PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

NIVOLUMAB WITH IPILIMUMAB METASTATIC COLORECTAL CANCER (mCRC)

PROTOCOL REF: MPHAMCRCGA
Version No: 1.0

Approved for use in:

Patients with microsatellite instability high (MSI-H) or mismatch repair deficiency (dMMR) metastatic colorectal cancer (mCRC) after prior fluoropyrimidine-based chemotherapy for metastatic disease

Under the following conditions:

- BRAF and RAS status must be confirmed as wild type or mutant
- ECOG performance status of 0 or 1
- No symptomatic brain or leptomeningeal metastases
- The patient has not received any prior treatment with an anti-PD-1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless the patient has been treated with nivolumab and ipilimumab in a company early access scheme
- The patient has received previous systemic fluoropyrimidine-based therapy for metastatic colorectal cancer unless the fluoropyrimidine part of chemotherapy was contra-indicated on account of documented DPD deficiency

*****Blueteq registration is required******

Treatment break approval is required for a break of more than 12 weeks beyond cycle

Exclusions

History of pneumonitis, organ transplantation, HIV infection, active hepatitis B or C infection

Active infection requiring systemic treatment

Less than 4 weeks from major surgery

History of clinically severe autoimmune disease

Dosage:

Combination with Nivolumab and Ipilimumab can be given up to a maximum of 4 cycles, Nivolumab should continue until disease progression or unacceptable toxicity occurs.

Drug	Dosage	Route	Frequency
Nivolumab	**3mg/kg** (while having combination treatment with ipilimumab)	IV	3 weekly in combination with ipilimumab for 4 doses
	480mg (monotherapy following completion of ipilimumab treatment)		Followed by monotherapy 480mg 4 weekly until disease progression or unacceptable toxicity
	OR		
	240mg (monotherapy following completion of ipilimumab treatment)*	IV	Followed by monotherapy 240mg 4 weekly until disease progression or unacceptable toxicity
Ipilimumab	**1mg/kg**	IV	3 weekly for a maximum of 4 doses in combination with nivoloumab

*Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 2-weekly regime may be used.

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

- Guidelines for permanent discontinuation or withholding of doses are contained in the 'Dose Modifications' Section.
- For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Extravasation risk:

Both agents are monoclonal antibodies and considered to be neutral.

Refer to the CCC policy for the '**Prevention and Management of Extravasation Injuries'.**

Administration:

Give Nivolumab before Ipilimumab.

Women of childbearing potential should use effective contraception throughout treatment and for at least 5 months following the last treatment dose.

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

Dosing in renal and hepatic impairment (Prior to start of treatment ONLY/Baseline):

Renal	Nivolumab	eGFR < 30ml/min/1.73- limited data use with caution.
	Ipilimumab	CrCl ≥ 10ml/min proceed with treatment **CrCl < 10ml/min- use with caution. Discuss with clinical team.**

Hepatic	Nivolumab	Administered with caution in patients with: Moderate (total bilirubin > 1.5 -3 × ULN and any AST) or **Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment. Discuss with clinical team** * Within normal limits or high
	Ipilumimab	

Interactions:

Additional monitoring of signs of gastrointestinal bleeding for those on anticoagulants required with Ipilimumab.

Treatment schedule:

Combination

Day	Drug	Dose	Route	Diluent and rate
1	**Nivolumab**	**3mg/kg**	**IV**	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron 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 30 minutes in a non-pyrogenic line with a 0.2 to 1.2 micron filter
1	Sodium chloride 0.9%	100mL	IV	Flush

Repeated every 21 days for 4 cycles only.

Treatment then continues with nivolumab monotherapy starting at least **6 weeks** after last Nivolumab/Ipilimumab combination dose given.

Monotherapy

Day	**Drug**	**Dose**	**Route**	Diluent and rate
1	**Nivolumab**	**480mg (4 weekly) OR 240mg (2 weekly)***	**IV infusion**	100mL sodium chloride 0.9%. Infused over 60 minutes (for 480mg) *or 30 minutes (for 240mg)* in a non-pyrogenic line with a 0.2 micron filter

*480mg dosing is **unlicensed** in mCRC but permitted by CDF funding. Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 2 weekly regime may be used.*

Repeated every 28 days until unacceptable toxicity or disease progression.

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.).
Please refer to the CCC **Hypersensitivity; Management Prevention Policy.**

Main toxicities:

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Immune related toxicities	
Immune-Mediated Pneumonitis	Monitor patients for signs and symptoms and evaluate with radiographic imaging and administer corticosteroids for toxicities of grade 2 or above.
Immune-Mediated Colitis	Monitor patients for signs and symptoms and administer corticosteroids for grade 2 or greater.
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		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 (AST, ALT and bilirubin), 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,	x				At baseline then if clinically indicated

Testosterone (men only), ESR					
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				Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5 x upper limit of normal or baseline
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				

Pregnancy test if applicable

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.**

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Treatment Threshold:

Administer treatment on day 1 if:

Platelets	Neutrophils	Serum Creatinine	Bilirubin	AST/ALT	Alkaline Phosphatase	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≥1.5 x ULN or Baseline	<3 x ULN	<5 x ULN	<5 x ULN	Within range or no change from base line

ULN = upper limit of normal

Platelets must be within normal range prior to Cycle 1.

Toxicity management:

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. Nivolumab SPC & Ipilimumab SPC accessed on *https://www.medicines.org.uk/emc* [accessed 24.09.21]
2. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; **20:** e201–08. *https://www.thelancet.com/cms/10.1016/S1470-2045(19)30145-7/attachment/58f32d43-6320-4c6c-8204-a94f06ed2199/mmc1.pdf* [accessed 24.09.2021]
3. BNF available via: *https://bnf.nice.org.uk/*
4. NICE: TA716 Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency w*ww.nice.org.uk/guidance/ta716* [accessed 24.09.21]

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
October 2021	1.0	Anna Taylor - Colorectal SRG Pharmacist	New protocol