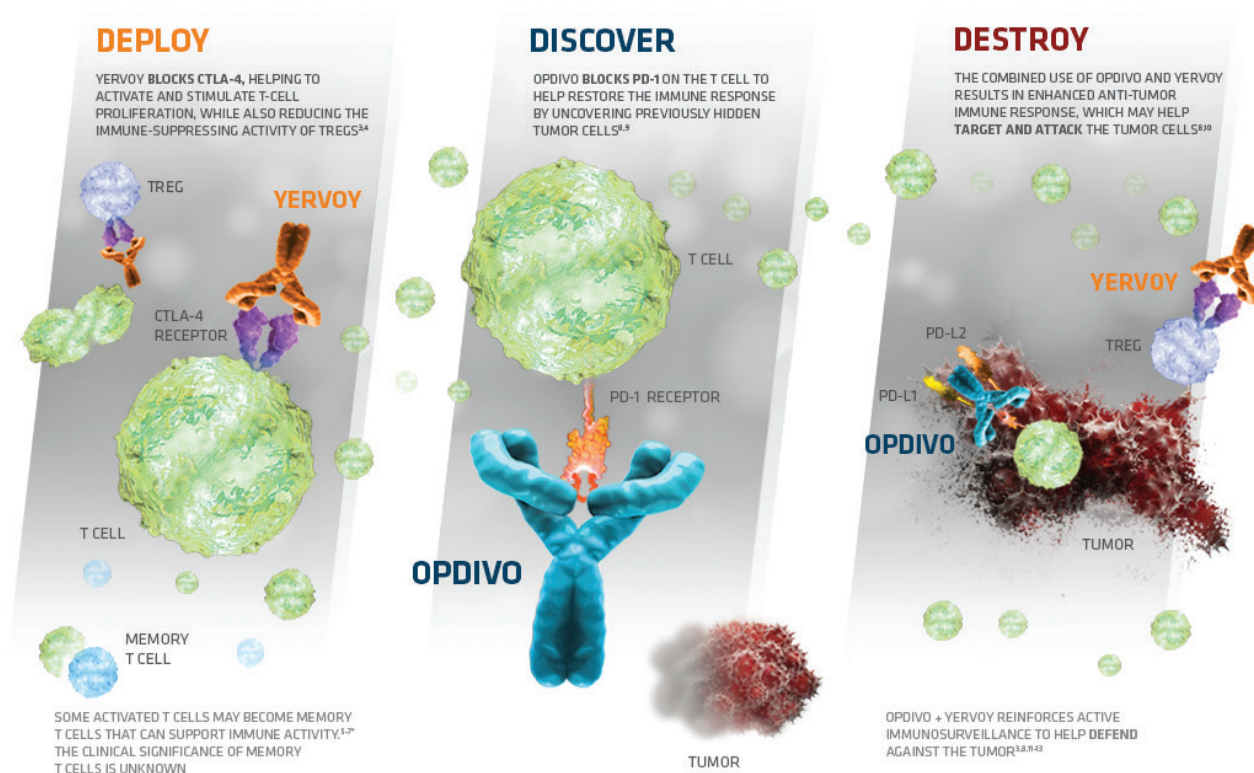


# ENHANCE IMMUNE RESPONSE WITH THE DUAL BLOCKADE OF OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

TARGETING OF NORMAL CELLS COULD ALSO OCCUR<sup>1,2</sup>



This graphic is to be used for demonstration purposes only. The specific sequence and mechanism of these drugs may vary for each patient.

\*Based on the measurements of CD45RD+ or CD45RA- as a marker for memory T cells in 5 studies (N=22-115) utilizing a range of YERVOY doses.

CTLA-4=cytotoxic T-lymphocyte antigen 4; PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1; PD-L2=programmed death ligand 2; T cell=cytotoxic T cell; Treg=regulatory T cell.



## INDICATION

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with intermediate or poor-risk, previously untreated advanced renal cell carcinoma (RCC).

OPDIVO (10 mg/mL) and YERVOY (5 mg/mL) are injections for intravenous use.

## IMPORTANT SAFETY INFORMATION

### WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

**YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.**

**Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose.**

**Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.**

### Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 4.4% (24/547) of patients.

### Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 10% (52/547) of patients.

### Immune-Mediated Hepatitis

OPDIVO can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 7% (38/547) of patients.

## Immune-Mediated Endocrinopathies

OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypophysitis occurred in 4.6% (25/547) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 7% (38/547) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients. Hyperthyroidism occurred in 12% (66/547) of patients receiving this dose of OPDIVO with YERVOY. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, diabetes occurred in 2.7% (15/547) of patients.

## Immune-Mediated Nephritis and Renal Dysfunction

OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients.

## Immune-Mediated Skin Adverse Reactions and Dermatitis

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 16.6% (91/547) of patients.

## Immune-Mediated Encephalitis

OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. Encephalitis occurred in one patient receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg (0.2%) after approximately 4 months of exposure.

## Other Immune-Mediated Adverse Reactions

Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving OPDIVO and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

## Infusion Reactions

OPDIVO can cause severe infusion reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In a separate study in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients.

## Embryo-Fetal Toxicity

Based on their mechanisms of action, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with an OPDIVO- or YERVOY- containing regimen and for at least 5 months after the last dose of OPDIVO.

## Lactation

It is not known whether OPDIVO or YERVOY is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from an OPDIVO-containing regimen, advise women to discontinue breastfeeding during treatment. Advise women to discontinue breastfeeding during treatment with YERVOY and for 3 months following the final dose.

## Serious Adverse Reactions

In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY and in 43% of patients receiving sunitinib. The most frequent serious adverse reactions reported in at least 2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea.

## Common Adverse Reactions

In Checkmate 214, the most common adverse reactions reported in at least 20% of patients treated with OPDIVO plus YERVOY (n=547) vs sunitinib (n=535) were fatigue (58% vs 69%), rash (39% vs 25%), diarrhea (38% vs 58%), musculoskeletal pain (37% vs 40%), pruritus (33% vs 11%), nausea (30% vs 43%), cough (28% vs 25%), pyrexia (25% vs 17%), arthralgia (23% vs 16%), and decreased appetite (21% vs 29%).

Please see U.S. Full Prescribing Information for [OPDIVO](#) and [YERVOY](#), including **Boxed WARNING regarding immune-mediated adverse reactions** for YERVOY.

**References:** 1. Metro G et al. *Expert Opin Drug Saf.* 2016;16(1):101-109. 2. Byrne EH, Fisher DE. *Cancer.* 2017;123(S1):2143-2153. 3. YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2018. 4. Bulliard Y et al. *J Exp Med.* 2013;210(9):1685-1693. 5. Farber DL et al. *Nat Rev Immunol.* 2014;14(1):24-35. 6. Pedicord VA et al. *Proc Natl Acad Sci USA.* 2011;108(1):266-271. 7. Ansell SM et al. *Clin Cancer Res.* 2009;15(20):6446-6453. 8. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2018. 9. Zhang Z et al. *Oncotarget.* 2017;8(56):96453-96459. 10. Rotte A et al. *Ann Oncol.* 2018;29(1):71-83. 11. Buchbinder E, Desai A. *Am J Clin Oncol.* 2016;39(1):98-106. 12. Peters S et al. *Cancer Treat Rev.* 2018;62:39-49. 13. Jenkins RW et al. *Br J Cancer.* 2018;118:9-16. 14. Weber JS et al. *J Immunother.* 2012;35(1):89-97. 15. Ladanyi A et al. Poster presentation at ESMO 2015. Abstract 524. 16. Das R et al. *J Immunol.* 2015;194(3):950-959. 17. Tarhini AA et al. *PLoS One.* 2014;9(2):e87705.