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Rovalpituzumab tesirine (SC16LD6.5) for the treatment of relapsed or refractory small cell lung cancer

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LAY SUMMARY

Small cell lung cancer (SCLC) is a type of lung cancer that usually develops in the central part of the lungs, and in which the cancer cells are small compared with other types of lung cancer. SCLC is almost always caused by smoking. The cancer is difficult to detect in the early stages of the disease, and the majority of the patients are diagnosed when the cancer has spread and cannot be removed by surgery.

In England and Wales approximately 10% of patients diagnosed with lung cancer each year are found to have SCLC. This represents around 3,000 new cases per year.

SCLC is a life-threatening disease that is associated with poor long-term survival.

Rovalpituzumab tesirine is a new antibody-drug conjugate that binds to delta-like protein 3(DLL3) present in the cancer cells of most small cell lung cancer patients. This drug works by attacking and killing cancer cells, limiting the growth of tumours due to SCLC. This drug is being currently studied as third line therapy for patients that get worse after treatment with other therapies such as chemotherapy or radiotherapy.

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TARGET GROUP

Small cell lung cancer: relapsed or refractory; delta-like protein 3-expressing cancer; third line or later.

TECHNOLOGY

DESCRIPTION

Rovalpituzumab tesirine (SC16LD6.5) is a first-in-class DLL3-targeted antibody-drug conjugate (ADC) consisting of the humanized DLL3-specific IgG1 monoclonal antibody SC16, the DNA cross-linking pyrrolobenzodiazepine (PBD) dimer toxin (SC-DR002 [D6.5]), and a protease-cleavable linker that covalently links SC-DR002 to SC16.

The primary mechanism of rovalpituzumab tesirine is binding of the ADC to DLL3 on target-expressing cells, followed by internalization of the ADC-DLL3 complex and release of SC-DR002 via proteolytic cleavage in late endosomes. Interstrand crosslinks of cellular DNA induced by intercalated SC-DR002 leads to cellular cytotoxicity.

When injected into the patient, the medicine is expected to attach to the cancerous cells. The medicine is then expected to release the toxic component inside the cells, causing them to die.

In the completed phase I/II dose escalation trial (NCT01901653), rovalpituzumab tesirine was administered intravenously in doses ranging from 0.05 to 0.8 mg/kg either every three weeks or six weeks, followed by investigation of the dose schedules 0.3 mg/kg and 0.4 mg/kg every 6 weeks and 0.2 mg/kg every 3 weeks.[1,2] A subsequent Phase II trial (NCT02674568) evaluating the efficacy, safety and pharmacokinetics of rovalpituzumab tesirine for third-line and later treatment of subjects with relapsed or refractory delta-like protein 3-expressing small cell lung cancer (TRINITY), is due to be completed by 2020.

Rovalpituzumab tesirine is also being evaluated in a phase I/II trial for the treatment of DLL3 expressing advanced solid tumours (NCT02709889). Additional studies assessing the safety and efficacy of rovalpituzumab tesirine in SCLC and other tumour types include:

- A phase I study in the frontline treatment of SCLC (NCT02819999)
- A phase I study in combination with immunotherapy for the treatment of SCLC (NCT03026166)
- A phase I safety study focusing on cardiac ventricular repolarization (NCT02874664)
- A phase III study for the second-line treatment of SCLC (NCT03061812)
- A phase III study evaluating rovalpituzumab tesirine as maintenance therapy following first-line platinum based chemotherapy in subjects with extensive stage SCLC (NCT03033511)
- A phase I/II study for the treatment of DLL3-expressing advanced solid tumours (NCT02709889)

INNOVATION and/or ADVANTAGES

If licensed, rovalpituzumab tesirine will offer an alternative treatment option with manageable toxicity, which has demonstrated encouraging single-agent anti-tumour activity and durability in recurrent or refractory SCLC.[2]

DEVELOPER

AbbVie; Aceso Biologics Consulting Ltd. are the EMA licence holders.

AVAILABILITY, LAUNCH or MARKETING

Rovalpituzumab tesirine has been granted orphan drug status by the European Medicines Agency (EMA) in June 2016.[3]

PATIENT GROUP

BACKGROUND

Small cell lung cancer (SCLC) belongs to the high-grade pulmonary neuroendocrine tumours which represent approximately 18% of primary lung neoplasms, predominantly developed in older patients with a history of smoking.[4] SCLC remains among the most deadly malignancies because no new therapeutic options have emerged for this indication in more than 30 years [5] and because it grows rapidly and usually at the time of diagnosis has already spread beyond the lung. [6] SCLC survival is measured in months, with a 5-year survival rate of less than 5%.[4] The treatment of SCLC remains a challenge, despite remarkable initial efficacy of combination chemotherapy and radiation therapy. The response is usually short-lived and the prognosis of SCLC has not changed over the past few decades. [7]

CLINICAL NEED and BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK (2014), accounting for 13% of all new cases. It is the second most common cancer in both males (14% of all male cases) and females (12% of all female cases).[8]

In England and Wales approximately 10% of patients diagnosed with lung cancer each year are found to have SCLC. This represents around 3,000 new cases per year.[6] SCLC frequently responds to treatment with chemotherapy but in the majority of patients, whilst length of life can be extended, the cancer is not curable.[6]

The clinical benefits from second line chemotherapy for patients with SCLC who relapse after primary treatment are uncertain and it is administered with palliative intent. In general, patients with a good performance status and those who have responded to first-line chemotherapy are more likely to be considered suitable for second line treatment. [6]

In 2015-2016, there were 89,945 hospital admissions due to lung cancer (ICD code C-34), resulting in 266,522 bed days and 110,013 finished consultant episodes.

Lung cancer patients with a known stage are most commonly diagnosed at stage IV (49-53%). More people with a known stage are diagnosed at a late stage (72-76% are diagnosed at stage III or IV), than at an early stage (24-28% are diagnosed at stage I or II).[8]

A total of 35,895 lung cancer deaths were registered in the UK in 2014. Incidence of this form of lung cancer is decreasing over time as it is most strongly related to tobacco smoking.[9]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab for small-cell lung cancer after platinum-based chemotherapy (GID-TA10158). Expected July 2018.
- NICE technology appraisal. Topotecan for the treatment of relapsed small-cell lung cancer (TA184). November 2009.

- NICE guidelines. Suspected cancer: recognition and referral (NG12). June 2015.
- NICE guidelines. Lung cancer: diagnosis and management (CG121). April 2011

- NICE quality standard. Lung cancer in adults. March 2012.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2016 Clinical Commissioning Policy: Robotic assisted lung resection for primary lung cancer. 16024/P
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a

OTHER GUIDANCE

- American Society of Clinical Oncology. Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline. 2015.[10]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[11]
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. Small cell lung cancer: NCCN evidence blocks version 3. 2017.[12]
- London Cancer Alliance. LCA lung cancer clinical guidelines. 2013.[13]
- European Society for Medical Oncology (ESMO). Small-cell lung cancer (SCLC). Clinical practice guidelines for diagnosis, treatment and follow-up. 2013.[14]
- British Thoracic Society and the Society for Cardiothoracic Surgery in Great Britain and Ireland (BTS/SCTS). Guidelines on the radical management of patients with lung cancer. 2010.[15]

CURRENT TREATMENT OPTIONS

NICE clinical guideline (CG121) recommends the use of four to six cycles of cisplatin-based combination chemotherapy as first line treatment for limited-stage disease. This can be replaced by carboplatin on those patients with impaired renal function, poor performance status or significant comorbidity.[16] Radical thoracic radiotherapy can be added during the first or second cycle of chemotherapy. Sequential radical thoracic radiotherapy can be offered to patients unfit for concurrent chemotherapy. Surgery can be considered in patients with early-stage SCLC (T1–2a, N0, M0).

First line treatment when the disease has reached extensive-stage consists of platinum-based combination chemotherapy up to a maximum of six cycles, depending on response and toxicity. Thoracic radiotherapy should be considered after chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax. Prophylactic cranial irradiation can be offered to those patients in limited or extensive-stage disease if their disease has not progressed on first-line treatment.

As second line treatment, when the disease has relapsed, patients who are suitable for chemotherapy are offered treatment with an anthracycline-containing regimen or further treatment with a platinum-based regimen up to a maximum of six cycles. Radiotherapy is used for palliation of local symptoms. [16]

Currently there are no approved treatments for SCLC in refractory patients. [a]

EFFICACY and SAFETY

Trial	NCT01901653; SCRX16-001	NCT02674568; SCRX001-002; TRINITY
Sponsor	Stemcentrx and AbbVie Inc.	Stemcentrx and AbbVie Inc.
Status	Complete and published[17]	Recruiting
Source of Information	Lancet Oncology,[17] trial registry [18]	Trial registry[19]
Location	USA	USA, France, Germany, Hungary, Poland, Spain.
Design	Non-randomised/uncontrolled	Non-randomised/uncontrolled
Participants	N=74 with SCLC; aged over 18; male and female; either limited or extensive disease; progressive disease during or following 1 or 2 prior chemotherapy regimens.	N=154 (planned); aged over 18; male and female; disease progression after at least 2 prior systemic regimens; third-line and later relapsed or refractory delta-like protein 3 (DLL3) expressing small cell lung cancer.
Schedule	Rovalpituzumab tesirine was administered as a single agent, at increasing dose levels (0.05-0.8 mg/kg every 3 weeks or every 6 weeks with expansion cohorts at 0.3 mg/kg and 0.4 mg/kg every 6 weeks and 0.2 mg/kg every 3 weeks) as permitted based on real-time assessment of safety and tolerability, intravenously over 30 minutes.	Rovalpituzumab tesirine intravenously on Day 1 of each 6 week cycle for 2 cycles follow by end of treatment visit and long term follow-ups
Follow-up	Doses will be repeated every 3 weeks or every 6 weeks. [17]	Not reported
Primary Outcomes	For the phase 1 dose escalation: Maximum Tolerated Dose and Dose Limiting Toxicities; For the phase 2 dose escalation: RECIST v1.1 Assessed Objective Response Rate.	Objective response rate; Overall survival for subjects.

[a] Information provided by company.

Secondary Outcomes	Pharmacokinetics and immunogenicity; Progression Free Survival; Overall Survival.	Clinical Benefit Rate; Duration of Response; Progression-free Survival.
Key Results	The recommended phase 2 dose and schedule is 0·3 mg/kg every 6 weeks. At active doses of rovalpituzumab tesirine (0·2 mg/kg or 0·4 mg/kg every 3 weeks or 0·3 mg/kg or 0·4 mg/kg every 6 weeks), 11 (18%) of 60 assessable patients had a confirmed objective response, including ten (38%) of 26 patients confirmed to have high DLL3 expression (expression in 50% or more of tumour cells). [17]	-
Adverse effects (AEs)	The most frequent grade 3 or worse treatment-related adverse events in 74 patients with small-cell lung cancer were thrombocytopenia (eight [11%]), pleural effusion (six [8%]), and increased lipase (five [7%]). Drug-related serious adverse events occurred in 28 (38%) of 74 patients.[17]	-
Expected reporting date	Published in January 2017.	January 2020

ESTIMATED COST and IMPACT

COST

The cost of rovalpituzumab tesirine is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ 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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