Idelalisib and Rituximab

Indication

Idelalisib is indicated in combination with rituximab for the treatment of adults with Chronic Lymphocytic Leukaemia who have received at least one prior line of therapy.
NICE TA359

All patients must be informed of the risk of serious and fatal infections prior to commencing treatment (see below)

ICD-10 codes

Code 91.1

Regimen details

Rituximab

Cycle 1

Day	Drug	Dose	Route
1*	Rituximab	375mg/m²	IV infusion
15	Rituximab	500mg/m²	IV infusion

Cycle 2

Day	Drug	Dose	Route
1	Rituximab	500mg/m²	IV infusion
15	Rituximab	500mg/m²	IV infusion

Cycles 3 to 6

Day	Drug	Dose	Route
1	Rituximab	500mg/m²	IV infusion

*If high tumour burden consider splitting the first dose of rituximab to give 50mg/m^2 (or 100mg) on day 0 and the remainder of the total dose on day 1

Idelalisib

150mg TWICE daily orally

Cycle frequency

28 days (as above)
Rituximab is given 2 weekly for 5 doses (day 1 and 15 for cycles 1 and 2) and then 4 weekly (day 1 only) for cycles 3-6.

Number of cycles

Maximum of 8 doses (6 cycles) of rituximab.
Idelalisib continued until disease progression or unacceptable toxicity.

Administration

Rituximab is administered in 500mL sodium chloride 0.9%. The first infusion should be initiated at 50mg/hour and if tolerated the rate can be increased at 50mg/hour every 30 minutes to a maximum of 400mg/hour. Subsequent infusions should be initiated at 100 mg/hour and if tolerated increased at 100mg/hour increments every 30minutes to a maximum of 400 mg/hour.

Idelalisib is available as 100mg and 150mg film coated tablets. Tablets should be swallowed whole with or without food. If a patient misses a dose within 6 hours of the time it is due, they should take the dose. If more than 6 hours have elapsed, the patient should omit the dose and continue with the usual doing schedule.

Pre-medication

Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion
- Dexamethasone 8mg IV bolus or hydrocortisone 100mg IV bolus 15 minutes prior to rituximab infusion

Emetogenicity

This regimen has low emetic potential

Additional supportive medication

Allopurinol 300mg (100mg if creatinine clearance <20mL/min) OD for the first cycle if required.
Loperamide if required
Prophylaxis for *Pneumocystis jirovecii* pneumonia, e.g. co-trimoxazole 480mg BD Monday, Wednesday and Friday, or as per local policy.
Antiviral prophylaxis as per local policy

Extravasation

Rituximab is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U + E (including creatinine)	14 days
LFTs	14 days
LDH	14 days
Hepatitis B core antibody and surface antigen	4 weeks
Hepatitis C antibody	4 weeks
HIV 1 + 2 status	4 weeks
ECG +/- Echo if clinically indicated	4 weeks
CMV	4 weeks

Treatment must not be commenced in patients with any signs of ongoing systemic bacterial, fungal or viral infection.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC*	48 hours (every 2 weeks)
U+E (including creatinine)	48 hours (every 4 weeks)
LFTs	48 hours (every 2 weeks for the first 12 weeks, then as clinically indicated)
LDH	Every 8 weeks
CMV screening	Every 4 weeks

* Neutrophil count must be monitored in all patients at least every 2 weeks for the first 6 months of treatment, and at least weekly if < 1.0 x 10^9/L.

Treatment must be discontinued in patients with any signs of systemic bacterial, fungal or viral infection.

Idelalisib-Associated Lymphocytosis

Idelalisib frequently causes an exacerbation of lymphocytosis, particularly when given as a single agent. The addition of rituximab to Idelalisib lessens the degree of lymphocytosis but a rise in lymphocytes should be expected to peak at week 2 and resolve by week 12. This should not be regarded as a contra-indication to continuation.

Serious infections

Serious and fatal infections have occurred with idelalisib, including *Pneumocystis jirovecii* and cytomegalovirus. Prophylaxis should be administered throughout treatment and patients should be monitored for signs and symptoms and advised to report new respiratory symptoms promptly.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥35 x 10^9/L
ALT/AST	< 3 x ULN

Neutrophil count must be monitored in all patients at least every 2 weeks for the first 6 months of treatment, and at least weekly if < 1.0 x 10^9/L.

Dose modifications

- **Haematological toxicity**

Neutrophils (x 10^9/L)	**Idelalisib dose**
>1.0	Full dose
0.5-1.0	Full dose but monitor neutrophils weekly
<0.5	Withhold and monitor neutrophils weekly Recommence at 100mg BD

If grade 3 or 4 haematological toxicity, withhold idelalisib for 1 week or until resolved to ≤ Grade 1, then recommence at full dose. Discuss with consultant as may be due to marrow infiltration.

- **Renal impairment**

No dose modifications required.

- **Hepatic impairment**

Elevated liver transaminases are frequently seen. No dose modification is required when initiating treatment in patients with mild-moderate hepatic impairment, but increased monitoring of LFTs is required. There is no information regarding dosing in severe hepatic impairment. If enzymes become raised during treatment, see table below:

AST/ALT (x ULN)	**Idelalisib dose**
3-5	Monitor LFTs weekly until < 3 x ULN
> 5 – first occurrence	Withhold until < 3 x ULN Recommence at 100mg BD. Dose may be escalated back to 150mg BD at consultant discretion if toxicity does not reoccur.
> 5 – second occurrence	Withhold until < 3 x ULN Recommence at 100mg BD at consultant discretion.

- **Other toxicities**

Toxicity	Definition	Idelalisib dose
Diarrhoea/colitis	Grade 3 - 4	Withhold idelalisib until ≤ grade 1 Recommence at 100mg BD. Dose may be escalated back to 150mg BD at consultant discretion if toxicity does not reoccur.
Pneumonitis	Suspected	Withhold idelalisib until resolved Recommence at 100mg BD at consultant discretion. If moderate or severe, discontinue treatment.
Rash	Grade 3 or 4	Withhold idelalisib until ≤ grade 1 Recommence at 100mg BD. Dose may be escalated back to 150mg BD at consultant discretion if toxicity does not reoccur.

Treatment must be discontinued in patients with any signs of systemic bacterial, fungal or viral infection.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Rituximab-related infusion reactions
Pneumonitis
Serious and fatal infections, including *Pneumocystis jirovecii* and cytomegalovirus

- **Frequently occurring side effects**

Myelosuppression
Angina
Cardiac arrhythmias
Raised transaminases
Diarrhoea
Rash

- **Other side effects**

Fatigue
Headaches
Raised triglycerides

Significant drug interactions – for full details consult product literature/ reference texts

CYP3A inducers (eg Rifampicin, Phenytoin, St John's Wort or Carbamazepine): avoid concomitant use – may reduce efficacy of idelalisib.

The primary metabolite of idelalisib, GS-563117, is a strong CYP3A4 inhibitor. 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, consult the full product literature. 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.

CYP3A/P-gp inhibitors: no initial dose adjustment of idelalisib is considered necessary when administered with CYP3A/P-gp inhibitors but close monitoring for adverse reactions is recommended.

Additional comments

Women of child-bearing potential must use effective contraception while taking idelalisib and for 1 month after stopping treatment.

References

- Summary of Product Characteristics Idelalisib (Gilead) accessed 13 April 2016 via www.medicines.org.uk
- Summary of Product Characteristics Rituximab (Roche) accessed 28 October 2015 via www.medicines.org.uk
- Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and Rituximab in relapsed chronic lymphocytic leukaemia. N Engl J Med. 2014 Mar 13;370(11):997-1007
- http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/03/news_detail_002490.jsp&mid=WC0b01ac058004d5c1

Written/reviewed by: Dr S Otton (Consultant Haematologist, North Bristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Strategic Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Strategic Clinical Network)

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