Indication	1st line treatment for metastatic RAS wild-type colorectal cancer or as 2nd line treatment if treated with 1st line pembrolizumab for MSI-H/dMMR disease (or 1st line nivolumab which was previously available as an Interim COVID option). NB: The patient may have received neoadjuvant cytotoxic chemotherapy for potentially resectable metastatic colorectal cancer. *Please note, If the patient has BRAF V600 mutation-positive disease, the patient will be ineligible for encorafenib plus cetuximab as a subsequent line of therapy if they receive a cetuximab/panitumumab-containing regimen as first-line therapy.*
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 14 days Continue until disease progression, unacceptable toxicity or patient choice to stop treatment. 2 weekly administration of cetuximab is unlicensed, Trust policy regarding the use of unlicensed treatments must be followed. NB: continued use of cetuximab beyond 1st line therapy is not commissioned once disease progression has occurred with 1st line treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, LFTs and U&Es baseline and at each cycle, including calcium, potassium and magnesium. • Neuts <1.5 and PLT<100 delay one week. • **DPD testing:** DPD testing must be undertaken in all patients before starting treatment; the result must be checked before treatment is started. • **ECG should be checked prior to cycle 1.** • **Cardiotoxicity:** caution in patients with prior history of coronary heart disease, arrhythmias and angina pectoris. • Patients should be assessed at each visit for symptoms of visual disturbance (see below). • **Hepatic impairment:** o **Cetuximab:** no data available in patients with impaired hepatic function. o **Fluorouracil:** In moderate hepatic impairment consider reducing the dose by 30% and for severe impairment by 50%. If the bilirubin is >85umol/L and / or AST >180 fluorouracil is contra-indicated. o **Irinotecan:** Consider dose reduction if bilirubin >/= 26µmol/L. Bilirubin >51µmol/L clinical decision. • **Renal impairment:** o **Oxaliplatin:**If CrCl <30ml/min consider 50% of original dose. o **Cetuximab:** no data available in patients with impaired renal function. o **Fluorouracil:** consider dose reduction in severe renal impairment. • **Management of adverse reactions and dose adjustments:** o Dose reduction of cytotoxic chemotherapy should be considered if any other grade 3(other than those listed below) or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1.

- Patients with persistent diarrhoea for >/= 24hrs should have an FBC and if neutropenic start a broad-spectrum antibiotic in line with Trust antibiotic policy.
- If the patient experiences excessive toxicity with irinotecan and/or oxaliplatin, cetuximab can be subsequently continued in combination with a fluoropyrimidine without irinotecan and/or oxaliplatin until disease progression.

- **CETUXIMAB**
  - **Cetuximab infusion rate and infusion related reactions (IRRs):**
  - Cetuximab can cause severe infusion related reactions, pre-meds must be given 1 hour before 1st administration and then 30-60mins prior to subsequent administrations and patients must be monitored every 30 minutes during the infusion and for a 1-hour period after. If the patient experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions. For severe reactions discontinue treatment.
  - **Interstitial lung disease (ILD):** Patients should report any new or worsening respiratory symptoms. Cetuximab should be permanently discontinued in patients with confirmed ILD.
  - **Ocular toxicities:** Cetuximab should be used with caution in patients with a history of keratitis ulcerative keratitis or severe dry eye. If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.
  - **Skin reactions:** Skin reactions are very common and treatment interruption or discontinuation may be required, see tables 1 and 2 for guidance. Do not use CTCAE grading to assess cetuximab induced rash. The rash is classified as follows:
    Moderate: requires 1st line treatment on development of rash
    Severe: failed 1st line treatment.
- **OXALIPLATIN**
  - **For guidance on the assessment and management of oxaliplatin induced neuropathy see KMCC website:**
    https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/guidelines-for-the-management-of-sact-induced-adverse-reactions/
  - Symptoms of sensory or functional neuropathy may include tingling or numbness which may persist to the next pre-chemotherapy assessment.
  - This guidance is for patients receiving treatment outside the context of a clinical trial. For patients being treated within a clinical trial setting, follow trial protocol (using assessment below as far as possible).
  - Do not assess oxaliplatin induced neuropathy using CTC toxicity criteria.
  - Dysaesthesia in the jaw is an unpleasant sensation and/or pain in the jaw.
  - Laryngopharyngeal spasm is a sensation of difficulty in swallowing / breathing.
  - Neurology referral should be considered in severe cases of oxaliplatin induced neuropathy.
  - Initial dose reductions should be at a 25% level. If there is no improvement or worsening symptoms, based on an assessment of risk and benefit, consider further dose reduction. Once reduced, doses should not be re-escalated.
- **Common drug interactions (for comprehensive list refer to BNF/SPC):**
  - **5FU:** 5FU must not be given with concurrent sorivudine or derivatives (e.g. brivudine), see SPC.
  - Monitor PT and INR regularly in patients taking coumarin-derivative anticoagulants.
  - Monitor phenytoin levels with concomitant use.
  - Caution with folinic acid or folic acid – potential for increased toxicity.

	○ **Oxaliplatin:** Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored. ○ Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis. ○ **Irinotecan:** St. John's Wort should not be administered with irinotecan. Concurrent administration with strong inhibitors (e.g. ketoconazole, itraconazole, clarithromycin) or inducers (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital) of cytochrome P450 3A4 (CYP3A4) may alter the metabolism of irinotecan and should be avoided. • **Driving:** Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following treatment, and advised not to drive or operate machinery if these symptoms occur.
References	Blueteq form accessed online 02.11.2022 KMCC protocol COL-030 v2 SPC accessed online 02.11.2022

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Acne-like cetuximab induced rash: Treatment Principles		
Severity of rash.	**Moderate: on development of rash requires 1st line treatment**	**Severe: requires 2nd line treatment**
Systemic antibiotics	YES Doxycycline 100mg od or alternatively Minocycline 100mg od	YES Doxycycline 100mg od or alternatively Minocycline 100mg od
Delay Cetuximab	NO	YES Consultant referral required
General remarks	• All patients should use an emollient whilst on cetuximab • Oral tetracyclines: treat for a prolonged period to benefit from their anti-inflammatory properties. Advise patients to take appropriate precautions against prolonged sun exposure • Consider oral anti-histamine for symptomatic relief	

Table 2: Cetuximab treatment interruption and re-introduction in response to skin toxicity

Occurrence of skin toxicity	**Adjustment to cetuximab treatment**	
	SEVERE (failed 1st line treatment)	On resolution to MODERATE
First time	Interrupt treatment	Treatment may be resumed at previous dose
Second time	Interrupt treatment	Treatment may be resumed but at reduced dose (20% DOSE REDUCTION)
Third time	Interrupt treatment	Treatment may be resumed but at reduced dose (40% DOSE REDUCTION)
Fourth time	Discontinue treatment	

Repeat every 14 days

Day	Drug	Dose	Route	Infusion Duration	Administration	
1	Dexamethasone	8mg	PO		To be administered 60 minutes prior to cetuximab on **cycle 1.** From **cycle 2** onwards administer 30-60 minutes prior to cetuximab**.**	
	Chlorphenamine	10mg	IV	stat		
	CETUXIMAB	**500mg/m²**	IV	1st dose over 2hrs 2nd dose onwards – over 90 mins (or 60 mins if tolerated)	To be given undiluted or diluted in 0.9% sodium chloride to a total volume of 250ml Flush line with sodium chloride 0.9% IV post cetuximab infusion.	
	Cytotoxic chemotherapy to be administered 1 hour after the end of the cetuximab infusion					
	Aprepitant	125mg	PO		Take one 125mg capsule one hour prior to chemo on Day 1	
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml	
	Flush with 5% glucose before and after oxaliplatin administration					
	OXALIPLATIN	**85mg/m²**	IV	2-6 hrs	250-500ml 5% glucose (to give a concentration between 0.2 mg/ml and 0.70 mg/ml)	**Can be run concurrently**
	CALCIUM FOLINATE (folinic acid)	350mg	IV	2 hours	Glucose 5% 250ml	
	Atropine	0.25mg	SC	bolus	if required for acute cholinergic syndrome.	
	IRINOTECAN	**150mg/m²**	IV	60-90 min	In 250ml NaCl 0.9% or glucose 5% with a final volume of 180ml-240ml (pre-made bag)	
1-2	**5-FLUOROURACIL**	**3000mg/m²/over 48 hrs**	IV	**48 hr pump**	continuous infusion	
TTO	Drug	Dose	Route	Directions		
Day 1	Loperamide	2mg-4mg	PO	Take 2 after first loose stool then one every 2 hrs for at least 12 hrs or until 12 hrs after last loose stool (max. 48 hrs).		
	Dioralyte Sachets	1 sachet	PO	Take the contents of ONE sachet dissolved in 200ml of water after each loose motion.		
	Dexamethasone	6mg	OM	For 3 days		
	Metoclopramide	10mg	PO	10mg TDS for 3 days and then 10mg TDS PRN. Do not take for more than 5 consecutive days.		
	Aprepitant	80mg	PO	Take one 80mg capsule each morning on day 2 and day 3 only		
	NB If required prescribe doxycycline 100mg OD at onset of rash.					