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Oral stomatitis and mTOR inhibitors: A review of current evidence in 20,915 patients

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Background: Traditional treatment of malignancies with chemotherapeutic agents is often affected by the damage inflicted on non-cancerous cells. Toxicities of the oral cavity, such as mucositis and stomatitis, are some of the most significant and unavoidable toxicities associated with anti-cancer therapies. For such reason, in the last decades, newer targeted agents have been developed aiming to decrease the rates of side effects on healthy cells. Unfortunately, targeted anti-cancer therapies also showed significant rate of toxicity on healthy tissues. mTOR inhibitors showed some adverse events, such as hyperglycemia, hyperlipidemia, hypophosphatemia, hematologic toxicities, and mucocutaneous eruption, but the most important are still stomatitis and skin rash, often reported as dose-limiting side effects.

Patients and Methods: A search of the literature was performed by authors on the PubMed online database using the following key words: "sirolimus" OR "everolimus" OR "temsirolimus" OR "deforolimus" OR "ridaforolimus" combined with the Boolean operator AND with the terms: "stomatitis" OR "mucositis" OR "oral pain." Titles and abstracts of 382 potentially relevant studies were screened; of these, 114 studies were excluded because they did not report the inclusion criteria. In the second round, 268 studies were read full-text, but only 135 reported the inclusion criteria and were included for data extraction. Of the included studies, 95 referred to everolimus use, 16 to ridaforolimus, and 26 to temsirolimus (two studies referred to both everolimus and temsirolimus).

Results: The incidence rate of stomatitis according to the agent used was 25.07% (3,959/15,787) for everolimus, 27.02% (724/2,679) for temsirolimus, and 54.76% (598/1,092) for ridaforolimus. All the three agents analyzed showed high rates of low-grade stomatitis (G1–G2), while the onset of severe stomatitis (G3–G4) was rare.

Conclusions: Analysis of the reports with patients treated with everolimus, temsirolimus, and ridaforolimus showed a clear prevalence of stomatitis grade 1 or 2. These data differ from that of patients treated with conventional chemotherapy in which mucositis is predominantly of grade 3 or 4.

KEYWORDS

mTOR inhibitors, oral medicine, oral pathology, rapamycin, stomatitis, target therapy

1 | INTRODUCTION

Traditional treatment of malignancies with chemotherapeutic agents is often affected by the damage inflicted on normal, healthy cells (Keefe & Bateman, 2012). Toxicities of the oral cavity, such as mucositis and stomatitis, are some of the most significant and unavoidable toxicities associated with cancer treatment (Epstein et al., 2012). Oral toxicities have a tremendous impact on the patient with cancer and are a common cause of dose delays and interruptions of cancer therapy (Bensinger et al., 2008).

The terms oral mucositis and stomatitis are often used interchangeably to indicate oral complications of anti-cancer therapy, but they do not refer to the same process (Parkhill, 2013). Oral mucositis is a Medical Subject Headings term that describes inflammation of oral mucosa due to chemotherapeutic agents or ionizing radiation. Stomatitis is a less specific term used to describe any inflammatory condition of oral tissue.

The difference between lesions was underlined in a seminal paper by Sonis, Treister, Chawla, Demetri, and Haluska (2010) that proposed the term mIAS (mTOR inhibitor-associated stomatitis) in order to provide a clear distinction from oral mucositis due to conventional chemotherapy.

The reported incidence of mucositis is striking; it is in fact evident the real incidence of mucositis in clinical practice is high. Currently available knowledge on oral mucositis is derived from clinical trials. Unfortunately, relatively few clinical trials focused on mucositis as a specific outcome and clinical trials often do not include the full range of patients (e.g. elderly patients, patients with comorbidities, non-adherent patients) (Bensinger et al., 2008). Additionally, mucositis often emerges between treatment cycles when clinical monitoring is sporadic (Elting et al., 2013).

For these reasons, everyone hoped that the newer targeted agents would have minor effects on normal, healthy cells. The use of targeted agents in the treatment of cancer has recently exploded with a significant positive impact on patient quality of life and survival rates (Keefe & Bateman, 2012). Since 2012, 14 agents have been approved by the US Food and Drug Administration (Parkhill, 2013). These agents influence or inhibit the signaling of many cellular targets including mTOR, EGFR, VEGF, and several tyrosine kinases (Parkhill, 2013). Unfortunately, targeted anti-cancer therapies can still cause significant toxicity to non-cancer cells (Parkhill, 2013).

The PI3K/Akt/mTOR signaling pathway has a pivotal role in cancer cell functions such as growth, proliferation, survival, and mortality. mTOR was identified in 1994 by several groups of investigators as the kinase targeted by rapamycin linked to the cellular protein FKBP12 (Vignot, Faivre, Aguirre, & Raymond, 2005).

Rapamycin and its analogues are the first generation of mTOR inhibitors. The target of rapamycin (mTor in mammalian cells) is a 289-kDa serine/threonine protein kinase belonging to a bigger family of phosphatidyl-inositol 3-kinase (PI3K)-related kinase (PIKK). The mechanism of action of rapamycin and its analogues is based on the inhibition of the activity of mTORC1 through the binding to FKBP-12 and the formation of a ternary complex with mTOR (Meng & Zheng, 2015).

The spectrum of adverse events related to this new class of oncology drugs is unique as compared with conventional anti-cancer chemotherapy. The most common adverse events are hyperglycemia, hyperlipidemia, hypophosphatemia, hematologic toxicities and mucocutaneous eruption, and stomatitis and skin rash are often reported as dose-limiting side effects (Li & Trovato, 2012; Watters, Epstein, & Agulnik, 2011).

Prior to the introduction of mTOR inhibitors in cancer therapy, aphthous ulcers have been observed in several studies with sirolimus in immunosuppressive regimens. These appear to be different when compared to mTOR inhibitor-associated stomatitis (mIAS) in patients with cancer. This difference is probably due to the concurrent administration of immunosuppressive therapy, which probably attenuates the toxicity in the organ transplant population (de Oliveira et al., 2011). Organ transplant patients treated with sirolimus often received concomitant calcineurin inhibitors (cyclosporine or tacrolimus) and a corticosteroid (typically prednisone), which are effective in the management of severe cases of aphthous stomatitis.

Mouth lesions present as singular or multiple discrete, ovoid, superficial, well-demarcated ulcers with a grayish white pseudomembrane. They are often ≤0.5 cm in diameter in size. Lesions typically affect the non-keratinized movable mucosa, such as the inner aspect of the lips, the ventral and lateral surfaces of the tongue and the soft palate. The ulcers develop acutely, usually within 5 days, and generally resolve spontaneously in 1 week, most frequently in the first cycle of mTOR inhibitor therapy.

2 | MATERIALS AND METHODS

The following review was performed to answer this following question: "What is the rate of incidence of oral stomatitis in patients treated with mTOR inhibitors?" A systematic search was performed on the PubMed online database using a combination of MESH terms and free text words: "sirolimus" (MESH) OR "everolimus" (MESH) OR "temsirolimus" (MESH) OR "deferolimus" (free text) OR "ridaforolimus" (MESH) combined through the use of Boolean operator AND with the key words: "stomatitis" (MESH) OR "mucositis" (MESH) OR "oral pain" (free text). Only studies fulfilling the following inclusion criteria were considered eligible for inclusion in this study: (i) performed on human subjects, (ii) reporting about the use of an mTOR inhibitor, (iii) written in the English language, and (iv) reporting about the incidence of stomatitis or oral mucositis. Case reports and studies on animal model were excluded from this study. No restrictions were applied to the year of publication.

For each study, the following records were extracted: name of the first author, year of publication, number of patients enrolled, type of disease treated, number of events recorded, and grade of the events reported. To simplify the process of data extraction, an ad hoc extraction sheet was used. In addition, data were independently extracted by two authors (LLM and CA) and checked in a joint session.

3 | RESULTS

3.1 | Bibliographic research

Titles and abstracts of 382 potentially relevant studies were screened; of these, 114 studies were excluded because they did not report the inclusion criteria. In the second round, 268 studies were read full-text, but only 135 reported the inclusion criteria and were included for data extraction. Of the included studies: 95 referred to everolimus use, 16 to ridaforolimus, and 26 to temsirolimus (two studies referred to both everolimus and temsirolimus) (Figure 1).

3.2 | Analysis of data

For everolimus, 95 manuscripts were analyzed (Table 1). A total of 17,144 patients were treated with everolimus in solid tumors and tuberous sclerosis complex. Studies reported data about grade of stomatitis for 15,787 patients. The overall incidence of stomatitis of any grade with everolimus treatment was 25.07% (3,959 patients), and 2,981 cases were grade 1/2 (18.88%) and 978 were grade 3/4 (6.19%).

A total of 2,679 patients were treated with temsirolimus in advanced solid tumors (Table 2). Although the overall incidence of stomatitis of any grade in the temsirolimus treatment was 27.02% (724 patients), most stomatitis events were grade 1 or 2, 623 cases (23.25% of the patients), with grade 3/4 events reported in 101 cases (3.77 of the patients). However, four authors (Armstrong et al., 2013; Gandhi et al., 2014; Mita et al., 2017; Pandya et al., 2007) reported the incidence rates limited to grades 3 and 4 treatment-related toxicities, for this reason, data about cases of stomatitis and stomatitis grades 1 and 2 are underestimated.

For ridaforolimus, 16 papers were analyzed. A total of 1,092 patients were treated with ridaforolimus for solid tumors (Table 3). Although the overall incidence of stomatitis of any grade in the ridaforolimus treatment was 54.76% (598 patients), most stomatitis events were grade 1 or 2, 534 cases (48.90% of the patients), with grade 3/4 events reported only in 64 cases (5.86 of the patients).

4 | DISCUSSION

Targeted therapy is a term used to describe methods designed to selectively inhibit a molecular target that is abnormally expressed in malignant-versus-normal tissues. It is employed to achieve a preferential localization of a drug in the region of disease and subsequently an increase in local concentration. mTOR inhibitors work as "signal transduction inhibitors." These drugs work in those malignancies where cells are stimulated to divide continuously without any external influence. The first mTOR inhibitor approved in 1980s by the US Food and Drug Administration was rapamycin, also named sirolimus, an anti-fungal agent with immunosuppressive properties produced by S.hygroscopicus (Sehgal, Baker, & Vezina, 1975). Due to the poor pharmacokinetic characteristics of rapamycin, research focused on the synthesis of analogues of rapamycin more suitable to therapy, such as everolimus, temsirolimus, and ridaforolimus. These molecules share a similar structure to the prototype rapamycin consisting of a 31-membered macrocyclic lactone backbone. The difference is in their C-40-O positions, which results in disparate pharmacokinetic/pharmacodynamics profiles (Liu, Thoreen, Wang, Sabatini, & Gray, 2009). Sirolimus and its analogues, everolimus, temsirolimus, and ridaforolimus, are the first generation of mTOR inhibitors. The mechanism of action of these

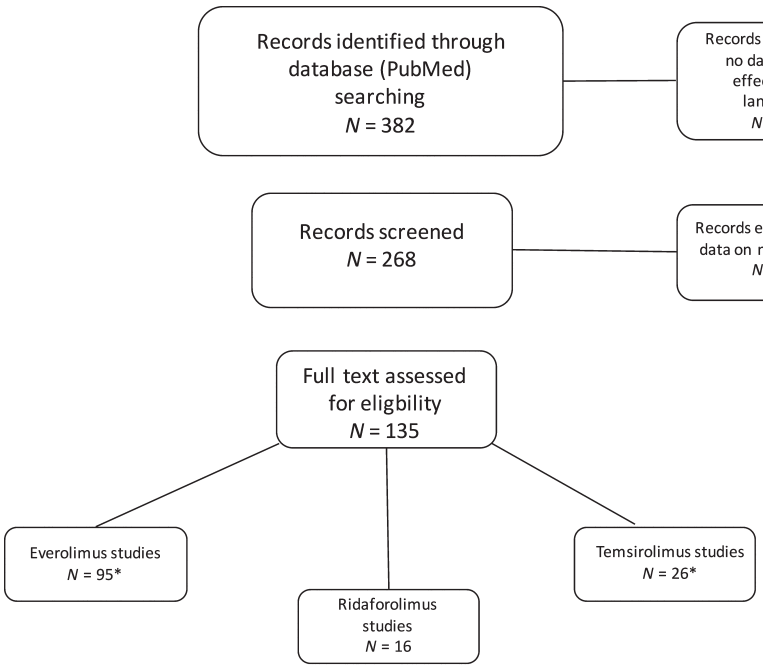

FIGURE 1 Flowchart showing the process of papers selection used in this review *2 Studies involved everolimus and temsirolimus

TABLE 1 Reports of all papers evaluating everolimus and cases of stomatitis

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
1.	Milton et al. (2007)	2007	Advanced non-small-cell lung cancer						
			A: Everolimus 5 mg + gefitinib 250 mg	A: 6	3 (50%)	A: 2 (33.3%)	A: 1 (16.6%)	A: 0	
			B: Everolimus 10 mg + gefitinib 250 mg	B: 3	1 (33.3%)	B: 0	B: 0	B: 1 (33.3%)	
2.	Awada et al. (2008)[a]	2008	Advanced breast cancer						
			A: Everolimus 5 mg/die + letrozole	A = 6	A: 3 (50%)	Not reported	Not reported	Not reported	Not reported
			B: Everolimus 10 mg/die + letrozole	B = 12	B: 6 (50%)				
				Total: 18	Total: 9 (50%)				
3.	Motzer et al. (2008)	2008	Advanced renal cell carcinoma						
			A: Everolimus 10 mg once daily	A: 269	A: 107 (40%)	A: 98 (37%)		A: 9 (3%)	A: 0
			B: Placebo	B: 135	B: 11 (8%)	B: 11 (8%)		B: 0	B: 0
4.	O'Donnell et al. (2008)[a]	2008	Advanced solid tumors						
			A: Everolimus 5 mg weekly	A: 4	A: 0	Not reported	Not reported	Not reported	Not reported
			B: Everolimus 10 mg weekly	B: 4	B: 1 (25%)				
			C: Everolimus 20 mg weekly	C: 5	C: 0				
			D: Everolimus 30 mg weekly	D: 5	D: 3 (60%)				
			E: Everolimus 50 mg weekly	E: 6	E: 3 (50%)				
			F: Everolimus 70 mg weekly	F: 31	F: 12 (38.7%)				
			G: Everolimus 5 mg daily	G: 4	G: 2 (50%)				
			H: Everolimus 10 mg daily	H: 33	H: 17 (51.51%)				
				Total: 92	Total: 38 (41%)				
5.	Tabernero et al. (2008)	2008	Advanced solid tumors						
			A: Everolimus 5 mg daily	A: 12	A: 4 (33.3%)	A: 3 (25%)		A: 1 (8.3%)	
			B: Everolimus 10 mg daily	B: 12	B: 6 (50%)	B: 5 (41.7%)		B: 1 (8.3%)	
			C: Everolimus 20 mg weekly	C: 12	C: 2 (16.6%)	C: 2 (16.6%)		C: 0	
			D: Everolimus 50 mg weekly	D: 12	D: 5 (41.6%)	D: 4 (33.3%)		D: 1 (8.3%)	
			E: Everolimus 70 mg weekly	E: 7	E: 4 (57.1%)	E: 2 (28.53%)		E: 2 (28.57%)	
6.	Baselga et al. (2009)	2009	Estrogen receptor-positive breast cancer						
			A: Everolimus + letrozole	A: 137	A: 50 (36.5%)	A: 47 (34.3%)		A: 3 (2.2%)	
			B: Placebo + letrozole	B: 132	B: 8 (6.1%)	B: 8 (6.1%)		B: 0 (0)	
7.	Amato, Jac, Giessinger, Saxena, and Willis (2009)	2009	Clear cell carcinoma						
			A: Everolimus	A: 39	A: 12 (30.8%)	A: 4 (10.3%)	B: 8 (20.5%)	A: 0	

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
8.	Campone et al. (2009)	2009	Advanced solid tumors						
			A: Everolimus 15 mg + paclitaxel 80 mg	A: 3	A: 1 (33.3%)	A: 1 (33.3%)		A: 0	
			B: Everolimus 30 mg + paclitaxel 80 mg	B: 13	B: 5 (38.4%)	B: 4 (30.71%)		B: 1 (7.69%)	
				Total: 16	Total: 6 (37.5%)			Total: 1 (6.25%)	
9.	Soria et al. (2009)	2009	Advanced non-small-cell lung cancer (NSCLC)						
			A: Platinum based + everolimus 10 mg/day	A = 42	A = 22 (52.4%)	A = 20 (47.6%)		A = 2 (4.8%)	
			B: Platinum + epidermal growth factor receptor tyrosine kinase inhibitors + everolimus 10 mg/day	B = 43	B = 17 (39.5%)	B = 14 (32.5%)		B = 3 (7%)	
10.	Motzer et al. (2010)	2010	Metastatic renal cell carcinoma						
			A: Everolimus + BSC	A: 274	A: 44	A: 40		A: 4	
			B: Placebo + BSC	B: 137	B: 8	B: 8		B: 0	
11.	Hainsworth et al. (2010)	2010	Advanced renal cell carcinoma						
			A: Bevacizumab + everolimus	A: 80	A: 48	A: 36 (45%)		A: 12 (15%)	B: 0 (0)
12.	Dalenc et al. (2010)[a]	2010	HER-2+ metastatic breast cancer						
			A: Everolimus 10 mg per die	A: 55	A: 11 (20.0%)	Not reported		Not reported	
13.	Krueger et al. (2010)	2010	Subependymal giant cell astrocytoma						
			A: Everolimus 3 mg/m^2	A: 28	A: 22 (79%)	A: 21 (75%)		A: 1 (4%)	
14.	Tobinai et al. (2010)	2010	Relapsed/refractory non-Hodgkin lymphoma						
			A: Everolimus 5 mg/day	A: 7	A: 3 (42.8%)	A: 3 (42.8%)		A: 0	
			B: Everolimus 10 mg/day	B: 6	B: 4 (66.6%)	B: 4 (66.6%)		B: 0	
15.	Yao et al. (2010)	2010	Advanced pNET						
			A: EVE 10 mg/day after failure of cytotoxic chemotherapy	A: 115	A: 52 (45.2%)	A: 47 (40.9%)		A: 5 (4.3%)	
			B: EVE 10 mg/day after previous octreotide LAR and failure of cytotoxic chemotherapy	B: 45	B: 22 (48.9%)	B: 21 (46.7%)		B: 1 (2.2%)	

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
16.	Andre et al. (2010)	2010	Metastatic breast cancer						
			A: Everolimus 5 mg daily + paclitaxel 80 mg/m^2 days 1, 8, and 15 every 4 weeks + trastuzumab 2 mg/kg weekly	A: 6	A: 3 (50%)	A: 2 (33.3%)		A: 1 (16.6%)	
			B: Everolimus 10 mg daily + paclitaxel 80 mg/m^2 days 1, 8, and 15 every 4 weeks + trastuzumab 2 mg/kg weekly	B: 17	B: 16 (94%)	B: 13 (76.4%)		B: 3 (17.6%)	
			C: Everolimus 30 mg weekly + paclitaxel 80 mg/m^2 days 1, 8, and 15 every 4 weeks + trastuzumab 2 mg/kg weekly	C: 10	C: 8 (80%)	C: 5 (50%)		C: 3 (30%)	
				Total: 33	Total: 27 (81.8%)	Total: 20 (60.59%)		Total: 7 (21.21%)	
17.	Jerusalem et al. (2011)	2011	HER-2 overexpressing metastatic breast cancer						
			A: Everolimus 5 mg per die + vinorelbine + trastuzumab	A: 30	A: 26	A: 21 (70%)		A: 5 (16.7%)	
			B: Everolimus 20 mg/week + vinorelbine + trastuzumab	B: 6	B: 5	B: 5 (83.3%)		B: 0	
			C: Everolimus 30 mg/week + vinorelbine + trastuzumab	C: 14	C: 9	C: 8 (57.1%)		C: 1 (7.1%)	
				Total: 50	Total: 40 (80%)	Total: 34 (68%)		Total: 6 (12%)	
18.	Pavel et al. (2011)	2011	Advanced neuroendocrine tumors associated with carcinoid syndrome						
			A: Everolimus + octreotide	A: 215	A: 133 (62%)	A: 119 (55%)		A: 14 (7%)	
			B: Placebo + octreotide	B: 211	B: 29 (14%)	B: 29 (14%)		B: 0	
19.	Yao et al. (2011)	2011	Advanced pancreatic neuroendocrine tumors						
			A: Everolimus	A: 204	A: 131 (64%)	A: 117 (57%)		A: 14 (7%)	
			B: Placebo	B: 203	B: 34 (17%)			B: 0 (0)	
20.	Motzer et al. (2011)[a]	2011	De novo kidney transplants						
			A: Ciclosporine	A: 145	A: 4 (3%)	Not reported		Not reported	
			B: Everolimus	B: 155	B: 26 (17%)				
21.	Guglielmelli et al. (2011)	2011	Myelofibrosis						
			A: Everolimus	A: 39	A: 27 (70%)	A: 26 (67%)		A: 1 (3%)	
22.	Porta et al. (2011)	2011	Advanced renal cell carcinoma RECORD-1						
			A: Everolimus 10 mg/day	A: 274	A: 42 (15.32%)	A: 39 (14.226%)		A: 3 (1.094%)	A: 0
			B: Placebo	B: 137	B: 8 (5.83%)	B: 8 (5.83%)		B: 0	B: 0

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
23.	Tsukamoto et al. (2011)	2011	Metastatic renal cell carcinoma						
			A: Everolimus 10 mg/day overall population	A: 274	A: 120 (44%)	A: 108 (39%)		A: 11 (4%)	A: 1 (<1%)
			B: Placebo overall population	B: 137	B: 11 (8%)	B: 11 (8%)		B: 0	B: 0
			C: Everolimus 10 mg/day Japanese population	C: 15	C: 11 (73%)	C: 11 (73%)		C: 0	C: 0
			D: Placebo Japanese population	D: 9	D: 1 (11%)	D: 1 (11%)		D: 0	D: 0
24.	Piccart et al. (2012)	2012	Advanced breast cancer	482	59 (12.3%)	A: 51 (10.7%)		8 (1.6%)	0
25.	Bachelot et al. (2012)	2012	Hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors						
			A: Tamoxifen + everolimus	A: 54	A: 30 (56%)	A: 24 (45%)		A: 6 (11%)	
			B: Tamoxifen	B: 57	B: 4 (7%)	B: 4 (7%)		B: 0 (0)	
26.	Baselga et al. (2012)	2012	Postmenopausal hormone receptor-positive advanced breast cancer						
			A: Everolimus + exemestane	A: 482	A: 56 (11.6%)	A: 48 (9.95%)		A: 8 (1.65%)	A: 0
			B: Everolimus + placebo	B: 238	B: 11 (4.6%)	B: 10 (4.18%)		B: 1 (0.42%)	B: 0
				Total: 720	Total: 67 (9.30%)	Total: 58 (8.05%)		Total: 9 (1.25%)	
27.	Deenen et al. (2012)	2012	Advanced solid malignancies						
			A: Everolimus 10 mg/day + capecitabine 500 mg/m^2	A: 4	A: 1 (25%)	A: 1 (25%)		A: 0	
			B: Everolimus 10 mg/day+capecitabine 650 mg/m^2	B: 5	B: 2 (40%)	B: 2 (40%)		B: 0	
			C: Everolimus 10 mg/day+capecitabine 800 mg/m^2	C: 3	C: 1 (33.3%)	C: 1 (33.3%)		C: 0	
			D: Everolimus 10 mg/day+capecitabine 1,000 mg/m^2	D: 6	D: 5 (83.3%)	D: 5 (83.3%)		D: 0	
				Total: 18	Total: 9 (50%)	Total: 9 (50%)			
28.	Ito et al. (2012)	2012	Advanced pancreatic neuroendocrine tumors						
			A: Everolimus 10 mg/daily Japanese pop	A: 23	A: 17 (74%)	A: 17 (74%)		A: 0	
			B: Placebo Japanese pop	B.17	B: 4 (24%)	B: 4 (24%)		B: 0	
			C: Everolimus 10 mg/daily overall pop	C: 204	C: 131 (64%)	C: 117 (57%)		C: 14 (7%)	
			D: Placebo overall pop	D: 203	D: 34 (17%)	D: 34 (17%)		D: 0	
29.	Oh et al. (2012)	2012	Non-functioning neuroendocrine tumors or pheochromocytomas/paragangliomas						
			A: Everolimus 10 mg/daily	A: 34	A: 6 (17.6%)	A: 4 (11.7%)		A: 2 (5.9%)	

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
30.	Huober et al. (2013)	2013	Breast cancer						
			A: Paclitaxel	A: 198	A: 106 (54.1%)	A: 101 (51.5%)		A: 5 (2.6%)	
			B: Paclitaxel + everolimus	B: 197	B: 131 (66.8%)	B: 117 (59.7%)		B: 14 (7.1%)	
31.	Franz et al. (2013)	2013	Subependymal giant cell astrocytomas associated with tuberous sclerosis complex						
			A: Everolimus	A: 78	A: 24 (31%)	A: 18 (23%)		A: 6 (8%)	
			B: Placebo	B: 39	B: 8 (21%)	B: 7 (18%)		B: 1 (3%)	
32.	Ohtsu et al. (2013)	2013	Previously treated advanced gastric cancer						
			A: Everolimus + BSC	A: 437	A: 174 (40%)	A: 154 (35%)		A: 20 (5%)	
			B: Placebo	B: 215	B: 23 (11%)	B: 23 (11%)		B: 0 (0)	
33.	Bissler et al. (2013)	2013	Angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2)						
			A: Everolimus	A: 79	A: 38 (48%)	A: 37 (47%)		A: 1 (1%)	A: 0
			B: Placebo	B: 39	B: 3 (8%)	B: 0		B: 3 (8%)	B: 0
34.	Maass et al. (2013)	2013	Breast cancer patients with bone metastases only						
			A: Everolimus	A: 18	A: 4 (22%)	A: 4 (22%)		A: 0	
			B: Placebo	B: 21	B: 4 (18%)	B: 3 (14%)		B: 1 (4.8%)	
35.	Castellano et al. (2013)[a]	2013	Neuroendocrine solid tumors						
			A: Everolimus + octreotide LAR	A: 19	A: 11 (57.9%)	Not reported		Not reported	
			B: Placebo + octreotide LAR	B: 20	B: 0				
36.	Yardley et al. (2013)	2013	HR + breast cancer						
			A: Everolimus + exemestane	A: 485	A: 286 (59%)	A: 140 (29%)	A: 106 (22%)	A: 39 (8%)	A: 0
			B: Placebo + exemestane	B: 239	B: 28 (12%)	B: 21 (9%)	B: 4 (2%)	B: 2 (<1%)	B: 0
37.	Chinnaiyan et al. (2013)[b]	2013	Glioblastoma						
			A: Everolimus 2.5 mg/ day + radiotherapy + temozolomide	A: 8	A: 0	Not reported	Not reported	A: 0	A: 0
			B: Everolimus 5 mg/ day + radiotherapy + temozolomide	B: 9	B: 0	Not reported	Not reported	B: 0	B: 0
			C: Everolimus 10 mg/ day + radiotherapy+ temozolomide	C: 8	C: 1	Not reported	Not reported	C: 1	C: 0
				Total: 25	Total: 1 (4%)[c]				
38.	Fazio et al. (2013)	2013	Advanced lung neuroendocrine tumors						
			A: Everolimus + octreotide LAR	A: 33	A: 23 (69.7%)	A: 20 (60.6%)		A: 3 (9.1%)	
			B: Placebo + octreotide LAR	B: 11				B: 0 (0%)	

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
39.	Franz et al. (2013)	2013	Subependymal giant cell astrocytomas associated with tuberous sclerosis complex						
			A: Everolimus	A: 78	A: 24 (31%)	A: 18 (23%)		A: 6 (8%)	
			B: Placebo	B: 39	B: 8 (21%)	B: 7 (18%)		B: 1 (3%)	
40.	Fury et al. (2013)	2013	Head and neck cancer		Oral pain				
			A: Everolimus 5 mg/day + radiation + weekly cisplatin	A: 13	A: 10 (77%)	A: 6 (60%)		A: 4 (31%)	
41.	Gadgeel et al. (2013)	2013	Advanced cancer						
			A: Lapatinib + everolimus	A: 54	A: 14 (26%)	A: 7 (13%)	A: 6 (11.1%)	A: 1 (1.85%)	A: 0
42.	Hainsworth et al. (2013)[d]	2013	Advanced clear cell renal carcinoma						
			A: Everolimus + sorafenib	A: 75	A: 10 (14%)[e]	Not reported	A: 8 (11%)	A: 2 (3%)	A: 0/0
43.	Hurvitz et al. (2013)	2013	HER-2 overexpressing advanced breast cancer						
			A: Everolimus + trastuzumab + paclitaxel	A: 55	A: 42 (76.36%)	A: 13 (23.6%)	A: 18 (32.7%)	A: 11 (20.0%)	A: 0
44.	Krueger et al. (2013)	2013	Subependymal giant cell astrocytoma in tuberous sclerosis complex						
			A: Everolimus starting dose 3 mg/day	A: 28	A: 22 (78.6%)	A: 21 (75.0%)		A: 1 (3.6%)	
			B: Everolimus extension phase	B: 28	B: 24 (85.7%)	B: 22 (78.6%)		B: 2 (7.1%)	
45.	Kumano, Miyake, Harada, and Fujisawa (2013)	2013	Metastatic renal cell carcinoma						
			A: Everolimus	A: 57	A: 17 (29.8%)	A: 14 (24.5%)		A: 3 (5.3%)	
			B: Temsirolimus	B: 26	B: 8 (30.8%)	B: 8 (30.8%)		B: 0	
46.	Nozawa et al. (2013)	2013	Advanced renal cell carcinoma						
			A: Everolimus	A: 180	A: 79 (44%)	A: 73 (41%)		A: 6 (3%)	A: 0
47.	Pritchard et al. (2013)	2013	HER-2-negative hormone receptor-positive advanced breast cancer						
			A: Everolimus + exemestane <70 age	A: 364	A: 225 (62%)	A: 196 (54%)		A: 29 (8%)	
			B: Placebo + exemestane <70 age	B: 196	B: 25 (13%)	B: 23 (12%)		B: 2 (1%)	
			C: Everolimus + exemestane >70 age	C: 121	C: 59 (49%)	C: 50 (41%)		C: 9 (8%)	
			D: Placebo + exemestane >70 age	D: 43	D: 2 (5%)	D: 2 (5%)		D: 0	
48.	Sun et al. (2013)	2013	Small-cell lung cancer						
			A: Everolimus 2.5 mg once daily + paclitaxel	A: 6	A: 2	A: 2 (33.3%)		A: 0	
			B: Everolimus 5 mg once daily + paclitaxel	B: 11	B: 5	B: 5 (45.45%)		B: 0	
			C:Everolimus 10 mg once daily+paclitaxel	C: 3	C: 1	C: 1 (33.3%)		C: 0	
				Total: 20	Total: 8	Total: 8		Total: 0	

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
49.	van den Eertwegh et al. (2013)	2013	Advanced renal cell cancer						
			A: Everolimus < 3 months	A: 626	A: 57 (9.1%)	A: 25 (4%)		A: 32 (5.1%)	
			B: Everolimus > 3 < 6 months	B: 395	B: 46 (11.6%)	B: 22 (5.5%)		B: 24 (6.1%)	
			C: Everolimus > 6 months < 1 year	C: 294	C: 28 (9.5%)	C: 15 (5.1%)		C: 13 (4.4%)	
			D: Everolimus >1 year	D: 52	D: 7 (13.5%)	D: 4 (7.7%)		D: 3 (5.8%)	
50.	Yoo et al. (2013)	2013	Metastatic or recurrent bone and soft tissue sarcoma						
			A: Everolimus 10 mg orally once daily	A: 41	A: 16 (39%)	A: 8 (20%)	A: 5 (12%)	A: 3 (7%)	A: 0 (0%)
51.	Lee et al. (2013)	2013	Refractory gastric cancer						
			A: Capecitabine 650 mg/m^2 twice/ daily + everolimus 5 mg twice daily	A: 45	A: 26 (57.7%)	A: 11 (24.4%)	A: 12 (26.7%)	A: 3 (6.7%)	A: 0 (0)
52.	Zhu et al. (2014)	2014	Advanced hepatocellular carcinoma						
			A: Everolimus	A: 361	A: 143 (39.4%)	A: 133 (36.6%)		A: 10 (2.8%)	
			B: Placebo	B: 182	B: 9 (4.9%)	B: 8 (4.4%)		B: 1 (0.5%)	
53.	Andre et al. (2014)	2014	Trastuzumab-resistant, HER2-positive, advanced breast cancer						
			A: Daily everolimus + weekly trastuzumab and vinorelbine	A: 280	A: 179 (63.9%)	A: 138 (49%)		A: 37 (13%)	A: 4 (1%)
			B: Placebo + trastuzumab and vinorelbine	B: 282	B: 74 (26%)	B: 74 (26%)		B: 0 (0)	B: 0/0
54.	Bajetta et al. (2014)	2014	Neuroendocrine tumors						
			A: Everolimus 10 mg/day + octreotide	50	A: 31 (62%)	A: 26 (52%)		A: 4 (8%)	A: 1 (2%)
55.	Ciunci et al. (2014)[d]	2014	Advanced cancer						
			A: Everolimus 30 mg + cetuximab 250 mg/m^2	A: 6	A: 1 (16.6%)	Not reported	A: 1 (16.6%)	A: 0	
			B: Everolimus 50 mg + cetuximab 250 mg/m^2	B: 7	B: 1 (14.28%)	Not reported	B: 1 (14.28%)	B: 0	
			C: Everolimus 70 mg + cetuximab 250 mg/m^2	C: 16	C: 2 (12.5%)	Not reported	C: 2 (12.5%)	C: 0	
				Total: 29	Total: 4 (13.7%)[e]		Total: 4 (13.7%)	Total: 0	
56.	Conconi et al. (2014)	2014	Relapsed/refractory marginal zone B-cell lymphoma						
			A: Everolimus	A: 30	A: 23 (76.6%)	A: 11 (36.6%)	A: 8 (26.6%)	A: 3 (10%)	A: 1 (3.33%)
57.	Panzuto et al. (2014)	2014	Neuroendocrine advanced tumors						
			A: Everolimus	A: 169	A: 37 (21.9%)	A: 33 (19.6%)		A: 4 (2.3%)	
58.	Jeng et al. (2014)[a]	2014	Early stage of living donor liver transplantation						
			A: Everolimus	A: 43	A: 15 (34.8%)	Not reported		Not reported	Not reported

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
59.	Kim et al. (2014)	2014	Progressive unresectable adenoid cystic carcinoma						
			A: Everolimus 10 mg/daily	A: 34	A: 27 (79.4%)	A: 26 (76.5%)		A: 1 (2.9%)	
60.	Motzer et al. (2014)	2014	Metastatic renal cell carcinoma						
			A: Everolimus first-line therapy	A: 238	A: 126 (53%)	A: 112 (47%)		A: 14 (6%)	A: 0
			B: Sunitinib first-line therapy	B: 231	B: 131 (57%)	B: 122 (53%)		B: 9 (4%)	B: 0
			C: Everolimus second line	C: 99	C: 24 (25%)	C: 23 (24%)		C: 1 (1%)	C: 0
			D: Sunitinib second line	D: 108	D: 30 (28%)	D: 27 (25%)		D: 3 (3%)	D: 0
61.	Park et al. (2014)	2014	Metastatic renal cell carcinoma						
			A: Everolimus 10 mg once daily	A: 100	A: 42 (44%)	A: 46 (38%)		A: 6 (6%)	
62.	Rugo et al. (2014)	2014	Postmenopausal HER-positive breast cancer						
			A: Everolimus + exemestane	A: 482	A: 39 (2.7%)	A: 26 (1.9%)		A: 13 (0.8%)	
			B: Placebo + exemestane	B: 238	B: 2 (0.4%)	B: 2 (0.4%)			
63.	Yao et al. (2014)	2014	Advanced pancreatic neuroendocrine tumors						
			A: Everolimus 10 mg/day orally	A: 44	A: 30 (68%)	A: 19 (43%)		A: 11 (25%)	
			B: Placebo	B: 35	B: 3 (9%)	B: 3 (9%)		B: 0	
64.	Noguchi et al. (2014)	2014	HER-2-negative hormone receptor-positive breast cancer						
			A: Asian population everolimus + exemestane	A: 98	A: 77 (78.5%)	A: 42 (43%)	A: 28 (29%)	A: 7 (8%)	A: 0
			B: Asian population placebo + exemestane	B: 45	B: 6 (13.3%)	B: 5 (13%)	B: 1 (2%)	B: 0%	B: 0
			C: Non-Asian everolimus + exemestane	C: 387	C: 208 (53.7%)	C: 96 (25%)	C: 81 (21%)	C: 31 (8%)	C: 0
			D: Non-Asian placebo + exemestane	D: 194	D: 20 (10.3%)	D: 15 (8%)	D: 3 (2%)	D: 2 (1%)	D: 0
65.	Besse et al. (2014)	2014	Non-small-cell lung cancer						
			A: Everolimus 5 mg/day + erlotinib 150 mg/day	A: 66	A: 48 (72.7%)	A: 11 (16.7%)	A: 16 (24.2%)	A: 21 (31.8%)	A: 0
			B: Everolimus 150 mg/day	B: 65	B: 15 (23.1%)	B: 11 (16.9%)	B: 4 (6.2%)	B: 0	B: 0
66.	Albiges et al. (2015)	2015	Metastatic renal cell carcinoma						
			A: Everolimus	A: 632	A: 157 (25%)	A: 132 (21%)		A: 25 (4%)	
			B: Second-line everolimus	B: 493	B: 134 (27%)	B: 111 (22%)		B: 23 (5%)	
67.	Bainbridge, Larbi, and Middleton (2015)	2015	Neuroendocrine tumors	15	7 (46.7%)	A: 6 (40%)		1 (6.7%)	
			A: Everolimus 10 mg once daily						
68.	Chocteau-Bouju et al. (2015)	2015	Advanced ER+HER2− breast cancer						
			A: Everolimus + endocrine therapy	A: 123	A: 70 (56.9%)	A: 84 (68.3%)	A: 29 (23.6%)	A: 10 (8.1%)	

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
69.	Daver et al. (2015)	2015	Relapsed refractory acute lymphoblastic leukemia						
			A: Everolimus 5 mg/day + HyperCVAD	Total: 24	A: 10 (42%)	A: 6 (43%)		A: 4 (40%)	
			B: Everolimus 10 mg/day + HyperCVAD		B: 3 (13%)	B: 4 (40%)		B: 3 (30%)	
70.	Franz et al. (2015)[a]	2015	Subependymal giant cell astrocytoma						
			A: Everolimus <12 months	A: 28	A: 19 (67.9%)	Not reported	Not reported	Not reported	
			B: Everolimus 13–24 months	B: 27	B: 16 (59.3%)				
			C: Everolimus 25–36 months	C: 25	C: 11 (44.0%)				
			D: Everolimus 37–48 months	D: 24	D: 6 (25.0%)				
			E: Everolimus 49–60 months	E: 24	E: 10 (41.7%)				
			F: Everolimus >60 months	F: 24	F: 5 (20.8%)				
				Total: 152	Total: 67 (44.97%)				
71.	Goldberg et al. (2015)[a]	2015	Lymphangioleiomyomatosis						
			A: Everolimus	A: 24	A: 18 (75%)	Not reported	Not reported	Not reported	
72.	Hurvitz et al. (2015)	2015	HER-2-positive advanced breast cancer						
			A: Everolimus 10 mg/ daily + trastuzumab + paclitaxel	A: 472	A: 314 (66.52%)	A: 255 (54%)		A: 59 (13%)	A: 0
			B: Placebo + trastuzumab + paclitaxel	B: 238		B: 74 (31%)		B: 3 (1%)	B: 0
73.	Ju, Hu, Sun, Wang, and Jiao (2015)	2015	Advanced non-small-cell lung cancer						
			A: Everolimus 5–10 mg/day	A: 22	A: 4 (18.1%)	A: 4 (18.1)		A: 0	
74.	Kordes et al. (2015)	2015	Advanced adenocarcinoma of pancreas						
			A: Capecitabine 1,000 mg/m^2 + everolimus 10 mg/day	A: 31	A: 19 (61.2%)	A: 18 (58%) (including aphthous ulcers and stomatitis)		A: 1 (3%)	
75.	Nozawa et al. (2015)	2015	Advanced renal cell carcinoma						
			A: Everolimus	A: 123	A: 69 (56.1%)	A: 65 (52.8%)		A: 4 (3.3%)	
			B: Temsirolimus	B: 73	B: 22 (30.1%)	B: 20 (27.4)		B: 2 (2.7%)	

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
76.	Tolcher et al. (2015)[a]	2015	Advanced solid tumors						
			A: Trametinib 0.5 mg once daily + everolimus 5 mg	A: 6	A: 1 (17%)	Not reported	Not reported	Not reported	
			B: Trametinib 1 mg + everolimus 5 mg	B: 6	B: 2 (33%)				
			C: Trametinib 1 mg + everolimus 5 mg	C: 4	C: 1 (25%)				
			D: Trametinib 1 mg + everolimus 7.5 mg	D: 4	D: 0				
			E: Trametinib 1.5 mg + everolimus 5 mg	E: 4	E: 1(25%)				
			F: Trametinib 1.5 mg + everolimus 7.5 mg	F: 6	F: 2 (33%)				
			G: Trametinib 2 mg + everolimus 5 mg	G: 9	G: 4 (44%)				
			H: Trametinib 2 mg + everolimus 5 mg once daily for 5 days	H: 12	H: 3 (25%)				
			I: Trametinib 2 mg + everolimus 5 mg for 7 days followed by 7 days off	I: 12	I: 3 (25%)				
			L: Trametinib 2 mg + everolimus 5 mg 3 times weekly	L: 4	L: 0				
			M: Trametinib 2 mg + everolimus 7.5 mg on three times weekly						
				Total: 67	Total: 17 (25%)				
77.	Trelinska et al. (2015)	2015	Tuberous sclerosis complex						
			A: Everolimus	A: 18	A: 7 (39%)	A: 7 (39%)		A: 0	A: 0
78.	Lombard-Bohas et al. (2015)	2015	Pancreatic neuroendocrine tumors						
			A: Prior chemotherapy use everolimus 10 mg/day	A: 104	A: 62 (59.6%)	A: 55 (52.9%)		A: 7 (6.7%)	
			B: Prior chemotherapy use placebo	B: 102	B: 17 (16.7%)	B: 17 (16.7%)		B: 0	
			C: Chemonaive everolimus 10 mg/day	C: 100	C: 69 (69.0%)	C: 62 (62%)		C: 7 (7.0%)	
			D: Chemonaive placebo	D: 101	D: 17 (16.8%) including aphthous ulcers and mouth ulceration	D: 17 (16.8%)		D: 0	

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
79.	Ravaud et al. (2015)	2015	Metastatic renal cell carcinoma						
			A: Bevacizumab 10 mg/kg every 2 weeks + everolimus 10 mg daily	A: 180	A: 113 (62.8%)	A: 94 (52.2%)		A: 18 (10.0%)	A: 1 (0.6%)
			B: Bevacizumab 10 mg/kg every 2 weeks + interferon 9MIU 3 times/week	B: 181	B: 42 (23.2%)	B: 38 (21%)		B: 4 (2.2%)	B: 0 (0.0%)
80.	Chung et al. (2016)	2016	Metastatic gastroesophageal adenocarcinoma						
			A: mFOLFOX6 + everolimus	A: 6	A: 4 (66.6%)	A: 2 (33%)		A: 2 (33%)	
81.	Conteduca et al. (2016)[a]	2016	Metastatic renal cell carcinoma						
			A: Everolimus 10 mg/day	A: 79	A: 20 (25.31%)	Not reported	Not reported	Not reported	Not reported
82.	de Wit et al. (2016)	2016	Thyroid cancer						
			A: Everolimus 10 mg/day	A: 40	A: 17 (42.5%)	A: 12 (30%)	A: 2 (5%)	A: 3 (7.5%)	
83.	Franz et al. (2016)[a]	2016	Tuberous sclerosis complex						
			A: Everolimus <12 months	A: 111	A: 44 (39.6%)	Not reported	Not reported	Not reported	
			B: Everolimus 13–24 months	B: 106	B: 13 (12.3%)				
			C: Everolimus 25–36 months	C: 98	C: 11 (11.2%)				
			D: Everolimus 37–48 months	D: 88	D: 6 (6.8%)				
			E: >48 months	E: 57	E: 5 (8.8%)				
84.	Hatano, Chikaraishi, Inaba, Endo, and Egawa (2016)	2016	Renal angiomyolipoma associated with tuberous sclerosis complex						
			A: Everolimus 10 mg once a day for childhood 5 mg once a day	A: 47	A: 43 (91%)	A: 42 (88.88%)		A: 1 (2.12%)	
85.	Jerusalem et al. (2016)	2016	Hormone receptor-positive HER-2-negative advanced or metastatic breast cancer						
			A: Everolimus + examestane	A: 2,133	A: 1,126 (52.8%)	A: 926 (43.4%)		A: 198 (9.3%)	A: 2 (0.1%)
86.	Jozwiak, Kotulska, Berkowitz, Brechenmacher, and Franz (2016)[a]	2016	Tuberous sclerosis complex associated with subependymal giant cell astrocytoma younger than 3						
			A: Everolimus	A: 18	A: 12 (66.7%)	Not reported	Not reported	Not reported	Not reported
87.	Liu et al. (2016)	2016	Gastroenteropancreatic neuroendocrine tumors						
			A: Everolimus 10 mg/daily	A: 53	A: 19 (35.8%)	A: 18 (34%)		A: 1 (1.8%)	
88.	Oudard et al. (2016)	2016	Metastatic renal cell carcinoma						
			A: Second-line everolimus	A: 162	A: 41 (25.3%)	A: 21 (13.0%)	A: 16 (9.9%)	A: 4 (2.5%)	A: 0/0

(Continues)

TABLE 1 (Continued)

	References	Year	Neoplasia and protocol	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
89.	Pavel et al. (2016)	2016	Advanced neuroendocrine tumors						
			A: Everolimus 10 mg/day pNet	A: 123	A: 29 (23.6%)	A: 23 (18.7%)		A: 6 (4.9%)	A: 0
			B: Everolimus 10 mg/day non-pNET	B: 117	B: 22 (18.8%)	B: 19 (16.2%)		B: 3 (2.6%)	B: 0
90.	Robles et al. (2016)	2016	Renal angiomyolipomas						
			A: Everolimus 10 mg once daily	A: 19	A: 11 (57.9%)	A: 11 (57.9%)	A: 0	A: 0	
91.	Schneider et al. (2016)	2016	Advanced follicular-derived thyroid cancer						
			A: Everolimus 10 mg orally once daily	A: 28	A: 17 (61%)	A: 12 (71%)	A: 2 (12%)	A: 3 (18%)	
92.	Vargo, Berger, Phillips, and Mrozek (2016)[a]	2016	Metastatic breast cancer						
			A: Everolimus + exemestane first cycle	Total: 46	A: 12 (26.1%)	Not reported	Not reported	Not reported	Not reported
			B: Everolimus + exemestane subsequent cycles		B: 2 (4.3%)				
			C: Everolimus + exemestane overall		C: 14 (30.4%)				
93.	Yao, Fazio, et al. (2016)	2016	Advanced non-functional neuroendocrine tumors of the lung or gastrointestinal tract RADIANT-4						
			A: Everolimus 10 mg/day	A: 202	A: 127 (63%)	A: 72 (36%)	A: 37 (18%)	A: 18 (9%)	A: 0
			B: Placebo	B: 98	B: 19 (19%)	B: 17 (17%)	B: 2 (2%)	B: 0	B: 0
94.	Yao, Pavel, et al. (2016)	2016	Advanced pancreatic neuroendocrine tumors						
			A: Everolimus	A: 204	A: 137 (67.2%)	A: 122 (59.8%)		A: 15 (7.4%)	
			B: Placebo	B: 203	B: 36 (17.7%)	B: 36 (17.7%)		B: 0	
			C: Open-label everolimus	C: 225	C: 134 (59.6%)	C: 126 (56%)		C: 8 (3.6%)	
95.	Joly et al. (2017)	2017	Metastatic renal cell carcinoma						
			A: Everolimus	A: 274	A: 117 (42.7%)	A: 48 (17.5%)	A: 46 (16.7%)	A: 23 (8.4%)	
	Total with grade			15,787	3,959 (25.07%)	2,981 (18.88%)		978 (6.19%)	
	Total without grade ([a])			1,228	351 (28.58%)	Not reported	Not reported	Not reported	Not reported
	Total with grade >1 ([b]/[d])			129	15 (11.61%)	Not reported	12	3	0
	Total			17,144	4,325 (25.22%)	2,993 (17.45%)[a]/[b]/[d]		981 (5.72%)[a]	

[a]Awada et al. (2008), O'Donnell et al. (2008), Dalenc et al. (2010), Motzer et al. (2011), Castellano et al. (2013), Jeng et al. (2014), Franz et al. (2015), Goldberg et al., 2015; Tolcher et al. (2015), Conteduca et al. (2016), Franz et al. (2016), Jozwiak et al. (2016), Vargo et al. (2016) did not report the grade of stomatitis.

[b]Chinnaiyan et al. (2013) reported the incidence rates limited to grades 3 and 4 treatment-related toxicities; for this reason, data about cases of stomatitis and stomatitis grades 1 and 2 are lower than real.

[c]Data are concerning only grades 3 and 4.

[d]Hainsworth et al. (2013), Ciunci et al. (2014) reported the incidence rates limited to grades 2, 3, and 4 treatment-related toxicities; for this reason, data about cases of stomatitis and stomatitis grade 1 are lower than real.

[e]Data are concerning only grades 2–4.

TABLE 2 Reports of all papers evaluating temsirolimus and cases of stomatitis

	References	Year	Neoplasia	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
1.	Hudes et al. (2007)	2007	Advanced renal cell carcinoma						
			A: Temsirolimus	A: 208	A: 42 (20%)	A: 40 (19%)		A: 2 (1%)	
			B: Temsirolimus + interferone	B: 208	B: 44 (21%)	B: 34 (16%)		B: 10 (5%)	
			C: Interferone	C: 200	C: (4%)	C: 4%		C: 0	
				Total: 416	Total: 86 (20.65%)	Total: 74 (17.78%)		Total: 12 (2.87%)	
2.	Pandya et al. (2007)[a]	2007	Extensive-stage small-cell lung cancer						
			A: Temsirolimus 25 mg	A: 44	A: 1 (2.72%)[b]	Not reported	Not reported	A: 1 (2.72%)	A: 0
			B: Temsirolimus 250 mg	B: 41	B: 3 (7.31%)[b]			B: 3 (7.31%)	B: 0
3.	Motzer et al. (2007)	2007	Advanced renal cell carcinoma						
			A: Temsirolimus 5 mg + IFN-a &MU	A: 7	A: 3 (43%)	A: 3 (43%)		A: 0	
			B: Temsirolimus 10 mg + IFN-a 6MU	B: 6	B: 4 (67%)	B: 4 (67%)		B: 0	
			C: Temsirolimus 15 mg + IFN-a 6MU	C: 39	C: 27 (69%)	C: 24 (61%)		C: 3 (8%)	
			D: Temsirolimus 20 mg + IFN-a 6MU	D: 6	D: 6 (100%)	D: 6 (100%		D: 0	
			E: Temsirolimus 25 mg + IFN-a 6MU	E: 7	E: 5 (71%)	E: 4 (57%)		E: 1 (14%)	
			F: Temsirolimus 15 mg + IFN-a 9MU	F: 6	F: 6 (100%)	F: 5 (83%)		F: 1 (17%)	
				Total: 71	Total: 51 (72%)	Total: 46 (65%)		Total: 5 (7%)	
4.	Farag et al. (2009)	2009	Relapsed or refractory multiple myeloma						
			A: Temsirolimus 25 mg weekly	A: 16	A: 7 (43.75%)	A: 4 (25%)	A: 2 (12.5%)	A: 1 (6.25%)	A: 0
5.	Gerullis, Bergmann, Maute, Eimer, and Otto (2009)	2009	Advanced renal cell carcinoma						
			A: Temsirolimus 25 mg/ weekly	A: 32	A: 10 (31.3%)	A: 0	A: 10 (31.3%)	A: 0	A: 0
6.	Patel, Senico, Curiel, and Motzer (2009)	2009	Advanced renal cell carcinoma						
			A: Temsirolimus 15 mg daily + sunitinib orally 25 mg once daily	A: 3	A: 1 (33.33%)	A: 1		A: 0	
7.	Fujisaka, Yamada, Yamamoto, Horiike, and Tamura (2010)	2010	Advanced solid tumors						
			A: Temsirolimus 15 mg/m^2	A: 7	A: 5 (71.4%)	A: 5 (71.4%)		A: 0	
			B: Temsirolimus 45 mg/m^2	B: 3	B: 2 (66.6%)	B: 1 (33.3%)		B: 1 (33.3%)	
				Total: 10	Total: 7 (70%)			Total: 1 (10%)	
8.	Smith et al. (2010)	2010	Non-mantle cell non-Hodgkin lymphoma						
			A: Temsirolimus 25 mg/ weekly	A: 89	A: 30 (33.7%)	A: 26 (29.2%)		A: 4 (4.5%)	

(Continues)

drugs is based on the inhibition of the activity of mTORC1 through the binding to FKBP-12 and the formation of a ternary complex with mTOR (Meng & Zheng, 2015). This can restore proper control of the activated PI3K/AKT/mTOR signaling pathway. This class of drugs is typically used for the treatment of solid tumors such as renal cell carcinoma, breast cancer, and pancreatic neuroendocrine tumors and for the treatment of tuberous sclerosis complex (Awada et al., 2008; Boers-Sonderen et al., 2014; Hudes et al., 2009; Krueger et al., 2010; Mita et al., 2013; Motzer et al., 2008; Yao et al., 2011).

TABLE 2 (Continued)

	References	Year	Neoplasia	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
9.	Kwitkowski et al. (2010)	2010	Advanced renal cell carcinoma						
			A: Temsirolimus 25 mg	A: 208	A: 86 (41%)	A: 80 (38%)		A: 6 (3%)	
			B: IFN-ALFA	B: 200	B: 19 (19%) including aphthous ulcers and mouth ulceration and mucositis	B: 19 (19%)		B: 0	
10.	Okuno et al. (2011)	2011	Soft-tissue sarcomas						
			A: Temsirolimus 25 mg	A: 40	A: 27 (67.5%)	A: 19 (48%)	A: 5 (13%)	A: 3 (8%)	A: 0 (0)
11.	Sun et al. (2012)	2012	Advanced renal cell carcinoma						
			A: Temsirolimus 20 mg/m^2 weekly	A: 6	A: 5 (83%)	A: 5 (83%)		A: 0	
			B: Temsirolimus 25 mg flat weekly	B: 76	B: 42 (55%)	B: 38 (50%)		B: 4 (5%)	
					Total: 47 (57%)	Total: 43 (52%)		Total: 4 (5%)	
12.	Wolff et al. (2013)	2013	Estrogen receptor-positive advanced breast cancer						
			A: Letrozole + temsirolimus	A: 550	A: 65 (12%)	A: 59 (11%)		A: 6 (1%)	
			B: Letrozole + placebo	B: 553	B: 13 (2%)	B: 12 (1.5%)		B: 1 (<0.5%)	
13.	Armstrong et al. (2013)[a]	2013	Metastatic prostate cancer						
			A: Temsirolimus 25 mg	A: 11	A: 2[b]	Not reported		A: 2	B: 0
14.	(Diaz-Padilla et al. (2013)	2013	Advanced solid tumors						
			A: RO4929097 10 mg + temsirolimus 25 mg	A: 8	A: 5 (62.5%)	A: 4 (50%)		A: 1 (12.5%)	
			B: RO4929097 20 mg + temsirolimus 25 mg	B: 3	B: 2 (66.6%)	B: 2 (66.6%)		B: 0	
			C: RO4929097 20 mg + temsirolimus 37.5 mg	C: 6	C: 5 (83.3%)	C: 5 (83.3%)		C: 0	
				Total: 17	Total: 12 (71%)	Total: 11 (55%)		Total: 1 (6%)	
15.	Goodwin et al. (2013)	2013	Recurrent or metastatic endometrial cancer						
			A: Temsirolimus	A: 49	A: 23 (46.9%)	A: 14 (28.57%)	A: 8 (16.32%)	A: 1 (2.04%)	
16.	Kumano et al. (2013)	2013	Metastatic renal cell carcinoma						
			A: Everolimus	A: 57	A: 17 (29.8%)	A: 14 (24.5%)		A: 3 (5.3%)	
			B: Temsirolimus	B: 26	B: 8 (30.8%)	B: 8 (30.8%)		B: 0	
				Total: 83	Total: 25 (30.1%)	Total: 22 (26.5%)		Total: 3 (3.6%)	
17.	Rini et al. (2014)	2014	Metastatic renal cell carcinoma						
			A: Temsirolimus + bevacizumab	A: 393	A: 102 (26%)	A: 75 (19%)		A: 27 (7%)	
			B: Interferone alfa + bevacizumab	B: 391	B: 38 (10%)	B: 32 (8%)		B: 6 (2%)	

(Continues)

TABLE 2 (Continued)

	References	Year	Neoplasia	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
18.	Boers-Sonderen et al. (2014)	2014	Breast endometrial and ovarian cancer						
			A: Temsirolimus 10 mg + pegylated liposomal doxorubicin 30 mg/m^2	A: 5	A: 3 (60%)	A: 3 (60%)		A: 0	
			B: Temsirolimus 10 mg + PLD 40 mg/m^2	B: 3	B: 3 (100%)	B: 1 (33.4%)		B: 2 (66.6%)	
			C: Temsirolimus 15 mg + PLD 40 mg/m^2	C: 3	C: 3 (100%)	C: 2 (66.4%)		C: 1 (33.3%)	
			D: Temsirolimus 20 mg + PLD 40 mg/m^2	D: 9	D: 6 (66.6%)	D: 5 (55.5%)		D: 1 (11.1%)	
			E: Temsirolimus 25 mg + PLD 40 mg/m^2	E: 0					
			F: Temsirolimus 25 mg + PLD 50 mg/m^2	F: 0					
				Total: 20	Total: 15	Total: 11		Total: 4	
19.	Gandhi et al. (2014)[a]	2014	Hegf-2 receptor-dependent and other solid tumors						
			A: Neratinib 120 + temsirolimus 15	A: 3	A: 0[b]	Not reported		A: 0	
			B: Neratinib 120 + temsirolimus 25	B: 5	B: 0[b]	Not reported		B: 0	
			C: Neratinib 120 + temsirolimus 50	C: 5	C: 0[b]	Not reported		C: 0	
			D: Neratinib 120 + temsirolimus 75	D: 4	D: 0[b]	Not reported		D: 0	
			E: Neratinib 160 + temsirolimus 15	E: 4	E: 0[b]	Not reported		E: 0	
			F: Neratinib 160 + temsirolimus 25	F: 4	F: 0[b]	Not reported		F: 0	
			G: Neratinib 160 + temsirolimus 50	G: 7	G: 0[b]	Not reported		G: 0	
			H: Neratinib 160 + temsirolimus 75	H: 6	H: 0[b]	Not reported		H: 0	
			I: Neratinib 200 + temsirolimus 15	I: 5	I: 0[b]	Not reported		I: 0	
			L: Neratinib 200 + temsirolimus 25	L: 8	L: 1 (13%)[b]	Not reported		L: 1 (13%)	
			M: Neratinib 200 + temsirolimus 50	M: 5	M: 0[b]	Not reported		M: 0	
			N: Neratinib 240 + temsirolimus 15	N: 4	N: 0[b]	Not reported		N: 0	
				Total: 60	Total: 1 (1.66%)[b]			Total: 1 (1.66%)	
20.	Miyake, Harada, Kumano, and Fujisawa (2014)	2014	Metastatic renal cell carcinoma						
			A: Temsirolimus 25 mg/weekly	A: 55	A: 13 (23.6%)	A: 10 (18.1%)		A: 3 (5.5%)	
21.	Hutson et al. (2014)	2014	Metastatic renal cell carcinoma						
			A: Temsirolimus 25 mg IV once per week	A: 249	A: 54 (22%)	A: 49 (20%)		A: 5 (2%)	
			B: Sorafenib 400 mg orally twice per day	B: 252	B: 18 (7%)	B: 18 (6%)		B: 0 (<1%)	

(Continues)

TABLE 2 (Continued)

	References	Year	Neoplasia	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
22.	Rangwala et al. (2014)	2014	Advanced solid tumors and melanoma						
			A: Hydroxychloroquine 200 mg + temsirolimus	A: 11	A: 4 (36%)	A: 4 (36%)		A: 0	
			B: Hydroxychloroquine 400 mg + temsirolimus	B: 3	B: 1 (33%)	B: 1 (33%)		B: 0	
			C: Hydroxychloroquine 800 mg + temsirolimus	C: 9	C: 4 (44%)	C: 4 (44%)		C: 0	
			D: Hydroxychloroquine 1,200 mg + temsirolimus	D: 16	D: 7 (44%)	D: 7 (44%)		D: 0	
				Total: 39	Total: 16 (41%)	Total: 16 (41%)		Total: 0	
23.	Wang-Gillam et al. (2014)	2014	Refractory solid malignancies						
			A: Pegylated liposomal doxorubicin (30 mg/m^2) every 4 weeks + temsirolimus 20 mg weekly	A: 5	A: 3 (60%)	A: 0	A: 3 (60%)	A: 0	A: 0
			B: Pegylated liposomal doxorubicin (25 mg/m^2) every 4 weeks + temsirolimus 20 mg weekly	B: 6	B: 3 (49.9%)	B: 1 (16.6%)	B: 2 (33.3%)	B: 0	B: 0
			C: Pegylated liposomal doxorubicin (25 mg/m^2) every 4 weeks + temsirolimus 25 mg weekly	C: 12	C: 10 (83.3%)	C: 7 (58.3%)	C: 3 (25%)	C: 0	C: 0
24.	Nozawa et al. (2015)	2015	Advanced renal cell carcinoma						
			A: Everolimus	A: 123	A: 69 (56.1%)	A: 65 (52.8%)		A: 4 (3.3%)	
			B: Temsirolimus	B: 73	B: 22 (30.1%)	B: 20 (27.4)		B: 2 (2.7%)	
25.	Kyriakopoulos et al. (2016)	2016	Advanced solid tumors						
			A: Tivatinib 120–360 mg twice daily + temsirolimus 20 mg IV daily	A: 29	A: 11 (37.8%)	A: 5 (17.2%)	A: 5 (17.2%)	A: 1 (3.4%)	A: 0
26.	Mita et al. (2017)[a]	2017	Advanced solid tumors						
			A: Pimasertib 45 mg + temsirolimus 12.5 mg	A: 4	A: 0[b]	Not reported		A: 0	
			B: Pimasertib 45 mg + temsirolimus 25 mg	B: 23	B: 6 (26.1%)[b]	Not reported		B: 6 (26.1%)	
			C: Pimasertib 75 mg + temsirolimus 25 mg	C: 6	C: 2 (33.3%)[b]	Not reported		C: 2 (33.3%)	
				Total: 33	Total: 8 (24.2%)[b]			Total: 8 (24.2%)	
	Total			2,679	724[a] (27.02%)	623[a] (23.25%)		101 (3.77%)	

[a]Pandya et al. (2007), Armstrong et al. (2013), Gandhi et al. (2014), Mita et al. (2017) reported the incidence rates limited to grades 3 and 4 treatment-related toxicities; for this reason, data about cases of stomatitis and stomatitis grades 1 and 2 are lower than real.
[b]Data are concerning only grade 3 and grade 4.

Results of this analysis of the literature revealed that the rate of incidence of overall stomatitis is higher in patients treated with ridaforolimus (54.76%) compared both to everolimus (25.07%) and temsirolimus (27.02%). Although it was not possible to carry out an accurate analysis of stomatitis by grade, it can be noted that most of the studies included in the review showed an high rate of minor stomatitis (G1–G2) while the onset of severe stomatitis (G3–G4) was relatively rare. Indeed, in patients treated with temsirolimus the rate of incidence of low-grade stomatitis was 23.25% while the rate of incidence of higher grade stomatitis is 3.77%. In patients treated with ridaforolimus, the rate of low-grade stomatitis was 48.90% against a rate of incidence of 5.86% for high-grade stomatitis. These results differ from those reported in

TABLE 3 Reports of all papers evaluating ridaforolimus and cases of stomatitis

	References	Year	Neoplasia	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
1.	Sessa et al. (2010)	2010	Taxane-sensitive solid tumors						
			A: Ridaforolimus 12.5 mg + paclitaxel 80 mg/m^2	A: 8	20 (69%)	A: 4 (50%)		A: 1 (12.5%)	
			B: Ridaforlimus 25 mg + paclitaxel 60 mg/m^2	B: 8		B: 6 (75%)		B: 0	
			C: Ridaforolimus 25 mg + paclitxel 80 mg/m^2	C: 7		C: 6 (86%)		C: 0	
			D: Ridaforolimus 37.5 mg + paclitaxel 60 mg/m^2	D: 6		D: 3 (50%)		D: 0	
				Total: 29		Total: 19 (65.51%)			
2.	Perotti et al. (2010)	2010	Solid tumors						
			A: RIdaforolimus 25 mg+ capecitabine 1,650 mg/m^2	A: 3	A: 2 (66.6%)	A: 2		A: 0	
			B: Ridaforolimus 37.5 + capeciabine 1,650 mg/m^2	B: 8	B: 6 (75%)	B: 6		B: 0	
			C: Ridaforolimus 50 mg + capecitabine 1,650 mg/m^2	C: 4	C: 3 (75%)	C: 3		C: 0	
			D: Ridaforolimus 75 mg + capecitabine 1,650 mg/m^2	D: 6	D: 2 (33.3%)	D: 2		D: 0	
			E: Ridaforolimus 75 mg + capecitabine 1,800 mg/m^2	E: 4	E: 3 (75%)	E: 2 (50%)		E: 1 (25%)	
			F: Ridaforolimus 50 mg + capecitabine 1,800 mg/m^2 collateral	F: 7	F: 6 (85.7%)	F: 5 (14.2%)		F: 0	
				Total: 32	Total: 22 (69%)	Total: 21 (66%)		Total: 1 (3%)	
3.	Chawla et al. (2012)	2012	Advanced bone and soft tissues sarcomas						
			A: Ridaforolimus	A: 212	A: 94 (44.3%)	A: 91 (42.9%)		A: 3 (1.4%)	A: 0/0
4.	Seki et al. (2012)	2012	Advanced solid tumors						
			A: Ridaforolimus 20 mg	A: 7	A: 7 (100%)	A: 6 (100%)		A: 1 (14.2%)	
			B: Ridaforolimus 40 mg	B: 6	B: 6 (100%)	B: 6 (100%)		B: 0	
				Total: 13					
5.	Demetri et al. (2013)	2013	Metastatic sarcoma						
			A: Ridaforolimus	A: 343	A: 267 (77.8%)	A: 230 (67%)		A: 37 (10.8%)	
			B: Placebo	B: 359	B: 88 (22.8%)	B: 86 (22%)		B: 2 (0.8%)	

(Continues)

TABLE 3 (Continued)

	References	Year	Neoplasia	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
6.	Nemunaitis et al. (2013)	2013	Refractory advanced solid tumors						
			A: Ridaforolimus + bevacizumab	A: 17	A: 8 (47%)	A: 7 (41%)		1 (6%)	
7.	Colombo et al. (2013)	2013	Recurrent or persistent endometrial cancer						
			A: Ridaforolimus 12.5 mg/day	A: 45	A: 25 (56%)	A: 21 (47%)		4 (9%)	
8.	Liu et al. (2013)	2013	Advanced solid tumors						
			A: Ridaforolimus	A: 15	A: 12 (80%)	A: 10 (66.7%)		A: 2 (13.3%)	
9.	Meulenbeld et al. (2013)	2013	Asymptomatic metastatic castration resistant prostate cancer						
			A: Ridaforolimus 30 mg/day for 5 consecutive days + bicalutamide 50 mg/day	A: 11	A: 5 (45.4%)	A: 2 (18.2%)	A: 3 (27.2%)	A: 0	A: 0
10.	Mita et al. (2013)	2013	Refractory or advanced solid malignancies						
			A: Ridaforolimus 10 mg	A: 147	A: 35 (23.8%)	A: 21 (14.3%)	A: 13 (8.8%)	A: 1 (0.7%)	A: 0/0
11.	Di Cosimo et al. (2015)	2015	Breast cancer						
			A: Ridaforolimus + dalotuzumab	A: 87	A: 25 (29%)	A: 24 (28%)		A: 1 (1%)	
12.	Gupta et al. (2015)	2015	Advanced malignancies						
			A: Ridaforolimus 10 mg QD × 5 days a week + MK-2206 90 mg/weekly	A: 18	A: 7 (38.9%)	A: 6 (33.3%)		A: 1 (5.6%)	
			B: Ridaforolimus 20 mg QD × 5 day/ week + MK-2206 90 mg weekly	B: 17	B: 12 (70.6%)	B: 9 (53%)		B: 3 (17.6%)	
				Total: 35	Total: 19 (54.3%)	Total: 15 (42.9%)		Total: 4 (11.4%)	
13.	Piha-Paul et al. (2015)	2015	Advanced solid tumors						
			A: Ridaforolimus 20 mg QD 5 days/ week + MK-0752 1,800 mg weekly	A: 19	A: 6 (31.6%)	A: 4 (21.1%)		A: 2 (10.5%)	
			B: Ridaforolimus 30 mg QD 5 days/ week + MK-0752 1,800 mg weekly	B: 9	B: 7 (77.8%)	B: 6 (66.7%)		B: 1 (11.1%)	
				Total: 28	Total: 13 (46.4%)	Total: 10 (35.7%)		Total: 3 (10.7%)	
14.	Seiler et al. (2015)	2015	HER2 + trastuzumab refractory metastatic breast cancer						
			A: Ridaforolimus + trastuzumab	A: 34	A: 20 (58.8%)	A: 15 (44.1%)		A: 5 (14.7%)	

TABLE 3 (Continued)

	References	Year	Neoplasia	No. of cases	Stomatitis %	Stomatitis grade 1%	Stomatitis grade 2%	Stomatitis grade 3%	Stomatitis grade 4%
15.	Frappaz et al. (2016)	2016	Pediatric solid tumors						
			A: Dalotuzumab 900 mg/m^2	A: 11	A: 1 (9.1%)	A: 1 (9.1%)		A: 0	
			B: Dalotuzumab 1,200 mg/m^2	B: 3	B: 0	B: 0		B: 0	
			C: Dalotuzumab 1,500 mg/m^2	C: 6	C: 0	C: 0		C: 0	
			D: Dalotuzumab 900 mg/m^2 + ridaforolimus 28 mg/m^2	D: 4	D: 4 (100%)	D: 4 (100%)		D: 0	
				Total: 24	Total: 5 (20%–83%)	Total: 5 (20%–83%)			
16.	Pearson et al. (2016)	2016	Advanced solid tumors in pediatric patients						
			A: Ridaforolimus 22 mg/m^2	A: 4	A: 2 (50%)	A: 2 (50%)		A: 0	
			B: Ridaforolimus 28 mg/m^2	B: 3	B: 3 (100%)	B: 3 (100%)		B: 0	
			C: Ridaforolimus 33 mg/m^2	C: 13	C: 10 (77%)	C: 10 (77%)		C: 0	
				Total: 20	Total: 15 (75%)	Total: 15 (75%)			
	Total			1,092 (100%)	598 (54.76%)	534 (48.90%)		64 (5.86%)	

literature about mucositis caused by conventional chemotherapy in which mucositis is often severe and the most debilitating effect for patients (Borbasi et al., 2002). Despite results show that stomatitis caused by mTOR inhibitors are often mild and self-limiting, different attempts to manage mIAS have been reported in the literature. The treatments more frequently used are Magic Mouthwash composed of lidocaine gel 2% × 30 g, doxycycline suspension 50 mg/5ml × 60 ml, and sucralfate oral suspension 1,000 mg/5 ml dissolved in sodium chloride 0.9% × 2,000 ml used for 3–15 days (Kalogirou, Tosios, Piperi, & Sklavounou, 2015), a sodium bicarbonate-based mouthwash combined with oral fluconazole (Ferte et al., 2011) or a combination of dexamethasone solution 0.5 mg/ml and miconazole 2% gel (Nicolatou-Galitis, Nikolaidi, Athanassiadis, Papadopoulou, & Sonis, 2013). An alternative treatment is that based on a combination of topical anesthetics, a Magic Mouthwash (composed of lidocaine, aluminum hydroxide, magnesium hydroxide, dimethicone suspension, diphenhydramine, equal parts) clobetasol gel 0.05%, dexamethasone 0.1 mg/ml, triamcinolone paste, intralesional triamcinolone, systemic prednisone (1 mg/kg for 7 days) (de Oliveira et al., 2011). However, literature on treatment of mIAS is poor, and management of mIAS is still largely based on assessment and education of patients on oral hygiene measures, diet modifications, and pain management (Boers-Doets et al., 2013; Ji, Aboalela, & Villa, 2016). Until today, it cannot be determined which lesions will be self-limiting and which can determine a poor quality of life, leading to complications such as malnutrition and dose reduction in medically necessary treatment. Therefore, it would be useful to increase research about this kind of oral toxicity that still represents a dose-limiting effect of this kind of cancer therapy.

CONFLICT OF INTERESTS

None to declare.

AUTHORS' CONTRIBUTION

Lo Muzio concepted the study and elaborated the discussion, Arena and Troiano collected papers and performed the study, Villa revised paper.

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