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HEALTH TECHNOLOGY BRIEFING
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Plinabulin in addition to docetaxel for advanced, metastatic non-small-cell lung cancer - second line or greater

NIHRIO ID	11397	**NICE ID**	9866
Developer/Company	BeyondSpring Pharmaceuticals Inc	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Plinabulin in addition to docetaxel is in clinical development for the treatment of advanced non-small-cell lung cancer (NSCLC) as a second-line or greater therapy. NSCLC makes up the majority of lung cancers in the UK. Advanced/metastatic NSCLC is when the cancer has spread beyond the lung which was initially affected, most often to the liver, the adrenal glands, the bones, and the brain. Most patients with NSCLC are diagnosed at the stage where curative treatment with surgery is unsuitable. Current treatment options can be toxic which limits their use, a regimen with an improved safety profile would address this unmet need.

Plinabulin is an intravenously administered drug that binds to and affects the function of the protein tubulin within cells of the body. In certain cells of the immune system called Dendritic Cells (DCs) tubulin targeting with plinabulin activates a protein named GEF-H1 which boosts the ability of DCs to activate T-cells, which go on to kill cancer cells. These effects are thought to contribute towards the anti-cancer benefits of plinabulin. If licensed, plinabulin in addition to docetaxel will provide a new regimen for advanced NSCLC.

PROPOSED INDICATION

Treatment of advanced non-small cell lung cancer (NSCLC) and with at least one measurable lung lesion whose disease has progressed during or after treatment with one or two treatment regimens.[1]

TECHNOLOGY

DESCRIPTION

Plinabulin (NPI-2358) is a synthetic analogue of the diketipiperazine phenylahistin with potential antineoplastic activity, given by infusion intravenously (IV).[2] Plinabulin selectively binds to the colchicine-binding site of tubulin. Plinabulin also induces inhibition of tubulin polymerization in vascular endothelial cells, resulting in the disruption of tumour blood vessel architecture and a selective collapse of tumour vasculature.[3] Plinabulin is a potent antigen-presenting cell (such as Dendritic Cells (DC)) inducer. In DCs, plinabulin activates a protein named GEF-H1, which leads to enhanced Dendritic Cell (DC) maturation. In the presence of tumour-antigen, plinabulin's effects on DCs facilitates T-cell priming and proliferation in an antigen-specific manner, resulting in boosting of T-cells to kill cancer cells.[4] This effect is thought to contribute towards the ability of plinabulin to shrink tumours and increase patient survival.[5]

In the phase III clinical trial (NCT02504489), patients receive docetaxel 75 mg/m^2 by IV on day 1 of each cycle and plinabulin 30 mg/m^2 by IV on days 1 and 8 of the 21-day cycle. Treatment will be repeated until disease progression is detected by imaging studies or unacceptable toxicities are encountered. Patients who stop treatment with docetaxel due to toxicity or another medically acceptable reason, may continue treatment with plinabulin alone.[1]

INNOVATION AND/OR ADVANTAGES

Plinabulin, a first-in-class small molecule agent with potent immune oncology effects and vascular disruptive properties, is being developed in combination with docetaxel to address this need. Docetaxel is currently approved for NSCLC after a failure of first-line chemotherapy. However, docetaxel has an unfavourable toxicity profile that limits its use. A docetaxel-containing regimen with an improved safety profile would therefore be attractive.[6]

In a phase II study (NCT00630110), adding plinabulin to docetaxel combination mitigated docetaxel chemotherapy-induced-neutropenia (CIN) and improved docetaxel dose intensity. The neutropenia benefit was likely due to boosting bone marrow progenitor stem cells by plinabulin. In addition, preliminary results indicated a potential anti-cancer efficacy benefit of the plinabulin/docetaxel combination over docetaxel alone.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Plinabulin is not approved for any indication in the EU/UK.

Docetaxel is currently approved in the EU/UK for NSCLC after a failure of prior chemotherapy.[7]

Plinabulin and docetaxel is currently in phase III development for chemotherapy-induced neutropenia.[8]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or NSCLC. NSCLC comprises approximately 87% of lung cancers.[9] There are three common types of NSCLC; adenocarcinoma (the most common type which starts in the mucus making glands in the lining of the airways), squamous cell cancer (develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung) and large cell carcinoma (cancer cells which appear large and round under the microscope).[10] Metastatic cancer refers to cancers that have spread from where they started to other parts of the body, metastatic cancers cannot be cured.[11] In Stage III NSCLC the cancer is in more than one lobe of the lung, or it has spread to lymph nodes or nearby structures in the chest. In Stage IV the cancer has spread to the other lung or to a distant part of your body such as the liver or bones.

Common risk factors for the development of lung cancer include tobacco smoking, exposure to air pollution, radon gas, silica and asbestos, previous lung disease such as COPD and family history of lung cancer.[12]

Symptoms of lung cancer include a persistent cough (which may be more painful, have a different sound or bring up coloured mucus), shortness of breath, coughing up phlegm with blood, aches and pains in the chest or shoulder, recurrent chest infections, loss of appetite, weight loss and fatigue.[13]

CLINICAL NEED AND BURDEN OF DISEASE

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide.[14]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017. There are around 47,800 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 years (2015-2016). Incidence rates for lung cancer are projected to fall by 7% in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035.[15]

In England in 2017, there were 38,888 newly diagnosed cases of malignant neoplasm of the bronchus and lung (ICD-10 code C34).[16] According to the National Cancer Registration and Analysis Service (NCRAS), 25,777 of these cases were stage III-IV lung cancer, representing 66% of all cases for that year.[17] In the UK, it is estimated that up to 87% of lung cancer cases are NSCLC, applying this figure to the number of stage III-IV lung cancer cases diagnosed in 2017, it can be estimated that approximately 22,426 cases were NSCLC.[9]

In 2018/19 there were 107,010 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 128,985 finished consultant episodes (FCEs), resulting in 249,196 FCE bed days.[18]

In England, between 2013 to 2017, the age-standardised net cancer survival rate at 1-year for stage III and IV were 48.7% and 19.3% respectively. The age-standardised net cancer survival rate at 5-years for stage III and IV were 12.6% and 2.9% respectively.[19]

Lung cancer was one of the most common causes of cancer death in 2017, accounting for approximately 21% of all cancer deaths.[15] In 2018, there were 29,443 registrations of death from malignant neoplasms of bronchus and lung in adults in England and Wales (ICD-10 code C34).[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. At advanced stage (III and IV) NSCLC treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally include chemotherapy, targeted drugs, radiotherapy and symptom control treatment.[21] According to NICE there are specific treatment pathways for cancers positive for EGFR-TK, ALK or ROS-1 gene mutations.[22]

CURRENT TREATMENT OPTIONS

Patients with NSCLC (with no gene mutation or fusion protein) who progress after platinum-based therapy receive:[22]

- Immunotherapy treatment with pembrolizumab, nivolumab and atezolizumab
- Docetaxel with or without the multikinase inhibitor nintedanib.

PLACE OF TECHNOLOGY

If licenced, plinabulin in addition to docetaxel could provide an additional treatment option for patients with advanced NSCLC, with at least one measurable lung lesion whose disease has progressed during or after treatment with one or two treatment regimens.

CLINICAL TRIAL INFORMATION

Trial	**DUBLIN-3;** NCT02504489**;** Randomized Blinded Phase III Assessment of Second or Third-Line Chemotherapy With Docetaxel + Plinabulin Compared to Docetaxel + Placebo in Patients With Advanced Non-Small Cell Lung Cancer and With at Least One Measurable Lung Lesion **Phase III**- Recruiting **Location(s):** Australia, China, and United States. **Primary completion date of patient accrual**: December 2020
Trial design	Randomized, Parallel Assignment, Single Masking
Population	N = 554 (planned), histopathologically or cytologically confirmed NSCLC with disease progression during or after treatment with one or two treatment regimens, aged 18 years and older

Intervention(s)	Docetaxel 75 mg/m^2 and plinabulin 30 mg/m^2 (IV)
Comparator(s)	Docetaxel 75 mg/m^2 (IV)
Outcome(s)	Primary outcome: Overall Survival (OS) [Time Frame: Approximately 2 years after study initiation] See trial record for full list of other outcomes
Results (efficacy)	
Results (safety)	

Trial	NCT00630110**;** Study of the Vascular Disrupting Agent NPI-2358 in Combination With Docetaxel in Patients With Advanced Non-Small Cell Lung Cancer **Phase II** - Completed **Location(s):** Argentina, Australia, Brazil, Chile, India and the United States **Primary completion date:** June 2011
Trial design	Randomized, Parallel Assignment, Open Label
Population	N = 172, advanced NSCLC (unresectable Stage IIIb or IV) that has progressed after treatment with at least one chemotherapy regimen, aged 18 years and older
Intervention(s)	NPI-2358 (30 mg/m^2) + docetaxel (75 mg/m^2) (DN)
Comparator(s)	Docetaxel (75 mg/m^2) (D)
Outcome(s)	Primary outcome: Compare OS of patients treated with docetaxel to patients treated with docetaxel + NPI-2358 [Time Frame: Continuous] See trial record for full list of other outcomes.
Results (efficacy)[23]	• 172 patients were randomized into 2 dosing cohorts with 163 treated: 30 Cohort (50 DN; 55 D) and 20 Cohort (40 DN; 18 D). For 30 Cohort, OS (months (M)), 90% confidence interval [90% CI]) was 8.7 (6.6, 12.6) for DN and 7.5 (6.3, 10.5) for D; response rate was 14.0% for DN and 14.5% for D; and duration of response (M, 90% CI) for DN was 12.7 (4.0, 13.9) and 1.5 (1.1, 3.1) for D (p=0.049). • Results appeared better for the DN 30 Cohort vs 20 Cohort. Post hoc subset analysis identified patients with large, lung tumours (>3 cm) and 1 prior ChRx as having better survival with DN. OS (M, 95% CI) for this subset was 11.5 (7.1, 15.1) DN vs 7.8 (4.1, 17.4) D. • Patients with large, lung tumours (>3 cm) and 1 prior ChRx may be more likely to have an increased survival with DN as compared to D.
Results (safety)[23]	• The most common adverse events were nausea, fatigue, diarrhea, constipation, and anorexia. There were fewer dose reductions of D among DN patients (10%) vs D patients (18.2%). • There was a lower incidence of neutropenia in patients in the DN 30 Cohort compared to D (8.0% vs 36.4%, p<0.001) and the DN 20 Cohort compared with its companion D (7.5% vs 22.2%).

	• A post hoc analysis showed that the DN 30 Cohort (n=50) had a significantly lower incidence of ⩾ Grade 3 neutropenia vs the pooled D (n=73) at 8.0% vs 27.4%, respectively (p=0.010).

ESTIMATED COST

The cost of plinabulin is not yet known.

For docetaxel, the NHS indicative price varies between suppliers and according to the concentration. For example, the cost of docetaxel 20mg/2ml (10 mg per 1 ml) vial supplied by Pfizer Ltd is £162.75 (hospital only).[24]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Avelumab for treating non-small-cell lung cancer after platinum-based chemotherapy (TA10341). Expected date of issue to be confirmed.
- NICE Technology appraisal. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557). January 2019.
- NICE technology appraisal. Durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation (TA578). May 2019.
- NICE Technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018.
- NICE technology appraisal. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (TA520). May 2018.
- NICE technology appraisal. Nivolumab for previously treated non-squamous non-small-cell lung cancer (TA484). November 2017.
- NICE technology appraisal. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428). January 2017.
- NICE technology appraisal. Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (TA403). August 2016.
- NICE Technology appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (TA402). August 2016.
- NICE technology appraisal. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (TA374). December 2015.
- NICE technology appraisal. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347). July 2015.
- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.

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.
- NHS England. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). B01/P/a. April 2013.

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment follow-up. 2018.[14]
- European Society for Medical Oncology. Early and locally advanced non-small-cell-lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2017.[25]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[26]
- Scottish Intercollegiate Guidelines Network (SIGN) Management of lung cancer: A national clinical guideline. 2014.[27]

ADDITIONAL INFORMATION

BeyondSpring Pharmaceuticals Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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