NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
AUGUST 2020

Lurbinectedin in addition to doxorubicin for small-cell lung cancer after prior platinum-containing therapy

NIHRIO ID	8200	**NICE ID**	9761
Developer/Company	Pharma Mar SA	**UKPS ID**	646849

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Lurbinectedin in addition to doxorubicin is in clinical development for the treatment of adults with small-cell lung cancer (SCLC) who have progressed after prior platinum-containing therapy. SCLC is an aggressive type of lung cancer that is associated with smoking. The condition is often diagnosed at a late stage, when the cancer has spread to other parts of the body (extensive-stage). If patients are fit enough, they may be given chemotherapy as first-line treatment, although the cancer will usually return quickly.

Lurbinectedin is expected to work by breaking down an enzyme called 'RNA polymerase II', which plays a key role in the production of proteins that are needed for the cell to grow and multiply. Small cell lung cancer cells have high levels of these proteins, which make the cells grow uncontrollably. By breaking down RNA polymerase II, lurbinectedin reduces production of these growth-related proteins and so reduces the growth of the cancer. If licensed, this combination could be an effective treatment option for a patient group with clear unmet need.

PROPOSED INDICATION

Adults with small-cell lung cancer (SCLC) who have progressed after prior platinum-containing therapy.[1,]

TECHNOLOGY

DESCRIPTION

Lurbinectedin (Zepsyre, PM01183) is a synthetic analog of the natural marine-based tetrahydroisoquinoline trabectedin. It contains a pentacyclic skeleton composed of two fused tetrahydroisoquinoline rings, with an additional tetrahydro β-carboline moiety. Lurbinectedin induces a specific degradation of transcribing RNA Pol II and the subsequent accumulation of DNA breaks. This degradation is dependent on active transcription, the presence of functional proteasome machinery and transcription-coupled nucleotide excision repair. Furthermore, in transcriptionally addicted tumours cells (e.g., SCLC), lurbinectedin-caused detachment of transcription factors (e.g., ASCL1, NeuroD1, and NFIB in SCLC) from their target promoters, including the block of its transactivating activity. Lurbinectedin may also target the tumour microenvironment via suppression of tumour proliferation, matrix remodelling, angiogenesis and immune suppression.[2]

Lurbinectedin in addition to doxorubicin is currently in phase III clinical development for the treatment of adults with SCLC who have progressed after prior platinum-containing therapy. In phase III clinical trial (ATLANTIS; NCT02566993), participants in the experimental arm are treated with doxorubicin 40.0 mg/m^2 on day 1, followed by lurbinectedin 2.0 mg/m^2 on day 1 of each 21-day cycle. A maximum of ten cycles of doxorubicin-containing regimens are allowed. Then, if applicable, doxorubicin will be discontinued and for patients in the experimental arm, lurbinectedin will be continued as maintenance therapy at a dose of 3.2 mg/m^2 (or 2.6 mg/m^2 if more than one dose reduction was applied while on combination therapy) on day 1 of each 21-day cycle. All patients will receive primary G-CSF prophylaxis, with type, dose and scheme according to institutional standard practices and guidelines.[1,2] Further information of the dosing regimen and administration schedule assessed are detailed in the clinical trial table section of this briefing.[1]

INNOVATION AND/OR ADVANTAGES

Therapeutic options for SCLC are limited. First-line standard chemotherapy is a combination of etoposide or irinotecan with platinum. SCLC is usually sensitive to the initial treatment; however, most patients develop recurrent disease, often with additional sites of metastasis after initial treatment.[3]

Lurbinectedin is a synthetic analogue based on the unique features of trabectedin. The main difference is attributed to the substitution of the tetrahydroisoquinoline with a tetrahydro β-carboline, resulting in increased antitumour activity of lurbinectedin. The mechanism of action of lurbinectedin is similar to that of trabectedin, since it also binds to guanine-rich sequences in the promoters of actively transcribed genes, inhibiting oncogenic transcription.[4]

In transcription-addicted tumours in which disease drivers are oncogenic transcription factors (e.g., SCLC, which is driven by ASCL1, NEUROD1, and NFIB), lurbinectedin can cause the detachment of those transcription factors from their target promoters, blocking their transactivation activity and exerting important effects upon cancer stem cells as well as on tumour micro-environment (TME).[4]

A phase I study that evaluated the efficacy of lurbinectedin and doxorubicin in patients with relapsed SCLC observed durable overall response rates (ORR) for the second-line was 91.7% Of patients with sensitive disease and in 33.3% and 20.0% of resistant disease as second- and third-line treatments respectively.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lurbinectedin either as monotherapy or in combination with doxorubicin does not currently have Marketing Authorization in the EU/UK for any indication.

Lurbinectedin was granted EU orphan drug designation in February 2019 for the treatment of SCLC.[5]

Lurbinectedin is currently in phase III and phase II clinical development for the treatment of various types of cancers including mesothelioma, solid tumours (such as ovarian cancer, sarcoma, non-small cell lung cancer, and breast cancer).[6]

PATIENT GROUP

DISEASE BACKGROUND

SCLC is an aggressive high-grade neuroendocrine tumour associated with a short doubling time, a high growth fraction, and early development of widespread metastases, which contribute to the extremely poor prognosis of patients with the disease. Among the major lung cancer subtypes, SCLC has the strongest association with smoking, with only 2% of cases occurring in never-smokers. Consequently, SCLCs have a high load of somatic mutations induced by tobacco carcinogens.[7] Quitting smoking has been related not only to a reduction in the incidence of SCLC, but also to a significant reduction in the risk of mortality. The association with smoking means that the treatment of patients with SCLC can be complicated, as they usually present with multiple important comorbidities secondary to tobacco use such as chronic obstructive pulmonary disease, ischaemic cardiopathy and hypertension, thus deteriorating their functional status.[8]

The most common presenting symptoms of SCLC are cough, chest pain, haemoptysis (coughing up blood), dyspnoea (breathlessness) and weight loss.[9] SCLC is usually classified as limited-stage or extensive-stage disease. Limited-stage SCLC is defined as disease confined to a single radiation port, with or without mediastinal lymph-node involvement, whilst in extensive-stage SCLC the disease has spread beyond a single radiation port, generally synonymous with distant metastasis.[7]

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2016.[10] In England in 2017 there were 38,888 registrations of newly diagnosed cases of malignant neoplasm of bronchus and lung (ICD-10 code C34).[11] Across the UK, incidence rates are expected to decrease from 94.41 per 100,000 in 2014 (46,400 cases) to 87.99 per 100,000 in 2035 (62,832 cases) (European age-standardised rates).[12] SCLC it makes up about 1 in 7 lung cancers (about 15%).[13]

In England, in 2018-2019, there were 128,985 finished consultant episodes (FCE) for malignant neoplasm of bronchus and lung (ICD 10: C34), resulting in 107,010 hospital admissions of which 79,628 were day cases and 249,196 were FCE bed days.[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

A multidisciplinary team should discuss the best treatment for patients with SCLC. The treatment will depend on where the cancer is, how far it has grown or spread (the stage), and general health and level of fitness of the patient. The main treatments are chemotherapy, radiotherapy, surgery, chemoradiotherapy, and symptom control treatment.[15]

- Chemotherapy is usually the main treatment for SCLC. When it is given before or with radiotherapy this is called chemoradiation.[13]
- Radiotherapy may be given before, during or after chemotherapy to treat SCLC. It may be used to control symptoms, if the cancer is more advanced or has spread. It may also be given to the head to stop any lung cancer cells that have spread growing into a secondary cancer in the brain.[13]
- Surgery is rarely used to treat SCLC, unless the cancer is small and has not spread outside the lung.[13]
- Ablation treatments use heat or laser light to treat very early lung cancers. Ablation treatment can also be used if the cancer is blocking an airway.[13]
- Supportive treatment helps relieve any symptoms caused by the cancer.[13]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the following treatments for SCLC that has relapsed after first-line treatment:[16,17]

- For people in whom chemotherapy is a suitable treatment, an anthracycline-containing regimen or further treatment with a platinum-based regimen should be offered to a maximum of 6 cycles.
- Oral topotecan is recommended as an option only for people with relapsed small-cell lung cancer for whom:[16,17]
    - re-treatment with the first-line regimen is not considered appropriate and
    - the combination of cyclophosphamide, doxorubicin and vincristine (CAV) is contraindicated (for details of the contraindications to CAV see the summary of product characteristics for each of the component drugs).

PLACE OF TECHNOLOGY

If licensed, lurbinectedin in addition to doxorubicin will offer an additional therapy option for patients with SCLC who have progressed after prior platinum-containing therapy.

CLINICAL TRIAL INFORMATION

Trial	**ATLANTIS**, NCT02566993, 2015-001641-89, PM1183-C-003-14; Phase III Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) Versus Cyclophosphamide (CTX), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients With Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line (ATLANTIS Trial) **Phase III - completed** **Location(s):** EU (including the UK), US, Canada, and other countries **Study completion date:** February 2020
Trial design	Randomised, active comparator-controlled, parallel assignment, open-label
Population	n=613; aged 18 years and older with a histologically or cytologically confirmed diagnosis of limited or extensive stage SCLC which failed one prior platinum-containing regimen and with a chemotherapy-free interval (CTFI, time from the last dose of first-line chemotherapy to the occurrence of progressive disease) ≥ 30 days. Small-cell carcinoma of unknown primary site with or without neuroendocrine features confirmed in histology test(s) performed on metastatic lesion(s) are eligible, if Ki-67/MIB-1 is expressed in >50% of tumour cells; Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2; at least three weeks since last prior anticancer treatment and adequate recovery from prior treatment toxicity; prior radiotherapy (RT): At least four weeks since completion of whole-brain irradiation, at least two weeks since completion of prophylactic cranial irradiation, and to any other site.
Intervention(s)	Patients are treated with doxorubicin 40.0 mg/m^2 on day 1, followed by lurbinectedin 2.0 mg/m^2 on day 1 of each 21-day cycle. In both arms, up to a maximum of ten cycles of doxorubicin-containing regimens are allowed. Then, if applicable, doxorubicin will be discontinued and for patients in the experimental arm, lurbinectedin will be continued as maintenance therapy at a dose of 3.2 mg/m^2 (or 2.6 mg/m^2 if more than one dose reduction was applied while on combination therapy) on day 1 of each 21-day cycle. All patients in all treatment arms will receive primary G-CSF prophylaxis, with type, dose and scheme according to institutional standard practices and guidelines.[2]
Comparator(s)	Patients receiving topotecan in the control arm are treated with topotecan at 1.5 mg/m^2 daily on days 1–5 of each 21-day cycle, with dose reductions specified for patients with creatinine clearance less than 60 ml/min. Patients receiving Cyclophosphamide, Doxorubicin and Vincristine (CAV) in the control arm are treated with cyclophosphamide 1000 mg/m^2 on day 1, doxorubicin 45.0 mg/m^2 on day 1 and vincristine 2.0 mg total FD on day 1 of each 21-day cycle.[2]
Outcome(s)	Overall survival (OS) [Time frame: Every three months up to death or study termination (approximately 10 months)]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of lurbinectedin is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Topotecan for the treatment of relapsed small-cell lung cancer (TA184). November 2009.
- NICE guideline. Lung cancer: diagnosis and management. 2019.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 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

- Royal College of Physicians. National Lung Cancer Audit Annual Report 2017 (for the audit period 2016). January 2018.[18]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer (SIGN 137). February 2014.[19]
- European Society for Medical Oncology (ESMO). Small-cell lung cancer: ESMO Clinical Practice Guidelines. June 2013.[20]

ADDITIONAL INFORMATION

REFERENCES

1 ClinicalTrials.gov. *Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) Versus Cyclophosphamide (CTX), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients With Small-Cell Lung Cancer (ATLANTIS). Trial ID*. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT02566993 [Accessed 10 February 2020].

2 Farago, A. F., Drapkin B. J., Lopez-Vilarino de Ramos J. A., Galmarini C. M., Nunez R., Kahatt C., et al. *ATLANTIS: a Phase III study of lurbinectedin/doxorubicin versus topotecan or cyclophosphamide/doxorubicin/vincristine in patients with small-cell lung cancer who have failed one prior platinum-containing line*. Future Oncol. 2019 Jan;15(3):231-9. Available from: 10.2217/fon-2018-0597 https://www.ncbi.nlm.nih.gov/pubmed/30362375

3 Yang, S., Zhang Z., Wang Q. *Emerging therapies for small cell lung cancer*. J Hematol Oncol. 2019 May 2;12(1):47. Available from: 10.1186/s13045-019-0736-3 https://www.ncbi.nlm.nih.gov/pubmed/31046803

4 Jimenez, P. C., Wilke D. V., Branco P. C., Bauermeister A., Rezende-Teixeira P., Gaudencio S. P., et al. *Enriching cancer pharmacology with drugs of marine origin*. Br J Pharmacol. 2020

Jan;177(1):3-27. Available from: 10.1111/bph.14876 https://www.ncbi.nlm.nih.gov/pubmed/31621891

5 European Medicines Agency (EMA). *Public summary of opinion on orphan designation - Lurbinectedin for the treatment of small cell lung cancer.* Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/19/2143-public-summary-opinion-orphan-designation-lurbinectedin-treatment-small-cell-lung-cancer_en.pdf [Accessed 05 February 2020].

6 ClinicalTrials.gov. *Phase II and III clinical trial.* Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Lurbinectedin+&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 05 February 2020].

7 Sabari, J. K., Lok B. H., Laird J. H., Poirier J. T., Rudin C. M. *Unravelling the biology of SCLC: implications for therapy*. Nat Rev Clin Oncol. 2017 Sep;14(9):549-61. Available from: 10.1038/nrclinonc.2017.71 https://www.ncbi.nlm.nih.gov/pubmed/28534531

8 Alvarado-Luna, G., Morales-Espinosa D. *Treatment for small cell lung cancer, where are we now?-a review*. Transl Lung Cancer Res. 2016 Feb;5(1):26-38. Available from: 10.3978/j.issn.2218-6751.2016.01.13 https://www.ncbi.nlm.nih.gov/pubmed/26958491

9 British Medical Journal Best Practice. *Small cell lung cancer.* Available from: https://bestpractice.bmj.com/topics/en-gb/1081 [Accessed 05 February 2020].

10 Cancer Research UK. *Lung cancer statistics - Lung cancer incidence.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 05 February 2020].

11 Office for National Statistics (ONS). *Cancer registration statistics, England.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 07 February 2020].

12 Cancer Research UK. *Lung cancer incidence statistics - Projections of incidence for lung cancer.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Four [Accessed 07 February 2020].

13 MacMillan Cancer Support. *What is small cell lung cancer?* Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/small-cell-lung-cancer#what_is [Accessed 07 February 2020].

14 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 07 February 2020].

15 Cancer Research UK. *Treatment for small cell lung cancer (SCLC).* Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment/small-cell-lung-cancer [Accessed 07 February 2020].

16 National Institute for Health and Care Excellence (NICE). *Lung cancer overview.* Available from: https://pathways.nice.org.uk/pathways/lung-cancer#path=view%3A/pathways/lung-cancer/treating-small-cell-lung-cancer.xml&content=view-node%3Anodes-second-line-treatment [Accessed 07 February 2020].

17 National Institute for Health and Care Excellence (NICE). *Treating small-cell lung cancer.* Available from: https://pathways.nice.org.uk/pathways/lung-cancer#path=view%3A/pathways/lung-cancer/treating-small-cell-lung-cancer.xml&content=view-node%3Anodes-subsequent-treatment [Accessed 21 August 2020].

18 Royal College of Physicians. *National Lung Cancer Audit Annual Report 2017 (for the audit period 2016).* Available from: https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2017 [Accessed 10 February 2020].

19 Scottish Intercollegiate Guidelines Network (SIGN). *Management of lung cancer (SIGN 137).* Available from: https://www.sign.ac.uk/our-guidelines/management-of-lung-cancer/ [Accessed 10 February 2020].

20 Fruh, M., De Ruysscher D., Popat S., Crino L., Peters S., Felip E., et al. *Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Ann Oncol. 2013 Oct;24 Suppl 6:vi99-105. Available from: 10.1093/annonc/mdt178 https://www.ncbi.nlm.nih.gov/pubmed/23813929

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.