Nivolumab and Ipilimumab (for kidney cancer and colorectal cancer)

NB: This regimen uses different doses to the nivolumab/ipilimumab combination regimen used in the treatment of melanoma or mesothelioma
Check that the correct dosing regimen is being used

Indication

First line treatment of intermediate or poor risk advanced renal cell carcinoma (RCC)

dMMR or MSI-H metastatic colorectal cancer (mCRC)

Regimen details

Drug	Fluid	Route	Time
Nivolumab 3mg/kg*	50ml Sodium chloride 0.9%	IV	30 mins
Ipilimumab 1mg/kg	50ml Sodium chloride 0.9%	IV	30 mins

*Use 240mg flat dose in 1st line mCRC

Repeat every 3 weeks for 4 cycles

Followed by:

Drug	Route	Time
Nivolumab 1200mg	SC	3-5 mins

1st dose of 4-weekly nivolumab should be given:

- **6 weeks after the last dose of combination treatment for RCC**
- **3 weeks after the last dose of combination treatment for mCRC**

Repeat every 4 weeks as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (for 1st line mCRC, treatment is limited to a maximum of 2 calendar years)

Cycle frequency

As above

Number of cycles

As above

Administration

Intravenous

Administer the drug solution using a volumetric pump through an intravenous line containing a sterile non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer)

When administered in combination, nivolumab should be given first

Patients should be monitored for infusion related reactions

Subcutaneous (Nivolumab)

SC Nivolumab should be administered subcutaneously over 3-5 minutes into the subcutaneous tissue of the abdomen or thigh. Alternate injection sites for successive injections. Do not inject into areas where the skin is tender, red, or bruised, or areas where there are scars or moles. If the administration of OPDIVO solution for injection is interrupted, it can be resumed at the same site, or at an alternate site.

Allow the solution to reach ambient temperature before administration.

Pre-medication

Nil

Emetogenicity

No routine antiemetics required

Additional supportive medication

Nil

Extravasation

Neutral

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine and bicarbonate)	14 days
LFT (including AST)	14 days
Calcium	14 days
Serum samples for HIV, Hep C antibody and HBs Ag if risk factors	Baseline
Cortisol	Baseline
Luteinizing hormone	Baseline
Follicle stimulating hormone	Baseline
Testosterone	Baseline

Cautions

Presence of HIV, hepatitis B or C

Patients on high dose immunosuppression

Autoimmune disease: history of active inflammatory bowel disease, history of symptomatic autoimmune disease e.g. rheumatoid arthritis, SLE, autoimmune vasculitis, history of autoimmune neuropathy e.g. Guillain-Barre

Patients should be on the lowest clinically effective dose of systemic steroids

No dose adjustment is required for mild-moderate renal impairment. No data are available for severe renal impairment (GFR <30ml/min)

No data are available for liver impairment (bilirubin >1.5 ULN)

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), TFTs every cycle for the first 4 doses, then routinely every other cycle or as per clinician instructions

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	≥ 1.0 x 10^9/L
Platelet count	≥ 75 x 10^9/L
Creatinine clearance	≥ 30 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 2.5 x ULN if no liver mets, <5 x ULN if liver mets

Dose modifications

Dose de-escalation and/or escalation of nivolumab or ipilimumab is otherwise not allowed.

For information on treatment of Immune related side effects see:

https://www.healthierlsc.co.uk/canceralliance/chemotherapy-protocols/immunotherapy-toxicity-guidelines

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 haemorrhage – avoid or closely monitor.

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

Yervoy SPC - https://www.medicines.org.uk/emc/product/4683
Opdivo SPC - https://www.medicines.org.uk/emc/product/6888
OPDIVO 600 mg/5 ml solution for injection - Summary of Product Characteristics (SmPC) - (emc) | 100807

South West Clinical Network SACT protocols - http://www.swscn.org.uk/guidance-protocols/cancer-protocols/
Clatterbridge SACT protocol - Nivolumab in combination with Ipilimumab Advanced Renal Cell Carcinoma

THIS PROTOCOL HAS BEEN DIRECTED BY DR PARIKH, DESIGNATED LEAD CLINICIAN FOR KIDNEY CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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