Nivolumab

Nivolumab (nye vol' ue mab), marketed as **Opdivo**, is a human IgG4 anti-PD-1 monoclonal antibody used to treat cancer.[1][2] Nivolumab works as a checkpoint inhibitor, blocking a signal that would have prevented activated T cells from attacking the cancer, thus allowing the immune system to clear the cancer. It was discovered at Medarex, developed by Medarex and Ono Pharmaceutical, and brought to market by Bristol-Myers Squibb (which acquired Medarex in 2009) and Ono.

As of April 2016, nivolumab was used as a first line treatment for inoperable or metastatic melanoma in combination with ipilimumab if the cancer does not have a mutation in BRAF,[2] as a second-line treatment following treatment with ipilimumab and if the cancer has a mutation in BRAF, with a BRAF inhibitor,[3] as a second-line treatment for squamous non-small cell lung cancer,[4] and as a second-line treatment for renal cell carcinoma.[2]

It had not been tested in pregnant women but based on the mechanism of action and animal studies, is probably toxic to the fetus; it is not known if it is secreted in breast milk. Side effects include severe immune-related inflammation of the lungs, colon, liver, kidneys, and thyroid, and there are effects on skin, central nervous system, the heart, and the digestive system.[2]

1 Medical use

Nivolumab is used as a first line treatment for inoperable or metastatic melanoma in combination with ipilimumab if the cancer does not have a mutation in BRAF,[2] and as a second-line treatment for inoperable or metastatic melanoma following treatment of ipilimumab and, if the cancer has a BRAF mutation, a BRAF inhibitor.[2][3] It is also used to treat metastatic squamous non-small cell lung cancer with progression with or after platinum-based drugs.[2][4] It also used as a second-line treatment for renal cell carcinoma after anti-angiogenic treatment has failed.[2]

Nivolumab was not tested in pregnant women but based on how the drug works and on animal studies, it is likely to cause harm to a fetus; it is not known if nivolumab is secreted in breast milk.[2]

2 Side effects

The drug label contains warnings with regard to increased risks of severe immune-mediated inflammation of the lungs, the colon, the liver, the kidneys (with accompanying kidney dysfunction), as well as immune-mediated hypothyroidism and hyperthyroidism.[2]

In clinical trials for melanoma, the following side effects occurred in more than 10% of subjects and more frequently than with chemotherapy alone: rash and itchy skin, cough, upper respiratory tract infections, and peripheral edema. Other clinically important side effects with less than 10% frequency were ventricular arrhythmia, inflammation of parts of the eye (iridocyclitis), infusion-related reactions, dizziness, peripheral and sensory neuropathy, peeling skin, erythema multiforme, vitiligo, and psoriasis.[2]

In clinical trials for lung cancer, the following side effects occurred in more than 10% of subjects and more frequently than with chemotherapy alone: fatigue, weakness, edema, fever, chest pain, generalized pain, shortness of breath, cough, muscle and joint pain, decreased appetite, abdominal pain, nausea and vomiting, constipation, weight loss, rash, and itchy skin.[2]

Levels of electrolytes and blood cells counts were also disrupted.[2]

3 Pharmacology

Based on data from 909 patients, the terminal half-life of nivolumab is 26.7 days and steady-state concentrations were reached by 12 weeks when administered at 3 mg/kg every 2 weeks.[2]:29 Age, gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment do not affect clearance of the drug.[2]:30

4 Mechanism of action

Nivolumab acts by blocking a negative regulator of T-cell activation and response, thus allowing the immune system to attack the tumor.[5] This is an example of immune checkpoint blockade.[5]

PD-1 is a protein on the surface of activated T cells. If another molecule, called programmed cell death 1 ligand 1

or programmed cell death 1 ligand 2 (PD-L1 or PD-L2), binds to PD-1, the T cell becomes inactive. This is one way that the body regulates the immune system, to avoid an overreaction. Many cancer cells make PD-L1, which inhibits T cells from attacking the tumor. Nivolumab blocks PD-L1 from binding to PD-1, allowing the T cell to work.[5] PD-L1 is expressed on 40–50% of melanomas and has limited expression otherwise in most visceral organs with the exception of respiratory epithelium and placental tissue.[3]

5 Physical properties

Nivolumab is a humanized monoclonal, immunoglobulin G4 antibody to PD-1.[3] The gamma 1 heavy chain is 91.8% humanized and the kappa light chain is 98.9% humanized.[1]

6 History

PD-1 was first shown to be an immune checkpoint in 2000.[6]

Nivolumab was created by scientists at Medarex using Medarex's transgenic mice with a humanized immune system; the discovery and *in vitro* characterization of the antibody, originally called MDX-1106, was published (much later) in 2014.[7] Medarex licensed Japanese rights to nivolumab to Ono Pharmaceutical in 2005.[8] Bristol Myers Squibb acquired Medarex in 2009 for $2.4B, largely on the strength of its checkpoint inhibitor program.[9][10]

Promising clinical trial results made public in 2012 caused excitement among industry analysts and in the mainstream media; PD-1 was being avidly pursued as a biological target at that time, with companies including Merck with pembrolizumab (Keytruda), Roche (via its subsidiary Genentech) with atezolizumab, GlaxoSmithKline in collaboration with the Maryland biotech company Amplimmune; and Teva in collaboration with the Israeli biotech company CureTech competing.[11][6]

Ono received approval from Japanese regulatory authorities to use nivolumab to treat unresectable melanoma in July 2014, which was the first regulatory approval of a PD-1 inhibitor anywhere in the world.[8]

Merck received its first FDA approval for its PD-1 inhibitor, Keytruda, in September 2014.[12]

Nivolumab received FDA approval for the treatment of melanoma in December 2014.[3][13] In April 2015, the Committee for Medicinal Products for Human Use of the European Medicines Agency recommended approval of Nivolumab for metastatic melanoma as a monotherapy.[14]

In March 2015, the US FDA approved it for the treatment of squamous cell lung cancer.[15]

In November 2015, the FDA approved nivolumab as a second-line treatment for renal cell carcinoma after having granted the application breakthrough therapy designation, fast track designation, and priority review status.[16]

In May 2016, the FDA approved nivolumab for the treatment of patients with classical Hodgkin lymphoma (cHL) who have relapsed or progressed after autologous hematopoietic stem cell transplantation (auto-HSCT) and post-transplantation brentuximab vedotin.[17]

7 Research

7.1 Hodgkin's lymphoma

In Hodgkin's lymphoma, Reed-Sternberg cells harbor amplification of chromosome 9p24.1, which encodes PD-L1 and PD-L2 and leads to their constitutive expression. In a small clinical study published in 2015, nivolumab elicited an objective response rate of 87% in a cohort of 20 patients.[6]

7.2 Biomarkers

Amplification of chromosome 9p24 may serve as a predictive biomarker in Hodgkin's lymphoma.[6]

Each company pursuing mAbs against PD-1 as drugs developed assays to measure PD-L1 levels as a potential biomarker using their drugs as the analyte-specific reagent in the assay. BMS partnered with Dako on a nivolumab-based assay. However, as of 2015 the complexity of the immune response had hindered efforts to identify people who would be likely to respond well to PD-1 inhibitors;[6] in particular PD-L1 levels appear to be dynamic and modulated by several factors, and efforts to correlate PD-L1 levels before or during treatment with treatment response or duration of response had failed to reveal any useful correlations as of 2015.[3]

7.3 Lung cancer

In 2016, BMS announced the results of a clinical trial in which nivolumab failed to achieve its endpoint and was no better than traditional chemotherapy at treating newly diagnosed lung cancer.[18]

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