



Everolimus

Updated: February 26, 2018.

OVERVIEW

Introduction

Everolimus is an inhibitor of cell proliferation and immunosuppressive agent that is used alone or in combination with calcineurin inhibitors to prevent cellular rejection after organ transplantation, and in combination with other anticancer agents as treatment of advanced renal cell and other cancers. Everolimus therapy can be associated with mild serum enzyme elevations, but has yet to be linked to instances of clinically apparent liver injury with jaundice.

Background

Everolimus (e' ver oh' li mus) binds to the same intracellular receptor as tacrolimus and cyclosporine, but does not inhibit calcineurin; rather, it blocks the "mammalian target of rapamycin" (mTOR), which interrupts signaling pathways of several cytokines and growth factors including IL2 and causes a decrease in protein synthesis and cell cycle arrest. Everolimus therapy has been shown to improve graft survival after solid organ transplantation and to improve time to progression in several forms of cancer. Everolimus was approved for use in the United States in 2009 initially as an agent to prevent rejection after kidney and liver transplantation and later, in higher doses, as therapy of advanced renal cell, breast and pancreatic neuroendocrine cancers given alone or in combination with other antineoplastic agents. More recently, everolimus was approved as therapy of renal angiomyolipoma and subependymal giant cell astrocytoma associated with tuberous sclerosis complex (in which mTOR signaling is dysregulated). Everolimus like sirolimus is also used in drug eluting arterial stents, to prevent stenosis. Everolimus is available as tablets of 0.25, 0.50 and 0.75 mg under the brand name of Zortress for management of solid organ transplantation, and as tablets of 2.5, 5, 7.5 and 10 mg under the brand name of Afinitor, and tablets of 2, 3 and 5 mg for oral suspension under the brand name Afinitor-Disprez for use in cancer chemotherapy. The typical dose in organ transplantation is 1.0 to 1.5 mg in two divided doses daily but therapeutic drug level monitoring for dosing is recommended. The doses using in cancer chemotherapy are higher than those used in prevention of organ rejection, usually starting at 10 mg once daily and varying somewhat by indication. Everolimus is less nephrotoxic than the calcineurin inhibitors but does have many, largely dose dependent side effects including oral ulcers, stomatitis, diarrhea, nausea, poor appetite, fatigue, peripheral edema, rash, anemia, impaired wound healing and renal dysfunction. Less common but potentially severe adverse events include interstitial pneumonitis, renal failure, hypersensitivity reactions and embryo-fetal toxicity.

Hepatotoxicity

Serum enzyme elevations occur in up to a quarter of patients taking everolimus, but the abnormalities are usually mild, asymptomatic and self-limiting, rarely requiring dose modification or discontinuation. Liver test elevations above 5 times ULN occur in only 1% to 2% of treated patients. In contrast, idiosyncratic, clinically apparent acute liver injury has not been linked to everolimus therapy despite its wide scale use in several malignant and non-malignant syndromes. Elevations in serum enzymes and bilirubin and hepatitis are listed as potential adverse events in the product label for everolimus. Thus, acute clinically apparent liver injury with jaundice due to everolimus is probably quite rare, if it occurs at all.

Importantly, everolimus is immunosuppressive and therapy in patients with cancer has been associated with episodes of reactivation of hepatitis B, which can be severe and even fatal. Reverse seroconversion (development of HBsAg in a person with preexisting antibody to hepatitis B, either anti-HBs or anti-HBc) has also been reported.

Likelihood score: E* (unproven and also unlikely cause of clinically apparent liver injury but capable of inducing reactivation of hepatitis B).

Mechanism of Injury

Everolimus undergoes extensive hepatic metabolism, largely via the cytochrome P450 system (CYP 3A4) and P-glycoprotein. Liver injury might be due to a direct effect of everolimus or to a toxic intermediate of its metabolism. Everolimus is prone to drug-drug interactions if used with inhibitors or inducers of the cytochrome P450 drug metabolizing enzymes.

Outcome and Management

Acute liver injury with jaundice associated with everolimus therapy has not been described, and the serum enzyme elevations associated with its use are usually mild and transient, resolving spontaneously or with dose modification. Because everolimus can lead to reactivation of chronic hepatitis B, routine screening of patients for HBsAg and anti-HBc before starting therapy is advisable, particularly those undergoing organ transplantation. Patients with HBsAg or anti-HBc should be offered prophylaxis or some degree of monitoring for de novo appearance or rise in levels of HBV DNA. Patients who develop reactivation should be treated with an oral nucleoside analogue with potent activity against hepatitis B (entecavir or tenofovir alafenamide). Everolimus is a macrolide similar in structure and function to sirolimus and temsirolimus, but these agents do not always exhibit cross sensitivity to adverse effects.

Agents used specifically for the prophylaxis against allograft rejection include cyclosporine, everolimus, mycophenolate mofetil, sirolimus and tacrolimus, as well as azathioprine and corticosteroids.

Drug Class: [Antineoplastic Agents, Miscellaneous](#); [Transplant Agents](#)

Other Drugs in the Class, Transplant Drugs: [Cyclosporine](#), [Mycophenolate](#), [Sirolimus](#), [Tacrolimus](#)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Everolimus – Zortress®

DRUG CLASS

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Antineoplastic Agents; Transplant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Everolimus	159351-69-6	C ₅₃ -H ₈₃ -N-O ₁₄	

ANNOTATED BIBLIOGRAPHY

References updated: 26 February 2018

Zimmerman HJ. Cyclosporine. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp.697-8.

(Expert review of hepatotoxicity published in 1999; everolimus and temsirolimus are not discussed).

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 569-91.

(Review of hepatotoxicity of immunosuppressive agents; mentions that reports of hepatotoxicity of everolimus have been less frequent than those of sirolimus [rapamycin]).

Chabner BA, Barnes J, Neal J, Olson E, Mugagic H, Sequist L, Wilson W, Longo DL, Mitsiades C, Richardson P. Targeted therapies: tyrosin kinase inhibitors, monoclonal antibodies and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-53.

(Textbook of pharmacology and therapeutics).

Levy G, Schmidli H, Punch J, Tuttle-Newhall E, Mayer D, Neuhaus P, Samuel D, et al. Safety, tolerability, and efficacy of everolimus in de novo liver transplant recipients: 12- and 36-month results. Liver Transpl 2006; 12: 1640-8. PubMed PMID: 16598777.

(Controlled trial of everolimus vs placebo for 12-36 months in 119 liver transplant recipients also taking cyclosporine and corticosteroids found "no clinically meaningful changes from baseline" in ALT, Alk P or bilirubin).

Tedesco-Silva H Jr, Vitko S, Pascual J, Eris J, Magee JC, Whelchel J, Civati G, et al.; 2306 and 2307 study groups. 12-month safety and efficacy of everolimus with reduced exposure cyclosporine in de novo renal transplant recipients. *Transpl Int* 2007; 20: 27-36. PubMed PMID: 17181650.

(Controlled trial of 2 doses of everolimus with cyclosporine with or without basiliximab in 237 patients undergoing renal transplantation; no mention of ALT elevations or hepatotoxicity).

Reinisch W, Pané J, Lénn M, Schreiber S, Feagan B, Schmidt S, Sturniolo GC, et al. A multicenter, randomized, double-blind trial of everolimus versus azathioprine and placebo to maintain steroid-induced remission in patients with moderate-to-severe active Crohn's disease. *Am J Gastroenterol* 2008; 103: 2284-92. PubMed PMID: 18671816.

(Controlled trial of everolimus vs azathioprine vs placebo as maintenance therapy in 144 adults with Crohn Disease, found no effect of everolimus; serum ALT levels rose slightly in everolimus vs placebo treated patients [mean 38 U/L at 3 months vs 17 U/L at baseline], but there were no hepatic serious adverse events).

Ettenger R, Hoyer PF, Grimm P, Webb N, Loirat C, Mahan JD, Mentser M, et al.; Everolimus Pediatric Study Group. Multicenter trial of everolimus in pediatric renal transplant recipients: results at three year. *Pediatr Transplant* 2008; 12: 456-63. PubMed PMID: 18466433.

(Open label study of everolimus and cyclosporine in 19 children undergoing renal transplantation; ALT elevations [above 3 times ULN] occurred in 33%, but there were no severe hepatic adverse reactions or discontinuations due to liver injury).

Chan L, Greenstein S, Hardy MA, Hartmann E, Bunnapradist S, Cibrik D, Shaw LM, et al.; CRADUS09 Study Group. Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. *Transplantation* 2008; 85: 821-6. PubMed PMID: 18360262.

(Open label study of 92 renal transplant patients given everolimus with standard or low dose tacrolimus for at least 6 months; ALT elevations and liver toxicity were not listed among "most relevant" adverse events).

Ellard SL, Clemons M, Gelmon KA, Norris B, Kennecke H, Chia S, Pritchard K, et al. Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC Clinical Trials Group IND.163. *J Clin Oncol* 2009; 27: 4536-41. PubMed PMID: 19687332.

(Trial comparing daily vs weekly everolimus in 15 patients with advanced breast cancer; no mention of ALT elevations or liver toxicity).

Baselga J, Semiglazov V, van Dam P, Manikhas A, Bellet M, Mayordomo J, Campone M, et al. Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. *J Clin Oncol* 2009; 27: 2630-7. PubMed PMID: 19380449.

(270 women with breast cancer were treated with a 4 month course of letrozole with or without everolimus; ALT elevations occurred in 12% on everolimus [above 5 times ULN in 1.5%] vs 4% on placebo [all less than 5 times ULN], but no mention of clinically apparent liver injury).

Gabardi S, Baroletti SA. Everolimus: a proliferation signal inhibitor with clinical applications in organ transplantation, oncology, and cardiology. *Pharmacotherapy* 2010; 30: 1044-56. PubMed PMID: 20874042.

(Systematic review of safety and efficacy of everolimus in organ transplantation and oncology mentioned liver test elevations as an adverse event; no mention of clinically apparent liver injury).

Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, et al.; RECORD.1 Study Group. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer* 2010; 116: 4256-65. PubMed PMID: 20549832.

(Controlled trial of everolimus [10 mg/day] vs placebo in 416 patients with metastatic renal cell carcinoma for 19 to 455 days; side effects included pneumonitis [14% vs 0%] and ALT elevations [21% vs 4%], but most were less than 5 times ULN and no mention of clinically apparent liver injury).

Zuckermann A, Wang SS, Ross H, Frigerio M, Eisen HJ, Bara C, Hoefler D, et al. Efficacy and safety of low-dose cyclosporine with everolimus and steroids in de novo heart transplant patients: a multicentre, randomized trial. *J Transplant* 2011; 2011: 535983. PubMed PMID: 22295178.

(Open label 6 month study of everolimus with standard or reduced doses of cyclosporine in 199 heart transplant recipients; no mention of ALT elevations or liver toxicity).

Grgic T, Mis L, Hammond JM. Everolimus: a new mammalian target of rapamycin inhibitor for the treatment of advanced renal cell carcinoma. *Ann Pharmacother* 2011; 45: 78-83. PubMed PMID: 21177421.

(Systematic review of everolimus [5-10 mg/day] as therapy of renal cell carcinoma; major side effects are mucositis [40%], rash [25%], fatigue [20%] and liver test abnormalities [proportion not given]).

Oberstein PE, Saif MW. Safety and efficacy of everolimus in adult patients with neuroendocrine tumors. *Clin Med Insights Oncol* 2012; 6: 41-51. PubMed PMID: 22253554.

(Review of safety and efficacy of everolimus as therapy of neuroendocrine tumors; common side effects are mucositis [64%], rash [49%], diarrhea [34%] and infections [23%], including reactivation of hepatitis B; no mention of ALT elevations or hepatotoxicity).

Holdaas H, Midtvedt K, Åsberg A. A drug safety evaluation of everolimus in kidney transplantation. *Expert Opin Drug Saf* 2012; 11: 1013-22. PubMed PMID: 22954349.

(Review and opinion of pharmacology, mechanism of action, efficacy and safety of everolimus in renal transplantation; no mention of ALT elevations or hepatotoxicity).

Thompson LA, Kim M, Wenger SD, O'Bryant CL. Everolimus: a new treatment option for advanced pancreatic neuroendocrine tumors. *Ann Pharmacother* 2012; 46: 1212-9. PubMed PMID: 22947595.

(Review of safety and efficacy of everolimus in advanced pancreatic endocrine tumors; side effects include mucositis, rash, diarrhea, fatigue, infections, nausea, edema, poor appetite and pneumonitis; no mention of ALT elevations or hepatotoxicity).

Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahnoud T, Noguchi S, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; 366: 520-9. [PubMed Citation](#) (Among 724 postmenopausal women with advanced, refractory breast cancer treated with exemestane with or without everolimus, progression-free survival was greater with everolimus [6.9 vs 2.8 months] as were serious adverse event rates [23% vs 12%] and total ALT elevations [11% vs 3%], but less than 1% were above 5 times ULN and there were no instances of clinically apparent liver injury).

Shiah HS, Chen CY, Dai CY, Hsiao CF, Lin YJ, Su WC, Chang JY, et al. Randomised clinical trial: comparison of two everolimus dosing schedules in patients with advanced hepatocellular carcinoma. *Aliment Pharmacol Ther* 2013; 37: 62-73. PubMed PMID: 23134470.

(Open label study of different dose regimens of everolimus in 39 patients with hepatocellular carcinoma found ALT flares after 4-16 weeks in 5 patients [one with jaundice], 4 had hepatitis B, and ALT rises were associated with reactivation and responded to stopping everolimus and starting lamivudine therapy).

Pallet N, Legendre C. Adverse events associated with mTOR inhibitors. *Expert Opin Drug Saf* 2013; 12: 177-86. PubMed PMID: 23252795.

(Review of side effects of the mTor inhibitors focusing largely on sirolimus; no discussion of hepatotoxicity).

Krueger DA, Care MM, Agricola K, Tudor C, Mays M, Franz DN. Everolimus long-term safety and efficacy in subependymal giant cell astrocytoma. *Neurology* 2013; 80: 574-80. PubMed PMID: 23325902.

(Abstract only: Long term follow up on 28 patients with tuberous sclerosis and subependymal giant cell astrocytoma treated for 5-47 months with everolimus; most side effects were mild and none led to discontinuation).

Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, Sauter M, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 381 (9869): 817-24. PubMed PMID: 23312829.

(Among 118 adults with angiomyolipoma treated with everolimus or placebo for up to 2 years, common side effects were stomatitis, nasopharyngitis, acne, headache, cough and hypercholesterolemia; no mention of ALT changes or hepatotoxicity).

van den Eertwegh AJ, Karakiewicz P, Bavbek S, Rha SY, Bracarda S, Bahl A, Ou YC, et al. Safety of everolimus by treatment duration in patients with advanced renal cell cancer in an expanded access program. *Urology* 2013; 81: 143-9. PubMed PMID: 23273080.

(Analysis of side effects among 1367 patients with renal cell cancer treated with everolimus in an expanded access program; common side effects were dyspnea, anemia, fatigue, stomatitis, pneumonitis and hyperglycemia; no mention of ALT elevations or hepatotoxicity).

Mizuno S, Yamagishi Y, Ebinuma H, Nakamoto N, Katahira M, Sasaki A, Sakamoto M, et al. Progressive liver failure induced by everolimus for renal cell carcinoma in a 58-year-old male hepatitis B virus carrier. *Clin J Gastroenterol* 2013; 6: 188-92. PubMed PMID: 23606919.

(58 year old man with inactive HBsAg carrier state and refractory renal cell cancer developed reactivation of HBV 5 months after starting everolimus [bilirubin 11.0 mg/dL, ALT 878 U/L, HBV DNA 10 million copies/mL, INR 1.8], with progressive liver failure despite entecavir and methylprednisolone therapy, and death 6 weeks after presentation).

Sezgin Göksu S, Bilal S, Coşkun HŞ. Hepatitis B reactivation related to everolimus. *World J Hepatol* 2013; 5: 43-5. PubMed PMID: 23383366.

(49 year old man with inactive HBsAg carrier state and refractory renal cell cancer developed reactivation of HBV 3-5 months after starting everolimus [bilirubin 16.3 mg/dL, ALT 1871 U/L, HBV DNA 1.2 billion copies/mL, protime 14.8 seconds], starting to resolve 20 days after stopping everolimus and starting tenofovir).

Teplinsky E, Cheung D, Weisberg I, Jacobs RE, Wolff M, Park J, Friedman K, et al. Fatal hepatitis B reactivation due to everolimus in metastatic breast cancer: case report and review of literature. *Breast Cancer Res Treat* 2013; 141: 167-72. PubMed PMID: 24002736.

(56 year old woman with advanced metastatic breast cancer developed jaundice 4 months after starting everolimus [bilirubin 8.0 mg/dL, ALT 1758 U/L, Alk P 154 U/L, HBsAg and HBV DNA positive, IgM anti-HBc negative], with progression to hepatic failure and death despite tenofovir therapy).

Schieren G, Bölke E, Scherer A, Raffel A, Gerber PA, Kröpil P, Schott M, et al. Severe everolimus-induced steatohepatitis: a case report. *Eur J Med Res* 2013; 18: 22. PubMed PMID: 23822543.

(76 year old man with metastatic neuroendocrine cancer developed ascites and liver test abnormalities 4 weeks after starting everolimus [bilirubin normal, ALT 16 U/L, GGT 1599 U/L], and CT scans of the liver suggested diffuse steatosis and expanding hepatic masses, the patient dying of multiorgan failure 2 weeks later, and there was no verification of steatosis histologically).

Sterneck M, Kaiser GM, Heyne N, Richter N, Rauchfuss F, Pascher A, Schemmer P, et al. Everolimus and early calcineurin inhibitor withdrawal: 3-year results from a randomized trial in liver transplantation. *Am J Transplant* 2014; 14: 701-10. PubMed PMID: 24502384.

(Among 203 liver transplant recipients switched to everolimus or maintained on calcineurin inhibitors 1 month after transplantation, 81 were enrolled in an extension study for up to 3 years; mean ALT, AST and GGT levels did not differ between those receiving or not receiving everolimus).

Piccart M, Hortobagyi GN, Campone M, Pritchard KI, Lebrun F, Ito Y, Noguchi S, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†. *Ann Oncol* 2014; 25: 2357-62. PubMed PMID: 25231953.

(Among 724 women with advanced breast cancer treated with exemestane with or without everolimus [Baselga 2012], further follow up demonstrated higher overall survival for the combination [31 vs 27 months] but also higher rates of serious adverse events [33% vs 16%], discontinuations for adverse events [29% vs 5%] and drug related deaths [1.7% vs 0.4%], but none were considered liver related deaths).

Chalasan N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. *Gastroenterology* 2015; 148: 1340-52.e7. [PubMed Citation](#) *(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 [5.5%] were attributed to antineoplastic agents, but none were linked to use of everolimus).*

Abdel-Rahman O, Fouad M. Risk of fatigue and hepatic and metabolic toxicities in patients with solid tumors treated with everolimus: a meta-analysis. *Future Oncol* 2015; 11: 79-90. PubMed PMID: 25572784.

(A review of the literature on adverse events in cancer patients treated with everolimus mentions ALT elevations above 5 times ULN in 4 publications [0% to 4%], but does not mention clinically apparent liver injury).

Goldberg HJ, Harari S, Cottin V, Rosas IO, Peters E, Biswal S, Cheng Y, et al. Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study. *Eur Respir J* 2015; 46: 783-94. PubMed PMID: 26113676.

(Among 24 women with lymphangioleiomyomatosis treated with everolimus [2.5 to 10 mg daily] for 26 weeks, pulmonary function improved and common adverse events included stomatitis [92%], headache [38%], nausea [29%] and fatigue [29%], while serious adverse events occurred in one-third of patients and included heart failure, edema, pneumonitis and P. jirovecii pneumonia; no mention of ALT elevations or hepatotoxicity).

Mir O, Toulmonde M, Coriat R, Ropert S, Loulergue P. Hepatitis B reactivation during everolimus treatment. *Acta Oncol* 2016; 55: 1505-6. PubMed PMID: 27771976.

(51 year old French woman with previous history of hepatitis B, but undocumented serology developed symptomatic acute hepatitis 3 months after starting everolimus and exemestane for refractory, advanced breast cancer [bilirubin 6.3 mg/dL, ALT 3.5 times ULN, HBsAg positive and HBV DNA 60 million copies/mL], improving with stopping everolimus and starting entecavir).

D'Aniello C, Maruzzo M, Basso U. Prevention of hepatitis B virus reactivation with lamivudine in a patient with advanced renal cell carcinoma treated with everolimus. *Am J Ther* 2016; 23: e300-3. PubMed PMID: 24368609.

(An HBsAg positive patient with metastatic renal cancer was treated with lamivudine prophylactically and had no evidence of hepatitis B reactivation during therapy with high doses of everolimus: Abstract only).

Moscetti L, Vici P, Gamucci T, Natoli C, Cortesi E, Marchetti P, Santini D, et al. Safety analysis, association with response and previous treatments of everolimus and exemestane in 181 metastatic breast cancer patients: A multicenter Italian experience. *Breast* 2016; 29: 96-101. PubMed PMID: 27476084.

(Among 181 women with advanced breast cancer treated with the combination of everolimus and exemestane for a median duration of 18 months, adverse events were common and included "hepatic" events in 35 patients [19%], but only 5 [2.8%] were above "grade 3" [above 5 times ULN for ALT and AST]).

Jerusalem G, Mariani G, Ciruelos EM, Martin M, Tjan-Heijnen VC, Neven P, Gavila JG, et al. Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET). *Ann Oncol* 2016; 27: 1719-25. PubMed PMID: 27358383.

(Among 2133 postmenopausal women with advanced breast cancer treated with exemestane with or without everolimus for a median of 5 months, everolimus related serious adverse events occurred in 8.5% of treated subjects and was the suspected cause of death in 4, but details not provided).

Armstrong AJ, Halabi S, Eisen T, Broderick S, Stadler WM, Jones RJ, Garcia JA, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. *Lancet Oncol* 2016; 17: 378-88. PubMed PMID: 26794930.

(Among 108 patients with metastatic renal cell carcinoma treated with everolimus or sunitinib, overall survival was similar and adverse events were common in both groups, but ALT elevations were infrequent and mild, arising in 0% on everolimus and 10% on sunitinib [all of which were less than 5 times ULN] and there were no instances of clinically apparent liver injury).

Takasaki S, Kikuchi M, Kawasaki Y, Ito A, Arai Y, Yamaguchi H, Mano N. [A case of renal cell carcinoma with high everolimus blood concentrations and hyperglycemia due to everolimus-induced hepatic dysfunction]. *Gan To Kagaku Ryoho* 2017; 44: 87-9. Japanese. PubMed PMID: 28174388.

(74 year old man with metastatic renal cell carcinoma developed hyperglycemia and liver enzyme elevations during everolimus therapy [peak ALT 115 U/L] which improved on stopping and recurred on restarting [ALT ~60 U/L], which resolved when he was switched to axitinib [a tyrosine kinase receptor inhibitor also used to treat renal cell carcinoma]).

Christopoulos P, Engel-Riedel W, Grohé C, Kropf-Sanchen C, von Pawel J, Gütz S, Kollmeier J, et al. Everolimus with paclitaxel and carboplatin as first-line treatment for metastatic large-cell neuroendocrine lung carcinoma: a multicenter phase II trial. *Ann Oncol* 2017; 28: 1898-902. PubMed PMID: 28535181.

(Among 49 patients with metastatic neuroendocrine lung cancer treated with everolimus, paclitaxel and carboplatin, the median overall survival was 10 months and adverse events were common [overall 89%, grade 3-4 51%], leading to dose reductions or interruptions in 30%; but ALT elevations and hepatotoxicity were not listed in Tables or mentioned).