= one cycle). It is available in single-use vials of 50mg. Thus for the treatment of a patient of 70 to 80 kg body weight three vials will be required. The price for nine single-use vials of 50mg brentuximab vedotin is EUR 30,000.- and thus one 3-week cycle of therapy for a patient with 70 to 80 kg body weight would be EUR 10,000.-.

90,000.- to 100,000.- for median duration of treatment according to pivotal trials

According to the FDA label brentuximab vedotin is recommended for a maximum of 16 treatment cycles which would result in EUR 160,000.-; median duration of therapy in the two open-label single-arm phase II trials were 9 and 10 months, resulting in EUR 90,000.- and EUR 100,000.- estimated treatment costs.

8 On-going research

one ongoing phase III trial in HL patients identified

One on-going phase III trial assessing the efficacy and safety of brentuximab vedotin in HL was found at ClinicalTrials.gov. No phase III trial evaluating brentuximab in HL was identified on the EU Clinical Trials Register; to

date, no phase III trial investigating brentuximab vedotin in sALCL is registered in one of these trial registries.

comparison of brentuximab + BSC versus placebo + BSC

NCT01100502: The AETHERA trial is a double-blind placebo-controlled, randomized phase III trial investigating the efficacy and safety of brentuximab vedotin and best supportive care (BSC) compared to placebo plus BSC in patients with residual HL after autologous stem cell transplantation (ASCT). The study started in April 2010 and plans to enrol 322 patients. The estimated primary completion date is June 2013 and the study completion date is planned for April 2016.

No further phase III trials evaluating brentuximab vedotin in other indications were found. Several phase II trials investigating brentuximab vedotin as a single agent or in combination with BSC or chemotherapy in different lines of therapy (e.g. first-line, in refractory patients, prior or after stem cell transplantation) in hematologic are ongoing.

9 Commentary

brentuximab vedotin

… not yet approved in Europe

… since August 2011 approved in the US for HL and sALCL

Brentuximab vedotin is currently not approved in Europe but Takeda has announced, that they submitted the marketing authorisation application in June 2011. In August 2011, the US FDA approved brentuximab vedotin under the accelerated approval scheme for the treatment of patients with HL after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates and for the treatment of patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen [4].

discrepancies in the definition of "refractory disease"

The marketing authorisation holder initially submitted the marketing authorisation application for brentuximab for relapsed and refractory HL and sALCL. As the definition of primary refractory disease and refractory disease to prior therapy/ies was not consistent with a widely accepted definition of refractory disease by the medical community, those patients initially labelled as "refractory", were "re-labelled" by the US FDA's medical reviewer based on the available data. Within the SG035-0003 trial 88% of patients classified as having refractory disease by the applicant, had a response of CR or PR to earlier lines of therapy and 65% of patients classified as primary refractory disease had a response of CR or PR to subsequent lines of therapy. Only 9 of 102 patients never had a response of PR or CR to any line of therapy [7]. The same discrepancy was observed in patients in the SG035-0004 trial, where 29 (50%) patients were initially classified as having "refractory" disease. After re-labelling 11 patients were classified as having primary refractory disease, 2 were refractory to last line of therapy, 15 had relapsed disease and the status of one was unknown [26].

FDA-approval based on two single-arm open-label phase II trials with ORR as the primary efficacy endpoint

The FDA-approval is based on two single-arm phase two studies; one study in patients with HL (n=102) and one in patients with sALCL (n=58). Originally the applicant requested regular approval for brentuximab vedotin, but the FDA favoured the accelerated approval based on a recommendation by the Oncologic Drugs Advisory Committee (ODAC) to require RCTs for regular approval and as the pivotal trial SG035-0004 was small and of single arm design which limited the comprehensiveness of the safety and efficacy analysis. Further, the accelerated approval scheme will allow access to brentuximab vedotin for patients who have limited treatment options for their rare disease in the absence of RCTs and at the same time confirmatory trials that could incorporate randomization which would enhance the safety and efficacy profiles and thus understanding of this new drug can be requested [7, 26, 31]. Accelerated approval is intended for new therapies for a "serious or life-threatening illness" which is expected to have a meaningful therapeutic benefit to patients over existing treatments. The accelerated approval pathway accepts surrogate endpoints that are reasonably likely to predict clinical benefit. As described above, there are currently no specifically approved drugs available and there is no consistent standard of care for these two indications defined. Due to this unmet medical need, accelerated approval based on two single-arm phase II studies was granted. At the time of marketing authorisation, only an on-going confirmatory trial for the treatment of HL was registered but not for sALCL [26]. The submission of a study protocol by the marketing authorisation holder for a randomized phase III trial investigating the safety and efficacy of brentuximab in combination with chemotherapy compared to chemotherapy alone in patients with CD30-positive T- and NK-cell lymphomas including ALCL is expected by December 2012 [26].

accelerated approval for "serious or life-threatening illness"

currently no consistent standard of care established for HL and sALCL

achieved ORR in both trials considered to be clinically relevant

Overall, the response rates (75% and 86% in HL and sALCL, respectively) in both trials were considered as clinically relevant. Complete remissions were achieved by 34% and 57% in HL and sALCL patients, respectively. Duration of ORR was 6.7 months and 12.6 months in HL and sALCL patients, respectively. Overall duration of response appears to be driven by those patients who achieved a complete remission as the duration of response in these patients was 20.5 months and 13.2 months in HL and sALCL patients, respectively.

duration of ORR mainly driven by CR

reliable estimates for time-to-event endpoints such as PFS and OS were not possible

Due to the single-arm design of the study neither time-to-event endpoints such as progression-free survival and overall survival nor observed adverse events can be reliably estimated [26]. A further limiting factor was the small sample size of both studies. Thus, efficacy evaluation in these two single-arm trials was limited to response rates and duration of response, as these outcomes represent a direct treatment effect of the drug [7].

Also patient reported outcomes such as B symptoms (fever, night sweats, or unexplored weight loss) cannot be adequately evaluated in these trials because of (1) lack of validated instruments for patient reported outcomes and (2) the open-label nature of a single-arm trial [7].

limited characterisation of safety and efficacy due to trial design

Overall, the small population included and the single-arm design as well as the endpoint of response rate do not allow to fully characterize the safety and efficacy profile of brentuximab vedotin based on the available data [26] [31].

The most common treatment-emergent adverse events (TEAEs), occurring in ≥10% of either HL or systemic ALCL patients, in the phase 2 studies are summarized in Table 6.1-2 for HL and in Table 6.1-4 sALCL. TEAEs occurring in ≥20% of patients were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhoea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily grade 1 or 2, with the exception of neutropenia, for which grade 3 and Grade 4 events were reported for 13% and 7% of patients, respectively. Similar patterns and incidence rates of adverse events were observed for HL and systemic ALCL patients, with the exception of a higher incidence of upper respiratory tract infections in HL patients. In the phase II studies, 31% of patients had a serious adverse event (SAE), 28% had a SAE of Grade 3 or higher, and 15% had a SAE that was determined by the investigator to be related to brentuximab vedotin [9].

most frequent TEAEs: peripheral sensory neuropathy, fatigue, nausea, diarrhoea, pyrexia, upper respiratory tract infection, neutropenia and vomiting

Additional confirmatory trials will add important information to the safety and efficacy profile of brentuximab vedotin. As already mentioned above, the risk-benefit assessment within the accelerated approval scheme of the US FDA aims at balancing two important variables in granting an accelerated marketing approval for brentuximab vedotin: on the one hand the new biological entity will be made available to patients with limited treatment options, and on the other hand the applicant is required to continue to collect mature data on response to brentuximab and its safety profile and to conduct further trials to further investigate the safety and efficacy of brentuximab vedotin. These confirmatory trials will be a randomized trials which will enhance the characterization of risk-benefit analysis [26].

additional trials will add more information on the safety and efficacy profile of brentuximab vedotin

For now, there are impressive initial response rates shown for these two indications that lack a definite standard of care. Patients achieving a CR benefit from a median duration of response of 1 to 2 years. However, a superior survival rate or an improvement in quality of life has not been proven. The long term safety profile and the possible benefit of combining brentuximab vedotin with conventional chemotherapy have to be determined. Therefore, phase III clinical trials are mandatory and enrolment of patients in clinical trials is recommended.

despite impressive initial response a lot of open questions remain

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