DC Bead® Chemoembolisation for the Treatment of Primary [DEBDOX™] and Secondary [DEBIRI™] Liver Cancer

Review of Published Clinical Data

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DC Bead® has been shown to produce high response rates with a very favourable safety profile in HCC, cholangiocarcinoma, neuroendocrine metastases and colorectal metastases. Furthermore, data produced by the same authors in treatment of colorectal cancer provide further evidence that supports the use of DC Bead in this indication.

Data also show that patient selection may be a key factor in ensuring optimal results. In the case of primary liver cancer, patients with advanced stages of cirrhotic and/or cancer disease were excluded from treatment. For metastatic disease, patients with a high degree of extrahepatic disease, a very high liver involvement and/or liver failure were also excluded from treatment.

The evidence from these data supports the use of DC Bead for treatment of primary and secondary liver cancer. Owing to limited data and heterogeneity of studies for indications outside HCC, further trials are required in order to confirm these results. In the meantime, and given the poor prognosis and limited efficacy of existing therapies for these malignancies, DC Bead should be considered as a treatment option, provided the patient is a good candidate for such therapy.

1

Drug-eluting bead therapy in primary and metastatic disease of the liver.

Carter S and Martin RCG
HPB 11 (2009): 541-550

2

Transarterial chemoembolisation (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: an interim report.

Martin RCG, Robbins K, Tomalty D et al
World Journal of Surgical Oncology (2009) 7:80

3

Surgical downstaging and neo-adjuvant therapy in metastatic colorectal carcinoma with irinotecan drug-eluting beads: a multi-institutional study.

Bower M, Metzger T, Robbins K et al
HPB 12 (2010) 31-36

Biocompatibles

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DC Bead® Chemoem Primary [DEBDOX™]

Following the results from the randomised PRECISION V trial, DC Bead® Drug-Eluting Bead doxorubicin [DEBDOX™] (Biocompatibles UK) is becoming widely accepted as a 'standard' TACE treatment for patients with intermediate HCC. As the benefits of DEBDOX in the treatment of HCC become clearer, interest is increasing in defining the role of this innovative technology in the treatment of other liver malignancies.

Three recent publications have studied the role of DC Bead in the treatment of primary and secondary liver cancer. In a review by Carter & Martin[1], DC Bead treatment for both these indications is evaluated, while two other publications refer to single-arm studies for the use of DC Bead Drug-Eluting Bead irinotecan [DEBIRI™] for the treatment of liver metastases from colorectal cancer.

1 Drug-eluting bead therapy in primary and metastatic disease of the liver

Carter S and Martin RCG, HPB 11 (2009): 541-550

ABSTRACT

Background: Drug-eluting bead transarterial chemoembolization (DEB-TACE) [DEBDOX™] is a novel therapy for the treatment of hypervascularized tumours. Through the intra-arterial delivery of microspheres, DEB-TACE allows for embolization as well as local release of chemotherapy in the treatment of hepatic malignancy, providing an alternative therapeutic option in unresectable tumours. Its role as an adjunct to surgical resection or radiofrequency ablation (RFA) is less clear. The purpose of this review is to summarize recent studies investigating DEB-TACE in order to better define safety, efficacy and outcomes associated with its use.

Methods: A systematic review of all published articles and trials identified nine clinical trials and 23 abstracts. These were reviewed for tumour histology, stage of treatment, delivery technique, outcome at follow-up, complications and mortality rates.

Results: Publications involved treatment of hepatocellular carcinoma (HCC), metastatic colorectal carcinoma (MCRC), metastatic neuroendocrine (MNE) disease and cholangio-carcinoma (CCA). Using Response Evaluation Criteria in Solid Tumours (RECIST) or European Association for the Study of the Liver (EASL) criteria, studies treating HCC reported complete response (CR) rates of 5% (5/101) at 1 month, 9% (8/91) at 4 months, 14% (19/138) at 6 months and 25% (2/8) at 10 months. Partial response (PR) was reported as 58% (76/131) at 1 month, 50% (67/119) at 4 months, 57% (62/108) at 6–7 months and 63% (5/8) at 10 months. Studies involving MCRC, CCA and MNE disease were less valuable in terms of response rate because there is a lack of comparative data. The most common procedure-associated complications included fever (46–72%), nausea and vomiting (42–47%), abdominal pain (44–80%) and liver abscess (2–3%). Rather than reporting individual symptoms, two studies reported rates of postembolic syndrome (PES), consisting of fever, abdominal pain, and nausea and vomiting, at 82% (75/91). Six of eight studies reported length of hospital stay, which averaged 2.3 days per procedure. Mortality was reported as occurring in 10 of 456 (2%) procedures, or 10 of 214 (5%) patients.

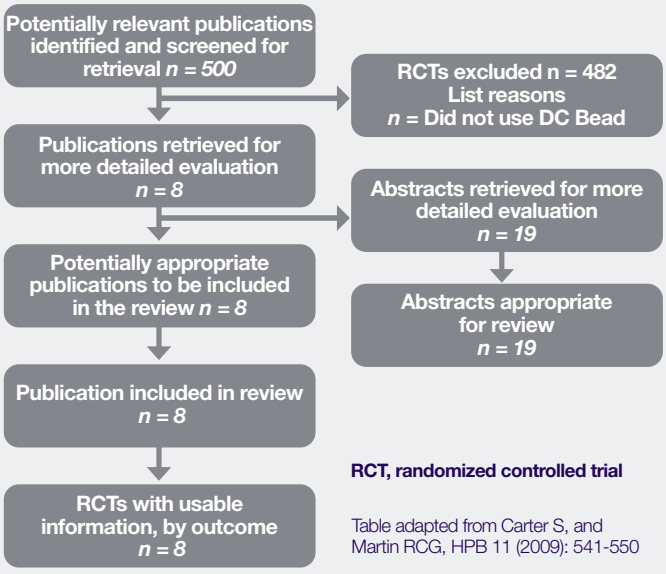
Conclusions: Drug-eluting bead TACE is becoming more widely utilized in primary and liver-dominant metastatic disease of the liver. Outcomes of success must be expanded beyond response rates because these are not a reliable surrogate for progression-free survival or overall survival. Ongoing clinical trials will further clarify the optimal timing and strategy of this technology.

REVIEW

In this article by Carter & Martin[1], the authors describe a systematic review carried out in February 2009 of all available literature for DC Bead. The review included eight papers published in peer-reviewed journals and 19 abstracts. Of the eight published clinical trials, four involved HCC patients, two metastatic colorectal patients, one cholangiocarcinoma and one neuroendocrine disease. Results from these publications are summarised in the table opposite.

The authors of this review conclude that DEBDOX produces beneficial tumour response with an exceptionally low complication rate. In their view, this treatment has the potential to become an effective alternative therapy or palliative measure in the treatment of hepatic malignancy. They also highlight the need for standardisation across both DEBDOX technique and data collection.

QUORUM Algorithm of Review of the DC Bead® Publications and Abstracts



RCT, randomized controlled trial

Table adapted from Carter S, and Martin RCG, HPB 11 (2009): 541-550

> "The authors of this review[1] conclude that TACE with DC Bead produces beneficial tumour response with an exceptionally low complication rate."

bolisation for the Treatment of and Secondary [DEBIRI™] Liver Cancer

Populations Treated

HCC (n=163)	**Inclusion Criteria**	• HCC confirmed by EASL or biopsy • Not suitable for resection, transplantation or PEI (except for 1 study)
	Exclusion Criteria	• BRB higher than 3mg/dl • Advanced HCC • Doxorubicin contraindication • Contraindicated for embolisation • Renal failure • Severe atheromatosis
Colorectal (n=30)	**Inclusion Criteria**	• Histologically confirmed colorectal carcinoma, with metastatic disease confirmed by CT scan • Karnofsky ≥60% or WHO PS 0-2 • Previous chemotherapy discontinued at least 4 weeks prior to beginning the study • No signs of infection or ascites
	Exclusion Criteria	• Any history of inflammatory bowel disease or previous extensive bowel resection • Signs of cardiac disease or renal, bone marrow, pulmonary or central nervous system metastases • Uncontrollable infections • Other types of cancer (except treated in situ cervical, basal cell carcinoma or squamous cell carcinoma) • One study excluded patients with prior treatment with topoisomerase inhibitors
NET (n=20)	**Inclusion Criteria**	• Histologically proven disease with 2 or fewer mitoses per high-powered field, and proven progressive disease on 2 subsequent imaging studies according to RECIST criteria • BRB <2 x ULN • Transaminases <3 x ULN • Creatinine levels <120mol/l • PT<1.5 IU • Platelets >10^6/mm^3
	Exclusion Criteria	• Patients with any resectable disease • Predominant extrahepatic disease • Biliary tract dilation, bilioenteric anastomosis or biliary stent • Crossing the ampulla of Vater • Previous treatment with TACE

Populations Treated (Cont'd)

CholangioK (n=20)	**Inclusion Criteria**	• Karnofsky PS >60% • Tumour substitution <60% • Normal liver function with levels up to twice the upper limit of normal
	Exclusion Criteria	• No exclusion criteria were specified in this study

Treatment

HCC	• Doxorubicin used in all articles and most abstracts • Doxorubicin doses from 25mg/m^2 up to a maximum dose of 150mg/m^2 per treatment
Colorectal	Irinotecan at doses of 100mg per TACE procedure
NET	Doxorubicin
CholangioK	Doxorubicin

Response Rates

HCC	EASL: Overall Response 75% at 6M and 88% at 10M RECIST: Overall Response 42% at 6M
Colorectal	RECIST: Overall Response 80% at 1M
NET	RECIST: Overall Response 80% at 3M
CholangioK	RECIST: Overall Response 100% at 3M

Safety

Complications reported in ≥5%	• Fever (85% patients) • Nausea and vomiting (93% patients) • Abdominal Pain (80% patients)
Length of Stay	Average 2.3 days
Mortality	11/233 (5%) patients - 5 of these 11 patients died from progressive disease

Data for Published Studies Reviewed (n = 8)

Author(s)	Date	Histology	Patients, n	Chemotherapy Agent	Response Rate Reported	Complications Reported	Survival Reported
Malagari et al	Nov 2007	HCC	71	Doxorubicin	Yes	Yes	Yes
Poon et al	Sep 2007	HCC	35	Doxorubicin	Yes	Yes	Yes
Aliberti et al	Oct 2006	MCRC	10	Irinotecan	Yes	Yes	Yes
Fiorentini et al	Nov 2007	MCRC	20	Irinotecan	Yes	Yes	Yes
Aliberti et al	July 2008	CAC	20	Doxorubicin	Yes	Yes	Yes
Varela et al	March 2007	HCC	27	Doxorubicin	Yes	Yes	Yes
de Baere et al	June 2008	NE	20	Doxorubicin	Yes	Yes	Yes
Kettenbach et al	Jan 2007	HCC	30	Doxorubicin	Yes	Yes	Yes

HCC, hepatocellular carcinoma; MCRC, metastatic colorectal cancer; CAC, cholangiocarcinoma; NE, neuroendocrine disease

Table adapted from Carter S, and Martin RCG, HPB 11 (2009): 541-550

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2 Transarterial chemoembolization (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: an interim report.

Martin RCG, Robbins K, Tomalty D et al, World Journal of Surgical Oncology (2009) 7:80

ABSTRACT

Background: Following failure of standard systemic chemotherapy, the role of hepatic transarterial therapy for colorectal hepatic metastasis continues to evolve as the experience with this technique matures. The aim of this study to gain a better understanding of the value of drug eluting bead therapy when administered to patients with unresectable colorectal hepatic metastasis.

Methods: This was an open-label, multi-center, single arm study, of unresectable colorectal hepatic metastasis patients who had failed standard therapy from 10/2006-10/2008. Patients received repeat embolizations with Irinotecan loaded beads (max 100 mg per embolization) per treating physician's discretion.

Results: Fifty-five patients underwent 99 treatments using Irinotecan drug eluting beads. The median number of total treatments per patient was 2 (range of 1-5). Median length of hospital stay was 23 hours (range 23 hours - 10 days). There were 30 (30%) sessions associated with adverse reactions during or after the treatment. The median disease free and overall survival from the time of first treatment was 247 days and 343 days. Six patients (10%) were downstaged from their original disease status. Of these, four were treated with surgery and two with RFA.

Neither number of liver lesions, size of liver lesions or extent of liver replacement (<= 25% vs >25%) were predictors of overall survival. Only the presence of extrahepatic disease (p = 0,001), extent of prior chemotherapy (failed 1st and 2nd line vs > 2 line failure) (P = 0,007) were predictors of overall survival in multivariate analysis.

Conclusions: Chemoembolization using Irinotecan loaded beads was safe and effective in the treatment of patients as demonstrated by a minimal complication rate and acceptable tumor response.

REVIEW

In 2009 Martin et al[2] published interim results from an open-label, multi-centre, single-arm study and evaluated the role of DC Bead® irinotecan (DEBIRI) in the treatment of liver metastases from colorectal cancer. Fifty-five patients with confirmed diagnosis of liver-dominant metastatic colorectal cancer, liver involvement of less than 75%, preserved liver function and ECOG PS 0-2 or Karnofsky 60-100% were treated within the study.

DEBIRI was administered in an outpatient setting, using a lobar approach with 100mg of irinotecan loaded into each DC Bead vial (mainly 100-300µm).

Adverse events were seen in 29% of patients. Patients who received greater than 100mg irinotecan in the first treatment only, were more likely to suffer an adverse event (p<0.0001).

During a median follow-up of 18 months, 12 patients died, most of them due to disease progression. One patient died of liver failure. This patient had baseline BRB of 1.9mg/dl, a liver involvement of 26-50% with total target lesion size of 12.9cm.

Tumour response was seen in 80% patients at 6 months and 54% at 12 months according to EASL. According to RECIST, 56% responded at 6 months and 40% at 12 months.

The authors conclude that DEBIRI is safe and effective in the treatment of patients with unresectable metastatic colorectal cancer.

> “...DEBIRI is safe and effective in the treatment of patients with unresectable metastatic colorectal cancer.[2]”

bolisation for the Treatment of and Secondary [DEBIRI™] Liver Cancer

③ Surgical downstaging and neo-adjuvant therapy in metastatic colorectal carcinoma with irinotecan drug-eluting beads: a multi-institutional study.

Bower M, Metzger T, Robbins K et al, HPB 12 (2010) 31-36

ABSTRACT

Background: Neoadjuvant chemotherapy for potentially resectable metastatic colorectal cancer (MCC) is becoming a more common treatment algorithm. The aim of the present study was to evaluate the efficacy of precision hepatic arterial Irinotecan therapy in unresectable MCC.

Methods: An open-label, multi-centre, multi-national single arm study of MCC patients, who received hepatic arterial irinotecan. Primary endpoints were safety, tolerance and metastatic tumour resection.

Results: Fifty-five patients with metastatic colorectal to the liver underwent a total of 90 hepatic arterial irinotecan treatments. The extent of liver involvement was <25% in 75% of the patients (n = 41), between 26 and 50% in 15% of the patients (n = 11) and >50% in 10% of the patients (n = 24). The median number of hepatic lesions was four (range 1–20), with a median total size of all target lesions of 9 cm (range 5.5–28 cm) with 50% of patients having bilobar tumour distribution. The median number of irinotecan treatments was two (range 1–5). The median treatment dose was 100 mg (range 100–200) with a median total hepatic treatment of 200 mg (range 200–650). The majority of treatments (86%) were performed as lobar infusion treatments, and 30% of patients were treated with concurrent simultaneous chemotherapy. Eleven (20%) patients demonstrated significant response and downstage of their disease or demonstrated stable disease without extra-hepatic disease progression allowing resection, ablation or resection and ablation. There were no post-operative deaths. Post-operative complications morbidity occurred in 18% of patients, with none of them hepatic related. Non-tumourous liver resected demonstrated no evidence of steatohepatitis from the irinotecan arterial infusion.

Conclusions: Hepatic arterial infusion irinotecan drug-eluting beads is safe and effective in pre-surgical therapy and helpful in evaluating the biology of metastatic colorectal cancer to the liver prior to planned hepatic resection.

REVIEW

A further paper by Martin et al[3] focuses on those patients from the original 55 who were either downstaged to resection or treated in the neo-adjuvant setting. Eleven (20%) patients demonstrated either significant response and downstaging of their disease or stable disease without extra-hepatic disease progression allowing for resection, ablation or a combination of both.

All of these 11 patients had multiple liver metastases, with nine patients having less than 25% liver involvement. They all had also received systemic chemotherapy, including either FOLFOX, FOLFIRI, bevacizumab or capecitabine. Three patients were treated with concurrent irinotecan and cetuximab while on hepatic arterial therapy.

After TACE, median length of hospital stay was 23 hours. One patient suffered an adverse event of post-embolic syndrome.

No peri-operative mortality was reported. One patient suffered a biloma which was resolved with percutaneous drainage and another patient experienced a minor wound infection.

Pathological evaluation showed no evidence of chemotherapy-associated steatohepatitis. Overall, pathological response in resected specimens was 90%.

Median disease-free interval was 9 months and median overall survival 12 months.

In the authors' view, this initial evaluation confirms the activity of this therapy in the management of colorectal cancer liver metastasis. They also consider it to be an acceptable treatment option for evaluating the overall metastatic biology prior to planned hepatic resection.

Details on therapy before and after DC Bead® treatment are given in the table overleaf.

> "...this initial evaluation confirms the activity of this therapy in the management of colorectal cancer liver metastasis[3]. [The authors] also consider it to be an acceptable treatment option for evaluating the overall metastatic biology prior to planned hepatic resection.[3]"

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DC Bead® Chemoem Primary [DEBDOX™]

Patient	Prior Liver Therapy	Cause for Unresectability and Reason for Initial Bead Treatment	Number of Bead Treatments	Operation After Bead Therapy
1	Lobectomy	Insufficient remnant liver	2	Ablation
2	Lobectomy	Number and location	2	Ablation
3	Lobectomy	Location	1	Ablation
4	Ablation	Location	2	Ablation + Resection
5	Ablation	Number and location	2	Ablation + Resection
6	Ablation	Number and location	2	Atypical Resection
7	None	Lung metastases	3	Lobectomy
8	None	Lung metastases	3	Atypical Resection
9	None	Lung metastases	3	Atypical Resection
10	None	Portal lymph nodes	3	Lobectomy
11	None	Portal lymph nodes	3	Lobectomy

Table adapted from Bower M, Metzger T, Robbins K et al, HPB 12 (2010) 31-36

Conclusion

DC Bead® has been shown to produce high response rates with a very favourable safety profile in HCC, cholangiocarcinoma, neuroendocrine metastases and colorectal metastases. Furthermore, data produced by the same authors in the treatment of colorectal cancer provide further evidence that supports the use of DC Bead in this indication.

Data also show that patient selection may be a key factor in ensuring optimal results. In the case of primary liver cancer, patients with advanced stages of cirrhotic and/or cancer disease were excluded from treatment. For metastatic disease, patients with high degree of extrahepatic disease, a very high liver involvement and/or liver failure were also excluded from treatment.

The evidence from these data supports the use of DC Bead for treatment of primary and secondary liver cancer. Owing to limited data and heterogeneity of studies for indications outside HCC, further trials are required in order to confirm these results. In the meantime and given the poor prognosis and limited efficacy of existing therapies for these malignancies, DC Bead should be considered as a treatment option provided the patient is a good candidate for such therapy.

Notes

Biocompatibles' Clinical Trial Programme

Hepatocellular Carcinoma

Trial Details	Status
Prospective Randomised Study of Transarterial Doxorubicin-Eluting Bead Embolisation vs Conventional TACE in the Treatment of Patients with Hepatocellular Carcinoma on the Liver Transplant Waiting List *CharitH niversitGsmedizin, Berlin, Germany*	**Recruiting**
Assessment of Chemoembolisation using Doxorubicin-Eluting Beads in Patients Listed for Orthotopic Liver Transplantation with Hepatocellular Carcinoma with Explant Correlation *uc5land City Hospital, ew) ealand*	**Recruiting**
LC Drug-Eluting Bead for Treatment of Liver Cancer Which Cannot be Surgically Removed (HCC) *niversity of Pittsburgh Medical Center, P , S*	**Recruiting**
A Pilot Study of Neoadjuvant Therapy for Hepatocellular Carcinoma using Doxorubicin-Eluting Embolic Beads *Mount Sinai Hospital, ew (or5, S*	**Recruiting**
Chemoembolization of Hepatocellular Carcinoma with Drug-Eluting Beads: Efficacy and Doxorubicin Pharmacokinetics (PRECISION I) *Barcelona Clinic Liver Cancer (BCLC), Spain*	**Published**: Journal of Hepatology 46 (3): 474-481g2007
A Phase I/II Trial of Chemoembolization for Hepatocellular Carcinoma using a Novel Intra-arterial Drug-Eluting Bead (PRECISION II) *ueen Mary Hospital, Hong Kong*	**Published**: Clin Gastroenterology & Hepatology 2007, 5: 1100-1108
Prospective Randomised Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by Drug-Eluting Bead Embolisation (PRECISION V). *International multicentre RCT ustria, rance, Germany, Greece and Switzerland*	**Published**: Cardiovasc Intervent Radiol 33 (2010): 41-52
Doxorubicin-eluting Bead-enhanced Radiofrequency Ablation of Hepatocellular Carcinoma: a Pilot Clinical Study *Cisanello niversity Hospital, Pisa, Italy*	**Published**: Journal of Hepatology 49 (2008) 217-212
Prospective Randomized Comparison of Chemoembolization with Doxorubicin-Eluting Beads and Bland Embolization with BeadBlock for Hepatocellular Carcinoma *niversity of thens, Greece*	**Published**: Cardiovasc Intervent Radiol 33 (2010): 541-551
Single Centre Phase II Trial of Transarterial Chemoembolization with Drug-Eluting Beads for Patients with Unresectable Hepatocellular Carcinoma *Johns Hop5ins niversity Medical School, Baltimore, S*	**Published**: Cancer J 2009 15(6): 526-532
A Phase II Randomized, Double-blind, Placebo-controlled Study of Sorafenib or Placebo in Combination With Transarterial Chemoembolization (TACE) Performed With DC Bead and Doxorubicin for Intermediate Stage Hepatocellular Carcinoma (HCC) *International Multicentre RCT sponsored by Bayer*	**Recruiting**

Hepatic Metastases

	Trial Details	Status
Colorectal	**Drug-Eluting Bead, Irinotecan (DEBIRI) Therapy of Liver Metastases from Colon Cancer with Concomitant Systemic Oxaliplatin, Fluorouracil and Leucovorin Chemotherapy, and Anti-Angiogenic Therapy**	**Recruiting** **Pilot study (n=10) complete**
Colorectal	**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 (mCRC)**	**Protocol in development**
Colorectal	**A Single-arm Phase II Study of Neoadjuvant Therapy Using Irinotecan Bead in Patients with Resectable Liver Metastases from Colorectal Cancer**	**Recruiting**
Colorectal	**A Randomised Phase II Trial of Irinotecan Drug-Eluting Beads Administered by Hepatic Chemoembolisation with Cetuximab (IV) vs Systemic Treatment with Irinotecan (IV) plus Cetuximab (IV) in Patients with Refractory Metastatic Colorectal Cancer and KRAS Wild-type Tumours**	**Recruiting**
Colorectal	**DC Bead®/LC Bead® International Registry**	**Recruiting**
Breast	**Chemoembolisation of Liver Metastases from Breast Carcinoma with Doxorubicin-Loaded DC Bead**	**Protocol in development**
Melanoma	**Transcatheter Arterial Chemoembolisation (TACE) with Doxorubicin-Loaded LC Bead in the Treatment of Liver Metastases in Patients with Stage IV Metastatic Melanoma: A Multicenter Pilot, Non-Randomised Feasibility Trial**	**Recruiting**
Neuroendocrine	**Transarterial Chemoembolisation of Liver Metastases from Well Differentiated astroenteropancreatic Endocrine Tumours with Doxorubicin-Eluting Beads**	**Published** JVIR 19 (6) 2008

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