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A phase I and pharmacokinetic study of daily oral cediranib, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer: A study of the National Cancer Institute of Canada Clinical Trials Group

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ABSTRACT

Introduction: Cediranib, a potent vascular endothelial growth factor inhibitor, demonstrated broad pre-clinical anti-tumour activity. This study evaluated escalating cediranib doses with combination chemotherapy in advanced non-small cell lung cancer patients.
Methods: Patients received cisplatin 80 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on days 1 and 8 of a 3-week cycle, and daily oral cediranib at either 30 mg or 45 mg. Pharmacokinetics of all drugs were analysed, and response was assessed by RECIST.
Results: Fifteen patients were enrolled. No dose-limiting toxicities were observed during cycle 1. Fatigue, nausea, diarrhoea, anorexia and granulocytopaenia were common; hypertension was manageable. No grade 3/4 bleeding occurred. At 45 mg/d, fatigue, diarrhoea and thrombocytopaenia were increased; and headache, hoarseness and grade 2 hand–foot syndrome were observed. Cediranib had no effect on cisplatin elimination, but clearance of gemcitabine is significantly reduced in the presence of cediranib ($p > 0.02$). Central review confirmed responses in four of 15 enrolled patients (26.7%, 95% CI 7.8–55%) and four of 12 evaluable patients (33.3%, 95% CI 9.9–65%).
Conclusion: Cediranib at 30 mg daily can be combined with standard doses of cisplatin/gemcitabine with encouraging anti-tumour activity, and is the recommended phase III dose. Toxicity is increased, but is predictable and manageable.

1. Introduction

The leading cause of cancer-related mortality in Canada and the United States (US) is non-small cell lung cancer (NSCLC), with 19,900 and 161,000 patients, respectively, predicted to die in 2007.[1,2] For advanced disease (stages IIIB and IV), a median survival of less than 12 months can be expected with standard platinum-based regimens.[3] Recently, modest improvements in survival over best supportive care have been documented with both docetaxel[4] and erlotinib[5] in the sec-

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ond and third line settings. Clearly new treatment approaches are needed.

In order to grow and metastasise, tumours require a vascular supply, and to accomplish this, new blood vessels are formed (neoangiogenesis) in response to a number of factors. Vascular endothelial growth factor (VEGF) is a key angiogenic factor implicated in tumour blood vessel formation,[6] and has a permeabilising effect that may contribute to tumour progression by facilitating nutrient exchange and tumour cell intravasation during the metastatic process. Two high-affinity receptors, VEGFR-1 and VEGFR-2, are found on vascular endothelial cells, whilst a third one, VEGFR-3, is expressed on lymphatic endothelium. Markers of angiogenesis, such as serum VEGF levels and high tumour microvessel density (MVD), may be negative prognostic factors in lung cancers.[7]

Bevacizumab, a humanised monoclonal antibody against VEGF-A, in combination with carboplatin and paclitaxel improves median survival (12.5 versus 10.2 months) and objective response rate (27.2% versus 10%) compared to chemotherapy alone. The triple combination was associated with greater toxicity, and surprisingly, in subgroup analyses, women and patients aged greater than 70 years did not appear to benefit. Further, this study had restrictive eligibility criteria excluding patients with brain metastases, and those with a history of haemoptysis, squamous histology, therapeutic anticoagulation or prior thromboembolic events, due to episodes of fatal haemoptysis observed in the pilot randomised phase II trial.[8,9]

Cediranib (AZD2171, Recentin™, AstraZeneca, Macclesfield, UK) is a small molecule inhibitor of the tyrosine kinase domain of all three VEGFRs, with an IC_{50} value of less than 1 nmol/l for VEGFR2, and less than 5 nmol/l for the other VEGFRs, in addition to c-Kit.[10] In preclinical studies it has shown broad anti-tumour activity, including against NSCLC. The single-agent continuous daily oral dose of 45 mg/d appears tolerable in patients, with the most frequently reported adverse events being fatigue, nausea, diarrhoea and hypertension.[11] The phase I study of cediranib in combination with carboplatin and taxol established the recommended phase II dose (RP2D) of cediranib as 45 mg/d.[11,12] Therefore, this phase I study explored cediranib at two dose levels in combination with a standard chemotherapy regimen of cisplatin and gemcitabine in advanced NSCLC.

2. Methods

2.1. Patients

Eligible patients had advanced, incurable NSCLC (stage IV, or IIIB with effusion or unsuitable for chemoradiation), Eastern Co-operative Oncology Group (ECOG) performance status (PS) 0–2, adequate haematology (CBC), biochemistry and end-organ function. Prior palliative radiotherapy was allowed but had to be discontinued at least 21 d before registration. Patients must have recovered from all toxicities. Previous surgery was permitted provided wound healing had occurred and 14 d had elapsed since surgery.

Patients were excluded if they had received prior angiogenesis inhibitor therapy or had uncontrolled hypertension, serious medical or cardiac conditions, QTc prolongation, significant proteinuria, haemoptysis or cavitation of central pulmonary lesions, brain metastases which were symptomatic or required steroids; were pregnant or refused contraception if of childbearing potential; or had prior malignancy within 5 years of entry. Therapeutic anticoagulation was not a contraindication, but as cediranib is highly protein bound, increased monitoring of the INR was recommended, as was a switch to low molecular weight heparin (LMWH), if this was medically appropriate.

This study was approved by the research ethics boards of each participating centre. All patients provided written informed consent, and the study was conducted in accordance with good clinical practice guidelines.

2.2. Patient evaluation

Pre-treatment evaluation included a physical examination, CBC and differential, biochemistry, thyroid function, coagulation parameters, electrocardiogram, chest X-ray and other imagings to document disease. During treatment, CBCs were done weekly (first and second cycles) whilst a physical examination, CBC and biochemistry were performed every 3 weeks. Disease status was assessed every 6 weeks using response evaluation criteria in solid tumours (RECIST).[13] Toxicity was graded using common toxicity criteria, version 3.0.

2.3. Therapy

Cisplatin 80 mg/m^2 over 3 h with standard premedication on day 1 and gemcitabine 1250 mg/m^2 on days 1 and 8 were given intravenously every 3 weeks (one cycle) for up to eight cycles.

Cediranib was provided by AstraZeneca (Ontario, Canada), and was given orally daily starting on day 2 of the first cycle. Planned dose levels (DLs) were 30 mg and 45 mg. Three patients were to be enrolled to each DL, and three additional patients were enrolled if dose-limiting toxicity (DLT) was observed. Escalation to 45 mg was planned with <2 DLTs. De-escalation to 20 mg was planned if required. The highest administered dose was the dose at which two or more patients experienced DLT, and the next lower dose level would be the recommended phase II dose (RP2D) of cediranib.

DLT was defined as cediranib-related toxicity (including an increase in severity or frequency of the expected toxicity of chemotherapy) in cycle 1 only and included $\geqslant$grade 3 renal toxicity, fatigue or hand–foot syndrome, delay of cycle 2 by $\geqslant$14 d, grade 4 hypertension or uncontrollable grade 3 hypertension.

2.4. Duration of therapy and dose modifications for toxicity

Cisplatin and gemcitabine were adjusted for related toxicities according to manufacturers' guidelines, and no dose re-escalation was permitted. Patients who discontinued chemotherapy could continue cediranib monotherapy in the absence of disease progression or unacceptable toxicity. Therapy with cediranib was discontinued for grade 4 toxicity, held and dose was reduced on recovery for grade 3 toxicities (other than renal or hypertension), and held transiently for grade 2 toxicity. For renal toxicity of grade 2 or 3, cediranib was held, and

weekly 24 h urine collections for creatinine clearance and proteinuria were obtained. Study drug could be restarted after resolution to grade 1 either at the same dose (for a worst grade of toxicity of grade 2) or at one dose level lower (for grade 3 toxicity). Patients requiring a delay greater than 2 weeks for any toxicity and who required more than 2 dose reductions were removed from protocol therapy.

A standardised algorithm that was developed for the management of cediranib-induced hypertension for a previous protocol (IND.171) was used to facilitate continued administration of cediranib without dose reduction or interruption.[14] The guidelines suggested a dihydropyridine calcium-channel blocker as the initial agent.

2.5. *Pharmacokinetics*

Blood samples were drawn for cisplatin and gemcitabine levels on the first day of cycles 1 and 2 (pre-infusion, 60 and 120 min after the beginning of the infusion and at the end of the 180-min infusion, and then at 5, 15 and 30 min, and 1, 2, 4, 6, 8 and 24 h post-infusion), whilst samples for cediranib were drawn on the first day of cycle 2 (pre-dose, and at 0.5, 1, 2, 4, 6, 8 and 24 h post-dosing).

Samples were centrifuged immediately and were stored at –20 °C until analysis. Both plasma cisplatin and gemcitabine were analysed using validated high-performance liquid chromatograph with UV detection methods.[15,16] Pharmacokinetic parameters were calculated using non-compartmental methods (WinNonlin 4.1, Pharsight Corp., Mountain View, CA). Effects of cediranib on pK parameters were analysed using repeated two-way ANOVA (dose level, co-administration of cediranib), SAS Inc., Gary, NC.

3. Results

3.1. *Patients*

Characteristics of the 15 enrolled patients are summarised in Table 1. No patient had previously received any cytotoxic chemotherapy; two had received prior radiotherapy.

Table 1 – Patient characteristics.

Characteristic	Number of patients
Total enrolled	15
Female	5
Median age (range)	56 (34–73)
ECOG performance status	
0	7
1	6
2	2
Stage IIIB	4
Stage IV	11
Histology	9
Adenocarcinoma	2
Bronchoalveolar carcinoma	2
Undifferentiated	2
Not otherwise specified	2
Three or more sites of disease	9

Key: ECOG – Eastern Cooperative Oncology Group.

3.2. *Drug delivery*

The median number of cycles of cisplatin and gemcitabine delivered was 6 (range 4–6) for DL 1 and 3 (range 1–6) for DL 2. The median actual dose intensity (ADI) of cisplatin at both DLs was similar, but for gemcitabine was slightly less at DL 2 (658 mg/m^2/week) than at DL 1 (740 mg/m^2/week). Dose delays and/or reductions of cisplatin and gemcitabine were commonly due to myelosuppression.

All six patients enrolled at DL 1 and 8/9 at DL 2 received 100% of the planned dose intensity of cediranib (210 and 315 mg/week, respectively) for the first cycle. The median number of subsequent cycles of cediranib at DL 1 and the actual dose intensity for DL 1 were 7 (range 5–14) and 150 mg/week (range 131–196), respectively, and 5 (range 1–17) and 131 mg/week (range 37–193), respectively, for DL 2. This represents 26% and 56% reduction in the actual median delivered doses following cycle one at the 30 mg/d (DL 1) and 45 mg/d (DL 2) dose levels, respectively. Four of 6 patients on DL 1 had their dose of cediranib reduced to 20 mg (1 patient each with nausea, hypertension, hand–foot syndrome and vomiting). On DL 2 (45 mg/d), 9 patients were treated and received a total of 58 cycles; 89% received greater than 90% of the planned dose in cycle 1, however, no patient received greater than 90% of the planned dose in cycle 2+. Five of 9 patients had seven dose reductions to 30 mg (one due to vomiting, 2 due to fatigue, 1 due to proteinuria and 1 due to hand–foot syndrome). Eleven percent of all the doses of cediranib in the 30 mg/d and 14% in the 45 mg/d cohort were missed, the majority due to non-haematological toxicities.

3.3. *Toxicity*

Table 2 summarises all the reported adverse events with a frequency >15% or ⩾grade 3 toxicity for cycle 1 and worst reported at any time. For both DL cohorts, the most common events attributed to cediranib were fatigue, anorexia, nausea, vomiting, diarrhoea, hypertension and voice changes. DL 2 was associated with more severe fatigue, diarrhoea, dehydration and more common anorexia. Haematologic toxicity (Table 3) appeared similar at both DLs except for thrombocytopaenia. Biochemical adverse events were primarily of grade 1. However, there were 2 patients with grade 2 creatinine elevation and 1 patient with reversible grade 3 AST elevation which appears more severe at the 45 mg dose level.

3.4. *Dose escalation, dose-limiting toxicity and serious adverse events*

Although no protocol-defined dose-limiting toxicities were observed, the 45 mg dose level was expanded to gain more experience, and of 7 evaluable patients 1 patient developed DLT (grade 3 fatigue). In addition, a number of patients required dose modifications or interruptions. One patient had the study drug held for a total of 3 non-consecutive weeks due to proteinuria and hypertension, and two had dose interruptions for grade 2 hand–foot syndrome and nausea, and vomiting and fatigue, respectively. In view of this, it was

Table 2 – All reported non-haematological adverse events.

	Cediranib 30 mg/d ($n = 6$)				Cediranib 45 mg/d ($n = 9$)			
	Cycle 1		Worst by patient, any cycle		Cycle 1		Worst, any cycle	
	Any	CTCAE grade 3/4	Any	CTCAE grade 3/4	Any	CTCAE grade 3/4	Any	CTCAE grade 3/4
Cardiac general								
Hypertension	2	1	4	4	5	3	6	3
Hypotension		–	1	–	–	–	–	1
Constitutional								
Fatigue	5	–	6	4	9	3	9	**5**
Dermatological								
	–	–		–	–	–	–	–
Dry skin	1	–	2	–	1	–	3	–
Hand–foot	1	–	2	–	2	–	3	–
Rash	1	–	3	–	–	–	–	–
Gastrointestinal								
Anorexia	4	–	4	1	7	1	8	2
Constipation	5	–	6	–	4	0	4	–
Dehydration	–	–	2	–	2	–	3	1
Diarrhoea	4	0	6	1	6	1	8	2
Gastritis/heartburn	2	–	5	–	2	0	5	
Mucositis	2	–	4	–	3	0	3	
Nausea	3	–	6	–	9	0	9	1
Vomiting	2		5	–		0	8	–
Musculoskeletal								
Weakness: limb/general	–	–	2	–	1	–	3	–
Neurological								
Confusion	–	–	–	–	1	0	1	**1**
Dizziness	1	1	3	2	1	0	2	–
Neuropathy – sensory		–	1	–	–	–	2	–
Mood alteration	1	–	2		4		7	–
Other								
Haemorrhage	6	–	10	–	4	–	7	
Thrombosis	2	–	3	–	–	–	1	–
Voice Change	4	–	5	–	5	1	5	1

Key: Events related to cediranib, and of grade 3/4 (grade 4 in bold) in severity and/or occurring in at least 15% of patients in a cohort.
–, indicates the toxicity that is not reported.

Table 3 – Haematological toxicity.

	Cediranib 30 mg/d ($n = 6$)					Cediranib 45 mg/d ($n = 9$)				
	Cycle 1	Worst, any cycle	No. of patients worst NCI grade			Cycle 1	Worst, any cycle	No. of patients worst NCI grade		
	Median nadir (range)	Median nadir (range)	1/2	3	4	Median nadir (range)	Median nadir (range)	1/2	3	4
Leucocytes ($\times 10^9$/l)	3.2 (1.4–6.8)	3.2 (1.1–4.5)	4	1	0	4.7 (1.9–6.6)	4.5 (1.7–6.1)	2	2	0
Granulocytes ($\times 10^9$/l)	1.04 (0.7–3.5)	1.04 (0.2–1.8)	4	0	2	1.9 (0.3–4.7)	1.9 (0.3–4.7)	2	3	1
Haemoglobin (g/l)	132 (113–155)	95 (76–147)	4	1	0	112 (83–153)	93 (83–153)	7	0	0
Platelets ($\times 10^9$/l)	139 (71–158)	104 (57–158)	5	0	0	113 (16–251)	70 (16–251)	4	3	1

decided to expand the 30 mg dose with an additional 3 patients. No DLTs were observed in this cohort.

All serious adverse events (SAEs) occurred at dose level 2. Seven SAEs were reported in 4 patients. Four SAEs were possibly, probably or definitely related to the study drug (3 patients were hospitalised for nausea, vomiting, dehydration and fatigue; 1 patient suffered a parietal lobe infarction with a transient visual defect which resolved). Three SAEs were

unlikely or unrelated to the study drug (1 patient with uncontrolled disease-related pain requiring admission; 1 diagnosed with pulmonary tuberculosis following enrollment into study; 1 admitted with gastrointestinal perforation superimposed on widespread abdominal carcinomatosis and abscess formation who had been off the study drug).

3.5. *Potential class-specific toxicities*

Grade 1 mucocutaneous bleeding was reported in a number of patients and a single patient had a grade 2 epistaxis. No patient experienced grades 3–4 bleeding or haemoptysis. Three patients experienced thrombotic events (at 30 mg dose – 1 patient experienced grade 3 event related to a venous indwelling catheter and one experienced grade 3 parietal lobe infarct which resolved spontaneously over a 2-week period; at 45 mg dose – 1 patient experienced a grade 2 superior vena cava occlusion). Hypertension occurred in 10 patients (in 4 at 30 mg/d and in 6 at 45 mg/d with 7 of 10 patients experiencing grades 2–3 toxicity). However, the hypertension was manageable and not dose-limiting whilst using the algorithm previously described for the management of hypertension.[14]

3.6. *Anti-tumour activity*

Following central radiology review, there were four confirmed partial responses (response rate 27%, 95% CI 7.8–55%), with a median duration of response of 4.3 months (range 3.6–6.7); there were two responses on each DL. Three patients were inevaluable for response for the following reasons: one patient received less than one complete cycle of therapy, 1 patient's disease status could not be reassessed, 1 patient was inevaluable on radiology review as the pleural effusion increased and obscured the measurable lung lesion. Seven patients had stable disease by RECIST as their best response, for a median duration of 4.3 months (range 1.6–10.8 months). Cavitation of lung lesions was observed in 4 patients (1 with squamous and 3 with other histologies). There was no relationship between cavitation and haemoptysis. All patients showed some initial tumour shrinkage. Responses for all 15 patients are detailed in Fig. 1.

3.7. *Pharmacokinetics*

Paired samples for cisplatin and gemcitabine were available for 7 and 8 patients, respectively, and for cediranib pharmacokinetics in 9 patients; results are summarised in Table 4. At either dose, steady-state pharmacokinetic parameters of cediranib were similar to those seen with single-agent dosing.[11] Co-administration of cediranib had no effect on cisplatin elimination. However, the clearance of gemcitabine is reduced significantly in the presence of cediranib ($p < 0.02$).

4. Discussion

Other than for renal cell carcinoma,[17,18] angiogenesis inhibitors have shown their greatest benefit in combination with cytotoxic chemotherapy.[8,19] These agents may improve chemotherapy drug delivery by normalising intratumoural hydrostatic pressure[20–22] making combinations attractive, although overlapping toxicity profiles are of concern.

We demonstrated that cediranib can be added to cisplatin and gemcitabine in patients with advanced NSCLC with ex-

		# patients	Duration in Median	Months (Range)
Complete Response	(CR)	0		
Partial Response	(PR)	4	4.3	(3.6- 6.7)
Stable Disease	(SD)	7	4.3	(1.6- 10.8)
Progressive Disease	(PD)	1		
Inevaluable	(IN)	3		

Response rate for all patients: 4/15 = 26 . 7% (95 % CI : 7.8, 55.1 %)
Response rate for evaluable patients: 4/12 = 33 . 3% (95 % CI:9.9, 65.1 %)

Fig. 1 – Central radiology review: response ($n = 15$ patients).

Table 4 – Pharmacokinetic parameters.

	Dose level 1 (30 mg/d) Cisplatin ($n = 4$) Gemcitabine ($n = 2$)				Dose level 2 (45 mg/d) Cisplatin ($n = 3$) Gemcitabine ($n = 6$)			
	Clearance (l/h)		Vd (l)		Clearance (l/h)		Vd (l)	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2
Cisplatin	21.9 ± 2.5	21.1 ± 6.1	22.8 ± 11.9	20.6 ± 9.6	17.2 ± 1.7	19.0 ± 3.6	20.9 ± 5.6	18.1 ± 3.8
Gemcitabine	124 ± 14.4	93.4[a] ± 8.0	148 ± 144	204 ± 126	123 ± 25.1	114[a] ± 37.1	151 ± 80.0	134 ± 83.2
Cediranib	$C_{ss\ max}$ = 66.9 ng/ml AUC_{ss} = 1058.7 ng * h/ml				$C_{ss\ max}$ = 194 ng/ml AUC_{ss} = 2861.7 ng * h/ml			

Key: l, litres; Vd, volume of distribution; h, hour; AUC, area under the concentration–time curve; ss, steady state.
a $p < 0.02$ versus cycle 1.

pected, incremental, fatigue, gastrointestinal adverse events, and possibly, myelosuppression. Although in the initial single-agent phase I study of cediranib,[11] 45 mg was found to be the RP2D, this dose was not tolerable in patients with advanced hepatocellular carcinoma[23] or in the majority of those with renal cell carcinoma,[24] and 20 mg/d was the maximum tolerated dose in a single-agent study in men with hormone-refractory prostate cancer.[25] Whilst in this study the classical RP2D, based on cycle 1 DLT, was 45 mg for cediranib, this dose appeared less well tolerated than 30 mg for prolonged usage with cisplatin/gemcitabine, and 30 mg was chosen as the RP2D for future studies in this patient population. The requirement for dose modification of the single-agent RP2D for combinations or specific patient populations is well described. In combination with 250 mg/d of gefitinib, 30 mg/d of cediranib was the MTD.[26] In heavily pretreated patients, when cediranib was administered in combination with standard cytotoxic agents such as pemetrexed, irinotecan, capecitabine and the combination of 5-fluorouracil/leucovorin/oxaliplatin (mFOLFOX), 30 mg appeared to be more tolerable.[27] In a second NCIC CTG study in advanced NSCLC, there were no DLTs observed at 45 mg in combination with carboplatin and paclitaxel, but 30 mg was felt to be more tolerable for longer term administration.[12] Interestingly, in another NCIC CTG study, 45 mg was tolerable in carefully selected and managed patients in combination with mFOLFOX.[28]

Based on the small patient numbers and the degree of interpatient variability, a cross-study comparison showed that the steady-state pK parameters of cediranib in combination with cisplatin and gemcitabine are not substantially different from the steady-state pK parameter estimate obtained from single-agent studies following multiple doses of cediranib 30 and 45 mg.[13] The co-administration of cisplatin and gemcitabine did not lead to steady-state levels of cediranib which were significantly different from those observed with single-agent administration, and cediranib does not appear to affect the pharmacokinetics of cisplatin. However, the clearance of gemcitabine appeared to be reduced in the presence of cediranib ($p < 0.02$). As gemcitabine is mainly eliminated through cytidine deaminase, the mechanism of a potential interaction is not clear. Although we noted a drop in the median platelet count between cycles 1 and subsequent cycles at DL 1 and DL 2, and lower median (7×10^9/l) platelet count at the 45 mg DL versus 104×10^9/l at the 30 mg DL, these findings may be due to additive haematologic toxicity, which has been described with this class of agents, rather than a pharmacokinetic interaction such as reduced clearance of gemcitabine.

In the current trial, anti-tumour activity was seen at both cediranib dose levels, with no suggestion of a dose–response relationship. However, the numbers are small and need to be interpreted cautiously.

Oncologists will need to learn to manage the unique toxicities seen with angiogenesis inhibitors. For example, the mechanism of hypertension associated with these agents is not fully understood. The algorithm developed for a previous phase I trial of the combination of carboplatin and paclitaxel plus cediranib[14] greatly facilitated clinical management of the hypertension. Diarrhoea, with institution of anti-diarrhoeal agents and patient education, was manageable. Fatigue, commonly reported with angiogenesis inhibitors, is of uncertain aetiology. Encouragingly, significant drug-related bleeding was not observed, nor was clinically significant renal dysfunction or proteinuria. Finally, four episodes of venous thromboembolism were seen but given the known risk of these events in patients with NSCLC receiving chemotherapy, the contribution of cediranib is unclear.

In conclusion, encouraging anti-tumour activity was observed with this combination, with all patients showing some degree of initial tumour shrinkage. Consequently, it is proposed that the combination of cisplatin/gemcitabine plus cediranib be studied in a randomised phase II/III trial, in which patients with advanced NSCLC of any histology are randomised to receive the combination chemotherapy plus cediranib at 30 mg/d or placebo.

Conflict of interest statement

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