NHS England Evidence Review:

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

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

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety, and cost effectiveness of neoadjuvant vismodegib compared with standard care in people with locally advanced basal cell carcinoma that is likely to result in significant aesthetic or functional sequelae following curative treatment and who are suitable or potentially suitable for curative treatment (at baseline).

Vismodegib inhibits the Hedgehog signalling pathway, which is an underlying molecular driver of basal cell carcinoma. The aim of neoadjuvant treatment with vismodegib is to downstage locally advanced basal cell carcinoma to reduce the extent of curative treatment required, either by radiotherapy or surgery. NICE has appraised vismodegib (TA489) for the licensed indication of treating symptomatic metastatic basal cell carcinoma and locally advanced basal cell carcinoma and concluded that vismodegib cannot be recommended because of the uncertainty in the evidence and because it is not cost effective. Neoadjuvant use of vismodegib is off label and not included in the scope of the technology appraisal.

Most basal cell carcinomas affect the face and a common site for locally advanced basal cell carcinoma is the eyelid. If the locally advanced basal cell carcinoma extends to involve the tissues and muscles of the orbit, then the only curative surgery is orbital exenteration (removal of the eye and surrounding soft tissues). The resulting defect requires major reconstructive surgery, and the person is often left with severe facial disfigurement. Other types of radical curative surgery include rhinectomy (amputation of the nose) and removal of the ear. Radiotherapy to the face, particularly around the eye, can cause a painful eye and eventual visual loss.

The review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with vismodegib more than others.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety, and cost effectiveness of neoadjuvant vismodegib compared with standard care in people with locally advanced basal cell carcinoma that is likely to result in significant aesthetic or functional sequelae following curative treatment and who are suitable or potentially suitable for curative treatment (at baseline).

The searches for evidence published since January 2013 were conducted on 11 September 2023 and identified 620 references. The titles and abstracts were screened, and 50 full text papers were obtained and assessed for relevance.

Three single-arm trials were included in the evidence review (Ally et al. 2014, Bertrand et al. 2021, and Kahana et al. 2021) including 11, 55, and 34 people, respectively. Two trials were based in the US and one in France. No studies directly compared neoadjuvant vismodegib to a control group.

In terms of clinical effectiveness:

- **Tumour response.** Three single-arm trials provided very low certainty evidence for the critical outcome of tumour response. The trials showed that most people had a response to vismodegib and that vismodegib reduced tumour size compared with baseline after up to 12 months of treatment. One single-arm trial showed that, after treatment with vismodegib, tumour size was 44%, 22%, 22%, and 20% of that at baseline at 3, 6, 9, and 12 months, respectively. The study also showed that 19/34 people had a complete response and 10/34 had a partial response (RECIST criteria). One single-arm trial showed a statistically significant reduction in the surgical defect area compared with baseline after 3 to 6 months (average 4 months) treatment with vismodegib. One single-arm trial showed that most people had a response after 4 to 10 months (average 6 months) treatment with vismodegib. Of these, 14/55 had a complete response and 25/55 had a partial response.
- **Downstaging of the surgical procedure and/or reduction in radiotherapy field size.** Two single-arm trials provided very low certainty evidence for the critical outcome of downstaging of the surgical procedure and/or reduction in radiotherapy field size. One trial showed that the surgical procedure was downstaged in most people (44/55) after an average of 6 months of vismodegib treatment and one trial showed that, of the 19 people who were predicted at baseline to need exenteration, none needed exenteration after up to 12 months treatment with vismodegib.
- **Organ-specific preservation and function.** One single-arm trial provided very low certainty evidence for the critical outcome of organ-specific preservation and function. The study showed that successful visual function was maintained in all people (34/34) with globe and lacrimal drainage system threatening orbital and extensive periocular basal cell carcinoma after up to 12 months of treatment with vismodegib. One person experienced a major decline in visual function (1/34), 5/34 people had a minor decline in visual function, and 27/34 people had stable or improved visual function.
- **Relapse rates.** Three single-arm trials provided very low certainty evidence for the important outcome of relapse rates following between 3 and 12 months of treatment with vismodegib alone or vismodegib followed by surgery. One single-arm trial showed that 1/11 people had a tumour recurrence after 17 months, one single-arm trial showed that 2/34 people had a recurrence after 2 years, and one single-arm trial showed that 16/44 people had a recurrence in a 3-year follow-up period.

One single-arm trial showed that a greater proportion of people who did not have a response to vismodegib had a recurrence or progression (7/11) compared with people who had a complete response (7/27). However, no statistical analyses were reported, and it is not clear what proportion of people had surgery in each group.

- **Histological remission.** Two single-arm trials provided very low certainty evidence relating to the important outcome of histological remission after up to 12 months of treatment with vismodegib. One single-arm trial found no residual basal cell carcinoma in the first piece of excised tissue in 6/13 (46%) of tumours and one single-arm trial found that 18/27 (67%) of people had a histological response with no sign of disease.
- **Quality of life.** One single-arm trial provided very low certainty evidence relating to the important outcome of quality of life. The study showed that quality of life, measured using the Skindex-16 score, statistically significantly improved each month, up to 10 months.
- **Did not receive curative surgery and/or curative radiotherapy treatment.** Two single-arm trials provided very low certainty evidence relating to the important outcome of not receiving curative surgery and/or curative radiotherapy treatment. One single-arm trial showed that, of the 27/55 people who had a complete response to vismodegib, 21 did not receive curative surgery. One single-arm trial showed that 7/34 people did not have surgery within the 12-month treatment period. Reasons for not receiving curative surgery were not fully described.

In terms of safety:

- Three single-arm trials provided very low certainty evidence that almost all (11/11, 54/55, 33/34) people had one or more treatment-related adverse event with vismodegib treatment.
- Two single-arm trials provided very low certainty evidence that 11/55 and 3/34 people had grade ≥3 treatment-related adverse events with vismodegib treatment.
- Two single-arm trials provided very low certainty evidence that 4/14 and 7/55 people discontinued vismodegib because of side effects.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- One single-arm trial provided evidence that the 2 people who had less than 3 months of vismodegib treatment did not have a significant reduction in surgical defect area but the 9 people who had least 3 months of treatment had a statistically significant reduction of the surgical defect area, no comparative analysis reported. However, one single-arm trial provided evidence that there was no statistically significant difference in duration of vismodegib treatment between people who had treatment success (downstaging of the surgical procedure) and the treatment failure group.
- One single-arm trial provided evidence that 4 people who had recurrent basal cell carcinomas had no reduction in the surgical defect area with vismodegib treatment but the 7 people who had nonrecurrent basal cell carcinomas had a statistically significant reduction in the surgical defect area compared with baseline. No comparative analysis reported.

- One single-arm trial provided evidence that there was no statistically significant difference in initial target lesion size in people who had treatment success (downstaging of the surgical procedure) and the treatment failure group.

In terms of regimen and duration of vismodegib used in the trials:

- Three single-arm trials used oral vismodegib 150 mg once a day for the following durations: 3 to 6 months (mean 4±2 months), 4 to 10 months (median 6.0±2.3 months), and up to 12 months (median 261 days).

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

This evidence review includes 3 open-label, single-arm trials (Ally et al. 2014, Bertrand et al. 2021, and Kahana et al. 2021). All 3 studies have significant limitations that affect their interpretation.

All 3 included studies were single-arm trials. Because single-arm trials do not have a control arm and, therefore, no randomisation or blinding of participants or investigators, bias cannot be avoided. The lack of randomisation and a control group also means the effect of vismodegib alone cannot be determined. All outcomes were considered to have very low certainty using modified GRADE and were downgraded for risk of bias because there was no comparator group or blinding, and outcome assessment could be considered subjective. However, given the natural progression of basal cell carcinoma, low prevalence, and a lack of active neoadjuvant treatment options, a single-arm study design is appropriate.

Collectively, the studies provided evidence for all the critical and important outcomes. However, all curative treatment options in the studies were surgical and no outcomes were identified that assessed a reduction in radiotherapy field size or the need for curative radiotherapy. No evidence was identified regarding the cost-effectiveness of neoadjuvant vismodegib.

A key limitation of all 3 included studies is the short follow-up time, with the maximum follow-up time being reported as 3 years to measure tumour recurrence. Further studies with a longer follow-up are needed to determine the long-term effect of neoadjuvant vismodegib on recurrence rates, the nature of the recurrence, and the need for further curative treatments.

Sample sizes were based on the power to detect a significant difference in the primary outcomes. The primary outcomes were the percentage change in surgical defect area (powered to detect a 20% decrease, Ally et al. 2014), the proportion of people with a downstaging of the surgical procedure (Bertrand et al. 2021), and visual function (measured by VAWS, Kahana et al. 2021). Despite this, sample sizes were small (Bertrand et al. 2021, n=55; Kahana et al. 2021, n=34; Ally et al. 2014, n=11) and therefore unlikely to be powered to detect differences in secondary outcomes and subgroups.

To assess tumour response, the largest trial (Bertrand et al. 2021), used new classification criteria for downstaging of the surgical procedure and it is not clear whether these criteria are externally valid. However, these criteria are more conservative in assessing response than the validated RECIST (Response Evaluation Criteria in Solid Tumors) v1.1 criteria and are therefore unlikely to overestimate the effect of vismodegib. Ally et al. 2014 assessed tumour response by measuring the change in surgical defect area. However, surgical defect area does not describe the possible subclinical extension of the tumour and the number of Mohs stages needed.

In Ally et al. 2014, 7/13 tumours (54%) appeared clinically cured but only 4/7 of these showed histological cure. Kahana et al. 2021 also reported rates of histological cure in the people who had surgery (18/27) but it was not clear whether these people showed a complete, partial, or no response to vismodegib. Further studies are needed to understand the effect of vismodegib on tumour histology. If histological cure does not correlate with clinical response in people treated with vismodegib, it is possible that curative treatment may be inappropriately downstaged and lead to tumour recurrence.

Basal cell carcinoma is more common in the Caucasian population, particularly amongst older people. Basal cell carcinoma is less prevalent in non-Caucasian ethnic groups, but when they occur, they tend to be diagnosed at a later stage. None of the included studies reported the ethnicity of the participants, therefore it is not possible to say whether vismodegib is effective in all ethnicities, particularly if people are diagnosed at a later stage.

Most of the tumours assessed in the 3 trials were located near to organs on the face, mostly near the eyes. Small tumours on the face are more likely to be classified as invasive than those on the body because their removal is more likely to result in significant morbidity. It is unclear whether these findings are applicable to tumours on other areas of the body which may only be classified as invasive because they are larger.

Ally et al. 2014 showed that an average of 4 months of vismodegib before surgery significantly reduced the surgical defect size. However, this effect was not seen in people with recurrent basal cell carcinomas. Because of the small sample size in this study (7 nonrecurrent, 4 recurrent) further studies are needed to understand the efficacy of neoadjuvant vismodegib in people with recurrent basal cell carcinoma compared with nonrecurrent.

Interpretation of the data on the safety of vismodegib is limited by the small numbers of participants and short treatment periods. The studies did include a follow-up period (up to 3 years after the end of the study) but this was primarily to assess tumour recurrence, not long-term safety. The absence of a control group in the single-arm trials also limits ability to assess causality. Vismodegib is not licensed for the neoadjuvant treatment of basal cell carcinoma, but it is licensed for the treatment of basal cell carcinoma. The dose and route (150 mg orally) used in the 3 included studies is the same as in the product licence, and the most common treatment-related adverse events in the studies were similar to those listed in the SPC.

Ally et al. 2014 reported that the 2/11 people who had less than 3 months of vismodegib treatment did not have a significant reduction in surgical defect area but the 9/11 people who had least 3 months of treatment had a statistically significant reduction of the surgical defect area. However, Bertrand et al. 2021, (n=55) provided evidence that duration of treatment with vismodegib was not statistically significantly different between the treatment success group who had downstaging of the surgical procedure and the treatment failure group. Because these trials were non-comparative and had small sample sizes, it is not possible to draw conclusions on what duration of vismodegib treatment is most effective. It is also possible that the people who took vismodegib for less time differed from those who took it for more time. For example, because of susceptibility to side effects, leading to treatment discontinuation, or from differences in disease progression.

Conclusion

Overall, 3 studies provided evidence on the clinical effectiveness and safety of neoadjuvant vismodegib for locally advanced basal cell carcinoma prior to curative treatment for lesions likely to result in significant aesthetic sequelae or functional sequelae following curative treatment and who are suitable or potentially suitable for curative treatment (at baseline). All 3 studies were single-arm trials that, combined, provided very low certainty evidence on the critical outcomes

of: tumour response, downstaging of the surgical procedure, organ-specific preservation and function; and the important outcomes of: relapse rates, histological remission quality of life, did not receive curative surgery, and safety. All curative treatment options in the studies were surgical and no outcomes were identified that assessed a reduction in radiotherapy field size or the need for curative radiotherapy.

All 3 single-arm trials (Ally et al. 2014, Bertrand et al. 2021, and Kahana et al. 2021) suggested that most people had a response to vismodegib and that vismodegib reduced tumour size compared with baseline after up to 12 months of treatment. Ally et al. 2014 showed a statistically significant reduction in the surgical defect area after an average of 4 months of vismodegib and Bertrand et al. 2021 showed that most people had a response to an average of 6 months of vismodegib. However, these outcomes are compared with baseline, and the lack of a comparator group, small sample sizes, and limited information on whether response rates are associated with a reduction in tumour recurrences means that these findings should be interpreted with caution.

Two studies showed that surgical procedure was downstaged in most people after an average of 6 months of vismodegib treatment (Bertrand et al. 2021) and that predicted surgical requirements are reduced after up to 12 months treatment with vismodegib (Kahana et al. 2021).

Kahana et al. 2021 showed that successful visual function was maintained in all people with globe and lacrimal drainage system threatening orbital and extensive periocular basal cell carcinoma after up to 12 months of treatment with vismodegib. One person experienced a major decline in visual function, 5 people had a minor decline in visual function, and 27 people had stable or improved visual function, compared with baseline.

All 3 studies reported relapse rates during a follow-up period. Ally et al. 2014 showed that 1/11 people had a tumour recurrence after 17 months, Kahana et al. 2021 showed that 2/34 people had a recurrence after 2 years, and Bertrand et al. 2021 showed that 16/44 people had a recurrence in a 3-year follow-up period. Some people in Bertrand et al. 2021 and Kahana et al. 2021 did not have surgery following successful treatment with vismodegib. It is not clear from the studies whether these people were more or less likely to have a tumour recurrence therefore limiting the interpretation of the findings. All 11 participants in Ally et al 2014 had curative surgery after vismodegib. Further studies with larger samples sizes and longer follow-up periods are needed to understand whether recurrence is associated with treatment duration of vismodegib.

Ally et al. 2014 showed that there was no residual basal cell carcinoma in the first piece of excised tissue in 6/13 (46%) of tumours and Kahana et al. 2021 found that 18/27 (67%) of people had a histological response with no sign of disease. However, it was not clear whether histological remission was associated with clinical response or tumour recurrence.

Only one study (Bertrand et al. 2021) reported quality of life outcomes, measured using the Skindex-16 score. The study found that quality of life statistically significantly improved each month, up to 10 months.

Bertrand et al. 2021 showed that, of the 27/55 people who had a complete response to vismodegib, 21 did not receive curative surgery, and Kahana et al. 2021 showed that 7/34 people did not have surgery within the 12-month treatment period. In Kahana et al. 2021, the intention was that all people would have vismodegib for 12 months. People who received surgery did so because of poor tolerance to vismodegib. In Bertrand et al. 2021, reasons for not receiving curative surgery were not fully described.

All 3 studies found that almost all (11/11, 54/55, 33/34) people had one or more treatment related adverse event and two studies showed that 11/55 and 3/34 people had grade ≥3 treatment-related adverse events. Ally et al. 2014 and Bertrand et al. 2021 showed that 4/14 and 7/55 people discontinued vismodegib because of side effects, respectively.

The duration of vismodegib treatment varied between studies. Average duration was longest in Kahana et al. 2021 (up to 12 months, median 261 days), then Bertrand et al. 2021 (4 to 10 months, median 6.0±2.3 months), followed by Ally et al. 2014 (3 to 6 months, mean 4±2 months). One study provided some evidence to suggest that vismodegib is only effective when taken for at least 3 months. Most people experienced adverse events and the people who discontinued treatment did so because of side effects. The benefits of longer-term treatment with vismodegib should be balanced against the risks.

Locally advanced basal cell carcinoma can be difficult to treat, and current treatment options are limited. Most basal cell carcinomas affect the face and a common site for locally advanced basal cell carcinoma is the eyelid. If the locally advanced basal cell carcinoma extends to involve the tissues and muscles of the orbit, then the only curative surgery is removal of the eye. Other types of radical curative surgery include amputation of the nose and removal of the ear. The findings of this review are important because they suggest that the use of neoadjuvant vismodegib (used before curative surgery) may reduce the scope of curative treatment required. However, interpretation of the data is limited by the lack of comparator group in the single-arm trials, the differences in vismodegib treatment duration, the lack of correlation between clinical cure and histological cure, and the fact that not all participants went on to receive curative surgery.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people with locally advanced basal cell carcinoma that is determined as likely to result in significant aesthetic or functional sequelae following curative treatment, and who are suitable or potentially suitable for curative treatment, what is the clinical effectiveness of neoadjuvant vismodegib compared with standard care?
2. In people with locally advanced basal cell carcinoma that is determined as likely to result in significant aesthetic or functional sequelae following curative treatment, and who are suitable or potentially suitable for curative treatment, what is the safety of neoadjuvant vismodegib compared with standard care?
3. In people with locally advanced basal cell carcinoma that is determined as likely to result in significant aesthetic or functional sequelae following curative treatment, and who are suitable or potentially suitable for curative treatment, what is the cost effectiveness of neoadjuvant vismodegib compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from neoadjuvant vismodegib more than the wider population of interest?
5. From the evidence selected, what was the regimen and duration of neoadjuvant vismodegib treatment?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 11 September 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Three papers were identified for inclusion (Ally et al. 2014, Bertrand et al. 2021, and Kahana et al. 2021). Table 1 provides a summary of these included studies and full details are given in Appendix E. All 3 were open-label, single-arm trials with no comparator.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Ally et al. 2014 Open-label, single-arm trial USA	Adults with at least 1 biopsy-confirmed basal cell carcinoma of any histologic subtype, more than 5 mm in diameter, eligible for surgical removal. • N=11 • Age 39 to 100 years; 6 female, 5 male. • Target basal cell carcinoma sites (10/13 on face): cheek (3), nasal tip (1), lower eyelid (1), temple (2), forehead (2), shoulder (1), medial canthus (1), back (1), chest (1); histological type: infiltrative (7), micronodular (1), nodular/infiltrative (3), superficial (1), nodular (1). • All target sites were high-risk basal cell carcinomas (NCCN guidelines), 36% recurrent (previously treated with cryotherapy).	**Intervention** Oral vismodegib (150 mg daily) for 3 to 6 months (mean 4±2 months), based on clinical response (one participant received vismodegib for 9 months to further reduce tumour size before surgery) **Comparator** No comparator.	**Critical outcomes** • Tumour response (after 3 to 6 months of vismodegib [9 months in one person], average 4 months) **Important outcomes** • Relapse rates (mean follow-up 11.5 months, 4 to 21 months after surgery) • Histological remission (after 3 to 6 months of vismodegib [9 months in one person], average 4 months) • Safety (after 3 to 6 months of vismodegib [9 months in one person], average 4 months)
Bertrand et al. 2021 Open-label single-arm trial France	Adults with basal cell carcinoma of the face with a diameter of 2 cm or more in an area of the face with a high risk of recurrence and 3 cm or more in an area with an intermediate risk of recurrence. • N=55 • 51% male, median age 73 years (range 35.5 to 95.2). • Location of basal cell carcinoma: eye (19), ear (8), nose (7), mouth (1), other facial location (20). • Lesions were classified as stage A (inoperable) (4), stage B (operable with a major functional risk) (15), and stage C (operable with a minor functional risk or a major aesthetic risk) (36).	**Intervention** Oral vismodegib 150 mg once a day for 4 to 10 months (median 6.0±2.3 months). Treatment was reviewed once a month. Treatment was stopped if there was some disease progression, unacceptable toxicity, consent withdrawal, death, or other reasons deemed appropriate. Dose interruption for up to 4 weeks was allowed. **Comparator** No comparator.	**Critical outcomes** • Tumour response (after 6 months vismodegib) • Downstaging of the surgical procedure (after 6 months vismodegib) **Important outcomes** • Relapse rates (3-year follow-up) • Quality of life (up to the 10th cycle [28 days each cycle]) • Did not receive curative surgery and/or curative radiotherapy treatment (after 6 months vismodegib) • Safety (after 6 months vismodegib)
Kahana et al. 2021 Open-label single-arm trial USA	Adults with globe and lacrimal drainage system threatening (within 7 mm of lacrimal apparatus) orbital and extensive periocular basal cell carcinoma. • N=34 • Mean age 67.1±12.2, 56% male. • Tumour locations: medial canthus (22), lateral canthus (3), lower lid (8), brow/orbit (2). Median tumour size 21.5 mm (range 10 to 60 mm). • 19 people had lesions where complete excision with clear margins would have likely required exenteration. 15 people with lesions that would have qualified for globe-sparing surgery, but to achieve clear margins, the surgery would have resulted in loss of lacrimal drainage apparatus function (4), extraocular motility (1), or both (10).	**Intervention** Oral vismodegib 150 mg once a day for up to 12 months or until disease progression or unacceptable toxicity (median treatment duration 261 days). **Comparator** No comparator.	**Critical outcomes** • Tumour response (after up to 12 months vismodegib) • Downstaging of the surgical procedure (up to 12 months of vismodegib) • Organ-specific preservation and function (up to 12 months of vismodegib or after surgery) **Important outcomes** • Relapse rates (duration of follow-up unclear, relapse detected at 2 years) • Histological remission (up to 12 months of vismodegib or after surgery) • Did not receive curative surgery and/or curative radiotherapy treatment (up to 12 months vismodegib) • Safety (up to 12 months of vismodegib)

Abbreviations

NCCN, National Comprehensive Cancer Network

5. Results

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

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Tumour response **Certainty of evidence:** Very low	Response rate is important to patients as it represents whether the treatment can reduce tumour burden. In total 3 single-arm trials provided evidence relating to response rate at up to 12 months. Ally et al. 2014 (n=11) included people with tumours mostly on the face (10/13 tumours). All tumours were high-risk (NCCN guidelines) and 36% were recurrent. Bertrand et al. 2021 (n=55) included people with basal cell carcinoma of the face with a diameter of 2 cm or more in an area with a high risk of recurrence, and 3 cm or more in areas with an intermediate risk of recurrence. Kahana et al. 2021 (n=34) included people with globe and lacrimal drainage system threatening orbital and extensive periocular basal cell carcinoma. After 3 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that cross-sectional tumour size was 44% of the baseline tumour size, no statistical analysis reported. **(VERY LOW)** After an average of 4 months vismodegib treatment (3 to 6 months, 9 months for 1 person): • 1 single-arm trial (Ally et al. 2014) (n=11, 13 tumours) showed a statistically significant reduction in the surgical defect area compared with baseline after treatment with vismodegib (−27%, 95% CI −45.7 to −7.9%, p=0.006). **(VERY LOW)** After 4 to 10 months (average 6 months) of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) (n=55) showed that most people had a response to vismodegib 39/55 (70.9%, 95% CI 59 to 83%). Of these, 14/55 (25.5%, 95% CI 14 to 37%) had a complete response and 25/55 (45.5%, 95% CI 32 to 59%) had a partial response. **(VERY LOW)** After 6 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that cross-sectional tumour size was 22% of the baseline tumour size, no statistical analysis reported. **(VERY LOW)** After 9 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=10, people who had not yet had surgery) showed that cross-sectional tumour size was 22% of the baseline tumour size, no statistical analysis reported. **(VERY LOW)** After 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=3, people who had not yet had surgery) showed that cross-sectional tumour size was 20% of the baseline tumour size, no statistical analysis reported. **(VERY LOW)**

	After up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 19/34 (56%) people had a complete response by physical examination, and 16/34 (47%) had a complete response by MRI/CT. 10/34 (29%) people had a partial response by physical examination, and 9/34 (26.5%) had a partial response by MRI/CT. No statistical analyses reported. **(VERY LOW)** **These studies provided very low certainty evidence that most people had a response to vismodegib, and that vismodegib reduced tumour size compared with baseline after up to 12 months of treatment.** **One single-arm trial showed that, after treatment with vismodegib, tumour size was 44%, 22%, 22%, and 20% of that at baseline at 3, 6, 9, and 12 months, respectively. The study also showed that 19/34 people had a complete response and 10/34 had a partial response.** **One single-arm trial showed a statistically significant reduction in the surgical defect area compared with baseline after 3 to 6 months (average 4 months) treatment with vismodegib.** **One single-arm trial showed that most people had a response after 4 to 10 months (average 6 months) treatment with vismodegib. Of these, 14/55 had a complete response and 25/55 had a partial response.**
Downstaging of the surgical procedure and/or reduction in radiotherapy field size **Certainty of evidence:** Very low	This outcome is important to patients as it represents a downstaging of the complexity and scope of the curative intervention required. This correlates with a reduction in the extent of surgical resection and/or a reduction in normal tissue toxicity. In total 2 single-arm trials provided evidence relating to downstaging of the surgical procedure at up to 12 months. After 4 months of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) (n=42) showed that 35/42 (85.7%, 95% CI 71 to 95%) had a downstaging of the surgical procedure. No statistical analysis reported. **(VERY LOW)** After 4 to 10 months (average 6 months) of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) (n=55) showed that 44/55 (80%, 95% CI 67 to 90%) had a downstaging of the surgical procedure. No statistical analysis reported. **(VERY LOW)** After up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 19/19 (100%) of people who were predicted at baseline to have exenteration had no exenteration and 34/34 (100%) had successful visual function at completion of the study. This followed predicted surgical outcomes at baseline as: exenteration (19, 56%), globe-sparing (15 [44%], with lacrimal damage [4], extraocular motility damage [1], or both [10]). No statistical analysis reported. **(VERY LOW)** **These studies provided very low certainty evidence for the outcome of downstaging of the surgical procedure and/or reduction in radiotherapy field size. One trial showed that the surgical procedure was downstaged in most people (44/55) after an average of 6 months of vismodegib treatment and one trial showed that, of the 19 people who were predicted at baseline to need exenteration, none needed exenteration after up to 12 months treatment with vismodegib.**

Organ-specific preservation and function **Certainty of evidence:** Very low	This outcome is important to patients as it represents sparing of major aesthetic and/or functional sequelae following curative treatment. For some patients this would include preservation of organs that may otherwise have been excised- e.g., orbital exenteration. Preservation of organ function correlates with an improvement in patients' quality of life. In total 1 single-arm trial provided evidence relating to organ-specific preservation and function at up to 12 months. The trial included 34 people with globe and lacrimal drainage system threatening orbital and extensive periocular basal cell carcinoma. At up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 34/34 (100%) people maintained a VAWS of >21 (considered successful) at study completion, p<0.0001. Mean scores were 44/50 at baseline, 46/50 at 3 months,46/50 at 6 months, and 47/50 at 12 months or post-surgery. **(VERY LOW)** • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 1/34 (3%, 95% CI 0.1 to 15.3%) people had a major decline in VAWS of 5 points compared with baseline. No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 5/34 (14.7%, 95% CI 5 to 31.1%) people had a minor decline in VAWS of 2 to 4 points compared with baseline. No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 27/34 (79.4%, 95% CI 62.1 to 91.3%) people had a stable or improved VAWS compared with baseline. No statistical analysis reported. **(VERY LOW)** **This study provided very low certainty evidence that successful visual function (VAWS>21) was maintained in all people (34/34) with globe and lacrimal drainage system threatening orbital and extensive periocular basal cell carcinoma after up to 12 months of treatment with vismodegib. One person experienced a major decline in visual function, 5 people had a minor decline in visual function, and 27 people had stable or improved visual function.**
Important outcomes	
Relapse rates **Certainty of evidence:** Very low	This outcome is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions. In total 3 single-arm trials provided evidence relating to relapse rates at up to 3 years. One trial (Ally et al. 2014) enrolled 15 people but only 11 completed the trial through having their basal cell carcinoma surgically excised (2 people withdrew because of vismodegib-related side effects, 1 withdrew because of unrelated adverse events, and one person was lost to follow-up). The average duration of vismodegib before surgery was 4 months. One single-arm trial (Bertrand et al. 2021) included 55 people with basal cell carcinoma of the face with a diameter of 2 cm or more in an area with a high risk of recurrence, and 3 cm or more in areas with an intermediate risk of recurrence. One single-arm trial (Kahana et al. 2021) included 34 people with globe and lacrimal drainage system threatening orbital and extensive periocular basal cell carcinoma. Mean 11.5 months (range 4 to 21 months) after surgery: • 1 single-arm trial (Ally et al. 2014) (n=11, 13 tumours) showed that 1 person had a tumour recurrence 17 months after surgery. This person had 2 months of vismodegib treatment for a twice recurrent basal cell carcinoma. No statistical analysis reported. **(VERY LOW)**

	2 years after the end of the study • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 2 people had a tumour recurrence. No statistical analysis reported. **(VERY LOW)** 3 years after the end of the study: • 1 single-arm trial (Bertrand et al. 2021) showed that 16/44 (36%, 95% CI 22 to 51%) people had a recurrence. No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Bertrand et al. 2021) showed that, in people who had a complete response to vismodegib (6/27 had surgery and 21/27 did not), 7/27 had a recurrence (1 died with recurrence). No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Bertrand et al. 2021) showed that, in people who had an incomplete response to vismodegib, 9/17 had a recurrence (1 died with recurrence). No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Bertrand et al. 2021) showed that, in people who did not have a response to vismodegib, 7/11 had a recurrence or progression. No statistical analysis reported. **(VERY LOW)** **These studies provided very low certainty evidence relating to the outcome of tumour recurrence after between 3 and 12 months of treatment with vismodegib alone or vismodegib followed by surgery. One single-arm trial showed that 1/11 people had a tumour recurrence after 17 months, one single-arm trial showed that 2/34 people had a recurrence after 2 years, and one single-arm trial showed that 16/44 people had a recurrence in a 3-year follow-up period.** **One single-arm trial showed that a greater proportion of people who did not have a response to vismodegib had a recurrence or progression (7/11) compared with people who had a complete response (7/27). However, no statistical analyses were reported, and it is not clear what proportion of people had surgery in each group.**
Histological remission **Certainty of evidence:** Very low	This outcome is important to patients because it can indicate that the disease is reducing in severity and prognosis is improved. In total 2 single-arm trials provided evidence relating histological remission at up to 12 months. After an average of 4 months vismodegib treatment (3 to 6 months, 9 months for 1 person): • 1 single-arm trial (Ally et al. 2014) (n=11, 13 tumours) found no residual basal cell carcinoma in the first piece of excised tissue in 6/13 (46%) tumours. No statistical analysis reported. **(VERY LOW)** • 1 single-arm trial (Ally et al. 2014) found no residual basal cell carcinoma in the first piece of excised tissue in 4/7 (57%) tumours that appeared clinically cured (flat scar with no erythema or nodularity). No statistical analysis reported. **(VERY LOW)** After up to 12 months of treatment: • 1 single-arm trial (Kahana et al. 2021) showed that 18/27 (67%) of people had a histological response with no sign of disease. No statistical analysis reported. **(VERY LOW)** **These studies provided very low certainty evidence relating to the outcome of histological remission after up to 12 months of treatment with vismodegib. One single-arm trial found no residual basal cell carcinoma in the first piece of**

	excised tissue in 6/13 (46%) of tumours and one single-arm trial found that 18/27 (67%) of people had a histological response with no sign of disease.
Quality of life **Certainty of evidence:** Very low	This outcome is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. In total 1 single-arm trial provided evidence relating to quality of life at up to 10 months. From baseline up to the 10th cycle (28 days per cycle), after 4 to 10 months [median 6 months] of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) showed that the Skindex-16 score statistically significantly improved (decreased) by 2.07 per cycle ($p<0.0001$). **(VERY LOW)** **This study provided very low certainty evidence that quality of life, measured using the Skindex-16 score, statistically significantly improved each month, up to 10 months.**
Did not receive curative surgery and/or curative radiotherapy treatment **Certainty of evidence:** Very low	This outcome is important to patients as it captures the number of patients for whom neoadjuvant treatment with vismodegib has removed the need for curative surgery and/or curative radiotherapy altogether. It also captures patients who chose not to, or who remained unable to undergo curative surgery and/or curative radiotherapy following neoadjuvant vismodegib. In total 2 single-arm trials provided evidence for people who did not receive curative surgery. After 4 to 10 months (median 6 months) of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) (n=55) showed that of the 27 people who had complete clinical response to vismodegib, 6 had surgery and 21 did not. No statistical analysis reported. **(VERY LOW)** After up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 7/34 (20.6%) people did not have surgery within the 12-month treatment period. The 27/34 who elected to undergo excision before the 12 months treatment did so because of poor tolerance to vismodegib. No statistical analysis reported. **(VERY LOW)** **These studies provided very low certainty evidence for the outcome of not receiving curative surgery and/or curative radiotherapy treatment. One single-arm trial showed that, of the 27/55 people who had a complete response to vismodegib, 21 did not receive curative surgery. One single-arm trial showed that 7/34 people did not have surgery within the 12-month treatment period. Reasons for not receiving curative surgery were not fully described.**
Safety	
Treatment-related adverse events **Certainty of evidence:** Very low	Safety of vismodegib is important to patients as it reflects the risks involved in taking this medication and allows a risk benefit assessment to be undertaken. It also allows comparison of interventional approaches. In total 3 single-arm trials provided evidence relating to treatment-related adverse events. After an average of 4 months vismodegib treatment (3 to 6 months, 9 months for 1 person): • 1 single-arm trial (Ally et al. 2014) (n=11) showed that 11/11 (100%) people had treatment-related adverse events. These were grade-1: dysgeusia (100%),

	muscle cramps (100%), fatigue (72%), diarrhoea (9%), weight loss [less than 5% body weight] (45%), depressed mood (18%), reversible amenorrhea (9%). 11/11 had hair loss; 7/11 <50% hair loss (grade 1), 4/11 ≥50% hair loss (grade 2). After 4 to 10 months (median 6 months) of vismodegib treatment: • 1 single-arm trial (Bertrand et al. 2021) (n=55) showed that 54/55 (98.2%) people had treatment-related adverse events including: dysgeusia, muscle spasms, alopecia, fatigue, weight loss (or decrease), diarrhoea, cytolysis, appetite loss (or decrease), arthralgia, constipation, hypogeusia, dyspepsia, hyponatremia, dyspnoea, anaemia, vomiting, pruritus, CPK elevation, oral dryness, cough. The mean number of adverse events was 6.4±3.6 per person. **(VERY LOW)** After up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 33/34 (97%) people had treatment-related adverse events. **(VERY LOW)** **These studies provided very low certainty evidence that almost all (11/11, 54/55, 33/34) people had one or more treatment related adverse event.**
Grade ≥3 treatment-related adverse events **Certainty of evidence:** Very low	After 4 to 10 months (median 6 months) of vismodegib treatment • 1 single-arm trial (Bertrand et al. 2021) (n=55) showed that 11/55 (20%) of people had grade ≥3 treatment-related adverse events including: dysgeusia, muscle spasms, weight loss (or decrease), cytolysis, dyspepsia, hyponatremia, dyspnoea, and anaemia. After up to 12 months of vismodegib treatment: • 1 single-arm trial (Kahana et al. 2021) (n=34) showed that 3/34 (8.8%) people had grade ≥3 treatment-related adverse events. **These studies provided very low certainty evidence that 11/55 and 3/34 people had grade ≥3 treatment-related adverse events.**
Discontinuation of vismodegib because of side effects/ toxicity **Certainty of evidence:** Very low	One single-arm trial (Ally et al. 2014) (n=14) showed that 4/14 (29%) could not complete more than 3 months of treatment because of vismodegib-related side effects including: aspartate/alanine aminotransferase elevation, hair loss, fatigue, creatine phosphokinase elevation). One single-arm trial (Bertrand et al. 2021) (n=55) showed that 7/55 discontinued vismodegib because of toxicity (after 4 to 10 months [median 6 months] of vismodegib treatment). **These studies provided very low certainty evidence that 4/14 and 7/55 people discontinued vismodegib because of side effects.**

Abbreviations

CT, computed tomography; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; VAWS, visual assessment weighted score

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

Outcome	Evidence statement

Cost effectiveness	No evidence was identified for this outcome.

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

Outcome	Evidence statement
Duration of vismodegib treatment	1 single-arm trial (Ally et al. 2014) (n=11) provided evidence that the 2 people who had less than 3 months of vismodegib treatment did not have a significant reduction in surgical defect (−12%, 95% CI −55.0% to 33.0%, p=1.0). However, the 9 people who had least 3 months of treatment had a statistically significant reduction of the surgical defect area (−31%, 95% CI −68.0% to −7.0%, p=0.002). 1 single-arm trial (Bertrand et al. 2021) (n=55) provided evidence that duration of treatment with vismodegib was not statistically significantly different between the group who had downstaging of the surgical procedure (treatment success) and the treatment failure group (6.1±2.1 months compared with 5.6±3.2 months, respectively, p=0.53). **One single-arm trial provided evidence that the 2 people who had less than 3 months of vismodegib treatment did not have a significant reduction in surgical defect but the 9 people who had least 3 months of treatment had a statistically significant reduction of the surgical defect area compared with baseline, no comparative analysis reported. However, one single-arm trial provided evidence that there was no statistically significant difference in duration of vismodegib treatment between people in the treatment success group and the treatment failure group.**
People with recurrent disease	1 single-arm trial (Ally et al. 2014) (n=11) provided evidence that the 4 people with recurrent basal cell carcinomas (4 target tumours) had no reduction in surgical defect area after treatment with vismodegib (no statistical analysis reported). The 7 people with nonrecurrent tumours (9 target tumours) had a statistically significant reduction in the surgical defect area with vismodegib treatment (−36%, 95% CI −58.7% to −14.0%, p=0.004). **One single-arm trial provided evidence that the 4 people who had recurrent basal cell carcinomas had no reduction in the surgical defect area but the 7 people who had nonrecurrent basal cell carcinomas had a statistically significant reduction in the surgical defect area compared with baseline. No comparative analysis reported.**
Size of target lesion at baseline	1 single-arm trial (Bertrand et al. 2021) (n=55) provided evidence that there was no significant difference in average initial target lesion size in people who had downstaging of the surgical procedure (treatment success group) (45.8 mm, range 20 to 130 mm) and the treatment failure group (53.1 mm, range 20 to 120 mm) (p=0.50). **One single-arm trial provided evidence that there was no statistically significant difference in initial target lesion size between people in the treatment success group and the treatment failure group.**

From the evidence selected, what was the regimen and duration of neoadjuvant vismodegib treatment?

Study	Regimen and duration of neoadjuvant vismodegib

Ally et al. 2014	Oral vismodegib 150 mg once a day for 3 to 6 months (mean 4±2 months), based on clinical response (one participant received vismodegib for 9 months to further reduce tumour size before surgery).
Bertrand et al. 2021	Oral vismodegib 150 mg once a day for 4 to 10 months (median 6.0±2.3 months). Treatment was reviewed once a month. Treatment was stopped if there was some disease progression, unacceptable toxicity, consent withdrawal, death, or other reasons deemed appropriate. Dose interruption for up to 4 weeks was allowed.
Kahana et al. 2021	Oral vismodegib 150 mg once a day for up to 12 months or until disease progression or unacceptable toxicity (median treatment duration 261 days).

6. Discussion

This evidence review includes 3 open-label, single-arm trials (Ally et al. 2014, Bertrand et al. 2021, and Kahana et al. 2021). All 3 studies have significant limitations that affect their interpretation.

All 3 included studies were single-arm trials. Because single-arm trials do not have a control arm and, therefore, no randomisation or blinding of participants or investigators, bias cannot be avoided. The lack of randomisation and a control group also means the effect of vismodegib alone cannot be determined. All outcomes were considered to have very low certainty using modified GRADE and were downgraded for risk of bias because there was no comparator group or blinding, and outcome assessment could be considered subjective. However, given the natural progression of basal cell carcinoma, low prevalence, and a lack of active neoadjuvant treatment options, a single-arm study design is appropriate.

Collectively, the studies provided evidence for all the critical and important outcomes. However, all curative treatment options in the studies were surgical, and no outcomes were identified that assessed a reduction in radiotherapy field size or the need for curative radiotherapy. No evidence was identified regarding the cost-effectiveness of neoadjuvant vismodegib.

A key limitation of all 3 included studies is the short follow-up time, with the maximum follow-up time being reported as 3 years to measure tumour recurrence. Further studies with a longer follow-up are needed to determine the long-term effect of neoadjuvant vismodegib on recurrence rates, the nature of the recurrence, and the need for further curative treatments.

Sample sizes were based on the power to detect a significant difference in the primary outcomes. The primary outcomes were the percentage change in surgical defect area (powered to detect a 20% decrease, Ally et al. 2014), the proportion of people with a downstaging of the surgical procedure (Bertrand et al. 2021), and visual function (measured by VAWS, Kahana et al. 2021). Despite this, sample sizes were small (Bertrand et al. 2021, n=55; Kahana et al. 2021, n=34; Ally et al. 2014, n=11) and therefore unlikely to be powered to detect differences in secondary outcomes and subgroups.

To assess tumour response, the largest trial (Bertrand et al. 2021), used new classification criteria for downstaging of the surgical procedure and it is not clear whether these criteria are externally valid. However, these criteria are more conservative in assessing response than the validated RECIST v1.1 criteria and are therefore unlikely to overestimate the effect of vismodegib. Ally et al. 2014 assessed tumour response by measuring the change in surgical defect area. However, surgical defect area does not describe the possible subclinical extension of the tumour and the number of Mohs stages needed.

In Ally et al. 2014, 7/13 tumours (54%) appeared clinically cured but only 4/7 of these showed histological cure. Kahana et al. 2021 also reported rates of histological cure in the people who had surgery (18/27) but it was not clear whether these people showed a complete, partial, or no response to vismodegib. Further studies are needed to understand the effect of vismodegib on tumour histology. If histological cure does not correlate with clinical response in people treated with vismodegib, it is possible that curative treatment may be inappropriately downstaged and lead to tumour recurrence.

Basal cell carcinoma is more common in the Caucasian population, particularly amongst older people. Basal cell carcinoma is less prevalent in non-Caucasian ethnic groups, but when they occur, they tend to be diagnosed at a later stage. None of the included studies reported the ethnicity of the participants, therefore it is not possible to say whether vismodegib is effective in all ethnicities, particularly if people are diagnosed at a later stage.

Most of the tumours assessed in the 3 trials were located near to organs on the face, mostly near the eyes. Small tumours on the face are more likely to be classified as invasive than those on the body because their removal is more likely to result in significant morbidity. It is unclear whether the study findings are applicable to tumours on other areas of the body which may only be classified as invasive because they are larger.

Ally et al. 2014 showed that an average of 4 months of vismodegib before surgery significantly reduced the surgical defect size. However, this effect was not seen in people with recurrent basal cell carcinomas. Because of the small sample size in this study (7 nonrecurrent, 4 recurrent) further studies are needed to understand the efficacy of neoadjuvant vismodegib in people with recurrent basal cell carcinoma compared with nonrecurrent.

Interpretation of the data on the safety of vismodegib is limited by the small numbers of participants and short treatment periods. The studies did include a follow-up period (up to 3 years after the end of the study) but this was primarily to assess tumour recurrence, not long-term safety. The absence of a control group in the single-arm trials also limits ability to assess causality. Vismodegib is not licensed for the neoadjuvant treatment of basal cell carcinoma, but it is licensed for the treatment of basal cell carcinoma, and the dose and route (150 mg orally) used in the 3 included studies is the same as in the product licence. The most common treatment-related adverse events in the studies were also similar to those listed in the SPC (muscle spasms, alopecia, dysgeusia, decreased weight, fatigue, nausea, and diarrhoea).

Ally et al. 2014 reported that the 2/11 people who had less than 3 months of vismodegib treatment did not have a significant reduction in surgical defect area compared with baseline (mean −12%, 95% CI −55.0% to 33.0%, p=1.0) but the 9/11 people who had least 3 months of treatment did (mean −31%, 95% CI −68.0% to −7.0%, p=0.002). However, Bertrand et al. 2021, (n=55) provided evidence that duration of treatment with vismodegib was not statistically significantly different between the treatment success group who had downstaging of the surgical procedure and the treatment failure group (6.1±2.1 months compared with 5.6±3.2 months, respectively, p=0.53). These trials were non-comparative and had small sample sizes and so, it is not possible to draw conclusions on what duration of vismodegib treatment is most effective. It is also possible that the people who took vismodegib for less time differed from those who took it for more time. For example, because of susceptibility to side effects, leading to treatment discontinuation, or from differences in disease progression.

7. Conclusion

Overall, 3 studies provided evidence on the clinical effectiveness and safety of neoadjuvant vismodegib for locally advanced basal cell carcinoma prior to curative treatment for lesions likely to result in significant aesthetic sequelae or functional sequelae following curative treatment and who are suitable or potentially suitable for curative treatment (at baseline). All 3 studies were single-arm trials that, combined, provided very low certainty evidence on the critical outcomes of: tumour response, downstaging of the surgical procedure, organ-specific preservation and function; and the important outcomes of: relapse rates, histological remission, quality of life, did not receive curative surgery, and safety. All curative treatment options in the studies were surgical and no outcomes were identified that assessed a reduction in radiotherapy field size or the need for curative radiotherapy.

All 3 single-arm trials (Ally et al. 2014, Bertrand et al. 2021 and Kahana et al. 2021) suggested that most people had a response to vismodegib, and that vismodegib reduced tumour size compared with baseline after up to 12 months of treatment. Ally et al. 2014 showed a statistically significant reduction in the surgical defect area after an average of 4 months of vismodegib (−27%, 95% CI −45.7 to −7.9%, p=0.006) and Bertrand et al. 2021 showed that most people had a response to an average of 6 months of vismodegib treatment; 39/55 (70.9%, 95% CI 59 to 83%). However, these outcomes are compared with baseline, and the lack of a comparator group, small sample sizes, and limited information on whether response rates are associated with a reduction in tumour recurrences means that these findings should be interpreted with caution.

Two studies showed that the surgical procedure was downstaged in most people (44/55, 80%) after an average of 6 months of vismodegib treatment (Bertrand et al. 2021) and that predicted surgical requirements are reduced after up to 12 months treatment with vismodegib (Kahana et al. 2021).

Kahana et al. 2021 showed that successful visual function (a VAWS of 21 or more) was maintained in all people (34/34) with globe and lacrimal drainage system threatening orbital and extensive periocular basal cell carcinoma after up to 12 months of treatment with vismodegib. Mean scores were 44/50 at baseline, 46/50 at 3 months,46/50 at 6 months, and 47/50 at 12 months or post-surgery. One person experienced a major decline in visual function, 5 people had a minor decline in visual function, and 27 people had stable or improved visual function, compared with baseline.

All 3 studies reported relapse rates during a follow-up period. Ally et al. 2014 showed that 1/11 people had a tumour recurrence after 17 months, Kahana et al. 2021 showed that 2/34 people had a recurrence after 2 years, and Bertrand et al. 2021 showed that 16/44 people had a recurrence in a 3-year follow-up period. Some people in Bertrand et al. 2021 and Kahana et al. 2021 did not have surgery following successful treatment with vismodegib. It is not clear from the studies whether these people were more or less likely to have a tumour recurrence therefore limiting the interpretation of the findings. All 11 participants in Ally et al 2014 had curative surgery after vismodegib. The 1 person in Ally et al. 2014 who had a tumour recurrence after 17 months had vismodegib for 2 months (less than the average 4 months in the study) and had twice recurrent basal cell carcinoma at baseline. Further studies with larger samples sizes and longer follow-up periods are needed to understand whether recurrence is associated with treatment duration of vismodegib, and whether the basal cell carcinoma is recurrent or non-recurrent.

Ally et al. 2014 showed that there was no residual basal cell carcinoma in the first piece of excised tissue in 6/13 (46%) tumours and Kahana et al. 2021 found that 18/27 (67%) of people

had a histological response with no sign of disease. However, it was not clear whether histological remission was associated with clinical response or tumour recurrence.

Only one study (Bertrand et al. 2021) reported quality of life outcomes, measured using the Skindex-16 score. The study found that quality of life statistically significantly improved each month, up to 10 months.

Bertrand et al. 2021 showed that, of the 27/55 people who had a complete response to vismodegib, 21 did not receive curative surgery, and Kahana et al. 2021 showed that 7/34 people did not have surgery within the 12-month treatment period. In Kahana et al. 2021, the intention was that all people would have vismodegib for 12 months. People who received surgery within the 12-month treatment period did so because of poor tolerance to vismodegib. In Bertrand et al. 2021, reasons for not receiving curative surgery were not fully described.

All 3 studies found that almost all (11/11, 54/55, 33/34) people had one or more treatment related adverse event and 2 studies showed that 11/55 and 3/34 people had grade ≥3 treatment-related adverse events. Ally et al. 2014 and Bertrand et al. 2021 showed that 4/14 and 7/55 people discontinued vismodegib because of side effects, respectively. All people in Ally et al. 2014 experienced alopecia with 7/11 experiencing less than 50% hair loss (grade 1), and 4/11 experiencing 50% or more hair loss (grade 2). In Bertrand et al. 35/54 (64%) of people had alopecia, 26/35 grade 1 and 9/35 grade 2. In Kahana et al. 2021, 16/34 (47%) of people had alopecia (grade not described).

The duration of vismodegib treatment varied between studies. Average duration was longest in Kahana et al. 2021 (up to 12 months, median 261 days), then Bertrand et al. 2021 (4 to 10 months, median 6.0±2.3 months), followed by Ally et al. 2014 (3 to 6 months, mean 4±2 months). One study provided some evidence to suggest that vismodegib is only effective when taken for at least 3 months. Most people experienced adverse events and the people who discontinued treatment did so because of side effects. The benefits of longer-term treatment with vismodegib should be balanced against the risks.

Locally advanced basal cell carcinoma can be difficult to treat, and current treatment options are limited. Most basal cell carcinomas affect the face and a common site for locally advanced basal cell carcinoma is the eyelid. If the locally advanced basal cell carcinoma extends to involve the tissues and muscles of the orbit, then the only curative surgery is removal of the eye. Other types of radical curative surgery include amputation of the nose and removal of the ear. The findings of this review are important because they suggest that the use of neoadjuvant vismodegib (used before curative surgery) may reduce the scope of curative treatment required. However, interpretation of the data is limited by the lack of comparator group in the single-arm trials, the differences in vismodegib treatment duration, the lack of correlation between clinical cure and histological cure, and the fact that not all participants went on to receive curative surgery.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with locally advanced basal cell carcinoma that is determined as likely to result in significant aesthetic or functional sequelae following curative treatment, and who are suitable or potentially suitable for curative treatment, what is the clinical effectiveness of neoadjuvant vismodegib compared with standard care?
2. In people with locally advanced basal cell carcinoma that is determined as likely to result in significant aesthetic or functional sequelae following curative treatment, and who are suitable or potentially suitable for curative treatment, what is the safety of neoadjuvant vismodegib compared with standard care?
3. In people with locally advanced basal cell carcinoma that is determined as likely to result in significant aesthetic or functional sequelae following curative treatment, and who are suitable or potentially suitable for curative treatment, what is the cost effectiveness of neoadjuvant vismodegib compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from neoadjuvant vismodegib more than the wider population of interest?
5. From the evidence selected, what was the regimen and duration of neoadjuvant vismodegib treatment?

P –Population and Indication	Patients with a diagnosis of locally advanced BCC that is determined as likely to result in significant aesthetic sequelae or functional sequelae following curative treatment and who are suitable or potentially suitable for curative treatment at baseline Subgroups of particular interest: Non-Caucasian ethnicity [The determination of whether curative treatment for a locally advanced BCC would be likely to result in significant aesthetic or functional sequelae, alongside potential suitability for curative treatment, would be determined by MDT assessment prior to commencement on vismodegib. This decision would be guided by frameworks such as the staging criteria proposed by Bertrand et al. 2021 in the VISMONEO study- e.g., those patients that would fall in to Stage A, B or C of this classification system were determined to be eligible for neoadjuvant treatment with vismodegib. Curative treatment includes radical curative surgery and/or radical curative radiotherapy.] [There is no standard definition of locally advanced basal cell carcinoma. Locally advanced disease may also be referred to as advanced, extensive, difficult-to-treat. This list is not exhaustive]
I – Intervention	Neoadjuvant vismodegib [Neoadjuvant treatment may also be referred to as organ-sparing treatment or downstaging treatment.]
C – Comparator(s)	Curative surgery and/or curative radiotherapy OR Best supportive care [Standard care is curative surgery and/or curative radiotherapy or best supportive care]

	[This would be without neoadjuvant treatment for patients suitable for curative treatment and best supportive care for patients unsuitable for curative treatment] [Best supportive care is defined as supportive measures including dressings and pain relief]
O – Outcomes	**<u>Clinical Effectiveness</u>** Unless stated for the outcome, the minimum clinically important difference (MCID) is unknown. <u>*Critical to decision-making:*</u> • **Tumour response** *Response rate is important to patients as it represents whether the treatment can reduce tumour burden.* [Examples include but are not limited to: o Clinical assessment of response which might be assessed by a validated scoring system such as the Response Evaluation Criteria in Solid Tumours (RECIST) or modified RECIST criteria. Other scoring systems are acceptable. Terminology such as complete response or partial response are also acceptable.] • **Downstaging of the surgical procedure and/or reduction in radiotherapy field size** *This outcome is important to patients as it represents a downstaging of the complexity and scope of the curative intervention required. This correlates with a reduction in the extent of surgical resection and/or a reduction in normal tissue toxicity.* • **Organ-specific preservation and function** *This outcome is important to patients as it represents sparing of major aesthetic and/or functional sequelae following curative treatment. For some patients this would include preservation of organs that may otherwise have been excised- e.g., orbital exenteration. Preservation of organ function correlates with an improvement in patients' quality of life.* <u>*Important to decision-making:*</u> • **Relapse Rates** *This outcome is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions.* • **Histological Remission** *This outcome is important to patients because it can indicate that the disease is reducing in severity and prognosis is improved.* • **Quality of life** *Quality of life is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in*

	activities of daily living. Validated tools for general quality of life measurements (e.g., EQ-5D, SF-36, QLQ-OV28 and QLQ-C30) are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. *[Disease specific quality of life measures are also useful for this purpose and include, but are not limited to, the Facial Skin Cancer Index, Skin Cancer Index, the Skin Cancer Quality of Life Impact Tool, Skindex-16 questionnaire.]* • **Did not receive curative surgery and/or curative radiotherapy treatment** *This outcome is important to patients as it captures the number of patients for whom neoadjuvant treatment with vismodegib has removed the need for curative surgery and/or curative radiotherapy altogether. It also captures patients who chose not to, or who remained unable to undergo curative surgery and/or curative radiotherapy following neoadjuvant vismodegib.* **Safety** Safety of vismodegib is important to patients as it reflects the risks involved in taking this medication and allows a risk benefit assessment to be undertaken. It also allows comparison of interventional approaches. [Examples include, but not limited to: • Frequency of adverse events • Frequency of serious adverse events • Frequency of grade 3 or 4 adverse events • Adverse events leading to discontinuation • Treatment related adverse events] **Cost effectiveness**
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, 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	2013- 2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, Epistemonikos, and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials, and case reports were excluded.

Search date: 11 September 2023. Results earlier than 2013 were excluded.

Database: Medline ALL
Platform: Ovid
Version: 1946 to September 08, 2023
Search date: 11th September 2023
Number of results retrieved: 202
Search strategy:

1 vismodegib.tw. (804)
2 erivedge.tw. (35)
3 "gdc 0449".tw. (144)
4 gdc0449.tw. (8)
5 "HhAntag 691".tw. (1)
6 HhAntag691.tw. (1)
7 "r 3616".tw. (0)
8 r3616.tw. (31)
9 "rg 3616".tw. (0)
10 rg3616.tw. (1)
11 "ro 5450815".tw. (0)
12 ro5450815.tw. (0)
13 or/1-12 (943)
14 exp Carcinoma, Basal Cell/ (19746)
15 "basal cell carcinoma".tw. (13421)
16 "basal cell carcinomas".tw. (4246)
17 "basal cell epithelioma".tw. (449)
18 "basal cell epitheliomas".tw. (188)
19 bcc.tw. (9082)
20 bccs.tw. (2377)
21 or/14-20 (29146)
22 13 and 21 (595)
23 VISMONEO.af. (1)
24 NCT02667574.af. (1)
25 "2013-004338-13".af. (0)
26 "2013_36".af. (0)
27 NICCI.af. (96)
28 NCT03035188.af. (1)
29 "2016-002856-26".af. (0)
30 "ADO-EP02".af. (0)
31 ML29328.af. (0)
32 "ADO-EP02(ML29328)".af. (0)
33 VISORB.af. (2)
34 NCT02436408.af. (3)
35 "UMCC 2014.022".af. (0)
36 HUM00082579.af. (0)
37 or/22-36 (692)
38 limit 37 to (english language and yr="2013 -Current") (595)

39 38 not (comment or editorial or guideline or letter or preprint).pt. (520)
40 39 not (animals/ not humans/) (511)
41 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (6624161)
42 ((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (8664698)
43 41 or 42 (11400607)
44 exp Randomized Controlled Trial/ (601038)
45 randomi?ed.mp. (1079317)
46 placebo.mp. (249146)
47 or/44-46 (1145416)
48 43 or 47 (11603689)
49 40 and 48 (202)

Database: Embase
Platform: Ovid
Version: 1974 to 2023 September 08
Search date: 11th September 2023
Number of results retrieved: 591
Search strategy:

1 vismodegib/ (2776)
2 vismodegib.tw. (1308)
3 erivedge.tw. (204)
4 "gdc 0449".tw. (745)
5 gdc0449.tw. (24)
6 "HhAntag 691".tw. (5)
7 HhAntag691.tw. (1)
8 "r 3616".tw. (16)
9 r3616.tw. (37)
10 "rg 3616".tw. (2)
11 rg3616.tw. (1)
12 "ro 5450815".tw. (0)
13 ro5450815.tw. (0)
14 or/1-13 (3133)
15 exp basal cell carcinoma/ (34334)
16 "basal cell carcinoma".tw. (18359)
17 "basal cell carcinomas".tw. (5663)
18 "basal cell epithelioma".tw. (397)
19 "basal cell epitheliomas".tw. (178)
20 bcc.tw. (11710)
21 bccs.tw. (3503)
22 or/15-21 (41372)
23 14 and 22 (1594)
24 VISMONEO.af. (8)
25 NCT02667574.af. (11)
26 "2013-004338-13".af. (0)
27 "2013_36".af. (10)
28 NICCI.af. (152)
29 NCT03035188.af. (10)
30 "2016-002856-26".af. (0)
31 "ADO-EP02".af. (0)
32 ML29328.af. (0)

33 "ADO-EP02(ML29328)".af. (0)
34 VISORB.af. (5)
35 NCT02436408.af. (7)
36 "UMCC 2014.022".af. (0)
37 HUM00082579.af. (0)
38 or/23-37 (1765)
39 limit 38 to (english language and yr="2013 -Current") (1456)
40 39 not (editorial or letter or "preprint (unpublished, non-peer reviewed)").pt. (1315)
41 40 not (nonhuman/ not human/) (1267)
42 40 not (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (993)
43 exp clinical study/ (12137155)
44 exp cohort analysis/ (1044229)
45 exp epidemiology/ (4486025)
46 exp evaluation study/ (97237)
47 exp statistics/ (317522)
48 ((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (10672040)
49 or/43-48 (19177735)
50 random:.tw. (1972416)
51 placebo:.mp. (523986)
52 double-blind:.tw. (244557)
53 or/50-52 (2250617)
54 49 or 53 (19652468)
55 42 and 54 (591)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL
Platform: Wiley
Version:
CDSR –Issue 9 of 12, Month year
CENTRAL – Issue 8 of 12, Month year
Search date: 11th September 2023
Number of results retrieved: CDSR – 0; CENTRAL – 20.

ID	Search	Hits
#1	vismodegib:ti,ab	93
#2	erivedge:ti,ab	6
#3	"gdc 0449":ti,ab	23
#4	gdc0449:ti,ab	1
#5	"HhAntag 691":ti,ab	0
#6	HhAntag691:ti,ab	0
#7	"r 3616":ti,ab	1
#8	r3616:ti,ab	0
#9	"rg 3616":ti,ab	0
#10	rg3616:ti,ab	0
#11	"ro 5450815":ti,ab	0
#12	ro5450815:ti,ab	1
#13	{OR #1-#12}	105
#14	[mh "Carcinoma, Basal Cell"]	450
#15	"basal cell carcinoma":ti,ab	766
#16	"basal cell carcinomas":ti,ab	203
#17	"basal cell epithelioma":ti,ab	0

#18 "basal cell epitheliomas":ti,ab 0
#19 bcc:ti,ab 608
#20 bccs:ti,ab 184
#21 {OR #14-#20} 1193
#22 #13 AND #21 53
#23 VISMONEO 2
#24 NCT02667574 0
#25 "2013-004338-13" 0
#26 NICCI 7
#27 NCT03035188 0
#28 "2016-002856-26" 0
#29 "ADO-EP02" 0
#30 ML29328 0
#31 "ADO-EP02(ML29328)" 0
#32 VISORB 0
#33 NCT02436408 0
#34 "UMCC 2014.022" 0
#35 HUM00082579 0
#36 {OR #22-#35} 60
#37 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 483367
#38 "conference":pt 226442
#39 #36 NOT (#37 OR #38) with Publication Year from 2013 to 2023, in Trials 20
#40 #36 NOT (#37 OR #38) with Cochrane Library publication date Between Jan 2013 and Oct 2023, in Cochrane Reviews, Cochrane Protocols 0

Database: Epistemonikos
Website: https://www.epistemonikos.org/
Search date: 11th September 2023
Number of results retrieved: 34 results for drug/condition search. 2 for trial identifier search.
Search strategies:

Drug/condition search

Searched using title/abstract drop-down menus in advanced search, using separate boxes for drug name and condition, connected with Boolean *AND*:

Title/abstract: vismodegib OR erivedge OR "gdc 0449" OR gdc0449 OR "HhAntag 691" OR HhAntag691 OR "r 3616" OR r3616 OR "rg 3616" OR rg3616 OR "ro 5450815" OR ro5450815

AND

Title/abstract: "basal cell carcinoma" OR "basal cell carcinomas" OR "basal cell epithelioma" OR "basal cell epitheliomas" OR bcc OR bccs

Limited to 2013-2023 using on-screen limits.

Trial identifier search

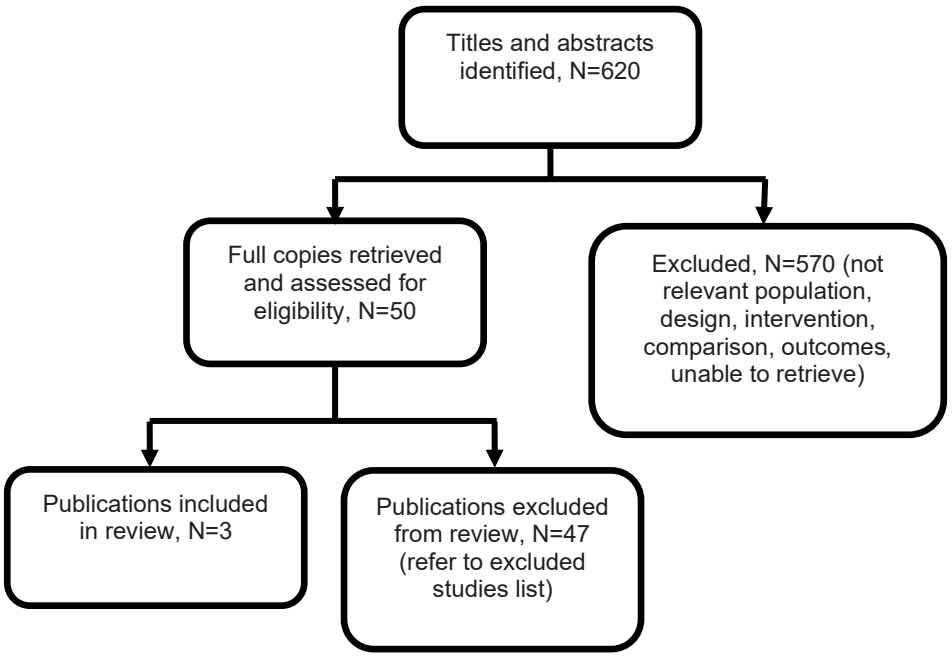
Title/abstract: VISMONEO OR NCT02667574 OR "2013-004338-13" OR "2013_36" OR NICCI OR NCT03035188 OR "2016-002856-26" OR "ADO-EP02" OR ML29328 OR (ADO-EP02(ML29328)) OR VISORB OR NCT02436408 OR ("UMCC 2014.022") OR HUM00082579

Limited to 2013-2023 using on-screen limits.

Appendix C Evidence selection

The literature searches identified 620 references. These were screened using their titles and abstracts and 50 references were obtained in full text and assessed for relevance. Of these, 3 references are included in the evidence summary. The remaining 47 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Bertrand, N. et al. (2021) "Vismodegib in neoadjuvant treatment of locally advanced basal cell carcinoma: First results of a multicenter, open-label, phase 2 trial (VISMONEO study)," EClinicalMedicine, 35, p. 100844. Available at: https://doi.org/10.1016/j.eclinm.2021.100844.	Included
Kahana A et al (2021) Vismodegib for Preservation of Visual Function in Patients with Advanced Periocular Basal Cell Carcinoma: The VISORB Trial. Oncologist. 2021 Jul;26(7):e1240-e1249. doi: 10.1002/onco.13820. Epub 2021 May 31. PMID: 33988881; PMCID: PMC8265335	Included
Ally MS et al (2014) An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma. J Am Acad Dermatol. 2014 Nov;71(5):904-911.e1. doi: 10.1016/j.jaad.2014.05.020. Epub 2014 Jun 11. PMID: 24929884	Included

Appendix D Excluded studies table

Study reference	Reason for exclusion
Apalla, Z.; Papageorgiou, C.; Lallas, A. et al. (2017) Spotlight on vismodegib in the treatment of basal cell carcinoma: An evidence-based review of its place in therapy Clinical, Cosmetic and Investigational Dermatology, 10, 171-177	Publication type - non-systematic/ narrative review
Apalla, Z.; Spyridis, I.; Kyrgidis, A. et al. (2021) Vismodegib in real-life clinical settings: A multicenter, longitudinal cohort providing long-term data on efficacy and safety Journal of the American Academy of Dermatology, 85, 6, 1589-1592	Publication type – letter
Ashraf, D.C.; Vagefi, M.R. (2020) Hedgehog pathway inhibitors for periocular basal cell carcinoma International Ophthalmology Clinics, 60, 2, 13-30	Publication type – narrative review
Basset-Seguin, N.; Sharpe, H.J.; De Sauvage, F.J. (2015) Efficacy of Hedgehog pathway inhibitors in basal cell carcinoma Molecular Cancer Therapeutics, 14, 3, 633-641	Publication type – non-systematic/ narrative review
Belzer, A.; Pach, J.; Mortlock, R.D. et al. (2023) Evaluating the medical management of locally advanced and metastatic basal cell carcinoma: A single institutional retrospective analysis investigating efficacy, safety, and tolerability JAAD International, 11, 174-175	Publication type – letter
Chang, A.L.S.; Atwood, S.X.; Tartar, D.M. et al. (2013) Surgical excision after neoadjuvant therapy with vismodegib for a locally advanced basal cell carcinoma and resistant basal carcinomas in Gorlin syndrome JAMA Dermatology, 149, 5, 639-641	Study type – case report
Ching, J.A.; Curtis, H.L.; Braue, J.A. et al. (2015) The impact of neoadjuvant hedgehog inhibitor therapy on the surgical treatment of extensive basal cell carcinoma Annals of plastic surgery, 74, supplement4, 193-s197	Study design – retrospective, better quality evidence available
Cowey, L.; Chen, C.-I.; Aguilar, K.M. et al. (2022) Real-World Treatment Patterns and Outcomes Among Patients with Basal Cell Carcinoma Following First-Line Hedgehog Inhibitor Discontinuation Dermatology and Therapy, 12, 5, 1211-1224	Intervention – not neoadjuvant
Cox, Kyle F; Margo, Curtis E (2016) Role of Vismodegib in the Management of Advanced Periocular Basal Cell Carcinoma. Cancer control : journal of the Moffitt Cancer Center, 23, 2, 133-9	Publication type – non-systematic/ narrative review
Curragh, David S; Huilgol, Shyamala C; Selva, Dinesh (2021) Neoadjuvant vismodegib in the management of locally advanced periocular basal cell carcinoma. Eye (London, England), 35, 10, 2740-2745	Study design – retrospective, better quality evidence available
De Giorgi, V.; Trane, L.; Pieretti, G. et al. (2021) Treatment of periocular advanced basal cell carcinoma with Hedgehog pathway inhibitors: A single-center study and a new dedicated therapeutic protocol Dermatology Reports, 13, 3, 9240	Intervention – not neoadjuvant
Decker, A.; Nijhawan, R.; Barker, C.A. et al. (2016) Locally Advanced Basal Cell Carcinoma: Management Challenges and Role of Multidisciplinary Approach Clinical Skin Cancer, 1, 1, 30-35	Study type – case report
Erdem, Gokmen Umut; Sendur, Mehmet Ali Nahit; Ozdemir, Nuriye Yildirim et al. (2015) A comprehensive review of the role of the hedgehog pathway and vismodegib in the management of basal cell carcinoma. Current medical research and opinion, 31, 4, 743-56	Intervention – not neoadjuvant

Esmaeli, B.; Sagiv, O. (2019) Targeted biological drugs and immune check point inhibitors for locally advanced or metastatic cancers of the conjunctiva, eyelid, and orbit International Ophthalmology Clinics, 59, 2, 13-26	Publication type – narrative review
Furdova, Alena; Lukacko, Pavol (2017) Periocular Basal Cell Carcinoma Predictors for Recurrence and Infiltration of the Orbit. The Journal of craniofacial surgery, 28, 1, e84-e87	Intervention – not neoadjuvant
Gonzalez, Abel R; Etchichury, Dardo; Gil, Maria E et al. (2019) Neoadjuvant Vismodegib and Mohs Micrographic Surgery for Locally Advanced Periocular Basal Cell Carcinoma. Ophthalmic plastic and reconstructive surgery, 35, 1, 56-61	Study type - better quality evidence available
Gurbuz, Mustafa; Dogan, Izzet; Akkus, Erman et al. (2021) Efficacy and tolerability of vismodegib treatment in locally advanced and metastatic basal cell carcinoma: Retrospective real-life data. Dermatologic therapy, 34, 6, e15122	Intervention – not all neoadjuvant
Hanke, C William; Mhatre, Shivani K; Oliveri, David et al. (2018) Vismodegib Use in Clinical Practice: Analysis of a United States Medical Claims Database. Journal of drugs in dermatology : JDD, 17, 2, 143-148	Intervention – not all neoadjuvant
Heath, M.S.; Bar, A. (2023) Basal Cell Carcinoma Dermatologic Clinics, 41, 1, 13-21	Publication type – narrative review
Hsiao, J.L.; Worswick, S. (2016) Treatment of Giant Basal Cell Carcinoma With Vismodegib Clinical Skin Cancer, 1, 2, 103-105	Study type – case report
Jacobsen, Audrey A; Aldahan, Adam S; Hughes, Olivia B et al. (2016) Hedgehog Pathway Inhibitor Therapy for Locally Advanced and Metastatic Basal Cell Carcinoma: A Systematic Review and Pooled Analysis of Interventional Studies. JAMA dermatology, 152, 7, 816-24	Intervention – not neoadjuvant
Koekelkoren, F.H.J.; Roodbergen, S.L.; Baerveldt, E.M. et al. (2019) Vismodegib for giant, locally advanced, basal cell carcinoma and its complex position in clinical practice JAAD Case Reports, 5, 3, 267-270	Study type – case reports
Mathis, Jason; Doerr, Timothy; Lin, Edward et al. (2019) Oral Hedgehog Pathway Inhibition as a Means for Ocular Salvage in Locally Advanced Intraorbital Basal Cell Carcinoma. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.], 45, 1, 17-25	Study type – non-systematic/ narrative review
Migden, M. (2016) Hedgehog pathway inhibitor therapy in basal-cell nevus syndrome The Lancet Oncology, 17, 12, 1631-1632	Publication type – commentary
Monteiro, A.F.; Rato, M.; Trigo, M. et al. (2019) Aggressive Inferior Eyelid Basal Cell Carcinoma: Advantage of Neoadjuvant Vismodegib: [[es]]Carcinoma basocelular agresivo del parpado inferior: ventaja del vismodegib neoadyuvante Actas Dermo-Sifiliograficas, 110, 10, 863-865	Publication type – letter
Moreiras Arias, N.; Vazquez Veiga, H.; Sanchez-Aguilar, D. (2023) Treatment of locally advanced basal cell carcinoma with vismodegib Medicina Clinica, 160, 9, 413-414	Publication type – letter
Oliphant, H; Laybourne, J; Chan, K et al. (2020) Vismodegib for periocular basal cell carcinoma: an international multicentre case series. Eye (London, England), 34, 11, 2076-2081	Intervention – unclear if neoadjuvant
Patel, A.; Kim, J.S.; Liss, J. et al. (2021) Outcomes of adjunctive therapies post hedgehog inhibitors in the management of locally advanced basal cell carcinoma: A	Intervention – systematic review, some papers not neoadjuvant vismodegib

systematic review and pooled analysis Dermatologic Therapy, 34, 6, e15172	
Patel, Akash D; Ravichandran, Surya; Kheterpal, Meenal (2022) Hedgehog inhibitors with and without adjunctive therapy in treatment of locally advanced basal cell carcinoma. International journal of dermatology, 61, 1, 118-124	Intervention – not all adjuvant
Peillex, D.; Passemard, L.; Magnin, B. et al. (2022) The Role of Surgery After Remission of Nonsystemic Extensive Periorbital Basal Cell Carcinoma Treated by Vismodegib: A Systematic Review Dermatologic Surgery, 48, 9, 905-911	Intervention – not neoadjuvant
Puig, S.; Sampogna, F.; Tejera-Vaquerizo, A. (2016) Study on the Risk of Cutaneous Squamous Cell Carcinoma After Vismodegib Therapy for Basal Cell Carcinoma: Not a Case-Control Study JAMA dermatology, 152, 10, 1172-1173	Publication type - letter
Pulido Prieto, L.; Esguerra Cantillo, J.A.; Toquica Diaz, N.A. et al. (2023) [Translated article] Multimodal Therapy With Vismodegib and Radiotherapy in the Treatment of Locally Advanced Basal Cell Carcinoma: A Series of 4 Cases Actas Dermo-Sifiliograficas, 114, 3, t264-t267	Publication type - letter
Rubben, A.; Hilgers, R.-D.; Leverkus, M. (2016) Hedgehog blockade for basal cell carcinoma coming at a (secondary neoplastic) price JAMA Dermatology, 152, 5, 521-523	Publication type – editorial
Ruiz-Salas, V.; Podlipnik, S.; Sandoval-Clavijo, A. et al. (2023) Real-world experience with vismodegib on advanced and multiple BCCs: data from the RELIVIS study Dermatology (Basel, Switzerland),	Intervention – unclear
Sagiv, Oded; Nagarajan, Priyadharsini; Ferrarotto, Renata et al. (2019) Ocular preservation with neoadjuvant vismodegib in patients with locally advanced periocular basal cell carcinoma. The British journal of ophthalmology, 103, 6, 775-780	Study type - better quality evidence available
Schulze, Bjorn; Meissner, Markus; Ghanaati, Shahram et al. (2016) Hedgehog pathway inhibitor in combination with radiation therapy for basal cell carcinomas of the head and neck : First clinical experience with vismodegib for locally advanced disease. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al], 192, 1, 25-31	Intervention – combination of radiotherapy and vismodegib
Sekulic, Aleksandar; Yoo, Simon; Kudchadkar, Ragini et al. (2022) Real-world assessment and treatment of locally advanced basal cell carcinoma: Findings from the RegiSONIC disease registry. PloS one, 17, 1, e0262151	Study design and outcomes
Shoji, M.K.; Pirakitikulr, N.; Tran, A.Q. et al. (2021) Basal cell carcinoma with extensive periorbital involvement response to vismodegib Orbit (London), 40, 6, 543	Study type – case report
Singalavanija, Tassapol; Ceylanoglu, Kubra Serbest; Juntipwong, Sarinee et al. (2023) Review of Targeted Therapy, Vismodegib, for the Treatment of Periocular Basal Cell Carcinoma. Ophthalmic plastic and reconstructive surgery,	Intervention – systematic review, some papers not neoadjuvant
Sofen, H.; Gross, K.G.; Goldberg, L.H. (2016) Erratum: A phase II, multicenter, open-label, 3-cohort trial evaluating the efficacy and safety of vismodegib in operable basal cell carcinoma (Journal of the American Academy of Dermatology (2015) 73 (99-105)) Journal of the American Academy of Dermatology, 74, 4, 780	Publication type - correction to excluded paper
Sofen, Howard; Gross, Kenneth G; Goldberg, Leonard H et al. (2015) A phase II, multicenter, open-label, 3-cohort trial evaluating the efficacy and safety of vismodegib in	Population – small basal cell carcinomas, not clear if locally advanced

operable basal cell carcinoma. Journal of the American Academy of Dermatology, 73, 1, 99-105e1	
Soon, SL; Ibrahim, SF; Arron, ST (2019) A randomized phase II study evaluating vismodegib as neoadjuvant treatment of basal cell carcinoma preceding Mohs micrographic surgery: results and lessons learned British journal of dermatology, 181, 1, 208-209	Publication type - letter
Tay, E.Y.-X.; Teoh, Y.-L.; Yeo, M.S.-W. (2019) Hedgehog Pathway Inhibitors and Their Utility in Basal Cell Carcinoma: A Comprehensive Review of Current Evidence Dermatology and Therapy, 9, 1, 33-49	Intervention – not neoadjuvant
Tong, Justin; Mitchell, Brandon; Roth, Kathryn et al. (2022) Real-World Experience of Vismodegib in Advanced Basal Cell Carcinoma at a Canadian Cancer Center. Journal of cutaneous medicine and surgery, 26, 2, 143-148	Intervention – unclear if neoadjuvant
Weissman, Joshua P; Samlowski, Wolfram; Meoz, Raul (2021) Hedgehog Inhibitor Induction with Addition of Concurrent Superficial Radiotherapy in Patients with Locally Advanced Basal Cell Carcinoma: A Case Series. The oncologist, 26, 12, e2247-e2253	Intervention – combination of radiotherapy and vismodegib
Velleman, Jos; Kaarela, Outi; Vranckx, Jan J (2021) Treatment of basal cell carcinoma with vismodegib: future or present?. Acta chirurgica Belgica, 121, 3, 198-203	Publication type – non-systematic/narrative review
Wilhelmi, E. (2016) Targeted therapy of advanced basal cell carcinoma: With vismodegib, complete remission also without surgery Journal fur Pharmakologie und Therapie, 25, 3, 97-98	Non-English language
Wong, Kai Yuen; Fife, Kate; Lear, John T et al. (2017) Vismodegib for Locally Advanced Periocular and Orbital Basal Cell Carcinoma: A Review of 15 Consecutive Cases. Plastic and reconstructive surgery. Global open, 5, 7, e1424	Intervention – unclear if neoadjuvant

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Ally et al. (2014) An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma. Journal of the American Academy of Dermatology, 71, 5, 904-911e1 **Study location** USA **Study type** Open-label, single-arm trial **Study aim** "To determine the efficacy and tolerability of short-term preoperative vismodegib to reduce the surgical defect area of high-risk BCCs." **Study dates** April 2012 to July 2013	**Inclusion criteria** Adults with at least 1 biopsy-confirmed BCC of any histologic subtype, more than 5 mm in diameter, eligible for surgical removal. People with previously treated or recurrent BCCs were also included. **Exclusion Criteria** People with congestive heart failure, abnormal liver function test results, elevated lactate dehydrogenase or creatine phosphokinase levels, or pregnant or nursing women. **Total sample size** N=11 No comparator group. **Baseline characteristics** Baseline characteristics are reported for the 11/15 people who completed the trial only and do not include the person who was lost to follow-up or the 3 people who withdrew prior to surgery because of adverse events. Age 39 to 100 years; 6 female, 5 male. Target BCC sites (10/13 on face): cheek (3), nasal tip (1), lower eyelid (1), temple (2), forehead (2), shoulder (1), medial canthus (1), back (1), chest (1); histological type: infiltrative (7), micronodular (1),	**Intervention** Oral vismodegib (150 mg daily) for 3 to 6 months (mean 4±2 months), based on clinical response (one participant received vismodegib for 9 months to further reduce tumour size before surgery) **Comparator** No comparator	**Critical outcomes** **Tumour response** Reduction in the surgical defect area at 3 to 6 months after vismodegib (9 months for 1 person) relative to baseline (%) (n=11, 13 tumours): 27% (95% CI −45.7 to −7.9, p=0.006, range −86 to +33% [Person 1 cheek: −14, nasal tip: −55; Person 2 lower eyelid: −86; Person 3 cheek: −47, temple: −20; Person 4 forehead: −10; Person 5 shoulder: −33; Person 6 medial canthus: −5; Person 7 forehead: +33; Person 8 cheek: −8; Person 9 temple: −7; Person 10 back: −68; Person 11 chest: −28]). People who had <3 months of vismodegib (2/11) had no significant reduction in surgical defect area. **Important outcomes** **Relapse Rates** Mean follow-up 11.5 months, 4 to 21 months after surgery: 1 tumour recurred at 17 months post-surgery. This person had 2 months of vismodegib treatment for a recurrent basal cell carcinoma. **Histological Remission** No residual basal cell carcinoma on the first piece of excised tissue in 6/13 (46%) tumours. Histological cure in tumours that appeared clinically cured: 4/7 (57%) **Safety** Treatment-related adverse events: 11/11 Grade-1: dysgeusia (100%), muscle cramps (100%), fatigue (72%), diarrhoea (9%), weight loss [less than 5% body weight] (45%),	This study was appraised using the National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no (concurrent) control group 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes – for the primary outcome 6. Yes 7. No 8. No 9. No 10. Yes 11. No 12. N/A Quality Rating: Fair Other comments: 15 people met the inclusion criteria and were enrolled in the study. However, only 11 completed the study by having surgery. One person was lost to follow-up, 2 withdrew because of vismodegib-related side effects and 1 withdrew because of unrelated adverse events. These 4 people were not included in the analyses. Source of funding: Supported in part by a Damon Runyon Cancer Research Foundation Clinical Investigator

	nodular/infiltrative (3), superficial (1), nodular (1). Mean tumour diameter 3.2 cm, mean tumour area 12.6 cm^2 (range 1 to 78 cm^2). All target sites were high-risk BCCs (NCCN guidelines), 36% recurrent (previously treated with cryotherapy). Mean tumour diameter: 3.2 cm		depressed mood (18%), reversible amenorrhea (9%). 11/11 had hair loss. 7/11 <50% hair loss (grade 1), 4/11 ≥50% hair loss (grade 2). 4/14 (29%) could not complete more than 3 months of vismodegib because of vismodegib-related side effects (aspartate/alanine aminotransferase elevation, hair loss, fatigue, creatine phosphokinase elevation). 2/15 people withdrew from the trial because of vismodegib-related side effects (elevated creatinine phosphokinase and fatigue)	
Full citation Bertrand et al. (2021) Vismodegib in neoadjuvant treatment of locally advanced basal cell carcinoma: First results of a multicenter, open-label, phase 2 trial (VISMONEO study). EClinical Medicine 100844(35) doi.org/10.1016 **Study location** 17 centres in France. **Study type** Open-label, single-arm trial **Study aim** 'The purpose of the study was to reduce the tumour size of locally advanced basal cell carcinoma of the face by using vismodegib in a neoadjuvant setting and therefore to allow for downstaging of the surgical procedure.' **Study dates** Participants selected for inclusion in the study from November 2014 to June 2015.	**Inclusion criteria** Adults with basal cell carcinoma of the face with a diameter of 2 cm or more in an area of the face with a high risk of recurrence and 3 cm or more in an area with an intermediate risk of recurrence. The study included participants classed as having inoperable basal cell carcinoma (stage A), surgery would cause major functional sequelae (stage B) or minor functional or major aesthetic sequelae (stage C). The surgery classification system was developed in France by centres involved in the study. **Exclusion Criteria** People who did not meet the inclusion criteria. Decided at a multi-disciplinary team meeting. **Total sample size** 55 in intention to treat population, 42 in the per protocol population (participants who had at least 4 months of treatment). No comparator group. **Baseline characteristics**	**Intervention** Oral vismodegib 150 mg once a day for 4 to 10 months (median 6.0±2.3 months). Treatment was reviewed once a month. Treatment was stopped if there was some disease progression, unacceptable toxicity, consent withdrawal, death, or other reasons deemed appropriate. Dose interruption for up to 4 weeks was allowed. **Comparator** No comparator.	**Critical outcomes** **Tumour response** Measured using the RECIST (Response Evaluation Criteria in Solid Tumors) criteria. Median duration of 6 months of vismodegib treatment. 39/55 (70.9%, 95% CI 59 to 83%) people had a response. 14/55 (25.5%, 95% CI 14 to 37%) had a complete response and 25/55 (45.5%, 95% CI 32 to 59%) had a partial response. **Downstaging of surgical procedure** Defined as a downstaging of surgical procedure by at least 1 level of complexity (for example from stage C to stage B) compared to the one assigned at baseline. After 4 months of treatment with vismodegib: 35/42 (85.7%, 95% CI 71 to 95%) had a downstaging of surgical procedure. After a median duration of 6 months of vismodegib treatment: 44/55 (80%, 95% CI 67 to 90%) had a downstaging of surgical procedure. **Important outcomes** **Relapse Rate** After 3 years of follow-up: 16/44 (36%, 95% CI 22 to 51%) people had a recurrence (12/44 lost to follow-up without any	This study was appraised using the National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no (concurrent) control group 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes – for the primary outcome 6. Yes 7. No 8. No 9. Yes 10. Yes 11. No 12. N/A Quality Rating: Fair Other comments: The primary outcome of downstaging of surgical procedure was measured using a classification system developed for the purposes of the study. This classification system is not validated.

	51% male, median age 73 years (range 35.5 to 95.2). Location of basal cell carcinoma: eye (19), ear (8), nose (7), mouth (1), other facial location (20). The mean size of the target lesion was 47.3 mm (SD 27.2 mm). The lesions were classified as stage A (inoperable) (4), stage B (operable with a major functional risk) (15), and stage C (operable with a minor functional risk or a major aesthetic risk) (36). 46 people (84%) had a history of previous surgery for basal cell carcinoma,1 had previous radiotherapy.		known recurrence, 6/44 died without any known recurrence). In people who had a complete response to vismodegib (6/27 had surgery and 21/27 did not) 7/27 had a recurrence (1 died with recurrence). 8 had no recurrence, 9 were lost to follow-up and 3 died without known recurrence. In people who had a response but an incomplete response to vismodegib 9/17 had a recurrence (1 died with recurrence). 2 had no recurrence, 3 were lost to follow-up, and 3 died without known recurrence. In people who did not have a response to vismodegib 7/11 had a recurrence or progression. 3 did not relapse after surgery, 1 person left the study, and 4 people died. **Quality of life** The Skindex-16 score measures quality of life and ranges from 0 (best) to 100 (worst). Improvement (decrease) in Skindex-16 score at each cycle, 28 days each cycle, from baseline up to the 10th cycle: 2.07/cycle ($p<0.0001$) **Did not receive curative surgery and/or curative radiotherapy treatment** At 6 months: 21/55 had a complete clinical response to vismodegib and no surgery. **Safety** Treatment-related adverse events: 54/55 (98.2%). Dysgeusia, muscle spasms, alopecia, fatigue, weight loss (or decrease), diarrhoea, cytolysis, appetite loss (or decrease), arthralgia, constipation, hypogeusia, dyspepsia, hyponatremia, dyspnoea, anaemia, vomiting, pruritus, CPK elevation, oral dryness, cough. Mean adverse events per person: 6.4±3.6. Grade ≥3 treatment-related adverse events: 11/55 (20%)	Source of funding: The Hoffman-La Roche Foundation provided the product (vismodegib) and financial support.

			Dysgeusia, muscle spasms, weight loss (or decrease), cytolysis, dyspepsia, hyponatremia, dyspnoea, anaemia. Discontinuation of vismodegib because of toxicity: 7/55	
Full citation Kahana et al. (2021) Vismodegib for Preservation of Visual Function in Patients with Advanced Periocular Basal Cell Carcinoma: The VISORB Trial. The oncologist, 26, 7, e1240-e1249 **Study location** USA **Study type** Open-label, single-arm trial **Study aim** "to assess whether vismodegib treatment helps to preserve visual organs and function" **Study dates** Enrolment between July 2015 and May 2019.	**Inclusion criteria** Adults with globe- and lacrimal drainage system threatening (within 7 mm of lacrimal apparatus) orbital and extensive periocular basal cell carcinoma. **Exclusion Criteria** Inability to swallow capsules; inability to comply with study protocol; pregnant, lactating, or breastfeeding women; women of childbearing potential, uncontrolled medical illnesses; and dementia or significantly altered mental status that would prohibit the understanding of the protocol. **Total sample size** N=34 (35 tumours) No comparator group. **Baseline characteristics** Mean age 67.1±12.2, 19/34 (56% male). Tumour locations: medial canthus (22), lateral canthus (3), lower lid (8), brow/orbit (2). Median tumour size 21.5 mm (range 10 to 60 mm). 19 people had lesions where complete excision with clear margins would have likely required exenteration. 15 people with lesions that would have qualified for globe-sparing surgery, but to achieve clear margins, the surgery would have resulted in loss of lacrimal	**Intervention** Oral vismodegib 150 mg once a day for up to 12 months or until disease progression or unacceptable toxicity (median treatment duration 261 days). **Comparator** No comparator.	**Critical outcomes** **Tumour response** Complete response (RECIST criteria): 19/34 (56%) people had a complete response by physical examination, and 16/34 (47%) had a complete response by MRI/CT after up to 12 months of vismodegib treatment. Partial response (RECIST criteria): 10/34 (29%) people had a partial response by physical examination, and 9/34 (26.5%) had a partial response by MRI/CT after up to 12 months of vismodegib treatment. Cross-sectional tumour size (% of baseline): 3 months (n=34): 44%, 6 months (n=34): 22%, 9 months (people who had not yet had surgery, n=10): 22%, 12 months (people who had not yet had surgery, n=3): 20% **Downstaging of the surgical procedure and/or reduction in radiotherapy field size** Predicted surgical outcome at baseline: exenteration (19, 56%), globe-sparing (15 [44%], with lacrimal damage [4], extraocular motility damage [1], or both [10]). At study completion: no exenteration, 100%; successful visual function (VAWS), 100%. **Organ-specific preservation and function** Maintenance of visual assessment weighted score (VAWS) of >21 (considered successful) at 12 months or after surgery: 34/34 (100%, p<0.0001). Mean scores: baseline: 44/50, 3 months: 46/50, 6 months: 46/50, 12 months (or postoperatively): 47/50.	This study was appraised using the National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no (concurrent) control group 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes – for the primary outcome 6. Yes 7. No 8. No 9. No 10. Yes 11. No 12. N/A Quality Rating: Fair Other comments: The primary outcome was visual function (measured using the VAWS). The VAWS consists of 8 items related to preservation of visual organs, acuity, extraocular motility, and lacrimal drainage A total score of 21 was considered a positive outcome, because it suggests globe preservation (20 points) and one additional aspect of visual function. Source of funding: Funding for the study was provided in part through an investigator-initiated study grant from Genentech.

	drainage apparatus function (4), extraocular motility (1), or both (10).		1/34 (3%, 95% CI 0.1 to 15.3%) had a major decline in VAWS of 5 points compared with baseline. 5/34 (14.7%, 95% CI 5 to 31.1%) had a minor decline in VAWS of 2 to 4 points compared with baseline. 27/34 (79.4%, 95% CI 62.1 to 91.3%) had a stable or improved VAWS compared with baseline. **Important outcomes** **Relapse Rates** 2/34 people had a tumour recurrence up to 2 years after the end of the study. **Histological Remission** Up to 12 months of vismodegib or after surgery: no sign of disease in 18/27 (67%). **Did not receive curative surgery and/or curative radiotherapy treatment** 7/34 (20.6%) people did not have surgery within the 12-month treatment period. The 27/34 who elected to undergo excision before the 12 months treatment did so because of poor tolerance to vismodegib. **Safety** Treatment-related adverse events: 33/34 (97%) Grade ≥3 treatment-related adverse events: 3/34 (8.8%)	

Abbreviations

BCC, basal cell carcinoma; NCCN, National Comprehensive Cancer Network; RECIST, Response Evaluation Criteria in Solid Tumors; VAWS, visual assessment weighted score

Appendix F Quality appraisal checklists

The National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no (concurrent) control group

1. Was the study question or objective clearly stated?

2. Were eligibility/selection criteria for the study population prespecified and clearly described?

3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?

4. Were all eligible participants that met the prespecified entry criteria enrolled?

5. Was the sample size sufficiently large to provide confidence in the findings?

6. Was the test/service/intervention clearly described and delivered consistently across the study population?

7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?

8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?

9. Was the loss to follow up after baseline 20% or less? Were those lost to follow up accounted for in the analysis?

10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?

11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?

12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Appendix G GRADE profiles

Table 2: Question In people with locally advanced basal cell carcinoma that is determined as likely to result in significant aesthetic or functional sequelae following curative treatment, and who are suitable or potentially suitable for curative treatment, what is the clinical effectiveness and safety of neoadjuvant vismodegib compared with standard care?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Vismodegib	No comparator	Result (95%CI)		
Tumour response (3 single-arm trials)									
Complete response (RECIST v1.1 criteria, after median duration of vismodegib 6 months)									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	14/55	-	14/55 (25.5%, 95% CI 14 to 37)	CRITICAL	VERY LOW
Complete response (RECIST v1.1 criteria, up to 12 months of vismodegib treatment)									
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	N=34	-	Physical examination: 19/34 (56%) MRI/CT: 16/34 (47%)	CRITICAL	VERY LOW
Partial response (RECIST v1.1 criteria, after median duration of vismodegib 6 months)									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	25/55	-	25/55 (45.5%, 95% CI 32 to 59)	CRITICAL	VERY LOW
Partial response (RECIST v1.1 criteria, up to 12 months of vismodegib treatment)									
Single-arm trial 1 study	Serious[1]	No serious	Not applicable	Not calculable	N=34	-	Physical examination: 10/34 (29%) MRI: 9/34 (26.5%)	CRITICAL	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Vismodegib**	**No comparator**	**Result (95%CI)**		
Kahana et al. 2021									
Overall Response Rate (RECIST v1.1, after median duration of vismodegib 6 months)									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	39/55	-	39/55 (70.9%, 95% CI 59 to 83)	CRITICAL	VERY LOW
Mean reduction in the surgical defect area (% reduction from baseline, 3 to 6 months after vismodegib [9 months in one participant], lower value indicates greater benefit)									
Single-arm trial 1 study Ally et al. 2014	Serious[1]	No serious	Not applicable	Not calculable	N=11 (13 tumours)	-	−27% (95% CI −45.7 to −7.9%, p=0.006 Range −86 to +33% Person 1 cheek: −14, nasal tip: −55; Person 2 lower eyelid: −86; Person 3 cheek: −47, temple: −20; Person 4 forehead: −10; Person 5 shoulder: −33; Person 6 medial canthus: −5; Person 7 forehead: +33; Person 8 cheek: −8; Person 9 temple: −7; Person 10 back: −68; Person 11 chest: −28	CRITICAL	VERY LOW
Mean cross-sectional tumour size (% of size at baseline, 3 months)									
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	N=34	-	44%	CRITICAL	VERY LOW
Mean cross-sectional tumour size (% of size at baseline, 6 months)									
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	N=34	-	22%	CRITICAL	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Vismodegib**	**No comparator**	**Result (95%CI)**		
Mean cross-sectional tumour size (% of size at baseline, in the people who had not had surgery at 9 months)									
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	N=10	-	22%	CRITICAL	VERY LOW
Mean cross-sectional tumour size (% of size at baseline, in the people who had not had surgery at 12 months)									
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	N=3		20%	CRITICAL	VERY LOW
Downstaging of the surgical procedure and/or reduction in radiotherapy field size (2 single-arm trials)									
Downstaging of the surgical procedure[A] (ITT population, median duration of treatment 6 months)									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	44/55	-	44/55 (80%, 95% CI 67 to 90%)	CRITICAL	VERY LOW
Downstaging of the surgical procedure[A] (after 4 months treatment with vismodegib)									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	35/42	-	35/42 (85.7%), 95% CI 71 to 95%)	CRITICAL	VERY LOW
Downstaging of the surgical procedure (after up to 12 months treatment with vismodegib)									
Single-arm trial 1 study	Serious[1]	No serious	Not applicable	Not calculable	N=34	-	Predicted surgical outcome at baseline: exenteration (19, 56%), globe-sparing (15 [44%], with lacrimal damage [4],	CRITICAL	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Vismodegib**	**No comparator**	**Result (95%CI)**		
Kahana et al. 2021							extraocular motility damage [1], or both [10]) At study completion: no exenteration, 100%; successful visual function (VAWS), 100%.		
Organ-specific preservation and function (1 single-arm trial)									
Maintenance of VAWS score >21 (Visual Assessment Weighted Score[B], mean VAWS score, score of 21 or more considered successful, at 12 months or after surgery)									
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	N=34	-	34/34 (100%) p<0.0001 (Mean scores: baseline: 44/50, 3 months:46/50, 6 months:47/50)	CRITICAL	VERY LOW
VAWS (major score decline of +5 points compared with baseline)									
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	N=34	-	3% (95% CI 0.1 to 15.3)	CRITICAL	VERY LOW
VAWS (minor score decline of 2 to 4 points compared with baseline)									
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	N=34	-	14.7% (95% CI 5 to 31.1)	CRITICAL	VERY LOW
VAWS (stable or improved score compared with baseline)									
Single-arm trial 1 study	Serious[1]	No serious	Not applicable	Not calculable	N=34	-	79.4% (95% CI 62.1 to 91.3) Note: reported differently in results section of paper (27/33, 82%)	CRITICAL	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Vismodegib**	**No comparator**	**Result (95%CI)**		
Kahana et al. 2021									
Relapse rates (3 single-arm trials)									
Tumour recurrence, mean follow-up 11.5 months (range 4 to 21) after surgery									
Single-arm trial 1 study Ally et al. 2014	Serious[1]	No serious	Not applicable	Not calculable	1/11	-	1/11 people at 17 months post-surgery	IMPORTANT	VERY LOW
Tumour recurrence, 2 years after the end of the study									
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	2/34	-	2/34	IMPORTANT	VERY LOW
Tumour recurrence, 3 years follow-up									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	16/44	-	16/44 (36%, 95% CI 22 to 51%) (12/44 lost to follow-up without any known recurrence, 6/44 died without any known recurrence)	IMPORTANT	VERY LOW
Tumour recurrence in people who had a complete response to vismodegib (6/27 had surgery and 21/27 did not), 3 years follow-up									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	7/27	-	7/27 (1 died with recurrence) (8 had no recurrence, 9 were lost to follow-up and 3 died without known recurrence)	IMPORTANT	VERY LOW
Tumour recurrence in people who had a response but an incomplete response to vismodegib, 3 years follow-up									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Vismodegib**	**No comparator**	**Result (95%CI)**		
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	9/17	-	9/17 (1 died with recurrence) (2 had no recurrence, 3 were lost to follow-up, and 3 died without known recurrence)	IMPORTANT	VERY LOW
Tumour recurrence or progression in people who did not have a response to vismodegib, 3 years follow-up									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	7/11	-	7/11 (3 did not relapse after surgery, 1 person left the study, 4 people died)	IMPORTANT	VERY LOW
Histological remission (2 single-arm trials)									
Histological cure[C] (3 to 6 months after vismodegib [9 months in one participant])									
Single-arm trial 1 study Ally et al. 2014	Serious[1]	No serious	Not applicable	Not calculable	N=11	-	6/13 (46%) tumours	IMPORTANT	VERY LOW
Histological cure in tumours that appeared clinically cured (flat scar with no erythema or nodularity, 3 to 6 months after vismodegib [9 months in one participant])									
Single-arm trial 1 study Ally et al. 2014	Serious[1]	No serious	Not applicable	Not calculable	N=7	-	4/7 (57%)	IMPORTANT	VERY LOW
Histological response. no sign of disease (up to 12 months of treatment or until disease progression or unacceptable toxicity)									
Single-arm trial 1 study	Serious[1]	No serious	Not applicable	Not calculable	18/27		18/27 (67%)	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Vismodegib	No comparator	Result (95%CI)		
Kahana et al. 2021									
Quality of life (1 single-arm trial)									
Improvement (decrease) in Skindex-16 score at each cycle, 28 days each cycle, from baseline up to the 10th cycle									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	N=54		2.07/cycle (p<0.0001)	IMPORTANT	VERY LOW
Did not receive curative surgery and/or curative radiotherapy treatment (2 single-arm trials)									
Complete clinical response and no surgery (after median 6 months treatment with vismodegib)									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	21/55		21/55	IMPORTANT	VERY LOW
Did not have surgery (after up to 12 months treatment with vismodegib)									
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	N=34		7/34 (20.6%)	IMPORTANT	VERY LOW
Safety (3 single-arm trials)									
Treatment-related adverse events									
Single-arm trial 1 study Ally et al. 2014	Serious[1]	No serious	Not applicable	Not calculable	11/11	-	11/11 Grade-1: dysgeusia (100%), muscle cramps (100%), fatigue (72%), diarrhoea (9%), weight loss [less than 5% body weight] (45%), depressed mood (18%), reversible amenorrhea (9%).	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Vismodegib**	**No comparator**	**Result (95%CI)**		
							11/11 had hair loss. 7/11 <50% hair loss (grade 1), 4/11 ≥50% hair loss (grade 2).		
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	54/55		54/55 (98.2%) Dysgeusia, muscle spasms, alopecia, fatigue, weight loss (or decrease), diarrhoea, cytolysis, appetite loss (or decrease), arthralgia, constipation, hypogeusia, dyspepsia, hyponatremia, dyspnoea, anaemia, vomiting, pruritus, CPK elevation, oral dryness, cough. Mean adverse events per person: 6.4±3.6	IMPORTANT	VERY LOW
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	33/34	-	33/34 (97%)	IMPORTANT	VERY LOW
Grade ≥3 treatment-related adverse events									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	11/55	-	11/55 (20%) Dysgeusia, muscle spasms, weight loss (or decrease), cytolysis, dyspepsia, hyponatremia, dyspnoea, anaemia.	IMPORTANT	VERY LOW
Single-arm trial 1 study Kahana et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	3/34	-	3/34 (8.8%)	IMPORTANT	VERY LOW
Discontinuation of vismodegib because of side effects (after 3 months of vismodegib)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Vismodegib**	**No comparator**	**Result (95%CI)**		
Single-arm trial 1 study Ally et al. 2014	Serious[1]	No serious	Not applicable	Not calculable	4/14	-	4/14 (29%) (Aspartate/alanine aminotransferase elevation, hair loss, fatigue, creatine phosphokinase elevation).	IMPORTANT	VERY LOW
Discontinuation of vismodegib because toxicity (after 6±2.3 months of vismodegib)									
Single-arm trial 1 study Bertrand et al. 2021	Serious[1]	No serious	Not applicable	Not calculable	7/55	-	7/55	IMPORTANT	VERY LOW

Abbreviations

CT, computed tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors; VAWS, visual assessment weighted score

A This was defined as a downstaging of surgical procedure by at least 1 level of complexity (for example from stage C to stage B) compared to the one assigned at baseline.
B The VAWS consists of 8 items related to preservation of visual organs, acuity, extraocular motility, and lacrimal drainage A total score of 21 was considered a positive outcome, because it suggests globe preservation (20 points) and one additional aspect of visual function.
C No residual basal cell carcinoma on the first piece of excised tissue.
1 Single-arm trial – no comparator and no blinding of investigators or participants.

References

Included studies

- Ally MS et al (2014) An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma. J Am Acad Dermatol. 2014 Nov;71(5):904-911.e1. doi: 10.1016/j.jaad.2014.05.020. Epub 2014 Jun 11. PMID: 24929884
- Bertrand, N. et al. (2021) “Vismodegib in neoadjuvant treatment of locally advanced basal cell carcinoma: First results of a multicenter, open-label, phase 2 trial (VISMONEO study),” EClinicalMedicine, 35, p. 100844. Available at: https://doi.org/10.1016/j.eclinm.2021.100844.
- Kahana A et al (2021) Vismodegib for Preservation of Visual Function in Patients with Advanced Periocular Basal Cell Carcinoma: The VISORB Trial. Oncologist. 2021 Jul;26(7):e1240-e1249. doi: 10.1002/onco.13820. Epub 2021 May 31. PMID: 33988881; PMCID: PMC8265335

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