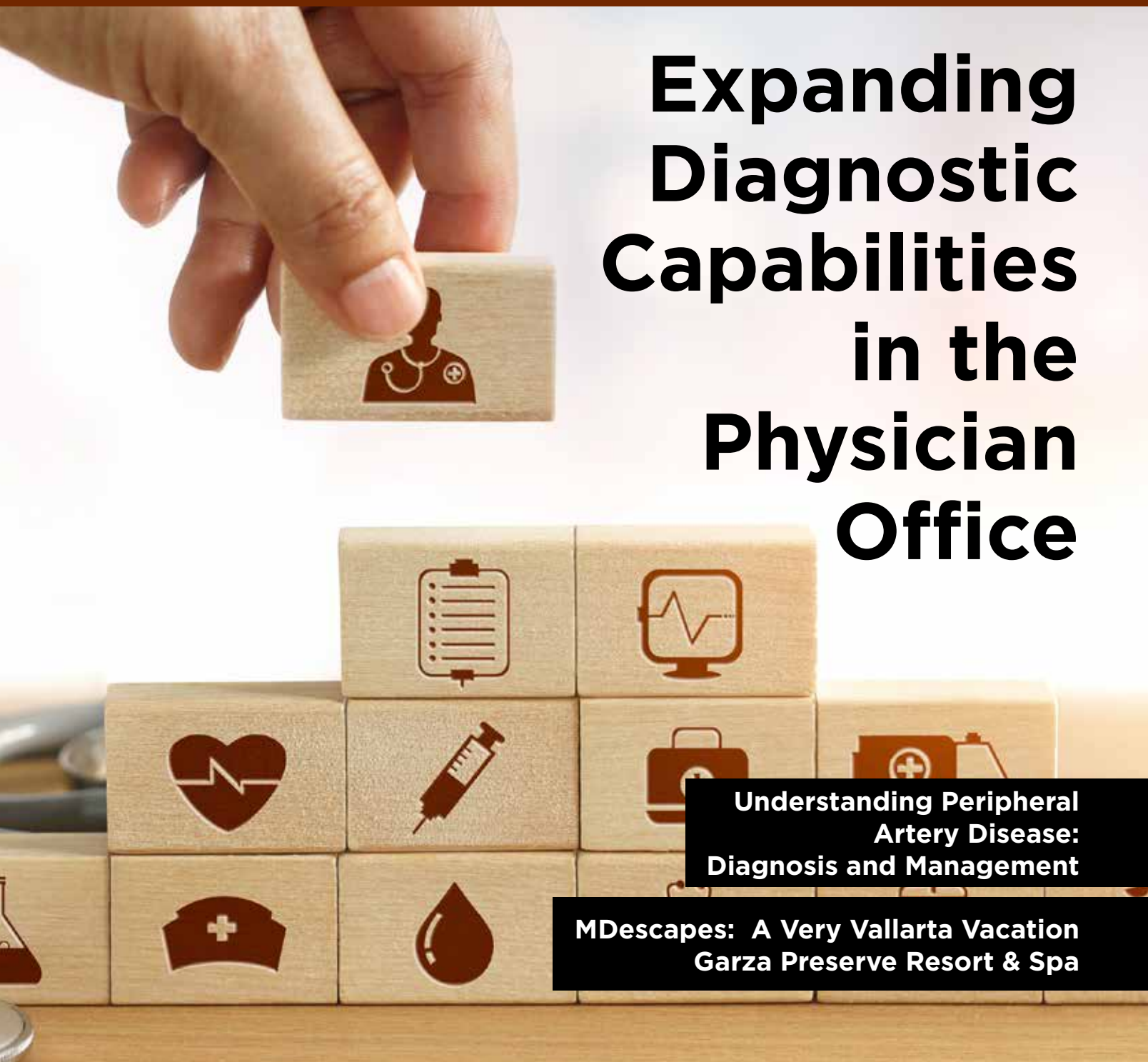
2025 | Issue 7

# Physicians office Resource

*Resources for You, Your Patients, & Your Practice*



## Expanding Diagnostic Capabilities in the Physician Office

**Understanding Peripheral Artery Disease: Diagnosis and Management**

**MDescapes: A Very Vallarta Vacation Garza Preserve Resort & Spa**

# THE POWER TO DETECT THE HIDDEN THREAT OF PERIPHERAL ARTERIAL DISEASE (PAD)




"PAD IS ASYMPTOMATIC IN 75% OF ELDERLY PATIENTS." [1]

IN PRIMARY CARE: "THE RISK OF MORTALITY WAS SIMILAR IN SYMPTOMATIC AND ASYMPTOMATIC PATIENTS WITH PAD" [2]

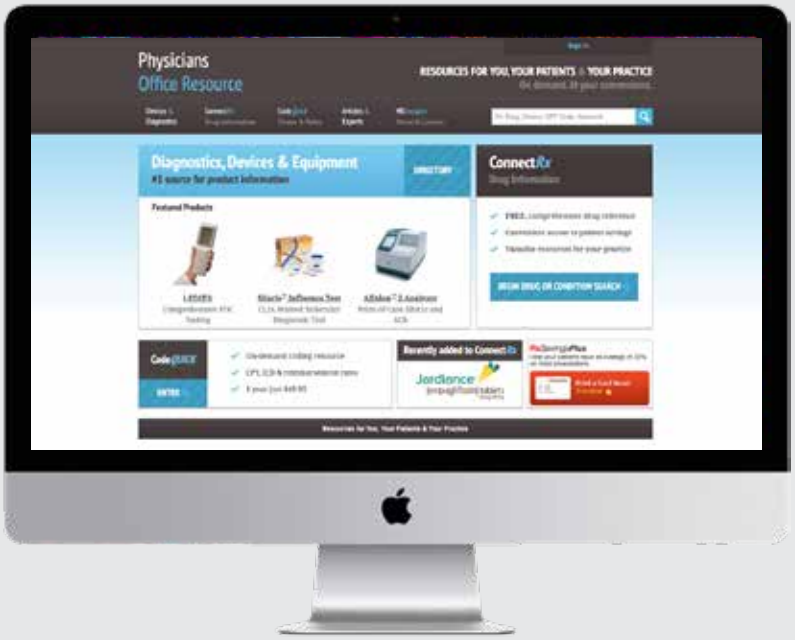
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**Understanding Peripheral Artery Disease: Diagnosis and Management**

Peripheral Artery Disease (PAD) is a manifestation of systemic atherosclerosis that primarily affects the lower extremities.

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**Expanding Diagnostic Capabilities in the Physician Office**

As physician practices evolve into more comprehensive diagnostic hubs, integrating new testing equipment offers both opportunities and regulatory challenges.

34

**MDescapes: A Very Vallarta Vacation Garza Blanca Preserve Resort & Spa**

Between the dramatic backdrop of the Sierra Madre Mountains and the Pacific Ocean, this vibrant Mexican destination welcomes guests from around the world.

POC-24-NAM-5696

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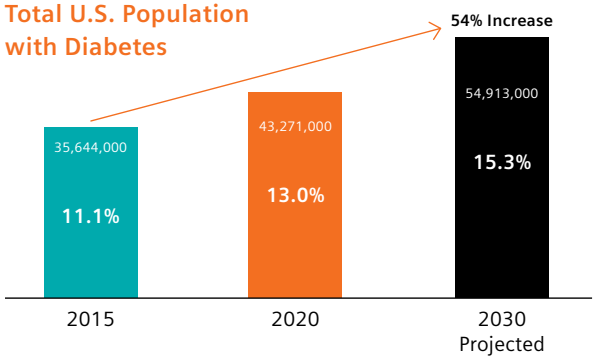
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Rapid assessment of glycemic control and kidney health

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- CLIA-waived

Albumin-to-creatinine ratio (ACR)
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5302



## The Prevalence of Diabetes Among U.S. Adults is on the Rise[1]

## Help your patients reverse the trend

Customize your patient consultations to enhance physician-patient partnership toward improved outcomes.

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1. Rowley, William R et al. "Diabetes 2030: Insights from Yesterday, Today, and Future Trends." Population health management vol. 20,1 (2017): 6-12. doi:10.1089/pop.2015.0181.

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# Discover what faster delivery* could mean for your patients.[1,2]

## Streamline administration time with a 3- to 5-minute subcutaneous injection[1,2]*

Must be administered by a healthcare professional.[1] *A 3–5 minute injection time of OPDIVO Qvantig™ compared to a 30-minute infusion time of OPDIVO®. This does not account for all aspects of treatment and does not include observation time. Actual clinic time may vary.[1,2]

### INDICATIONS

OPDIVO QVANTIG™ (nivolumab and hyaluronidase-nvhy), in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

OPDIVO QVANTIG, as monotherapy, is indicated for the adjuvant treatment of adult patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

OPDIVO QVANTIG, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by OPDIVO QVANTIG as monotherapy in the adjuvant setting after surgical resection.

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO QVANTIG.

Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of metastatic NSCLC.

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

OPDIVO QVANTIG, as monotherapy, is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.

OPDIVO QVANTIG, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC).

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

OPDIVO QVANTIG, as monotherapy, is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

### IMPORTANT SAFETY INFORMATION

#### 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 QVANTIG. Early identification and management are essential to ensure safe use of OPDIVO QVANTIG. 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. 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 QVANTIG depending on severity (please see Section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO QVANTIG 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 for at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

# OPDIVO Qvantig™

## nivolumab + hyaluronidase-nvhy

**SUBCUTANEOUS INJECTION** | 120 mg + 2,000 units / mL



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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 QVANTIG can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 2.8% (7/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (0.8%) and Grade 2 (2.0%) adverse reactions.

### Immune-Mediated Colitis

OPDIVO QVANTIG 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.

Immune-mediated colitis occurred in 2.8% (7/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (0.4%) and Grade 2 (2.4%) adverse reactions.

### Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO QVANTIG can cause immune-mediated hepatitis.

Immune-mediated hepatitis occurred in 2.4% (6/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (1.6%), and Grade 2 (0.8%) adverse reactions. Intravenous nivolumab in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to intravenous nivolumab alone. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. With the combination of intravenous nivolumab and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% (35/320) of patients.

### Immune-Mediated Endocrinopathies

OPDIVO QVANTIG 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 QVANTIG 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.

Adrenal insufficiency occurred in 2% (5/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (0.8%) and Grade 2 (1.2%) adverse reactions. Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received intravenous nivolumab with cabozantinib, including Grade 3 (2.2%) and Grade 2 (1.9%) adverse reactions. Hypophysitis occurred in 0.6% (12/1994) of patients treated with single agent intravenous nivolumab, including Grade 3 (0.2%) and Grade 2 (0.3%). Thyroiditis occurred in 0.4% (1/247) of patients receiving OPDIVO QVANTIG, including a Grade 1 (0.4%) adverse reaction.

Hyperthyroidism occurred in 0.8% (2/247) of patients receiving OPDIVO QVANTIG, including Grade 2 (0.4%) adverse reactions. Hypothyroidism occurred in 9% (23/247) of patients receiving OPDIVO QVANTIG, including Grade 2 (5.7%) adverse reactions.

Grade 3 diabetes occurred in 0.4% (1/247) of patients receiving OPDIVO QVANTIG.

### Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO QVANTIG can cause immune-mediated nephritis.

Grade 2 immune-mediated nephritis and renal dysfunction occurred in 1.2% (3/247) of patients receiving OPDIVO QVANTIG.

### Immune-Mediated Dermatologic Adverse Reactions

OPDIVO QVANTIG can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (drug rash with eosinophilia and systemic symptoms), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently

**IMPORTANT SAFETY INFORMATION (cont'd)**

**Immune-Mediated Dermatologic Adverse Reactions (cont'd)**

discontinue OPDIVO QVANTIG™ (nivolumab and hyaluronidase-nvhy) depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

Immune-mediated rash occurred in 7% (17/247) of patients, including Grade 3 (0.8%) and Grade 2 (2.8%) adverse reactions.

**Other Immune-Mediated Adverse Reactions**

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO QVANTIG or intravenous nivolumab as single agent or in combination with chemotherapy or immunotherapy, 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, other transplant (including corneal graft) 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, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

**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 QVANTIG. 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 QVANTIG and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO QVANTIG prior to or after an allogeneic HSCT.

**Embryo-Fetal Toxicity**

Based on its mechanism of action and data from animal studies, OPDIVO QVANTIG 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 QVANTIG and for 5 months after the last dose.

**Increased Mortality in Patients with Multiple Myeloma when Nivolumab 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 intravenous nivolumab, 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.

**Lactation**

There are no data on the presence of nivolumab or hyaluronidase 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 QVANTIG.

**Serious Adverse Reactions**

In Checkmate 67T, serious adverse reactions occurred in 28% of patients who received OPDIVO QVANTIG (n=247). Serious adverse reactions in >1% of patients included pleural effusion (1.6%), pneumonitis (1.6%), hyperglycemia (1.2%), hyperkalemia (1.2%), hemorrhage (1.2%) and diarrhea (1.2%). Fatal adverse reactions occurred in 3 patients (1.2%) who received OPDIVO QVANTIG and included myocarditis, myositis, and colitis complications. In Checkmate 77T, serious adverse reactions occurred in 21% of patients who received intravenous nivolumab in combination with platinum-doublet chemotherapy as neoadjuvant treatment (n=228). The most frequent (≥2%) serious adverse reactions was pneumonia. Fatal adverse reactions occurred in 2.2% of patients, due to cerebrovascular accident, COVID-19 infection, hemoptysis, pneumonia, and pneumonitis (0.4% each). In the adjuvant phase of Checkmate 77T, 22% of patients experienced serious adverse reactions (n=142). The most frequent serious adverse reaction was pneumonitis/ILD (2.8%). One fatal adverse reaction due to COVID-19 occurred. In Checkmate 017 and 057, serious adverse reactions occurred in 46% of patients receiving intravenous nivolumab (n=418). The most frequent serious adverse reactions reported in ≥2% of patients receiving intravenous nivolumab were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 057, fatal adverse reactions occurred; these included events of infection (7 patients, including one case of Pneumocystis jirovecii pneumonia), pulmonary embolism (4 patients), and limbic encephalitis (1 patient). In Checkmate 9ER, serious adverse reactions occurred in 48% of patients receiving intravenous nivolumab and cabozantinib (n=320). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving intravenous nivolumab (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving intravenous nivolumab (n=236). The most frequent serious adverse reactions reported in ≥2% of patients receiving intravenous nivolumab were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving intravenous nivolumab (n=270). The most frequent serious adverse reactions reported in ≥ 2% of patients receiving intravenous nivolumab were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. In Checkmate 274, serious adverse reactions occurred in 30% of patients receiving intravenous nivolumab (n=351). The most frequent serious adverse reaction reported in ≥ 2% of patients receiving intravenous nivolumab was urinary tract infection. Fatal adverse reactions occurred in 1% of patients; these included events of pneumonitis (0.6%). In Checkmate 901, serious adverse reactions occurred in 48% of patients receiving intravenous nivolumab in combination with chemotherapy. The most frequent serious adverse reactions reported in ≥2% of patients who received intravenous nivolumab with chemotherapy were urinary tract infection (4.9%), acute kidney injury (4.3%), anemia (3%), pulmonary embolism (2.6%), sepsis (2.3%), and platelet count decreased (2.3%). Fatal adverse reactions occurred in 3.6% of patients who received intravenous nivolumab in combination with chemotherapy; these included sepsis (1%). In Checkmate 238, serious adverse reactions occurred in 18% of patients receiving intravenous nivolumab (n=452). Grade 3 or 4 adverse reactions occurred in 25% of intravenous nivolumab-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions

reported in ≥2% of intravenous nivolumab-treated patients were diarrhea and increased lipase and amylase. In Attraction-3, serious adverse reactions occurred in 38% of patients receiving intravenous nivolumab (n=209). Serious adverse reactions reported in ≥2% of patients who received intravenous nivolumab were pneumonia, esophageal fistula, interstitial lung disease, and pyrexia. The following fatal adverse reactions occurred in patients who received intravenous nivolumab: interstitial lung disease or pneumonitis (1.4%), pneumonia (1.0%), septic shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death (0.5%). In Checkmate 577, serious adverse reactions occurred in 33% of patients receiving intravenous nivolumab (n=532). A serious adverse reaction reported in ≥2% of patients who received intravenous nivolumab was pneumonitis. A fatal reaction of myocardial infarction occurred in one patient who received intravenous nivolumab. In Checkmate 76K, serious adverse reactions occurred in 18% of patients receiving intravenous nivolumab (n=524). Adverse reactions which resulted in permanent discontinuation of intravenous nivolumab in >1% of patients included arthralgia (1.7%), rash (1.7%), and diarrhea (1.1%). A fatal adverse reaction occurred in 1 (0.2%) patient (heart failure and acute kidney injury). The most frequent Grade 3-4 lab abnormalities reported in ≥1% of intravenous nivolumab-treated patients were increased lipase (2.9%), increased AST (2.2%), increased ALT (2.1%), lymphopenia (1.1%), and decreased potassium (1.0%).

### Common Adverse Reactions

In Checkmate 67T, the most common adverse reactions (≥10%) in patients treated with OPDIVO QVANTIG (n=247) were musculoskeletal pain (31%), fatigue (20%), pruritus (16%), rash (15%), hypothyroidism (12%), diarrhea (11%), cough (11%), and abdominal pain (10%). In Checkmate 77T, the most common adverse reactions (reported in ≥20%) in patients receiving intravenous nivolumab in combination with chemotherapy (n= 228) were anemia (39.5%), constipation (32.0%), nausea (28.9%), fatigue (28.1%), alopecia (25.9%), and cough (21.9%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving intravenous nivolumab (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 9ER, the most common adverse reactions (≥20%) in patients receiving intravenous nivolumab and cabozantinib (n=320) were diarrhea (64%), fatigue (51%), hepatotoxicity (44%), palmar-plantar erythrodysaesthesia syndrome (40%), stomatitis (37%), rash (36%), hypertension (36%), hypothyroidism (34%), musculoskeletal pain (33%), decreased appetite (28%), nausea (27%), dysgeusia (24%), abdominal pain (22%), cough (20%) and upper respiratory tract infection (20%). In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving intravenous nivolumab (n=406) vs everolimus (n=397) were fatigue (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving intravenous nivolumab (n=236) were cough (14%) and dyspnea (14%) at a higher incidence than investigator's choice. In Checkmate 275, the most common adverse reactions (≥ 20%) reported in patients receiving intravenous nivolumab (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%). In Checkmate 274, the most common adverse reactions (20%) reported in patients receiving intravenous nivolumab (n=351) were rash (36%), fatigue (36%), diarrhea (30%), pruritus (30%), musculoskeletal pain (28%), and urinary tract infection (22%). In Checkmate 901, the most common adverse reactions (reported in ≥20% of patients) were nausea (52%), fatigue (48%), musculoskeletal pain (33%), constipation (30%), decreased appetite (30%), rash (25%), vomiting (23%), and peripheral neuropathy (20%). In Checkmate 238, the most common adverse reactions (≥20%) reported in intravenous nivolumab-treated patients (n=452) vs ipilimumab-treated patients (n=453) were fatigue (57% vs 55%), diarrhea (37% vs 55%), rash (35% vs 47%), musculoskeletal pain (32% vs 27%), pruritus (28% vs 37%), headache (23% vs 31%), nausea (23% vs 28%), upper respiratory infection (22% vs 15%), and abdominal pain (21% vs 23%). The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%). In Attraction-3, the most common adverse reactions (≥20%) in intravenous nivolumab-treated patients (n=209) were rash (22%) and decreased appetite (21%). In Checkmate 577, the most common adverse reactions (≥20%) in patients receiving intravenous nivolumab (n=532) were fatigue (34%), diarrhea (29%), nausea (23%), rash (21%), musculoskeletal pain (21%), and cough (20%). In Checkmate 76K, the most common adverse reactions (≥20%) reported with intravenous nivolumab (n=524) were fatigue (36%), musculoskeletal pain (30%), rash (28%), diarrhea (23%) and pruritus (20%).

### Surgery Related Adverse Reactions

In Checkmate 77T, 5.3% (n=12) of the intravenous nivolumab-treated patients who received neoadjuvant treatment, did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery in intravenous nivolumab-treated patients were cerebrovascular accident, pneumonia, and colitis/diarrhea (2 patients each) and acute coronary syndrome, myocarditis, hemoptysis, pneumonitis, COVID-19, and myositis (1 patient each).

Please see U.S. Full Prescribing Information for OPDIVO QVANTIG at https://packageinserts.bms.com/pi/pi_opdivo-qvantig.pdf

### Clinical Trials and Patient Populations

Checkmate 577–adjuvant treatment of esophageal or gastroesophageal junction cancer; Checkmate 238–adjuvant treatment of patients with completely resected Stage III or Stage IV melanoma; Checkmate 76K–adjuvant treatment of patients 12 years of age and older with completely resected Stage IIB or Stage IIC melanoma; Checkmate 274–adjuvant treatment of urothelial carcinoma; Checkmate 275–previously treated advanced or metastatic urothelial carcinoma; Attraction-3–esophageal squamous cell carcinoma; Checkmate 017–second-line treatment of metastatic squamous non-small cell lung cancer; Checkmate 057–second-line treatment of metastatic non-squamous non-small cell lung cancer; Checkmate 77T–Neoadjuvant treatment with platinum-doublet chemotherapy for non-small cell lung cancer followed by single-agent OPDIVO as adjuvant treatment after surgery; Checkmate 901–Adult patients with unresectable or metastatic urothelial carcinoma; Checkmate 141–recurrent or metastatic squamous cell carcinoma of the head and neck; Checkmate 025–previously treated renal cell carcinoma; Checkmate 9ER–previously untreated renal cell carcinoma, in combination with cabozantinib

Please see Brief Summary of Prescribing information for OPDIVO Qvantig on the following pages. For more information, call 1-855-OPDIVO-1 (1-855-673-4861) or go to www.OPDIVOQvantighcp.com.

**References: 1.** OPDIVO Qvantig [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **2.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

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## (nivolumab and hyaluronidase-nvhy) injection, for subcutaneous use

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

**INDICATIONS AND USAGE**

Advanced Renal Cell Carcinoma (RCC)

- In combination with cabozantinib, for the first-line treatment of adult patients with advanced RCC.
- For the treatment of adult patients with advanced RCC who have received prior anti-angiogenic therapy.

Adjuvant Treatment of Melanoma

- For the adjuvant treatment of adult patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer (NSCLC)

- In combination with platinum-doublet chemotherapy, for the neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) NSCLC and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) as monotherapy in the adjuvant setting after surgical resection.

Metastatic NSCLC

- For the treatment of adult patients with NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO QVANTIG.

  **Limitations of Use:** OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of metastatic NSCLC.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- For the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy.

Urothelial Carcinoma (UC)

- For the adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC.
- In combination with cisplatin and gemcitabine, for the first-line treatment of adult patients with unresectable or metastatic UC.
- For the treatment of adult patients with locally advanced or metastatic UC who:
  - have disease progression during or following platinum-containing chemotherapy.
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Esophageal Cancer

- For the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).
- For the treatment of adult patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

**DOSAGE AND ADMINISTRATION**

**OPDIVO QVANTIG is for subcutaneous use only in the abdomen or thigh. Do not administer intravenously.**

**OPDIVO QVANTIG is to be administered by a healthcare professional only.**

**Recommended Dosages for OPDIVO QVANTIG as Monotherapy**

Advanced RCC, Metastatic NSCLC, SCCHN, Locally Advanced or Metastatic UC, ESCC, Adjuvant Treatment of Melanoma, Adjuvant Treatment of UC, and Adjuvant Treatment of Resected Esophageal or Gastroesophageal Junction Cancer

- 600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks **OR** 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks until disease progression or unacceptable toxicity.

**Recommended Dosages for OPDIVO QVANTIG in Combination with Other Therapeutic Agents**

Advanced RCC

- 600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks **OR** 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks until disease progression, unacceptable toxicity, or up to 2 years.
- In combination with cabozantinib 40 mg orally once daily without food until disease progression or unacceptable toxicity.

Neoadjuvant and Adjuvant Treatment of Resectable NSCLC

- Neoadjuvant: 900 mg nivolumab and 15,000 units hyaluronidase with platinum-doublet chemotherapy on the same day every 3 weeks until disease progression or unacceptable toxicity, for up to 4 cycles.
- Adjuvant: 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks until disease progression, recurrence, or unacceptable toxicity, for up to 13 cycles (up to 1 year).

First-Line Unresectable or Metastatic UC

- 900 mg nivolumab and 15,000 units hyaluronidase every 3 weeks in combination with cisplatin and gemcitabine on the same day for up to 6 cycles.
- After completing up to 6 cycles of combination therapy: 600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks **OR** 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks until disease progression, unacceptable toxicity, or up to 2 years from first dose.

Refer to the respective Prescribing Information for each therapeutic agent administered in combination with OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) for the recommended dosage information, as appropriate.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

**Severe and Fatal Immune-Mediated Adverse Reactions**

OPDIVO QVANTIG is a combination of 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, and an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. 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 QVANTIG depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*. In general, if OPDIVO QVANTIG 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 QVANTIG can cause immune-mediated pneumonitis, which is defined as requiring use of steroids and no clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 2.8% (7/247) of patients receiving OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy), including Grade 3 (0.8%) and Grade 2 (2.0%) adverse reactions. Pneumonitis led to permanent discontinuation of OPDIVO QVANTIG in 1.6% and withholding of OPDIVO QVANTIG in 1.6% of patients.

Systemic corticosteroids were required in 100% (7/7) of patients with pneumonitis. Pneumonitis resolved in 27% of the 7 patients. Of the 4 patients in whom OPDIVO QVANTIG was withheld for pneumonitis, 2 reinitiated OPDIVO QVANTIG after symptom improvement; of these, 1 (50%) had recurrence of pneumonitis.

Immune-Mediated Colitis

OPDIVO QVANTIG 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 2.8% (7/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (0.4%) and Grade 2 (2.4%) adverse reactions. Colitis led to withholding of OPDIVO QVANTIG in 2.0% of patients.

Systemic corticosteroids were required in 100% (7/7) of patients with colitis. Colitis resolved in 71% of the 7 patients. Of the 5 patients in whom OPDIVO QVANTIG was withheld for colitis, 3 reinitiated OPDIVO QVANTIG after symptom improvement; of these, 2 (67%) had recurrence of colitis.

Immune-Mediated Hepatitis and Hepatotoxicity

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

Immune-mediated hepatitis occurred in 2.4% (6/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (1.6%), and Grade 2 (0.8%) adverse reactions. Hepatitis led to permanent discontinuation of OPDIVO QVANTIG in 0.8% and withholding of OPDIVO QVANTIG in 1.6% of patients.

Systemic corticosteroids were required in 100% (6/6) of patients with hepatitis. Hepatitis resolved in 67% of the 6 patients. Of the 2 patients in whom OPDIVO QVANTIG was withheld for hepatitis, 2 reinitiated OPDIVO QVANTIG after symptom improvement; of these, 1 (50%) had recurrence of hepatitis.

*Intravenous Nivolumab with Cabozantinib*

Nivolumab in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to nivolumab alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt nivolumab and cabozantinib and consider administering corticosteroids *[see Dosage and Administration (2.3) in full Prescribing Information]*.

With the combination of intravenous nivolumab and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% (35/320) of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either intravenous nivolumab (n=11) or cabozantinib (n=9) administered as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving intravenous nivolumab, 2 patients receiving cabozantinib, and 7 patients receiving both intravenous nivolumab and cabozantinib.

Immune-Mediated Endocrinopathies

*Adrenal Insufficiency*

OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) 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 QVANTIG depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Adrenal insufficiency occurred in 2% (5/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (0.8%) and Grade 2 (1.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO QVANTIG in 0.4% of patients and withholding of OPDIVO QVANTIG in 0.4% of patients.

Systemic corticosteroids were required in 100% (5/5) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 20% of the 5 patients.

*Intravenous Nivolumab with Cabozantinib*

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received intravenous nivolumab with cabozantinib, including Grade 3 (2.2%) and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of intravenous nivolumab and cabozantinib in 0.9% and withholding of intravenous nivolumab and cabozantinib in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom intravenous nivolumab with cabozantinib was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

*Hypophysitis*

OPDIVO QVANTIG 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 QVANTIG depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*.

*Intravenous Nivolumab*

Hypophysitis occurred in 0.6% (12/1994) of patients treated with single agent intravenous nivolumab, including Grade 3 (0.2%) and Grade 2 (0.3%). Hypophysitis led to permanent discontinuation of intravenous nivolumab 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 intravenous nivolumab was withheld for hypophysitis, 2 reinitiated intravenous nivolumab after symptom improvement; of these, none had recurrence of hypophysitis.

*Thyroid Disorders*

OPDIVO QVANTIG 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 QVANTIG depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*.

*Thyroiditis*

Thyroiditis occurred in 0.4% (1/247) of patients receiving OPDIVO QVANTIG, including a Grade 1 (0.4%) adverse reaction.

Systemic corticosteroids were not required in the patient with thyroiditis. Thyroiditis did not resolve in this patient.

*Hyperthyroidism*

Hyperthyroidism occurred in 0.8% (2/247) of patients receiving OPDIVO QVANTIG, including Grade 2 (0.4%) adverse reactions.

Systemic corticosteroids were not required in patients with hyperthyroidism. Hyperthyroidism resolved in 50% of the 2 patients.

*Hypothyroidism*

Hypothyroidism occurred in 9% (23/247) of patients receiving OPDIVO QVANTIG, including Grade 2 (5.7%) adverse reactions. Hypothyroidism led to withholding of OPDIVO QVANTIG in 0.8% of patients.

Systemic corticosteroids were not required in patients with hypothyroidism. Hypothyroidism resolved in 4.3% of the 23 patients. Of the 1 patient in whom OPDIVO QVANTIG was withheld for hypothyroidism, OPDIVO QVANTIG was not reinitiated after symptom improvement.

*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 QVANTIG (nivolumab and hyaluronidase-nvhy) depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Grade 3 diabetes occurred in 0.4% (1/247) of patients receiving OPDIVO QVANTIG.

No patients with diabetes required systemic corticosteroids. Diabetes did not resolve in this patient.

Immune-Mediated Nephritis with Renal Dysfunction

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

Grade 2 immune-mediated nephritis and renal dysfunction occurred in 1.2% (3/247) of patients receiving OPDIVO QVANTIG. Immune-mediated nephritis and renal dysfunction led to withholding of OPDIVO QVANTIG in 1.2% of patients.

Systemic corticosteroids were required in 100% (3/3) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 100% of the 3 patients. Of the 3 patients in whom OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) was withheld for nephritis or renal dysfunction, 1 reinitiated OPDIVO QVANTIG after symptom improvement without recurrence of nephritis or renal dysfunction.

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO QVANTIG 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/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue OPDIVO QVANTIG depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Immune-mediated rash occurred in 7% (17/247) of patients, including Grade 3 (0.8%) and Grade 2 (2.8%) adverse reactions. Immune-mediated rash led to withholding of OPDIVO QVANTIG in 1.2% of patients.

Systemic corticosteroids were required in 47% (8/17) of patients with immune-mediated rash. Rash resolved in 77% of the 17 patients. Of the 3 patients in whom OPDIVO QVANTIG was withheld for immune-mediated rash, all reinitiated OPDIVO QVANTIG after symptom improvement; of these, all (100%) 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 QVANTIG or intravenous nivolumab as a single agent or in combination with chemotherapy or immunotherapy, 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 lympho-histiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

**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 QVANTIG 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 QVANTIG and for 5 months after the last dose *[see Use in Specific Populations)]*.

**Increased Mortality in Patients with Multiple Myeloma when Nivolumab 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 intravenous nivolumab, 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, 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 QVANTIG as a single agent in 247 patients enrolled in CHECKMATE-67T, with additional data from intravenous nivolumab single-agent (1994 patients), and from intravenous nivolumab in combination with cabozantinib (320 patients) for select adverse reactions.

Advanced Renal Cell Carcinoma

CHECKMATE-67T was a multicenter, randomized, open-label study in adult patients with advanced or metastatic RCC. Patients received OPDIVO QVANTIG dose of 1,200 mg of nivolumab and 20,000 units of hyaluronidase subcutaneously every 4 weeks (n=247) or 3 mg/kg of nivolumab intravenously every 2 weeks (n=245). Among patients who received OPDIVO QVANTIG, 52% were exposed for 6 months or longer and 20% were exposed for greater than 1 year.

Serious adverse reactions occurred in 28% of patients who received OPDIVO QVANTIG. Serious adverse reactions in >1% of patients included pleural effusion (1.6%), pneumonitis (1.6%), hyperglycemia (1.2%), hyperkalemia (1.2%), hemorrhage (1.2%) and diarrhea (1.2%). Fatal adverse reactions occurred in 3 patients (1.2%) who received OPDIVO QVANTIG and included myocarditis, myositis, and colitis complications.

Permanent discontinuation of OPDIVO QVANTIG due to an adverse reaction occurred in 10% of patients. The most common adverse reaction which resulted in permanent discontinuation was pneumonitis (2%).

Dosage interruptions of OPDIVO QVANTIG due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage interruption in >2% of patients included COVID-19 (4.5%), increased blood creatinine (2.8%), anemia, diarrhea, and fatigue (2.4% each).

The most common adverse reactions (≥10%) were musculoskeletal pain, fatigue, pruritus, rash, hypothyroidism, diarrhea, cough, and abdominal pain.

Tables 1 and 2 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-67T.

**Table 1: Adverse Reactions* in ≥5% of Adult Patients with RCC Receiving OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) in CHECKMATE-67T**

| Adverse Reaction | OPDIVO QVANTIG (n=247) | | Intravenous Nivolumab (n=245) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **General** | | | | |
| Fatigue[a] | 20 | 2.4 | 25 | 3.3 |
| Injection site reaction[a] | 8 | 0 | 0 | 0 |
| Edema | 5 | 0.4 | 11 | 0.8 |
| **Musculoskeletal and Connective Tissue** | | | | |
| Musculoskeletal pain[a] | 31 | 1.6 | 39 | 3.3 |
| **Skin and Subcutaneous Tissue** | | | | |
| Pruritus | 16 | 0.4 | 21 | 0 |
| Rash[a] | 15 | 1.2 | 13 | 1.2 |
| **Gastrointestinal** | | | | |
| Diarrhea[a] | 11 | 0.4 | 14 | 0.4 |
| Abdominal pain[a] | 10 | 0 | 10 | 0.4 |
| Nausea | 8 | 0 | 9 | 0 |
| Constipation | 8 | 0 | 6 | 0 |
| Vomiting | 6 | 0.4 | 4.9 | 0 |
| **Respiratory, Thoracic, and Mediastinal** | | | | |
| Cough | 11 | 0 | 11 | 0 |
| **Endocrine** | | | | |
| Hypothyroidism[a] | 12 | 0 | 17 | 0 |
| **Metabolism and Nutrition** | | | | |
| Hyperglycemia | 9 | 2.4 | 13 | 2.0 |
| Decreased appetite | 9 | 0 | 11 | 0.8 |

* Toxicity was graded per NCI CTCAE v5.
[a] Includes multiple related terms.

**Table 2: Laboratory Values Worsening from Baseline[a] (≥20%) in Patients with RCC Receiving OPDIVO QVANTIG in CHECKMATE-67T**

| Laboratory Abnormality | OPDIVO QVANTIG | | Intravenous Nivolumab | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Hematology** | | | | |
| Hemoglobin decreased | 46 | 7 | 48 | 9 |
| Lymphocytes decreased | 36 | 6 | 45 | 9 |
| **Chemistry** | | | | |
| Creatinine increased | 38 | 1.3 | 43 | 0.4 |
| Sodium decreased | 34 | 2.6 | 40 | 2.5 |
| Potassium increased | 34 | 3.0 | 45 | 2.9 |
| Alkaline phosphatase increased | 32 | 2.1 | 33 | 2.0 |
| Calcium increased | 29 | 2.1 | 31 | 4.1 |
| Albumin decreased | 25 | 1.7 | 35 | 0.4 |
| ALT increased | 21 | 1.3 | 26 | 4.1 |

[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 QVANTIG group (range: 232 to 235 patients) and intravenous nivolumab group (range: 240 to 244 patients).

**Adverse Reactions in Patients Treated with Intravenous Nivolumab**

The safety of OPDIVO QVANTIG for its approved indications *[see Indications and Usage]* has been established in adequate and well-controlled clinical studies of intravenous nivolumab. Below is a description of adverse reactions in these adequate and well-controlled clinical studies.

*First-line Renal Cell Carcinoma*

*CHECKMATE-9ER*

The safety of intravenous nivolumab with cabozantinib was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received intravenous nivolumab 240 mg over 30 minutes every 2 weeks with cabozantinib 40 mg orally once daily (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320) *[see Clinical Studies (14.1) in full Prescribing Information]*. Cabozantinib could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in intravenous nivolumab and cabozantinib-treated patients. In this trial, 82% of patients in the intravenous nivolumab and cabozantinib arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving intravenous nivolumab and cabozantinib. The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either intravenous nivolumab or cabozantinib occurred in 20% of patients: 7% intravenous nivolumab only, 8% cabozantinib only, and 6% both drugs due to same adverse reaction at the same time. Adverse reaction leading to dose interruption or reduction of either intravenous nivolumab or cabozantinib occurred in 83% of patients: 3% intravenous nivolumab only, 46% cabozantinib only, and 21% both drugs due to same adverse reaction at the same time, and 6% both drugs sequentially.

The most common adverse reactions reported in ≥20% of patients treated with intravenous nivolumab and cabozantinib were diarrhea, fatigue, hepatotoxicity, palmar-plantar erythro-dysesthesia syndrome, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Tables 3 and 4 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9ER.

**Table 3: Adverse Reactions in >15% of Patients Receiving Intravenous Nivolumab and Cabozantinib - CHECKMATE-9ER**

| Adverse Reaction | Intravenous Nivolumab and Cabozantinib (n=320) | | Sunitinib (n=320) | |
|---|---|---|---|---|
| | Grades 1-4 (%) | Grades 3-4 (%) | Grades 1-4 (%) | Grades 3-4 (%) |
| **Gastrointestinal** | | | | |
| Diarrhea | 64 | 7 | 47 | 4.4 |
| Nausea | 27 | 0.6 | 31 | 0.3 |
| Abdominal pain[a] | 22 | 1.9 | 15 | 0.3 |
| Vomiting | 17 | 1.9 | 21 | 0.3 |
| Dyspepsia[b] | 15 | 0 | 22 | 0.3 |
| **General** | | | | |
| Fatigue[c] | 51 | 8 | 50 | 8 |
| **Hepatobiliary** | | | | |
| Hepatotoxicity[d] | 44 | 11 | 26 | 5 |
| **Skin and Subcutaneous Tissue** | | | | |
| Palmar-plantar erythrodysesthesia syndrome | 40 | 8 | 41 | 8 |
| Stomatitis[e] | 37 | 3.4 | 46 | 4.4 |
| Rash[f] | 36 | 3.1 | 14 | 0 |
| Pruritus | 19 | 0.3 | 4.4 | 0 |
| **Vascular** | | | | |
| Hypertension[g] | 36 | 13 | 39 | 14 |
| **Endocrine** | | | | |
| Hypothyroidism[h] | 34 | 0.3 | 30 | 0.3 |
| **Musculoskeletal and Connective Tissue** | | | | |
| Musculoskeletal pain[i] | 33 | 3.8 | 29 | 3.1 |
| Arthralgia | 18 | 0.3 | 9 | 0.3 |
| **Metabolism and Nutrition** | | | | |
| Decreased appetite | 28 | 1.9 | 20 | 1.3 |
| **Nervous System** | | | | |
| Dysgeusia | 24 | 0 | 22 | 0 |
| Headache | 16 | 0 | 12 | 0.6 |
| **Respiratory, Thoracic and Mediastinal** | | | | |
| Cough[j] | 20 | 0.3 | 17 | 0 |
| Dysphonia | 17 | 0.3 | 3.4 | 0 |
| **Infections and Infestations** | | | | |
| Upper respiratory tract infection[k] | 20 | 0.3 | 8 | 0.3 |

Toxicity was graded per NCI CTCAE v4.
[a] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.
[b] Includes gastroesophageal reflux disease.
[c] Includes asthenia.
[d] Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.
[e] Includes mucosal inflammation, aphthous ulcer, mouth ulceration.
[f] Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.
[g] Includes blood pressure increased, blood pressure systolic increased.
[h] Includes primary hypothyroidism.
[i] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.
[j] Includes productive cough.
[k] Includes nasopharyngitis, pharyngitis, rhinitis.

**Table 4: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on Intravenous Nivolumab and Cabozantinib - CHECKMATE-9ER**

| Laboratory Abnormality | Intravenous Nivolumab and Cabozantinib | | Sunitinib | |
|---|---|---|---|---|
| | Grades 1-4 (%) | Grades 3-4 (%) | Grades 1-4 (%) | Grades 3-4 (%) |
| **Chemistry** | | | | |
| Increased ALT | 79 | 9.8 | 39 | 3.5 |
| Increased AST | 77 | 7.9 | 57 | 2.6 |
| Hypophosphatemia | 69 | 28 | 48 | 10 |
| Hypocalcemia | 54 | 1.9 | 24 | 0.6 |
| Hypomagnesemia | 47 | 1.3 | 25 | 0.3 |
| Hyperglycemia | 44 | 3.5 | 44 | 1.7 |
| Hyponatremia | 43 | 11 | 36 | 12 |
| Increased lipase | 41 | 14 | 38 | 13 |
| Increased amylase | 41 | 10 | 28 | 6 |
| Increased alkaline phosphatase | 41 | 2.8 | 37 | 1.6 |
| Increased creatinine | 39 | 1.3 | 42 | 0.6 |
| Hyperkalemia | 35 | 4.7 | 27 | 1 |
| Hypoglycemia | 26 | 0.8 | 14 | 0.4 |
| **Hematology** | | | | |
| Lymphopenia | 42 | 6.6 | 45 | 10 |
| Thrombocytopenia | 41 | 0.3 | 70 | 9.7 |
| Anemia | 37 | 2.5 | 61 | 4.8 |
| Leukopenia | 37 | 0.3 | 66 | 5.1 |
| Neutropenia | 35 | 3.2 | 67 | 12 |

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab and cabozantinib group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

*Previously Treated Renal Cell Carcinoma*

*CHECKMATE-025*

The safety of intravenous nivolumab was evaluated in CHECKMATE-025, a randomized open-label trial in 803 patients with advanced RCC who had experienced disease progression during or after at least one anti-angiogenic treatment regimen received intravenous nivolumab 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks (n=406) or everolimus 10 mg daily (n=397) *[see Clinical Studies (14.1) in full Prescribing Information]*. The median duration of treatment was 5.5 months (range: 1 day to 29.6+ months) in intravenous nivolumab-treated patients and 3.7 months (range: 6 days to 25.7+ months) in everolimus-treated patients.

Rate of death on treatment or within 30 days of the last dose was 4.7% on the intravenous nivolumab arm. Serious adverse reactions occurred in 47% of patients receiving intravenous nivolumab. Study therapy was discontinued for adverse reactions in 16% of intravenous nivolumab patients. Forty-four percent (44%) of patients receiving intravenous nivolumab had a dose interruption for an adverse reaction.

The most frequent serious adverse reactions in at least 2% of patients were: acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. The most common adverse reactions (≥20%) were fatigue, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia. The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of patients include increased creatinine, lymphopenia, anemia, increased AST, increased alkaline phosphatase, hyponatremia, increased triglycerides, and hyperkalemia. In addition, among patients with TSH < ULN at baseline, a greater proportion of patients experienced a treatment-emergent elevation of TSH > ULN in the intravenous nivolumab group compared to the everolimus group (26% and 14%, respectively).

Tables 5 and 6 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-025.

**Table 5: Adverse Reactions in >15% of Patients Receiving Intravenous Nivolumab - CHECKMATE-025**

| Adverse Reaction | Intravenous Nivolumab (n=406) | | Everolimus (n=397) | |
|---|---|---|---|---|
| | Grades 1-4 (%) | Grades 3-4 (%) | Grades 1-4 (%) | Grades 3-4 (%) |
| **Adverse Reaction** | 98 | 56 | 96 | 62 |
| **General** | | | | |
| Fatigue[a] | 56 | 6 | 57 | 7 |
| Pyrexia | 17 | 0.7 | 20 | 0.8 |
| **Respiratory, Thoracic and Mediastinal** | | | | |
| Cough/productive cough | 34 | 0 | 38 | 0.5 |
| Dyspnea/exertional dyspnea | 27 | 3 | 31 | 2 |
| Upper respiratory infection[b] | 18 | 0 | 11 | 0 |
| **Gastrointestinal** | | | | |
| Nausea | 28 | 0.5 | 29 | 1 |
| Diarrhea[c] | 25 | 2.2 | 32 | 1.8 |
| Constipation | 23 | 0.5 | 18 | 0.5 |
| Vomiting | 16 | 0.5 | 16 | 0.5 |
| **Skin and Subcutaneous Tissue** | | | | |
| Rash[d] | 28 | 1.5 | 36 | 1 |
| Pruritus/generalized pruritus | 19 | 0 | 14 | 0 |
| **Metabolism and Nutrition** | | | | |
| Decreased appetite | 23 | 1.2 | 30 | 1.5 |
| **Musculoskeletal and Connective Tissue** | | | | |
| Arthralgia | 20 | 1 | 14 | 0.5 |
| Back pain | 21 | 3.4 | 16 | 2.8 |

Toxicity was graded per NCI CTCAE v4.
[a] Includes asthenia, decreased activity, fatigue, and malaise.
[b] Includes nasopharyngitis, pharyngitis, rhinitis, and viral upper respiratory infection (URI).
[c] Includes colitis, enterocolitis, and gastroenteritis.
[d] Includes dermatitis, acneiform dermatitis, erythematous rash, generalized rash, macular rash, maculopapular rash, papular rash, pruritic rash, erythema multiforme, and erythema.

**Table 6: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on Intravenous Nivolumab - CHECKMATE-025**

| Laboratory Abnormality | Intravenous Nivolumab | | Everolimus | |
|---|---|---|---|---|
| | Grades 1-4 (%) | Grades 3-4 (%) | Grades 1-4 (%) | Grades 3-4 (%) |
| **Hematology** | | | | |
| Lymphopenia | 42 | 6 | 53 | 11 |
| Anemia | 39 | 8 | 69 | 16 |
| **Chemistry** | | | | |
| Increased creatinine | 42 | 2 | 45 | 1.6 |
| Increased AST | 33 | 2.8 | 39 | 1.6 |
| Increased alkaline phosphatase | 32 | 2.3 | 32 | 0.8 |
| Hyponatremia | 32 | 7 | 26 | 6 |
| Hyperkalemia | 30 | 4 | 20 | 2.1 |
| Hypocalcemia | 23 | 0.9 | 26 | 1.3 |
| Increased ALT | 22 | 3.2 | 31 | 0.8 |
| Hypercalcemia | 19 | 3.2 | 6 | 0.3 |
| **Lipids** | | | | |
| Increased triglycerides | 32 | 1.5 | 67 | 11 |
| Increased cholesterol | 21 | 0.3 | 55 | 1.4 |

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab group (range: 259 to 401 patients) and everolimus group (range: 257 to 376 patients).

Adjuvant Treatment of Melanoma

*CHECKMATE-76K*

The safety of intravenous nivolumab as a single agent was evaluated in CHECKMATE-76K, a randomized (2:1), double-blind trial in 788 patients with completely resected Stage IIB/C melanoma who received intravenous nivolumab 480 mg by intravenous infusion over 30 minutes every 4 weeks (n=524) or placebo by intravenous infusion over 30 minutes every 4 weeks (n=264) for up to 1 year *[see Clinical Studies (14.3)]*. The median duration of exposure was 11 months in patients treated with intravenous nivolumab and 11 months in patients treated with placebo.

Serious adverse reactions occurred in 18% of patients treated with intravenous nivolumab. A fatal adverse reaction occurred in 1 (0.2%) patient (heart failure and acute kidney injury). Permanent discontinuation of intravenous nivolumab due to an adverse reaction occurred in 17% of patients. Adverse reactions which resulted in permanent discontinuation of intravenous nivolumab in >1% of patients included diarrhea (1.1%), arthralgia (1.7%), and rash (1.7%).

Dosage interruptions of intravenous nivolumab due to an adverse reaction occurred in 25% of patients. Adverse reactions which required dosage interruption in >1% of patients included COVID-19 infection, infusion related reaction, diarrhea, arthralgia, and increased ALT.

The most common adverse reactions (reported in ≥20% of patients) were fatigue, musculoskeletal pain, rash, diarrhea, and pruritus.

Tables 7 and 8 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-76K.

**Table 7: Adverse Reactions Occurring in ≥10% of Patients Treated with Intravenous Nivolumab - CHECKMATE-76K**

| Adverse Reaction | Intravenous Nivolumab (n=524) | | Placebo (n=264) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **General** | | | | |
| Fatigue[a] | 36 | 0.4 | 34 | 0.4 |
| **Musculoskeletal and Connective Tissue** | | | | |
| Musculoskeletal pain[b] | 30 | 0.4 | 26 | 0.4 |
| **Skin and Subcutaneous Tissue** | | | | |
| Rash[c] | 28 | 1.1 | 15 | 0.4 |
| Pruritus | 20 | 0.2 | 11 | 0 |
| **Gastrointestinal** | | | | |
| Diarrhea[d] | 23 | 1.3 | 16 | 0 |
| Nausea | 14 | 0 | 11 | 0 |
| **Endocrine** | | | | |
| Hypothyroidism[e] | 14 | 0 | 2.3 | 0 |
| **Nervous System** | | | | |
| Headache[f] | 12 | 0.2 | 14 | 0.8 |

Toxicity was graded per NCI CTCAE v5.

[a] Includes asthenia.

[b] Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, spinal pain, pain in extremity.

[c] Includes dermatitis, dermatitis acneiform, dyshidrotic eczema, eczema, eczema asteatotic, eyelid rash, genital rash, pemphigoid, penile rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, toxic skin eruption.

[d] Includes autoimmune colitis, colitis, diarrhea, enteritis, enterocolitis

[e] Includes autoimmune hypothyroidism, blood thyroid stimulating hormone increased.

[f] Includes cluster headache, migraine.

**Table 8: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Intravenous Nivolumab-Treated Patients - CHECKMATE-76K**

| Laboratory Abnormality | Intravenous Nivolumab (n=524) | | Placebo (n=264) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Hematology** | | | | |
| Anemia | 19 | 0 | 14 | 0 |
| Lymphopenia | 17 | 1.1 | 17 | 1.7 |
| Neutropenia | 10 | 0 | 10 | 0.4 |
| **Chemistry** | | | | |
| AST increased | 25 | 2.2 | 16 | 0.4 |
| Lipase increased | 22 | 2.9 | 21 | 2.3 |
| ALT increased | 20 | 2.1 | 15 | 0.4 |
| Amylase increased | 17 | 0.4 | 9 | 0 |
| Creatinine increased | 15 | 0.4 | 13 | 0 |
| Sodium decreased | 13 | 0.6 | 11 | 0.4 |
| Potassium increased | 13 | 1 | 15 | 1.1 |

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab group (range: 262 to 513 patients) and placebo group (range: 138 to 261 patients).

*CHECKMATE-238*

The safety of intravenous nivolumab as a single agent was evaluated in CHECKMATE-238, a randomized (1:1), double-blind trial in 905 patients with completely resected Stage IIIB/C or Stage IV melanoma received intravenous nivolumab 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=452) or ipilimumab 10 mg/kg by intravenous infusion every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year (n=453) *[see Clinical Studies (14.3)]*. The median duration of exposure was 11.5 months in intravenous nivolumab-treated patients and was 2.7 months in ipilimumab-treated patients. In this ongoing trial, 74% of patients received intravenous nivolumab for >6 months.

Serious adverse reactions occurred in 18% of intravenous nivolumab-treated patients. Study therapy was discontinued for adverse reactions in 9% of intravenous nivolumab-treated patients and 42% of ipilimumab-treated patients. Twenty-eight percent of intravenous nivolumab-treated patients had at least one omitted dose for an adverse reaction. Grade 3 or 4 adverse reactions occurred in 25% of intravenous nivolumab-treated patients.

The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of intravenous nivolumab-treated patients were diarrhea and increased lipase and amylase. The most common adverse reactions (at least 20%) were fatigue, diarrhea, rash, musculoskeletal pain, pruritus, headache, nausea, upper respiratory infection, and abdominal pain. The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%).

Tables 9 and 10 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-238.

**Table 9: Adverse Reactions Occurring in ≥10% of Intravenous Nivolumab-Treated Patients - CHECKMATE-238**

| Adverse Reaction | Intravenous Nivolumab (n=452) | | Ipilimumab 10 mg/kg (n=453) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **General** | | | | |
| Fatigue[a] | 57 | 0.9 | 55 | 2.4 |
| **Gastrointestinal** | | | | |
| Diarrhea | 37 | 2.4 | 55 | 11 |
| Nausea | 23 | 0.2 | 28 | 0 |
| Abdominal pain[b] | 21 | 0.2 | 23 | 0.9 |
| Constipation | 10 | 0 | 9 | 0 |
| **Skin and Subcutaneous Tissue** | | | | |
| Rash[c] | 35 | 1.1 | 47 | 5.3 |
| Pruritus | 28 | 0 | 37 | 1.1 |
| **Musculoskeletal and Connective Tissue** | | | | |
| Musculoskeletal pain[d] | 32 | 0.4 | 27 | 0.4 |
| Arthralgia | 19 | 0.4 | 13 | 0.4 |
| **Nervous System** | | | | |
| Headache | 23 | 0.4 | 31 | 2.0 |
| Dizziness[e] | 11 | 0 | 8 | 0 |
| **Infections** | | | | |
| Upper respiratory tract infection[f] | 22 | 0 | 15 | 0.2 |
| **Respiratory, Thoracic and Mediastinal** | | | | |
| Cough/productive cough | 19 | 0 | 19 | 0 |
| Dyspnea/exertional dyspnea | 10 | 0.4 | 10 | 0.2 |
| **Endocrine** | | | | |
| Hypothyroidism[g] | 12 | 0.2 | 7.5 | 0.4 |

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness.

[c] Includes dermatitis described as acneiform, allergic, bullous, or exfoliative and rash described as generalized, erythematous, macular, papular, maculopapular, pruritic, pustular, vesicular, or butterfly, and drug eruption.

[d] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, spinal pain, and pain in extremity.

[e] Includes postural dizziness and vertigo.

[f] Includes upper respiratory tract infection including viral respiratory tract infection, lower respiratory tract infection, rhinitis, pharyngitis, and nasopharyngitis.

[g] Includes secondary hypothyroidism and autoimmune hypothyroidism.

**Table 10: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Intravenous Nivolumab-Treated Patients - CHECKMATE-238**

| Laboratory Abnormality | Intravenous Nivolumab | | Ipilimumab 10 mg/kg | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Hematology** | | | | |
| Lymphopenia | 27 | 0.4 | 12 | 0.9 |
| Anemia | 26 | 0 | 34 | 0.5 |
| Leukopenia | 14 | 0 | 2.7 | 0.2 |
| Neutropenia | 13 | 0 | 6 | 0.5 |
| **Chemistry** | | | | |
| Increased Lipase | 25 | 7 | 23 | 9 |
| Increased ALT | 25 | 1.8 | 40 | 12 |
| Increased AST | 24 | 1.3 | 33 | 9 |
| Increased Amylase | 17 | 3.3 | 13 | 3.1 |
| Hyponatremia | 16 | 1.1 | 22 | 3.2 |
| Hyperkalemia | 12 | 0.2 | 9 | 0.5 |
| Increased Creatinine | 12 | 0 | 13 | 0 |
| Hypocalcemia | 10 | 0.7 | 16 | 0.5 |

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab group (range: 400 to 447 patients) and ipilimumab 10 mg/kg group (range: 392 to 443 patients).

Non-Small Cell Lung Cancer

*Neoadjuvant and Adjuvant Treatment of Resectable (Tumors ≥4 cm or Node Positive) Non-Small Cell Lung Cancer*

*CHECKMATE-77T*

The safety of intravenous nivolumab in combination with neoadjuvant platinum-doublet chemotherapy followed by surgery and continued adjuvant treatment with intravenous nivolumab as a single agent after surgery was evaluated in CHECKMATE-77T, a randomized, double-blind, multicenter trial in patients with previously untreated resectable Stage IIA (>4 cm) to IIIB (T3N2 or T4N2) NSCLC (per the AJCC Cancer Staging Manual 8th Edition) *[see Clinical Studies (14.5)]*. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. The median duration of exposure to intravenous nivolumab was 10.3 months (range: 1 day to 22.3 months).

The study population characteristics were: median age 66 years (range: 35 - 86); 71% male; 72% White, 25% Asian, 1.7% Black/African American, and 1.5% other race; and 6% Hispanic or Latino.

Adverse reactions occurring in patients with resectable NSCLC receiving intravenous nivolumab in combination with platinum-doublet chemotherapy, given as neoadjuvant treatment and followed as a single agent adjuvant treatment after surgery, were generally similar to those occurring in patients in other clinical trials across tumor types receiving intravenous nivolumab in combination with chemotherapy.

*Neoadjuvant Phase of CHECKMATE-77T*

A total of 228 patients received at least 1 dose of intravenous nivolumab in combination with platinum-doublet chemotherapy as neoadjuvant treatment and 230 patients received at least 1 dose of placebo in combination with platinum-doublet chemotherapy as neoadjuvant treatment.

Serious adverse reactions occurred in 21% of patients who received intravenous nivolumab in combination with platinum-doublet chemotherapy as neoadjuvant treatment; the most frequent (≥2%) serious adverse reactions was pneumonia. Fatal adverse reactions occurred in 2.2% of patients, due to cerebrovascular accident, COVID-19 infection, hemoptysis, pneumonia, and pneumonitis (0.4% each).

Permanent discontinuation of any study drug due to an adverse reaction occurred in 13% of patients who received intravenous nivolumab in combination with platinum-doublet chemotherapy as neoadjuvant treatment; the most frequent (≥1%) adverse reaction that led to permanent discontinuation of any study drug was peripheral sensory neuropathy (2.2%).

Of the 228 intravenous nivolumab-treated patients and 230 placebo-treated patients who received neoadjuvant treatment, 5.3% (n=12) and 3.5% (n=8), respectively, did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery in intravenous nivolumab-treated patients were cerebrovascular accident, pneumonia, and colitis/diarrhea (2 patients each) and acute coronary syndrome, myocarditis, hemoptysis, pneumonitis, COVID-19, and myositis (1 patient each).

Of the 178 intravenous nivolumab-treated patients who received surgery, 4.5% (n=8) experienced delay of surgery (surgery more than 6 weeks from last neoadjuvant treatment) due to adverse reactions. Of the 178 placebo-treated patients who received surgery, 3.9% (n=7) experienced delay of surgery due to adverse reactions.

Of the 178 intravenous nivolumab-treated patients who received surgery, 7% (n=13) did not receive adjuvant treatment due to adverse reactions. Of the 178 placebo-treated patients who received surgery, 2.8% (n=5) did not receive adjuvant treatment due to adverse reactions.

*Adjuvant Phase of CHECKMATE-77T*

A total of 142 patients in the intravenous nivolumab arm and 152 patients in the placebo arm received at least 1 dose of adjuvant treatment.

Of the patients who received single agent intravenous nivolumab as adjuvant treatment, 22% experienced serious adverse reactions; the most frequent serious adverse reaction was pneumonitis/ILD (2.8%). One fatal adverse reaction due to COVID-19 occurred. Permanent discontinuation of adjuvant intravenous nivolumab due to an adverse reaction occurred in 14% of patients; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of adjuvant intravenous nivolumab were pneumonitis (4.2%) and diarrhea (1.4%).

*Second-line Treatment of Metastatic NSCLC*

*CHECKMATE-017 and CHECKMATE-057*

The safety of intravenous nivolumab was evaluated in CHECKMATE-017, a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen and in CHECKMATE-057, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.6)]*. These trials excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. Patients received intravenous nivolumab 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks or docetaxel 75 mg/m$^2$ intravenously every 3 weeks. The median duration of therapy in intravenous nivolumab-treated patients in CHECKMATE-017 was 3.3 months (range: 1 day to 21.7+ months) and in CHECKMATE-057 was 2.6 months (range: 0 to 24.0+ months). In CHECKMATE-017, 36% of patients received intravenous nivolumab for at least 6 months and 18% of patients received intravenous nivolumab for at least 1 year and in CHECKMATE-057, 30% of patients received intravenous nivolumab for >6 months and 20% of patients received intravenous nivolumab for >1 year.

Across both trials, the median age of intravenous nivolumab-treated patients was 61 years (range: 37 to 85); 38% were ≥65 years of age, 61% were male, and 91% were White. Ten percent of patients had brain metastases and ECOG performance status was 0 (26%) or 1 (74%).

In CHECKMATE-057, in the intravenous nivolumab arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis. Serious adverse reactions occurred in 46% of patients receiving intravenous nivolumab. Intravenous nivolumab was discontinued in 11% of patients and was delayed in 28% of patients for an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients receiving intravenous nivolumab were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. Across both trials, the most common adverse reactions (≥20%) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

Tables 11 and 12 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-057.

**Table 11: Adverse Reactions Occurring in ≥10% of Intravenous Nivolumab-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-017 and CHECKMATE-057**

| Adverse Reaction | Intravenous Nivolumab (n=418) | | Docetaxel (n=397) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Respiratory, Thoracic and Mediastinal** | | | | |
| Cough | 31 | 0.7 | 24 | 0 |
| **Metabolism and Nutrition** | | | | |
| Decreased appetite | 28 | 1.4 | 23 | 1.5 |
| **Skin and Subcutaneous Tissue** | | | | |
| Pruritus | 10 | 0.2 | 2 | 0 |

Toxicity was graded per NCI CTCAE v4.

**Table 12: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Intravenous Nivolumab-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-017 and CHECKMATE-057**

| Laboratory Abnormality | Intravenous Nivolumab | | Docetaxel | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Chemistry** | | | | |
| Hyponatremia | 35 | 7 | 34 | 4.9 |
| Increased AST | 27 | 1.9 | 13 | 0.8 |
| Increased alkaline phosphatase | 26 | 0.7 | 18 | 0.8 |
| Increased ALT | 22 | 1.7 | 17 | 0.5 |
| Increased creatinine | 18 | 0 | 12 | 0.5 |
| Increased TSH[b] | 14 | N/A | 6 | N/A |

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab group (range: 405 to 417 patients) and docetaxel group (range: 372 to 390 patients), except for TSH: intravenous nivolumab group n=314 and docetaxel group n=297.

[b] Not graded per NCI CTCAE v4.

Squamous Cell Carcinoma of the Head and Neck

*CHECKMATE-141*

The safety of intravenous nivolumab was evaluated in CHECKMATE-141, a randomized, active-controlled, open-label, multicenter trial in patients with recurrent or metastatic SCCHN with progression during or within 6 months of receiving prior platinum-based therapy *[see Clinical Studies (14.7)]*. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma). Patients received intravenous nivolumab 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=236) or investigator's choice of either cetuximab (400 mg/m$^2$ initial dose intravenously followed by 250 mg/m$^2$ weekly), or methotrexate (40 to 60 mg/m$^2$ intravenously weekly), or docetaxel (30 to 40 mg/m$^2$ intravenously weekly). The median duration of exposure to nivolumab was 1.9 months (range: 1 day to 16.1+ months) in intravenous nivolumab-treated patients. In this trial, 18% of patients received intravenous nivolumab for >6 months and 2.5% of patients received intravenous nivolumab for >1 year.

The median age of all randomized patients was 60 years (range: 28 to 83); 28% of patients in the intravenous nivolumab group were ≥65 years of age and 37% in the comparator group were ≥65 years of age, 83% were male and 83% were White, 12% were Asian, and 4% were Black. Baseline ECOG performance status was 0 (20%) or 1 (78%), 45% of patients received only one prior line of systemic therapy, the remaining 55% of patients had two or more prior lines of therapy, and 90% had prior radiation therapy.

Serious adverse reactions occurred in 49% of patients receiving intravenous nivolumab. Intravenous nivolumab was discontinued in 14% of patients and was delayed in 24% of patients for an adverse reaction. Adverse reactions and laboratory abnormalities occurring in patients with SCCHN were generally similar to those occurring in patients with melanoma and NSCLC.

The most frequent serious adverse reactions reported in ≥2% of patients receiving intravenous nivolumab were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. The most common adverse reactions occurring in ≥10% of intravenous nivolumab-treated patients and at a higher incidence than investigator's choice were cough and dyspnea. The most common laboratory abnormalities occurring in ≥10% of intravenous nivolumab-treated patients and at a higher incidence than investigator's choice were increased alkaline phosphatase, increased amylase, hypercalcemia, hyperkalemia, and increased TSH.

Urothelial Carcinoma

*Adjuvant Treatment of Urothelial Carcinoma (UC)*

*CHECKMATE-274*

The safety of intravenous nivolumab was evaluated in CHECKMATE-274, a randomized, double-blind, multicenter trial of adjuvant intravenous nivolumab versus placebo in adult patients who had undergone radical resection of UC originating in the bladder or upper urinary tract (renal pelvis or ureter) and were at high risk of recurrence *[see Clinical Studies (14.8)]*. Patients received intravenous nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=351) or placebo (n=348) until recurrence or unacceptable toxicity for a maximum of 1 year. The median duration of intravenous nivolumab treatment was 8.8 months (range: 0 to 12.5).

Serious adverse reactions occurred in 30% of intravenous nivolumab patients. The most frequent serious adverse reaction reported in ≥2% of patients was urinary tract infection. Fatal adverse reactions occurred in 1% of patients; these included events of pneumonitis (0.6%). Intravenous nivolumab was discontinued for adverse reactions in 18% of patients. Intravenous nivolumab was delayed for adverse reaction in 33% of patients.

The most common adverse reactions (reported in ≥20% of patients) were rash, fatigue, diarrhea, pruritus, musculoskeletal pain, and urinary tract infection.

Tables 13 and 14 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-274.

**Table 13: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-274**

| Adverse Reaction | Intravenous Nivolumab (n=351) | | Placebo (n=348) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Skin and Subcutaneous Tissue** | | | | |
| Rash[a] | 36 | 1.7 | 19 | 0.3 |
| Pruritus | 30 | 0 | 16 | 0 |
| **General** | | | | |
| Fatigue/Asthenia | 36 | 1.1 | 32 | 0.3 |
| Pyrexia | 10 | 0.3 | 10 | 0.3 |
| **Gastrointestinal** | | | | |
| Diarrhea[b] | 30 | 2.8 | 27 | 1.7 |
| Nausea | 16 | 0.6 | 13 | 0 |
| Abdominal pain[c] | 15 | 0.9 | 15 | 0.6 |
| Constipation | 13 | 0.3 | 15 | 0.3 |
| **Musculoskeletal and Connective Tissue** | | | | |
| Musculoskeletal pain[d] | 28 | 0.6 | 24 | 0.9 |
| Arthralgia | 11 | 0.3 | 13 | 0 |
| **Infections** | | | | |
| Urinary tract infection[e] | 22 | 6 | 23 | 9 |
| Upper respiratory tract infection[f] | 16 | 0.3 | 16 | 0.6 |
| **Endocrine** | | | | |
| Hyperthyroidism | 11 | 0 | 1.1 | 0 |
| Hypothyroidism | 11 | 0 | 2.3 | 0 |
| **Renal and Urinary Disorders** | | | | |
| Renal dysfunction[g] | 17 | 1.7 | 16 | 0.9 |
| **Respiratory, Thoracic and Mediastinal** | | | | |
| Cough[h] | 14 | 0 | 11 | 0 |
| Dyspnea[i] | 11 | 0.3 | 6 | 0.3 |
| **Metabolism and Nutrition** | | | | |
| Decreased appetite | 13 | 0.9 | 7 | 0.3 |
| **Nervous System Disorders** | | | | |
| Dizziness[j] | 11 | 0.3 | 9 | 0 |
| **Hepatobiliary** | | | | |
| Hepatitis[k] | 11 | 4 | 8 | 0.6 |

Toxicity was graded per NCI CTCAE v4.

[a] Includes acne, blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis contact, eczema, eczema asteatotic, eczema nummular, erythema, erythema multiforme, lichen sclerosus, lichenoid keratosis, pemphigoid, photosensitivity reaction, pigmentation disorder, psoriasis, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rosacea, skin exfoliation, skin lesion, skin reaction, toxic skin eruption, and urticaria.

[b] Includes colitis, colitis microscopic, diarrhea, duodenitis, enteritis, immune-mediated enterocolitis.

[c] Includes abdominal pain, abdominal discomfort, abdominal tenderness, lower and upper abdominal pain.

[d] Includes musculoskeletal pain, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain.

[e] Includes cystitis, escherichia urinary tract infection, pyelonephritis, pyelonephritis acute, pyelonephritis chronic, urethritis, urinary tract infection, urinary tract infection bacterial, urinary tract infection staphylococcal, and urosepsis.

[f] Includes upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis.

[g] Includes acute kidney injury, autoimmune nephritis, blood creatinine increased, glomerular filtration rate decreased, immune-mediated nephritis, nephritis, renal failure, and renal impairment.

[h] Includes cough, productive cough, and upper-airway cough syndrome.

[i] Includes dyspnea and exertional dyspnea.

[j] Includes dizziness, postural dizziness and vertigo.

[k] Includes aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, cholangitis, drug-induced liver injury, hepatic failure, hepatic function abnormal, hepatitis, hepatocellular injury, hyperbilirubinemia, gamma-glutamyl transferase increased, liver injury, and transaminases increased.

**Table 14: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-274**

| Laboratory Abnormality | Intravenous Nivolumab (n=351) | | Placebo (n=348) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Chemistry** | | | | |
| Increased creatinine | 36 | 1.7 | 36 | 2.6 |
| Increased amylase | 34 | 8 | 23 | 3.2 |
| Increased lipase | 33 | 12 | 31 | 10 |
| Hyperkalemia | 32 | 5 | 30 | 6 |
| Increased alkaline phosphatase | 24 | 2.3 | 15 | 0.6 |
| Increased AST | 24 | 3.5 | 16 | 0.9 |
| Increased ALT | 23 | 2.9 | 15 | 0.6 |
| Hyponatremia | 22 | 4.1 | 17 | 1.8 |
| Hypocalcemia | 17 | 1.2 | 11 | 0.9 |
| Hypomagnesemia | 16 | 0 | 9 | 0 |
| Hypercalcemia | 12 | 0.3 | 8 | 0.3 |
| **Hematology** | | | | |
| Lymphopenia | 33 | 2.9 | 27 | 1.5 |
| Anemia | 30 | 1.4 | 28 | 0.9 |
| Neutropenia | 11 | 0.6 | 10 | 0.3 |

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab group (range: 322 to 348 patients) and placebo group (range: 312 to 341 patients).

*First-line Treatment of Unresectable or Metastatic UC*

*CHECKMATE-901*

The safety of intravenous nivolumab was evaluated in CHECKMATE-901, a randomized, open-label trial in cisplatin-eligible patients with unresectable or metastatic UC *[see Clinical Studies (14.8)]*. Patients received either intravenous nivolumab 360 mg with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by single-agent intravenous nivolumab 480 mg every 4 weeks up to 2 years (n=304), or cisplatin and gemcitabine chemotherapy every 3 weeks for up to 6 cycles (n=288). Patients discontinuing cisplatin alone were permitted to switch to carboplatin.

Among patients who received intravenous nivolumab with chemotherapy, the median duration of intravenous nivolumab exposure was 7.4 months (range: 0.03 to 47.9 months). Serious adverse reactions occurred in 48% of patients receiving intravenous nivolumab in combination with chemotherapy. The most frequent serious adverse reactions reported in ≥2% of patients who received intravenous nivolumab with chemotherapy were urinary tract infection (4.9%), acute kidney injury (4.3%), anemia (3%), pulmonary embolism (2.6%), sepsis (2.3%), and platelet count decreased (2.3%). The most common adverse reactions (reported in ≥20% of patients) were nausea, fatigue, musculoskeletal pain, constipation, decreased appetite, rash, vomiting, and peripheral neuropathy.

Fatal adverse reactions occurred in 3.6% of patients who received intravenous nivolumab in combination with chemotherapy; these included sepsis (1%).

Intravenous nivolumab and/or chemotherapy were discontinued in 30% of patients and were delayed in 67% of patients for an adverse reaction.

Tables 15 and 16 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-901.

**Table 15: Adverse Reactions Occurring in ≥10% of Treated Patients - CHECKMATE-901**

| Adverse Reaction | Intravenous Nivolumab and Platinum-Doublet Chemotherapy (n=304) | | Platinum-Doublet Chemotherapy (n=288) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Gastrointestinal disorders** | | | | |
| Nausea | 52 | 0.3 | 53 | 1 |
| Constipation | 30 | 0 | 28 | 0.7 |
| Vomiting | 23 | 1.3 | 19 | 2.1 |
| Diarrhea[a] | 19 | 2 | 14 | 0 |
| Abdominal pain[b] | 14 | 0.3 | 9 | 0.3 |
| **General** | | | | |
| Fatigue[c] | 48 | 3.9 | 43 | 4.2 |
| Edema[d] | 18 | 0 | 9 | 0.3 |
| Pyrexia[e] | 14 | 1 | 14 | 0 |
| **Musculoskeletal and Connective Tissue** | | | | |
| Musculoskeletal pain[f] | 33 | 3 | 21 | 0.3 |
| **Metabolism and Nutrition** | | | | |
| Decreased appetite | 30 | 1.6 | 19 | 1 |
| **Skin and Subcutaneous Tissue** | | | | |
| Rash[g] | 25 | 2.3 | 7 | 0.3 |
| Pruritus | 17 | 0.7 | 3.5 | 0 |
| **Nervous System Disorders** | | | | |
| Peripheral neuropathy[h] | 20 | 0.7 | 14 | 0 |
| Headache[i] | 11 | 0 | 5 | 0 |
| **Infections** | | | | |
| Urinary tract infection[j] | 19 | 8 | 18 | 8 |
| **Endocrine disorders** | | | | |
| Hypothyroidism[k] | 17 | 0 | 0.3 | 0 |
| **Renal and Urinary Disorders** | | | | |
| Renal dysfunction[l] | 14 | 6 | 11 | 1.7 |
| Hematuria | 11 | 1 | 7 | 1.4 |
| **Investigations** | | | | |
| Weight decreased | 11 | 0.3 | 6 | 0 |

Toxicity was graded per NCI CTCAE v4.

[a] Includes colitis, immune-mediated enterocolitis.

[b] Includes upper abdominal pain, lower abdominal pain, abdominal discomfort, epigastric discomfort, gastrointestinal pain, and hepatic pain.

[c] Includes asthenia.

[d] Includes peripheral edema, swelling, peripheral swelling, localized edema, swelling, face edema, testicular edema, gravitational edema, and edema genital.

[e] Includes hyperthermia, body temperature increased and hyperpyrexia.

[f] Includes back pain, arthralgia, bone pain, arthritis, musculoskeletal chest pain, non-cardiac chest pain, myalgia, neck pain, pain in extremity, and spinal pain.

[g] Includes maculopapular rash, erythematous rash, macular rash, papular rash, pustular rash, acneiform dermatitis, dermatitis, allergic dermatitis, atopic dermatitis, exfoliative rash, eczema asteatotic, erythema multiforme, palmar-plantar erythrodysesthesia syndrome, eczema, dermatitis exfoliative generalized, and skin exfoliation.

[h] Includes paresthesia, peripheral sensory neuropathy, hypoesthesia, dysesthesia, neuralgia, hyperesthesia, peripheral motor neuropathy, polyneuropathy.

*(Continued)*

**Table 15: Adverse Reactions Occurring in ≥10% of Treated Patients - CHECKMATE-901**
*(Continued)*

[i] Includes occipital neuralgia.

[j] Includes urosepsis, cystitis, pyelonephritis, pyelonephritis acute, urinary tract infection enterococcal, escherichia urinary tract infection.

[k] Includes blood stimulating hormone increased.

[l] Includes acute kidney injury, renal failure, renal impairment, glomerular filtration rate decreased, anuria, azotemia.

**Table 16: Selected Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥20% of Patients - CHECKMATE-901**

| Laboratory Abnormality | Intravenous Nivolumab and Platinum-Doublet Chemotherapy (n=304) | | Platinum-Doublet Chemotherapy (n=288) | |
|---|---|---|---|---|
| | Grades 1-4 (%) | Grades 3-4 (%) | Grades 1-4 (%) | Grades 3-4 (%) |
| **Hematology** | | | | |
| Anemia | 88 | 21 | 80 | 21 |
| Neutropenia | 82 | 35 | 76 | 28 |
| Lymphopenia | 71 | 17 | 56 | 13 |
| Thrombocytopenia | 60 | 13 | 51 | 8 |
| **Chemistry** | | | | |
| Increased creatinine | 53 | 2.4 | 42 | 1.1 |
| Hypomagnesemia | 48 | 3.8 | 39 | 1.5 |
| Hyponatremia | 43 | 13 | 39 | 8 |
| Hyperglycemia | 41 | 3.9 | 37 | 3.2 |
| Hypocalcemia | 36 | 2.1 | 24 | 1.1 |
| Hyperkalemia | 33 | 3.0 | 32 | 1.1 |
| Increased amylase | 32 | 4.2 | 23 | 3.6 |
| Increased AST | 31 | 2.4 | 17 | 0.7 |
| Increased ALT | 29 | 2.4 | 19 | 0.7 |

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab group (range: 289-301 patients) and chemotherapy group (range: 265-281 patients).

*Previously Treated Advanced or Metastatic UC*

*CHECKMATE-275*

The safety of intravenous nivolumab was evaluated in CHECKMATE-275, a single arm trial in which 270 patients with locally advanced or metastatic UC had disease progression during or following platinum-containing chemotherapy or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *[see Clinical Studies (14.8)]*. Patients received intravenous nivolumab 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 3.3 months (range: 0 to 13.4+). Forty-six percent (46%) of patients had a dose interruption for an adverse reaction.

Fourteen patients (5.2%) died from causes other than disease progression. This includes 4 patients (1.5%) who died from pneumonitis or cardiovascular failure which was attributed to treatment with intravenous nivolumab. Serious adverse reactions occurred in 54% of patients. Intravenous nivolumab was discontinued for adverse reactions in 17% of patients.

The most frequent serious adverse reactions reported in ≥2% of patients were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. The most common adverse reactions (reported in ≥20% of patients) were fatigue, musculoskeletal pain, nausea, and decreased appetite.

Tables 17 and 18 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-275.

**Table 17: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275**

| Adverse Reaction | Intravenous Nivolumab (n=270) | |
|---|---|---|
| | All Grades (%) | Grades 3-4 (%) |
| **Adverse Reaction** | 99 | 51 |
| **General** | | |
| Asthenia/fatigue/malaise | 46 | 7 |
| Pyrexia/tumor associated fever | 17 | 0.4 |
| Edema/peripheral edema/peripheral swelling | 13 | 0.4 |
| **Musculoskeletal and Connective Tissue** | | |
| Musculoskeletal pain[a] | 30 | 2.6 |
| Arthralgia | 10 | 0.7 |
| **Metabolism and Nutrition** | | |
| Decreased appetite | 22 | 2.2 |
| **Gastrointestinal** | | |
| Nausea | 22 | 0.7 |
| Diarrhea | 17 | 2.6 |
| Constipation | 16 | 0.4 |
| Abdominal pain[b] | 13 | 1.5 |
| Vomiting | 12 | 1.9 |
| **Respiratory, Thoracic and Mediastinal** | | |
| Cough/productive cough | 18 | 0 |
| Dyspnea/exertional dyspnea | 14 | 3.3 |
| **Infections** | | |
| Urinary tract infection/escherichia/fungal urinary tract infection | 17 | 7 |
| **Skin and Subcutaneous Tissue** | | |
| Rash[c] | 16 | 1.5 |
| Pruritus | 12 | 0 |
| **Endocrine** | | |
| Thyroid disorders[d] | 15 | 0 |

Toxicity was graded per NCI CTCAE v4.

[a] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain.

[b] Includes abdominal discomfort, lower and upper abdominal pain.

[c] Includes dermatitis, dermatitis acneiform, dermatitis bullous, and rash described as generalized, macular, maculopapular, or pruritic.

[d] Includes autoimmune thyroiditis, blood TSH decrease, blood TSH increase, hyperthyroidism, hypothyroidism, thyroiditis, thyroxine decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine free increased, tri-iodothyronine increased.

**Table 18: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients - CHECKMATE-275**

| Laboratory Abnormality | Intravenous Nivolumab[a] | |
|---|---|---|
| | All Grades (%) | Grades 3-4 (%) |
| **Chemistry** | | |
| Hyperglycemia | 42 | 2.4 |
| Hyponatremia | 41 | 11 |
| Increased creatinine | 39 | 2 |
| Increased alkaline phosphatase | 33 | 5.5 |
| Hypocalcemia | 26 | 0.8 |
| Increased AST | 24 | 3.5 |
| Increased lipase | 20 | 7 |
| Hyperkalemia | 19 | 1.2 |
| Increased ALT | 18 | 1.2 |
| Increased amylase | 18 | 4.4 |
| Hypomagnesemia | 16 | 0 |
| **Hematology** | | |
| Lymphopenia | 42 | 9 |
| Anemia | 40 | 7 |
| Thrombocytopenia | 15 | 2.4 |
| Leukopenia | 11 | 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: range: 84 to 256 patients.

Esophageal Cancer

*Adjuvant Treatment of Resected Esophageal or Gastroesophageal Junction Cancer*

*CHECKMATE-577*

The safety of intravenous nivolumab was evaluated in CHECKMATE-577, a randomized, placebo-controlled, double-blinded, multicenter trial in 792 treated patients with completely resected (negative margins) esophageal or gastroesophageal junction cancer who had residual pathologic disease following chemoradiotherapy (CRT) *[see Clinical Studies (14.11)]*. The trial excluded patients who did not receive concurrent CRT prior to surgery, had stage IV resectable disease, autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications. Patients received either intravenous nivolumab 240 mg or placebo by intravenous infusion over 30 minutes every 2 weeks for 16 weeks followed by 480 mg or placebo by intravenous infusion over 30 minutes every 4 weeks beginning at week 17. Patients were treated until disease recurrence, unacceptable toxicity, or for up to 1-year total duration. The median duration of exposure was 10.1 months (range: <0.1 to 14 months) in intravenous nivolumab-treated patients and 9 months (range: <0.1 to 15 months) in placebo-treated patients. Among patients who received intravenous nivolumab, 61% were exposed for >6 months and 54% were exposed for >9 months.

Serious adverse reactions occurred in 33% of patients receiving intravenous nivolumab. A serious adverse reaction reported in ≥2% of patients who received intravenous nivolumab was pneumonitis. A fatal adverse reaction of myocardial infarction occurred in one patient who received intravenous nivolumab.

Intravenous nivolumab was discontinued in 12% of patients and was delayed in 28% of patients for an adverse reaction.

Tables 19 and 20 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-577.

**Table 19: Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Nivolumab - CHECKMATE-577**

| Adverse Reaction | Intravenous Nivolumab (n=532) | | Placebo (n=260) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Adverse Reaction** | 96 | 34 | 93 | 32 |
| **Gastrointestinal** | | | | |
| Diarrhea | 29 | 0.9 | 29 | 0.8 |
| Nausea | 23 | 0.8 | 21 | 0 |
| Abdominal Pain[a] | 17 | 0.8 | 20 | 1.5 |
| Vomiting | 15 | 0.6 | 16 | 1.2 |
| Dysphagia | 13 | 0.8 | 17 | 3.5 |
| Dyspepsia[b] | 12 | 0.2 | 16 | 0.4 |
| Constipation | 11 | 0 | 12 | 0 |
| **General** | | | | |
| Fatigue[c] | 34 | 1.3 | 29 | 1.5 |
| **Respiratory, Thoracic and Mediastinal** | | | | |
| Cough[d] | 20 | 0.2 | 21 | 0.4 |
| Dyspnea[e] | 12 | 0.8 | 12 | 0.4 |
| **Skin and Subcutaneous Tissue** | | | | |
| Rash[f] | 21 | 0.9 | 10 | 0.4 |
| Pruritus | 13 | 0.4 | 6 | 0 |
| **Investigations** | | | | |
| Weight decreased | 13 | 0.4 | 9 | 0 |
| **Musculoskeletal and Connective Tissue** | | | | |
| Musculoskeletal pain[g] | 21 | 0.6 | 20 | 0.8 |
| Arthralgia | 10 | 0.2 | 8 | 0 |
| **Metabolism and Nutrition** | | | | |
| Decreased appetite | 15 | 0.9 | 10 | 0.8 |
| **Endocrine** | | | | |
| Hypothyroidism | 11 | 0 | 1.5 | 0 |

[a] Includes upper abdominal pain, lower abdominal pain, and abdominal discomfort.
[b] Includes gastroesophageal reflux.
[c] Includes asthenia.
[d] Includes productive cough.
[e] Includes dyspnea exertional.
[f] Includes rash pustular, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, exfoliative rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic.
[g] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, spinal pain.

**Table 20: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-577**

| Laboratory Abnormality | Intravenous Nivolumab (n=532) | | Placebo (n=260) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Chemistry** | | | | |
| Increased AST | 27 | 2.1 | 22 | 0.8 |
| Increased alkaline phosphatase | 25 | 0.8 | 18 | 0.8 |
| Increased albumin | 21 | 0.2 | 18 | 0 |
| Increased ALT | 20 | 1.9 | 16 | 1.2 |
| Increased amylase | 20 | 3.9 | 13 | 1.3 |
| Hyponatremia | 19 | 1.7 | 12 | 1.2 |
| Hyperkalemia | 17 | 0.8 | 15 | 1.6 |
| Hypokalemia | 12 | 1 | 11 | 1.2 |
| Transaminases increased[b] | 11 | 1.5 | 6 | 1.2 |
| **Hematology** | | | | |
| Lymphopenia | 44 | 17 | 35 | 12 |
| Anemia | 27 | 0.8 | 21 | 0.4 |
| Neutropenia | 24 | 1.5 | 23 | 0.4 |

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab group (range: 163 to 526 patients) and Placebo group (range: 86 to 256 patients).
[b] Includes alanine aminotransferase increased, aspartate aminotransferase increased.

*Previously-Treated Unresectable Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)*

*ATTRACTION-3*

The safety of intravenous nivolumab was evaluated in ATTRACTION-3, a randomized, active-controlled, open-label, multicenter trial in 209 patients with unresectable advanced, recurrent or metastatic ESCC refractory or intolerant to at least one fluoropyrimidine- and platinum-based chemotherapy *[see Clinical Studies (14.11)]*. The trial excluded patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had autoimmune disease, used systemic corticosteroids or immunosuppressants, had apparent tumor invasion of organs adjacent to the esophageal tumor or had stents in the esophagus or respiratory tract. Patients received intravenous nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=209) or investigator's choice: docetaxel 75 mg/m$^2$ intravenously every 3 weeks (n=65) or paclitaxel 100 mg/m$^2$ intravenously once a week for 6 weeks followed by 1 week off (n=143). Patients were treated until disease progression or unacceptable toxicity. The median duration of exposure was 2.6 months (range: 0 to 29.2 months) in intravenous nivolumab-treated patients and 2.6 months (range: 0 to 21.4 months) in docetaxel- or paclitaxel-treated patients. Among patients who received intravenous nivolumab, 26% were exposed for >6 months and 10% were exposed for >1 year.

Serious adverse reactions occurred in 38% of patients receiving intravenous nivolumab. Serious adverse reactions reported in ≥2% of patients who received intravenous nivolumab were pneumonia, esophageal fistula, interstitial lung disease and pyrexia. The following fatal adverse reactions occurred in patients who received intravenous nivolumab: interstitial lung disease or pneumonitis (1.4%), pneumonia (1.0%), septic shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death (0.5%).

Intravenous nivolumab was discontinued in 13% of patients and was delayed in 27% of patients for an adverse reaction.

Tables 21 and 22 summarize the adverse reactions and laboratory abnormalities, respectively, in ATTRACTION-3.

**Table 21: Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Nivolumab - ATTRACTION-3**

| Adverse Reaction | Intravenous Nivolumab (n=209) | | Docetaxel or Paclitaxel (n=208) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Skin and Subcutaneous Tissue** | | | | |
| Rash[a] | 22 | 1.9 | 28 | 1 |
| Pruritus | 12 | 0 | 7 | 0 |
| **Metabolism and Nutrition** | | | | |
| Decreased appetite[b] | 21 | 1.9 | 35 | 5 |
| **Gastrointestinal** | | | | |
| Diarrhea[c] | 18 | 1.9 | 17 | 1.4 |
| Constipation | 17 | 0 | 19 | 0 |
| Nausea | 11 | 0 | 20 | 0.5 |
| **Musculoskeletal and Connective Tissue** | | | | |
| Musculoskeletal pain[d] | 17 | 0 | 26 | 1.4 |
| **Infections** | | | | |
| Upper respiratory tract infection[e] | 17 | 1 | 14 | 0 |
| Pneumonia[f] | 13 | 5 | 19 | 9 |
| **Respiratory, Thoracic and Mediastinal** | | | | |
| Cough[g] | 16 | 0 | 14 | 0.5 |
| **General** | | | | |
| Pyrexia[h] | 16 | 0.5 | 19 | 0.5 |
| Fatigue[i] | 12 | 1.4 | 27 | 4.8 |
| **Blood and Lymphatic System** | | | | |
| Anemia[j] | 13 | 8 | 30 | 13 |
| **Endocrine** | | | | |
| Hypothyroidism[k] | 11 | 0 | 1.4 | 0 |

Toxicity was graded per NCI CTCAE v4.
[a] Includes urticaria, drug eruption, eczema, eczema asteatotic, eczema nummular, palmar-plantar erythrodysesthesia syndrome, erythema, erythema multiforme, blister, skin exfoliation, Stevens-Johnson syndrome, dermatitis, dermatitis described as acneiform, bullous, or contact, and rash described as maculo-papular, generalized, or pustular.
[b] Includes hypophagia, and food aversion.
[c] Includes colitis.
[d] Includes spondylolisthesis, periarthritis, musculoskeletal chest pain, neck pain, arthralgia, back pain, myalgia, pain in extremity, arthritis, bone pain, and periarthritis calcarea.
[e] Includes influenza, influenza like illness, pharyngitis, nasopharyngitis, tracheitis, and bronchitis and upper respiratory infection with bronchitis.
[f] Includes pneumonia aspiration, pneumonia bacterial, and lung infection. Two patients (1.0%) died of pneumonia in the intravenous nivolumab treatment arm. Two patients (1.0%) died of pneumonia in the chemotherapy treatment arm; these deaths occurred with paclitaxel only.
[g] Includes productive cough.
[h] Includes tumor-associated fever.
[i] Includes asthenia.
[j] Includes hemoglobin decreased, and iron deficiency anemia.
[k] Includes blood thyroid stimulating hormone increased.

**Table 22: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - ATTRACTION-3**

| Laboratory Abnormality | Intravenous Nivolumab (n=209) | | Docetaxel or Paclitaxel (n=208) | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Chemistry** | | | | |
| Increased creatinine | 78 | 0.5 | 68 | 0.5 |
| Hyperglycemia | 52 | 5 | 62 | 5 |
| Hyponatremia | 42 | 11 | 50 | 12 |
| Increased AST | 40 | 6 | 30 | 1 |
| Increased alkaline phosphatase | 33 | 4.8 | 24 | 1.0 |
| Increased ALT | 31 | 5 | 22 | 1.9 |
| Hypercalcemia | 22 | 6 | 14 | 2.9 |
| Hyperkalemia | 22 | 0.5 | 31 | 1 |
| Hypoglycemia | 14 | 1.4 | 14 | 0.5 |
| Hypokalemia | 11 | 2.9 | 13 | 3.4 |
| **Hematology** | | | | |
| Lymphopenia | 46 | 19 | 72 | 43 |
| Anemia | 42 | 9 | 71 | 17 |
| Leukopenia | 11 | 0.5 | 79 | 45 |

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab group (209 patients) and Docetaxel or Paclitaxel group (range: 207 to 208 patients).

**Immunogenicity**

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) or of other nivolumab products or hyaluronidase products.

During the 2-year treatment period in CHECKMATE-67T *[see Clinical Studies (14.1) in full Prescribing Information]*, 23% (46/202) of patients who received OPDIVO QVANTIG developed anti-nivolumab antibodies (ADA) and 4.3% (2/46) had neutralizing antibodies against nivolumab (NAb). The corresponding incidence of ADA was 7% (15/215) and NAb was 0% (0/15) for intravenous nivolumab in the same study. The incidence of anti-hyaluronidase antibodies in CHECKMATE-67T was 8.8% (19/215); 5 (26%) of these 19 patients developed NAb.

Nivolumab clearance increased by approximately 26% in patients who received OPDIVO QVANTIG and tested positive for ADA compared to patients who tested negative for ADA; this change in clearance is not considered clinically significant. Local injection-site reactions were reported in 15% (7/46) of patients who developed ADA to nivolumab and 7% (10/155) of patients who did not develop ADA to nivolumab; however, all events were Grade 1 or 2 and resolved. Because of low occurrence of anti-nivolumab or anti-hyaluronidase antibodies, the effect of ADA on the effectiveness of OPDIVO QVANTIG is unknown.

**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 QVANTIG 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 QVANTIG are likely to be greater during the second and third trimesters of pregnancy. There are no available data on OPDIVO QVANTIG 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*

OPDIVO QVANTIG for subcutaneous injection contains nivolumab and hyaluronidase *[see Description in full Prescribing Information]*.

Nivolumab

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 intravenously twice weekly from the onset of organogenesis through delivery, at exposure levels of between 4 and 15 times higher than those observed at the clinical dose of 600 mg once every 2 weeks, 900 mg once every 3 weeks, or 1,200 mg once every 4 weeks (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.

Hyaluronidase

In an embryo-fetal development study, mice were dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase (recombinant human) at dose levels up to 2,200,000 U/kg, which is at least 6,600 times higher than the human dose of 10,000 U once every 2 weeks, 15,000 U once every 3 weeks, or 20,000 U once every 4 weeks (U/kg basis), when administered with nivolumab. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is at least 1,080 times higher than the human dose of 10,000 U once every 2 weeks, 15,000 U once every 3 weeks, or 20,000 U once every 4 weeks (U/kg basis), when administered with nivolumab.

**Lactation**

Risk Summary

There are no data on the presence of nivolumab or hyaluronidase 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 QVANTIG (nivolumab and hyaluronidase-nvhy).

**Females and Males of Reproductive Potential**

Pregnancy Testing

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

Contraception

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

**Pediatric Use**

The safety and effectiveness of OPDIVO QVANTIG have not been established in pediatric 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 QVANTIG, 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]*.
- Other immune-mediated adverse reactions:
  - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new or worsening signs or symptoms *[see Warnings and Precautions]*.
  - Advise patients of the risk of solid organ transplant rejection and other transplant (including corneal graft) rejection. Advise patients to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection and other transplant (including corneal graft) rejection *[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 and Use in Specific Populations]*.
- Advise females of reproductive potential to use effective contraception during treatment with OPDIVO QVANTIG and for 5 months following the last dose *[see Use in Specific Populations]*.

Lactation

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

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# UNDERSTANDING PERIPHERAL ARTERY DISEASE: DIAGNOSIS AND MANAGEMENT

BY ADAM IRVING

## Introduction

Peripheral Artery Disease (PAD) is a manifestation of systemic atherosclerosis that primarily affects the lower extremities. It is a common but often underdiagnosed condition, with significant implications for cardiovascular morbidity and mortality. As the population ages and diabetes and smoking rates continue to impact vascular health globally, early recognition and optimal management of PAD are crucial for reducing adverse outcomes. This article provides a brief overview of PAD, focusing on its pathophysiology, clinical presentation, diagnostic approaches, and evidence-based management.

## Pathophysiology and Epidemiology

PAD is caused by atherosclerotic narrowing or occlusion of arteries, most commonly in the legs. It shares the same risk factors as coronary artery disease (CAD), including smoking, diabetes mellitus, hypertension, dyslipidemia, and advanced age.

An estimated 8.5 million people in the United States and over 200 million globally are affected by PAD. Despite its prevalence, PAD is underrecognized, especially in patients who are asymptomatic or who attribute their symptoms to aging or arthritis.

PAD is more than a localized limb problem. Patients with PAD have a significantly higher risk of myocardial infarction, stroke, and cardiovascular death, highlighting the importance of systemic risk factor management.

## Clinical Presentation

PAD presents on a spectrum from asymptomatic disease to critical limb ischemia (CLI):

**1. Asymptomatic PAD**
Many patients (up to 50%) have no limb symptoms but have abnormal ankle-brachial index (ABI) measurements or imaging findings. These individuals remain at increased cardiovascular risk.

**2. Intermittent Claudication**
This is the most classic symptom—exertional muscle pain (typically in the calf, thigh, or buttocks) relieved by rest. It reflects hemodynamically significant arterial obstruction.

**3. Atypical Leg Symptoms**
Some patients present with leg fatigue or exertional discomfort without classic claudication. These cases are frequently misdiagnosed, underscoring the need for a high index of suspicion.

**4. Critical Limb Ischemia (CLI)**
Characterized by rest pain, non-healing wounds, or gangrene. CLI indicates advanced disease and a high risk of limb loss and cardiovascular death.

## Diagnostic Evaluation

The goal of diagnostic testing is to confirm the presence of PAD, assess its severity, and guide treatment decisions.

**1. Ankle-Brachial Index (ABI)**
- Method: Ratio of systolic blood pressure at the ankle to that in the brachial artery.

- Interpretation:
  - 1.30: Non-compressible vessels (often seen in diabetes, requires further testing)
  - 1.00–1.30: Normal
  - 0.91–0.99: Borderline
  - 0.41–0.90: Mild to moderate PAD
  - ≤0.40: Severe PAD

- Advantages: Inexpensive, non-invasive, and widely available.

- Limitations: May be falsely elevated in patients with calcified vessels (e.g., diabetes, ESRD).

**2. Toe-Brachial Index (TBI)**
- Used when ABI is unreliable due to non-compressible arteries. Toe pressures are typically unaffected by arterial calcification.

**3. Segmental Limb Pressures and Pulse Volume Recordings (PVRs)**
- Help localize the level of disease.
- Useful in conjunction with ABI to assess severity and guide revascularization planning.

**4. Exercise ABI Testing**
- Performed in patients with normal resting ABI but exertional symptoms.
- A post-exercise drop in ABI indicates flow-limiting disease.

**5. Duplex Ultrasonography**
- Provides anatomical and hemodynamic data.
- Useful for identifying the location and severity of stenosis or occlusion.
- First-line imaging for patients being considered for intervention.

**6. Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA)**
- Offer detailed visualization of arterial anatomy.
- CTA is quick and widely available but requires iodinated contrast and radiation.
- MRA avoids radiation and uses gadolinium, but is contraindicated in certain renal patients.

**7. Digital Subtraction Angiography (DSA)**
- Gold standard for vascular imaging.
- Invasive but offers therapeutic potential during the same procedure.

## Risk Factor Modification

The cornerstone of PAD management is aggressive risk factor modification to reduce cardiovascular risk and slow disease progression.

**1. Smoking Cessation**
- Strongly associated with PAD incidence and progression.
- All patients should receive counseling and access to pharmacotherapy (e.g., varenicline, nicotine replacement, bupropion).

**2. Diabetes Management**
- Tight glycemic control (A1c <7%) reduces microvascular complications and may slow PAD progression.
- Consider SGLT2 inhibitors or GLP-1 receptor agonists with cardiovascular benefit.

**3. Hypertension Control**
- Target <130/80 mmHg for most PAD patients.
- ACE inhibitors or ARBs are preferred for their cardiovascular benefits.

**4. Lipid Management**
- Statins are indicated for all PAD patients.
- High-intensity statin therapy reduces CV events and may improve walking distance.

**5. Antiplatelet Therapy**
- Aspirin (75–325 mg daily) or clopidogrel (75 mg daily) is recommended to reduce CV events.
- Dual antiplatelet therapy is not routinely recommended unless there's a recent revascularization.

### Symptom Management and Functional Improvement

**1. Exercise Therapy**
- Supervised Exercise Therapy (SET) is first-line for patients with intermittent claudication.
- Typically consists of 30–45 minutes, 3 times/week for at least 12 weeks.
- Shown to improve walking distance more than pharmacologic therapy or revascularization alone.

**2. Pharmacologic Therapy for Claudication**
- Cilostazol (a phosphodiesterase III inhibitor) can improve walking distance in patients with claudication. · Contraindicated in heart failure.
- Pentoxifylline is less effective and rarely used.

### Revascularization

Indicated for patients with lifestyle-limiting symptoms unresponsive to medical therapy or those with CLI.

**1. Endovascular Therapy**
- Preferred first approach for many patients due to lower risk.
- Techniques include angioplasty, stenting, atherectomy.
- Best suited for focal disease, particularly in the iliac and superficial femoral arteries.

**2. Surgical Revascularization**
- Considered in patients with long-segment occlusions or those unsuitable for endovascular procedures.
- Includes bypass grafting using autologous vein or prosthetic conduit.

**3. Hybrid Approaches**
- Combine open and endovascular techniques for complex disease.

### Management of Critical Limb Ischemia

CLI requires urgent evaluation by a vascular specialist. Goals are to relieve ischemia, promote wound healing, and prevent limb loss.
- Wound care and infection control are critical.
- Prompt revascularization (endovascular or surgical) is often necessary.
- Multidisciplinary care (vascular, wound, infectious disease, podiatry) improves outcomes.

As the population ages and diabetes and smoking rates continue to impact vascular health globally, early recognition and optimal management of PAD are crucial for reducing adverse outcomes.

### Long-Term Monitoring and Follow-up
- Monitor ABI annually or more frequently in symptomatic patients.
- Assess for new or worsening symptoms.
- Reinforce adherence to medications, exercise, and life style modification.
- Coordinate care with cardiology, endocrinology, and vascular surgery as needed.

### Special Populations

**1. Diabetic Patients**
- Higher risk of CLI and limb loss.
- Foot care education and regular podiatric evaluations are essential.

**2. Patients with Chronic Kidney Disease**
- Increased risk of arterial calcification.
- Non-invasive testing (e.g., TBI, duplex) preferred over contrast-based imaging when possible.

### Conclusion
Peripheral Artery Disease is a common, systemic atherosclerotic disease with significant implications for patient morbidity and mortality. For physicians, early recognition and proactive management—including risk factor control, symptom relief, and timely revascularization—are essential for improving outcomes.

An individualized approach, incorporating non-invasive diagnostics, lifestyle interventions, pharmacotherapy, and procedural options, ensures comprehensive care. Given the high cardiovascular risk associated with PAD, physicians must remain vigilant not only for limb symptoms but also for broader systemic disease implications.

# DIABETES/BLOOD GLUCOSE

## EARLY DETECTION AND MANAGEMENT OF CHRONIC CONDITIONS WITH DCA VANTAGE® AND CLINITEK STATUS®+ ANALYZERS

*From Siemens Healthineers*

**5303**

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Siemens Healthineers DCA Vantage® and CLINITEK Status® family of analyzers provide Hemoglobin A1c (HbA1c) and albumin-to-creatinine ratio (ACR) testing at the point of care. Monitor glycemic control in patients with diabetes and screening for kidney disease in patients at-risk, in-office. Enable real-time consultation, eliminating loss to follow-up. Improve the patient experience and overall outcome by providing actionable results in minutes.

*CLIA-waived: DCA HbA1c; CLINITEK Microalbumin 2 (ACR)*
*CLIA Moderate Complexity: DCA® Microalbumin/Creatinine (ACR)*



## QUANTAFLO® PAD

*From Semler Scientific*

**5304**

**SCAN TO LEARN MORE**

QuantaFlo® PAD is an easy to use, accurate, point of care, non-invasive solution that aids in the early detection of peripheral arterial disease (PAD). This FDA cleared device can be administered by a medical aide in less than 5 minutes. As published in the Journal of Vascular Surgery and the American Journal of Preventive Medicine, QuantaFlo detected undiagnosed PAD in 31.6% of patients +65.1 QuantaFlo is portable and integrates with other technologies and platforms. It is ideal for both home and clinic environments.

1. Smolderen KG, Ameli O, Chaisson CE, Heath K, Mena-Hurtado C. Peripheral Artery Disease Screening in the Community and 1-Year Mortality, Cardiovascular Events, and Adverse Limb Events, AJPM Focus (2022), https://doi.org/10.1016/j.focus.2022.100016



## NOVA PRIMARY BLOOD GLUCOSE REFERENCE ANALYZER

*From Nova Biomedical*

**5305**

**SCAN TO LEARN MORE**

The U.S. FDA has cleared Nova Primary as a blood glucose reference analyzer that fills the need for a new reference analyzer to replace the YSI STAT PLUS 2300 (YSI, Inc., Yellow Springs, OH). Manufacturers of blood glucose measuring devices and clinical diabetes researchers have relied on the YSI 2300 as a reference and correlation analyzer. However, YSI, Inc. no longer supports the analyzer, and its discontinuation has left a critical industry void. With today's FDA clearance, Nova Primary from Nova Biomedical is now available in the U.S. and worldwide.



FEATURE

# EXPANDING DIAGNOSTIC CAPABILITIES IN THE PHYSICIAN OFFICE

BY MICHAEL BAKER




## Abstract

As physician practices evolve into more comprehensive diagnostic hubs, integrating new testing equipment offers both opportunities and regulatory challenges. Understanding the differences between CLIA-waived, moderately complex, and highly complex tests is critical for compliance, operational efficiency, and patient care optimization. This article guides medical directors and physicians through key considerations for evaluating, selecting, and implementing new diagnostic equipment in outpatient settings.


## Introduction

Physician office laboratories (POLs) play an increasingly critical role in providing immediate diagnostic insights that support timely clinical decisions. As the healthcare landscape shifts toward value-based care, in-office diagnostics can improve patient outcomes by reducing turnaround times and enhancing patient engagement. However, adding new testing equipment or expanding test menus must be undertaken with careful attention to regulatory requirements, operational workflow, staff training, and financial feasibility.

Whether considering CLIA-waived tests for rapid diagnostics or branching into more advanced moderate or high complexity testing, understanding the full implications of such an expansion is essential for medical directors and practice leaders.

## Understanding CLIA and Laboratory Test Classifications

The Clinical Laboratory Improvement Amendments (CLIA) of 1988 regulate all laboratory testing performed on humans in the United States, with the aim of ensuring quality and reliability. Under CLIA, tests are categorized into three levels of complexity:

- CLIA-Waived Tests
- Moderate Complexity Tests
- High Complexity Tests

These categories are defined based on factors such as test methodology, operator skill required, interpretation of results, and potential risk to the patient if performed incorrectly.

## CLIA-Waived Tests

CLIA-waived tests are simple, low-risk diagnostic tests that the FDA has determined can be performed accurately with minimal training. Examples include:

- Glucose by glucose oxidase method
- Urine pregnancy tests
- Rapid streptococcal antigen tests
- Influenza A/B antigen tests
- COVID-19 antigen tests
- HbA1c point-of-care devices
- Fecal immunochemical tests (FIT)

Figure 1

## Key Differences Between Moderate and High Complexity:

| Category | Operator | Quality Requirements | Oversight | Cost |
|---|---|---|---|---|
| CLIA-Waived | Minimal | Basic QC | Self-inspection or state visit | Low |
| Moderate | Licensed technician | Full QC and QA | CLIA-inspected | Medium |
| High | Licensed specialist or pathologist | Advanced QA/QC, PT | Often CAP/Joint Commission | High |

These tests require only a CLIA Certificate of Waiver, which is relatively easy to obtain. Laboratories performing waived testing are still subject to basic quality control and record-keeping requirements, but inspections are less frequent compared to moderate or high complexity labs.

### Benefits:

- Minimal regulatory burden
- Fast setup and minimal staff training
- Ideal for point-of-care diagnostics
- Shorter result turnaround time

### Considerations:

- Test selection must be limited to FDA-approved waived tests
- Proper documentation and QC logs still required
- CLIA-waived status must be verified before test implementation

### Moderate and High Complexity Tests

Moderately and highly complex tests require a CLIA Certificate of Compliance or Certificate of Accreditation, as well as a more rigorous regulatory framework. Moderate complexity tests include many benchtop analyzers used for:

- Basic chemistry panels
- Complete blood counts (CBCs)
- Electrolyte testing
- Basic immunoassays

High complexity tests include:

- Molecular diagnostics (e.g., PCR testing)
- Genetic testing
- Complex immunoassays
- Certain infectious disease panels

Both require extensive documentation, adherence to proficiency testing programs, formal quality assurance protocols, and employment of certified laboratory personnel. *(See Figure 1.)*

### Steps for Adding Diagnostic Equipment or Tests

**1. Assess Clinical Needs and Goals**

Evaluate which conditions are most frequently treated and how enhanced diagnostics could support faster or more accurate treatment. For example:

- Chronic disease management: HbA1c, lipid panels, renal function
- Infectious disease diagnosis: Flu, strep, COVID-19, RSV
- Women's health: hCG, STIs
- Cardiovascular risk: Troponin, BNP

**2. Evaluate Test Complexity and CLIA Requirements**

Determine whether your desired test is waived, moderate, or high complexity. Visit the FDA CLIA Waived Test Database or consult the Centers for Medicare & Medicaid Services (CMS) for guidance.

- If adding waived tests: ensure your lab has an active Certificate of Waiver
- If upgrading to moderate or high complexity: prepare for application or upgrade of CLIA certificate and inspection

**3. Facility and Staffing Requirements**

For moderate/high complexity testing, consider:

- Physical space: appropriate benchtop or enclosed lab areas
- Environmental controls (temperature, humidity, contamination prevention)
- Certified laboratory personnel: medical technologists, lab supervisors, directors
- Training programs and competency assessments

**4. Equipment Selection and Validation**

Choose diagnostic platforms based on:

- Analytical performance (sensitivity, specificity)
- FDA approval status and CLIA categorization
- Reagent and consumable costs
- Connectivity with EMR/LIS systems
- Vendor support and training services

Conduct verification/validation studies to establish accuracy, precision, reportable range, and reference intervals if performing moderate or high complexity testing.

**5. Implement Quality Assurance and Proficiency Testing**

- Waived Tests: Implement basic QC (e.g., internal controls, lot verification)
- Moderate/High Complexity: Develop full QA programs including daily QC, instrument maintenance, calibration verification, and PT participation through approved organizations (e.g., CAP, COLA)

**6. Regulatory and Billing Compliance**

Ensure CPT coding and documentation align with CMS and payer requirements. Proper test menu management and use of appropriate modifiers (e.g., QW for waived tests) is critical to reimbursement success.

### Opportunities with CLIA-Waived Test Expansion

The number of available CLIA-waived tests continues to grow. Notable recent additions include:

- Molecular point-of-care tests for influenza, COVID-19, and RSV
- Lipid panel analyzers suitable for wellness visits
- Rapid A1C and microalbumin tests for diabetic screening
- At-home collection kits processed in waived labs

These offer physician practices the ability to enhance:
- Annual wellness exams
- Chronic disease screening
- Preventive services
- Rapid triage for acute illnesses

## Advantages of Moderate and High Complexity Testing

While CLIA-waived testing offers convenience and ease of implementation, expanding into moderate or high complexity testing can unlock a wide array of clinical, operational, and financial advantages for physician practices committed to delivering more comprehensive care.

**1. Enhanced Diagnostic Capabilities**

Moderate and high complexity testing enables physicians to diagnose and manage a broader spectrum of conditions with greater precision. Practices can bring in-house a wide variety of diagnostic tools that were previously outsourced, including:
- Complete blood counts (CBCs)
- Basic and comprehensive metabolic panels (BMP/CMP)
- Lipid panels and liver function tests
- Thyroid function tests (TSH, Free T4)
- Molecular diagnostic tests (e.g., respiratory panels, STI testing, COVID-19 PCR)

By implementing these tests onsite, clinicians are empowered to make more data-driven decisions during the initial patient encounter, minimizing treatment delays and enhancing continuity of care.

**2. Faster Turnaround Time and Improved Workflow**

In-house moderate and high complexity testing reduces reliance on third-party labs and accelerates time-to-result. Rapid turnaround supports:
- Same-day diagnosis and treatment decisions
- Improved patient adherence and satisfaction
- Reduced need for follow-up appointments

**3. Revenue Diversification and Practice Growth**

Moderate and high complexity testing opens the door to expanded billing opportunities. Many of these tests are reimbursable at higher rates than waived tests, providing:
- Additional revenue streams
- Better ROI from diagnostic equipment
- Enhanced profitability per patient encounter

**4. Improved Chronic Disease Management and Preventive Care**

For practices focused on long-term care and disease prevention, having access to more sophisticated testing tools allows for better:
- Monitoring of chronic conditions (e.g., diabetes, kidney disease, heart failure)
- Risk stratification and early intervention
- Population health analytics

**5. Clinical Autonomy and Customization**

Operating a moderate or high complexity lab gives practices more control over their diagnostic strategy. Physicians can tailor test menus to their patient population and clinical expertise, while also:
- Selecting platforms with preferred assay performance
- Adjusting reporting parameters and critical values
- Designing lab operations to meet unique workflow or specialty needs

**6. Advancement in Point-of-Care Molecular Testing**

Recent advances in molecular testing have blurred the line between complexity and convenience. Many molecular platforms now offer CLIA moderate complexity classification with near-point-of-care usability, allowing practices to benefit from:
- High sensitivity and specificity
- Multiplex pathogen detection
- Fast turnaround times comparable to waived tests

## Financial Considerations

Adding diagnostic equipment should be evaluated as a return-on-investment (ROI) decision. Key financial elements include:
- Capital investment in equipment and infrastructure
- Ongoing costs: consumables, QC materials, service contracts
- Billing potential: volume of reimbursable tests, payer mix
- Operational impact: staff time, workflow integration

A break-even analysis and projected reimbursement model can help determine whether adopting new diagnostics aligns with the practice's long-term strategic goals.

## Conclusion

Expanding diagnostic capabilities through the addition of new equipment and tests can provide significant clinical and financial benefits for physician practices. However, it requires careful planning, regulatory understanding, and strategic investment. CLIA- waived tests offer a low-barrier entry point with immediate patient care impact, while moderate and high complexity testing can elevate a practice's diagnostic capacity when supported by appropriate infrastructure and compliance protocols.

Practice leaders should take a multidisciplinary approach—engaging clinical staff, compliance officers, and financial planners—to ensure any additions align with the practice's mission and operational capabilities. When done correctly, in-office diagnostics can transform a clinic's responsiveness, patient satisfaction, and revenue potential.


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## METRIX® COVID/FLU TEST- RAPID MOLECULAR TEST PROVIDE LAB QUALITY RESULTS IN JUST 20 MINUTES

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*From Sekisui Diagnostics*

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- 3-in-1 Multiplex – Detects COVID-19, Flu A and Flu B from one swab, in one test
- Minimal Hands-On Time – Can be performed in a CLIA-waived setting in a few simple steps
- Convenient– No maintenance or calibration, ready for testing any time
- Accessible and Flexible – Suitable for any facility
- Exceptional Support – Experienced support teams and online training modules to help streamline your implementation




## METRIX® COVID-19 TEST – A MOLECULAR LAB ANYWHERE AND EVERYWHERE

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*From Sekisui Diagnostics*

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The Metrix® COVID-19 is a novel technology includes clinical claims for symptomatic and asymptomatic individuals, along with dual-sample types for nasal or saliva, allowing for an enhanced point-of-care testing experience. The reader is compact and robust, it's ideal for professional use in diverse locations, including clinics and mobile health units. It's a maintenance free device with no calibration step required.




## BE PREPARED FOR RESPIRATORY SEASONS WITH THE OSOM® COVID-19 ANTIGEN RAPID TEST

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*From Sekisui Diagnostics*

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The OSOM® COVID-19 Antigen Rapid Test is a lateral flow immunoassay that detects the SARS-CoV-2 nucleocapsid protein with a nasal swab in only 15 minutes at the point-of-care. The test is intended to be used by healthcare professionals or operators on patients suspected of COVID-19 within the first 7 days of symptom onset. The clinical performance compares favorably against polymerase chain reaction methodology, with a positive percent agreement of 95.1% and a negative percent agreement of 97%.

*OSOM® COVID-19 Antigen Rapid Test has not been FDA cleared or approved. It is authorized by FDA under an EUA for prescription use only. It has been authorized only for the detection of SARS-CoV-2 antigen, not for any other viruses or pathogens and is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C S360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.*



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# Rapid Diagnosis,

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# 9 TRAVEL DESTINATIONS YOU CAN'T MISS IN 2025

Whether you're craving pristine beaches or vibrant cities, these nine must-visit destinations around the world promise stunning scenery, rich culture, and unforgettable adventures for every type of traveler.

**HARBOUR VILLAGE BEACH CLUB · TURTLE BAY RESORT · FOUR SEASON ORLANDO AT WALT DISNEY WORLD · SECRETS CAP CANA · BALBOA BAY RESORT · DESOLATION HOTEL THE TAMPA EDITION HOTEL · FOUR SEASONS NASHVILLE · FOUR SEASONS LAS VEGAS**

MDescapes

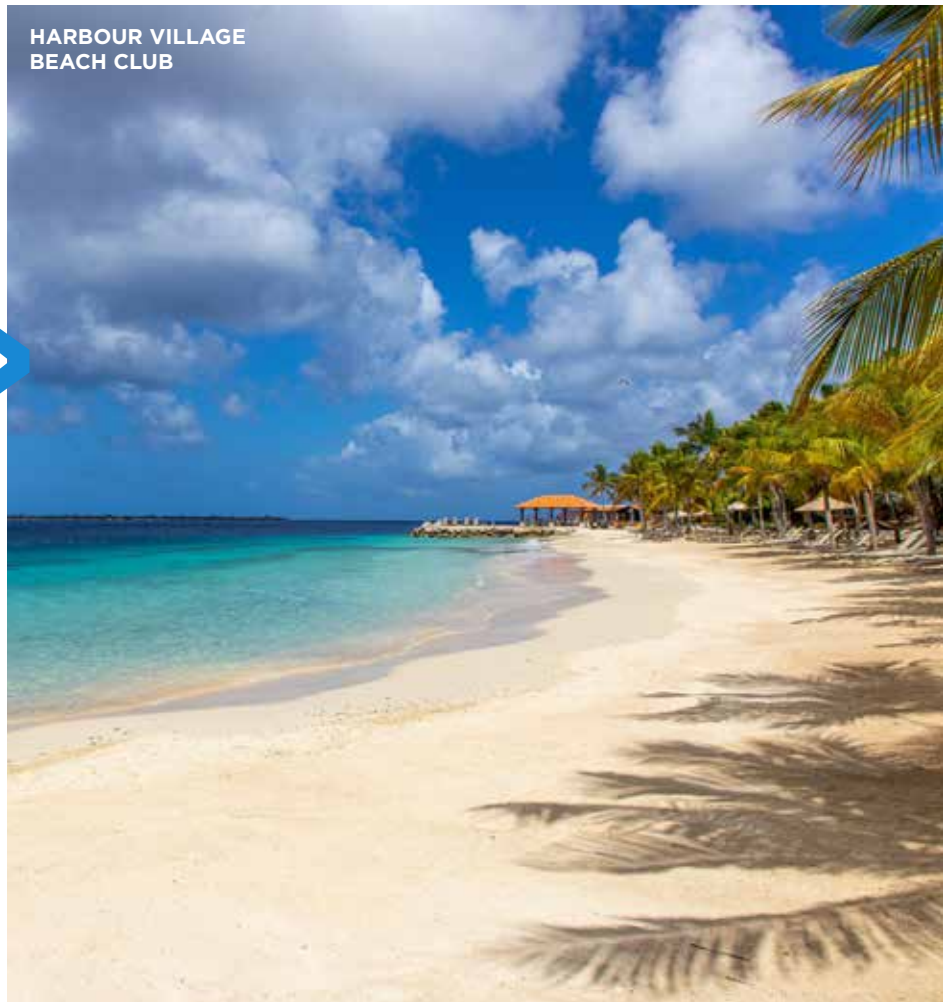
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# HARBOUR VILLAGE BEACH CLUB

## BONAIRE, CARIBBEAN

Tucked away on a private stretch of white sand and palm trees, you will find the iconic Harbour Village Beach Club. An oasis beloved by sun lovers, scuba divers, and seafarers alike. Our boutique Bonaire retreat captures the breezy, barefoot elegance of the Dutch Caribbean, consistently earning the title of “Bonaire's leading hotel” in the World Travel Awards.

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HARBOUR VILLAGE BEACH CLUB



TURTLE BAY RESORT

# TURTLE BAY RESORT

## OAHU, HAWAII

Deeply rooted in the land, the history, and the layered richness of Oahu, at Turtle Bay you’ll find an authentic connection to a place of uncommon natural splendor and the warm, welcoming community within it. Where your days are filled with constant discovery and moments that touch your soul, allowing you to explore the uncommon depths of this remarkable coast.

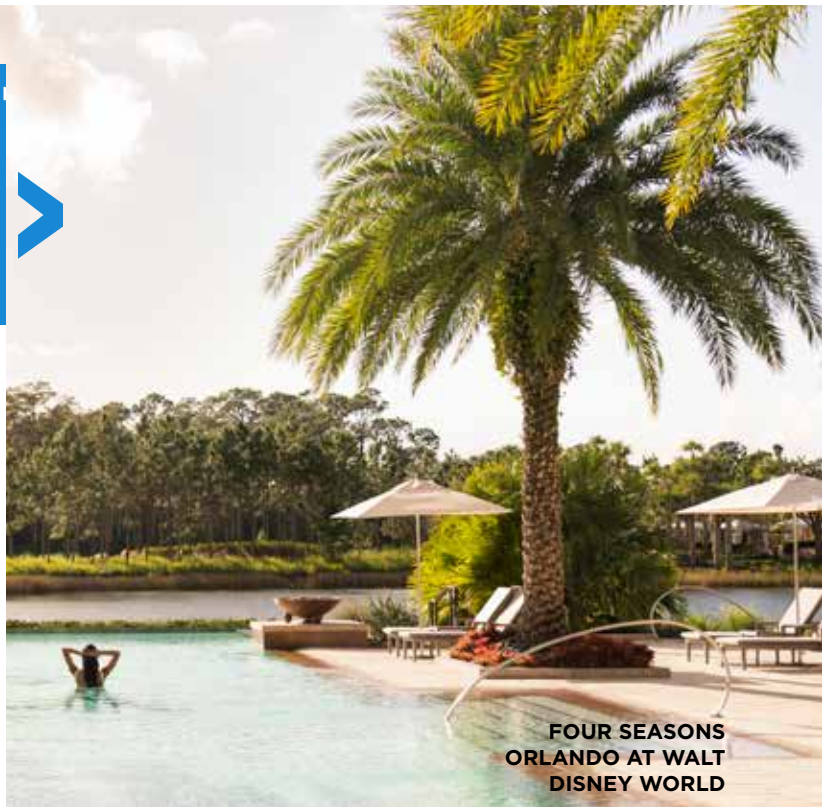
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# FOUR SEASON ORLANDO AT WALT DISNEY WORLD

## ORLANDO, FLORIDA

Discover an elevated escape with the perfect balance of fun and relaxation at our AAA Five Diamond, luxury Orlando Resort. Splash around with the family at Explorer Island water park, or unwind beneath swaying palms at Oasis adult-only pool while we entertain your young ones at our complimentary kids camp. Treat yourself to a soothing, post-park massage at The Spa, then toast to the nightly Walt Disney World® fireworks views over dinner at our Michelin-starred rooftop steakhouse Capa.

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FOUR SEASONS ORLANDO AT WALT DISNEY WORLD



SECRETS CAP CANA

# SECRETS CAP CANA

## PUNTA CANA DOMINICAN REPUBLIC

Secrets Cap Cana Resort & Spa is a sophisticated, adults-only hideaway located in the exclusive gated community of Cap Cana Facing the clear Caribbean Sea along the white sand of the exclusive Juanillo Beach. Secrets Cap Cana Resort & Spa is proud to support the Punta Cana Promise as part of the ongoing commitment to ensure that guests will continue to receive the highest levels of service and security they have come to know and expect from Secrets Cap Cana. The Punta Cana Promise reaffirms the commitment to a set of security standards and safety guidelines in one of the top travel destinations in the Dominican Republic.

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## BALBOA BAY RESORT

NEWPORT BEACH , CALIFORNIA

Balboa Bay Resort is Newport Beach's premier waterfront retreat offering stunning bay views and sunsets over Balboa Bay's harbor. It is the #1 Resort in Newport Beach per U.S. News & World Report, and it is rated as a Forbes Four-Star and AAA Four-Diamond resort.

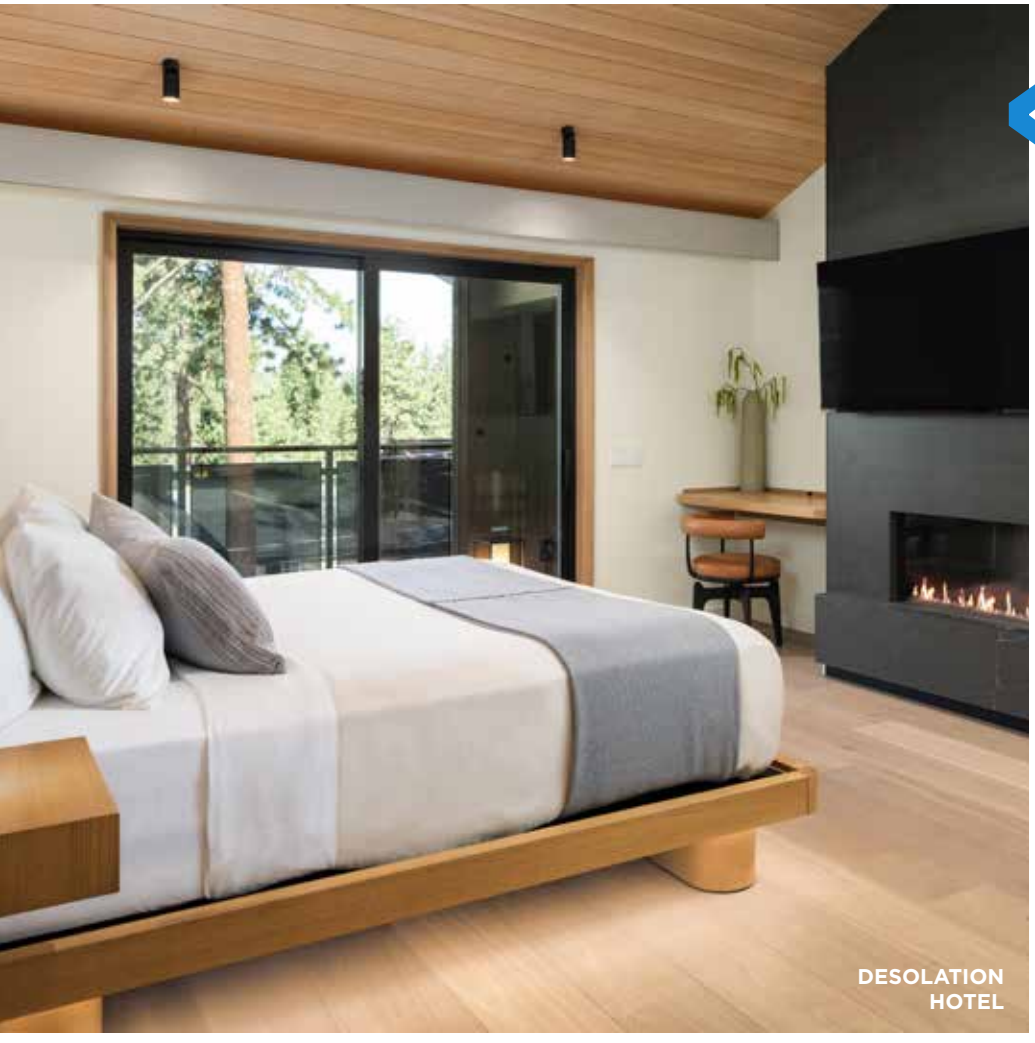
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TURTLE BAY RESORT

## DESOLATION HOTEL

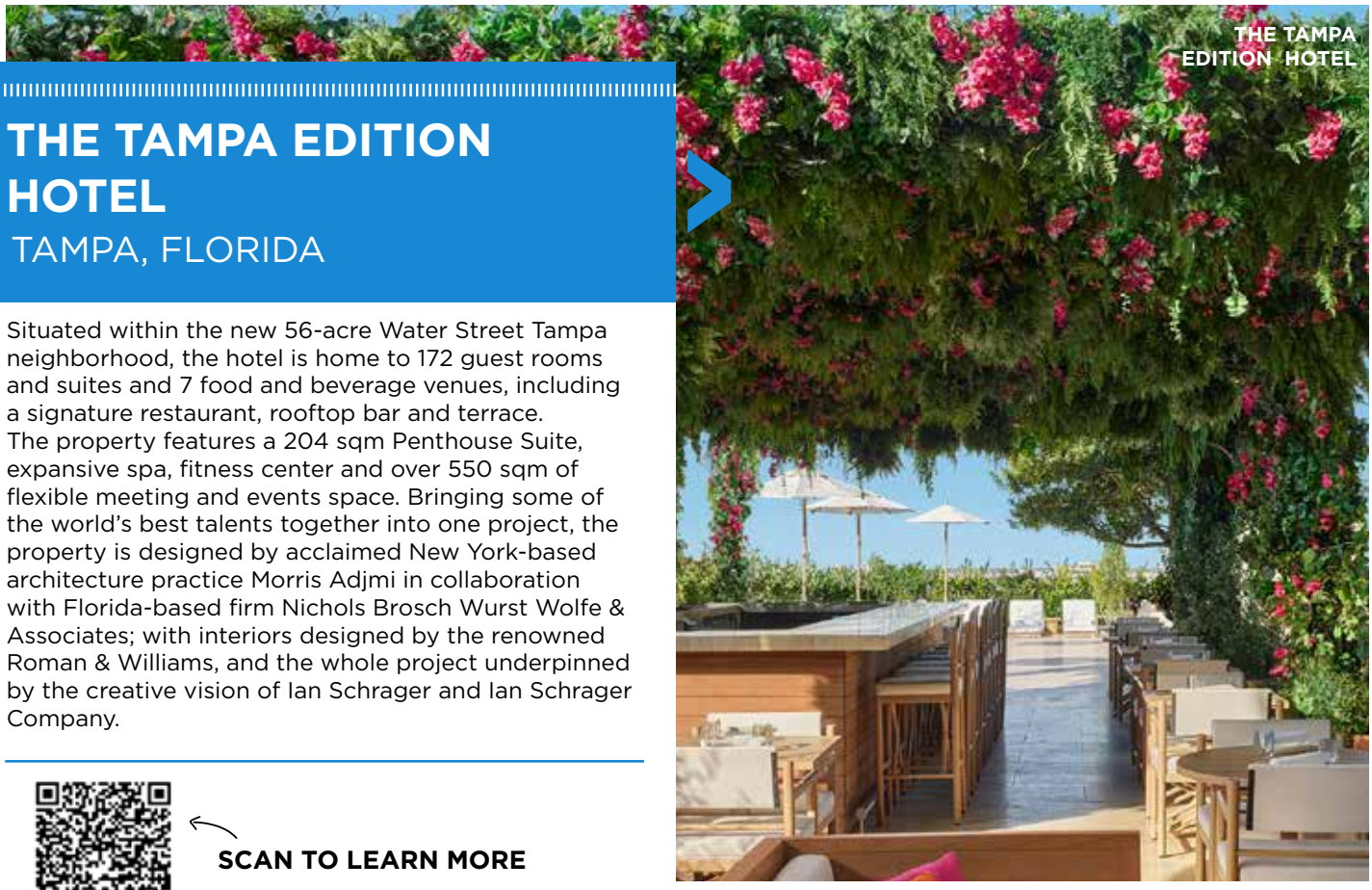
LAKE TAHOE, CALIFONIA



DESOLATION HOTEL

At Desolation Hotel, modern conveniences and eco-luxury commingle with Japanese tranquility and Scandinavian design. Our one-of-a-kind South Lake Tahoe experience inspires adventure and invites tranquility, providing the right space to recharge your battery. Balancing reverence for the past with appreciation for the present, Desolation Hotel nods to the simple days of yesteryear, while modern technology serves as a quiet backbone to the entire resort experience.

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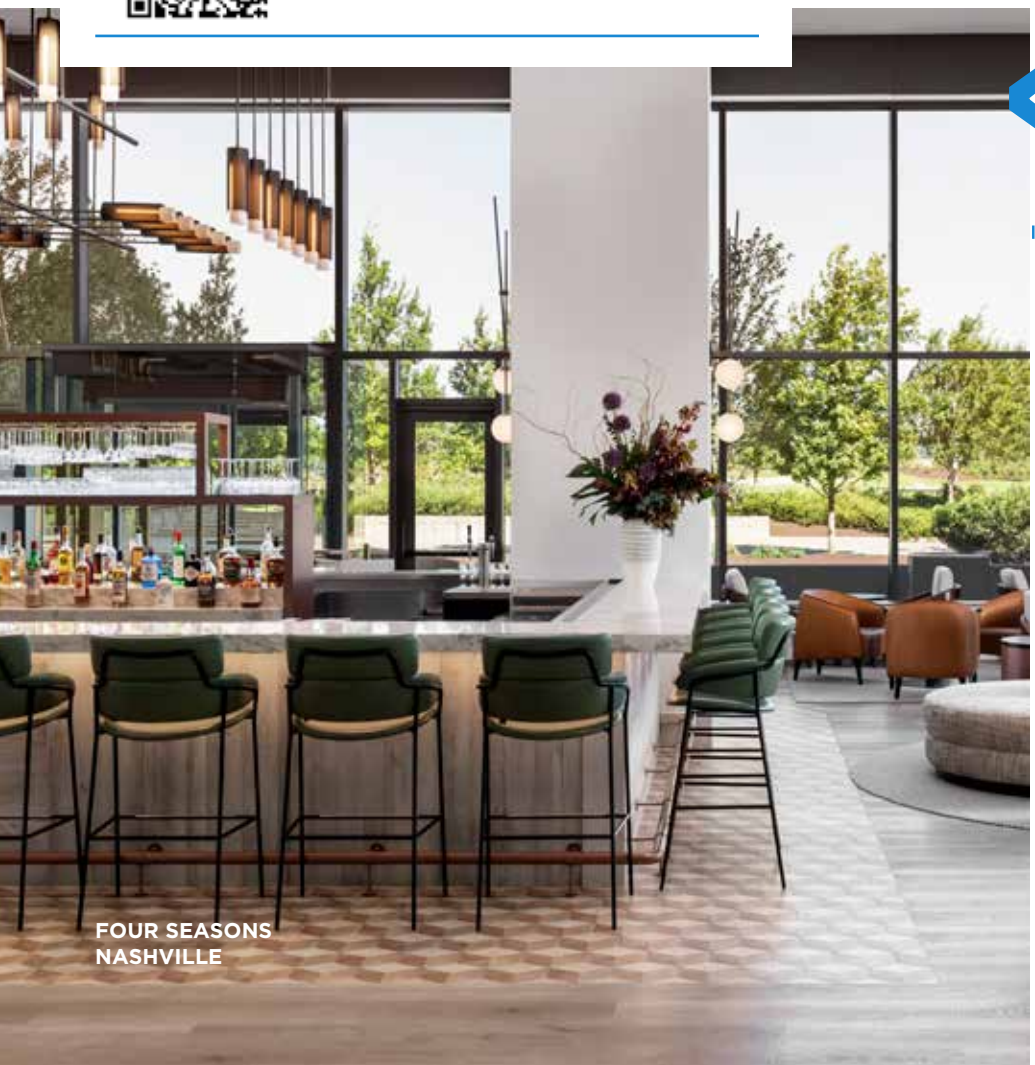
THE TAMPA EDITION HOTEL

# THE TAMPA EDITION HOTEL

## TAMPA, FLORIDA

Situated within the new 56-acre Water Street Tampa neighborhood, the hotel is home to 172 guest rooms and suites and 7 food and beverage venues, including a signature restaurant, rooftop bar and terrace. The property features a 204 sqm Penthouse Suite, expansive spa, fitness center and over 550 sqm of flexible meeting and events space. Bringing some of the world's best talents together into one project, the property is designed by acclaimed New York-based architecture practice Morris Adjmi in collaboration with Florida-based firm Nichols Brosch Wurst Wolfe & Associates; with interiors designed by the renowned Roman & Williams, and the whole project underpinned by the creative vision of Ian Schrager and Ian Schrager Company.

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FOUR SEASONS NASHVILLE

# FOUR SEASONS

## NASHVILLE, TENNESSEE

Welcome to Four Seasons Hotel Nashville, a luxury hotel located in the heart of downtown's vibrant SoBro neighborhood. This new social hub is just steps away from the city's iconic music, sports, and entertainment venues. Experience the rhythm of our lively restaurants and event spaces, the tranquility of our Spa, and the stunning views from our rooftop pool overlooking the Cumberland River and Riverfront Park. With the unmatched service of Four Seasons and warm Southern hospitality, we'll inspire an authentic experience of Music City.

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# FOUR SEASONS
## LAS VEGAS, NEVADA

As one of the only non-gaming and non-smoking hotels on The Strip, Four Seasons Hotel Las Vegas is a unique oasis in the heart of the action-packed sports and entertainment capital of the world. Offering Five Diamond luxury accommodations, acclaimed dining and a Forbes Five-Star spa, Four Seasons offers the best of both worlds: a resort retreat amid the famous energy of Las Vegas.

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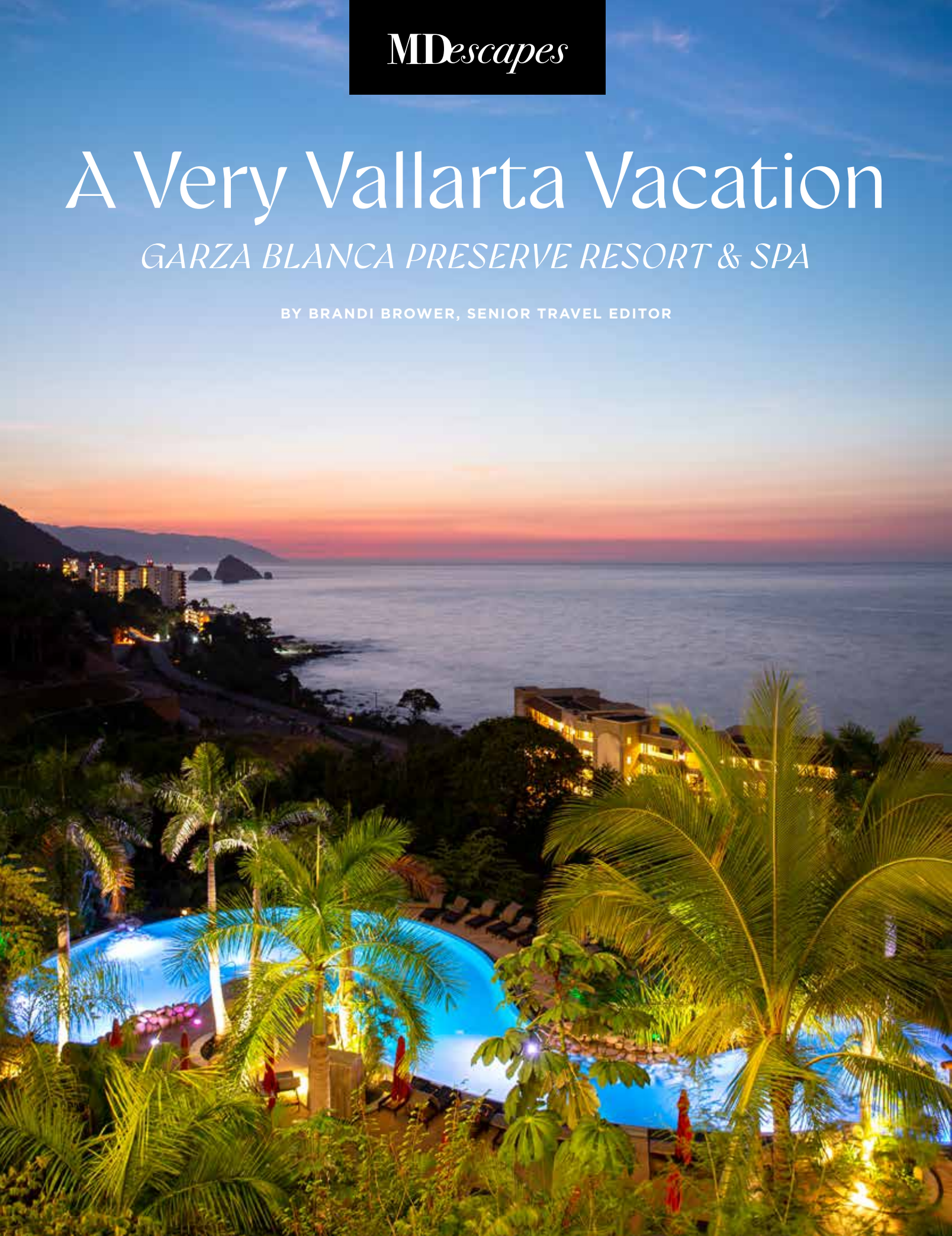

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MDescapes

# A Very Vallarta Vacation

## *GARZA BLANCA PRESERVE RESORT & SPA*

BY BRANDI BROWER, SENIOR TRAVEL EDITOR



Between the dramatic backdrop of the Sierra Madre Mountains and the Pacific Ocean, this vibrant Mexican destination welcomes guests from around the world. What was once called Las Penas, meaning "the rocks," was renamed Puerto Vallarta in 1918 as an honor to the then-governor of the state of Jalisco, Ignacio Vallarta. Situated in the second-largest bay in North America, after Chesapeake Bay in the United States, Bahía de Banderas has a history of being a strategic location and a haven for pirates navigating the Pacific coast. Much later, the area's popularity grew significantly with the arrival of Hollywood in the 1960s. Director John Huston chose a small village south of Vallarta to film "The Night of the Iguana," adapted from Tennessee Williams' book of the same title. Famous actors Ava Gardner, Deborah Kerr, and Richard Burton starred in this film. Still, it was Elizabeth Taylor's extramarital affair with Burton that brought the U.S. media and a flood of publicity that put this sleepy Mexican town on the map. Fast forward 60+ years, the pirates and paparazzi are gone; however, Puerto Vallarta welcomes an average of six million visitors annually and is renowned for its unique blend of cultural charm and natural beauty.

After traveling to many beautiful destinations and wishing I had brought my family along on my adventures, I decided that next landing spot would include my love for my grandchildren and my infatuation with guacamole. What better place than the family-friendly Garza Blanca Preserve Resort & Spa Puerto Vallarta? This destination marks my first all-inclusive experience and my first opportunity to explore the level of service, accommodations, food, beverages, and entertainment that come with the travel category. Situated on the southern coastline of Banderas Bay, this 5-star resort is nestled on 85 acres of lush jungle terrain on the steep mountainside, where the Garza Blanca Preserve Resort takes full advantage of nature's gifts. The drive along the winding road is less than an hour from the Puerto Vallarta International Airport to our destination, with the beautiful blue ocean always in view. Anticipation for relaxation grows as we pull up to the resort's portico. The expansive lobby greets us; sunlight shines down from the glass ceiling, and shadows from the large iron beams and timber accents make patterns on the marble floor. The overall aesthetic is a nod to tradition with Mexican cultural influence—some modern touches, but more warm and colorful, as native artwork accents the walls. Moon, an enthusiastic team member, greets us as we step down in the sunken seating area to review our dining options and reservations that she will make for us. A cool towel and refreshing drink signal the official start of our vacation before Joel takes us to our accommodations on the fifth floor.

The two-bedroom panoramic suite is one of the most desirable layouts, spanning over 3,200 square feet and featuring one king bedroom, a two-queen bedroom, and a sofa bed in the living room, as well as three full bathrooms. The open floor plan features a fully equipped state-of-the-art kitchen, a dining area, and a living area, all seamlessly integrated. Panoramic sliding doors open seamlessly along the length of the spacious wraparound terrace, allowing the stunning vista of both the ocean and the verdant hillside to merge with the comfortable design



of the interior. The three-foot-high, plastered base with clever planters filled with small bushes and laminated tempered glass on top creates a beautiful balcony barrier, adding a splash of greenery to contrast with the blue ocean in the background. An oversized hammock on the patio beckons as you walk past the al fresco dining table and turn the corner to see two lounge chairs and a private jacuzzi in the corner. The main bedroom features a beautiful king bed with two accent posts positioned high above the custom headboard, which is draped with a partial canopy. A dresser with a flat-screen TV and a ceiling fan are nice additions. A plush chaise lounge serves as a proper accent between the closet and the makeup desk. Interesting stained glass panels frame the large mirror, allowing colorful, fractional light to stream into the space. Double vanities, a soaking tub, and a generous walk-in glass-enclosed shower with a rain shower head and bench, accented by river stones, round out the luxurious quarters.

The suite is well-appointed, designed with sophistication and class, and accented with lighting features and fixtures that add interest to each space. With two children in tow, Joel points out the convenience of the laundry room within the suite and informs us that if we need any baby equipment, such as a high chair, crib, or baby monitor, he would be happy to assist. He shares that housekeeping staff will replenish the basket of snacks and candy on the kitchen island daily. We discreetly hide the goodies in a cabinet before the children notice. He also points out that the fridge is stocked with a large assortment of beverages, and so the gluttony of an all-inclusive resort begins!

There's something about knowing that you can have whatever you want, as much as you want, wherever you are, be it in a restaurant, room service, or poolside, that conjures up feelings of the memorable character Augustus Gloop in Roald Dahl's book "Charlie and the Chocolate Factory." The young, overweight boy, known for his insatiable appetite, is a greedy antagonist whose excessive eating and disregard for Willy Wonka's rules lead him to get sucked up into a pipe and fall



into the chocolate river. (You can tell that image scarred my childhood.) I don't want to be the Augustus Gloop of Garza Blanca Preserve.

Which is a perfect segue into the cuisine. The resort has seven gourmet dining options; it was refreshing to see the variety offered. My stay wasn't long enough to experience all of the culinary choices. However, I will share the highlights of the exceptional offerings I enjoyed. We went to breakfast every day at Blanca Blue because it was incredible. The omelet station, crepe station, authentic Mexican section, traditional breakfast offerings, desserts, charcuterie, grilled vegetables, fresh fruit, smoothies, kids' food station, and a wall of shelves with bread and pastries —are just a few of the offerings. I know I'm leaving things out. As if that wasn't enough, you can choose to dine inside, closer to the buffet, or eat outside under an umbrella overlooking the beach and ocean just feet away.
BocaDos Mexican Steakhouse is located up on the hill near our resort suite, a stone's throw away, offering delicious and convenient dining. The eatery is elevated in style and literal elevation, as it is situated on the hill overlooking the gorgeous sunsets on Banderas Bay—a romantic venue with flame torches and candles lighting your table and live music playing. With all-inclusive and attractive menu selections, it's hard not to order a starter or two to share, a salad, a soup, a main course, a couple of side dishes to share, and dessert, which we did. The filet with the chimichurri sauce was cooked to perfection and was my favorite dish of the evening. Best of all, seeing my granddaughter all dressed up, ordering a "Shirley Temple, please," and being treated like a princess by the warm wait staff made it a delightful dinner.

Not all restaurants on the property are suitable for families. There are three dining options available for guests 16 and older, located onsite at the sister property, Hotel Mousai, an adults-only hotel. All three restaurants have double-height ceilings, design elements that draw attention to the gastronomy theme, and breathtaking views. NOI is where flavorful Italian cuisine, contemporary art, and modern design collide. DAO is a contemporary Chinese cuisine experience in a zen-like atmosphere featuring mesmerizing elements. Lastly, Hiroshi accentuates the eclecticism of Japanese cuisine. While my son-in-law watched the little ones, my daughter and I had a mother-daughter date night to savor some sashimi. Again, the all-inclusive makes it difficult not to order everything on the menu. We found some semblance of self-control and shared several items. Standouts were the Crispy Rice appetizer, the Mango Citrus Roll, and the Miso Creme Brulee. When we arrived back at our spacious suite, we found that our family members had taken advantage of the delicious room service options, and their appetites had been bigger than their stomachs, with many dishes barely touched. The struggle is real.

My biggest regret is not making time for the jewel of the culinary crown on the property, Karuma, a brand-new steakhouse and grill. The word Karuma is a combination of two words from the Mayan language, meaning "fire in the night." The structure features no walls or windows, but it's housed underneath a pergola-style structure that allows for ample natural light. An open concept that enables guests to watch their entries created in real-time in the show kitchen: The Art of the Grill. Where the colors of the uniquely crafted drinks compete with the hues of the sunsets. *This restaurant is not part of the all-inclusive package.

One of my favorite moments was dinner at Blanca Blue, where we enjoyed guacamole prepared tableside, watched yet another spectacular sunset, savored a yummy authentic Mexican meal, and listened to a talented musician play current hits with a Latin spin. Burned in my brain, seeing my daughter slow dance with her husband and their young daughter, the three moving with the melody. Memories: Made in Mexico.

Aquazul is the poolside bar and lounge and was our daily food source while at the pool. Stunning views of both the infinity pool and ocean, combined with poolside favorites like salads, burgers, guacamole, and refreshing drinks, make for a convenient dining experience.

The property offers numerous amenities, including three outdoor pools with Jacuzzis, a tennis court, a fitness center, hiking trails, and a sports facility featuring complimentary water activities, such as kayaks, paddle boards, and snorkel equipment. With small children, we planted ourselves mostly on the beach or by the pools and splash pads, and with the excellent pool concierge service by Rigo, Carlos, and Tito, to name just a few, adjusting our umbrellas and bringing by snacks like jicama and mango sprinkled with lime juice and chili powder or supplying my granddaughter with chocolate milkshakes, these sun-splashed days made such an impression on her, she often says, "When can we go back to Mexico?"



Garza Blanca Preserve Resort makes quite an impression on even the youngest of critics. Not many resorts can boast having a carousel onsite, but in the Tierraluna Village, located in the heart of the property, a colorful, old-fashioned carousel whirls with whimsy from late afternoon into the evening, providing a fun experience for families to enjoy. Tierraluna Village features nine boutique shops, a garden area for yoga classes, a natural spring for cold plunges, and an amphitheater hosting movie nights. Children aged 4-12 can also participate in the Kids Club, where a weekly calendar of various crafts, games, and activities is available for drop-in participation. I'm not surprised my granddaughter asks to go back.

Garza Blanca Preserve is fun for "kids" of all ages, as it offers a list of activities for adults daily as well. Kayak & Snorkeling to Los Arcos, Viyansa Yoga Class, Arcos Mountain Hike, Tequila Tasting, Mexican Mixology Class, Complimentary Chair Massage, and that was just a Monday! I saw a gentleman in a wheelchair while we were waiting for our trolley ride back to our room. He didn't look well, and I asked his wife if he was going to be ok. "All-inclusive tequila," she chagrined. It's far too easy to indulge here if you're not careful; you, too, can be like Augustus Gloop.

Spa indulgence is made simple at the resort's Spa Imagine. Surrender to bliss high on the 15th floor, overlooking the cerulean blue below at this oasis in the sky. My tailored wellness journey began with the Hydrotherapy Circuit, which consisted of the following: a steam room, a sauna with an ocean view, a pressure massage shower, a six-cycle vitality pool, a large whirlpool, and a cold plunge pool, all stations precision timed and facilitated with the help of Ishmael, who guided me through the experience. The hydrotherapy circuit properly prepared my body for my relaxation massage; a fantastic therapist, Kenia, performed the treatment in a room with a bird's-eye view. I loved the experience so much that I scheduled some indulgence for my daughter the next day.

Puerto Vallarta is one of Mexico's coastal darlings. Some other West Coast beach towns can have rocky coastlines and rough seas. Still, this popular destination is protected by Banderas Bay, which promises calm, gorgeous, swimmable waters and soft sand beaches framed by stunning mountain views. Like the bay it rests along, the Garza Blanca Preserve Resort & Spa promises a calm, gorgeous getaway—a wonderful escape from the rocky day-to-day, rough seas of life. A beach destination with the tradition, culture, and authentic flavor of the country it resides in: a very Vallarta vacation.

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*From Semler Scientific*

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QuantaFlo® PAD is an easy to use, accurate, point of care, non-invasive solution that aids in the early detection of peripheral arterial disease (PAD). This FDA cleared device can be administered by a medical aide in less than 5 minutes. As published in the Journal of Vascular Surgery and the American Journal of Preventive Medicine, QuantaFlo detected undiagnosed PAD in 31.6% of patients +65.1 QuantaFlo is portable and integrates with other technologies and platforms. It is ideal for both home and clinic environments.

1. Smolderen KG, Ameli O, Chaisson CE, Heath K, Mena-Hurtado C. Peripheral Artery Disease Screening in the Community and 1-Year Mortality, Cardiovascular Events, and Adverse Limb Events, AJPM Focus (2022), https://doi.org/10.1016/j.focus.2022.100016



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**Your Patients Trust YOU To Find Their Peripheral Artery Disease**

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**PERIPHERAL ARTERY DISEASE** (PAD) is an often silent condition where narrowed arteries reduce blood flow to the legs, causing symptoms like leg pain, numbness, and slow-healing wounds.

**DON'T LET PAD SNEAK UP ON YOU OR THESE PATIENTS.**
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