To be sold by retail on the prescription of a 'Registered Oncologist' only.

For the use only of registered medical practitioners or a hospital or a laboratory

Nivolumab
OPDYTA®

1. GENERIC NAME

Nivolumab 10 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nivolumab is a fully human anti-PD-1 monoclonal antibody (IgG4) produced in Chinese hamster ovary cells by recombinant DNA technology.

Nivolumab is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid for intravenous infusion that may contain light (few) particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg.

Each 1 mL of concentrate contains 10 mg of nivolumab.

For the full list of excipients, see Section 7. Description

3. DOSAGE FORM AND STRENGTH

Concentrate for solution for infusion

Injection: 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL) and 240 mg/24 mL (10 mg/mL) clear to opalescent, colorless to pale-yellow solution in a single-dose vial.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

4.1.1 Non-Small Cell Lung Cancer (NSCLC)

Nivolumab as a single agent is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

Nivolumab, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by a validated test, with no EGFR or ALK genomic tumor aberrations.

Nivolumab, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

Nivolumab, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC).

4.1.2 Renal cell carcinoma (RCC)

Nivolumab as a single agent is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) after prior therapy in adults.

Nivolumab is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab.

Nivolumab, in combination with cabozantinib, is indicated for the first-line treatment of patients with advanced Renal cell carcinoma (RCC).

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

Nivolumab as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based therapy.

4.1.4 Melanoma

Nivolumab as a single agent is indicated for the treatment of patients with BRAF V600 wildtype unresectable or metastatic melanoma.

Nivolumab as a single agent is indicated for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma.

Nivolumab is indicated for the treatment of patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant settings.

Nivolumab, in combination with ipilimumab, is indicated for the treatment of adult patients with unresectable or metastatic melanoma.

4.1.5 Classical Hodgkin Lymphoma (cHL)

Nivolumab is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:

- autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- 3 or more lines of systemic therapy that includes autologous HSCT

4.1.6 Urothelial Carcinoma (UC)

Nivolumab is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC (see 5.2.1 Clinical Trial Information).

Nivolumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

4.1.7 Colorectal Cancer (CRC)

Nivolumab as montherapy is indicated for the treatment of adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Nivolumab, in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).

4.1.8 Esophageal Squamous Cell Carcinoma (ESCC)

Nivolumab is indicated for the treatment of unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

Nivolumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

4.1.9 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma (GC, GEJC or EAC)

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

4.1.10 Adjuvant treatment of Resected Esophageal or Gastroesophageal Junction Cancer (EC or GEJC)

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

4.1.11 Hepatocellular Carcinoma

Nivolumab, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC).

4.1.12 Malignant Pleural Mesothelioma

Nivolumab, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresetable malignant pleural mesothelioma.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

4.2.1 Recommended dosage

The recommended doses of nivolumab as a single agent are presented in Table 1.

Table 1: Recommended doses for nivolumab as monotherapy (*NSCLC, RCC, SCCHN, melanoma, cHL, UC, Adj UC, CRC, ESCC, EC/GEJC)*

<table>
<tr><th>Indication^</th><th>Recommended Nivolumab Dosage</th><th>Duration of Therapy</th></tr>
<tr><td>Locally advanced or metastatic squamous non-small cell lung cancer</td><td rowspan="9">3 mg/kg every 2 weeks (30-minute intravenous infusion)
or
240 mg every 2 weeks (30-minute intravenous infusion)
or
480 mg every 4 weeks (30-minute intravenous infusion)</td><td rowspan="9">Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated.</td></tr>
<tr><td>Advanced renal cell carcinoma</td></tr>
<tr><td>Recurrent or metastatic squamous cell carcinoma of the head and neck</td></tr>
<tr><td>Unresectable or metastatic melanoma</td></tr>
<tr><td>Relapsed/refractory classical Hodgkin lymphoma</td></tr>
<tr><td>Unresectable or metastatic urothelial carcinoma</td></tr>
<tr><td>Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer</td></tr>
<tr><td>Esophageal Squamous Cell Carcinoma</td></tr>
<tr><td>Adjuvant treatment of melanoma</td><td rowspan="2">3 mg/kg every 2 weeks (30-minute intravenous infusion)
or</td><td rowspan="2">Treatment should be continued as long as clinical benefit is observed or until</td></tr>
<tr><td>Adjuvant treatment of urothelial carcinoma (UC)</td></tr>
</table>

Adjuvant treatment of resected esophageal or gastro- esophageal junction cancer	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	treatment is no longer tolerated. For adjuvant treatment, the maximum duration of nivolumab is 1 year.

^ As per monotherapy indications in Section 4.1 Therapeutic Indications.

Please see section 8.4 Storage and handling instructions regarding limitation of total infusion volume with the 240-mg or 480-mg dosage.

The recommended doses of nivolumab in combination with other therapeutic agents are presented in Table 2. Refer to the respective Product Information for each therapeutic agent administered in combination with nivolumab for the recommended dose information, as appropriate.

Table 2: Recommended Doses of Nivolumab in Combination with Other Therapeutic Agents

Indication^	**Recommended Nivolumab Dosage**	**Duration of Therapy**
Metastatic non-small cell lung cancer expressing PD-L1	3 mg/kg every 2 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenousinfusion)	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
Metastatic or recurrent non-small cell lung cancer	360 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) and platinum chemotherapy every 3 weeks	After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab administered as an intravenous infusion every 3 weeks in combination with 1 mg/kg ipilimumab every 6 weeks until disease progression, is no longer tolerated, or up to 2 years in patients without disease progression.
Neoadjuvant treatment of resectable non-small cell lung	360 mg every 3 weeks with platinum-doublet chemotherapy (30-minute intravenous infusion)	Every 3 weeks for 3 cycles
Unresectable or metastatic melanoma	1 mg/kg every 3 weeks (30-minute OR 60-minute intravenous infusion) with ipilimumab 3 mg/kg (30-minute intravenous infusion)	In combination with ipilimumab for a maximum of 4 doses

Indication^	Recommended Nivolumab Dosage	Duration of Therapy
	3 mg/kg every 2 weeks (30-minute or 60-minute intravenous infusion)* **OR** 240 mg every 2 weeks (30-minute or 60-minute intravenous infusion)* **OR** 480 mg every 4 weeks (30-minute or 60-minute intravenous infusion)*	Followed by the single-agent phase. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.
Advanced renal cell carcinoma	3 mg/kg every 3 weeks (30-minute intravenous infusion) Administer nivolumab in combination with ipilimumab 1 mg/kg (30-minute intravenous infusion)	In combination with ipilimumab for 4 doses
	3 mg/kg every 2 weeks* (30-minute intravenous infusion) or 240 mg every 2 weeks* (30-minute intravenous infusion) or 480 mg every 4 weeks* (30-minute intravenous infusion)	After completing 4 doses of combination therapy with Ipilimumab, administer as single agent as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion) Administer nivolumab in combination with cabozantinib 40 mg orally once daily	Nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Cabozantinib should be continued until disease progression or unacceptable toxicity.
Gastric cancer, Gastro-esophageal junction cancer, or Esophageal adenocarcinoma	360 mg every 3 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks or 240 mg every 2 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks	Treatment should be continued until disease progression, is no longer tolerated or up to 2 years in patients without disease progression.

Indication^	Recommended Nivolumab Dosage	Duration of Therapy
Esophageal squamous cell carcinoma	240 mg every 2 weeks or 480 mg every 4 weeks (30-minute intravenous infusion) Administer nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy	Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.
Hepatocellular carcinoma	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg (30-minute intravenous infusion)	In combination with ipilimumab for a maximum of 4 doses
	240 mg every 2 weeks* (30-minute intravenous infusion) Or 480 mg every 4 weeks* (30-minute intravenous infusion) Or 3 mg/kg every 2 weeks* (30-minute intravenous infusion) Or 6 mg/kg every 4 weeks* (30-minute intravenous infusion)	The first dose of nivolumab monotherapy should be administered 3 weeks following the last dose of the combination of nivolumab and ipilimumab. Treatment is continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression
Microsatellite instability-high (MSI--H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	**Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more:** 240 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg (30-minute intravenous infusion) **Pediatric patients age 12 years and older and weighing less than 40 kg:** 3 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg (30-minute intravenous infusion)	In combination with ipilimumab for a maximum of 4 doses
	Adult patients and pediatric patients age 12 years and older and weighing at least 40 kg or more: 240 mg every 2 weeks* (30-minute intravenous infusion) Or 480 mg every 4 weeks* (30-minute intravenous infusion) Or 3 mg/kg every 2 weeks* (30-minute intravenous infusion)	After completing a maximum of 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity, or up to 2 years

Indication^	Recommended Nivolumab Dosage	Duration of Therapy
	Or 6 mg/kg every 4 weeks* (30-minute intravenous infusion) **Pediatric patients age 12 years and older and weighing less than 40 kg:** 3 mg/kg every 2 weeks* (30-minute intravenous infusion)	
Malignant pleural mesothelioma	360 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) or 3 mg/kg every 2 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion)	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression

*Following the last dose of the combination of nivolumab and ipilimumab, the first dose of nivolumab monotherapy should be administered after 3 weeks when using 3 mg/kg or 6 mg/kg or 240 mg or 6 weeks when using 480 mg

^ As per combination indications in Section 4.1 Therapeutic Indications.

For all combination therapy

When administered in combination with ipilimumab, with ipilimumab and/or chemotherapy, or with other therapeutic agents, nivolumab should be given first followed by ipilimumab (if applicable) and then chemotherapy or other therapeutic agents on the same day (see 8.4 Storage and handling instructions).

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 3. Detailed guidelines for the management of immune-related adverse reactions are described in 4.4.2 Product-specific warnings and precautions.

Table 3: Recommended treatment modifications for nivolumab or nivolumab in combination with ipilimumab

Immune-related adverse reaction	**Severity**	**Treatment modification**
Immune-related pneumonitis	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.
Immune-related colitis	Grade 2 diarrhea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete.
	Grade 3 diarrhea or colitis - nivolumab monotherapy - nivolumab+ipilimumab	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete. Permanently discontinue treatment.
	Grade 4 diarrhea or colitis	Permanently discontinue treatment.
Immune-related hepatitis NOTE: for RCC patients treated with **nivolumab in combination with cabozantinib** withliver 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.
	HCC patients with elevated AST/ALT at baseline: • AST/ALT >1 to 3 × ULN at baseline and on-treatment increases to >5 to 10 ×ULN • AST/ALT >3 to 5 ×ULN at baseline and on-treatment increases to>8 to 10 ×ULN	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids is complete.
	AST/ALT on-treatment increases to >10 ×ULN (regardless of	Permanently discontinue treatment.

Immune-related adverse reaction	**Severity**	**Treatment modification**
	baseline) or Grade 3 or 4 elevation in total bilirubin	
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete.
	Grade 4 creatinine elevation	Permanently discontinue treatment.
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present.
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment.
Immune-related skin adverse reactions	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.
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete. Retreatment may be considered after recovery.

Immune-related adverse reaction	Severity	Treatment modification
	Grade 3 or 4 myocarditis	Permanently discontinue treatment.
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s) until symptoms resolve or improve and management with corticosteroids is complete.
	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.

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

Nivolumab as monotherapy or nivolumab in combination with other therapeutic agents should be permanently discontinued for:

- Grade 4 or recurrent Grade 3 adverse reactions;
- Persistent Grade 2 or 3 adverse reactions despite management.

When nivolumab is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld.

Nivolumab in combination with cabozantinib

For RCC patients treated with nivolumab in combination with cabozantinib, see the product information regarding treatment modifications of cabozantinib.

For liver enzyme elevations, in patients with RCC being treated with nivolumab in combination with cabozantinib:

- If ALT or AST >3 times ULN but ≤10 times ULN without concurrent total bilirubin ≥2 times ULN, both nivolumab and cabozantinib should be withheld until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or rechallenge with both medicines after recovery may be considered. If rechallenging with cabozantinib, refer to cabozantinib product information.

- If ALT or AST >10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN, both nivolumab and cabozantinib should be permanently discontinued and corticosteroid therapy may be considered.

Nivolumab in combination with chemotherapy

For GC, GEJC ESCC EAC or NSCLC patients treated with nivolumab in combination with chemotherapy, refer to the product information for the other combination therapy agents regarding dosing. If any agents are withheld, the other agents may be continued. If dosing is resumed after a delay, either the combination treatment, or nivolumab monotherapy or chemotherapy alone, could be resumed based on the evaluation of the individual patient.

4.2.2 Renal impairment

Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see 5.3.1 Special populations).

4.2.3 Hepatic impairment

Based on the population PK results, no dose adjustment is required in patients with mild or moderate hepatic impairment (see 5.3.1 Special populations).

4.2.4 Geriatric

No dose adjustment is required for elderly patients (≥65 years) (see 4.4.5 Geriatric use and 5.3.1 Special populations).

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

When nivolumab is administered in combination with ipilimumab, refer to the product information for ipilimumab prior to initiation of treatment. Both agents are associated with immune-related adverse reactions. In clinical trials, immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications.

When an immune-related adverse reaction is suspected, alternate etiology should be ruled out and use of immunosuppressive therapy should be considered. Patients should be monitored continuously as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of nivolumab therapy. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use. Nivolumab or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

4.4.1 Drug-class–specific warnings and precautions

Increased mortality in patients with multiple myeloma [not an approved indication] when a PD-1 blocking antibody 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 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.

4.4.2 Product-specific warnings and precautions

Immune-related pneumonitis

Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1 Clinical experience). Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g, focal ground glass opacities, patchy filtrates), dyspnea, and hypoxia. Infectious and disease-related etiologies should be ruled out.

For Grade 3 or 4 pneumonitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

For Grade 2 (symptomatic) pneumonitis, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents, and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related colitis

Severe diarrhea or colitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1 Clinical experience). Patients should be monitored for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Infectious and disease-related etiologies should be ruled out. 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.

For Grade 4 diarrhea or colitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Grade 3 diarrhea observed with nivolumab in combination with ipilimumab also requires permanent discontinuation of treatment and initiation of corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Nivolumab monotherapy should be withheld for Grade 3 diarrhea or colitis, and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab monotherapy may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab monotherapy must be permanently discontinued.

For Grade 2 diarrhea or colitis, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent diarrhea or colitis should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

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-related hepatitis

Severe hepatitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1. Clinical experience). Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related etiologies should be ruled out.

For Grade 3 or 4 transaminase or total bilirubin elevation, nivolumab monotherapy or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 transaminase or total bilirubin elevation, nivolumab monotherapy or nivolumab in combination with ipilimumab should be withheld. Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab monotherapy or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and nivolumab monotherapy or nivolumab in combination with ipilimumab must be permanently discontinued.

Management of transaminase elevation in patients with HCC

In patients with HCC, nivolumab monotherapy should be withheld or permanently discontinued based on the following criteria, and corticosteroids initiated at a dose of 1 to 2 mg/kg methylprednisolone equivalents.

- For transaminase levels >1 to 3 times ULN at baseline and on-treatment increases to >5 to 10 times ULN, nivolumab should be withheld.
- For transaminase levels >3 to 5 times ULN at baseline and on-treatment increases to >8 to 10 times ULN, nivolumab should be withheld.

- Regardless of baseline transaminase levels, nivolumab must be permanently discontinued for on-treatment transaminase increases to >10 times ULN or Grade 3 or 4 total bilirubin increases.

Use of nivolumab in combination with cabozantinib for first-line treatment of patients with RCC

Nivolumab in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to nivolumab alone and cabozantinib alone. Liver enzymes should be monitored before initiation of and periodically throughout treatment. Medical management guidelines for both medicines should be followed (refer to the product information for cabozantinib).

Immune-related nephritis and renal dysfunction

Severe nephritis and renal dysfunction have been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1 Clinical experience). Patients should be monitored for signs and symptoms of nephritis and renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related etiologies should be ruled out.

For Grade 4 serum creatinine elevation, nivolumab monotherapy or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 or 3 serum creatinine elevation, nivolumab monotherapy or nivolumab in combination with ipilimumab should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab monotherapy or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and nivolumab monotherapy or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related endocrinopathies

Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), diabetes mellitus, and diabetic ketoacidosis have been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1 Clinical experience). Patients should be monitored for clinical signs and symptoms of endocrinopathies and for changes in thyroid function. Patients may present with fatigue, 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. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.

For symptomatic hypothyroidism, nivolumab or nivolumab in combination with ipilimumab should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, nivolumab or nivolumab in combination with ipilimumab should be withheld and antithyroid medication should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day

methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilized. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening (Grade 4) hyperthyroidism or hypothyroidism.

For symptomatic Grade 2 adrenal insufficiency, nivolumab or nivolumab in combination with ipilimumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilized.

For symptomatic Grade 2 or 3 hypophysitis, nivolumab or nivolumab in combination with ipilimumab should be withheld, and hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the pituitary gland is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening (Grade 4) hypophysitis. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilized.

For symptomatic diabetes, nivolumab or nivolumab in combination with ipilimumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilized. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening (Grade 4) diabetes.

Immune-related skin adverse reactions

Severe rash has been observed with nivolumab. The frequency of rash is higher when nivolumab is administered in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1 Clinical experience). Nivolumab or nivolumab in combination with ipilimumab should be withheld for Grade 3 rash and discontinued for Grade 4 rash. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

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, nivolumab or nivolumab in combination with ipilimumab 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 nivolumab or nivolumab in combination with ipilimumab is recommended.

Other immune-related adverse reactions

Other clinically significant immune-related adverse reactions have been observed. Across clinical trials of nivolumab or nivolumab in combination with ipilimumab investigating various doses and tumor types, the following immune-related adverse reactions were reported in less than 1% of patients: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens

nerve paresis), Guillain-Barré syndrome, myasthenia gravis, myasthenic syndrome, aseptic meningitis, gastritis, sarcoidosis, duodenitis, encephalitis, myositis, myocarditis and rhabdomyolysis (see 4.8.1 Undesirable effects, Clinical experience). Cases of Vogt-Koyanagi-Harada syndrome have been reported during post approval use of nivolumab or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.2. Postmarketing experience).

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. 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. Troponin is a sensitive but not diagnostic marker of myocarditis. 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, 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, nivolumab or nivolumab in combination with ipilimumab should be withheld. For grade 3 myocarditis, nivolumab or nivolumab in combination with ipilimumab therapy should be permanently discontinued (see section 4.2.1 Recommended dosage, Table 1). Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1/PD-L1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. (see 4.8 Undesirable effects, 4.8.2 Post marketing experience).

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 PD-1/PD-L1 inhibitors. (see 4.8 Undesirable effects, 4.8.2 Post marketing experience).

Complications of allogeneic hematopoietic stem cell transplant (HSCT) after treatment with PD-1/PD-L1 inhibitors

PD-1/PD-L1 inhibitors including nivolumab, administered before allogeneic hematopoietic stem cell transplant (HSCT), may be associated with an increased risk of transplant-related complications, including GVHD. Fatal cases have been reported in clinical studies. Patients should be monitored closely for early evidence of transplant-related complications.

Infusion reactions

Severe infusion reactions have been reported in clinical trials of nivolumab or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1. Clinical experience). In case of a

severe or life-threatening infusion reaction, the nivolumab or nivolumab in combination with ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab or nivolumab in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Use in Specific populations

In all registrational studies of nivolumab or nivolumab in combination with other therapeutic agents, patients with autoimmune disease, active brain metastases (or leptomeningeal metastases), Eastern Cooperative Oncology Group (ECOG) performance score ≥2 or Karnofsky performance score (KPS) <70%, and patients receiving systemic immunosuppressants prior to study entry were excluded. Specific populations excluded from clinical studies by tumor type are listed below (See 4.5 Drug interaction and 5.2.1 Clinical Trial Information):

NSCLC: patients with symptomatic interstitial lung disease

Previously untreated NSCLC*:* patients with sensitizing EGFR mutations or ALK translocations

Resectable NSCLC: patients who received prior anti-cancer treatment for resectable disease, patients with known sensitizing EGFR mutations or ALK translocations

Malignant Pleural Mesothelioma: patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, or interstitial lung disease.

RCC: patients with any history of or concurrent brain metastases

SCCHN: patients with carcinoma of the nasopharynx or salivary gland as the primary tumor site

Melanoma: patients with ocular/uveal melanoma

Adjuvant treatment of melanoma: patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomization) and patients treated with prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)

cHL: patients with symptomatic interstitial lung disease

Adjuvant treatment of UC: patients with a baseline ECOG performance score ≥2 (except patients with a baseline ECOG performance score of 2 who have not received cisplatin based neoadjuvant chemotherapy and are considered ineligible for cisplatin adjuvant chemotherapy); evidence of disease after surgery.

GC or GEJC: patients with diverticulitis, or symptomatic gastrointestinal ulcerative disease or ascites requiring treatment

ESCC: patients with apparent tumor invasion on organs located adjacent to the esophageal disease (eg. the aorta or respiratory tract)

GC, GEJC, or EAC: patients with known human epidermal growth factor receptor 2 (HER2) positive cancer or untreated CNS metastases.

EC or GEJC: Patients who did not receive concurrent chemoradiotherapy (CRT) prior to surgery, without evidence of residual pathologic disease, or with stage IV resectable disease.

Unresectable HCC: Child Pugh score other than A at screening; a history of hepatic encephalopathy (within 12 months of randomization), clinically significant ascites, infection with HIV, or active co infection with HBV and HCV or HBV and HDV.

4.4.3 Pregnancy and lactation

Refer to section 4.6 -Use in Special Populations (Such as Pregnant Women, Lactating women.)

4.4.4 Females and Males of Reproductive Potential

4.4.5 Pediatric use

The safety and effectiveness of nivolumab have not been established in pediatric patients.

4.4.6 Geriatric use

No overall differences in safety or efficacy were reported between elderly (≥65 years) and younger patients (<65 years).

4.4.7 Renal impairment

The safety and efficacy of nivolumab have not been studied in patients with severe renal impairment (see 5.3.1 Special Populations, Renal impairment).

4.4.8 Hepatic impairment

The safety and efficacy of nivolumab have not been studied in patients with severe hepatic impairment. Nivolumab must be administered with caution in patients with severe (total bilirubin >3 times ULN and any AST) hepatic impairment (see 5.3.1 Special Populations, Hepatic impairment).

4.5 DRUG INTERACTIONS

Nivolumab is a human monoclonal antibody, as such pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by coadministered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab.

<u>Other forms of interaction</u>

Systemic immunosuppression

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab 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.

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN)

There are no data on the use of nivolumab in pregnant women. Studies in animals have shown embryofetal toxicity (see 6 Nonclinical properties). Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Women should be advised to use effective contraception for at least 5 months following the last dose of nivolumab.

It is unknown whether nivolumab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue from nivolumab therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND TO USE MACHINES

Based on its pharmacodynamic properties, nivolumab is unlikely to affect the ability to drive and use machines. Because of potential adverse reactions such as fatigue (see 4.8 Undesirable effects, 4.8.1 Clinical experience), patients should be advised to use caution when driving or operating machinery until they are certain that nivolumab does not adversely affect them.

4.8 UNDESIRABLE EFFECTS

4.8.1 CLINICAL EXPERIENCE

Nivolumab or nivolumab in combination with ipilimumab is associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of nivolumab (see "Description of selected adverse reactions" below).

Nivolumab monotherapy

In the pooled dataset of nivolumab as monotherapy across tumor types (n=4494), the most frequent adverse reactions (≥10%) were fatigue (43%), musculoskeletal pain (30%), diarrhea (25%), nausea (23%), rash (23%), cough (22%), pruritus (19%), decreased appetite (18%), constipation (17%), abdominal pain (17%), dyspnea (17%), upper respiratory tract infection (15%), vomiting (14%), pyrexia (14%), arthralgia (13%), headache (12%), edema (11%).

Adverse reaction frequencies in the paragraph above and in Table 4 below are based on all-causality adverse event incidence rates.

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n=4494) are presented in Table 4. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 4: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Infections and infestations	
Very common	upper respiratory tract infection
Common	pneumonia[a], bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Uncommon	eosinophilia
Immune system disorders	
Common	infusion related reaction, hypersensitivity (including anaphylactic reaction)
Uncommon	sarcoidosis
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism
Uncommon	adrenal insufficiency, hypopituitarism, hypophysitis, diabetes mellitus, diabetic ketoacidosis, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration
Uncommon	metabolic acidosis
Nervous system disorders	
Very common	Headache
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a]
Eye disorders	
Common	blurred vision, dry eye
Uncommon	uveitis
Cardiac disorders	
Common	tachycardia, atrial fibrillation
Uncommon	arrhythmia (including ventricular arrhythmia), pericardial disorders, myocarditis[a,b]

Vascular disorders	
Common	Hypertension
Uncommon	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Very common	cough, dyspnoea[a]
Common	pneumonitis[a], pleural effusion
Uncommon	lung infiltration
Gastrointestinal disorders	
Very common	diarrhea, nausea, constipation, abdominal pain, vomiting
Common	colitis[a], stomatitis, dry mouth, gastritis
Uncommon	pancreatitis
Rare	duodenal ulcer
Hepatobiliary disorders	
Uncommon	hepatitis, cholestasis
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus
Common	vitiligo, dry skin, erythema, alopecia, urticaria
Uncommon	erythema multiforme, psoriasis, rosacea
Rare	toxic epidermal necrolysis [a,b], Stevens-Johnson-syndrome[a]
Musculoskeletal and connective tissue disorders	
Very Common	musculoskeletal pain,[d] arthralgia
Common	Arthritis
Uncommon	polymyalgia rheumatica
Rare	myopathy, myositis (including polymyositis),[a] rhabdomyolysis,[a,b] Sjogren's syndrome
Renal and urinary disorders	
Common	renal failure (including acute kidney injury) [a]
Rare	tubulointerstitial nephritis
General disorders and administration site conditions	
Very common	Fatigue, pyrexia, oedema (including peripheral oedema)
Common	chest pain, pain
Investigations	
Common	weight decreased

[a] Fatal cases have been reported in completed or ongoing clinical studies.

[b] Including those reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

[c] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalized, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption.

[d] 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.

The overall safety profile of nivolumab 3 mg/kg for the adjuvant treatment of melanoma (n = 452) was generally consistent with that established across tumor types for nivolumab monotherapy.

The overall safety profile of nivolumab 3 mg/kg for the treatment of colorectal cancer (n=74) was generally consistent with that established across tumor types for nivolumab monotherapy.

Nivolumab in combination with ipilimumab

RCC

In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n = 547), with a minimum follow-up of 17.5 months, the most frequent adverse reactions (≥ 10%) were fatigue (48%), rash (34%), pruritus (28%), diarrhea (27%), nausea (20%), hypothyroidism (16%), musculoskeletal pain (15%), arthralgia (14%), decreased appetite (14%), pyrexia (14%), vomiting (11%), and hyperthyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Among the patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in CA209214, 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 a minimum of 60 months follow-up from study CA209214 in RCC, no new safety signals were identified.

NSCLC

In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC (n=576), the most frequent adverse reactions (≥10%) were rash (28%), fatigue (24%), diarrhea (17%), pruritus (14%), decreased appetite (13%), hypothyroidism (13%), and nausea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Median duration of therapy was 4.19 months (95% CI 3.71, 5.09) for nivolumab in combination with ipilimumab and 2.63 months (95% CI 2.56, 2.79) for chemotherapy.

HCC

In the dataset of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in unresectable HCC (n=332), the most frequent adverse reactions (≥20%) were rash (36%), pruritus (34%), fatigue (33%), and diarrhea (22%). Incidences of Grade 3-5 adverse reactions were 68% for nivolumab in combination with ipilimumab followed by nivolumab alone and median duration of therapy was 4.7 months.

Melanoma

In the pooled dataset of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n=448; CA209067 [combination group], CA209069, and CA209004 [cohort 8]), the most frequent adverse reactions (≥10%) were rash (52%), fatigue (46%), diarrhea (43%), pruritus (36%), nausea (26%), pyrexia (19%), decreased appetite (16%), hypothyroidism (16%), colitis (15%), vomiting (14%), abdominal pain (13%), arthralgia (13%), headache (11%), and dyspnea (10%).166 The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Among the 313 patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in CA209067, 154 (49%) 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, 47 (32%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase.

CRC

In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the first-line treatment of dMMR or MSI-H CRC (n=200), the most frequent adverse reactions (≥10%) were fatigue (40%), diarrhea (34%), pruritus (27%), abdominal pain (25%), and nausea (20%), rash (19%), arthralgia (18%), hypothyroidism (16%), decreased appetite (16%), musculoskeletal pain (15%), myalgia (15%), constipation (14%), upper respiratory tract infection (13%), headache (12%), pyrexia (11%), adrenal insufficiency (10%), and vomiting (10%). Incidences of Grade 3-5 adverse reactions were 49% for nivolumab in combination with ipilimumab followed by nivolumab alone and median duration of therapy was 13.5 months.

Malignant Pleural Mesothelioma

In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma (n=300), the most frequent adverse reactions (≥10%) were rash (25%), fatigue (22%), diarrhea (21%), pruritus (16%), hypothyroidism (11%), and nausea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Median duration of therapy was 5.55 months (range: 0-26.2 months) for nivolumab in combination with ipilimumab and 3.48 months (range: 0-4.7 months) for chemotherapy.

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with nivolumab in combination with ipilimumab (n=448 for melanoma regimen, n=547 for RCC regimen,n=576 for NSCLC regimen,n=332 for unresectable HCC, n=300 for malignant pleural mesothelioma and n=200 for the first-line treatment of unresectable or metastatic CRC)) are presented in Table 5 and 6. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 5: Adverse reactions with nivolumab in combination with ipilimumab

	Nivolumab 3 mg/kg in combination with Ipilimumab 1 mg/kg in RCC**	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC***	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*
Infections and infestations			
Common	pneumonia, upper respiratory tract infection		pneumonia, upper respiratory tract infection
Uncommon	bronchitis, aseptic meningitis	pneumonia, bronchitis, upper respiratory tract infection	bronchitis
Blood and lymphatic system disorders			
Common			eosinophilia
Uncommon	eosinophilia	eosinophilia	
Immune system disorders			
Common	infusion-related reaction, hypersensitivity	infusion-related reaction	infusion-related reaction, hypersensitivity
Uncommon		hypersensitivity	sarcoidosis
Endocrine disorders			
Very common	hypothyroidism, hyperthyroidism	hypothyroidism	hypothyroidism
Common	adrenal insufficiency, hypophysitis, thyroiditis, diabetes mellitus	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, diabetes mellitus	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis
Uncommon	diabetic ketoacidosis, hypopituitarism	Thyroiditis	diabetic ketoacidosis, diabetes mellitus
Metabolism and nutrition disorders			
Very common	decreased appetite	decreased appetite	decreased appetite
Common	Dehydration	Dehydration	dehydration
Uncommon	metabolic acidosis	Hyperglycaemia	
Hepatobiliary disorders			
Common	Hepatitis	Hepatitis	hepatitis
Nervous system disorders			

Table 5: Adverse reactions with nivolumab in combination with ipilimumab

	Nivolumab 3 mg/kg in combination with Ipilimumab 1 mg/kg in RCC**	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC***	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*
Very common			headache
Common	headache, peripheral neuropathy, dizziness	Headache	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis	peripheral neuropathy, dizziness, encephalitis, neuropathy (including facial and abducens nerve paresis), myasthenia gravis	Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis
Eye disorders			
Common	blurred vision		uveitis, blurred vision
Uncommon	Uveitis	uveitis, blurred vision	
Cardiac disorders			
Common	Tachycardia		tachycardia
Uncommon	arrhythmia (including ventricular arrhythmia), myocarditis	atrial fibrillation, myocarditis[a,]	arrhythmia (including ventricular arrhythmia)[a], atrial fibrillation, myocarditis[a,c]
Vascular disorders			
Common	Hypertension		hypertension
Uncommon		Hypertension	
Respiratory, thoracic and mediastinal disorders			
Very common			dyspnoea
Common	pneumonitis, dyspnoea, pleural effusion, cough	Pneumonitis[a,], dyspnoea, cough	pneumonitis[a], pulmonary embolism[a], cough
Uncommon		pleural effusion	pleural effusion
Gastrointestinal disorders			

Table 5: Adverse reactions with nivolumab in combination with ipilimumab

	Nivolumab 3 mg/kg in combination with Ipilimumab 1 mg/kg in RCC**	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC***	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*
Very common	diarrhea, vomiting, nausea	diarrhea, nausea	colitis[a], diarrhea, vomiting, nausea, abdominal pain
Common	colitis, stomatitis, pancreatitis, abdominal pain, constipation, dry mouth	colitis, vomiting, stomatitis, abdominal pain,constipation, dry mouth, pancreatitis	stomatitis, pancreatitis, constipation, dry mouth
Uncommon	Gastritis	Gastritis	intestinal perforation[a], gastritis, duodenitis
Skin and subcutaneous tissue disorder			
Very common	rash[b], pruritus	rash[b], pruritus	rash[b], pruritus
Common	dry skin, erythema, urticaria	dry skin, erythema	vitiligo, dry skin, erythema, alopecia, urticaria
Uncommon	Stevens-Johnson syndrome, vitiligo, erythema multiforme, alopecia, psoriasis	urticaria, erythema multiforme, vitiligo, alopecia	psoriasis
Rare			toxic epidermal necrolysis[a,c], Stevens-Johnson syndrome[c]
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[d], arthralgia		arthralgia
Common	arthritis, muscle spasms, muscular weakness	musculoskeletal pain[d], arthralgia, arthritis	musculoskeletal pain[d]
Uncommon	polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis	Polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis	spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis)[a,c], rhabdomyolysis[a,c]
Renal and urinary disorders			

Table 5: Adverse reactions with nivolumab in combination with ipilimumab

	Nivolumab 3 mg/kg in combination with Ipilimumab 1 mg/kg in RCC**	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC***	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*
Common	renal failure (including acute kidney injury)	renal failure (including acute kidney injury)	renal failure (including acute kidney injury)[a]
Uncommon	tubulointerstitial nephritis	tubulointerstitial nephritis	tubulointerstitial nephritis
General disorders and administration site conditions			
Very common	fatigue, pyrexia	Fatigue	fatigue, pyrexia
Common	oedema (including peripheral oedema), pain, chest pain, chills	pyrexia, oedema (including peripheral oedema)	oedema (including peripheral oedema), pain
Uncommon		chest pain	chest pain
Investigations			
Common	weight decreased	weight decreased	weight decreased

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

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

*** Nivolumab every 2 weeks in combination with ipilimumab every 6 weeks in NSCLC.

[a] Fatal cases have been reported in completed or ongoing clinical studies.

[b] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.

[c] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

[d] 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.

Table 6: Adverse reactions with nivolumab in combination with ipilimumab

	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for the treatment of unresectable HCC	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the first-line treatment of unresectable or metastatic CRC	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma
Infections and infestations			
Very common		upper respiratory tract infection	
Common		pneumonia, bronchitis	
Blood and lymphatic			
Common		eosinophilia	
Immune system disorders			
Common		infusion-related reaction, hypersensitivity	infusion-related reaction, hypersensitivity
Endocrine disorders			
Very common	hyperthyroidism, hypothyroidism	hypothyroidism, adrenal insufficiency	hypothyroidism
Common	hyperglycemia, adrenal insufficiency	hyperthyroidism, hypophysitis, diabetes mellitus, thyroiditis	hyperthyroidism, adrenal insufficiency, hypophysitis, hypopituitarism
Uncommon		hypopituitarism	thyroiditis
Metabolism and nutrition disorders			
Very common	decreased appetite	decreased appetite, hyperglycemia	
Common			decreased appetite
Hepatobiliary disorders			
Common		hepatitis	hepatitis
Nervous system disorders			
Very common		headache	
Common		dizziness, peripheral neuropathy, polyneuropathy	
Uncommon		immune-mediated encephalitis, myasthenia gravis	encephalitis
Cardiac disorders			
Uncommon		myocarditis[a]	myocarditis

	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for the treatment of unresectable HCC	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the first-line treatment of unresectable or metastatic CRC	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma
Respiratory, thoracic and mediastinal disorders			
Very common	cough	cough, dyspnoea	
Common	pneumonitis[a]	pneumonitis[a]	pneumonitis
Gastrointestinal disorders			
Very common	diarrhea, abdominal pain, nausea	diarrhea, nausea, vomiting, constipation, abdominal pain	diarrhoea, nausea
Common	colitis, pancreatitis	dry mouth, stomatitis, colitis, dyspepsia	constipation, colitis, pancreatitis
Uncommon		gastritis, pancreatitis	
Skin and subcutaneous tissue disorders			
Very common	rash[b], pruritus	pruritus, rash[b]	rash, pruritus
Common		dry skin, erythema, alopecia	
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[c], arthralgia	arthralgia, musculoskeletal pain[c]	
Common		arthritis, myositis, muscular weakness	musculoskeletal pain, arthritis
Uncommon		polymyalgia rheumatica, muscle spasms	myositis
Renal and urinary disorders			
Common		renal failure (including acute kidney injury)	acute kidney injury
Uncommon			renal failure
General disorders and administration site conditions			
Very common	fatigue, pyrexia, oedema	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue
Common		pain, chest pain, chills	
Investigations			
Common		weight decreased	

[a] Fatal cases have been reported in completed or ongoing clinical studies.

[b] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalized, exfoliative rash,

dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.

[c] 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.

Nivolumab in combination with ipilimumab and chemotherapy

NSCLC

In the dataset of nivolumab 360 mg in combination with ipilimumab 1 mg/kg and 2 cycles of chemotherapy in NSCLC (n = 358), the most frequent adverse reactions (≥10%) were fatigue (36%), nausea (26%), rash (25%), diarrhea (20%), pruritus (18%), decreased appetite (16%), hypothyroidism (15%), and vomiting (13%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Median duration of therapy was 6.1 months (95% CI 4.93, 7.06) for nivolumab in combination with ipilimumab and 2.4 months (95% CI 2.30, 2.83) for platinum-based chemotherapy.

Tabulated list of adverse reactions

Adverse reactions reported in the dataset for patients treated with nivolumab in combination with ipilimumab and platinum-based chemotherapy (n = 358) are presented in Table 7. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7: Adverse reactions with nivolumab in combination with ipilimumab and chemotherapy

Infections and infestations	
Common	conjunctivitis, pneumonia, respiratory tract infection
Blood and lymphatic system disorders	
Common	febrile neutropenia
Uncommon	Eosinophilia
Immune system disorders	
Common	infusion-related reaction, hypersensitivity
Endocrine disorders	
Very common	Hypothyroidism
Common	hyperthyroidism, adrenal insufficiency, hypophysitis, thyroiditis
Uncommon	hypopituitarism, hypoparathyroidism
Metabolism and nutrition disorders	

Very common	decreased appetite
Common	dehydration, , hypoalbuminemia, hypophosphatemia
Nervous system disorders	
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis
Eye disorders	
Common	dry eye
Uncommon	blurred vision, episcleritis
Cardiac disorders	
Uncommon	tachycardia, atrial fibrillation, bradycardia
Vascular disorders	
Uncommon	Hypertension
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis, dyspnoea, cough
Uncommon	pleural effusion
Gastrointestinal disorders	
Very common	nausea, diarrhea, vomiting
Common	constipation, stomatitis, abdominal pain, colitis, dry mouth, pancreatitis
Hepatobiliary disorders	
Common	Hepatitis
Skin and subcutaneous tissue disorders	
Very common	rash[a], pruritus
Common	alopecia, dry skin, erythema, urticaria
Uncommon	psoriasis, Stevens-Johnson syndrome, vitiligo
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain[b], arthralgia, arthritis
Uncommon	muscular weakness, muscle spasms, polymyalgia rheumatica
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)
Uncommon	Nephritis
General *disorders* and administration site conditions	

Very common	Fatigue
Common	pyrexia, oedema (including peripheral oedema)
Uncommon	chills, chest pain
Investigations	
Common	increased thyroid-stimulating hormone
Uncommon	increased gamma-glutamyl transferase

* Nivolumab every 3 weeks in combination with ipilimumab every 6 weeks and platinum-based chemotherapy every 3 weeks for 2 cycles, then followed by nivolumab every 3 weeks in combination with ipilimumab every 6 weeks in NSCLC.

[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, and drug eruption.

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

Nivolumab in combination with chemotherapy

NSCLC

In the dataset of nivolumab 360 mg in combination with platinum-doublet chemotherapy for 3 cycles in resectable NSCLC (n=176), the most frequent adverse reactions (≥10%) were nausea (38%), constipation (34%), fatigue (26%), rash (21%), decreased appetite (21%), malaise (15%), peripheral neuropathy (13%), vomiting (11%), and alopecia (11%). Incidence of Grade 3-5 adverse reactions were 41% for nivolumab in combination with platinum-doublet chemotherapy and 44% for platinum-doublet chemotherapy.

GC, GEJC, or EAC

In the dataset of nivolumab 240 mg or 360 mg in combination with fluoropyrimidine- and platinum-containing chemotherapy in GC, GEJC, or EAC (n=782), with a minimum follow-up of 12.1 months, the most frequent adverse reactions (≥10%) were peripheral neuropathy (53%), nausea (48%), fatigue (44%), diarrhea (39%), vomiting (31%), decreased appetite (29%), abdominal pain (27%), constipation (25%), musculoskeletal pain (20%), pyrexia (19%), rash (18%), stomatitis (17%), lipase increased (14%), palmar-plantar erythrodysaesthesia syndrome (13%), alkaline phosphatase increased (13%), cough (13%), edema (including peripheral edema) (12%), amylase increased (12%), headache (11%), and upper respiratory tract infection (10%). Median duration of therapy was 6.75 months (95% CI: 6.11, 7.36) for nivolumab in combination with chemotherapy and 4.86 months (95% CI: 4.47, 5.29) for chemotherapy.

ESCC

In the dataset of nivolumab 240 mg every 2 weeks in combination with chemotherapy in ESCC (n = 310), with a minimum follow-up of 12.9 months, the most frequent adverse reactions were nausea (65%), decreased appetite (51%), constipation (44%), stomatitis (44%), fatigue (32%), diarrhea (29%), vomiting (23%), pyrexia (19%), peripheral neuropathy (18%), edema (17%), rash (16%), cough (16%), pneumonia (13%), musculoskeletal pain (11%), pruritus (11%), and alopecia (10%). Incidences of Grade 3-5 adverse reactions were 75% for nivolumab in combination with chemotherapy and median duration of therapy was 5.68 months (95% CI: 5.09, 6.28).

Tabulated list of adverse reactions

Adverse reactions reported in the dataset for patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC (n=176), nivolumab 240 mg or 360 mg in combination with fluoropyrimidine- and platinum-containing chemotherapy in GC, GEJC, or EAC (n=782), and nivolumab 240 mg in combination with chemotherapy in ESCC (n=310) are presented in Table 8. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 8: Adverse reactions with nivolumab in combination with chemotherapy

	Nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC	Nivolumab 240 mg or 360 mg in combination with fluoropyrimidine- and platinum-containing chemotherapy in GC, GEJC, or EAC	Nivolumab 240 mg in combination with chemotherapy in ESCC
Infections and infestations			
Very common		upper respiratory tract infection	pneumonia
Common	upper respiratory tract infection, pneumonia	pneumonia	upper respiratory tract infection
Blood and lymphatic system disorders			
Common	febrile neutropenia	febrile neutropenia, eosinophilia	febrile neutropenia
Uncommon			eosinophilia
Immune system disorders			
Common	hypersensitivity, infusion related reaction	hypersensitivity, infusion related reaction	infusion-related reaction, hypersensitivity
Endocrine disorders			
Common	hyperthyroidism, hypothyroidism, diabetes mellitus, thyroiditis	hypothyroidism, hyperthyroidism	hypothyroidism, hyperthyroidism, adrenal insufficiency, diabetes mellitus

Uncommon		hypopituitarism, adrenal insufficiency, hypophysitis, diabetes mellitus	hypopituitarism
Metabolism and nutrition disorders			
Very common	decreased appetite	decreased appetite	decreased appetite
Common	hypoalbuminemia, hypophosphatemia		hypoalbuminemia, hypophosphatemia
Nervous system disorders			
Very common	peripheral neuropathy	peripheral neuropathy, headache	peripheral neuropathy
Common	headache, dizziness	paraesthesia, dizziness	headache, dizziness
Uncommon	paraesthesia	Guillain-Barre syndrome	paresthesia
Eye disorders			
Common		dry eye, blurred vision	blurred vision, dry eye
Uncommon	dry eye	uveitis	uveitis
Cardiac disorders			
Common	atrial fibrillation	tachycardia	
Uncommon		myocarditis	tachycardia
Vascular disorders			
Common	hypertension, vasculitis, thrombosis	thrombosis, hypertension	hypertension, thrombosis
Respiratory, thoracic and mediastinal disorders			
Very common		cough	cough
Common	cough, pneumonitis, dyspnea	pneumonitis[a], dyspnoea	pneumonitis, dyspnea
Gastrointestinal disorders			
Very common	nausea, constipation, vomiting	diarrhoea, stomatitis, vomiting, nausea, abdominal pain, constipation	nausea, constipation, stomatitis, vomiting, diarrhea
Common	diarrhea, abdominal pain, stomatitis, dry mouth	colitis, dry mouth	colitis
Uncommon		pancreatitis	
Hepatobiliary disorders			
Uncommon		hepatitis	
Skin and subcutaneous tissue disorders			
Very common	rash[b], alopecia	palmar-plantar erythrodysaesthesia syndrome, rash[b]	rash[b], pruritus, alopecia
Common	pruritus, erythema	pruritus, skin hyperpigmentation, alopecia, dry skin, erythema	dry skin, erythema
Uncommon	dry skin		palmar-plantar erythrodysesthesia syndrome, skin hyperpigmentation

Musculoskeletal and connective tissue disorders			
Very common		musculoskeletal pain[c]	musculoskeletal pain[c]
Common	musculoskeletal pain[c], arthralgia, muscular weakness	arthralgia, muscular weakness	arthralgia
Uncommon			muscular weakness
Renal and urinary disorders			
Common	renal failure	renal failure	renal failure
Uncommon		nephritis	
General disorders and administration site conditions			
Very common	fatigue, malaise	fatigue, pyrexia, edema (including peripheral edema)	fatigue, pyrexia, edema (including peripheral edema)
Common	edema, pyrexia		
Investigations			
Very common		increased lipase, increased alkaline phosphatase, increased amylase	
Uncommon	increased alkaline phosphatase		

[a] Fatal cases have been reported in completed or ongoing clinical studies

[b] Rash is a composite term that 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.

[c] Musculoskeletal pain is a composite term that includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, spinal pain, and musculoskeletal discomfort.

Nivolumab in combination with cabozantinib

RCC

In the dataset of nivolumab 240 mg every 2 weeks in combination with cabozantinib 40 mg once daily in RCC (n=320), with a minimum follow-up of 10.6 months, the most frequent adverse reactions (≥10%) were diarrhoea (63.8%), fatigue (50.6%), palmar-plantar erythrodysaesthesia syndrome (40%), stomatitis (36.6%), hypertension (35.6%), rash (35.6%) hypothyroidism (34.1%), musculoskeletal pain (33.4%), decreased appetite (28.1%), nausea (26.6%),dysgeusia (23.8%), abdominal pain (21.9%), upper respiratory tract infection (20.0%), dysphonia (17.2%),vomiting (17.2%), headache (15.6%), dyspepsia (15.0%), dizziness (12.8%), constipation (12.2%),pyrexia (12.2%), muscle spasm (11.9%), oedema (11.6%), dyspnoea (10.6%), proteinuria (10.3%), and hyperthyroidism (10.0%).The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Adverse reaction frequencies in the paragraph above and in Table 8 below are based on all- causality adverse event incidence rates.

Tabulated summary of adverse reactions

Adverse reactions reported in the dataset for patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg (n=320) are presented in Table 9. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 9: Adverse reactions with nivolumab in combination with cabozantinib

Infections and infestations	
Very common	upper respiratory tract infection
Common	Pneumonia
Blood and lymphatic system disorders	
Common	Eosinophilia
Immune system disorders	
Common	hypersensitivity (including anaphylactic reaction)
Uncommon	infusion related hypersensitivity reaction
Endocrine disorders	
Very common	hypothyroidism, hyperthyroidism,
Common	adrenal insufficiency
Uncommon	hypophysitis, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	Dehydration
Nervous system disorders	
Very common	Dysgeusia, dizziness, headache
Common	peripheral neuropathy
Uncommon	encephalitis autoimmune, Guillain-Barre syndrome, myasthenic syndrome
Ear and labyrinth disorders	
Common	Tinnitus
Eye disorders	
Common	dry eye,blurred vision
Uncommon	uveitis
Cardiac disorders	
Common	atrial fibrillation, tachycardia
Uncommon	myocarditis
Vascular disorders	

Very common	hypertension
Common	thrombosis[a]
Respiratory, thoracic and mediastinal disorders	
Very common	Dyspnoea, cough,dysphonia
Common	pneumonitis, pulmonary embolism, pleural effusion, epistaxis
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia
Common	colitis, gastritis, oral pain, dry mouth, haemorrhoids
Uncommon	pancreatitis, small intestine perforation[b], glossodynia
Hepatobiliary disorders	
Common	hepatitis
Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus
Common	Alopecia, dry skin, erythema, hair colour change
Uncommon	psoriasis, urticaria
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[d], arthralgia, muscle spasm, ,
Common	arthritis
Uncommon	myopathy, osteonecrosis of the jaw, fistula
Renal and urinary disorders	
Very common	proteinuria
Common	renal failure, acute kidney injury
Uncommon	Nephritis
General disorders and administration site conditions	
Very common	Fatigue, pyrexia, oedema
Common	pain, chest pain
Investigations	
Very common	weight decreased

[a] Thrombosis is a composite term which includes portal vein thrombosis, pulmonary vein thrombosis, pulmonary thrombosis, aortic thrombosis, arterial thrombosis, deep vein thrombosis, pelvic vein thrombosis, vena cava thrombosis, venous thrombosis, venous thrombosis limb

[b] Fatal cases have been reported

[c] Rash is a composite term which includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic,dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash morbilliform, rash pruritic and drug eruption

[d] 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

Description of selected adverse reactions - nivolumab monotherapy

Management guidelines for the following immune-related adverse reactions are described in Section (4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Immune-related pneumonitis

In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.5% (156/4494). The majority of cases were Grade 1 or 2 in severity reported in 1.0% (43/4494) and 1.7% (76/4494) of patients, respectively. Grade 3 and 4 cases were reported in 0.8% (34/4494) and <0.1% (1/4494) of patients, respectively. Grade 5 cases were reported in <0.1% (2/ 4494) of patients in these studies.

Median time to onset was 3.3 months (range: 0.2-19.6). Sixty-six patients (1.5%) required permanent discontinuation of nivolumab. One-hundred patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.0 mg/kg (range: 0.5- 25.3) for a median duration of 3.1 weeks (range: 0.1-13.1). Resolution occurred in 104 patients (66.7%) with a median time to resolution of 6.7 weeks (range: 0.1^{+}-109.1^{+}); ($^{+}$ denotes a censored observation).

Immune-related colitis

In patients treated with nivolumab monotherapy, the incidence of diarrhea, colitis and frequent bowel movements was 14.7% (661/4494). The majority of cases were Grade 1 or 2 in severity reported in 9.5% (425/4494) and 3.8% (170/4494) of patients, respectively. Grade 3 and 4 cases were reported in 1.4% (65/4494) and <0.1% (1/4494) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 1.7 months (range: 1 day-26.6 months). Forty-four patients (1.0%) required permanent discontinuation of nivolumab. Ninety patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.0 mg/kg (range: 0.4-5.1) for a median duration of 2.4 weeks (range: 0.1-30.7). Resolution occurred in 588 patients (89.9 %) with a median time to resolution of 2.7 weeks (range: 0.1-124.4^{+}).

Immune-related hepatitis

In patients treated with nivolumab monotherapy, the incidence of hepatic adverse reactions was 7.3% (326/ 4494). The majority of cases were Grade 1 or 2 in severity reported in 3.9% (175/ 4494) and 1.6% (73/ 4494) of patients, respectively. Grade 3 and Grade 4 cases were reported in 1.5% (66/ 4494) and 0.3% (12/ 4494) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 2.0 months (range: 1 day - 27.6 months). Thirty-nine patients (0.9%) required permanent discontinuation of nivolumab. Sixty-three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.2 mg/kg (range: 0.4-10.6) for a median duration of 2.7 weeks (range: 0.1-22.1). Resolution occurred in 254 patients (78.9%) with a median time to resolution of 6.3 weeks (range: 0.1- 126.4^{+}).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab monotherapy, the incidence of nephritis and renal dysfunction was 2.5% (113/4494). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (66/4494) and

0.6% (29/4494) of patients, respectively. Grade 3 and 4 cases were reported in 0.4% (17/4494) and <0.1% (1/4494) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported.

Median time to onset was 2.6 months (range: 1 day - 18.2 months). Eleven patients (0.2%) required permanent discontinuation of nivolumab. Twenty-five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.0 mg/kg (range: 0.5-3.6) for a median duration of 2.9 weeks (range: 0.1-67.0). Resolution occurred in 74 patients (68.5%) with a median time to resolution of 8.1 weeks (range: 0.3^{+}-79.1^{+}).

Immune-related endocrinopathies

In patients treated with nivolumab monotherapy, the incidence of thyroid disorders including hypothyroidism and hyperthyroidism was 11.9% (533/4494). The majority of cases were Grade 1 or 2 in severity reported in 5.9% (263/4494) and 5.8% (262/4494) of patients, respectively. Grade 3 thyroid disorders were reported in 0.2% (8/4494) of patients.

The incidence of pituitary disorders, including hypophysitis and hypopituitarism was 0.6% (25/4494) 0.1% Grade 1, 0.2% Grade 2, 0.2% Grade 3 and <0.1% Grade 4).

The incidence of adrenal disorders, including adrenal insufficiency, secondary adrenocortical insufficiency, and acute adrenocortical insufficiency, was 0.6% (26/4494) (<0.1% Grade 1, 0.4% Grade 2, and 0.2% Grade 3).

The incidence of diabetes mellitus including Type 1 diabetes mellitus and diabetic ketoacidosis was 0.3% (15/4494) (<0.1% Grade 1, <0.1% Grade 2, 0.2% Grade 3 and < 0.1% Grade 4). Thirteen patients experienced a shift from baseline to Grade 3 or 4 hyperglycemia.

No Grade 5 endocrinopathies were reported.

Median time to onset of these endocrinopathies was 2.5 months (range: 1 day-29.1). Fourteen patients (0.3%) required permanent discontinuation of nivolumab. Thirty-four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.8 mg/kg (range: 0.4-2.2) for a median duration of 2.1 weeks (range: 0.1-51.1). Resolution occurred in 284 patients (49.1%) with a median time to resolution of 44.1 weeks (range: 0.4 to 204.4^{+}).

Immune-related skin adverse reactions

In patients treated with nivolumab monotherapy, the incidence of rash and pruritus was 28.4% (1278 / 4494). The majority of cases were Grade 1 in severity reported in 21.7 % (975 / 4494) of patients. Grade 2 and Grade 3 cases were reported in 5.5 % (246 / 4494) and 1.3 % (57 / 4494) of patients, respectively. No Grade 4 or 5 cases were reported.

Median time to onset was 1.4 months (range: 1 day-27.9 months). Twenty-six patients (0.6%) required permanent discontinuation of nivolumab. Forty-three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.9 mg/kg (range: 0.4-363.6) for a median duration of 1.9 weeks (range: 0.1- 53.6). Resolution occurred in 817 patients (64.4 %) with a median time to resolution of 18.00 weeks (range: 0.1- 192.7^{+}).

Infusion reactions

In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions, including anaphylactic reaction, anaphylactic shock, and bronchospasm, was 3.6% (163/4494), including 9 Grade 3 (0.2%) and 3 Grade 4 (<0.1%) cases. No Grade 5 cases were reported.

Description of selected adverse reactions - nivolumab in combination with ipilimumab

The management guidelines for these adverse reactions are described in section (4.4.2 PRODUCT-SPECIFIC WARNINGS AND PRECAUTIONS).

Immune-related pneumonitis

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of pneumonitis including interstitial lung disease was 6.2% (34/547). Grade 2 and Grade 3 cases were reported in 3.1% (17/547) and 1.1% (6/547) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 2.6 months (range: 0.25-20.6). Resolution occurred in 31 patients (91.2%) with a median time to resolution of 6.1 weeks (range: 0.7-85.9^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of pneumonitis including interstitial lung disease was 8.0% (48/576). Grade 2, Grade 3, and Grade 4 cases were reported in 4.0% (23/576), 3% (17/576), and 0.3% (2/576) of patients, respectively. Four patients died due to pneumonitis. Median time to onset was 3.6 months (range: 0.9-23.7). Resolution occurred in 41 patients (85.4%) with a median time to resolution of 6.0 weeks (range: 0.7-109.4^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in unresectable HCC, the incidence of pneumonitis was 2.1% (7/332). Grade 2 and Grade 3 cases were reported in 1.2% (4/332) and 0.3% (1/332) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 2.1 months (range: 1.1-7.7). Resolution occurred in 5 patients (71.4%) with a median time to resolution of 16.1 weeks (range: 3.9-100.1^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of pneumonitis, including interstitial lung disease, was 7.8% (35/448). Grade 2, Grade 3, and Grade 4 cases were reported in 4.7% (21/448), 1.1% (5/448), and 0.2% (1/448) of patients, respectively. One of the Grade 3 pneumonitis cases worsened over 11 days with a fatal outcome.

Median time to onset was 2.6 months (range: 0.7-12.6). Nine patients (2.0%) required permanent discontinuation of nivolumab in combination with ipilimumab. Twenty-two patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.2 mg/kg (range: 0.4-5.0) for a median duration of 4.2 weeks (range: 0.7-106.6). Resolution occurred in 33 patients (94%) with a median time to resolution of 6.1 weeks (range: 0.3-35.1).

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in the first-line treatment of metastatic or unresectable CRC, the incidence of pneumonitis, including interstitial lung disease, was 2.5% (5/200). Grade 2 and Grade 3 cases were reported in 0.5% (1/200) and 1.0% (2/200) of patients, respectively. No Grade 4 or Grade 5 cases were reported in this study. Median time to onset was 1.4 months (range: 1.2-2.8). Resolution occurred in 5 patients (100%) with a median time to resolution of 7.1 weeks (range: 4.0-20.1).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma, the incidence of pneumonitis including interstitial lung disease was 6.7% (20/300). Grade 2 and Grade 3 cases were reported in 5.3% (16/300) and 0.7% (2/300) of patients, respectively. Median time to onset was 1.8 months (range: 0.3-20.8). Resolution occurred in 16 patients (80%) with a median time to resolution of 6.1 weeks (range: 1.1-113.1+).

Immune-related colitis

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of diarrhea or colitis was 28.2% (154/547). Grade 2 and Grade 3 cases were reported in 10.4% (57/547) and 4.9% (27/547) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 1.2 months (range: 0.0-24.7). Resolution occurred in 140 patients (91.5%) with a median time to resolution of 2.4 weeks (range: 0.1-103.1^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of diarrhea or colitis was 18.2% (105/576). Grade 2, Grade 3 and Grade 4 cases were reported in 7.5% (43/576), 2.1% (12/576) and 0.3% (2/576) of patients, respectively. Median time to onset was 2 months (range: 0.0-22.5). Resolution occurred in 98 patients (94.2%) with a median time to resolution of 2.1 weeks (range: 0.1-149.3^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in unresectable HCC, the incidence of diarrhea or colitis was 16.9% (56/332). Grade 2 and Grade 3 cases were reported in 5.4% (18/332) and 5.1% (17/332) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 1.4 months (range: 0.1-21.5). Resolution occurred in 51 patients (91.1%) with a median time to resolution of 3.6 weeks (range: 0.3-170.0^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg melanoma, the incidence of diarrhea or colitis was 46.7% (209/448). Grade 2, Grade 3, and Grade 4 cases were reported in 13.6% (61/448), 15.8% (71/448), and 0.4% (2/448) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 1.2 months (range: 1 day-22.6 months). Seventy-three patients (16.3%) required permanent discontinuation of nivolumab in combination with ipilimumab. Ninety-six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.1 mg/kg (range: 0.3-12.5) for a median duration of 4.4 weeks (range: 0.1-130.1). Resolution occurred in 186 patients (89%) with a median time to resolution of 3.0 weeks (range: 0.1-159.4^{+}).

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in the first-line treatment of metastatic or unresectable CRC, the incidence of diarrhea or colitis was 23% (46/200). Grade 2, Grade 3, and Grade 4 cases were reported in 5.0% (10/200), 4.0% (8/200), and 0.5% (1/200) of patients, respectively. Median time to onset was 2.8 months (range: 0.1-18.5). Resolution occurred in 43 patients (93.5%) with a median time to resolution of 4.1 weeks (range: 0.1-93.0^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma, the incidence of diarrhea or colitis was 22.0% (66/300). Grade 2 and Grade 3 cases were reported in 7.3% (22/300) and 5.3% (16/300) of patients, respectively. Median time to onset was 3.9 months (range: 0.0-21.7). Resolution occurred in 66 patients (93.9%) with a median time to resolution of 3.1 weeks (range: 0.1-100.0+).

Immune-related hepatitis

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of liver function test abnormalities was 18.5% (101/547). Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (26/547), 6.6% (36/547), and 1.6% (9/547) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.0 months (range: 0.4-26.8). Resolution occurred in 86 patients (85.1%) with a median time to resolution of 6.1 weeks (range: 0.1^{+}-82.9^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of liver function test abnormalities was 15.8% (91/576). Grade 2, Grade 3, and Grade 4 cases were reported in 2.8% (16/576), 7.5% (43/576), and 0.7% (4/576) of patients, respectively. Median time to onset was 2.4 months (range: 0.2-20.3). Resolution occurred in 82 patients (90.1%) with a median time to resolution of 5.3 weeks (range: 0.4-155.1^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, in unresectable HCC, the incidence of liver function test abnormalities was 34.3% (114/332). Grade 2, Grade 3, and Grade 4 cases were reported in 8.4% (28/332), 14.2% (47/332), and 2.7% (9/332) of patients, respectively. No Grade 5 cases were reported in this study. Median time to onset was 1.1 months (range: 0.2-20.4). Resolution occurred in 94 patients (82.5%) with a median time to resolution of 6.0 weeks (range: 0.4^{+}-129.3^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of liver function test abnormalities was 29.5% (132/448). Grade 2, Grade 3, and Grade 4 cases were reported in 6.7% (30/448), 15.4% (69/448), and 1.8% (8/448) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 1.5 months (range: 1 day-30.1 months). Forty-one patients (9.2%) required permanent discontinuation of nivolumab in combination with ipilimumab. Sixty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.2 mg/kg (range: 0.4-5.2) for a median duration of 3.8 weeks (range: 0.1-138.1). Resolution occurred in 124 patients (94%) with a median time to resolution of 5.1 weeks (range: 0.1-106.9).

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in the first-line treatment of metastatic or unresectable CRC, the incidence of liver function test abnormalities was 19.5% (39/200). Grade 2, Grade 3, and Grade 4 cases were reported in 7.5% (15/200), 4.0% (8/200), and 0.5% (1/200) of patients, respectively. Median time to onset was 2.8 months (range: 0.4-15.8). Resolution occurred in 36 patients (92.3%) with a median time to resolution of 7.1 weeks (range: 0.9-98.3^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma, the incidence of liver function test abnormalities was 12.0% (36/300). Grade 2, Grade 3, and Grade 4 cases were reported in 1.7% (5/300), 4.3% (13/300), and 1.0% (3/300) of patients, respectively. Median time to onset was 1.8 months (range: 0.5-20.3). Resolution occurred in 31 patients (86.1%) with a median time to resolution of 4.1 weeks (range: 1.0-78.3+).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of nephritis or renal dysfunction was 8.8% (48/547). Grade 2, Grade 3, and Grade 4 cases were reported in 4.4% (24/547), 0.7% (4/547), and 0.5% (3/547) of patients, respectively. No Grade 5

cases were reported. Median time to onset was 2.1 months (range: 0.0-16.1). Resolution occurred in 37 patients (77.1%) with a median time to resolution of 13.2 weeks (range: 0.1^{+}-106.0^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of nephritis or renal dysfunction was 4.3% (25/576). Grade 2, Grade 3, and Grade 4 cases were reported in 1.4% (8/576), 0.5% (3/576), and 0.2% (1/576) of patients, respectively. Median time to onset was 4.9 months (range: 0.5-21.2). Resolution occurred in 23 patients (92.0%) with a median time to resolution of 2.4 weeks (range: 0.3-152.4^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, in unresectable HCC, the incidence of nephritis or renal dysfunction was 1.8% (6/332). Grade 2 and Grade 3 cases were reported in 0.6% (2/332) and 0.3% (1/332) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 2.9 months (range: 0.4-13.4). Resolution occurred in 6 patients (100%) with a median time to resolution of 3.6 weeks (range: 0.6-23.9).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of nephritis and renal dysfunction was 5.1% (23/448). Grade 2, Grade 3, and Grade 4 cases were reported in 1.6% (7/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 2.6 months (range: 0.5-21.8). Five patients (1.1%) required permanent discontinuation of nivolumab in combination with ipilimumab. Four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 2.1 mg/kg (range: 1.2-6.6) for a median duration of 2.5 weeks (range: 0.1-6.9). Resolution occurred in 21 patients (91%) with a median time to resolution of 2.1 weeks (range: 0.1-125.1^{+}).

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in the first-line treatment of metastatic or unresectable CRC, the incidence of nephritis or renal dysfunction was 3.5% (2/200). Grade 2 and Grade 4 cases were reported in 0.5% (1/200) and 0.5% (1/200) of patients, respectively. No Grade 3, or 5 cases were reported. Median time to onset was 4.6 months (range: 0.6-17.5). Resolution occurred in 7 patients (100.0%) with a median time to resolution of 1.1 weeks (range: 0.3-12.3).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma, the incidence of renal dysfunction was 5.0% (15/300). Grade 2 and Grade 3 cases were reported in 2.0% (6/300) and 1.3% (4/300) of patients, respectively. Median time to onset was 3.6 months (range: 0.5-14.4). Resolution occurred in 12 patients (80.0%) with a median time to resolution of 6.1 weeks (range: 0.9-126.4+).

Immune-related endocrinopathies

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of thyroid disorders was 27.2% (149/547). Grade 2 and Grade 3 thyroid disorders were reported in 15.7% (86/547) and 1.3% (7/547) of patients, respectively. Hypophysitis occurred in 4.0% (22/547) of patients. Grade 2, Grade 3, and Grade 4 cases were reported in 0.5% (3/547), 2.4% (13/547), and 0.4% (2/547) of patients, respectively. Grade 2 hypopituitarism occurred in 0.4% (2/547) of patients. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 2.9% (16/547), 2.2% (12/547) and 0.4% (2/547) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus (3 Grade 2, 2 Grade 3, and 3 Grade 4), and diabetic ketoacidosis (1 Grade 4) were reported. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 1.9 months (range: 0.0-22.3). Resolution occurred in 76 patients (42.7%). Time to resolution ranged from 0.4 to 130.3^{+} weeks.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of thyroid disorders was 20.0% (115/576). Grade 2, Grade 3 and Grade 4 thyroid disorders were reported in 10.6% (61/576), 0.3% (2/576) and 0.2% (1/576) of patients, respectively. Hypophysitis occurred in 2.1% (12/576) of patients. Grade 2, Grade 3, and Grade 4 cases were reported in 0.7% (4/576), 0.9% (5/576), and 0.2% (1/576) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (1/576) and 0.5% (3/576) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 1% (6/576) and 1.7% (10/576) of patients, respectively. Diabetes mellitus including, Type 1 diabetes mellitus, occurred in 0.9% (5/576) of patients (1 Grade 2, 3 Grade 3, and 1 Grade 4). Median time to onset of these endocrinopathies was 2.3 months (range: 0.5-16.1). Resolution occurred in 57 patients (41.9%). Time to resolution ranged from 0.7 to 176.6^{+} weeks.

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, in unresectable HCC, the incidence of thyroid disorders was 28.3% (94/332). Grade 2 and Grade 3 thyroid disorders were reported in 16.6% (55/332) and 3.6% (12/332) of patients, respectively. Hypophysitis (including lymphocytic hypophysitis) occurred in 2.1% (7/332) of patients. Grade 2 and Grade 3 cases were reported in 1.2% (4/332) and 0.9% (3/332) of patients, respectively. Grade 3 hypopituitarism occurred in 0.3% (1/332) of patients. Grade 2 and Grade 3 adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute, blood corticotrophin decreased and immune-mediated adrenal insufficiency) occurred in 3.0% (10/332) and 1.2% (4/332) of patients, respectively. Grade 3 diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) occurred in 0.6% (2/332) of patients. Median time to onset of these endocrinopathies was 2.0 months (range: 0-23.5). Resolution occurred in 43 patients (45.7%). Time to resolution ranged from 0.6 to 191.1^{+} weeks.

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of thyroid disorders was 25.2% (113/448). Grade 2 and Grade 3 thyroid disorders were reported in 14.5% (65/448) and 1.3% (6/448) of patients, respectively. Grade 2 and Grade 3 hypophysitis occurred in 5.8 % (26/448) and 2.0% (9/448) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.4% (2/448) and 0.7% (3/448) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency occurred in 1.6% (7/448), 1.3% (6/448), and 0.2% (1/448) of patients, respectively. Grade 2, Grade 3, and Grade 4 diabetes mellitus and Grade 4 diabetic ketoacidosis were each reported in 0.2% (1/448) of patients. No Grade 5 endocrinopathy was reported.

Median time to onset of these endocrinopathies was 1.9 months (range: 1 day-28.1 months). Twelve patients (2.7%) required discontinuation of nivolumab in combination with ipilimumab. Thirty-eight patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.0 mg/kg (range: 0.4-9.3) for a median duration of 2.8 weeks (range: 0.1-12.7). Resolution occurred in 64 patients (45%). Time to resolution ranged from 0.4 to 155.4^{+} weeks.

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in the first-line treatment of metastatic or unresectable CRC, the incidence of thyroid disorders was 24% (48/200). Grade 2 and Grade 3 thyroid disorders were reported in 10.0% (20/200) and 1.5% (3/200) of patients, respectively. Hypophysitis occurred in 4.5% (9/200) of patients. Grade 2 and Grade 3 cases were reported in 1.5% (3/200) and 2.0% (4/200) of patients, respectively. Grade 3 hypopituitarism occurred in 0.5% (1/200) of patients. Grade 2 and Grade 3 adrenal insufficiency, including blood corticotrophin decreased and secondary adrenocortical insufficiency, occurred in 6.0% (12/200) and 3.0% (6/200) of patients, respectively. Diabetes mellitus, including Type 1 diabetes mellitus and diabetic ketoacidosis, occurred in 1.0% (2/200) of patients (2 Grade 2). Median time to onset of these endocrinopathies was 2.9 months (range: 0.7-23.5). Resolution occurred in 27 patients (40.3%). Time to resolution ranged from 0.9^{+} to 201.6^{+} weeks.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma, the incidence of thyroid disorders was 14% (43/300). Grade 2 and Grade 3 thyroid disorders were reported in 9.3% (28/300) and 1.3% (4/300) of patients, respectively. Hypophysitis occurred in 2% (6/300) of patients. Grade 2 cases were reported in 1.3% (4/300) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 1.0% (3/300) and 1.0% (3/300) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (5/300) and 0.3% (1/300) of patients, respectively. No cases of immune-related diabetes mellitus were reported. Median time to onset of these endocrinopathies was 2.8 months (range: 0.5-20.8). Resolution occurred in 17 patients (32.7%). Time to resolution ranged from 0.3 to 144.1+ weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of rash was 48.8% (267/547). Grade 2 and Grade 3 cases were reported in 13.7% (75/547) and 3.7% (20/547) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 0.9 months (range: 0.0-17.9). Resolution occurred in 192 patients (72.2%) with a median time to resolution of 11.6 weeks (range: 0.1-126.7^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of rash was 34.0% (196/576). Grade 2 and Grade 3 cases were reported in 10.6% (61/576) and 4.2% (24/576) of patients, respectively. Median time to onset was 1.0 month (range: 0.0-18). Resolution occurred in 148 patients (75.5%) with a median time to resolution of 9.9 weeks (range: 0.1-165.0^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, in unresectable HCC, the incidence of rash was 51.8% (172/332). Grade 2, Grade 3, and Grade 4 cases were reported in 18.7% (62/332), 5.4% (18/332), and 0.3% (1/332) of patients, respectively. No Grade 5 cases were reported in this study. Median time to onset was 0.7 months (range: 0-23.9).

Resolution occurred in 119 patients (69.6%) with a median time to resolution of 15.7 weeks (range: 0.1-170.7^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of rash was 65.0% (291/448). Grade 2 and Grade 3 cases were reported in 20.3% (91/448) and 7.6% (34/448) of patients, respectively. No Grade 4 or 5 cases were reported.

Median time to onset was 0.5 months (range: 1 day-19.4 months). Four patients (0.9%) required permanent discontinuation of nivolumab in combination with ipilimumab. Twenty-one patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.9 mg/kg (range: 0.3-1.8) for a median duration of 1.6 weeks (range: 0.3-17.0). Resolution occurred in 191 patients (66%) with a median time to resolution of 11.4 weeks (range: 0.1-150.1^{+}).

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in the first-line treatment of metastatic or unresectable CRC, the incidence of rash was 34.5% (69/200). Grade 2 and Grade 3 cases were reported in 7.5% (15/20) and 2.5% (5/200) of patients, respectively. Median time to onset was 1.2 months (range: 0.0-14.6). Resolution occurred in 52 patients (75.4%) with a median time to resolution of 11.9 weeks (range: 0.1-154.6^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma, the incidence of rash was 36.0% (108/300). Grade 2 and Grade 3 cases were reported in 10.3% (31/300) and 3.0% (9/300) of patients, respectively. Median time to onset was 1.6 months (range: 0.0-22.3). Resolution occurred in 71 patients (66.4%) with a median time to resolution of 12.1 weeks (range: 0.4-146.4+).

Infusion reactions

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg//kg in RCC, the incidence of hypersensitivity/infusion reactions was 4.0% (22/547); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.4% (13/547) of patients. No Grade 3-5 cases were reported.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of hypersensitivity/infusion reactions was 4.0% (23/576); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.4% (14/576) of patients.

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg//kg, in unresectable HCC, the incidence of hypersensitivity/infusion reactions was 2.4% (8/332); all were Grade 1, 2 or 3 in severity. Grade 2 and Grade 3 cases were reported in 1.5% (5/332) and 0.3% (1/332) of patients, respectively. No Grade 4 and 5 cases were reported.

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of hypersensitivity/infusion reactions was 3.8% (17/448); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.2% (10/448) of patients. No Grade 3-5 cases were reported.

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in the first-line treatment of metastatic or unresectable CRC, the incidence of hypersensitivity/infusion reactions was 4.0% (8/200); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.5% (5/200) of patients.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma, the incidence of hypersensitivity/infusion reactions was 12% (36/300); Grade 2 and Grade 3 cases were reported in 5.0% (15/300) and 1.3% (4/300) of patients, respectively.

Description of selected adverse reactions - nivolumab in combination with ipilimumab and chemotherapy

The management guidelines for these adverse reactions are described in section 4.4.2.

Immune-related pneumonitis

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of pneumonitis including interstitial lung disease was 5.3% (19/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.1% (4/358), and 0.6% (2/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 18.1 weeks (range: 0.6-52.4). Resolution occurred in 14 patients (74%) with a median time to resolution of 4.3 weeks (range: 0.7-27.9^{+}).

Immune-related colitis

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of diarrhea or colitis was 22.3% (80/358). Grade 2, Grade 3, Grade 4, and Grade 5 cases were reported in 7% (25/358), 5% (18/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively. Median time to onset was 5.1 weeks (range: 0.1- 53.6). Resolution occurred in 70 patients (87.5%) with a median time to resolution of 1.4 weeks (range: 0.1-76.9^{+}).

Immune-related hepatitis

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of liver function test abnormalities was 13.4% (48/358). Grade 2, Grade 3, and Grade 4 cases were reported in 3.1% (11/358), 3.4% (12/358), and 1.1% (4/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 10.6 weeks (range: 1.1-68.3). Resolution occurred in 37 patients (80.4%) with a median time to resolution of 5 weeks (range: 0.3^{+}-45.0^{+}).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of nephritis or renal dysfunction was 7% (25/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.7% (6/358), and 0.6% (2/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 10.6 weeks (range: 0.1-51.3). Resolution occurred in 14 patients (56%) with a median time to resolution of 6.3 weeks (range: 0.1^{+}-82.9^{+}).

Immune-related endocrinopathies

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of thyroid disorders was 24% (86/358). Grade 2 and Grade 3 thyroid disorders were reported in 12.3% (44/358) and 0.3% (1/358) of patients, respectively. Hypophysitis occurred in 1.4% (5/358) of patients. Grade 2 and Grade 3 cases were reported in 0.6% (2/358) and 0.8% (3/358) of patients, respectively. Grade 2 hypopituitarism occurred in 0.3% (1/358) of patients. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (6/358) and 1.4% (5/358) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus was not reported. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 12.1 weeks (range: 1.9-58.3). Resolution occurred in 30 patients (35.3%). Time to resolution ranged from 1.4 to 72.4^{+} weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of rash was 37.7% (135/358). Grade 2, Grade 3, and Grade 4 cases were reported in 11.5% (41/358), 4.2% (14/358), and 0.3% (1/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 3.3 weeks (range: 0.1-83.1). Resolution occurred in 96 patients (71.6%) with a median time to resolution of 9.4 weeks (range: 0.1^{+}-84.1^{+}).

Infusion reactions

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of hypersensitivity/infusion reactions was 4.7% (17/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively. No Grade 5 cases were reported.

Description of selected adverse reactions - nivolumab in combination with chemotherapy

Immune-related pneumonitis

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of pneumonitis including interstitial lung disease was 1.1% (2/176). Both cases were Grade 2. Median time to onset was 10.4 weeks (range: 10.3-10.6). Resolution occurred in 2 patients (100%) with a median time to resolution of 16.1 weeks (range: 5.7-26.6).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC, or EAC, the incidence of pneumonitis including interstitial lung disease was 5.1% (40/782). Grade 2, Grade 3, and Grade 4 cases were reported in 2.3% (18/782), 1.4% (11/782), and 0.4% (3/782) of patients, respectively. No Grade 5 cases were reported in this study. Median time to onset was 23.9 weeks (range: 1.6-96.9). Resolution occurred in 28 patients (70%) with a median time to resolution of 10.1 weeks (range: 0.3^{+}-121.3^{+}).

In patients treated with nivolumab 240 mg in combination with chemotherapy in ESCC, the incidence of pneumonitis including interstitial lung disease was 5.8% (18/310). Grade 2 and Grade 3 cases were reported in 3.2% (10/310) and 0.6% (2/310) of patients, respectively. Median time to onset was 31.2 weeks (range: 5.0-85.1). Resolution occurred in 12 patients (66.7%) with a median time to resolution of 12.1 weeks (range: 1.0-39.9^{+}).

Immune-related colitis

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of diarrhea was 5.7% (10/176). Grade 2 and Grade 3 cases were reported in 0.6% (1/176) in each grade, respectively. Median time to onset was 1.0 week (range: 0.3-4.9). Resolution occurred in all patients (100%) with a median time to resolution of 0.7 week (range: 0.1-1.3).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC or EAC, the incidence of diarrhea or colitis was 33.5% (262/782). Grade 2, Grade 3, and Grade 4 cases were reported in 10.2% (80/782), 4.9% (38/782), and 0.6% (5/782) of patients, respectively. No Grade 5 cases were reported in this study. Median time to onset was 4.3 weeks (range: 0.1-93.6). Resolution occurred in 228 patients (87.4%) with a median time to resolution of 1.6 weeks (range: 0.1-117.6^{+}).

In patients treated with nivolumab 240 mg in combination with chemotherapy in ESCC, the incidence of diarrhea or colitis was 20.6% (64/310). Grade 2, Grade 3, and Grade 4 cases were reported in 7.4% (23/310), 1.9% (6/310), and 0.3% (1/310) of patients, respectively. Median time to onset was 5.1 weeks (range: 0.3-53.1). Resolution occurred in 58 patients (90.6%) with a median time to resolution of 1.5 weeks (range: 0.1-65.9^{+}).

Immune-related hepatitis

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of liver function test abnormalities was 7.4% (13/176). All cases were reported as Grade 1. Median time to onset was 1.3 weeks (range: 1.0-6.9). Resolution occurred in 13 patients (100%) with a median time to resolution of 2.4 weeks (range:0.7-21.1).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC or EAC, the incidence of liver function test abnormalities was 26% (203/782). Grade 2 and Grade 3 cases were reported in 9.0% (70/782) and 3.7% (29/782) of patients, respectively. No Grade 4 or Grade 5 cases were reported in this study. Median time to onset was 7.9 weeks (range: 0.1-61.3). Resolution occurred in 156 patients (78%) with a median time to resolution of 10.1 weeks (range: 0.4-150.6^{+}).

In patients treated with nivolumab 240 mg in combination with chemotherapy in ESCC, the incidence of liver function test abnormalities was 10.3% (32/310). Grade 2, Grade 3, and Grade 4 cases were reported in 1.9% (6/310), 1.9% (6/310), and 0.3% (1/310) of patients, respectively. Median time to onset was 7.9 weeks (range: 0.3-84.1). Resolution occurred in 28 patients (90.3%) with a median time to resolution of 2.4 weeks (range: 0.4-24.0^{+}).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of renal dysfunction including acute kidney injury was 7.4% (13/176). Grade 2 and Grade 3 cases were reported in 1.1 (2/176) and 0.6 (1/176) of patients, respectively. Median time to onset was 1.3 weeks (range: 0.9-9.1). Resolution occurred in 10 patients (76.9%) with a median time to resolution of 2.9 weeks (range: 0.7-140.7^{+}).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC or EAC, the incidence of nephritis or renal dysfunction was 3.3% (26/782). Grade 2, Grade 3, and Grade 4 cases were reported in 1% (8/782), 0.6% (5/782), and 0.1% (1/782) of patients, respectively. No Grade 5 cases were reported in this study. Median time to onset was 12.4 weeks (range: 1.7-59.4). Resolution occurred in 19 patients (73.1%) with a median time to resolution of 3.1 weeks (range: 0.1-42.4^{+}).

In patients treated with nivolumab 240 mg in combination with chemotherapy in ESCC, the incidence of renal dysfunction was 23.9% (74/310). Grade 2, Grade 3, and Grade 4 cases were reported in 10.6% (33/310), 1.9% (6/310), and 0.3% (1/310) of patients, respectively. Median time to onset was 10.1 weeks (range: 0.7-60.7). Resolution occurred in 42 patients (56.8%) with a median time to resolution of 17.1 weeks (range: 0.4-128.1^{+})

Immune-related endocrinopathies

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of thyroid disorders was 5.1% (9/176). Grade 2 thyroid disorders were reported in 0.6% (1/176) of patients. Diabetes mellitus (Grade 1) was reported in 0.6% (1/176) of patients. Median time to onset of these endocrinopathies was 6.1 weeks (range: 3.1-10.7). Resolution occurred in 7 patients (70.0%). Time to resolution ranged from 0.9 to 169.1^{+} weeks

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC or EAC, the incidence of thyroid disorders was 12.3% (96/782). Grade 2 thyroid disorder was reported in 6% (47/782) of patients. There were no cases of Grade 3 thyroid disorder. Grade 3 hypophysitis occurred in 0.1% (1/782) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.3% (2/782) and 0.3% (2/782) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 0.4% (3/782) and 0.1% (1/782) of patients, respectively. Grade 2 and Grade 3 Diabetes mellitus including Type 1 diabetes mellitus were reported in 0.3% (2/782) of patients. Median time to onset of these endocrinopathies was 15.0 weeks (range: 2.0-124.3). Resolution occurred in 46 patients (43%). Time to resolution ranged from 0.4 to 139.1^{+} weeks.

In patients treated with nivolumab 240 mg in combination with chemotherapy in ESCC, the incidence of thyroid disorders was 9.7% (30/310). Grade 2 thyroid disorders were reported in 4.2% (13/310) of patients. Grade 2 and Grade 3 adrenal insufficiency cases were reported in 1.6% (5/310) and 0.3% (1/310) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus and fulminant Type 1 diabetes mellitus (1 patient with Grade 3 and 1 with Grade 4), and diabetic ketoacidosis (1

patient with Grade 4), were reported. Median time to onset of these endocrinopathies was 13.0 weeks (range: 5.0-100.0). Resolution occurred in 10 patients (28.6%). Time to resolution ranged from 4.1 to 125.6^{+} weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of rash was 22.2% (39/176). Grade 2 and Grade 3 cases were reported in 5.7% (10/176) and 2.3% (4/176) of patients, respectively. Median time to onset was 1.3 weeks (range: 0.1-6.3). Resolution occurred in 36 patients (92.3%) with a median time to resolution of 3.0 weeks (range: 0.3-142.7^{+}).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC, or EAC, the incidence of rash was 27.4% (214/782). Grade 2 and Grade 3 cases were reported in 7% (55/782) and 3.3% (26/782) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 9.6 weeks (range: 0.1-97.4). Resolution occurred in 124 patients (57.9%) with a median time to resolution of 23.4 weeks (range: 0.1-153.6^{+}).

In patients treated with nivolumab 240 mg in combination with chemotherapy in ESCC, the incidence of rash was 17.1% (53/310). Grade 2 and Grade 3 cases were reported in 4.5% (14/310) and 0.3% (1/310) of patients, respectively. Median time to onset was 5.9 weeks (range: 0.1-61.1). Resolution occurred in 40 patients (75.5%) with a median time to resolution of 8.1 weeks (range: 0.1-157.0^{+}).

Infusion reactions

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of hypersensitivity/infusion reactions was 6.3% (11/176). Grade 2, Grade 3, and Grade 4 cases were reported in 1.1% (2/176), 1.7% (3/176), and 0.6% (1/176) of patients, respectively.

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, the incidence of hypersensitivity/infusion reactions was 14.2% (111/782). Grade 2, Grade 3 and Grade 4 cases were reported in 8.8% (69/782), 1.9% (15/782) and 0.3% (2/782) of patients, respectively.

In patients treated with nivolumab 240 mg in combination with chemotherapy in ESCC, the incidence of hypersensitivity/infusion reactions was 1.9% (6/310). All 6 patients were Grade 1 or 2 in severity, both were 1.0% (3/310).

Description of selected adverse reactions - nivolumab in combination with cabozantinib

Immune-related pneumonitis

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of pneumonitis including interstitial lung disease was 5.3% (17/320). Grade 2 and Grade 3 cases were reported in 1.9% (6/320) and 1.6% (5/320) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 24 weeks (range: 12.3 - 74.3 weeks). Resolution occurred in 12 patients (70.6%) with a median time to resolution of 6.36 weeks (range: 0.1^{+}- 36.9^{+} weeks).

Immune-related colitis

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of diarrhoea, colitis, frequent bowel movements or enteritis was 57.5% (184/320). Grade 2 and Grade 3 cases were reported in 25% (80/320) and 5.3% (17/320) of patients, respectively. Grade 4 were reported in 0.6% (2/320). No Grade 5 cases were reported. Median time to onset was 12.36 weeks (range: 0.3 - 75.7 weeks). Resolution occurred in 127 patients (69.4%) with a median time to resolution of 11.14 weeks (range: 0.1 - 109.1^{+} weeks).

Immune-related hepatitis

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of liver function test abnormalities was 40% (128/320). Grade 2, Grade 3, and Grade 4 cases were reported in 15% (48/320), 9.7% (31/320), and 0.6% (2/320) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 8.14 weeks (range: 0.1 -88.3 weeks). Resolution occurred in 99 patients (77.3%) with a median time to resolution of 9.14 weeks (range: 0.1 - 65.7^{+} weeks).

Elevated liver enzymes when nivolumab is combined with cabozantinib in RCC

In a clinical study of previously untreated patients with RCC receiving nivolumab in combination with cabozantinib, a higher incidence of Grades 3 and 4 ALT increased (9.8%) and AST increased (7.9%) were observed, compared to nivolumab alone and cabozantinib 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 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. There were no Grade 5 hepatic events.

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of nephritis, immune mediated nephritis, renal failure, acute kidney injury, blood creatinine increased or blood urea increased was 9.7% (31/320). Grade 2 and Grade 3 cases were reported in 3.4% (11/320), and 1.3% (4/320), respectively. No Grade 4 or 5 cases were reported. Median time to onset was 14.14 weeks (range: 2.1 - 86 weeks.). Resolution occurred in 21 patients (70%) with a median time to resolution of 3.5 weeks (range: 0.6 - 83.9^{+} weeks).

Immune-related endocrinopathies

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of thyroid disorders was 42.2% (135/320). Grade 2 and Grade 3 thyroid disorders were reported in 21.9% (70/320) and 0.9% (3/320) of patients, respectively. Hypophysitis occurred in 0.6% (2/320) of patients. Grade 2 and Grade 3 cases were reported in 1% (0.3/320), and 0.3% (1/320) of patients, respectively.

Grade 2, and Grade 3 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 1.9% (6/320) and 1.9% (6/320) of patients, respectively. No Grade 4 or 5 endocrinopathies were reported. Median time to onset of these endocrinopathies was 12.4 weeks (range: 2.0-84.7 weeks). Resolution occurred in 47 patients (34.3%). Time to resolution ranged from 0.9 to 101.4^{+} weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of rash was 62.2% (199/320). Grade 2 and Grade 3 cases were reported in 22.5% (72/320) and 10.6% (34/320) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 6.14 weeks (range: 0.1- 92.3 weeks). Resolution occurred in 131 patients (65.8%) with a median time to resolution of 17.71 weeks (range: 0.1 - 106.6^{+}weeks).

Infusion reactions

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of hypersensitivity/infusion reactions was 2.5% (8/320). All 8 patients were Grade 1 or 2 in severity. Grade 2 cases were reported in 0.3% (1/320) of patients. No Grade 3-5 cases were reported.

4.8.2 Postmarketing experience

The following event has been identified during post approval use of nivolumab or nivolumab in combination with ipilimumab or other therapeutic agents. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Eye disorders: Vogt-Koyanagi-Harada syndrome

Immune system disorders: solid organ transplant rejection, graft-versus-host-disease

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH) autoimmune hemolytic anemia

Cardiac disorder: pericarditis

Nervous system disorders: myelitis (including transverse myelitis)

4.8.3 Laboratory findings

A summary of laboratory abnormalities that worsened from baseline is presented in Table 10 through 19.

Table 10: Laboratory abnormalities: nivolumab monotherapy

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
	Nivolumab monotherapy		
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**
Anemia[b]	4407	1538 (34.9)	212 (4.8)
Thrombocytopenia	4404	549 (12.5)	34 (0.8)
Leukopenia	4415	675 (15.3)	33 (0.7)
Lymphopenia	4391	1741 (39.6)	419 (9.5)
Neutropenia	4394	564 (12.8)	39 (0.9)
Increased alkaline phosphatase	4368	1121 (25.7)	118 (2.7)
Increased AST	4383	1264 (28.8)	148 (3.4)
Increased ALT	4392	1011 (23.0)	114 (2.6)
Increased total bilirubin	4389	425 (9.7)	67 (1.5)
Increased creatinine	4398	1234 (28.1)	35 (0.8)
Increased total amylase	2282	446 (19.5)	95 (4.2)
Increased total lipase	2500	554 (22.2)	184 (7.4)
Hypercalcemia	3760	384 (10.2)	42 (1.1)
Hypocalcemia	3760	641 (17.0)	26 (0.7)
Hyperkalemia	4339	861 (19.8)	76 (1.8)
Hypokalemia	4339	468 (10.8)	66 (1.5)
Hypermagnesemia[c]	3035	158 (5.2)	21 (0.7)
Hypomagnesemia[c]	3035	458 (15.1)	11 (0.4)
Hypernatremia	4345	248 (5.7)	4 (<0.1)
Hyponatremia	4345	1208 (27.8)	244 (5.6)
Hyperglycemia[c]	485	195(40.2)	13(2.7)
Hypoglycemia[d]	1016	118(11.6)	13 (1.3)
Albumin	754	202 (26.8)	7 (0.9)

Toxicity scale: CTC Version 4.0.
Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy, except for ONO-4538-12. For ONO-4538-12 includes events reported between the first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period. The frequencies are regardless of causality.
[a] The total number of patients who had both baseline and on-study laboratory measurements available.
[b] Per anemia criteria in CTC version 4.0, there is no Grade 4 for hemoglobin.
[c] Does not include ONO-4538-12.
[d] Does not include CA209066, CA209037, CA209017, CA209057, CA209025, and CA209039

Table 11: Laboratory abnormalities: nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg (RCC)

Number (%) of Patients with Worsening Laboratory Test from Baseline			
	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC		
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**
Anemia[b]	541	231 (42.7)	18 (3.3)
Thrombocytopenia	541	96 (17.7)	7 (1.3)
Leukopenia	541	85 (15.7)	8 (1.5)
Lymphopenia	540	204 (37.8)	36 (6.7)
Neutropenia	540	76 (14.1)	11 (2)
Increased alkaline phosphatase	542	167 (30.8)	14 (2.6)
Increased AST	541	225 (41.6)	33 (6.1)
Increased ALT	542	235 (43.4)	44 (8.1)
Increased total bilirubin	541	74 (13.7)	8 (1.5)
Increased creatinine	541	215 (39.7)	14 (2.6)
Increased total amylase	491	188 (38.3)	61 (12.4)
Increased total lipase	518	236 (45.6)	97 (18.7)
Hypercalcemia	529	71 (13.4)	9 (1.7)
Hypocalcemia	529	115 (21.7)	6 (1.1)
Hyperkalemia	534	147 (27.5)	15 (2.8)
Hypokalemia	534	61 (11.4)	13 (2.4)
Hypermagnesemia	528	34 (6.4)	6 (1.1)
Hypomagnesemia	528	86 (16.3)	2 (0.4)
Hypernatremia	534	40 (7.5)	0
Hyponatremia	534	206 (38.6)	56 (10.5)

Toxicity scale: CTC Version 4.0.
Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.
[a] The total number of patients who had both baseline and on-study laboratory measurements available.
[b] Per anemia criteria in CTC version 4.0, there is no Grade 4 for hemoglobin.

Table 12: Laboratory abnormalities: nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg (NSCLC and malignant pleural mesothelioma)

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	Nivolumab 3mg/kg in combination with ipilimumab 1 mg/kg in NSCLC			Nivolumab 3mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma		
Test	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Anemia	556	255 (45.9)	20 (3.6)	297	127 (42.8)	7 (2.4)
Thrombocytopenia	555	58 (10.5)	5 (0.9)	296	26 (8.8)	3 (1.0)
Leukopenia	559	35 (6.3)	3 (0.5)	297	24 (8.1)	3 (1.0)
Lymphopenia	553	254 (45.9)	29 (5.2)	296	128 (43.2)	25 (8.4)
Neutropenia	555	53 (9.5)	5 (0.9)	297	16 (5.4)	4 (1.3)
Increased alkaline phosphatase	552	185 (33.5)	21 (3.8)	295	91 (30.8)	9 (3.1)
Increased AST	551	217 (39.4)	30 (5.4)	294	111 (37.8)	21 (7.1)
Increased ALT	555	202 (36.4)	39 (7.0)	295	108 (36.6)	21 (7.1)
Increased total bilirubin	554	63 (11.4)	6 (1.1)	295	29 (9.8)	5 (1.7)
Increased creatinine	554	119 (21.5)	5 (0.9)	294	60 (20.4)	1 (0.3)
Increased total amylase	494	139 (28.1)	46 (9.3)	259	68 (26.3)	14 (5.4)
Increased total lipase	524	181 (34.5)	73 (13.9)	281	96 (34.2)	36 (12.8)
Hypernatremia	552	42 (7.6)	2 (0.4)	296	23 (7.8)	2 (0.7)
Hyponatremia	552	227 (41.1)	64 (11.6)	296	94 (31.8)	24 (8.1)
Hyperkalemia	551	151 (27.4)	19 (3.4)	296	88 (29.7)	12 (4.1)
Hypokalemia	551	83 (15.1)	22 (4.0)	296	30 (10.1)	6 (2.0)
Hypercalcemia	545	75 (13.8)	10 (1.8)	290	31 (10.7)	0
Hypocalcemia	545	155 (28.4)	9 (1.7)	290	83 (28.6)	1 (0.3)
Hypermagnesemia	542	62 (11.4)	19 (3.5)	287	14 (4.9)	0
Hypomagnesemia	542	115 (21.2)	3 (0.6)	287	52 (18.1)	0
Hyperglycemia	-	-	-	109	57 (52.3)	3 (2.8)

Table 12: Laboratory abnormalities: nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg (NSCLC and malignant pleural mesothelioma)

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
Hypoglycemia	-	-	-	109	10 (9.2)	0

Toxicity scale: CTC Version 4.0.

Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

Table 13: Laboratory abnormalities: nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy (NSCLC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
	Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC		
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**
Anemia[b]	347	243 (70.0)	32 (9.2)
Thrombocytopenia	347	80 (23.1)	15 (4.3)
Leukopenia	347	126 (36.3)	34 (9.8)
Lymphopenia	257	105 (40.9)	15 (5.8)
Neutropenia	346	140 (40.5)	51 (14.7)
Increased alkaline phosphatase	342	106 (31.0)	4 (1.2)
Increased AST	345	102 (29.6)	12 (3.5)
Increased ALT	345	118 (34.2)	15 (4.3)
Increased total bilirubin	344	26 (7.6)	0
Increased creatinine	346	91 (26.3)	4 (1.2)
Increased total amylase	312	95 (30.4)	21 (6.7)
Increased total lipase	337	105 (31.2)	40 (11.9)
Hypercalcemia	345	39 (11.3)	4 (1.2)

Table 13: Laboratory abnormalities: nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy (NSCLC)

		Number (%) of Patients with Worsening Laboratory Test from Baseline	
Hypocalcemia	345	95 (27.5)	5 (1.4)
Hyperkalemia	345	77 (22.3)	6 (1.7)
Hypokalemia	345	53 (15.4)	12 (3.5)
Hypermagnesemia	334	35 (10.5)	1 (0.3)
Hypomagnesemia	334	107 (32.0)	4 (1.2)
Hypernatremia	345	15 (4.3)	0
Hyponatremia	345	128 (37.1)	37 (10.7)
Hyperglycemia	197	89 (45.2)	14 (7.1)
Hypoglycemia	273	35 (12.8)	0

Toxicity scale: CTC Version 4.0.
Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.
[a] The total number of patients who had both baseline and on-study laboratory measurements available.
[b] Per anemia criteria in CTC version 4.0, there is no Grade 4 for hemoglobin.

Table 14: Laboratory abnormalities: nivolumab 240 mg in combination with cabozantinib 40 mg (RCC)

Number (%) of Patients with Worsening Laboratory Test from Baseline			
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**
Hemoglobin [b]	316	117 (37.0)	8 (2.5)
Platelet count	316	129 (40.8)	1 (0.3)
Leukocytes	316	116 (36.7)	1 (0.3)
Lymphocytes (absolute)	228	95 (41.7)	15 (6.6)
Absolute neutrophil count	316	112 (35.4)	10 (3.2)
Increased alkaline Phosphatase	317	131 (41.3)	9 (2.8)
Increased AST	317	245 (77.3)	25 (7.9)
Increased ALT	316	249 (78.8)	31 (9.8)

Table 14: Laboratory abnormalities: nivolumab 240 mg in combination with cabozantinib 40 mg (RCC)

Number (%) of Patients with Worsening Laboratory Test from Baseline			
Increased total Bilirubin	316	54 (17.1)	3 (0.9)
Increased Creatinine	317	121 (38.2)	4 (1.3)
Increased amylase	285	117 (41.1)	28 (9.8)
Increased lipase	308	127 (41.2)	42 (13.6)
Hypernatremia	317	34 (10.7)	0
Hyponatremia	317	140 (44.2)	37 (11.7)
Hyperkalemia	317	113 (35.6)	15 (4.7)
Hypokalemia	317	61 (19.2)	10 (3.2)
Hypercalcemia	314	28 (8.9)	1 (0.3)
Hypocalcemia	314	172 (54.8)	6 (1.9)
Hypermagnesemia	308	44 (14.3)	10 (3.2)
Hypomagnesemia	308	153 (49.7)	5 (1.6)
Hypophosphatemia	307	210 (68.4)	63 (20.7)
Hyperglycemia	170	74 (43.5)	6 (3.5)
Hypoglycemia	262	67 (25.6)	2 (0.8)

Toxicity scale: CTC Version 4.0.
Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.
[a] The total number of patients who had both baseline and on-study laboratory measurements available.
[b] Per anemia criteria in CTC version 4.0, there is no Grade 4 for hemoglobin

Table 15: Laboratory abnormalities: nivolumab 240 mg or 360 mg in combination with chemotherapy (resectable NSCLC and GC, GEJC or EAC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline	Number (%) of Patients with Worsening Laboratory Test from Baseline
	Nivolumab 360 mg in combination with chemotherapy in resectable NSCLC	**Nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC or EAC**

Table 15: Laboratory abnormalities: nivolumab 240 mg or 360 mg in combination with chemotherapy (resectable NSCLC and GC, GEJC or EAC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline			Number (%) of Patients with Worsening Laboratory Test from Baseline		
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**	**N[a]**	**Grades 1-4**	**Grades 3-4**
Hemoglobin	170	107 (62.9)	6 (3.5)	765	450 (58.8)	106 (13.9)
Platelet count	170	41 (24.1)	5 (2.9)	762	515 (67.6)	52 (6.8)
Leukocytes	171	91 (53.2)	9 (5.3)	764	524 (68.6)	90 (11.8)
Lymphocytes (absolute)	170	65 (38.2)	8 (4.7)	763	446 (58.5)	93 (12.2)
Absolute neutrophil count	170	99 (58.2)	37 (21.8)	764	556 (72.8)	224 (29.3)
Aspartate aminotransferase	171	19 (11.1)	0	764	395 (51.7)	35 (4.6)
Alanine aminotransferase	171	39 (22.8)	0	764	283 (37.0)	26 (3.4)
Bilirubin, total	171	1 (0.6)	0	761	182 (23.9)	23 (3.0)
Creatinine	170	29 (17.1)	0	765	115 (15.0)	8 (1.0)
Amylase, total	167	39 (23.4)	6 (3.6)			
Lipase, total	170	31 (18.2)	11 (6.5)			
Hypernatremia	170	3 (1.8)	0	767	84 (11.0)	4 (0.5)
Hyponatremia	170	42 (24.7)	4 (2.4)	767	258 (33.6)	48 (6.3)
Hyperkalemia	170	32 (18.8)	2 (1.2)	766	110 (14.4)	11 (1.4)

Table 15: Laboratory abnormalities: nivolumab 240 mg or 360 mg in combination with chemotherapy (resectable NSCLC and GC, GEJC or EAC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline			Number (%) of Patients with Worsening Laboratory Test from Baseline		
Hypokalemia	170	9 (5.3)	1 (0.6)	766	203 (26.5)	50 (6.5)
Hypercalcemia	169	5 (3.0)	0	748	46 (6.1)	2 (0.3)
Hypocalcemia	169	29 (17.2)	1 (0.6)	748	326 (43.6)	12 (1.6)
Hypermagnesemia	168	3 (1.8)	0			
Hypomagnesemia	168	43 (25.6)	3 (1.8)			
Hyperglycemia	73	27 (37.0)	4 (5.5)	408	166 (40.7)	17 (4.2)
Hypoglycemia	73	2 (2.7)	0	407	48 (11.8)	3 (0.7)

Toxicity scale: CTC Version 4.0.
Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.
[a] The total number of patients who had both baseline and on-study laboratory measurements available.

Table 16: Laboratory abnormalities: nivolumab in combination with chemotherapy (ESCC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline
	Nivolumab in combination with chemotherapy in ESCC

Table 16: Laboratory abnormalities: nivolumab in combination with chemotherapy (ESCC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
Test	**N**[a]	**Grades 1-4**	**Grades 3-4**
Hemoglobin	304	246 (80.9)	65 (21.4)
Platelet count	304	132 (43.4)	10 (3.3)
Leukocytes	305	163 (53.4)	33 (10.8)
Lymphocytes (absolute)	305	69 (51.9)	24 (18.0)
Absolute neutrophil count	305	187 (61.3)	54 (17.7)
Alkaline Phosphatase	305	78 (25.6)	4 (1.3)
Aspartate aminotransferase	305	70 (23.0)	10 (3.3)
Alanine aminotransferase	305	70 (23.0)	7 (2.3)
Bilirubin, total	305	19 (6.2)	1 (0.3)
Creatinine	304	126 (41.4)	7 (2.3)
Hypernatremia	304	27 (8.9)	2 (0.7)
Hyponatremia	304	158 (52.0)	46 (15.1)
Hyperkalemia	305	102 (33.4)	7 (2.3)
Hypokalemia	305	88 (28.9)	28 (9.2)
Hypercalcemia	304	33 (10.9)	8 (2.6)
Hypocalcemia	304	132 (43.4)	9 (3.0)
Hypermagnesemia	60	5 (8.3)	0
Hypomagnesemia	60	21 (35.0)	1 (1.7)
Hyperglycemia	143	49 (34.3)	0
Hypoglycemia	246	44 (17.9)	1 (0.4)

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

Table 17: Laboratory abnormalities: nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg (melanoma and HCC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma		
Test	Na	Grades 1-4	Grades 3-4
Anemia[b]	424	215 (50.7)	12 (2.8)
Thrombocytopenia	422	51 (12.1)	5 (1.2)
Leukopenia	426	60 (14.1)	2 (0.5)
Lymphopenia	421	173 (41.1)	28 (6.7)
Neutropenia	423	64 (15.1)	3 (0.7)
Increased alkaline phosphatase	418	160 (38.3)	18 (4.3)
Increased AST	420	207 (49.3)	52 (12.4)
Increased ALT	425	225 (52.9)	65 (15.3)
Increased total bilirubin	422	54 (12.8)	5 (1.2)
Increased creatinine	424	107 (25.2)	10 (2.4)
Increased total amylase	366	96 (26.2)	32 (8.7)
Increased total lipase	401	164 (40.9)	78 (19.5)
Hypercalcemia	406	29 (7.1)	1 (0.2)
Hypocalcemia	406	133 (32.8)	5 (1.2)
Hyperkalemia	421	73 (17.3)	2 (0.5)
Hypokalemia	421	84 (20.0)	20 (4.8)
Hypermagnesemia	370	11 (3.0)	1 (0.3)
Hypomagnesemia	370	58 (15.7)	0
Hypernatremia	422	20 (4.7)	1 (0.2)
Hyponatremia	422	185 (43.8)	40 (9.5)
Hyperglycemia	75	39 (52.0)	4 (5.3)
Hypoglycemia	71	8 (11.3)	0

Toxicity scale: CTC Version 4.0.
Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.

a The total number of patients who had both baseline and on-study laboratory measurements available.

b Per anemia criteria in CTC version 4.0, there is no Grade 4 for hemoglobin.

Table 18: Laboratory abnormalities: nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg (unresectable HCC)

Test	Number (%) of Patients with Worsening Laboratory Test from Baseline		
	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in unresectable HCC		
	N[a]	Grades 1-4	Grades 3-4
Anemia[b]	329	145 (44.1)	17 (5.2)
Lymphopenia	328	130 (39.6)	20 (6.1)
Thrombocytopenia	329	89 (27.1)	13 (4.0)
Neutropenia	328	78 (23.8)	13 (4.0)
Leukopenia	329	54 (16.4)	11 (3.3)
Increased AST	330	205 (62.1)	94 (28.5)
Increased ALT	331	201 (60.7)	55 (16.6)
Increased total lipase	310	181 (58.4)	50 (16.1)
Increased albumin	329	160 (48.6)	3 (0.9)
Hyponatremia	328	149 (45.4)	18 (5.5)
Hyperglycemia	168	74 (44.0)	25 (14.9)
Increased total bilirubin	331	142 (41.9)	30 (9.1)
Increased total amylase	291	120 (41.2)	17 (5.8)
Increased alkaline phosphatase	329	119 (36.2)	4 (1.2)
Hypocalcemia	326	104 (31.9)	3 (0.9)
Increased creatinine	330	85 (25.8)	8 (2.4)
Hypokalemia	328	68 (20.7)	7 (2.1)
Hypomagnesemia	326	62 (19.0)	3 (0.9)
Hyperkalemia	328	62 (18.9)	9 (2.7)
Hypercalcemia	326	30 (9.2)	2 (0.6)
Hypoglycemia	322	27 (8.4)	2 (0.6)
Hypermagnesemia	326	23 (7.1)	7 (2.1)
Hypernatremia	328	14 (4.3)	0

Toxicity scale: CTCAE Version: 4.0 for AST, ALP, Total bilirubin, ALT and Hyperglycemia; and 5.0 for other parameters in CA2099DW.
Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.

a The total number of patients who had both baseline and on-study laboratory measurements available.

b Per anemia criteria in CTC version 5.0, there is no Grade 4 for hemoglobin.

Table 19: Laboratory abnormalities: nivolumab 240 mg in combination with ipilimumab 1 mg/kg (first-line treatment of MSI-H/dMMR CRC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
	Nivolumab 240 mg in combination with ipilimumab 1 mg/kg in MSI/H/dMMR CRC		
Test	N[a]	Grades 1-4	Grades 3-4
Anemia[b]	195	72 (36.9)	6 (3.1)
Thrombocytopenia	195	19 (9.7)	1 (0.5)
Leukopenia	195	25 (12.8)	0
Lymphopenia	195	58 (29.7)	7 (3.6)
Neutropenia	195	36 (18.5)	2 (1.0)
Increased alkaline phosphatase	195	48 (24.6)	3 (1.5)
Increased AST	194	78 (40.2)	7 (3.6)
Increased ALT	195	80 (41.0)	8 (4.1)
Increased total bilirubin	195	35 (17.9)	3 (1.5)
Increased creatinine	195	56 (28.7)	6 (3.1)
Increased total amylase	101	40 (39.6)	4 (4.0)
Increased total lipase	103	43 (41.7)	10 (9.7)
Hypernatremia	194	13 (6.7)	0
Hyponatremia	194	65 (33.5)	7 (3.6)
Hyperkalemia	194	57 (29.4)	2 (1.0)
Hypokalemia	194	26 (13.4)	2 (1.0)
Hypercalcemia	194	34 (17.5)	0
Hypocalcemia	194	47 (24.2)	1 (0.5)
Hypoglycemia	189	25 (13.2)	0

Toxicity scale: CTCAE Version 5.0.
Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality. Hyperglycemia was not reported as a laboratory term because value ranges in severity grading was removed in CTCAE V.5.0 compared to V.4.0, and changed to quality definitions.

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

[b] Per anemia criteria in CTC version 5.0, there is no Grade 4 for hemoglobin.

4.8.4 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response to nivolumab. Of 3874 patients who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks and evaluable for the presence of anti-product-antibodies, 373 patients (9.6%) tested positive for treatment-emergent anti-product-antibodies by an electro chemi luminescent (ECL) assay. Twenty-one patients (0.5%) had neutralizing antibodies.

Co-administration with chemotherapy did not affect nivolumab immunogenicity. Of the 276 patients who were treated with nivolumab 240 mg every 2 weeks in combination with chemotherapy and evaluable for the presence of anti-product-antibodies in the CA209648 study, 12 patients (4.3%) tested positive for treatment-emergent anti-product-antibodies with 3 patients (1.1 %) testing positive for neutralizing antibodies.

Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 36.7% and 25.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks in NSCLC and and malignant pleural mesothelioma, respectively. and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks.. The incidence of neutralizing antibodies against nivolumab was 0.5% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 1.4% and 0.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks in NSCLC and malignant pleural mesothelioma, respectively, and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks.. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 13.7% and neutralizing antibodies against ipilimumab ranged from 0 to 0.4%.

Of the patients who were treated with nivolumab in combination with ipilimumab and platinum-based chemotherapy and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 33.8% and the incidence of neutralizing antibodies was 2.6%. Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-ipilimumab antibodies or neutralizing antibodies against ipilimumab, the incidence of anti-ipilimumab antibodies was 7.5%, and neutralizing antibodies was 1.6%.

Although the clearance of nivolumab was increased by approximately 20% when anti-nivolumab antibodies were present, there was no evidence of loss of efficacy or altered toxicity profile in presence of nivolumab antibodies.

4.9 OVERDOSE

No cases of overdose have been reported in clinical trials.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Nivolumab is a fully human IgG4 monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumors or other cells in the tumor microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumor responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumor growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumor activity.

5.2 Pharmacodynamics

5.2.1 Clinical Trial Information

Non-small cell lung cancer (NSCLC)

Randomized phase 3 study vs. docetaxel (CA209017)

The safety and efficacy of nivolumab 3 mg/kg-or the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomized, open-label study (CA209017). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an ECOG performance status score of 0 or 1. Patients were enrolled regardless of their PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, 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.

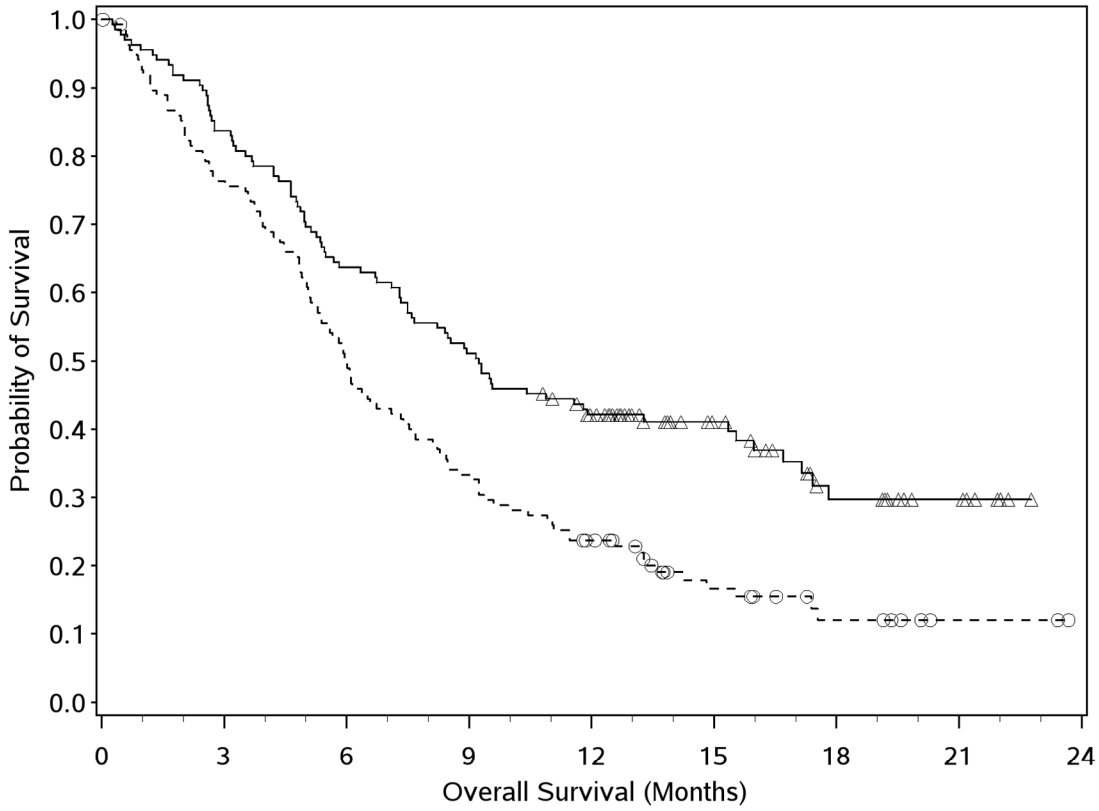
Patients were randomized on a 1:1 basis to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks or docetaxel 75 mg/m^2 every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments, according to RECIST, version 1.1, were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. In addition, symptom improvement and overall health status were assessed using the Lung Cancer Symptom Score (LCSS) average symptom burden index and the EQ-5D Visual Analogue Scale (EQ-VAS), respectively.

A total of 272 patients were randomized to either nivolumab (n=135) or docetaxel (n=137). Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 39-85) with 44% ≥65 years of age and 11% ≥75 years of age. The majority of patients were

white (93%) and male (76%). Thirty-one percent had progressive disease reported as the best response to their most recent prior regimen and 45% received nivolumab within 3 months of completing their most recent prior regimen. Baseline ECOG performance status was 0 (24%) or 1 (76%).

Nivolumab demonstrated a statistically significant improvement in OS compared with docetaxel. At the pre-defined PD-L1 tumor membrane expression cut-off levels of 1%, 5%, and 10%, similar survival was observed regardless of PD-L1 expression status. OS results are shown in Figure 1. The observed OS benefit was consistently demonstrated across subgroups of patients.

Figure 1: Kaplan-Meier curves of OS (CA209017)



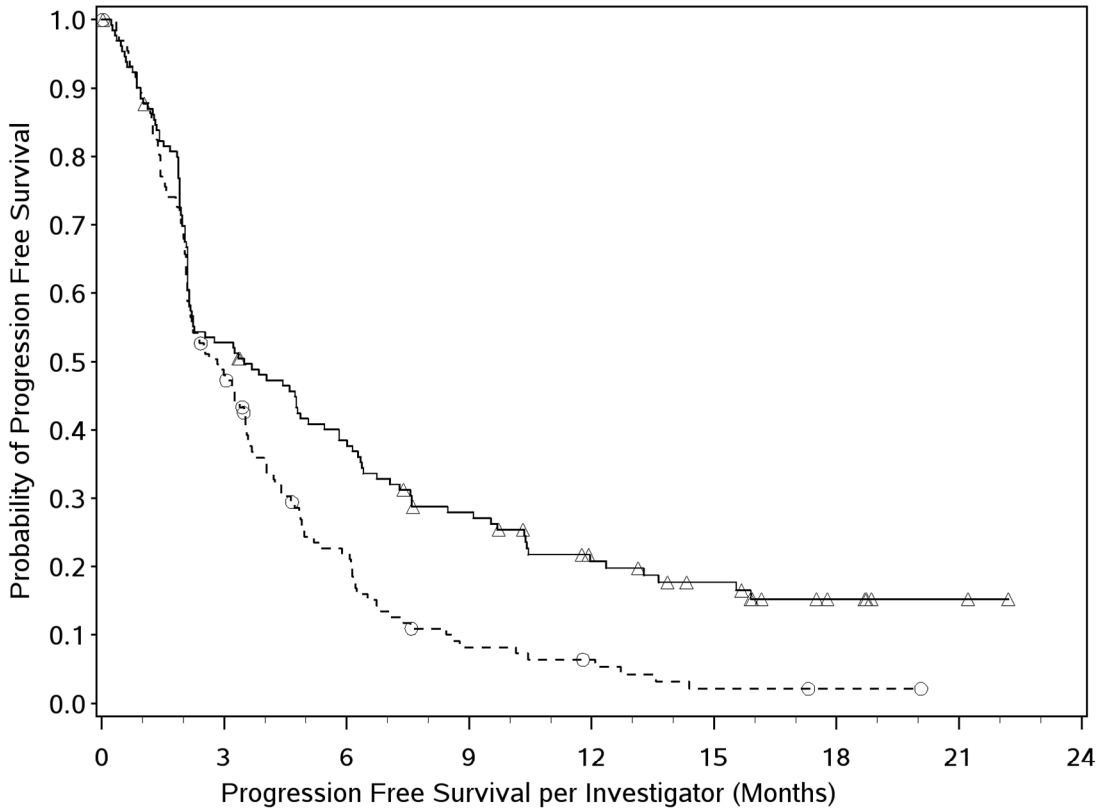
Number of Subjects at Risk

Nivolumab 3 mg/kg	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Nivolumab 3 mg/kg (events : 86/135), median and 95% CI : 9.23 (7.33, 13.27)
Docetaxel (events : 113/137), median and 95% CI : 6.01 (5.13, 7.33)
Hazard Ratio (Nivolumab 3 mg/kg over Docetaxel) and 96.85% CI: 0.59 (0.43, 0.81)
Stratified log-rank p-value: 0.0002

The investigator-assessed ORR using RECIST version 1.1 criteria was significantly higher in the nivolumab group than in the docetaxel group. Nivolumab treatment also demonstrated statistically significant improvement in PFS compared with docetaxel (Figure 2). Efficacy results based on the primary and updated analyses are shown in Table 20.

Figure 2: Kaplan-Meier curves of PFS (CA209017)



Number of Subjects at Risk

Nivolumab 3 mg/kg	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

Nivolumab 3 mg/kg (events : 105/135), median and 95% CI : 3.48 (2.14, 4.86)

Docetaxel (events : 122/137), median and 95% CI : 2.83 (2.10, 3.52)

Hazard Ratio (Nivolumab 3 mg/kg over Docetaxel) and 95% CI: 0.62 (0.47, 0.81)

Stratified log-rank p-value: 0.0004

Table 20: Efficacy results (CA209017)

	nivolumab (n = 135)	docetaxel (n = 137)
Primary analysis Minimum follow-up: 10.6 months		
Overall survival		
Events n (%)	86 (63.7%)	113 (82.5%)
Hazard ratio	0.59	
96.85% CI	(0.43, 0.81)	
p-value	0.0002	
Median (95% CI)	9.2 months (7.3, 13.3)	6.0 months (5.1, 7.3)
Rate (95% CI) at 12 months	42.1% (33.7, 50.3)	23.7% (16.9, 31.1)
Confirmed objective response n (%)	27 (20.0%)	12 (8.8%)
(95% CI)	(13.6, 27.7)	(4.6, 14.8)
Odds ratio (95% CI)	2.64 (1.27, 5.49)	
p-value	0.0083	
Complete response (CR)	1 (0.7%)	0
Partial response (PR)	26 (19.3%)	12 (8.8%)
Stable disease (SD)	39 (28.9%)	47 (34.3%)
Median duration of response (range)	Not reached (2.9-20.5+)	8.4 months (1.4+-15.2+)
Median time to response (range)	2.2 months (1.6-11.8)	2.1 months (1.8-9.5)
Progression-free survival		
Events	105 (77.8%)	122 (89.1%)
Hazard ratio	0.62	
95% CI	(0.47, 0.81)	
p-value	< 0.0004	
Median (95% CI)	3.5 months (2.1, 4.9)	2.8 months (2.1, 3.5)
Rate (95% CI) at 12 months	20.8% (14.0, 28.4)	6.4% (2.9, 11.8)
Updated analysis Minimum follow-up: 24.2 months		
Overall survival[a]		
Events	110 (81.4%)	128 (93.4%)
Hazard ratio	0.62	
95% CI	(0.47, 0.80)	

Table 20: Efficacy results (CA209017)

	nivolumab (n = 135)	docetaxel (n = 137)
Rate (95% CI) at 24 months	22.9% (16.2, 30.3)	8.0% (4.3, 13.3)
Confirmed objective response	20.0%	8.8%
(95% CI)	(13.6, 27.7)	(4.6, 14.8)
Median duration of response		
(range)	25.2 months (2.9-30.4)	8.4 months (1.4^{+}-18.0^{+})
Progression-free survival		
Rate (95% CI) at 24 months	15.6% (9.7, 22.7)	All patients had either progressed, were censored, or lost to follow-up

[a] Six patients (4%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
"+" denotes a censored observation.

The rate of disease-related symptom improvement, as measured by LCSS, was similar between the nivolumab group (18.5%) and the docetaxel group (21.2%). The average LCSS symptom score in the nivolumab group generally decreased (improved) over time and the change from baseline exceeded the clinically meaningful threshold at about 10 months; in the docetaxel group, the average symptom index was stable over the period for which there were enough patients to interpret the data (about 6 months). The average EQ-VAS increased over time for both treatment groups, indicating better overall health status for patients remaining on treatment.

Single-arm phase 2 study (CA209063)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of squamous NSCLC were evaluated in a phase 2, single-arm, multinational, multicenter study (CA209063). All patients had progressed after receiving a platinum doublet-based therapy and at least one additional systemic treatment regimen. Patients were enrolled regardless of their PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, 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.

Patients received 3 mg/kg of nivolumab administered intravenously over 60 minutes every 2 weeks as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments took place at week 8 and every 6 weeks thereafter. The primary efficacy outcome measure was confirmed ORR as assessed by an independent review committee (IRC) according to RECIST version 1.1. Duration and timing of responses were also assessed. Additional outcome measures included IRC-assessed PFS and OS, as exploratory endpoints.

A total of 117 patients received treatment with nivolumab. The median age of patients was 65 years (range: 37-87) with 50% ≥65 years of age and 14% ≥75 years of age. The majority of patients were male (73%) and white (85%). All patients received two or more prior systemic treatments: 35% received two, 44% received three, and 21% received four or more. Sixty-one percent had progressive disease reported as the best response to their most recent prior regimen. The majority of patients (76%) received nivolumab within 3 months of completing their most recent prior regimen.

The most common tumor sites at baseline were lung (86%), lymph node (46%), liver (25%), mediastinum (20%), bone (18%), and kidney (10%). Fifty percent of patients had 3 or more baseline disease sites. Baseline ECOG performance status was 0 (22%) or 1 (78%).

Efficacy results based on a minimum follow up of approximately 11 months are shown in Table 21 and Figure 3.

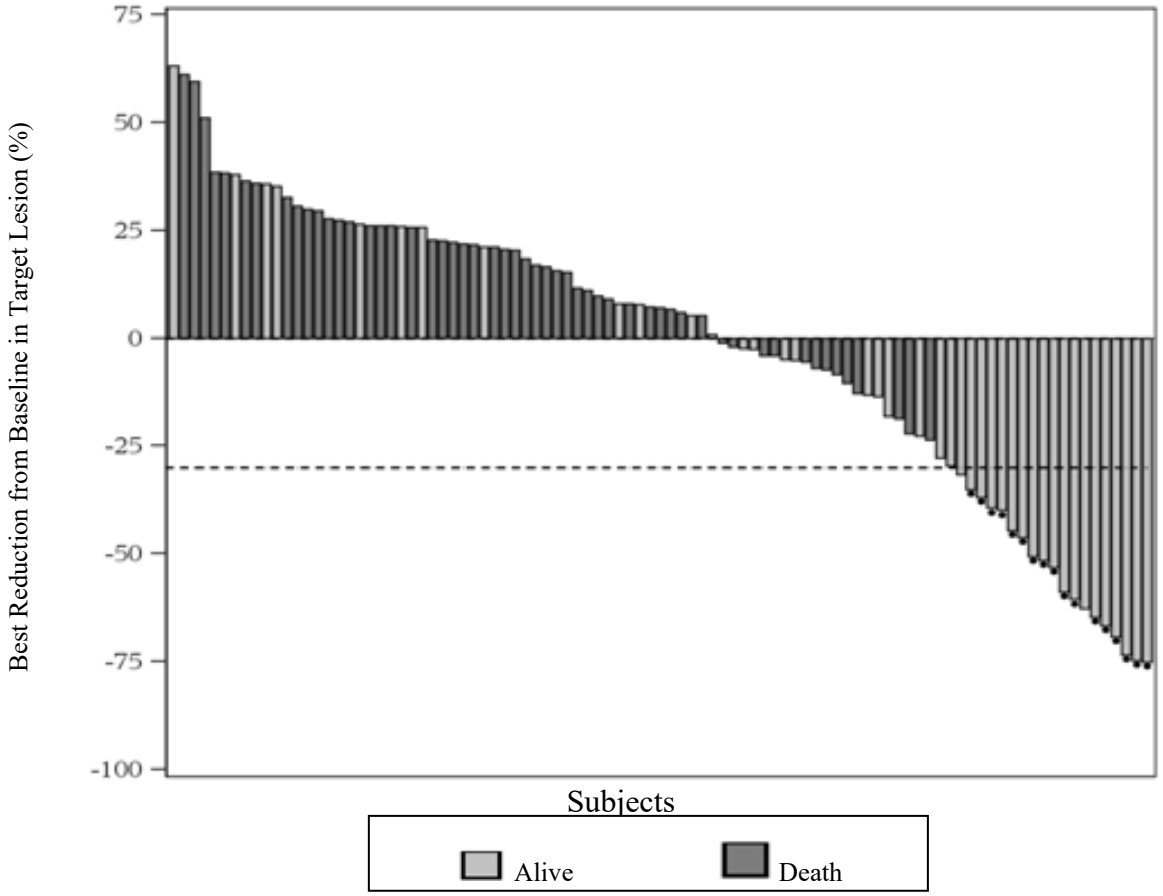
Table 21: Efficacy Results (CA209063)

	nivolumab (n = 117)
Confirmed objective response n (%)	17 (14.5%)
(95% CI)	(8.7, 22.2)
Complete response (CR)	0
Partial response (PR)	17 (14.5%)
Stable disease (SD) [a]	30 (25.6%)
Median duration of response	
Months (range)	Not reached (1.9^{+}- 11.5^{+})
Median time to response	
(range)	3.25 months (1.7 - 8.8)
Median PFS (95% CI)	1.87 months (1.77, 3.15)
PFS rate at 12 months (95% CI)	20 % (12.7, 28.5)
Median OS (95% CI)	8.21 months (6.05, 10.91)
OS rate at 12 months (95% CI)	40.8% (31.6, 49.7)

[a] Median duration of SD was 6 months (95% CI: 4.7, 10.9).
"$^{+}$" denotes a censored observation

At the pre-defined PD-L1 tumor membrane expression cut-off levels of 1%, 5%, and 10%, similar response rates were observed regardless of PD-L1 expression status.

Figure 3: Waterfall plot of best reduction in target lesion, per IRC according to survival status



Note: Symbol ("●") represents confirmed responders.

Randomized phase 3 study vs. docetaxel (CA209057)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced or metastatic non-squamous NSCLC were evaluated in a phase 3, randomized, open-label study (CA209057). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen which may have included maintenance therapy and who had an ECOG performance status score of 0 or 1. An additional line of TKI therapy was allowed for patients with known EGFR mutation or ALK translocation. Patients were enrolled regardless of their PD-L1 status. Patients with active autoimmune disease, symptomatic interstitia l lung disease, 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.

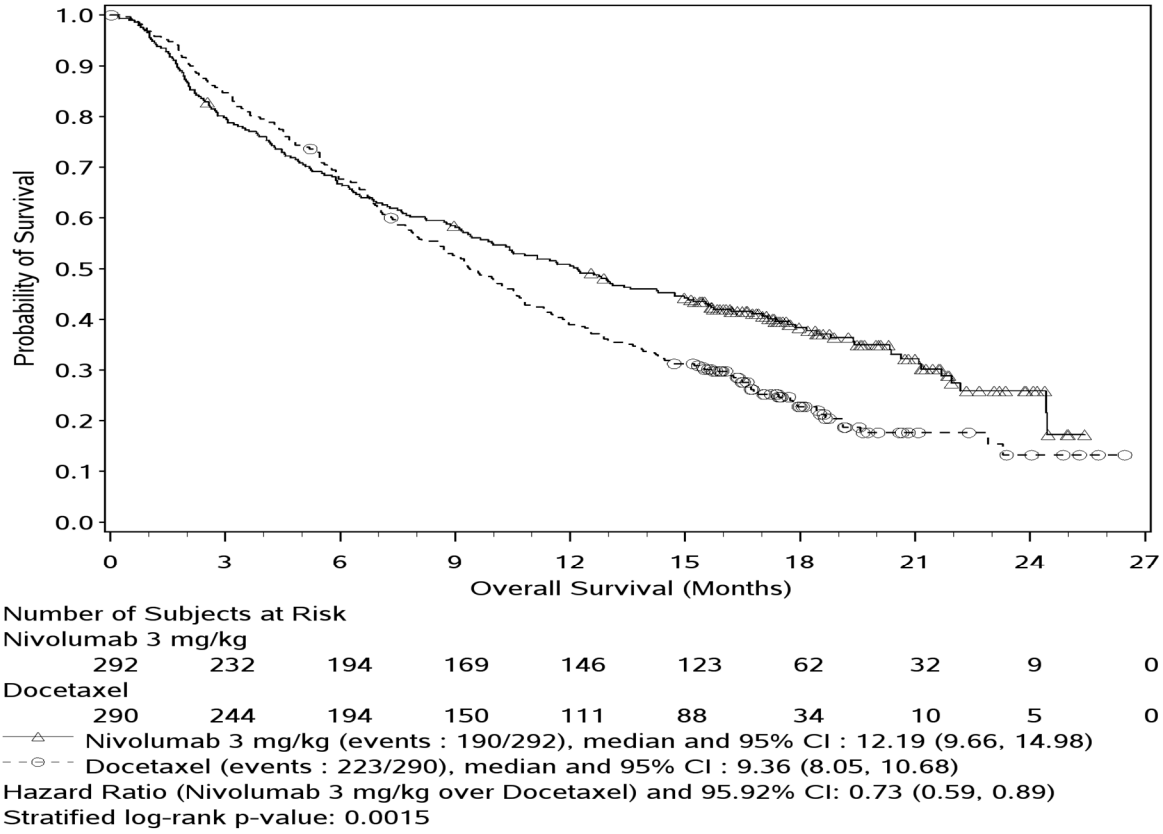
Patients were randomized to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks or docetaxel 75 mg/m^2 every 3 weeks . Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments,

according to RECIST, version 1.1, were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. The study evaluated whether PD-L1 expression was a predictive biomarker for efficacy. In addition, symptom improvement and overall health status were assessed using the LCSS average symptom burden index and the EQ-5D VAS, respectively.

A total of 582 patients were randomized to receive nivolumab (n = 292) or docetaxel (n = 290). Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 21 to 85) with 34% ≥65 years of age and 7% ≥75 years of age. The majority of patients were white (92%) and male (55%). Thirty-nine percent had progressive disease reported as the best response to their most recent prior regimen and 62.5% received nivolumab within 3 months of completing their most recent prior regimen. Baseline ECOG performance status was 0 (31%) or 1 (69%). Seventy-nine percent of patients were former/current smokers.

The Kaplan-Meier curves for OS are shown in Figure 4.

Figure 4: Kaplan-Meier curves of OS (CA209057)



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). Efficacy results are shown in Table 22.

Table 22: Efficacy Results (CA209057)

	nivolumab (n = 292)	docetaxel (n = 290)
Primary analysis		
Minimum follow-up: 13.2 months		
Overall survival n (%)		
Events n (%)	190 (65.1%)	223 (76.9%)
Hazard ratio[a]	0.73	
(95.92% CI)	(0.59, 0.89)	
p-value[b]	0.0015	
Median (95% CI)	12.2 months (9.7, 15.0)	9.4 months (8.1, 10.7)
Rate (95% CI) at 12 months	50.5% (44.6, 56.1)	39.0% (33.3, 44.6)
Confirmed objective response n (%)	56 (19.2%)	36 (12.4%)
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Odds ratio (95% CI)	1.68 (1.07, 2.64)	
p-value	0.0246	
Complete response (CR)	4 (1.4%)	1 (0.3%)
Partial response (PR)	52 (17.8%)	35 (12.1%)
Stable disease (SD)	74 (25.3%)	122 (42.1%)
Median duration of response (range)	17.15 months (1.8-22.6^{+})	5.55 months (1.2^{+}-15.2^{+})
Median time to response (range)	2.1 months (1.2-8.6)	2.6 months (1.4-6.3)
Progression-free survival		
Events n (%)	234 (80.1%)	245 (84.5%)
Hazard ratio	0.92	
95% CI	(0.77, 1.11)	
p-value	0.3932	
Median (95% CI)	2.33 months (2.17, 3.32)	4.21 months (3.45, 4.86)
Rate (95% CI) at 12 months	18.5% (14.1, 23.4)	8.1% (5.1, 12.0)
Updated analysis		
Minimum follow-up: 24.2 months		

Overall survival[c]		
Events n (%)	228 (78.1%)	247 (85.2%)
Hazard ratio[a]	0.75	
(95% CI)	(0.63, 0.91)	
Rate (95% CI) at 24 months	28.7% (23.6, 34.0)	15.8% (11.9, 20.3)
Confirmed objective response	19.2%	12.4%
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Median duration of response		
(range)	17.2 months (1.8-33.7^{+})	5.6 months (1.2^{+}-16.8)
Progression-free survival		
Rate (95% CI) at 24 months	11.9% (8.3, 16.2)	1.0% (0.2, 3.3)

[a] Derived from a stratified proportional hazards model.

[b] 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.

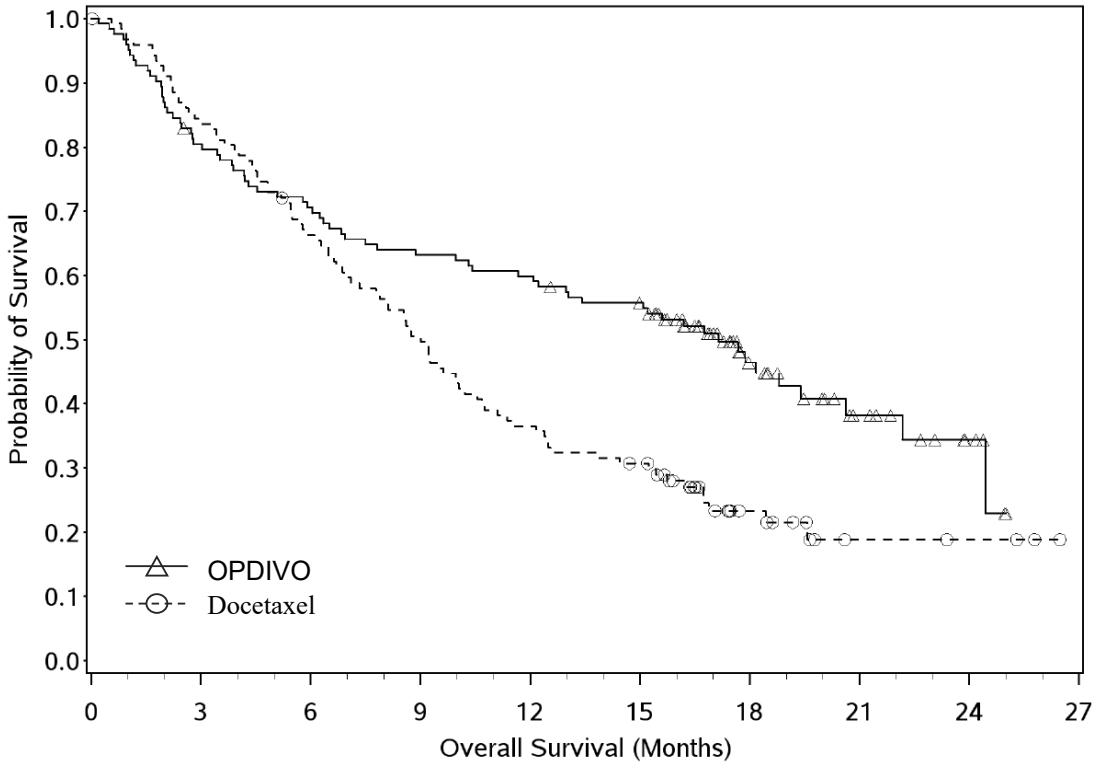
[c] Sixteen patients (6%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.

"$^{+}$"denotes a censored observation.

Pre-study tumor tissue specimens were systematically collected prior to randomization in order to conduct pre-planned analyses of efficacy according to tumor PD-L1 expression. Quantifiable PD-L1 expression was measured in 79% of patients in the nivolumab group and 77% of patients in the docetaxel group. Tumor PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs docetaxel) at each of the predefined PD-L1 expression levels of ≥1% (53% vs 55%), ≥5% (41% vs 38%), or ≥10% (37% vs 35%). Tumor PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Patients with tumor PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of enhanced survival compared to docetaxel, whereas survival was similar to docetaxel in patients with low or no tumor PD-L1 expression. Results are shown below in Figures 5, 6, and 7.

Figure 5: Overall Survival: Patients with ≥1% PD-L1 Expression (CA209057)



Number at Risk									
OPDIVO									
123	98	86	77	73	65	27	13	5	0
Docetaxel									
123	102	80	61	44	36	13	4	3	0

Figure 6: Overall Survival: Patients with <1% PD-L1 Expression (CA209057)

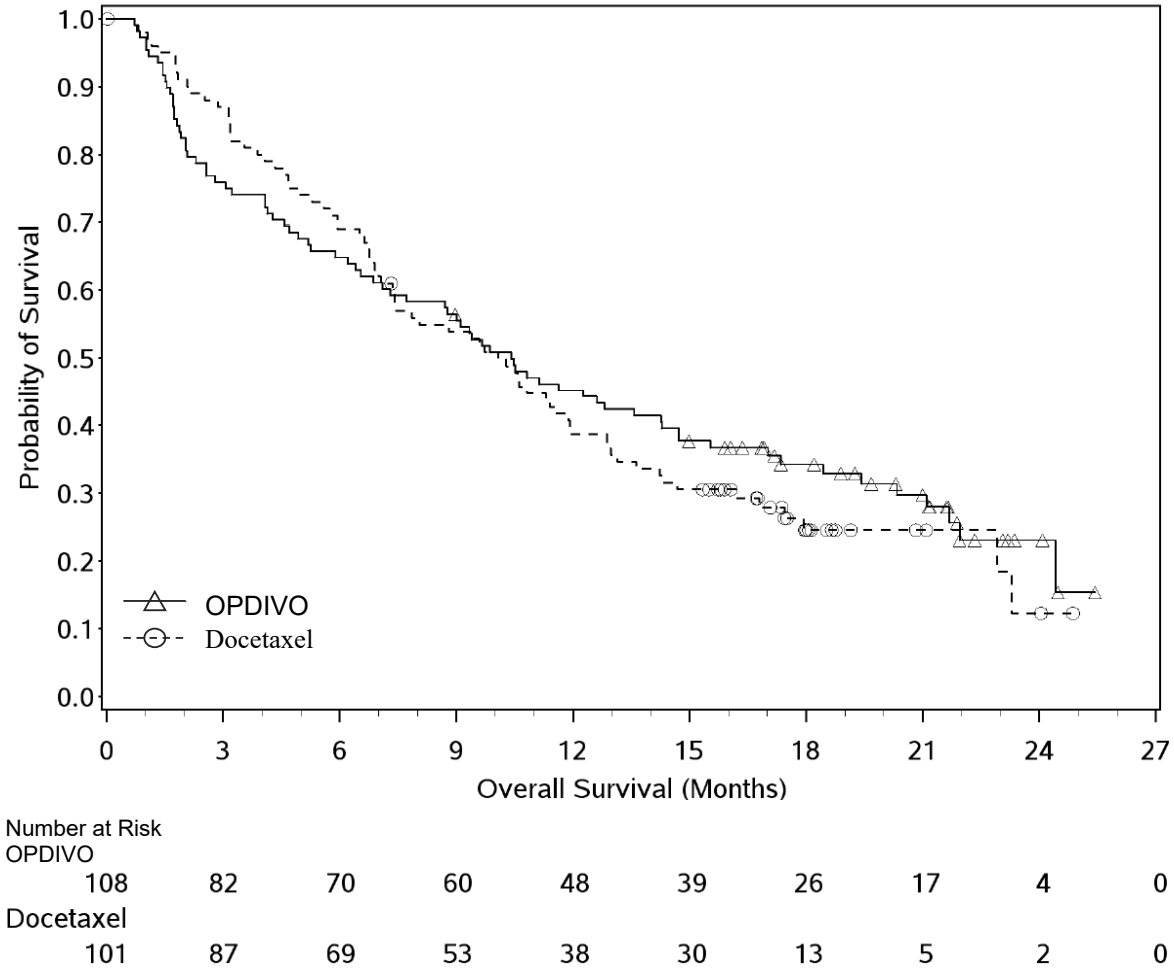
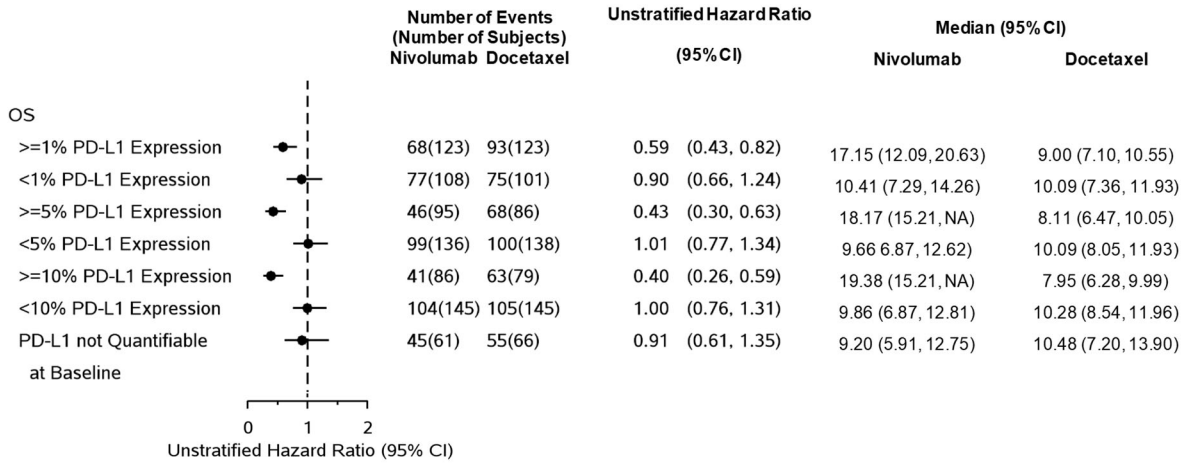


Figure 7: Forest Plot for OS based on PD-L1 Expression (CA209057)



The rate of disease-related symptom improvement, as measured by LCSS, was similar between the nivolumab group (17.8%) and the docetaxel group (19.7%). The average EQ-VAS increased over time for both treatment groups, indicating better overall health status for patients remaining on treatment.

As compared to the overall study population, no meaningful differences in safety were observed based on PD-L1 expression levels of 1% or 5%.

Open-label phase 1 dose-escalation study (MDX1106-03)

The safety and tolerability of nivolumab were investigated in a phase 1, open-label, dose-escalation study in various tumour types, including NSCLC. Of the 306 patients enrolled in the study, 129 had NSCLC and received nivolumab at a dose of 1 mg/kg (n=33), 3 mg/kg (n=37), or 10 mg/kg (n=59) every 2 weeks for a maximum of 2 years. Objective response was reported in 22/129 patients (17% [95% CI: 11.0, 24.7]) in the entire NSCLC cohort (across histologies and dose levels) and 4/18 patients (22% [95% CI: 6.4, 47.6]) with squamous NSCLC treated at the 3 mg/kg dose level.

In the entire NSCLC cohort, the median duration of response was 17 months. The median PFS was 2.3 months (95% CI: 1.8, 3.7). The estimated milestone PFS rates were 22% (95% CI: 15, 30) at 1 year and 9% (95% CI: 4, 15) at 2 years. The median OS was 9.9 months (95% CI: 7.8, 12.4), and the estimated milestone OS rates were 42% (95% CI: 34, 51) at 1 year and 24% (95% CI: 16, 32) at 2 years.

Randomized, open-label, Phase 3 study of nivolumab alone or in combination with ipilimumab or platinum-doublet chemotherapy vs platinum-doublet chemotherapy (CA209227, Part 1)

The safety and efficacy of nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks for the treatment of NSCLC were evaluated in a Phase 3, randomized, open-label study (CA209227, Part 1). The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification ((ASLC)), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors). Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression 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.

Patients were enrolled into Part 1a or Part 1b according to PD-L1 status. In Part 1a, patients with PD-L1 tumor expression ≥1% were randomized 1:1:1 to either nivolumab 3 mg/kg administered intravenously over 30 minutes every 2 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks; platinum-doublet chemotherapy administered every 3 weeks for up to 4 cycles; or nivolumab 240 mg administered intravenously over 30 minutes every 2 weeks. In Part 1b, patients with PD-L1 tumor expression <1% were randomized 1:1:1 to either nivolumab 3 mg/kg administered intravenously over 30 minutes every 2 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks; platinum-doublet chemotherapy administered every 3 weeks for up to 4 cycles; or nivolumab 360 mg administered intravenously over 30 minutes in combination with platinum- doublet chemotherapy every 3 weeks for 4 cycles, followed by nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks. Stratification factors were identical between Part 1a and Part 1b (tumor histology [non-squamous versus squamous]). Platinum-doublet chemotherapy consisted of:

- pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2), or pemetrexed (500 mg/m^2) and carboplatin (AUC 5 or 6) for non-squamous NSCLC;
- or gemcitabine (1000 or 1250 mg/m^2) and cisplatin (75 mg/m^2), or gemcitabine (1000 mg/m^2) and carboplatin (AUC 5) (gemcitabine was administered on Days 1 and 8 of each cycle) for squamous NSCLC.
- Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment continued beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to ipilimumab were permitted to continue nivolumab monotherapy. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.
- In Part 1a, a total of 793 patients were randomized to receive either nivolumab in combination with ipilimumab (n=396) or platinum-doublet chemotherapy (n=397). The median age was 64 years (range: 26 to 87) with 49% of patients ≥65 years and 10% of patients ≥75 years, 76% White, 65% male. Baseline ECOG performance status was 0 (34%) or 1 (65%), 50% with PD-L1 ≥50%, 29% with squamous and 71% with non-squamous histology, 10% had brain metastases, and 85% were former/current smokers.

The study demonstrated a statistically significant benefit in OS, and a clinically meaningful benefit in PFS, ORR, and duration of response for patients randomized to nivolumab in combination with ipilimumab compared to platinum-doublet chemotherapy alone. Efficacy results for patients whose tumors expressed PD-L1 ≥1% are presented in Table 23 and Figure 8 below.

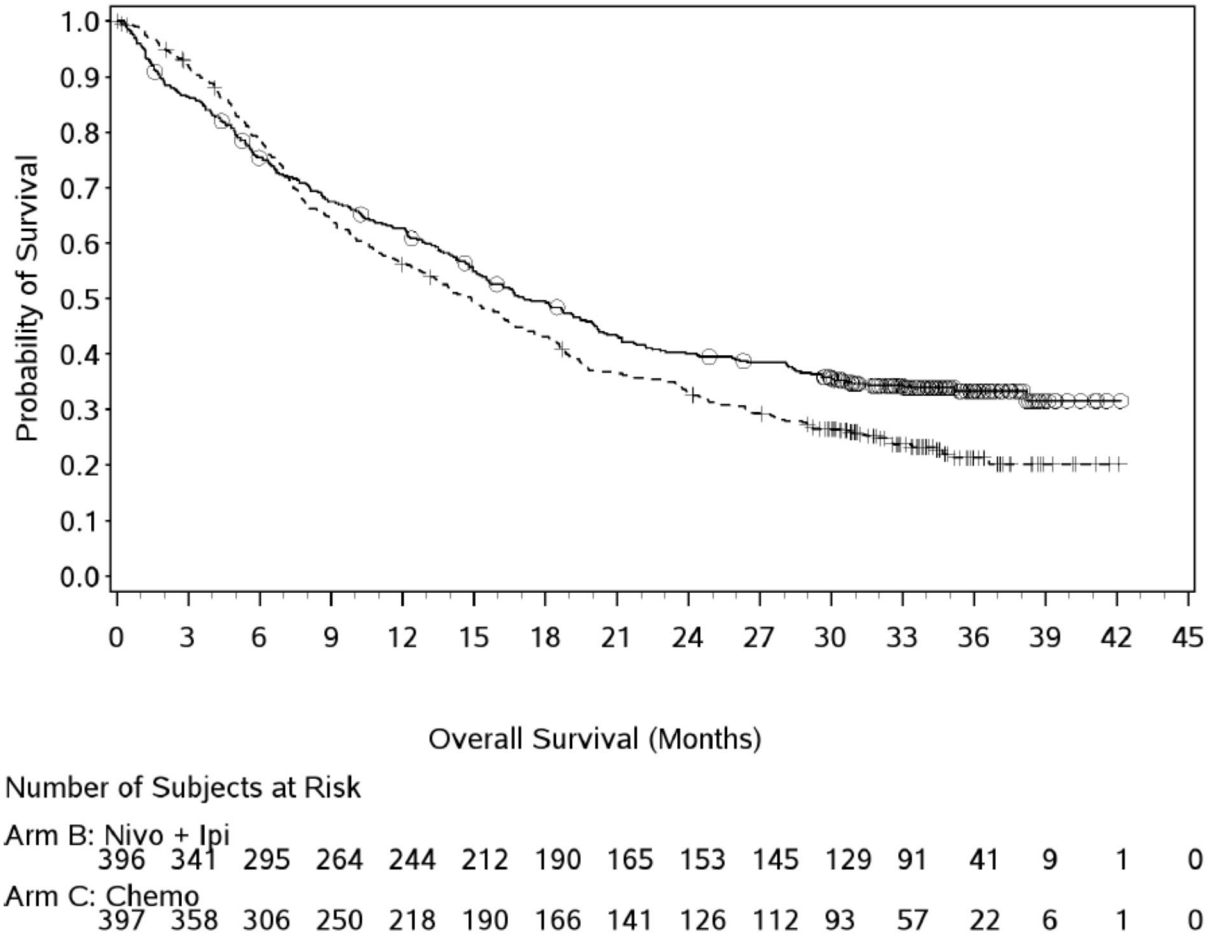
Table 23: Efficacy results (PD-L1 ≥1%) - CA209227 Part 1a

	nivolumab + ipilimumab (n=396)	**Chemotherapy (n=397)**
Overall Survival		
Events (%)	258 (65.2)	298 (75.1)
Median (months)	17.1	14.9
(95% CI)	(15, 20.1)	(12.7, 16.7)
Hazard ratio (97.72% CI)[a]	0.799 (0.65, 0.96)	
Stratified log-rank p-value	0.0066	
Rate (95% CI) at 12 months	62.6 (57.7, 67.2)	56.2 (51.1, 61.0)
Rate (95% CI) at 24 months	40.0 (35.1, 44.9)	32.8 (28.2, 37.5)

Progression-Free Survival		
Events (%)	288 (72.7)	286 (72.0)
Hazard ratio (95% CI)[a]	0.82 (0.69, 0.97)	
Median (months)[b]	5.1	5.6
(95% CI)	(4.07, 6.31)	(4.63, 5.82)
Objective Response Rate (%)[c]	142 (35.9)	119 (30.0)
(95% CI)	(31.1, 40.8)	(25.5, 34.7)
Complete response (%)	23 (5.8)	7 (1.8)
Partial response (%)	119 (30.1)	112 (28.2)
Duration of Response		
Median (months) (95% CI)[b]	23.2 (15.2, 32.2)	6.2 (5.6, 7.4)
% with duration ≥12 months[d]	64	28
% with duration ≥24 months[d]	49	11

[a] Based on a stratified Cox proportional hazard model.
[b] Kaplan-Meier estimate.
[c] Proportion with complete or partial response; confidence interval based on the Clopper and Pearson Method.
[d] Based on Kaplan-Meier estimates of duration of response.

Figure 8: Kaplan-Meier plot of OS (PD-L1 ≥1%) - CA209227 Part 1a



Randomized, open-label, Phase 3 study of nivolumab in combination with ipilimumab and platinum-based chemotherapy vs platinum-based chemotherapy (CA2099LA)

The safety and efficacy of nivolumab 360 mg every 3 weeks in combination with ipilimumab 1mg/kg every 6 weeks and 2 cycles of platinum-based chemotherapy were evaluated for the treatment of NSCLC in a Phase 3, randomized, open-label study (CA2099LA). The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification ((IASLC)), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors). Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression 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.

Patients were randomized 1:1 to receive either nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-based chemotherapy administered every 3 weeks for 2 cycles; or platinum-based chemotherapy administered every 3 weeks for 4 cycles; patients with non-

squamous NSCLC could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1%), histology (squamous versus non-squamous), and gender (male versus female). Platinum-based chemotherapy consisted of:

- carboplatin (AUC 5 or 6) and pemetrexed 500 mg/mg^2; or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC;
- or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC.

Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months in patients without disease progression. Treatment continued beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to ipilimumab were permitted to continue nivolumab monotherapy. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued.

The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

A total of 719 patients were randomized to receive either nivolumab in combination with ipilimumab and platinum-based chemotherapy (n=361) or platinum-based chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients ≥65 years and 10% of patients ≥75 years, 89% White, 70% male. Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% with PD-L1 ≥1% and 37% with PD-L1 <1%, 31% with squamous and 69% with non-squamous histology, 17% had brain metastases, and 86% were former/current smokers.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR, and a clinically meaningful benefit in duration of response for patients randomized to nivolumab in combination with ipilimumab and platinum-based chemotherapy compared to platinum-based chemotherapy alone. Minimum follow-up for OS was 8.1 months. Efficacy results are presented in Table 24 and Figure 9.

Table 24: Efficacy results - CA2099LA

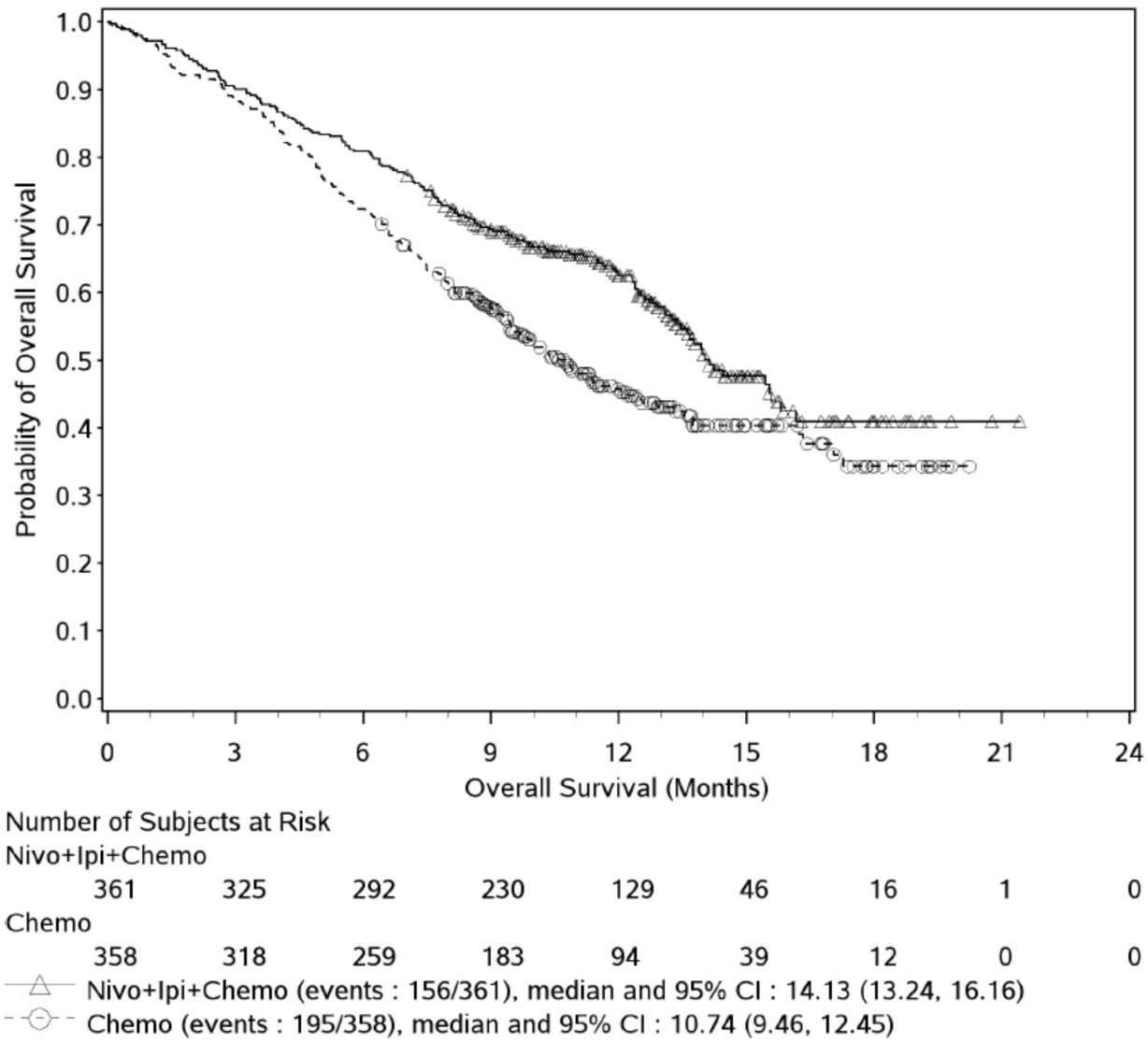
	Nivolumab + ipilimumab + chemotherapy (n=361)	**Chemotherapy (n=358)**
OS		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.24, 16.16)	10.7 (9.46, 12.45)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	

Table 24: Efficacy results - CA2099LA

	Nivolumab + ipilimumab + chemotherapy (n=361)	**Chemotherapy (n=358)**
Rate (95% CI) at 6 months	80.9 (76.4, 84.6)	72.3 (67.4, 76.7)
PFS		
Events (%)	232 (64.3)	249 (69.6)
Hazard ratio (97.48% CI)[a]	0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]	0.0001	
Median (months)[d] (95% CI)	6.83 (5.55, 7.66)	4.96 (4.27, 5.55)
Rate (95% CI) at 6 months	51.7 (46.2, 56.8)	35.9 (30.5, 41.3)
ORR (%)[e]	136 (37.7)	90 (25.1)
(95% CI)	(32.7, 42.9)	(20.7, 30.0)
Stratified CMH test p-value[f]	0.0003	
Complete response (%)	7 (1.9)	3 (0.8)
Partial response (%)	129 (35.7)	87 (24.3)
Duration of Response		
Median (months) (95% CI)[d]	10.02 (8.21, 13.01)	5.09 (4.34, 7.00)
% with duration ≥6 months[g]	74	41

[a] Based on a stratified Cox proportional hazard model.
[b] p-value is compared with the allocated alpha of 0.0329 for this interim analysis.
[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.
[d] Kaplan-Meier estimate.
[e] Proportion with complete or partial response; confidence interval based on the Clopper and Pearson Method.
[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.
[g] Based on Kaplan-Meier estimates of duration of response.

Figure 9: Kaplan-Meier plot of OS - CA2099LA



Subsequent systemic therapy was received by 28.8% and 41.1% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti- CTLA4) was received by 3.9% and 27.9% of patients in the combination and chemotherapy arms, respectively.

In study CA2099LA, subgroup descriptive analysis relative to chemotherapy, OS benefit was shown in patients treated with nivolumab in combination with ipilimumab and chemotherapy with squamous histology (HR (95% CI) 0.65 (0.46, 0.93), n = 227) and in patients with non-squamous histology (HR (95% CI) 0.72 (0.55, 0.93), n = 492).

Table 25 summarizes efficacy results of OS by tumour PD-L1 expression in pre-specified subgroup analyses.

Table 25: Efficacy results by tumor PD-L1 expression (CA2099LA)

	PD-L1 <1% (n=264)	PD-L1 ≥1% (n=406)	PD-L1 ≥1% to 49 % (n=233)	PD-L1 ≥50% (n=173)
OS hazard ratio (95 % CI)[a]	0.65 (0.46, 0.92)	0.67 (0.51, 0.89)	0.69 (0.48, 0.98)	0.64 (0.41, 1.02)

[a] Hazard ratio based on unstratified Cox proportional hazards model.

Randomized, open-label, Phase 3 study of nivolumab in combination with platinum-based chemotherapy vs platinum-based chemotherapy (CA209816)

The safety and efficacy of nivolumab 360 mg in combination with platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles were evaluated for the neoadjuvant treatment of resectable NSCLC in a Phase 3, randomized, open-label study (CA209816). The study 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 tumor 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 (nonsquamous 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 tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), disease stage (IB/II versus IIIA), and sex (male versus female). Tumor 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).

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 tumors with PD-L1 expression ≥1%and 43% had tumors 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 tumors with squamous histology and 49% had tumors with non-squamous histology; and 89% were former/current smokers.

Numerically more patients in the nivolumab in combination with platinum-doublet chemotherapy arm (83%) had definitive surgery compared to patients in the platinum-doublet chemotherapy arm (75%).

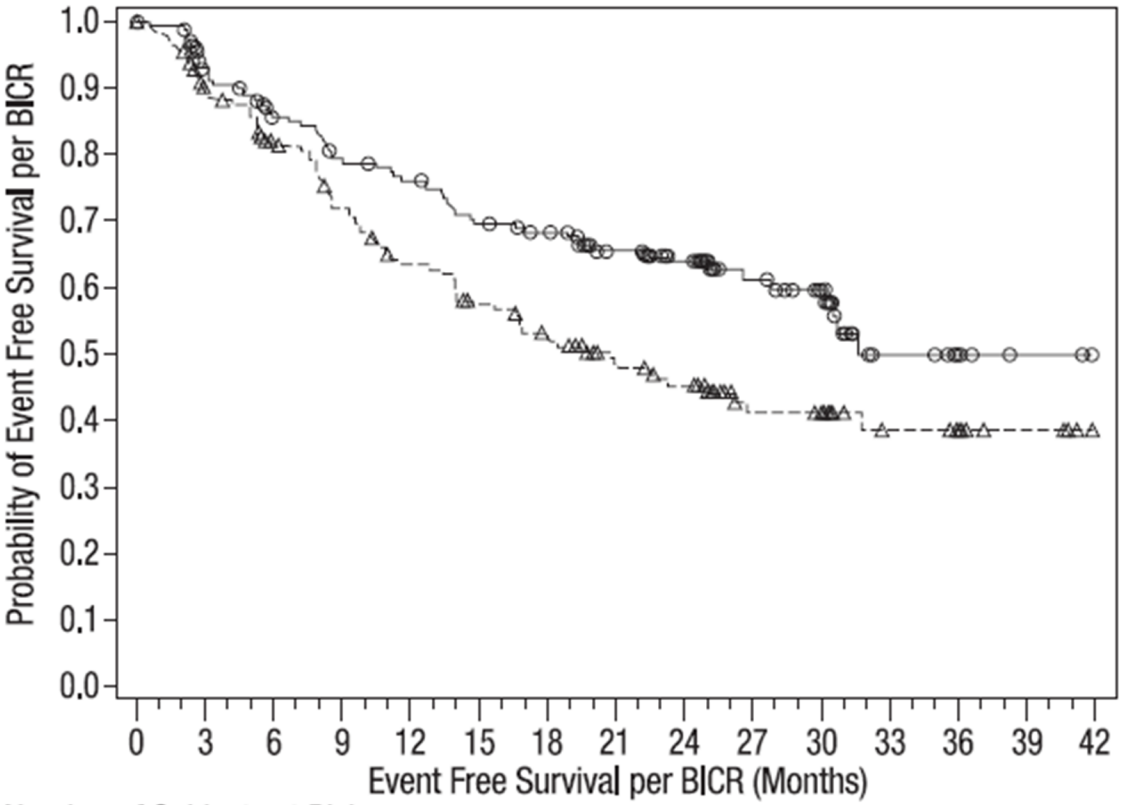
The study demonstrated statistically significant improvement in EFS and pCR. Efficacy results are presented in Table 26 and Figure 10.

Table 26: Efficacy Results - CA209816

	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] (97.38% CI)	0.63 (0.43, 0.91)	
Stratified log-rank p-value[c]	0.0052	
Rate (95% CI) at 12 months	76.1 (68.8, 81.9)	63.4 (55.3, 70.4)
Rate (95% CI) at 24 months	63.8 (55.7, 70.9)	45.3 (37.0, 53.2)
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 (99% CI)[e]	21.6 (13.0, 30.3)	
Odds ratio of pCR (99% CI)[f]	13.9 (3.49, 55.75)	
Stratified p-value[g]	<0.0001	

Minimum follow-up for EFS was 21 months.
[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] Strata-adjusted using Mantel-Haenszel method.
[g] From stratified CMH test.

Figure 10: Event-Free Survival - CA209816



Renal cell carcinoma (RCC)

Randomized, open-label, phase 3 study vs. everolimus (CA209025)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced RCC was evaluated in a Phase 3, randomized, open-label study (CA209025). The study included patients (18 years or older) who have 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. Patients with any history of or concurrent brain metastases, prior treatment with a mammalian target of rapamycin (mTOR) inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

Patients were randomized to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks or everolimus 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumor assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for

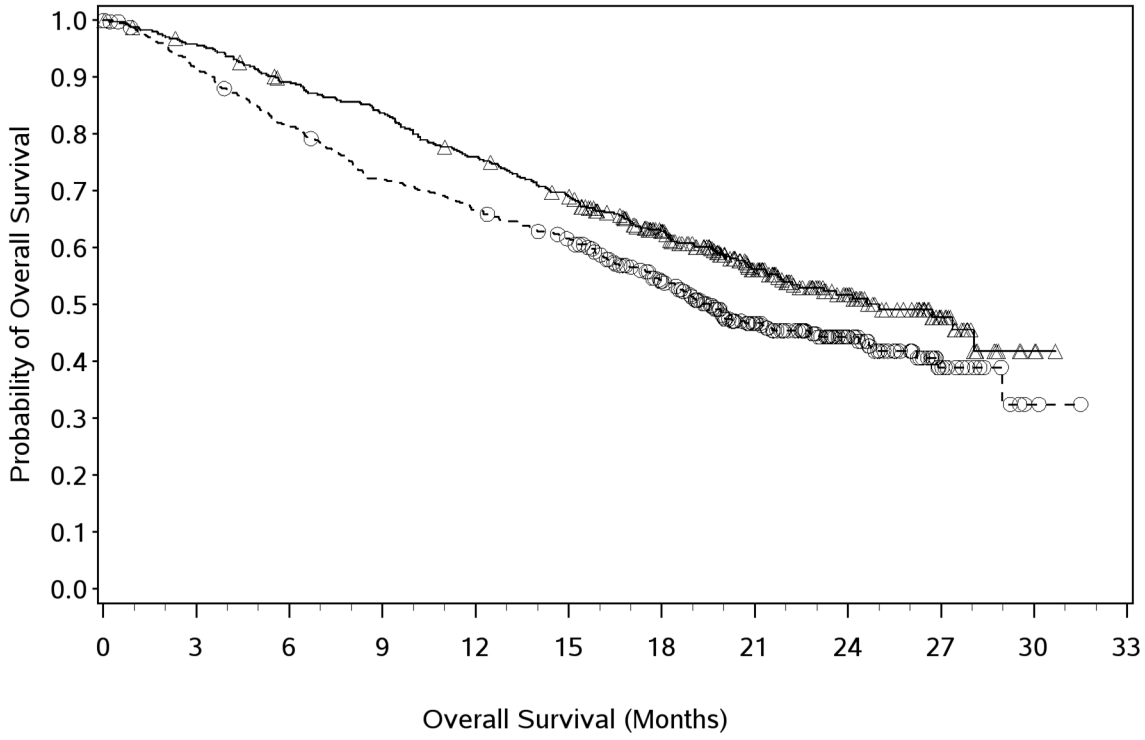
the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Tumor assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was OS. Secondary efficacy assessments included investigator-assessed ORR and PFS.

A total of 821 patients were randomized to receive either nivolumab (n=410) or everolimus (n=411). Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and white (88%), all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups were represented, and 34% and 66% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. The majority of patients (72%) were treated with one prior anti-angiogenic therapy. The median duration of time from initial diagnosis to randomization was 2.6 years in both the nivolumab and everolimus groups. The median duration of treatment was 5.5 months (range: 0-29.6^{+} months) for nivolumab and 3.7 months (range: 6 days-25.7^{+} months) for everolimus.

Nivolumab was continued beyond progression in 44% of patients.

The Kaplan-Meier curves for OS are shown in Figure 11.

Figure 11: Kaplan-Meier curves of OS (CA209025)



Number of Subjects at Risk

Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

Nivolumab (events: 183/410), median and 95% CI: 25.00 (21.75, N.A.)
Everolimus (events: 215/411), median and 95% CI: 19.55 (17.64, 23.06)
Nivolumab vs Everolimus - hazard ratio and 98.52% CI: 0.73 (0.57, 0.93); p-value: 0.0018

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 27 and Figure 11). OS benefit was observed regardless of PD-L1 expression level.

Table 27: Efficacy results (CA209025)

	nivolumab (n = 410)	**everolimus (n = 411)**
Overall survival		
Events n (%)	183 (45%)	215 (52%)
Hazard ratio	0.73	
98.52% CI	(0.57, 0.93)	
p-value	0.0018	
Median (95% CI)	25.0 months (21.7, NE)	19.6 months (17.6, 23.1)
Rate (95% CI)		
At 6 months	89.2% (85.7, 91.8)	81.2% (77.0, 84.7)
At 12 months	76.0% (71.5, 79.9)	66.7 % (61.8, 71.0)
Objective response n (%)	103 (25.1%)	22 (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		
(range)	12.0 months (0.0-27.6^{+})	12.0 months (0.0^{+}-22.2^{+})
Median time to response		
(range)	3.5 months (1.4-24.8)	3.7 months (1.5-11.2)
Progression-free survival		
Events n (%)	318 (77.6%)	322 (78.3%)
Hazard ratio	0.88	
95% CI	(0.75, 1.03)	
p-value	0.1135	
Median (95% CI)	4.6 months (3.7, 5.4)	4.4 months (3.7, 5.5)

NE=not estimable

"$^{+}$" denotes a censored observation.

The Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) subscale of the FKSI-15 was used to assess disease-related symptom progression rate in each treatment arm. With a completion rate of 80% in the first year, nivolumab demonstrated a

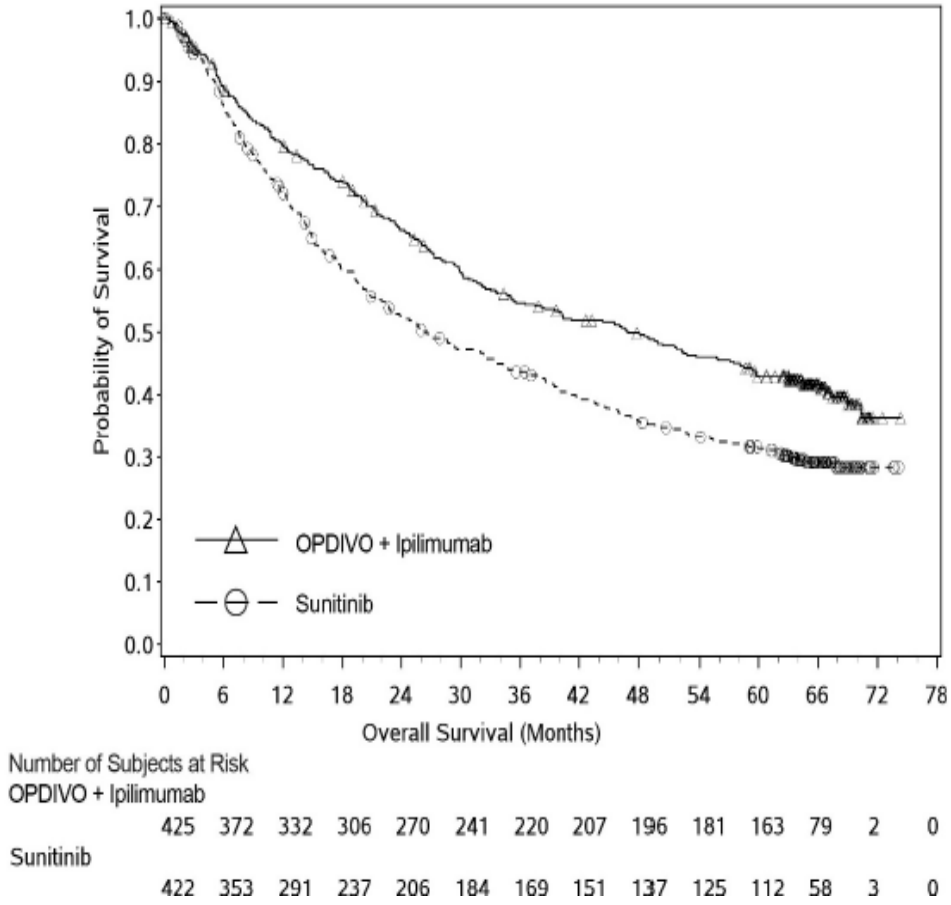
favourable impact on disease-related symptom progression rate. The scores for the nivolumab group increased over time and differed significantly from median changes in the everolimus group at each assessment point through week 104.

Randomized Phase 3 study of nivolumab in combination with ipilimumab vs. sunitinib (CA209214)

The safety and efficacy of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the treatment of advanced/metastatic RCC was evaluated in a Phase 3, randomized, open-label study (CA209214). The study included patients (18 years or older) with previously untreated, advanced or metastatic renal cell carcinoma with a clear-cell component. The primary efficacy population included those intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the International Metastatic RCC Database Consortium (IMDC) criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status <80%, haemoglobin 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). This study included patients regardless of their tumor PD-L1 status. Patients with Karnofsky performance status <70% and patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were stratified by IMDC prognostic score and region.
A total of 1096 patients were randomized in the trial, of which 847 patients had intermediate/poor-risk RCC and received either nivolumab 3 mg/kg (n=425) administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks or sunitinib (n=422) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off, every cycle. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumor 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 beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measures were OS, ORR and PFS as determined by a Blinded Independent Central Review (BICR) in intermediate/poor-risk patients.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 21-85) 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 median duration of time from initial diagnosis to randomization was 0.4 years in both the nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg and sunitinib groups. The median duration of treatment was 7.9 months (range: 1 day- 21.4^{+} months) in nivolumab with ipilimumab-treated patients and was 7.8 months (range: 1 days- 20.2^{+} months) in sunitinib-treated patients. Nivolumab with ipilimumab was continued beyond progression in 29% of patients.
The Kaplan-Meier curves for OS (with a minimum follow-up of 60 months) in intermediate/poor-risk patients are shown in Figure 12.

Figure 12: Kaplan-Meier curves of OS in intermediate/poor-risk patients (CA209214)



The trial demonstrated statistically significant improvement in OS, clinically relevant improvement in ORR, and a numerical improvement (not statistically significant) in PFS for intermediate/poor-risk patients randomized to nivolumab in combination with ipilimumab as compared with sunitinib (Table 28). With a longer follow-up (a minimum follow-up of 60 months), as shown in Figure 12, the trial continued to demonstrate significant improvement in OS for patients randomized to nivolumab and ipilimumab as compared with sunitinib.

In intermediate/poor-risk patients, OS benefit was observed in the nivolumab in combination with ipilimumab arm vs. sunitinib regardless of tumor PD-L1 expression. Median OS for tumor PD-L1 expression ≥1% was not reached for nivolumab in combination with ipilimumab, and was 19.61 months in the sunitinib arm (HR=0.45; 95% CI: 0.29, 0.71). For tumor PD-L1 expression <1%, the median OS was not reached for the nivolumab in combination with ipilimumab and the sunitinib arms (HR=0.73; 95% CI: 0.56, 0.96).

CA209214 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 primary

efficacy population. With 60 month minimum follow-ups. OS in favorable-risk patients receiving nivolumab plus ipilimumab compared to sunitinib had a hazard ratio of 0.94 (95% CI:0.65, 1.37). There are no data on the use of nivolumab in combination with ipilimumab in patients with only a non-clear-cell histology in first-line RCC.

Efficacy results for the intermediate/poor risk patients are shown in Table 28.

Table 28: Efficacy results in intermediate/poor-risk patients (CA209214)

	nivolumab + ipilimumab (n = 425)	sunitinib (n = 422)
Overall survival[a]		
Events	140 (33%)	188 (45%)
Hazard ratio[b]	0.63	
99.8% CI	(0.44, 0.89)	
p-value[c,d]	<0.0001	
Median (95% CI)	NE (32.5, NE)	27.0 (22.1, 34.8)
Rate (95% CI)		
At 6 months	89.5 (86.1, 92.1)	86.2 (82.4, 89.1)
At 12 months	80.1 (75.9, 83.6)	72.1 (67.4, 76.2)
Progression-free survival		
Events	228 (53.6%)	228 (54.0%)
Hazard ratio[b]	0.82	
99.1% CI	(0.64, 1.05)	
p-value[c,i]	0.0331	
Median (95% CI)	11.6 (8.71, 15.51)	8.4 (7.03, 10.81)
Confirmed objective response (BICR)	177 (41.6%)	112 (26.5%)
(95% CI)	(36.9, 46.5)	(22.4, 31.0)
Difference in ORR (95% CI)[e]	16.0 (9.8, 22.2)	
p-value[f,g]	<0.0001	
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[h]		
Months (range)	NE (1.4^+, 25.5^+)	18.2 (1.3^+, 23.6^+)
Median time to response		
Months (range)	2.8 (0.9-11.3)	3.0 (0.6-15.0)

[a] Results are based on the final analysis with 24 months of minimum follow-up.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.
[d] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[e] Strata adjusted difference.
[f] Based on the stratified DerSimonian-Laird text.

[g] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[h] Computed using Kaplan-Meier method.
[i] p-value is compared to alpha 0.009 in order to achieve statistical significance.
"+" denotes a censored observation.
NE = non-estimable.

An updated OS analysis was performed when all patients had a minimum follow-up of 24 months. At the time of this analysis, the hazard ratio was 0.66; (99.8% CI: 0.48-0.91) with 166/425 events in the combination arm and 209/422 events in the sunitinib arm. At 18 months, the OS rate was 74.3% (95% CI: 69.8-78.2) for nivolumab in combination with ipilimumab and 59.9 (95% CI: 54.9-64.5) for sunitinib. At 24 months, the OS rate was 66.5% (95% CI: 61.8-70.9) for nivolumab in combination with ipilimumab and 52.9 (95% CI: 47.9- 57.7) for sunitinib. An updated OS analysis was performed when all patients had a minimum follow-up of 60 months. At the time of analysis the median OS was 47.0 months in the nivolumab and ipilimumab arm and 26.6 months in the sunitinib arm (HR: 0.68; 95% CI: 0.58, 0.81).

The median time to onset of objective response was 2.8 months (range: 0.9-11.3 months) after the start of nivolumab with ipilimumab treatment. Among the 177 responders, 128 (72.3%) had an ongoing response with a duration ranging from 1.4^{+}-25.5^{+} months.

Patients ≥75 years of age represented 8% of all intermediate/poor-risk patients in CA209214, and the combination of nivolumab and ipilimumab showed numerically less effect on OS (HR 0.97, 95% CI: 0.48, 1.95) in this subgroup versus the overall population. Because of the small size of this subgroup, no definitive conclusions can be drawn from these data.

Overall survival was accompanied by fewer patients experiencing patient-reported deterioration on disease-related symptoms, cancer symptoms and non-disease specific Quality of Life (QoL) as assessed using valid and reliable scales in the FKSI-19, FACT-G, and EQ-5D. In those patients who deteriorated, the time to deterioration was significantly longer for all three scales for those in the nivolumab in combination with ipilimumab arm relative to those in the sunitinib arm ($p<0.0001$). While both arms of the study received active therapy, the QoL data should be interpreted in the context of the open-label study design and therefore cautiously taken.

Randomized Phase 3 study of nivolumab in combination with cabozantinib vs. sunitinib (CA2099ER)

The safety and efficacy of nivolumab 240 mg in combination with cabozantinib 40 mg for the first-line treatment of advanced/metastatic RCC was evaluated in a Phase 3, randomized, open-label study (CA2099ER). The study included patients (18 years or older) with advanced or metastatic RCC with a clear cell component, Karnofsky Performance Status (KPS) ≥70%, and measurable disease as per RECIST v1.1 regardless of their PD-L1 status or IMDC risk group. The study excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression, patients who had prior treatment with an anti-PD-1, anti- PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, poorly controlled hypertension despite antihypertensive therapy, active brain metastases and uncontrolled adrenal insufficiency. Patients were stratified by IMDC prognostic score, PD-L1 tumor expression, and region.

A total of 651 patients were randomized to receive either nivolumab 240 mg (n=323) administered intravenously every 2 weeks in combination with cabozantinib 40 mg once daily orally or sunitinib

(n=328) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off. Treatment continued until disease progression or unacceptable toxicity with nivolumab administration for up to 24 months. Treatment beyond initial investigator-assessed RECIST version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. First tumor assessment post-baseline was performed at 12 weeks (±7 days) following randomization. Subsequent tumor assessments occurred at every 6 weeks (±7 days) until Week 60, then every 12 weeks (±14 days) until radiographic progression, confirmed by the BICR.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 28-90) with 38.4% ≥65 years of age and 9.5% ≥75 years of age. The majority of patients were male (73.9%) and White (81.9%), and 23.2% and 76.5% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. Patient distribution by IMDC risk categories was 22.6% favorable, 57.6% intermediate, and 19.7% poor. For tumor PD-L1 expression. 72.5% of patients had PD-L1 expression <1% or indeterminate and 24.9% of patients had PD-L1 expression ≥ 1%. 11.5% of patients had tumours with sarcomatoid features.The median duration of treatment was 14.26 months (range: 0.2-27.3 months) in nivolumab with cabozantinib-treated patients and was 9.23 months (range: 0.8-27.6 months) in sunitinib-treated patients.

The primary efficacy outcome measure was PFS as determined by a BICR. Additional efficacy measures included OS and ORR as key secondary endpoints for hierarchical statistical testing. The study demonstrated a statistically significant benefit in PFS, OS, and ORR for patients randomised to nivolumab in combination with cabozantinib as compared to sunitinib.

Efficacy results from the primary analysis (minimum follow-up 10.6 months) are shown in Table 29.

Table 29: Efficacy results (CA2099ER)

	nivolumab + cabozantinib (n=323)	**sunitinib (n=328)**
Progression-free survival Events	144 (44.6%)	191 (58.2%)
Hazard ratio[a]	0.51	
95% CI	(0.41, 0.64)	
p-value[b, c]	<0.0001	
Median (95% CI)[d]	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)
Overall survival Events	67 (20.7%)	99 (30.2%)
Hazard ratio[a]	0.60	
98.89% CI	(0.40, 0.89)	
p-value[b],[c,e]	0.0010	
Median (95% CI)	N.E.	N.E. (22.6, N.E.)
Rate (95% CI)		
At 6 months	93.1 (89.7, 95.4)	86.2 (81.9, 89.5)
At 9 months	89.9 (86.0, 92.8)	80.5
	(75.7, 84.4)	
Confirmed objective response (BICR)[f]	180 (55.7%)	89
	(27.1%)	

(95% CI)	(50.1, 61.2)		(22.4, 32.3)
Difference in ORR (95% CI)[f]		28.6 (21.7, 35.6)	
p-value[g]		<0.0001	
Complete response (CR)	26 (8.0%)		15 (4.6%)
Partial response (PR)	154 (47.7%)		74 (22.6%)
Stable disease (SD)	104 (32.2%)		138 (42.1%)
Median duration of response[d]			
Months (range)	20.17 (17.31, N.E.)		11.47 (8.31, 18.43)
Median time to response			
Months (range)	2.83 (1.0-19.4)		4.17 (1.7-12.3)

[a] Stratified Cox proportional hazards model. Hazard ratio is nivolumab and cabozantinib over sunitinib.
[b] Based on Kaplan-Meier estimates.
[c] Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumor expression (≥1% versus <1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.
[d] 2-sided p-values from stratified regular log-rank test.
[e] 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 Kaplan-Meier curves for PFS and OS (with a minimum follow-up of 10.6 months) in all risk patients are shown in Figures 13 and 14

Figure 13: Kaplan-Meier curves of PFS (CA2099ER)

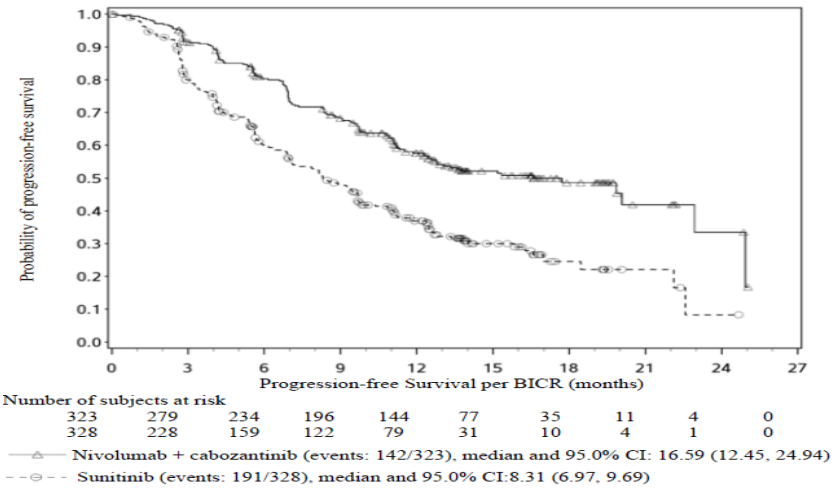
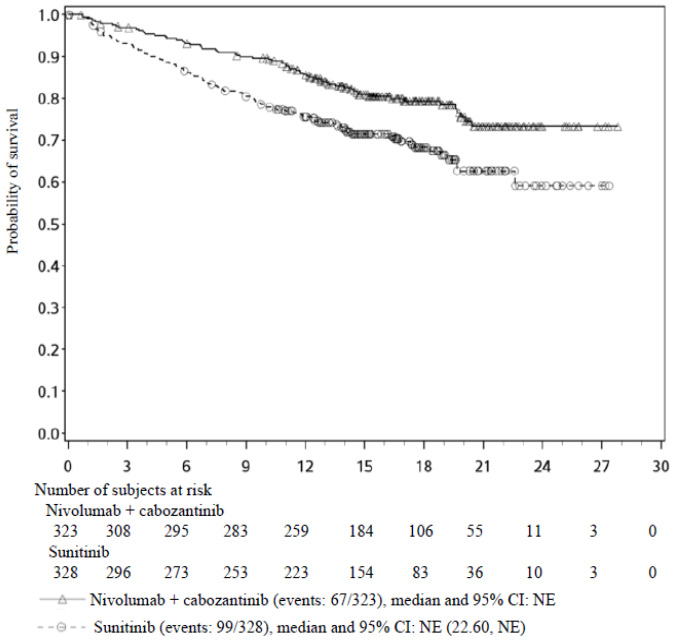


Figure 14: Kaplan-Meier curves of OS (CA2099ER)



PFS benefit was observed in the nivolumab in combination with cabozantinib arm vs. sunitinib regardless of tumor PD-L1 expression or IMDC risk category.

Patient-reported outcomes (PROs) were assessed over the time of the study using valid and reliable scales, the NCCN Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19), a disease specific HRQoL instrument for patients with kidney cancer and the EQ-5D-3L a generic instrument. Disease specific Health Related Quality of Life as measured by FKSI-19 is maintained over the time of the study for patients treated with nivolumab in combination with cabozantinib while a deterioration is observed at all time points in the sunitinib arm, exceeding the MID (3 points) at most time points (Weeks 13, 19, and 49 to 91). Generic QoL measured by the EQ-5D VAS shows trends for improvement in patients treated with nivolumab in combination with cabozantinib while sunitinib treated patients remained relatively stable. The QoL results should be interpreted with caution in the context of the open label study design.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

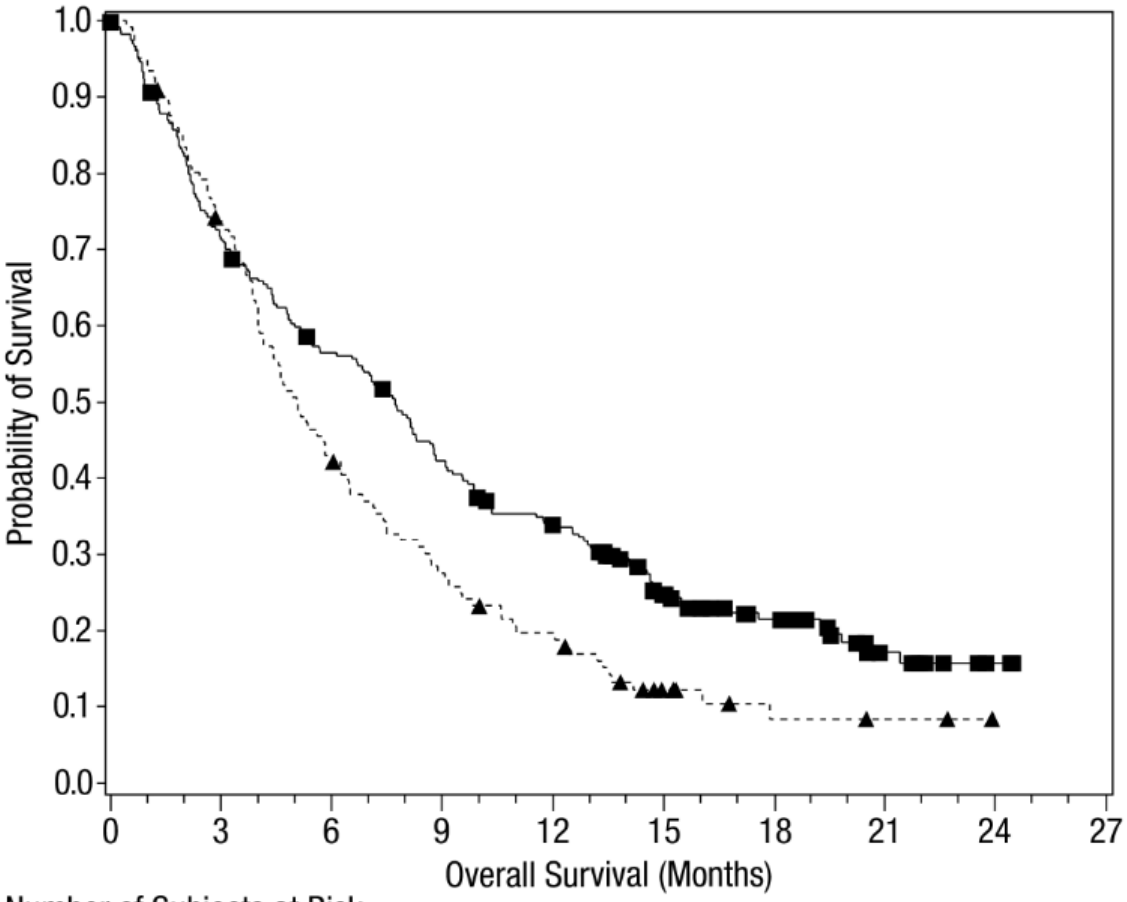
The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of metastatic or recurrent SCCHN were evaluated in a Phase 3, randomized, open-label study (CA209141). The study included patients (18 years or older) who had disease progression during or after a prior platinum-based therapy 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, recurrent, or metastatic setting. Patients were enrolled regardless of their tumor 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, 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 randomized to receive either nivolumab 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice 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. Randomization was stratified by prior cetuximab treatment. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments, according to RECIST version 1.1, were conducted 9 weeks after randomization 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 tumor PD-L1 expression at predefined levels of 1%, 5%, and 10%.

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 men, and 83% were white. Baseline ECOG performance status score was 0 (20%) or 1 (78%), 77% were former/current smokers, 90% had Stage IV disease, 66% had two or more lesions, 45%, 34% and 20% received 1, 2, or 3 or more prior lines of systemic therapy, respectively, and 25% were HPV-16 status positive.

With a minimum follow-up of 11.4 months, the trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab compared with investigator's choice. The Kaplan-Meier curves for OS are shown in Figure 15. Efficacy results are shown in Table 30.

Figure 15: Kaplan-Meier curves of OS (CA209141)



Number of Subjects at Risk

NIVO	240	169	132	98	76	45	27	12	3
INV Choice	121	88	51	32	22	9	4	3	0

Nivolumab 3 mg/kg (events : 184/240), median and 95% CI : 7.72 (5.68,8.77)

Investigator's Choice (events : 105/121), median and 95% CI : 5.06 (4.04,6.24)

NIVO vs. INV Choice - hazard ratio 95%: 0.71 (0.55, 0.90), pvalue:0.0048

Symbols represent censored observations

Table 30: **Efficacy results (CA209141)**

	nivolumab (n = 240)	**investigator's choice (n = 121)**
Overall survival		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio[a]	0.71	
(95% CI)	(0.55, 0.90)	
p-value[b]	0.0048	
Median (95% CI)	7.7 months (5.7, 8.8)	5.1 months (4.0, 6.2)
Rate (95% CI) at 6 months	56.5% (49.9, 62.5)	43.0% (34.0, 51.7)
Rate (95% CI) at 12 months	34.0% (28.0, 40.1)	19.7% (13.0, 27.3)
Rate (95% CI) at 18 months	21.5% (16.2, 27.4)	8.3% (3.6, 15.7)
Progression-free survival		
Events	204 (85%)	104 (86%)
Hazard ratio	0.87	
95% CI	(0.69, 1.11)	
p-value	0.2597	
Median (95% CI)	2.0 months (1.9, 2.1)	2.3 months (2.0, 3.1)
Rate (95% CI) at 6 months	21.0% (15.9, 26.6)	11.1% (5.9, 18.3)
Rate (95% CI) at 12 months	9.5% (6.0, 13.9)	2.5% (0.5, 7.8)
Confirmed objective response[c] n (%)	32 (13.3%)	7 (5.8%)
(95% CI)	(9.3, 18.3)	(2.4, 11.6)
Odds ratio (95% CI)	2.49 (1.07, 5.82)	
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%)
Median time to response (range)	2.1 months (1.8- 7.4)	2.0 months (1.9 - 4.6)
Median duration of response (range)	9.7 months (2.8- 20.3^{+})	4.0 months (1.5^{+}- 8.5^{+})

[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 tumor PD-L1 expression < 1%.

"$^{+}$" denotes a censored observation.

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

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

Patients with tumor PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared with those in the investigator's choice group. The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumor PD-L1 expression levels (Table 31).

Table 31: OS by tumor PD-L1 expression (CA209141)

PD-L1 Expression	nivolumab	investigator's choice	
	OS by tumor PD-L1 expression		
	Number of events (number of patients)		Unstratified Hazard Ratio (95% CI)
< 1%	56 (73)	32 (38)	0.83 (0.54, 1.29)
≥ 1%	66 (88)	55 (61)	0.53 (0.37, 0.77)
≥ 5%	39 (54)	40 (43)	0.51 (0.32, 0.80)
≥ 10%	30 (43)	31 (34)	0.57 (0.34, 0.95)

Patients with investigator-assessed primary site of oropharyngeal cancer were tested for HPV. OS benefit was observed regardless of HPV status (HPV-positive oropharyngeal: HR = 0.63; 95% CI: 0.38, 1.04 and HPV-negative oropharyngeal and non-oropharyngeal SCCHN: HR = 0.74; 95% CI: 0.56, 0.98).

Patient-reported outcomes (PROs) were assessed using three measures: the EORTC QLQ-C30, EORTC QLQ-H&N35, and 3-level version of the EQ-5D. Over 15 weeks of follow-up, patients treated with nivolumab exhibited generally stable PROs, while those assigned to investigator's choice therapy exhibited statistically significant and clinically meaningful declines in functioning (e.g., physical, role, social) and health status as well as increases in symptomatology (e.g., fatigue, dyspnea, appetite loss, pain, sensory problems, social contact problems).

Unresectable or metastatic melanoma

Randomized phase 3 study vs. dacarbazine (CA209066)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomized, double-blind study (CA209066). The study included patients (18 years or older) with confirmed, treatment-naive, Stage III or IV BRAF wild-type melanoma and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients who had received previous adjuvant therapy were not excluded. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

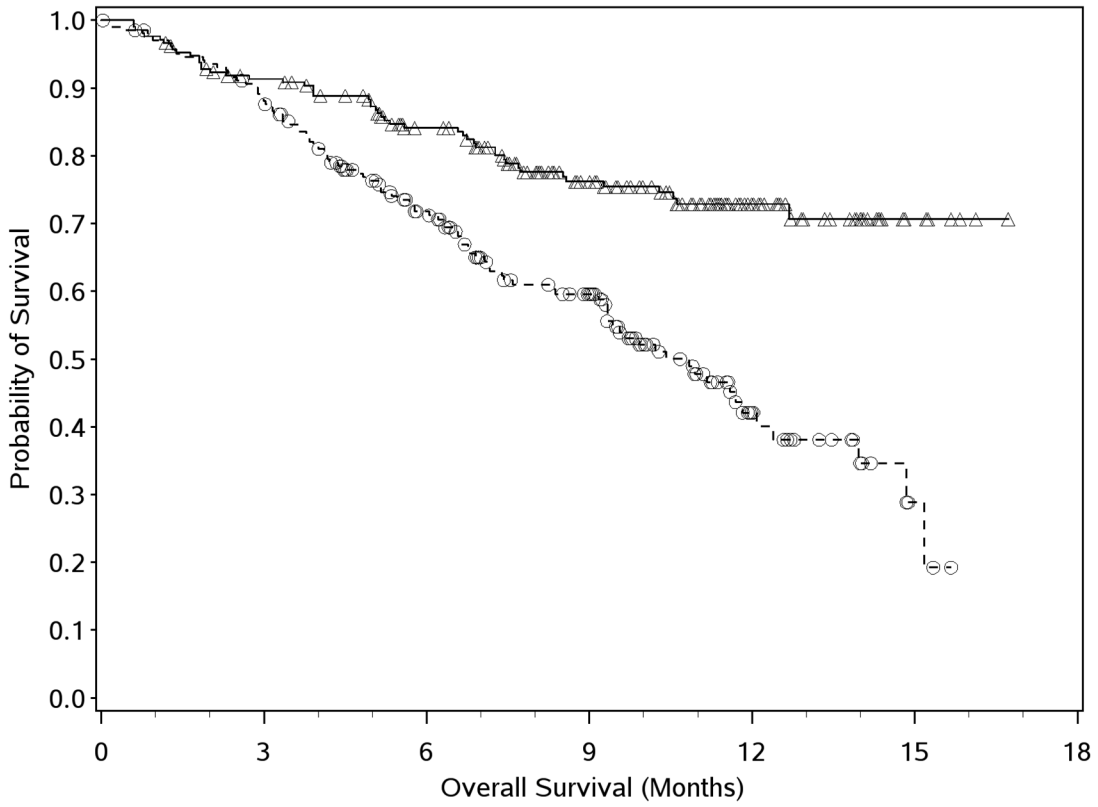
Patients were randomized on a 1:1 basis to receive either nivolumab administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine at 1000 mg/m^2 every 3 weeks. Randomization was stratified by PD-L1 status and M stage (M0/M1a/M1b versus M1c). Treatment was continued as long as clinical 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. Tumor assessments, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, were conducted 9 weeks after randomization and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed progression-free survival (PFS) and objective response rate (ORR).

A total of 418 patients were randomized to either nivolumab (n=210) or dacarbazine (n=208). Baseline characteristics were balanced between the two groups. The median age was 65 years (range: 18-87), 59% were men, and 99% were white. Most patients had ECOG performance score of 0 (64%) or 1 (34%). Sixty-one percent of patients had M1c stage disease at study entry. Seventy-four percent of patients had cutaneous melanoma, and 11% had mucosal melanoma; 35% of patients had PD-L1 positive melanoma ($\geq$5% tumor cell membrane expression). Four percent of patients had a history of brain metastasis, and 37% of patients had a baseline LDH level greater than ULN at study entry.

Nivolumab demonstrated a statistically significant improvement in OS over dacarbazine in treatment-naive patients with BRAF wild-type advanced (unresectable or metastatic) melanoma (HR = 0.42; 99.79% CI: 0.25, 0.73; p-value <0.0001). Median OS was not reached for nivolumab and was 10.8 months (95% CI: 9.33, 12.09) for dacarbazine. The estimated OS rates at 12 months were 73% (95% CI: 65.5, 78.9) and 42% (95% CI: 33.0, 50.9), respectively.

The observed OS benefit was consistently demonstrated across subgroups of patients including baseline ECOG performance status, M stage, history of brain metastases, and baseline LDH level. Survival benefit was observed regardless of whether PD-L1 expression was above or below a PD-L1 tumor membrane expression cut-off of 5% or 10%. The Kaplan-Meier curves for OS are shown in Figure 16.

Figure 16: Kaplan-Meier curves of OS (CA209066)



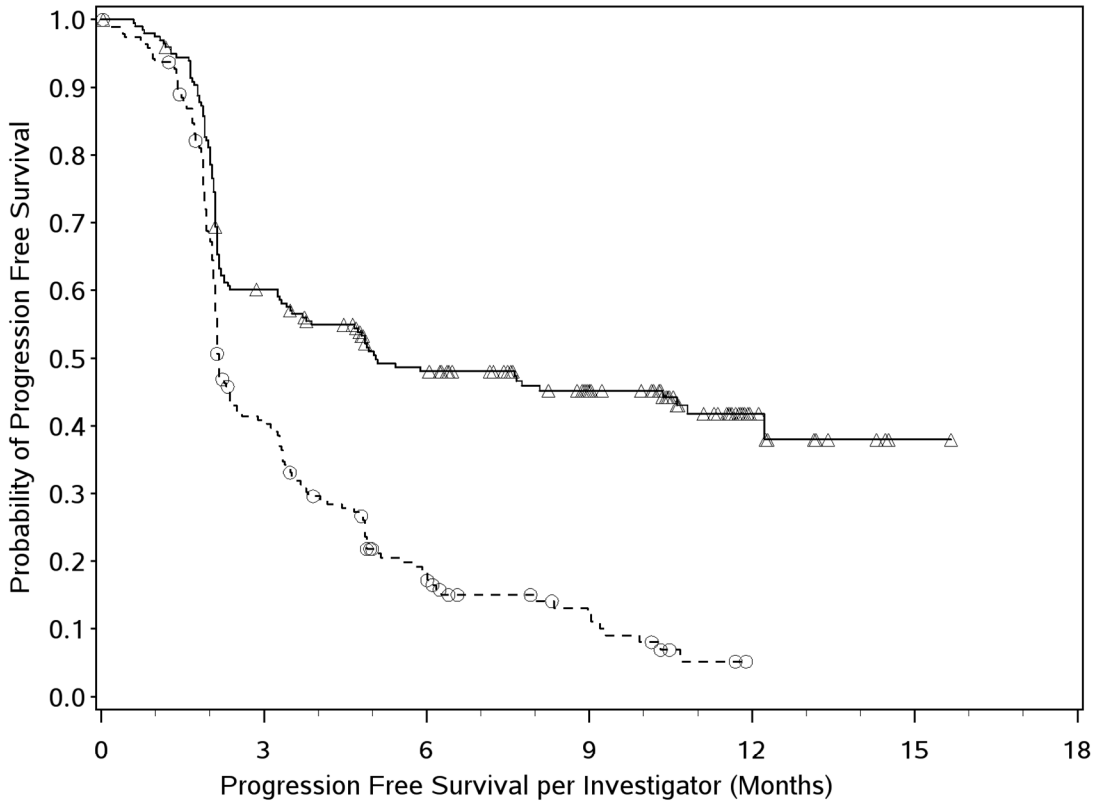
Number of Subjects at Risk

Nivolumab	210	185	150	105	45	8	0
Dacarbazine	208	177	123	82	22	3	0

Nivolumab (events : 50/210), median and 95% CI : N.A.
Dacarbazine (events : 96/208), median and 95% CI : 10.84 (9.33, 12.09)
Hazard Ratio (Nivolumab over Dacarbazine) and 95% CI (1): 0.42 (0.30, 0.60)
Hazard Ratio (Nivolumab over Dacarbazine) and 99.79% CI (1): 0.42 (0.25, 0.73)
Stratified log-rank p-value: <0.0001

Nivolumab also demonstrated statistically significant improvement in PFS compared with dacarbazine (HR = 0.43 [95% CI: 0.34, 0.56]; p <0.0001). The median PFS was 5.1 months (95% CI: 3.48, 10.81) for nivolumab and 2.2 months (95% CI: 2.10, 2.40) for dacarbazine. The estimated PFS rates at 6 months were 48% (95% CI: 40.8, 54.9) and 18% (95% CI: 13.1, 24.6), respectively. The estimated PFS rate at 12 months was 42% (95% CI: 34.0, 49.3) for nivolumab. The Kaplan-Meier curves for PFS are shown in Figure 17.

Figure 17: Kaplan-Meier curves of progression-free survival (CA209066)



Number of Subjects at Risk

Nivolumab						
210	116	82	57	12	1	0
Dacarbazine						
208	74	28	12	0	0	0

Nivolumab (events : 108/210), median and 95% CI : 5.06 (3.48, 10.81)

Dacarbazine (events : 163/208), median and 95% CI : 2.17 (2.10, 2.40)

Hazard Ratio (Nivolumab over Dacarbazine) and 95% CI (1): 0.43 (0.34, 0.56)

Stratified log-rank p-value: <0.0001

The investigator-assessed ORR using RECIST v1.1 criteria was significantly higher in the nivolumab group than in the dacarbazine group (Odds Ratio: 4.06 [95% CI: 2.52, 6.54], p <0.0001). Response rates, time to response, and duration of response are shown in Table 32.

Table 32: Best overall response, time, and duration of response (CA209066)

	nivolumab (n=210)	**dacarbazine (n=208)**
Objective response n (%)	84 (40.0%)	29 (13.9%)
(95% CI)	(33.3, 47.0)	(9.5, 19.4)
Odds ratio (95% CI)	4.06 (2.52, 6.54)	
p-value	< 0.0001	
Complete response (CR)	16 (7.6%)	2 (1.0%)
Partial response (PR)	68 (32.4%)	27 (13.0%)
Stable disease (SD)	35 (16.7%)	46 (22.1%)
Median duration of response		
(range)	Not reached (0^+ - 12.5^+)	6.0 months (1.1 - 10.0^+)
Median time to response		
(range)	2.1 months (1.2 - 7.6)	2.1 months (1.8 - 3.6)

"$^+$" denotes a censored observation.

At the time of analysis, 82% (69/84) of nivolumab-treated patients and 31% (9/29) of dacarbazine-treated patients had ongoing responses, which included 46 and 4 patients, respectively, with ongoing response of 6 months or longer.

In 54 nivolumab-treated patients, treatment was continued beyond an initial investigator assessment of RECIST disease progression if the investigator determined the patient had sufficient ongoing clinical benefit and was tolerating therapy. Of these patients, 12 (22.2%) had target lesion reductions (>30% compared to baseline).

Randomized phase 3 study vs. chemotherapy (CA209037)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomized, open-label study (CA209037). The study included adult patients who had progressed on or after ipilimumab and, if BRAF V600 mutation positive, had also progressed on or after BRAF kinase inhibitor therapy. Patients with active autoimmune disease, ocular melanoma or a known history of prior

ipilimumab-related high-grade (Grade 4 per CTCAE v4.0) adverse reactions, except for resolved nausea, fatigue, infusion reactions, or endocrinopathies, were excluded from the study.

Patients were randomized on a 2:1 basis to receive either nivolumab administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or chemotherapy. Chemotherapy consisted of the investigator's choice of either dacarbazine (1000 mg/m^2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks). Randomization was stratified by BRAF and PD-L1 status and best response to prior ipilimumab. Tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks for the first year and then every 12 weeks thereafter.

The co-primary efficacy outcome measures were confirmed ORR, as measured by independent radiology review committee (IRRC) using RECIST 1.1, and comparison of OS of nivolumab to chemotherapy. Additional outcome measures included duration and timing of response.

A total of 405 patients were randomized to receive either nivolumab (n=272) or chemotherapy (n = 133). The median age was 60 years (range: 23-88). Sixty-four percent of patients were men and 98% were white. ECOG performance scores were 0 for 61% of patients and 1 for 39% of patients. The majority (75%) of patients had M1c stage disease at study entry. Seventy-three percent of patients had cutaneous melanoma and 10% had mucosal melanoma. The number of prior systemic regimen received was 1 for 27% of patients, 2 for 51% of patients, and >2 for 21% of patients. Twenty-two percent of patients were BRAF mutation positive and 50% of patients were PD-L1 positive. Sixty-four percent of patients had no prior clinical benefit (CR/PR or SD) on ipilimumab. Baseline characteristics were balanced between groups except for the proportions of patients who had a history of brain metastasis (19% and 13% in the nivolumab group and chemotherapy group, respectively) and patients with LDH greater than ULN at baseline (51% and 35%, respectively).

At the time of this 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. Efficacy results are presented in Table 33 and Figure 18.

Table 33: Best overall response, time, and duration of response (CA209037)

	nivolumab (n=120)	**chemotherapy (n=47)**
Confirmed Objective Response (IRRC) n (%)	38 (31.7%)	5 (10.6%)
(95% CI)	(23.5, 40.8)	(3.5, 23.1)
Complete Response (CR)	4 (3.3%)	0
Partial Response (PR)	34 (28.3%)	5 (10.6%)
Stable Disease (SD)	28 (23.3%)	16 (34.0%)
Median Duration of Response		
(range)	Not Reached	3.6 months (Not available)
Median Time to Response		

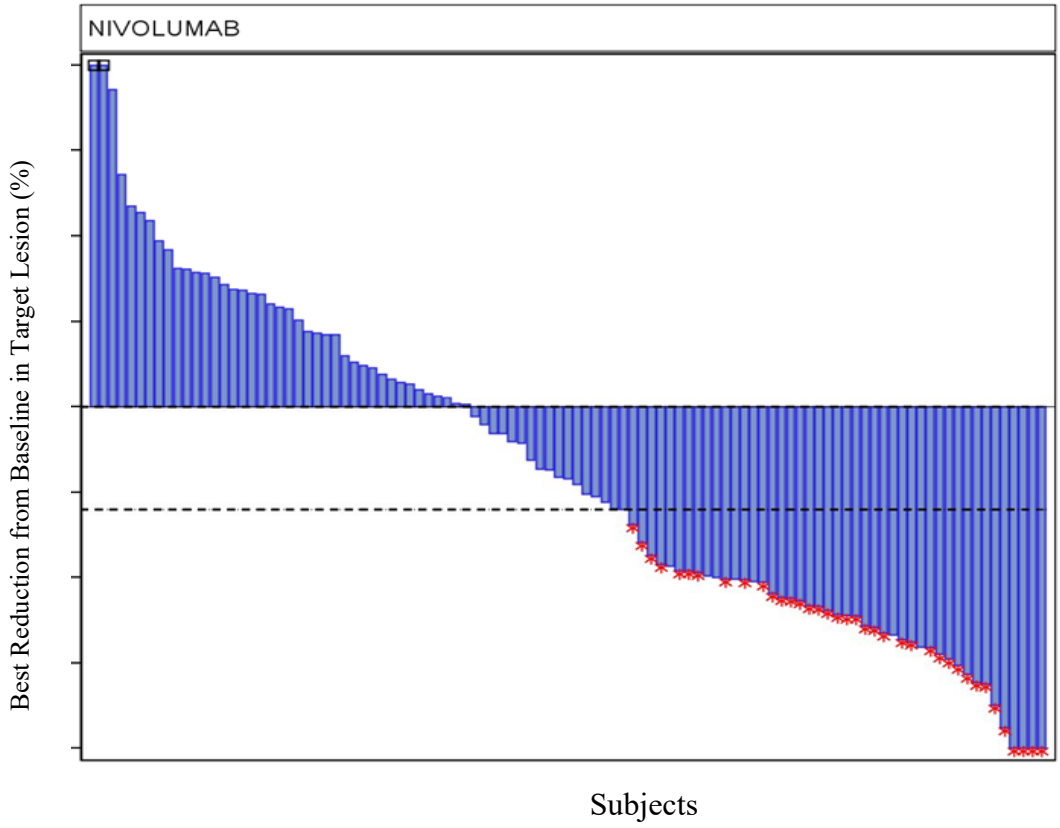
Table 33: Best overall response, time, and duration of response (CA209037)

	nivolumab (n=120)	chemotherapy (n=47)
(range)	2.1 months (1.6-7.4)	3.5 months (2.1-6.1)

Of the 38 nivolumab-treated patients with a confirmed response, 33 were still in response at the time of analysis.

Objective responses to nivolumab were observed in patients with or without BRAF mutation-positive melanoma. Of the patients who received nivolumab, the ORR in the BRAF mutation-positive subgroup was 23% (95% CI: 9.0, 43.6), and 34% (95% CI: 24.6, 44.5) in patients whose tumors were BRAF wild-type. Objective responses to nivolumab were observed regardless of whether PD-L1 expression was above or below a PD-L1 tumor membrane expression cut-off of 5% or 10%.

Figure 18: Waterfall plot of best reduction in target lesion, per IRRC (CA209037)



Note: Symbol ("*") represents confirmed responders.

In 37 (31%) nivolumab-treated patients, treatment was continued beyond an initial investigator assessment of RECIST disease progression if the investigator determined that the patient had sufficient ongoing clinical benefit and was tolerating therapy. Of these patients, 10 (27%) had target lesion reductions (>30% compared to baseline).

Updated analysis (24-month follow-up)

Among all randomized patients, the ORR was 27.2% (95% CI: 22.0, 32.9) in the nivolumab group and 9.8% (95% CI: 5.3, 16.1) in the chemotherapy group. Median duration of response was 31.9 months (range: 1.4^{+}-31.9) and 12.8 months (range: 1.3^{+}-13.6^{+}), respectively.

There was no statistically significant difference between nivolumab and chemotherapy in the primary OS analysis. The OS analysis was not adjusted to account for subsequent therapies, with 54 (41%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies and differences in baseline factors. More patients in the nivolumab arm had poor prognostic factors (elevated LDH and brain metastases) than in the chemotherapy arm.

Open-label phase 1 dose-escalation study (MDX1106-03)

The safety and tolerability of nivolumab were investigated in a phase 1, open-label dose-escalation study in various tumor types, including malignant melanoma.

Of the 306 previously treated patients enrolled in the study, 107 had melanoma and received nivolumab at a dose of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg for a maximum of 2 years. In this patient population, objective response was reported in 33 patients (31%) with a median duration of response of 22.9 months (95% CI: 17.0, NR). The median PFS was 3.7 months (95% CI: 1.9, 9.3). The median OS was 17.3 months (95% CI: 12.5, 36.7), and the estimated OS rates were 63% (95% CI: 53, 71) at 1 year, 48% (95% CI: 38, 57) at 2 years, and 41% (95% CI: 31, 51) at 3 years.

Randomized phase 3 study of nivolumab in combination with ipilimumab or nivolumab as monotherapy vs ipilimumab (CA209067)

The safety and efficacy of nivolumab in combination with ipilimumab and nivolumab monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomized, double-blind study (CA209067). The study included adult patients (18 years or older) with confirmed unresectable Stage III or Stage IV melanoma, regardless of PD-L1 expression. Patients were to have ECOG performance status score of 0 or 1. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled. Prior adjuvant or neoadjuvant therapy was allowed if it was completed at least 6 weeks prior to randomization. Patients with active autoimmune disease, ocular/uveal melanoma, or active brain or leptomeningeal metastases were excluded from the study.

A total of 945 patients were randomized to receive nivolumab in combination with ipilimumab (n = 314), nivolumab as monotherapy (n = 316), or ipilimumab as monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks. Patients in the nivolumab monotherapy arm received nivolumab 3 mg/kg every 2 weeks. Patients in the comparator arm received ipilimumab 3 mg/kg and nivolumab-

matched placebo intravenously every 3 weeks for 4 doses followed by placebo every 2 weeks. Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression), BRAF status, and M stage per the American Joint Committee on Cancer (AJCC) staging system. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments were conducted 12 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter. The co-primary outcome measures were progression-free survival and OS. ORR and the duration of response were also assessed. This study evaluated whether PD-L1 expression was a predictive biomarker for the co-primary endpoints. The efficacy of nivolumab in combination with ipilimumab and nivolumab monotherapy was each compared with that of ipilimumab. In addition, the differences between the two nivolumab-containing groups were evaluated descriptively, but not included in formal hypothesis testing. Health Related Quality of Life (HRQoL) was assessed by the European Organization for Research and Treatment of Care (EORTC) QLQ-C30.

Baseline characteristics were balanced across the three treatment groups. The median age was 61 years (range: 18-90 years), 65% of patients were men, and 97% were white. ECOG performance status score was 0 (73%) or 1 (27%). The majority of the patients had AJCC Stage IV disease (93%); 58% had M1c disease at study entry. Twenty-two percent of patients had received prior adjuvant therapy. Thirty-two percent of patients had BRAF mutation-positive melanoma; 26.5% of patients had PD-L1 ≥5% tumor cell membrane expression. Four percent of patients had a history of brain metastasis, and 36% of patients had a baseline LDH level greater than ULN at study entry.

Both nivolumab-containing arms demonstrated a significant PFS and OS benefit and greater ORR compared with ipilimumab monotherapy. Efficacy results for the randomized patients are shown in Table 34, Figure 19, and Figure 20.

The observed PFS, OS, and ORR results for nivolumab monotherapy were consistently demonstrated across subgroups of patients including baseline ECOG performance status, BRAF status, M stage, age, history of brain metastases, and baseline LDH level.

Table 34: Efficacy results (CA209067)

	nivolumab + ipilimumab (n=314)	**nivolumab (n=316)**	**ipilimumab (n=315)**
Progression-free survival[a]			
Events n (%)	151 (48%)	174 (55%)	234 (74%)
Hazard ratio (vs ipilimumab)	0.42	0.57	
(99.5% CI)	(0.31, 0.57)	(0.43, 0.76)	
p-value	p<0.0001	p<0.0001	
Hazard ratio (vs nivolumab monotherapy) (95% CI)	0.74 (0.60, 0.92)		
Median (95% CI)	11.5 months (8.9, 16.7)	6.9 months (4.3, 9.5)	2.9 months (2.8, 3.4)
Rate (95% CI)			
At 6 months	62% (56, 67)	52% (46, 57)	29% (24, 34)
At 9 months	56% (50, 61)	45% (40, 51)	21% (17, 26)

Table 34: Efficacy results (CA209067)

	nivolumab + ipilimumab (n=314)	nivolumab (n=316)	ipilimumab (n=315)
Overall survival[b]			
Events n (%)	128 (41%)	142 (45%)	197 (63%)
Hazard ratio (vs ipilimumab)	0.55	0.63	
(98% CI)	(0.42, 0.72)	(0.48, 0.81)	
p-value	p<0.0001	p<0.0001	
Hazard ratio (vs nivolumab monotherapy) (95% CI)	0.88 (0.69, 1.12)		
Median (95% CI)	Not reached	Not reached (29.1, NE)	20.0 months (17.1, 24.6)
Rate (95% CI)			
At 12 months	73% (68, 78)	74% (69, 79)	67% (61, 72)
At 24 months	64% (59, 69)	59% (53, 64)	45% (39, 50)
Objective response[b] n (%)	185 (59%)	141 (45%)	60 (19%)
(95% CI)	(53.3, 64.4)	(39.1, 50.3)	(14.9, 23.8)
Odds ratio (vs ipilimumab)	6.50	3.54	
(95% CI)	(3.81, 11.08)	(2.10, 5.95)	
Complete response (CR)	54 (17%)	47 (15%)	14 (4%)
Partial response (PR)	131 (42%)	94 (30%)	46 (15%)
Stable disease (SD)	36 (12%)	31 (10%)	67 (21%)
Duration of response			
Median (range)	Not reached (0^+ - 33.3^+)	31.1 months (0^+ - 32.3^+)	18.2 months (0^+ - 31.5^+)
Proportion >12 months in duration	64%	70%	53%
Proportion >24 months in duration	50%	49%	32%

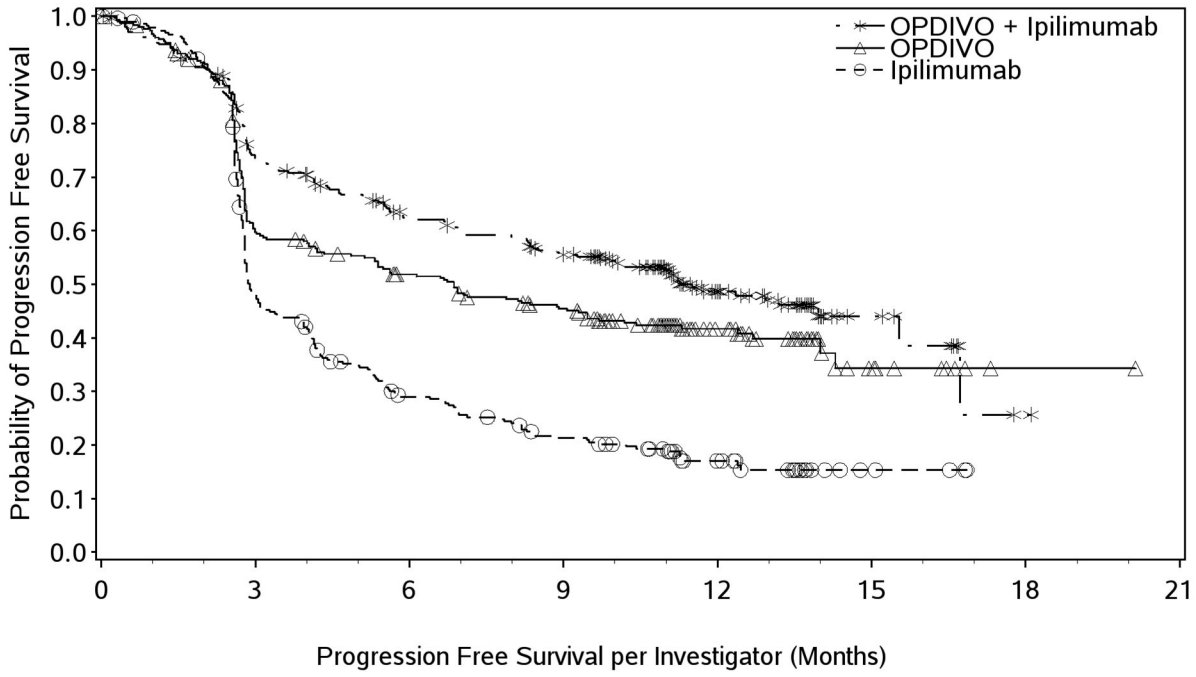
a Minimum follow-up of 9 months.

b Minimum follow-up of 28 months.

NE=not estimable.

"+" denotes a censored observation.

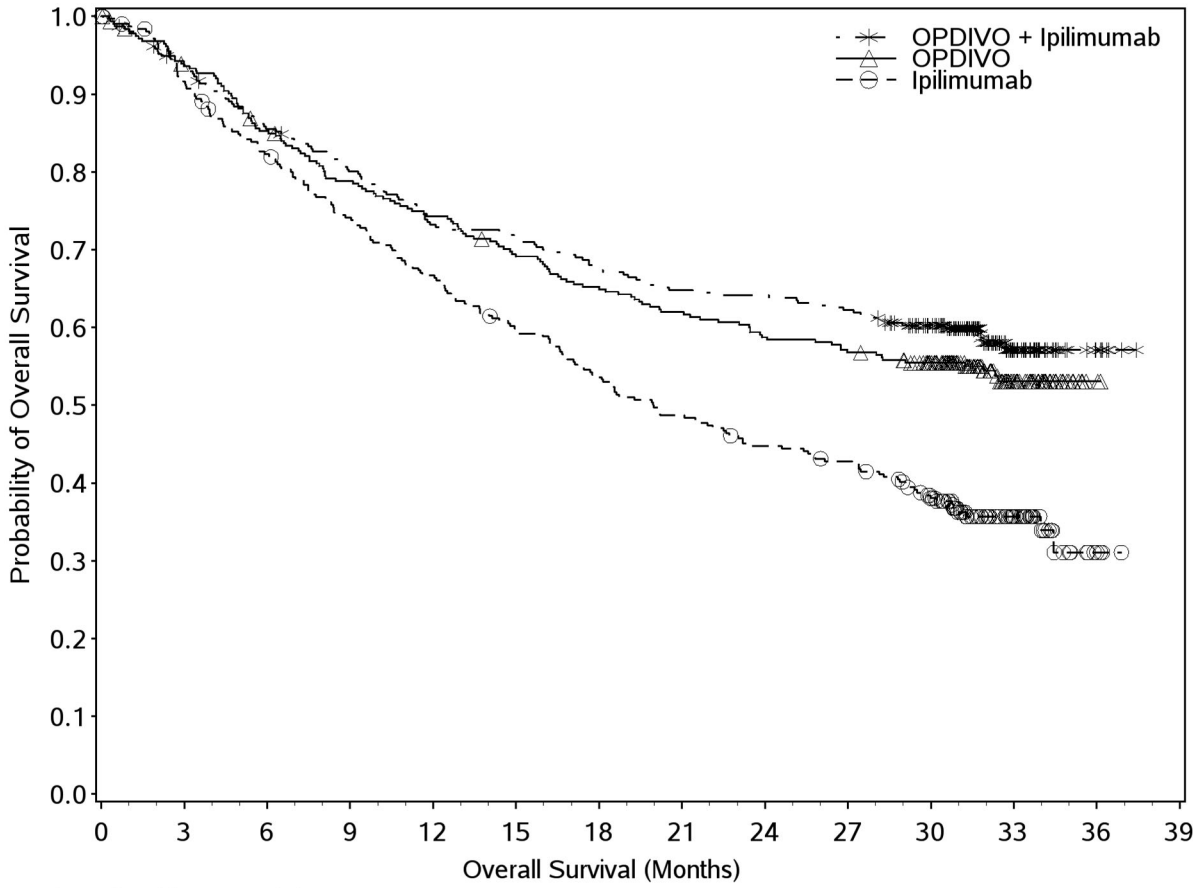
Figure 19: Progression-free survival (CA209067)



Number of Subjects at Risk

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

Figure 20: Overall survival (CA209067)



Number of Subjects at Risk

OPDIVO + Ipilimumab	314	292	265	247	226	221	209	200	198	192	170	49	7	0
OPDIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
Ipilimumab	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Quality of life measured by the EORTC QLQ-C30 Global Health Status remained stable in both treatment groups, with no mean change in score from baseline reaching the minimal important difference for the patient (i.e., mean change ≥10 points) at any time point for any of the three treatment arms.

Among 131 patients who discontinued nivolumab in combination with ipilimumab due to adverse reaction, median PFS was 21.9 months (95% CI: 11.1, NE), the ORR was 71% (93/131) with 20% (26/131) achieving a complete response, and median OS was not reached. Quality of life (QoL) returned to baseline levels shortly after discontinuation due to toxicity.

Efficacy by BRAF status: Efficacy results by BRAF status are shown in Table 35 for PFS, Table 36for OS, and Table 37 for ORR.

Table 35: PFS by BRAF [V600]-mutation status (CA209067)

Treatment	BRAF [V600] mutation-positive			BRAF wild-type		
	Median PFS (95% CI)	**HR vs ipilimumab (95% CI)**	**HR vs monotherapy (95% CI)**	**Median PFS (95% CI)**	**HR vs ipilimumab (95% CI)**	**HR vs monotherapy (95% CI)**
nivolumab + ipilimumab	11.7 months (8.0, NE)	0.47 (0.32, 0.68)	0.61 (0.42, 0.90)	11.2 months (8.3, NE)	0.41 (0.32, 0.53)	0.82 (0.63, 1.07)
nivolumab	5.6 months (2.8, 9.5)	0.77 (0.54, 1.09)	--	7.9 months (4.9, 12.7)	0.50 (0.39, 0.63)	--
ipilimumab	4.0 months (2.8, 5.5)	--	--	2.8 months (2.8, 3.1)	--	--

Minimum follow-up of 9 months.
NE=not estimable.

Table 36: OS by BRAF[V600]-mutation status (CA209067)

Treatment	BRAF [V600] mutation-positive			BRAF wild-type		
	Median OS (95% CI)	**HR vs ipilimumab (95% CI)**	**HR vs monotherapy (95% CI)**	**Median OS (95% CI)**	**HR vs ipilimumab (95% CI)**	**HR vs monotherapy (95% CI)**
nivolumab + ipilimumab	Not reached	0.43 (0.28, 0.66)	0.71 (0.45, 1.13)	Not reached (27.6, NE)	0.62 (0.48, 0.80)	0.97 (0.74, 1.28)
nivolumab	Not reached (26.4, NE)	0.60 (0.40, 0.89)	--	Not reached (25.8, NE)	0.64 (0.49, 0.83)	--
ipilimumab	24.6 months (17.9, 31.0)	--	--	18.5 months (14.8, 23.0)	--	--

Minimum follow-up of 28 months.
NE=not estimable.

Table 37: Objective response by BRAF[V600]-mutation status[a] (CA209067)

Treatment	BRAF [V600] mutation-positive		BRAF wild-type	
	Number of responses/patients	**ORR (95% CI)**	**Number of responses/patients**	**ORR (95% CI)**
nivolumab + ipilimumab	69/102	68% (58, 77)	116/212	55% (48, 62)
nivolumab	36/98	37% (27, 47)	105/218	48% (41, 55)
ipilimumab	23/100	23% (15, 33)	37/215	17% (12, 23)

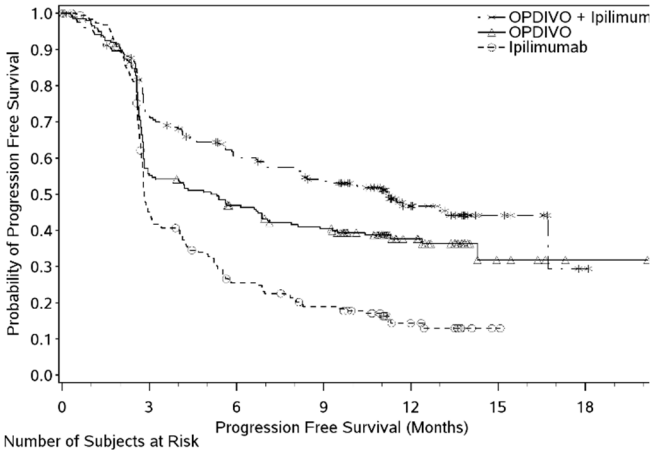
Minimum follow up of 28 months.

Efficacy by PD-L1 tumor expression: Baseline tumor tissue specimens were systematically collected prior to randomization in order to conduct planned analyses of efficacy according to PD-L1 expression. Quantifiable tumor PD-L1 expression was measured in 89% (278/314) of patients randomized to nivolumab in combination with ipilimumab, 91% (288/316) of patients randomized to nivolumab monotherapy, and 88% (277/315) of patients randomized to ipilimumab monotherapy. Among patients with quantifiable tumor PD-L1 expression, the distribution of patients was balanced across the three treatment groups at each of the predefined tumor PD-L1 expression levels of ≥1% (56% in the nivolumab in combination with ipilimumab arm, 59% in the nivolumab monotherapy arm, and 59% in the ipilimumab arm) and ≥5% (24%, 28%, and 27%, respectively). Tumor PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

In patients with low or no tumor PD-L1 expression (based on the predefined expression level of <5% and <1%), nivolumab in combination with ipilimumab and nivolumab monotherapy demonstrated significant improvements in PFS and OS compared with ipilimumab monotherapy. Nivolumab in combination with ipilimumab demonstrated a greater improvement in PFS and OS than nivolumab monotherapy. In patients with ≥5% and ≥1% tumor PD-L1 expression, a significant improvement in PFS and OS relative to ipilimumab was also observed for both nivolumab-containing arms. The improvements in PFS and OS were similar between nivolumab in combination with ipilimumab and nivolumab monotherapy. Results by PD-L1 expression level are shown in Figure 21 for PFS and in Figure 22 for OS.

Figure 21: Progression-free survival by tumor PD-L1 expression level (CA209067)

<5%



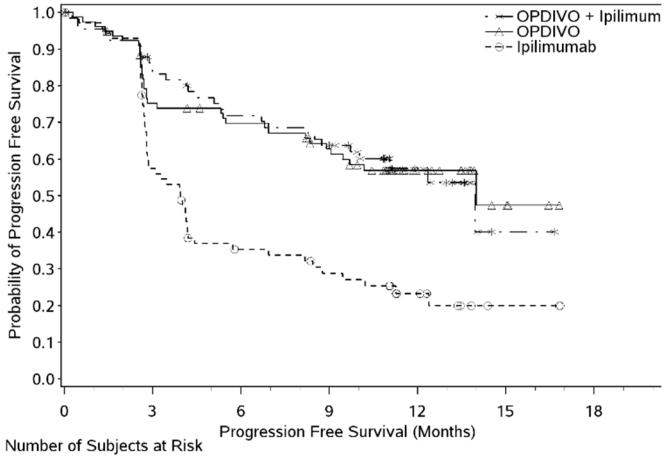
Number of Subjects at Risk

OPDIVO + Ipilimumab	210	142	112	96	42	9	1
OPDIVO	208	108	88	74	31	5	1
Ipilimumab	202	82	44	31	12	1	0

OPDIVO + Ipilimumab (events : 103/210), median and 95% CI : 11.24 (7.98, N.A.)
OPDIVO (events : 122/208), median and 95% CI : 5.32 (2.83, 7.06)
Ipilimumab (events : 154/202), median and 95% CI : 2.83 (2.76, 3.09)

OPDIVO + Ipilimumab vs. Ipilimumab - hazard ratio and 95% CI: 0.42 (0.32, 0.54)
OPDIVO vs. Ipilimumab - hazard ratio and 95% CI: 0.59 (0.47, 0.75)
OPDIVO + Ipilimumab vs. OPDIVO - hazard ratio and 95% CI: 0.70 (0.54, 0.91)

≥5%



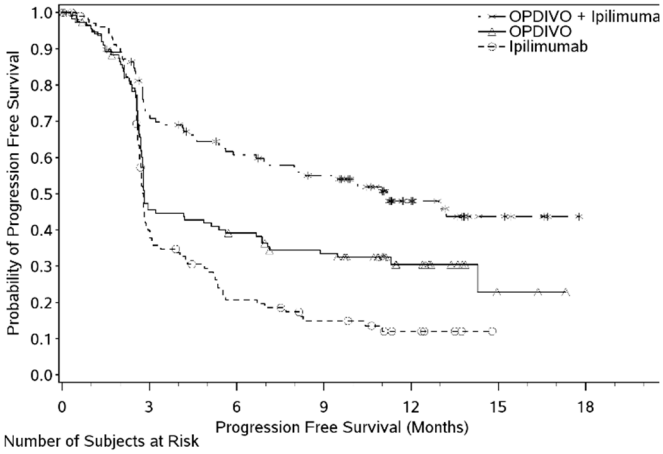
Number of Subjects at Risk

OPDIVO + Ipilimumab	68	53	44	39	16	1	0
OPDIVO	80	57	51	43	16	4	0
Ipilimumab	75	40	22	17	9	2	0

OPDIVO + Ipilimumab (events : 28/68), median and 95% CI : 13.96 (9.72, N.A.)
OPDIVO (events : 33/80), median and 95% CI : 14.00 (9.07, N.A.)
Ipilimumab (events : 53/75), median and 95% CI : 3.94 (2.79, 4.21)

OPDIVO + Ipilimumab vs. Ipilimumab - hazard ratio and 95% CI: 0.39 (0.25, 0.62)
OPDIVO vs. Ipilimumab - hazard ratio and 95% CI: 0.41 (0.26, 0.63)
OPDIVO + Ipilimumab vs. OPDIVO - hazard ratio and 95% CI: 0.96 (0.58, 1.58)

<1%



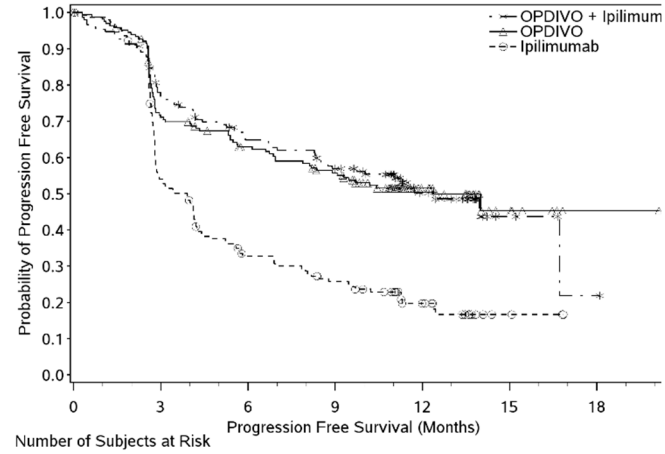
Number of Subjects at Risk

OPDIVO + Ipilimumab	123	82	65	57	26	6	0
OPDIVO	117	50	42	34	13	2	0
Ipilimumab	113	39	19	12	5	0	0

OPDIVO + Ipilimumab (events : 59/123), median and 95% CI : 11.17 (6.93, N.A.)
OPDIVO (events : 76/117), median and 95% CI : 2.83 (2.76, 5.13)
Ipilimumab (events : 85/113), median and 95% CI : 2.79 (2.66, 2.96)

OPDIVO + Ipilimumab vs. Ipilimumab - hazard ratio and 95% CI: 0.38 (0.27, 0.53)
OPDIVO vs. Ipilimumab - hazard ratio and 95% CI: 0.67 (0.49, 0.92)
OPDIVO + Ipilimumab vs. OPDIVO - hazard ratio and 95% CI: 0.56 (0.40, 0.79)

≥1%



Number of Subjects at Risk

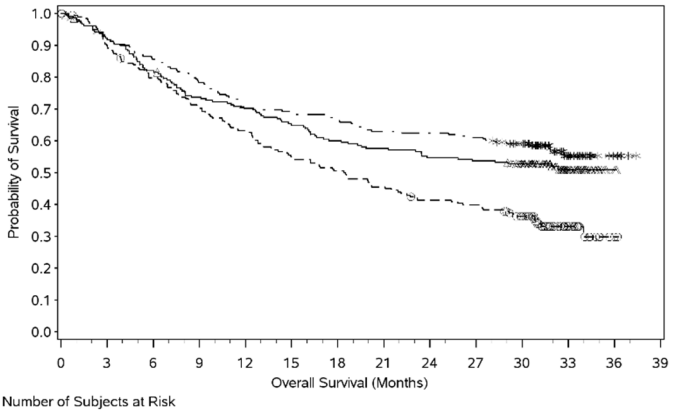
OPDIVO + Ipilimumab	155	113	91	78	32	4	1
OPDIVO	171	115	97	83	34	7	1
Ipilimumab	164	83	47	36	16	3	0

OPDIVO + Ipilimumab (events : 72/155), median and 95% CI : 12.35 (8.51, N.A.)
OPDIVO (events : 79/171), median and 95% CI : 12.39 (8.11, N.A.)
Ipilimumab (events : 122/164), median and 95% CI : 3.91 (2.83, 4.17)

OPDIVO + Ipilimumab vs. Ipilimumab - hazard ratio and 95% CI: 0.44 (0.32, 0.58)
OPDIVO vs. Ipilimumab - hazard ratio and 95% CI: 0.46 (0.34, 0.61)
OPDIVO + Ipilimumab vs. OPDIVO - hazard ratio and 95% CI: 0.95 (0.69, 1.31)

Figure 22: Overall survival by tumor PD-L1 expression level (CA209067)

<5%



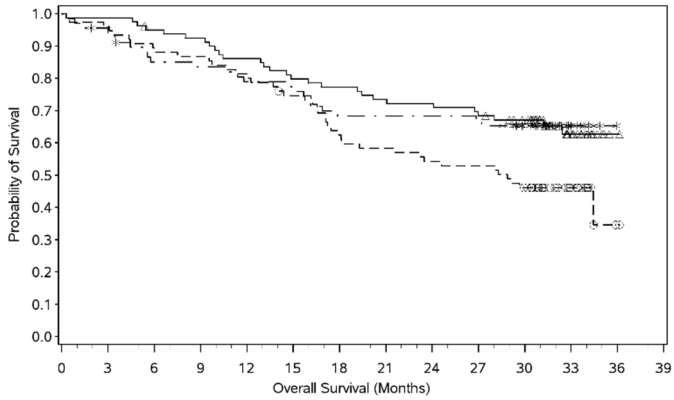
Number of Subjects at Risk

Nivolumab + Ipilimumab	210	194	178	163	146	144	139	131	130	127	116	34	7	0
Nivolumab	208	189	169	151	144	133	123	118	112	110	99	34	2	0
Ipilimumab	202	179	158	140	125	108	100	90	81	78	63	18	2	0

Nivolumab + Ipilimumab (events: 89/210), median and 95% CI: N.A. (31.84, N.A.)
Nivolumab (events: 99/208), median and 95% CI: N.A. (23.06, N.A.)
Ipilimumab (events: 131/202), median and 95% CI: 18.50 (13.70, 22.51)

Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 95% CI: 0.55 (0.42, 0.72)
Nivolumab vs Ipilimumab - hazard ratio and 95% CI: 0.65 (0.50, 0.85)
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.84 (0.63, 1.12)

≥5%



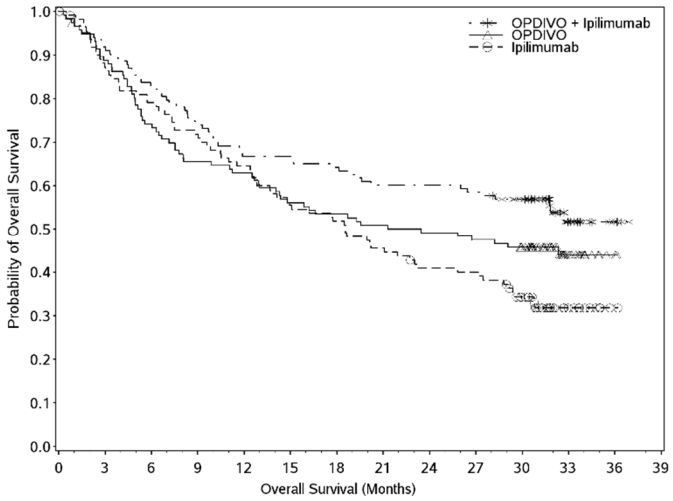
Number of Subjects at Risk

Nivolumab + Ipilimumab	68	63	56	55	52	50	45	45	45	44	35	11	0	0
Nivolumab	80	79	75	73	68	63	61	58	57	54	49	18	1	0
Ipilimumab	75	72	67	65	61	55	46	43	40	39	33	13	1	0

Nivolumab + Ipilimumab (events: 23/68), median and 95% CI: N.A.
Nivolumab (events: 28/80), median and 95% CI: N.A.
Ipilimumab (events: 41/75), median and 95% CI: 28.88 (18.10, N.A.)

Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 95% CI: 0.60 (0.36, 1.00)
Nivolumab vs Ipilimumab - hazard ratio and 95% CI: 0.57 (0.35, 0.92)
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 1.05 (0.61, 1.83)

<1%



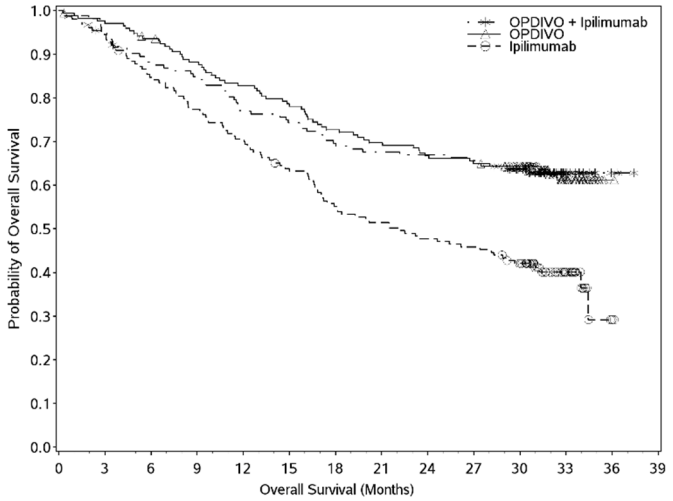
Number of Subjects at Risk

OPDIVO + Ipilimumab	123	113	102	91	82	82	79	74	74	72	66	18	4	0
OPDIVO	117	103	86	76	73	65	62	59	57	55	50	16	2	0
Ipilimumab	113	96	87	79	71	61	57	50	44	43	32	10	1	0

Nivolumab + Ipilimumab (events: 56/123), median and 95% CI: N.A. (26.45, N.A.)
Nivolumab (events: 64/117), median and 95% CI: 23.46 (13.01, N.A.)
Ipilimumab (events: 74/113), median and 95% CI: 18.56 (13.67, 23.20)

Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 95% CI: 0.60 (0.42, 0.84)
Nivolumab vs Ipilimumab - hazard ratio and 95% CI: 0.80 (0.57, 1.12)
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.74 (0.52, 1.06)

≥1%



Number of Subjects at Risk

OPDIVO + Ipilimumab	155	144	132	127	116	112	105	102	101	99	85	27	3	0
OPDIVO	171	165	158	148	139	131	122	117	112	109	98	36	1	0
Ipilimumab	164	155	138	126	115	102	89	83	77	74	64	21	2	0

Nivolumab + Ipilimumab (events: 56/155), median and 95% CI: N.A.
Nivolumab (events: 63/171), median and 95% CI: N.A.
Ipilimumab (events: 98/164), median and 95% CI: 22.11 (17.08, 29.67)

Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 95% CI: 0.53 (0.38, 0.74)
Nivolumab vs Ipilimumab - hazard ratio and 95% CI: 0.52 (0.38, 0.71)
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 1.03 (0.72, 1.48)

Table 38 shows the objective response rates in CA209067 based on PD-L1 expression level. Both nivolumab-containing arms demonstrated greater objective response rates than ipilimumab regardless of tumor PD-L1 expression levels. Greater objective response rates were demonstrated for nivolumab in combination with ipilimumab relative to nivolumab monotherapy across tumor PD-L1 expression levels, with a best overall response of complete response correlating to an improved survival rate.

Table 38: Objective response by PD-L1 Expression Level (CA209067)

	ORR % (95% CI)		
	nivolumab + ipilimumab (n=314)	**nivolumab (n=316)**	**ipilimumab (n=315)**
<5%	56% (49.2, 63.0) n=210	42% (35.5, 49.3) n=208	18% (12.8, 23.8) n=202
≥5%	74% (61.4, 83.5) n=68	59% (47.2, 69.6) n=80	21% (12.7, 32.3) n=75
<1%	55% (45.2, 63.5) n=123	35% (26.5, 44.4) n=117	19% (11.9, 27.0) n=113
≥1%	65% (57.1, 72.6) n=155	55% (47.2, 62.6) n=171	19% (13.2, 25.7) n=164

No clear cutoff for PD-L1 expression can reliably be established when considering the relevant endpoints of tumor response, PFS, and OS.

As compared to the overall study population, no meaningful differences in safety were observed based on BRAF status or tumor PD-L1 expression levels of 1% or 5%.

Randomized Phase 2 study of nivolumab in combination with ipilimumab vs ipilimumab (CA209069)

The safety and efficacy of nivolumab in combination with ipilimumab, compared with ipilimumab monotherapy, for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a Phase 2, randomized, double-blind study (CA209069). Key eligibility criteria were similar to those in CA209067. Patients were enrolled regardless of PD-L1 expression. Patients in the combination arm received nivolumab 1 mg/kg and ipilimumab 3 mg/kg intravenously every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg monotherapy every 2 weeks. Patients in the comparator arm received ipilimumab 3 mg/kg monotherapy and nivolumab-matched placebo intravenously every 3 weeks for 4 doses followed by placebo every 2 weeks. The primary efficacy outcome measure was ORR, as determined by investigator, in patients with BRAF wild-type unresectable or metastatic melanoma using RECIST 1.1. Magnitude of tumor reduction and duration of response were also assessed. Additional outcome measures were PFS in patients with BRAF wild-type melanoma, ORR and PFS in patients with BRAF mutation-positive melanoma, and Health Related Quality of Life (HRQoL) as assessed by the European Organization for Research and Treatment of Care (EORTC) QLQ-C30. OS was also assessed as an exploratory endpoint.

A total of 142 patients were randomized: 95 to nivolumab in combination with ipilimumab and 47 to ipilimumab. The baseline study population characteristics were generally balanced between treatment groups except for history of brain metastasis (4% in the nivolumab in combination with ipilimumab arm and none in the ipilimumab arm), acral/mucosal melanoma (8% and 21%, respectively), and cutaneous melanoma (84% and 62%, respectively). Seventy-seven percent of patients had BRAF wild-type melanoma and 23% of patients had BRAF mutation positive melanoma.

Efficacy results in BRAF wild-type melanoma are presented in Table 39 and Figure 23.

Table 39: Efficacy results in BRAF wild-type melanoma (CA209069)

Endpoint	**nivolumab +ipilimumab (n=72)**	**ipilimumab (n=37)**
Objective response rate n (%) (95% CI)	44 (61%) (48.9, 72.4)	4 (11%) (3.0, 25.4)
Odds ratio (95% CI)	12.96 (3.91, 54.49)	
P-value	<0.0001	
Complete response (CR)	16 (22%)	0
Partial response (PR)	28 (39%)	4 (11%)
Stable disease (SD)	9 (13%)	13 (35%)
Duration of Response (months)[a]		
Median (range)	Not reached (0.0^{+}-12.1^{+})	Not reached (6.9-9.8^{+})

Table 39: Efficacy results in BRAF wild-type melanoma (CA209069)

Endpoint	nivolumab +ipilimumab (n=72)		ipilimumab (n=37)
Progression-free Survival[a]			
Events n (%)	30 (42%)		25 (68%)
Hazard Ratio (95% CI)		0.40 (0.23, 0.68)	
p-value		0.0006	
Median (95% CI)	Not reached		4.4 months (2.8, 5.8)
Rate (95% CI)			
At 6 months	68% (55, 77)		31% (16, 47)
At 12 months	55% (42, 66)		22% (9, 39)
OS[b]			
Events n (%)	28 (38%)		20 (54%)
Hazard Ratio (95% CI)		0.62 (0.35, 1.10)	
Median OS (95% CI)	Not reached (29.3, NE)		32.9 months (10.3, NE)
Rate (95% CI)			
at 12 months	78% (66, 86)		62% (44, 75)
at 24 months	68% (56, 78)		53% (36, 68)
at 36 months	61% (49, 71)		44% (28, 60)

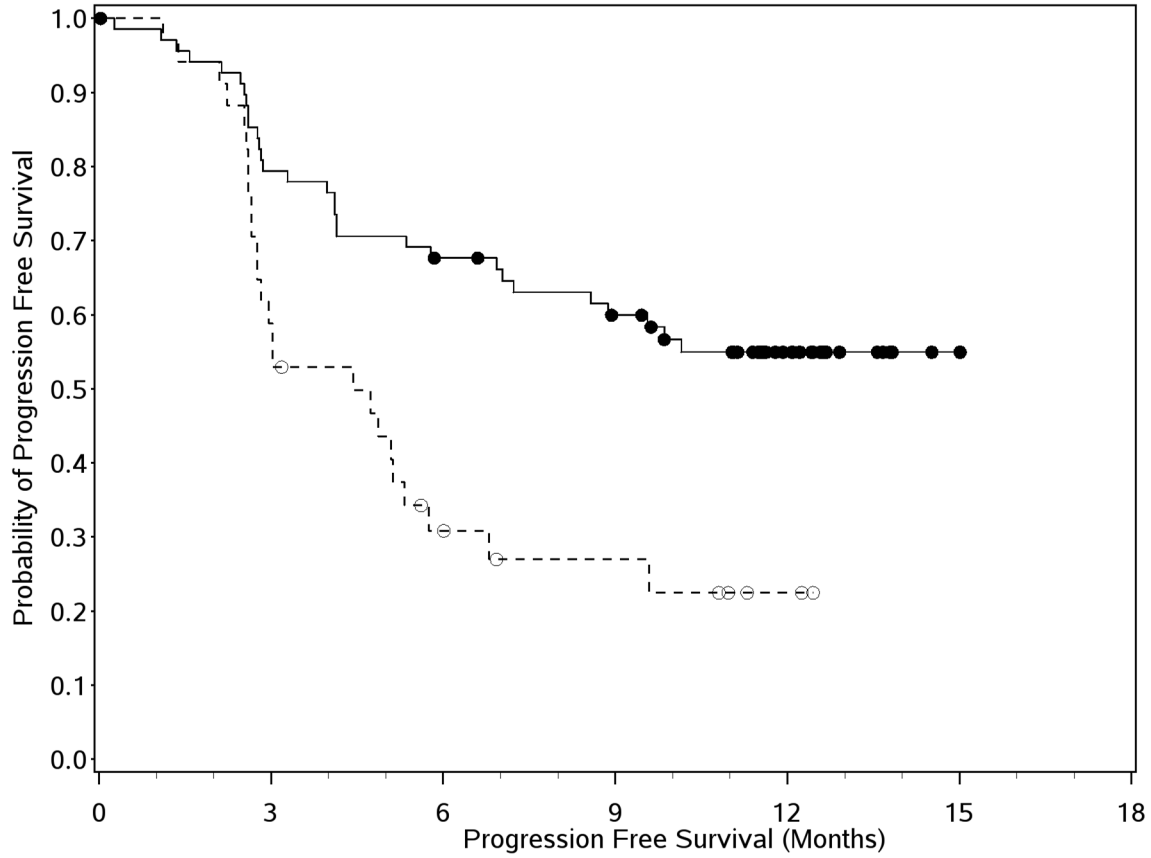
a Minimum follow-up of 11 months.

b Minimum follow-up of 36 months.

NE: not estimable.

"+" denotes a censored observation.

Figure 23: Progression-free Survival in BRAF Wild-Type Previously Untreated, Unresectable or Metastatic Melanoma (CA209069)



Number of Subjects at Risk

Nivolumab + Ipilimumab	72	54	45	38	20	1	0
Ipilimumab	37	20	9	6	2	0	0

Nivolumab + Ipilimumab (events : 30/72), median and 95% CI : N.A.

Ipilimumab (events : 25/37), median and 95% CI : 4.44 (2.76, 5.75)

Hazard Ratio (Nivolumab + Ipilimumab over Ipilimumab) and 95% CI : 0.40 (0.23, 0.68)
P-Value: 0.0006

Among the 44 BRAF wild-type patients randomized to nivolumab in combination with ipilimumab who had an objective response, 38 (86%) had their responses within the first 3 months and 36 (82%) had ongoing responses at the time of analysis. Patients randomized to nivolumab in combination with ipilimumab had a median reduction in tumor volume of 68%, while patients treated with ipilimumab monotherapy had a median increase of 5%.

Among 38 patients with BRAF wild-type melanoma who discontinued nivolumab in combination with ipilimumab due to adverse reaction, the confirmed ORR was 71% (27/38) with 26% (10/38) achieving a complete response. The ORR result was consistently demonstrated across subgroups of patients (M stage, AJCC state, age, gender, race, baseline ECOG performance status, history of brain metastases, and baseline LDH).

Results for patients with BRAF mutation-positive melanoma were consistent with the primary analyses in patients with BRAF wild-type melanoma. Among 23 patients with BRAF

mutation-positive melanoma randomized to nivolumab in combination with ipilimumab, ORR was 52% (95% CI: 30.6, 73.2); 5 complete responses and 7 partial responses. The median PFS was 8.5 months (95% CI: 2.79, NE) in patients randomized to nivolumab in combination with ipilimumab and 2.7 months (95% CI: 0.99, 5.42) in patients randomized to ipilimumab monotherapy (HR 0.38, 95% CI: 0.15, 1.00).

Responses were observed across levels of PD-L1 tumor membrane expression.

Randomized Phase 3 study of nivolumab vs ipilimumab 10 mg/kg (CA209238)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with completely resected melanoma were evaluated in a Phase 3, randomized, double-blind study (CA209238). The study included adult patients who had an ECOG performance status score of 0 or 1, with Stage IIIB/C or Stage IV American Joint Committee on Cancer (AJCC), 7th edition, histologically confirmed melanoma that was completely surgically resected. Per the AJCC 8th edition, this corresponds to patients with lymph node involvement or metastases. Patients were enrolled regardless of their tumor PD-L1 status. Patients with prior 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 patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomization) prior therapy with, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways), were excluded from the study.

A total of 906 patients were randomized to receive either nivolumab 3 mg/kg (n = 453) administered every 2 weeks or ipilimumab 10 mg/kg (n = 453) administered every 3 weeks for 4 doses then every 12 weeks beginning at week 24 for up to 1 year. Randomization was stratified by tumor PD-L1 expression (≥5% vs. < 5%/indeterminate), and stage of disease per the AJCC staging system. Tumor assessments were conducted every 12 weeks for the first 2 years then every 6 months thereafter. The primary endpoint was recurrence-free survival (RFS). RFS, assessed by 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 due to any cause, whichever occurred first.

Baseline characteristics were generally balanced between the two groups. The median age was 55 years (range: 18-86), 58% were men, and 95% were white. Baseline ECOG performance status score was 0 (90%) or 1 (10%). The majority of patients had AJCC Stage III disease (81%), and 19% had Stage IV disease. Forty-eight percent of patients had macroscopic lymph nodes and 32% had tumor ulceration. Forty-two percent of patients were BRAF V600 mutation positive while 45% were BRAF wild type and 13% BRAF status was unknown. For tumor PD-L1 expression, 34% of patients had PD-L1 expression ≥ 5% and 62% had < 5% as determined by clinical trial assay. Among patients with quantifiable tumor PD-L1 expression, the distribution of patients was balanced across the treatment groups. Tumor PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

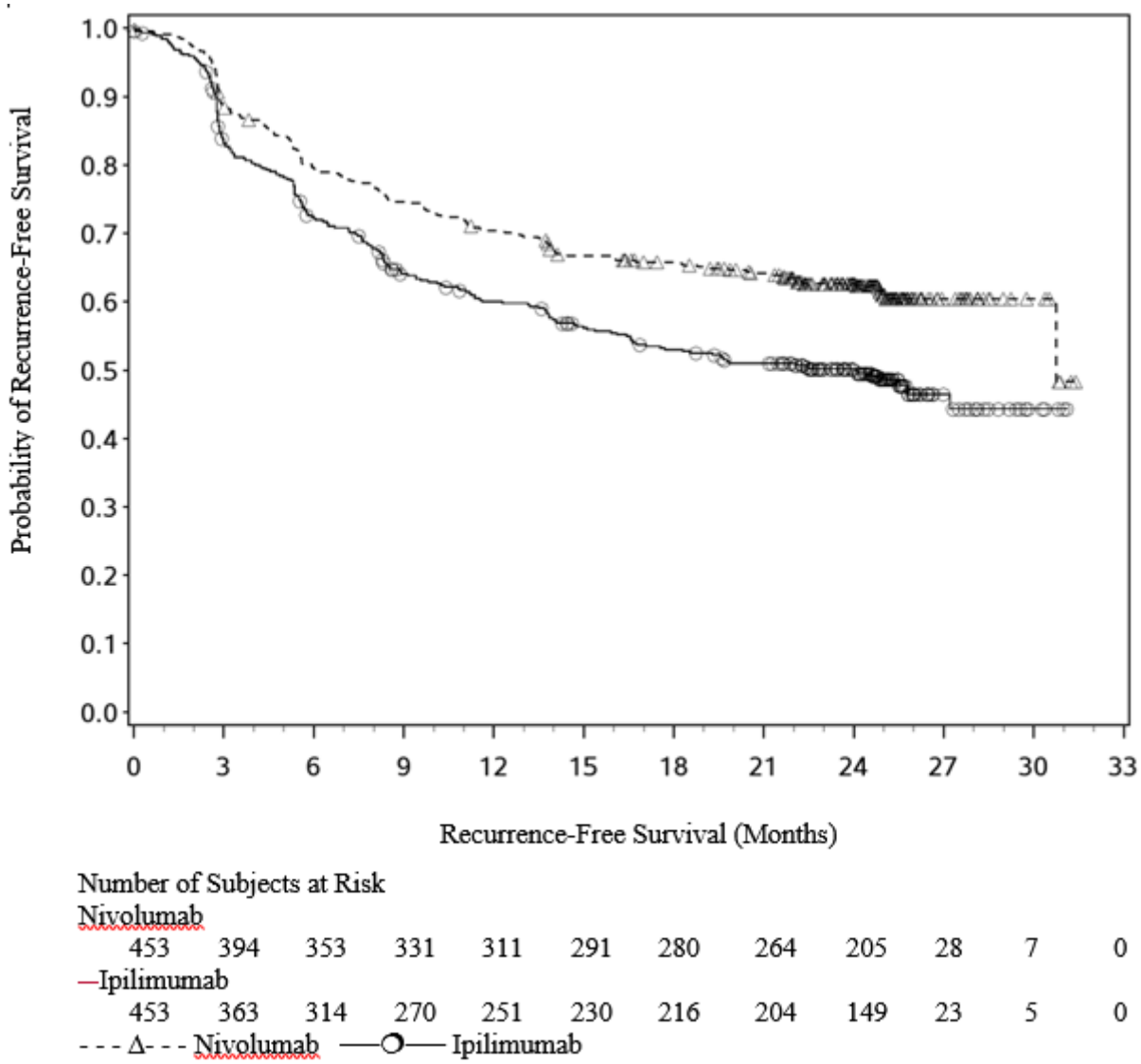
Minimum follow-up was approximately 24 months. OS was not mature at the time of this analysis. RFS results are shown in Table 40 and Figure 24 (all randomized population).

Table 40: Efficacy results (CA209238)

	nivolumab (n = 453)	**ipilimumab 10 mg/kg (n = 453)**
Recurrence-free Survival		
Events	171 (37.7%)	221 (48.8%)
Hazard ratio[a]	0.66	
95% CI	(0.54, 0.81)	
p-value	p<0.0001	
Median (95% CI) months	30.75 (30.75, NR)[b]	24.08 (16.56, NR)[b]
Rate (95% CI) at 12 months	70.4 (65.9, 74.4)	60.0 (55.2, 64.5)
Rate (95% CI) at 18 months	65.8 (61.2, 70.0)	53.0 (48.1, 57.6)
Rate (95% CI) at 24 months	62.6 (57.9, 67.0)	50.2 (45.3, 54.8)

[a] Derived from a stratified Cox proportional hazards model.
[b] Based on Kaplan-Meier estimates.

Figure 24: Recurrence-free Survival (CA209238)



The trial demonstrated a statistically significant improvement in RFS for patients randomized to the nivolumab arm compared with the ipilimumab 10 mg/kg arm. RFS benefit was consistently demonstrated across subgroups, including tumor PD-L1 expression, BRAF status, and stage of disease.

Quality of life (QoL) with nivolumab remained stable and close to baseline values during treatment, as assessed by valid and reliable scales like the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EQ-5D utility index and visual analog scale (VAS).

Classical Hodgkin lymphoma (cHL)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of relapsed or refractory cHL following ASCT and treatment with brentuximab vedotin were evaluated in two global, multicenter, open-label, single-arm studies (CA209205 and CA209039).

CA209205 is an ongoing Phase 2, open-label, multi-cohort, single-arm study of nivolumab in cHL. Cohort A included 63 patients who had received ASCT and were brentuximab vedotin naïve; Cohort B included 80 patients who had received brentuximab vedotin after ASCT failure; Cohort C included

100 patients who had received brentuximab vedotin before and/or after ASCT out of which 33 patients received brentuximab vedotin only prior to ASCT. The first tumor assessments were conducted 9 weeks after the start of treatment and continued thereafter until disease progression or treatment discontinuation. The primary efficacy outcome measure was ORR as determined by IRRC. Additional efficacy measures included duration of response and PFS.

CA209039 was a Phase 1b open-label, multicenter, dose-escalation, and multidose study of nivolumab in relapsed or refractory hematologic malignancies, including 23 patients with cHL; amongst which, 15 patients received prior brentuximab vedotin treatment as a salvage therapy following ASCT, similar to Cohort B of study CA209205. The first tumor assessments were conducted 4 weeks after the start of treatment and continued thereafter until disease progression or treatment discontinuation. Efficacy assessments included investigator-assessed ORR, retrospectively evaluated by an IRRC, and duration of response.

Both studies included patients regardless of their PD-L1 status, and excluded patients with autoimmune disease, symptomatic interstitial lung disease, known central nervous system (CNS) lymphoma or patients with nodular lymphocyte-predominant HL. Patients received 3 mg/kg of nivolumab administered intravenously over 60 minutes every 2 weeks.

Data from the 80 patients from CA209205 Cohort B and the 15 patients from CA209039 who received prior brentuximab vedotin treatment following ASCT were integrated. Baseline characteristics were similar across the two studies (Table 41). Efficacy from both studies was evaluated by the same IRRC. Results are shown in Table 42.

Table 41: **Baseline patient characteristics (CA209205 Cohort B and CA209039)**

	CA209205 Cohort B and CA209039 (n = 95)	**CA209205 Cohort B [a] (n = 80)**	**CA209039 (n = 15)**
Median age (range)	37.0 years (18–72)	37.0 years (18–72)	40.0 years (24–54)
Gender	61 (64%)M / 34 (36%)F	51 (64%)M / 29 (36%)F	10 (67%)M / 5 (33%)F
ECOG status			
0	49 (52%)	42 (52.5%)	7 (47%)
1	46 (48%)	38 (47.5%)	8 (53%)
≥5 prior lines of systemic therapy	49 (52%)	39 (49%)	10 (67%)
Prior ASCT			
1	87 (92%)	74 (92.5%)	13 (87%)
≥2	8 (8%)	6 (7.5%)	2 (13%)
Years from most recent transplant to first dose of study therapy, median (range)	3.5 years (0.2-19.0)	3.4 years (0.2-19.0)	5.6 years (0.5-15.0)

[a] 18/80 (22.5%) of the patients in CA209205 Cohort B presented B-Symptoms at baseline.

Table 42: Efficacy results (CA209205 Cohort B and CA209039)

	CA209205 Cohort B[a] and CA209039 (n = 95)	CA209205 Cohort B[a] (n = 80)	CA209039 (n = 15)
Objective Response Rate; (95% CI)	63 (66%); (56, 76)	54 (68%); (56, 78)	9 (60%); (32, 84)
Complete Remission Rate; (95% CI)	6 (6%); (2, 13)	6 (8%); (3, 16)	0 (0%); (0, 22)
Partial Remission Rate; (95% CI)	57 (60%); (49, 70)	48 (60%); (48, 71)	9 (60%); (32, 84)
Stable disease, n (%)	22 (23%)	17 (21%)	5 (33%)
Median Duration of Response[b] (95% CI)	13.1 months (9.5, NE)	13.1 months (8.7, NE)	12.0 months (1.8, NE)
Range	0.0^{+} - 23.1^{+}	0.0^{+} - 14.2^{+}	1.8 - 23.1^{+}
Median Time to Response	2.0 months	2.1 months	0.8 months
Range	0.7 - 11.1	1.6 - 11.1	0.7 - 4.1
Median Duration of Follow-up	15.8 months	15.4 months	21.9 months
Range	1.9 - 27.6	1.9 - 18.5	11.2 - 27.6
PFS rate at 12 months (95% CI)	57% (45, 68)	55% (41, 66)	69% (37, 88)

[a] Follow-up was ongoing at the time of data submission
[b] Data unstable due to the limited duration of response for Cohort B resulting from censoring.
NE=not estimable.
"+" denotes a censored observation.

Nine patients received allogeneic stem cell transplant (5 in CA209205 and 4 in CA209039) as subsequent therapy.

Objective response per IRRC with nivolumab was observed regardless of baseline tumor PD-L1 expression status.

In a post-hoc analysis of the 80 patients in CA209205 Cohort B, 37 had no response to prior brentuximab vedotin treatment. Among these 37 patients, treatment with nivolumab resulted in an ORR of 59.5% (22/37). The median duration of response is 13.1 months (13.1, NE) for the 22 responders to nivolumab who had failed to achieve response with prior brentuximab vedotin treatment.

B-symptoms were present in 22.5% (18/80) of the patients in CA209205 Cohort B at baseline. Nivolumab treatment resulted in rapid resolution of B-symptoms in 88.9% (16/18) of the patients, with a median time to resolution of 1.9 months.

Efficacy was also evaluated in 258 patients who had relapsed or progressive cHL after autologous HSCT (243 patients in Cohorts A+B+C from CA209205 and 15 patients from CA209039). The median age was 34 years (range: 18-72). The majority were male (59%) and white (86%). Patients had a median of 4 prior systemic regimens (range: 2-15), with 85% having 3 or more prior systemic regimens and 76% having prior brentuximab vedotin. Of the 195 patients having prior brentuximab

vedotin, 17% received it only before autologous HSCT, 78% received it only after HSCT, and 5% received it both before and after HSCT. Efficacy results for this population are shown in Table 43.

Table 43: Efficacy in cHL after autologous HSCT (CA209205 Cohort A+B+C and CA209039)

	Nivolumab (n=258)
Objective Response Rate, n (%)	179 (69%)
(95% CI)	(63, 75)
Complete Remission Rate	37 (14%)
(95% CI)	(10, 19)
Partial Remission Rate	142 (55%)
(95% CI)	(49, 61)
Duration of Response (months)	
Median[a,b]	Not reached
(95% CI)	(12.0, NE)
Range	0^{+} - 23.1^{+}
Time to Response	
Median	2.0 months
Range	0.7 - 11.1

[a] Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 6.7 months.

[b] The estimated median duration of PR was 13.1 months (95% CI, 9.5, NE). The median duration of CR was not reached.

NE=not estimable.

"$^{+}$" denotes a censored observation.

Health related Quality of Life (QoL) was assessed among overall patients (Cohort A+B+C) in CA209205 using the patient reported EQ 5D VAS and EORTC-QLQ-C30 (global health status). Over 81 weeks of follow up, mean EQ-5D VAS scores increased over time, indicating superior overall health status for patients remaining on treatment with clinically relevant improvements. EORTC QLQ-C30 scores remained generally stable over time with mean changes from baseline trending toward an improvement on treatment in global health status.

Urothelial Carcinoma (UC)

Open-label Phase 2 study (CA209275)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of locally advanced or metastatic UC were evaluated in a Phase 2, multicenter, open-label, single-arm study (CA209275).

The study included patients (18 years or older) who had disease progression during or after platinum-containing chemotherapy for advanced or metastatic disease or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Patients had an ECOG performance status score of 0 or 1 and were enrolled regardless of their tumor PD-L1 status. Patients with active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

Patients received nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit, did not have rapid disease progression, and was tolerating study drug. The first tumor assessments were conducted 8 weeks after the start of treatment and continued every 8 weeks up to 48 weeks, then every 12 weeks thereafter until disease progression or treatment discontinuation, whichever occurred later. Tumor assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. The primary efficacy outcome measure was ORR as determined by IRRC. Additional efficacy measures included duration of response, PFS, and OS.

A total of 270 patients with a minimum follow-up of 8.3 months were evaluable for efficacy. The median age was 66 years (range: 38-90) with 55% ≥65 years of age and 14% ≥75 years of age. The majority of patients were white (86%) and male (78%). Baseline ECOG performance status was 0 (54%) or 1 (46%).

Efficacy results are shown in Table 44.

Table 44: Efficacy results (CA209275)[a]

	nivolumab (n = 270)
Confirmed objective response n (%)	54 (20.0%)
(95% CI)	(15.4, 25.3)
Complete response (CR)	8 (3.0%)
Partial response (PR)	46 (17.0%)
Stable disease (SD)	60 (22.2%)

Median duration of response[b] (range)	10.4 months (1.9^{+}-12.0^{+})
Median time to response (range)	1.9 months (1.6-7.2)
Progression-Free Survival	
Events (%)	216 (80%)
Median (95% CI)	2.0 months (1.9, 2.6)
Rate (95% CI) at 6 months	26.1% (20.9, 31.5)
Overall survival	
Events n (%)	154 (57%)
Median (95% CI)	8.6 months (6.1, 11.3)
Rate (95% CI) at 12 months	41.0% (34.8, 47.1)

	Tumor PD-L1 expression level	
	< 1%	**≥ 1%**
Confirmed objective response (95% CI)	16% (10.3, 22.7) n=146	25% (17.7, 33.6) n=124
Median duration of response (range)	10.4 months (3.7-12.0^{+})	Not Reached (1.9^{+}-12.0^{+})
Progression-free survival		
Median (95% CI)	1.9 months (1.8, 2.0)	3.6 months (1.9, 3.7)
Rate (95% CI) at 6 months	22.0% (15.6, 29.2)	30.8% (22.7, 39.3)
Overall survival		
Median (95% CI)	5.9 months (4.4, 8.1)	11.6 months (9.1, NE)
Rate (95% CI) at 12 months	34.0% (26.1, 42.1)	49.2% (39.6, 58.1)

[a] Median follow-up 11.5 months.
[b] Data unstable due to the limited duration of response.
NE=not estimable.
"+" denotes a censored observation.

Objective response per IRRC with nivolumab was observed regardless of baseline tumor PD-L1 expression status.

Disease related and non-disease specific quality of life (QoL) was assessed using the validated European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and the EuroQoL EQ-5D. Overall QoL scores remained stable while Global Health Status (GHS) based on the EORTC-QLQ-C30, continued to improve through Week 49. EQ-5D VAS scores showed clinically relevant improvement in QoL by Week 9, with continued improvement through Week 49. Both scales showed no detriment.

Open-label Phase 1/2 study (CA209032)

CA209032 was a Phase 1/2 open-label multi-cohort study which included a cohort of 78 patients with UC. Inclusion criteria were similar to those in study CA209275. Patients were treated with nivolumab 3 mg/kg as monotherapy. At a minimum follow-up of 9 months, investigator-assessed confirmed ORR was 24.4% (95% CI: 15.3, 35.4). The median duration of response was not reached (range: 4.4-16.6^{+} months). The median OS was 9.7 months (95% CI: 7.3, 16.2) and the estimated OS rates were 69.2% (CI: 57.7, 78.2) at 6 months and 45.6% (CI: 34.2, 56.3) at 12 months.

Randomized Phase 3 study of adjuvant nivolumab vs. placebo (CA209274)

The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of urothelial carcinoma was evaluated in a Phase 3 multicenter, randomized, placebo-controlled, double-blinded study (CA209274). The study included patients (18 years or older) who had undergone radical resection of muscle invasive 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 defined high risk patients was 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 included patients regardless of their PD-L1 status, who had an ECOG performance status score of 0 or 1 (an ECOG performance status score of 2 was allowed for patients ineligible for neo-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.

A total of 709 patients were randomized to receive either nivolumab 240 mg (n = 353) every 2 weeks or placebo (n = 356) every 2 weeks until recurrence or unacceptable toxicity for a maximum treatment duration of 1 year. Randomization was stratified by pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), tumor PD-L1 expression (≥ 1% vs. < 1%/indeterminate), and use of cisplatin neo-adjuvant chemotherapy (yes vs. no). Tumor imaging assessments were to be performed every 12 weeks from the date of first dose to week 96, then every 16 weeks from week 96 to week 160, then every 24 weeks until non-urothelial tract recurrence or treatment was discontinued (whichever occurred later) for a maximum of 5 years. The primary efficacy outcome measures were disease-free survival (DFS) in all randomized patients and DFS in randomized patients with tumors expressing PD-L1 ≥ 1%.

DFS was defined as the time between the date of randomization and the date of the first documented recurrence assessed by investigator (local urothelial tract, local non-urothelial tract or distant), or death (from any cause), whichever occurred first. Secondary efficacy outcome measures include overall survival (OS), non-urothelial tract recurrence free survival (NUTRFS), and disease-specific survival (DSS).

Baseline characteristics were generally balanced between the two groups. The median age was 67 years (range: 30 to 92), 76% were male and 76% were White. Twenty one percent of patients had upper tract urothelial carcinoma, 43% received prior cisplatin in the neoadjuvant setting, and 47%

were N+ at radical resection. Baseline ECOG performance status was 0 (63%), 1 (35%), or 2 (2%), and 7% of patients had a hemoglobin <10 g/dL.

Of the 709 patients, 40% had tumor cell PD-L1 expression of ≥ 1%, 59% had tumour cell PD-L1 expression of < 1%, and 1% had tumour cell PD-L1 expression indeterminate, not evaluable, or not reported. Tumor PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

In all randomized patients and all randomized patients with tumor cell PD-L1 expression ≥ 1%, the median follow-up was 20.9 and 22.1 months for the nivolumab arm, respectively. With a minimum follow-up of 5.9 months in the all randomized patients and a minimum follow-up of 6.3 months in randomized patients with tumors expressing PD-L1 ≥ 1%, the study demonstrated a statistically significant improvement in DFS for patients randomized to nivolumab as compared to placebo, as shown in Table 45 and Figures 25 and 26.

Table 45: Efficacy Results CA209274

	All randomized nivolumab N=353	**All randomized placebo N=356**	**PD-L1 ≥ 1% nivolumab N=140**	**PD-L1 ≥ 1% placebo N=142**
Disease-Free Survival, n (%)	170 (48.2)	204 (57.3)	55 (39.3)	81 (57.0)
Median DFS (95% CI) months[a]	20.76 (16.49, 27.63)	10.84 (8.25, 13.86)	N.R (21.19, N.E.)	8.41 (5.59, 21.19)
HR[b] (alpha adjusted[c] % CI)	0.70 (0.55, 0.90)		0.55 (0.35, 0.85)	
p-value	0.0008[d]		0.0005[e]	
Non-Urothelial Tract Recurrence Free Survival, n (%)	162 (45.9)	190 (53.4)	54 (38.6)	78 (54.9)
Median NUTRFS[f] (95% CI) months[a]	22.93 (19.15, 33.41)	13.70 (8.41, 20.34)	N.R. (24.57, N.E.)	10.84 (5.65, 22.14)
HR[b] (95% CI)	0.72 (0.59, 0.89)		0.55 (0.39, 0.79)	

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

[a] Based on Kaplan-Meier estimates

[b] Stratified Cox proportional hazard model. Hazard Ratio is nivolumab over placebo.

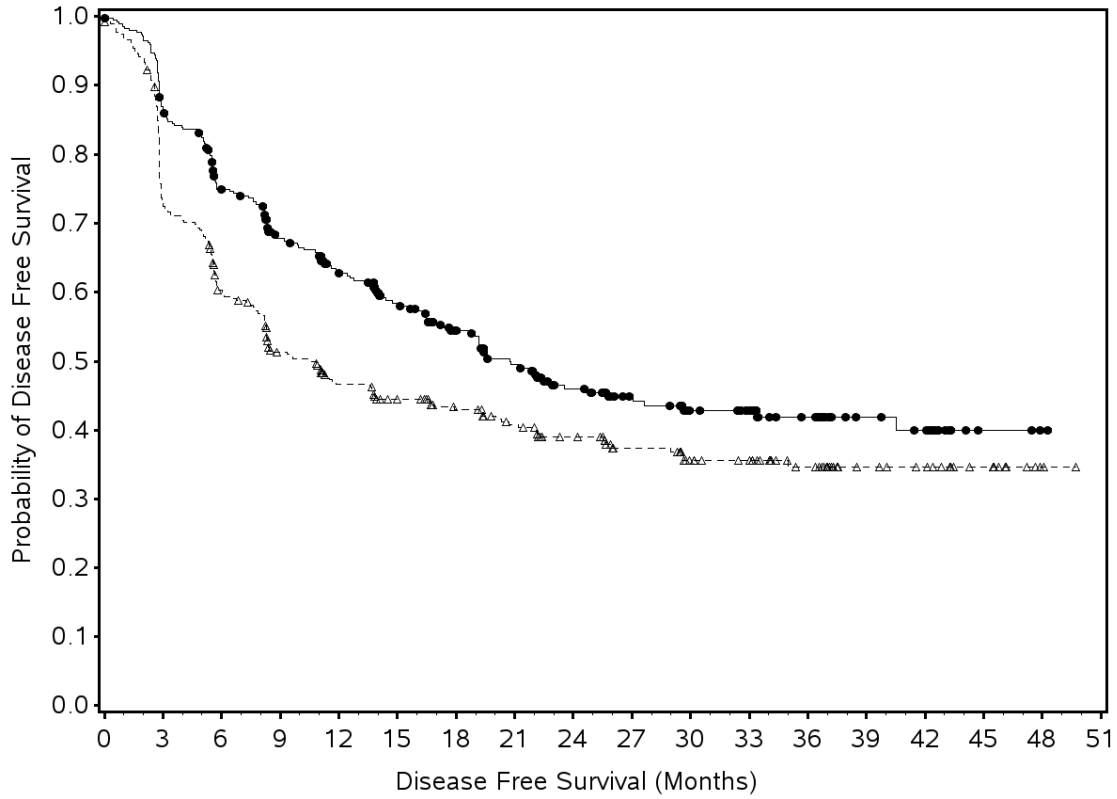
[c] alpha adjusted CI is 98.22% for all randomized patients and 98.72% for all randomized patients with PD-L1≥1%.

[d] Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, PD-L1 status (≥ 1% vs < 1%/indeterminate) as entered in the IRT. Boundary for statistical significance in all randomized patients: p-value < 0.01784.

[e] Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status as entered in the IRT. Boundary for statistical significance in all randomized patients with PD-L1 ≥ 1%: p-value < 0.01282.

[f] Non-urothelial tract recurrence free survival.

Figure 25: Disease-Free Survival - All Randomized Patients CA209274



Number of Subjects at Risk

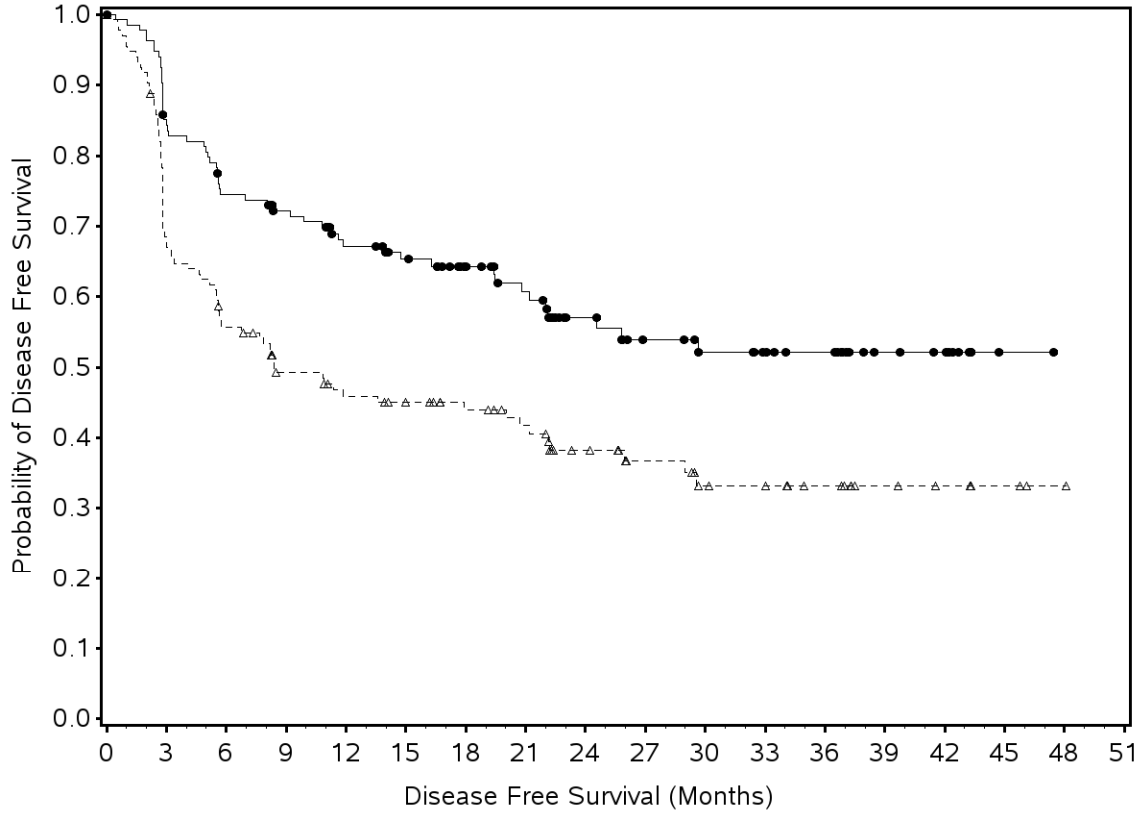
Placebo	356	248	198	157	134	121	105	94	80	65	54	50	37	22	19	10	2	0
Nivolumab	353	296	244	212	178	154	126	106	85	68	57	51	36	23	20	3	1	0

Placebo (events : 204/356), median and 95% CI : 10.84 (8.25, 13.86)

Nivolumab (events : 170/353), median and 95% CI : 20.76 (16.49, 27.63)

Nivolumab vs Placebo - hazard ratio (98.22% CI) : 0.70 (0.55, 0.90), p-value : 0.0008

Figure 26: Disease Free Survival - Randomized Patients with tumor PD-L1 expression ≥ 1% (CA209274)



Number of Subjects at Risk

Placebo	142	90	73	59	53	49	42	37	28	22	17	16	12	7	5	3	1	0
Nivolumab	140	113	98	91	76	68	58	50	38	31	27	24	21	12	10	1	0	0

Placebo (events : 81/142), median and 95% CI : 8.41 (5.59, 21.19)

Nivolumab (events : 55/140), median and 95% CI : N.A. (21.19, N.A.)

Nivolumab vs Placebo - hazard ratio (98.72% CI) : 0.55 (0.35, 0.85), p-value : 0.0005

Health-related quality of life (HRQoL), as measured by the mean changes from baseline in EORTC QLQ-C30, EQ-5D-3L Utility index, and EQ-VAS scores for patients on adjuvant nivolumab, showed no clinically meaningful change from baseline and no clinically meaningful difference compared to placebo.

Colorectal Cancer (CRC)

The safety and efficacy of nivolumab as a single agent or in combination with ipilimumab were evaluated for the treatment of dMMR or MSI-H metastatic CRC in a Phase 2, multicenter, open-label, single-arm study (CA209142).

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 tumor PD-L1 status. Patients with active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

Nivolumab monotherapy

A total of 74 patients received treatment with nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments according to RECIST version 1.1 were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The primary and secondary outcome measures were investigator-assessed ORR and blinded independent central review (BICR) ORR, respectively. Exploratory outcome measures included duration of and time to response, PFS, OS, and QoL.

The median age was 53 years (range: 26-79) with 23% ≥ 65 years of age and 5% ≥ 75 years of age, 59% were male and 88% were white. Baseline ECOG performance status was 0 (43%) or 1 (55%), 16% of patients were BRAF mutation positive, 35% were KRAS mutation positive, and 11% were unknown. 15%, 30%, 30%, and 24% received 1, 2, 3, or 4 or more prior lines of therapy, respectively, and 42% of patients had received EGFR inhibitor therapy.

Efficacy results based on a minimum follow-up of approximately 15.7 months for all 74 patients and a subgroup of 53 patients who had prior fluoropyrimidine, oxaliplatin and irinotecan therapy are shown in Table 46.

Table 46: Nivolumab monotherapy efficacy results (CA209142)

	nivolumab All patients (n = 74)	nivolumab Prior treatment with fluoropyrimidine, oxaliplatin and irinotecan (n = 53)
Confirmed objective response[a], n (%)	24 (32.4)	15 (28.3)
(95% CI)	(22.0, 44.3)	(16.8, 42.3)
Complete response (CR), n (%)	2 (2.7)	1 (1.9)
Partial response (PR), n (%)	22 (29.7)	14 (26.4)
Stable disease (SD), n (%)	25 (33.8)	16 (30.2)
Median duration of response[a]		
Months (range)	NE (1.4+, 26.5+)	NE (2.8+, 22.1+)
Median time to response[a]		
Months (range)	2.79 (1.2, 22.6)	2.89 (1.2, 22.6)
Disease control rate[a,b], n (%)	47 (63.5)	30 (56.6)
(95% CI)	(51.5, 74.4)	(42.3, 70.2)
Progression-free survival[a]		
Events	40	30
Median (months) (95% CI)	6.6 (3.0, NE)	4.2 (1.4, NE)
Overall survival		
Events	25	19
Median (months) (95% CI)	Not reached (19.6, NE)	Not reached (18.0, NE)
6-month rate (%) (95% CI)	83.3 (72.4, 90.1)	80.3 (66.5, 88.9)
12-month rate (%) (95% CI)	72.0 (60.0, 80.9)	68.3 (53.5, 79.2)

"+" denotes a censored observation.
[a] BICR assessment.
[b] CR + PR + SD (for at least 12 weeks).
NE = non-estimable.

Confirmed responses were observed regardless of BRAF and KRAS mutation status, and tumor PD-L1 expression levels.

Open-label study of nivolumab in combination with ipilimumab versus chemotherapy in dMMR or MSI-H CRC patients naive to treatment in the metastatic setting

The safety and efficacy of nivolumab 240 mg in combination with ipilimumab 1 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks in the first-line treatment of unresectable or metastatic CRC with known tumor MSI-H or dMMR status were evaluated in a randomized, multi-arm, phase 3, open-label study (CA2098HW). MSI-H or dMMR tumor status was determined in accordance with local standard of practice using PCR, NGS or IHC, assays. Central assessment of MSI-H status using PCR (Idylla MSI) test and dMMR status using IHC (Omnis MMR) test was conducted retrospectively on patient tumor specimens used for local MSI-H/dMMR status

determination. Patients with confirmed MSI-H/dMMR status by either central test comprised the primary efficacy population. Patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors were excluded from the study. Randomization was stratified by tumor location (right vs left). Patients randomized to the chemotherapy arm could receive nivolumab plus ipilimumab combination upon progression assessed by BICR.

A total of 303 previously untreated patients, in the metastatic setting, were randomized to study, including 202 patients to nivolumab in combination with ipilimumab and 101 patients to chemotherapy. Among them 255 had centrally confirmed MSI-H/dMMR status, 171 in the nivolumab in combination with ipilimumab arm and 84 in the chemotherapy arm. Patients in the nivolumab plus ipilimumab arm received nivolumab 240 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks. Patients in the chemotherapy arm received: mFOLFOX6 (oxaliplatin, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus followed by fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m^2 administered prior to mFOLFOX6 every 2 weeks; or FOLFIRI (irinotecan, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus and fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg on or cetuximab 500 mg/m^2 administered prior to FOLFIRI every 2 weeks. Treatment continued until disease progression, unacceptable toxicity, or for nivolumab in combination with ipilimumab up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Nivolumab with or without ipilimumab could be administered beyond RECIST 1.1-assessed progressive disease if there was a clinical benefit as determined by investigator and therapy was tolerated. Tumor assessments per RECIST v1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter until week 96, then every 16 weeks thereafter until week 146, and then every 24 weeks.

The baseline characteristics of all randomized previously untreated for metastatic disease patients were: the median age was 63 years (range: 21 to 87), with 46% ≥ 65 years of age and 18% ≥ 75 years of age; 46% were male and 86% were White. Baseline ECOG performance status was 0 (54%) and ≥ 1 (46%); tumor location was right-sided or left-sided for 68% and 32% of patients, respectively; and 39 patients had confirmed Lynch syndrome among the 223 patients with a known status. The baseline characteristics of previously untreated for metastatic disease patients with centrally confirmed MSI-H/dMMR were consistent with all randomized previously untreated patients. Among the 101 patients randomized to receive chemotherapy, 88 received chemotherapy per protocol, including oxaliplatin-containing regimens (58%) and irinotecan-containing regimens (42%). Additionally, 66 patients received a targeted agent, either bevacizumab (64%) or cetuximab (11%).

A primary efficacy outcome measure of the study was BICR-assessed PFS per RECIST 1.1. Additional efficacy measures included ORR assessed by BICR, OS, and duration of response.

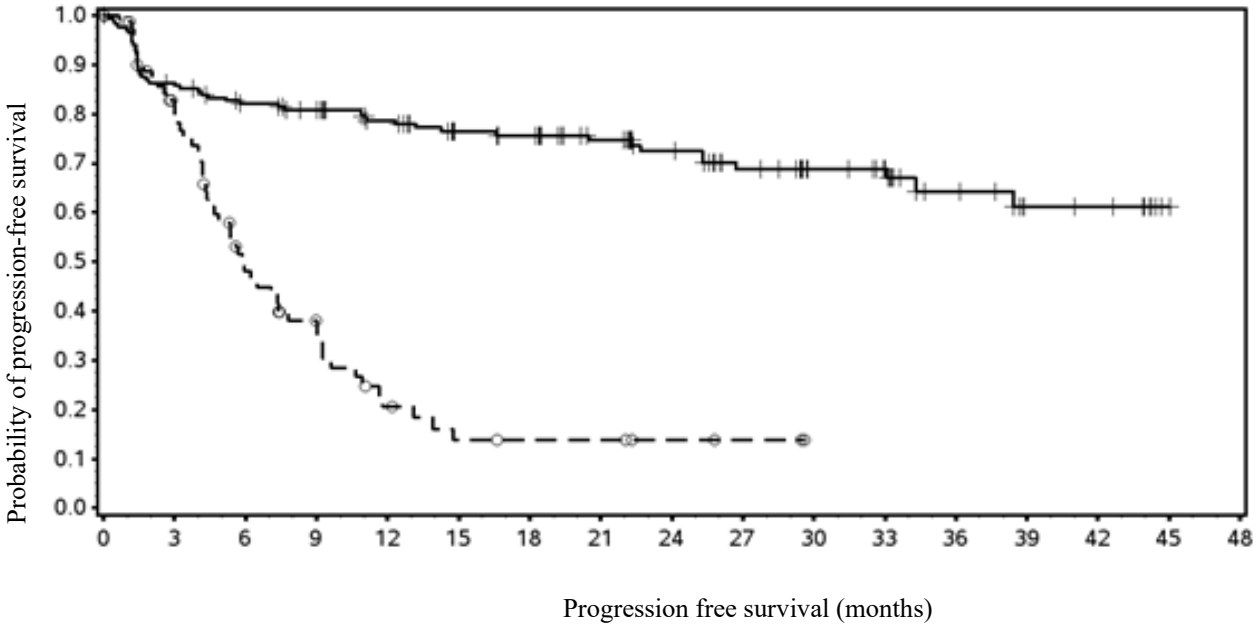
The study met the primary endpoint, at the planned interim analysis, demonstrating a statistically significant improvement in BICR assessed-PFS for the first-line treatment of patients with centrally confirmed MSI-H/dMMR in the nivolumab in combination with ipilimumab arm compared with the chemotherapy arm. The BICR-assessed PFS results are presented in Table 47 and Figure 27. At the time of this interim analysis, the other endpoints were not tested, due to testing hierarchy.

Table 47: Efficacy results (CA2098HW)[a,b]

		nivolumab + ipilimumab (n = 171)	chemotherapy (n = 84)
Progression-free survival			
Events		48 (28%)	52 (62%)
Hazard ratio		0.21	
95% CI		(0.14, 0.32)	
p-value [c]		< 0.0001	
Median (95% CI) (months)		NR (38.4, NR)	5.9 (4.4, 7.8)

[a] Median follow-up of 31.5 months (range: 6.1 to 48.4 months).
[b] Based on centrally confirmed randomized patients.
[c] Based on log-rank test stratified by the same factors as used in the Cox proportional hazard model.

Figure 27: Kaplan-Meier curve of PFS (CA2098HW)



Number of subjects at risk

Nivolumab + ipilimumab																
171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Investigator's choice																
84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

—O—— Nivolumab + ipilimumab (events: 48/171), median and 95% CI: N.A. (38.44, N.A.)
- - -+- - - Chemotherapy (events: 52/84), median and 95% CI: 5.85 (4.37, 7.79)

Esophageal Squamous Cell Carcinoma (ESCC)

Randomized, open-label, multicenter Phase 3 study (CA209473/ONO-24/ ATTRACTION-3)

The safety and efficacy of nivolumab monotherapy for the treatment of ESCC were evaluated in a Phase 3, multicenter, randomized (1:1), active-controlled, open-label study in patients with unresectable advanced, recurrent, or metastatic ESCC, refractory or intolerant to at least one

fluoropyrimidine- and platinum-based regimen (CA209473/ONO-24). The study included patients regardless of PD-L1 status. The study excluded patients with a baseline performance score ≥ 2, brain metastases that were symptomatic or required treatment, apparent tumor invasion on organs located adjacent to the esophagus (e.g., the aorta or respiratory tract), active autoimmune disease, or use of systemic corticosteroids or immunosuppressants. Patients received nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=210) or investigator's choice taxane chemotherapy of either:

- docetaxel (n=65) 75 mg/m^2 intravenously every 3 weeks, or
- paclitaxel (n=144) 100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off.

Patients were treated until disease progression, assessed by the investigator per RECIST v1.1, or unacceptable toxicity. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab or chemotherapy if there was no worsening of symptoms due to progression, treatment could be safely administered and there was an expectation continued treatment would lead to clinical benefit, as determined by the investigator.

The tumor assessments were conducted every 6 weeks for 1 year and every 12 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures included ORR and PFS, as assessed by the investigator using RECIST v1.1, and DOR. The trial population characteristics were: median age 65 years (range: 33 to 87), 53% were 65 years of age, 87% were male, 96% were Asian, and 4% were White. Baseline ECOG performance status was 0 (50%) or 1 (50%).

The study demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with investigator's choice taxane chemotherapy. OS benefit was observed regardless of PD-L1 expression level. The minimum follow-up was 17.6 months.

Efficacy results are shown in Table 47 and Figure 28.

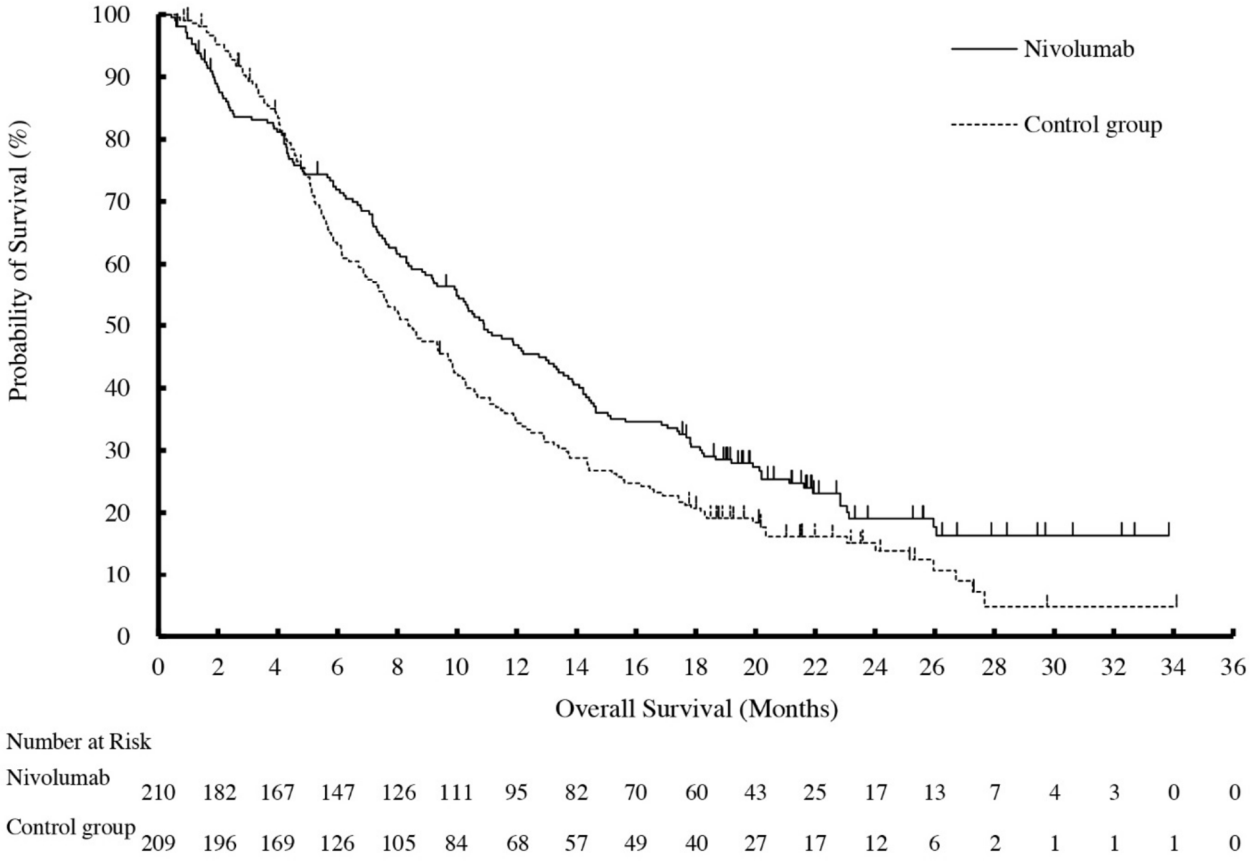
Table 47: Efficacy Results - CA209473/ONO-24/ ATTRACTION-3

	Nivolumab (n=210)	**Chemotherapy (n=209)**
Overall Survival[a]		
Deaths (%)	160 (76%)	173 (83%)
Median (months) (95% CI)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)
Hazard ratio (95% CI)[b]	0.77 (0.62, 0.96)	
p-value[c]	0.0189	

Progression-free Survival[a]		
Disease progression or death (%)	187 (89)	176 (84)
Median (months) (95% CI)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
Hazard ratio (95% CI)[b]	1.1 (0.9, 1.3)	
Objective Response Rate[d,e]	33 (19.3)	34 (21.5)
(95% CI)	(13.7, 26.0)	(15.4, 28.8)
Complete response (%)	1 (0.6)	2 (1.3)
Partial response (%)	32 (18.7)	32 (20.3)
Median duration of response (months) (95% CI)	6.9 (5.4, 11.1)	3.9 (2.8, 4.2)

[a] Based on ITT analysis.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.
[d] Based on Response Evaluable Set (RES) analysis, n=171 in nivolumab group and n=158 in investigator's choice group.
[e] Not significant, p-value 0.6323.

Figure 28 Overall Survival - CA209473/ONO-24/ ATTRACTION-3



Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for prespecified analyses. Of the 419 patients, 48% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 52% of patients were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1).

The hazard ratio (HR) for survival was 0.69 (95% CI: 0.51, 0.94) with median survivals of 10.9 and 8.1 months for the nivolumab and chemotherapy arms, respectively, in the tumor PD-L1 ≥1% subgroup. The HR for survival was 0.84 (95% CI: 0.62, 1.14) with median survivals of 10.9 and 9.3 months for the nivolumab and chemotherapy arms, respectively, in the tumor PD-L1 <1% subgroup.

Note**: This section mentions certain details on nivolumab in combination with ipilimumab**, as they are part of study CA209648.

Randomized phase 3 study of nivolumab in combination with ipilimumab vs. chemotherapy and nivolumab in combination with chemotherapy vs. chemotherapy as first-line treatment (CA209648)

The safety and efficacy of nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and nivolumab 240 mg every 2 weeks in combination with chemotherapy were evaluated in a randomized, active-controlled, open-label study (CA209648). The study included adult patients (18 years or older) with previously untreated, unresectable advanced, recurrent or metastatic ESCC. Patients were enrolled regardless of their tumor PD-L1 status, and

tumor PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. Patients were required to have squamous cell carcinoma or adenosquamous cell carcinoma of esophagus, not amenable to chemoradiation and/or surgery. Prior adjuvant, neoadjuvant, or definitive, chemotherapy, radiotherapy or chemoradiotherapy was permitted if given as part of curative intent regimen prior to trial enrollment. Patients who had a baseline performance score ≥ 2, had brain metastases that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumor to organs adjacent to the esophageal tumor were excluded from the study. Randomization was stratified by tumor cell PD-L1 status (≥1% vs. <1% or indeterminate), region (East Asia vs. rest of Asia vs. rest of world), ECOG performance status (0 vs. 1), and number of organs with metastases (≤1 vs. ≥2).

A total of 970 patients were randomized to receive either nivolumab in combination with ipilimumab (n = 325), nivolumab in combination with chemotherapy (n = 321), or chemotherapy (n = 324). Patients in the nivolumab plus ipilimumab arm received nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks, and patients in the nivolumab plus chemotherapy arm received nivolumab 240 mg every 2 weeks on days 1 and 15, 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). Patients in the chemotherapy arm received 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). Treatment continued until disease progression, unacceptable toxicity, or up to 24 months. Patients in the nivolumab plus ipilimumab arm who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Patients in the nivolumab plus chemotherapy arm in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued.

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 esophagus. The baseline tumor cell PD-L1 status was positive for 48.8% of patients, defined as ≥1% of tumor cells expressing PD-L1, negative for 50.7%, or indeterminate for 0.5% of patients. Baseline ECOG performance status was 0 (46.9%) or 1 (53.6%).

Nivolumab in combination with chemotherapy vs. chemotherapy

The primary efficacy outcome measures were PFS (by BICR) and OS in patients with tumor PD-L1 expression ≥1%. Secondary endpoints per the pre-specified hierarchical testing included OS, PFS (by BICR), and ORR (by BICR) in all randomized patients. The tumor assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

At the primary pre-specified analysis, with a minimum follow-up of 12.9 months, the study demonstrated a statistically significant improvement in OS and PFS in patients with tumor PD-L1 expression ≥1%.Statistically significant improvement in OS was also demonstrated for all randomized patients. Efficacy results in all randomized patients are shown in Table 48 and Figure 29, and in patients with tumor PD-L1 ≥1% in Figures 30 and 31.

Table 48: Efficacy results (CA209648)

	nivolumab + chemotherapy (n = 321)	chemotherapy[a] (n = 324)
	All randomized patients	
Overall Survival		
Events	209 (65%)	232 (72%)
Hazard ratio (95% CI)[b]	0.74 (0.61, 0.90)	
p-value[c]	0.0021	
Median (95% CI) (months)[d]	13.2 (11.1, 15.7)	10.7 (9.4, 11.9)
Progression-free Survival[e]		
Events	235 (73%)	210 (65%)
Hazard ratio (95% CI)[b]	0.81 (0.67, 0.99)	
p-value[c]	0.0355	
Median (95% CI) (months)[d]	5.8 (5.6, 7.0)	5.6 (4.3, 5.9)
Overall response rate, n (%)[e]	152 (47)	87 (27)
(95% CI)	(42, 53)	(22, 32)
Complete response	43 (13)	20 (6)
Partial response	109 (34)	67 (21)
Duration of response[e]		
Median (95% CI) (months)[d]	8.2 (6.9, 9.7)	7.1 (5.7, 8.2)
Range	1.4^{+} , 35.9^{+}	1.4^{+} , 31.8^{+}
% Duration ≥ 6 months (95% CI)[d]	64 (55, 71)	54 (41, 65)
% Duration ≥ 12 months (95% CI)[d]	39 (30, 47)	23 (13, 34)

[a] Fluorouracil and cisplatin.

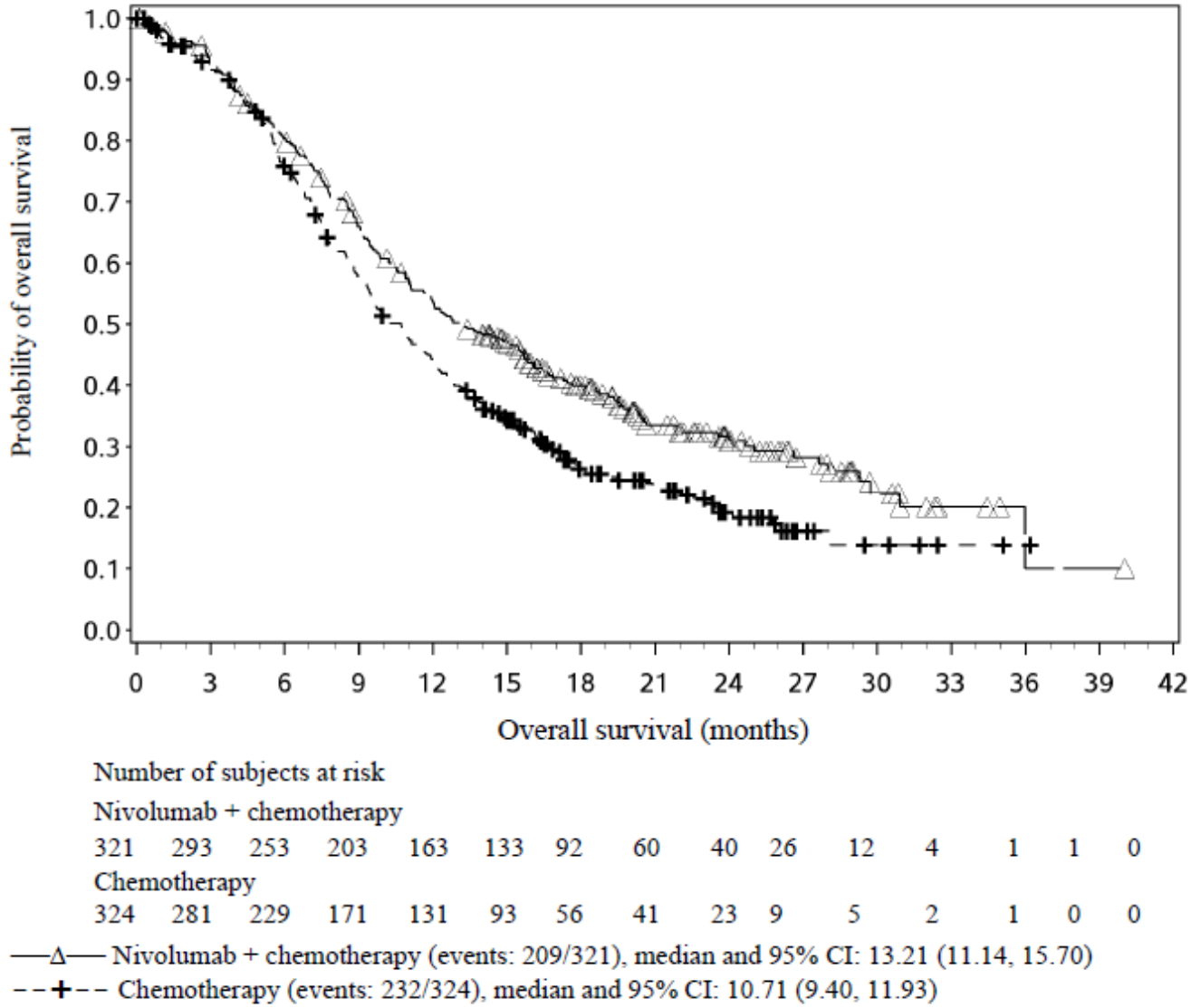
[b] Based on stratified Cox proportional hazard model.

[c] Based on stratified 2-sided log-rank test.

[d] Based on Kaplan-Meier estimates.

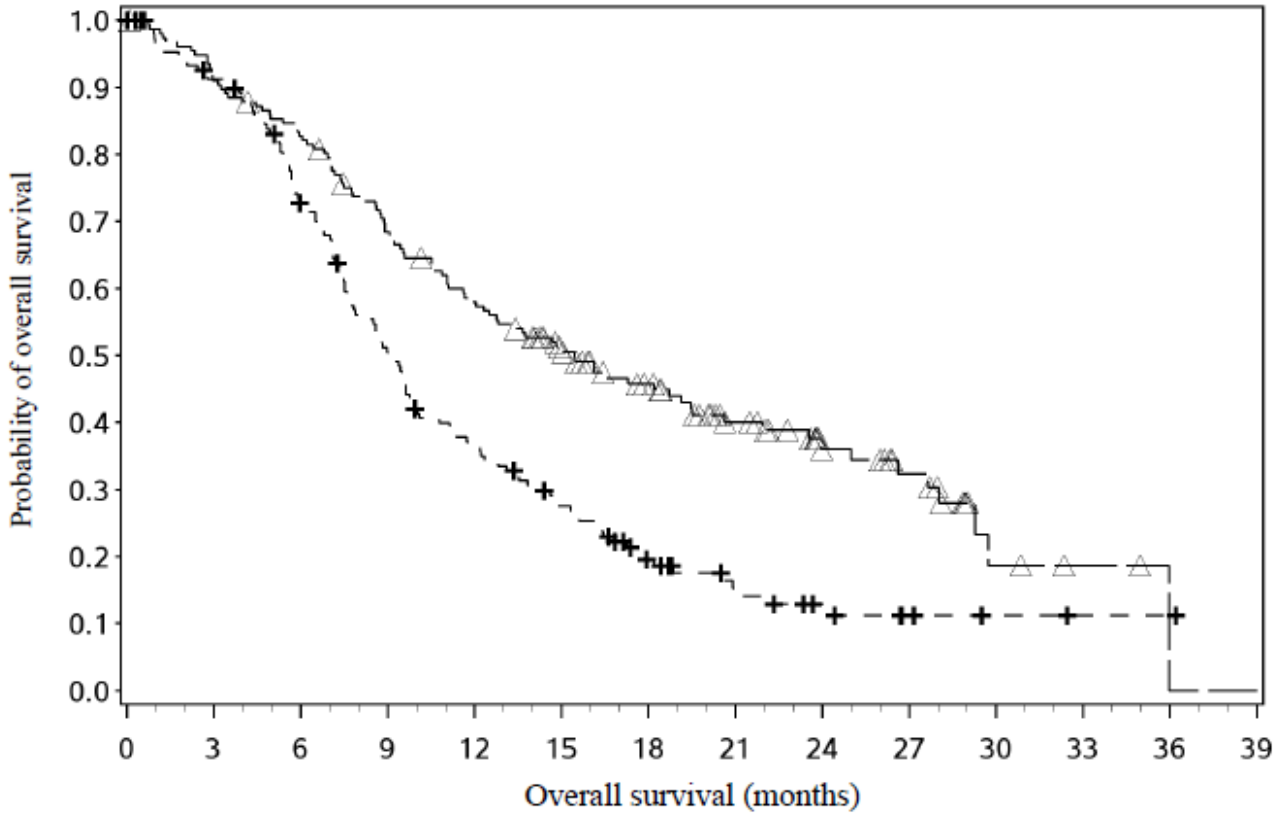
[e] Assessed by BICR.

Figure 29: Kaplan-Meier curves of OS in all randomized patients (CA209648)



Statistically significant improvement in OS was also demonstrated for patients with positive tumor PD-L1 status (HR = 0.54; 95% CI: 0.41, 0.71; p-value <0.0001). The median OS was 15.4 months (95% CI: 11.9, 19.5) for nivolumab plus chemotherapy and 9.1 months (95% CI: 7.7, 10.0) for chemotherapy. The HR for PFS was 0.65 months (95% CI: 0.49, 0.86) with median PFS of 6.9 months (95% CI: 5.7, 8.3) for nivolumab plus chemotherapy and 4.4 months (95% CI: 2.9, 5.8) for chemotherapy.

Figure 30: Kaplan-Meier curves of OS in patients with tumor PD-L1 ≥1% (CA209648)



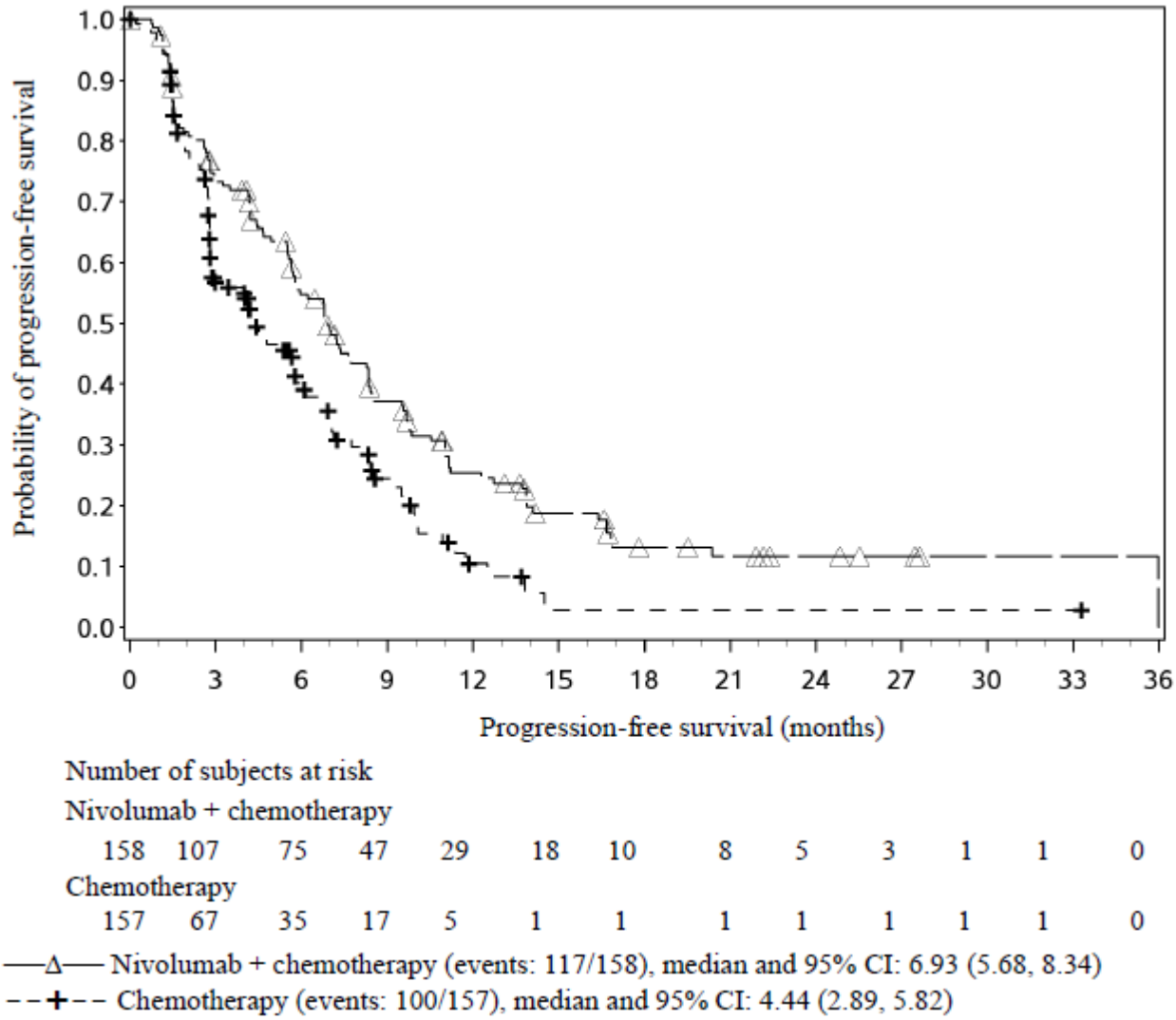
Number of subjects at risk

Nivolumab + chemotherapy	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemotherapy	157	135	105	72	52	36	21	12	8	4	2	1	1	0

—Δ— Nivolumab + chemotherapy (events: 98/158), median and 95% CI: 15.44 (11.93, 19.52)

– –+– – Chemotherapy (events: 121/157), median and 95% CI: 9.07 (7.69, 9.95)

Figure 31: Kaplan-Meier curves of PFS in patients with tumor PD-L1 ≥1% (CA209648)



Exploratory analyses for OS were performed in patients who had tumor PD-L1 <1% (nivolumab plus chemotherapy n= 111 [68%] vs. chemotherapy n = 111 [67%]); the HR was 0.98 (95% CI: 0.76, 1.28).

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

The safety and efficacy of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy was evaluated in a phase 3, randomised, open-label study (CA209649). The study included adult patients (18 years or older) with previously untreated advanced or metastatic gastric,

gastro-esophageal junction (GEJ) or esophageal adenocarcinoma, no prior systemic treatment (including HER2 inhibitors), and ECOG performance status score 0 or 1. Patients were enrolled regardless of their tumour PD-L1 status, and tumour PD-L1 expression was determinated using the PD-L1 IHC 28-8 pharmDx assay. Patients with known HER2-positive tumours, baseline performance score ≥2 or who had untreated central nervous system metastases were excluded from the study. Randomization was stratified by tumor 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. Chemotherapy consisted of FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

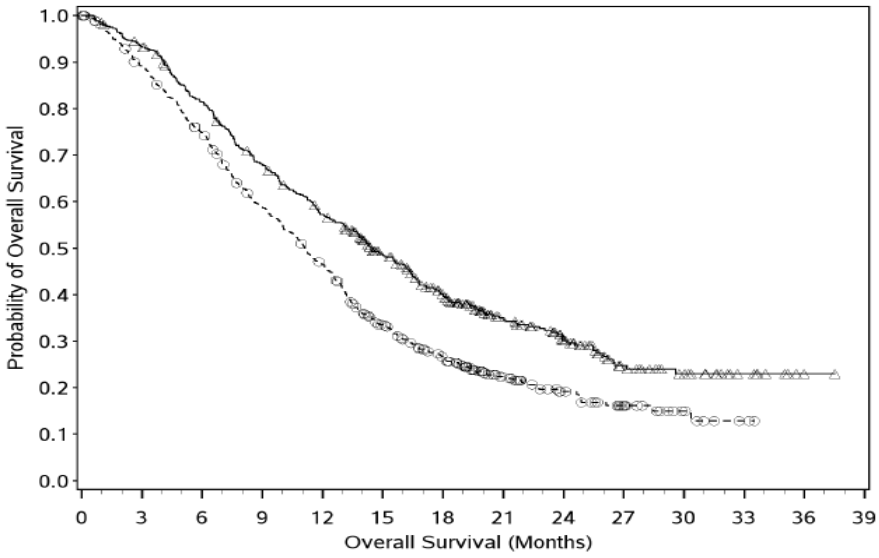
A total of 1581 patients were randomised to receive either nivolumab in combination with chemotherapy (n=789) or chemotherapy (n=792). Patients in the nivolumab plus chemotherapy arm received either nivolumab 240 mg by intravenous infusion over 30 minutes in combination with FOLFOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 intravenously on Day 1 and fluorouracil 1200 mg/m^2 intravenously daily on Days 1 and 2) every 2 weeks, or nivolumab 360 mg by intravenous infusion over 30 minutes in combination with CapeOX (oxaliplatin 130 mg/m^2 intravenously on Day 1 and capecitabine 1000 mg/m^2 orally twice daily on Days 1-14) every 3 weeks. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months for nivolumab only. In patients who received nivolumab plus 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 24 months after treatment initiation. Tumor assessments were performed every 6 weeks up to and including week 48, then every 12 weeks thereafter.

Baseline characteristics were generally balanced across treatment groups. The median age was 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%). Tumor locations were distributed as gastric (70%), gastro-esophageal junction (16%), and esophagus (13%).

Primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with PD-L1 combined positive score (CPS) ≥5 based on the PD-L1 IHC 28-8 pharmDX. Secondary endpoints per the pre-specified hierarchical testing were OS in patients with PD-L1 CPS ≥1 and in all randomized patients; further endpoints included ORR (BICR) in PD-L1 CPS ≥5 and all randomized patients.

With a minimum follow-up of 12.1 months, the study demonstrated a statistically significant improvement in OS and PFS in patients with PD-L1 CPS ≥5. Statistically significant improvement in OS was also demonstrated for all randomized patients. Efficacy results are shown in Figures 32, 33, and 34 and Table 49.

Figure 32: Kaplan-Meier curves of OS in patients with PD-L1 CPS ≥5 (CA209649)



Overall survival (months)

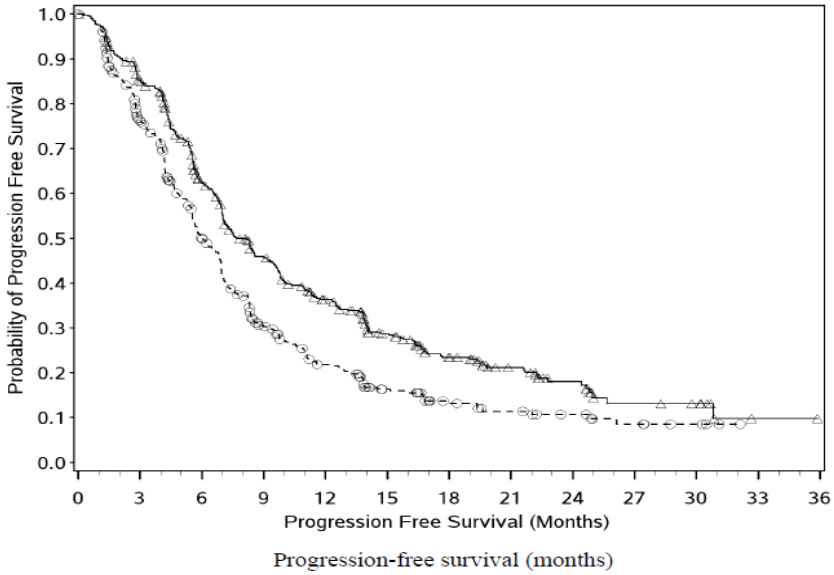
Number of subjects at risk

Nivolumab + chemotherapy	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemotherapy	482	421	350	271	211	138	98	56	34	19	8	2	0	0

Nivolumab + chemotherapy (events: 309/473), median and 95% CI: 14.39 (13.11, 16.23)

Chemotherapy (events: 362/482), median and 95% CI: 11.10 (10.02, 12.09)

Figure 33: Kaplan-Meier curves of PFS in patients with PD-L1 CPS ≥5 (CA209649)



Progression-free survival (months)

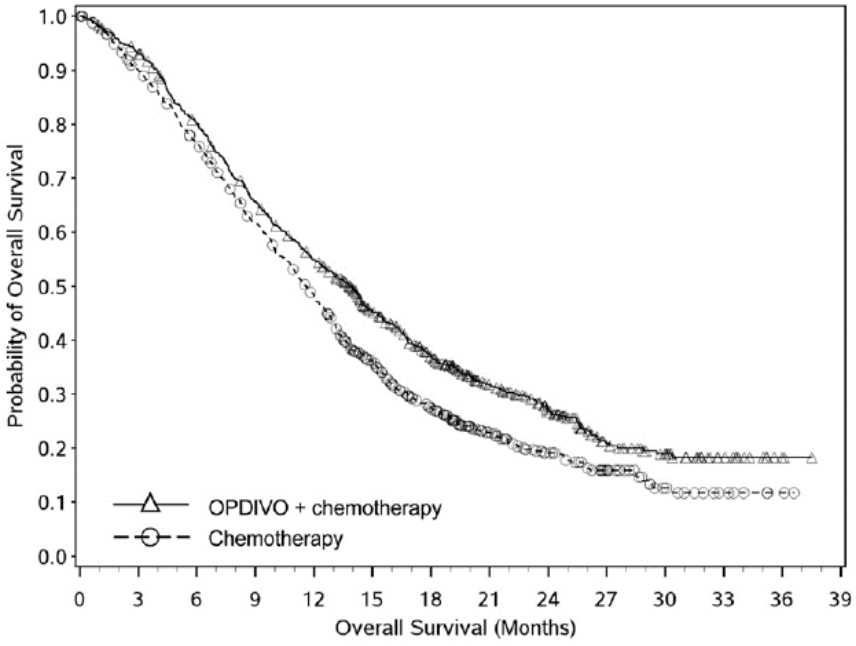
Number of subjects at risk

Nivolumab + chemotherapy	473	384	258	181	132	89	60	39	23	10	8	1	0
Chemotherapy	482	325	200	109	72	41	25	18	12	7	4	0	0

Nivolumab + chemotherapy (events: 328/473), median and 95% CI: 7.69 (7.03, 9.17)

Chemotherapy (events: 350/482), median and 95% CI: 6.05 (5.55, 6.90)

Figure 34: Kaplan-Meier curves of OS in all randomized patients (CA209649)



Overall survival (months)

Number of subjects at risk

Nivolumab + chemotherapy	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemotherapy	792	697	586	469	359	239	160	94	59	35	15	7	2	0

Nivolumab + chemotherapy (events: 544/789), median and 95% CI: 13.83 (12.55, 14.55)

Chemotherapy (events: 591/792), median and 95% CI: 11.56 (10.87, 12.48)

Table 49: Efficacy results (CA209649)

	nivolumab + chemotherapy (n=473)	chemotherapy (n=482)	nivolumab + chemotherapy (n=789)	chemotherapy (n=792)
	PD-L1 CPS ≥5		**All patients**	
Overall survival				
Events (%)	309 (65)	362 (75)	544 (69)	591 (75)
Hazard ratio (CI)[a]	0.71 (98.4% CI: 0.59, 0.86)		0.80 (99.3% CI: 0.68, 0.94)	
p-value[b]	<0.0001		0.0002	
Median (95% CI) (months)[c]	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)
Rate (95% CI) at 12 months	57.3 (52.6, 61.6)	46.4 (41.8, 50.8)	55.0 (51.4, 58.4)	47.9 (44.4, 51.4)
Progression-free survival[d]				
Events(%)	328 (69.3)	350 (72.6)	559 (70.8)	557 (70.3)
Hazard ratio (CI)[a]	0.68 (98% CI: 0.56, 0.81)		0.77 (95% CI: 0.68, 0.87)	
p-value[b]	<0.0001		-[e]	
Median (95% CI) (months)[c]	7.69 (7.03, 9.17)	6.05 (5.55, 6.90)	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)
Rate (95% CI) at 12 months	36.3 (31.7, 41.0)	21.9 (17.8, 26.1)	33.4 (29.9, 37.0)	23.2 (19.9, 26.7)
Overall response rate, n (%)[d,f]	226/378 (60)	177/391 (45)	350/603 (58)	280/608 (46)
(95% CI)	(55, 65)	(40, 50)	(54, 62)	(42, 50)
Complete response	44 (12)	27 (7)	59 (10)	39 (6)
Partial response	182 (48)	150 (38)	291 (48)	241 (40)
Duration of response[d,f]				
Median (95% CI) (months)[c]	9.49 (7.98, 11.37)	6.97 (5.65, 7.85)	8.51 (7.23, 9.92)	6.93 (5.82, 7.16)
Range	1.1+, 29.6+	1.2+, 30.8+	1.0+, 29.6+	1.2+, 30.8+

[a] Based on stratified log Cox proportional hazard model.
[b] Based on stratified log-rank test.
[c] Kaplan-Meier estimate.
[d] Confirmed by BICR.
[e] Not evaluated for statistical significance.
[f] Based on patients with measurable disease at baseline.

Statistically significant improvement in OS was also demonstrated for patients with PD-L1 CPS ≥1 (HR = 0.77; 99.3% CI: 0.64, 0.92; p-value <0.0001). The median OS was 13.96 months (95% CI: 12.55, 14.98) for nivolumab plus chemotherapy and 11.33 months (95% CI: 10.64, 12.25) for chemotherapy.

Further exploratory analyses were performed in patients who had PD-L1 CPS <1 [nivolumab plus chemotherapy n=140 (17.9%) vs. chemotherapy n=125 (16.0%)] and PD-L1 CPS <5 [nivolumab plus chemotherapy n=308 (39.4%) vs. chemotherapy n=298 (38.2%)] (see Table 50).

Table 50: OS by PD-L1 CPS <1 and <5 (CA209649)

PD-L1 Expression	nivolumab +chemotherapy	chemotherapy	
	OS by PD-L1 CPS expression Number (%) of patients with event		Unstratified hazard ratio (95% CI)
CPS <1	103 (74%)	91 (73%)	0.92 (0.70, 1.23)
CPS <5	228 (74%)	221 (74%)	0.94 (0.78, 1.13)

Microsatellite instability (MSI) status was also assessed in CA209649 and determined retrospectively on pre-treatment tissues using the Idylla™ MSI Test. Of the 1581 randomised patients, 44 (2.8%) patients were MSI-high (MSI-H), and 1377 (87.1%) patients were microsatellite stable (MSS). The HR of OS in MSI-H was 0.37 (95% CI: 0.16, 0.87) and in MSS was 0.80 (95% CI: 0.71, 0.91).

Adjuvant treatment of Resected Esophageal or Gastroesophageal Junction Cancer (EC or GEJC)

The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of esophageal or gastro-esophageal junction cancer was evaluated in a phase 3 multicentre, randomized, placebocontrolled, double-blinded study (CA209577). The study included adult patients who had received CRT, followed by complete resection of carcinoma prior to randomisation, and who had residual pathologic disease, with at least ypN1 or ypT1. Patients who did not receive concurrent CRT prior to surgery or had stage IV resectable disease, autoimmune disease, any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications were excluded from the study. Patients were enrolled regardless of tumor PD-L1 expression level.

A total of 794 patients were randomized 2:1 to receive either nivolumab (n=532) or placebo (n=262). Patients were administered nivolumab 240 mg intravenously over 30 minutes every 2 weeks for 16 weeks followed respectively by 480 mg infused over 30 minutes every 4 weeks beginning at week 17. Patients were administered placebo over 30 minutes with the same dosing schedule as nivolumab. 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). Treatment continued until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. The primary efficacy outcome measure was disease-free survival (DFS), as assessed by the investigator, 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. Patients on treatment underwent imaging for tumour every 12 weeks for 2 years, and a minimum of one scan every 6 to 12 months for years 3 to 5.

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 26-86) with 36% ≥65 years of age and 5% ≥75 years of years. The majority of patients were white (82%) and male (85%). Baseline ECOG performance status was 0 (58%) or 1 (42%).

With a minimum of 6.2 months and a median of 24.4 months follow-up (range 6.2 to 44.9 months), the study demonstrated a statistically significant improvement for patients randomised to nivolumab compared with placebo, with DFS observed in 241 (45%) patients and a hazard ratio of 0.69 (95% CI: 0.56, 0.86). Efficacy results are shown in Table 51 and Figure 35.

Table 51: Efficacy results (CA209577)

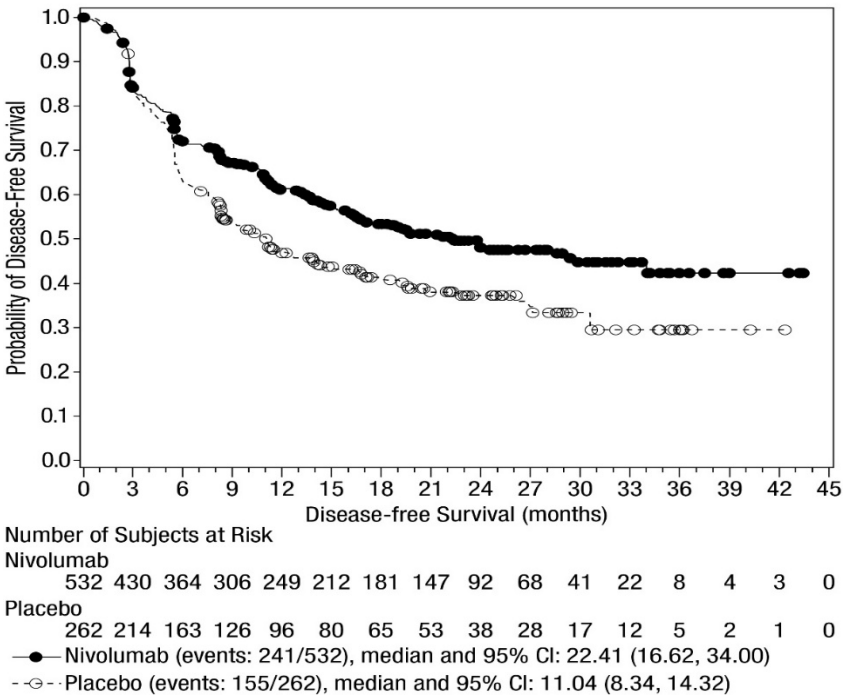
	nivolumab (n=532)	**placebo (n=262)**
Disease-free Survival[a]		
Events (%)	241 (45%)	155 (59%)
Hazard ratio (96.4% CI)[b]	0.69 (0.56, 0.86)	
p-value[c]	0.0003	
Median (95% CI) (months)	22.4 (16.6, 34.0)	11.0 (8.3, 14.3)

[a] Based on all randomized patients

[b] Based on a stratified cox proportional hazards model.

[c] Based on a stratified log-rank test.

Figure 35: Kaplan-Meier curves of DFS (CA 209577)



DFS benefit was observed regardless of histology and tumor cell PD-L1 expression.

In the adenocarcinoma subgroup (n=376), the hazard ratio (HR) for DFS was 0.75 (95% CI: 0.59, 0.96) with median DFS of 19.35 and 11.10 months for the nivolumab and placebo arms, respectively. In the squamous cell carcinoma subgroup (n=155), the HR for DFS was 0.61 (95 CI: 0.42, 0.88) with median DFS of 29.73 and 11.04 months for the nivolumab and placebo arms, respectively.

Of the 794 patients, 16.2% had tumor cell PD-L1 expression ≥1%, 71.8% had tumor cell PD-L1 expression <1%, and 12.0% had tumor cell PD-L1 expression indeterminate or non-evaluable. In the tumor cell PD-L1 ≥1% subgroup, the HR for DFS was 0.75 (95% CI: 0.45, 1.24) with median DFS of 19.65 and 14.13 months for the nivolumab and placebo arms, respectively. In the tumor cell PD-L1 <1% subgroup, the HR for DFS was 0.73 (95 % CI: 0.57, 0.92) with median DFS of 21.26 and 11.10 months for the nivolumab and placebo arms, respectively. In the tumor cell PD-L1 indeterminate or non-evaluable subgroup, the HR for DFS was 0.54 (95% CI: 0.27, 1.05) with median DFS not reached and of 9.49 months for the nivolumab and placebo arms, respectively.

Patient-reported outcomes were assessed using the EQ-5D-3L and FACT-E. At baseline, mean FACT-E or mean FACT-E total scores in all randomized subjects were similar between treatment arms. From baseline through week 53 of follow-up, patients in both treatment arms had improvements in mean change from baseline score in both measures.

Hepatocellular Carcinoma (HCC)

Open-label Phase 3 study of nivolumab in combination with ipilimumab versus investigators' choice of lenvatinib or sorafenib in unresectable HCC (CA209-9DW).

The safety and efficacy of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks in the first-line treatment of unresectable hepatocellular carcinoma (HCC) were evaluated in a phase 3, randomised, active controlled, open label study (CA2099DW). The study included adult patients (18 years or older) with histologically confirmed HCC, Child Pugh Class A, ECOG performance status 0 or 1, and no prior systemic therapy for advanced disease. Esophagogastroduodenoscopy was not mandated prior to enrollment. The study enrolled adults whose disease was not amenable to or progressed after surgical and/or locoregional therapies. Prior neo-adjuvant or adjuvant systemic therapy was permitted. Patients with active autoimmune disease, brain or leptomeningeal metastases, a history of hepatic encephalopathy (within 12 months of randomisation), clinically significant ascites, medical conditions requiring systemic immunosuppression, infection with HIV, or active co infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV) were excluded from the study. Randomisation was stratified by aetiology (HBV vs. HCV vs. non-viral), macrovascular invasion and/or extrahepatic spread (present or absent), and alpha-fetoprotein levels (≥400 or <400 ng/mL).

A total of 668 patients were randomised to receive nivolumab in combination with ipilimumab (n=335) or investigator's choice (n=333) of lenvatinib or sorafenib. In the investigator's choice arm, 85% and 15% of treated patients received lenvatinib or sorafenib, respectively. Patients in the nivolumab plus

ipilimumab arm received nivolumab 1 mg/kg every 3 weeks in combination with ipilimumab 3 mg/kg every 3 weeks, for up to a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks. Patients in the investigators' choice arm received either lenvatinib 8 mg orally daily (if body weight < 60 kg) or 12 mg orally daily (if body weight ≥ 60 kg), or sorafenib 400 mg orally twice daily. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months for nivolumab in combination with ipilimumab. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Nivolumab with or without ipilimumab could be administered beyond RECIST 1.1-assessed progressive disease if there was a clinical benefit as determined by investigator and therapy was tolerated. Tumour assessments were conducted at baseline, after randomisation at week 9 and week 16, then every 8 weeks up to 48 weeks, and then every 12 weeks thereafter until disease progression, treatment discontinuation, or initiation of subsequent therapy.

Baseline characteristics were generally balanced across treatment groups. The median age was 66 years (range: 20 to 89), with 53% ≥ 65 years and 16% ≥ 75 years, 53% were White, 44% were Asian, 2.2% were Black, and 82% were male. Baseline ECOG performance status was 0 (71%) or 1 (29%). Thirty-four percent (34%) of patients had HBV infection, 28% had HCV infection, and 36% had no evidence of HBV or HCV infection. Nineteen percent (19%) of patients had alcoholic liver disease and 11% had non-alcoholic fatty liver disease. The majority of patients had BCLC stage C (73%) disease at baseline, 19% had stage B, and 6% had stage A. Patients with Child-Pugh scores of 5, 6, and ≥ 7 were 77%, 20%, and 3%, respectively. A total of 54% of patients had extrahepatic spread; 25% had macrovascular invasion; and 33% had AFP levels ≥ 400 μg/L.

The study demonstrated a statistically significant benefit in OS and ORR for patients randomised to nivolumab in combination with ipilimumab compared to investigator's choice of lenvatinib or sorafenib. Efficacy results are presented in Table 52 and Figure 36.

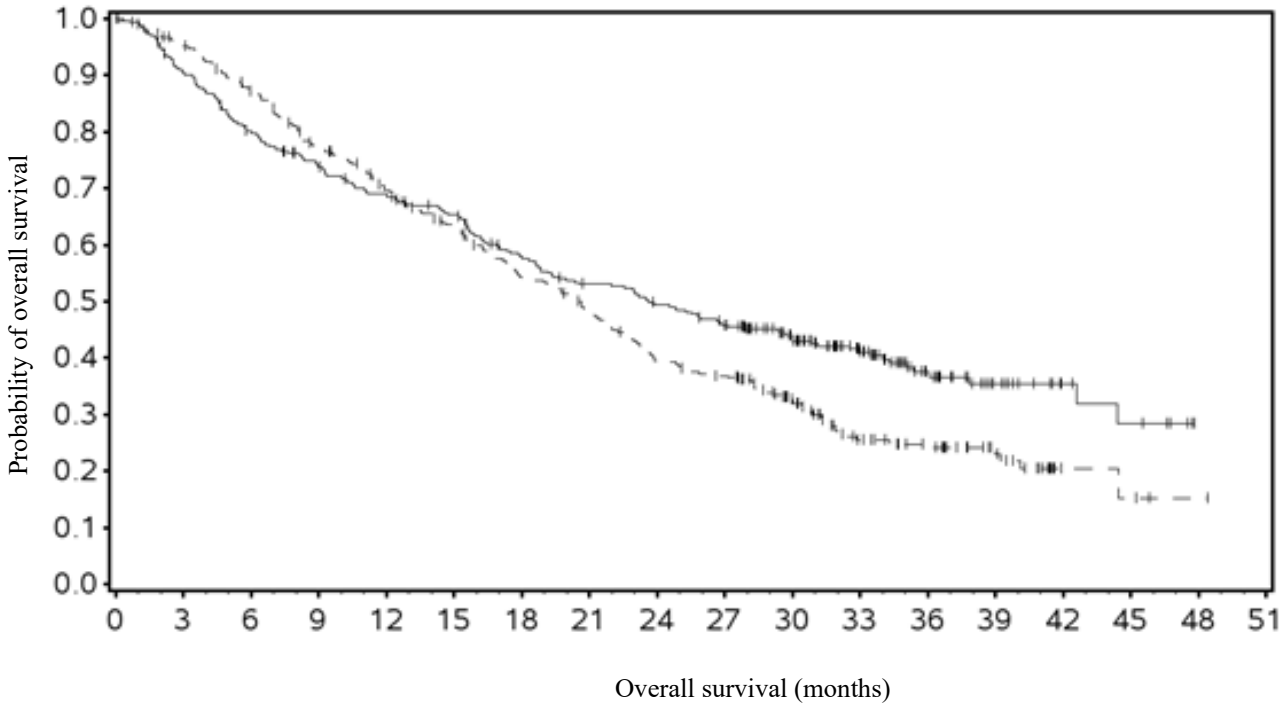
Table 52: Efficacy results in first-line HCC (CA2099DW)a

	nivolumab + ipilimumab (n = 335)	**lenvatinib or sorafenib (n = 333)**
Overall survival		
Events	194 (58%)	228 (68%)
Median (months) (95% CI)	23.7 (18.8, 29.4)	20.6 (17.5, 22.5)
Hazard ratio (95% CI) [b]	0.79 (0.65, 0.96)	
p-value [c]	0.0180	
Overall Response Rate, n (%)[d]	121 (36.1)	44 (13.2)
(95% CI)	(31.0, 41.5)	(9.8, 17.3)
p-value[e]	<0.0001	
Complete response (%)	23 (6.9)	6 (1.8)
Partial response (%)	98 (29.3)	38 (11.4)
Duration of Response (months)[d]		
Median (95% CI)	30.4 (21.2, N.A.)	12.9 (19.2, 31.2)
Range	1.5+, 36.9+	2.1+, 32.5+

a Minimum follow-up of 26.8 months.

b Based on stratified Cox proportional hazard model.
c Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value ≤0.0257.
d Assessed by BICR using RECIST 1.1.
e Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: p-value ≤0.025.
+ Censored observation.

Figure 36: Kaplan-Meier curve of OS in first-line patients with HCC (CA2099DW)



Number of subjects at risk

Nivolumab + ipilimumab																	
335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
Investigator's choice																	
333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

—O—— Nivolumab + ipilimumab (events: 194/335), median and 95% CI: 24.66 (18.33, 29.44)
- - -+- - - Lenvatinib or sorafenib (events: 228/333), median and 95% CI: 20.63 (17.48, 22.54)

Treatment with nivolumab in combination with ipilimumab also resulted in a statistically significant reduction in the risk (24%) of symptom deterioration (HR 0.76 [95%CI: 0.62, 0.93]; p=0.0059) versus lenvatinib or sorafenib on the FACT-Hep HCS subscale. Time to symptom deterioration was defined as the time from randomisation until a clinically meaningful decline (at least a 6 point decrease from baseline) in the FACT-Hep HCS subscale in all randomised participants.

Malignant Pleural Mesothelioma

Randomized, open-label, Phase 3 study of nivolumab in combination with ipilimumab vs chemotherapy (CA209743)

The safety and efficacy of nivolumab in combination with ipilimumab were evaluated in CA209743, a randomized, open-label study in patients with unresectable malignant pleural mesothelioma. The study included patients (18 years of age and older) with histologically confirmed and previously untreated malignant pleural mesothelioma of epithelioid or non-epithelioid histology, ECOG performance status 0 or 1, and no palliative radiotherapy within 14 days of first trial therapy. Patients were enrolled regardless of their tumor PD-L1 status. Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the study. Patients received nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks and ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years, or chemotherapy consisting of cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 or carboplatin 5 AUC and pemetrexed 500 mg/m^2 for up to 6 cycles (each cycle was 21 days). Stratification factors for randomization were tumor histology (epithelioid versus sarcomatoid or mixed histology subtypes) and gender (male vs female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent as part of the study. Treatment continued beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, duration of response, and disease control rate (DCR) as assessed by BICR utilizing modified RECIST criteria.

A total of 605 patients were randomized to receive either nivolumab in combination with ipilimumab (n=303) or chemotherapy (n=302). The median age was 69 years (range: 25 to 89) with 72% ≥65 and 26% ≥75 years, 85% White, and 77% male. Baseline ECOG performance status was 0 (40%) or 1 (60%), 75% had epithelioid and 25% had non-epithelioid histology, and 80% of patients with PD-L1 ≥1% and 20% with PD-L1 <1%.

The study demonstrated a statistically significant improvement in OS for patients randomized to nivolumab in combination with ipilimumab compared to chemotherapy with a minimum follow-up of 22 months. Efficacy results from the prespecified interim analysis when at least 403 events were observed (85% of the planned number of events for final analysis) are presented in Table 53 and Figure 37.

Table 53: Efficacy Results - CA209743

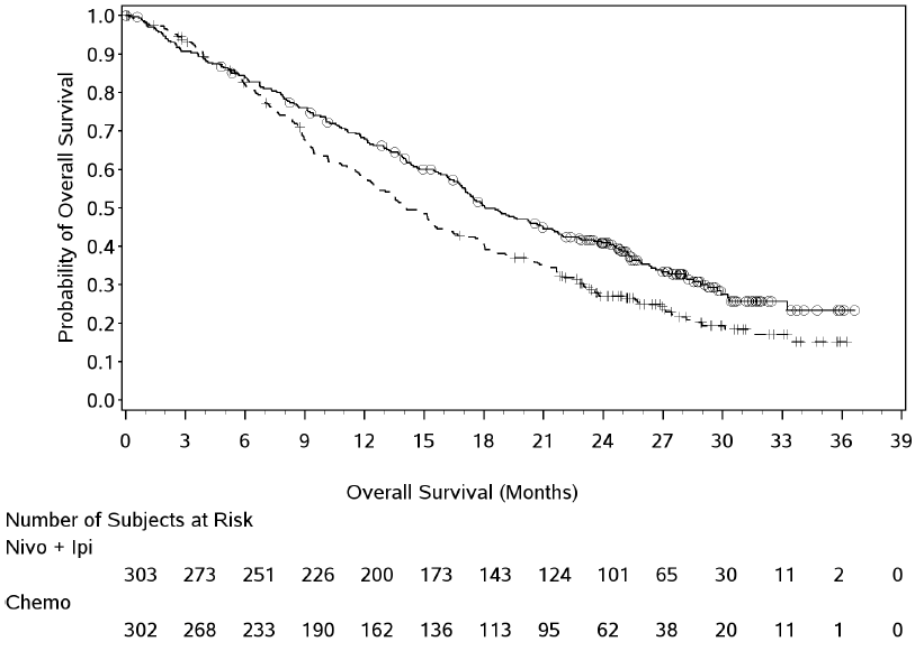
	Nivolumab and Ipilimumab (n=303)	**Chemotherapy (n=302)**
Overall Survival		
Events (%)	200 (66%)	219 (73%)

Table 53: Efficacy Results - CA209743

	Nivolumab and Ipilimumab (n=303)	Chemotherapy (n=302)
Median (months) [a] (95% CI)	18.1 (16.8, 21.5)	14.1 12.5, 16.2)
Hazard ratio (96.6% CI) [b]	0.74 (0.60, 0.91)	
Stratified log-rank p-value [c]	0.002	
Rate (95% CI) at 24 months [a]	41% (35.1, 46.5)	27% (21.9, 32.4)
Progression-free Survival		
Events (%)	218 (72%)	209 (69%)
Hazard ratio (95% CI) [b]	1.0 (0.82, 1.21)	
Median (months) [a] (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)
Overall Response Rate (%)	40%	43%
(95% CI)	(34.1, 45.4)	(37.1, 48.5)
Complete response (%)	1.7%	0
Partial response (%)	38%	43%
Duration of Response		
Median (months) [a] (95% CI)	11.0 (8.1, 16.5)	6.7 (5.3, 7.1)
% with duration ≥6 months	69%	53%
% with duration >24 months	32%	8%
Disease Control Rate (95% CI)	77% (71.4, 81.2)	85% (80.6, 88.9)

[a] Kaplan-Meier estimate.
[b] Stratified Cox proportional hazard model.
[c] p-value is compared with the allocated alpha of 0.0345 for this interim analysis.

Figure 37: Kaplan-Meier Plot of OS - CA209743



5.3 Pharmacokinetics

The PK of nivolumab is linear in the dose range of 0.1 to 10 mg/kg. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 26 (32.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 7.91 mL/h (46%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.6 L (24.4%) and geometric mean elimination half-life ($t_{1/2}$) is 25 days (55.4%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks and systemic accumulation was approximately 4-fold.

The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Nivolumab CL increased with increasing body weight. Body weight normalized dosing produced approximately uniform steady-state trough concentration over a wide range of body weights (34-162 kg).

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.

Nivolumab in combination with ipilimumab:

When administered in combination with ipilimumab, the CL of nivolumab increased by 20% in the presence of anti-nivolumab antibodies and the CL of ipilimumab increased by 5.7% in the presence of anti-ipilimumab antibodies. These changes were not considered clinically relevant.

Nivolumab in combination with ipilimumab and 2-cycles of chemotherapy: When nivolumab 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy, the CL of nivolumab decreased approximately 10% and the CL of ipilimumab increased approximately 22%, which were not considered clinically relevant.

When administered in combination with ipilimumab and chemotherapy, the CL of nivolumab increased by approximately 29% in the presence of anti-nivolumab antibodies. There was no apparent impact on efficacy or safety with nivolumab ADA-positive subjects.

5.3.1 Special populations

A population PK analysis suggested no difference in CL of nivolumab based on age, gender, race, solid tumor type, tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin and body weight had an effect on nivolumab CL, the effect was not clinically meaningful.

Renal impairment

The effect of renal impairment on the CL of nivolumab was evaluated in patients with mild* (n=1399), moderate* (n=651), or severe* (n=6) renal impairment compared to patients with normal* renal function (n=1354) in the population PK analysis. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see 4.2 Posology and method of administration, renal impairment).

** Definitions*

- *Normal: GFR ≥90 mL/min/1.73 m^2*
- *Mild: GFR <90 and ≥60 mL/min/1.73 m^2*
- *Moderate: GFR <60 and ≥30 mL/min/1.73 m^2*
- *Severe: GFR <30 and ≥15 mL/min/1.73 m^2*

Hepatic impairment

The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with different tumor types (NSCLC, SCLC, melanoma, RCC, SCCHN, UC, gastric cancer, and cHL) with mild* hepatic impairment (n=351) and in patients with moderate* hepatic impairment (n=10) compared to patients with normal* hepatic function (n=3096) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate hepatic impairment and normal hepatic function. Nivolumab has not been studied in patients with severe* hepatic impairment (see 4.2 Posology and method of administration, Hepatic impairment).

**Per National Cancer Institute criteria of hepatic dysfunction:*

- *Normal: total bilirubin and AST ≤ ULN*
- *Mild: total bilirubin >1.0 to 1.5 times ULN or AST > ULN*

- *Moderate: total bilirubin >1.5 to 3 times ULN and any AST*
- *Severe: total bilirubin >3 times ULN and any AST*

6. NONCLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Nivolumab was well tolerated by cynomolgus monkeys when administered intravenously, twice weekly, up to three months and at doses up to approximately 35 times the human exposure at the clinical dose of 3 mg/kg based on AUC.

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels either 8 or 35 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, dose-dependent increases in fetal losses and increased neonatal mortality was observed.

The remaining offspring of nivolumab-treated females survived to scheduled termination, with no treatment-related clinical signs, alterations to normal development, organ-weight effects, or gross and microscopic pathology changes. Results for growth indices, as well as teratogenic, neurobehavioral, immunological, and clinical pathology parameters throughout the 6-month postnatal period were comparable to the control group. However, based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-related disorders or altering the normal immune response, and immune-related disorders have been reported in PD-1 knockout mice.

Carcinogenesis, mutagenesis, impairment of fertility

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

7. DESCRIPTION

Nivolumab is a fully human anti-PD-1 monoclonal antibody (IgG4) produced in Chinese hamster ovary cells by recombinant DNA technology.

Nivolumab is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid for intravenous infusion that may contain light (few) particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg.

List of excipients: Sodium citrate dihydrate, Sodium chloride, Mannitol , Pentetic acid (diethylenetriaminepentaacetic acid), Polysorbate 80, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment), Water for injections.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Nivolumab should not be infused concomitantly in the same intravenous line with other medicinal products.

8.2 Shelf life

Unopened vial

Refer to the outer carton, for the expiry date.

The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

After opening

- From a microbiological point of view, once opened, the medicinal product should be prepared for infusion immediately.

After preparation of infusion

- The prepared infusion solution may be stored under refrigeration conditions: 2°C to 8°C and protected from light for up to 7 days (a maximum of 8 hours of the total 7 days can be at room temperature 20°C to 25°C and room light – the maximum 8-hour period under room temperature and room light conditions should be inclusive of the product administration period). The administration of the nivolumab infusion must be completed within 7 days of preparation.

8.3 Packaging information

Each 10 mL vial contains 40 mg of nivolumab in 4 mL

Each 10 mL vial contains 100 mg of nivolumab in 10 mL

Each 25 mL vial contains 240 mg of nivolumab in 24 mL

Pack of 1 Vial

8.4 Storage and handling instructions

Store in a refrigerator (2°C-8°C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after preparation of the infusion, see 8.2 Shelf life.

Preparation and administration

Calculating the dose

More than one vial of nivolumab concentrate may be needed to give the total dose for the patient.

Flat dose (240 mg, 360 mg or 480 mg)	Weight-based dose
• The prescribed dose for the patient is 240 mg,360 mg or 480 mg given regardless of body weight.	The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given. • The total nivolumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg. • The volume of nivolumab concentrate to prepare the dose (mL) = the total dose in mg, divided by 10 (the nivolumab concentrate strength is 10 mg/mL).

Preparing the infusion

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Nivolumab can be used for intravenous administration either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting,

Flat dose (240 mg, 360 mg or 480 mg)*	Weight-based dose
The concentrate may be diluted so as not to exceed a total infusion volume of 160 mL.	The final infusion concentration should range between 1 and 10 mg/mL.

**For adult and pediatric patients with body weight less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of body weight*

- Nivolumab concentrate may be diluted with either:
  - sodium chloride 9 mg/mL (0.9%) solution for injection; or
  - 50 mg/mL (5%) glucose solution for injection.

STEP 1

- Inspect the nivolumab concentrate for particulate matter or discoloration. Do not shake the vial. Nivolumab concentrate is a clear to opalescent, colorless to pale-yellow liquid. Discard the vial if the solution is cloudy, is discolored, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of nivolumab concentrate using an appropriate sterile syringe.

STEP 2

- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).

- If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Gently mix the infusion by manual rotation. Do not shake.

Administration

Nivolumab infusion must not be administered as an intravenous push or bolus injection.

Administer the nivolumab infusion intravenously over a period of 30 minutes.

Nivolumab infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm).

Nivolumab infusion is compatible with:

- PVC containers
- Polyolefin containers
- Glass bottles
- PVC infusion sets
- In-line filters with polyethersulfone membranes with pore sizes of 0.2 μm to 1.2 μm.

After administration of the nivolumab dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

When administered in combination with ipilimumab, or other therapeutic agents, nivolumab should be given first followed by ipilimumab and/or other therapeutic agents (if applicable) on the same day. Use separate infusion bags and filters for each infusion.

Disposal

Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

9. PATIENT COUNSELLING INFORMATION

Please refer to section: SPECIAL WARNINGS AND PRECAUTIONS FOR USE (4.4) and 4.6 -Use in Special Populations (Such as Pregnant Women, Lactating Women) and see Use in Specific Populations (5.3.1) for Patient Counselling Information.

10. DETAILS OF MANUFACTURER

Manufactured and packed by: Bristol-Myers Squibb Holdings Pharma, Ltd. Liability Company, Road 686 Km 2.3, Bo. Tierras Nuevas, Manatí, Puerto Rico 00674, USA

And

Batch Release by: Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics, Cruiserath Road, Mulhuddart, Dublin 15, D15, H6EF, Ireland

Imported by: Bristol-Myers Squibb India Private Limited, Bldg.B-4, Gala No. 3B & 4B, Citylink Warehousing Complex, Mumbai Nashik Highway, Vadape Village, Taluka: Bhiwandi – 16, District: Thane Z5, Pin- 421302

Marketed by (registered office address)- Bristol-Myers Squibb India Private Limited, 6th floor, Tower 1, One International Center, S.B. Marg, Elphinstone (W), Mumbai - 400013, Tel: + 91 22 6628 8600

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Initial Form 45 Permission No.IMP-88/2016 dated 09-June 2016

12. DATE OF REVISION

Date of Revision – 27 Nov 2025

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Source - Nivolumab CCDS dated – 12 Aug 2015, 22 Jun 2022 and 28 Aug 2024