NHS ENGLAND SPECIALISED SERVICES

CLINICAL PANEL REPORT

Date: 17th January 2024

Intervention: vemurafenib plus rituximab

Indication: relapsed or refractory classic hairy cell leukaemia (HCL) (adults)

URN: 2318

Gateway: 2, Round 1

Programme: Cancer

CRG: Chemotherapy

Information provided to the Panel

Policy Proposition

Evidence Review completed by Solutions for Public Health

Clinical Priorities Advisory Group (CPAG) Summary Report

Evidence to Decision Summary

Equalities and Health Inequalities (EHIA) Assessment

Patient Impact Assessment

Blueteq™ Report

Policy Working Group (PWG) Appendix

This Policy Proposition recommends the use of off-label vemurafenib plus rituximab as a treatment option for adult patients with classic hairy cell leukaemia (HCL). HCL is a very rare type of leukaemia. Classic HCL is characterised by a mutation called BRAF V600 which is present in all leukaemic cells. The first-line treatment for patients with classic HCL is purine nucleoside analogue (PA) therapy. For patients who are refractory to, or relapse within 2 years following PA therapy, standard second-line treatment is generally with an alternative PA therapy in combination with rituximab. The proposed intervention is for vemurafenib (BRAF inhibitor) plus rituximab in adult patients with classic HCL who are either a) refractory to, or relapse following, treatment with a second-line purine analogue (PA) therapy with or without rituximab; or b) for patients who are unsuitable for PA therapy either first-line or second-line.

The proposition and the supporting evidence review were presented to Panel members. Two non-comparative studies were included in the evidence review. One was a prospective case series (n=31) and the second was a retrospective case series (n=3). No cost effectiveness studies were identified.

The critical outcomes for clinical effectiveness were progression free survival (PFS), treatment response, and overall survival (OS). Important outcomes reported were unplanned hospital admissions due to treatment related adverse events, treatment related infections, activities of daily living (ADLs), and Quality of Life (QoL). The presentation to Panel members covered all elements of the evidence.

One study provided evidence of 78% PFS at a median of 37 months. Relapse free survival was reported in both studies. An 86.7% complete response rate was reported in the prospective study whilst the retrospective study reported evidence of a complete response rate in two out of three patients. Members noted that no evidence was identified for hospital admissions, QoL, or ADLs. Adverse events were identified to be common but of low grade and transient.

The evidence presented across all critical and important outcomes was reported as very low using modified GRADE.

Limitations of the studies presented were discussed including the lack of comparator groups, high risk of bias and unclear definitions of response and relapse. Panel members, however, agreed that, despite the very limited and low certainty of data and the very small number of patients studied, this is a rare condition and clinical improvement was demonstrated. They agreed that biological plausibility was demonstrated. Close monitoring of patients is a requirement whilst receiving this treatment.

The proposition and supporting documents were considered and some amendments requested.

The delivery mechanism of subcutaneous injection as an alternative option to intravenous injection was raised. This was debated at length as this was not discussed as an inclusion in the PICO or used within the studies in the evidence base presented. Members agreed this should not be included.

EHIA – a review or wording requested.
PIA – no amendments requested.

Recommendation

Clinical Panel agreed with the proposition and recommended this proceeds as a routine commissioning proposition once amendments have been made to the proposition as requested and these are approved through Chair's action.

Why the panel made these recommendations

The evidence and reported outcomes were considered carefully. Panel members agreed that, despite the very limited and low certainty of data and the very small number of patients studied, this is a rare condition and clinical improvement was demonstrated. They agreed that biological plausibility was demonstrated.

Documentation amendments required

Policy Proposition:

- Summary section – the language needs slightly amending. The reference currently is to 'routine commissioning treatment' and would read better if phrased 'a routinely commissioned treatment'.
- Current treatment section - the Summary of Product Characteristics states cladribine is given for seven days whereas the proposition states five days – to check.
- Inclusion criteria –
    - review to ensure this is as tight as possible and to include performance status.

- Refractory to treatment with PA therapy is stated, whereas in the flow diagram on page 6 it states relapsed or refractory. This needs to be reviewed and amended for consistency. The inclusion criteria wording needs to state this is for 1st line treatment, in line with the flow diagram.
- The difference between refractory and relapse needs to be defined to understand what line of therapy is required.

- Dosing – it is unclear what the treatment breaks are based on – what is defined as a cycle length in this proposition?
- Policy Working Group to consider whether the two studies included in the evidence review need to be included in the reference section of the proposition.

EHIA:

- Review the wording to ensure consistency – there is reference to vemurafenib being an oral treatment and therefore reducing hospital visits. Rituximab, though, is administered intravenously so will require service access.

Declarations of Interest of Panel Members: None received.

Panel Chair: James Palmer, Medical Director, Specialised Services

Post Panel Amendments

Policy Proposition		
Panel Comment	**Amendment**	**Page number (if applicable)**
Summary section – the language needs slightly amending. The reference currently is to 'routine commissioning treatment' and would read better if phrased 'a routinely commissioned treatment'.	Amended to 'routinely commissioned treatment'	p2
Current treatment section - the Summary of Product Characteristics states cladribine is given for seven days whereas the proposition states five days – to check.	This has been discussed with the PWG and the SmPC has been reviewed. The SmPC for cladribine is the subcutaneous formulation referred to in this proposition—this is given for 5 days. The alternative formulation for cladribine is an intravenous infusion which is given for 7 days. The subcutaneous form of cladribine is the one referred to in this proposition and the one used in clinical practice. Therefore, references to 5 days have been retained.	N/A

Inclusion criteria – • review to ensure this is as tight as possible and to include performance status. • Refractory to treatment with PA therapy is stated, whereas in the flow diagram on page 6 it states relapsed or refractory. This needs to be reviewed and amended for consistency. The inclusion criteria wording needs to state this is for 1st line treatment, in line with the flow diagram.	The inclusion criteria have been reviewed and the addition of performance status has been added. The definitions of relapsed and refractory have been discussed with the PWG and amended for clarity. This is reflected in the indications for treatment, the eligibility criteria and the flow diagram. References to relapsed and refractory and now consistent throughout the proposition.	References to relapsed and refractory + definitions amended throughout.
Dosing – it is unclear what the treatment breaks are based on – what is defined as a cycle length in this proposition?	This has been reviewed with the PWG and with the evidence included in the independent review (Tiacci et al. 2021). A dosing schedule has been added to the policy proposition in the 'Dosing' section, in line with the independent evidence review. This also clarifies the duration of a cycle length in this proposition.	P5-6
Policy Working Group to consider whether the two studies included in the evidence review need to be included in the reference section of the proposition.	References have added to the policy proposition.	P9
EHIA		
Review the wording to ensure consistency – there is reference to vemurafenib being an oral treatment and therefore reducing hospital visits. Rituximab, though, is administered intravenously so will require service access.	Wording has been reviewed and amended throughout the document.	N/A