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Annals of Oncology 25: 1597–1603, 2014
doi:10.1093/annonc/mdu175
Published online 14 May 2014

Activity and safety of RAD001 (everolimus) in patients affected by biliary tract cancer progressing after prior chemotherapy: a phase II ITMO study

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Received 8 January 2014; revised 24 April 2014; accepted 25 April 2014

Background: Biliary tract cancer (BTC) is a highly lethal disease for which the best available therapy remains undetermined. The mammalian target of rapamycin (mTOR) pathway is up-regulated in several cancers, including BTC, and preclinical evidence indicates that mTOR inhibition may be effective in the treatment of BTC. We sought to evaluate the activity and tolerability of the mTOR inhibitor RAD001—everolimus—in patients with BTC progressing after prior chemotherapy.

Patients and methods: This was an open-label, single-arm, phase II study (EUDRACT 2008-007152-94) conducted in eight sites in Italy. Patients with locally advanced, metastatic or recurrent BTC progressing despite previous chemotherapy received a daily oral dose of everolimus 10 mg administered continuously in 28-day cycles. The two primary end

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points were disease control rate (DCR) and objective response rate (ORR). Secondary end points were progression-free survival (PFS), overall survival (OS) and time-to-progression (TTP).

Results: Thirty-nine patients were enrolled. The DCR was 44.7%, and the ORR was 5.1%. One patient showed a partial response at 2 months and one patient showed a complete response sustained up to 8 months. The median (95% confidence interval) PFS was 3.2 (1.8–4.0) months, and the median OS was 7.7 (5.5–13.2) months. The median TTP was 2.0 (1.7–3.7) months. Most common toxicities were asthenia (43.6%), thrombocytopenia (35.9%), pyrexia (30.8%) and erythema, mainly of mild-to-moderate severity. Two patients required dose reduction due to adverse events.

Conclusion: Everolimus demonstrated a favourable toxicity profile and encouraging anti-tumour activity. Further trials are needed to establish the role of everolimus in the treatment of BTC.EUDRACT 2008-007152-94.

Key words: advanced biliary tract cancer, everolimus, mTOR

introduction

Biliary tract cancer (BTC), which encompasses cholangiocarcinoma (CC) and gallbladder carcinoma (GBC), is a disease with high mortality, limited treatment options and few significant improvements in the therapeutic strategy over the last 10–20 years. Currently, tumour resection is the only potential cure for BTC. However, most BTCs are diagnosed at advanced stages, when tumour is unresectable. Five-year survival rates are <5%–10% for advanced BTC [1], and the median survival of patients with advanced disease is frequently <1 year [2]. Chemotherapeutic agents currently used for the treatment of BTC include gemcitabine, 5 fluorouracil (5-FU), mitomycin C and platinum analogues [2]. Objective response rates (ORR) to most of these drugs range from 0% to 40%, with no complete remissions [3]. In most cases, treatment after disease progression consists of palliative care, with only 25% of patients receiving further chemotherapy [4]. More effective strategies for the treatment of BTC are needed to improve the prognosis and quality of life (QoL) of BTC patients.

RAD001 (everolimus) is a mammalian target of rapamycin (mTOR) inhibitor currently indicated for the treatment of advanced breast cancer, neuroendocrine tumours of pancreatic origin and renal cell carcinoma [5]. The mTOR pathway, which plays a key role in cell growth, proliferation and survival, is known to be up-regulated in many cancer types, including extrahepatic CC [6].

In transgenic mouse models of GBC, mTOR inhibition has yielded promising results [7]. The mTOR status was found to be an independent prognostic factor in patients with BTC, overall survival being significantly shorter in patients with m-TOR-positive tumours [8]. We undertook the present study to assess the activity and tolerability of everolimus in patients with BTC progressing after prior chemotherapy.

patients and methods

study design

This was an open-label, single-arm, multicentre phase II study in eight sites in Italy (EUDRACT 2008-007152-94). The study was conducted according to ICH/GCP guidelines and the Declaration of Helsinki and approved by the Ethic Committees of participating Centres. All patients provided written informed consent.

eligibility criteria

Eligible participants were adult patients (age 18–75 years) with histologically or cytologically confirmed locally advanced, metastatic or recurrent BTC that had progressed despite previous chemotherapy and who had at least one measurable site of disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [9] and no indication to surgery or radiotherapy for locally advanced disease. Only patients who had received no more than one previous systemic chemotherapy regimen were enrolled. Adjuvant chemotherapy and/or radiotherapy were not considered as first-line chemotherapy. Further inclusion criteria are provided as supplementary material, available at *Annals of Oncology* online.

treatment and dose modifications

Everolimus was administered orally at a daily dose of 10 mg continuously (28-day cycles). Therapy was continued from day 1 until progression of disease, unacceptable toxicity or discontinuation from study drug for any other reason. Thereafter, patients were followed-up. Dose adjustments were allowed in patients unable to tolerate the protocol-specified dosing schedule. If toxicity was tolerable to the patient, the initial dose was maintained. Dose reductions for toxicity were as follows: dose level 1, 5 mg daily; and dose level 2, 5 mg every other day.

assessments

Baseline evaluations included a complete history and physical examination; ECOG performance status; complete blood count, coagulation parameters, biochemical measurements and fasting lipid profile; pregnancy test in women of childbearing potential; electrocardiogram and chest X-ray. Laboratory assessments were repeated every 2 weeks and at study end. Tumour measurement was carried out by computed tomography and/or magnetic resonance imaging of the abdomen, pelvis and chest before initiation of treatment and subsequently every 8 weeks. Tumour response was assessed using the RECIST criteria version 1.1 [9].

Safety was monitored throughout the study and for 28 days after discontinuation of study drug. Adverse events (AEs) terms were classified by Primary System Organ Class (SOC) according to the MedDRA thesaurus version 12 [10]. All patients were assessed for toxicity as per the NCI Common Toxicity Criteria, version 3. Survival was recorded every 2 months for at least 1 year after enrolment of the last patient.

QoL was assessed with the EORTC QLQ-C30 questionnaire [11] at baseline, every 8 weeks and at study end.

activity end points

The two primary activity end points were disease control rate (DCR) and ORR, which were assessed hierarchically. The primary variable for the definition of the DCR was the overall objective response (OOR) at the 8-week assessment, according to RECIST criteria. DCR was calculated as the

proportion of patients with complete response (CR), partial response (PR) or stable disease (SD) on the number of assessable patients.

The primary variable for defining the ORR was the best overall response (CR or PR) achieved at any time during treatment, as per RECIST criteria among patients who received at least one dose of study drug.

Secondary activity end points were progression-free survival (PFS), overall survival (OS), and time-to-progression (TTP). PFS was defined as the time from date of the first everolimus dose to the date of the event, defined as the first documented progression or death due to any cause. In the case of no event, PFS was censored at the date of last adequate tumour assessment. OS was defined as the time from date of the first everolimus dose to the date of death for any cause. If a patient was not known to have died, survival was censored at the date of last contact. TTP was defined as time from date of the first everolimus dose to the date of event (first documented progression or death due to the underlying cancer). In the case of no event, time to progression was censored at the date of last adequate tumour assessment.

statistical analysis

A Simon optimum two-stage design was used [12]. The stopping rule was based exclusively on DCR. A DCR of 5% or lower precluded further study, whereas a DCR of 20% or higher would be considered sufficiently promising to warrant further study. Assuming a type I error rate of 10% and a power of 90%, a total of 12 patients were enrolled in the first stage, which required at least one patient achieving disease control to proceed to the second stage. An additional 25 assessable patients would be enrolled in the second stage, giving a total of 37 assessable patients. If ≥3 patients achieved disease control, everolimus would be considered active and worthy of further testing. Patients who experienced progression or death from progressive disease before week 8 were considered as failures in the DCR. All data were considered for patients who had received at least one dose of study drug [intent-to-treat (ITT) population]. Patient withdrawals due to AEs or toxicity before the 8-week response evaluation were considered as treatment failures. The Kaplan–Meier curves were estimated for the PFS, OS and TTP.

Continuous variables were summarized by descriptive statistics. Categorical variables were summarized using counts of patients and percentages. Comparisons were carried out with Student's paired *t*-test. Statistical significance was set at $P < 0.05$. Statistical analyses were carried out with SAS System (version 9.2, Cary, NC).

results

patient characteristics

Thirty-nine patients were enrolled between January 2009 and December 2011. Patients' characteristics (ITT population) are listed in Table 1. Thirty-seven patients (94.9%) had a histological or cytological diagnosis of CC, while two (5.1%) had GBC. At diagnosis, 8 patients (20.5%) had stage II disease, 3 (7.7%) had stage III and 28 (71.8%) had stage IV. Thirty-one (79.5%) patients had ECOG 0, five (12.8%) ECOG 1 and three (7.7%) ECOG 2. At study enrolment, all patients had received previous chemotherapy. The combination of gemcitabine and oxaliplatin (GEMOX) was the most common first-line chemotherapy regimen.

Table 1. Baseline demographic and clinical characteristics (safety population, $n = 39$)

Characteristic	Value
Age (years), median (range)	63 (36–75)
Gender, *n* (%)	
Male	17 (43.6)
Female	22 (56.4)
Stage at diagnosis, *n* (%)	
II	8 (20.5)
III	3 (7.7)
IV	28 (71.8)
ECOG performance status, *n* (%)	
0	31 (79.5)
1	5 (12.8)
2	3 (7.7)
Previous surgery for cancer, *n* (%)	
Yes	21 (53.8)
No	18 (46.2)
Previous radiotherapy, *n* (%)	
Yes	6 (15.4)
No	33 (84.4)

treatment exposure

The median compliance was 92.9% (range 50–100%). The median exposure to study drug was 67.5 days (range 15–674 days). Of the 39 assessable patients (ITT population), 36 discontinued the study drug because of disease progression. One patient withdrew consent after 12 weeks and two patients died for the onset of adverse events after 8 weeks of treatment (deaths: 11 and 14 weeks).

activity

One patient was excluded from the analysis of DCR due to missing data on tumour response at week 8. Of the 38 assessable patients, one patient (2.6%) had a PR and 16 patients (42.1%) showed SD (DCR 44.7%) at week 8 (supplementary Table S1, available at *Annals of Oncology* online). Twenty-one patients (55.3%) had disease progression at week 8. The ORR was 5.1%, with one patient showing a PR at 2 months (59-year-old male with GBC; PFS 8.5 months and OS 10.1 months) and one patient showing CR at 4, 6 and 8 months (57-year-old male with intrahepatic CC; PFS 10 months and OS 17 months).

The median (95% CI) PFS in the ITT population was 3.2 (1.8–4.0) months (Figure 1A). The proportion of progression-free patients was 51.3% (34.8–65.6) at 3 months, 28.2% (15.3–42.7) at 6 months, 5.1% (1.0–15.2) at 12 months and 0% (NA) at 18 months.

The median OS was 7.7 (5.5–13.2) months (Figure 1B). One patient was censored from the OS analysis. The proportion of patients alive was 79.5% (63.1–89.2) at 3 months, 56.4% (39.6–70.2) at 6 months, 32.4% (18.4–47.3) at 12 months and 10.8% (3.4–23.0) at 18 months (supplementary Table S2, available at *Annals of Oncology* online). Percentile analysis showed that one-quarter of patients had an OS >15.3 months.

The median TTP in the ITT population was 2.0 (1.7–3.7) months.

safety

The total number of AEs in the safety population ($n = 39$) was 384; 261 of which (67.9%) were considered as treatment-related (Table 2). Overall, the most common AEs were asthenia (43.6%), thrombocytopenia (35.9%), pyrexia (30.8%) and

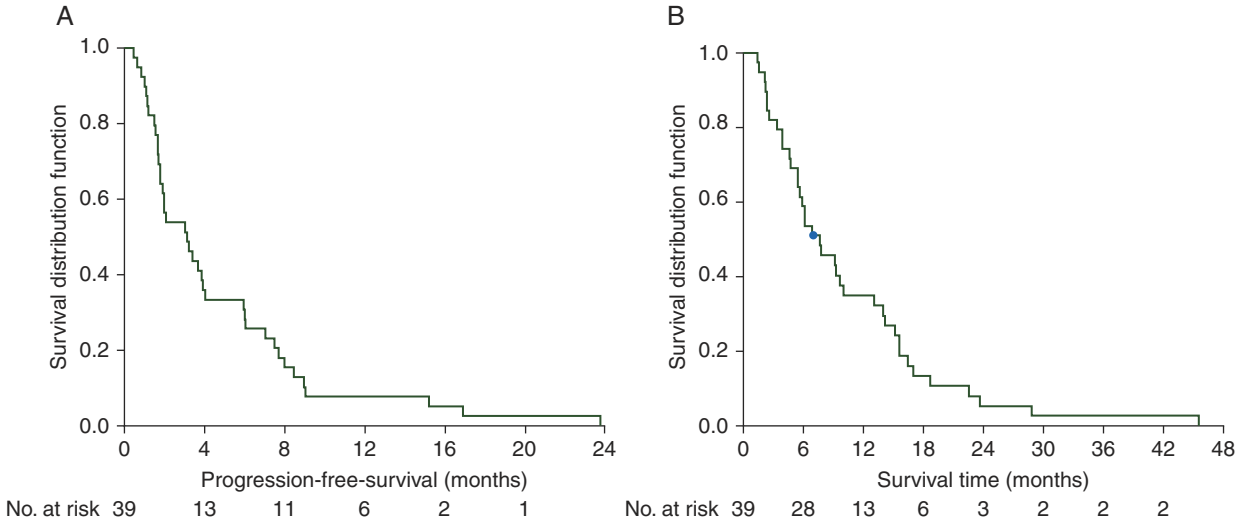

Figure 1. The Kaplan–Meier plots of progression-free survival (A) and overall survival (B) in the ITT population ($n = 39$).

erythema (23.1%). Grade 1 AEs were reported in 33 patients (86.6%), grade 2 AEs in 34 patients (87.2%), grade 3 AEs in 20 patients (51.3%) and grade 4 AEs in 13 patients (33.3%).

The most common grade 3–4 toxicities were hyperbilirubinaemia (15.4%), elevated alanine aminotransferase (12.8%), hypocalcaemia (12.8%), elevated alkaline phosphatase (10.3%), thrombocytopaenia (10.3%) and hyperglycaemia (10.3%). In total, 21 grade 4 AEs were reported; six of these, occurring in three patients (23.1% of patients with grade 4 toxicity), were classified as probably (thrombocytopenia, pneumonia, anorexia, nausea and vomiting), or certainly (stomatitis) related to study drug. Two patients (5.1%) died due to an AE (both for cachexia), but those events were not considered drug-related. Dose reduction due to AEs was required in two patients (one for neutropenia and one for hypersensitivity).

QoL and performance status

Data on QoL at baseline and study end were available for 19 patients (48.7%). There was a trend towards a decrease from baseline in global health status, physical functioning, role functioning and emotional functioning and a statistically significant, moderate improvement in fatigue ($P = 0.039$). A small but significant ($P = 0.030$) deterioration was observed in the pain subscale. No changes were observed in the remaining QLQ-C30 items. With respect to PS, at study end, data were available for 26 patients, 22 of whom (84.6%) had ECOG 0–2 and 4 (15.4%) had ECOG ≥3.

discussion

BTC is a highly lethal cancer for which the best available chemotherapy remains to be determined. In a large meta-analysis of clinical trials of chemotherapy in advanced BTC, the overall OS for all patients included in the survival analysis ($n = 1543$) was 8.2 months, with a tumour control rate of 57.3% ($n = 2386$) [13]. At present, gemcitabine- and platinum-containing regimens appear to be the most effective first-line treatment for advanced BTC, with reported median OSs of 9.5–11.7 months [14]. In contrast, there is an urgent need to establish an effective second-line treatment to improve survival of BTC patients.

The results of the present study support the role of mTOR as a potential therapeutic target in BTC. The 44.7% DCR at 8 weeks, along with the median PFS, TTP and OS of ∼3, 2 and 7.2 months, respectively, indicate that everolimus is active in patients with BTC progressing despite previous chemotherapy. Noteworthy, OS data and the percentile analysis seem to suggest that patients who are still alive after the first months of therapy present a prolonged OS, with 32.4% and 25% of patients still alive after 12 and 15 months of therapy, respectively. This finding suggests that proper selection of patients eligible to everolimus therapy could maximize the clinical benefits of the drug. The identification of predictive biomarkers of response to everolimus could help optimize the management of BTC patients, and could be the aim of future studies.

Previously evaluated second-line chemotherapy regimens include the combination of 5-FU, doxorubicin and mitomycin C, gemcitabine as a single agent and the oral fluoropyrimidine S-1 [15–17]. In these trials, the average DCR was ∼43%, with a median TTP of ∼2 months, a median OS of 4–7 months and no patient showing CR. Recently, a retrospective study analysed the efficacy of second-line chemotherapy in advanced BTC, reporting DCRs and SD of 43% and 34%, respectively, and the median PFS and OS of 2.8 and 7.5 months, respectively [4].

Although a comparison with previous studies is difficult due to different design and patient populations, in the present study, everolimus treatment resulted in longer OS when compared with previous trials on second-line chemotherapy, complete tumour response in one patient at 4, 6 and 8 months and partial response in one patient at 2 months. Furthermore, 42.1% of patients had SD at 2 months.

Targeting the mTOR pathway may represent a novel and effective strategy for the treatment of BTC. Although the genetics of BTC are highly heterogeneous, there is evidence that the mTOR pathway is involved either directly or indirectly in CC tumorigenesis [18], and activation of this pathway may negatively impact the prognosis of patients with BTC [8]. Inhibition of

Table 2. Total adverse events by system organ class (SOC) and severity and proportion of adverse events with a suspected relationship with everolimus experienced by ≥5% of patients (safety population, $n = 39$)

Adverse event	*n* (%)	G1–G2	G3–G4	Drug-related
Total number of adverse events	384	347	37	261
Number of patients with at least one adverse event[a]	39 (100)	34 (87.2)	20 (51.3)	36 (92.3)
General disorders and administration site conditions[a]	27 (69.2)	25 (64.1)	6 (15.4)	19 (48.7)
Asthenia	17 (43.6)	14 (35.9)	3 (7.7)	12 (30.8)
Pyrexia	12 (30.8)	11 (28.2)	1 (2.6)	7 (17.9)
Mucosal inflammation	8 (20.5)	7 (17.9)	1 (2.6)	7 (17.9)
Peripheral oedema	8 (20.5)	8 (20.5)	—	3 (7.7)
Condition aggravated	2 (5.1)	—	2 (5.1)	—
Fatigue	2 (5.1)	2 (5.1)	—	2 (5.1)
Pain	2 (5.1)	2 (5.1)	—	—
Chest pain	2 (5.1)	2 (5.1)	—	—
Gravitational oedema	2 (5.1)	2 (5.1)	—	2 (5.1)
Gastrointestinal disorders[a]	26 (66.7)	31 (79.5)	6 (15.4)	19 (48.7)
Abdominal pain	8 (20.5)	5 (12.8)	3 (7.7)	3 (7.7)
Nausea	8 (20.5)	7 (17.9)	1 (2.6)	6 (15.4)
Stomatitis	8 (20.5)	8 (20.5)	—	8 (20.5)
Vomiting	6 (15.4)	5 (12.8)	1 (2.6)	4 (10.3)
Ascites	5 (12.8)	4 (10.3)	1 (2.6)	2 (5.1)
Diarrhoea	4 (10.3)	4 (10.3)	—	3 (7.7)
Gastrointestinal obstruction	3 (7.7)	—	3 (7.7)	—
Constipation	2 (5.1)	2 (5.1)	—	—
Upper abdominal pain	2 (5.1)	2 (5.1)	—	—
Blood and Lymphatic system disorders[a]	21 (53.8)	21 (53.8)	3 (7.7)	21 (53.8)
Thrombocytopenia	14 (35.9)	13 (33.3)	1 (2.6)	14 (35.9)
Anaemia	6 (15.4)	6 (15.4)	—	6 (15.4)
Neutropenia	6 (15.4)	5 (12.8)	1 (2.6)	6 (15.4)
Leukopenia	2 (5.1)	1 (2.6)	1 (2.6)	2 (5.1)
Thrombocythaemia	2 (5.1)	1 (2.6)	1 (2.6)	2 (5.1)
Skin and subcutaneous tissue disorders[a]	17 (43.6)	18 (46.2)	—	16 (41.0)
Erythema	9 (23.1)	9 (23.1)	—	9 (23.1)
Skin toxicity	2 (5.1)	2 (5.1)	—	2 (5.1)
Metabolism and nutrition disorders[a]	15 (38.5)	16 (41.0)	3 (7.7)	9 (23.1)
Anorexia	7 (17.9)	6 (15.4)	1 (2.6)	3 (7.7)
Hypertriglyceridaemia	3 (7.7)	3 (7.7)	—	3 (7.7)
Cachexia	2 (5.1)	—	2 (5.1)	—
Hyperglycaemia	2 (5.1)	2 (5.1)	—	2 (5.1)
Hypercholesterolaemia	2 (5.1)	2 (5.1)	—	2 (5.1)
Hyponatraemia	2 (5.1)	2 (5.1)	—	—
Investigations[a]	14 (35.9)	18 (46.2)	2 (5.1)	12 (30.8)
Elevated alkaline phosphatase	6 (15.4)	5 (12.8)	1 (2.6)	4 (10.3)
Elevated alanine amonotransferase	5 (12.8)	5 (12.8)	—	4 (10.3)
Elevated aspartate aminotransferase	5 (12.8)	4 (10.3)	1 (2.6)	4 (10.3)
Weight loss	5 (12.8)	5 (12.8)	—	3 (7.7)
Elevated bilirubin	3 (7.7)	1 (2.6)	2 (5.1)	—
Hypokalaemia	2 (5.1)	2 (5.1)	—	2 (5.1)
Elevated γ-glutamyltransferase	2 (5.1)	1 (2.6)	1 (2.6)	2 (5.1)
Respiratory, thoracic and mediastinal disorders[a]	14 (35.9)	17 (43.6)	—	8 (20.5)
Cough	7 (17.9)	7 (17.9)	—	3 (7.7)
Dyspnoea	5 (12.8)	5 (12.8)	—	2 (5.1)
Epistaxis	4 (10.3)	4 (10.3)	—	4 (10.3)
Rales	2 (5.1)	2 (5.1)	—	2 (5.1)
Hepatobiliary disorders[a]	11 (28.2)	8 (20.5)	4 (10.3)	5 (12.8)
Hepatomegaly	6 (15.4)	5 (12.8)	1 (2.6)	3 (7.7)
Jaundice	3 (7.7)	1 (2.6)	2 (5.1)	—
Hyperbilirubinaemia	2 (5.1)	1 (2.6)	1 (2.6)	2 (5.1)

Continued

Table 2. *Continued*

Adverse event	*n* (%)	G1–G2	G3–G4	Drug-related
Infections and infestations[a]	10 (25.6)	10 (25.6)	—	6 (15.4)
Urinary tract infection	2 (5.1)	2 (5.1)	—	1 (2.6)
Vascular disorders[a]	7 (17.9)	5 (12.8)	2 (5.1)	—
Deep vein thrombosis	2 (5.1)	—	2 (5.1)	—
Hypertension	2 (5.1)	2 (5.1)	—	—
Musculoskeletal and connective tissue disorders[a]	6 (15.4)	4 (10.3)	3 (7.7)	—
Back pain	4 (10.3)	4 (10.3)	—	—
Nervous system disorders[a]	4 (10.3)	4 (10.3)	—	3 (7.7)
Dysgeusia	2 (5.1)	2 (5.1)	—	2 (5.1)
Cardiac disorders[a]	3 (7.7)	3 (7.7)	—	—
Sinus tachycardia	2 (5.1)	2 (5.1)	—	—

[a]Number of patients with a least one adverse event.

mTOR has antiproliferative effects on different BTC cell lines *in vitro*, and is known to reduce angiogenesis by diminishing vascular endothelial growth factor (VEGF) [19, 20]. Everolimus was able to induce a 50% reduction in cell growth of human extrahepatic CC and GBC cell lines, and the combination of everolimus with gemcitabine had the strongest synergistic effect on extrahepatic cell lines when compared with the combination of gemcitabine with a VEGF-inhibitor, allowing a significant reduction in the median gemcitabine dose [21]. A single-arm, phase I study designed to determine the maximally tolerated dose of everolimus plus gemcitabine and to obtain pilot data on toxicity and efficacy outcomes in patients with advanced refractory CC/GBC is currently ongoing [22].

In the present study, drug-related toxicity was observed in 92.3% of patients, with a spectrum of toxicities that was similar to that observed with everolimus in other cancers [23, 24]. Overall, everolimus had not any marked effect on QoL.

The patient sample in this study was relatively small. However, this reflects the modest incidence of the disease in the overall population; in addition, many BTC patients die or require only supportive care after the first-line treatment. We used the RECIST criteria to evaluate DCR, PFS and TTP. These criteria may not take into account the cytostatic effect of everolimus, since they are more focused on variations in tumour size. Lastly, we did not report data on immunohistochemistry (IHC) assessments: IHC samples were available only for 11 patients, all treated in a single Centre (Istituto Nazionale Tumori, Milan, Italy) and therefore not representative of the entire study population.

In conclusion, everolimus demonstrated a favourable toxicity profile and promising anti-tumour activity as a second-line therapy in BTC patients. Larger trials are needed to better establish the role of everolimus in the treatment of BTC and identify prognostic biomarkers predictive of response to targeted therapies.

acknowledgements

The authors thank data management service of Italian Trials in Medical Oncology (ITMO) for their assistance and help in statistical analysis and in preparing the manuscript.

disclosures

The authors have declared no conflicts of interest.

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appendix

Further eligibility criteria.

inclusion criteria

Eastern Cooperative Oncology Group (ECOG) performance status 0–2; life expectancy >12 weeks; adequate organ function, as defined by normal complete blood count, liver function tests [total serum bilirubin ≤1.5×upper limit of normal (ULN); serum aspartate transaminase and serum alanine transaminase ≤2×ULN (<5 times the ULN for patients with liver metastases), alkaline phosphatase <2.5×ULN (unless bone metastases were present in the absence of any liver disorders) and renal function; no major surgery, radiotherapy or chemotherapy within 4 weeks before study entry.

exclusion criteria

Therapy with a VEGF inhibitor (VEGFi) within 4 weeks before study entry, previous therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus), known hypersensitivity to everolimus or other mTOR inhibitors, chronic systemic treatment with corticosteroids or other immunosuppressive agents, known HIV or active infections, autoimmune hepatitis, active bleeding diathesis, severe or uncontrolled medical conditions, congestive heart failure or angina pectoris, history of relevant neurological or psychiatric disorders, past or current history of neoplasm other than curatively treated non-melanoma skin cancer or carcinoma *in situ* of the uterine cervix; metastatic involvement of the central nervous system; malabsorption syndrome or any other disorders that could affect gastrointestinal absorption; pregnancy or breastfeeding.

Annals of Oncology 25: 1603–1608, 2014
doi:10.1093/annonc/mdu184
Published online 14 May 2014

A phase I study of cabozantinib (XL184) in patients with renal cell cancer

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Received 24 October 2013; revised 7 February 2014; accepted 1 May 2014

Background: Cabozantinib targets tyrosine kinases including the hepatocyte growth factor receptor (MET) and vascular endothelial growth factor (VEGF) receptor 2, which are important drug targets in renal cell carcinoma (RCC).
Patients and methods: This single-arm open-label phase I trial evaluated the safety and tolerability of cabozantinib in heavily pretreated patients with metastatic clear cell RCC.

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