In the 1L treatment of adult patients with unresectable advanced or metastatic ESCC

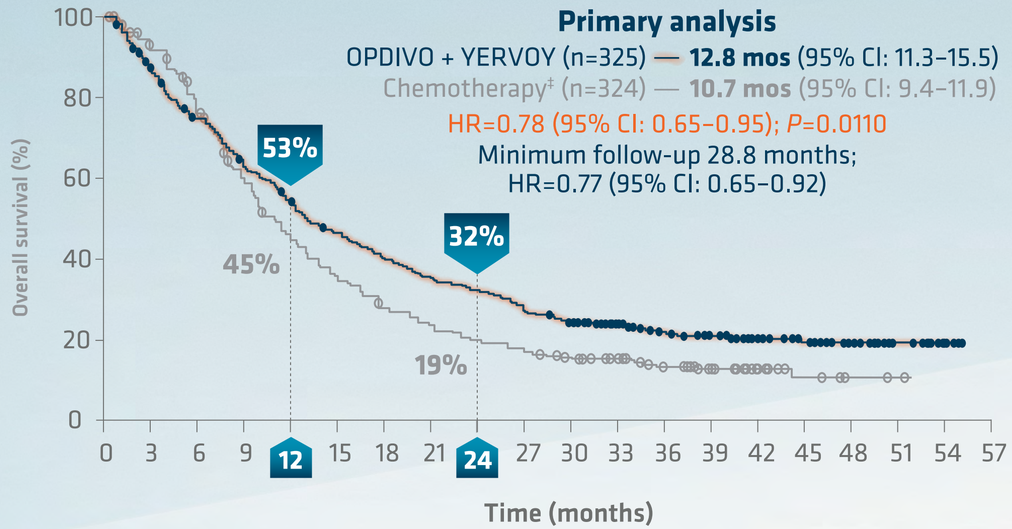
# Long-term survival in all comers* with OPDIVO® (nivolumab) + YERVOY® (ipilimumab) at 29 months[1,2†]

## INDICATION[1]

**OPDIVO, in combination with YERVOY, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).**

## OPDIVO + YERVOY in ESCC: the only dual I-O approved regardless of PD-L1 status[1]

### Median overall survival in all comers* (secondary endpoint)[1,2]




Number at risk

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| OPDIVO + YERVOY | 325 | 274 | 233 | 193 | 165 | 142 | 122 | 107 | 98 | 82 | 71 | 60 | 45 | 35 | 27 | 20 | 13 | 6 | 3 | 0 |
| Chemotherapy‡ | 324 | 284 | 232 | 173 | 133 | 104 | 81 | 67 | 57 | 50 | 42 | 34 | 25 | 17 | 10 | 5 | 2 | 1 | 0 | 0 |

*Long-term survival shown at 2 years[2†]*

Dosing information >

Response rates in all comers >

- The 28.8-month follow-up analysis was not statistically powered to detect differences between treatment arms[3]

**Trial design:** Checkmate 648 was a global, phase 3, randomized (1:1:1[§]), open-label trial of OPDIVO 3 mg/kg q2w IV infusion over 30 minutes in combination with YERVOY 1 mg/kg q6w IV infusion over 30 minutes (n=325) compared with FP[‖] q4w alone (n=324) in previously untreated patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma. Patients were stratified by PD-L1 TC status (TC ≥1% vs <1%[¶]), region, ECOG PS (0 vs 1), and number of organs with metastases (≤1 vs ≥2). The trial excluded patients with brain metastases that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumor to organs adjacent to the esophageal tumor. Forty-nine percent of patients (n=158) had PD-L1 TC ≥1%. Patients were treated with OPDIVO or YERVOY until disease progression, unacceptable toxicity, or up to 2 years. Patients were treated with chemotherapy until disease progression or unacceptable toxicity. In patients who received OPDIVO in combination with chemotherapy and in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue OPDIVO as a single agent. The primary endpoints, assessed in patients with PD-L1 TC ≥1%, were OS and PFS.[#] Secondary endpoints included OS and PFS[#] in all comers* and ORR[#] in TC ≥1% and all comers.* mDOR[#] was an exploratory endpoint. Secondary endpoints were tested hierarchically only if corresponding primary endpoints were significant. Since PFS[#] in the PD-L1 TC ≥1% population did not meet statistical significance, PFS[#] in all comers* was not hierarchically tested in the OPDIVO + YERVOY arm.[1-3]

### Dual primary endpoints in the PD-L1 TC ≥1% population (n=315)[1]

- **mOS: 13.7 mos** (95% CI: 11.2–17.0) with OPDIVO + YERVOY vs **9.1 mos** (95% CI: 7.7–10.0) with chemotherapy‡ alone (HR=0.64; 95% CI: 0.49–0.84; *P*=0.0010)
- **mPFS[#]: 4.0 mos** (95% CI: 2.4–4.9) with OPDIVO + YERVOY vs **4.4 mos** (95% CI: 2.9–5.8) with chemotherapy‡ alone (HR=1.02; 95% CI: 0.78–1.34; *P*=NS)

### Secondary endpoint in all comers* (primary analysis)[1]

- **mPFS[#]: 2.9 mos** (95% CI: 2.7–4.2) with OPDIVO + YERVOY vs **5.6 mos** (95% CI: 4.3–5.9) with chemotherapy‡ alone (HR=1.26; 95% CI: 1.04–1.52; *P*=NT)

### Extended follow-up in the PD-L1 TC ≥1% population at 28.8 months (n=315)[2]

- **mOS: 13.1 mos** (95% CI: 11.2–17.4 with OPDIVO + YERVOY vs **9.1 mos** (95% CI: 7.7–10.0) with chemotherapy‡ alone (HR=0.62; 95% CI: 0.48–0.80)
- **mPFS[#]: 4.0 mos** (95% CI: 2.3–4.4) with OPDIVO + YERVOY vs **4.4 mos** (95% CI: 2.9–5.8) with chemotherapy‡ alone (HR=1.04; 95% CI: 0.79–1.36)

### Extended follow-up in all comers* at 28.8 months[2]

- **mOS: 12.7 mos** (95% CI: 11.3–15.5) with OPDIVO + YERVOY vs **10.7 mos** (95% CI: 9.4–12.1) with chemotherapy‡ alone (HR=0.77; 95% CI: 0.65–0.92)
- **mPFS[#]: 2.9 mos** (95% CI: 2.7–4.2) with OPDIVO + YERVOY vs **5.6 mos** (95% CI: 4.3–5.9) with chemotherapy‡ alone (HR=1.26; 95% CI: 1.04–1.51)

*All comers refers to all randomized patients in Checkmate 648. †Vs chemotherapy alone.[1] ‡Fluorouracil and cisplatin.[1] §Checkmate 648 included a third arm: OPDIVO 240 mg IV q2w + FP q4w (n=321). The trial was not designed to compare OPDIVO + chemotherapy with OPDIVO + YERVOY. Please refer to the US Prescribing Information for further information.[1,3] ‖Fluorouracil 800 mg/m² IV daily (Days 1-5) and cisplatin 80 mg/m² IV (on Day 1) of a 4-week cycle.[1] ¶<1% includes indeterminate tumor cell PD-L1 expression as determined by PD-L1 IHC 28-8 pharmDx assay.[1,3] #Assessed using blinded independent central review (BICR).[1]

1L=first line; CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FP=fluorouracil plus cisplatin; HR=hazard ratio; IHC=immunohistochemistry; I-O=immuno-oncology; IV=intravenous; mDOR=median duration of response; mo=month; mOS=median OS; mPFS=median PFS; NS=not significant; NT=not tested; ORR=overall response rate; OS=overall survival; PD-L1=programmed death ligand 1; PFS=progression-free survival; q2w=every 2 weeks; q4w=every 4 weeks; q6w=every 6 weeks; TC=tumor cell.

## 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.

**Please see full Important Safety Information for OPDIVO + YERVOY on the next page and US Full Prescribing Information for OPDIVO and YERVOY.**

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

INJECTION FOR INTRAVENOUS USE 10 mg/mL | Injection for intravenous use 5 mg/mL

# IMPORTANT SAFETY INFORMATION

## 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® (nivolumab) or YERVOY® (ipilimumab). 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.

### 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.

### 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/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).

### 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 648, serious adverse reactions occurred in 69% of patients receiving OPDIVO in combination with YERVOY (n=322). The most frequent serious adverse reactions reported in ≥2% who received OPDIVO in combination with YERVOY were pneumonia (10%), pyrexia (4.3%), pneumonitis (4.0%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with YERVOY; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome.

### Common Adverse Reactions

- In Checkmate 648, the most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with YERVOY were rash (31%), fatigue (28%), pyrexia (23%), nausea (22%), diarrhea (22%), and constipation (20%).

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **2.** Kato K, Ajani J, Doki Y, et al. Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma: 29-month follow-up from CheckMate 648. Presentation at ASCO GI 2023. Abstract 290. **3.** Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. *N Engl J Med*. 2022;386(5):449-462. **4.** BMS-REF-NIVO-0207. Princeton, NJ: Bristol-Myers Squibb Company; 2023.

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

Bristol Myers Squibb™


7356-US-2300037 2/23

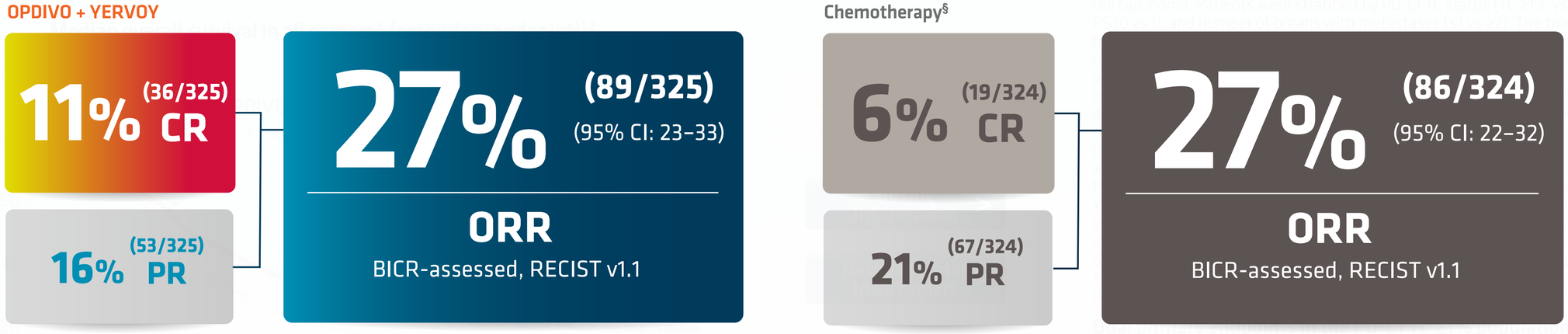
OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous use 5 mg/mL

CLOSE

### In the 1L treatment of adult patients with unresectable advanced or metastatic ESCC

# At 29 months, 27% of patients receiving OPDIVO® (nivolumab) + YERVOY® (ipilimumab) responded, and 11% were complete responders[1,2,4]

## Response rates in all comers*[†‡]




- ORR in all comers*[†] was not included in the hierarchy for statistical testing[3]
- 28.8 months minimum follow-up[2]

## Response rates in all comers* (primary analysis)[1‡]

- 11% CR (36/325), 17% PR (54/325), 28% ORR (90/325) for OPDIVO + YERVOY; 6% CR (20/324), 21% PR (67/324), 27% ORR (87/324) for chemotherapy§ alone

## Duration of response in all comers* (primary analysis)[1‡‖]

- **mDOR: 11.1 mos** (95% CI: 8.3–14.0) with OPDIVO + YERVOY vs **7.1 mos** (95% CI: 5.7–8.2) with chemotherapy§ alone

## Extended follow-up in all comers* at 28.8 months[2‡]

- **mDOR: 11.1 mos** (95% CI: 7.1–14.3) with OPDIVO + YERVOY vs **7.1 mos** (95% CI: 5.7–8.2) with chemotherapy§ alone

*All comers refers to all randomized patients in Checkmate 648. [†]Secondary endpoint.[2] [‡]Assessed using blinded independent central review (BICR), RECIST v1.1.[1,2] §Fluorouracil and cisplatin.[2] ‖Exploratory endpoint.[3]

1L=first line; CI=confidence interval; CR=complete response; ESCC=esophageal squamous cell carcinoma; mDOR=median duration of response; mo=month; ORR=overall response rate; PR=partial response; RECIST=Response Evaluation Criteria In Solid Tumors.

1L=first line; CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FP=fluorouracil plus cisplatin; HR=hazard ratio; IHC=immunohistochemistry; I-O=immuno-oncology; IV=intravenous; mDOR=median duration of response; mo=month; mOS=median OS; mPFS=median PFS; NS=not significant; NT=not tested; ORR=overall response rate; OS=overall survival; PD-L1=programmed death ligand 1; PFS=progression-free survival; q2w=every 2 weeks; q4w=every 4 weeks; q6w=every 6 weeks; TC=tumor cell.

with chemotherapy‡ alone (HR=0.77; 95% CI: 0.65–0.92)

- **mPFS#: 2.9 mos** (95% CI: 2.7–4.2) with OPDIVO + YERVOY vs **5.6 mos** (95% CI: 4.3–5.9) with chemotherapy‡ alone (HR=1.26; 95% CI: 1.04–1.51)

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OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous use 5 mg/mL

CLOSE

In the 1L treatment of adult patients with unresectable advanced or metastatic ESCC

# Same-day dosing for OPDIVO® (nivolumab) + YERVOY® (ipilimumab)[1]

## 1L ESCC dosing (Checkmate 648)

**OPDIVO + YERVOY**

OPDIVO 3 mg/kg **q2w** (30 minute IV infusion)

*OR*

OPDIVO 360 mg **q3w** (30 minute IV infusion)

*WITH*

YERVOY 1 mg/kg **q6w** (30 minute IV infusion)

**Continue treatment** until disease progression, unacceptable toxicity, or up to 2 years

- Administer OPDIVO first, followed by YERVOY on the same day

*In Checkmate 648, patients with mESCC in the OPDIVO + YERVOY arm who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue OPDIVO as a single agent[1]**

*Per the Checkmate 648 study design; see OPDIVO Full Prescribing Information, section 14.12.[1]

1L=first line; ESCC=esophageal squamous cell carcinoma; IV=intravenous; mESCC=metastatic ESCC; q2w=every 2 weeks; q3w=every 3 weeks; q6w=every 6 weeks.

*All comers refers to all randomized patients in Checkmate 648. †Vs chemotherapy alone.[1] ‡Fluorouracil and cisplatin.[1] §Checkmate 648 included a third arm: OPDIVO 240 mg IV q2w + FP q4w (n=321). The trial was not designed to compare OPDIVO + chemotherapy with OPDIVO + YERVOY. Please refer to the US Prescribing Information for further information.[1,3] ||Fluorouracil 800 mg/m² IV daily (Days 1-5) and cisplatin 80 mg/m² IV (on Day 1) of a 4-week cycle.[1] ¶<1% includes indeterminate tumor cell PD-L1 expression as determined by PD-L1 IHC 28-8 pharmDx assay.[1,3] #Assessed using blinded independent central review (BICR).[1]

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### Extended follow-up in all comers* at 28.8 months[2]

- **mOS: 12.7 mos** (95% CI: 11.3–15.5) with OPDIVO + YERVOY vs **10.7 mos** (95% CI: 9.4–12.1) with chemotherapy‡ alone (HR=0.77; 95% CI: 0.65–0.92)
- **mPFS#: 2.9 mos** (95% CI: 2.7–4.2) with OPDIVO + YERVOY vs **5.6 mos** (95% CI: 4.3–5.9) with chemotherapy‡ alone (HR=1.26; 95% CI: 1.04–1.51)

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