Combination of antiangiogenic therapy using the mTOR-inhibitor everolimus and low-dose chemotherapy for locally advanced and/or metastatic pancreatic cancer: a dose-finding study

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Pancreatic adenocarcinomas are associated with a poor survival prognosis. Besides curative surgical resection, only limited therapies with modest impact are available. New evidence suggests that the mammalian target of rapamycin pathway may be involved in the pathogenesis of neuroendocrine tumors, and breast and renal cell cancer. The phase I study described here was therefore designed to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of escalating doses of the mammalian target of rapamycin inhibitor everolimus in combination with gemcitabine in patients with advanced pancreatic cancer. Eligible patients had histologically confirmed locally advanced and/or metastatic pancreatic carcinoma and were administered 5 mg everolimus every second day (cohort 1, 2, 3) or 5 mg daily (cohort 4, 5) in combination with escalating low-dose gemcitabine. It was found that if two patients showed DLTs, MTD was reached and gemcitabine dose escalation was stopped at this level. Twenty-seven patients were enrolled in the study (cohort 1: $n = 3$; cohort 2: $n = 4$; cohort 3: $n = 6$; cohort 4: $n = 7$; cohort 5: $n = 7$) and received a maximum 600 mg gemcitabine/week. In cohort 5, two of the six patients experienced DLTs (grade 3 liver toxicity lasting for > 7 days). MTD was measured as 400 mg/m^2/week gemcitabine plus 5 mg/day everolimus. The MTD of a low-dose gemcitabine treatment in combination with everolimus was determined and no new safety concerns were identified in patients with advanced pancreatic cancer. *Anti-Cancer Drugs* 25:1095–1101 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Pancreatic cancer remains one of the greatest challenges in oncology. At present, pancreatic adenocarcinoma is associated with an unfavorable prognosis and poor overall survival. Surgical resection remains the only potentially curative option, but only 15–20% of patients will have resectable tumors, whereas the majority of patients have locally advanced or metastatic disease at the initial time of diagnosis [1]. During the last decade, standard treatment for patients with advanced pancreatic cancer was systemic chemotherapy with gemcitabine, with a median overall survival of about 6 months. To improve upon this modest benefit, several investigations have explored other strategies for reducing pancreatic cancer growth by administering various cytotoxic and targeted agents together with gemcitabine, or – more recently – by introducing novel combination chemotherapy regimens such as FOLFIRINOX or gemcitabine plus nab-paclitaxel [1–6].

Tumor angiogenesis is the process leading to the formation of blood vessels within a tumor and plays a key role in cancer cell survival and the development of distant metastases. Multiple preclinical studies have shown the efficacy of a broad variety of antiangiogenic compounds as antitumor agents for solid tumors; in particular, the efficacy of mammalian target of rapamycin (mTOR) inhibitors against pancreatic and colon cancer in combination with chemotherapy has been evaluated. Tumor growth and metastases of pancreatic and colon cancer were significantly inhibited by low doses of antiangiogenic therapy in combination with chemotherapy [7]. In addition, Browder and colleagues showed in animal models that low-dose chemotherapy itself acts antiangiogenically and was effective even in chemotherapy-resistant solid malignancies [8–10].

Experiments with gemcitabine combined with targeted therapy such as an EGFR antibody in human umbilical endothelial cells and animal models suggest potential

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additional effects of gemcitabine on proliferating endothelial cells *in vitro* or tumor angiogenesis *in vivo*. Similar effects could be the basis of a combination therapy of gemcitabine and RAD001, which is a more downstream targeted therapy than an EGFR antibody [11]. The mTOR is a serine–threonine kinase, which is a member of the larger phosphatidylinositol 3-kinase (PI3K) family, and is expressed in all types of cells. The PI3K/Akt/mTOR pathway regulates many cellular properties, including cell growth, proliferation and survival, as well as metabolism and angiogenesis. Dysregulation of this pathway is characteristic of numerous proliferative disorders including cancer because of the fact that many tumors carry gene mutations that result in the hyperactivation of phosphatidylinositol 3-kinase/protein kinase B and mTOR signaling pathways. Overall, these data point to mTOR as a relevant target for antitumor treatment [12–15].

Everolimus (RAD001; Afinitor) is a novel macrolide derivative of rapamycin formulated for oral administration, which is being developed as an antiproliferative drug with applications either as an immunosuppressant or as an anticancer agent, which acts by selectively inhibiting mTOR downstream signaling events [16,17]. In oncology, experiences with everolimus are based on preclinical and clinical studies in renal cell cancer, neuroendocrine tumors, and breast cancer, and showed good efficacy of everolimus as a novel antiproliferative drug [16–*22*]. Within the recently reported phase III trial BOLERO-*2*, the progression-free survival in postmenopausal hormone-receptor-positive advanced breast cancer patients treated with a combination of everolimus and exemestane was also significantly improved (nearly 11 vs. 4 months) [23].

On the basis of currently available results from pharmacokinetic drug-to-drug interaction studies, gemcitabine did not alter everolimus pharmacokinetics to a clinically relevant extent. Coadministration of everolimus did not influence the pharmacokinetics of gemcitabine, imatinib, or letrozole (Novartis, data on file). However, preliminary data from Pacey *et al.* [24] showed that combination therapy with gemcitabine 600 mg/m^2/week together with everolimus 20 mg/week produced significant hematological toxicity (grade 4 neutropenia and grade 3 thrombocytopenia) in patients with solid tumors.

The aim of this open-label, multicenter study was thus to investigate whether patients with locally advanced and/or metastatic pancreatic cancer can be treated safely with a combination of everolimus and low-dose gemcitabine chemotherapy. The study was designed as a phase I dose-finding trial to evaluate the maximum tolerated dose (MTD) of this combination treatment.

Table 1 Dosing details of cohorts 1–5

	Patients (*N*)	Everolimus	Gemcitabine (mg/m^2/week)
Cohort 1	3	5 mg/second day	400
Cohort 2	4	5 mg/second day	500
Cohort 3	6	5 mg/second day	600
Cohort 4	7	5 mg/day	400
Cohort 5	7	5 mg/day	500

Patients and methods

Patient eligibility

Adult patients with histologically confirmed locally advanced or metastatic pancreatic adenocarcinoma were eligible for study enrollment. Further key inclusion criteria were as follows: adequate bone marrow, liver, and renal function on RAD001 treatment; at least one measurable lesion [longest diameter $\geq$ 20 mm on conventional computed tomography (CT) or MRI scan; $\geq$ 10 mm on spiral CT] according to the RECIST criteria (version 1.0) that has not been irradiated previously; at least 4 or 2 weeks' time since previous major/minor surgery and recovery, completion of radiation, or completion of all previous systemic anticancer therapy. Eligible patients must have an ECOG performance status of 0–*2*.

Individuals were not eligible for study enrollment if there was documented intolerance to everolimus or gemcitabine, a history of another malignancy within 5 years before study enrollment, or if patients had a marked impairment in gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of RAD001. Furthermore, previous treatment with an mTOR inhibitor or with gemcitabine was not allowed (except adjuvant treatment with gemcitabine, which had to be completed $\geq$ 3 months before study entry). The clinical trial was conducted in accordance with the Declaration of Helsinki as well as local laws and regulations and with the approval of an independent ethics committee (approved protocol NCT00560963), and all patients provided written informed consent before study enrollment.

Study design and treatment

The study was designed as a prospective, open-label, multicenter phase I study of continuous doses of everolimus (5 mg) every second day (cohorts 1, 2, and 3) or every day (cohorts 4 and 5) in combination with escalating low-dose gemcitabine (400, 500, and 600 mg/m^2) administered as a weekly intravenous infusion over 30 min (Table 1). The primary objective was to determine the MTD of the combination treatment. At least three patients were enrolled per cohort. If 1/3 patients experienced dose-limiting toxicity (DLT), the cohort was expanded to 6. If at least 2/3 patients had DLT, dose escalation was stopped. For extended cohorts, dose escalation was allowed if 1/6 patients had DLT. Dose escalation was stopped if DLT were documented for at least 2/6 patients. Determination of MTD was based on the DLT rate. One treatment cycle was defined as study drug administration for 28 days. All patients were to be

followed for a minimum of 8 weeks following the start of study treatment before escalating to the next level. Patients whose therapy with gemcitabine and RAD001 was safe were offered to continue the therapy until disease progression. DLTs were defined as treatment-related adverse events (AEs) of at least grade 3 according to CTCAE (common terminology criteria for adverse events) version 3.0; DLTs were listed individually by dose cohort.

The secondary objectives of the study were to characterize the safety and tolerability of everolimus in combination with gemcitabine including acute and chronic toxicities and to evaluate preliminary efficacy defined as the overall response rate [complete response (CR) and partial response (PR)] according to RECIST, version 1.0.

Study assessments

During study participation, monitoring of vital signs, physical examination, assessment of ECOG status, and laboratory assessments were performed at every weekly visit. To determine the pharmacology data, serum everolimus samples were taken at visit 3 to the end-of-study visit (or premature discontinuation visit).

For the safety assessments, the rate of AE and serious adverse events (SAE) as well as the number of laboratory values beyond predetermined ranges were monitored and recorded at every visit.

Disease status was assessed by CT or contrast MRI scans and tumor evaluation according to RECIST (version 1.0), as well as evaluation of tumor markers (CEA, CA19-9) at the screening and at the end-of-study visit (or premature discontinuation visit).

Table 2 Patient characteristics ($N=27$)

Safety population	Total ($N=27$)	Cohort 1 ($N=3$)	Cohort 2 ($N=4$)	Cohort 3 ($N=6$)	Cohort 4 ($N=7$)	Cohort 5 ($N=7$)
Age (years)						
Minimum	46	46	53	64	55	57
Median	67	67	67	70	67	63
Maximum	83	70	76	73	83	80
Sex (*n*)						
Male	17	3	2	3	7	2
Female	10	0	2	3	0	5
Race (*n*)						
White	27	3	4	6	7	7
Metastasis [*n* (%)]						
No	7 (26)	1 (33)	0 (0)	2 (33)	2 (29)	2 (29)
Yes	20 (74)	2 (67)	4 (100)	4 (67)	5 (71)	5 (71)
Peritoneum	4 (15)	0 (0)	0 (0)	0 (0)	4 (57)	0 (0)
Liver	13 (48)	2 (67)	3 (75)	2 (33)	2 (29)	4 (57)
Lungs	2 (7)	0 (0)	0 (0)	0 (0)	2 (59)	0 (0)
Lymph nodes	10 (37)	2 (67)	1 (25)	3 (50)	4 (57)	0 (0)
Other	10 (37)	2 (67)	1 (25)	3 (50)	4 (57)	0 (0)
ECOG score 0	13	3	3	3	1	3
ECOG score 1	12	0	0	3	6	3
ECOG score 2	2	0	1	0	0	1

Statistical analysis

All patients who received at least one dose of everolimus and/or gemcitabine and had at least one postbaseline safety assessment were included in the safety population. Furthermore, an MTD-determining population was defined: if a patient fulfilled the minimum study safety requirements for cycle 1 and if the patient either experienced DLT during cycle 1 or had received at least 21 days of both everolimus and gemcitabine, the patient was observed for at least 28 days following the first dose, and if all the required safety evaluations had been completed, the patient was included in this population. For further analysis, data from all four participating centers were pooled and summarized. Demographic and baseline characteristics (including disease characteristics), efficacy observations and measurements as well as safety observations and measurements were therefore included in the analysis.

Descriptive statistics such as mean, standard deviation, minimum, median, and maximum were presented for continuous variables.

Results

Patient characteristics

All 27 patients with histologically confirmed advanced pancreatic adenocarcinoma were screened at four study centers and included in one of the five study cohorts. Patient baseline characteristics as well as disease history are listed in Table 2. The patients' median age was 67 years (range 46–83 years). The majority of patients in cohorts 1, 3, and 4 were more than 65 years, whereas the reverse age distribution was observed for patients in cohort 5. In cohort 2, all four age groups were equally frequent. Cohorts 1 and 4 included only male patients, whereas the majority of patients in cohort 5 were female. An equal percentage of patients were male and female in cohorts 2 and 3. At screening, 13 patients had an ECOG score of 0, 12 a score of 1, and the two remaining study participants had an ECOG score of 2; 20 patients had metastatic and seven patients had locally advanced disease at study entry. All 27 treated patients were included in the safety study population and of those, 23 patients were included in the MTD population. The remaining four patients were treated with study drugs for less than 8 weeks (3, 4, 14, and 17 days, respectively) and were thus not included in the MTD population.

Study treatment

Cohort design and dosing details are listed in Tables 3 and 4: the overall median daily dose of everolimus was 3.9 mg/day. The median daily doses of everolimus were higher in cohorts 1, 4, and 5 (4.3, 5.0, and 4.0 mg/day, respectively) than in cohorts 2 and 3 (3.7 and 2.6 mg/day, respectively) for the safety population. The median everolimus exposure time in the MTD-determining population was 49 days (range 0–63 days). Dose

Table 3 Patient disposition (*N* = 27)

	Screened	Treated	Discontinued	Completed
Number of patients (%)				
All cohorts (*N* = 27)	27	27	6	21
Cohort 1 (*N* = 3)	3	3	0	3
Cohort 2 (*N* = 4)	4	4	1	3
Cohort 3 (*N* = 6)	6	6	0	6
Cohort 4 (*N* = 7)	7	7	3	4
Cohort 5 (*N* = 7)	7	7	2	5
Main reason for discontinuation [*n* (%)]				
Adverse event(s)			3 (11)	
Patient withdrew consent			1 (4)	
Lost to follow-up			1 (4)	
Death			1 (4)	

changes for everolimus were documented for about 70% of patients. Most of these had one to four changes (Table 5). Reasons for the vast majority of changes in both the safety and the MTD-determining population were as foreseen by the protocol (e.g. protocol predefined dose adjustment of everolimus on the basis of serum levels).

A study amendment (issued after the inclusion of 3/27 patients) allowed RAD001 dose adjustments only for toxicity and not anymore with regard to serum level. A subsequent amendment (issued after 11/27 patients) introduced two further cohorts (cohorts 4 and 5) with RAD001 5 mg daily in combination with gemcitabine when further experience on the use of RAD001 had indicated that the combination is safe and the MTD had not been reached so far.

For about one-quarter of patients in the safety population, an AE or a laboratory or test abnormality was the reason for the dose change. A dosing error occurred in one patient (Table 5). Across all cohorts, the median daily dose of gemcitabine relative to body surface area was 61.5 mg/day/m^2 (range 46.5–400) in the MTD-determining population (Table 4). More than 80% of patients had gemcitabine dose changes. Most patients had one to four changes. Slightly more than half of the dose changes were as per protocol and more than 40% of the dose changes were because of an AE or laboratory or test abnormality (Table 5). Patients were exposed to gemcitabine for a median of 50 days (range 1–64) in the MTD-determining population (Table 4).

Table 5 Dose changes for everolimus and gemcitabine (safety population)

Treatment	Everolimus [*n* (%)]	Gemcitabine
Number of patients	27 (100)	27 (100)
Number of changes per patient		
0	8 (30)	5 (19)
1	3 (11)	4 (15)
2	3 (11)	4 (15)
3	3 (11)	4 (15)
4	3 (11)	6 (22)
5	–	2 (7)
6	1 (4)	2 (7)
7	2 (7)	–
9	2 (7)	–
14	1 (4)	–
16	1 (4)	–
Number of changes	98 (100)	70 (100)
Reasons for dose/change		
As per protocol	73 (74)	37 (53)
Adverse event/laboratory or test abnormality	24 (24)	30 (43)
Dosing error	1 (1)	0 (0)
Other	0 (0)	3 (4)

Safety and efficacy evaluation

Of the 27 patients treated, 21 completed the study. Six patients were withdrawn because of AEs (three), withdrawn consent (one), loss to follow-up (one), and death (one) (Table 3). AEs leading to discontinuation were reported as moderate worsening of general condition (no relation to study drug), severe neutropenia (study drug related), and moderate to severe laboratory changes, including drug-related increase in alanine aminotransferase, aspartate aminotransferase, and bilirubin. In total, 25 of 27 patients (93%) reported at least one AE.

Table 4 Treatment administration of everolimus and gemcitabine by cohorts (maximum tolerated dose-determining population)

MTD-determining population	Cohort 1 (*N* = 3)	Cohort 2 (*N* = 3)	Cohort 3 (*N* = 6)	Cohort 4 (*N* = 5)	Cohort 5 (*N* = 6)	All (*N* = 23)
Everolimus dose (mg/day)	5 mg/second day	5 mg/second day	5 mg/second day	5 mg/day	5 mg/day	
Gemcitabine dose (mg/m^2/week)	400	500	600	400	500	
Daily dose of everolimus (mg/day)						
Evaluable patients (*N*)	3	3	6	5	6	23
Median	4.3	3.7	2.6	5.0	4.0	3.9
Range	3.5–4.5	1.9–3.9	1.8–2.6	4.3–5.1	2.3–5.0	1.8–5.1
Everolimus exposure time (days)						
Evaluable patients (*N*)	3	3	6	5	6	23
Median	49	35	49	50	46	49
Range	49–63	34–49	49–57	4–50	23–50	4–63
Daily dose of gemcitabine (mg/day/m^2)						
Evaluable patients (*N*)	3	3	6	5	6	23
Median	55.6	67.7	84.9	56.0	62.6	61.5
Range	46.5–56.3	58.1–80.1	49.8–100	48–400	50–81.9	46.5–400
Gemcitabine exposure time (days)						
Evaluable patients (*N*)	3	3	6	5	6	23
Median	43	43	46	50	50	50
Range	36–64	29–50	36–50	1–50	47–50	1–64

MTD, maximum tolerated dose.

In cohorts 3, 4, and 5, every patient reported at least one AE, whereas in cohorts 1 and 2, one of the patients reported no AEs. Overall, thrombocytopenia was the most frequent AE, followed by leukopenia and nausea. The majority of patients experienced AEs with suspected relation to the study drug (81%). Furthermore, 11 patients (41%) experienced at least one SAE. Details of study drug-related AEs are listed as per cohort and CTCAE version 3.0 grading in Table 6. Two patients (both in cohort 4) died during the study (unrelated to study drug) and one patient died 8 days after study termination. Of the AEs reported, three events (two AEs,

Table 6 Number of patients with suspected drug-related adverse events per cohort (safety population)

	Cohort 1 ($N=3$)		Cohort 2 ($N=4$)		Cohort 3 ($N=6$)		Cohort 4 ($N=7$)		Cohort 5 ($N=7$)		All ($N=27$)	
Number of patients with any drug-related AEs	2		2		5		6		7		22 (81%)	
CTC grade	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4
Blood and lymphatic system disorder												
Anemia									1		1	
Granulocytopenia							1				1	
Leukopenia	1		1		4		3				9	
Lymphopenia							2				2	
Neutropenia								3				3
Thrombocytopenia	2		2		3		3		4	2	14	2
White blood cell count decreased									1		1	
Cardiac disorders												
Angina pectoris	1										1	
Gastrointestinal disorder												
Abdominal pain	1										1	
Diarrhea					1		1		1		3	
Dry mouth							1				1	
Dry lips							1				1	
Nausea					1		3		2		6	
Periodontitis					1						1	
Vomiting							1				1	
General disorders												
Chills									1		1	
Fatigue					1				1		2	
Edema					2						2	
Infections/infestations												
Biliary tract infection					1						1	
Escherichia bacteremia	1										1	
Eyelid infection					1						1	
Infection					1						1	
Oral infection					2						2	
Tinea pedis									1		1	
Urinary tract infection					2				1		3	
Laboratory investigations												
Alanine aminotransferase increased										1		1
Aspartate aminotransferase increased									1		1	
Blood alkaline phosphatase increased							1			1	1	1
Blood bilirubin increased										1		1
Blood cholesterol increased									1		1	
γ-Glutamyltransferase increased										1		1
Hepatic enzyme increased										1		1
Lipase increased									1		1	
Metabolism/nutrition disorders												
Weight decreased							1				1	
Appetite decreased							1				1	
Diabetes mellitus			1								1	
Hyperglycemia			1								1	
Nervous system disorders												
Dizziness									2		2	
Headache									1		1	
Paresthesia							1				1	
Respiratory, thoracic, and mediastinal disorders												
Pleurisy									1		1	
Skin/subcutaneous tissue disorders												
Alopecia									1		1	
Erythema							1				1	
Pruritus							1				1	
Rash							1		1		2	
Skin lesion							1				1	
Vascular disorders												
Hypertension	1										1	

AEs, adverse events.

Table 7 Efficacy rates and lesions according to RECIST (maximum tolerated dose-determining population)

Response	*N* (%)
Total	23 (100)
Overall response rate (CR + PR)	3 (13)
Clinical benefit rate (CR + PR + SD)	18 (78)
Complete response (CR)	0 (0)
Partial response (PR)	3 (13)
Stable disease (SD)	15 (65)
Progressive disease (PD)	3 (13)
Unknown	1 (4)
Evaluation missing	1 (4)

one SAE) represented a DLT. One of these DLTs was observed in cohort 4 and two were observed in cohort 5. For two of these, hepatic toxicity was reported with the DLT criterion being CTCAE grade 3 aspartate aminotransferase or alanine aminotransferase elevation lasting for more than 7 days. For the remaining DLT, the DLT was added as a worst case assumption: this DLT enclosed the unknown cause of death of a patient who was not a member of the MTD population in the follow-up data.

As per protocol, the primary efficacy variable was the overall response rate, defined as the proportion of patients in whom a CR or a PR response was observed according to RECIST (version 1.0) after 8 weeks. On the basis of RECIST, the majority of all treated patients showed stable disease (65%); three patients each showed PR and PD. None of the patients experienced a CR; however, a clinical benefit (CR, PR, or stable disease) was documented for 78% of the patients treated (95% CI: 56–93%] (Table 7).

Discussion

Recent research into the molecular mechanisms of pancreatic cancer progression has led to the development of novel therapeutic approaches using targeted agents as monotherapy or in combination with gemcitabine or other chemotherapeutic agents, but so far, no clear benefit of a gemcitabine-based combination therapy has been documented in clinical trials [1,4,5].

New evidence suggests that the mTOR pathway may be involved in the pathogenesis of several solid malignancies: for example, the tuberous sclerosis complex (TSC) 1/2 is an inhibitor of mTOR that is present in normal neuroendocrine cells. Patients with defects in the *TSC2* gene are thus known to develop islet cell tumors [17]. Recent clinical studies have documented promising efficacy and a good safety profile for everolimus as an anti-proliferative drug, when administered alone or in combination with other drugs in patients with different tumor entities such as melanoma, GIST, or breast cancer [16–23]. For pancreatic neuroendocrine tumors, two phase II and one phase III studies have been carried out so far [17,18,22]. In the randomized phase III study, Yao *et al.* [22] compared 10 mg everolimus daily with a placebo in patients with advanced pancreatic neuroendocrine tumors and showed significantly prolonged progression-free survival in the everolimus group associated with a low rate of severe AEs compared with placebo (11.0 vs. 4.6 months).

The majority of pancreatic ductal adenocarcinomas harbor activating mutations in KRAS, which promote cellular proliferation and survival through involvement of several downstream effectors pathways, including the PI3K/Akt/mTOR pathway, and increased activation of this pathway has been noted in approximately half of pancreatic cancers [14,25]. Furthermore, preclinical models as well as some clinical studies suggest that pancreatic cancer progression may be sensitive to anti-angiogenic therapy. Browder *et al.* [10] documented that in animals, low-dose chemotherapy acts anti-angiogenically and was effective even in solid malignancies. Combination therapy of low-dose gemcitabine together with everolimus might therefore show synergistic effects, leading to better patient benefits [7,10,12].

The primary objective of the phase I study reported here was to determine the MTD and the DLT of everolimus in combination with escalating low-dose gemcitabine. Combination treatment with everolimus and low-dose gemcitabine was well tolerated and MTD was not reached within cohorts 1–3. In cohort 5, DLTs were observed in two patients (liver toxicity); thus, MTD was determined as 400 mg/m^2/week gemcitabine in combination with 5 mg everolimus daily. These findings are consistent with safety data of other clinical trials in different tumor entities, which showed that everolimus was well tolerated even when administered in doses up to 10 mg or in combination with low-dose chemotherapeutics [13,17,18,22,26]. Furthermore, efficacy and safety analyses were carried out in all treated patients: because of the relatively low number of patients, however, the results should be interpreted with caution. In terms of treatment efficacy, none of the patients achieved a CR, but an objective disease control was observed in the majority of patients (78%). Thrombocytopenia was the most frequent AE, followed by leukopenia and nausea. Reduced blood cell counts and nausea are known side effects of this kind of treatment. Thus, no new safety concerns were identified for everolimus in combination with gemcitabine, including acute and chronic toxicities in patients with advanced pancreatic cancer.

Conclusion

It may be concluded from the results of the study presented that the MTD was found to be 400 mg/m^2/week gemcitabine and 5 mg/day everolimus. Overall, no new safety concerns were identified for the combination of mTOR-inhibitor everolimus and low-dose chemotherapy for locally advanced and/or metastatic pancreatic cancer. Combination treatment with 400 mg/m^2/week gemcitabine

and 5 mg/day everolimus should therefore be investigated further in clinical phase II trials in patients with advanced pancreatic adenocarcinoma.

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Conflicts of interest

M.J. has received travel expenses from Novartis to attend study meetings. G.V.W. has received grants for his institution from Novartis. A.K. is an employee of Novartis Pharma GmbH, Germany. C.J.B. received a consulting fee/honorarium and travel expenses form Novartis to attend study meetings. For the remaining authors there are no conflicts of interest.

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