OPDIVO (nivolumab) | OPDIVO (nivolumab) + YERVOY (ipilimumab) | OPDIVO (nivolumab) + YERVOY (ipilimumab) and platinum-doublet chemotherapy

Indications

OPDIVO, indicated for:

- Unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma, as monotherapy or in combination with ipilimumab;
- Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor;
- Melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases, as adjuvant therapy after complete resection;
- The adjuvant treatment of adult patients with Stage IIB or IIC melanoma following complete resection, as monotherapy;
- Locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving OPDIVO;
- Metastatic NSCLC, expressing PD-L1 ≥1% as determined by a validated test, with no EGFR or ALK genomic tumour aberrations and no prior systemic treatment for metastatic NSCLC, when used in combination with ipilimumab;
- Metastatic NSCLC with no EGFR or ALK genomic tumour aberrations and no prior systemic therapy for metastatic NSCLC, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy;
- Unresectable malignant pleural mesothelioma (MPM) who have not received prior systemic therapy for MPM, when used in combination with ipilimumab;
- Advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy;
- Intermediate/poor-risk advanced or metastatic RCC when used in combination with ipilimumab;
- The first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC, when used in combination with cabozantinib;
- Recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) progressing on or after platinum-based therapy;
- Adjuvant treatment of completely resected esophageal or gastroesophageal junction (GEJ) cancer in patients who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (CRT);
- HER2 negative advanced or metastatic gastric cancer, gastroesophageal junction cancer or esophageal adenocarcinoma (GC/GEJC/EAC), in combination with fluoropyrimidine- and platinum-containing chemotherapy;
- Unresectable or metastatic esophageal squamous cell carcinoma (ESCC) in adult patients, with tumor cell PD-L1 expression ≥1% as determined by a validated test, and no prior systemic therapy for metastatic ESCC, when used in combination with ipilimumab;
- Unresectable or metastatic ESCC in adult patients with tumor cell PD-L1 expression ≥1% as determined by a validated test, and no prior systemic therapy for metastatic ESCC, when used in combination with fluoropyrimidine- and platinum-containing chemotherapy;
- Neoadjuvant treatment of adult patients with resectable NSCLC (tumors ≥4 cm or node positive) when used in combination with platinum-doublet chemotherapy;

has been issued market authorization **without conditions**.

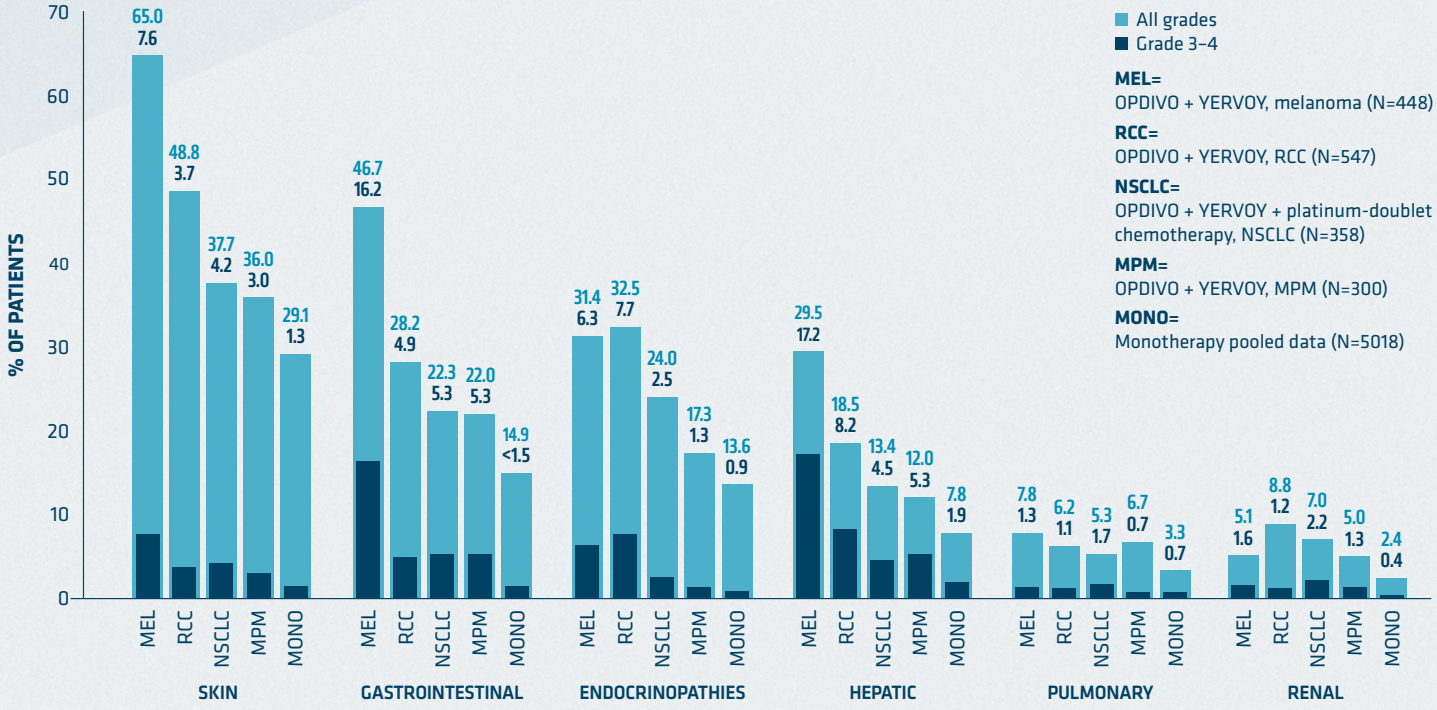
OPDIVO, indicated for:[1]

- Classical Hodgkin Lymphoma (cHL) that has relapsed or progressed after:
  - autologous stem cell transplantation (ASCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy including ASCT;
- In combination with ipilimumab, for the treatment of adult patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer after:
  - prior fluoropyrimidine-based therapy in combination with oxaliplatin or irinotecan;
- The adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC;

has been issued market authorization **with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information on OPDIVO please refer to Health Canada's Notice of Compliance with conditions – drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html.

SAFETY PROFILE

IMMUNE-MEDIATED ADVERSE REACTION (imAR) INCIDENCES BY INDICATION[1]



% OF PATIENTS WITH COLITIS
MEL: 13.1% RCC: 3.7%
NSCLC: 3.4% MPM: 3.3%
MONO: 1.2%

% OF PATIENTS WITH HEPATITIS
MEL: 4.5% RCC: 1.3%
NSCLC: 1.7% MPM: 2.3%
MONO: < 0.3%

OPDIVO Safety Information[1]

Clinical use:
Efficacy and safety not established in pediatric patients.

Most serious warnings and precautions:
Severe/fatal immune-mediated adverse reactions (imARs): OPDIVO as monotherapy or in combination with YERVOY (ipilimumab) can cause severe and fatal immune-mediated adverse reactions, including pneumonitis, interstitial lung disease, encephalitis, myocarditis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and autoimmune hemolytic anemia. Immune-mediated adverse reactions may involve any organ system. While most of these reactions occurred during treatment, onset months after the last dose has been reported. Early diagnosis and appropriate management are essential to minimize potential life-threatening complications. Monitor patients for signs and symptoms of imARs and appropriately manage with treatment modifications. Permanently discontinue for any severe imARs that recur and for any life-threatening imARs.

Administration: Administer OPDIVO under the supervision of physicians experienced in the treatment of cancer.

Allogeneic hematopoietic stem cell transplantation (HSCT): Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Preliminary results from the follow-up of patients undergoing allogeneic HSCT after previous exposure to nivolumab showed a higher than expected number of cases of acute graft-versus-host disease (GVHD) and transplant-related mortality. Complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grades 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic venoocclusive disease (VOD), and other immune-mediated adverse reactions, and intervene promptly.

Multiple myeloma: Increased mortality in patients with multiple myeloma [not an approved indication] when OPDIVO is added to a thalidomide analogue and dexamethasone. Treatment of patients with multiple myeloma with a PD-1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Other relevant warnings and precautions:
- imARs have occurred at higher frequencies when OPDIVO was administered in combination with YERVOY vs. OPDIVO alone
- Severe cases of these imARs have been observed, including fatal cases. Monitor patients for signs and symptoms of:
  - Cardiac adverse events and pulmonary embolism with combination therapy
  - Endocrinopathies, including hypothyroidism, hyperthyroidism, hypoparathyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis
  - Diarrhea, additional symptoms of colitis, and cytomegalovirus (CMV) infection/reactivation
  - Hepatotoxicity, including hepatitis
  - Pneumonitis or interstitial lung disease
  - Nephrotoxicity, including nephritis and renal failure
  - Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Encephalitis
  - Aplastic anemia
  - Myelitis (including transverse myelitis)
  - Autoimmune hemolytic anemia
  - Myotoxicity (myositis, myocarditis, and rhabdomyolysis)
  - Other imARs, including solid organ transplant rejection and rapid-onset and severe graft-versus-host disease (GVHD)
- Infusion reaction
- Patients on controlled sodium diet
- Caution when driving or operating a vehicle or potentially dangerous machinery
- Haemophagocytic lymphohistiocytosis (HLH)
- Effective contraception in women of reproductive potential
- Pregnancy and nursing women
- Has not been studied in patients with moderate or severe hepatic or severe renal impairment

For more information:
Please consult the OPDIVO Product Monograph at https://www.bms.com/assets/bms/ca/documents/productmonograph/OPDIVO_EN_PM.pdf for important information relating to adverse reactions, drug interactions, and dosing, which have not been discussed in this piece.

The Product Monograph is also available by calling us at: 1-866-463-6267.

YERVOY Safety Information[2]

Clinical use:
Efficacy and safety not established in pediatric patients.

Contraindication:
In patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life threatening.

Most serious warnings and precautions:
Severe/fatal immune-mediated adverse reactions (imARs): YERVOY as monotherapy or in combination with OPDIVO (nivolumab) can cause severe/fatal imARs, including enterocolitis, intestinal perforation, hepatitis, dermatitis (incl. toxic epidermal necrolysis), Stevens-Johnson syndrome, neuropathy, endocrinopathy, pneumonitis, interstitial lung disease, myocarditis, encephalitis, myasthenia gravis, autoimmune hemolytic anemia and other organ system toxicities. Most occurred during the induction period; onset months after the last dose has been reported. Early diagnosis and appropriate management are essential to minimize life-threatening complications. Monitor patients for signs and symptoms suggestive of imARs. Permanently discontinue treatment for any severe imAR reaction that recurs and for any life-threatening imAR.

Consult the OPDIVO (nivolumab) Product Monograph prior to initiation of YERVOY in combination with OPDIVO.

Administration: Administer YERVOY under the supervision of physicians experienced in the treatment of cancer.

Other relevant warnings and precautions:
- imARs have occurred at higher frequencies when YERVOY was administered in combination with OPDIVO vs. YERVOY alone
- Patients who have had a severe or life-threatening skin adverse reaction on a prior cancer immune stimulatory therapy
- Severe cases of these imARs have been observed, including fatal cases. Monitor for signs/symptoms of:
  - Gastrointestinal adverse reactions
  - Hepatic adverse reactions
  - Renal adverse reactions
  - Pulmonary adverse reactions
  - Skin adverse reactions
  - Encephalitis
  - Neuropathies
  - Endocrinopathies, including diabetes mellitus (including fulminant type 1 diabetes), and diabetic ketoacidosis
- Other imARs including ocular events
- Haemophagocytic lymphohistiocytosis (HLH)
- Vogt-Koyanagi-Harada syndrome
- Serous retinal detachment
- Graft-versus-host disease (GVHD)
- Solid organ transplant rejection in the post-marketing setting
- Infusion reaction
- Patients on immunosuppressive therapy for life-threatening disease or condition
- Autoimmune hemolytic anemia
- Myotoxicity (myositis, myocarditis, and rhabdomyolysis)
- Patients on controlled sodium diet
- Concurrent administration with vemurafenib
- Caution when driving or operating machinery
- Patient counseling information: imARs and fatigue
- Not studied in patients with hepatic impairment
- Not studied in patients with renal impairment
- Pregnancy and nursing women
- Effective contraception in women of reproductive potential
- Close monitoring required: liver function tests, thyroid function test, electrolytes, any signs of imARs

For more information:
Please consult the YERVOY Product Monograph at https://www.bms.com/assets/bms/ca/documents/productmonograph/YERVOY_EN_PM.pdf for important information relating to adverse reactions, management of imARs, drug interactions, and dosing information, which have not been discussed in this piece.

The Product Monograph is also available by calling us at: 1-866-463-6267.

REFERENCES: 1. OPDIVO Product Monograph. Bristol-Myers Squibb Canada Co.
2. YERVOY Product Monograph. Bristol-Myers Squibb Canada Co.

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MEMBER OF INNOVATIVE MEDICINES CANADA

OPDIVO (nivolumab) + Pr YERVOY (ipilimumab)

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