

Nivolumab and Ipilimumab (Colorectal)

Indication

Microsatellite instability high (MSI-H) or mismatch repair deficiency (dMMR) metastatic colorectal cancer after prior fluoropyrimidine-based chemotherapy for metastatic disease.

(NICE TA716)

ICD-10 codes

Codes prefixed with

Regimen details

Cycles 1-4 – Nivolumab and Ipilimumab every 3 weeks

Day	Drug	Dose	Route
1	Nivolumab	3mg/kg	IV infusion
1	Ipilimumab	1mg/kg	IV infusion

Subsequent cycles - Nivolumab monotherapy every 2 or 4 weeks

Day	Drug	Dose	Route
1	Nivolumab	240mg every 2 weeks or 480mg every 4 weeks	IV infusion

The first monotherapy dose should be given 3 weeks after the last combination dose if 240mg every 2 weeks or 6 weeks after last combination dose if 480mg every 4 weeks.

Cycle frequency

Nivolumab and Ipilimumab – every 21 days

Nivolumab monotherapy – every 14 or 28 days (see above)

If patients need to switch from 2 weekly dosing to 4 weekly dosing, the first 480mg dose should be administered 2 weeks after the last 240mg dose. If patients need to switch from the 4 weekly dosing to the 2 weekly dosing, the first 240mg dose should be administered 4 weeks after the last 480mg dose.

Number of cycles

Nivolumab and Ipilimumab - 4 cycles (4 doses)

Nivolumab monotherapy – continued until disease progression or unacceptable toxicity.

Administration

Combination treatment:

Nivolumab should be given first, followed by ipilimumab.

Nivolumab may be administered without dilution as a 10mg/mL solution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-10mg/mL over 30 minutes. Nivolumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2µm).

Ipilimumab may be administered without dilution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-4mg/mL over 30 minutes. Ipilimumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2µm).

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusions for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment.

Monotherapy:

Nivolumab may be administered without dilution as a 10mg/mL solution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-10mg/mL over 30 minutes (240mg dose) or 60 minutes (480mg dose). Nivolumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2µm).

Pre-medication

Nil

Emetogenicity

This regimen has low emetogenic potential

Additional supportive medication

Loperamide if required.

Extravasation

Nivolumab and ipilimumab are neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Thyroid function tests	7 days
Calcium	7 days
Glucose	7 days
Cortisol	7 days

Investigations – pre subsequent dual immunotherapy cycles

Investigation	Validity period (or as per local policy)
FBC	72 hours
U+E (including creatinine)	72 hours
LFTs	72 hours
Thyroid function tests	72 hours
Calcium	72 hours
Glucose	72 hours
Cortisol	72 hours

Investigations – pre subsequent Nivolumab maintenance cycles

Investigation	Validity period (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Thyroid function tests	Every other cycle
Calcium	As clinically indicated
Glucose	As clinically indicated
Cortisol	As clinically indicated

Patients should be monitored for up to 5 months after last dose for adverse reactions.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 75 \times 10^9/L$
WBC	$\geq 2.0 \times 10^9/L$
Creatinine Clearance (CrCl)	$\geq 30\text{mL}/\text{min}$
Bilirubin	$\leq 1.5 \times \text{ULN}$
ALT/AST	$< \text{ULN}$
Alkaline Phosphatase	$< 5 \times \text{ULN}$

Dose modifications

Dose reductions are not recommended. Doses should be delayed until an adverse reaction resolves to \leq grade 1.

- **Haematological toxicity**

Discuss with the consultant if:

WBC $< 2.0 \times 10^9/L$

Neutrophils $< 1.0 \times 10^9/L$

Platelets $< 75 \times 10^9/L$

- **Renal impairment**

Nivolumab:

No dose modifications required in mild-moderate renal impairment. Use with caution in severe renal impairment.

Ipilimumab:

The safety and efficacy of ipilimumab have not been studied in patients with renal impairment. No specific dose adjustments are recommended in mild to moderate renal impairment.

Discuss with consultant if CrCl <30mL/min.

If creatinine increases to >1.5 x baseline levels during treatment consider nephritis - see immune related adverse reactions section below.

- **Hepatic impairment**

Nivolumab:

Nivolumab has not been studied in moderate to severe hepatic impairment. Use with caution if baseline bilirubin > 1.5 x ULN – consultant decision. If ALT increases to >3 x ULN (or baseline, if baseline abnormal) or bilirubin increases to >1.5 x ULN (or baseline, if baseline abnormal) whilst on treatment consider hepatitis – see immune related adverse reactions section below.

Ipilimumab:

The safety and efficacy of ipilimumab have not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. Ipilimumab should be administered with caution in patients with AST/ALT ≥ 5 x ULN or bilirubin > 3 x ULN.

See table below for details of when ipilimumab should be omitted or permanently discontinued:

Elevation in AST/ALT and/or bilirubin	Action
Grade 1	Continue
Grade 2	Withhold until ≤ Grade 1 and after steroid taper (if appropriate)
Grade 3-4	Discontinue

- **Other toxicities**

Severe pneumonitis and interstitial lung disease

Severe pneumonitis or interstitial lung disease, including fatal cases, have been observed with nivolumab in combination with ipilimumab or with nivolumab monotherapy. Patients should be monitored for signs and symptoms of pneumonitis including radiographic changes, dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

Grade 2 pneumonitis: withhold treatment, initiate corticosteroids (equivalent to 1mg/kg/day methylprednisolone). Once improved and corticosteroids tapered, treatment may be recommenced.

≥ Grade 3 pneumonitis: permanently discontinue treatment and initiate corticosteroids (equivalent to 2-4mg/kg/day methylprednisolone). If doses > 2mg/kg/day methylprednisolone are required consider alternative immunosuppressive agents, discuss with the consultant.

Immune-related adverse reactions

Immune-related adverse reactions can be severe or life-threatening and may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. While most immune-related adverse reactions reported occurred during the induction period, onset months after the last dose have also been reported. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and treatment-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions. Specific management guidelines for immune-related adverse reactions are described in full in the summary of product characteristics for nivolumab and ipilimumab.

Management of immune-related adverse reactions may require a dose delay or permanent discontinuation of treatment and initiation of systemic high-dose corticosteroid or, in some cases, the addition of other immunosuppressive therapy.

Permanently discontinue treatment in patients with the following symptoms:

Management of these reactions may require high dose systemic corticosteroid therapy if suspected to be immune related:

Toxicity – severe or life threatening	Definition
Gastrointestinal	Grade 3-4 diarrhoea/colitis (Nivolumab and Ipilimumab) Grade 4 diarrhoea/colitis -(Nivolumab monotherapy)
Hepatic	Grade 3-4 elevation in AST/ALT and or bilirubin
Nephritis/renal dysfunction	Grade 4 elevation in serum creatinine
Skin	Grade 4 rash, Stevens-Johnson syndrome, toxic epidermal necrolysis Grade 3 pruritus
Endocrine	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3-4 adrenal insufficiency Grade 4 diabetes
Neurological	Grade 3 or 4 motor or sensory neuropathy
Pneumonitis	Grade 3 or 4 pneumonitis
Other	Grade 4 Recurrent grade 3 Persistent grade 2-3 despite treatment modification; inability to reduce corticosteroid dose to 10mg prednisolone/day (or equivalent)

Withhold treatment in patients with the following symptoms:

Treat with corticosteroids.

Upon improvement and after steroid taper treatment may recommence.

Toxicity	Definition
Gastrointestinal	Grade 2 diarrhoea/colitis (Nivolumab and Ipilimumab) Grade 3 diarrhoea/colitis (Nivolumab monotherapy)
Hepatic	Grade 2 elevation in AST/ALT and or bilirubin
Nephritis/renal dysfunction	Grade 2-3 elevation in serum creatinine
Skin	Grade 3 rash
Endocrine	Symptomatic grade 2-3 hypothyroidism Symptomatic grade 2-3 hyperthyroidism Symptomatic grade 2-3 hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes
Neurological	Grade 2 motor or sensory neuropathy
Pneumonitis	Grade 2 pneumonitis
Other	Grade 3 (first occurrence)

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Immune reactions may occur during or after completion of treatment.

Infusion related reactions

Colitis

Hepatitis

Peripheral neuropathy

Hypopituitarism

Hypothyroidism

Uveitis

Renal failure

Cardiac events

Thromboembolism

Interstitial lung disease

Pneumonia, upper respiratory tract infection

- **Frequently occurring side effects**

Pruritus

Rash

Nausea and vomiting

Diarrhoea

Fatigue

Decreased appetite

Abdominal pain

Hypertension

Arthralgia

- **Other side effects**

Tumour pain

Headache, dizziness

Blurred vision

Raised transaminases

Significant drug interactions – for full details consult product literature/ reference texts

Anticoagulants: increased risk of GI haemorrhage – monitor closely.

Corticosteroids: use of systemic corticosteroids at baseline, before starting ipilimumab and/or nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agents. However, systemic corticosteroids or other immunosuppressants can be used after starting ipilimumab and/or nivolumab to treat immune-related adverse reactions.

Additional comments

Ipilimumab is contraindicated in patients with active, life-threatening autoimmune disease, or patients who are receiving immunosuppressive treatment following organ transplantation graft where immune activation is potentially imminently life threatening.

The prescriber must discuss the risks of nivolumab therapy with the patient and provide the Patient Alert Card.

Contraception: Adequate methods of contraception should be used during therapy and for 8 weeks after last dose.

Sodium: Ipilimumab and nivolumab concentrate each contain 0.1mmol (2.30mg) sodium per mL. Care if low sodium diet.

References

- National Institute for Health and Clinical Excellence TA716. Accessed 18 November 2021 via www.nice.org.uk
- Summary of Product Characteristics Ipilimumab (Bristol Myers Squibb) accessed 18 November 2021 via www.medicines.org.uk
- Summary of Product Characteristics Nivolumab (Bristol Myers Squibb) accessed 18 November 2021 via www.medicines.org.uk
- Lenz, H-J. et al. First-line Nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: The Phase II Checkmate 142 Study. J Clin Onc Published online 12th October 2021

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