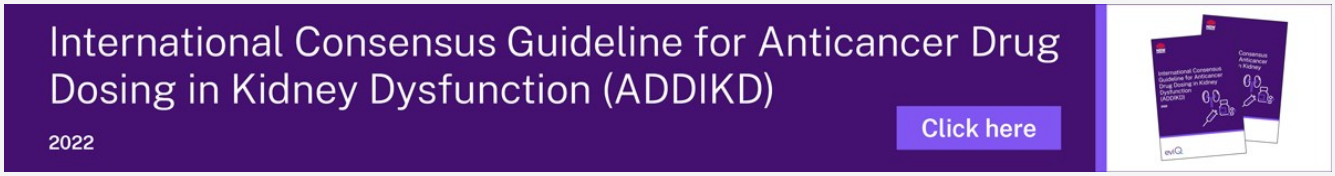
Advanced or metastatic nivolumab (flat dosing)

ID: 3594 v.7 **Endorsed** Essential Medicine List

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:

- Advanced or metastatic nivolumab (weight based dosing) SUPERSEDED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]

Frequency: 28 days

Cycles: Continuous until disease progression or unacceptable toxicity

Notes:
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. In patients with clinical deterioration and radiographic progression treatment with nivolumab should be discontinued.

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 for head and neck, melanoma, non small cell lung cancer, renal cell and oesophageal carcinoma

Nivolumab is TGA registered but not PBS listed for hepatocellular carcinoma

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

Note: Alternative dosing schedule 240 mg every 14 days[1, 2]

Frequency: 28 days

Cycles: Continuous until disease progression or unacceptable toxicity

Indications and patient population - Head and neck

Indications:

- Treatment as monotherapy of patients with recurrent or metastatic squamous cell cancer of the head and neck in patients progressing on or after platinum based chemotherapy.
  - Patients must not have received prior treatment with a PD-1 inhibitor.
  - ECOG performance status 0 to 1.

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 - Hepatic

Indications:

- Treatment as monotherapy for advanced hepatocellular carcinoma Child-Pugh class A or B7 after prior sorafenib therapy
  - ECOG 0 to 1.

Precautions:

If any of these conditions are present, clinical judgment 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 (note: CheckMate 040 included patients with hepatitis B (if treated with adequate antiviral therapy) and hepatitis C)[3]

- HIV/acquired immune deficiency syndrome (AIDS)
- previous radiation to the lungs.

Indications and patient population - Melanoma

Indications:

- Treatment as monotherapy of patients with unresectable Stage III or Stage IV metastatic malignant melanoma
  - patients must not have received prior treatment with ipilimumab or a PD-1 inhibitor.

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.

Note:

Treatment cessation after 2 years of therapy may be considered.

Not to be used post induction ipilimumab and nivolumab, use ID 3682 Metastatic nivolumab maintenance (weight based dosing) following ipilimumab and nivolumab (SUPERSEDED) or ID 3677 Metastatic nivolumab maintenance (flat dosing) following ipilimumab and nivolumab.

Indications and patient population - Non small cell lung cancer

Indications:

- Monotherapy for locally advanced or metastatic **non-squamous** or **squamous** non-small cell lung cancer (NSCLC) with progression on or after prior platinum chemotherapy. In patients with **non-squamous** NSCLC and tumour epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic aberrations, nivolumab should be used after progression on or after both targeted therapy and platinum chemotherapy.

Precautions:

if any of the following 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 practice guidelines for the treatment of lung cancer

Indications and patient population - Oesophageal

Indications:

- Treatment as monotherapy for unresectable advanced, recurrent or metastatic oesophageal squamous or adenosquamous cell carcinoma after prior fluoropyrimidine and platinum based chemotherapy
  - ECOG performance status 0 to 1.

Precautions:

if any of the following 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:

- Treatment as monotherapy for advanced renal cell carcinoma (RCC) with clear cell variant histology
  - ECOG 0 to 2
  - post failure of one or two lines of anti-angiogenic treatments.

Exclusions:

- patients with CNS metastases, previous mTOR inhibitor treatment and condition requiring glucocorticoid treatment (> 10 mg prednisolone daily) were excluded from the pivotal trial of this treatment.

Precautions:

If any of these conditions are present, clinical judgment 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.

A washout period is recommended for patients changing from pazopanib who have drug-induced hepatotoxicity.

Note:

Not to be used post induction ipilimumab and nivolumab, use ID 3682 Metastatic nivolumab maintenance (weight based dosing) following ipilimumab and nivolumab (SUPERSEDED) or ID 3677 Metastatic nivolumab maintenance (flat dosing) following ipilimumab and nivolumab.

Clinical information

Caution with EGFR TKI	Nivolumab is not approved for combination with EGFR TKI use in NSCLC. Serious adverse events, including deaths (one case of pneumonitis and one case of toxic epidermal necrolysis), have been reported in a Phase II non-randomised trial of nivolumab in combination with an investigational 3rd generation TKI. In patients transitioning from an EGFR TKI to nivolumab monotherapy, a sufficient washout period should be observed to minimise the risk of adverse events occurring from the combination.

Venous access required	IV cannula (IVC) or central venous access device (CVAD) is required to administer this treatment. 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. 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. Examples of irAEs with high risk of mortality include: • cardiac toxicity: myocarditis • musculoskeletal toxicity: myositis • neurological toxicity: encephalitis, Guillain-Barré syndrome, myelitis, myasthenia gravis • pulmonary toxicity: pneumonitis • skin toxicity: Stevens-Johnson syndrome, toxic epidermal necrolysis. Examples of irAEs in order of frequency include: • Common ◦ endocrinopathies: thyroid dysfunction ◦ gastrointestinal toxicity: diarrhoea ◦ musculoskeletal toxicity: arthralgia, myalgia ◦ skin toxicity: rash, erythema, pruritus • Less common ◦ endocrinopathies: hypophysitis, type I diabetes mellitus ◦ gastrointestinal toxicity: colitis ◦ musculoskeletal toxicity: inflammatory arthritis ◦ ocular toxicity: dry eye ◦ renal toxicity ◦ skin toxicity: vitiligo • Rare ◦ endocrinopathies: primary adrenal insufficiency ◦ gastrointestinal toxicity: pancreatitis ◦ haematological toxicity ◦ musculoskeletal toxicity: vasculitis ◦ ocular toxicity: uveitis, iritis. 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. 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. 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. 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. 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. 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. 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. Read more about the effect of cancer treatment on fertility 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. 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. 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. 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. 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. Read more about Management of immune related adverse events.
Musculoskeletal toxicity	Inflammatory arthritis, temporal arteritis, arthralgia, myalgia, synovitis, vasculitis, polymyalgia-like syndrome and myositis. 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. 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. 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. Read more about Management of immune related adverse events
Pulmonary toxicity	Radiographic changes, dyspnoea, new or worsening cough, hypoxia, tachycardia, chest pain or fever. Read more about Management of immune related adverse events.
Renal toxicity	Increase in serum creatinine, oliguria, haematuria, peripheral oedema and anorexia. 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. 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. Read more about Management of immune related adverse events

Non-immune related adverse events	
Anorexia	Loss of appetite accompanied by decreased food intake. 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 - Head and neck

The evidence supporting this protocol is provided by a phase 3 multicentre international randomised trial (CheckMate 141) involving 361 patients comparing nivolumab with standard, single-agent systemic therapy alone in patients with recurrent squamous cell carcinoma of the head and neck.[4]

Between June 2014 and August 2015, 240 patients were randomised to receive nivolumab (3 mg/kg every 2 weeks) and 121 patients were randomised to receive either methotrexate (40 to 60 mg/m^2 IV weekly), docetaxel (30 to 40 mg/m^2 IV weekly), or cetuximab (250 mg/m^2 IV weekly after a loading dose of 400 mg/m^2).

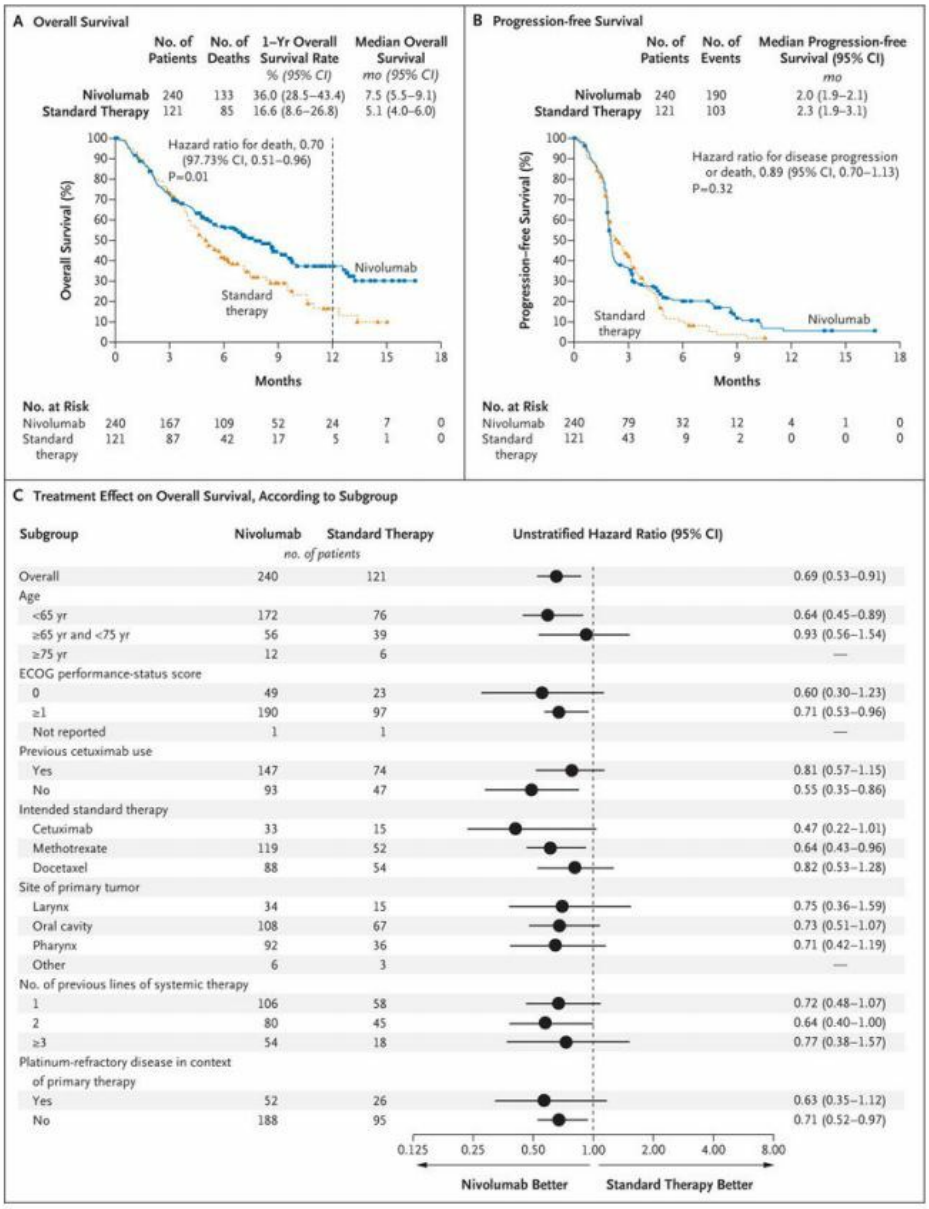
The primary end point was overall survival, secondary end points were progression-free survival and the rate of objective response according to RECIST, version 1.1. Additional prespecified end points included the time to response; associations between PD-L1 level and human papillomavirus (HPV) status and response rate; safety; and quality-of-life assessments.

Efficacy

After a median follow up of 5.1 months, the median overall survival was 7.5 months (95% CI 5.5 – 9.1) in the nivolumab group vs 5.1 months (95% CI 4.0 – 6.0) in the standard therapy group.[4] The risk of death was 30% less in the nivolumab group compared to standard therapy (HR=0.70; 97.73% CI 0.51 to 0.96; p=0.01). The estimated overall rate of survival at one year was 36.0% (95% CI, 28.5 to 43.4) in the nivolumab group vs 16.6 % (95% CI, 8.6 to 26.8) in the standard therapy group. No significant difference between groups was observed with regard to the rate of progression-free survival. Across pre-specified demographic and clinical subgroups, the estimate of the hazard ratio for death in the analysis of overall survival with nivolumab versus standard therapy was less than 1.

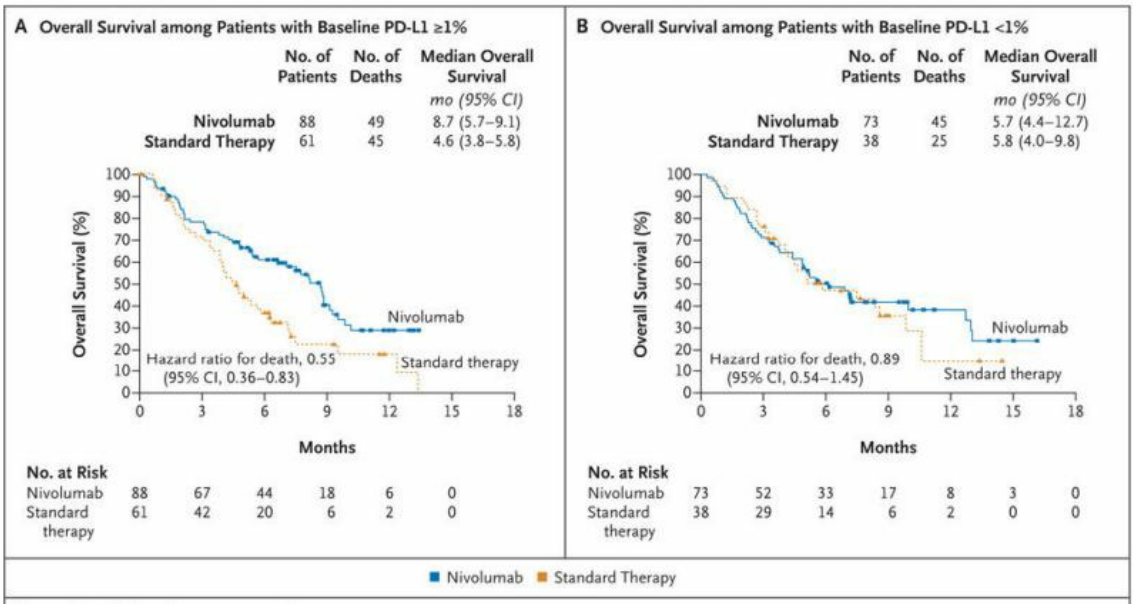
At prolonged follow up the benefit is maintained.[5] 2 year follow up results from the CheckMate 141 trial, demonstrate an improved 24-month OS rate in the nivolumab group 16.9% (95% CI: 12.4-22.0%) compared to the standard therapy group 6.0% (95% CI: 2.7-11.3%).[5] The OS benefit was seen with nivolumab regardless of PD-L1 expression and HPV status.

Overall survival, progression-free survival, and treatment effect on overall survival according to subgroup[4]



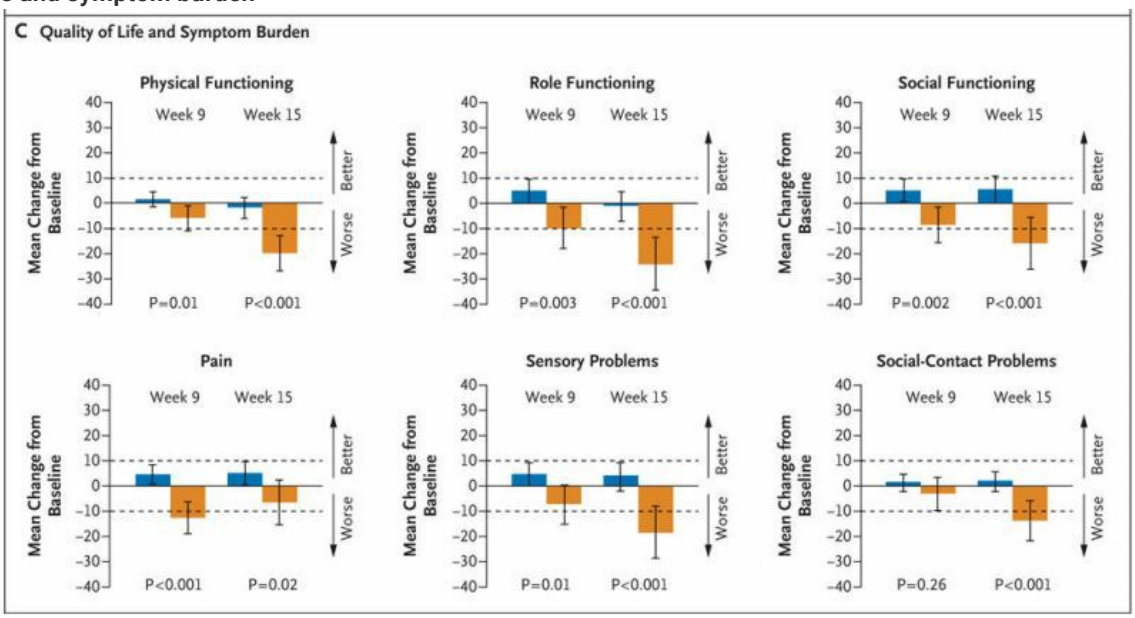
A prespecified, exploratory analysis was performed to evaluate the consistency of the treatment effect in subgroups defined according to tumour PD-L1 expression level (≥1% vs. <1%).[4] Tumour PD-L1 expression status could be evaluated in 260 of 361 patients (72%). Among the patients who could be evaluated, 57.3% had a PD-L1 expression level of 1% or more.

Overall survival according to baseline PD-L1 status[4]



Quality of life data was available for 129 patients (35.7%) at weeks 9 and 15, and stratified according to treatment group. Analyses were limited to data collected through to week 15 owing to a low number of responses to the questionnaire in the standard therapy group after that point.

Quality of life and symptom burden[4]



Toxicity

Treatment related adverse events[4]

Table 3. Treatment-Related Adverse Events Occurring in at Least 5% of the Patients in Either Group.

Event	Nivolumab (N=236)		Standard Therapy (N=111)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any event	139 (58.9)*	31 (13.1)	86 (77.5)†	39 (35.1)
Fatigue	33 (14.0)	5 (2.1)	19 (17.1)	3 (2.7)
Nausea	20 (8.5)	0	23 (20.7)	1 (0.9)
Rash	18 (7.6)	0	5 (4.5)	1 (0.9)
Decreased appetite	17 (7.2)	0	8 (7.2)	0
Pruritus	17 (7.2)	0	0	0
Diarrhea	16 (6.8)	0	15 (13.5)	2 (1.8)
Anemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)
Asthenia	10 (4.2)	1 (0.4)	16 (14.4)	2 (1.8)
Vomiting	8 (3.4)	0	8 (7.2)	0
Dry skin	7 (3.0)	0	10 (9.0)	0
Stomatitis	5 (2.1)	1 (0.4)	10 (9.0)	3 (2.7)
Weight loss	4 (1.7)	0	6 (5.4)	0
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Peripheral neuropathy	1 (0.4)	0	7 (6.3)	0
Alopecia	0	0	14 (12.6)	3 (2.7)
Neutropenia	0	0	9 (8.1)	8 (7.2)

* Data include one patient with a grade 5 event of hypercalcemia and one patient with grade 3 pneumonitis who subsequently died of a grade 5 pulmonary embolism.
† Data include one patient with a grade 5 event of lung infection.

Evidence - Hepatic

A search of the literature did not find strong evidence to support the use of nivolumab in the treatment of hepatocellular carcinoma. The expert reference panel supported publication of the protocol on the basis of the information summarised below. The committee was most strongly influenced by the open-label, non-comparative phase I/II dose-escalation and expansion CheckMate 040 trial.[3]

The primary endpoint of the dose-escalation phase was safety and tolerability. The primary endpoint of the dose-expansion phase was objective response rate (ORR). Secondary endpoints included ORR (dose-escalation phase only), complete response rate, disease control rate (DCR), duration of response, time to response, time to progression, progression-free survival (PFS), overall survival (OS), and response stratified by PD-L1 expression.

The protocol has been used extensively for the treatment of head and neck, melanoma, non small cell and renal cell cancer.

Source	Study & Year Published	Supports Use	Is the dose and regimen consistent with the protocol?	Comments
Phase I/II trials	CheckMate 040, 2017[3]	Yes	Yes	
Guidelines	**Date published/revised**	**Supports Use**	**Is the dose and regimen consistent with the protocol?**	**Comments**
NCCN	Version 4.2019	Yes	No doses stated	
BCCA	-	N/A	-	
CCO	-	N/A	-	
ESMO	2020	No	No doses stated	
NICE	-	N/A		

Efficacy

In the dose expansion cohort treated with nivolumab 3 mg/kg, the ORR was 20%, including 1% (3 patients) who had a complete response. A further 45% had stable disease, giving a DCR of 64%. ORR rates were higher for sorafenib-naïve patients compared with sorafenib-experienced patients. Overall, responses occurred regardless of the PD-L1 expression or aetiology.[3]

69% of patients achieved an objective response before three months. Responses were durable with 67% of patients with an objective response having an ongoing objective response at the time of data cut-off with a median duration of 9.9 months. Disease control was also durable with 57% of patients having ongoing disease control for more than six months. Median time to progression was 4.1 months.

In the initial survival analysis, OS was 83% at 6 months and 74% at 9 months. OS rates were higher for sorafenib-naïve patients compared with sorafenib-experienced patients. 6 month PFS was 37% and 9 month PFS was 28% overall.

Nivolumab efficacy in the dose expansion phase[3]

	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective response*	13 (23%; 13 to 36)	12 (21%; 11 to 34)	10 (20%; 10 to 34)	7 (14%; 6 to 26)	42 (20%; 15 to 26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable disease	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Progressive disease	13 (23%)	18 (32%)	14 (28%)	23 (45%)	68 (32%)
Not evaluable	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)
Duration of response*					
KM median	8·4 (8·3 to NE)	NR	9·9 (4·5 to 9·9)	NR	9·9 (8·3 to NE)
Ongoing, n/N (%)	8/13 (62%)	7/12 (58%)	8/10 (80%)	5/7 (71%)	28/42 (67%)
Disease control*	42 (75%; 62 to 86)	35 (61%; 48 to 74)	33 (66%; 51 to 79)	28 (55%; 40 to 69)	138 (64%; 58 to 71)
Disease control with stable disease for ≥6 months	22 (39%; 27 to 53)	22 (39%; 26 to 52)	17 (34; 21 to 49)	18 (35%; 22 to 50)	79 (37%; 30 to 44)
Overall survival					
6 months	89% (77 to 95)	75% (62 to 85)	85% (72 to 93)	84% (71 to 92)	83% (78 to 88)
9 months	82% (68 to 90)	63% (49 to 74)	81% (66 to 90)	70% (55 to 81)	74% (67 to 79)
KM median	NR	13·2 (8·6 to NE)	NR	NR	NR
Progression-free survival*					
KM median	5·4 (3·9 to 8·5)	4·0 (2·6 to 6·7)	4·0 (2·6 to 5·7)	4·0 (1·3 to 4·1)	4·0 (2·9 to 5·4)

Unless otherwise indicated, data are n (%; 95% CI); n (%); months (95% CI); or % (95% CI). HCV=hepatitis C virus. HBV=hepatitis B virus. KM=Kaplan-Meier estimate. NR=not reached. NE=not estimable. RECIST=Response Evaluation Criteria In Solid Tumors. *Determined by investigator assessment using RECIST version 1.1.

Table 4: Nivolumab efficacy in the dose-expansion phase

Toxicity

Toxicity in the dose-escalation phase was similar to the dose expansion-phase, and similar to that seen with nivolumab in other tumour types.[3]

In the dose-expansion cohort that received nivolumab 3 mg/kg (214 patients), grade 3 or 4 adverse events (AEs) were seen in 19%, and serious grade 3 or 4 AEs were seen in 4%. There were no treatment related deaths.

Adverse events in the dose-escalation phase[3]

	0·1 mg/kg (n=6)		0·3 mg/kg (n=9)		1 mg/kg (n=10)		3 mg/kg (n=10)		10 mg/kg (n=13)		All patients (n=48)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related serious AEs	1 (17%)*	1 (17%)*	1 (11%)†	1 (11%)†	0	0	0	0	1 (8%)‡	0	3 (6%)	2 (4%)
AEs leading to discontinuation	0	0	1 (11%)§	1 (11%)§	0	0	1 (10%)¶	1 (10%)¶	1 (8%)‖	1 (8%)‖	3 (6%)	3 (6%)
Treatment-related deaths	0	0	0	0	0	0	0	0	0	0	0	0
Patients with a treatment-related AE	4 (67%)	2 (33%)	8 (89%)	3 (33%)	8 (80%)	5 (50%)	9 (90%)	2 (20%)	11 (85%)	0	40 (83%)	12 (25%)
Treatment-related AEs**												
Rash	1 (17%)	0	2 (22%)	0	2 (20%)	0	2 (20%)	0	4 (31%)	0	11 (23%)	0
Pruritus	2 (33%)	0	3 (33%)	0	0	0	1 (10%)	0	3 (23%)	0	9 (19%)	0
Diarrhoea	0	0	3 (33%)	0	0	0	1 (10%)	0	1 (8%)	0	5 (10%)	0
Decreased appetite	1 (17%)	0	2 (22%)	0	1 (10%)	0	0	0	1 (8%)	0	5 (10%)	0
Fatigue	1 (17%)	1 (17%)	2 (22%)	0	1 (10%)	0	0	0	0	0	4 (8%)	1 (2%)
Asthenia	0	0	1 (11%)	0	0	0	1 (10%)	0	1 (8%)	0	3 (6%)	0
Weight decreased	0	0	1 (11%)	0	0	0	0	0	2 (15%)	0	3 (6%)	0
Nausea	0	0	1 (11%)	0	0	0	1 (10%)	0	1 (8%)	0	3 (6%)	0
Dry mouth	0	0	1 (11%)	0	1 (10%)	0	0	0	1 (8%)	0	3 (6%)	0
Laboratory treatment-related AEs**												
AST increase	0	0	2 (22%)	2 (22%)	3 (30%)	2 (20%)	1 (10%)	1 (10%)	4 (31%)	0	10 (21%)	5 (10%)
ALT increase	0	0	2 (22%)	2 (22%)	1 (10%)	0	2 (20%)	1 (10%)	2 (15%)	0	7 (15%)	3 (6%)
Lipase increase	1 (17%)	1 (17%)	1 (11%)	0	4 (40%)	4 (40%)	2 (20%)	1 (10%)	2 (15%)	0	10 (21%)	6 (13%)
Amylase increase	1 (17%)	0	0	0	4 (40%)	1 (10%)	2 (20%)	1 (10%)	2 (15%)	0	9 (19%)	2 (4%)
Anaemia	0	0	1 (11%)	0	1 (10%)	1 (10%)	0	0	2 (15%)	0	4 (8%)	1 (2%)
Hypoalbuminaemia	0	0	1 (11%)	0	1 (10%)	0	0	0	1 (8%)	0	3 (6%)	0
Hyponatraemia	0	0	0	0	2 (20%)	0	0	0	1 (8%)	0	3 (6%)	0

Data are n (%). AE=adverse event. AST=aspartate aminotransferase. ALT=alanine aminotransferase. *Pemphigoid (n=1). †Adrenal insufficiency (n=1). ‡Liver disorder (n=1). §Malignant neoplasm progression (n=1). ¶Grade 3 ALT increase (n=1), grade 2 AST increase. ||Grade 3 blood bilirubin increase (n=1). **Treatment-related AEs reported in ≥5% of all patients, any grade.

Table 3: Safety and tolerability of nivolumab in the dose-escalation phase

Evidence - Melanoma

The evidence supporting this protocol is provided by two international, multicentre, randomised phase III, clinical trials; CheckMate 066 which compared nivolumab with dacarbazine in previously untreated patients with metastatic melanoma without a BRAF mutation, and CheckMate 067 which compared the safety and efficacy of nivolumab alone or nivolumab combined with ipilimumab, with ipilimumab alone in previously untreated patients with confirmed stage III (unresectable) or stage IV (metastatic) BRAF V600 mutant and wild-type melanoma.

In CheckMate 066, 418 patients were randomised 1:1 between January 2013 and February 2014 to receive nivolumab 3 mg/kg every 2 weeks or dacarbazine 1000 mg/m^2 every 3 weeks.[6] Randomisation was stratified according to tumour PD-L1 status and metastases stage (M1a vs M1b vs M1c). Treatment was continued until disease progression or unacceptable toxicity. Treatment after disease progression was permitted for patients who had a clinical benefit in the absence of toxicity. The primary end point was overall survival (OS). Secondary end points included progression-free survival (PFS), objective response rate (ORR) and tumour PD-L1 expression as a predictive biomarker of OS.[6]

In CheckMate 067, 945 eligible patients were randomised 1:1:1 between July 2013 to March 2014 to receive either nivolumab alone, nivolumab+ipilimumab or ipilimumab alone.[7, 8] 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+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).[7, 8] Baseline characteristics were balanced across the three groups. Treatment was continued until disease progression or unacceptable toxicity. The co-primary endpoints were PFS and OS. Secondary end points were 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+ipilimumab.[7, 8]

Efficacy

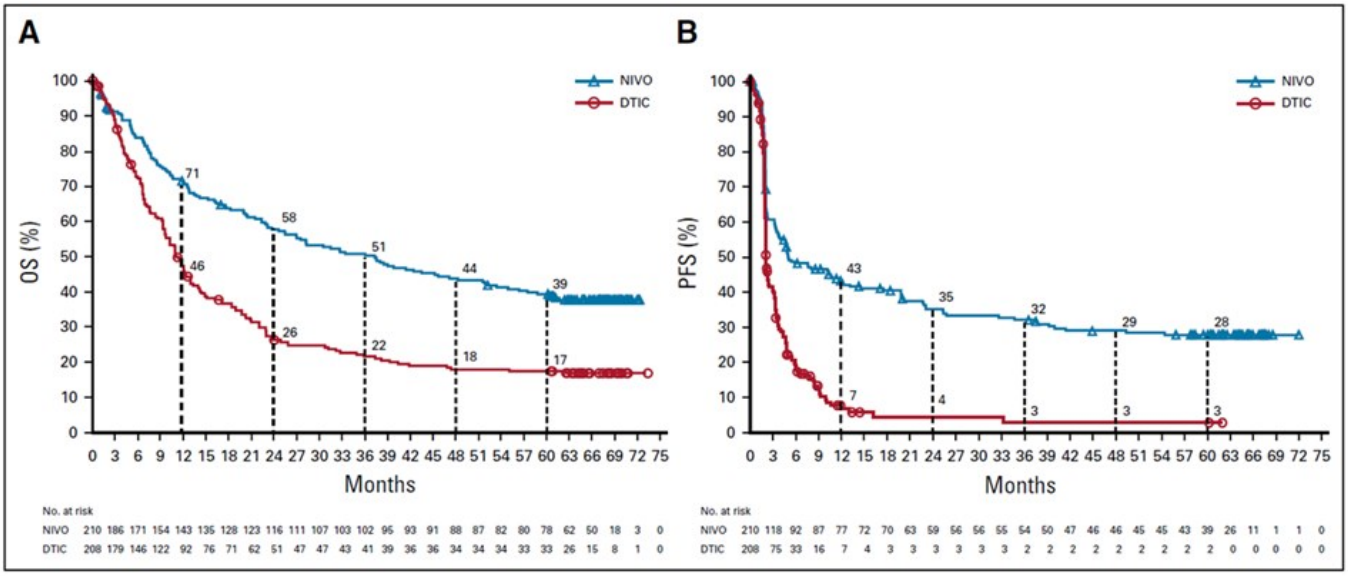
CheckMate 066[6, 9]

Response to treatment[9]	Nivolumab	Dacarbazine	Effect
5-year OS rate (%)	39	17	HR=0.5 (95% CI 0.40-0.63; p<0.0001)

Response to treatment[9]	Nivolumab	Dacarbazine	Effect
Median OS (months, 95% CI)	37.3 (25.4-51.6)	11.2 (9.6-13.0)	-
5-year PFS rate (%)	28	3	HR=0.4 (95% CI 0.33-0.54; p<0.0001)
Median PFS (months, 95% CI)	5.1 (3.5-12.2)	2.2 (2.1-2.5)	-
Complete response (%)	20	1	-
Partial response (%)	22	13	-
ORR (%)	42	14	Odd ratio=4.43 (95% CI 2.75-7.13; p<0.001)
Median duration of response (months, 95% CI)	NR (47.2-NR)	6 (3.9-30.4)	-

NR= Not reached

Kaplan-Meier curves for (A) overall survival and (B) progression-free survival[9]



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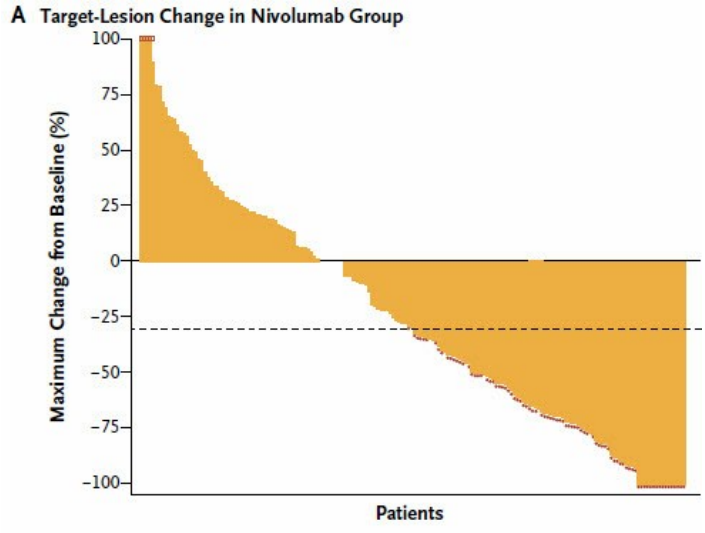
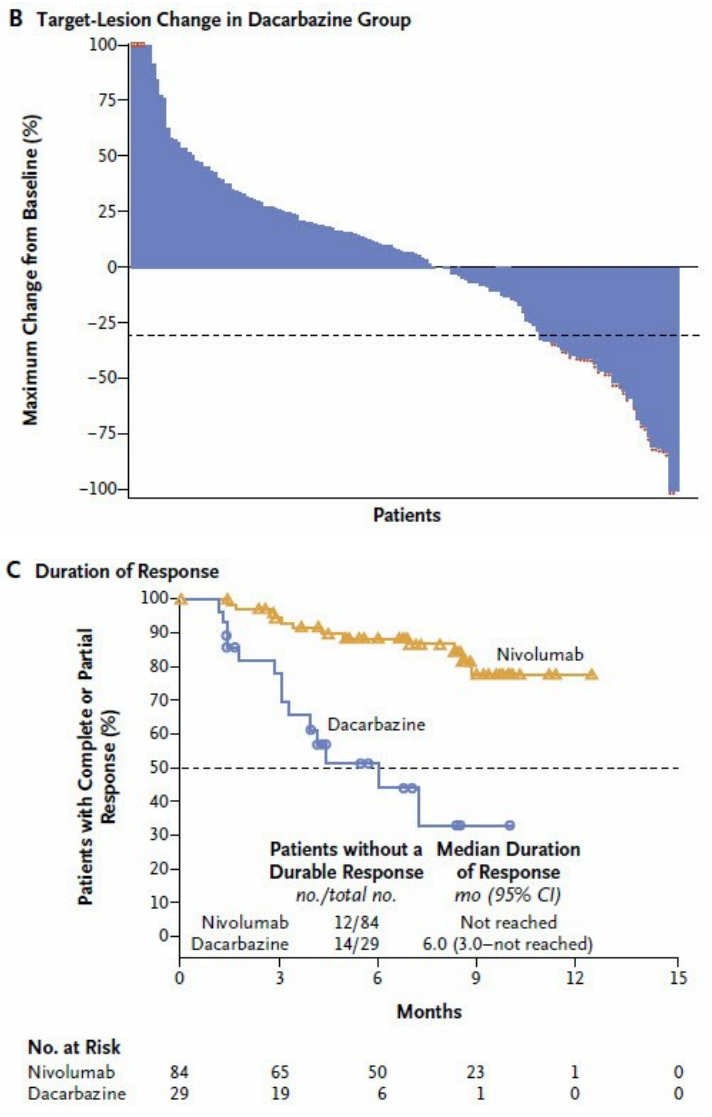
Characteristics of response[6]





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CheckMate 067[7, 8, 10]

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 (HR=0.43; 95% CI 0.35-0.52; p<0.001 for combination therapy vs ipilimumab and HR=0.55; 95% CI 0.45-0.66; p<0.001 for nivolumab vs ipilimumab). 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.[8]

At a minimum follow-up of 36 months, the median OS had not been reached (NR) in the nivolumab+ipilimumab group and was 37.6 months in the nivolumab group, as compared with 19.9 months in the ipilimumab group (HR=0.55; p<0.001 for combination therapy vs ipilimumab and HR=0.65; p<0.001 for nivolumab vs ipilimumab). The OS rate at 3 years was 58% with combination therapy and 52% with nivolumab, as compared with 34% with ipilimumab.[8]

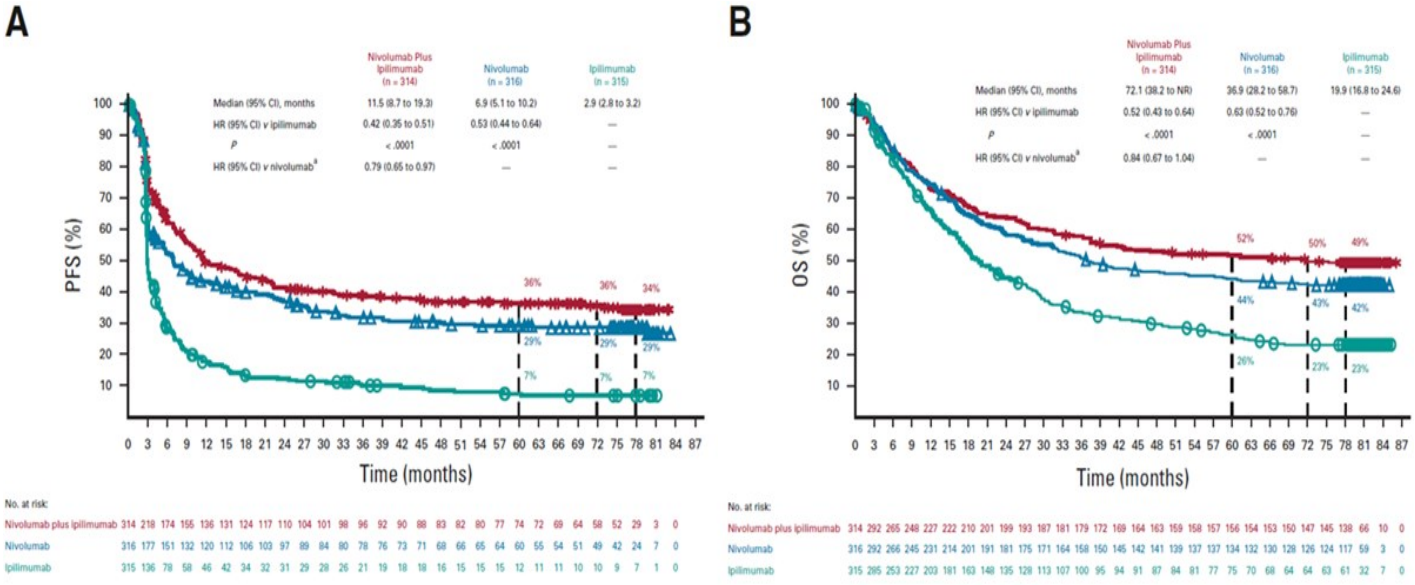
At a minimum follow-up of 77 months, the median OS was 72.1 months (95% CI 38.2-NR) in the combination therapy arm as compared with 36.9 months (95% CI 28.2-58.7) and 19.9 months (95% CI 16.8-24.6) in the nivolumab and ipilimumab arms [HR=0.52 (95% CI 0.43-0.64; p<0.0001) for combination therapy vs ipilimumab 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.[10]

Response to treatment[10]	Nivolumab (n=316)	Nivolumab + ipilimumab (n=314)	Ipilimumab (n=315)
Complete response (%)	19	23	6

Response to treatment[10]	Nivolumab (n=316)	Nivolumab + ipilimumab (n=314)	Ipilimumab (n=315)
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[10]



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Toxicity

CheckMate 066[6, 9]

Treatment-related adverse events (AEs) of any grade occurred in 74.3% of patients in the nivolumab group and 75.6% of patients in the dacarbazine group. Treatment-related AEs of grade 3/4 occurred in 11.7% of patients in the nivolumab group and 17.6% of patients in the dacarbazine group. The most common AEs in the nivolumab group were fatigue (20%), pruritis (17%) and nausea (16.5%). Treatment-related AEs that led to discontinuation of the study drug occurred in 6.8% of patients in the nivolumab group and 11.7% of patients in the dacarbazine group. No deaths were attributed to study-drug toxicity in either group.[6]

At the time of 5-year analysis, grade 3/4 treatment-related AEs were reported in 16% of the nivolumab group and 18% of dacarbazine group. Treatment-related AEs that led to treatment discontinuation occurred in 5% and 2% of patients, respectively.[9]

CheckMate 067[7, 8, 10, 11]

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).

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).[8]

Patients have experienced toxicity even after finishing treatment, and deaths considered to be related to study drug >100 days

after the last dose.[7]

At the time of 6.5-year analysis, grade 3/4 treatment-related AEs 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.[11]

Treatment related adverse events - Grade 3 or 4 (%)	CheckMate 066[9]		CheckMate 067[10]		
	Nivolumab	Dacarbazine	Nivolumab	Nivolumab + ipilimumab	Ipilimumab
Total	16	18	24	59	28
Fatigue	0	1	1	4	1
Pruritus	<1	0	<1	2	<1
Nausea	0	0	0	2	1
Diarrhoea	<1	<1	3	10	6
Rash	<1	0	1	4	2
Vomiting	<1	<1	<1	2	<1
Hepatitis	NR	NR	3	20	2
Hypothyroidism	0	0	0	<1	0
Hypophysitis	NR	NR	<1	2	2
Colitis	<1	0	1	8	8.0
Pneumonitis	<1	0	<1	1	<1
Renal	NR	NR	1	2	<1

NR= Not reported

Evidence - Non small cell lung cancer

Squamous non small cell lung cancer

The evidence supporting this protocol is provided by a phase III multicentre international randomised trial (CheckMate-017).[12] This trial involved 272 patients and compared nivolumab with docetaxel alone in patients with advanced squamous cell lung cancer who had progressed on or after one platinum-containing chemotherapy regime. Between October 2012 and December 2013, 135 patients were randomised to receive nivolumab 3 mg/kg every 2 weeks and 137 patients were randomised to receive docetaxel 75 mg/m^2 every 3 weeks. The primary end point was overall survival (OS) and secondary end points were progression-free survival (PFS), patient-reported outcomes, efficacy according to tumour PD-L1 expression, and safety.

Non squamous non small cell lung cancer

The evidence supporting this protocol is provided by a phase III multicentre international trial (CheckMate-057).[13] This trial randomised 582 patients with advanced non squamous non small cell lung cancer who had progressed during or after one prior platinum containing chemotherapy regime to either nivolumab or docetaxel. Between November 2012 and December 2013, 292 patients received nivolumab 3 mg/kg every 2 weeks and 290 patients received docetaxel 75 mg/m^2 every 3 weeks. The primary end point was OS and secondary end points were PFS, objective response rate (ORR), patient-reported outcomes, and efficacy according to tumour PD-L1 expression level.

Efficacy

Squamous non small cell lung cancer (CheckMate-017)[12]

After a minimum follow up of 11 months, the median OS was 9.2 months in nivolumab group vs 6.0 months in docetaxel group (HR=0.59; 95% CI 0.44-0.79; p<0.001). 1-year OS rates were 42% vs 24% respectively. 2-year OS rate was 23% vs 8%

respectively.[14]The median PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (HR for death or disease progression=0.62; 95% CI 0.47-0.81; p<0.001). 2-year PFS rates with nivolumab was 16% (95% CI 10-23).[14]The response rate was 20% for nivolumab vs 9% for docetaxel (p=0.008). The median DoR was not reached in the nivolumab group (range 2.9 to 20.5+ months) compared with 8.4 months in the docetaxel group. A total of 28 patients were treated with nivolumab after initial progression as defined by RECIST1.1, with 9 patients having a nonconventional pattern of benefit.

Kaplan-Meier curves for overall survival and (B) progression-free survival[12]

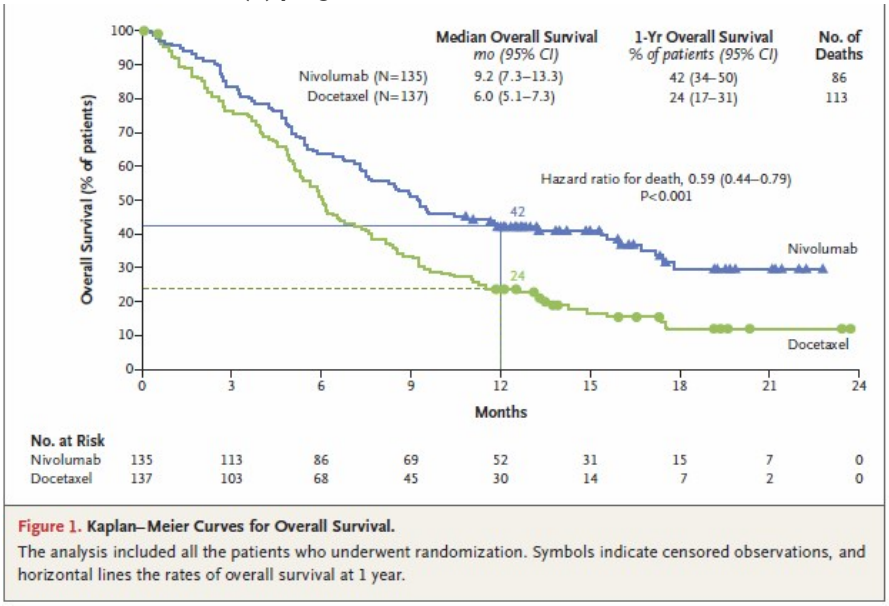
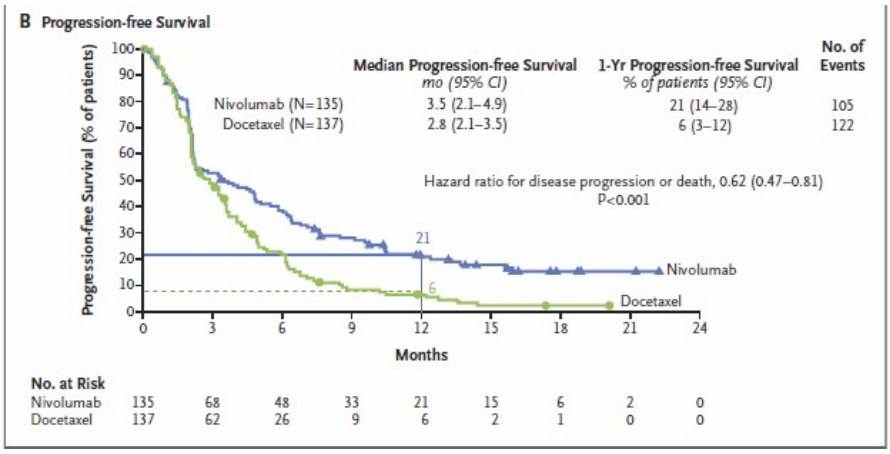


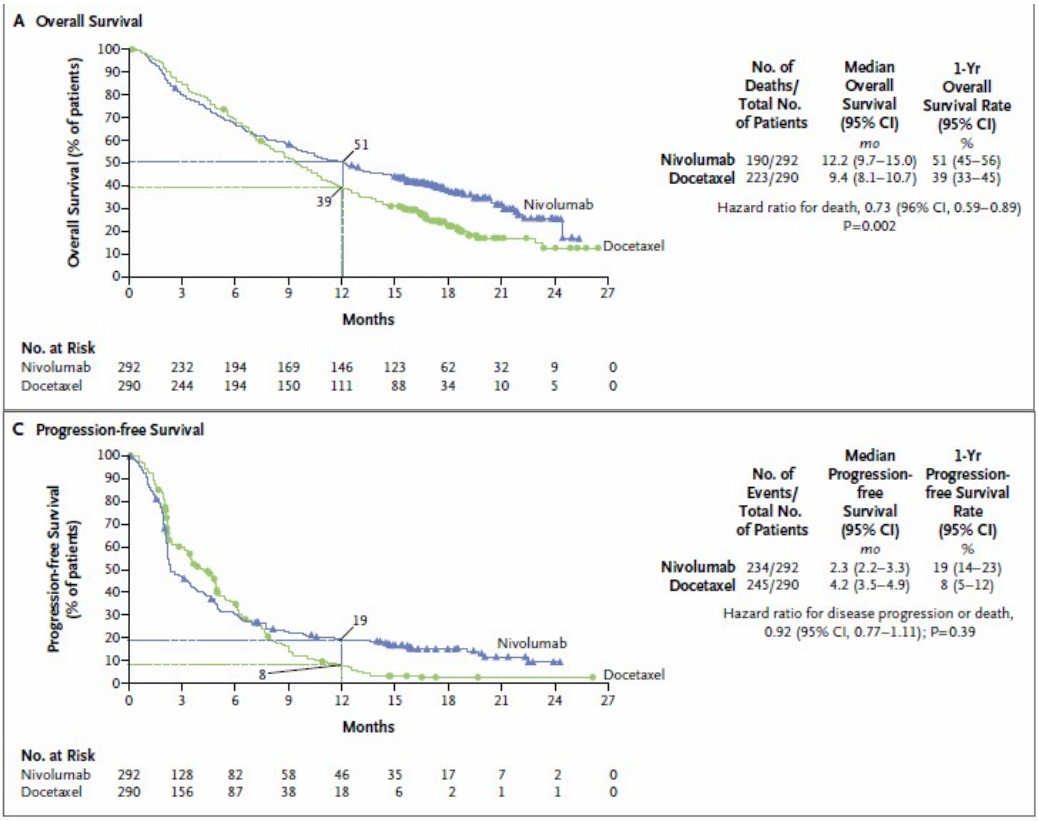
Figure 1. Kaplan–Meier Curves for Overall Survival.
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.



Non squamous non small cell lung cancer (CheckMate-057)[13]

After a minimum follow up of 13.2 months, the median OS was 12.2 months in nivolumab group vs 9.4 months in docetaxel group (HR=0.73; 95% CI 0.59-0.89; p=0.002). 1-year OS rates were 51% vs 39% respectively. At 18 months follow up, the rate of OS was 39% with nivolumab and 23% with docetaxel. Although PFS did not favour nivolumab over docetaxel (median 2.3 months and 4.2 months respectively), the rate of PFS at 1 year was higher with nivolumab than with docetaxel (19% and 8%, respectively). 2-year OS rates were 29% vs 16% respectively. 2-year PFS was 12% (95% CI 8-16%).[14]The median DoR was 17.2 months in the nivolumab group (range 1.8 to 22.6+ months) compared with 5.6 months in the docetaxel group. A total of 71 patients were treated with nivolumab after initial progression as defined by RECIST1.1, with 16 patients having a nonconventional pattern of benefit.

Kaplan-Meier curves for (A) overall survival and (C) progression-free survival[13]



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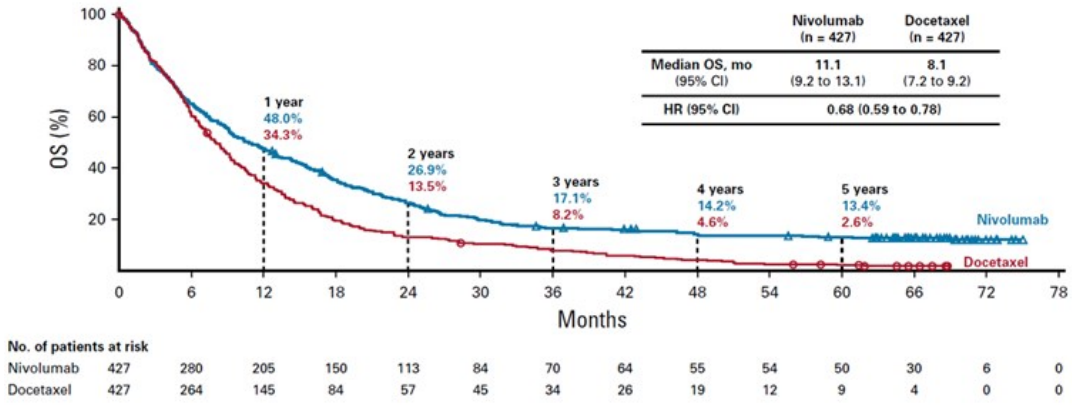
Pooled analysis for both squamous and non squamous non small cell lung cancer (CheckMate-017/057)

3-year pooled analysis for both squamous and non squamous non small cell lung cancer showed an OS rate of 17% (95% CI 14-21) with nivolumab vs 8% (95% CI 6-11) with docetaxel (HR 0.70; 95% CI 0.61-0.81). PFS in the pooled analysis was 10% (95% CI 7-14) with nivolumab vs <1% (95% CI <1-2) with docetaxel. The median DoR with the 3-year pooled analysis was 23.8 months (95% CI 11.4-36.1) for nivolumab vs 5.6 months (95% CI 4.4-7.0) for docetaxel.[15]

5-year pooled analysis after minimum follow-up of 64.2 (CheckMate 017) and 64.5 (CheckMate 057) months, showed median OS of 11.1 months (95% CI 9.2-13.1) with nivolumab vs 8.1 months (95% CI 7.2-9.2) with docetaxel (HR=0.68; 95% CI 0.59-0.78). Pooled 5-year OS rates were 13.4% (95% CI 10.4-16.9) in the nivolumab arm compared to 2.6% (95% CI 1.4-4.5) in the docetaxel arm. OS rates benefits with nivolumab compared to docetaxel were similar with squamous (12.3% vs 3.6%) and non squamous (14.0% vs 2.1%) histology and PD-L1 ≥ 1% (18.3% vs 3.4%) and PD-L1 < 1% (8.0% vs 2.0%) expression. Pooled PFS rates were 8.0% (95% CI 5.4-11.2) and 0% with nivolumab and docetaxel respectively. The median DoR with the 5-year pooled analysis was 19.9 months (95% CI 11.4-30.8) for nivolumab vs 5.6 months (95% CI 4.4-7.0) for docetaxel.[16]

Kaplan-Meier curves for overall survival[16]



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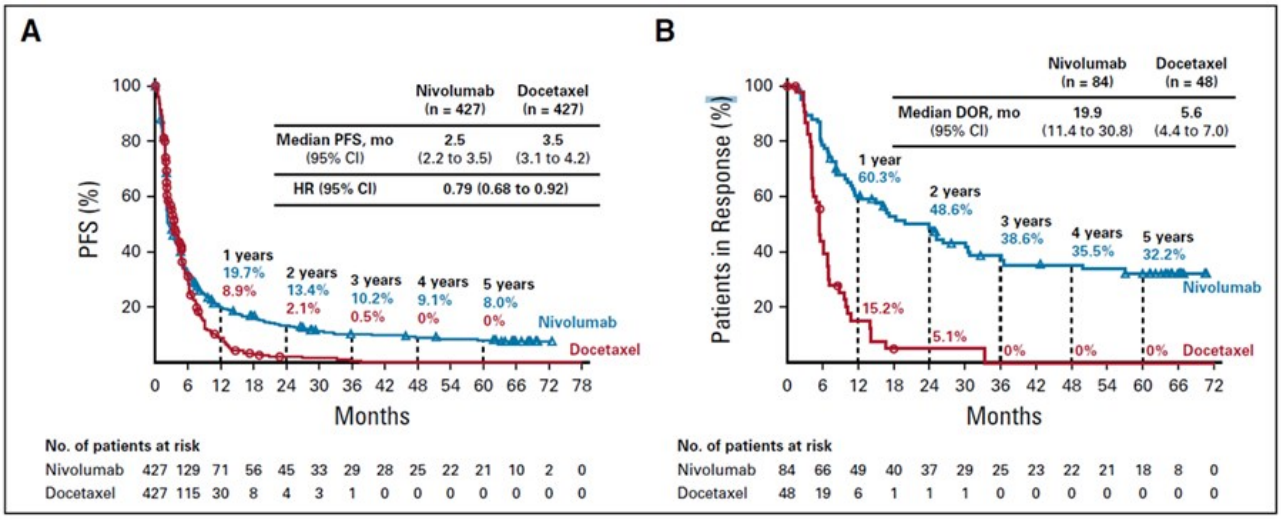
Kaplan-Meier curves for (A) progression-free survival (B) duration of response[16]



Toxicity

Squamous non small cell lung cancer (Checkmate-017)[12]

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

* Safety analyses included all the patients who received at least one dose of study drug. No treatment-related deaths occurred in patients treated with nivolumab. Treatment-related deaths were reported in three patients treated with docetaxel (one death each from interstitial lung disease, pulmonary hemorrhage, and sepsis).

Non squamous non small cell lung cancer (Checkmate-057)[13]

Table 3. Treatment-Related Adverse Events Reported in at Least 10% of the Patients Treated with Nivolumab or Docetaxel.*

Event	Nivolumab (N=287)		Docetaxel (N=268)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	199 (69)	30 (10)	236 (88)	144 (54)
Fatigue	46 (16)	3 (1)	78 (29)	13 (5)
Nausea	34 (12)	2 (1)	70 (26)	2 (1)
Decreased appetite	30 (10)	0	42 (16)	3 (1)
Asthenia	29 (10)	1 (<1)	47 (18)	6 (2)
Diarrhea	22 (8)	2 (1)	62 (23)	3 (1)
Peripheral edema	8 (3)	0	28 (10)	1 (<1)
Myalgia	7 (2)	1 (<1)	30 (11)	0
Anemia	6 (2)	1 (<1)	53 (20)	7 (3)
Alopecia	1 (<1)	0	67 (25)	0
Neutropenia	1 (<1)	0	83 (31)	73 (27)
Febrile neutropenia	0	0	27 (10)	26 (10)
Leukopenia	0	0	27 (10)	22 (8)

* Data are based on a March 18, 2015, database lock. Safety analyses included all the patients who received at least one dose of study drug. Some patients had more than one adverse event. No treatment-related grade 5 events (deaths) were reported at the time of the database lock. The association of one death (from encephalitis) in a patient in the nivolumab group was changed from not related to treatment to treatment-related after the database lock. A treatment-related death of a patient in the docetaxel group, which occurred before the database lock, was reported as grade 4 febrile neutropenia.

Pooled squamous and non squamous non small cell lung cancer (Checkmate-017/057)[16]

TABLE 1. Treatment-Related Adverse Events With Nivolumab (Overall and at 3-5 Years' Follow-Up)

Event	Overall[a] (n = 418)		3-5 Years' Follow-Up (n = 31)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
TRAE[b]				
Any event	284 (67.9)	45 (10.8)	8 (25.8)	1 (3.2)
Fatigue	72 (17.2)	4 (1.0)	0	0
Nausea	46 (11.0)	2 (0.5)	0	0
Decreased appetite	46 (11.0)	1 (0.2)	0	0
Asthenia	45 (10.8)	1 (0.2)	1 (3.2)	0
Diarrhea	37 (8.9)	4 (1.0)	2 (6.5)	0
Rash	34 (8.1)	2 (0.5)	1 (3.2)	0
Pruritus	29 (6.9)	1 (0.2)	1 (3.2)	0
Hypothyroidism	25 (6.0)	0	0	0
Arthralgia	24 (5.7)	1 (0.2)	0	0
Vomiting	21 (5.0)	0	0	0
Pyrexia	15 (3.6)	0	0	0
Pneumonitis	15 (3.6)	4 (1.0)	0	0
Constipation	14 (3.3)	0	0	0
Chills	14 (3.3)	0	0	0
Increased alanine aminotransferase	14 (3.3)	1 (0.2)	0	0
Increased AST	13 (3.1)	2 (0.5)	0	0
Dry skin	13 (3.1)	0	0	0
Erythema	6 (1.4)	0	1 (3.2)	0
Hypophosphatemia	5 (1.2)	2 (0.5)	1 (3.2)	0
Skin exfoliation	4 (1.0)	0	1 (3.2)	0
Increased lipase	2 (0.5)	2 (0.5)	1 (3.2)	1 (3.2)
Nummular eczema	1 (0.2)	0	1 (3.2)	0
Memory impairment	1 (0.2)	0	1 (3.2)	0
State of confusion	1 (0.2)	0	1 (3.2)	0
Hot flush	1 (0.2)	0	1 (3.2)	0
TRAEs leading to discontinuation	27 (6.5)	18 (4.3)	1 (3.2)[c]	0

Abbreviations: AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
[a]One treatment-related death, because of encephalitis, was reported with nivolumab.
[b]Events of any grade reported between the first dose and 30 days after the last dose of trial therapy in ≥ 3% of patients in any group.
[c]Because of grade 2 nummular eczema; this was a recurrent event.

Evidence - Oesophageal

The evidence supporting this protocol is provided by a phase III multicentre international randomised trial (ATTRACTION-3). This trial involved 419 patients and compared nivolumab with investigator's choice of chemotherapy (paclitaxel or docetaxel) in patients with metastatic or advanced oesophageal squamous cell carcinoma who were refractory or intolerant to previous fluoropyrimidine-based and platinum-based chemotherapy.[17]

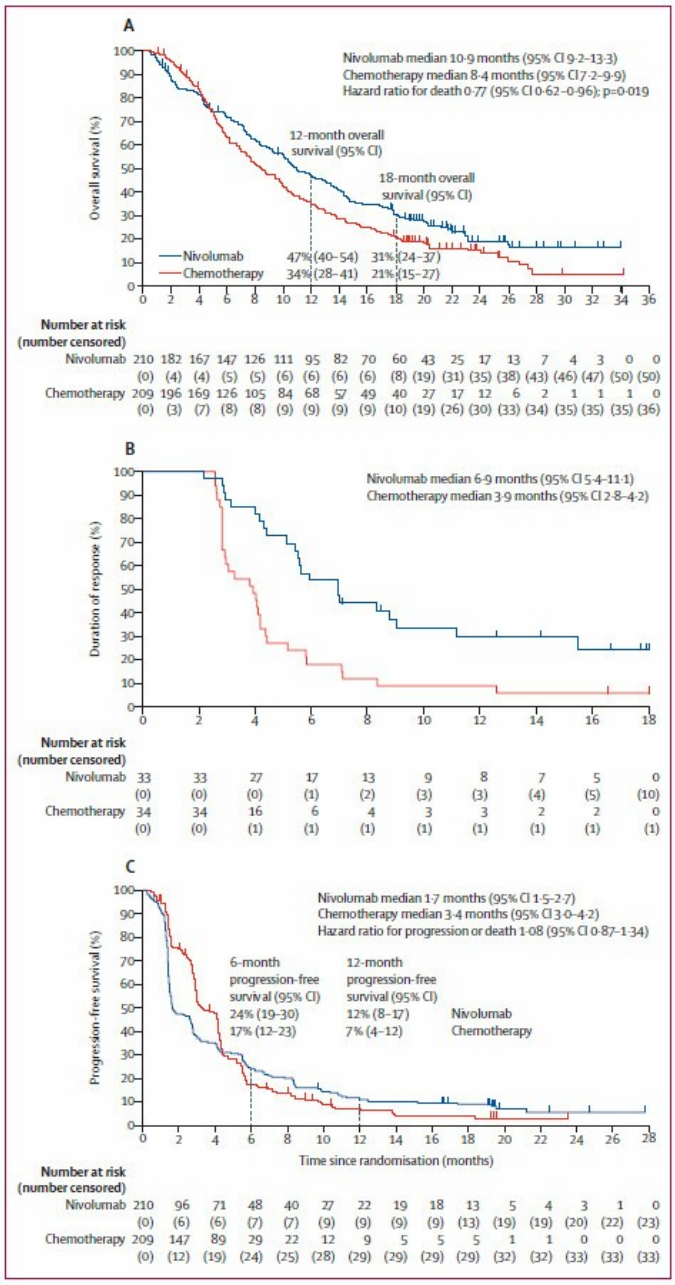
Between Jan 2016 and May 2017, 210 patients were randomised to receive nivolumab (240 mg every 2 weeks) and 209 patients were randomised to receive either paclitaxel (100 mg/m^2 every week for six weeks then one week off) or docetaxel (75 mg/m^2 every 3 weeks). Treatment was continued until disease progression or unacceptable toxicity. Treatment after disease progression was permitted at investigator's discretion. 96% of the patients included in this study were Asian.[17]

The primary endpoint was overall survival (OS) and secondary endpoints were objective response rate (ORR), progression free survival (PFS), disease control rate, time to response and duration of response. Health-related quality of life (HR-QoL) was assessed as an exploratory endpoint.[17]

Efficacy

Nivolumab was associated with a small survival benefit. After a minimum follow up of 17.6 months, the median OS was 10.9 months (95% CI 9.2 to13.3) in the nivolumab group vs 8.4 months (95% CI 7.2 to 9.9) in the chemotherapy group (HR=0.77; 95% CI 0.62 to 0.96; p=0.019). 12-month OS rates were 47% vs 34% respectively. 18-month OS rates were 31% vs 21% respectively. The median DoR was 6.9 months (95% CI 5.4 to 11.1) in the nivolumab group compared with 3.9 months (95% CI 2.8 to 4.2) in the chemotherapy group. There was no improvement in PFS nor response rate. The median PFS was 1.7 months (95% CI 1.5 to 2.7) with nivolumab vs 3.4 months (95% CI 3.0 to 4.2) with chemotherapy (HR=1.08, 95% CI 0.87 to 1.34).[17]

Kaplan-Meier curves for (A) overall survival, (B) duration of response and (C) progression free survival[17]



Response to treatment[17]

	Nivolumab group (n=171)*	Chemotherapy group (n=158)*
Objective response	33 (19%, 14–26)	34 (22%, 15–29)
Best overall response†		
Complete response	1 (1%)	2 (1%)
Partial response	32 (19%)	32 (20%)
Stable disease	31 (18%)	65 (41%)
Progressive disease	94 (55%)	51 (32%)
Not evaluable	13 (8%)	8 (5%)
Disease control	64 (37%, 30–45)	99 (63%, 55–70)
Median time to response, months (IQR)	2·6 (1·5–2·8)	1·5 (1·4–1·7)
Median duration of response, months (95% CI)	6·9 (5·4–11·1)	3·9 (2·8–4·2)
Patients with ongoing response (n/N [%])	7/33 (21%)‡	2/34 (6%)§

Data are n (%, 95% CI) or n (%), unless stated otherwise. *Randomly assigned patients who had target lesion measurements at baseline. †Percentages might not add up to 100% due to rounding. ‡One patient with a complete response and six patients with a partial response. §Two patients with a complete response.

Table 2: **Antitumour activity**

HR-QoL data was collected in more than 85% of patients across both groups using EQ-5D-3L visual analogue scale (VAS) and utility index score (UIS) questionnaires. On-treatment HRQoL collected through week 42 was significantly improved for patients in nivolumab group compared with chemotherapy group in both VAS (least squares mean 6.9, 95% CI 3.0 to 10.9; p=0.00069) and UIS (0.076, 95% CI 0.011 to 0.142; p=0.023).[17]

Toxicity

Treatment related grade 3 or 4 adverse events were reported in 18% of patients in the nivolumab group as compared to 63% of patients in the chemotherapy group. There were 5 treatment-related deaths: 2 in the nivolumab group (interstitial lung disease and pneumonitis) and 3 in the chemotherapy group (interstitial lung disease, pneumonia and spinal cord abscess).[17]

	Nivolumab group (n=209)*				Chemotherapy group (n=208)*			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
All events	99 (47%)	33 (16%)	5 (2%)	0	65 (31%)	85 (41%)	46 (22%)	2 (1%)
Serious events	13 (6%)	16 (8%)	4 (2%)†	0	6 (3%)	31 (15%)	8 (4%)	2 (1%)
Events leading to discontinuation	10 (5%)	8 (4%)	0	0	6 (3%)	9 (4%)	3 (1%)	1 (<1%)
Events leading to death‡	0	2 (1%)	0	0	0	1 (<1%)	0	2 (1%)
Events in 10% or more of treated patients in either group								
Rash	22 (11%)	1 (<1%)	0	0	29 (14%)	2 (1%)	0	0
Diarrhoea	20 (10%)	2 (1%)	0	0	18 (9%)	2 (1%)	0	0
Decreased appetite	14 (7%)	2 (1%)	0	0	46 (22%)	10 (5%)	0	0
Fatigue	14 (7%)	1 (<1%)	0	0	34 (16%)	9 (4%)	0	0
Malaise	9 (4%)	0	0	0	45 (22%)	0	0	0
Stomatitis	4 (2%)	1 (<1%)	0	0	24 (12%)	1 (<1%)	0	0
Nausea	4 (2%)	0	0	0	33 (16%)	1 (<1%)	0	0
Alopecia	3 (1%)	0	0	0	98 (47%)	0	0	0
Arthralgia	3 (1%)	0	0	0	20 (10%)	1 (<1%)	0	0
Neutrophil count decreased	2 (1%)	1 (<1%)	0	0	17 (8%)	29 (14%)	30 (14%)	0
Anaemia	1 (<1%)	4 (2%)	0	0	30 (14%)	19 (9%)	0	0
White blood cell count decreased	1 (<1%)	1 (<1%)	0	0	26 (13%)	32 (15%)	14 (7%)	0
Neutropenia	1 (<1%)	0	0	0	11 (5%)	18 (9%)	11 (5%)	0
Peripheral sensory neuropathy	1 (<1%)	0	0	0	46 (22%)	1 (<1%)	0	0
Febrile neutropenia	0	0	0	0	0	18 (9%)	4 (2%)	0
Neuropathy peripheral	0	0	0	0	21 (10%)	1 (<1%)	0	0

Data are n (%). *Patients who received at least one dose of the assigned treatment. †One case of grade 4 diabetic ketoacidosis was not reported before the data cutoff and therefore not captured here. ‡The deaths in the nivolumab group were due to interstitial lung disease and pneumonitis; the deaths in the chemotherapy group were due to pneumonia, spinal cord abscess, and interstitial lung disease. Some patients had adverse events lower than grade 5 that subsequently led to death.

Table 3: Summary of treatment-related adverse events

Evidence - Renal cell

This protocol has been superseded due to the availability of superior alternatives. The preferred regimen is ID 3594 Advanced or metastatic nivolumab (flat dosing).

The evidence supporting this protocol is provided by the phase 3 multicentre international randomised trial Checkmate 025 involving 803 patients comparing nivolumab with everolimus in patients with advanced clear-cell renal-cell carcinoma for which they had previously received 1-2 lines of anti-angiogenic therapy.[18]

Between October 2012 and March 2014, 406 patients were randomised to receive 3 mg/kg of nivolumab every 2 weeks and 397 patients were randomised to receive 10 mg everolimus orally daily. Both treatments continued until disease progression or unacceptable toxicity.

The primary end point was overall survival (OS) and secondary end points were objective response rate (ORR), progression free survival (PFS), association between OS and tumour expression of PD-L1 and the incidence of adverse events.

Efficacy

After a minimum follow-up of 14 months (median not provided), the median OS was 25.0 months in the nivolumab group vs 19.6 months in the everolimus group (HR for death=0.73; 98.5% CI 0.57-0.93; p=0.002) which met the pre-specified criterion for superiority.[18]

Kaplan-Meier curves for overall survival[18]

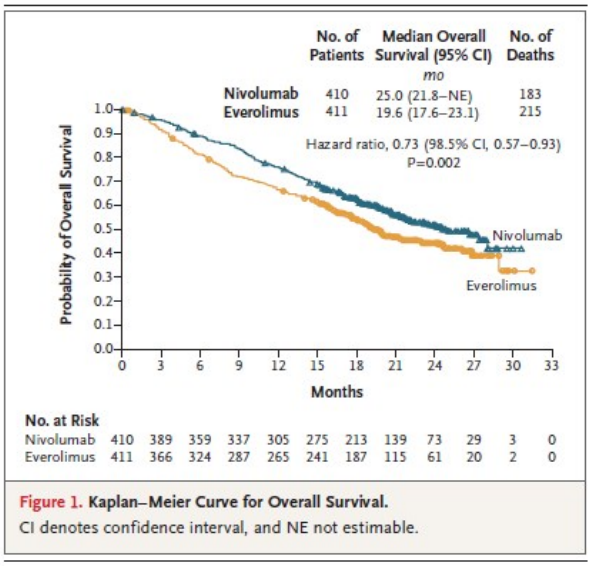


Figure 1. Kaplan–Meier Curve for Overall Survival.
CI denotes confidence interval, and NE not estimable.

Overall survival in subgroup analyses and Kaplan-Meier curves for progression-free survival[18]

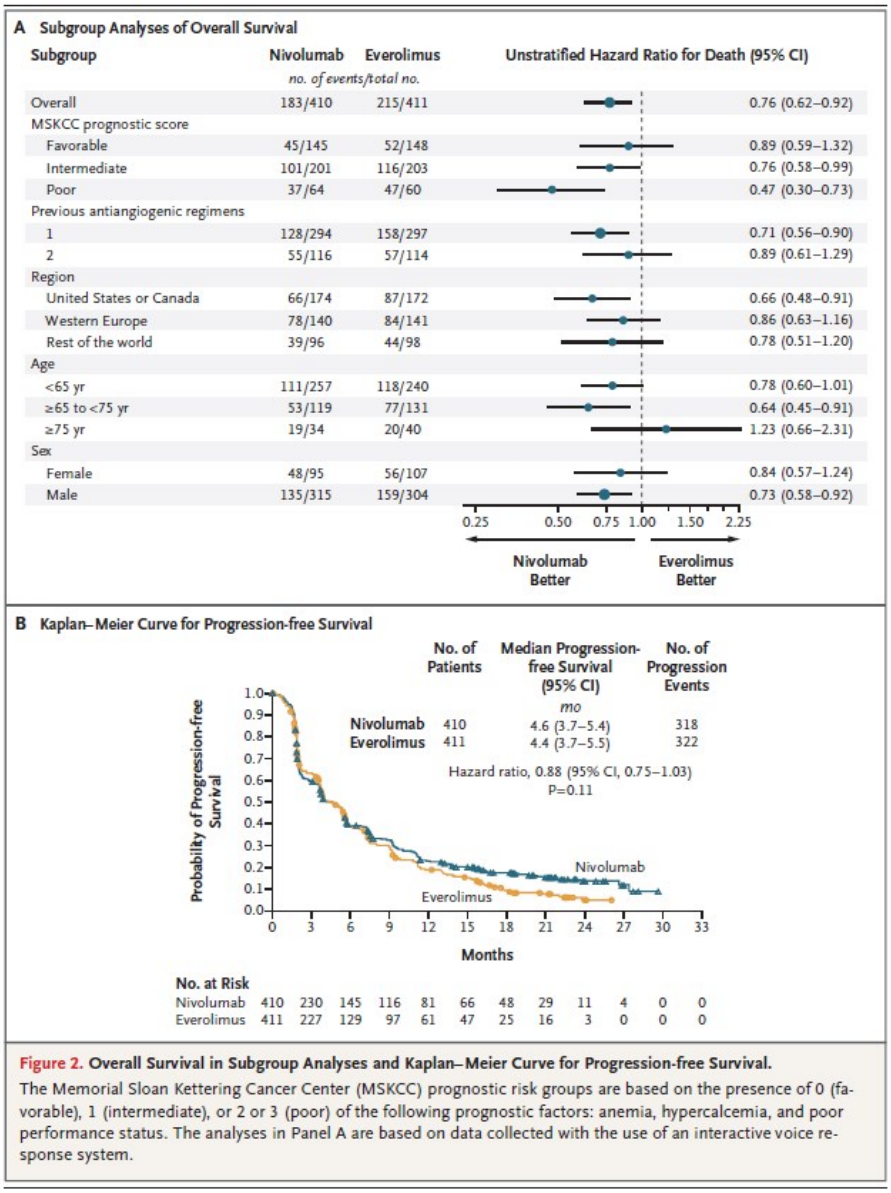


Figure 2. Overall Survival in Subgroup Analyses and Kaplan–Meier Curve for Progression-free Survival.
The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk groups are based on the presence of 0 (favorable), 1 (intermediate), or 2 or 3 (poor) of the following prognostic factors: anemia, hypercalcemia, and poor performance status. The analyses in Panel A are based on data collected with the use of an interactive voice response system.

Toxicity

Study therapy was discontinued for adverse reactions in 8% of nivolumab patients and 13% of everolimus patients. Fifty one percent (51%) of patients receiving nivolumab had a drug delay for an adverse reaction. Serious adverse reactions (grade 3 or 4) occurred in 19% of patients receiving nivolumab.[18]

Table 2. Treatment-Related Adverse Events Reported in 10% or More of Treated Patients in Either Group.

Event	Nivolumab Group (N=406)		Everolimus Group (N=397)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
All events	319 (79)	76 (19)	349 (88)	145 (37)
Fatigue	134 (33)	10 (2)	134 (34)	11 (3)
Nausea	57 (14)	1 (<1)	66 (17)	3 (1)
Pruritus	57 (14)	0	39 (10)	0
Diarrhea	50 (12)	5 (1)	84 (21)	5 (1)
Decreased appetite	48 (12)	2 (<1)	82 (21)	4 (1)
Rash	41 (10)	2 (<1)	79 (20)	3 (1)
Cough	36 (9)	0	77 (19)	0
Anemia	32 (8)	7 (2)	94 (24)	31 (8)
Dyspnea	30 (7)	3 (1)	51 (13)	2 (1)
Peripheral edema	17 (4)	0	56 (14)	2 (1)
Pneumonitis	16 (4)	6 (1)	58 (15)	11 (3)
Mucosal inflammation	11 (3)	0	75 (19)	12 (3)
Dysgeusia	11 (3)	0	51 (13)	0
Hyperglycemia	9 (2)	5 (1)	46 (12)	15 (4)
Stomatitis	8 (2)	0	117 (29)	17 (4)
Hypertriglyceridemia	5 (1)	0	64 (16)	20 (5)
Epistaxis	3 (1)	0	41 (10)	0

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History

Version 7

Date	Summary of changes
22/08/2022	Evidence for melanoma indication reviewed by Medical Oncology Reference Committee. Efficacy and toxicity updated with CheckMate 066 5 years data and CheckMate 067 6.5 years data. Version number change to V.7. No change to next review date.
20/09/2022	Blood tests in clinical information section updated to remove information about CTLA-4 containing regimens.
31/03/2023	Indications and evidence for head and neck reviewed by Medical Oncology Reference Committee. No changes. Head and neck indication to be reviewed in 2 years.
02/11/2023	Indications and evidence section for oesophageal reviewed by Medical Oncology Reference Committee, indications updated to include "adenosquamous". Oesophageal indication and evidence to be reviewed in 2 years.

Version 6

Date	Summary of changes
23/06/2022	Evidence for non small cell lung cancer indication reviewed at medical oncology reference committee meeting on 20/05/2022. Efficacy and toxicity updated with 5 years pooled data. Version number change to V.6. No change to next review date.

Version 5

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: • Indications and patient populations- previous radiation to the lungs added to precautions.

Date	Summary of changes
	• Clinical information- general irAEs, hepatitis and HIV, and fertility blocks updated. Individual irAE-related blocks removed. New block (baseline investigations) added. • Patient information- pregnancy and breastfeeding block in general advice section updated. Version number increased to V.5. Next review in 2 years.

Version 4

Date	Summary of changes
03/12/2021	New oesophageal indication approved by upper gastrointestinal reference committee and published on eviQ. Oesophageal section added to indications, evidence and patient information. Drug status updated. Version increased to V.4.

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: • Clinical information- cardiotoxicity, haematological toxicity, musculoskeletal toxicity and ocular toxicity added; rheumatological toxicity removed; immunotherapy clinical information changed to alphabetical order. • Side effects- haematological added; rheumatological replaced with musculoskeletal; immunotherapy side effects changed to alphabetical order. Version number increased to V.3.
18/10/2021	Review period extended to align with the delayed immunotherapy Reference Committee Meeting.

Version 2

Date	Summary of changes
03/04/2020	New hepatic indication approved by upper gastrointestinal reference committee on 27/03/2020 and published on eviQ. Hepatic section added to indications, evidence and patient information. Protocol and patient information title updated to 'advanced or metastatic'. Drug status updated. Version increased to V.2.
21/07/2020	Protocol reviewed electronically by melanoma reference committee. Melanoma indications updated- BRAF V600 mutation restrictions removed.

Version 1

Date	Summary of changes
15/03/2019	New flat dosing multi-indication protocol reviewed by Medical Oncology Reference Committees (head and neck, urogenital, melanoma, respiratory)
08/05/2019	Approved and published on eviQ.
20/01/2020	Links to maintenance nivolumab (weight based and flat dosing) updated in melanoma and renal cell indications. Protocol and patient information title updated to include metastatic.

First approved: 3 May 2019
Last reviewed: 4 March 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/3594
02 Mar 2024

Patient information - Advanced or metastatic - Nivolumab - 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. Immunotherapy can potentially affect any organ of the body.

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.

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: ◦ chest pain or tightness ◦ shortness of breath ◦ swelling of your ankles ◦ an abnormal heartbeat. • 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. • Tell your doctor if you have a history of heart problems or high blood pressure. • Before or during treatment, you may be asked to have a test to see how well your heart is working. • **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: ◦ bowel motions (stools, poo) that are more frequent or more liquid (diarrhoea) ◦ blood or mucous in your stool ◦ dark, tarry, or sticky bowel motions ◦ bloating, cramping, pain or tenderness in your stomach area. • Inform your doctor or nurse immediately if you get diarrhoea • Take your anti-diarrhoeal or steroid medication as directed by your doctor. • Drink plenty of fluids (unless you are on a fluid restriction). • Eat and drink small amounts more often. • Avoid spicy foods, dairy products, high fibre foods, and coffee. • **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. • You may feel dizzy, light-headed, tired, weak and appear more pale than usual. • You may get: • dark, tarry bowel motions (stools, poo) • blood in your urine or not urinating as often • dark-coloured urine • yellowing of the whites of your eyes, and/or your skin • pinpoint red spots on your skin • unexplained bleeding • major bruising • a fever • shortness of breath • a severe headache • confusion • faster heartbeat than normal • **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: ◦ fatigue ◦ severe nausea and vomiting ◦ weight loss ◦ bruising or bleeding more easily ◦ pain or tenderness on the right side of your stomach area ◦ dark coloured urine ◦ yellowing of the whites of your eyes and/or your skin ◦ itchy skin ◦ drowsiness • You will have regular blood tests to check how well your liver is working. • Take your steroid medication as directed by your doctor. • **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: • muscle or joint stiffness, especially after a period of rest • muscle weakness • pain in your muscles or joints • joint swelling • tiredness • headaches • Take your pain relief or steroid medication as directed by your doctor. • **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. • You may get: ◦ headaches ◦ fever ◦ stiff neck ◦ confusion or difficulty concentrating ◦ dizziness or drowsiness ◦ loss of consciousness ◦ muscle weakness or pain ◦ numbness or tingling in your hands or feet ◦ jerky movements. • Take your steroid medication as directed by your doctor. • **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: ◦ eye pain ◦ itchy eyes ◦ red or swollen eyes ◦ blurred or change in vision ◦ change in colour vision ◦ watery or gritty eyes ◦ dry eyes ◦ sensitivity to light. • Protect your eyes from the weather (sun and wind) by wearing sunglasses. • Use your eye drops or take your steroid medication as directed by your doctor. • **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. • You may get: ◦ headaches ◦ tiredness, dizziness or fainting ◦ abnormal heartbeat (faster than usual) ◦ a feeling of being hot or cold more easily ◦ excessive sweating ◦ weight changes ◦ a deepened voice ◦ irregular or absent periods ◦ nausea and vomiting ◦ thirsty and need to urinate more often than normal ◦ high blood sugar levels ◦ pain in your stomach area ◦ muscle pain or weakness ◦ difficulty sleeping ◦ agitated more easily ◦ changes in your mood or behaviour, such as decreased sex drive or irritability. • Take your hormone or steroid medication as directed by your doctor. • **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.**

Lung problems	• You may get: ◦ shortness of breath ◦ difficulty breathing ◦ faster heartbeat than normal ◦ chest pain ◦ new or worsening cough ◦ fever. • Your doctor will monitor how well your lungs are working during your treatment. • Take your steroid medication as directed by your doctor. • **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. • You may get: ◦ a feeling of needing to urinate less often than normal ◦ blood in your urine ◦ swollen hands and feet ◦ loss of appetite. • You will have regular blood tests to check how well your kidneys are working. • 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. • Take your steroid medication as directed by your doctor. • **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 ◦ a red rash ◦ a bumpy rash ◦ dry and itchy skin ◦ skin peeling or blisters. ◦ if you have had previous radiation therapy to an area this effect may be worse • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Avoid scratching your skin. • Avoid wearing tight fitting clothing • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • Take your antihistamine medication or apply your steroid cream as directed by your doctor. • **Tell your doctor or nurse as soon as possible if you notice any changes to the rash like pain or pus forming.**

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

Non-immune related side effects	
Appetite loss (anorexia)	• You may not feel like eating. • Try to avoid drinking fluids at meal times. • Try to eat small meals or snacks regularly throughout the day. • Try to eat food that is high in protein and calories. • 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. • Do not drive or operate machinery if you are feeling tired. • Nap for short periods (only 1 hour at a time) • Prioritise your tasks to ensure the best use of your energy. • Eat a well balanced diet and drink plenty of fluids (unless you are fluid restricted). • Try some gentle exercise daily. • Allow your friends and family to help. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Headache	• You can take paracetamol if you have a headache. • **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). • Drink plenty of fluids (unless you are fluid restricted). • Eat small meals more frequently. • Try food that does not require much preparation. • Try bland foods like dry biscuits or toast. • Gentle exercise may help with nausea. • Anti-sickness medication is usually not needed but may help in some people. • Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer treatment. • **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 - Head and neck

Telephone support

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

Head and neck cancer information

- Head and Neck Cancer Australia - headandneckcancer.org.au/

General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyond Blue – beyondblue.org.au
- Beyond Five – beyondfive.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 - Liver

Telephone support

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

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
- Liver Wellness Program – liverwellnessprogram.com/
- 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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- Patient Information – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

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
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- LGBTQI+ People and Cancer - cancercouncil.com.au/cancer-information/lgbtqi
- Look Good Feel Better – lgfb.org.au
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- Patient Information – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

Where to get more information - Non small cell lung cancer

Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support
- Call the Lung Foundation Australia on 1800 654 301

Lung cancer information

- Lung Foundation Australia – lungfoundation.com.au
- Lungevity – lungevity.org

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

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- Patient Information – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

Where to get more information - Oesophageal

Telephone support

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

Stomach and oesophageal cancer information

- Pancare Foundation – pancare.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
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- 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
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- Quitnow – quitnow.gov.au

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