Published in final edited form as:

Target Oncol. 2014 September ; 9(3): 195–204. doi:10.1007/s11523-013-0289-2.

Pulmonary complications with the use of mTOR inhibitors in targeted cancer therapy: a systematic review and meta-analysis

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Abstract

Mammalian target of rapamycin (mTOR) inhibitors have gained regulatory approval for use in several cancer types. Pulmonary adverse events associated with mTOR inhibitors are well recognized but their frequency has varied considerably among trials. PubMed and ASCO abstracts

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Conflict of interest The authors report no conflicts of interest relevant to the submitted manuscript.

were searched to identify clinical trials of mTOR inhibitors in solid tumors. Twenty-two eligible trials on which 4,242 patients were treated met the criteria for inclusion in this systematic review and meta-analysis. Adverse event data were extracted and used to determine the incidence rate and incidence rate ratio for pneumonitis, dyspnea, and cough. The incidence rate of any grade pneumonitis in patients with solid tumors treated with mTOR inhibitors was 0.11 (95 % confidence interval (CI), 0.06–0.17) per patient, while the incidence of grade 3–4 pneumonitis was 0.03 (95 % CI, 0.01–0.04) per patient. The incidence rate ratio (IRR) of any grade pneumonitis with mTOR inhibitors relative to controls was 19.0 (95 % CI, 6.5–55.4), and for grade 3–4 pneumonitis was 8.0 (95 % CI, 2.6–24.1). The incidence rate for any grade and grade 3–4 cough was 0.23 (95 % CI, 0.20–0.27) per patient and 0.01 (95 % CI, 0.00–0.01) per patient, respectively. The incidence rate for any grade and grade 3–4 dyspnea was 0.15 (95 % CI, 0.10–0.21) per patient and 0.03 (95 % CI, 0.02–0.04) per patient, respectively. Compared to control, treatment with mTOR inhibitors were associated with a significant increase in any grade cough [IRR=1.9 (95 % CI, 1.6–2.4)] and grade 3–4 dyspnea [IRR=2.0 (95 % CI, 1.2–3.3)]. This study provides an estimation of the risk of pulmonary adverse events in solid tumor patients treated with mTOR inhibitors. While pulmonary adverse events are relatively common with mTOR inhibitors, most are low grade and asymptomatic.

Keywords

Systematic review; Meta-analysis; mTOR inhibitor; Adverse event; Solid tumor; Pneumonitis

Introduction

Drugs targeting signaling pathways involved in cancer pathogenesis play an increasing role in cancer therapy. These agents differ from traditional cytotoxic chemotherapy not only in mechanism of action but also with regard to toxicity profile. Importantly, each new class of “targeted” therapeutic is often associated with a unique side effect profile related to both on-target and off-target effects.

One such novel class of “targeted” anticancer agents is the inhibitors of the mammalian target of rapamycin (mTOR). The mTOR pathway is critical to several oncogenic processes such as cell survival, cell growth, and tumor angiogenesis [1]. Inhibiting this pathway with mTOR inhibitors or rapalogs has demonstrated anticancer effects across a wide variety of tumor types. Currently, two mTOR inhibitors have received regulatory approval from the United States Food and Drug Administration for the treatment of cancer, temsirolimus for use in advanced renal cell carcinoma (RCC) and everolimus for the treatment of advanced RCC, advanced breast cancer, unresectable/advanced pancreatic neuroendocrine tumors (PNET), and for subependymal giant cell astrocytoma associated with tuberous sclerosis. Ridaforolimus, which has not yet gained regulatory approval, has been evaluated in several large clinical trials.

Common toxicities of mTOR inhibitors include metabolic abnormalities, increased susceptibility to infection, mucositis, fatigue, and pulmonary complications. Pulmonary complications, particularly pneumonitis, have been reported in the majority of large clinical

trials of these agents. However, the incidence and risk of pneumonitis with mTOR inhibitors has varied among trials and has not been comprehensively evaluated. Furthermore, the incidence of risk of pulmonary symptoms with these agents has not been assessed. Therefore, we conducted a systematic review and meta-analysis of clinical trials to better determine the incidence and incidence rate ratio of pneumonitis, cough, and dyspnea associated with the use of mTOR inhibitors in cancer patients.

Methods

Data source

An independent PubMed search was performed to identify studies published between January 1, 1997 and April 30, 2012. Prospective studies of temsirolimus, everolimus, and ridaforolimus were identified. The search was limited to clinical trials published in english. Abstracts and presentations from the American Society of Clinical Oncology (ASCO) annual meeting from 1997 to 2011 were also searched to identify additional clinical trials. Each publication, abstract, and presentation was reviewed.

Study selection

The objectives of our study were to determine the incidence rate and incidence rate ratio of pulmonary adverse events with the use of mTOR inhibitors in the treatment of solid tumors. Criteria used for determining trial eligibility were the following: (1) prospective phase II and III trials exploring an mTOR inhibitor for the treatment of solid tumors, (2) reported data on treatment-emergent pulmonary adverse events, and (3) used an mTOR inhibitor alone or in combination with another non-cytotoxic agent. Phase I trials and trials involving mTOR inhibitors administered in combination with cytotoxic chemotherapy were excluded. Only clinical trials which had been published or from which final results had been presented were included in this analysis. If the same clinical trial was described in multiple publications, only the most recent and/or most complete report of the trial was included. The quality of randomized trials was determined using the Jadad 7-item scale [2].

Data extraction

Data extraction was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [3]. The data extracted from each publication included key study characteristics such as first author name, year of publication, phase of trial, cancer type, treatments administered, number of patients evaluable for adverse event data, and adverse event data including grade for pneumonitis, cough, and dyspnea.

Adverse events were assessed as per versions 2.0 or 3.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) criteria. These versions are similar in defining pulmonary adverse events (Table 1). Data extraction was performed independently by two authors (B.G., S.S.). Discrepancies were resolved by consensus among the study team.

Statistical analysis

Meta-analysis using a random effects model was employed to determine the incidence rate of pulmonary toxicities in the mTOR inhibitor treatment group and the incidence rate ratio between the mTOR inhibitor treatment group and the control group [4]. The event number (X) was assumed to follow a Poisson distribution. Where N is the number of patients, the variance of the incidence rate X/N is X/N [2]. Publication bias was assessed by Egger's regression test [5].

Results

Search results

The literature search identified 243 potentially relevant clinical trials evaluating the mTOR inhibitors temsirolimus, everolimus, and ridaforolimus. Studies excluded from the analysis and the reasons for their exclusion are shown in Fig.1. Twenty-two trials were identified that met our inclusion criteria. Twenty trials reported pneumonitis events, eight trials reported cough, and twelve trials reported dyspnea. Sixteen trials (seven temsirolimus, eight everolimus, and one ridaforolimus) were single arm studies or randomized patients to different doses/schedules of an mTOR inhibitor (Table 2) [6–21]. Six trials (one temsirolimus, four everolimus, and one ridaforolimus) randomized patients to an mTOR inhibitor arm or a non-mTOR inhibitor control arm (Table 3) [22–27]. The most common malignancies involved in these studies included renal cell carcinoma (four trials), breast cancer (three trials), neuroendocrine carcinomas (three trials), and sarcoma (three trials).

We did include one phase III trial, the results of which had been presented but not yet published. This study was presented at ASCO 2011 and data regarding adverse events were extracted from the presentation [27]. In one instance, a phase III trial [22] reported no data on pneumonitis, but a later publication [28] gave data on treatment-related pneumonitis in that trial. For this one instance, treatment-related as opposed to treatment-emergent adverse event data were used. In multiple instances, trials randomized patients to different doses or schedules of an mTOR inhibitor. For the purposes of our analysis, these arms were combined and used for incidence rate determination but not for evaluation of incidence rate ratio.

Study quality

Study quality was assessed for randomized studies using the Jadad 7-item scale. Of the five published randomized studies, the Jadad score ranged from 3–5 (Table 3). Only the Global ARCC Trial received a Jadad score of less than 4. This trial was open-label given the typical and anticipated adverse event profile of interferon.

Publication bias

No significant publication bias was detected for the 22 trials included in the meta-analysis for the incidence of pulmonary adverse events ($p=0.76$) or for the six trials included in the calculation of pulmonary adverse event incidence rate ratio ($p=0.27$).

Patients

A total of 4,242 patients (2,973 treated with mTOR inhibitors and 1,269 treated with controls) from 22 trials were included in this analysis. The 2,973 patients treated with mTOR inhibitors were included in the systematic review for determination of the incidence rate of pulmonary complications with mTOR inhibitor treatment. Six of these trials randomized patients to an mTOR inhibitor (1,856 patients) or a non-mTOR containing control treatment (1,269 patients) and were used in the determination of incidence rate ratios for pulmonary adverse events: 2,261 (710 controls) patients were treated on everolimus studies, 1,067 (200 controls) were treated on temsirolimus studies, and 914 (359 controls) were treated on ridaforolimus studies.

Only trials in which the adverse events of interest were reported were included in the determination of incidence rate or incidence rate ratios. Thus, if a trial reported pneumonitis but not cough or dyspnea, the patients treated in such a trial would be used only for calculation of pneumonitis incidence rate and incidence rate ratio. Trials reporting dyspnea included 2,526 patients (707 controls), trials reporting cough included 2,970 patients (1,066 controls), and trials reporting pneumonitis included 4,117 patients (1,269 controls). Patients included in these studies were typical of patient populations included in advanced solid tumor clinical trials. Patients generally had an Eastern Oncology Cooperative Group performance status of 0–1, preserved end organ function, and had not been treated with an mTOR inhibitor previously.

Incidence of pulmonary events

The pulmonary adverse event data for each of the trials included is shown in Table 4. The average incidence rate of any grade pneumonitis in the 20 trials reporting this adverse event was 0.11 (95 % confidence interval (CI), 0.06–0.17) per patient, while the incidence rate for grade 3–4 pneumonitis was found to be 0.03 (95 % CI, 0.01–0.04) per patient (Figure 2). The average incidence rate for any grade dyspnea in the 12 trials reporting it was 0.15 (95 % CI, 0.10–0.21) per patient, while the incidence rate for grade 3–4 dyspnea was found to be 0.03 (95 % CI, 0.02–0.04) per patient. The average incidence rate for cough in the eight trials reporting it was 0.23 (95 % CI, 0.20–0.27) per patient, while the incidence rate for grade 3–4 cough was found to be 0.01 (95 % CI, 0.00–0.01) per patient.

Risk of pulmonary events

Analysis of 3,125 patients in six randomized trials revealed an incidence rate ratio (IRR) of any grade pneumonitis with mTOR inhibitors relative to controls of 19.0 (95 % CI, 6.5–55.4) and for grade 3–4 pneumonitis was 8.0 (95 % CI, 2.6–24.1) (Figure 3). The IRR for the development of any grade dyspnea with mTOR inhibitors relative to controls is 1.7 (95 % CI, 0.99–2.9) and for grade 3–4 dyspnea is 2.0 (95 % CI, 1.2–3.3). The IRR for the development of any grade cough with mTOR inhibitors relative to controls is 1.9 (95 % CI, 1.6–2.4) and for grade 3–4 cough is 2.7 (95 % CI, 0.7–10.4).

Discussion

We determined the incidence of pulmonary complications associated with mTOR inhibition in the treatment of solid malignancies by performing a systematic review of the literature and meta-analysis. We found that pulmonary complications, most notably pneumonitis, are fairly common with the use of mTOR inhibitors, occurring in approximately one of nine solid tumor patients treated with these drugs. Rates of pneumonitis were found to be 19-fold higher with mTOR inhibitors compared to controls.

While ours is the first meta-analysis to evaluate pulmonary complications in cancer patients treated with mTOR inhibitors, a number of groups have performed retrospective evaluations of imaging from large clinical trials of mTOR inhibitors to better assess the incidence of pneumonitis. Though treatment-emergent pneumonitis was not commented upon in the final report of the Global ARCC trial [22], a later publication described four cases of treatment-associated pneumonitis among the 208 patients treated with temsirolimus alone [28]. A review of imaging found that 52 of 178 (29.2 %) treated with temsirolimus had radiological evidence of pneumonitis compared to 8 of 138 (5.8 %) patients treated with interferon. Of patients with radiological evidence of pneumonitis, 52 % had any pulmonary symptom compared to 48 % in those patients without radiological evidence of pneumonitis. A retrospective review of imaging from the RECORD-1 trial was also conducted [29]. As per the final report of the trial, 37 of 274 (13.5 %) patients receiving everolimus developed pneumonitis [24]. Post-treatment CT scans were available for review in 377 of the 411 patients. Compared to 15.2 % in the placebo group, 53.9 % of patients in the everolimus group showed radiographic development or worsening of baseline pneumonitis (which was present in 20 % of patients). Of patients treated with everolimus not clinically identified as having pneumonitis during the trial, 38.9% had radiological evidence of pneumonitis upon review of imaging. Of 37 patients with clinical pneumonitis, 51.4 % had cough, 43.2 % had dyspnea, and 32.4 % had both cough and dyspnea. Of patients without clinical pneumonitis, rates of cough (20.6 vs. 16.2 %) and dyspnea (29.0 vs. 25.0 %) were similar in patients with and without radiological evidence of pneumonitis.

While the pathophysiology of mTOR inhibitor-associated pneumonitis is not certain, several mechanisms have been proposed. Helper T cells have been identified in both bronchoalveolar lavage and transbronchial biopsy specimens from solid organ transplant patients suffering from sirolimus-associated pneumonitis [30, 31]. It has been suggested that mTOR inhibitors may lead to exposure of cryptic pulmonary antigens triggering an autoimmune response and subsequent pneumonitis [31]. Others have speculated that mTOR inhibitors may act as haptens upon exposure to plasma proteins thereby triggering a delayed-type hypersensitivity reaction [32]. Regardless of the exact pathophysiology, the response to corticosteroids strongly suggests an immune mediated mechanism.

A strength of our study includes the analysis of not only pneumonitis, given the limitations noted above, but also pulmonary symptoms. Importantly, our findings demonstrate that while the risk of pneumonitis is increased 19-fold in patients receiving mTOR inhibitors, the magnitude of increase in pulmonary symptoms is much smaller.

This study also has several potential limitations. First, studies of different tumor types and different mTOR inhibitors were included. This is of potential significance as the incidence of pulmonary toxicity could vary between tumor types and with different mTOR inhibitors. Three of the phase II studies involved patients with lung cancer; while the risk of pulmonary symptoms such as cough or dyspnea are likely higher in these patients, these studies only comprised 5 % of the total study population. Among 4/6 randomized studies reporting the incidence of lung metastases, the proportion of patients with lung metastases were similar in the mTOR inhibitor and control arms; thus, the IRR for pulmonary adverse events with mTOR inhibitors is unlikely to be significantly affected. The incidence of pulmonary complications appeared lower in earlier reports, and this is likely a result of heightened awareness/detection of this side effect in later studies. As noted, retrospective analyses have revealed a higher incidence of pneumonitis compared to the reported incidence in the initial clinical trial publications. In total, the variability in awareness, diagnosis, and reporting may have resulted in an underestimation of the incidence and risk of pulmonary complications. Finally, we did not have individual patient data and therefore utilized aggregate published clinical trial data for our analysis; however, prior analyses have suggested that these approaches generally yield similar results [33] and meta-analyses using individual patient data are also subject to potential unique biases [34].

It is apparent from our analysis, and others mentioned herein, that many cases of mTOR inhibitor-associated pneumonitis are either asymptomatic or minimally symptomatic. When symptoms do occur, they are most commonly cough, dyspnea, and hypoxia [35]. Suggested approaches for the management of mTOR inhibitor-associated pneumonitis have been proposed [29, 35]. Patients who are asymptomatic and have only radiographic evidence of pneumonitis can likely be maintained on an mTOR inhibitor without dose interruption or dose modification, but should be monitored closely for pulmonary symptoms and educated about the need to immediately report any such symptoms. For patients with symptomatic pneumonitis, the grade of the adverse event should be used to guide decisions with regard to management, which in addition to dose interruption or modification, often involves the use of corticosteroids. The potential significance of mTOR inhibitor-associated pulmonary adverse events should not be minimized as grade 5 pneumonitis, while very rare, has been reported [10, 27].

In conclusion, mTOR inhibitor-associated pulmonary adverse events are relatively common and physicians involved in the care of patients treated with these agents should be well aware of the risk for mTOR inhibitor-associated pulmonary adverse events, should closely monitor for pulmonary symptoms and be familiar with the management of mTOR inhibitor-associated pneumonitis.

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Fig. 1.
Selection process for trials included in the meta-analysis

Fig. 2.
Incidence rate of any grade (a) and grade 3–4 (b) pneumonitis

Fig. 3.
Incidence rate ratio of any grade (a) and grade 3–4 (b) pneumonitis

Table 1

Grade determination for relevant pulmonary adverse events as per CTCAE v2.0 and v3.0

Grade	1	2	3	4
CTCAE v2.0				
Pneumonitis	Radiographic changes but asymptomatic or symptoms not requiring steroids	Radiographic changes and requiring steroids or diuretics	Radiographic changes and requiring oxygen	Radiographic changes and requiring assisted ventilation
Cough	Mild, relieved by nonprescription medication	Requiring narcotic antitussive	Severe cough or coughing spasms, poorly controlled or unresponsive to treatment	No grade 4
Dyspnea	No grade 1	DOE	Dyspnea at normal level of activity	Dyspnea at rest or requiring ventilator support
CTCAE v3.0				
Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O ₂ indicated	Life-threatening; ventilatory support indicated
Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	No grade 4
Dyspnea	DOE, but can walk one flight of stairs without stopping	DOE, but unable to walk one flight of stairs or one city block without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated

DOE dyspnea on exertion, *ADL* activities of daily living

Studies identified in the systematic review that reported pulmonary adverse events (pneumonitis, cough, or dyspnea) but no non-mTOR inhibitor control arm

Table 2

Source	Phase	Malignancy	mTOR inhibitor	Dose	No. of patients
Okuno et al. [6]	2	Advanced sarcoma	Temsirolimus	25 mg weekly	40
Atkins et al. [7]	2R ^a	Advanced RCC	Temsirolimus	25, 50, or 75 mg weekly	110
Pandya et al. [8]	2R ^b	Extensive-stage SCLC	Temsirolimus	25 or 250 mg weekly	86
Duran et al. [9]	2	Advanced NEC	Temsirolimus	25 mg weekly	36
Galanis et al. [10]	2	Recurrent GBM	Temsirolimus	250 mg weekly	65
Behbakht et al. [11]	2	Ovarian and primary peritoneal carcinoma	Temsirolimus	25 mg weekly	54
Oza et al. [12]	2 ^c	Recurrent or metastatic endometrial carcinoma	Temsirolimus	25 mg weekly	60
Soria et al. [13]	2	NSCLC	Everolimus	10 mg daily	85
Tarhini et al. [14]	2	Recurrent SCLC	Everolimus	10 mg daily	40
Slonovitz et al. [15]	2	Recurrent endometrial cancer	Everolimus	10 mg daily	35
Yao et al. [16]	2R ^d	Metastatic PNET	Everolimus	10 mg daily	115
Elliard et al. [17]	2R ^e	Metastatic breast cancer	Everolimus	10 mg daily or 70 mg weekly	49
Amato et al. [18]	2	Metastatic RCC	Everolimus	10 mg daily	39
Seront et al. [19]	2	Advanced UC	Everolimus	10 mg daily	37
Yoon et al. [20]	2	Gastric adenocarcinoma	Everolimus	10 mg daily	54
Chawla et al. [21]	2	Advanced sarcoma	Ridaforolimus	12.5 mg IV weekly for 5 days every 2 weeks	212

RCC renal cell carcinoma, SCLC small cell lung cancer, NEC neuroendocrine carcinoma, GBM glioblastoma multiforme, NSCLC non-small cell lung cancer, PNET pancreatic neuroendocrine tumor, UC urothelial carcinoma

^aRandomized to temsirolimus 25 mg (n=36), 50 mg (n=38), or 75 mg (n=36) IV weekly. Patients were combined for our study

^bRandomized to temsirolimus 25 mg (n=45) or 250 mg (n=41) IV weekly. Patients combined for this study

^cCombined sequential phase 2 studies

^dRandomized to everolimus (n=115) or everolimus + octreotide (n=45). Only everolimus alone group included in this analysis

^eRandomized to everolimus 10 mg PO daily (n=33) or 70 mg PO weekly (n=16). These patients are combined for our analysis

Table 3

Studies identified in the systematic review that reported pulmonary adverse events (pneumonitis, cough, or dyspnea) and included a non-mTOR inhibitor control arm

Source	Phase	Malignancy	mTOR inhibitor	Dose	Patients	Control arm	Jadad score
Hudes et al. [22]	3	Advanced RCC	Temsirolimus	(1) 25 mg/week (2) 15 mg/week + IFN	416 (n=208 arms 1 & 2)	(3) IFN (n=200)	3
Baselga et al. [23]	2R	Breast cancer (neoadjuvant)	Everolimus	10 mg daily + letrozole	137	placebo + letrozole (n=132)	4
Motzer et al. [24]	3	Metastatic RCC	Everolimus	10 mg daily	274	Placebo (n=137)	4
Yao et al. [25]	3	Advanced PNET	Everolimus	10 mg daily	204	Placebo (n=203)	5
Baselga et al. [26]	3	Advanced breast cancer	Everolimus	10 mg daily + exemestane	482	Placebo + exemestane (n=238)	5
Chawla et al. [27]	3	Metastatic sarcoma	Ridaforolimus	40 mg PO 5 days weekly	343	Placebo (n=359)	Unable to assess

RCC renal cell carcinoma, PNET pancreatic neuroendocrine tumor

Table 4

Pulmonary adverse events reported in the identified trials

Source	Phase	Malignancy	mTOR inhibitor	Patients	Pneumonitis				Cough				Dyspnea				Lung mets (%)
					Total	1-2	3-4	Total	1-2	3-4	Total	1-2	3-4	Total	1-2	3-4	
Okuno et al. [6]	2	Sarcoma	Temsirolimus	40	NR	NR	NR	11	11	0	7	5	2	56			
Atkins et al. [7]	2R	RCC	Temsirolimus	110	6	NR	NR	NR	NR	NR	NR	NR	NR	75			
Pandya et al. [8]	2R	SCLC	Temsirolimus	86	NR	NR	4	NR	NR	NR	NR	NR	NR	6	NR		
Duran et al. [9]	2	NEC	Temsirolimus	36	7	7	0	NR	NR	NR	NR	NR	NR	NR	NR		
Galanis et al. [10]	2	GBM	Temsirolimus	65	NR	NR	3	NR	NR	NR	NR	NR	NR	NR	NR		
Behbakht et al. [11]	2	Ovarian	Temsirolimus	54	3	0	3	NR	NR	NR	NR	NR	NR	NR	NR		
Oza et al. [12]	2R	Endometrial	Temsirolimus	60	25	20	5	13	13	0	11	9	2	50			
Soria et al. [13]	2	NSCLC	Everolimus	85	NR	NR	NR	21	20	1	34	26	8	NR			
Tarhini et al. [14]	2	SCLC	Everolimus	40	3	1	2	NR	NR	NR	3	1	2	NR			
Slomovitz et al. [15]	2	Endometrial	Everolimus	35	2	0	2	NR	NR	NR	1	1	0	NR			
Yao et al. [16]	2R	PNET	Everolimus	115	7	7	0	NR	NR	NR	8	6	2	17			
Ellard et al. [17]	2R	Breast	Everolimus	49	17	14	3	NR	NR	NR	12	9	3	37			
Amato et al. [18]	2	RCC	Everolimus	39	19	12	7	NR	NR	NR	NR	NR	NR	80			
Seront et al. [19]	2	UC	Everolimus	37	2	1	1	NR	NR	NR	NR	NR	NR	51			
Yoon et al. [20]	2	Gastric	Everolimus	54	8	5	3	NR	NR	NR	NR	NR	NR	4			
Chawla et al. [21]	2	Sarcoma	Ridaforolimus	212	5	NR	NR	NR	NR	NR	NR	NR	NR	77			
Hudes et al. [22]	3	RCC	Temsirolimus	208	4	3	1	54	52	2	58	39	19	NR			
			Temsirolimus + IFN	208	0	0	0	48	44	4	54	33	21	NR			
			IFN	200	1	1	0	28	28	0	48	36	12	NR			
Baselga et al. [23]	2R	Breast (neoadjuvant)	Everolimus + letrozole	137	4	1	3	NR	NR	NR	10	9	1	NR			
			Placebo + letrozole	132	0	0	0	NR	NR	NR	2	2	0	NR			
Motzer et al. [24]	3	RCC	Everolimus	274	37	27	10	82	79	3	66	47	19	73			
			Placebo	137	0	0	0	22	22	0	20	16	4	81			
Yao et al. [25]	3	PNET	Everolimus	204	35	30	5	22	22	0	NR	NR	NR	14			
			Placebo	203	0	0	0	4	4	0	NR	NR	NR	15			
Baselga et al. [26]	3	Breast	Everolimus + exemestane	482	58	44	14	106	101	5	88	69	19	29			

Source	Phase	Malignancy	mTOR inhibitor	Patients	Pneumonitis				Cough				Dyspnea				Lung mets (%)
					Total		1-2		3-4		Total		1-2		3-4		
Chawla et al. [27]	3	Sarcoma	Placebo + exemestane	238	0	0	0	0	0	26	26	0	21	18	3	33	
			Ridaforolimus	343	34	24	10 ^a		106	105	1	NR	NR	NR	67		
			Placebo	359	1	0	0	1	57	56	1	NR	NR	NR	64		

^aThis includes one grade 5 pneumonitis