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Brentuximab vedotin (Adcetris) for treatment naïve Hodgkin's Lymphoma

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LAY SUMMARY

Lymphoma is the most common blood cancer, which occurs if cells of the immune system, a type of white blood cell, grow and multiply uncontrollably. Hodgkin's lymphoma, with which about 20% of all lymphoma patients are diagnosed, affects the lymphatic system. The disease usually occurs in individuals either aged 20 to 25 or over 70 years. Symptoms include swelling lymph nodes in the neck, armpit or groin, recurring fever, night sweats, weight loss, cough, breathlessness, abdominal pain and itching.

First-line treatment consists of chemotherapy alone or in combination with radiotherapy and can lead to long-term remission in 70 to 85% of patients. Brentuximab is a type of monoclonal antibody (MA). MAs target particular proteins on the cancer cells surface. Brentuximab targets a protein called CD 30, it sticks to the CD30 protein and delivers a drug to the cell. The drug then kills the cell. Early trials suggest that patients may find treatment with brentuximab easier to tolerate.

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TARGET GROUP

- treatment naïve advanced Hodgkin's Lymphoma patients

TECHNOLOGY

DESCRIPTION

Brentuximab vedotin [Adcetris; b-vedotin; brentuximab vedotin; SGN-35; SGN35] is an antibody-drug conjugate (ADC) comprised of an anti-CD30 monoclonal antibody attached by an enzyme-cleavable linker to the antimicrotubule agent monomethyl auristatin E (MMAE). The ADC employs a novel linker system that is designed to be stable in the bloodstream but to release MMAE upon internalization into CD30-expressing tumor cells. It is developed by Seattle Genetics for the treatment of haematologic malignancies, including Hodgkin's lymphoma (HD) and some types of non-Hodgkin's lymphoma (NHL) expressing CD30, such as anaplastic large cell lymphoma (ALCL). A previous lead in the series, SGN-25, was under development for carcinoma. Brentuximab vedotin also previously showed potential in autoimmune disorders such as multiple sclerosis and systemic lupus erythematosus. A companion diagnostic has been co-developed with brentuximab vedotin to evaluate CD30 expression levels in tissue specimens.

In Phase III clinical trial Brentuximab vedotin is administered 1.2 mg/kg by IV infusion on Days 1 and 15 of each 28-day cycle.1

Brentuximab vedotin is currently licensed in the EU for patients with relapsed or refractory CD30 Hodgkin's Lymphoma following autologous stem cell transplant or other prior treatments.

In current trials, Brentuximab Vedotin is tested in combination with Adriamycin, vinblastine and dacarbazine for treatment naïve patients (first-line treatment) with advanced state of Hodgkin's Lymphoma.

INNOVATION and/or ADVANTAGES

If licensed, Brentuximab Vedotin will offer a novel additional treatment option for patients with treatment naïve advanced Hodgkin's Lymphoma.

DEVELOPER

Takeda UK Ltd.

AVAILABILITY, LAUNCH or MARKETING

Brentuximab vedotin for Hodgkin's lymphoma is currently in Phase III clinical trials.

PATIENT GROUP

BACKGROUND

Hodgkin's Lymphoma is a cancer of the lymphatic system arising from cancerous B lymphocyte cells. Of all diagnosed lymphomas, about 20% are diagnosed as Hodgkin's Lymphoma. The disease usually occurs in people aged 20 to 25 and over 70 years old. In the UK (2011) a total of 1517 people were

treated for Hodgkin's Lymphoma. Symptoms include swelling lymph nodes in the neck, armpit or groin. Recurring fever, night sweats, weight loss, cough, breathlessness, abdominal pain and itching might occur. First line treatment consists of chemotherapy alone or in combination with radiotherapy and can lead to long-term remission in 70 to 85% of patients treated.[2]

Lymphoma is the most common blood cancer. Besides Hodgkin's Lymphoma, Non- Hodgkin's Lymphoma is the second main form of this type. Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. A tumour can form in different parts of the body. Hodgkin's Lymphoma is divided into two categories: classical HL, which accounts to 90-95% of cases, and nodular lymphocyte predominant HL.[3]

CLINICAL NEED and BURDEN OF DISEASE

For the UK, the incidence of Hodgkin's Lymphoma was 2,106 new cases in 2014 (57% male/43% female). The crude incidence rate shows that there are 4 new Hodgkin's Lymphoma cases for every 100,000 males in the UK and 3 for every 100,000 females. Since 1990 the UK incidence rate has increased by 31%. However, the condition accounts for less than 1% of all cancers in the UK. Age distribution shows that there are two peaks in incidence rates – young adults (20 to 25) and older adults (>70 years). The incidence rates for Hodgkin's Lymphoma have been predicted to rise by 5% in the UK between 2014 and 2035.[4]

People with non-Hodgkin-Lymphoma have an increased risk of HL. Patients who have Epstein Barr Virus have a 40% chance of developing HL. First degree relatives with HL, non-HL or chronic lymphocytic leukaemia are under an increased risk of getting HL themselves. It is yet unknown whether this stems from an inherited gene change or shared lifestyle factors. Research has shown an increased risk of HL in overweight people or individuals who smoke.[5]

Survival rates depend on many different factors, such as the individual condition, type of cancer, treatment and level of fitness. However, based on a 2012 British review paper resulting from large international trials, stage 1 and 2 patients are expected to survive for 5 years or more in 90% after diagnosis. In stage 3 and 4 this number is lower with 75% and 90%, respectively.[6]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal in development. Pembrolizumab for classical Hodgkin lymphoma [ID1062]. Expected February 2018.
- NICE Technology appraisal in consultation. Nivolumab for treating relapsed or refractory classical Hodkin Lymphoma [ID972]. Expected July 2017.
- NICE Technology appraisal in development. Lymphoma (Hodgkin's, CD30-positive) – brentuximab vedotin [ID722]. Expected May 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2014 Clinical Commissioning Policy: Use of Plerixafor for Stem Cell Mobilization (Update). B04/P/b

OTHER GUIDANCE

No guidance is currently available.

CURRENT TREATMENT OPTIONS

Hodgkin's Lymphoma can be cured, over 80% of the patients survive for 5 years. The most common treatment is some form of chemotherapy, and sometimes radiation therapy, as their first treatment. ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) is recommended as front-line therapy with or without radiation therapy, depending on a patient's stage of HL as well as the overall health status. The Stanford V regimen, which consists of doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone, is usually used for the treatment of more advanced HL. BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) is also suggested for more advanced stages. In a relapsed or refractory setting stem cell transplantation may be used.[3]

Brentuximab Vedotin was approved in 2011 by the FDA for the treatment of relapsed or refractory HL after failure of stem cell transplantation or after failure of two previous chemotherapy regimens in patients who are not eligible for stem cell transplantation. Brentuximab Vedotin was also approved by the FDA in 2015 as a consolidation treatment after autologous stem cell transplantation in patients with HL who are at high risk of disease relapse or progression.

In 2016, FDA approved the use of nivolumab for the treatment of patients with classic HL that has relapsed or progressed after autologous stem cell transplantation and post- transplantation brentuximab vedotin.[3]

Hodgkin's disease may be successfully treated with high dose chemotherapy followed by autologous transplantation of peripheral blood stem cells (PBSC). A small number of these treatments are prevented from proceeding because it is not possible to collect enough cells. Plerixafor is suggested to be used instead of a second, stronger chemotherapy attempt in order to collect enough cells.[7]

Many other promising therapies are currently under investigation in clinical trials for HL including:[3]

- Bendamustine (Treanda)
- Gemcitabine (Gemzar)
- Ifosfamide (Ifex)
- Mocetinostat (MGCD0103)
- Panobinostat (Farydak)
- Pembrolizumab (Keytruda)

EFFICACY and SAFETY

Trial	EudraCT Number:2011-005450-60 NCT01712490 UKCRN ID:13505
Sponsor	Seattle Genetics, Takeda/Takeda Oncology
Status	Closed.
Source of Information	Trialtrove
Location	EU (incl. UK), USA and Canada and other countries.

Design	Randomised, efficacy, safety, pharmacokinetics, open-label, active comparator, immunogenicity, multiple arm.
Participants	N= 1334. >18 years. Patients with advanced classical Hodgkin's Lymphoma who have not been previously treated with systemic chemotherapy or radiotherapy. Treatment naïve, HL patients with Ann Arbor Stage III or IV disease. ECOG performance status < or =2.
Schedule	Experimental: A+AVD A+AVD consists of brentuximab vedotin (ADCETRIS) 1.2mg/kg plus doxorubicin 25mg/m^2, vinblastine 6mg/m^2, and dacarbazine (DTIC) 375mg/m^2 Assigned Intervention: Brentuximab vedotin 1.2mg/kg by IV infusion on days 1 and 15 of each 28-day cycle Doxorubicin 25mg/m^2 by IV infusion on days 1 and 15 of each 28-day cycle Vinblastine 6mg/m^2 will be administered by IV infusion on days 1 and 15 of each 28-day cycle Dacarbazine 375mg/m^2 by IV infusion on days 1 and 15 of each 28-day cycle Active Comparator: ABVD consists of doxorubicin 25mg/m^2, bleomycin 10units/m^2, vinblastine 6mg/m^2, and dacarbazine 375mg/m^2 Assigned Intervention: Doxorubicin 25mg/m^2 by IV infusion on days 1 and 15 of each 28-day cycle Bleomycin 10 units/m^2 by IV infusion on days 1 and 15 of each 28-day cycle Vinblastine 6mg/m^2 will be administered by IV infusion on days 1 and 15 of each 28-day cycle Dacarbazine 375mg/m^2 by IV infusion on days 1 and 15 of each 28-day cycle Patients will receive Adcetris plus AVD or ABVD The study treatment will be given for up to 6 cycles. Each cycle is made up of 28 days, and dosing will be given on both day 1 and day 15 of each 28-day cycle.
Follow-up	Not reported.
Primary Outcomes	To evaluate Adcetris plus AVD versus ABVD in front-line advanced Hodgkin's Lymphoma patients.
Secondary Outcomes	To compare the modified progression-free survival obtained with brentuximab vedotin plus AVD versus that obtained with ABVD for the frontline treatment of advanced classical HL. Overall survival rate.
Key Results	Not reported.
Adverse effects (AEs)	Not reported.
Expected reporting date	Not reported.

Trial	NCT01716806
Sponsor	Bristol-Myers Squibb, Seattle Genetics
Status	Open.
Source of Information	Trialtrove
Location	Canada, USA
Design	Efficacy, safety, pharmacokinetics, open label, multiple arm

Participants	N=69 (as of October 22,2016). Elderly patients with histopathologically-confirmed newly diagnosed HL with no prior treatment. ASH 2013 Treatment-naïve patients with classical HL (Stages I-IV). Median age was 75 years (age range 64-92) and approximately half of the patients were male (54%). Seven patients had moderate age-related renal insufficiency at baseline. ASH 2014 Median age for all pts was 77years, 58% were male, and 27% had ECOG 2-3. Most had stage III-IV disease (70%) and 48% had moderate age-related renal insufficiency at baseline. ASH 2015: 70 treatment-naïve pts aged > or = 60 years with HL (30 monotherapy, 20 for each combination) are to be enrolled. ISHL 2016: Patients aged > or= 60 years with newly diagnosed HL. Median age was 76 years (age range 62-92). At baseline, 70% of patients had Stage III-IV HL, 13% presented with bulky disease, 41% had B symptoms, 25% had ECOG 2-3, and 72% were ineligible for frontline chemotherapy.
Schedule	Arm 1: Experimental: Brentuximab Vedotin Assigned Interventions: Brentuximab Vedotin 1.8 mg/kg every 3 weeks by IV infusion Arm 2: Experimental: Brentuximab Vedotin + Dacarbazine Assigned Interventions: B-Vedotin 1.8 mg/kg every 3 weeks by IV infusion Dacarbazine 375mg/m^2 every 3 weeks by IV infusion Arm 3: Experimental: Brentuximab Vedotin + Bendamustine Assigned Interventions: B-Vedotin 1.8 mg/kg every 3 weeks by IV infusion Bendamustine 70mg/m^2 by IV infusion on days 1 and 2 of 3 week cycle Arm 4: Experimental: Brentuximab vedotin + Nivolumab Assigned Interventions: B-Vedotin 1.8 mg/kg every 3 weeks by IV infusion Nivolumab 3 mg/kg every 3 weeks bi IV infusion ASH 2014 For monotherapy, B-Vedotin 1.8mg/kg is administered every 3 weeks for up to 16 or more cycles in pts achieving stable disease or better. For combination therapy, dacarbazine 375 mg/m^2 I given for cycles 1-12, followed by monotherapy for cycles 13-16. Pts with unacceptable toxicity to dacarbazine prior to completion of 12 cycles may receive monotherapy for total of 16 cycles or more. ASH 2015: Bretuximab vedotin 1.8mg/kg is administered every 3 weeks for up to 12 cycles with DTIC (375mg/m^2) up to 6 cycles with benda (90 or 70 mg/m^2) ISHL 2016: The study evaluated cohorts of 1.8mg/kg BV (16 cycles), 1.8 mg/kg BV=375 mg/m^2 DTIC (12 cycles), and 1.8 mg/kg BV+90 or 70 mg/m^2 bendamustine (starting dose reduced to improve tolerability after 10 patients treated) (6cycles). Patients with clinical benefit could subsequently continue BV treatment.
Follow-up	Not reported.
Primary Outcomes	Efficacy and tolerability of ADCTRIS as a monotherapy for older HL patients who have received no prior treatment. Side effects of B-vedotin in HL pts.
Secondary Outcomes	Objective response rate. Incidence of AEs.
Key Results	Both BV monotherapy and BV+DTIC appear tolerable and yield high response rates in this fragile patient population. Furthermore, the combination with DTIC appears to increase the durability of response without increasing toxicity; and therefore, may represent a reasonable frontline treatment option for elderly HL patients. Other treatment combinations are being considered.

Adverse effects (AEs)	Not reported.
Expected reporting date	-

TIMATED COST and IMPACT

COST

The cost of Brentuximab Vedotin is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: improved patient convenience

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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