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

Bristol Myers Squibb™

Ipilimumab
YERVOI®

1. GENERIC NAME

Ipilimumab 5 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

YERVOI® (Ipilimumab) is a recombinant, fully human monoclonal antibody that binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture by recombinant DNA technology.

Each ml of concentrate contains 5 mg Ipilimumab.

Each10 ml vial contains 50 mg of Ipilimumab.

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

3. DOSAGE FORM AND STRENGTH

Injection: 50 mg/10 mL (5 mg/mL) as a clear to slightly opalescent, colorless to pale-yellow solution in a single-dose vial.

4. CLINICAL PARTICULARS

4.1Therapeutic Indications

Renal Cell Carcinoma (RCC)

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

Non-Small Cell Lung Cancer (NSCLC)

Ipilimumab, in combination with nivolumab, 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.

Ipilimumab, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

4.2 Posology and method of administration

Ipilimumab should be administered under the supervision of physicians experienced in the treatment of cancer.

4.2.1 Recommended dosage

RCC

Combination phase: The recommended dose during the combination phase is Ipilimumab 1 mg/kg administered intravenously over a period of 30 minutes every 3 weeks for the first 4 doses in combination with Nivolumab 3 mg/kg administered intravenously over a period of 30 minutes, followed by the single-agent phase.

Single-agent phase: The recommended dose of Nivolumab during the single-agent phase is 3 mg/kg every 2 weeks or 240 mg every 2 weeks or 480 mg every 4 weeks administered intravenously over a period of 30 minutes.

The first dose of nivolumab monotherapy should be administered 3 weeks following the last dose of the combination of ipilimumab and nivolumab.

When administered in combination with nivolumab*,* nivolumab should be given first followed by ipilimumab on the same day.

Review the Prescribing Information for nivolumab for dosage information.

NSCLC

The recommended dose of ipilimumab in combination with nivolumab is nivolumab 3 mg/kg administered as an intravenous infusion over 30 minutes every 2 weeks and ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes every 6 weeks until disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression.

The recommended dose of ipilimumab in combination with nivolumab and platinum-doublet chemotherapy is nivolumab 360 mg administered as an intravenous infusion over 30 minutes every 3 weeks and ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes every 6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progressio*n.*

Review the Prescribing Information for nivolumab and platinum-based chemotherapy for recommended dosing information.

Recommended Dosage Modifications for Adverse Reactions

No dose reduction for ipilimumab is recommended. In general, withhold ipilimumab for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue ipilimumab for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, persistent moderate (Grade 2) or severe (Grade 3) reactions lasting 12 weeks or longer after last ipilimumab dose (excluding endocrinopathy), or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids. Dosage modifications for ipilimumab or ipilimumab in combination with nivolumab for adverse reactions that require management different from these general guidelines are summarized in Table 1.

When ipilimumab is administered in combination with nivolumab, withhold or permanently discontinue both ipilimumab and nivolumab for toxicity.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity***	**Dosage Modifications**
Immune-Mediated Adverse Reactions ***[See Warnings and Precautions (5.1)]***		
Colitis/diarrhea	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver Or Hepatitis with tumor involvement of the liver/non-HCC	AST or ALT increases to more than 3 times and up to 5 times the ULN or Total bilirubin increases to more than 1.5 times and up to 3 times the ULN	Withhold[a]
	AST or ALT more than 5 times the ULN or Total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[b]	Baseline AST/ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST/ALT is more than 3 and up to 5	Withhold[a]

Adverse Reaction	Severity*	Dosage Modifications
	times ULN and increases to more than 8 and up to 10 times ULN.	
	AST/ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN.	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Endocrinopathies[c]	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Pneumonitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Ophthalmologic	Grade 2, 3, or 4 that does not improve to Grade 1 within 2 weeks while receiving topical therapy or that requires systemic treatment	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[see 4.4 Special warnings and precautions for use]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit of normal

* Based on Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03

[a] Resume in patients with complete or partial resolution (Grade 0 or 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

[b] If AST/ALT are less than or equal to ULN at baseline, withhold or permanently discontinue ipilimumab based on recommendations for hepatitis with no liver involvement.

[c] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

4.3 Contraindications

None.

4.4 Special warnings and precautions for use

Severe and Fatal Immune-Mediated Adverse Reactions

Ipilimumab is a fully human monoclonal antibody that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, thereby removing inhibition of the immune response with the potential for induction of immune-mediated adverse reactions. Immune-mediated adverse reactions listed herein may not be inclusive of all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting ipilimumab. While immune-mediated adverse reactions usually manifest during treatment, immune-mediated adverse reactions can also manifest after discontinuation of ipilimumab.

Early identification and management are essential to ensure safe use of ipilimumab. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue ipilimumab depending on severity *[see4.2 Posology and method of administration].* In general, if ipilimumab requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroid therapy.

<u>Immune-Mediated Colitis</u>

Ipilimumab can cause immune-mediated colitis, which may be fatal. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 10% (52/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 1.7 months (range: 2 days to 19.2 months). Immune-mediated colitis led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 3.5% and 4.2% of patients, respectively. Approximately 83% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 21 days (range: 1 day to 27 months). Approximately 23% of patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 89% of patients. Two patients had recurrence of colitis after re-initiation of nivolumab with Ipilimumab.

Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in 7% (38/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 2 months (range: 14 days to 26.8 months). Immune-mediated hepatitis led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 3.7% and 3.1% of patients, respectively. Approximately 92% of patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.0 month (range: 1 day to 4.0 months). Complete resolution occurred in 87% of patients without recurrence of hepatitis after re-initiation of nivolumab with Ipilimumab.

Immune-Mediated Dermatologic Adverse Reactions

Ipilimumab can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens Johnson Syndrome, toxic epidermal necrolysis (TEN) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue ipilimumab depending on severity *[see 4.2 Posology and method of administration]*.

Immune-mediated rash occurred in 16.6% (91/547) of patients. Median time to onset was 1.5 months (range: 1 day to 20.9 months). Immune-mediated rash led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 0.5% and 2.9% of patients, respectively. Approximately 19% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 25 days (range: 1 day to 23.1 months). Complete resolution occurred in 64% of patients. Approximately 3.6% of patients who resumed nivolumab and Ipilimumab after resolution had recurrence of rash.

Immune-Mediated Endocrinopathies

Hypophysitis:

Ipilimumab can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue ipilimumab depending on severity *[see 4.2 Posology and method of administration]*.

Hypophysitis occurred in 4.6% (25/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 2.8 months (range: 1.3 months to 7.3 months). Hypophysitis led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 1.3% and 2.6% of patients, respectively. Approximately 72% of patients with

hypophysitis received hormone replacement therapy and 60% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 10 days (range: 1 day to 1.6 months).

Adrenal Insufficiency:

Adrenal insufficiency occurred in 7% (41/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 3.4 months (range: 2.0 months to 22.3 months). Adrenal insufficiency led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 1.3% and 2.0% of patients, respectively. Approximately 93% of patients with adrenal insufficiency received hormone replacement therapy and 18% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 1 day to 5.6 months).

Hypothyroidism and Hyperthyroidism:

Hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 2.2 months (range: 1 day to 21.4 months). Approximately 76% of patients with hypothyroidism or thyroiditis received levothyroxine. Resolution occurred in 31% of patients.

Hyperthyroidism occurred in 12% (66/547) of patients with RCC. Median time to onset was 1.4 months (range: 6 days to 14.2 months) in RCC. Approximately 14% of patients with hyperthyroidism received methimazole and 3% received carbimazole. Resolution occurred in 85% of patients.

Type 1 Diabetes Mellitus:

Diabetes occurred in 2.7% (15/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 3.2 months (range: 19 days to 16.8 months). Nivolumab with Ipilimumab was withheld in 33% of patients and permanently discontinued in 20% of patients who developed diabetes.

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis occurred in 4.4% (24/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 2.6 months (range: 8 days to 9.2 months). Immune-mediated pneumonitis led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 2.0% and 1.6% of patients, respectively. Approximately 92% of patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 19 days (range: 4 days to 3.2 months). Approximately 8% of patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 79% of patients without recurrence of pneumonitis after re-initiation of nivolumab with Ipilimumab.

In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving Ipilimumab 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks, including Grade 4 (0.5%), Grade 3

(3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. The median duration was 1.5 months (range: 5 days to 25+ months). Immune-mediated pneumonitis led to permanent discontinuation of Ipilimumab with nivolumab in 5% of patients and withholding of Ipilimumab with nivolumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis followed by a corticosteroid taper. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after re-initiation of Ipilimumab with nivolumab.

Immune-Mediated Nephritis with Renal Dysfunction

Immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 2.5 months (range: 1 day to 13.2 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 1.1% and 2.7% of patients, respectively. Approximately 76% of patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 15 days (range: 1 day to 5.9 months). Complete resolution occurred in 64% of patients. One patient had recurrence of nephritis or renal dysfunction after re-initiation of nivolumab with Ipilimumab.

Other Immune-Mediated Adverse Reactions

Across clinical trials of ipilimumab administered as a single agent or in combination with nivolumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified, as shown below:

Nervous System: Autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, motor dysfunction

Cardiovascular: Angiopathy, myocarditis, pericarditis, temporal arteritis, vasculitis

Ocular: Blepharitis, episcleritis, iritis, orbital myositis, scleritis, uveitis. Some cases can be associated with retinal detachment. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving ipilimumab and may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Gastrointestinal: Duodenitis, gastritis, pancreatitis (1.3%)

Musculoskeletal and Connective Tissue: Arthritis, myositis, polymyalgia rheumatica, polymyositis, rhabdomyolysis

Other (hematologic/immune): Aplastic anemia, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), hypersensitivity vasculitis, meningitis, neurosensory hypoacusis, psoriasis, sarcoidosis, systemic inflammatory response syndrome and solid organ transplant rejection.

Infusion-Related Reactions

Severe infusion-related reactions can occur with ipilimumab. Discontinue ipilimumab in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions *[see 4.2 Posology and method of administration]*.

Infusion-related reactions occurred in 5.1% (28/547) of patients.

Complications of Allogeneic Hematopoietic Stem Cell Transplant after Ipilimumab

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive ipilimumab either before or after allogeneic hematopoietic stem cell transplantation (HSCT). These complications may occur despite intervening therapy between CTLA-4 receptor blocking antibody and allogeneic HSCT.

Follow patients closely for evidence of GVHD and intervene promptly *[see 4.8 Undesirable effects]*. Consider the benefit versus risks of treatment with ipilimumab after allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, ipilimumab can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight) and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ipilimumab and for 3 months after the last dose *[see 4.6 Use in Specific Populations (such as pregnant women, lactating women, pediatric patients, geriatric patients, etc.)]*.

Risks Associated When Administered in Combination with Nivolumab

Ipilimumab is indicated for use in combination with nivolumab for patients with advanced RCC and NSCLC. Refer to the nivolumab Full Prescribing Information for additional risk information that applies to the combination use treatment.

4.5 DRUG INTERACTIONS

Ipilimumab is a human monoclonal antibody that is not metabolized by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes. In a drug-interaction study, ipilimumab did not have a significant effect on the pharmacokinetics of substrates of CYP1A2, CYP2E1, CYP2C8, and CYP3A4 when coadministered with substrates of these CYP isozymes (dacarbazine or paclitaxel/carboplatin).

Other forms of interaction

Corticosteroids

The use of systemic corticosteroids at baseline, before starting ipilimumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of ipilimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting ipilimumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting ipilimumab treatment does not appear to impair the efficacy of ipilimumab.

Anticoagulants

The use of anticoagulants is known to increase the risk of gastrointestinal hemorrhage. Since gastrointestinal hemorrhage is an adverse reaction with ipilimumab *(see 4.8 Undesirable effects)*, patients who require concomitant anticoagulant therapy should be monitored closely.

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, ipilimumab can cause fetal harm when administered to a pregnant woman. There is insufficient human data for ipilimumab exposure in pregnant women. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner *(see Data)*. The effects of Ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

In a combined study of embryo-fetal and peri-postnatal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, administration of ipilimumab at doses resulting in exposures approximately 2.6 to 7.2 times the human exposure at a dose of 3 mg/kg resulted in dose-related increases in abortion, stillbirth, premature delivery (with corresponding lower birth weight), and an increased incidence of infant mortality. In addition, developmental abnormalities were identified in the urogenital system of 2 infant monkeys exposed in utero to 30 mg/kg of ipilimumab (7.2 times the humans exposure based on area under the curve at a dose of 3 mg/kg). One female infant monkey had unilateral renal agenesis of the left kidney and ureter, and 1 male infant monkey had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/−), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/− heterozygous offspring. Mated CTLA-4+/− heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4−/−). The CTLA-4−/− homozygous negative offspring appeared healthy at birth, exhibited signs of multiorgan lymphoproliferative disease by 2 weeks of age, and all died by 3 to 4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

Lactation

Risk Summary

There are no data on the presence of ipilimumab in human milk or its effects on the breastfed child or milk production. In monkeys, ipilimumab was present in milk *(see Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with ipilimumab and for 3 months following the last dose.

Data

In monkeys treated at dose levels resulting in exposures 2.6 and 7.2 times higher than those in humans at a 3 mg/kg dose, ipilimumab was present in milk at concentrations of 0.1 mcg/mL and 0.4 mcg/mL, representing a ratio of up to 0.3% of the steady-state serum concentration of the drug.

Females and Males of Reproductive Potential

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating Ipilimumab *[see 4.6 Use in Special Populations-Pregnancy]*.

Contraception
Ipilimumab can cause fetal harm when administered to a pregnant woman *[see 4.6 Use in Special Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Ipilimumab and for 3 months following the last dose.

Pediatric use

The safety and effectiveness for pediatric patients 12 years and older have not been established or for the treatment of renal cell carcinoma. In addition, the safety and effectiveness have not been established with ipilimumab for any indication in pediatric patients less than 12 years of age.

Ipilimumab was evaluated in a total of 45 pediatric patients across two clinical trials. In a dose finding trial (NCT01445379), 33 pediatric patients with relapsed or refractory solid tumors were evaluated. The median age was 13 years (range 2 to 21 years) and 20 patients were ≥12 years old.

Geriatric use

Of the 550 patients randomized to ipilimumab 1 mg/kg with nivolumab in CA209227, Part 1 [CHECKMATE-214] (renal cell carcinoma), 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was observed between these patients and younger patients. In geriatric patients with intermediate or poor risk, no overall difference in effectiveness was observed.

Of the 576 patients randomized to Ipilimumab 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227 (NSCLC), 48% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29%) relative to all patients who received Ipilimumab with nivolumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to Ipilimumab 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks with in CHECKMATE-227, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older *[see 5.2.1 Clinical Trials]*.

Of the 361 patients randomized to Ipilimumab 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CA2099LA [CHECKMATE-9LA] (NSCLC), 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received Ipilimumab with nivolumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to Ipilimumab in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

4.7 Effects on ability to drive and to use machines

Because of potential adverse reactions such as fatigue *(see 4.8 Undesirable effects)*, patients should be advised to use caution when driving or operating machinery until they are certain that ipilimumab does not adversely affect them.

4.8 Undesirable effects

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and fatal immune-mediated adverse reactions *[see 4.4 Special warnings and precautions for use]*.
- Infusion-related reactions *[see 4.4 Special warnings and precautions for use]*.

4.8.1 Clinical experience

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

RCC

The safety of ipilimumab in combination with nivolumab was evaluated in 1082 patients with previously untreated advanced RCC in CHECKMATE-214 *[see 5.2.1 Clinical Trial Studies]*. Patients received ipilimumab 1 mg/kg with nivolumab 3 mg/kg intravenously every 3 weeks for 4 doses followed by nivolumab as a single agent at a dose of 3 mg/kg every 2 weeks (n=547) or sunitinib 50 mg orally daily for first 4 weeks of each 6-week cycle (n=535). The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in ipilimumab and nivolumab arm. In this trial, 57% of patients in the ipilimumab and nivolumab arm were exposed to treatment for greater than 6 months and 38% of patients were exposed to treatment for greater than 1 year.

Serious adverse reactions occurred in 59% of patients receiving ipilimumab with nivolumab. The most frequent serious adverse reactions reported in >2% of patients treated with Ipilimumab and nivolumab were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

In patients who received ipilimumab with nivolumab, study therapy was discontinued for adverse reactions in 31% and delayed for adverse reactions in 54%.

The most common adverse reactions (>20%) in the ipilimumab and nivolumab arm were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, vomiting, dyspnea, and decreased appetite. Table 2 summarizes adverse reactions in CHECKMATE-214.

Table 2: Adverse Reactions (>15%) in Patients Receiving Ipilimumab with Nivolumab in CHECKMATE-214

Adverse Reaction	**Ipilimumab 1 mg/kg with Nivolumab n=547**		**Sunitinib n=535**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
General and Administration Site Conditions				
Fatigue[a]	58	8	69	13
Pyrexia	25	0.7	17	0.6
Edema[b]	16	0.5	17	0.6
Skin and Subcutaneous Tissue				
Rash[c]	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
Gastrointestinal				
Diarrhea	38	4.6	58	6
Nausea	30	2.0	43	1.5
Vomiting	20	0.9	28	2.1
Abdominal pain	19	1.6	24	1.9
Constipation	17	0.4	18	0

Table 2: Adverse Reactions (>15%) in Patients Receiving Ipilimumab with Nivolumab in CHECKMATE-214

Adverse Reaction	Ipilimumab 1 mg/kg with Nivolumab n=547		Sunitinib n=535	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	37	4.0	40	2.6
Arthralgia	23	1.3	16	0
Respiratory, Thoracic, and Mediastinal				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
Metabolism and Nutrition				
Decreased appetite	21	1.8	29	0.9
Nervous System				
Headache	19	0.9	23	0.9
Endocrine				
Hypothyroidism	18	0.4	27	0.2

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema, peripheral swelling.

[c] Includes dermatitis described as acneiform, bullous, and exfoliative, drug eruption, rash described as exfoliative, erythematous, follicular, generalized, macular, maculopapular, papular, pruritic, and pustular, fixed-drug eruption.

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

Table 3 summarizes the laboratory abnormalities in CHECKMATE-214.

Table 3: Laboratory Abnormalities (>15%) Worsening from Baseline in Patients Receiving Ipilimumab with Nivolumab in CHECKMATE-214

Laboratory Abnormality	Ipilimumab 1 mg/kg with Nivolumab[a]		Sunitinib[a]	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased lipase	48	20	51	20
Increased creatinine	42	2.1	46	1.7
Increased ALT	41	7	44	2.7
Increased AST	40	4.8	60	2.1
Increased amylase	39	12	33	7
Hyponatremia	39	10	36	7
Increased alkaline phosphatase	29	2.0	32	1.0
Hyperkalemia	29	2.4	28	2.9

Table 3: Laboratory Abnormalities (>15%) Worsening from Baseline in Patients Receiving Ipilimumab with Nivolumab in CHECKMATE-214

Laboratory Abnormality	Ipilimumab 1 mg/kg with Nivolumab[a]		Sunitinib[a]	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hypocalcemia	21	0.4	35	0.6
Hypomagnesemia	16	0.4	26	1.6
Hematology				
Anemia	43	3.0	64	9
Lymphopenia	36	5	63	14

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

In addition, among patients with TSH ≤ ULN at baseline, a lower proportion of patients experienced a treatment-emergent elevation of TSH > ULN in the ipilimumab with nivolumab group compared to the sunitinib group (31% and 61%, respectively).

First-line Treatment of Metastatic NSCLC: In Combination with Nivolumab

The safety of Ipilimumab in combination with nivolumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations *[see 5.2.1 Clinical Trials]*. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received Ipilimumab 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks and nivolumab 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in Ipilimumab and nivolumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received Ipilimumab and nivolumab for >6 months and 23% of patients received Ipilimumab and nivolumab for >1 year. The population characteristics were: median age 64 years (range: 26 to 87); 48% were ≥65 years of age, 76% White, and 67% male. Baseline ECOG performance status was 0 (35%) or 1 (65%), 85% were former/current smokers, 11% had brain metastases, 28% had squamous histology and 72% had non-squamous histology.

Serious adverse reactions occurred in 58% of patients. Ipilimumab and nivolumab were discontinued for adverse reactions in 24% of patients and 53% had at least one dose withheld for an adverse reaction.

The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. The most common (≥20%) adverse reactions were fatigue, rash, decreased appetite, musculoskeletal pain, diarrhea/colitis, dyspnea, cough, hepatitis, nausea, and pruritus.

Tables 4 and 5 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 4: Adverse Reactions in ≥10% of Patients Receiving Ipilimumab and Nivolumab - CHECKMATE-227

	Ipilimumab and Nivolumab (n=576)		Platinum-doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema[b]	14	0.2	12	0.5
Skin and Subcutaneous Tissue				
Rash[c]	34	4.7	10	0.4
Pruritus[d]	21	0.5	3.3	0
Metabolism and Nutrition				
Decreased appetite	31	2.3	26	1.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[e]	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
Gastrointestinal				
Diarrhea/colitis[f]	26	3.6	16	0.9
Nausea	21	1.0	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1.0	18	2.3
Abdominal pain[g]	10	0.2	9	0.7
Respiratory, Thoracic, and Mediastinal				
Dyspnea[h]	26	4.3	16	2.1
Cough[i]	23	0.2	13	0
Hepatobiliary				
Hepatitis[j]	21	9	10	1.2
Endocrine				
Hypothyroidism[k]	16	0.5	1.2	0
Hyperthyroidism[l]	10	0	0.5	0

Infections and Infestations				
Pneumonia[m]	13	7	8	4.0
Nervous System				
Headache	11	0.5	6	0

[a] Includes fatigue and asthenia.
[b] Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.
[c] Includes autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.
[d] Includes pruritus and pruritus generalized.
[e] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.
[f] Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.
[g] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.
[h] Includes dyspnea and dyspnea exertional.
[i] Includes cough and productive cough.
[j] Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased.
[k] Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.
[l] Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.
[m] Includes lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral, atypical pneumonia, organizing pneumonia.

Other clinically important adverse reactions in CHECKMATE-227 were:

Skin and Subcutaneous Tissue: urticaria, alopecia, erythema multiforme, vitiligo

Gastrointestinal: stomatitis, pancreatitis, gastritis

Musculoskeletal and Connective Tissue: arthritis, polymyalgia rheumatica, rhabdomyolysis

Nervous System: peripheral neuropathy, autoimmune encephalitis

Blood and Lymphatic System: eosinophilia

Eye Disorders: blurred vision, uveitis

Cardiac: atrial fibrillation, myocarditis

Table 5: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on Ipilimumab and Nivolumab - CHECKMATE-227

Laboratory Abnormality	Ipilimumab and Nivolumab		Platinum-doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	46	3.6	78	14
Lymphopenia	46	5	60	15
Chemistry				
Hyponatremia	41	12	26	4.9
Increased AST	39	5	26	0.4
Increased ALT	36	7	27	0.7
Increased lipase	35	14	14	3.4
Increased alkaline phosphatase	34	3.8	20	0.2
Increased amylase	28	9	18	1.9
Hypocalcemia	28	1.7	17	1.3
Hyperkalemia	27	3.4	22	0.4
Increased creatinine	22	0.9	17	0.2

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Ipilimumab and nivolumab group (range: 494 to 556 patients) and chemotherapy group (range: 469 to 542 patients).

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublet Chemotherapy

The safety of Ipilimumab in combination with nivolumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see 5.2.1 Clinical Trials].* Patients received either Ipilimumab 1 mg/kg administered every 6 weeks in combination with nivolumab 360 mg administered every 3 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in Ipilimumab in combination with nivolumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received Ipilimumab and nivolumab for >6 months and 13% of patients received Ipilimumab and nivolumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with Ipilimumab in combination with nivolumab and platinum-doublet chemotherapy. The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Study therapy with Ipilimumab in combination with nivolumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Tables 6 and 7 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 6: Adverse Reactions in >10% of Patients Receiving Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				

Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia

[b] Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis

[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis

[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain

[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blenorrhagica, palmar-plantar erythrodysaesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria

[f] Includes pruritus and generalized pruritus

[g] Includes cough, productive cough, and upper-airway cough syndrome

[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea

[i] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine

[j] Includes dizziness, vertigo and positional vertigo

Table 7: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	**Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy**		**Platinum-Doublet Chemotherapy**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Hematology				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9
Thrombocytopenia	23	4.3	24	5

Chemistry				
Hyperglycemia	45	7	42	2.6
Hyponatremia	37	10	27	7
Increased ALT	34	4.3	24	1.2
Increased lipase	31	12	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	7	19	1.3
Increased AST	30	3.5	22	0.3
Hypomagnesemia	29	1.2	33	0.6
Hypocalcemia	26	1.4	22	1.8
Increased creatinine	26	1.2	23	0.6
Hyperkalemia	22	1.7	21	2.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Ipilimumab and nivolumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

4.8.2 Post-marketing experience

The following adverse reactions have been identified during post approval use of ipilimumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH)

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

Skin and Subcutaneous Tissue: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

4.8.3 Immunogenicity

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

Of 483 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-227 Part 1, 8.5% were positive for treatment-emergent anti-ipilimumab antibodies. No patients had neutralizing antibodies against ipilimumab. In Part 1 of the same study, of 491 patients evaluable for anti-nivolumab antibodies, 36.7% were positive for anti-nivolumab antibodies and 1.4% had neutralizing antibodies against nivolumab.

Of 305 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-9LA, 8% were positive for anti-ipilimumab antibodies and 1.6% were positive for anti-ipilimumab neutralizing antibodies. There was no evidence of increased incidence of infusion reactions to Ipilimumab in patients with anti-ipilimumab antibodies. Of 308 patients evaluable for anti-nivolumab antibodies in

CHECKMATE-9LA, 34% were positive for anti-nivolumab antibodies and 2.6% had neutralizing antibodies against nivolumab.

4.9 Overdose

The maximum tolerated dose of ipilimumab has not been determined. In clinical trials, patients received up to 20 mg/kg without apparent toxic effects.

In case of overdosage, 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

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

5.2 Pharmacodynamics Properties

5.2.1 Clinical Trials

Renal cell carcinoma (RCC)

The efficacy of ipilimumab with nivolumab was evaluated in CHECKMATE-214 (NCT02231749), a randomized (1:1), open-label study in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were randomized to nivolumab 3 mg/kg and ipilimumab 1 mg/kg administered intravenously every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every two weeks or to sunitinib administered orally 50 mg daily for the first 4 weeks of each 6-week cycle. Treatment continued until disease progression or unacceptable toxicity. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. The major efficacy outcome measures were OS, PFS (IRRC-assessed), and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. Intermediate/poor risk patients had at least 1 or more of 6 prognostic risk factors as per the IMDC criteria: less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status (KPS) <80%, hemoglobin less than the lower limit of normal, corrected calcium >10 mg/dL, platelet count > ULN, and absolute neutrophil count > ULN.

A total of 847 patients were randomized, 425 to ipilimumab with nivolumab and 422 to sunitinib. The median age was 61 years (range: 21 to 85) with 38% ≥65 years of age and 8% ≥75 years of age.

The majority of patients were male (73%) and White (87%) and 26% and 74% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively.

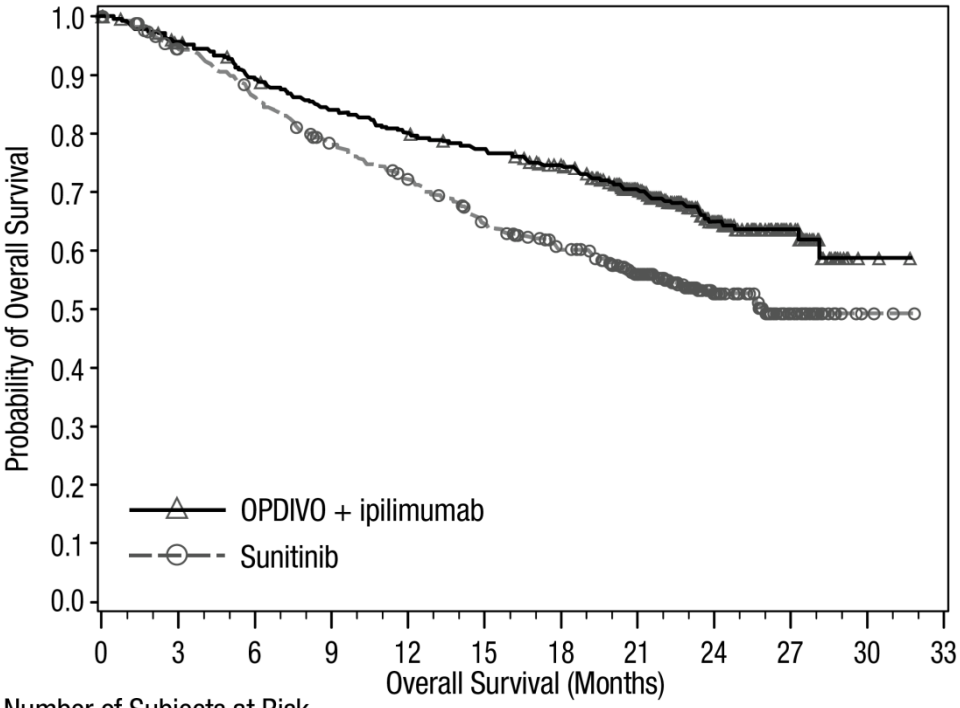
Efficacy results from CHECKMATE-214 are presented in Table 8 and Figure 1. In intermediate/poor risk patients, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to ipilimumab and nivolumab arm as compared with sunitinib arm. OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS.

Table 8 :Efficacy Results for CHECKMATE-214

Efficacy Parameter	**Intermediate/Poor-Risk**	
	Ipilimumab 1 mg/kg with Nivolumab n=425	**Sunitinib n=422**
Overall Survival		
Number of deaths	140 (32.9%)	188 (44.5%)
Median in months	NE	25.9
Hazard ratio (99.8% CI)[a]	0.63 (0.44, 0.89)	
p-value[b,c]	<0.0001	
Confirmed Objective Response Rate (95% CI)	41.6% (36.9%, 46.5%)	26.5% (22.4%, 31.0%)
Complete Response	40 (9.4%)	5 (1.2%)
Partial Response	137 (32.2%)	107 (25.4%)
Median duration of response in months (95% CI)	NE (21.8, NE)	18.2 (14.8, NE)
p-value[d,e]	<0.0001	
Progression-free Survival		
Number of events (progression or death)	228 (53.6%)	228 (54.0%)
Median in months	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	
p-value[b]	NS[f]	

[a] Based on a stratified proportional hazards model.
[b] Based on a stratified log-rank test.
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[d] Based on the stratified DerSimonian-Laird test.
[e] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[f] Not Significant at alpha level of 0.009

Figure 1: Kaplan-Meier Curves for Overall Survival (Intermediate/Poor Risk Population) in CHECKMATE-214



Number of Subjects at Risk

OPDIVO + ipilimumab	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

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

Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Nivolumab

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. 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 [ASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. 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 enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression ≥1%. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Randomization was stratified by tumor histology (non-squamous versus squamous). The evaluation of efficacy relied on the comparison between:

• Ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks in combination with nivolumab 3 mg/kg administered intravenously over 30 minutes every 2 weeks; or

• Platinum-doublet chemotherapy

Chemotherapy regimens 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 as a single agent. 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 Ipilimumab in combination with nivolumab (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, and 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 improvement in OS for PD-L1 ≥1% patients randomized to the Ipilimumab and nivolumab arm compared to platinum-doublet chemotherapy arm. The OS results are presented in Table 9 and Figure 2.

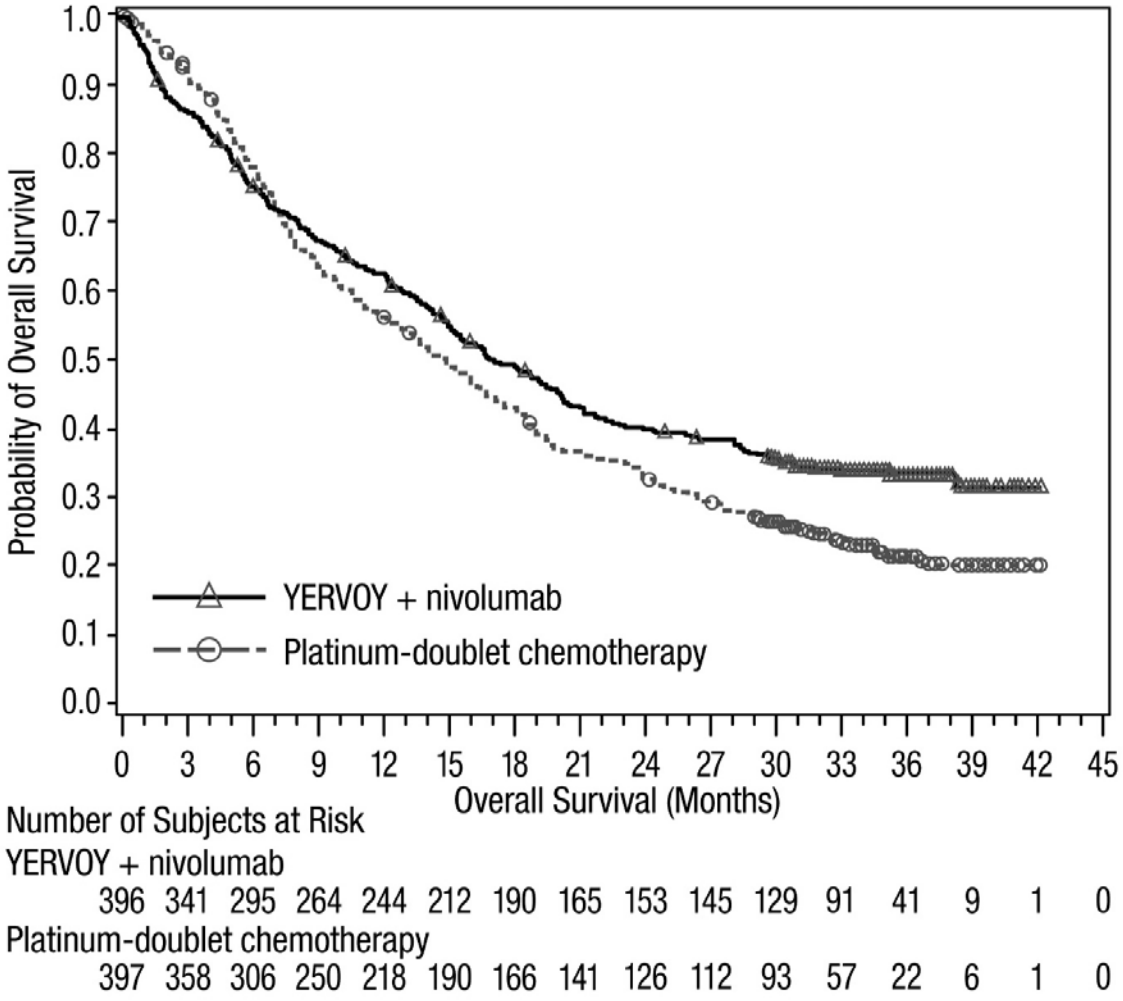
Table 9: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

	Ipilimumab and Nivolumab (n=396)	Platinum-Doublet Chemotherapy (n=397)
Overall Survival		
Events (%)	258 (65%)	298 (75%)
Median (months)[a] (95% CI)	17.1 (15, 20.1)	14.9 (12.7, 16.7)
Hazard ratio (95% CI)[b]	0.79 (0.67, 0.94)	
Stratified log-rank p-value	0.0066	

[a] Kaplan-Meier estimate.

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

Figure 2: Overall Survival (PD-L1 ≥1%) - CHECKMATE-227



BICR-assessed PFS showed a HR of 0.82 (95% CI: 0.69, 0.97), with a median PFS of 5.1 months (95% CI: 4.1, 6.3) in the Ipilimumab and nivolumab arm and 5.6 months (95% CI: 4.6, 5.8) in the platinum-doublet chemotherapy arm. The BICR-assessed confirmed ORR was 36% (95% CI: 31, 41) in the Ipilimumab and nivolumab arm and 30% (95% CI: 26, 35) in the platinum-doublet chemotherapy arm. Median duration of response observed in the Ipilimumab and nivolumab arm was 23.2 months and 6.2 months in the platinum-doublet chemotherapy arm.

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublet Chemotherapy

CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial 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) for metastatic disease. 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 stable brain metastases were eligible for enrollment.

Patients were randomized 1:1 to receive either:

• Ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks, nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks, and platinum-doublet chemotherapy administered intravenously every 3 weeks for 2 cycles, or

• platinum-doublet chemotherapy administered every 3 weeks for 4 cycles.

Platinum-doublet chemotherapy consisted of either 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. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Treatment could continue 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 reaction attributed to Ipilimumab were permitted to continue nivolumab as a single agent as part of the study. 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 Ipilimumab in combination with nivolumab and platinum-doublet chemotherapy (n=361) or platinum-doublet 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. The majority of patients were White (89%) and male (70%). Baseline ECOG performance

status was 0 (31%) or 1 (68%), 57% had tumors with PD-L1 expression ≥1% and 37% had tumors with PD-L1 expression that was <1%, 32% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 86% were former or current smokers.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR. Efficacy results from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) are presented in Table 10.

Table 10: Efficacy Results - CHECKMATE-9LA

	Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy (n=361)	**Platinum-Doublet Chemotherapy (n=358)**
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Progression-free Survival per BICR		
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)	6.8 (5.6, 7.7)	5.0 (4.3, 5.6)
Overall Response Rate per BICR (%)	38	25
(95% CI)[e]	(33, 43)	(21, 30)
Stratified CMH test p-value[f]	0.0003	
Duration of Response per BICR		
Median (months) (95% CI)[d]	10.0 (8.2, 13.0)	5.1 (4.3, 7.0)

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

[b] p-value is compared with the allocated alpha of 0.033 for this interim analysis.

[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.

[d] Kaplan-Meier estimate.

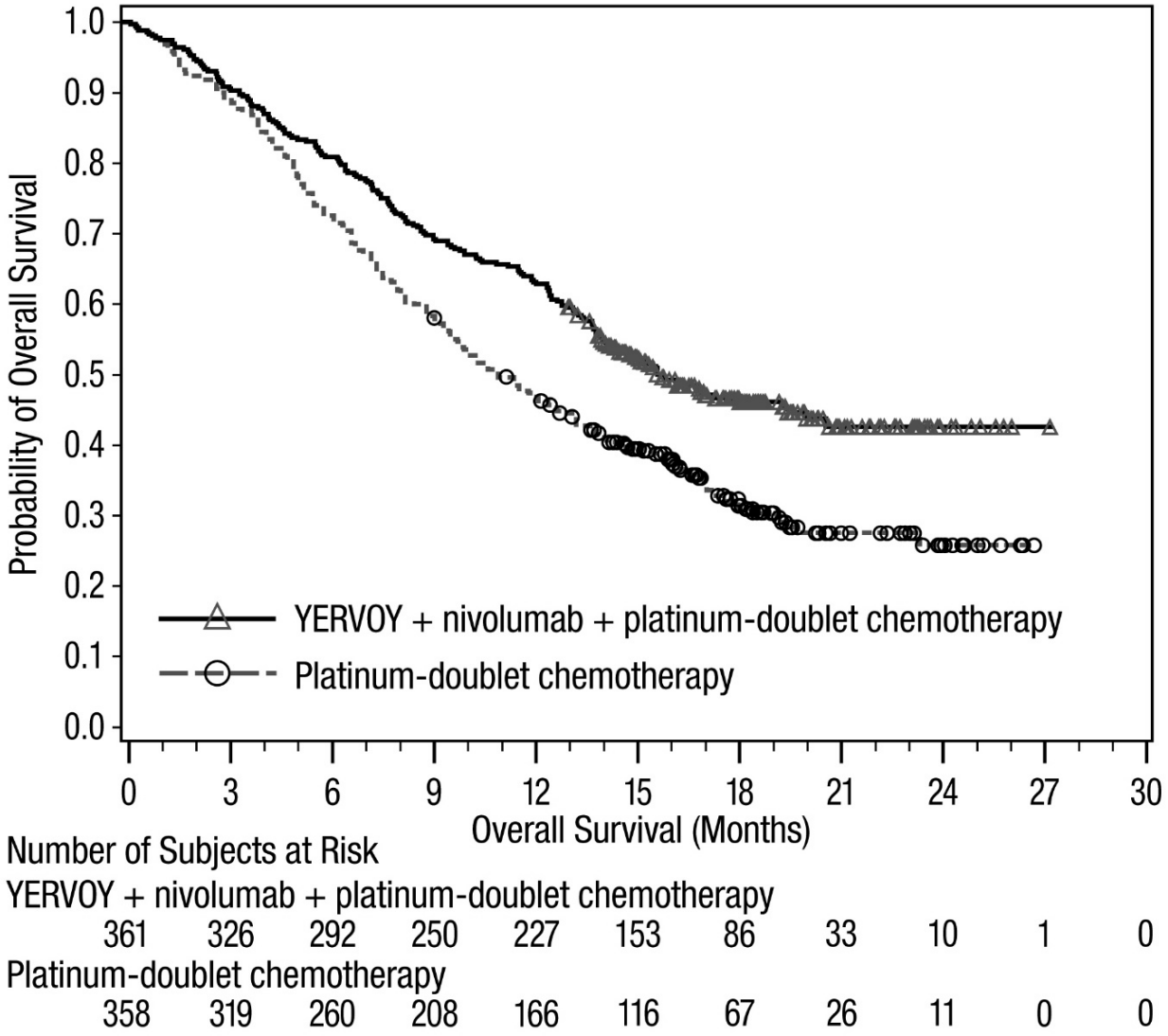
[e] Confidence interval based on the Clopper and Pearson Method.

[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.

With an additional 4.6 months of follow-up the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for

patients receiving ipilimumab and nivolumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 3).

Figure 3: Overall Survival - CHECKMATE-9LA



5.3 Pharmacokinetic Properties

The pharmacokinetics (PK) of ipilimumab was studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every 3 weeks for 4 doses. The PK of ipilimumab is linear in the dose range of 0.3 mg/kg to 10 mg/kg. Following administration of Ipilimumab every 3 weeks, the systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean minimum concentration (C_{min}) at steady state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks.

Elimination

The mean (percent coefficient of variation) terminal half-life (t1/2) was 15.4 days (34%) and then mean (percent coefficient of variation) clearance (CL) was 16.8 mL/h (38%).

The CL of ipilimumab was unchanged in presence of anti-ipilimumab antibodies.

Specific Populations

The CL of ipilimumab increased with increasing body weight supporting the recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23 to 88 years), sex, performance status, renal impairment (glomerular filtration rate ≥15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin [TB] >1 to 1.5 times the upper limit of normal [ULN] or AST > ULN), previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-White racial groups. ipilimumab has not been studied in patients with moderate (TB > 1.5 to 3 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment.

Pediatric Patients: Based on a population PK analysis using available pooled data from 565 patients from four adult studies (n=521) and two pediatric studies (n=44), body weight normalized clearance of ipilimumab is comparable between adult and pediatric patients. In pediatric patients with a dosing regimen of 3 mg/kg every 3 weeks, the model simulated geometric mean (CV%) steady-state serum peak and trough concentrations of ipilimumab were 65.8 (17.6%) and 20.7 (33.1%) mcg/mL (for 2 to 6 years old), 70.1 (19.6%) and 19.6 (42.9%) mcg/mL (for 6 to <12 years old), and 73.3 (20.6%) and 17.8 (50.8%) mcg/mL (for 12 years and older), which are comparable to those in adult patients.

Drug Interaction Studies

Ipilimumab with Nivolumab

When ipilimumab 1 mg/kg was administered with nivolumab 3 mg/kg every 3 weeks, the CL of ipilimumab was unchanged compared to when ipilimumab was administered alone.

When Ipilimumab 1 mg/kg every 6 weeks was administered in combination with nivolumab 3 mg/kg every 2 weeks, the CL of ipilimumab increased by 30% compared to Ipilimumab administered alone and the CL of nivolumab was unchanged compared to nivolumab administered alone.

When Ipilimumab 1 mg/kg every 6 weeks was administered in combination with nivolumab 360 mg every 3 weeks and chemotherapy, the CL of ipilimumab increased by 22% compared to Ipilimumab administered alone and the CL of nivolumab was unchanged compared to nivolumab administered alone.

6. NON CLINICALPROPERTIES

6.1 Animal Toxicology

Please refer section 4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.), sub-section Animal data.

Carcinogenesis, mutagenesis, impairment of fertility

The carcinogenic potential of ipilimumab has not been evaluated in long-term animal studies, and the genotoxic potential of ipilimumab has not been evaluated.

Fertility studies have not been performed with ipilimumab.

7. DESCRIPTION

Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. Ipilimumab is a recombinant IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

Ipilimumab injection, for intravenous use is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-dose vials of 50 mg/10 mL. Each milliliter contains 5 mg of ipilimumab and the following excipients: Tris hydrochloride (2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride), Sodium chloride, Mannitol, Pentetic acid (diethylenetriaminepentaacetic acid), Polysorbate 80, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment) and Water for injection.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

8.2 Shelf life

Unopened vial: Refer to the outer carton, for the expiry date.

Solution for infusion: Once opened, the product should be infused or diluted and infused immediately. The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 mg/mL and 4 mg/mL) has been demonstrated for 24 hours at 25°C (77°F) and 2°C to 8°C (36°F to 46°F). If not used immediately, the infusion solution (undiluted or diluted) may be stored for up to 24 hours either under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).

Ipilimumab must be stored in a refrigerator (2°C - 8°C). Do not freeze.Store in the original package in order to protect from light.

8.3 Packaging Information

Each 10 ml vial contains 50 mg of ipilimumab.

Pack of 1 Vial.

8.4 Storage and handling instructions

Preparation for administration

- Do not shake product.
- Visually inspect for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

Preparation of Solution

- Allow the vial(s) to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of ipilimumab and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- After preparation, store the diluted solution either refrigerated at 2°C to 8°C (36°F to 46°F) or at room temperature of 20°C to 25°C (68°F to 77°F) for no more than 24 hours from the time of preparation to the time of infusion.
- Discard partially used or empty vials of ipilimumab.

Administration

- Do not co-administer other drugs through the same intravenous line.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose
- Injection, USP after each dose.
- Administer diluted solution through an intravenous line containing a sterile, non-pyrogenic,
- low-protein-binding in-line filter.
- When administered in combination with nivolumab, infuse nivolumab first followed by ipilimumab on the same day. When administered with nivolumab and platinum-doublet

chemotherapy, infuse nivolumab first followed by ipilimumab and then platinum-doublet chemotherapy on the same day. Use separate infusion bags and filters for each infusion.

9. PATIENT COUSELLING INFORMATION

Immune-Mediated Adverse Reactions

Advise patients that ipilimumab can cause immune-mediated adverse reactions including the following *[see 4.4 Special warnings and precautions for use]*:

• Immune-Mediated Diarrhea or Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of diarrhea or colitis.

• Immune-Mediated Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.

• Immune-Mediated Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.

• Immune-Mediated Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus

• Immune-Mediated Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening symptoms of pneumonitis.

• Immune-Mediated Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.

Infusion-Related Reactions

• Advise patients who are receiving ipilimumab of the potential risk of an infusion-related reaction *[see 4.4 Special warnings and precautions for use]*.

Embryo-Fetal Toxicity

• Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see 4.4 Special warnings and precautions for use and 4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.)]*.

• Advise females of reproductive potential to use effective contraception during treatment with ipilimumab and for 3 months after the last dose *[see 4.4 Special warnings and precautions for use]*.

Lactation

• Advise women not to breastfeed during treatment with Ipilimumab and for 3 months after the last dose *[see 4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.)]*.

10. DETAILS OF MANUFACTURER

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11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

CT-20 Permission No. IMP/BIO/20/000008 dated 21-FEB 2020

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