Liposomal cisplatin (Nanoplatin) for advanced non-small cell lung cancer – first line

SUMMARY

LIposomal cisplatin is intended to be used as first line therapy for the treatment of stage IIIb or IV, non-squamous non-small cell lung cancer (NSCLC), in combination with paclitaxel, gemcitabine or pemetrexed. If licensed, it will offer an alternative to the currently marketed preparation for patients requiring treatment with cisplatin. Liposomal cisplatin is a new formulation that targets and fuses with human tumour cells allowing for the specific delivery of the cytotoxic drug directly into cancer cells.

In the UK, lung cancer is the most common cause of cancer-related death in men and women. In 2009, there were 41,428 new cases of lung cancer in England and Wales (approximately 48 cases per 100,000 population in the UK) and around 34,859 registered deaths in 2010 (around 39 deaths per 100,000 population in the UK). NSCLC accounts for approximately 85% of all lung cancers. The non-squamous types of NSCLC - adenocarcinoma and large cell carcinoma - account for around 26% and 4% respectively of all UK lung cancer cases. In England and Wales, approximately 78% of newly diagnosed NSCLC patients have advanced (stage III or IV) disease that is incurable at outset, with a five-year survival rate of less than 1%. An estimated 30% of patients with advanced NSCLC receive first line chemotherapy.

For advanced NSCLC, treatment aims to relieve symptoms, improve disease control, improve quality of life, and increase survival. The standard therapy for stage IIIb or IV disease is radiotherapy and chemotherapy. Liposomal cisplatin is in several phase III clinical trials comparing its effect on response rate and survival against treatment with cisplatin. The trials are expected to complete in 2013 and 2014.
TARGET GROUP

- Non-small cell lung cancer (NSCLC): stage IIIb or IV, non-squamous – first line; in combination with paclitaxel, gemcitabine or pemetrexed.

TECHNOLOGY

DESCRIPTION

Liposomal cisplatin (Nanoplatin) is a new formulation that targets and fuses with human tumour cells allowing for the specific delivery of the cytotoxic drug directly into cancer cells. This reduces the toxicity of cisplatin and helps evade the immune system. Liposomal cisplatin is intended to be used for the treatment of stage IIIb or IV, non-squamous NSCLC and is administered at 200mg/m² by intravenous (IV) infusion every 2 weeks in combination with paclitaxel, gemcitabine or pemetrexed.

Liposomal cisplatin is also in phase III clinical trials for head and neck cancer, pancreatic cancer and ovarian cancer, and in phase II clinical trials for gastric cancer.

INNOVATION and/or ADVANTAGES

If licensed, it will offer an alternative to the currently marketed preparation for patients requiring treatment with cisplatin.

DEVELOPER

Regulon Inc.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

There are two main types of lung cancer, small cell lung cancer and NSCLC. NSCLC is further divided into three common subtypes, namely squamous cell carcinoma, adenocarcinoma and large cell carcinoma¹. Stage IIIb lung cancer describes cancer that has spread from the lungs to lymph nodes in the chest and another major structure such as the oesophagus, heart, or trachea; the presence of two or more tumours in the same lung; or a malignant pleural effusion². Stage IV lung cancer represents metastatic lung cancer, where the cancer has spread to distant parts of the body such as the liver, bones or brain².

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011).
CLINICAL NEED and BURDEN OF DISEASE

In the UK, lung cancer is the most common cause of cancer-related death in men and women\(^3\). In 2009, there were 41,428 new cases of lung cancer in England and Wales (approximately 48 cases per 100,000 population in the UK)\(^4\) and around 34,859 registered deaths in 2010 (around 39 deaths per 100,000 population in the UK)\(^5\). In England and Wales, one-year survival rates are estimated to be 27% for men and 30% for women, with five-year survival rates falling to 7% and 9% respectively\(^5\). Around 5.5% of lung cancers are cured with currently available treatments\(^6\). About 90% of lung cancer mortality among men and 80% among women is attributable to smoking\(^7\).

NSCLC accounts for approximately 85% of all lung cancers\(^8\). The non-squamous types of NSCLC - adenocarcinoma and large cell carcinoma - account for around 26% and 4% respectively, of all UK lung cancer cases\(^8\). In addition, 35% of NSCLCs in the UK are classed as 'not otherwise specified' when the exact histological subtype is unknown\(^8\). In England and Wales, approximately 78% of newly diagnosed NSCLC patients have advanced (stage III or IV) disease that is incurable at outset\(^9\), with a five-year survival rate of less than 1\(^%\)\(^10\). Survival from clinical trials is reported to be around 12 months, although in the 'real-world' setting this is closer to 7-9 months, with many patients not fit enough for any form of active anti-cancer therapy at the point of diagnosis. An estimated 30% of patients with advanced NSCLC receive first line chemotherapy\(^9\).

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Cetuximab for the treatment of advanced non-small cell lung cancer (ID9). Expected date of issue to be confirmed\(^11\).
- NICE technology appraisal in development. Erlotinib and gefitinib for the second line treatment of non-small cell lung cancer (review of TA162 and TA175) (ID620). Expected June 2014\(^12\).
- NICE technology appraisal in development. Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small cell lung cancer. Expected August 2013\(^13\).
- NICE technology appraisal in development. Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer (ID489). Expected June 2013\(^15\).
- NICE technology appraisal in development. Afatinib for the treatment of locally advanced or metastatic non-small cell lung cancer after previous platinum containing chemotherapy and gefitinib or erlotinib (ID357). Suspended July 2011\(^16\).
- NICE technology appraisal. Gefitinib for the first line treatment of locally advanced or metastatic non-small cell lung cancer (TA192). 2010\(^19\).
• NICE technology appraisal. Pemetrexed for the maintenance treatment of non-small cell lung cancer (TA190). 2010\textsuperscript{20}.
• NICE technology appraisal. Pemetrexed for the first line treatment of non-small cell lung cancer (TA181). 2009\textsuperscript{21}.
• NICE technology appraisal. Erlotinib for the treatment of non-small cell lung cancer (TA162). 2008\textsuperscript{22}.
• NICE clinical guideline. Lung cancer: the diagnosis and treatment of lung cancer (CG121). 2011\textsuperscript{6}.

Other Guidance

• European Society for Medical Oncology (ESMO). Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2010\textsuperscript{8}.
• ESMO. Early stage and locally advanced (non-metastatic) non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2010\textsuperscript{24}.
• SIGN. Management of patients with lung cancer. 2005\textsuperscript{26}.
• Cancer Services Collaborative Improvement Partnership. Lung cancer service improvement guide. 2004\textsuperscript{27}.

EXISTING COMPARATORS and TREATMENTS

In advanced NSCLC, treatment aims to relieve symptoms, improve disease control, improve quality of life and increase survival. Treatment options for stage IIIb or IV NSCLC include radiation therapy, chemotherapy with radiation therapy and chemotherapy alone. Chemotherapy may be recommended for patients provided they have a good performance status\textsuperscript{a,26,28}.

First line treatment regimens for advanced and/or metastatic NSCLC include\textsuperscript{6,20,21}:
• A combination of a single third-generation drug (gemcitabine, docetaxel, paclitaxel or vinorelbine) with a platinum drug (carboplatin or cisplatin) or pemetrexed with cisplatin in non-squamous pathology.
• Single agent chemotherapy with a third-generation drug for patients who cannot tolerate a platinum combination.
• Maintenance pemetrexed in non-squamous pathology and non progression after first line chemotherapy (not containing pemetrexed).
• Gefitinib or erlotinib may be offered for EGFR mutation positive disease\textsuperscript{b}.
• Bevacizumab plus a platinum containing chemotherapy (not recommended by NICE)\textsuperscript{29}.

\textsuperscript{a} 0 or 1 on the World Health Organisation performance status scale, or a Karnofsky score of 80-100.
\textsuperscript{b} Expert personal opinion.
## EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>ACTRN12610000046000; Liposomal cisplatin vs cisplatin, both with paclitaxel; phase III.</th>
<th>Liposomal cisplatin vs cisplatin, both in combination with paclitaxel; phase III.</th>
<th>NanoPem-PIII-1L; Liposomal cisplatin vs cisplatin, both in combination with pemetrexed; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Complete and published.</td>
<td>Complete and published.</td>
<td>To be initiated Q4 2012.</td>
</tr>
<tr>
<td>Location</td>
<td>Greece.</td>
<td>Greece.</td>
<td>EU (incl UK), USA and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled, open-label.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=202; ≥18 years; NSCLC; non-squamous; stage IIIB or IV; inoperable; chemotherapy and radiotherapy naive.</td>
<td>n=236; ≥18 years; NSCLC; stage IIIa, IIIb or IV; inoperable; chemotherapy naive.</td>
<td>n=884 (planned); 18-75 years; NSCLC; non-squamous; stage III or IV; inoperable; chemotherapy naive.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to liposomal cisplatin, IV 200mg/m² or cisplatin, IV 75mg/m², both in combination with paclitaxel, IV 135mg/m², every 2 weeks for 9 cycles.</td>
<td>Randomised to liposomal cisplatin, IV 200mg/m² or cisplatin, IV 75mg/m², both in combination with paclitaxel, IV 135mg/m², every 2 weeks for 9 cycles.</td>
<td>Randomised to liposomal cisplatin, IV 200mg/m² on days 1 and 8 of a 21 day cycle; or cisplatin, IV 75mg/m² on day 1 of a 21 day cycle; both in combination with pemetrexed, IV 500mg/m² on day 1 of a 21 day cycle, all for 6 cycles.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Median 18 months follow-up.</td>
<td>1 year follow-up.</td>
<td>Active treatment period 18 weeks; then follow up 30 days after last infusion and every 3 months thereafter.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Response rate.</td>
<td>One year survival.</td>
<td>PFS.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Progression free survival (PFS); overall survival (OS).</td>
<td>Overall response rate (ORR); time to tumour progression (TTP); OS; toxicity; quality of life (QoL).</td>
<td>OS; ORR; duration of response; toxicity; QoL.</td>
</tr>
<tr>
<td>Key results</td>
<td>For liposomal cisplatin vs cisplatin: partial response (PR), 59.2% vs 42.4% (p=0.036); stable disease (SD), 34.0% vs 43.4% (p=0.22); disease progression (PD), 6.8% vs 14.1% (p=0.11); median duration of response, 7 vs 6 months; median survival, 10 vs 8 months (p=0.155); percentage of patients alive at 18 months follow-up, 28.4% vs 11.1%.</td>
<td>Intent-to-treat analysis, liposomal cisplatin vs cisplatin: complete response, 0.9% vs 0%; PR, 58.8% vs 47.0%; SD, 36.8% vs 43.5%; PD, 3.5% vs 9.6% (all p&gt;0.05); median survival, 9 vs 10 months (p=0.577); median time to progression, 6.5 vs 6 months (p=0.464).</td>
<td>-</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>AEs reported include nausea and vomiting, asthenia and -</td>
<td>Nephrotoxicity was reported in 6.1% of patients in the liposomal cisplatin -</td>
<td>-</td>
</tr>
</tbody>
</table>
nephrotoxicity, which were all statistically significantly more common in the cisplatin arm vs liposomal cisplatin arm. Peripheral neuropathy was also observed in both arms. Overall, less toxicity was observed in the liposomal cisplatin arm.

<table>
<thead>
<tr>
<th>Expected reporting date</th>
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<th>-</th>
<th>Expected completion date Q4 2014</th>
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</table>

**Trial**

| LipoGem-PIII-1L; Liposomal cisplatin vs cisplatin, both with gemcitabine; phase III. | Liposomal cisplatin vs cisplatin, both with gemcitabine; phase II. |

**Sponsor**

| Regulon. | Regulon. |

**Status**

| Ongoing. | Published. |

**Source of information**

| Manufacturer. | Publication. |

**Location**

| Greece. | Greece. |

**Design**

| Randomised, open label. | Randomised, active-controlled, open label. |

**Participants**

| n=400 (planned); adults; NSCLC; adenocarcinoma; stage III or IV; inoperable; chemotherapy naive. | n=88; adults; NSCLC; stage III or IV; chemotherapy naive. |

**Schedule**

| Randomised to liposomal cisplatin, IV 120mg/m² on days 1, 8, and 15 of a 21 day cycle; or cisplatin, IV 100mg/m², on day 1 of a 21 day cycle; both in combination with gemcitabine, IV 1,000mg/m² on days 1 and 8 of a 21 day cycle, all for 6 cycles. | Randomised to liposomal cisplatin, IV 120mg/m² on days 1, 8, and 15 of a 21 day cycle; or cisplatin, IV 100mg/m², on day 1 of a 21 day cycle; both in combination with gemcitabine, IV 1,000mg/m² on days 1 and 8 of a 21 day cycle, all for 6 cycles. |

**Follow-up**

| Active treatment period 18 weeks; then follow up 30 days after last infusion and every 3 months thereafter. | Active treatment period 18 weeks; then follow up 30 days after last infusion, then every 3 months thereafter. |

**Primary outcome**

| 1 year survival. | ORR. |

**Secondary outcomes**

| ORR; TTP; OS; toxicity; QoL. | PFS; disease control rate (DCR); duration of response; OS; safety and tolerability. |

**Key results**

| - | Liposomal cisplatin vs cisplatin: ORR, 31.7% vs 25.6%; DCR, 70.7% vs 56.4%; disease progression in patients with the adenocarcinoma subtype of NSCLC, 16.7% vs 45.8%. |

**Adverse effects (AEs)**

| - | The most common AEs reported in the liposomal cisplatin arm included grade I and II myelotoxicity and there was only one grade IV adverse event reported (neutropenia). There was a statistically significant difference (p<0.001) in grade III nephrotoxicity (0% vs 5%), and grade III nausea and vomiting (2% vs 12%) in the liposomal cisplatin arm vs cisplatin arm. |
COST and IMPACT

ESTIMATED COST

The cost of liposomal cisplatin is not yet known. Treatment with a single dose of cisplatin at 75mg/m² would cost £67.77[^c], and at 100mg/m² would cost £86.42[^d,^4].

IMPACT - SPECULATIVE

Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified
- Other:

Impact on Services
- Increased use of existing services
- Decreased use of existing services
- Need for new services
- Re-organisation of existing services
- None identified
- Other:

Impact on Costs
- Increased drug treatment costs
- Reduced drug treatment costs
- Other reduction in costs
- None identified
- Other:

Other Issues
- Clinical uncertainty or other research question identified:
- None identified
- Other:

REFERENCES


[^c]: Based on average surface area 1.7m².


