Product Monograph

Including Patient Medication Information

[Pr]OPDIVO® SC

nivolumab for injection

Monoclonal antibody produced in mammalian cells using recombinant DNA

Solution for Subcutaneous Injection

300 mg/2.5 mL and 600 mg/5 mL

(120 mg/mL)

Single-use vial

Antineoplastic

(Anatomical Therapeutic Chemical index code: L01FF01)

[Pr]OPDIVO® SC, indicated for:

- In monotherapy, for the treatment of adult patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer after:
  - prior fluoropyrimidine-based therapy in combination with oxaliplatin or irinotecan following treatment with intravenous nivolumab and ipilimumab.
- The adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for [Pr] OPDIVO® SC please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html.

[Pr]OPDIVO® SC, indicated for:

- Unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma, as monotherapy.
- Unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma, as monotherapy following treatment with intravenous nivolumab and ipilimumab.
- Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

- Melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases, as adjuvant therapy after complete resection.
- Adjuvant treatment of adult patients with Stage IIB or IIC melanoma following complete resection.
- Locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving OPDIVO SC.
- Neoadjuvant treatment of adult patients with resectable NSCLC (tumours ≥4 cm or node positive) when used in combination with platinum-doublet chemotherapy.
- Advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
- Intermediate/poor-risk advanced or metastatic RCC following treatment with intravenous nivolumab and ipilimumab.
- The first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC, when used in combination with cabozantinib.
- Recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) progressing on or after platinum-based therapy.
- Adjuvant treatment of completely resected esophageal or gastroesophageal junction (GEJ) cancer in patients who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (CRT).
- HER2 negative advanced or metastatic gastric cancer, gastroesophageal junction cancer or esophageal adenocarcinoma (GC/GEJC/EAC), in combination with fluoropyrimidine- and platinum- containing chemotherapy.
- Unresectable or metastatic esophageal squamous cell carcinoma (ESCC) in adult patients with tumour cell PD-L1 expression ≥ 1% as determined by a validated test, and no prior systemic therapy for metastatic ESCC, when used in combination with fluoropyrimidine- and platinum-containing chemotherapy.
- Unresectable or metastatic urothelial carcinoma in adult patients, as first-line treatment in combination with cisplatin and gemcitabine.

has been issued market authorization without conditions.

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Feb 6, 2026

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What is a Notice of Compliance with Conditions (NOC/c)?

A NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

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Part 1: Healthcare Professional Information

1. Indications

PrOPDIVO® SC (nivolumab) is indicated for:

Unresectable or Metastatic Melanoma:

- Opdivo SC (nivolumab), as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma.
- Opdivo SC (nivolumab), as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic melanoma following combination treatment with intravenous nivolumab and ipilimumab.
- Opdivo SC is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor.

Adjuvant Treatment of Melanoma:

- Opdivo SC, as monotherapy, is indicated for the adjuvant treatment of adult patients after complete resection of melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases.
- Opdivo SC, as monotherapy, is indicated for the adjuvant treatment of adult patients with Stage IIB or IIC melanoma following complete resection.

Metastatic Non-Small Cell Lung Cancer (NSCLC):

- Opdivo SC, as monotherapy, is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving Opdivo SC.

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

- Opdivo SC, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of adult patients with resectable NSCLC (tumours ≥4 cm or node positive).
    - Positive associations were observed between the level of PD-L1 expression and advanced disease stage, and the magnitude of the treatment benefit.

Metastatic Renal Cell Carcinoma (RCC):

- Opdivo SC, as monotherapy, is indicated for the treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy (see 14 Clinical Trials).
- Opdivo SC, as monotherapy, is indicated for the treatment of adult patients with intermediate/poor-risk advanced or metastatic RCC following combination treatment with intravenous nivolumab and ipilimumab.
- Opdivo SC, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC.

Squamous Cell Carcinoma of the Head and Neck (SCCHN):

- Opdivo SC is indicated for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy.

Microsatellite Instability-High (MSI-H)/ Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer:

- Opdivo SC, as monotherapy, is indicated for the treatment of adult patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer after prior fluoropyrimidine-based therapy in combination with oxaliplatin or irinotecan following combination treatment with intravenous nivolumab and ipilimumab.

The marketing authorization with conditions is primarily based on tumour objective response rate and durability of response. An improvement in survival has not yet been established.

Adjuvant Treatment of Resected Esophageal or Gastroesophageal Junction (GEJ) Cancer:

- Opdivo SC is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction (GEJ) cancer in patients who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (CRT).

Gastric Cancer, Gastroesophageal Junction Cancer, or Esophageal Adenocarcinoma (GC/GEJC/EAC):

- Opdivo SC, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with HER2 negative advanced or metastatic gastric, gastroesophageal junction or esophageal adenocarcinoma.
    - A positive association was observed between PD-L1 CPS score and the magnitude of the treatment benefit.

Adjuvant Treatment of Urothelial Carcinoma (UC):

- Opdivo SC is indicated as a monotherapy for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.
    - A positive association was observed between tumour PD-L1 expression and the magnitude of the treatment benefit. An improvement in overall survival has not yet been established.
- Opdivo SC, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

Unresectable or Metastatic Esophageal Squamous Cell Carcinoma (ESCC):

- Opdivo SC, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with unresectable or metastatic ESCC, with tumour cell PD-L1 expression ≥ 1% as determined by a validated test, and no prior systemic therapy for metastatic ESCC.

1.1. Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Opdivo SC in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (> 65 years of age): Refer to Opdivo PM for indication-specific information regarding the geriatric population. There are insufficient data comparing the safety and efficacy in Geriatrics following Opdivo SC administration as compared to administration of intravenous nivolumab.

2. Contraindications

Opdivo SC (nivolumab) is contraindicated in patients who are hypersensitive to nivolumab or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing see 6 Dosage Forms, Strengths, Composition, and Packaging.

3. Serious Warnings and Precautions Box

Serious Warnings and Precautions

Opdivo SC as monotherapy can cause severe and fatal immune-mediated adverse reactions, including pneumonitis, interstitial lung disease, encephalitis, myocarditis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and autoimmune hemolytic anemia [see 7 Warnings and Precautions, Immune-mediated adverse reactions].

Immune-mediated adverse reactions may involve any organ system. While most of these reactions occurred during treatment, onset months after the last dose has been reported [see 7 Warnings and Precautions and 8 Adverse Reactions].

Early diagnosis and appropriate management are essential to minimize potential life-threatening complications. Patients should be monitored for signs and symptoms suggestive of immune-mediated adverse reactions [see 7 Warnings and Precautions and 4 Dosage and Administration for management guidelines for these adverse reactions]. Opdivo SC must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction

4. Dosage and Administration

4.1. Dosing Considerations

It is important to check the product labels to ensure that the appropriate formulation (Opdivo or Opdivo SC) is being administered to the patient, as prescribed.

Opdivo SC is not to be used for intravenous administration and must be administered as a subcutaneous injection only in the abdomen or thigh.

Opdivo SC has different dosage and administration instructions than intravenous nivolumab products.

Opdivo SC has not been authorised for use in combination concurrently with ipilimumab.

Opdivo SC treatment must be initiated and supervised by health care professional experienced in the treatment of cancer.

Adult patients currently receiving intravenous nivolumab as a single agent, or in combination with chemotherapy or cabozantinib, may switch to subcutaneous OPDIVO SC at their next scheduled dose.

Please refer to the separate Opdivo Product Monograph for full instructions on dosing and administration of the intravenous formulation.

Patient Selection

MSI-H/dMMR mCRC:
Patients should be selected for treatment based on MSI-H or dMMR tumour status as determined by an experienced laboratory using validated testing methods.

4.2. Recommended Dose and Dosage Adjustment

Recommended Dose

Opdivo SC as monotherapy:

The recommended dose of Opdivo SC as monotherapy is presented in Table 1:

Table 1: Recommended Dosages for Opdivo SC as Monotherapy

Indication	Recommended Opdivo SC Dosage	Duration of Therapy
Unresectable or metastatic melanoma	600 mg Opdivo SC every 2 weeks or 1,200 mg Opdivo SC every 4 weeks (Administer by subcutaneous injection over 3-5 minutes)	Continue treatment as long as clinical benefit is observed or until disease progression or unacceptable toxicity
Metastatic non-small cell lung cancer		
Advanced or metastatic renal cell carcinoma		
Squamous cell carcinoma of the head and neck		
Adjuvant treatment of melanoma (Stage III/IV)	600 mg Opdivo SC every 2 weeks or 1,200 mg Opdivo SC every 4 weeks (Administer by subcutaneous injection over 3-5 minutes)	Continue treatment as long as clinical benefit is observed or until disease recurrence or unacceptable toxicity for up to 1 year
Adjuvant treatment of melanoma (Stage IIB/IIC)		
Adjuvant treatment of urothelial carcinoma		
Adjuvant treatment of resected esophageal or Gastroesophageal junction		

The recommended dosages of Opdivo SC in combination with other therapeutic agents are presented in following tables. Refer to the respective Product Monograph for each therapeutic agent administered in combination with Opdivo SC for the recommended dosage information, as appropriate.

Opdivo SC as monotherapy following combination treatment with intravenous nivolumab and ipilimumab:

The recommended dosages of Opdivo SC (monotherapy phase) following combination treatment with intravenous nivolumab and ipilimumab is presented in Table 2.

Table 2: Recommended doses of Opdivo SC (monotherapy phase) following combination treatment with intravenous nivolumab and ipilimumab

Indication	Recommended Opdivo SC Dosage	Duration of Therapy
Unresectable or metastatic melanoma	600 mg nivolumab every 2 weeks or 1,200 mg nivolumab every 4 weeks (Administer by subcutaneous injection over 3-5 minutes)	Following intravenous nivolumab and ipilimumab combination therapy, administer Opdivo SC as monotherapy until disease progression or unacceptable toxicity
Advanced or metastatic renal cell carcinoma		
Microsatellite Instability-High (MSI-H)/ Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer		

OPDIVO in combination with cabozantinib:

Advanced or metastatic renal cell carcinoma

Table 3: Recommended Dosages of OPDIVO SC in combination with cabozantinib

	Recommended Dosage	Duration of Therapy
Opdivo SC	600 mg Opdivo SC every 2 weeks or 1,200 mg Opdivo SC every 4 weeks (Administer by subcutaneous injection over 3-5 minutes)	In combination with cabozantinib, until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
cabozantinib	40 mg orally once daily without food	In combination with Opdivo SC, until disease progression or unacceptable toxicity

Refer to the cabozantinib product monograph for recommended cabozantinib dose information.

Opdivo SC in combination with chemotherapy:

Gastric cancer, gastroesophageal junction cancer or esophageal adenocarcinoma

Table 4: Recommended Dosages of Opdivo SC in combination with fluoropyrimidine- and platinum-containing chemotherapy

	Recommended Dosage	Duration of Therapy
Opdivo SC	600 mg Opdivo SC every 2 weeks or	Until disease progression, unacceptable toxicity, or up to 2 years

	Recommended Dosage	Duration of Therapy
Chemotherapy	900 mg Opdivo SC every 3 weeks (Administer by subcutaneous injection over 3-5 minutes) Administer Opdivo SC in combination with fluoropyrimidine- and platinum-containing chemotherapy	

Unresectable or metastatic esophageal squamous cell carcinoma

Table 5: Recommended Dosages of Opdivo SC in combination with fluoropyrimidine- and platinum-containing chemotherapy

	Recommended Dosage	Duration of Therapy
OPDIVO SC	600 mg Opdivo SC every 2 weeks or 1,200 mg Opdivo SC every 4 weeks (Administer by subcutaneous injection over 3-5 minutes) Administer Opdivo SC in combination with fluoropyrimidine- and platinum-containing chemotherapy	Until disease progression, unacceptable toxicity, or up to 2 years
Chemotherapy		

Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer

Table 6: Recommended Dosages of Opdivo SC in combination with platinum-doublet chemotherapy

	Recommended Dosage	Duration of Therapy
OPDIVO SC	900 mg Opdivo SC (Administer by subcutaneous injection over 3-5 minutes) with platinum-doublet chemotherapy on the same day every 3 weeks	In combination with platinum-doublet chemotherapy for 3 cycles

First-line treatment of unresectable or metastatic urothelial carcinoma

Table 7: Recommended dose of Opdivo SC in combination with cisplatin and gemcitabine

	Recommended Dosage	Duration
Opdivo SC	900 mg Opdivo SC every 3 weeks with cisplatin and gemcitabine every 3 weeks for 6 cycles followed by Opdivo SC as monotherapy at either 600 mg every 2 weeks or at 1,200 mg every 4 weeks (Administer by subcutaneous injection over 3-5 minutes)	In combination with cisplatin and gemcitabine for up to 6 cycles. After completing combination therapy, administer Opdivo SC as monotherapy, until disease progression, unacceptable toxicity, or up to 2 years from first dose.

Recommended Dosage Adjustment

For treatment with Opdivo SC, monotherapy or in combination with other therapeutic agents, dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. When Opdivo SC is administered in combination, refer to the product monograph of the other combination therapy agents regarding dosing.
Dosage modifications for Opdivo SC or Opdivo SC in combination for adverse reactions that require management different from these general guidelines are summarized in Table 8.

Table 8: Recommended Dosage Modifications for Adverse Reactions for Opdivo SC or in Combination with other therapeutic agents

Target Organ/System	Adverse Reaction[a]	Treatment modification
Endocrine	Grade 2 or 3 hypothyroidism, Grade 2 or 3 hyperthyroidism, Grade 2 or 3 hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and acute management with corticosteroids, if needed, is complete[b]
	Grade 3 or 4 hypophysitis Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment[c]

Target Organ/System	Adverse Reaction[a]	Treatment modification
Gastrointestinal	Grade 2 or 3 diarrhea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhea or colitis	Permanently discontinue treatment[c]
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete.
	Immune-mediated encephalitis	Permanently discontinue treatment[c]
Hepatic **NOTE**: For RCC patients treated with **Opdivo SC in combination with cabozantinib** with liver enzyme elevations, see dosing guidelines following this table	*Patients with normal AST/ALT/bilirubin at baseline:*	
	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment[c]
Myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete. Retreatment may be considered after recovery.
	Grade 3 or 4 myocarditis	Permanently discontinue treatment[c]
Pulmonary	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete.
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment[c]
Renal	Grade 2 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete.
	Grade 3 or 4 creatinine elevation	Permanently discontinue treatment[c]
Skin	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s)
	Grade 4 rash Confirmed SJS/TEN	Permanently discontinue treatment[c]

Target Organ/System	Adverse Reaction[a]	Treatment modification
	Grade 3	Withhold dose(s) until symptoms resolve or improve and management with corticosteroids is complete
Other	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment[c]

a National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

b May resume treatment while receiving physiologic replacement therapy.

c See 7 Warnings and Precautions for treatment recommendations.

Pediatrics:

The safety and efficacy of Opdivo SC in pediatric patients (<18 years of age) has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

4.4. Administration

Opdivo SC should be administered by subcutaneous injection only, using the doses specified. It is not intended for intravenous administration. Opdivo SC should be administered by a healthcare professional.

Opdivo SC is a single-use, ready to use solution for injection. It should not be diluted.

Prior to use, visually inspect for particulate matter and discoloration. Opdivo SC is a clear to opalescent, colorless to yellow solution. Discard if the solution is discolored or contains extraneous particulate matter other than a few translucent-to-white particles. Do not shake.

Preparation

Opdivo SC is compatible with polypropylene, polycarbonate, polyethylene, polyurethane, polyvinyl chloride, fluorinated ethylene propylene, and stainless steel.

A syringe, a transfer needle, and a hypodermic injection needle are needed to withdraw Opdivo SC solution from the vial and inject it subcutaneously. Opdivo SC may be injected using a 23G-25G (3/8”-5/8”) hypodermic injection needle or a winged butterfly needle.

- *600 mg nivolumab for subcutaneous injection*
    - Allow one Opdivo SC 600 mg vial to reach room temperature
    - Withdraw 5 mL (600 mg) of Opdivo SC into the syringe

    Total volume in syringe should be 5 mL of Opdivo SC (600 mg in total).

    Or

    - Allow two Opdivo SC 300 mg vials to reach room temperature
    - Withdraw 2.5 mL (300 mg) from the first vial
    - Using the same syringe, withdraw 2.5 mL (300 mg) from the second vial

    Total volume in syringe should be 5 mL of Opdivo SC (600 mg in total).

- *900 mg nivolumab for subcutaneous injection*
    - Allow one Opdivo SC vial of 600 mg and one vial of 300 mg to reach room temperature
    - Withdraw 5.0 mL (600 mg) from the 600 mg vial
    - Using the same syringe, withdraw 2.5 mL (300 mg) from the 300 mg vial

    Total volume in syringe should be 7.5 mL of Opdivo SC (900 mg in total).

    Or

    - Allow three Opdivo SC 300 mg vials to reach room temperature
    - Using the same syringe, withdraw 2.5 mL (300 mg) of Opdivo SC from each vial into the syringe

    Total volume in syringe should be 7.5 mL of Opdivo SC (900 mg in total).

- *1,200 mg nivolumab for subcutaneous injection*
    - Allow two Opdivo SC vials of 600 mg to reach room temperature,
    - Withdraw 5.0 mL (600 mg) from the first vial
    - Using the same syringe, withdraw 5 mL (600 mg) from the second vial

    Total volume in syringe should be 10 mL of Opdivo SC (1,200 mg in total).

    Or

    - Allow one Opdivo SC vial of 600 mg and two vials of 300 mg to reach room temperature
    - Withdraw 5.0 mL (600 mg) from the 600 mg vial
    - Using the same syringe, withdraw 2.5 mL (300 mg) from each 300 mg vials

    Total volume in syringe should be 10 mL of Opdivo SC (1,200 mg in total).

    Or

    - Allow four Opdivo SC 300 mg vials to reach room temperature
    - Using the same syringe, withdraw 2.5 mL (300 mg) of OPDIVO SC from each vial into the syringe

    Total volume in syringe should be 10 mL of Opdivo SC (1,200 mg in total).

Discard any unused solution remaining in the vial.

If the dose is to be used immediately, attach a 23G-25G (3/8”-5/8”) hypodermic injection needle to the syringe. If the dose is not to be used immediately, attach a tip cap to the syringe prior to storage. To avoid clogging of the hypodermic injection needle, attach the needle to the syringe immediately prior to administration.

Storage in Syringe

Once withdrawn into the syringe, Opdivo SC should be used immediately. If not used immediately, store the syringe:

- In the refrigerator at 2°C to 8°C, protected from light for up to 7 days.
    - If the syringe was stored in a refrigerator, allow the syringe to reach room temperature prior to administration.
    - At room temperature 15°C to 25°C and room light for up to 8 hours.
- Discard if storage time exceeds these limits. Do not freeze.

Administration

- Administer the full contents of the syringe into the subcutaneous tissue of the abdomen or thigh over a period of 3 to 5 minutes.
- Alternate injection sites for successive injections. Do not inject into areas where the skin is tender, red, or bruised, or areas where there are scars or moles. If the administration of Opdivo SC is interrupted, continue administering at the same site, or at an alternate site.
- During treatment with Opdivo SC, do not administer other subcutaneous medications at the same site used for Opdivo SC.

4.5. Missed Dose

If a planned dose of Opdivo SC is missed, it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the prescribed dosing interval.

5. Overdose

There is no information on overdosage with Opdivo SC (nivolumab).

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 9 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Subcutaneous (SC) injection	Sterile Solution for Injection 300 mg nivolumab/2.5 mL (120 mg/mL) 600 mg nivolumab /5 mL (120 mg/mL)	Recombinant human hyaluronidase PH20 (rHuPH20)*, histidine, histidine hydrochloride monohydrate, methionine, pentetic acid, polysorbate 80, sodium chloride, sucrose, and water for injection.

*Recombinant human hyaluronidase PH20 (rHuPH20): an enzyme used to increase the dispersion and absorption

of co-administered nivolumab

Description

Opdivo SC (nivolumab) for subcutaneous injection is a sterile, non-pyrogenic, preservative-free, single-use, clear to opalescent, colorless to yellow solution, essentially free of visible particulates. Opdivo SC is supplied at a nominal concentration of 120 mg/mL nivolumab in 300 mg and 600 mg single-use vials and contains the following inactive ingredients:

- Each 2.5 mL single-dose vial (overfill of 0.52 mL) contains histidine (3.88 mg), Histidine hydrochloride monohydrate (5.25 mg), Hyaluronidase (5,000 Units hyaluronidase/2,5mL), methionine (1.87 mg), pentetic acid (0.049 mg), polysorbate 80 (1.25 mg), sucrose (214 mg), and water for injection.
- Each 5 mL single-dose vial (overfill of 0.60 mL) contains histidine (7.75 mg), Histidine hydrochloride monohydrate (10.5 mg), Hyaluronidase (10,000 Units hyaluronidase/5mL), methionine (3.73 mg), pentetic acid (0.1 mg), polysorbate 80 (2.5 mg), sucrose (428 mg), and water for injection.

7. Warnings and Precautions

Please see 3 Serious Warnings and Precautions Box.

General

Opdivo SC (nivolumab) should be administered under the supervision of a healthcare professional experienced in the treatment of cancer.

When Opdivo SC is administered in combination with chemotherapy, refer to the product monograph of the other combination therapy agents regarding dosing.

When Opdivo SC is administered in combination with cabozantinib, refer to the product monograph for cabozantinib prior to initiation of treatment.

Opdivo SC is not authorised for use in combination concurrently with ipilimumab.

Increased mortality in patients with multiple myeloma [not an approved indication] when nivolumab intravenous 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 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Carcinogenesis and Mutagenesis

The mutagenic and carcinogenic potential of nivolumab have not been evaluated.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

Haemophagocytic lymphohistiocytosis (HLH)

Haemophagocytic lymphohistiocytosis (HLH) has been reported in relation to the use of nivolumab as monotherapy. Patients should be closely monitored. If HLH is suspected, Opdivo SC should be withheld. If HLH is confirmed, Opdivo SC should be discontinued and treatment for HLH should be initiated, as deemed medically appropriate (see 8 Adverse Reactions).

Hepatic/Biliary/Pancreatic

Hepatotoxicity (nivolumab intravenous in combination with cabozantinib for RCC)

Nivolumab intravenous in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to nivolumab intravenous alone (see 8 Adverse Reactions). Liver enzymes and bilirubin should be monitored before initiation of and periodically throughout treatment. Consider more frequent monitoring as compared to when the drugs are administered as single agents. Delayed occurrence of liver enzyme elevations after discontinuation of treatment has been reported. For elevated liver enzymes, interrupt Opdivo SC and cabozantinib and consider administering corticosteroids as needed (see 4 Dosage and Administration and the product monograph for cabozantinib).

Immune

Immune-Mediated Adverse Reactions

Adverse reactions observed with immunotherapies such as Opdivo SC may differ from those observed with non-immunotherapies, can be severe and life-threatening, and may require immunosuppression. Early identification of adverse reactions and intervention are essential to minimize potential life-threatening complications. Most immune-mediated adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications.

Patients should be monitored for signs and symptoms suggestive of immune-mediated adverse reactions and appropriately managed with treatment modification. Opdivo SC must be permanently discontinued for any severe immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with Opdivo SC may occur at any time during or after discontinuation of therapy. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening of the adverse reaction. Non-corticosteroid immunosuppressive medications should be added if there is worsening or no improvement despite corticosteroid use.

Do not resume Opdivo SC while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive medications. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive medications.

Immune-Mediated Endocrinopathies

Opdivo SC can cause severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), diabetes mellitus (including fulminant type I diabetes), and diabetic ketoacidosis. These have been observed with nivolumab monotherapy. Monitor patients for signs and symptoms of

endocrinopathies such as fatigue, weight change, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease, changes in blood glucose levels and thyroid function. If signs or symptoms are present, complete endocrine function evaluation (see 8 Adverse Reactions). Long-term hormone replacement therapy may be necessary in cases of immune-related endocrinopathies.

For Grade 2 or 3 hypothyroidism, withhold Opdivo SC and initiate thyroid hormone replacement therapy. For Grade 2 or 3 hyperthyroidism, withhold Opdivo SC and initiate antithyroid therapy. For Grade 4 hypothyroidism, or Grade 4 hyperthyroidism, permanently discontinue Opdivo SC. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered, as clinically indicated. Upon improvement, for Grade 2 or 3, resume Opdivo SC after corticosteroid taper. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilized.

For Grade 2 adrenal insufficiency, withhold Opdivo SC, and initiate physiologic corticosteroid replacement. For Grade 3 or 4 (life-threatening) adrenal insufficiency, permanently discontinue Opdivo SC. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilized.

For Grade 2 hypophysitis, withhold Opdivo SC and initiate appropriate hormone therapy. For Grade 3 or 4 hypophysitis, permanently discontinue Opdivo SC. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered, as clinically indicated. Upon improvement, for Grade 2, resume Opdivo SC after corticosteroid taper. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilized.

For Grade 3 diabetes, Opdivo SC should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilized. For Grade 4 diabetes, permanently discontinue Opdivo SC.

Immune-Mediated Gastrointestinal Adverse Reactions

Opdivo SC can cause severe diarrhea or colitis. This has been observed with nivolumab monotherapy. Monitor patients for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Rule out infectious and disease-related etiologies. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Stool infections work-up (including CMV, other viral etiology, culture, Clostridium difficile, ova, and parasite) should be performed upon presentation of diarrhea or colitis to exclude infectious or other alternate etiologies (see 8 Adverse Reactions).

For Grade 4 diarrhea or colitis, permanently discontinue Opdivo SC and initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 3 diarrhea or colitis, withhold Opdivo SC and initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, resume Opdivo SC after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, permanently discontinue Opdivo SC.

For Grade 2 diarrhea or colitis, withhold Opdivo SC and start immediate corticosteroid treatment at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, resume Opdivo SC after corticosteroid taper if needed. If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone equivalents and permanently discontinue Opdivo SC.

Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded (including CMV infection/reactivation evaluated with viral PCR on biopsy, and other viral, bacterial, and parasitic etiology).

Immune-Mediated Hepatic Adverse Reactions

Opdivo SC can cause severe hepatotoxicity, including hepatitis. This has been observed with nivolumab monotherapy. Monitor patients for signs and symptoms of hepatotoxicity, such as transaminase and total bilirubin elevations. Rule out infectious and disease-related etiologies (see 8 Adverse Reactions).

For Grade 3 or 4 transaminase or total bilirubin elevation, permanently discontinue Opdivo SC and initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 transaminase or total bilirubin elevation, withhold Opdivo SC and start immediate corticosteroid treatment at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, resume Opdivo SC after corticosteroid taper if needed. If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone equivalents and permanently discontinue Opdivo SC.

Immune-Mediated Pulmonary Adverse Reactions

Opdivo SC can cause severe pneumonitis or interstitial lung disease, including fatal cases. These have been observed with nivolumab monotherapy. Monitor patients for signs and symptoms of pneumonitis, such as radiographic changes (eg, focal ground glass opacities, patchy filtrates), dyspnea, and hypoxia. Rule out infectious and disease-related etiologies (see 8 Adverse Reactions).

For Grade 3 or 4 pneumonitis, permanently discontinue Opdivo SC and initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

For Grade 2 (symptomatic) pneumonitis, withhold Opdivo SC and initiate corticosteroids at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, resume Opdivo SC after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 2 to 4 mg/kg/day methylprednisolone equivalents and permanently discontinue Opdivo SC.

Immune-Mediated Renal Adverse Reactions

Opdivo SC can cause severe nephrotoxicity, including nephritis and renal failure. This has been observed with nivolumab monotherapy. Monitor patients for signs and symptoms of nephrotoxicity. Most patients present with asymptomatic increase in serum creatinine. Rule out disease-related etiologies (see 8 Adverse Reactions).

For Grade 3 or 4 serum creatinine elevation, permanently discontinue Opdivo SC and initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 serum creatinine elevation, withhold Opdivo SC and initiate corticosteroid treatment at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, resume Opdivo SC after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone equivalents and permanently discontinue Opdivo SC.

Immune-Mediated Skin Adverse Reactions

Opdivo SC can cause severe rash. This has been observed with nivolumab monotherapy.

Monitor patients for rash. Withhold Opdivo SC for Grade 3 rash and permanently discontinue OPDIVO SC for Grade 4 rash. Administer corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents for severe or life-threatening rash.

Rare cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been observed. If symptoms or signs of SJS or TEN appear, Opdivo SC should be withheld and the patient referred to a specialized unit for assessment and treatment. If the patient has confirmed SJS or TEN, permanent discontinuation of Opdivo SC is recommended.

Immune-Mediated Encephalitis

Opdivo SC can cause immune-mediated encephalitis. This has been observed in less than 1% of patients treated with nivolumab intravenous monotherapy in clinical trials across doses and tumour types, including fatal cases.

Withhold Opdivo SC in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue Opdivo SC for immune-mediated encephalitis (see 4 Dosage and Administration).

Other Immune-Mediated Adverse Reactions

Opdivo SC can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Across clinical trials of nivolumab intravenous investigating various doses and tumour types, the following immune-mediated adverse reactions were reported in less than 1% of patients: uveitis, Guillain-Barré syndrome, pancreatitis, autoimmune neuropathy (including facial and abducens nerve paresis), demyelination, myasthenic syndrome, myasthenia gravis, aseptic meningitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, rhabdomyolysis, and aplastic anemia. Cases of Vogt-Koyanagi-Harada syndrome and hypoparathyroidism have been reported during post approval use of nivolumab (see 8 Adverse Reactions).

For suspected immune-mediated adverse reactions, perform adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold Opdivo SC and administer corticosteroids. Upon improvement, resume Opdivo SC after corticosteroid taper. Permanently discontinue Opdivo SC for any severe immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

Cases of autoimmune hemolytic anemia, some with fatal outcome, have been reported with nivolumab intravenous (see 8 Adverse Reactions). Patients with signs and symptoms of anemia should undergo a prompt diagnostic workup to evaluate for autoimmune hemolytic anemia. If autoimmune hemolytic anemia is suspected, hematology consultation should be initiated. Based on the severity of anemia as defined by hemoglobin level, withhold or permanently discontinue Opdivo SC. Red blood cell transfusion may be necessary in severe cases.

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab intravenous. Some cases of myocarditis can be asymptomatic, so a diagnosis of myocarditis requires a high index of suspicion. Therefore, patients with cardiac or cardio-pulmonary symptoms should undergo a prompt diagnostic workup to evaluate for myocarditis with close

monitoring. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day), and prompt cardiology consultation with diagnostic workup including electrocardiogram, troponin assay, and echocardiogram should be initiated. Additional testing may be warranted, as guided by the cardiologist, and may include cardiac magnetic resonance imaging. Once a diagnosis is established, Opdivo SC should be withheld. For grade 3 myocarditis, OPDIVO SC should be permanently discontinued (see 8 Adverse Reactions and 4 Dosage and Administration).

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with nivolumab. Treatment with Opdivo SC may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with Opdivo SC versus the risk of possible organ rejection in these patients.

Rapid-onset and severe graft-versus-host disease (GVHD), some with fatal outcome, has been reported in the post-marketing setting in patients who had undergone prior allogeneic stem cell transplant and subsequently received nivolumab (see 8 Adverse Reactions).

Complications, including fatal events, occurred in patients who received allogeneic hematopoietic stem cell transplantation (HSCT) after nivolumab.

Preliminary results from the follow-up of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) after previous exposure to nivolumab showed a higher-than-expected number of cases of acute GVHD and transplant related mortality (TRM).

These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease (VOD), and other immune-mediated adverse reactions, and intervene promptly (see 8 Adverse Reactions).

Monitoring and Laboratory Tests

Liver function tests, thyroid function tests, blood glucose and electrolytes should be monitored prior to and periodically during treatment. Patients should be closely monitored during treatment for signs and symptoms of immune-mediated adverse reactions, including but not limited to, dyspnea, hypoxia; increased frequency of bowel movements, diarrhea; elevated transaminase and bilirubin levels; elevated creatinine levels; rash pruritis; headache, fatigue, hypotension, mental status changes; visual disturbances; muscle pain or weakness; paresthesias.

Metastatic NSCLC and SCCHN

In the clinical trials, PD-L1 testing was conducted using the Health Canada approved PD-L1 IHC 28-8 pharmDx assay. However, the role of the PD-L1 expression status has not been fully elucidated.

In patients with metastatic non-squamous NSCLC or SCCHN and no measurable tumour PD-L1 expression or in those deemed non-quantifiable, close monitoring for unequivocal progression during the first months of treatment with Opdivo SCmay be clinically prudent.

GC/GEJC/EAC:

Patients who had known human epidermal growth factor receptor 2 (HER2) positive cancer, baseline ECOG performance score ≥ 2 or had untreated central nervous system (CNS) metastases were excluded

from the clinical study in GC, GEJC or EAC. In the absence of data, nivolumab in combination with chemotherapy should be used with caution in the HER2 negative subpopulations (baseline ECOG performance score ≥ 2 or had untreated CNS metastases), after careful consideration of the potential benefit/risk on an individual basis.

Reproductive Health

Fertility studies have not been performed with nivolumab. Advise women of reproductive potential to use effective contraception during treatment with Opdivo SC and for at least 5 months after the last dose of Opdivo SC (see 7.1.1 Pregnancy).

7.1. Special Populations

7.1.1. Pregnancy

There are no adequate and well-controlled studies of nivolumab in pregnant women. 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 **PART 2,** 16 Non-Clinical Toxicology). 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. Opdivo SC is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus.

7.1.2. Breastfeeding

It is unknown whether nivolumab is secreted in human milk. Because antibodies are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from nivolumab, a decision should be made whether to discontinue nursing or to discontinue Opdivo SC, taking into account the importance of Opdivo SC to the mother.

7.1.3. Pediatrics

The safety and efficacy of Opdivo SC has not been established in pediatric patients (< 18 years of age) (see 1.1 Pediatrics); therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Refer to Opdivo PM for indication-specific information regarding the geriatric population. There are insufficient data comparing the safety and efficacy in Geriatrics following Opdivo SC administration as compared to administration of intravenous nivolumab.

8. Adverse Reactions

8.1. Adverse Reaction Overview

SUBCUTANEOUS FORMULATION (Opdivo SC)

The safety of Opdivo SC was evaluated in CHECKMATE-67T, a multicenter, randomized, open-label study in patients with previously treated advanced or metastatic RCC (see 14 CLINICAL TRIALS). Patients received Opdivo SC 1200 mg subcutaneously every 4 weeks (n=247) or nivolumab 3 mg/kg intravenously every 2 weeks (n=245). Median duration of treatment was 6.6 months (range 0 to 22.4).

Serious adverse events occurred in 27.9% of patients who received Opdivo SC. Study therapy was discontinued due to adverse events in 9.3% of patients and 34.4% of patients had a dose interruption due to an adverse event.

The incidence of Grade 3-5 adverse events was 36.4%. Fatal adverse reactions occurred in 3 (1.2%) patients, and included myocarditis, myasthenia, and colitis complications one each.

The most frequent serious adverse reactions in at least 1% of patients were: pleural effusion, pneumonitis, hyperglycemia, hyperkalaemia and diarrhea.

The most common adverse reactions (≥10%) were: anaemia, fatigue, musculoskeletal pain, pruritus, rash, blood creatinine increased, arthralgia, and cough.

INTRAVEOUS FORMULATION (Opdivo)

Unresectable or Metastatic Melanoma:

In CHECKMATE-066, intravenous nivolumab was administered at 3 mg/kg every 2 weeks in patients with advanced (unresectable or metastatic) treatment-naive, BRAF V600 wild-type melanoma (n=206) or dacarbazine at 1000 mg/m^2 every 3 weeks (n=205). Nivolumab patients in this study received a median of 12 doses. The median duration of therapy was 6.51 months (95% CI: 4.86, NA) for nivolumab and 2.10 months (95% CI: 1.87, 2.40) for chemotherapy. In this trial, 47% of patients received nivolumab for greater than 6 months and 12% of patients received nivolumab for greater than 1 year.

In CHECKMATE-067, nivolumab as a single agent at 3 mg/kg every 2 weeks (n=313) or nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg as a single agent every 2 weeks (n=313) or ipilimumab as a single agent at 3 mg/kg every 3 weeks for 4 doses (n=311) was administered in patients with advanced (unresectable or metastatic) treatment-naive melanoma. The median duration of therapy was 2.8 months (95% CI: 2.40, 3.91) with a median of 4 doses (range: 1-76 for nivolumab; 1-4 for ipilimumab) for nivolumab in combination with ipilimumab, 6.6 months (95% CI: 5.16, 9.66) with a median of 15 doses (range: 1-77) for single-agent nivolumab, and 3.0 months (95% CI: 2.56, 3.71) with a median of 4 doses (range: 1-4) in ipilimumab. In the nivolumab in combination with ipilimumab arm, 39% of patients received treatment for greater than 6 months and 30% received treatment for greater than 1 year. In the single-agent nivolumab arm, 53% received treatment for greater than 6 months and 40% received treatment for greater than 1 year.

In CHECKMATE-037, nivolumab was administered at 3 mg/kg every 2 weeks in patients with advanced (unresectable or metastatic) melanoma (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m^2 every 3 weeks. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. Patients treated with nivolumab in this study received a median of eight doses. The median duration of therapy was 5.3 months (range: 1 day-13.8+ months) for nivolumab and 2 months (range: 1 day-9.6+ months) for chemotherapy. In this ongoing trial, 24% of patients received nivolumab for greater than 6 months and 3% of patients received nivolumab for greater than 1 year.

Adjuvant Treatment of Melanoma:

The safety of nivolumab as a single agent was evaluated in CHECKMATE-238, a randomized (1:1), double-blind Phase 3 trial in which 905 patients with completely resected Stage IIIB/C or Stage IV

melanoma received nivolumab 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks (n=452) or ipilimumab 10 mg/kg (n=453) administered as an intravenous infusion every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to a 1 year. The median duration of exposure was 11.5 months (95% CI: 11.47, 11.53) in nivolumab-treated patients and was 2.7 months (95% CI: 2.33, 3.25) in ipilimumab-treated patients. In this ongoing trial, 74% of patients received nivolumab for greater than 6 months.

The safety of nivolumab as a single agent was evaluated in CHECKMATE-76K, a randomized (2:1), double-blind Phase 3 trial in which 788 patients with completely resected Stage IIB or IIC melanoma received nivolumab 480 mg administered as an intravenous infusion over 30 minutes every 4 weeks (n=524) or placebo administered as an intravenous infusion over 30 minutes every 4 weeks (n=264) for up to a 1 year. The median duration of exposure was 11.0 months (range: 0.0, 12.1) in nivolumab-treated patients and was 11.0 months (range: 0.0, 12.7) in placebo-treated patients. In this ongoing trial, 77.5% of patients received nivolumab for greater than 6 months.

Metastatic NSCLC (previously treated):

Second-line Treatment of Metastatic NSCLC:

Nivolumab 3 mg/kg has been administered to approximately 535 patients with metastatic NSCLC, from two Phase 3 randomized trials in patients with metastatic squamous NSCLC (CHECKMATE-017) and non-squamous NSCLC (CHECKMATE-057), and a Phase 2 single-arm trial in squamous NSCLC (CHECKMATE-063).

CHECKMATE-017 was conducted in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen. Patients received 3 mg/kg of nivolumab (n=131) administered intravenously over 60 minutes every 2 weeks or docetaxel (n=129) administered intravenously at 75 mg/m^2 every 3 weeks. The median duration of therapy was 3.3 months (range: 1 day-21.65+ months) with a median of 8 doses (range: 1-48) in nivolumab-treated patients and was 1.4 months (range: 1 day-20.01+ months) in docetaxel-treated patients. Therapy was discontinued due to adverse reactions in 3% of patients receiving nivolumab and 10% of patients receiving docetaxel.

CHECKMATE-057 was conducted in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen. Patients received 3 mg/kg of nivolumab (n=287) administered intravenously over 60 minutes every 2 weeks or docetaxel (n=268) administered intravenously at 75 mg/m^2 every 3 weeks. The median duration of therapy was 2.6 months (range: 0-24.0+ months) with a median of 6 doses (range: 1-52) in nivolumab-treated patients and was 2.3 months (range: 0-15.9 months) in docetaxel-treated patients. Therapy was discontinued due to adverse reactions in 5% of patients receiving nivolumab and 15% of patients receiving docetaxel.

Neoadjuvant NSCLC

Neoadjuvant Treatment of Resectable NSCLC:

CHECKMATE-816

The safety of nivolumab in combination with platinum-doublet chemotherapy was evaluated in CHECKMATE-816, a randomized, open-label, multicenter trial in patients with resectable NSCLC. Patients received either nivolumab 360 mg administered in combination with platinum-doublet chemotherapy

administered every 3 weeks for 3 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 3 cycles.

The most common (>10%) adverse events were nausea, constipation, vomiting, neutropenia, anemia, thrombocytopenia, fatigue, malaise, decreased appetite, rash, alopecia, hiccups, and neuropathy peripheral.

Serious adverse events occurred in 30% of patients who were treated with nivolumab in combination with platinum-doublet chemotherapy. The most frequent (>2%) serious adverse events were pneumonia and vomiting.

Study therapy with nivolumab in combination with platinum-doublet chemotherapy was permanently discontinued for adverse events in 10% of patients and 30% had at least one treatment withheld for an adverse event. The most common adverse events (≥1%) resulting in permanent discontinuation of nivolumab in combination with platinum doublet chemotherapy were anaphylactic reaction (1.7%), decreased neutrophil count (1.1%) and fatigue (1.1%).

No deaths due to study drug toxicity were reported in patients treated with nivolumab in combination with platinum-doublet chemotherapy.

Advanced or Metastatic RCC (previously treated):

The safety of nivolumab was evaluated in a randomized open-label Phase 3 trial (CHECKMATE-025) in which 803 patients with advanced RCC who had experienced disease progression during or after 1 or 2 anti-angiogenic treatment regimens, received nivolumab 3 mg/kg intravenously every 2 weeks (n=406) or everolimus 10 mg po daily (n=397). The median duration of treatment was 5.5 months (range: 0-29.6+ months) with a median of 12 doses (range: 1-65) in nivolumab-treated patients and was 3.7 months (range: 6 days-25.7+ months) in everolimus-treated patients.

Study therapy was discontinued for adverse reactions in 8% of patients receiving nivolumab and 13% of patients receiving everolimus. Serious adverse reactions occurred in 12% of patients receiving nivolumab and 13% of patients receiving everolimus. The most frequent serious adverse reactions reported in at least 1% of patients in the nivolumab arm were pneumonitis and diarrhea.

No treatment related deaths were associated with nivolumab versus two with everolimus.

Advanced or Metastatic RCC (previously untreated):

CHECKMATE-214

The safety of nivolumab 3 mg/kg, administered with ipilimumab 1 mg/kg was evaluated in CHECKMATE-214, a randomized open-label trial in which 1082 patients with previously untreated advanced RCC received nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab monotherapy at the 3 mg/kg dose (n=547) every 2 weeks or sunitinib administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle (n=535). The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in nivolumab plus ipilimumab treated patients and 7.8 months (range: 1 day to 20.2+ months) in sunitinib-treated patients. A total of 79% of the patients received all four doses of ipilimumab with nivolumab.

Study therapy was discontinued for adverse reactions in 22% of nivolumab plus ipilimumab patients and 12% of sunitinib patients. Serious adverse reactions occurred in 30% of patients receiving nivolumab plus ipilimumab and 15% of patients receiving sunitinib. The most frequent serious adverse

reactions reported in at least 1% of patients were diarrhea, pneumonitis, hypophysitis, adrenal insufficiency, colitis, hyponatremia, increased ALT, pyrexia, and nausea.

In CHECKMATE-214, Grade 3-4 adverse reactions were reported in 46% of nivolumab plus ipilimumab patients and in 63% of sunitinib patients. Among the patients treated with nivolumab in combination with ipilimumab, 169/547 (31%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 382 patients in this group who continued treatment in the single-agent phase, 144 (38%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase. With longer follow-up (minimum 41.4 months), the safety results observed for patients who received nivolumab plus ipilimumab remained consistent with the pre-specified interim analysis (minimum follow-up of 17.5 months).

At 41.4 months minimum follow-up, there were eight treatment-related deaths associated with nivolumab in combination with ipilimumab versus four in patients treated with sunitinib.

CHECKMATE-9ER

The safety of nivolumab with cabozantinib was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced or metastatic RCC. Patients received nivolumab 240 mg 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). Cabozantinib could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14.3 months (range: 0.2-27.3 months) in nivolumab and cabozantinib-treated patients and 9.2 months (range: 0.8-27.6 months) in sunitinib-treated patients. In this trial, 82.2% of patients in the nivolumab and cabozantinib arm were exposed to treatment for >6 months and 60.3% of patients were exposed to treatment for >1 year.

In patients treated with nivolumab in combination with cabozantinib, higher frequencies of Grades 3 and 4 increased ALT (9.8%) and increased AST (7.9%) were seen compared to nivolumab alone. In patients with Grade ≥2 increased ALT or AST (n=83): median time to onset was 2.3 months (range: 2.0 to 88.3 weeks), 28% received systemic corticosteroids for median duration of 1.7 weeks (range: 0.9 to 52.3 weeks), and resolution to Grades 0-1 occurred in 89% with median time to resolution of 2.1 weeks (range: 0.4 to 83.6+ weeks). Among the 44 patients who were rechallenged with either nivolumab (n=11) or cabozantinib (n=9) monotherapy or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving nivolumab, 2 patients receiving cabozantinib, and 7 patients receiving both nivolumab and cabozantinib.

Grade 3-4 adverse events occurred in 70% of patients receiving nivolumab and cabozantinib. The most frequent (≥5%) Grade 3-4 adverse events were hypertension, hyponatremia, palmar-plantar erythrodysesthesia syndrome, fatigue, diarrhea, increased lipase, increased transaminases, hypophosphatemia and pulmonary embolism.

Serious adverse events occurred in 46% of patients receiving nivolumab and cabozantinib. The most frequent (≥1%) serious adverse events were diarrhea, pneumonitis, pulmonary embolism, pneumonia, adrenal insufficiency, hyponatremia, urinary tract infection and pyrexia.

There was one (0.3%) treatment-related death in patients receiving nivolumab and cabozantinib. The cause of death was small intestine perforation. Within 100 days of the last study dose, nine subjects

(2.8%) had death classified as “other”, not related to disease progression or to study treatment by the investigator, which included: intestinal perforation, intestinal perforation secondary to radiation injury, upper gastrointestinal hemorrhage, cardio-respiratory arrest, cardiac arrest, septic shock, hyponatremia, hypoglycemia and pain.

Adverse events leading to permanent discontinuation of either nivolumab, cabozantinib or both occurred in 19.7% of patients: 6.6% nivolumab only, 7.5% cabozantinib only, and 5.6% both drugs due to same adverse event at the same time. Adverse events leading to dose interruption or reduction of either nivolumab, cabozantinib or both occurred in 83.4% of patients: 3.1% nivolumab only, 46.3% cabozantinib only, and 21.3% both drugs due to same adverse event at the same time, and 6.3% both drugs sequentially. 56% of subjects taking cabozantinib had dose reductions and the median time to first dose reduction due to an adverse event was 98 days. Dose reductions were not permitted with nivolumab treatment.

Recurrent or Metastatic SCCHN:

The safety of nivolumab was evaluated in a randomized, open-label, Phase 3 trial (CHECKMATE-141) in patients with recurrent or metastatic SCCHN and progression during or after one prior platinum-based therapy. Patients received 3 mg/kg of nivolumab (n=236) administered intravenously over 60 minutes every 2 weeks or investigator’s choice of either cetuximab (n=13), 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly, or methotrexate (n=46) 40 to 60 mg/m^2 weekly, or docetaxel (n=52) 30 to 40 mg/m^2 weekly. The median duration of therapy was 1.9 months (range: 0.03-16.1+ months) in nivolumab-treated patients and was 1.9 months (range: 0.03-9.1 months) in patients receiving investigator’s choice. In this trial, 18% of patients received nivolumab for greater than 6 months and 2.5% of patients received nivolumab for greater than 1 year.

In CHECKMATE-141, therapy was discontinued for adverse reactions in 4% of patients receiving nivolumab and in 10% of patients receiving investigator’s choice. Twenty-four percent (24%) of nivolumab-treated patients had a drug delay for an adverse reaction. Serious adverse reactions occurred in 7% of nivolumab-treated patients and in 15% receiving investigator’s choice.

There were two treatment-related deaths associated with nivolumab (pneumonitis and hypercalcemia) versus none in patients treated with investigator’s choice therapy.

MSI-H/dMMR mCRC:

The safety of nivolumab administered in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, open-label trial.

In CHECKMATE-142, 119 patients with mCRC received a combination therapy of nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses, then nivolumab 3 mg/kg every 2 weeks until disease progression or until unacceptable toxicity. The median duration of therapy was 24.9 months (range: 0 to 44+ months). Patients received a median of 51.0 doses (range: 1 to 93) of nivolumab and 4.0 doses (range: 1-4) of ipilimumab.

In this ongoing trial, 64.7% of patients received nivolumab in combination with ipilimumab for greater than 1 year.

Nivolumab was discontinued due to adverse reactions in 13% of patients on the combination therapy. Serious adverse reactions occurred in 22.7% of patients receiving nivolumab in combination with ipilimumab. The most frequent (≥1%) serious adverse reactions were colitis (2.5%), abdominal pain (1.7%), hypophysitis (1.7%), pyrexia (2.5%), increased transaminase (1.7%), anemia (1.7%) and acute kidney injury (1.7%).

Adjuvant Treatment of Resected Esophageal or GEJ Cancer:

The safety of nivolumab was evaluated in CHECKMATE-577, a randomized, placebo-controlled, double-blind, multicenter trial in 792 treated patients with resected esophageal or gastroesophageal junction cancer who had residual pathologic disease following CRT. The trial excluded patients who did not receive concurrent CRT prior to surgery, who 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 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 10.14 months (range: <0.1 to 14.2 months) in nivolumab-treated patients and 8.99 months (range: <0.1 to 15 months) in placebo-treated patients. Among patients who received nivolumab, 61.1% were exposed for >6 months and 54.3% were exposed for >9 months.

In CHECKMATE-577, Grade 3-4 adverse reactions were reported in 13.3% of nivolumab patients and in 5.8% of placebo patients. Serious adverse reactions occurred in 33% of patients receiving nivolumab. A serious adverse reaction reported in ≥2% of patients who received nivolumab was pneumonitis. One fatal adverse reaction of myocardial infarction occurred in a patient with multiple significant comorbidities who received nivolumab.

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

GC/GEJC/EAC (previously untreated):

First-line Treatment of GC/GEJC/EAC:

The safety of nivolumab in combination with chemotherapy was evaluated in CHECKMATE-649, a randomized, multicenter, open-label trial in patients with previously untreated advanced or metastatic gastric cancer or gastroesophageal junction cancer or esophageal adenocarcinoma. The trial excluded patients who were known HER2 positive, had a baseline ECOG performance score ≥2 or had untreated CNS metastases. Patients were randomized to receive nivolumab in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

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

Patients were treated with nivolumab in combination with chemotherapy or chemotherapy until disease progression, unacceptable toxicity, or up to 2 years (for nivolumab only). Among patients who

received nivolumab and chemotherapy (n=782), 54% were exposed for >6 months and 28% were exposed for >1 year.

Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with nivolumab in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation. Fatal adverse reactions occurred in 4 (0.5%) patients who were treated in the chemotherapy arm; these included pulmonary thromboembolism, asthenia and severe hypoxia, study drug toxicity with diarrhea and intestinal pneumonia (1 patient each).

In CHECKMATE-649, Grade 3-4 adverse reactions were reported in 59.1% of patients with nivolumab in combination with chemotherapy and in 44.5% with chemotherapy. Serious adverse reactions occurred in 22% of patients treated with nivolumab in combination with chemotherapy. nivolumab and chemotherapy was discontinued in 36% of patients and at least one dose was withheld in 67% of patients due to an adverse reaction. The most common adverse reaction leading to discontinuation for nivolumab in combination with chemotherapy was peripheral neuropathy and peripheral sensory neuropathy.

The most frequent serious adverse reactions reported in ≥2% of patients treated with nivolumab in combination with chemotherapy were diarrhea, febrile neutropenia, and pneumonitis.

After a minimum follow-up of 12.1 months, the most frequent adverse reactions were peripheral neuropathy (50%), neutropenia (43%), nausea (41%), thrombocytopaenia (36%), fatigue (33%), diarrhea (32%), anaemia (28%), vomiting (25%), decreased appetite (20%), increased transaminases (18%), rash (14%), palmar-plantar erythrodysaesthaesia syndrome (12%) and lipase increased (11%). Median duration of therapy was 6.8 months (95% CI 6.11, 7.36) for nivolumab in combination with chemotherapy and 4.9 months (95% CI 4.47, 5.29) for chemotherapy.

Adjuvant Treatment of Urothelial Carcinoma:

The safety of nivolumab was evaluated in CHECKMATE-274, a phase 3, randomized, double-blind, multicenter trial of adjuvant 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. CHECKMATE-274 randomized 709 patients (353 and 356 to the nivolumab and placebo arms respectively), 699 of whom received at least one dose of study treatment (351 in the nivolumab arm and 348 in the placebo arm). Patients received nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks until recurrence or toxicity for a maximum of 1 year. The median duration of treatment was 8.77 months (range: 0 to 12.5) and 8.21 months (range: 0 to 12.6) for nivolumab and placebo arms, respectively. The extent of exposure among all treated subjects was approximately the same for the nivolumab arm compared with the placebo arm (19.0 vs 18.0 doses).

Twenty-two patients (6.3%) in the treatment group and 17 patients (4.9%) in the placebo arm died from causes other than disease progression. In the treatment group, 2 patients (0.6%) died from pneumonitis which was attributed to treatment with nivolumab. Fatalities that were attributed to other reasons and were not considered related to study drug were reported in 17 (4.8%) subjects in the nivolumab arm. These included sepsis and septic shock (3), pulmonary thromboembolism (2), disease

progression in new lung primary, overall clinical deterioration, sudden death, surgery related complications, fatal bowel perforation, rupture of the abdominal aorta, meningitis, kidney failure and sepsis, syncope and heart failure, atrial fibrillation with rapid ventricular response, cardiopulmonary failure, and liver failure and death. The cause of death in 3 patients in the nivolumab arm was unknown.

Nivolumab was discontinued for adverse reactions in 13% of patients; the most common adverse reactions reported were pneumonitis, rash, increased alanine amino transferase, and colitis. Nivolumab was delayed for adverse reactions in 16% of patients; the most common adverse reactions reported were diarrhea, alanine amino transferase increase, lipase increased, blood creatinine increased, and hyperthyroidism.

Serious adverse reactions occurred in 9% of patients. The most frequent serious adverse reactions reported were pneumonitis, colitis, and acute kidney injury (0.9% each). The most common adverse reactions (reported in >10% of patients) were rash, fatigue/asthenia, pruritus, thyroid disorders, and diarrhea. Grade 3-4 adverse reactions were reported in 17.9% of nivolumab patients and in 7.2% of placebo patients.

First-line Treatment of Unresectable or Metastatic Urothelial Carcinoma:

The safety of nivolumab was evaluated in CHECKMATE-901, a randomized, open-label trial in 608 cisplatin-eligible patients with unresectable or metastatic urothelial carcinoma (see 14 CLINICAL TRIALS). Patients received either nivolumab 360 mg with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by single-agent nivolumab 480 mg every 4 weeks until disease progression, unacceptable toxicity, or 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.

The median duration of therapy was 7.4 months (range: 0.0 to 47.9) in patients receiving nivolumab with chemotherapy, and 3.7 months (range: 0.0 to 14.3) in patients receiving chemotherapy alone.

Serious treatment-related adverse reactions occurred in 24.7% of patients receiving nivolumab in combination with chemotherapy. The most frequent serious treatment-related adverse reactions reported in ≥2% of patients who received nivolumab with chemotherapy were thrombocytopenia (4.0%), acute kidney injury (2.6%), and anemia (2.0%). The most frequent treatment-related adverse reactions (reported in ≥20% of patients) were anemia, neutropenia, nausea, fatigue, thrombocytopenia, decreased appetite, white blood cell count decreased, and rash. Grade 3-4 treatment-related adverse reactions were reported in 61.5% of patients receiving nivolumab with chemotherapy and in 51.4% of patients receiving chemotherapy alone.

Fatal adverse reactions considered treatment-related, occurred in 7 (2.3%) patients who received nivolumab in combination with chemotherapy; these included sepsis (2 patients), myocarditis, adrenal insufficiency, acute kidney injury, thrombocytopenia and hypovolemic shock (1 patient each). Two patients (0.7%) who received chemotherapy alone, died due to acute kidney failure and septic shock (1 patient each).

Nivolumab and/or chemotherapy were discontinued in 21.1% of patients and were delayed in 61.5% of patients for a treatment-related adverse reaction. In the chemotherapy alone arm, 17.4% of patients

discontinued treatment and 50.0% of patients had treatment delayed due to a treatment-related adverse reaction.

Unresectable or Metastatic Treatment of ESCC:

The safety of nivolumab in combination with chemotherapy or ipilimumab was evaluated in CHECKMATE-648, a randomized, active-controlled, multicenter, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic ESCC (see 14 CLINICAL TRIALS).

Among patients who received nivolumab in combination with ipilimumab or chemotherapy, 158 (49%) and 156 (48%) had tumour cell PD-L1 expression ≥ 1%, respectively.

Patients received one of the following treatments:

- Nivolumab 240 mg on days 1 and 15, 5-FU (fluorouracil) 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle).
- Nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks.
- 5-FU (fluorouracil) 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle).

First-line Treatment of Unresectable or Metastatic ESCC: In Combination with Ipilimumab

Among patients who received nivolumab and ipilimumab, 28% were exposed for >6 months and 15% were exposed for >1 year. The median duration of exposure was 2.8 months (range: 0 to 24 months).

Fatal treatment-related adverse reactions occurred in 5 (1.6%) patients who received nivolumab in combination with ipilimumab; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome. Serious adverse reactions occurred in 69% of patients receiving nivolumab in combination with ipilimumab. Nivolumab and/or ipilimumab were discontinued in 23% of patients and were delayed in 47% of patients for an adverse reaction.

The most frequent serious adverse events reported in ≥2% of patients who received nivolumab with ipilimumab were pneumonia (9.6%), pyrexia (4.3%), pneumonitis (4.0%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%). The most common adverse events reported in ≥20% of patients treated with nivolumab in combination with ipilimumab were rash, pyrexia, nausea, diarrhea, fatigue, and constipation.

First-line Treatment of Unresectable or Metastatic ESCC: In Combination with Fluoropyrimidine- and Platinum-containing Chemotherapy

Among patients who received nivolumab with chemotherapy, 48% were exposed for >6 months and 20% were exposed for >1 year. The median duration of exposure was 5.7 months (range: 0.1 to 30.6 months).

Fatal treatment-related adverse events occurred in 5 (1.6%) patients who received nivolumab in combination with chemotherapy; these included pneumonitis, pneumatosis intestinalis, pneumonia, and acute kidney injury. Serious adverse events occurred in 62% of patients receiving nivolumab in combination with chemotherapy. nivolumab and/or chemotherapy were discontinued in 39% of patients and were delayed in 71% of patients for an adverse event.

The most frequent serious adverse events reported in ≥2% of patients who received nivolumab with chemotherapy were pneumonia (10.6%), dysphagia (6.5%), esophageal stenosis (2.9%), acute kidney injury (2.9%), and pyrexia (2.3%). The most common adverse events reported in ≥20% of patients treated with nivolumab in combination with chemotherapy were nausea, decreased appetite, constipation, stomatitis, fatigue, diarrhea, and vomiting.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Nivolumab is most commonly associated with adverse reactions resulting from increased or excessive immune activity (see 7 Warnings and Precautions for guidance on management of immune-mediated adverse reactions). Most of these adverse reactions, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of Opdivo SC (see 7 Warnings and Precautions).

SUBCUTANEOUS FORMULATION (Opdivo SC)

CHECKMATE-67T:

Table 10 reflects adverse reactions observed in CHECKMATE-67T following exposure to Opdivo SC (1200 mg SC injection every 4 weeks) for a median treatment duration of 6.6 months (range: 0-22.4 months) or intravenous nivolumab (3 mg/kg IV infusion every 2 weeks) for a median treatment duration of 7.69 months (range: 0-24).

Table 10: Adverse Reactions in ≥1% of Patients Receiving Opdivo SC - CHECKMATE 67T

Adverse Reaction (System Organ Class Preferred Term)	Opdivo SC (n=247)		Nivolumab IV (n = 245)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood and Lymphatic Disorders				
Eosinophilia	2.0	0	2.4	0
Endocrine				
Hypothyroidism[a]	9.7	0	12.2	0
Adrenal insufficiency	2.0	1.2	0.8	0
Gastrointestinal				
Diarrhea	9.7	0.4	13.5	0.4
Abdominal pain[b]	9.7	0	9.0	0.4
Nausea	8.1	0	9.0	0
Constipation	7.7	0	6.1	0
Vomiting	6.1	0.4	4.9	0

Adverse Reaction (System Organ Class Preferred Term)	Opdivo SC (n=247)		Nivolumab IV (n = 245)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Dry mouth	2.0	0	1.6	0
General				
Fatigue[c]	19.8	2.4	24.9	3.3
Injection site reaction[d]	6.9	0	0	0
Edema[e]	5.7	0.4	10.6	0.8
Pyrexia[f]	2.4	0	5.3	0
Investigations				
Weight decreased	4.5	0	7.8	1.2
Metabolism and Nutrition				
Hyperglycemia	9.3	2.4	13.1	2.0
Decreased appetite	8.9	0	11.4	0.8
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[g]	20.2	1.2	29.4	2.4
Arthralgia	11.7	0.4	15.9	0.4
Arthritis[h]	2.8	0	1.2	0
Nervous System Disorders				
Peripheral neuropathy[i]	1.6	0	1.2	0
Skin and Subcutaneous Tissue				
Pruritus	16.2	0.4	21.2	0
Rash[j]	13.4	1.2	11.8	1.2
Dry skin	1.6	0	1.6	0
Erythema	1.2	0	1.2	0
Psoriasis	1.2	0	0	0
Respiratory, Thoracic, and Mediastinal				
Cough[k]	10.9	0	11.4	0
Dyspnea[l]	4.9	2.0	8.6	0.4
Pneumonitis[m]	4.9	1.6	2.4	0.4

Incidences presented in this table are based on reports of treatment-emergent adverse events.

[a] Includes hypothyroidism, autoimmune hypothyroidism, central hypothyroidism, and primary hypothyroidism.

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

[c] Includes fatigue, asthenia.

[d] Includes injection site reactions, injection site erythema, application site pain, injection site edema, injection site pain, application site erythema, application site rash, injection site discoloration, injection site inflammation, and injection site

pruritus.
[e] Includes edema, generalised edema, peripheral edema, peripheral swelling and swelling.
[f] Includes pyrexia, body temperature increased, and tumour associated fever
[g] Includes musculoskeletal pain, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, sacral pain, and spinal pain.
[h] Includes arthritis, autoimmune arthritis osteoarthritis, polyarthritis, and seronegative arthritis .
[i] Includes peripheral neuropathy, dysaesthesia, hyperaesthesia, hypoaesthesia, peripheral motor neuropathy, peripheral nerve paresis, peripheral sensorimotor, and peripheral sensory neuropathy.
[j] Includes rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash vesicular, and rash pustular.
[k] Includes couch, and productive cough.
[l] Includes dyspnea, dyspnea exertional.
[m] Includes pneumonitis and interstitial lung disease.

Immune-Mediated Adverse Reactions

Table 11: Immune-Mediated Adverse Reactions of Patients Receiving Opdivo SC and Intravenous nivolumab in CHECKMATE 67T

Category	Severity	Nivolumab SC (n=247)	Nivolumab IV (n=245)
Immune-Mediated Endocrinopathies			
Endocrinopathies (incidence (N (%))	Any Grade	31 (12.6)	44 (18.0)
	Grade 3-4	2 (0.8)	3 (1.2)
Thyroid disorders	Any Grade	29 (11.7)	41 (16.7)
	Grade 3-4	0	0
Adrenal insufficiency	Any Grade	3 (1.2)	2 (0.8)
	Grade 3-4	2 (0.8)	0
Diabetes	Any Grade	0	1 (0.4)
	Grade 3-4	0	1 (0.4)
Pituitary disorder	Any Grade	0	3 (1.2)
	Grade 3-4	0	2 (0.8)
Immune-Mediated Gastrointestinal Adverse Reactions			
Gastrointestinal events (incidence (N (%))	Any Grade	15 (6.1)	13 (5.3)
	Grade 3-4	0	1 (0.4)
Immune-Mediated Hepatic Adverse Reactions			
Hepatic events (incidence (N (%))	Any Grade	20 (8.1)	27 (11.0)
	Grade 3-4	5 (2.0)	9 (3.7)
Immune-Mediated Pulmonary Adverse Reactions			
Pulmonary events (incidence (N (%))	Any Grade	13 (5.3)	8 (3.3)
	Grade 3-4	4 (1.6)	2 (0.8)

Category	Severity	Nivolumab SC (n=247)	Nivolumab IV (n=245)
Immune-Mediated Renal Adverse Reactions			
Renal events (incidence (N (%))	Any Grade	7 (2.8)	12 (4.9)
	Grade 3-4	0	0
Immune-Mediated Skin Adverse Reactions			
Skin events (incidence (N (%))	Any Grade	57 (23.1)	65 (26.5)
	Grade 3-4	4 (1.6)	3 (1.2)
Immune-Mediated Hypersensitivity / Infusion Reactions			
Hypersensitivity / Infusion Reactions events (incidence (N (%))	Any Grade	1 (0.4)	6 (2.4)
	Grade 3-4	1 (0.4)	0

INTRAVENOUS FORMULATION (Opdivo)

Additional clinically important adverse reactions have also been reported following intravenous administration of nivolumab or nivolumab in combination with other therapeutic agents. The following sections below present data from a separate Product Monograph for intravenous Opdivo formulation studies.

Unresectable or Metastatic Melanoma:

CHECKMATE-066:

In CHECKMATE-066 (monotherapy), the most frequently reported adverse reactions (occurring at ≥15%) were fatigue, nausea, diarrhea, pruritus and rash. The majority of adverse reactions were mild to moderate (Grade 1 or 2). Intravenous nivolumab therapy was discontinued for adverse reactions in 2.4% of patients. Fifteen percent (15%) of nivolumab-treated patients had a drug delay for an adverse reaction.

Table 12 lists adverse reactions that occurred in at least 1% of patients in CHECKMATE-066.

Table 12: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-066

	Nivolumab (n=206)		Dacarbazine (n=205)	
System Organ Class Preferred Term	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue	30.1	0	25.4	1.5
Pyrexia	7.3	0	5.4	0.5
Edema	3.4	0.5	1.0	0
Gastrointestinal Disorders				
Nausea	16.5	0	41.5	0
Diarrhea	16.0	1.0	15.6	0.5
Constipation	10.7	0	12.2	0

Vomiting	6.3	0.5	21.0	0.5
Abdominal pain	4.4	0	2.4	0
Skin and Subcutaneous Tissue Disorders				
Rash	20.9	1.0	4.9	0
Pruritus	17.0	0.5	5.4	0
Vitiligo	10.7	0	0.5	0
Erythema	6.3	0	2.0	0
Dry Skin	4.4	0	1.0	0
Alopecia	3.4	0	1.0	0
Nervous System Disorders				
Headache	4.4	0	7.3	0
Peripheral Neuropathy	2.9	0	5.4	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	8.7	0.5	2.9	0
Arthralgia	5.8	0	1.5	0
Metabolism and Nutrition Disorders				
Decreased appetite	5.3	0	9.3	0
Hyperglycemia	1.5	1.0	0	0
Endocrine Disorders				
Hypothyroidism	4.4	0	0.5	0
Hyperthyroidism	3.4	0.5	0	0
Hypopituitarism	1.5	0	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	4.4	0	3.9	0
Infections and Infestations				
Upper respiratory tract infection	1.9	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	2.9	0	1.0	0
Dyspnea	1.9	0	2.0	0
Pneumonitis	1.5	0	0	0
Renal and Urinary Disorders				
Renal Failure	1.5	0.5	0	0

a. Incidences presented in this table are based on reports of drug-related adverse events.

CHECKMATE-067:

At the primary analysis (28 months minimum follow-up), in CHECKMATE-067 (monotherapy and combination therapy), the most common adverse reactions (reported in at least 20% of patients) in either the nivolumab in combination with ipilimumab arm or the single-agent nivolumab arm were fatigue, rash, diarrhea, nausea and pruritis. The overall frequency of serious adverse events (SAEs) was higher in the nivolumab in combination with ipilimumab group (71.2%) compared to the nivolumab monotherapy (42.5%) and ipilimumab monotherapy groups (55.0%). The overall frequency of drug-related SAEs was higher in the nivolumab in combination with ipilimumab group (48.6%) compared to the nivolumab monotherapy (9.9%) and ipilimumab monotherapy groups (22.5%). The overall frequency of AEs leading to discontinuation was higher in the nivolumab in combination with ipilimumab group (47.0%) compared to the nivolumab monotherapy (18.2%) and ipilimumab monotherapy (25.1%) groups.

A total of 127 (40.6%), 141 (45.0%), and 195 (62.7%) deaths were reported in nivolumab in combination with ipilimumab, nivolumab, and ipilimumab groups, respectively prior to final database lock. Disease progression was the most common cause of death in all 3 groups (109 [34.8%], 123 [39.3%], and 181 [52.8%]), respectively. There were two treatment-related deaths in patients receiving nivolumab in combination with ipilimumab. The cause of death was autoimmune myocarditis and liver toxicity/liver necrosis, respectively. There was one treatment-related death in patients treated with single-agent nivolumab. The cause of death was neutropenia. There was one treatment related death in patients treated with ipilimumab. The cause of death was colon perforation. Within 100 days of the last study dose, in the nivolumab in combination with ipilimumab group fifteen subjects (4.8%) had death classified as 'other' by the investigator, these included: pulmonary embolus (3 events), sudden cardiac death, cardiopulmonary arrest, respiratory failure (2 events), emphysema and lung fibrosis, pneumonia (2 events), cerebral hemorrhage, worsening of general condition, multi-organ failure, accident, and euthanasia. In the nivolumab monotherapy group, seven subjects (2.2%) had death classified as "other", these included: gastrointestinal bleeding, upper gastrointestinal bleeding, intraabdominal problem, perforated diverticulitis, intracranial hemorrhage and subarachnoid hemorrhage, sepsis, and macrophagic activation syndrome. The causes of death classified as 'other' were not considered related to study drug by the investigator.

Among the patients treated with nivolumab in combination with ipilimumab, 196/313 (63%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 147 patients in this group who continued treatment in the single-agent phase, 71 (48%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase.

As compared to the overall study population, no meaningful differences in safety were observed based on BRAF status or PD-L1 expression level.

Table 13 summarizes the adverse reactions that occurred in at least 1% of patients in either nivolumab-containing arm or in the ipilimumab arm in CHECKMATE-067.

Table 13: Adverse Reactions Reported in at Least 1% of Patients (CHECKMATE-067)

System Organ Class Preferred Term	Nivolumab + ipilimumab (n=313)		Nivolumab (n=313)		ipilimumab (n=311)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]					
General Disorders and Administration Site Conditions						
Fatigue	45.7	4.2	40.9	1.3	33.4	1.6
Pyrexia	19.2	0.6	7.0	0	6.8	0.3
Chills	7.0	0	3.8	0	3.2	0
Influenza-like Illness	2.9	0	3.5	0	3.5	0.3
Edema[b]	3.5	0	3.5	0	2.6	0.3
Malaise	2.9	0.3	1.0	0.3	0.3	0
Pain	2.2	0	0.6	0	1.6	0
General physical health deterioration	1.0	0.3	0	0	0.3	0.3
Thirst	1.3	0	0	0	0	0

Gastrointestinal Disorders						
Diarrhea	45.4	9.6	21.4	2.9	33.8	5.8
Nausea	28.1	2.2	13.1	0	16.4	0.6
Vomiting	16.0	2.6	7.0	0.3	7.7	0.3
Abdominal pain	12.8	0.3	8.3	0	11.3	1.0
Colitis	13.1	8.6	2.9	1.3	11.6	8.4
Dry Mouth	6.1	0	4.2	0	2.3	0
Constipation	3.8	0	6.1	0	5.5	0
Stomatitis	3.8	0.3	2.6	0	1.6	0
Dyspepsia	2.6	0	3.5	0	2.3	0
Gastritis	1.3	0.6	0	0	0.3	0
Abdominal distension	1.0	0	2.6	0	0.6	0
Pancreatitis	1.0	0.3	1.0	1.0	0.3	0
Skin and Subcutaneous Tissue Disorders						
Rash[c]	46.6	5.4	30.4	1.6	36.7	2.6
Pruritus	35.8	1.9	21.4	0.3	36.3	0.3
Vitiligo	8.6	0	8.9	0.3	5.1	0
Dry Skin	4.8	0	5.4	0	3.5	0
Erythema	1.9	0.3	2.9	0	1.6	0.3
Hyperhidrosis	3.8	0	1.0	0	1.3	0
Night sweats	2.9	0	1.0	0	1.6	0
Eczema	2.9	0	2.2	0.3	0.6	0
Alopecia	1.9	0	2.2	0	0	0
Skin hypopigmentation	1.6	0	2.2	0	0.6	0
Hair colour changes	1.3	0	1.3	0	0.3	0
Photosensitivity	1.0	0	0.3	0	0.3	0
Psoriasis	0.3	0	1.6	0	0.3	0
Urticaria	1.0	0	0	0	1.0	0
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	13.4	0.3	9.3	0.3	6.8	0
Musculoskeletal Pain[d]	8.6	0.3	10.9	0.3	8.4	0
Muscular weakness	1.9	0.3	1.3	0	1.0	0
Muscle spasms	2.2	0.6	1.9	0	1.3	0
Musculoskeletal stiffness	1.0	0	1.0	0.3	0.3	0
Myositis	1.0	0	0	0	0	0
Arthritis	0.3	0	1.0	0	0.3	0
Metabolism and Nutrition Disorders						
Decreased appetite	19.2	1.3	11.5	0	13.2	0.3
Dehydration	4.5	1.6	0.3	0	1.6	0.6
Hyperglycaemia	2.6	1.3	0.6	0.3	0.6	0
Hyponatremia	3.2	1.3	0.6	0.3	1.0	0.6
Hypoalbuminemia	1.9	0	0.6	0	0.6	0
Hypokalemia	2.2	0.3	0.3	0.3	0.6	0.3
Hypomagnesemia	1.0	0	0.6	0	0.6	0
Diabetes Mellitus	1.0	0.6	1.0	0.3	0	0
Hypocalcemia	1.6	0	0	0	0	0
Endocrine Disorders						
Hypothyroidism	16.3	0.3	10.2	0	4.5	0
Hyperthyroidism	10.9	1.0	4.8	0	1.0	0

Hypophysitis	7.3	1.6	0.6	0.6	3.9	1.6
Thyroiditis	4.8	0.6	1.3	0	0.3	0
Adrenal Insufficiency	3.5	1.9	1.0	0.3	1.3	0.3
Hypopituitarism	1.6	1.0	0.3	0.3	1.3	0.6
Respiratory, Thoracic, and Mediastinal Disorders						
Dyspnea	11.8	1.0	7.0	0.3	4.5	0
Cough	8.3	0	6.4	0.6	5.1	0
Pneumonitis	7.3	1.0	1.6	0.3	1.9	0.3
Wheezing	1.0	0	1.0	0	0.3	0
Nervous System Disorders						
Headache	10.9	0.6	7.7	0	8.0	0.3
Dizziness	5.4	0	5.4	0	3.5	0
Neuropathy Peripheral	5.8	0.3	3.5	0.3	1.9	0
Dysgeusia	4.5	0	5.8	0	2.9	0
Lethargy	3.2	0	1.6	0	1.6	0
Paresthesia	1.6	0	2.9	0.3	2.6	0
Syncope	1.3	0.3	0.3	0.3	0	0
Somnolence	1.0	0.3	0.3	0	0	0
Tremor	1.0	0	0	0	0.3	0
Injury, Poisoning, and Procedural Complications						
Infusion-related reaction	2.9	0	2.6	0.3	2.6	0.3
Blood and Lymphatic System Disorders						
Anemia	4.4	0.6	1.6	0	2.6	0
Eosinophilia	2.2	0	0.6	0	0.3	0
Thrombocytopenia	2.2	0.6	1.9	0.3	0	0
Neutropenia	1.3	0.3	1.3	1.0[e]	0.6	0.3
Hepatobiliary Disorders						
Hepatitis	4.5	3.8	0.6	0.6	0.6	0.3
Hyperbilirubinaemia	2.2	0	0.3	0	1.0	0
Hepatotoxicity	3.2	2.6	0.6	0.6	0.3	0
Hepatocellular injury	1.0	0.6	1.0	0.6	0.3	0
Eye Disorders						
Blurred vision	2.2	0	1.9	0	1.6	0
Dry eye	1.3	0	2.2	0	1.6	0
Uveitis	1.0	0	0.6	0	1.0	0.3
Psychiatric Disorders						
Anxiety	1.6	0	0.3	0	0.6	0
Confusional state	1.0	0	0.3	0	0	0
Depression	1.6	0	1.0	0	0.6	0.3
Infections and Infestations						
Upper respiratory tract infection	1.3	0	0.6	0	0.6	0
Conjunctivitis	1.3	0	0.3	0	0.6	0
Pneumonia	1.0	0	0	0	0.3	0
Vascular Disorders						
Hypotension	1.9	0.6	0.3	0.3	1.0	0
Hypertension	1.3	0.3	1.6	0.6	1.3	0.6
Flushing	1.6	0	1.0	0	1.6	0
Renal and Urinary Disorders						

Acute kidney injury	1.3	1.0	0	0	0.6	0
Immune System Disorders						
Hypersensitivity	1.3	0	1.9	0	0.0	0
Cardiac Disorders						
Tachycardia	1.6	0	0	0	0.6	0
Palpitations	1.0	0	0.3	0	0.6	0

a. Incidences presented in this table are based on reports of drug-related adverse events.
b. Edema is a composite term which includes peripheral edema, peripheral swelling and swelling
c. Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform and drug eruption.
d. Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskelet
e. l discomfort, myalgia, neck pain, pain in extremity, and spinal pain
f. Includes one Grade 5 event (refer to **Blood and Lymphatic System Disorders** - Neutropenia).

Based on a follow-up of 60 months, there were no new safety signals observed and therefore no meaningful changes occurred in the safety profile of nivolumab and nivolumab in combination with ipilimumab.

CHECKMATE-037:

In CHECKMATE-037 (monotherapy), the most frequently reported adverse reactions (occurring at ≥15%) were fatigue, nausea, diarrhea, pruritus and rash. The majority of adverse reactions were mild to moderate (Grade 1 or 2). nivolumab was discontinued due to adverse reactions in 2% of patients receiving nivolumab and in 8% of patients receiving chemotherapy. Ten percent (10%) of nivolumab-treated patients had a drug delay for an adverse reaction. Serious adverse reactions occurred in 6% of patients receiving nivolumab. Grade 3 and 4 adverse reactions occurred in 5% of patients receiving nivolumab.

The frequency of adverse events in the cardiac disorders system organ class regardless of causality was higher in the nivolumab group (27/268; 10.1% all grades, 4.1% grade 3-5) than in the chemotherapy group (1/102; 1% all grades) in post-CTLA4/BRAF inhibitor metastatic melanoma population (CHECKMATE-037). Incidence rates of cardiac events per 100 person-years of exposure were 13.4 in the nivolumab group vs none in the chemotherapy group. Serious cardiac events were reported by 4.5% patients in the nivolumab group vs none in the chemotherapy group. One serious cardiac adverse event (ventricular arrhythmia) was considered related to nivolumab by investigators.

At the final analysis for CHECKMATE-037, there were no new safety signals observed and therefore with additional follow-up, no meaningful changes occurred in the safety profile of nivolumab.

Table 14 lists adverse reactions that occurred in at least 1% of patients in CHECKMATE-037.

Table 14: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-037

System Organ Class Preferred Term	Nivolumab (n=268)		Chemotherapy (n=102)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue	29.5	0.7	40.2	3.9
Pyrexia	3.4	0	4.9	1.0
Edema	3.0	0	1.0	0
Gastrointestinal Disorders				
Diarrhea	11.2	0.4	14.7	2.0
Nausea	9.3	0	37.3	2.0
Vomiting	3.4	0.4	19.6	2.0
Abdominal pain	2.6	0.4	2.9	0
Constipation	2.2	0	13.7	1.0
Stomatitis	1.1	0	2.9	0
Colitis	1.1	0.7	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	16.8	0.4	6.9	0
Pruritus	16.0	0	2.0	0
Vitiligo	5.2	0	0	0
Dry Skin	4.9	0	0	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	5.6	0.4	11.8	1.0
Musculoskeletal Pain	5.2	0	9.8	0
Metabolism and Nutrition Disorders				
Decreased appetite	5.2	0	15.7	0
Hyperglycemia	1.1	0.7	0	0
Endocrine Disorders				
Hypothyroidism	5.6	0	0	0
Hyperthyroidism	1.9	0	1.0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea	3.7	0	7.8	0
Cough	2.6	0	0	0
Pneumonitis	2.2	0	0	0
Nervous System Disorders				
Peripheral Neuropathy	2.6	0.4	22.5	2.0
Headache	2.6	0	2.9	0
Dizziness	1.5	0	2.9	0
Investigations				
Lipase increased	1.5	1.1	2.0	1.0
Amylase increased	1.1	0.7	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	1.1	0.4	6.9	0
Infections and Infestations				
Upper respiratory tract infection	1.1	0	0	0

Eye Disorders				
Uveitis	1.5	0.4	0	0

a. Incidences presented in this table are based on reports of drug-related adverse events.

Overall, there were no differences in the types or frequencies of adverse drug reactions reported in CHECKMATE-066 and CHECKMATE-037. The frequency of cardiac adverse events was lower in the nivolumab group than in the dacarbazine group in the metastatic melanoma without prior treatment population (CHECKMATE-066).

The safety profile of nivolumab in combination with ipilimumab in CHECKMATE-069 was consistent with that observed in CHECKMATE-067.

Adjuvant Treatment of Melanoma:

CHECKMATE-238:

In CHECKMATE-238, the most frequently reported adverse reactions (occurring at ≥10%) in the nivolumab group were fatigue, rash, diarrhea, pruritus, nausea, arthralgia, musculoskeletal pain, and hypothyroidism. The majority of adverse reactions were mild to moderate (Grade 1 or 2). Grade 3-4 adverse reactions were reported in 14% of nivolumab patients and 46% of ipilimumab patients.

Study therapy was discontinued for adverse reactions in 8% of nivolumab patients and 42% of ipilimumab patients. In the nivolumab group, the most frequently reported adverse reactions (occurring at ≥1%) leading to discontinuation were diarrhea (1.5%) and colitis (1.1%). Twenty percent (20%) of nivolumab-treated patients had a drug delay (dose omission or reduction) for an adverse reaction. The most frequently reported adverse reactions (occurring at ≥1%) leading to dose delay were diarrhea (3.3%), ALT increased (2.9%), AST increased (2.4%), hypothyroidism (2.0%), hyperthyroidism (1.8%), arthralgia (1.5%), increased lipase (1.3%) and increased amylase (1.1%).

Serious adverse reactions occurred in 5% of nivolumab patients and 31% of ipilimumab patients. The most frequently reported serious adverse reactions (occurring at ≥0.5%) in nivolumab patients were diarrhea (0.7%) and pneumonitis (0.7%).

Table 15 lists adverse reactions that occurred in at least 1% of patients in CHECKMATE-238 at the pre-specified interim analysis (18 months of minimum follow-up). At the final analysis for CHECKMATE-238 with a minimum of 48 months of follow-up, there were no new safety signals observed and therefore with additional follow-up, no meaningful changes occurred in the safety profile of nivolumab.

Table 15: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-238

System Organ Class Preferred Term	Nivolumab (n=452)		Ipilimumab (n=453)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue[b]	46.5	0.7	44.4	1.8
Influenza like illness	2.0	0	2.4	0.2
Pyrexia	1.5	0	11.9	0.4
Chest pain	1.1	0	0.4	0
Pain	1.1	0.2	1.5	0
Gastrointestinal Disorders				
Diarrhea	24.3	1.5	45.9	9.5
Nausea	15.0	0.2	20.1	0
Abdominal pain[c]	9.3	0	13.0	0.2
Dry mouth	5.3	0	3.1	0
Stomatitis	3.3	0.2	1.8	0
Dyspepsia	2.9	0	3.8	0
Vomiting	2.7	0.2	9.7	0.4
Constipation	2.4	0	2.2	0
Colitis	2.0	0.7	11.3	8.6
Abdominal distension	1.8	0	2.0	0
Flatulence	1.1	0	0.7	0
Skin and Subcutaneous Tissue Disorders				
Rash[d]	28.5	1.1	42.8	4.9
Pruritus	23.2	0	33.6	1.1
Erythema	4.4	0	3.5	0
Vitiligo	4.2	0	1.8	0
Eczema	2.9	0	1.8	0.2
Alopecia	1.8	0	2.9	0
Dry Skin	1.8	0	1.5	0.4
Generalized pruritus	1.8	0	1.5	0
Nervous System Disorders				
Headache	9.7	0.2	17.4	1.5
Dizziness	3.5	0	3.5	0
Dysgeusia	2.7	0	2.6	0
Paraesthesia	2.7	0	2.2	0
Neuropathy peripheral	1.1	0	3.3	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	12.6	0.2	10.8	0.4
Musculoskeletal pain[e]	11.3	0.4	9.5	0.2
Musculoskeletal stiffness	1.1	0	0.9	0
Tendonitis	1.1	0	0	0
Metabolism and Nutrition Disorders				

Decreased appetite	4.0	0	8.6	0.2
Hyponatremia	1.1	0	1.5	0.7
Endocrine Disorders				
Hypothyroidism[f]	11.1	0.2	6.8	0.4
Hyperthyroidism	8.4	0.2	4.0	0.2
Thyroiditis	2.2	0	1.8	0.2
Hypophysitis	1.5	0.4	10.6	2.4
Adrenal insufficiency	1.1	0.2	2.6	0.7
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	2.0	0	1.5	0
Eye Disorders				
Dry eye	2.2	0	1.5	0
Vision blurred	1.3	0	2.2	0
Psychiatric Disorders				
Insomnia	1.8	0	1.8	0
Vascular Disorders				
Flushing	1.5	0	3.3	0
Cardia Disorders				
Palpitations	1.3	0	0.2	0
Immune System Disorders				
Sarcoidosis	1.1	0.2	0.2	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea	4.2	0.4	5.3	0
Cough	2.2	0	5.1	0
Pneumonitis	1.3	0	2.4	0.9
Blood and Lymphatic System Disorders				
Anemia	1.1	0	2.2	0.2

a. Incidences presented in this table are based on reports of drug-related adverse events (CTCAE v4.0).
b. Includes asthenia.
c. Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness.
d. Includes dermatitis also described as acneiform, allergic, bullous, or exfoliative and rash described as generalized, erythematous, macular, papular, maculopapular, pruritic, pustular, vesicular, or butterfly, and drug eruption.
e. Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, spinal pain, and pain in extremity.
f. Includes secondary hypothyroidism and autoimmune hypothyroidism.

CHECKMATE 76K:

In CHECKMATE-76K, the most frequently reported adverse reactions (occurring at ≥10%) in the nivolumab group were fatigue, pruritus, diarrhea, rash, arthralgia, and hypothyroidism. The majority of adverse reactions were mild to moderate (Grade 1 or 2). Grade 3-4 adverse reactions were reported in 10.3% of nivolumab patients and 2.3% of placebo patients. A fatal adverse reaction occurred in 1 (0.2%) nivolumab patient (heart failure and acute kidney injury).

Serious adverse reactions occurred in 4.8% of nivolumab patients and 1.1% of placebo patients. The most frequently (occurring in > 1% patient) reported serious adverse reactions in nivolumab patients were colitis, diarrhea, adrenal insufficiency and myocarditis.

Study therapy was discontinued for adverse reactions in 14.7% of nivolumab patients and 2.7% of placebo patients. In the nivolumab group, the most frequently reported adverse reactions (occurring at

≥1%) leading to discontinuation were athralgia (1.7%), diarrhea (1.1%), colitis (1.0%), increased ALT (1.0%), increased AST (1.0%) and rash (1.0%). 15.6% of nivolumab-treated patients had a drug delay (dose omission) for an adverse reaction. The most frequently reported adverse reactions (occurring at ≥1%) leading to dose delay were diarrhea (1.7%), arthralgia (1.5%), increased ALT (1.3%), increased blood creatinine phosphokinase (1.3%), hypothyroidism (1.1%), and hyperthyroidism (1.0%).

Table 16 lists adverse reactions that occurred in at least 1% of nivolumab-treated patients in CHECKMATE-76K (7.8 months of minimum follow-up).

Table 16: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-76K

	Nivolumab (n=524)		Placebo (n=264)	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue[b]	27.1	0	26.9	0.4
Gastrointestinal Disorders				
Diarrhea	15.3	0.8	9.5	0
Nausea	7.4	0	2.7	0
Dry mouth	6.9	0	2.7	0
Abdominal pain[c]	1.9	0	2.3	0
Stomatitis[d]	1.9	0	1.1	0
Colitis[e]	1.5	0.4	0	0
Constipation	1.5	0	0.8	0
Pancreatitis[f]	1.1	0.2	0	0
Vomiting	1.1	0	0.8	0
Skin and Subcutaneous Tissue Disorders				
Rash[g]	20.2	1.3	9.8	0
Pruritus	18.5	0.2	9.5	0
Eczema[h]	2.1	0	0.8	0
Dry skin	1.7	0.2	1.1	0
Vitiligo	1.7	0	1.1	0
Lichenoid keratosis	1.0	0	0.4	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough[i]	3.1	0	0.4	0
Dyspnea[j]	2.7	0	0	0
Pneumonitis[k]	1.3	0.2	0.4	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	5.2	0	0.8	0
Nervous System Disorders				
Headache	4.0	0	3.8	0
Dizziness	2.1	0	1.5	0
Eye Disorders				
Dry eye[l]	2.3	0	0.4	0

Musculoskeletal and Connective Tissue Disorders				
Arthralgia	10.3	0.2	5.7	0
Musculoskeletal pain[m]	7.3	0	8.3	0
Arthritis	2.3	0	0	0
Muscle spasms	1.3	0	0.8	0
Endocrine Disorders				
Hypothyroidism[n]	10.5	0	0	0
Hyperthyroidism	6.9	0.2	1.1	0
Adrenal insufficiency	1.9	0.4	1.1	0
Thyroid disorder	1.0	0	0	0
Thyroiditis[o]	1.0	0	0	0
Hepatobiliary disorders				
Hepatitis[p]	1.1	0.6	0.8	0.4
Metabolism and nutrition disorders				
Decreased appetite	3.4	0	0.8	0
Hypophosphatemia	1.3	0.2	1.9	0
Blood and lymphatic system disorders				
Eosinophilia[q]	3.1	0	0.4	0
Thrombocytopenia[r]	1.5	0.2	0.4	0
Investigations				
Increased Transaminases[s]	7.8	1.3	5.3	0.4
Increased Blood creatine phosphokinase	5.7	1.1	4.9	0
Increased Lipase	3.4	0.8	3.0	1.1
Increased Blood thyroid stimulating hormone	2.5	0	1.9	0
Increased Amylase	1.9	0.2	1.5	0
Increased Gamma-glutamyltransferase	1.7	0.6	0	0
Increased Blood bilirubin	1.3	0	0	0
Increased Blood alkaline phosphatase	1.1	0.4	0	0
Increased Blood creatinine	1.1	0	0	0
Decreased Blood thyroid stimulating hormone	1.1	0	0	0

a. Incidences presented in this table are based on reports of drug-related adverse events (CTCAE v5.0).
b. Includes fatigue and asthenia.
c. Includes abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain.
d. Includes stomatitis, aphthous ulcer, mouth ulceration, and mucosal inflammation.
e. Includes colitis, and autoimmune colitis.
f. Includes pancreatitis, and autoimmune pancreatitis.
g. Includes rash, dermatitis, dermatitis described as acneiform, allergic, psoriasiform and rash described as erythematous, follicular, macular, papular, maculo-papular, pruritic, pustular, and vesicular.
h. Includes eczema, dyshidrotic eczema, and eczema nummular.
i. Includes cough, and productive cough.
j. Includes dyspnea and dyspnea exertional.
k. Includes pneumonitis and interstitial lung disease.
l. Includes dry eye
m. Includes musculoskeletal pain, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, spinal pain, sacral pain, pain in extremity, and tendon pain.
n. Includes hypothyroidism and autoimmune hypothyroidism.
o. Includes thyroiditis and autoimmune thyroiditis.
p. Includes hepatitis and autoimmune hepatitis.
q. Includes eosinophilia and increased count eosinophilia.

r. Includes thrombocytopenia and platelet count decreased.
s. Includes increased transaminase, hypertransaminamia, increased aspartate aminotransferase, increased alanine aminotransferase.

Metastatic NSCLC:

Metastatic NSCLC (previously treated):

In patients who received 3 mg/kg nivolumab monotherapy in CHECKMATE-017 and CHECKMATE-057, the most frequently reported adverse drug reactions (occurring at ≥10%) were fatigue, nausea, rash, and decreased appetite (Table 17). The majority of adverse drug reactions were mild to moderate (Grade 1 or 2).

Table 17 summarizes adverse drug reactions that occurred in at least 1% of patients receiving nivolumab in CHECKMATE-017 and CHECKMATE-057.

Table 17: Adverse Drug Reactions Reported in at Least 1% of Patients in CHECKMATE-017 and CHECKMATE-057

Adverse Reaction	Nivolumab (n=418)		Docetaxel (n=397)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
General Disorders and Administration Site Conditions				
Fatigue[a]	26	1	45	8
Pyrexia	3	0	7	0.3
Edema[b]	3	0	11	0.3
Gastrointestinal Disorders				
Nausea	11	0.5	25	1
Diarrhea	8	0.5	22	2
Vomiting	5	0	9	0.3
Constipation	4	0	7	0.5
Stomatitis	3	0	14	2
Skin and Subcutaneous Tissue Disorders				
Rash[c]	11	0.7	10	0.8
Pruritus	7	0	1	0
Urticaria	1	0	0.5	0
Metabolism and Nutrition Disorders				
Decreased appetite	11	0.2	17	1
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[d]	6	0.2	18	1
Arthralgia[e]	6	0	6	0
Respiratory, Thoracic, and Mediastinal Disorders				

Pneumonitis	4	1	0.5[f]	0.3
Cough	4	0.2	1	0
Dyspnea	3	0.5	3	0.3
Nervous System Disorders				
Peripheral neuropathy	4	0	22	2
Headache	1	0	2	0
Endocrine Disorders				
Hypothyroidism	6	0	0	0
Hyperthyroidism	1	0	0	0
Injury, Poisoning and Procedural Complications				
Infusion-related reaction	2	0	2	0.3

a. Includes asthenia.
b. Includes face edema, peripheral edema, local swelling, localized edema, orbital edema, generalized edema, peripheral swelling, swelling face.
c. Includes maculopapular rash, rash erythematous, rash macular, rash papular, rash pustular, rash pruritic, rash generalized, dermatitis, dermatitis exfoliative, dermatitis acneiform, dermatitis bullous, drug eruption, toxic skin eruption, and erythema.
d. Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.
e. Includes arthritis and osteoarthritis.
f. Includes 1 Grade 5 event.

Neoadjuvant NSCLC

CHECKMATE-816:

In CHECKMATE-816, the most frequently reported adverse reactions (occurring at ≥ 10%) in patients who received nivolumab in combination with platinum-doublet chemotherapy were nausea, constipation, vomiting, fatigue, malaise, decreased appetite, rash, alopecia, and peripheral neuropathy.

Table 18 lists adverse reactions that occurred in at least 1% of patients treated with nivolumab and platinum-doublet chemotherapy in CHECKMATE-816.

Table 18: Adverse Reactions Reported in at Least 1% of Patients Receiving nivolumab and Platinum-Doublet Chemotherapy in CHECKMATE-816

	Nivolumab and Platinum-Doublet Chemotherapy (n=176)		Platinum-Doublet Chemotherapy (n=176)	
System Organ Class Preferred Term	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
Blood and Lymphatic System Disorders				
Neutropenia[b]	29.5	15.9	36.9	22.2
Anemia	24.4	3.4	23.3	3.4
Thrombocytopenia[d]	9.7	2.3	10.2	1.1
Leukopenia	8.5	0.6	6.3	1.7
Febrile neutropenia	1.7	1.7	3.4	3.4
Myelosuppression	1.1	1.1	0.6	0.6
Gastrointestinal Disorders				

Nausea	33.0	0.6	41.5	0.6
Constipation	21.0	0	20.5	1.1
Vomiting	8.5	1.1	10.8	0.6
Diarrhea	5.7	0.6	11.4	2.3
Abdominal pain[e]	4.0	0	4.0	0.6
Stomatitis[f]	2.8	0	3.4	0
Dyspepsia	2.3	0	2.8	0
Dry mouth	1.1	0	0.6	0
Epigastric discomfort	1.1	0	0	0
General Disorders and Administration Site Conditions				
Fatigue[h]	21.6	1.7	17.6	0.6
Malaise	13.6	0.6	12.5	0.6
Pyrexia	3.4	0	6.3	0
Edema	2.3	0	4.5	0
Pain	1.1	0.6	2.8	0.6
Skin and Subcutaneous Tissue Disorders				
Rash[j]	19.3	2.3	6.8	0
Alopecia	9.7	0	14.2	0
Pruritus[k]	4.5	0	1.1	0.
Erythema	1.1	0	0	0
Erythema multiforme	1.1	0	0.6	0
Metabolism and Nutrition Disorders				
Decreased appetite	16.5	1.1	21.6	2.3
Hypomagnesemia[l]	3.4	0.6	5.7	0
Hypoglycemia	2.3	1.1	0	0
Hyponatremia	1.7	1.1	2.8	1.1
Hypoalbuminemia	1.1	0	1.7	0
Nervous System Disorders				
Peripheral neuropathy[n]	12.5	0	5.1	0
Dizziness[o]	3.4	0	2.3	0
Respiratory, Thoracic, and Mediastinal Disorders				
Hiccups	6.8	0	13.6	0
Dyspnea	1.7	0	1.7	0
Epistaxis	1.1	0	0	0
Pneumonitis[p]	1.1	0	0	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[q]	4.5	0	2.3	0
Arthralgia	2.3	0.6	4.0	0
Muscular weakness	1.7	0	1.7	0
Endocrine Disorders				
Hyperthyroidism	2.3	0	0	0
Hypothyroidism	1.1	0	0	0
Thyroiditis[r]	1.1	0	0	0
Infections and Infestations				
Pneumonia[s]	1.1	0	1.1	0.6
Immune System Disorders				
Hypersensitivity	3.4	1.7	0.6	0.6
Injury, Poisoning and Procedural Complications				
Infusion related reaction	2.8	0.6	2.3	0.6

Vascular Disorders				
Vasculitis	1.7	0	0	0
Ear and Labyrinth Disorders				
Tinnitus	2.8	0	5.1	0
Renal and Urinary Disorders				
Renal impairment	1.1	0	0.6	0
Cardiac Disorders				
Atrial fibrillation	1.1	0	0.6	0
Hepatobiliary Disorders				
Hepatic function abnormal	1.1	0	0.6	0

a. Incidences presented in this table are based on reports of drug-related adverse events (CTCAE v4.0).
b. Includes neutropenia and neutrophil count decreased.
c. Includes anemia, hemoglobin decreased and iron deficiency.
d. Includes thrombocytopenia, platelet count decreased.
e. Includes abdominal pain, abdominal discomfort and abdominal pain upper.
f. Includes stomatitis, mouth ulceration and mucosal inflammation.
g. Includes dyspepsia and gastroesophageal reflux disease.
h. Includes fatigue and asthenia.
i. Includes edema, generalised edema, edema peripheral, peripheral swelling and swelling.
j. Includes rash, dermatitis atopic, dermatitis bullous, drug eruption, rash maculo-papular, rash pruritic, dermatitis and dermatitis acneiform.
k. Includes pruritus and pruritus allergic.
l. Includes hypomagnesemia and blood magnesium decreased.
m. Includes blood albumin decreased.
n. Includes peripheral neuropathy, dysaesthesia, hypoaesthesia, peripheral motor neuropathy and peripheral sensory neuropathy.
o. Includes dizziness and vertigo.
p. Includes pneumonitis and interstitial lung disease.
q. Includes musculoskeletal pain, musculoskeletal chest pain, back pain, myalgia, neck pain and pain in extremity.
r. Includes thyroiditis and autoimmune thyroiditis.
s. Includes pneumonia, pneumonia bacterial and pneumonia influenzal.

Advanced or Metastatic RCC:

Previously treated:

Table 19 lists adverse reactions that occurred in at least 1% of patients in pivotal renal cell carcinoma trial CHECKMATE-025:

Table 19: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-025

	Nivolumab (n=406)		**Everolimus (n=397)**	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue	36.7	2.7	39.0	4.0
Pyrexia	8.6	0	9.3	0.5
Edema	5.7	0	15.4	0.5
Chills	4.9	0	2.8	0
Chest Pain	2.2	0	1.5	0
Influenza-Like Illness	1.7	0.5	1.0	0
Malaise	1.5	0	1.8	0

Pain	1.2	0.5	0.8	0
Gastrointestinal Disorders				
Nausea	14.0	0.2	16.6	0.8
Diarrhea	12.3	1.2	21.2	1.3
Constipation	5.9	0.2	5.3	0
Vomiting	5.9	0	9.1	0.3
Stomatitis	4.7	0	45.6	7.3
Abdominal pain	3.9	0	4.0	0
Dry Mouth	3.9	0	3.5	0
Dyspepsia	2.0	0	2.5	0
Colitis	1.7	0.7	0	0
Abdominal Distention	1.5	0	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	18.2	1.0	30.7	1.0
Pruritus	14.0	0	9.8	0
Dry Skin	6.4	0	8.3	0
Erythema	2.7	0	1.5	0.3
Alopecia	1.2	0	1.0	0
Hyperhydrosis	1.2	0	0.3	0
Night Sweats	1.0	0	1.0	0
Palmar-Plantar Erythrodysesthesia Syndrome	1.0	0	5.5	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	9.6	0	20.7	0
Dyspnea	9.1	1.0	15.6	0.5
Pneumonitis	4.4	1.5	17.6	3.3
Dysphonia	1.7	0	0.8	0
Nasal Congestion	1.0	0	0.5	0
Wheezing	1.0	0	0.5	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	9.4	0.5	5.5	0
Arthralgia	6.7	0.2	3.5	0
Arthritis	1.7	0.2	0.3	0
Joint Swelling	1.7	0	0.5	0
Muscle Spasms	1.7	0	0.8	0
Muscular Weakness	1.0	0.2	0	0
Musculoskeletal Stiffness	1.0	0.2	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	11.8	0.5	20.7	1.0
Hyperglycemia	2.2	1.2	11.6	3.8
Hypertriglyceridemia	1.2	0	19.1	5.8
Hyponatremia	1.2	0.5	0.5	0.3
Nervous System Disorders				
Headache	5.9	0	4.8	0.3
Dizziness	3.2	0	3.0	0
Dysgeugia	2.7	0	12.8	0
Peripheral Neuropathy	2.0	0	2.3	0

Blood and Lymphatic Disorders				
Anemia	8.4	1.7	24.9	7.8
Lymphopenia	2.7	0.7	2.0	0.5
Thrombocytopenia	1.2	0.2	6.5	1.0
Neutropenia	1.0	0	2.3	0.5
Endocrine Disorders				
Hypothyroidism	5.9	0.2	0.5	0
Hyperthyroidism	1.7	0	0.3	0
Adrenal Insufficiency	1.5	0.5	0	0
Infections and Infestations				
Upper respiratory tract infection	2.2	0	2.0	0
Pneumonia	1.0	0	3.5	1.5
Eye Disorders				
Dry Eye	1.5	0	1.3	0
Lacrimation Increased	1.2	0	1.5	0
Vascular Disorders				
Hypertension	2.0	0.7	2.3	1.0
Flushing	1.7	0	0.5	0
Hypotension	1.7	0	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	3.2	0	0	0
Immune System Disorders				
Hypersensitivity	2.2	0.2	0.3	0
Psychiatric Disorders				
Insomnia	1.0	0	1.3	0
Renal and Urinary Disorders				
Pollakiuria	1.0	0	0.3	0

a. Incidences presented in this table are based on reports of drug-related adverse events.

Previously untreated:

CHECKMATE-214

Table 20 lists adverse reactions that occurred in at least 1% of nivolumab plus ipilimumab-treated patients in CHECKMATE-214 at the pre-specified interim analysis (17.5 months of minimum follow-up). There were no new safety signals observed with longer follow-up (minimum 41.4 months), and therefore with additional follow-up, the safety profile of nivolumab plus ipilimumab remained consistent with the pre-specified interim analysis.

Table 20: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-214

	Nivolumab + ipilimumab (n=547)		**Sunitinib (n=535)**	
System Organ Class	**Any**	**Grades**	**Any**	**Grades**
Preferred Term	**Grade**	**3-4**	**Grade**	**3-4**
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue	47.5	5.5	62.1	11.2
Pyrexia	14.4	0.4	6.2	0.2
Edema	4.9	0.2	8.6	0.4
Influenza-like illness	4.8	0.4	2.4	0.2

Chills	3.3	0	3.7	0.2
Pain	2.0	0	3.2	0
Chest pain	1.8	0	1.9	0.2
Malaise	1.5	0	4.7	0
Gastrointestinal Disorders				
Diarrhea	26.5	3.8	52.0	5.2
Nausea	19.9	1.5	37.8	1.1
Vomiting	10.8	0.7	20.6	1.9
Abdominal pain	9.0	0.4	14.4	0.2
Stomatitis	6.8	0	53.1	5.4
Constipation	6.4	0	7.3	0
Dry Mouth	5.7	0	6.0	0
Dyspepsia	3.8	0.2	27.1	0
Colitis	3.7	2.2	0.4	0
Dysphagia	1.5	0	1.7	0.2
Pancreatitis	1.3	0.4	1.3	0.7
Abdominal distention	1.1	0	3.9	0
Skin and Subcutaneous Tissue Disorders				
Rash	33.8	3.5	19.8	0.6
Pruritus	28.2	0.5	9.2	0
Dry skin	7.3	0	8.6	0
Erythema	2.7	0	0.9	0
Hyperhydrosis	1.5	0	1.3	0
Night sweats	1.5	0	0.4	0
Urticaria	1.5	0.2	0.4	0
Generalized pruritus	1.5	0	0.4	0
Endocrine Disorders				
Hypothyroidism	15.7	0.4	25.0	0.2
Hyperthyroidism	11.2	0.7	2.2	0
Adrenal insufficiency	5.3	2.0	0	0
Hypophysitis	4.0	2.7	0	0
Thyroiditis	3.3	0.2	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	13.7	1.3	24.9	0.9
Hyperglycemia	5.1	1.5	1.9	0
Hyponatremia	4.4	2.9	3.7	2.2
Dehydration	3.1	1.1	3.6	1.5
Hyperkalemia	2.6	0.7	2.2	0.4
Diabetes mellitus	1.8	1.1	0	0
Hypomagnesemia	1.8	0.2	3.6	0.6
Hypoalbuminemia	1.3	0	1.7	0
Hypokalemia	1.3	0.4	1.7	0.2
Hypophosphatemia	1.3	0.2	3.4	0.4
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain	14.8	1.5	14.0	0.4
Arthralgia	13.9	0.9	7.3	0
Muscle spasms	4.0	0	3.2	0
Arthritis	2.0	0.2	0.4	0
Muscular weakness	1.8	0	1.3	0.4
Nervous System Disorders				
Headache	9.7	0.7	12.1	0.2
Dizziness	6.0	0.4	6.0	0.4

Dysgeusia	5.7	0	33.5	0.2
Peripheral neuropathy	4.0	0.2	5.8	0.4
Paresthesia	3.3	0.4	3.9	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	8.4	0	6.2	0
Dyspnea	6.8	0.2	8.2	0.4
Pneumonitis	6.2	1.1	0.2	0
Dysphonia	1.3	0	3.9	0.2
Pleural effusion	1.3	0	0.2	0.2
Oropharyngeal pain	1.1	0	2.4	0.2
Blood and Lymphatic Disorders				
Anemia	6.4	0.4	15.9	4.5
Lymphopenia	1.5	0.4	4.5	2.4
Neutropenia	1.1	0.4	19.3	10.3
Thrombocytopenia	1.1	0.2	29.5	11.2
Infections and Infestations				
Conjunctivitis	1.5	0	0.7	0
Pneumonia	1.5	0.2	0.4	0
Upper respiratory tract infection	1.5	0.2	0.6	0
Eye Disorders				
Vision Blurred	1.6	0	0.4	0
Dry Eye	1.5	0	1.1	0
Vascular Disorders				
Hypertension	2.2	0.7	40.7	16.1
Hypotension	2.2	0.7	0.7	0.2
Flushing	1.6	0	1.3	0
Renal and Urinary Disorders				
Acute kidney injury	1.8	0.7	1.7	0.6
Psychiatric Disorders				
Insomnia	1.6	0	2.1	0
Confusional state	1.1	0	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	2.6	0	0	0
Hepatobiliary Disorders				
Hepatitis	1.3	0.9	0.2	0.2
Cardiac Disorders				
Palpitations	1.3	0	0.9	0
Tachycardia	1.3	0	0.4	0
Immune System Disorders				
Hypersensitivity	1.6	0	1.1	0.4

CHECKMATE-9ER

Table 21 lists adverse events that occurred in greater than 10% of nivolumab plus cabozantinib-treated patients in CHECKMATE-9ER (10.6 months of minimum follow-up).

Table 21: Adverse Events Reported in ≥10% of Patients in CHECKMATE-9ER

	Nivolumab + cabozantinib (n=320)		Sunitinib (n=320)	
System Organ Class Preferred Term	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
Blood and Lymphatic Disorders				
Anemia	15	2	25	4
Thrombocytopenia	12	1	36	9
Endocrine Disorders				
Hypothyroidism[b]	34	0	30	0
Hyperthyroidism	10	1	3	0
Gastrointestinal Disorders				
Diarrhea	64	7	47	4
Stomatitis[c]	37	3	46	4
Nausea	27	1	31	0
Abdominal pain[d]	22	2	15	0
Vomiting	17	2	21	0
Dyspepsia[e]	15	0	22	0
Constipation	12	1	13	0
General Disorders and Administration Site Conditions				
Fatigue[f]	51	8	50	8
Pyrexia	12	1	9	1
Edema	12	0	10	0
Infections and infestations				
Upper respiratory tract infection	20	0	8	0
Investigations				
Weight decreased	11	1	3	0
Metabolism and Nutrition Disorders				
Decreased appetite	28	2	20	1
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[g]	33	4	29	3
Arthralgia	18	0	9	0

Muscle spasms	12	0	2	0
Nervous System Disorders				
Dysgeusia	24	0	22	0
Headache	16	0	12	1
Dizziness	13	1	6	0
Renal and Urinary Disorders				
Proteinuria	10	3	8	2
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	20	0	17	0
Dysphonia	17	0	3	0
Dyspnea	11	0	9	2
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia syndrome	40	8	41	8
Rash[h]	36	3	14	0
Pruritus	19	0	4	0
Vascular Disorders				
Hypertension[i]	36	13	39	14

a. Incidences presented in this table are based on reports of treatment-emergent adverse events, independent of the relationship to the study drug.
b. Hypothyroidism includes primary hypothyroidism
c. Stomatitis is a composite term which includes mucosal inflammation, aphthous ulcer, mouth ulceration
d. Abdominal pain includes abdominal discomfort, abdominal pain lower, abdominal pain upper
e. Dyspepsia includes gastroesophageal reflux
f. Fatigue includes asthenia
g. Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain
h. Rash is a composite term which includes dermatitis, dermatitis anceiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic
i. Hypertension includes blood pressure increased, blood pressure systolic increased

Recurrent or Metastatic SCCHN:

Table 22 lists adverse reactions that occurred in at least 1% of patients in pivotal squamous cell cancer of the head and neck CHECKMATE-141:

Table 22: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-141

System Organ Class Preferred Term	Nivolumab (n=236)		Investigator Choice[a] (n=111)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[b]			
General Disorders and Administration Site Conditions				
Fatigue	17.8	2.5	31.5	4.5
Pyrexia	1.7	0	3.6	1.8
Edema	2.5	0	1.8	0
Gastrointestinal Disorders				
Nausea	8.5	0	20.7	0.9
Diarrhea	6.8	0	13.5	1.8
Stomatitis	3.8	0.4	21.6	4.5
Vomiting	3.4	0	7.2	0
Dysphagia	1.7	0.4	0	0
Constipation	1.3	0	3.6	0
Skin and Subcutaneous Tissue Disorders				
Rash	10.6	0	12.6	1.8
Pruritus	7.2	0	0	0
Dry Skin	3.0	0	9.0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	2.5	0.4	0	0
Pneumonitis	2.1	0.8	0.9	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	2.1	0	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	7.2	0	7.2	0
Hyponatremia	1.7	0.8	3.6	2.7
Hypomagnesaemia	1.3	0	3.6	0
Investigations				
Lipase Increased	2.5	1.7	0	0
Transaminase Increased	1.7	0.8	2.7	0.9
Weight Decreased	1.7	0	5.4	0
Thyroid stimulating hormone	1.3	0	0	0
Nervous System Disorders				
Headache	1.7	0.4	0.9	0
Blood and Lymphatic System Disorders				
Anemia	5.1	1.3	16.2	4.5
Lymphopenia	2.5	1.3	3.6	3.6
Thrombocytopenia	2.5	0	6.3	2.7
Endocrine Disorders				
Hypothyroidism	4.2	0.4	0.9	0
Vascular Disorders				
Hypertension	1.7	0.4	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	1.3	0	1.8	0.9

a. Cetuximab, methotrexate or docetaxel.

b. Incidences presented in this table are based on reports of drug-related adverse events.

MSI-H/dMMR mCRC:

In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC (n =119), the most frequent adverse reactions (≥ 10%) were fatigue (28.6%), rash (25.3%), diarrhea (25.2%), pruritus (20.2%), hypothyroidism (17.6%), pyrexia (15.1%), hyperthyroidism (14.3%), nausea (13.4%), decreased appetite (10.9%) and anemia (10.1%). The majority of adverse reactions were mild to moderate (Grade 1 or 2) with 31.9% Grade 3-4 adverse reactions.

Table 23, lists the adverse reactions that occurred in at least 1% of patients treated with nivolumab in combination with ipilimumab in CHECKMATE-142.

Table 23: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-142

	Nivolumab + ipilimumab[a] (n=119)	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients	
General Disorders and Administration Site Conditions		
Fatigue	34 (28.6)	3 (2.5)
Pyrexia	18 (15.1)	0
Influenza like illness	6 (5.0)	0
Chills	5 (4.2)	0
Face edema	2 (1.7)	0
Edema	2 (1.7)	0
Pain	2 (1.7)	0
Gastrointestinal Disorders		
Diarrhea	30 (25.2)	3 (2.5)
Nausea	16 (13.4)	1 (0.8)
Vomiting	8 (6.7)	1 (0.8)
Abdominal pain	8 (6.7)	2 (1.7)
Stomatitis	5 (4.2)	0
Dry mouth	7 (5.9)	0
Dyspepsia	4 (3.4)	0
Constipation	4 (3.4)	0
Colitis	3 (2.5)	3 (2.5)
Skin and Subcutaneous Tissue Disorders		
Rash	30 (25.3)	2 (2.5)
Pruritus	24 (20.2)	2 (1.7)
Dry skin	11 (9.2)	0
Erythema	4 (3.4)	0
Alopecia	2 (1.7)	0
Endocrine Disorders		
Hypothyroidism	21 (17.6)	1 (0.8)
Hyperthyroidism	17 (14.3)	0
Adrenal Insufficiency	8 (6.7)	1 (0.8)
Hypophysitis	4 (3.4)	2 (1.7)

Thyroiditis	4 (3.4)	2 (1.7)
Autoimmune thyroid disorder	2 (1.7)	1 (0.8)
Blood and Lymphatic System Disorders		
Anemia	12 (10.1)	3 (2.5)
Neutropenia	5 (4.2)	0
Thrombocytopenia	10 (8.4)	1 (0.8)
Lymphopenia	3 (2.5)	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	10 (8.4)	1 (0.8)
Musculoskeletal pain[b]	10 (8.4)	1 (0.8)
Joint stiffness	2 (1.7)	0
Metabolism and Nutrition Disorders		
Decreased appetite	13 (10.9)	2 (1.7)
Hypomagneaemia	3 (2.5)	0
Dehydration	2 (1.7)	1 (0.8)
Hypocalcaemia	2 (1.7)	0
Hyponatraemia	2 (1.7)	2 (1.7)
Nervous System Disorders		
Dizziness	4 (3.4)	0
Headache	7 (5.9)	0
Neuropathy peripheral	4 (3.4)	0
Respiratory, Thoracic, and Mediastinal Disorders		
Pneumonitis	7 (5.9)	1 (0.8)
Dyspnoea	3 (2.5)	2 (1.7)
Hepatobiliary Disorders		
Hepatitis	3 (2.5)	3 (2.5)
Injury, Poisoning, and Procedural Complications		
Infusion related reaction	4 (3.4)	0
Renal and Urinary Disorders		
Acute kidney injury	2 (1.7)	2 (1.7)
Immune System Disorders		
Sarcoidosis	2 (1.7)	0
Eye disorders		
Vision blurred	2 (1.7)	0

a. Nivolumab in combination with ipilimumab for the first 4 doses then followed by nivolumab monotherapy.

b. Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

Adjuvant Treatment of Resected Esophageal or GEJ Cancer

Table 24 summarizes the adverse reactions in CHECKMATE-577:

Table 24: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-577

	Nivolumab (n=532)		Placebo (n=260)	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue[b]	22.0	1.1	12.7	0.4
Influenza like illness	1.5	0.2	0.8	0
Pyrexia	1.5	0	0.8	0
Gastrointestinal Disorders				
Diarrhea	16.5	0.4	15.0	0.8
Nausea	8.8	0	5.0	0
Vomiting	4.1	0.2	3.1	0
Dry Mouth	3.0	0	1.2	0
Abdominal Pain[c]	2.4	0	2.3	0
Stomatitis	2.3	0.2	1.9	0
Constipation	1.3	0	0.4	0
Dyspepsia[d]	1.1	0	0.8	0.4
Skin and Subcutaneous Tissue Disorders				
Rash[e]	16.0	0.9	5.8	0.4
Pruritus	10.0	0.4	3.5	0
Dry Skin	3.2	0.2	1.2	0
Eczema	1.1	0	0.4	0
Erythema	1.1	0	0.4	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnoea[f]	4.1	0.4	1.2	0
Pneumonitis	4.1	0.9	1.5	0.4
Cough[g]	3.6	0	2.7	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	5.6	0.2	1.5	0
Musculoskeletal Pain[h]	5.5	0	2.3	0
Metabolism and Nutrition Disorders				

	Nivolumab (n=532)		Placebo (n=260)	
System Organ Class Preferred Term	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
Decreased appetite	4.9	0	1.9	0
Hyperglycaemia	1.1	0.4	0	0
Investigations				
Increased transaminases[i]	7.0	0.6	4.2	0.8
Increased amylase	4.3	1.7	0.8	0
Increased alkaline phosphatase	3.2	0.2	1.2	0
Increased lipase	2.6	1.3	1.9	0.8
Decreased weight	2.1	0	0	0
Decreased white blood cell count	1.9	0.2	0.4	0
Increased blood thyroid stimulating hormone	1.5	0	0.4	0
Increased creatinine	1.1	0	0.8	0
Nervous System Disorders				
Headache	2.1	0	3.5	0
Neuropathy peripheral	1.7	0.2	1.9	0
Dizziness	1.5	0	1.9	0
Blood and Lymphatic System Disorders				
Lymphopenia[j]	3.0	1.1	1.9	0.4
Neutropenia[k]	2.3	0	1.5	0
Anemia[l]	1.5	0	1.2	0
Endocrine Disorders				
Hypothyroidism	9.4	0	1.5	0
Hyperthyroidism	6.8	0	0.4	0
Thyroiditis	1.5	0.4	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	1.5	0	0.8	0

a. Incidences presented in this table are based on reports of drug-related adverse events.

b. Includes asthenia.

c. Includes upper abdominal pain, lower abdominal pain, and abdominal discomfort.

d. Includes gastroesophageal reflux.

e. Includes rash pustular, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, exfoliative rash, rash erythematous, rash macular, rash maculo-papular, rash popular, rash pruritic.

f. Includes dyspnea exertional.

g. Includes productive cough.

h. Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, spinal pain.

i. Includes alanine aminotransferase increased, aspartate aminotransferase increased.

j. Includes lymphopenia and decreased lymphocyte count.

k. Includes neutropenia and decreased neutrophil count.

l. Includes anemia, increased hemoglobin, and iron deficiency anemia.

GC/GEJC/EAC (previously untreated):

Table 25 lists adverse reactions that occurred in at least 1% of patients in CHECKMATE-649:

Table 25: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-649

	Nivolumab in combination with Fluoropyrimidine- and Platinum-based Chemotherapy (n=782)		Fluoropyrimidine- and Platinum-based Chemotherapy (n=767)	
System Organ Class Preferred Term	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue	33.4	4.7	31.7	3.5
Pyrexia	8.2	0.5	2.9	0.1
Edema (including peripheral edema)	3.3	0	1.3	0
Gastrointestinal Disorders				
Nausea	41.3	2.6	38.1	2.5
Diarrhea	32.4	4.5	26.9	3.1
Vomiting	24.9	2.2	21.6	3.1
Stomatitis	14.7	1.7	12.0	0.8
Constipation	9.3	0.3	8.0	0
Abdominal Pain	7.3	0.5	7.0	0.4
Dry Mouth	2.8	0.1	0.9	0
Colitis	1.8	1.0	0.1	0
Skin and Subcutaneous Tissue Disorders				
Rash[a]	13.9	1.7	2.9	0.1
Palmar-plantar erythrodysaesthaesia syndrome	12.0	1.4	10.6	0.8
Pruritus	6.9	0.1	1.0	0
Skin hyperpigmentation	3.5	0.1	1.6	0
Alopecia	2.7	0	1.8	0.1
Dry skin	2.4	0	2.0	0
Erythema	1.4	0.3	0.4	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain[b]	3.8	0.3	1.8	0

Arthralgia	2.7	0	0.8	0.1
Muscular weakness	1.5	0.1	1.3	0
Respiratory, Thoracic, and Mediastinal Disorders				
Pneumonitis	5.0	1.8	0.5	0.1
Cough	3.2	0	1.6	0
Dyspnea	2.9	0.4	1.0	0
Endocrine Disorders				
Hypothyroidism	9.0	0	0.3	0
Hyperthyroidism	3.3	0	0	0
Nervous System Disorders				
Peripheral Neuropathy	49.9	6.5	43.9	4.7
Paraesthesia	7.5	0.3	8.0	0.1
Headache	5.1	0.3	2.2	0.1
Dizziness	2.8	0	3.1	0.1
Eye Disorders				
Dry eye	1.8	0.1	0.4	0
Blurred vision	1.2	0	0.1	0
Blood and Lymphatic System Disorders				
Febrile neutropaenia	2.6	2.2	1.2	1.2
Metabolism and Nutrition Disorders				
Decreased Appetite	20.1	1.8	18.1	1.7
Infections and Infestations				
Pneumonia	2.2	0.5	0.7	0.3
Immune System Disorders				
Hypersensitivity	6.8	0.6	2.1	0.7
Infusion related reaction	0.4	0.1	0.1	0.1
Vascular Disorders				
Thrombosis	1.4	0.1	0.7	0.1
Hypertension	1.2	0.6	0.7	0.3
Investigations				
Increased lipase	11.4	5.8	4.4	2.1
Increased amylase	9.1	2.7	2.9	0.3
Increased alkaline phosphatase	6.6	0.6	4.4	0.3

a. Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash macular, rash morbilliform, rash papular, rash generalised, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, drug eruption, and exfoliative rash, nodular rash, rash vesicular.

b. Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, spinal pain, and musculoskeletal discomfort.

Urothelial Carcinoma:

Table 26 lists the adverse reactions that occurred in at least 1% of patients treated with nivolumab in CHECKMATE-274.

Table 26: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-274

Adverse Reaction	Nivolumab (n=351)		PLACEBO (n=348)	
System Organ Class **Preferred Term**	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
	Percentage (%) of Patients[a]			
Skin and Subcutaneous Tissue				
Rash[b]	29.1	1.7	9.8	0
Pruritus	23.1	0	11.5	0
Dry skin	3.1	0	2.3	0
General disorders and administration site conditions				
Fatigue/asthenia[c]	23.6	0.9	16.4	0
Oedema peripheral	2.3	0	0.6	0
Influenza like illness	1.7	0	1.1	0
Pyrexia	1.7	0	0.6	0
Gastrointestinal disorders				
Diarrhea[d]	18.2	1.7	11.2	0.9
Nausea	6.8	0	3.7	0
Abdominal pain[e]	3.4	0	2.6	0
Dry mouth	3.1	0	0.6	0
Vomiting	3.1	0	2.0	0
Constipation	2.6	0.3	1.1	0
Investigations				
Lipase increased	9.7	5.1	5.7	2.6
Amylase increased	9.4	3.7	5.7	1.4
Blood alkaline phosphatase increased	2.3	0.3	0.6	0
Weight decreased	1.4	0	0.3	0
Blood uric acid increased	1.1	0	1.1	0.3
Lymphocyte count decreased	1.1	0	0.9	0.3
Platelet count decreased	1.1	0.3	0.3	0
Weight increased	1.1	0	1.4	0
Endocrine Disorders				
Thyroid disorders[f]	18.5	0	3.4	0
Metabolism and Nutrition Disorders				
Decreased appetite	5.7	0.6	3.2	0

Hyponatremia	1.4	0.6	0.9	0
Hyperglycemia	1.1	0	2.9	0.6
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[g]	7.4	0.3	2.3	0
Arthralgia	4.6	0.3	4.6	0
Arthritis	1.1	0	0	0
Hepatobiliary disorders				
Hepatitis[h]	7.4	1.7	4.6	0.3
Nervous System Disorders				
Headache	2.6	0	1.7	0
Peripheral neuropathy	1.4	0	0.6	0
Dysgeusia	1.1	0	0.6	0
Dizziness[i]	2.0	0	2.0	0
Renal and urinary disorders				
Renal dysfunction[j]	7.1	1.1	3.4	0
Respiratory, thoracic and mediastinal disorders				
Pneumonitis	4.6	0.9	1.4	0
Dyspnea[k]	3.4	0	0.6	0
Cough[l]	2.3	0	0.9	0
Blood and lymphatic system disorders				
Anemia	2.3	0	1.4	0
Injury, poisoning and procedural complications				
Infusion related reaction	3.7	0.6	0.6	0
Infections and infestations				
Pneumonia	1.1	0	0.3	0
Vascular disorders				
Hypertension	1.1	0.3	0	0

a. Incidences presented in this table are based on reports of drug-related adverse events (CTCAE v4.0).
b. 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.
c. Includes fatigue and asthenia
d. Includes colitis, colitis microscopic, diarrhea, duodenitis, enteritis, immune-mediated enterocolitis.
e. Includes abdominal pain, abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness
f. Includes blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, goitre, hyperthyroidism, hypothyroidism, thyroid mass, thyroiditis, thyroiditis subacute,
g. Includes musculoskeletal pain, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain

h. Includes aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, cholangitis, drug-induced liver injury, hepatic failure, hepatic function abnormal, hepatitis, hepatocellular injury, hyperbilirubinaemia, gamma-glutamyltransferase increased, liver injury, transaminases increased
i. Includes dizziness, dizziness postural and vertigo
j. Includes acute kidney injury, autoimmune nephritis, blood creatinine increased, glomerular filtration rate decreased, immune-mediated nephritis, nephritis, renal failure, and renal impairment.
k. Includes dyspnea and dyspnea exertional
l. Includes cough, productive cough and upper-airway cough syndrome

First-line Treatment of Unresectable or Metastatic Urothelial Carcinoma:

Table 27 lists the adverse reactions that occurred in at least 1% of patients treated with Nivolumab in CHECKMATE-901.

Table 27: **Adverse Reactions Reported in at Least 1% of Patients - CHECKMATE-901**

Adverse Reaction	**Nivolumab and Cisplatin and Gemcitabine (n=304)**		**Cisplatin and Gemcitabine (n=288)**	
System Organ Class	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Preferred Term				
Blood and lymphatic system disorders				
Anemia[a]	57.6	22.0	47.6	17.7
Neutropenia[b]	53.0	33.2	47.9	25.7
Thrombocytopenia[c]	34.5	13.8	26.7	9.4
Leukopenia	12.5	2.3	11.5	1.7
Lymphopenia[d]	6.9	2.6	4.9	1.4
Febrile neutropenia	2.0	1.6	0.7	0.7
Myelosuppression	1.3	0.7	1.7	1.4
Gastrointestinal disorders				
Nausea	46.7	0.3	47.9	1.0
Vomiting	18.1	1.3	16.7	2.1
Constipation	14.5	0	13.9	0.3
Diarrhea	13.2	1.3	8.7	0
Stomatitis[e]	5.9	0.3	3.8	0
Abdominal pain[f]	3.9	0	4.5	0.3
Dyspepsia[g]	3.0	0	2.4	0
Dry mouth	2.3	0	0.3	0
Oral dysesthesia	1.0	0	0	0
General disorders and administration site conditions				
Fatigue[h]	39.1	3.0	36.8	3.1
Edema[i]	6.3	0	3.1	0
Malaise	4.9	0.3	3.8	0
Pyrexia[j]	4.3	0.3	5.2	0
Xerosis	2.0	0	0.3	0
Pain	1.0	0.3	0	0
Investigations				
White blood cell count decreased	21.1	9.9	13.9	3.8
Blood creatinine increased	12.8	0.3	12.5	0
Transaminases increased[k]	10.2	2.0	5.2	0.7
Amylase increased	7.6	1.6	3.1	0.3
Lipase increased	7.2	2.0	3.5	0.7
Blood thyroid stimulating hormone increased	4.6	0	0	0
Weight decreased	4.3	0	4.5	0
Blood alkaline phosphatase increased	2.6	0	2.1	0
Blood lactate dehydrogenase increased	1.3	0	0.7	0
Blood sodium decreased	1.3	0.3	0.3	0.3
Gamma-glutamyltransferase increased	1.3	0.7	1.7	0

Table 27: **Adverse Reactions Reported in at Least 1% of Patients - CHECKMATE-901**

Adverse Reaction	Nivolumab and Cisplatin and Gemcitabine (n=304)		Cisplatin and Gemcitabine (n=288)	
System Organ Class	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Preferred Term				
Platelet count increased	1.0	0	0.3	0
Skin and Subcutaneous Tissue				
Rash[l]	20.1	2.3	4.5	0.3
Pruritus[m]	14.8	0.7	2.8	0
Alopecia	5.6	0	8.7	0
Dry skin	2.6	0	0	0
Erythema	1.0	0	0	0
Skin lesion	1.0	0	0	0
Metabolism and nutrition disorders				
Decreased appetite	22.4	1.3	15.6	0.3
Hypomagnesemia[n]	5.3	0.7	7.3	0.3
Hyponatremia	4.3	2.0	2.8	1.0
Hypoalbuminemia[o]	2.3	0	1.0	0
Hypokalemia[p]	2.3	0.3	2.1	0
Dehydration	1.6	0.3	0.7	0.3
Hyperkalemia[q]	1.6	0.3	0.3	0
Hyperglycemia	1.3	0.7	0	0
Hypoproteinemia	1.0	0	0.3	0
Nervous System Disorders				
Peripheral neuropathy	12.2	0.7	7.3	0
Dysgeusia	5.3	0	3.8	0
Paraesthesia	4.6	0	4.9	0.3
Dizziness[r]	3.6	0	4.5	0
Headache	3.3	0	2.1	0
Endocrine disorders				
Hypothyroidism	13.2	0	0	0
Hyperthyroidism	6.6	0.3	0	0
Respiratory, thoracic and mediastinal disorders				
Hiccups	3.6	0.3	2.4	0
Dyspnea	3.0	0	2.1	0
Cough[s]	2.3	0	0	0
Pulmonary embolism	2.0	1.6	3.8	2.1
Pneumonitis[t]	1.3	0	0	0
Epistaxis	1.0	0.7	0	0
Renal and Urinary Disorders				
Renal failure[u]	7.6	3.3	6.9	1.0
Renal impairment	2.0	0	0.7	0
Hematuria	1.1	0.3	1.0	0.3
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[v]	4.9	0.3	2.4	0
Arthralgia	3.9	0	0.7	0
Arthritis[w]	1.0	0	0	0
Vascular disorders				
Hypotension[x]	2.0	0.7	0.7	0
Vascular pain	2.0	0	0.3	0

Table 27: **Adverse Reactions Reported in at Least 1% of Patients - CHECKMATE-901**

Adverse Reaction	Nivolumab and Cisplatin and Gemcitabine (n=304)		Cisplatin and Gemcitabine (n=288)	
System Organ Class	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Preferred Term				
Flushing[y]	1.3	0	0.7	0
Phlebitis	1.3	0	1.0	0
Hypertension[z]	1.0	0.3	0.7	0.3
Vasculitis	1.0	0	0.7	0
Infections and infestations				
Sepsis[aa]	2.0	1.6	0.3	0.3
Upper respiratory tract infection[bb]	1.6	0	0.3	0.3
Urinary tract infection[cc]	1.6	0.3	2.4	1.4
Pneumonia[dd]	1.3	0.3	1.0	0.7
Ear and labyrinth disorders				
Tinnitus	4.6	0	6.3	0
Deafness	1.0	0	1.7	0
Hypoacusis	1.0	0	1.7	0.3
Cardiac disorders				
Myocarditis[ee]	1.0	0.7	0	0
Hepatobiliary disorders				
Hepatic function abnormal	1.0	0.3	0	0
Injury, poisoning and procedural complications				
Infusion related reaction	2.6	0	1.4	0
Psychiatric disorders				
Insomnia	1.0	0	1.4	0

Incidences presented in this table are based on reports of drug-related adverse events.

Toxicity was graded per NCI CTCAE v4.

a. Includes anemia and hemoglobin decreased
b. Includes neutropenia and neutrophil count decreased
c. Includes thrombocytopenia and platelet count decreased
d. Includes lymphopenia and lymphocyte count decreased
e. Includes stomatitis, aphthous ulcer, mouth ulceration, and mucosal inflammation
f. Includes abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper
g. Includes dyspepsia and gastrooesophageal reflux disease
h. Includes fatigue and asthenia
i. Includes edema, edema peripheral, peripheral swelling, and swelling
j. Includes pyrexia, body temperature increased, and tumour associated fever
k. Includes alanine aminotransferase increased and aspartate aminotransferase increased
l. Includes rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, drug eruption, exfoliative rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pustular
m. Includes pruritus, and pruritus allergic
n. Includes hypomagnesemia and blood magnesium decreased
o. Includes hypoalbuminemia and blood albumin decreased
p. Includes hypokalemia and blood potassium decreased
q. Includes hyperkalemia and blood potassium increased
r. Includes dizziness and vertigo
s. Includes cough and productive cough
t. Includes pneumonitis and interstitial lung disease
u. Includes renal failure and acute kidney injury
v. Includes musculoskeletal pain, back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, sacral pain, and spinal pain
w. Includes arthritis and osteoarthritis

x. Includes hypotension and orthostatic hypotension
y. Includes flushing and hot flush
z. Includes hypertension and blood pressure increased
aa. Includes sepsis, abdominal sepsis, bacterial sepsis, klebsiella sepsis, pulmonary sepsis, septic shock, and staphylococcal sepsis
bb. Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis
cc. Includes urinary tract infection
dd. Includes pneumonia and pneumonia bacterial
ee. Includes myocarditis and immune-mediated myocarditis

Unresectable or Metastatic ESCC:

Table 28 summarizes the adverse reactions that occurred in at least 1% of patients in either nivolumab-containing arm or in the chemotherapy arm in CHECKMATE-648.

Table 28: **Adverse Reactions Reported in at Least 1% of Patients (CHECKMATE-648)**

	Nivolumab and Ipilimumab (n=322)		**Nivolumab with Cisplatin and 5 FU (n=310)**		**Cisplatin and 5-FU (n=304)**	
System Organ Class Preferred Term	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]					
Skin and Subcutaneous Tissue Disorders						
Rash[b]	25.2	3.1	10.0	0.3	2.3	0
Pruritus	13.4	0.9	7.4	0	0.7	0
Dry skin	2.5	0.6	2.3	0	2.0	0
Erythema multiforme	1.2	0.3	0	0	0.3	0
Alopecia	0.6	0	10.0	0	10.5	0
Gastrointestinal Disorders						
Diarrhea	9.9	0.6	19.4	1.0	15.1	2.0
Nausea	8.1	0.3	58.7	3.5	52.0	2.6
Stomatitis[c]	5.9	0	41.6	8.7	32.9	3.0
Vomiting	5.6	1.2	18.1	2.3	16.1	3.0
Constipation	2.2	0.3	19.0	0.6	21.7	0.3
Colitis	1.9	0.6	1.9	1.3	0	0
Pancreatitis	1.2	0.9	0	0	0	0
Endocrine Disorders						
Hypothyroidism	13.4	0	5.8	0	0	0
Hyperthyroidism	6.2	0.6	2.3	0	0	0
Adrenal Insufficiency	4.3	2.2	1.9	0	0	0
Hypopituitarism	3.4	1.6	0.6	0	0	0
Hypophysitis	2.8	1.6	0	0	0	0
Thyroiditis	2.5	0.3	0	0	0	0
General Disorders and Administration Site Conditions						
Fatigue[d]	11.2	1.6	25.5	2.9	20.7	4.3
Pyrexia[e]	8.1	0.3	2.6	0	3.3	0
Edema	0	0	6.8	0	5.3	0
Investigations						
Increased amylase	2.5	1.2	1.0	0.3	0	0
Increased blood alkaline	2.5	0	2.9	0	1.3	0

phosphatase						
Increased blood creatinine	1.6	0	12.6	0.3	10.5	0.3
Increased lipase	1.6	1.6	0.6	0.3	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	5.9	1.6	42.6	4.2	42.8	3.0
Hyponatremia	2.8	2.5	9.4	5.5	6.3	3.0
Hyperglycaemia	2.2	0.6	0.3	0	0.7	0
Hypoalbuminemia	1.9	0	1.6	0	1.3	0
Diabetes Mellitus	1.6	0.6	0.6	0.6	0	0
Hypokalemia[f]	1.6	0.6	4.5	1.6	4.9	1.6
Hypomagnesemia	0.9	0	1.9	0.3	2.3	0.7
Hypophosphataemia	0.9	0	2.3	1.9	1.0	0.3
Hypocalcemia	0.3	0	1.6	0.6	0.7	0
Hyperkalemia	0	0	1.0	0	2.0	0
Respiratory, Thoracic, and Mediastinal Disorders						
Pneumonitis	8.1	2.8	5.8	0.6	0	0
Cough[g]	1.2	0	1.3	0	0.7	0
Blood and Lymphatic System Disorders						
Thrombocytopenia	1.9	0	13.9	1.3	11.8	2.3
Neutropenia	0.6	0	29.7	10.6	23.4	10.2
Leukopenia	0.3	0	3.2	0.6	3.3	0.3
Febrile neutropenia	0	0	1.6	1.6	1.3	1.3
Hepatobiliary Disorders						
Hepatitis	1.2	1.2	0	0	0	0
Infections and Infestations						
Pneumonia[h]	1.6	0.6	2.6[i]	1.3	3.0	0
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal Pain[j]	2.8	0	0.6	0	0.7	0
Nervous System Disorders						
Headache	1.9	0.3	2.6	0	1.0	0
Peripheral Neuropathy[k]	0.6	0	16.5	0	11.8	1.0
Dizziness	0.3	0	2.6	0	5.3	0
Lethargy	0.3	0	1.0	0	0	0
Injury, Poisoning, and Procedural Complications						
Infusion-related reaction	2.5	0	1.3	0	0.3	0
Renal and Urinary Disorders						
Renal Failure	0.6	0.6	5.2	1.9	5.6	1.0
Nephropathy	0	0	1.0	0.3	0.7	0
Vascular Disorders						
Hypertension	0	0	1.6	0.3	1.0	0

a. Incidences presented in this table are based on reports of drug-related adverse events.
b. Includes rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, and rash pruritic.
c. Includes stomatitis, aphthous ulcer, mouth ulceration, and mucosal inflammation.
d. Includes fatigue, asthenia.
e. Includes pyrexia, tumour associated fever.
f. Includes hypokalemia, blood potassium decreased.
g. Includes cough, productive cough.

h. Includes pneumonia, organizing pneumonia, pneumonia bacterial, and pneumonia pseudomonal.
i. Includes one Grade 5 event
j. Includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, and spinal pain.
k. Includes peripheral neuropathy, hyperaesthesia, hypoaesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.

8.3. Less Common Clinical Trial Adverse Reactions

SUBCUTANEOUS FORMULATION (Opdivo SC)

Table 29: Less Common Clinical Trial Adverse Reactions

Opdivo SC Study	System Organ Class
Advanced or Metastatic RCC previously treated CHECKMATE-67T	The following additional adverse reactions were reported in less than 1% of patients treated with Opdivo SC (nivolumab 1200 mg) monotherapy every four weeks in CHECKMATE-67T. Adverse reactions presented elsewhere in this section are excluded. Cardiac: myocarditis Endocrine: hyperthyroidism, thyroiditis Gastrointestinal: colitis, pancreatitis, stomatitis Hepatobiliary: hepatitis Eye disorders: uveitis Respiratory, thoracic, and mediastinal disorders: lung infiltration Immune system: hypersensitivity

INTRAVENOUS FORMULATION (Opdivo)

The following sections below present data from a separate Product Monograph for Opdivo intravenous formulation studies.

Table 30: Less Common Clinical Trial Adverse Reactions

Nivolumab Study	System Organ Class
Unresectable or Metastatic Melanoma: CHECKMATE-066	The following additional adverse reactions were reported in less than 1% of patients treated with nivolumab 3 mg/kg monotherapy every two weeks in CHECKMATE-066. Adverse reactions presented elsewhere in this section are excluded. Skin and subcutaneous tissue disorder: psoriasis, rosacea. Gastrointestinal disorders: stomatitis, colitis. Nervous system disorders: dizziness, Guillain-Barré syndrome. Metabolism and nutrition disorders: diabetes mellitus, diabetic ketoacidosis. Endocrine disorders: hypophysitis. Eye disorders: uveitis. Vascular disorders: hypertension.
Unresectable or Metastatic Melanoma: CHECKMATE-067	The following additional adverse reactions were reported in less than 1% of patients treated with either nivolumab as a single agent at 3 mg/kg every two weeks or nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg as a single agent every

	two weeks in CHECKMATE-067. Adverse reactions presented elsewhere in this section are excluded. *Nivolumab + Ipilimumab* Gastrointestinal Disorders: intestinal perforation. Musculoskeletal and Connective Tissue Disorders: polymyalgia rheumatica, Sjogren's syndrome, spondyloarthropathy. Nervous System Disorders: neuritis, peroneal nerve palsy, Guillain-Barré syndrome, encephalitis. Renal and Urinary Disorders: renal failure, nephritis. Respiratory, Thoracic and Mediastinal Disorders: pleural effusion. Cardiac Disorders: atrial fibrillation. *Nivolumab monotherapy* Musculoskeletal and Connective Tissue Disorders: myopathy, polymyositis. Respiratory, Thoracic and Mediastinal Disorders: pleural effusion. Cardiac Disorders: atrial fibrillation.
Unresectable or Metastatic Melanoma: CHECKMATE-037	Skin and subcutaneous tissue disorder: alopecia, urticaria, erythema multiforme. Endocrine disorders: thyroiditis. Renal and urinary disorders: tubulointerstitial nephritis. Cardiac disorders: ventricular arrhythmia.
Adjuvant Treatment of Melanoma: CHECKMATE-238	The following other clinically important adverse reactions were reported in less than 1% of patients in the nivolumab group in CHECKMATE-238. Adverse reactions presented elsewhere are excluded. Endocrine disorders: fulminant type I diabetes.
Adjuvant Treatment of Melanoma: CHECKMATE-76K	The following other clinically important adverse reactions were reported in less than 1% of patients in the nivolumab group in CHECKMATE-76K. Adverse reactions presented elsewhere are excluded. Gastrointestinal Disorders: autoimmune enteropathy, oesophagitis. Musculoskeletal and Connective Tissue Disorders: immune-mediated myositis. Investigations: troponin increased. Infections and infestations: diverticulitis. Cardiac Disorders: myocarditis. Metabolism and nutrition disorders: diabetes mellitus. Vascular disorders: hypertension.
Metastatic NSCLC: previously treated CHECKMATE-017 and CHECKMATE-057	The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with nivolumab 3 mg/kg monotherapy in CHECKMATE-017 and CHECKMATE-057. Adverse reactions presented elsewhere are excluded. Gastrointestinal Disorders: pancreatitis. Musculoskeletal and Connective Tissue Disorders: polymyalgia rheumatica. Endocrine Disorders: hyperglycaemia. Eye Disorders: blurred vision.

	Neoplasms Benign, Malignant and Unspecified: histocytic necrotising lymphadenitis (Kikuchi lymphadenitis). Investigations: lipase increased, amylase increased. Respiratory, Thoracic, and Mediastinal Disorders: pleural effusion. Infections and Infestations: pneumonia.
Neoadjuvant Treatment of Resectable NSCLC CHECKMATE-816	The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with nivolumab in combination with platinum-doublet chemotherapy in CHECKMATE-816 Nervous System Disorders: paraesthesia Eye Disorders: dry eye Skin and Subcutaneous Tissue Disorders: dry skin Investigations: increased alkaline phosphatase
Advanced or Metastatic RCC: previously treated CHECKMATE-025	The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with nivolumab 3 mg/kg monotherapy in CHECKMATE-025. Adverse reactions presented elsewhere are excluded. Immune System Disorders: anaphylactic reaction. Metabolism & Nutrition Disorders: diabetic ketoacidosis. Renal and Urinary Disorders: tubulointerstitial nephritis. Respiratory, Thoracic, and Mediastinal Disorders: hemoptysis.
Advanced or Metastatic RCC previously untreated CHECKMATE-214	The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with nivolumab plus ipilimumab in CHECKMATE-214. Adverse reactions presented elsewhere are excluded. Infections and Infestations: aseptic meningitis. Nervous System Disorders: myasthenia gravis.
Advanced or Metastatic RCC previously untreated CHECKMATE-9ER	The following clinically important adverse drug events were reported in less than 10% of patients with renal cell carcinoma treated with nivolumab plus cabozantinib in CHECKMATE-9ER. Adverse events presented elsewhere are excluded. Ear and Labyrinth Disorder: tinnitus. Gastrointestinal Disorder: small intestine perforation, glossodynia, hemorrhoids. Musculoskeletal and Connective Tissue Disorder: osteonecrosis of the jaw, fistula. Skin and Subcutaneous tissue disorders: skin ulcer. Vascular disorders: thrombosis.
Recurrent or Metastatic SCCHN: CHECKMATE-141	The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with nivolumab 3 mg/kg monotherapy in CHECKMATE-141. Adverse reactions presented elsewhere are excluded. Skin and Subcutaneous: urticaria. Eye Disorders: vision blurred. Infections and Infestations: bronchitis. Endocrine: hypophysitis. Metabolism and Nutrition: hyperglycemia, hypercalcemia. Respiratory, Thoracic and Mediastinal: dyspnea, pulmonary embolism, pneumonia aspiration.

Microsatellite Instability-High (MSI-H)/ Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer: CHECKMATE-142	The following adverse reactions were reported in less than 1% of MSI-H patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses in CHECKMATE-142. Adverse reactions presented elsewhere in this section are excluded. Skin and Subcutaneous Tissue Disorders: Psoriasis, Urticaria. General Disorders and Administration Site Conditions: Chest pain. Gastrointestinal Disorders: Pancreatitis. Endocrine Disorders: Secondary adrenocortical insufficiency. Musculoskeletal and Connective Tissue Disorders: Arthritis, Myositis, Necrotising myositis. Nervous System Disorders: paraesthesia. Respiratory, Thoracic and Mediastinal Disorders: Cough. Infections and Infestations: Upper respiratory tract infection. Vascular Disorders: Flushing, Hypertension, Hypotension. Eye Disorders: Dry eye.
Adjuvant Treatment of Resected Esophageal or GEJ Cancer: CHECKMATE-577	The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with nivolumab in CHECKMATE-577. Cardiac disorders: myocarditis.
GC/GEJC/EAC: (previously untreated) CHECKMATE-649	The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with nivolumab in combination with chemotherapy in CHECKMATE-649. Blood and Lymphatic System Disorder: eosinophilia. Cardiac Disorders: tachycardia, myocarditis. Endocrine Disorders: hypopituitarism, adrenal insufficiency, hypophysitis, diabetes mellitus. Eye Disorders: uveitis. Gastrointestinal Disorders: pancreatitis. Hepatobiliary Disorders: hepatitis. Infections and Infestations: upper respiratory tract infection. Nervous System Disorders: guillain-barré syndrome. Renal and Urinary Disorders: renal failure, nephritis.
Urothelial Carcinoma (UC): CHECKMATE-274	The following other clinically important adverse drug reactions were reported in less than 1% of UC patients treated with nivolumab 240 mg monotherapy every two weeks in CHECKMATE-274. Cardiac Disorders: myocarditis. Gastrointestinal disorders: pancreatic mass, pancreatitis. Hepatobiliary disorders: hepatic calcification. Nervous System Disorders: demyelination and myasthenic syndrome.
Unresectable or Metastatic Urothelial Carcinoma (UC): CHECKMATE-901	The following other clinically important adverse drug reactions were reported in less than 1% of UC patients treated with nivolumab in combination with cisplatin and gemcitabine chemotherapy in CHECKMATE-901. Adverse reactions presented elsewhere are excluded. Blood and lymphatic system disorders: febrile bone marrow aplasia, pancytopenia.

Unresectable or Metastatic Treatment of Esophageal Squamous Cell Carcinoma (ESCC): CHECKMATE-648	The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with nivolumab in combination with chemotherapy or nivolumab in combination with ipilimumab in CHECKMATE-648. *Nivolumab + ipilimumab* Cardiac Disorders: myocarditis Eye Disorders: uveitis Gastrointestinal Disorders: gastrointestinal hemorrhage Musculoskeletal and Connective Tissue: arthritis, myositis Nervous System Disorders: encephalitis *Nivolumab + chemotherapy* Cardiac Disorders: tachycardia Eye Disorders: uveitis Musculoskeletal and Connective Tissue: rhabdomyolysis, myositis, muscle weakness Nervous System Disorders: paresthesia Skin and subcutaneous tissue disorder: palmar-plantar erythrodysesthesia syndrome, skin hyperpigmentation System Disorders: paresthesia Vascular Disorders: thrombosis

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

SUBCUTANEOUS FORMULATION (Opdivo SC)

Clinical Trial Findings

The incidence of worsening laboratory abnormalities in CHECKMATE-67T is shown in Table 31.

Table 31: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on Opdivo SC - CHECKMATE 67T

Laboratory Abnormality	Opdivo SC		Nivolumab IV	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	46	7	48	9
Lymphopenia	36	6	45	9
Chemistry				
Increased creatinine	37	1.3	44	0.4
Hyponatremia	34	2.6	40	2.5
Hyperkalemia	34	3.0	45	2.9

Laboratory Abnormality	Opdivo SC		Nivolumab IV	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alkaline phosphatase	32	2.1	33	2.0
Hypercalcemia	30	2.1	32	4.5
Increased albumin	23	1.7	34	0.4
Increased ALT	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 SC group (range: 232 to 235 patients) and nivolumab intravenous group (range: 240 to 244 patients).

INTRAVENOUS FORMULATION (Opdivo)

The following sections below present data from a separate Product Monograph for Opdivo intravenous formulation studies.

Clinical Trial Findings

The incidence of worsening laboratory abnormalities in CHECKMATE-066 is shown in Table 32.

Table 32: Laboratory Abnormalities (CHECKMATE-066)

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	Nivolumab			Dacarbazine		
Test	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	195	72 (36.9)	3 (1.5)	189	78 (41.3)	12 (6.3)
Decreased platelet count	203	23 (11.3)	1 (0.5)	195	65 (33.3)	13 (6.7)
Decreased lymphocytes	195	56 (28.7)	11 (5.6)	186	87 (46.8)	13 (7.0)
Decreased absolute neutrophil count	196	15 (7.7)	1 (0.5)	190	47 (24.7)	17 (8.9)
Increased alkaline phosphatase[c]	194	41 (21.1)	5 (2.6)	186	26 (14.0)	3 (1.6)
Increased AST[c]	195	47 (24.1)	7 (3.6)	191	37 (19.4)	1 (0.5)
Increased ALT[c]	197	49 (24.9)	6 (3.0)	193	37 (19.2)	1 (0.5)
Increased total bilirubin[c]	194	26 (13.4)	6 (3.1)	190	12 (6.3)	0
Increased creatinine	199	21 (10.6)	1 (0.5)	197	19 (9.6)	1 (0.5)

a. The total number of patients who had both baseline and on-study laboratory measurements available.
b. Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.
c. Laboratory Abnormalities Occurring in ≥10% of nivolumab-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% [Grades 1-4] or ≥2% [Grades 3-4]).

Table 33 presents selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of patients in either nivolumab-containing arm or in the ipilimumab arm in CHECKMATE-067.

Table 33: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients treated with Nivolumab in Combination with Ipilimumab or Single-Agent Nivolumab and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (CHECKMATE-067)

	Percentage (%) of Patients[a]					
	nivolumab + ipilimumab (n=313)		nivolumab (n=313)		ipilimumab (n=311)	
Test	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Decreased hemoglobin [b]	52	2.7	41	2.6	41	5.6
Decreased platelet count	12	1.4	10	0.3	5	0.3
Decreased leukocytes	14	0.3	19	0.3	6	0.3
Decreased lymphocytes (Absolute)	39	5.1	41	4.9	29	4.0
Decreased Absolute Neutrophil Count	14	0.7	16	0.3	6	0.3
Increased alkaline phosphatase	41	5.9	27	2.0	23	2.0

Increased ALT	55	15.8	25	3.0	29	2.7
Increased AST	52	13.4	29	3.7	29	1.7
Bilirubin, Total	15	1.7	11	1.0	6	0
Increased creatinine	26	2.7	18	0.7	16	1.3
Increased amylase	27	9.5	19	2.7	15	1.6
Increased lipase	43	21.7	32	12	24	6.6
Hyperglycemia	52	5.3	47	7.4	28	0
Hyponatremia	45	9.9	22	3.3	26	6.7
Hypocalcemia	32	1.1	16	0.7	21	0.7
Hypokalemia	18	4.4	9	1.3	10	1.3

a. Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: nivolumab +ipilimumab (range: 75 to 297); single-agent nivolumab (range: 81 to 307); ipilimumab (range: 61 to 304).
b. Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

The incidence of worsening laboratory abnormalities for CHECKMATE-037 is shown in **Table 34**.

Table 34: Laboratory Abnormalities (CHECKMATE-037)

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	Nivolumab			Chemotherapy		
Test	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	259	94 (36.3)	16 (6.2)	99	59 (59.6)	9 (9.1)
Decreased platelet count	257	24 (9.3)	0	99	40 (40.4)	9 (9.1)
Leukopenia	257	22 (8.6)	1 (0.4)	100	53 (53.0)	14 (14.0)
Decreased lymphocytes	256	112 (43.8)	17 (6.6)	99	52 (52.5)	15 (15.2)
Decreased absolute neutrophil count	256	20 (7.8)	3 (1.2)	99	44 (44.4)	21 (21.2)
Increased alkaline phosphatase[c]	252	55 (21.8)	6 (2.4)	94	12 (12.8)	1 (1.1)
Increased AST[c]	253	70 (27.7)	6 (2.4)	96	11 (11.5)	1 (1.0)
Increased ALT[c]	253	41 (16.2)	4 (1.6)	96	5 (5.2)	0
Increased total bilirubin	249	24 (9.6)	1 (0.4)	94	0	0
Increased creatinine	254	34 (13.4)	2 (0.8)	94	8 (8.5)	0
Hyponatremia[c]	256	63 (24.6)	13 (5.1)	95	17 (17.9)	1 (1.1)
Hyperkalemia[c]	256	39 (15.2)	5 (2.0)	95	6 (6.3)	0

a. The total number of patients who had both baseline and on-study laboratory measurements available.
b. Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

c. Laboratory Abnormalities Occurring in ≥10% of nivolumab-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% [Grades 1-4] or ≥2% [Grades 3-4]).

The incidence of worsening laboratory abnormalities in CHECKMATE-238 is shown in **Table 35**.

Table 35: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients (CHECKMATE-238)

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	Nivolumab			Ipilimumab		
Test	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	447	25.5	0	440	33.6	0.5
Decreased Leukocytes	447	13.9	0	440	2.7	0.2
Decreased lymphocytes	446	26.7	0.4	439	12.3	0.9
Decreased absolute neutrophil count	447	12.5	0	439	5.9	0.5
Increased ALT	445	23.6	1.3	440	32.7	8.6
Increased AST	447	25.3	1.8	443	39.5	11.7
Increased creatinine	446	12.1	0	440	12.7	0
Increased amylase	400	17.0	3.3	392	13.3	3.1
Increased lipase	438	24.9	7.1	427	23.2	8.7
Hyponatremia	446	16.1	1.1	438	21.7	3.2
Hyperkalemia	445	12.4	0.2	439	8.9	0.5
Hypocalcemia	434	10.6	0.7	422	17.3	0.5

a. The total number of patients who had both baseline and on-study laboratory measurements available.
b. Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

The incidence of worsening laboratory abnormalities in CHECKMATE-76K is shown in Table 36.

Table 36: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients (CHECKMATE-76K)

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	Nivolumab			Placebo		
Test	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	512	18.8	0	261	14.2	0
Decreased lymphocytes (absolute)	469	17.3	1.1	238	16.8	1.7
Decreased neutrophils	510	10.4	0	261	10.3	0.4
Increased ALT	513	20.3	2.1	261	15.3	0.4
Increased AST	511	24.9	2.2	260	15.8	0.4
Increased creatinine	512	15.4	0.4	261	13.4	0
Increased amylase	262	16.8	0.4	138	8.7	0
Increased lipase	313	21.7	2.9	174	21.3	2.3
Hyponatremia	513	13.3	0.6	260	10.8	0.4
Hyperkalemia	511	12.9	1.0	261	15.3	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: nivolumab (range: 262 to 513 patients) and Placebo group (range: 138 to 261 patients).
b. Grade 4 hemoglobin is not applicable per anemia criteria in CTCAE v5.0.

The incidence of worsening laboratory abnormalities in CHECKMATE-017 and CHECKMATE-057 is shown in **Table 37**.

Table 37: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients (CHECKMATE-017 and CHECKMATE-057)

	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	Nivolumab		Docetaxel	
Test	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
Hyperkalemia	23	1.7	20	2.6
Increased ALT	22	1.7	17	0.5
Hypomagnesemia	21	1.2	17	0.3
Hypocalcemia	20	0.2	23	0.3
Increased creatinine	18	0	12	0.5

Hypokalemia	15	1.4	13	2.1
Hypercalcemia	12	1.2	8	0.5
Hematology				
Lymphopenia	48	10	59	24
Anemia	34	2.4	57	5
Thrombocytopenia	12	0.7	12	0
Leukopenia	11	1.2	78	50

a. Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: nivolumab group (range: 405-417 patients) and docetaxel group (range: 372-390 patients).

The incidence of worsening laboratory abnormalities in CHECKMATE-816 is shown in **Table 38**

Table 38: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-816

Laboratory Abnormality	Nivolumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	62.9	3.5	70.0	5.9
Neutropenia	58.2	21.8	58.0	26.6
Leukopenia	53.2	5.3	50.9	10.7
Lymphopenia	38.2	4.7	31.4	1.8
Thrombocytopenia	24.1	2.9	21.9	3.0
Chemistry				
Hyperglycemia	37.0	5.5	35.0	2.9
Hypomagnesemia	25.6	1.8	31.0	1.2
Hyponatremia	24.7	2.4	28.2	1.8
Increased amylase	23.0	3.6	13	1.8
Increased ALT	23.0	0	20	1.2
Creatinine	17.1	0	20.5	0
Increased Lipase	18.2	6.5	13.8	3.6
Hyperkalemia	18.8	1.2	9.4	1.8
Hypocalcemia	17.2	0.6	8.2	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: nivolumab and platinum-doublet chemotherapy group (range: 73 to 171 patients) and platinum-doublet chemotherapy group (range: 68 to 171 patients).

The incidence of worsening laboratory abnormalities in CHECKMATE-025 is shown in **Table 39**.

Table 39: Laboratory Abnormalities Reported in CHECKMATE-025

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	Nivolumab			Everolimus		
Test	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	395	153 (38.7)	33 (8.4)	383	264 (68.9)	60 (15.7)
Decreased platelet count	391	39 (10.0)	1 (0.3)	379	104 (27.4)	7 (1.8)

Decreased lymphocytes	390	163 (41.8)	25 (6.4)	376	198 (52.7)	42 (11.2)
Decreased absolute neutrophil count	391	28 (7.2)	0	377	56 (14.9)	3 (0.8)
Increased alkaline phosphatase	400	127 (31.8)	9 (2.3)	374	119 (31.8)	3 (0.8)
Increased AST	399	131 (32.8)	11 (2.8)	374	146 (39.0)	6 (1.6)
Increased ALT	401	87 (21.7)	13 (3.2)	376	115 (30.6)	3 (0.8)
Increased total bilirubin	401	37 (9.2)	2 (0.5)	376	13 (3.5)	2 (0.5)
Increased creatinine	398	168 (42.2)	8 (2.0)	379	170 (44.9)	6 (1.6)

a. The total number of patients who had both baseline and on-study laboratory measurements available.
b. Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

The incidence of worsening laboratory abnormalities in CHECKMATE-214 is shown in **Table 40**.

Table 40: Laboratory Abnormalities Worsening from Baseline Occurring in >15% of Patients on nivolumab plus ipilimumab (CHECKMATE-214)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	Nivolumab plus ipilimumab		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Hematology				
Anemia	43	3.0	64	8.8
Lymphopenia	36	5.1	63	14.3
Chemistry				
Increased lipase	48	20.1	51	20.2
Increased creatinine	43	2.1	46	1.5
Increased ALT	41	6.5	44	2.7
Increased AST	40	4.8	60	2.1
Increased amylase	39	12.2	33	7.2
Hyponatremia	39	9.9	36	7.3
Increased alkaline phosphatase	29	2.0	32	1.0
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	22	0.4	36	0.6
Hypomagnesemia	19	0.4	28	1.8

a. Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: nivolumab plus ipilimumab group (range: 490 to 538 patients) and sunitinib group (range: 485 to 523 patients).

The incidence of worsening laboratory abnormalities in CHECKMATE-9ER is shown in **Table 41**.

Table 41: Laboratory Abnormalities Worsening from Baseline Occurring in >15% of Patients on nivolumab plus cabozantinib (CHECKMATE-9ER)

	Percentage of Patients with Worsening Laboratory Test from Baseline[a]

Laboratory Abnormality	nivolumab plus cabozantinib		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Hematology				
Lymphopenia	42	7	45	10
Thrombocytopenia	41	0	70	10
Anemia	37	3	61	5
Leukopenia	37	0	66	5
Neutropenia	35	3	67	12
Chemistry				
Increased ALT	79	10	39	4
Increased AST	77	8	57	3
Hypophosphatemia	68	21	48	7
Hypocalcemia	55	2	24	1
Hypomagnesemia	50	2	29	0
Hyponatremia	44	12	37	12
Hyperglycemia	44	4	44	2
Increased alkaline phosphatase	41	3	37	2
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased creatinine	38	1	43	1
Hyperkalemia	36	5	27	1
Hypoglycemia	26	1	14	0
Hypokalemia	19	3	12	2
Increased Total Bilirubin	17	1	22	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: nivolumab plus cabozantinib group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

The incidence of worsening laboratory abnormalities in CHECKMATE-141 is shown in **Table 42**.

Table 42: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Nivolumab-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Comparator (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial CHECKMATE-141)

	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	Nivolumab		Investigator Choice[b]	
Laboratory Abnormality	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Chemistry				
Increased alkaline phosphatase	23	1.8	15	0
Increased amylase	12	3.2	8	1.1
Hypercalcemia	15	2.2	10	1.0
Hyperkalemia	17	0.4	12	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: nivolumab group (range: 186-225 patients) and investigator's choice group (range: 92-104 patients).
b. Cetuximab, methotrexate or docetaxel.

The incidence of worsening laboratory abnormalities in CHECKMATE-142 is shown **Table 43**.

Table 43: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Reported in CHECKMATE-142 (Nivolumab in Combination with Ipilimumab) with MSI-H/dMMR mCRC

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]	
	Nivolumab + Ipilimumab (n=119)	
	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	50 (43.5)	11 (9.6)
Thrombocytopenia	33 (28.9)	1 (0.9)
Leukopenia	24 (20.9)	0
Lymphopenia	37 (32.7)	7 (6.2)
Neutropenia	33 (28.9)	0
Increased alkaline phosphatase	36 (31.9)	6 (5.3)
Increased AST	51 (44.3)	15 (13.0)
Increased ALT	45 (39.1)	13 (11.3)
Increased total bilirubin	31 (27.2)	6 (5.3)
Increased creatinine	31 (27.2)	4 (3.5)
Increased total amylase	34 (38.6)	3 (3.4)
Increased total lipase	50 (44.6)	19 (17.0)
Hypercalcemia	7 (10.0)	0
Hypocalcemia	31 (27.7)	1 (0.9)
Hyperkalemia	33 (28.9)	1 (0.9)
Hypokalemia	21 (18.4)	4 (3.5)
Hypomagnesemia	27 (24.1)	0
Hyponatremia	35 (30.4)	7 (6.1)

a. Each test incidence is based on the number of patients who had both baseline and on-treatment laboratory measurement available. All laboratory parameters are based on a range of 88-115 patients for nivolumab in combination with ipilimumab.
b. Per anemia criteria in CTC version 4.0, there is no Grade 4 for hemoglobin.

The incidence of worsening laboratory abnormalities in in CHECKMATE-577 is shown in **Table 44**.

Table 44: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥15% of Patients - CHECKMATE-577

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	Nivolumab		Placebo	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Hematology				
Anemia[b]	26.5	0.8	20.7	0.4
Leukopenia	25.3	1.0	34.4	0.4
Lymphopenia	44.1	16.7	34.8	11.7
Absolute Neutropenia	23.8	1.5	22.7	0.4
Chemistry				
Increased alkaline phosphatase	25.0	0.8	18.0	0.8
Increased AST	27.3	2.1	21.9	0.8
Increased ALT	20.4	1.9	16.0	1.2
Increased albumin	21.0	0.2	17.5	0
Increased amylase	19.5	3.9	12.5	1.3
Hyponatremia	18.7	1.7	11.7	1.2
Hyperkalemia	16.8	0.8	15.2	1.6
Hyperglycemia	38.7	0.6	41.9	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: nivolumab group (range: 163 to 526 patients) and Placebo group (range: 86 to 256 patients).

b. Per Anemia criteria in CTC v4.0 there is no grade 4 for hemoglobin.

The incidence of worsening laboratory abnormalities in CHECKMATE-649 is shown in Table 45.

Table 45: Laboratory Abnormalities Worsening from Baseline Occurring in >10% of Patients on Nivolumab in combination with Fluoropyrimidine- and Platinum-based Chemotherapy (CHECKMATE-649)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	Nivolumab in combination with Fluoropyrimidine- and Platinum-based Chemotherapy		Fluoropyrimidine- and Platinum-based Chemotherapy	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Hematology				
Neutropenia	72.8	29.3	62.3	22.3
Leukopenia	68.6	11.8	59.1	9.0
Thrombocytopenia	67.6	6.8	62.6	4.4
Anemia[b]	58.8	13.9	59.7	9.5
Lymphopenia	58.5	12.2	49.3	9.2
Chemistry				
Increased AST	51.7	4.6	47.5	1.9
Hypocalcemia	43.6	1.6	37.4	1.0

Hyperglycemia	40.7	4.2	38.1	2.7
Increased ALT	37.0	3.4	29.5	1.9
Hyponatremia	33.6	6.3	24.1	5.5
Hypokalemia	26.5	6.5	24.1	4.8
Increased bilirubin, total	23.9	3.0	22.3	2.0
Increased creatinine	15.0	1.0	9.1	0.5
Hyperkalemia	14.4	1.4	10.5	0.7
Hypoglycemia	11.8	0.7	9.1	0.2
Hypernatremia	11.0	0.5	7.1	0

a. Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. nivolumab in combination with chemotherapy (407 to 767 patients) or chemotherapy group (range: 405 to 735 patients).

b. Per Anemia criteria in CTC version 4.0 there is no grade 4 for hemoglobin.

The incidence of worsening laboratory abnormalities in CHECKMATE-274 is shown **Table 46**.

Table 46: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-274

Laboratory Abnormality	Nivolumab (n=351)		PLACEBO (n=348)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased creatinine	35.5	1.7	35.9	2.6
Increased amylase	33.5	8.1	22.8	3.2
Increased lipase	32.6	11.8	31.2	10.1
Hyperkalemia	32.1	5.0	29.5	5.6
Increased alkaline phosphatase	23.9	2.3	14.5	0.6
Increased AST	24.3	3.5	16.0	0.9
Increased ALT	23.2	2.9	15.0	0.6
Hyponatremia	22.4	4.1	17.4	1.8
Hypocalcemia	17.0	1.2	11.2	0.9
Hypomagnesemia	15.7	0.0	8.7	0.0
Hypercalcemia	11.9	0.3	7.9	0.3
Hematology				
Lymphopenia	33.3	2.9	26.6	1.5
Anemia	30.1	1.4	27.7	0.9
Neutropenia	11.3	0.6	10.3	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: nivolumab group (range: 322 to 348 patients) and placebo group (range: 312 to 341 patients).

The incidence of worsening laboratory abnormalities in CHECKMATE-901 is shown **Table 47**.

Table 47: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-901

Laboratory Abnormality	Nivolumab and Cisplatin and Gemcitabine		Cisplatin and Gemcitabine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	88.0	21.3	80.1	20.6
Leukopenia	82.7	18.3	73.5	13.3
Neutropenia	82.3	35.3	76.3	27.6
Lymphopenia	70.5	17.4	56.3	12.5

Thrombocytopenia	60.1	13.0	50.9	7.5
Chemistry				
Increased creatinine	52.5	2.4	41.2	1.1
Hypomagnesemia	48.4	3.8	39.2	1.5
Hyponatremia	42.6	13.2	39.0	7.7
Hyperglycemia	41.4	3.9	36.5	3.2
Hypocalcemia	35.6	2.1	24.2	1.1
Increased alkaline phosphatase	33.6	2.4	22.5	0.7
Hyperkalemia	32.8	3.0	32.2	1.1
Amylase increased	31.7	4.2	23.1	3.6
Increased AST	31.3	2.4	17.3	0.7
Increased ALT	29.3	2.4	18.8	0.7
Lipase increased	20.2	4.8	22.7	5.4
Hypokalemia	15.5	2.0	9.9	1.5
Hypercalcemia	13.0	0.3	7.8	0.7
Hypoglycemia	12.5	1.3	6.3	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: nivolumab group (range: 152-301 patients) and chemotherapy group (range: 126-281 patients).

The incidence of worsening laboratory abnormalities in CHECKMATE-648 is shown in Table 48.

Table 48: Laboratory Abnormalities Worsening from Baseline Occurring in ≥15% of Patients treated with Nivolumab in Combination with Ipilimumab or Nivolumab in Combination with Chemotherapy (CHECKMATE-648)

	Percentage (%) of Patients[a]					
	Nivolumab and Ipilimumab (n=322)		Nivolumab with Cisplatin and 5 FU (n=310)		Cisplatin and 5-FU (n=304)	
Test	**Any Grade**	**Grade 3–4**	**Any Grade**	**Grade 3–4**	**Any Grade**	**Grade 3–4**
Hematology						
Anemia[b]	52	6.5	81	21.4	66	13.8
Lymphopenia	50	1.0	67	23.3	44	8.2
Neutropenia	13	1.3	61	17.7	48	13.5
Leukopenia	9	1.3	53	10.8	39	5
Thrombocytopenia	12	1.0	43	3.3	29	2.8
Chemistry						
Hyponatremia	46	11.8	52	14.8	41	8.9

Hyperglycemia	43	4.3	34	0	36	0.8
Increased AST	39	5.6	23	3.3	11	1.4
Increased ALT	33	5.9	23	2.3	8	0.7
Hypocalcemia	33	0	45	3.0	23	0.7
Increased alkaline phosphatase	32	3.3	26	1.3	16	0
Hyperkalemia	22	1.6	34	2.3	24	0.7
Hypokalemia	20	5.2	29	9.5	17	6.0
Hypercalcemia	15	2.0	12	3.0	8	0.4
Hypoglycemia	16	1.2	18	0.4	7	0
Increased creatinine	15	0.7	41	2.3	30	0.7
Hypomagnesemia	19	0	37	1.7	27	1.8

a Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: nivolumab with cisplatin and 5-FU group (range: 60 to 305 patients) or Cisplatin and 5-FU group (range: 56 to 283 patients).

b Per Anemia criteria in CTC v4.0 there is no grade 4 for hemoglobin.

8.5. Post-Market Adverse Reactions

The following events have been identified during post approval use of nivolumab intravenous formulation. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Blood and lymphatic system disorders: haemophagocytic lymphohistiocytosis (HLH), autoimmune hemolytic anemia.

Cardiac disorders: pericarditis.

Endocrine: hypoparathyroidism.

Eye disorders: Vogt-Koyanagi-Harada syndrome.

Immune system disorders: solid organ transplant rejection, graft-versus-host-disease, cytokine release syndrome.

Metabolism and nutrition disorders: tumour lysis syndrome.

Nervous system disorders: myelitis (including transverse myelitis)

9. Drug Interactions

9.2. Drug Interactions Overview

No formal drug-drug interaction studies have been conducted with nivolumab. Nivolumab is considered to have low potential to affect pharmacokinetics of other drugs based on the lack of effect on cytokines in peripheral circulation.

9.3. Drug-Behaviour Interactions

The interaction of nivolumab with individual behavioural risks has not been studied.

9.4. Drug-Drug Interactions

Systemic Immunosuppression

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting Opdivo SC, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting Opdivo SC to treat immune-related adverse reactions. The preliminary results show that systemic immunosuppression after starting nivolumab treatment does not appear to preclude the response on nivolumab.

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Hyaluronidase is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. In the doses administered, hyaluronidase in Opdivo SC acts locally.

The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

10.2. Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamics of Opdivo SC have not been fully characterized.

10.3. Pharmacokinetics

SUBCUTANEOUS FORMULATION (Opdivo SC)

Nivolumab pharmacokinetics (PK) were assessed using a population pharmacokinetics (PopPK) approach for monotherapy Opdivo SC. The PK of nivolumab was studied at a dose of 1,200 mg co-formulated with 20,000 units of recombinant human hyaluronidase PH20 administered as multiple doses of Opdivo SC as a solution for subcutaneous injection every 4 weeks.

Based on PopPK analysis, Opdivo SC PK can be described with first order absorption from the extravascular compartment and time-varying CL. Steady state is achieved after 16 weeks and the average systemic accumulation ratio of was 2.3.

Table 49: Summary of Nivolumab Pharmacokinetic Parameters for Opdivo SC 1200 mg Q4W in patients with metastatic renal cell carcinoma

	Parameters[a]							
	C_{min} (µg/mL)	**C_{max}** (µg/mL)	**T_{max}** **(**Day**)**	Cavg (µg/mL)	**AUC_{tau}** (µg*day/mL)	**CLss** (mL/hr)	**Vss** (L)	**$T_{1/2ss}$** (Day)
Cycle 1	50.8 (44.2)	108 (32.7)	5.83 (41.2)	78.8 (35.6)	2,206 (35.6)	7.18 (52.3)	6.32 (21.3)	26.5 (32.1)
Steady State	126 (51)	230 (39.2)	5.83 (41.2)	182 (43.5)	n/a			

[a] Parameters are reported as geometric mean values (% geometric mean coefficient of variation - CV) based on population pharmacokinetic analysis.

AUC: area under the curve from time zero to 28 days; Cmax: maximum concentration; Cmin; minimum concentration; t½: terminal half-life; Tmax: time to reach Cmax; Vss: volume of distribution at steady-state; CL: clearance at steady-state

Absorption

The geometric mean (CV%) absorption rate constant (Ka) and bioavailability (F) of Opdivo SC are 0.281 Day-1 (28.1%) and 74% (13.8%), respectively. Peak concentrations occurred by around 6 days.

Distribution

Opdivo SC geometric mean (CV%) volume of distribution at steady state (Vss) is 6.32 L (21.3%).

Metabolism

The metabolic pathway of nivolumab has not been characterized. As a fully human IgG4 monoclonal antibody, nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

Opdivo SC human clearance (CL) decreases over time, with a mean maximal reduction from baseline values (CV%) of 24.6% (15.8%) resulting in a geometric mean (CV%) steady-state clearance (CLss) of 7.18 mL/h (52.3%) in patients with RCC; the decrease in CLss is not considered clinically relevant.

The geometric mean (CV%) half-life (t1/2) at steady state is 26.5 days (32.1%).

Special populations and conditions

PopPK analysis suggested Karnofsky performance status had no clinically important effect on the bioavailability or clearance of Opdivo SC.

Pediatrics: Opdivo SC is not authorized for use in pediatric patients below 18 years of age. No dedicated studies of Opdivo SC have been conducted in pediatric patients.

Geriatrics: No dedicated studies of Opdivo SC have been conducted in elderly patients. Based on a PopPK analysis, age (range: 24-93 years) was not a statistically significant covariate on the clearance of nivolumab.

Sex: Based on a PopPK analysis, sex had no clinically important effect on the clearance of Opdivo SC. The bioavailability of nivolumab following subcutaneous administration was <10% lower in females than males.

Hepatic Impairment: No dedicated studies of Opdivo SC have been conducted in patients with hepatic impairment.

Renal Impairment: Based on a PopPK analysis, there was no impact of renal impairment on the clearance, F and KA of Opdivo SC across patients with normal (N=31), mild (N=98) and moderate (N=110) renal impairment (eGFR 24 to 124 mL/min/1.73 m^2). There was insufficient data in patients with severe renal impairment (N=3) to draw a conclusion.

Obesity: Based on a PopPK analysis, body weight (35 to 153 kg) had no clinically important effect on the clearance of Opdivo SC.

INTRAVENOUS FORMULATION (Opdivo)

For pharmacokinetic information on the IV formulation, please refer to the separate Product Monograph for Opdivo.

10.4. Immunogenicity

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

SUBCUTANEOUS FORMULATION (Opdivo SC)

During the 2-year treatment period in CHECKMATE-67T, approximately 23% (46/202) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay 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 treatment-emergent anti-recombinant human hyaluronidase PH20 antibodies was 8.8% (19/215); 5 (26%) of these 19 patients developed NAb.

When Opdivo SC is administered as monotherapy, the clearance of nivolumab increased by approximately 26% in the presence of treatment-emergent anti-nivolumab antibodies. These anti-drug antibody-associated pharmacokinetic changes were not considered to be clinically significant. Of patients in CHECKMATE-67T who were treated with Opdivo SC and evaluable for anti-drug antibodies, local injection-site reaction adverse events were reported in a greater proportion of patients who developed anti-drug antibodies to nivolumab 15% (7/46) of patients who developed ADA to nivolumab and 7% (10/155) of patients who did not develop ADA to nivolumab) or recombinant human hyaluronidase PH20;

however, all events were Grade 1 or 2 and resolved. No systemic injection-related reactions were observed. The effects of anti-drug antibodies on effectiveness of Opdivo SC have not been characterized.

INTRAVENOUS FORMULATION (Opdivo)

For immunogenicity information on the intravenous formulation, please refer to the separate Product Monograph for Opdivo.

11. Storage, Stability, and Disposal

Store Opdivo SC (nivolumab) under refrigeration at 2°C to 8°C. Protect Opdivo SC from light by storing in the original package until time of use. Do not freeze or shake.

Once withdrawn into the syringe, Opdivo SC should be used immediately. If not used immediately, the syringe can be stored in the refrigerator at 2°C to 8°C, protected from light for up to 7 days and/or at room temperature 15°C to 25°C and room light for up to 8 hours. Discard if storage time exceeds these limits. Do not freeze.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Proper name: nivolumab

Molecular formula and molecular mass: The predominant product has a molecular formula of C6462H9990N1714O2074S42 (with heavy chain N-terminal pyroglutamate, without C-terminal lysine and with G0F/G0F glycoform) with a calculated molecular weight of 146,221 Da.

Structural formula: Nivolumab is a fully human monoclonal antibody of the IgG4 class consisting of four polypeptide chains: two identical heavy chains of 440 amino acids and two identical kappa light chains of 214 amino acids, which are linked through inter-chain disulfide bonds.

Physicochemical properties: The nivolumab drug substance is a clear to opalescent, colorless to yellow solution. The 120mg/mL nivolumab drug substance solution containing 20 mM histidine, 250 mM sucrose, 0.05% w/v polysorbate 80, 50 µM pentetic acid (also known as diethylenetriaminepentaacetic acid [DTPA]), has a pH of approximately 6.0, a pI of approximately 7.7 and an extinction coefficient of 1.68 mL/mg·cm.

Product Characteristics:

OPDIVO SC (nivolumab) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) developed by recombinant deoxyribonucleic acid (DNA) technology. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. Nivolumab has a calculated molecular mass of 146,221 Da.

OPDIVO SC injection is a Clear to opalescent, colorless to yellow liquid. Essentially free of visible particulates. The drug product is a sterile, non-pyrogenic, single-use, preservative-free, isotonic aqueous solution for subcutaneous (SC) administration. The drug product is packaged in a 6R Type I clear tubing glass vial, closed with a 20-mm gray Flurotec® film-laminated butyl rubber stopper and a 20-mm aluminum crimp seal with an orange (600 mg/vial presentation) or violet (300 mg/vial presentation) polypropylene Flip-Off® button.

14. Clinical Trials

14.1. Clinical Trials by Indication

SUBCUTANEOUS FORMULATION (Opdivo SC)

Metastatic Renal Cell Carcinoma (RCC)

CHECKMATE-67T

Study Demographics and Trial Design

Table 50 – Summary of Patient Demographics for Clinical Trial in Metastatic Renal Cell Carcinoma

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (range)	Sex
CHEKMATE -67T	Phase 3 open-label, randomized, noninferiority study of nivolumab SC monotherapy coformulated with rHuPH20	Nivolumab SC 1200 mg Q4W or Nivolumab IV 3 mg/kg Q2W	495 randomized: Nivolumab SC Arm: 248 Nivolumab IV Arm: 247	65.0(20, 93)	Male 68% Female 32%

CHECKMATE-67T was a multicenter, randomized, open-label study in patients with advanced or metastatic clear cell renal cell carcinoma. Patients 18 years of age or older with histologically confirmed advanced or metastatic renal cell carcinoma with a clear cell component, including those with sarcomatoid features, and who received no more than 2 prior systemic treatment regimens were randomized to receive Opdivo SC 1,200 mg every 4 weeks subcutaneously, or nivolumab 3 mg/kg every 2 weeks intravenously. Patients with untreated, symptomatic central nervous system (CNS) metastases; leptomeningeal metastases; concurrent malignancies requiring treatment or history of prior malignancy within the prior 2 years; active, known, or suspected autoimmune disease; or who received prior treatment with a checkpoint inhibitor were excluded from the study. Patients with asymptomatic, stable CNS metastases that did not require immediate treatment were eligible if there was no evidence of progression within 28 days prior to the first dose of study drug administration. Stratification factors for randomization were weight (<80 kg vs ≥80 kg) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification (favorable vs intermediate, vs poor risk). The primary objective of the study was to demonstrate noninferiority of the model-predicted serum nivolumab Cavgd28 and Cminss (co-primary endpoints) for the subcutaneous administration of OPDICO SC to the intravenous administration of nivolumab (see 10 Clinical Pharmacology). The secondary objective of the study was to demonstrate noninferiority of the overall response rate (ORR) for the subcutaneous administration of Opdivo SC to the intravenous administration of nivolumab, as assessed by blinded independent central review (BICR). The efficacy analysis was considered to be exploratory.

A total of 495 patients were randomized to receive either Opdivo SC (n = 248) or intravenous nivolumab (n = 247). The median age was 65 years (range: 20 to 93), with 51% ≥65 years of age and

14% ≥75 years of age, 85% White, 0.8% Asian, and 0.4% Black, and 68% male. Fifty-seven percent of patients weighed <80 kg and 43% weighed ≥80 kg. Baseline Karnofsky performance status was 70 (7%%), 80 (20%), 90 (34%), or 100 (39%). Patient distribution by IMDC risk categories was 21% favorable, 62% intermediate, and 17% poor.

Study Results

CHECKMATE-67T demonstrated noninferiority exposures of Opdivo SC administered subcutaneously to nivolumab 3 mg/kg administered intravenously as shown in Table 51.

Table 51: Nivolumab exposure (geometric mean with range and CV%) following subcutaneous or intravenous administration of nivolumab - CHECKMATE-67T

Co-primary Endpoints	Nivolumab within Opdivo SC (n=242)	Nivolumab within Opdivo (IV formulation) (n=245)	% Ratio of Geometric Means	Confidence Interval
Model-predicted Cavgd28 (ug/mL)	77.4 (74.55, 80.30)	36.9 (35.56, 38.23)	2.09	(2.00-2.20)
Model-predicted Cminss (ug/mL)	122.2 (114.55, 130.42)	68.9 (64.68, 73.40)	1.77	(1.63-1.93)

Abbreviation: SC = subcutaneous; IV = intravenous

Note: PK parameters are from Population Pharmacokinetics Model

Descriptive results of the exploratory analysis of the secondary efficacy endpoint of BICR-assessed ORR were: Opdivo SC: ORR = 24% (60/248; 95% CI: 19 – 30); Opdivo (intravenous formulation): ORR = 18% (45/247; 95% CI: 13.6 – 23.6).

INTRAVENOUS FORMULATION (Opdivo)

Information in this section reports data from a separate Product Monograph for Opdivo (intravenous formulation). Use of Opdivo SC for these indications is supported by evidence from clinical studies conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between Opdivo SC and intravenous nivolumab (see 8 Adverse Reactions, 10 Clinical Pharmacology).

Metastatic Renal Cell Carcinoma

Advanced RCC (previously treated)

Controlled Trial in RCC Patients Previously Treated with Anti-angiogenic Therapy (Second-line treatment): CHECKMATE-025

CHECKMATE-025 was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after 1 or 2 prior anti-angiogenic therapy regimens and no more than 3 total prior systemic treatment regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70%. This study included patients regardless of their PD-L1 status. CHECKMATE-025

excluded patients with any history of or concurrent brain metastases, prior treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

A total of 821 patients were randomized to nivolumab (n=410) administered intravenously at 3 mg/kg every 2 weeks or everolimus (n=411) administered orally 10 mg daily. The median age was 62 years (range: 18 to 88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and white (88%) and 34% and 66% of patients had a baseline KPS of 70 to 80% and 90 to100%, respectively. The majority of patients (72%) were treated with one prior anti-angiogenic therapy, and 28% received 2 prior anti-angiogenic therapies. Twenty-four percent of patients had at least 1% PD-L1 expression.

The first tumour assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. Nivolumab was continued beyond progression in 44% of patients.

The primary efficacy outcome measure was overall survival (OS). Secondary efficacy assessments included investigator-assessed objective response rate (ORR) and progression-free survival (PFS). A summary of efficacy outcome measures is presented in **Table 52**.

Primary Efficacy Outcome Measure:

The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 52 and Figure 1). OS benefit was observed regardless of PD-L1 expression level. The estimated OS rates at 12 months were 76% for nivolumab and 67% for everolimus.

Secondary Efficacy Outcome Measures:

The investigator-assessed ORR using RECIST v1.1 was superior in the nivolumab group (103/410, 25.1%) compared with the everolimus group (22/411, 5.4%), with a stratified CMH test p-value of < 0.0001. The median time to onset of objective response was 3 months (range: 1.4 to 13 months) after the start of nivolumab treatment. Forty-three (48.9%) responders had ongoing responses with a duration ranging from 7.4 to 27.6 months. Thirty-three (37.5%) patients had durable responses of 12 months or longer. The ORR with a confirmatory scan was performed after at least 4 weeks. The median duration of response was 23.0 months and 13.7 months in the nivolumab and everolimus group, respectively. The best overall response (BOR) was CR in 4 subjects (1.0%) in the nivolumab group and 2 subjects (0.5%) in the everolimus group. BOR was PR in 99 (24.1%) subjects in the nivolumab group and 20 (4.9%) subjects in the everolimus group.

While not statistically significant, PFS data suggest a benefit with nivolumab vs everolimus (HR: 0.88 [95%CI: 0.75, 1.03], stratified log-rank test p-value = 0.1135), with separation of the K-M curves after 6 months favoring nivolumab (Table 52 and Figure 2).

Table 52: Efficacy Results - CHECKMATE-025

	Nivolumab (n=410)	Everolimus (n=411)
Primary Efficacy Outcome Measure		
Overall Survival[a]		
Events (%)	183/410 (45)	215/411 (52)
Median survival in months (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (98.52% CI)	0.73[b] (0.57, 0.93)	
p-value	0.0018[c]	
Secondary Efficacy Outcome Measures:		
Progression-free survival		
Events	318/410 (77.6)	322 /411(78.3)
Hazard ratio	0.88	
95% CI	(0.75, 1.03)	
p-value	0.1135	
Median (95% CI)	4.6 (3.71, 5.39)	4.4 (3.71, 5.52)
Objective Response Rate per Investigator (CR+PR)	103/410 (25.1%)	22/411 (5.4%)
(95% CI)	(21.0, 29.6)	(3.4, 8.0)
Odds ratio (95% CI)	5.98 (3.68, 9.72)	
p-value	< 0.0001	
Complete response (CR)	4 (1.0%)	2 (0.5%)
Partial response (PR)	99 (24.1%)	20 (4.9%)
Stable disease (SD)	141 (34.4%)	227 (55.2%)
Median duration of response		
Months (range)	11.99 (0.0-27.6+)	11.99 (0.0+-22.2+)

a. Based on the 398 observed deaths and O'Brian-Fleming alpha spending function, the boundary for statistical significance requires the p-value to be less than 0.0148 (based on interim analysis)

b. Hazard ratio is obtained from a Cox proportional-hazards model stratified by MSKCC risk group, number of prior anti-angiogenic therapies, and region with treatment as the sole covariate.

c. P-value is obtained from a two-sided log-rank test stratified by MSKCC risk group, number of prior anti-angiogenic therapies in the advanced/metastatic setting, and region.

Figure 1: Overall Survival - CHECKMATE-025

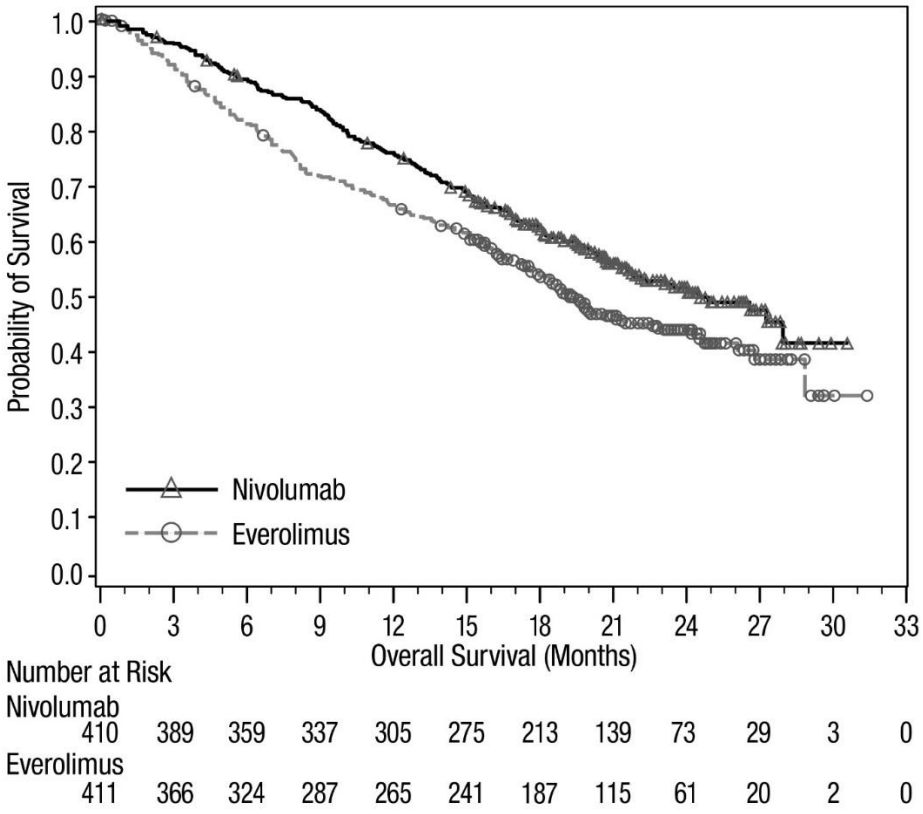
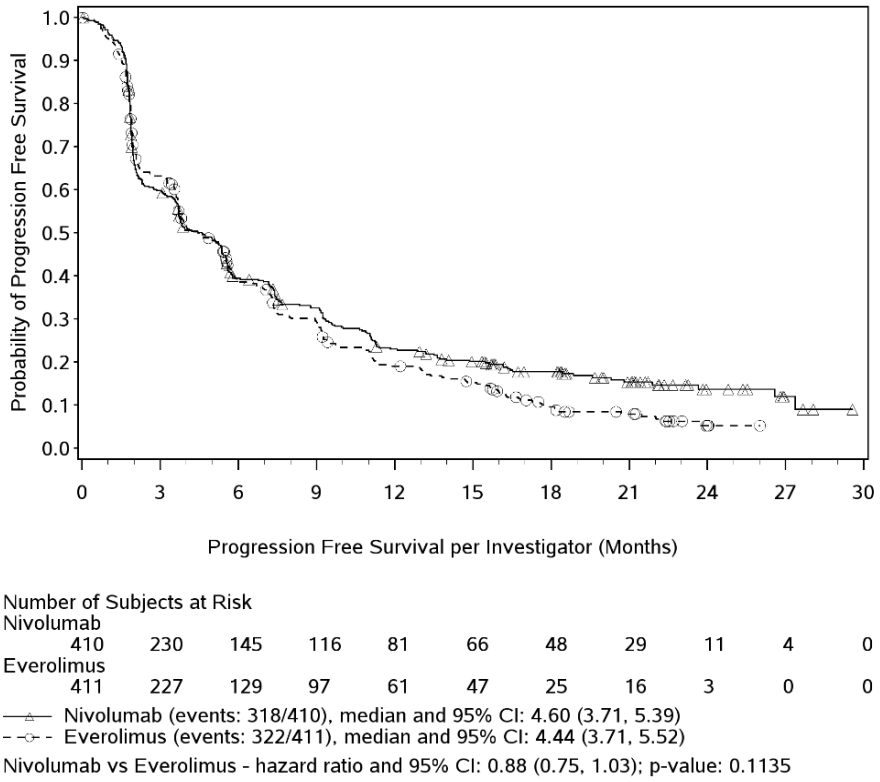


Figure 2: Progression- Free Survival - CHECKMATE-025



Advanced RCC (previously untreated): CHECKMATE-214

CHECKMATE-214 was a randomized (1:1), open-label study in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score (0 vs 1-2 vs 3-6) and region (US vs Canada/Western Europe/Northern Europe vs Rest of World).

The primary efficacy population includes those intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status < 80%, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal).

Patients were randomized to nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n=425) administered intravenously every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every two weeks or to sunitinib (n=422) administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle. For intermediate or poor risk patients, the median age was 61 years (range: 21 to 85) with 38% ≥65 years of age and 8% ≥75 years of age. The majority of patients were male (73%) and white (87%) and 31% and 69% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively.

The first tumour assessments were conducted 12 weeks after randomization and continued every 6 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later.

Treatment continued until disease progression or unacceptable toxicity. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator.

The primary efficacy outcome measures were OS, confirmed ORR and PFS as determined by an IRRC, in intermediate/poor risk patients. The median follow-up for patients was 25.2 months (range: 17.5 to 33.5 months). Among intermediate/poor risk patients, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to nivolumab plus ipilimumab as compared with sunitinib (Table **52** and Figure 3). The trial did not demonstrate a statistically significant improvement in PFS.

Table 52: Efficacy Results - CHECKMATE-214 (Primary analysis)

	Intermediate/Poor-Risk	
	Nivolumab plus ipilimumab (n=425)	**Sunitinib (n=422)**
Overall Survival		
Deaths (%)	140 (32.9)	188 (44.5)
Median survival (months)	NE	25.9
Hazard ratio (99.8% CI)[a]	0.63 (0.44, 0.89)	
p-value[b,c]	<0.0001	
Confirmed Objective Response Rate (95% CI)	41.6% (36.9, 46.5)	26.5% (22.4, 31.0)
Difference in ORR (99.9% CI)[d]	16.0% (5.6%, 26.4%)	
p-value[d,e]	<0.0001	
Best Overall Response		
Complete Response (CR)	40 (9.4)	5 (1.2)
Partial Response (PR)	137 (32.2)	107 (25.4)
Stable Disease (SD)	133 (31.3%)	188 (44.5%)
Median duration of response in months (95% CI)[f]	NE (21.8, NE)	18.2 (14.8, NE)
Median time to onset of confirmed response in months (min, max)	2.8 (0.9, 11.3)	3.0 (0.6, 15.0)
Progression-free Survival		
Disease progression or death (%)	228 (53.6)	228 (54.0)
Median (months)	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	
p-value[b,g]	0.0331	

a. Base on a stratified Cox proportional hazards model stratified by IMDC prognostic score and region.

b. Based on a stratified log-rank test stratified by IMDC prognostic score and region.

c. p-value is compared to alpha 0.002 in order to achieve statistical significance.

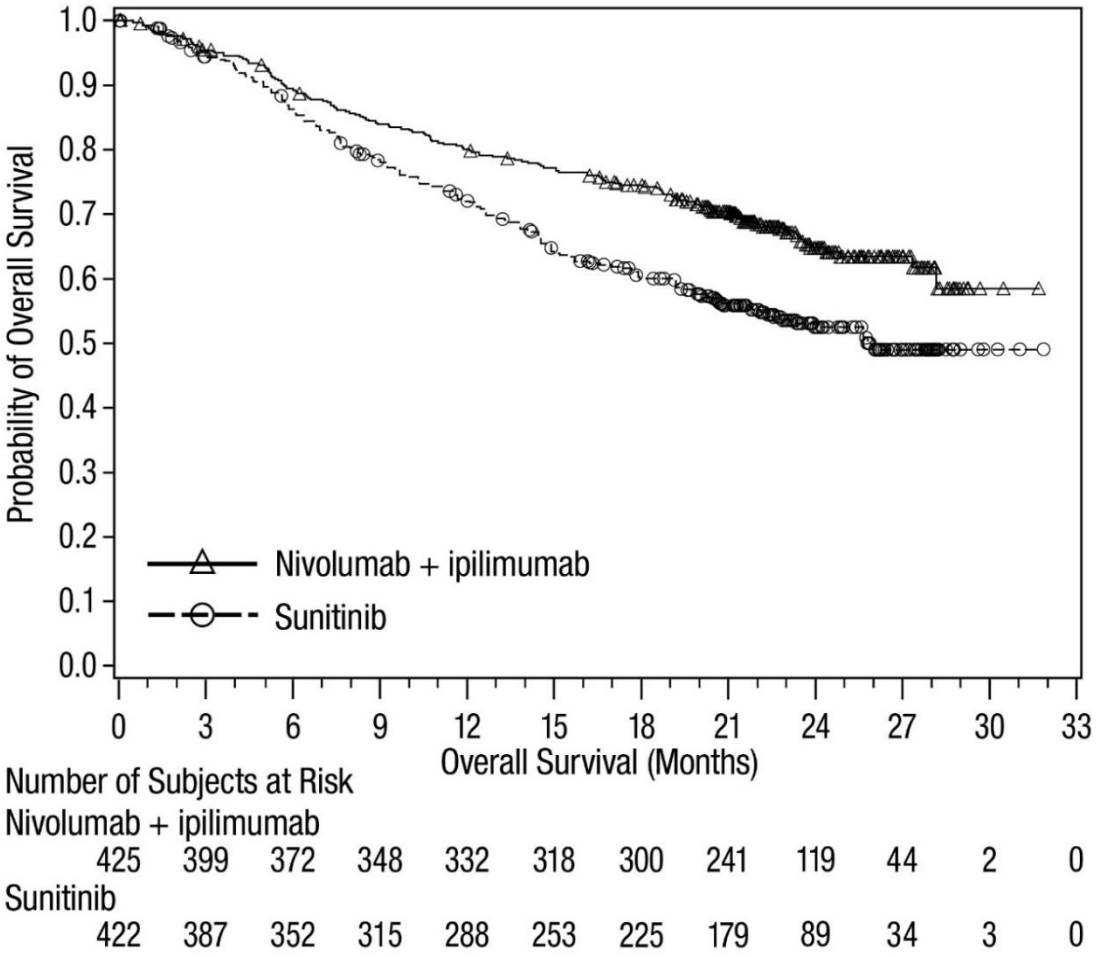
d. Strata adjusted difference based on the stratified DerSimonian-Laird test.

e. p-value is compared to alpha 0.001 in order to achieve statistical significance.

f. Computed using Kaplan-Meier method

g. Not significant at alpha level of 0.009

Figure 3: Overall Survival (Intermediate/Poor Risk Population) - CHECKMATE-214 (Primary analysis)



The estimated OS rates at 12 months were 80.1% (95% CI: 75.9, 83.6) for nivolumab plus ipilimumab and 72.1% (95% CI: 67.4, 76.2) for sunitinib.

OS benefit was observed regardless of PD-L1 expression level, with a hazard ratio of 0.45 (95% CI: 0.29, 0.71) for PD-L1 tumour expression levels ≥ 1%, and a hazard ratio of 0.73 (95% CI: 0.56, 0.96) for PD-L1 tumour expression levels < 1%.

CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to nivolumab plus ipilimumab (n=125) or to sunitinib (n=124). These patients were not evaluated as part of the efficacy analysis population. OS in favorable risk patients receiving nivolumab plus ipilimumab compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of nivolumab plus ipilimumab in previously untreated renal cell carcinoma with favorable-risk disease has not been established.

An exploratory follow-up analysis was conducted for CHECKMATE-214. The median follow-up for patients at the time of this analysis was 49.2 months (range: 41.4 to 57.5 months). For intermediate/poor-risk patients, the results for OS, PFS, and ORR based on 41.4 months of minimum

follow-up remained consistent with the results of the primary analysis based on 17.5 months of minimum follow-up. The median OS, with further follow-up, was approximately 47.0 months for patients who received nivolumab plus ipilimumab vs. 26.6 months for sunitinib, resulting in a hazard ratio of 0.66.

Advanced RCC (previously untreated): CHECKMATE-9ER

CHECKMATE-9ER was a phase 3 randomized, open-label study of nivolumab combined with cabozantinib versus sunitinib in adult patients with previously untreated advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC with clear cell component. Patients were included regardless of their PD-L1 status or International Metastatic RCC Database Consortium (IMDC) risk group. CHECKMATE-9ER excluded patients with poorly controlled hypertension despite antihypertensive therapy, active brain metastases, uncontrolled adrenal insufficiency autoimmune disease or other medical conditions requiring systemic immunosuppression, and patients who had prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody. Patients were stratified by IMDC prognostic score, PD-L1 tumour expression, and geographic region.

Patients were randomized to nivolumab 240 mg intravenously every 2 weeks and cabozantinib 40 mg orally daily (n=323), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (4 weeks on treatment followed by 2 weeks off) (n=328). Treatment was continued until disease progression per RECIST v1.1 or unacceptable toxicity with nivolumab administration for up to 24 months. Treatment beyond RECIST-defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumour assessments were performed at baseline, after randomization at Week 12, then every 6 weeks until Week 60, and then every 12 weeks thereafter.

Baseline characteristics were generally balanced between the two groups. From both arms, median age was 61 years (range: 28-90) with 38% ≥65 years of age and 10% ≥75 years of age. The majority of patients were male (74%) and White (82%) and 23% and 76% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. Twenty-nine (4.5%) subjects had advanced, non-metastatic RCC. Seventy-five (11.5%) subjects had tumours with sarcomatoid features. Patient distribution by IMDC risk categories was 23% favorable, 58% intermediate, and 20% poor.

The primary efficacy outcome measure was PFS (blinded independent central review [BICR] assessed). Secondary efficacy outcome measures were OS and ORR (BICR assessed). The trial demonstrated a statistically significant improvement in PFS, OS, and ORR for patients randomized to nivolumab and cabozantinib compared with sunitinib.

Efficacy results after a minimum follow-up of 10.6 months are shown in Table **53** and Figure 4 and Figure 5.

Table 53: Efficacy Results - CHECKMATE-9ER

	Nivolumab and Cabozantinib (n=323)	**Sunitinib (n=328)**
Progression-free Survival		
Events (%)	144 (44.6)	191 (58.2)

Median (months)[a]	16.6 (12.5, 24.9)	8.3 (7.0, 9.7)
Hazard ratio (95% CI)[b]	0.51 (0.41, 0.64)	
p-value[c,d]	<0.0001	
Overall Survival		
Events (%)	67 (20.7)	99 (30.2)
Median (months)[a]	N.E.	N.A. (22.6, N.A.)
Hazard ratio (98.89% CI)[b]	0.60 (0.40, 0.89)	
p-value[c,d,e]	0.0010	
Confirmed Objective Response Rate (95% CI)[f]	55.7% (50.1, 61.2)	27.1% (22.4, 32.3)
p-value[g]	<0.0001	
Complete Response (CR)	26 (8.0%)	15 (4.6%)
Partial Response (PR)	154 (47.7%)	74 (22.6%)

a. Based on Kaplan-Meier estimates.

b. Stratified Cox proportional hazards model. Hazard ratio is nivolumab and cabozantinib over sunitinib.

c. Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥1% versus <1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the per protocol Interactive Response Technology (IRT) system.

d. 2-sided p-values from stratified regular log-rank test.

e. Type-1 error controlled by hierarchical testing. OS interim analysis boundary for statistical significance p-value <0.0111.

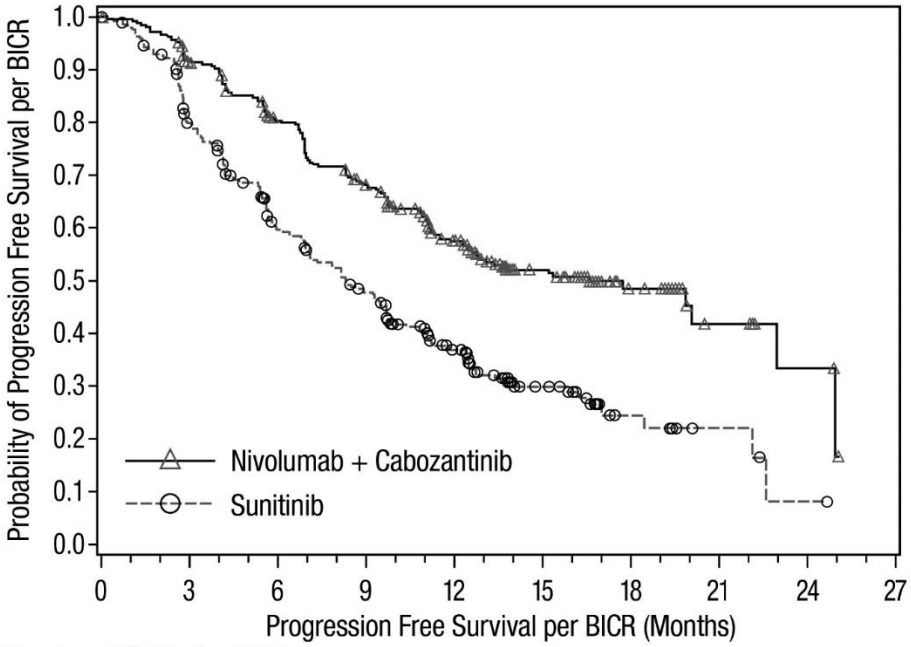
f. CI based on the Clopper and Pearson method.

g. 2-sided p-value from CMH test.

NE = non-estimable

The exploratory analyses in responders suggested the median duration of response of 20.2 months (range from 17.3 to N.E.) for nivolumab in combination with cabozantinib treated patients and 11.5 months (8.3 to 18.4 months) for sunitinib treated patients. The median time to response was 2.8 months (range from 1.0 to19.4) for nivolumab in combination with cabozantinib treated patients and 4.2 months (1.7 to 12.3) for sunitinib treated patients. Additional exploratory analyses suggested a consistent treatment benefit in both OS and PFS across all three pre-specified IMDC risk subgroups.

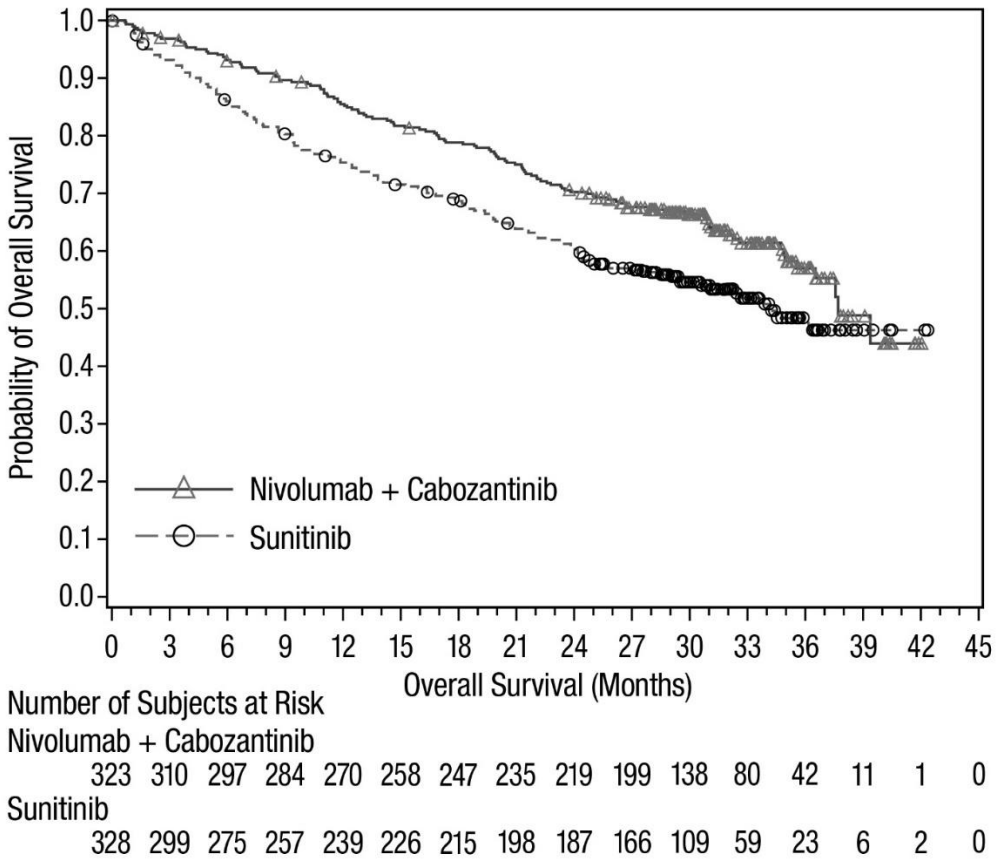
Figure 4: Kaplan-Meier Curve of Progression-free Survival - CHECKMATE-9ER



Number of Subjects at Risk

Nivolumab + Cabozantinib									
323	279	234	196	144	77	35	11	4	0
Sunitinib									
328	228	159	122	79	31	10	4	1	0

Figure 5: Kaplan-Meier Curve of Overall Survival - CHECKMATE-9ER



Adjuvant Treatment of Melanoma

Randomized phase III study of intravenous nivolumab versus ipilimumab: CHECKMATE-238

CHECKMATE-238 was a phase III randomized, double-blind trial enrolling patients with completely resected (rendered free of disease with negative margins on resected specimens) Stage IIIB/C or Stage IV melanoma. Patients were randomized (1:1) to receive nivolumab (n=453) administered as an intravenous infusion over 60 minutes at 3 mg/kg every 2 weeks or ipilimumab (n=453) administered as an intravenous infusion at 10 mg/kg every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year. Randomization was stratified by PD-L1 status (positive [based on 5% level] vs negative/indeterminate) and American Joint Committee on Cancer (AJCC) stage (Stage IIIB/C vs Stage IV M1a-M1b vs Stage IV M1c, 7th edition). The trial excluded patients with a history of ocular/uveal melanoma, autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery, adjuvant radiotherapy after

neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomization.

The primary efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, whatever the cause, whichever occurs first and assessed by the investigator. Disease was assessed at baseline and every 12 weeks (± 7 days) for the first year, then every 12 weeks (± 14 days) for the second year, then every 6 months until 5 years or until local, regional, or distant recurrence (whichever comes first) for Stage IV subjects and until distant recurrence for Stage III subjects. Overall survival (OS) was evaluated as a secondary objective.

A total of 906 patients were randomized (453 to nivolumab and 453 to ipilimumab). The median age was 55 years (range: 18 to 86), 58% were male, 95% were white, and 90% had ECOG performance status of 0. Forty-two percent (42%) of patients were BRAF V600 mutation positive, 45% were BRAF wild type, and 13% were BRAF status unknown. With regard to disease stage, 34% had Stage IIIB, 47% had Stage IIIC, and 19% had Stage IV. The majority of patients (85.3%) were randomized within 12 weeks of surgery. The median duration of follow-up was 19.5 months (range: 0.0 to 25.0 months).

CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients randomized to the nivolumab arm compared with the ipilimumab 10 mg/kg arm.

Efficacy results for the primary endpoint at the interim analysis are presented in **Table 54** and Figure 6.

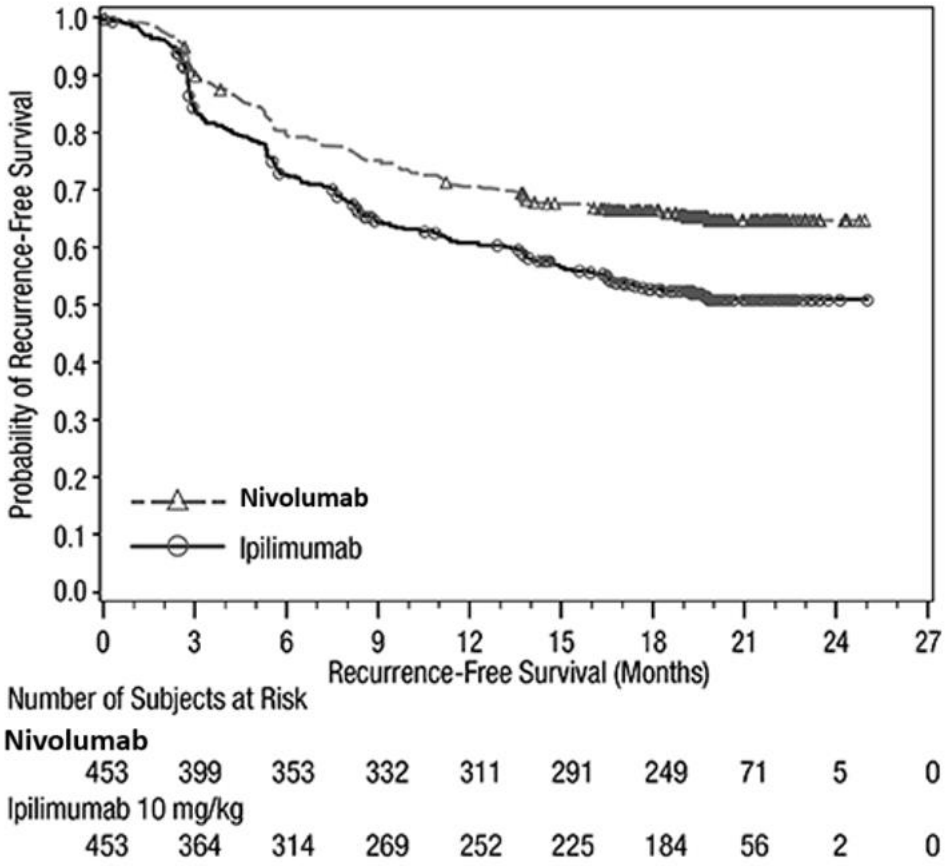
Table 54: Efficacy Results in CHECKMATE-238

Recurrence-free Survival	**Nivolumab N=453**	**Ipilimumab 10 mg/kg N=453**
Number of Events, n (%)	154 (34.0%)	206 (45.5%)
Type of Event		
Disease at Baseline	1 (0.2%)	2 (0.4%)
Local Recurrence	30 (6.6%)	44 (9.7%)
Regional Recurrence	31 (6.8%)	34 (7.5%)
Distant Metastasis	85 (18.8%)	117 (25.8%)
New Primary Melanoma	7 (1.5%)	4 (0.9%)
Hazard Ratio[a] (97.56% CI) p-value[b]	0.65 (0.51, 0.83) p<0.0001	
Median (months) (95% CI)	Not Reached	Not Reached (16.56, NR)
Rate (95% CI) at 12 months	70.5 (66.1, 74.5)	60.8 (56.0, 65.2)
Rate (95% CI) at 18 months	66.4 (61.8, 70.6)	52.7 (47.8, 57.4)

a. Based on a stratified proportional hazards model $_{\text{stratified by}}$ tumour PD-L1 expression and stage of disease.

b. p-value is derived from a log-rank test stratified by tumour PD-L1 expression and stage of disease; the corresponding O'Brien-Fleming efficacy boundary significance level at the interim analysis is 0.0244.

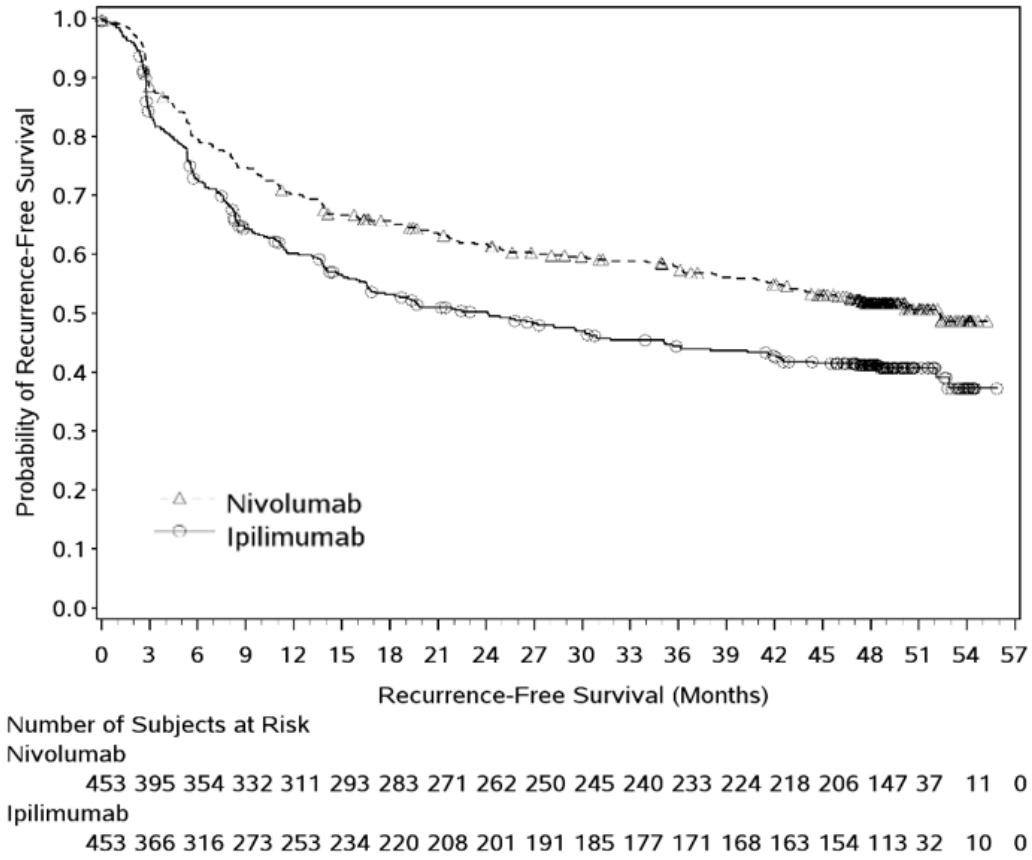
Figure 6: Recurrence-free Survival -CHECKMATE-238



*18-months minimum follow-up interim RFS analysis

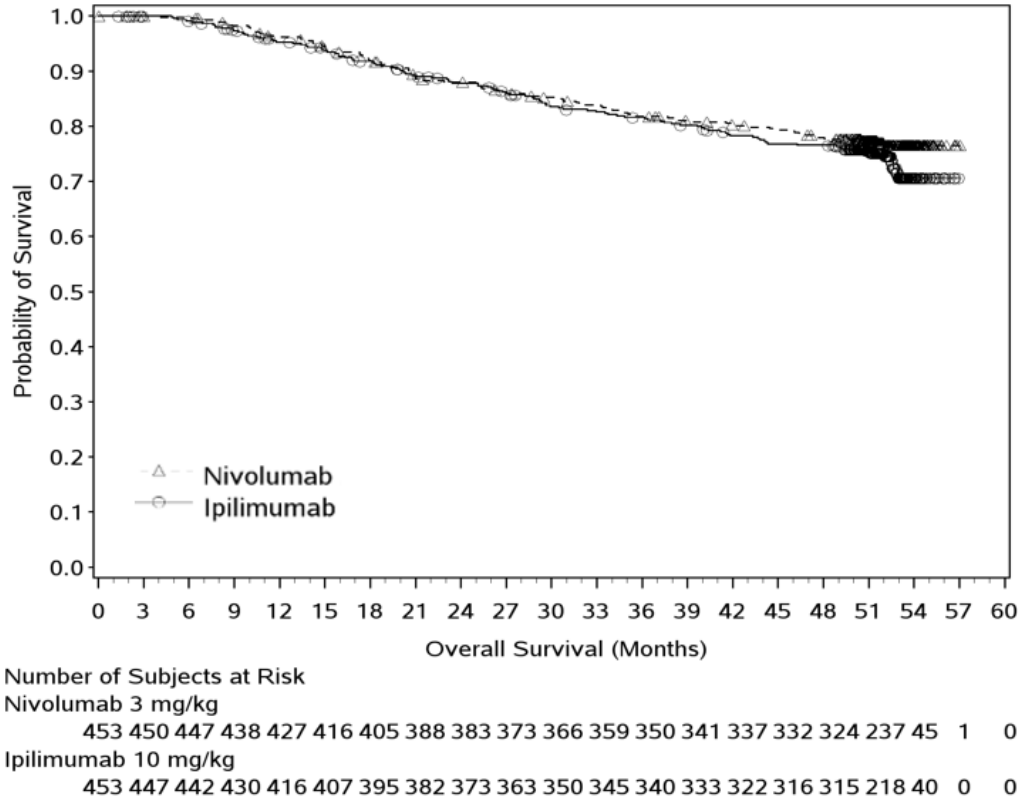
The pre-specified final OS analysis occurred with a minimum follow-up of 48 months. Fewer OS events were observed than originally anticipated (approximately 302). There were 211 total OS events (100 in the nivolumab arm and 111 in the ipilimumab arm); median OS was not reached in either arm (HR 0.87, 95% CI: 0.66, 1.14, p=0.31). OS rates at 48 months were 77.9% and 76.6% in the nivolumab and ipilimumab arms, respectively (Figure 8). With a minimum follow-up of 48 months, median RFS was 52.4 months in the nivolumab arm compared to 24.1 months in the ipilimumab arm (HR 0.71, 95% CI: 0.60, 0.86). RFS rates at 48 months were 51.7% vs. 41.2% in the nivolumab and ipilimumab arms, respectively (Figure 7).

Figure 7: **Recurrence-free Survival - CHECKMATE-238***



*48-months minimum follow-up descriptive RFS analysis

Figure 8: Overall Survival - CHECKMATE-238*



*48-months minimum follow-up final analysis

Randomized phase III study of intravenous nivolumab versus placebo: CHECKMATE-76K

CHECKMATE-76K was a phase III randomized, double-blind trial enrolling patients with completely resected Stage IIB or IIC melanoma. Patients were randomized (2:1) to receive nivolumab (n=526) administered as an intravenous infusion over 30 minutes at 480 mg every 4 weeks or placebo (n=264) and were treated for 1 year or until disease recurrence or unacceptable toxicity. Randomization was stratified by American Joint Committee on Cancer (AJCC) 8th edition T Stage (T3b vs. T4a vs. T4b). Enrolment required complete resection of the primary melanoma with negative margins and a negative sentinel lymph node biopsy within 12 weeks prior to randomization. Patients were enrolled regardless of their tumour PD-L1 status. The study included patients, who had an ECOG performance status score of 0 or 1, with Stage IIB or IIC American Joint Committee on Cancer (AJCC), 8th edition, histologically confirmed melanoma that is completely surgically resected. The trial excluded patients with ocular/uveal or mucosal melanoma, active autoimmune disease, any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery.

The primary efficacy outcome measure was recurrence-free survival (RFS). RFS, assessed by the investigator, was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurs first. Tumour assessments were conducted every 26 weeks during years 1-3 and every 52 weeks thereafter to year 5.

A total of 790 patients were randomised (526 to nivolumab and 264 to placebo). The median age of patients was 62 years (range: 19-92), 42% age 65 years or older, 61% were men, and 98% were white. Baseline ECOG performance status score was 0 (94%) or 1 (6%). Sixty percent had Stage IIB and 40% had Stage IIC.

At a primary pre-specified interim analysis (minimum follow-up 8 months; median follow-up 16 months), CHECKMATE-76K demonstrated a statistically significant improvement in RFS for patients randomized to the nivolumab arm compared with the placebo arm.

Efficacy results for the primary endpoint at the interim analysis are presented in Table 55 and Figure 9.

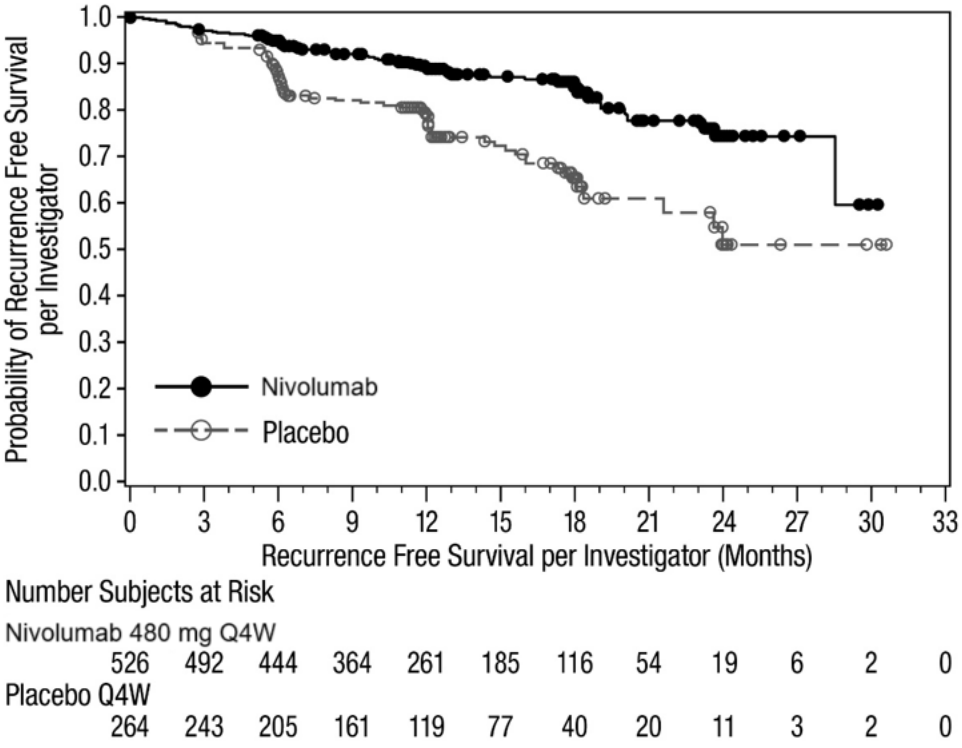
Table 55: Efficacy Results in CHECKMATE-76K

	Nivolumab N=526	**Placebo N=264**
Recurrence-free Survival		
Number of Events, n (%)	66 (13%)	69 (26%)
Hazard Ratio[a] (95% CI) p-value[b]	0.42 (0.30, 0.59) p<0.0001	
Median (months) (95% CI)	Not Reached (NR) (28.52, NR)	Not Reached (NR) (21.62, NR)

[a] Based on stratified Cox proportional hazard model.

[b] Based on log-rank test stratified by AJCC 8th edition T stage at study entry. P-value is derived from the log-rank test. The corresponding O'Brien-Fleming efficacy boundary significance level at the interim analysis is 0.024.

Figure 9: Recurrence-free Survival - CHECKMATE-76K



Unresectable or Metastatic Melanoma

In CHECKMATE-066 and CHECKMATE-037 (monotherapy), the safety and efficacy of intravenous nivolumab as a single agent for the treatment of patients with advanced (unresectable or metastatic) melanoma were evaluated in two randomized, Phase III studies CHECKMATE-066 and CHECKMATE-037. Additional support is provided from an open-label Phase I dose-escalation study, MDX1106-03 (conducted in solid tumour malignancies across several tumour types).

In CHECKMATE-067 (monotherapy and combination therapy) and CHECKMATE-069 (combination therapy), the safety and efficacy of intravenous nivolumab as a single agent or in combination with ipilimumab for the treatment of patients with advanced (unresectable or metastatic) melanoma were evaluated in 2 randomized, multinational, well-controlled, double-blind studies (Studies CHECKMATE-067 and CHECKMATE-069). CHECKMATE-067 is a Phase III study of nivolumab monotherapy or nivolumab in combination with ipilimumab versus ipilimumab. CHECKMATE-069 is a Phase II study of nivolumab in combination with ipilimumab versus ipilimumab.

Controlled Trial in Melanoma Patients Previously Untreated (First-line treatment)

CHECKMATE-066

In CHECKMATE-066, a total of 418 patients were randomized on a 1:1 basis to either nivolumab administered intravenously over 60 minutes at 3 mg/kg every 2 weeks (n = 210) or dacarbazine 1000 mg/m^2 every 3 weeks (n = 208). Randomization was stratified by PD-L1 status and M stage. Previously

untreated patients with BRAF wild-type melanoma were enrolled in the study. Prior adjuvant or neoadjuvant melanoma therapy was permitted if it had been completed at least 6 weeks prior to randomization. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

The primary efficacy outcome measure was overall survival (OS). Key secondary endpoints included progression-free survival (PFS), and objective response rate (ORR). Exploratory outcome measures included time to response (TTR) and duration of response (DOR). Tumour response was assessed by investigators based on Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 at 9 weeks after randomization and continued every 6 weeks for the first year and then every 12 weeks thereafter.

Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse effects with the study drug, as determined by the investigator. Baseline characteristics were balanced between groups. Demographic and baseline disease characteristics are shown in **Table 56**.

Table 56: Baseline Characteristics in CHECKMATE-066

	Nivolumab 3 mg/kg n=210	**Dacarbazine 1000 mg/m^2 n=208**
Men	58%	60%
Women	42%	40%
Age (median)	64 years	66 years
Age (range)	(18-86 years)	(25-87 years)
Melanoma Subtypes		
Mucosal	12%	11%
Cutaneous	73%	75%
M-Stage at study entry (%)		
M0	8%	6%
M1a (soft tissue)	10%	10%
M1b (lung)	21%	23%
M1c (all viscera)	61%	61%
PD-L1 Status		
Positive	35%	36%
Negative/Indeterminate	65%	64%
ECOG		
0 (%)	71%	58%
1 (%)	29%	40%
2 (%)	1%	1%
Not reported (%)	1%	0%
Baseline LDH		
> ULN	38%	36%

> 2*ULN	10%	11%
History of Brain Metastases		
Yes	3%	4%
No	97%	96%

Based on a formal interim analysis for OS that occurred when 146 deaths were observed, nivolumab demonstrated clinically meaningful and statistically significant improvement in OS compared with dacarbazine in previously untreated patients with BRAF wild type advanced (unresectable or metastatic) melanoma (HR=0.42 [99.79% CI: 0.25, 0.73]; p<0.0001). Median OS was not reached for nivolumab and was 10.8 months for dacarbazine (95% CI: 9.33, 12.09). The estimated OS rates at 12 months were 73% (95% CI: 65.5, 78.9) and 42% (95% CI: 33.0, 50.9), respectively. OS was demonstrated regardless of PD-L1 tumour cell membrane expression levels. Efficacy results are presented in **Table 57** and Figure 10.

Table 57: Efficacy of Nivolumab in CHECKMATE-066

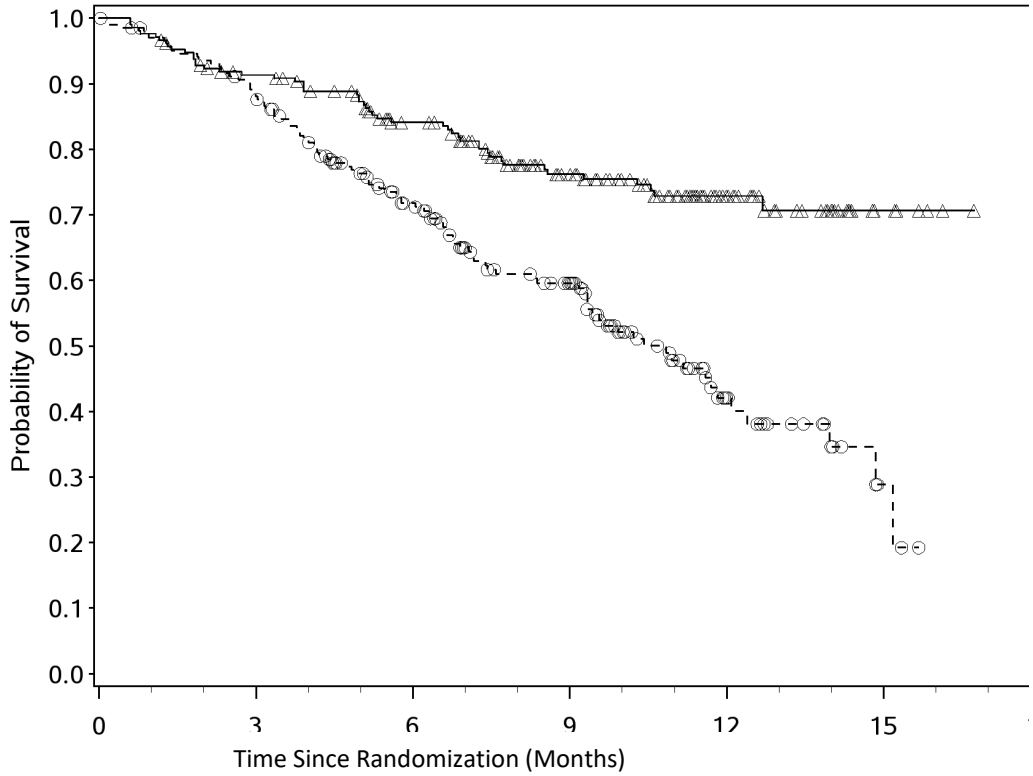
Efficacy Parameter	**Nivolumab N=210**	**Dacarbazine N=208**
Overall Survival		
Events, n (%)	50/210 (23.8)	96/208 (46.2)
Median (95% CI) (Months)	Not Reached	10.84 (9.33, 12.09)
Hazard ratio[a]	0.42	
99.79% CI [b]	(0.25, 0.73)	
p-value [b]	<0.0001	
Progression-free Survival		
Events, n (%)	108/210 (51.4)	163/208 (78.4)
Median (95% CI) (Months)	5.06 (3.48, 10.81)	2.17 (2.10, 2.40)
Hazard ratio (99.79% CI[c])	0.43 (0.29, 064)	
p-value[c]	<0.0001	
Objective Response Rate[d]		
n (%)	84/210 (40.0)	29/208 (13.9)
95% CI	(33.3, 47.0)	(9.5, 19.4)
Difference of ORR (99.79% CI[c])	26.1 (13.4, 38.7)	
p-value[c,e]	<0.0001	
Complete Response	16 (7.6)	2 (1.0)
Partial Response	68 (32.4)	27 (13.0)
Stable Disease	35 (16.7)	46 (22.1)

Abbreviation: CI = confidence interval

a. Based on a Cox proportional hazards model adjusted for PD-L1 status and M-stage.
b. The 99.79% CI corresponds to a p-value of 0.0021, which is the boundary for statistical significance for this interim analysis.
c. A hierarchical testing approach was used to control the Type I error rate of 0.21% for PFS and ORR with corresponding 99.79% CIs

d. Responses of CR + PR as per RECIST v1.1 criteria, as assessed by the investigator
e. p-value from CMH test for the comparison of the ORRs.

Figure 10 : Kaplan-Meier Curves of Overall Survival - Nivolumab versus Dacarbazine in BRAF wild-type advanced (unresectable or metastatic) melanoma (CHECKMATE-066)



Symbols represent censored observations.

Median TTR was 2.1 months (range 1.2 to 7.6) in the nivolumab group and 2.1 months (range 1.8 to 3.6) in the dacarbazine group. Median DOR was not reached in the nivolumab group (range: 0+ to 12.5+ months) and was 5.98 months (range: 1.1 to 10.0+) in the dacarbazine group. At the time of analysis, 86% (72/84) of nivolumab-treated patients and 52% (15/29) of dacarbazine-treated patients were still in response. In addition, atypical responses (i.e., tumour shrinkage following initial RECIST progression) have been observed with nivolumab.

Controlled Trial in Melanoma Patients Previously Untreated First-line treatment as monotherapy or in combination with ipilimumab: CHECKMATE-067

CHECKMATE-067 was a multicenter, double-blind trial that randomized (1:1:1) patients with unresectable or metastatic melanoma to receive intravenous nivolumab in combination with ipilimumab, nivolumab as a single agent, or ipilimumab alone. Patients in the combination arm received nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as a single agent every 2 weeks. Patients in the nivolumab single-agent arm received nivolumab 3 mg/kg every 2 weeks. Patients in the comparator arm received ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled regardless of PD-L1 expression. Prior adjuvant or neoadjuvant therapy was allowed if completed at least 6 weeks prior to randomization and all adverse reactions had returned to baseline or stabilized. Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumour cell membrane expression), BRAF status, and M stage per the American Joint Committee on Cancer (AJCC) staging system. The trial excluded patients with active brain metastasis, ocular/uveal melanoma, autoimmune disease, or medical conditions requiring systemic immunosuppression within 14 days of the start of study therapy. Tumour assessments were conducted 12 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

The co-primary efficacy outcome measures were to compare progression-free survival (PFS) and overall survival (OS) of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma. Overall response rate (ORR) was a secondary objective. The trial was not designed to assess whether adding ipilimumab to nivolumab improves PFS or OS compared to nivolumab as a single agent. Two formal scheduled analyses were planned for this study; the primary analysis of the PFS endpoint occurred at a minimum follow-up of 9 months, and the primary analysis of the OS endpoint occurred at a minimum follow-up of 28 months. This study also evaluated whether PD-L1 expression was a predictive biomarker for the co-primary endpoints as an exploratory objective.

Among the 945 randomized patients, the baseline study population characteristics were generally balanced across the three treatment groups. The baseline characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥5% tumour cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%).

At the primary efficacy analysis which took place at 28 months minimum follow-up, in the nivolumab plus ipilimumab group, patients received a median of 4 doses of nivolumab (range: 1 to 76 doses) and 4 doses of ipilimumab (range: 1 to 4 doses); 57% completed all 4 doses in the initial combination phase. In the single-agent nivolumab arm, patients received a median of 15 doses (range: 1 to 77 doses).

Efficacy results are presented in **Table 58**, Figure 11 and Figure 12.

Table 58: Efficacy Results in CHECKMATE-067 (Intent-to-Treat Analysis)

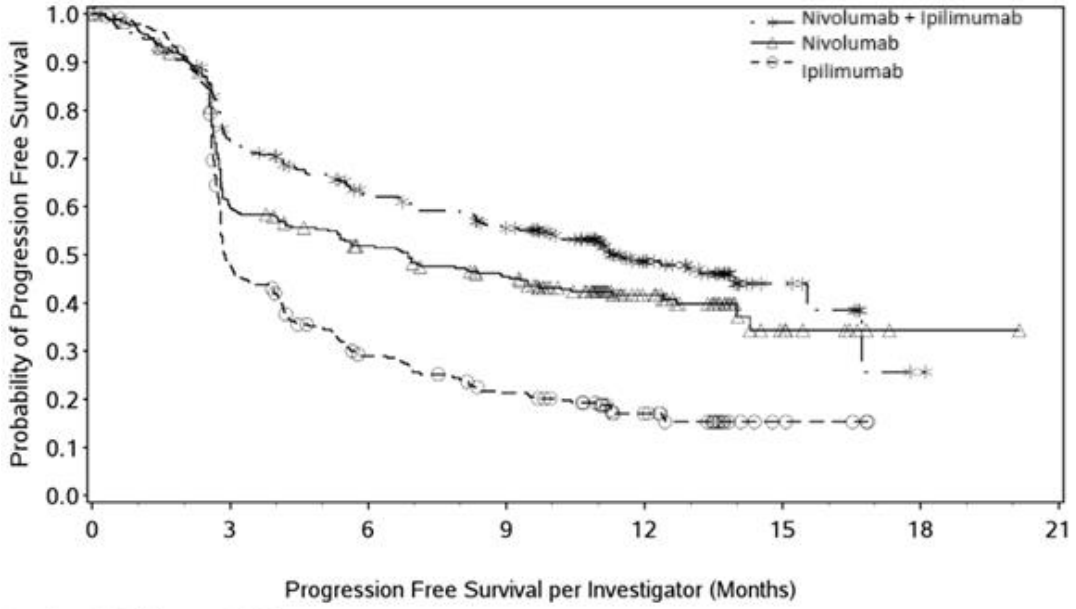
	Nivolumab + Ipilimumab (n=314)	Nivolumab (n=316)	Ipilimumab (n=315)
Primary Outcome Measures			
Overall Survival[a]			
Events (%)	128 (41%)	142 (45%)	197 (63%)
Median (95% CI)	NR	NR (29.1, NR)	20.0 months (17.1, 24.6)
Hazard Ratio (vs. ipilimumab)[b]	0.55	0.63	
(98% CI)	(0.42, 0.72)	(0.48, 0.81)	
p-value[c,d]	p<0.0001	p<0.0001	
Progression-Free Survival[e]			
Events (%)	151 (48%)	174 (55%)	234 (74%)
Median (95% CI)	11.5 months (8.9, 16.7)	6.9 months (4.3, 9.5)	2.9 months (2.8, 3.4)
Hazard Ratio (vs. ipilimumab)[f]	0.42	0.57	
(99.5% CI)[g]	(0.31, 0.57)	(0.43, 0.76)	--
p-value[h]	p<0.0001	p<0.0001	
Secondary Outcome Measures			
Objective Response Rate[e]	58%	44%	19%
(95% CI)	(52.0, 63.2)	(38.1, 49.3)	(14.9, 23.8)
p-value[i,j]	p<0.0001	p<0.0001	
Complete Response	11%	9%	2%
Partial Response	46%	35%	17%
Stable disease (SD)	41 (13%)	34 (11%)	69 (22%)
Progressive disease (PD)	71 (23%)	119 (38%)	154 (49%)
Confirmed Objective Response Rate[e,k]	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-value[j]	<0.0001	<0.0001	
Exploratory Outcome Measures			
Duration of Response[e]			
Proportion ≥6 months in duration	68%	67%	53%

Abbreviation: CI = confidence interval

a. Minimum follow-up of 28 months.
b. Based on a stratified proportional hazards model.
c. Based on stratified log-rank test.

d. The maximum of the two p-values is compared with the allocated alpha of 0.04 for final OS treatment comparisons using Hochberg's procedure.
e. Minimum follow-up of 9 months.
f. Based on a Cox proportional hazards model adjusted for PD-L1 status, BRAF status, and M-stage.
g. The 99.5% confidence level corresponds to the allocated Type I error of 0.01 for the PFS co- primary endpoint, adjusted for two pairwise comparisons versus ipilimumab (0.005 for each comparison).
h. P-value is obtained from a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M-stage
i. A hierarchical testing approach was used to control the Type I error rate of 0.01
j. Based on the stratified Cochran-Mantel-Haenszel test.
k. Confirmed CR or PR was determined if the criteria for each were met at a subsequent timepoint (minimum 4 weeks after criteria for an objective response were first met)

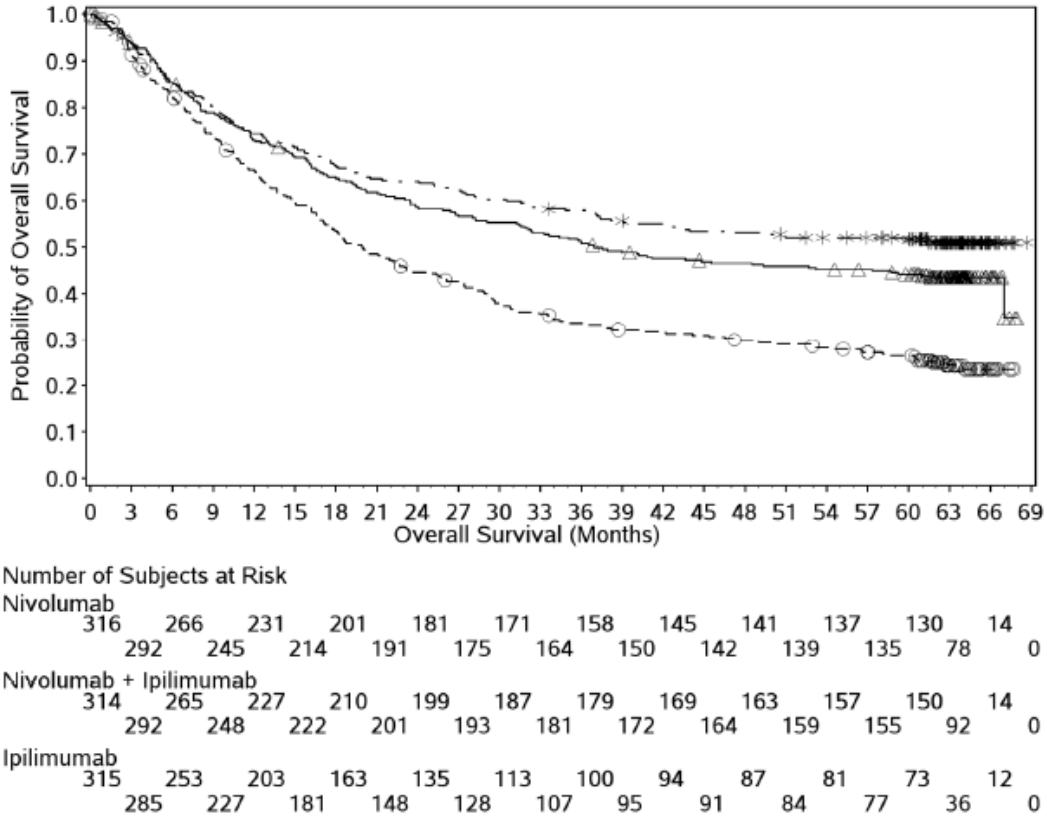
Figure 11: Progression-Free Survival: Unresectable or Metastatic Melanoma (CHECKMATE-067) (Intent-to-Treat, Primary Analysis)



Number of Subjects at Risk

Nivolumab + Ipilimumab							
314	219	173	151	65	11	1	0
Nivolumab							
316	177	147	124	50	9	1	0
Ipilimumab							
315	137	77	54	24	4	0	0

Figure 12: Overall survival (CA209067) (Intent-to-Treat)



In an exploratory analysis, updated efficacy results for OS, PFS and ORR, based on a minimum follow-up of 60 months were consistent with the final results previously reported. The median OS was not reached in the nivolumab in combination with ipilimumab arm. The median OS was 36.9 months in the single-agent nivolumab arm and 19.9 months in the ipilimumab arm.

Efficacy of PFS analysis by BRAF status at a minimum follow-up of 9 months: Progression-free survival results by BRAF mutation status are shown in **Table 59** and

Table 60.

Table 59: Progression Free Survival by BRAF Status - Nivolumab in Combination with Ipilimumab Compared to Ipilimumab - Exploratory Analysis (CHECKMATE-067)

		Nivolumab + Ipilimumab		Ipilimumab		
	N	N of events/ N of subjects (% subjects)	mPFS (95% CI)	N of events/ N of subjects (% subjects)	mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	945	151/314 (48.1)	11.50 (8.90, 16.72)	234/315 (74.3)	2.89 (2.79, 3.42)	0.43 (0.35, 0.53)
BRAF Mutation Status						
Mutant	300	48/102	11.73	66/100	4.04	0.47

		Nivolumab + Ipilimumab		Ipilimumab		
	N	N of events/ N of subjects (% subjects)	mPFS (95% CI)	N of events/ N of subjects (% subjects)	mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
		(47.1)	(8.02, N.A.)	(66.0)	(2.79, 5.52)	(0.32, 0.68)
Wildtype	645	103/212 (48.6)	11.24 (8.34, N.A.)	168/215 (78.1)	2.83 (2.76, 3.09)	0.41 (0.32, 0.53)

Table 60: Progression Free Survival by BRAF Status - Single Agent Nivolumab Compared to Ipilimumab - Exploratory Analysis (CHECKMATE-067)

		Nivolumab		Ipilimumab		
	N	N of events/ N of subjects (% subjects)	mPFS (95% CI)	N of events/ N of subjects (% subjects)	mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	945	174/316 (55.1)	6.87 (4.34, 9.46)	234/315 (74.3)	2.89 (2.79, 3.42)	0.57 (0.47, 0.69)
BRAF Mutation Status						
Mutant	300	57/98 (58.2)	5.62 (2.79, 9.46)	66/100 (66.0)	4.04 (2.79, 5.52)	0.77 (0.54, 1.09)
Wildtype	645	117/218 (53.7)	7.89 (4.86, 12.68)	168/215 (78.1)	2.83 (2.76, 3.09)	0.50 (0.39, 0.63)

Table 61 provides objective response rates by BRAF mutation status.

Table 61: Objective Response by BRAF [V600] Mutation Status - Exploratory Analysis (CHECKMATE-067)

Treatment	BRAF [V600] Mutation-Positive		BRAF Wild-Type	
	Number of Responses/Patients	ORR% (95% CI)	Number of Responses/Patients	ORR% (95% CI)[a]
Nivolumab + Ipilimumab	68/102	66.7 (56.6, 75.7)	113/212	53.3 (46.3, 60.2)
Nivolumab	36/98	36.7 (27.2, 47.1)	102/218	46.8 (40.0, 53.6)
Ipilimumab	22/100	22.0 (14.3, 31.4)	38/215	17.7 (12.8, 23.4)

a. Descriptive evaluation only, based on Cochran Mantel-Haenszel (CMH) methodology

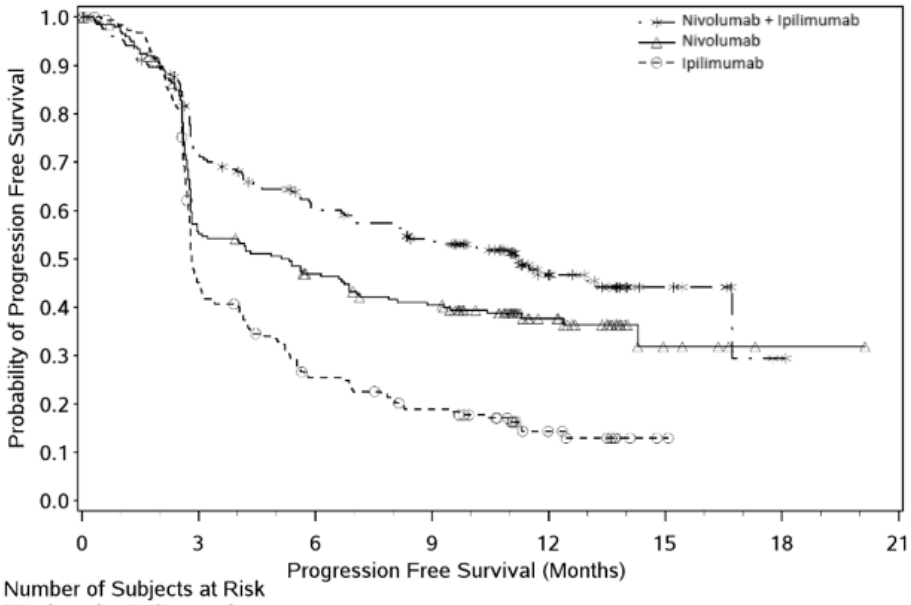
Efficacy of PFS and ORR analysis by PD-L1 Expression at a minimum follow-up of 9 months: Quantifiable PD-L1 expression was retrospectively measured in 89% (278/314) of patients randomized to nivolumab in combination with ipilimumab, 91% (288/316) of patients randomized to single-agent nivolumab, and 88% (277/315) of patients randomized to ipilimumab alone. Among patients with quantifiable PD-L1

expression, the distribution of patients across the three treatment groups at each of the predefined PD-L1 expression levels was as follows: ≥1% (56% in the nivolumab in combination with ipilimumab arm, 59% in the single-agent nivolumab arm, and 59% in the ipilimumab arm) and ≥5% (24%, 28%, and 27%, respectively). PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Figure 13 and Figure 14 present exploratory efficacy subgroup analyses of PFS based on defined PD-L1 expression levels.

In this study, no clear cutoff of PD-L1 expression has been established to predict treatment benefit when considering the relevant endpoints of tumour response, PFS, and OS.

Figure 13: Progression-Free Survival: Patients with <5% PD-L1 Expression - Exploratory Analysis (CHECKMATE-067)



Number of Subjects at Risk							
Nivolumab + Ipilimumab							
210	142	112	96	42	9	1	0
Nivolumab							
208	108	88	74	31	5	1	0
Ipilimumab							
202	82	44	31	12	1	0	0

Figure 14: Progression-Free Survival: Patients with ≥5% PD-L1 Expression - Exploratory Analysis (CHECKMATE-067)

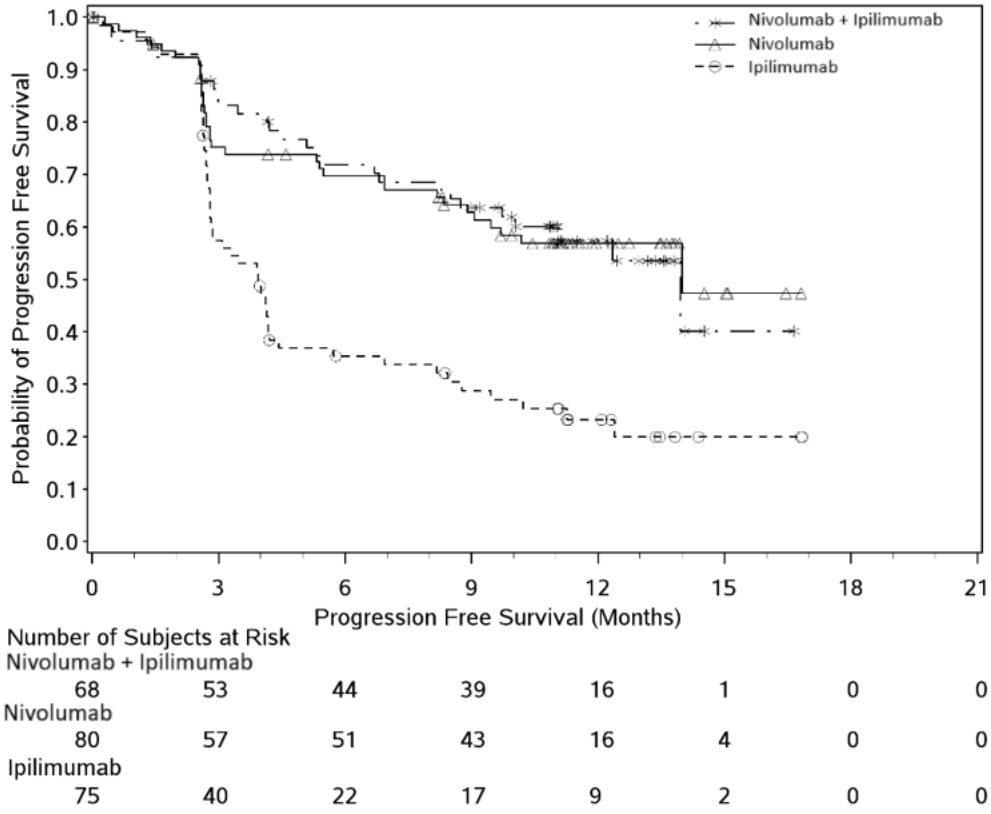


Table 62 shows the objective response rates based on PD-L1 expression level.

Table 62: Objective response - Exploratory Analysis (CHECKMATE-067) (Intent to Treat Analysis)

	Nivolumab + Ipilimumab (n=314)	**Nivolumab (n=316)**	**Ipilimumab (n=315)**
ORR (95% CI) by tumour PD-L1 expression level			
<5%	55% (47.8, 61.6) n=210	41% (34.6, 48.4) n=208	18% (12.8, 23.8) n=202
≥5%	72% (59.9, 82.3) n=68	58% (45.9, 68.5) n=80	21% (12.7, 32.3) n=75
<1%	52% (42.8, 61.1) n=123	33% (24.9, 42.6) n=117	19% (11.9, 27.0) n=113
≥1%	65% (56.4, 72.0) n=155	54% (46.6, 62.0) n=171	19% (13.2, 25.7) n=164

Controlled Trial in Melanoma Patients Previously Treated with Ipilimumab (Second-line treatment): CHECKMATE-037

CHECKMATE-037 was a multicentre, open-label phase III study that randomized patients (2:1) with unresectable or metastatic melanoma to receive either 3 mg/kg of nivolumab by intravenous (IV) infusion every 3 weeks (Q3W) or Investigator's choice chemotherapy (ICC). Chemotherapy consisted of either dacarbazine (1000 mg/m^2 Q3W) or carboplatin (AUC 6 every Q3W) and paclitaxel (175 mg/m^2 Q3W). Randomization was stratified by BRAF status (wildtype vs. mutation positive) and PD-L1 status by a verified immunohistochemistry (IHC) assay (≥ 5% vs. < 5% cut-off) and best response to prior ipilimumab therapy (prior clinical benefit [complete response, CR; partial response, PR; stable disease, SD] vs. no prior clinical benefit [progressive disease, PD]). Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor.

The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV. Treatment was continued until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond progression), discontinuation due to toxicity, or other reasons. Radiographic assessments of tumour response were performed at 9 weeks following randomization and every 6 weeks for the first 12 months, and then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. Demographic and baseline disease characteristics are presented in **Table 63**.

Table 63: Baseline Characteristics in CHECKMATE-037

	Nivolumab 3 mg/kg n=272	**ICC n=133**
Men	65%	64%
Women	35%	36%
Age (median)	59 years	62 years
Age (range)	(23-88 years)	(29-85 years)
Melanoma Subtypes		
Mucosal	10%	11%
Cutaneous	72%	74%
M-Stage at study entry		
M0	4%	2%
M1a (soft tissue)	6%	8%
M1b (lung)	16%	14%
M1c (all viscera)	75%	77%
Number of Prior Systemic therapies		
1	28%	26%

	Nivolumab 3 mg/kg n=272	ICC n=133
2	51%	51%
>2	21%	23%
PD-L1 Status		
Positive	49%	50%
Negative/Indeterminate	51%	50%
BRAF Status		
Wild Type	78%	78%
Mutation Positive	22%	22%
No response to prior ipilimumab (BOR of PD)	64%	65%
ECOG		
0	60%	63%
1	40%	36%
2	0	1%
Baseline LDH		
> ULN	52%	38%
> 2*ULN	17%	17%
History of Brain Metastases		
Yes	20%	14%
No	80%	87%

The median duration of exposure was 4.71 months (range: 0.03 to 35.94 months) in the nivolumab arm and 1.95 months (range: 0.03 to 14.23 months) in the chemotherapy arm.

The co-primary efficacy outcome measures were confirmed overall response rate (ORR) in the first 120 patients treated with nivolumab, as measured by independent radiology review committee (IRRC) using RECIST, version 1.1, and comparison of overall survival (OS) of nivolumab to chemotherapy. Additional outcome measures included duration of response.

At the time of the final ORR analysis, results from 120 nivolumab-treated patients and 47 chemotherapy-treated patients who had a minimum of 6 months of follow-up were analyzed. The ORR was 31.7 % (95% confidence interval [CI]: 23.5, 40.8), consisting of 4 complete responses and 34 partial responses in nivolumab-treated patients. There were objective responses in patients with and without BRAF V600 mutation-positive melanoma. The ORR was 10.6% (95% CI: 3.5, 23.1) in the chemotherapy treated patients.

There was no statistically significant difference between nivolumab and chemotherapy in the final OS analysis. The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment and 30 (11.0%) of patients in the nivolumab arm receiving subsequent therapies.

Efficacy by BRAF status:

The ORRs in the BRAF mutation-positive subgroup were 17% (n = 59; 95% CI: 8.4, 29.0) for nivolumab and 11% (n= 27; 95% CI: 2.4, 29.2) for chemotherapy, and in the BRAF wild-type subgroup were 30% (n = 213; 95% CI: 24.0, 36.7) and 9% (n =106; 95% CI: 4.6, 16.7), respectively.

The OS HR for nivolumab (n= 59) versus chemotherapy (n = 27) was 1.32 (95% CI: 0.75, 2.32) for BRAF mutation-positive patients. The OS HR for nivolumab (n= 213) versus chemotherapy (n = 106) was 0.83 (95% CI: 0.62, 1.11) for BRAF wild-type patients.

Efficacy by tumour PD-L1 expression:

In patients with tumour PD-L1 expression ≥1%, ORR was 33.5% for nivolumab (n=179; 95% CI: 26.7, 40.9) and 13.5% for chemotherapy (n=74; 95% CI: 6.7, 23.5). In patients with tumour PD-L1 expression <1%, ORR per IRRC was 13.0% (n=69; 95% CI: 6.1, 23.3) and 12.0% (n=25; 95% CI: 2.5, 31.2), respectively.

The OS HR for nivolumab (n= 179) versus chemotherapy (n = 74) was 0.69 (95% CI: 0.49, 0.96) in patients with tumour PD-L1 expression ≥1%. The OS HR for nivolumab (n= 69) versus chemotherapy (n = 25) was 1.52 (95% CI: 0.89, 2.57) in patients with tumour PD-L1 expression <1%.

Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer

CHECKMATE-816 was a randomized, open label trial in patients with resectable NSCLC. The trial included patients with resectable, histologically confirmed Stage IB (≥4 cm), II, or IIIA NSCLC (per the 7th edition American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging criteria), ECOG performance status 0 or 1, and measurable disease (per RECIST version 1.1). Patients were enrolled regardless of their tumour PD-L1 status. Patients with unresectable or metastatic NSCLC, known EGFR mutations or ALK translocations, Grade 2 or greater peripheral neuropathy, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

Patients were randomized to receive either:

- Nivolumab 360 mg administered intravenously over 30 minutes and platinum-doublet chemotherapy administered intravenously every 3 weeks for up to 3 cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for up to 3 cycles.

Platinum-doublet chemotherapy consisted of paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (non-squamous histology); or gemcitabine 1000 mg/m^2 or 1250 mg/m^2 and cisplatin 75 mg/m^2 (squamous histology). In the platinum-doublet chemotherapy arm, two additional treatment regimen options included vinorelbine 25 mg/m^2 or 30 mg/m^2 and cisplatin 75 mg/m^2; or docetaxel 60 mg/m^2 or 75 mg/m^2 and cisplatin 75 mg/m^2 (any histology). Stratification factors for randomization were tumour PD-L1 expression level (≥1% versus <1% or non-quantifiable), disease stage (IB/II versus IIIA), and sex (male versus female). Tumour assessments were performed at baseline, within 14 days of surgery, every 12 weeks after surgery for 2 years, then every 6 months for 3 years, and every year for 5 years until disease recurrence or progression. The primary efficacy outcome measures were event-free survival (EFS) based on BICR assessment and pathologic complete response (pCR) as evaluated by blinded independent pathology review (BIPR). Secondary efficacy outcome measures included OS.

A total of 358 patients were randomized to receive either nivolumab in combination with platinum-doublet chemotherapy (n=179) or platinum-doublet chemotherapy (n=179). The median age was 65 years (range: 34 to 84) with 51% of patients ≥65 years and 7% of patients ≥75 years, 50% were Asian, 47% were White, 2% were Black, and 71% were male. Baseline ECOG performance status was 0 (67%) or 1 (33%); 50% had tumours with PD-L1 expression ≥1% and 43% had tumours with PD-L1 expression that was <1%; 5% had stage IB, 17% had stage IIA, 13% had stage IIB, and 64% had stage IIIA disease; 51% had tumours with squamous histology and 49% had tumours with non-squamous histology; and 89% were former/current smokers.

Eighty-three percent of patients in the nivolumab in combination with platinum-doublet chemotherapy arm had definitive surgery compared to 75% of patients in the platinum-doublet chemotherapy arm.

Median follow-up at the pre-specified EFS interim analysis was 29.5 months (range: 21.0 to 46.3 months). Efficacy results are presented in Table 64 and Figure 15.

Table 64: Efficacy Results - CHECKMATE-816

	Nivolumab and Platinum-Doublet Chemotherapy (n=179)	**Platinum-Doublet Chemotherapy (n=179)**
Event-free Survival (EFS) per BICR		
Events (%)	64 (35.8)	87 (48.6)
Median (months)[a] (95% CI)	31.6 (30.2, NR)	20.8 (14.0, 26.7)
Hazard Ratio[b] (95% CI)	0.63 (0.45, 0.87)	
Stratified log-rank p-value[c]	0.0052	
Pathologic Complete Response (pCR) per BIPR		
Responses (%)	43 (24.0)	4 (2.2)
95% CI[d]	18.0, 31.0	0.6, 5.6
Difference of pCR (95%CI)[e]	21.6 (15.1, 28.2)	
Stratified log-rank p-value[f]	<0.0001	

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

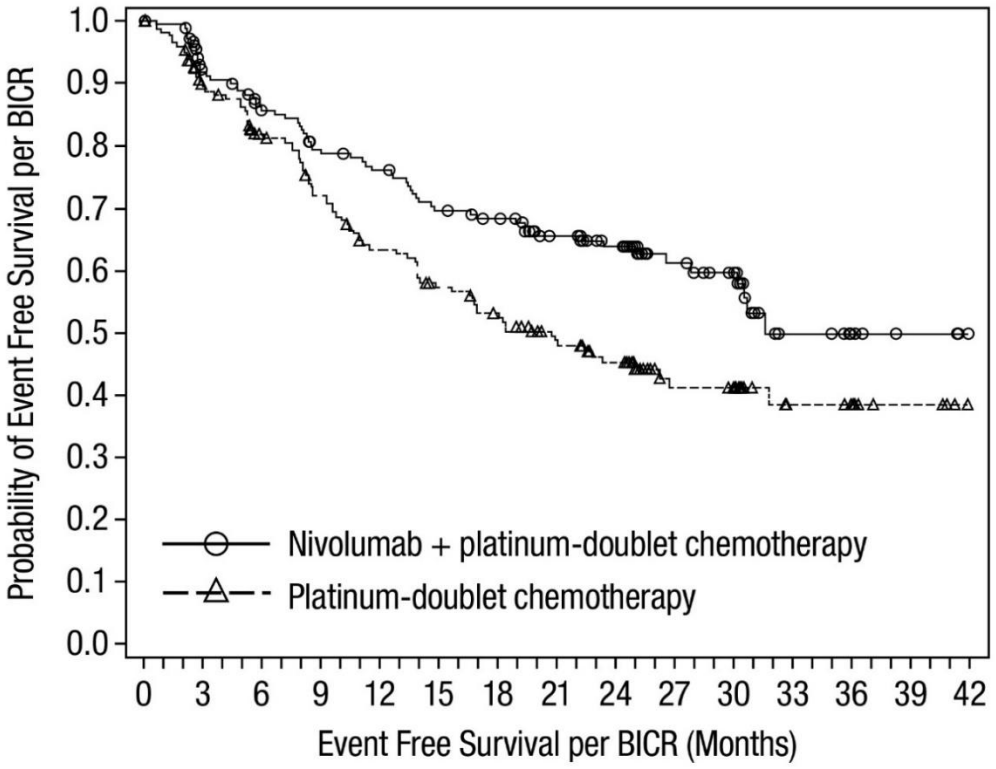
[c] Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0262.

[d] Based on Clopper and Pearson method.

[e] Strata-adjusted difference based on Cochran-Mantel-Haenszel method of weighting.

[f] From stratified CMH test.

Figure 15: Event-Free Survival - CHECKMATE-816



Number of Subjects at Risk

Nivolumab + platinum-doublet chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Platinum-doublet chemotherapy	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

EFS benefit was shown in patients treated with nivolumab in combination chemotherapy with PD L1 <1% (HR [95% CI] 0.85 [0.54, 1.32], n = 155) and PD-L1 ≥1% (HR [95% CI] 0.41 [0.24, 0.70], n = 178), and in patients with squamous histology (HR [95% CI] 0.77 [0.49, 1.22], n = 182) and non-squamous histology (HR [95% CI] 0.50 [0.32, 0.79], n = 176).

The results of a post-hoc exploratory analysis of EFS by both stage and PD-L1 are presented in **Table 65**.

Table 65: EFS by Stage and PD-L1

	PD-L1 < 1%		PD-L1 ≥ 1%	
	Nivolumab and Platinum-Doublet Chemotherapy	**Platinum-Doublet Chemotherapy**	**Nivolumab and Platinum-Doublet Chemotherapy**	**Platinum-Doublet Chemotherapy**
Stage IB/II	**N = 28**	**N = 28**	**N = 32**	**N = 33**
HR (95% CI)[a]	1.15 (0.52, 2.57)		0.63 (0.24, 1.62)	
Stage IIIA	**N = 50**	**N = 49**	**N = 56**	**N = 55**
HR (95% CI)[a]	0.69 (0.40, 1.19)		0.34 (0.18, 0.65)	

[a] Based on an unstratified Cox proportional hazard model.

At the time of the EFS analysis, a prespecified interim analysis for OS resulted in a HR of 0.57 (95% CI:0.38, 0.87) for nivolumab in combination with platinum-doublet chemotherapy versus platinum-doublet chemotherapy, which did not cross the boundary for statistical significance.

Metastatic Non-Small Cell Lung Cancer

Controlled Trial in Squamous NSCLC Patients Previously Treated with Chemotherapy (Second-line Treatment): CHECKMATE-017

CHECKMATE-017 was a randomized (1:1), open-label study enrolling 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients were randomized to receive nivolumab (n=135) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=137) administered intravenously at 75 mg/m^2 every 3 weeks. This study included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumour assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter.

The major efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed objective response rate (ORR) and progression-free survival (PFS). In addition, this trial evaluated whether PD-L1 expression was a predictive biomarker for efficacy.

In CHECKMATE-017, the median age was 63 years (range: 39 to 85) with 44% ≥65 years of age and 11% ≥75 years of age. The majority of patients were white (93%) and male (76%). Baseline disease characteristics of the population were Stage IIIb (19%), Stage IV (80%) and brain metastases (6%). Baseline ECOG performance status was 0 (24%) or 1 (76%).

The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with docetaxel at the pre-specified interim analysis when 199 events were observed (86% of the planned number of events for final analysis) (**Table 66** and Figure 16).

Table 66: Efficacy Results in CHECKMATE-017 (Intent-to-Treat Analysis)

	Nivolumab (n=135)		Docetaxel (n=137)
Overall Survival			
Events (%)	86 (64%)		113 (82%)
Median survival in months (95% CI)	9.2 (7.3, 13.3)		6.0 (5.1, 7.3)
p-value[a]		0.00025	
Hazard ratio (96.85% CI)[b]		0.59 (0.43, 0.81)	
Objective Response Rate[c]			
n (%)	27 (20%)		12 (8.8%)
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Difference in ORR (95% CI)		11.3% (2.9, 19.6)	
p-value[d]		0.0083	
Complete Response	1 (0.7%)		0
Partial Response	26 (19.3%)		12 (8.8%)
Progression-free Survival			
Events (%)	105 (78%)		122 (89%)
Median survival in months (95% CI)	3.5 (2.1, 4.9)		2.8 (2.1, 3.5)
p-value[a]		0.0004	
Hazard ratio (95% CI)[b]		0.62 (0.47, 0.81)	

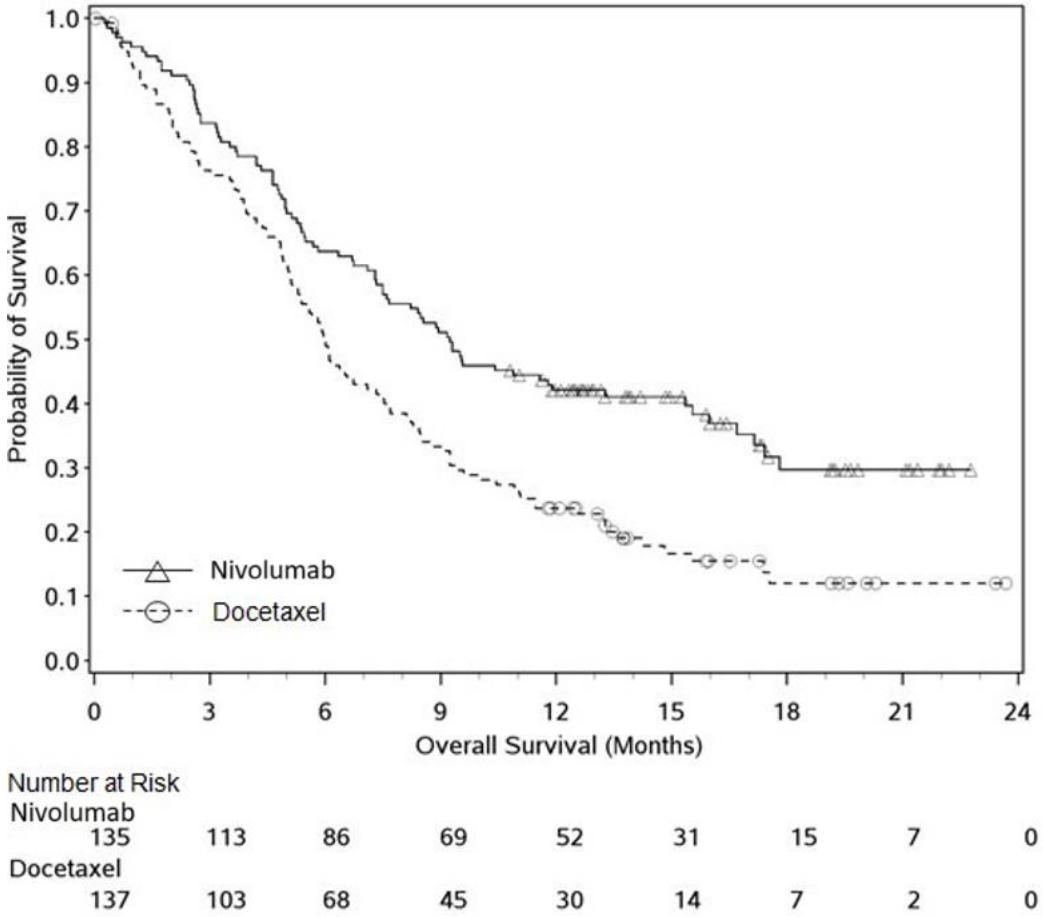
a. P-value is derived from a log-rank test stratified by region and prior paclitaxel use; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0315.

b. Derived from a stratified proportional hazards model.

c. Responses of CR+PR as per RECIST v1.1 criteria, as assessed by investigator; confidence interval based on the Clopper and Pearson method.

d. Based on the stratified Cochran-Mantel-Haenzel test.

Figure 16: Overall Survival - CHECKMATE-017



The estimated OS rates at 12 months were 42% (95% CI: 33.7, 50.3) for nivolumab and 24% (95% CI: 16.9, 31.1) for docetaxel. The median time to onset of response was 2.2 months (range: 1.6 to 11.8 months) for patients randomized to nivolumab and 2.1 months (range 1.8 to 9.5 months) for patients randomized to docetaxel. At the time of this analysis, 17/27 (63%) of nivolumab patients and 4/12 (33%) of docetaxel patients with a confirmed response had ongoing responses. The median duration of response was not reached (range from 2.9 to 20.5+ months) for nivolumab patients and 8.4 months (range 1.4 to 15.2+ months) for docetaxel patients.

Pre-study tumour tissue specimens were systematically collected prior to randomization in order to conduct pre-planned analyses of efficacy according to predefined PD-L1 expression status. Quantifiable PD-L1 expression was measured in 87% of patients in the nivolumab group and 79% of patients in the docetaxel group. PD-L1 expression levels for the two treatment groups (nivolumab vs docetaxel) at each of the predefined PD-L1 expression levels were ≥1% (54% vs 52%), ≥5% (36% vs 36%), or ≥10% (31% vs 31%). PD-L1 testing was conducted using the PD-L1 IHC 28-8 pharmDx assay. Survival benefit was observed regardless of PD-L1 expression or non-expression status by all pre-defined expression levels (1%, 5% and 10%). However, the role of the PD-L1 expression status has not been fully elucidated.

Squamous NSCLC Single-Arm Trial: CHECKMATE-063

CHECKMATE-063 was a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous-NSCLC after two or more lines of therapy; otherwise similar inclusion criteria as CHECKMATE-017 were applied. The major efficacy outcome measure was confirmed objective response rate (ORR) as measured by independent review committee (IRC) using Response Evaluation Criteria in Solid Tumours (RECIST 1.1).

Based on IRC review and with a minimum follow-up of at least 10 months on all patients, confirmed ORR was 15% (17/117) (95% CI: 9, 22), of which all were partial responses. In the 17 responders, the median duration of response was not reached at a follow-up of approximately 11 months, with a range of 1.9+ to 11.5+ months.

Controlled Trial in Non-Squamous NSCLC Patients Previously Treated with Chemotherapy (Second-line Treatment): CHECKMATE-057

CHECKMATE-057 was a randomized (1:1), open-label study of 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen which may have included maintenance therapy. An additional line of TKI therapy was allowed for patients with known EGFR mutation or ALK translocation. Patients were randomized to receive nivolumab (n=292) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=290) administered intravenously at 75 mg/m^2 every 3 weeks. This study included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumour assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed objective response rate (ORR) and progression-free survival (PFS). In addition, this trial evaluated whether PD-L1 expression was a predictive biomarker for efficacy.

In CHECKMATE-057, the mean age was 62 years (range: 21 to 85) with 42% ≥65 years of age and 7% ≥75 years of age. The majority of patients were white (92%) and male (55%); baseline ECOG performance status was 0 (31%) or 1 (69%). Seventy-nine percent of patients were former/current smokers.

The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis) (**Table 67** and Figure 17).

Table 67: Efficacy Results in CHECKMATE-057 (Intent-to-Treat Analysis)

	Nivolumab (n=292)		Docetaxel (n=290)
Overall Survival			
Events (%)	190 (65%)		223 (77%)
Median survival in months (95% CI)	12.2 (9.7, 15.0)		9.4 (8.0, 10.7)
p-value[a]		0.0015	
Hazard ratio (95.92% CI)[b]		0.73 (0.59, 0.89)	
Objective Response Rate[c]			
n (%)	56 (19%)		36 (12%)
(95% CI)	(14.8, 24.2)		(8.8, 16.8)
Difference in ORR (95% CI)		6.8% (0.9, 12.7)	
p-value [d]		0.0235	
Complete Response	4 (1.4%)		1 (0.3)
Partial Response	52 (17.8%)		35 (12.1%)
Progression-free Survival			
Events (%)	234 (80%)		245 (85%)
Median survival in months (95% CI)	2.3 (2.8, 3.3)		4.2 (3.5, 4.9)
p-value		0.3932	
Hazard ratio (95% CI)[b]		0.92 (0.77, 1.11)	

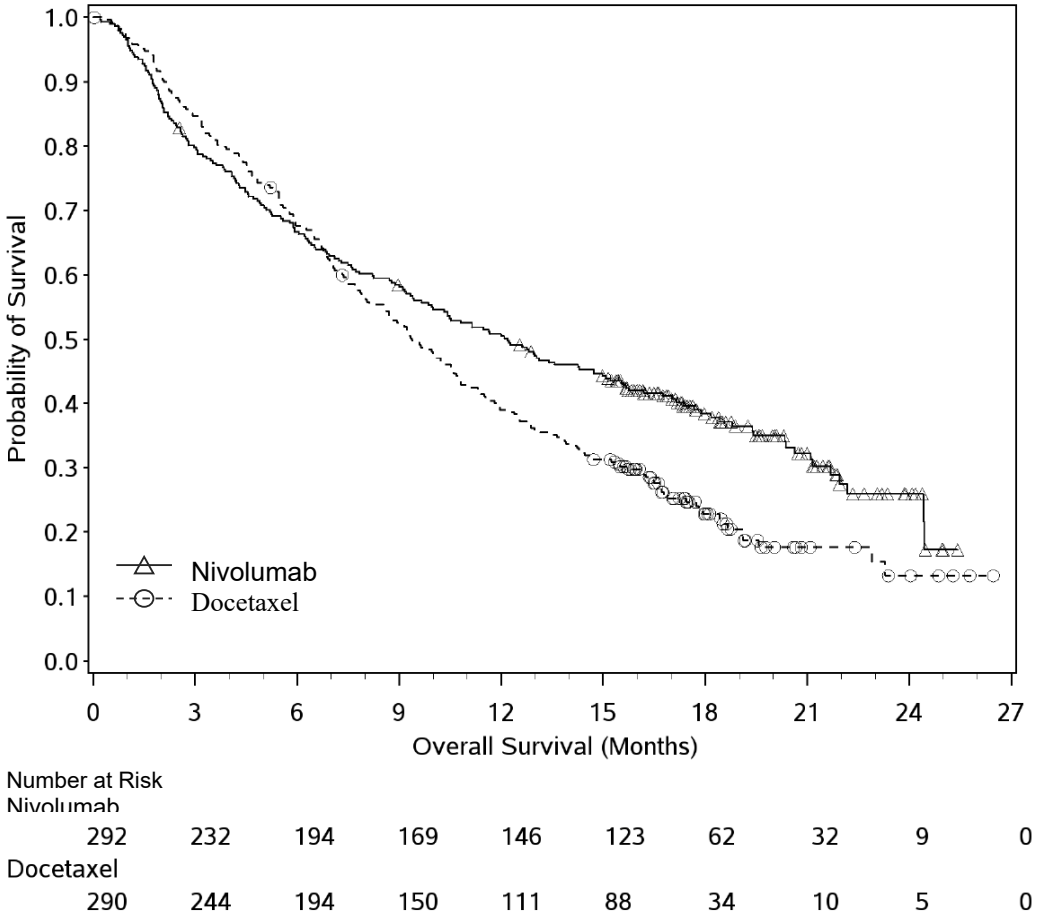
a. P-value is derived from a log-rank test stratified by prior maintenance therapy and line of therapy; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0408.

b. Derived from a stratified proportional hazards model.

c. Responses of CR+PR as per RECIST v1.1 criteria, as assessed by investigator; confidence interval based on the Clopper and Pearson method

d. Based on the stratified Cochran-Mantel-Haenzel test.

Figure 17: Overall Survival: CHECKMATE-057



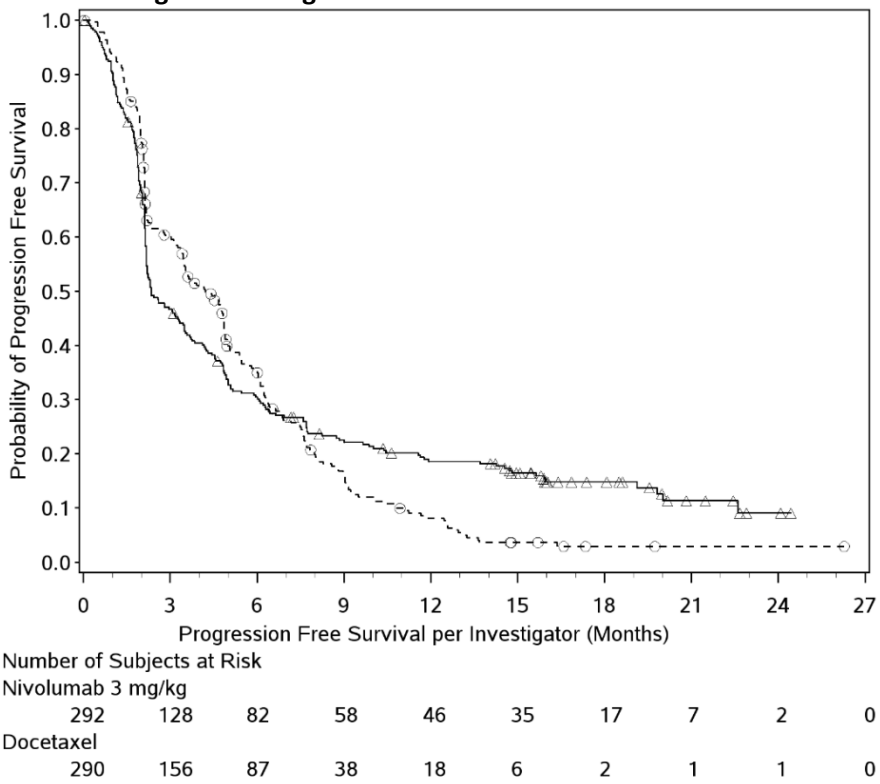
Number at Risk

Nivolumab									
292	232	194	169	146	123	62	32	9	0
Docetaxel									
290	244	194	150	111	88	34	10	5	0

The estimated OS rates at 12 months were 50.5% (95% CI: 44.6, 56.1) for nivolumab and 39.0% (95% CI: 33.3, 44.6) for docetaxel. The median time to onset of response was 2.1 months (range: 1.2 to 8.6 months) for patients randomized to nivolumab and 2.6 months (range 1.4 to 6.3 months) for patients randomized to docetaxel. At the time of this analysis, 29/56 (52%) of nivolumab-treated patients and 5/36 (14%) of docetaxel-treated patients with a confirmed response had ongoing responses. The median duration of response of 17.2 months (range from 1.8 to 22.6+ months) for nivolumab-treated patients and 5.6 months (1.2+ to 15.2+ months) for docetaxel-treated patients.

However, the trial did not demonstrate a statistically significant improvement in PFS for patients randomized to nivolumab as compared with docetaxel. (**Table 67** and Figure 18). Immediate benefit of nivolumab may not become evident in the first months of treatment with nivolumab as shown by the delayed crossing of the PFS curves followed by sustained separation.

Figure 18: Progression Free Survival: CHECKMATE-057



Archival tumour specimens were evaluated for PD-L1 expression following completion of the trial. Across the study population, 22% (127/582) of patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% (209/455) PD-L1 negative, defined as <1% of tumour cells expressing PD-L1 and 54% (246/455) had PD-L1 expression, defined as ≥ 1% of tumour cells expressing PD-L1. Among the 246 patients with tumours expressing PD-L1, 26% had ≥1%, but <5% tumour cells with positive staining, 7% had ≥ 5% but <10% tumour cells with positive staining, and 67% had greater than or equal to 10% tumour cells with positive staining. PD-L1 testing was conducted using the PD-L1 IHC 28-8 pharmDx assay.

Although the role of PD-L1 expression status has not been fully elucidated, in non-squamous NSCLC, pre-study (baseline) PD-L1 expression status shows an apparent association for benefit from nivolumab for all efficacy endpoints. Additional analyses of the association between PD-L1 expression status using pre-defined expression levels and efficacy measures suggested a clinically important signal of predictive association. In PD-L1 positive patients, nivolumab demonstrated improved efficacy vs docetaxel across all efficacy endpoints (OS, ORR, and PFS). In contrast, there were no meaningful differences in efficacy between the treatment groups in the PD-L1 negative subgroups by any expression level. As compared to the overall study population, no meaningful differences in safety were observed based on PD-L1 expression level. In patients with no measurable tumour PD-L1 expression or in those deemed non-quantifiable, close monitoring for unequivocal progression during the first months of treatment with nivolumab may be clinically prudent.

Figure 19 provides the Kaplan-Meier plots of OS stratified by PD-L1 expression status using the 1% expression level at baseline.

Figure 19: Overall Survival by PD-L1 Expression Level (1%) - CHECKMATE-057

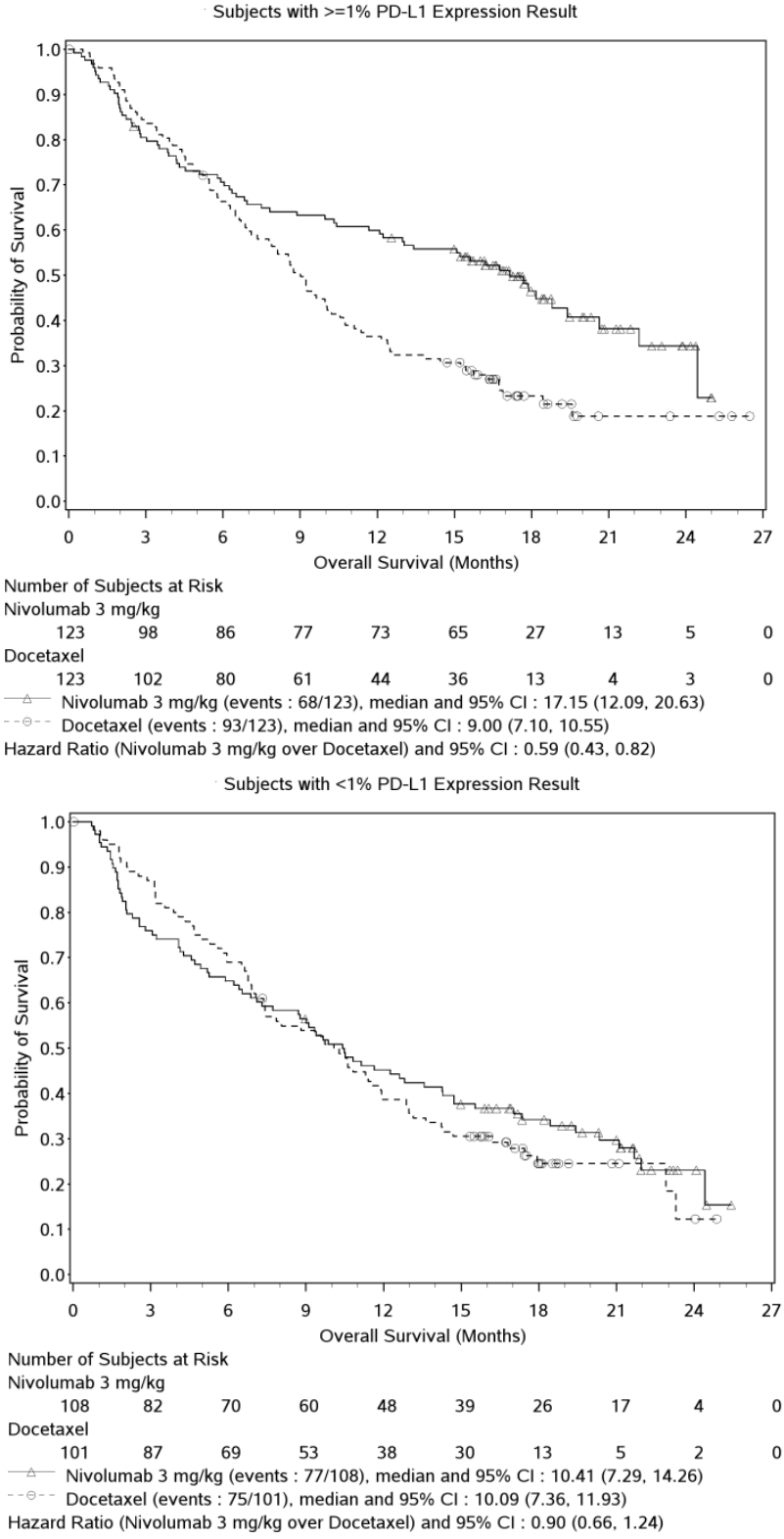
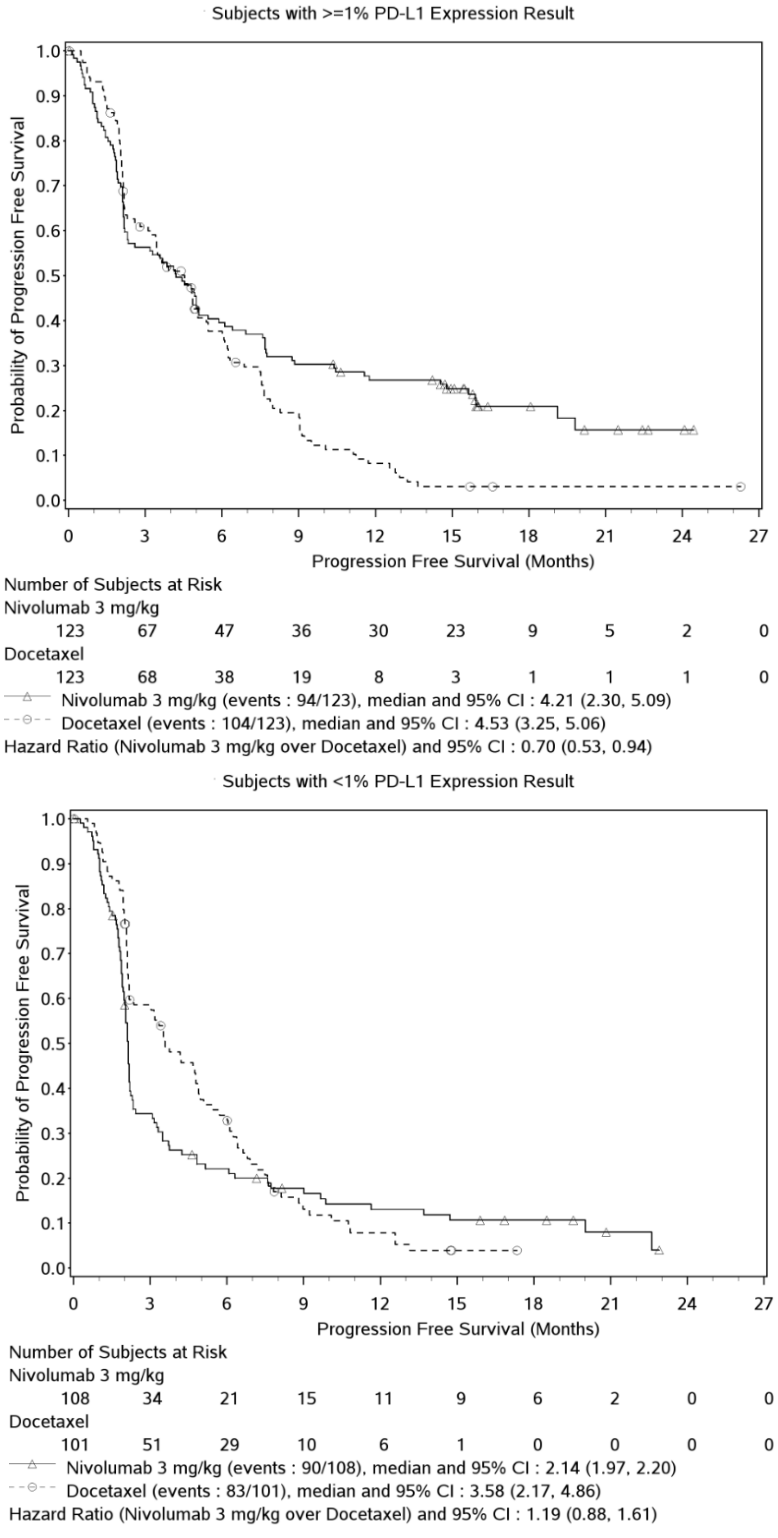


Figure 20 provides the Kaplan-Meier plots of PFS stratified by PD-L1 expression status using the 1% expression level at baseline.

Figure 20: Progression-free Survival by PD-L1 Expression Level (1%) - CHECKMATE-057



Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Controlled Trial in SCCHN Patients Progressing on or after Platinum-Based Therapy: CHECKMATE-141

The safety and efficacy of intravenous nivolumab 3 mg/kg as a single agent for the treatment of metastatic or recurrent SCCHN were evaluated in a Phase III, randomised, open-label study (CHECKMATE-141). The study included patients (18 years or older) who experienced disease progression during or within 6 months after prior platinum-based therapy regimen and had an ECOG performance status score of 0 or 1. Prior platinum-based therapy was administered in either the adjuvant, neo-adjuvant, primary, or metastatic setting. Patients were enrolled regardless of their tumour PD-L1 or human papilloma virus (HPV) status. Patients with active autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or untreated brain metastasis were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

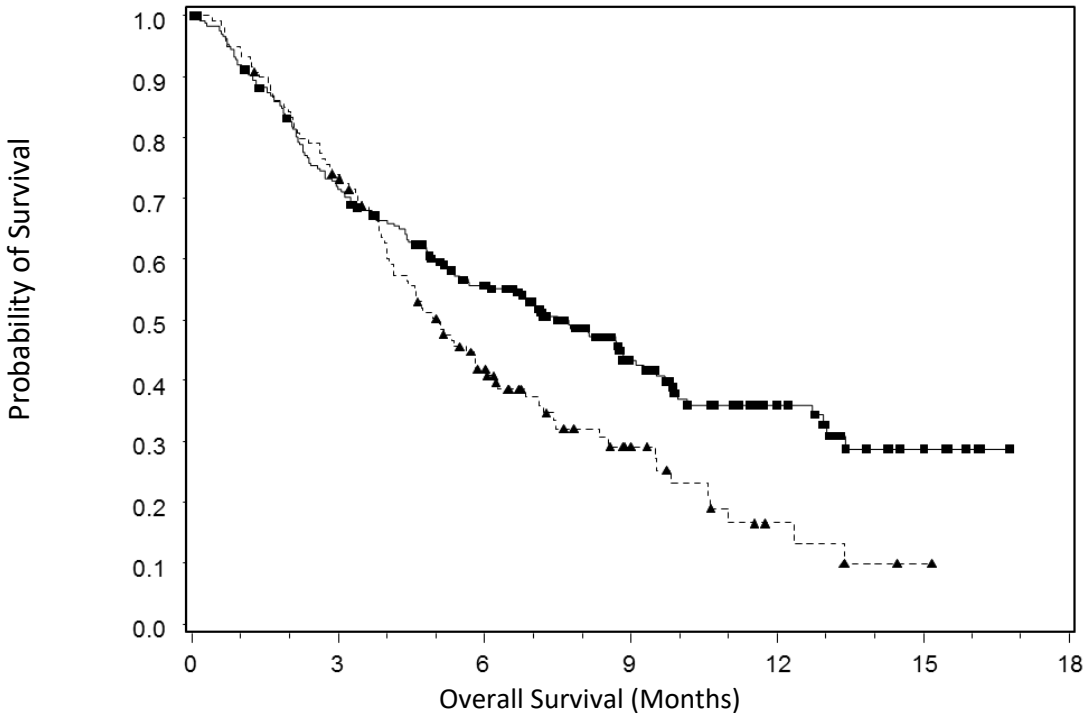
A total of 361 patients were randomised 2:1 to receive either nivolumab 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice (n = 121) of either cetuximab (n = 15), 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly or methotrexate (n = 52) 40 to 60 mg/m^2 weekly, or docetaxel (n = 54) 30 to 40 mg/m^2 weekly. Randomisation was stratified by prior cetuximab treatment. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to RECIST version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted in patients receiving nivolumab if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and ORR. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at predefined levels of 1%, 5%, and 10%.

Pre-study tumour tissue specimens were systematically collected prior to randomisation in order to conduct pre-planned analyses of efficacy according to tumour PD-L1 expression. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Baseline characteristics were generally balanced between the two groups. The median age was 60 years (range: 28-83) with 31% ≥ 65 years of age and 5% ≥ 75 years of age, 83% were male, and 83% were white. Baseline ECOG performance status score was 0 (20%) or 1 (78%), 76% were former/current smokers, 90% had Stage IV disease, 66% had two or more lesions, 45%, 35% and 20% received 1, 2, or 3 or more prior lines of systemic therapy, respectively, and 25% were HPV-16 status positive.

The Kaplan-Meier curves for OS are shown in Figure 21.

Figure 21: Overall Survival - CHECKMATE-141



Number of Subjects at Risk

Nivolumab						
240	167	109	52	24	7	0
Investigator's choice						
121	87	42	17	5	1	0

Nivolumab (events: 133/240), median and 95% CI: 7.49 (5.49, 9.10)
Investigator's choice (events: 85/121), median and 95% CI: 5.06 (4.04, 6.05)
Nivolumab vs. Investigator's Choice - hazard ratio and 95% CI: 0.70 (0.53 - 0.92); p-value: 0.0101

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice at the pre-specified interim analysis when 218 events were observed (78% of the planned number of events for final analysis). Nivolumab did not demonstrate a statistically significant benefit over investigator's choice in the secondary efficacy endpoints of progression-free survival (PFS) and objective response rates (ORR). Efficacy results are shown in **Table 68**.

Table 68: Efficacy results - CHECKMATE-141

	Nivolumab (n = 240)	investigator's choice (n = 121)
Overall survival		
Events	133 (55.4%)	85 (70.2%)
Hazard ratio[a]	0.70	
(95% CI)	(0.53, 0.92)	
p-value[b]	0.0101	
Median (95% CI) months	7.49 (5.49, 9.10)	5.06 (4.04, 6.05)
Rate (95% CI) at 6 months	55.6 (48.9, 61.8)	41.8 (32.6, 50.7)
Rate (95% CI) at 12 months	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)
Progression-free survival		
Events	190 (79.2%)	103 (85.1%)
Hazard ratio	0.89	
95% CI	(0.70, 1.13)	
p-value	0.3236	
Median (95% CI) (months)	2.04 (1.91, 2.14)	2.33 (1.94, 3.06)
Confirmed objective response[c]	32 (13.3%)	7 (5.8%)
(95% CI)	(9.3, 18.3)	(2.4, 11.6)
Complete response (CR)	6 (2.5%)	1 (0.8%)
Partial response (PR)	26 (10.8%)	6 (5.0%)
Stable disease (SD)	55 (22.9%)	43 (35.5%)

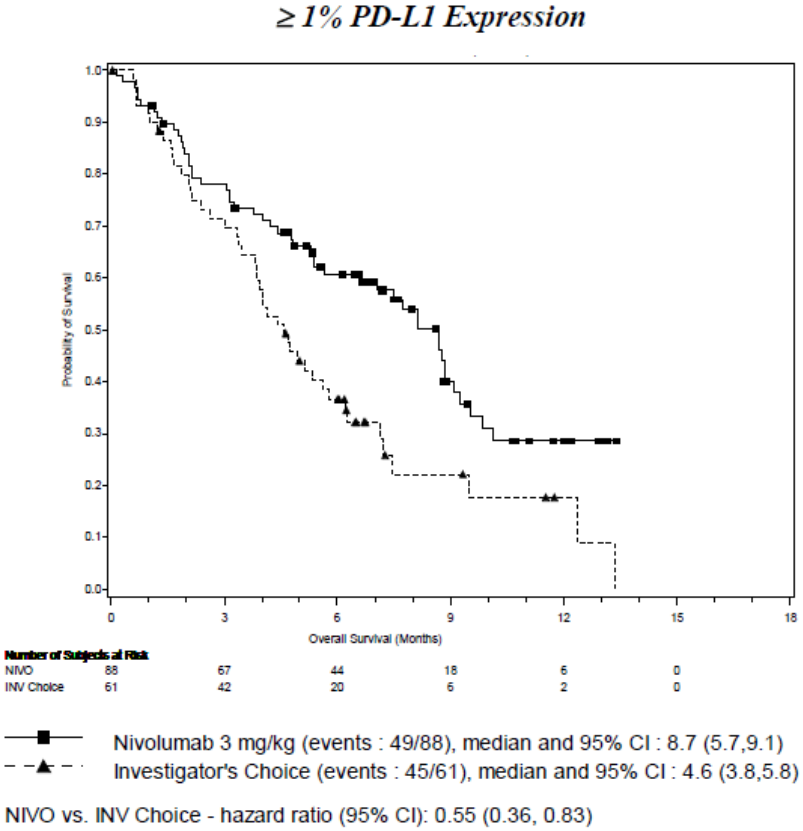
a. Derived from a stratified proportional hazards model.
b. P-value is derived from a log-rank test stratified by prior cetuximab; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0227.
c. In the nivolumab group there were two patients with CRs and seven patients with PRs who had tumour PD-L1 expression < 1%.

Tumour PD-L1 expression was quantifiable in 72% of patients - 67% of patients in the nivolumab group and 82% of patients in the investigator's choice group. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. investigator's choice) at each of the predefined tumour PD-L1 expression levels of ≥ 1% (55% vs. 62%), ≥ 5% (34% vs. 43%), or ≥ 10% (27% vs. 34%).

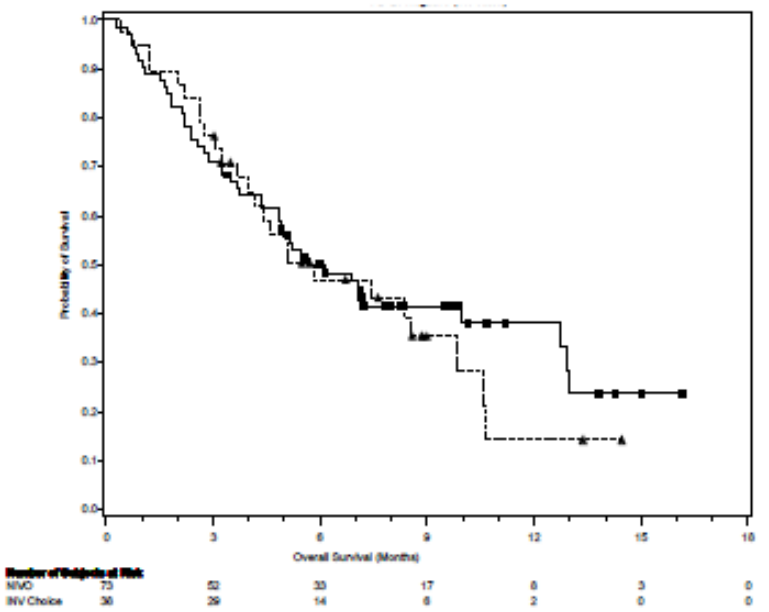
Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to investigator's choice. The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumour PD-L1 expression levels, with results shown using a 1% cut-off for PD-L1 expression (Figure 22). In contrast, there were no

meaningful differences in OS between nivolumab and investigator's choice treated patients who were PD-L1 negative (PD-L1 < 1%). In patients with no measurable tumour PD-L1 expression or in those deemed non-quantifiable, close monitoring for unequivocal progression during the first months of treatment with nivolumab may be clinically prudent.

Figure 22: Overall Survival by PD-L1 Expression Level (1%) - CHECKMATE-141



< 1% PD-L1 Expression



Nivolumab 3 mg/kg (events : 45/73), median and 95% CI : 5.7 (4.4,12.7)
Investigator's Choice (events : 25/38), median and 95% CI : 5.8 (4.0,9.8)

NIVO vs. INV Choice - hazard ratio (95% CI): 0.89 (0.54, 1.45)

Urothelial Carcinoma

CHECKMATE-274 was a phase 3, randomized, double-blind, placebo-controlled study of adjuvant intravenous nivolumab in patients who were within 120 days of radical resection of urothelial carcinoma (UC) originating in the bladder or upper urinary tract (renal pelvis or ureter) and were at high risk of recurrence. The UC pathologic staging criteria that defines high risk patients were ypT2-ypT4a or ypN$^+$ for adult patients who received neo-adjuvant cisplatin chemotherapy, and pT3-pT4a or pN$^+$ for adult patients who did not receive neo-adjuvant cisplatin chemotherapy and were not eligible or refused adjuvant cisplatin chemotherapy. The study excluded patients with active, known or suspected autoimmune disease, patients who had treatment with any chemotherapy, radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment. Patients had an ECOG performance status (PS) of 0 or 1. Patients who had not received cisplatin-based neoadjuvant chemotherapy and were considered ineligible for cisplatin adjuvant chemotherapy were eligible to enter the study with ECOG PS 2. Patients received nivolumab 240 mg or placebo by intravenous infusion every 2 weeks until recurrence or unacceptable toxicity for a maximum treatment duration of 1 year. Eligible patients were randomized in a 1:1 ratio to nivolumab or placebo and stratified by pathologic nodal status (N+ vs. N0/x with <10 nodes removed vs. N0 with ≥10 nodes removed), tumour PD-L1 expression (≥1% vs. <1%/indeterminate; as determined by the central lab using the PD-L1 IHC 28-8 pharmDx assay), and use of cisplatin neoadjuvant chemotherapy (yes vs. no).

The median age was 67 years (range: 30 to 92), 76% were male and 76% were White, 22% Asian, 0.7% Black and 0.1% American Indian or Alaska Native. Twenty one percent of patients had upper tract UC.

Prior neoadjuvant cisplatin had been given to 43% of patients; from the 57% who had not received prior neoadjuvant cisplatin, reasons listed were ineligibility (22%), patient preference (33%), and other/not reported (2%). At radical resection, 343 patients (47%) were node-positive and 50 patients (7%) had non-muscle-invasive (<pT2) primary tumours. Baseline ECOG performance status was 0 (63%), 1 (35%), or 2 (2%). Of the 709 patients, 40% were randomized as having PD-L1 expression of ≥1% (defined as ≥1% of tumour cells expressing PD-L1).

Primary endpoints were investigator-assessed DFS in all randomized patients and in patients with tumours expressing PD-L1 ≥1%. DFS was defined as time to first recurrence (local urothelial tract, local non-urothelial tract, or distant metastasis), or death. Key secondary endpoints included OS.

DFS efficacy results for CHECKMATE-274 are shown in **Table 69** and Figure 23. OS data remain immature at this interim analysis and are planned to be analyzed in pre-specified subsequent interim-analyses. The median follow-up time was 20.9 months and 19.5 months for all randomized subjects in the nivolumab and placebo arms, respectively.

Table 69: Efficacy Results - CHECKMATE-274

	All Randomized		PD-L1 ≥1%	
	Nivolumab (n=353)	**Placebo (n=356)**	**Nivolumab (n=140)**	**Placebo (n=142)**
Disease-free Survival				
Events[a], n (%)	170 (48)	204 (57)	55 (39)	81 (57)
Local recurrence	47 (13)	64 (18)	10 (7)	24 (17)
Distant recurrence	108 (31)	127 (36)	40 (29)	52 (37)
Death	14 (4)	10 (3)	5(4)	5 (4)
Median DFS (months)[b]	20.8	10.8	N.R.	8.4
(95% CI)	(16.5, 27.6)	(8.3, 13.9)	(21.2, N.E.)	(5.6, 21.2)
Hazard ratio[c]	0.70		0.55	
(95% CI)	(0.57, 0.86)		(0.39, 0.77)	
p-value	0.0008[d]		0.0005[e]	

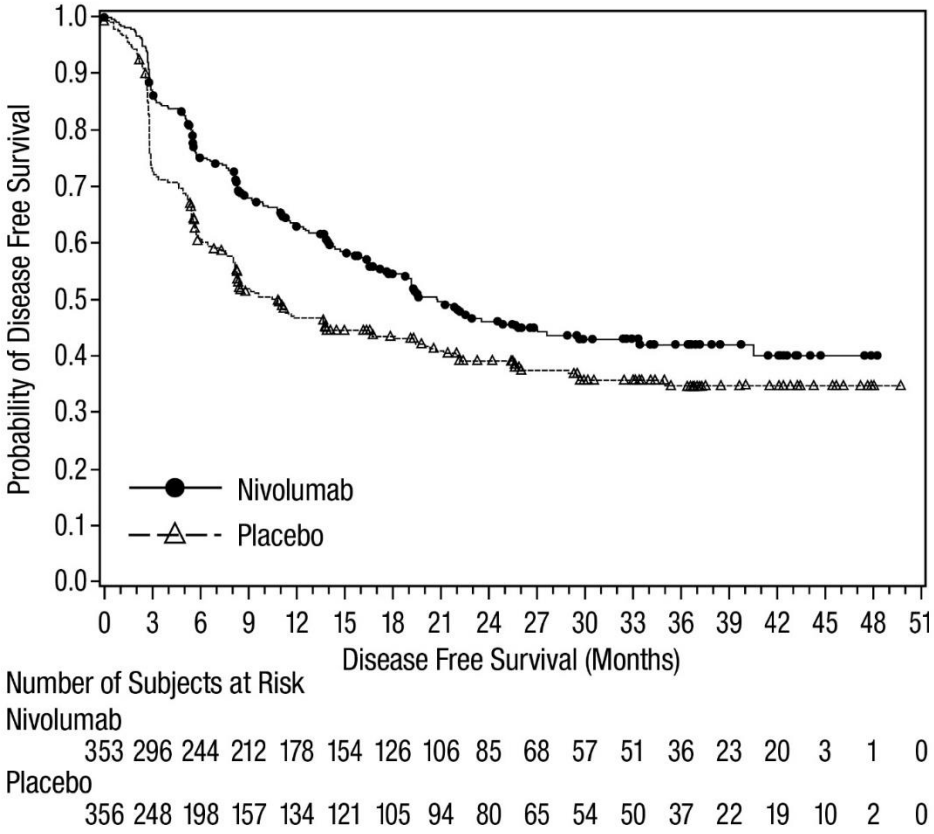
N.R. Not reached, N.E. Not estimable

a. Includes disease at baseline events (protocol deviations): n=1 in nivolumab arm and n=3 in placebo arm.
b. Based on Kaplan-Meier estimates.
c. Stratified Cox proportional hazard model. Hazard ratio is nivolumab over placebo.
d. Log-rank test stratified by prior neoadjuvant cisplatin, pathological nodal status, and PD-L1 status (≥1% vs <1%/indeterminate) as entered in the Interactive Response Technologies (IRT). Boundary for statistical significance in all randomized patients: p-value <0.01784.
e. Log-rank test stratified by prior neoadjuvant cisplatin, and pathological nodal status. Boundary for statistical significance in all randomized patients with PD-L1≥1%: p-value <0.01282.

In an exploratory subgroup analysis of all randomized patients with tumour cell PD-L1 <1% (n=414), the estimated HR for DFS was 0.83 (95% CI: 0.64, 1.08).

In an exploratory subgroup analysis in patients with upper tract UC (n=149), no improvement in DFS was observed in the nivolumab arm compared to the placebo arm. The estimated HR for DFS was 1.15 (95% CI: 0.74, 1.80).

Figure 23: Disease-free Survival in All Randomized Patients - CHECKMATE-274



Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

The safety and efficacy of intravenous nivolumab in combination with ipilimumab were evaluated for the treatment of dMMR or MSI-H mCRC in a Phase 2, multicenter, open-label, single-arm study (CHECKMATE-142).

The study included patients (18 years or older) with locally determined dMMR or MSI-H status, who had disease progression during, after, or were intolerant to, prior therapy with fluoropyrimidine and oxaliplatin or irinotecan, and had an ECOG performance status score of 0 or 1. This study included patients regardless of their tumour PD-L1 status. Patients with active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 119 patients received the combination regimen (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then nivolumab 3 mg/kg every 2 weeks). Treatment continued until unacceptable toxicity or radiographic progression. Tumour assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures included overall response rate (ORR) as assessed by independent radiographic review

committee (IRRC) using Response Evaluation Criteria in Solid Tumours (RECIST v1.1) and duration of response (DOR).

The median age was 58 years (range: 21 to 88), with 32% ≥ 65 years of age and 9% ≥ 75 years of age; 59% were male and 92% were white.

Baseline ECOG performance status was 0 (57%) and ≥1 (61%), and 29% were reported to have Lynch Syndrome. 25% of patients were BRAF mutation positive, 37% were KRAS mutation positive, and 12% were unknown. 23%, 36%, 24%, and 16% received 1, 2, 3, or ≥4 prior lines of therapy, respectively, and 29% had received an anti-EGFR antibody.

Efficacy results based on a minimum follow-up of approximately 27.5 months for all 119 patients who had prior fluoropyrimidine, oxaliplatin or irinotecan therapy are shown in **Table 70**.

Table 70: Nivolumab + ipilimumab Combination Therapy Efficacy Results for Patients with MSI-H/dMMR mCRC (CHECKMATE-142)

	Nivolumab + Ipilimumab[a] **All patients (n = 119)**
Confirmed objective response[b], n (%)	71 (59.7)
(95% CI)[c]	(50.3, 68.6)
Complete response (CR), n (%)	17 (14.3)
Partial response (PR), n (%)	54 (45.4)

a. Minimum follow-up 27.5 months, Median follow-up 31.5 months
b. BICR assessment
c. Estimated using the Clopper-Pearson method

At the time of this analysis corresponding to the minimum follow-up duration of 27.5 months, the median response duration was not reached (range: 1.9 to 36.9+ months).

Adjuvant Treatment of Resected Esophageal or Gastroesophageal Junction Cancer

CHECKMATE-577

CHECKMATE-577 was a randomized, multicenter, double-blind trial in 794 patients with resected esophageal or gastroesophageal junction cancer who had residual pathologic disease. Patients were randomized (2:1) to receive either 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. Treatment was until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. Enrollment required complete resection with negative margins within 4 to 16 weeks prior to randomization. The trial excluded patients who did not receive concurrent chemoradiotherapy (CRT) prior to surgery, who 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. Randomization was stratified by tumour PD-L1 status (≥1% vs. <1% or indeterminate or non-evaluable), pathologic lymph node status (positive ≥ypN1 vs. negative ypN0), and histology (squamous vs. adenocarcinoma). The primary efficacy outcome measure was disease-free survival (DFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant from the primary resected site) or death, from any cause, whichever occurred first as assessed by the investigator prior to subsequent anti-cancer therapy. Patients on treatment underwent imaging for tumour recurrence every 12 weeks for 2 years, and a minimum of one scan every 6 to 12 months for years 3 to 5.

The trial population characteristics were: median age 62 years (range: 26 to 86), 36.1% were ≥65 years of age, 84.5% were male, 14.7% were Asian, and 81.6% were White. Disease characteristics were AJCC Stage II (35%) or Stage III (64.7%) carcinoma at initial diagnosis, EC (59.8%) or GEJC (40.2%) at initial diagnosis, with pathologic positive lymph node status (57.6%) at study entry and histological confirmation of predominant adenocarcinoma (70.9%) or squamous cell carcinoma (29%). The baseline tumour PD-L1 status was positive for 16.2% patients, defined as ≥1% of tumour cells expressing PD-L1, and negative for 71.8% of patients. Baseline ECOG performance status was 0 (58.4%) or 1 (41.6%).

Efficacy results are shown in **Table 71** and Figure 24.

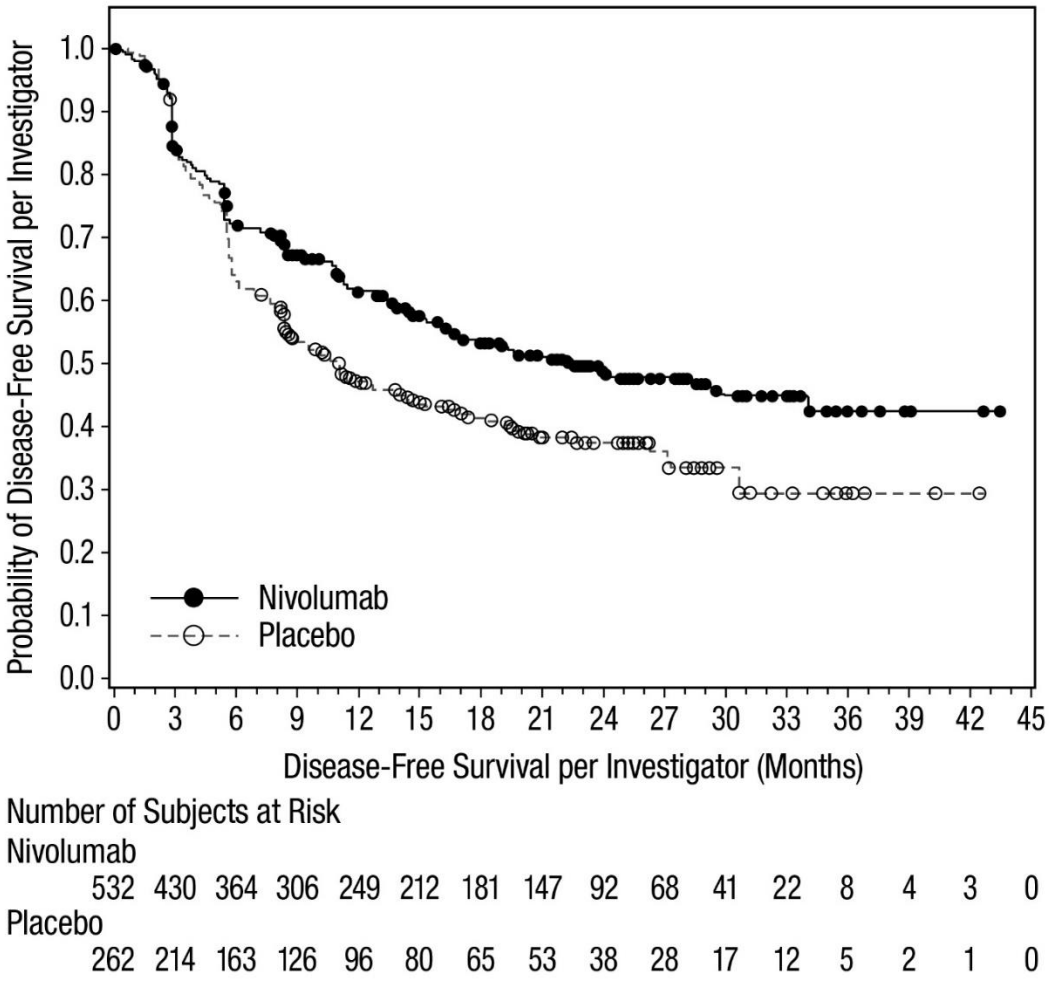
Table 71: Efficacy Results - CHECKMATE-577

	Nivolumab (n=532)	**Placebo (n=262)**
Disease-free Survival[a]		
Number of events, n (%)	241 (45.3%)	155 (59.2%)
Median (months) (95% CI)	22.41 (16.62, 34.00)	11.04 (8.34, 14.32)
Hazard ratio[b] (95% CI)	0.69 (0.56, 0.85)	
p-value[c]	0.0003	

a. Based on all randomized patients.

b. Hazard ratio is obtained from a Cox proportional-hazards model stratified by tumour PD-L1 status, pathologic lymph node status, and histology with treatment as the sole covariate.
c. Based on a stratified log-rank test.

Figure 24: Disease-free Survival - CHECKMATE-577



Unresectable Advanced or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

CHECKMATE-648 is an open-label, randomized Phase 3 study of nivolumab + ipilimumab or nivolumab + chemotherapy (fluorouracil plus cisplatin) compared with chemotherapy (fluorouracil plus cisplatin) in adult (≥ 18 years) male and female subjects with unresectable advanced, recurrent or metastatic ESCC. Patients were randomized (1:1:1) to the following treatment arms:

- Arm A: nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab 1 mg/kg as a 30 minute infusion every 6 weeks
- Arm B: nivolumab 240 mg as a 30-minute infusion, fluorouracil 800 mg/m²/day as an IV continuous infusion, and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle
- Arm C: fluorouracil 800 mg/m²/day as a continuous IV infusion, and cisplatin 80 mg/m² as a 30-

to 120-minute infusion on Day 1 of 4-week cycle

Subjects were permitted to receive treatment with cisplatin 80 mg/m² as an IV infusion over a period of longer than 120 minutes if in accordance with local standard of care/local label. Randomization was stratified by tumour cell PD-L1 status (≥ 1% vs < 1%, including indeterminate), region (East Asia [Japan, Korea, Taiwan] vs Rest of Asia vs Rest of world), Eastern Cooperative Oncology Group performance status (0 vs 1), and number of organs with metastases (≤ 1 vs ≥ 2) per interactive response technology. Tumour specimens were evaluated prospectively using the PD-L1 IHC 28-8 PharmDx at a central laboratory. Treatment was given for up to 24 months in the absence of disease progression or unacceptable toxicity. Treatment beyond initial, investigator-assessed, Response Evaluation Criteria in Solid Tumours (RECIST) 1.1-defined progression was permitted for patients treated with nivolumab in combination with ipilimumab or nivolumab in combination with chemotherapy if the subject had investigator-assessed clinical benefit and was tolerating treatment.

The primary endpoints were OS and progression-free survival per blinded independent central review in subjects with tumour cell PD-L1 ≥ 1%, comparing nivolumab in combination with chemotherapy vs chemotherapy arms and nivolumab in combination with ipilimumab vs chemotherapy arms.

A total of 970 patients were randomized to receive either nivolumab in combination with ipilimumab (Arm A; n=325) or nivolumab in combination with chemotherapy (Arm B; n=321) or chemotherapy (Arm C; n=324). Baseline characteristics were generally balanced across treatment groups. The median age was 64 years (range: 26-90), 46.6% were ≥ 65 years of age, 82.2% were male, 70.6% were Asian, and 25.6% were white. Patients had histological confirmation of squamous cell carcinoma (98.0%) or adenosquamous cell carcinoma (1.9%) in the oesophagus. Baseline ECOG performance status was 0 (47%) or 1 (54%).

The baseline tumour cell PD-L1 status positive, as defined as ≥1% of tumour cells expressing PD-L1, was 48.6% (n=158) in Arm A, 49.2% (n=158) in Arm B, and 48.5% (n=157) in Arm C, respectively.

Nivolumab in combination with ipilimumab:

In CHECKMATE-648 for patients receiving nivolumab in combination with ipilimumab a statistically significant improvement in OS was demonstrated in patients with tumour cell PD-L1 expression ≥ 1%. The minimum follow-up was 13.1 months. Efficacy results are shown in **Table 72** and Figure 25.

Table 72: Efficacy Results - Arms A and C of CHECKMATE-648

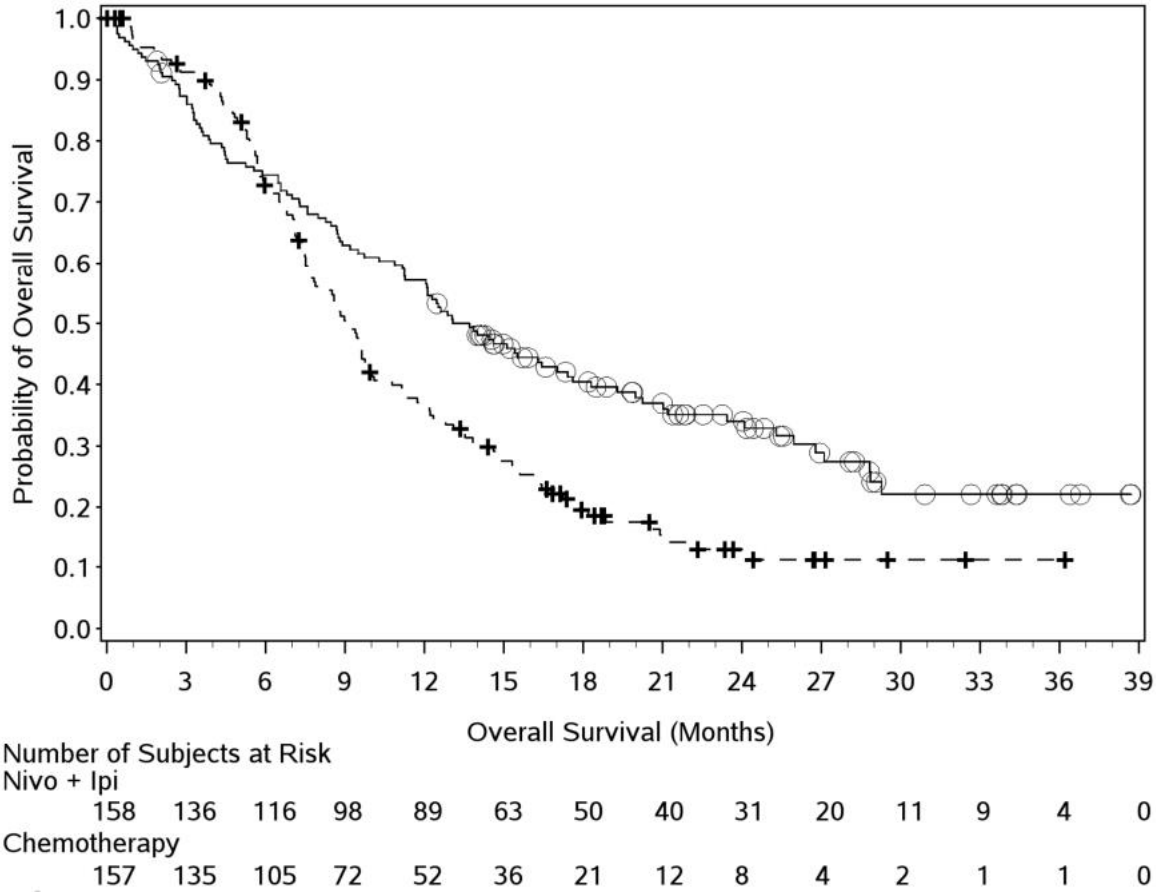
	Nivolumab and Ipilimumab (n=158)	Cisplatin and Fluorouracil (n=157)
	Tumour cell PD-L1 ≥ 1%	
Overall Survival		
Deaths (%)	106 (67)	120 (77)
Median (months) (95% CI)	13.7 (11.2, 17.0)	9.0(7.7, 10.0)
Hazard ratio (95% CI)[b]	0.64 (0.49, 0.84)	
p-value[c]	0.0010	
Progression-free Survival[a]		
Disease progression or death (%)	123 (78)	100 (64)
Median (months) (95% CI)	4.0 (2.4, 4.9)	4.4 (2.9, 5.8)
Hazard ratio (CI)[b]	1.02 (0.78, 1.34)	
p-value[c]	0.8958	
Overall Response Rate, n (%)[a]	56 (35)	31 (20)
(95% CI)	(28.0, 43.4)	(13.8, 26.8)

[a] Assessed by BICR.

[b] Based on stratified Cox proportional hazard model.

[c] Based on a stratified 2-sided log-rank test by ECOG PS (0 vs 1), region (J/K/T vs rest of Asia vs RoW) and number of organs with metastases (≤1 vs ≥2).

Figure 25: Overall Survival (tumour cell PD-L1 ≥ 1%) - CHECKMATE-648



In patients with a positive tumour cell PD-L1 status, the median durations of response are 11.8 (95% CI:7.1, 27.4) and 5.7 (95% CI: 4.4, 8.7) months for nivolumab with ipilimumab and chemotherapy alone, respectively.

Nivolumab in combination with chemotherapy:

In patients treated with nivolumab in combination with cisplatin and fluorouracil, CHECKMATE-648 demonstrated a statistically significant improvement in OS and PFS for patients with tumour cell PD-L1 expression ≥ 1%. The minimum follow-up was 12.9 months. Efficacy results are shown in **Table 73** and Figure 26.

Table 73: Efficacy Results - Arms B and C of CHECKMATE-648

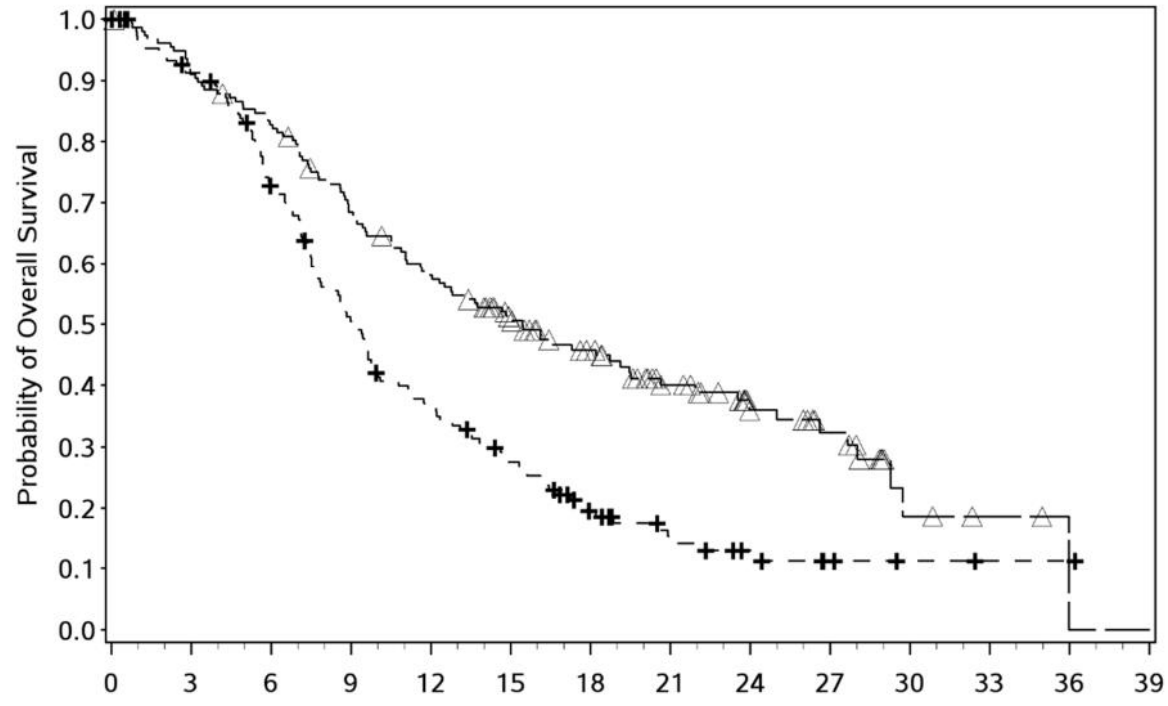
	Nivolumab with Cisplatin and Fluorouracil (n=158)	Cisplatin and Fluorouracil (n=157)
	Tumour cell PD-L1 ≥ 1%	
Overall Survival		
Deaths (%)	98 (62)	120 (77)
Median (months) (95% CI)	15.4 (11.9, 19.5)	9.1 (7.7, 10.0)
Hazard ratio (95% CI)[b]	0.54 (0.41, 0.71)	
p-value[c]	< 0.0001	
Progression-free Survival[a]		
Disease progression or death (%)	117 (74)	100 (64)
Median (months) (95% CI)	6.93 (5.7, 8.3)	4.4 (2.9, 5.8)
Hazard ratio (95% CI)[b]	0.65 (0.49, 0.86)	
p-value[c]	0.0023	
Overall Response Rate, n (%)[a]	84 (53)	31 (20)
(95% CI)	(45.1, 61.1)	(13.8, 26.8)

[a] Assessed by BICR.

[b] Based on stratified Cox proportional hazard model.

[c] Based on a stratified 2-sided log-rank test. by ECOG PS (0 vs 1), region (J/K/T vs rest of Asia vs RoW) and number of organs with metastases (≤1 vs ≥2).

Figure 26: Overall Survival (Tumour cell PD-L1 ≥ 1%) - CHECKMATE-648



In patients with a positive tumour cell PD-L1 status, the median durations of response are 8.4 (95% CI: 6.9, 12.4) and 5.7 (95% CI: 4.4, 8.7) months for nivolumab with chemotherapy and chemotherapy alone, respectively.

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

The safety and efficacy of intravenous nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy was evaluated in phase 3, randomized, open-label study (CHECKMATE-649). The study included adult patients (18 years or older) with previously untreated advanced or metastatic gastric (GC), gastroesophageal junction (GEJC) or esophageal adenocarcinoma (EAC), no prior systemic treatment (including HER2 inhibitors), and ECOG performance status score 0 or 1. The trial enrolled patients regardless of PD-L1 status, and tumour specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were known HER2 positive or had untreated CNS metastases. Patients were randomized to receive nivolumab in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

- Nivolumab 240 mg in combination with FOLFOX (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or FOLFOX every 2 weeks.

- Nivolumab 360 mg in combination with CapeOX (capecitabine and oxaliplatin) every 3 weeks or CapeOX every 3 weeks.

Patients were treated until disease progression, unacceptable toxicity, or up to 2 years. In patients who received Nivolumab in combination with chemotherapy and in whom chemotherapy was discontinued, nivolumab monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks up to 2 years after treatment initiation.

Randomization was stratified by tumour cell PD-L1 status (≥1% vs. <1% or indeterminate), region (Asia vs. US vs. Rest of World), ECOG performance status (0 vs. 1), and chemotherapy regimen. PD-L1 status by CPS was evaluated using the PD-L1 stained tumour specimens used for randomization. Chemotherapy consisted of FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

The study objectives were to assess OS and PFS in all randomized patients, as well as in patients with PD-L1 combined positive score (CPS) ≥5. The tumour assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

A total of 1581 patients were randomized: 789 to the nivolumab in combination with chemotherapy arm and 792 to the chemotherapy arm. The baseline characteristics were generally balanced across treatment groups. The median age 61 years (range: 18 to 90), 39% were ≥65 years of age, 70% were male, 24% were Asian, and 69% were White. Baseline ECOG performance status was 0 (42%) or 1 (58%). Tumour locations were distributed as gastric (70%), gastroesophageal junction (16%) and esophagus (13%).

CHECKMATE-649 met its objectives after a minimum follow-up of 12.1 months and results are shown in **Table 74** and Figure 27 and Figure 28.

Table 74: Efficacy Results - CHECKMATE-649

	Nivolumab and FOLFOX or CapeOx (n=789)	**FOLFOX or CapeOx (n=792)**	**Nivolumab and FOLFOX or CapeOx (n=473)**	**FOLFOX or CapeOx (n=482)**
	All Patients		**PD-L1 CPS ≥5**	
Overall Survival				
Events (%)	544 (69)	591 (75)	309 (65)	362 (75)
Median (months)[a] (95% CI)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)
Hazard ratio (CI)[b]	0.80 (99.3% CI: 0.68, 0.94)		0.71 (98.4% CI: 0.59, 0.86)	
p-value[c]	0.0002		<0.0001	
Progression-free Survival[d]				
Events (%)	559 (70.8)	557 (70.3)	328 (69.3)	350 (72.6)
Median (months)[a] (95% CI)	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)	7.69 (7.03, 9.17)	6.05 (5.55, 6.90)
Hazard ratio (CI)[b]	0.77 (95% CI: 0.68, 0.87)		0.68 (98% CI: 0.56, 0.81)	

	Nivolumab and FOLFOX or CapeOx (n=789)	FOLFOX or CapeOx (n=792)	Nivolumab and FOLFOX or CapeOx (n=473)	FOLFOX or CapeOx (n=482)
p-value[c]	Not Tested		<0.0001	
Overall Response Rate, n (%)[d,e]	350/603 (58)	280/608 (46)	226/378 (60)	177/391 (45)

a. Kaplan-Meier estimate.
b. Based on stratified log Cox proportional hazard model.
c. Based on stratified log-rank test.
d. Confirmed by BICR.
e. Based on patients with measurable disease at baseline.

In all randomized patients the median DOR was 8.5 months in the nivolumab + chemotherapy arm compared to 6.9 months in the chemotherapy arm. In patients with CPS ≥ 5 the median DOR was 9.5 months for the nivolumab + chemotherapy arm compared to 7.0 months in the chemotherapy arm.

A positive association was observed between PD-L1 CPS score and the magnitude of the treatment benefit. The hazard ratios (HR) for OS were 0.80, 0.77, 0.71 for all randomized patients, PD-L1 CPS ≥ 1, and PD-L1 CPS ≥ 5 patients, respectively. In an exploratory analysis, the stratified HRs for OS were 0.85 in patients with PD-L1 CPS < 1 and 0.94 for patients with PD-L1 CPS < 5.

Figure 27: Kaplan-Meier Curve of Overall Survival (ITT) - CHECKMATE-649

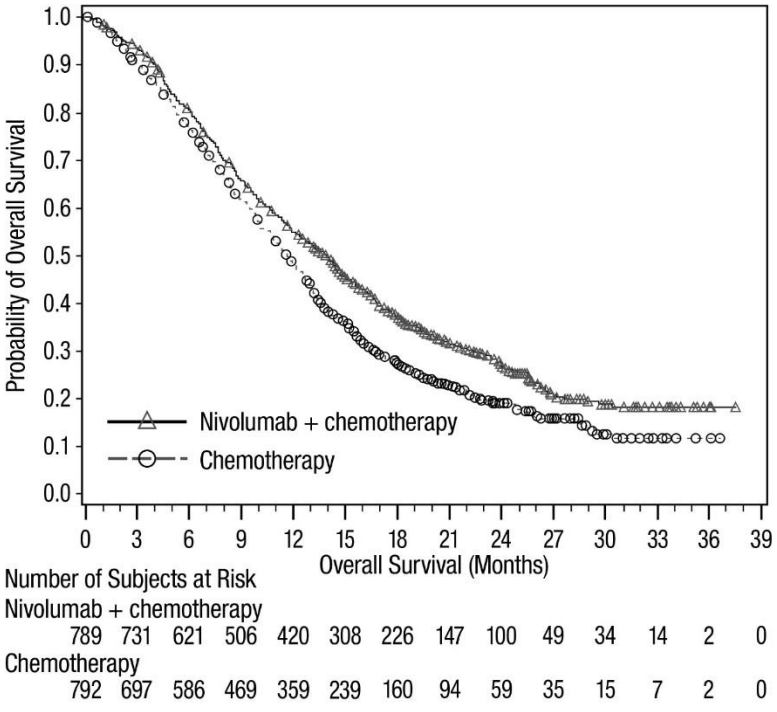
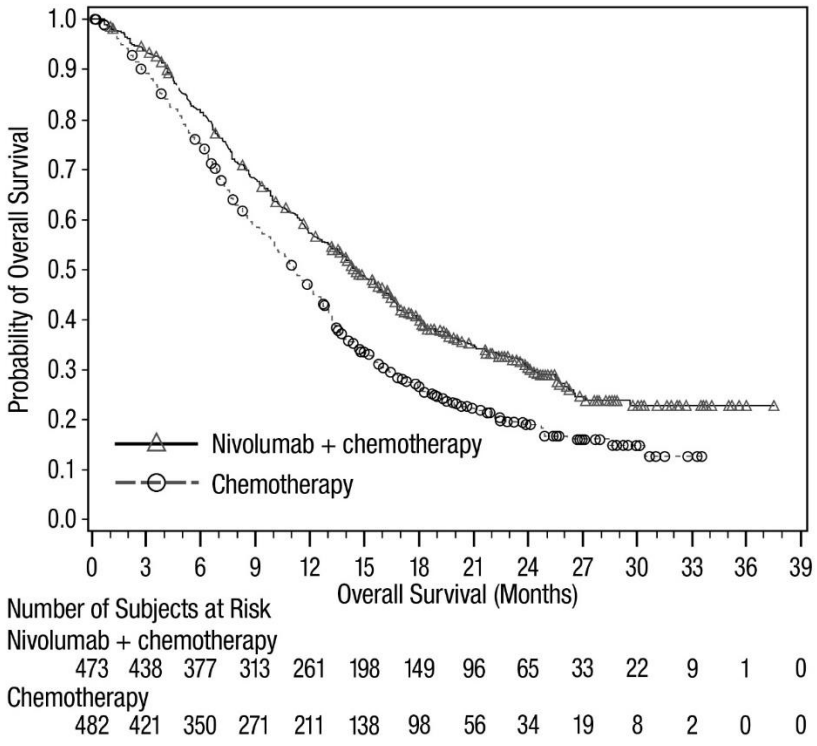


Figure 28: Kaplan-Meier Curve of Overall Survival (PD-L1 CPS ≥5) - CHECKMATE-649



First-line Treatment of Unresectable or Metastatic Urothelial Carcinoma

CHECKMATE-901 was a randomized, open-label study in adult patients with previously untreated unresectable or metastatic urothelial carcinoma (UC). Prior neoadjuvant chemotherapy or prior adjuvant platinum-based chemotherapy following radical cystectomy were permitted as long as the disease recurrence took place ≥12 months from completion of therapy. Patients who were ineligible for cisplatin and those with active CNS metastases were excluded.

Stratification factors for randomization were PD-L1 status (≥1% vs. <1% or indeterminate) and liver metastasis. Patients were randomized 1:1 to receive either:

- Intravenous nivolumab 360 mg and cisplatin 70 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle for up to 6 cycles followed by single-agent nivolumab 480 mg every 4 weeks until disease progression, unacceptable toxicity, or for up to 2 years from first dose.
- Cisplatin 70 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle for up to 6 cycles.

The median age was 65 years of age (range: 32 to 86) with 51% of patients ≥ 65 years of age and 12% of patients ≥75 years of age, 23% were Asian, 72% were White, 0.3% were Black; 77% were male. Baseline ECOG performance status was 0 (53%) or 1 (46%). At baseline, 87% of patients had metastatic UC, 20% of patients had liver metastases, and 51% had UC histologic variants. Forty-nine (16%) patients in the

nivolumab in combination with chemotherapy arm and 43 (14%) patients in the chemotherapy alone arm switched from cisplatin to carboplatin after at least one cycle of cisplatin.

The primary efficacy outcome measures were OS and PFS assessed by BICR using RECIST v1.1. The median follow-up was 33.6 months in the nivolumab in combination with chemotherapy arm and 33.5 months in the chemotherapy alone arm.

Efficacy results are presented in **Table 75** and Figure 29 and Figure 30.

Table 75: Efficacy Results - CHECKMATE-901

	Nivolumab and Cisplatin and Gemcitabine (n=304)	**Cisplatin and Gemcitabine (n=304)**
Overall Survival		
Deaths, n (%)	172 (56.6)	193 (63.5)
Median (months) (95% CI)[a]	21.7 (18.6, 26.4)	18.9 (14.7, 22.4)
Hazard ratio (95% CI)[b]	0.78 (0.63, 0.96)	
p-value[c]	0.0171	
Progression-free Survival		
Disease progression or death, n (%)	211 (69.4)	191 (62.8)
Median (months) (95% CI)[a]	7.9 (7.6, 9.5)	7.6 (6.1, 7.8)
Hazard ratio (95% CI)[b]	0.7 (0.6, 0.9)	
p-value[c]	0.0012	
Objective Response Rate[d]		
Response rate, n (%) (95% CI)	175 (57.6) (51.8, 63.2)	131 (43.1) (37.5, 48.9)
Complete response, n (%)	66 (21.7)	36 (11.8)
Partial response, n (%)	109 (35.9)	95 (31.3)
Duration of Response	n=175	n=131
Median (months) (95% CI)[a]	9.5 (7.6, 15.1)	7.3 (5.7, 8.9)

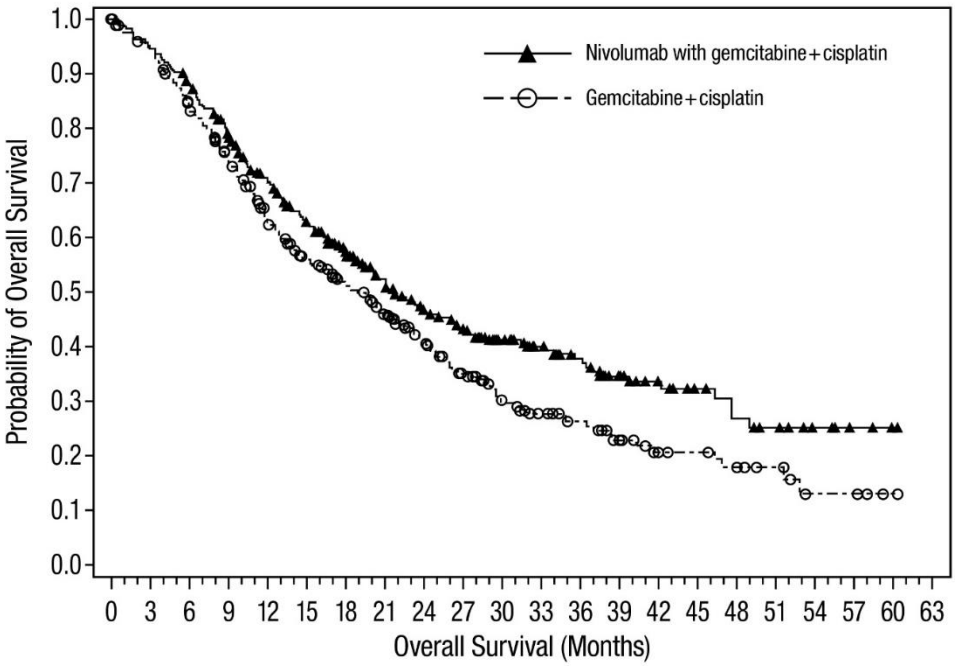
[a] Based on Kaplan-Meier Estimates

[b] Stratified Cox proportional hazard model.

[c] 2 sided p-value from stratified log-rank test.

[d] Best overall response of complete response or partial response assessed by BICR using RECIST v1.1.

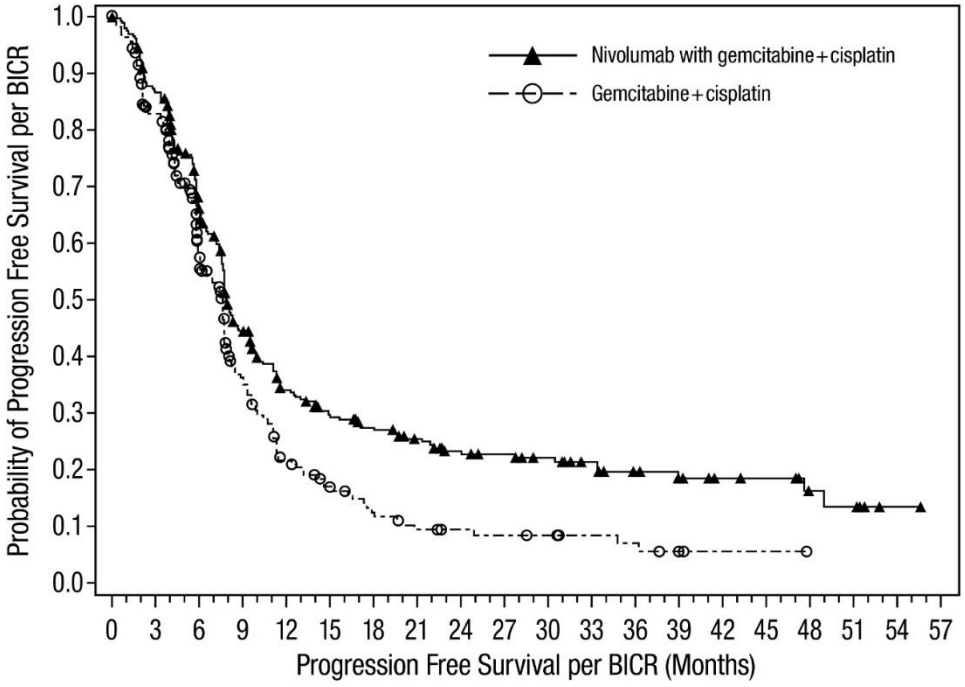
Figure 29: Overall Survival in All Randomized Patients - CHECKMATE-901



Number of Subjects at Risk

Nivolumab with gemcitabine + cisplatin	304	286	264	228	196	167	142	119	97	84	69	58	48	36	25	20	15	12	7	4	2	0
Gemcitabine + cisplatin	304	277	242	208	166	140	122	102	82	65	49	39	33	24	17	16	13	9	4	4	1	0

Figure 30: Progression-free Survival in All Randomized Patients - CHECKMATE-901



Number of Subjects at Risk

Nivolumab with gemcitabine+cisplatin	304	253	179	116	82	65	57	49	41	36	31	26	19	14	11	10	6	5	1	0
Gemcitabine+cisplatin	304	223	119	63	35	25	17	12	10	9	8	6	5	2	1	1	0	0	0	0

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

SUBCUTANEOUS FORMULATION (Opdivo SC)

General toxicology

Single-Dose toxicity

Dedicated single-dose toxicity studies with nivolumab administered subcutaneously were not conducted.

Repeat-Dose Toxicity

The effects of SC administered nivolumab (Q3W × 2) were evaluated in a repeat-dose SC toxicity study in monkeys with inclusion of local tolerance, PK, and pharmacodynamic assessments. Nivolumab with and without rHuPH20 (administered SC, 2 doses Q3W) at 50 mg/kg was well tolerated (mean sex-combined AUC[0-T] 182,000 µg•h/mL and 166,000 µg•h/mL, with and without rHuPH20, respectively). There were no local tolerance issues observed at the SC injection sites. There were no differences in exposure or pharmacodynamic endpoints to nivolumab, when administered SC, in the presence or absence of rHuPH20.

Recombinant Human Hyaluronidase

Hyaluronidases are found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase. In addition, when subcutaneous hyaluronidase (recombinant human) was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, which is 2,640 times higher than the human dose (U/kg basis), of 10,000 U once every 2 weeks, 15,000 U once every 3 weeks, or 20,000 U once every 4 weeks, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

Dedicated carcinogenicity, genotoxicity, fertility, reproduction and development toxicity studies with nivolumab administered subcutaneously were not conducted.

INTRAVENOUS FORMULATION (Opdivo)

For non-clinical toxicology information on the intravenous formulation, please refer to the separate Product Monograph for Opdivo.

17. Supporting Product Monographs

OPDIVO® (Intravenous Infusion, 10 mg nivolumab/mL), submission control 282374, Product Monograph, Bristol-Myers Squibb Canada. (JUN 28, 2024)

CABOMETYX® (20 mg, 40 mg, 60 mg cabozantinib tablets), Submission Control no. 280615, Product Monograph, Exelixis Inc., licensed to Ipsen Pharma S.A.S. (SEP 12, 2024)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]OPDIVO® SC

(op-DEE-voh)

nivolumab for subcutaneous injection 300 mg/2.5 mL (120 mg/mL), 600 mg/ 5 mL (120 mg/mL)

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **Opdivo SC**, talk to a healthcare professional.

Serious warnings and precautions box

Opdivo SC acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening.

Opdivo SC given alone can cause serious side effects in parts of your body which can lead to death. These serious side effects may include: inflammation of the lungs (pneumonitis or interstitial lung disease), inflammation of the brain (encephalitis), inflammation of the heart muscle (myocarditis), inflammation of the skin (severe skin problems), and decreased number of red blood cells (autoimmune hemolytic anemia).

It is important to tell your healthcare professional immediately if you have, or develop, any of the symptoms listed under the section "*What are possible side effects from using Opdivo SC and Serious Side Effects and What to do About Them*."

What Opdivo SC is used for:

Skin Cancer:

Opdivo® SC is a medicine used in adult patients to treat a type of skin cancer (melanoma) to help delay or prevent the cancer from coming back after it and its metastases have been completely removed by surgery.

Opdivo SC may be given to treat a type of skin cancer (melanoma) after complete removal by surgery in adult patients (treatment after surgery is called adjuvant therapy).

Opdivo SC may be given to treat a type of skin cancer that has spread or cannot be removed by surgery (advanced melanoma) in adult patients.

Opdivo SC may also be given to patients following treatment with nivolumab intravenous and ipilimumab combination therapy.

Lung Cancer:

Opdivo SC is used in adult patients to treat a type of advanced stage lung cancer (called non-small cell lung cancer) that has spread or grown after treatment with platinum containing chemotherapy.

Opdivo SC may be given in combination with chemotherapy that contains platinum and another chemotherapy medicine before you have surgery for your lung cancer (non-small cell lung cancer). Treatment prior to surgery is called neoadjuvant therapy.

Kidney Cancer:

Opdivo SC is used in adult patients to treat advanced kidney cancer (called renal cell carcinoma) that has spread or grown after treatment with medicines that block cancer blood vessel growth.

Opdivo SC may be given in adult patients with advanced kidney cancer following treatment with nivolumab intravenous and ipilimumab combination therapy.

Opdivo SC may also be given in combination with cabozantinib in adult patients with advanced kidney cancer that cannot be treated with radiation or surgery or disease that is metastatic, and who have not been treated. It is important that you also read the package leaflet for cabozantinib. If you have any questions about cabozantinib, please ask your doctor.

Head and Neck Cancer:

Opdivo SC is used in adult patients to treat advanced head and neck cancer (called squamous cell carcinoma of the head and neck) when the cancer grows or spreads on or after platinum containing chemotherapy.

Colon or Rectal Cancer:

Opdivo SC is used in adults following treatment with nivolumab intravenous and ipilimumab combination therapy, for the treatment of colon or rectal cancer that is shown by a laboratory test to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), and:

- you used the drug fluoropyrimidine in combination with oxaliplatin, or irinotecan and the cancer has spread or grown or you no longer tolerating the treatment.

Esophageal or Gastroesophageal Junction Cancer:

Esophageal cancer is cancer of the esophagus, the tube that connects your throat to your stomach. Gastroesophageal junction (GEJ) cancer is cancer of the junction between the esophagus and the stomach.

Opdivo SC is used in adult patients who have been treated with chemoradiation followed by surgery to remove the cancer.

Opdivo SC is also used in adult patients who test positive for PD-L1 and have a type of esophageal cancer called squamous cell carcinoma, which cannot be removed with surgery, and has come back or spread to other parts of the body.

Cancer of the stomach, esophagus or the junction between the stomach and esophagus (gastric, esophageal, or gastroesophageal junction cancers):

Opdivo SC may be used in combination with chemotherapy that contains fluoropyrimidine and platinum when your gastric, gastroesophageal junction or esophageal cancer:

- is a type called adenocarcinoma, and
- cannot be removed with surgery

Bladder and Urinary Tract Cancers:

Opdivo SC is used in adult patients to help prevent cancer of the urinary tract from coming back after it was removed by surgery.

Opdivo SC may be used in combination with chemotherapy medicines cisplatin and gemcitabine as your first treatment when your urinary tract cancer (urothelial carcinoma) has spread to other parts of the body (metastatic) or cannot be removed by surgery.

For the following indications Opdivo SC has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- Adults with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, following completed treatment with nivolumab intravenous + ipilimumab combination therapy, when your colon or rectal cancer:
    - has come back or spread
    - you have tried treatment with fluoropyrimidine-based therapy in combination with oxaliplatin or irinotecan.
- Adults with bladder or urinary tract cancer at high risk of recurrence when the cancer was removed by surgery and you may have received chemotherapy that contains platinum prior to surgery.

For the following indications Opdivo SC has been approved without conditions. This means it has passed Health Canada's review and can be bought and sold in Canada.

- Adults with skin cancer (advanced melanoma) when used alone or used alone following completed treatment with nivolumab intravenous + ipilimumab combination therapy.
- Adults with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
- Adults with skin cancer (melanoma) to help delay or prevent the cancer from coming back after it and its metastases have been completely removed by surgery.
- Adults with skin cancer (melanoma) after complete removal by surgery (adjuvant therapy).
- Adults with lung cancer (advanced non-small cell cancer) that has spread or grown after treatment with a platinum-based chemotherapy. Patients with certain lung cancer mutations (EGFR or ALK) should only be treated with Opdivo SC if their cancer grows or spreads during or after treatment with therapies targeting these mutations.
- Adults with lung cancer (advanced non-small cell cancer), if the tumour tests positive for "PD-L1", for patients following treatment with nivolumab intravenous and ipilimumab combination therapy.
- Adults with lung cancer (non-small cell cancer) in combination with chemotherapy before surgery.
- Adults with kidney cancer (advanced renal cell carcinoma) that has spread or grown after treatment with medicines that block vessel growth (anti-angiogenic therapies).
- Adults with kidney cancer (advanced renal cell carcinoma) when used alone following completed treatment with nivolumab intravenous + ipilimumab combination therapy.

- Adults with kidney cancer (advanced renal cell carcinoma) when used together with cabozantinib in patients who have not been treated.
- Adults with cancer of the head and neck (advanced squamous cell carcinoma) when the cancer grows or spreads on or after platinum containing chemotherapy.
- Adults with cancer of the esophagus or junction between the esophagus and the stomach [gastroesophageal junction (GEJ)] who have been treated with chemoradiation followed by surgery to remove the cancer.
- Adults with gastric, gastroesophageal junction or esophageal adenocarcinoma (stomach and gullet cancer).Adults with cancer of the esophagus (advanced squamous cell carcinoma) when used together with chemotherapy in patients who have not been treated and who have tested positive for PD-L1.
- Adults with cancer of the urinary tract (urothelial carcinoma) in combination with cisplatin and gemcitabine chemotherapies as a first treatment for cancer that cannot be removed by surgery or has spread to other parts of the body (unresectable or metastatic).

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How Opdivo SC works?

Opdivo SC contains the active substance nivolumab which helps your immune system to attack and destroy cancer cells.

Opdivo SC attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the melanoma, lung, kidney, lymphoid, head and neck, liver, colon, rectal or stomach and gullet cancer cells.

Opdivo SC may be given in combination with cabozantinib. Please refer to the package leaflet of cabozantinib in order to understand the use of this medicine. If you have questions about this medicine, please ask your doctor.

Opdivo SC may be given in combination with chemotherapy. Please refer to the package leaflets for the chemotherapy medicines in order to understand their use. If you have questions about the chemotherapy medicines given with Opdivo SC, please ask your healthcare professional.

The ingredients in Opdivo SC are:

Medicinal ingredients: nivolumab

Non-medicinal ingredients: histidine, histidine hydrochloride monohydrate, methionine, pentetic acid, polysorbate 80, recombinant human hyaluronidase PH20 (rHuPH20), sodium chloride, sucrose, and

water for injection.

Opdivo SC comes in the following dosage form:

Opdivo SC, ready-to-use solution for subcutaneous injection only, 120 mg nivolumab/mL, comes in glass vials containing 300 mg (in 2.5 mL) of nivolumab (overfill of 0.52 mL) and in glass vials containing 600 mg (in 5 mL) of nivolumab (overfill of 0.60 mL).

Do not use Opdivo SC if:

- you are allergic to nivolumab or any of the other ingredients of this medicine. Talk to your healthcare professional if you are not sure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Opdivo SC. Talk about any health conditions or problems you may have, including if you:

- **Problems with your hormone producing glands** (including the thyroid, parathyroids, pituitary, adrenal glands, and pancreas) that may affect how these glands work. Signs and symptoms that your glands are not working properly may include fatigue (extreme tiredness), weight change, headache or excessive thirst or lots of urine, decreased blood levels of calcium.
- **Diarrhea** (watery, loose or soft stools) or any symptoms of **inflammation of the intestines** (colitis), such as stomach pain and mucus or blood in stool.
- **Abnormal liver function tests**. Signs and symptoms may include eye or skin yellowing (jaundice), pain on the right side of your stomach area, or tiredness.
- **Problems with your lungs** such as breathing difficulties, or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Abnormal kidney function tests or problems with your kidneys**, such as decreased volume of urine or inflammation of the kidneys (tubulointerstitial nephritis).
- **Had an organ transplant** (such as a kidney transplant).
- **Take other medicines that make your immune system weak.** Examples of these may include steroids, such as prednisone.
- If you are pregnant or plan to become pregnant.
- If you are breast-feeding.

Other warnings you should know about:

Give yourself time after taking Opdivo SC to see how you feel before driving a vehicle or using machinery.

Tell your healthcare professional immediately if you have any of these signs or symptoms or if they get worse. **Do not try to treat your symptoms with other medicines on your own.** Your healthcare professional may:

- give you other medicines in order to prevent complications and reduce your symptoms,
- withhold the next dose of Opdivo SC,
- or, stop your treatment with Opdivo SC.

Please note that these signs and symptoms are **sometimes delayed**, and may develop weeks or months after your last dose. Before treatment, your healthcare professional will check your general health.

Check with your healthcare professional before you are given Opdivo SC if:

- you have an autoimmune disease (a condition where the body attacks its own cells);
- you have melanoma of the eye;
- have experienced side effects with another drug, such as ipilimumab;
- have been told cancer has spread to your brain;
- or, you are on a low salt diet.

Pregnancy and Breast-feeding:

- you are pregnant or plan to become pregnant. You should not become pregnant while you are getting Opdivo SC, Opdivo SC can cause harm or death to your unborn baby.
- you must use effective contraception while you are being treated with Opdivo SC and for at least 5 months after the last dose of Opdivo SC if you are a woman who could become pregnant.
- you are breast-feeding. Opdivo SC may pass into your breast milk. You and your doctor should decide if you will take Opdivo SC or breast-feed. You should not do both.

Always update your healthcare professional on your medical conditions.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Opdivo SC:

No drug-drug interaction studies have been conducted with nivolumab.

How to take Opdivo SC:

Your healthcare provider will give you Opdivo SC by injection under the skin, in the stomach area (abdomen) or in the thigh area.

Opdivo SC is injected over 3 to 5 minutes.

Your healthcare provider will decide the time between doses as well as how many treatments you will receive.

Your healthcare provider will do blood tests to check you for side effects.

If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

Usual dose:

- When Opdivo SC is given on its own, the recommended dose is either 600 mg of nivolumab every 2 weeks or 1200 mg given every 2 weeks every 4 weeks. Your healthcare professional will discuss with you and help choose the appropriate dose.

- When Opdivo SC is given on its own following nivolumab intravenous in combination with ipilimumab for the treatment of skin cancer, the recommended dose is either 600 mg of nivolumab every 2 weeks or 1200 mg given every 2 weeks every 4 weeks. Your healthcare professional will discuss with you and help choose the appropriate dose.
- When Opdivo SC is given on its own following nivolumab intravenous in combination with ipilimumab for the treatment of advanced kidney cancer, the recommended dose is either 600 mg of nivolumab every 2 weeks or 1200 mg given every 2 weeks every 4 weeks. Your healthcare professional will discuss with you and help choose the appropriate dose.
- When Opdivo SC is given in combination with cabozantinib for the treatment of advanced kidney cancer, the recommended dose of Opdivo SC is 600 mg of nivolumab every 2 weeks, or 1200 mg every 4 weeks and cabozantinib 40 mg is given once daily by mouth.
- When Opdivo SC is given in combination with chemotherapy before surgery for non-small cell lung cancer, the recommended dose of Opdivo SC is 900 mg every 3 weeks for 3 cycles only.
- When Opdivo SC is given in combination with chemotherapy for the treatment of advanced gastric, gastroesophageal junction or esophageal adenocarcinoma cancer, the recommended dose of Opdivo SC is 600 mg of nivolumab every 2 weeks or 900 mg of nivolumab every 3 weeks.
- When Opdivo SC is given in combination with chemotherapy for the treatment of metastatic esophageal cancer, the recommended dose of Opdivo is 600 mg or 1200 mg Q4W in combination with fluoropyrimidine- and platinum-based chemotherapy, until disease progression, unacceptable toxicity, or up to 24 months.
- When Opdivo SC is given in combination with cisplatin and gemcitabine chemotherapies for the treatment of unresectable or metastatic urothelial carcinoma, the recommended dose of Opdivo SC is 900 mg every 3 weeks for up to 6 cycles followed by Opdivo SC monotherapy at either 600 mg every 2 weeks or at 1,200 mg every 4 weeks, until disease progression, unacceptable toxicity, or up to 24 months.

Overdose:

If you think you, or a person you are caring for, have taken too much Opdivo SC, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

If you stop using Opdivo SC:

Stopping your treatment may stop the effect of the medicine. Do not stop treatment with Opdivo SC unless you have discussed this with your healthcare professional.

If you have any further questions about your treatment or on the use of this medicine, ask your healthcare professional.

When Opdivo SC is given in combination with chemotherapy you will first be given Opdivo SC followed by chemotherapy.

Please refer to the package leaflet of your prescribed chemotherapy in order to understand the use of these medicines. If you have questions about these medicines, please ask your healthcare professional.

When Opdivo SC is given in combination with cabozantinib, you will first be given Opdivo SC followed by cabozantinib.

Please refer to the package leaflet of cabozantinib in order to understand the use of this medicine. If you have questions about this medicine, please ask your healthcare professional.

Opdivo SC is not authorised for the use in combination concurrently with ipilimumab.

Missed dose:

It is very important for you to keep all your appointments to receive Opdivo SC. If you miss an appointment, ask your healthcare professional when to schedule your next dose.

Possible side effects from using Opdivo SC:

These are not all the possible side effects you may have when taking Opdivo SC. If you experience any side effects not listed here, tell your healthcare professional.

Very common side effects (may affect more than 1 in 10 people):

The most common side effects of Opdivo SC when used alone are:

- Feeling tired
- Skin rash, itching
- Pain in muscles, bones and joints
- Cough

Injection site reactions: Skin reactions at or near the injection site (local), including injection site reactions, may happen with Opdivo SC. Symptoms may include pain, itching, swelling or redness around site of injection.

Opdivo SC acts on your immune system and may cause redness, warmth (fever), swelling and pain (inflammation) in parts of your body. This may cause serious damage to your body and some conditions may be life-threatening. You may need treatment to reduce the inflammation and Opdivo SC may be stopped.

If you get any serious side effects with Opdivo SC when used alone (monotherapy) or in combination with chemotherapy (combination) (see table below), talk to your healthcare professional. Side effects may be very common (may affect more than 1 in 10 people), common (may affect less than 1 in 10 but more than 1 in 100 people), uncommon (may affect less than 1 in 100 but more than 1 in 1,000 people), or rare (may affect less than 1 in 1,000 people).

Serious side effects and what to do about them

Frequency/Side Effect/Symptom		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
COMMON	**Inflammation of the intestines (colitis)** *Symptoms may include:* • diarrhea (watery, loose, or soft stools) or more bowel movements than usual. Do not treat the diarrhea yourself • blood or mucous in stools, or dark, tarry, sticky stools stomach pain (abdominal pain) or tenderness		√	
COMMON	**Inflammation of the thyroid, adrenal or pituitary glands** *Symptoms may include:* • headaches that will not go away or unusual • unusual tiredness or sleepiness • weight changes (weight gain or weight loss) • changes in mood or behaviour such as less sex drive, being irritable or forgetful, or depression dizziness or fainting		√	
UNCOMMON	**Inflammation of the liver (hepatitis)** *Symptoms may include:* • extreme tiredness • yellowing of your skin (jaundice) or the whites of your eyes • severe nausea or vomiting • pain on the right side of your stomach (abdomen) bruise easily		√	
UNCOMMON	**Inflammation of the kidney (nephritis)**		√	

Frequency/Side Effect/Symptom		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	Symptoms may include: • changes in urine output (increase or decrease) • dark urine (tea-coloured) swelling of extremities			
COMMON	**Inflammation of the lung (pneumonitis)** *Symptoms may include:* • trouble breathing, shortness of breath cough (new or worsening) with or without mucus		**√**	
UNCOMMON	**Eye problems** *Symptoms may include:* • changes in eyesight • eye pain or redness blurred or blurry vision, or other vision problems		**√**	
UNCOMMON	**Blood sugar problems (diabetes or ketoacidosis)** *Symptoms may include:* • hunger or excessive thirst • need to urinate more often • increased appetite with weight loss, or loss of appetite • muscle weakness • sleepiness or drowsiness • depression • irritability feeling unwell		**√**	
COMMON*)*	**Inflammation of the skin (severe skin problems)** *Symptoms may include:* • severe skin reactions or rash • itching • skin blistering and peeling • ulcers in the mouth or other mucous membranes		**√**	

Frequency/Side Effect/Symptom		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	• raised skin lumps/bumps (skin nodules) dry skin			
UNCOMMON	**Inflammation of the brain (encephalitis)** *Symptoms may include:* • headache • fever • confusion • memory problems • sleepiness or drowsiness • seeing things that are not really there (hallucinations) • seizures (fits) stiff neck		**√**	
UNCOMMON	**Inflammation of the nerves (demyelination)** *Symptoms may include:* • muscle weakness • muscle stiffness • numbness • loss of reflexes uncoordinated movements		**√**	
UNCOMMON	**Muscle weakness (myasthenia gravis or myasthenic syndrome**) *Symptoms may include:* • difficulty walking and climbing stairs • difficulty lifting objects or raising the arms • drooping eyelids chewing or swallowing problems		**√**	
RARE	**Inflammation of the muscles (myositis), inflammation of the heart muscle (myocarditis), or breakdown of skeletal muscle (rhabdomyolysis):** *Symptoms may include:*		**√**	

Frequency/Side Effect/Symptom		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	• muscle or joint pain, stiffness, or weakness • chest pain, irregular heartbeat, or palpitations • confusion or memory problems • severe fatigue difficulty walking			
RARE	**Problems with other organs** *Symptoms may include:* • loss of nerve function or sensation of paralysis • swollen lymph nodes • numbness or tingling in hands or feet • swelling in extremities • abdominal pain, nausea or vomiting (pancreatitis) indigestion or heartburn		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

It is unlikely that you will be asked to store Opdivo SC yourself. It will be stored in the hospital or clinic where it is given to you.

Keep out of reach and sight of children.

Do not use Opdivo SC after the expiry date which is stated on the label and carton after EXP.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Store in the original package in order to protect from light.

Storage in Syringe

Once withdrawn into the syringe, Opdivo SC should be used immediately. If not used immediately, the syringe can be stored in the refrigerator at 2°C to 8°C, protected from light for up to 7 days and/or at room temperature 15°C to 25°C and room light for up to 8 hours. Discard if storage time exceeds these limits. Do not freeze.

If you want more information about Opdivo SC:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website [https://www.bms.com/ca/en], or by calling Bristol-Myers Squibb Canada at: 1-866-463-6267

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