Indication	For chemotherapy-naïve RAS wild-type metastatic colorectal cancer. NB: The patient may have been treated with 1st line pembrolizumab or 1st line nivolumab which was previously available as an Interim COVID option if they have MSI-H/dMMR disease. 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.

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.
	• **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.**
	• Patients should be assessed at each visit for symptoms of visual disturbance (see below).
	• Monitor FBC, LFTs and U&Es at baseline and prior to each cycle in particular $Mg2^{+}$, K^{+} and $Ca2^{+}$ and for up to 8 weeks after completion of treatment.
	• Neuts <1.5 and PLT<100 delay one week.
	• **Hepatic impairment:**
	  ○ **Panitumumab:** no available guidance clinical decision.
	  ○ **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.
	  ○ **Irinotecan:** Consider dose reduction if bilirubin > 26µmol/L.
	• **Renal impairment:**
	  ○ **Panitumumab:** no available guidance clinical decision.
	  ○ **Oxaliplatin:** If CrCl <30ml/min consider 50% of original dose.
	  ○ **Fluorouracil:** consider dose reduction in severe renal impairment.
	• **Management of adverse reactions and dose adjustments:**
	• 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, panitumumab can be subsequently continued in combination with a fluoropyrimidine without irinotecan and/or oxaliplatin until disease progression.
	• **PANITUMUMAB**
	• Panitumumab can cause severe infusion related reactions. 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. Infusion related reactions can occur more than 24 hours post infusion, patients should be made aware of this and report hypersensitivity reactions if they occur.

	• Interstitial lung disease (ILD): Patients should report any new or worsening respiratory symptoms. Panitumumab should be permanently discontinued in patients with confirmed ILD. • Patients presenting with signs and symptoms of keratitis should be referred to an ophthalmologist. If a diagnosis of ulcerative keratitis is confirmed, treatment with panitumumab should be interrupted or discontinued, 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. If grade 1 skin rash occurs treat with emollients. If >/= grade 2 skin rash occurs d/w consultant. If >/= grade 3 interrupt panitumumab and see table 1 for guidance. Patients should be advised to ensure regular use of moisturisers and sun protection (> SPF 15). It is recommended that patients experiencing rash/dermatological toxicities wear sunscreen, hat and limit sun exposure as sunlight can exacerbate any skin reactions that may occur. • **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. ○ 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. ○ Dose reduction should be considered if any other grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ 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 11.06.21 SPC accessed online 11.06.21 ARIA regimen COL-035

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

Table 1 Panitumumab dermatological toxicity

Occurrence of skin symptom(s): ≥ grade 3	**Management**
1st occurrence	Withhold 1 or 2 doses Improved (< grade 3): continue at 100% of original dose Not recovered: Discontinue
2nd occurrence	Withhold 1 or 2 doses Improved (< grade 3): continue at 80% of original dose Not recovered: Discontinue
3rd occurrence	Withhold 1 or 2 doses Improved (< grade 3): continue at 60% of original dose Not recovered: Discontinue
4th occurrence	Discontinue

Repeat every 14 days

Day	Drug	Dose	Route	Infusion Duration	Administration	
1	**PANITUMUMAB**	**6mg/kg**	IV	1st dose 60 min 2nd dose onwards- Over 30-60 min (if previously tolerated.) Doses higher than 1,000 mg should be infused over approximately 90 minutes.	Sodium chloride 0.9% 100ml via in-line 0.22-micron filter. The final concentration should not exceed 10mg/ml. Flush line with sodium chloride 0.9% IV pre and post panitumumab 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	
	Dexamethasone	8mg	PO			
	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	**48hr 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 then 10mg TDS when required. 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.			