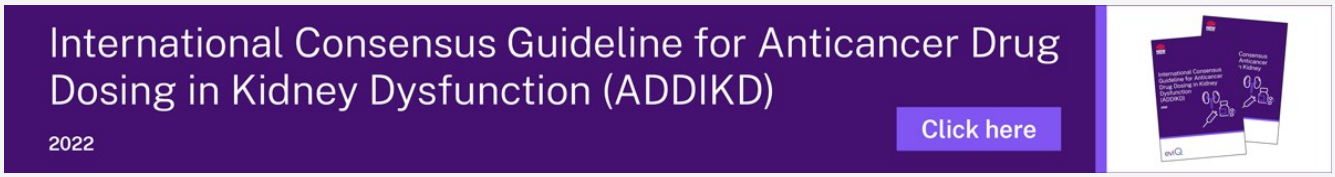
# Metastatic nivolumab maintenance (flat dosing) following ipilimumab and nivolumab

**ID: 3677** v.6 **Endorsed**

Treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer using immunological agents. Before commencing immunotherapy treatment in any patient, clinicians should have an understanding of the immune-related adverse events (irAEs) associated with immunotherapy treatment and their management.

Check for clinical trials in this patient group. Link to Australian Clinical Trials website

The anticancer drug(s) in this protocol may have been included in the ADDIKD guideline. Dose recommendations in kidney dysfunction have yet to be updated to align with the ADDIKD guideline. Recommendations will be updated once the individual protocol has been evaluated by the reference committee. For further information refer to the ADDIKD guideline. To assist with calculations, use the eviQ Estimated Glomerular Filtration Rate (eGFR) calculator.




**Related pages:**

- Melanoma metastatic ipilimumab and nivolumab (induction)
- Renal cell metastatic ipilimumab and nivolumab (induction)
- Metastatic nivolumab maintenance (weight based dosing) following ipilimumab and nivolumab SUPERSEDED

## Treatment schedule - Overview

### Cycle 1 and further cycles

| Drug | Dose | Route | Day |
|---|---|---|---|
| Nivolumab | 480 mg * | IV infusion | 1 |

- * Alternative dosing schedule 240 mg every 14 days[1,2]
- If using 4 weekly maintenance dosing, commence maintenance treatment 6 weeks after the last dose of ipilimumab/nivolumab induction.
- If using 2 weekly maintenance dosing, commence maintenance treatment 3 weeks after the last dose of ipilimumab/nivolumab induction.

**Frequency:** 28 days

**Cycles:** Continuous until disease progression or unacceptable toxicity. Treatment cessation after 2 years of therapy may be considered.

**Notes:**

- In clinical trials patients could be treated after progression, provided that they had a clinical benefit and did not have substantial adverse effects, as assessed by the investigator.
- Patients should be assessed for tumour response after 12 weeks i.e. after induction treatment with combination of ipilimumab and nivolumab.
- In the first few months after the start of immunotherapy, some patients can experience transient tumour flare (termed "pseudo progression" or an immune response). This may manifest as growth of existing lesions or the development of new lesions prior to later tumour regression. While this is rare (~5%), continuing treatment and performing a second scan 4 to 6 weeks later to confirm progression may be considered, particularly if the patient remains well.
- Radiation recall has been observed with PD1 inhibitors, consideration should be given to the timing when starting this

treatment after a prolonged course of radiation therapy.

**Drug status:** Nivolumab is PBS authority

**Cost:** ~ $9,560 per cycle

## Treatment schedule - Detail

*The supportive therapies (e.g. antiemetics, premedications, etc.), infusion times, diluents, volumes and routes of administration, if included, are listed as defaults. They may vary between institutions and can be substituted to reflect individual institutional policy.*

*Antiemetics if included in the treatment schedule are based upon recommendations from national and international guidelines. These are **defaults only** and may be substituted to reflect individual institutional policy. Select here for recommended doses of alternative antiemetics.*

### Cycle 1 and further cycles

| Day 1 | | |
|---|---|---|
| Nivolumab | 480 mg (IV infusion) | in 50 mL to 100 mL sodium chloride 0.9% over 30 minutes |

- Alternative dosing schedule 240 mg every 14 days[1,2]
- If using 4 weekly maintenance dosing, commence maintenance treatment 6 weeks after the last dose of ipilimumab/nivolumab induction.
- If using 2 weekly maintenance dosing, commence maintenance treatment 3 weeks after the last dose of ipilimumab/nivolumab induction.

**Frequency:** 28 days

**Cycles:** Continuous until disease progression or unacceptable toxicity. Treatment cessation after 2 years of therapy may be considered.

## Treatment schema - Melanoma

| | |
|---|---|
| **Induction (part 1)** | Ipilimumab and nivolumab every 3 weeks (for 4 doses only). |
| **Maintenance (part 2) - weight based dosing (SUPERSEDED)** | Nivolumab every 2 weeks (weight based dosing). Continuous until disease progression or unacceptable toxicity. |
| **OR** | |
| **Maintenance (part 2) - flat dosing** | Nivolumab every 2 or 4 weeks (flat dosing). Continuous until disease progression or unacceptable toxicity. |

This protocol is the maintenance (flat dosing) part of the ipilimumab and nivolumab followed by nivolumab regimen.

If using 4 weekly maintenance dosing, commence maintenance treatment 6 weeks after the last dose of ipilimumab/nivolumab induction.

If using 2 weekly maintenance dosing, commence maintenance treatment 3 weeks after the last dose of ipilimumab/nivolumab induction.

## Treatment schema - Renal cell

| | |
|---|---|
| **Induction (part 1)** | Ipilimumab and nivolumab every 3 weeks (for 4 doses only). |
| **Maintenance (part 2) - weight based dosing (SUPERSEDED)** | Nivolumab every 2 weeks (weight based dosing). Continuous until disease progression or unacceptable toxicity. |
| **OR** | |

| | |
|---|---|
| **Maintenance (part 2) - flat dosing** | Nivolumab every 2 or 4 weeks (flat dosing). Continuous until disease progression or unacceptable toxicity. |

This protocol is the maintenance (flat dosing) part of the ipilimumab and nivolumab followed by nivolumab regimen.

If using 4 weekly maintenance dosing, commence maintenance treatment 6 weeks after the last dose of ipilimumab/nivolumab induction.

If using 2 weekly maintenance dosing, commence maintenance treatment 3 weeks after the last dose of ipilimumab/nivolumab induction.

## Indications and patient population - Melanoma

### Indications:

- Unresectable stage III or stage IV metastatic malignant melanoma following ipilimumab/nivolumab induction.

### Precautions:

If any of these conditions are present, clinical judgement should be used and individual cases discussed with an expert in the field as indicated:

- significant autoimmune disease (e.g. myasthenia gravis, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, autoimmune ocular disease)
- organ transplantation
- previous history of viral hepatitis
- HIV/acquired immune deficiency syndrome (AIDS)
- previous radiation to the lungs.

## Indications and patient population - Renal cell

### Indications:

- First line treatment of advanced unresectable or metastatic intermediate to poor risk clear cell renal cell carcinoma, following ipilimumab/nivolumab induction.

### Precautions:

If any of these conditions are present, clinical judgement should be used and individual cases discussed with an expert in the field as indicated:

- significant autoimmune disease (e.g. myasthenia gravis, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, autoimmune ocular disease)
- organ transplantation
- previous history of viral hepatitis
- HIV/acquired immune deficiency syndrome (AIDS)
- previous radiation to the lungs.

## Clinical information

| | |
|---|---|
| **Venous access required** | IV cannula (IVC) or central venous access device (CVAD) is required to administer this treatment.<br>Read more about central venous access device line selection |

| | |
|---|---|
| **Emetogenicity MINIMAL** | No antiemetics should be routinely administered before treatment in patients without a history of nausea and vomiting. If patients experience nausea and/or vomiting, consider using the low antiemetic prophylaxis regimen.<br>Read more about preventing anti-cancer therapy induced nausea and vomiting |
| **Immune-related adverse events (irAEs)** | Immune-related adverse events (irAEs) can occur early and escalate quickly in patients receiving immune checkpoint inhibitors. irAEs can also occur after discontinuation of treatment. Fatalities have been reported. Management of irAEs is largely based on expert opinion and consensus guidelines.<br>Examples of irAEs with high risk of mortality include:<br>• cardiac toxicity: myocarditis<br>• musculoskeletal toxicity: myositis<br>• neurological toxicity: encephalitis, Guillain-Barré syndrome, myelitis, myasthenia gravis<br>• pulmonary toxicity: pneumonitis<br>• skin toxicity: Stevens-Johnson syndrome, toxic epidermal necrolysis.<br><br>Examples of irAEs in order of frequency include:<br>• Common<br>◦ endocrinopathies: thyroid dysfunction<br>◦ gastrointestinal toxicity: diarrhoea<br>◦ musculoskeletal toxicity: arthralgia, myalgia<br>◦ skin toxicity: rash, erythema, pruritus<br>• Less common<br>◦ endocrinopathies: hypophysitis, type I diabetes mellitus<br>◦ gastrointestinal toxicity: colitis<br>◦ musculoskeletal toxicity: inflammatory arthritis<br>◦ ocular toxicity: dry eye<br>◦ renal toxicity<br>◦ skin toxicity: vitiligo<br>• Rare<br>◦ endocrinopathies: primary adrenal insufficiency<br>◦ gastrointestinal toxicity: pancreatitis<br>◦ haematological toxicity<br>◦ musculoskeletal toxicity: vasculitis<br>◦ ocular toxicity: uveitis, iritis.<br><br>Proactive monitoring, patient self-monitoring and early reporting of adverse events is critical. Treatment interruptions/discontinuation, consultation with specialist and administration of corticosteroids and/or supportive care is required to minimise the risk of death.<br>Read more about the management of immune-related adverse events (irAEs) |
| **Baseline investigations** | Consider ECG and troponin at baseline. There is no clear evidence regarding the efficacy/value of baseline ECG or troponin in patients receiving immune checkpoint inhibitor therapy. Some cancer specialists obtain baseline testing, and others continue this through the initial period of therapy. Consider urinalysis at baseline, particularly in patients with additional risk factors for developing immune-related acute kidney injury. |
| **Blood tests** | FBC, EUC, eGFR, LFTs, serum cortisol, TFTs and BSL at baseline.<br>Repeat FBC, EUC, eGFR, LFTs and BSL prior to each cycle and serum cortisol and TFTs alternate cycles. Check lipase and amylase if symptomatic of pancreatitis.<br>In the absence of suspicion of immune-related adverse events less frequent monitoring may be applicable, according to institutional guidelines. Evidence for the frequency of routine blood testing with immunotherapies varies within published studies and guidelines.<br>Read more about immunotherapy blood test monitoring recommendations. |

| | |
|---|---|
| **Hepatitis and HIV** | Hepatitis screening is recommended in all patients who are to receive immune checkpoint inhibitors.<br>Immunotherapy is associated with inflammatory adverse reactions resulting from increased or excessive immune activity and patients are at risk of developing autoimmune hepatitis. It should be used with caution in patients who have a history of chronic hepatic infections (hepatitis B and C), detectable human immunodeficiency virus (HIV) viral load or acquired immune deficiency syndrome (AIDS). |
| **Vaccinations** | The safety of having vaccinations during treatment is unknown. Patients in the clinical trials were typically allowed to receive inactivated and recombinant vaccines but not live vaccines.<br>Read more about COVID-19 vaccines and cancer. |
| **Effects of cancer treatment on fertility** | Studies to evaluate the effects of immune checkpoint inhibitor therapy on fertility have not been performed. Therefore, the effect on male and female fertility is unknown. Limited evidence supports that immune checkpoint inhibitor-related hypogonadism due to orchitis and hypophysitis can impact fertility. Immune checkpoint inhibitors can cause fetal harm when given to pregnant women. A pregnancy test should be considered in females of reproductive potential if sexually active. It is important that all patients of reproductive potential use effective contraception whilst on therapy and after treatment finishes. There is very limited evidence to provide guidance regarding contraception timelines. Some studies have demonstrated PD-1 receptor occupancy for greater than 9 months after anti-PD-1 therapy (Brahmer et al., 2010). As a result, some cancer specialists advise using contraception for at least six months or even as long as two years after treatment finishes.<br>Read more about the effect of cancer treatment on fertility<br>Link to Brahmer et al., 2010 |

## Dose modifications

The dose recommendations in kidney dysfunction (i.e.renal impairment) displayed may not reflect those in the ADDIKD guideline and have been included for historical reference only. Recommendations will be updated once the individual protocol has been evaluated by the reference committee, with this version of the protocol then being archived. Clinicians are expected to refer to the ADDIKD guideline prior to prescribing in kidney dysfunction.
**International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD)**.

- Dose reduction is not recommended
- No dose adjustment is required in the elderly, mild or moderate renal impairment or mild hepatic impairment. Immune checkpoint inhibitors have not been studied in patients with severe renal impairment or moderate to severe hepatic impairment.

### Management of immune-related adverse events (irAEs)

Link to Management of immune-related adverse events (irAEs)

## Interactions

*The drug interactions shown below are not an exhaustive list. For a more comprehensive list and for detailed information on specific drug interactions and clinical management, please refer to the specific drug product information and the following key resources:*

- *MIMS - interactions tab (includes link to a CYP-450 table) (login required)*
- *Australian Medicines Handbook (AMH) – interactions tab (login required)*
- *Micromedex Drug Interactions (login required)*
- *Cancer Drug Interactions*
- *Cytochrome P450 Drug Interactions*

*For more information see References & Disclaimer .*

| Nivolumab | | |
|---|---|---|
| No formal pharmacokinetic drug interaction studies have been conducted with nivolumab. | | |
| | **Interaction** | **Clinical management** |
| **Immunosuppressants (inc. corticosteroids)** | Reduced efficacy of both immunosuppressants and nivolumab possible due to pharmacodynamic interaction | It is recommended that patients requiring corticosteroids **prior** to treatment receive the lowest possible dose (preferably no greater than 10 mg prednisolone or equivalent steroid per day). **Once started** on nivolumab the use of corticosteroids to treat immune related adverse events (irAEs) does not appear to impact the clinical response to nivolumab. In patients requiring ongoing corticosteroids **post management** of an irAE, the dose should be as low as possible.<br><br>Monitor for signs of organ rejection in transplant recipients. |
| **Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)** | Additive nephrotoxicity | Avoid combination or monitor kidney function closely |

## Administration

*eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual product information monographs via the TGA website for further information.*

### Day 1

**Approximate treatment time: 60 minutes**

Handling of monoclonal antibodies and waste management

Safe administration

Immunotherapy patient assessment prior to each treatment.

Any toxicity may require delay of treatment and review by medical officer before commencing treatment.

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

#### Pre treatment medication

Administer antiemetics if required

#### Treatment - Time out

#### Nivolumab

**Administer nivolumab:**

- a low protein binding 0.2 micron or 1.2 micron inline filter should be used
- via IV infusion over 30 minutes
- observe for infusion-related reactions
- flush with 50 mL of sodium chloride 0.9%.

**Mild or moderate infusion-related reaction:**

- decrease the rate of infusion and monitor closely
- give any further doses with close monitoring
- premedication with paracetamol and an antihistamine should be considered for further doses.

**Severe infusion-related reaction:**

- stop infusion immediately
- medical officer review.

Remove IV cannula and/or deaccess TIVAD or CVAD.

## Discharge information

### Patient information

- Ensure patient receives patient information sheet.

## Side effects

*The side effects listed below are not a complete list of all possible side effects for this treatment. Side effects are categorised into the approximate onset of presentation and should only be used as a guide.*

The most common side effects with this treatment are immune-related adverse events (irAEs). irAEs can escalate quickly and close monitoring of the patient is required. Symptoms should improve promptly after the introduction of immunosuppressive therapy. If this does not occur review the diagnosis and seek further specialist advice. Refer to the Management of immune related adverse events document for further information.

| Immune related adverse events | |
|---|---|
| **Cardiotoxicity** | Cardiotoxicity is a rare but serious side effect, which may manifest as asymptomatic reduction in left ventricular ejection fraction (LVEF), arrhythmia, cardiomyopathy, myocarditis, pericarditis, cardiac fibrosis, hypertension, cardiac ischaemia, congestive heart failure (CHF) and cardiac arrest.<br>Read more about Management of immune related adverse events. |
| **Gastrointestinal toxicity** | Colitis, diarrhoea or more bowel movements than usual; blood or mucous in stools; dark, tarry, sticky stools; abdominal pain or tenderness.<br>Read more about Management of immune related adverse events |
| **Haematological toxicity** | Autoimmune haemolytic anaemia (AIHA), acquired thrombotic thrombocytopenic purpura (TTP), aplastic anaemia (AA), immune thrombocytopenia (ITP), acquired haemophilia (AH), haemolytic uremic syndrome (HUS) and lymphopenia are rare but potentially serious immune-related adverse events associated with immunotherapy treatment.<br>Read more about Management of immune related adverse events. |
| **Hepatotoxicity** | Transaminase and total bilirubin elevation, jaundice, severe nausea or vomiting, pain on the right side of the abdomen, drowsiness, dark urine, bleeding or bruising more easily than normal, anorexia.<br>Read more about Management of immune related adverse events. |
| **Musculoskeletal toxicity** | Inflammatory arthritis, temporal arteritis, arthralgia, myalgia, synovitis, vasculitis, polymyalgia-like syndrome and myositis.<br>Read more about Management of immune related adverse events. |
| **Neurological toxicity** | Aseptic meningitis, myasthenia gravis, Guillain-Barre syndrome, encephalitis, meningeal symptoms, optic neuritis, neuropathy and acute inflammatory demyelinating polyneuropathy are infrequent but potentially serious immune-related adverse events associated with immunotherapy treatment.<br>Read more about Management of immune related adverse events. |
| **Ocular toxicity** | Eye pain, blurred vision, Uveitis/iritis, episcleritis, blepharitis, optic neuritis, tear duct stenosis, conjunctivitis, hyperlacrimation, watery or dry eyes and photophobia.<br>Read more about Management of immune related adverse events. |
| **Other endocrinopathies** | Type 1 diabetes mellitus, hypophysitis, hypopituitarism and adrenal insufficiency are infrequent but potentially serious immune-related adverse events associated with immunotherapy treatment.<br>Read more about Management of immune related adverse events |
| **Pulmonary toxicity** | Radiographic changes, dyspnoea, new or worsening cough, hypoxia, tachycardia, chest pain or fever.<br>Read more about Management of immune related adverse events. |
| **Renal toxicity** | Increase in serum creatinine, oliguria, haematuria, peripheral oedema and anorexia.<br>Read more about Management of immune related adverse events. |
| **Skin toxicity** | Rash including full thickness, pruritus, skin blisters, ulceration and necrosis. Radiation recall can occur at site of previous radiation therapy. Symptoms include vesiculation, desquamation and ulceration of the skin.<br>Read more about Management of immune related adverse events |
| **Thyroid toxicity** | Thyroid toxicity is common with immune checkpoint inhibitors. Hypothyroidism is most frequent however hyperthyroidism can also occur.<br>Read more about Management of immune related adverse events |

| Non-immune related adverse events | |
|---|---|
| **Anorexia** | Loss of appetite accompanied by decreased food intake.<br>Read more about anorexia |
| **Fatigue** | Read more about fatigue |
| **Headache** | |
| **Nausea and vomiting** | Read more about prevention of treatment induced nausea and vomiting |

## Evidence - Flat dosing

The evidence for flat as opposed to weight based dosing for nivolumab comes from pharmacokinetic modelling papers by Long et al[1] and Zhao et al.[2]

The Long study compared pharmacokinetic (PK) data for flat dose 480 mg every 4 weeks to 3 mg/kg every 2 weeks and 240 mg 2 every weeks.[1] Zhou et al studied flat dose 240 mg every 2 weeks compared with the standard 3 mg/kg every 2 weeks.[2] Both studies used population PK modelling and simulation to compare nivolumab PK exposure and also evaluated the clinical safety of the various regimens.

In the Long paper data from clinical trials including 3817 patients across multiple tumour streams (including renal cell cancer, non small cell lung cancer, squamous cell cancer of head and neck, urothelial cancer, small cell lung cancer, hepatocellular cancer, colorectal cancer and gastric cancer) were pooled into a PK dataset. The results of the predicted steady state PK exposures in the flat dosing (480 mg every 4 weeks and 240 mg every 2 weeks) were compared with those already approved for the 3 mg/kg every 2 weeks regimen. Safety analysis was also performed in the following patient populations- advanced melanoma, renal cell cancer, non-squamous and squamous non small cell lung cancer who transitioned to 4 weekly dosing from 2 weekly or from the comparator arm in four phase III trials, CheckMate 066, 025, 057 and 017.[1]

Nivolumab PK exposure values were found to be comparable. Serum concentrations in the 480 mg every 4 weeks regimen rapidly approached steady state after the first month and remained at this level for the duration of the treatment. Similar time-averaged concentration, approximately 16% lower trough concentration and 45% higher peak concentration at steady state was produced with 480mg flat dose.

Clinical safety data was available for 61 patients from the phase III trials who transitioned from nivolumab dosing of 3 mg/kg to 480 mg every 4 weeks, which showed a comparable incidence of treatment related adverse events to those within the weight based dosing regimen and was consistent with other studies.[1]

The incidence of serious adverse events was comparable between body weight groups with no increase in the low body weight group. There were no reported infusion related reactions or adverse events resulting in treatment discontinuation or death.[1]

Similar conclusions for safety and efficacy were made in the Zhou study which compared flat dose 240 mg every 2 weeks with 3mg/kg every 2 weeks regimen.[2]

**Summary of treatment related adverse events[1]**

**Table 2. Summary of TRAEs during weight-based nivolumab treatment across CheckMate 066, 025, 057, and 017, and the pooled patient cohort that transitioned to nivolumab 480 mg Q4W[a]**

| *N* (%) | 3 mg/kg Q2W | | | | 480 mg Q4W |
|---|---|---|---|---|---|
| | CheckMate 066 [9] (*N* = 206) | CheckMate 025 [10] (*N* = 406) | CheckMate 057 [11] (*N* = 287) | CheckMate 017 [12] (*N* = 131) | Pooled cohort (*N* = 61) |
| Number of nivolumab doses received, median, *N* | 12 | 12 | 6 | 8 | 3[b] |
| TRAEs (all grades) | 153 (74.3) | 319 (78.6) | 199 (69.3) | 76 (58.0) | 9 (14.8) |
| Grades 3–4 | 24 (11.7) | 76 (18.7) | 30 (10.5) | 9 (6.9) | 1 (1.6)[c] |
| Treatment-related SAEs (all grades) | 19 (9.2) | 47 (11.6) | 21 (7.3) | 9 (6.9) | 1 (1.6) |
| Grades 3–4 | 12 (5.8) | 32 (7.9) | 15 (5.2) | 3 (2.3) | 1 (1.6)[c] |
| TRAEs leading to discontinuation (all grades) | 5 (2.4) | 31 (7.6) | 14 (4.9) | 4 (3.1) | 0 |
| Grades 3–4 | 4 (1.9) | 19 (4.7) | 11 (3.8) | 2 (1.5) | 0 |
| Treatment-related deaths | 0 | 0 | 1 (0.3)[d] | 0 | 0 |

[a]Pooled data include patients in CheckMate 066, 025, 057, and 017 who transitioned to nivolumab 480 mg Q4W after receiving nivolumab 3 mg/kg Q2W.
[b]Mean duration of exposure to nivolumab 480 mg Q4W was 2.06 months, with 19.7% of patients treated with nivolumab for longer than 3 months. Nearly 92% of patients had a relative dose intensity greater than 90%.
[c]One patient with a body weight ≥70 and <90 kg experienced an SAE of grade 3 renal failure.
[d]Cause of death was encephalitis attributed to nivolumab.
Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; TRAE, treatment-related adverse event.

## Evidence - Melanoma

The evidence supporting this protocol is provided by three trials, CheckMate 067, CheckMate 069 and ABC. In the phase 3 double-blinded, multicentre, international, randomised trial CheckMate 067. In this trial, 945 eligible patients with previously untreated unresectable stage III or IV melanoma were randomised in a 1:1:1 ratio to receive either nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone.[3]

From July 2013 through to March 2014, a total of 1296 patients were enrolled at 137 centres worldwide. A total of 945 eligible patients underwent randomisation: 316 patients were assigned to the nivolumab group and received 3 mg/kg of nivolumab every 2 weeks (plus ipilimumab-matched placebo), 314 patients in the nivolumab plus ipilimumab group received 1 mg/kg of nivolumab every 3 weeks plus 3 mg/kg of ipilimumab every 3 weeks for 4 doses, followed by 3 mg/kg of nivolumab every 2 weeks as maintenance treatment, and 315 patients in the ipilimumab group received 3 mg/kg of ipilimumab every 3 weeks for 4 doses (plus nivolumab-matched placebo).[3] Baseline characteristics were balanced across the three groups. Treatment was continued until disease progression or unacceptable toxicity.

The co-primary end points were progression-free survival (PFS) and overall survival (OS). Secondary end points were objective response rate (ORR), tumour PD-L1 expression as a predictive biomarker for efficacy outcomes, and safety. This study was not powered to compare nivolumab monotherapy with nivolumab plus ipilimumab.[3]

CheckMate 069 is a double-blind phase 2 study involving 142 patients with previously untreated stage III or IV melanoma. In this study patients were randomly assigned in a 2:1 ratio to receive ipilimumab (3 mg/kg) combined with either nivolumab (1 mg/kg) or placebo once every 3 weeks for four doses, followed by nivolumab (3 mg/kg ) or placebo every 2 weeks until the occurrence of disease progression or unacceptable toxic effects. Randomisation was stratified according to BRAF mutation status (V600 wild type vs mutation-positive).[4]

The primary end point was the rate of investigator-assessed, confirmed ORR among patients with BRAF V600 wild-type tumours. Secondary end points included investigator-assessed PFS in patients with BRAF wild-type tumours, the ORR and PFS among patients with BRAF V600 mutation–positive tumours, and safety.[4]

Patients with active brain metastases or leptomeningeal disease were previously excluded from clinical trials. The ABC (Anti-PD1 Brain Collaboration) trial provides data on activity of immunotherapy in brain metastasis. Immunotherapy-naïve patients with at least one brain metastasis between 5 and 40 mm with no prior local brain therapy were randomized to nivolumab or combination nivolumab-ipilimumab. Patients with brain metastases in whom local therapy had failed, or who had neurological symptoms, or leptomeningeal disease were enrolled in a third non-randomised cohort receiving nivolumab alone. The primary endpoint was intracranial response from week 12.[5]

### Efficacy

**CheckMate 067**

After a median follow-up ranging from 18.6 to 38.0 months across the three groups, the median PFS was 11.5 months (95% CI 8.7-19.3) in the nivolumab+ipilimumab group and 6.9 months (95% CI 5.1-9.7) in the nivolumab group, as compared with 2.9 months (95% CI 2.8-3.2) in the ipilimumab group. The hazard ratio for progression or death was 0.43 (95% CI 0.35-0.52) with nivolumab+ipilimumab vs ipilimumab (p<0.001) and was 0.55 (95% CI 0.45-0.66) with nivolumab vs ipilimumab (p<0.001). The rate of PFS at 3 years was 39% in the nivolumab+ipilimumab group and 32% in the nivolumab group as compared with 10% in the ipilimumab group[6]

At a minimum follow-up of 60 months, the median OS had not been reached (NR) in the nivolumab+ipilimumab group and was 36.9 months in the nivolumab group, compared with 19.9 months in the ipilimumab group (HR=0.52; 95% CI 0.42-0.64; p<0.001 with nivolumab+ipilimumab vs ipilimumab; HR=0.63, 95% CI 0.52-0.76; p<0.001 with nivolumab vs ipilimumab). The OS rate at 5 years was 52% in the nivolumab+ipilimumab group and 44% in the nivolumab group, compared with 26% in the ipilimumab group.[7]

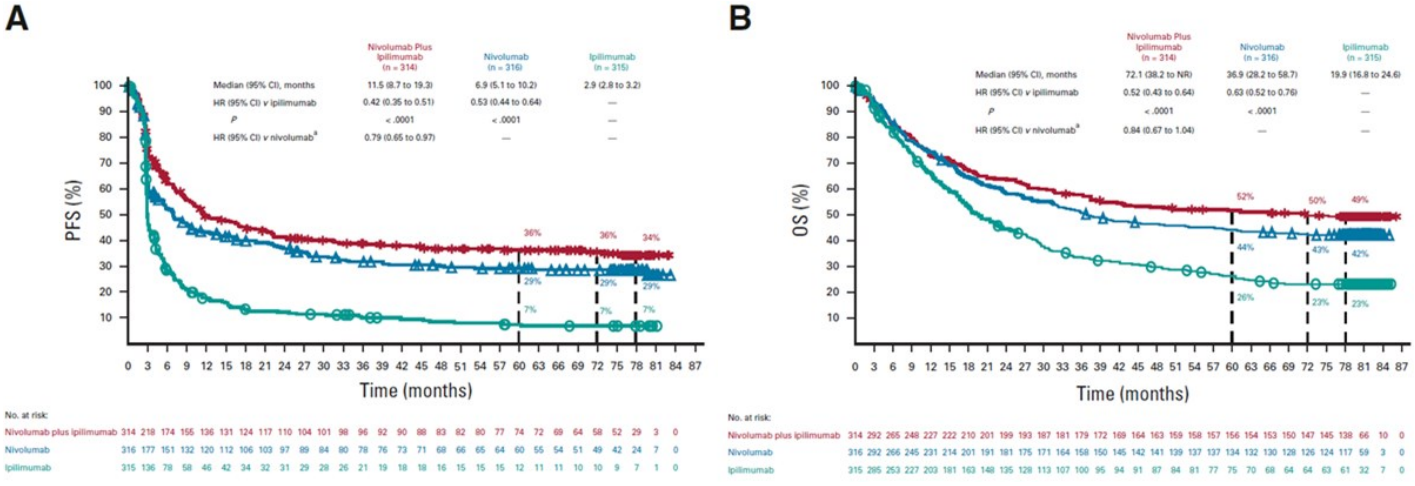
At a minimum follow-up of 77 months, the median OS was 72.1 months (95% CI 38.2-NR) in the combination therapy arm as compared with 36.9 months (95% CI 28.2-58.7) and 19.9 months (95% CI 16.8-24.6) in the nivolumab and ipilimumab arms, respectively (HR=0.52; 95% CI 0.43-0.64; p<0.0001 for combination therapy vs ipilimumab alone, HR=0.84; 95% CI 0.67-1.04 for combination therapy vs nivolumab alone and HR=0.63; 95% CI 0.52-0.76; p<0.0001 for nivolumab vs ipilimumab). 6.5-year OS rates were 49%, 42% and 23% in the nivolumab+ipilimumab, nivolumab and ipilimumab groups, respectively. PFS was 11.5 months (95% CI 8.7-19.3), 6.9 months (95% CI 5.1-10.2) and 2.9 months (95% CI 2.8-3.2) in the three groups, respectively.[8]

The phase II CheckMate 069 study showed similar efficacy and toxicity for patients receiving combination ipilumumab/nivolumab and ipilimumab monotherapy respectively.[4]

| Response to treatment[8] | Nivolumab (n=316) | Nivolumab + ipilimumab (n=314) | Ipilimumab (n=315) |
|---|---|---|---|
| **Complete response (%)** | 19 | 23 | 6 |
| **Partial response (%)** | 26 | 36 | 13 |
| **Stable disease (%)** | 9 | 12 | 22 |
| **Progressive disease (%)** | 38 | 24 | 50 |
| **Unknown (%)** | 8 | 6 | 9 |
| **ORR (%, 95% CI)** | 45 (39–51) | 58 (53–64) | 19 (15–24) |
| **Median duration of response (months, 95% CI)** | NR (45.7-NR) | NR (61.9-NR) | 19.2 (8.8-47.4) |

*NR= Not reached*

**Kaplan Meier curves for (A) overall survival and (B) progression-free survival[8]**

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**ABC study**

With a median follow up of 17 months, intracranial responses were achieved by 16 (46%) of 35 patients treated with combined nivolumab + ipilimumab, five (20%) of 25 patients treated with nivolumab monotherapy and one (6%) of 16 patients with poor prognostic features (neurological symptoms, progression after previous local brain treatment or leptomeningeal disease) treated with nivolumab monotherapy.[5]

## Toxicity

**CheckMate 067**

Treatment-related adverse events were reported in 96% of the patients treated with combination therapy, 86% of those treated with nivolumab, and 86% of those treated with ipilimumab. Grade 3 or 4 adverse events occurred in 59%, 21%, and 28%, respectively. Treatment-related adverse events of any grade that led to the discontinuation of therapy occurred more frequently with combination therapy (39%) than with either monotherapy (12% nivolumab, 16% ipilimumab).[6]

The most common select adverse events of grade 3 or 4 were gastrointestinal events, which occurred in 15% of the patients who received combination therapy, in 4% of those who received nivolumab monotherapy, and in 12% of those who received ipilimumab monotherapy (specifically, diarrhoea in 9%, 3%, and 6% of patients respectively).[6]

There were two deaths related to a study drug within 100 days of the last dose: one death due to neutropenia (nivolumab group) and one due to colon perforation (ipilimumab group). There were two deaths considered to be related to a study drug (>100 days after the last dose) in the combination therapy group: one due to autoimmune myocarditis (approximately 2 months after receiving a single dose of anti-PD1 outside the context of the trial) and one due to liver necrosis.[6]

At the time of 6.5-year analysis, grade 3/4 treatment-related adverse events were reported in 59% of patients treated with combination therapy as compared with 24%, and 28% in the nivolumab and ipilimumab groups, respectively. No new safety signals were detected.[8]

**Adverse events**[6]

**Table 2. Treatment-Related Adverse Events.***

| Event | Nivolumab plus Ipilimumab (N=313) | | Nivolumab (N=313) | | Ipilimumab (N=311) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| | *number of patients with event (percent)* | | | | | |
| Any treatment-related adverse event | 300 (96) | 184 (59) | 270 (86) | 67 (21) | 268 (86) | 86 (28) |
| Rash | 93 (30) | 10 (3) | 72 (23) | 1 (<1) | 68 (22) | 5 (2) |
| Pruritus | 112 (35) | 6 (2) | 67 (21) | 1 (<1) | 113 (36) | 1 (<1) |
| Vitiligo | 28 (9) | 0 | 29 (9) | 1 (<1) | 16 (5) | 0 |
| Maculopapular rash | 38 (12) | 6 (2) | 15 (5) | 2 (1) | 38 (12) | 1 (<1) |
| Fatigue | 119 (38) | 13 (4) | 114 (36) | 3 (1) | 89 (29) | 3 (1) |
| Asthenia | 30 (10) | 1 (<1) | 25 (8) | 1 (<1) | 17 (5) | 2 (1) |
| Pyrexia | 60 (19) | 2 (1) | 21 (7) | 0 | 21 (7) | 1 (<1) |
| Diarrhea | 142 (45) | 29 (9) | 67 (21) | 9 (3) | 105 (34) | 18 (6) |
| Nausea | 88 (28) | 7 (2) | 41 (13) | 0 | 51 (16) | 2 (1) |
| Vomiting | 48 (15) | 7 (2) | 22 (7) | 1 (<1) | 24 (8) | 1 (<1) |
| Abdominal pain | 26 (8) | 1 (<1) | 18 (6) | 0 | 28 (9) | 2 (1) |
| Colitis | 40 (13) | 26 (8) | 7 (2) | 3 (1) | 35 (11) | 24 (8) |
| Headache | 35 (11) | 2 (1) | 24 (8) | 0 | 25 (8) | 1 (<1) |
| Arthralgia | 43 (14) | 2 (1) | 31 (10) | 1 (<1) | 22 (7) | 0 |
| Increased lipase level | 44 (14) | 34 (11) | 27 (9) | 14 (4) | 18 (6) | 12 (4) |
| Increased amylase level | 26 (8) | 9 (3) | 20 (6) | 6 (2) | 15 (5) | 4 (1) |
| Increased aspartate aminotransferase level | 51 (16) | 19 (6) | 14 (4) | 3 (1) | 12 (4) | 2 (1) |
| Increased alanine aminotransferase level | 60 (19) | 27 (9) | 13 (4) | 4 (1) | 12 (4) | 5 (2) |
| Decreased weight | 19 (6) | 0 | 10 (3) | 0 | 4 (1) | 1 (<1) |
| Hypothyroidism | 53 (17) | 1 (<1) | 33 (11) | 0 | 14 (5) | 0 |
| Hyperthyroidism | 35 (11) | 3 (1) | 14 (4) | 0 | 3 (1) | 0 |
| Hypophysitis | 23 (7) | 5 (2) | 2 (1) | 1 (<1) | 12 (4) | 5 (2) |
| Decreased appetite | 60 (19) | 4 (1) | 36 (12) | 0 | 41 (13) | 1 (<1) |
| Cough | 25 (8) | 0 | 19 (6) | 2 (1) | 15 (5) | 0 |
| Dyspnea | 36 (12) | 3 (1) | 19 (6) | 1 (<1) | 12 (4) | 0 |
| Pneumonitis | 22 (7) | 3 (1) | 5 (2) | 1 (<1) | 5 (2) | 1 (<1) |
| Treatment-related adverse event leading to discontinuation | 123 (39) | 95 (30) | 37 (12) | 24 (8) | 49 (16) | 43 (14) |

* Shown are treatment-related adverse events of any grade that occurred in more than 5% of the patients in any treatment group who had one or more treatment-related adverse events of grade 3 or 4. The relatedness of the adverse event to treatment was determined by the investigators. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Two deaths that were considered by the investigators to be related to a study drug occurred in the nivolumab group (neutropenia) and in the ipilimumab group (colonic perforation) within 100 days after the last dose of study drug; two additional deaths in the nivolumab-plus-ipilimumab group (one due to cardiac insufficiency and autoimmune myocarditis, and one due to liver necrosis) that were considered by the investigator to be related to a study drug were reported more than 100 days after the last dose of study drug.



## Evidence - Renal cell

The evidence supporting this protocol is provided by a phase III multicentre international randomised trial (CheckMate 214) involving 1096 patients comparing nivolumab plus ipilimumab with sunitinib alone in patients with previously untreated advanced renal cell carcinoma with a clear-cell component.[9]

Between October 2014 and February 2016, 550 patients were assigned to the nivolumab plus ipilimumab group, 3 mg/kg and 1 mg/kg respectively given every 3 weeks for 4 doses (induction phase), followed by nivolumab monotherapy 3 mg/kg given every 2 weeks (maintenance phase) until progression or discontinuation due to unacceptable toxicity. Five hundred and thirty five patients were assigned to the sunitinib group and received 50 mg orally once daily for 4 weeks of a 6 week cycle.

The co-primary endpoints were overall survival (OS), objective response rate (ORR) and progression-free survival (PFS) among patients with intermediate- or poor-risk by IMDC prognostic score criteria. Exploratory endpoints included the OS, ORR and PFS among favourable-risk patients.

## Efficacy

The efficacy outcomes of CheckMate 214 have previously been reported in primary, second and third interim analyses.[9, 10, 11]

After a minimum of 5 years follow up (median follow up 67.7 months), OS superiority was maintained with nivolumab plus ipilimumab compared to sunitinib in the intention to treat (ITT) population (HR, 0.72; 95% CI, 0.62-0.85, P<0.0001) and in the intermediate-risk/poor-risk population (HR 0.68, 95% CI, 0.58-0.81, P<0.0001). OS benefits were observed with nivolumab plus ipilimumab compared to sunitinib in ITT patients regardless of PD-L1 expression status. PFS and ORR benefits were also maintained in the ITT and intermediate-risk/poor risk patient group.[12] The results are summarised in the table below.

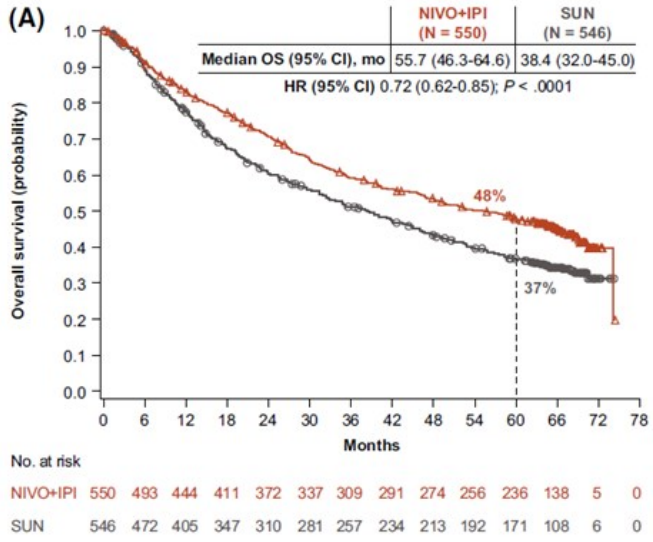
Importantly, more responses to nivolumab plus ipilimumab were complete (11.6%) and durable (63% ongoing response) compared to sunitinib (3.1% complete response, 50.3% ongoing response) in the ITT population.[12]

Exploratory analysis in patients with favourable-risk disease showed improved outcomes in the sunitinib group compared to the nivolumab plus ipilimumab group, with prolonged median PFS (28.9 months vs 12.4 months, HR=1.6; 95% CI 1.13 to 2.26; p=0.0073) and higher ORR (51.6% vs 29.6%, p=0.0002). However, more responses in the nivolumab plus ipilimumab group were complete (12.8% vs 6.5%) and durable (59.5% vs 51.6%) compared to sunitinib.[12] Ongoing follow-up and data maturation for this patient subgroup is required before definitive conclusions can be made regarding optimal therapy.

**Summary of co-primary endpoint analysis after a median follow up of 67.7 months in the ITT population and Intermediate/poor-risk disease patients[12]**

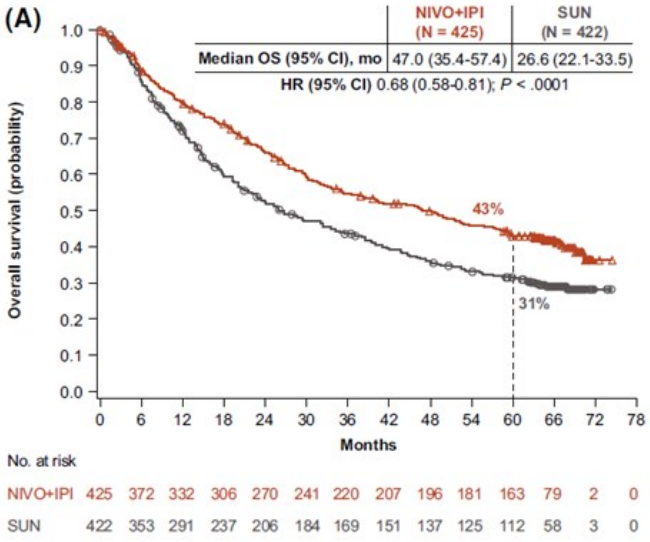
| | ITT population | | Intermediate-risk/poor-risk disease | |
|---|---|---|---|---|
| | NIVO-IPI n = 550 | SUN n = 546 | NIVO-IPI n = 425 | SUN n = 422 |
| **Median OS (months)** | 55.7 | 38.4 | 47 | 26.6 |
| | HR 0.72; (95% CI, 0.62-0.85; P<0.0001 | | HR 0.68; (95% CI, 0.38-0.81); P<0.0001 | |
| **Median PFS (months)** | 12.3 | 12.3 | 11.6 | 8.3 |
| | HR 0.86; (95% CI, 0.72-1.01); P=0.0628 | | HR 0.73; (95% CI, 0.61-0.87); P=0.0004 | |
| **ORR (%)** | 39.3 | 32.4 | 42.1 | 26.8 |
| | P=0.0055 | | P<0.0001 | |

**Kaplan-Meier curve for overall survival in ITT population[12]**



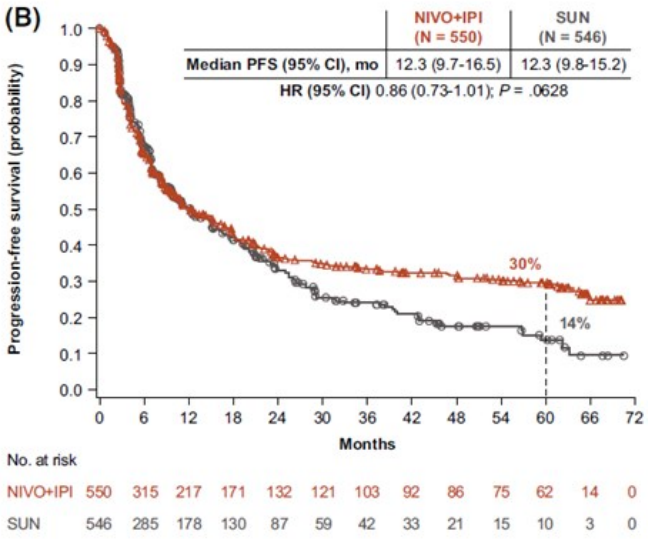



**Kaplan-Meier curve for overall survival in intermediate-risk/poor-risk disease patients[12]**



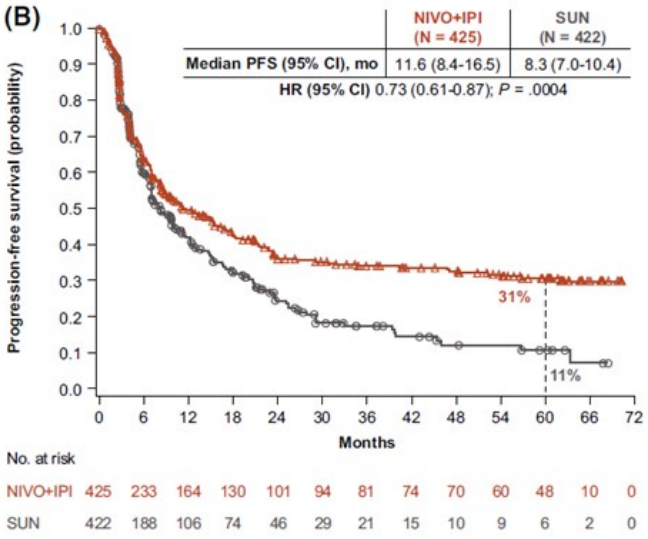



**Kaplan-Meier curve for progression-free survival in ITT population**[12]






**Kaplan-Meier curve for progression-free survival in intermediate-risk/poor-risk patients**[12]






## Toxicity

Treatment-related adverse events were reported in 94% of those who received nivolumab plus ipilimumab and 98% in those who

received sunitinib. Fewer grade 3 and 4 treatment-related adverse events were reported in those who received nivolumab plus ipilimumab (48%) compared to those who received sunitinib (64%).[12] The most common severe toxicities (grade 3 or 4) experienced in both regimens are summarised below. Severe toxicity for nivolumab plus ipilimumab tended to occur within or soon after the initial four cycle induction phase, with far fewer events during the maintenance nivolumab phase. In comparison, patients who received sunitinib experience chronic toxicity in a cumulative fashion, especially vascular-related adverse events.[10]

Treatment discontinuation due to adverse events occurred in 23% of patients in the nivolumab plus ipilimumab group vs 13% in the sunitinib group. The use of corticosteroids (> 40 mg prednisolone daily or equivalent) to manage treatment-related select adverse events occurring within 30 days of last dose in the nivolumab plus ipilimumab group was 30% (162/547).[12] There were eight (1%) treatment-related deaths reported in the nivolumab plus ipilimumab group and five (<1%) treatment-related deaths reported in the sunitinib group.[12]

**Adverse events**

| Grade 3-4 treatment-related adverse events[12] | NIVO-IPI (N = 547) | SUN (N = 535) |
|---|---|---|
| **Fatigue** | 4% | 10% |
| **Pruritis** | <1% | 0 |
| **Diarrhoea** | 4% | 6% |
| **Rash** | 2% | 0 |
| **Nausea** | 1% | 1% |
| **Lipase increased** | 12% | 7% |
| **Hypothyroidism** | <1% | <1% |
| **Arthralgia** | 1% | <1% |
| **Pyrexia** | <1% | <1% |
| **Decreased appetite** | 1% | 1% |
| **Asthenia** | 2% | 2% |
| **Vomiting** | <1% | 2% |
| **Anaemia** | <1% | 4% |
| **Stomatitis** | 0 | 3% |
| **Mucosal inflammation** | <1% | 3% |
| **Hypertension** | <1% | 17% |
| **Palmar-plantar erythrodysesthesia syndrome** | <1% | 9% |
| **Thrombocytopenia** | 0 | 4% |

** Reported between first dose and 30 days after last dose of study therapy*

| Grade 3-4 treatment-related select^ adverse events[12] | NIVO-IPI (N = 547) | SUN (N = 535) |
|---|---|---|
| **Skin** | 4% | 10% |
| **Endocrine** | 7% | <1% |
| **Gastrointestinal** | 5% | 6% |
| **Hepatic** | 9% | 4% |
| **Renal** | 1% | 1% |
| **Pulmonary** | 1% | 0 |

*^ Defined as events that might be immune-mediated*

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12 Motzer, R. J., D. F. Mcdermott, B. Escudier, et al. 2022. "Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma." Cancer 128(11): 2085-2097.


## History

### Version 6

| Date | Summary of changes |
|---|---|
| **04/09/2023** | Protocol reviewed at the urogenital reference committee meeting on 18th August 2023. Evidence section for renal cell carcinoma updated to include long term efficacy data from CheckMate 214. Version increased to V.6. Review urogenital indication in 2 years. |

### Version 5

| Date | Summary of changes |
|---|---|
| **22/08/2022** | Evidence for melanoma indication reviewed by Medical Oncology Reference Committee. Efficacy and toxicity updated with CheckMate 067 6.5 years data. Version number change to V.5. No change to next review date. |
| **20/09/2022** | Blood tests in clinical information section updated to remove information about CTLA-4 containing regimens. |

### Version 4

| Date | Summary of changes |
|---|---|

| | |
|---|---|
| **13/04/2022** | Protocol reviewed at the immunotherapy reference committee meeting held on 4th of March 2022. The following changes have been made across all immune checkpoint inhibitor protocols:<br>• Indications and patient populations- previous radiation to the lungs added to precautions.<br>• Clinical information- general irAEs, hepatitis and HIV, and fertility blocks updated. Individual irAE-related blocks removed. New block (baseline investigations) added.<br>• Patient information- pregnancy and breastfeeding block in general advice section updated.<br><br>Version number increased to V.4. Next review in 2 years. |

### Version 3

| Date | Summary of changes |
|---|---|
| **12/11/2020** | Protocol updated to align with ID 1993 Management of immune-related adverse events (irAEs) clinical resource which has been electronically reviewed and approved by the eviQ immunotherapy reference committee. The following changes have been made across all immune checkpoint inhibitor protocols:<br>• Treatment schedule - additional note added: radiation recall.<br>• Clinical information- cardiotoxicity, haematological toxicity, musculoskeletal toxicity and ocular toxicity added; rheumatological toxicity removed; immunotherapy clinical information changed to alphabetical order.<br>• Side effects- haematological added; rheumatological replaced with musculoskeletal; immunotherapy side effects changed to alphabetical order.<br><br>Arthralgia and myalgia non-irAE side effect removed to align with other immune checkpoint inhibitor protocols.<br><br>Version number increased to V.3. |

### Version 2

| Date | Summary of changes |
|---|---|
| **14/09/2020** | Protocol reviewed electronically by urogenital reference committee. Renal cell efficacy and toxicity data updated. Version number changed to V.2. |

### Version 1

| Date | Summary of changes |
|---|---|
| **14/01/2020** | New flat dosing multi-indication protocol reviewed and approved electronically by Medical Oncology Reference Committee (melanoma, urogenital) |
| **20/01/2020** | Protocol published on eviQ. Next review in 1 year. |
| **21/07/2020** | Protocol reviewed electronically by melanoma reference committee. M1c disease and elevated LDH removed from melanoma indication. Next review in 2 years. |



**First approved:** 14 January 2020
**Last reviewed:** 8 August 2022
**Review due:** 30 June 2024

***The currency of this information is guaranteed only up until the date of printing, for any updates please check:***
*https://www.eviq.org.au/p/3677*
*02 Mar 2024*

# Patient information - Metastatic - Nivolumab maintenance (flat dosing)

**Patient's name:**

## Your treatment

It is important to understand that nivolumab is not a traditional chemotherapy drug and has a different way of working. It is an immunotherapy treatment (also called anticancer drug) that works with your immune system to detect and destroy cancer cells.

This treatment may be used to treat different types of cancer. Your doctor will advise you why you are receiving this treatment.

The treatment schedule below explains how the immunotherapy drug is given.

**Nivolumab**

This treatment cycle is repeated every 28 days. It can also be repeated every 14 days at a lower dose. Your doctor will advise you of how often you will have your treatment and the number of treatments you will have. This treatment follows the 4 cycles of combination treatment of ipilimumab and nivolumab that you received every 21 days.

| Day | Treatment | How it is given | How long it takes |
|---|---|---|---|
| 1 | **Nivolumab** (*nee-vol-u-mab*) | By a drip into a vein | About 60 minutes |

**Prior to your treatment** tell your doctor if you are taking any other medicines (e.g. corticosteroids, immunosuppressive therapy), have or ever had chronic liver infections e.g. hepatitis B (HBV) or C (HCV), human immunodeficiency virus (HIV) or an organ transplant.

## When to get help

**It is important that you tell your doctor or nurse immediately if you develop any of the symptoms listed below in the side effects section. If you can't contact your doctor or nurse, go to your nearest hospital Emergency Department for help.**

**Emergency contact details**

Ask your doctor or nurse from your treating team who to contact if you have a problem

Daytime:.....

Night/weekend:.....

Other instructions:.....

.....

.....

.....

.....

.....

**During your treatment immediately** tell the doctor or nurse looking after you if you get any of the following problems:

- leaking from the area where the drugs are being given
- pain, stinging, swelling or redness in the area where the drugs are being given
- a skin rash, itching, feeling short of breath, wheezing, fever, shivers, or feeling dizzy or unwell in any way (allergic reaction).

## Other information about your treatment

### Treatment delays

There may be times when your treatment is delayed. This can happen if your doctor thinks you are likely to have severe side effects, if you get severe side effects, if your blood counts are affected and causing delays in treatment, or if you are finding it hard to cope with the treatment. Your doctor will explain if you need any delays to your treatment and the reason why.

### Blood tests and monitoring

You will need to have a blood test before you start treatment and regularly throughout your treatment. Your doctor or nurse will tell you when to have these blood tests.

### Other medications given during this treatment

- **Steroids:** you may be given some steroid tablets to help reduce immune-related side effects. Your doctor or nurse will tell you how and when to take the steroids. You may need to monitor your blood sugar levels closely while you are taking steroids. If you have diabetes, your diabetic medication may need to be adjusted because of the effects of steroids. Speak to your diabetes advisor.

## Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you. Follow the instructions below and those given to you by your doctor or nurse.

Immunotherapy may cause serious immune reactions against your own body. These are called immune-related adverse events. They may occur during your treatment, or after your treatment has ended. Immunotherapy can affect many parts of your body. Some side effects can cause severe or life threatening conditions, so even mild side effects must be reported immediately. Do not try to treat these symptoms yourself without talking to your doctor or nurse first.You will be given an information pack at the start of your treatment. This contains an alert card which you should carry with you at all times. Bring this alert card with you to hospital, especially if you are unwell or attending the emergency department.

| Immune related side effects | |
|---|---|
| **Heart problems** | • You may get:<br>◦ chest pain or tightness<br>◦ shortness of breath<br>◦ swelling of your ankles<br>◦ an abnormal heartbeat.<br>• Heart problems are uncommon but potentially fatal. If heart problems were to occur, symptoms usually start within the first 3 months of treatment, but can happen at any time even after the treatment has finished.<br>• Tell your doctor if you have a history of heart problems or high blood pressure.<br>• Before or during treatment, you may be asked to have a test to see how well your heart is working.<br>• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.** |

| | |
|---|---|
| **Bowel and stomach inflammation** | • You may get:<br>◦ bowel motions (stools, poo) that are more frequent or more liquid (diarrhoea)<br>◦ blood or mucous in your stool<br>◦ dark, tarry, or sticky bowel motions<br>◦ bloating, cramping, pain or tenderness in your stomach area.<br>• Inform your doctor or nurse immediately if you get diarrhoea<br>• Take your anti-diarrhoeal or steroid medication as directed by your doctor.<br>• Drink plenty of fluids (unless you are on a fluid restriction).<br>• Eat and drink small amounts more often.<br>• Avoid spicy foods, dairy products, high fibre foods, and coffee.<br>• **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if your diarrhoea is not controlled despite taking anti-diarrhoea medicine, severe stomach pains and bloating, and/or if you feel dizzy or light-headed.** |
| **Blood problems** | • Blood problems are infrequent but can be serious.<br>• You may feel dizzy, light-headed, tired, weak and appear more pale than usual.<br>• You may get:<br>• dark, tarry bowel motions (stools, poo)<br>• blood in your urine or not urinating as often<br>• dark-coloured urine<br>• yellowing of the whites of your eyes, and/or your skin<br>• pinpoint red spots on your skin<br>• unexplained bleeding<br>• major bruising<br>• a fever<br>• shortness of breath<br>• a severe headache<br>• confusion<br>• faster heartbeat than normal<br>• **Tell your doctor or nurse immediately or go to the nearest hospital Emergency Department if it has been longer than 12 hours since you have emptied your bladder or if you get any of the symptoms listed above.** |
| **Liver damage** | • You may get:<br>◦ fatigue<br>◦ severe nausea and vomiting<br>◦ weight loss<br>◦ bruising or bleeding more easily<br>◦ pain or tenderness on the right side of your stomach area<br>◦ dark coloured urine<br>◦ yellowing of the whites of your eyes and/or your skin<br>◦ itchy skin<br>◦ drowsiness<br>• You will have regular blood tests to check how well your liver is working.<br>• Take your steroid medication as directed by your doctor.<br>• **Tell your doctor or nurse as soon as possible if you notice that your urine is a dark colour, the whites of your eyes or skin look yellow, if you have unexplained bruising or bleeding or if you have severe stomach pain.** |
| **Muscle and joint problems** | • You may get:<br>• muscle or joint stiffness, especially after a period of rest<br>• muscle weakness<br>• pain in your muscles or joints<br>• joint swelling<br>• tiredness<br>• headaches<br>• Take your pain relief or steroid medication as directed by your doctor.<br>• **Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above.** |

| | |
|---|---|
| **Nervous system problems** | • Nervous system changes are rare, but can be serious.<br>• You may get:<br>◦ headaches<br>◦ fever<br>◦ stiff neck<br>◦ confusion or difficulty concentrating<br>◦ dizziness or drowsiness<br>◦ loss of consciousness<br>◦ muscle weakness or pain<br>◦ numbness or tingling in your hands or feet<br>◦ jerky movements.<br>• Take your steroid medication as directed by your doctor.<br>• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.** |
| **Eye problems** | • You may get:<br>◦ eye pain<br>◦ itchy eyes<br>◦ red or swollen eyes<br>◦ blurred or change in vision<br>◦ change in colour vision<br>◦ watery or gritty eyes<br>◦ dry eyes<br>◦ sensitivity to light.<br>• Protect your eyes from the weather (sun and wind) by wearing sunglasses.<br>• Use your eye drops or take your steroid medication as directed by your doctor.<br>• **Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above.** |
| **Hormone problems** | • Hormone changes are infrequent, but can be serious.<br>• You may get:<br>◦ headaches<br>◦ tiredness, dizziness or fainting<br>◦ abnormal heartbeat (faster than usual)<br>◦ a feeling of being hot or cold more easily<br>◦ excessive sweating<br>◦ weight changes<br>◦ a deepened voice<br>◦ irregular or absent periods<br>◦ nausea and vomiting<br>◦ thirsty and need to urinate more often than normal<br>◦ high blood sugar levels<br>◦ pain in your stomach area<br>◦ muscle pain or weakness<br>◦ difficulty sleeping<br>◦ agitated more easily<br>◦ changes in your mood or behaviour, such as decreased sex drive or irritability.<br>• Take your hormone or steroid medication as directed by your doctor.<br>• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you feel confused, weak, dizzy, or faint, or get sudden pain in your lower back or legs.** |

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| **Lung problems** | • You may get:<br>◦ shortness of breath<br>◦ difficulty breathing<br>◦ faster heartbeat than normal<br>◦ chest pain<br>◦ new or worsening cough<br>◦ fever.<br>• Your doctor will monitor how well your lungs are working during your treatment.<br>• Take your steroid medication as directed by your doctor.<br>• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have chest pain or become short of breath.** |
| **Kidney damage** | • This treatment can cause changes to how your kidneys work.<br>• You may get:<br>◦ a feeling of needing to urinate less often than normal<br>◦ blood in your urine<br>◦ swollen hands and feet<br>◦ loss of appetite.<br>• You will have regular blood tests to check how well your kidneys are working.<br>• You may need to drink more fluids while you are having treatment. Your doctor or nurse will tell you if you need to do this.<br>• Take your steroid medication as directed by your doctor.<br>• **Tell your doctor or nurse as soon as possible if you notice that your urine changes colour or you don't need to empty your bladder as often.** |
| **Skin rash** | • You may get<br>◦ a red rash<br>◦ a bumpy rash<br>◦ dry and itchy skin<br>◦ skin peeling or blisters.<br>◦ if you have had previous radiation therapy to an area this effect may be worse<br>• Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream.<br>• Avoid scratching your skin.<br>• Avoid wearing tight fitting clothing<br>• Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher.<br>• Take your antihistamine medication or apply your steroid cream as directed by your doctor.<br>• **Tell your doctor or nurse as soon as possible if you notice any changes to the rash like pain or pus forming.** |

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| **Thyroid problems** | Thyroid problems are common with this treatment. The most common problem is an underactive thyroid gland (hypothyroidism), occasionally you may get an overactive thyroid gland (hyperthyroidism).<br>• If you have an **underactive** thyroid, you may get:<br>◦ fatigue and low energy levels<br>◦ depression<br>◦ slow heart rate<br>◦ unexplained weight gain<br>◦ intolerance to cold temperatures<br>◦ fatigued and aching muscles<br>◦ dry, coarse skin<br>◦ puffy face<br>◦ hair loss<br>◦ constipation<br>◦ problems with concentration<br>◦ changes in your periods<br>• If you have an **overactive** thyroid, you may get<br>◦ abnormal heartbeat (faster than usual)<br>◦ a feeling of being hot or cold more easily<br>◦ excessive sweating<br>◦ difficulty sleeping<br>◦ anxiety, nervousness or agitated more easily<br>◦ diarrhoea<br>◦ changes in your periods<br>• You will have regular blood tests to check how well your thyroid is working.<br>• Take your hormone or steroid medication as directed by your doctor.<br>• Tell your doctor or nurse if you get any of the symptoms listed above. |

| Non-immune related side effects | |
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| **Appetite loss (anorexia)** | • You may not feel like eating.<br>• Try to avoid drinking fluids at meal times.<br>• Try to eat small meals or snacks regularly throughout the day.<br>• Try to eat food that is high in protein and calories.<br>• If you are worried about how much food you can eat, or if you are losing weight, ask to speak to a dietitian. |
| **Tiredness and lack of energy (fatigue)** | • You may feel very tired, have no energy, sleep a lot, and not be able to do normal activities or things you enjoy.<br>• Do not drive or operate machinery if you are feeling tired.<br>• Nap for short periods (only 1 hour at a time)<br>• Prioritise your tasks to ensure the best use of your energy.<br>• Eat a well balanced diet and drink plenty of fluids (unless you are fluid restricted).<br>• Try some gentle exercise daily.<br>• Allow your friends and family to help.<br>• **Tell your doctor or nurse if you get any of the symptoms listed above.** |
| **Headache** | • You can take paracetamol if you have a headache.<br>• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get a very bad headache that is not helped by pain medication.** |
| **Nausea and vomiting** | • You may feel sick (nausea) or be sick (vomit).<br>• Drink plenty of fluids (unless you are fluid restricted).<br>• Eat small meals more frequently.<br>• Try food that does not require much preparation.<br>• Try bland foods like dry biscuits or toast.<br>• Gentle exercise may help with nausea.<br>• Anti-sickness medication is usually not needed but may help in some people.<br>• Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer treatment.<br>• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have uncontrolled vomiting or feel dizzy or light-headed.** |

## General advice for people having cancer treatment

### Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).
- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

### Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal treatments.
- Don't stop or start any medications during treatment without talking to your doctor and pharmacist first.
- Paracetamol is safe to take if you have a headache or other mild aches and pains. It is recommended that you avoid taking aspirin, ibuprofen and other anti-inflammatory type medications for pain while you are having treatment. However, if these medications have been prescribed by your doctor, do not stop taking them without speaking with your doctor.
- Don't have **any** vaccinations without talking to the doctor who is managing your cancer treatment.
- People you live with should be fully vaccinated, according to the current vaccination schedule. Extra care needs to be taken with hand washing and careful disposal of soiled nappies for infants who have recently received the rotavirus vaccine.

### Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

### Diet

- While you are receiving this treatment it is important that you try to maintain a healthy diet.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.

### Fertility

- Some cancer treatments can reduce your fertility. This can make it difficult or impossible to get pregnant or father a child.
- Talk to your doctor or nurse before you start any treatment. Depending on your situation there may be fertility sparing options available to you and/or your partner, discuss these with your doctor or nurse.

### Pregnancy and breastfeeding

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. Contraception should be used during treatment and after stopping treatment. Ask your doctor or nurse about what type of contraception you should use.
- If you are planning pregnancy/fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.
- Do not breastfeed if you are on this treatment, as anti-cancer medications can also pass into breast milk.

### Sex life and sexuality

- The desire to have sex may decrease as a result of this treatment or its side effects.
- Your emotions and the way you feel about yourself may also be affected by this treatment.
- It may help to discuss your concerns with your partner and doctor or nurse.

### Quitting smoking

- It is never too late to quit smoking. Quitting smoking is one of the best things you can do to help your treatment work better.
- There are many effective tools to improve your chances of quitting.
- Talk to your treating team for more information and referral to a smoking cessation support service.

### Staying active

- Research shows that exercise, no matter how small, has many benefits for people during and after cancer treatment.
- Talk to your doctor before starting an exercise program. Your doctor can advise whether you need a modified exercise program.

**For more information about cancer treatment, side effects and side effect management see our Patient and carers section.**

## Where to get more information - Melanoma

### Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support

### Melanoma information

- Melanoma Institute Australia – melanoma.org.au
- Melanoma Patients Australia – melanomapatients.org.au

### General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyond Blue – beyondblue.org.au
- Cancer Australia – canceraustralia.gov.au
- Cancer Council Australia – cancer.org.au
- Cancer Voices Australia – cancervoicesaustralia.org
- CanTeen – canteen.org.au
- Carers Australia – carersaustralia.com.au
- Carer Help - carerhelp.com.au
- CHILL Cancer related hair loss - scalpcooling.org

- eviQ Cancer Treatments Online – eviQ.org.au
- LGBTQI+ People and Cancer - cancercouncil.com.au/cancer-information/lgbtqi
- Look Good Feel Better – lgfb.org.au
- Patient Information – patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer – targetingcancer.com.au
- Redkite – redkite.org.au
- Return Unwanted Medicines – returnmed.com.au
- Staying active during cancer treatment – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

### Quit smoking information and support

Quitting smoking is helpful even after you have been diagnosed with cancer. The following resources provide useful information and support to help you quit smoking. Talk to your treating team about any other questions you may have.

- Call Quitline on 13 QUIT (13 78 48)
- iCanQuit –iCanQuit.com.au
- Patient Information – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

## Where to get more information - Renal cell

### Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support

### Kidney cancer information

- Kidney Cancer Association – kidneycancer.org/
- Kidney Health Australia – kidney.org.au

### General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyond Blue – beyondblue.org.au
- Cancer Australia – canceraustralia.gov.au
- Cancer Council Australia – cancer.org.au
- Cancer Voices Australia – cancervoicesaustralia.org
- CanTeen – canteen.org.au
- Carers Australia – carersaustralia.com.au
- Carer Help - carerhelp.com.au
- CHILL Cancer related hair loss - scalpcooling.org
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- Patient Information – patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer – targetingcancer.com.au
- Redkite – redkite.org.au
- Return Unwanted Medicines – returnmed.com.au
- Staying active during cancer treatment – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

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- Quitnow – quitnow.gov.au

**Additional notes:**



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