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A randomized phase II study of temsirolimus and cetuximab versus temsirolimus alone in recurrent/metastatic cetuximab-resistant head and neck cancer: The MAESTRO study

Running Title: The MAESTRO study

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Tanguy Y. Seiwert: Conceptualization, methodology, patient enrollment, writing - original draft, and writing – review and editing. **Sara Kochanny**: Data curation, visualization, writing – original draft, and writing – review and editing. **Kevin Wood**: writing – original draft. **Francis P. Worden**: Patient enrollment and resources. **Douglas Adkins**: Investigation, patient enrollment and resources. **James L. Wade**: Investigation and resources. **Bethany G. Sleckman**: Investigation and resources. **Daniel Anderson**: Investigation and resources. **Ryan J. Brisson**: Data curation and writing – review and editing. **Theodore Karrison**: Formal analysis. **Walter M. Stadler**: Supervision and project administration. **Everett E. Vokes**: Conceptualization, patient enrollment, methodology, supervision, and writing – review and editing.

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Precis for use in the Table of Contents: In this randomized clinical trial of patients with cetuximab-refractory recurrent/metastatic HNSCC, cetuximab + temsirolimus induced durable responses in some patients (including 1 CR), indicating modest clinical activity. However, in an unselected population temsirolimus + cetuximab did not improve survival, though further investigation as a salvage option for patients with prior benefit from cetuximab monotherapy may be warranted.

Keywords: Squamous Cell Carcinoma of Head and Neck , cetuximab , temsirolimus , Neoplasm Metastasis , Neoplasm Recurrence , Local Genes , erbB-1 , TOR Serine-Threonine Kinases

Abstract

Background: Patients with cetuximab-resistant recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) have poor outcomes. This study hypothesized that dual blockade of mTOR and EGFR would overcome cetuximab resistance based on the role of PI3K signaling in preclinical models of EGFR resistance.

Methods: In this multicenter randomized clinical study, patients with recurrent/metastatic HNSCC with documented progression on cetuximab (in any line in recurrent/metastatic setting) received temsirolimus 25 mg weekly + cetuximab (TC) 400/250mg/m^2 weekly or single-agent temsirolimus (T). Primary outcome was progression free survival (PFS) of TC arm compared to T arm. Response rate, overall survival, toxicity were secondary outcomes.

Results: 80 patients were randomized to therapy with TC or T alone. There was no difference for the primary outcome of median PFS (TC arm: 3.5 months, T arm: 3.5 months). Response rate in the TC arm was 12.5% (5 responses, including 1 CR (2.5%)) compared to 2.5% in the T arm (1 PR) *(P*=0.10). Responses were clinically meaningful in the TC arm (range: 3.6–9.1 months), but not in the T alone am (1.9 months). Fatigue, electrolyte abnormalities, and leukopenia were the most common grade 3+ adverse events and occurred in less than 20% of patients in both arms.

Conclusion: The study did not meet its primary endpoint of improvement in PFS. However, temsirolimus + cetuximab induced responses in cetuximab-refractory patients with good

tolerability. The post-hoc observation of activity in patients with acquired resistance (after prior benefit from cetuximab monotherapy) may warrant further investigation.

Introduction

90% of head and neck squamous cell carcinomas (HNSCC) express epidermal growth factor receptor (EGFR) and its presence is associated with poor outcome[1]. Cetuximab, an IgG1 monoclonal antibody that inhibits ligand binding to EGFR and stimulates antibody-dependent cell-mediated toxicity[2], has been demonstrated to improve overall survival, progression-free survival, and response rates in the recurrent or metastatic setting when added to standard chemotherapy[3]. Single agent response rates of 9.7-13% have been noted in platinum-refractory disease with single-agent cetuximab[4], but patients eventually develop resistance and progress[5].

While resistance to cetuximab can occur through a variety of mechanisms, preclinical models suggest that downstream activation of the phosphoinositide 3-kinase (PI3K)/AKT pathway can play a key role in the development of cetuximab resistance[5]. AKT/mTOR activation is an early event in HNSCC carcinogenesis, and is implicated in progression from dysplasia to invasive carcinoma and predicts recurrence when identified at the surgical margin[6,7]. Independent activation of AKT predicts resistance to EGFR inhibitors in *EGFR*-overexpressing cell lines[8]. Furthermore, it has been demonstrated that genetic alterations causing PI3K/AKT/mTOR activation, such as by expression of activated *PIK3CA* and *RAS* alleles, are sufficient to prevent a sustained response to cetuximab after an initial short-lasting beneficial effect[9].

Consequently, it has been hypothesized that dual blockade of EGFR and mTOR may lead to improved efficacy in tumor inhibition. Temsirolimus, an ester of the immunosuppressive drug sirolimus, acts by binding to the intracellular cytoplasmic protein, FK506 binding protein 12 (FKBP12), thereby inhibiting mammalian target of rapamycin (mTOR), a highly conserved serine-threonine kinase. In xenograft models, the combination of the EGFR small molecule tyrosine inhibitor erlotinib and temsirolimus was successful in demonstrating tumor inhibition[10]. However, a phase II trial evaluating the combination was halted early due to toxicity, notably head & neck edema, diarrhea, and asthenia[11]. A second phase II trial evaluating the combination of everolimus, a different mTOR inhibitor and derivative of sirolimus, and erlotinib in unselected patients with platinum-resistant recurrent/metastatic

HNSCC showed a manageable toxicity profile but did not show significant benefit[12]. Additional studies looked at combinations of mTOR inhibitors with chemotherapy or radiation[13-15].

The aim of this phase II randomized clinical trial was to evaluate progression-free survival with cetuximab + temsirolimus combination therapy compared to temsirolimus alone in patients with cetuximab-refractory metastatic or recurrent HNSCC.

Materials and Methods

Study investigations were performed following approval by the local Institutional Review Board (Univ. of Chicago IRB#10-428-B, PI: Seiwert) and respective University of Chicago Phase 2 consortium member sites (full list is at www.clinicaltrials.gov, identifier: NCT01256385). Written informed consent was obtained from each patient.

Patient Population

Patients were ≥18 years and required to have a histologic or cytologic diagnosis of HNSCC not amenable to curative intent therapy. Patients must have had progressive disease on a cetuximab-based therapy in the recurrent or metastatic setting. Acceptable prior cetuximab therapy was defined as palliative intent use either alone or in combination with chemotherapy for at least 2 weeks. Treatment with cetuximab during radiotherapy or chemotherapy was not sufficient. Patients were required to have Eastern Cooperative Group Performance Status (ECOG) 0-1, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST v1.1), normal organ and marrow function, and a life expectancy of greater than 8 weeks. Pregnant women, patients with active brain metastases, and patients with uncontrolled intercurrent illness (including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, ongoing or active infection) were ineligible for the study.

Investigational Treatment

A total of 80 patients were randomized to receive either temsirolimus + cetuximab (TC) or temsirolimus monotherapy (T). Randomization was 1:1 between the two arms using the method of permuted blocks (not blinded) and stratified based on anatomic site of tumor origin

(oropharyngeal versus non-oropharyngeal origin). Randomization was done at the University of Chicago.

The initial cetuximab dose was a loading dose of 400 mg/m^2 IV, and subsequent weekly doses were of 250 mg/m^2 IV (given over 60 minutes). In both arms, temsirolimus was given at a dose of 25 mg weekly, infused IV over 30-60 minutes via infusion pump. Four weeks (28 days) constituted one cycle and treatment was continued until disease progression, intercurrent illness that prevented further administration of treatment, unacceptable adverse events, or the patient chose to withdraw from the study. At time of progression, patients treated on the T arm could cross over to the TC arm for a salvage therapy option.

Restaging radiological evaluation was performed at baseline and then every 8 weeks. Disease progression (PD) was evaluated by the investigators using RECIST v1.1. Toxicity assessments according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NIH) were performed every two weeks for the first 8 weeks, and then monthly until the patient was taken off study.

Statistical Methods

The primary endpoint was progression-free survival (PFS), defined as time from randomization to disease progression or death from any cause. It was assumed that temsirolimus as a single agent would not prolong PFS based on prior studies of ineffective targeted agents in HNSCC[16]. It was hypothesized that combination treatment would increase median PFS from 2.0 months to 4.0 months, which corresponded to a hazard ratio of HR=2. A sample size of N=80 patients (40 per arm) was chosen, to provide 90% power to detect such a difference based on a log rank test with a one-sided α=0.05 (assuming 24-month accrual and 6-month follow-up periods).

Secondary endpoints were tumor response, OS, treatment related toxicity, and signal with TC combination therapy after PD on T monotherapy. PFS and OS were estimated by the Kaplan-Meier method and compared between treatment arms using the log rank test[17]. Confidence intervals for median survival times were derived using the method of Broomeyer and Crowley[18]. Response rates were compared by Fisher's exact test.

Results

Patient characteristics and treatment administration

Patients were enrolled between February 2011 and May 2013 across 14 institutions. A total of 86 patients were randomized (43 per treatment arm, see **Figure 1**). Three patients in each arm did not start treatment and were considered non-evaluable and per the protocol not included in the analysis. The baseline characteristics for the 80 evaluable patients are listed in **Table 1**. The majority of patients were male (TC: 77.5%, T: 92.5%), with ages ranging from 39-86 years. Approximately 40% of tumors were located in the oropharynx and 60% at non-oropharynx sites.

Efficacy

PFS and OS are depicted in **Figure 2**. All 80 randomized patients were evaluable for PFS and OS. PFS was not significantly different between the two arms (logrank *P*=0.73). Median PFS time was 105 days for the TC arm (95% CI: 70-136 days) and 105 days for the T arm (95% CI: 77-147 days). OS was also not significantly improved with the combination therapy (logrank *P*=0.87). Median OS time was 177 days for the TC arm (95% CI: 146-247 days) and 176 days for the T arm (95% CI: 131-316 days).

There was a trend toward a difference in response rates, with 5 patients (12.5%) having either a partial (*N*=4) or complete response (*N*=1) in the TC arm and only 1 patient (2.5%) having a partial response in the T arm *(P*=0.10) (**Table 2**). The duration of responses and prior history data are shown in **Table 3**.

Ten patients were taken off treatment due to an adverse event (6 in TC arm and 4 in T arm), 48 due to disease progression (26 in TC arm and 22 in T arm), 2 to pursue alternative treatments (1 in each arm), 6 withdrew (1 in TC arm and 5 in T arm), 6 discontinued for other reasons (2 in TC arm and 4 in T arm), and 8 patients died on therapy (4 in each arm).

Activity of combination therapy after failure of temsirolimus monotherapy

In total, 15 (37.5%) patients in T arm progressed and subsequently crossed over to receive the combination treatment. Of those 15, 5 were not evaluable due to coming off treatment prior to the first evaluation. Of the remaining 10 evaluable patients, 6 had a best response of PD and 4 had a best response of SD.

Toxicity

In both arms, all 80 patients were evaluable for toxicity. The most common any grade and 3+ grade AEs while patients were on their initially assigned treatment arm and deemed at least possibly related to study drug are listed in **Table 4**. The number of patients who experienced at least one grade 3+ AE was 28/40 (70%) in the TC arm, and 31/40 (77.5%) in the T arm. In both arms, the most common at least possibly related grade 3+ AEs were leukopenia, electrolyte abnormalities, and fatigue, with no grade 3+ AE occurring in more than 20% of patients in either arm. No grade 5 hematologic AEs were observed in either arm. Two grade 5 non-hematologic adverse events were noted in the TC arm, one with pulmonary hemorrhage and one with death not otherwise specified. A clear cause of death could not be determined (in the presence of metastatic disease, no autopsy performed). Neither grade 5 AEs were thought to be related to the study drugs. There were no grade 5 non-hematologic adverse events in the T arm.

Discussion

Cetuximab is an approved treatment for recurrent/metastatic HNSCC setting with modest response rates from 9.7%-13%, but patients eventually develop resistance[4,5]. Pre-clinical studies have demonstrated that upregulation of the PI3K/AKT/mTOR pathway is one mechanism by which cetuximab-resistance can develop[5]. Clinical studies of mTOR inhibition alone have shown poor activity in HNSCC[19]. In preclinical models blocking mTOR has been shown to reverse EGFR resistance, and has been proposed as a clinical candidate mechanism by several groups[9,10]. However prior phase II studies evaluating the tolerability and efficacy of dual inhibition of EGFR and mTOR in recurrent/metastatic, platinum-resistant HNSCC patients have either poor tolerability or, at tolerable doses, shown poor efficacy[11,12]. Poor tolerability in particular may be related to the use of small molecule EGFR inhibitor erlotinib, or continual mTOR inhibition with daily oral dosing of everolimus. Hence, in this study, we chose a different approach to accomplish EGFR and mTOR co-targeting, using the EGFR monoclonal antibody cetuximab, which, as commonly observed[20], may be easier to combine than a TKI. Additionally, we used temsirolimus given IV once weekly based on pharmacokinetic considerations with an intermittent weekly peak of mTOR inhibition[21]. Differences in tolerability between IV intermittent dosing and continual oral dosing are well described and may account for differences in tolerability and efficacy[22].

This phase II randomized trial of cetuximab + temsirolimus versus temsirolimus alone in cetuximab-resistant, recurrent/metastatic HNSCC patients failed to meet its primary endpoint of demonstrating a difference in PFS. However, the combination was well-tolerated and the addition of temsirolimus to cetuximab in this cetuximab-resistant population induced responses in 12.5% (5/40) of patients, including 1 complete response, with duration of responses ranging from 3.6 months to 9.1 months (**Table 3**), which may support the preclinical evidence and mechanistic rationale for dual, vertical targeting of EGFR and PIK3K/mTOR pathways [9,10]. The long duration of response argues against re-sensitization which would result in more transient/shorter term responses from regrowth of resistant clones. Given that the temsirolimus-alone comparator arm did not show meaningful activity neither response rate nor duration of response is likely driven by temsirolimus alone. Similarly, everolimus as a single agent also did not show activity[19]. Furthermore, some patients who progressed on temsiroliums and crossed over to the combination showed some disease stabilization, indicating that efficacy is due to the combination.

Interestingly, responses occurred exclusively in non-oropharyngeal sites of origin, suggesting preferential activity in HPV-negative tumors. Activity of EGFR agents is primarily in HPV-negative tumors[23], and may relate to higher levels of EGFR expression in HPV-negative HNSCC[24].

Overall this is a negative study, and the median progression-free and overall survival do not support development in the overall population of EGFR-refractory HNSCC patients. Identification of a predictive biomarker to enrich a population with higher rate of benefit might support further development to provide a clinically meaningful treatment option for patients who fail prior cetuximab therapy. Biomarker development for cetuximab therapy in HNSCC to date has been unsuccessful, nevertheless more recent biomarker analyses with newer agents do suggest that HPV status and PTEN/PI3K influence upfront anti-EGFR therapy efficacy for HNSCC and should be explored further[23, 25].

This is a pre-immunotherapy patient cohort as is evident in the overall poor survival. However, after approval of anti-PD-1 agents in both the first and second line recurrent/metastatic setting, cetuximab and cetuximab combinations continue to play an important role in PD-L1 negative patients and patients who fail checkpoint inhibition.

In conclusion the combination of temsirolimus and cetuximab shows modest clinical activity in cetuximab-refractory recurrent/metastatic HNSCC patients and meaningful duration of response, lending credence to the preclinical, mechanistic rationale for dual, vertical targeting of EGFR and PIK3K/mTOR pathways. However, overall this was a negative study, but further mechanistic and clinical investigation as a salvage treatment option in particular in patients with prior benefit from cetuximab monotherapy may be warranted.

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Figure 1. Study Design and Patient Allocation

Figure 2. Kaplan-Meier curves for survival. (a) Progression-free survival. (b) Overall survival. Provided *p*-values for Logrank tests. Tic marks denote censored observations.

Table 1: Baseline demographics and clinical characteristics.

	No. of Patients (%)	
	Temsirolimus + Cetuximab (N=40)	**Temsirolimus** (N=40)
Sex		
Male	31 (77.5)	37 (92.5)
Female	9 (22.5)	3 (7.5)
Age, years		
Median	60	61
Range	45-83	36-79
Race		
White	34 (85.0)	34 (85.0)
Black	5 (12.5)	3 (7.5)
Other	1 (2.5)	3 (7.5)
Primary Site		
Oropharynx	17 (42.5)	16 (40.0)
Non-oropharynx	23 (57.5)	24 (60.0)
Time between cetuximab failure and trial onset (months)		
Mean	2.7	1.0
Median	3.9	1.6

Table 2: Best response rates reported in both arms

Best response	**Temsirolimus + Cetuximab**		**Temsirolimus**	
	No. pts.	**%**	**No. pts**	**%**
Complete Response	1	2.5	0	0.0

Partial Response	4	10.0	1	2.5
Stable Response	21	52.5	20	50.0
Progressive Disease	10	25.0	16	40.0
Death < 1st Evaluation	3	7.5	1	2.5
Off treatment for AE[a] < 1st evaluation	1	2.5	1	2.5
Not adequately assessed	0	0.0	1	2.5
Overall Response Rate	**5**	**12.5%**	**1**	**2.5%**

[a]AE, adverse event.

Table 3. Characteristics of responses in patients with either a CR[a] or PR[b]

Response	Site of Origin	Duration of response (months)	Duration of best response to prior cetuximab (best response, months)	Time between cetuximab failure and trial onset (months)
Temsirolimus + Cetuximab				
CR	non-oropharyngeal	9.1	PR, 15.4	1.6
PR	non-oropharyngeal	7.3	PR, 9.0	1.1
PR	non-oropharyngeal	5.7	SD[c], 1.7	0.5
PR	non-oropharyngeal	4.2	PR, 9.2	2.8
PR	non-oropharyngeal	3.6	PR, 3.0	7.8
Temsirolimus				
PR	non-oropharyngeal	1.9	SD, 3.7	6.2

[a]CR, complete response. [b]PR, partial response. [c]SD, stable disease.

Table 4. Summary of most common adverse events at least possibly related in both treatment arms[a]

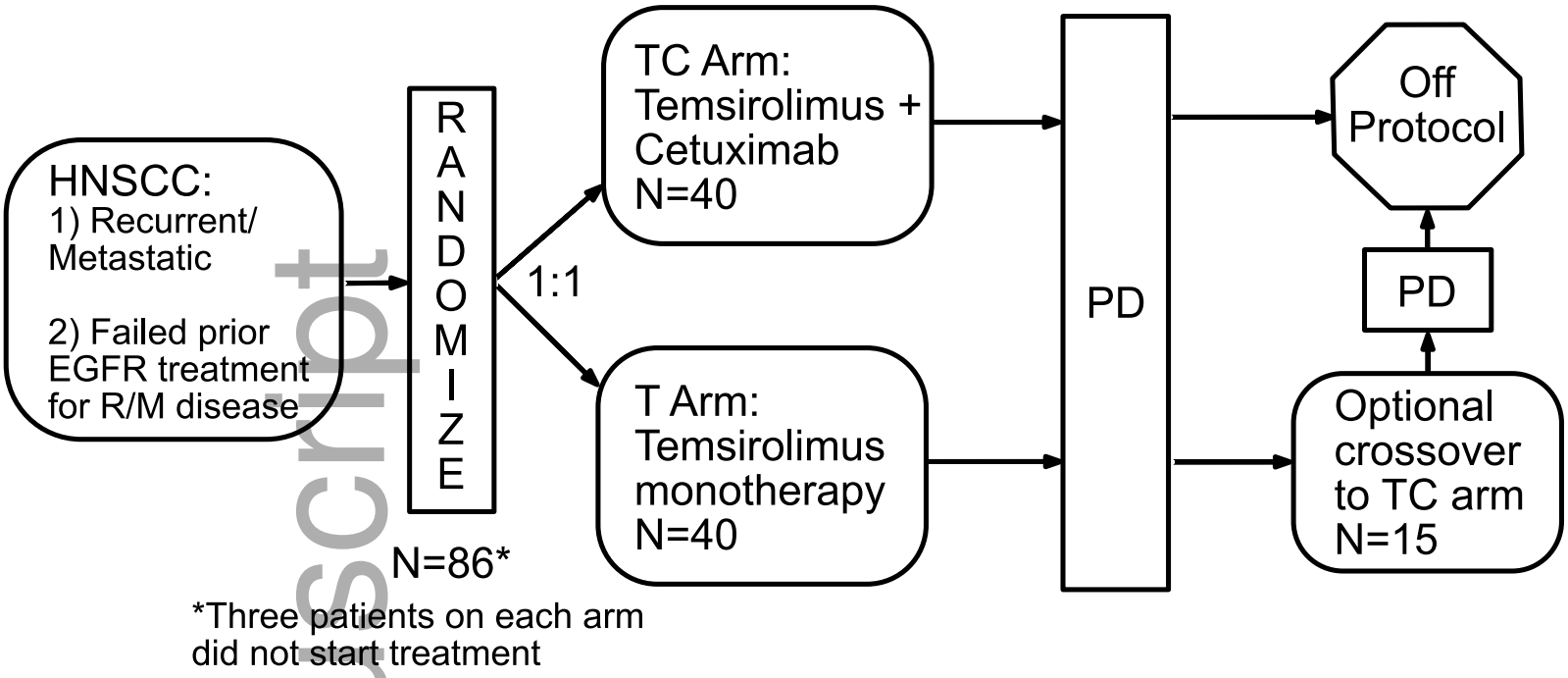
	No. of patients (%)

Characteristics	Temsirolimus + Cetuximab (N=40)		Temsirolimus (N=40)	
Grade	**Any**	**3+**	**Any**	**3+**
Hematologic AEs[b]				
Anemia	20 (50.0)	1 (2.5)	25 (62.5)	3 (7.5)
Leukocytosis	0 (0.0)	0 (0.0)	2 (5.0)	2 (5.0)
Lymphocyte count decreased	10 (25.0)	7 (17.5)	16 (40.0)	8 (20.0)
Platelet count decreased	15 (37.5)	1 (2.5)	15 (37.5)	0 (0.0)
White blood cell decreased	9 (22.5)	0 (0.0)	11 (27.5)	0 (0.0)
Non-Hematologic AEs				
Alanine aminotransferase increased	11 (27.5)	2 (5.0)	8 (20.0)	0 (0.0)
Alkaline phosphatase increased	10 (25.0)	0 (0.0)	7 (17.5)	0 (0.0)
Anorexia	9 (22.5)	1 (2.5)	15 (37.5)	0 (0.0)
Aspartate aminotransferase increased	8 (20.0)	0 (0.0)	6 (15.0)	0 (0.0)
Cholesterol high	7 (17.5)	0 (0.0)	12 (30.0)	0 (0.0)
Constipation	8 (20.0)	0 (0.0)	11 (27.5)	0 (0.0)
Dry skin	13 (32.5)	0 (0.0)	5 (12.5)	0 (0.0)
Dyspnea	3 (7.5)	1 (2.5)	8 (20.0)	1 (2.5)
Edema face	7 (17.5)	1 (2.5)	4 (10.0)	0 (0.0)
Fatigue	24 (60.0)	3 (7.5)	27 (67.5)	3 (7.5)
Headache	4 (10.0)	2 (5.0)	4 (10.0)	1 (2.5)
Hyperglycemia	16 (40.0)	3 (7.5)	22 (55.0)	5 (12.5)
Hypertriglyceridemia	7 (17.5)	0 (0.0)	10 (25.0)	2 (5.0)
Hypoalbuminemia	7 (17.5)	0 (0.0)	7 (17.5)	0 (0.0)
Hypocalcemia	8 (20.0)	2 (5.0)	8 (20.0)	0 (0.0)
Hypokalemia	12 (30.0)	2 (5.0)	8 (20.0)	0 (0.0)
Hypomagnesemia	22 (55.0)	4 (10.0)	4 (10.0)	0 (0.0)
Hypophosphatemia	10 (25.0)	6 (15.0)	9 (22.5)	1 (2.5)
Lung infection	1 (2.5)	1 (2.5)	3 (7.5)	2 (5.0)

Mucositis oral	16 (40.0)	3 (7.5)	14 (35.0)	1 (2.5)
Nausea	13 (32.5)	0 (0.0)	13 (32.5)	0 (0.0)
Rash acneiform	19 (47.5)	4 (10.0)	8 (20.0)	1 (2.5)
Rash maculo-papular	5 (12.5)	0 (0.0)	7 (17.5)	0 (0.0)
Vomiting	6 (15.0)	0 (0.0)	5 (12.5)	0 (0.0)
Weight loss	6 (15.0)	0 (0.0)	8 (20.0)	0 (0.0)

[a]Frequency cutoff for grade 1-2 AEs is 15%, and grade 3+ AEs is 5% for either arm. Maximum grade per patient reported.

[b]AE, adverse event.



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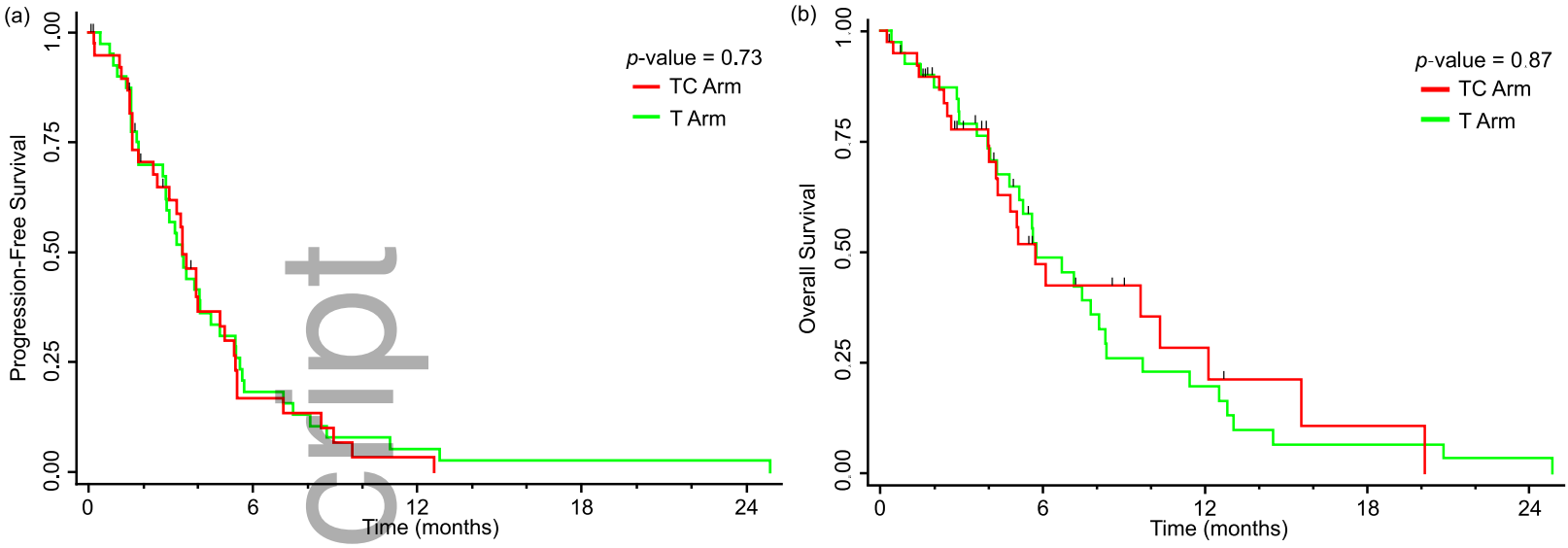

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