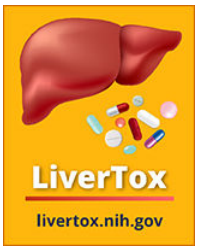
U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Pembrolizumab. [Updated 2022 Jun 23].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Pembrolizumab

Updated: June 23, 2022.

OVERVIEW

Introduction

Pembrolizumab is a humanized monoclonal antibody to programmed cell death receptor 1 (PD-1), which acts as a checkpoint inhibitor and is used in the immunotherapy of several forms of advanced or metastatic cancer. Pembrolizumab like other checkpoint inhibitors has major side effects and particularly immune related conditions, including acute hepatocellular and cholestatic liver injury which can be serious and even life threatening.

Background

Pembrolizumab (pem" broe liz' ue mab) is a humanized recombinant monoclonal IgG4 kappa-isotype antibody to the programmed cell death receptor-1 (PD-1), which has distinctive immunomodulatory activity and is used as a checkpoint inhibitor in cancer immunotherapy. PD-1 is an important checkpoint molecule that modulates and down regulates T cell responses. Inhibition of PD-1 receptors on the surface of activated T cells prevents their binding to the PD receptor which activates pathways that terminate the activation and proliferation of T cells. Without the PD-1 receptor engagement, T cell responses remained activated. The subsequent enhancement of cytotoxic reactivity may play a beneficial role in cancer immunotherapy by breaking immunological tolerance to cancer cell neo-antigens. In several large multicenter studies, pembrolizumab therapy resulted in a prolongation of survival in patients with advanced, metastatic or unresectable malignant melanoma, and a proportion of patients had a long term remission. Pembrolizumab was approved for use in advanced melanoma in the United States in 2014 and subsequently for several other forms of advanced or metastatic cancer including non-small cell lung cancer (NSCLC), renal cell carcinoma, urothelial carcinoma, hepatocellular carcinoma, gastric and esophageal cancer, head and neck cancer, cervical and endometrial cancer, breast cancer, cutaneous squamous cell cancer and several forms of lymphoma. Pembrolizumab is available in 4 mL single use vials of 100 mg (25 mg/mL) under the brand name Keytruda. The typical regimen in adults is 200 mg as an intravenous infusion every 3 weeks or 400 mg every 6 weeks, but varies in children by body weight.

Side effects of pembrolizumab are common and can include fatigue, headache, musculoskeletal pain, arthralgia, abdominal pain, diarrhea, nausea, vomiting, decreased appetite, weight loss, fever, cough, dyspnea, pruritus, and rash. Importantly, as a result of immune enhancement, between 15% and 25% of pembrolizumab treated patients develop immune related side effects, including enterocolitis, dermatitis, endocrinopathy, pneumonitis, neuropathy, nephritis and hepatitis. Most of these reactions respond to immunosuppressive therapy, but some have resulted in fatalities and some have required permanent discontinuation of checkpoint inhibitor therapy and long term immunosuppressive therapy. These immune related adverse events are more frequent with combination therapy of ipilimumab and pembrolizumab. Baseline screening and regular monitoring for these

adverse events during pembrolizumab therapy is recommended. Early recognition and prompt management of side effects is an integral component of proper use of checkpoint inhibitors. Checkpoints inhibitors should be used only by health care professional with training in immunotherapy and experience in the management of the side effects of immunomodulatory agents. Other rare but potentially severe adverse effects of pembrolizumab include infusion hypersensitivity reactions and embryo-fetal toxicity.

Hepatotoxicity

Mild-to-moderate serum aminotransferase elevations are not uncommon (20% to 30%) during pembrolizumab therapy, but are usually self-limited and resolve even with continuing cyclic therapy. These rates of serum enzyme elevations are similar to those with other forms of chemotherapy for advanced malignancies. Serum ALT elevations above 5 times the upper limit of normal (ULN) occur in 1% to 4% of patients and generally lead to temporary discontinuation. Importantly, in 1% to 2% of patients the serum enzyme elevations evolve into an immune mediated liver injury that can be clinically apparent and can be severe. The onset of injury is usually after 2 to 4 cycles or 1 to 3 months after starting treatment. The pattern of enzyme elevation is usually hepatocellular but can be mixed or even cholestatic. Liver histology typically demonstrates a panlobular hepatitis with focal or confluent necrosis and prominent lymphocytic infiltrates of activated T cells, compatible with an immune mediated hepatic injury. More severe forms of hepatitis may demonstrate centrilobular (zone 3) necrosis. Despite features of immune mediated liver injury, autoantibodies are usually not present and immunoglobulin levels are normal. Because of the serious nature of the liver injury, monitoring with routine liver tests (including alkaline phosphatase) is recommended for patients who receive checkpoint inhibitor therapy. Treatment with corticosteroids generally results in a rapid improvement, allowing for their discontinuation within 1 to 2 months. In some instances, however, the clinical and biochemical response is inadequate, calling for addition of a second immunosuppressive agent such as azathioprine or mycophenolate mofetil. Restarting pembrolizumab or another checkpoint inhibitor after resolution of the hepatic injury is sometimes possible, but can result in recurrence of injury and has not been shown to improve outcome of the cancer chemotherapy.

A proportion of patients receiving pembrolizumab develop cholestatic rather than hepatocellular liver injury. Cholestatic forms of immune mediated liver injury generally arise later than the hepatocellular forms (after 3 to 10 cycles) and are often accompanied by abdominal pain and jaundice. Alkaline phosphatase levels are markedly elevated while aminotransferase levels are only modestly increased. Imaging studies may show irregular dilatation of the intra- and/or extra-hepatic bile ducts and thickening of the gall bladder and bile duct wall but without evidence of frank obstruction. Liver biopsy shows portal inflammation and bile duct injury, and endoscopic biopsy of bile duct epithelium shows inflammation and scarring. The general features suggest a secondary form of sclerosing cholangitis referred to as checkpoint inhibitor cholangiopathy. Therapy with immunosuppression may improve alkaline phosphatase and bilirubin levels but rarely leads to complete recovery, and long term cholestasis and hepatic failure can occur. Some patients with a cholestatic form of immune related liver injury do not manifest the large bile duct changes but demonstrate loss and paucity of the smaller intrahepatic bile ducts resulting in a vanishing bile duct syndrome similar to primary biliary cholangitis (PBC).

The effects of PD-1 inhibition on chronic hepatitis B are not well defined, but convincing examples of reactivation of hepatitis B have been described due to pembrolizumab and other checkpoint inhibitors. Most cases have occurred in patients with preexisting HBsAg, but rare instances were reported in individuals suspected of having with anti-HBc without HBsAg. Thus, screening patients for HBsAg, anti-HBc and anti-HBs is appropriate before initiating immunotherapy with checkpoint inhibitors. Patients with HBsAg should be considered for prophylaxis with an antiviral agent with potent activity against HBV such as entecavir or tenofovir. In patients with anti-HBc without HBsAg, monitoring and close attention to liver test abnormalities is probably adequate if antiviral therapy can be introduced rapidly for early evidence of reactivation. There has not

been adequate experience with pembrolizumab in regard to the risk of reactivation of hepatitis B to provide rates of reactivation with and without antiviral prophylaxis.

Likelihood score: A (well known cause of clinically apparent liver injury and likely cause of reactivation of hepatitis B).

Mechanism of Injury

The mechanism of liver injury due to pembrolizumab is likely to be immunologically mediated and is usually at least partially responsive to corticosteroid or immunosuppressive therapy. Liver biopsies in cases of hepatocellular injury and bile duct epithelial cell biopsies in cholangiopathic injury demonstrate necrosis and inflammatory cell infiltration with cytotoxic CD8+ T cells, suggesting that the checkpoint inhibition allowed for activation of T cells directed at hepatocyte or cholangiocyte cell surface antigens.

Outcome and Management

Guidelines for management of patients receiving pembrolizumab recommend monitoring of liver tests and interrupting therapy for patients who develop serum aminotransferase elevations above 3 times the upper limit of normal (ULN), and discontinuing treatment for values above 8 times the ULN in patients without preexisting abnormalities or tumor involvement of the liver (in whom elevations of 5 and 10 times the ULN are used). Corticosteroid therapy can be considered for patients with high or persistent ALT elevations or if symptoms or jaundice arise, initiating therapy with high dose intravenous methylprednisolone and switching to oral prednisone after 1 to 2 days, continuing tapering doses for at least 30 days.

Most cases of hepatitis due to pembrolizumab resolve with prompt institution of immunosuppressive therapy which can be discontinued in 1 to 3 months. In some more protracted and resistant instances, corticosteroids have only a limited effect and adding a second agent is needed. Mycophenolate mofetil or azathioprine are most commonly recommended. Other immunosuppressive agents that have been reported to be beneficial include antithymocyte globulin, tacrolimus, infliximab and cycloserine. In refractory cases, immunosuppressive therapy may be needed long term. The few fatal cases due to checkpoint inhibitors have typically occurred in patients who have cholestatic forms of liver injury or have other severe immune related adverse events (Stevens Johnson syndrome, capillary leak syndrome). Restarting pembrolizumab after severe liver injury requiring corticosteroid therapy can be followed by recurrence of liver injury and is not recommended. Switching to other checkpoint inhibitors (ipilimumab or anti-PD-L1 inhibitors) is more likely to be tolerated. Interestingly, survival rates do not seem to be improved by re-introduction of checkpoint inhibitor therapy after severe immune related adverse events. Thus, restarting therapy should be undertaken only after careful evaluation of the residual cancer status.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies, Checkpoint Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Pembrolizumab – Keytruda®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Pembrolizumab	1374853-91-4	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 23 June 2022

Abbreviations used: CPI, checkpoint inhibitor; CTLA-4, cytotoxic T lymphocyte associated antigen 4; HCC, hepatocellular carcinoma; irAE, immune related adverse event; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death receptor ligand-1; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Pathway-targeted therapies: monoclonal antibodies, protein kinase inhibitors, and various small molecules. In, Brunton LL, Hilal-Danan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1203-36.

(Textbook of pharmacology and therapeutics).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s59-64,69,76-83SumR.pdf

(FDA website with current and previous product labels and the 2014 initial medical review of the new drug application for pembrolizumab; ALT elevations arose in 26% [1% above 5 times ULN] and Alk P elevations in 27% [2% above 3 times ULN).

Phan GQ, Yang JC, Sherry RM, Hwu P, Topalian SL, Schwartzentruber DJ, Restifo NP, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci U S A. 2003;100:8372–7. PubMed PMID: 12826605.

(Initial study of anti-CTLA-4 therapy in 14 patients with melanoma, 6 of whom developed clinically apparent immune adverse reactions including one with hepatitis arising after the third infusion [ALT 6820 U/L], resolving over the ensuing 4 months with corticosteroid therapy: Case 1).

Kleiner DE, Berman D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig Dis Sci. 2012;57:2233–40. PubMed PMID: 22434096.

(Clinical and histological features of 5 patients with acute liver injury due to ipilimumab; 3 men and 2 women, ages 43 to 76 years, arising after 2-4 courses, 39-71 days after initial dose [peak bilirubin 1.5-5.1 mg/dL, ALT 326-3070 U/L, Alk P 206-427 U/L], only one had autoantibodies, resolving with immunosuppressive therapy within 1-4 months; one had recurrence on rechallenge; liver biopsies showed acute hepatitis usually with prominent inflammation, interface hepatitis and confluent necrosis: Case 1 Ipilimumab).

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366:2443–54. PubMed PMID: 22658127.

(Among 296 patients with advanced cancers [melanoma, NSCLC, renal, prostate and colorectal] treated with 1 of 5 doses of nivolumab every 2 weeks, response rates were highest with melanoma and renal cancer, and drug related adverse events were common, including immune related conditions such as pneumonitis [3 fatal], vitiligo, colitis, hepatitis [reversible in all cases], hypophysitis and thyroiditis; ALT elevations occurred in 11 patients [4%] and were greater than 5 times ULN in 2 [1%]).

Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366:2455–65. PubMed PMID: 22658128.

(Among 207 patients with various advanced solid tumors treated with nivolumab given daily for 14 days in 6 week cycles for an average of 12 weeks, durable tumor regression occurred in 6-17% of patients; serious adverse events considered related to therapy occurred in 5%, but no patient had ALT elevations above 5 times ULN).

Gardiner D, Lalezari J, Lawitz E, DiMicco M, Ghalib R, Reddy KR, Chang KM, et al. A randomized, double-blind, placebo-controlled assessment of BMS-936558, a fully human monoclonal antibody to programmed death-1 (PD-1), in patients with chronic hepatitis C virus infection. PLoS One. 2013;8:e63818. PubMed PMID: 23717490.

(Among 56 patients with chronic hepatitis C treated with a single injection of nivolumab or placebo, decreases in HCV RNA occurred in 11% of both groups, 12% had immune related adverse events and one a transient ALT elevation above 10 times ULN).

Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, Weber JS, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomized dose-comparison cohort of a phase 1 trial. Lancet. 2014;384(9948):1109–17. PubMed PMID: 25034862.

(Among 173 adults with advanced metastatic melanoma not responding to ipilimumab treated with pembrolizumab [2 or 10 mg/kg every 3 weeks], objective response rates were 26% at both doses; ALT elevations occurred in 3.5% of patients, but were below 5 times ULN; one patient developed "autoimmune hepatitis", but no further information provided).

Teply BA, Lipson EJ. Identification and management of toxicities from immune checkpoint-blocking drugs. Oncology (Williston Park). 2014 Nov;28 Suppl 3:30–8. PubMed PMID: 25384885.

(Clinical review of the toxicities of immune checkpoint blocking drugs such as ipilimumab, pembrolizumab and nivolumab; mentions that elevations of serum aminotransferase elevations should lead to careful exclusion of other causes of liver injury and increased monitoring; that elevations above 3 times ULN should lead to withholding the drug and starting corticosteroids; and, that elevations above 5 times ULN should lead to hospital admission and immediate administration of high doses of corticosteroids).

Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, Chmielowski B, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568–71. PubMed PMID: 25428505.

(Analysis of expression of PD-1 and its ligand on CD8+ T cells at the margins of melanoma tumors before and after treatment with pembrolizumab showed that high levels of PD-1 and its ligand are found in responders to therapy).

Pembrolizumab (Keytruda) for metastatic melanoma. Med Lett Drugs Ther. 2014;56(1455):e114–5. PubMed PMID: 25538981.

(Concise review of the rationale, mechanism of action, efficacy, safety and cost of pembrolizumab as therapy for metastatic melanoma shortly after its approval in the US; mentions that immune related adverse events occur, but are uncommon and can include hepatitis).

Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348(6230):124–8. PubMed PMID: 25765070.

(Exome sequencing from NSCLC tumors in patients treated with pembrolizumab showed that patients with a durable clinical benefit of therapy typically had higher numbers of nonsynonymous mutations, an association confirmed in a second cohort; mutations were not in the known PD-1 or checkpoint pathways, but likely represented genes that express neo-antigens).

Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56–61. PubMed PMID: 25838373.

(Commentary and review of the rationale, history, clinical efficacy and mechanism of action of immune checkpoint therapy).

Martin-Liberal J, Furness AJ, Joshi K, Peggs KS, Quezada SA, Larkin J. Anti-programmed cell death-1 therapy and insulin-dependent diabetes: a case report. Cancer Immunol Immunother. 2015;64:765–7. PubMed PMID: 25828465.

(54 year old woman with melanoma who was treated unsuccessfully with nivolumab and ipilimumab, developed diabetic ketoacidosis after 3 doses of pembrolizumab [anti-GAD positive] having had normal glucose levels before treatment, but also having high risk HLA alleles for type 1 diabetes; no mention of ALT elevations).

Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B, Herold KC. Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. Diabetes Care. 2015;38:e55–7. PubMed PMID: 25805871.

(Description of 5 patients with cancer who had new-onset of insulin dependent diabetes 1 week to 5 months after starting nivolumab [n=4] or pembrolizumab [n=1], 3 with anti-GAD, and all requiring insulin therapy chronically; 3% of patients treated with these agents at this cancer center).

Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, et al; KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372:2521–2532. PubMed PMID: 25891173.

(Among 834 patients with advance melanoma treated with pembrolizumab [Pem: 10mg/kg every 2 or 3 weeks] or ipilimumab [Ipil: 3 mg/kg every 3 weeks], 6 month progression free survival was higher with Pem [47% and 46%] than Ipil [26.5%] and adverse events were less; thyroiditis was more common with Pem, whereas colitis and hypophysitis were more common with Ipil; ALT elevations occurred in 3% [Pem] vs 3.5% [Ipil] and were above 5 times ULN in 0.2% vs 0.8%).

Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, et al. KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372:2018–28. PubMed PMID: 25891174.

(Among 495 patients with advanced NSCLC treated with pembrolizumab in 1 of 3 dose regimens, the overall response rate was 19% but was higher among those with greater PD-ligand 1 staring of tumor cells; adverse events occurred in 71%, including hypothyroidism 7%, pneumonitis 4% [1 fatal], and ALT elevations 2.2%).

Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509–20. PubMed PMID: 26028255.

(Among 41 patients with advanced cancers with or without mismatch repair deficiency, response rates to pembrolizumab were higher in those with mismatch repair deficiency [53%] than in those without [0%]; adverse events occurred in 98% of patients; ALT elevations occurred in 3 [7%] patients and were greater than 5 times ULN in 2 [5%]).

Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, Hodi FS, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16:908–18. PubMed PMID: 26115796.

(Among 540 patients with advanced ipilimumab-refractory melanoma treated with pembrolizumab [2 or 10 mg/kg every 3 weeks] or standard chemotherapy, progression free survival at 6 months was greater with pembrolizumab and adverse events were less; ALT elevations occurred in 4 patients [1.1%] and were greater than 5 times ULN in 1 [0.3%]).

Abdel-Rahman O, El Halawani H, Fouad M. Risk of elevated transaminases in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Expert Opin Drug Saf. 2015;14:1507–18. PubMed PMID: 26394770.

(Analysis of publications on checkpoint inhibitors indicated that therapy was associated with higher rates of ALT elevations).

Davar D, Wilson M, Pruckner C, Kirkwood JM. PD-1 blockade in advanced melanoma in patients with hepatitis C and/or HIV. Case Rep Oncol Med. 2015;2015:737389. PubMed PMID: 26448890.

(59 year old woman and 47 year old man with metastatic melanoma and combined HIV and hepatitis C infection were treated with pembrolizumab, tolerating therapy with no worsening of liver disease or HIV infection).

Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, Schmidgen MI, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer. 2016;60:190–209. PubMed PMID: 27085692.

(Among 496 patients with metastatic melanoma treated in 15 European centers with either nivolumab or pembrolizumab, 138 [28%] had at least one immune related adverse event including 11 [2%], with hepatitis arising after 1-4 infusions in all but 1, all treated with corticosteroids, 2 needing addition of mycophenolate, 9 resolving and 2 improving, none fatal).

Gelsomino F, Vitale G, D'Errico A, Bertuzzi C, Andreone P, Ardizzoni A. Nivolumab-induced cholangitic liver disease: a novel form of serious liver injury. Ann Oncol. 2017;28:671–672. PubMed PMID: 27993797.

(79 year old man with NSCLC developed jaundice after 4 infusions of nivolumab [day 62] with bilirubin 10.5, ALT ~480 U/L, Alk P~950 U/L, jaundice resolving 14 weeks after stopping therapy and with corticosteroid treatment, but patient died of progressive cancer shortly thereafter and before Alk P and GGT were completely normal).

Spänkuch I, Gassenmaier M, Tampouri I, Noor S, Forschner A, Garbe C, Amaral T. Severe hepatitis under combined immunotherapy: Resolution under corticosteroids plus anti-thymocyte immunoglobulins. Eur J Cancer. 2017;81:203–205. PubMed PMID: 28641200.

(49 year old woman with metastatic melanoma developed hepatitis after 3 cycles of ipilimumab and nivolumab [bilirubin 5.8 mg/dL, ALT 772 U/L, Alk P 449 U/L], with inadequate response to corticosteroids but eventual response after starting antithymocyte globulin, later tolerating pembrolizumab without recurrence on low doses of prednisone).

Kawakami H, Tanizaki J, Tanaka K, Haratani K, Hayashi H, Takeda M, Kamata K, et al. Imaging and clinicopathological features of nivolumab-related cholangitis in patients with non-small cell lung cancer. Invest New Drugs. 2017;35:529–536. PubMed PMID: 28317087.

(Among 91 Japanese patients with advanced NSCLC treated with nivolumab, 3 developed severe cholangitis arising after 6, 9 and 12 cycles in 2 women and 1 man, ages 64 to 82 years with marked elevations in Alk P (peak 1769, 1947 and 2996 U/L], modest ALT elevations [144, 101 and 70 U/L], no autoantibodies, and imaging showing localized common bile duct dilatation with distal breaking but no obstruction, hypertrophy of bile duct wall and no intrahepatic duct abnormalities, all with poor or only moderate response to corticosteroids).

Doherty GJ, Duckworth AM, Davies SE, Mells GF, Brais R, Harden SV, Parkinson CA, et al. Severe steroid-resistant anti-PD1 T-cell checkpoint inhibitor-induced hepatotoxicity driven by biliary injury. ESMO Open. 2017;2:e000268. PubMed PMID: 29081991.

(Three cases of checkpoint inhibitor induced cholestatic liver injury in 2 women and 1 man, ages 47, 59 and 76 years, who developed liver injury after 1-3 cycles of pembrolizumab or nivolumab, one with severe ductopenia who died of liver failure, one with focal ductopenia who eventually recovered, and one with prolonged cholestasis who died of progressive cancer, all with poor or only moderate response to corticosteroids).

Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L, Daud A, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017;390:1853–1862. PubMed PMID: 28822576.

(Among 811 patients with advanced melanoma treated with pembrolizumab [every 2 or 3 weeks] vs ipilimumab for a median of 23 months, overall survival at 24 months was higher with pembrolizumab [55% vs 42%] and serious adverse events were more frequent with ipilimumab, while hepatitis requiring drug discontinuation occurred only with pembrolizumab [4 cases: 0.7%, no deaths]).

Aivazian K, Long GV, Sinclair EC, Kench JG, McKenzie CA. Histopathology of pembrolizumab-induced hepatitis: a case report. Pathology. 2017;49:789–792. PubMed PMID: 29079004.

(67 year old man with metastatic melanoma and preexisting scleroderma developed fevers and jaundice shortly after an initial dose of pembrolizumab [bilirubin 23 mg/dL, ALT 117 U/L, Alk P 2275 U/L], with partial response to corticosteroids, but progression of melanoma leading to death a few months later, liver biopsy show focal and confluent necrosis, moderate inflammation, bile duct damage and cholestasis).

El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389:2492–2502. PubMed PMID: 28434648.

(Among 262 patients with advanced hepatocellular carcinoma [HCC] treated with nivolumab in dose escalation and expansion studies, objective responses were achieved in 15% to 20% of patients and toxicity was "manageable", with ALT elevations in 15% that were above 5 times ULN in 6%; among 51 patients with HBV all were receiving antiviral prophylaxis and none had HBV reactivation).

Lake AC. Hepatitis B reactivation in a long-term nonprogressor due to nivolumab therapy. AIDS. 2017;31:2115–2118. PubMed PMID: 28906278.

(72 year old man with HIV infection, recurrent metastatic lung cancer and anti-HBc without HBsAg was started on dolutegravir and abacavir and then on nivolumab and was found to have acute liver injury 1 month later [bilirubin 0.5 mg/dL, ALT 332 UL, Alk P 205 U/L, HBsAg positive and HBV DNA > 170 million IU/mL], started on tenofovir and later tolerated restarting nivolumab).

Koksal AS, Toka B, Eminler AT, Hacibekiroglu I, Uslan MI, Parlak E. HBV-related acute hepatitis due to immune checkpoint inhibitors in a patient with malignant melanoma. Ann Oncol. 2017;28:3103–3104. PubMed PMID: 28945827.

(56 year old man with melanoma and HBsAg in serum developed liver injury 12 weeks after starting ipilimumab [bilirubin 0.7 rising to 1.9 mg/dL, ALT 246 rising to 888 U/L, HBV DNA 244,259 IU/mL], responding to tenofovir and was continued on nivolumab).

Ragunathan K, Dadana S, Huang C-H. Hepatitis B reactivation after administration of pembrolizumab (Keytruda): a unique case report. Amer J Gastroenterol. 2017;112:S1187–8.

(51 year old man with metastatic lung cancer developed liver injury after 1st dose of pembrolizumab and was found to have reactivation of HBV [bilirubin 0.8 mg/dL, ALT 615 U/L, Alk P 64 U/L, HBsAg positive, HBV DNA > 170 million IU/mL], no follow up provided [possibly same patient as in Pandey 2018]).

Pandey A, Ezemenari S, Liaukovich M, Richard I, Boris A. A rare case of pembrolizumab-induced reactivation of hepatitis B. Case Rep Oncol Med. 2018;2018:5985131. PubMed PMID: 30416833.

(51 year old man with metastatic lung cancer developed liver injury after 1st dose of pembrolizumab and was found to have reactivation of HBV [bilirubin normal, ALT 528 rising to 994 U/L, Alk P normal, HBsAg positive, HBeAg negative, HBV DNA > 170 million IU/mL], responding to tenofovir therapy, and later restarted on checkpoint inhibitor therapy).

Pollack MH, Betof A, Dearden H, Rapazzo K, Valentine I, Brohl AS, Ancell KK, et al. Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. Ann Oncol. 2018;29:250–255. PubMed PMID: 29045547.

(Among 80 patients treated with checkpoint inhibitors who developed immune related adverse events requiring discontinuation who were then restarted on therapy, 31 [39%] had recurrence or toxicities requiring discontinuation again, of the 29 who had hepatitis initially, 5 had recurrence on restarting).

Santini FC, Rizvi H, Plodkowski AJ, Ni A, Lacouture ME, Gambarin-Gelwan M, Wilkins O, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. Cancer Immunol Res. 2018;6:1093–1099. PubMed PMID: 29991499.

(Among 482 patients with metastatic or advanced NSCLC treated with checkpoint inhibitors at a single US referral center between 2011 and 2016, 68 [14%] developed a serious immune related adverse event [irAE] that required discontinuation of whom 38 were retreated, of whom 18 had no recurrence, 10 had recurrence of the same irAE, 10 had a new irAE [2 of which were fatal]; restarting therapy appeared to be beneficial only in those who had no tumor response before onset of the first event).

Zen Y, Yeh MM. Hepatotoxicity of immune checkpoint inhibitors: a histology study of seven cases in comparison with autoimmune hepatitis and idiosyncratic drug-induced liver injury. Mod Pathol. 2018;31:965–973. PubMed PMID: 29403081.

(Liver histology from 7 patients with checkpoint inhibitor [CPI] induced hepatitis [4 nivolumab, 2 ipilimumab, arising after 1-6 doses] and classical autoimmune hepatitis showed similar rates of lobular hepatitis, but less confluent necrosis with CPIs and absence of autoantibodies and IgG elevations).

Huffman BM, Kottschade LA, Kamath PS, Markovic SN. Hepatotoxicity after immune checkpoint inhibitor therapy in melanoma: natural progression and management. Am J Clin Oncol. 2018;41:760–765. PubMed PMID: 28749795.

(Among 281 patients with cancer treated with checkpoint inhibitors at the Mayo Clinic over a 5 year period, 17 [6%] developed liver injury within 16 to 151 [median=52] days of starting [ipilimumab alone in 12, with nivolumab in 2 and pembrolizumab alone in 3], all with ALT elevations [59 to 2355 U/L], often with Alk P elevations [up to 1728 U/L], 6 with jaundice [bilirubin 2.5 to 15.7 mg/dL], all but one treated with corticosteroids, responding in 6 to 56 [median 31] days, 2 requiring a second agent [azathioprine or cycloserine], none fatal).

Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378:158–168. PubMed PMID: 29320654.

(Review of the clinical features, outcomes, pathogenesis and therapy of immune related adverse events of checkpoint inhibitor therapy).

De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, Roche B, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol. 2018;68:1181–1190. PubMed PMID: 29427729.

(Among 536 patients treated with checkpoint inhibitors, 19 [3.5%] were referred to a liver service for high grade hepatitis and 16 underwent liver biopsy; ages 33 to 84 years, 56% female, injury arising after 1-36 [median=5] weeks and 1-36 [median=2] doses, presenting with fever in 38%, rash in 31%, ALT 266 to 3137 [460] U/L, Alk P 54 to 768 [309] U/L, bilirubin 0.4 to 19 [1.1] mg/dL, enzyme pattern most commonly being mixed, 10 patients treated with corticosteroids and 6 resolving spontaneously and no deaths).

Karamchandani DM, Chetty R. Immune checkpoint inhibitor-induced gastrointestinal and hepatic injury: pathologists' perspective. J Clin Pathol. 2018;71:665–671. PubMed PMID: 29703758.

(Review of the gastrointestinal and hepatic pathology of checkpoint inhibitor induced immune adverse events with acute hepatitis and acute cholangitic patterns found on liver biopsy).

LoPiccolo J, Brener MI, Oshima K, Lipson EJ, Hamilton JP. Nodular regenerative hyperplasia associated with immune checkpoint blockade. Hepatology. 2018;68:2431–2433. PubMed PMID: 30014512.

(35 year old man with melanoma developed anasarca and ascites 3 weeks after starting pembrolizumab [bilirubin 0.8 mg/dL, ALT 62 U/L, Alk P 331 U/L, albumin 2.5 g/dL, INR 1.2], liver biopsy demonstrating nodular regenerative hyperplasia without fibrosis, and after stopping therapy and transjugular intrahepatic portosystemic stent shunt [TIPSS], the ascites and anasarca resolved).

Abu-Sbeih H, Tran CN, Ge PS, Bhutani MS, Alasadi M, Naing A, Jazaeri AA, et al. Case series of cancer patients who developed cholecystitis related to immune checkpoint inhibitor treatment. J Immunother Cancer. 2019;7:118. PubMed PMID: 31053161.

(Among 4253 patients treated with checkpoint inhibitors at the MD Anderson Cancer Center between 2010 and 2018, 25 [0.6%] developed acalculous cholecystitis attributed to the immunotherapy most frequently with anti-CTLA-4 agents alone [1.6%], than anti-PD1/PD-L1 [0.4%] and combination [0.9%], mean age of patients was 60 years, 60% male, 64% white, median peak ALT 55 U/L, bilirubin 1.4 mg/dL, 20% underwent cholecystectomy, all recovered, 10 [40%] restarted therapy, all without recurrence).

Fouchard M, Jantzem H, Quere G, Descourt R, Robinet G, Poureau PG. Three cases of immune cholangitis related to anti-programmed cell death and programmed cell death ligand agents for the treatment of non-small cell lung cancer. Eur J Cancer. 2019;115:107–110. PubMed PMID: 31132740.

(3 patients with metastatic lung cancer developed cholangitis 2, 4 and 9 months after starting checkpoint inhibitor therapy [nivolumab, durvalumab/tremelimumab, pembrolizumab] presenting with abdominal pain and fever, modest ALT but marked Alk P elevations and minimal jaundice, imaging showing biliary dilation and thickening of the gallbladder wall, biopsies showing inflammation with CD8+ lymphocytes, and slow clinical response to corticosteroids but long term remission in cancer).

Kurokawa K, Hara M, Iwakami SI, Genda T, Iwakami N, Miyashita Y, Fujioka M, et al. Cholestatic liver injury induced by pembrolizumab in a patient with lung adenocarcinoma. Intern Med. 2019;58:3283–3287. PubMed PMID: 31735738.

(48 year old man with refractory lung cancer developed fever, fatigue and jaundice 11 days after a second dose of pembrolizumab [bilirubin 5.4 mg/dL, ALT 175 U/L, Alk P 1033 U/L], with improvement on treatment with corticosteroids and ursodiol but death within months from progressive cancer).

Jennings JJ, Mandaliya R, Nakshabandi A, Lewis JH. Hepatotoxicity induced by immune checkpoint inhibitors: a comprehensive review including current and alternative management strategies. Expert Opin Drug Metab Toxicol. 2019;15:231–244. PubMed PMID: 30677306.

(Comprehensive review of the clinical features, diagnosis, histology, outcomes and management of checkpoint inhibitor related liver injury including serum aminotransferase elevations and immune related hepatic injury, with recommendations on use of corticosteroids based upon the grade of liver injury).

Kwan JM, Cheng R, Feldman LE. Hepatotoxicity and recurrent NSTEMI while on pembrolizumab for metastatic giant cell bone tumor. Am J Med Sci. 2019;357:343–347. PubMed PMID: 30638772.

(71 year old woman with metastatic giant cell tumor of the bone developed two episodes of chest pain and coronary occlusion and liver injury one year after starting pembrolizumab [bilirubin 6.2 rising to 13 mg/dL, ALT 463 U/L, Alk P 794 U/L], biopsy showing primary biliary cholangitis [Alk P had been elevated chronically] and an eosinophilic hepatitis, responding to prednisone and ursodiol).

Koya Y, Shibata M, Shinohara N, Nebuya S, Oe S, Honma Y, Senju M, et al. Secondary sclerosing cholangitis with hemobilia induced by pembrolizumab: Case report and review of published work. Hepatol Res. 2019;49:950–956. PubMed PMID: 30861263.

(66 year old man with small cell lung cancer developed cholestatic liver injury after 5 cycles of pembrolizumab [bilirubin 1.1 rising to 20 mg/dL, ALT 313 U/L, Alk P 2241 U/L], imaging showing dilatation of intra- and extra-hepatic bile ducts, biopsies showing secondary sclerosing cholangitis and active inflammation and scarring of bile ducts; only modest response to ursodiol, bezafibrate and corticosteroid therapy).

Kida A, Matsuda K, Matsuda M, Sakai A. Hepatobiliary and Pancreatic: Biliary injury related to checkpoint inhibitor "pembrolizumab". J Gastroenterol Hepatol. 2019;34:1478. PubMed PMID: 31197882.

(62 year old man with ureteral carcinoma developed abdominal pain after starting pembrolizumab [bilirubin 0.6 mg/dL, ALT 306 U/L, GGT 581 U/L], with normal cholangiograms and liver biopsy showing portal inflammation and bile duct injury, responding to oral prednisone and restarted on pembrolizumab).

Cheung V, Gupta T, Payne M, Middleton MR, Collier JD, Simmons A, Klenerman P, et al. Immunotherapy-related hepatitis: real-world experience from a tertiary centre. Frontline Gastroenterol. 2019;10(4):364–371. PubMed PMID: 31656561.

(Among 453 patients treated with checkpoint inhibitors for cancer between 2022 and 2018, 20 [4%] developed immune related hepatitis, with highest rates with the combination of ipilimumab and nivolumab, 18 treated with immunosuppression using corticosteroids, 8 with addition of mycophenolate and 2 with infliximab, none fatal).

Zen Y, Yeh MM. Checkpoint inhibitor-induced liver injury: A novel form of liver disease emerging in the era of cancer immunotherapy. Semin Diagn Pathol. 2019;36:434–440. PubMed PMID: 31358424.

(Liver histology from 7 patients with checkpoint inhibitor [CPI] induced hepatitis [4 nivolumab, 2 ipilimumab, arising after 1-6 doses] and classical autoimmune hepatitis showed similar rates of lobular hepatitis, but less confluent necrosis with CPIs and absence of autoantibodies and IgG elevations).

Vozy A, De Martin E, Johnson DB, Lebrun-Vignes B, Moslehi JJ, Salem JE. Increased reporting of fatal hepatitis associated with immune checkpoint inhibitors. Eur J Cancer. 2019;123:112–115. PubMed PMID: 31678768.

(Review of the VigiBase registry of adverse drug reactions through September 2018 identified 531 cases of immune related hepatitis, 85% due to CPIs alone with an increase in fatality rate over time, being 14% between 2011 to 2016 and 34% in 2017-2018, time to onset median of 42 days, arising after 1-4 courses [median 2] and with concurrent other organ immune related injury in 31%, usually thyroid or skin).

Zhang D, Hart J, Ding X, Zhang X, Feely M, Yassan L, Alpert L, et al. Histologic patterns of liver injury induced by anti-PD-1 therapy. Gastroenterol Rep (Oxf). 2019;8:50–55. PubMed PMID: 32467761.

(Liver histology in 8 cases of immune mediated liver injury after monoclonal anti-PD1 therapy revealed a lobular hepatitis without features of autoimmune hepatitis).

Imoto K, Kohjima M, Hioki T, Kurashige T, Kurokawa M, Tashiro S, Suzuki H, et al. Clinical features of liver injury induced by immune checkpoint inhibitors in Japanese patients. Can J Gastroenterol Hepatol. 2019;2019:6391712. PubMed PMID: 31929981.

(Among 343 Japanese patients with cancer treated with checkpoint inhibitors, 56 [16%] developed evidence of liver injury, arising after 21-94 [median=46] days, with initial ALT 39 to 136 [mean 60] U/L, Alk P 263 to 857 [471] U/L, bilirubin 0.4 to 1.0 [0.7] mg/dL, and thus a cholestatic pattern was found in most patients, and there was a low rate of high grade liver injury [3.2%] and no fatalities).

Zhang X, Zhou Y, Chen C, Fang W, Cai X, Zhang X, Zhao M, et al. Hepatitis B virus reactivation in cancer patients with positive Hepatitis B surface antigen undergoing PD-1 inhibition. J Immunother Cancer. 2019;7:322. PubMed PMID: 31753012.

(Among 114 HBsAg-positive Chinese patients undergoing checkpoint inhibitor therapy for advanced malignancies, 6 developed HBV reactivation [1 of 85 on prophylaxis vs 5 of 29 not] after 3-35 [median 18] weeks of therapy with peak ALT 28 to 465 U/L, HBV DNA 1,800 to 60 million IU/mL [all were undetectable at baseline], none with jaundice, 5 treated with rapid improvement, all 6 recovered).

Lee PC, Chao Y, Chen MH, Lan KH, Lee IC, Hou MC, Huang YH. Risk of HBV reactivation in patients with immune checkpoint inhibitor-treated unresectable hepatocellular carcinoma. J Immunother Cancer. 2020;8:e001072. PubMed PMID: 32863270.

(Among 62 Taiwanese patients with HBsAg or anti-HBc without HBsAg treated with checkpoint inhibitors for advanced HCC, reactivation of HBV rose in none of 56 given prophylaxis vs 1 of 6 not given antiviral prophylaxis: the one case in an HBsAg positive patient with HBV DNA 8960 IU/mL at baseline rising to 168,000 IU/mL, peak ALT 174U/L, bilirubin 5.2 mg/dL, resolving with tenofovir therapy).

Onoyama T, Takeda Y, Yamashita T, Hamamoto W, Sakamoto Y, Koda H, Kawata S, et al. Programmed cell death-1 inhibitor-related sclerosing cholangitis: a systematic review. World J Gastroenterol. 2020;26:353–365. PubMed PMID: 31988594.

(Review of literature on secondary sclerosing cholangitis due to anti-PD-1/PD-L1 therapy identified 31 cases with male:female ratio of 2:1, median age 67 [range 43 to 89] years, arising after a median of 5.5 [range 1-27] cycles of nivolumab [19], pembrolizumab [10], avelumab [1], or durvalumab [1], with median bilirubin 0.8 [0.3-15.9] mg/dL, ALT 125 [31-1536] U/L, AST 129 [49-961] U/L, Alk P 1543 [237-5066] U/L, GGT 452 [114-2094] U/L, cholangiography demonstrating biliary dilation without obstruction [77%], hypertrophy of the extrahepatic biliary tree [90%], and biliary strictures [30%] and biopsy demonstrating CD8+ infiltrates around bile ducts, and adequate response to corticosteroids in only 11%).

Zen Y, Chen YY, Jeng YM, Tsai HW, Yeh MM. Immune-related adverse reactions in the hepatobiliary system: second-generation check-point inhibitors highlight diverse histological changes. Histopathology. 2020;76:470–480. PubMed PMID: 31550390.

(Description of 10 cases of second generation checkpoint inhibitor induced immune liver injury mentions 3 patterns, hepatocellular, cholestatic and granulomatous injury, the cholestatic form often with a delayed latency and poor response to corticosteroids).

Peeraphatdit TB, Wang J, Odenwald MA, Hu S, Hart J, Charlton MR. Hepatotoxicity from immune checkpoint inhibitors: a systematic review and management recommendation. Hepatology. 2020;72:315–329. PubMed PMID: 32167613.

(Review of the clinical features, biochemical findings, histology, pathogenesis, diagnosis and management of immune related liver injury due to the checkpoint inhibitors).

Miller ED, Abu-Sbeih H, Styskel B, Nogueras Gonzalez GM, Blechacz B, Naing A, et al. Clinical characteristics and adverse impact of hepatotoxicity due to immune checkpoint inhibitors. Am J Gastroenterol. 2020;115:251–261. PubMed PMID: 31789632.

(Among 5762 recipients of checkpoint inhibitor therapy of cancer at the MD Anderson Cancer Center between 2010 and 2018, 433 [8%] developed ALT levels and 100 had levels above 5 times ULN [2%), the rate being 8% with combination therapy, 1.7% with anti-CTLA agents and 1.1% with PD1 and PDL1 blockers, the abnormalities arising after a median of 59 days; all had the checkpoint inhibitor therapy held, 67 received corticosteroids [for a median of 43 days], 3 with mycophenolate, and 31 were rechallenged after resolution of the hepatitis, of whom 8 [26%] had a recurrence).

Sawada K, Hayashi H, Nakajima S, Hasebe T, Fujiya M, Okumura T. Non-alcoholic fatty liver disease is a potential risk factor for liver injury caused by immune checkpoint inhibitor. J Gastroenterol Hepatol. 2020 Jun;35(6):1042–1048. PubMed PMID: 31752049.

(Among 135 patients with cancer treated with nivolumab or pembrolizumab, 8 developed immune mediated hepatitis of whom 3 [37.5%] had preexisting chronic liver disease versus 14 of the total [10.3%]).

Kitagataya T, Suda G, Nagashima K, Katsurada T, Yamamoto K, Kimura M, Maehara O, et al. Prevalence, clinical course, and predictive factors of immune checkpoint inhibitor monotherapy-associated hepatitis in Japan. J Gastroenterol Hepatol. 2020;35:1782–1788. PubMed PMID: 32187734.

(Among 202 patients with cancer treated with checkpoint inhibitors at a single referral center in Japan, 17 [8.5%] developed immune related hepatitis which was severe in 8 [4.5%] often requiring corticosteroids, 2 receiving mycophenolate as well, but none died).

Thorsteinsdottir T, Løitegård T, Reims HM, Porojnicu AC. Fatal cholestatic liver injury during treatment with PD1 immune checkpoint inhibitor for malignant melanoma: A Case Report. Case Rep Oncol. 2020;13:659–663. PubMed PMID: 32774252.

(70 year old woman with metastatic melanoma developed jaundice after 13 cycles of pembrolizumab [bilirubin 12.6 rising to 32.7 mg/dL, ALT 1536 U/L, GGT 2094 U/L, Alk P 237 U/L], biopsy showing few bile ducts, mild inflammation and marked cholestasis, with minimal response to corticosteroids and ursodiol, dying 26 days after symptom onset).

Ruggiero R, Fraenza F, Scavone C, di Mauro G, Piscitelli R, Mascolo A, Ferrajolo C, et al. Immune checkpoint inhibitors and immune-related adverse drug reactions: data from Italian Pharmacovigilance Database. Front Pharmacol. 2020;11:830. PubMed PMID: 32581796.

(Among 2088 safety reports of check point inhibitors enrolled in an Italian pharmacovigilance registry, 801 were immune related including gastrointestinal [33%], skin [17%] and liver [2.7%] due to nivolumab [70%], pembrolizumab [11%], ipilimumab [15%], atezolizumab [4%] and avelumab [<1%]).

Riveiro-Barciela M, Barreira-Díaz A, Vidal-González J, Muñoz-Couselo E, Martínez-Valle F, Viladomiu L, Mínguez B, et al. Immune-related hepatitis related to checkpoint inhibitors: clinical and prognostic factors. Liver Int. 2020;40:1906–1916. PubMed PMID: 32329119.

(Among 414 patients treated with checkpoint inhibitors, 28 developed high grade liver injury but 19 were considered mild, 7 moderate, 1 severe, and only 1 fatal).

Vitale G, Lamberti G, Comito F, Di Nunno V, Massari F, Morelli MC, Ardizzoni A, et al. Anti-programmed cell death-1 and anti-programmed cell death ligand-1 immune-related liver diseases: from clinical pivotal studies to real-life experience. Expert Opin Biol Ther. 2020;20:1047–1059. PubMed PMID: 32425081.

(Review of the hepatic complications of anti-PD-1 and anti-PD-L1 checkpoint inhibitors that includes immune mediated hepatitis [typically panlobular inflammation and injury], small and large duct cholangitis [similar to primary biliary and sclerosing cholangitis], immune mediated cholecystitis, nodular regenerative hyperplasia and vanishing bile duct syndrome).

Kitagataya T, Suda G, Nagashima K, Katsurada T, Yamamoto K, Kimura M, Maehara O, et al. Prevalence, clinical course, and predictive factors of immune checkpoint inhibitor monotherapy-associated hepatitis in Japan. J Gastroenterol Hepatol. 2020;35:1782–1788. PubMed PMID: 32187734.

(Among 202 patients with cancer treated with checkpoint inhibitors at a single referral center in Japan, 17 [8.5%] developed immune related hepatitis which was severe in 8 [4.5%], often requiring corticosteroids, 2 receiving mycophenolate as well, but none died).

Mizuno K, Ito T, Ishigami M, Ishizu Y, Kuzuya T, Honda T, Kawashima H, et al. Real world data of liver injury induced by immune checkpoint inhibitors in Japanese patients with advanced malignancies. J Gastroenterol. 2020;55:653–661. PubMed PMID: 32124082.

(Among 546 patients with advanced malignancies treated with checkpoint inhibitors at two Japanese referral centers between 2014 and 2019, high grade, immune mediated liver injury occurred in 29 [5%], mean age 69 years, 73% male, mean onset 52 [range 1-273] days, after 3 [1-15] doses of ipilimumab [6%], nivolumab [54%], pembrolizumab [30%], atezolizumab [6%], durvalumab [2.4%], combination [1.3%], presenting with hepatocellular [21%], cholestatic [59%] or mixed [21%] enzyme elevations, 4 with cholangitis and biliary dilatation without obstruction, only 1 case fatal; predictive factors for injury included ipilimumab [hazard ratio 4.2]).

Cho YA, Han JM, Kang SY, Kim DC, Youn YJ, Choi KH, Gwak HS. Analysis of risk factors for hepatotoxicity induced by immune checkpoint Inhibitors. J Immunother. 2021;44:16–21. PubMed PMID: 33290362.

(Among 194 patients with cancer treated with checkpoint inhibitors at two Korean referral centers, 125 [64%] developed liver test abnormalities, more frequently in younger patients vs older [30 to 50 years - 80% vs 50 to 70 years - 72%, and >70 years - 50%] and in men than women [68% vs 58%]).

Gauci ML, Baroudjian B, Bédérède U, Zeboulon C, Delyon J, Allayous C, Madelaine I, et al; PATIO group. Severe immune-related hepatitis induced by immune checkpoint inhibitors: Clinical features and management proposal. Clin Res Hepatol Gastroenterol. 2021;45:101491. PubMed PMID: 32773362.

(Among 339 patients treated at a single French referral center with checkpoint inhibitors, 21 [6.2%] developed high grade liver toxicity, including 8% [7/86] receiving ipilimumab, 3% [3/105] nivolumab, 1% [1/122] pembrolizumab, and 38% [10/26] combination therapy; 13 patients received corticosteroids, all except one with severe biliary lesions recovered, and 8 restarted therapy none of whom relapsed).

Chatterjee A, Bivas BK, Gehani A, Sen S. Pembrolizumab-induced large duct cholangiopathy: Diagnosis and follow-up imaging. J Postgrad Med. 2021r;67:43–45. PubMed PMID: 33533751.

(66 year old man with lung cancer developed liver test abnormalities after two cycles of pembrolizumab [ALT 85 U/L, Alk P 232 subsequently rising to 1843 U/L], with imaging showing bile duct dilatation, which improved but not completely with holding pembrolizumab which was later restarted without worsening of the liver abnormalities).

Ortland I, Mirjalili M, Kullak-Ublick GA, Peymani P. Drug-induced liver injury in Switzerland: an analysis of drug-related hepatic disorders in the WHO pharmacovigilance database VigiBase™ from 2010 to 2020. Swiss Med Wkly. 2021;151:w20503. PubMed PMID: 34000058.

(Among 2042 cases of drug induced liver injury reported from Switzerland to VigiBase between 2010 and 2020, average age 57 years, males and females similar proportions, 10% were fatal and the most common causes included acetaminophen [5.8%], amoxicillin/clavulanate 3.1%, esomeprazole [2.0%], atorvastatin [1.9%], and nivolumab [1.3%]).

Yamamoto A, Yano Y, Ueda Y, Yasutomi E, Hatazawa Y, Hayashi H, Yoshida R, et al. Clinical features of immune-mediated hepatotoxicity induced by immune checkpoint inhibitors in patients with cancers. J Cancer Res Clin Oncol. 2021;147:1747–1756. PubMed PMID: 33222015.

(Among 250 patients with cancer treated with checkpoint inhibitors, 21 [9.5%] developed immune mediated liver injury, most frequently with ipilimumab [60%], ipilimumab and nivolumab [57%] compared to nivolumab alone [7%] or pembrolizumab [3%], and rates were higher in patients with melanoma [35%] compared to renal cell cancer [10%] and others).

Aya F, González-Navarro EA, Martínez C, Carcelero E, Arance A. Safe anti-programmed cell death-1 rechallenge with antibody switching after immune-related adverse events: brief communication. Immunotherapy. 2021;13:745–752. PubMed PMID: 33906373.

(68 year old woman with metastatic melanoma developed ALT elevations [215 U/L] after an initial dose of nivolumab, which resolved rapidly with prednisone therapy and she later tolerated pembrolizumab without recurrent hepatic injury).

da Silva JA, Falcão D, Cardoso C, Pires AL, Araújo A, Castro-Poças F. Hepatic immune-mediated adverse effects of immune checkpoint inhibitors: analysis of real-life experience. Ann Hepatol. 2021;26:100561. PubMed PMID: 34653687.

(Among 151 patients treated with checkpoint inhibitors, 8 [5%] developed liver injury, 5 due to metastases and 3 from immune mediated hepatitis, 2 from nivolumab and 1 pembrolizumab, with latency of 84 days, all three cholestatic and responding to immunosuppression).

Suda T, Kobayashi M, Kurokawa K, Matsushita E. Simultaneous occurrence of autoimmune pancreatitis and sclerosing cholangitis as immune-related adverse events of pembrolizumab. BMJ Case Rep. 2021;14:e243360. PubMed PMID: 34088696.

(57 year old man with metastatic lung cancer developed evidence of liver injury 6 weeks after starting pembrolizumab, paclitaxel and carboplatin [ALT 84 U/L, Alk P 490 U/L]; pembrolizumab was continued but several weeks later he developed severe abdominal pain and pancreatitis [bilirubin 1.1 mg/dL, ALT 406 U/L, Alk P 1330 U/L, amylase 1034 U/L], cholangiography showing irregularities of intrahepatic bile ducts and biliary tree hypertrophy, responding slowly and only partially to high dose corticosteroids and ursodiol).

Wong GL, Wong VW, Hui VW, Yip TC, Tse YK, Liang LY, Lui RN, et al. Hepatitis flare during immunotherapy in patients with current or past hepatitis B virus infection. Am J Gastroenterol. 2021;116:1274–1283. PubMed PMID: 33560651.

(Among 990 patients in Hong Kong with advanced malignancies treated with checkpoint inhibitors between 2014 and 2019 [397 HBsAg positive, 482 with anti-HBc or anti-HBs, 111 negative for both at baseline], 39% of HBsAg-positive vs 30% of HBsAg-negative patients developed ALT elevations during therapy, but only two cases [both HBsAg positive and on prophylaxis] were due to HBV reactivation).

Mustafayev K, Torres H. Hepatitis B virus and hepatitis C virus reactivation in cancer patients receiving novel anticancer therapies. Clin Microbiol Infect. 2022: S1198-743X (22)00119-7.

(Review of the literature on reactivation of HBV and HCV in patients on "novel" anticancer therapy concludes that reactivation can occur with checkpoint inhibitor therapy, but largely among HBsAg positive patients and only rarely in patients with resolved hepatitis B).

Yoo S, Lee D, Shim JH, Kim KM, Lim YS, Lee HC, Yoo C, et al. Risk of hepatitis B virus reactivation in patients treated with immunotherapy for anti-cancer treatment. Clin Gastroenterol Hepatol. 2022;20:898–907. PubMed PMID: 34182151.

(Among 3,465 patients with advanced malignancies treated with checkpoint inhibitors between 2015 and 2020 at a single referral center in Korean, 511 [15%] were HBsAg positive at baseline, reactivation of HBV occurred in 5 of 511 [1%] HBsAg positive vs none of 2,954 HBsAg negative patients, arising in 2 of 464 [0.4%] patients given prophylaxis [both having stopped antivirals] vs 3 of 47 not given prophylaxis [6.4%]; reactivation arising after 3-141 weeks [median 54 weeks] of nivolumab [n=2], pembrolizumab [n=2] or ipilimumab and nivolumab [n=1] treatment, ALT peak 53 to 1768 IU/mL, HBV DNA 6,100 to 3.9 million IU/mL, resolving with 2 to 6 weeks of starting antiviral therapy).

Al-Nattah S, Lata Sharma K, Caldis M, Spengler E, Nicholas Rose W. Plasmapheresis for pembrolizumab-induced hepatitis in a patient with squamous cell carcinoma and prior orthotopic liver transplantation. Case Reports Hepatol. 2022;2022:5908411. PubMed PMID: 35096431.

(76 year old man with liver transplant for alcoholic cirrhosis with excellent control with tacrolimus developed refractory metastatic laryngeal carcinoma and was treated with pembrolizumab and 5 weeks later developed evidence of liver injury [bilirubin 2.1 mg/dL, ALT 783 U/L, Alk P 444 U/L], with minimal response to increases in immunosuppression and liver biopsy showing bile duct loss, thereafter treated with plasmapheresis and intravenous immunoglobulin with slow, eventual improvement).

Fernández-Gordón Sánchez FM, Gómez-Domínguez E, Paredes Ruiz D, Rodríguez Gil Y, Martín Algíbez A, Fernández Vázquez I, Martínez Montiel P. Ustekinumab for corticodependent immune-mediated colitis by pembrolizumab, an alternative for patients with concomitant liver injury. Rev Esp Enferm Dig. 2022 Jan 25. Epub ahead of print. PubMed PMID: 35073724.

(56 year old woman with large cell lung cancer developed immune mediated colitis and cholestatic liver injury while receiving pembrolizumab that was successfully treated with corticosteroids and ustekinumab).