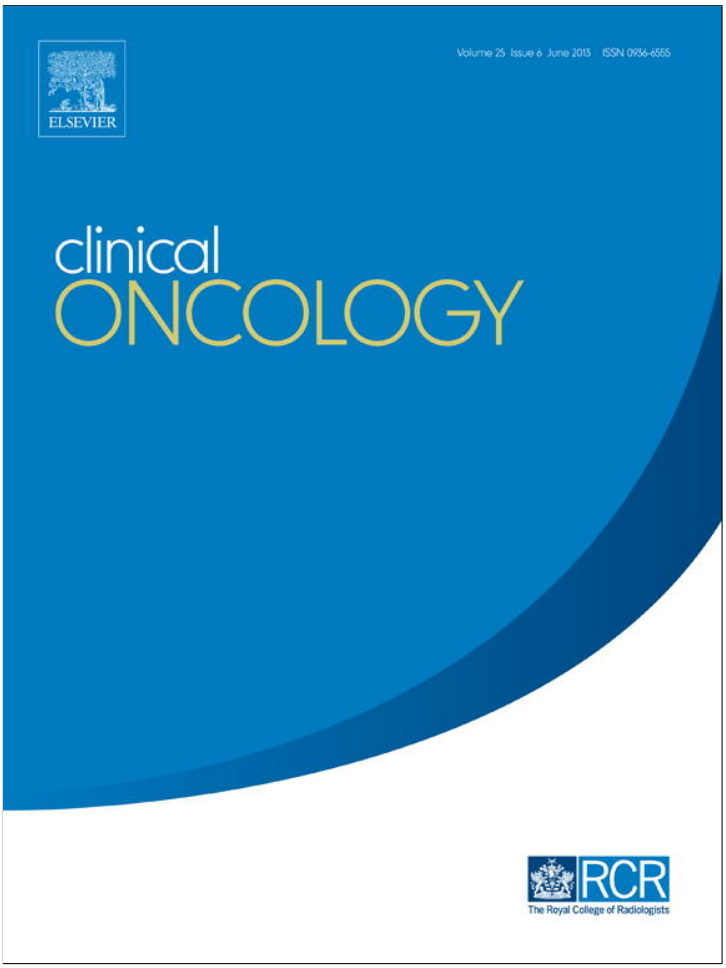

Clinical Oncology 25 (2013) 336–342

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

A Phase I Trial of Oral Ridaforolimus (AP23573; MK-8669) in Combination with Bevacizumab for Patients with Advanced Cancers

J. Nemunaitis [*], H.S. Hochster [†], S. Lustgarten [‡], R. Rhodes [§], S. Ebbinghaus [¶], C.D. Turner [‡], P.F. Dodion [‡], M.M. Mita [||a]

[*] *Mary Crowley Cancer Research Centers, Clinical Research, Dallas, TX, USA*
[†] *Yale School of Medicine, Medical Oncology, New Haven, CT, USA*
[‡] *ARIAD Pharmaceuticals Inc., Cambridge, MA, USA*
[§] *Merck Sharp & Dohme Corp., Clinical Writing Group, Whitehouse Station, NJ, USA*
[¶] *Merck Sharp & Dohme Corp., Clinical Research, Whitehouse Station, NJ, USA*
[||] *Cancer Therapy and Research Center, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA*

Received 22 August 2012; received in revised form 21 January 2013; accepted 13 February 2013

Abstract

Aims: This phase I dose-escalation study was designed to evaluate the combination of the mammalian target of rapamycin inhibitor ridaforolimus with the vascular endothelial growth factor inhibitor bevacizumab.
Materials and methods: Seventeen adult patients with refractory advanced solid tumours received oral ridaforolimus (30 or 40 mg) once daily for 5 days per week (QDx5/wk) combined with intravenous bevacizumab (10 mg/kg every 2 weeks [Q2wk] or 15 mg/kg every 3 weeks [Q3wk]). Patients were evaluated for dose-limiting toxicities, safety and anti-tumour activity.
Results: A 40 mg dose of ridaforolimus with either bevacizumab dosing schedule was the recommended phase II dose. No dose-limiting toxicities were reported; the most common drug-related adverse events were mucosal inflammation and anorexia. Seven patients, with clinical features that included primary tumour of the abdominal origin (colorectal, pancreatic or gynaecological cancers) and previous abdominal radiotherapy, reported serious adverse events related to bowel perforations. There were no objective responses, but 65% of patients had a best response of stable disease.
Conclusion: Oral ridaforolimus (40 mg QDx5/wk) is feasible to combine with standard doses of bevacizumab, although careful patient selection would be needed to mitigate the risk of bowel perforation-related adverse events. Combination therapy produced prolonged stable disease in several heavily pretreated patients.

Key words: Bevacizumab; mammalian target of rapamycin; phase I; ridaforolimus; solid tumours

Introduction

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase ubiquitously expressed in mammalian cells. It is a central component of the PI3K/PTEN/AKT signalling pathway, which regulates cell proliferation, survival and angiogenesis and is critical to malignant transformation [1,2]. Studies have shown that mTOR mediates angiogenesis through several pathways. mTOR also contributes to the cellular response to hypoxia by regulating proteins (e.g. tuberous sclerosis complex 1, tuberous sclerosis complex 2 and hypoxia-inducible factor-1 alpha) upstream of vascular endothelial growth factor (VEGF), a key factor in tumour vascularisation [3–5]; mTOR is also involved in transducing the cellular response to VEGF/VEGF receptor signalling [6]. As the inhibition of mTOR function can exert anti-tumorigenic effects via multiple mechanisms, mTOR is an attractive target for cancer therapy [1,2]. Moreover, the implication of mTOR in angiogenic signalling provides a rationale for exploring potential anti-angiogenic activity of mTOR inhibitors in combination with other therapies that inhibit independent angiogenic pathways [7].

Author for correspondence: J. Nemunaitis, Mary Crowley Cancer Research Centers, 1700 Pacific Avenue, Suite 1100, Dallas, TX 75201, USA. Tel: +1-214-658-1965; Fax: +1-214-658-1992.
E-mail address: jnemunaitis@marycrowley.org (J. Nemunaitis).
[a] Present address: Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2013.02.005

Ridaforolimus (MK-8669, formerly AP23573 or deforolimus), a non-prodrug rapamycin analogue that specifically inhibits mTOR, has shown anti-proliferative activity both *in vitro* (against a broad range of human tumour cell lines) and *in vivo* (using tumour xenograft models), with additive or synergistic activity when combined with other anti-cancer agents [8,9]. In phase I, II and III trials, both oral and intravenous single-agent ridaforolimus have shown anti-tumour activity against various tumour types, as well as favourable safety profiles [10–18]. In particular, a large, multicentre, randomised, placebo-controlled phase III trial showed the potential benefit of ridaforolimus as maintenance therapy in patients with metastatic sarcoma who had achieved a response or stable disease after chemotherapy [18]. Safety and efficacy have also been shown in phase I studies of ridaforolimus in combination with either cytotoxic agents (capecitabine and paclitaxel)[19,20] or a monoclonal antibody (dalotuzumab) directed against the insulin growth factor receptor [21]. There was also a phase II study of ridaforolimus in combination with a monoclonal antibody (trastuzumab) directed against the human epidermal growth factor receptor 2 [22].

Bevacizumab, a recombinant humanised monoclonal antibody that binds VEGF and inhibits VEGF binding to its receptor, is a well-established anti-angiogenic regimen approved by the US Food and Drug Administration (FDA) for use in first- or second-line treatment of metastatic colorectal cancer, as well as in patients with metastatic non-squamous non-small cell lung cancer in combination with chemotherapy [7,23,24]. Inhibition of mTOR and VEGF signalling, two independent pathways that affect angiogenesis, could potentially lead to improved efficacy compared with blockage of one single pathway alone. The addition of ridaforolimus to bevacizumab has been shown to enhance the inhibition of tumour growth and angiogenesis via effects mediated by the mTOR and VEGF pathways [3,5]. Clinical data from phase I and II studies support the use of bevacizumab in combination with mTOR inhibitors [25–29]. Here we report the results of a phase I study designed to evaluate the safety, tolerability and recommended phase II dose of oral ridaforolimus in combination with the two approved intravenous bevacizumab regimens. The trial also assessed evidence of anti-tumour activity of the combination in patients with refractory advanced solid tumours.

Materials and Methods

Study Population and Treatment Plan

This was a phase I, open-label, single-arm, cohort-based, dose-escalation trial conducted between 14 October 2008 and 19 February 2010, with a planned enrolment of 15–30 patients in three centres in the USA (ClinicalTrials.gov identifier: NCT00781846; http://clinicaltrials.gov/ct2/show/NCT00781846; Protocol 010). Patients 18 years or older with advanced or metastatic solid tumours were eligible if the following criteria were met: relapsed or refractory disease after standard therapy; Eastern Cooperative Oncology Group performance status 0–1 and life expectancy greater than 3 months; adequate haematological, hepatic and renal function; serum cholesterol less than or equal to 350 mg/dl; triglycerides less than or equal to 400 mg/dl. Exclusion criteria included the presence of tumour(s) in close proximity to a major blood vessel; history of brain metastases, spinal cord compression or carcinomatous meningitis; haemoptysis, haematemesis, clinically significant unexplained bleeding or major surgery within 28 days before study entry; uncontrolled hypertension; proteinuria at screening; clinically significant cardiovascular disease; newly diagnosed or poorly controlled type 1 or 2 diabetes; or active infection.

The planned dose cohorts and schedules are shown in Table 1. Oral ridaforolimus doses were self-administered by the patients after initial dosing in the clinic. Bevacizumab was administered as a single intravenous infusion 30–60 min after oral administration of ridaforolimus, according to the following schedules: in cohort 1, patients received oral ridaforolimus at 30 mg once daily for 5 consecutive days every week (QDx5/wk) and 10 mg/kg intravenous infusion of bevacizumab every 2 weeks (Q2wk); in cohort 2, patients received oral ridaforolimus at 40 mg QDx5/wk and 10 mg/kg intravenous infusion of bevacizumab Q2wk (cohort 2a) or 15 mg/kg intravenous infusion of bevacizumab every 3 weeks (Q3wk; cohort 2b). Each treatment cycle was 4 weeks (28 days) in duration for cohorts with bevacizumab administered on the Q2wk schedule and 3 weeks (21 days) for cohorts with bevacizumab administered on the Q3wk schedule. The study protocol included provisions for changes in dose levels in case dose-limiting toxicities (DLTs) were observed in the initial cohort. However, based on the data as they accumulated during the conduct of the study, it was not necessary to open these additional cohorts.

The protocol, its amendments and the patient informed consent form were reviewed and approved by an independent ethics committee or institutional review board at each site before patients were allowed to enrol at that site. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and all appropriate regulatory guidelines. Each patient provided written informed consent before entering the trial.

Toxicity, Safety and Tolerability Assessments

All patients receiving at least one dose of ridaforolimus and/or bevacizumab were considered evaluable for safety, assessed by a physical examination, interim history and laboratory assessments. Patients were also monitored for adverse events while receiving treatment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0) and characterised according to their relationship to study medication by the investigator.

Patients were evaluated for DLTs in the first cycle to determine the maximum tolerated dose and the recommended phase II dose. The maximum tolerated dose was

Table 1
Planned dose cohorts and schedules

Cohort	Ridaforolimus	Bevacizumab	Planned number of patients	Cycle length
1	30 mg QDx5/wk	10 mg/kg Q2wk	3–6	4 weeks
2a	40 mg QDx5/wk	10 mg/kg Q2wk	6–12	4 weeks
2b	40 mg QDx5/wk	15 mg/kg Q3wk	6–12	3 weeks

QDx5/wk, once daily for 5 consecutive days per week; Q2wk, every 2 weeks; Q3wk, every 3 weeks.

defined as the dose level below the one that produced DLTs in at least one-third of evaluable patients. DLTs were defined as treatment-related adverse events occurring in the first cycle of treatment, including persistent grade 4 neutropenia or thrombocytopenia; grade 3 or 4 neutropenia associated with fever, intravenous antibiotics or hospitalisation; grade 3 or 4 thrombocytopenia associated with bleeding or platelet transfusions; clinically significant grade 3 or higher non-haematological toxicities that were not transient; and any toxicity that results in significant deviation, interruption or delay in dosing. Patients who discontinued from the study for reasons unrelated to the study (e.g. for personal reasons) or due to any toxicity unrelated to the study treatment were considered not evaluable for DLTs and were replaced as required for the study to meet its objectives.

Efficacy Assessments

Tumour response was an exploratory end point in this trial. Patients were assessed by computed tomography and magnetic resonance imaging within 21 days before the first dose of study treatment and after every two cycles of study treatment. The objective response rate, defined as either a complete response or a partial response, was determined using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.0) guidelines [30]. To achieve a response of stable disease, follow-up measurements must have met the stable disease criteria at least once after study entry at a minimum interval of not less than 6 weeks after the baseline assessment. To further assess the anti-tumour activity of this combination, additional efficacy end points were planned, including the fraction of patients achieving stable disease (for 24 weeks or longer) or an objective response, the duration of the objective response and the best target lesion response (defined as the best change in sum of the target lesions from baseline to disease progression).

Statistical Analyses

Summary statistics and analyses were generated by dose level for each treatment regimen and for the entire cohort of patients, where appropriate. Patient demographic data and baseline characteristics (including baseline performance status, age and previous treatment) were summarised using descriptive statistics. The incidence of adverse events and the frequency of study drug–related adverse events were categorised by severity, and clinically significant changes in laboratory results were also tabulated and summarised using descriptive statistics. All patients receiving at least one dose of either drug or the combination regimen were included in the analyses.

Results

Patient Disposition and Baseline Characteristics

Table 2 summarises the main baseline patient characteristics. Seventeen patients were enrolled in the trial and received treatment (cohort 1, $n = 4$; cohort 2a, $n = 6$; cohort 2b, $n = 7$). The median age for the patient population was 60 years (range 24–72). Three patients had diagnoses of ovarian cancer, three had rectal cancer and two had pancreatic cancer. Over half (53%) the patients in the study had received previous radiotherapy. Only one patient had had no previous chemotherapy, whereas two patients had had one previous chemotherapy regimen and 14 patients (82%) had had two or more previous chemotherapy regimens.

Toxicity, Safety and Tolerability

Dose levels of ridaforolimus and bevacizumab were administered to patients according to the planned dose cohorts; the median duration of treatment was 61 days

Table 2
Baseline patient demographics and disease characteristics

Baseline characteristic	Ridaforolimus and bevacizumab ($N = 17$)
Median age (range), years	60 (24–72)
Gender, *n* (%)	
Female	10 (59)
Male	7 (41)
ECOG performance status, *n* (%)	
0	6 (35)
1	11 (65)
Diagnosis, *n* (%)	
Ovarian cancer	3 (18)
Rectal cancer	3 (18)
Pancreatic cancer	2 (12)
Other	9 (53)
Previous radiotherapy, *n* (%)	9 (53)
Previous chemotherapy regimens, *n* (%)	
0	1 (6)
1	2 (12)
2 or more	14 (82)

ECOG, Eastern Cooperative Oncology Group.

(range 15–356 days). No DLTs were noted during the first (28-day) cycle of treatment in any of the three cohorts, which included 15 patients evaluable for DLTs. Cohorts 1 and 2b each had one patient who was replaced because the patient was not evaluable for DLTs due to early discontinuation from unrelated adverse events. As no DLTs were observed among the evaluated patients, full dosages of each agent (ridaforolimus 40 mg administered QDx5/wk with 10 mg/kg Q2 wk or 15 mg/kg Q3wk bevacizumab) were determined to be the recommended phase II doses.

All patients reported experiencing at least one adverse event and had at least one adverse event considered by the investigator to be related to study medication. The most frequently observed drug-related adverse events included mucosal inflammation (65%), anorexia (53%), stomatitis (47%), proteinuria (41%), epistaxis (35%) and thrombocytopenia (35%) (Table 3). The frequency of grade 3 adverse events considered related to a study drug was low, and the most common were proteinuria (24%), thrombocytopenia (18%) and anaemia (12%). No grade 4 drug-related adverse events were experienced in the study. Serious adverse events irrespective of relationship to a study drug were experienced by 12 patients (71%). Among these patients, eight (47%) experienced serious drug-related adverse events, which included grade 2 (neutropenia, nausea, abdominal wall abscess, colonic fistula and small intestinal perforation) and grade 3 (enterocutaneous fistula, diabetes mellitus, vomiting, lung infiltration, epistaxis, perirectal abscess and small intestinal perforation) events. Seven patients were reported to have serious adverse events related to bowel perforations, including perforations, fistulas, pelvic or abdominal abscesses, and peritonitis (Table 4). Of these patients, six had primary tumours arising from an abdominal or pelvic location (two endometrial/uterine, two ovarian, one pancreatic and one rectal). Four patients had a previous history of abdominal or pelvic radiotherapy, and at least three of the patients had had previous abdominal and/or pelvic surgery (diagnosed with rectal, pancreatic or endometrial cancer). However, a previous history of abdominal radiotherapy could not necessarily be ruled out in the other patients. Perforation-related events occurred in cohorts 1 and 2b at both dose levels of ridaforolimus and on both schedules of bevacizumab.

Table 3
Most common drug-related adverse events and all grade 3 or above events in all patients as treated ($N = 17$)

Adverse event*	All grades	Grade 3–4†
	n (%)	*n* (%)
Mucosal inflammation	11 (65)	0 (0)
Anorexia	9 (53)	0 (0)
Stomatitis	8 (47)	1 (6)
Proteinuria	7 (41)	4 (24)
Thrombocytopenia	6 (35)	3 (18)
Epistaxis	6 (35)	1 (6)
Diarrhoea	5 (29)	1 (6)
Anaemia	3 (18)	2 (12)
Neutropenia	3 (18)	1 (6)
Vomiting	3 (18)	1 (6)
Leukopenia	2 (12)	2 (12)
Small intestinal perforation	2 (12)	1 (6)
Abdominal pain	1 (6)	1 (6)
Blood phosphorus decreased	1 (6)	1 (6)
Diabetes mellitus	1 (6)	1 (6)
Enterocutaneous fistula	1 (6)	1 (6)
Hypochloraemia	1 (6)	1 (6)
Hyponatraemia	1 (6)	1 (6)
Lung infiltration	1 (6)	1 (6)
Lymphopenia	1 (6)	1 (6)
Perirectal abscess	1 (6)	1 (6)

* If multiple episodes of an event were experienced by one patient, the patient/event is presented once at the highest grade reported.
† No grade 4 adverse events were reported.

One patient died as a result of an unrelated adverse event within 30 days of study treatment. This patient was a 66-year-old man with pancreatic cancer who had discontinued from the study due to disease progression on day 35. The patient died on day 53 (20 days after his last dose of ridaforolimus and 31 days after his last dose of bevacizumab), with disease progression noted as a possible cause of death. An autopsy was not carried out. All 17 patients discontinued treatment; eight patients due to progressive disease (five with documented disease progression and three with clinical disease progression, as judged by the investigator), seven patients due to adverse events (six of which were drug-related), one patient due to study withdrawal and one patient due to other reasons.

Laboratory abnormalities in patients receiving the combination of ridaforolimus and bevacizumab were mostly grade 1 or 2. Four patients experienced grade 4 decreases in platelets and two patients experienced grade 4 decreases in haemoglobin levels. Grade 4 decreases in lymphocytes and potassium levels were observed in one patient each. Three patients each experienced grade 3 decreases in white blood cells, potassium and sodium levels and increases in glucose levels. Two patients each experienced grade 3 decreases in albumin, calcium and haemoglobin levels. Finally, grade 3 decreases in glucose, phosphorous and platelets, and increases in aspartate transaminase were experienced by one patient each.

Tumour Response

All patients were evaluable using modified RECIST guidelines for the best tumour response rate. Among the 17 patients who received at least one dose of study medication, 11 (65%) had a best response of stable disease, three (18%) had a best response of disease progression and three (18%) had a response that was unknown or not assessable. No objective responses (complete or partial response) were reported. Four patients (24%) had stable disease for at least 24 weeks. Among the patients who achieved stable disease, some had progressed on multiple previous therapies.

Discussion

This phase I study was designed to explore the inhibitory effects of ridaforolimus on mTOR-regulated growth,

Table 4
Characteristics of patients with serious adverse experiences related to bowel perforation (irrespective of relationship to study medication)

Patient number	Cohort	Diagnosis	Serious adverse event term(s)	Previous abdominal or pelvic radiotherapy				Previous chemotherapy regimens (with bevacizumab)
				Location (s)	Duration (days)	Dose (Gy)	Time before study therapy	
19-102	1	Rectal cancer	Perirectal abscess	Rectum	62	NA	4 years, 2 months	8 (5)
19-103	1	Pancreatic cancer	Enterocutaneous fistula	Abdomen	50	54	2 years, 9 months	3 (0)
19-104	1	Ovarian cancer	*Clostridium difficile* colitis, fistula, ileus	None	None	None	Not applicable	6 (0)
02-103	2b	Uterine cancer	Abdominal wall abscess, colonic fistula	Pelvis Vagina	57 57	45 15	5 years, 22 days 5 years, 22 days	8 (0)
02-105	2b	Nasopharyngeal cancer	Perirectal abscess	None	None	None	Not applicable	3 (0)
19-107	2b	Ovarian cancer	Abdominal abscess, small intestinal perforation	None	None	None	Not applicable	3 (0)
19-109	2b	Endometrial cancer	Small intestinal perforation, peritonitis bacterial	Cervix/ uterus	70	45	2 years, 1 month	4 (0)

Gy, gray; NA, not available.

survival and angiogenesis in combination with the anti-angiogenic effects of bevacizumab in patients with advanced or metastatic solid tumours. As no DLTs were observed, the single-agent recommended phase II dose of oral ridaforolimus was determined to be 40 mg combined with either of two approved intravenous dosages and schedules of bevacizumab. The 40-mg dose of ridaforolimus is the same dose that has been evaluated in single-agent phase II and III trials. Therefore, full-dosage ridaforolimus seems to be tolerable when used in combination with bevacizumab. The adverse events profile was similar to those observed in clinical trials with other mTOR inhibitors and bevacizumab [25,28,31]. Most treatment-related adverse events experienced by patients in the trial were mild to moderate in severity and included stomatitis (mucosal inflammation), anorexia, proteinuria, epistaxis and thrombocytopenia. Drug-related serious adverse events reported in the study included nausea, vomiting, lung infiltration and epistaxis. Laboratory changes in glucose, cholesterol, triglycerides and haematological parameters that are typical of the mTOR inhibitor class were also reported in this study [10].

The high rate of bowel perforation–related adverse events (41%; seven patients with serious adverse events related to bowel perforations) reported in this study was of concern. We examined potential risk factors for gastrointestinal toxicity in the study population. Although it is difficult to draw firm conclusions from a small phase I study, the observation that six of the seven patients had other risk factors for bowel perforation (tumour involvement, previous abdominal surgery and/or previous abdominal and/or pelvic radiotherapy) suggests that a history of previous bowel injury or perturbations of normal anatomy may be associated with the risk of bowel perforation or fistula formation in this study. The role of some of these risk factors has been reported in a recent observational study of patients with metastatic colorectal cancer who were treated with bevacizumab [32]. The one patient in our study with a perforation-related event, without any of these risk factors (diagnosed with nasopharyngeal cancer), experienced a perirectal abscess, which in this case may have a different mechanism and could be attributed to increased susceptibility to infection due to the cancer, its treatment and a history of diabetes.

Bowel perforations are known to occur with bevacizumab treatment and have been reported in about 2% of patients treated with bevacizumab [7,32]. A recent meta-analysis of 10,000 cancer patients showed that the addition of bevacizumab to treatment regimens increased the risk of bowel perforations, with risk dependent on bevacizumab dose and tumour type [33]. Other studies have shown that previous abdominal radiotherapy may also play a role in bowel perforations in patients who were treated with bevacizumab [34]. Bowel perforation has been reported with low frequency with the mTOR inhibitors. In a phase III study of advanced renal cell carcinoma patients treated with temsirolimus, two patients experienced bowel perforations; seven patients with bowel perforations (including four fatalities) were identified across the entire temsirolimus safety database [35]. Although there was a higher frequency of bowel perforation-related events in this study compared with that typically reported for bevacizumab, the overall sample size was very small, and the size and design of this study do not allow firm conclusions to be drawn about whether the addition of ridaforolimus to bevacizumab further increases the risk of bowel perforation. However, future studies of mTOR inhibitors combined with bevacizumab should take the risk of bowel perforations associated with mTOR inhibitors and bevacizumab into account [35]. The risk could depend on several factors; particular attention should be paid to patients with potential risk factors for bowel perforations [33,34].

There have been several other small, uncontrolled studies investigating the safety and anti-tumour activity of various combinations of mTOR and VEGF inhibitors in patients with advanced malignancies. In phase I studies conducted in patients with advanced solid malignancies, the combination of everolimus and bevacizumab showed minor

clinical activity [25,26]. In phase II studies, this combination displayed limited activity in patients with refractory metastatic colorectal cancer and modest activity in advanced clear cell renal cancer, but grade 1–2 mucositis and dose reductions or discontinuations due to toxicity were common [27,36]. Results from a randomised, open-label, phase II trial, evaluating everolimus and bevacizumab versus interferon alpha-2a and bevacizumab, showed similar efficacy and tolerability between the two combinations in patients with metastatic renal cell carcinoma [37]. The preliminary results of a phase I/II trial suggest that the combination of temsirolimus with bevacizumab is feasible and active in advanced renal cell carcinoma [28]. However, a randomised phase II trial of this combination showed higher than expected toxicity and low clinical activity in renal cell carcinoma compared with the benefit expected from sequential use of each agent [29]. Recently presented results from a phase III trial showed that the combination of temsirolimus and bevacizumab was not superior to interferon alpha and bevacizumab for patients with metastatic renal cell carcinoma [38].

Conclusions

The results from our study show that the combination of oral ridaforolimus 40 mg QDx5/wk and two approved dosages of bevacizumab is a possible treatment option. In this small, phase I trial, 65% of patients (including mostly heavily pretreated patients) achieved stable disease as their best response, and 24% had prolonged stable disease for at least 24 weeks. Together with the results from trials that examined other mTOR inhibitors in combination with bevacizumab, the combination of ridaforolimus and bevacizumab seems feasible in patients with advanced cancer, with attention to the potential risk factors for bowel perforation. Larger studies are needed to fully assess the efficacy of this combination as an alternative treatment option for cancer patients.

Conflict of Interest Statement

H.S. Hochster is a consultant for Roche and a speaker for Genentech. R. Rhodes and S. Ebbinghaus are employees of and hold stock in Merck & Co., Inc. S. Lustgarten, C.D. Turner and P.F. Dodion are employees of and hold stock in ARIAD Pharmaceuticals, Inc. J. Nemunaitis and M.M. Mita have no conflicts of interest to disclose related to this manuscript.

Acknowledgments

Medical writing and editorial assistance was provided by Joseph J. Abrajano and Kakuri M. Omari of Integrus Scientific, a division of Medicus International New York (New York, NY, USA). Medical writing and editorial assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Whitehouse Station, NJ, USA). The authors were fully responsible for all content and editorial decisions and received no financial support or other compensation related to the development of the manuscript.

References

[1] Shaw RJ, Cantley LC. Ras, PI(3)K and mTOR signalling controls tumour cell growth. *Nature* 2006;441:424–430.
[2] Dancey J. mTOR signaling and drug development in cancer. *Nat Rev Clin Oncol* 2010;7:209–219.
[3] El-Hashemite N, Walker V, Zhang H, Kwiatkowski DJ. Loss of Tsc1 or Tsc2 induces vascular endothelial growth factor production through mammalian target of rapamycin. *Cancer Res* 2003;63:5173–5177.
[4] Guba M, von Breitenbuch P, Steinbauer M, *et al*. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med* 2002;8:128–135.
[5] Hudson CC, Liu M, Chiang GG, *et al*. Regulation of hypoxia-inducible factor 1alpha expression and function by the mammalian target of rapamycin. *Mol Cell Biol* 2002;22:7004–7014.
[6] Riesterer O, Zingg D, Hummerjohann J, Bodis S, Pruschy M. Degradation of PKB/Akt protein by inhibition of the VEGF receptor/mTOR pathway in endothelial cells. *Oncogene* 2004;23:4624–4635.
[7] Avastin [package insert]. South San Francisco, CA: Genentech Inc., 2011.
[8] Rivera VM, Squillace RM, Miller D, *et al*. Ridaforolimus (AP23573; MK-8669), a potent mTOR inhibitor, has broad antitumor activity and can be optimally administered using intermittent dosing regimens. *Mol Cancer Ther* 2011;10:1059–1071.
[9] Squillace RM, Miller D, Cookson M, *et al*. Antitumor activity of ridaforolimus and potential cell-cycle determinants of sensitivity in sarcoma and endometrial cancer models. *Mol Cancer Ther* 2011;10:1959–1968.
[10] Hartford CM, Desai AA, Janisch L, *et al*. A phase I trial to determine the safety, tolerability, and maximum tolerated dose of deforolimus in patients with advanced malignancies. *Clin Cancer Res* 2009;15:1428–1434.
[11] Rizzieri DA, Feldman E, Dipersio JF, *et al*. A phase 2 clinical trial of deforolimus (AP23573, MK-8669), a novel mammalian target of rapamycin inhibitor, in patients with relapsed or refractory hematologic malignancies. *Clin Cancer Res* 2008;14:2756–2762.
[12] Mita MM, Mita AC, Chu QS, *et al*. Phase I trial of the novel mammalian target of rapamycin inhibitor deforolimus (AP23573; MK-8669) administered intravenously daily for 5 days every 2 weeks to patients with advanced malignancies. *J Clin Oncol* 2008;26:361–367.
[13] Chawla SP, Blay J, Ray-Coquard IL, *et al*. Results of the phase III, placebo-controlled trial (SUCCEED) evaluating the mTOR inhibitor ridaforolimus (R) as maintenance therapy in advanced sarcoma patients (pts) following clinical benefit from prior standard cytotoxic chemotherapy (CT). *J Clin Oncol* 2011;29. abstract 10005.
[14] Mackay H, Welch S, Tsao MS, *et al*. Phase II study of oral ridaforolimus in patients with metastatic and/or locally advanced recurrent endometrial cancer: NCIC CTG IND 192. *J Clin Oncol* 2011;29. 15s(abstract 5013).
[15] Oza AM, Poveda A, Clamp AR, *et al*. A randomized phase II (RP2) trial of ridaforolimus (R) compared with progestin (P) or chemotheraphy (C) in female adult patients with advanced endometrial carcinoma. *J Clin Oncol* 2011;29. abstract 5009.

[16] Mita MM, Britten CD, Poplin E, *et al*. Deforolimus trial 106 – A phase I trial evaluating 7 regimens of oral deforolimus (AP23573, MK-8669). *J Clin Oncol* 2008;26. abstract 3509.
[17] Colombo N, McMeekin S, Schwartz P, *et al*. A phase II trial of the mTOR inhibitor AP23573 as a single agent in advanced endometrial cancer. *J Clin Oncol* 2007;25. abstract 5516.
[18] Chawla SP, Staddon AP, Baker LH, *et al*. Phase II study of the mammalian target of rapamycin inhibitor ridaforolimus in patients with advanced bone and soft tissue sarcomas. *J Clin Oncol* 2012;30:78–84.
[19] Perotti A, Locatelli A, Sessa C, *et al*. Phase IB study of the mTOR inhibitor ridaforolimus with capecitabine. *J Clin Oncol* 2010;28:4554–4561.
[20] Sessa C, Tosi D, Vigano L, *et al*. Phase Ib study of weekly mammalian target of rapamycin inhibitor ridaforolimus (AP23573; MK-8669) with weekly paclitaxel. *Ann Oncol* 2010;21:1315–1322.
[21] Di Cosimo S, Bendell JC, Cervantes-Ruiperez A, *et al*. A phase I study of the oral mTOR inhibitor ridaforolimus (RIDA) in combination with the IGF-1R antibody dalotozumab (DALO) in patients (pts) with advanced solid tumors. *J Clin Oncol* 2010;28. abstract 3008.
[22] Yardley D, Seiler M, Ray-Coquard I, *et al*. Ridaforolimus (AP23573; MK-8669) in combination with trastuzumab for patients with HER2-positive trastuzumab-refractory metastatic breast cancer: a multicenter phase 2 clinical trial. *Clin Cancer Res* 2009;69. abstract 3091.
[23] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 3.2012. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#colon [accessed 11.06.12].
[24] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. Version 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#nscl [accessed 11.06.12].
[25] Zafar Y, Bendell J, Lager J, *et al*. Preliminary results of a phase I study of bevacizumab (BV) in combination with everolimus (E) in patients with advanced solid tumors. *J Clin Oncol* 2006;24. 18s(abstract 3097).
[26] Bullock KE, Petros WP, Younis I, *et al*. A phase I study of bevacizumab (B) in combination with everolimus (E) and erlotinib (E) in advanced cancer (BEE). *Cancer Chemother Pharmacol* 2011;67:465–474.
[27] Hainsworth JD, Spigel DR, Burris 3rd HA, Waterhouse D, Clark BL, Whorf R. Phase II trial of bevacizumab and everolimus in patients with advanced renal cell carcinoma. *J Clin Oncol* 2010;28:2131–2136.
[28] Merchan JR, Pitot HC, Qin R, *et al*. Final phase II safety and efficacy results of study MC0452: phase I/II trial of CCI 779 and bevacizumab in advanced renal cell carcinoma. *J Clin Oncol* 2011;29. abstract 4548.
[29] Negrier S, Gravis G, Perol D, *et al*. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. *Lancet Oncol* 2011;12:673–680.
[30] Therasse P, Arbuck SG, Eisenhauer EA, *et al*. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
[31] Bendell JC, George D, Nixon A, *et al*. Results of a phase I study of bevacizumab (BV), everolimus (EV), and erlotinib (E) in patients with advanced solid tumors. *J Clin Oncol* 2007;25. abstract 3548.
[32] Kabbinavar FF, Flynn PJ, Kozloff M, *et al*. Gastrointestinal perforation associated with bevacizumab use in metastatic colorectal cancer: results from a large treatment observational cohort study. *Eur J Cancer* 2012;48:1126–1132.
[33] Hapani S, Chu D, Wu S. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. *Lancet Oncol* 2009;10:559–568.
[34] Saif MW, Elfiky A, Salem RR. Gastrointestinal perforation due to bevacizumab in colorectal cancer. *Ann Surg Oncol* 2007;14:1860–1869.
[35] Kwitkowski VE, Prowell TM, Ibrahim A, *et al*. FDA approval summary: temsirolimus as treatment for advanced renal cell carcinoma. *Oncologist* 2010;15:428–435.
[36] Altomare I, Bendell JC, Bullock KE, *et al*. A phase II trial of bevacizumab plus everolimus for patients with refractory metastatic colorectal cancer. *Oncologist* 2011;16:1131–1137.
[37] Ravaud A, Barrios C, Anak Ö, *et al*. Randomized phase II study of first-line everolimus (EVE) + bevacizumab (BEV) versus interferon alfa-2a (IFN) + BEV in patients (pts) with metastatic renal cell carcinoma (mRCC): RECORD-2. *Ann Oncol* 2012;23:ix258–ix293.
[38] Rini BI, Bellmunt J, Clancy J, Wang K, Niethammer A, Escudier B. Randomized phase IIIb trial of temsirolimus and bevacizumab versus interferon and bevacizumab in metastatic renal cell carcinoma: results from INTORACT. *Ann Oncol* 2012;23:ixe14.