CLINICAL PRIORITIES ADVISORY GROUP
10 May 2021

Agenda Item No	3.1
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	1905

Title
Vismodegib for adults with either Gorlin syndrome or non-Gorlin syndrome related multiple basal cell carcinomas

Actions Requested	1. Support adoption of the policy proposition.
	2. Recommend its approval as an IYSD.

Proposition
The policy proposition recommends that vismodegib, a targeted cancer treatment, should be made routinely available for the treatment of adults with either Gorlin syndrome or non-Gorlin syndrome related multiple basal cell carcinomas (BCCs) who have a minimum of 6 lesions and where surgery could result in significant disfigurement. Use of vismodegib is unlicensed in this indication. The policy proposition has been developed in line with the standard Methods and is based on the findings of an Evidence Review. Due to the unanimous support for the policy proposition at stakeholder testing, the policy has not been subject to public consultation (endorsed by the Cancer Programme of Care and the Patient and Public Voice Advisory Group).

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

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

2.	The Head of Cancer Programme 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 Clinical Programmes Director (Specialised 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

Part A i) Use of vismodegib vs. placebo to treat non-locally advanced, non-metastatic multiple BCCs

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported.
2.	Progression free survival	Not reported.
3.	Mobility	Not reported.
4.	Self-care	Not reported.
5.	Usual activities	Not reported.
6.	Pain	Not reported.
7.	Anxiety / Depression	Not reported.
8.	Replacement of more toxic treatment	Not reported.
9.	Dependency on care giver / supporting independence	Not reported.

10.	Safety	Adverse events were graded according to the National Cancer Institute Common Terminology Criteria (version 3) where Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening or disabling; Grade 5 = death related to adverse event[1]. In one RCT of patients with Gorlin syndrome (Tang et al 2012, n=42), there were no Grade 5 adverse events. There was no significant difference in vismodegib vs placebo for any Grade 3 or 4 adverse events. Grade 1 or 2 adverse events that were statistically significantly greater with vismodegib (n=26) vs placebo (n=15), included hair loss (62% vs 7%, p=0.004), muscle cramps (81% vs 0%, p<0.001), taste disturbance (85% vs 7%, p<0.001) and >5% weight decrease (42% vs 0%, p=0.003). At a mean of 8 months follow-up 7/26 (27%) patients had discontinued vismodegib due to adverse events and 1/15 (7%) patients had discontinued placebo due to disease progression. At last follow-up (28 months after study start) 14/26 (54%) of patients had discontinued vismodegib due to adverse events. Adverse events may affect quality of life and are likely to be of importance to clinicians, patients and their families. Patients receiving vismodegib experienced more mild to moderate adverse events than patients receiving placebo. There was no significant difference in more severe adverse effects between groups. However, more than half of vismodegib patients discontinued vismodegib due to adverse events. This small but good quality double-blind RCT, was stopped after the planned interim analysis due to statistically significant better results with vismodegib for the primary outcome (new surgically eligible BCCs). At this point 38 patients had completed ≥3 months follow-up (range 1 to 15) of a planned 18 month RCT duration. The analysis was modified intention-to-treat (n=41) with the exclusion of 1 patient assigned to placebo who withdrew before receiving any study medication due to work and travel difficulties. All patients in this RCT had Gorlin syndrome and ≥10 surgically eligible BCCs at baseline or that had been removed during the previous 2 years. A published, standardised grading system was used to assess adverse events.
11.	Delivery of intervention	Not reported.

[1] https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

No	Outcome measure	Summary from evidence review
1.	New surgically eligible BCCs	Surgically eligible BCCs were defined as BCCs with a diameter of ≥3mm on the nose or periorbital skin, ≥5mm elsewhere on the face or ≥9mm on the truck or limbs (excluding the leg below the knees which was not monitored).This outcome assessed the number of new surgically eligible BCCs per patient per year. In one RCT of patients with Gorlin syndrome (Tang et al 2012, n=42), the mean number of new surgically eligible BCCs per patient per year was statistically significantly lower with vismodegib (2) vs placebo (29), p<0.001. Mean follow-up was 8 months (range 1 to 15). Multiple invasive surgeries may impact patient's quality of life. A mean reduction of 27 new surgically eligible BCCs per year would be of importance to clinicians, patients and their families if it results in fewer surgeries. See above for limitations of Tang et al (2012). The analysis of this outcome accounted for the differential follow-up among study participants. Clinical photographs and training from the principal investigator were used to ensure consistency in the assessment of surgically eligible BCCs.
2.	Reduction in size of existing surgically eligible BCCs	This outcome assessed percentage change from baseline in the sum of the longest diameter of existing surgically eligible BCCs. Surgically eligible BCCs were defined as BCCs with a diameter of ≥3mm on the nose or periorbital skin, ≥5mm elsewhere on the face or ≥9mm on the truck or limbs (excluding the leg below the knees which was not monitored). In one RCT of patients with Gorlin syndrome (Tang et al 2012, n=42), percent change from baseline was statistically significantly greater with vismodegib (-65%) vs placebo (-11%), p<0.003. Mean follow-up was 8 months (range 1 to 15). Multiple invasive surgeries may impact patient's quality of life. A reduction in size of surgically eligible BCCs would be of importance to clinicians, patients and their families if it results in fewer surgeries. See above for limitations of Tang et al (2012). Clinical photographs and training from the principal investigator were used to ensure consistency in the assessment of surgically eligible BCCs.

3.	Surgeries as part of standard care	Patients could have tumors surgically removed at the discretion of their primary dermatologist. This outcome reports the mean number of surgeries performed during the RCT as part of standard care. In one RCT of patients with Gorlin syndrome (Tang et al 2012, n=42), the mean number of surgeries as part of standard care was statistically significantly lower with vismodegib (0.31) vs placebo (4.4), p<0.001. Mean follow-up was 8 months (range 1 to 15). Multiple invasive surgeries may impact patient's quality of life. A mean reduction of approximately 4 surgeries is likely to be of importance to clinicians, patients and their families. See above for limitations of Tang et al (2012). The performance of surgeries was at the discretion of the patient's primary dermatologist. Practice may have varied between study centres and clinicians.
4.	Pharmacokinetic assessment of vismodegib	This outcome assessed the level of vismodegib present in plasma at 1 month. In one RCT of patients with Gorlin syndrome (Tang et al 2012) 26 patients received vismodegib. Median (±standard error) total plasma drug level was 25±7µmol/litre (range 13 to 42). The study authors reported no correlation between plasma drug level and tumour response at 1 or 3 months. As no correlation between plasma drug level and tumour response was reported, the clinical meaningfulness of this outcome is not clear. See above for limitations of Tang et al (2012). This outcome was only reported after 1 month of vismodegib.
5.	Histologic outcomes	Biopsy samples were examined for evidence of residual tumour at 1 and 3 months. In one RCT of patients with Gorlin syndrome (Tang et al 2012) 26 patients received vismodegib. Residual microscopic BCC was present in 22/25 (88%) random samples of tumours that were clinically raised (plaques or papules)[2] after 1 month of vismodegib. 6/13 (43%) biopsy samples had residual tumour detected in random histological sections after 3 months of vismodegib. The authors also reported that 1/6 (17%) of lesions that appeared clinically resolved had residual tumour.

[2] Not further defined

		This result suggests that residual tumour remains after 3 months of vismodegib. The clinical meaningfulness of this result is unclear. See above for limitations of Tang et al (2012). The number of samples is provided but the number of patients that had samples taken is unclear. Tumour detected at 1 month was described as microscopic. It is not clear if this was also the case for residual tumour detected after 3 months.
6.	Molecular outcomes	Dysregulated hedgehog signalling is the pivotal molecular abnormality in BCC (Tang et al 2012). Hedgehog signalling (assessed by GLI1 messenger RNA), tumour proliferation (assessed by Ki67 index) and apoptosis (cell death assessed by cleaved caspase 3) assess the effectiveness of vismodegib in the inhibition of hedgehog signalling. These were assessed at 1 month. In one RCT of patients with Gorlin syndrome (Tang et al 2012, n=42), there was a statistically significant decrease in hedgehog signalling from baseline for vismodegib (90% decrease in GLI1 messenger RNA, p<0.001). There was no significant difference from baseline for placebo (p=0.75, % not reported). There was also a statistically significant reduction in tumour proliferation from baseline with vismodegib (p<0.0001) but not with placebo (p=0.37). There was no significant change in apoptosis from baseline for vismodegib (p=0.41) or placebo (p=0.32). These results suggest a statistically significant decrease in hedgehog signalling and tumour proliferation from baseline to 1 month with vismodegib but not with placebo. However vismodegib and placebo were not directly compared. There was no impact on apoptosis. The clinical meaningfulness of these results is unclear. See above for limitations of Tang et al (2012).

BCC – basal-cell carcinoma; ITT – intention-to-treat; RCT – randomised controlled trial; SD – standard deviation; SE – standard error

Part A ii) Use of vismodegib to treat non-locally advanced, non-metastatic multiple BCCs (no comparator)

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported.
2.	Progression free survival	Not reported.
3.	Mobility	Not reported.

4.	Self-care	Not reported.
5.	Usual activities	Not reported.
6.	Pain	Not reported.
7.	Anxiety / Depression	Not reported.
8.	Replacement of more toxic treatment	Not reported.
9.	Dependency on care giver / supporting independence	Not reported.
10.	Safety	Adverse events were graded according to the National Cancer Institute Common Terminology Criteria (version 3) where Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening or disabling; Grade 5 = death related to adverse event[1]. In an extension study following the RCT of patients with Gorlin syndrome (Tang et al 2016) adverse events were reported for 40 patients who had received vismodegib during the RCT or extension study. Grade 3-4 adverse events affecting >1 patient included ≥20% weight loss (15%), muscle cramps (5%), pneumonia (5%), reactions to antibiotics (5%) and chest pain (5%). Grade 1-2 adverse events affecting >25% of patients included hair loss (100%), muscle cramps (100%), dysgeusia (93%), gastrointestinal upset (65%), 5% to <20% weight loss (63%), fatigue (48%). 2 patients died, however these deaths were not thought to be related to vismodegib. Adverse events may affect quality of life and are likely to be of importance to clinicians, patients and their families. A high proportion of patients experienced mild to moderate adverse events with vismodegib. The proportion experiencing more severe adverse events was lower. The proportion of patients who discontinued vismodegib due to adverse events is not clear due to differences in reporting between study centres. In this small, moderate quality extension study the length of time that patients were allowed to take vismodegib varied between study sites (up to 36 months at 2 of the 3 sites and up to 18 months at the third site). Patients originally randomised to vismodegib received vismodegib for a mean of 21 (SD 9) months. Patients originally assigned to placebo received vismodegib for a mean of 16 (SD 7) months. All patients in this RCT had Gorlin syndrome and ≥10 surgically eligible BCCs at

		baseline or that had been removed during the previous 2 years. 2 patients randomised to placebo withdrew before the study extension. As they did not receive vismodegib they were not included in this safety analysis. A published, standardised grading system was used to assess adverse events.
11.	Delivery of intervention	Not reported.

No	Outcome measure	Summary from evidence review
1.	Median time to tumour shrinkage	Median time to tumour shrinkage (by 50%, 90% and 100%) was reported for surgically eligible BCCs. Surgically eligible BCCs were defined as BCCs with a diameter of ≥3mm on the nose or periorbital skin, ≥5mm elsewhere on the face or ≥9mm on the truck or limbs (excluding the leg below the knees which was not monitored). In an extension study following the RCT of patients with Gorlin syndrome (Tang et al 2016), median time to 50% tumour shrinkage (n=36) was 3 months (IQR 2 to 5). Median time to 90% tumour shrinkage (n=22) was 7 months (IQR 4 to 14). Median time to 100% tumour shrinkage (n=19) was 15 months (IQR 9 to 15). Multiple invasive surgeries may impact patient's quality of life. Tumour shrinkage would be of importance to clinicians, patients and their families if it results in fewer surgeries. Most patients in the extension study (n=40) achieved 50% tumour shrinkage for surgically eligible BCCs at a median of 3 months. Approximately half achieved 100% tumour reduction at a median of 15 months. See above for limitations for Tang et al (2016).
2.	Surgeries as part of standard care	Patients could have tumors surgically removed at the discretion of their primary dermatologist. In an extension study following the RCT of patients with Gorlin syndrome, Tang et al (2016) reported the mean (SD) number of surgeries per patient per year. Before vismodegib treatment (n=23) this was 28.0 (19.6). During vismodegib treatment (n=40) this was 0.5 (0.5). After a mean of 14 months (SD 7) of discontinuing vismodegib (n=15) this was 4.9 (6.3). Multiple invasive surgeries may impact patient's quality of life. A reduction in number of surgeries would be of importance to clinicians, patients and their families. See above for limitations for Tang et al (2016).

		Data before and after treatment were only available for patients who responded to a telephone questionnaire after study completion. The performance of surgeries during the study was at the discretion of the patient's primary dermatologist. Practice may have varied between study centres and clinicians.

BCC – basal-cell carcinoma; IQR – inter quartile range; RCT – randomised controlled trial; SD – standard deviation; SE – standard error

Part B i) Use of vismodegib with a 12-8 week based intermittent dose vs. vismodegib with a 24-8-8 week based intermittent dose to treat non-locally advanced, non-metastatic multiple BCCs

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported.
2.	Progression free survival	Not reported.
3.	Mobility	Not reported.
4.	Self-care	Not reported.
5.	Usual activities	Not reported.
6.	Pain	Not reported.
7.	Anxiety / Depression	Not reported.
8.	Replacement of more toxic treatment	Not reported.
9.	Dependency on care giver / supporting independence	Not reported.
10.	Safety	Adverse events were classified using the Medical Dictionary for Regulatory Activities (version 18.0)[3]. The severity of adverse events was reported using 5 grades which appear to align to the National Cancer Institute Common Terminology Criteria where Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening or disabling; Grade 5 = death related to adverse event[1]. In one RCT (Dréno et al 2017, n=229) 94% of patients with intermittent dosing regimen A and 97% of patients with intermittent dosing regimen B had ≥1 adverse event related to study treatment. For serious adverse events (not defined) this

[3] https://www.meddra.org/

		was 5% and 2% respectively. Overall, 107 (47%) patients discontinued treatment. The proportion of patients who stated that their discontinuation was because of adverse events was 23/116 (20%) in group A and 30/113 (27%) in group B. Statistical differences between groups were not assessed. Adverse events ≥ Grade 3 affecting more than 1 patient included muscle spasms (group A 4% vs group B 11%), increased blood creatine phosphokinase (1% vs 4%), hypophosphataemia (0% vs 3%), dysgeusia (1% vs 2%), pneumonia (2% vs 0%), γ-Glutamyltransferase (2% vs 0%), abscess limb (0% vs 2%), decreased appetite (0% vs 2%). Adverse events may affect quality of life and are likely to be of importance to clinicians, patients and their families. A high proportion of patients experienced at least 1 adverse event with vismodegib. The proportion experiencing more severe adverse events was lower. At least 20% of patients in each group discontinued vismodegib due to adverse events. In this moderate quality, double-blind RCT, group A received vismodegib 150mg daily for 12 weeks then placebo for 8 weeks alternating for 3 rounds, followed by a final 12 weeks of vismodegib (n=116). Group B received vismodegib 150mg daily for 24 weeks then placebo for 8 weeks and vismodegib for 8 weeks alternating for 3 rounds (n=113). This study included patients with multiple (≥6 clinically evident) BCCs amenable to surgery. 'Clinically evident' and 'amenable to surgery' were not further defined. The study included 52 centres from 10 countries (non-UK). The study was funded by the manufacturer. This outcome did not include a comparison to assess the statistical difference between groups. Treatment interruptions of ≤2 weeks were permitted up to 4 weeks. The safety analysis included all patients who received ≥1 dose of study drug (n=227). A number of categories were used to describe treatment discontinuation but reasons e.g. for withdrawal of consent were not recorded. The number of patients who discontinued due to adverse events may be an underestimate.
11.	Delivery of intervention	Not reported.

No	Outcome measure	Summary from evidence review
1.	Mean number of clinically evident BCCs (reduction from baseline)	The mean number of clinically evident (not further defined) BCCs was reported as the difference between baseline and treatment end. Median treatment duration was 71.4 weeks (range 1.3 to 73.3).

		In one RCT (Dréno et al 2017, n=229), both groups showed a reduction from baseline in the mean number of clinically evident BCCs. There was no significant difference in reduction from baseline between the 2 intermittent vismodegib dosing regimens (62.7% (95%CI 53.0 to 72.3) vs 54.0% (95%CI 43.6 to 64.4); difference -8.9% (95%CI -23.0 to 5.2), p=0.24) in intention-to-treat analysis. The same non-significant difference was reported for the per-protocol analysis. In a subgroup analysis of patients with Gorlin syndrome (n=85) there was no significant difference between regimens (55.2% vs 56.6%; difference 2.1% (95%CI -28.8 to 33.0), p=0.87). For patients without Gorlin syndrome, intermittent dosing regimen A had a statistically significantly greater reduction from baseline than intermittent dosing regimen B (67.2% vs 52.6%; difference -15.4% (95%CI -28.8 to -1.9), p=0.03). No comparison between patients with and without Gorlin syndrome was reported. New clinically evident BCCs may require invasive treatment which could impact quality of life. A reduction in number would be of importance to clinicians, patients and their families if this resulted in fewer invasive treatments. Both dosing regimens showed a reduction in the mean number of clinically evident BCCs from baseline. There was no significant difference between the dosing regimens. See above for limitations of Dréno et al (2017). Although difference between groups was reported, the primary aim of the study was to assess percentage reduction from baseline. The authors described the comparison between groups as exploratory analysis and these should be treated with caution as the study was not powered to detect a difference between groups. The per-protocol analysis included all patients who completed the 72 weeks of treatment without major protocol violations (n=109). There were a number of inaccuracies in the reporting of results, e.g. the difference figures reported do not align to the difference in the percentage reduction figures between groups.
2.	Size of target BCC lesions	Patients all had ≥6 clinically evident BCCs amendable to surgery. Three lesions ≥5mm diameter (of which ≥1 was histopathologically confirmed) were designated as target BCCs. In one RCT (Dréno et al 2017, n=229), both groups showed a reduction from baseline in the size of target BCC lesions. Intermittent dosing regimen A had a statistically significantly greater reduction from baseline than intermittent dosing regimen B (82.9% vs 68.8%; difference -15.2% (95%CI -27.4 to -3.0), p=0.015) in intention-to-treat analysis. The same

		significant difference was reported for the per-protocol analysis. Multiple invasive procedures may impact patient's quality of life. A reduction in size of BCCs would be of importance to clinicians, patients and their families if it results in fewer surgeries Both dosing regimens showed a reduction in the size of target BCCs from baseline, with regimen A showing a statistically significantly greater reduction than regimen B. This outcome was only assessed in lesions designated as target lesions. The clinical significance of the result is not clear. See above for limitations of Dréno et al (2017).
3.	Number of patients with a reduction in total BCCs ≥50%	This outcome reports the number of patients with a reduction of ≥50% in total number of BCCs from baseline to end of treatment (median treatment duration 71.4 weeks (range 1.3 to 73.3)). In one RCT (Dréno et al 2017, n=229), 65.5% of patients with intermittent dosing regimen A and 50.4% of patients with intermittent dosing regimen B had a reduction in total BCCs of ≥50% in the intention-to-treat analysis (difference -15.1% (95% CI -27.7 to -2.4). In the per-protocol analysis this outcome was 83.1% vs 77.1% (difference -6.0% (95%CI -21.2 to -9.3). Statistical difference between groups was not assessed. More than half of the patients with each dosing regimen had a reduction of ≥50% in total number of BCCs. A reduction in total BCCs would be of importance to clinicians, patients and their families if it results in fewer invasive procedures. See above for limitations of Dréno et al (2017). This outcome did not include a comparison to assess the statistical difference between groups.
4.	New BCCs	This outcome reports the number of patients without new BCCs at the end of treatment (median treatment duration 71.4 weeks (range 1.3 to 73.3)). In one RCT (Dréno et al 2017, n=229), 76.6% of patients with intermittent dosing regimen A and 74.4% of patients with intermittent dosing regimen B were without new BCCs at the end of treatment in the intention-to-treat analysis (difference -2.2% (95% CI -14.8 to 10.4)). In the per-protocol analysis this outcome was 74.6% vs 77.1% (difference -2.5% (95%CI -13.8 to 18.8)). Statistical difference between groups was not assessed.

		Approximately three quarters of patients with each dosing regimen did not develop any new BCCs during treatment. This would be of importance to clinicians, patients and their families if it results in fewer invasive procedures. See above for limitations of Dréno et al (2017). This outcome did not include a comparison to assess the statistical difference between groups.

BCC – basal-cell carcinoma; RCT – randomised controlled trial; SD – standard deviation; SE – standard error

Part B ii) Use of continuous vismodegib vs. intermittent vismodegib to treat non-locally advanced, non-metastatic multiple BCCs

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported.
2.	Progression free survival	Not reported.
3.	Mobility	Not reported.
4.	Self-care	Not reported.
5.	Usual activities	Not reported.
6.	Pain	Not reported.
7.	Anxiety / Depression	Not reported.
8.	Replacement of more toxic treatment	Not reported.
9.	Dependency on care giver / supporting independence	Not reported.
10.	Safety	Not reported.
11.	Delivery of intervention	Not reported.

No	Outcome measure	Summary from evidence review
1.	New surgically eligible BCCs	Surgically eligible BCCs were defined as BCCs with a diameter of ≥3mm on the nose or periorbital skin, ≥5mm elsewhere on the face or ≥9mm on the truck or limbs (excluding the leg below the knees which was not

		monitored).This outcome assessed the number of new surgically eligible BCCs per patient per year. In an extension study following the RCT of patients with Gorlin syndrome (Tang et al 2016), patients who were 'very compliant' (≥80% of prescribed pills (n=16)) had a statistically significantly lower mean (SD) number of new surgically eligible BCCs per patient per year than patients who were 'very incompliant' (<50% of prescribed pills (n=14)) (0.6 SD 0.72) vs 1.7 SD 1.8), p<0.0001). Multiple invasive surgeries may impact patient's quality of life. A reduction of new surgically eligible BCCs would be of importance to clinicians, patients and their families. The clinical meaningfulness of a difference of approximately 1 new surgically eligible BCC per year is unclear. See above for limitations of Tang et al (2016). It is not clear why 80% and 50% were chosen as the cut-off points for 'very compliant' and 'very incompliant' patients. 11 patients were not included in this analysis for reasons that were decided after data collection. The selective inclusion of patients in analyses introduces bias and the results should be treated with caution.
2.	Recurrence	Recurrence relates to a return to baseline BCC tumour burden. In an extension study following the RCT of patients with Gorlin syndrome (Tang et al 2016), for 10/41 patients who took vismodegib continuously for ≥15 months there was no return to baseline tumour burden for 18 months after discontinuing the drug. The authors also reported that of 22/41 patients (54%) who discontinued vismodegib for ≥6 months: • 11 (50%) had a recurrence of ≥50% of baseline tumour burden over a median of 7.0 months (IQR 6.0 to 9.0) • 3/11 had a 90% recurrence of baseline tumour burden over a median of 21.0 months (IQR 16.5 to 25.5) A return to baseline BCC tumour burden may result in patients requiring multiple invasive procedures and would therefore be of importance to clinicians, patients and their families. See above for limitations of Tang et al (2016). It is not clear why 15 months and 6 months were chosen as the cut-off points for inclusion in this analysis and this decision was made after data collection. The selective inclusion of patients in analyses introduces bias and the results should be treated with caution.

BCC – basal-cell carcinoma; RCT – randomised controlled trial; SD – standard deviation; SE – standard error

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **Mobility:** Patients have no problems in walking about.
- **Ability to provide self-care:** Patients have no problems in washing or dressing.
- **Undertaking usual activities:** Patients have slight to moderate problems in doing their usual or daily activities.
- **Experience of pain/discomfort:** Patients have moderate pain or discomfort.
- **Experience of anxiety/depression:** Patients can be extremely anxious or depressed.

Further details of impact upon patients:
Multiple basal cell carcinoma (BCC) is a lifelong condition, with progressive disfigurement in some patients. The continuous development and surgical removal of lesions can result in progressive disfigurement of patients impacting a patient's perceived appearance and self-esteem (Shingler et al, 2013). This may eventually lead to decreased activities involving interpersonal interactions and decreased overall health related quality of life (HRQL).

Further details of impact upon carers:
As described above, the psychological impact of the condition can result in patients reducing their interpersonal interactions and this may impact carers.

Considerations from review by Rare Disease Advisory Group

Not applicable.

Pharmaceutical considerations

This clinical commissioning policy proposition recommends vismodegib for adults with either Gorlin syndrome or non-Gorlin syndrome with multiple BCCs who have a minimum of 6 lesions and where surgery could result in significant disfigurement. The recommendations are outside its marketing authorisation which is for patients whose BCC is inappropriate for surgery. Due to safety concerns this medicinal product should not be used in children and adolescents aged below 18 years.

Considerations from review by National Programme of Care

1) The proposal received the full support of the Cancer PoC on the 6th August 2020.