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Update from ASCO GI 2022: Expanded Analyses of Efficacy and Safety at a 24-Month Follow-Up

ASK THE EXPERT™

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 2022, approximately 47,000 people in the United States will be diagnosed with gastric cancer (GC), gastroesophageal junction cancer (GEJC), and esophageal adenocarcinoma (EAC), with approximately 27,500 deaths resulting from these cancer types.[1,2] Men are more likely to be affected by these malignancies, with 60% of GC cases and 80% of GEJC and EAC cases affecting men.[1,2]

There are significant unmet needs in this population. Treatment options for patients with metastatic GC are limited, and they often have a poor prognosis.[3] More than half of new cases are unresectable, with a median overall survival (OS) of <1 year for patients treated with chemotherapy alone.[4,5]

"I'm a GI oncologist, and I see a large number of patients with gastric cancer. And gastric cancer patients' overall prognosis is very poor. Advanced gastric cancer patients might live 6 to 12 months with appropriate therapy, but untreated patients' life expectancy is <3 months."

-Minsig Choi, MD

Recently, the US Food and Drug Administration (FDA) approved first-line OPDIVO® (nivolumab), in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the treatment of patients with advanced 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

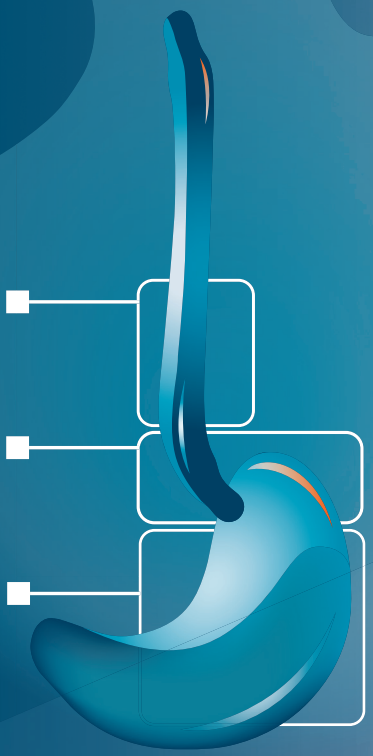
OPDIVO® (nivolumab) + chemotherapy:*

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‡]

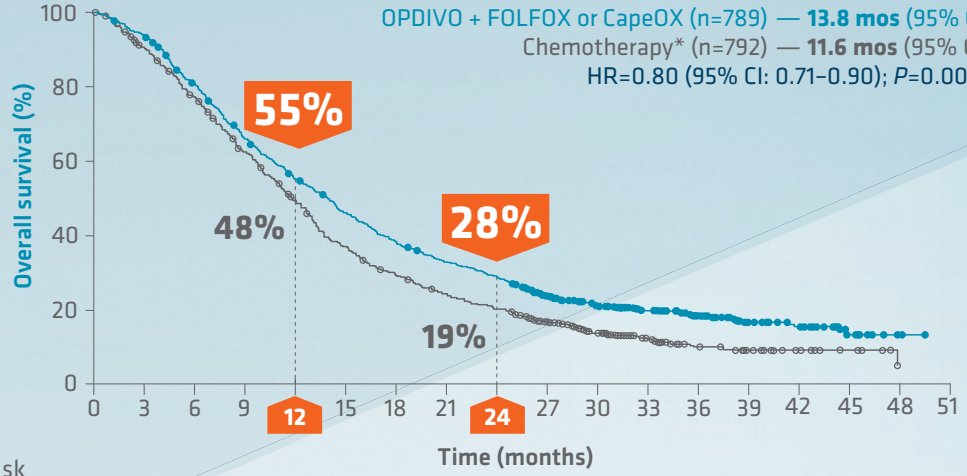
Median OS in all comers[1,2§]

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

Bristol Myers Squibb™

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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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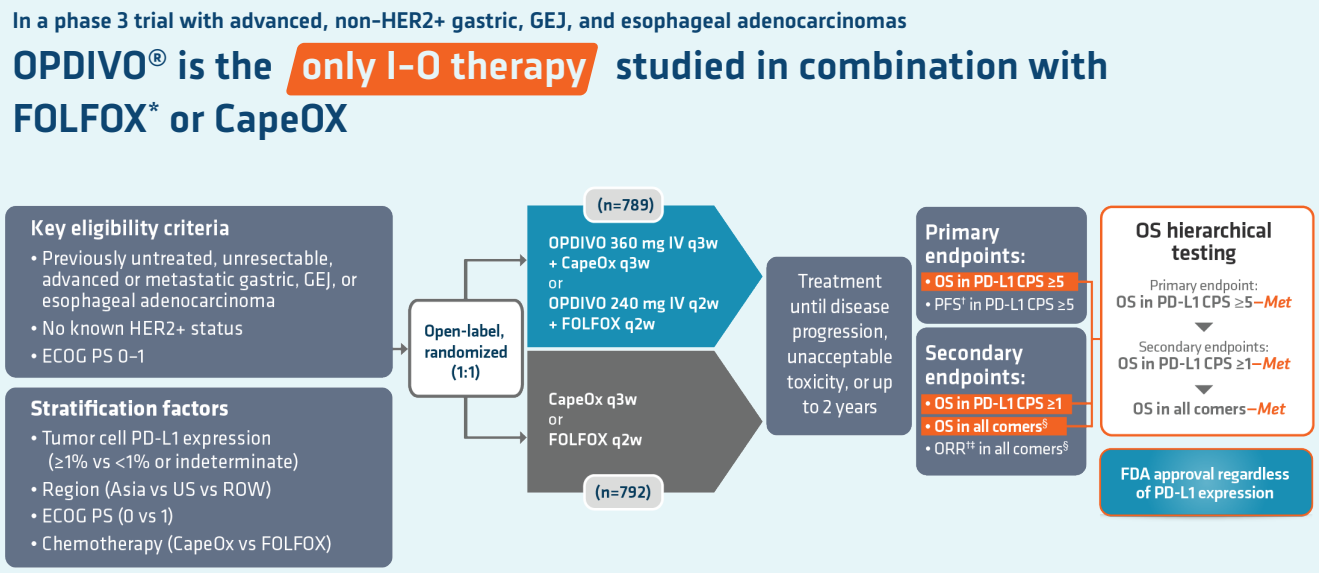
Bristol Myers Squibb™

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, *HER2*-negative unresectable, advanced or metastatic GC, GEJC, or EAC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.[7,8] Further stratification factors were tumor cell programmed death-ligand 1 (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**).[9]

Figure 1. Checkmate 649 study design



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

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.

OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy is indicated for the treatment of patients with advanced or metastatic GC, GJEC, and EAC.

- In Checkmate 649, in the OPDIVO plus chemotherapy arm, patients who discontinued chemotherapy were permitted to receive OPDIVO monotherapy at 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks up to 2 years after treatment initiation[9]
- Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory[9]
- The efficacy analysis in patients with PD-L1 combined positive score (CPS) ≥5 included 473 patients in the OPDIVO plus FOLFOX or CapeOX arm and 482 patients in the FOLFOX or CapeOX arm[10]
- Minimum follow-up time at extended analysis was 24 months[10]

UPDATE: The results of Checkmate 649 were updated at the 2022 American Society of Clinical Oncology Gastrointestinal (ASCO GI) Cancers Symposium with expanded analyses of efficacy and safety at a 24-month follow-up.[10]

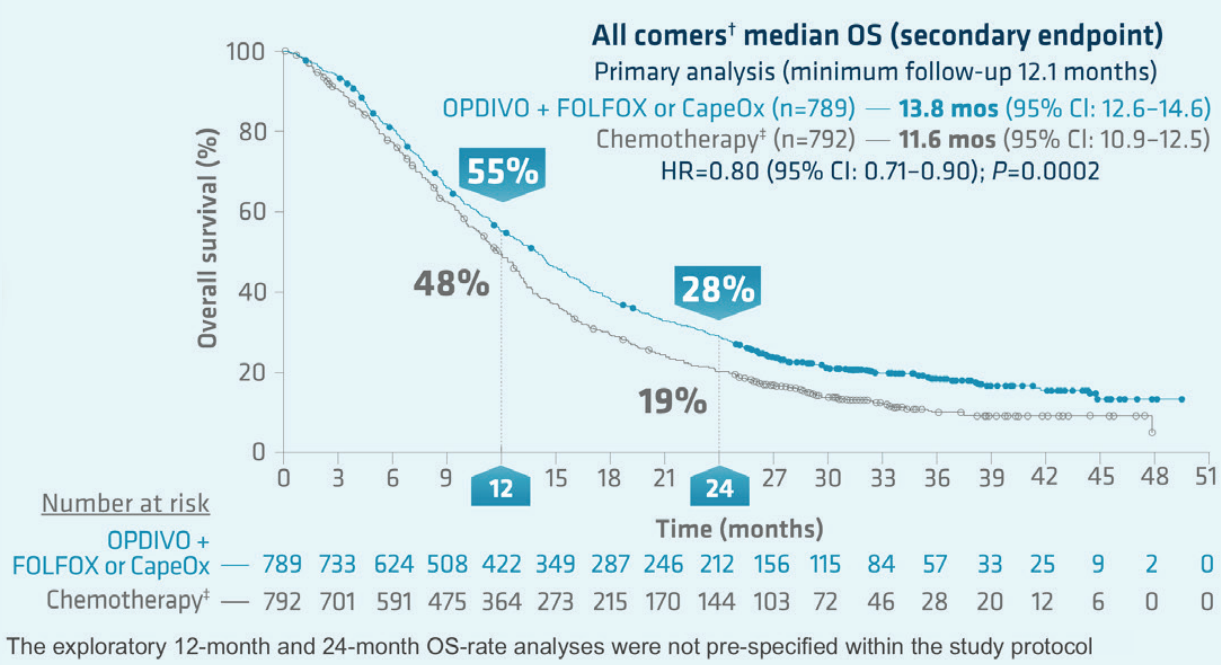
INTERVIEW WITH DR CHOI

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.

- OS of 28% in all comers at 24 months with treatment with OPDIVO plus chemotherapy versus 19% OS at 24 months with chemotherapy alone is significant. 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**)[9-11]

Figure 2. Checkmate 649 efficacy: overall survival in all comers treated with OPDIVO plus FOLFOX or CapeOX



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

CapeOX indicates capecitabine and oxaliplatin; CI, confidence interval; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; HR, hazard ratio; mos, months; OS, overall survival.

- A significant difference in median OS of 13.8 months for all comers (95% confidence interval [CI], 12.6-14.6) with OPDIVO plus FOLFOX or CapeOX versus 11.6 months (95% CI, 10.9-12.5) for chemotherapy alone (hazard ratio [HR], 0.80; 95% CI, 0.71-0.90; *P* = .0002)[10]
- A significant difference in median PFS of 7.7 months for all comers (95% CI, 7.1-8.6) with OPDIVO plus FOLFOX or CapeOX versus 6.9 months (95% CI, 6.7-7.2) for chemotherapy alone (HR, 0.79; 95% CI, 0.70-0.89)[10,11]

We are extremely pleased that the 2-year follow-up shows persistent improvement in both OS and PFS, and it shows that the clinical improvement lasts long in people who are receiving OPDIVO plus FOLFOX or CapeOX in this setting.

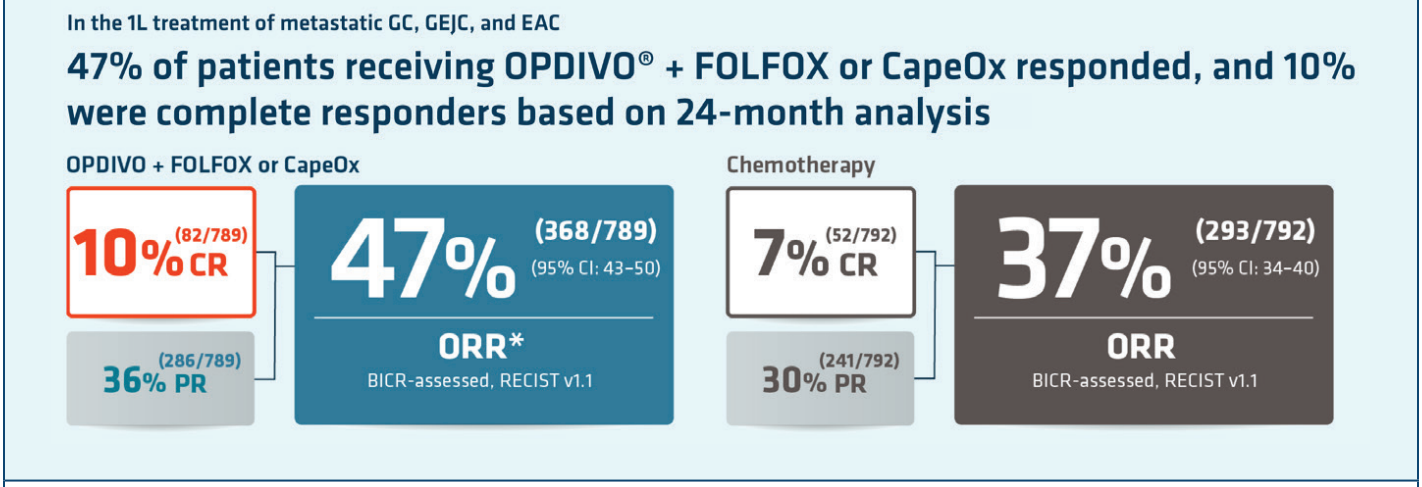
Q: At the 24-month extended analysis, 47% of all comers receiving OPDIVO plus chemotherapy responded and 10% were complete responders, compared with a 37% response rate and 7% complete responders in those receiving chemotherapy alone. What is the impact of these data?

A: The proportion of patients with an objective response and those with a complete response was numerically higher with OPDIVO plus chemo compared with chemotherapy alone in all randomized patients. Moreover, the median duration of response was 8.5 months (95% CI, 7.2-9.9) with OPDIVO plus chemotherapy compared with 6.9 months (95% CI, 5.8-7.2) with chemotherapy alone (**Figure 3**).[11,12]

Objective response rates are important. It means that the cancer is shrinking with OPDIVO plus chemotherapy, and there is about a 10% absolute increased benefit in overall response rate with OPDIVO plus chemotherapy compared with chemotherapy alone. And then the complete responders are also higher compared with chemotherapy alone.

If I can tell my patients that the cancer is responding to therapy, their pain is better, their appetite is better, their fatigue is better, and everything is improved because they know that the cancer is responding. Within a month or 2, patients who are treated with OPDIVO plus chemotherapy start eating better because their cancer is shrinking and their nutrition improves and their overall quality of life improves.

Figure 3. Checkmate 649 efficacy: overall and complete response rates



1L indicates first line; BICR, blinded independent central review; CapeOX, capecitabine and oxaliplatin; CI, confidence interval; CR, complete response; EAC, esophageal adenocarcinoma; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; GC, gastric cancer; GEJC, gastroesophageal junction cancer; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.

Q: Which efficacy end points from the 24-month follow-up are clinically meaningful and relevant to convey to all your patients when considering treatment?

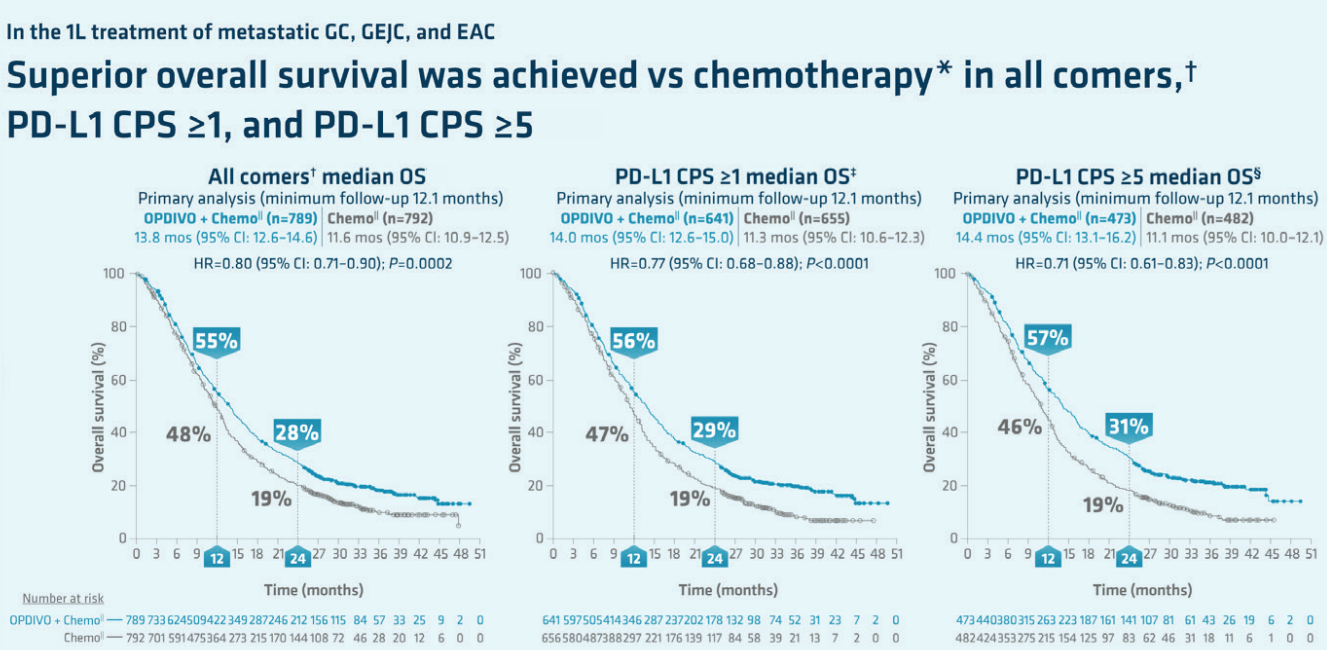
A: Therapy with OPDIVO plus chemo improves OS. We can tell our patients that cancer shrinkage is faster and better with OPDIVO plus chemotherapy. So, if you have bulky disease, where you need the cancer to shrink, then chemotherapy alone is not optimal, but you have to give OPDIVO plus chemotherapy to improve the response rate, as well as make it possible for patients to live longer.

Also, in the 2-year follow-up, these are actual data where we see that both the overall response rate, as well as PFS and OS, are so much better in the OPDIVO plus chemotherapy arm than with chemo alone.

Q: In Checkmate 649, the results demonstrated significant survival advantage with OPDIVO plus chemotherapy for each end point at 2 years' follow-up, including in PD-L1 expressors and non-expressors. What is the significance of these data? On the basis of these data, would you suggest to your colleagues that OPDIVO plus chemotherapy represents the new standard in first-line treatment in all patients with advanced GC/GEJC/EAC, even in those who are PD-L1 non-expressors?

A: OS consistently favored OPDIVO plus chemo compared with chemotherapy alone across multiple prespecified baseline demographics and disease characteristics in the primary population and all randomized patients. Particularly, survival benefit with OPDIVO plus chemotherapy occurred in all comers regardless of PD-L1 expression (**Figure 4**).[8,9,11-14] At 2 years of follow-up, superior OS was achieved by patients treated with OPDIVO plus chemo compared with chemotherapy alone in all comers.

Figure 4. Checkmate 649 efficacy: overall survival by PD-L1 expression



*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; chemo, chemotherapy; CI, confidence interval; CPS, combined positive score; EAC, esophageal adenocarcinoma; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HR, hazard ratio; mos, months; OS, overall survival; PD-L1, programmed death-ligand 1.

- In patients with PD-L1 ≥1, median OS was 29% in those treated with OPDIVO plus chemo compared with 19% in those treated with chemotherapy alone at 24 months.
- In patients with PD-L1 ≥5, median OS was 31% in those treated with OPDIVO plus chemo compared with 19% in those treated with chemotherapy alone at 24 months.

The important point here is that everybody, regardless of the PD-L1 score, had greater survival benefit with OPDIVO plus chemotherapy than with chemotherapy alone, so I personally don't use the PD-L1 score to choose whether one of my patients with advanced gastric cancer gets OPDIVO plus chemo; I use OPDIVO plus chemo on all my patients with advanced gastric/GEJ/esophageal cancer and use CPS only for prognostication. The PD-L1 score gives me a prognostic indicator that if your PD-L1 CPS is very high, then your chance of benefiting from OPDIVO plus chemo is slightly higher than people with a lower CPS.

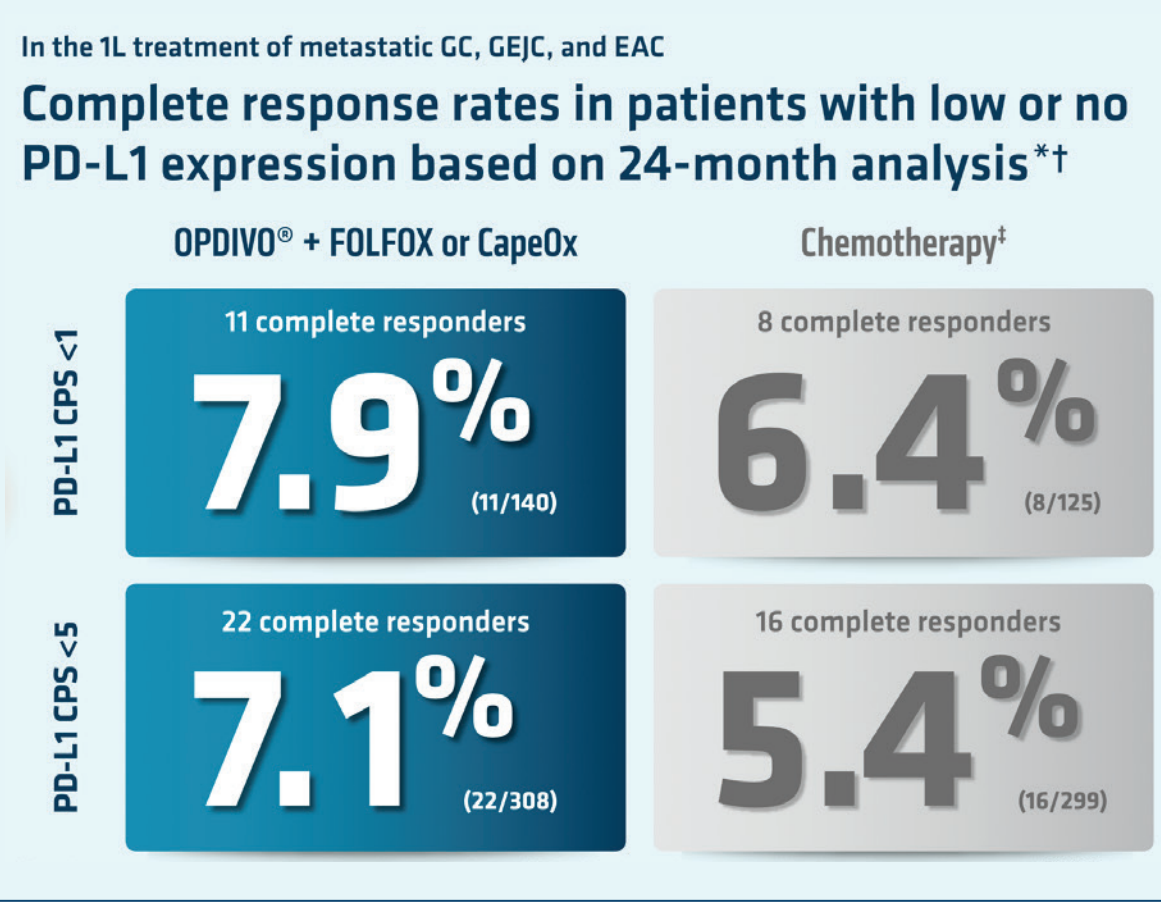
If you are not at a big academic center, where you can get the PD-L1 score right away, a lot of patients want to start their cancer treatment right away, and sometimes a PD-L1 score might take 2 to 4 weeks to obtain, and patients with advanced disease cannot wait that long to start therapy. Since the results in Figure 4 show that all patients benefited from OPDIVO plus chemo, I think it's reasonable to add OPDIVO at the beginning of first-line treatment.

Thus, in all my patients who have newly diagnosed gastric, GEJ, or esophageal cancer, as I talk with them about different treatment options, I recommend OPDIVO plus FOLFOX or OPDIVO plus CapeOX as first-line therapy.

Q: In an exploratory analysis at 24 months in Checkmate 649, complete response rates were numerically higher in patients with low or no PD-L1 expression who were treated with OPDIVO plus chemo compared with chemotherapy alone. What is the significance of these data?

A: In patients with PD-L1 CPS <1, there was a 7.9% complete response rate in the group treated with OPDIVO plus chemo compared with 6.4% in the group treated with chemotherapy alone. In patients with PD-L1 CPS <5, there was a 7.1% complete response rate in the group treated with OPDIVO plus chemo compared with 5.4% in the group treated with chemotherapy alone (**Figure 5**).[12] This suggests a benefit of OPDIVO plus chemo compared with chemo alone in all comers with respect to achieving a complete response.

Figure 5. Checkmate 649 efficacy: complete response rates by PD-L1 expression



*Based on an exploratory analysis in all randomized patients (OPDIVO + chemotherapy: n=789; chemotherapy alone: n=792).
†Assessed using blinded independent central review (BICR).
‡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; GEJC, gastroesophageal junction cancer; PD-L1, programmed death-ligand 1.

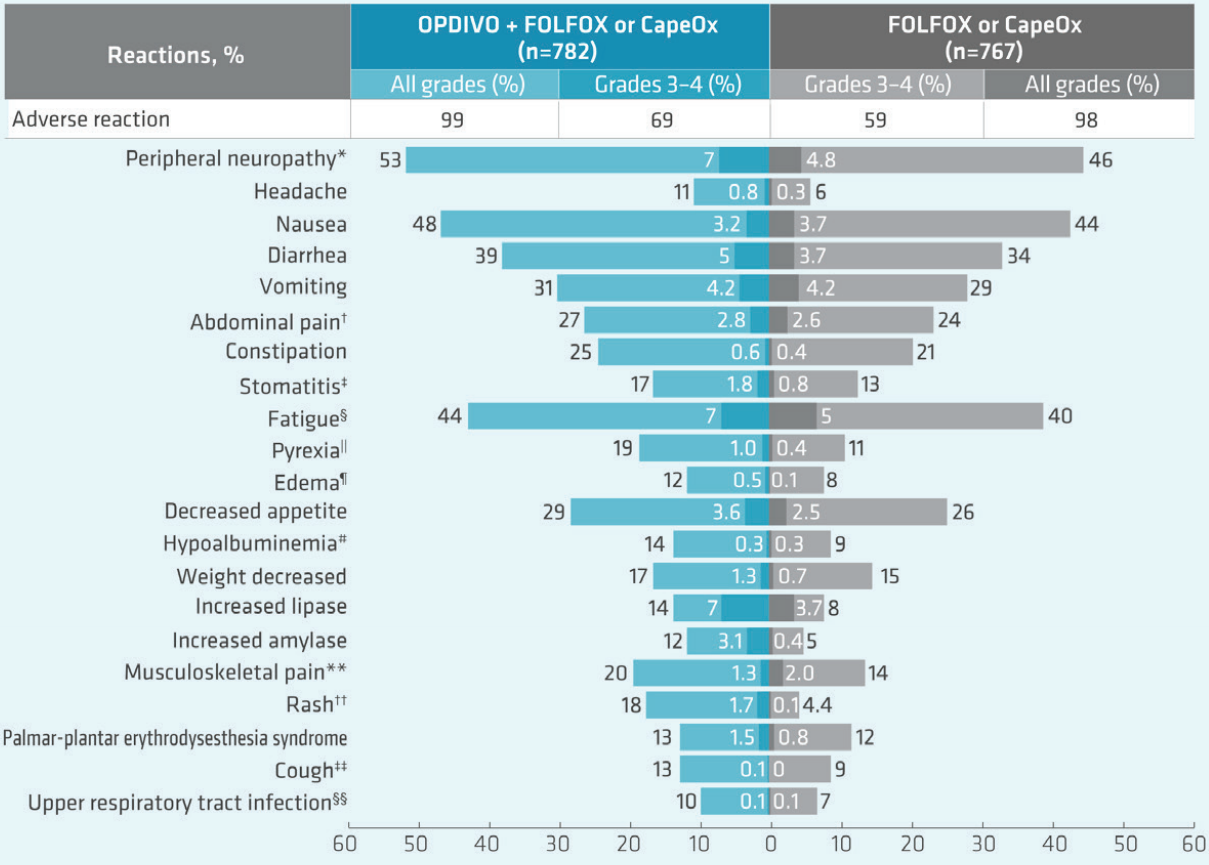
It is amazing that we are talking about complete responders in Checkmate 649 because this is seldom observed in the oncology world; complete responder means the cancer is all gone, or the patient is in remission. For stage IV gastric cancer, that's unheard of. If I see one complete response, I'll be very happy. So here, if you have 22 patients and 11 patients who are complete responders, we are extremely happy.

These are impressive results; however, the number of these patients is relatively small compared to the overall patient population, so it's hard to make a definite conclusion in this case.

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. Figure 6 shows the incidence of adverse reactions in ≥10% of patients receiving OPDIVO plus FOLFOX or CapeOX.[9]

What has been your experience with adverse reactions in patients with GC/GEJC/EAC receiving first-line OPDIVO plus chemotherapy? Which side effects do you see most frequently, and which ones have required dose modification or discontinuation?

Figure 6. Checkmate 649 safety: adverse reactions in ≥10% of patients receiving OPDIVO + chemotherapy



*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 maculopapular, 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.

A: The safety profile of OPDIVO plus chemo shown in Figure 6 is consistent with the known safety profiles of the individual treatments, and no new safety signals were identified. The incidence of treatment-related adverse events (TRAEs) at the 24-month follow-up analysis was similar to the primary analysis at 12.1 months. Moreover, grade 3 to 4 TRAEs with potential immunologic etiology occurred in ≤5% of patients, and the overall safety profile was acceptable.

My patients on OPDIVO plus FOLFOX tolerate their treatment very well, and the numbers here in the chemotherapy arm and OPDIVO plus chemo arms are very similar. Many times, fatigue, anorexia, and constipation might be disease-related symptoms. Many patients with gastric cancer have liver metastasis and bulky disease, and those things make people tired and have anorexia and weight loss. I monitor for endocrinopathies, such as hypothyroidism and hyperthyroidism, so that I can address these issues. I also make sure that, if my patients have diarrhea, I try to determine whether it is immune-mediated diarrhea or just chemotherapy-related diarrhea.

In general, OPDIVO is well-tolerated and needs no dose modification; but FOLFOX is chemotherapy, so if my patients have severe myelosuppression, I drop the bolus fluorouracil (5-FU). If my patients have neuropathy issues, I dose-modify oxaliplatin. Patients cannot be on chemotherapy forever. So usually, about 4 to 6 months into treatment, I start dropping oxaliplatin and continue most patients on just 5-FU and OPDIVO. And then if they do very well on 5-FU and OPDIVO, I might even drop the 5-FU and just treat with maintenance OPDIVO.

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

A: When I see patients with advanced GC, I talk to them about different treatment options, including single-agent 5-FU, doublet therapy (which is usually FOLFOX or CapeOX), and then triplet chemotherapy. As you increase the number of chemotherapy agents, toxicity increases, so the patient might live longer, but they will have more toxicities and decreased quality of life.

The advantage of OPDIVO plus chemo is that it is doublet chemotherapy plus immunotherapy, and usually OPDIVO does not add much toxicity. You're getting a 47% response rate with 7.9% complete responses, with the side effects of just 2 chemotherapies. And this is very durable, with responses out to 2 years.[11,12]

I tell my patients that I have had patients who are doing very well on OPDIVO plus chemo, and that their quality of life is maintained. When I discuss all these options, I've never seen any patient who wants triplet chemotherapy; everybody wants OPDIVO plus chemotherapy as their first-line treatment. If the patient is not a clinical trial candidate, then my first-line treatment recommendation would be OPDIVO with FOLFOX chemotherapy.

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/EAC in all comers (both PD-L1 expressors and non-expressors) based on the phase 3 Checkmate 649 trial.[6] Can you describe your overall experience with this regimen in your patients with these tumors?

A: I can tell you my experience has been pretty good. Just like with the clinical trial data, the tolerability and safety of OPDIVO plus FOLFOX is just like a FOLFOX-based regimen alone.

But the better thing is that with OPDIVO plus chemo, you are achieving a higher response rate, longer OS, and longer PFS. So, my experience has been excellent, and my patients treated with this regimen are doing well. We see more survivors of metastatic cancer 1 to 2 years out from their diagnosis on OPDIVO plus chemo, which is great news for our patients with gastric cancer, as well as people who are treating gastric cancer.

I have had some patients on this regimen who were PD-L1–negative and patients with PD-L1 scores of 10 or 20. My experience has been that most people benefited from OPDIVO plus chemo very well.

Q: Based on what we have discussed, 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/EAC?

A: I think the data are very clear—this was a large, phase 3 international study showing that OPDIVO, when added to FOLFOX or CapeOX, improved OS, PFS, and the response rate. And the 2-year data presented at the 2022 ASCO GI Cancers Symposium showed that this response is durable. Therefore, I would strongly recommend if you haven't used this regimen, that you should consider using this as a first-line treatment for patients with gastric cancer, GE junction cancer, and esophageal cancer, regardless of the PD-L1 score. I think it is reasonable to start this regimen at the time of initial diagnosis for all patients, regardless of the PD-L1 expression score.

Moreover, OPDIVO plus chemo is well-tolerated, with an acceptable safety profile. So, I think it's a no-brainer that OPDIVO plus FOLFOX should be considered your first-line treatment option for advanced gastric, GEJC, and EAC. Chemoimmunotherapy is becoming a new standard-of-care treatment for many advanced cancers, and now with the Checkmate 649 data, we know that we can use OPDIVO plus chemo safely and effectively in patients with GC, GEJC, and EAC.

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