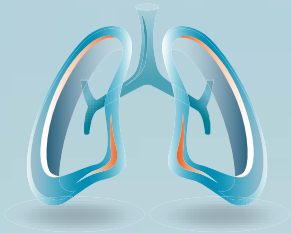


OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

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 (MPM).

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 and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); 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.

Severe and Fatal Immune-Mediated Adverse Reactions

- Immune-mediated adverse reactions listed herein may not include 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 after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and 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 periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

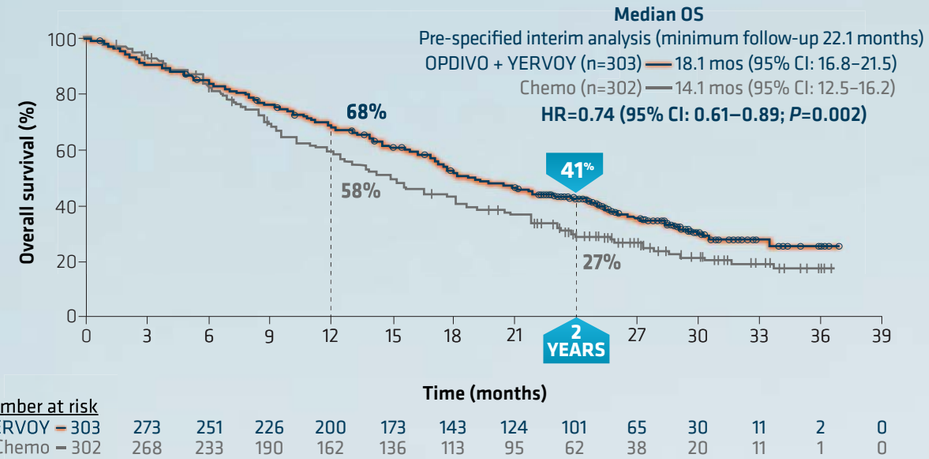
Please see additional Important Safety Information for OPDIVO and YERVOY throughout and US Full Prescribing Information for **OPDIVO** and **YERVOY**.

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

Severe and Fatal Immune-Mediated Reactions (cont'd)

Immune-Mediated Pneumonitis

- OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-Mediated Colitis

- OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. 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.

Immune-Mediated Hepatitis and Hepatotoxicity

- OPDIVO and YERVOY can cause immune-mediated hepatitis.

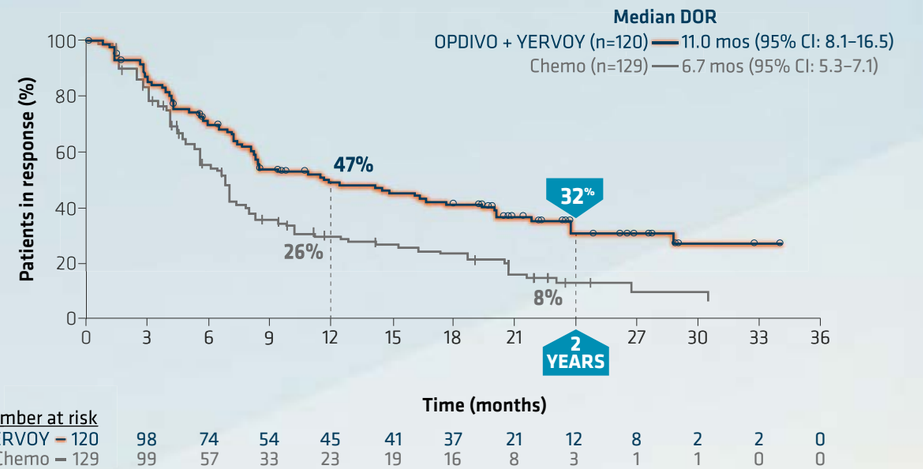
Please see additional Important Safety Information for OPDIVO and YERVOY throughout and US Full Prescribing Information for **OPDIVO** and **YERVOY**.

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]

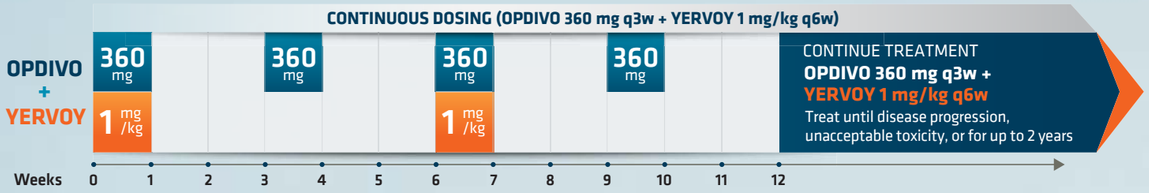
*Compared vs chemo. Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2), q3w for 6 cycles.[1]
†Per adapted mRECIST for pleural mesothelioma lesions and/or RECIST 1.1 criteria for non-pleural lesions.[2]
‡95% CI: 34%–45%.[1]
§95% CI: 37%–49%.[1]
CR=complete response; DOR=duration of 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 and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In MPM patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, infusion-related reactions occurred in 12% (37/300) of patients.

Severe and Fatal Immune-Mediated Reactions (cont'd)

Immune-Mediated Endocrinopathies

- OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

Immune-Mediated Nephritis with Renal Dysfunction

- OPDIVO and YERVOY can cause immune-mediated nephritis.

Please see additional Important Safety Information for OPDIVO and YERVOY throughout and US Full Prescribing Information for **OPDIVO** and **YERVOY**.

SELECT IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Reactions (cont'd)

Immune-Mediated Dermatologic Adverse Reactions

- OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.
- YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.
- Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular:* myocarditis, pericarditis, vasculitis; *nervous system:* meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular:* uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal:* pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue:* myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine:* hypoparathyroidism; *other (hematologic/immune):* hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.
- 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: *nervous system:* autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular:* angiopathy, temporal arteritis; *ocular:* blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal:* pancreatitis (1.3%); *other (hematologic/immune):* conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.
- Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. 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, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

- OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In MPM patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, infusion-related reactions occurred in 12% (37/300) of patients.

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 OPDIVO 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 OPDIVO or YERVOY and allogeneic HSCT.
- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

- Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and 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 randomized 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

- There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 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 US Full Prescribing Information for **OPDIVO** and **YERVOY**.

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.

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OPDIVO® (nivolumab) + YERVOY® (ipilimumab)