Table SI. Incidence of anaemia in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 cases (%)	Grade 3/4 cases (%)
1. Amato *et al* (1)	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 was administered at a dose of 10 mg daily orally with- out interruption (28-day cycle), with dose modifications for toxicity (graded according to National Cancer Institute Commonfvn Toxicity Criteria, version 3.0). Patients were evaluated every 2 cycles (8 weeks) using Response Evaluation Criteria in Solid Tumors (RECIST).	39	12 (30.8)	12 (30.8)	0
2. Bajetta *et al* (2)	2014	Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients with Neuroendocrine Tumors; treatment-naive 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	4 (8)	3 (6)	1 (2)
3. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer; in this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily).	482	16 (3.31)	10 (2.07)	6 (1.2)
4. Baselga *et al* (4)	2009	Phase II Randomized Study of Neoadjuvant Everolimus Plus Letrozole Compared With Placebo	137	16 (11.7)	7 (5.1)	9 (6.5)

		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.				
5. Bendell *et al* (5)	2015	A phase Ib study of linsitinib (OSI-906), a dual inhibitor of IGF-1R and IR tyrosine kinase, in combination with everolimus as treatment for patients with refractory metastatic colorectal cancer; OSI-906 and everolimus were administered to cohorts of 3–6 patients in a standard 3+3 design	18	5 (27)	5 (27)	0
6. Bergmann *et al* (6)	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	46 (15)	25 (8)	21 (7)
7. Besse *et al* (7)	2013	A phase Ib dose-escalation study of everolimus combined with cisplatin and etoposide as first-line therapy in patients with extensive-stage small-cell lung cancer	40	9 (23)		
8. Besse *et al* (8)	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	18 (27.3)	15 (22.7)	3 (4.5)
9. Buzzoni *et al* (9)	2017	Impact of prior therapies on everolimus activity: an exploratory analysis of raDianT-4;	202	32 (16)	24 (12)	8 (4)

		patients were randomized (2:1) to everolimus 10 mg/day or placebo, both with best supportive care.				
10. Chocteau-Bouju *et al* (10)	2015	Efficacy and tolerance of everolimus in 123 consecutive advanced ER positive, HER2 negative breast cancer patients. A two center retrospective study; everolimus was initially prescribed at the standard dose of 10 mg daily in 77.2% of patients and at 5 mg daily in 22.8% of patients, combined with endocrine therapy	123	123 (100)	123 (100)	0
11. Choueiri *et al* (11)	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma everolimus at a dose of 10 mg daily	322	120 (37)	71 (22)	49 (15)
12. Chow *et al* (12)	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)	12 (50)	2 (8.3)
13. Chung *et al* (13)	2016	Phase Ib Trial of mFOLFOX6 and Everolimus (NSC-733504) in Patients with Metastatic Gastroesophageal Adenocarcinoma; xix patients were accrued to the first dose level of 2.5 mg everolimus daily with mFOLFOX6.	6	4 (67)	4 (67)	0
14. Ciunci *et al* (14)	2014	Phase 1 and Pharmacodynamic Trial of Everolimus in Combination With Cetuximab in Patients With Advanced Cancer	29	5 (17.2)	4 (13.7)	1 (3.4)
15. Conconi *et al* (15)	2014	Clinical activity of everolimus in relapsed/refractory marginal zone B-cell lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group; everolimus at 10 mg daily dose, from day 1 to day 28 for up to a total of six cycles or until progression	30	7 (23.3)	6 (20)	1 (3.3)

16. Dasari *et al* (16)	2015	Phase I study of the anti-IGF1R antibody cixutumumab with everolimus and octreotide in advanced well-differentiated neuroendocrine tumours; keeping the doses of everolimus (10 mg p.o. daily) and octreotide LAR (20 mg i.m. every 21 days) constant, cixutumumab was evaluated at escalating doses of 10 and 15 mg/kg every 21 days for a 21-day cycle. Octreotide LAR was administered every 21 days rather than the standard practice of every 28 days to fit with the study schedule for patients' convenience	19	2 (11)	1 (5.5)	1 (5.5)
17. El-Madani *et al* (17)	2017	EVESOR, a model-based, multiparameter, Phase I trial to optimize the bene t/toxicity ratio of everolimus and sorafenib everolimus + sorafenib	26	2 (7.7)	2 (7.7)	0
18. Fazio *et al* (18)	2018	Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumours: RADIANT-4 lung subgroup analysis everolimus 10 mg/d	62	13 (21.0)	11 (17.8)	2 (3.2)
19. Fazio *et al* (19)	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 A: everolimus + octreotide	33	5 (15.2)		
20. Guo *et al* (20)	2013	Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy: an open-label phase 1b study	64	41 (64)	28 (43)	13 (21)

		A: everolimus 10 mg (2 × 5 mg tablets) daily until objective tumor progression (according to RECIST, version 1.0), unacceptable toxicity, death, or study discontinuation for any other reason				
21. Hainsworth *et al* (21)	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	51 (64)	47 (59)	4 (5)
22. Hatano *et al* (22)	2016	Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: A single institution experience in Japan The dose of everolimus was set at 10 mg once a day for adults.	47	6 (13)	6 (13)	0
23. Hatano *et al* (23)	2017	Intermittent everolimus administration for renal angiomyolipoma associated with tuberous sclerosis complex The dose of everolimus was set at 10 mg once a day	26	3 (12)	3 (12)	0
24. Hill *et al* (24)	2018	A phase I trial of bortezomib in combination with everolimus for treatment of relapsed/refractory non-Hodgkin lymphoma bortezomib + everolimus	29	26 (89.6)	21 (72.4)	5 (17.2)
25. Hurvitz *et al* (25)	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	55	19 (34.6)	15 (27.3)	4 (7.3)

		followed by 2 mg/kg weekly), administered in 28-day cycles.				
26. Jerusalem *et al* (26)	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) patients self-administered EVE on day 1 and continued daily doses of EVE (either 2 x 5 or 1 x 10 mg) plus EXE (25 mg/day) in 28-day cycles.	2, 131	306 (14.4)	306 (14.4)	0
27. Johnston *et al* (27)	2016	The mTORC1 Inhibitor Everolimus Combined with R-CHOP-21 for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Safety and Efficacy Results of a Phase I and Feasibility Trial NCCTG 1085 (Alliance) everolimus 10 mg days 1-10 or 1-14 in combination with R-CHOP-21 for 6 cycles	24	12 (50)	9 (38)	3 (12)
28. Jovanovic *et al* (28)	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	96	62 (65)	56 (59)	6 (6)
29. Kim *et al* (29)	2014	A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma	34	22 (64.7)	21 (61.8)	1 (2.9)

		Everolimus was given at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities.				
30. Kim *et al* (30)	2013	A phase I study of everolimus and CHOP in newly diagnosed peripheral T-cell lymphomas Four dose levels (2.5 to 10 mg) of everolimus from days 1 to 14 with CHOP (750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 (maximum 2 mg) vincristine on day 1, and 100 mg/day prednisone on days 1 to 5) every 21 days were planned	15	11 (73.3)	5 (33.3)	6 (40)
31. Knox *et al* (31)	2017	Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC Patients were randomly assigned 1 : 1 to receive either first-line everolimus 10 mg/day	238	32		
32. Koeberle *et al* (32)	2016	Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29)† Sorafenib + everolimus	59	5 (8)	2 (3)	3 (5)
33. Kordes *et al* (33)	2013	A phase I/II, non-randomized, feasibility/safety and efficacy study of the combination of everolimus, cetuximab and capecitabine in patients with advanced pancreatic cancer Safety and efficacy of fixed standard dose cetuximab in combination with various dose levels of everolimus (5–10 mg/day) and capecitabine (600–800 mg/ m^2 bid, 2 weeks every 3	A 31 B 9	A 14 (45) B 6 (67)	A 13 (42) B 6 (67)	A 1 (3) B 0

		weeks) were investigated in a phase I/II study in patients with advanced pancreatic cancer. A: STUDY PHASE II – 113 cycles B: DL2 – 25 CYCLES				
34. Koutsoukos *et al* (34)	2017	real-world experience of everolimus as second-line treatment in metastatic renal cell cancer after failure of pazopanib The median everolimus daily dose was 10 mg (5–10 mg), while the mean daily dose was 9.3 mg	31	9 (29)	6 (20)	3 (10)
35. Kulke *et al* (35)	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:everolismus 10 mg/d, per oral (po) +pasireotide LAR (60 mg/28 d, IM) B:everolimus 10 mg/d, per oral (po)	A: 78 B: 81	A 21 (26.9) B 21 (25.9)	A 17 (21.8) B 17 (21)	A 4 (5.1) B 4 (4.9)
36. Kumano *et al* (36)	2013	Sequential use of mammalian target of rapamycin inhibitors in patients with metastatic renal cell carcinoma following failure of tyrosine kinase inhibitors everolimus 10 mg/daily	57	12 (21.1)	6 (10.6)	6 (10.5)
37. Massarweh *et al* (37)	2014	A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure; fulvestrant was administered intramuscularly (in the gluteus maximus) in a loading dose schedule as follows: 500 mg in two divided doses—one on each side on day 1, then 250 mg on day 14, and then 250 mg on day 28 and every 4 weeks ± 3	31	23 (74)	22 (70.9)	1 (3.1)

		days thereafter. Everolimus was administered initially at a dose of 5 mg daily in the first 5-patient cohort for the first month of treatment and then increased to 10 mg PO daily after that.				
38. Molina *et al* (38)	2012	Phase 1 Trial of Everolimus Plus Sunitinib in Patients With Metastatic Renal Cell Carcinoma A:everolimus + sunitnib	20	18 (90)	15 (75)	3 (15)
39. Molina *et al* (39)	2014	A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of metastatic renal cell carcinoma (RCC) A: 20 twenty patients (mean 58.4 years) received lenvatinib (12 mg (*n* = 7); 18 mg (*n* = 11); 24 mg (*n* = 2)) plus everolimus 5 mg	20	1 (5)		
40. Morrow *et al* (40)	2011	Phase I/II Study of Trastuzumab in Combination with Everolimus (RAD001) in Patients With HER2-Overexpressing Metastatic Breast Cancer Who Progressed on Trastuzumab-Based Therapy Everolimus: the 10 mg dose was used in the phase II portion	47	10 (21)	8 (17)	2 (4)
41. Motzer *et al* (41)		Phase II trial of second-line everolimus in patients with metastatic renal cell carcinoma (RECORD-4) everolimus	133	17 (13)		
42. Motzer *et al* (42)	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	337	93 (27.6)	42 (12.5)	51 (15.1)

43. Narayan *et al* (43)	2016	Phase I Trial of Everolimus and Radiation Therapy for Salvage Treatment of Biochemical Recurrence in Prostate Cancer Patients Following Prostatectomy Everolimus +srt	18	2 (11.1)	1 (5.5)	1 (5.5)
44. Niegisch *et al* (44)	2015	Second-Line Treatment of Advanced Urothelial Cancer with Paclitaxel and Everolimus in a German Phase II Trial (AUO Trial AB 35/09) paclitaxel (175 mg/m2 i.v., 3-weekly) and the mTOR-inhibitor everolimus (10 mg p.o., once daily).	27	15 (55.5)	2 (7.4)	13 (48.1)
45. Oh *et al* (45)	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	4 (11.8)	2 (5.9)	2 (5.9)
46. Ohtsu *et al* (46)	2013	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study Everolimus 10 mg/d	437	114 (26)	44 (10)	70 (16)
47. Oudard *et al* (47)	2016	Clinical Benefit of Everolimus as Second-Line Therapy in Metastatic Renal Cell Carcinoma: The French Retrospective SECTOR Stud Everolimus with/or VEGFR-TKI	162	58 (35.8)	45 (27.8)	13 (8)
48. Oyama *et al* (48)	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; everolimus Subjects were administered 10 mg of everolimus q.d. orally during a fasting state.	53	12 (22.6)	10 (19.2)	2 (3.4)

		Doses were delayed or reduced to 5 mg once daily if patients had significant laboratory abnormalities or clinically adverse events				
49. Panzuto *et al* (49)	2014	Real-World Study of Everolimus in Advanced Progressive Neuroendocrine Tumors Everolimus starting dose was 10 mg daily; the investigator had the option of starting at or reducing the dose to 5 mg daily	169	33 (19.5)	24 (14.2)	9 (5.3)
50. Pavel *et al* (50)	2016	Safety and QOL in Patients with Advanced NET in a Phase 3b Expanded Access Study of Everolimus; oral everolimus (two 5 mg tablets, totally 10 mg/day, in 28-day cycles) was taken by patients until disease progression, unacceptable toxicity, death, discontinuation from the study for any other reason, commercial availability for advanced NET in each participating country	A pNET 123 B Non pNET 117	A 7 (5.7) B 13 (11.1)	A 3 (2.5) B 9 (7.7)	A 4 (3.2) B 4 (3.4)
51. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO; everolimus 10 mg per day until progression or unacceptable toxicity	43	43 (100)	37 (86)	6 (14)
52. Rodrigues *et al* (52)	2015	Phase I combination of pazopanib and everolimus in PIK3CA mutation positive/PTEN loss patients with advanced solid tumors refractory to standard therapy; pazopanib 600 mg every other day (QOD) alternating with everolimus 10 mg PO QOD.	52	4 (7.6)	2 (3.8)	2 (3.8)
53. Safra *et al* (53)	2018	Everolimus Plus Letrozole for Treatment of Patients With HR^+, $HER2^-$ Advanced Breast Cancer	72	20 (27.8)	13 (18.1)	7 (9.79)

		Progressing on Endocrine Therapy: An Open-label, Phase II Trial; everolimus 10 mg daily and letrozole 2.5 mg daily				
54. Salazar *et al* (54)	2017	Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Natıve Advanced Pancreatic Neuroendocrine Tumors Everolimus 10 mg once daily	31	11 (35.5)	8 (25.8)	3 (9.7)
55. Sanoff *et al* (55)	2015	Everolimus and pasireotide for advanced and metastatic hepatocellular carcinoma everolimus 7.5 mg PO daily and pasireotide LAR 60 mg IM every 28 days.	24	5 (21)	5 (21)	0
56. Sarkaria *et al* (56)	2011	NCCTG 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 chemo- radiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide	18	12 (66.6)	6 (33.3)	6 (33.3)
57. Shen *et al* (57)	2014	Phase II Multicentered Study of Low-Dose Everolimus plus Cisplatin and Weekly 24-Hour Infusion of High-Dose 5-Fluorouracil and Leucovorin as First-Line Treatment for Patients with Advanced Gastric Cancer; everolimus (10 mg p.o. on days 1, 8 and 15) plus cisplatin and a weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin (HDFL) chemotherapy (cisplatin 35 mg/m2 intrave- nous infusion for 24 h on days 1 and 8, 5-fluorouracil 2,000 mg/m2 and leucovorin 300 mg/m2	40	29 (72.5)	23 (57.5)	6 (15)

		intravenous infusion for 24 h on days 1, 8 and 15) every 28 days				
58. Shoushtari *et al* (58)	2016	Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients	13	1 (7)	0	1 (7)
59. Slomovitz *et al* (59)	2010	A Phase 2 Study of the Oral Mammalian Target of Rapamycin Inhibitor, Everolimus, in Patients With Recurrent Endometrial Carcinoma Everolimus was administered at a dose of 10 mg orally daily for 28-day cycles.	35	15 (43)	12 (34)	3 (9)
60. Sun *et al* (60)	2013	A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer a everolimus 2.5 mg b everolimus 5 mg c everolimus 10 mg	A:6 B:11 C:3	A 5 (83.33) B 11 (100) C 3 (100)	A 5 B 10 C 3	A 0 B 1 C 0
61. Tarhini *et al* (61)	2010	Phase II Study of Everolimus (RAD001) in Previously Treated Small Cell Lung Cancer everolimus 10 mg orally daily until disease progression.	40	9 (22.5)	9 (22.5)	0
62. Tomita *et al* (62)	2017	Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup analysis from the CheckMate 025 study nivolumab 3 mg/kg intravenously every 2 weeks or everolimus 10 mg tablet orally once daily	26	12 (46)	10 (38)	2 (8)
63. Vlahovic *et al* (63)	2012	A phase I study of bevacizumab, everolimus and panitumumab in advanced solid tumors	32	10 (31)	9 (28)	1 (3)

		everolimus and flat dosing of panitumumab at 4.8 mg/kg and bevacizumab at 10 mg/kg every 2 weeks.				
64. Werner *et al* (64)	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/m2 every 3 weeks.	16	5 (31.2)	4 (25)	1 (6.2)
65. Yao *et al* (65)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors 10 mg once daily	204	35 (17)	23 (11)	12 (6)
66. Albiges *et al* (66)	2015	Everolimus for patients with metastatic renal cell carcinoma refractory to anti-VEGF therapy: Results of a pooled analysis of non-interventional studies metastatic renal cell carcinoma (mRCC) who failed one or two anti-VEGF therapies; 493 patients received everolimus in the second-line setting: 10 mg/day until disease progression or unacceptable toxicity.	493	70 (14)	42 (8)	28 (6)
67. Andre *et al* (67)	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 3 trial, we 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 randomisation system to daily everolimus (5 mg/day) plus	A:280	138 (49)	85 (30)	53 (19)

		weekly trastuzumab (2 mg/kg) and vinorelbine (25 mg/m2) or to placebo plus trastuzumab plus vinorelbine, in 3-week cycles, stratified by previous lapatinib use.				
68. Armstrong *et al* (68)	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.	55	16 (29)	10 (18)	6 (11)
69. Bissler *et al* (69)	2013	Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial oral everolimus 10 mg per day	79	10 (13)	10 (13)	0
70. Escudier *et al* (70)	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 unac-ceptable toxicity	92	27 (29)	21 (23)	6 (6)
71. Ferolla *et al* (71)	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 Everolimus long-acting pasireotide (60 mg intramuscularly every 28 days), everolimus (10 mg orally once daily), or both in combination, for the core 12-month treatment period.	42	13 (31)	12 (29)	1 (2)
72. Grignani *et al* (72)	2015	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial	38	19 (50)	17 (45)	2 (5)

		A: Patients took 400 mg sorafenib twice a day together with 5 mg everolimus once a day				
73. Grunwald *et al* (73)	2012	An international expanded-access programme of everolimus: Addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy; patients received everolimus 10 mg once daily, with dose and schedule modifications allowed for toxicity	1367	202 (14.8)	19 (1.4)	183 (13.4)
74. Motzer *et al* (74)	2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial A: everolimus 10 mg once daily	269	244 (90.7)	219 (81.4)	25 (9.3)
75. Motzer *et al* (75)	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	13 (26)	7 (14)	6 (12)
Total overall			10,386	2,534 (24.4)	-	-
Total with grade			9,922	2,470 (24.9)	1,767 (17.8)	703 (7.1)
Total with grade		Only everolimus at 2.5 mg	6	5 (83.33)	5 (83.33)	0
Total with grade		Only everolimus at 5 mg	11	11 (100)	10 (90,9)	1 (9.1)
Total with grade		Only everolimus at 10 mg	4,770	1,247 (26.2)	790 (16.6)	467 (9.8)

Table SII. Incidence of anorexia in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 cases (%)	Grade 3/4 cases (%)
1. Bachelot *et al* (76)	2012	Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study; open-label, phase II study randomly assigned postmenopausal women with hormone receptor– positive, human epidermal growth factor receptor 2–negative, AI-resistant mBC to tamoxifen 20 mg/d plus everolimus 10 mg/d (n 54) or tamoxifen 20 mg/d alone	54	23 (43)	19 (34)	4 (7)
2. Barnes *et al* (77)	2013	Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma; everolimus was administered orally once daily at a dose of 5 mg on days 1 through 14 of cycle 1. If tolerated, the dose was then increased to 10 mg for days 15 through 28 of cycle 1. For cycle 2 and beyond, patients continued to receive everolimus at a dose of 10 mg daily continuously. Rituximab, at a dose of 375 mg/m^2, was administered intravenously weekly for four doses during cycle 1, and then on day 1 of cycles 2 through 6. After cycle 6, patients could receive an additional 6 months of everolimus monotherapy in the absence of disease progression or unacceptable toxicity.	24	3 (12.5)	3 (12.5)	0
3. Baselga *et al* (4)	2009	Phase II Randomized Study of Neoadjuvant Everolimus Plus Letrozole Compared With	137	17 (12.4)	17 (12.4)	0

		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.				
4. Bendell *et al* (5)	2015	A phase Ib study of linsitinib (OSI-906), a dual inhibitor of IGF-1R and IR tyrosine kinase, in combination with everolimus as treatment for patients with refractory metastatic colorectal cancer; OSI-906 and everolimus were adminis-tered to cohorts of 3–6 patients in a standard 3+3 design	18	9 (50)	9 (50)	0
5. Besse *et al* (8)	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	24 (36.4)	24 (36.3)	0
6. Chan *et al* (78)	2013	A Prospective, Phase 1/2 Study of Everolimus and Temozolomide in Patients With Advanced Pancreatic Neuroendocrine Tumor; patients were treated with temozolomide at a dose of 150 mg/m^2 per day on days 1 through 7 and days 15 through 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	42	13 (31)	13 (31)	0
7. Chow *et al* (12)	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	5 (20.8)	4 (16.6)	1 (4.2)

8. (13)	Chung *et al*	2016	Phase Ib Trial of mFOLFOX6 and Everolimus (NSC-733504) in Patients with Metastatic Gastroesophageal Adenocarcinoma Six patients were accrued to the first dose level of 2.5 mg everolimus daily with mFOLFOX6.	6	4 (67)	4 (67)	0
9. (14)	Ciunci *et al*	2014	Phase 1 and Pharmacodynamic Trial of Everolimus in Combination With Cetuximab in Patients With Advanced Cancer	29	3 (10.3)	2 (6.9)	1 (3.4)
10. (15)	Conconi *et al*	2014	Clinical activity of everolimus in relapsed/refractory marginal zone B-cell lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group The study drug everolimus (RAD001) was administered orally at a daily dose of 10mg from day1 to day 28 for upto a total of six cycles or until progression	30	4 (13.3)	3 (10)	1 (3.3)
11. (16)	Dasari *et al*	2015	Phase I study of the anti-IGF1R antibody cixutumumab with everolimus and octreotide in advanced well-differentiated neuroendocrine tumors; keeping the doses of everolimus (10 mg p.o. daily) and octreotide LAR (20 mg i.m. every 21 days) constant, cixutumumab was evaluated at escalating doses of 10 and 15 mg/kg every 21 days for a 21-day cycle. Octreotide LAR was administered every 21 days rather than the standard practice of every 28 days to fit with the study schedule for patients' convenience.	19	9 (47)	8 (42)	1 (5)
12. (17)	El-Madani *et al*	2017	EVESOR, a model-based, multiparameter, Phase I trial to optimize the bene t/toxicity ratio of everolimus and sorafenib Everolimus +sorafenib	26	8 (30.8)	8 (30.8)	0
13. (79)	Ellard *et al*	2009	Randomized Phase II Study Comparing Two Schedules of Everolimus in Patients With Recurrent/Metastatic Breast Cancer: NCIC Clinical Trials Group IND.163	A 33 B 16	A 14 (42.4) B 6 (37.5)	A 1 (3) B 0	A 13 (39.4) B 6 (37.5)

		Randomized phase II study of everolimus 10 mg daily (A) versus 70 mg weekly (B)				
14. Fury *et al* (80)	2012	A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors	30	7 (25)	7 (25)	0
15. Gadgeel *et al* (81)	2013	Phase I study evaluating the combination of lapatinib (a Her2/Neu and EGFR inhibitor) and everolimus (an mTOR inhibitor) in patients with advanced cancers: South West OncologymGroup (SWOG) Study S0528 The MTD of the combination was 1,250 mg of lapatinib and 5 mg of everolimus once daily.	54	14 (26)	13 (24)	1 (2)
16. Gong *et al* (82)	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 the dose of 10 mg or in some instances at 5 mg daily, according to patients' tolerance and request.	70	5 (7.1)	5 (7.1)	0
17. Gross *et al* (83)	2017	Safety and Efficacy of Docetaxel, Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m^2, bevacizumab 15 mg/kg, and everolimus 2.5 mg	43	40 (93)	39 (90.6)	1 (2.3)
18. Hainsworth *et al* (21)	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	26 (33)	23 (29)	3 (4)
19. Harzstark *et al* (84)	2011	A Phase 1 Study of Everolimus and Sorafenib for Metastatic Clear Cell Renal Cell Carcinoma Starting doses were everolimus at a dose of 2.5 mg orally daily and sorafenib at a dose of 400 mg orally twice daily continuously	20	2 (10)	1 (5)	1 (5)
20. Ju *et al* (85)	2015	Toxicity and adverse effects of everolimus in the treatment of advanced non-small cell	12	3 (25)	3 (25)	0

			lung cancer pretreated with chemotherapy-Chinese experiences; everolimus 5-10 mg/day with or without chemotherapy until progression or unacceptable toxicity.				
21.	Kato *et al* (86)	2013	Efficacy of Everolimus in Patients with Advanced Renal Cell Carcinoma Refractory or Intolerant to VEGFR-TKIs and Safety Compared with Prior VEGFR-TKI Treatment Everolimus during everolimus therapy, dose interruption and reduction to 5 mg/day were permitted if Grades 3 or 4 adverse event occurred.	19	4 (21)	3 (16)	1 (5)
22.	Kim *et al* (29)	2014	A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma Everolimus was given at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities.	34	5 (14.7)	5 (14.7)	0
23.	Kim *et al* (87)	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	36	9 (25)	9 (25)	0
24.	Kim *et al* (88)	2016	Efficacy and Toxicity of Mammalian Target Rapamycin Inhibitors in Patients with Metastatic Renal Cell Carcinoma with Renal Insufficiency: The Korean Cancer Study Group GU 14-08; the starting oral dose of everolimus was 10 mg daily for 10 patients and the starting intravenous dose for temsirolimus was 25 mg weekly for eight patients in the overall series.	19	3 (16)	3 (16)	0
25.	Kim *et al* (30)	2013	A phase I study of everolimus and CHOP in newly diagnosed peripheral T-cell lymphomas; four dose levels (2.5 to 10 mg) of everolimus from days 1 to 14 with CHOP (750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 (maximum 2	15	2 (13.3)	2 (13.3)	0

		mg) vincristine on day 1, and 100 mg/day prednisone on days 1 to 5) every 21 days were planned				
26. Koeberle *et al* (32)	2016	Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29)	59	33 (56)	22 (37)	11 (19)
27. Lim *et al* (89)	2013	A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes everolimus 10 mg daily orally	38	17 (44)	16 (42)	1 (2)
28. Massarweh *et al* (37)	2014	A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure Fulvestrant was administered intramuscularly (in the gluteus maximus) in a loading dose schedule as follows: 500 mg in two divided doses—one on each side on day 1, then 250 mg on day 14, and then 250 mg on day 28 and every 4 weeks ± 3 days thereafter. Everolimus was administered initially at a dose of 5 mg daily in the first 5-patient cohort for the first month of treatment and then increased to 10 mg PO daily after that.	31	6 (19)	6	0
29. Motzer *et al* (74)	2008	Efficacy of everolimus in advanced renal cell carcinoma: double-blind, randomised, placebo-controlled phase III trial everolimus 10 mg once daily	269	44 (16)	43 (16)	1 (<1)
30. Narayan *et al* (43)	2016	Phase I Trial of Everolimus and Radiation Therapy for Salvage Treatment of Biochemical Recurrence in Prostate Cancer Patients Following Prostatectomy	18	1 (5.5)	1 (5.5)	0
31. Nozawa *et al* (90)	2013	Adverse Event Profile and Dose Modification of Everolimus for Advanced Renal Cell Carcinoma in Real-world Japanese Clinical Practice	47	2 (4.2)	1 (2.1)	1 (2.1)

		Everolimus, not specified posology				
32. Oh *et al* (45)	2012	Phase 2 Study of Everolimus Monotherapy in Patients With Non functioning Neuroendocrine Tumors or Pheochromocytomas/ Paragangliomas Everolimus was administered daily at a dose of 10 mg for 4 weeks.	34	7 (20.6)	7 (20.7)	0
33. Ou *et al* (91)	2015	SWOG S0722: Phase II study of mTOR inhibitor everolimus (RAD001) in advanced malignant pleural mesothelioma (MPM) Everolimus 10 mg daily.	59	19 (32.3)	18 (30.6)	1 (1.7)
34. Oudard *et al* (47)	2016	Clinical Benefit of Everolimus as Second-Line Therapy in Metastatic Renal Cell Carcinoma: The French Retrospective SECTOR Study Everolimus, not specified posology	162	9 (5.6)	8 (5)	1 (0.6)
35. Quek *et al* (92)	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	9 (42.8)	9 (42.8)	0
36. Rathkopf *et al* (93)	2015	Everolimus Combined With Gefitinib in Patients With Metastatic Castration-Resistant Prostate Cancer: Phase 1/2 Results and Signaling Pathway Implications In phase 1, 12 patients (10 with CRPC and 2 with glioblastoma) received daily gefitinib (250 mg) with weekly everolimus (30, 50, or 70 mg). In phase 2, 27 CRPC patients received gefitinib with everolimus (70 mg)	39	16 (41)	16 (41)	0
37. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO everolimus 10mg per day until progression or unacceptable toxicity	43	20 (47)	9 (21)	11 (26)

38.	Ryan *et al* (94)	2011	A phase II study of everolimus in combination with imatinib for previously treated advanced renal carcinoma everolimus 2.5 mg p.o. daily and imatinib 600 mg p.o. daily.	19	9 (48)	9 (48)	0
39.	Sanoff *et al* (55)	2015	Everolimus and pasireotide for advanced and metastatic hepatocellular carcinoma everolimus 7.5 mg PO daily and pasireotide LAR 60 mg IM every 28 days.	24	3 (13)	3 (13)	0
40.	Sarkaria *et al* (56)	2011	NCCTG Phase I Trial N057K of everolimus (RAD001) and Temozoloide in Combination with Radiation Therapy in Newly Diagnosed Glioblastoma Multiforme Patients All patients received weekly oral RAD001 in combination with standard chemo-radiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide	18	3 (27)	2 (11)	1 (6)
41.	Shen *et al* (57)	2014	Phase II Multicentred Study of Low-Dose Everolimus plus Cisplatin and Weekly 24-Hour Infusion of High-Dose 5-Fluorouracil and Leucovorin as First-Line Treatment for Patients with Advanced Gastric Cancer everolimus (10 mg p.o. on days 1, 8 and 15) plus cisplatin and a weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin (HDFL) chemotherapy (cisplatin 35 mg/m2 intrave- nous infusion for 24 h on days 1 and 8, 5-fluorouracil 2,000 mg/m2 and leucovorin 300 mg/m2 intravenous infusion for 24 h on days 1, 8 and 15) every 28 days	40	18 (45)	12 (30)	6 (15)
42.	Slomovitz *et al* (59)	2010	A Phase 2 Study of the Oral Mammalian Target of Rapamycin Inhibitor, Everolimus, in Patients With Recurrent Endometrial Carcinoma Everolimus was administered at a dose of 10 mg orally daily for 28-day cycles.	35	7 (20)	6 (17)	1 (3)
43.	Strickler *et al* (95)	2012	Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors	12	3 (25)	3 (25)	0

			10 mg of panobinostat three times weekly, 5 or 10 mg everolimus daily, and bevacizumab at 10 mg/kg every 2 weeks.				
44.	Sun *et al* (60)	2013	A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer a everolimus 2.5 mg b everolimus 5 mg c everolimus 10 mg	A 6 B 11 C 3	A 2 (33) B 3 (27) C 1 (33)	A 2 (33) B 3 (27) C 1 (33)	A 0 B 0 C 0
45.	Tarhini *et al* (61)	2010	Phase II Study of Everolimus (RAD001) in Previously Treated Small Cell Lung Cancer everolimus 10 mg orally daily until disease progression.	40	6 (15)	6 (15)	0
46.	Tobinai *et al* (96)	2010	Phase I study of the oral mammalian target of rapamycin inhibitor everolimus (RAD001) in Japanese patients with relapsed or refractory non-Hodgkin lymphoma A everolimus 5 mg once daily B everolimus 10 mg once daily	A 7 B 6	A 1 (14.2) B 3 (50)	A 1 (14.2) B 2 (34)	A 0 B 1 (16)
47.	Vlahovic *et al* (63)	2012	A phase I study of bevacizumab, everolimus and panitumumab in advanced solid tumors everolimus and flat dosing of pani-tumumab at 4.8 mg/kg and bevacizumab at 10 mg/kg every 2 weeks.	32	12 (38)	12 (38)	0
48.	Wolpin *et al* (97)	2009	Oral mTOR Inhibitor Everolimus in Patients With Gemcitabine-Refractory Metastatic Pancreatic Cancer Everolimus 10 mg daily	33	5 (15)	5 (15)	0
49.	Yee *et al* (98)	2014	Outcomes in patients with relapsed or refractory multiple myeloma in a phase I study of everolimus in combination with lenalidomide	25	3 (12)	2 (8)	1 (4)
50.	Yee *et al* (99)	2006	Phase I/II Study of the Mammalian Target of Rapamycin Inhibitor Everolimus (RAD001) in Patients with Relapsed or Refractory Hematologic Malignancies Everolimus Patients were treated with 5 (first three patients) or 10 mg orally once daily continuously either in a fasted state or	27	11 (41)	10 (37)	1 (4)

		after a light fat-free meal. One treatment cycle consisted of 28 days of therapy.				
Total overall			2,120	534 (25.2)	-	-
Total with grade			2,120	534 (25.2)	463 (21.8)	71 (3.3)
Total with grade		Only everolimus at 2.5 mg	6	2 (33.3)	2 (33.3)	0
Total with grade		Only everolimus at 5 mg	18	4 (22.2)	4 (22.2)	0
Total with grade		Only everolimus at 10 mg	657	152 (23.1)	122 (18.6)	30 (4.5)

Table SIII. Incidence of asthenia in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 cases (%)	Grade 3/4 cases (%)
1. Andre *et al* (67)	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 3 trial, we 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 randomisation system to daily everolimus (5 mg/day) plus weekly trastuzumab (2 mg/kg) and vinorelbine (25 mg/m2) or to placebo plus trastuzumab plus vinorelbine, in 3-week cycles, stratified by previous lapatinib use.A	280	74 (26)	60 (21)	14 (5)
2. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer In this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily).	482	12 (2.4)	10 (2.0)	2 (0.4)
3. Baselga *et al* (4)	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	24 (17.5)	24 (17.5)	0
4. Besse *et al* (8)	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	13 (19.7)	6 (9.1)	7 (10.6)

5. Buzzoni *et al* (9)	2017	impact of prior therapies on everolimus activity: an exploratory analysis of raDianT-4 Patients were randomized (2:1) to everolimus 10 mg/day or placebo, both with best supportive care.	202	32 (16)	30 (15)	2 (1)
6. Campone *et al* (100)	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	7 (43.7)	6 (37.5)	1 (6.2)
7. Choueiri *et al* (11)	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma everolimus at a dose of 10 mg daily	322	50 (16)	44 (14)	6 (2)
8. Ciruelos *et al* (101)	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 (either 2 9 5 mg or 1 9 10 mg) and exemestane (25 mg) and continued until disease pro- gression, unacceptable toxicity	429	108 (25)	88 (20)	20 (5)
9. Conconi *et al* (15)	2014	Clinical activity of everolimus in relapsed/refractory marginal zone B-cell lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group; the study drug everolimus (RAD001) was administered orally at a daily dose of 10 mg, from day 1 to day 28 for up to a total of six cycles or until progression	30	8 (26.6)	8 (26.6)	0
10. Escudier at al.(70)	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	41 (45)	29 (32)	12 (13)

11. Fazio *et al* (18)	2018	Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis everolimus 10 mg/day	62	14 (22.6)	13 (21)	1 (1.6)
12. Ferolla *et al* (71)	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 Everolimus (10 mg orally once daily)	42	13 (31)	12 (29)	1 (2)
13. Hurvitz *et al* (25)	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	28	26 (47.3)	2 (3.6)
14. Jerusalem *et al* (26)	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)	2131	485 (22.8)	408 (19.2)	77 (3.6)
15. Kim *et al* (29)	2014	A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities.	34	13 (38.2)	11 (32.3)	2 (5.9)
16. Kim *et al* (87)	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	10 (27.8)	10 (27.8)	0
17. Kulke *et al* (35)	2017	A randomized, open-label, phase 2 study of everolimus in combination with pasireotide	A 78 B 81	A 17 (21.8) B	A 12 (15.4) B 13 (16.1)	A 5 (6.4)

		LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial A: everolismus +pasireotide LAR everolimus (10 mg/day, orally) and pasireotide long-acting release (60 mg/28 days, intramuscularly); B: Everolimus alone (10 mg/day, orally)		17 (21)		B 4 (4.9)
18. Moscetti *et al* (102)	2016	Safety analysis, association with response and previous treatments of everolimus and exemestane in 181 metastatic breast cancer patients: A multicenter Italian experience	181	90 (49.8)	87 (48.1)	3 (1.7)
19. Motzer *et al* (42)	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 dosage was 10 mg daily continually, and the sunitinib dosage was 50 mg daily in a schedule of 4 weeks on followed by 2 weeks off	337	40 (11.9)	31 (9.2)	9 (2.7)
20. Motzer *et al* (74)	2008	Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial everolimus 10 mg once daily	269	48 (18)	44 (17)	4 (1)
21. Motzer *et al* (75)	2015	Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial Only everolimus: 10 mg day (50 cases)	50	19 (38)	18 (36)	1 (2)
22. Oh *et al* (45)	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	8 (23.5)	7 (20.6)	1 (2.9)
23. Ohtsu *et al* (46)	2013	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study	437	70 (16)	50 (11)	20 (5)

		Everolimus 10 mg/d				
24. Panzuto *et al* (49)	2014	Real-World Study of Everolimus in Advanced Progressive Neuroendocrine Tumors Everolimus starting dose was 10 mg daily; the investigator had the option of starting at or reducing the dose to 5 mg daily depending on the patient's baseline clinical status and tolerability.	169	30 (17.7)	27 (15.9)	3 (1.8)
25. Park *et al* (103)	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 10 mg dose once daily	100	45 (47)	45 (47)	0
26. Pavel *et al* (50)	2016	Safety and QOL in Patients with Advanced NET in a Phase 3b Expanded Access Study of Everolimus; oral everolimus (two 5 mg tablets, totally 10 mg/day, in 28-day cycles) was taken by patients until disease progression, unacceptable toxicity, death, discontinuation from the study for any other reason, commercial availability for advanced NET in each participating country. It was allowed modification of the protocol in presence of mild or moderate hepatic impairment	pNET 123 Non pNET 117	pNET 12 (9.8) Non pNET 7 (6.0)	pNET 9 (7.3) Non pNET 3 (2.5)	pNET 3 (2.5) Non pNET 4 (3.5)
27. Powles *et al* (104)	2016	Randomized Open-Label Phase II Trial of Apitolisib (GDC-0980), a Novel Inhibitor of the PI3K/Mammalian Target of Rapamycin Pathway, Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma; everolimus 10 mg once per day	43	9 (21)	7 (16)	2 (5)
28. Rizzo *et al* (105)	2015	Everolimus as second-line therapy for metastatic renal cell carcinoma: a 'real-life' study; everolimus 10 mg/day	100	20 (20)	18 (18)	2 (2%)
29. Robles *et al* (106)	2016	Everolimus safety and efficacy for renal angiomyolipomas associated with tuberous sclerosis complex: a Spanish expanded access trial	19	3 (15.8)	3 (15.8)	0

		10 mg everolimus once daily				
30. Salazar *et al* (54)	2017	Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Na€ıve Advanced Pancreatic Neuroendocrine Tumors Everolimus 10 mg once daily	31	13 (41.9)	12 (38.7)	1 (3.2)
31. Wang *et al* (107)	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study; everolimus 10 mg/d in adults	58	9 (15.5)	6 (10.3)	3 (5.2)
32. Yao *et al* (108)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors; 10 mg once daily	204	26 (13)	24 (12)	2 (1)
Total over all			6,847	1,415 (20.6)	-	-
Total with grade			6,847	1,415 (20.6)	1, 201 (17.5)	214 (3.1)
Total with grade		Only everolimus at 2.5 mg	-	-	-	-
Total with grade		Only everolimus at 5 mg	-	-	-	-
Total with grade		Only everolimus at 10 mg	2,168	445 (20.5)	382 (17.6)	63 (2.9)

Table SIV. Incidence of diarrhoea in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 cases (%)	Grade 3/4 cases (%)
1. Abida *et al* (109)	2016	Phase I Study of Everolimus in Combination with Gemcitabine and Split-Dose Cisplatin in Advanced Urothelial Carcinoma gemcitabine 800 mg/m^2 and cisplatin 35 mg/m^2 on days 1 and 8 of 21-day cycles for a total of 6 cycles in combination with everolimus at increasing dose levels (DL1:5 mg QOD, DL2:5 mg daily, DL3:10 mg daily) following a standard 3+3 design.	A:12	1 (8)		
2. Amato *et al* (1)	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 was given 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 2 cycles (8 weeks) using Response Evaluation Criteria in Solid Tumors (RECIST).	A:39	11 (30.7)	11 (30.7)	0
3. Bachelot *et al* (76)	2012	Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study; this open-label, phase II study randomly assigned postmenopausal women with hormone receptor– positive, human epidermal growth factor receptor 2–negative, AI-resistant mBC to tamoxifen 20 mg/d plus	54	21 (39)	20 37)	1 (2)

		everolimus 10 mg/d (n 54) or tamoxifen 20 mg/d alone (n 57). tamoxifen plus everolimus				
4. Bajetta *et al* (2)	2014	Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients With Neuroendocrine Tumors; treatment-naive 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	1 (2)	1 (2)	0
5. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer In this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily).	482	30 (6.2)	27 (5.6)	3 (0.6)
6. Bendell *et al* (5)	2015	A phase Ib study of linsitinib (OSI-906), a dual inhibitor of IGF-1R and IR tyrosine kinase, in combination with everolimus as treatment for patients with refractory metastatic colorectal cancer; OSI-906 and everolimus were administered to cohorts of 3-6 patients in a standard 3+3 design	18	7 (38)	7 (38)	0
7. Bergmann *et al* (6)	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	16 (5)	11 (3)	5(2)
8. Besse *et al* (8)	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 (72.7)	43 (65.1)	5 (7.6)
9. Bissler *et al* (110)	2016	Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: extension of a randomized controlled trial	112	22 (19.6)	22 (19.6)	0

		A starting dose of 10 mg was chosen as a means of providing adequate exposure to almost all patients based on dose proportionality in this adult age group. Dose modifications were to be determined clinically and were based solely on tolerability. Doses could be lowered to 5 mg/day or even to 5 mg/ every other day				
10. Bissler *et al* (69)	2013	Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial oral everolimus 10 mg per day	79	10 (13)	10 (13)	0
11. Buzzoni *et al* (9)	2017	impact of prior therapies on everolimus activity: an exploratory analysis of raDianT-4 Patients were randomized (2:1) to everolimus 10 mg/day or placebo, both with best supportive care.	202	63 (31)	48 (24)	15 (7)
12. Campone *et al* (100)	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	2 (12.5)	2 (12.5)	0
13. Castellano *et al* (111)	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	5 (26.3)		
14. Chan *et al* (78)	2013	A Prospective, Phase 1/2 Study of Everolimus and Temozolomide in Patients With Advanced Pancreatic Neuroendocrine Tumor; patients were treated with temozolomide at a dose of 150 mg/m^2 per day on days 1 through 7 and days 15 through 21 in combination with everolimus daily in each 28-day cycle. In cohort 1, temozolomide was administered	43	22 (51)	21 (49)	1 (2)

		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				
15. Choueiri *et al* (11)	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma; everolimus at a dose of 10 mg daily	322	88 (27)	81(25)	7(2)
16. Chow *et al* (12)	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	4 (16.6)	4 (16.6)	0
17. Chung *et al* (13)	2016	Phase Ib Trial of mFOLFOX6 and Everolimus (NSC-733504) in Patients with Metastatic Gastroesophageal Adenocarcinoma; six patients were accrued to the first dose level of 2.5 mg everolimus daily with mFOLFOX6.	6	3 (50)	3 (50)	0
18. Cibrik *et al* (112)	2013	Randomized Trial of Everolimus-Facilitated Calcineurin Inhibitor Minimization Over 24 Months in Renal Transplantation A: Everolimus 3-8 ng/ml B: Everolimus 6-12 ng/ml	A: 274 B: 278	A 60 (21.9) B 57 (20.5)		
19. Cicora *et al* (113)	2015	Variances in the Use of Everolimus in Kidney Transplantation: A 2-Year Registry of Everyday Practice Everolimus	181	19 (10.5)		
20. Ciunci *et al* (14)	2014	Phase 1 and Pharmacodynamic Trial of Everolimus in Combination With Cetuximab in Patients With Advanced Cancer	29	4 (13.7)	4 (13.7)	0
21. Conconi *et al* (15)	2014	Clinical activity of everolimus in relapsed/refractory marginal zone B-cell lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group The study drug everolimus (RAD001) was administered orally at a daily dose of 10 mg,	30	3 (10)	3 (10)	0

		from day 1 to day 28 for up to a total of six cycles or until progression				
22. Dasari *et al* (16)	2015	Phase I study of the anti-IGF1R antibody cixutumumab with everolimus and octreotide in advanced well differentiated neuroendocrine tumors; keeping the doses of everolimus (10 mg p.o. daily) and octreotide LAR (20 mg i.m. every 21 days) constant, cixutumumab was evaluated at escalating doses of 10 and 15 mg/kg every 21 days for a 21-day cycle. Octreotide LAR was administered every 21 days rather than the standard practice of every 28 days to fit with the study schedule for patients' convenience.	19	11 (58)	11(58)	0
23. De Fijter *et al* (114)	2017	Early Conversion From Calcineurin Inhibitor- to Everolimus-Based Therapy Following Kidney Transplantation: Results of the Randomized ELEVATE Trial everolimus	352	82 (23.3)		
24. El-Madani *et al* (17)	2017	EVESOR, a model-based, multiparameter, Phase I trial to optimize the bene t/toxicity ratio of everolimus and sorafenib Everolimus +sorafenib	26	3 (11.5)	3 (11.5)	0
25. Escudier *at al* (70)	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	36 (39)	34 (37)	2 (2)
26. Fazio *et al* (18)	2018	Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis everolimus 10 mg/d	62	16 (25.8)	13 (21)	3 (4.8)
27. Fazio *et al* (19)	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	9 (27.3)	6 (18.2)	3 (9.1)

28.	Finn *et al* (115)	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 10 (62.5) B 10 (71.4)	A 9 (56.2) B 9 (64.3)	A 1(6.3) B 1 (7.1)
29.	Fogarasi *et al* (116)	2016	EFFECTS: an expanded access program of everolimus for patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex; patients received once daily everolimus (dose adjusted to attain a trough level of 5-15 ng/ml)	120	6 (5)	5 (4.2)	1 (0.8)
30.	Franz *et al* (117)	2013	Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial; everolimus was administered orally at a starting dose of 4·5 mg/m2 body surface area per day and subsequently adjusted to attain blood trough concentrations of 5–15 ng/ml	78	10 (13)	10 (13)	0
31.	Fury *et al* (118)	2013	A Phase 1 Study of Everolimus D Weekly Cisplatin D Intensity Modulated Radiation Therapy in Head-and-Neck Cancer; everolimus + cisplatin	13	5 (39)	4 (31)	1 (8)
32.	Fury *et al* (80)	2012	A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors	30	15 (54)	15 (54)	0
33.	Gadgeel *et al* (81)	2013	Phase I study evaluating the combination of lapatinib (a Her2/Neu and EGFR inhibitor) and everolimus (an mTOR inhibitor) in patients with advanced cancers: South West Oncology Group (SWOG) Study S0528; The MTD of the combination was 1,250 mg of lapatinib and 5 mg of everolimus once daily	54	32 (60)	28 (51.8)	4 (8.2)
34.	Gelsomino *et al* (119)	2017	A dose finding and biomarkers evaluation phase Ib study of Everolimus in association with 5-Fluorouracil and pelvic radiotherapy	A: 12	6 (50)	6 (50)	0

		as neo-adjuvant treatment for locally advanced rectal cancer (E-LARC); 2 weeks of administration of everolimus alone, followed by a concomitant treatment with everolimus, 5-Fluorouracil and radiotherapy				
35. Ghobrial *et al* (120)	2010	Phase II Trial of the Oral Mammalian Target of Rapamycin Inhibitor Everolimus in Relapsed or Refractory Waldenstrom Macroglobulinemia; everolimus 10 mg daily for two cycles	50	3 (6)	0	3 (6)
36. Glanville *et al* (121)	2015	Three-year results of an investigator-driven multicenter, international, randomized open-label de novo trial to prevent BOS after lung transplantation everolimus	84	29 (18)		
37. Goldberg et al.(122)	2015	Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study	24	7 (29)		
38. Gong *et al* (82)	2017	Ef cacy and safety of everolimus in Chinese metastatic HR positive, HER2 negative breast cancer patients: a real-world retrospective study; A: everolimus was usually initiated at the dose of 10 mg or in some instances at 5 mg daily, according to patients' tolerance and request.	70	9 (12.9)	8 (11.4)	1 (1.5)
39. Grignani *et al* (72)	2014	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial; patients took 400 mg sorafenib twice a day together with 5 mg everolimus once a day	38	18 (47)	16 (42)	2 (5)
40. Gross *et al* (83)	2018	Safety and Efficacy of Docetaxel, Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m^2, bevacizumab 15 mg/kg, and everolimus 2.5 mg	43	25 (58.1)	24 (55.8)	1 (2.3)
41. Grushkin *et al* (123)	2013	*De novo* therapy with everolimus and reduced-exposure cyclosporine following pediatric kidney transplantation: A prospective, multicenter, 12-month study everolimus (target trough concentration 3	18	4 (22.2)		

		ng/ml) with reduced-exposure CsA and corticosteroids				
42. Guglielmelli *et al* (124)	2011	Safety and efficacy of everolimus, a mTOR inhibitor, as single agent in a phase 1/2 study in patients with myelofibrosis; everolimus in 3 dose-escalating cohorts at 5.0, 7.5, and 10.0 mg daily for 3 months	30	2 (6.7)	2 (6.7)	0
43. Guo *et al* (20)	2013	Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy: an open-label phase 1b study; patients received everolimus 10 mg daily until objective tumor progression (according to RECIST, version 1.0), unacceptable toxicity, death, or study discontinuation for any other reason	64	12 (19)	11 (17)	1 (2)
44. Hainsworth *et al* (21)	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	36 (45)	29 (36)	7 (9)
45. Harzstark *et al* (84)	2011	A Phase 1 Study of Everolimus and Sorafenib for Metastatic Clear Cell Renal Cell Carcinoma; starting doses were everolimus at a dose of 2.5 mg orally daily and sorafenib at a dose of 400 mg orally twice daily continuously	20	7 (35)	5 (25)	2 (10)
46. Hatano *et al* (22)	2016	Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: A single institution experience in Japan; dose of everolimus was set at 10 mg once a day for adults.	47	5 (11)	5 (11)	0
47. Hatano *et al* (23)	2017	Intermittent everolimus administration for renal angiomyolipoma associated with tuberous sclerosis complex; dose of everolimus was set at 10 mg once a day	26	4 (15)	4 (15)	0

48. Hurvitz *et al* (25)	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	31 (56.4)	28 (50.9)	3 (5.5)
49. Jerusalem *et al* (26)	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); Everolimus patients self-administered EVE on day 1 and continued daily doses of EVE (either 2x5 or 1 x 10 mg) plus EXE (25 mg/day) in 28-day cycles.	2,131	359 (16.8)	332 (15.7)	27 (1.2)
50. Johnston *et al* (27)	2016	The mTORC1 Inhibitor Everolimus Combined with R-CHOP-21 for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Safety and Efficacy Results of a Phase I and Feasibility Trial NCCTG 1085 (Alliance) everolimus 10 mg days 1-10 or 1-14 in combination with R-CHOP-21 for 6 cycles	24	12 (50)	12 (50)	0
51. Jovanovic *et al* (28)	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 Everolimus cisplatin 25 mg/m2 IV weekly for 12 weeks, everolimus 5 mg orally daily for 12 weeks, and paclitaxel 80 mg/m^2 IV	96	31 (32)	29 (30)	2 (2)

		weekly for 11 weeks (starting 1 week after cisplatin initiation)				
52. Jozwiak *et al* (125)	2016	Safety of Everolimus in Patients Younger than 3 Years of Age: Results from EXIST-1, a Randomized, Controlled Clinical Trial; everolimus was initiated at 4.5 mg/m^2/day and titrated to blood trough levels of 5-15 ng/ml	18	5 (27.8)		
53. Ju *et al* (85)	2015	Toxicity and adverse effects of everolimus in the treatment of advanced nonsmall cell lung cancer pretreated with chemotherapy-Chinese experiences; everolimus 5-10 mg/day with or without chemotherapy until progression or unacceptable toxicity.	12	2 (16.6)	2 (16.6)	0
54. Kanesvaran *et al* (126)	2015	A single arm phase 1b study of everolimus and sunitinib in patients with advanced renal cell carcinoma (RCC); Sunitinib + everolimus	4	3 (75)	2 (50)	1 (25)
55. Kato *et al* (86)	2013	Efficacy of Everolimus in Patients with Advanced Renal Cell Carcinoma Refractory or Intolerant to VEGFR-TKIs and Safety Compared with Prior VEGFR-TKI Treatment	19	2 (11)	2 (11)	0
56. Kim *et al* (87)	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	7 (19.4)	6 (16.6)	1 (2.8)
57. Kim *et al* (30)	2013	A phase I study of everolimus and CHOP in newly diagnosed peripheral T-cell lymphomas Four dose levels (2.5 to 10 mg) of everolimus from days 1 to 14 with CHOP (750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 (maximum 2 mg) vincristine on day 1, and 100 mg/day prednisone on days 1 to 5) every 21 days were planned.	15	6 (40)	5 (33.3)	1 (6.7)
58. Knox *et al* (31)	2017	Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line	238	15 (6.3)		

		sunitinib followed by everolimus in metastatic RCC; Patients were randomly assigned 1:1 to receive either first-line everolimus 10 mg/day				
59. Koeberle *et al* (32)	2016	Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29); sorafenib + everolimus	59	38 (64)	26 (44)	12 (20)
60. Kordes *et al* (33)	2013	A phase I/II, non-randomized, feasibility/safety and efficacy study of the combination of everolimus, cetuximab and capecitabine in patients with advanced pancreatic cancer Safety and efficacy of fixed standard dose cetuximab in combination with various dose levels of everolimus (5-10 mg/day) and capecitabine (600–800 mg/ m^2 bid, 2 weeks every 3 weeks) were investigated in a phase I/II study in patients with advanced pancreatic cancer.	31	10 (32)	6 (19)	4 (13)
61. Koutsoukos *et al* (34)	2017	Real-world experience of everolimus as second-line treatment in metastatic renal cell cancer after failure of pazopanib Everolimus: media of everolimus daily dose was 10 mg (5-10 mg), while the mean daily dose was 9.3 mg	31	2 (7)	2 (7)	0
62. Kulke *et al* (35)	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: everolismus 10 mg/day, orally, per os (po) + pasireotide LAR (60 mg/28 day, IM) B: everolimus 10 mg/day, orally, per os (po)	A: 78 B: 81	A 49 (62.8) B 43 (53.1)	A 45 (57.7) B 40 (49.4)	A 4 (5.1) B 3 (3.7)
63. Lim *et al* (89)	2013	A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes;	38	6 (15)	2 (5)	4 (10)

		everolimus 10 mg daily orally until unacceptable toxicity or disease progression				
64. Massarweh *et al* (37)	2014	A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure; Fulvestrant was administered intramuscularly (in the gluteus maximus) in a loading dose schedule as follows: 500 mg in two divided doses, one on each side on day 1, then 250 mg on day 14, and then 250 mg on day 28 and every 4 weeks ± 3 days thereafter. Everolimus was administered initially at a dose of 5 mg daily in the first 5-patient cohort for the first month of treatment and then increased to 10 mg PO daily after that.	31	5 (16)	5 (16)	0
65. Milowsky *et al* (127)	2013	Phase II study of everolimus in metastatic urothelial cancer; all patients received everolimus 10 mg orally once daily continuously (one cycle = 4 weeks)	45	7 (16)	7 (16)	0
66. Molina *et al* (38)	2012	Phase 1 Trial of Everolimus Plus Sunitinib in Patients With Metastatic Renal Cell Carcinoma; A: everolimus + sunitinib	20	10 (50)	6 (30)	4
67. Molina *et al* (39)	2014	A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of metastatic renal cell carcinoma (RCC) A: lenvatinib [12 mg (n=7); 18 mg (n=11); 24 mg (n=2)] plus everolimus 5 mg	20	8 (40)	6 (30)	2 (10)
68. Morrow *et al* (40)	2011	Phase I/II Study of Trastuzumab in Combination With Everolimus (RAD001) in Patients With HER2-Overexpressing Metastatic Breast Cancer Who Progressed on Trastuzumab-Based Therapy	47	5 (11)	1 (2)	4 (9)
69. Moscetti *et al* (102)	2016	Safety analysis, association with response and previous treatments of everolimus and exemestane in 181 metastatic breast cancer patients: A multicenter Italian experience	181	11 (6.6)	11 (6.6)	0

70. (42)	Motzer *et al*	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; the everolimus dosage was 10 mg daily continually, and the sunitinib dosage was 50 mg daily in a schedule of 4 weeks on followed by 2 weeks off. Dose modifications were permitted for adverse events (AEs)	337	103 (30.6)	91 (27)	12(3.6)
71. (74)	Motzer *et al*	2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial everolimus 10 mg once daily	269	46 (17)	42 (16)	4 (1)
72. (75)	Motzer *et al*	2015	Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial everolimus 10 mg once daily	50	17 (34)	16 (32)	1 (2)
73. (43)	Narayan *et al*	2016	Phase I Trial of Everolimus and Radiation Therapy for Salvage Treatment of Biochemical Recurrence in Prostate Cancer Patients Following Prostatectomy Everolimus +srt	18	2 (11.1)	2 (11.1)	0
74. (44)	Niegisch *et al*	2015	Second-Line Treatment of Advanced Urothelial Cancer with Paclitaxel and Everolimus in a German Phase II Trial (AUO Trial AB 35/09); paclitaxel (175 mg/m2 i.v., 3-weekly) and the mTOR-inhibitor everolimus (10 mg p.o., once daily).	27	5 (18.5)	4 (14.8)	1 (3.7)
75. (90)	Nozawa *et al*	2013	Adverse Event Profile and Dose Modification of Everolimus for Advanced Renal Cell Carcinoma in Real-world Japanese Clinical Practice Everolimus	47	2 (4.2)	1 (2.1)	1 (2.1)
76.	Oh *et al* (45)	2012	Phase 2 Study of Everolimus Monotherapy in Patients With Nonfunctioning	34	9 (26.5)	8 (23.6)	1 (2.9)

			Neuroendocrine Tumors or Pheochromocytomas/ Paragangliomas; everolimus was administered daily at a dose of 10 mg for 4 weeks.				
77. (46)	Ohtsu *et al*	2013	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study Everolimus 10 mg/daily	437	115 (26)	100 (23)	15 (3)
78.	Ou *et al* (91)	2015	SWOG S0722: Phase II study of mTOR inhibitor everolimus (RAD001) in advanced malignant pleural mesothelioma (MPM) Everolimus orally at 10 mg once daily until disease progression or unacceptable toxicity.	59	15 (25.4)	14 (23.7)	1 (1.7)
79. (47)	Oudard *et al*	2016	Clinical Benefit of Everolimus as Second-Line Therapy in Metastatic Renal Cell Carcinoma: The French Retrospective SECTOR Study Everolimus	162	28 (17.3)	28 (17.3)	0
80. (103)	Park *et al*	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 oral (10 mg dose once daily)	100	11 (12)	11 (12)	0
81. (50)	Pavel *et al*	2016	Safety and QOL in Patients with Advanced NET in a Phase 3b Expanded Access Study of Everolimus; everolimus oral (two 5 mg tablets, totally 10 mg/day, in 28-day cycles) was taken by patients until disease progression, unacceptable toxicity, death, discontinuation from the study for any other reason, commercial availability for advanced NET in each participating country	pNET 123 Non pNET 117	pNET 13 (10.6) Non pNET 37 (31.6)	pNET 8 (6.5) Non pNET 27 (23.9)	pNET 5 (4.1) Non pNET 10 (8.6)
82. (128)	Powles *et al*	2014	A phase Ib study investigating the combination of everolimus and dovitinib in vascular endothelial growth factor refractory clear cell renal cancer; everolimus 5 mg orally (PO) once daily (OD) and dovitinib 200 mg PO day 1–5/7.	15	8 (53)	7 (47)	1 (7)

83. Powles *et al* (104)	2016	Randomized Open-Label Phase II Trial of Apitolisib (GDC-0980), a Novel Inhibitor of the PI3K/Mammalian Target of Rapamycin Pathway, Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma; everolimus 10 mg once per day	43	22 (51)	21 (49)	1 (2)
84. Quek *et al* (92)	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	6 (28.6)	5 (23.8)	1 (4.8)
85. Ramalingam *et al* (129)	2010	Phase 1 and Pharmacokinetic Study of Everolimus, a Mammalian Target of Rapamycin Inhibitor, in Combination With Docetaxel for Recurrent/Refractory Nonsmall Cell Lung Cancer; escalating doses of docetaxel (Day 1) and everolimus (orally daily, Days 1-19) every 3 weeks.	24	1 (4.1)	0	1 (4.1)
86. Rathkopf *et al* (93)	2015	Everolimus Combined With Gefitinib in Patients With Metastatic Castration-Resistant Prostate Cancer: Phase 1/2 Results and Signaling Pathway Implications; in phase 1, 12 patients (10 with CRPC and 2 with glioblastoma) received daily gefitinib (250 mg) with weekly everolimus (30, 50, or 70 mg). In phase 2, 27 CRPC patients received gefitinib with everolimus (70 mg)	39	25 (65)	25 (65)	0
87. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO everolimus 10mg per day until progression or unacceptable toxicity	43	19 (44)	14 (32)	5 (12)
88. Rizzo *et al* (105)	2015	Everolimus as second-line therapy for metastatic renal cell carcinoma: a 'real-life' study; everolimus 10 mg/day	100	14 (14)	11 (11)	3 (3)

89. Robles *et al* (106)	2016	Everolimus safety and efficacy for renal angiomyolipomas associated with tuberous sclerosis complex: a Spanish expanded access trial; 10 mg everolimus once daily	19	4 (21.1)	4 (21.1)	0
90. Rodrigues *et al* (52)	2015	Phase I combination of pazopanib and everolimus in PIK3CA mutation positive/PTEN loss patients with advanced solid tumors refractory to standard therapy; pazopanib 600 mg every other day (QOD) alternating with everolimus 10 mg PO QOD.	52	4 (7.6)	2 (3.8)	2 (3.8)
91. Ryan *et al* (94)	2011	A phase II study of everolimus in combination with imatinib for previously treated advanced renal carcinoma; everolimus 2.5 mg po daily and imatinib 600 mg po daily.	19	11 (58)	10 (53)	1 (5)
92. Safra *et al* (107)	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	21 (29.2)	18 (13)	3 (5.6)
93. Salazar *et al* (54)	2017	Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Na€ıve Advanced Pancreatic Neuroendocrine Tumors; everolimus 10 mg once daily	31	17 (54.8)	16 (51.6)	1 (3.2)
94. Sanoff *et al* (55)	2015	Everolimus and pasireotide for advanced and metastatic hepatocellular carcinoma; everolimus 7.5 mg PO daily and pasireotide LAR 60 mg IM every 28 days.	24	7 (29)	6 (26)	1 (4)
95. Sarkaria *et al* (56)	2011	NCCTG 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 chemo-radiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide	18	4	4 (23)	0

96. Shen *et al* (57)	2014	Phase II Multicentered Study of Low-Dose Everolimus plus Cisplatin and Weekly 24-Hour Infusion of High-Dose 5-Fluorouracil and Leucovorin as First-Line Treatment for Patients with Advanced Gastric Cancer; everolimus (10 mg p.o. on days 1, 8 and 15) plus cisplatin and a weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin (HDFL) chemotherapy (cisplatin 35 mg/m2 intrave- nous infusion for 24 h on days 1 and 8, 5-fluorouracil 2,000 mg/m2 and leucovorin 300 mg/m2 intravenous infusion for 24 h on days 1, 8 and 15) every 28 days	40	12 (30)	9 (22.5)	3 (7.5)
97. Shoushtari *et al* (58)	2016	Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients; Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients	13	9 (64)	8 (57)	1(7)
98. Strickler *et al* (95)	2012	Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors; 10 mg of panobinostat three times weekly, 5 or 10 mg everolimus daily, and bevacizumab at 10 mg/kg every 2 weeks.	12	6 (50)	6 (50)	0
99. Sun *et al* (60)	2013	A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer A: everolimus 2.5 mg B: everolimus 5 mg C: everolimus 10 mg	A 6 B 11 C 3	A 0 B 2 (18.1) C 1 (33.3)	A 0 B 2 (18.1) C 1 (33.3)	A 0 B 0 C 0
100. Takahashi *et al* (130)	2013	Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results; everolimus regimen (1.5 mg/day starting dose (target trough: 3 to 8 ng/ml) + reduced-dose cyclosporine)	61	11 (18)		
101. Tan *et al* (131)	2017	The mTOR inhibitor everolimus in combination with azacitidine in patients with	37	5 (13.5)		

		relapsed/refractory acute myeloid leukemia: a phase Ib/II study				
102. Tarhini *et al* (61)	2010	Phase II Study of Everolimus (RAD001) in Previously Treated Small Cell Lung Cancer everolimus 10 mg orally daily until disease progression.	40	6 (15)	5 (12.5)	1 (2.5)
103. Thudium *et al* (132)	2015	Bioavailability of everolimus administered as a single 5 mg tablet versus five 1 mg tablets: a randomized, open-label, two-way crossover study of healthy volunteers; Subjects were randomized 1:1 to receive everolimus dosed as one 5 mg tablet or as five 1 mg tablets on day 1, followed by a washout period on days 8–14 and then the opposite formulation on day 15	22	1 (4.5)		
104. Vlahovic *et al* (63)	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	11 (34)	10 (31)	1 (3)
105. Wang *et al* (107)	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study; Everolimus 10 mg/d in adults with confirmed mantle cell lymphoma (MCL) refractory to or intolerant of bortezomib who received ≥1 other antineoplastic agent, either separately or in combination with bortezomib.	58	26 (44.8)	23 (39.6)	3 (5.2)
106. Werner *et al* (64)	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	5 (31.3)	4 (25)	1 (6.3)
107. Wolpin *et al* (97)	2009	Oral mTOR Inhibitor Everolimus in Patients With Gemcitabine-Refractory Metastatic Pancreatic Cancer; everolimus 10 mg daily	33	8 (24)	8 (24)	0

108. Yao *et al* (65)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors; everolimus 10 mg once daily	204	69 (34)	62 (31)	7(3)
109. Yee *et al* (98)	2014	Outcomes in patients with relapsed or refractory multiple myeloma in a phase I study of everolimus in combination with lenalidomide	26	7 (27)	6 (23.1)	1 (3.9)
110. Yee *et al* (99)	2006	Phase I/II Study of the Mammalian Target of Rapamycin Inhibitor Everolimus (RAD001) in Patie nts with Relapsed or Refractory Hematologic Malignancies; everolimus Two dose levels (5 and 10 mg orally once daily continuously)	27	9 (33)	8 (29)	1 (4)
Total overall			10,436	2,330 (22.3)		
Total with grade			8,818	2,029 (23)	1,797 (20.4)	232 (2.6)
Total with grade		Only everolimus at 2.5 mg	6	0	0	0
Total with grade		Only everolimus at 5 mg	11	2 (18.2)	2 (18.2)	0
Total with grade		Only everolimus at 10 mg	3,456	803 (22.5)	701 (19,6)	102 (2.9)

Table SV. Incidence of fatigue in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 cases (%)	Grade 3/4 cases (%)
1. Albiges *et al* (66)	2015	Everolimus for patients with metastatic renal cell carcinoma refractory to anti-VEGF therapy: Results of a pooled analysis of non-interventional studies metastatic renal cell carcinoma (mRCC) who failed one or two anti-VEGF therapies; everolimus 10 mg/day until disease progression or unacceptable toxicity	632	32 (7)	22 (5)	10 (2)
2. Andre *et al* (67)	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 3 trial, we 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 randomisation 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,	280	121 (44)	87 (31)	34 (13)

		in 3-week cycles, stratified by previous lapatinib use.A				
3. Angelousi *et al* (133)	2017	Sequential Everolimus and Sunitinib Treatment in Pancreatic Metastatic Well-Differentiated Neuroendocrine Tumours Resistant to Prior Treatments Thirty-one patients were administered one compound and upon progression were switched to the other. All patients had grade 1 or 2 tumours and stage IV disease with similar metastatic load. The everolimus full dosage was 10 mg daily, and the sunitinib 37.5 mg daily. However, dose modifications were permitted in the presence of AEs, so that everolimus could be decreased to 5 mg and sunitinib to 25 mg daily, respectively	A: 20 1st line everolimus B: 11 2nd line everolimus	A 2 (10) B 2 (18)	A 2 (10) B 2 (18)	A 0 B 0
4. Armstrong *et al* (68)	2016	Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial; everolimus was given orally at 10 mg once daily.	52	33 (58)	29 (51)	4 (7)
5. Bachelot *et al* (76)	2012	Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer With Prior Exposure	54	39 (72)	36 (66)	3 (6)

		to Aromatase Inhibitors: A GINECO Study; this open-label, phase II study randomly assigned postmenopausal women with hormone receptor– positive, human epidermal growth factor receptor 2–negative, AI-resistant mBC to tamoxifen 20 mg/day plus everolimus 10 mg/day (n 54) or tamoxifen 20 mg/day alone (n=57).				
6. Barnes *et al* (77)	2013	Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma; everolimus was administered orally once daily at a dose of 5 mg on days 1 through 14 of cycle 1. If tolerated, the dose was then increased to 10 mg for days 15 through 28 of cycle 1. For cycle 2 and beyond, patients continued to receive everolimus at a dose of 10 mg daily continuously. Rituximab, at a dose of 375 mg/m^2, was administered intravenously weekly for four doses during cycle 1, and then on day 1 of cycles 2 through 6. After cycle 6, patients could receive an additional 6 months of everolimus monotherapy in the absence of disease progression or unacceptable toxicity.	24	8 (33)	6 (25)	2 (8)
7. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-	482	33 (6.8)	30 (6.2)	3 (0.6)

		Receptor–Positive Advanced Breast Cancer; in this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily)				
8. Baselga *et al* (4)	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	17 (12.4)	15 (10.9)	2 (1.5)
9. Bendell *et al* (5)	2015	A phase Ib study of linsitinib (OSI-906), a dual inhibitor of IGF-1R and IR tyrosine kinase, in combination with everolimus as treatment for patients with refractory metastatic colorectal cancer OSI-906 and everolimus were administered to cohorts of 3-6 patients in a standard 3+3 design	18	9 (50)	9 (50)	0
10. Bergmann *et al* (6)	2015	Everolimus in metastatic renal cell carcinoma after failure of initial anti-VEGF therapy: final results of a noninterventional study;	334	37 (12)	24 (8)	13 (4)

		patients received everolimus 10 mg once daily until disease progression or unacceptable				
11. Besse *et al* (8)	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	15 (22.7)	11(33.3)	4 (6.1)
12. Bissler *et al* (134)	2018	The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant cell astrocytoma; patients were initially randomly assigned to receive everolimus 4.5 mg/m^2/day (target blood through 5-15 mg/dl) or placebo and could continue in an open-label extension phase	33	5 (15.2)		
13. Bissler *et al* (110)	2016	Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: extension of a randomized controlled trial; a starting dose of 10 mg was chosen as a means of pro-viding adequate exposure to almost all patients based on dose proportionality in this adult age group. Dose modifications were to be determined clinically and were based solely on toler-ability. Doses could be lowered to 5 mg/day or even to 5 mg/ every other day	112	20 (17.9)	19 (17)	1 (0.9)

14.	Bissler *et al* (69)	2013	Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial; oral everolimus 10 mg per day	79	14 (18)	13 (17)	1 (1)
15.	Buzzoni *et al* (9)	2017	impact of prior therapies on everolimus activity: an exploratory analysis of raDianT-4; patients were randomized (2:1) to everolimus 10 mg/day or placebo, both with best supportive care.	202	63 (31)	56 (28)	7 (3)
16.	Cazzaniga *et al* (135)	2017	Efficacy and safety of Everolimus and Exemestane in hormone- receptor positive (HRþ) human-epidermal-growth-factor negative (HER2) advanced breast cancer patients: New insights beyond clinical trials. The EVA study; The EVE starting dose was 10 mg dose, even if the 5 mg dose could be independently chosen by physicians.	404	134 (39.5)	123 (36.3)	11 (3.2)
17.	Choueiri *et al* (11)	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma; everolimus at a dose of 10 mg daily	322	146 (45)	124 (38)	22 (7)
18.	Chow *et al* (12)	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	24	13 (54.1)	13 (54.1)	0

		once daily, with a cycle defined as 4 weeks.				
19. Chung *et al* (13)	2016	Phase Ib Trial of mFOLFOX6 and Everolimus (NSC-733504) in Patients with Metastatic Gastroesophageal Adenocarcinoma; six patients were accrued to the first dose level of 2.5 mg everolimus daily with mFOLFOX6	6	6 (100)	6 (100)	0
20. Ciunci *et al* (14)	2014	Phase 1 and Pharmacodynamic Trial of Everolimus in Combination With Cetuximab in Patients With Advanced Cancer	29	7 (24.1)	6 (20.6)	1 (3.5)
21. Dasari *et al* (16)	2015	Phase I study of the anti-IGF1R antibody cixutumumab with everolimus and octreotide in advanced well-differentiated neuroendocrine tumors; Keeping the doses of ever-olimus (10 mg po daily) and octreotide LAR (20 mg i.m. every 21 days) constant, cixutumumab was evaluated at escalating doses of 10 and 15 mg/kg every 21 days for a 21-day cycle. Octreotide LAR was administered every 21 days rather than the standard practice of every 28 days to fit with the study schedule for patients' convenience.	19	14 (74)	9 (48)	5 (26)
22. Doi *et al* (136)	2010	Multicenter Phase II Study of Everolimus in Patients With Previously Treated Metastatic Gastric Cancer; everolimus 10 mg orally daily	53	3 (5.7)		

23.	El-Madani *et al* (17)	2017	EVESOR, a model-based, multiparameter, Phase I trial to optimize the bene t/toxicity ratio of everolimus and sorafenib; everolimus + sorafenib	26	18 (69.2)	12 (46.1)	6 (23.1)
24.	Ellard *et al* (79)	2009	Randomized Phase II Study Comparing Two Schedules of Everolimus in Patients With Recurrent/Metastatic Breast Cancer: NCIC Clinical Trials Group IND; randomized phase II study of everolimus 10 mg daily versus 70 mg weekly A: daily B: weekly	A 33 B 16	A 21 (63.6) B 12 (75)	A 5 (15.1) B 5 (31.2)	A 16 (48.4) B 7 (43.7)
25.	Escudier *et al* (70)	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	30 (33)	25 (28)	5 (5)
26.	Fazio *et al* (18)	2018	Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis; everolimus 10 mg/day	62	20 (32.3)	18 (29.1)	2 (3.2)
27.	Fazio *et al* (19)	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	33	4 (12.1)		

		everolimus + octreotide				
28. Ferolla *et al* (71)	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; everolimus long-acting pasireotide (60 mg intramuscularly every 28 days), everolimus (10 mg orally once daily), or both in combination, for the core 12-month treatment period.	A 42	8 (19)	7 (17)	1 (2)
29. Finn *et al* (115)	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 4 (25) B 5 (35.7)	A 4 (25) B 4 (28.6)	A 0 B 1 (7.1)
30. Franz *et al* (137)	2014	Everolimus for subependymal giant cell astrocytoma in patients with tuberous sclerosis complex: 2-year open-label extension of the randomised EXIST-1 study; everolimus oral at a starting dose of 4.5 mg/m^2 per day.	120	6 (5)	6 (5)	0
31. Franz *et al* (117)	2013	Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial	78	11 (14)	11 (14)	0

		Everolimus everolimus 4·5 mg/m^2 per day (titrated to achieve blood trough concentrations of 5-15 ng/ml)				
32. Fury *et al* (118)	2013	A Phase 1 Study of Everolimus D Weekly Cisplatin D Intensity Modulated Radiation Therapy in Head-and-Neck Cancer A: everolimus + cisplatin	13	13 (100)	11 (85)	2 (15)
33. Fury *et al* (80)	2012	A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors	30	27 (96)	24 (85)	3 (11)
34. Gadgeel *et al* (81)	2013	Phase I study evaluating the combination of lapatinib (a Her2/Neu and EGFR inhibitor) and everolimus (an mTOR inhibitor) in patients with advanced cancers: South West Oncology Group (SWOG) Study S0528; The MTD of the combination was 1,250 mg of lapatinib and 5 mg of everolimus once daily.	54	25 (47)	22 (40.7)	3 (6.3)
35. Ghobrial *et al* (138)	2014	Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory Waldenstrom Macroglobulinemia; everolimus 10 mg daily and were evaluated monthly.	60	5 (9)	0	5 (9)
36. Goldberg *et al* (122)	2015	Everolimus for the treatment of lymphangioleio-myomatosis: a phase II study Everolimus Following a 28-day screening period, patients received everolimus 2.5	24	7 (29)		

		mg/day for 4 weeks, followed by dose titration (based on safety and tolerability) to 5 mg/day for 4 weeks then 10 mg/day for 18 weeks thereafter				
37. Gong *et al* (82)	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 the dose of 10 mg or in some instances at 5 mg daily, according to patients' tolerance and request	70	18 (25.7)	17 (24.3)	1 (1.4)
38. Grignani *et al* (72)	2014	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial; patients took 400 mg sorafenib twice a day together with 5 mg everolimus once a day	38	16 (42)	14 (37)	2 (5)
39. Grunwald *et al* (73)	2012	An international expanded-access programme of everolimus: Addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy; patients received everolimus 10 mg once daily, with dose and schedule modifications allowed for toxicity	1,367	116 (8.5)	24 (1.8)	92 (6.7)

40. Guglielmelli *et al* (124)	2011	Safety and efficacy of everolimus, a mTOR inhibitor, as single agent in a phase 1/2 study in patients with myelofibrosis; everolimus in 3 dose-escalating cohorts at 5.0, 7.5, and 10.0 mg daily for 3 months	30	5 (16.9)	5 (16.9)	0
41. Guo *et al* (20)	2013	Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy: an open-label phase 1b study; patients received everolimus 10 mg daily until objective tumor progression (according to RECIST, version 1.0), unacceptable toxicity, death, or study discontinuation for any other reason.	64	20 (31)	19 (29)	1 (2)
42. Hainsworth *et al* (21)	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	62 (77)	52 (65)	10 (12)
43. Harzstark *et al* (84)	2011	A Phase 1 Study of Everolimus and Sorafenib for Metastatic Clear Cell Renal Cell Carcinoma; starting doses of everolimus were 2.5 mg orally daily and sorafenib at a dose of 400 mg	20	3 (15)	2 (10)	1 (5)

		orally twice daily continuously				
44. Hatano *et al* (22)	2016	Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: A single institution experience in Japan; the dose of everolimus was set at 10 mg once a day for adults.	47	7 (15)	7 (15)	0
45. Hatano *et al* (23)	2017	Intermittent everolimus administration for renal angiomyolipoma associated with tuberous sclerosis complex; the dose of everolimus was set at 10 mg once a day	26	3 (12)	3 (12)	0
46. Hill *et al* (24)	2017	A phase I trial of bortezomib in combination with everolimus for treatment of relapsed/refractory non-Hodgkin lymphoma bortezomib + everolimus	29	24	23	1
47. Hurvitz *et al* (25)	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	12 (21.9)	9 (16.4)	3 (5.5)
48. Jerusalem *et al* (26)	2016	Safety of everolimus plus exemestane in patients with	2,131	298 (14.0)	271 (12.7)	27 (1.3)

		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) Enrolled patients self-administered EVE on day 1 and continued daily doses of EVE (either 2x5 or 1x10 mg) plus EXE (25 mg/day) in 28-day cycles.				
49. Johnston *et al* (27)	2016	The mTORC1 Inhibitor Everolimus Combined with R-CHOP-21 for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Safety and Efficacy Results of a Phase I and Feasibility Trial NCCTG 1085 (Alliance); everolimus 10 mg days 1-10 or 1-14 in combination with R-CHOP-21 for 6 cycles	24	12 (50)	11 (46)	1 (4)
50. Jovanovic *et al* (28)	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	96	61 (64)	58 (61)	3 (3)
51. Ju *et al* (85)	2015	Toxicity and adverse effects of everolimus in the treatment of advanced nonsmall cell	12	1 (8.3)	1 (8.3)	0

		lung cancer pretreated with chemotherapy-Chinese experiences; everolimus 5-10 mg/day with or without chemotherapy until progression or unacceptable toxicity.				
52. Kanesvaran *et al* (126)	2015	A single arm phase 1b study of everolimus and sunitinib in patients with advanced renal cell carcinoma (RCC) Sunitinib + everolimus	4	4 (100)	3 (75)	1 (25)
53. Kato *et al* (86)	2013	Efficacy of Everolimus in Patients with Advanced Renal Cell Carcinoma Refractory or Intolerant to VEGFR-TKIs and Safety Compared with Prior VEGFR-TKI Treatment; everolimus	19	7 (37)	6 (32)	1 (5)
54. Kim *et al* (87)	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	14 (38.9)	13 (36.1)	1 (2.8)
55. Kim *et al* (88)	2016	Efficacy and Toxicity of Mammalian Target Rapamycin Inhibitors in Patients with Metastatic Renal Cell Carcinoma with Renal Insufficiency: The Korean Cancer Study Group GU 14-08; the starting oral dose of everolimus was 10 mg daily for 10 patients and the starting intravenous dose for temsirolimus was 25 mg	19	3 (16)	3 (16)	0

		weekly for eight patients in the overall series.				
56. Kim *et al* (30)	2013	A phase I study of everolimus and CHOP in newly diagnosed peripheral T-cell lymphomas; four dose levels (2.5 to 10 mg) of everolimus from days 1 to 14 with CHOP (750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 (maximum 2 mg) vincristine on day 1, and 100 mg/day prednisone on days 1 to 5) every 21 days were planned	15	3 (20)	3 (20)	0
57. Knox *et al* (31)	2017	Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC; patients were randomly assigned 1 : 1 to receive either first-line everolimus 10 mg/day	238	35 (14.7)		
58. Koeberle *et al* (32)	2016	Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29) Sorafenib + everolimus	59	39 (66)	22 (37)	17 (29)

59.	Kordes *et al* (33)	2013	A phase I/II, non-randomized, feasibility/safety and efficacy study of the combination of everolimus, cetuximab and capecitabine in patients with advanced pancreatic cancer Safety and efficacy of fixed standard dose cetuximab in combination with various dose levels of everolimus (5-10 mg/day) and capecitabine (600-800 mg/ m^2 bid, 2 weeks every 3 weeks) were investigated in a phase I/II study in patients with advanced pancreatic cancer	31	13 (42)	9 (29)	4 (13)
60.	Koutsoukos *et al* (34)	2017	Real-world experience of everolimus as second-line treatment in metastatic renal cell cancer after failure of pazopanib; everolimus: The median everolimus daily dose was 10 mg (5-10 mg), while the mean daily dose was 9.3 mg	31	3 (10)	3 (10)	0
61.	Kulke *et al* (35)	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: everolismus 10 mg/day, per oral (po) + pasireotide LAR (60 mg/28 day, IM) B: everolimus 10 mg/day, per os (po)	A 78 B 81	A 21 (26.9) B 28 (34.6)	A 18 (23.1) B 25 (30.9)	A 3 (3.8) B 3 (3.7)
62.	Kumano *et al* (36)	2013	Sequential use of mammalian target of rapamycin inhibitors	57	3 (5.3)	3 (5.3)	0

		in patients with metastatic renal cell carcinoma following failure of tyrosine kinase inhibitors; everolimus (10 mg orally, once daily)				
63. Macaskill *et al* (139)	2011	The mammalian target of rapamycin inhibitor everolimus (RAD001) in early breast cancer: results of a pre-operative study; 5 mg RAD001 once daily for 14 days prior to surgery.	31	6 (19.4)		
64. Massarweh *et al* (37)	2014	A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure; fulvestrant was administered intramuscularly (in the gluteus maximus) in a loading dose schedule as follows: 500 mg in two divided doses, one on each side on day 1, then 250 mg on day 14, and then 250 mg on day 28 and every 4 weeks ± 3 days thereafter. Everolimus was administered initially at a dose of 5 mg daily in the first 5-patient cohort for the first month of treatment and then increased to 10 mg po daily after that	31	10 (32)	10 (32)	0
65. Milowsky *et al* (127)	2013	Phase II study of everolimus in metastatic urothelial cancer; everolimus 10 mg orally once daily continuously (one cycle = 4 weeks)	45	44 (98)	39 (87)	5 (11)

66. (38)	Molina *et al*	2012	Phase 1 Trial of Everolimus Plus Sunitinib in Patients With Metastatic Renal Cell Carcinoma; everolimus + sunitnib	20	15 (75)	15	0
67. (39)	Molina *et al*	2014	A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of metastatic renal cell carcinoma (RCC); 20 patients (mean age, 58.4 years) received lenvatinib [12 mg (n=7); 18 mg (n=11); 24 mg (n=2)] plus everolimus 5 mg	20	12 (60)	10 (50)	2 (10)
68. (42)	Motzer *et al*	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; The everolimus dosage was 10 mg daily continually, and the sunitinib dosage was 50 mg daily in a schedule of 4 weeks on followed by 2 weeks off. Dose modifications were permitted for adverse events (AEs)	238	45 (19)	36 (15.1)	9 (3.8)
69. (74)	Motzer *et al*	2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial everolimus 10 mg once daily	269	33 (20)	25 (17)	8 (3)
70. (75)	Motzer *et al*	2015	Lenvatinib, everolimus, and the combination in patients	50	19 (38)	18 (36)	1 (2)

			with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial; everolimus 10 mg day				
71.	Narayan *et al* (43)	2016	Phase I Trial of Everolimus and Radiation Therapy for Salvage Treatment of Biochemical Recurrence in Prostate Cancer Patients Following Prostatectomy; Everolimus + srt	18	7 (38.8)	7 (38.8)	0
72.	Niegisch *et al* (44)	2015	Second-Line Treatment of Advanced Urothelial Cancer with Paclitaxel and Everolimus in a German Phase II Trial (AUO Trial AB 35/09); paclitaxel (175 mg/m2 i.v., 3-weekly) and the mTOR-inhibitor everolimus (10 mg po, once daily).	27	12 (44.4)	1 (3.7)	11 (40.7)
73.	Ohtsu *et al* (46)	2013	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study; everolimus 10 mg/day	437	150 (34)	116(26)	34 (8)
74.	Ou *et al* (91)	2015	SWOG S0722: Phase II study of mTOR inhibitor everolimus (RAD001) in advanced malignant pleural mesothelioma (MPM); Everolimus orally at 10 mg once daily until disease progression or unacceptable toxicity	59	35 (59.3)	29 (49.1)	6 (10.2)
75.	Oudard *et al* (47)	2016	Clinical Benefit of Everolimus as Second-Line Therapy in Metastatic Renal Cell Carcinoma: The French	162	66 (40.7)	58 (25.8)	8 (4.9)

		Retrospective SECTOR Study; Everolimus				
76. Oyama *et al* (48)	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 Everolimus: Subjects were administered 10 mg of everolimus q.d. orally during a fasting state. Doses were delayed or reduced to 5 mg once daily if patients had significant laboratory abnormalities or clinically adverse events	53	7 (13.2)	6 (11.3)	1 (1.9)
77. Powles *et al* (128)	2014	A phase Ib study investigating the combination of everolimus and dovitinib in vascular endothelial growth factor refractory clear cell renal cancer; everolimus 5 mg orally (po) once daily (OD) and dovitinib 200 mg PO day 1-5/7	15	11(73)	10(67)	1(7)
78. Powles *et al* (104)	2016	Randomized Open-Label Phase II Trial of Apitolisib (GDC-0980), a Novel Inhibitor of the PI3K/Mammalian Target of Rapamycin Pathway, Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma;	43	15 (35)	12 (28)	3 (7)

		everolimus 10 mg once per day				
79. Quek *et al* (92)	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	18 (85.9)	16 (76.4)	2 (9.5)
80. Rathkopf *et al* (93)	2015	Everolimus Combined With Gefitinib in Patients With Metastatic Castration-Resistant Prostate Cancer: Phase 1/2 Results and Signaling Pathway Implications; In phase 1, 12 patients (10 with CRPC and 2 with glioblastoma) received daily gefitinib (250 mg) with weekly everolimus (30, 50, or 70 mg). In phase 2, 27 CRPC patients received gefitinib with everolimus (70 mg)	39	36 (92)	34 (87)	2 (5)
81. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO; everolimus 10 mg per day until progression or unacceptable toxicity	43	40 (93)	22 (51)	18 (42)
82. Rodrigues *et al* (52)	2015	Phase I combination of pazopanib and everolimus in PIK3CA mutation positive/PTEN loss patients with advanced solid tumors refractory to standard therapy;	52	9 (17.3)	8 (15.4)	1 (1.9)

			pazopanib 600 mg every other day (QOD) alternating with everolimus 10 mg PO QOD				
83.	Ryan *et al* (94)	2011	A phase II study of everolimus in combination with imatinib for previously treated advanced renal carcinoma; everolimus 2.5 mg p.o. daily and imatinib 600 mg p.o. daily	19	13 (68)	10 (53)	3 (16)
84.	Safra *et al* (53)	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	44 (61.1)	40 (55.5)	4 (5.6)
85.	Salazar *et al* (54)	2017	Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Na€ıve Advanced Pancreatic Neuroendocrine Tumors; everolimus 10 mg once daily	31	10 (32.3)	8 (29.8)	2 (2.5)
86.	Sanoff *et al* (55)	2015	Everolimus and pasireotide for advanced and metastatic hepatocellular carcinoma; everolimus 7.5 mg po daily and pasireotide LAR 60 mg IM every 28 days	24	7 (29)	6 (25)	1 (4)
87.	Sarkaria *et al* (56)	2011	NCCTG 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	18	6 (34%)	3 (17%)	3 (17%)

		with standard chemo-radiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide				
88. Shen *et al* (57)	2014	Phase II Multicentered Study of Low-Dose Everolimus plus Cisplatin and Weekly 24-Hour Infusion of High-Dose 5-Fluorouracil and Leucovorin as First-Line Treatment for Patients with Advanced Gastric Cancer; everolimus (10 mg po on days 1, 8 and 15) plus cisplatin and a weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin (HDFL) chemotherapy (cisplatin 35 mg/m2 intravenous infusion for 24 h on days 1 and 8, 5-fluorouracil 2,000 mg/m^2 and leucovorin 300 mg/m^2 intravenous infusion for 24 h on days 1, 8 and 15) every 28 days	40	19 (47.5)	17 (42.5)	2 (5)
89. Shoushtari *et al* (58)	2016	Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients; phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients	13	2 (14)	2 (14)	0
90. Slomovitz *et al* (59)	2010	A Phase 2 Study of the Oral Mammalian Target of Rapamycin Inhibitor, Everolimus, in Patients With	35	19 (54)	11 (46)	8 (8)

		Recurrent Endometrial Carcinoma; Everolimus was administered at a dose of 10 mg orally daily for 28-day cycles				
91. Strickler *et al* (95)	2012	Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors; 10 mg of panobi- nostat three times weekly, 5 or 10 mg everolimus daily, and bevacizumab at 10 mg/kg every 2 weeks	12	1 (8)	1 (8)	0
92. Tan *et al* (131)	2017	The mTOR inhibitor everolimus in combination with azacitidine in patients with relapsed/refractory acute myeloid leukemia: a phase Ib/II study; The everolimus dose was escalated in a standard 3x3 study design to determine the MTD. The cohort doses of everolimus examined were 2.5, 5 and 10 mg with no intra-patient dose escalation permitted; the dosage was capped at 10 mg as this was the established dose used in the treatment of solid cancers	37	4 (10.8)		
93. Tarhini *et al* (61)	2010	Phase II Study of Everolimus (RAD001) in Previously Treated Small Cell Lung Cancer; everolimus 10 mg orally daily	40	10 (25)	9 (22.5)	1 (2.5)
94. Tomita *et al* (62)	2017	Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup analysis from the CheckMate 025 study;	26	5 (19)	4 (15)	1 (4)

		nivolumab 3 mg/kg intravenously every 2 weeks or everolimus 10 mg tablet orally once daily				
95. Vlahovic *et al* (63)	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	10 (31)	8 (25)	2 (6)
96. Wang *et al* (107)	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study; everolimus 10 mg/d in adults	58	25 (43.1)	21 (36.2)	4 (6.9)
97. Werner *et al* (64)	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	5 (32)	5 (32)	0
98. Wolpin *et al* (97)	2009	Oral mTOR Inhibitor Everolimus in Patients With Gemcitabine-Refractory Metastatic Pancreatic Cancer; everolimus 10 mg daily	33	19 (57)	16 (48)	3 (9)
99. Yao *et al* (140)	2008	Efficacy of RAD001 (Everolimus) and Octreotide LAR in Advanced Low- to Intermediate-Grade Neuroendocrine Tumors: Results of a Phase II Study; treatment consisted of RAD001 5 mg/d (30 patients) or 10 mg/day (30 patients)	64	7 (11)		

		and octreotide LAR 30 mg every 28 days				
100. Yao *et al* (65)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors 10 mg once daily	204	64 (31)	59 (29)	5 (2)
101. Yee *et al* (99)	2006	Phase I/II Study of the Mammalian Target of Rapamycin Inhibitor Everolimus (RAD001) in Patients with Relapsed or Refractory Hematologic Malignancies; everolimus No DLT occurred in the first three patients treated with 5 mg daily; all subsequent patients received 10 mg daily	27	6 (22)	4 (15)	2 (7)
Total over all			11,436	2,780 (23.7)		
Total with grade			10,923	2,709 (24.8)	2,187 (20)	522 (4.8)
Total with grade		Only everolimus at 2.5 mg	-	-	-	-
Total with grade		Only everolimus at 5 mg	-	-	-	-
Total with grade		Only everolimus at 10 mg	5,449	1,111 (20.4)	828 (15.2)	283 (5.2)

Table SVI. Incidence of hypercholesterolaemia in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of Cases (%)	Grade 1/2 cases (%)	Grade 3/4 cases (%)
1. Bajetta *et al* (2)	2014	Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients With Neuroendocrine Tumors; treatment-naive 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	13 (26)	13 (26)	0
2. Baselga *et al* (4)	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	22 (16.1)	21 (15.4)	1 (0.7)
3. Bissler *et al* (69)	2013	Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial;	79	16 (20)	16 (20)	0

		oral everolimus 10 mg per day				
4. Bissler *et al* (110)	2016	Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyo-matosis: extension of a randomized controlled trial; a starting dose of 10 mg was chosen as a means of providing adequate exposure to almost all patients based on dose proportionality in this adult age group. Dose modifications were to be determined clinically and were based solely on toler-ability. Doses could be lowered to 5 mg/day or even to 5 mg/ every other day	112	33 (29.5)	32 (8.6)	1 (0.9)
5. Cazzaniga *et al* (135)	2017	Efficacy and safety of Everolimus and Exemestane in hormone- receptor positive (HRþ) human-epidermal-growth-factor negative (HER2) advanced breast cancer patients: New insights beyond clinical trials. The EVA study; Everolimus	404	63 (18.6)	63 (18.6)	0
6. Chan *et al* (78)	2013	A Prospective, Phase 1/2 Study of Everolimus and Temozolomide in Patients With Advanced Pancreatic Neuroendocrine Tumor; patients were treated with temozolomide at a dose of 150 mg/m^2 per day on days 1 through 7 and days 15 through 21 in combination with everolimus daily in each 28-day cycle. In cohort 1, temozolo-mide was administered together	43	18 (42)	18 (42)	0

		with everolimus at 5 mg daily. Following the demonstration of safety in this cohort, subsequent patients in cohort 2 were treated with temozolomide plus everolimus at 10 mg daily				
7. Chow *et al* (12)	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	15 (62.5)	15 (62.5)	0
8. Conconi *et al* (15)	2014	Clinical activity of everolimus in relapsed/refractory marginal zone B-cell lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group; the study drug everolimus (RAD001) was administered orally at a daily dose of 10 mg, from day 1 to day 28 for up to a total of six cycles or until progression	30	8 (26.6)	8 (26.6)	0
9. Ellard *et al* (79)	2009	Randomized Phase II Study Comparing Two Schedules of Everolimus in Patients With Recurrent/Metastatic Breast Cancer: NCIC Clinical Trials Group IND.163 randomized phase II study of everolimus 10 mg daily versus 70 mg weekly A: 10 mg daily B: 70 mg weekly	A 33 B 16	A 27(81.8) B 13 (81.2)	0 0	27(81.8) 13(81.2)
10. Escudier at al.(70)	2016	Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis	92	15 (16)	13 (14)	2 (2)

		oral everolimus 10 mg once daily until disease progression or unacceptable toxicity				
11. Ferolla *et al* (71)	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; Everolimus long-acting pasireotide (60 mg intramuscularly every 28 days), everolimus (10 mg orally once daily), or both in combination, for the core 12-month treatment period.	42	6 (14)	6 (14)	0
12. Fogarasi *et al* (116)	2016	EFFECTS: an expanded access program of everolimus for patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex; patients received once daily everolimus (dose adjusted to attain a trough level of 5-15 ng/ml). Median daily dose of everolimus was 5.82 mg (range, 2.0-11.8 mg), including days of temporary interruption of the study drug	120	5 (4.2)	5 (4.2)	0
13. Franz *et al* (137)	2014	Everolimus for subependymal giant cell astrocytoma in patients with tuberous sclerosis complex: 2-year open-label extension of the randomised EXIST-1 study; everolimus 4.5 mg/m2 per day (titrated to achieve blood	114	8 (7)	8 (7)	0

		through concentrations of 5-15 ng/ml)				
14. Fury *et al* (80)	2012	A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors	30	16 (57)	16 (57)	0
15. Gelsomino *et al* (119)	2017	A dose finding and biomarkers evaluation phase Ib study of Everolimus in association with 5-FU and pelvic radiotherapy as neo-adjuvant treatment for locally advanced rectal cancer (E-LARC); 2 weeks of administration of Everolimus alone, followed by a concomitant treatment with Everolimus, 5-FU and radiotherapy	A:12	1 (8.3)	1 (8.3)	0
16. Grignani *et al* (72)	2014	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial Patients took 400 mg sorafenib twice a day together with 5 mg everolimus once a day	38	15	15 (40)	0
17. Guglielmelli *et al* (124)	2011	Safety and efficacy of everolimus, a mTOR inhibitor, as single agent in a phase 1/2 study in patients with myelofibrosis; everolimus in 3 dose-escalating cohorts at 5.0, 7.5, and 10.0 mg daily for 3 months	30	7 (23.3)	7 (23.3)	0
18. Guo *et al* (20)	2013	Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase	64	32 (50)	32 (50)	0

		inhibitor therapy: an open-label phase 1b study; Everolimus 10 mg (2x5 mg tablets) daily until objective tumor progression (according to RECIST, version 1.0), unacceptable toxicity, death, or study discontinuation for any other reason				
19. Hatano *et al* (22)	2016	Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: A single institution experience in Japan; The dose of everolimus was set at 10 mg once a day for adults.	47	6 (13)	6 (13)	0
20. Hatano *et al* (23)	2017	Intermittent everolimus administration for renal angiomyolipoma associated with tuberous sclerosis complex The dose of everolimus was set at 10 mg once a day	26	3 (12)	3 (12)	0
21. Jebali *et al* (141)	2017	Biological toxicities as surrogate markers of efficacy in patients treated with mTOR inhibitors for metastatic renal cell carcinoma; everolimus was administered orally at a starting dose of 10 mg per day. The duration of a cycle was 28 days.	44	31 (70)	28 (63)	3(7)
22. Jerusalem *et al* (26)	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-	2131	216 (10.1)	214 (10.0)	2 (0.1)

		arm, expanded- access multicenter trial (BALLET); Everolimus patients self-administered EVE on day 1 and continued daily doses of EVE (either 2x5 or 1x10 mg) plus EXE (25 mg/day) in 28-day cycles.				
23. Johnston *et al* (27)	2016	The mTORC1 Inhibitor Everolimus Combined with R-CHOP-21 for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Safety and Efficacy Results of a Phase I and Feasibility Trial NCCTG 1085 (Alliance); everolimus 10 mg days 1-10 or 1-14 in combination with R-CHOP-21 for 6 cycles	24	14 (58)	14 (58)	0
24. Jovanovic *et al* (28)	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; cisplatin 25 mg/m2 IV weekly for 12 weeks, everolimus 5 mg PO daily for 12 weeks and paclitaxel 80 mg/m2 IV weekly for 11 weeks (starting 1 week after cisplatin initiation)	96	9 (9)	9 (9)	0
25. Kim *et al* (30)	2013	A phase I study of everolimus and CHOP in newly diagnosed peripheral T-cell lymphomas; Four dose levels (2.5 to 10 mg) of everolimus from days 1 to 14	15	1 (6.6)	1 (6.6)	0

		with CHOP (750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 (maximum 2 mg) vincristine on day 1, and 100 mg/day prednisone on days 1 to 5) every 21 days were planned				
26. Kulke *et al* (35)	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: everolismus 10 mg/day, per os (po) + pasireotide LAR (60 mg/28 day, IM) B: everolimus 10 mg/d, per os (po)	A: 78 B: 81	A: 16 (20.5) B: 12 (14.8)	A: 16 (20.5) B: 12 (14.8)	A: 0 B: 0
27. Lim *et al* (89)	2013	A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes; everolimus 10 mg daily orally until unacceptable toxicity or disease progression	38	7 (18)	7 (18)	0
28. Massarweh *et al* (37)	2014	A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure; Fulvestrant was administered i.m. (in the gluteus maximus) in a loading dose schedule as follows: 500 mg in two divided doses, one on each side on day 1, then 250 mg on day 14, and then 250 mg on day 28 and every 4 weeks ± 3 days thereafter.	31	21 (68)	21 (68)	0

		Everolimus was administered initially at a dose of 5 mg daily in the first 5-patient cohort for the first month of treatment and then increased to 10 mg po daily after that				
29. Milowsky *et al* (127)	2013	Phase II study of everolimus in metastatic urothelial cancer all patients received everolimus 10 mg orally once daily continuously (one cycle = 4 weeks).	45	29 (64)	29 (64)	0
30. Molina *et al* (38)	2012	Phase 1 Trial of Everolimus Plus Sunitinib in Patients With Metastatic Renal Cell Carcinoma; A: everolimus + sunitnib	20	17 (85)	17 (85)	0
31. Motzer *et al* (41)	2016	Phase II trial of second-line everolimus in patients with metastatic renal cell carcinoma (RECORD-4); everolimus	133	4 (3)		
32. Motzer *et al* (74)	2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial; everolimus 10 mg once daily	269	205 (76)	196 (76)	9 (3)
33. Motzer *et al (75)*	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	8 (16)	8 (16)	0
34. Oudard *et al* (47)	2016	Clinical Benefit of Everolimus as Second-Line Therapy in Metastatic Renal Cell Carcinoma: The French Retrospective SECTOR Study; everolimus	162	28 (17.3)	27 (16.6)	1 (0.6)

35. Panzuto *et al* (49)	2014	Real-World Study of Everolimus in Advanced Progressive Neuroendocrine Tumors; everolimus starting dose was 10 mg daily; the investigator had the option of starting at or reducing the dose to 5 mg daily depending on the patient's baseline clinical status and tolerability	169	23 (13.6)	23 (13.6)	0
36. Quek *et al* (92)	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	4 (19.1)	4 (19.1)	0
37. Ramalingam *et al* (129)	2010	Phase 1 and Pharmacokinetic Study of Everolimus, a Mammalian Target of Rapamycin Inhibitor, in Combination With Docetaxel for Recurrent/Refractory Nonsmall Cell Lung Cancer; escalating doses of docetaxel (day 1) and everolimus (orally daily, days 1-19) every 3 weeks	24	2 (8.3)	2 (8.3)	0
38. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO; everolimus 10mg per day until progression or unacceptable toxicity	43	30 (81)	27 (73)	3 (8)
39. Robles *et al* (106)	2016	Everolimus safety and efficacy for renal angiomyolipomas	19	11 (57.9)	11 (57.9)	0

		associated with tuberous sclerosis complex: a Spanish expanded access trial; 10 mg everolimus once daily				
40. Rodrigues *et al* (52)	2015	Phase I combination of pazopanib and everolimus in PIK3CA mutation positive/PTEN loss patients with advanced solid tumors refractory to standard therapy; pazopanib 600 mg every other day (QOD) alternating with everolimus 10 mg PO QOD.	52	7 (13.4)	6 (11.5)	1 (1.9)
41. Sarkaria *et al* (56)	2011	NCCTG 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 chemo- radiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide	18	16 (89)	16 (89)	0
42. Shoushtari *et al* (58)	2016	Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60 mg every 28 days enrolling patients; phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60 mg every 28 days enrolling patients	13	8 (58)	8 (58)	0
43. Tobinai *et al* (96)	2010	Phase I study of the oral mammalian target of rapamycin inhibitor everolimus (RAD001) in Japanese patients with relapsed or refractory non-Hodgkin lymphoma; everolimus 5 mg (A) or 10 (B) mg orally once daily	A: 7 B: 6	A: 1 (14) B: 3 (50)	A 1 (14) B 3 (50)	A 0 B 0

		A: everolimus 5 mg once daily B: everolimus 10 mg once daily				
44. Wang *et al* (107)	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study Everolimus 10 mg/day in adults	58	6 (10.3)	4 (6.9)	2 (3.4)
45. Wolpin *et al* (97)	2009	Oral mTOR Inhibitor Everolimus in Patients With Gemcitabine-Refractory Metastatic Pancreatic Cancer; everolimus 10 mg daily	33	7 (21)	6 (18)	1 (3)
Total over all			5,346	1,078 (20.2)		
Total with grade			5,213	1,074 (20.6)	1,008 (19.3)	66 (1.3)
Total with grade		Only everolimus at 2.5 mg	-	-	-	-
Total with grade		Only everolimus at 5 mg	7	1 (14.3)	1 (14.3)	0
Total with grade		Only everolimus at 10 mg	1,169	489 (41.8)	441 (37.7)	48 (4.1)

Table SVII. Incidence of hyperglycemia in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 cases (%)	Grade 3/4 cases (%)
1. Amato *et al* (1)	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 was administered at a dose of 10 mg daily orally with- out 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 2 cycles (8 weeks) using Response Evaluation Criteria in Solid Tumors (RECIST)	39	23 (59)	20 (51.3)	3 (7.7)
2. Bajetta *et al* (2)	2014	Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients With Neuroendocrine Tumors; treatment-naive 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	9 (18)	9 (18)	0
3. Barnes *et al* (77)	2013	Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma; everolimus was administered orally once daily at a dose of 5 mg on days 1 through 14 of cycle 1. If tolerated, the dose was then increased to 10 mg for days 15 through 28 of cycle 1. For cycle 2 and beyond, patients continued to receive everolimus at a dose of 10	24	6 (25)	6 (25)	0

		mg daily continuously. Rituximab, at a dose of 375 mg/m^2, was administered intravenously weekly for four doses during cycle 1, and then on day 1 of cycles 2 through 6. After cycle 6, patients could receive an additional 6 months of everolimus monotherapy in the absence of disease progression or unacceptable toxicity				
4. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer; In this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily)	482	13 (2.7)	9 (1.8)	4 (0.9)
5. Baselga *et al* (4)	2009	Phase II Randomized Study of Neoadjuvant Everolimus Plus Letrozole Compared With Placebo Plus Letrozole in Patients With Estrogen Receptor–Positive Breast Cancer; Two hundred seventy 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	18 (13.1)	11 (8)	7 (5.1)
6. Besse *et al* (8)	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	14 (21.2)	13 (19.7)	1 (1.5)
7. Buzzoni *et al* (9)	2017	Impact of prior therapies on everolimus activity: an exploratory analysis of raDianT-4;	202	20 (10)	14 (7)	6 (3)

		patients were randomized (2:1) to everolimus 10 mg/day or placebo, both with best supportive care				
8. Chan *et al* (78)	2013	A Prospective, Phase 1/2 Study of Everolimus and Temozolomide in Patients With Advanced Pancreatic Neuroendocrine Tumor; Patients were treated with temozolomide at a dose of 150 mg/m^2 per day on days 1 through 7 and days 15 through 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	44	31 (52)	23 (71)	8 (19)
9. Choueiri *et al* (11)	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma everolimus at a dose of 10 mg daily	322	61 (19)	45 (14)	16 (5)
10. Chow *et al* (12)	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	12 (50)	10 (41.6)	2 (8.4)
11. Chung *et al* (13)	2016	Phase Ib Trial of mFOLFOX6 and Everolimus (NSC-733504) in Patients with Metastatic Gastroesophageal Adenocarcinoma; six patients were accrued to the first dose level of 2.5 mg everolimus daily with mFOLFOX6	6	3 (50)	3 (50)	0
12. Ciruelos *et al* (101)	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;	429	39 (9)	29 (7)	10 (2)

		eligible patients started study treatment on Day 1 with daily doses of everolimus (either 2 9 5 mg or 1 9 10 mg) and exemestane (25 mg) and continued until disease pro- gression, unacceptable toxicity				
13. Dasari *et al* (16)	2015	Phase I study of the anti-IGF1R antibody cixutumumab with everolimus and octreotide in advanced well-differentiated neuroendocrine tumors; Keeping the doses of everolimus (10 mg p.o. daily) and octreotide LAR (20 mg i.m. every 21 days) constant, cixutumumab was evaluated at escalating doses of 10 and 15 mg/kg every 21 days for a 21-day cycle. Octreotide LAR was administered every 21 days rather than the standard practice of every 28 days to fit with the study schedule for patients' convenience.	19	12 (63)	10 (53)	2 (10)
14. Doi *et al* (136)	2010	Multicenter Phase II Study of Everolimus in Patients With Previously Treated Metastatic Gastric Cancer; everolimus 10 mg orally daily	53	2 (3.8)		
15. Ellard *et al* (79)	2009	Randomized Phase II Study Comparing Two Schedules of Everolimus in Patients With Recurrent/Metastatic Breast Cancer: NCIC Clinical Trials Group IND.163 randomized phase II study of everolimus 10 mg daily versus 70 mg weekly; A: daily B: weekly	A: 33 B: 16	A: 17 (51.5) B: 10 (62.5)	A: 17 (51.5) B: 8 (50)	A: 0 B: 2 (12.5)
16. Fazio *et al* (18)	2018	Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis;	62	11 (17.7)	5 (7.9)	6 (9.8)

		everolimus 10 mg/day				
17. Fazio *et al* (19)	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	5 (15.2)	3 (9.1)	2 (6.1)
18. Finn *et al* (115)	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: 2 (12.5) B: 2 (14.3)	1 (6.2) 2 (14.3)	1 (6.3) 0
19. Fury *et al* (80)	2012	A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors	30	23 (82)	20 (71)	3 (11)
20. Gadgeel *et al* (81)	2013	Phase I study evaluating the combination of lapatinib (a Her2/Neu and EGFR inhibitor) and everolimus (an mTOR inhibitor) in patients with advanced cancers: South West Oncology Group (SWOG) Study S0528; the maximum tolerated dose of the combination was 1,250 mg of lapatinib and 5 mg of everolimus once daily	54	32 (60)	27 (50)	5 (10)
21. Gelsomino *et al* (119)	2017	A dose finding and biomarkers evaluation phase Ib study of Everolimus in association with 5-FU and pelvic radiotherapy as neo-adjuvant treatment for locally advanced rectal cancer (E-LARC); 2 weeks of administration of Everolimus alone, followed by a concomitant treatment with Everolimus, 5-FU and radiotherapy	A:12	1 (8.3)	1 (8.3)	0

22. (82)	Gong *et al*	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 the dose of 10 mg or in some instances at 5 mg daily, according to patients' tolerance and request.	70	15 (21.4)	14 (20)	1 (1.4)
23. (83)	Gross *et al*	2018	Safety and Efficacy of Docetaxel, Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC); docetaxel 75 mg/m^2, bevacizumab 15 mg/kg, and everolimus 2.5 mg	43	13 (30.2)	13 (30.2)	0
24. (20)	Guo *et al*	2013	Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy: an open-label phase 1b study; everolimus	64	33 (52)	25 (39)	8 (13)
25. (24)	Hill *et al*	2017	A phase I trial of bortezomib in combination with everolimus for treatment of relapsed/refractory non-Hodgkin lymphoma; A: bortezomib + everolimus	29	15 (51.7)	13 (44.8)	2 (6.8)
26. (141)	Jebali *et al*	2017	Biological toxicities as surrogate markers of efficacy in patients treated with mTOR inhibitors for metastatic renal cell carcinoma; everolimus was administered orally at a starting dose of 10 mg per day. The duration of a cycle was 28 days	44	24 (54)	18 (40)	6 (14)
27. Jerusalem *et al* (26)		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,	2131	265 (12.4)	204 (9.6)	61

		expanded- access multicenter trial (BALLET)				
28. Johnston *et al* (27)	2016	The mTORC1 Inhibitor Everolimus Combined with R-CHOP-21 for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Safety and Efficacy Results of a Phase I and Feasibility Trial NCCTG 1085 (Alliance); everolimus 10 mg days 1-10 or 1-14 in combination with R-CHOP-21 for 6 cycles	24	1 (4)	0	1 (4)
29. Jovanovic *et al* (28)	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; everolimus	96	49 (51)	49 (51)	0
30. Ju *et al* (85)	2015	Toxicity and adverse effects of everolimus in the treatment of advanced nonsmall cell lung cancer pretreated with chemotherapy-Chinese experiences; everolimus 5-10 mg/day with or without chemotherapy until progression or unacceptable toxicity	12	1 (8.3)	1 (8.3)	0
31. Kim *et al* (88)	2016	Efficacy and Toxicity of Mammalian Target Rapamycin Inhibitors in Patients with Metastatic Renal Cell Carcinoma with Renal Insufficiency: The Korean Cancer Study Group GU 14-08; the starting oral dose of everolimus was 10 mg daily for 10 patients and the starting intravenous dose for tem-sirolimus was 25 mg weekly for eight patients in the overall series	18	2 (11)	2 (11)	0

32. (30)	Kim *et al*	2013	A phase I study of everolimus and CHOP in newly diagnosed peripheral T-cell lymphomas; Four dose levels (2.5 to 10 mg) of everolimus from days 1 to 14 with CHOP (750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 (maximum 2 mg) vincristine on day 1, and 100 mg/day prednisone on days 1 to 5) every 21 days were planned	15	2 (13.3)	2 (13.3)	0
33.	Koeberle *et al* (32)	2016	Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29); sorafenib + everolimus	59	18 (21)	8 (3)	10 (18)
34. (33)	Kordes *et al*	2013	A phase I/II, non-randomized, feasibility/safety and efficacy study of the combination of everolimus, cetuximab and capecitabine in patients with advanced pancreatic cancer Safety and efficacy of fixed standard dose cetuximab in combination with various dose levels of everolimus (5–10 mg/day) and capecitabine (600–800 mg/ m^2 bid, 2 weeks every 3 weeks) were investigated in a phase I/II study in patients with advanced pancreatic cancer	31	19 (61)	11 (53)	8 (26)
35. (35)	Kulke *et al*	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: everolismus 10 mg/d, per oral (po) +pasireotide LAR (60 mg/28 d, IM)	A: 78 B: 81	A: 59 (75.6) B: 22 (27.2)	A: 30 (38.4) B: 13 (16.1)	A: 29 (37.2) B: 9 (11.1)

		B: everolimus 10 mg/d, per oral (po)				
36. Lim *et al* (89)	2013	A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes; everolimus 10 mg daily orally until unacceptable toxicity or disease progression	38	4 (10)	4 (10)	0
37. Massarweh *et al* (37)	2014	A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure; fulvestrant was administered intramuscularly (in the gluteus maximus) in a loading dose schedule as follows: 500 mg in two divided doses—one on each side on day 1, then 250 mg on day 14, and then 250 mg on day 28 and every 4 weeks ± 3 days thereafter. Everolimus was administered initially at a dose of 5 mg daily in the first 5-patient cohort for the first month of treatment and then increased to 10 mg PO daily after that.	31	22 (71)	20	2
38. Molina *et al* (38)	2012	Phase 1 Trial of Everolimus Plus Sunitinib in Patients With Metastatic Renal Cell Carcinoma; everolimus + sunitnib	20	18 (90)	18 (90)	0
39. Morrow *et al* (40)	2011	Phase I/II Study of Trastuzumab in Combination With Everolimus (RAD001) in Patients With HER2-Overexpressing Metastatic Breast Cancer Who Progressed on Trastuzumab-Based Therapy; everolimus	47	22 (65.8)	9 (19.1)	13 (27.6)
40. Moscetti *et al* (102)	2016	Safety analysis, association with response and previous treatments of everolimus and exemestane in 181 metastatic breast cancer patients: A multicenter Italian experience;	181	44 (24.3)	40 (22.0)	4 (2.3)

		everolimus				
41. Motzer *et al* (41)	2016	Phase II trial of second-line everolimus in patients with metastatic renal cell carcinoma (RECORD-4); everolimus	133	6 (5)		
42. Motzer *et al* (42)	2014	Phase II Randomized Trial Comparing Sequential First-Line Everolimus and Second-Line Sunitinib (A) Versus First-Line Sunitinib and Second-Line Everolimus (B) in Patients With Metastatic Renal Cell Carcinoma; everolimus 10 mg/daily	337	51 (15)	30 (9)	21 (6)
43. Narayan *et al* (43)	2016	Phase I Trial of Everolimus and Radiation Therapy for Salvage Treatment of Biochemical Recurrence in Prostate Cancer Patients Following Prostatectomy; everolimus + salvage radiation therapy	18	1(5.5)	1(5.5)	0
44. Oh *et al* (45)	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	4 (11.8)	2 (5.9)	2 (5.9)
45. Ou *et al* (91)	2015	SWOG S0722: Phase II study of mTOR inhibitor everolimus (RAD001) in advanced malignant pleural mesothelioma (MPM); everolimus orally at 10 mg once daily until disease progression or unacceptable toxicity	59	17 (28.8)	14 (23.7)	3 (5.1)
46. Oudard *et al* (47)	2016	Clinical Benefit of Everolimus as Second-Line Therapy in Metastatic Renal Cell Carcinoma: The French Retrospective SECTOR Study; everolimus	162	15 (9.3)	10 (6.2)	5 (3.1)
47. Panzuto *et al* (49)	2014	Real-World Study of Everolimus in Advanced Progressive Neuroendocrine Tumors;	169	28 (16.6)	26 (15.4)	2 (1.2)

		Everolimus starting dose was 10 mg daily; the investigator had the option of starting at or reducing the dose to 5 mg daily depending on the patient's baseline clinical status and tolerability				
48. Pavel *et al* (50)	2016	safety and QOL in Patients with Advanced NET in a Phase 3b Expanded Access Study of Everolimus; everolimus oral administration (two 5 mg tablets, totally 10 mg/day, in 28-day cycles) was taken by patients until disease progression, unacceptable toxicity, death, discontinuation from the study for any other reason, commercial availability for advanced NET in each participating country	123pNET 117 non pNET	pNET 15 (12.2) Non pNET 6 (5.1)	pNET 7 (5.7) Non pNET 2 (1.7)	pNET 8 (6.5) Non pNET 4 (3.4)
49. Powles *et al* (104)	2016	Randomized Open-Label Phase II Trial of Apitolisib (GDC-0980), a Novel Inhibitor of the PI3K/Mammalian Target of Rapamycin Pathway, Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma; everolimus 10 mg once per day	43	9 (21)	5 (12)	4 (9)
50. Quek *et al* (92)	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) n 21	21	13 (61.9)	12 (57.1)	1 (4.8)
51. Ramalingam *et al* (129)	2010	Phase 1 and Pharmacokinetic Study of Everolimus, a Mammalian Target of Rapamycin Inhibitor, in Combination With Docetaxel for Recurrent/Refractory Nonsmall Cell Lung Cancer	24	12 (50)	11 (45.8)	1 (4.2)

		escalating doses of docetaxel (Day 1) and everolimus (orally daily, Days 1-19) every 3 weeks.				
52. Rathkopf *et al* (93)	2015	Everolimus Combined With Gefitinib in Patients With Metastatic Castration-Resistant Prostate Cancer: Phase 1/2 Results and Signaling Pathway Implications In phase 1, 12 patients (10 with CRPC and 2 with glioblastoma) received daily gefitinib (250 mg) with weekly everolimus (30, 50, or 70 mg). In phase 2, 27 CRPC patients received gefitinib with everolimus (70 mg)	39	35 (90)	32 (82)	3 (8)
53. Rizzo *et al* (105)	2015	Everolimus as second-line therapy for metastatic renal cell carcinoma: a 'real-life' study; everolimus 10 mg/day	100	20 (20)	18 (18)	2 (2)
54. Safra *et al* (53)	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	25 (34.7)	22 (30.5)	3 (4.2)
55. Salazar *et al* (54)	2017	Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Naıve Advanced Pancreatic Neuroendocrine Tumors; everolimus 10 mg once daily	31	11 (35.5)	9 (29)	2 (6.5)
56. Sanoff *et al* (55)	2015	Everolimus and pasireotide for advanced and metastatic hepatocellular carcinoma; everolimus 7.5 mg PO daily and pasireotide LAR 60 mg IM every 28 days	24	14 (58)	8 (34)	6 (25)
57. Shoushtari *et al* (58)	2016	Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients;	13	12 (86)	5 (36)	7 (50)

		phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60 mg every 28 days enrolling patients				
58. Strickler *et al* (95)	2012	Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors; 10 mg of panobinostat three times weekly, 5 or 10 mg everolimus daily, and bevacizumab at 10 mg/kg every 2 weeks.	12	4 (34)	2 (17)	2 (17)
59. Sun *et al* (60)	2013	A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer A: everolimus 2.5 mg B: everolimus 5 mg C: everolimus 10 mg	A: 6 B: 11 C: 3	A: 6 B: 9 (81.8) C: 3 (100)	A: 6 (100) B: 9 (81.8) C: 2 (66)	A: 0 B: 0 C: 1 (33)
60. Tarhini *et al* (61)	2010	Phase II Study of Everolimus (RAD001) in Previously Treated Small Cell Lung Cancer; everolimus 10 mg orally daily until disease progression	40	6 (15)	4 (10)	2 (5)
61. Tobinai *et al* (96)	2010	Phase I study of the oral mammalian target of rapamycin inhibitor everolimus (RAD001) in Japanese patients with relapsed or refractory non-Hodgkin lymphoma; everolimus 5 (A) or 10 (B) mg orally once daily. A: everolimus 5 mg once daily B: everolimus 10 mg once daily	A: 7 B: 2	A: 2 (28) B: 2 (100)	A: 2 (28) B: 1 (50)	A: 0 B: 1 (50)
62. Vlahovic *et al* (63)	2012	A phase I study of bevacizumab, everolimus and panitumumab in advanced solid tumors; everolimus and flat dosing of pani-tumumab at 4.8 mg/kg and bevacizumab at 10 mg/kg every 2 weeks.	32	11 (34)	10 (31)	1 (3)
63. Werner *et al* (64)	2013	Phase I study of everolimus and mitomycin C for patients with metastatic esophagogastric adenocarcinoma;	16	3 (18.7)	3 (18.7)	0

		oral everolimus (5, 7.5, and 10 mg/day) in combination with intravenous MMC 5 mg/m^2 every 3 weeks				
64. Wolpin *et al* (97)	2009	Oral mTOR Inhibitor Everolimus in Patients With Gemcitabine-Refractory Metastatic Pancreatic Cancer; everolimus 10 mg daily	33	22 (6)	16 (48)	6 (18)
65. Yao *et al* (140)	2008	Efficacy of RAD001 (Everolimus) and Octreotide LAR in Advanced Low- to Intermediate-Grade Neuroendocrine Tumors: Results of a Phase II Study; treatment consisted of RAD001 5 mg/d (30 patients) or 10 mg/day (30 patients) and octreotide LAR 30 mg every 28 days.	64	6 (9)		
66. Yao *et al* (65)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors; 10 mg once daily	204	27 (13)	16 (18)	11 (5)
67. Yee *et al* (99)	2006	Phase I/II Study of the Mammalian Target of Rapamycin Inhibitor Everolimus (RAD001) in Patients with Relapsed or Refractory Hematologic Malignancies; Everolimus: Nodose-limiting toxicity (DLT) occurred in the first three patients treated with 5 mg daily; all subsequent patients received 10 mg daily	27	13 (48)	7 (26)	6 (22)
68. Albiges *et al* (66)	2015	Everolimus for patients with metastatic renal cell carcinoma refractory to anti-VEGF therapy: Results of a pooled analysis of non-interventional studies metastatic renal cell carcinoma (mRCC) who failed one or two anti-VEGF therapies; Everolimus Everolimus 10mg/day until disease progression or unacceptable toxicity	493	17 (3)		
69. Andre *et al* (67)	2014	Everolimus for women with trastuzumab-resistant, HER2-positive,	A:280	25	19 (7)	6 (2)

		advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial; in this randomised, double-blind, placebo-controlled, phase 3 trial, we 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 randomisation system to daily everolimus (5 mg/day) plus weekly trastuzumab (2 mg/kg) and vinorelbine (25 mg/m2) or to placebo plus trastuzumab plus vinorelbine, in 3-week cycles, stratified by previous lapatinib use				
70. Angelousi *et al* (133)	2017	Sequential Everolimus and Sunitinib Treatment in Pancreatic Metastatic Well-Differentiated Neuroendocrine Tumours Resistant to Prior Treatments Thirty-one patients were administered one compound and upon progression were switched to the other. All patients had grade 1 or 2 tumours and stage IV disease with similar metastatic load; A: 1st line everolimus; B: 2nd line everolimus; 31 patients were administered one compound and upon progression were switched to the other. All patients had grade 1 or 2 tumours and stage IV disease with similar metastatic load. The everolimus full dosage was 10 mg daily, and the sunitinib 37.5 mg daily. However, dose modifications were permitted in the presence of AEs, so that everolimus could be decreased to 5 mg and sunitinib to 25 mg daily, respectively	A:20 B:11	A: 6 (30) B: 2 (18)	A: 4 (20) B: 2 (18)	A: 2 (10) B: 0

71. Armstrong *et al* (68)	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	7 (12)	7 (12)	0
72. Capdevila *et al* (142)	2015	Evaluation of the efficacy and safety of lanreotide in combination with targeted therapies in patients with neuroendocrine tumours in clinical practice: a retrospective cross-sectional analysis; everolimus	404	7 (1.7)	7 (1.7)	0
73. Cazzaniga *et al* (135)	2017	Efficacy and safety of Everolimus and Exemestane in hormone- receptor positive (HRþ) human-epidermal-growth-factor negative (HER2) advanced breast cancer patients: New insights beyond clinical trials. The EVA study; Everolimus: The EVE starting dose was 10 mg dose, even if the 5 mg dose could be independently selected by physicians	404	60 (17.7)	57 (16.8)	3 (0.9)
74. Escudier at al.(70)	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	13 (14)	11 (12)	2 (2)
75. Ferolla *et al* (71)	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; everolimus: The EVE starting dose was 10 mg dose, even if the 5 mg dose could be independently selected by physicians	42	26 (63)	19 (46)	7 (17)

76. Grignani *et al* (72)	2014	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	11 (29)	11 (29)	0
77. Grunwald *et al* (73)	2012	An international expanded-access programme of everolimus: Addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy; patients received everolimus 10 mg once daily, with dose and schedule modifications allowed for toxicity	1367	78 (5.7)	3 (0.2)	75 (5.5)
78. Motzer *et al* (74)	2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial everolimus 10 mg once daily	269	135 (50)	104 (38)	31 (12)
79. Motzer *et al* (75)	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	11(22)	6 (12)	5 (10)
80. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO; everolimus 10 mg per day until progression or unacceptable toxicity	43	25 (61)	21 (51)	4 (10)
81. Wang *et al* (107)	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study; everolimus 10 mg/day in adults	58	8 (13.8)	4 (6.9)	4 (6.9)

Total overall		10,878	1,853 (16.9)		
Total with grade		10,135	1,822 (18)	1,347 (13.3)	475 (4.7)
Total with grade	Only everolimus at 2.5 mg	6	6 (100)	6 (100)	0
Total with grade	Only everolimus at 5 mg	18	11 (61.1)	11 (61.1)	0
Total with grade	Only everolimus at 10 mg	3,611	615 (17)	400 (11)	223 (6)

Table SVIII. Incidence of leukopenia in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 cases (%)	Grade 3/4 cases (%)
1. Andre *et al* (67)	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 3 trial, we 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 randomisation system to daily everolimus (5 mg/day) plus weekly trastuzumab (2 mg/kg) and vinorelbine (25 mg/m2) or to placebo plus trastuzumab plus vinorelbine, in 3-week cycles, stratified by previous lapatinib use	275	128 (46)	22 (8)	106 (38)
2. Andreassen *et al* (143)	2016	Everolimus Initiation With Early Calcineurin Inhibitor Withdrawal in De Novo Heart Transplant Recipients: Three-Year Results From the Randomized SCHEDULE Study; in a randomized, open-label trial, *de novo* heart transplant recipients were randomized to everolimus (3-6 ng/ ml) with reduced-exposure calcineurin inhibitor (CNI; cyclosporine) to weeks 7-11 after transplant, followed by increased everolimus exposure	A:51	12 (23.6)		

		(target 6-10 ng/ml) with cyclosporine withdrawal or standard-exposure cyclosporine. All patients received mycophenolate mofetil and corticosteroids.				
3. Bissler *et al* (69)	2013	Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial; oral everolimus 10 mg per day	79	8 (10)	8 (10)	0
4. Bissler *et al* (110)	2016	Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic ymphangioleiomyomatosis: extension of a randomized controlled trial; a starting dose of 10 mg was chosen as a means of providing adequate exposure to almost all patients based on dose proportionality in this adult age group. Dose modifications were to be determined clinically and were based solely on toler- ability. Doses could be lowered to 5 mg/day or even to 5 mg/ every other day	112	14 (12.5)	14 (12.5)	0
5. Campone *et al* (100)	2009	Safety and pharmacokinetics of paclitaxel and the oral mTOR inhibitor everolimus in advanced solid tumours; everolimus dose was escalated from 15 to 30 mg and administered with paclitaxel 80 mg m^2 on days 1, 8, and 15 every 28 days.	16	5 (30)	3 (18)	2 (12)

6. Chow *et al* (12)	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	17 (70.8)	15 (62.5)	2 (8.3)
7. Conconi *et al* (15)	2014	Clinical activity of everolimus in relapsed/refractory marginal zone B-cell lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group; the study drug everolimus (RAD001) was administered orally at a daily dose of 10mg, from day 1 to day 28 for up to a total of six cycles or until progression	30	8 (26.6)	6 (20)	2 (6.6)
8. Fazio *et al* (19)	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	4 (12.1)		
9. Fury *et al* (80)	2012	A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors	30	19 (68)	19 (68)	0
10. Ghobrial *et al* (120)	2010	Phase II Trial of the Oral Mammalian Target of Rapamycin Inhibitor Everolimus in Relapsed or Refractory; everolimus 10 mg daily for two cycles	50	10 (20)	0	10 (20)
11. Ghobrial *et al* (138)	2014	Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed	60	13 (21)	0	13 (21)

		or refractory Waldenstrom Macroglobulinemia; everolimus 10 mg/day				
12. Gong *et al* (82)	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 the dose of 10 mg or in some instances at 5 mg daily, according to patients' tolerance and request	70	4 (5.7)	4 (5.7)	0
13. Grignani *et al* (72)	2014	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial; patients took 400 mg sorafenib twice a day together with 5 mg everolimus once a day	38	12 (32)	11(29)	1 (3)
14. Guo *et al* (20)	2013	Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy: an open-label phase 1b study; everolimus 10 mg/day	64	14 (22)	14 (22)	0
15. Hatano *et al* (22)	2016	Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: A single institution experience in Japan; everolimus 10 mg once a day	47	3 (6)	3 (6)	0
16. Hatano *et al* (23)	2017	Intermittent everolimus administration for renal angiomyolipoma associated with tuberous sclerosis complex; everolimus 10 mg once a day	26	2 (8)	2 (8)	0

17. Hurvitz *et al* (25)	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	12 (21.8)	2 (3.6)	10 (18.2)
18. Johnston *et al* (27)	2016	The mTORC1 Inhibitor Everolimus Combined with R-CHOP-21 for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Safety and Efficacy Results of a Phase I and Feasibility Trial NCCTG 1085 (Alliance); everolimus 10 mg days 1-10 or 1-14 in combination with R-CHOP-21 for 6 cycles	24	13 (54)	4 (17)	9 (37)
19. Ju *et al* (85)	2015	Toxicity and adverse effects of everolimus in the treatment of advanced nonsmall cell lung cancer pretreated with chemotherapy-Chinese experiences; everolimus 5-10 mg/day with or without chemotherapy until progression or unacceptable toxicity	12	0	0	0
20. Kanesvaran *et al* (126)	2015	A single arm phase 1b study of everolimus and sunitinib in patients with advanced renal cell carcinoma (RCC); sunitinib + everolimus	4	2 (50)	1 (25)	1 (25)

21. Kim *et al* (29)	2014	A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities	34	11 (32.4)	10 (29.5)	1 (2.9)
22. Massarweh *et al* (37)	2014	A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure; fulvestrant was administered intramuscularly (in the gluteus maximus) in a loading dose schedule as follows: 500 mg in two divided doses, one on each side on day 1, then 250 mg on day 14, and then 250 mg on day 28 and every 4 weeks ± 3 days thereafter. Everolimus was administered initially at a dose of 5 mg daily in the first 5-patient cohort for the first month of treatment and then increased to 10 mg PO daily after that	31	14 (45)	14 (45)	0
23. Milowsky *et al* (127)	2013	Phase II study of everolimus in metastatic urothelial cancer; all patients received everolimus 10 mg orally once daily continuously (one cycle = 4 weeks).	45	17 (38)	16 (36)	1 (2)
24. Molina *et al* (38)	2012	Phase 1 Trial of Everolimus Plus Sunitinib in Patients With Metastatic Renal Cell Carcinoma; everolimus + sunitnib	20	18 (90)	14 (70)	4 (20)
25. Niegisch *et al* (44)	2015	Second-Line Treatment of Advanced Urothelial Cancer with Paclitaxel and Everolimus in a	27	15 (55.5)	4 (14.8)	11 (40.7)

		German Phase II Trial (AUO Trial AB 35/09); paclitaxel (175 mg/m2 i.v., 3-weekly) and the mTOR-inhibitor everolimus (10 mg p.o., once daily).				
26. Nozawa *et al* (90)	2013	Adverse Event Profile and Dose Modification of Everolimus for Advanced Renal Cell Carcinoma in Real-world Japanese Clinical Practice; everolimus	47	1 (2.1)	1 (2.1)	0
27. Ramalingam *et al* (129)	2010	Phase 1 and Pharmacokinetic Study of Everolimus, a Mammalian Target of Rapamycin Inhibitor, in Combination With Docetaxel for Recurrent/Refractory Nonsmall Cell Lung Cancer; escalating doses of docetaxel (day 1) and everolimus (orally daily, days 1-19) every 3 weeks	24	2 (8.3)	0	2 (8.3)
28. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO; everolimus 10mg per day until progression or unacceptable toxicity	43	21 (49)	19 (44)	2 (5)
29. Rodrigues *et al* (52)	2015	Phase I combination of pazopanib and everolimus in PIK3CA mutation positive/PTEN loss patients with advanced solid tumors refractory to standard therapy; pazopanib 600 mg every other day (QOD) alternating with everolimus 10 mg PO QOD	52	9 (17.3)	8 (15.3)	1 (2)
30. Ryan *et al* (94)	2011	A phase II study of everolimus in combination with imatinib for	19	11 (58)	11 (58)	0

		previously treated advanced renal carcinoma; everolimus 2.5 mg p.o. daily and imatinib 600 mg p.o. daily				
31. Sanoff *et al* (55)	2015	Everolimus and pasireotide for advanced and metastatic hepatocellular carcinoma; everolimus 7.5 mg PO daily and pasireotide LAR 60 mg IM every 28 days.	24	2 (8)	2 (8)	0
32. Sarkaria *et al* (56)	2011	NCCTG 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 chemo- radiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide	18	6 (34)	4 (22)	2 (12)
33. Shen *et al* (57)	2014	Phase II Multicentered Study of Low-Dose Everolimus plus Cisplatin and Weekly 24-Hour Infusion of High-Dose 5-Fluorouracil and Leucovorin as First-Line Treatment for Patients with Advanced Gastric Cancer; everolimus (10 mg p.o. on days 1, 8 and 15) plus cisplatin and a weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin (HDFL) chemotherapy (cisplatin 35 mg/m2 intrave- nous infusion for 24 h on days 1 and 8, 5-fluorouracil 2,000 mg/m2 and leucovorin 300 mg/m2 intravenous infusion for 24 h on days 1, 8 and 15) every 28 days	40	23 (57.5)	21 (52.5)	2 (5)

34. Shoushtari *et al* (58)	2016	Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients; phase 2 trial of everolimus 10 mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients	13	9 (65)	9 (65)	0
35. Slomovitz *et al* (59)	2010	A Phase 2 Study of the Oral Mammalian Target of Rapamycin Inhibitor, Everolimus, in Patients With Recurrent Endometrial Carcinoma; everolimus was administered at a dose of 10 mg orally daily for 28-day cycles	35	7 (20)	5 (15)	2 (5)
36. Sun *et al* (60)	2013	A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer A: everolimus 2.5 mg B: everolimus 5 mg C: everolimus 10 mg	A: 6 B: 11 C: 3	5 (83.3) 8 (72.7) 2 (66)	4 (66.6) 4 (36.3) 2 (66)	1 (16.7) 4 (36.3) 0
37. Werner *et al* (64)	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	10 (62.5)	7 (43.7)	3 (18.8)
38. Yao *et al* (140)	2008	Efficacy of RAD001 (Everolimus) and Octreotide LAR in Advanced Low- to Intermediate-Grade Neuroendocrine Tumors: Results of a Phase II Study; treatment consisted of RAD001 5 mg/day (30 patients) or 10 mg/day	64	3 (5)		

		(30 patients) and octreotide LAR 30 mg every 28 days				
Total overall			1,672	495 (29.6)		
Total with grade			1,524	476 (31.2)	283 (18.6)	193 (12.6)
Total with grade		Only everolimus at 2.5 mg	6	5 (83.3)	4 (66.6)	1 (16.7)
Total with grade		Only everolimus at 5 mg	11	8 (72.6)	4 (36.3)	4 (36.3)
Total with grade		Only everolimus at 10 mg	698	134 (19.2)	103 (14.7)	31 (4.5)

Table SIX. Incidence of pneumonitis in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 Cases (%)	Grade 3/4 Cases (%)
1. Albiges *et al* (66)	2015	Everolimus for patients with metastatic renal cell carcinoma refractory to anti-VEGF therapy: Results of a pooled analysis of non-interventional studies metastatic renal cell carcinoma (mRCC) who failed one or two anti-VEGF therapies; everolimus 10 mg/day until disease progression or unacceptable toxicity	493	57 (12)	37 (8)	20 (4)
2. Amato *et al* (1)	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 was given at a dose of 10 mg daily orally with- out 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 2 cycles (8 weeks) using Response Evaluation Criteria in Solid Tumors (RECIST)	39	19 (48.6)	12 (30.7)	7 (17.9)
3. Andre *et al* (67)	2014	Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a	280	16 (7)	13 (5)	3 (2)

		randomised, double-blind, placebo-controlled phase 3 trial; in this randomised, double-blind, placebo-controlled, phase 3 trial, we 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 randomisation 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				
4. Angelousi *et al* (133)	2017	Sequential Everolimus and Sunitinib Treatment in Pancreatic Metastatic Well-Differentiated Neuroendocrine Tumours Resistant to Prior Treatments; 31 patients were administered one compound and upon progression were switched to the other. All patients had grade 1 or 2 tumours and stage IV disease with similar metastatic load. A: 1st line everolimus B: 2nd line everolimus; the everolimus full dosage was 10 mg daily, and the sunitinib 37.5 mg daily. However, dose modifications were permitted	A: 20 B: 11	A: 5 (25) B: 2 (18)	A: 4 (20) B: 1(9)	A: 1 (5) B: 1 (9)

		in the presence of AEs, so that everolimus could be decreased to 5 mg and sunitinib to 25 mg daily, respectively.				
5. Armstrong *et al* (68)	2016	Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial; everolimus was given orally at 10 mg once daily	52	8 (14)	3 (5)	5 (9)
6. Bachelot *et al* (76)	2012	Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study; this open-label, phase II study randomly assigned postmenopausal women with hormone receptor– positive, human epidermal growth factor receptor 2–negative, AI-resistant mBC to tamoxifen 20 mg/d plus everolimus 10 mg/d (n 54) or tamoxifen 20 mg/d alone (n 57). tamoxifen plus everolimus	54	9 (17)	8 (15)	1 (2)

7. Bajetta *et al* (2)	2014	Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients With Neuroendocrine Tumors Treatment-naive 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	3 (6)	3 (6)	0
8. Barnes *et al* (77)	2013	Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma; everolimus was administered orally once daily at a dose of 5 mg on days 1 through 14 of cycle 1. If tolerated, the dose was then increased to 10 mg for days 15 through 28 of cycle 1. For cycle 2 and beyond, patients continued to receive everolimus at a dose of 10 mg daily continuously. Rituximab, at a dose of 375 mg/m^2, was administered intravenously weekly for four doses during cycle 1, and then on day 1 of cycles 2 through 6. After cycle 6, patients could receive an additional 6 months of everolimus monotherapy in the absence of disease progression or unacceptable toxicity	24	1 (4.1)	0	1 (4.1)
9. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-	482	12 (2.4)	9 (1.8)	3 (0.6)

		Receptor–Positive Advanced Breast Cancer; in this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily)				
10. Baselga *et al* (4)	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	4 (2.9)	1 (0.7)	3 (2.2)
11. Bennani *et al* (144)	2017	Efficacy of the oral mTORC1 inhibitor everolimus in relapsed or refractory indolent lymphoma; eligible patients received oral everolimus 10 mg daily on a 28 day-cycle schedule	55	1 (1.8)		
12. Buzzoni *et al* (9)	2017	impact of prior therapies on everolimus activity: an exploratory analysis of raDianT-4; patients were randomized (2:1) to everolimus 10 mg/day or placebo, both with best supportive care.	202	32 (16)	30 (15)	2 (1)
13. Chan *et al* (78)	2013	A Prospective, Phase 1/2 Study of Everolimus and	43	3 (7)	3 (7)	0

		Temozolomide in Patients With Advanced Pancreatic neuroendocrine Tumor; patients were treated with temozolomide at a dose of 150 mg/m^2 per day on days 1 through 7 and days 15 through 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				
14. Choueiri *et al* (11)	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma everolimus at a dose of 10 mg daily	322	33 (10)	27 (8)	6 (2)
15. Chow *et al* (12)	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	6 (25)	5 (21)	1 (4)
16. Ciruelos *et al* (101)	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 began study treatment on day 1 with daily	429	60 (14)	47 (11)	13 (3)

			doses of everolimus (either 2x5 mg or 1x10 mg) and exemestane (25 mg) and continued until disease pro-gression, unacceptable toxicity				
17. (79)	Ellard *et al*	2009	Randomized Phase II Study Comparing Two Schedules of everolimus in patients with recurrent/Metastatic Breast Cancer: NCIC Clinical Trials Group IND.163 randomized phase II study of everolimus 10 mg daily versus 70 mg weekly A: daily B: weekly	A: 33 B: 16	14 (42.4) 3 (18.7)	3 (9) 0	11 (33.3) 3 (18.7)
18. (18)	Fazio *et al*	2018	Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis; everolimus 10 mg/day	62	8 (12.9)	7 (11.3)	1 (1.6)
19. (71)	Ferolla *et al*	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; everolimus: The EVE starting dose was 10 mg dose, even if the 5 mg dose could be independently selected by physicians.	42	4 (10)	2 (5)	2 (5)
20. (116)	Fogarasi *et al*	2016	EFFECTS: an expanded access program of everolimus for patients with subependymal giant cell	120	5 (4.2)	5 (4.2)	0

		astrocytoma associated with tuberous sclerosis complex; patients received once daily everolimus (dose adjusted to attain a trough level of 5-15 ng/ml)				
21. Gong *et al* (82)	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 the dose of 10 mg or in some instances at 5 mg daily, according to patients' tolerance and request.	70	10 (14.2)	10 (14.2)	0
22. Gross *et al* (83)	2018	Safety and Efficacy of Docetaxel, bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC); docetaxel 75 mg/m^2, bevacizumab 15 mg/kg, and everolimus 2.5 mg	43	3 (6.8)	1 (2.3)	2 (4.5)
23. Grunwald *et al* (73)	2012	An international expanded-access programme of everolimus: Addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy; patients received everolimus 10 mg once daily, with dose and schedule modifications allowed for toxicity	1367	83 (6.1)	46 (3.4)	37 (2.7)
24. Guglielmelli *et al* (124)	2011	Safety and efficacy of everolimus, a mTOR inhibitor, as single agent in a phase 1/2	30	7 (23.3)	0	7 (23.3)

		study in patients with myelofibrosis; everolimus in 3 dose-escalating cohorts at 5.0, 7.5, and 10.0 mg daily for 3 months				
25. Harzstark *et al* (84)	2011	A Phase 1 Study of Everolimus and Sorafenib for Metastatic Clear Cell Renal Cell Carcinoma; starting doses were everolimus at a dose of 2.5 mg orally daily and sorafenib at a dose of 400 mg orally twice daily continuously	20	1 (5)	0	1 (5)
26. Johnston *et al* (27)	2016	The mTORC1 Inhibitor Everolimus Combined with R-CHOP-21 for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Safety and Efficacy Results of a Phase I and Feasibility Trial NCCTG 1085 (Alliance); everolimus 10 mg days 1-10 or 1-14 in combination with R-CHOP-21 for 6 cycles	24	4 (16)	3 (12)	1 (4)
27. Jovanovic *et al* (28)	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	96	1 (1)	1 (1)	0
28. Kato *et al* (86)	2013	Efficacy of Everolimus in Patients with Advanced Renal Cell Carcinoma Refractory or Intolerant to VEGFR-TKIs	19	4 (21)	3 (16)	1 (5)

		and Safety Compared with Prior VEGFR-TKI Treatment; everolimus				
29. Kim *et al* (87)	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	4 (11.1)	2 (5.5)	2 (5.6)
30. Koutsoukos *et al* (34)	2017	Real-world experience of everolimus as second-line treatment in metastatic renal cell cancer after failure of pazopanib; the median everolimus daily dose was 10 mg (5-10 mg), while the mean daily dose was 9.3 mg	31	6 (19)	4 (13)	2 (6)
31. Kulke *et al* (35)	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: everolismus +pasireotide LAR B: everolimus 10 mg/day, per os (po)	A:78 B:81	6 (7.7) 10 (12.3)	5 (6.4) 9 (11.1)	1(1.3) 1 (1.2)
32. Kumano *et al* (36)	2013	Sequential use of mammalian target of rapamycin inhibitors in patients with metastatic renal cell carcinoma following failure of tyrosine kinase inhibitors; everolimus 10mg/day	57	14 (24.6)	9 (15.8)	5 (8.8)
33. Lim *et al* (89)	2013	A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid	38	4 (10)	3 (8)	1 (2)

		cancer of all histologic subtypes; everolimus 10 mg daily orally until unacceptable toxicity or disease progression				
34. Milowsky *et al* (127)	2013	Phase II study of everolimus in metastatic urothelial cancer all patients received everolimus 10 mg orally once daily continuously (one cycle = 4 weeks)	45	6 (13)	5 (11)	1 (2)
35. Molina *et al* (38)	2012	Phase 1 Trial of Everolimus Plus Sunitinib in Patients With Metastatic Renal Cell Carcinoma; everolimus + sunitnib	20	1 (5)	1	0
36. Moscetti *et al* (102)	2016	Safety analysis, association with response and previous treatments of everolimus and exemestane in 181 metastatic breast cancer patients: A multicenter Italian experience	181	30 (13.4)	22 (12.2)	2 (1.2)
37. Motzer *et al* (74)	2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial; everolimus 10 mg once daily	269	22 (8)	14 (5)	8 (3)
38. Niegisch *et al* (44)	2015	Second-Line Treatment of Advanced Urothelial Cancer with Paclitaxel and Everolimus in a German Phase II Trial (AUO Trial AB 35/09) paclitaxel (175 mg/m2 i.v., 3-weekly) and the mTOR-inhibitor verolimus (10 mg p.o., once daily)	27	1 (3.7)	0	1 (3.7)
39. Nozawa *et al* (90)	2013	Adverse Event Profile and Dose Modification of Everolimus for Advanced Renal Cell Carcinoma in Real-	47	20 (42.5)	12 (25.5)	8 (17)

		world Japanese Clinical Practice				
40. Panzuto *et al* (49)	2014	Real-World Study of Everolimus in Advanced Progressive Neuroendocrine Tumors	169	32 (18.9)	18 (10.6)	14 (8.3)
41. Park *et al* (103)	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 10 mg/day	100	26 (27)	17 (18)	9 (9)
42. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO; everolimus 10 mg per day until progression or unacceptable toxicity	43	5 (12)	3 (7)	2 (5)
43. Ryan *et al* (94)	2011	A phase II study of everolimus in combination with imatinib for previously treated advanced renal carcinoma; everolimus 2.5 mg p.o. daily and imatinib 600 mg p.o. daily.	19	1 (5)	0	1 (5)
44. Safra *et al* (53)	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	9 (12.5)	8 (11.1)	1 (1.4)
45. Slomovitz *et al* (59)	2010	A Phase 2 Study of the Oral Mammalian Target of	35	2 (5)	2 (5)	0

			Rapamycin Inhibitor, Everolimus, in Patients With Recurrent Endometrial Carcinoma; everolimus was administered at a dose of 10 mg orally daily for 28-day cycles				
46.	Sun *et al* (60)	2013	A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer A: everolimus 2.5 mg B: everolimus 5 mg C: everolimus 10 mg	A: 6 B: 11 C: 3	A: 0 B: 1 (9.09) C: 0	A: 0 B: 1 (9.09) C: 0	A: 0 B: 0 C: 0
47.	Tarhini *et al* (61)	2010	Phase II Study of Everolimus (RAD001) in Previously Treated Small Cell Lung Cancer; everolimus 10 mg orally daily until disease progression	40	3 (7.5)	1 (2.5)	2 (5)
48.	Tomita *et al* (62)	2017	Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup analysis from the CheckMate 025 study; nivolumab 3 mg/kg intravenously every 2 weeks or everolimus 10-mg tablet orally once daily	26	5 (19)	5 (19)	0
49.	Wang *et al* (107)	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study; Everolimus 10 mg/day in adults	58	7 (12.1)	4 (6.9)	3 (5.2)
50.	Yao *et al* (140)	2008	Efficacy of RAD001 (Everolimus) and Octreotide LAR in	50	1 (2)		

		Advanced Low- to Intermediate-Grade Neuroendocrine Tumors: Results of a Phase II Study; treatment consisted of RAD001 5 mg/day (30 patients) or 10 mg/day (30 patients) and octreotide LAR 30 mg every 28 days				
Total overall			6,201	628 (10.1)		
Total with grade			6,096	626 (10.3)	429 (7)	197 (3.3)
Total with grade		Only everolimus at 2.5 mg	6	0	0	0
Total with grade		Only everolimus at 5 mg	11	1 (9)	1 (9)	0 (0)
Total with grade		Only everolimus at 10 mg	3,409	363 (10.7)	242 (7.1)	121 (3.6)

Table SX. Incidence of pruritus in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 Cases (%)	Grade 3/4 Cases (%)
1. Armstrong *et al* (68)	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	A: 52	8 (14)	7 (12)	1 (2)
2. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer In this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily)	482	11 (2.2)	10 (2.0)	1 (0.2)
3. Baselga *et al* (4)	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	18 (13.1)	18 (13.1)	0
4. Bergmann *et al* (145)	2013	Everolimus in Metastatic Renal Cell Carcinoma after Failure of Initial Vascular Endothelial Growth Factor Receptor-Tyrosine Kinase Inhibitor	195	12 (6)	11 (5.6)	1 (0.4)

		(VEGFr-TKI) Therapy: Results of an Interim Analysis of a Non-Interventional Study; everolimus 10 mg/day demonstrated clinical benefit over placebo in patients with metastatic renal cell carcinoma (mRCC), who had failed previous therapy with sunitinib and/ or sorafenib				
5. Besse *et al* (8)	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	13 (19.7)	12 (18.2)	1 (1.5)
6. Bissler *et al* (110)	2016	Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangio-leiomyomatosis: extension of a randomized controlled trial; a starting dose of 10 mg was chosen as a means of pro-viding adequate exposure to almost all patients based on dose proportionality in this adult age group. Dose modifications were to be determined clinically and were based solely on toler- ability. Doses could be lowered to 5 mg/day or even to 5 mg/ every other day	112	12 (10.7)	12 (10.7)	0
7. Buzzoni *et al* (9)	2017	impact of prior therapies on everolimus activity: an exploratory analysis of raDianT-4; patients were randomized (2:1) to everolimus 10 mg/day or	202	26 (13)	24 (12)	2 (1)

		placebo, both with best supportive care.				
8. Campone *et al* (100)	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	2 (12.5)	2 (12.5)	0
9. Choueiri *et al* (11)	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma everolimus at a dose of 10 mg daily	322	47 (15)	46 (14)	1 (<1)
10. Chow *et al* (12)	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	2 (8.3)	2 (8.3)	0
11. Elmadani *et al* (17)	2017	EVESOR, a model-based, multiparameter, Phase I trial to optimize the bene t/toxicity ratio of everolimus and sorafenib; everolimus + sorafenib	26	1 (3.8)	1 (3.8)	0
12. Escudier at al.(70)	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	20 (22)	20 (22)	0
13. Fazio *et al* (18)	2018	Everolimus in advanced, progressive, well-differentiated, non-functional	62	7 (11.3)	6 (9.7)	1 (1.6)

		neuroendocrine tumors: RADIANT-4 lung subgroup analysis; everolimus 10 mg/day				
14. Fazio *et al* (19)	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	4 (12.1)		
15. Ferolla *et al* (71)	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; The EVE starting dose was 10 mg dose, even if the 5 mg dose could be independently chosen by physicians.	42	2 (5)	2 (5)	0
16. Goldberg et al.(122)	2015	Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study	24	3 (13)		
17. Grignani *et al* (72)	2014	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial; patients took 400 mg sorafenib twice a day together with 5 mg everolimus once a day	38	5 (13)	5 (13)	0

18. Guo *et al* (20)	2013	Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy: an open-label phase 1b study; everolimus 10 mg/daily	64	14 (22)	14 (22)	0
19. Hatano *et al* (22)	2016	Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: A single institution experience in Japan; the dose of everolimus was set at 10 mg once a day for adults	47	3 (6)	3 (6)	0
20. Hatano *et al* (23)	2017	Intermittent everolimus administration for renal angiomyolipoma associated with tuberous sclerosis complex; the dose of everolimus was set at 10 mg once a day	26	1 (4)	1 (4)	0
21. Kim *et al* (88)	2016	Efficacy and Toxicity of Mammalian Target Rapamycin Inhibitors in Patients with Metastatic Renal Cell Carcinoma with Renal Insufficiency: The Korean Cancer Study Group GU 14-08; the starting oral dose of everolimus was 10 mg daily for 10 patients and the starting intravenous dose for temsirolimus was 25 mg weekly for eight patients in the overall series	20	1 (5)	1 (5)	0
22. Kulke *et al* (35)	2017	A randomized, open-label, phase 2 study of everolimus in	A: 78 B: 81	A: 12 (15.4) B: 18 (22.2)	A: 12 (15.4)	A: 0 B: 1 (1.2)

		combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial; A: everolismus + pasireotide LAR B: everolimus 10 mg/day, per os (po)			B: 17 (21)	
23. Milowsky *et al* (127)	2013	Phase II study of everolimus in metastatic urothelial cancer all patients received everolimus; 10 mg orally once daily continuously (one cycle = 4 weeks).	45	2 (4)	2 (4)	0
24. Motzer *et al* (75)	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	7 (14)	7 (14)	0
25. Ohtsu *et al* (46)	2013	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study; everolimus 10 mg/day	437	47 (11)	47 (11)	0
26. Powles *et al* (104)	2016	Randomized Open-Label Phase II Trial of Apitolisib (GDC-0980), a Novel Inhibitor of the PI3K/Mammalian Target of Rapamycin Pathway, Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma; everolimus 10 mg once per day	43	7 (16)	7 (16)	0
27. Quek *et al* (92)	2011	Combination mTOR and IGF-1R Inhibition: Phase I Trial of Everolimus and Figitumumab in Patients with Advanced	21	3 (14.3)	3 (14.3)	0

		Sarcomas and Other Solid Tumors; figitumumab (20 mg/kg IV every 21 days) with full dose everolimus (10 mg orally once daily)				
28. Safra *et al* (53)	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, n=72	72	12 (16.7)	12 (16.7)	0
29. Tomita *et al* (62)	2017	Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup analysis from the CheckMate 025 study; nivolumab 3 mg/kg intravenously every 2 weeks or everolimus 10-mg tablet orally once daily	26	6 (23)	6 (23)	0
30. Vlahovic *et al* (63)	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	29 (91)	24 (75)	5 (16)
31. Werner *et al* (146)	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	1 (6.25)	1 (6.25)	0

32. Yao *et al* (65)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors; everolimus 10 mg once daily	204	30 (15)	30 (15)	0
Total overall			3,187	386 (12.1)		
Total with grade			3,130	379 (12.1)	365 (11.6)	14 (0.5)
Total with grade		Only everolimus at 2.5 mg	-	-	-	-
Total with grade		Only everolimus at 5 mg	-	-	-	-
Total with grade		Only everolimus at 10 mg	2,034	261 (12.8)	254 (12.5)	7 (0.3)

Table SXI. Incidence of pyrexia in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. patients	No. of cases (%)	Grade 1/2 cases (%)	Grade 3/4 cases (%)
1. Andre *et al* (67)	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 3 trial, we 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 randomisation system to daily everolimus (5 mg/day) plus weekly trastuzumab (2 mg/kg) and vinorelbine (25 mg/m2) or to placebo plus trastuzumab plus vinorelbine, in 3-week cycles, stratified by previous lapatinib use	280	108 (39)	101 (36)	7 (3)
2. Armstrong *et al* (68)	2016	Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial; everolimus was given orally at 10 mg once daily	52	8 (14)	8 (14)	0
3. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-	482	14 (2.9)	13 (2.7)	1 (0.2)

		Receptor–Positive Advanced Breast Cancer; in this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily)				
4. Bergmann *et al* (6)	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	19 (6)	8 (2)	11 (4)
5. Besse *et al* (8)	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	10 (15.2)	10 (15.2)	0
6. Bissler *et al* (134)	2018	The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant cell astrocytoma; Patients were initially randomly assigned to receive everolimus 4.5 mg/m^2/day (target blood through 5-15 mg/dl) or placebo and could continue in an open-label extension phase	33	6 (18.2)		
7. Buzzoni *et al* (9)	2017	impact of prior therapies on everolimus activity:	202	22 (11)	18 (9)	4 (2)

		an exploratory analysis of raDianT-4; patients were randomized (2:1) to everolimus 10 mg/day or placebo, both with best supportive care.				
8. Campone *et al* (100)	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	2 (12.5)	2 (12.5)	0
9. Choueiri *et al* (11)	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma everolimus at a dose of 10 mg daily	322	51 (16)	50 (15)	1 (<1)
10. De Simone *et al* (147)	2012	Everolimus With Reduced Tacrolimus Improves Renal Function in De Novo Liver Transplant Recipients: A Randomized Controlled Trial; A: Everolimus + reduced Tacrolimus B: Everolimus w/o tacrolimus	A: 245 B: 231	A: 32 (13.1) B: 45 (19.6)	A: 22 (9) B: 29 (12.6)	A: 10 (4.1) B: 16 (7.0)
11. Escudier e*t al* (70)	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 unac-ceptable toxicity	92	27 (29)	27 (29)	0

12. Fazio *et al* (18)	2018	Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis; everolimus 10 mg/day	62	12 (19.4)	10 (16.2)	2 (3.2)
13. Ferolla *et al* (71)	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 Everolimus; The EVE starting dose was 10 mg dose, even if the 5 mg dose could be independently chosen by physicians	42	8 (19)	7 (17)	1 (2)
14. Finn *et al* (115)	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: 4 (25) B: 6 (42.9)	A: 4 (25) B: 6 (42.9)	A: 0 B: 0
15. Fogarasi *et al* (116)	2016	EFFECTS: an expanded access program of everolimus for patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex; patients received once daily everolimus (dose adjusted to attain a trough level of 5-15 ng/ml)	120	18 (15)	17 (14.2)	1 (0.8)
16. Franz *et al* (137)	2014	Everolimus for subependymal giant cell	111	10 (9)	8 (7)	2 (2)

		astrocytoma in patients with tuberous sclerosis complex: 2-year open-label extension of the randomised EXIST-1 study; Everolimus 44-5mg/m^2				
17. Franz *et al* (117)	2013	Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial Everolimus 4-5mg/m^2	78	17 (22)	12 (16)	5 (6)
18. Goldberg *et al* (122)	2015	Everolimus for the treatment of lymphangioleiomyo-matosis: a phase II study	24	3 (13)		
19. Gong *et al* (82)	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 the dose of 10 mg or in some instances at 5 mg daily, according to patients' tolerance and request	70	10 (14.2)	10 (14.2)	0
20. Guo *et al* (20)	2013	Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy: an open-label phase 1b study; everolimus 10 mg/daily	64	26 (41)	25 (39)	1 (2)
21. Hurvitz *et al* (25)	2013	A phase 2 study of everolimus combined with	55	22 (40)	21 (38.2)	1 (1.8)

		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.				
22. Jerusalem *et al* (26)	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)	2,131	299 (14)	289 (13.6)	10 (0.4)
23. Jozwiak *et al* (125)	2016	Safety of Everolimus in Patients Younger than 3 Years of Age: Results from EXIST-1, a Randomized, Controlled Clinical Trial; everolimus was initiated at 4.5 mg/m^2/day and titrated to blood trough levels of 5-15 ng/ml	18	8 (44.4)		
24. Kulke *et al* (35)	2017	A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or	A: 78 B: 81	A: 15 (19.2) B: 21 (25.9)	A: 15 (19.2) B: 19 (23.2)	A: 0 B: 2 (2.5)

		everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial A: everolismus + pasireotide LAR B: everolimus 10 mg/day, per oral (po)				
25. Motzer *et al* (41)	2016	Phase II trial of second-line everolimus in patients with metastatic renal cell carcinoma (RECORD-4)	133	3 (2)		
26. Motzer *et al* (42)	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	337	67 (19.9)	64 (19)	3 (0.9)
27. Motzer *et al* (75)	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	5 (10)	4 (8)	1 (2)
28. Ohtsu *et al* (46)	2013	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study; everolimus 10 mg/day	437	81 (19)	78 (18)	3 (<1)
29. Pavel *et al* (50)	2016	Safety and QOL in Patients with Advanced NET in a Phase 3b Expanded Access Study of Everolimus;	pNET 123 Non pNET	pNET 10 (8.1) Non pNET 8 (6.8)	pNET 8 (6.5) Non pNET 8 (6.8)	pNET 2 (1.6) Non pNET 0

		Everolimus 10 mg/day	117			
30. Robles *et al* (106)	2016	Everolimus safety and efficacy for renal angiomyolipomas associated with tuberous sclerosis complex: a Spanish expanded access trial; 10 mg everolimus once daily	19	2 (10.5)	2 (10.5)	0
31. Safra *et al* (53)	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	19 (26.4)	19 (26.4)	0
32. Salazar *et al* (54)	2017	Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Naєıve Advanced Pancreatic Neuroendocrine Tumors; everolimus 10 mg once daily	31	4 (12.9)	4 (12.9)	0
33. Takahashi *et al* (130)	2013	Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results; everolimus regimen (1.5 mg/day starting dose (target trough: 3 to 8 ng/ml) + reduced-dose cyclosporine)	61	13 (21.3)		
34. Wang *et al* (107)	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study	58	12 (20.7)	11 (19)	1 (17)

		Everolimus 10 mg/day in adults				
35. Yao *et al* (65)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors; 10 mg once daily	204	22 (11)	22 (11)	0
Total overall			6,961	1,069 (15.4)		
Total with grade			6,692	1,036 (15.5)	951 (14.2)	85 (1.3)
Total with grade		Only everolimus at 2.5 mg	-	-	-	-
Total with grade		Only everolimus at 5 mg	-	-	-	-
Total with grade		Only everolimus at 10 mg	2,318	340 (14.7)	312 (13.5)	28 (1.2)

Table SXII. Incidence of rash in selected studies in the literature due to everolimus therapy.

Author (Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 cases (%)	Grade 3/4 cases (%)
1. Abida *et al* (109)	2016	Phase I Study of Everolimus in Combination with Gemcitabine and Split-Dose Cisplatin in Advanced Urothelial Carcinoma; gemcitabine 800 mg/m^2 and cisplatin 35 mg/m^2 on days 1 and 8 of 21-day cycles for a total of 6 cycles in combination with everolimus at increasing dose levels (DL1: 5 mg QOD, DL2: 5 mg daily, DL3:10 mg daily) following a standard 3+3 design	12	1 (8)		
2. Albiges *et al* (66)	2015	Everolimus for patients with metastatic renal cell carcinoma refractory to anti-VEGF therapy: Results of a pooled analysis of non-interventional studies; metastatic renal cell carcinoma (mRCC) who failed one or two anti-VEGF therapies	632	42 (9)		
3. Amato *et al* (148)	2012	Phase I Trial of Everolimus Plus Sorafenib for Patients with Advanced Renal Cell Cancer; everolimus 2.5 mg q.d Sorafeib 400 mg bid; everolimus 5 mg q.d Sorafenib 400 mg bid; everolimus 10 mg q.d Sorafenib 400 mg bid	A: 6 B: 6 C: 3	A: 3 (50) B: 6 (100) C: 1 (33)	A: 3 (50) B: 6 (100) C: 1 (33)	A: 0 B: 0 C: 0
4. Amato *et al* (1)	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 was administered at a dose of 10 mg daily orally without interruption (28-day cycle), with dose modifications for toxicity (graded	A:39	10 (25.6)	10 (25.6)	0

		according to National Cancer Institute Common Toxicity Criteria, version 3.0). Patients were evaluated every 2 cycles (8 weeks) using Response Evaluation Criteria in Solid Tumors (RECIST)				
5. Andre *et al* (67)	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 3 trial, we 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 randomisation 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	A: 280	69 (25)	69 (25)	0
6. Armstrong *et al* (68)	2016	Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial; everolimus was administered orally at 10 mg once daily.	52	18 (32)	17 (30)	1(2)
7. Bachelot *et al* (76)	2012	Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study;	54	24 (44)	22 (40)	2 (4)

		this open-label, phase II study randomly assigned postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2–negative, AI-resistant mBC to tamoxifen 20 mg/day plus everolimus 10 mg/day (n=54) or tamoxifen 20 mg/day alone (n 57); tamoxifen plus everolimus				
8. Bajetta *et al* (2)	2014	Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients With Neuroendocrine Tumors; treatment-naive 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	24 (48)	23 (46)	1 (2)
9. Barnes *et al* (77)	2013	Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma; everolimus was administered orally once daily at a dose of 5 mg on days 1 through 14 of cycle 1. If tolerated, the dose was then increased to 10 mg for days 15 through 28 of cycle 1. For cycle 2 and beyond, patients continued to receive everolimus at a dose of 10 mg daily continuously. Rituximab, at a dose of 375 mg/m^2, was administered intravenously weekly for four doses during cycle 1, and then on day 1 of cycles 2 through 6. After cycle 6, patients could receive an additional 6 months of everolimus monotherapy in the absence of disease progression or unacceptable toxicity	24	3 (12.5)	3 (12.5)	0

10. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer; in this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily)	482	36 (7.4)	35 (7.2)	1(0.2)
11. Baselga *et al* (4)	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	28 (20.4)	27 (20.4)	1 (0.7)
12. Bendell *et al* (5)	2015	A phase Ib study of linsitinib (OSI-906), a dual inhibitor of IGF-1R and IR tyrosine kinase, in combination with everolimus as treatment for patients with refractory metastatic colorectal cancer; OSI-906 and everolimus were administered to cohorts of 3–6 patients in a standard 3+3 design	18	3 (16)	3 (16)	0
13. Bergmann *et al* (6)	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	18 (6)	14 (5)	4 (1)
14. Besse *et al* (8)	2014	Phase II study of everolimus–erlotinib in previously treated patients with advanced non-small-cell lung cancer;	66	35 (53.0)	31(46.9)	4 (6.1)

		everolimus 5 mg/day + erlotinib 150 mg/day				
15. Bissler *et al* (134)	2018	The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant cell astrocytoma; patients were initially randomly assigned to receive everolimus 4.5 mg/m^2/day (target blood through 5-15 mg/dl) or placebo and could continue in an open-label extension phase	33	5 (15.2)		
16. Buzzoni *et al* (9)	2017	Impact of prior therapies on everolimus activity: an exploratory analysis of raDianT-4; patients were randomized (2:1) to everolimus 10 mg/day or placebo, both with best supportive care	202	54 (27)	52 (26)	2 (1)
17. Castellano *et al* (111)	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	10 (52.6)		
18. Cazzaniga *et al* (135)	2017	Efficacy and safety of Everolimus and Exemestane in hormone- receptor positive (HRþ) human-epidermal-growth-factor negative (HER2) advanced breast cancer patients: New insights beyond clinical trials. The EVA study; everolimus 10 mg/daily	404	86 (25.4)	77 (22.7)	9 (2.7)
19. Chan *et al (78)*	2013	A Prospective, Phase 1/2 Study of Everolimus and Temozolomide in Patients With Advanced Pancreatic Neuroendocrine Tumors; patients were treated with temozolomide at a dose of 150 mg/m^2 per day on days 1 through 7 and days 15 through 21 in combination with everolimus daily in each 28-day cycle. In cohort 1,	43	23 (54)	21 (49)	2 (5)

		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				
20. Choueiri *et al* (11)	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma everolimus at a dose of 10 mg daily	322	89 (28)	87 (27)	2 (<1)
21. Chow *et al* (12)	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	5 (20.8)	5 (20.8)	0
22. Chung *et al* (13)	2016	Phase Ib Trial of mFOLFOX6 and Everolimus (NSC-733504) in Patients with Metastatic Gastroesophageal Adenocarcinoma; six patients were accrued to the first dose level of 2.5 mg everolimus daily with mFOLFOX6	6	3 (50)	3 (50)	0
23. Ciruelos *et al* (101)	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 (either 2x5 mg or 1x10 mg) and exemestane (25 mg) and continued until disease progression, unacceptable toxicity	429	76 (18)	71 (17)	5 (1)
24. Ciunci *et al* (14)	2014	Phase 1 and Pharmacodynamic Trial of Everolimus in Combination With Cetuximab in Patients With Advanced Cancer	29	10 (34.4)	8 (27.5)	2 (6.9)
25. Conconi *et al* (15)	2014	Clinical activity of everolimus in relapsed/refractory marginal zone B-	30	12 (40)	11 (36.6)	1 (3.4)

		cell lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group; the study drug everolimus (RAD001) was administered orally at a daily dose of 10 mg, from day 1 to day 28 for up to a total of six cycles or until progression				
26. Dasari *et al* (16)	2015	Phase I study of the anti-IGF1R antibody cixutumumab with everolimus and octreotide in advanced well-differentiated neuroendocrine tumors; keeping the doses of everolimus (10 mg p.o. daily) and octreotide LAR (20 mg i.m. every 21 days) constant, cixutumumab was evaluated at escalating doses of 10 and 15 mg/kg every 21 days for a 21-day cycle. Octreotide LAR was administered every 21 days rather than the standard practice of every 28 days to fit with the study schedule for patients' convenience	19	8 (42)	8 (42)	0
27. El-Madani *et al* (17)	2017	EVESOR, a model-based, multiparameter, Phase I trial to optimize the bene t/toxicity ratio of everolimus and sorafenib; everolimus + sorafenib	26	10 (38.5)	9 (34.7)	1 (3.8)
28. Ellard *et al* (79)	2009	Randomized Phase II Study Comparing Two Schedules of Everolimus in Patients With Recurrent/Metastatic Breast Cancer: NCIC Clinical Trials Group IND.163; randomized phase II study of everolimus 10 mg daily versus 70 mg weekly A: Daily B: Weekly	A: 33 B: 16	A: 20 (60.6) B: 9 (56.2)	A: 0 B: 0	A: 20 (60.6) B: 9 (56.2)
29. Escudier *et al* (70)	2016	Open-label phase 2 trial of first-line everolimus monotherapy in patients	92	53 (58)	53 (58)	0

		with papillary metastatic renal cell carcinoma: RAPTOR final analysis oral everolimus 10 mg once daily until disease progression or unacceptable toxicity; everolimus 10mg/daily				
30. Fazio *et al* (18)	2018	Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis; everolimus 10 mg/day	62	22 (35.5)	22 (35.5)	0
31. Fazio *et al* (19)	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	11 (33.3)		
32. Ferolla *et al* (71)	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; Everolimus: The EVE starting dose was 10 mg dose, even if the 5 mg dose could be independently chosen by physicians	42	14 (33)	11 (26)	3 (7)
33. Finn *et al* (115)	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: 7 (43.8) B: 7 (50)	A: 7 (43.8) B: 7 (50)	A: 0 B: 0
34. Franz *et al* (117)	2013	Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre,	78	9 (12)	9 (12)	0

		randomised, placebo-controlled phase 3 trial; everolimus 4-5mg/m^2				
35. Fury *et al* (80)	2012	A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors; everolimus: escalating doses starting form 2.5 mg/day	30	7 (25)	7 (25)	0
36. Gadgeel *et al* (81)	2013	Phase I study evaluating the combination of lapatinib (a Her2/Neu and EGFR inhibitor) and everolimus (an mTOR inhibitor) in patients with advanced cancers: South West Oncology Group (SWOG) Study S0528; the maximum tolerated dose (MTD) of the combination was 1,250 mg of lapatinib and 5 mg of everolimus once daily	54	19 (36)	17 (31.4)	2(4.6)
37. Gelsomino *et al* (119)	2017	A dose finding and biomarkers evaluation phase Ib study of Everolimus in association with 5-FU and pelvic radiotherapy as neo-adjuvant treatment for locally advanced rectal cancer (E-LARC); 2 weeks of administration of Everolimus alone, followed by a concomitant treatment with Everolimus, 5-FU and radiotherapy	12	4 (33)	4 (33)	0
38. Goldberg *et al* (122)	2015	Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study	24	3 (13)		
39. Gong *et al* (82)	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 the dose of 10 mg or in some instances at 5 mg daily, according to patients' tolerance and request	70	13 (18.6)	13 (18.6)	0

40. Grignani *et al* (72)	2014	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial; patients took 400 mg sorafenib twice a day together with 5 mg everolimus once a day	38	24 (63)	23 (60)	1 (3)
41. Guo *et al* (20)	2013	Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy: an open-label phase 1b study; everolimus 10 mg/day	64	20 (31)	20 (31)	0
42. Hainsworth *et al* (21)	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	37 (47)	35 (44)	2 (3)
43. Harzstark *et al* (84)	2011	A Phase 1 Study of Everolimus and Sorafenib for Metastatic Clear Cell Renal Cell Carcinoma; starting doses of everolimus were of 2.5 mg orally daily and sorafenib at a dose of 400 mg orally twice daily continuously	20	13 (65)	11(55)	2 (10)
44. Hatano *et al* (22)	2016	Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: A single institution experience in Japan; the dose of everolimus was set at 10 mg once a day for adults	47	5 (11)	5 (11)	0
45. Hatano *et al* (23)	2017	Intermittent everolimus administration for renal angiomyolipoma associated with tuberous sclerosis complex; the dose of everolimus was set at 10 mg once a day	26	3 (12)	3 (12)	0

46. Hurvitz *et al* (25)	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	26	25 (45.5)	1 (1.8)
47. Jerusalem *et al* (26)	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); everolimus plus exemestane	2131	351 (16.5)	331 (15.6)	20 (0.9)
48. Johnston *et al* (27)	2016	The mTORC1 Inhibitor Everolimus Combined with R-CHOP-21 for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Safety and Efficacy Results of a Phase I and Feasibility Trial NCCTG 1085 (Alliance); everolimus 10 mg days 1-10 or 1-14 in combination with R-CHOP-21 for 6 cycles	24	6 (25)	5 (21)	1 (4)
49. Jovanovic *et al* (28)	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	96	47 (49)	47 (49)	0

50. Ju *et al* (85)	2015	Toxicity and adverse effects of everolimus in the treatment of advanced nonsmall cell lung cancer pretreated with chemotherapy-Chinese experiences; everolimus 5-10 mg/day with or without chemotherapy until progression or unacceptable toxicity	12	1 (8.3)	1 (8.3)	0
51. Kanesvaran *et al* (126)	2015	A single arm phase 1b study of everolimus and sunitinib in patients with advanced renal cell carcinoma (RCC); sunitinib + everolimus	4	3 (75)	3 (75)	0
52. Kato *et al* (86)	2013	Efficacy of Everolimus in Patients with Advanced Renal Cell Carcinoma Refractory or Intolerant to VEGFR-TKIs and Safety Compared with Prior VEGFR-TKI Treatment	19	8 (42)	8 (42)	0
53. Kim *et al* (29)	2014	A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities.	34	10 (29.4)	10 (29.4)	0
54. Kim *et al* (87)	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	36	13 (36.1)	13 (36.1)	0
55. Kim *et al* (30)	2013	A phase I study of everolimus and CHOP in newly diagnosed peripheral T-cell lymphomas; Four dose levels (2.5 to 10 mg) of everolimus from days 1 to 14 with CHOP (750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 (maximum 2 mg) vincristine on day 1, and 100 mg/day prednisone on days 1 to 5) every 21 days were planned	15	1 (6.6)	1 (6.6)	0

56. Koeberle *et al* (32)	2016	Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29); sorafenib + everolimus	59	16 (27)	16 (27)	0
57. Kordes *et al* (33)	2013	A phase I/II, non-randomized, feasibility/safety and efficacy study of the combination of everolimus, cetuximab and capecitabine in patients with advanced pancreatic cancer; everolimus (5-10 mg/day) and capecitabine (600-800 mg/m^2 bid, 2 weeks every 3 weeks) were investigated in a phase I/II study in patients with advanced pancreatic cancer	A 31 B 9	A 24 (77) B 6 (67)	A 18 (58) B 3 (40)	A 6 (19) B 3 (27)
58. Koutsoukos *et al* (34)	2017	real-world experience of everolimus as second-line treatment in metastatic renal cell cancer after failure of pazopanib; the median everolimus daily dose was 10 mg (5-10 mg), while the mean daily dose was 9.3 mg	31	2 (7)	2 (6)	0
59. Kulke *et al* (35)	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: Everolismus + pasireotide LAR B: Everolimus 10 mg/day, per os (po)	A: 78 B: 81	A: 19 (24.4) B: 24 (29.8)	A: 19 (24.4) B: 24 (29.8)	A: 0 B: 0
60. Kumano *et al* (36)	2013	Sequential use of mammalian target of rapamycin inhibitors in patients with metastatic renal cell carcinoma following failure of tyrosine kinase inhibitors; everolimus 10mg/die	57	13 (22.8)	12 (21)	1(1.8)
61. Lim *et al* (89)	2013	A multicenter, phase II trial of everolimus in locally advanced or	38	8 (21)	8 (21)	0

		metastatic thyroid cancer of all histologic subtypes; everolimus 10 mg daily orally until unacceptable toxicity or disease progression				
62. Macaskill *et al* (139)	2011	The mammalian target of rapamycin inhibitor everolimus (RAD001) in early breast cancer: results of a pre-operative study; 5 mg RAD001 once daily for 14 days prior to surgery	31	2 (6.5)		
63. Massarweh *et al* (37)	2014	A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure; fulvestrant was administered intramuscularly (in the gluteus maximus) in a loading dose schedule as follows: 500 mg in two divided doses, one on each side on day 1, then 250 mg on day 14, and then 250 mg on day 28 and every 4 weeks ± 3 days thereafter. Everolimus was administered initially at a dose of 5 mg daily in the first 5-patient cohort for the first month of treatment and then increased to 10 mg PO daily after that	31	13 (42)	13 (42)	0
64. Milowsky *et al* (127)	2013	Phase II study of everolimus in metastatic urothelial cancer; all patients received everolimus 10 mg orally once daily continuously (one cycle = 4 weeks).	45	22 (49)	22 (49)	0
65. Molina *et al* (38)	2012	Phase 1 Trial of Everolimus Plus Sunitinib in Patients With Metastatic Renal Cell Carcinoma A: everolimus + sunitnib	20	9 (45)	9 (45)	0
66. Molina *et al* (39)	2014	A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of	20	7 (35)		

		metastatic renal cell carcinoma (RCC); 20 patients (mean age, 58.4 years) received lenvatinib [12 mg (n=7); 18 mg (n=11); 24 mg (n=2)] plus everolimus 5 mg				
67. Morrow *et al* (40)	2011	Phase I/II Study of Trastuzumab in Combination With Everolimus (RAD001) in Patients With HER2-Overexpressing Metastatic Breast Cancer Who Progressed on Trastuzumab-Based Therapy	47	9 (19.1)	9 (19.1)	0
68. Motzer *et al* (42)	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	238	88 (37)	83 (35)	5 (2)
69. Motzer *et al* (74)	2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial; everolimus 10 mg once daily	269	66 (25)	64 (24)	2 (1)
70. Motzer *et al* (75)	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	11 (22)	11 (22)	0
71. Narayan *et al* (43)	2016	Phase I Trial of Everolimus and Radiation Therapy for Salvage Treatment of Biochemical Recurrence in Prostate Cancer Patients Following Prostatectomy; Everolimus + salvage radiation therapy	18	12 (66.6)	11(61.1)	1 (5.5)
72. Oh *et al* (45)	2012	Phase 2 Study of Everolimus Monotherapy in Patients With Nonfunctioning Neuroendocrine Tumors or Pheochromocytomas/Paragangliomas;	34	10 (29.4)	10 (29.4)	0

		everolimus was administered daily at a dose of 10 mg for 4 weeks.				
73. Ohtsu *et al* (46)	2013	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study; everolimus 10 mg/day	437	87 (20)	86 (19.8)	1 (0.2)
74. Ou *et al* (91)	2015	SWOG S0722: Phase II study of mTOR inhibitor everolimus (RAD001) in advanced malignant pleural mesothelioma (MPM); everolimus 10 mg/day	59	11 (18.6)	10 (16.9)	1 (1.7)
75. Oudard *et al* (47)	2016	Clinical Benefit of Everolimus as Second-Line Therapy in Metastatic Renal Cell Carcinoma: The French Retrospective SECTOR Study	162	37 (22.8)	34 (21)	3 (1.9)
76. Park *et al* (103)	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 10 mg/day	100	30 (30)	29 (29)	1 (1)
77. Pavel *et al* (50)	2016	Safety and QOL in Patients with Advanced NET in a Phase 3b Expanded Access Study of Everolimus; everolimus 10 mg/day	pNet 123 Non pNEt 117	pNET 10 (8.1) Non pNET 8 (6.8)	pNET 9 (7.3) Non pnet 6 (5.1)	pNET 1(0.8) Non pnet 2 (1.7)
78. Powles *et al* (128)	2014	A phase Ib study investigating the combination of everolimus and dovitinib in vascular endothelial growth factor refractory clear cell renal cancer; everolimus 5 mg orally (PO) once daily (OD) and dovitinib 200 mg PO day 1-5/7	15	3 (20)	2 (14)	1 (7)
79. Powles *et al* (104)	2016	Randomized Open-Label Phase II Trial of Apitolisib (GDC-0980), a Novel Inhibitor of the PI3K/Mammalian Target of Rapamycin Pathway, Versus	43	26 (61)	25 (59)	1 (2)

		Everolimus in Patients With Metastatic Renal Cell Carcinoma; everolimus 10 mg once per day				
80. Quek *et al* (92)	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	8 (38.1)	8 (38.1)	0
81. Rathkopf *et al* (93)	2015	Everolimus Combined With Gefitinib in Patients With Metastatic Castration-Resistant Prostate Cancer: Phase 1/2 Results and Signaling Pathway Implications; in phase 1, 12 patients (10 with CRPC and 2 with glioblastoma) received daily gefitinib (250 mg) with weekly everolimus (30, 50, or 70 mg). In phase 2, 27 CRPC patients received gefitinib with everolimus (70 mg)	39	21 (54)	21 (54)	0
82. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO; everolimus 10 mg per day until progression or unacceptable toxicity	43	21 (49)	19 (44)	2 (5)
83. Rizzo *et al* (105)	2015	Everolimus as second-line therapy for metastatic renal cell carcinoma: a 'real-life' study; everolimus 10 mg/day	100	3 (3)	3 (3)	0
84. Robles *et al* (106)	2016	Everolimus safety and efficacy for renal angiomyolipomas associated with tuberous sclerosis complex: a Spanish expanded access trial; 10 mg everolimus once daily	19	2 (10.5)	2 (10.5)	0
85. Rodrigues *et al* (52)	2015	Phase I combination of pazopanib and everolimus in PIK3CA mutation positive/PTEN loss patients with	52	3 (5.7)	3 (5.7)	0

		advanced solid tumors refractory to standard therapy; pazopanib 600 mg every other day (QOD) alternating with everolimus 10 mg PO QOD.				
86. Ryan *et al* (94)	2011	A phase II study of everolimus in combination with imatinib for previously treated advanced renal carcinoma; everolimus 2.5 mg p.o. daily and imatinib 600 mg p.o. daily	19	5 (26)	5 (27)	0
87. Salazar *et al* (54)	2017	Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Na€ıve Advanced Pancreatic Neuroendocrine Tumors; everolimus 10 mg once daily	31	13 (41.9)	13 (41.9)	0
88. Sanoff *et al* (55)	2015	Everolimus and pasireotide for advanced and metastatic hepatocellular carcinoma; everolimus 7.5 mg PO daily and pasireotide LAR 60 mg IM every 28 days	24	6 (25)	6 (25)	0
89. Sarkaria *et al* (56)	2011	NCCTG 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 chemo-radiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide	18	4 (22)	4 (22)	0
90. Shoushtari *et al* (58)	2016	Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients; phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients	13	3 (21)	3 (21)	0

91. Slomovitz *et al* (59)	2010	A Phase 2 Study of the Oral Mammalian Target of Rapamycin Inhibitor, Everolimus, in Patients With Recurrent Endometrial Carcinoma; everolimus was administered at a dose of 10 mg orally daily for 28-day cycles	35	4 (11)	4 (11)	0
92. Strickler *et al* (95)	2012	Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors; 10 mg of panobinostat three times weekly, 5 or 10 mg everolimus daily, and bevacizumab at 10 mg/kg every 2 weeks	12	3 (25)	3 (25)	0
93. Tan *et al* (131)	2017	The mTOR inhibitor everolimus in combination with azacitidine in patients with relapsed/refractory acute myeloid leukemia: a phase Ib/II study	37	1 (2.7)		
94. Tarhini *et al* (61)	2010	Phase II Study of Everolimus (RAD001) in Previously Treated Small Cell Lung Cancer; everolimus 10 mg orally daily until disease progression	40	6 (15)	6 (15)	0
95. Vlahovic *et al* (63)	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	29 (91)	24 (75)	5 (16)
96. Wang *et al* (107)	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study; everolimus 10 mg/day in adults	58	16 (27.6)	14 (24.2)	2 (3.4)
97. Werner *et al* (64)	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	4 (25)	4 (25)	0

98. Yao *et al* (65)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors; 10 mg once daily	204	99 (49)	98 (48)	1 (1)
Total overall			10,114	2,302 (22.7)		
Total with grade			9,273	2,220 (24)	2,082 (22.5)	138 (1.5)
Total with grade		Only everolimus at 2.5 mg	-	-	-	-
Total with grade		Only everolimus at 5 mg	-	-	-	-
Total with grade		Only everolimus at 10 mg	3,794	923 (24.3)	869 (22.9)	54 (1.4)

Table SXIII. Incidence of stomatitis in selected studies in the literature due to everolimus therapy.

	Author/(Refs.)	Year	Study	No. of patients	Stomatitis (%)	G1/2 (%)	G3/4 (%)
1.	Amato *et al* (1)	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)	39	12 (30.8)	12 (30.8)	0
2.	Andre *et al* (67)	2014	Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial; eligible patients were randomly assigned (1:1) using a central patient screening and randomisation system to daily everolimus (5 mg/day) plus weekly trastuzumab (2 mg/kg) and vinorelbine (25 mg/m2) or to placebo plus trastuzumab plus vinorelbine, in 3-week cycles, stratified by previous lapatinib use	280	175 (62)	138 (49)	37 (13)
3.	Angelousi *et al* (133)	2017	Sequential everolimus and Sunitinib Treatment in Pancreatic Metastatic Well-Differentiated Neuroendocrine Tumours Resistant to Prior Treatments;	A: 20 B: 11	A: 2 (10) B: 1 (9)	A: 2 (10) B: 1(9)	0 0

			A :20 1st line everolimus B: 11 2nd line everolimus; 31 patients were administered one compound and upon progression were switched to the other. All patients had grade 1 or 2 tumours and stage IV disease with similar metastatic load. The everolimus full dosage was 10 mg daily, and the sunitinib 37.5 mg daily. However, dose modifications were permitted in the presence of AEs, so that everolimus could be decreased to 5 mg and sunitinib to 25 mg daily, respectively.				
4.	Armstrong *et al* (68)	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)	5 (9)
5.	Bajetta *et al* (2)	2014	Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients with advanced well-differentiated NETs of gastroentero-pancreatic tract and lung origin: everolimus 10 mg daily, in combination with octreotide LAR 30 mg every 28 days	50	31 (62)	26 (52)	5 (10)
6.	Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced	482	56 (11.6)	48 (9.9)	8 (1.6)

			Breast Cancer - Double-blind, phase 3 study; patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily)				
7.	Baselga *et al* (4)	2009	Phase II Randomized Study of Neoadjuvant Everolimus Plus Letrozole Compared With Placebo Plus Letrozole in Patients With Estrogen Receptor–Positive Breast Cancer; letrozole (2.5 mg/day) and either everolimus (10 mg/day) or placebo	137	50 (36.5)	47 (34.3)	3 (2.2)
8.	Bergmann *et al* (6)	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)
9.	Besse *et al* (8)	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)	27 (40.8)	21 (31.8)
10.	Campone *et al* (100)	2009	Safety and pharmacokinetics of paclitaxel and the oral mTOR inhibitor everolimus in advanced solid tumours; dose of everolimus was escalated from 15 to 30 mg	16	6 (37.5)	5 (31.2)	1 (6.2)

			and administered with paclitaxel 80 mg m^2 on days 1, 8, and 15 every 28 days				
11.	Castellano *et al* (111)	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)		
12.	Chan *et al* (78)	2013	A Prospective, Phase 1/2 Study of Everolimus and Temozolomide in Patients With Advanced Pancreatic Neuroendocrine Tumor; patients treated with temozolomide at a dose of 150 mg/m^2 per day on days 1 through 7 and days 15 through 21 in combination with everolimus daily in each 28-day cycle. In cohort 1, temozolo- mide 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 (62)	26 (60)	1 (2)
13.	Choueiri *et al* (11)	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)
14.	Chow *et al* (12)	2016	A Phase 2 Clinical Trial of Everolimus Plus	24	14 (58.3)	10 (41.6)	4 (6.9)

			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.				
15.	Chung *et al* (13)	2016	Phase Ib Trial of mFOLFOX6 and Everolimus (NSC-733504) in Patients with Metastatic Gastroesophageal Adenocarcinoma; six patients were accrued to the first dose level of 2.5 mg everolimus daily with mFOLFOX6.	6	4 (66)	2 (33)	2 (33)
16.	Ciruelos *et al* (101)	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; Treatment commenced on day 1 with daily doses of everolimus (either 2x5 mg or 1x10 mg) and exemestane (25 mg) and continued until disease progression, unacceptable toxicity	429	272 (63)	232 (54)	40 (9)
17.	Ciunci *et al* (14)	2014	Phase 1 and Pharmacodynamic Trial of Everolimus in Combination With Cetuximab in Patients With Advanced Cancer; not reported	29	4 (13.8)	4 (13.8)	0
18.	Colon-Otero *et al* (149)	2017	Phase 2 trial of everolimus and letrozole in relapsed estrogen receptor-positive high-grade ovarian cancer Patients received oral	19	2 (10.5)	0	2 (10.5)

			everolimus 10 mg daily and letrozole 2.5 mg daily				
19.	Courtney *et al* (150)	2015	A Phase I Study of Everolimus and Docetaxel in Patients With Castration-Resistant Prostate Cancer; everolimus 10 mg daily for 2 weeks and underwent a restaging FDG-PET/computed tomography scan. Patient cohorts were subsequently treated at 3 dose levels of everolimus with docetaxel: 5 mg to 60 mg/m^2, 10 mg to 60 mg/m^2, and 10 mg to 70 mg/m^2. The primary end point was the safety and tolerability of combination therapy	18	5 (27.7)	5 (27.7)	0
20.	Deenen *et al* (151)	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 bid for 14 days in three-weekly cycles	18	9 (50)	9 (50)	0
21.	Doi *et al* (136)	2010	Multicenter Phase II Study of Everolimus in Patients With Previously Treated Metastatic Gastric Cancer; everolimus 10 mg orally daily	53	3 (5.7)		
22.	Elmadani *et al* (17)	2017	EVESOR, a model-based, multiparameter, Phase I trial to optimize the benefit/toxicity ratio of everolimus and sorafenib	26	6 (23.1)	6 (23.1)	0
23.	Escudier at al.(70)	2016	Open-label phase 2 trial of first-line everolimus	92	23 (25)	23 (25)	0

			monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis; oral everolimus 10 mg once daily until disease progression or unacceptable toxicity				
24.	Fazio *et al* (19)	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)		
25.	Ferolla *et al* (71)	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; everolimus: The EVE starting dose was 10 mg dose, even if the 5 mg dose could be independently chosen by physicians	42	30 (72)	26 (62)	4 (10)
26.	Finn *et al* (115)	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)	A: 6 (37.5) B: 5 (35.8)	A: 0 B: 1 (7.1)

27.	Fury *et al* (80)	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)	0
28.	Ghobrial *et al* (120)	2010	Phase II Trial of the Oral Mammalian Target of Rapamycin Inhibitor Everolimus in Relapsed or Refractory Waldenstrom Macroglobulinemia; everolimus 10 mg daily for two cycles	50	4 (8)	0	4 (8)
29.	Goldberg et al.(122)	2015	Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study; not reported	24	18 (75)		
30.	Gong *et al* (82)	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 the dose of 10 mg or in some instances at 5 mg daily, according to patients' tolerance and request.	70	40 (57.1)	34 (47.8)	6 (9.3)
31.	Grignani *et al* (72)	2015	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial; patients took 400 mg sorafenib twice a day together with 5 mg everolimus once a day	38	20 (52)	18 (37)	2 (5)
32.	Hainsworth *et al* (21)	2010	Phase II Trial of Bevacizumab and	80	48 (60)	36 (45)	12 (15)

			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				
33.	Hatano *et al* (22)	2016	Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: A single institution experience in Japan; the dose of everolimus was set at 10 mg once a day for adults	47	43 (91)	42 (97.6)	1 (2.3)
34.	Hatano *et al* (23)	2017	Intermittent everolimus administration for renal angiomyolipoma associated with tuberous sclerosis complex; the dose of everolimus was set at 10 mg once a day	26	23 (88)	22 (84)	1 (4)
35.	Hurvitz *et al* (25)	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)	31 (56.3)	11 (20)

36.	Jerusalem *et al* (26)	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	2131	1126 (52.8)	926 (43.4)	200 (9.4)
37.	Jovanovic *et al* (28)	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)	0
38.	Jozwiak *et al* (125)	2016	Safety of Everolimus in Patients Younger than 3 Years of Age: Results from EXIST-1, a Randomized, Controlled Clinical Trial; everolimus was initiated at 4.5 mg/m^2/day and titrated to blood trough levels of 5-15 ng/ml	18	12 (66.7)		
39.	Kato *et al* (86)	2014	Efficacy of Everolimus in Patients with Advanced Renal Cell Carcinoma Refractory or Intolerant to VEGFR-TKIs and Safety	19	7 (37)	6 (32)	1 (5)

			Compared with Prior VEGFR-TKI Treatment; not reported				
40.	Kim *et al* (29)	2014	A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma; everolimus was given at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities	34	27 (79.4)	26 (96.2)	1 (2.9)
41.	Kim *et al* (87)	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	36	15 (41.7)	14 (38.9)	1 (2.8)
42.	Koutsoukos *et al* (34)	2017	real-world experience of everolimus as second-line treatment in metastatic renal cell cancer after failure of pazopanib; the median everolimus daily dose was 10 mg (5–10 mg), while the mean daily dose was 9.3 mg	31	8 (26)	5 (16)	3 (10)
43.	Kulke *et al* (35)	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)

			Patients were randomized 1:1 to receive a combination of everolimus (10 mg/day, orally) and pasireotide long-acting release (60 mg/28 days, intramuscularly) or everolimus alone (10 mg/day, orally)				
44.	Kumano *et al* (36)	2013	Sequential use of mammalian target of rapamycin inhibitors in patients with metastatic renal cell carcinoma following failure of tyrosine kinase inhibitors everolimus; everolimus (10 mg orally, once daily)	57	17 (29.8)	14 (82.35)	3 (5.3)
45.	Moscetti *et al* (102)	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)	100 (55.2)	15 (8.3)
46.	Motzer *et al* (41)	2016	Phase II trial of second-line everolimus in patients with metastatic renal cell carcinoma (RECORD-4); not reported	133	7 (5.26)		
47.	Motzer *et al* (42)	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 The everolimus dosage was 10 mg daily continually, and	337	151 (44.8)	136 (40.3)	15 (4.5)

			the sunitinib dosage was 50 mg daily in a schedule of 4 weeks on followed by 2 weeks off. Dose modifications were permitted for adverse events (AEs)				
48.	Motzer *et al* (74)	2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial; ever;olimus 10 mg once daily	269	107 (40)	98 (36.43)	9 (3.34)
49.	Motzer *et al* (75)	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)	1 (2)
50.	Oh *et al* (45)	2012	Phase 2 Study of Everolimus Monotherapy in Patients With Nonfunctioning neuroendocrine Tumors or Pheochromocytomas/Paraganngliomas; everolimus was administered daily at a dose of 10 mg for 4 weeks.	34	6 (17.6)	4 (11.7)	2 (5.9)
51.	Ohtsu *et al* (46)	2013	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study; everolimus 10 mg/day	437	174 (40)	154 (35)	20 (5)
52.	Ohyama *et al* (48)	2017	Efficacy and safety of sequential use of everolimus in Japanese patients with advanced renal cell carcinoma after failure of	53	26 (49.1)	22 (41.6)	4 (7.5)

			first-line treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitor: a multicenter phase II clinical trial; not reported				
53.	Panzuto *et al* (49)	2014	Real-World Study of Everolimus in Advanced progressive neuroendocrine tumors; everolimus starting dose was 10 mg daily; the investigator had the option of starting at or reducing the dose to 5 mg daily	169	37 (21.9)	33 (19.6)	4 (2.3)
54.	Park *et al* (103)	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; not reported	100	42 (44)	36 (38)	6 (6)
55.	Pavel *et al* (50)	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)	6 (4.9)
56.	Quek *et al* (92)	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)	18 (85.7)	3 (14.3)

57.	Safra *et al* (53)	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)	21 (8.3)
58.	Salazar *et al* (54)	2017	Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Na€ıve Advanced Pancreatic Neuroendocrine Tumors; everolimus 10 mg once daily	31	20 (64.5)	18 (58)	2 (6.5)
59.	Sarkaria *et al* (56)	2011	NCCTG Phase I Trial N057K of Everolimus (RAD001) and Temozolomide in Combination with Radiation Therapy in Newly Diagnosed glioblastoma multiforme; all patients received weekly oral RAD001 in combination with standard chemo-radiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide	18	11 (61.1)	11 (61.1)	0
60.	Strickler *et al* (95)	2012	Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors; 10 mg of 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)

61.	Sun *et al* (60)	2013	A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung Cancer; A: everolimus 2.5 mg B: everolimus 5 mg C: everolimus 10 mg	A: 6 B: 11 C: 3	A: 2 (33.3) B: 5 (45.5) C: 1 (33.3)	A: 2 (33.3) B: 5 (45.5) C: 1 (33.3)	0 0 0
62.	Takahashi *et al* (130)	2013	Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results; everolimus regimen (1.5 mg/day starting dose (target trough: 3 to 8 ng/ml) + reduced-dose cyclosporine)	61	14 (23)		
63.	Tobinai *et al* (96)	2010	Phase I study of the oral mammalian target of rapamycin inhibitor everolimus (RAD001) in Japanese patients with relapsed or refractory non-Hodgkin lymphoma everolimus 5 or 10 mg orally once daily.	13	7 (53.7)	7 (53.7)	0
64.	Vlahovic *et al* (63)	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)
65.	Wang *et al* (107)	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)	1 (1.7)

66.	Werner *et al* (64)	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)	8 (50)	1 (6.25)
67.	Wolpin *et al* (97)	2009	Oral mTOR Inhibitor Everolimus in Patients With Gemcitabine-Refractory Metastatic Pancreatic Cancer; everolimus 10 mg daily	33	10 (30)	9 (27)	1 (3)
68.	Yao *et al* (140)	2008	Efficacy of everolimus and Octreotide LAR in Advanced Low- to Intermediate-Grade Neuroendocrine Tumors: Results of a Phase II Study; treatment consisted of RAD001 5 mg/day or 10 mg/day and octreotide LAR 30 mg every 28 days.	64	6 (10)		
69.	Yao *et al* (65)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors; everolimus 10 mg once daily	204	131 (64)	117 (57)	14 (7)
70.	Yee *et al* (99)	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				8,259	3,568 (43.2)		
Total with grade				7,854	3,494 (44.5)	2,959 (37.7)	535 (6.8)
Total with grade			Only everolimus at 2.5 mg	6	2 (33.3)	2 (33.3)	0
Total with grade			Only everolimus at 5 mg	11	5 (45.5)	5 (45.5)	0
Total with grade			Only everolimus at 10 mg	2,275	844 (37.1)	750 (33)	94 (4.1)

Table SXIV. Incidence of thrombocytopenia in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 Cases (%)	Grade 3/4 Cases (%)
1. Abida *et al* (109)	2016	Phase I Study of Everolimus in Combination with Gemcitabine and Split-Dose Cisplatin in Advanced Urothelial Carcinoma; gemcitabine 800 mg/m^2 and cisplatin 35 mg/m^2 on days 1 and 8 of 21-day cycles for a total of 6 cycles in combination with everolimus at increasing dose levels (DL1: 5 mg QOD, DL2: 5 mg daily, DL3: 10 mg daily) following a standard 3+3 design	12	3 (25)		
2. Amato *et al* (1)	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 was given at a dose of 10 mg daily orally with- out 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 2 cycles (8 weeks) using Response Evaluation Criteria in Solid Tumors (RECIST)	39	39 (100)	36 (92.3)	3 (7.7)
3. Andre *et al* (67)	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 3 trial, we recruited women with HER2-positive, trastuzumab-resistant, advanced breast carcinoma who had previously received	280	40 (15)	30 (11)	10 (4)

		taxane therapy. Eligible patients were randomly assigned (1:1) using a central patient screening and randomisation system to daily everolimus (5 mg/day) plus weekly trastuzumab (2 mg/kg) and vinorelbine (25 mg/m2) or to placebo plus trastuzumab plus vinorelbine, in 3-week cycles, stratified by previous lapatinib use				
4. Armstrong *et al* (68)	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	7 (13)	6 (11)	1 (2)
5. Bajetta *et al* (2)	2014	Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients With Neuroendocrine Tumors Treatment-naive 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	6 (12)	6 (12)	0
6. Barnes *et al* (77)	2013	Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma; everolimus was administered orally once daily at a dose of 5 mg on days 1 through 14 of cycle 1. If tolerated, the dose was then increased to 10 mg for days 15 through 28 of cycle 1. For cycle 2 and beyond, patients continued to receive everolimus at a dose of 10 mg daily continuously. Rituximab, at a dose of 375 mg/m^2, was administered intravenously weekly for four doses during cycle 1, and then on day 1 of cycles 2 through 6. After cycle 6, patients could receive an additional 6 months of everolimus	24	10 (41.6)	8 (33.3)	2 (8.3)

		monotherapy in the absence of disease progression or unacceptable toxicity				
7. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer; In this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily)	482	12 (2.4)	9 (1.8)	3 (0.6)
8. Baselga *et al* (4)	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	25 (18.2)	23 (16.7)	2 (1.5)
9. Bendell *et al* (5)	2015	A phase Ib study of linsitinib (OSI-906), a dual inhibitor of IGF-1R and IR tyrosine kinase, in combination with everolimus as treatment for patients with refractory metastatic colorectal cancer; OSI-906 and everolimus were adminis-tered to cohorts of 3-6 patients in a standard 3+3 design	18	3 (15)	1 (5)	2 (10)
10. Besse *et al* (7)	2013	A phase Ib dose-escalation study of everolimus combined with cisplatin and etoposide as first-line therapy in patients with extensive-stage small-cell lung cancer	40	11 (28)		
11. Campone *et al* (100)	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	16	4 (25)	3 (18.7)	1 (6.2)

		paclitaxel 80 mg m^2 on days 1, 8, and 15 every 28 days				
12. Cazzaniga *et al* (135)	2017	Efficacy and safety of Everolimus and Exemestane in hormone- receptor positive (HRþ) human-epidermal-growth-factor negative (HER2) advanced breast cancer patients: New insights beyond clinical trials. The EVA study; everolimus 10 or 5 mg/day	404	35 (10.3)	31 (9.1)	4 (1.2)
13. Chocteau-Bouju *et al* (10)	2015	Efficacy and tolerance of everolimus in 123 consecutive advanced ER positive, HER2 negative breast cancer patients. A two center retrospective study; Everolimus was initially prescribed at the standard dose of 10 mg daily in 77.2% of patients and at 5 mg daily in 22.8% of patients.	123	123 (9.8)	121 (98.4)	2 (1.6)
14. Chow *et al* (12)	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	8 (33)	7 (29.1)	1 (4.1)
15. Ciunci *et al* (14)	2014	Phase 1 and Pharmacodynamic Trial of Everolimus in Combination With Cetuximab in Patients With Advanced Cancer	29	4 (13.8)	2 (6.9)	2 (6.9)
16. Conconi *et al* (15)	2014	Clinical activity of everolimus in relapsed/refractory marginal zone B-cell lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group; the study drug everolimus (RAD001) was supplied by Nov- artis (Basel, Switzerland) and was administered orally at a daily dose of 10 mg, from day 1 to day 28 for up to a total of six cycles or until progression	30	28 (93.3)	23 (76.6)	5 (16.6)
17. Dasari *et al* (16)	2015	Phase I study of the anti-IGF1R antibody cixutumumab with everolimus and	19	10 (53)	10 (53)	0

		octreotide in advanced well-differentiated neuroendocrine tumors; keeping the doses of everolimus (10 mg p.o. daily) and octreotide LAR (20 mg i.m. every 21 days) constant, cixutumumab was evaluated at escalating doses of 10 and 15 mg/kg every 21 days for a 21-day cycle. Octreotide LAR was administered every 21 days rather than the standard practice of every 28 days to fit with the study schedule for patients' convenience				
18. Elmadani *et al* (17)	2017	EVESOR, a model-based, multiparameter, Phase I trial to optimize the bene t/toxicity ratio of everolimus and sorafenib; everolimus + sorafenib	26	2 (7.7)	2 (7.7)	0
19. Ellard *et al* (79)	2009	Randomized Phase II Study Comparing Two Schedules of Everolimus in Patients With Recurrent/Metastatic Breast Cancer: NCIC Clinical Trials Group IND.163 randomized phase II study of everolimus 10 mg daily versus 70 mg weekly A: daily B: weekly	A: 33 B: 16	A: 20 (60.6) B: 7 (43.7)	A: 0 B: 0	A: 20 (60.6) B: 7 (43.7)
20. Escudier at al.(70)	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	10 (11)	10 (11)	0
21. Fazio *et al* (19)	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 A:everolimus + octreotide	33	6 (18.2)	3 (9.1)	3 (9.1)
22. Ferolla *et al* (71)	2017	Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced	42	10 (23)	9 (21)	1 (2)

		carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial; Everolimus: the EVE starting dose was 10 mg dose, even if the 5 mg dose could be independently chosen by physicians				
23. Finn *et al* (115)	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: 7 (43.8) B: 8 (57.1)	A: 6 (37.5) B: 2 (24.2)	A: 1 (6.3) B: 6 (42.9)
24. Fury *et al* (80)	2012	A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors	30	18 (64)	18 (64)	0
25. Ghobrial *et al* (138)	2014	Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory Waldenstrom Macroglobulinemia; everolimus 10 mg/day	60	12 (20)	0	12 (20)
26. Glanville *et al* (121)	2015	Three-year results of an investigator-driven multicenter, international, randomized open-label *de novo* trial to prevent BOS after lung transplantation	84	12 (7)		
27. Gong *et al* (82)	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 the dose of 10 mg or in some instances at 5 mg daily, according to patients' tolerance and request.	70	7 (10)	3 (4.3)	4 (5.7)
28. Grignani *et al* (72)	2014	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial; patients took 400 mg sorafenib twice a day together with 5 mg everolimus once a day	38	22 (58)	18 (47)	4 (11)

29. Hainsworth *et al* (21)	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	32 (40)	31 (39)	1 (1)
30. Hill *et al* (24)	2017	A phase I trial of bortezomib in combination with everolimus for treatment of relapsed/refractory non-Hodgkin lymphoma; A: bortezomib + everolimus	29	47	41	6
31. Hurvitz *et al* (25)	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	10 (18.2)	6 (10.9)	4 (7.3)
32. Johnston *et al* (27)	2016	The mTORC1 Inhibitor Everolimus Combined with R-CHOP-21 for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Safety and Efficacy Results of a Phase I and Feasibility Trial NCCTG 1085 (Alliance); everolimus 10 mg days 1-10 or 1-14 in combination with R-CHOP-21 for 6 cycles	24	21 (89)	15 (63)	6 (26)
33. Jovanovic *et al* (28)	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;	96	38 (40)	38 (40)	0

		cisplatin 25 mg/m2 IV weekly for 12 weeks, everolimus 5 mg PO daily for 12 weeks and paclitaxel 80 mg/m2 IV weekly for 11 weeks (starting 1 week after cisplatin initiation)				
34. Ju *et al* (85)	2015	Toxicity and adverse effects of everolimus in the treatment of advanced nonsmall cell lung cancer pretreated with chemotherapy-Chinese experiences everolimus 5–10 mg/day with or without chemotherapy until progression or unacceptable toxicity	12	0	0	0
35. Kanesvaran *et al* (126)	2015	A single arm phase 1b study of everolimus and sunitinib in patients with advanced renal cell carcinoma (RCC); sunitinib + everolimus	4	4 (100)	3 (75)	1 (5)
36. Kim *et al* (29)	2014	A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma; everolimus was given at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities	34	4 (11.8)	4 (11.8)	0
37. Kim *et al* (87)	2018	Clinical outcomes of the sequential use of pazopanib followed by meverolimus for the treatment of metastatic renal cell carcinoma: A multicentre study in Korea	36	9 (25)	9 (25)	0
38. Kim *et al* (30)	2013	A phase I study of everolimus and CHOP in newly diagnosed peripheral T-cell lymphomas; four dose levels (2.5 to 10 mg) of everolimus from days 1 to 14 with CHOP (750 mg/m2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 (maximum 2 mg) vincristine on day 1, and 100 mg/day prednisone on days 1 to 5) every 21 days were planned	15	13 (86.6)	8 (53.3)	5 (33.3)
39. Knox *et al* (31)	2017	Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC;	238	3		

		patients were randomly assigned 1:1 to receive either first-line everolimus 10 mg/day				
40. Koeberle *et al* (32)	2016	Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29) Sorafenib + everolimus	59	15 (25)	4 (6)	11 (19)
41. Kumano *et al* (36)	2013	Sequential use of mammalian target of rapamycin inhibitors in patients with metastatic renal cell carcinoma following failure of tyrosine kinase inhibitors; everolimus 10 mg/day	57	9 (15.8)	8 (14)	1 (1.8)
42. Lim *et al* (89)	2013	A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes; everolimus 10 mg daily orally until unacceptable toxicity or disease progression	38	1 (2)	1 (2)	0
43. Massarweh *et al* (37)	2014	A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure; fulvestrant was administered intramuscularly (in the gluteus maximus) in a loading dose schedule as follows: 500 mg in two divided doses, one on each side on day 1, then 250 mg on day 14, and then 250 mg on day 28 and every 4 weeks ± 3 days thereafter. Everolimus was administered initially at a dose of 5 mg daily in the first 5-patient cohort for the first month of treatment and then increased to 10 mg PO daily after that	31	17 (55)	17 (55)	0
44. Milowsky *et al* (127)	2013	Phase II study of everolimus in metastatic urothelial cancer; all patients received everolimus 10 mg orally once daily continuously (one cycle = 4 weeks)	45	21 (47)	21 (47)	0

45. Molina *et al* (38)	2012	Phase 1 Trial of Everolimus Plus Sunitinib in Patients With Metastatic Renal Cell Carcinoma; A: everolimus + sunitnib	20	18 (90)	14 (70)	4 (20)
46. Morrow *et al* (40)	2011	Phase I/II Study of Trastuzumab in Combination With Everolimus (RAD001) in Patients With HER2-Overexpressing Metastatic Breast Cancer Who Progressed on Trastuzumab-Based Therapy	47	10 (21.2)	6 (12.7)	4 (8.5)
47. Motzer *et al* (42)	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	337	12 (3.6)	4 (1.2)	8 (4.4)
48. Narayan *et al* (43)	2016	Phase I Trial of Everolimus and Radiation Therapy for Salvage Treatment of Biochemical Recurrence in Prostate Cancer Patients Following Prostatectomy	18	2 (11.1)	1 (5.5)	1 (5.5)
49. Nozawa *et al* (90)	2013	Adverse Event Profile and Dose Modification of Everolimus for Advanced Renal Cell Carcinoma in Real-world Japanese Clinical Practice	47	3 (6.3)	2 (4.2)	1 (2.1)
50. Oh *et al* (45)	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	5 (14.7)	0	5 (14.7)
51. Ohtsu *et al* (46)	2013	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study; everolimus 10 mg/day	437	80 (18)	58 (13)	22 (5)
52. Oudard *et al* (47)	2016	Clinical Benefit of Everolimus as Second-Line Therapy in Metastatic Renal Cell Carcinoma: The French Retrospective SECTOR Study	162	12 (7.4)	11 (6.8)	1 (0.6)

53. Panzuto *et al* (49)	2014	Real-World Study of Everolimus in Advanced Progressive Neuroendocrine Tumors Everolimus; everolimus starting dose was 10 mg daily; the investigator had the option of starting at or reducing the dose to 5 mg daily	169	37 (21.9)	24 (14.1)	13 (7.8)
54. Park *et al* (103)	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 oral (10 mg dose once daily)	100	33 (35)	30 (32)	3 (3)
55. Pavel *et al* (50)	2016	Safety and QOL in Patients with Advanced NET in a Phase 3b Expanded Access Study of Everolimus; everolimus (10 mg/day)	pNET 123 Non pNET 117	pNET 12 (9.8) Non pNET 6 (5.1)	pNET 11 (9) Non pNET 4 (3.7)	pNET 1 (0.8) Non pNET 2 (1.4)
56. Rathkopf *et al* (93)	2015	Everolimus Combined With Gefitinib in Patients With Metastatic Castration-Resistant Prostate Cancer: Phase 1/2 Results and Signaling Pathway Implications; in phase 1, 12 patients (10 with CRPC and 2 with glioblastoma) received daily gefitinib (250 mg) with weekly everolimus (30, 50, or 70 mg). In phase 2, 27 CRPC patients received gefitinib with everolimus (70 mg)	39	18 (47)	16 (41)	2 (6)
57. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO; everolimus 10mg per day until progression or unacceptable toxicity	43	9 (21)	7 (16)	2 (5)
58. Rodrigues *et al* (52)	2015	Phase I combination of pazopanib and everolimus in PIK3CA mutation positive/PTEN loss patients with	52	20 (28.4)	14 (27)	6 (1.4)

		advanced solid tumors refractory to standard therapy; pazopanib 600 mg every other day (QOD) alternating with everolimus 10 mg PO QOD.				
59. Ryan *et al* (94)	2011	A phase II study of everolimus in combination with imatinib for previously treated advanced renal carcinoma; everolimus 2.5 mg p.o. daily and imatinib 600 mg p.o. daily	19	9 (47)	8 (21)	1 (5)
60. Sanoff *et al* (55)	2015	Everolimus and pasireotide for advanced and metastatic hepatocellular carcinoma; everolimus 7.5 mg PO daily and pasireotide LAR 60 mg IM every 28 days	24	5 (21)	5 (21)	0
61. Sarkaria *et al* (56)	2011	NCCTG 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 chemo-radiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide	18	16 (89)	15 (83)	1 (6)
62. Shen *et al* (57)	2014	Phase II Multicentered Study of Low-Dose Everolimus plus Cisplatin and Weekly 24-Hour Infusion of High-Dose 5-Fluorouracil and Leucovorin as First-Line Treatment for Patients with Advanced Gastric Cancer; everolimus (10 mg p.o. on days 1, 8 and 15) plus cisplatin and a weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin (HDFL) chemotherapy (cisplatin 35 mg/m2 intrave- nous infusion for 24 h on days 1 and 8, 5-fluorouracil 2,000 mg/m2 and leucovorin 300 mg/m2 intravenous infusion for 24 h on days 1, 8 and 15) every 28 days	40	22 (55)	17 (42.5)	5 (12.5)

63. Shoushtari *et al* (58)	2016	Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients; phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients	13	7 (50)	7 (50)	0
64. Slomovitz *et al* (59)	2010	A Phase 2 Study of the Oral Mammalian Target of Rapamycin Inhibitor, Everolimus, in Patients With Recurrent Endometrial Carcinoma; everolimus was administered at a dose of 10 mg orally daily for 28-day cycles	35	4 (11)	3 (8)	1 (3)
65. Strickler *et al* (95)	2012	Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors; 10 mg of panobinostat three times weekly, 5 or 10 mg everolimus daily, and bevacizumab at 10 mg/kg every 2 weeks.	12	5 (42)	3 (25)	2 (17)
66. Sun *et al* (60)	2013	A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer; A: everolimus 2.5 mg B: everolimus 5 mg C: everolimus 10 mg	A: 6 B: 11 C: 3	A: 2 (33.3) B: 4 (36.3) C: 3 (100)	A: 2 (33.3) B: 3 (27.2) C: 2 (66.6)	A: 0 B: 1 (9.1) C: 1 (33.3)
67. Tarhini *et al* (61)	2010	Phase II Study of Everolimus (RAD001) in Previously Treated Small Cell Lung Cancer everolimus 10 mg orally daily until disease progression	40	6 (15)	4 (10)	2 (5)
68. Tobinai *et al* (96)	2010	Phase I study of the oral mammalian target of rapamycin inhibitor everolimus (RAD001) in Japanese patients with relapsed or refractory non-Hodgkin lymphoma everolimus 5 or 10 mg orally once daily A: Everolimus 5 mg B: Everolimus 10 mg	A: 7 B: 6	A: 3 (42.8) B: 5 (83.3)	A: 3 (42.8) B: 3 (50)	A: 0 B: 2 (33.3)
69. Tomita *et al* (62)	2017	Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup analysis from the CheckMate 025 study;	26	13 (50)	12 (46)	1 (4)

		nivolumab 3 mg/kg intravenously every 2 weeks or everolimus 10-mg tablet orally once daily				
70. Vlahovic *et al* (63)	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	12 (37)	10 (31)	2 (6)
71. Werner *et al* (64)	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	8 (50)	8 (50)	0
72. Yao *et al* (140)	2008	Efficacy of RAD001 (Everolimus) and Octreotide LAR in Advanced Low- to Intermediate-Grade Neuroendocrine Tumors: Results of a Phase II Study Treatment consisted of RAD001 5 mg/day (30 patients) or 10 mg/d (30 patients) and octreotide LAR 30 mg every 28 days.	64	3 (5)		
73. Yao *et al* (65)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors; 10 mg once daily	204	27 (13)	19 (9)	8 (4)
74. Yee *et al* (98)	2014	Outcomes in patients with relapsed or refractory multiple myeloma in a phase I study of everolimus in combination with lenalidomide	26	11 (42)	2 (7.6)	9 (34.4)
Total over all			5,533	1,195 (21.8)		
Total with grade			5,095	1,163 (22.8)	921 (18.1)	242 (4.7)
Total with grade		Only everolimus at 2.5 mg	6	2 (33.3)	2 (33.3)	0
Total with grade		Only everolimus at 5 mg	18	7 (38.9)	6 (33.3)	1 (5.6)
Total with grade		Only everolimus at 10 mg	1,718	361(21)	265 (15.4)	96 (5.6)

Table SXV. Incidence of emesis in selected studies in the literature due to everolimus therapy.

Author/(Refs.)	Year	Study	No. of patients	No. of cases (%)	Grade 1/2 Cases (%)	Grade 3/4 Cases (%)
1. Amato *et al* (1)	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 was given 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 2 cycles (8 weeks) using Response Evaluation Criteria in Solid Tumors (RECIST)	39	9 (23.1)	9 (23.1)	0
2. Andre *et al* (67)	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 3 trial, we 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 randomisation system to daily	280	60 (22)	58 (21)	2 (1)

		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				
3. Armstrong *et al* (68)	2016	Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial; everolimus was administered orally at 10 mg once daily	52	13 (23)	13 (23)	0
4. Bachelot *et al* (76)	2012	Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study; this open-label, phase II study randomly assigned postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative, AI-resistant mBC to tamoxifen 20 mg/day plus everolimus 10 mg/day (n=54) or tamoxifen 20 mg/day alone	54	9 (17)	9 (17)	0
5. Baselga *et al* (3)	2012	Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer; in this international, double-blind, phase 3 study, patients	482	14 (3)	12 (2.4)	2 (0.6)

		were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily)				
6. Bendell *et al* (5)	2015	A phase Ib study of linsitinib (OSI-906), a dual inhibitor of IGF-1R and IR tyrosine kinase, in combination with everolimus as treatment for patients with refractory metastatic colorectal cancer; OSI-906 and everolimus were administered to cohorts of 3-6 patients in a standard 3+3 design	18	4 (21)	3 (16)	1 (5)
7. Besse *et al* (8)	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	11 (16.7)	11 (16.7)	0
8. Bissler *et al* (134)	2018	The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant cell astrocytoma; Patients were initially randomly assigned to receive everolimus 4.5 mg/m^2/day (target blood trough 5–15 mg/dl) or placebo and could continue in an open-label extension phase	33	6 (18.2)		
9. Bissler *et al* (110)	2016	Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis:	112	19 (17)	19 (17)	0

		extension of a randomized controlled trial; a starting dose of 10 mg was chosen as a means of providing adequate exposure to almost all patients based on dose proportionality in this adult age group. Dose modifications were to be determined clinically and were based solely on tolerability. Doses could be lowered to 5 mg/day or even to 5 mg/ every other day				
10. Bissler *et al* (69)	2013	Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial; oral everolimus 10 mg per day	79	12 (15)	12 (15)	0
11. Buzzoni *et al* (9)	2017	impact of prior therapies on everolimus activity: an exploratory analysis of raDianT-4; patients were randomized (2:1) to everolimus 10 mg/day or placebo, both with best supportive care	202	14 (7)	10 (7)	4 (2)
12. Cazzaniga *et al* (135)	2017	Efficacy and safety of Everolimus and Exemestane in hormone- receptor positive (HRþ) human-epidermal-growth-factor negative (HER2) advanced breast cancer patients: New insights beyond clinical trials. The EVA study	404	9 (2.7)	9 (2.7)	0

13. (78)	Chan *et al*	2013	A Prospective, Phase 1/2 Study of Everolimus and Temozolomide in Patients With Advanced Pancreatic Neuroendocrine Tumor Patients were treated with temozolomide at a dose of 150 mg/m^2 per day on days 1 through 7 and days 15 through 21 in combination with everolimus daily in each 28-day cycle. In cohort 1, temozolo- mide 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	19 (44)	19 (44)	0
14. (11)	Choueiri *et al*	2015	Cabozantinib versus everolimus in advanced renal cell carcinoma everolimus at a dose of 10 mg daily	322	45 (14)	42 (13)	3 (1)
15. (13)	Chung *et al*	2016	Phase Ib Trial of mFOLFOX6 and Everolimus (NSC-733504) in Patients with Metastatic Gastroesophageal Adenocarcinoma Six patients were accrued to the first dose level of 2.5 mg everolimus daily with mFOLFOX6	6	3 (50)	3 (50)	0
16. (14)	Ciunci *et al*	2014	Phase 1 and Pharmacodynamic Trial of Everolimus in Combination With Cetuximab in Patients With Advanced Cancer	29	5 (17.2)	5 (17.2)	0

17. Ellard *et al* (79)	2009	Randomized Phase II Study Comparing Two Schedules of Everolimus in Patients With Recurrent/Metastatic Breast Cancer: NCIC Clinical Trials Group IND.163; randomized phase II study of everolimus 10 mg daily versus 70 mg weekly A: daily B: weekly	A: 33 B: 16	A: 4 (12.1) B: 5 (31.2)	A: 0 B: 0	A: 4 (12.1) B: 5 (31.2)
18. Escudier at al.(70)	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	16 (17)	15 (16)	1 (1)
19. Ferolla *et al* (71)	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; Everolimus: the EVE starting dose was 10 mg dose, even if the 5 mg dose could be independently chosen by physicians	42	4 (10)	4 (10)	0
20. Franz *et al* (117)	2013	Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial	78	13 (17)	12 (16)	1 (1)

		A: everolimus 4-5mg/m^2				
21. Fury *et al* (118)	2013	A Phase 1 Study of Everolimus D Weekly Cisplatin D Intensity Modulated Radiation Therapy in Head-and-Neck Cancer; A: everolimus + cisplatin	13	5 (39)	5 (39)	0
22. Gadgeel *et al* (81)	2013	Phase I study evaluating the combination of lapatinib (a Her2/Neu and EGFR inhibitor) and everolimus (an mTOR inhibitor) in patients with advanced cancers: South West Oncology Group (SWOG) Study S0528; A: The MTD of the combination was 1,250 mg of lapatinib and 5 mg of everolimus once daily	54	8 (15)	7 (13)	1 (2)
23. Goldberg et al.(122)	2015	Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study Everolimus; following a 28-day screening period, patients received everolimus 2.5 mg/day for 4 weeks, followed by dose titration (based on safety and tolerability) to 5 mg/day for 4 weeks then 10 mg/day for 18 weeks thereafter	24	4 (17)		
24. Grignani *et al* (72)	2014	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	38	8 (21)	8 (21)	0

		with 5 mg everolimus once a day				
25. Hainsworth *et al* (21)	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	34 (43)	32 (40)	2 (3)
26. Harzstark *et al* (84)	2011	A Phase 1 Study of Everolimus and Sorafenib for Metastatic Clear Cell Renal Cell Carcinoma; starting doses were everolimus at a dose of 2.5 mg orally daily and sorafenib at a dose of 400 mg orally twice daily continuously	20	2 (10)	2 (10)	0
27. Hatano *et al* (22)	2016	Outcomes of everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex: A single institution experience in Japan; the dose of everolimus was set at 10 mg once a day for adults.	47	13 (28)	12 (27)	1
28. Hatano *et al* (23)	2017	Intermittent everolimus administration for renal angiomyolipoma associated with tuberous sclerosis complex; the dose of everolimus was set at 10 mg once a day	26	5 (19)	4 (15.3)	1 (3.7)
29. Hurvitz *et al* (25)	2013	A phase 2 study of everolimus combined with trastuzumab and paclitaxel in patients with HER2-overexpressing; advanced breast cancer that progressed during prior	55	15	12 (21.8)	3 (5.5)

		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				
30. Jozwiak *et al* (125)	2016	Safety of Everolimus in Patients Younger than 3 Years of Age: Results from EXIST-1, a Randomized, Controlled Clinical Trial Everolimus was initiated at 4.5 mg/m^2/day and titrated to blood trough levels of 5-15 ng/ml	18	4 (22.2)		
31. Ju *et al* (85)	2015	Toxicity and adverse effects of everolimus in the treatment of advanced nonsmall cell lung cancer pretreated with chemotherapy-Chinese experiences; everolimus 5-10 mg/day with or without chemotherapy until progression or unacceptable toxicity	12	1 (8.3)	0	1 (8.3)
32. Kanesvaran *et al* (126)	2015	A single arm phase 1b study of everolimus and sunitinib in patients with advanced renal cell carcinoma (RCC); sunitinib + everolimus	4	3 (75)	3 (75)	0
33. Kato *et al* (86)	2013	Efficacy of Everolimus in Patients with Advanced Renal Cell Carcinoma Refractory or Intolerant to VEGFR-TKIs and Safety Compared with Prior VEGFR-TKI Treatment	19	3 (16)	1 (5)	2 (11)

34. (87)	Kim *et al*	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	36	2 (5.6)	2 (5.6)	0
35. (30)	Kim *et al*	2013	A phase I study of everolimus and CHOP in newly diagnosed peripheral T-cell lymphomas Four dose levels (2.5 to 10 mg) of everolimus from days 1 to 14 with CHOP (750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 (maximum 2 mg) vincristine on day 1, and 100 mg/day prednisone on days 1 to 5) every 21 days were planned	15	2 (13.3)	2 (13.3)	0
36. (31)	Knox *et al*	2017	Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC Patients were randomly assigned 1:1 to receive either first-line everolimus 10 mg/day	238	10 (4.2)		
37. (35)	Kulke *et al*	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: everolismus + pasireotide LAR everolimus [10 mg/day, per oral (p.o.) with pasireotide LAR (60 mg/28 days, i.m.)	A 78 B 81	A 22 (28.2) B 16 (19.8)	A 20 (25.6) B 14 (17.3)	A 2 (2.6) B 2 (2.5)

		B: Everolimus (10 mg/day, per oral (p.o.)]				
38. Massarweh *et al* (37)	2014	A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure; fulvestrant was administered intramuscularly (in the gluteus maximus) in a loading dose schedule as follows: 500 mg in two divided doses, one on each side on day 1, then 250 mg on day 14, and then 250 mg on day 28 and every 4 weeks ± 3 days thereafter. Everolimus was administered initially at a dose of 5 mg daily in the first 5-patient cohort for the first month of treatment and then increased to 10 mg PO daily after that	31	6 (19)	5 (16.1)	1 (2.9)
39. Milowsky *et al* (127)	2013	Phase II study of everolimus in metastatic urothelial cancer all patients received everolimus 10 mg orally once daily continuously (one cycle = 4 weeks)	45	10 (22)	10 (22)	0
40. Molina *et al* (38)	2012	Phase 1 Trial of Everolimus Plus Sunitinib in Patients With Metastatic Renal Cell Carcinoma; A: everolimus + sunitnib	20	4 (20)	3 (15)	1 (5)
41. Molina *et al* (39)	2014	A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of metastatic renal cell carcinoma (RCC)	20	8 (40)	7 (35)	1 (5)

		20 twenty patients (mean 58.4 years) received lenvatinib [12 mg (n=7); 18 mg (n=11); 24 mg (n=2)] plus everolimus 5 mg				
42. Moscetti *et al* (102)	2016	Safety analysis, association with response and previous treatments of everolimus and exemestane in 181 metastatic breast cancer patients: A multicenter Italian experience	181	8 (4.5)	8 (4.5)	0
43. Motzer *et al* (42)	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	337	59 (17.5)	52 (15.4)	7 (2.1)
44. Motzer *et al* (74)	2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial A: everolimus 10 mg once daily	269	32 (12)	32 (12)	0
45. Motzer *et al* (75)	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	5 (10)	5 (10)	0
46. Niegisch *et al* (44)	2015	Second-Line Treatment of Advanced Urothelial Cancer with Paclitaxel and Everolimus in a German Phase II Trial (AUO Trial AB 35/09)	27	8 (30)	4 (15)	4 (15)

		paclitaxel (175 mg/m^2 i.v., 3-weekly) and the mTOR-inhibitor everolimus (10 mg p.o., once daily)				
47. Nozawa *et al* (90)	2013	Adverse Event Profile and Dose Modification of Everolimus for Advanced Renal Cell Carcinoma in Real-world Japanese Clinical Practice	47	1 (2.1)	1(2.1)	0
48. Ohtsu *et al* (46)	2013	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study; everolimus 10 mg/day	437	107 (24)	94 (21)	13 (3)
49. Oudard *et al* (47)	2016	Clinical Benefit of Everolimus as Second-Line Therapy in Metastatic Renal Cell Carcinoma: The French Retrospective SECTOR Study	162	11 (6.8)	11 (6.8)	0
50. Park *et al* (103)	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 oral everolimus (10 mg dose once daily)	100	6 (6)	6 (6)	0
51. Powles *et al* (128)	2014	A phase Ib study investigating the combination of everolimus and dovitinib in vascular endothelial growth factor refractory clear cell renal cancer; everolimus 5 mg orally (PO) once daily (OD) and dovitinib 200 mg PO day 1–5/7	15	3 (20)	2 (14)	1 (7)

52. Powles *et al* (104)	2016	Randomized Open-Label Phase II Trial of Apitolisib (GDC-0980), a Novel Inhibitor of the PI3K/Mammalian Target of Rapamycin Pathway, Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma; everolimus 10 mg once per day	43	5 (12)	4 (10)	1 (2)
53. Ramalingam *et al* (129)	2010	Phase 1 and Pharmacokinetic Study of Everolimus, a Mammalian Target of Rapamycin Inhibitor, in Combination With Docetaxel for Recurrent/Refractory Nonsmall Cell Lung Cancer; escalating doses of docetaxel (day 1) and everolimus (orally daily, days 1-19) every 3 weeks	24	2 (8.3)	2 (8.3)	0
54. Ray-Coquard *et al* (51)	2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD,a phase II trial of GINECO; everolimus 10mg per day until progression or unacceptable toxicity	43	21 (49)	17 (40)	4 (9)
55. Robles *et al* (106)	2016	Everolimus safety and efficacy for renal angiomyolipomas associated with tuberous sclerosis complex: a Spanish expanded access trial; 10 mg everolimus once daily	19	2 (10.5)	2 (10.5)	0
56. Ryan *et al* (94)	2011	A phase II study of everolimus in combination with imatinib for previously treated advanced renal carcinoma;	19	11 (58)	11 (58)	0

		everolimus 2.5 mg p.o. daily and imatinib 600 mg p.o. daily				
57. Safra *et al* (53)	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	12 (16.7)	10 (13.5)	2 (2.8)
58. Salazar *et al* (54)	2017	Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Na€ıve Advanced Pancreatic Neuroendocrine Tumors; everolimus 10 mg once daily	31	7 (22.6)	6 (19.4)	1 (3.2)
59. Sanoff *et al* (55)	2015	Everolimus and pasireotide for advanced and metastatic hepatocellular carcinoma; everolimus 7.5 mg PO daily and pasireotide LAR 60 mg IM every 28 days.	24	2 (8)	2 (8)	0
60. Sarkaria *et al* (56)	2011	NCCTG 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 chemo-radiotherapy, followed by RAD001 in combination with standard adjuvant temozolomide	18	6 (33)	6 (33)	0
61. Shen *et al* (57)	2014	Phase II Multicentered Study of Low-Dose Everolimus plus Cisplatin and Weekly 24-Hour Infusion of High-Dose 5-	40	21 (52.5)	21 (12.5)	0

		Fluorouracil and Leucovorin as First-Line Treatment for Patients with Advanced Gastric Cancer; everolimus (10 mg p.o. on days 1, 8 and 15) plus cisplatin and a weekly 24-h infusion of high-dose 5-fluorouracil and leucovorin (HDFL) chemotherapy (cisplatin 35 mg/m2 intrave- nous infusion for 24 h on days 1 and 8, 5-fluorouracil 2,000 mg/m^2 and leucovorin 300 mg/m^2 intravenous infusion for 24 h on days 1, 8 and 15) every 28 days				
62. Slomovitz *et al* (59)	2010	A Phase 2 Study of the Oral Mammalian Target of Rapamycin Inhibitor, Everolimus, in Patients With Recurrent Endometrial Carcinoma; everolimus was administered at a dose of 10 mg orally daily for 28-day cycles	35	5 (14)	4 (11)	1 (3)
63. Strickler *et al* (95)	2012	Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors; 10 mg of panobinostat three times weekly, 5 or 10 mg everolimus daily, and bevacizumab at 10 mg/kg every 2 weeks	12	1 (8)	1 (8)	0
64. Sun *et al* (60)	2013	A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer A: everolimus 2.5 mg	A: 6 B: 11 C: 3	A: 0 B: 2 (19) C: 0	A: 0 B: 2 (19) C: 0	A: 0 B: 0 C: 0

		B: everolimus 5 mg C: everolimus 10 mg				
65. Tarhini *et al* (61)	2010	Phase II Study of Everolimus (RAD001) in Previously Treated Small Cell Lung Cancer; everolimus 10 mg orally daily until disease progression	40	3 (7.5)	3 (7.5)	0
66. Thudium *et al* (132)	2015	Bioavailability of everolimus administered as a single 5 mg tablet versus five 1 mg tablets: a randomized, open-label, two-way crossover study of healthy volunteers; Subjects were randomized 1:1 to receive everolimus dosed as one 5 mg tablet or as five 1 mg tablets on day 1, followed by a washout period on days 8–14 and then the opposite formulation on day 15	22	1 (4.5)		
67. Vlahovic *et al* (63)	2012	A phase I study of bevacizumab, everolimus and panitumumab in advanced solid tumors; everolimus and flat dosing of pani- tumumab at 4.8 mg/kg and bevacizumab at 10 mg/kg every 2 weeks	32	10 (31)	10 (31)	0
68. Wang *et al* (107)	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study Everolimus 10 mg/day in adults	58	10 (17.2)	9 (15.5)	1 (1.7)
69. Werner *et al* (64)	2013	Phase I study of everolimus and mitomycin C for patients with metastatic esophagogastric adenocarcinoma;	16	3 (18)	3 (18)	0

		oral everolimus (5, 7.5 and 10 mg/day) in combination with intravenous MMC 5 mg/m^2 every 3 weeks				
70. Wolpin *et al* (97)	2009	Oral mTOR Inhibitor Everolimus in Patients With Gemcitabine-Refractory metastatic Pancreatic Cancer; everolimus 10 mg daily	33	5 (15)	4 (12)	1 (3)
71. Yao *et al* (65)	2011	Everolimus for Advanced Pancreatic Neuroendocrine Tumors; 10 mg once daily	204	31 (15)	31 (15)	0
72. Yee *et al* (99)	2006	Phase I/II Study of the Mammalian Target of Rapamycin Inhibitor Everolimus (RAD001) in Patients with Relapsed or Refractory Hematologic Malignancies; Everolimus: no dose-limiting toxicity (DLT) occurred in the first three patients treated with 5 mg daily; all subsequent patients received 10 mg daily	27	4 (15)	4 (15)	0
Total over all			5,913	883 (15.0)		
Total with grade			5,578	858 (15.4)	781 (14)	77 (1.4)
Total with grade		Only everolimus at 2.5 mg	6	0	0	0
Total with grade		Only everolimus at 5 mg	11	2 (18.2)	2 (18.2)	0
Total with grade		Only everolimus at 10 mg	2,495	415 (16.6)	377 (15.1)	38 (1.5)

Table SXVI. Main systemic changes induced by everolimus therapy according to dosage: Summary table.

	Everolimus at 2.5 mg			Everolimus at 5 mg			Everolimus at 10 mg		
Adverse event	Cases/adverse effects (%)	Grade 1/2 % (cases)	Grade 3/4 % (cases)	Cases/adverse effects (%)	Grade 1/2 % (cases)	Grade 3/4 % (cases)	Cases/adverse effects (%)	Grade 1/2 % (cases)	Grade 3/4 % (cases)
Anaemia	6/5 (83.33)	5 (83.33)	-	11/11 (100)	10 (90.9)	1 (9.1)	4,770/1,247 (26.2)	790 (16.6)	467 (9.8)
Anorexia	6/2 (33.3)	2 (33.3)	-	18/4 (22.2)	4 (22.2)	-	657/152 (23.1)	122 (18.6)	30 (4.5)
Asthenia	-	-	-	-	-	-	2,168/445 (20.5)	382 (17.6)	63 (2.9)
diarrhoea	6/0	-	-	11/2 (18.2)	2 (18.2)	-	3,456/803 (22.5)	701 (19.6)	102 (2.9)
Fatigue	-	-	-	-	-	-	5,449/111 (20.4)	828 (15.2)	283 (5.2)
Hypercholesterolemia	-	-	-	7/1 (14.3)	1 (14.3)	-	1,169/489 (41.8)	441 (37.7)	48 (4.1)
Hyperglycaemia	6/6 (100)	6 (100)	-	18/11 (61.1)	11 (61.1)	-	3,611/615 (17)	400 (11)	223 (6)
Leukopenia	6/5 (83.3)	4 (66.6)	1(16.7)	11/8 (72.6)	4 (36.3)	4 (36.3)	698/134 (19.2)	103 (14.7)	31 (4.5)
Pneumonitis	6/0	-	-	11/1 (9)	1 (9)	-	3,409/363 (10.7)	242 (7.1)	121 (3.6)
Pruritus	-	-	-	-	-	-	2,034/261 (12.8)	254 (12.5)	7 (0.3)
Pyrexia	-	-	-	-	-	-	2,318/340 (14.7)	312 (13.5)	28 (1.2)
Rash	-	-	-	-	-	-	3,794/923 (24.3)	869 (22.9)	54 (1.4)
Stomatitis	6/2 (33.3)	2 (33.3)	-	11/5 (45.5)	5 (45.5)	-	2,275/844 (37.1)	750 (33)	94 (4.1)
Thrombocytopenia	6/2 (33.3)	2 (33.3)	-	18/7 (38.9)	6 (33.3)	1 (5.6)	1,718/361 (21)	265 (15.4)	96 (5.6)
Vomiting	6/0	-	-	11/2 (18.2)	2 (18.2)	-	2,495/415 (16.6)	377 (15.1)	38 (1.5)

Table SXVII. Comparison of the side-effects incidence between everolimus and traditional chemotherapy.

Adverse effect	Incidence due to everolimus treatment (%)	Incidence due to traditional chemotherapy (%)
Anaemia	Average = 24.4 G3-4 = 7.1	Average = 70 G3-4 = 60
Anorexia	Average = 25.2 G3-4 = 3.3	Average = 60 G3-4 = 45
Asthenia	Average = 20.6	Average = 35.7
diarrhoea	Average = 22.3 G1-2 = 20.4 G3-4 = 2.6	Range = 50-80 G1-2 = 20-50 G3-4 = 30
Fatigue	Average = 23.7 G3-4 = 4.8	Average = 60 G3-4 = 10
Hypercholesterolemia	Average = 20.2	Slightly increased
Hyperglycaemia	Average = 16.9	Average = 10-30
Leukopenia	Average = 29.6	Average (neutropenia) = 33.3
Thrombocytopenia	Average = 21.8 G1-2 = 18.1 G3-4 = 4.7	Average = 25 G1-2 = 20 G3-4 = 5
Pneumonitis	Average = 10.1	Average = 1.5-50
Pruritus	Average = 12.1	Average = 10-25
Pyrexia	Average = 15.4 G3-4 = 1.3	Average = 34 G3-4 = 5
Rash	Average = 22.7	Average = 10
Stomatitis	Average = 43.2	Average = 40
Emesis	Average = 15	Average = 30

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