REBECA: a phase I study of bevacizumab and whole-brain radiation therapy for the treatment of brain metastasis from solid tumours


Departments of Oncology; Radiology, Centre François Baclesse, Caen; GIP Cyceron, Caen; Department of Clinical Research, Centre François Baclesse, Caen; Departments of Oncology; Radiotherapy, Institut de Cancérologie de l’Ouest René Gauducheau, Nantes-Saint Herblain, Caen; Departments of Oncology; Radiotherapy, Centre Henri Becquerel, Rouen; Departments of Oncology; Radiotherapy, Institut Curie, Paris; Departments of Oncology; Radiotherapy, Centre Oscar Lambret, Lille; Departments of Oncology; Radiotherapy, Centre Léon Bérard, Lyon; Department of Radiotherapy, Centre François Baclesse, Caen; Department of Radiology, Centre Hospitalier Universitaire, Caen; Department of Biostatistics, Institut Curie/Inserm U900, Paris, France

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Background: Brain metastases (BMs) are associated with a poor prognosis. Standard treatment comprises whole-brain radiation therapy (WBRT). As neo-angiogenesis is crucial in BM growth, combining angiogenesis inhibitors such as bevacizumab with radiotherapy is of interest. We aimed to identify the optimal regimen of bevacizumab combined with WBRT for BM for phase II evaluation and provide preliminary efficacy data.

Patients and methods: In this multicentre single-arm phase I study with a 3 + 3 dose-escalation design, patients with unresectable BM from solid tumours received three cycles of bevacizumab at escalating doses [5, 10 and 15 mg/kg every 2 weeks at dose levels (DL) 0, 1 and 2, respectively] and WBRT (30 Gy/15 fractions/3 weeks) administered from day 15. DL3 consisted of bevacizumab 15 mg/kg with WBRT from day 15 in 30 Gy/10 fractions/2 weeks. Safety was evaluated using NCI-CTCAE version 3. BM response (RECIST 1.1) was assessed by magnetic resonance imaging at 6 weeks and 3 months after WBRT.

Results: Nineteen patients were treated, of whom 13 had breast cancer. There were no DLTs. Grade 1–2 in-field and out-field toxicities occurred for five and nine patients across all DLs, respectively, including three and six patients (including one patient with both, so eight patients overall) of nine patients in DL3. One patient experienced BM progression during treatment (DL0). At the 3-month post-treatment assessment, 10 patients showed a BM response (RECIST 1.1) assessed by magnetic resonance imaging at 6 weeks and 3 months after WBRT.

Conclusion: Bevacizumab combined with WBRT appears to be a tolerable treatment of BM. DL3 warrants further efficacy evaluation based on the favourable safety/efficacy balance.

Clinical trials.gov Identifier: NCT01332929.
Key words: brain metastasis, cranial radiotherapy, bevacizumab, phase 1, anti-angiogenic

Introduction
It is established that 20%–40% of metastatic cancer patients will develop brain metastases (BMs) [1] associated with short life expectancy. For patients with a limited number of BM, surgery or mono- or hypo-fractionated stereotactic radiotherapy may improve local control and survival. For patients ineligible for these techniques, whole-brain radiation therapy (WBRT) remains the standard treatment and is associated with survival of 4–6 months [2, 3]. Combining WBRT with cytotoxic agents or radiosensitizers has shown disappointing local control and survival [4, 5], highlighting the need for alternative strategies.

*Correspondence to: Dr Christelle Lévy, Oncology Department, Centre François Baclesse, 3 avenue Général Harris, 14076 Caen cedex 05, France. Tel: +33-2-31-45-54-56; E-mail: c.levy@baclesse.unicaner.fr
One hypothesis for improving efficacy, supported by preclinical and clinical data, is to explore synergy between radiotherapy and treatments targeting the pathways involved in tumour and vascular development. Vascular endothelial growth factor (VEGF) is critical for endothelial cell growth and angiogenesis [6, 7] and Jain’s publications have early highlighted the role of angiogenesis in brain malignancies [8]. Preclinical data indicate an interaction between the angiogenic pathway and radiation-induced damage [9]. A dose-dependent increase in VEGF levels following a single radiation dose was noted in some tumour cell lines, enhancing tumour cell invasion and migration and increasing tumour hypoxia and radio-resistance. Synergism between ionizing radiation and the anti-angiogenic therapy bevacizumab has been observed in vitro and in vivo [10] and the tolerability of this approach was demonstrated in clinical studies in rectal and pancreatic cancers [11, 12]. More recently, the combination of bevacizumab and radiotherapy has been evaluated extensively in malignant glioblastoma (in both the newly diagnosed and recurrent settings) [13–15] but, to our knowledge, no prospective study has explored the combination of WBRT and anti-VEGF therapy for BM.

We conducted the phase I REBECA study to assess the safety of WBRT combined with bevacizumab in patients with newly diagnosed BM from solid tumours to determine the recommended phase II dose (RP2D) and to describe preliminary efficacy findings.

**materials and methods**

**study design**

This multicentre open-label phase I dose-escalation trial was approved by local ethics committee and health authority (EUDRACT: 2009-015977-11, ClinicalTrials.gov: NCT01332929). The review boards of all participating institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. Written informed consent was obtained from all patients under study.

The primary objective was to identify the RP2D using a standard ‘3 + 3’ dose-escalation design. Patients who did not receive the entire scheduled treatment were replaced by an additional patient enrolled at the same dose level (DL). If three assessable patients experienced no DLT during the 6-week period following the first bevacizumab dose, the study could continue to the next DL. If one patient experienced a DLT, three additional assessable patients were required to that DL. Further escalation could occur if no additional DLTs were seen. Four additional patients were treated at the highest DL for which the DLT rate was <33%. This DL was defined as the RP2D if <33% of the 7 or 10 patients at this dose experienced DLTs. Decisions for dose escalation were made together with an Independent Data Monitoring Committee appointed by the Comprehensive Cancer Centre François Baclesse, Caen, France.

The secondary objective was to assess treatment-related parameters of BM progression by morphologic and functional magnetic resonance imaging (MRI) 6 weeks after treatment end.

**eligibility criteria**

Eligible patients had measurable BM from solid tumours and Eastern Cooperative Oncology Group performance status 0–2. Patients with BM eligible for neuro-surgery or stereotactic radiotherapy or with meningeval carcinomatosis or contraindications to bevacizumab (including a prior cardiac or and/or thromboembolic event, haemorrhagic BM or uncontrolled hypertension) were ineligible.

**treatment schedule**

At each DLs, bevacizumab was administered intravenously on days 1, 15 and 29. WBRT (delivered through two parallel opposite fields with ≥6 Megavolt (MV) photons) was initiated at day 15. The total dose was 30 Gy, with a dose/fraction of 2 Gy for 15 fractions during 3 weeks for DL 0, 1 and 2, then 3 Gy/fraction for 10 fractions during 2 weeks for DL3 (Figure 1). Bevacizumab injections and WBRT initiation were to be scheduled on Mondays. No dose adjustment was allowed. No other anti-cancer therapy was permitted during treatment or for 2 weeks thereafter.

**safety assessment**

Adverse events (AEs) observed during and after the bevacizumab and WBRT treatment period were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v3.0). AEs were recorded at baseline, then every week during treatment, at 3 months after the end of treatment, and then every 3 months until BM progression. DLTs were defined as any of the following: grade ≥3 venous thrombosis; any grade pulmonary embolism or symptomatic thrombosis; any grade of arterial thrombosis; grade ≥3 haemorrhage; grade 4 or uncontrolled grade 3 hypertension; reversible posterior leukoencephalopathy syndrome; grade 3/4 proteinuria; or any grade 3/4 non-haematological or grade 4 haematological treatment-related toxicity requiring permanent discontinuation of bevacizumab.

**response assessment**

Morphologic (T1, T1 gadolinium, T2 and T2* sequences) and functional (dissolution, perfusion) brain MRI was carried out at baseline, at day 15 before starting WBRT, at 6 weeks and 3 months after treatment and every 3 months thereafter until BM progression.

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**Figure 1.** Treatment schedule (BEV Bevacizumab DL dose-level WBRT, whole-brain radiation therapy).
Imaging was centralized and reviewed by two radiologists. Response was determined according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, with complete or partial responses defined as objective responses. For target lesions, BM response was also summarized by the relative brain tumour reduction [sum of the longest diameters (SLD) of measurable target lesions/SLD at baseline].

**statistical analysis**

The population analysed to define the RP2D included all patients who received at least one bevacizumab dose, unless they were replaced. The intent-to-treat (ITT) population included all patients who received at least one bevacizumab dose and one session of WBRT; safety was reported in this population. The per-protocol (PP) population included all patients who completed planned treatment. Patients with at least one documented BM response assessment within the 3-month post-treatment period were included in the analysis of anti-tumour activity. Time to progression (TTP, defined as time from treatment start to BM progression or death from BM) and overall survival (OS, defined as time from treatment start to death from any cause) were estimated using the Kaplan–Meier method.

**results**

**study population**

Between September 2010 and July 2013, 21 patients were enrolled, of whom 19 (representing the ITT population) were treated in six French comprehensive cancer centres. Their characteristics are presented in Table 1, including the RTOG recursive partitioning analysis classification for BM [16].

Three patients in the ITT population were replaced during the study (one received WBRT at a total dose of 44 Gy; one began

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<th>Table 1. Patient characteristics by dose level (N = 19)</th>
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Patients 13 and 16 received no bevacizumab because of uncontrolled arterial hypertension (patient 13) and because after enrolment by the radiotherapist, the oncologist considered the delay between WBRT and chemotherapy to be too long (patient 16). Consequently, these two patients were replaced before receiving any study therapy.

<sup>a</sup>Replaced during the study and thus excluded from the analysis defining the recommended phase II dose.

<sup>b</sup>Excluded from the per-protocol population.

<sup>c</sup>Not included in anti-tumour analyses because no MRI was conducted at the 3-month post-treatment assessment (patient’s withdrawal).

BM, brain metastases; DL, dose level; ECOG, Eastern Cooperative Oncology Group; DLT, dose-limiting toxicity; RTOG, Radiation Therapy Oncology Group; f, female; m, male.
WBRT at day 10; and one chose not to continue bevacizumab treatment). The 16 remaining patients completed WBRT and bevacizumab as scheduled, and thus represented the PP population.

safety

No DLTs occurred at DL 0, 1 or 2. Consequently the protocol was amended to add one further DL (DL3) representing a more widely used WBRT fractionation (30 Gy/10 fractions/2 weeks) combined with bevacizumab 15 mg/kg on days 1, 15 and 29. As no DLTs were observed in seven patients treated at DL3, this was defined as the RP2D. Of the 11 patients who experienced AEs considered by the investigator to be treatment-related, 8 were treated at DL3 (Table 2). However, all treatment-related AEs were mild or moderate in intensity (grade 1/2) and known side-effects of the treatments (in-field events: nausea/vomiting and headache; out-field event related to bevacizumab: reversible mild hypertension). No new safety signals were observed and no bleeding or oedema was detected during MRI examination.

During the assessment period for BM response, no meningeal or parenchymal haemorrhagic lesions were detected by MRI. Two patients experienced intra-lesional haemorrhagic necrosis without signs of extra-lesional haemorrhage. No progression of peri-lesional oedema or midline deviation of the falx cerebri was observed.

disease outcome

At the day 15 assessment before starting WBRT, 1 patient treated at DL3 had an improvement in neurologic symptoms and a complete BM response (Figure 2), which was maintained through the 3-month post-treatment period; one progressed (DL0) and the remaining 17 patients had stable BM. At the 3-month post-treatment response assessment, 18 patients were included in the ITT analysis (1 patient withdrew). Objective responses were observed in one of three patients treated at DL0, two of four at DL1, two of three at DL2 and seven of eight at DL3. Five patients experienced BM progression (two at DL0, two at DL1, one at DL3), leading to death in two patients (one at DL0, one at DL1). The remaining patient treated at DL1 died from extracranial disease progression. Figure 3 depicts brain tumour reduction from baseline by patient over time. Dealing with timing and duration of corticotherapy over study period, most patients were on stable corticoid treatment at first bevacizumab injection (supplementary Figure S1, available at Annals of Oncology online). In DL3, all patients (except one with 1-week corticotherapy after treatment) were either on corticotherapy before experimental treatment start or did not receive any corticoid. TTP and OS in the PP population are presented in supplementary Figure S2, available at Annals of Oncology online. After a median follow-up of 8.5 months (range 2.4–28.8 months), median TTP was 7.1 months [95% confidence interval (CI) 5.3–not reached] and median OS was 13.3 months [95% CI 7.7–not reached].

discussion

The REBECA phase I trial is, to our knowledge, the first trial evaluating bevacizumab combined with WBRT in BM patients. We did not observe any increase of WBRT-associated toxicities nor cerebral haemorrhage, using standard fractionation WBRT. These findings are consistent with studies reported in the literature showing no significant increase in the risk of intracranial haemorrhage in patients with BM treated with bevacizumab for extra-cranial disease. They further support the absence of cerebral haemorrhage or

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*Adverse events considered not related to treatment were: grade 3 asthenia and grade 3 hyperglycaemia in 1 patient; grade 2 AEs in 13 patients [asthenia (n = 4), pain (n = 4), infection (n = 4), headache (n = 3), balance disorder (n = 3), constipation (n = 2), insomnia (n = 2), anorexia (n = 1), hyperglycaemia (n = 1), hyponatrema (n = 1), paraesthesia (n = 1), cutaneous/mucus disorder (n = 1), liver disorder (n = 1), ocular disorder (n = 1), epigastralgia (n = 1)].
other significant brain injury during or after administration of bevacizumab.

The study also provides some encouraging data suggesting a potential synergistic effect between bevacizumab and radiation therapy in BM. There appeared to be a trend towards better BM response with the highest bevacizumab dose (15 mg/kg on days 1, 15 and 29) combined with WBRT 30 Gy in 10 fractions over 2 weeks.

The biologic rationale of this synergistic effect may rely on the anti-angiogenic properties of BEV, since neo-angiogenesis enhances intra-tumoral hypoxia (by reduction of oxygen diffusion) and is simultaneously stimulated by hypoxic conditions and external stress such as ionizing radiation.

Considering the key role of hypoxia in radio-resistance, angiogenesis inhibitors such as VEGF inhibitors, may be of interest to disrupt this vicious circle between angiogenesis and radio-resistance by normalization of tumour vasculature. This normalization reduces hypoxia and improves radio-sensitivity of cancer cells and endothelial cells [20–22].

The benefit of BEV adjunction to WBRT in REBECA trial may thus be allowed by the optimal treatment timing, as far as the early administration of BEV 2 weeks before WBRT may induce a vascular normalization which may enhance radiation-induced activity. This could also be considered in light of the recently published placebo-controlled randomized phase III trials, AVAglio and RTOG 0825, evaluating the addition of bevacizumab to radiotherapy and temozolomide for newly diagnosed malignant glioblastoma [13, 14]. In both trials, bevacizumab-containing therapy improved PFS but not OS. But the better effect on quality of life and cognitive functions are observed in AVAglio for which BEV was started concurrently with radiotherapy (while initiated later—week 4 of WBRT—in RTOG trial).

In addition, it is hypothesized that bevacizumab may also act as anti-oedematous agent on peripheral oedema of BM. This action is difficult to identify since most of BM patients received corticosteroids to control neurologic symptoms (headache, nausea, …) which concomitantly exert an anti-oedematous effect. In our study, most patients were on stable corticoid treatment at first bevacizumab injection.

The penetration of monoclonal antibodies through the blood–brain barrier (BBB) is often discussed and theoretically may be compromised because of the large molecular weight of monoclonal antibodies such as bevacizumab. However, the BBB is disrupted in patients with brain tumour involvement and/or during brain radiotherapy [23]. Of note, the observed improvement in neurologic symptoms associated with objective BM response within the first 15 days after starting bevacizumab therapy, before initiation of WBRT for one patient treated in the REBECA study suggests a direct effect of bevacizumab on BM. Nevertheless, oral compounds such as TKIs with anti-angiogenic properties may be of interest. Cediranib, a pan-VEGF receptor tyrosine kinase inhibitor, was recently tested [24] in newly diagnosed glioblastomas with concurrent chemoradiation. In this setting, MRI demonstrated that cediranib (given daily during the 6 weeks of radiotherapy) allowed, in a limited subset of patients, an improved perfusion which was associated with improved OS.

Figure 2. Contrast-enhanced $T_1$-weighted MRI in the patient #20 with complete response at day 15: (A) at study entry, demonstrating brain metastases and (B) at day 15 (second injection of bevacizumab, before WBRT start), demonstrating a complete response.

Figure 3. Waterfall plot of maximum relative brain tumour reduction observed between day 15 and 3 months post-treatment in comparison to baseline, one column representing one patient (pt) with the best response obtained (SD, stable disease; PR, partial response or CR, complete response), pt 6 belonged to dose level 1, ‘per-protocol’ analysis, n = 16.
In BM setting, additional data about efficacy of anti-angiogenic TKIs in combination with radiotherapy are also needed. The present study focused on BEV combined with WBRT; however, stereotactic radiotherapy is nowadays a standard for limited BM, with an OS estimated to 5.5–11.3 months [25]. Stereotactic radiotherapy and WBRT are not aimed to the same patients (mainly since WBRT remains the standard for disseminated BM), but the potential benefit of BEV combined with WBRT lets hypothesize a similar effect with stereotactic approach (the absence of toxicity should be assessed, considering the higher dose per fraction delivered by stereotactic radiotherapy).

In conclusion, the REBECA phase I study demonstrates the feasibility of combined standard WBRT fractionation (30 Gy/10 fractions/2 weeks) WBRT and bevacizumab and provides preliminary efficacy data for this approach. Based on the trend towards a better response rate with higher doses of bevacizumab combined with WBRT, the schedule of bevacizumab 15 mg/kg every 2 weeks for three cycles and WBRT 30 Gy in 2 weeks (10 fractions) seems the most appropriate for further phase II evaluation. The objective of such trials would be to assess the clinical benefit of this approach and to develop neurocognitive evaluation. This is of great importance because of the frequent deterioration of cognitive function in the context of BMs and/or after WRBT. The strategy of combining bevacizumab with systemic therapy, which has been shown to improve efficacy in several trials in the metastatic setting, may also be relevant to local therapy, such as radiotherapy. Consequently, further studies to validate the clinical benefit of this combination are justified.

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disclosure

ELR had a consultant advisory role with Roche and received research funding from Mundipharma. All the remaining authors have declared no conflicts of interest.

references