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# Nivolumab

Updated: May 1, 2016.

# OVERVIEW

## Introduction

Nivolumab is a human monoclonal antibody to programmed cell death receptor 1 (PD-1), which modulates T cell immune reactivity and is used in the immunotherapy of cancer. Nivolumab has major side effects and particularly immune related conditions, including acute liver injury which can be serious and even life threatening.

## Background

Nivolumab (nye vol' ue mab) is a human recombinant monoclonal immunoglobulin G4 antibody to the programmed cell death receptor-1 (PD-1) which has distinctive immunomodulatory activity and is used 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 costimulatory factor B7 and consequently allows for a continued activation and proliferation of T cells. The subsequent enhancement of cytotoxic reactivity may play a beneficial role in cancer immunotherapy by breaking immunological tolerance to cancer cell associated antigens. In several large multicenter studies, nivolumab 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. Nivolumab was approved for use in advanced melanoma in the United States in 2015 and is under active investigation in several other forms of cancer, including renal, breast and colon cancer. Nivolumab is available in liquid solution in 40 and 100 mg vials (10 mg/mL) under the brand name Opdivo. The typical regimen is 3 mg/kg as an intravenous infusion every 2 weeks. In 2015, the combination of nivolumab with ipilimumab, a monoclonal antibody to CTLA-4, another checkpoint molecule, was approved as combination immunotherapy for malignant melanoma. Side effects of nivolumab are common and can be severe. As many as half of treated patients develop immune related side effects as a result of immune enhancement 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 long term therapy. Early recognition and prompt management of these side effects is an integral component of proper use of nivolumab and other checkpoint inhibitors such as ipilimumab and pembrolizumab.

## Hepatotoxicity

Mild-to-moderate serum aminotransferase elevations are not uncommon (~10%) during nivolumab therapy, but are usually self-limited and resolve even with continuing cyclic therapy. Serum ALT elevations above 5 times the upper limit of normal (ULN) occur in 0.5% to 1.5% of patients, and a proportion of these individuals develop

clinically apparent liver injury that can be severe. The onset of such injury is usually after 2 to 6 cycles, 1 to 3 months after initiation of treatment. The pattern of enzyme elevation is usually hepatocellular but can be mixed, particularly at the onset. Liver histology demonstrates an acute hepatitis-like pattern with focal or confluent necrosis and prominent lymphocytic infiltrates of activated T cells, which is compatible with an immune mediated hepatic injury. However, autoantibodies are usually not present. Restarting nivolumab can result in recurrence of injury, although corticosteroid treatment may block recurrence.

The effects of PD-1 inhibition on hepatitis B have not been reported as enrollment criteria in the clinical trials of nivolumab have usually excluded patients with chronic viral hepatitis. However, it is possible that anti-PD-1 treatment would exacerbate chronic hepatitis B by enhancing T cell cytotoxicity to viral antigens, and such patients should be monitored during therapy and managed appropriately with antiviral therapy if necessary. In contrast, checkpoint immunotherapy in patients with hepatitis C has not been found to be deleterious and in some cases resulted in a decrease in HCV RNA levels.

Likelihood score: E* (although no specific cases have been described in the literature, this is a relatively recently approved medication and is likely to be a rare cause of clinically apparent acute liver injury).

## Mechanism of Injury

The mechanism of liver injury due to nivolumab is likely to be immunologically mediated and some cases have appeared to respond to corticosteroid or immunosuppressive therapy allowing for continuation or restarting of nivolumab therapy.

## Outcome and Management

Guidelines for management of patients receiving nivolumab recommend monitoring of liver tests and use of corticosteroids for patients who develop serum aminotransferase elevations above 5 times the ULN, initiating therapy with high doses of 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 nivolumab resolve with prompt institution of immunosuppressive therapy. The few fatal cases that have been reported during immunotherapy with check point inhibitors occurred in patients who had other severe immune related adverse events (Stevens Johnson syndrome, capillary leak syndrome) or who had a delay in starting corticosteroid therapy. There is little information on the safety of restarting nivolumab or other checkpoint inhibitors after occurrence of clinically apparent liver injury from their use. In some situations, therapy can be restarted safely after resolution of an immune mediated adverse event, but in other situations immunosuppressive therapy is required to control the adverse event.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies, Checkpoint Inhibitors

# PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Nivolumab – Opdivo®

**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 |
|---|---|---|---|
| Nivolumab | 946414-94-4 | Monoclonal Antibody | Not Available |

# ANNOTATED BIBLIOGRAPHY

References updated: 01 May 2016

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

*(Textbook of pharmacology and therapeutics).*

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 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).*

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).*

Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013; 369: 122-33. PubMed PMID: 23724867.

*(Among 53 patients with advance melanoma treated with the combination of ipilimumab and nivolumab, the objective response rate was 53% to the optimal dose regimen, but adverse events were common [98%] as were serious adverse events [49%], any ALT elevations [23%] and elevations above 5 times ULN [13%]; lower response rates [20%] and ALT elevations [3%] occurred with sequential therapy).*

Weber JS, Kudchadkar RR, Yu B, Gallenstein D, Horak CE, Inzunza HD, Zhao X, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. J Clin Oncol 2013; 31: 4311-8. PubMed PMID: 24145345.

*(Among 90 patients with refractory or naïve melanoma treated with nivolumab in 1 of 3 doses every 2 weeks for 24 weeks, then every 12 weeks with or without a peptide vaccine, response rates were approximately 25% and adverse events were manageable; no mention of ALT elevations or hepatotoxicity).*

Ascierto PA, Simeone E, Sileni VC, Pigozzo J, Maio M, Altomonte M, Del Vecchio M, et al. Clinical experience with ipilimumab 3 mg/kg: real-world efficacy and safety data from an expanded access programme cohort. J Transl Med 2014; 12: 116. PubMed PMID: 24885479.

*(Among 855 patients with melanoma treated with ipilimumab in an expanded access program, 19 [2%] developed "liver toxicity", which led to stopping therapy in 1 patient and death from hepatitis in another).*

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).*

Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, Schuster SJ, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015; 372: 311-9. PubMed PMID: 25482239.

*(Among 23 patients with refractory Hodgkin lymphoma treated with nivolumab [3 mg/kg every 2 weeks], objective responses occurred in 87% and 3 patients had drug related serious adverse events, but none were hepatic; no mention of ALT elevations).*

Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR, Vaishampayan UN, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. J Clin Oncol 2015; 33: 1430-7. PubMed PMID: 25452452.

*(Among 168 patients with metastatic renal cell cancer treated with 1 of 3 doses of nivolumab every 3 weeks, objective response rates were 20-22% and ALT elevations occurred in 7 [4%] and were above 5 times ULN in 2 [1%]).*

Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372: 320-30. PubMed PMID: 25399552.

*(Among 418 patients with metastatic melanoma [BRAF-] treated with nivolumab or dacarbazine, one year survival was 73% vs 42%, and common side effects of nivolumab were fatigue [20%], pruritus [17%] and nausea [17%]; 2 patients [1%] had ALT elevations above 5 times ULN, 1 requiring corticosteroid therapy).*

Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, Horn L, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 2015; 16: 257-65. PubMed PMID: 25704439.

*(Among 117 patients with advanced, refractor NSCLC treated with nivolumab [3 mg/kg every 2 weeks], the objective response rate was 15% and adverse events were common [74%]; no serious adverse events were liver related and ALT elevations [less than 5 times ULN] occurred in only 1 patient [1%]).*

Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, Hoeller C, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015; 16: 375-84. PubMed PMID: 25795410.

*(Among 272 patients with refractory, advanced melanoma treated with nivolumab, the objective response rate was 32% and adverse events were common [68%] and 2 patients [1%] had ALT elevations above 5 times ULN, resolving with corticosteroid therapy).*

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).*

Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, Powderly JD, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol 2015; 33: 2004-12. PubMed PMID: 25897158.

*(Among 129 patients with advanced, refractory NSCLC treated with 1 of 3 doses of nivolumab every 2 weeks for up to 96 weeks, objective response rates at 1 year were 42%; serum enzyme elevations occurred in 6 patients [5%] and were above 5 times ULN in one; 2 patients died of suspected treatment-related, immune mediated pneumonitis).*

McDermott DF, Drake CG, Sznol M, Choueiri TK, Powderly JD, Smith DC, Brahmer JR, et al. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. J Clin Oncol 2015; 33: 2013-20. PubMed PMID: 25800770.

*(Among 34 patients with advanced renal cell cancer treated with pembrolizumab [1 or 10 mg/kg every two weeks], objective responses occurred in 10 patients [29%], and immune mediated adverse events in 19 [56%], including ALT elevations in 4 patients [12%] which were above 5 times ULN in 1 [3%]).*

Nivolumab (Opdivo) for metastatic melanoma and metastatic NSCLC. Med Lett Drugs Ther 2015; 57 (1470): 85-7. PubMed PMID: 26035747.

*(Concise review of the mechanism of action, efficacy, safety and costs of nivolumab for metastatic melanoma shortly after its approval for this use in the US; mentions that side effects can include immune mediated reactions including hepatitis as well as transient, but marked serum ALT elevations).*

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%]).*

Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015; 373: 123-35. PubMed PMID: 26028407.

*(Among 272 patients with advanced NSCLC treated with nivolumab or docetaxel, overall one year survival rates were greater with nivolumab [42% vs 24%] and side effects were less, ALT elevations occurring in 2% vs 1%, but were mostly mild and self-limited).*

Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015; 373: 23-34. PubMed PMID: 26027431.

*(Among 945 patients with advanced, untreated melanoma treated with checkpoint inhibitors, median progression-free survival was 3 months with ipilimumab, 7 months with nivolumab and 11.5 months with the combination of both, adverse events including ALT elevations also being more common with the combination [any ALT elevation 17.6%, ALT above 5 times ULN 8.3%] than either alone [3.8% and 1.3% for nivolumab vs 3.9% and 1.6% for ipilimumab], almost all resolving with immunosuppressive therapy).*

Nishino M, Sholl LM, Hodi FS, Hatabu H, Ramaiya NH. Anti-PD-1-related pneumonitis during cancer immunotherapy. N Engl J Med 2015; 373: 288-90. PubMed PMID: 26176400.

*(Summary of 3 patients with melanoma treated with nivolumab [2 also received ipilimumab] who developed severe immune mediated interstitial pneumonitis 7-24 months after starting therapy with diffuse pulmonary ground-glass and reticular opacities, 2 eventually recovering with corticosteroid therapy, one dying after 4 weeks).*

Larkin J, Lao CD, Urba WJ, McDermott DF, Horak C, Jiang J, Wolchok JD. Efficacy and safety of nivolumab in patients with BRAF V600 mutant and BRAF wild-type advanced melanoma: A pooled analysis of 4 clinical trials. JAMA Oncol 2015; 1: 433-40. PubMed PMID: 26181250.

*(Pooled analysis of 4 clinical trials of 5 doses of nivolumab in 440 adults with advanced melanoma found similar efficacy and safety in tumors with mutant vs wild-type BRAF; no specific mention of ALT elevations or hepatotoxicity).*

Narita T, Oiso N, Taketomo Y, Okahashi K, Yamauchi K, Sato M, Uchida S, et al. Serological aggravation of autoimmune thyroid disease in two cases receiving nivolumab. J Dermatol 2016; 43 (2): 210-4. PubMed PMID: 26198822.

*(Two patients, 65 and 70 years old, one woman and one man developed thyroid test abnormalities soon after starting nivolumab therapy for metastatic melanoma, having subtle abnormalities before treatment; ALT values remained normal or minimally elevated).*

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015; 373: 1627-39. PubMed PMID: 26412456.

*(Among 582 patients with NSCLC treated with nivolumab or docetaxel, the one year overall survival rate was better with nivolumab [51% vs 39%] and overall adverse events were less, and ALT elevations above 5 times ULN occurred in none on nivolumab and 1 on docetaxel).*

Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, et al.; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373: 1803-13. PubMed PMID: 26406148.

*(Among 831 patients with advanced renal cancer treated with nivolumab or everolimus, median overall survival was better with nivolumab [25 vs 19.6 months] and side effects were less [79% vs 88%]; no mention of ALT elevations or hepatotoxicity).*

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 including nivolumab and ipilimumab indicated that therapy was associated with higher rates of ALT elevations).*

Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T, Kanai M, et al. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. J Clin Oncol 2015; 33: 4015-22. PubMed PMID: 26351349.

*(Among 20 patients with advanced, refractory ovarian cancer treated with 1 of 2 doses of nivolumab, adverse events were common [95%] and included ALT elevations in 5 patients [25%] which were above 5 times ULN in 1 [5%]).*

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).*

Kanameishi S, Otsuka A, Nonomura Y, Fujisawa A, Endo Y, Kabashima K. Idiopathic thrombocytopenic purpura induced by nivolumab in a metastatic melanoma patient with elevated PD-1 expression on B cells. Ann Oncol 2016; 27 (3): 546-7. PubMed PMID: 26602778.

*(79 year old woman with metastatic melanoma developed severe thrombocytopenia after 2 doses of nivolumab [platelet count 2000/μL], having been normal before therapy, ultimately responding to corticosteroids, IVIG and romiplostim; no information given on subsequent course).*

Nivolumab (Opdivo) plus ipilimumab (Yervoy) for metastatic melanoma. Med Lett Drugs Ther 2015; 57 (1483): 168. PubMed PMID: 26633687.

*(Concise review of the rationale, clinical efficacy, adverse effects and costs of nivolumab and ipilimumab for metastatic melanoma shortly after approval of this combination in the US; no mention of hepatotoxicity or ALT elevations).*