Expert Opinion

DC Bead embolic drug-eluting bead: clinical application in the locoregional treatment of tumours

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Introduction: DC Bead is an embolic drug-eluting bead designed to be loaded with chemotherapeutic agents (such as doxorubicin and irinotecan), delivered intra-arterially into tumor blood vessels to block nutrient flow and then to deliver the drug locally in a sustained fashion. This product is finding increasing use in the treatment of patients with both primary and secondary liver cancers.

Areas covered: This review positions DC Bead in the field of targeted embolic drug delivery and with respect to other competitive technologies in the treatment of liver cancer. An overview of the studies that demonstrate the product's performance, safety and efficacy is presented. The clinical application of the doxorubicin loaded DC Bead is firstly reviewed, in the context of treatment of patients with various stages of hepatocellular carcinoma. Its combination with other therapies is also discussed, together with consideration of the treatment of other liver tumors. Secondly, the use of irinotecan loaded DC Bead, primarily for the treatment of colorectal cancer metastases to the liver, but also some additional rare metastases, is summarized.

Expert Opinion: An opinion is proffered as to how this technology and its application is evolving, illustrating a move towards synergistic combination therapies and into other cancer indications.

Keywords: DC Bead, doxorubicin, hepatocellular carcinoma, irinotecan, transarterial chemoembolisation

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1. Introduction

The global cancer burden is an estimated 12.7 million new cancer cases and 7.6 million cancer deaths each year [1]. In the UK, one in three people develop cancer in their lifetime. Almost 300,000 new cases of cancer and an average of 154,500 deaths from cancer were reported in the UK per year between 2005 and 2007 [2].

Substantial progress in the development of new treatments and improved detection and diagnosis of cancer has been made over the past few decades. Despite this, > 50% of all cancer patients either do not respond to initial therapy or experience relapse after an initial response to treatment and ultimately die from progressive metastatic disease. In this context, it is important to examine the ways in which more effective treatments can be offered to the patient that aim to improve patient survival and quality of life. The advances in understanding of the molecular biology of cancer have allowed the development of better treatment strategies by targeting the tumour, using direct and indirect approaches. Such approaches of targeted cancer therapy include drugs that interfere with cell growth signalling or tumour blood vessel development, that promote cancer cell apoptosis, and that

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Article highlights.

- DC Bead is an embolic drug delivery system that has been designed to be administered intra-arterially in order to occlude the blood vessels of tumours, while concomitantly releasing chemotherapy at the target site and over a sustained period of time.
- These biocompatible biomedical polymer beads based on a sulphonate-modified polyvinyl alcohol hydrogel are capable of efficiently binding positively charged drugs such as doxorubicin and irinotecan and subsequently releasing them in a controlled fashion by an ion-exchange process.
- Preclinical studies have shown the product to be safe and effective, inducing significant necrosis in tumour models following embolisation and by the subsequent delivery of a sustained dose of drug into the tumour tissue, which minimises its systemic exposure.
- Clinical studies in the treatment of patients with hepatocellular carcinoma using doxorubicin-loaded DC Bead have confirmed the favourable pharmacokinetics, which translates into fewer chemotherapy-related side effects. Overall tumour response is also improved over the comparable conventional therapy, particularly in patients with more advanced disease.
- Promising clinical data have been obtained with irinotecan-loaded DC Bead in the treatment of metastatic liver disease, where it is being used as an adjunct therapy in combination with established chemotherapeutic regiments.

This box summarises key points contained in the article.

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stimulate the immune system to destroy specific cancer cells. Innovative methods of cancer treatment also require new concepts of drug delivery. However, this idea in itself is not new.

It has been over a century since Paul Ehrlich first proposed the 'magic bullet' concept whereby therapeutics might be targeted more selectively to the disease site in order to enhance their efficacy and reduce undesirable side effects. Helmut Ringsdorf elaborated on this concept in the mid-1970s with a proposal for a generic drug-polymer conjugate comprised of a targeting group, a solubilising agent and a drug, all attached to a polymeric backbone, the latter component by means of a cleavable linker to enable its release at the site of action once targeted. Since that time, the field of drug delivery has grown significantly and systems that allow better discrimination in how therapeutic agents are directed to their targets have attracted great attention, thereby enhancing the therapeutic efficacy while reducing nonspecific side effects or overcoming drug resistance. The mechanisms by which this selectivity is achieved are both numerous and varied in degree of sophistication. Nanoparticulate drug carriers or conjugates bearing ligands or antibodies specific for biomolecules overexpressed by the target cells take advantage of the enhanced permeability and retention (EPR) phenomenon often present in the vasculature of diseased tissues. This allows them to pass preferentially from the general circulation into the diseased tissue, concentrating their effect. Variations on these systems are designed to use the presence or application of a stimulus to localise or trigger the release of the drug; for example, by a change in the environmental pH [3], or by application of heat (an example being Thermodox® (Celsion Corp., Columbia, MD, USA) [4]), light (as for photodynamic therapy [5]) or an external magnetic field [6]. In the case of certain tumours, treatment can be tumour-specific by means of physical targeting (so-called locoregional treatment), such as topical administration to skin cancers, drug infusion into the organ bearing the tumour, and directly implantable delivery systems, either in the resection margins of excised tumours (such as the Gliadel® wafer (Archimedes Pharma Ltd., Reading, UK) for treating brain tumours [7]) or by direct intra-tumoural injection (as for Oncogel® (Protherics Ltd., London, UK) in the treatment of oesophageal cancer [8]).

In this review, the use of embolic drug-eluting bead (DEB) systems is focused on, in which the drug carrier is delivered intra-arterially through catheters that can be positioned close to the main arterial supplies that feed particular tumours, causing primarily a physical blockage of the artery in combination with a sustained local delivery of drug.

1.1 Transarterial chemoembolisation and liver cancer

Transarterial chemoembolisation (TACE) is a minimally invasive therapeutic procedure performed by interventional radiologists. It involves the use of various imaging methods to navigate guidewires and catheters to various sites within the body by means of the major blood vessels. The aim is to position a catheter within the arterial supply in close proximity to a hypervascular tumour, in order that chemotherapy can be infused in a locoregional fashion; this is followed by the delivery of an embolisation agent to cause a blockade in the arterial flow and slow down the wash-out of the chemotherapy from the tumour. TACE is a well-established technique and is particularly useful in the treatment of liver cancers because of the dual aspect to its blood supply. The liver is supplied with oxygenated blood from both the hepatic artery (25%) and portal vein (70%); yet most liver tumours derive their blood supply from the hepatic artery predominantly, meaning that flow through these vessels can be occluded without subsequent complete ischaemia of the whole organ.

Primary liver cancer, or hepatocellular carcinoma (HCC), is the seventh most common cancer worldwide [1], and its incidence is on the increase owing to the prevalence of hepatitis B and C viral infections. Although the rate of occurrence is relatively low in the West, globally there are ~ 1 million new cases a year. Its treatment is according to the extent of disease progression and stage of underlying disease, and includes potentially curative treatments for early stage disease such as resection, transplantation and ablative techniques, and palliative treatments for intermediate disease such as TACE and new agents (e.g., sorafenib). Metastatic liver cancer is caused by the metastasis of primary tumours elsewhere in the body, such as stomach, pancreas, neuroendocrine,

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melanoma, breast, ovarian or, most commonly, of colorectal origin (mCRC). It is more common in the Western world than HCC, with ~ 1.8 million cases a year. Such tumours of the liver are generally less vascular than HCC and are not commonly treated by TACE, as the focus for therapy has been systemic in approach to address the metastatic nature of the disease. There remains a need, however, to control the liver-dominant disease as liver failure is often the main cause of death in patients with metastases.

There are many variations in the TACE procedure used from hospital to hospital, including position of the catheter within the organ, choice of chemotherapeutic agent, the option to use oily contrast medium in addition for increased embolic effect and imaging properties, and choice of embolisation device (permanent or temporary) and its size. With this wide variety of clinical practice, it has been only relatively recently that two independently conducted randomised clinical trials have demonstrated a significant benefit for TACE in the treatment of HCC over palliative care, albeit with quite different TACE approaches [9,10]. In an attempt to simplify and standardise the practice of TACE, the concept of an embolic DEB system has been mooted for quite some time. Kerr described the ideal attributes of just such a system in 1987 [11]: deliverable through microcatheters; in sizes useful for embolisation of target vessels; made from biocompatible, non-immunogenic materials; with no drug-device incompatibility issues; capable of carrying a therapeutic dose of a drug; and releasing it locally in a controlled and predictable manner at therapeutic levels locally in the tissue. Since that time there have been numerous studies investigating an array of different polymeric embolic microsphere systems for the controlled and sustained delivery of a wide variety of chemotherapeutic agents. Again, a lack of a common approach and variation in use meant that none of these systems progressed significantly until late 2004, when the first commercially available embolic DEB was launched in Europe: DC Bead® [12]. This device was initially approved for TACE in combination with anthracycline drugs in the treatment of hypervascular tumours, particularly HCC. The drug is added to the device in the hospital, before the procedure, where the bead, by virtue of its chemical structure, sequesters the drug from solution, allowing it to be delivered safely as a drug–device combination to the patient in a simple one-step TACE procedure [13] (so-called DEB-TACE). Subsequently, it has also been shown that DC Bead can load other classes of antineoplastic drugs, such as the camptothecins [14], allowing for its use in other clinical settings, such as metastatic colorectal cancer.

Competitive technologies:

- TACE has been performed for many years with a variety of different products. In Japan in particular, the technique is generally performed using the chemotherapeutic agent mixed together with a contrast agent made from iodinated poppy seed oil (Lipiodol®, guerbert, Paris, France) [15], used because the oil is believed to accumulate in the tumour, although this is unproven [16]. This viscous unstable emulsion is administered into the artery to slow the flow of blood and is sometimes followed by administration of an embolic agent.
- Other embolic agents used in conventional TACE can be classed as temporary materials such as a slurry of Gelfoam® (Pfizer Inc, New York, USA) [17] (a gelatin-based material for haemostasis, again used off-label), or degradable starch microspheres (Spherex® Pharmacia, Sweden [18]); or permanent embolics such as polyvinyl alcohol particles or microspheres (Contour and Contour SE® Boston Scientific Corp., Marlborough, MA, USA [19]), polyvinyl alcohol hyrdogel beads (Bead Block® Biocompatibles UK Ltd., Farnham, UK), trisacryl gelatin microspheres (Embosphere Microspheres® Merit Medical, Utah, USA [20]), or polyphosphazene-coated polyacrylate microspheres (Embozene Microspheres® Celanova BioSciences, GA, USA [21]). These agents, however, cannot be loaded with drugs and are used only for the final embolisation step of the TACE procedure.
- There is a superabsorbent embolic microsphere composed of polyvinyl alcohol-*co*-sodium acrylate known as HepaSphere® (Merit Medical, Utah, USA), which can absorb drug from aqueous solution. A recent review of such superabsorbent microspheres from Japan suggests handling and outcome with this product are quite different from those seen with DC Bead [22].
- Radioactive ^{90}Y microspheres (SIR-Sphere® Sirtex Medical, Wilmington, MA, USA, and TheraSphere® MDS Nordion Inc., Ottowa, ON, Canada) are approved for use in the radioembolisation of mCRC [23] to the liver and also are being used in the treatment of HCC [24]. These devices are much smaller than the embolisation microspheres and are prescribed on demand for each patient requiring specific dose calculations and use of the product within a narrow time window before degradation of the isotope.
- Non-embolisation competitive technologies used in the locoregional treatment of liver tumours include radiofrequency ablation, cryoablation, microwave ablation and percutaneous ethanol injection. These approaches are used preferentially for smaller tumours where they are considered potentially curative or where TACE is unsuitable.
- Systemic treatments specifically indicated for advanced primary liver cancer include the recently approved sorafenib (Nexavar®), a multikinase inhibitor that targets multiple pro-survival pathways and induces apoptosis in HCC [25].

1.2 DC Bead embolic drug-eluting beads

DC Bead is composed of a polyvinyl alcohol hydrogel hybrid polymer with 2-acrylamido-2-methylpropanesulphonate sodium salt (AMPS, **Figure 1**) formed into a microspherical shape. The hydrogel structure consists of a swollen network

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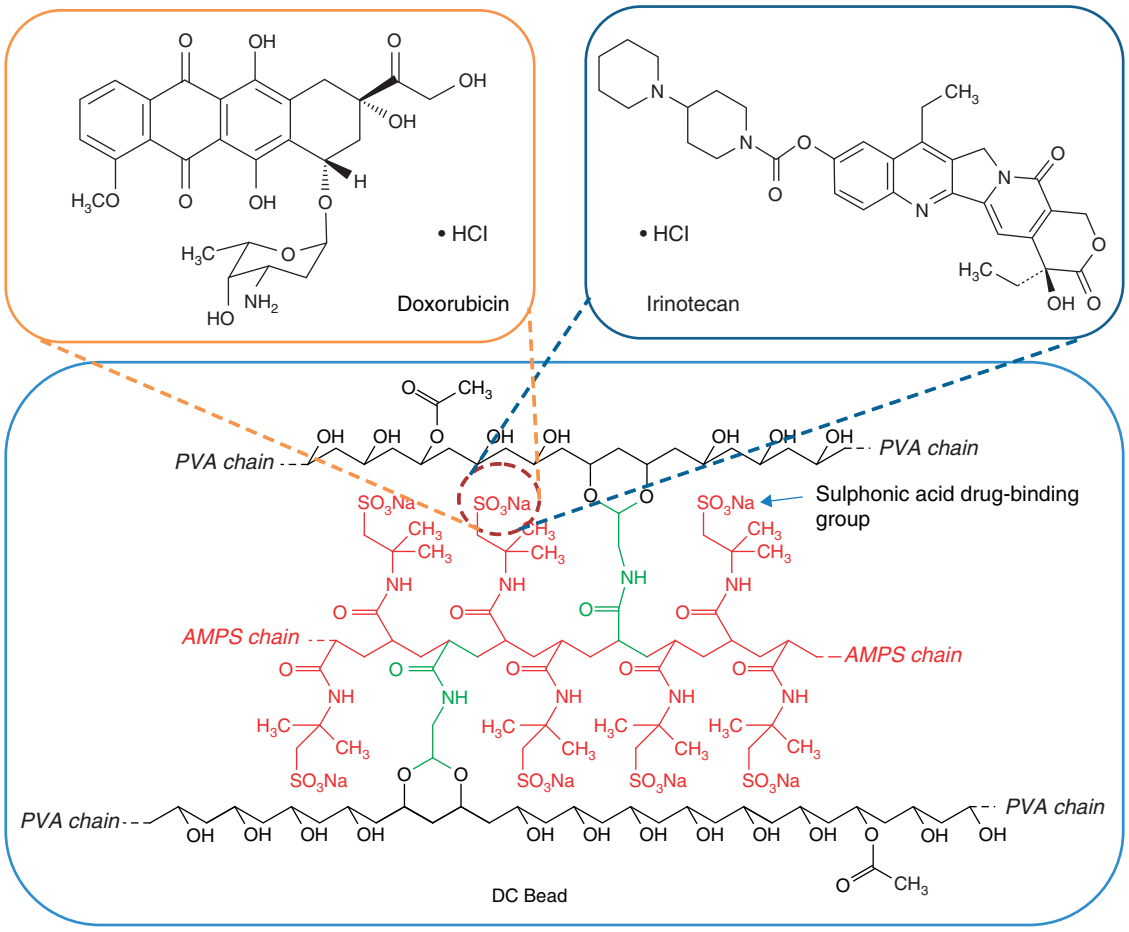

Figure 1. Chemical structure of DC Bead, doxorubicin and irinotecan and the sites of binding interaction.

of hydrophilic polymer chains composed of ~ 95% water by weight. The AMPS provides a plethora of sulphonic acid groups that are capable of ion exchange between the sodium counter ions and other positively charged ions in the solution in which the beads are immersed. When the solution contains a suitably charged drug, such as doxorubicin hydrochloride, the drug diffuses into the structure, displaces the sodium ions and binds through electrostatic interactions to the sulphonate groups [26]. This property means that DC Bead can be provided to the physician unloaded, wherein the drug can be subsequently loaded before use. This does mean, however, that the product must be prepared at least a few hours in advance of the procedure to allow time for the drug to load.

A multitude of biocompatibility tests and implantation studies has been performed on the unloaded device itself, which demonstrate safety and excellent tissue compatibility of the PVA-based hydrogel material, and that the beads are effective in forming a permanent occlusion in arteries. **Table 1** lists some of the extra characterisation studies that have been carried out on the device combined with either doxorubicin (doxorubicin drug-eluting bead, DEBDOX™) or irinotecan (irinotecan drug-eluting bead, DEBIRI™). Although not all drugs are suitable for loading into DC Bead, drug–bead interaction studies have shown loading of hydrochloride salts of anthracycline compounds (such as doxorubicin, epirubicin and daunorubicin) and certain camptothecin derivatives (irinotecan and topotecan) is particularly facile [12]. Drug loading into the beads is accompanied by a decrease in water content and bead diameter (owing to displacement of water by the more hydrophobic drug) and a concomitant increase in mechanical resistance to compression [26]. Drug uptake by ion exchange is extremely efficient (> 99%), as long as there are no other competitive ions present in solution, to a level dependent on the total number of ionic binding sites in the beads. This gives rise to a maximum loading capacity of 37.5 mg/ml of beads for doxorubicin and 50 mg/ml of beads for irinotecan. These drug concentrations are high enough to be therapeutically active when delivered locoregionally, as volumes of 1 – 4 ml of beads are typically used in a TACE treatment. Drug release studies have been reported using a variety of different elution methods, including US Pharmacopeia (USP) methods 1, 2 and 4 and the T-cell apparatus; the latter provides probably the most useful drug elution data, which can be used for *in vitro–in vivo* correlation (IVIVC) to predict

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Table 1. Preclinical studies for drug-eluting beads.

	Study objective	Techniques used	Main findings	Ref.
In vitro studies	Physicomechanical evaluation	Compression testing; catheter delivery studies; optical microscopy; gravimetric analysis; confocal scanning microscopy	Resistance to compression increases with drug loading; no fragmentation post-delivery; bead diameter and water content decrease with drug loading; drug distribution concentrated in the outer portions of the bead	[13,14,26]
	Drug loading and release studies	UV/visible spectroscopy; HPLC; USP 1, 2, 7 dissolution methods and T-cell apparatus	Maximum loading capacities; drug release increases with ionic strength and temperature; drug binding is reversible	[13,14,26,27]
	Drug stability studies	HPLC, UV/visible spectroscopy	Drug is stable once loaded for > 2 weeks; must be protected from light; all drug can be eluted; irinotecan is loaded and eluted in its lactone form	[12,28,29]
In vivo studies	Safety, local toxicity and pharmacokinetics	Non-tumour, porcine model of liver embolisation	Safe with no adverse clinical findings; smaller DEBDOX cause more necrosis; DEBIRI well tolerated, minimal toxicity; 28 + 90 day implants Plasma C_{max} and AUC much lower for DEB than IA administrations of drug	[14,30]
	Efficacy and pharmacokinetics	VX-2 tumour rabbit liver model of embolisation	DEB efficacious in killing tumour; C_{max} and AUC much lower for DEB than IA administrations of drug	[31,32]
	Safety, local toxicity and pharmacokinetics of repeat administration	Non-tumour, porcine model of liver embolisation (DEBIRI only)	Safe with no adverse clinical findings; no overlapping PK or toxicity	Data on file at Biocompatibles
	Efficacy	Rat embolisation model of liver cancer metastases	Complex model using 75 – 100 mm beads; DEBDOX toxic at high dose; DEBIRI well tolerated at highest dose; both DEBs efficacious	[35]
	Safety and pharmacokinetics	Sheep model of lung embolisation (DEBIRI only)	Safe with no adverse clinical findings; well tolerated, minimal toxicity Plasma C_{max} and AUC much lower for DEB than IA administrations of drug	[34]
	Drug distribution studies	Fluorescence microscopy; FTIR microspectroscopy; epifluorescent microscopy, m-computed tomography	DEBDOX only; drug at therapeutic levels several hundred micrometres from the bead edge. Drug at therapeutic levels for several weeks; more drug associated with clusters of beads; small beads distribute more evenly and distally	[33,68]

DEB: Drug-eluting bead; DEBDOX: Doxorubicin drug-eluting bead; DEBIRI: Irinotecan drug-eluting bead; FTIR: Fourier transform infrared; IA: Intra-arterial; PK: Pharmacokinetic.

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the initial burst of drug from the beads over the first 24 h, and hence the potential for systemic toxicity [14,27]. In the case of DEBIRI, it has been advantageously demonstrated that irinotecan is preferentially bound and released from DC Bead in its active lactone form [28]. Once loaded, the drug has been shown to have adequate physicochemical stability over a period of at least 28 days [29].

2. Preclinical safety and efficacy studies

2.1 Preclinical safety evaluations in non-tumour-bearing models

In vitro studies are of only limited use when attempting to predict the combined embolic and local drug release effects of embolic DEBs. Some evaluations in non-tumour liver embolisation models have demonstrated the safety of DEB administration, which causes a transient and fully reversible rise in liver enzymes (ALT and AST) and localised toxic effects in the treated areas of liver parenchyma [14,30]. Smaller DEBDOX were shown to produce more widespread necrosis owing to their more diffuse distribution in the tissue, whereas DEBIRI, irrespective of size, was far better tolerated by the normal liver tissue, with much less evidence of local tissue toxicity compared with DEBDOX.

2.2 Pharmacokinetic and tissue distribution studies

Pharmacokinetic (PK) studies in non-tumour and tumour-bearing models confirmed both a lower systemic peak concentration (C_{max}) and overall exposure (area under the curve [AUC]) to either drug when delivered by DEB compared with intra-arterial infusions of drug alone [14,30-32]. Advanced techniques such as Fourier transform infrared microscopy, fluorescent microspectroscopy and epifluorescent microscopy have been applied to sections of tissue explants and show that for DEBDOX there is an initial surge of drug across the vessel wall and into the surrounding tissues for the first few hours (**Figure 2**), which diminishes to a level that remains above the IC_{50} for tumour cells for several weeks [33]. The drug diffuses from the beads several hundred micrometers from the bead edge, the levels of which slowly diminish over months, with a small amount of drug remaining detectable within the beads even at 90 days. For DEBIRI, diffusion from the beads and into the tissue is far more rapid, with most of the drug being released within a few days, as demonstrated in a sheep pulmonary artery embolisation model [34].

2.3 Preclinical efficacy evaluation in tumour-bearing models

To demonstrate efficacy for the DEBs, the rabbit VX-2 liver tumour model, a known model of hypervascular tumour, has been used [31,32]. For DEBDOX, this model shows high levels of drug retention within the tumour compared with that released in the plasma and a significant tumour necrosis approaching 100% at 7 days post-embolisation; similar efficacy has been reported for DEBIRI. In a new embolisation model of rat colorectal liver metastases, smaller DC Beads were required (75 – 100 μm) in order to treat the smaller vessels [35]. Despite the complexity of this model, both DEBDOX and DEBIRI were shown to be effective in reducing overall tumour burden in the liver. DEBDOX, however, gave rise to severe dose-limiting toxicity in the liver, whereas DEBIRI was extremely well tolerated even at the highest dose.

3. Clinical experience with DC Bead

3.1 DEBDOX for treatment of hepatocellular carcinoma

The most effective way to treat HCC is surgical removal; however, ~ 70% of patients are not candidates for surgery owing to the size or location of the tumour, or other co-morbidities. The principal application of TACE, including DEB-TACE, is in these patients with unresectable HCC in order to control symptoms and prolong patient survival [36].

As the clinical experience with DC Bead has grown, it is evident that DEB-TACE has the potential as a treatment option across a broader spectrum of clinical situations in patients with intermediate and advanced HCC (**Figure 3**). DEB-TACE may allow patients to proceed to other potentially curative treatment options for which they were initially unsuitable. Tumour size may be reduced such that surgical resection becomes feasible, or the tumour may be downstaged, permitting a subsequent liver transplant. Also, although a patient may initially be assessed as suitable for a liver transplant, the shortage of donors results in long waiting lists, during which time the disease may continue to progress. In some cases this means that the patient may no longer be eligible for a liver transplant. By undergoing DEB-TACE while on the transplant list, the aim is to control the tumour until such time as a transplant becomes available (bridge to transplant) [37].

Clinical studies have been performed or are continuing in these different clinical settings (**Table 2**). DEB-TACE can also be considered as a neoadjuvant treatment in the setting of resectable HCC, with the aim of preventing recurrence and prolonging patient survival.

3.1.1 Patients unsuitable for liver transplant or resection

So far, eight prospective clinical studies have reported on the safety and efficacy of DEBDOX in the treatment of patients with unresectable HCC [38-45], including a prospective randomised study comparing DEB-TACE with conventional TACE (c-TACE), the so-called PRECISION V study (**Table 2**) [40].

3.1.1.1 Product

The initial studies (PRECISION I [45] and II [43]) used bead sizes of 500 – 700 μm; however, as DC Bead was marketed

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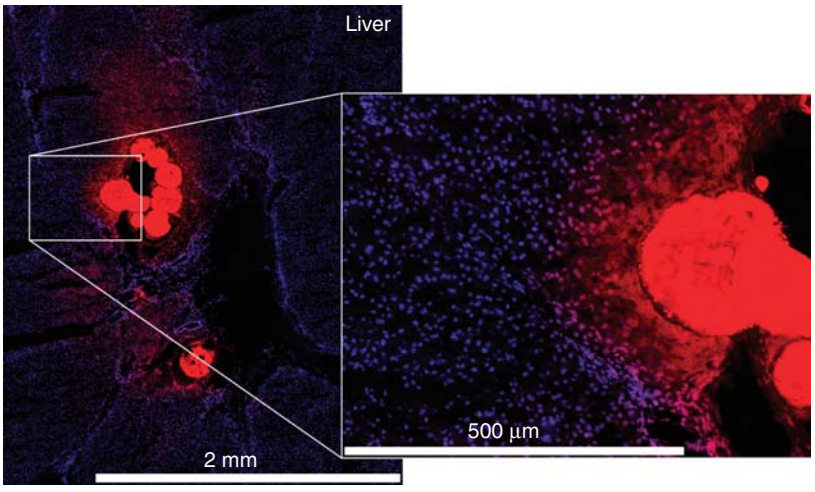

Figure 2. Epifluorescence microscopy image of DEBDOX 2 h post-delivery into the hepatic arterioles of the liver, demonstrating drug diffusion into the surrounding tissue (blue = hepatocyte nuclei, red = doxorubicin).

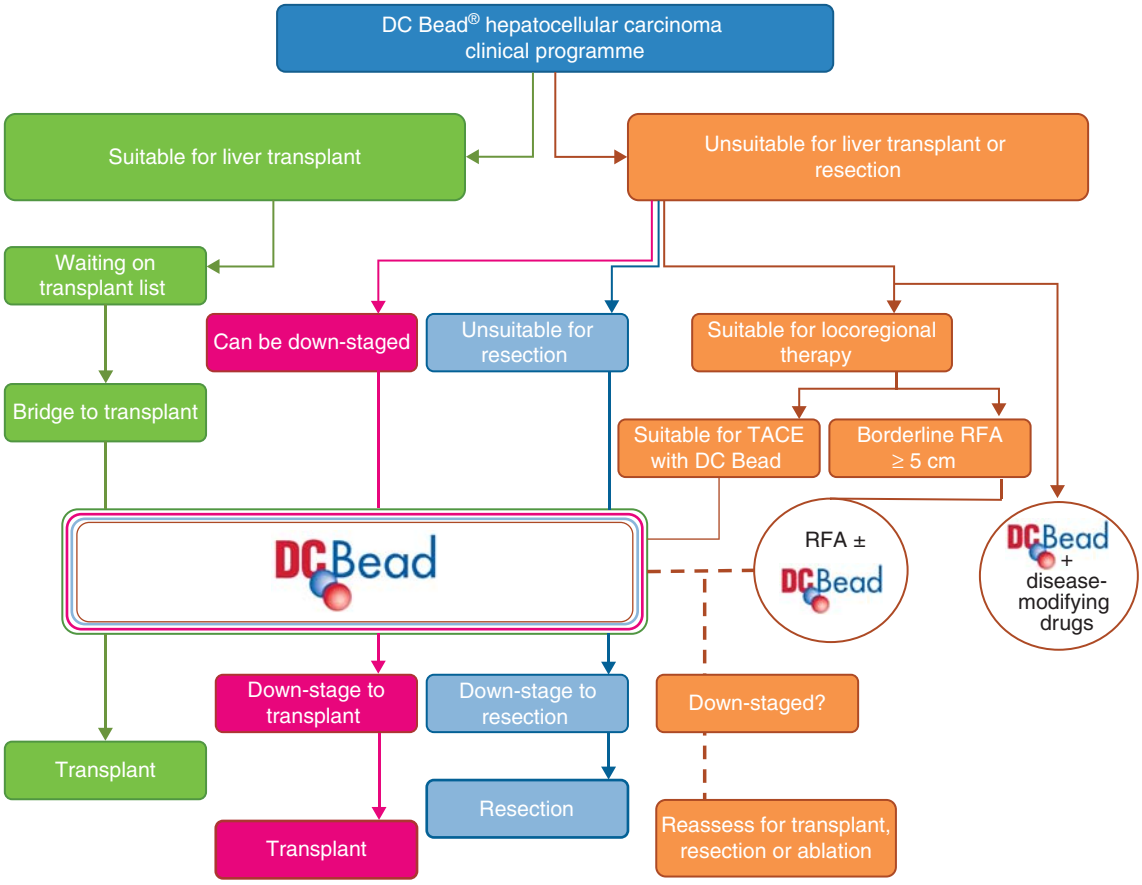

Figure 3. Algorithm showing DC Bead hepatocellular carcinoma clinical programme.
RFA: Radiofrequency ablation; TACE: Transarterial chemoembolisation.

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Table 2. Clinical trials for hepatocellular carcinoma with DEBDOX.

	Study	End point	Status	Number of patients	Location
Bridge to liver transplant	Prospective randomised study of transarterial doxorubicin-eluting bead embolisation versus conventional TACE in the treatment of patients with HCC in the liver	Histological response and transplantability	Recruiting	88	Germany
	Assessment of chemoembolisation using doxorubicin-eluting beads in patients listed for orthotopic liver transplantation with HCC with explant correlation	Histological response and transplantability	Recruiting	20	New Zealand
Down-stage to resection or transplant	A pilot study of neoadjuvant therapy for HCC using doxorubicin-eluting embolic beads	Down-stage to transplant	Recruiting	20	USA
	LC Drug-eluting bead for treatment of liver cancer that cannot be surgically removed	Histological response and transplantability	Recruiting	18	USA
Unsuitable for liver transplant or resection	Chemoembolisation of HCC with drug-eluting beads: efficacy and doxorubicin pharmacokinetics (PRECISION I)	Safety, efficacy and pharmacokinetics (dose escalation)	Complete [45]	27	Spain
	A Phase I/II trial of chemoembolisation of HCC using new intra-arterial drug-eluting bead (PRECISION II)	Phase I: dose escalation Phase II: safety and efficacy	Complete [43]	35	Hong Kong
	Prospective randomised study of doxorubicin drug-eluting bead embolisation in the treatment of HCC: results of the PRECISION V study	Safety and efficacy	Complete [40]	212	International multi-centre
	Doxorubicin-eluting bead-enhanced radiofrequency ablation of HCC: a pilot clinical study	Safety and efficacy	Complete [50]	20	Italy
	Prospective randomised comparison of chemoembolisation with doxorubicin-eluting beads and bland embolisation with Bead Block for HCC	Efficacy, safety, time to progression and survival	Complete [42]	41	Greece
	Single-centre Phase II trial of TACE with drug-eluting beads for patients with unresectable HCC	Efficacy, safety, progression free survival and overall survival	Complete [44]	20	USA
	A Phase II randomised, double-blind, placebo-controlled study of sorafenib or placebo in combination with TACE performed with DC Bead and doxorubicin for intermediate stage HCC	Time to untreatable progression	Recruiting	300	International multi-centre

HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolisation.

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in Europe and interventional radiologists became more experienced with DEB-TACE, smaller bead sizes began to be used. For example, a combination of two sizes, 100 – 300 and 300 – 500 μm, enabled more beads to be delivered before complete occlusion was achieved [42], with no associated increase in non-target embolisation or other complications. Further, it is inferred that use of smaller beads may achieve a more distal embolisation, whereas larger beads may cause more proximal embolisation that penetrates less into the tumour and enables vascular supply by means of collaterals that are not blocked.

Phase I/II clinical studies included a dose escalation to determine the maximum tolerated dose of DEBDOX (**Table 2**). Dose-limiting toxicity was not observed in these studies. Subsequently, the recommendation is that up to a maximum dose of 150 mg of doxorubicin administered in an embolic procedure, equivalent to 4 ml of DEBDOX, is safe. At this dose up to six repeat procedures are possible, remaining within the doxorubicin maximum lifetime dose limit recommended owing to the risk of congestive heart failure [46]. However, this limit may not be restrictive to the use of DEBDOX, as so far no patients have been documented as receiving six or more procedures and the data from the clinical studies suggest that, in general, the volume (dose) of embolic that can be delivered decreases with each successive procedure.

3.1.1.2 Safety

The most common procedure-related complication is post-embolisation syndrome (PES), consisting of fever, abdominal pain, and nausea and vomiting, as would be expected following any chemoembolisation procedure. The PRECISION V study allows for a direct comparison of DEB-TACE with c-TACE: the incidence and frequency of PES were comparable in the two treatment arms [40].

An increase in liver enzymes post-embolisation is a frequent occurrence following c-TACE. In the DEBDOX studies, raised liver enzymes were observed 3 – 4 days post-embolisation. Similar to the animal studies, these levels returned to pre-embolisation levels within a few days. PRECISION V indicates that liver toxicity is lower following treatment by DEBDOX than c-TACE, with the mean maximum increases in AST and ALT being less than with c-TACE. Liver abscess and liver failure have also been reported in patients, but at frequencies no greater than expected for c-TACE.

It is worth noting that few doxorubicin-related systemic adverse events (AE) were reported in these studies, further supporting the presumption that DEBDOX fulfils the desired characteristics of targeted locoregional therapy. Indeed, in Malagari *et al.*'s study comparing DEBDOX with bland embolisation (i.e., no chemotherapy), there was no statistically significant difference in the nature and severity of adverse events between the two groups [42]. In PRECISION V, compared with c-TACE, the level of doxorubicin-related AE in the DEBDOX group was significantly lower, despite a higher mean total dose administered. Importantly, cardiac function was maintained in the DEBDOX group.

Overall, the studies so far show that DEB-TACE is well tolerated, and in subpopulation analyses safety is confirmed in patients with worse prognostic factors, when compared with c-TACE.

3.1.1.3 Pharmacokinetics and sustained delivery

Varela *et al.* reported significantly lower doxorubicin C_{max} (78.97 ± 38.3 ng/ml versus 895.66 ± 653.1 ng/ml, p = 0.001) and AUC values (662.6 ± 417.6 ng/(ml min) versus 1532.98 ± 295.2 ng/(ml min), p = 0.005) in DC Bead patients than in c-TACE patients (PRECISION I) [45]. In another study in Hong Kong, low C_{max} levels were also observed, even at the highest dose of doxorubicin administered (52.8 ± 41.5 ng/ml for 150 mg dose cohort, PRECISION II) [43].

Therefore, preclinical and clinical studies have demonstrated lower systemic doxorubicin plasma levels compared with c-TACE (**Figure 4A**), with the rabbit VX2 model offering a reasonable prediction of the pharmacokinetic profile for systemic exposure to doxorubicin (**Figure 4B**) [31].

Furthermore, preclinical evidence for longevity of the drug release (Section 2.2) is further supported by a recent study using contrast-enhanced ultrasonography, which substantiates this premise by demonstrating a sustained antitumour effect of DEBDOX [47].

3.1.1.4 Efficacy

Response rates are reported as the measure of efficacy in all the DC Bead trials; long-term follow-up is still continuing. Survival data are available from the Phase I/II study, with 88.9% patients alive at 2 years [45].

Malagari *et al.* reported an objective response (OR) rate at 6 months of 73.2% for patients receiving DEBDOX, compared with 55.8% with bland embolisation [42]. The PRECISION V study reported an OR rate at 6 months (EASL criteria) of 52% with DEBDOX and 44% with c-TACE [40]. This did not reach statistical significance as the control arm had a better response rate than anticipated in the study design; though these data do support the OR rates observed in earlier studies, with a trend towards improved response rate versus c-TACE. Analyses of the population with most advanced liver disease, however, revealed a significant improvement in OR rate in these difficult-to-treat patients.

3.1.2 DEB-TACE before orthotopic liver transplant

As discussed above, DEB-TACE can be used before liver transplant as a bridge-to-transplant or for down-staging of the disease in patients with HCC. The efficacy of such an approach is under evaluation. One important measure of improved outcome is the extent of tumour necrosis before transplant, as incomplete necrosis may increase the risk of tumour spread post-transplant [48]. A retrospective

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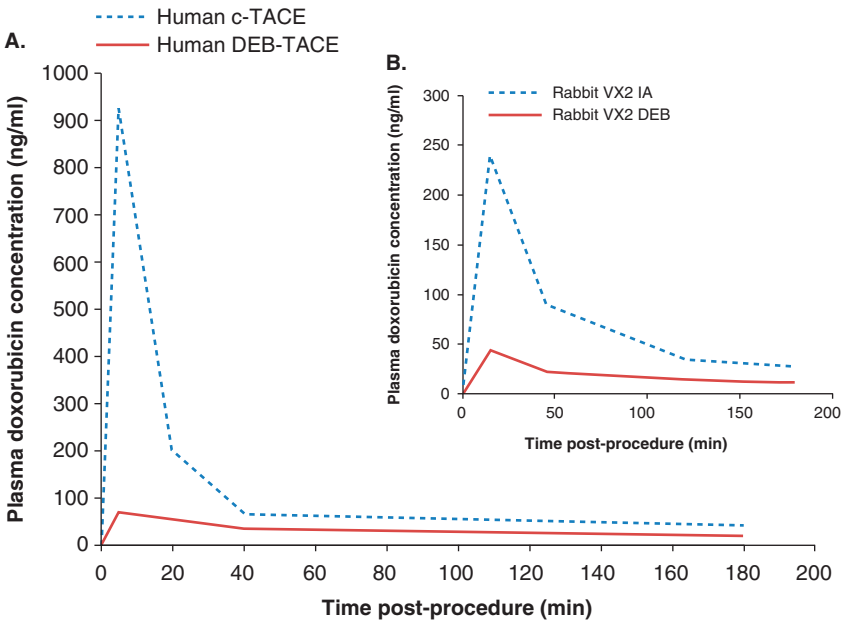

Figure 4. (**A**) Doxorubicin plasma PK from patients in the PRECISION I clinical study compared with (**B**) doxorubicin plasma PK in the VX2 rabbit model.

c-TACE: Conventional transarterial chemoembolisation; DEB: Drug-eluting bead; PK: Pharmacokinetic; TACE: Transarterial chemoembolisation.

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preliminary study using DC Bead loaded with epirubicin (an isomer of doxorubicin) compared the extent of necrosis with bland embolisation versus DEB-TACE in patients on a transplant waiting list [49]. Although both techniques revealed a high percentage of necrosis on computerised tomography (CT) scan, once the explanted livers were examined histologically, complete necrosis was achieved for 77% of lesions in the DEB-TACE-treated livers, but for 27.2% with bland embolisation. Further studies are required to determine the clinical benefit of DEB-TACE post-transplant.

3.1.3 *Combination of DEBDOX and radiofrequency ablation*

In patients with liver cirrhosis, candidates for resection have to be carefully selected to reduce the risk of postoperative liver failure. Image-guided percutaneous ablation is now accepted as a non-surgical approach for these patients; however, outcome is dependent on tumour size. Experimental studies have shown a synergy between radiofrequency ablation (RFA) and adjuvant chemotherapy. Based on these findings, Lencioni *et al.* conducted a pilot clinical study to evaluate the safety and efficacy of DEBDOX-enhanced RFA in the treatment of patients with HCC [50]. In this study, the RFA was performed before the DEB-TACE. This treatment protocol was very well tolerated – no major complications occurred, and no deterioration in liver function was observed. The response rate in the target lesions was high, indicating that DEB-TACE enhances the effect of RF ablation in patients refractory to standard RF treatment.

3.1.4 *Combination of DEBDOX with systemic therapies*

Chemoembolisation is performed to induce ischaemia, leading to necrosis of the tumour tissue. Creation of hypoxic areas in the tumour may lead, among other things, to the upregulation of hypoxia-inducible factor 1-α (HIF-1α), which in turn triggers a neoangiogenic reaction with a significant growth of adjacent satellites. The association of DEB-TACE with oral agents such as sorafenib, sunitinib and everolimus therefore has a strong rationale and is now under clinical investigation (sorafenib: SPACE – NCT00855218; sunitinib: SATURNE – NCT01164202; everolimus: Swiss study, NCT01009801).

3.1.5 *DEBDOX for treatment of other liver tumours*

DEBDOX is becoming well established as a treatment for HCC; interventional radiologists are evaluating the potential of DEBDOX in the treatment of other liver tumours. Low-grade gastroenteropancreatic endocrine tumours metastasise predominantly to the liver and have a poor response rate to systemic therapy. Curative surgery is rarely achievable. Locoregional therapies such as TACE have been evaluated. DEB-TACE is feasible in this patient population, with response rates of 80% (16/20 patients, by RECIST criteria) [51]. There was a high level of prolonged postprocedural pain, which was unexpected based on previous experience. Peripheral liver necrosis was found on follow-up imaging in these patients; however, this did not result in an increase in liver failure.

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In another report [52], 11 patients with unresectable intrahepatic cholangiocarcinoma underwent TACE with DEBDOX. The procedure was well tolerated, and a response rate of 100% was observed in patients at 3 months (by RECIST criteria). Although only a few patients were evaluated, median survival was reported as 13 months, which was better than patients receiving palliative care or systemic chemotherapy.

These two reports therefore confirm the application of TACE with DEBDOX in the treatment of other liver tumours, although further learning is required to optimise technique and patient selection.

3.2 DEBIRI for treatment of liver metastases

3.2.1 Patients with metastatic colorectal cancer

Approximately 60% of patients with colorectal cancer will develop metastatic disease, which is localised to the liver alone in half of them [53]. Involvement of the liver is associated with poor survival. Although systemic therapy can slow growth and even cause regression in hepatic tumours, long-term survival without local therapy is unlikely. Surgery remains the optimal first-line treatment for hepatic mCRC, however the resectability rate is low (estimated between 15 and 25%). Locoregional therapies for mCRC include RFA, cryoablation, laser interstitial tumour therapy (LITT), radioactive ^{90}Y microspheres and chemoembolisation.

Compared with HCC, where TACE is considered the standard treatment, the use of TACE for mCRC is not established, with only a few clinical investigations having been conducted since the 1990s. These initial results were comparable to response and survival data from systemic use of newer second-line agents that were not available when these trials were designed; hence, added complexity and use of variable technique have meant this approach has not been widely adopted. A large study was conducted wherein 463 patients with unresectable liver mCRC who did not respond to systemic chemotherapy were repeatedly treated with chemoembolisation in 4-week intervals. The local chemotherapy protocol consisted of mitomycin C alone, mitomycin C with gemcitabine, or mitomycin C with irinotecan. Embolisation was performed with lipiodol and starch microspheres for vessel occlusion. Evaluation of local tumour control resulted in partial response (14.7%), stable disease (48.2%) and progressive disease (37.1%). The 1-year survival rate after chemoembolisation was 62%, and the 2-year survival rate was 28% [54]. Thus, as techniques and products for TACE have improved, there has been renewed interest in the use of TACE in mCRC.

As with HCC, the application of DEB-TACE for the treatment of hepatic metastases can be envisaged in several patient populations with liver-dominant disease: patients with unresectable disease; as a tool to achieve shrinkage of initially unresectable tumours allowing resection and therefore improving long-term outcome (surgical down-staging); or as a neoadjuvant treatment providing the best chance of improved survival for surgical candidates. Nearly two-thirds of patients selected for liver resection of mCRC will have a recurrence due to microscopic residual disease undetected at the time of the original liver resection. The neoadjuvant treatment of resectable mCRC is a relatively new concept, with few studies reported so far in the literature. As such, the long-term benefits are still under investigation. Nonetheless, the potential benefits of neoadjuvant therapy of resectable mCRC include elimination of micro-metastatic disease and dormant cancer cells in the liver, and may decrease the risk of intraoperative dissemination of cells; it may improve the rate of complete resection and decrease the amount of liver that needs to be removed at surgery, as well as testing the chemoresponsiveness of patients in order to determine suitable adjuvant treatment post-resection [55].

Several recent reports have evaluated the role of DEB-TACE in the treatment of colorectal cancer patients with liver metastases [56-62].

3.2.1.1 Product/technique

DEB-TACE for metastatic liver disease is performed in a similar manner to DEB-TACE for HCC. In general, these investigators have used smaller size range DEBIRI beads (100 – 300 µm), although 300 – 500 and 500 – 700 µm have also been used, with up to 4 ml of bead delivered per embolisation treatment. No dose-limiting toxicity has been reported, and serial treatments at 2-week intervals have been reported. Given the more diffuse nature of the disease compared with HCC, the DEB-TACE technique is adapted based on the distribution of the tumours, varying from more selective subsegmental to multiple lobar infusions to achieve an embolisation end point [59].

3.2.1.2 Safety

No formal dose escalation study has been reported, however there have been no reports of dose-limiting toxicity, and multiple treatments are not associated with any cumulative toxicity. As for HCC, PES is the most common adverse event reported in patients. Events typically associated with systemic irinotecan, such as diarrhoea and leukopenia, are rarely reported. An interim analysis of a Phase III study reported at ASCO 2009 compared DEBIRI versus FOLFIRI (a systemic chemotherapy regimen for colorectal cancer that includes irinotecan) [62]. The FOLFIRI arm of the study reported late toxicity, whereas the DEBIRI arm reported immediate (within 1 h) toxicity and post-embolisation syndrome effects lasting up to 2 weeks and then resolving. As the systemic effects are limited, the addition of locoregional therapy to existing combination therapies is not expected to add to the toxicity burden. Further, the pretreatment of patients with irinotecan-containing regimens does not preclude them from treatment using DEBIRI.

3.2.1.3 Pharmacokinetics

Systemic levels of irinotecan after DEB-TACE in 10 patients were lower than would be expected from a similar intravenous

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dose (221 ng/ml versus 685 ng/ml) and a correspondingly lower AUC (1958 ng h/ml versus 2963 ng h/ml) [63]. The plasma levels of SN-38 (the main metabolite of irinotecan) are not reduced to the same extent, which suggests that there is efficient conversion of irinotecan locally, and these systemic levels do not contribute to any significant toxicity.

3.2.1.4 *Efficacy*

Results from the first clinical studies with DEBIRI indicate a good local control of the liver metastases, with local disease control rates > 60% by modified RECIST criteria [57,58,61]. Although survival data are limited, Martin *et al.* reported a median overall survival of 343 days in a 55-patient study in which patients had unresectable hepatic metastases and had failed standard therapy [61]. Such outcomes are very promising, as these patients have already been treated for their metastatic disease. A small number of patients in this study subsequently became eligible for surgical resection, and post-resection median survival was 12 months [57]. Although some of these patients received systemic treatment concurrently, the principle of using DEB-TACE for down-staging to allow tumour resection is a valuable approach, giving more patients the opportunity of improved survival following surgery.

As data mature and larger studies are conducted, it will be possible to evaluate to what extent these response rates translate into a survival benefit for these patients. A recent report of a Phase III study showed a 43% improvement in 2-year overall survival (OS) when DEBIRI (median OS = 690 days) was compared with FOLFIRI (median OS = 482 days) in patients who had failed 2 or 3 lines of chemotherapy [64]. Several randomised studies are underway (**Table 3**), in which DEBIRI will be combined with systemic therapy and compared with systemic therapy alone. These studies may help to establish specific DEBIRI TACE clinical guidelines, providing a standardised, highly specific cost-effective treatment option for patients.

3.2.2 *DEBIRI for treatment of other liver metastases*

DEBIRI has also been evaluated in other cancer indications in which liver metastases are common, building on the experience in colorectal cancer. Uveal melanoma is a rare tumour that has a significant tendency to metastasise to the liver. The 1-year survival of patients after diagnosis of liver metastases is estimated at 10%. A Phase II study in 10 patients presenting with liver metastases from uveal melanoma showed an objective response in all patients following 1 – 2 DEB-TACE procedures. Compared with previous studies, DEB-TACE seems to provide a high overall response rate [65]. There were no procedure-related complications, and the toxicity profile was similar to that observed with DEB-TACE in mCRC.

A multi-institutional registry has been set up by Martin and colleagues, in which patients with hepatic malignancies are treated with DEBIRI [66]. So far, patients included in the registry have been most commonly diagnosed with mCRC and cholangiocarcinoma; other metastatic diseases include oesophageal, bladder, lung, carcinoid and anal cell carcinoma. The procedure was technically successful in the 109 patients (187 procedures). Treatment-related adverse events were reported in 19% of patients, the most frequent event being PES.

These investigations demonstrate the potential of TACE with DEBIRI in the treatment of liver metastases in patients with different primary cancers.

4. Conclusions

DC Bead has become a valuable therapy in the treatment of patients with intermediate HCC, owing to its ease of handling and use, combined with the clinical benefits of reduced chemotherapy-related side effects and high tumour response rates. Studies with DEBDOX suggest a potential survival advantage, but this remains to be demonstrated in a randomised setting, which would require significant patient numbers. The success of the product has led to investigation into its use beyond intermediate stage disease as recommended at present by BCLC and AASLD guidelines, in patients with early stage disease pre-liver resection or transplantation or in late stage patients in combination with new oral disease-modifying drugs.

Promising recent data have been generated in the setting of colorectal metastases to the liver. As these patients are essentially suffering from a systemic disease, DEBIRI is positioned as an adjunct therapy to intravenous chemotherapeutic regimens with the aim of controlling the local liver-dominant disease. This is a challenging indication given the large number of investigational studies that are underway with new agents; the potential for an effective treatment is, however, immense, and DEBIRI could offer a cost-effective locoregional option for patients.

5. Expert opinion and 5-year view

Since the introduction of DC Bead in 2004, there has been a shift in usage from larger beads (500 – 700 µm) in favour of the smaller size range product (300 – 500 and 100 – 300 µm). This change has been driven primarily by the desire to deliver the beads more distally into the tumour bed, although there is as yet no clear clinical evidence to suggest this is advantageous in terms of outcome. To this end, there has been a desire for products with a narrower size range than the 100 – 300 µm product, hence a new size range has recently been made commercially available (70 – 150 µm). DC Bead M1™ loaded with irinotecan is under investigation for the treatment of mCRC, and it has been reported that the narrower size range allows a much more distal embolisation end point, much closer to the tumour itself, which results in greater tumour necrosis [67]. The move to smaller products may also be catalysed by several continuing studies using beads that are also loaded with radiopaque material to make them visible under techniques such as angiography and

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Table 3. Clinical trials for hepatic metastases with DEBIRI.

	Study	End point	Regimen	Status	Number of patients
Colorectal	DEBIRI therapy of liver metastases from colon cancer with concomitant systemic oxaliplatin, fluorouracil and leucovorin chemotherapy, and antiangiogenic therapy	Safety, efficacy	FOLFOX + Avastin (IV) versus FOLFOX + Avastin + DEBIRI	Recruiting	70
	Chemoembolisation with irinotecan-loaded DC Bead® (DEBIRI) in combination with cetuximab in the first-line treatment of patients with KRAS wild-type metastatic colorectal cancer	Feasibility, safety, efficacy	FOLFOX + cetuximab + DEBIRI	Protocol in development	10
	A single-arm Phase II study of neoadjuvant therapy using irinotecan bead in patients with resectable liver metastases from colorectal cancer	Rate of R0 resection	DEBIRI before resection	Recruiting	20
	A randomised Phase II trial of irinotecan drug-eluting beads administered by hepatic chemoembolisation with Cetuximab (IV) versus systemic treatment with cetuximab in patients with refractory metastatic colorectal cancer and KRAS wild-type tumours	Safety, efficacy	Cetuximab + DEBIRI versus cetuximab + irinotecan	Recruiting	74
	DC Bead®/LC Bead® International Registry	Safety, efficacy	DEBIRI in current clinical practice	Recruiting	550
Melanoma	Transcatheter arterial chemoembolisation with doxorubicin-loaded LC Bead in the treatment of liver metastases in patients with stage IV metastatic melanoma: a multi-centre pilot, non-randomised feasibility trial	Feasibility, safety, efficacy	LC Bead + doxorubicin	Recruiting	40
Neuro-endocrine	Transarterial chemoembolisation of liver metastases from well-differentiated gastroenteropancreatic endocrine tumours with doxorubicin-eluting beads	Feasibility, safety, efficacy	DC Bead + doxorubicin	Complete [51]	30

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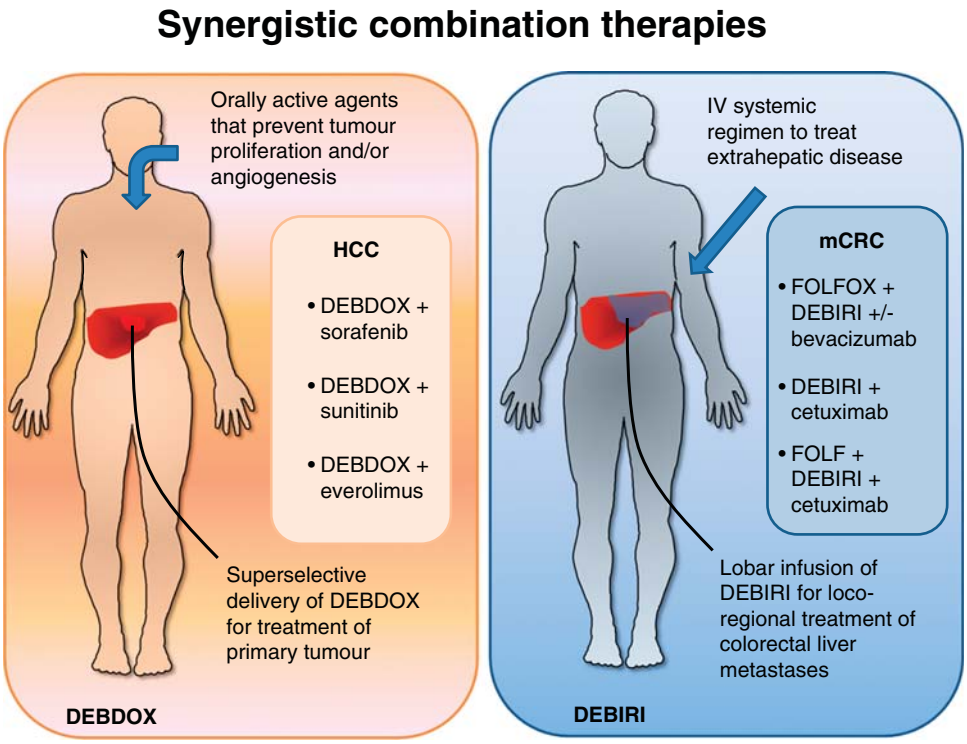

Figure 5. Synergistic combination therapies for DEB-TACE under investigation.
DEB: Drug-eluting bead; DEBDOX: Doxorubicin drug-eluting bead; DEBIRI: Irinotecan drug-eluting bead; FOLFOX: Folinic acid (FOL), Fluoruracil (F), Oxaliplatin (OX); HCC: Hepatocellular carcinoma; mCRC: Metastatic colorectal cancer; TACE: Transarterial chemoembolisation.

CT [68]. The relative distribution of different sizes of beads in the tissue can therefore, for the first time, be visualized, demonstrating that the smaller size range of beads embolise more distal arteries with a more frequent and homogeneous spatial distribution. The advantage of being able to see where the treatment has been successful and plan retreatment of any underembolised areas could make the imageable DEB an invaluable tool for the interventional radiologist in the future.

Regardless of the continuing debate regarding size and embolisation technique, the weight of clinical evidence so far supports the use of DEBDOX as a mainstay treatment for intermediate HCC. It is clear that clinical practice is heading the way trodden by conventional chemotherapy in that combination approaches are being selected as the most effective treatment regimes. As we have seen, DC Bead may be combined with other interventional techniques such as RFA to good effect. Moreover, combination of DEB-TACE with orally active agents designed to prevent tumour proliferation and/or angiogenesis has been identified as a promising strategy, and several clinical studies have already started to evaluate the effectiveness of such potential synergies (**Figure 5**). Here, these agents may act on several pro-survival pathways that are upregulated in the cancer cells on exposure to the hypoxic environment induced by the embolisation procedure itself. When followed by the very high local drug concentrations eluted from the beads, drug resistance mechanisms can be overcome and tumour response to the treatment is likely to be greater. The treatment of mCRC using DEBIRI has moved to combination therapies in a similar fashion (**Figure 5**), whereby the TACE is provided as an adjunct to existing systemic intravenous (IV) regimens in order to provide local control of the liver-dominant disease in addition to the treatment of more distant metastases.

As more data are gathered on the DEB delivery technique, it will at some point in the future be most convenient to supply the DEB preloaded with a set dose of drug, to negate the need for the physician to undertake the loading procedure. Preloaded DEBDOX (Precision Bead™) and DEBIRI (Paragon Bead™) have been developed but are not yet on the market. Despite advantages in their handling and safety, their fate lies ultimately in the provision of clinical data that support equivalence or a survival advantage for such products. Indeed, drug combinations within the bead are possible, with studies confirming that the combination of doxorubicin with drugs such as rapamycin has synergistic effects in the treatment of liver cancer cells [69]; but given the complexities of approving a preloaded DEB containing just one drug, such products containing two or more actives are unlikely to see the light of day for many years to come.

More promising for the near to mid-term future is the use of DEBs in the treatment of other cancers. DEBs have been

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used in the treatment of several other liver tumour metastases and have found utility in the embolisation of lung tumours, although with inconclusive results. Several preclinical studies have been published on the use of DEBs by direct injection in the treatment of brain tumours [70,71], pancreatic cancer [72] and by intraperitoneal administration in the treatment of peritoneal carcinomatosis of colon or pancreatic origin [73]. Although these studies have been positive in their outcome, the change in the intended primary action of the DEB means that it is classed as a medicinal product presenting a different set of challenges.

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Declaration of interest

Both authors are paid employees of the manufacturer of the product under review.

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