IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 10, Issue 12 Series. I (December 2020), PP. 10-20 www.iosrphr.org

A Review on Current Development of Nivolumab Anticancer Activity Drug.

M. Kalaichandar*, M. Jeevitha *, Dr.D .Satheeshkumar*
PSV College of Pharmaceutical Science and Research, Orappam .
Received 28 December 2020; Accepted 09January 2021

ABSTRACT;
New insight on the interaction between the immune system and tumor has identified the programmed death-1/programmed death-1 ligand pathway to be a key player in evading host immune response. The immune checkpoint modulator, nivolumab (BMS-936558/ONO-4538), is the first PD-1 inhibitor to gain regulatory approval, for the treatment of patients with unresectable melanoma. This review will discuss results from early phase studies of nivolumab in solid tumors including non-small cell lung cancer (NSCLC) as well as studies of nivolumab in combination with chemotherapy, other immune modulators and molecular targeted therapy in patients with NSCLC.
KEYWORDS; Nivolumab,Melanoma, Non-Small Cell Lung Cancer, Head and Neck Cancer,RCC, Urothelial Carcinoma, immunoglobulin G4 (IgG4),PD-1,PD-L1, immune check point inhibitor .

I. INTRODUCTION ;

Nivolumab (BMS-936558, ONO-4538, or MDX1106, trade name Opdivo; Bristol-Myers Squibb, Princeton, NJ, USA) is a human immunoglobulin G4 (IgG4) monoclonal antibody (mAb). The gamma 1 heavy chain is 91.8% unmodified human design while the kappa light chain is 98.9%. It is the first-in-human programmed death-1 (PD-1) immune checkpoint inhibitor antibody that disrupts the interaction of the PD-1 receptor with its ligands programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), thereby inhibiting the cellular immune response. Nivolumab was created by scientists at Medarex using Medarex's transgenic mice with a humanized immune system. Medarex licensed Japanese rights to nivolumab to Ono Pharmaceutical in 2005. Bristol-Myers Squibb acquired Medarex in 2009. 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. Nivolumab received Food and Drug Administration (FDA) approval for the treatment of melanoma in December 2014. In April 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended approval of Nivolumab for metastatic melanoma as a monotherapy. In March 2015, the US FDA approved it for the treatment of squamous cell lung cancer (SCLC). On 19 June 2015 the European Commission granted a marketing authorization valid throughout the European Union. In November 2015, the FDA approved nivolumab as a second-line treatment for renal cell carcinoma (RCC) after having granted the application breakthrough therapy designation, fast track designation, and priority review status. 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. On December 20, 2017, the FDA granted approval to nivolumab for adjuvant treatment of melanoma with involvement of lymph nodes or for metastatic disease with complete resection. On April 16, 2018, the FDA granted approval to nivolumab in combination with ipilimumab for the first-line treatment of intermediate and poor risk advanced RCC patients. 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.[1]

Despite the advances in treatment options for cancer, there is a significant scope for improving clinical benefit for the existing standards of care which are dependent on line of therapy and/or histology. Some cancer patients are not eligible for targeted therapies and not all patients receiving targeted agents actually respond to it. Furthermore, conventional chemotherapy causes wide range of toxicities including bone marrow suppression.[2][3]

Among these, the one strategy that is most credulous in activation of a counterattack is “immune checkpoint activation.” Programmed death-1 (PD-1) immune checkpoint pathways are the most actively studied pathway.[2] Immuno-oncology agents target checkpoints within the cascade of immune regulatory molecules. Since these approaches directly target the patient's immune system, they have the potential for utility across multiple tumor types.

The PD-1 receptor is expressed on activated T-cells, and the key ligands for this receptor are programmed death-ligands 1 (PD-L1) and 2 (PD-L2). PD-L1 is upregulated in many tumors. This overexpression helps tumor evade immune responses. Binding of ligands, PD-L1 or PD-L2 to PD-1 receptors inhibits T-cell activation and dampens antitumor immune responses. Thus, PD-1 receptor represents a logical target for cancer immunotherapy. This is a promising mechanism to stimulate the antitumor activity of the immune system, thereby improving therapeutic outcomes in cancer patients.[2][4]

Currently, the various drugs being evaluated in this area are ipilimumab, nivolumab, and pembrolizumab. Nivolumab (Opdivo; Nivolumab BMS) was first PD-1 immune checkpoint inhibitor to be approved for use in advanced, squamous (SQ) nonsmall cell lung cancer (NSCLC) following prior chemotherapy. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody. It binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thus releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

Nivolumab is one of the most extensively studied immune checkpoint inhibitors across various tumor types and has anticancer activity against.[5]

Nivolumab is approved in the USA for the treatment of patients with metastatic SQ NSCLC which has shown progression on or after platinum-based chemotherapy and in the European Union (EU) for the treatment of adults with locally advanced or metastatic SQ NSCLC after prior chemotherapy treatment. Nivolumab is also approved in the USA and the EU for the treatment of advanced melanoma and in the USA for use in previously treated patients with advanced, non-SQ NSCLC. Several clinical trials are underway for other indications, such as the 1st line in RCC/NSCLC, glioblastoma multiforme, head and neck cancer, small cell lung cancer, gastrointestinal malignancies, and genitourinary malignancies.

Given the recent surge in research evaluating immuno-oncology molecules such as nivolumab and the growing list of indications that will actualize over the coming years, there is a need to bring together the existing evidence on current place of nivolumab. In this narrative review, the current clinical efficacy and safety data of anti-PD-1 nivolumab for cancer types relevant to India (NSCLC and RCC) are elucidated to appreciate the value of immune checkpoint blockade as a novel tool in the oncotherapeutic arsenal for advanced cancers.[2]

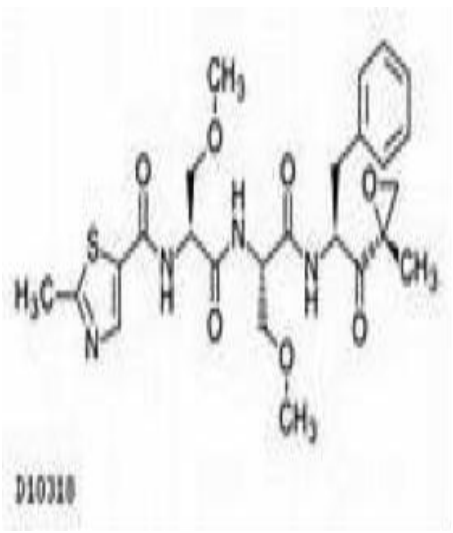
Nivolumab received US FDA Approval in November 2015 for the treatment of patients with advanced RCC (Renal cell cancer) who have received prior anti-angiogenic theapy

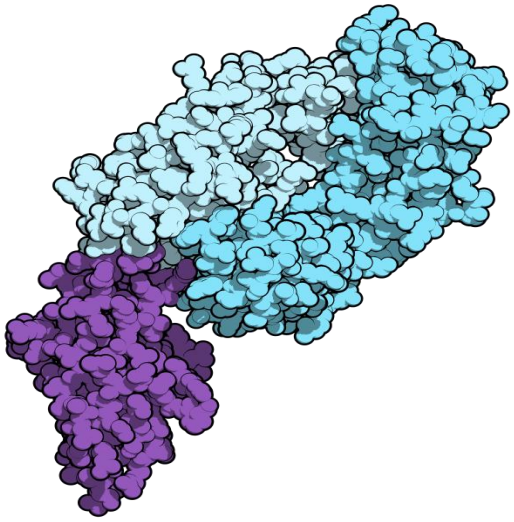
We report on overall survival and response in key subgroups based on patient characteristics and pror therapy.[6]

DEFINITION ;

Nivolumab sold under the brand name opdivo , is a medication used to treat a number of typesof cancer . this includes melanoma , lung cancer , renal cell carcinoma , Hodgkin lymphoma , head and neck cancer , colon cancer and liver cancer . it is used by slow injection into a vein.

STRUCTURE ;





Name	Nivolumab (USAN/INN); Nivolumab (genetical recombination) (JAN);

	Opdivo (TN)
Product	OPDIVO (E.R. Squibb & Sons)
Formula	C6362H9862N1712O1995S42
Exact mass	143509.1148
Mol weight	143597.3811

DESCIRPTION ;
A genetically engineered, fully human immunoglobulin G4 (IgG4) monoclonal anti programmed death-1/PD-1 protein antibody.[7]

INVITRO AND INVIVO STUDY OF NIVOLUMAB ;
INVITRO ;-

Nivolumab (anti-human PD-1) binds PD-1 with high affinity (KD 2.6 nmol/l by Scatchard analysis to polyclonally activated human T cells) and blocks its interactions with both B7-H1 and B7-DC[8]. It effectively inhibits the interaction between PD-1 and its ligands. In vitro assays demonstrated the ability of nivolumab to potently enhance T-cell responses and cytokine production in the mixed lymphocyte reaction and superantigen or cytomegalovirus stimulation assays. Nivolumab inhibits the interaction between PD-1 and its ligands, PD-L1 and PD-L2, with IC50 values of 2.52 and 2.59 nmol/L, respectively, as shown by surface plasmon resonance. In a study using FACS to evaluate ligand binding to PD-1 expressed on CHO cells, the IC50 values for nivolumab-mediated inhibition of PD-1 binding to PD-L1 or PD-L2 were similar (1.04 and 0.97 nmol/L, respectively). Nivolumab binds specifically to PD-1 and not to other immunoglobulin superfamily proteins, such as CD28, CTLA-4, ICOS, and BTLA. Nivolumab can, at very low concentrations (~1.5 ng/mL), enhance T-cell reactivity in the presence of a T-cell receptor stimulus. However, nivolumab had no stimulatory effect in the absence of antigen or T-cell receptor stimulus. Specifically, there was no significant release of inflammatory cytokines, including IFNγ, TNFα, IL-2, IL-4, IL-6, or IL-10, from unstimulated whole blood after coincubation with nivolumab. Nivolumab does not cause nonspecific lymphocyte activation[9].

INVIVO;

Nivolumab (anti-human PD-1) is well tolerated, dose-limiting toxicities (DLTs) were not reached and the maximum tolerable dose (MTD) was not defined in patients with advanced stage solid tumors. The measured half-life of nivolumab was 12-20 days, the pharmacodynamic effects of PD-1 receptor occupancy was even more prolonged at 85 days, indicating the biological durability of this high-affinity mAb[8]. In monkeys, serum nivolumab has a relatively slow clearance with limited extra vascular distribution, as demonstrated by a Vss value consistent with plasma volume. Mean apparent terminal elimination half-life estimates for males and females at 1 mg/kg were similar (124 and 139 hours, respectively), and the mean half-life estimate for males at 10 mg/kg was 261 hours. Although nivolumab seems to lack toxicity in monkeys, toxicities have been observed in human clinical trials. In a phase I trial, nivolumab had a favorable safety profile. Adverse events were generally similar to those observed with ipilimumab, although with lower incidence and of less severity, and comprised gastrointestinal, endocrine, and skin toxicities, and pulmonary inflammation. Interestingly, pneumonitis has been observed in PD-1-deficient mice bred onto the MRL genetic background, but not in PD-1-deficient mice with other genetic backgrounds[9].

MECHANISM OF ACTION ;

T cells protect the body from cancer by killing certain cancer cells. But cancer cells evolve proteins to protect themselves from T cells. Nivolumab blocks those protective proteins. Thus, the T cells can kill the cancer cells.[10] [11] This is an example of immune checkpoint blockade.

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.[11] 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. .[10] [11] 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.[12]

PHARMACOKINETICS;

The recommended dosage of nivolumab is 3.0 mg/kg administered intravenously over 60 minutes every 2 weeks until disease progression or unacceptable toxicity . Nivolumab has linear pharmacokinetics (PK), with a dose-proportional increase in the maximum concentration (Cmax) and area under the concentration-time curve (AUC) . Based upon the study of Brahmer et al, the median time to the peak concentration of nivolumab

was 1-4 hours after the start of infusion, and serum half-life ($t_{1/2}$) was 12 days (0.3, 1.0 or 3.0 mg/kg) to 20 days (10.0 mg/kg) [13].

PHARMACODYNAMICS;

The pharmacodynamics (PD) of nivolumab was evaluated according to PD-1 receptor occupancy on circulating CD3+ T cells . PD-1 occupancy appeared to be dose-independent, with a mean peak occupancy of 85% at 4-24 hours and average plateau occupancy of 72% observed at 57 days and beyond 4. In addition, the median PD-1 receptor occupancy rate by nivolumab treatment was 64%-70% for 65 patients with melanoma in peripheral blood mononuclear cells (PBMCs), who were treated with one cycle of nivolumab at a dose of 0.1 to 10.0 mg/kg every 2 weeks . All these data indicated nivolumab has a high affinity for PD-1[13] .

DRUG INTRACTION ;

A total of **14 drugs** are known to interact with **nivolumab**.

- **3 major** drug interactions
- **11 moderate** drug interactions
- **betamethasone**
- **budesonide**
- **cortisone**
- **deflazacort**
- **dexamethasone**
- **hydrocortisone**
- **idelalisib**
- **lenalidomide**
- **methylprednisolone**
- **pomalidomide**
- **prednisolone**
- **prednisone**
- **thalidomide**
- **triamcinolone**

Drug Interaction Classification ;

These classifications are only a guideline. The relevance of a particular drug interaction to a specific individual is difficult to determine. Always consult your healthcare provider before starting or stopping any medication.

Major	Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit.
Moderate	Moderately clinically significant. Usually avoid combinations; use it only under special circumstances.
Minor	Minimally clinically significant. Minimize risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.
Unknown	No interaction information available.[14]

SIDE EFFECT ;

Along with its needed effects, nivolumab may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.

Check with your doctor or nurse immediately if any of the following side effects occur while taking nivolumab:

More common

- **Back pain**
- blistering, peeling, or loosening of the skin
- chest tightness
- chills
- **constipation**
- cough
- depressed mood
- **diarrhea**
- **dry skin** and hair
- feeling cold
- feeling of warmth

- fever
- **hair loss**
- **headache**
- hoarseness or husky voice
- itching
- joint or muscle pain
- loss of appetite
- muscle cramps and stiffness
- **nausea**
- red, irritated eyes
- redness of the face, neck, arms and occasionally, upper chest
- slowed heartbeat
- **sore throat**
- sores, ulcers, or white spots in the mouth or on the lips
- trouble breathing
- unusual tiredness or weakness
- **vomiting**
- weight gain

Less common

- Chest pain
- dark urine
- general feeling of discomfort or illness
- light-colored stools
- nervousness
- pain
- sensitivity to heat
- stomach cramps
- sweating
- tenderness
- thickening of bronchial secretions
- trouble sleeping
- upper right abdominal or stomach pain
- watery or bloody diarrhea
- **weight loss**
- yellow eyes and skin

Rare

- **Bloating**
- bloody or cloudy urine
- blurred vision or other change in vision
- darkening of the skin
- **dizziness**
- drowsiness
- **eye pain**
- fainting
- **fast heartbeat**
- fruity breath odor
- increased hunger, thirst, and urination
- **indigestion**
- mental **depression**
- pains in the stomach, side, or abdomen, possibly radiating to the back
- redness of the eye
- sensitivity of the eyes to light
- **skin rash**
- swelling of the face, feet, or lower legs
- tearing[14][15]

IMMUNE CHECKPOINT INHIBITOR;

Immunotherapy is currently a promising cancer treatment that activates the immune system and alleviates the suppression of the immune system by the tumour. The blockade of immune checkpoints is one of the most efficient approaches for activating anti-tumour immunity. There are 7 immune checkpoint inhibitors approved by USFDA[17] including nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, cemiplimab, and ipilimumab. However, these drugs are highly expensive. Most people cannot afford to access this treatment. Therefore, it is necessary to develop novel platforms that are cost-effective, scalable, and safe.

In this study, we further developed an anti-PD1 monoclonal antibody (mAb), nivolumab, as a possible cancer immunotherapeutic by applying plant technology that enables cost-effective and scalable antibody production. We produced nivolumab at 140 μg/g fresh *Nicotiana benthamiana* leaves within 6 days of infiltration. Plant-produced nivolumab retained similar structure and *in vitro* efficacy, compared to those of commercial mammalian cell-produced nivolumab. This study is the first to demonstrate the use of plant-derived mAb for cancer immunotherapy.[16]

Nivolumab is an ICI, is a humanized anti-programmed death-1 (PD-1) monoclonal antibody that is used as second-line therapy in various types of cancer such as melanoma, non-small cell lung cancer, renal cancer, Hodgkin's lymphoma, urothelial cancer, and head and neck cancers.[17] Recently, nivolumab has demonstrated high (64%–87%) response rates in relapsed or refractory Hodgkin's lymphoma. Nivolumab may activate T cells to develop antitumor effects, but this immune activation sometimes causes immune-related adverse events, such as pneumonitis, hepatitis, and enterocolitis.[18] Sometimes, these adverse events are serious and life-threatening, which require timely patient management and adequate therapeutic decisions.

ICIs, nivolumab is associated with many immune-regulated adverse events including nausea, abdominal pain, and diarrhea. Diarrhea is observed in about one-third of patients. It usually occurs in the 3rd month of therapy. Diarrhea may be infectious or autoimmunological. About 8%–22% of patients receiving immunotherapy develop autoimmunological enterocolitis. Clinical symptoms of enterocolitis include mixed watery and bloody diarrhea and cramping pain. Enterocolitis can be managed with cessation of nivolumab and administration of intravenous corticosteroid therapy or infliximab therapy in severe cases, like in our case.18F-FDG PET-CT is standard of care for the staging, monitoring of response to therapy, and detection of disease recurrence for Hodgkin's disease and non-Hodgkin's lymphomas. ^{18}F-FDG PET-CT can be used to identify regions of active inflammation in ulcerative colitis. ICI is a potentially important therapeutic agent for refractory and relapsed Hodgkin's lymphomas. As the use of ICIs in cancer therapy increases, therefore immune-related adverse events are frequently identified on ^{18} F-FDG PET-CT, which may lead to early diagnosis, close clinical follow-up, and appropriate clinical management of immune-related adverse events.[19]

Nivolumab is one of the most extensively studied immune checkpoint inhibitors across various tumor types and has anticancer activity against several tumor types, including melanoma, NSCLC, and renal cell cancer (RCC). Nivolumab monotherapy presents a favorable benefit-risk profile in patients with previously treated advanced or metastatic NSCLC as well as in patients with advanced or metastatic RCC.[2]

Nivolumab is approved in the USA for the treatment of patients with metastatic SQ NSCLC which has shown progression on or after platinum-based chemotherapy and in the European Union (EU) for the treatment of adults with locally advanced or metastatic SQ NSCLC after prior chemotherapy treatment. Nivolumab is also approved in the USA and the EU for the treatment of advanced melanoma and in the USA for use in previously treated patients with advanced, non-SQ NSCLC. Several clinical trials are underway for other indications, such as the 1st line in RCC/NSCLC, glioblastoma multiforme, head and neck cancer, small cell lung cancer, gastrointestinal malignancies, and genitourinary malignancies.

IMMUNOCHECK POINT INHIBITOR- (NIVOLUMAB) ASSOCIATED HYPEREOSINOPHILIA ;

The use of immunotherapeutic agents has proven to be effective for patients with many different types of cancers . The antitumor function of T-cells is inhibited by PD-L1 which is expressed on many malignant tumors. Nivolumab, a fully human IgG4 monoclonal antibody against PD-1 receptors, blocks the interaction of PD-1 on the T-cell and PD-L1/PD-L2 on the tumor cell improving the antitumor function of the T-cells. The US FDA has approved nivolumab for the treatment of several malignancies.

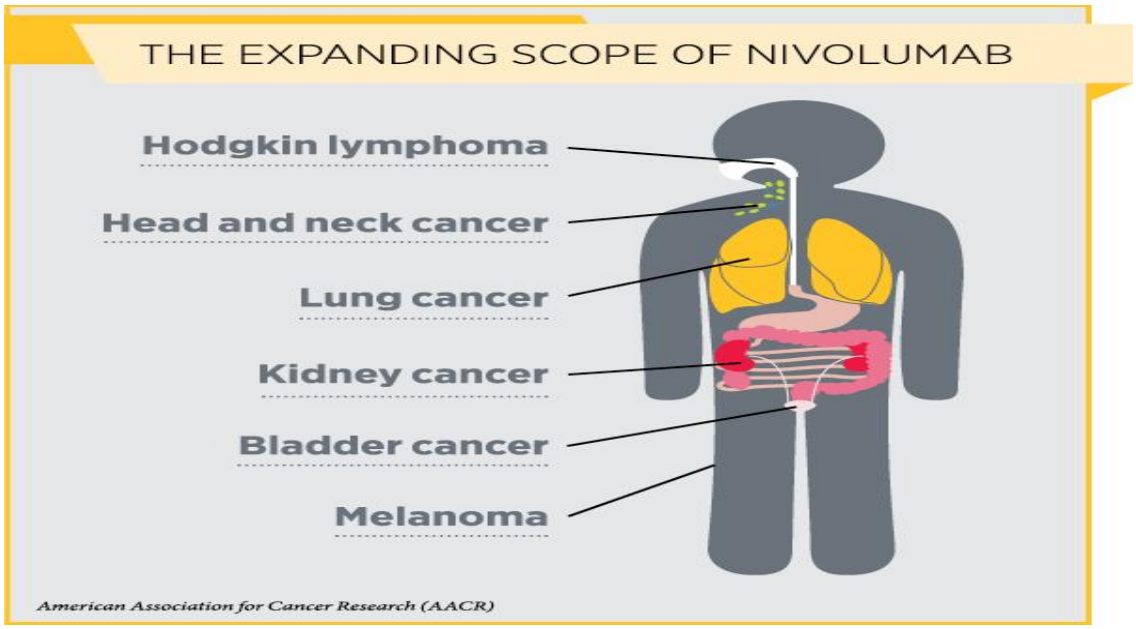
Eosinophilia with PD-1/PD-L1 checkpoint inhibitors is a rarely reported adverse event. Absolute eosinophilic count (AEC) of more 500 cells/μL in the peripheral blood is eosinophilia, and based on the eosinophil count, it is further subdivided as mild , moderate , and severe . AEC >1500 x 10 power 9 in the peripheral blood on two separate occasions at least one month apart is defined as hypereosinophilia. Pathologic confirmation of tissue hypereosinophilia is also termed as hypereosinophilia. The term hypereosinophilic syndrome is used when eosinophilia is associated with tissue and organ damage . Early identification of drug-induced hypereosinophilia is critical, especially when deciding whether to continue the drug and/or to treat with corticosteroids.

Allergic or immunologic processes like asthma, eosinophilic granulomatosis with polyangiitis, bronchopulmonary aspergillosis, and helminthic parasitic infections are associated with hypereosinophilia. Hematologic or neoplastic disorders (adenocarcinomas, Hodgkin lymphoma, and T-cell lymphoma) can also lead to hypereosinophilia, but are an uncommon cause .

However, hypereosinophilia associated with immune-checkpoint inhibitors has rarely been studied. To date, only five studys of nivolumab-induced hypereosinophilia have been studied in the literature [20].

SCOPE OF NIVOLUMAB;

nivolumab is now approved for treating six types of cancer.



Bladder cancer is expected to be the sixth most commonly diagnosed cancer in the United States in 2017, with an estimated 79,030 new cases of the disease. With 16,870 people anticipated to die from the disease in 2017, it will be the ninth most common cause of cancer-related death in the United States.

More than 90 percent of bladder cancers diagnosed in the United States begin in urothelial cells that line the inside of the bladder; they are referred to as urothelial carcinomas.

The approval of nivolumab for urothelial carcinoma was based on results from the phase II CheckMate-275 clinical trial, according to Bristol-Meyers Squibb (BMS), the company that manufactures nivolumab. In brief, the results showed that 19 percent of the 270 patients who received nivolumab had an objective response for a median of 10.3 months. Of the 53 patients who responded, seven had a complete response and 46 had a partial response.

Given that the approval of nivolumab centers on response data, rather than overall survival, BMS is required by the FDA to conduct additional studies to confirm that the immunotherapeutic improves survival for patients with urothelial carcinoma.

Nivolumab works by releasing a brake (or checkpoint protein) called PD-1 on cancer-fighting immune cells called T cells. Nivolumab releases the PD-1 brake by preventing it from being engaged by two proteins called PD-L1 and PD-L2. Once the PD-1 brake is released by nivolumab, the T cells are able to destroy cancer cells.

Nivolumab is the second immunotherapeutic that targets the PD-1/PD-L1 braking system to be approved by the FDA for treating certain patients with urothelial carcinoma. As discussed on this blog, atezolizumab (Tecentriq), which targets PD-L1, was approved for this indication in May 2016, after it was shown to yield remarkable and durable responses for some patients, like Dave Maddison, who was featured in the *AACR Cancer Progress Report 2016*.[21]

CANCER TREATMENT ;

WHAT IS NIVOLUMAB AND HOW DOES IT WORK?

Nivolumab is a prescription drug indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.

Nivolumab is also indicated for the treatment of patients with advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck and urothelial carcinoma.
Nivolumab is available under the following different brand names: Opdivo.

Dosage of Nivolumab ;
Intravenous solution

- 40 mg/4 ml (10 mg/ml)
- 100 mg/10 ml (10 mg/ml)
- Further dilution required before administration

Dosing Considerations – Should be Given as Follows:
Safety and efficacy has not been established for pediatric use. Adult dosages only:

Melanoma

- Single agent
- Indicated as a single agent for BRAF V600 wildtype or BRAF V600 mutation-positive unresectable or metastatic melanoma
- 240 mg intravenous every 2 weeks infused over 1 hour
- Continue until disease progression or unacceptable toxicity
- Combination with ipilimumab
- Indicated in combination with ipilimumab for treatment of patients with BRAF unresectable or metastatic melanoma
- 1 mg/kg intravenous infused over 1 hour, followed by ipilimumab (3 mg/kg intravenous infused over 90 min) administer on the same day every 3 weeks for 4 doses
- Subsequent doses of nivolumab as a single agent are 240 mg intravenous every 2 weeks infused over 1 hour until disease progression or unacceptable toxicity

Non-Small Cell Lung Cancer

- Indicated for metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy
- Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab
- 240 mg intravenous every 2 weeks infused over 1 hour
- Continue until disease progression or unacceptable toxicity

Renal Cell Carcinoma

- Indicated for patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy
- 240 mg intravenous every 2 weeks infused over 1 hour
- Continue until disease progression or unacceptable toxicity
  Hodgkin Lymphoma
- Indicated for classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin
- 3 mg/kg intravenous infused over 1 hour every 2 weeks until disease progression or unacceptable toxicity

Head and Neck Cancer

- Indicated for recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after a platinum-based therapy
- 3 mg/kg intravenously every 2 weeks infused over 1 hour
- Continue until disease progression or unacceptable toxicity

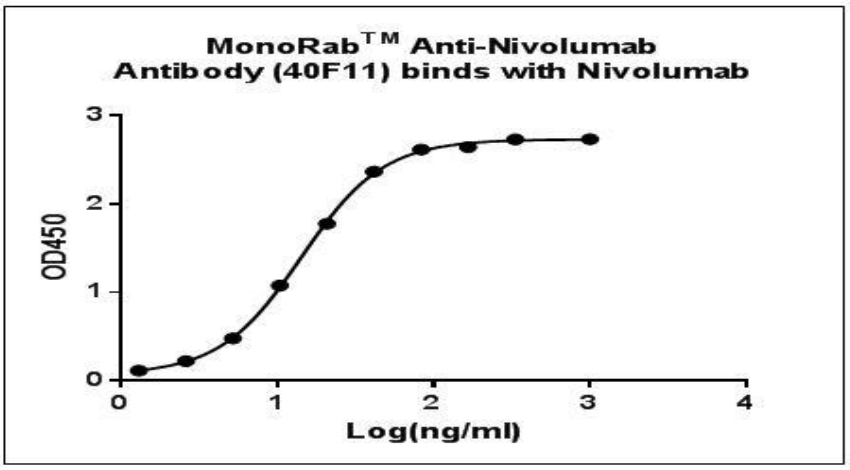
Urothelial Carcinoma

- Indicated for locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- 240 mg intravenously every 2 weeks infused over 1 hour
- Continue until disease progression or unacceptable toxicity[22]

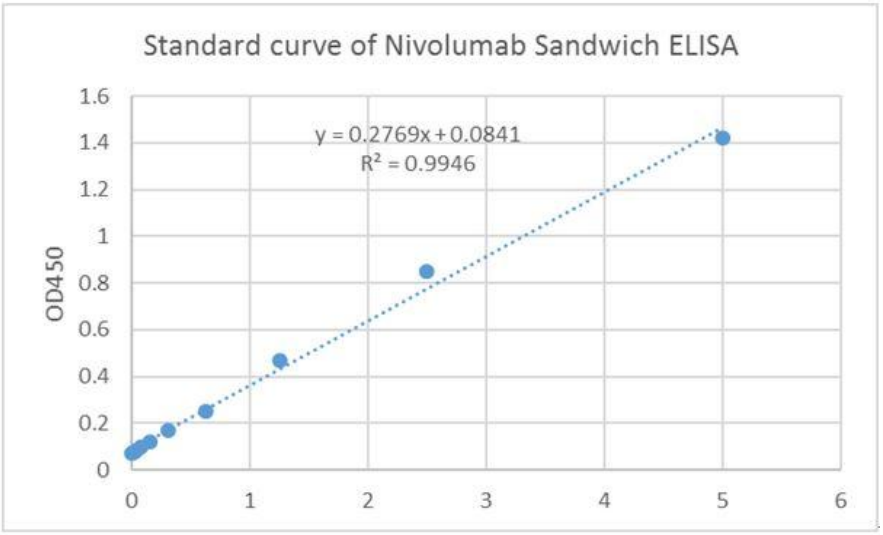
APPLICATION;

Working concentrations for specific applications should be determined by the investigators. The appropriate concentrations may be affected by secondary antibody affinity, antigen concentration, the sensitivity of the method of detection, temperature, the length of the incubations, and other factors. The suitability of this antibody for applications other than those listed below has not been determined. The following concentration ranges are recommended starting points for this product.

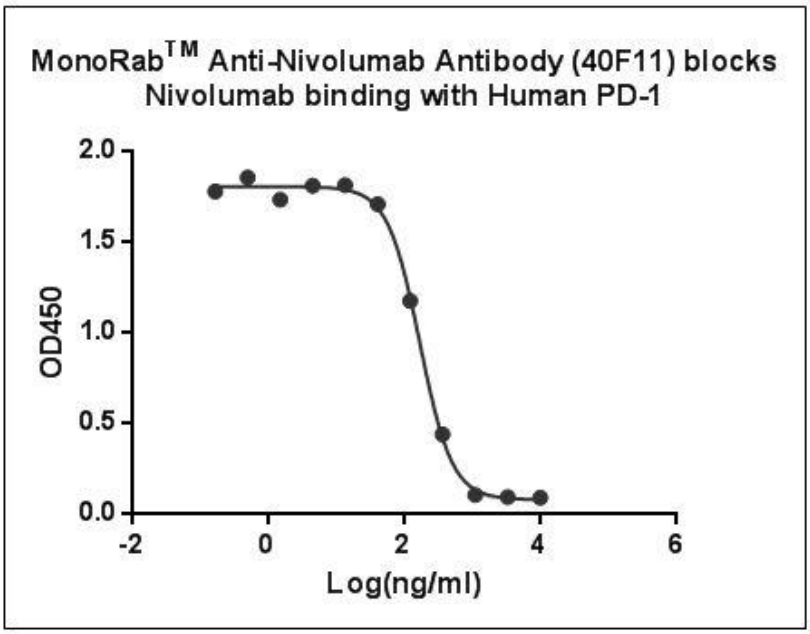
ELISA detection: 0.01-0.1 µg/ml
Other applications: user-optimized
EXAMPLE ;



ELISA binding of MonoRab™ Anti-Nivolumab Antibody (40F11) (Genscript , A01988-40) with nivolumab. While the antibody does not recognize the human IgG Fc fragment (data not shown).
Coating antigen:nivolumab. 1 µg/ml
MonoRab™ Anti-Nivolumab Antibody (40F11) (Genscript , A01988-40) dilution start from 1,000 ng /ml.
EC50 = 14.3 ng/ml.



Standard curve of nivolumab sandwich ELISA .the nivolumab sandwich ELISA assay is developed by using MonoRab™ Anti-Nivolumab Antibody (34H4),mab, Rabbit (Genscript, A01987-40) and MonoRab™ Anti-Nivolumab Antibody (40F11) (Genscript, A01988-40) as the capture and detection antibodies, respectively.in this ELISA assay MonoRab™ Anti-Nivolumab Antibody (40F11) (Genscript, A01988-40) was labelled with biotin. GenSCRIPT can provide customized conjugation services for this product per the customer's request. The sensitivity of detecting nivolumab is up to 78 pg/ml



.

MonoRab™ Anti-Nivolumab Antibody (40F11) , mAb Rabbit (Genscript, A01988-40) blocks nivolumab binding with human PD-1 recombinant protein (Z03370,PD-1 Fc chimera, Human).Coating antigen:nivolumab. 1 µg/ml.PD-1 –FC-biotin final concentration:10ng/ml.MonoRab™ Anti-Nivolumab Antibody (40F11) , mAb Rabbit (Genscript, A01988-40) dilutions start from 10 µg/ml .IC50 = 0.17 µg/ml. [23]

II. CONCLUTION ;

The encouraging literature on nivolumab lends credibility to the promise of immune checkpoint blockade, not just in terms of its feasibility as an oncotherapeutic strategy but also as a key tool of the future in the therapeutic approaches against advanced cancers. Since PD-L1 is a weak biomarker, it is difficult for the clinician to know in particular whether the patient will respond to nivolumab therapy or not. This can lead to significant financial burden to the patient as immunotherapy is expensive. The way forward to leverage maximum benefits nivolumab may be to synergize both anti-PD-1 blockade with complementary targets in immune checkpoint pathways and other oncogenic signal transduction pathways. The US FDA has approved nivolumab for metastatic melanoma, NSCLC, and RCC. As more clinical data emerge globally, it is almost certain that approvals for nivolumab will be seen in other cancer therapeutic areas including lymphoma, hepatocellular carcinoma, and colorectal carcinoma.

BIBLIOGRAPHY ;

[1]. Natasha Udpa and Ryan P. Million. Monoclonal antibody biosimilars of nivolumab overview Creative Biolabs summarizes a short overview of Nivolumab, which consists of definition, mechanism of action, and clinical projects., Nature Reviews Drug Discovery, Published online 18 Dec 2015. view at : https://www.creativebiolabs.net/nivolumab-overview.htm

[2]. Pratishtha , B Chaudhari,Nivolumab – Pearls of Evidence;Indian J Med Paediatr Oncol. 2017 Oct-Dec; 38(4): 520–525. doi: 10.4103/ijmpo.ijmpo_193_16 ;Available from : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5759075/

[3]. Davis C. Drugs, cancer and end-of-life care: A case study of pharmaceuticalization? Soc Sci Med. 2015;131:207–14. [PMC free article] [PubMed] [Google Scholar]https://pubmed.ncbi.nlm.nih.gov/25533871/

[4]. He J, Hu Y, Hu M, Li B. Development of PD-1/PD-L1 pathway in tumor immune microenvironment and treatment for non-small cell lung cancer. Sci Rep. 2015;5:13110. [PMC free article] [PubMed] [Google Scholar] https://pubmed.ncbi.nlm.nih.gov/26279307/

[5]. Momtaz P, Postow MA. Immunologic checkpoints in cancer therapy: Focus on the programmed death-1 (PD-1) receptor pathway. Pharmgenomics Pers Med. 2014;7:357–65. [PMC free article] [PubMed] [Google Scholar] https://pubmed.ncbi.nlm.nih.gov/25484597/

[6]. R.J.Motzer, P.Sharma, D.F.McDermott, S.George.etc...CheckMate 025 phase III trial of nivolumab versus everolimus in advanced RCC.

https://www.slideshare.net/mobile/DaniloBaltazarChacon/opdivo-ref-congress-presentationasco-gu-2016presentationmotzer025rcc
[7]. U.S. National Library of Medicine,MD 20894 ,Last updated: Nov 2020 :
[8]. https://druginfo.nlm.nih.gov/drugportal/name/nivolumab
[9]. Raghav Sundar , Byoung-Chul Cho , Julie R Brahmer , Ross A Soo Nivolumab in NSCLC: latest evidence and clinical potential,Ther Adv Med Oncol. 2015 Mar;7(2):85-96. doi: 10.1177/1758834014567470.PMID: 25755681 PMCID: PMC4346216 https://pubmed.ncbi.nlm.nih.gov/25755681/
[10]. Changyu Wang, Kent B. Thudium, Minhua Han, Xi-Tao Wang, Haichun Huang, Diane Feingersh, Candy Garcia, Yi Wu, Michelle Kuhne, Mohan Srinivasan, Sujata Singh, Susan Wong, Neysa Garner, Heidi Leblanc, R. Todd Bunch, Diann Blanset, Mark J. Selby and Alan J. Korman In Vitro Characterization of the Anti-PD-1 Antibody Nivolumab, BMS-936558, and In Vivo Toxicology in Non-Human Primates ,DOI: 10.1158/2326-6066.CIR-14-0040 Published September 2014
[11]. https://cancerimmunolres.aacrjournals.org/content/2/9/846
[12]. Drew M. Pardoll, The blockade of immune checkpoints in cancer immunotherapy,Nat Rev Cancer. 2012 Apr; 12(4): 252–264.
[13]. Published online 2012 Mar 22. doi: 10.1038/nrc3239, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4856023/
[14]. Nicholas L Syn,Prof Tony S K Mok,Michele W L Teng,Ross A Soo,De-novo and acquired resistance to immune checkpoint targeting
[15]. VOLUME 18, ISSUE 12, E731-E741, DECEMBER 01, 2017 ,Published:December, 2017 DOI:https://doi.org/10.1016/S1470-2045(17)30607-1 PlumX Metrics ,
[16]. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30607-1/fulltext
[17]. Douglas B. Johnson, Chengwei Peng, Jeffrey A. Sosman ,Nivolumab in melanoma: latest evidence and clinical potential ,First Published February 2, 2015 https://doi.org/10.1177/1758834014567469
[18]. https://journals.sagepub.com/doi/10.1177/1758834014567469
[19]. Liting Guo, Haijun Zhang, and Baoan Chen,Nivolumab as Programmed Death-1 (PD-1) Inhibitor for Targeted Immunotherapy in TumorJ Cancer. 2017; 8(3): 410–416.
[20]. Published online 2017 Feb 10. doi: 10.7150/jca.17144,PMID: 28261342,PMCID: PMC5332892 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5332892/
[21]. Data sources include IBM Watson Micromedex (updated 2 Nov 2020), Cerner Multum™ (updated 2 Nov 2020), ASHP (updated 23 Oct 2020) and others.https://www.drugs.com/drug-interactions/nivolumab.html
[22]. Medically reviewed by Drugs.com. Last updated on Nov 12, 2019.,Nivolumab Side Effects
[23]. https://www.drugs.com/sfx/nivolumab-side-effects.html,https://www.rxlist.com/opdivo-drug.htm
[24]. Kaewta Rattanapisit, Tanapati Phakham, Supranee Buranapraditkun, Konlavat Siriwattananon, Chatikorn Boonkrai, Trairak Pisitkun, Nattiya Hirankarn, Richard Strasser, Yoshito Abe & Waranyoo Phoolcharoen,Structural and In Vitro Functional Analyses of Novel Plant-Produced Anti-Human PD1 Antibody,Structural and In Vitro Functional Analyses of Novel Plant-Produced Anti-Human PD1 Antibody ,Published: 23 October 2019,https://doi.org/10.1038/s41598-019-51656-1.
[25]. https://www.nature.com/articles/s41598-019-51656-1
[26]. Hargadon, K. M., Johnson, C. E. & Williams, C. J. Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. Int Immunopharmacol 62, 29–39, https://doi.org/10.1016/j.intimp.2018.06.001 (2018).Return to ref 1 in article
[27]. CAS Article PubMed Google Scholar,
[28]. https://www.sciencedirect.com/science/article/pii/S1567576918302522?via%3Dihub
[29]. Nandi, S. et al. Techno-economic analysis of a transient plant-based platform for monoclonal antibody production. MAbs 8, 1456–1466, https://doi.org/10.1080/19420862.2016.1227901 (2016).Return to ref 4 in articleCAS Article PubMed PubMed Central Google Scholar,https://www.tandfonline.com/doi/full/10.1080/19420862.2016.1227901
[30]. Sharjeel Usmani1, Rashid Rasheed2, Fahad Marafi3, Fareeda Al Kandari2
[31]. Immune checkpoint inhibitors (Nivolumab)-induced enterocolitis demonstrated on 18Fluorine-fluorodeoxyglucose positron emission tomography-computed tomography,Year : 2019 | Volume : 34 | Issue : 2 | Page : 173-175.,
[32]. https://www.ijnm.in/article.asp?issn=0972-3919;year=2019;volume=34;issue=2;spage=173;epage=175;aulast=Usmani
[33]. Navdeep Singh,1 Sandeep Singh Lubana ,2 George Constantinou,3 and Andrea N. Leaf4,Immunocheckpoint Inhibitor-(Nivolumab-) Associated Hypereosinophilia in Non-Small-Cell Lung Carcinoma,Volume 2020 |Article ID 7492634 | https://doi.org/10.1155/2020/7492634,https://www.hindawi.com/journals/crionm/2020/7492634/
[34]. Karen Honey, PhD.,CANCER RESEARCH CATALYST The Official Blog of the American Association for Cancer Research,published byFebruary 6, 2017.,
[35]. https://www.aacr.org/blog/2017/02/06/use-of-nivolumab-expanded-to-sixth-cancer-type/
[36]. John P. Cunha, DO, FACOEP.,(Medical and Pharmacy Editor)NIVOLUMAB https://www.rxlist.com/consumer_nivolumab_opdivo/drugs-condition.htm
[37]. MonoRab™ Anti-Nivolumab Antibody (40F11), mAb, Rabbit.,
[38]. View at:https://www.genscript.com/antibody/A01988-MonoRab_Anti_Nivolumab_AntibodyF11_mAb_Rabbit.html

M. Kalaichandar,M.Jeevitha,Dr.D.Satheeshkumar et. al. "A Review on Current Development of Nivolumab Anticancer Activity Drug." *IOSR Journal of Pharmacy (IOSRPHR)*, 10(12), 2020, pp. 10-20.