CLINICAL PRIORITIES ADVISORY GROUP
20 May 2024

Agenda Item No	6.1
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	2269

Title
Neoadjuvant vismodegib for locally advanced basal cell carcinoma (BCC) prior to curative treatment for lesions likely to result in functional sequelae or significant aesthetic sequelae (adults)

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

Proposition
The proposition is: neoadjuvant vismodegib is recommended to be available as a routinely commissioned treatment option for locally advanced basal cell carcinoma (BCC) prior to curative treatment for lesions likely to result functional sequelae or significant aesthetic sequelae within the criteria set out in the policy proposition documentation. Patients must be suitable or potentially suitable for curative treatment at baseline. Chemotherapy services are considered suitable and ready for delegation, therefore it is expected that responsibility will transfer to Integrated Care Boards in future.

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 locally advanced basal cell carcinoma that is determined as likely to result in significant aesthetic or functional sequelae following curative treatment, and who are suitable or potentially suitable for curative treatment, what is the clinical effectiveness of neoadjuvant vismodegib compared with standard care?

Outcome	**Evidence statement**
Clinical Effectiveness	
Critical outcomes	
Tumour response **Certainty of evidence:** Very low	Response rate is important to patients as it represents whether the treatment can reduce tumour burden. In total 3 single-arm trials provided evidence relating to response rate at up to 12 months. Ally et al. 2014 (n=11) included people with tumours mostly on the face (10/13 tumours). All tumours were high-risk (NCCN guidelines) and 36% were recurrent. Bertrand et al. 2021 (n=55) included people with basal cell carcinoma of the face with a diameter of 2 cm or more in an area with a high risk of recurrence, and 3 cm or more in areas with an intermediate risk of recurrence. Kahana et al. 2021 (n=34) included people with globe and lacrimal drainage system threatening orbital and extensive periocular basal cell carcinoma. After 3 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that cross-sectional tumour size was 44% of the baseline tumour size, no statistical analysis reported. **(VERY LOW)** After an average of 4 months vismodegib treatment (3 to 6 months, 9 months for 1 person): • 1 single-arm trial (Ally et al. 2014) (n=11, 13 tumours) showed a statistically significant reduction in the surgical defect area compared with baseline after treatment with vismodegib (−27%, 95% CI −45.7 to −7.9%, p=0.006). **(VERY LOW)** After 4 to 10 months (average 6 months) of vismodegib treatment:

	• 1 single-arm trial (Bertrand et al. 2021) (n=55) showed that most people had a response to vismodegib 39/55 (70.9%, 95% CI 59 to 83%). Of these, 14/55 (25.5%, 95% CI 14 to 37%) had a complete response and 25/55 (45.5%, 95% CI 32 to 59%) had a partial response. **(VERY LOW)** After 6 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that cross-sectional tumour size was 22% of the baseline tumour size, no statistical analysis reported. **(VERY LOW)** After 9 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=10, people who had not yet had surgery) showed that cross-sectional tumour size was 22% of the baseline tumour size, no statistical analysis reported. **(VERY LOW)** After 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=3, people who had not yet had surgery) showed that cross-sectional tumour size was 20% of the baseline tumour size, no statistical analysis reported. **(VERY LOW)** After up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 19/34 (56%) people had a complete response by physical examination, and 16/34 (47%) had a complete response by MRI/CT. 10/34 (29%) people had a partial response by physical examination, and 9/34 (26.5%) had a partial response by MRI/CT. No statistical analyses reported. **(VERY LOW)** **These studies provided very low certainty evidence that most people had a response to vismodegib, and that vismodegib reduced tumour size compared with baseline after up to 12 months of treatment.** **One single-arm trial showed that, after treatment with vismodegib, tumour size was 44%, 22%, 22%, and 20% of that at baseline at 3, 6, 9, and 12 months, respectively. The study also showed that 19/34 people had a complete response and 10/34 had a partial response.** **One single-arm trial showed a statistically significant reduction in the surgical defect area compared with baseline after 3 to 6 months (average 4 months) treatment with vismodegib.** **One single-arm trial showed that most people had a response after 4 to 10 months (average 6 months) treatment with vismodegib. Of these, 14/55 had a complete response and 25/55 had a partial response.**
Downstaging of the surgical procedure and/or reduction in radiotherapy field size Certainty of evidence: Very low	This outcome is important to patients as it represents a downstaging of the complexity and scope of the curative intervention required. This correlates with a reduction in the extent of surgical resection and/or a reduction in normal tissue toxicity. In total 2 single-arm trials provided evidence relating to downstaging of the surgical procedure at up to 12 months. After 4 months of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) (n=42) showed that 35/42 (85.7%, 95% CI 71 to 95%) had a downstaging of the surgical procedure. No statistical analysis reported. **(VERY LOW)**

	After 4 to 10 months (average 6 months) of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) (n=55) showed that 44/55 (80%, 95% CI 67 to 90%) had a downstaging of the surgical procedure. No statistical analysis reported. **(VERY LOW)** After up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 19/19 (100%) of people who were predicted at baseline to have exenteration had no exenteration and 34/34 (100%) had successful visual function at completion of the study. This followed predicted surgical outcomes at baseline as: exenteration (19, 56%), globe-sparing (15 [44%], with lacrimal damage [4], extraocular motility damage [1], or both [10]). No statistical analysis reported. **(VERY LOW)** **These studies provided very low certainty evidence for the outcome of downstaging of the surgical procedure and/or reduction in radiotherapy field size. One trial showed that the surgical procedure was downstaged in most people (44/55) after an average of 6 months of vismodegib treatment and one trial showed that, of the 19 people who were predicted at baseline to need exenteration, none needed exenteration after up to 12 months treatment with vismodegib.**
Organ-specific preservation and function **Certainty of evidence:** Very low	This outcome is important to patients as it represents sparing of major aesthetic and/or functional sequelae following curative treatment. For some patients this would include preservation of organs that may otherwise have been excised- e.g., orbital exenteration. Preservation of organ function correlates with an improvement in patients' quality of life. In total 1 single-arm trial provided evidence relating to organ-specific preservation and function at up to 12 months. The trial included 34 people with globe and lacrimal drainage system threatening orbital and extensive periocular basal cell carcinoma. At up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 34/34 (100%) people maintained a VAWS of >21 (considered successful) at study completion, p<0.0001. Mean scores were 44/50 at baseline, 46/50 at 3 months,46/50 at 6 months, and 47/50 at 12 months or post-surgery. **(VERY LOW)** • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 1/34 (3%, 95% CI 0.1 to 15.3%) people had a major decline in VAWS of 5 points compared with baseline. No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 5/34 (14.7%, 95% CI 5 to 31.1%) people had a minor decline in VAWS of 2 to 4 points compared with baseline. No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 27/34 (79.4%, 95% CI 62.1 to 91.3%) people had a stable or improved VAWS compared with baseline. No statistical analysis reported. **(VERY LOW)** **This study provided very low certainty evidence that successful visual function (VAWS>21) was maintained in people with globe and lacrimal drainage system threatening**

	orbital and extensive periocular basal cell carcinoma after up to 12 months of treatment with vismodegib. One person experienced a major decline in visual function, 5 people had a minor decline in visual function, and 27 people had stable or improved visual function.
Important outcomes	
Relapse rates **Certainty of evidence:** Very low	This outcome is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions. In total 3 single-arm trials provided evidence relating to relapse rates at up to 3 years. One trial (Ally et al. 2014) enrolled 15 people but only 11 completed the trial through having their basal cell carcinoma surgically excised (2 people withdrew because of vismodegib-related side effects, 1 withdrew because of unrelated adverse events, and one person was lost to follow-up). The average duration of vismodegib before surgery was 4 months. One single-arm trial (Bertrand et al. 2021) included 55 people with basal cell carcinoma of the face with a diameter of 2 cm or more in an area with a high risk of recurrence, and 3 cm or more in areas with an intermediate risk of recurrence. One single-arm trial (Kahana et al. 2021) included 34 people with globe and lacrimal drainage system threatening orbital and extensive periocular basal cell carcinoma. Mean 11.5 months (range 4 to 21 months) after surgery: • 1 single-arm trial (Ally et al. 2014) (n=11, 13 tumours) showed that 1 person had a tumour recurrence 17 months after surgery. This person had 2 months of vismodegib treatment for a twice recurrent basal cell carcinoma. No statistical analysis reported. **(VERY LOW)** 2 years after the end of the study • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 2 people had a tumour recurrence. No statistical analysis reported. **(VERY LOW)** 3 years after the end of the study: • 1 single-arm trial (Bertrand et al. 2021) showed that 16/44 (36%, 95% CI 22 to 51%) people had a recurrence. No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Bertrand et al. 2021) showed that, in people who had a complete response to vismodegib (6/27 had surgery and 21/27 did not), 7/27 had a recurrence (1 died with recurrence). No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Bertrand et al. 2021) showed that, in people who had an incomplete response to vismodegib, 9/17 had a recurrence (1 died with recurrence). No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Bertrand et al. 2021) showed that, in people who did not have a response to vismodegib, 7/11 had a recurrence or progression. No statistical analysis reported. **(VERY LOW)** **These studies provided very low certainty evidence relating to the outcome of tumour recurrence after between 3 and 12 months of treatment with vismodegib alone or vismodegib**

	followed by surgery. One single-arm trial showed that 1/11 people had a tumour recurrence after 17 months, one single-arm trial showed that 2/34 people had a recurrence after 2 years, and one single-arm trial showed that 16/44 people had a recurrence in a 3-year follow-up period. **One single-arm trial showed that a greater proportion of people who did not have a response to vismodegib had a recurrence or progression (7/11) compared with people who had a complete response (7/27). However, no statistical analyses were reported, and it is not clear what proportion of people had surgery in each group.**
Histological remission **Certainty of evidence:** Very low	This outcome is important to patients because it can indicate that the disease is reducing in severity and prognosis is improved. In total 2 single-arm trials provided evidence relating histological remission at up to 12 months. After an average of 4 months vismodegib treatment (3 to 6 months, 9 months for 1 person): • 1 single-arm trial (Ally et al. 2014) (n=11, 13 tumours) found no residual basal cell carcinoma in the first piece of excised tissue in 6/13 (46%) tumours. No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Ally et al. 2014) found no residual basal cell carcinoma in the first piece of excised tissue in 4/7 (57%) tumours that appeared clinically cured (flat scar with no erythema or nodularity). No statistical analysis reported. **(VERY LOW)** After up to 12 months of treatment: • 1 single-arm trial (Kahana et al. 2021) showed that 18/27 (67%) of people had a histological response with no sign of disease. No statistical analysis reported. **(VERY LOW)** **These studies provided very low certainty evidence relating to the outcome of histological remission after up to 12 months of treatment with vismodegib. One single-arm trial found no residual basal cell carcinoma in the first piece of excised tissue in 6/13 (46%) of tumours and one single-arm trial found that 18/27 (67%) of people had a histological response with no sign of disease.**
Quality of life **Certainty of evidence:** Very low	This outcome is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. In total 1 single-arm trial provided evidence relating to quality of life at up to 10 months. From baseline up to the 10th cycle (28 days per cycle), after 4 to 10 months [median 6 months] of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) showed that the Skindex-16 score statistically significantly improved (decreased) by 2.07 per cycle ($p<0.0001$). **(VERY LOW)** **This study provided very low certainty evidence that quality of life, measured using the Skindex-16 score, statistically significantly improved each month, up to 10 months.**
Did not receive curative surgery and/or curative radiotherapy treatment	This outcome is important to patients as it captures the number of patients for whom neoadjuvant treatment with vismodegib has removed the need for curative surgery and/or curative

Certainty of evidence: Very low	radiotherapy altogether. It also captures patients who chose not to, or who remained unable to undergo curative surgery and/or curative radiotherapy following neoadjuvant vismodegib. In total 2 single-arm trials provided evidence for people who did not receive curative surgery. After 4 to 10 months (median 6 months) of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) (n=55) showed that of the 27 people who had complete clinical response to vismodegib, 6 had surgery and 21 did not. No statistical analysis reported. **(VERY LOW)** After up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 7/34 (20.6%) people did not have surgery within the 12-month treatment period. The 27/34 who elected to undergo excision before the 12 months treatment did so because of poor tolerance to vismodegib. No statistical analysis reported. **(VERY LOW)** **These studies provided very low certainty evidence for the outcome of not receiving curative surgery and/or curative radiotherapy treatment. One single-arm trial showed that, of the 27/55 people who had a complete response to vismodegib, 21 did not receive curative surgery. One single-arm trial showed that 7/34 people did not have surgery within the 12-month treatment period. Reasons for not receiving curative surgery were not fully described.**
Safety	
Treatment-related adverse events **Certainty of evidence:** Very low	Safety of vismodegib is important to patients as it reflects the risks involved in taking this medication and allows a risk benefit assessment to be undertaken. It also allows comparison of interventional approaches. In total 3 single-arm trials provided evidence relating to treatment-related adverse events. After an average of 4 months vismodegib treatment (3 to 6 months, 9 months for 1 person): • 1 single-arm trial (Ally et al. 2014) (n=11) showed that 11/11 (100%) people had treatment-related adverse events. These were grade-1: dysgeusia (100%), muscle cramps (100%), fatigue (72%), diarrhoea (9%), weight loss [less than 5% body weight] (45%), depressed mood (18%), reversible amenorrhea (9%). 11/11 had hair loss; 7/11 <50% hair loss (grade 1), 4/11 ≥50% hair loss (grade 2). After 4 to 10 months (median 6 months) of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) (n=55) showed that 54/55 (98.2%) people had treatment-related adverse events including: dysgeusia, muscle spasms, alopecia, fatigue, weight loss (or decrease), diarrhoea, cytolysis, appetite loss (or decrease), arthralgia, constipation, hypogeusia, dyspepsia, hyponatremia, dyspnoea, anaemia, vomiting, pruritus, CPK elevation, oral dryness, cough. The mean number of adverse events was 6.4±3.6 per person. **(VERY LOW)** After up to 12 months of vismodegib treatment:

	• 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 33/34 (97%) people had treatment-related adverse events. **(VERY LOW)** **These studies provided very low certainty evidence that almost all (11/11, 54/55, 33/34) people had one or more treatment related adverse event.**
Grade ≥3 treatment-related adverse events **Certainty of evidence:** Very low	After 4 to 10 months (median 6 months) of vismodegib treatment • 1 single-arm trial (Bertrand et al. 2021) (n=55) showed that 11/55 (20%) of people had grade ≥3 treatment-related adverse events including: dysgeusia, muscle spasms, weight loss (or decrease), cytolysis, dyspepsia, hyponatremia, dyspnoea, and anaemia. After up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 3/34 (8.8%) people had grade ≥3 treatment-related adverse events. **These studies provided very low certainty evidence that 11/55 and 3/34 people had grade ≥3 treatment-related adverse events.**
Discontinuation of vismodegib because of side effects/ toxicity **Certainty of evidence:** Very low	One single-arm trial (Ally et al. 2014) (n=14) showed that 4/14 (29%) could not complete more than 3 months of treatment because of vismodegib-related side effects including: aspartate/alanine aminotransferase elevation, hair loss, fatigue, creatine phosphokinase elevation). One single-arm trial (Bertrand et al. 2021) (n=55) showed that 7/55 discontinued vismodegib because of toxicity (after 4 to 10 months [median 6 months] of vismodegib treatment). **These studies provided very low certainty evidence that 4/14 and 7/55 people discontinued vismodegib because of side effects.**
Abbreviations CT, computed tomography; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; VAWS, visual assessment weighted score	

From the evidence selected, are there any subgroups of patients that may benefit from neoadjuvant vismodegib more than the wider population of interest?

Outcome	Evidence statement
Duration of vismodegib treatment	1 single-arm trial (Ally et al. 2014) (n=11) provided evidence that the 2 people who had less than 3 months of vismodegib treatment did not have a significant reduction in surgical defect (−12%, 95% CI −55.0% to 33.0%, p=1.0). However, the 9 people who had least 3 months of treatment had a statistically significant reduction of the surgical defect area (−31%, 95% CI −68.0% to −7.0%, p=0.002).

	1 single-arm trial (Bertrand et al. 2021) (n=55) provided evidence that duration of treatment with vismodegib was not statistically significantly different between the group who had downstaging of the surgical procedure (treatment success) and the treatment failure group (6.1±2.1 months compared with 5.6±3.2 months, respectively, p=0.53). **One single-arm trial provided evidence that the 2 people who had less than 3 months of vismodegib treatment did not have a significant reduction in surgical defect but the 9 people who had least 3 months of treatment had a statistically significant reduction of the surgical defect area compared with baseline, no comparative analysis reported. However, one single-arm trial provided evidence that there was no statistically significant difference in duration of vismodegib treatment between people in the treatment success group and the treatment failure group.**
People with recurrent disease	1 single-arm trial (Ally et al. 2014) (n=11) provided evidence that the 4 people with recurrent basal cell carcinomas (4 target tumours) had no reduction in surgical defect area after treatment with vismodegib (no statistical analysis reported). The 7 people with nonrecurrent tumours (9 target tumours) had a statistically significant reduction in the surgical defect area with vismodegib treatment (−36%, 95% CI −58.7% to −14.0%, p=0.004). **One single-arm trial provided evidence that the 4 people who had recurrent basal cell carcinomas had no reduction in the surgical defect area but the 7 people who had nonrecurrent basal cell carcinomas had a statistically significant reduction in the surgical defect area compared with baseline. No comparative analysis reported.**
Size of target lesion at baseline	1 single-arm trial (Bertrand et al. 2021) (n=55) provided evidence that there was no significant difference in average initial target lesion size in people who had downstaging of the surgical procedure (treatment success group) (45.8 mm, range 20 to 130 mm) and the treatment failure group (53.1 mm, range 20 to 120 mm) (p=0.50). **One single-arm trial provided evidence that there was no statistically significant difference in initial target lesion size between people in the treatment success group and the treatment failure group.**

In people with locally advanced basal cell carcinoma that is determined as likely to result in significant aesthetic or functional sequelae following curative treatment, and who are suitable or potentially suitable for curative treatment, what is the cost effectiveness of neoadjuvant vismodegib compared with standard care?

Outcome	Evidence statement
Cost-effectiveness	No evidence was identified for this outcome.

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** Patients mostly have no problems in walking about • **ability to provide self-care:** Patients mostly have no problems in washing or dressing • **undertaking usual activities:** Patients mostly have no problems in doing their usual activities • **experience of pain/discomfort:** Patients mostly have no pain or discomfort • **experience of anxiety/depression:** Patients may be anxious or depressed
Further details of impact upon patients: The impact of having a locally advanced BCC can be variable depending on its location. Some patients with large, disfiguring lesions on the face may have low self esteem and suffer from anxiety. Furthermore, the thought of having to undergo radical curative treatment to remove the lesion, such as removal of the eye or nose, or removal of part of the bowel or use of a limb can negatively impact on patients' mental health and quality of life. Patients can also experience distressing oozing or bleeding from lesions which may require an intensive schedule for dressing changes. **Further details of impact upon carers:** The majority of patients with locally advanced BCC will not require a carer for this issue specifically. Some patients may require assistance with dressing changes. However, in general this demographic of patients is elderly with multiple co-morbidities and may require assistance with self-care for other reasons.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This clinical commissioning policy proposition recommends vismodegib as a treatment option for locally advanced basal cell carcinoma (BCC) prior to curative treatment for lesions likely to result functional sequelae or significant aesthetic sequelae in adults. The recommendation is outside of the marketing authorisation for vismodegib so use is off-label and Trust policy regarding unlicensed medicines should apply. Vismodegib is on the NHS Payment Scheme Annex A, that is, it is an excluded drug. The safety and efficacy of vismodegib in children and adolescents 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 8th May 2024