	Author/(Refs.)	Year	Study	No. of	No. of cases	Grade 1/2	Grade 3/4
				patients	(%)	cases (%)	cases (%)
1.	Amato et al (1)	2009	A Phase 2 Study With a Daily	39	12 (30.8)	12 (30.8)	0
			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).				
2.	Bajetta et al (2)	2014	Everolimus in Combination with	50	4 (8)	3 (6)	1 (2)
			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.				
3.	Baselga et al (3)	2012	Everolimus in Postmenopausal	482	16 (3.31)	10 (2.07)	6 (1.2)
			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).				
4.	Baselga et al (4)	2009	Phase II Randomized Study of	137	16 (11.7)	7 (5.1)	9 (6.5)
			Neoadjuvant Everolimus Plus				
			Letrozole Compared With Placebo				

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

			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-	18	5 (27)	5 (27)	0
			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				
6.	Bergmann et al	2015	Everolimus in metastatic renal cell	334	46 (15)	25 (8)	21 (7)
	(6)		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				
7.	Besse et al (7)	2013	A phase Ib dose-escalation study of	40	9 (23)		
			everolimus combined with cisplatin				
			and etoposide as first-line therapy in				
			patients with extensive-stage small-				
			cell lung cancer				
8.	Besse et al (8)	2014	Phase II study of everolimus-	66	18 (27.3)	15 (22.7)	3 (4.5)
			erlotinib in previously treated patients				
			with advanced non-small-cell lung				
			cancer;				
			everolimus				
			150 mg/day				
9.	Buzzoni et al (9)	2017	Impact of prior therapies on	202	32 (16)	24 (12)	8 (4)
			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.				
10. Chocteau-Bouju	2015	Efficacy and tolerance of everolimus	123	123 (100)	123 (100)	0
<i>et al</i> (10)		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				
11. Choueiri et al	2015	Cabozantinib versus everolimus in	322	120 (37)	71 (22)	49 (15)
(11)		advanced renal cell carcinoma				
		everolimus at a dose of 10 mg daily				
12. Chow <i>et al</i> (12)	2016	A Phase 2 Clinical Trial of	24	14 (58.3)	12 (50)	2 (8.3)
		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.				
13. Chung <i>et al</i> (13)	2016	Phase Ib Trial of mFOLFOX6 and	6	4 (67)	4 (67)	0
		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.				
14. Ciunci et al (14)	2014	Phase 1 and Pharmacodynamic Trial	29	5 (17.2)	4 (13.7)	1 (3.4)
		of Everolimus in Combination With				
		Cetuximab in Patients With				
		Advanced Cancer				
15. Conconi et al	2014	Clinical activity of everolimus in	30	7 (23.3)	6 (20)	1 (3.3)
(15)		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				

16. Dasari et al (16)	2015	Phase I study of the anti-IGF1R	19	2 (11)	1 (5.5)	1 (5.5)
		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				
17. El-Madani <i>et al</i>	2017	EVESOR, a model-based,	26	2 (7.7)	2 (7.7)	0
(17)		multiparameter, Phase I trial to				
		optimize the bene t/toxicity ratio of				
		everolimus and sorafenib				
		everolimus + sorafenib				
18. Fazio <i>et al</i> (18)	2018	Everolimus in advanced, progressive,	62	13 (21.0)	11 (17.8)	2 (3.2)
		well-differentiated, non-functional				
		neuroendocrine tumours: RADIANT-				
		4 lung subgroup analysis				
		everolimus 10 mg/d				
19. Fazio <i>et al</i> (19)	2013	Everolimus Plus Octreotide Long-	33	5 (15.2)		
		Acting Repeatable in Patients With				
		Advanced Lung Neuroendocrine				
		Tumors;				
		analysis of the Phase 3, Randomized,				
		Placebo-Controlled RADIANT-2				
		Study				
		A: everolimus + octreotide				
20. Guo et al (20)	2013	Safety and efficacy of everolimus in	64	41 (64)	28 (43)	13 (21)
		Chinese patients with metastatic renal				
		cell carcinoma resistant to vascular				
		endothelial growth factor receptor-				
		tyrosine kinase inhibitor therapy: an				
		open-label phase 1b study				

		A everolimus 10 mg $(2 \times 5 \text{ mg})$				
		tablets) daily until objective tumor				
		progression (according to RECIST.				
		version 1.0), unacceptable toxicity.				
		death, or study discontinuation for				
		any other reason				
21. Hainsworth <i>et al</i>	2010	Phase II Trial of Bevacizumab and	80	51 (64)	47 (59)	4 (5)
(21)	-010	Everolimus in Patients With	00			. (0)
		Advanced Renal Cell Carcinoma				
		All patients received bevacizumab 10				
		mg/kg intravenously every 2 weeks				
		and everolimus 10 mg orally daily				
22. Hatano <i>et al</i> (22)	2016	Outcomes of everolimus treatment for	47	6 (13)	6 (13)	0
		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.				
23. Hatano <i>et al</i> (23)	2017	Intermittent everolimus	26	3 (12)	3 (12)	0
		administration for renal				
		angiomyolipoma associated with				
		tuberous sclerosis complex				
		The dose of everolimus was set at 10				
		mg once a day				
24. Hill et al (24)	2018	A phase I trial of bortezomib in	29	26 (89.6)	21 (72.4)	5 (17.2)
		combination with everolimus for				
		treatment of relapsed/refractory non-				
		Hodgkin lymphoma				
		bortezomib + everolimus				
25. Hurvitz et al (25)	2013	A phase 2 study of everolimus	55	19 (34.6)	15 (27.3)	4 (7.3)
		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.				
26. Jerusalem <i>et al</i>	2016	Safety of everolimus plus exemestane	2, 131	306 (14.4)	306 (14.4)	0
(26)		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.				
27. Johnston et al	2016	The mTORC1 Inhibitor Everolimus	24	12 (50)	9 (38)	3 (12)
(27)		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				
28. Jovanovic et al	2017	A randomized phase II neoadjuvant	96	62 (65)	56 (59)	6 (6)
(28)		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				
29. Kim <i>et al</i> (29)	2014	A multicenter phase II study of	34	22 (64.7)	21 (61.8)	1 (2.9)
		everolimus in patients with				
		progressive unresectable adenoid				
		cystic carcinoma				
				1		

		Everolimus was given at a dose of 10				
		mg daily until progression or				
		occurrence of unacceptable toxicities.				
30. Kim <i>et al</i> (30)	2013	A phase I study of everolimus and	15	11 (73.3)	5 (33.3)	6 (40)
		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				
31. Knox <i>et al</i> (31)	2017	Final overall survival analysis for the	238	32		
		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				
32. Koeberle <i>et al</i>	2016	Sorafenib with or without everolimus	59	5 (8)	2 (3)	3 (5)
(32)		in patients with advanced				
		hepatocellular carcinoma (HCC): a				
		randomized multicenter,				
		multinational phase II trial (SAKK				
		77/08 and SASL 29)†				
		Sorafenib + everolimus				
33. Kordes <i>et al</i> (33)	2013	A phase I/II, non-randomized,	A 31	A 14 (45)	A 13 (42)	A 1 (3)
		feasibility/safety and efficacy study	B 9	B 6 (67)	B 6 (67)	B 0
		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.				
		A: STUDY PHASE II – 113 cycles				
		B: DL2 – 25 CYCLES				
34. Koutsoukos <i>et al</i>	2017	real-world experience of everolimus	31	9 (29)	6 (20)	3 (10)
(34)		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				
35. Kulke <i>et al</i> (35)	2017	A randomized, open-label, phase 2	A: 78	A 21 (26.9)	A 17 (21.8)	A 4 (5.1)
		study of everolimus in combination	B: 81	B 21 (25.9)	B 17 (21)	B 4 (4.9)
		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)				
36. Kumano <i>et al</i>	2013	Sequential use of mammalian target	57	12 (21.1)	6 (10.6)	6 (10.5)
(36)		of rapamycin inhibitors in patients				
		with metastatic renal cell carcinoma				
		following failure of tyrosine kinase				
		inhibitors				
		everolimus 10 mg/daily				
37. Massarweh <i>et al</i>	2014	A phase II study of combined	31	23 (74)	22 (70.9)	1 (3.1)
(37)		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.				
38. Molina <i>et al</i> (38)	2012	Phase 1 Trial of Everolimus Plus	20	18 (90)	15 (75)	3 (15)
		Sunitinib in Patients With Metastatic				
		Renal Cell Carcinoma				
		A:everolimus + sunitnib				
39. Molina <i>et al</i> (39)	2014	A phase 1b clinical trial of the multi-	20	1 (5)		
		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				
40. Morrow <i>et al</i> (40)	2011	Phase I/II Study of Trastuzumab in	47	10 (21)	8 (17)	2 (4)
		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				
41. Motzer <i>et al</i> (41)		Phase II trial of second-line	133	17 (13)		
· · · · · · · · · · · · · · · · · · ·		everolimus in patients with metastatic				
		renal cell carcinoma (RECORD-4)				
		everolimus				
42. Motzer <i>et al</i> (42)	2014	Phase II Randomized Trial	337	93 (27.6)	42 (12.5)	51 (15.1)
		Comparing Sequential First-Line				
		Everolimus and Second-Line				
		Sunitinib Versus First-Line Sunitinib				
		and Second-Line Everolimus in				
		and Second-Line Everolimus in Patients With Metastatic Renal Cell				
		and Second-Line Everolimus in Patients With Metastatic Renal Cell Carcinoma				

43.	Narayan <i>et al</i>	2016	Phase I Trial of Everolimus and	18	2 (11.1)	1 (5.5)	1 (5.5)
	(43)		Radiation Therapy for Salvage				
			Treatment of Biochemical				
			Recurrence in Prostate Cancer				
			Patients Following Prostatectomy				
			Everolimus +srt				
44.	Niegisch et al	2015	Second-Line Treatment of Advanced	27	15 (55.5)	2 (7.4)	13 (48.1)
	(44)		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).				
45.	Oh et al (45)	2012	Phase 2 Study of Everolimus	34	4 (11.8)	2 (5.9)	2 (5.9)
			Monotherapy in Patients With				
			Nonfunctioning Neuroendocrine				
			Tumors or Pheochromocytomas/				
			Paragangliomas				
			Everolimus was administered daily at				
			a dose of 10 mg for 4 weeks.				
46.	Ohtsu et al (46)	2013	Everolimus for Previously Treated	437	114 (26)	44 (10)	70 (16)
			Advanced Gastric Cancer: Results of				
			the Randomized, Double-Blind,				
			Phase III GRANITE-1 Study				
			Everolimus 10 mg/d				
47.	Oudard et al (47)	2016	Clinical Benefit of Everolimus as	162	58 (35.8)	45 (27.8)	13 (8)
			Second-Line Therapy in Metastatic				
			Renal Cell Carcinoma: The French				
			Retrospective SECTOR Stud				
			Everolimus with/or VEGFR-TKI				
48.	Oyama et al (48)	2017	Efficacy and safety of sequential use	53	12 (22.6)	10 (19.2)	2 (3.4)
			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				
49. Panzuto <i>et al</i> (49)	2014	Real-World Study of Everolimus in	169	33 (19.5)	24 (14.2)	9 (5.3)
		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				
50. Pavel et al (50)	2016	Safety and QOL in Patients with	A pNET	A 7 (5.7)	A 3 (2.5)	A 4 (3.2)
		Advanced NET in a Phase 3b	123	B 13 (11.1)	B 9 (7.7)	B 4 (3.4)
		Expanded Access Study of	B Non			
		Everolimus;	pNET 117			
		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				
51. Ray-Coquard et	2013	Everolimus as second- or third-line	43	43 (100)	37 (86)	6 (14)
al (51)		treatment of advanced endometrial				
		cancer: ENDORAD, a phase II trial of				
		GINECO;				
		everolimus 10 mg per day until				
		progression or unacceptable toxicity				
52. Rodrigues et al	2015	Phase I combination of pazopanib and	52	4 (7.6)	2 (3.8)	2 (3.8)
(52)		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.				
53. Safra <i>et al</i> (53)	2018	Everolimus Plus Letrozole for	72	20 (27.8)	13 (18.1)	7 (9.79)
		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				
54. Salazar <i>et al</i> (54)	2017	Phase II Study of BEZ235 versus	31	11 (35.5)	8 (25.8)	3 (9.7)
		Everolimus in Patients with				
		Mammalian Target of Rapamycin				
		Inhibitor-Native Advanced				
		Pancreatic Neuroendocrine Tumors				
		Everolimus 10 mg once daily				
55. Sanoff <i>et al</i> (55)	2015	Everolimus and pasireotide for	24	5 (21)	5 (21)	0
		advanced and metastatic				
		hepatocellular carcinoma				
		everolimus 7.5 mg PO daily and				
		pasireotide LAR 60 mg IM every 28				
		days.				
56. Sarkaria <i>et al</i> (56)	2011	NCCTG Phase I Trial N057K of	18	12 (66.6)	6 (33.3)	6 (33.3)
		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				
57. Shen et al (57)	2014	Phase II Multicentered Study of Low-	40	29 (72.5)	23 (57.5)	6 (15)
		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				
58. Shoushtari et al	2016	Phase 2 trial of everolimus 10mg	13	1 (7)	0	1 (7)
(58)		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				
59. Slomovitz <i>et al</i>	2010	A Phase 2 Study of the Oral	35	15 (43)	12 (34)	3 (9)
(59)		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.				
60. Sun <i>et al</i> (60)	2013	A phase-1b study of everolimus plus	A:6	A 5 (83.33)	A 5	A 0
		paclitaxel in patients with small-cell	B:11	B 11 (100)	B 10	B 1
		lung cancer	C:3	C 3 (100)	C 3	C 0
		a everolimus 2.5 mg				
		b everolimus 5 mg				
		c everolimus 10 mg				
61. Tarhini <i>et al</i> (61)	2010	Phase II Study of Everolimus	40	9 (22.5)	9 (22.5)	0
		(RAD001) in Previously Treated				
		Small Cell Lung Cancer				
		everolimus 10 mg orally daily until				
		disease progression.				
62. Tomita <i>et al</i> (62)	2017	Nivolumab versus everolimus in	26	12 (46)	10 (38)	2 (8)
		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				
63. Vlahovic <i>et al</i>	2012	A phase I study of bevacizumab,	32	10 (31)	9 (28)	1 (3)
(63)		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.				
64. Werner <i>et al</i> (64)	2013	Phase I study of everolimus and	16	5 (31.2)	4 (25)	1 (6.2)
		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.				
65. Yao <i>et al</i> (65)	2011	Everolimus for Advanced Pancreatic	204	35 (17)	23 (11)	12 (6)
		Neuroendocrine Tumors				
		10 mg once daily				
66. Albiges et al (66)	2015	Everolimus for patients with	493	70 (14)	42 (8)	28 (6)
		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.				
67. Andre <i>et al</i> (67)	2014	Everolimus for women with	A:280	138 (49)	85 (30)	53 (19)
		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.				
68. Armstrong et al	2016	Everolimus versus sunitinib for	55	16 (29)	10 (18)	6 (11)
(68)		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.				
69. Bissler <i>et al</i> (69)	2013	Everolimus for angiomyolipoma	79	10 (13)	10 (13)	0
		associated with tuberous sclerosis				
		complex or sporadic				
		lymphangioleiomyomatosis (EXIST-				
		2): a multicentre, randomised,				
		double-blind, placebo-controlled trial				
		oral everolimus 10 mg per day				
70. Escudier <i>et al</i>	2016	Open-label phase 2 trial of first-line	92	27 (29)	21 (23)	6 (6)
(70)		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				
71. Ferolla <i>et al</i> (71)	2017	Efficacy and safety of long-acting	42	13 (31)	12 (29)	1 (2)
		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.				
72. Grignani <i>et al</i>	2015	Sorafenib and everolimus for patients	38	19 (50)	17 (45)	2 (5)
(72)		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				
73. Grunwald et al	2012	An international expanded-access	1367	202 (14.8)	19 (1.4)	183 (13.4)
(73)		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				
74. Motzer <i>et al</i> (74)	2008	Efficacy of everolimus in advanced	269	244 (90.7)	219 (81.4)	25 (9.3)
		renal cell carcinoma: a double-blind,				
		randomised, placebo-controlled				
		phase III trial				
		A: everolimus 10 mg once daily				
75. Motzer <i>et al</i> (75)	2015	Lenvatinib, everolimus, and the	50	13 (26)	7 (14)	6 (12)
		combination in patients with				
		metastatic renal cell carcinoma: a				
		randomised, phase 2, open-label,				
		multicentre trial				
		everolimus 10 mg day				
Total overall			10,386	2,534 (24.4)	-	-
Total with grad	e		9,922	2,470 (24.9)	1,767 (17.8)	703 (7.1)
Total with grad	e	Only everolimus at 2.5 mg	6	5 (83.33)	5 (83.33)	0
Total with grad	e	Only everolimus at 5 mg	11	11 (100)	10 (90,9)	1 (9.1)
Total with grad	e	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	No. of cases	Grade 1/2	Grade
				patients	(%)	cases (%)	3/4
							cases
							(%)
1.	Bachelot et al	2012	Randomized Phase II Trial of Everolimus in	54	23 (43)	19 (34)	4 (7)
(76)			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				
2.	Barnes et al	2013	Everolimus in combination with rituximab	24	3 (12.5)	3 (12.5)	0
(77)			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.				
3.	Baselga et al	2009	Phase II Randomized Study of Neoadjuvant	137	17 (12.4)	17 (12.4)	0
(4)			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.				
4.	Bendell et al	2015	A phase Ib study of linsitinib (OSI-906), a	18	9 (50)	9 (50)	0
(5)			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				
5.	Besse et al (8)	2014	Phase II study of everolimus-erlotinib in	66	24 (36.4)	24 (36.3)	0
			previously treated patients with advanced				
			non-small-cell lung cancer;				
			everolimus 5 mg/day + erlotinib 150 mg/day				
6.	Chan et al (78)	2013	A Prospective, Phase 1/2 Study of	42	13 (31)	13 (31)	0
			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				
7.	Chow <i>et al</i>	2016	A Phase 2 Clinical Trial of Everolimus Plus	24	5 (20.8)	4 (16.6)	1 (4.2)
(12)			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.				
		1			1	1	

8.	Chung et al	2016	Phase Ib Trial of mFOLFOX6 and	6	4 (67)	4 (67)	0
(13)			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.				
9.	Ciunci et al	2014	Phase 1 and Pharmacodynamic Trial of	29	3 (10.3)	2 (6.9)	1 (3.4)
(14)			Everolimus in Combination With				
			Cetuximab in Patients With Advanced				
			Cancer				
10.	Conconi et al	2014	Clinical activity of everolimus in	30	4 (13.3)	3 (10)	1 (3.3)
(15)			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				
11.	Dasari et al	2015	Phase I study of the anti-IGF1R antibody	19	9 (47)	8 (42)	1 (5)
(16)			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.				
12.	El-Madani et	2017	EVESOR, a model-based, multiparameter,	26	8 (30.8)	8 (30.8)	0
al (17)			Phase I trial to optimize the bene t/toxicity				
			ratio of everolimus and sorafenib				
			Everolimus +sorafenib				
13.	Ellard et al	2009	Randomized Phase II Study Comparing	A 33	A 14 (42.4)	A 1 (3)	A 13
(79)			Two Schedules of Everolimus in Patients	B 16	B 6 (37.5)	B 0	(39.4)
			With Recurrent/Metastatic Breast Cancer:				B 6
			NCIC Clinical Trials Group IND.163				(37.5)
		I					

			Randomized phase II study of everolimus				
			10 mg daily (A) versus 70 mg weekly (B)				
14.	Fury <i>et al</i> (80)	2012	A phase I study of daily everolimus plus	30	7 (25)	7 (25)	0
			low-dose weekly cisplatin for patients with				
			advanced solid tumors				
15.	Gadgeel et al	2013	Phase I study evaluating the combination of	54	14 (26)	13 (24)	1 (2)
(81)			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.				
16.	Gong <i>et al</i> (82)	2017	Efficacy and safety of everolimus in	70	5 (7.1)	5 (7.1)	0
			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.				
17	Gross at al	2017	Safety and Efficacy of Docetaxel	12	40 (93)	39 (90.6)	1(2 3)
(02)	01085 81 11	2017	Sufery and Efficacy of Docetaxel,	45	40 (75)	57 (50.0)	1 (2.3)
(83)	Gloss et al	2017	Bevacizumab, and Everolimus for	43	+0 (93)	57 (50.0)	1 (2.3)
(83)		2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer	43	+0 (55)	57 (50.0)	1 (2.3)
(83)	Gloss et al	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC)	45	40 (55)	57 (70.0)	1 (2.3)
(83)		2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15	43	40 (55)	57 (70.0)	1 (2.3)
(83)	Gloss et al	2017	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 (22)	57 (70.0)	1 (2.3)
18. al (21)	Hainsworth <i>et</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg Phase II Trial of Bevacizumab and	80	26 (33)	23 (29)	3 (4)
18. al (21)	Hainsworth <i>et</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg Phase II Trial of Bevacizumab and Everolimus in Patients With Advanced	80	26 (33)	23 (29)	3 (4)
17. (83) 18. <i>al</i> (21)	Hainsworth <i>et</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg Phase II Trial of Bevacizumab and Everolimus in Patients With Advanced Renal Cell Carcinoma	80	26 (33)	23 (29)	3 (4)
18. al (21)	Hainsworth <i>et</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg Phase II Trial of Bevacizumab and Everolimus in Patients With Advanced Renal Cell Carcinoma All patients received bevacizumab 10 mg/kg	80	26 (33)	23 (29)	3 (4)
18. al (21)	Hainsworth <i>et</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg 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	80	26 (33)	23 (29)	3 (4)
17. (83) 18. <i>al</i> (21)	Hainsworth <i>et</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg 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)
17. (83) 18. <i>al</i> (21) 19. (84)	Hainsworth <i>et</i> Harzstark <i>et al</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg 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 A Phase 1 Study of Everolimus and	80	26 (33)	23 (29)	3 (4)
18. al (21) 19. (84)	Hainsworth <i>et</i> Harzstark <i>et al</i>	2017 2010 2011	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg 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 A Phase 1 Study of Everolimus and Sorafenib for Metastatic Clear Cell Renal	80	26 (33)	23 (29)	3 (4)
18. al (21) 19. (84)	Hainsworth <i>et</i> Harzstark <i>et al</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg 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 A Phase 1 Study of Everolimus and Sorafenib for Metastatic Clear Cell Renal Cell Carcinoma	80	26 (33)	23 (29)	3 (4)
18. al (21) 19. (84)	Hainsworth <i>et</i> Harzstark <i>et al</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg 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 A Phase 1 Study of Everolimus and Sorafenib for Metastatic Clear Cell Renal Cell Carcinoma Starting doses were everolimus at a dose of	80	26 (33)	23 (29)	3 (4)
18. al (21) 19. (84)	Hainsworth <i>et</i> Harzstark <i>et al</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg 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 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	80	26 (33)	23 (29)	3 (4)
18. al (21) 19. (84)	Hainsworth <i>et</i> Harzstark <i>et al</i>	2017	Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg 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 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	80	26 (33)	23 (29)	3 (4)
17. (83) 18. <i>al</i> (21) 19. (84) 20.	Hainsworth <i>et</i> Harzstark <i>et al</i> Ju <i>et al</i> (85)	2017 2010 2011 2011	Barty and Enready of Doctate, Bevacizumab, and Everolimus for Castration-resistant Prostate Cancer (CRPC) docetaxel 75 mg/m ² , bevacizumab 15 mg/kg, and everolimus 2.5 mg 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 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 Toxicity and adverse effects of everolimus	43 80 20 12	26 (33)	23 (29) 1 (5) 3 (25)	1 (2.3) 3 (4) 1 (5) 0

			lung cancer pretreated with chemotherapy-				
			Chinese experiences;				
			everolimus 5-10 mg/day with or without				
			chemotherapy until progression or				
			unacceptable toxicity.				
21.	Kato <i>et al</i> (86)	2013	Efficacy of Everolimus in Patients with	19	4 (21)	3 (16)	1 (5)
			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.				
22.	Kim <i>et al</i> (29)	2014	A multicenter phase II study of everolimus	34	5 (14.7)	5 (14.7)	0
			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.				
23.	Kim <i>et al</i> (87)	2018	Clinical outcomes of the sequential use of	36	9 (25)	9 (25)	0
			pazopanib followed by everolimus for the				
			treatment of metastatic renal cell carcinoma:				
			A multicentre study in Korea				
24.	Kim <i>et al</i> (88)	2016	Efficacy and Toxicity of Mammalian Target	19	3 (16)	3 (16)	0
			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.				
25.	Kim <i>et al</i> (30)	2013	A phase I study of everolimus and CHOP in	15	2 (13.3)	2 (13.3)	0
			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				

26.	Koeberle <i>et al</i>	2016	mg) vincristine on day 1, and 100 mg/day prednisone on days 1 to 5) every 21 days were planned Sorafenib with or without everolimus in	59	33 (56)	22 (37)	11 (19)
			patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29)				
27.	Lim <i>et al</i> (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. <i>al</i> (37)	Massarweh <i>et</i>	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 \pm 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. (74)	Motzer <i>et al</i>	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. (43)	Narayan <i>et al</i>	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. (90)	Nozawa <i>et al</i>	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 <i>et al</i> (45)	2012	Phase 2 Study of Everolimus Monotherapy	34	7 (20.6)	7 (20.7)	0
			in Patients With Non functioning				
			Neuroendocrine Tumors or				
			Pheochromocytomas/ Paragangliomas				
			Everolimus was administered daily at a dose				
			of 10 mg for 4 weeks.				
33.	Ou et al (91)	2015	SWOG S0722: Phase II study of mTOR	59	19 (32.3)	18 (30.6)	1 (1.7)
			inhibitor everolimus (RAD001) in advanced				
			malignant pleural mesothelioma (MPM)				
			Everolimus 10 mg daily.				
34.	Oudard et al	2016	Clinical Benefit of Everolimus as Second-	162	9 (5.6)	8 (5)	1 (0.6)
(47)			Line Therapy in Metastatic Renal Cell				
			Carcinoma: The French Retrospective				
			SECTOR Study				
			Everolimus, not specified posology				
35.	Quek et al (92)	2011	Combination mTOR and IGF-1R Inhibition:	21	9 (42.8)	9 (42.8)	0
			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)				
36.	Rathkopf <i>et al</i>	2015	Everolimus Combined With Gefitinib in	39	16 (41)	16 (41)	0
(93)			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)				
37.	Ray-Coquard	2013	Everolimus as second- or third-line	43	20 (47)	9 (21)	11 (26)
ei ui (S	1)		treatment of advanced endometrial cancer:				
			ENDORAD, a phase II trial of GINECO				
			everolimus 10mg per day until progression				
			or unacceptable toxicity				

combination with imatinib for previously treated advanced renal carcinoma everolimus 2.5 mg p.o. daily and imatinib	0
treated advanced renal carcinoma everolimus 2.5 mg p.o. daily and imatinib	1
everolimus 2.5 mg p.o. daily and imatinib)
600 mg n o deilu)
out ing p.o. dany.)
39.Sanoff et al2015Everolimus and pasireotide for advanced243 (13)3 (13)0	
(55) and metastatic hepatocellular carcinoma	
everolimus 7.5 mg PO daily and pasireotide	
LAR 60 mg IM every 28 days.	
40. Sarkaria et al 2011 NCCTG Phase I Trial N057K of everolimus 18 3 (27) 2 (11) 1 (0)	6)
(56) (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	
41. Shen et al (57) 2014 Phase II Multicentred Study of Low-Dose 40 18 (45) 12 (30) 6 (1	5)
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	
42. Slomovitz <i>et al</i> 2010 A Phase 2 Study of the Oral Mammalian 35 7 (20) 6 (17) 1 (.	3)
(59) 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.	
43.Strickler et al2012Phase I study of bevacizumab, everolimus,123 (25)3 (25)0)
(95) 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.				
44.	Sun <i>et al</i> (60)	2013	A phase-1b study of everolimus plus	A 6	A 2 (33)	A 2 (33)	A 0
			paclitaxel in patients with small-cell lung	B 11	B 3 (27)	B 3 (27)	B 0
			cancer	C 3	C 1 (33)	C 1 (33)	C 0
			a everolimus 2.5 mg				
			b everolimus 5 mg				
			c everolimus 10 mg				
45.	Tarhini et al	2010	Phase II Study of Everolimus (RAD001) in	40	6 (15)	6 (15)	0
(61)			Previously Treated Small Cell Lung Cancer				
			everolimus 10 mg orally daily until disease				
			progression.				
46.	Tobinai et al	2010	Phase I study of the oral mammalian target	A 7	A 1 (14.2)	A 1 (14.2)	A 0
(96)			of rapamycin inhibitor everolimus	B 6	B 3 (50)	B 2 (34)	B 1 (16)
			(RAD001) in Japanese patients with				
			relapsed or refractory non-Hodgkin				
			lymphoma				
			A everolimus 5 mg once daily				
			B everolimus 10 mg once daily				
47.	Vlahovic et al	2012	A phase I study of bevacizumab, everolimus	32	12 (38)	12 (38)	0
(63)			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.				
48.	Wolpin <i>et al</i>	2009	Oral mTOR Inhibitor Everolimus in Patients	33	5 (15)	5 (15)	0
(97)			With Gemcitabine-Refractory Metastatic				
			Pancreatic Cancer				
			Everolimus 10 mg daily				
49.	Yee et al (98)	2014	Outcomes in patients with relapsed or	25	3 (12)	2 (8)	1 (4)
			refractory multiple myeloma in a phase I				
			study of everolimus in combination with				
			lenalidomide				
50.	Yee <i>et al</i> (99)	2006	Phase I/II Study of the Mammalian Target	27	11 (41)	10 (37)	1 (4)
			of Rapamycin Inhibitor Everolimus				
			(RAD001) in Patients with Relapsed or				
			Refractory Hematologic Malignancies				
			Everolimus Patients were treated with 5				
		1	(7		1	1	1
			(first three patients) or 10 mg orally once				

	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	No. of cases	Grade 1/2	Grade
				patients	(%)	cases (%)	3/4
							cases (%)
1. Andre	e et al 2	2014	Everolimus for women with trastuzumab-	280	74 (26)	60 (21)	14 (5)
(67)			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				
2. Basel	ga et 2	2012	Everolimus in Postmenopausal Hormone-	482	12 (2.4)	10 (2.0)	2 (0.4)
al (3)			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).				
3. Basel	ga et 2	2009	Phase II Randomized Study of Neoadjuvant	137	24 (17.5)	24 (17.5)	0
al (4)			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.				
4. Besse	et al 2	2014	Phase II study of everolimus-erlotinib in	66	13 (19.7)	6 (9.1)	7 (10.6)
(8)			previously treated patients with advanced				
			non-small-cell lung cancer;				
			everolimus 5 mg/day + erlotinib 150 mg/day				

	1					
5. Buzzoni et	2017	impact of prior therapies on everolimus	202	32 (16)	30 (15)	2 (1)
ui ())		activity: an exploratory analysis of raDianT-4				
		Patients were randomized (2:1) to everolimus				
		10 mg/day or placebo, both with best				
		supportive care.				
6. Campone	2009	Safety and pharmacokinetics of paclitaxel and	16	7 (43.7)	6 (37.5)	1 (6.2)
<i>et al</i> (100)		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.				
7. Choueiri <i>et</i>	2015	Cabozantinib versus everolimus in advanced	322	50 (16)	44 (14)	6 (2)
<i>al</i> (11)		renal cell carcinoma				
		everolimus at a dose of 10 mg daily				
8. Ciruelos <i>et</i>	2017	Safety of everolimus plus exemestane in	429	108 (25)	88 (20)	20 (5)
al (101)		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				
9. Conconi <i>et</i>	2014	Clinical activity of everolimus in	30	8 (26.6)	8 (26.6)	0
<i>al</i> (15)		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				
10. Escudier at	2016	Open-label phase 2 trial of first-line	92	41 (45)	29 (32)	12 (13)
al.(70)		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				
	1	· ·				1

11. Fa	azio <i>et al</i>	2018	Everolimus in advanced, progressive, well-	62	14 (22.6)	13 (21)	1 (1.6)
(18)			differentiated, non-functional neuroendocrine				
			tumors: RADIANT-4 lung subgroup analysis				
			everolimus 10 mg/day				
12. Fe	erolla et	2017	Efficacy and safety of long-acting pasireotide	42	13 (31)	12 (29)	1 (2)
al (71)			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)				
13. H	urvitz <i>et</i>	2013	A phase 2 study of everolimus combined with	55	28	26 (47.3)	2 (3.6)
al (25)			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.				
14. Je	erusalem	2016	Safety of everolimus plus exemestane in	2131	485 (22.8)	408 (19.2)	77 (3.6)
<i>et al</i> (26)			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)				
15. K	im et al	2014	A multicenter phase II study of everolimus in	34	13 (38.2)	11 (32.3)	2 (5.9)
(29)		1		-	()		
			patients with progressive unresectable	-			
			patients with progressive unresectable adenoid cystic carcinoma;		()		
			patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10		,		
			patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of		,		
			patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities.				
16. K	im et al	2018	patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities. Clinical outcomes of the sequential use of	36	10 (27.8)	10 (27.8)	0
16. K (87)	im et al	2018	patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities. Clinical outcomes of the sequential use of pazopanib followed by everolimus for the	36	10 (27.8)	10 (27.8)	0
16. K (87)	im et al	2018	patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities. Clinical outcomes of the sequential use of pazopanib followed by everolimus for the treatment of metastatic renal cell carcinoma:	36	10 (27.8)	10 (27.8)	0
16. K (87)	im et al	2018	patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities. 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	10 (27.8)	10 (27.8)	0
16. K (87)	im et al	2018	patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities. 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
16. K (87) 17. K	im <i>et al</i> ulke <i>et al</i>	2018	patients with progressive unresectable adenoid cystic carcinoma; everolimus was administered at a dose of 10 mg daily until progression or occurrence of unacceptable toxicities. 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 A randomized, open-label, phase 2 study of	36 A 78	10 (27.8) A 17 (21.8)	10 (27.8) A 12 (15.4)	0 A

		LAR or everolimus alone in advanced, well-		17 (21)		B 4 (4.9)
		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)				
		b. Everonnus alone (10 mg/day, orany)				
19 Magaatt	2016	Sofaty analysis association with reasons and	101	00 (40 8)	07 (40 1)	2(17)
al (102)	2010	safety analysis, association with response and	181	90 (49.8)	87 (48.1)	5 (1.7)
		previous treatments of everolimus and				
		exemestane in 181 metastatic breast cancer				
		patients: A multicenter Italian experience				
19. Motzer e	<i>2014</i> 2014	Phase II Randomized Trial Comparing	337	40 (11.9)	31 (9.2)	9 (2.7)
<i>ui</i> (<i>42)</i>		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				
20. Motzer e	et 2008	Efficacy of everolimus in advanced renal cell	269	48 (18)	44 (17)	4 (1)
al (74)		carcinoma: A double-blind, randomised,				
		placebo-controlled phase III trial				
		everolimus 10 mg once daily				
21. Motzer e	et 2015	Lenvatinib, everolimus, and the combination	50	19 (38)	18 (36)	1 (2)
al (75)		in patients with metastatic renal cell				~ /
		carcinoma: a randomised phase 2 open-label				
		multicentre trial				
		Only everolimus: 10 mg day (50 cases)				
22 Oh et al	2012	Phase 2 Study of Everolimus Monotherapy in	3/	8 (23 5)	7 (20.6)	1 (2.9)
(45)	2012	Patients With Nonfunctioning	54	8 (23.3)	7 (20.0)	1 (2.9)
		Neuroendooring Tumore or				
		Dhaaahnemaaytaraa /Dara ara l'				
		rneocnromocytomas/Paragangliomas;				
		everonimus was administered daily at a dose				
		of 10 mg for 4 weeks.				
23. Ohtsu <i>et</i>	<i>al</i> 2013	Everolimus for Previously Treated Advanced	437	70 (16)	50 (11)	20 (5)
		Gastric Cancer: Results of the Randomized,				
		Double-Blind, Phase III GRANITE-1 Study				

			Everolimus 10 mg/d				
24.	Panzuto et	2014	Real-World Study of Everolimus in	169	30 (17.7)	27 (15.9)	3 (1.8)
al (49)			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.				
25.	Park et al	2014	Efficacy and Safety of Everolimus in Korean	100	45 (47)	45 (47)	0
(103)			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				
26.	Pavel et al	2016	Safety and QOL in Patients with Advanced	pNET	pNET	pNET	pNET
(50)			NET in a Phase 3b Expanded Access Study of	123	12 (9.8)	9 (7.3)	3 (2.5)
			Everolimus;	Non		Non pNET	Non
			oral everolimus (two 5 mg tablets, totally 10	pNET	Non pNET	3 (2.5)	pNET
			mg/day, in 28-day cycles) was taken by	117	7 (6.0)		4 (3.5)
			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				
27.	Powles et	2016	Randomized Open-Label Phase II Trial of	43	9 (21)	7 (16)	2 (5)
al (104)			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				
28.	Rizzo et al	2015	Everolimus as second-line therapy for	100	20 (20)	18 (18)	2 (2%)
(105)			metastatic renal cell carcinoma: a 'real-life'				
			study;				
			everolimus 10 mg/day				
29.	Robles et	2016	Everolimus safety and efficacy for renal	19	3 (15.8)	3 (15.8)	0
al (106)			angiomyolipomas associated with tuberous				
			sclerosis complex: a Spanish expanded access				
			trial				
		1					

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

Author/(Refs.)		Year	Study	No. of	No. of cases	Grade	Grade
				patients	(%)	1/2	3/4
						cases	cases
						(%)	(%)
1.	Abida et al	2016	Phase I Study of Everolimus in Combination	A:12	1 (8)		
(109)			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				
			(DL1:5mg QOD, DL2:5mg daily,				
			DL3:10mg daily) following a standard 3+3				
			design.				
2.	Amato et al	2009	A Phase 2 Study With a Daily Regimen of the	A:39	11 (30.7)	11 (30.7)	0
(1)			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).				
3.	Bachelot et al	2012	Randomized Phase II Trial of Everolimus in	54	21 (39)	20 37)	1 (2)
(76)			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				

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

			everolimus 10 mg/d (n 54) or tamoxifen 20				
			mg/d alone (n 57). tamoxifen plus everolimus				
4.	Bajetta et al	2014	Everolimus in Combination with Octreotide	50	1 (2)	1 (2)	0
(2)			Long-Acting Repeatable in a First-Line				
			Setting for Patients With Neuroendocrine				
			Tumors;				
			treatment-naive patients with advanced well-				
			differentiated NETs of gastroenteropancre-				
			atic tract and lung origin received everolimus				
			10 mg daily, in combination with octreotide				
			LAR 30 mg every 28 days.				
5.	Baselga et al	2012	Everolimus in Postmenopausal Hormone-	482	30 (6.2)	27 (5.6)	3 (0.6)
(3)			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).				
6.	Bendell et al	2015	A phase Ib study of linsitinib (OSI-906), a	18	7 (38)	7 (38)	0
(5)			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				
7.	Bergmann et	2015	Everolimus in metastatic renal cell carcinoma	334	16 (5)	11 (3)	5(2)
al (6)	-		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				
8.	Besse et al (8)	2014	Phase II study of everolimus-erlotinib in	66	48 (72.7)	43 (65.1)	5 (7.6)
			previously treated patients with advanced				
			non-small-cell lung cancer;				
			everolimus 5 mg/day + erlotinib 150 mg/day				
9.	Bissler et al	2016	Everolimus for renal angiomyolipoma in	112	22 (19.6)	22 (19.6)	0
(110)			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 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 at al	2013	Everolimus for angiomvolinoma associated	70	10(13)	10 (13)	0
(69)	Dissier et ut	2015	with tuberous sclerosis complex or sporadic	17	10 (15)	10 (13)	0
			with tuberous sciencists complex of sporadic				
			lymphangioleiomyomatosis (EXIST-2): a				
			multicentre, randomised, double-blind,				
			placebo-controlled trial				
			oral everolimus 10 mg per day				
11.	Buzzoni et al	2017	impact of prior therapies on everolimus	202	63 (31)	48 (24)	15 (7)
(9)			activity: an exploratory analysis of raDianT-				
			4				
			Patients were randomized (2:1) to everolimus				
			10 mg/day or placebo, both with best				
			supportive care.				
12.	Campone et al	2009	Safety and pharmacokinetics of paclitaxel	16	2 (12.5)	2 (12.5)	0
(100)			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.				
13.	Castellano et	2013	Everolimus Plus Octreotide Long-Acting	19	5 (26.3)		
al (111))		Repeatable in Patients With Colorectal				
			Neuroendocrine Tumors: A Subgroup				
			Analysis of the Phase III RADIANT-2 Study;				
			everolimus plus octreotide				
14.	Chan <i>et al</i>	2013	A Prospective, Phase 1/2 Study of	43	22 (51)	21 (49)	1 (2)
(78)			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				
			avarolimus daily in each 28 day cycle. In				
			everonnius dany in each 28-day cycle. In				
			conort 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				
15.	Choueiri et al	2015	Cabozantinib versus everolimus in advanced	322	88 (27)	81(25)	7(2)
(11)			renal cell carcinoma;				
			everolimus at a dose of 10 mg daily				
16.	Chow <i>et al</i>	2016	A Phase 2 Clinical Trial of Everolimus Plus	24	4 (16.6)	4 (16.6)	0
(12)			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.				
17.	Chung et al	2016	Phase Ib Trial of mFOLFOX6 and	6	3 (50)	3 (50)	0
(13)			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.				
18.	Cibrik et al	2013	Randomized Trial of Everolimus-Facilitated	A: 274	A 60 (21.9)		
(112)			Calcineurin Inhibitor Minimization Over 24	B: 278	B 57 (20.5)		
			Months in Renal Transplantation				
			A: Everolimus 3-8 ng/ml				
			B: Everolimus 6-12 ng/ml				
19.	Cicora et al	2015	Variances in the Use of Everolimus in	181	19 (10.5)		
(113)			Kidney Transplantation: A 2-Year Registry				
			of Everyday Practice				
			Everolimus				
20.	Ciunci et al	2014	Phase 1 and Pharmacodynamic Trial of	29	4 (13.7)	4 (13.7)	0
(14)			Everolimus in Combination With Cetuximab				
			in Patients With Advanced Cancer				
21.	Conconi et al	2014	Clinical activity of everolimus in	30	3 (10)	3 (10)	0
(15)			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				
			administered orany at a daily dose of 10 mg,				
			from day 1 to day 28 for up to a total of six				
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			cycles or until progression				
22.	Dasari et al	2015	Phase I study of the anti-IGF1R antibody	19	11 (58)	11(58)	0
(16)			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.				
23.	De Fijter et al	2017	Early Conversion From Calcineurin	352	82 (23.3)		
(114)			Inhibitor- to Everolimus-Based Therapy				
			Following Kidney Transplantation: Results				
			of the Randomized ELEVATE Trial				
			everolimus				
24.	El-Madani et	2017	EVESOR, a model-based, multiparameter,	26	3 (11.5)	3 (11.5)	0
al (17)			Phase I trial to optimize the bene t/toxicity				
			ratio of everolimus and sorafenib				
			Everolimus +sorafenib				
25.	Escudier at al	2016	Open-label phase 2 trial of first-line	92	36 (39)	34 (37)	2 (2)
(70)			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				
26.	Fazio <i>et al</i>	2018	Everolimus in advanced, progressive, well-	62	16 (25.8)	13 (21)	3 (4.8)
(18)			differentiated, non-functional				
			neuroendocrine tumors: RADIANT-4 lung				
			subgroup analysis				
			everolimus 10 mg/d				
27.	Fazio et al	2013	Everolimus Plus Octreotide Long-Acting	33	9 (27.3)	6 (18.2)	3 (9.1)
(19)			Repeatable in Patients With Advanced Lung				
			Neuroendocrine Tumors;				
			analysis of the Phase 3, Randomized,				
			Placebo-Controlled RADIANT-2 Study				
			everolimus + octreotide				

28.	Finn <i>et al</i>	2013	Phase I study investigating everolimus	A: 16	А	Α	А
(115)			combined with sorafenib in patients with	B: 14	10 (62.5)	9 (56.2)	1(6.3)
			advanced hepatocellular carcinoma;		В	В	В
			A: sorafenib + everolimus 2.5 mg once daily		10 (71.4)	9 (64.3)	1 (7.1)
			B: sorafenib + everolimus 5 mg once daily				
29.	Fogarasi et al	2016	EFFECTS: an expanded access program of	120	6 (5)	5 (4.2)	1 (0.8)
(116)			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)				
30.	Franz <i>et al</i>	2013	Efficacy and safety of everolimus for	78	10 (13)	10 (13)	0
(117)			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				
31.	Furv <i>et al</i>	2013	A Phase 1 Study of Everolimus D Weekly	13	5 (39)	4 (31)	1 (8)
(118)			Cisplatin D Intensity Modulated Radiation			. ()	- (-)
			Therapy in Head-and-Neck Cancer:				
			everolimus + cisplatin				
32	Furv <i>et al</i> (80)	2012	A phase I study of daily everolimus plus low-	30	15 (54)	15 (54)	0
52.	1 aly <i>et at</i> (00)	2012	dose weekly cisplatin for patients with	50	15 (51)	15 (51)	0
			advanced solid tumors				
33.	Gadgeel <i>et al</i>	2013	Phase I study evaluating the combination of	54	32 (60)	28 (51.8)	4 (8.2)
(81)	Sugerieru	-010	lapatinib (a Her2/Neu and EGFR inhibitor)	0.	02 (00)	20 (0110)	. (0.2)
			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 lapatinih and 5 mg of everolimus once				
			daily				
34	Gelsomino at	2017	A dose finding and biomarkers evaluation	Δ·12	6 (50)	6 (50)	0
al (119))	2017	phase Ib study of Everolimus in association	A. 12	0 (50)	0 (30)	0
			with 5 Eluorourseil and polyis redictheren				
			with 3-ritorouracil and pervic 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-Fluorouracil and				
			radiotherapy				
35.	Ghobrial et al	2010	Phase II Trial of the Oral Mammalian Target	50	3 (6)	0	3 (6)
(120)			of Rapamycin Inhibitor Everolimus in				
			Relapsed or Refractory Waldenstrom				
			Macroglobulinemia;				
			everolimus 10 mg daily for two cycles				
36.	Glanville et al	2015	Three-year results of an investigator-driven	84	29 (18)		
(121)			multicenter, international, randomized open-				
			label de novo trial to prevent BOS after lung				
			transplantation everolimus				
37.	Goldberg et	2015	Everolimus for the treatment of	24	7 (29)		
al.(122)			lymphangioleiomyomatosis: a phase II study				
38.	Gong et al	2017	Ef cacy and safety of everolimus in Chinese	70	9 (12.9)	8 (11.4)	1 (1.5)
(82)			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.				
39.	Grignani et al	2014	Sorafenib and everolimus for patients with	38	18 (47)	16 (42)	2 (5)
(72)			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				
40.	Gross et al	2018	Safety and Efficacy of Docetaxel,	43	25 (58.1)	24 (55.8)	1 (2.3)
(83)			Bevacizumab, and Everolimus for				
			Castration-resistant Prostate Cancer (CRPC)				
			docetaxel 75 mg/m ² , bevacizumab 15 mg/kg,				
			and everolimus 2.5 mg				
41.	Grushkin et al	2013	De novo therapy with everolimus and	18	4 (22.2)		
(123)			reduced-exposure cyclosporine following				
			pediatric kidney transplantation: A				
			prospective, multicenter, 12-month study				
			everolimus (target trough concentration 3				

		ng/ml) with reduced-exposure CsA and				
		corticosteroids				
42. Guglielmelli	2011	Safety and efficacy of everolimus, a mTOR	30	2 (6.7)	2 (6.7)	0
<i>et al</i> (124)		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				
43. Guo <i>et al</i> (20)	2013	Safety and efficacy of everolimus in Chinese	64	12 (19)	11 (17)	1 (2)
		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				
44. Hainsworth <i>et</i>	2010	Phase II Trial of Bevacizumab and	80	36 (45)	29 (36)	7 (9)
<i>al</i> (21)		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				
45. Harzstark <i>et al</i>	2011	A Phase 1 Study of Everolimus and Sorafenib	20	7 (35)	5 (25)	2 (10)
(84)		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				
46. Hatano <i>et al</i>	2016	Outcomes of everolimus treatment for renal	47	5 (11)	5 (11)	0
(22)		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. Hatano <i>et al</i>	2017	Intermittent everolimus administration for	26	4 (15)	4 (15)	0
(23)		renal angiomyolipoma associated with				
		tuberous sclerosis complex;				
		dose of everolimus was set at 10 mg once a				
		day				

48.	Hurvitz et al	2013	A phase 2 study of everolimus combined with	55	31 (56.4)	28 (50.9)	3 (5.5)
(25)			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.				
49.	Jerusalem et al	2016	Safety of everolimus plus exemestane in	2,131	359 (16.8)	332	27 (1.2)
(26)			patients with hormone-receptor-positive,			(15.7)	
			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.				
50.	Johnston et al	2016	The mTORC1 Inhibitor Everolimus	24	12 (50)	12 (50)	0
(27)			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				
51.	Jovanovic et	2017	A randomized phase II neoadjuvant study of	96	31 (32)	29 (30)	2 (2)
al (28)			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^2IV				

			weekly for 11 weeks (starting 1 week after				
			cisplatin initiation)				
52.	Jozwiak et al	2016	Safety of Everolimus in Patients Younger	18	5 (27.8)		
(125)			than 3 Years of Age: Results from EXIST-1,				
			a Randomized, Controlled Clinical Trial;				
			everolimus was initiated at 4.5 mg/m²/day				
			and titrated to blood trough levels of 5-				
			15 ng/ml				
53.	Ju <i>et al</i> (85)	2015	Toxicity and adverse effects of everolimus in	12	2 (16.6)	2 (16.6)	0
			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.				
54.	Kanesvaran et	2015	A single arm phase 1b study of everolimus	4	3 (75)	2 (50)	1 (25)
al (126)	1		and sunitinib in patients with advanced renal				
			cell carcinoma (RCC);				
			Sunitinib + everolimus				
55.	Kato <i>et al</i> (86)	2013	Efficacy of Everolimus in Patients with	19	2 (11)	2 (11)	0
			Advanced Renal Cell Carcinoma Refractory			~ /	
			or Intolerant to VEGFR-TKIs and Safety				
			Compared with Prior VEGFR-TKI				
			Treatment				
56.	Kim <i>et al</i> (87)	2018	Clinical outcomes of the sequential use of	36	7 (19.4)	6 (16.6)	1 (2.8)
			pazopanib followed by everolimus for the				
			treatment of metastatic renal cell carcinoma:				
			A multicentre study in Korea:				
			Everolimus				
57.	Kim <i>et al</i> (30)	2013	A phase I study of everolimus and CHOP in	15	6 (40)	5 (33.3)	1 (6.7)
0,1		2010	newly diagnosed peripheral T-cell	10	0(10)	e (eeie)	1 (017)
			lymphomas				
			Four dose levels $(2.5 \text{ to } 10 \text{ mg})$ of everolimus				
			from days 1 to 14 with CHOP (750 mg/m^2				
			cvclophosphamide, 50 mg/m2 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.				
58.	Knox <i>et al</i>	2017	Final overall survival analysis for the phase	238	15 (6.3)		
(31)			II RECORD-3 study of first-line everolimus				
			followed by sunitinib versus first-line				
			ionovica og samtinio versus mist-inte				

			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	2016	Sorafenib with or without everolimus in	59	38 (64)	26 (44)	12 (20)
(32)			patients with advanced hepatocellular				
			carcinoma (HCC): a randomized multicenter,				
			multinational phase II trial (SAKK 77/08 and				
			SASL 29);				
			sorafenib + everolimus				
60.	Kordes et al	2013	A phase I/II, non-randomized,	31	10 (32)	6 (19)	4 (13)
(33)			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.				
61.	Koutsoukos et	2017	Real-world experience of everolimus as	31	2 (7)	2 (7)	0
al (34)			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				
62.	Kulke et al	2017	A randomized, open-label, phase 2 study of	A: 78	А	А	А
(35)			everolimus in combination with pasireotide	B: 81	49 (62.8)	45 (57.7)	4 (5.1)
			LAR or everolimus alone in advanced, well-		В	В	В
			differentiated, progressive pancreatic		43 (53.1)	40 (49.4)	3 (3.7)
			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)				
63.	Lim <i>et al</i> (89)	2013	A multicenter, phase II trial of everolimus in	38	6 (15)	2 (5)	4 (10)
			locally advanced or metastatic thyroid cancer				
			of all histologic subtypes;				

			everolimus 10 mg daily orally until				
			unacceptable toxicity or disease progression				
64.	Massarweh et	2014	A phase II study of combined fulvestrant and	31	5 (16)	5 (16)	0
al (37)			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 \pm 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.				
65.	Milowsky et	2013	Phase II study of everolimus in metastatic	45	7 (16)	7 (16)	0
al (127)			urothelial cancer;				
			all patients received everolimus 10 mg orally				
			once daily continuously (one cycle = 4				
			weeks)				
66.	Molina et al	2012	Phase 1 Trial of Everolimus Plus Sunitinib in	20	10 (50)	6 (30)	4
(38)			Patients With Metastatic Renal Cell				
			Carcinoma;				
			A: everolimus + sunitinib				
67.	Molina et al	2014	A phase 1b clinical trial of the multi-targeted	20	8 (40)	6 (30)	2 (10)
(39)			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				
68.	Morrow et al	2011	Phase I/II Study of Trastuzumab in	47	5 (11)	1 (2)	4 (9)
(40)			Combination With Everolimus (RAD001) in				
			Patients With HER2-Overexpressing				
			Metastatic Breast Cancer Who Progressed on				
			Trastuzumab-Based Therapy				
69. (102)	Moscetti et al	2016	Safety analysis, association with response	181	11 (6.6)	11 (6.6)	0
(102)			and previous treatments of everolimus and				
			exemestane in 181 metastatic breast cancer				
			patients: A multicenter Italian experience				

70.	Motzer et al	2014	Phase II Randomized Trial Comparing	337	103 (30.6)	91 (27)	12(3.6)
(42)			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)				
71.	Motzer et al	2008	Efficacy of everolimus in advanced renal cell	269	46 (17)	42 (16)	4 (1)
(74)			carcinoma: a double-blind, randomised,				
			placebo-controlled phase III trial				
			everolimus 10 mg once daily				
72.	Motzer et al	2015	Lenvatinib, everolimus, and the combination	50	17 (34)	16 (32)	1 (2)
(75)			in patients with metastatic renal cell				
			carcinoma: a randomised, phase 2, open-				
			label, multicentre trial				
			everolimus 10 mg once daily				
73.	Narayan <i>et al</i>	2016	Phase I Trial of Everolimus and Radiation	18	2 (11.1)	2 (11.1)	0
(43)			Therapy for Salvage Treatment of				
			Biochemical Recurrence in Prostate Cancer				
			Patients Following Prostatectomy				
			Everolimus +srt				
74.	Niegisch et al	2015	Second-Line Treatment of Advanced	27	5 (18.5)	4 (14.8)	1 (3.7)
(44)			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).				
75.	Nozawa <i>et al</i>	2013	Adverse Event Profile and Dose	47	2 (4.2)	1 (2.1)	1 (2.1)
(90)			Modification of Everolimus for Advanced				
			Renal Cell Carcinoma in Real-world				
			Japanese Clinical Practice				
			Everolimus				
76.	Oh <i>et al</i> (45)	2012	Phase 2 Study of Everolimus Monotherapy	34	9 (26.5)	8 (23.6)	1 (2.9)
			in Patients With Nonfunctioning				

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

83. Powles <i>et al</i>	2016	Randomized Open-Label Phase II Trial of	43	22 (51)	21 (49)	1 (2)
(104)		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				
84. Quek <i>et al</i>	2011	Combination mTOR and IGF-1R Inhibition:	21	6 (28.6)	5 (23.8)	1 (4.8)
(92)		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)				
85. Ramalingam	2010	Phase 1 and Pharmacokinetic Study of	24	1 (4.1)	0	1 (4.1)
<i>et al</i> (129)		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.				
86. Rathkopf <i>et al</i>	2015	Everolimus Combined With Gefitinib in	39	25 (65)	25 (65)	0
(93)		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)				
87. Ray-Coquard	2013	Everolimus as second- or third-line treatment	43	19 (44)	14 (32)	5 (12)
<i>et al</i> (51)		of advanced endometrial cancer:				
		ENDORAD,				
		a phase II trial of GINECO				
		everolimus 10mg per day until progression or				
		unacceptable toxicity				
88. Rizzo <i>et al</i>	2015	Everolimus as second-line therapy for	100	14 (14)	11 (11)	3 (3)
(105)		metastatic renal cell carcinoma: a 'real-life'				
		study;				
		everolimus 10 mg/day				

89.	Robles et al	2016	Everolimus safety and efficacy for renal	19	4 (21.1)	4 (21.1)	0
(106)			angiomyolipomas associated with tuberous				
			sclerosis complex: a Spanish expanded				
			access trial;				
			10 mg everolimus once daily				
90.	Rodrigues et	2015	Phase I combination of pazopanib and	52	4 (7.6)	2 (3.8)	2 (3.8)
al (52)			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.				
91.	Ryan et al	2011	A phase II study of everolimus in	19	11 (58)	10 (53)	1 (5)
(94)			combination with imatinib for previously				
			treated advanced renal carcinoma;				
			everolimus 2.5 mg po daily and imatinib 600				
			mg po daily.				
92.	Safra <i>et al</i>	2018	Everolimus Plus Letrozole for Treatment of	72	21 (29.2)	18 (13)	3 (5.6)
(107)			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				
93.	Salazar et al	2017	Phase II Study of BEZ235 versus Everolimus	31	17 (54.8)	16 (51.6)	1 (3.2)
(54)			in Patients with Mammalian Target of				
			Rapamycin Inhibitor-Na€ıve Advanced				
			Pancreatic Neuroendocrine Tumors;				
			everolimus 10 mg once daily				
94.	Sanoff et al	2015	Everolimus and pasireotide for advanced and	24	7 (29)	6 (26)	1 (4)
(55)			metastatic hepatocellular carcinoma;				
			everolimus 7.5 mg PO daily and pasireotide				
			LAR 60 mg IM every 28 days.				
95.	Sarkaria et al	2011	NCCTG Phase I Trial N057K of Everolimus	18	4	4 (23)	0
(56)			(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				

96.	Shen et al (57)	2014	Phase II Multicentered Study of Low-Dose	40	12 (30)	9 (22.5)	3 (7.5)
			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				
97.	Shoushtari et	2016	Phase 2 trial of everolimus 10mg daily plus	13	9 (64)	8 (57)	1(7)
al (58)			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				
98.	Strickler et al	2012	Phase I study of bevacizumab, everolimus,	12	6 (50)	6 (50)	0
(95)			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.				
99.	Sun <i>et al</i> (60)	2013	A phase-1b study of everolimus plus	A 6	A 0	A 0	A 0
			paclitaxel in patients with small-cell lung	B 11	B 2 (18.1)	B 2	B 0
			cancer	C 3	C 1 (33.3)	(18.1)	C 0
			A: everolimus 2.5 mg			C 1	
			B: everolimus 5 mg			(33.3)	
			C: everolimus 10 mg				
100.	Takahashi et	2013	Efficacy and safety of concentration-	61	11 (18)		
al (130))		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)				
101.	Tan <i>et al</i> (131)	2017	The mTOR inhibitor everolimus in	37	5 (13.5)		
			combination with azacitidine in patients with				

			relapsed/refractory acute myeloid leukemia:				
			a phase Ib/II study				
102.	Tarhini <i>et al</i>	2010	Phase II Study of Everolimus (RAD001) in	40	6 (15)	5 (12.5)	1 (2.5)
(61)			Previously Treated Small Cell Lung Cancer				
			everolimus 10 mg orally daily until disease				
			progression.				
103.	Thudium et al	2015	Bioavailability of everolimus administered	22	1 (4.5)		
(132)			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				
104.	Vlahovic et al	2012	A phase I study of bevacizumab, everolimus	32	11 (34)	10 (31)	1 (3)
(63)			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.				
105.	Wang <i>et al</i>	2014	Everolimus for patients with mantle cell	58	26 (44.8)	23 (39.6)	3 (5.2)
(107)			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.				
106.	Werner et al	2013	Phase I study of everolimus and mitomycin C	16	5 (31.3)	4 (25)	1 (6.3)
(04)			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.				
107.	Wolpin et al	2009	Oral mTOR Inhibitor Everolimus in Patients	33	8 (24)	8 (24)	0
(97)			With Gemcitabine-Refractory Metastatic				
			Pancreatic Cancer;				
			everolimus 10 mg daily				

108.	Yao <i>et al</i> (65)	2011	Everolimus for Advanced Pancreatic	204	69 (34)	62 (31)	7(3)
			Neuroendocrine Tumors;				
			everolimus 10 mg once daily				
109.	Yee <i>et al</i> (98)	2014	Outcomes in patients with relapsed or	26	7 (27)	6 (23.1)	1 (3.9)
			refractory multiple myeloma in a phase I				
			study of everolimus in combination with				
			lenalidomide				
110.	Yee <i>et al</i> (99)	2006	Phase I/II Study of the Mammalian Target of	27	9 (33)	8 (29)	1 (4)
			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)				
	Total overall			10,436	2,330 (22.3)		
	Total with grade			8,818	2,029 (23)	1,797	232
						(20.4)	(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	102
						(19,6)	(2.9)

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

Author/(Refs.)	Year	Study	No. of	No. of cases	Grade 1/2	Grade 3/4
			patients	(%)	cases (%)	cases (%)
1. Albiges <i>et al</i> (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	632	(%) 32 (7)	cases (%)	cases (%)
		unacceptable toxicity				
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	280	121 (44)	87 (31)	34 (13)

			in 3-week cycles, stratified by				
			previous lapatinib use.A				
3.	Angelousi et al	2017	Sequential Everolimus and	A: 20 1st	A 2 (10)	A 2 (10)	A 0
(133)			Sunitinib Treatment in	line	B 2 (18)	B 2 (18)	B 0
			Pancreatic Metastatic Well-	everolimus			
			Differentiated	B: 11 2nd			
			Neuroendocrine Tumours	line			
			Resistant to Prior Treatments	everolimus			
			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				
4.	Armstrong et al	2016	Everolimus versus sunitinib	52	33 (58)	29 (51)	4 (7)
(68)			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.				
5.	Bachelot et al	2012	Randomized Phase II Trial of	54	39 (72)	36 (66)	3 (6)
(76)			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				
			(n=57).				
6.	Barnes et al	2013	Everolimus in combination	24	8 (33)	6 (25)	2 (8)
(77)			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.				
7.	Baselga et al	2012	Everolimus in	482	33 (6.8)	30 (6.2)	3 (0.6)
(3)			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)				
8.	Baselga et al	2009	Phase II Randomized Study	137	17 (12.4)	15 (10.9)	2 (1.5)
(4)			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				
9.	Bendell et al	2015	A phase Ib study of linsitinib	18	9 (50)	9 (50)	0
(5)			(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				
10.	Bergmann et al	2015	Everolimus in metastatic	334	37 (12)	24 (8)	13 (4)
(6)			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				
11.	Besse et al (8)	2014	Phase II study of everolimus-	66	15 (22.7)	11(33.3)	4 (6.1)
			erlotinib in previously treated				
			patients with advanced non-				
			small-cell lung cancer;				
			everolimus 5 mg/day +				
			erlotinib 150 mg/day				
12.	Bissler et al	2018	The effect of everolimus on	33	5 (15.2)		
(134)			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				
13.	Bissler et al	2016	Everolimus for renal	112	20 (17.9)	19 (17)	1 (0.9)
(110)			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				

14.	Bissler et al	2013	Everolimus for	79	14 (18)	13 (17)	1(1)
(69)			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				
15.	Buzzoni et al	2017	impact of prior therapies on	202	63 (31)	56 (28)	7 (3)
(9)			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.				
16.	Cazzaniga et al	2017	Efficacy and safety of	404	134 (39.5)	123 (36.3)	11 (3.2)
(135)			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.				
17.	Choueiri et al	2015	Cabozantinib versus	322	146 (45)	124 (38)	22 (7)
(11)			everolimus in advanced renal				
			cell carcinoma;				
			everolimus at a dose of 10 mg				
			daily				
18.	Chow <i>et al</i> (12)	2016	A Phase 2 Clinical Trial of	24	13 (54.1)	13 (54.1)	0
			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.				
19.	Chung et al	2016	Phase Ib Trial of mFOLFOX6	6	6 (100)	6 (100)	0
(13)			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				
20.	Ciunci et al	2014	Phase 1 and	29	7 (24.1)	6 (20.6)	1 (3.5)
(14)			Pharmacodynamic Trial of				
			Everolimus in Combination				
			With Cetuximab in Patients				
			With Advanced Cancer				
21.	Dasari et al	2015	Phase I study of the anti-	19	14 (74)	9 (48)	5 (26)
(16)			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.				
22.	Doi <i>et al</i> (136)	2010	Multicenter Phase II Study of	53	3 (5.7)		
			Everolimus in Patients With				
			Previously Treated Metastatic				
			Gastric Cancer;				
			everolimus 10 mg orally daily				

23.	El-Madani et al	2017	EVESOR, a model-based,	26	18 (69.2)	12 (46.1)	6 (23.1)
(17)			multiparameter, Phase I trial				
			to optimize the bene t/toxicity				
			ratio of everolimus and				
			sorafenib;				
			everolimus + sorafenib				
24.	Ellard et al (79)	2009	Randomized Phase II Study	A 33	A 21 (63.6)	A 5 (15.1)	A 16
			Comparing Two Schedules of	B 16	B 12 (75)	B 5 (31.2)	(48.4)
			Everolimus in Patients With				B 7 (43.7)
			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				
25.	Escudier et al	2016	Open-label phase 2 trial of	92	30 (33)	25 (28)	5 (5)
(70)			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				
26.	Fazio et al (18)	2018	Everolimus in advanced,	62	20 (32.3)	18 (29.1)	2 (3.2)
			progressive, well-				
			differentiated, non-functional				
			neuroendocrine tumors:				
			RADIANT-4 lung subgroup				
			analysis;				
			everolimus 10 mg/day				
27.	Fazio et al (19)	2013	Everolimus Plus Octreotide	33	4 (12.1)		
			Long-Acting Repeatable in				
			Patients With Advanced Lung				
			Neuroendocrine Tumors;				
			analysis of the Phase 3,				
			Randomized, Placebo-				
			Controlled RADIANT-2				
			Study				

			everolimus + octreotide				
28.	Ferolla et al	2017	Efficacy and safety of long-	A 42	8 (19)	7 (17)	1 (2)
(71)			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.				
29.	Finn <i>et al</i> (115)	2013	Phase I study investigating	A 16	A 4 (25)	A 4 (25)	A 0
			everolimus combined with	B 14	B 5 (35.7)	B 4 (28.6)	B 1 (7.1)
			sorafenib in patients with				
			advanced hepatocellular				
			carcinoma;				
			A: sorafenib +everolimus 2.5				
			mg once daily				
			B: sorafenib + everolimus 5				
			mg once daily				
30.	Franz et al	2014	Everolimus for subependymal	120	6 (5)	6 (5)	0
(137)			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.				
31.	Franz <i>et al</i>	2013	Efficacy and safety of	78	11 (14)	11 (14)	0
(117)			everolimus for subependymal				
			giant cell astrocytomas				
			associated with tuberous				
			sclerosis complex (EXIST-1):				
			a multicentre, randomised,				
			placebo-controlled phase 3				
			trial				

			Everolimus everolimus 4.5				
			mg/m ² per day (titrated to				
			achieve blood trough				
			concentrations of 5-15 ng/ml)				
32.	Fury <i>et al</i> (118)	2013	A Phase 1 Study of	13	13 (100)	11 (85)	2 (15)
			Everolimus D Weekly				
			Cisplatin D Intensity				
			Modulated Radiation Therapy				
			in Head-and-Neck Cancer				
			A: everolimus + cisplatin				
33.	Fury <i>et al</i> (80)	2012	A phase I study of daily	30	27 (96)	24 (85)	3 (11)
			everolimus plus low-dose				
			weekly cisplatin for patients				
			with advanced solid tumors				
34. (81)	Gadgeel et al	2013	Phase I study evaluating the	54	25 (47)	22 (40.7)	3 (6.3)
(0-)			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.				
35.	Ghobrial et al	2014	Long-term results of the	60	5 (9)	0	5 (9)
(158)			phase II trial of the oral				
			mTOR inhibitor everolimus				
			(RAD001) in relapsed or				
			refractory Waldenstrom				
			Macroglobulinemia;				
			everolimus 10 mg daily and				
			were evaluated monthly.				
36.	Goldberg et al	2015	Everolimus for the treatment	24	7 (29)		
(122)			of lymphangioleio-				
			myomatosis: 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				
37.	Gong et al (82)	2017	Efficacy and safety of	70	18 (25.7)	17 (24.3)	1 (1.4)
			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				
38.	Grignani et al	2014	Sorafenib and everolimus for	38	16 (42)	14 (37)	2 (5)
(72)			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				
39.	Grunwald et al	2012	An international expanded-	1,367	116 (8.5)	24 (1.8)	92 (6.7)
(73)			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				

40. Guglielmelli et	2011	Safety and efficacy of	30	5 (16.9)	5 (16.9)	0
al (124)		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				
41. Guo <i>et al</i> (20)	2013	Safety and efficacy of	64	20 (31)	19 (29)	1 (2)
		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.				
42. Hainsworth <i>et</i>	2010	Phase II Trial of	80	62 (77)	52 (65)	10 (12)
<i>al</i> (21)		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				
43. Harzstark <i>et al</i>	2011	A Phase 1 Study of	20	3 (15)	2 (10)	1 (5)
(84)		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				

			orally twice daily				
			continuously				
44.	Hatano et al	2016	Outcomes of everolimus	47	7 (15)	7 (15)	0
(22)			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.				
45.	Hatano et al	2017	Intermittent everolimus	26	3 (12)	3 (12)	0
(23)			administration for renal				
			angiomyolipoma associated				
			with tuberous sclerosis				
			complex;				
			the dose of everolimus was set				
			at 10 mg once a day				
46.	Hill et al (24)	2017	A phase I trial of bortezomib	29	24	23	1
			in combination with				
			everolimus for treatment of				
			relapsed/refractory non-				
			Hodgkin lymphoma				
			bortezomib + everolimus				
47.	Hurvitz et al	2013	A phase 2 study of everolimus	55	12 (21.9)	9 (16.4)	3 (5.5)
(25)			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				
			$(80 \text{ mg/m}^2 \text{ days } 1, 8, \text{ and } 15$				
			every 4 weeks) and				
			trastuzumab (4 mg/kg loading				
			dose followed by 2 mg/kg				
			weekly), administered in 28-				
			day cycles				
48.	Jerusalem et al	2016	Safety of everolimus plus	2,131	298 (14.0)	271 (12.7)	27 (1.3)
(26)			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)				
			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	2016	The mTORC1 Inhibitor	24	12 (50)	11 (46)	1 (4)
(27)			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				
50.	Jovanovic et al	2017	A randomized phase II	96	61 (64)	58 (61)	3 (3)
(28)			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				
51.	Ju <i>et al</i> (85)	2015	Toxicity and adverse effects	12	1 (8.3)	1 (8.3)	0
			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.				
52. Kanesvaran <i>et</i>	2015	A single arm phase 1b study	4	4 (100)	3 (75)	1 (25)
al (126)		of everolimus and sunitinib in				
		patients with advanced renal				
		cell carcinoma (RCC)				
		Sunitinib + everolimus				
53. Kato <i>et al</i> (86)	2013	Efficacy of Everolimus in	19	7 (37)	6 (32)	1 (5)
		Patients with Advanced				
		Renal Cell Carcinoma				
		Refractory or Intolerant to				
		VEGFR-TKIs and Safety				
		Compared with Prior				
		VEGFR-TKI Treatment;				
		everolimus				
54. Kim <i>et al</i> (87)	2018	Clinical outcomes of the	36	14 (38.9)	13 (36.1)	1 (2.8)
		sequential use of pazopanib				
		followed by everolimus for				
		the treatment of metastatic				
		renal cell carcinoma: A				
		multicentre study in Korea;				
		everolimus				
55. Kim <i>et al</i> (88)	2016	everolimus Efficacy and Toxicity of	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus Efficacy and Toxicity of Mammalian Target	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus Efficacy and Toxicity of Mammalian Target Rapamycin Inhibitors in	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus Efficacy and Toxicity of Mammalian Target Rapamycin Inhibitors in Patients with Metastatic	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus Efficacy and Toxicity of Mammalian Target Rapamycin Inhibitors in Patients with Metastatic Renal Cell Carcinoma with	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus Efficacy and Toxicity of Mammalian Target Rapamycin Inhibitors in Patients with Metastatic Renal Cell Carcinoma with Renal Insufficiency: The	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus Efficacy and Toxicity of Mammalian Target Rapamycin Inhibitors in Patients with Metastatic Renal Cell Carcinoma with Renal Insufficiency: The Korean Cancer Study Group	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus 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;	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus 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	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus 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	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus 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	19	3 (16)	3 (16)	0
55. Kim <i>et al</i> (88)	2016	everolimus 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	19	3 (16)	3 (16)	0

			weekly for eight patients in				
			the overall series.				
56.	Kim <i>et al</i> (30)	2013	A phase I study of everolimus	15	3 (20)	3 (20)	0
			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				
57.	Knox <i>et al</i> (31)	2017	Final overall survival analysis	238	35 (14.7)		
			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				
58.	Koeberle et al	2016	Sorafenib with or without	59	39 (66)	22 (37)	17 (29)
(32)			everolimus in patients with				
			advanced hepatocellular				
			carcinoma (HCC): a				
			randomized multicenter,				
			multinational phase II trial				
			(SAKK 77/08 and SASL 29)				
			Sorafenib + everolimus				

59.	Kordes et al	2013	A phase I/II, non-randomized,	31	13 (42)	9 (29)	4 (13)
(33)			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				
			$(600-800 \text{ mg/ } \text{m}^2 \text{ bid}, 2 \text{ weeks})$				
			every 3 weeks) were				
			investigated in a phase I/II				
			study in patients with				
			advanced pancreatic cancer				
60.	Koutsoukos et	2017	Real-world experience of	31	3 (10)	3 (10)	0
al (34)			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				
61.	Kulke et al (35)	2017	A randomized, open-label,	A 78	A 21 (26.9)	A 18	A 3 (3.8)
			phase 2 study of everolimus	B 81	B 28 (34.6)	(23.1)	B 3 (3.7)
			in combination with			B 25	
			pasireotide LAR or			(30.9)	
			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)				
62.	Kumano et al	2013	Sequential use of mammalian	57	3 (5.3)	3 (5.3)	0
(36)			target of rapamycin inhibitors				

			in patients with metastatic				
			renal cell carcinoma				
			following failure of tyrosine				
			kinase inhibitors;				
			everolimus (10 mg orally,				
			once daily)				
63.	Macaskill et al	2011	The mammalian target of	31	6 (19.4)		
(139)			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.				
64.	Massarweh et	2014	A phase II study of combined	31	10 (32)	10 (32)	0
al (37)			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 \pm 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				
65.	Milowsky et al	2013	Phase II study of everolimus	45	44 (98)	39 (87)	5 (11)
(127)			in metastatic urothelial				
			cancer;				
			everolimus 10 mg orally once				
			daily continuously (one cycle				
			= 4 weeks)				

66.	Molina et al	2012	Phase 1 Trial of Everolimus	20	15 (75)	15	0
(38)			Plus Sunitinib in Patients				
			With Metastatic Renal Cell				
			Carcinoma;				
			everolimus + sunitnib				
67.	Molina et al	2014	A phase 1b clinical trial of the	20	12 (60)	10 (50)	2 (10)
(39)			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				
68.	Motzer et al	2014	Phase II Randomized Trial	238	45 (19)	36 (15.1)	9 (3.8)
(42)			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)				
69.	Motzer et al	2008	Efficacy of everolimus in	269	33 (20)	25 (17)	8 (3)
(74)			advanced renal cell				
			carcinoma: a double-blind,				
			randomised, placebo-				
			controlled phase III trial				
			everolimus 10 mg once daily				
70.	Motzer et al	2015	Lenvatinib, everolimus, and	50	19 (38)	18 (36)	1 (2)
(75)			the combination in patients				

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

			Retrospective SECTOR				
			Study;				
			Everolimus				
76.	Oyama et al	2017	Efficacy and safety of	53	7 (13.2)	6 (11.3)	1 (1.9)
(48)			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				
77.	Powles et al	2014	A phase Ib study investigating	15	11(73)	10(67)	1(7)
(128)			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				
78.	Powles et al	2016	Randomized Open-Label	43	15 (35)	12 (28)	3 (7)
(104)			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				
•							
			everolimus 10 mg once per				
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			day				
79.	Quek et al (92)	2011	Combination mTOR and IGF-	21	18 (85.9)	16 (76.4)	2 (9.5)
			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)				
80.	Rathkopf et al	2015	Everolimus Combined With	39	36 (92)	34 (87)	2 (5)
(93)			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)				
81.	Ray-Coquard et	2013	Everolimus as second- or	43	40 (93)	22 (51)	18 (42)
<i>ai</i> (31)			third-line treatment of				
			advanced endometrial cancer:				
			ENDORAD, a phase II trial of				
			GINECO;				
			everolimus 10 mg per day				
			until progression or				
			unacceptable toxicity				
82.	Rodrigues et al	2015	Phase I combination of	52	9 (17.3)	8 (15.4)	1 (1.9)
(32)			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				
83.	Ryan et al (94)	2011	A phase II study of	19	13 (68)	10 (53)	3 (16)
			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				
84.	Safra <i>et al</i> (53)	2018	Everolimus Plus Letrozole for	72	44 (61.1)	40 (55.5)	4 (5.6)
			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				
85.	Salazar <i>et al</i>	2017	Phase II Study of BEZ235	31	10 (32.3)	8 (29.8)	2 (2.5)
(54)			versus Everolimus in Patients				
			with Mammalian Target of				
			Rapamycin Inhibitor-Na€ıve				
			Advanced Pancreatic				
			Neuroendocrine Tumors;				
			everolimus 10 mg once daily				
86.	Sanoff et al	2015	Everolimus and pasireotide	24	7 (29)	6 (25)	1 (4)
(55)			for advanced and metastatic				
			hepatocellular carcinoma;				
			everolimus 7.5 mg po daily				
			and pasireotide LAR 60 mg				
			IM every 28 days				
87.	Sarkaria et al	2011	NCCTG Phase I Trial N057K	18	6 (34%)	3 (17%)	3 (17%)
(56)			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				
88.	Shen et al (57)	2014	Phase II Multicentered Study	40	19 (47.5)	17 (42.5)	2 (5)
			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				
89.	Shoushtari et al	2016	Phase 2 trial of everolimus	13	2 (14)	2 (14)	0
(58)			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				
90.	Slomovitz et al	2010	A Phase 2 Study of the Oral	35	19 (54)	11 (46)	8 (8)
(99)			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				
91.	Strickler et al	2012	Phase I study of bevacizumab,	12	1 (8)	1 (8)	0
(95)			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				
92.	Tan <i>et al</i> (131)	2017	The mTOR inhibitor	37	4 (10.8)		
			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				
93.	Tarhini <i>et al</i>	2010	Phase II Study of Everolimus	40	10 (25)	9 (22.5)	1 (2.5)
(01)			(RAD001) in Previously				
			Treated Small Cell Lung				
			Cancer;				
			everolimus 10 mg orally daily				
94.	Tomita et al	2017	Nivolumab versus everolimus	26	5 (19)	4 (15)	1 (4)
(02)			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				
95.	Vlahovic et al	2012	A phase I study of	32	10 (31)	8 (25)	2 (6)
(63)			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				
96.	Wang et al	2014	Everolimus for patients with	58	25 (43.1)	21 (36.2)	4 (6.9)
(107)			mantle cell lymphoma				
			refractory to or intolerant of				
			bortezomib: multicentre,				
			single-arm, phase 2 study;				
			everolimus 10 mg/d in adults				
97.	Werner et al	2013	Phase I study of everolimus	16	5 (32)	5 (32)	0
(64)			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				
98.	Wolpin et al	2009	Oral mTOR Inhibitor	33	19 (57)	16 (48)	3 (9)
(97)	-		Everolimus in Patients With				
			Gemcitabine-Refractory				
			Metastatic Pancreatic Cancer;				
			everolimus 10 mg daily				
99.	Yao <i>et al</i> (140)	2008	Efficacy of RAD001	64	7 (11)		
			(Everolimus) and Octreotide				
			LAR in Advanced Low- to				
			Intermediate-Grade				
			Neuroendocrine Tumors:				
			Results of a Phase II Study;				
		1				1	
1			treatment consisted of				
			treatment consisted of RAD001 5 mg/d (30 patients)				

			and octreotide LAR 30 mg				
			every 28 days				
100.	Yao <i>et al</i> (65)	2011	Everolimus for Advanced	204	64 (31)	59 (29)	5 (2)
			Pancreatic Neuroendocrine				
			Tumors				
			10 mg once daily				
101.	Yee <i>et al</i> (99)	2006	Phase I/II Study of the	27	6 (22)	4 (15)	2 (7)
			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				
	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	No. of Cases	Grade 1/2	Grade
			patients	(%)	cases (%)	3/4
						cases (%)
1. Bajetta <i>et al</i>	2014	Everolimus in Combination	50	13 (26)	13 (26)	0
(2)		with Octreotide Long-Acting				
		Repeatable in a First-Line				
		Setting for Patients With				
		Neuroendocrine Tumors;				
		treatment-naive patients with				
		advanced well-differentiated				
		NETs of gastroenteropancre-				
		atic tract and lung origin				
		received everolimus 10 mg				
		daily, in combination with				
		octreotide LAR 30 mg every 28				
		days.				
2. Baselga <i>et</i>	2009	Phase II Randomized Study of	137	22 (16.1)	21 (15.4)	1 (0.7)
<i>al</i> (4)		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				
3. Bissler <i>et al</i>	2013	Everolimus for angiomyolipoma	79	16 (20)	16 (20)	0
(69)		associated with tuberous				
		sclerosis complex or sporadic				
		lymphangioleiomyomatosis				
		(EXIST-2): a multicentre,				
		randomised, double-blind,				
		placebo-controlled trial;				

			oral everolimus 10 mg per day				
4. Bissl	ler <i>et al</i>	2016	Everolimus for renal	112	33 (29.5)	32 (8.6)	1 (0.9)
(110)			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				
5. Cazz	zaniga	2017	Efficacy and safety of	404	63 (18.6)	63 (18.6)	0
<i>et al</i> (155)			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				
$\begin{array}{c} 6. \\ (78) \end{array} $ Char	n <i>et al</i>	2013	A Prospective, Phase 1/2 Study	43	18 (42)	18 (42)	0
(70)			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 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	2016	A Phase 2 Clinical Trial of	24	15 (62.5)	15 (62.5)	0
(12)			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.				
8.	Conconi et	2014	Clinical activity of everolimus	30	8 (26.6)	8 (26.6)	0
al (15)			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				
9.	Ellard et al	2009	Randomized Phase II Study	A 33	A 27(81.8)	0	27(81.8)
(79)			Comparing Two Schedules of	B 16	B 13 (81.2)	0	13(81.2)
			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				
10.	Escudier at	2016	Open-label phase 2 trial of first-	92	15 (16)	13 (14)	2 (2)
ai.(70)			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				
11 Forolla at al	2017	Efficacy and safety of long	42	6 (14)	6 (14)	0
(71)	2017	Efficacy and safety of long-	42	0(14)	0(14)	0
		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.				
12. Fogarasi <i>et</i>	2016	EFFECTS: an expanded access	120	5 (4.2)	5 (4.2)	0
al (116)		program of everolimus for				
		patients with subependymal				
		giant cell astrocytoma				
		associated with tuberous				
		sclerosis complex:				
		patients received once daily				
		everolimus (dose adjusted to				
		ettein a trough level of 5 15				
		attain a trough level of 5-15				
		Median daily dose of everolimus				
		was 5.82 mg (range, 2.0-11.8				
		mg), including days of				
		temporary interruption of the				
		study drug				
13. Franz <i>et al</i>	2014	Everolimus for subependymal	114	8 (7)	8 (7)	0
(157)		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				

		through concentrations of 5-15				
		ng/ml)				
14. Fury <i>et al</i>	2012	A phase I study of daily	30	16 (57)	16 (57)	0
(80)		everolimus plus low-dose				
		weekly cisplatin for patients				
		with advanced solid tumors				
15. Gelsomino	2017	A dose finding and biomarkers	A:12	1 (8.3)	1 (8.3)	0
<i>et al</i> (119)		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				
16. Grignani et	2014	Sorafenib and everolimus for	38	15	15 (40)	0
al (72)		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				
17. Guglielmelli	2011	Safety and efficacy of	30	7 (23.3)	7 (23.3)	0
<i>et al</i> (124)		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				
18. Guo et al	2013	Safety and efficacy of	64	32 (50)	32 (50)	0
(20)		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 (2x5 mg				
			tablets) daily until objective				
			tumor progression (according to				
			RECIST version 1.0)				
			unaccentable toxicity death or				
			study discontinuation for any				
			study discontinuation for any				
10	TT 4 1	2016		47	<i>c</i> (12)	6 (12)	0
(22)	Hatano <i>et al</i>	2016	Outcomes of everolimus	47	6 (13)	6 (13)	0
× ,			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.				
20.	Hatano et al	2017	Intermittent everolimus	26	3 (12)	3 (12)	0
(23)			administration for renal				
			angiomyolipoma associated				
			with tuberous sclerosis complex				
			The dose of everolimus was set				
			at 10 mg once a day				
21.	Jebali et al	2017	Biological toxicities as	44	31 (70)	28 (63)	3(7)
(141)			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				
22	Iarusalam at	2016	Safety of everolimus plus	2131	216 (10.1)	214 (10.0)	2 (0 1)
al (26)	jerusalelli et	2010	exemption in patients with	2131	210 (10.1)	214 (10.0)	2 (0.1)
			bormono recentor positivo				
			LIED2 magating lagella				
			HER2-negative locally				
			auvanced 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 1x10 mg) plus				
			EXE (25 mg/day) in 28-day				
			cycles.				
23.	Johnston et	2016	The mTORC1 Inhibitor	24	14 (58)	14 (58)	0
al (27)			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.	Jovanovic et	2017	A randomized phase II	96	9 (9)	9 (9)	0
al (28)			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)				
25.	Kim et al	2013	A phase I study of everolimus	15	1 (6.6)	1 (6.6)	0
(30)			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				
26. Kulke <i>et al</i>	2017	A randomized, open-label,	A: 78	A: 16 (20.5)	A: 16 (20.5)	A: 0
(35)		phase 2 study of everolimus in	B: 81	B: 12 (14.8)	B: 12 (14.8)	B: 0
		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)				
27. Lim <i>et al</i>	2013	A multicenter, phase II trial of	38	7 (18)	7 (18)	0
(89)		everolimus in locally advanced				
		or metastatic thyroid cancer of				
		all histologic subtypes;				
		everolimus 10 mg daily orally				
		until unacceptable toxicity or				
		disease progression				
28. Massarweh	2014	A phase II study of combined	31	21 (68)	21 (68)	0
<i>et al</i> (37)		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				
	1					

			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. Mi	ilowsky <i>et</i>	2013	Phase II study of everolimus in	45	29 (64)	29 (64)	0
al (127)			metastatic urothelial cancer				
			all patients received everolimus				
			10 mg orally once daily				
			continuously (one cycle = 4				
			weeks).				
30. Mo	olina <i>et al</i>	2012	Phase 1 Trial of Everolimus Plus	20	17 (85)	17 (85)	0
(38)			Sunitinib in Patients With				
			Metastatic Renal Cell				
			Carcinoma;				
			A: everolimus + sunitnib				
31. Mo	otzer <i>et al</i>	2016	Phase II trial of second-line	133	4 (3)		
(41)			everolimus in patients with				
			metastatic renal cell carcinoma				
			(RECORD-4);				
			everolimus				
32. Mo	otzer <i>et al</i>	2008	Efficacy of everolimus in	269	205 (76)	196 (76)	9 (3)
(74)			advanced renal cell carcinoma: a				
			double-blind, randomised,				
			placebo-controlled phase III				
			trial;				
			everolimus 10 mg once daily				
33. Mo	otzer <i>et al</i>	2015	Lenvatinib, everolimus and the	50	8 (16)	8 (16)	0
(75)			combination in patients with				
			metastatic renal cell carcinoma:				
			a randomised, phase 2, open-				
			label, multicentre trial				
			everolimus 10 mg day				
34. Ou	idard <i>et al</i>	2016	Clinical Benefit of Everolimus	162	28 (17.3)	27 (16.6)	1 (0.6)
(47)			as Second-Line Therapy in				
			Metastatic Renal Cell				
			Carcinoma: The French				
			Retrospective SECTOR Study;				
			everolimus				

35. Panzuto <i>et</i>	2014	Real-World Study of	169	23 (13.6)	23 (13.6)	0
al (49)		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				
36. Quek <i>et al</i>	2011	Combination mTOR and IGF-	21	4 (19.1)	4 (19.1)	0
(92)		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)				
37. Ramalingam	2010	Phase 1 and Pharmacokinetic	24	2 (8.3)	2 (8.3)	0
<i>et al</i> (129)		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				
38. Ray-	2013	Everolimus as second- or third-	43	30 (81)	27 (73)	3 (8)
Coquard <i>et al</i> (51)		line treatment of advanced				
		endometrial cancer:				
		ENDORAD, a phase II trial of				
		GINECO;				
		everolimus 10mg per day until				
		progression or unacceptable				
		toxicity				
39. Robles <i>et al</i>	2016	Everolimus safety and efficacy	19	11 (57.9)	11 (57.9)	0
(106)		for renal angiomyolipomas				

			associated with tuberous				
			sclerosis complex: a Spanish				
			expanded access trial;				
			10 mg everolimus once daily				
40.	Rodrigues et	2015	Phase I combination of	52	7 (13.4)	6 (11.5)	1 (1.9)
al (52)			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.				
41.	Sarkaria et	2011	NCCTG Phase I Trial N057K of	18	16 (89)	16 (89)	0
al (56)			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				
42.	Shoushtari	2016	Phase 2 trial of everolimus	13	8 (58)	8 (58)	0
<i>et al</i> (58)		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 natients				
13	Tobinai <i>et al</i>	2010	Phase I study of the oral	$\Delta \cdot 7$	$\Delta \cdot 1 (14)$	$\Delta 1 (14)$	A 0
(96)	i obinar e <i>i</i> ai	2010	mammalian target of ranamycin	R: 6	$R \cdot 3 (50)$	R = (1+) R = 3 (50)	B O
			inhibitor everolimus (RAD001)	D . 0	D . 5 (50)	D 5 (50)	ЪŪ
			in Japanese patients with				
			rolopsad or refractory non				
			Hodakin lymphome:				
			1000000000000000000000000000000000000				
			mg orally once deily				
			ing orany once daily				

			A: everolimus 5 mg once daily				
			B: everolimus 10 mg once daily				
44. (107)	Wang et al	2014	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-	58	6 (10.3)	4 (6.9)	2 (3.4)
			arm, phase 2 study				
			Everolimus 10 mg/day in adults				
45.	Wolpin et al	2009	Oral mTOR Inhibitor	33	7 (21)	6 (18)	1 (3)
(97)			Everolimus in Patients With				
			Gemcitabine-Refractory				
			Metastatic Pancreatic Cancer;				
			everolimus 10 mg daily				
	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)

Aut	hor/(Refs.)	Year	Study	No. of	No. of	Grade 1/2	Grade 3/4
				patients	cases (%)	cases (%)	cases (%)
1.	Amato et al	2009	A Phase 2 Study With a Daily	39	23 (59)	20 (51.3)	3 (7.7)
(1)			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)				
2.	Bajetta et al	2014	Everolimus in Combination with	50	9 (18)	9 (18)	0
(2)			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				
3.	Barnes et al	2013	Everolimus in combination with	24	6 (25)	6 (25)	0
(77)			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				

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

			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	2012	Everolimus in Postmenopausal	482	13 (2.7)	9 (1.8)	4 (0.9)
al (3)			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)				
5.	Baselga et	2009	Phase II Randomized Study of	137	18 (13.1)	11 (8)	7 (5.1)
al (4)			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				
6.	Besse et al	2014	Phase II study of everolimus-erlotinib	66	14 (21.2)	13 (19.7)	1 (1.5)
(8)			in previously treated patients with				
			advanced non-small-cell lung cancer;				
			everolimus 5 mg/day + erlotinib 150				
			mg/day				
7.	Buzzoni et	2017	Impact of prior therapies on	202	20 (10)	14 (7)	6 (3)
al (9)			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				
8. Chan <i>et al</i>	2013	A Prospective, Phase 1/2 Study of	44	31 (52)	23 (71)	8 (19)
(78)		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				
9. Choueiri <i>et</i>	2015	Cabozantinib versus everolimus in	322	61 (19)	45 (14)	16 (5)
al (11)		advanced renal cell carcinoma				
		everolimus at a dose of 10 mg daily				
10. Chow <i>et al</i>	2016	A Phase 2 Clinical Trial of Everolimus	24	12 (50)	10 (41.6)	2 (8.4)
(12)		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				
11. Chung <i>et al</i>	2016	Phase Ib Trial of mFOLFOX6 and	6	3 (50)	3 (50)	0
(13)		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				
12. Ciruelos <i>et</i>	2017	Safety of everolimus plus exemestane	429	39 (9)	29 (7)	10 (2)
al (101)		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				
13.	Dasari et al	2015	Phase I study of the anti-IGF1R	19	12 (63)	10 (53)	2 (10)
(16)			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.				
14.	Doi et al	2010	Multicenter Phase II Study of	53	2 (3.8)		
(136)			Everolimus in Patients With				
			Previously Treated Metastatic Gastric				
			Cancer;				
			everolimus 10 mg orally daily				
15.	Ellard et al	2009	Randomized Phase II Study	A: 33	A: 17	A: 17 (51.5)	A: 0
(79)			Comparing Two Schedules of	B: 16	(51.5)	B: 8 (50)	B: 2 (12.5)
			Everolimus in Patients With		B: 10		
			Recurrent/Metastatic Breast Cancer:		(62.5)		
			NCIC Clinical Trials Group IND.163				
			randomized phase II study of				
			everolimus 10 mg daily versus 70 mg				
			weekly;				
			A: daily				
			B: weekly				
16.	Fazio <i>et al</i>	2018	Everolimus in advanced, progressive,	62	11 (17.7)	5 (7.9)	6 (9.8)
(10)			well-differentiated, non-functional				
			neuroendocrine tumors: RADIANT-4				
			lung subgroup analysis;				

			everolimus 10 mg/day				
17.	Fazio <i>et al</i>	2013	Everolimus Plus Octreotide Long-	33	5 (15.2)	3 (9.1)	2 (6.1)
(19)			Acting Repeatable in Patients With				
			Advanced Lung Neuroendocrine				
			Tumors;				
			analysis of the Phase 3, Randomized,				
			Placebo-Controlled RADIANT-2				
			Study;				
			everolimus + octreotide				
18.	Finn et al	2013	Phase I study investigating	A: 16	A: 2	1 (6.2)	1 (6.3)
(115)			everolimus combined with sorafenib	B: 14	(12.5)	2 (14.3)	0
			in patients with advanced		B: 2		
			hepatocellular carcinoma		(14.3)		
			A: sorafenib + everolimus 2.5 mg once				
			daily				
			B: sorafenib + everolimus 5 mg once				
			daily				
19.	Fury et al	2012	A phase I study of daily everolimus	30	23 (82)	20 (71)	3 (11)
(80)			plus low-dose weekly cisplatin for				
			patients with advanced solid tumors				
20.	Gadgeel et	2013	Phase I study evaluating the	54	32 (60)	27 (50)	5 (10)
al (81)			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				
21.	Gelsomino	2017	A dose finding and biomarkers	A:12	1 (8.3)	1 (8.3)	0
<i>ei ai</i> (1	19)		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				

22.	Gong et al	2017	Efficacy and safety of everolimus in	70	15 (21.4)	14 (20)	1 (1.4)
(82)			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.				
23.	Gross et al	2018	Safety and Efficacy of Docetaxel,	43	13 (30.2)	13 (30.2)	0
(83)			Bevacizumab, and Everolimus for				
			Castration-resistant Prostate Cancer				
			(CRPC);				
			docetaxel 75 mg/m ² , bevacizumab 15				
			mg/kg, and everolimus 2.5 mg				
24.	Guo et al	2013	Safety and efficacy of everolimus in	64	33 (52)	25 (39)	8 (13)
(20)			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				
25.	Hill et al	2017	A phase I trial of bortezomib in	29	15 (51.7)	13 (44.8)	2 (6.8)
(24)			combination with everolimus for				
			treatment of relapsed/refractory non-				
			Hodgkin lymphoma;				
			A: bortezomib + everolimus				
26.	Jebali et al	2017	Biological toxicities as surrogate	44	24 (54)	18 (40)	6 (14)
(141)			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				
27.	Jerusalem et	2016	Safety of everolimus plus exemestane	2131	265 (12.4)	204 (9.6)	61
al (26)			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.				
		1	1		1		

		expanded- access multicenter trial				
		(BALLET)				
28. Johnston <i>et</i>	2016	The mTORC1 Inhibitor Everolimus	24	1 (4)	0	1 (4)
al (27)		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				
29. Jovanovic et	2017	A randomized phase II neoadjuvant	96	49 (51)	49 (51)	0
al (28)		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				
30. Ju <i>et al</i> (85)	2015	Toxicity and adverse effects of	12	1 (8.3)	1 (8.3)	0
		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				
31. Kim <i>et al</i>	2016	Efficacy and Toxicity of Mammalian	18	2 (11)	2 (11)	0
(88)		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				

32.	Kim et al	2013	A phase I study of everolimus and	15	2 (13.3)	2 (13.3)	0
(30)			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				
33.	Koeberle et	2016	Sorafenib with or without everolimus	59	18 (21)	8 (3)	10 (18)
al (32)			in patients with advanced				
			hepatocellular carcinoma (HCC): a				
			randomized multicenter,				
			multinational phase II trial (SAKK				
			77/08 and SASL 29);				
			sorafenib + everolimus				
34.	Kordes et al	2013	A phase I/II, non-randomized,	31	19 (61)	11 (53)	8 (26)
(33)			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				
35.	Kulke et al	2017	A randomized, open-label, phase 2	A: 78	A: 59	A: 30 (38.4)	A: 29
(35)			study of everolimus in combination	B: 81	(75.6)	B: 13 (16.1)	(37.2)
			with pasireotide LAR or everolimus		B: 22		B: 9 (11.1)
			alone in advanced, well-		(27.2)		
			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)				
36. Lim <i>et al</i>	2013	A multicenter, phase II trial of	38	4 (10)	4 (10)	0
(89)		everolimus in locally advanced or				
		metastatic thyroid cancer of all				
		histologic subtypes;				
		everolimus 10 mg daily orally until				
		unacceptable toxicity or disease				
		progression				
37. Massarweh	2014	A phase II study of combined	31	22 (71)	20	2
<i>et al</i> (37)		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.				
38. Molina <i>et al</i>	2012	Phase 1 Trial of Everolimus Plus	20	18 (90)	18 (90)	0
(38)		Sunitinib in Patients With Metastatic				
		Renal Cell Carcinoma;				
		everolimus + sunitnib				
39. Morrow <i>et</i>	2011	Phase I/II Study of Trastuzumab in	47	22 (65.8)	9 (19.1)	13 (27.6)
al (40)		Combination With Everolimus				
		(RAD001) in Patients With HER2-				
		Overexpressing Metastatic Breast				
		Cancer Who Progressed on				
		Trastuzumab-Based Therapy;				
		everolimus				
40. Moscetti et	2016	Safety analysis, association with	181	44 (24.3)	40 (22.0)	4 (2.3)
al (102)		response and previous treatments of				
		everolimus and exemestane in 181				
		metastatic breast cancer patients: A				
		multicenter Italian experience;				

			everolimus				
41.	Motzer et	2016	Phase II trial of second-line	133	6 (5)		
al (41)			everolimus in patients with metastatic				
			renal cell carcinoma (RECORD-4);				
			everolimus				
42.	Motzer et al	2014	Phase II Randomized Trial	337	51 (15)	30 (9)	21 (6)
(42)			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				
43.	Narayan et	2016	Phase I Trial of Everolimus and	18	1(5.5)	1(5.5)	0
al (43)			Radiation Therapy for Salvage				
			Treatment of Biochemical Recurrence				
			in Prostate Cancer Patients Following				
			Prostatectomy;				
			everolimus + salvage radiation therapy				
44.	Oh et al	2012	Phase 2 Study of Everolimus	34	4 (11.8)	2 (5.9)	2 (5.9)
(45)			Monotherapy in Patients With				
			Nonfunctioning Neuroendocrine				
			Tumors or				
			Pheochromocytomas/Paragangliomas;				
			everolimus was administered daily at a				
			dose of 10 mg for 4 weeks				
45.	Ou et al	2015	SWOG S0722: Phase II study of	59	17 (28.8)	14 (23.7)	3 (5.1)
(91)			mTOR inhibitor everolimus				
			(RAD001) in advanced malignant				
			pleural mesothelioma (MPM);				
			everolimus orally at 10 mg once daily				
			until disease progression or				
			unacceptable toxicity				
46.	Oudard et al	2016	Clinical Benefit of Everolimus as	162	15 (9.3)	10 (6.2)	5 (3.1)
(47)			Second-Line Therapy in Metastatic				
			Renal Cell Carcinoma: The French				
			Retrospective SECTOR Study;				
			everolimus				
47.	Panzuto et	2014	Real-World Study of Everolimus in	169	28 (16.6)	26 (15.4)	2 (1.2)
ui (49)			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				
48.	Pavel et al	2016	safety and QOL in Patients with	123pNET	pNET	pNET	pNET
(50)			Advanced NET in a Phase 3b	117 non	15 (12.2)	7 (5.7)	8 (6.5)
			Expanded Access Study of	pNET	Non	Non pNET	Non pNET
			Everolimus;		pNET	2 (1.7)	4 (3.4)
			everolimus oral administration (two 5		6 (5.1)		
			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				
49.	Powles et al	2016	Randomized Open-Label Phase II	43	9 (21)	5 (12)	4 (9)
(104)			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				
50.	Quek et al	2011	Combination mTOR and IGF-1R	21	13 (61.9)	12 (57.1)	1 (4.8)
(92)			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				
51.	Ramalingam	2010	Phase 1 and Pharmacokinetic Study of	24	12 (50)	11 (45.8)	1 (4.2)
et al (1	29)		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.				
52.	Rathkopf et	2015	Everolimus Combined With Gefitinib	39	35 (90)	32 (82)	3 (8)
al (93)			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)				
53.	Rizzo <i>et al</i>	2015	Everolimus as second-line therapy for	100	20 (20)	18 (18)	2 (2)
(105)			metastatic renal cell carcinoma: a				
			'real-life' study;				
			everolimus 10 mg/day				
54.	Safra <i>et al</i>	2018	Everolimus Plus Letrozole for	72	25 (34.7)	22 (30.5)	3 (4.2)
(53)			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				
55.	Salazar <i>et al</i>	2017	Phase II Study of BEZ235 versus	31	11 (35.5)	9 (29)	2 (6.5)
(54)			Everolimus in Patients with				
			Mammalian Target of Rapamycin				
			Inhibitor-Naive Advanced Pancreatic				
			Neuroendocrine Tumors;				
			everolimus 10 mg once daily				
56.	Sanoff et al	2015	Everolimus and pasireotide for	24	14 (58)	8 (34)	6 (25)
(55)			advanced and metastatic				
			hepatocellular carcinoma;				
			everolimus 7.5 mg PO daily and				
			pasireotide LAR 60 mg IM every 28				
			days				
57.	Shoushtari	2016	Phase 2 trial of everolimus 10mg daily	13	12 (86)	5 (36)	7 (50)
<i>et al</i> (58))		plus pasireotide long-acting release				
			60mg every 28 days enrolling patients;				

			phase 2 trial of everolimus 10mg daily				
			plus pasireotide long-acting release 60				
			mg every 28 days enrolling patients				
58.	Strickler et	2012	Phase I study of bevacizumab,	12	4 (34)	2 (17)	2 (17)
al (95)			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.				
59.	Sun et al	2013	A phase-1b study of everolimus plus	A: 6	A: 6	A: 6 (100)	A: 0
(60)			paclitaxel in patients with small-cell	B: 11	B: 9	B: 9 (81.8)	B: 0
			lung cancer	C: 3	(81.8)	C: 2 (66)	C: 1 (33)
			A: everolimus 2.5 mg		C: 3 (100)		
			B: everolimus 5 mg				
			C: everolimus 10 mg				
60.	Tarhini et al	2010	Phase II Study of Everolimus	40	6 (15)	4 (10)	2 (5)
(61)			(RAD001) in Previously Treated				
			Small Cell Lung Cancer;				
			everolimus 10 mg orally daily until				
			disease progression				
61.	Tobinai et al	2010	Phase I study of the oral mammalian	A: 7	A: 2 (28)	A: 2 (28)	A: 0
(96)			target of rapamycin inhibitor	B: 2	B: 2 (100)	B: 1 (50)	B: 1 (50)
			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				
62.	Vlahovic et	2012	A phase I study of bevacizumab,	32	11 (34)	10 (31)	1 (3)
al (63)			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.				
63.	Werner et al	2013	Phase I study of everolimus and	16	3 (18.7)	3 (18.7)	0
(64)			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				
64.	Wolpin et al	2009	Oral mTOR Inhibitor Everolimus in	33	22 (6)	16 (48)	6 (18)
(97)			Patients With Gemcitabine-Refractory				
			Metastatic Pancreatic Cancer;				
			everolimus 10 mg daily				
65.	Yao et al	2008	Efficacy of RAD001 (Everolimus) and	64	6 (9)		
(140)			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.				
66.	Yao et al	2011	Everolimus for Advanced Pancreatic	204	27 (13)	16 (18)	11 (5)
(65)			Neuroendocrine Tumors;				
			10 mg once daily				
67.	Yee et al	2006	Phase I/II Study of the Mammalian	27	13 (48)	7 (26)	6 (22)
(99)			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				
68	Albiges <i>et</i>	2015	Everolimus for patients with	493	17 (3)		
<i>al</i> (66)	1 1101800 01	-010	metastatic renal cell carcinoma	.,,,	17 (0)		
			refractory to anti-VEGE therapy:				
			Results of a pooled analysis of non-				
			interventional studies metastatic renal				
			coll corcinoma (mPCC) who failed				
			one or two anti VECE thoropios:				
			Everalizeus Everalizeus 10mg/dau				
			until diagona programity				
			unun uisease progression or				
(0)	Andre 1	2014		A-200	25	10 (7)	(1)
69. (67)	Andre et al	2014	Everolimus for women with	A:280	25	19 (7)	6 (2)
(3.)			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				
70. Angelousi <i>et</i>	2017	Sequential Everolimus and Sunitinib	A:20	A: 6 (30)	A: 4 (20)	A: 2 (10)
al (133)		Treatment in Pancreatic Metastatic	B:11	B: 2 (18)	B: 2 (18)	B: 0
		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				

71. Armstrong	2016	Everolimus versus sunitinib for	52	7 (12)	7 (12)	0
<i>et al</i> (68)		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.				
72. Capdevila <i>et</i>	2015	Evaluation of the efficacy and safety	404	7 (1.7)	7 (1.7)	0
al (142)		of lanreotide in combination with				
		targeted therapies in patients with				
		neuroendocrine tumours in clinical				
		practice: a retrospective cross-				
		sectional analysis;				
		everolimus				
73. Cazzaniga	2017	Efficacy and safety of Everolimus and	404	60 (17.7)	57 (16.8)	3 (0.9)
<i>et al</i> (135)		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				
74. Escudier at	2016	Open-label phase 2 trial of first-line	92	13 (14)	11 (12)	2 (2)
al.(70)		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				
75 Ferolla <i>et al</i>	2017	Efficacy and safety of long-acting	42	26 (63)	19 (46)	7 (17)
(71)	2017	pasireotide or everolimus alone or in	12	20 (00)	1) (10)	/ (1/)
		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				
		hu physicians				
		by physicians				

76. Grignani et	2014	Sorafenib and everolimus for patients	38	11 (29)	11 (29)	0
al (72)		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				
77. Grunwald <i>et</i>	2012	An international expanded-access	1367	78 (5.7)	3 (0.2)	75 (5.5)
al (73)		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				
78. Motzer <i>et al</i>	2008	Efficacy of everolimus in advanced	269	135 (50)	104 (38)	31 (12)
(74)		renal cell carcinoma: a double-blind,				
		randomised, placebo-controlled phase				
		III trial				
		everolimus 10 mg once daily				
79. Motzer <i>et al</i>	2015	Lenvatinib, everolimus, and the	50	11(22)	6 (12)	5 (10)
(75)		combination in patients with				
		metastatic renal cell carcinoma: a				
		randomised, phase 2, open-label,				
		multicentre trial;				
		everolimus 10 mg day				
80. Ray-	2013	Everolimus as second- or third-line	43	25 (61)	21 (51)	4 (10)
Coquard <i>et al</i> (51)		treatment of advanced endometrial				
		cancer: ENDORAD, a phase II trial of				
		GINECO;				
		everolimus 10 mg per day until				
		progression or unacceptable toxicity				
81. Wang <i>et al</i>	2014	Everolimus for patients with mantle	58	8 (13.8)	4 (6.9)	4 (6.9)
(107)		cell lymphoma refractory to or				
		intolerant of bortezomib: multicentre,				
		single-arm, phase 2 study;				
		everolimus 10 mg/day in adults				

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	No. of	Grade 1/2	Grade 3/4
			patients	cases (%)	cases (%)	cases (%)
1. Andre <i>et al</i>	2014	Everolimus for women with	275	128 (46)	22 (8)	106 (38)
(67)		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				
2. Andreassen	2016	Everolimus Initiation With Early	A:51	12 (23.6)		
<i>et al</i> (143)		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				

3. Bissler <i>et al</i>	2013	(target6-10ng/ml)withcyclosporinewithdrawalorstandard-exposurecyclosporine.Allpatientsreceivedmycophenolatemofetilandcorticosteroids.Everolimusfor	79	8 (10)	8 (10)	0
(69)		associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial; oral everolimus 10 mg per day				
4. Bissler <i>et al</i> (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 <i>et</i> <i>al</i> (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	2016	A Phase 2 Clinical Trial of	24	17 (70.8)	15 (62.5)	2 (8.3)
(12)			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				
7.	Conconi et	2014	Clinical activity of everolimus in	30	8 (26.6)	6 (20)	2 (6.6)
al (15)			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				
			prograssion				
0	Enzio et al	2012	Everolimus Dlus Ostrootide Long	22	4 (12 1)		
o. (19)	Fazio ei ui	2013	Acting Repeatable in Patients	33	4 (12.1)		
			With Advanced Lung				
			With Advanced Lung				
			Neuroendocrine Tumors Analysis				
			of the Phase 3, Randomized,				
			Placebo-Controlled RADIANT-2				
			Study;				
			everolimus + octreotide				
9. (80)	Fury <i>et al</i>	2012	A phase I study of daily	30	19 (68)	19 (68)	0
(00)			everolimus plus low-dose weekly				
			cisplatin for patients with				
			advanced solid tumors				
10.	Ghobrial <i>et</i>	2010	Phase II Trial of the Oral	50	10 (20)	0	10 (20)
<i>ai</i> (120))		Mammalian Target of Rapamycin				
			Inhibitor Everolimus in Relapsed				
			or Refractory;				
			everolimus 10 mg daily for two				
			cycles				
11.	Ghobrial et	2014	Long-term results of the phase II	60	13 (21)	0	13 (21)
at (138))		trial of the oral mTOR inhibitor				
			everolimus (RAD001) in relapsed				

			or refractory Waldenstrom				
			Macroglobulinemia;				
			everolimus 10 mg/day				
12.	Gong et al	2017	Efficacy and safety of everolimus	70	4 (5.7)	4 (5.7)	0
(82)			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				
13.	Grignani et	2014	Sorafenib and everolimus for	38	12 (32)	11(29)	1 (3)
al (72)			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				
14.	Guo et al	2013	Safety and efficacy of everolimus	64	14 (22)	14 (22)	0
(20)			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				
15.	Hatano et al	2016	Outcomes of everolimus	47	3 (6)	3 (6)	0
(22)			treatment for renal				
			angiomyolipoma associated with				
			tuberous sclerosis complex: A				
			single institution experience in				
			Japan;				
			everolimus 10 mg once a day				
16.	Hatano et al	2017	Intermittent everolimus	26	2 (8)	2 (8)	0
(23)			administration for renal				
			angiomyolipoma associated with				
			tuberous sclerosis complex;				

17.	Hurvitz et al	2013	A phase 2 study of everolimus	55	12 (21.8)	2 (3.6)	10 (18.2)
(25)			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				
18.	Johnston et	2016	The mTORC1 Inhibitor	24	13 (54)	4 (17)	9 (37)
al (27)			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				
19.	Ju et al (85)	2015	Toxicity and adverse effects of	12	0	0	0
			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				
20.	Kanesvaran	2015	A single arm phase 1b study of	4	2 (50)	1 (25)	1 (25)
<i>et al</i> (12	26)		everolimus and sunitinib in				
			patients with advanced renal cell				
			carcinoma (RCC);				
			sunitinib + everolimus				

21. Kim <i>et al</i>	2014	A multicenter phase II study of	34	11 (32.4)	10 (29.5)	1 (2.9)
(29)		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				
22. Massarweh	2014	A phase II study of combined	31	14 (45)	14 (45)	0
<i>et al</i> (37)		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 \pm 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				
23. Milowsky <i>et</i>	2013	Phase II study of everolimus in	45	17 (38)	16 (36)	1 (2)
al (127)		metastatic urothelial cancer;				
		all patients received everolimus				
		10 mg orally once daily				
		continuously (one cycle = 4				
		weeks).				
24. Molina <i>et al</i>	2012	Phase 1 Trial of Everolimus Plus	20	18 (90)	14 (70)	4 (20)
(38)		Sunitinib in Patients With				
		Metastatic Renal Cell Carcinoma;				
		everolimus + sunitnib				
25. Niegisch <i>et</i>	2015	Second-Line Treatment of	27	15 (55.5)	4 (14.8)	11 (40.7)
al (44)		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).				
26. Nozawa <i>et al</i>	2013	Adverse Event Profile and Dose	47	1 (2.1)	1 (2.1)	0
(90)		Modification of Everolimus for				
		Advanced Renal Cell Carcinoma				
		in Real-world Japanese Clinical				
		Practice;				
		everolimus				
27. Ramalingam	2010	Phase 1 and Pharmacokinetic	24	2 (8.3)	0	2 (8.3)
et al (129)		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				
28. Ray-	2013	Everolimus as second- or third-	43	21 (49)	19 (44)	2 (5)
Coquard <i>et al</i> (51)		line treatment of advanced				
		endometrial cancer: ENDORAD,				
		a phase II trial of GINECO;				
		everolimus 10mg per day until				
		progression or unacceptable				
		toxicity				
29. Rodrigues <i>et</i>	2015	Phase I combination of pazopanib	52	9 (17.3)	8 (15.3)	1 (2)
al (52)		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				
30. Ryan <i>et al</i>	2011	A phase II study of everolimus in	19	11 (58)	11 (58)	0
(94)		combination with imatinib for				

			previously treated advanced renal				
			carcinoma;				
			everolimus 2.5 mg p.o. daily and				
			imatinib 600 mg p.o. daily				
31.	Sanoff et al	2015	Everolimus and pasireotide for	24	2 (8)	2 (8)	0
(55)			advanced and metastatic				
			hepatocellular carcinoma;				
			everolimus 7.5 mg PO daily and				
			pasireotide LAR 60 mg IM every				
			28 days.				
32.	Sarkaria <i>et al</i>	2011	NCCTG Phase I Trial N057K of	18	6 (34)	4 (22)	2 (12)
(56)			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				
33.	Shen et al	2014	Phase II Multicentered Study of	40	23 (57.5)	21 (52.5)	2 (5)
(57)			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				

34.	Shoushtari et	2016	Phase 2 trial of everolimus 10mg	13	9 (65)	9 (65)	0
al (58)			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				
35.	Slomovitz et	2010	A Phase 2 Study of the Oral	35	7 (20)	5 (15)	2 (5)
al (59)			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				
36.	Sun et al	2013	A phase-1b study of everolimus	A: 6	5 (83.3)	4 (66.6)	1 (16.7)
(60)			plus	B: 11	8 (72.7)	4 (36.3)	4 (36.3)
			paclitaxel in patients with small-	C: 3	2 (66)	2 (66)	0
			cell lung				
			cancer				
			A: everolimus 2.5 mg				
			B: everolimus 5 mg				
			C: everolimus 10 mg				
37.	Werner et al	2013	Phase I study of everolimus and	16	10 (62.5)	7 (43.7)	3 (18.8)
(64)			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				
38.	Yao et al	2008	Efficacy of RAD001	64	3 (5)		
(140)			(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				

	(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.

patients (%) 1/2	
	3/4
Cases C	Cases
	(%)
1. Albiges et al 2015 Everolimus for patients with 493 57 (12) 37 (8) 20	0 (4)
(66) 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	
2. Amato et al 2009 A Phase 2 Study With a Daily 39 19 (48.6) 12 (30.7) 7 ((17.9)
(1) 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)	
3. Andre et al 2014 Everolimus for women with 280 16 (7) 13 (5) 3	3 (2)
(67) 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				
4. Angelousi <i>et</i>	2017	Sequential Everolimus and	A: 20	A: 5 (25)	A: 4 (20)	A: 1 (5)
al (133)		Sunitinib Treatment in	B: 11	B: 2 (18)	B: 1(9)	B: 1 (9)
		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				

			in the presence of AEs, so that				
			everolimus could be decreased				
			to 5 mg and sunitinib to 25 mg				
			daily, respectively.				
5.	Armstrong et	2016	Everolimus versus sunitinib	52	8 (14)	3 (5)	5 (9)
al (68)			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				
6.	Bachelot et al	2012	Randomized Phase II Trial of	54	9 (17)	8 (15)	1 (2)
(76)			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				

7.	Bajetta et al	2014	Everolimus in Combination	50	3 (6)	3 (6)	0
(2)			with Octreotide Long-Acting				
			Repeatable in a First-Line				
			Setting for Patients With				
			Neuroendocrine Tumors				
			Treatment-naive patients with				
			advanced well-differentiated				
			NETs of gastroenteropancre-				
			atic tract and lung origin				
			received everolimus 10 mg				
			daily, in combination with				
			octreotide LAR 30 mg every				
			28 days				
8.	Barnes et al	2013	Everolimus in combination	24	1 (4.1)	0	1 (4.1)
(77)			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				
9.	Baselga et al	2012	Everolimus in	482	12 (2.4)	9 (1.8)	3 (0.6)
(3)			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)				
10.	Baselga et al	2009	Phase II Randomized Study of	137	4 (2.9)	1 (0.7)	3 (2.2)
(4)			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				
11.	Bennani et al	2017	Efficacy of the oral mTORC1	55	1 (1.8)		
(144)			inhibitor everolimus in				
			relapsed or refractory indolent				
			lymphoma;				
			eligible patients received oral				
			everolimus 10 mg daily on a				
			28 day-cycle schedule				
12.	Buzzoni et al	2017	impact of prior therapies on	202	32 (16)	30 (15)	2 (1)
(9)			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.				
13.	Chan et al	2013	A Prospective, Phase 1/2	43	3 (7)	3 (7)	0
(78)			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				
14.	Choueiri et al	2015	Cabozantinib versus	322	33 (10)	27 (8)	6 (2)
(11)			everolimus in advanced renal				
			cell carcinoma				
			everolimus at a dose of 10 mg				
			daily				
15.	Chow et al	2016	A Phase 2 Clinical Trial of	24	6 (25)	5 (21)	1 (4)
(12)			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				
16.	Ciruelos et al	2017	Safety of everolimus plus	429	60 (14)	47 (11)	13 (3)
(101)			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				

			doses of everolimus (either				
			2x5 mg or 1x10 mg) and				
			exemestane (25 mg) and				
			continued until disease pro-				
			gression, unacceptable toxicity				
17.	Ellard et al	2009	Randomized Phase II Study	A: 33	14 (42.4)	3 (9)	11 (33.3)
(79)			Comparing Two Schedules of	B: 16	3 (18.7)	0	3 (18.7)
			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				
18.	Fazio <i>et al</i>	2018	Everolimus in advanced,	62	8 (12.9)	7 (11.3)	1 (1.6)
(18)			progressive, well-				
			differentiated, non-functional				
			neuroendocrine tumors:				
			RADIANT-4 lung subgroup				
			analysis;				
			everolimus 10 mg/day				
19.	Ferolla et al	2017	Efficacy and safety of long-	42	4 (10)	2 (5)	2 (5)
(71)			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.				
20.	Fogarasi <i>et al</i>	2016	EFFECTS: an expanded	120	5 (4.2)	5 (4.2)	0
(110)			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)				
21.	Gong et al	2017	Efficacy and safety of	70	10 (14.2)	10 (14.2)	0
(82)			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.				
22.	Gross et al	2018	Safety and Efficacy of	43	3 (6.8)	1 (2.3)	2 (4.5)
(83)			Docetaxel, bevacizumab, and				
			Everolimus for Castration-				
			resistant Prostate Cancer				
			(CRPC);				
			docetaxel 75 mg/m^2 ,				
			bevacizumab 15 mg/kg, and				
			everolimus 2.5 mg				
23.	Grunwald et	2012	An international expanded-	1367	83 (6.1)	46 (3.4)	37 (2.7)
al (73)			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				
24.	Guglielmelli	2011	Safety and efficacy of	30	7 (23.3)	0	7 (23.3)
<i>et al</i> (12	24)		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				
25.	Harzstark <i>et</i>	2011	A Phase 1 Study of	20	1 (5)	0	1 (5)
al (84)			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				
26	Iohnston <i>et al</i>	2016	The mTORC1 Inhibitor	24	4 (16)	3(12)	1 (4)
(27)	Johnston et ut	2010	Everolimus Combined with R-	21	(10)	5 (12)	1(1)
			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				
27.	Jovanovic <i>et</i>	2017	A randomized phase II	96	1(1)	1 (1)	0
al (28)			neoadiuvant study of cisplatin.	20	- (1)	- (-)	Ũ
			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				
28.	Kato <i>et al</i>	2013	Efficacy of Everolimus in	19	4 (21)	3 (16)	1 (5)
(86)			Patients with Advanced Renal		× /	\ ~/	<u>\-</u> /
			Cell Carcinoma Refractory or				
			Intolerant to VEGFR-TKIs				
1							

		and Safety Compared with				
		Prior VEGFR-TKI Treatment;				
		everolimus				
29. Kim <i>et al</i>	2018	Clinical outcomes of the	36	4 (11.1)	2 (5.5)	2 (5.6)
(87)		sequential use of pazopanib				
		followed by everolimus for the				
		treatment of metastatic renal				
		cell carcinoma: A multicentre				
		study in Korea;				
		everolimus				
30. Koutsoukos	2017	Real-world experience of	31	6 (19)	4 (13)	2 (6)
<i>et al</i> (34)		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. Kulke <i>et al</i>	2017	A randomized, open-label,	A:78	6 (7.7)	5 (6.4)	1(1.3)
(35)		phase 2 study of everolimus in	B:81	10 (12.3)	9 (11.1)	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)				
32. Kumano <i>et al</i>	2013	Sequential use of mammalian	57	14 (24.6)	9 (15.8)	5 (8.8)
(36)		target of rapamycin inhibitors				
		in patients with metastatic				
		renal cell carcinoma following				
		failure of tyrosine kinase				
		inhibitors;				
		everolimus 10mg/day				
33. Lim <i>et al</i>	2013	A multicenter, phase II trial of	38	4 (10)	3 (8)	1 (2)
(89)		everolimus in locally				
		advanced or metastatic thyroid				

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

		world Japanese Clinical				
		Practice				
40. Panzuto <i>et</i>	al 2014	Real-World Study of	169	32 (18.9)	18 (10.6)	14 (8.3)
(49)		Everolimus in Advanced				
		Progressive Neuroendocrine				
		Tumors				
41. Park <i>et al</i>	2014	Efficacy and Safety of	100	26 (27)	17 (18)	9 (9)
(103)		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				
42. Ray-Coqua	ard 2013	Everolimus as second- or	43	5 (12)	3 (7)	2 (5)
<i>et al</i> (51)		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. Ryan <i>et al</i>	2011	A phase II study of	19	1 (5)	0	1 (5)
(94)		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.				
44. Safra <i>et al</i>	2018	Everolimus Plus Letrozole for	72	9 (12.5)	8 (11.1)	1 (1.4)
(53)		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				
45. Slomovitz	et 2010	A Phase 2 Study of the Oral	35	2 (5)	2 (5)	0
al (59)		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				
46.	Sun <i>et al</i> (60)	2013	A phase-1b study of	A: 6	A: 0	A: 0	A: 0
			everolimus plus	B: 11	B: 1 (9.09)	B: 1	B: 0
			paclitaxel in patients with	C: 3	C: 0	(9.09)	C: 0
			small-cell lung			C: 0	
			cancer				
			A: everolimus 2.5 mg				
			B: everolimus 5 mg				
			C: everolimus 10 mg				
47.	Tarhini <i>et al</i>	2010	Phase II Study of Everolimus	40	3 (7.5)	1 (2.5)	2 (5)
(61)			(RAD001) in Previously				
			Treated Small Cell Lung				
			Cancer;				
			everolimus 10 mg orally daily				
			until disease progression				
48.	Tomita <i>et al</i>	2017	Nivolumab versus everolimus	26	5 (19)	5 (19)	0
(62)			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				
49.	Wang et al	2014	Everolimus for patients with	58	7 (12.1)	4 (6.9)	3 (5.2)
(107)			mantle cell lymphoma				
			refractory to or intolerant of				
			bortezomib: multicentre,				
			single-arm, phase 2 study;				
			Everolimus 10 mg/day in				
			adults				
50.	Yao <i>et al</i>	2008	Efficacy of RAD001	50	1 (2)		
	(140)		(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 (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)

Author/(Refs.)	Year	Study	No. of	No. of cases (%)	Grade 1/2	Grade 3/4
			patients		Cases (%)	Cases (%)
1. Armstrong	2016	Everolimus versus sunitinib for	A: 52	8 (14)	7 (12)	1 (2)
<i>et al</i> (68)		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				
2. Baselga <i>et</i>	2012	Everolimus in Postmenopausal	482	11 (2.2)	10 (2.0)	1 (0.2)
al (3)		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)				
3. Baselga <i>et</i>	2009	Phase II Randomized Study of	137	18 (13.1)	18 (13.1)	0
al (4)		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				
4. Bergmann	2013	Everolimus in Metastatic Renal	195	12 (6)	11 (5.6)	1 (0.4)
<i>et al</i> (145)		Cell Carcinoma after Failure of				
		Initial Vascular Endothelial				
		Growth Factor Receptor-				
		Tyrosine Kinase Inhibitor				

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

		(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 <i>et al</i>	2014	Phase II study of everolimus-	66	13 (19.7)	12 (18.2)	1 (1.5)
(8)		erlotinib in previously treated				
		patients with advanced non-				
		small-cell lung cancer				
		Everolimus				
		erlotinib 150 mg/day				
6. Bissler <i>et</i>	2016	Everolimus for renal	112	12 (10.7)	12 (10.7)	0
al (110)		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				
7. Buzzoni <i>et</i>	2017	impact of prior therapies on	202	26 (13)	24 (12)	2 (1)
al (9)		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.				
8. Campone	2009	Safety and pharmacokinetics of	16	2 (12.5)	2 (12.5)	0
<i>et al</i> (100)		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				
9. Choueiri	2015	Cabozantinib versus	322	47 (15)	46 (14)	1 (<1)
<i>et al</i> (11)		everolimus in advanced renal			~ /	
		cell carcinoma				
		everolimus at a dose of 10 mg				
		daily				
10. Chow <i>et</i>	2016	A Phase 2 Clinical Trial of	24	2 (8.3)	2 (8.3)	0
al (12)		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				
11. Elmadani	2017	EVESOR, a model-based.	26	1 (3.8)	1 (3.8)	0
<i>et al</i> (17)	-017	multiparameter Phase I trial to	-0	1 (010)	1 (0.0)	Ū
		optimize the bene t/toxicity				
		ratio of everolimus and				
		sorafenib:				
		everolimus + sorafenib				
12 Escudier	2016	Open-label phase 2 trial of first-	92	20 (22)	20 (22)	0
at al.(70)	2010	line everolimus monotherapy in	/2	20 (22)	20 (22)	Ū
		patients with papillary				
		metastatic renal cell carcinoma:				
		RAPTOR final analysis:				
		oral everolimus 10 mg once				
		daily until disease progression				
		or unacceptable toxicity				
13. Fazio et al	2018	Everolimus in advanced	62	7 (11 3)	6 (9 7)	1(16)
(18)	2010	progressive well-	02	, (11.3)	5 (2.1)	1 (1.0)
		differentiated non-functional				
		unterentiated, non-tunetional				

		neuroendocrine tumors:				
		RADIANT-4 lung subgroup				
		analysis;				
		everolimus 10 mg/day				
14. Fazio <i>et al</i>	2013	Everolimus Plus Octreotide	33	4 (12.1)		
(19)		Long-Acting Repeatable in				
		Patients With Advanced Lung				
		Neuroendocrine Tumors				
		Analysis of the Phase 3,				
		Randomized, Placebo-				
		Controlled RADIANT-2				
		Study;				
		everolimus + octreotide				
15. Ferolla <i>et</i>	2017	Efficacy and safety of long-	42	2 (5)	2 (5)	0
al (71)		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.				
16. Goldberg	2015	Everolimus for the treatment of	24	3 (13)		
et al.(122)		lymphangioleiomyomatosis: a				
		phase II study				
17. Grignani	2014	Sorafenib and everolimus for	38	5 (13)	5 (13)	0
<i>et al</i> (72)		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				

18. (Guo <i>et al</i>	2013	Safety and efficacy of	64	14 (22)	14 (22)	0
(20)			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				
19.	Hatano <i>et</i>	2016	Outcomes of everolimus	47	3 (6)	3 (6)	0
al (22)			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				
20.	Hatano <i>et</i>	2017	Intermittent everolimus	26	1 (4)	1 (4)	0
al (23)			administration for renal	-			
			angiomvolipoma associated				
			with tuberous sclerosis				
			complex;				
			the dose of everolimus was set				
			at 10 mg once a day				
21.	Kim <i>et al</i>	2016	Efficacy and Toxicity of	20	1 (5)	1 (5)	0
(88)			Mammalian Target Rapamycin		ζ-γ		
			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				
22.	Kulke <i>et</i>	2017	A randomized, open-label,	A: 78	A: 12 (15.4)	A: 12	A: 0
al (35)			phase 2 study of everolimus in	B: 81	B: 18 (22.2)	(15.4)	B: 1 (1.2)

		combination with pasireotide			B: 17 (21)	
		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)				
23. Milowsky	2013	Phase II study of everolimus in	45	2 (4)	2 (4)	0
<i>et al</i> (127)		metastatic urothelial cancer				
		all patients received				
		everolimus; 10 mg orally once				
		daily continuously (one cycle =				
		4 weeks).				
24. Motzer et	2015	Lenvatinib, everolimus, and the	50	7 (14)	7 (14)	0
al (75)		combination in patients with				
		metastatic renal cell carcinoma:				
		a randomised, phase 2, open-				
		label, multicentre trial;				
		everolimus 10 mg day				
25. Ohtsu <i>et</i>	2013	Everolimus for Previously	437	47 (11)	47 (11)	0
<i>al</i> (46)		Treated Advanced Gastric				
		Cancer: Results of the				
		Randomized, Double-Blind,				
		Phase III GRANITE-1 Study;				
		everolimus 10 mg/day				
26. Powles <i>et</i>	2016	Randomized Open-Label Phase	43	7 (16)	7 (16)	0
<i>al</i> (104)		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				
27. Quek <i>et al</i>	2011	Combination mTOR and IGF-	21	3 (14.3)	3 (14.3)	0
(92)		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)				
28. Safra <i>et al</i>	2018	Everolimus Plus Letrozole for	72	12 (16.7)	12 (16.7)	0
(53)		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				
29. Tomita et	2017	Nivolumab versus everolimus	26	6 (23)	6 (23)	0
al (62)		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				
30. Vlahovic	2012	A phase I study of	32	29 (91)	24 (75)	5 (16)
<i>et al</i> (63)		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.				
31. Werner <i>et</i>	2013	Phase I study of everolimus and	16	1 (6.25)	1 (6.25)	0
al (146)		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				

32. Ya (65)	no et al	2011	Everolimus Pancreatic Tumors; everolimus 1	for Neu 0 mg o	Advanced proendocrine	204	30 (15)	30 (15)	0
Tot	tal overall					3,187	386 (12.1)		
Total	l with grac	le				3,130	379 (12.1)	365 (11.6)	14 (0.5)
Total with grade		le	Only everolin	nus at	2.5 mg	-	-	-	-
Total with grade		Only everoli	nus at	5 mg	-	-	-	-	
Total	l with grac	le	Only everolin	nus 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.	No. of cases (%)	Grade 1/2	Grade 3/4
			patients		cases (%)	cases (%)
1. Andre <i>et</i> <i>al</i> (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	patients 280	108 (39)	cases (%) 101 (36)	cases (%) 7 (3)
		lapatinib use				
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 <i>et al</i> (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 Devemonn	2015	Everalimus in matastatio	224	10 (6)	9 (2)	11 (4)
<i>et al</i> (6)	2015	Everonnius in metastatic	334	19(0)	8 (2)	11 (4)
		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				
5. Besse <i>et al</i>	2014	Phase II study of everolimus-	66	10 (15.2)	10 (15.2)	0
(8)		erlotinib in previously				
		treated patients with				
		advanced non-small-cell				
		lung cancer;				
		everolimus 5 mg/day +				
		erlotinib 150 mg/day				
6. Bissler <i>et</i>	2018	The effect of everolimus on	33	6 (18.2)		
al (134)		renal angiomyolipoma in				
		pediatric patients with				
		tuberous sclerosis being				
		treated for subependymal				
		giant cell astrocytoma:				
		Patients were initially				
		randomly assigned to receive				
		everolimus $4.5 \text{ mg/m}^2/\text{day}$				
		(target blood through 5.15				
		mg/dl) or placebo and could				
		aontinuo in on onen labal				
		eutension nhose				
7	2017	extension phase	202	22 (11)	19.70	
/. Buzzoni <i>et</i> $al(9)$	2017	impact of prior therapies on	202	22 (11)	18 (9)	4 (2)
		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.				
8. Campone	2009	Safety and pharmacokinetics	16	2 (12.5)	2 (12.5)	0
<i>et al</i> (100)		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				
9. Choueiri	2015	Cabozantinib versus	322	51 (16)	50 (15)	1 (<1)
<i>et al</i> (11)		everolimus in advanced				
		renal cell carcinoma				
		everolimus at a dose of 10				
		mg daily				
10. De	2012	Everolimus With Reduced	A: 245	A: 32 (13.1)	A: 22 (9)	A: 10 (4.1)
Simone et al (147)		Tacrolimus Improves Renal	B: 231	B: 45 (19.6)	B: 29 (12.6)	B: 16 (7.0)
		Function in De Novo Liver				
		Transplant Recipients: A				
		Randomized Controlled				
		Trial;				
		A: Everolimus + reduced				
		Tacrolimus				
		B: Everolimus w/o				
		tacrolimus				
11. Escudier	2016	Open-label phase 2 trial of	92	27 (29)	27 (29)	0
et al (70)		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				

12.	Fazio <i>et al</i>	2018	Everolimus in advanced,	62	12 (19.4)	10 (16.2)	2 (3.2)
(18)			progressive, well-				
			differentiated, non-				
			functional neuroendocrine				
			tumors: RADIANT-4 lung				
			subgroup analysis;				
			everolimus 10 mg/day				
13.	Ferolla <i>et</i>	2017	Efficacy and safety of long-	42	8 (19)	7 (17)	1 (2)
al (71)			acting pasireotide or		- ()	. ()	- (-)
			everolimus alone or in				
			combination in patients with				
			advanced carcinoids of the				
			lung and thumus (LUNA):				
			lung and urymus (LONA).				
			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				
14.	Finn et al	2013	Phase I study investigating	A: 16	A: 4 (25)	A: 4 (25)	A: 0
(115)			everolimus combined with	B: 14	B: 6 (42.9)	B: 6 (42.9)	B: 0
			sorafenib in patients with				
			advanced hepatocellular				
			carcinoma;				
			A: sorafenib + everolimus				
			2.5 mg once daily				
			B: sorafenib + everolimus 5				
			mg once daily				
15.	Fogarasi	2016	EFFECTS: an expanded	120	18 (15)	17 (14.2)	1 (0.8)
<i>et al</i> (1	16)		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)				
16.	Franz <i>et al</i>	2014	Everolimus for	111	10 (9)	8 (7)	2 (2)
(137)			subependymal giant cell		-~ (~)	- (,)	- (-)
			Sucepena, mai giunt cen				
		astrocytoma in patients with					
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		tuberous sclerosis complex:					
		2-year open-label extension					
		of the randomised EXIST-1					
		study;					
		Everolimus 44-5mg/m ²					
17. Franz <i>et al</i>	2013	Efficacy and safety of	78	17 (22)	12 (16)	5 (6)	
(117)		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					
18. Goldberg	2015	Everolimus for the treatment	24	3 (13)			
<i>et al</i> (122)		of lymphangioleiomyo-					
		matosis: a phase II study					
19. Gong <i>et al</i>	2017	Efficacy and safety of	70	10 (14.2)	10 (14.2)	0	
(82)		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					
20. Guo et al	2013	Safety and efficacy of	64	26 (41)	25 (39)	1 (2)	
(20)		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					
21. Hurvitz et	2013	A phase 2 study of	55	22 (40)	21 (38.2)	1 (1.8)	
al (25)		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.				
22. Jerusalem	2016	Safety of everolimus plus	2,131	299 (14)	289 (13.6)	10 (0.4)
<i>et al</i> (26)		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)				
23. Jozwiak <i>et</i>	2016	Safety of Everolimus in	18	8 (44.4)		
al (125)		Patients Younger than 3				
		Years of Age: Results from				
		EXIST-1, a Randomized,				
		Controlled Clinical Trial;				
		everolimus was initiated at				
		$4.5 \text{ mg/m}^2/\text{day}$ and titrated to				
		blood trough levels of 5-				
		15 ng/ml				
24. Kulke et	2017	A randomized, open-label,	A: 78	A: 15 (19.2)	A: 15 (19.2)	A: 0
<i>ui</i> (55)		phase 2 study of everolimus	B: 81	B: 21 (25.9)	B: 19 (23.2)	B: 2 (2.5)
		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 oral (po)				
25. Motzer	2016	Phase II trial of second-line	133	3 (2)		
<i>et al</i> (41)		everolimus in patients with				
		metastatic renal cell				
		carcinoma (RECORD-4)				
26. Motzer <i>et</i>	2014	Phase II Randomized Trial	337	67 (19.9)	64 (19)	3 (0.9)
al (42)		Comparing Sequential First-				
		Line Everolimus and				
		Second-Line Sunitinib				
		Versus First-Line Sunitinib				
		and Second-Line				
		Everolimus in Patients With				
		Metastatic Renal Cell				
		Carcinoma				
27. Motzer <i>et</i>	2015	Lenvatinib, everolimus, and	50	5 (10)	4 (8)	1 (2)
al (75)		the combination in patients				
		with metastatic renal cell				
		carcinoma: a randomised,				
		phase 2, open-label,				
		multicentre trial				
		everolimus 10 mg day				
28. Ohtsu <i>et al</i>	2013	Everolimus for Previously	437	81 (19)	78 (18)	3 (<1)
(46)		Treated Advanced Gastric				
		Cancer: Results of the				
		Randomized, Double-Blind,				
		Phase III GRANITE-1				
		Study;				
		everolimus 10 mg/day				
29. Pavel <i>et al</i>	2016	Safety and QOL in Patients	pNET	pNET	pNET	pNET
(50)		with Advanced NET in a	123	10 (8.1)	8 (6.5)	2 (1.6)
		Phase 3b Expanded Access	Non	Non pNET	Non pNET	Non pNET
		Study of Everolimus;	pNET	8 (6.8)	8 (6.8)	0

			Everolimus 10 mg/day	117			
30. Rob	oles et 2	2016	Everolimus safety and	19	2 (10.5)	2 (10.5)	0
al (106)			efficacy for renal				
			angiomyolipomas associated				
			with tuberous sclerosis				
			complex: a Spanish				
			expanded access trial;				
			10 mg everolimus once daily				
31. Safr	a <i>et al</i> 2	2018	Everolimus Plus Letrozole	72	19 (26.4)	19 (26.4)	0
(53)			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				
32. Sala	azar <i>et</i> 2	2017	Phase II Study of BEZ235	31	4 (12.9)	4 (12.9)	0
al (54)			versus Everolimus in				
			Patients with Mammalian				
			Target of Rapamycin				
			Inhibitor-Na€ıve Advanced				
			Pancreatic Neuroendocrine				
			Tumors;				
			everolimus 10 mg once daily				
33. Tak	ahashi 2	2013	Efficacy and safety of	61	13 (21.3)		
<i>et al</i> (130)			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)				
34. War	ng et al 2	2014	Everolimus for patients with	58	12 (20.7)	11 (19)	1 (17)
(107)			mantle cell lymphoma				
			refractory to or intolerant of				
			bortezomib: multicentre,				
			single-arm, phase 2 study				

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

Auth	or (Refs.)	Year	Study	No. of	No. of cases (%)	Grade 1/2	Grade 3/4
				patients		cases (%)	cases (%)
1.	Abida et al	2016	Phase I Study of Everolimus in	12	1 (8)		
(109)			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: 5mg				
			QOD, DL2: 5mg daily, DL3:10mg				
			daily) following a standard 3+3 design				
2.	Albiges et	2015	Everolimus for patients with	632	42 (9)		
al (66)			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				
3.	Amato et al	2012	Phase I Trial of Everolimus Plus	A: 6	A: 3 (50)	A: 3 (50)	A: 0
(148)			Sorafenib for Patients with Advanced	B: 6	B: 6 (100)	B: 6 (100)	B: 0
			Renal Cell Cancer;	C: 3	C: 1 (33)	C: 1 (33)	C: 0
			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				
4.	Amato et al	2009	A Phase 2 Study With a Daily	A:39	10 (25.6)	10 (25.6)	0
(1)			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				

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

	1					
		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 <i>et al</i>	2014	Everolimus for women with	A: 280	69 (25)	69 (25)	0
(67)		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				
6. Armstrong	2016	Everolimus versus sunitinib for	52	18 (32)	17 (30)	1(2)
<i>et al</i> (68)		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				
7 Pachalot at	2012	Pandomized Dhase II Trial of	54	24 (44)	22 (40)	2 (4)
<i>al</i> (76)	2012	Everelimus in Combination With	54	24 (44)	22 (40)	2 (4)
		Tempyifan in Datients With Hormone				
		Pagenter Desitive Humon Enidemel				
		Crowth Easter Deserter 2 Nagetive				
		Growin 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 (n 57); tamoxifen plus everolimus				
8. <i>al</i> (2)	Bajetta <i>et</i>	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. (77)	Barnes <i>et al</i>	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	2012	Everolimus in Postmenopausal	482	36 (7.4)	35 (7.2)	1(0.2)
al (3)			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)				
11.	Baselga et	2009	Phase II Randomized Study of	137	28 (20.4)	27 (20.4)	1 (0.7)
al (4)			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				
12.	Bendell et	2015	A phase Ib study of linsitinib (OSI-	18	3 (16)	3 (16)	0
al (5)			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				
13.	Bergmann	2015	Everolimus in metastatic renal cell	334	18 (6)	14 (5)	4 (1)
<i>et al</i> (6)	1		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				
14.	Besse et al	2014	Phase II study of everolimus-erlotinib	66	35 (53.0)	31(46.9)	4 (6.1)
(8)			in previously treated patients with				
			advanced non-small-cell lung cancer;				

		everolimus 5 mg/day + erlotinib 150				
		mg/day				
15. Bissler <i>et al</i>	2018	The effect of everolimus on renal	33	5 (15.2)		
(134)		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				
16. Buzzoni <i>et</i>	2017	Impact of prior therapies on	202	54 (27)	52 (26)	2 (1)
al (9)		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				
17. Castellano	2013	Everolimus Plus Octreotide Long-	19	10 (52.6)		
<i>et at</i> (111)		Acting Repeatable in Patients With				
		Colorectal Neuroendocrine Tumors: A				
		Subgroup Analysis of the Phase III				
		RADIANT-2 Study;				
		everolimus plus octreotide				
18. Cazzaniga	2017	Efficacy and safety of Everolimus and	404	86 (25.4)	77 (22.7)	9 (2.7)
<i>et at</i> (155)		Exemestane in hormone- receptor				
		positive (HRb) human-epidermal-				
		growth-factor negative (HER2)				
		advanced breast cancer patients: New				
		insights beyond clinical trials. The				
		EVA study;				
		everolimus 10 mg/daily				
19. Chan <i>et al</i> (78)	2013	A Prospective, Phase 1/2 Study of	43	23 (54)	21 (49)	2 (5)
(70)		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,				

		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 <i>et</i>	2015	Cabozantinih versus everolimus in	322	89 (28)	87 (27)	2 (<1)
al(11)	2015	advanced renal cell carcinoma	522	09 (20)	07 (27)	2 (<1)
		auvanceu fenar cen carcinoma				
21 Chow at al	2016	A Dhose 2 Clinical Trial of Everalimus	24	5 (20.8)	5 (20.8)	0
$\begin{array}{c} 21. \text{Chow et al} \\ (12) \end{array}$	2010	A Phase 2 Clinical That of Everonimus	24	5 (20.8)	5 (20.8)	0
		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				
$\begin{array}{ccc} 22. & \text{Chung et al} \\ (13) & \end{array}$	2016	Phase Ib Trial of mFOLFOX6 and	6	3 (50)	3 (50)	0
(13)		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				
23. Ciruelos <i>et</i>	2017	Safety of everolimus plus exemestane	429	76 (18)	71 (17)	5 (1)
al (101)		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				
24. Ciunci <i>et al</i>	2014	Phase 1 and Pharmacodynamic Trial	29	10 (34.4)	8 (27.5)	2 (6.9)
(14)		of Everolimus in Combination With				
		Cetuximab in Patients With Advanced				
		Cancer				
25. Conconi <i>et</i>	2014	Clinical activity of everolimus in	30	12 (40)	11 (36.6)	1 (3.4)
al (15)		relapsed/refractory marginal zone B-			()	<u> </u>
1		Treater and a second and a second 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				
26. Dasari <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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	2018	Everolimus in advanced, progressive,	62	22 (35.5)	22 (35.5)	0
(18)			well-differentiated, non-functional				
			neuroendocrine tumors: RADIANT-4				
			lung subgroup analysis;				
			everolimus 10 mg/day				
31.	Fazio et al	2013	Everolimus Plus Octreotide Long-	33	11 (33.3)		
(19)			Acting Repeatable in Patients With				
			Advanced Lung Neuroendocrine				
			Tumors: analysis of the Phase 3,				
			Randomized, Placebo-Controlled				
			RADIANT-2 Study;				
			everolimus + octreotide				
32.	Ferolla et	2017	Efficacy and safety of long-acting	42	14 (33)	11 (26)	3 (7)
al (71)			pasireotide or everolimus alone or in				
` <i>`</i>			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				
33.	Finn <i>et al</i>	2013	Phase I study investigating	A: 16	A: 7 (43.8)	A: 7 (43.8)	A: 0
(115)			everolimus combined with sorafenib	B: 14	B: 7 (50)	B: 7 (50)	B: 0
			in patients with advanced				
			hepatocellular carcinoma				
			A: sorafenib + everolimus 2.5 mg once				
			daily				
			B: sorafenib + everolimus 5 mg once				
			daily				
34.	Franz <i>et al</i>	2013	Efficacy and safety of everolimus for	78	9 (12)	9 (12)	0
(117)			subependymal giant cell astrocytomas				
			associated with tuberous sclerosis				
			complex (EXIST-1): a multicentre,				

		randomised, placebo-controlled phase				
		3 trial;				
		everolimus 4-5mg/m ²				
35. Fury <i>et al</i>	2012	A phase I study of daily everolimus	30	7 (25)	7 (25)	0
(80)		plus low-dose weekly cisplatin for				
		patients with advanced solid tumors;				
		everolimus: escalating doses starting				
		form 2.5 mg/day				
36. Gadgeel <i>et</i>	2013	Phase I study evaluating the	54	19 (36)	17 (31.4)	2(4.6)
<i>al</i> (81)		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				
37. Gelsomino	2017	A dose finding and biomarkers	12	4 (33)	4 (33)	0
<i>et al</i> (119)		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				
38. Goldberg <i>et</i>	2015	Everolimus for the treatment of	24	3 (13)		
al (122)		lymphangioleiomyomatosis: a phase				
		II study				
39. Gong <i>et al</i>	2017	Efficacy and safety of everolimus in	70	13 (18.6)	13 (18.6)	0
(82)		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				

40. Grignani <i>et</i>	2014	Sorafenib and everolimus for patients	38	24 (63)	23 (60)	1 (3)
al (72)		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				
41. Guo et al	2013	Safety and efficacy of everolimus in	64	20 (31)	20 (31)	0
(20)		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				
42. Hainsworth	2010	Phase II Trial of Bevacizumab and	80	37 (47)	35 (44)	2 (3)
<i>et al</i> (21)		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				
43. Harzstark	2011	A Phase 1 Study of Everolimus and	20	13 (65)	11(55)	2 (10)
<i>et al</i> (84)		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				
44. Hatano <i>et</i>	2016	Outcomes of everolimus treatment for	47	5 (11)	5 (11)	0
al (22)		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				
45. Hatano <i>et</i>	2017	Intermittent everolimus	26	3 (12)	3 (12)	0
al (23)		administration for renal				
		angiomyolipoma associated with				
		tuberous sclerosis complex;				
		the dose of everolimus was set at 10				
		mg once a day				

46. Hurvitz <i>et</i>	2013	A phase 2 study of everolimus	55	26	25 (45.5)	1 (1.8)
al (25)		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				
47. Jerusalem	2016	Safety of everolimus plus exemestane	2131	351 (16.5)	331 (15.6)	20 (0.9)
<i>et al</i> (26)		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				
48. Johnston <i>et</i>	2016	The mTORC1 Inhibitor Everolimus	24	6 (25)	5 (21)	1 (4)
al (27)		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				
49. Jovanovic	2017	A randomized phase II neoadjuvant	96	47 (49)	47 (49)	0
<i>et al</i> (28)		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				

50. Ju <i>et al</i> (85) 51. Kanesvaran <i>et al</i> (126)	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 A single arm phase 1b study of everolimus and sunitinib in patients with advanced renal cell carcinoma (RCC); sunitinib + everolimus	12	1 (8.3) 3 (75)	1 (8.3)	0
52. Kato <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et</i>	2016	Sorafenib with or without everolimus	59	16 (27)	16 (27)	0
al (32)		in patients with advanced				
		hepatocellular carcinoma (HCC): a				
		randomized multicenter, multinational				
		phase II trial (SAKK 77/08 and SASL				
		29)·				
		27 , sorafanib \pm everolimus				
57 X 1	2012		A 21		A 10 (50)	A ((10)
37. Kordes <i>et</i> al (33)	2013	A phase I/II, non-randomized,	A 31	A 24 (77)	A 18 (58)	A 6 (19)
		feasibility/safety and efficacy study of	В 9	B 6 (6/)	B 3 (40)	B 3 (27)
		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				
58. Koutsoukos	2017	real-world experience of everolimus	31	2 (7)	2 (6)	0
<i>et al</i> (34)		as second-line treatment in metastatic		- (.)	- (*)	-
		renal cell cancer after failure of				
		pazonanih:				
		the median everolimus deily dose was				
		10 mg (5, 10 mg) while the mean daily				
		10 mg (5-10 mg), while the mean daily				
		dose was 9.3 mg				
59. Kulke <i>et al</i> (35)	2017	A randomized, open-label, phase 2	A: 78	A: 19 (24.4)	A: 19	A: 0
(55)		study of everolimus in combination	B: 81	B: 24 (29.8)	(24.4)	B: 0
		with pasireotide LAR or everolimus			B:	
		alone in advanced, well-differentiated,			24 (29.8)	
		progressive pancreatic neuroendocrine				
		tumors: COOPERATE-2 trial;				
		A: Everolismus + pasireotide LAR				
		B: Everolimus 10 mg/day, per os (po)				
60. Kumano et	2013	Sequential use of mammalian target of	57	13 (22.8)	12 (21)	1(1.8)
al (36)		rapamycin inhibitors in patients with				
		metastatic renal cell carcinoma				
		following failure of tyrosine kinase				
		inhibitors:				
		everolimus 10mg/die				
61 Lim - t - I	2012	A multicenter shace U trial f	20	0 (21)	0 (01)	0
(89)	2013	A municenter, phase in trial of	38	ð (21)	8 (21)	U
		everolimus in locally advanced or				

		metastatic thyroid cancer of all				
		histologic subtypes;				
		everolimus 10 mg daily orally until				
		unacceptable toxicity or disease				
		progression				
62. Macaskill	2011	The mammalian target of rapamycin	31	2 (6.5)		
<i>et al</i> (139)		inhibitor everolimus (RAD001) in				
		early breast cancer: results of a pre-				
		operative study;				
		5 mg RAD001 once daily for 14 days				
		prior to surgery				
63. Massarweh	2014	A phase II study of combined	31	13 (42)	13 (42)	0
<i>et al</i> (37)		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 \pm 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				
64. Milowsky	2013	Phase II study of everolimus in	45	22 (49)	22 (49)	0
<i>et al</i> (127)		metastatic urothelial cancer;				
		all patients received everolimus 10 mg				
		orally once daily continuously (one				
		cycle = 4 weeks).				
65. Molina <i>et</i>	2012	Phase 1 Trial of Everolimus Plus	20	9 (45)	9 (45)	0
<i>al</i> (38)		Sunitinib in Patients With Metastatic				
		Renal Cell Carcinoma				
		A: everolimus + sunitnib				
66. Molina <i>et</i>	2014	A phase 1b clinical trial of the multi-	20	7 (35)		
ui (37)		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				
67. Mo	orrow <i>et</i>	2011	Phase I/II Study of Trastuzumab in	47	9 (19.1)	9 (19.1)	0
al (40)			Combination With Everolimus			~ /	
			(RAD001) in Patients With HER2-				
			Overexpressing Metastatic Breast				
			Cancer Who Progressed on				
			Trastuzumab-Based Therapy				
68. Mo	otzer <i>et</i>	2014	Phase II Randomized Trial Comparing	238	88 (37)	83 (35)	5 (2)
al (42)			Sequential First-Line Everolimus and				
			Second-Line Sunitinib Versus First-				
			Line Sunitinib and Second-Line				
			Everolimus in Patients With				
			Metastatic Renal Cell Carcinoma				
69. Mo	otzer <i>et</i>	2008	Efficacy of everolimus in advanced	269	66 (25)	64 (24)	2 (1)
al (74)			renal cell carcinoma:				
			a double-blind, randomised, placebo-				
			controlled phase III trial;				
			everolimus 10 mg once daily				
70. Mo	otzer <i>et</i>	2015	Lenvatinib, everolimus, and the	50	11 (22)	11 (22)	0
al (75)			combination in patients with				
			metastatic renal cell carcinoma: a				
			randomised, phase 2, open-label,				
			multicentre trial;				
			everolimus 10 mg day				
71. Na	arayan <i>et</i>	2016	Phase I Trial of Everolimus and	18	12 (66.6)	11(61.1)	1 (5.5)
al (43)			Radiation Therapy for Salvage				
			Treatment of Biochemical Recurrence				
			in Prostate Cancer Patients Following				
			Prostatectomy;				
			Everolimus + salvage radiation				
			therapy				
72. Oh	n et al	2012	Phase 2 Study of Everolimus	34	10 (29.4)	10 (29.4)	0
(45)			Monotherapy in Patients With				
			Nonfunctioning Neuroendocrine				
			Tumors or				
			Pheochromocytomas/Paragangliomas;				

		everolimus was administered daily at a				
		dose of 10 mg for 4 weeks.				
73. Ohtsu <i>et al</i>	2013	Everolimus for Previously Treated	437	87 (20)	86 (19.8)	1 (0.2)
(46)		Advanced Gastric Cancer: Results of				
		the Randomized, Double-Blind, Phase				
		III GRANITE-1 Study;				
		everolimus 10 mg/day				
74. Ou <i>et al</i>	2015	SWOG S0722: Phase II study of	59	11 (18.6)	10 (16.9)	1 (1.7)
(91)		mTOR inhibitor everolimus				
		(RAD001) in advanced malignant				
		pleural mesothelioma (MPM);				
		everolimus 10 mg/day				
75. Oudard <i>et</i>	2016	Clinical Benefit of Everolimus as	162	37 (22.8)	34 (21)	3 (1.9)
al (47)		Second-Line Therapy in Metastatic				
		Renal Cell Carcinoma: The French				
		Retrospective SECTOR Study				
76. Park <i>et al</i>	2014	Efficacy and Safety of Everolimus in	100	30 (30)	29 (29)	1 (1)
(103)		Korean Patients with Metastatic Renal				
		Cell Carcinoma Following Treatment				
		Failure with a Vascular Endothelial				
		Growth Factor Receptor-Tyrosine				
		Kinase Inhibitor;				
		everolimus 10 mg/day				
77. Pavel <i>et al</i>	2016	Safety and QOL in Patients with	pNet	pNET	pNET 9	pNET
(50)		Advanced NET in a Phase 3b	123	10 (8.1)	(7.3)	1(0.8)
		Expanded Access Study of	Non	Non pNET	Non pnet	Non pnet
		Everolimus;	pNEt	8 (6.8)	6 (5.1)	2 (1.7)
		everolimus 10 mg/day	117			
78. Powles et	2014	A phase Ib study investigating the	15	3 (20)	2 (14)	1 (7)
<i>ui</i> (126)		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				
79. Powles et	2016	Randomized Open-Label Phase II	43	26 (61)	25 (59)	1 (2)
ut (104)		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				
80. Quek <i>et al</i>	2011	Combination mTOR and IGF-1R	21	8 (38.1)	8 (38.1)	0
(92)		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)				
81. Rathkopf <i>et</i>	2015	Everolimus Combined With Gefitinib	39	21 (54)	21 (54)	0
al (93)		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)				
82. Ray-	2013	Everolimus as second- or third-line	43	21 (49)	19 (44)	2 (5)
Coquard <i>et al</i> (51)		treatment of advanced endometrial				
		cancer: ENDORAD,				
		a phase II trial of GINECO;				
		everolimus 10 mg per day until				
		progression or unacceptable toxicity				
83. Rizzo <i>et al</i>	2015	Everolimus as second-line therapy for	100	3 (3)	3 (3)	0
(105)		metastatic renal cell carcinoma: a				
		'real-life' study;				
		everolimus 10 mg/day				
84. Robles <i>et al</i> (106)	2016	Everolimus safety and efficacy for	19	2 (10.5)	2 (10.5)	0
(100)		renal angiomyolipomas associated				
		with tuberous sclerosis complex: a				
		Spanish expanded access trial;				
		10 mg everolimus once daily				
85. Rodrigues	2015	Phase I combination of pazopanib and	52	3 (5.7)	3 (5.7)	0
ei (1) (12)		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.				
86. Ryan <i>et al</i>	2011	A phase II study of everolimus in	19	5 (26)	5 (27)	0
(94)		combination with imatinib for				
		previously treated advanced renal				
		carcinoma;				
		everolimus 2.5 mg p.o. daily and				
		imatinib 600 mg p.o. daily				
87. Salazar <i>et</i>	2017	Phase II Study of BEZ235 versus	31	13 (41.9)	13 (41.9)	0
al (54)		Everolimus in Patients with				
		Mammalian Target of Rapamycin				
		Inhibitor-Na€ıve Advanced				
		Pancreatic Neuroendocrine Tumors;				
		everolimus 10 mg once daily				
88. Sanoff <i>et al</i>	2015	Everolimus and pasireotide for	24	6 (25)	6 (25)	0
(55)		advanced and metastatic				
		hepatocellular carcinoma;				
		everolimus 7.5 mg PO daily and				
		pasireotide LAR 60 mg IM every 28				
		days				
89. Sarkaria <i>et</i>	2011	NCCTG Phase I Trial N057K of	18	4 (22)	4 (22)	0
<i>ui</i> (50)		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				
90. Shoushtari	2016	Phase 2 trial of everolimus 10mg daily	13	3 (21)	3 (21)	0
<i>ei ui</i> (56)		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				

91. Slomovitz	2010	A Phase 2 Study of the Oral	35	4 (11)	4 (11)	0
et al (59)		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				
92. Strickler <i>et</i>	2012	Phase I study of bevacizumab,	12	3 (25)	3 (25)	0
al (95)		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				
03 Top at al	2017	The mTOP inhibitor everelimus in	37	1 (2 7)		
(131)	2017	apprinting with againiding in	57	1 (2.7)		
		comonation with azactudine in				
		patients with relapsed/refractory acute				
		myeloid leukemia: a phase lb/ll study	- 10			
94. Tarhini <i>et</i>	2010	Phase II Study of Everolimus	40	6 (15)	6 (15)	0
		(RAD001) in Previously Treated				
		Small Cell Lung Cancer;				
		everolimus 10 mg orally daily until				
		disease progression				
95. Vlahovic et	2012	A phase I study of bevacizumab,	32	29 (91)	24 (75)	5 (16)
<i>al</i> (63)		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				
96. Wang <i>et al</i>	2014	Everolimus for patients with mantle	58	16 (27.6)	14 (24.2)	2 (3.4)
(107)		cell lymphoma refractory to or				
		intolerant of bortezomib: multicentre,				
		single-arm, phase 2 study;				
		everolimus 10 mg/day in adults				
97. Werner <i>et</i>	2013	Phase I study of everolimus and	16	4 (25)	4 (25)	0
<i>al</i> (64)		mitomycin C for patients with				
		metastatic esophagogastric				
		adenocarcinoma:				
		oral everolimus (5.7.5 and 10 mg/day).				
		in combination with intravenous				
		$MMC 5 mg/m^2$ avery 3 weeks				
		where s mg/m every s weeks.				

98. (65)	Yao et al	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		e		9,273	2,220 (24)	2,082	138 (1.5)
						(22.5)	
	Total with grade	e	Only everolimus at 2.5 mg	-	-	-	-
	Total with grade	e	Only everolimus at 5 mg	-	-	-	-
	Total with grade	e	Only everolimus at 10 mg	3,794	923 (24.3)	869 (22.9)	54 (1.4)

Table	SXIII. Incide	ence of	stomatitis in selected stud	dies in th	e literature due	e to everolimu	s therapy.
	Author/(Refs.)	Year	Study	No. of	Stomatitis	G1/2	G3/4
				patients	(%)	(%)	(%)
1.	Amato et al	2009	A Phase 2 Study With a	39	12 (30.8)	12 (30.8)	0
	(1)		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)				
2.	Andre et al	2014	Everolimus for women with	280	175 (62)	138 (49)	37 (13)
	(67)		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				
3.	Angelousi et	2017	Sequential everolimus and	A: 20	A: 2 (10)	A: 2 (10)	0
	al		Sunitinib Treatment in	B: 11	B: 1 (9)	B: 1(9)	0
	(133)		Pancreatic Metastatic Well-				
			Differentiated				
			Neuroendocrine Tumours				
			Resistant to Prior				
			Treatments;				

			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	2016	Everolimus versus sunitinib	52	27 (48)	22 (39)	5 (9)
	al		for patients with metastatic				
	(68)		non-clear cell renal cell				
			carcinoma (ASPEN - a				
			multicentre, open-label,				
			randomised phase 2 trial);				
			everolimus orally at 10 mg				
			once daily				
5.	Bajetta et al	2014	Everolimus in Combination	50	31 (62)	26 (52)	5 (10)
	(2)		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				
6.	Baselga et al	2012	Everolimus in	482	56 (11.6)	48 (9.9)	8 (1.6)
	(3)		Postmenopausal Hormone-				
			Receptor–Positive Advanced				

			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 <i>et al</i>	2009	Phase II Randomized Study	137	50 (36.5)	47 (34.3)	3 (2.2)
	(4)		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				
8.	Bergmann et	2015	Everolimus in metastatic	334	22 (7)	18 (81)	4 (18)
	<i>al</i> (6)		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				
9.	Besse et al (8)	2014	Phase II study of	66	48 (72.6)	27 (40.8)	21 (31.8)
			everolimus–erlotinib in				
			previously treated patients				
			with advanced non-small-				
			cell lung cancer;				
			everolimus 5 mg/day +				
			erlotinib 150 mg/day				
10.	Campone et al	2009	Safety and pharmacokinetics	16	6 (37.5)	5 (31.2)	1 (6.2)
	(100)		of paclitaxel and the oral				
			mTOR inhibitor everolimus				
			in advanced solid tumours;				
			dose of everolimus was				
			escalated from 15 to 30 mg				

			and administered with				
			paclitaxel 80 mg m ² on days				
			1, 8, and 15 every 28 days				
11.	Castellano et	2013	Everolimus Plus Octreotide	19	11 (57.9)		
	al (111)		Long-Acting Repeatable in				
			Patients With Colorectal				
			Neuroendocrine Tumors: A				
			Subgroup Analysis of the				
			Phase III RADIANT-2				
			Study; everolimus plus				
			octreotide				
12.	Chan et al	2013	A Prospective, Phase 1/2	43	27 (62)	26 (60)	1 (2)
	(78)		Study of Everolimus and				
			Temozolomide in Patients				
			With Advanced Pancreatic				
			Neuroendocrine Tumor;				
			patients treated with				
			temozolomide at a dose of				
			$150 \text{ mg/m}^2 \text{ per day on days}$				
			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				
13.	Choueiri et al	2015	Cabozantinib versus	322	77 (24)	70 (21.7)	7 (2.2)
	(11)		everolimus in advanced renal				
			cell carcinoma;				
			everolimus at a dose of 10				
			mg daily				
14	Chow at al	2016	A Dhase 2 Clinical Trial of	24	14 (58 2)	10 (41.6)	1 (6 0)
14.	(12)	2010	A Flast 2 Children I Hal Ol Everolimus Dhus	24	14 (30.3)	10 (41.0)	4 (0.9)
	(12)		Everonnius rius				

			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	2016	Phase Ib Trial of	6	4 (66)	2 (33)	2 (33)
	(13)		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.				
16.	Ciruelos et al	2017	Safety of everolimus plus	429	272 (63)	232 (54)	40 (9)
	(101)		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				
17.	Ciunci et al	2014	Phase 1 and	29	4 (13.8)	4 (13.8)	0
	(14)		Pharmacodynamic Trial of				
			Everolimus in Combination				
			With Cetuximab in Patients				
			With Advanced Cancer;				
			not reported				
18.	Colon-Otero	2017	Phase 2 trial of everolimus	19	2 (10.5)	0	2 (10.5)
	et al (149)		and letrozole in relapsed				
			estrogen receptor-positive				
			high-grade ovarian cancer				
			Patients received oral				

			everolimus 10 mg daily and				
			letrozole 2.5 mg daily				
19.	Courtney et al	2015	A Phase I Study of	18	5 (27.7)	5 (27.7)	0
	(150)		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				
20.	Deenen et al	2012	Phase I and pharmacokinetic	18	9 (50)	9 (50)	0
	(151)		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				
21.	Doi et al	2010	Multicenter Phase II Study of	53	3 (5.7)		
	(136)		Everolimus in Patients With				
			Previously Treated				
			Metastatic Gastric Cancer;				
			everolimus 10 mg orally				
			daily				
22.	Elmadani et al	2017	EVESOR, a model-based,	26	6 (23.1)	6 (23.1)	0
	(17)		multiparameter, Phase I trial				
			to optimize the				
			benefit/toxicity ratio of				
			everolimus and sorafenib				
23.	Escudier at	2016	Open-label phase 2 trial of	92	23 (25)	23 (25)	0
	al.(70)		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				
24.	Fazio <i>et al</i>	2013	Everolimus Plus Octreotide	33	3 (9.1)		
	(19)		Long-Acting Repeatable in				
			Patients With Advanced				
			Lung Neuroendocrine				
			Tumors				
			Analysis of the Phase 3,				
			Randomized, Placebo-				
			Controlled RADIANT-2				
			Study				
			everolimus + octreotide				
25.	Ferolla et al	2017	Efficacy and safety of long-	42	30 (72)	26 (62)	4 (10)
	(71)		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				
26.	Finn et al	2013	Phase I study investigating	A:16	A: 6 (37.5)	A: 6 (37.5)	A: 0
	(115)		everolimus combined with	B:14	B: 6 (42.9)	B: 5 (35.8)	B: 1 (7.1)
			sorafenib in patients with				
			advanced hepatocellular				
			carcinoma				
			A: sorafenib +everolimus				
			2.5 mg once daily				
			B: sorafenib + everolimus 5				
			mg once daily				

27.	Fury <i>et al</i> (80)	2012	A phase I study of daily	30	11 (39)	11 (39)	0
			everolimus plus low-dose				
			weekly cisplatin for patients				
			with advanced solid tumors;				
			not reported				
28.	Ghobrial et al	2010	Phase II Trial of the Oral	50	4 (8)	0	4 (8)
	(120)		Mammalian Target of				
			Rapamycin Inhibitor				
			Everolimus in Relapsed or				
			Refractory Waldenstrom				
			Macroglobulinemia;				
			everolimus 10 mg daily for				
			two cycles				
29.	Goldberg et	2015	Everolimus for the treatment	24	18 (75)		
	al.(122)		of				
			lymphangioleiomyomatosis:				
			a phase II study;				
			not reported				
30.	Gong et al	2017	Efficacy and safety of	70	40 (57.1)	34 (47.8)	6 (9.3)
	(82)		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.				
31.	Grignani et al	2015	Sorafenib and everolimus for	38	20 (52)	18 (37)	2 (5)
	(72)		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				
32.	Hainsworth <i>et</i>	2010	Phase II Trial of	80	48 (60)	36 (45)	12 (15)
	al (21)		Bevacizumab and				

			Everolimus in Patients With				
			Advanced Renal Cell				
			Carcinoma:				
			all patients received				
			bevacizumah 10 mg/kg				
			intravanously avory 2 wooks				
			and everalimus 10 mg arally				
			and everonmus 10 mg orany				
			daily				
33.	Hatano <i>et al</i>	2016	Outcomes of everolimus	47	43 (91)	42 (97.6)	1 (2.3)
	(22)		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				
34.	Hatano <i>et al</i>	2017	Intermittent everolimus	26	23 (88)	22 (84)	1 (4)
	(23)		administration for renal				
			angiomyolipoma associated				
			with tuberous sclerosis				
			complex;				
			the dose of everolimus was				
			set at 10 mg once a day				
35.	Hurvitz <i>et al</i>	2013	A phase 2 study of	55	42 (76.3)	31 (56.3)	11 (20)
	(25)		everolimus combined with				
			trastuzumab and paclitaxel in				
			patients with HER2-				
			overexpressing advanced				
			breast cancer that progressed				
			during prior treatury				
			toware therease everelimus				
			10 mg/dec in combination				
			no ing/day in combination				
			with pacificatel (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				

36.	Jerusalem et	2016	Safety of everolimus plus	2131	1126 (52.8)	926 (43.4)	200 (9.4)
	al (26)		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				
37.	Jovanovic et	2017	A randomized phase II	96	37 (39)	37 (39)	0
	al (28)		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				
38.	Jozwiak et al	2016	Safety of Everolimus in	18	12 (66.7)		
	(125)		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				
39.	Kato <i>et al</i> (86)	2014	Efficacy of Everolimus in	19	7 (37)	6 (32)	1 (5)
			Patients with Advanced				
			Renal Cell Carcinoma				
			Refractory or Intolerant to				
			VEGFR-TKIs and Safety				

			Compared with Prior				
			VEGFR-TKI Treatment;				
			not reported				
40.	Kim <i>et al</i> (29)	2014	A multicenter phase II study	34	27 (79.4)	26 (96.2)	1 (2.9)
			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				
41.	Kim <i>et al</i> (87)	2018	Clinical outcomes of the	36	15 (41.7)	14 (38.9)	1 (2.8)
			sequential use of pazopanib				
			followed by everolimus for				
			the treatment of metastatic				
			renal cell carcinoma: A				
			multicentre study in Korea				
42.	Koutsoukos et	2017	real-world experience of	31	8 (26)	5 (16)	3 (10)
	al (34)		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				
43.	Kulke et al	2017	A randomized, open-label,	A:78	A: 46 (59)	A: 39 (50)	A: 7 (9)
	(35)		phase 2 study of everolimus	B: 81	B: 51 (63)	B: 44 (54.4)	B: 7 (8.6)
			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				
			Patients were randomized				
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			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	2013	Sequential use of	57	17 (29.8)	14 (82.35)	3 (5.3)
	(36)		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)				
45.	Moscetti et al	2016	Safety analysis, association	181	115 (63.5)	100 (55.2)	15 (8.3)
	(102)		with response and previous				
			treatments of everolimus and				
			exemestane in 181 metastatic				
			breast cancer patients: A				
			multicenter Italian				
			experience;				
			not reported				
46.	Motzer et al	2016	Phase II trial of second-line	133	7 (5.26)		
	(41)		everolimus in patients with				
			metastatic renal cell				
			carcinoma (RECORD-4);				
			not reported				
47.	Motzer et al	2014	Phase II Randomized Trial	337	151 (44.8)	136 (40.3)	15 (4.5)
	(42)		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				

			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	2008	Efficacy of everolimus in	269	107 (40)	98 (36.43)	9 (3.34)
	(74)		advanced renal cell				
			carcinoma: a double-blind,				
			randomised, placebo-				
			controlled phase III trial;				
			ever;olimus 10 mg once				
			daily				
49.	Motzer et al	2015	Lenvatinib, everolimus, and	50	21 (42)	20 (40)	1 (2)
	(75)		the combination in patients				
			with metastatic renal cell				
			carcinoma: a randomised,				
			phase 2, open-label,				
			multicentre trial; everolimus				
			10 mg day				
50.	Oh et al (45)	2012	Phase 2 Study of Everolimus	34	6 (17.6)	4 (11.7)	2 (5.9)
			Monotherapy in Patients				
			With Nonfunctioning				
			neuroendocrine Tumors or				
			Pheochromocytomas/Paraga				
			ngliomas; everolimus was				
			administered daily at a dose				
			of 10 mg for 4 weeks.				
51.	Ohtsu <i>et al</i>	2013	Everolimus for Previously	437	174 (40)	154 (35)	20 (5)
	(46)		Treated Advanced Gastric				
			Cancer: Results of the				
			Randomized, Double-Blind,				
			Phase III GRANITE-1				
			Study;				
			everolimus 10 mg/day				
52.	Ohyama et al	2017	Efficacy and safety of	53	26 (49.1)	22 (41.6)	4 (7.5)
	(48)		sequential use of everolimus				
			in Japanese patients with				
			advanced renal cell				
			carcinoma after failure of				

			first-line treatment with				
			vascular endothelial growth				
			factor receptor tyrosine				
			kinase inhibitor: a				
			multicenter phase II clinical				
			trial;				
			not reported				
53.	Panzuto <i>et al</i>	2014	Real-World Study of	169	37 (21.9)	33 (19.6)	4 (2.3)
	(49)		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				
54.	Park <i>et al</i>	2014	Efficacy and Safety of	100	42 (44)	36 (38)	6 (6)
	(103)		Everolimus in Korean			(/	
	()		Patients with Metastatic				
			Renal Cell Carcinoma				
			Following Treatment Failure				
			with a Vascular Endothelial				
			Growth Factor Receptor-				
			Tyrosine Kinase Inhibitor				
			not reported				
55	Pavel <i>et al</i>	2016	safety and OOL in Patients	123	29 (23.6)	23 (18 7)	6 (4 9)
	(50)	2010	with Advanced NET in a	123	29 (23.6)	23 (10.7)	0(11))
	(50)		Phase 3h Expanded Access				
			Study of Everolimus:				
			not reported				
56	Quek et al	2011	Combination mTOR and	21	21 (100)	18 (85 7)	3 (14 3)
50.	(92)	2011	IGE-1R Inhibition. Phase I	21	21 (100)	10 (05.7)	5 (11.5)
	()2)		Trial of Everolimus and				
			Figitumumab in Patients				
			with Advanced Sarcomas				
			and Other Solid Tumors				
			figitumumah (20 mg/kg IV				
			every 21 days) with full dose				
			everolimus (10 mg orally				
			once daily)				
			once duriy)				

57.	Safra <i>et al</i>	2018	Everolimus Plus Letrozole	72	39 (54.2)	18 (45.9)	21 (8.3)
	(53)		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				
58.	Salazar <i>et al</i>	2017	Phase II Study of BEZ235	31	20 (64.5)	18 (58)	2 (6.5)
	(54)		versus Everolimus in				
			Patients with Mammalian				
			Target of Rapamycin				
			Inhibitor-Na€ıve Advanced				
			Pancreatic Neuroendocrine				
			Tumors;				
			everolimus 10 mg once daily				
59.	Sarkaria <i>et al</i>	2011	NCCTG Phase I Trial	18	11 (61.1)	11 (61.1)	0
	(56)		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				
60.	Strickler et al	2012	Phase I study of	12	4 (33)	3 (25)	1 (8)
	(95)		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.				

61.	Sun <i>et al</i> (60)	2013	A phase-1b study of	A: 6	A: 2 (33.3)	A: 2 (33.3)	0
			everolimus plus paclitaxel in	B: 11	B: 5 (45.5)	B: 5 (45.5)	0
			patients with small-cell lung	C: 3	C: 1 (33.3)	C: 1 (33.3)	0
			Cancer;				
			A: everolimus 2.5 mg				
			B: everolimus 5 mg				
			C: everolimus 10 mg				
62.	Takahashi <i>et</i>	2013	Efficacy and safety of	61	14 (23)		
	al (130)		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)				
63.	Tobinai et al	2010	Phase I study of the oral	13	7 (53.7)	7 (53.7)	0
	(96)		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.				
64.	Vlahovic et al	2012	A phase I study of	32	24 (76)	20 (63)	4 (13)
	(63)		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				
65.	Wang et al	2014	Everolimus for patients with	58	12 (20.7)	11 (19)	1 (1.7)
	(107)		mantle cell lymphoma				
			refractory to or intolerant of				
			bortezomib: multicentre,				
			single-arm, phase 2 study;				
			not reported				

66.	Werner et al	2013	Phase I study of everolimus	16	9 (56.25)	8 (50)	1 (6.25)
	(64)		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.				
67.	Wolpin <i>et al</i>	2009	Oral mTOR Inhibitor	33	10 (30)	9 (27)	1 (3)
	(97)		Everolimus in Patients With				
			Gemcitabine-Refractory				
			Metastatic Pancreatic				
			Cancer; everolimus 10 mg				
			daily				
68.	Yao <i>et al</i>	2008	Efficacy of everolimus and	64	6 (10)		
	(140)		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.				
69.	Yao <i>et al</i> (65)	2011	Everolimus for Advanced	204	131 (64)	117 (57)	14 (7)
			Pancreatic Neuroendocrine				
			Tumors;				
			everolimus 10 mg once daily				
70.	Yee <i>et al</i> (99)	2006	Phase I/II Study of	27	10 (37)	10 (37)	
			everolimus in patients with				
			relapsed or refractory				
			hematologic malignancies;				
			Not reported				
	Total over all		1	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.

Auth	nor/(Refs.)	Year	Study	No.	No. of	Grade 1/2	Grade 3/4
				of	cases (%)	Cases (%)	Cases (%)
				patien			
				ts			
1.	Abida et al	2016	Phase I Study of Everolimus in	12	3 (25)		
(109)			Combination with Gemcitabine and Split-				
			Dose Cisplatin in Advanced Urothelial				
			Carcinoma;				
			gemcitabine 800 mg/m ² and cisplatin				
			35mg/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				
2.	Amato et	2009	A Phase 2 Study With a Daily Regimen of	39	39 (100)	36 (92.3)	3 (7.7)
al (1)			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)				
3.	Andre et al	2014	Everolimus for women with trastuzumab-	280	40 (15)	30 (11)	10 (4)
(67)			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				

4. Armstrong et al (68)	2016	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 Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open	52	7 (13)	6 (11)	1 (2)
		label, randomised phase 2 trial Everolimus orally at 10 mg once daily				
5. Bajetta <i>et</i> <i>al</i> (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 <i>et</i> <i>al</i> (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. Bas	elga <i>et</i>	2012	Everolimus in Postmenopausal Hormone-	482	12 (2.4)	9 (1.8)	3 (0.6)
al (3)			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. Bas	elga <i>et</i>	2009	Phase II Randomized Study of	137	25 (18.2)	23 (16.7)	2 (1.5)
al (4)			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				
9. Ben	ndell <i>et</i>	2015	A phase Ib study of linsitinib (OSI-906),	18	3 (15)	1 (5)	2 (10)
al (5)			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				
10. Bes	se <i>et al</i>	2013	A phase Ib dose-escalation study of	40	11 (28)		
(7)			everolimus combined with cisplatin and				
			etoposide as first-line therapy in patients				
			with extensive-stage small-cell lung				
			cancer				
11. Can	npone	2009	Safety and pharmacokinetics of paclitaxel	16	4 (25)	3 (18.7)	1 (6.2)
et al (100)			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				
12. Cazzaniga	2017	Efficacy and safety of Everolimus and	404	35 (10.3)	31 (9.1)	4 (1.2)
<i>et al</i> (135)		Exemestane in hormone- receptor				
		positive (HRb) human-epidermal-				
		growth-factor negative (HER2) advanced				
		breast cancer patients: New insights				
		beyond clinical trials. The EVA study;				
		everolimus 10 or 5 mg/day				
13. Chocteau-	2015	Efficacy and tolerance of everolimus in	123	123 (9.8)	121 (98.4)	2 (1.6)
Bouju et al (10)		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.				
14. Chow <i>et al</i>	2016	A Phase 2 Clinical Trial of Everolimus	24	8 (33)	7 (29.1)	1 (4.1)
(12)		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				
15. Ciunci <i>et al</i>	2014	Phase 1 and Pharmacodynamic Trial of	29	4 (13.8)	2 (6.9)	2 (6.9)
(14)		Everolimus in Combination With				
		Cetuximab in Patients With Advanced				
		Cancer				
16. Conconi <i>et</i>	2014	Clinical activity of everolimus in	30	28 (93.3)	23 (76.6)	5 (16.6)
al (15)		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				
17. Dasari <i>et al</i>	2015	Phase I study of the anti-IGF1R antibody	19	10 (53)	10 (53)	0
		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				
18. Elmadani	2017	EVESOR, a model-based,	26	2 (7.7)	2 (7.7)	0
<i>et al</i> (17)		multiparameter, Phase I trial to optimize				
		the bene t/toxicity ratio of everolimus				
		and sorafenib;				
		everolimus + sorafenib				
19. Ellard <i>et al</i>	2009	Randomized Phase II Study Comparing	A: 33	A: 20	A: 0	A: 20 (60.6)
(79)		Two Schedules of Everolimus in Patients	B: 16	(60.6)	B: 0	B: 7 (43.7)
		With Recurrent/Metastatic Breast Cancer:		B: 7 (43.7)		
		NCIC Clinical Trials Group IND.163				
		randomized phase II study of everolimus				
		10 mg daily versus 70 mg weekly				
		A: daily				
		B: weekly				
20. Escudier at	2016	Open-label phase 2 trial of first-line	92	10 (11)	10 (11)	0
al.(70)		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				
21. Fazio $et al$	2013	Everolimus Plus Octreotide Long-Acting	33	6 (18.2)	3 (9.1)	3 (9.1)
(19)		Repeatable in Patients With Advanced				
		Lung Neuroendocrine Tumors Analysis				
		of the Phase 3, Randomized, Placebo-				
		Controlled RADIANT-2 Study				
		A:everolimus + octreotide				
22. Ferolla et	2017	Efficacy and safety of long-acting	42	10 (23)	9 (21)	1 (2)
ui (11)		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				
23. Finn <i>et al</i>	2013	Phase I study investigating everolimus	A: 16	A: 7 (43.8)	A: 6 (37.5)	A: 1 (6.3)
(115)		combined with sorafenib in patients with	B: 14	B: 8 (57.1)	B: 2 (24.2)	B: 6 (42.9)
		advanced hepatocellular carcinoma;				
		A: sorafenib +everolimus 2.5 mg once				
		daily				
		B: sorafenib + everolimus 5 mg once				
		daily				
24. Fury <i>et al</i>	2012	A phase I study of daily everolimus plus	30	18 (64)	18 (64)	0
(80)		low-dose weekly cisplatin for patients				
		with advanced solid tumors				
25. Ghobrial <i>et</i>	2014	Long-term results of the phase II trial of	60	12 (20)	0	12 (20)
al (138)		the oral mTOR inhibitor everolimus				
		(RAD001) in relapsed or refractory				
		Waldenstrom Macroglobulinemia;				
		everolimus 10 mg/day				
26. Glanville <i>et</i>	2015	Three-year results of an investigator-	84	12 (7)		
al (121)		driven multicenter, international,				
		randomized open-label de novo trial to				
		prevent BOS after lung transplantation				
27. Gong <i>et al</i>	2017	Efficacy and safety of everolimus in	70	7 (10)	3 (4.3)	4 (5.7)
(82)		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.				
28. Grignani et	2014	Sorafenib and everolimus for patients	38	22 (58)	18 (47)	4 (11)
al (72)		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				

29. Hainsworth	2010	Phase II Trial of Bevacizumab and	80	32 (40)	31 (39)	1 (1)
<i>et al</i> (21)		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				
30. Hill <i>et al</i>	2017	A phase I trial of bortezomib in	29	47	41	6
(24)		combination with everolimus for				
		treatment of relapsed/refractory non-				
		Hodgkin lymphoma;				
		A: bortezomib + everolimus				
31. Hurvitz <i>et</i>	2013	A phase 2 study of everolimus combined	55	10 (18.2)	6 (10.9)	4 (7.3)
al (25)		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				
32 Johnston <i>et</i>	2016	The mTORC1 Inhibitor Everolimus	24	21 (89)	15 (63)	6 (26)
al (27)	2010	Combined with R-CHOP-21 for New	24	21 (07)	15 (05)	0 (20)
		Untreated Diffuse Large B Cell				
		Lymphoma (DLBCL): Safety and				
		Efficacy Results of a Phase I and				
		Encacy Results of a Thase T and Eastibility Trial NCCTG 1085 (Alliance):				
		everolimus 10 mg days 1-10 or 1-14 in				
		combination with R-CHOP-21 for 6				
		cycles				
33 Iovanovic	2017	A randomized phase II neoadiuvant study	96	38 (40)	38 (40)	0
<i>et al</i> (28)	2017	of cisplatin paclitaxel with or without	20	55 (40)	55 (40)	
		everolimus in patients with stage II/III				
		triple-negative breast cancer (TNRC).				
		Responses and long-term outcome				
		correlated with increased frequency of				
		DNA damage response gene mutations				
		TNRC subtype AP status and Ki67.				
		TINDE SUBTYPE, AK STATUS and KIO/;				

			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	2015	Toxicity and adverse effects of	12	0	0	0
(85)			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				
35.	Kanesvaran	2015	A single arm phase 1b study of	4	4 (100)	3 (75)	1 (5)
<i>et al</i> (1	26)		everolimus and sunitinib in patients with				
			advanced renal cell carcinoma (RCC);				
			sunitinib + everolimus				
36.	Kim et al	2014	A multicenter phase II study of	34	4 (11.8)	4 (11.8)	0
(29)			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				
37.	Kim et al	2018	Clinical outcomes of the sequential use of	36	9 (25)	9 (25)	0
(87)			pazopanib followed by meverolimus for				
			the treatment of metastatic renal cell				
			carcinoma: A multicentre study in Korea				
38.	Kim et al	2013	A phase I study of everolimus and CHOP	15	13 (86.6)	8 (53.3)	5 (33.3)
(30)			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				
39.	Knox et al	2017	Final overall survival analysis for the	238	3		
(31)			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				
40. Koeberle <i>et</i>	2016	Sorafenib with or without everolimus in	59	15 (25)	4 (6)	11 (19)
al (32)		patients with advanced hepatocellular				
		carcinoma (HCC): a randomized				
		multicenter, multinational phase II trial				
		(SAKK 77/08 and SASL 29)				
		Sorafenib + everolimus				
41. Kumano <i>et</i>	2013	Sequential use of mammalian target of	57	9 (15.8)	8 (14)	1 (1.8)
al (36)		rapamycin inhibitors in patients with				
		metastatic renal cell carcinoma following				
		failure of tyrosine kinase inhibitors;				
		everolimus 10 mg/day				
42. Lim <i>et al</i>	2013	A multicenter, phase II trial of everolimus	38	1 (2)	1 (2)	0
(89)		in locally advanced or metastatic thyroid				
		cancer of all histologic subtypes;				
		everolimus 10 mg daily orally until				
		unacceptable toxicity or disease				
		progression				
43. Massarweh	2014	A phase II study of combined fulvestrant	31	17 (55)	17 (55)	0
<i>et al</i> (37)		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 \pm 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				
44. Milowsky	2013	Phase II study of everolimus in metastatic	45	21 (47)	21 (47)	0
<i>et al</i> (127)		urothelial cancer;				
		all patients received everolimus 10 mg				
		orally once daily continuously (one cycle				
		= 4 weeks)				

45.	Molina et	2012	Phase 1 Trial of Everolimus Plus	20	18 (90)	14 (70)	4 (20)
al (38)			Sunitinib in Patients With Metastatic				
			Renal Cell Carcinoma;				
			A: everolimus + sunitnib				
46.	Morrow et	2011	Phase I/II Study of Trastuzumab in	47	10 (21.2)	6 (12.7)	4 (8.5)
al (40)			Combination With Everolimus				
			(RAD001) in Patients With HER2-				
			Overexpressing Metastatic Breast Cancer				
			Who Progressed on Trastuzumab-Based				
			Therapy				
47.	Motzer et	2014	Phase II Randomized Trial Comparing	337	12 (3.6)	4 (1.2)	8 (4.4)
al (42)			Sequential First-Line Everolimus and				
			Second-Line Sunitinib Versus First-Line				
			Sunitinib and Second-Line Everolimus in				
			Patients With Metastatic Renal Cell				
			Carcinoma				
48.	Narayan <i>et</i>	2016	Phase I Trial of Everolimus and Radiation	18	2 (11.1)	1 (5.5)	1 (5.5)
al (43)	2		Therapy for Salvage Treatment of		~ /	~ /	~ /
			Biochemical Recurrence in Prostate				
			Cancer Patients Following Prostatectomy				
49.	Nozawa <i>et</i>	2013	Adverse Event Profile and Dose	47	3 (6.3)	2 (4.2)	1 (2.1)
al (90)			Modification of Everolimus for Advanced		~ /	~ /	~ /
			Renal Cell Carcinoma in Real-world				
			Japanese Clinical Practice				
50.	Oh et al	2012	Phase 2 Study of Everolimus	34	5 (14.7)	0	5 (14.7)
(45)			Monotherapy in Patients With				
			Nonfunctioning Neuroendocrine Tumors				
			or Pheochromocytomas/Paragangliomas;				
			everolimus was administered daily at a				
			dose of 10 mg for 4 weeks				
51.	Ohtsu <i>et al</i>	2013	Everolimus for Previously Treated	437	80 (18)	58 (13)	22 (5)
(46)			Advanced Gastric Cancer: Results of the				~ /
			Randomized, Double-Blind, Phase III				
			GRANITE-1 Study;				
			everolimus 10 mg/day				
52.	Oudard <i>et</i>	2016	Clinical Benefit of Everolimus as Second-	162	12 (7.4)	11 (6.8)	1 (0.6)
al (47)		_	Line Therapy in Metastatic Renal Cell		、 /	~ - /	
			Carcinoma: The French Retrospective				
			SECTOR Study				
1		1	5				

53. Panzuto <i>et</i>	2014	Real-World Study of Everolimus in	169	37 (21.9)	24 (14.1)	13 (7.8)
al (49)		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				
54. Park <i>et al</i>	2014	Efficacy and Safety of Everolimus in	100	33 (35)	30 (32)	3 (3)
(103)		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)				
55. Pavel <i>et al</i>	2016	Safety and QOL in Patients with	pNET	pNET	pNET	pNET 1
(50)		Advanced NET in a Phase 3b Expanded	123	12 (9.8)	11 (9)	(0.8)
		Access Study of Everolimus;	Non	Non pNET	Non pNET	Non pNET
		everolimus (10 mg/day)	pNET	6 (5.1)	4 (3.7)	2 (1.4)
			117			
56. Rathkopf <i>et</i>	2015	Everolimus Combined With Gefitinib in	39	18 (47)	16 (41)	2 (6)
al (93)		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)				
57. Ray-	2013	Everolimus as second- or third-line	43	9 (21)	7 (16)	2 (5)
Coquard <i>et al</i> (51)		treatment of advanced endometrial				
		cancer: ENDORAD, a phase II trial of				
		GINECO;				
		everolimus 10mg per day until				
		progression or unacceptable toxicity				
58. Rodrigues	2015	Phase I combination of pazopanib and	52	20 (28.4)	14 (27)	6 (1.4)
<i>et al</i> (52)		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.				
59.	Ryan et al	2011	A phase II study of everolimus in	19	9 (47)	8 (21)	1 (5)
(94)			combination with imatinib for previously				
			treated advanced renal carcinoma;				
			everolimus 2.5 mg p.o. daily and imatinib				
			600 mg p.o. daily				
60.	Sanoff et al	2015	Everolimus and pasireotide for advanced	24	5 (21)	5 (21)	0
(55)			and metastatic hepatocellular carcinoma;				
			everolimus 7.5 mg PO daily and				
			pasireotide LAR 60 mg IM every 28 days				
61.	Sarkaria et	2011	NCCTG Phase I Trial N057K of	18	16 (89)	15 (83)	1 (6)
al (56)			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				
62.	Shen et al	2014	Phase II Multicentered Study of Low-	40	22 (55)	17 (42.5)	5 (12.5)
(57)			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				
1							

63. Shoushtari	2016	Phase 2 trial of everolimus 10mg daily	13	7 (50)	7 (50)	0
<i>et al</i> (58)		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				
64. Slomovitz	2010	A Phase 2 Study of the Oral Mammalian	35	4 (11)	3 (8)	1 (3)
<i>et al</i> (59)		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				
65. Strickler <i>et</i>	2012	Phase I study of bevacizumab,	12	5 (42)	3 (25)	2 (17)
al (95)		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.				
66. Sun <i>et al</i>	2013	A phase-1b study of everolimus plus	A: 6	A: 2 (33.3)	A: 2 (33.3)	A: 0
(60)		paclitaxel in patients with small-cell lung	B: 11	B: 4 (36.3)	B: 3 (27.2)	B: 1 (9.1)
		cancer;	C: 3	C: 3 (100)	C: 2 (66.6)	C: 1 (33.3)
		A: everolimus 2.5 mg				
		B: everolimus 5 mg				
		C: everolimus 10 mg				
67. Tarhini <i>et</i>	2010	Phase II Study of Everolimus (RAD001)	40	6 (15)	4 (10)	2 (5)
<i>al</i> (61)		in Previously Treated Small Cell Lung	-			
		Cancer				
		everolimus 10 mg orally daily until				
		disease progression				
68. Tobinai <i>et</i>	2010	Phase I study of the oral mammalian	A: 7	A: 3 (42.8)	A: 3 (42.8)	A: 0
al (96)		target of rapamycin inhibitor everolimus	B: 6	B: 5 (83.3)	B: 3 (50)	B: 2 (33.3)
		(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				
69. Tomita et	2017	Nivolumab versus everolimus in	26	13 (50)	12 (46)	1 (4)
<i>al</i> (62)	2017	advanced renal cell carcinoma: Jananese	20	10 (00)	12(10)	• (1)
		subroup analysis from the CheckMate				
		025 study				
		025 Study,				

			nivolumab 3 mg/kg intravenously every 2				
			weeks or everolimus 10-mg tablet orally				
			once daily				
70.	Vlahovic et	2012	A phase I study of bevacizumab,	32	12 (37)	10 (31)	2 (6)
al (63)			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				
71.	Werner et	2013	Phase I study of everolimus and	16	8 (50)	8 (50)	0
al (64)			mitomycin C for patients with metastatic				
			esophagogastric adenocarcinoma				
			oral everolimus (5, 7.5, and 10 mg/day) in				
			combination with intravenous MMC 5				
			m_{π}/m^2 avery 2 weaks				
72	Vac at al	2008	Efficacy of PAD001 (Everelimus) and	64	2(5)		
(140)	1 a0 ei ai	2008	Cotractide LAP in Advanced Low to	04	5 (5)		
			Untermediate Grade Neuroandearing				
			Turrenne Develte of a Dhase II Studie				
			Tumors: Results of a Phase II Study				
			I reatment consisted of RADOUL 5				
			mg/day (30 patients) or 10 mg/d (30				
			patients) and octreotide LAR 30 mg every				
70	X 7 . 1	2011	28 days.	204	07 (10)	10 (0)	0 (1)
(65)	Yao <i>et al</i>	2011	Everolimus for Advanced Pancreatic	204	27 (13)	19 (9)	8 (4)
			Neuroendocrine Tumors;				
			10 mg once daily				
74.	Yee <i>et al</i>	2014	Outcomes in patients with relapsed or	26	11 (42)	2 (7.6)	9 (34.4)
(50)			refractory multiple myeloma in a phase I				
			study of everolimus in combination with				
			lenalidomide				
	Total over all			5,533	1,195		
					(21.8)		
Т	otal with grad	e		5,095	1,163	921 (18.1)	242 (4.7)
					(22.8)		
Т	otal with grad	e	Only everolimus at 2.5 mg	6	2 (33.3)	2 (33.3)	0
Т	otal with grad	e	Only everolimus at 5 mg	18	7 (38.9)	6 (33.3)	1 (5.6)
T	otal with grad	e	Only everolimus at 10 mg	1,718	361(21)	265 (15.4)	96 (5.6)

Author/(Refs.)	Year	Study	No. of	No. of cases	Grade 1/2	Grade 3/4
			patients	(%)	Cases (%)	Cases (%)
1. Amato <i>et al</i>	2009	A Phase 2 Study With a Daily	39	9 (23.1)	9 (23.1)	0
(1)		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)				
2. Andre <i>et al</i>	2014	Everolimus for women with	280	60 (22)	58 (21)	2 (1)
(67)		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				

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

			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	2016	Everolimus versus sunitinib	52	13 (23)	13 (23)	0
al (68)			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				
4.	Bachelot et al	2012	Randomized Phase II Trial of	54	9 (17)	9 (17)	0
(76)			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				
5.	Baselga et al	2012	Everolimus in	482	14 (3)	12 (2.4)	2 (0.6)
(3)			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)				
6.	Bendell et al	2015	A phase Ib study of linsitinib	18	4 (21)	3 (16)	1 (5)
(5)			(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				
7.	Besse et al	2014	Phase II study of everolimus-	66	11 (16.7)	11 (16.7)	0
(8)			erlotinib in previously treated				
			patients with advanced non-				
			small-cell lung cancer				
			Everolimus 5 mg/day +				
			erlotinib 150 mg/day				
8.	Bissler et al	2018	The effect of everolimus on	33	6 (18.2)		
(134)			renal angiomyolipoma in				
			pediatric patients with				
			tuberous sclerosis being				
			treated for subependymal				
			giant cell astrocytoma;				
			Patients were initially ran-				
			domly 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				
9.	Bissler et al	2016	Everolimus for renal	112	19 (17)	19 (17)	0
(110)			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 tolerability.				
		Doses could be lowered to 5				
		mg/day or even to 5 mg/ every				
		other day				
10. Bissler <i>et al</i>	2013	Everolimus for	79	12 (15)	12 (15)	0
(09)		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				
11. Buzzoni <i>et al</i>	2017	impact of prior therapies on	202	14 (7)	10 (7)	4 (2)
(9)		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				
12. Cazzaniga <i>et</i>	2017	Efficacy and safety of	404	9 (2.7)	9 (2.7)	0
<i>al</i> (135)		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				

13.	Chan <i>et al</i>	2013	A Prospective, Phase 1/2	43	19 (44)	19 (44)	0
(78)			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				
14.	Choueiri et al	2015	Cabozantinib versus	322	45 (14)	42 (13)	3 (1)
(11)			everolimus in advanced renal				
			cell carcinoma				
			everolimus at a dose of 10 mg				
			daily				
15.	Chung et al	2016	Phase Ib Trial of mFOLFOX6	6	3 (50)	3 (50)	0
(15)			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				
16.	Ciunci et al	2014	Phase 1 and	29	5 (17.2)	5 (17.2)	0
(14)			Pharmacodynamic Trial of				
			Everolimus in Combination				
			With Cetuximab in Patients				
		1	With Advanced Concer				

17.	Ellard et al	2009	Randomized Phase II Study	A: 33	A: 4 (12.1)	A: 0	A: 4 (12.1)
(79)			Comparing Two Schedules of	B: 16	B: 5 (31.2)	B: 0	B: 5 (31.2)
			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				
18.	Escudier at	2016	Open-label phase 2 trial of	92	16 (17)	15 (16)	1 (1)
al.(70)			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				
19.	Ferolla et al	2017	Efficacy and safety of long-	42	4 (10)	4 (10)	0
(71)			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				
20.	Franz <i>et al</i>	2013	Efficacy and safety of	78	13 (17)	12 (16)	1 (1)
(117)			everolimus for subependymal				
			giant cell astrocytomas				
			associated with tuberous				
			sclerosis complex (EXIST-1):				
			a multicentre, randomised,				
			placebo-controlled phase 3				
			trial				

			A: everolimus 4-5mg/m ²				
21.	Fury <i>et al</i>	2013	A Phase 1 Study of	13	5 (39)	5 (39)	0
(118)			Everolimus D Weekly				
			Cisplatin D Intensity				
			Modulated Radiation Therapy				
			in Head-and-Neck Cancer;				
			A: everolimus + cisplatin				
22.	Gadgeel et al	2013	Phase I study evaluating the	54	8 (15)	7 (13)	1 (2)
(81)			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				
23.	Goldberg et	2015	Everolimus for the treatment	24	4 (17)		
al.(122)			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.	Grignani <i>et al</i>	2014	Sorafenib and everolimus for	38	8 (21)	8 (21)	0
(72)			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				
25.	Hainsworth et	2010	Phase II Trial of Bevacizumab	80	34 (43)	32 (40)	2 (3)
al (21)			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				
26.	Harzstark et	2011	A Phase 1 Study of	20	2 (10)	2 (10)	0
al (84)			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				
27.	Hatano et al	2016	Outcomes of everolimus	47	13 (28)	12 (27)	1
(22)			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.				
28.	Hatano et al	2017	Intermittent everolimus	26	5 (19)	4 (15.3)	1 (3.7)
(23)			administration for renal				
			angiomyolipoma associated				
			with tuberous sclerosis				
			complex;				
			the dose of everolimus was set				
			at 10 mg once a day				
29.	Hurvitz et al	2013	A phase 2 study of everolimus	55	15	12 (21.8)	3 (5.5)
(25)			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				
30. Jozwiak <i>et al</i>	2016	Safety of Everolimus in	18	4 (22.2)		
(125)		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				
31. Ju <i>et al</i> (85)	2015	Toxicity and adverse effects of	12	1 (8.3)	0	1 (8.3)
		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				
32. Kanesvaran	2015	A single arm phase 1b study of	4	3 (75)	3 (75)	0
<i>et al</i> (126)		everolimus and sunitinib in				
		patients with advanced renal				
		cell carcinoma (RCC);				
		sunitinib + everolimus				
33. Kato <i>et al</i>	2013	Efficacy of Everolimus in	19	3 (16)	1 (5)	2 (11)
(86)		Patients with Advanced Renal				
		Cell Carcinoma Refractory or				
		Intolerant to VEGFR-TKIs				
		and Safety Compared with				
		Prior VEGFR-TKI Treatment				

34.	Kim et al	2018	Clinical outcomes of the	36	2 (5.6)	2 (5.6)	0
(87)			sequential use of pazopanib				
			followed by everolimus for the				
			treatment of metastatic renal				
			cell carcinoma: A multicentre				
			study in Korea				
35.	Kim et al	2013	A phase I study of everolimus	15	2 (13.3)	2 (13.3)	0
(30)			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				
36.	Knox et al	2017	Final overall survival analysis	238	10 (4.2)		
(31)			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				
37.	Kulke et al	2017	A randomized, open-label,	A 78	A 22 (28.2)	A 20 (25.6)	A 2 (2.6)
(35)			phase 2 study of everolimus	B 81	B 16 (19.8)	B 14 (17.3)	B 2 (2.5)
			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.)				

			B: Everolimus (10 mg/day,				
			per oral (p.o.)]				
38.	Massarweh et	2014	A phase II study of combined	31	6 (19)	5 (16.1)	1 (2.9)
al (37)			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 \pm 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				
39.	Milowsky et	2013	Phase II study of everolimus in	45	10 (22)	10 (22)	0
al(127)			metastatic urothelial cancer				
			all patients received				
			everolimus 10 mg orally once				
			daily continuously (one cycle				
			= 4 weeks)				
40.	Molina et al	2012	Phase 1 Trial of Everolimus	20	4 (20)	3 (15)	1 (5)
(38)			Plus Sunitinib in Patients With				
			Metastatic Renal Cell				
			Carcinoma;				
			A: everolimus + sunitnib				
41.	Molina et al	2014	A phase 1b clinical trial of the	20	8 (40)	7 (35)	1 (5)
(39)			multi-targeted tyrosine kinase				
			inhibitor lenvatinib (E7080) in				
			combination with everolimus				
			for treatment of metastatic				
			renal cell carcinoma (RCC)				

			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	2016	Safety analysis, association	181	8 (4.5)	8 (4.5)	0
(102)			with response and previous				
			treatments of everolimus and				
			exemestane in 181 metastatic				
			breast cancer patients: A				
			multicenter Italian experience				
43.	Motzer et al	2014	Phase II Randomized Trial	337	59 (17.5)	52 (15.4)	7 (2.1)
(42)			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				
44.	Motzer et al	2008	Efficacy of everolimus in	269	32 (12)	32 (12)	0
(74)			advanced renal cell				
			carcinoma: a double-blind,				
			randomised, placebo-				
			controlled phase III trial				
			A: everolimus 10 mg once				
			daily				
45.	Motzer et al	2015	Lenvatinib, everolimus, and	50	5 (10)	5 (10)	0
(75)			the combination in patients				
			with metastatic renal cell				
			carcinoma: a randomised,				
			phase 2, open-label,				
			phase 2, open-label, multicentre trial;				
			phase 2, open-label, multicentre trial; everolimus 10 mg day				
46.	Niegisch et al	2015	phase 2, open-label, multicentre trial; everolimus 10 mg day Second-Line Treatment of	27	8 (30)	4 (15)	4 (15)
46. (44)	Niegisch et al	2015	phase 2, open-label, multicentre trial; everolimus 10 mg day Second-Line Treatment of Advanced Urothelial Cancer	27	8 (30)	4 (15)	4 (15)
46. (44)	Niegisch <i>et al</i>	2015	phase 2, open-label, multicentre trial; everolimus 10 mg day Second-Line Treatment of Advanced Urothelial Cancer with Paclitaxel and	27	8 (30)	4 (15)	4 (15)
46. (44)	Niegisch <i>et al</i>	2015	phase 2, open-label, multicentre trial; everolimus 10 mg day Second-Line Treatment of Advanced Urothelial Cancer with Paclitaxel and Everolimus in a German	27	8 (30)	4 (15)	4 (15)
46. (44)	Niegisch <i>et al</i>	2015	phase 2, open-label, multicentre trial; everolimus 10 mg day Second-Line Treatment of Advanced Urothelial Cancer with Paclitaxel and Everolimus in a German Phase II Trial (AUO Trial AB	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 <i>et al</i>	2013	Adverse Event Profile and	47	1 (2.1)	1(2.1)	0
(90)			Dose Modification of				
			Everolimus for Advanced				
			Renal Cell Carcinoma in Real-				
			world Japanese Clinical				
			Practice				
48.	Ohtsu et al	2013	Everolimus for Previously	437	107 (24)	94 (21)	13 (3)
(46)			Treated Advanced Gastric				
			Cancer: Results of the				
			Randomized, Double-Blind,				
			Phase III GRANITE-1 Study;				
			everolimus 10 mg/day				
49.	Oudard et al	2016	Clinical Benefit of Everolimus	162	11 (6.8)	11 (6.8)	0
(47)			as Second-Line Therapy in				
			Metastatic Renal Cell				
			Carcinoma: The French				
			Retrospective SECTOR Study				
50.	Park <i>et al</i>	2014	Efficacy and Safety of	100	6 (6)	6 (6)	0
(103)			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)				
51.	Powles et al	2014	A phase Ib study investigating	15	3 (20)	2 (14)	1 (7)
(128)			the combination of everolimus				
			and dovitinib in vascular				
			endothelial growth factor				
			refractory clear cell renal				
			cancer;				
			cancer; everolimus 5 mg orally (PO)				
			cancer; everolimus 5 mg orally (PO) once daily (OD) and dovitinib				

52. Powles <i>et al</i>	2016	Randomized Open-Label	43	5 (12)	4 (10)	1 (2)
(104)		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				
53. Ramalingam	2010	Phase 1 and Pharmacokinetic	24	2 (8.3)	2 (8.3)	0
<i>et al</i> (129)		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				
54. Ray-Coquard	2013	Everolimus as second- or	43	21 (49)	17 (40)	4 (9)
<i>et al</i> (51)		third-line treatment of				
		advanced endometrial cancer:				
		ENDORAD, a phase II trial of				
		GINECO;				
		everolimus 10mg per day until				
		progression or unacceptable				
		toxicity				
55. Robles <i>et al</i>	2016	Everolimus safety and	19	2 (10.5)	2 (10.5)	0
(106)		efficacy for renal				
		angiomyolipomas associated				
		with tuberous sclerosis				
		complex: a Spanish expanded				
		access trial;				
		10 mg everolimus once daily				
56. Ryan <i>et al</i>	2011	A phase II study of everolimus	19	11 (58)	11 (58)	0
(94)		in combination with imatinib				
		for previously treated				
		advanced renal carcinoma;				

			everolimus 2.5 mg p.o. daily				
			and imatinib 600 mg p.o. daily				
57.	Safra <i>et al</i>	2018	Everolimus Plus Letrozole for	72	12 (16.7)	10 (13.5)	2 (2.8)
(53)			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				
58.	Salazar et al	2017	Phase II Study of BEZ235	31	7 (22.6)	6 (19.4)	1 (3.2)
(54)			versus Everolimus in Patients				
			with Mammalian Target of				
			Rapamycin Inhibitor-Na€ıve				
			Advanced Pancreatic				
			Neuroendocrine Tumors;				
			everolimus 10 mg once daily				
59.	Sanoff et al	2015	Everolimus and pasireotide for	24	2 (8)	2 (8)	0
(55)			advanced and metastatic				
			hepatocellular carcinoma;				
			everolimus 7.5 mg PO daily				
			and pasireotide LAR 60 mg				
			IM every 28 days.				
60.	Sarkaria <i>et al</i>	2011	NCCTG Phase I Trial N057K	18	6 (33)	6 (33)	0
(56)			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				
61.	Shen et al	2014	Phase II Multicentered Study	40	21 (52.5)	21 (12.5)	0
(57)			of Low-Dose Everolimus plus				
			Cisplatin and Weekly 24-Hour				
			Infusion of High-Dose 5-				
			Fluorouracil and Leucovorin				
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			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	2010	A Phase 2 Study of the Oral	35	5 (14)	4 (11)	1 (3)
al (59)			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				
63.	Strickler et al	2012	Phase I study of bevacizumab,	12	1 (8)	1 (8)	0
(95)			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				
64.	Sun <i>et al</i> (60)	2013	A phase-1b study of	A: 6	A: 0	A: 0	A: 0
			everolimus plus	B: 11	B: 2 (19)	B: 2 (19)	B: 0
			paclitaxel in patients with	C: 3	C: 0	C: 0	C: 0
			small-cell lung				
			cancer				
			A: everolimus 2.5 mg				

			B: everolimus 5 mg				
			C: everolimus 10 mg				
65.	Tarhini et al	2010	Phase II Study of Everolimus	40	3 (7.5)	3 (7.5)	0
(61)			(RAD001) in Previously				
			Treated Small Cell Lung				
			Cancer;				
			everolimus 10 mg orally daily				
			until disease progression				
66.	Thudium et	2015	Bioavailability of everolimus	22	1 (4.5)		
al (132)			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				
67.	Vlahovic et	2012	A phase I study of	32	10 (31)	10 (31)	0
<i>al</i> (63)			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				
68.	Wang et al	2014	Everolimus for patients with	58	10 (17.2)	9 (15.5)	1 (1.7)
(107)			mantle cell lymphoma				
			refractory to or intolerant of				
			bortezomib: multicentre,				
			single-arm, phase 2 study				
			Everolimus 10 mg/day in				
			adults				
69.	Werner et al	2013	Phase I study of everolimus	16	3 (18)	3 (18)	0
(04)			and mitomycin C for patients				
			with metastatic				
			esophagogastric				
1			adenocarcinoma;				

			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	2009	Oral mTOR Inhibitor	33	5 (15)	4 (12)	1 (3)
(97)			Everolimus in Patients With				
			Gemcitabine-Refractory				
			metastatic Pancreatic Cancer;				
			everolimus 10 mg daily				
71.	Yao <i>et al</i> (65)	2011	Everolimus for Advanced	204	31 (15)	31 (15)	0
			Pancreatic Neuroendocrine				
			Tumors;				
			10 mg once daily				
72.	Yee <i>et al</i> (99)	2006	Phase I/II Study of the	27	4 (15)	4 (15)	0
			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				
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		
	Cases/adverse	Grade 1/2	Grade	Cases/adver	Grade	Grade	Cases/adverse	Grade 1/2	Grade
A duarsa avant	effects (%)	% (cases)	3/4	se effects	1/2	3/4	effects (%)	% (cases)	3/4
Adverse event			%	(%)	%	%			%
			(cases)		(cases)	(cases)			(cases)
Anaomia	6/5 (83.33)	5 (83.33)		11/11 (100)	10	1 (9.1)	4,770/1,247 (26.2)	790 (16.6)	467
Anacima			-	11/11 (100)	(90.9)				(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
ululiloou							5,156,665 (22.5)		(2.9)
Fatigue	-	-	-	-	-	-	5,449/111 (20.4)	828 (15.2)	283
1 ungue									(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	-	3,611/615 (17)	400 (11)	223 (6)
11) pergij edemid				10,11 (0111)	(61.1)				
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
1 noumonitis				11/1 ())	1 ())		5,105/505 (10.7)	242 (7.1)	(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	Incidence due to traditional		
	treatment (%)	chemotherapy (%)		
Anaemia	Average = 24.4	Average = 70		
	G3-4 = 7.1	G3-4 = 60		
Anorexia	Average = 25.2	Average = 60		
	G3-4 = 3.3	G3-4 = 45		
Asthenia	Average = 20.6	Average = 35.7		
diarrhoea	Average = 22.3	Range = 50-80		
	G1-2 = 20.4	G1-2 = 20-50		
	G3-4 = 2.6	G3-4 = 30		
Fatigue	Average = 23.7	Average = 60		
	G3-4 = 4.8	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	Average = 25		
	G1-2 = 18.1	G1-2 = 20		
	G3-4 = 4.7	G3-4 = 5		
Pneumonitis	Average = 10.1	Average $= 1.5-50$		
Pruritus	Average = 12.1	Average = 10-25		
Pyrexia	Average = 15.4	Average = 34		
	G3-4 = 1.3	G3-4 = 5		
Rash	Average = 22.7	Average = 10		
Stomatitis	Average = 43.2	Average = 40		
Emesis	Average = 15	Average = 30		

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