

**NIHR Innovation Observatory
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Intravenous Doxorubicin Nanoparticles for Advanced Hepatocellular Carcinoma

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LAY SUMMARY

Hepatocellular Carcinoma (HCC) is the most common type of liver cancer, with approximately 15 new cases diagnosed every day.¹ Treatment and survival depends on the stage at which the cancer is diagnosed. Treatment of advanced HCC with chemotherapy and the drug Sorafenib can only slow the progression of the cancer and extend lifespan. However if the cancer is not responsive to these treatments there are no further treatment options available.

Doxorubicin Nanoparticles are an injectable drug made up of microscopic polymer based spheres containing the drug doxorubicin. Doxorubicin, a chemotherapy drug used to treat many types of cancer, slows or stops the growth of cancer cells by blocking an enzyme called topoisomerase 2.² Studies on doxorubicin nanoparticles on people with advance HCC have suggested it may extend lifespan.

If doxorubicin nanoparticles is licenced in the UK, it could provide a new treatment option for patients with advance HCC when other treatment options have failed, which may extend patient survival time.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Adults with Hepatocellular Carcinoma (HCC); second line; refractory

TECHNOLOGY

DESCRIPTION

Doxorubicin Nanoparticles (doxorubicin nanoparticles (intra-arterial), BioAlliance; doxorubicin nanoparticles (IV), BioAlliance; doxorubicin nanoparticles, BioAlliance; doxorubicin polyisohexylcyanoacrylate (intra-arterial), BioAllia; doxorubicin polyisohexylcyanoacrylate (IV), BioAlliance; doxorubicin polyisohexylcyanoacrylat, BioAlliance; doxorubicin Transdrug (intra-arterial); doxorubicin Transdrug (IV); doxorubicin, BioAlliance; doxorubicin Transdrug; Livatag (intra-arterial); Livatag (IV), BA-003; BA-003 (intra-arterial); BA (IV)) are a polymer based (polyisohexylcyanoacrylate), masked nanoparticle formulation of doxorubicin (a DNA topoisomerase II inhibitor) for the treatment of HCC, liver metastases and refractory solid liver tumours.

Doxorubicin is a anthracycline drug which works by inhibiting the topoisomerase II inhibitor enzyme which cells require to grow and divide.² It is currently available in conventional (IV) and liposomal formulations, each licenced for different indications and differing in pharmacokinetics, dosage and administration.⁴ Nanoparticle drug delivery systems involve incorporating drugs (by dissolving, entrapping, attaching or encapsulating), such as doxorubicin, into nanoparticles 10-1000nm in diameter. There are many advantages to nanoparticle drug delivery including controlled drug release, targeted delivery of drugs, improved bioavailability and protection against enzymatic degradation.⁵

In the phase III clinical trial, doxorubicin nanoparticles were administered intravenously at 20mg/m² or 30mg/m² (infused over 6 hours), in combination with undisclosed chemotherapy, once every 4 weeks until disease progression or unacceptable toxicity occurred.⁶

Doxorubicin Nanoparticles does not currently have Marketing Authorisation in the EU for any indication. Doxorubicin Nanoparticles were in phase II clinical trials for metastatic colorectal cancer but was terminated as the trial was never initiated and for acute myelogenous leukaemia but was terminated for safety reasons (due to unacceptable side effects).^{7 8}

INNOVATION and/or ADVANTAGES

If licensed, doxorubicin nanoparticles has the potential to extend survival and will offer an additional treatment option for adults with advanced refractory HCC.

DEVELOPER

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AVAILABILITY, LAUNCH or MARKETING

Doxorubicin Nanoparticles is a designated orphan drug in the EU and USA for Hepatocellular Carcinoma.

PATIENT GROUP

BACKGROUND

Hepatocellular Carcinoma (HCC) is the fifth most common type of cancer worldwide and the third leading cause of cancer mortality.⁹ In the UK it is the 7th most common cause of cancer death, accounting for 3% total cancer deaths.¹⁰ HCC is the most common type of primary liver cancer which occurs in the most prevalent liver cells (hepatocytes).¹¹ The main symptoms of HCC are significant appetite and weight loss (>10% body weight), pain and swelling of the abdomen, jaundice, nausea, bloating and itching.¹² The origin of HCC is usually related to previous liver disease, injury and infection, however there are many risk factors which increase the likelihood of developing HCC. These risk factors include cirrhosis (scarring of the liver), heavy alcohol consumption, non-alcoholic fatty liver disease (NAFLD), hepatitis infection, smoking, impaired immunity (HIV/AIDS, immunosuppressive medication), systemic lupus erythematosus (SLE), family history, diabetes, previous gallbladder removal, previous radiation exposure and obesity.¹³

HCC is usually diagnosed using a combination of blood tests (Liver Function tests, urea and electrolytes, tumour markers – particularly alpha fetoprotein), ultrasound, CT or MRI scans, biopsy (of liver tumour tissue) and laparoscopic investigation.¹⁴ Treatment and survival rates depend on the cancer stage at diagnosis and are discussed further in ‘current treatment options’ section.

CLINICAL NEED and BURDEN OF DISEASE

For England, the incidence of liver cancer was 8.4 per 100,000 population in 2014 and for the UK the incidence of liver cancer was 8.6 per 100,000 in 2014.¹

For UK, the prevalence of liver cancer 1, 5 and 10 years after diagnosis (as of 2006) was 1113, 2108 and 2626 people respectively.¹⁵

In adults in England diagnosed with liver cancer, 35% will survive >1 year after diagnosis and 10% will survive >5 years after diagnosis.¹⁶

The European Clinical Practice Guidelines have estimated survival based on liver cancer stage, as follows:¹⁶

- Stage 0 – Median survival without treatment is > 3 years and median survival with treatment for 70 to 90% patients will be >5 years
- Stage A – Median survival without treatment is 3 years and median survival with treatment for 50 to 70% patients will be >5 years
- Stage B – Median survival without treatment is 16 months and median survival with treatment is 20 months
- Stage C – Median survival without treatment is 4-8 months and median survival with treatment is 6 to 11 months
- Stage D – Median survival without treatment is <4 months. There are no treatments for this stage of liver cancer.

Liver cancer (C22) deaths were 7.9 per 100,000 (total 5091 people) in the UK in 2014 at a male: female ratio of 15:10.

In 2015/2016, there were 11,256 admissions for malignant neoplasms of the liver and intrahepatic bile ducts (C22) in England, resulting in 60, 804 bed days and 16,730 finished consultant episodes.¹⁷

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance in development. Regorafenib for previously treated unresectable hepatocellular carcinoma (ID991). Expected date of issue to be confirmed.
- NICE Technology appraisal guidance in development. Lenvatinib for untreated advanced unresectable hepatocellular carcinoma (ID1089). Expected date of issue to be confirmed.
- NICE Technology appraisal guidance in development. Hepatocellular carcinoma (advanced and metastatic) – sorafenib (first line) (review of TA189)[ID1012] – CDF rapid reconsideration process. Expected date of issue to be confirmed.
- NICE Technology appraisal. Sorafenib for the treatment of advanced hepatocellular carcinoma (TA189). May 2010.

- NICE MedTech innovation briefing. SIR-Spheres for treating inoperable hepatocellular carcinoma (MIB63). March 2016.
- NICE MedTech innovation briefing. TheraSphere for treating operable and inoperable hepatocellular carcinoma (MIB62). March 2016.
- NICE Interventional procedures guidance. Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary and metastatic liver cancer (IPG488). May 2014.
- NICE Interventional procedures guidance. Selective internal radiation therapy for primary hepatocellular carcinoma (IPG460). July 2013
- NICE Interventional procedures guidance. Irreversible electroporation for treating primary liver cancer (IPG444). February 2013.
- NICE Interventional procedures guidance. Ex-vivo hepatic resection and reimplantation for liver cancer (IPG298). April 2009.
- NICE Interventional procedures guidance. Microwave ablation of hepatocellular carcinoma (IPG214). March 2007.
- NICE Interventional procedures guidance. Laparoscopic liver resection (IPG135)
- NICE Interventional procedures guidance. Radiofrequency ablation of hepatocellular carcinoma (IPG2). July 2003.

- Do not do recommendation. Do not offer surveillance for HCC for people who are receiving end of life care. December 2016.
- Do not do recommendation. Sorafenib is not recommended for the treatment of advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies have failed or are not suitable. June 2015.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) as a treatment option for patients with hepatocellular carcinoma or Cholangiocarcinoma. 16022/P. July 2016.

- NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and pancreas (adult). A02/S/a.
- NHS England. 2013/14 NHS Standard Contract for specialist liver disease service (children). E03/S(HSS)/d.
- NHS England. 2013/14 NHS Standard Contract for cancer: pancreatic (adult). A02/S/b.
- NHS England. Intrim Clinical Commissioning Policy Statement: Selective Internal Radiotherapy (SIRT). B01/PS/a. June 2013.

OTHER GUIDANCE

No guidance is currently available.

CURRENT TREATMENT OPTIONS

The treatment of HCC depends on the stage of cancer at diagnosis. The NHS uses the BCLC staging system to define liver cancer stages, as follows:¹⁸

- Stage 0: single tumour <2cms, patient feels well and liver is functioning normally
- Stage A: single tumour <5cms or up to 3 tumours all <3cms, patient feels well and liver is functioning well
- Stage B: multiple tumours, patient feels well and liver is functioning well.
- Stage C: cancer spread to the blood vessels, lymph nodes or other organs, patient does not feel well, and liver is functioning.
- Stage D: severe liver damage or patient does not feel well and liver is functioning poorly.

Curative treatment is possible for HCC if it is at Stage A when diagnosed. Treatments available for Stage A HCC are:^{3, 19}

- Surgical liver resection – removal of a section of the liver recommended for those with minimal liver damage and localised cancer.
- Liver transplant – recommended for those with a single tumour <5cms or less than 3 tumours each <3cms or a good response to other treatments with no tumour growth in the last 6 months.
- Microwave/Radiofrequency ablation – targeting tumours with microwaves or radio waves (via small electrodes introduced percutaneously, laparoscopically or surgically) with the aim of shrinking the tumour. This is recommended for treatment of early cancer in tumours <5cm, and can be carried out in 3 ways:

Treatments available for Stage B and C HCC aims to slow the progression of the cancer, relieve symptoms and prolong life but cannot cure the cancer. These treatments include:^{3, 19}

- Chemotherapy – specifically the TACE procedure where chemotherapy medication and small plastic beads are injected into the hepatic artery via a catheter inserted into the femoral artery (in the groin), with the aim of slowing cancer growth.
- Alcohol injections – recommended for small tumours as alcohol dehydrates the cells.
- Sorafenib – oral medication which disrupts blood supply to liver tumours and slows their growth (not available in the NHS)

Treatments available for Stage D HCC cannot cure or slow the progression of the disease but focus on relieving symptoms and discomfort. These treatments include: ^{3, 19}

- Painkillers – e.g. codeine, morphine
- Anti-sickness and Laxative medications

EFFICACY and SAFETY

Trial	Doxorubicin Nanoparticles, ACTRN12608000082303, BA 2005/00/00, BA 2006/03/03, BA2006/03/03, DOTAHCC1, EudraCT Number: 2006-004088-77, TrialTroveID-024718; standard care vs doxorubicin nanoparticles; phase II	Doxorubicin Nanoparticles, NCT01655693, BA2011/03/04, DRKS00005752, EudraCT Number: 2011-002843-92, REec-2013-0406, ReLive, TrialTroveID-148718; doxorubicin nanoparticles 20mg/m² vs doxorubicin nanoparticles 30mg/m² vs best standard of care; phase III
Sponsor	Onxeo (BioAlliance Pharma)	Onxeo (BioAlliance Pharma)
Status	Terminated and published in abstract	complete but unpublished
Source of Information	Abstract ²⁰ , trial registry ²¹	trial registry ²³
Location	EU (including UK) and Australia	EU (not UK), USA, Australia, Egypt, Lebanon, Russia, Saudi Arabia and Turkey
Design	Randomised, active controlled trial	Randomised active controlled trial
Participants	n=28; aged 18-80 years; hepatocellular carcinoma (HCC); advanced	Give brief details of participants as illustrated below. Indicate using “planned” if numbers not accurately known (still recruiting or unpublished and not reported by company). Always give age range of participants (do not say “adults” or “children”), but only list sex if relevant. Include diagnosis/condition; sub-type; and severity/place in therapy where relevant, all separated by semi-colons, e.g. n=390; aged = or >18 years; Hepatocellular carcinoma (primary); advanced (BLCL stage B or C); progression despite first line treatment with TACE and Sorafenib or intolerance to Sorafenib.
Schedule	Randomised to doxorubicin nanoparticles 30mg/m ² hepatic intra-arterial injection as a 15 minute infusion on days 1 of a 28 day cycle; or standard care including Embolisation,	Participants randomised to one of 3 parallel arms: 1. Doxorubicin Nanoparticles (IV) 20mg/m ² infused over 6 hrs on day 1 in 4 week cycles until

	Transarterial Chemoembolisation (TACE), Hepatic Intra-arterial chemotherapy with or without Lipiodol, Lipiodol, IV chemotherapy and best supportive care (pain and symptom management)	disease progression or unacceptable toxicity. 2. Doxorubicin Nanoparticles (IV) 30mg/m ² infused over 6 hrs on day 1 in 4 week cycles until disease progression or unacceptable toxicity. 3. Best standard care treatment according to the investigators choice until disease progression or unacceptable toxicity.
Follow-up	Active treatment in 28 day cycles for 3 cycles (up to 90 days) or until disease progression or unacceptable toxicity. Standard care treatment according to the centres usual practice till 90 days. All participants followed up every 3 mths for 1yr	Active treatment in 28 day cycles until disease progression or unacceptable toxicity. Participants assessed at each visit (every 2 weeks) then every 3 months until death (estimated at 1 year).
Primary Outcomes	Number of patients with no local cancer progression (according to EASL criteria) and progression free survival (PFS) at 3 months	Overall Survival (OS)
Secondary Outcomes	PFS, Overall Survival (OS), Response Rate, Tolerance and Quality of Life, Safety and efficacy.	Incidence and severity of AEs (until 1 month after last treatment), tumour response rate, progression free survival (PFS), time to progression (TTP), time to symptomatic progression (TTSP)
Key Results	Of the 28 participants, 17 were randomised to doxorubicin nanoparticles and 11 randomised to standard care. Trial was terminated in July 2008 because of severe respiratory distress in 3 patients causing death in 2 patients. In the active treatment arm 9 patients took all 3 drug courses, 4 patients took 2 courses and 4 patients took 1 course. PFS 3 months post trial was 64% in the doxorubicin nanoparticle group (95% CI: 31%>89%). Median duration of OS was substantially increased in the doxorubicin nanoparticle group (31.7 mths, 95% CI: 8.2 mths - not determined) compared to standard care (15mths, 95% CI 8mths- 18.8 mnths) (Logrank test, p=0.05). Only participants who received 3 courses has significantly longer median duration of OS compared to standard	-

	care (33 mnths vs. 15 mnths, Logrank test, $p < 0.05$).	
Adverse effects (AEs)	Severe respiratory distress (lung toxicity) in 3 patients leading to death in 2 patients.	-
Expected reporting date	-	2017

ESTIMATED COST and IMPACT

COST

The cost of doxorubicin nanoparticles is not yet known.

Drug	Dose ⁴	Unit cost ²²
Doxorubicin (non-proprietary) (IV) – Powder for constitution	Dosing variable according to bilirubin concentration and boy mass. Given in 21 day intervals.	10mg vial - £19 50mg vial - £100
Doxorubicin (non-proprietary) (IV)	Dosing variable according to bilirubin concentration and boy mass. Given in 21 day intervals.	2mg/ml: 5ml vial - £19 25ml vial - £93 50ml vial - £371
Doxorubicin (lipid formulation) (Caelyx [®] - Janssen) – Concentrate for IV		2mg/ml encapsulated lysosomes For dilution before use: 10ml vial - £360 25ml vial - £713
Doxorubicin (lipid formulation - Myocet [®] - TEVA UK) – powder for reconstitution		50mg vial (with vials of liposomes and buffer) - £456

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: Cost of IV administration and trained staff to deliver drug.

Other reduction in costs

Other: uncertain unit cost compared to existing treatments

None identified

OTHER ISSUES

Clinical uncertainty or other research question identified

None identified

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