

Stomatitis And Everolimus: A Review Of Current Literature On 8,201 Patients

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Background: Oral toxicities, such as mucositis and stomatitis, are some of the most significant and unavoidable side effects associated with anticancer therapies. In past decades, research has focused on newer targeted agents with the aim of decreasing the rates of side effects on healthy cells. Unfortunately, even targeted anticancer therapies show significant rates of toxicity on healthy tissue. mTOR inhibitors display some adverse events, such as hyperglycemia, hyperlipidemia, hypophosphatemia, hematologic toxicities, and mucocutaneous eruption, but the most important are still stomatitis and skin rash, which are often dose-limiting side effects.

Aim: This review was performed to answer the question “What is the incidence of stomatitis in patients treated with everolimus?”

Methods: We conducted a systematic search on the PubMed and Medline online databases using a combination of MESH terms and free text: “everolimus” (MESH) AND “side effects” OR “toxicities” OR “adverse events”. Only studies fulfilling the following inclusion criteria were considered eligible for inclusion in this study: performed on human subjects, reporting on the use of everolimus (even if in combination with other drugs or ionizing radiation), written in the English language, and reporting the incidence of side effects.

Results: The analysis of literature revealed that the overall incidence of stomatitis after treatment with everolimus was 42.6% (3,493) and that of stomatitis grade G1/2 84.02% (2,935), while G3/4 was 15.97% (558).

Conclusion: Results of the analysis showed that the incidence of stomatitis of grade 1 or 2 is higher than grade 3 or 4. However, it must be taken into account that it is not possible to say if side effects are entirely due to everolimus therapy or combinations with other drugs.

Keywords: stomatitis, everolimus, mucositis, targeted therapy, oral medicine, oral pathology

Introduction

Conventional anticancer therapy does not distinguish between normal and cancer cells. The damage inflicted on normal tissue have thus hampered this therapy.¹ The introduction of targeted-therapy molecules targeting specific enzymes, growth-factor receptors, and signal transducers has lowered the incidence of side effects,² significantly influencing patient quality of life and survival rates.² mTOR is a therapeutic target for both solid and hematologic malignancies. It is part of a pathway that regulates protein biosynthesis, cell growth, and cell-cycle progression. Moreover, mTOR is the downstream effector of the PI3K–Akt–mTOR pathway, which regulates cell growth and metabolism and is involved in multiple processes.^{1,3–5}

Rapamycin and its analogues form the first generation of mTOR inhibitors. The action of these molecules is targeting a 289 kDa serine/threonine-protein kinase that

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is a component of the big family of PI3Ks. Rapamycin and its analogues work by inhibiting the activity of mTORC1 through binding to FKBP12 and the establishment of a ternary complex with mTOR.⁶ Actually, there are three available mTOR inhibitors: everolimus, temsirolimus, and ridaforolimus. Everolimus is currently used for the treatment of advanced hormone receptor-positive HER2-negative breast cancer together with exemestane, renal-cell carcinoma after failure of therapies based on sunitinib or sorafenib, progressive neuroendocrine tumors of pancreatic origin, in combination with exemestane, and subependymal giant-cell astrocytoma.

These drugs have a different spectrum of side effects compared to conventional chemotherapy. Common side effects are anemia, fatigue, hyperglycemia, hyperlipidemia, stomatitis, rash, and thrombocytopenia.^{5,7} The terms “oral mucositis” and “stomatitis” are both used to describe inflammation and ulceration of the oral mucosal lining due to chemotherapy or ionizing radiation. However, stomatitis associated with mTOR inhibitors should be considered a separate entity this often being designated as mTOR inhibitor-associated stomatitis (mIAS).^{8,9} Mouth lesions present as superficial, ovoid, well-demarcated singular or multiple ulcers with a grayish white pseudomembrane. Their size often does not exceed 0.5 cm in diameter. Lesions typically involve the nonkeratinized mucosa, like the inner aspect of the lips, the ventral and lateral surfaces of the tongue, and the soft palate. Ulcers generally develop in 5 days and usually heal spontaneously in 1 week, most frequently in the first cycle of mTOR-inhibitor therapy.¹⁰

Methods

This review was performed to answer to the question “Which is the rate of incidence of stomatitis in patients treated with everolimus?” A systematic search on the online databases PubMed and Medline was conducted using a combination of MESH terms and free-text words: “everolimus” (MESH) AND “side effects” OR “toxicities” OR “adverse events”. The authors included in this study only reports that fulfilled certain criteria: performed on human subjects, everolimus alone or in combination with other drugs/ionizing radiation, written in the English language, and providing incidence of side effects. No restrictions were applied on year of publication. Reviews, case reports, and studies in vitro or performed on animal models were excluded. Information collected comprised name of first author, year, title, number of patients enrolled, and number and grade of events recorded. In addition, data

were independently extracted by two authors (CA and LLM) and checked in a joint session.

Results

Our literature search yielded 1,019 potentially relevant studies. After elimination of duplicates, titles and abstracts of 912 potentially relevant studies were screened. Of these, 731 were not considered because they did not meet the inclusion criteria. A total of 181 studies were read in full text. Of these, only 100 reported on stomatitis or oral mucositis, and 30 were excluded due to lack of data (Figure 1). Results showed that the overall incidence of stomatitis after treatment with everolimus was 42.6% (3,493), stomatitis grade G12 84.02% (2,935), and G34 15.97% (558, Table 1).

Discussion

Targeted therapy includes those drugs that selectively inhibit a target that is mutated in malignant tissue, aiming to achieve preferential localization in the region of disease and thus an increase in local concentration. In particular, mTOR inhibitors work as signal-transduction inhibitors. Rapamycin, also named sirolimus, was the first mTOR inhibitor approved. It is an antiungal agent produced by *Streptomyces hygroscopicus* with immunosuppressive properties.¹¹ However, sirolimus has been shown to have

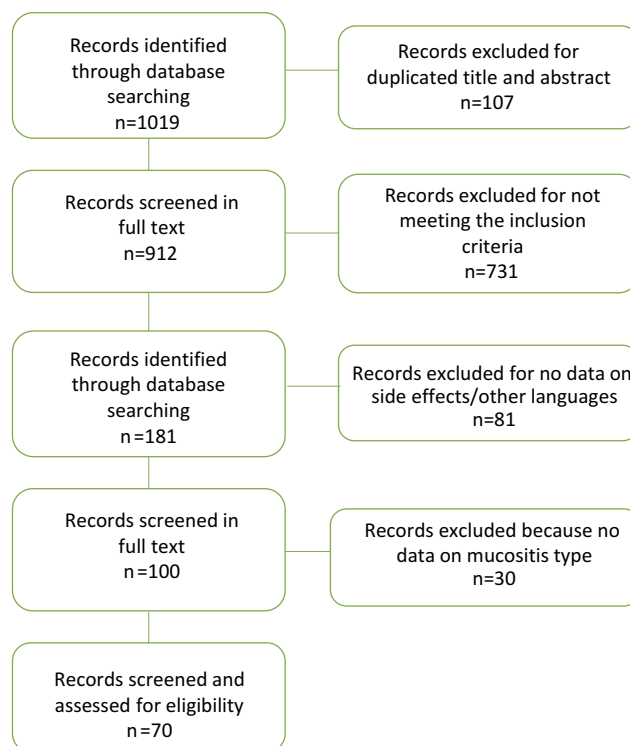


Figure 1 Flowchart showing the process of paper selection used in this review.

Table 1 Papers About Everolimus And Stomatitis

Study	Year	Title	Therapy	Patients, n	Stomatitis, n (%)	G1/2, n (%)	G3/4, n (%)
Amato et al ²⁷	2009	A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer	Everolimus at a dose of 10 mg daily orally without interruption (28-day cycle), with dose modifications for toxicity (graded according to National Cancer Institute Common Toxicity Criteria version 3.0). Patients were evaluated every two cycles (8 weeks) using Response Evaluation Criteria in Solid Tumors (RECIST)	39	12 (30.8)	G1 4 (10.3) G2 8 (20.5)	
Andre et al ²⁸	2014	Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial	In this randomised, double-blind, placebo-controlled, phase III trial, authors recruited women with HER2-positive, trastuzumab-resistant advanced breast carcinoma who had previously received taxane therapy. Eligible patients were randomly assigned (1:1) using a central patient-screening and -randomization system to daily everolimus (5 mg/day) plus weekly trastuzumab (2 mg/kg) and vinorelbine (25 mg/m ²) or to placebo plus trastuzumab plus vinorelbine, in 3-week cycles, stratified by previous lapatinib use	280	175 (62)	138 (49)	G3 37 (13)
Angelousi et al ²⁹	2017	Sequential everolimus and sunitinib treatment in pancreatic metastatic well-differentiated neuroendocrine tumours resistant to prior treatments	A: 20 1st-line everolimus B: 11 2nd-line everolimus	A: 20 B: 11	A: 2 (10) B: 1 (9)	A: 2 (10) B: 1 (9)	
Armstrong et al ³⁰	2016	Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN — a multicentre, open-label, randomised phase 2 trial)	Everolimus orally at 10 mg once daily	52	27 (48)	22 (39)	G3 5 (9)
Bajetta et al ³¹	2014	Everolimus in combination with octreotide long-acting repeatable in a first-line setting for patients with neuroendocrine tumors	Treatment-naïve patients with advanced well-differentiated NETs of gastroenteropancreatic tract and lung origin received everolimus 10 mg daily in combination with octreotide LAR 30 mg every 28 days	50	31	26 (52)	G3 4 (8) G4 1 (2)

(Continued)

Table 1 (Continued).

Study	Year	Title	Therapy	Patients, n	Stomatitis, n (%)	GI/2, n (%)	G3/4, n (%)
Baselga et al ³²	2012	Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer	Double-blind phase III study, patients randomly assigned to treatment with oral everolimus or matching placebo (10 mg daily) in conjunction with exemestane (25 mg daily)	482	56 (11.61)	48 (9.95)	G3 8
Baselga et al ³³	2009	Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer	270 postmenopausal women with operable ER-positive breast cancer were randomly assigned to receive 4 months of neoadjuvant treatment with letrozole (2.5 mg/day) and either everolimus (10 mg/day) or placebo	137	50 (36.5)	47 (34.3)	3 (2.2)
Bergmann et al ³⁴	2015	Everolimus in metastatic renal cell carcinoma after failure of initial anti-VEGF therapy: final results of a noninterventional study	Patients received everolimus 10 mg once daily until disease progression or unacceptable	334	22 (7)	18 (81)	4 (18)
Besse et al ³⁵	2014	Phase II study of everolimus-erlotinib in previously treated patients with advanced non-small-cell lung cancer	Everolimus 5 mg/day + erlotinib 150 mg/day	66	48 (72.6)	G1 11 (16.7) G2 16 (24.2)	G3 21 (31.8)
Carbone et al ³⁶	2009	Safety and pharmacokinetics of paclitaxel and the oral mTOR inhibitor everolimus in advanced solid tumours	Everolimus was dose-escalated from 15 to 30 mg and administered with paclitaxel 80 mg/m ² on days 1, 8, and 15 every 28 days	16	6 (37.5)	5 (31.25)	G3 1 (6.25)
Castellano et al ³⁷	2013	Everolimus plus octreotide long-acting repeatable in patients with colorectal neuroendocrine tumors: a subgroup analysis of the phase III RADIANT-2 study	Everolimus plus octreotide	19	11 (57.9)		
Chan et al ³⁸	2013	A prospective, phase 1/2 study of everolimus and temozolomide in patients with advanced pancreatic neuroendocrine tumor	Patients treated with temozolomide 150 mg/m ² per day on days 1–7 and 15–21 in combination with everolimus daily in each 28-day cycle. In cohort 1, temozolomide was administered together with everolimus at 5 mg daily. Following demonstration of safety in this cohort, subsequent patients in cohort 2 were treated with temozolomide plus everolimus at 10 mg daily	43	27	G1 22 (51) G2 4 (9)	G3 1 (2)
Choueiri et al ³⁹	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma	Everolimus at a dose of 10 mg daily	322	77 (24)	70 (21.7)	7 (2.2)

Chow et al ⁴⁰	2016	A phase 2 clinical trial of everolimus plus bicalutamide for castration-resistant prostate cancer	Oral bicalutamide 50 mg and oral everolimus 10 mg, both once daily, with a cycle defined as 4 weeks	24	14 (58.3)	10 (41.6)	G3 4
Chung et al ⁴¹	2016	Phase Ib trial of mFOLFOX6 and everolimus (NSC-733,504) in patients with metastatic gastroesophageal adenocarcinoma	Six patients were accrued to the first dose level of 2.5 mg everolimus daily with mFOLFOX6	A: 6	4 (66)	G1 2 (33)	G3 2 (33)
Ciruelos et al ⁴²	2017	Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer: results of phase IIIb BALLET trial in Spain	Eligible patients started study treatment on day 1 with daily doses of everolimus (2/5/9 mg or 1/9/10 mg) and exemestane (25 mg) and continued until disease progression or unacceptable toxicity	429	272 (63)	232 (54)	G3 40 (9)
Ciunci et al ⁴³	2014	Phase I and pharmacodynamic trial of everolimus in combination with cetuximab in patients with advanced cancer	Not reported	29	4 (13.8)	G2 4 (13.8)	
Colon-Otero et al ⁴⁴	2017	Phase 2 trial of everolimus and letrozole in relapsed estrogen receptor-positive high-grade ovarian cancer	Patients received oral everolimus 10 mg daily and letrozole 2.5 mg daily	19	2 (10.5)		G3 2 (10.5)
Courtney et al ⁴⁵	2015	A phase I study of everolimus and docetaxel in patients with castration-resistant prostate cancer	Patients received everolimus 10 mg daily for 2 weeks and underwent a restaging FDG- PET/computed tomography scan. Patient cohorts were subsequently treated at three dose levels of everolimus with docetaxel: 5–60 mg/m ² , 10–60 mg/m ² , and 10–70 mg/m ² . The primary end point was the safety and tolerability of combination therapy.	18	5 (27.7)	5 (27.7)	
Deenen et al ⁴⁶	2012	Phase I and pharmacokinetic study of capecitabine and the oral mTOR inhibitor everolimus in patients with advanced solid malignancies	Fixed-dose everolimus 10 mg/day continuously plus capecitabine twice daily for 14 days in 3-weekly cycles	18	9 (50)	9 (50)	
Doi et al ⁴⁷	2010	Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer	Everolimus 10 mg orally daily	A: 53	3 (5.7)		
Elmadani et al ⁴⁸	2017	EYESOR, a model-based, multiparameter, phase I trial to optimize the benefit/toxicity ratio of everolimus and sorafenib	Everolimus + sorafenib	26	6 (23.1)	6 (23.1)	
Escudier et al ⁴⁹	2016	Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis	Oral everolimus 10 mg once daily until disease progression or unacceptable toxicity	92	23 (25)	23 (25)	

(Continued)

Table 1 (Continued).

Study	Year	Title	Therapy	Patients, n	Stomatitis, n (%)	G1/2, n (%)	G3/4, n (%)
Fazio et al ⁵⁰	2013	Everolimus plus octreotide long-acting repeatable in patients with advanced lung neuroendocrine tumors: analysis of the phase 3, randomized, placebo-controlled RADIANT-2 study	Everolimus + octreotide	33	3 (9.1)		
Ferolla et al ⁵¹	2017	Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial	A: everolimus B: everolimus + pasireotide	A: 42 B: 41	Total A: 30 (72) Total B: 15 (37)	A: 26 (62) B: 13 (32)	A: G3 4 (10) B: G3 2 (5)
Finn et al ⁵²	2013	Phase I study investigating everolimus combined with sorafenib in patients with advanced hepatocellular carcinoma	A: sorafenib + everolimus 2.5 mg once daily B: sorafenib + everolimus 5 mg once daily	A: 16 B: 14	A: 6 (37.5) B: 6 (42.9) Ulcers total 6 (37.5)	A: 6 (37.5) B: 5 (35.8)	A: 0 B: 1 (7.1)
Fury et al ⁵³	2012	A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors	Not reported	30	11 (39)	11 (39)	
Ghobrial et al ⁵⁴	2010	Phase II trial of the oral mammalian target of rapamycin inhibitor everolimus in relapsed or refractory Waldenström macroglobulinemia	Everolimus 10 mg daily for two cycles	50	4 (8)		4 (8)
Goldberg et al ⁵⁵	2015	Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study	Not reported	24	18 (75)		
Gong et al ⁵⁶	2017	Efficacy and safety of everolimus in Chinese metastatic HR positive, HER2 negative breast cancer patients: a real-world retrospective study	Everolimus was usually initiated at 10 mg or in some instances 5 mg daily, according to patients' tolerance and request	70	40 (57.1)	34 (47.8)	G3 6 (9.3)
Grignani et al ⁵⁷	2015	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial	A: patients took 400 mg sorafenib twice a day together with 5 mg everolimus once a day	38	20	G1 11 (29) G2 7 (18)	G3 2 (5)
Hainsworth et al ⁵⁸	2010	Phase II trial of bevacizumab and everolimus in patients with advanced renal cell carcinoma	All patients received bevacizumab 10 mg/kg intravenously every 2 weeks and everolimus 10 mg orally daily	80	48	36 (45)	G3 12 (15)

Hatano et al ⁵⁹	2016	Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: a single institution experience in Japan	Everolimus set at 10 mg once a day for adults	47	43 (91)	42 (97.6)	I (2.3)
Hatano et al ⁶⁰	2017	Intermittent everolimus administration for renal angiomyolipoma associated with tuberous sclerosis complex	Everolimus set at 10 mg once a day	26	23 (88)	22	I
Hurvitz et al ⁶¹	2013	A phase 2 study of everolimus combined with trastuzumab and paclitaxel in patients with HER2-overexpressing advanced breast cancer that progressed during prior trastuzumab and taxane therapy	Everolimus 10 mg/day in combination with paclitaxel (80 mg/m ² days 1, 8, and 15 every 4 weeks) and trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly), administered in 28-day cycles	55	42 (76.3)	G1 I3 (23.6) G2 I8 (32.7)	G3 I1 (20)
Jerusalem et al ⁶²	2016	Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLEt)	Not reported	2,131	1,126 (52.8)	926 (43.4)	G3 I98 (9.3) G4 2 (0.1)
Jovanovic et al ⁶³	2017	A randomized phase II neoadjuvant study of cisplatin, paclitaxel with or without everolimus in patients with stage II/III triple-negative breast cancer (TNBC): responses and long-term outcome correlated with increased frequency of DNA damage response gene mutations, TNBC subtype, AR status and Ki67	Not reported	96	37 (39)	37 (39)	
Jozwiak et al ⁶⁴	2016	Safety of everolimus in patients younger than 3 years of age: results from EXIST-1, a randomized, controlled clinical trial	Everolimus initiated at 4.5 mg/m ² /day and titrated to blood trough levels of 5–15 ng/mL	18	12 (66.7)		
Kato et al ⁶⁵	2014	Efficacy of everolimus in patients with advanced renal cell carcinoma refractory or intolerant to VEGFR-TKIs and safety compared with prior VEGFR-TKI treatment	Not reported	19	7 (37)	6 (32)	I (5)

(Continued)

Table 1 (Continued).

Study	Year	Title	Therapy	Patients, n	Stomatitis, n (%)	GI/2, n (%)	G3/4, n (%)
Kim et al ⁶⁶	2014	A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma	Everolimus given at 10 mg daily until progression or occurrence of unacceptable toxicities	34	27 (79.4)	26 (96.2)	1 (2.9)
Kim et al ⁶⁷	2018	Clinical outcomes of the sequential use of pazopanib followed by everolimus for the treatment of metastatic renal cell carcinoma: a multicentre study in Korea	Everolimus	36	15 (41.7)	14 (38.9)	1 (2.8)
Koutsoukos et al ⁶⁸	2017	Real-world experience of everolimus as second-line treatment in metastatic renal cell cancer after failure of pazopanib	Not reported	31	8 (26)	GI 4 (13) G2 1 (3)	G3 3 (10)
Kulke et al ⁶⁹	2017	A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial	A: everolimus + pasireotide LAR B: everolimus	A: 78 B: 81	A: 46 (59) B: 51 (63)	A: 39 (50) B: 44 (54.4)	A: 7 (9) B: 7 (8.6)
Kumano et al ⁷⁰	2013	Sequential use of mammalian target of rapamycin inhibitors in patients with metastatic renal cell carcinoma following failure of tyrosine kinase inhibitors	Everolimus	57	17 (29.8)	14 (82.35)	3 (5.3)
Moscetti et al ⁷¹	2016	Safety analysis, association with response and previous treatments of everolimus and exemestane in 181 metastatic breast cancer patients: a multicenter Italian experience	Not reported	181	115 (63.5)	GI 54 (29.8) G2 46 (25.4)	G3 15 (8.3)
Motzer et al ⁷²	2016	Phase II trial of second-line everolimus in patients with metastatic renal cell carcinoma (RECORD-4) [†]	Not reported	133	7 (5.26)		
Motzer et al ⁷³	2014	Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma	Everolimus	238	53 (22.26)	47 (19.74)	G3 6 (2.52)

Motzer et al ¹⁷	2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial	Everolimus 10 mg once daily	269	107 (40)	98 (36.43)	G3 9 (3.34)
Motzer et al ⁷⁴	2015	Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial	Everolimus 10 mg day	50	21 (42)	20 (40)	G3 1 (2)
Oh et al ⁷⁵	2012	Phase 2 study of everolimus monotherapy in patients with nonfunctioning neuroendocrine tumors or pheochromocytomas/paragangliomas	Everolimus was administered daily at a dose of 10 mg for 4 weeks.	34	6 (17.6)	4 (11.7)	2 (5.9)
Ohtsu et al ⁷⁶	2013	Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study	Everolimus 10 mg/day + BSC	437	174 (40)	154 (35)	20 (5)
Ohshima et al ⁷⁷	2017	Efficacy and safety of sequential use of everolimus in Japanese patients with advanced renal cell carcinoma after failure of first-line treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitor: a multicenter phase II clinical trial	Not reported	A :53	26 (49.1)	22 (41.6)	4 (7.5)
Panzuto et al ⁷⁸	2014	Real-world study of everolimus in advanced progressive neuroendocrine tumors	Everolimus	169	37 (21.9)	33 (19.6)	4 (2.3)
Park et al ⁷⁹	2014	Efficacy and safety of everolimus in Korean patients with metastatic renal cell carcinoma following treatment failure with a vascular endothelial growth factor receptor-tyrosine kinase inhibitor	Everolimus	100	42 (44)	36 (38)	6 (6)
Pavel et al ⁸⁰	2016	Safety and QOL in patients with advanced NET in a phase 3b expanded access study of everolimus	Not reported	123	29 (23.6)	23 (18.7)	G3 6 (4.9)
Quek et al ⁸¹	2011	Combination mTOR and IGF-1R inhibition: phase I trial of everolimus and figitumumab in patients with advanced sarcomas and other solid tumors	Figitumumab (20 mg/kg IV every 21 days) with full-dose everolimus (10 mg orally once daily)	21	21 (100)	G1 11 (52.4) G2 7 (33.3)	G3 3 (14.3)

(Continued)

Table 1 (Continued).

Study	Year	Title	Therapy	Patients, n	Stomatitis, n (%)	G1/2, n (%)	G3/4, n (%)
Safra et al ⁸²	2018	Everolimus plus letrozole for treatment of patients with HR ⁺ , HER2 ⁻ advanced breast cancer progressing on endocrine therapy: an open-label, phase II trial	Everolimus 10 mg daily and letrozole 2.5 mg daily	72	39 (54.2)	18 (45.9)	G3 21 (8.3)
Salazar et al ⁸³	2017	Phase II study of BEZ235 versus everolimus in patients with mammalian target of rapamycin inhibitor-naïve advanced pancreatic neuroendocrine tumors	Everolimus 10 mg once daily	31	20 (64.5)	18 (58)	2 (6.5)
Sarkaria et al ⁸⁴	2011	NCCCTG phase I trial N057K of everolimus (RAD001) and temozolomide in combination with radiation therapy in newly diagnosed glioblastoma multiforme patients	All patients received weekly oral RAD001 in combination with standard chemoradiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide	18	11 (61.1)	G2 11 (61.1)	
Strickler et al ⁸⁵	2012	Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors	10 mg panobinostat three times weekly, 5 or 10 mg everolimus daily, and bevacizumab at 10 mg/kg every 2 weeks	12	4 (33)	3 (25)	1 (8)
Sun et al ⁸⁶	2013	A phase Ib study of everolimus plus paclitaxel in patients with small-cell lung cancer	A: everolimus 2.5 mg 6 B: everolimus 5 mg 11 C: everolimus 10 mg 3	20	8 (40)	A 2 (10) B 5 (25) C 1 (5)	
Takahashi et al ⁸⁷	2013	Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results	Everolimus 1.5 mg/day starting dose (target trough 3–8 ng/mL) + reduced-dose cyclosporine	61	14 (23)		
Tobinai et al ⁸⁸	2010	Phase I study of the oral mammalian target of rapamycin inhibitor everolimus (RAD001) in Japanese patients with relapsed or refractory non-Hodgkin lymphoma	Not reported	13	7 (53.7)	G1 3 (23.7) G2 4 (30.7)	
Vlahovic et al ⁸⁹	2012	A phase I study of bevacizumab, everolimus and panitumumab in advanced solid tumors	Everolimus and flat dosing of panitumumab at 4.8 mg/kg and bevacizumab at 10 mg/kg every 2 weeks	32	24 (76)	20 (63)	4 (13)
Wang et al ⁹⁰	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study	Not reported	58	12 (20.7)	11 (19)	G3 1 (1.7)

Werner et al ⁹¹	2013	Phase I study of everolimus and mitomycin C for patients with metastatic esophagogastric adenocarcinoma	Oral everolimus (5, 7.5, and 10 mg/day) in combination with intravenous MMC 5 mg/m ² every 3 weeks.	16	9 (56.25)	G1 8 (50)	G3 I (6.25)
Wolpin et al ⁹²	2009	Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer	Everolimus 10 mg daily	33	10 (30)	G1 8 (24) G2 I (3)	G3 I (3)
Yao et al ⁹³	2008	Efficacy of everolimus and octreotide LAR in advanced low- to intermediate-grade neuroendocrinetumors: results of a phase II study	RAD001 5 mg/day or 10 mg/day and octreotide LAR 30 mg every 28 days	64	Aphthous ulcers 5 (8) Dysgeusia I (2)		
Yao et al ⁹⁴	2011	Everolimus for advanced pancreatic neuroendocrine tumors	10 mg once daily	204	131 (64)	117 (57)	14 (7)
Yee et al ⁹⁵	2006	Phase I/II study of everolimus in patients with relapsed or refractory hematologic malignancies	Not reported	27	10 (37)	10 (37)	
Total over all				8,201	3,490 (42.55)		
Total with grade				7,796	3,347 (42.93)	2,839 (36.41)	508 (6.51)

poor pharmacokinetic characteristics, and research has focused on the synthesis of analogues of rapamycin more suitable to therapy, such as everolimus, temsirolimus, and ridaforolimus. These molecules differ from sirolimus in their C-40-O positions, resulting in disparate pharmacokinetic and pharmacodynamic profiles.¹² This class of drugs is typically used for the treatment of solid tumors, such as renal-cell carcinoma, breast cancer, pancreatic neuroendocrine tumors, and tuberous sclerosis complex.^{13–17}

Unlike results obtained from reviews about mucositis caused by conventional chemotherapy, in which mucositis is often severe and the most debilitating effect for patients,¹⁸ our analysis showed that the incidence of stomatitis of grade 1 or 2 is higher than that of grade 3 or 4. These results are consistent with our previous work.¹⁹ However, it must be taken into account that it is not possible to say if side effects are entirely due to everolimus therapy or combination with other drugs. Moreover, not all the papers included in this review specified the exact therapeutic regimen. mIAS generally sets in within a few weeks of initiating everolimus therapy. Grade 3 or 4 lesions may lead to dose interruption or reduction. Interfering with patient food intake and diminishing quality of life, this kind of toxicity may cause treatment discontinuation or interruption.²⁰

mIAS is often evaluated using common scales employed in the evaluation of conventional oral mucositis (OMAS, 1999; NCI-CTCAE 2006, 2010). However, its clinical appearance tends to differ from conventional mucositis. A more specific mIAS scale was set by Boers-Doets and Lalla. According to this scale, lesions are evaluated depending on their duration, eg, a grade 3 lesion is an ulceration lasting >7 days.²¹ Management of mIAS is still widely based on education of patients on oral hygiene measures, diet modifications, and pain management.^{9,22} Treatments used are often based on “magic” mouthwash, composed of lidocaine gel 2% × 30 g, doxycycline suspension 50 mg/5mL × 60 mL, and sucral-fate oral suspension 1,000 mg/5 mL dissolved in sodium chloride 0.9% × 2,000 mL used for 3–15 days,²³ a sodium bicarbonate-based mouthwash combined with oral fluconazole,²⁴ or a combination of dexamethasone solution 0.5 mg/mL and miconazole 2% gel.²⁵ Another treatment is 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, and systemic prednisone (1 mg/kg for 7 days). Management of mIAS nowadays is based on education of patients on oral

hygiene measures, diet modifications, and pain management.⁹ Rugo et al showed evidence of the efficacy of a prophylactic use of dexamethasone mouthwash in patients treated with everolimus plus exemestane for advanced or metastatic breast cancer.²⁶ The mouthwash was administered in combination with a prophylactic topical antifungal agent to prevent potential fungal infection.²⁶ It still cannot be determined which lesions will self-limit and which will reduce quality of life, leading to malnutrition and dose reduction in medically necessary treatment.

Disclosure

The authors report no conflicts of interest in this work

References

- Gomez-Pinillos A, Ferrari AC. mTOR signaling pathway and mTOR inhibitors in cancer therapy. *Hematol Oncol Clin North Am*. 2012;26(3):483–505, vii. doi:10.1016/j.hoc.2012.02.014
- Keefe DM, Bateman EH. Tumor control versus adverse events with targeted anticancer therapies. *Nat Rev Clin Oncol*. 2011;9(2):98–109. doi:10.1038/nrclinonc.2011.192
- Khokhar NZ, Altman JK, Platanias LC. Emerging roles for mammalian target of rapamycin inhibitors in the treatment of solid tumors and hematological malignancies. *Curr Opin Oncol*. 2011;23(6):578–586. doi:10.1097/CCO.0b013e32834b892d
- Dabney R, Devine R, Sein N, George B. New agents in renal cell carcinoma. *Target Oncol*. 2014;9(3):183–193. doi:10.1007/s11523-013-0303-8
- Yuan R, Kay A, Berg WJ, Lebwohl D. Targeting tumorigenesis: development and use of mTOR inhibitors in cancer therapy. *J Hematol Oncol*. 2009;2:45. doi:10.1186/1756-8722-2-45
- Meng LH, Zheng XF. Toward rapamycin analog (rapalog)-based precision cancer therapy. *Acta Pharmacol Sin*. 2015;36(10):1163–1169. doi:10.1038/aps.2015.68
- Martins F, de Oliveira MA, Wang Q, et al. A review of oral toxicity associated with mTOR inhibitor therapy in cancer patients. *Oral Oncol*. 2013;49(4):293–298. doi:10.1016/j.oraloncology.2012.11.008
- Sonis S, Treister N, Chawla S, Demetri G, Haluska F. Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. *Cancer*. 2010;116(1):210–215. doi:10.1002/cncr.24696
- Boers-Doets CB, Raber-Durlacher JE, Treister NS, et al. Mammalian target of rapamycin inhibitor-associated stomatitis. *Future Oncol*. 2013;9(12):1883–1892. doi:10.2217/fon.13.141
- Peterson DE, O'Shaughnessy JA, Rugo HS, et al. Oral mucosal injury caused by mammalian target of rapamycin inhibitors: emerging perspectives on pathobiology and impact on clinical practice. *Cancer Med*. 2016;5(8):1897–1907. doi:10.1002/cam4.2016.5.issue-8
- Sehgal SN, Baker H, Rapamycin VC. (AY-22,989), a new antifungal antibiotic. II. Fermentation, isolation and characterization. *J Antibiot (Tokyo)*. 1975;28(10):727–732. doi:10.7164/antibiotics.28.727
- Liu Q, Thoreen C, Wang J, Sabatini D, Gray NS. mTOR mediated anti-cancer drug discovery. *Drug Discov Today Ther Strateg*. 2009;6(2):47–55. doi:10.1016/j.ddstr.2009.12.001
- Awada A, Cardoso F, Fontaine C, et al. The oral mTOR inhibitor RAD001 (everolimus) in combination with letrozole in patients with advanced breast cancer: results of a phase I study with pharmacokinetics. *Eur J Cancer*. 2008;44(1):84–91. doi:10.1016/j.ejca.2007.10.003

14. Boers-Sonderen MJ, de Geus-Oei LF, Desar IM, et al. Temsirolimus and pegylated liposomal doxorubicin (PLD) combination therapy in breast, endometrial, and ovarian cancer: phase Ib results and prediction of clinical outcome with FDG-PET/CT. *Target Oncol.* 2014;9(4):339–347. doi:10.1007/s11523-014-0309-x
15. Hudes GR, Berkenblit A, Feingold J, Atkins MB, Rini BI, Dutcher J. Clinical trial experience with temsirolimus in patients with advanced renal cell carcinoma. *Semin Oncol.* 2009;36(Suppl 3):S26–S36. doi:10.1053/j.seminoncol.2009.10.013
16. Krueger DA, Care MM, Holland K, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *N Engl J Med.* 2010;363(19):1801–1811. doi:10.1056/NEJMoa1001671
17. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet.* 2008;372(9637):449–456. doi:10.1016/S0140-6736(08)61039-9
18. Borbasi S, Cameron K, Quested B, Olver I, To B, Evans D. More than a sore mouth: patients' experience of oral mucositis. *Oncol Nurs Forum.* 2002;29(7):1051–1057. doi:10.1188/02.ONF.1051-1057
19. Lo Muzio L, Arena C, Troiano G, Villa A. Oral stomatitis and mTOR inhibitors: a review of current evidence in 20,915 patients. *Oral Dis.* 2018;24(1–2):144–171. doi:10.1111/odi.12795
20. Rugo HS, Pritchard KI, Gnani M, et al. Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. *Ann Oncol.* 2014;25(4):808–815. doi:10.1093/annonc/mdu009
21. Boers-Doets C, Lalla RV. The mIAS scale: a scale to measure mTOR inhibitor-associated stomatitis. *Supp Care Cancer.* 2013;21(Suppl):1.
22. Ji YD, Aboalela A, Villa A. Everolimus-associated stomatitis in a patient who had renal transplant. *BMJ Case Rep.* 2016;2016.
23. Kalogirou EM, Tosios KI, Piperi EP, Sklavounou A. mTOR inhibitor-associated stomatitis (mIAS) in three patients with cancer treated with everolimus. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2015;119(1):e13–e19. doi:10.1016/j.oooo.2014.08.023
24. Ferte C, Soria JC, Penel N. Dose-levels and first signs of efficacy in contemporary oncology phase I clinical trials. *PLoS One.* 2011;6(3):e16633. doi:10.1371/journal.pone.0016633
25. Nicolatou-Galitis O, Nikolaidi A, Athanassiadis I, Papadopoulou E, Sonis S. Oral ulcers in patients with advanced breast cancer receiving everolimus: a case series report on clinical presentation and management. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2013;116(2):e110–e116. doi:10.1016/j.oooo.2013.02.022
26. Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. *Lancet Oncol.* 2017;18(8):654–662. doi:10.1016/S1470-2045(17)30109-2
27. Amato RJ, Jac J, Giessinger S, Saxena S, Willis JP. A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer. *Cancer.* 2009;115(11):2438–2446. doi:10.1002/cncr.v115:11
28. Andre F, O'Regan R, Ozguroglu M, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol.* 2014;15(6):580–591. doi:10.1016/S1470-2045(14)70138-X
29. Angelousi A, Kamp K, Kaltsatou M, O'Toole D, Kaltsas G, de Herder W. Sequential everolimus and sunitinib treatment in pancreatic metastatic well-differentiated neuroendocrine tumours resistant to prior treatments. *Neuroendocrinology.* 2017;105(4):394–402. doi:10.1159/000456035
30. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. *Lancet Oncol.* 2016;17(3):378–388. doi:10.1016/S1470-2045(15)00515-X
31. Bajetta E, Catena L, Fazio N, et al. Everolimus in combination with octreotide long-acting repeatable in a first-line setting for patients with neuroendocrine tumors: an ITMO group study. *Cancer.* 2014;120(16):2457–2463. doi:10.1002/cncr.28726
32. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med.* 2012;366(6):520–529. doi:10.1056/NEJMoa1109653
33. Baselga J, Semiglazov V, van Dam P, et al. Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. *J Clin Oncol.* 2009;27(16):2630–2637. doi:10.1200/JCO.2008.18.8391
34. Bergmann L, Kube U, Doehn C, et al. Everolimus in metastatic renal cell carcinoma after failure of initial anti-VEGF therapy: final results of a noninterventional study. *BMC Cancer.* 2015;15:303. doi:10.1186/s12885-015-1309-7
35. Besse B, Leighl N, Bannoun J, et al. Phase II study of everolimus-erlotinib in previously treated patients with advanced non-small-cell lung cancer. *Ann Oncol.* 2014;25(2):409–415. doi:10.1093/annonc/mdt536
36. Campone M, Levy V, Bourbouloux E, et al. Safety and pharmacokinetics of paclitaxel and the oral mTOR inhibitor everolimus in advanced solid tumours. *Br J Cancer.* 2009;100(2):315–321. doi:10.1038/sj.bjc.6604851
37. Castellano D, Bajetta E, Panneerselvam A, et al. Everolimus plus octreotide long-acting repeatable in patients with colorectal neuroendocrine tumors: a subgroup analysis of the phase III RADIANT-2 study. *Oncologist.* 2013;18(1):46–53. doi:10.1634/theoncologist.2012-0263
38. Chan JA, Blaszkowsky L, Stuart K, et al. A prospective, phase 1/2 study of everolimus and temozolomide in patients with advanced pancreatic neuroendocrine tumor. *Cancer.* 2013;119(17):3212–3218. doi:10.1002/cncr.28142
39. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med.* 2015;373(19):1814–1823. doi:10.1056/NEJMoa1510016
40. Chow H, Ghosh PM, de Vere White R, et al. A phase 2 clinical trial of everolimus plus bicalutamide for castration-resistant prostate cancer. *Cancer.* 2016;122(12):1897–1904. doi:10.1002/cncr.29927
41. Chung V, Frankel P, Lim D, et al. Phase Ib trial of mFOLFOX6 and everolimus (NSC-733504) in patients with metastatic gastroesophageal adenocarcinoma. *Oncology.* 2016;90(6):307–312. doi:10.1159/000445297
42. Ciruelos E, Vidal M, Martinez de Duenas E, et al. Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer: results of phase IIb BALLET trial in Spain. *Clin Transl Oncol.* 2017.
43. Ciunci CA, Perini RF, Avadhani AN, et al. Phase 1 and pharmacodynamic trial of everolimus in combination with cetuximab in patients with advanced cancer. *Cancer.* 2014;120(1):77–85. doi:10.1002/cncr.28294
44. Colon-Otero G, Weroha SJ, Foster NR, et al. Phase 2 trial of everolimus and letrozole in relapsed estrogen receptor-positive high-grade ovarian cancers. *Gynecol Oncol.* 2017;146(1):64–68. doi:10.1016/j.ygyno.2017.04.020
45. Courtney KD, Manola JB, Elfiky AA, et al. A phase I study of everolimus and docetaxel in patients with castration-resistant prostate cancer. *Clin Genitourin Cancer.* 2015;13(2):113–123. doi:10.1016/j.clgc.2014.08.007
46. Deenen MJ, Klumpen HJ, Richel DJ, et al. Phase I and pharmacokinetic study of capecitabine and the oral mTOR inhibitor everolimus in patients with advanced solid malignancies. *Invest New Drugs.* 2012;30(4):1557–1565. doi:10.1007/s10637-011-9723-4
47. Doi T, Muro K, Boku N, et al. Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer. *J Clin Oncol.* 2010;28(11):1904–1910. doi:10.1200/JCO.2009.26.2923

48. El-Madani M, Colombari O, Tod M, et al. EVESOR, a model-based, multiparameter, Phase I trial to optimize the benefit/toxicity ratio of everolimus and sorafenib. *Future Oncol.* 2017;13(8):679–693. doi:10.2177/fon-2016-0357
49. Escudier B, Molinier V, Bracarda S, et al. Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. *Eur J Cancer.* 2016;69:226–235. doi:10.1016/j.ejca.2016.08.004
50. Fazio N, Granberg D, Grossman A, et al. Everolimus plus octreotide long-acting repeatable in patients with advanced lung neuroendocrine tumors: analysis of the phase 3, randomized, placebo-controlled RADIANT-2 study. *Chest.* 2013;143(4):955–962. doi:10.1378/chest.12-1108
51. Ferolla P, Brizzi MP, Meyer T, et al. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol.* 2017;18(12):1652–1664. doi:10.1016/S1470-2045(17)30681-2
52. Finn RS, Poon RT, Yau T, et al. Phase I study investigating everolimus combined with sorafenib in patients with advanced hepatocellular carcinoma. *J Hepatol.* 2013;59(6):1271–1277. doi:10.1016/j.jhep.2013.07.029
53. Fury MG, Sherman E, Haque S, et al. A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors. *Cancer Chemother Pharmacol.* 2012;69(3):591–598. doi:10.1007/s00280-011-1734-5
54. Ghobrial IM, Gertz M, Laplant B, et al. Phase II trial of the oral mammalian target of rapamycin inhibitor everolimus in relapsed or refractory Waldenstrom macroglobulinemia. *J Clin Oncol.* 2010;28(8):1408–1414. doi:10.1200/JCO.2009.24.0994
55. Goldberg HJ, Harari S, Cottin V, et al. Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study. *Eur Respir J.* 2015;46(3):783–794. doi:10.1183/09031936.00210714
56. Gong C, Zhao Y, Wang B, et al. Efficacy and safety of everolimus in Chinese metastatic HR positive, HER2 negative breast cancer patients: a real-world retrospective study. *Oncotarget.* 2017;8(35):59810–59822. doi:10.18632/oncotarget.v8i35
57. Grignani G, Palmerini E, Ferraresi V, et al. Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial. *Lancet Oncol.* 2015;16(1):98–107. doi:10.1016/S1470-2045(14)71136-2
58. Hainsworth JD, Spigel DR, Burris HA 3rd, Waterhouse D, Clark BL, Whorf R. Phase II trial of bevacizumab and everolimus in patients with advanced renal cell carcinoma. *J Clin Oncol.* 2010;28(13):2131–2136. doi:10.1200/JCO.2009.26.3152
59. Hatano T, Chikaraishi K, Inaba H, Endo K, Egawa S. Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: A single institution experience in Japan. *Int J Urol.* 2016;23(10):833–838. doi:10.1111/iju.2016.23.issue-10
60. Hatano T, Atsuta M, Inaba H, Endo K, Egawa S. Effect of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: an evaluation based on tumor density. *Int J Clin Oncol.* 2017.
61. Hurvitz SA, Dalenc F, Campone M, et al. A phase 2 study of everolimus combined with trastuzumab and paclitaxel in patients with HER2-overexpressing advanced breast cancer that progressed during prior trastuzumab and taxane therapy. *Breast Cancer Res Treat.* 2013;141(3):437–446. doi:10.1007/s10549-013-2689-5
62. Jerusalem G, Mariani G, Ciruelos EM, et al. Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET). *Ann Oncol.* 2016;27(9):1719–1725. doi:10.1093/annonc/mdw249
63. Jovanovic B, Mayer IA, Mayer EL, et al. A randomized Phase II neoadjuvant study of cisplatin, paclitaxel with or without everolimus in patients with stage II/III Triple-Negative Breast Cancer (TNBC): responses and long-term outcome correlated with increased frequency of DNA damage response gene mutations, TNBC subtype, AR status, and Ki67. *Clin Cancer Res.* 2017;23(15):4035–4045. doi:10.1158/1078-0432.CCR-16-3055
64. Jozwiak S, Kotulska K, Berkowitz N, Brechenmacher T, Franz DN. Safety of everolimus in patients younger than 3 years of age: results from EXIST-1, a randomized, controlled clinical trial. *J Pediatr.* 2016;172:151–155 e151. doi:10.1016/j.jpeds.2016.01.027
65. Kato R, Obara W, Matsuura T, Kato Y, Iwasaki K, Fujioka T. Efficacy of everolimus in patients with advanced renal cell carcinoma refractory or intolerant to VEGFR-TKIs and safety compared with prior VEGFR-TKI treatment. *Jpn J Clin Oncol.* 2014;44(5):479–485. doi:10.1093/jjco/hyu018
66. Kim DW, Oh DY, Shin SH, et al. A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma. *BMC Cancer.* 2014;14:795. doi:10.1186/1471-2407-14-795
67. Kim JH, Lee W, Kim TN, Nam JK, Kim TH, Lee KS. Clinical outcomes of the sequential use of pazopanib followed by everolimus for the treatment of metastatic renal cell carcinoma: A multicentre study in Korea. *Can Urol Assoc J.* 2018;12(1):E15–E20. doi:10.5489/cuaj.4644
68. Koutsoukos K, Bamias A, Tzannis K, et al. Real-world experience of everolimus as second-line treatment in metastatic renal cell cancer after failure of pazopanib. *Onco Targets Ther.* 2017;10:4885–4893. doi:10.2147/OTT
69. Kulke MH, Ruzsiewicz P, Van Cutsem E, et al. A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. *Ann Oncol.* 2017;28(6):1309–1315. doi:10.1093/annonc/mdx078
70. Kumano M, Miyake H, Harada K, Fujisawa M. Sequential use of mammalian target of rapamycin inhibitors in patients with metastatic renal cell carcinoma following failure of tyrosine kinase inhibitors. *Med Oncol.* 2013;30(4):745. doi:10.1007/s12032-013-0745-y
71. Moschetti L, Vici P, Gamucci T, et al. Safety analysis, association with response and previous treatments of everolimus and exemestane in 181 metastatic breast cancer patients: a multicenter Italian experience. *Breast.* 2016;29:96–101. doi:10.1016/j.breast.2016.07.005
72. Motzer RJ, Alyasova A, Ye D, et al. Phase II trial of second-line everolimus in patients with metastatic renal cell carcinoma (RECORD-4). *Ann Oncol.* 2016;27(3):441–448. doi:10.1093/annonc/mdv612
73. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2014;32(25):2765–2772. doi:10.1200/JCO.2013.54.6911
74. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomized, phase 2, open-label, multicentre trial. *Lancet Oncol.* 2015;16(15):1473–1482. doi:10.1016/S1470-2045(15)00290-9
75. Oh DY, Kim TW, Park YS, et al. Phase 2 study of everolimus monotherapy in patients with nonfunctioning neuroendocrine tumors or pheochromocytomas/paragangliomas. *Cancer.* 2012;118(24):6162–6170. doi:10.1002/cncr.27675
76. Ohtsu A, Ajani JA, Bai YX, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol.* 2013;31(31):3935–3943. doi:10.1200/JCO.2012.48.3552
77. Ohshima K, Matsumoto Y, Amamizu H, et al. Association of coronary perivascular adipose tissue inflammation and drug-eluting stent-induced coronary hyperconstricting responses in pigs: (18)F-fluorodeoxyglucose positron emission tomography imaging study. *Arterioscler Thromb Vasc Biol.* 2017;37(9):1757–1764. doi:10.1161/ATVBAHA.117.309843

78. Panzuto F, Rinzivillo M, Fazio N, et al. Real-world study of everolimus in advanced progressive neuroendocrine tumors. *Oncologist*. 2014;19(9):966–974. doi:10.1634/theoncologist.2014-0037
79. Park K, Lee JL, Ahn JH, et al. Efficacy and safety of everolimus in Korean patients with metastatic renal cell carcinoma following treatment failure with a vascular endothelial growth factor receptor-tyrosine kinase inhibitor. *Cancer Res Treat*. 2014;46(4):339–347. doi:10.4143/crt.2013.154
80. Pavel M, Unger N, Borbath I, et al. Safety and QOL in patients with advanced NET in a Phase 3b expanded access study of everolimus. *Target Oncol*. 2016;11(5):667–675. doi:10.1007/s11523-016-0440-y
81. Quek R, Wang Q, Morgan JA, et al. Combination mTOR and IGF-1R inhibition: phase I trial of everolimus and figitumumab in patients with advanced sarcomas and other solid tumors. *Clin Cancer Res*. 2011;17(4):871–879. doi:10.1158/1078-0432.CCR-10-2621
82. Safta T, Kaufman B, Kadouri L, et al. Everolimus plus letrozole for treatment of patients with HR(+), HER2(-) advanced breast cancer progressing on endocrine therapy: an open-label, Phase II trial. *Clin Breast Cancer*. 2017.
83. Salazar R, Garcia-Carbonero R, Libutti SK, et al. Phase II study of BEZ235 versus Everolimus in patients with mammalian target of rapamycin inhibitor-naïve advanced pancreatic neuroendocrine tumors. *Oncologist*. 2017.
84. Sarkaria JN, Galanis E, Wu W, et al. North Central Cancer Treatment Group Phase I trial N057K of everolimus (RAD001) and temozolomide in combination with radiation therapy in patients with newly diagnosed glioblastoma multiforme. *Int J Radiat Oncol Biol Phys*. 2011;81(2):468–475. doi:10.1016/j.ijrobp.2010.05.064
85. Strickler JH, Starodub AN, Jia J, et al. Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors. *Cancer Chemother Pharmacol*. 2012;70(2):251–258. doi:10.1007/s00280-012-1911-1
86. Sun JM, Kim JR, Do IG, et al. A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer. *Br J Cancer*. 2013;109(6):1482–1487. doi:10.1038/bjc.2013.467
87. Takahashi K, Uchida K, Yoshimura N, et al. Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results. *Transplant Res*. 2013;2(1):14. doi:10.1186/2047-1440-2-14
88. Tobinai K, Ogura M, Maruyama D, et al. Phase I study of the oral mammalian target of rapamycin inhibitor everolimus (RAD001) in Japanese patients with relapsed or refractory non-Hodgkin lymphoma. *Int J Hematol*. 2010;92(4):563–570. doi:10.1007/s12185-010-0707-5
89. Vlahovic G, Meadows KL, Uronis HE, et al. A phase I study of bevacizumab, everolimus and panitumumab in advanced solid tumors. *Cancer Chemother Pharmacol*. 2012;70(1):95–102. doi:10.1007/s00280-012-1889-8
90. Wang M, Popplewell LL, Collins RH Jr., et al. Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study. *Br J Haematol*. 2014;165(4):510–518. doi:10.1111/bjh.2014.165.issue-4
91. Werner D, Atmaca A, Pauligk C, Pustowka A, Jager E, Al-Batran SE. Phase I study of everolimus and mitomycin C for patients with metastatic esophagogastric adenocarcinoma. *Cancer Med*. 2013;2(3):325–333. doi:10.1002/cam4.77
92. Wolpin BM, Hezel AF, Abrams T, et al. Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Clin Oncol*. 2009;27(2):193–198. doi:10.1200/JCO.2008.18.9514
93. Yao JC, Phan AT, Chang DZ, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol*. 2008;26(26):4311–4318. doi:10.1200/JCO.2008.16.7858
94. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514–523. doi:10.1056/NEJMoa1009290
95. Yee KW, Zeng Z, Konopleva M, et al. Phase I/II study of the mammalian target of rapamycin inhibitor everolimus (RAD001) in patients with relapsed or refractory hematologic malignancies. *Clin Cancer Res*. 2006;12(17):5165–5173. doi:10.1158/1078-0432.CCR-06-0764

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