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Clinical Trial

Everolimus after hepatic arterial embolisation therapy of metastases from gastrointestinal neuroendocrine tumours: The FFCD 1104-EVACEL-GTE phase II study

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Abstract ***Background:*** Hepatic arterial embolisation therapy (HAET) is a treatment of liver metastases of gastrointestinal neuroendocrine tumours (GI-NETs). HAET increases circulating vascular endothelial growth factor levels. Everolimus is a treatment in NETs that may have antiangiogenic activity.
Methods: This phase II study was conducted in patients with predominant and progressive liver metastases from GI-NETs. Everolimus was initiated 7–30 days after HAET. The hypothesis was that everolimus after HAET would increase hepatic progression-free survival (hPFS) rate at 24 months from 35% to 50%.
Results: Among the 74 patients included, 88% had small-bowel primary tumour, 43% had grade I and 57% grade II tumour, and 51% had extrahepatic metastases. Patients underwent one (n = 19), two (n = 54), or three (n = 1) HAET procedures. hPFS at 24 months was 33% (95% confidence interval [CI], 22.5–43.7); 40 (54%) patients had objective response. Median (95% CI) hPFS, PFS, and overall survival were 19 (14–23), 17 (13–22), and 51 (33–60) months. The most common grade III–IV toxicities (>5%) in patients receiving both HAET and everolimus (n = 67) were elevated liver enzymes (55%), fatigue (18%), diarrhoea (16%), anaemia (12%), hypertriglyceridaemia (7%) and mucositis (6%).
Conclusions: The primary end-point was not reached. This sequence allows high liver response with HAET, and everolimus controls the extrahepatic disease.
Trial registration: NCT01678664 (clinicaltrials.gov).

1. Introduction

Hepatic arterial embolisation therapy (HAET), including hepatic arterial embolisation (HAE) or transarterial chemoembolisation (TACE), are among the locoregional treatments used for isolated or predominantly liver metastases of gastrointestinal NETs (GI-NETs). This treatment is proposed to control symptoms of a carcinoid syndrome, but it is often used as an antitumour treatment, especially in ileal tumours [1–3]. Only a few phase II studies, including a small number of patients, have been reported in this indication [1,4,5]. Well-differentiated GI-NETs are often hypervascular tumours with secretion of vascular endothelial growth factor (VEGF) by endocrine tumour cells, which may play an important role in the angiogenic process associated with endocrine carcinogenesis [6,7]. Furthermore, HAET has been reported to further increase the level of circulating VEGF with a possible impact on post-HAET relapse [8]. Thus, antiangiogenic treatment administered after HAET has been hypothesised to further improve tumour control, but a phase II study that evaluated treatment with sunitinib in this situation was negative [8]. mTOR pathway inhibitors display antiangiogenic *in vitro* and *in vivo* activity [9], and since the publication of RADIANT-2 and RADIANT-4 studies [10,11] everolimus is approved in GI-NETs; thus, the combination HAET-everolimus warrants further investigation. Our hypothesis was that everolimus after HAET could both delay liver disease progression in GI-NETs and improve control of the extrahepatic disease.

2. Patients and methods

FFCD 1104- EVACEL was a single-arm, phase II, multicentre study that evaluated the role of 24 months of everolimus treatment in the prolongation of hepatic progression-free survival (hPFS) after TAE or TACE of liver metastases. This protocol was authorised by the French Medicines Agency (*Agence Française de Sécurité Sanitaire des Produits de Santé*) on 29 June 2012 (A120657-42), and the trial was registered on the clinicaltrials.gov website (NCT01678664). The study complies with the Declaration of Helsinki rules and the principles of Good Clinical Practice guidelines.

2.1. Patients

Inclusion criteria were measurable progressive (within the previous 12 months) liver metastases (according to Response Evaluation Criteria in Solid Tumours [RECIST]

v1.1) inaccessible to radiofrequency ablation or surgery, absence of contraindications to HAET or everolimus, age 18 years or above, World Health Organisation (WHO) performance status ≤2, well differentiated (grade I or II according to WHO classification 2010) [12], histologically proven NET of the GI tract as determined by the French NET pathology network (TENpath). HAET with intention of tumour size reduction should have been confirmed in a multidisciplinary team meeting. Satisfactory laboratory assessments should be documented: neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, Hb > 10 g/dL; serum bilirubin ≤1.5 × the upper limit of normal (ULN), international normalized ratio (INR) <1.3 (or <3 for patients on anticoagulant therapy), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5 × ULN, creatinine ≤1.5 × ULN, fasting serum cholesterol ≤300 mg/dL or 7.8 mmol/L and triglycerides ≤2.5 × ULN (if either or both of these limits are exceeded, the patient may only be included after institution of appropriate lipid-lowering therapy). A complete resolution of toxic effects of any prior treatments or persistence at grade I at most (common terminology criteria for adverse events (CTCAE), version 4.0) should have occurred, and the minimum interval since previous treatment was 28 days. Somatostatin analogue treatment for the control of carcinoid syndrome before HAET had to be continued after HAET according to the investigator's judgment. In the absence of carcinoid syndrome, treatment with a somatostatin analogue was not to be initiated after HAET. All patients gave written informed consent for participation in this trial.

Patients were not eligible for this study if any of the following exclusion criteria applied: (i) duodenopancreatic neuroendocrine tumour; (ii) poorly differentiated and/or grade III neuroendocrine neoplasm; (iii) HAET indicated for symptomatic control only; (iv) prior hepatic HAET; (v) prior treatment with an mTOR inhibitor; (vi) symptomatic bone metastasis; (vii) any uncontrolled disease such as hepatic failure, renal failure, respiratory failure, New York Heart Association (NYHA) class III-IV congestive heart failure, unstable angina, myocardial infarction and significant arrhythmia; (viii) interstitial lung disease, uncontrolled diabetes (HbA1c >8%), chronic corticosteroid or immunosuppressant therapy, hypersensitivity to everolimus or other rapamycin derivatives; (ix) major surgery, open biopsy, or significant traumatic lesion during the 28 days prior to starting the investigational treatment, incompletely healed wound or foreseeable need for major surgery during the study and (x) portal thrombosis and biliodigestive anastomosis.

Table 1
Patient characteristics.

Patient characteristics	Total population n = 74
Female, n (%)	31 (42)
Median age, years [range]	66 [43–86]
Primary site, n (%)	
Small bowel	64 (86)
Caecum and colon	3 (4)
Rectum	2 (3)
Stomach	2 (3)
Unknown	3 (4)
Performance status, n (%)	
0	48 (65)
1	25 (34)
2	1 (1)
Previous carcinoid syndrome, n (%)	32 (58)
Median chromogranin A level, ng/mL [range]	571 [23–13677]
Median urine 5-HIAA level, mg/24h [range]	38 [1–315]
Tumour grade, n (%)	
Grade I	32 (43)
Grade II	42 (57)
Median liver tumour burden [range]	30 [1–80]
<25%	29 (39)
25%–50%	24 (32)
50%–75%	14 (19)
>75%	7 (10)
Extrahepatic metastases, n (%)	38 (51)
Peritoneal	10 (14)
Bone	9 (12)
Lung	6 (8)
Distant lymph nodes	24 (32)
Other	3 (4)
Disease progression at study entry (RECIST criteria), n (%)	74 (100)
Prior therapy, n (%)	
Surgery of the primary tumour	53 (72)
Surgery and/or radiofrequency ablation of liver metastases	12 (16)
Somatostatin analogue	55 (74)
Sunitinib	3 (4)
Chemotherapy	4 (5)
Interferon	1 (1)
Concurrent somatostatin analogue, n (%)	37 (67)

2.2. Study treatments

The HAET was either HAE by particulate embolisation of the hepatic arterial branches feeding the targeted liver metastases or TACE using a mixture of lipiodol with either doxorubicin (50 mg/m^2, up to a target of total dose of 100 mg) or streptozotocin (1500 mg/m^2) followed by particulate embolisation using either gelatin sponge particles or spherical embolics up to stasis. TACE using drug-eluting microspheres was not allowed. For both HAE and TACE, the HAET end-point was defined as arterial stagnation in the target hepatic vessels with contrast medium clearance in more than five heartbeats. TACE with streptozotocin had to be performed under sedation because of the pain induced at time of arterial injection. The treatment plan allowed for a maximum of two procedures, and the choice of either one or two procedures was defined at the time of patient inclusion during the multidisciplinary team meeting according to the tumour burden and its extension to one or both liver lobes.

Everolimus (10 mg/day) was started 7 days after the HAET and once hepatic toxicity had improved to grade ≤ I. The treatment had to start ≤30 days after HAET. The

duration of everolimus treatment was 24 months after the first procedure in the absence of unacceptable toxicity. If two HAET procedures were planned, everolimus had to be discontinued the day before HAET and reintroduced in accordance with the conditions described above.

Patients were followed by morphological evaluation every 3 months until death or disease progression by triphasic computed tomography (CT) scan of the chest, abdomen, and pelvis. The liver was explored first without contrast agent, then with contrast by acquisitions at the arterial (30 s) and then the portal venous (70–90 s) phases. All CT were performed in the same radiology department using identical technical parameters for the baseline and follow-up CT scan.

2.3. Study end-points and statistical analysis

The baseline liver tumour burden was reported as a proportion (%) of the total liver volume. For each patient, 4–6 scan slices with the greatest tumour volume were selected by the radiologist and the extent of disease scored visually.

The primary end-point of this study was the hPFS rate (based on the central assessment) as defined by RECIST v1.1 (including death considered as progression) at 24 months after treatment. The PFS and objective response were evaluated in the whole liver and not only in the treated liver. According to the literature, the median PFS after HAE or TACE ranges from 15 to 19 months, and the PFS rate at 24 months is around 35% [1,8,13]. The clinical hypothesis was to extend the hPFS rate at 24 months from 35% to 50%. With an α risk of 5% and power of 80%, 68 patients were required. Taking into account loss to follow-up and patients who were not evaluable for any reason other than death, 74 patients were to be included.

Secondary objectives were objective response, PFS (hepatic or not) evaluated by the investigator, overall survival (OS) and the safety of the treatment. For patients with elevated urine 5-hydroxyindoleacetic acid (5-HIAA) or serum chromogranin A (CgA), these parameters were measured every 3 months. A >50% reduction or normalisation of levels was defined as a biochemical response.

Analyses of safety were conducted in all patients who received ≥1 dose of treatment. Qualitative and continuous variables were described using usual descriptive statistics. Survival analyses were performed according to the intent-to-treat (ITT) principle. The median follow-up was evaluated using the reverse Kaplan–Meier method; PFS and OS were estimated using the Kaplan–Meier method and described with median and two-sided 95% confidence interval (CI). Univariate analyses were performed using the log-rank test for each variable of interest. All statistical analyses were done using SAS software 9.4 (SAS Institute, Cary, NC).

Table 2
Administration of HAE/TACE and everolimus.

Treatment characteristics	Scheduled		Performed	
Number of patient receiving HAET, n (%)	74	(100)	74 (100)	
Number of procedures, n (%)	142		130	
1	6	(8)	19	(26)
2	68	(92)	54	(73)
3			1	(1)
Type of procedures, n (%)				
Bland embolisation			21	(16)
Chemoembolisation			109	(84)
TACE with doxorubicin			97	(89)
TACE with streptozotocin			12	(11)
HAET considered as complete			124/127	(98)
Embolisation end-point reached			112/127	(88)
Complications during the procedure			4/127	(3)
Number of patients starting everolimus, n (%)	74	(100)	67	(91)
Cause of not starting everolimus, n (%)				
Not recovered at day 30 from HAET			3	(4)
Unknown			4	(5)
Patient refusal			1	(1)
Median duration in months [IQR]			11	[4–22]
At least one dose reduction, n (%)			20	(30)
At least one discontinuation, n (%)			56	(84)
Cause of discontinuation			67	
End of treatment (at 24 months)			13	(19)
Disease progression			21	(31)
Toxicity			24	(36)
Physician choice			7	(10)
Patient choice			2	(3)
Unknown			1	(1)
Median duration of follow-up in months (95% CI)			42	(39–45)

CI, confidence interval; IQR, interquartile range; HAET, hepatic arterial embolisation therapy; TACE, transarterial chemoembolisation.

Table 3
Efficacy.

End-points for efficacy	Total population n = 74
Best radiological tumour response, n (%)	
Objective response	40 (54)
Stable disease	30 (41)
Progressive disease	3 (4)
Not evaluable	1 (1)
Biochemical response in serum CgA levels in patients with elevated CgA levels and repeated dosages, n/N (%)	23/40 (58)
Biochemical response in urine 5HIA levels in patients with elevated 5-HIAA levels and repeated dosages, n/N (%)	14/18 (78)
Median hepatic PFS, months (95% CI)	18.5 (14.0–22.8)
Hepatic PFS rate at 24 months, % (95% CI)	33% (23%–44%)
Median PFS, months (95% CI)	16.9 (12.6–22.4)
PFS rate at 24 months, % (95% CI)	30% (20%–40%)
Location of disease progression according to RECIST criteria, n/N (%)	
Hepatic and extrahepatic	42/57 (74)
Hepatic only	7/57 (12)
Extrahepatic only	8/57 (14)
Median overall survival, months (95% CI)	51.0 (33.0–60.3)
Overall survival rate at 24 months, % (95% CI)	76% (65%–85%)
Death, n (%)	30 (41)
Cause of death, n/N (%)	
Disease progression	20/30 (67)
Other disease	7/30[a] (23)
Unknown	3/30 (10)

CgA, chromogranin A; PFS, progression-free survival; CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumours.
[a] Sepsis (n = 3), liver failure on cirrhosis (n = 1), cardiac arrest (n = 1), ruptured aneurysm (n = 1) and amyotrophic lateral sclerosis (n = 1).

3. Results

3.1. Patients

A total of 74 patients were included between January 2013 and March 2016; 42% were female, and the median age was 66 years (range: 43–86). The primary tumour was mainly observed in the small bowel (86%). Tumours were grade I (43%) or II (57%). All patients had liver metastases, and the median liver tumour burden was 30% (range: 1–80); 51% had extra-liver metastases. All patients had progressive liver disease (RECIST criteria) at study inclusion. Patients had undergone prior primary tumour surgery (72%) and/or surgery/radiofrequency ablation of liver metastases (16%). Thirty-seven (67%) received concurrent somatostatin analogue (Table 1).

3.2. Transarterial liver therapy and everolimus

All patients with scheduled HAET received the treatment. Six were scheduled to receive one procedure of HAET, and 68 were scheduled to receive two procedures of HAET (Table 2); 19 patients received one procedure, 54 two, and one patient three procedures of HAET. Overall, 130 procedures of HAET were delivered, including 21 procedures of bland and 109 TACE. The median dose of doxorubicin and streptozotocin administered during TACE was 100 mg (interquartile range [IQR]: 50–100) and 1500 mg (IQR: 1500-1500), respectively. The embolisation end-point was reached in 88% of procedures. Four patients experienced a complication during the HAET (one had thoracic pain and bradycardia, three patients had partial arterial occlusions of the cystic, gastric or hepatic arteries, respectively).

Sixty-seven (87%) patients were eligible for everolimus (liver toxicity was grade ≤I within the 30 days following HAET). Everolimus was started a median 11 days after HAET (IQR: 8–20 days), and the median duration of everolimus was 11.4 months (IQR: 4.4–22.1). Everolimus was most frequently discontinued because of toxicity (36%) and/or disease progression (31%; Table 2). Twenty (30%) patients required at least one dose reduction.

3.3. Efficacy

The hPFS rate at 24 months, the primary end-point was 32.9% (95% CI, 22.5–43.7). The median hPFS was 18.5 months (95% CI, 14.0–22.8; Table 3, Fig. 1a). Among the characteristics described in Table 1, only age above the median value was significantly associated with shorter hPFS (HR of 1.94, 95% CI 1.14–3.33, p = 0.01).

Among secondary end-points, 40 (54%) had objective response, and 30 (41%) had stable disease (Table 3). The median PFS was 16.9 months (95% CI, 12.6–22.4; Fig. 1a), and the median OS was 51.0 months (95% CI, 33.0–60.3; Fig. 1c). Eight patients had extrahepatic disease progression alone. Thirty deaths occurred, mainly (67%) secondary to disease progression. Among the 40 patients with elevated serum CgA at baseline (≥200 ng/ml), and several measurements made during follow-up, 23 (58%) patients experienced a biochemical response following embolisation (major reduction defined as ≥50% reduction or normalisation). Among the 27 patients with elevated baseline urine 5-HIAA (≥40 mg/24 h), 18 had several measurements made during the follow-up: 14 (78%) of them experienced a biochemical response in urine 5-HIAA levels following embolisation (Table 3).

3.4. Tolerance

All patients experienced ≥1 event (any-grade). The most common grade III-IV adverse event (>5%) in patients receiving both HAET and everolimus (n = 67) were elevated liver enzymes (55%), fatigue (18%), diarrhoea (16%), anaemia (12%), hypertriglyceridaemia (7%), abdominal pain (6%), and mucositis (6%; Table 4).

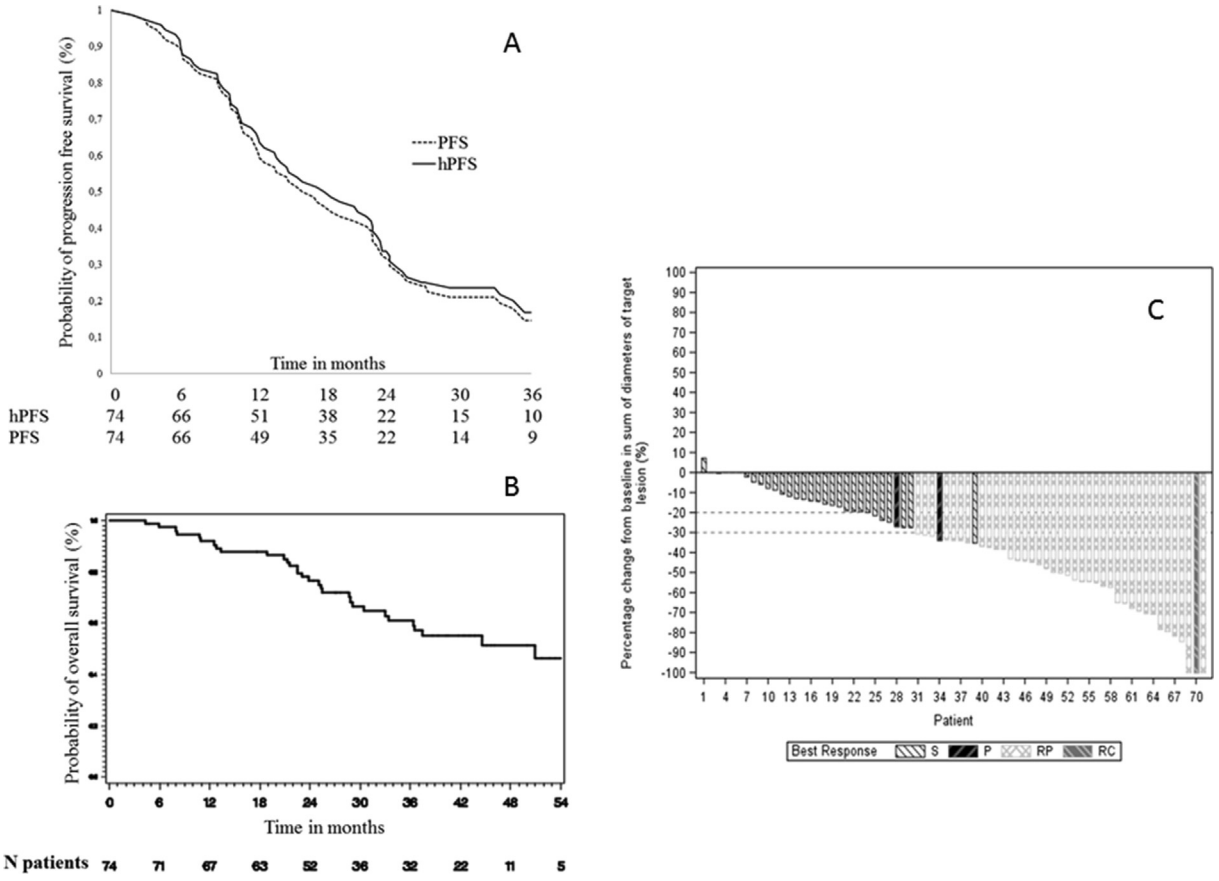

Fig. 1. Kaplan–Meier analysis of hepatic progression-free survival (hPFS), progression-free survival (PFS) (a) and overall survival (b) are presented as well as and percentage change from baseline according to RECIST criteria (c). S, stable disease; P, progressive disease; RP, partial response; RC, complete response.

4. Discussion

We report herein, to the best of our knowledge, the largest phase II study that prospectively evaluated HAET in NETs, which is also the first study testing everolimus after HAET. This study did not meet its primary end-point (hPFS at 24 months of 50%), which could be explain by two main reasons: the hypothesis for the primary end-point and the timing of post-HAET everolimus. First, the hypothesis was probably too optimistic because designed according to data available at the time of study inception that were scarce, mostly retrospective or did not meet the quality criteria required for trials in NETs [8,14–19] that have been reported to be indispensable for such tumours [20,21]. For instance, one of the main criteria required for inclusion in the present study was liver disease progression at baseline according to RECIST within the 12 months before inclusion, which was not an inclusion criterion of most previously reported studies [8,14–19]. It is also recommended that the study population be homogeneous (only one type of tumour without pancreatic NET, one type of differentiation according to the WHO classification) [20,21], which was the case herein. Interestingly, in the only randomised study evaluating HAET in patients with progressive liver metastases from midgut NETs, the hPFS rate at 24 months was 44% and 38% for HAE and TACE, respectively, which was lower than their hypothesis (50% and 75%) [13]. This indicates that a control arm study without everolimus would have been more appropriate herein to determine the value of this drug in increasing hPFS after HAET. Second, one limitation, present herein and in almost all trials combining HAET-antiangiogenic drugs in hepatocellular carcinoma (HCC) [22–24] and NET [8], is the late administration of the targeted therapy after HAET. The VEGF spike occurs within 1–2 days after HAET [8] and longitudinal studies in HCC demonstrate that serum VEGF levels rapidly normalise after HAET [25]. However, everolimus was scheduled in the present study to be started from 7 days after HAET to avoid the peak of liver toxicity induced by HAET (55% of grade III–IV). Therefore, mechanistically, it is difficult to expect synergy, as shown by the negative results of these studies [8,22–24]. It would make more sense to initiate antiangiogenic drugs before HAET and to continue after the intervention, but the feasibility in terms of safety has not been studied in NETs.

Table 4
Adverse events occurring in ≥5% of patients receiving both treatments, starting everolimus after at least one liver embolisation (n = 67).

Type of adverse events	Grade I –II, n (%)	Grade III –IV, n (%)	Any grade, n (%)
At least one toxicity	67 (100)	57 (85)	67 (100)
Fatigue	47 (70)	12 (18)	59 (88)
Fever	25 (37)	0 (0)	25 (37)
Infections	18 (27)	3 (4)	21 (31)
Myalgia	8 (12)	0 (0)	8 (12)
Peripheral oedema	25 (37)	1 (1)	26 (39)
Deep thrombosis	4 (6)	0 (0)	4 (6)
Haematological			
Anaemia	53 (79)	8 (12)	61 (91)
Leukopaenia	38 (57)	0 (0)	38 (57)
Neutropaenia	18 (27)	3 (4)	21 (31)
Lymphopaenia	5 (7)	3 (4)	8 (12)
Thrombocytopaenia	34 (51)	1 (1)	35 (52)
Digestive			
Dysgeusia	7 (10)	1 (1)	8 (12)
Mucositis/stomatitis	28 (42)	4 (6)	32 (48)
Weight loss	7 (10)	1 (1)	8 (12)
Diarrhoea	36 (54)	11 (16)	47 (70)
Abdominal pain	23 (34)	4 (6)	27 (40)
Anorexia	19 (28)	2 (3)	21 (31)
Nausea	23 (34)	2 (3)	25 (37)
Vomiting	20 (30)	2 (3)	22 (33)
Dermatological			
Dry skin	8 (12)	0 (0)	8 (12)
Rash	8 (12)	0 (0)	8 (12)
Alopecia	8 (12)	2 (3)	10 (15)
Pruritus	6 (9)	1 (1)	7 (10)
Nail disorders	4 (6)	0 (0)	4 (6)
Respiratory			
Epistaxis	7 (10)	0 (0)	7 (10)
Cough	11 (16)	0 (0)	11 (16)
Dyspnoea	14 (21)	1 (1)	15 (22)
Biochemical			
Biological liver toxicity (AST, ALT, PAL, bilirubin…)	62 (92)	37 (55)	64 (95)
Hypercholesterolaemia	37 (55)	0 (0)	37 (55)
Hypertriglyceridaemia	33 (49)	5 (7)	38 (57)
Hyperglycaemia	48 (72)	3 (4)	51 (76)
Hypoalbuminaemia	10 (15)	1 (1)	11 (16)
Hypocalcaemia	24 (36)	2 (3)	26 (39)
Hypokalaemia	8 (12)	3 (4)	11 (16)
Hyponatraemia	20 (30)	3 (4)	23 (34)
Hypomagnesaemia	12 (18)	2 (3)	14 (21)
Hypophosphataemia	19 (28)	3 (4)	22 (33)

The present study underlines the good tolerance and excellent control of extrahepatic disease of the HAET + everolimus combination. We demonstrated that this sequence (targeted therapy following HAET) is feasible in over 90% of patients, as has been reported by Strosberg *et al.* [8] for sunitinib; however, half of patients herein and 15% of those receiving sunitinib [8] discontinued before the scheduled times, respectively 104 weeks and 48 weeks, because of toxicity or physician/patient choice. We also found that the PFS was close to the hPFS, while half of patients had extrahepatic metastases at baseline, suggesting that everolimus allows the control extrahepatic disease. Moreover, the PFS and OS observed in this study compared advantageously with those observed in prior retrospective studies evaluating HAET [1] but also the phase III studies investigating everolimus [10,11,26]. The only study to have evaluated HAET followed by a targeted therapy was reported by Strosberg *et al.*, cited above, which found 28/39 (72%) objective response, a median PFS of 15 months and a PFS rate at 24 months less than 25% according to the reported survival curve [8]; these results are very close to those reported herein.

Another limitation of the study, in addition to the timing of post-HAET everolimus administration and the absence of control arm discussed above, could be the lack of standardisation of the HAET procedure. However, herein and in a prospective randomised study, no significant difference between TACE and HAE was found (hPFS at 24 months: 38% and 44%, respectively, p = 0.9) [13]. Finally, we used RECIST 1.1 instead of RECIST 1.0 which limits the measurements to only the two most representative liver metastases instead of five. This could be a less representative measure of liver tumour change. In addition, other criteria, including perfusion parameters, may provide an even more accurate assessment of change after HAET and targeted therapies [27,28].

In summary, this phase II study, conducted according to the current quality design in NETs, demonstrates that HAET is a highly active treatment as evidenced by the high rate of objective response and long hPFS/PFS/OS. It also found that everolimus can be safely administered following HAET. However, further randomised clinical trials are warranted to establish the best treatment sequence, i.e. everolimus immediately after HAET or at disease progression.

Ethical approval and consent to participate

This protocol was authorised by the French medicines agency (*Agence Française de Sécurité Sanitaire des Produits de Santé*) on 29 June 2012 (A120657-42), and the trial was registered on the clinicaltrials.gov website (NCT01678664). The study complies with the Declaration of Helsinki rules and the principles of Good Clinical Practice guidelines. Patients consent are available.

Consent to publish

The manuscript is not under consideration for publication elsewhere. There is no major overlap of the issues addressed in this paper with any prior publication. All authors have read and approved the manuscript.

Availability of data and materials

The data sets used during the current study are available from the corresponding author on reasonable request.

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Authors' contribution

T.W., C.L. and T.d.B. wrote the manuscript. C.L., O.H., G.C., O.H., E.B., M.D., C.L.B., and T.d.B. were responsible for the study design of the trial and contributed to writing the study protocol. E.B. is the statistical manager. T.W., C.L., R.C., G.C., F.C.B., O.H., K.B.L., T.A., L.D., E.B., A.D.G. and C.L.B. have included significant number of patients in this trial. All authors have read and approved the final manuscript.

Conflict of interest statement

The conflicts of interest are described below:

T.W., G.C. have acted as an advisory board member for Ipsen, Pfizer and Novartis.

R.C. has acted as an advisory board member for Merck, Keocyt, Pfizer and Novartis.

T.d.B. has acted as an advisory board member for Guerbet.

C.L., E.B., F.X.C.B., T.A., K.B.L., O.H., A.C.D.G., M.D., C.L., T.L., D.S., C.P., I.C., F.G., M.D. and C.L.B. declare no competing interests.

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Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.09.021.

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