NHS England

Evidence review: Vismodegib for multiple basal cell carcinomas

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1 Introduction

Introduction

- Basal cell carcinoma (BCC) is a non-melanoma skin cancer and is the most common type of skin cancer (Cancer Research UK 2019).
- BCCs develop from basal cells and are found in the deepest level of the epidermis (outer layer of the skin) and around hair follicles. They mostly develop in areas of skin that have been exposed to the sun but can develop anywhere on the body (Cancer Research UK 2019).
- One of the causes of BCC is mutations in a cellular signalling mechanism called the hedgehog pathway. These occur in almost all BCCs and can lead to uncontrolled cell growth (NHS England unpublished communication).
- Some people can have multiple BCCs (the focus of this evidence review), where multiple new tumours develop at different sites of the body, for example elderly people who have spent long periods of time working outside or in sunny areas of the world.
- Some people with multiple BCCs have a genetic disorder known as Gorlin syndrome or basal cell nevus syndrome. People with Gorlin syndrome develop BCCs from an early age (teens or 20s).

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- NICE do not recommend the use of vismodegib within its licensed indication for treating symptomatic metastatic or locally advanced BCCs that are inappropriate for surgery or radiotherapy (NICE 2017).
- NICE have not made any recommendations about the use of vismodegib in patients with multiple BCCs.

The indication and epidemiology

- From 2014 to 2016, the UK incidence of non-melanoma skin cancer increased from 237.0 per 100,000 population to 257.6 per 100,000 population. Between 2014 and 2016 the average number of new cases of non-melanoma skin cancer per year was 147,445 in the UK (Cancer Research UK 2019).
- Approximately 75% of non-melanoma skin cancers are BCCs (Cancer Research UK 2019). It is not clear what proportion of these cases have multiple BCCs.
- Gorlin syndrome affects about 1 in 31,000 people and about 90% of these develop multiple BCCs (Cancer Research UK 2016).

Standard treatment and pathway of care

- The standard first line treatment for BCC is an invasive procedure to remove the tumour, including surgery, laser, curettage and cautery and cryotherapy (NHS England unpublished communication).
- An alternative treatment is radiotherapy, however this is not recommended in people with Gorlin syndrome due to their sensitivity to radiation and the risk that this may cause additional tumours (Cancer Research UK 2016).
- Patients with multiple BCCs may require multiple invasive procedures every few months to keep their condition under control (NHS England unpublished communication).

The intervention (and licensed indication)

- Vismodegib is in oral drug which inhibits the hedgehog pathway. It is taken once daily either continuously or intermittently until disease progression or cessation due to adverse events (NHS England unpublished communication).
- Vismodegib is licensed for use in people with metastatic or locally advanced BCCs that are inappropriate for surgery or radiotherapy (NICE 2017).
- This review considers the use of vismodegib outside of the licensed indication i.e. in patients with multiple BCCs which may be suitable for surgery or radiotherapy.

Rationale for use

- Vismodegib may provide an alternative treatment for patients where first line invasive procedures may be appropriate, but the number and frequency of procedures required could be potentially disfiguring or negatively impact quality of life (NHS England unpublished communication).

2 Summary of results

- 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.

[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)

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[5]).
- Median time to tumour shrinkage: The RCT extension study (n=40), in which all patients 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)[7]. 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

[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] Not further defined

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%[8] (95%CI -23.0 to 5.2), p=0.24)[9]. Median treatment duration was 71.4 weeks.

- Size of target BCC lesions[10]: 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)[9]. 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)[9]. No statistical analysis of the difference between groups was performed[11]. 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)[9]. No statistical analysis of the difference between groups was performed[11]. 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).

Safety

Vismodegib compared to invasive procedures or radiotherapy (part A)

- Adverse events[12]: One RCT (n=41[13]) 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 follow-up, 27% of patients had discontinued vismodegib due to adverse events and 7% had discontinued placebo

[8] 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
[9] Intention-to-treat analysis
[10] 3 lesions of at least 5mm diameter were designated as target lesions for each patient
[11] 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)
[12] 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)
[13] 1 patient from this RCT (n=42) was excluded from the safety analysis because they withdrew before receiving any study medication

due to disease progression. At later follow-up (28 months after study start), 54% had discontinued vismodegib due to adverse events.

- For patients who received vismodegib during the RCT and/or extension study with follow-up of up to 36 months (n=40[14]), 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[15]: In one RCT (n=227[16]), 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-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)[17].

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.

[14] 2 patients randomised to placebo withdrew before the study extension and did not receive vismodegib

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

[16] 2 patients from this RCT (n=229) were excluded from the safety analysis because they had not received any study medication

[17] 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

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.

3 Methodology

- The methodology to undertake this review is specified by NHS England in the 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICOs) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICOs).
- The PICOs were used to search for relevant publications in the following sources: EMBASE MEDLINE and Cochrane Library (see section 10 for search strategies).
- The search dates for publications were between 1st January 2009 and 3rd June 2019.
- The titles and abstracts of the results from the literature search were assessed using the criteria from the PICOs. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICOs were selected for inclusion in this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using the National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8).

4 Results

Two sets of questions were considered in this evidence review (part A and part B). The evidence base relating to these two sets of questions is considered separately below.

Part A of the evidence review includes one study published in two papers. One RCT (n=42) reports outcomes comparing vismodegib to placebo in patients with Gorlin syndrome (Tang et al 2012). Tang et al (2016) reports longer-term outcomes from the extension study after patients were switched to vismodegib. Part B of the evidence review includes one RCT where two groups of patients with multiple BCCs received two different intermittent dosing regimens of vismodegib (Dréno et al 2017). Subgroup analysis from Tang et al (2016) also reported outcomes for patients who were more or less compliant with a continuous vismodegib dosing regimen.

Part A

1. In people who have non-locally advanced, non-metastatic multiple BCCs, what is the clinical effectiveness of vismodegib compared with invasive procedures or radiotherapy?

One RCT (Tang et al 2012, n=42) compared the clinical effectiveness of vismodegib and placebo in patients with non-locally advanced, non-metastatic multiple BCCs at a mean follow-up of eight months (range 1 to 15). In this study all patients had Gorlin syndrome. A further paper (Tang et al 2016) reported the longer-term extension of this RCT with follow-up for up to 36 months. No studies were identified comparing vismodegib to other invasive procedures or radiotherapy.

New surgically eligible BCCs

In Tang et al (2012), the mean number of new surgically eligible BCCs per patient per year[18] was statistically significantly lower with vismodegib (2) compared with placebo (29) ($p<0.001$). Mean follow-up was eight months.

Reduction in size of existing surgically eligible BCCs

In Tang et al (2012), the percentage reduction from baseline in the sum of the longest diameter of existing surgically eligible BCCs was statistically significantly greater with vismodegib (-65%) compared to placebo (-11%) ($p<0.003$). Mean follow-up was eight months.

Surgeries as part of standard care

In Tang et al (2012, 2016) patients could have tumours surgically removed at the discretion of their primary dermatologist. In Tang et al (2012) the mean number of surgeries performed as part of standard care during the study was statistically significantly lower with vismodegib (0.31) compared to placebo (4.4) ($p<0.001$) at a mean follow-up of eight months. Tang et al (2016) reported that the mean number of surgeries per patient per year was 28.0 (SD 19.6) before vismodegib (n=23), 0.5 (SD 0.5) during vismodegib treatment (n=40)[19] and 4.9 (SD 6.3) at a mean of 14 (SD 7) months after discontinuing vismodegib (n=15). Data on surgeries before and after treatment were only available for patients who responded to a telephone questionnaire conducted after study completion.

Median time to tumour shrinkage

Tang et al (2016) (n=40) reported that median time to 50% tumour shrinkage (n=36) was three months (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

In Tang et al (2012), median (±SE) total plasma drug level at one month was 25±7µmol/litre (range 13 to 42) in the 26 patients randomised to vismodegib in the RCT. The authors reported no correlation between plasma drug level and tumour response at one and three months.

Histologic outcomes

In Tang et al (2012), residual microscopic BCC was present in 22/25 (88%) random samples of tumours that were clinically raised (plaques or papules)[20] after one month of vismodegib. Residual tumour was also detected in 6/13 (43%) biopsy samples in random histological sections after three months of vismodegib. The authors also reported that 1/6 (17%) of lesions that

[18] The analysis accounted for the differential follow-up among study participants

[19] 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

[20] Not further defined

appeared clinically resolved had residual tumour. It is not clear how many patients provided biopsy samples.

Molecular outcomes at one month

In Tang et al (2012), 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 also 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).

2. In people who have non-locally advanced, non-metastatic multiple BCCs, what is the safety of vismodegib compared with invasive procedures or radiotherapy?

One RCT and extension study (n=42) compared the safety of vismodegib and placebo in patients with non-locally advanced, non-metastatic multiple BCCs. No studies were identified comparing the safety of vismodegib to other invasive procedures or radiotherapy.

Tang et al (2012) reported adverse events for vismodegib vs placebo for 41 patients with Gorlin syndrome who had received at least one dose of study medication at a mean follow-up of eight months (range 1 to 15). There were no Grade 5 adverse events (death related to an adverse event) and there was no significant difference between vismodegib and placebo for any Grade 3 (severe) or Grade 4 (life-threatening or disabling) adverse events. A number of Grade 1 (mild)/ Grade 2 (moderate) adverse events occurred statistically significantly more often with vismodegib (n=26) compared to placebo (n=15). These 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).

Tang et al (2016) reported adverse events for 40 patients who had received vismodegib during the RCT or study extension[21]. 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. 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%). Two patients died, however these deaths were not thought to be related to vismodegib.

At a mean of eight 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 later follow-up (28 months after study start) 14/26 (54%) of patients had discontinued vismodegib due to adverse events.

3. In people who have non-locally advanced, non-metastatic multiple BCCs, what is the cost-effectiveness of vismodegib compared with invasive procedures or radiotherapy?

No studies reported the cost-effectiveness of vismodegib compared with invasive procedures or radiotherapy in people who have non-locally advanced, non-metastatic multiple BCCs.

4. From the evidence selected, are there any subgroups that would gain greater benefit from vismodegib more than the wider population of interest?

[21] 2 patients randomised to placebo withdrew before the study extension and did not receive vismodegib

- **People with Gorlin syndrome vs. those without Gorlin syndrome**

No studies were identified that compared outcomes for people with and without Gorlin syndrome or other subgroups of patients. All of the patients in the RCT identified (Tang et al 2012, Tang et al 2016) had Gorlin syndrome.

5. From the evidence selected, what definitions and criteria of multiple BCCs were used in the research studies?

Tang et al (2012, 2016) included patients with Gorlin syndrome with 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).

Part B

1. In people who have non-locally advanced, non-metastatic multiple BCCs, what is the clinical effectiveness of one particular intermittent vismodegib dosing regimen compared with a different intermittent or continuous vismodegib dosing regimen?

One RCT (Dréno et al 2017, n=229) reported clinical effectiveness outcomes for two groups of patients with non-locally advanced, non-metastatic multiple BCCs who received two different intermittent dosing regimens of vismodegib over 72 weeks. All patients in this study had multiple BCCs and 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 the continuous vismodegib dosing regimen prescribed in this study.

Mean number of clinically evident BCCs

In Dréno et al (2017), both dosing regimens showed a reduction from baseline in the mean number of clinically evident BCCs. For dosing regimen A the mean number of clinically evident BCCs was 9.8 (SD 12.9) at baseline and 3.4 (SD 4.5) at treatment end. For dosing regimen B this was 9.1 (SD 8.1) at baseline and 3.5 (SD 3.8) at treatment end. There was no significant difference in reduction from baseline between dosing regimen A and 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%[22] (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[23]. Median treatment duration was 71.4 weeks.

Size of target BCC lesions

In Dréno et al (2017), three lesions of at least 5mm diameter were designated as target lesions for each patient. Both dosing regimens showed a reduction from baseline in the size of target BCC lesions. For dosing regimen A, the mean size of target BCCs was 52.7mm (SD 33.0) at baseline and 11.6mm (SD 22.1) at treatment end. For dosing regimen B, this was 50.2mm (SD

[22] 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

[23] The per-protocol analysis included all patients who completed the 72 weeks of treatment without major protocol violations (n=109)

39.0) at baseline and 17.8mm (SD 31.7) at treatment end. Dosing regimen A had a statistically significantly greater reduction from baseline than dosing regimen B (82.9% vs 68.8% (difference -15.2%[22] (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. Median treatment duration was 71.4 weeks.

Number of patients with a reduction in total BCCs of at least 50%
In Dréno et al (2017), 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 at least 50% in the intention-to-treat analysis (difference between groups -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)). No statistical analysis of the difference between groups was performed[24]. Median treatment duration was 71.4 weeks.

New BCCs
In Dréno et al (2017), 76.6% of patients with dosing regimen A and 74.4% of patients with dosing regimen B were without new BCCs at the end of treatment in the intention-to-treat analysis (difference between groups -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)). No statistical analysis of the difference between groups was performed[24]. Median treatment duration was 71.4 weeks.

New surgically eligible BCCs
In Tang et al (2016), all patients were prescribed a continuous vismodegib dosing regimen. Patients who were 'very compliant' (≥80% of prescribed pills, n=16) had a statistically significantly lower mean number of new surgically eligible BCCs per patient per year (0.6 (SD 0.72)) than patients who were 'very incompliant' (<50% of prescribed pills, n=14) (1.7 (SD 1.8)), (p<0.0001)[19].

Recurrence
Tang et al (2016) reported that for ten patients who took vismodegib continuously for at least 15 months, there was no return to baseline tumour burden for 18 months after discontinuing the drug. Tang et al (2016) also reported that of 22 patients (54%) who discontinued vismodegib for at least six months:

- 11 (50%) had a recurrence of at least 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).

2. In people who have non-locally advanced, non-metastatic multiple BCCs, what is the safety of one particular intermittent vismodegib dosing regimen compared with a different intermittent or continuous vismodegib dosing regimen?

One RCT (Dréno et al 2017, n=229) reported safety for two groups of patients with non-locally advanced, non-metastatic multiple BCCs who received two different intermittent dosing regimens of vismodegib (see clinical effectiveness section for details of dosing regimens). All patients in this study had multiple BCCs and 37% had Gorlin syndrome. Adverse events were reported for all patients who had received at least one dose of study medication (n=227). Median treatment duration was 71.4 weeks (range 1.3 to 73.3).

In this RCT, 94% of patients with dosing regimen A and 97% of patients with dosing regimen B had at least one adverse event relating 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

[24] 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)

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-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.

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.

3. In people who have non-locally advanced, non-metastatic multiple BCCs, what is the cost-effectiveness of one particular intermittent vismodegib dosing regimen compared with a different intermittent or continuous vismodegib dosing regimen?

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

4. From the evidence selected, are there any sub-groups that would gain greater benefit from a particular vismodegib dosing regimen?

- **People with Gorlin syndrome vs. those without Gorlin syndrome**

No studies compared outcomes for people with and without Gorlin syndrome or for other subgroups of patients. However, Dréno et al (2017) reported the number of clinically evident BCCs separately for patients with Gorlin syndrome (n=85) and patients without Gorlin syndrome (n=144). For patients with Gorlin syndrome, there was no significant difference between intermittent dosing regimen A and intermittent dosing regimen B (55.2% vs 56.6%; difference 2.1% (95%CI -28.8 to 33.0), p=0.87). For patients without Gorlin syndrome, the authors report that 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)[25].

5. From the evidence selected, what definitions and criteria of multiple BCCs were used in the research studies?

The RCT (Dréno et al 2017) included patients with multiple (≥6 clinically evident) BCCs amenable to surgery. 'Clinically evident' and 'amenable to surgery' were not further defined. Three lesions ≥5mm diameter, of which ≥1 was histopathologically confirmed were designated as target lesions.

5 Discussion

Two RCTs have reported clinical and safety outcomes for the use of vismodegib in patients with multiple basal cell carcinomas. No studies on the cost-effectiveness of vismodegib in this patient group were identified.

When compared to placebo, vismodegib was found to reduce the number of new surgically eligible BCCs and reduce the size of existing BCCs in one small, but good quality RCT (Tang et al 2012, n=42) where both patients and clinicians were blind to treatment group. Patients taking vismodegib also had fewer (by approximately 4) surgeries as part of standard care after mean follow-up of eight months. The assessment of BCCs was standardised, but as the decision to

[25] 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

perform surgeries was at the discretion of the patient's primary dermatologist, there may have been variation in clinical practice between study centres and clinicians.

This RCT was suspended at mean follow-up of eight months (range 1 to 15 months) after a planned interim analysis demonstrated that a pre-specified advantage for vismodegib had been met for the primary outcome (new surgically eligible BCCs). At this point placebo patients were crossed over to receive treatment with vismodegib. Patients were followed-up for up to 36 months. There was no loss to follow-up during the randomised phase of the trial. Five patients were lost to follow-up during the extension study. This included two patients who died and three patients who withdrew due to adverse events.

Some of the outcomes reported were exploratory and did not include all patients. It was not always clear why selected patients were included in certain analyses or how or why particular follow-up periods or cut-off levels were chosen for specific outcomes. Analyses unplanned at the study outset and carried out after data acquisition are less reliable because the authors may have selected results for this analysis in the search for positive and reportable findings. This may result in reporting bias.

No studies comparing the effectiveness of vismodegib with other invasive procedures or radiotherapy were identified.

The effectiveness of different dosing regimens was also assessed in one RCT (Dréno et al 2017) and one subgroup analysis (Tang et al 2016), however these results are difficult to interpret.

In one moderate quality RCT (Dréno et al 2017), two different intermittent dosing regimens both demonstrated a reduction in the number of clinically evident and new BCCs and in the size of target BCCs. For some outcomes, there appeared to be an advantage for dosing regimen A, however the significance of this is unclear and the result should be treated with caution as the study was not powered to investigate the difference between the different dosing regimens. In this RCT, although no dose reductions were permitted, treatment interruptions of two weeks or less were permitted for up to four weeks within the 72 week treatment period. The authors reported that 107 of the 229 patients randomised (47%) completed 72 weeks of treatment without major protocol violations. These patients were included in a per-protocol analysis which had a similar pattern of results to the intention-to-treat analysis.

Conversely, in the subgroup analysis by Tang et al (2016), patients who were more compliant with a continuously prescribed dosing regimen (i.e. who took more than 80% of their prescribed pills) had fewer new surgically eligible BCCs than patients who were less compliant (i.e. who took less than 50% of the prescribed pills). The clinical significance of the difference observed (approximately one new surgically eligible BCC per year) is unclear. In addition, the time period for compliance is not clear; patients were allowed to take treatment breaks due to toxicity and there were differences between the three study centres in the maximum period that patients were able to take vismodegib (up to 18 months in one centre and up to 36 months in two centres). In this study, although patients are described as taking vismodegib continuously it is not always clear what is meant by continuous. At one point in the paper 'continuous' is used to refer to the 16 patients who took more than 80% of the prescribed vismodegib pills. Elsewhere, the authors state that 31 of the 42 patients randomised needed interruptions in vismodegib treatment due to adverse events (during the RCT or extension study) and that only 3 of 18 patients who were offered vismodegib for the full 36 months tolerated it continuously for the full 36 months. It is not clear if 'continuous' means 100% compliance in this context. It is therefore not clear from any of the available published studies, what the optimum dosing regimen is for the management of multiple BCCs.

A high proportion of patients' experienced adverse events; 94-97% in the RCT comparing two intermittent dosing regimens of vismodegib (Dréno et al 2017). However, the proportion of severe adverse events was low and there was no significant difference between the number of Grade 3 or 4 adverse events compared to placebo in one RCT (Tang et al 2012).

However, the proportion of patients who were reported to have discontinued vismodegib due to adverse events was high. In the Tang et al RCT with a continuously prescribed regimen this was reported as 54% (14/26) at up to 28 months follow-up. In the Dréno et al RCT with two intermittent dosing regimens, 47% (107/227) of patients were reported to have discontinued treatment. In this study the percentage of patients in each group who were reported to have discontinued vismodegib due to adverse events was lower at 20% (23/116) and 27% (30/113), however a number of categories were used to describe treatment discontinuation and reasons e.g. for withdrawal of consent were not recorded. The number of patients who discontinued due to adverse events may therefore be underestimated.

The patient characteristics were not the same across the studies. Different definitions for 'multiple BCCs' were used in the included studies e.g. the patients in the Tang study had to have ten or more surgically eligible BCCs (the definition for this was specified) whereas the criteria for inclusion in the RCT by Dréno et al (2017) was at least six BCCs 'amendable for surgery'. Additionally, in the RCT comparing vismodegib to placebo all patients had Gorlin syndrome (Tang et al 2012, 2016). In the RCT comparing intermittent dosing regimens (Dréno et al 2017), 37% of the patients had Gorlin syndrome. No studies compared the effectiveness of vismodegib in patients with or without Gorlin syndrome or in other subgroups of patients. Therefore, the generalisability of the results to patients with multiple BCCs, with or without Gorlin syndrome is unclear.

There is some evidence for an improvement in clinical outcomes with vismodegib for patients with multiple BCCs. The most effective dosing regimen to balance clinical effectiveness and adverse events is unclear. It is not clear if there is any difference in outcomes for patients with Gorlin syndrome compared to those without. The clinical effectiveness outcomes (particularly the reduction in surgical treatment of BCCs) need to be balanced with the high proportion of patients reported to have experienced adverse events which often led to the discontinuation of treatment with both continuously and intermittently prescribed dosing regimens. As there were no studies which directly assessed the impact of both vismodegib's clinical effectiveness and adverse effects on overall quality of life, the impact on quality of life through a reduction in invasive procedures is unclear.

6 Conclusion

The evidence base for the effectiveness and safety of vismodegib in patients with multiple BCCs is limited to two small RCTs.

Positive clinical outcomes were reported for vismodegib compared to placebo and for two different intermittent dosing regimens. However limitations in the reporting of these studies limit the strength of any conclusions that can be drawn.

The advantage to quality of life associated with the positive clinical outcomes was not directly assessed and can only be inferred. High levels of mild to moderate adverse events, and discontinuation with treatment were observed. There is a need for well-conducted, randomised controlled studies examining the impact of vismodegib on quality of life in this patient group.

7 Evidence Summary Table

For abbreviations see list after each table

Part A i) Use of vismodegib vs. placebo to treat non-locally advanced, non-metastatic multiple BCCs									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Tang et al 2012	P1 RCT 3 US centres Patients recruited between September 2009 and January 2011 *(see Tang et al 2016 for the extension phase of this study)*	Patients with basal-cell nevus (Gorlin) syndrome with ≥10 surgically eligible[26] BCCs, present at study entry or removed during the previous 2 years n=42 Mean follow-up 8 months (range 1 to 15) Exclusion criteria: systemic chemotherapy ≤1 year	Intervention: vismodegib 150mg daily (n=26) Comparator: placebo (n=16) Treatment with vismodegib planned for up to 18 months or until intolerable toxic effects or clinical worsening of disease[27] Treatment with vismodegib or placebo could be interrupted due to toxicity	Primary Clinical effectiveness	New surgically eligible BCCs	Mean per patient per year (SD not reported): • Vismodegib: 2 • Placebo: 29 Significantly lower with vismodegib vs placebo (p<0.001)[28]	7	Direct	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. Data cut-off was February 2011, when patients had received ≥1 follow-up visit (38 patients had completed ≥3 months follow-up). The authors calculated that with 20 patients receiving vismodegib and 10 receiving placebo, the study would have an 80% power to detect a 50% difference between the groups for the primary outcome at a two-tailed alpha level of 0.05. A 20% dropout rate was anticipated with a planned enrolment of 41 patients. 42 patients were randomised but 1 placebo patient withdrew before receiving any study medication due to work and travel difficulties. All analyses were modified intention-to–treat, including all patients who received study medication (vismodegib or placebo) (n=41). The authors reported no loss to follow-up during the follow-up period.
				Secondary Clinical effectiveness	Reduction in size of existing surgically eligible BCCs	Percentage change from baseline in the sum of the longest diameter: • Vismodegib: -65% • Placebo: -11% Significantly greater with vismodegib vs placebo (p=0.003)[29]			
				Secondary Clinical effectiveness	Surgeries as part of standard care	Mean number of surgeries per patient: • Vismodegib: 0.31 • Placebo: 4.4 Significantly lower with vismodegib vs placebo (p<0.001)			
				Secondary	Pharmacokinetic assessment of vismodegib	Median (±SE) total plasma drug level at 1 month: 25±7µmol/litre (range 13 to 42)			

[26] 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)

[27] >60 new surgically eligible BCCs or doubling of the cumulative longest diameter of existing or new surgically eligible BCCs

[28] In Tang et al (2016) this outcome is reported as a significantly lower mean rate of new surgically eligible BCCs for vismodegib (mean 2 SD 0.12) vs placebo (mean 34 SD 1.32), p<0.0001. The reason for the difference in the placebo mean is not clear

[29] In Tang et al (2016) this outcome is reported as the change from baseline for the sum of cumulative diameters and was also significantly greater for vismodegib (-56%) vs placebo (13%), p<0.001

Part A i) Use of vismodegib vs. placebo to treat non-locally advanced, non-metastatic multiple BCCs									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		before starting study medication; ECOG performance status >2; uncontrolled systemic disease (including HIV); congestive heart failure; uncontrolled hypocalcaemia; hypomagnesaemia; hypokalaemia; viral hepatitis; liver cirrhosis; women of childbearing potential Patients in both groups were similar in age, weight and baseline number of surgically eligible BCCs Mean±SD: Age (years):	or planned surgery Randomisation sequence generated by computer code with no stratification Both patients and assessors were blind to study group	Clinical effectiveness		No correlation between plasma drug level and tumour response at 1 or 3 months			Analyses were pre-specified before the data were unblinded, however not all of the pre-specified secondary outcomes were reported in this paper (eg new BCCs ≤5mm on the upper back), resulting in possible bias. In calculating the number of new surgically eligible BCC per year the authors included the natural log of the amount of follow-up time for any patient as an offset to account for differential follow-up among study participants. The study authors also reported some observational results for small numbers of individual patients, for example relating to outcomes after these patients discontinued vismodegib. These are not included in this evidence review. Analyses unplanned at the study outset and carried out after data acquisition are less reliable because the authors may have selected results for this analysis in the search for positive and reportable findings. Tumour response was assessed by skin examination, monthly for months 1 to 3, every 2 months for months 4 to 9 and every 3 months for months 10 to 18. Clinical photos from previous visits were used to ensure consistency of clinical examination. The principal investigator trained all study dermatologists and participated in early study visits to ensure consistent assessments of surgically eligible BCCs. The trial was double-blind, with both patients and assessors blind to study group. There was no conflict of interest statement in the paper. The study was supported by the manufacturer.
				Secondary Clinical effectiveness	Histologic outcomes	**Vismodegib after 1 month:** residual microscopic BCC present in 22/25 (88%) random samples of BCCs that were clinically raised (plaques or papules) (not further defined) **Vismodegib after 3 months:** 6/13 (46%) biopsy specimens had residual tumour detected in random histologic sections 1/6 (17%) of lesions that appeared clinically resolved had residual tumour			
				Secondary Clinical effectiveness	Molecular outcomes at 1 month	Vismodegib associated with a decrease in hedgehog signalling from baseline (90% decrease in GLI1 messenger RNA, p<0.001). No significant difference from baseline for placebo (p=0.75, % not reported) Vismodegib associated with a significantly reduced tumour proliferation (Ki67 index) from baseline (p<0.0001). No significant difference from baseline for placebo (p=0.37) No significant change in apoptosis (assessed by cleaved caspase 3) from baseline for vismodegib (p=0.41) or placebo (p=0.32)			
				Safety	Adverse events	At mean follow-up 8 months, 7/26 (27%) had discontinued vismodegib due to adverse			

Part A i) Use of vismodegib vs. placebo to treat non-locally advanced, non-metastatic multiple BCCs									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		• Vismodegib: 54±8 • Placebo: 53±8 Weight (kg): • Vismodegib: 100±24 • Placebo: 100±29 Number of surgically eligible BCCs: • Vismodegib: 44±41 • Placebo: 37±50			Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3)[30]	events. 1 patient discontinued placebo due to disease progression No Grade 5 adverse events No significant difference for vismodegib vs placebo for any Grade 3 or 4 adverse events Significantly greater Grade 1/ 2 adverse events for vismodegib vs placebo: Hair loss (p=0.004): • Vismodegib: 16/26 (62%) • Placebo: 1/15 (7%) Muscle cramps (p<0.001): • Vismodegib: 21/26 (81%) • Placebo: 0/15 (0%) Taste disturbance (p<0.001): • Vismodegib: 22/26 (85%) • Placebo: 1/15 (7%) >5% weight decrease (p=0.003): • Vismodegib: 11/26 (42%) • Placebo: 0/15 (0%) At last follow-up (28 months after study start), 14/26 patients (54%) had discontinued vismodegib due to adverse events			

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

[30] 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)

Part A ii) Use of vismodegib to treat non-locally advanced, non-metastatic multiple BCCs (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Tang et al 2016	P1 Extension study following RCT 3 US centres Patients recruited between September 2009 and January 2011 *(see Tang et al 2012 for the results of the RCT of vismodegib vs placebo)*	Patients with basal-cell nevus (Gorlin) syndrome with ≥10 surgically eligible BCC[26], present at study entry or removed during the previous 2 years n=40 (26 continued vismodegib from the RCT; 14 reallocated from placebo to vismodegib) Age 35-75 Patients were followed-up for up to 36 months *See Tang et al 2012 for further*	Vismodegib 150mg daily In the study extension, patients at 2/3 study sites could receive vismodegib for up to 36 months (n=25[31]). Patients at the 3rd site could receive vismodegib for up to 18 months but were monitored up to 36 months (n=12) Treatment with vismodegib or placebo could be interrupted due to toxicity or planned surgery Patients originally assigned to vismodegib received vismodegib for	Secondary Clinical effectiveness	Median time to tumour shrinkage	Median time to shrinkage of existing surgically eligible BCCs of 50% (n=36): 3 months (IQR 2 to 5) Median time to shrinkage of existing surgically eligible BCCs of 90% (n=22): 7 months (IQR 4 to 14) Median time to shrinkage of existing surgically eligible BCCs of 100% (n=19): 15 months (IQR 9 to 15)	5	Direct	Results relating to the comparison of vismodegib and placebo in the randomised phase of the RCT are reported in the table above. Outcomes related to dose adherence are reported below in relation to Part B of this review. 5 patients who were recruited to the RCT but did not continue treatment in the extension included: • 1 patient in the placebo group withdrew before receiving any study medication • 1 patient in the placebo group discontinued intervention before unblinding due to disease progression • 3 patients in the vismodegib group withdrew due to adverse events Patients were monitored every 3 months up to 36 months. During the extension, 5 patients were lost to follow-up (2 patients died and 3 withdrew due to adverse events). Results only reported graphically have not been included. The authors reported a number of observations which were described as being for illustrative purposes without formal analysis. These were reported for small numbers of individual patients and are not included. *See Tang et al (2012) for further critique of this study*
				Secondary Clinical effectiveness	Surgeries as part of standard care	Mean (SD) number of surgeries per patient per year: • Before vismodegib treatment (n=23): 28.0 (19.6) • During vismodegib (n=40): 0.5 (0.5) • After a mean of 14 months (SD 7) of discontinuing vismodegib (n=15): 4.9 (6.3) Data before and after treatment available for patients who responded to a telephone questionnaire after study completion			
				Safety	Adverse events	Adverse events were reported for 40 patients who received vismodegib[32] 2 patients died however these deaths were not thought to be related to vismodegib			

[31] The authors stated that 18 of these 25 patients were offered vismodegib treatment for up to 36 months
[32] 26 patients initially randomised to vismodegib and 14 who were reallocated from placebo to vismodegib

Part A ii) Use of vismodegib to treat non-locally advanced, non-metastatic multiple BCCs (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		details on inclusion and exclusion criteria	mean 21 (SD 9) months Patients originally assigned to placebo received vismodegib for mean 16 (SD 7) months			Grade 3-4 adverse events affecting >1 patient included: • ≥20% weight loss: 6/40 (15%) • Muscle cramps: 2/40 (5%[33]) • Pneumonia: 2/40 (5%) • Reactions to antibiotics: 2/40 (5%) • Chest pain: 2/40 (5%) Grade 1-2 treatment related adverse events: • Hair loss: 40/40 (100%) • Muscle cramps: 40/40 (100%) • Dysgeusia: 37/40 (93%) • Gastrointestinal upset: 26/40 (65%) • Weight loss (5% to <20%): 25/40 (63%) • Fatigue: 19/40 (48%) • Common cold: 8/40 (20%) • Acne: 7/40 (18%) • Runny nose: 7/40 (18%) • Rash: 5/40 (13%) • Dizziness: 4/40 (10%) • Nausea: 4/40 (10%)			

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

[33] A figure of 8% for 2/40 patients is given in the paper. This has been corrected to 5% in this review

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									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Drénoet al 2017	P1 RCT 52 centres in 10 countries (Austria, Canada, France, Germany, Italy, Mexico, the Netherlands, Russia, Spain & USA) Patients recruited between April 2013 and April 2014	Patients with multiple (≥6 clinically evident) BCCs amenable to surgery 3 lesions ≥5mm diameter, of which ≥1 was histopathologically confirmed, were designated as target lesions n=229 Median treatment duration 71.4 weeks (range 1.3 to 73.3)	**Group A:** Vismodegib 150mg daily for 12 weeks then placebo for 8 weeks alternating for 3 rounds, followed by a final 12 weeks of vismodegib[34] n=116 **Group B:** Vismodegib 150mg daily for 24 weeks then placebo for 8 weeks and vismodegib for 8 weeks alternating for 3 rounds[35] n=113 No dose reductions were	Primary Clinical effectiveness	Mean number of clinically evident[36] BCCs (reduction from baseline)	**Intention-to-treat analysis** At baseline (mean (SD)): • Group A: 9.8 (12.9) • Group B: 9.1 (8.1) At treatment end (mean (SD)): • Group A: 3.4 (4.5) • Group B: 3.5 (3.8) Reduction from baseline: • Group A: 62.7% (95%CI 53.0 to 72.3) • Group B: 54.0% (95%CI 43.6 to 64.4) No significant difference in reduction from baseline (difference -8.9%, (95%CI -23.0 to 5.2), p=0.24)[37] **Per protocol analysis** At baseline (mean (SD)): • Group A: 11.1 (17.6) • Group B: 9.1 (9.2) At treatment end (mean (SD)): • Group A: 2.5 (4.7) • Group B: 2.3 (3.0) Reduction from baseline:	4	Direct	The primary aim of this study was to assess percentage reduction from baseline in the number of clinically evident BCCs at week 73. As the study was not designed to show a significant difference between treatment groups no formal statistical hypothesis for treatment comparisons were tested. The comparisons between groups reported were described as exploratory analysis and should be treated with caution as the study was not powered to detect a difference between groups. The primary analysis was intention-to-treat. For patients who discontinued treatment, the last observation carried forward method was used to impute missing data. The pre-specified per-protocol analysis (n=107) included all patients who completed the 72 weeks of treatment without major protocol violations. The safety analysis included all patients who received ≥1 dose of study drug (n=227). 1 patient withdrew before treatment (Group A) and 1 patient was mistakenly randomised twice. Tumour response was assessed by physical examination and count of BCCs every 8 weeks. Drug adherence was assessed via dispensing records and patient diaries. Adverse events were assessed

[34] The full schedule over the 72 week period was vismodegib 12 weeks; placebo 8 weeks; vismodegib 12 weeks; placebo 8 weeks; vismodegib 12 weeks; placebo 8 weeks; vismodegib 12 weeks

[35] The full schedule over the 72 week period was vismodegib 24 weeks; placebo 8 weeks; vismodegib 8 weeks; placebo 8 weeks; vismodegib 8 weeks; placebo 8 weeks; vismodegib 8 weeks

[36] Not further defined

[37] 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

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									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Exclusion criteria: Patients with locally advanced BCC unsuitable for surgery or radiation or metastatic BCC; ECOG performance status >2; inadequate organ function; pregnancy; uncontrolled medical illness or history of other disease that might affect interpretation of the results Patients in both groups had similar clinical and demographic characteristic at baseline Mean age (years)):	permitted. Treatment interruptions ≤2 weeks were permitted up to 4 weeks within the 72 week treatment period Centralised randomisation schedule with stratification by diagnosis of Gorlin syndrome, geographical region and immunosuppression status Both patients and assessors were blind to study group			• Group A: 72.7% (95%CI 56.8 to 88.6) • Group B: 64.4% (95%CI 45.3 to 83.4) No significant difference in reduction from baseline (difference -6.8%, (95%CI -31.1 to 17.6), p=0.54)[37] **In patients with Gorlin syndrome (ITT population)** Reduction from baseline: • Group A: 55.2% • Group B: 56.6% (95%CI not reported) No significant difference in reduction from baseline (difference 2.1%, (95%CI -28.8 to 33.0), p=0.87)[37] **In patients without Gorlin syndrome (ITT population)** Reduction from baseline: • Group A: 67.2% • Group B: 52.6% (95%CI not reported) Group A greater reduction from baseline (difference -15.4%, (95%CI -28.8 to -1.9), p=0.03)[37]			every 4 weeks and classified using the Medical Dictionary for Regulatory Activities (version 18.0) 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 underestimated All pre-specified secondary endpoints were reported, with the exception of disease recurrence. The authors stated that these data were not mature at the time of publication. A large number of centres were involved in the study in relation to the number of patients. Differences between centres may impact the results. None of the centres were in the UK. The paper contained a number of errors in the reporting of the percentage reductions reported for each group and the stated difference between groups. The study was funded by the manufacturer. The authors stated that the funder was involved in the study design, data collection, data analysis, data interpretation and writing of the report. Many of the authors declared an association with the manufacturer.
				Secondary Clinical effectiveness	Size of target BCC lesions	**Intention-to-treat analysis** At baseline (mean (SD)): • Group A: 52.7mm (33.0) • Group B: 50.2mm (39.0) At treatment end (mean (SD)): • Group A: 11.6mm (22.1) • Group B: 17.8mm (31.7)			

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									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		• Group A: 62 (27-89) • Group B: 60 (27-91) Gorlin syndrome: • Group A: 44 (38%) • Group B: 41 (36%)				Reduction from baseline: • Group A: 82.9% • Group B: 68.8% Group A greater reduction from baseline (difference -15.2% (95%CI -27.4 to -3.0), p=0.015)[37] **Per protocol analysis** At baseline (mean (SD)): • Group A: 51.3mm (32.4) • Group B: 49.4mm (37.2) At treatment end (mean (SD)): • Group A: 8.5mm (19.0) • Group B: 13.1mm (25.0) Reduction from baseline: • Group A: 87.8% • Group B: 77.3% Group A greater reduction from baseline (difference -11.5% (95%CI -22.3 to -0.7), p=0.037)[37]			
				Secondary Clinical effectiveness	Number of patients with reduction in total BCCs ≥50%	**Intention-to-treat analysis** From baseline to end of treatment: • Group A: 76/116 (65.5%) • Group B: 57/113 (50.4%) Difference -15.1% (95%CI -27.7 to -2.4). Statistical difference not assessed **Per protocol analysis** From baseline to end of treatment: • Group A: 49/59 (83.1%) • Group B: 37/48 (77.1%)			

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									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Difference -6.0% (95%CI -21.2 to -9.3). Statistical difference not assessed			
				Secondary Clinical effectiveness	New BCCs	Number of patients without new BCCs at end of treatment: **Intention-to-treat analysis:** • Group A: 72/94 (76.6%) • Group B: 64/86 (74.4%) Difference -2.2% (95%CI -14.8 to 10.4). Statistical difference not assessed **Per protocol analysis** • Group A: 44/59 (74.6%) • Group B: 37/48 (77.1%) Difference -2.5% (95%CI -13.8 to 18.8). Statistical difference not assessed			
				Safety	Adverse events	≥1 adverse event related to study treatment: • Group A: 107/114 (94%) • Group B: 109/113 (97%) Serious[38] adverse events related to study treatment: • Group A: 6/114 (5%) • Group B: 2/113 (2%) Statistical difference between groups not assessed **Adverse events ≥grade 3:** Muscle spasms: • Group A: 4/114 (4%) • Group B: 12/113 (11%)			

[38] Not further defined

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									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Increased blood creatine phosphokinase: • Group A: 1/114 (1%) • Group B: 4/113 (4%) Hypophosphataemia: • Group A: 0/114 (0%) • Group B: 3/113 (3%) Dysgeusia: • Group A: 1/114 (1%) • Group B: 2/113 (2%) Pneumonia: • Group A: 2/114 (2%) • Group B: 0/113 (0%) γ-Glutamyltransferase increased: • Group A: 2/114 (2%) • Group B: 0/113 (0%) Abscess limb: • Group A: 0/114 (0%) Group B: 2/113 (2%) Decreased appetite: • Group A: 0/114 (0%) • Group B: 2/113 (2%) Weight decreased: • Group A: 1/114 (1%) • Group B: 0/113 (0%) Diarrhoea: • Group A: 0/114 (0%) • Group B: 1/113 (1%) Asthenia:			

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									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• Group A: 0/114 (0%) • Group B: 1/113 (1%) Ageusia: • Group A: 0/114 (0%) • Group B: 1/113 (1%) 107 (47%) patients discontinued treatment. Discontinuation due to adverse events 23/116 (20%) in group A and 30/113 (27%) in group B			

BCC – basal-cell carcinoma; ITT – intention-to-treat; 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									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Tang et al 2016	P1 Drug adherence outcome from an RCT and extension study	Patients with basal-cell nevus (Gorlin) syndrome with ≥10 surgically eligible BCC[26], present at study entry	Vismodegib 150mg daily *See Tang et al 2016 for further details*	Primary Clinical effectiveness	New surgically eligible BCCs	Mean (SD) per patient per year: • Very compliant patients[39] (≥80% of prescribed pills) (n=16): 0.6 (0.72) • Very incompliant patients (<50% of prescribed pills) (n=14): 1.7 (1.8) Significantly lower for very compliant patients (p<0.0001)	5	Direct	All patients were prescribed continuous vismodegib although treatment could be interrupted due to toxicity or planned surgery. Although the paper refers to patients taking vismodegib continuously, the number of patients that are described as taking vismodegib continuously varies and it is not always clear what 'continuous' means.

[39] In the abstract for this paper, these patients are described as taking vismodegib continuously whereas very incompliant patients are described as having interrupted dosing

Part B ii) Use of continuous vismodegib vs. intermittent vismodegib to treat non-locally advanced, non-metastatic multiple BCCs									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	3 US centres	or removed during the previous 2 years *See Tang et al 2012 for further details*		Secondary Clinical effectiveness	Recurrence	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 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)			The authors reported that 31/42 (74%) of patients in the RCT needed interruptions in vismodegib treatment due to adverse events and that only 3 of 18 patients who were offered vismodegib for 36 months tolerated it continuously for the full 36 months. For 32 patients who continued follow-up for 36 months 14 patients were described as taking vismodegib intermittently and 5 patients continuously during the study extension phase. It is not clear if 'continuously' in this context suggests that patients were 100% compliant in taking the prescribed pills. When reporting number of new surgically eligible BCCs per patient per year 'continuous' is used to describe patients who were very compliant (≥80% of prescribed pills) and 'interrupted' dosing was used to describe patients who were very incompliant (<50% of prescribed pills). 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 due to not receiving vismodegib (n=1); received fewer than 2 months of vismodegib (n=3); took vismodegib continuously for only a short period (not defined) (n=2); ingested between 50 and 79% pills (n=3); had multiple excisions (n=1); had some lesions reclassified as not BCC (n=1). When reporting recurrence, patients were included if they had taken vismodegib continuously for ≥15 months or if they had discontinued vismodegib for ≥6 months. It is not clear why these time periods were chosen as cut-off points. Decisions about which patients to include in these analyses were made after data collection. The selective inclusion of patients in analyses introduces bias and the results should be treated with caution. See Tang et al (2012) and Tang et al (2016) for further critique of this study

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

8 Grade of Evidence Table

For abbreviations see list after each table

Part A i) Use of vismodegib vs. placebo to treat non-locally advanced, non-metastatic multiple BCCs					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
New surgically eligible BCCs	Tang et al (2012)	7	Direct	B	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 would be of importance to clinicians, patients and their families if it results in fewer surgeries. 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. The analysis 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. 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.
Reduction in size of existing surgically eligible BCCs	Tang et al (2012)	7	Direct	B	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.

Part A i) Use of vismodegib vs. placebo to treat non-locally advanced, non-metastatic multiple BCCs					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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. 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. 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. Clinical photographs and training from the principal investigator were used to ensure consistency in the assessment of surgically eligible BCCs.
Surgeries as part of standard care	Tang et al (2012)	7	Direct	B	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. 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. 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. 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. The RCT was conducted in 3 US centres. The performance of surgeries was at the discretion of the patient's primary dermatologist. Practice may have varied between centres and clinicians.
Pharmacokinetic assessment of vismodegib	Tang et al (2012)	7	Direct	B	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 (±SE) 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.

Part A i) Use of vismodegib vs. placebo to treat non-locally advanced, non-metastatic multiple BCCs					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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. This outcome was only reported after 1 month of vismodegib. 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.
Histologic outcomes	Tang et al (2012)	7	Direct	B	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)[40] 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. This result suggests that residual tumour remains after 3 months of vismodegib. The clinical meaningfulness of this result is unclear. 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 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. 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.
Molecular outcomes	Tang et al (2012)	7	Direct	B	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

[40] Not further defined

Part A i) Use of vismodegib vs. placebo to treat non-locally advanced, non-metastatic multiple BCCs					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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. 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. 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.
Adverse events	Tang et al (2012)	7	Direct	B	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[41]. 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

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

Part A i) Use of vismodegib vs. placebo to treat non-locally advanced, non-metastatic multiple BCCs					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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. A published, standardised grading system was used to assess adverse events. 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.

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)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Median time to tumour shrinkage	Tang et al (2016)	5	Direct	C	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. In this small, moderate quality extension study the length of time that patients were allowed to take vismodegib varied between study sites. This was 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.
Surgeries as part of standard care	Tang et al (2016)	5	Direct	C	Patients could have tumors surgically removed at the discretion of their primary dermatologist.

Part A ii) Use of vismodegib to treat non-locally advanced, non-metastatic multiple BCCs (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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. 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. The RCT was conducted in 3 US centres. 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 centres and clinicians.
Adverse events	Tang et al (2016)	5	Direct	C	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[41]. 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

Part A ii) Use of vismodegib to treat non-locally advanced, non-metastatic multiple BCCs (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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.

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					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Mean number of clinically evident BCCs (reduction from baseline)	Dréno et al (2017)	4	Direct	C	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. 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

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					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					vismodegib for 8 weeks alternating for 3 rounds (n=113). 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. Treatment interruptions of ≤2 weeks were permitted up to 4 weeks. 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. 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.
Size of target BCC lesions	Dréno et al (2017)	4	Direct	C	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. 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). Although difference between groups was reported 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. Treatment interruptions of ≤2 weeks were permitted up to 4 weeks. 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. This study included patients with multiple (≥6 clinically evident)

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					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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.
Number of patients with a reduction in total BCCs ≥50%	Dréno et al (2017)	4	Direct	C	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. 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 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 per-protocol analysis included all patients who completed the 72 weeks of treatment without major protocol violations (n=109). 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.
New BCCs	Dréno et al (2017)	4	Direct	C	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.

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					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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 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 per-protocol analysis included all patients who completed the 72 weeks of treatment without major protocol violations (n=109). 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.
Adverse events	Dréno et al (2017)	4	Direct	C	Adverse events were classified using the Medical Dictionary for Regulatory Activities (version 18.0)[42]. 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[41]. 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 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 outcome did

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

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					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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. 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.

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					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
New surgically eligible BCCs	Tang et al (2016)	5	Direct	C	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. In this small, moderate quality RCT extension study the length of time that patients were able to take vismodegib varied between study sites. This was 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. 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

Part B ii) Use of continuous vismodegib vs. intermittent vismodegib to treat non-locally advanced, non-metastatic multiple BCCs					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					decided after data collection. The selective inclusion of patients in analyses introduces bias and the results should be treated with caution.
Recurrence	Tang et al (2016)	5	Direct	C	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. In this small, moderate quality RCT extension study the length of time that patients were able 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. 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

9 Literature Search Terms

PICO TABLE A

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	People with multiple BCCs, without evidence of metastatic or locally advanced disease, who would require multiple invasive procedures • Subgroup of people with Gorlin syndrome (basal cell nevus syndrome) who have multiple BCCs, requiring multiple invasive procedures • People who do not have Gorlin syndrome multiple BCCs, requiring multiple invasive procedures [For info: Multiple BCCs is more than one BCC. Locally advanced BCC is where treatment with surgery or radiotherapy is not appropriate. Studies where the majority of participants do not have locally advanced or metastatic BCC should be included.]
I – Intervention Which intervention, treatment or approach should be used?	• Vismodegib [For info: Intermittent or continuous dosing regimens. An intermittent regimen is when there are periods of being on the drug with breaks of not being on the drug. Patients receiving vismodegib may also be having invasive procedures alongside.]
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Invasive procedures • Radiotherapy [For info: Invasive procedures include surgery, laser, curettage and cautery, and cryotherapy. Surgery may be described as 'placebo' in papers because this is the current standard treatment. Radiotherapy is not an appropriate comparator for patients with Gorlin syndrome, however, it may be used for other patients with multiple BCCs.]
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* • Number of required invasive procedures • Quality of life • Number of lesions • Number of new lesions • Number of surgically eligible lesions • Disfigurement *Important to decision-making:* • Adverse effects • Mohs surgery • Duration of response • Time to treatment discontinuation • Measures of cost-effectiveness
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, comparative cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only

Patients	Human studies only
Age	All ages
Date limits	2009-2019
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters and editorials
Study design	Case reports, resource utilisation studies

PICO TABLE B

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	People with multiple BCCs, without evidence of metastatic or locally advanced disease, who would require multiple invasive procedures • Subgroup of people with Gorlin syndrome (basal cell nevus syndrome) who have multiple BCCs, requiring multiple invasive procedures • People who do not have Gorlin syndrome multiple BCCs, requiring multiple invasive procedures [For info: Multiple BCCs is more than one BCC. Locally advanced BCC is where treatment with surgery or radiotherapy is not appropriate. Studies where the majority of participants do not have locally advanced or metastatic BCC should be included.]
I – Intervention Which intervention, treatment or approach should be used?	• Vismodegib – intermittent dosing regimen [For info: An intermittent regimen is when there are periods of being on the drug with breaks of not being on the drug. Patients receiving vismodegib may also be having invasive procedures alongside.]
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Other intermittent or a continuous vismodegib dosing regimen
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* • Number of required invasive procedures • Quality of life • Number of lesions • Number of new lesions • Number of surgically eligible lesions • Disfigurement *Important to decision-making:* • Adverse effects • Mohs surgery • Duration of response • Time to treatment discontinuation • Measures of cost-effectiveness
Inclusion criteria	

Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, comparative cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2009-2019
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters and editorials
Study design	Case reports, resource utilisation studies

10 Search Strategy

We searched Medline, Embase and Cochrane Library limiting the search to papers relevant to either PICO published in English from **1st January 2009 to 3rd June 2019**. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 3rd June 2019
Embase search:

1	exp basal cell carcinoma/ or basal cell nevus syndrome/
2	(basal cell adj (carcinoma? or cancer? or tumo?r?)).ti,ab.
3	((nonmelanoma or non-melanoma) adj2 skin cancer?).ti,ab.
4	(gorlin syndrome or basal cell nevus syndrome or basal cell nevoid syndrome).ti,ab.
5	1 or 2 or 3 or 4
6	(vismodegib or erivedge).mp.
7	vismodegib/
8	6 or 7
9	5 and 8
10	limit 9 to (english language and yr="2009 -Current")
11	(exp animals/ or nonhuman/) not human/
12	10 not 11
13	(conference or conference abstract or conference paper or "conference review" or editorial or letter or note or "review").pt.
14	12 not 13
15	limit 12 to "reviews (maximizes specificity)"
16	14 or 15

11 Evidence Selection

- Total number of publications reviewed: 52
- Total number of publications considered potentially relevant: 12
- Total number of publications selected for inclusion in this briefing: 3

References from the PWG supplied in the PPP		Paper selection decision and rationale if excluded
1	Tang, J.Y., Ally, M.S., Chanana, A.M., Mackay-Wiggan, J.M., Aszterbaum, M., Lindgren, J.A., Ulerio, G. *et al.* (2016). Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet Oncology* 17:1720-31.	Included
2	Dréno, B., Kunstfeld, R., Hauschild, A., Fosko, S., Zloty, D., Labeille, B., Grob, J-J. *et al.* (2017). Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomised regimen-controlled, double-blind, phase 2 trial. *The Lancet Oncology* 18:404-12.	Included
3	Basset-Seguin, N., Hauschild, A., Kunstfeld, R., Grob, J., Dréno, B., Mortier, L., Ascertio, P.A. *et al.* (2017). Vismodegib in patients with advanced basal cell carcinoma: Primary analysis of STEVIE, an international, open-label trial. *European Journal of Cancer* **86:**334-348.	Excluded – all the patients in this study had either locally advanced or metastatic cancer and therefore do not meet the population specified in the PICOs

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- Tang JY, Ally MS, Chanana AM, Mackay-Wiggan JM, Aszterbaum M, Lindgren JA, Ulerio G, Rezaee MR, Gildengorin G, Marji J, Clark C, Bickers DR, Epstein Jr EH. 2016. Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncology* 17: 1720-1731.
- Tang JY, Mackay-Wiggan JM, Aszterbaum M, Yauch RL, Lindgren J, Chang K, Coppola C, Chanana AM, Marji J, Bickers DR, Epstein Jr EH. 2012. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *New England Journal of Medicine* 366(23): 2180-2188.