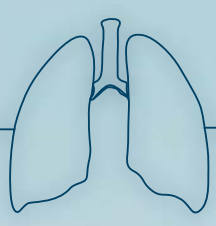


OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

with limited chemo*

IN 1L r/m NSCLC PATIENTS WITH PD-L1 <1% AND PD-L1 ≥1%[1]

Checkmate 9LA

OPDIVO®, in combination with YERVOY® and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

Primary analysis: median OS was 14.1 months (95% CI: 13.2–16.2) with OPDIVO + YERVOY and chemo vs 10.7 months (95% CI: 9.5–12.5) with chemo (HR=0.69; 96.71% CI: 0.55–0.87; *P*=0.0006).[1]

OPDIVO + YERVOY is also indicated for patients with 1L mNSCLC with PD-L1 ≥1%[1]

OPDIVO, in combination with YERVOY, is indicated for the first-line treatment of adult patients with mNSCLC whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

Primary analysis (PD-L1 ≥1%): median OS was 17.1 months (95% CI: 15.0–20.1) with OPDIVO + YERVOY vs 14.9 months (95% CI: 12.7–16.7) with chemo (HR=0.79; 95% CI: 0.67–0.94; *P*=0.0066).[1]

OPDIVO (10 mg/mL) and YERVOY (5 mg/mL) are injections for intravenous use.[1,2]

*Two cycles of platinum-doublet chemo.[1]

1L=first line; ALK=anaplastic lymphoma kinase; CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; mNSCLC=metastatic NSCLC; OS=overall survival; PD-L1=programmed death ligand 1; r/m=recurrent or metastatic.

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, 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.

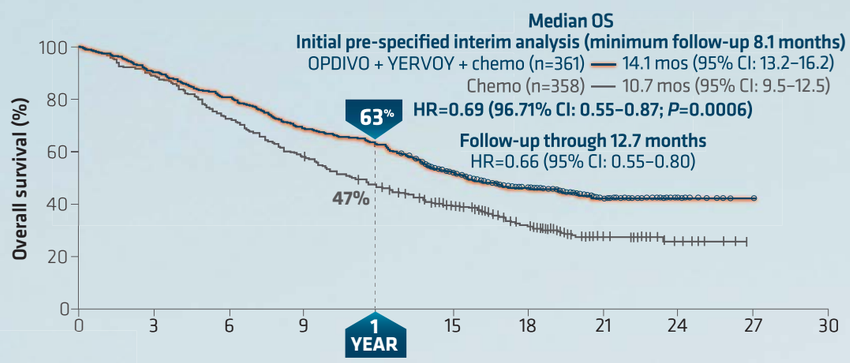
Please see Important Safety Information for OPDIVO and YERVOY throughout and refer to the end for a brief description of the patient populations studied in the clinical trials. US Full Prescribing Information for **OPDIVO** and **YERVOY** at **www.opdivoyervoymNSCLC.com**.

Bristol Myers Squibb™

For patients with r/m NSCLC, regardless of PD-L1 expression

OPDIVO® (nivolumab) + YERVOY® (ipilimumab) with limited chemo* achieved superior OS[1†]

OS: ITT[1,3]



Number at risk											
OPDIVO + YERVOY + chemo – 361	326	292	250	227	153	86	33	10	1	0
Chemo – 358	319	260	208	166	116	67	26	11	0	0

Minimum follow-up of 12.7 months.[3]

- Efficacy results from the pre-specified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) with an 8.1-month minimum follow-up[1,3]
  - **Primary analysis:** median OS was 14.1 months (95% CI: 13.2–16.2) with OPDIVO + YERVOY and chemo vs 10.7 months (95% CI: 9.5–12.5) with chemo (HR=0.69; 96.71% CI: 0.55–0.87; *P*=0.0006)[1]
- Median PFS at the 6.5 month minimum follow-up: 6.8 months (95% CI: 5.6–7.7) with OPDIVO + YERVOY with chemo vs 5.0 months (95% CI: 4.3–5.6) with chemo alone (HR=0.70; 97.48% CI: 0.57–0.86; *P*=0.0001)[1,3]
- ORR at the 6.5 month minimum follow-up: 38% (136/361) with OPDIVO + YERVOY with chemo and 25% (90/358) with chemo[1]
- Median OS at the 12.7-month follow-up analysis: 15.6 months (95% CI: 13.9–20.0) with OPDIVO + YERVOY with chemo and 10.9 months (95% CI: 9.5–12.5) with chemo alone[1,3]
- 32% of patients enrolled had SQ disease; 68% had NSQ disease[1]

Study design: Checkmate 9LA was a randomized (1:1), open-label phase 3 study of OPDIVO 360 mg q3w in combination with YERVOY 1 mg/kg q6w and 2 cycles of histology-based chemotherapy† versus 4 cycles of platinum-doublet chemotherapy† as a first-line treatment in patients with metastatic or recurrent NSCLC regardless of histology or PD-L1 status. Treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Patients were stratified by histology (SQ vs NSQ), PD-L1 (<1% vs ≥1%), and sex. The primary endpoint was OS.[1]

SELECT IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse 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. In NSCLC patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, immune-mediated pneumonitis occurred in 9% (50/576) of patients, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%). Four patients (0.7%) died due to pneumonitis.

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

- OPDIVO and YERVOY can cause immune-mediated hepatitis.

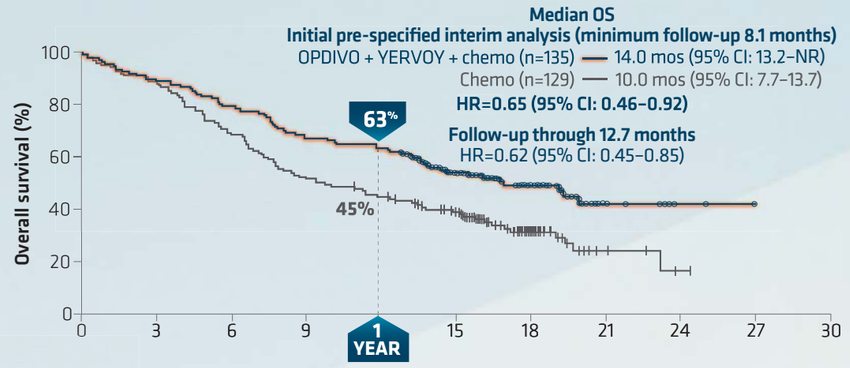
Please see Important Safety Information for OPDIVO and YERVOY throughout and refer to the end for a brief description of the patient populations studied in the clinical trials. US Full Prescribing Information for **OPDIVO** and **YERVOY** at **www.opdivoyervoymNSCLC.com**.

For patients with r/m NSCLC

Consistent OS across PD-L1 non-expressors and expressors

OS: Tumor PD-L1 <1% extended follow-up analysis[3,4]

63% of patients treated with OPDIVO + YERVOY with limited chemo* were alive at 1 year (PD-L1 <1%)[3†]

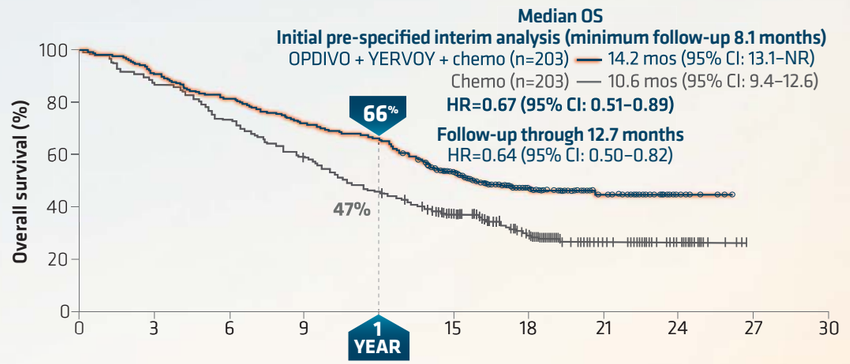


Number at risk											
OPDIVO + YERVOY + chemo – 135	120	107	90	85	53	31	8	2	1	0
Chemo – 129	116	90	68	57	43	19	5	1	0	0

Minimum follow-up of 12.7 months.[3]

OS: Tumor PD-L1 ≥1% extended follow-up analysis[3,4]

66% of patients treated with OPDIVO + YERVOY with limited chemo* were alive at 1 year (PD-L1 ≥1%)[3†]



Number at risk											
OPDIVO + YERVOY + chemo – 203	185	166	147	133	92	52	25	8	0	0
Chemo – 204	179	151	122	95	64	42	19	10	0	0

Minimum follow-up of 12.7 months.[3]

- Primary analysis of the ITT population at the 8.1-month minimum follow-up: median OS was 14.1 months (95% CI: 13.2–16.2) with OPDIVO + YERVOY with chemo vs 10.7 months (95% CI: 9.5–12.5) with chemo alone (HR=0.69; 96.71% CI: 0.55–0.87; *P*=0.0006)[1,3]
- In Checkmate 9LA, the primary efficacy outcome was OS; efficacy by PD-L1 status was a pre-specified analysis[1]

*Two cycles of platinum-doublet chemo.[1]
†Vs chemo. In Checkmate 9LA, patients in the comparator arm received 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin (optional pemetrexed maintenance in the comparator arm only); SQ: paclitaxel + carboplatin.[1]
AUC=area under the curve; ITT=intent to treat; mo=month; NR=not reached; NSQ=non-squamous; ORR=overall response rate; PFS=progression-free survival; q3w=every 3 weeks; q6w=every 6 weeks; SQ=squamous.

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

For patients with r/m NSCLC, regardless of PD-L1 expression

Adverse reactions in >10% of patients receiving OPDIVO® (nivolumab) + YERVOY® (ipilimumab) with limited chemo[1]*

Adverse reactions	OPDIVO + YERVOY + chemo (n=358)		Chemo‖‖ (n=349)	
	All grades (%)	Grades 3–4 (%)	All grades (%)	Grades 3–4 (%)
General				
Fatigue†	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and connective tissue				
Musculoskeletal pain‡	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea§	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain‖	12	0.6	11	0.9
Skin and subcutaneous tissue				
Rash¶	30	4.7	10	0.3
Pruritus#	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, thoracic, and mediastinal				
Cough**	19	0.6	15	0.9
Dyspnea††	18	4.7	14	3.2
Endocrine				
Hypothyroidism‡‡	19	0.3	3.4	0
Nervous system				
Headache	11	0.6	7	0
Dizziness§§	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.[1]

*Two cycles of platinum-doublet chemo.[1]
†Includes fatigue and asthenia.[1]
‡Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, and synovitis.[1]
§Includes colitis, ulcerative colitis, diarrhea, and enterocolitis.[1]
‖Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain.[1]
¶Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blennorrhagica, palmar-plantar erythrodysesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, and urticaria.[1]
#Includes pruritus and generalized pruritus.[1]
**Includes cough, productive cough, and upper-airway cough syndrome.[1]
††Includes dyspnea, dyspnea at rest, and exertional dyspnea.[1]
‡‡Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine.[1]
§§Includes dizziness, vertigo, and positional vertigo.[1]
‖‖Vs chemo. In Checkmate 9LA, patients in the comparator arm received 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin (optional pemetrexed maintenance in the comparator arm only); SQ: paclitaxel + carboplatin.[1]

- Treatment was permanently discontinued for adverse reactions in 24% of patients treated with OPDIVO + YERVOY with chemo, and 56% had at least one dose withheld for an adverse reaction[1]
- Serious adverse reactions occurred in 57% of patients receiving OPDIVO + YERVOY with chemo[1]
- The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure[1]
- The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus[1]
- Median number of doses was 9 for OPDIVO, 4 for YERVOY, and 2 cycles of chemo[5]
- With a minimum follow-up of 12.7 months, no new safety signals were identified for OPDIVO + YERVOY with limited chemo[3]*

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Please see Important Safety Information for OPDIVO and YERVOY throughout and refer to the end for a brief description of the patient populations studied in the clinical trials. US Full Prescribing Information for **OPDIVO** and **YERVOY** at **www.opdivoyervoymNSCLC.com**.

SELECT IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse 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.

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/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 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.

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 227, serious adverse reactions occurred in 58% of patients (n=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Common Adverse Reactions

- In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%).

Clinical Trials and Patient Populations

Checkmate 227–previously untreated metastatic non-small cell lung cancer, in combination with YERVOY

Checkmate 9LA–previously untreated recurrent or metastatic non-small cell lung cancer in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy by histology

Please see Important Safety Information for OPDIVO and YERVOY throughout and refer to the end for a brief description of the patient populations studied in the clinical trials. US Full Prescribing Information for **OPDIVO** and **YERVOY** at **www.opdivoyervoymNSCLC.com**.

References: 1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **2.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **3.** Reck M, Ciuleanu TE, Dols MC, et al. Nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy vs 4 cycles chemo as first-line treatment for stage IV/recurrent non-small cell lung cancer: CheckMate 9LA. Oral presentation at ASCO 2020. Abstract 9501. **4.** Data on file. NIVO 566. Princeton, NJ: Bristol-Myers Squibb Company; 2020. **5.** Data on file. NIVO 562. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

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OPDIVO® (nivolumab) + YERVOY® (ipilimumab)