Clinical Commissioning Policy: Vismodegib for adults with either Gorlin syndrome or non-Gorlin syndrome related multiple basal cell carcinomas. (Adults) (210504P) [URN: 1905]

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Commissioning position

Summary

Vismodegib is recommended to be available as a treatment option through routine commissioning for adults with either Gorlin syndrome or non-Gorlin syndrome related multiple basal cell carcinomas within the criteria set out in this document.

The policy is restricted to adults as the Marketing Authorisation does not recommend its use in children and adolescents aged below 18 years due to safety concerns in this population.

Executive summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain language summary

About multiple basal cell carcinomas (BCCs)

Basal cell carcinoma is the most common form of skin cancer, with approximately 114,000 new diagnoses per year in the United Kingdom. The condition develops from basal cells which are found in the deepest layer of the epidermis (the outer layer of the skin). Basal cell carcinom as can occur anywhere in the body but develop mostly in areas exposed to the sun, such as the face, head and neck. The condition is more common in older people with approximately 50% of cases being diagnosed in people aged 75 years and above (Cancer Research UK, 2019). Basal cell carcinomas are strongly linked to sun exposure, so mainly occur in sun-exposed areas of the body, such as the face, head and neck.

Although most people with basal cell carcinomas may have a small number of basal cell carcinomas during their lifetime, some people can have multiple basal cell carcinomas, where multiple tumours develop frequently at different sites.

People with multiple basal cell carcinoma fall into two distinct groups:

- Gorlin syndrome (also known as basal cell nevus syndrome): This is an inherited genetic disorder in which people develop basal cell carcinomas from an early age (teens or 20s), as well as other abnormalities such as cysts in the jawbone and ovarian tumours. They may develop hundreds of basal cell carcinomas over a lifetime.
- People with non-Gorlin related multiple basal cell carcinomas (BCCs); these are frequently elderly people who have worked outside or who have spent long periods in sunny areas of the world.

This policy is specifically for the treatment of adults with either Gorlin syndrome or non-Gorlin syndrome related multiple basal cell carcinoma, who have a minimum of 6 lesions at the point of decision to treat which have not spread to other sites in the body (i.e., non-metastatic, localised disease).

About current treatments

The standard first line treatment for basal cell carcinoma is to remove the tumour using a variety of invasive procedures. Treatment is dependent on the size of the cancer and may include:

- Surgery, excising the affected area of the skin;
- Curettage and cautery, whereby the tumour is scraped away under local anaesthetic (referred to as curettage) and then the skin's surface is healed with heat (cautery);
- Cryotherapy, using cold temperatures (freezing) to remove the cancer; and/or
- Radiotherapy, this treatment is unsuitable for people with Gorlin syndrome due to the risk of causing additional tumours. It may be used in people with multiple BCCs (non-Gorlin) but is not the first-choice treatment.

As patients with either or Gorlin syndrome or non-Gorlin syndrome related multiple basal cell carcinomas frequently develop new cancers, they may require multiple invasive procedures every few months to keep their condition under control. These procedures are potentially disfiguring, and some people may have many scars and skin grafts, particularly on the face and head, as a result of treatment. This can cause a major negative impact on quality of life.

About vismodegib

Vismodegib is a targeted cancer treatment which works by preventing cancer cell growth. It is taken once daily, on an intermittent schedule, until the patient progresses or can no longer tolerate side effects. The use of vismodegib in patients with multiple BCCs has been shown to reduce the size of these cancers, the frequency in which they appear and reduce or avoid the need for surgery in the long term.

Vismodegib is licensed for symptomatic metastatic basal cell carcinoma or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy; however, NICE Technology Appraisal (TA 489) recommended that the treatment not be made available for its licensed indications and is not commissioned by NHS England.

This policy considers vismodegib for adults with either Gorlin syndrome or non-Gorlin syndrome related multiple BCCs that are suitable for surgery where use of the medicine may reduce the need and extent of surgery or negate it altogether. Vismodegib is unlicensed for use in these indications.

What we have decided

NHS England has carefully reviewed the evidence to treat adults with either Gorlin syndrome

or non-Gorlin syndrome related multiple BCCs. We have concluded that there is enough evidence to make the treatment available at this time in line with the criteria set out in this policy NHS England intends to review the policy after two years, or earlier in the event that annual activity exceeds 100 cases.

Links and updates to other policies

Not applicable.

Committee discussion

Clinical Panel considered the evidence and recommended the policy proceed as a routine commissioning position.

See the committee papers (link) for full details of the evidence.

The condition

Basal cell carcinoma (BCC) is cancer that arises in the basal cell layer (lower part) of the epidermis (outer layer of the skin) (National Cancer Institute, 2019). BCC is the most common form of skin cancer (Bakshi *et al.,* 2017) and has a strong link to sun exposure so mainly occurs in sun-exposed areas of the body, such as the face, head and neck. BCC are more common in older people with approximately 50% of cases being diagnosed in people aged 75 years and above (Cancer Research UK, 2019). BCCs often look like open sores, red patches, pink growths, shiny bumps, or scars.

Some patients can have multiple BCCs, where multiple tumours develop frequently at different sites. This is typically seen in elderly people who have worked outside or spent long periods in sunny areas of the world.

A subgroup of patients with multiple BCCs are those with Gorlin syndrome (also known as basal cell nevus syndrome). This is a dominantly inherited genetic disorder in which people develop BCCs from an early age (teens or 20s), as well as other abnormalities such as cysts in the jawbone and benign ovarian tumours.

The underlying genetic defect in BCC is a mutation in a cellular signalling mechanism called the hedgehog pathway. The pathway is highly functional in embryogenesis and crucial for normal development.

Current treatments

The standard first line treatment for BCC is to remove the tumour. These invasive procedures include: (i) surgery; (ii) curettage and cautery; and/or (iii) cryotherapy.

As people with either Gorlin syndrome or non-Gorlin syndrome related multiple BCCs frequently develop new BCCs, they may require multiple invasive procedures every few months to keep their condition under control. These procedures are potentially disfiguring as patients may have many scars and skin grafts, particularly on the face and head. The severity of the condition varies but it can cause a major negative impact on quality of life.

Radiotherapy is unsuitable for people with Gorlin syndrome due to the risk of causing additional tumours.

Radiotherapy may be used in the treatment of non-Gorlin related multiple BCCs to prevent further surgery being carried out in the area if new BCCs arise. However, it is often avoided because of the close proximity of new BCCs to previously treated tumours and the increased risk of severe radiation damage caused as a result of overlapping radiotherapy treatment fields.

The new treatments

Vismodegib is an oral drug which inhibits the hedgehog signalling pathway, thereby preventing cancer cell growth. It is taken as a once daily capsule until the patient's disease progresses or can no longer tolerate the side effects of treatment. The most common side effects of vismodegib are taste changes, muscle cramps, gradual hair loss, weight loss, gastrointestinal effects such as nausea, diarrhoea or constipation, and fatigue (Basset-Seguin *et al.,* 2017).

The use of vismodegib in patients with multiple BCCs has been shown to produce high response rates and tumour shrinkage in BCCs and reduce or avoid the need for surgery in the long term (Basset-Seguin *et al.,* 2017; Tang *et al.* 2016; Dreno *et al.* 2017).

Vismodegib was available through the Cancer Drugs Fund from 2013 to 2017 for the treatment of people with metastatic or locally advanced basal cell carcinoma, in line with the medicine's license. However, a NICE Technology Appraisal (TA 489) recommended that it was not to be made available for its licensed indications because of the uncertainty of evidence and the cost effectiveness of the treatment (NICE, 2017).

This policy covers patients who may benefit from the treatment but fall outside the licensed indication considered by NICE TA 489. This use of vismodegib is an alternative treatment for patients where first line invasive procedures may be appropriate, but the number and frequency of procedures required could impact on their quality of life and potentially disfigure them.

Epidemiology and needs assessment

BCC is the most common form of skin cancer, accounting for about 80% of non-melanoma skin cancers (Bakshi *et al.,* 2017). In 2015, the incidence of non-melanoma skin cancer in the UK was 142,101 cases (Cancer Research UK, 2019), resulting in just over 100,000 new diagnoses of basal cell carcinoma in England. However, it is estimated that between 30-50% of BCCs go unreported (Venables et al. 2019) and therefore, the number of people with BCC could be higher. BCC is more common in males than females, and the risk of developing the condition increases with age (Cancer Research UK, 2019).

The estimated prevalence of Gorlin syndrome is about 1 in 31,000 people in the UK (Evans et al. 2010), of whom 90% develop BCCs increasingly with age (Cancer Research UK, 2016). The estimated birth incidence of Gorlin syndrome is about 1 in 19,000 people in the UK (Evans et al. 2010).

Due to limitations with the recording of BCC, it is difficult to estimate the exact prevalence of multiple BCCs (National Cancer Intelligence Network, 2013). The Policy Working Group has estimated an annual usage, based on the uptake when vismodegib was available via the Cancer Drugs Fund, of approximately 45 patients per year (23 with multiple BCCs appropriate for surgery and 22 with Gorlin syndrome) suitable for treatment with vismodegib in England, in line with the criteria set out in this policy. As there is some uncertainty in the estimate of the numbers of patients that might benefit from the treatment, it is intended to review the policy after two years, or earlier in the event that annual activity exceeds 100 cases.

The actual number of patients who require treatment with vismodegib will be much lower than the prevalence of Gorlin syndrome as there are varying degrees of severity of the condition. Overall treatment number are also likely to vary because some patients with multiple BCCs may not need or wish to have drug therapy.

Evidence summary

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication.

- Two sets of questions were considered in this evidence review of patients with non-

locally advanced, non-metastatic multiple BCCs. Part A assesses the effectiveness and safety of vismodegib compared with invasive procedures[1] or radiotherapy. Part B assesses the effectiveness and safety of one particular intermittent vismodegib dosing regimen compared with a different intermittent or continuous dosing regimen.

- One study, published in two papers, was identified for part A. One RCT (n=42) by Tang et al (2012) reported outcomes comparing vismodegib (n=26) to placebo (n=16) in patients with Gorlin syndrome with a mean follow-up of eight months (range 1 to 15)[2]. Tang et al (2016) reported additional outcomes from an extension study after patients were switched to vismodegib and followed-up for up to 36 months. In this paper patients originally randomised to vismodegib received vismodegib for a mean of 21 (standard deviation (SD) 9) months. Patients originally assigned to placebo received vismodegib for a mean of 16 (SD 7) months. No studies were identified comparing vismodegib to other invasive procedures or radiotherapy.
- One RCT and one subgroup analysis were identified for part B. The RCT (n=229) by Dréno et al (2017) reported outcomes for two different intermittent dosing regimens in patients with multiple BCCs, of which 37% had Gorlin syndrome. In intermittent dosing regimen A patients received vismodegib 150mg daily for 12 weeks then placebo for eight weeks alternating for three rounds, followed by a final 12 weeks of vismodegib (n=116). In intermittent dosing regimen B patients received vismodegib 150mg daily for 24 weeks then placebo for eight weeks and vismodegib for eight weeks alternating for three rounds (n=113). Median treatment duration was 71.4 weeks (range 1.3 to 73.3). Subgroup analysis from Tang et al (2016) also reported outcomes for patients who were more or less compliant with a continuous vismodegib dosing regimen.

Clinical effectiveness

Vismodegib compared to invasive procedures or radiotherapy (part A)

- New surgically eligible BCCs: There were statistically significantly fewer new surgically eligible BCCs with vismodegib vs placebo (mean 2 vs 29 per patient per year[3], p<0.001) in 1 RCT (n=42). Mean follow-up was eight months.
- Reduction in size of existing surgically eligible BCCs: Reduction from baseline in the sum of the longest diameter of existing surgically eligible BCCs was statistically significantly greater with vismodegib vs placebo (-65% vs -11%, p<0.003) in 1 RCT (n=42). Mean follow-up was eight months.
- Surgeries as part of standard care[4]: There were statistically significantly fewer surgeries with vismodegib vs placebo (mean 0.31 vs 4.4, p<0.001) in 1 RCT (n=42). Mean follow - up was eight months. The RCT extension study reported that the mean number of surgeries per patient per year was 28.0 (SD 19.6) before vismodegib (n=23[5]), 0.5 (SD 0.5) during vismodegib treatment[6] (n=40) and 4.9 (SD 6.3) at a mean of 14 (SD 7) months after discontinuing vismodegib (n=15[7]).
- Median time to tumour shrinkage: The RCT extension study (n=40), in which all patients

[1] The PICO definition of invasive procedures includes 'placebo' as "surgery may be described as 'placebo' in papers because this is the current standard treatment" (see PICO Table A in section 9)

[2] This paper reports a planned interim analysis after which the data safety and monitoring board recommended ending the placebo treatment as the pre-determined threshold for a significant difference (p<0.0113) between the 2 groups had been reached for the primary outcome (new surgically eligible BCCs)

[3] The analysis accounted for the differential follow-up among study participants (see section 7)

[4] Patients could have tumours surgically removed at the discretion of their primary dermatologist

[5] Data were only available for patients who responded to a telephone questionnaire conducted after study completion

[6] 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

[7] Data were only available for patients who responded to a telephone questionnaire conducted after study completion

were treated with vismodegib, reported that median time to 50% tumour shrinkage (n=36) was three months (interquartile range (IQR) 2 to 5). Median time to 90% tumour shrinkage (n=22) was seven months (IQR 4 to 14). Median time to 100% tumour shrinkage (n=19) was 15 months (IQR 9 to 15).

- Pharmacokinetic assessment of vismodegib: Median (±standard error (SE)) total plasma drug level at one month was 25±7µmol/litre (range 13 to 42) in patients randomised to vismodegib in one RCT (n=26).
- Histologic outcomes: After one month of vismodegib in one RCT (n=26), residual microscopic BCC was present in 88% random samples of 25 tumours that were clinically raised (plaques or papules)[8]. Residual tumour was detected in 43% of 13 biopsy samples in random histological sections after three months of vismodegib. 17% of six lesions that appeared clinically resolved had residual tumour. It is not clear how many patients provided biopsy samples.
- Molecular outcomes at 1 month: In one RCT (n=42) there was a statistically significant decrease in hedgehog signalling from baseline for vismodegib (90% decrease in GLI1 messenger RNA, p<0.001) but no significant difference from baseline for placebo (p=0.75, % not reported). There was a statistically significant reduction in tumour proliferation (Ki67 index) from baseline with vismodegib (p<0.0001) but not with placebo (p=0.37). There was no significant change in apoptosis (cell death) from baseline for vismodegib (p=0.41) or placebo (p=0.32).

Vismodegib using one intermittent dosing regimen compared with a different intermittent or continuous dosing regimen (part B)

- Mean number of clinically evident BCCs: In one RCT (n=229), both intermittent dosing regimens showed a reduction from baseline in the mean number of clinically evident BCCs. There was no significant difference in reduction from baseline for dosing regimen A vs dosing regimen B (62.7% (95%CI 53.0 to 72.3) vs 54.0% (95%CI 43.6 to 64.4):difference -8.9%[9] (95%CI -23.0 to 5.2), p=0.24)[10]. Median treatment duration was 71.4 weeks.
- Size of target BCC lesions[11]: In one RCT (n=229), both intermittent dosing regimens showed a reduction from baseline in the size of target BCC lesions. Dosing regimen A had a statistically significantly greater reduction from baseline than dosing regimen B (82.9% vs 68.8%; difference (-15.2%8 (95%CI -27.4 to -3.0), p=0.015)). Median treatment duration was 71.4 weeks.
- Number of patients with a reduction in total BCCs ≥50%: In one RCT (n=229), this was 65.5% for patients with intermittent dosing regimen A and 50.4% for patients with intermittent dosing regimen B (difference between groups -15.1% (95% CI -27.7 to -2.4)[12]. No statistical analysis of the difference between groups was performed. Median treatment duration was 71.4 weeks.
- New BCCs: In one RCT (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 (difference between groups -2.2% (95% CI -14.8 to 10.4)). No statistical

[8] Not further defined

[9] The difference figure reported does not align with the difference between the percent reductions reported. As it is not clear where the error lies, these figures are reported as given in the paper

[10] Intention-to-treat analysis

[11] 3 lesions of at least 5mm diameter were designated as target lesions for each patient

[12] Not further defined

analysis of the difference between groups was performed[13]. Median treatment duration was 71.4 weeks.

- New surgically eligible BCCs: In one RCT extension study, this was statistically significantly lower for patients who were 'very compliant' with the prescribed continuous vismodegib regimen (≥80% of prescribed pills (n=16)) vs patients who were 'very incompliant' (<50% of prescribed pills (n=14)) (mean 0.6 SD 0.72 vs mean 1.7 SD 1.8 (per patient per year), p<0.0001)6.
- Recurrence: In one RCT extension study, for patients who took vismodegib continuously for ≥15 months (n=10) there was no return to baseline tumour burden for 18 months after discontinuing the drug. For patients who discontinued vismodegib for at least six months (n=22), 11/22 (50%) had a recurrence of ≥50% of baseline tumour burden over a median of 7.0 months (IQR 6.0 to 9.0). Of these 3/11 had a 90% recurrence of baseline tumour burden over a median of 21.0 months (IQR 16.5 to 25.5).
- follow-up, 27% of patients had discontinued vismodegib due to adverse events and 7% had discontinued placebo due to disease progression. At later follow-up (28 months after study start), 54% had discontinued vismodegib due to adverse events.

Safety

Vismodegib compared to invasive procedures or radiotherapy (part A)

- Adverse events[14]: One RCT (n=41[15]) reported no Grade 5 adverse events and no significant difference between vismodegib (n=26) and placebo (n=15) for any Grade 3 or Grade 4 adverse events. Grade 1/ 2 adverse events that occurred statistically significantly more often with vismodegib vs placebo 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 eight months

- For patients who received vismodegib during the RCT and/ or extension study with follow-up of up to 36 months (n=40[16]), Grade 3 to 4 adverse events affecting more than one patient included ≥20% weight loss (15%), muscle cramps (5%), pneumonia (5%), reactions to antibiotics (5%) and chest pain (5%). Grade 1 to 2 adverse events affecting more than 25% of patients included hair loss (100%), muscle cramps (100%), dysgeusia (93%), gastrointestinal upset (65%), 5% to <20% weight loss (63%) and fatigue (48%).

Vismodegib using one intermittent dosing regimen compared with a different intermittent dosing regimen (part B)

- Adverse events[17]: In one RCT (n=227[18]), 94% of patients with dosing regimen A and 97% with dosing regimen B had at least one adverse event related to study treatment. For serious adverse events (not further defined) this was 5% and 2% respectively. Adverse events of Grade 3 or more affecting more than one 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 -

[13] The study authors described this as exploratory analysis and did not test for significance because the study was not designed to show a significant difference between groups (see section 7)

14 Classified using 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 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf)

[15] 1 patient from this RCT (n=42) was excluded from the safety analysis because they withdrew before receiving any study medication

[16] 2 patients randomised to placebo withdrew before the study extension and did not receive vismodegib

[17] Classified using the Medical Dictionary for Regulatory Activities (version 18.0) (https://www.meddra.org/). The severity of a dverse events was reported using 5 grades which appear to align to the National Cancer In stitute Common Terminology Criteria

[18] 2 patients from this RCT (n=229) were excluded from the safety analysis because they had not received any study medication

Glutamyltransferase (2% vs 0%), abscess limb (0% vs 2%) and decreased appetite (0% vs 2%). No statistical analysis of the difference between groups was reported. 107/227 (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.

Cost-effectiveness

- No studies reported the cost-effectiveness of vismodegib compared with invasive procedures or radiotherapy (part A), or of one particular intermittent vismodegib dosing regimen compared with a different intermittent or continuous vismodegib dosing regimen (part B), in people who have non-locally advanced, non-metastatic multiple BCCs.

Sub-groups of patients

- No studies identified for part A or part B compared outcomes for people with and without Gorlin syndrome or for other subgroups of patients.

In a subgroup analysis from one RCT (n=229) (part B), there was no significant difference in the reduction in number of clinically evident BCCs from baseline between intermittent dosing regimen A and intermittent dosing regimen B in patients with Gorlin syndrome (n=85) (55.2% vs 56.6%; difference 2.1% (95%CI -28.8 to 33.0), p=0.87). For patients without Gorlin syndrome (n=144) intermittent dosing regimen A had a statistically significantly greater reduction from baseline in the number of clinically evident BCCs than intermittent dosing regimen B (67.2% vs 52.6%; difference (-15.4% (95%CI - 28.8 to -1.9), p=0.03)[19].

Definitions

- In the Tang et al (2012, 2016) RCT all patients had Gorlin syndrome and ten or more surgically eligible BCCs present at study entry or removed during the previous two years. Surgically eligible tumours were defined as BCCs with a diameter of ≥3mm on the nose or periorbital skin, ≥5mm elsewhere on the face or ≥9mm on the trunk or limbs (excluding the leg below the knees which was not monitored).

- The Dréno et al (2017) RCT included patients with multiple (≥6 clinically evident) BCCs amenable to surgery (not further defined).

Summary

- Limitations in the design and reporting of these studies limit the strength of any conclusions that can be drawn. These include a lack of power to detect a difference between dosing regimens and exploratory analyses that did not include all patients.
- More robust studies examining the impact of vismodegib on quality of life in people with multiple BCCs would be beneficial.

[19] The difference figures reported do not align with the differences between the percent reductions reported. As it is not clear where the error lies, these figures are reported as given in the paper

Implementation

Eligibility Criteria

All patients should have their care managed by a range of different specialists working together as part of a tumour specific skin cancer or head and neck multi-disciplinary team (MDT).

Inclusion criteria

Patients meeting the following criteria should be considered for vismodegib:

- Adults with Gorlin syndrome with non-locally advanced, non-metastatic multiple (≥6) clinically evident lesions (Dréno *et al.* 2017) at the point of decision to treat BCCs of which 3 are at least 5mm; OR
- Adults with non-locally advanced, non-metastatic multiple (≥6 clinically evident lesions (Dréno *et al*. 2017) at the point of decision to treat BCCs of which 3 are at least 5mm AND are appropriate for surgery i.e. surgically eligible tumours.

Contraindications

Vismodegib is contra-indicated in women who are pregnant or breast feeding.

The Summary of Product Characteristics (SmPC) should be checked for other contraindications.

Contraception and Pregnancy

Vismodegib has a teratogenic risk and may cause severe birth defects and embryo-fetal death. The SmPC guidance on contraception and pregnancy testing must be followed for anyone receiving vismodegib.

Vismodegib must not be given to women of childbearing potential (WCBP) who do not comply with the contraception and pregnancy testing guidelines set out within the SmPC

Exclusion Criteria

- Patients covered by NICE TA 489 with symptomatic metastatic BCC, or locally advanced BCC that is inappropriate for surgery or radiotherapy, in adults.
- People under the age of 18.
- Vismodegib must not be used during pregnancy.

Stopping Criteria

Treatment with vismodegib should be discontinued if the patient cannot tolerate the side effects. See the SmPC for further details.

Dose

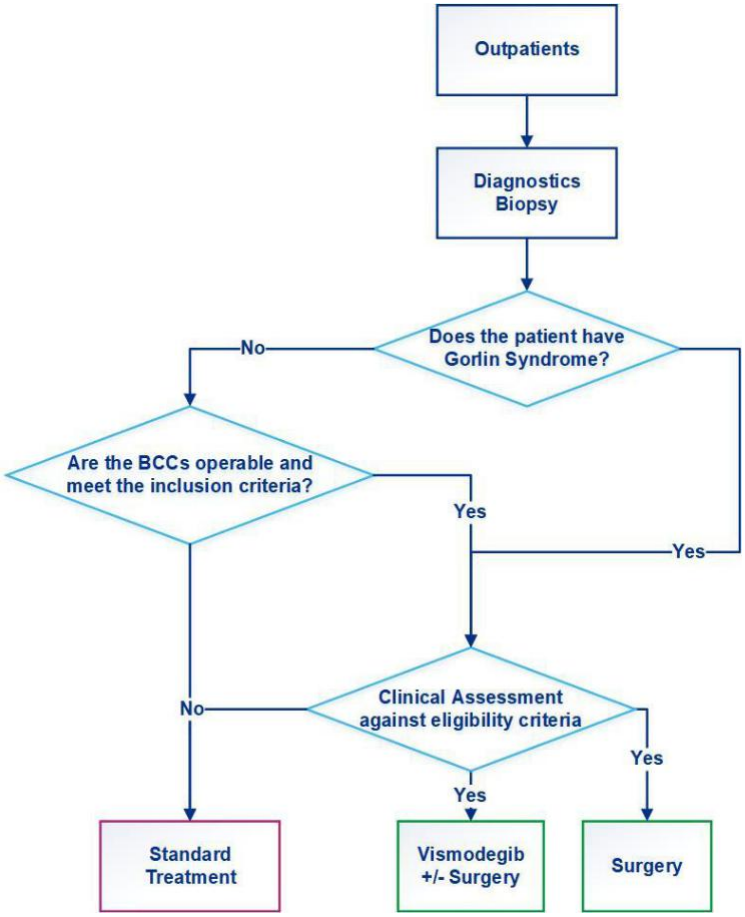
For the purposes of this policy, vismodegib will be taken once daily, on an intermittent schedule, until disease progression or adverse effects which necessitate stopping. This is because the tolerability of intermittent regimen is greater than the continuous regimen, as symptoms of muscle cramps, taste changes abate during the treatment breaks.

Vismodegib150mg daily for following regimens (Dréno *et al.* 2017):

1. A 72 week period of: vismodegib 12 weeks; off treatment 8 weeks; vismodegib 12 weeks; off treatment 8 weeks; vismodegib 12 weeks; off treatment 8 weeks; vismodegib 12 weeks. OR
2. A 72 week period of: vismodegib 24 weeks; off treatment 8 weeks; vismodegib 8 weeks; off treatment 8 weeks; vismodegib 8 weeks; off treatment 8 weeks; vismodegib 8 weeks.

Patient Pathway

Vismodegib will be given as an adjunct treatment within the current patient pathway:



Governance Arrangements

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

Vismodegib for patients with multiple operable BCC within the criteria set out in this document will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of Chemotherapy Services. All associated activity should be recorded to NCBPS01C Chemotherapy service line.

Audit requirements

Providers should use the Systemic Anti-Cancer Treatment (SACT) dataset and include treatment within the annual Skin Clinical Audit.

Policy review date

This policy will be reviewed after two years, or earlier in the event that annual activity exceeds 100 cases. The policy will also be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Basal cell carcinoma (BCC)	Cancer that arises in the basal cell layer (lower part) of the epidermis (outer layer of the skin).
Cryotherapy	An invasive procedure which uses extreme cold (with liquid nitrogen) to remove the cancer.
Curettage and cautery	An invasive procedure in which tumour is scrapped away under local anaesthetic (referred to as curettage) and then the skin's surface is healed with heat (cautery).
Embryogenesis	Refers to the process by which the embryo forms and develops.
Hedgehog pathway	A signalling pathway that regulates cell growth and differentiation in embryogenesis.
Gorlin Syndrome (also referred to as. basal cell nevus syndrome)	An inherited genetic disorder that increases the risk of developing cancerous and noncancerous tumours. People with Gorlin syndrome develop multiple BCCs from a young age.
Locally advanced BCC	Locally advanced BCC, in which tumours have become greatly enlarged, can result in significant tissue invasion and morbidity. Surgical management of these tumours can be extensive and may result in considerable deformity, particularly in the cases of facial BCC, including pinnectomy or rhinectomy. In such extreme cases, the cosmetic implications of treatment and impact on quality of life can make surgery an unattractive option for the patient (Lear 2014 narrative review).
Metastatic BCC	BCC that has spread beyond the skin to other parts of the body, including lymph nodes, lung, bones and/or internal organs.
Radiotherapy	The use of radiation, usually x-rays, to destroy cancer cells.
Teratogenic	Any substance that has a risk of causing birth defects via a toxic effect on an embryo or fetus.

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