CLINICAL PRIORITIES ADVISORY GROUP
20 May 2024

Agenda Item No	6.3
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	2218

Title
Vemurafenib plus rituximab for patients with relapsed or refractory classic hairy cell leukaemia (HCL) (adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
The proposition is: vemurafenib plus rituximab is recommended to be available as a routinely commissioned treatment option for adult patients with classic hairy cell leukaemia (HCL) who are either a) refractory to first-line treatment with a purine analogue (PA) therapy; or b) refractory to, or relapse following, treatment with a second-line purine analogue (PA) therapy with or without rituximab; or c) for patients who are unsuitable for PA therapy at any time within the criteria set out in this policy proposition. The policy proposition is restricted to certain age groups as there is insufficient evidence to confirm safety and/or it is not recommended through the licence authorisation process to be used in those age groups not included in the proposition. Commissioning responsibility for this treatment currently resides with NHS England, however, in time it is expected that this will transfer to Integrated Care Boards.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.

2.	The Deputy Director of Cancer Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Director of Clinical Commissioning confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In people with classic hairy cell leukaemia (HCL) who are refractory to, or later relapse following, treatment with second line purine analogue (PA) therapy +/- rituximab OR patients with classic HCL who are unsuitable for PA therapy either first or second line, what is the clinical effectiveness and safety of **vemurafenib plus rituximab plus standard care** compared with **standard care alone OR standard care with rituximab, interferon alpha-2a therapy, splenectomy or palliative care**?

Outcome	**Evidence statement**
Clinical Effectiveness	
Critical outcomes	
Overall survival **Certainty of evidence:** Not applicable	Overall survival is important to patients as individuals with relapsed or refractory HCL have a high mortality rate due to advanced disease. Improved overall survival is an important marker of effective treatment. **No evidence was identified for overall survival**
Progression free survival **Certainty of evidence:** Very low	Progression free survival is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. One prospective case series provided evidence relating to progression free survival and survival free of minimal residual disease (MRD), and one prospective and one retrospective case series provided evidence relating to relapse free survival in patients with classic HCL who are refractory to or relapse

	following treatment with second line PA therapy +/- rituximab, or who are unsuitable for PA therapy first or second line. *Progression free survival* **At median 37 months (range 0.5 to 54.5) follow-up from the start of treatment:** • One prospective case series (Tiacci et al 2021) (n=30) reported progression[1] free survival of 78%. **(VERY LOW)** *Relapse free survival* **At between 13 and 38+ months after the end of treatment:** • One retrospective case series (Robak et al 2021) (n=3) reported relapse[2] free survival in 3/3 patients at 13 months, 2/3 at 18 months and 1/3 at 38+ months. **(VERY LOW)** **At median 34 months (range 13 to 50) follow-up from the end of treatment:** • One prospective case series (Tiacci et al 2021) (n=26 patients who had had a complete response to treatment) reported relapse[3] free survival of 85% (22/26). **(VERY LOW)** *Survival free of MRD* **At median 28.5 months (range 21 to 50) follow-up from when MRD status was first observed:** • One prospective case series (Tiacci et al 2021) (n=17 patients who were MRD-negative after the end of treatment) reported survival free of MRD in both bone marrow and peripheral blood of 100%. **(VERY LOW)** **One prospective case series provided very low certainty evidence of 78% progression free survival at a median 37 months follow-up. It also provided very low certainty evidence of 85% relapse free survival at median 34 months follow-up, while a retrospective case series provided very low certainty evidence of relapse free survival in three out of three patients at 13 months, two of three at 18 months and one of three at 38+ months. The prospective case series also provided very low certainty evidence that 100% of patients who were MRD-negative after the end of treatment remained MRD-negative at median 28.5 months follow-up.**
Response to treatment **Certainty of evidence:**	Response to treatment is important to patients as it represents whether the treatment can improve disease burden. One prospective and one retrospective case series provided evidence relating to response to treatment in patients with

Very low	classic HCL who are refractory to or relapse following treatment with second line PA therapy +/- rituximab, or who are unsuitable for PA therapy first or second line. **After treatment completion:** • One retrospective case series (Robak et al 2021) (n=3) reported complete response[4] in 2/3 patients and haematological response in 1/3. **(VERY LOW)** **At 4 weeks after treatment completion:** • One prospective case series (Tiacci et al 2021) (n=30) reported complete response[5] in 86.7% (26/30) patients (p=0.005). **(VERY LOW)** • One prospective case series (Tiacci et al 2021) (n=30) reported partial response[6] in 3.3% (1/30) patients. **(VERY LOW)** • One prospective case series (Tiacci et al 2021) (n=30) reported that 3/30 patients were not evaluable[7]. **(VERY LOW)** • One prospective case series (Tiacci et al 2021) (n=26 patients who had had a complete response to treatment) reported that 65% (17/26) patients had no minimal residual disease[8]. **(VERY LOW)** **One prospective case series provided very low certainty evidence of complete response in 86.7% patients (65% of whom had no MRD) and partial response in 3.3%. One retrospective case series provided very low certainty evidence of complete response in two out of three patients and haematological response in one of three.**
Important outcomes	
Unplanned hospital admissions due to treatment-related adverse events **Certainty of evidence:** Not applicable	This is an important outcome to patients and their carers because it reflects the tolerability and adverse effects of the treatment. From a service delivery perspective, it reflects the demands placed on the healthcare system for the intervention. **No evidence was identified for unplanned hospital admissions due to treatment-related adverse events**
Incidence of treatment-related infection **Certainty of evidence:** Very low	This is an important outcome to patients and their carers because it is an important potential complication of treatment. One prospective case series provided evidence relating to treatment-related infection. **At an unspecified duration of follow-up:**

	• One prospective case series (Tiacci et al 2021) (n=31) reported that no patients had a treatment-related infection. **(VERY LOW)** **One prospective case series provided very low certainty evidence that no patients had a treatment-related infection.**
Quality of life **Certainty of evidence:** Not applicable	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making and inform health policy. **No evidence was identified for quality of life**
Activities of daily living (ADLs) **Certainty of evidence:** Not applicable	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. **No evidence was identified for activities of daily living**
Safety	
Safety outcomes **Certainty of evidence:** Very low	The safety of vemurafenib and rituximab is important to patients as it informs treatment decisions and allows comparison of interventional approaches. One prospective and one retrospective case series provided evidence relating to adverse events in patients with classic HCL who are refractory to or relapse following treatment with second line PA therapy +/- rituximab, or who are unsuitable for PA therapy first or second line. • One prospective case series (Tiacci et al 2021) (n=31) reported that 9 (29%) patients had an infusion-related reaction associated with rituximab. They also reported adverse events (most grade 1-2 and reported to be transient) associated with vemurafenib including asymptomatic hyperbilirubinemia in 24 (77%), asymptomatic increase in pancreatic enzymes in 18 (58%), arthralgia or arthritis in 17 (55%), rash or erythema in 15 (48%), skin papilloma or warts in 14 (45%), asymptomatic increase in aspartate or alanine aminotransferase level in 9 (29%), asymptomatic increase in γ-glutamyltransferase or alkaline phosphatase level in 9 (29%), asymptomatic hypophosphatemia in 9 (29%) and anaemia in 7 (23%). A large number of less common adverse events were also reported. In 14/29 patients there were toxic effects requiring reduction of the dose of vemurafenib for at least 2 weeks. **(VERY LOW)** • One retrospective case series (Robak et al 2021) reported that 0/3 patients had serious adverse effects associated with treatment. **(VERY LOW)**

	One prospective case series provided very low certainty evidence that while adverse events associated with treatment appeared quite common, most were grade 1-2 and transient. One retrospective case series provided very low certainty evidence that none out of three patients had a serious adverse event.
Abbreviations BM: bone marrow; HCL: hairy cell leukaemia; MRD: minimal residual disease; PA: purine analogue	

In people with classic HCL who are refractory to, or later relapse following, treatment with second line PA therapy +/- rituximab OR patients with classic HCL who are unsuitable for PA therapy either first or second line, what is the cost effectiveness of **vemurafenib plus rituximab plus standard care** compared with **standard care alone OR standard care with rituximab, interferon alpha-2a therapy, splenectomy or palliative care**?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for cost effectiveness

From the evidence selected, are there any subgroups of patients that may benefit from **vemurafenib plus rituximab** more than the wider population of interest?

Subgroup	Evidence statement
Previous treatment with a BRAF inhibitor	**At median 34 months follow-up:** • One prospective case series (Tiacci et al 2021) (n=26 who had a complete response to treatment) reported relapse free survival of 57% in n=7 patients previously treated with a BRAF inhibitor, and 95% in n=19 patients not previously treated with a BRAF inhibitor
Presence or absence of MRD	**At unspecified duration of follow-up:** • One prospective case series (Tiacci et al 2021) (n=26 who had a complete response to treatment) reported relapse free survival of 100% in n=17 patients who had no MRD, and 56% in n=9 patients who had MRD.
Previous exposure to rituximab	**At unspecified duration of follow-up:** • One prospective case series (Tiacci et al 2021) (n=26 who had a complete response to treatment) reported relapse free survival of 89% in n=9 patients who had received rituximab previously, and 82% in n=17 patients who had not received rituximab previously.
Abbreviations MRD: minimal residual disease	

From the evidence selected, what was the treatment duration and dosing of **vemurafenib plus rituximab** in the population of interest?

Outcome	Evidence statement
Dose of vemurafenib plus rituximab	In Tiacci et al 2021 (prospective case series) patients received oral vemurafenib (960 mg twice daily) for 8 weeks, and 8 intravenous rituximab infusions (375 mg/m^2 of body-surface area) administered over a period of 18 weeks. Treatment was administered in two cycles each consisting of 4 weeks of vemurafenib with rituximab infusions on days 1 and 15, followed by 2 weeks of rest and response evaluation. After the second cycle, four additional doses of rituximab were administered 2 weeks apart from one another. 14/29 patients received a reduced dose of vemurafenib (720mg or 480mg twice daily for at least 2 weeks) due to toxic effects. In 10/14 the dose was re-escalated once the toxic effects resolved. In Robak et al 2021 (retrospective case series) patients received vemurafenib 240 mg twice daily for 16 weeks + rituximab 375mg/m^2 intravenously every 2 weeks x 8.

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** Patients have variable problems in walking about • **ability to provide self-care:** Patients may have slight to severe problems in washing or dressing • **undertaking usual activities:** Patients may have slight to severe problems in doing their usual activities • **experience of pain/discomfort:** Patients have may have mild to severe pain or discomfort • **experience of anxiety/depression:** Patients may be moderately to severely anxious or depressed
Further details of impact upon patients: Hairy cell leukaemia is a type of blood cancer that can cause symptoms such as pronounced fatigue, bone pain, night sweats and fevers. Some patients experience no preceding symptoms, and this can lead to delays in diagnosis. Although first line treatment with PA therapy is generally successful, there is no defined standard of care for patients with relapsed or refractory disease. These patients may suffer from anxiety, low mood and worry about their future treatment options. **Further details of impact upon carers:** Prior to diagnosis, patients may require additional support with normal activities and functioning whilst dealing with their symptoms. Patients generally respond well to treatment. However, patients may require additional support during periods of relapse which can put strain on those looking after them. Additionally, patients

undergoing treatment may suffer from side effects such as infection, full body rash and confusion which can negatively impact patients and their families.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This clinical commissioning policy proposition recommends vemurafenib, in combination with rituximab, as a treatment option for adults with classic hairy cell leukaemia who are either a) refractory to first-line treatment with a purine analogue (PA) therapy; or b) refractory to, or relapse following, treatment with a second-line purine analogue (PA) therapy with or without rituximab; or c) for patients who are unsuitable for PA therapy. The recommendation is outside of the marketing authorisation for vemurafenib so use is off-label and Trust policy regarding unlicensed medicines should apply. Vemurafenib and rituximab are both on the NHS Payment Scheme Annex A, that is, they are both excluded drugs. The safety and efficacy of vemurafenib in children aged less than 18 years old have not been established so the policy proposition is for use in adults.

Considerations from review by National Programme of Care
The proposal received the full support of the Cancer PoC on the 9 May 2024