R-IDELALISIB FOR CLL

First-line use in CLL with a 17p deletion or TP53 mutation, *provided the patient is not suitable for any other regimen*
For treatment of CLL which has relapsed within 24 months of previous treatment
NICE approved October 2015

All patients should be screened for hepatitis B virus before starting treatment

Drugs/Dosage:	**Idelalisib**	150mg	PO	twice daily, continuous until disease progression or unacceptable toxicity
	Rituximab	375mg/m^2	IV	fractionated over Day 1 and Day 2 of the course (see Administration section)
	then, starting 2 weeks after the 375mg/m^2 dose;			
	Rituximab (dose 'banded' as table below)	500mg/m^2	IV	every 2 weeks for 4 doses (on week 2, week 4, week 6 & week 8), then every 4 weeks for 3 doses (on week 12, week 16 & week 20)

Other Drugs: **Rituximab Premedication** (to be administered before **all** infusions):

Paracetamol 1000mg	po	60 minutes before rituximab
Chlorphenamine 10mg	IV	15 minutes before rituximab
Dexamethasone 8mg	IV	15 minutes before rituximab

Allopurinol 300mg po daily, ideally starting 24 hours before treatment - review after 4 weeks.
For patients with high initial counts (WBC > 100) or bulky disease, it is suggested that at least 1 litre of IV N/saline is administered before starting treatment.
Co-trimoxazole 480mg po od as PCP prophylaxis during treatment and for up to 2 to 6 months after completion of treatment - or alternative according to unit practice
Loperamide as required for management of idelalisib-associated diarrhoea (note that the onset of diarrhoea may not be immediate but may first occur months after starting treatment)

Frequency: Rituximab 2 weekly for 5 doses, then 4 weekly for 3 doses (total 8 doses)
i.e. Rituximab on week 0, week 2, week 4, week 6, week 8, week 12, week 16 & week 20
Idelalisib twice daily dosing continuously, until disease progression or unacceptable toxicity

Administration: Idelalisib available as 100mg and 150mg tablets.
The tablets should be swallowed whole, either with or without food.

It is assumed that the majority of patients will present with WBC > 25 x 10^9/L, which requires rituximab to be administered with caution at a reduced rate, and with careful monitoring, as there is an increased risk of severe cytokine release syndrome. Ensure all patients are well hydrated before starting treatment. The following fractionated schedule over 2 days complies with the UK CLL advisory board advice, and is in line with current RMH practice:

Dose 1: Give rituximab over 2 days as follows:

Day 1: **rituximab 50mg/m^2** in 50ml sodium chloride 0.9% IV infusion at 50mg/hr fixed rate throughout.

Day 2: **rituximab 325mg/m^2** in 250 - 500ml sodium chloride 0.9% IV infusion, start at 50mg/hr, escalate in 50mg/hr increments every 30 minutes to max 400mg/hr.

Reason for Update: EMA PRAC review advice incorporated; no split ritux dosing from dose 3	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 3	Date: 22.8.16
Supersedes: Version 2	Review date: Sept 2018
Prepared by: S Taylor	Checked by: C Tucker

Dose 2:

If WBC < 25 x 10^9/L;
Give rituximab 500mg/m^2 in 500ml sodium chloride 0.9% total dose on one day.
If no problems with Dose 1 infusions, start at 100mg/hr; escalate in 100mg/hr increments every 30 minutes to a maximum of 400mg/hr.
If reactions occurred with Dose 1, infuse as for Day 2 of Dose 1.

If WBC > 25 x 10^9/L, consider fractionating again as follows:
Day 1: rituximab 125mg/m^2 in 100-250ml sodium chloride 0.9%
Day 2: rituximab 375mg/m^2 in 500ml sodium chloride 0.9%
If no problems with Dose 1 infusions, start both fractions at 100mg/hr; escalate in 100mg/hr increments every 30 minutes to a maximum of 400mg/hr.
If reactions occurred with Dose 1, give both fractions as for Day 2 of Dose 1.

Dose 3 onwards:

Assuming tolerated all previous infusions at standard rates, *(idelalisib can cause a lymphocytosis for the first few months, but it is not considered necessary to continue with split dosing rituximab):*
Give rituximab 500mg/m^2 in 500ml N/saline as a single dose.
Give 20% of dose (i.e. 100ml) over 30 minutes, then the remaining 80% (i.e. 400ml) over 1 hour, to give a total infusion time of 90 minutes.

Patients who did not tolerate their previous infusion at the standard rate:
Infuse as per Day 2 of first infusion, or at a slower rate if required.

Monitoring:

For all rituximab infusions, monitor and record patient's vital signs (blood pressure, pulse, temperature and O_2 saturation) at baseline and then every 30 minutes (before each increase in infusion rate for escalating infusions) until the end of the infusion.
If reactions occur at any time, stop the infusion. If symptoms improve, restart at half the previous infusion rate, and escalate as tolerated.

Full resuscitation equipment must be available, with immediate access to clinical staff trained in resuscitation, for the first hour of the first rituximab infusion.

Calculating infusion rates:

For rituximab doses **in 500ml volume only**, you may use the table below, *or* a locally locally approved method of calculating infusion rates.

	Infusion Rate (mg/hour)							
	50	100	150	200	250	300	350	400
Rituximab 'banded' dose	**Infusion Rate (ml/hour) for rituximab in 500ml volume only**							
400mg	62	125	187	250	312	375	437	500
450mg	55	111	166	222	277	333	388	444
500mg	50	100	150	200	250	300	350	400
600mg	42	83	125	167	208	250	292	333
700mg	36	71	107	143	178	214	250	286
800mg	31	62	94	125	156	187	219	250
900mg	28	56	83	111	139	167	194	222
1000mg	25	50	75	100	125	150	175	200
1100mg	23	45	68	90	114	136	159	182
1200mg	21	42	63	83	104	125	146	167
1300mg	19	38	58	77	96	115	134	154

For rituximab in smaller volumes (50ml, 100ml or 250ml), do **not** refer to the table; you may again use a locally approved method, or the following equation:

Infusion rate in ml/hr = $\frac{\text{required infusion rate in mg/hr} \times \text{total volume (ml)}}{\text{dose of rituximab (mg)}}$

Main Toxicities: *Rituximab:* severe cytokine release syndrome – usually occurs within 1–2 hours of the first rituximab infusion (see Comments) and consists of fever, headache, rigors, flushing, nausea, rash, URTI symptoms; increased risk of infections
tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration)
transient hypotension and bronchospasm are usually infusion rate related;
Idelalisib: increased transaminases; diarrhoea; pneumonitis; rash

Anti - emetics: mildly emetogenic (anti-emetic not usually required)

Extravasation: rituximab is a non-vesicant

Regular Investigations:		
	FBC	before every rituximab dose, then every 2 weeks for the first 6 months, then up to every 3 months in stable patients
	LFTs, including AST	every 2 weeks for 3 months, then as clinically indicated
	U&Es	every 4 weeks
	LDH	every 8 weeks
	CMV PCR	regularly throughout treatment

Interactions: Avoid co-administration with CYP3A inducers (e.g. rifampicin, phenytoin, St John's wort, carbamazepine) as this may result in reduced plasma concentrations of idelalisib.

The primary metabolite of idelalisib, GS-563117, is a strong CYP3A4 inhibitor, and so the concomitant use of idelalisib with medicinal products metabolised by CYP3A may lead to increased serum concentrations of the other product. When idelalisib is co-administered with other medicinal products, the Summary of Product Characteristics (SPC) for the other product must be consulted for recommendations regarding co-administration with CYP3A4 inhibitors.

Concomitant treatment of idelalisib with CYP3A substrates with serious and/or life-threatening adverse reactions (e.g., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible.

Dose Modifications

Haematological Toxicity:		
	Neutrophils 0.5 – 0.99 x 10^9/l	Increase FBC monitoring to at least weekly, but maintain idelalisib dosing.
	Neutrophils < 0.5 x10^9/l	Interrupt idelalisib. Increase FBC to at least weekly until neuts ≥ 0.5, then may re-start idelalisib at 100mg bd.

Elevated liver transaminases: Usually occur within the first 3 months

ALT / AST	Management
>3 – 5 x ULN	Increase monitoring of LFTs, including AST, to every week until the values fall to ≤ 3 x ULN
First occurrence of >5 x ULN	Withhold idelalisib until ALT/AST ≤ 3 x ULN. Then re-start idelalisib treatment at 100 mg twice daily. If this event does not recur at 100mg bd, the dose can be increased to 150 mg twice daily again, at the discretion of the Consultant.

Second occurrence of >5 x ULN	Withhold idelalisib until ALT/AST ≤ 3 x ULN. Re-initiation at 100 mg twice daily may be considered, at the discretion of the Consultant.

Diarrhoea/colitis: Patients should be advised to contact their doctor at the first sign of diarrhoea, at which point they should be advised to stay well hydrated, and implement the following dietmodifications:

• Drink plenty of fluid: 8–12 glasses a day of oral-rehydration drinks, other clear liquids, or clear broth
• Eat frequent, small meals (e.g. bananas, rice, toast, apple sauce, plain pasta)
• Eat cooked instead of raw vegetables, and remove skins from fruits before eating
• Avoid fried, fatty, greasy, or spicy foods
• Avoid milk (if it makes the diarrhoea worse), milk products (including ice cream), and acidic drinks (e.g., tomato juice, citrus juices, fizzy soft drinks)
• Avoid foods that cause gas (e.g., broccoli and cabbage) and high-fibre foods
• Avoid caffeine, alcohol, and herbal supplements (some may cause diarrhoea)

Diarrhoea	**Management**
Grade 1 or mild Grade 2 diarrhoea	Manage with loperamide and diet modification. Reassess patient after 24 hours. For any Grade 2 loperamide-unresponsive diarrhoea after 24 hours, manage as below.
Late-onset Grade 2 or borderline Grade 3 diarrhoea	Take cultures to rule out infectious causes. Withhold idelalisib. IV or oral hydration as warranted. Initiate Budesonide CR capsules 9mg po OD *or* IV steroid (equivalent to prednisolone 1mg/kg, tapering once diarrhoea resolves to grade 1), if patient cannot tolerate oral medicines, or being treated with IV fluids (switch from IV steroid to budesonide once oral route tolerated) Taper steroid according to clinical response. Continue until complete resolution of diarrhoea but do not use for chronic suppression of symptoms. Once diarrhoea /colitis has returned to ≤ Grade 1, idelalisib can be resumed at 100 mg bd. If diarrhoea / colitis does not recur, the dose can be re-escalated to 150 mg bd, at the discretion of the Consultant.
Grade 3 or 4 diarrhoea / colitis	

Pneumonitis: Idelalisib must be withheld in the event of suspected pneumonitis, and the patient treated accordingly. Once pneumonitis has resolved and if re-treatment is considered appropriate, resume at 100 mg bd.
Treatment must be discontinued for moderate or severe symptomatic pneumonitis.

Rash: Idelalisib must be withheld in the event of Grade 3 or 4 rash. Once rash has returned to ≤ Grade 1, treatment can be resumed at 100 mg bd. If rash does not recur, the dose can be re-escalated to 150 mg bd, at the discretion of the Consultant.

Renal Impairment: No idelalisib dose adjustments are required for patients with mild to severe renal impairment.

Hepatic Impairment: No dose adjustment of idelalisib is required when initiating treatment in patients with mild or moderate hepatic impairment, but an intensified monitoring of adverse reactions is recommended, as drug exposure is expected to be increased.
There is insufficient data to make dose recommendations for patients with severe hepatic impairment. Caution and extra monitoring is recommended if using idelalisib in this population.

Patient Information: Macmillan leaflet for Rituximab; Idelalisib patient information leaflet available from Gilead

References: Furman, R et al; NEJM 2014; 370: 997 – 1007
Coutre S et al; Leukaemia & Lymphoma 2015 ; 56 (10) : 2779 – 2786