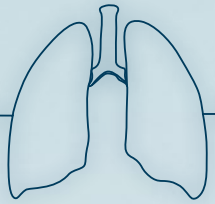


OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

SET OUT TOWARDS A FUTURE THE ONLY APPROVED DUAL I-O MAY DELIVER[1]*

For PD-L1 ≥1% mNSCLC patients, across histology

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

OPDIVO®, in combination with YERVOY®, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) 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]

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

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

WITH LIMITED CHEMO
(2 cycles of platinum-doublet chemo)

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 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]

*In Checkmate 227, patients received platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin; SQ: gemcitabine + carboplatin or cisplatin. In Checkmate 9LA, patients received platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin; SQ: paclitaxel + carboplatin.[1]

ALK=anaplastic lymphoma kinase; CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; I-O=immuno-oncology; mNSCLC=metastatic NSCLC; NSQ=non-squamous; OS=overall survival; PD-L1=programmed death ligand 1; q3w=every 3 weeks; r/m=recurrent or metastatic; SQ=squamous.

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.

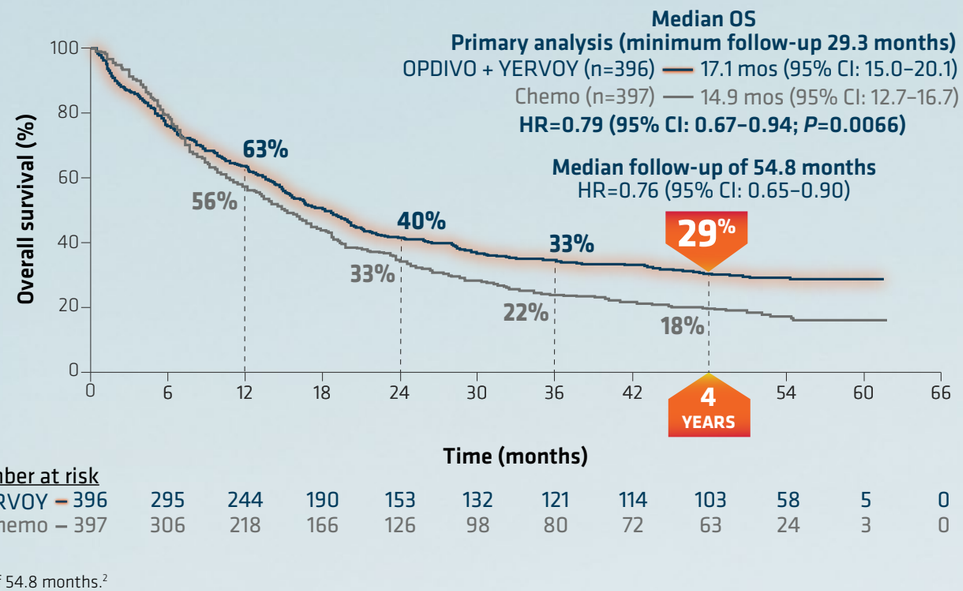
Please see additional Important Safety Information for OPDIVO and YERVOY throughout and US Full Prescribing Information for **OPDIVO** and **YERVOY**.

Bristol Myers Squibb™

Checkmate 227: In a cross-histology trial for patients with mNSCLC (PD-L1 ≥1%)

Durable survival with OPDIVO® (nivolumab) + YERVOY® (ipilimumab): 29% of patients alive at 4 years[2]*

OS for PD-L1 ≥1% (extended follow-up analysis)[1-3]



Number at risk											
OPDIVO + YERVOY – 396	295	244	190	153	132	121	114	103	58	5	0
Chemo – 397	306	218	166	126	98	80	72	63	24	3	0

Median follow-up of 54.8 months.[2]

- Median PFS with a median follow-up of 54.8 months was 5.1 months (95% CI: 4.1–6.3) with OPDIVO + YERVOY and 5.6 months (95% CI: 4.6–5.8) with chemo alone; HR=0.81; 95% CI: 0.68–0.96[2†]
- **29% of patients enrolled had SQ disease; 71% had NSQ disease[1]**

Study design: Checkmate 227 was a randomized, open-label phase 3 trial in patients with metastatic or recurrent NSCLC. Key eligibility criteria included patients 18 years or older, stage IV or recurrent NSCLC, ECOG PS 0/1, and no prior systemic anticancer therapy. Patients with known *EGFR* mutations or *ALK* translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. In Part 1a (n=793), patients with PD-L1 ≥1% were randomized to either OPDIVO 3 mg/kg q2w + YERVOY 1 mg/kg q6w (n=396) or platinum-doublet chemotherapy* (n=397). The primary endpoint in Part 1a was OS in patients with PD-L1 ≥1%. Pre-specified descriptive efficacy outcome measures included PFS, ORR, and DOR.[1]

*Vs chemo. In Checkmate 227, patients in the comparator arm received up to 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin, with optional pemetrexed maintenance following chemo; SQ: gemcitabine + carboplatin or cisplatin.[1,4]

†In Checkmate 227 Part 1a, PFS, ORR, and DOR were pre-specified descriptive analyses. The primary efficacy outcome measure was OS.[1,4]

SELECT IMPORTANT SAFETY INFORMATION

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.

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%).

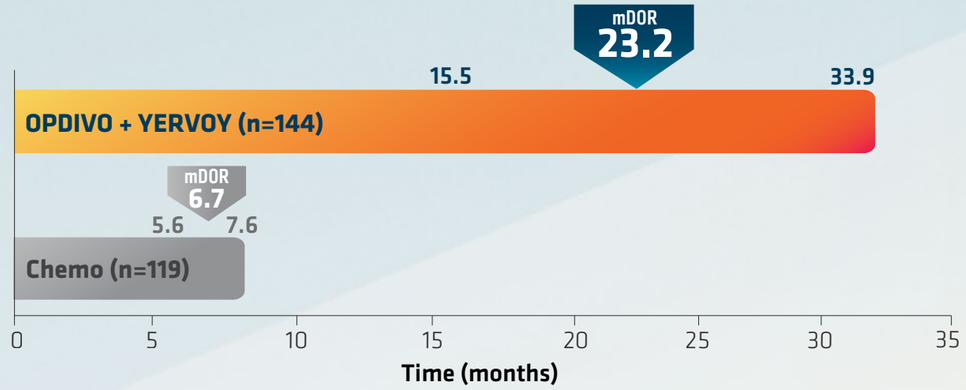
Please see additional Important Safety Information for OPDIVO and YERVOY throughout and US Full Prescribing Information for **OPDIVO** and **YERVOY**.

Checkmate 227: In a cross-histology trial for patients with mNSCLC (PD-L1 ≥1%)

OPDIVO + YERVOY: The only I-O combination with mDOR of 23.2 months[1]

- ORR was 36% (144/396) with OPDIVO + YERVOY and 30% (120/397) with chemo[1,4,5]
- 5.8% CR with OPDIVO + YERVOY and 1.8% with chemo[1,4]
- 34% of responders to OPDIVO + YERVOY were still responding at 4 years, and 7% of chemo responders were still responding to chemo[2]

mDOR and range (extended follow-up analysis)[2]



Median follow-up of 54.8 months.[2]

In Checkmate 227 Part 1a, PFS, ORR, and DOR were pre-specified descriptive analyses. The primary efficacy outcome measure was OS with a minimum follow-up of 29.3 months.[1,3,4]

- ORR: 36% (144/396, 95% CI: 32–41), CR=5.8%, PR=30.1% with OPDIVO + YERVOY and 30% (120/397, 95% CI: 26–35), CR=1.8%, PR=28.2% with chemo[1,4,5]
- The median TTR was 2.0 months with OPDIVO + YERVOY and 1.6 months with chemo[4]

CR=complete response; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IHC=immunohistochemistry; mDOR=median DOR; mo=month; ORR=overall response rate; PFS=progression-free survival; PR=partial response; q2w=every 2 weeks; q6w=every 6 weeks.

SELECT IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

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 and Hepatotoxicity

- OPDIVO and YERVOY can cause immune-mediated hepatitis.

Immune-Mediated Endocrinopathies

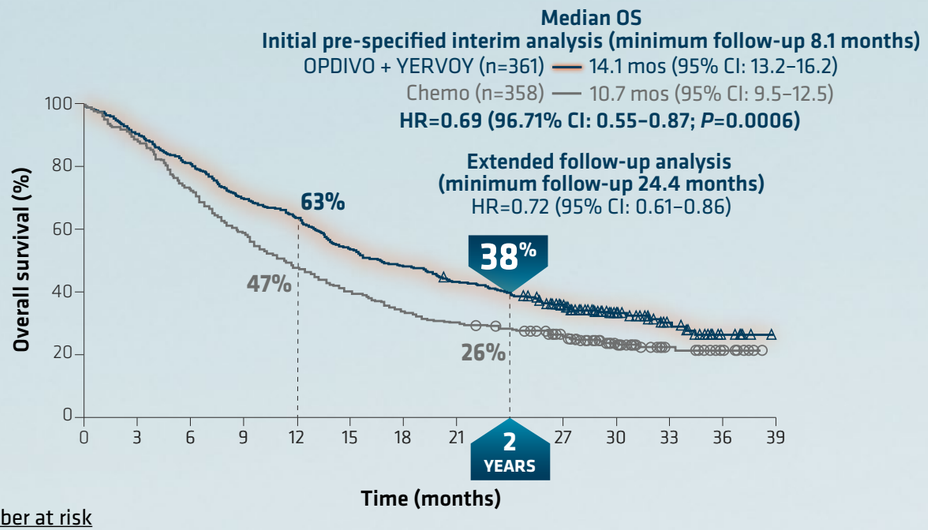
- OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration 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.

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

Checkmate 9LA: For r/m NSCLC patients, regardless of PD-L1 expression and histology

Durable survival with OPDIVO® (nivolumab) + YERVOY® (ipilimumab) with limited chemo* vs chemo: 38% of ITT patients alive at 2 years[1,6†]

Overall survival (ITT)[1,6,7]



Minimum follow-up of 24.4 months.[6]

- 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[1,7]
- Median PFS at the 23.3-month minimum follow-up: 6.7 months (95% 5.6–7.8) with OPDIVO + YERVOY with chemo and 5.3 months (95% CI: 4.4–5.6) with chemo alone; HR=0.67 (95% CI: 0.56–0.79)[6]
- ORR at the 6.5-month minimum follow-up: 38% (95% CI: 33–43) with OPDIVO + YERVOY with chemo and 25% (95% CI: 21–30) with chemo[1,7]
- Median OS at the 24.4-month follow-up analysis: 15.8 months (95% CI: 13.9–19.7) with OPDIVO + YERVOY with chemo and 11.0 months (95% CI: 9.5–12.7) with chemo; HR=0.72 (95% CI: 0.61–0.86)[6]
- 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. Key eligibility criteria included patients 18 years or older, stage IV or recurrent NSCLC, ECOG PS 0/1 and no prior systemic anticancer therapy. Patients with known *EGFR* mutations or *ALK* translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. 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. Additional efficacy outcome measures were PFS, ORR, and DOR.[1]

*Two cycles of platinum-doublet chemo.[1]
†In the intent-to-treat population vs chemo. In Checkmate 9LA, patients received 2 cycles of platinum-doublet chemo q3w in the experimental arm, and 4 cycles in the comparator arm; NSQ: pemetrexed + carboplatin or cisplatin (optional pemetrexed maintenance therapy in comparator arm only); SQ: paclitaxel + carboplatin.[1]
‡In Checkmate 9LA, patients in the comparator arm received 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin (optional pemetrexed maintenance therapy in the comparator arm only); SQ: paclitaxel + carboplatin.[1]

SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions

- 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 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%).

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

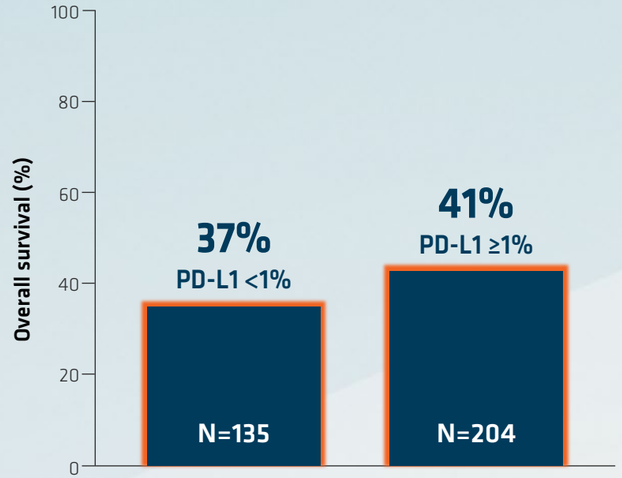
OPDIVO + YERVOY with limited chemo EFFICACY: OS

Checkmate 9LA: For r/m NSCLC patients, regardless of PD-L1 expression and histology

Consistent OS benefit across PD-L1 expression at 2 years[6]

OPDIVO + YERVOY with limited chemo*

OS by PD-L1 expression (extended follow-up analysis)[6]



OPDIVO + YERVOY with limited chemo

Minimum follow-up of 24.4 months.[6]

Limitation: Checkmate 9LA was not powered to detect differences in the treatment effect in PD-L1 subgroups; therefore, results from this exploratory analysis should be interpreted with caution because of the limited patient numbers and potential imbalances in baseline characteristics within the subgroup.

- Primary analysis 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[1,7]
- At the 24.4-month minimum follow-up, median OS for PD-L1 <1% was 17.7 (95% CI: 13.7–20.3) with OPDIVO + YERVOY with limited chemo and 9.8 months (95% CI: 7.7–13.5) with chemo; HR=0.67 (95% CI: 0.51–0.88)[6]
- At the 24.4-month minimum follow-up, median OS for PD-L1 ≥1% was 15.8 (95% CI: 13.8–22.2) with OPDIVO + YERVOY with limited chemo and 10.9 months (95% CI: 9.5–13.2) with chemo; HR=0.70 (95% CI: 0.56–0.89)[6]
- 22% of patients with PD-L1 <1% treated with chemotherapy were alive at 2 years[6]
- 28% of patients with PD-L1 ≥1% treated with chemotherapy were alive at 2 years[6]

*Two cycles of platinum-doublet chemo.[1]
ITT=intent to treat.

SELECT IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

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/PD-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).

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

Checkmate 227:

Adverse reactions in ≥10% of patients receiving OPDIVO® (nivolumab) + YERVOY® (ipilimumab)[1]

Adverse reactions	OPDIVO + YERVOY (n=576)		Chemo[##] (n=570)	
	All grades (%)	Grades 3–4 (%)	All grades (%)	Grades 3–4 (%)
General				
Fatigue*	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema[†]	14	0.2	12	0.5
Skin and subcutaneous tissue				
Rash[‡]	34	4.7	10	0.4
Pruritus[§]	21	0.5	3.3	0
Metabolism and nutrition				
Decreased appetite	31	2.3	26	1.4
Musculoskeletal and connective tissue				
Musculoskeletal pain[‖]	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
Gastrointestinal				
Diarrhea/colitis[¶]	26	3.6	16	0.9
Nausea	21	1.0	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1.0	18	2.3
Abdominal pain[#]	10	0.2	9	0.7
Respiratory, thoracic, and mediastinal				
Dyspnea**	26	4.3	16	2.1
Cough[††]	23	0.2	13	0
Hepatobiliary				
Hepatitis[‡‡]	21	9	10	1.2
Endocrine				
Hypothyroidism[§§]	16	0.5	1.2	0
Hyperthyroidism[‖‖]	10	0	0.5	0
Infections and infestations				
Pneumonia[¶¶]	13	7	8	4.0
Nervous system				
Headache	11	0.5	6	0

Safety was assessed in the overall population in Checkmate 227 Part 1. Efficacy analysis was conducted in the Part 1a population.[1]

*Includes fatigue and asthenia.[1]
[†]Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.[1]
[‡]Includes autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, and toxic skin eruption.[1]
[§]Includes pruritus and pruritus generalized.[1]
[‖]Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.[1]
[¶]Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.[1]
[#]Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.[1]
[**]Includes dyspnea and dyspnea exertional.[1]
[††]Includes cough and productive cough.[1]
[‡‡]Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, and transaminases increased.[1]
[§§]Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.[1]
[‖‖]Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.[1]
[¶¶]Includes lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral, atypical pneumonia, and organizing pneumonia.[1]
[##]In Checkmate 227, patients in the comparator arm received up to 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin, with optional pemetrexed maintenance following chemo; SQ: gemcitabine + carboplatin or cisplatin.[1,4]

- OPDIVO + YERVOY was discontinued in 24% of patients due to adverse reactions, and 53% had at least one dose withheld for an adverse reaction[1]
- Serious adverse reactions occurred in 58% of patients receiving OPDIVO + YERVOY[1]
- 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[1]
- The most common (≥20%) adverse reactions were fatigue, rash, decreased appetite, musculoskeletal pain, diarrhea/colitis, dyspnea, cough, hepatitis, nausea, and pruritus[1]
- Median number of doses was 9 OPDIVO and 3 YERVOY[4]
- With a median follow-up of 54.8 months, no new safety signals were identified with OPDIVO + YERVOY[2]

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

Checkmate 9LA:

Adverse reactions in >10% of patients receiving OPDIVO + YERVOY 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]
[‖‖]In Checkmate 9LA, patients in the comparator arm received 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin (optional pemetrexed maintenance therapy in comparator arm only); SQ: paclitaxel + carboplatin.[1]

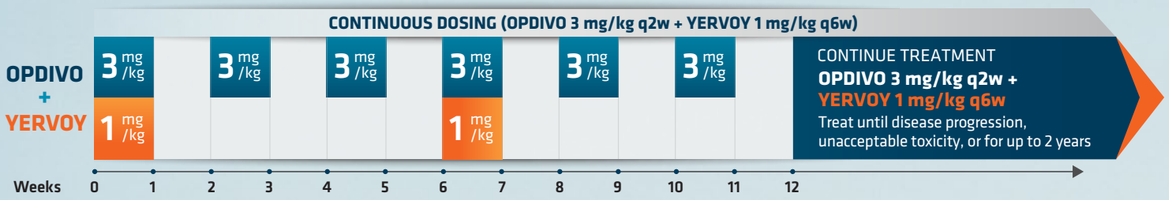
- Treatment was permanently discontinued for adverse reactions in 24% of patients treated with OPDIVO + YERVOY with chemo, and 56% had at least one dose withheld for an adverse reaction[1]
- Serious adverse reactions occurred in 57% of patients receiving OPDIVO + YERVOY with chemo[1]
- The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure.[1] 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[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 OPDIVO, 4 YERVOY, and 2 cycles of chemo[8]
- With a minimum follow-up of 23.3 months, no new safety signals were identified for OPDIVO + YERVOY with limited chemo[6*]

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

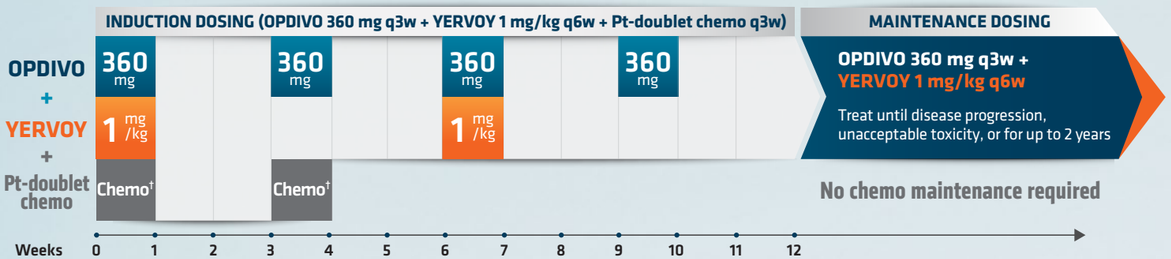
OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

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

OPDIVO + YERVOY in patients with mNSCLC (PD-L1 ≥1%)[1]



OPDIVO + YERVOY with limited chemo in patients with r/m NSCLC (PD-L1 <1% and PD-L1 ≥1%)[1]*



- OPDIVO is administered as an IV infusion over 30 minutes[1]
- YERVOY is administered as an IV infusion over 30 minutes[9]

*For the r/m NSCLC dosing regimen in combination with chemo: on the first week, 4 agents will be administered (OPDIVO 360 mg + YERVOY 1 mg/kg + histology-based† chemo), followed by 3 agents (OPDIVO + histology-based† chemo) on the third week, and 2 agents (OPDIVO + YERVOY) on the sixth week, OPDIVO monotherapy on the ninth week, followed by maintenance therapy of OPDIVO + YERVOY.[1]
†Histology-based chemo; SQ patients: carboplatin AUC 6 + paclitaxel 200 mg/m^2 q3w; NSQ patients: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 q3w or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 q3w.[1]
AUC=area under the curve; IV=intravenous; Pt=platinum.

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.

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 Adverse Reactions

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.

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%).

Please see US Full Prescribing Information for **OPDIVO** and **YERVOY**.

References: 1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **2.** Paz-Ares LG, Ciuleanu TE, Lee JS, et al. Nivolumab + ipilimumab vs chemotherapy as first-line treatment for advanced non-small cell lung cancer: 4-year update from CheckMate 227. Oral presentation at ASCO 2021. Abstract 9016. **3.** Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. *N Engl J Med*. 2019;381(21):2020-2031. **4.** Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. *N Engl J Med*. 2019;381(21):2020-2031 [supplementary appendix]. **5.** Data on file. NIVO 606. Princeton, NJ: Bristol-Myers Squibb Company; 2021. **6.** Reck M, Ciuleanu TE, Cobo M, et al. First-line nivolumab + ipilimumab + 2 cycles of chemotherapy versus chemotherapy alone (4 cycles) in patients with advanced non-small cell lung cancer: 2-year update from CheckMate 9LA. Oral presentation at ASCO 2021. Abstract 9000. **7.** Reck M, Ciuleanu TE, Cobo M, et al. Nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy vs 4 cycles chemotherapy as first-line treatment for stage IV/recurrent NSCLC: CheckMate 9LA. Oral presentation at ASCO 2020. Abstract 9501. **8.** Data on file. NIVO 562. Princeton, NJ: Bristol-Myers Squibb Company; 2020. **9.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **10.** Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):198-211.

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

Give patients a CHANCE TO LIVE LONGER*: Durable survival with OPDIVO® (nivolumab) + YERVOY® (ipilimumab)–based combinations[1]

Durable Survival in 1L mNSCLC[1,2,6]

For PD-L1 ≥1% mNSCLC patients, across histology

OPDIVO (nivolumab) + YERVOY (ipilimumab)

29% (n=103) alive at 4 years and **18%** (n=63) for chemo

DOR At 4 years with **mDOR of 23.2 months†**

Approved across PD-L1 expression levels including

For PD-L1 <1% r/m NSCLC patients, across histology

OPDIVO (nivolumab) + YERVOY (ipilimumab)

WITH LIMITED CHEMO‡

38% (n=137) alive at 2 years and **26%** (n=93) for chemo

Consistent OS for **PD-L1 <1%** **PD-L1 ≥1%**

OPDIVO + YERVOY

- **Primary analysis** at 29.3 months minimum follow-up: median OS was 17.1 months with OPDIVO + YERVOY vs 14.9 months with chemo; HR=0.79 (95% CI: 0.67–0.94); *P*=0.0066[1,3]
- ORR: 36% (144/396, 95% CI: 32–41) CR=5.8%, PR=30.1% with OPDIVO + YERVOY and 30% (120/397, 95% CI: 26–35) CR=1.8%, PR=28.2% with chemo[1,4,5]
- In Checkmate 227 Part 1a, PFS, ORR, and DOR were pre-specified descriptive analyses. The primary efficacy outcome measure was OS[1,4]
- Median TTR was 2.0 months with OPDIVO + YERVOY and 1.6 months with chemo[4]
- 29% of patients enrolled had SQ disease; 71% had NSQ disease[1]

OPDIVO + YERVOY with limited chemo‡

Limitation: Checkmate 9LA was not powered to detect differences in the treatment effect in PD-L1 subgroups; therefore, results from this exploratory analysis should be interpreted with caution because of the limited patient numbers and potential imbalances in baseline characteristics within the subgroup.

- **Primary analysis** from pre-specified interim analysis at 8.1 months minimum follow-up: median OS was 14.1 months (95% CI: 13.2–16.2) with OPDIVO + YERVOY with chemo vs 10.7 (95% CI: 9.5–12.5) with chemo; HR=0.69 (96.71% CI: 0.55–0.87); *P*=0.0006[1,10]
- 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[1,7]
- In Checkmate 9LA, additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR[1]
- Median PFS at the 23.3-month minimum follow-up: 6.7 months (95% CI: 5.6–7.8) with OPDIVO + YERVOY with chemo and 5.3 months (95% CI: 4.4–5.6) with chemo alone; HR=0.67 (95% CI: 0.56–0.79)[6]
- ORR at the 6.5-month minimum follow-up: 38% (95% CI: 33–43) with OPDIVO + YERVOY with chemo and 25% (95% CI: 21–30) with chemo[1,7]
- **Median OS at the 24.4-month follow-up analysis:** 15.8 months (95% CI: 13.9–19.7) with OPDIVO + YERVOY with chemo and 11.0 months (95% CI: 9.5–12.7) with chemo; HR=0.72 (95% CI: 0.61–0.86)[6]
- At the 24.4-month minimum follow-up, median OS for PD-L1 <1% was 17.7 (95% CI: 13.7–20.3) with OPDIVO + YERVOY with limited chemo and 9.8 months (95% CI: 7.7–13.5) with chemo; HR=0.67 (95% CI: 0.51–0.88)[6]
- At the 24.4-month minimum follow-up, median OS for PD-L1 ≥1% was 15.8 (95% CI: 13.8–22.2) with OPDIVO + YERVOY with limited chemo and 10.9 months (95% CI: 9.5–13.2) with chemo; HR=0.70 (95% CI: 0.56–0.89)[6]

*Vs chemo. In Checkmate 227, patients in the comparator arm received up to 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin, with optional pemetrexed maintenance therapy; SQ: gemcitabine + carboplatin or cisplatin. In Checkmate 9LA, patients in the comparator arm received 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin (optional pemetrexed maintenance therapy in comparator arm only); SQ: paclitaxel + carboplatin.[1,2,6] †In those who responded. ‡Two cycles of platinum-doublet chemotherapy.[1]

BICR=blinded independent central review; TTR=time to response.

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.

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Bristol Myers Squibb™

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OPDIVO (nivolumab) + YERVOY (ipilimumab)