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CANCER THERAPY AND PREVENTION

Phase III randomized, double-blind study of paclitaxel with and without everolimus in patients with advanced gastric or esophagogastric junction carcinoma who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen (RADPAC)

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Abbreviations: AE, adverse event; BSC, best supportive care; CI, confidence interval; CR, complete response; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse; DCR, disease control rate; ECOG-PS, Eastern Cooperative Oncology Group performance status; FLOT, 5-fluorouracil/leucovorin/oxaliplatin/taxotere; GEC, gastroesophageal cancer; GEJ, gastroesophageal junction; HR, hazard ratio; ITT, intent to treat; mTOR, mammalian target of rapamycin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PR, partial response; SAE, serious adverse event; SD, stable disease; VEGFR, vascular endothelial growth factor receptor.

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Abstract

The RADPAC trial evaluated paclitaxel with everolimus in patients with advanced gastroesophageal cancer (GEC) who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen. Patients were randomly assigned to receive paclitaxel (80 mg/m^2) on day 1, 8 and 15 plus everolimus (10 mg daily, arm B) d1-d28 or placebo (arm A), repeated every 28 days. Primary end point was overall survival (OS). Efficacy was assessed in the intention-to-treat population and safety in all patients who received at least one dose of treatment. This trial is registered with ClinicalTrials.gov, number NCT01248403. Between October 2011 and September 2015, 300 patients (median age: 62 years; median lines prior therapy: 2; 47.7% of patients had prior taxane therapy) were randomly assigned (arm A, 150, arm B, 150). In the intention to treat population, there was no significant difference in progression-free survival (PFS; everolimus, 2.2 vs placebo, 2.07 months, HR 0.88, P = .3) or OS (everolimus, 6.1 vs placebo, 5.0 months, HR 0.93, P = .54). For patients with prior taxane use, everolimus improved PFS (everolimus, 2.7 vs placebo 1.8 months, HR 0.69, P = .03) and OS (everolimus, 5.8 vs placebo 3.9 months, HR 0.73, P = .07). Combination of paclitaxel and everolimus was associated with significantly more grade 3-5 mucositis (13.3% vs 0.7%; P < .001). The addition of everolimus to paclitaxel did not improve outcomes in pretreated metastatic gastric/gastroesophageal junction (GEJ) cancer. Activity was seen in the taxane pretreated group. Additional biomarker studies are planned to look for subgroups that may have a benefit.

KEYWORDS
advanced gastroesophageal cancer, everolimus, paclitaxel, second-line

1 | INTRODUCTION

The incidence of gastroesophageal cancer ranges around 10 newly diagnosed patients/100000 inhabitants/year in the western hemisphere, and two thirds of patients present with inoperable or metastatic disease.[1,2] Overall 5-year relative survival rates are approximately 20% in most areas of the world.

Chemotherapy is the mainstay of treatment, however, responses are often short and median survival in advanced disease is between 8 and 11 months in non-Asian patients. After failure of standard first-line platinum and fluoropyrimidine-based combination therapy, nearly all patients continue to have disease progression after treatment. Selected second-line chemotherapy regimens, including irinotecan and taxanes, have been investigated with small increments in survival.[3-6] Today, the monoclonal antibody VEGFR2 antagonist ramucirumab is the only approved targeted therapy in second-line due to an improvement in overall survival by 2.2 months in combination with Paclitaxel.[7] However, there remains a need for more effective new agents to improve the poor prognosis of patients with advanced gastroesophageal cancer patients in later treatment lines.

What's new?

Patients with advanced gastroesophageal cancer who fail first-line chemotherapy regimens often suffer poor prognosis in later rounds of therapy. A promising therapeutic strategy for these patients entails targeting the PI3K-Akt-mTOR pathway with everolimus. Here, in a randomized, double-blind phase III study, the chemotherapeutic agent paclitaxel was tested with or without everolimus in patients with advanced gastroesophageal cancer. For most patients, everolimus had no significant impact on survival. Survival benefits were observed, however, for certain patient subgroups, namely patients previously treated with taxanes who might not be candidates for paclitaxel and ramucirumab combination therapy after failure of first-line platinum therapy.

The PI3K-Akt-mTOR pathway plays a pivotal role in oncogenesis and progression and is activated in 30% to 60% of human gastric carcinomas.[8,9] Its dysregulation is also associated with chemotherapy

resistance[8] and decreased survival.[10-12] When the current trial was designed, clinical and laboratory evidence indicated a promising potential of targeting the PI3K-Akt-mTOR pathway for efficacious treatment of gastroesophageal cancer. However, in the meanwhile, the Phase III GRANITE trial failed to demonstrate a significant survival benefit of everolimus monotherapy over best supportive care (BSC) in patients with refractory advanced gastric cancer.[13]

Paclitaxel was chosen as combination based on single-agent second-line trials.[14-16]

The combination of everolimus and paclitaxel has been well tolerated in patients with breast cancer and several responses were observed in a heavily pretreated population.[17] Both everolimus and paclitaxel have demonstrated activity against gastric cancer in vitro and in vivo.[9,18] Together, these data provide a rationale for the use of paclitaxel and everolimus in the second-line setting in advanced gastroesophageal cancer.

The Phase III RADPAC trial reports on the efficacy and safety of paclitaxel with or without everolimus in patients with advanced or metastatic gastroesophageal carcinoma who experienced treatment failure after one or more lines of previous chemotherapy.

2 | METHODS

Our study was an investigator-initiated, prospective, randomized, double-blind, phase III study. It has been registered at ClinicalTrials.gov, identifier NCT2009-01809214. All participants gave written informed consent by the use of forms approved by the ethics committees of participating institutions.

2.1 | Patients

Patients were eligible if they had histologically confirmed adenocarcinoma of the stomach or GEJ and had documented disease progression during/after one, two or three prior chemotherapy regimens containing a fluoropyrimidine/Platinum and/or its precursors or derivatives for advanced disease. Additional inclusion criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2, and adequate organ and hematologic function. Exclusion criteria included paclitaxel refractory disease, defined as a disease progression within 12 weeks or less of last administration of paclitaxel-based treatment in any treatment line. The appropriate ethics committees at each participating center approved the protocol and all amendments. The study was conducted in accordance with the protocol, the Declaration of Helsinki, and all applicable local regulations. An independent data monitoring committee performed annual safety reviews.

2.2 | Study design and assessment

Patients were centrally randomized in a 1:1 fashion to paclitaxel 80 mg/m^2 on day 1, 8 and 15 and everolimus 10 mg daily d1-d28 or to paclitaxel 80 mg/m^2 on day 1, 8 and 15 and matching placebo daily d1-d28 using an interactive web-response system (IWRS) based on a sequence generated with permuted blocks stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2), prior taxane use (yes vs no) and treatment line (2 vs 3 or 4 line). The randomization schedule was generated using a validated randomization program and verified for accuracy using strict quality control procedures.

Randomization numbers were linked to the treatment groups, which were in turn linked to medication numbers. The independent data monitoring committee and all individuals involved in the study were blinded to treatment assignment.

Study treatment continued until progression, intolerable toxicity, or consent withdrawal. Further treatment after progression was at the investigator's discretion. The protocol provided guidelines for dose interruptions or reductions for adverse events (AEs). An initial dose reduction to 5 mg/day and a subsequent reduction to 5 mg every other day were permitted. Dose adjustment for certain drugs for specific toxicities were permitted at the investigator's discretion.

Tumor response was assessed by the local investigator per the Response Evaluation Criteria in Solid Tumors, version 1.0,[19] every 8 weeks for 6 months or until documentation of disease progression. Follow-up for survival was done and documented every 2 months for the 1 year follow-up period.

Hematology, biochemistry and vital signs were monitored continuously and assessed using the Common Terminology Criteria for Adverse Events, Version 4.0.[20]

2.3 | Statistical analysis

All randomly assigned patients were assessed for efficacy following the intent-to-treat principle. Patients were analyzed per the treatment and stratum to which they were assigned on randomization.

Safety was assessed in all patients who received at least one dose of study drug.

The primary efficacy endpoint was overall survival (OS), measured from the date of enrolment into the study to the date of death of any cause. For patients dropping out of the study or lost to follow-up the survival date was censored at the last date known of the patient to be alive. Secondary efficacy end points included PFS, defined as the time from enrolment into the study to the first documented evidence of disease progression or death of any cause; overall response rate (ORR) defined as proportion of patients with complete or partial response and disease control rate (DCR), defined as proportion of patients with complete or partial response or stable disease for at least 12 weeks.

Secondary safety end points included the incidence and severity of adverse events AEs as determined by CTCAE version 4, the discontinuation rate, the dose adjustment rate and tolerability.

Between-arm comparisons of OS were performed using log-rank tests stratified by the three randomization stratifications factors at a two-sided cumulative 5% significance level. OS analyses were repeated in several patient subgroups; no interaction test was performed. No

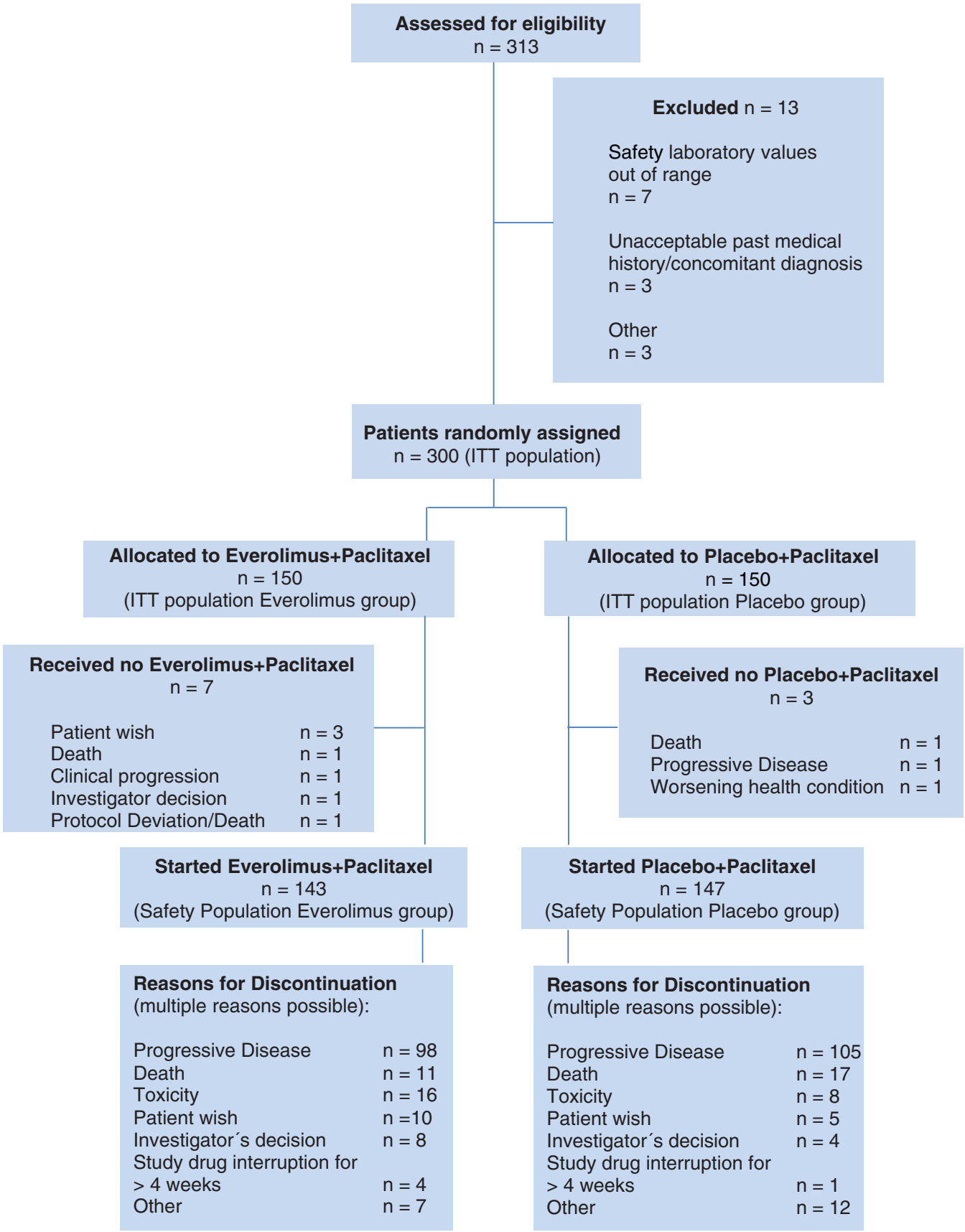


FIGURE 1 CONSORT diagram [Color figure can be viewed at wileyonlinelibrary.com]

statistical comparisons were performed for ORR or for safety parameters. For all time-to-event end points, median values were estimated using the Kaplan-Meier method. Hazard ratios (HRs) and 95% CIs were derived from Cox proportional hazards models stratified by the three randomization stratification factors.

Sample size was determined assuming exponential survival, uniform accrual over 24 months, a minimal follow-up time of 12 months, 80% power and a one-tailed log rank test at the 2.5% overall Type I error level. It was estimated that 480 patients (240 per arm) were required for the final analysis to detect a hazard ratio of 0.76, corresponding to an improvement in median OS from 7.0 months with placebo to 9.25 months with everolimus.

Sample size was cut to 300 patient's total (150 per arm) by a formal amendment (protocol version 4.0) due to lower recruiting rates per month than estimated initially. Nevertheless, all intended analyses were done.

TABLE 1 Baseline demographics and disease characteristics of all randomly assigned patients

	Paclitaxel/everolimus (n = 150)		Paclitaxel/placebo (n = 150)	
	No. of patients	(%)	No. of patients	(%)
Age years [median]	62	—	62	—
Range	32-83	—	29-86	
<70	109	73	105	70
≥70	41	27	45	30
Sex				
Male	110	73	121	81
Female	40	27	29	19
ECOG PS				
0	45	30	45	30
1	92	61	90	60
2	13	9	15	10
Location				
GEJ	85	57	91	61
Stomach	64	43	59	39
Number of affected organs [median]	2	—	2	—
0-2	100	67	92	60.7
≥3	50	33	58	38.7
Organs affected (top 3)				
Lymph nodes	97	65	95	63
Liver	72	48	80	53
Peritoneum	36	24	41	27
Prior resection of primary tumor	71	47	64	43
No. of prior regimens				
1	93	62	80	53
2	44	29	51	34
3	13	9	19	13
Prior taxane use	74	49	69	46
Type of taxane used				
Docetaxel	73	49	64	43
Paclitaxel	0	—	4	3
Both	1	1%	1	1
None	76	51	81	54
Histology				
Intestinal	58	39	49	33
Diffuse type	35	23	36	24
Mixed	8	5	7	5
Not evaluable/not classifiable/missing	49	33	58	38

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; No., number.

3 | RESULTS

3.1 | Patient disposition and characteristics

From October 2011 to September 2015, 300 patients from 50 centers in Germany were enrolled and received paclitaxel plus everolimus (n = 150) or paclitaxel plus placebo (n = 150; Figure 1). A total of 290 patients received at least one dose of study treatment, 143 in the paclitaxel and everolimus group and 147 in the paclitaxel and placebo group (safety analysis population). As of the analysis cutoff date (December 19, 2016), no patients were still receiving study treatment. The most common reason for treatment discontinuation was disease progression (65.3% in the everolimus arm and 70.7% in the placebo arm). A higher percentage of patients discontinued everolimus in comparison to placebo because of AEs (10.7% vs 5.3% with placebo), consent withdrawal (8.0% vs 3.3%) and due to investigators decision (6.0% vs 2.7%; Figure 1).

Baseline characteristics and disease characteristics (ITT population) of all 300 randomized patients were generally well balanced between treatment groups, although minor differences were observed (Table 1). Except four patients, all patients received previous treatment with platinum-based and fluoropyrimidine-based chemotherapy regimens and were included in the ITT population. Previous docetaxel therapy was administered in 49% in the everolimus group and in 43% in the placebo group. Overall, 57.7% of patients received only one prior line of chemotherapy and 31.7% and 10.7% received two and three lines of chemotherapy before enrolment into the trial. Compared to the placebo arm, more patients in the everolimus arm had received only one previous line (62.0% vs 53.3%), whereas 2 or 3 lines of prior treatment were more frequently given in the placebo arm (46.7% vs 38%; Table 1). Additionally, a large proportion of patients had other poor prognostic factors, including poorly differentiated tumors, at least three metastatic sites and the presence of the primary tumor.

3.2 | Chemotherapy and study drug exposure

Median duration of paclitaxel plus everolimus exposure was 8 weeks (range 0-74 weeks) and 7.9 weeks (range 0-104 weeks) for paclitaxel plus placebo. Mean duration of exposure was 12.2 weeks (SD 12.4 weeks) and 12.5 weeks (SD 13.6 weeks), respectively. Median cumulative dose intensity of everolimus was similar to placebo (530 mg [20-3040 mg] vs 555 mg [10-1000 mg]) and was similar for paclitaxel in both groups (872 mg [130-1438 mg] vs 870 mg [120-1463 mg]).

Dose modifications were significantly more common with everolimus (39 of 150 patients [26%] vs 20 of 150 patients [13%] with placebo; $P = .0061$), with dose reductions to 5 mg daily in 16% vs 7.3% in the everolimus vs the placebo group, respectively. Paclitaxel dose reductions were similar between the everolimus and placebo group (2% vs 1%, respectively); however, treatment interruptions of paclitaxel occurred significantly more frequently in the everolimus group compared to the placebo group (75.3% vs 57.3%; $P = .0012$).

3.3 | Efficacy

The final analysis was done when 276 overall survival events had occurred. There were 136 deaths in the everolimus plus paclitaxel group and 140 in the placebo plus paclitaxel group (Figure 2A). By the data cut-off date of December 2016, the median follow-up duration (ie, time from randomization date to last follow-up) in the surviving patients was 6.2 months in the everolimus group and

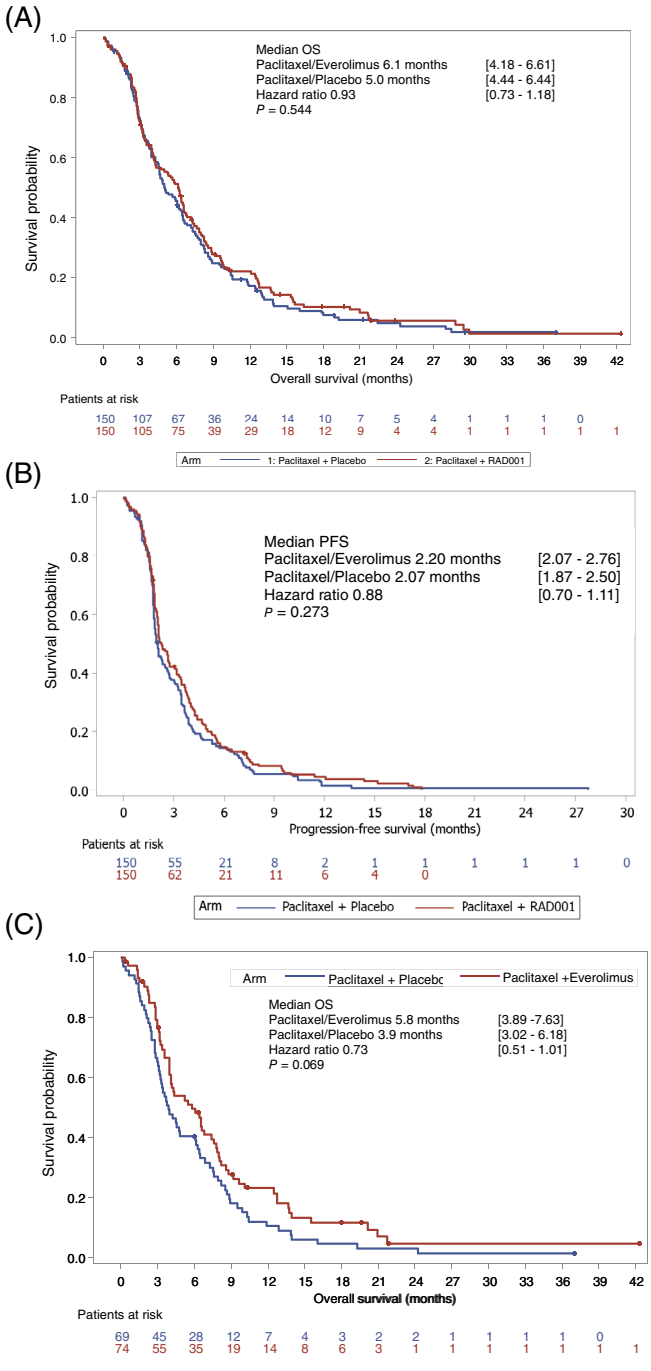


FIGURE 2 A, Kaplan–Meier plot of overall survival for all randomly assigned patients. B, Kaplan–Meier plot of progression-free survival for all randomly assigned patients. C, Kaplan–Meier plot of overall survival in taxan-pretreated patients [Color figure can be viewed at wileyonlinelibrary.com]

5.6 months in the placebo group and all patients had permanently discontinued study treatment.

The estimated median overall survival with everolimus plus paclitaxel was 6.1 months (95% CI 4.2-6.6 months) and 5.0 months with placebo and paclitaxel (95%CI 4.4-6.4; HR for OS, 0.93; 95% CI, 0.73-1.18; *P* = .544; Figure 2A). The 6 months OS rates were 51% (95% CI 43-59) in the everolimus plus paclitaxel group and 46% (95% CI 38-54) in the placebo plus paclitaxel group, respectively. The estimated median progression-free survival with everolimus plus paclitaxel was 2.2 months (95% CI 2.1-2.7 months) and 2.1 months with placebo and paclitaxel (95%CI 1.9-2.5; HR for PFS, 0.88; 95% CI, 0.70-1.11; *P* = .273; Figure 2B). A trend for a reduction in the risk of death was observed with everolimus in taxane-pretreated patients (27% reduction in the risk, Figure 2C). In taxane pretreated patients, the estimated median survival in the everolimus group was 5.8 months (95% CI 3.9-7.6), compared to 3.9 months (95% CI 3.1-6.2; HR 0.73; *P* = .069). Other, prespecified subgroup analysis of overall survival according to baseline demographic and disease characteristics are shown in Figure 3. Across the remaining subgroups analyzed, results were consistent with those of the overall population. Of note, patients with a favorable ECOG performance status of 0/1 (*P* = .003), evidence of lymph node metastasis (*P* = .03) and no evidence of peritoneal carcinomatosis (*P* = .01) as well as patients with previous taxane treatment and the evidence of liver metastases had the highest benefit from the additional treatment with everolimus. The percentage of patients who started other antineoplastic therapy after study treatment discontinuation was comparable between treatment arms (paclitaxel + everolimus 43.3% vs 46.0% with placebo).

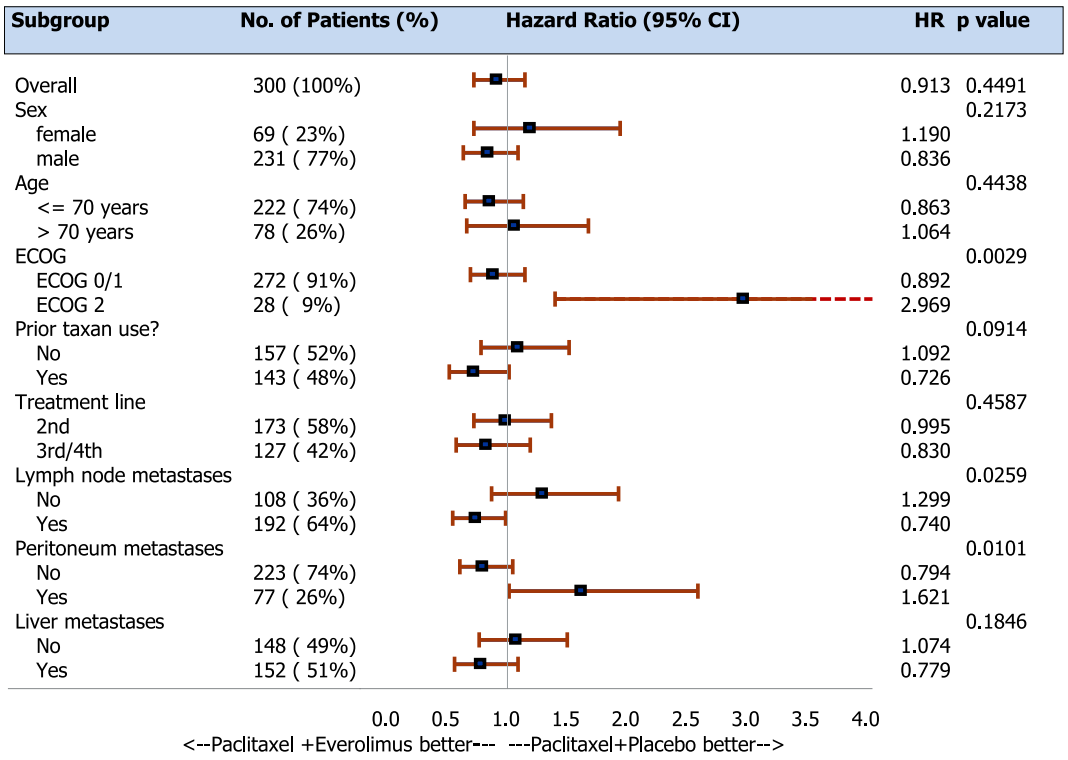
Estimated median PFS was 2.3 months with everolimus (95% CI 2.1-2.8) and 2.1 months (95% CI 1.9-2.5) in the placebo arm. The estimated percentage of patients progression-free at 6 months was 14% (95% CI 9-20) for both arms. Median PFS was significantly longer with everolimus in taxane pretreated patients with 2.7 months (95%CI 1.9-3.7) vs 1.8 months (95% CI 1.7-2.1; HR 0.69; *P* = .029).

Among patients with measurable disease at baseline two patients in the everolimus arm experienced a CR, vs one patient in the placebo arm. The overall response rate (ORR) (percentage of patients with CR or PR) was 8% with everolimus (95% CI 4.2%-13.6%) and 7.3% with placebo (95% CI 3.7%-12.7%). The disease control rate (percentage of patients with CR, PR or stable disease) was 38.7% vs 30.0% with everolimus vs placebo, respectively.

In patients with prior taxane therapy (n = 143) DCR was similar with a higher DCR rate in taxane-naïve patients (28% vs 21%; *P* = .180).

3.4 | Safety

Seven and three patients in the everolimus and placebo arm did not receive study medication and were excluded from the safety analysis (Figure 1). Consequently, the safety population consisted of 143 patients in the everolimus plus paclitaxel group and 147 patients



The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable

FIGURE 3 Forest plot of subgroup univariate analyses of overall survival [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Adverse events

	Everolimus + paclitaxel (n = 143)				Paclitaxel + placebo (n = 147)			
	Any grade		Grade 3-5		Any grade		Grade 3-5	
Adverse event	n	%	n	%	n	%	n	%
Blood and lymphatic system disorders								
Anemia	55	39	18	13	50	34	18	12
Leucopenia	31	22	8	6	17	12	7	5
Neutropenia	40	28	10	7	20	14	10	7
Thrombocytopenia	21	14	3	2	3	2	3	1
Gastrointestinal disorders								
Abdominal Pain	21	15	6	4	17	12	6	4
Constipation	22	15	1	1	21	14	2	1
Diarrhea	56	39	11	8	50	34	3	2
Mucositis	54	38	19	13	22	15	1	1
Nausea	52	36	7	5	62	42	10	7
Vomiting	34	24	5	4	36	25	7	5
General and other disorders								
Fatigue	73	51	10	7	67	46	14	10
Pain	46	32	10	7	37	25	13	9
Peripheral edema	20	14	1	1	11	7	0	0
Peripheral neuropathy	26	18	2	1	27	18	6	4
Pyrexia	30	21	4	3	15	10	0	0
Rash	17	12	2	1	5	3	0	0

Note: Data are n (%), unless otherwise indicated. Data show adverse events of any grade occurring in more than 10% of patients in at least one of the treatment arms.

in the placebo plus paclitaxel group. Hence, 290 patients were included in the safety analysis.

Almost all patients experienced at least one AE (97.2% in the everolimus arm and 97.3% in the placebo arm), with a significant higher number of AEs potentially related to everolimus vs placebo (56.6% vs 36.7%). The most common AEs (any grade) reported with everolimus were fatigue, anemia, diarrhea, mucositis and nausea (Table 2). The incidence of ≥grade 3 adverse events was similar in both treatment groups (78.3% vs 69.4%), however, more patients in the everolimus group had ≥3 oral mucositis (13.3% vs 0.7%) and diarrhea (7.7% vs 2.1%). Pneumonitis reported as serious was relatively uncommon, with incidence in the everolimus arm of 1.4% (n = 2), both CTC grade 3, and one grade 2 pneumonitis (0.7%) in the placebo Arm. There were no definitely treatment related adverse events leading to death in both groups. Sixteen (10.7%) of 150 patients in the everolimus group and 8 (5.3%) of 150 patients in the placebo group discontinued study treatment due to toxicity.

Serious treatment-related adverse events were reported in 91 (63.6%) of 143 patients in the everolimus group and 88 (59.9%) of 147 patients in the placebo group. SAEs with fatal outcome and at least possible relation to study therapy were reported in three patients in the everolimus group (2.1%) and in three patients (2.0%) in the placebo group.

4 | DISCUSSION

The randomized double-blind, placebo-controlled RADPAC trial did not demonstrate a significant survival benefit for the addition of everolimus to paclitaxel vs placebo plus paclitaxel in patients with EGC whose disease progressed after one or two lines of previous systemic chemotherapy. In the subgroup analysis, patients with liver involvement seemed to derive a particular benefit from the treatment with everolimus. Comparable findings have been observed in other trials with experimental second- and third-line treatments in GEC, such as the GRANITE-1 trial[13] and the recently presented ANGEL trial[21] with rivoceranib (apatinib) vs placebo in heavily pretreated GEC patients. Both, the GRANITE-1 trial and the ANGEL trial reported improved survival rates (HR 0.79 and 0.64, respectively) if either everolimus or rivoceranib was given instead of placebo, suggesting that for patients with liver involvement and anticipated higher tumor burden, the experimental treatment might be the more effective option. However, this has to be evaluated prospectively in future trials including liver only patients.

Notably, OS was numerically higher with everolimus (6.1 months vs 5.0 months) as was disease control rate (39% vs 30%). Although these trends may be a result of chance alone, comparable increase in activity with everolimus has been described in the GRANITE-1 trial.[13] OS in both arms was comparable to the paclitaxel mono arm in western patients in the RAINBOW trial (5.9 months 200/398 patients),[7] underlying the poor

prognosis of GEC patients progressing after systemic therapy. Both negative trials, the GRANITE-1 and the RADPAC trial confirm that there is no relevant benefit for everolimus either as monotherapy or in combination with a taxane in unselect populations of gastric cancer patients. However, in the prespecified subgroup of docetaxel-pretreated patients (48% of the ITT population), a clearer trend toward a reduced risk of death was noted for patients receiving everolimus (27% reduction in risk). The median survival was 5.8 months for the combination compared to only 3.9 months with paclitaxel alone, confirming the poor efficacy of paclitaxel in taxane-refractory patients. The rationale for enrollment of patients with prior docetaxel therapy in our study is supported by data showing that weekly paclitaxel is active in gastric cancer patients who had been refractory to docetaxel containing chemotherapy.[22] This indicates that cross-resistance between docetaxel and paclitaxel in gastric cancer is incomplete.[23-25] However, studies assessing the efficacy of taxane re-exposure show inconsistent results, mainly because numbers of patients are small and in various treatment lines and analyses are mostly retrospective. Our results regarding efficacy of taxane-rechallenge seem to be even worse than previous reports with a median survival of only 3.9 months in the paclitaxel control arm, which is close to those of patients who receive best supportive care only in second- and third-line setting (3.6-4.3 months).[4,13,26] As background conditions of the patients included in the study did not seem poorer compared to that of patients included in previous trials (median age 62 years, PS 0/1 90%) in a comparable setting, as were dose reductions and the relative dose intensity as expected, our results suggest the lack of efficacy of taxane re-administration. Of note, taxane-pretreated patients receiving everolimus in addition with paclitaxel had a median survival of 5.8 months, which is comparable with the median survival achieved for the combination in the overall population (6.1 months), and a significantly longer PFS (2.7 months vs 1.8 months). We therefore anticipate that the addition of everolimus to paclitaxel might overcome taxane-resistance, confirming the efficacy of this combination reported from heavily pretreated patients with breast cancer.[27] Our results are supported by preclinical evidence showing that paclitaxel resistant gastric cancer cell lines are characterized by microtubular disorders, reduced responses to antimitotic drugs and resistance to apoptosis. On the other hand, increased activation of the PI3K/Akt/mTOR pathway was observed, suggesting that targeting this pathway is sufficient to elicit antitumor responses in paclitaxel resistant GEC.[28] The question of re-exposure to a taxane is gaining more relevance, as, based on results from the FLOT-4 study,[29] the use of the FLOT regimen is standard in the perioperative management of resectable gastric/GEJ cancer from stage 2A. Patients who received perioperative FLOT for locally advanced disease and relapse, re-induction therapy with a taxane in the metastatic setting is of uncertain value and more data answering this question are urgently needed.

About 97% of all patients, independent of treatment arm, experienced at least one AE which is in line with other second- and third-line trials[13] and highlights the poor condition of heavily pretreated GEC patients. The everolimus AE profile was generally consistent with that reported previously in other trials with no new safety signals, however, there was a significantly higher number of AEs reported to be associated with everolimus vs placebo (57% vs 37%). Overall, grade ≥ 3 stomatitis (13% and 0.7%) and diarrhea (7.7% and 2.1%), AEs commonly associated with everolimus, were more often observed in the experimental arm respectively, leading to an increased rate of dose reduction of everolimus compared to placebo. As a consequence, treatment interruptions were more frequently reported for paclitaxel, as were treatment discontinuations in the combination arm due to toxicity.

Our trial had several limitations. First, the trial stopped recruitment prematurely due to a lower as expected recruitment rate, mainly because of the positive results of the Rainbow trial, establishing paclitaxel in combination with ramucirumab as the new second-line treatment standard in 2014. Furthermore, due to the limited number of taxane-pretreated patients, only a trend toward an improved efficacy with the combination could be observed, however evaluation of taxane re-challenge in combination with everolimus should be assessed in a larger patient population. We also must state that the initially expected survival rates were overestimated. At the time the study was designed, most data for paclitaxel were derived from Asian trials, where median survival was around 7 months. However, in the western patients, median survivals proved to be lower with paclitaxel. For example, in the Rainbow trial, median survival was 7.4 months in the paclitaxel arm in the whole population.[7] However, in the western population, median survival was 5.9 only for paclitaxel. In addition, many patients had received prior docetaxel in our trial leading to a less favorable study population. However, this issue did not seem to have an impact on the overall results of the trial, as the overestimation of the survival assumptions was done for both arms.

In conclusion, our trial failed to show a significant improvement in efficacy and toxicity in patients with GEC, relative to treatment with paclitaxel alone. However, in taxane-refractory patients, mTOR inhibition in addition to paclitaxel chemotherapy might be a promising therapeutic strategy. Identification of specific biomarkers may help to define those patients who might receive the most benefit from everolimus treatment. Results of ongoing biomarker analysis of the RADPAC trial are eagerly awaited.

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CONFLICT OF INTEREST

D. P.: Advisory role: Roche, Lilly, PharmaMar, Clinigen; Speaker: Lilly, PharmaMar; Research grants: Lilly, PharmaMar, Roche, Clinigen; P. T. P., Advisory role: Roche, MSD, merck, BMS, Lilly, Pfizer, Nordic, Servier; AV, Advisory role: Novartis. All other authors declare that they have no competing interests.

DATA ACCESSIBILITY

The data that support the findings of our study are available from the corresponding author upon reasonable request.

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