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First-Line OPDIVO® (nivolumab) in Combination with Chemotherapy in Patients with Advanced or Metastatic Gastric Cancer, Gastroesophageal Cancer, and Esophageal Adenocarcinoma

FACULTY

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INTRODUCTION

In 2021, approximately 45,820 people in the United States were diagnosed with gastric cancer (GC), gastroesophageal junction cancer (GEJC), and esophageal adenocarcinoma (EAC), with approximately 26,710 deaths resulting from these cancer types.[1,2]

The standard first-line treatment for advanced *HER2*-negative GC, GEJC, and EAC is fluoropyrimidine plus platinum-based chemotherapy.[3,4] Despite the availability of therapy, the median overall survival (OS) is <1 year.[3] In addition, chemotherapy treatment may cause severe toxicities that some patients may not be able to tolerate.[5]

With the introduction of immune checkpoint inhibitors, promising survival results in this patient population have been observed during clinical trials. PD-1 inhibitors, which block the PD-1/PD-L1 axis, have demonstrated efficacy in the treatment of certain solid cancer types along with a manageable safety profile.[5]

Recently, the US Food and Drug Administration (FDA) approved first-line OPDIVO® (nivolumab) plus chemotherapy for patients with GC, GEJC, or EAC based on the results of the phase 3 Checkmate 649 clinical trial in which OPDIVO plus chemotherapy demonstrated superior OS versus chemotherapy alone in patients with advanced GC, GEJC, or EAC.[6]

(continued on page 7)

From the publishers of

OPM ONCOLOGY PRACTICE MANAGEMENT
JONS JOURNAL OF ONCOLOGY NAVIGATION & SURVIVORSHIP
JHOP JOURNAL OF HEMATOLOGY ONCOLOGY PHARMACY — Official Publication of HOPA Hematology/Oncology Pharmacy Association
TON THE ONCOLOGY NURSE-APN/PA

IN THE 1L METASTATIC TREATMENT SETTING

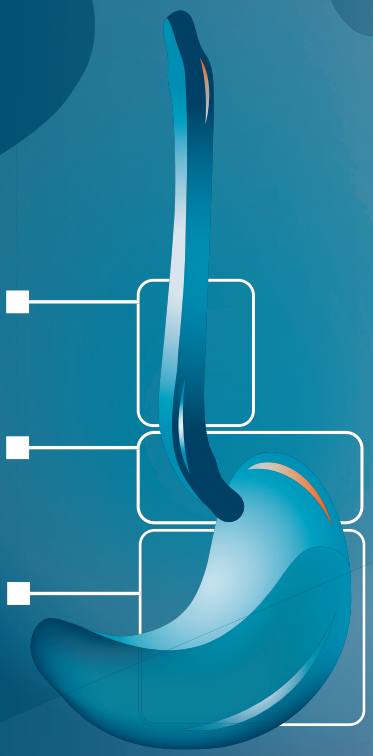
OPDIVO® (nivolumab) + chemotherapy:*

APPROVED ACROSS mUGI ADENOCARCINOMAS IN PD-L1 EXPRESSORS AND NON-EXPRESSORS[1]

ESOPHAGEAL
ADENOCARCINOMA

GASTROESOPHAGEAL JUNCTION

GASTRIC CANCER:
THE ONLY 1L I-O† APPROVED FOR NON-HER2+



INDICATION

OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC, GEJC, and EAC).

*FOLFOX or CapeOX.[1] †With chemotherapy.[1] ‡Vs chemotherapy alone.[1] §All comers refers to all randomized patients in Checkmate 649; secondary endpoint. ||Assessed using blinded independent central review (BICR).[1] ¶mFOLFOX6 (leucovorin, fluorouracil, and oxaliplatin) regimen was given in Checkmate 649.[1] #Based on confirmed response.[1]

1L=first line; CI=confidence interval; CPS=combined positive score; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; I-O=immuno-oncology; IV=intravenous; mo=month; mOS=median OS; mPFS=median PFS; mUGI=metastatic upper gastrointestinal; ORR=overall response rate; OS=overall survival; PD-L1=programmed death ligand 1; PFS=progression-free survival; q2w=every 2 weeks; q3w=every 3 weeks.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- OPDIVO is 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 additional Important Safety Information and Brief Summary of US Full Prescribing Information on the following pages.

Superior overall survival with OPDIVO + FOLFOX or CapeOX in 1L patients with metastatic GC, GEJC, and EAC[2‡]

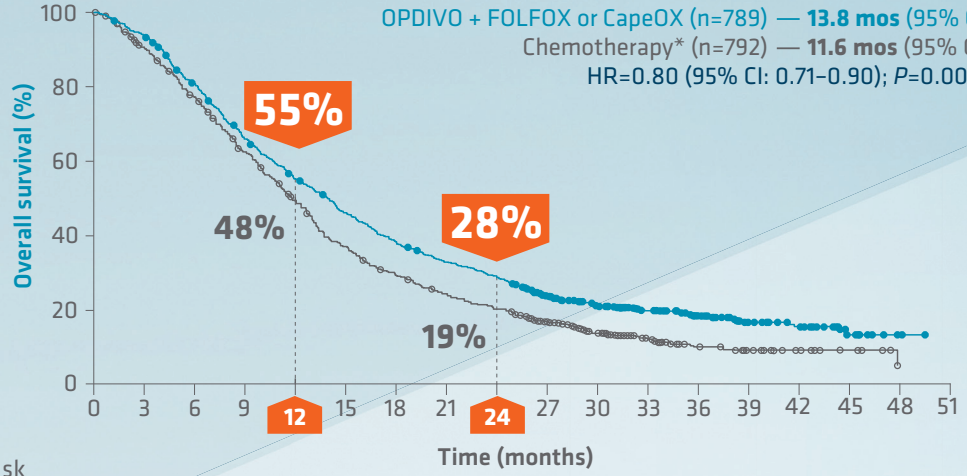
Median OS in all comers[1,2§]

Primary analysis (minimum follow-up 12.1 months)

OPDIVO + FOLFOX or CapeOX (n=789) — **13.8 mos** (95% CI: 12.6–14.6)

Chemotherapy* (n=792) — **11.6 mos** (95% CI: 10.9–12.5)

HR=0.80 (95% CI: 0.71–0.90); *P*=0.0002



Number at risk

OPDIVO + FOLFOX or CapeOX —	789	733	624	508	422	349	287	246	212	156	115	84	57	33	25	9	2	0
Chemotherapy* —	792	701	591	475	364	273	215	170	144	103	72	46	28	20	12	6	0	0

- The exploratory 12-month and 24-month OS rate analyses were not pre-specified within the study protocol[3]

Dual primary endpoints in the PD-L1 CPS ≥5 population (n=955)[1]

- **mOS: 14.4 mos** (95% CI: 13.1–16.2) with OPDIVO + FOLFOX or CapeOX vs **11.1 mos** (95% CI: 10.0–12.1) with chemotherapy* alone; HR=0.71 (95% CI: 0.61–0.83); *P*<0.0001
- **mPFS‖: 7.7 mos** (95% CI: 7.0–9.2) with OPDIVO + FOLFOX or CapeOX vs **6.0 mos** (95% CI: 5.6–6.9) with chemotherapy* alone; HR=0.68 (95% CI: 0.58–0.79); *P*<0.0001

OPDIVO (10 mg/mL) is an injection for IV use.[1]

Checkmate 649 trial design: Checkmate 649 was a phase 3, multicenter, randomized (1:1), open-label trial of OPDIVO 360 mg IV infusion over 30 minutes in combination with CapeOX q3w, or OPDIVO 240 mg IV infusion over 30 minutes in combination with FOLFOX¶ q2w (all comers§: n=789, PD-L1 CPS ≥5 population: n=473), compared with CapeOX q3w or FOLFOX¶ q2w alone (all comers§: n=792, PD-L1 CPS ≥5 population: n=482) in previously untreated patients with unresectable, advanced, or metastatic non-HER2+ gastric, gastroesophageal junction, or esophageal adenocarcinoma. Patients were stratified by tumor cell PD-L1 status, region, ECOG PS, and chemotherapy regimen, and treatment was continued until disease progression, unacceptable toxicity, or up to 2 years. The primary endpoints, assessed in patients with PD-L1 CPS ≥5, were PFS‖ and OS.[1,3] Secondary endpoints included OS in patients with PD-L1 CPS ≥1 and in all comers,§ and ORR‖# in all comers.[3§] Since OS in the PD-L1 CPS ≥5 population was statistically significant, OS in PD-L1 CPS ≥1, followed by OS in all comers,§ were tested hierarchically.[1,3]

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. Early identification and management are essential to ensure safe use of OPDIVO. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment with OPDIVO. 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 depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO 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.

OPDIVO® (nivolumab)

1506-US-2101686 11/21

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IMPORTANT SAFETY INFORMATION (cont'd)

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

Immune-Mediated Pneumonitis

- OPDIVO® (nivolumab) can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%).

Immune-Mediated Colitis

- OPDIVO can cause immune-mediated colitis. 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. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%).

Immune-Mediated Hepatitis and Hepatotoxicity

- OPDIVO can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).

Immune-Mediated Endocrinopathies

- OPDIVO 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 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.
- In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%).
- In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).
- In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%).
- In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%).
- In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%).
- In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis.

Immune-Mediated Nephritis with Renal Dysfunction

- OPDIVO can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%).

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.
- Withhold or permanently discontinue OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).
- In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%).

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 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.
- 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, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

- OPDIVO can cause severe infusion-related reactions. Discontinue OPDIVO 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 patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO. 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 and allogeneic HSCT.
- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

- Based on its mechanism of action and findings from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO 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 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 649, serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy (n=782). The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation.

Common Adverse Reactions

- In Checkmate 649, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=782) were peripheral neuropathy (53%), nausea (48%), fatigue (44%), diarrhea (39%), vomiting (31%), decreased appetite (29%), abdominal pain (27%), constipation (25%), and musculoskeletal pain (20%).

References: 1. OPDIVO® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2021. **2.** Janjigian YY, Ajani JA, Moehler M, et al. Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: CheckMate 649 study. Oral presentation at ESMO 2021. Abstract LBA7. **3.** Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastroesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27-40.

OPDIVO® (nivolumab) injection, for intravenous use

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATION AND USAGE

OPDIVO (nivolumab), in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

DOSAGE AND ADMINISTRATION

Recommended Dosage

360 mg every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks or 240 mg every 2 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS

Severe and Fatal Immune-Mediated Adverse Reactions

OPDIVO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. 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 depending on severity *[see Dosage and Administration (2.1) in full Prescribing Information]*. In general, if OPDIVO requires interruption or discontinuation, 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 can cause immune-mediated pneumonitis, which is defined as requiring use of steroids and no clear alternate etiology. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%) adverse reactions. Pneumonitis led to permanent discontinuation of OPDIVO in 1.1% and withholding of OPDIVO in 0.8% of patients.

Systemic corticosteroids were required in 100% (61/61) of patients with pneumonitis. Pneumonitis resolved in 84% of the 61 patients. Of the 15 patients in whom OPDIVO was withheld for pneumonitis, 14 reinitiated OPDIVO after symptom improvement; of these, 4 (29%) had recurrence of pneumonitis.

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. 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 colitis occurred in 2.9% (58/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (1.7%) and Grade 2 (1%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 0.9% of patients.

Systemic corticosteroids were required in 100% (58/58) of patients with colitis. Four patients required addition of infliximab to high-dose corticosteroids. Colitis resolved in 86% of the 58 patients. Of the 18 patients in whom OPDIVO was withheld for colitis, 16 reinitiated OPDIVO after symptom improvement; of these, 12 (75%) had recurrence of colitis.

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO can cause immune-mediated hepatitis, defined as requiring the use of corticosteroids and no clear alternate etiology.

Immune-mediated hepatitis occurred in 1.8% (35/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%) adverse reactions. Hepatitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 0.6% of patients.

Systemic corticosteroids were required in 100% (35/35) of patients with hepatitis. Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 35 patients. Of the 12 patients in whom OPDIVO was withheld for hepatitis, 11 reinitiated OPDIVO after symptom improvement; of these, 9 (82%) had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

OPDIVO can cause primary or secondary adrenal insufficiency. For grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold OPDIVO depending on severity *[see Dosage and Administration (2.2) in full Prescribing Information]*.

Adrenal insufficiency occurred in 1% (20/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.4%) and Grade 2 (0.6%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.4% of patients.

Approximately 85% of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 90% (18/20) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 35% of the 20 patients. Of the 8 patients in whom OPDIVO was withheld for adrenal insufficiency, 4 reinitiated OPDIVO after symptom improvement and all required hormone replacement therapy for their ongoing adrenal insufficiency.

Hypophysitis

OPDIVO can cause immune-mediated hypophysitis. 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. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.2) in full Prescribing Information]*.

Hypophysitis occurred in 0.6% (12/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.2%) and Grade 2 (0.3%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO in <0.1% and withholding of OPDIVO in 0.2% of patients.

Approximately 67% (8/12) of patients with hypophysitis received hormone replacement therapy, including systemic corticosteroids. Hypophysitis resolved in 42% of the 12 patients. Of the 3 patients in whom OPDIVO was withheld for hypophysitis, 2 reinitiated OPDIVO after symptom improvement; of these, none had recurrence of hypophysitis.

Thyroid Disorders

OPDIVO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management as clinically indicated. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.2) in full Prescribing Information]*.

Systemic corticosteroids were required in 17% (2/12) of patients with thyroiditis. Thyroiditis resolved in 58% of the 12 patients. Of the 3 patients in whom OPDIVO was withheld for thyroiditis, 1 reinitiated OPDIVO after symptom improvement without recurrence of thyroiditis.

Hyperthyroidism

Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (<0.1%) and Grade 2 (1.2%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.4% of patients.

Approximately 19% of patients with hyperthyroidism received methimazole, 7% received carbimazole, and 4% received propylthiouracil. Systemic corticosteroids were required in 9% (5/54) of patients. Hyperthyroidism resolved in 76% of the 54 patients. Of the 7 patients in whom OPDIVO was withheld for hyperthyroidism, 4 reinitiated OPDIVO after symptom improvement; of these, none had recurrence of hyperthyroidism.

Hypothyroidism

Hypothyroidism occurred in 8% (163/1994) of patients receiving OPDIVO (nivolumab) as a single agent, including Grade 3 (0.2%) and Grade 2 (4.8%) adverse reactions. Hypothyroidism led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.5% of patients.

Approximately 79% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 3.1% (5/163) of patients with hypothyroidism. Hypothyroidism resolved in 35% of the 163 patients. Of the 9 patients in whom OPDIVO was withheld for hypothyroidism, 3 reinitiated OPDIVO after symptom improvement; of these, 1 (33%) had recurrence of hypothyroidism.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold OPDIVO depending on severity *[see Dosage and Administration (2.2) in full Prescribing Information]*.

Diabetes occurred in 0.9% (17/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.4%) and Grade 2 (0.3%) adverse reactions, and two cases of diabetic ketoacidosis. Diabetes led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.1% of patients.

No patients (0/17) with diabetes required systemic corticosteroids. Diabetes resolved in 29% of the 17 patients. Of the 2 patients in whom OPDIVO was withheld for diabetes, both reinitiated OPDIVO after symptom improvement; of these, neither had recurrence of diabetes.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear alternate etiology.

Immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%) adverse reactions. Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.4% of patients.

Systemic corticosteroids were required in 100% (23/23) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 78% of the 23 patients. Of the 7 patients in whom OPDIVO was withheld for nephritis or renal dysfunction, 7 reinitiated OPDIVO after symptom improvement; of these, 1 (14%) had recurrence of nephritis or renal dysfunction.

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis, defined as requiring the use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) has occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.2) in full Prescribing Information]*.

Immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.5% of patients.

Systemic corticosteroids were required in 100% (171/171) of patients with immune-mediated rash. Rash resolved in 72% of the 171 patients. Of the 10 patients in whom OPDIVO was withheld for immune-mediated rash, 9 reinitiated OPDIVO after symptom improvement; of these, 3 (33%) had recurrence of immune-mediated rash.

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, 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-Barre syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some 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, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss

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 rheumatic

Endocrine: Hypoparathyroidism

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Infusion-Related Reactions

OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions *[see Dosage and Administration (2.3) in full Prescribing Information]*.

In patients who received OPDIVO as a 60-minute intravenous infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients.

In a trial assessing the pharmacokinetics and safety of a more rapid infusion, in which patients received OPDIVO as a 60-minute intravenous infusion or a 30-minute intravenous infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation, or withholding of OPDIVO.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1 receptor blocking antibody. 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) *[see Adverse Reactions]*. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose *[see Use in Specific Populations]*.

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 a PD-1 blocking antibody, including OPDIVO, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, 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.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling *[see Warnings and Precautions]*: Severe and Fatal Immune-Mediated Adverse Reactions, Infusion-Related Reactions, Complications of Allogeneic HSCT.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in WARNINGS AND PRECAUTIONS reflect exposure to OPDIVO as a single agent in 1994 patients enrolled in CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 or a single arm trial in NSCLC (n=117); OPDIVO 1 mg/kg with ipilimumab 3 mg/kg in patients enrolled in CHECKMATE-067 (n=313), CHECKMATE-040 (n=49), or another randomized trial (n=94); OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg (n=666) in patients enrolled in CHECKMATE-214 or CHECKMATE-142; OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in patients enrolled in CHECKMATE-227 (n=576) or CHECKMATE-743 (n=300); OPDIVO 360 mg with ipilimumab 1 mg/kg and 2 cycles of platinum-doublet chemotherapy in CHECKMATE-9LA (n=361); and OPDIVO 240 mg with cabozantinib 40 mg in patients enrolled in CHECKMATE-9ER (n=320).

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

The safety of OPDIVO in combination with chemotherapy was evaluated in CHECKMATE-649, a randomized, multicenter, open-label trial in patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer,

and esophageal adenocarcinoma *[see Clinical Studies (14.12) in full Prescribing Information]*. The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive, or had untreated CNS metastases. Patients were randomized to receive OPDIVO (nivolumab) in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

- OPDIVO 240 mg in combination with mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or mFOLFOX6 every 2 weeks.
- OPDIVO 360 mg in combination with CapeOX (capecitabine and oxaliplatin) every 3 weeks or CapeOX every 3 weeks.

Patients were treated with OPDIVO in combination with chemotherapy or chemotherapy until disease progression, unacceptable toxicity, or up to 2 years. The median duration of exposure was 6.8 months (range: 0 to 33.5 months) in OPDIVO and chemotherapy-treated patients. Among patients who received OPDIVO and chemotherapy, 54% were exposed for >6 months and 28% were exposed for >1 year.

Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation. Serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy. OPDIVO and/or chemotherapy were discontinued in 44% of patients and at least one dose was withheld in 76% of patients due to an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with chemotherapy were peripheral neuropathy, nausea, fatigue, diarrhea, vomiting, decreased appetite, abdominal pain, constipation, and musculoskeletal pain.

Tables 1 and 2 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-649.

Table 1: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Chemotherapy - CHECKMATE-649

Adverse Reaction	OPDIVO and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Adverse Reaction	99	69	98	59
Nervous System				
Peripheral neuropathy[a]	53	7	46	4.8
Headache	11	0.8	6	0.3
Gastrointestinal				
Nausea	48	3.2	44	3.7
Diarrhea	39	5	34	3.7
Vomiting	31	4.2	29	4.2
Abdominal pain[b]	27	2.8	24	2.6
Constipation	25	0.6	21	0.4
Stomatitis[c]	17	1.8	13	0.8
General				
Fatigue[d]	44	7	40	5
Pyrexia[e]	19	1.0	11	0.4
Edema[f]	12	0.5	8	0.1
Metabolism and Nutrition				
Decreased appetite	29	3.6	26	2.5
Hypoalbuminemia[g]	14	0.3	9	0.3
Investigations				
Weight decreased	17	1.3	15	0.7
Increased lipase	14	7	8	3.7
Increased amylase	12	3.1	5	0.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[h]	20	1.3	14	2.0
Skin and Subcutaneous Tissue				
Rash[i]	18	1.7	4.4	0.1
Palmar-plantar erythrodysesthesia syndrome	13	1.5	12	0.8
Respiratory, Thoracic and Mediastinal				
Cough[j]	13	0.1	9	0
Infections and Infestations				
Upper respiratory tract infection[k]	10	0.1	7	0.1

Toxicity was graded per NCI CTCAE v4.

[a] Includes dysaesthesia, hypoaesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.
[b] Includes abdominal discomfort, abdominal pain lower, and abdominal pain upper.
[c] Includes aphthous ulcer, mouth ulceration, and mucosal inflammation.
[d] Includes asthenia.
[e] Includes tumor associated fever.
[f] Includes swelling, generalized edema, edema peripheral, and peripheral swelling.
[g] Includes blood albumin decreased.
[h] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.
[i] Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, nodular rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash vesicular.
[j] Includes productive cough.
[k] Includes nasopharyngitis, pharyngitis, and rhinitis.

Table 2: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-649

Laboratory Abnormality	OPDIVO and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Neutropenia	73	29	62	23
Leukopenia	69	12	59	9
Thrombocytopenia	68	7	63	4.4
Anemia	59	14	60	10
Lymphopenia	59	12	49	9
Chemistry				
Increased AST	52	4.6	47	1.9
Hypocalcemia	42	1.6	37	1.0
Hyperglycemia	41	3.9	38	2.7
Increased ALT	37	3.4	30	1.9
Hyponatremia	34	6	24	5
Hypokalemia	27	7	24	4.8
Hyperbilirubinemia	24	2.8	21	2.0
Increased creatinine	15	1.0	9	0.5
Hyperkalemia	14	1.4	11	0.7
Hypoglycemia	12	0.7	9	0.2
Hypernatremia	11	0.5	7.1	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and mFOLFOX6 or CapeOX group (407 to 767 patients) or mFOLFOX6 or CapeOX group (range: 405 to 735 patients).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to OPDIVO (nivolumab) with the incidences of antibodies to other products may be misleading.

Of the 2085 patients who were treated with OPDIVO as a single agent at dose of 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 11% tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 0.7% had neutralizing antibodies against nivolumab. There was no evidence of altered pharmacokinetic profile or increased incidence of infusion-related reactions with anti-nivolumab antibody development.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of OPDIVO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Eye:* Vogt-Koyanagi-Harada (VKH) syndrome; *Complications of OPDIVO Treatment After Allogeneic HSCT:* Treatment refractory, severe acute and chronic GVHD; *Blood and lymphatic system disorders:* hemophagocytic lymphohistiocytosis (HLH) (including fatal cases), autoimmune hemolytic anemia (including fatal cases).

USE IN SPECIFIC POPULATIONS

PREGNANCY

Risk Summary

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in full Prescribing Information]*, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death *(see Data)*. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available data on OPDIVO use in pregnant women to evaluate a drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

Lactation

Risk Summary

There are no data on the presence of nivolumab in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment and for 5 months after the last dose of OPDIVO.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating OPDIVO *[see Use in Specific Populations–Pregnancy]*.

Contraception

OPDIVO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations–Pregnancy]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose.

Pediatric Use

The safety and effectiveness of OPDIVO has not been established in pediatric patients less than 18 years old for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Geriatric Use

Of the 1581 patients randomized to OPDIVO 240 mg every 2 weeks or 360 mg every 3 weeks administered in combination with fluoropyrimidine- and platinum-containing chemotherapy in CHECKMATE-649 (GC, GEJC, or EAC), 39% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation of OPDIVO, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions]*
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions]*
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions]*
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions]*
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions]*
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions]*.

Infusion-Related Reactions

- Advise patients of the potential risk of infusion-related reactions *[see Warnings and Precautions]*.

Complications of Allogeneic HSCT

- Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.
- Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose *[see Use in Specific Populations]*.

Lactation

- Advise women not to breastfeed during treatment with OPDIVO and for 5 months after the last dose *[see Use in Specific Populations]*.

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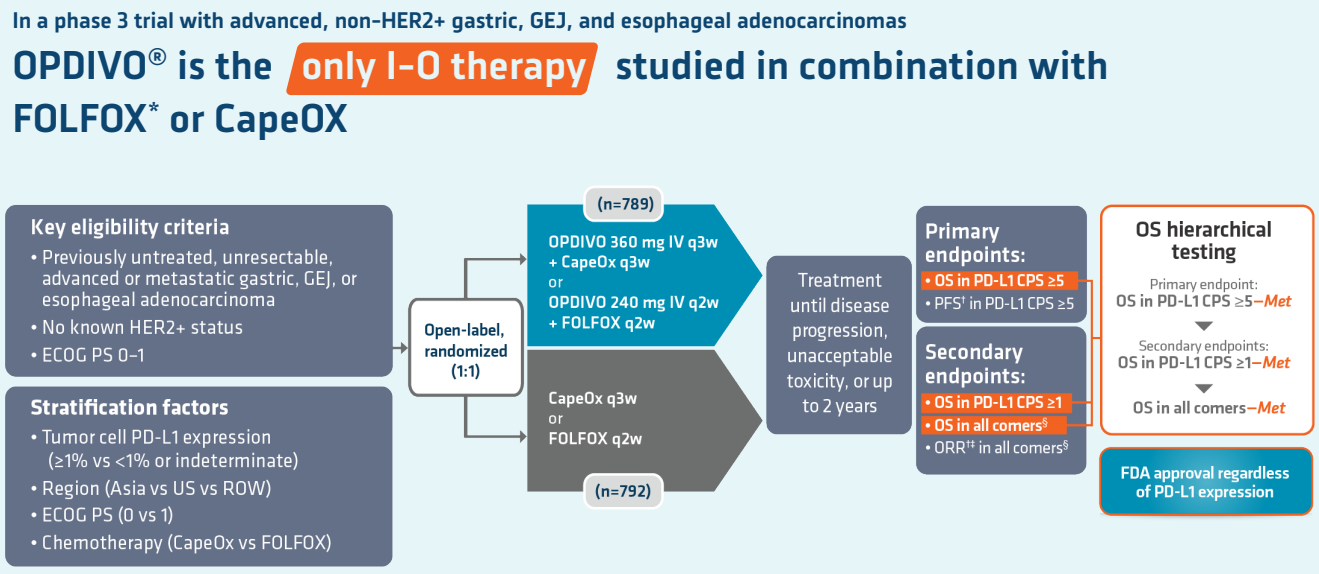
Bristol Myers Squibb™

Checkmate 649 was a multicenter, randomized, phase 3, open-label study that evaluated OPDIVO plus capecitabine and oxaliplatin (CapeOX) or OPDIVO plus fluorouracil, leucovorin, and oxaliplatin (FOLFOX) compared with CapeOX or FOLFOX alone as first-line therapy in patients with previously untreated, unresectable, advanced or metastatic GC, GEJC, or EAC without *HER2*-positive status and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.[7,8] Further stratification factors were tumor cell PD-L1 expression of ≥1% versus <1% or indeterminate; geographic region (Asia vs United States/Canada vs the rest of the world); ECOG performance status 0 versus 1; and chemotherapy consisting of either CapeOX or FOLFOX. Patients in the study were randomized 1:1 to receive OPDIVO plus chemotherapy or chemotherapy alone.[7,8] The clinical trial evaluated the following treatment regimens: 240 mg OPDIVO with FOLFOX or FOLFOX alone administered every 2 weeks, or 360 mg OPDIVO with CapeOX or CapeOX alone administered every 3 weeks.[6]

Patients with known *HER2*-positive status, untreated central nervous system metastases, peripheral neuropathy, autoimmune disease, hepatitis B or hepatitis C virus, and human immunodeficiency virus or known acquired immunodeficiency syndrome were excluded from the Checkmate 649 study (**Figure 1**).

Figure 1. Checkmate 649 Study



*mFOLFOX6 (leucovorin, fluorouracil, and oxaliplatin) regimen was given in Checkmate 649.
†Assessed using blinded independent central review (BICR).
‡All comers refers to all randomized patients in Checkmate 649.
§Based on confirmed response.

CapeOX indicates capecitabine and oxaliplatin; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; I-O, immuno-oncology; IV, intravenous; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; q2w, every 2 weeks; q3w, every 3 weeks; ROW, rest of world.

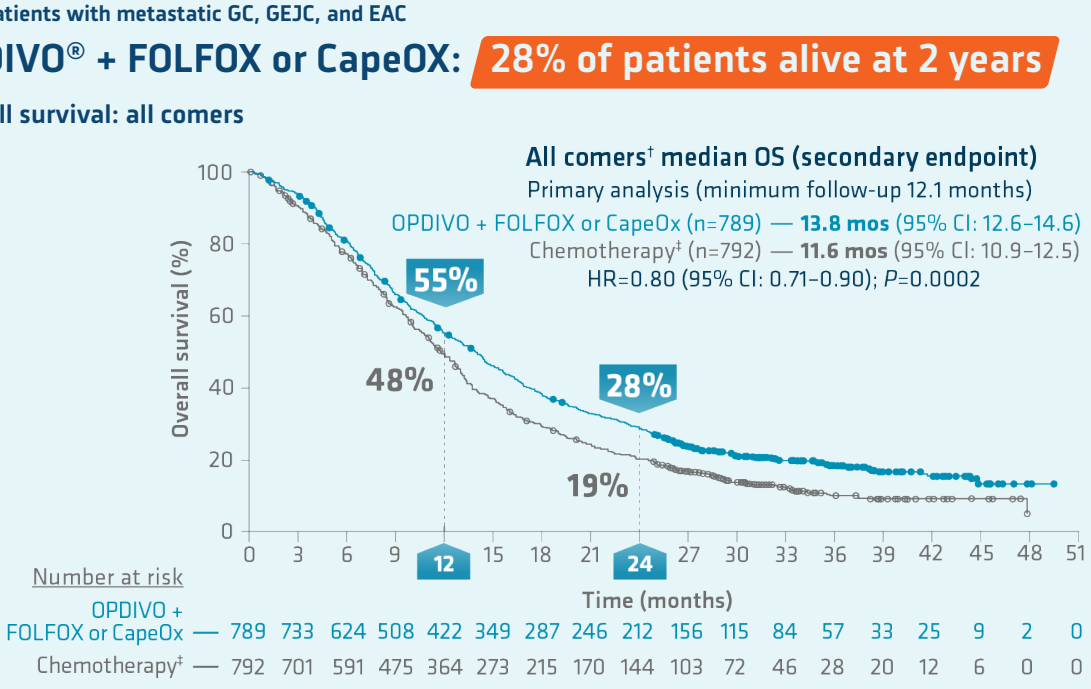
INTERVIEW WITH DR CHAO

Q: At a prespecified primary analysis with a minimum follow-up of 12.1 months, OPDIVO plus chemotherapy resulted in significant improvements in OS and progression-free survival (PFS) compared with chemotherapy alone in all comers, including PD-L1 expressors and non-expressors. Additional 12-month follow-up from the primary analysis demonstrated that OPDIVO plus chemotherapy continued to show improvement in OS compared with chemotherapy alone. What is the impact of these data and how do you view the data with longer follow-up?

A: Overall, these data demonstrate a sustained benefit with a longer follow-up period. What I observed was:

- OS of 28% in all comers at 24 months with treatment with OPDIVO plus chemotherapy versus 19% OS at 24 months with chemotherapy alone. This sustained survival improvement with OPDIVO plus chemotherapy is meaningful for patients in terms of being able to live longer, even with stage IV disease (**Figure 2**).
  - A significant difference in median OS of 13.8 months for all comers (95% confidence interval [CI], 12.4-14.6) with OPDIVO plus FOLFOX or CapeOX versus 11.6 months (95% CI, 10.9-12.5) for chemotherapy alone (hazard ratio [HR], 0.80; CI, 0.71-0.90; *P* = .0002).

Figure 2. Checkmate 649 Overall Survival



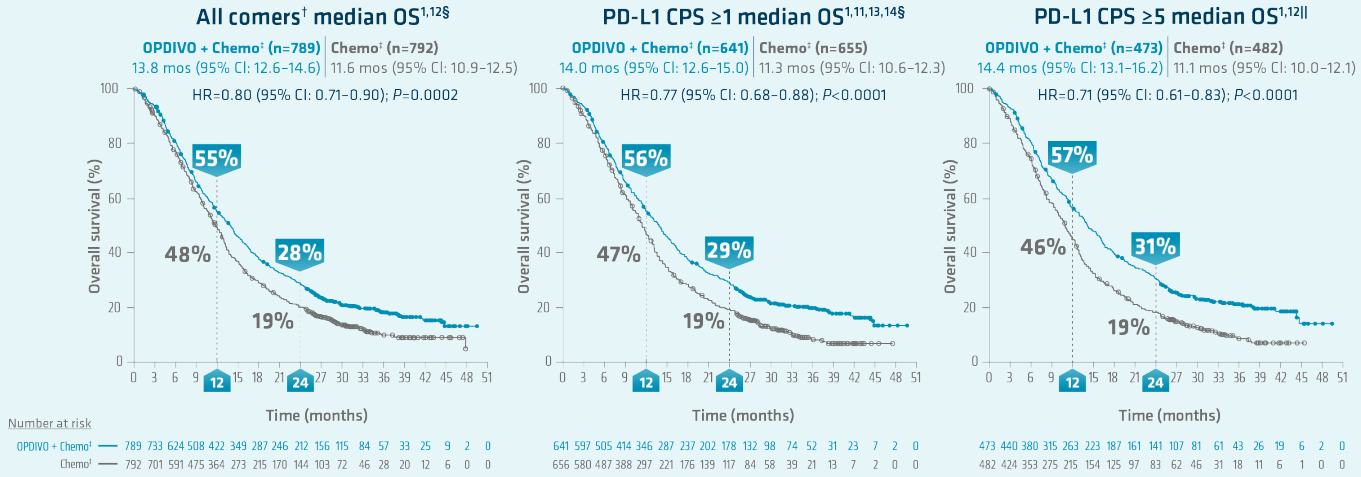
†All comers refers to all randomized patients in Checkmate 649.
‡FOLFOX or CapeOX.

1L indicates first-line; CapeOX, capecitabine and oxaliplatin; EAC, esophageal adenocarcinoma; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; GC, gastric cancer; GEJ, gastroesophageal junction; OS, overall survival.

Figure 3. Overall Survival by PD-L1 Status

In 1L patients with metastatic GC, GEJC, and EAC

Superior overall survival was achieved vs chemotherapy* in all comers,† PD-L1 CPS ≥1, and PD-L1 CPS ≥5

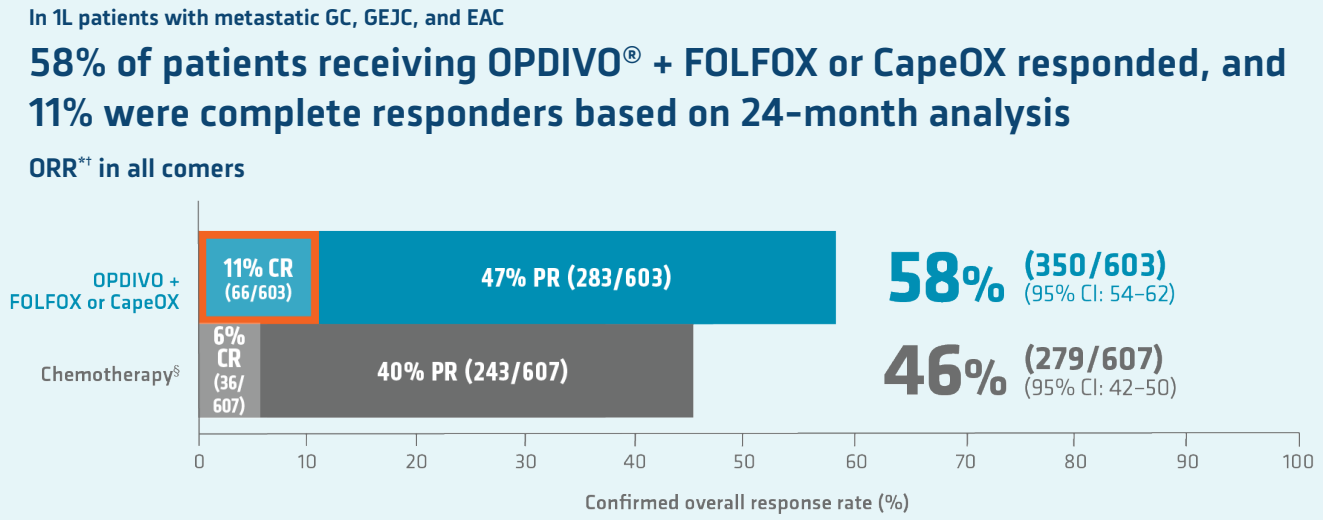


*OPDIVO + FOLFOX or CapeOX vs FOLFOX or CapeOX alone.
†All comers refers to all randomized patients in Checkmate 649.
‡Secondary end point.
§Primary end point.
‖FOLFOX or CapeOX.

1L indicates first-line; CapeOX, capecitabine and oxaliplatin; CPS, combined positive score; EAC, esophageal adenocarcinoma; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; GC, gastric cancer; GEJ, gastroesophageal junction; OS, overall survival.

- There are significant differences in all comers regardless of their PD-L1 status. Although the primary end point population was PD-L1 and combined positive score (CPS) ≥5, an OS benefit for all randomized patients is maintained, which is in line with the FDA approval for OPDIVO plus chemotherapy (**Figure 3**).
  - Median OS: 14.4 months for the PD-L1 CPS ≥5 (95% CI, 13.1-16.2) with OPDIVO plus FOLFOX or CapeOX versus 11.1 months (95% CI, 10.0-12.1) with chemotherapy alone (HR, 0.71; 95% CI, 0.61-0.83; *P* <.0001).
  - Median OS: 14.0 months for the PD-L1 CPS ≥1 (95% CI, 12.6-15.0) with OPDIVO plus FOLFOX or CapeOX versus 11.3 months (95% CI, 10.6-12.3) for chemotherapy alone (HR, 0.77; 95% CI, 0.68-0.88; *P* <.0001).
- Prior to these phase 3 data results, the treatment options for patients with advanced GC, GEJC, or EAC were limited. It is also good to see PFS maintained in patients treated with OPDIVO plus chemotherapy compared with chemotherapy alone.[9]
- In fact, in December 2021, the NCCN Guidelines were updated for the use of OPDIVO plus chemotherapy in *HER2*-negative GC, EAC, and GEJC patients from PD-L1 CPS 1-4 to PD-L1 <5 as a Category 2B-Preferred recommendation.[10]

Figure 4. Checkmate 649 Response Rate



*Based on confirmed response.
†Assessed using blinded independent central review (BICR).
‡All comers refers to all randomized patients in Checkmate 649.
§FOLFOX or CapeOX.

1L indicates first-line; CapeOX, capecitabine and oxaliplatin; CR, complete response; EAC, esophageal adenocarcinoma; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; GC, gastric cancer; GEJ, gastroesophageal junction; PR, partial response.

- The proportions of responders and the durability of responses are also higher with OPDIVO plus chemotherapy versus chemotherapy alone (**Figure 4**).
  - 11% of patients treated with OPDIVO plus FOLFOX or CapeOX experienced a complete response at 24 months versus 6% of patients treated with chemotherapy alone.
  - The median duration of response for all comers was 8.5 months with OPDIVO plus FOLFOX or CapeOX versus 6.9 months for patients treated with chemotherapy alone.

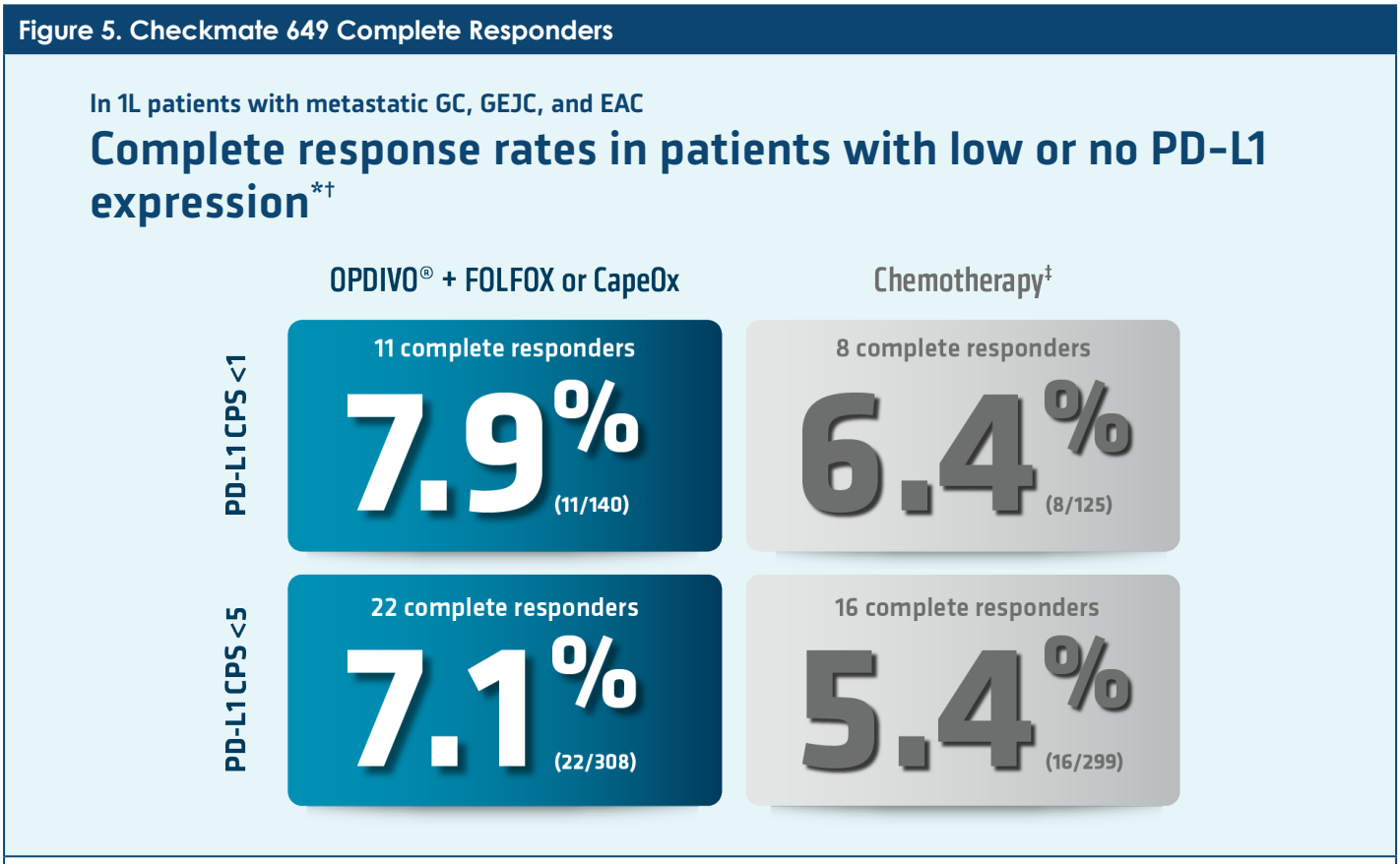
Q: Which efficacy end points from the 12.1-month primary analysis and the 12-month follow-up are clinically meaningful and relevant to convey to all your patients when considering treatment?

A: I explain to my patients that when there is a survival improvement in a large phase 3 study, even patients with stage IV disease do live longer. The PFS data demonstrate that the disease is less likely to grow with OPDIVO plus chemotherapy versus chemotherapy alone and that the disease does not develop resistance to the treatment.[9]

- Median PFS: 7.7 months (95% CI, 7.0-9.2) with OPDIVO plus FOLFOX or CapeOX versus 6.0 months (95% CI, 5.6-6.9) with chemotherapy alone (HR, 0.68; 95% CI, 0.58-0.79; *P* <.0001).
- Median OS: 13.8 months for all comers (95% CI, 12.4-14.6) with OPDIVO plus FOLFOX or CapeOX versus 11.6 months (95% CI, 10.9-12.5) for chemotherapy alone (HR, 0.80; 95% CI, 0.71-0.90; *P* = .0002).

The response data demonstrate that patients have a greater response to OPDIVO plus chemotherapy versus chemotherapy alone. As a result, patients are likely to see an improvement in disease-related symptoms. The higher median duration of response with OPDIVO plus chemotherapy means that at least for those patients who have shrinkage of cancer, they will likely have a longer period where the cancer does not proliferate or progress (Figure 4).

Figure 5. Checkmate 649 Complete Responders



*Based on an exploratory analysis in all patients who had measurable disease at baseline.
†Assessed using blinded independent central review (BICR).
‡FOLFOX or CapeOX.

1L indicates first-line; CapeOX, capecitabine and oxaliplatin; EAC, esophageal adenocarcinoma; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; GC, gastric cancer; GEJ, gastroesophageal junction.

- It was noted that 58% of patients who received OPDIVO plus FOLFOX or CapeOX responded to treatment versus 46% of patients receiving chemotherapy alone. Complete response was observed in 11% of patients receiving OPDIVO plus FOLFOX or CapeOX at 24 months versus 6% of patients receiving chemotherapy alone, and the complete response was maintained at 24 months.
- Median duration of response in all comers was 8.5 months (95% CI, 7.7-10.2) with OPDIVO plus FOLFOX or CapeOX versus 6.9 months (CI, 5.8-7.2) for chemotherapy alone.
- 7.9% of patients with PD-L1 CPS <1 and 7.1% of patients with PD-L1 CPS <5 achieved a complete response, compared with 6.4% and 5.4% of patients on chemotherapy alone, respectively (**Figure 5**).

These benefits occurred in all randomized patients, not just in those with PD-L1–expressing cancers, which formed the basis for the FDA approval for OPDIVO plus chemotherapy for all randomized patients. In addition, microsatellite instability (MSI)-high patients also had a demonstrated longer median OS and higher overall response rate when treated with OPDIVO plus chemotherapy compared with chemotherapy alone, even in patients who were PD-L1 non-expressors.[9]

Q: In the Checkmate 649 study, the results demonstrated a significant survival advantage with OPDIVO plus chemotherapy for each end point in all comers, including PD-L1 expressors and non-expressors. Based on these data, would you suggest to your colleagues that OPDIVO plus chemotherapy represents the new standard first-line treatment in all patients with advanced GC, GEJC, or EAC, even in those who are PD-L1 non-expressors?

A: I believe that OPDIVO plus FOLFOX or CapeOX can be a standard first-line treatment for patients with GC, GEJC, or EAC as even in the exploratory analysis, PD-L1 non-expressing patients had a response comparable to those who were PD-L1 expressing. The therapy is a consideration in all patients, including the non–PD-L1 expressors. In addition, if MSI is high, patients should have OPDIVO with chemotherapy.[9] If patients are not PD-L1 or MSI-high, OPDIVO plus chemotherapy still demonstrated a benefit in all patients in the study, so I would suggest to my colleagues to have a risk–benefit discussion with patients and discuss that the FDA regulatory approval for OPDIVO with chemotherapy in the GC/GEJC/EAC population was based on demonstrated benefit with this therapy in all comers (Figure 5). Moreover, in December 2021, the NCCN Guidelines were updated for the use of OPDIVO plus chemotherapy in *HER2*-negative GC, EAC, and GEJC patients from PD-L1 CPS 1-4 to PD-L1 <5 as a Category 2B-Preferred recommendation.[10]

Q: In the primary population in the Checkmate 649 study, 58% of all comers in the OPDIVO plus chemotherapy group versus 46% of patients in the chemotherapy-alone group achieved an objective response. The proportion of patients with a complete response was 11% and 6%, respectively, and median duration of response was 8.5 months versus 6.9 months, respectively. Regardless of whether the patients were PD-L1 expressors or non-expressors, the proportion of patients who achieved an objective response was higher in the OPDIVO plus chemotherapy group compared with the chemotherapy-alone group. What is the clinical significance of these data?

A: The data are clinically meaningful as there is consistency in response regardless of the origination of the cancer. For patients with stage IV disease, the disease burden comes from metastasis and >90% of the patients in both study arms in the Checkmate 649 study had metastases.[9]

The disease burden reduction was >30% in the patients treated with OPDIVO plus chemotherapy than in those treated with chemotherapy alone. For the patient, this means they can have superior tumor shrinkage with OPDIVO plus chemotherapy compared with chemotherapy alone.

- Patients with PD-L1 <5 demonstrated a 6.8% complete response rate with OPDIVO plus FOLFOX or CapeOX compared with a 4.3% complete response rate in those treated with chemotherapy alone.
- Patients with PD-L1 <1 demonstrated a 7.4% complete response rate with OPDIVO plus FOLFOX or CapeOX compared with a 4.7% complete response rate in those treated with chemotherapy alone.

Q: In Checkmate 649, OPDIVO and/or chemotherapy were discontinued in 44% of patients and at least 1 dose was withheld in 76% of patients due to an adverse reaction. Serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy. What has been your experience with adverse reactions in patients with GC, GEJC, or EAC receiving first-line OPDIVO plus chemotherapy? Which side effects do you see most frequently, and which ones have required dose modification or discontinuation? (Table)

A: The adverse events seen with the combination of OPDIVO plus chemotherapy are consistent with those seen with each agent on its own. With chemotherapy, patients have nausea, fatigue, and peripheral neuropathy (PN). After 4 months of treatment, I usually discontinue chemotherapy, specifically oxaliplatin, due to the PN side effects to ensure that it doesn't progress to a point of being irreversible.[11] In the Checkmate 649 trial, patients treated with OPDIVO plus chemotherapy demonstrated the same rates of PN as those treated with chemotherapy alone (Table).

OPDIVO therapy can continue for up to 2 years since treatment-related immune adverse events are generally uncommon. It's not often that we must stop OPDIVO in patients, as <5% of grade 3 to 4 adverse events occur with this treatment. I tell patients that OPDIVO has a well-established safety profile. Looking at the 2 treatment arms, OPDIVO does not seem to increase chemotherapy-related side effects nor is there a synergistic enhancement of adverse events with the combination treatment.

The immune-related adverse event observed most is pruritus in approximately 10% of patients.[12,13] I counsel patients that the incidence of grade 3 or 4 adverse events with OPDIVO is quite low, with rare or no increase in gastrointestinal-related side effects. There is approximately a 5% incidence of diarrhea associated with OPDIVO plus chemotherapy that can be effectively treated with steroids, and a low incidence of colitis.[12,13]

- Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation.
- Serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy.
- OPDIVO and/or chemotherapy were discontinued in 44% of patients and at least one dose was withheld in 76% of patients due to an adverse reaction.
- The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%).
- The most common adverse reactions occurring in ≥20% of patients treated with OPDIVO in combination with chemotherapy (n=782) were PN (53%), nausea (48%), fatigue (44%), diarrhea (39%), vomiting (31%), decreased appetite (29%), abdominal pain (27%), constipation (25%), and musculoskeletal pain (20%).

Table. Adverse reactions in ≥10% of patients receiving OPDIVO + FOLFOX or CapeOX

	OPDIVO + FOLFOX or CapeOX (n=782)		FOLFOX or CapeOX (n=767)	
	All grades (%)	Grades 3-4 (%)	All grades (%)	Grades 3-4 (%)
Adverse reactions	99	69	98	59
Nervous system				
Peripheral neuropathy*	53	7	46	4.8
Headache	11	0.8	6	0.3
Gastrointestinal				
Nausea	48	3.2	44	3.7
Diarrhea	39	5	34	3.7
Vomiting	31	4.2	29	4.2
Abdominal pain†	27	2.8	24	2.6
Constipation	25	0.6	21	0.4
Stomatitis‡	17	1.8	13	0.8
General				
Fatigue§	44	7	40	5
Pyrexia‖	19	1.0	11	0.4
Edema¶	12	0.5	8	0.1
Metabolism and nutrition				
Decreased appetite	29	3.6	26	2.5
Hypoalbuminemia#	14	0.3	9	0.3
Investigations				
Weight decreased	17	1.3	15	0.7
Increased lipase	14	7	8	3.7
Increased amylase	12	3.1	5	0.4
Musculoskeletal and connective tissue				
Musculoskeletal pain**	20	1.3	14	2.0
Skin and subcutaneous tissue				
Rash††	18	1.7	4.4	0.1
Palmar-plantar erythrodysesthesia syndrome	13	1.5	12	0.8
Respiratory, thoracic, and mediastinal				
Cough‡‡	13	0.1	9	0
Infections and infestations				
Upper repiratory tract infection§§	10	0.1	7	0.1

*Includes dysaesthesia, hypoaesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.
†Includes abdominal discomfort, abdominal pain lower, and abdominal pain upper.
‡Includes aphthous ulcer, mouth ulceration, and mucosal inflammation.
§Includes asthenia.
‖Includes tumor-associated fever.
¶Includes swelling, generalized edema, edema peripheral, and peripheral swelling.
#Includes blood albumin decreased.
**Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.
††Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, nodular rash, rash, erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash vesicular.
‡‡Includes productive cough.
§§Includes nasopharyngitis, pharyngitis, and rhinitis.

CapeOX indicates capecitabine and oxaliplatin; FOLFOX, leucovorin, fluorouracil, and oxaliplatin.

Q: How do you counsel your patients with advanced or metastatic GC, GEJC, or EAC who receive OPDIVO plus chemotherapy as first-line therapy regarding efficacy and safety?

A: There have been no negative quality-of-life (QOL) impacts with OPDIVO plus chemotherapy compared with chemotherapy alone. The QOL analysis in the Checkmate 649 study showed no significant difference in the QOL measures between the 2 treatment arms.[14] The time to symptom deterioration took longer for the patients on OPDIVO plus chemotherapy compared with chemotherapy alone, which could be related to QOL.

- Median duration of response in all comers in Checkmate 649 was 8.5 months (95% CI, 7.7-10.2) with OPDIVO plus FOLFOX or CapeOX compared with 6.9 months (95% CI, 5.8-7.2) with chemotherapy alone.

Patients who were able to continue with OPDIVO as maintenance therapy experienced fewer disease symptoms and had minimal side effects. Historically, with chemotherapy alone, patients' QOL becomes impacted, especially when their disease progresses.

In my experience, there are no significant safety concerns with the OPDIVO plus chemotherapy combination; it has an established safety profile. It is still necessary to monitor patients for grade 3 to 4 immune-mediated adverse events, but these have occurred in <5% of patients. Monitoring for chemotherapy-related side effects is already being performed, so monitoring for immune-related side effects will be added.

Q: In April 2021, OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy was approved by the FDA for the treatment of patients with advanced or metastatic GC, GEJC, or EAC in all comers (both PD-L1 expressors and non-expressors) based on the phase 3 Checkmate 649 trial. Can you describe your overall experience with this regimen in your patients with these tumors?

A: Overall, it has been a positive experience with the addition of this new treatment option for patients with stage IV GC, GEJC, or EAC. FOLFOX is one of the regimens in the Checkmate 649 study, so adaptation to the OPDIVO plus chemotherapy combination has been easy to recommend. When patients have durable responses to this combination, it's encouraging.

I have had to dose-reduce or discontinue the FOLFOX or CapeOX component of the regimen due to leukopenia, neutropenia, thrombocytopenia, and other adverse events. Generally, I am proactive in reducing the chemotherapy dose prior to side effects becoming intolerable. However, OPDIVO typically does not require dose reduction. A common adverse event with OPDIVO or other PD-1 inhibitors is hypothyroidism, which is easily managed with monitoring, replacement therapy, and/or referral to an endocrinologist.[12] After 4 months, I will discontinue treatment with oxaliplatin to be proactive in preventing long-term PN but will continue with fluoropyrimidine plus OPDIVO.

Q: What would you advise oncologists in the community who have not yet used OPDIVO plus chemotherapy in patients who are PD-L1 expressors and non-expressors, with advanced or metastatic GC, GEJC, or EAC?

A: Without question, for patients who are PD-L1 expressors or non-expressors, there is a clear-cut improvement in OS, PFS, and durability of response with OPDIVO plus chemotherapy compared with chemotherapy alone. Unless there is a contraindication, OPDIVO plus chemotherapy should be utilized for all comers with GC, GEJC, or EAC. In fact, in December 2021, the NCCN Guidelines were updated for the use of OPDIVO plus chemotherapy in *HER2*-negative GC, EAC, and GEJC patients from PD-L1 CPS 1-4 to PD-L1 <5 as a Category 2B-Preferred recommendation.[10]

If there are no contraindications, it's reasonable to consider OPDIVO plus chemotherapy in this setting. Even in patients with a history of autoimmune disease, OPDIVO plus chemotherapy should be considered, as long as the clinician monitors for immune-related adverse events.

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