Systemic Anti-Cancer Therapy Protocol

Nivolumab in Combination with Ipilimumab Advanced Renal Cell Carcinoma

PROTOCOL REF: MPHANILPUR
(Version No: 1.2)

Approved for use in:

This protocol has been temporarily amended - please see the SRG Guidelines during COVID-19 Urology Cancer.

- First line treatment of intermediate or poor risk advanced renal cell carcinoma; it must have a clear cell component or is a papillary RCC.
- The intermediate or poor risk is assessed by the International Metastatic RCC Database Consortium (IMDC).
- Patients have unresectable advanced or metastatic renal cell adenocarcinoma.
- No treatment breaks for longer than 12 weeks beyond the expected 3 weekly cycle length.

Blueteq registration required: See blueteq for further eligibility criteria

Dosage:

Drug	Dosage	Route	Frequency
Ipilimumab	1mg/Kg	IV	Every 3 weeks for a maximum of **four doses** in combination with nivolumab
Nivolumab	3mg/Kg (while having treatment with ipilimumab)	IV	Every 3 weeks for a maximum of **four doses** in combination with ipilimumab
Nivolumab (Monotherapy)	480mg (following completion of ipilimumab treatment)	IV	Every 4 weeks from cycle 5 onwards

Extravasation risk:

Both considered to be neutral

Patient Counselling Points:

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitor for signs of infection/sepsis

Administration:

Combination cycles 1- 4:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Nivolumab**	3mg/Kg	IV	100mL sodium chloride 0.9%, infused over 30minutes in a non-pyrogenic line with a 0.2micron to 1.2 micron filter
1	Sodium chloride 0.9%	100mL	IV	Flush
Switch to a new administration infusion set and ensure a 30 minute infusion break occurs between nivolumab and ipilimumab.				
1	**Ipilimumab**	1mg/Kg	IV	No diluent added. Infused over 30minutes in a non-pyrogenic line with a 0.2 or 1.2 micron filter
1	Sodium chloride 0.9%	100mL	IV	Flush

Repeat **every 21 days** for a maximum of four cycles

Treatment then continues with nivolumab monotherapy starting at least 6 weeks after the last nivolumab/ipilimumab combination dose has been given.

Monotherapy cycle 5 and onwards:

Day	Drug	Dose	Route	Diluent and rate
1	**Nivolumab**	480mg	IV	100mL sodium chloride 0.9%, infused over 60minutes in a non-pyrogenic line with a 0.2micron to 1.2 micron filter

Repeat **every 28 days** until acceptable toxicity or disease progression

Dosing in renal and hepatic impairment:

Renal	Nivolumab	Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to make any specific dose recommendation.
	Ipilimumab	Safety and efficacy has not been studied in patients with renal impairment. No specific dose adjustment is necessary in patients with mild to moderate renal dysfunction. For patients with a GFR below 30mL/min discuss with consultant before commencing treatment.

Hepatic	Nivolumab	No dose adjustment is required in patients with mild hepatic impairment. Data from patients with moderate or severe hepatic impairment is too limited to make any specific dose recommendations. Manufacturers of nivolumab advice caution in patients with moderate (total bilirubin > 1.5 x 3 x the upper limit of normal (ULN) and any AST) or severe (total bilirubin > 3 x ULN and any AST) hepatic impairment.
	Ipilimumab	Safety has not been studied in patients with hepatic impairment. No specific dose adjustment is necessary in patients with mild hepatic impairment. Administer with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline.

Main Toxicities:

Please refer to the Acute Oncology I-O Management guidance for specific advice

Immune related toxicities	
Immune-Mediated Pneumonitis	Monitor patients for signs and symptoms and evaluate with radiographic changes, dyspnoea and hypoxia.

Immune-Mediated Colitis	Monitor patients for signs and symptoms such as abdominal pain and mucus or blood in stool. Infectious and disease-related aetiologies should be ruled out.
Other Immune-Mediated Toxicities: • Hepatitis • Hypophysitis • Nephritis • Hyperthyroidism or Hypothyroidism Less frequently: • exfoliative dermatitis, • uveitis, • arthritis, • myositis, • pancreatitis, • haemolytic anaemia, • Guillain-Barré syndrome	Monitor LFTs, biochemistry, cortisol, TFTs and blood glucose, consider corticosteroids for grade 2 or greater.
Other non-immune adverse events: • Fatigue, • Anaemia, • Cough, • Dyspnoea, • Nausea, • Decreased appetite • Pruritis, • Rash • Constipation, • Diarrhoea • Arthralgia	Symptomatic management for grade 1 with close monitoring
Laboratory abnormalities: • Hyponatraemia, • Hypocalcaemia, • Hyperglycaemia, • Hypertriglyceridaemia	Monitor at each cycle and rule out immune-medicated reaction

Investigations and treatment plan:

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x				Every 12 weeks or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs, TFTs, cortisol, blood glucose, LDH, CRP	x	x	x	x	Every cycle
Lipid profile (cholesterol)	x				At baseline then if clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x				At baseline then if clinically indicated

Full set of observations (*BP, hear rate, temperature, respiratory rate and O_2 sats*)	x	x	x	x	Every cycle
Creatinine Clearance (Cockcroft and Gault)	x	x	x		x
CT scan	x				Every 12 weeks or as clinically indicated
Trop-T, CK, pro-BNP	x				**At baseline for all Renal and Melanoma and thereafter as clinically indicated** (ECG to be reviewed by clinical team)
ECG	x				
Weight recorded	x	x	x	x	Every cycle
Height recorded	x				

Dose Modifications and Toxicity Management:

Dosing delay or discontinuation may be required based on individual safety and tolerability.

When nivolumab is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or nivolumab monotherapy could be resumed based on the evaluation of the individual patient. **There is no evidence supporting the use of single agent Ipilimumab.**

Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC clinical network immunotherapy acute oncology guidelines.

Treatment Threshold:

Administer treatment on day 1 if:

Platelets	Neutrophils	Creatinine Clearance	Bilirubin	AST/ALT	Alkaline Phosphatase	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≥30 mL/min	<3 x ULN	<5 x ULN	<5 x ULN	Within range or no change from base line

*ULN = upper limit of normal

However at cycle one; platelets must be above the upper limit of normal.

<u>Toxicity management:</u>

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Toxicity Grade	Action
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.
Grade 2 Moderate	Withhold treatment until resolved to <grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 Severe	Withhold treatment. Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

References:

1. Summary of Product Characteristics, Opdivo® 10mg/mL concentrate for solution for infusion, Nivolumab, BMS, www.medicines.org.uk [accessed on 05/04/2019].
2. Summary of Product Characteristics, Yervoy 5mg/mL concentrate solution for infusion, Nivolumab, BMS, www.medicines.org.uk [accessed on 05/04/2019].
3. Motzer R. J., et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, New Eng. Journal of Medicine 2019.