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Nintedanib in combination with pemetrexed and cisplatin for unresectable malignant pleural mesothelioma – first line

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LAY SUMMARY

Malignant mesothelioma is a rare form of cancer that affects the pleura (the external lining of the lung) and rarely the peritoneum (the lining of the lower digestive tract). The disease has a strong association with a history of exposure to asbestos and can take several decades to present itself. Many cases are diagnosed at an advanced stage, beyond resection (a type of surgery), as symptoms are typically non-specific. It is almost always fatal, and often within twelve months of symptom onset.

Nintedanib is an oral drug in development for the treatment of malignant pleural mesothelioma (MPM) in combination with chemotherapy drugs pemetrexed and cisplatin. A targeted biological therapy, nintedanib blocks some enzymes that lead to the development of blood vessels within cancerous cells, inhibiting further growth. The combination of pemetrexed with cisplatin is currently the only licensed treatment option for MPM. If licensed, nintedanib in combination with pemetrexed and cisplatin followed by continuing nintedanib monotherapy may offer an additional first line treatment option for patients as current alternatives are limited.

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TARGET GROUP

Unresectable malignant pleural mesothelioma (MPM) – first line; in combination with pemetrexed and cisplatin followed by continuing nintedanib monotherapy

TECHNOLOGY

DESCRIPTION

Nintedanib (Vargatef; BIBF 1200) is an oral triple angiokinase inhibitor which simultaneously inhibits vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR) and fibroblast growth factor receptors (FGFR 1-3) signalling pathways. These three different angiokinase receptors, which are not yet targeted by any currently available therapies, play an important role not only in angiogenesis but also in tumour growth and the development of metastases.[1]

Pemetrexed and cisplatin are a combination of two chemotherapy drugs used to treat mesothelioma and non-small cell lung cancer (NSCLC) by inhibiting and destroying the growth of cancer cells.[2] Nintedanib is in phase III development for the treatment of unresectable malignant pleural mesothelioma (MPM), in combination with pemetrex and cisplatin.[3]

In the phase II/III trial (NCT01907100), treatment with pemetrexed and cisplatin and either nintedanib or matching placebo was given in 21-day courses. Pemetrexed and cisplatin were administered for a maximum of six cycles at the following standard dosages: 500 mg/m2 intravenous (IV) over 10 minutes on day 1 of each 21-day cycle for pemetrexed, and 75 mg/m2 IV over 2 hours on day 1 of each 21-day cycle for cisplatin. Nintedanib was given orally at 200 mg twice daily on days 2 through 21 of each 21-day cycle. Patients who did not experience progression during the combination therapy phase continued to receive nintedanib or placebo monotherapy until disease progression, undue toxicity, and withdrawal of consent or death.[18]

NIntedanib is licensed in the EU for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy in combination with docetaxel. Very common (≥1/10) and common (≥1/100 to <1/10) adverse reactions are detailed in the summary of product characteristics (SmPC) including: diarrhoea and other gastrointestinal disorders, liver enzyme elevations and hyperbilirubinaemia, peripheral neuropathy, and neutropenia.[4]

Nintedanib is in phase II/III clinical development in the EU and globally for the following additional indications:[5]

- systemic sclerosis (scleroderma)
- non-small cell lung cancer
- fallopian tube cancer
- oesophageal cancer
- soft tissue sarcoma
- neuroendocrine tumors
- bladder cancer
- metastatic breast cancer

- endometrial cancer
- hepatocellular carcinoma
- medullary thyroid cancer
- metastatic melanoma
- metastatic renal cell carcinoma
- squamous non-small cell lung cancer
- epithelial ovarian cancer
- metastatic colorectal cancer
- peritoneal cancer
- interstitial lung fibrosis
- lymphangioleiomyomatosis

INNOVATION and/or ADVANTAGES

If not treated with curative resection, cytotoxic chemotherapy remains one of the few therapeutic options that have been shown to improve survival in mesothelioma patients.[6] However, most chemotherapy agents have demonstrated only modest activity for MPM.[7] Pemetrexed and cisplatin as first-line therapy has been the standard of care for over a decade, warranting the investigation of novel agents in clinical trials to further mitigate or slow cancerous growth.[6] If licensed, nintedanib in combination with pemetrexed and cisplatin will offer an additional treatment option for patients with unresectable MPM.

DEVELOPER

Boehringer Ingelheim Ltd

AVAILABILITY, LAUNCH or MARKETING

Nintedanib was granted Orphan Drug Designation by the US FDA for mesothelioma in 2016.[5]

PATIENT GROUP

BACKGROUND

Mesothelioma is a rare form of cancer that originates from the mesothelium, a protective lining that sheaths the internal organs of the body. Pleural mesothelioma develops within the chest cavity and lungs. The pleural lining is comprised of two layers: the visceral layer is next to the lung and the parietal layer lines the chest wall. The pleura produces fluid that lubricates the space between, allowing the two layers to slide comfortably over each other during inhalation and exhalation.[8]

Pleural mesothelioma causes the pleura to thicken. This thickening may begin to press against the lungs or attach itself to the inside of the chest wall. The expansion of the lung becomes progressively restricted by tumorous growth. Fluid, sometimes several litres, can collect between the two layers affecting the ability of the lung to expand.[8]

The epidemiology of MPM is closely linked to occupational exposures to asbestos.[9] Current evidence suggests that approximately 85% of all male mesotheliomas are attributable to asbestos exposures

that occurred in occupational settings, including heavy industry and/or the armed forces.[10,11] The long latency period of typically at least 30 years means that most mesothelioma deaths occurring today are a result of past exposures to the widespread industrial use of asbestos during 1950-1980.[10] Malignant pleural mesotheliomas are most often surgically unresectable, and respond poorly to current chemotherapy and radiation therapy.[12]

Symptoms of pleural mesothelioma include:[8]

- shortness of breath
- chest pain
- cough
- sweating
- loss of appetite
- weight loss
- fatigue and lethargy

Given the symptom burden associated with a mesothelioma diagnosis, timely referral to specialist palliative care or a pain management is advisable (regional access may vary). Referral to centres offering access to cordotomy for pain management should correspondingly be considered. Patient-reported outcome measures and patient reported experience measures (PROMs/PREMs) are also possible. [13]

CLINICAL NEED and BURDEN OF DISEASE

Due to the short prognosis for mesothelioma, incidence and mortality data are more reliable than prevalence data in depicting trends.[13] The worldwide incidence of the disease continues to increase; in Western Europe, more than 5,000 new cases per year are estimated to occur, with more than a quarter of a million deaths over the next 40 years. Currently, there are no approved screening modalities for the early detection of mesothelioma.[14]

There were 2,542 mesothelioma deaths in the United Kingdom in 2015, a similar number to the previous three years.[10] The number of patients diagnosed in 2014 with MPM in England was 2,179 with a median age of 75 years.[13] MPM predominantly affects men – in 2014, there were 1,818 men diagnosed with MPM (83.4%) compared with 361 women (16.6%).[13] Data submitted to the National Lung Cancer Audit in England and Wales for MPM between 2008 and 2012 show a median survival rate of 9.5 months, with a 1 year survival rate of 41.4% and a 3 year survival rate of 12%.[9] MPM is an extremely difficult disease to treat, with the median overall survival ranging between 9 and 17 months, regardless of stage.[14]

In 2014, 36.5% (795 cases) of MPM patients received chemotherapy.[13] After first-line chemotherapy, there is no established second-line treatment for MPM. The population eligible to receive nintedanib in combination with pemetrexed and cisplatin followed by continuing nintedanib monotherapy could not be estimated from available published resources.

With a 20-50 year latency period between exposure to asbestos and the development of MPM, estimates of the likely burden of disease suggest that numbers of cases in the UK will peak between 2020 and 2025.[13] There are currently no established clinical guidelines in the UK for the management of MPM.[9]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Bevacizumab for untreated malignant pleural mesothelioma (GID-TA10197). Expected date of issue to be confirmed.
- NICE technology appraisal in development. NGR-TNF for previously treated advanced malignant pleural mesothelioma (GID-TA10183). Expected date of issue to be confirmed.
- NICE technology appraisal. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non‑small‑cell lung cancer (TA347). July 2015.
- NICE technology appraisal. Pemetrexed for the treatment of malignant pleural mesothelioma (TA135). January 2008.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). April 2011.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Malignant Mesothelioma (Adult). B10/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

OTHER GUIDANCE

- Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2015[15]
- Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma, 2010[16]

CURRENT TREATMENT OPTIONS

Mesothelioma is a fatal disease, with treatments currently aimed at easing symptoms and improving quality of life rather than a cure.[11] Palliative chemotherapy, debulking surgery and palliative radiotherapy are commonly included as active treatments for MPM patients, with other palliative measures such as pain control and fluid management via indwelling catheters.[13]

Cytotoxic platinum-based chemotherapy remains the only licensed therapeutic option shown to improve survival, with pemetrexed and cisplatin as the standard of care first-line therapy for patients with advanced unresectable MPM.[17]

EFFICACY and SAFETY

Trial	NCT01907100; nintedanib in mesothelioma; nintedanib in combination with pemetrexed and cisplatin followed by nintedanib vs placebo and pemetrexed with cisplatin followed by placebo; phase III
Sponsor	Boehringer Ingelheim Ltd
Status	Ongoing

Source of Information	Company[1], trial registry[3]
Location	EU (incl UK), USA, Canada, and other countries
Design	Randomised, placebo-controlled, double-blind multicentre study
Participants	n=450 (planned); aged ≥18 years; malignant pleural mesothelioma (MPM); epithelioid subtype only for Phase III patients
Schedule	Randomised to receive placebo from days two to 21 with pemetrexed (500 mg/m2) or cisplastin 75 mg/m2 followed by placebo monotherapy or up to (maximum of) six cycles of first-line combination pemetrexed at 500 mg/m2 or cisplatin at 75 mg/m2 on day one administered along with nintedanib at 200 mg twice daily followed by nintedanib monotherapy
Follow-up	Active treatment for up to 3 years
Primary Outcomes	Progression free survival measured from the time of randomisation to the time of disease progression or death of any cause, whichever occurs earlier (up to 3 years)
Secondary Outcomes	• Overall survival measured from the time of randomisation to the time of death of any cause (up to 3 years) • Objective response according to modified RECIST analysed by objective response rate (up to 3 years) • Disease control according to modified RECIST analysed by disease control rate (up to 3 years)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date estimated October 2019

Trial	NCT01907100; nintedanib in mesothelioma; nintedanib in combination with pemetrexed and cisplatin followed by nintedanib vs placebo and pemetrexed with cisplatin followed by placebo; phase II
Sponsor	Boehringer Ingelheim Ltd
Status	Published
Source of Information	Company[1], trial registry[3], publication[18]
Location	EU (incl UK), USA, Canada, and other countries
Design	Randomised, placebo-controlled, double-blind multicentre study

Participants	n=87; aged ≥18 years; malignant pleural mesothelioma (MPM); epithelioid or biphasic subtype for Phase II patients
Schedule	Randomised to receive placebo from days two to 21 with pemetrexed (500 mg/m2) or cisplastin 75 mg/m2 followed by placebo monotherapy or up to (maximum of) six cycles of first-line combination pemetrexed at 500 mg/m2 or cisplatin at 75 mg/m2 on day one administered along with nintedanib at 200 mg twice daily followed by nintedanib monotherapy
Follow-up	Active treatment for up to 3 years
Primary Outcomes	Progression free survival measured from the time of randomisation to the time of disease progression or death of any cause, whichever occurs earlier (up to 3 years)
Secondary Outcomes	• Overall survival measured from the time of randomisation to the time of death of any cause (up to 3 years) • Objective response according to modified RECIST analysed by objective response rate (up to 3 years) • Disease control according to modified RECIST analysed by disease control rate (up to 3 years)
Key Results	Phase II trial met primary endpoint of profession-free survival (PFS); nintedanib plus pemetrexed with cisplatin demonstrated a meaningful clinical benefit compared to placebo plus pemetrexed with cisplatin, with a significantly improved PFS (9.4 vs 5.7 months). Preliminary overall survival (OS) data also favoured nintedanib (18.3 vs 14.5 months). Phase II participants are not included in the Phase III ongoing trial.[18]
Adverse effects (AEs)	All patients experienced at least one AE of any grade and nearly all patients in the nintedanib (97.7%) and placebo (97.6%) groups experienced an investigator-defined drug-related AE. The most frequently reported AEs (≥60% of patients, any CTCAE grade) in the nintedanib arm and more frequent with nintedanib than placebo were diarrhoea and neutropenia. Neutropenia was the most frequent grade ≥ 3 adverse event (AE; nintedanib 43.2% v placebo 12.2%); rates of febrile neutropenia were low (4.5% in nintedanib group v 0% in placebo group). AEs leading to discontinuation were reported in 6.8% of those receiving nintedanib versus 17.1% of those in the placebo group.[18]
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Vargatef is already marketed in the UK for the treatment of locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma histology after first-line chemotherapy (in combination with docetaxel) and incurs a cost of £2151.10 (hospital only) for a 30−day pack of 150 mg

or 100 mg capsules for oral use (excluding VAT).[19,20] The company has agreed a patient access scheme with the Department of Health.

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

REFERENCES

[1] Boehringer Ingelheim Ltd. *Clinically meaningful data for oral nintedanib in mesothelioma presented at World Conference on Lung Cancer*. Available from: https://www.boehringer-ingelheim.com/press-release/positive-data-nintedanib-mesothelioma-world-conference-lung-cancer [Accessed 13th December 2017].

[2] Macmillan Cancer Support. *Pemetrexed and cisplatin chemotherapy*. Available from: https://www.macmillan.org.uk/cancerinformation/cancertreatment/treatmenttypes/chemotherapy/combinationregimen/pemetrexedcisplatin.aspx [Accessed 12th December 2017].
[3] Clinicaltrials.gov. *Nintedanib (BIBF 1120) in Mesothelioma*. Available from: https://clinicaltrials.gov/ct2/show/NCT01907100 [Accessed 12th December 2017].
[4] eMC. *Vargatef 100 mg and 150 mg soft capsules*. Available from: https://www.medicines.org.uk/emc/medicine/29790 [Accessed 12th December 2017].
[5] GlobalData. *Drug overview: nintedanib*. Available from: https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=12376 [Accessed 12th December 2017]. Login required
[6] Nowak K. Chemotherapy for malignant pleural mesothelioma: a review of current management and a look to the future. *Annals of Cardiothoracic Surgery*. 2012;1(4): 508-515. Available from: http://dx.doi.org/10.3978/j.issn.2225-319X.2012.10.05
[7] Tamura K and Fujiwara Y. Pemetrexed for malignant pleural mesothelioma: is it a standard second-line therapy? *Asia-Pacific Journal of Clinical Oncology*. 2010;6(4): 248-250. Available from: http://dx.doi.org/10.1111/j.1743-7563.2010.01362.x
[8] Mesothelioma UK. *About mesothelioma*. Available from: http://www.mesothelioma.uk.com/information-and-support/about-mesothelioma/ [Accessed 12th December 2017].
[9] Beckett P, Edwards J, Fennell D, Hubbard R, Woolhouse I and Peake MD. Demographics, management and survival of patients with malignant pleural mesothelioma in the National Lung Cancer Audit in England and Wales. *Lung Cancer*. 2015;88(3): 344-348. Available from: https://doi.org/10.1016/j.lungcan.2015.03.005
[10] Health and Safety Executive. *Mesothelioma in Great Britain: mesothelioma mortality in Great Britain 1968-2015*. Available from: http://www.hse.gov.uk/statistics/causdis/mesothelioma/mesothelioma.pdf [Accessed 12th December 2017].
[11] British Lung Foundation. *Mesothelioma statistics*. Available from: https://statistics.blf.org.uk/mesothelioma [Accessed 12th December 2017].
[12] Srinivasan G, Sidhu GS, Williamson EA, Jaiswal AS, Najmunnisa N, Wilcoxen K, et al. Synthetic lethality in malignant pleural mesothelioma with PARP1 inhibition. *Cancer Chemotherapy and Pharmacology*. 2017;80(4): 861-867. Available from: https://doi.org/10.1007/s00280-017-3401-y
[13] Royal College of Physicians. *National Lung Cancer Audit pleural mesothelioma report 2016 (for the audit period 2014)*. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-lung-cancer-audit-pleural-mesothelioma-report-2016-audit-period-2014 [Accessed 12th December 2017].
[14] Tsao A, Wistuba I, Roth JA, and Kindler HL. Malignant pleural mesothelioma. *Journal of Clinical Oncology*. 2009:27(12); 2081-2090. Available from: https://doi.org/10.1200/JCO.2008.19.8523
[15] Baas P, Fennell D, Kerr KM, Van Schil PE, Haas RL, Peters S on behalf of the ESMO Guidelines Committee. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2015;26(5): 31–39. Available from: https://doi.org/10.1093/annonc/mdv199
[16] Scherpereel A, Astoul P, Baas P, Berghmans T, Clayson H, de Vuyst P on behalf of the ERS/ESTS Task Force. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *European Respiratory Journal*. 2010;35(3): 479-495. Available from: https://doi.org/10.1183/09031936.00063109
[17] Kondola S, Manners D and Nowak AK. Malignant pleural mesothelioma: an update on diagnosis and treatment options. *Therapeutic Advances in Respiratory Disease*. 2016;10(3): 275-288. Available from: https://doi.org/10.1177/1753465816628800
[18] Grosso F, Steele N, Novello S, et al. Nintedanib plus pemetrexed/cisplatin in patients with malignant pleural mesothelioma: phase II results from the randomized, placebo-controlled LUME-meso trial. *Journal of Clinical Oncology*. 2017;35(31): 3591-3600. Available from: https://doi.org/10.1200/JCO.2017.72.9012
[19] MedicinesComplete. *Nintedanib*. Available from: http://dx.doi.org/10.18578/BNF.545837428 [Accessed 11th December 2017].
[20] NICE. *Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer*. Available from: https://www.nice.org.uk/guidance/ta347 [Accessed 12th December 2017].