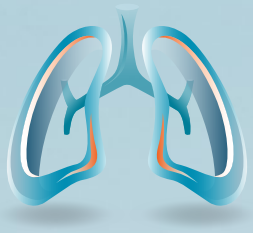


NOW APPROVED

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

The first approved therapy in >15 years to demonstrate superior survival vs SOC chemo* in the 1L treatment of unresectable malignant pleural mesothelioma[1,2]

Checkmate 743

OPDIVO®, in combination with YERVOY®, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Primary analysis: median OS was 18.1 months (95% CI: 16.8–21.5) with OPDIVO + YERVOY vs 14.1 months (95% CI: 12.5–16.2) with chemo (HR=0.74; 95% CI: 0.61–0.89; *P*=0.002).[1]

*Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2), q3w for 6 cycles.[1]

1L=first line; AUC=area under the curve; CI=confidence interval; HR=hazard ratio; OS=overall survival; q3w=every 3 weeks; SOC=standard of care.

SELECT IMPORTANT SAFETY INFORMATION

Summary of Warnings and Precautions

- OPDIVO is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, encephalitis, other adverse reactions; infusion-related reactions; embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials. YERVOY is associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogenic hematopoietic stem cell transplant after YERVOY, embryo-fetal toxicity and risks associated when administered in combination with nivolumab.

Severe and Fatal Immune-Mediated Adverse Reactions

- Immune-mediated adverse reactions listed herein may not be inclusive of all possible severe and fatal immune-mediated adverse reactions.
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur at any time after starting or discontinuing YERVOY. Early identification and management are essential to ensure safe use of YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.
- Withhold or permanently discontinue YERVOY depending on severity. In general, if YERVOY requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less followed by corticosteroid taper for at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroid therapy. Institute hormone replacement therapy for endocrinopathies as warranted.

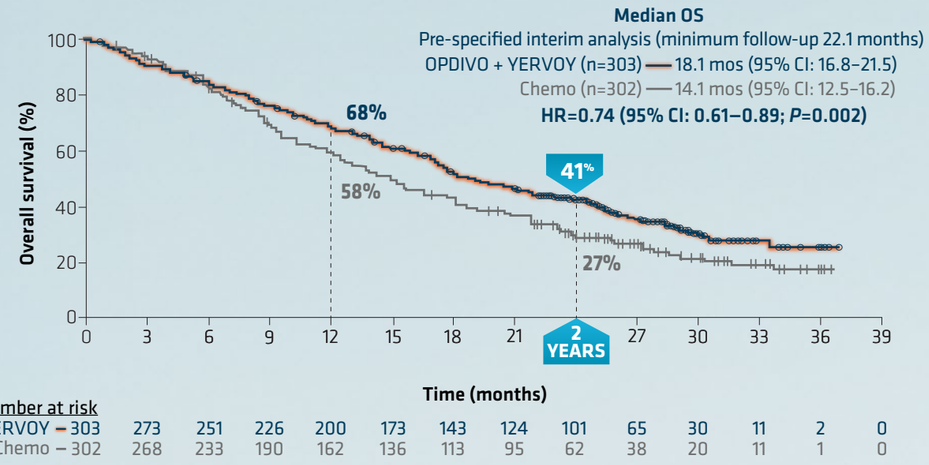
Please see additional Important Safety Information for OPDIVO and YERVOY throughout and US Full Prescribing Information for **OPDIVO** and **YERVOY** at **www.opdivocombomnsclc-mpm.com**.

Bristol Myers Squibb™

For the 1L treatment of adult patients with unresectable malignant pleural mesothelioma

OPDIVO® (nivolumab) + YERVOY® (ipilimumab): 41% of patients alive at 2 years[1,2*]

Checkmate 743 **Overall survival[1,2]**



Number at risk													
OPDIVO + YERVOY	303	273	251	226	200	173	143	124	101	65	30	11	2	0
Chemo	302	268	233	190	162	136	113	95	62	38	20	11	1	0

Median follow-up was 29.7 months.[2]

- Efficacy results from the interim analysis when 419 deaths occurred (89% of the deaths needed for the final analysis)[1]
- Median PFS 6.8 months (95% CI: 5.6–7.4) with OPDIVO + YERVOY and 7.2 months (95% CI: 6.9–8.1) with chemo; HR=1.0 (95% CI: 0.82–1.21)[1]

Study design: Checkmate 743 was a phase 3, randomized, open-label trial of OPDIVO (3 mg/kg) q2w in combination with YERVOY (1 mg/kg) q6w for up to 2 years (n=303) vs pemetrexed (500 mg/m^2) q3w with cisplatin (75 mg/m^2) q3w or carboplatin (AUC 5) q3w for 6 cycles (n=302) as 1L therapy in unresectable malignant pleural mesothelioma. The primary endpoint was OS. Key secondary endpoints included PFS and ORR.[2]

- The recommended dose of OPDIVO is 360 mg q3w, administered as an IV infusion over 30 minutes until disease progression, unacceptable toxicity, or for up to 2 years[1]

*Compared vs chemo. Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2), q3w for 6 cycles.[1]

SELECT IMPORTANT SAFETY INFORMATION

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. The incidence and severity of immune-mediated pneumonitis in patients with malignant pleural mesothelioma treated with OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks were similar to those occurring in NSCLC.

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.
- Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

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.

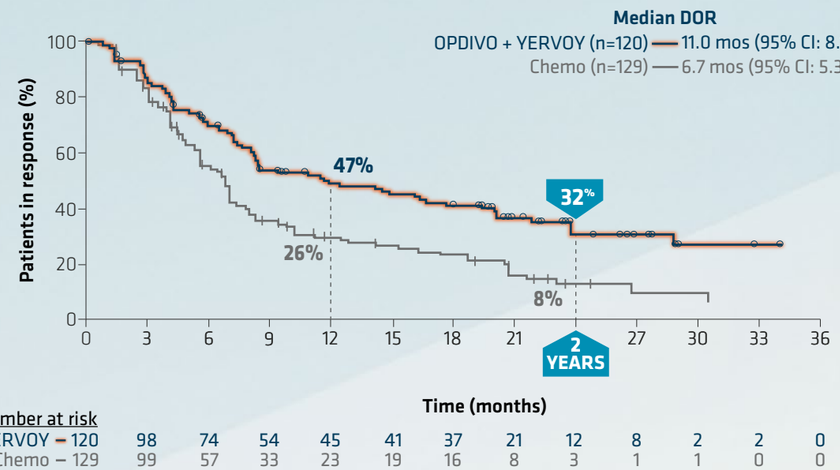
Please see additional Important Safety Information for OPDIVO and YERVOY throughout and US Full Prescribing Information for **OPDIVO** and **YERVOY** at **www.opdivocombomnsclc-mpm.com**.

For the 1L treatment of adult patients with unresectable malignant pleural mesothelioma

32% of OPDIVO + YERVOY responders were still responding at 2 years[2*]

Checkmate 743 **Duration of response[2]**

- ORR[†] was 40%[‡] with OPDIVO + YERVOY (120/303) and 43%[§] with chemo (129/302); CR=2%, PR=38% with OPDIVO + YERVOY and CR=0%, PR=43% with chemo[2]



Number at risk													
OPDIVO + YERVOY	120	98	74	54	45	41	37	21	12	8	2	2	0
Chemo	129	99	57	33	23	19	16	8	3	1	1	0	0

Median follow-up was 29.7 months.[2]

- Median time to response was 2.7 months with OPDIVO + YERVOY and 2.5 months with chemo[2]

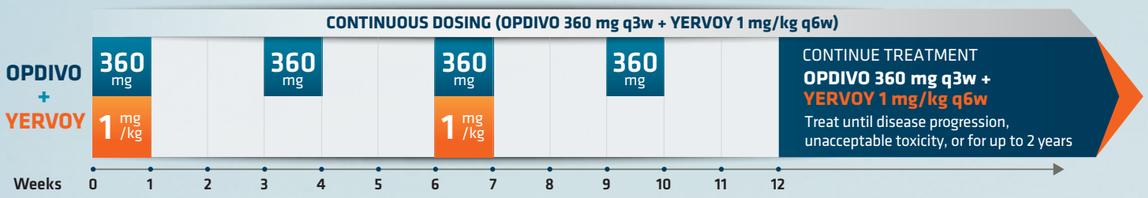
*Compared vs chemo. Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2), q3w for 6 cycles.[1]
[†]Per adapted mRECIST for pleural mesothelioma lesions and/or RECIST 1.1 criteria for non-pleural lesions.[2]
[‡]95% CI: 34%–45%.[1]
[§]95% CI: 37%–49%.[1]
CR=complete response; DOR=duration of response; IV=intravenous; mo=month; mRECIST=modified RECIST; ORR=overall response rate; PFS=progression-free survival; PR=partial response; q2w=every 2 weeks; q6w=every 6 weeks; RECIST=Response Evaluation Criteria In Solid Tumors.

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

For the 1L treatment of adult patients with unresectable malignant pleural mesothelioma

OPDIVO® (nivolumab) + low-dose YERVOY® (ipilimumab) (1 mg/kg) dosing[1]

uMPM **Dosing[1]**



- OPDIVO is administered as an IV infusion over 30 minutes[1]
- YERVOY is administered as an IV infusion over 30 minutes[3]

uMPM=unresectable malignant pleural mesothelioma.

Learn more about OPDIVO + YERVOY–based regimens. Visit www.opdivocombomnsclc-mpm.com

SELECT IMPORTANT SAFETY INFORMATION

Infusion-Related Reactions

- OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. Severe infusion-related reactions can also occur with YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion reactions and interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial 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.

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. Withhold for Grades 2, 3, or 4 endocrinopathies if not clinically stable. 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.

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.

SELECT IMPORTANT SAFETY INFORMATION

Immune-Mediated Skin and Dermatologic Adverse Reactions

- 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.
- YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous exfoliative rashes. Withhold YERVOY until specialist assessment for Grade 2 and permanently discontinue for Grade 3 or 4 exfoliative or bullous dermatologic conditions.

Immune-Mediated Encephalitis

- OPDIVO can cause immune-mediated encephalitis. Fatal cases have been reported. 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.

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. Dose modifications for YERVOY for adverse reactions that require management different from these general guidelines are summarized as follows. Withhold for Grade 2 and permanently discontinue YERVOY for Grade 3 or 4 neurological toxicities. Withhold for Grade 2 and permanently discontinue YERVOY for Grade 3 or 4 myocarditis. Permanently discontinue YERVOY for Grade 2, 3, or 4 ophthalmologic adverse reactions that do not improve to Grade 1 within 2 weeks while receiving topical therapy OR that require systemic therapy. Across clinical trials of OPDIVO 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, myasthenic syndrome, hemophagocytic lymphohistiocytosis (HLH), and autoimmune hemolytic anemia. In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, nerve paresis, angiopathy, temporal arteritis, pancreatitis (1.3%), arthritis, polymyositis, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis, blepharitis, episcleritis, orbital myositis, scleritis, and solid organ transplant rejection. Some cases of ocular IMARs have been associated with retinal detachment.
- 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 YERVOY and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

- OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. Severe infusion-related reactions can also occur with YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion reactions and interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial 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.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1 receptor blocking antibody or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1 or CTLA-4 receptor blockade and allogeneic HSCT.
- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody or YERVOY prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

- Based on mechanism 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 OPDIVO or YERVOY and for at least 5 months after the last dose.

Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

- In clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

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 OPDIVO or YERVOY, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

Serious Adverse Reactions

- In Checkmate 743, serious adverse reactions occurred in 54% of patients receiving OPDIVO plus YERVOY. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.3%) patients and included pneumonitis, acute heart failure, sepsis, and encephalitis.

Common Adverse Reactions

- In Checkmate 743, the most common adverse reactions (≥20%) in patients receiving OPDIVO and YERVOY were fatigue (43%), musculoskeletal pain (38%), rash (34%), diarrhea (32%), dyspnea (27%), nausea (24%), decreased appetite (24%), cough (23%), and pruritus (21%).

Please see additional Important Safety Information for OPDIVO and YERVOY throughout and US Full Prescribing Information for **OPDIVO** and **YERVOY** at **www.opdivocombomnsclc-mpm.com**.

References: 1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **2.** Baas P, Scherpereel A, Nowak A, et al. First-line nivolumab + ipilimumab vs chemotherapy in unresectable malignant pleural mesothelioma: CheckMate 743. Oral presentation at IASLC WCLC 2020 Presidential Symposium. Abstract 3. **3.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

Bristol Myers Squibb™

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