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-. Avelumab. [Updated 2022 Jun 23].
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/

# Avelumab

Updated: June 23, 2022.

# OVERVIEW

## Introduction

Avelumab is a human monoclonal antibody to programmed cell death ligand 1 (PD-L1), which acts as a checkpoint inhibitor and is used in the immunotherapy of several forms of advanced or metastatic cancer. Avelumab therapy 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

Avelumab (av el' ue mab) is a human recombinant monoclonal IgG1 antibody to the programmed cell death ligand-1 (PD-L1), which has distinctive immunomodulatory activity and is used as a checkpoint inhibitor in cancer immunotherapy. The programmed cell death receptor 1 (PD-1) is an important checkpoint molecule that is expressed on activated T and B cells. Binding of the ligand to PD-1 activates programmed cell death pathways that terminate or down regulate cytotoxic T cell responses. Monoclonal antibody binding to the PD-L1 prevents its engagement with the PD receptor and subsequent induction of the cellular pathways that down regulate T cell responses. Inhibition of this pathway allows for a continued activation and proliferation of T cell responses. 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 multicenter studies, avelumab therapy resulted in objective responses in patients with advanced, metastatic or unresectable malignant neoplasms, and a proportion of patients had a long term remission. Avelumab was approved for use in metastatic Merkel cell carcinoma and advanced, refractory urothelial bladder carcinoma in the United States in 2017, and was subsequently approved for use in combination with axitinib in advanced renal cell carcinoma. Avelumab is available in single use 10 mL vials of 200 mg (20 mg/mL) under the brand name Bavencio. The recommended dose is 800 mg as an intravenous infusion every 2 weeks. Premedication with acetaminophen and antihistamines is recommended for the first 4 infusions.

As with most checkpoint inhibitors, side effects of avelumab are common and can include fatigue, headache, musculosketetal pain, arthralgia, abdominal pain, diarrhea, nausea, vomiting, decreased appetite, weight loss, fever, cough, dyspnea, pruritus, and rash. Importantly, as a result of the immune enhancement, between 15% and 30% of avelumab treated patients develop immune related side effects, including enterocolitis, dermatitis, endocrinopathy, pneumonitis, neuropathy, nephritis and hepatitis. Most of these reactions respond to discontinuation of avelumab and initiation of immunosuppressive therapy, but some have resulted in fatalities and some have required permanent discontinuation of the checkpoint inhibitor and long term immunosuppressive therapy. Baseline screening and regular monitoring for these adverse events during avelumab therapy is recommended. Early recognition and prompt management of side effects is an integral

component of proper use of checkpoint inhibitors. Checkpoint inhibitors should be used only by health care professionals with training in immunotherapy and experience in the management of the side effects of immunomodulatory agents. Other rare but potentially severe adverse effects of avelumab include infusion reactions and embryo-fetal toxicity.

## Hepatotoxicity

Mild-to-moderate serum aminotransferase elevations are not uncommon during avelumab 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 receiving checkpoint inhibitor therapy, 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 generally demonstrates a pan-lobular 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 avelumab 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 avelumab 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 the 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 hepatitis do not manifest the large bile duct changes but demonstrate loss and paucity of the smaller, intrahepatic portal bile ducts resulting in a vanishing bile duct syndrome similar to primary biliary cholangitis (PBC).

The effects of PD-L1 inhibition on chronic hepatitis B are not well defined but convincing examples of reactivation of hepatitis B have been described due to 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 avelumab in

regard to the risk of reactivation of hepatitis B to provide rates of reactivation with and without antiviral prophylaxis.

Likelihood score: B (likely cause of clinically apparent immune mediated liver injury and possible cause of reactivation of hepatitis B).

## Mechanism of Injury

The liver injury due to avelumab is likely 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 avelumab recommend monitoring of liver tests and interrupting therapy for patients who develop serum aminotransferase elevations above 3 times the 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 checkpoint inhibitors resolve with prompt institution of immunosuppressive therapy. The few fatal cases that have been reported during immunotherapy with checkpoint inhibitors occurred in patients who had other severe immune related adverse events (Stevens Johnson syndrome, capillary leak syndrome) or who had a cholestatic form of liver injury or delay in receiving corticosteroids. Restarting avelumab 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-1 inhibitors) is more likely to be tolerated. However, 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**

Avelumab – Bavencio®

**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 |
|---|---|---|---|
| Avelumab | 1537032-82-8 | 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/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761049

*(FDA website with current and previous product labels and initial 2021 review of the New Drug Application for avelumab; in a pooled analysis of 1738 treated subjects, ALT elevations arose in 21% and were above 5 times ULN in 2.4%, while Alk P elevations occurred in 31% and were above 5 times ULN in 4.2%; serious adverse events included autoimmune hepatitis).*

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).*

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 an anti-PD-L1 monoclonal antibody 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).*

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; 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 Nov 27;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).*

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).*

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 indicate that therapy is associated with higher rates of ALT elevations than with standard of care).*

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).*

Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016;17:1374–85. PubMed PMID: 27592805.

*(Among 88 patients with chemotherapy refractory Merkel cell carcinoma treated with avelumab [10 mg/kg intravenously every 2 weeks], 28 [32%] developed an objective response including 8 with a complete response, and side effects were common including one patient with ALT elevations above 5 times ULN and one death due to hepatic failure; no details provided).*

Apolo AB, Infante JR, Balmanoukian A, Patel MR, Wang D, Kelly K, Mega AE, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. J Clin Oncol. 2017;35:2117–24. PubMed PMID: 28375787.

*(Among 44 patients with refractory urothelial bladder cancer treated with avelumab, 5 had a complete and 3 a partial response, and adverse reactions included fatigue [32%], infusion reactions [21%], and nausea [11%]; while ALT or AST elevations occurred in 3 patients, only one was above 5 times ULN in whom avelumab was discontinued early).*

Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, Lamping E, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol. 2017;18:587–98. PubMed PMID: 28373007.

*(Among 53 patients with various refractory solid tumors treated with 1 of 4 doses of avelumab every 2 weeks, common side effects were fatigue, flu-like symptoms and fever, and 3 developed autoimmune disorders, one with ALT elevations above 5 times ULN).*

Gulley JL, Rajan A, Spigel DR, Iannotti N, Chandler J, Wong DJL, Leach J, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. Lancet Oncol. 2017;18:599–610. PubMed PMID: 28373005.

*(Among 184 patients with refractory NSCLC treated with avelumab [10 mg/kg every 2 weeks], 22 [12%] had an objective response, but side effects were frequent with immune related events occurring in 22 [12%], although none were liver related).*

Kotsakis A, Georgoulias V. Avelumab, an anti-PD-L1 monoclonal antibody, shows activity in various tumour types. Lancet Oncol. 2017;18:556–557. PubMed PMID: 28373006.

*(Commentary on Gulley [2017] and the promise of avelumab in NSCLC).*

In brief: Avelumab (Bavencio) for metastatic merkel cell carcinoma. Med Lett Drugs Ther. 2017;59(1521):e120. PubMed PMID: 28699934.

*(Concise review of the mechanism of action, efficacy, safety and costs of avelumab shortly after its approval in the US as therapy of metastatic Merkel cell carcinoma).*

Kim ES. Avelumab: first global approval. Drugs. 2017;77:929–37. PubMed PMID: 28456944.

*(Review of the mechanism of action, pharmacology, clinical efficacy and adverse events of avelumab shortly after its approval for use in Merkel cell carcinoma in the US; mentions that one patient of 88 with Merkel cell cancer developed ALT elevations above 5 times ULN which resolved when avelumab was discontinued, and that there were no deaths that were considered treatment related).*

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 15-20% 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 1$^{st}$ 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]).*

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 pathological findings of immune checkpoint inhibitor associated gastrointestinal and hepatic injury and the role in diagnosis and management of these immune related adverse events).*

Cho JH, Sun JM, Lee SH, Ahn JS, Park K, Ahn MJ. Late-onset cholecystitis with cholangitis after avelumab treatment in non-small cell lung cancer. J Thorac Oncol. 2018;13:e34–e36. PubMed PMID: 29472055.

*(69 year old Japanese woman with adenocarcinoma of the lung had a beneficial response to avelumab given every 2 weeks for 21 cycles, when she developed abdominal pain and had an enlarged thick-walled gallbladder on imaging with mild elevations in ALT and Alk P, responding to high dose corticosteroids but with recurrence of pain and gallbladder abnormalities when avelumab was restarted).*

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-PD-1/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).*

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.

*(Systematic review of reports of sclerosing cholangitis due to check point inhibitors identified 31 cases, ages 43 to 89 years, 68% men, arising after 1 to 27 cycles [median=5.5] with cases due to nivolumab [n=19], pembrolizumab [10], durvalumab [1] and avelumab [1], usually with stenosis or multiple strictures, intra or extrahepatic [or both], median [and range] ALT 125 [31-1536] U/L, Alk P 1543 [237-5060] U/L, poorly responsive to corticosteroids).*

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 immune check point inhibitors at a single referral center in Japan, 8 [4%] developed ALT elevations above 5 times ULN [7 women], a median of 42 days after starting therapy, with benign outcomes upon discontinuation, although half required corticosteroid therapy and 2 mycophenolate; 5 of*

*137 had received nivolumab, 1 of 45 pembrolizumab, 2 of 17 ipilimumab, but none of 3 who had received atezolizumab or avelumab developed immune related hepatitis).*

Bang YJ, Ruiz EY, Van Cutsem E, Lee KW, Wyrwicz L, Schenker M, Alsina M, et al. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann Oncol. 2018;29:2052–2060. PubMed PMID: 30052729.

*(Among 371 patients with refractory, advanced or metastatic gastric or gastro-esophageal junction carcinoma treated with standard of care or avelumab, overall and progression free survival were similar in the two groups, but adverse events were fewer with avelumab [49% vs 74%] and ALT elevations arose in 3.3% vs 4%, one patient on avelumab developing autoimmune hepatitis requiring discontinuation).*

Rajan A, Heery CR, Thomas A, Mammen AL, Perry S, O'Sullivan Coyne G, Guha U, et al. Efficacy and tolerability of anti-programmed death-ligand 1 (PD-L1) antibody (Avelumab) treatment in advanced thymoma. J Immunother Cancer. 2019;7:269. PubMed PMID: 31639039.

*(Among 8 patients with thymic tumors treated with avelumab, 4 had an objective response all of whom had immune related adverse events [CPK and ALT elevations], which responded to prednisone suggesting that thymomas may predispose to immune related myositis or hepatitis).*

Pu D, Yin L, Zhou Y, Li W, Huang L, Cai L, Zhou Q. Safety and efficacy of immune checkpoint inhibitors in patients with HBV/HCV infection and advanced-stage cancer: A systematic review. Medicine (Baltimore). 2020;99:e19013. PubMed PMID: 32000444.

*(Systematic review of literature on check point inhibitor therapy in patients infected with hepatitis B or C identified 34 articles including 89 patients with HBV and 98 with HCV infection [67% with HCC and 25% with melanoma], among whom reactivation of hepatitis B occurred in two patients and ALT elevations arose in 14% of those with HBV versus 30% with HCV, the elevations rising above 5 times ULN in 3% and 17%).*

D'Angelo SP, Bhatia S, Brohl AS, Hamid O, Mehnert JM, Terheyden P, Shih KC, et al. Avelumab in patients with previously treated metastatic Merkel cell carcinoma: long-term data and biomarker analyses from the single-arm phase 2 JAVELIN Merkel 200 trial. J Immunother Cancer. 2020;8:e000674. PubMed PMID: 32414862.

*(Long term outcome of a single arm study of 88 patients with metastatic Merkel cell cancer treated with avelumab found a median overall survival of 12.6 months; with no treatment related deaths, but treatment related adverse events in 77% including ALT elevations in 5% but only one patient had ALT levels above 5 times ULN).*

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%]).*

Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, Kalofonos H, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383:1218–1230. PubMed PMID: 32945632.

*(Among 700 patients with metastatic urothelial cancer treated with avelumab vs supportive care, the overall 1-year survival was 71% vs 58%, while the adverse event rate was 98% vs 78% and serious adverse events 47% vs 25%; no mention of ALT elevations or hepatotoxicity).*

Kelly K, Manitz J, Patel MR, D'Angelo SP, Apolo AB, Rajan A, Kasturi V, et al. Efficacy and immune-related adverse event associations in avelumab-treated patients. J Immunother Cancer. 2020;8:e001427. PubMed PMID: 33219092.

*(Among 1783 patients in two large trials of avelumab in various solid tumors and Merkel cell carcinoma, adverse events arose in all patients which were immune related in 295 [16.5%] and severe in 51 [2.9%] with two deaths from liver injury; 50 and 51 year old women with metastatic breast and gastric cancer who developed acute liver failure after a 3rd and first infusion).*

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]).*

Lee DW, Cho EJ, Lee JH, Yu SJ, Kim YJ, Yoon JH, Kim TY, et al. Phase II study of avelumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib. Clin Cancer Res. 2021;27(3):713–718. PubMed PMID: 33139266.

*(Among 30 patients with HCC [26 due to HBV and 3 to HCV] resistant to sorafenib who were then treated with avelumab, there were no complete and only 3 partial responses, and adverse events were frequent including ALT or AST elevations in 37% and bilirubin in 30%, but there were no episodes of reactivation or deaths due to adverse events).*

Pujade-Lauraine E, Fujiwara K, Ledermann JA, Oza AM, Kristeleit R, Ray-Coquard IL, Richardson GE, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. Lancet Oncol. 2021;22:1034–1046. PubMed PMID: 34143970.

*(Among 566 woman with refractory ovarian carcinoma treated with avelumab or doxorubicin or both, avelumab alone or in combination did not improve either progression-free or overall survival and adverse events were greatest with the combination; ALT elevations arose in 1-2% of patients and one who received avelumab alone developed autoimmune hepatitis).*

Park K, Özgüroğlu M, Vansteenkiste J, Spigel D, Yang JCH, Ishii H, Garassino M, et al. Avelumab versus docetaxel in patients with platinum-treated advanced NSCLC: 2-year follow-up from the JAVELIN lung 200 phase 3 trial. J Thorac Oncol. 2021;16:1369–1378. PubMed PMID: 33845211.

*(Among 792 patients with advanced, refractory NSCLC treated with avelumab or docetaxel, objective response rates were greater with avelumab than docetaxel in subjects with increased PD-L1 expression, and immune related adverse events arose in 17.3% of patients and ALT elevations in 1%).*

D'Angelo SP, Bhatia S, Brohl AS, Hamid O, Mehnert JM, Terheyden P, Shih KC, et al. Avelumab in patients with previously treated metastatic Merkel cell carcinoma (JAVELIN Merkel 200): updated overall survival data after >5 years of follow-up. ESMO Open. 2021;6:100290. PubMed PMID: 34715570.

*(Among 88 patients with Merkel cell carcinoma treated with avelumab followed long term, the overall survival rate was 36% at 2 years and 26% at 5 years while 12% discontinued therapy because of adverse events).*

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 Korea, 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).*