PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Vismodegib (Erivedge) for Advanced Basal Cell Carcinoma

January 10, 2014

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the safety and efficacy of vismodegib on patient outcomes compared to standard therapies or best supportive care in patients with metastatic or locally advanced basal cell carcinoma (BCC) inappropriate for surgery or radiotherapy.

Vismodegib is a hedgehog inhibitor and has a Health Canada approved indication for the treatment of adult patients with histologically confirmed metastatic basal cell carcinoma or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

1.2 Key Results and Interpretation

Systematic Review Evidence

The pCODR systematic review included one non-randomized, non-comparative Phase 2 trial, ERIVANCE (Sekulic 2012). The study patients had either metastatic BCC (mBCC, N=33) or locally advanced BCC (laBCC, N=63) and were inappropriate for surgery or radiotherapy. Patients received vismodegib at the approved dose of 150mg orally once daily. No randomized controlled trials are currently available evaluating vismodegib in this patient population.

Patients included in the study had an ECOG of 2 or less. Patients with mBCC had measurable disease (including nodal metastases) according to RECIST criteria. Patients with laBCC had at least one lesion of at least 10mm that was considered inoperable or surgery was considered inappropriate. There were 21 patients (22%) in ERIVANCE with Gorlin syndrome or suspected Gorlin syndrome, all of whom had locally advanced BCC.

Efficacy

The primary outcome of ERIVANCE was independent review committee assessed objective response, defined as a ≥30% reduction in the externally visible or radiographic dimension. Tumours were assessed using physical examination documented by photography at baseline and every 8 weeks.

Objective response rates were higher in the laBCC (27 patients, 43%) than the mBCC cohort (10 patients, 30%), and in each case exceeded the pre-defined criteria for a minimally acceptable response (20% and 10%, respectively). No patients with mBCC had a complete response, while 21% of patients with laBCC had a complete response. Investigator-assessed objective response rates were higher in both the laBCC (38 patients, 60%) and mBCC (15 patients, 45%) cohorts when compared to independent review.[1]

In a post-hoc analysis in the subgroup of patients with Gorlin's syndrome, objective response rate was 67% [95% CI: 45%, 85%] compared to 30% [95% CI: 19%, 46%] in the other 42 patients with laBCC.

Duration of response was a key secondary outcome and was 7.6 months in both the laBCC and mBCC cohorts in ERIVANCE, assessed by independent review.

Overall survival was higher in patients with laBCC, and was approximately 93% in patients with laBCC and 78% in patients with mBCC through all the updates up to 18 months.[2,3] Median progression-free survival as assessed by independent review was 9.5 months in both

cohort. Progression-free survival was longer in the laBCC cohort when assessed by investigators (12.9 months) but was similar to independent reviewers in the mBCC cohort (9.3 months).

Quality of life was not reported in the published reports of ERIVANCE; however, information on SF-36 was collected. There are more specific quality of life instruments available both for cancer and dermatology, and these likely would have been a more appropriate choice for this study. There was also a large amount of missing data in both cohorts, and the lack of a control group, which makes it impossible to interpret these data in the context of BCC.

Harms

Overall, 26 (25%) of patients experienced a serious adverse event. The most common grade 3-4 adverse events were weight loss (5%), muscle spasms (4%) and fatigue (4%).[1] Fatal adverse events were reported in 7 (7%) patients (unknown cause in 3 patients, while the other deaths were due to hypovolemic shock, myocardial infarction, meningeal disease and ischemic stroke). The most common adverse events associated with vismodegib were muscle spasms (68% of patients), alopecia (63%), dysgeusia (51%) and weight loss (46%). AE leading to discontinuation occurred in 13 (12%). The most common reason was muscle spasm, although this only occurred in two patients.[1]

No information was available on dose adjustments.

Additional Evidence

pCODR received input on vismodegib from the following patient advocacy groups, Melanoma Network of Canada and Save Your Skin Foundation. Provincial Advisory group input was obtained from eight of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

An ongoing single-arm safety study that has only been published in abstract form, STEVIE (Reference), was also identified. Efficacy and harms data to-date were consistent with that of ERIVANCE. Information on quality of life and functional outcomes is currently being collected in STEVIE using dermatology-specific quality of life instruments.

Interpretation and Guidance

Burden of Illness and Need

Basal cell carcinoma is the most common cancer in North America and affects about 50,000 to 60,000 Canadians per year.[4,5] Basal cell carcinomas have typically been a disease of the elderly but are becoming more common in younger patients.[3] The incidence has been steadily increasing in Canada, as has the aggressiveness and invasiveness of the phenotypes. BCC accounts for 75% of all non-melanoma skin cancers and 25% of all cancers in North America. Although basal cell carcinomas rarely metastasize they are locally invasive and cause significant tissue destruction and result in significant morbidity. Mutations in the PTCH (Patched gene) pathway (Gorlin's Syndrome) lead to a hereditary nevoid basal cell syndrome.

For metastatic or locally advanced basal cell cancer patients in whom surgery and radiation has been deemed inappropriate, there remain few options. Chemotherapy does

not have a proven benefit in metastatic basal cell carcinoma. Therefore there is a distinct need for new options in these patients.

Effectiveness

The ERIVANCE study met its study objective with an independently reviewed primary response rates observed in both metastatic patients and in the locally advanced BCC patients (30% and 43%, respectively).

Higher response rates were observed in the subgroup of patients with Gorlin's syndrome (67%). The results in this subgroup were also supported by another study that assessed the use of vismodegib in surgically eligible patients with Gorlin's syndrome, which showed that vismodegib resulted in a significant decline in the rate of appearance of new surgically eligible basal cell carcinomas and a reduction in the burden of surgically eligible basal cell carcinomas.[6]

Safety

As of the November 26, 2010 data cut-off approximately half of patients had discontinued treatment with the most common reason in the metastatic patients being disease progression and patient's decision to discontinue (25%) in the locally advanced group. Although a number of serious adverse events were reported, vismodegib can be safely administered. However, adverse events will lead to discontinuation in a significant number of patients.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to vismodegib in the treatment of locally advanced basal cell carcinoma or metastatic basal cell cancer based on the results of a single arm, non-randomized trial that demonstrated objective response in 30% and 43% of patients with metastatic basal cell cancer and locally advanced basal cell cancer, respectively, with a median duration of response of 7.6 months.

The Clinical Guidance Panel made the following clinical conclusions:

- Vismodegib has an acceptable tolerability profile with predictable and manageable toxicities.
- For those patients who develop metastatic disease or for those with locally advanced disease in whom there is no surgical option, vismodegib is a viable option. There are no other acceptable options in this patient population.
- Based on responses observed in patients with Gorlin's syndrome (basal cell nevus), vismodegib should be available to this patient population.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding vismodegib (Erivedge) for advanced basal cell carcinoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website,www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature vismodegib (Erivedge) for advanced basal cell carcinoma conducted by the Melanoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on vismodegib (Erivedge) for advanced basal cell carcinoma and a summary of submitted Provincial Advisory Group Input on vismodegib (Erivedge) for advanced basal cell carcinoma are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Vismodegib targets a novel pathway for drug development, the hedgehog signalling pathway, which plays a key role in embryogenesis and is normally not active in adults. Dysregulation of the hedgehog pathway has been implicated in various cancers, including BCC. Because this is a novel target for drug development, the potential long term harms of this approach has not been established in humans. Due to the limited options available for patients with aBCC, patients anticipate vismodegib to be a significant advance in the management of their condition.

Vismodegib has a Health Canada approved indication for the treatment of adult patients with histologically confirmed metastatic basal cell carcinoma or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

2.1.2 Objectives and Scope of pCODR Review

The objective of this review was to evaluate vismodegib on patient outcomes compared to standard therapies or best supportive care in patients with metastatic or locally advanced basal cell carcinoma (BCC) inappropriate for surgery or radiotherapy. We included non-RCTs in this review because no RCTs are currently available evaluating vismodegib. Most of the key efficacy outcomes reflected those described as priorities by patients, including progression-free survival, quality of life and time to progression. We also included Gorlin syndrome as a subgroup.

2.1.3 Highlights of Evidence in the Systematic Review

One multinational (31 sites in US, Europe, Australia), manufacturer-sponsored study (ERIVANCE) met the inclusion criteria for this review. ERIVANCE lacked a control group, instead enrolling adult patients who had either mBCC (N=33) or laBCC (N=63), who all received vismodegib at the approved dose of 150mg PO once daily. Patients had an ECOG of 2 or less, and those with mBCC had measurable disease (including nodal metastases)

according to RECIST criteria. Patients with laBCC had at least one lesion of at least 10mm that was considered inoperable or surgery was considered inappropriate. Patients were treated until disease progression or unacceptable toxicity. Patients were 61 years of age, and the majority were male. The primary outcome of ERIVANCE was objective response, and the primary objective was to test whether the response rate was greater than 10% among patients with mBCC and greater than 20% among patients with laBCC, as determined with the use of exact binomial one-sided tests. Duration of response was a key secondary outcome.

The lack of a controlled trial is the most significant limitation to this review. The manufacturer described the lack of a comparator in this indication as the reason why there was no comparative trial. Nevertheless, a lack of comparator makes interpretation of outcomes difficult. This is particularly the case for patient-reported outcomes such as quality of life, where knowledge of treatment assignment can significantly bias results.

Objective response rates exceeded the pre-defined threshold for a significant response in both the mBCC (response in 30% of patients) and laBCC (43% of patients) cohorts. There were no complete responses in the mBCC group, and 21% of laBCC patients had a complete response. In a population that has few other options, these response rates appear clinically significant, however without a comparator there is no way to know the true significance of these results. There were 21 laBCC patients (22%) in ERIVANCE with Gorlin syndrome or suspected Gorlin syndrome, and the objective response rate was 67% for these patients, compared to 30% in the other 42 patients with laBCC.

Relatively few patients died in ERIVANCE, thus a median overall survival was not reached. Median progression-free survival was 9.5 months in both cohorts, and time to progression was 7.6 months in both cohorts. Dispersion around the median was not reported.

Quality of life results were not reported in the publication; however, information on SF-36 was collected. There are more specific quality of life instruments available both for cancer and dermatology, and these likely would have been a more appropriate choice for this study. There was also a large amount of missing SF-36 data in both cohorts, and the lack of a control group, which makes it impossible to interpret these data in the context of BCC. Given the significant impact of BCC on quality of life, the lack of quality of life data, and the lack of a trial that could properly assess quality of life is a notable gap in evidence. Proportion of patients with a dose adjustment was also not reported.

Serious adverse events were experienced by 25% of patients, and there was no clear pattern of serious events. The most common adverse events were muscle spasms (68% of patients) and alopecia (63%), and 12% of patients withdrew due to an adverse event. The most common grade 3-4 events were weight loss (5%), muscle spasms (4%) and fatigue (4%). Alopecia is commonly associated with cancer therapies; however muscle spasms are an unusual adverse effect that appears to reflect targeting of this novel pathway.

2.1.4 Comparison with Other Literature

STEVIE is an ongoing safety study that has only been published in abstract form, and thus was not included in this systematic review. Two updates have been reported as abstracts, one after 150 patients had at least 3 months follow-up, and the other when 300 patients had this much follow up.[7,8] Efficacy results focused on objective response, and this data was consistent with that of ERIVANCE, particularly after 300 patients had been followed. Safety results were also consistent, with similar harms occurring most commonly as adverse events. Information on quality of life and functional outcomes is currently being collected in STEVIE using more specific quality of life instruments. However, interpretation

of these data would still be limited by the lack of control group and the bias associated with patients being aware of their treatment allocation since STEVIE is a single-arm non-randomized study.

2.1.5 Summary of Supplemental Questions

No Supplemental questions were identified for this review.

2.1.6 Other Considerations

Patient Advocacy Group Input

Patients identified quality of life as an important outcome for them, yet ERIVANCE was not designed to able to establish whether vismodegib is able to improve quality of life. Without a comparator, there is no way to determine whether changes in quality of life are attributable to vismodegib or to random chance. Also, the instrument used to assess quality of life in ERIVANCE was a generic instrument (SF-36), not one specific to either cancer or to dermatology. Physical appearance was identified as a key issue with BCC, both due to the lesions themselves and scarring associated with surgeries and radiation used to remove/shrink them. All 13 patients providing input had experience with surgeries. Most of these patients also had tried photodynamic therapy, and a few had tried radiation for their BCC. At least 5/13 patients had experience with topical creams such as Aldara, Effudex or Tazorac, and a few patients (3/13) had tried an oral agent such as 5-FU or celecoxib. Patients also identified disease progression as a concern, as well as side effects. Ease of administration was considered to be a positive for vismodegib, and patients noted that their condition had stabilized without progression, another positive. Patients noted experiencing side effects, including serious side effects from various interventions, but also appeared willing to accept side effects and potential risk associated with a brand new drug like vismodegib if they know these can be effectively managed.

PAG Input

PAG noted that there is currently no standard of care for BCC, and therefore vismodegib may fill a therapeutic gap. Other potential comparators for cases of BCC not amenable to surgery may be radiation or topical therapies like fluorouracil or imiquimod. PAG also noted that the funding request closely aligns with inclusion criteria of the key clinical study that is patients with aBCC for whom surgery is inappropriate. They also noted that the small number of patients afflicted with aBCC may be an enabler for implementation of a funding recommendation. PAG also noted the enabling aspect of an oral route of administration, but also noted that there is variation among jurisdictions in the way that oral anticancer agents are covered versus those administered intravenously. With respect to dosing, PAG noted the limitation of only having one dose available, and that dose reduction may therefore not be possible. They also noted that the short treatment duration of 10 months would be an enabler; The dosing recommendations in the Product Monograph suggest vismodegib should be given until disease progression or unacceptable toxicity, although the median treatment duration in the Phase 2 ERIVANCE study was about 10 months and a number of patients discontinued treatment early. PAG also questioned whether testing for hedgehog signalling alteration would be to be carried out, as >90% of BCC patients have the alteration. Finally, PAG noted the limitations associated with relying on a single arm study as the pivotal registration trial, including added uncertainty surrounding cost effectiveness.

Other

- Vismodegib targets the hedgehog signalling pathway, a novel approach for drug development. As the first drug approved in a brand new class, there may be some additional uncertainty regarding long term side effects of this pharmacological approach. Clinical trial experience with vismodegib in aBCC is limited to single arm studies, making it difficult to assess the short term safety of vismodegib in this indication.
- Due to the key role of the hedgehog signalling pathway in embryogenesis, vismodegib is contraindicated in pregnancy. Males must also be warned that vismodegib can be transmitted through semen; therefore they should also use contraception while on vismodegib. Mothers should also not attempt to breastfeed during treatment and for 24 months after their last dose, due to the risk of serious developmental defects. The manufacturer has set up the Erivedge Pregnancy Prevention Program, which is an ongoing monitoring and pregnancy prevention program. Vismodegib is only available through this program, and only prescribers and pharmacists registered with the program are allowed to prescribe/dispense this drug.
- The lack of a comparator trial limits any conclusions that can be drawn regarding efficacy or safety of vismodegib. This is particularly the case for patient-reported outcomes such as quality of life.
- STEVIE is an ongoing study that was not included in this review because it is a non-randomized, non-comparative study that has not yet been fully published. The design of STEVIE is similar to ERIVANCE, in that it does not have a control group, and includes patients with laBCC and mBCC. The only reports of STEVIE appear as abstracts, and interim analyses have been published twice, with the latest including 300 patients with laBCC or mBCC. According to the manufacturer, results from STEVIE should be made available sometime in 2014.

2.2 Interpretation and Guidance

Burden of Illness and Need

Basal cell carcinoma is the most common cancer in North America and affects about 50,000 to 60,000 Canadians per year.[4,5] It accounts for 75% of all non-melanoma skin cancers and 25% of all cancers in North America.[9] Risk factors include UV radiation, immune suppression, ionizing radiation and mutations in tumour suppressor genes. Mutations in the PTCH pathway (Gorlin's Syndrome) lead to hereditary nevoid basal cell syndrome. Although basal cell carcinomas rarely metastasize they are locally invasive and cause significant tissue destruction and result in significant morbidity. The incidence has been steadily increasing in Canada, United States, Finland and Australia. In addition there is also an increase in the aggressive, invasive phenotypes. Basal cell carcinomas have typically been a disease of the elderly but are becoming more common in younger patients.[5,10] For metastatic or locally advanced basal cell cancer patients in whom surgery has been deemed inappropriate, there remain few options. Treatment modalities such as radiation or aggressive surgery would be an option in many of these patients but the cosmetic outcomes are unacceptable. Therefore there is a distinct need for new options in these patients.

Effectiveness

The trial by Sekulic et al[1] (ERIVANCE) enrolled 33 patients with metastatic basal cell carcinoma and 71 patients with locally advanced basal cell carcinoma. The primary objective was to test whether a response could be achieved in 10% and 20% of patients with metastatic basal cell carcinoma and locally advanced basal cell carcinoma, respectively. The study met its objective with an independently reviewed primary response rate in 30% of patients (95% CI 16 to 48, p=0.001) in the metastatic group, and a median duration of response of 7.6 months. In the locally advanced basal cell patients, there was an independently reviewed objective response rate in 43% of patients (95% CI, 30 to 56, p<0.001), and a complete response rate in 21% of patients. The median duration of response was 7.6 months. In both groups response rates were deemed to be higher by the investigators, and some patients had criteria for response rate but were not confirmed, and therefore were not included as a response.

In a post-hoc analysis in the subgroup of patients with Gorlin's syndrome, objective response rate was 67% [95% CI: 45%, 85%] compared to 30% [95% CI: 19%, 46%] in the other 42 patients with laBCC. The results in this subgroup were also supported by another study that assessed the use of vismodegib in surgically eligible patients with Gorlin's syndrome.

Tang et al[6] reported a randomized double blind, placebo controlled study on the use of vismodegib in patients with basal cell nevus syndrome who are eligible for surgery. In 41 patients randomized to vismodegib and treated for a median of 8 months there was a significant decline in the rate of appearance of new surgically eligible basal cell carcinomas and a reduction in the burden of surgically eligible basal cell carcinomas. As of January 31, 2012, 54% of patients had discontinued vismodegib due to adverse events. All patients who had discontinued vismodegib developed a recurrence, even at sites of a complete response. Of particular note, the patient population in this study differed from the ERIVANCE study, which only included patients inappropriate for surgery. In clinical practice, patients who are appropriate for surgery would be managed differently than those who are inappropriate for surgery.

Safety

As of the data cut-off approximately half of the patients had discontinued treatment. The most common reason for discontinuation in the metastatic patients was disease progression, and in the locally advanced group patient's decision accounted for 25% of discontinuations. Adverse events of grade 1 or 2 occurred in 57% of patients, and 12% of patients withdrew from study due to adverse events. The most common grade 3 or 4 adverse events were muscle spasm, weight loss, fatigue, loss of appetite, and alopecia. Grade 5 adverse events were reported in 7 patients and included death from unknown cause in 3 patients, myocardial infarction, ischemic stroke and meningeal disease.

Quality of Life was measured in ERIVANCE using a generic HRQofL tool SF-36 however the lack of a control group, the use of a generic assessment tool, and missing data make a proper assessment of Quality of Life difficult.

Although basal cell carcinoma is a common malignancy the majority of patients present with localized, surgically resectable disease**.** For the 1% of patients who develop metastatic disease or the patients with locally advanced disease, the treatment options were limited. Chemotherapy does not have a proven benefit in metastatic basal cell carcinoma. There is therefore a need for new drugs to offer acceptable treatment options for these patients. Vismodegib can be safely administered; however, adverse events will lead to discontinuation in a significant number of patients. The median duration of

treatment in the study was less than 8 months with patients discontinuing due to disease progression or adverse events.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to vismodegib in the treatment of locally advanced basal cell carcinoma or metastatic basal cell cancer based on the results of a single arm, non-randomized trial that demonstrated objective response in 30% and 43% of patients with metastatic basal cell cancer and locally advanced basal cell cancer, respectively, with a median duration of response of 7.6 months.

The Clinical Guidance Panel made the following clinical conclusions:

- Vismodegib has an acceptable tolerability profile with predictable and manageable toxicities.
- For those patients who develop metastatic disease or for those with locally advanced disease in whom there is no surgical option, vismodegib is a viable option. There are no other acceptable options in this patient population.
- Based on responses observed in patients with Gorlin's syndrome (basal cell nevus), vismodegib should be available to this patient population.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Melanoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Basal cell carcinoma (BCC) is the most common cancer in men and accounts for 75% of all non-melanoma skin cancer.[11] BCC is a malignancy derived from the non-keratinizing cells that form the basal layer of the epidermis. Tumour size can be quite variable from a few millimeters to several centimeters and tends to invade locally and rarely to metastasize distantly. BCC is principally a disease of the elderly but has been increasingly common detected amongst younger patients.[10] BCC generally develops on sun exposed skin and other risk factors include male sex, light hair, northern European ancestry, and the inability to tan. Seventy percent of cases occur on the head, frequently on the face, whereas 25% occur on the trunk and limbs and 5% in the perineal region.[12]

The greatest risk of BCC results from local invasion. Generally it is a slow growing tumour with a doubling rate between 6 months to 1 year. However, left untreated, BCC may invade into the subcutaneous tissue, muscle and bone. Direct extension into the central nervous system can also occur. Perineural invasion is uncommon in BCC but does infer a more aggressive phenotype which is associated with more extensive invasion and with more frequent recurrences.[13] In BCCs occurring in the periocular region, perineural progression can lead to invasion of the orbital structures and result in pain, paresthesias, motor weakness and blindness.[14]

Metastasis of BCC is rare with rates of 0.0028 to 0.55%. Most common sites of metastatic spread are lymph nodes and lungs.[15] Squamous differentiation may be present in the primary or metastatic sites and may contribute to the aggressive phenotype in these rare cases.

3.2 Accepted Clinical Practice

The principal modality of therapy is surgery. Curettage and electric dissection are commonly employed with cure rates up to 98%.[16] However, for larger BCCs surgical excision offers the most potential for margin control and often optimal cosmetic results. In order to achieve local control, adequate surgical margins are required. Clear surgical margins may be difficult to achieve and still maintain acceptable cosmesis and can be particularly challenging in eradicating extensive BCCs involving the face.[17]

Radiotherapy (RT) is also commonly utilized and has the advantage of sparing normal tissue and may reduce the need for reconstructive surgery. However, in some sites such as the nose, ear and periocular regions, collateral normal tissue damage may occur. RT remains an option for poor surgical candidates but higher failure rates may occur in large, recurrent and aggressive subtypes of BCCs. RT can also be used in the palliation and the debulking of tumours which are otherwise inoperable. Adjuvant post-operative RT may also be considered in cases when risk of recurrence is high.[18]

Chemotherapy has been used to manage both metastatic and uncontrolled locally advanced BCCs.[19] However, the results have been very disappointing. Patients with metastatic BCC have a life expectancy of 10-20 months, which is dependent upon the sites and extent of disease and

the overall patient performance status.[20] Cisplatin based chemotherapy has been utilized to provide some attempt at local or systemic control. There is no standard chemotherapy regimen and treatment with chemotherapy is essentially palliative in nature. The toxicity and potential palliative benefit must be carefully weighed for each individual patient.

The hedgehog signal pathway appears to be critical in the pathogenesis of basal cell carcinomas.[21] At least 90% of BCCs appear to have an acquired aberrant activation of the pathway. Linkage analyses have identified a locus on chromosome 9 which is deleted in sporadic BCC.[22] The locus encodes for PTCH1, a transmembrane receptor which inhibits smoothened (SMO) signaling and the downstream activation of cellular proliferation.[23] Because abnormalities in the Hedgehog signaling pathway are common in sporatic cases of BCC, routine testing to determine the precise nature of the signaling aberration is not recommended for clinical practice. However, testing may prove helpful in the future in characterizing intrinsic and acquired resistant to a Hedge Hodge Inhibitor such as vismodegib.

In Basal Cell Nevus Syndrome (BCNS) or Gorlin Syndrome, an inherited autosome dominant condition, the gene on chromosome 9 which encodes PTCH1 is mutated which leads to loss of autoregulation of SMO.[24] These individuals have increased sensitivity to ionizing radiation and develop hundreds of basal cell carcinomas particularly in sun exposed areas over their lifespan. BCNS was first described by Gorlin and Goltz in 1960 and has a prevalence estimation of 1 in 56,000 or 1 in 164,000.[25] BCNS has characteristic clinical features which also include palmoplantar pits, odontogenic cysts, skeletal abnormalities, and development of medulloblastoma. The associated BCCs begin to appear in puberty and occur throughout a lifetime. The BCCs can number from a few to thousands and primarily affect the face, back and chest. Because patients with BCNS have an intrinsic inability to repair DNA damage, RT is contraindicated and may induce more tumour development. Consequently, surgery has been the only treatment option and has involved hundreds of procedures on multiple sites for any affected individual. The morbidity of multiple surgical procedures has been considerable and an alternate approach to management is sorely needed.

3.3 Evidence-Based Considerations for a Funding Population

Although locally advanced BCC and metastatic BCC are relatively rare disease states, they lead to significant morbidity in patients. In those patients with locally advanced and multiply recurrent disease, the primary goal of therapy is local control and not overall survival. Especially of lesions on the face and distal extremities, an additional therapeutic goal is to maintain or optimize organ function. In some cases of advanced local disease, extensive surgical resection may not be technically possible. Furthermore, resection may involve removing vital structures such as the orbits, facial and cranial bones, and would result in significant deformity and functional impairment. Moreover, in cases where recurrent disease occurs, further radiotherapy may not possible and the goal of obtaining clear surgical margins may be impossible to achieve. En bloc resection may be technically very difficult and may still not lead to complete tumour eradication.

Patients with metastatic or locally advanced disease have very limited systemic treatment options. Chemotherapy appears to offer little therapeutic value and has not been shown to be clinically efficacious in any controlled studies of this uncommon indication. Locally advanced or metastatic BCC most commonly occurs in older population which often has significant comorbid illnesses which further limit the palliative benefit of systemic chemotherapy. An alternate option is greatly needed for these patients.

The earliest clinical evidence of an alternate was is the phase 1 trial of the novel SMO inhibitor vismodegib (CDC-0449), a small molecule which binds to SMO and thereby inhibits activation of

downstream hedgehog target genes.[26] Early indications of activity in the first 2 patients with advanced BCC lead to opening the study to an additional 31 patients with advanced BCC. The overall response rate was 55% which included 16 partial and 2 complete responses. A dose of 150 mg a day appeared to be well tolerated but was associated with adverse effects of hyponatremia, abdominal discomfort and fatigue.

The efficacy of vismodegib was further evaluated in the multicenter ERIVANCE trial which included 33 patients with metastatic BCC and 63 patients with locally advanced disease.[1] Sekulic et al reported a tumour response rate of 30% in the metastatic disease cohort and a response rate of 43% in the locally advanced group. Adverse events were common and generally mild and included muscle spasms, dysgeusia, weight loss and fatigue. The median progression-free survival was 9.5 and 11.3 months respectively. The details of this study and the on-going open access international study, STEVIE, are discussed in detail in Section **.

Although Hedgehog pathway inhibition with vismodegib appears to result in improved tumour control, it has not yet shown to be curative. Mechanisms of resistance have yet to be further explored and managed. The identification and management of acute and chronic toxicities also require additional evaluation as clinical experience grows in the treatment of increasing numbers of patients around the world. Experience with dose modification is also very limited. Alternations have primarily consisted of dose interruptions of variable duration. The optimal duration of therapy for cases of locally advanced or metastatic disease remains unknown.

The selection of suitable patient requires a multidisciplinary approach. Both surgical and radiotherapy options need to be clearly delineated. The risks and morbidity associated with all potential modalities of treatment must be carefully considered on a case by case basis.

3.4 Other Patient Populations in Whom the Drug May Be Used

Patients with BCNS are often subject to hundreds of surgical procedures to remove lesions throughout their skin. Because of the intrinsic defect in DNA repair, radiotherapy is contraindicated. Some disease control can be achieved with photodynamic therapy but multiple repeat treatments with considerable skin toxicity is required. Because the abnormality represents a somatic mutation, the propensity to develop BCC is life long and therefore treatments need to be given repeatedly throughout their life span. Vismodegib specifically inhibits SMO which is activated in BCNS and therefore offers a targeted therapeutic option for BCNS patients.

Because vismodegib is associated with high response rates, an obvious potential strategy for the management locally advanced BCC would be utilize vismodegib in a neoadjuvant context. By administering vismodegib pre-operatively, one could potentially reduce the tumour volume so that the extent of the surgical procedure required to eradicate the tumour could be more limited. Thereby, the surgical morbidity and functional impact could be reduced while potentially preserving long-term disease control. However, this strategy has not yet been tested in clinical trials. The selection of suitable candidates and the optimal duration of pre-operative treatment has not yet been explored nor have the long term disease control rates have been reported. Until this corroborative evidence is available, it is possible that dermatologists and surgeons may want to start incorporating neoadjuvant vismodegib into clinical practice.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group(s) provided input on vismodegib (Erivedge) for advanced basal cell carcinoma and their input is summarized below:

- Melanoma Network of Canada
- Save Your Skin Foundation

4.1 Condition and Current Therapy Information

Two patient advocacy groups provided input on vismodegib (Erivedge) for the treatment of adult patients with histologically confirmed metastatic basal cell carcinoma ("BCC") or with locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy, which is summarized below.

- Melanoma Network of Canada ("MNC")
- Save Your Skin Foundation ("SYSF")

The MNC conducted an anonymous questionnaire to gather information about the patient and caregiver experiences related to vismodegib. The survey was distributed through the BCCNS Life Support Network and advertised through their discussion forum; as well as distributed through a weekend conference hosted by the BCCNS Network. The survey consisted of four (4) parts: Part I requested information about patients' experience with metastatic basal cell carcinoma / BCC Nevus Syndrome (BCCNS) as well as their (prospective) thoughts about any future drug therapy (total of 13 respondents); Part II requested retrospective information from patients and caregivers who have had direct experience vismodegib (total of 5 respondents); and Part III and IV requested feedback from caregivers who had experiences with caring for someone with BCCNS and who had experience caring for someone with BCCNS who has taken vismodegib (total of 5 respondents).

The Save Your Skin Foundation conducted one on one interviews with a number of patients with advanced BCC, which included some respondents who were not taking Vismodegib and some that received the Vismodegib.

From a patient perspective, based on the survey and interviews conducted, the groups noted that current therapies have proven to be ineffective at stopping disease progression and have severe side-effects leading to decreased quality of life, loss of income and mental health challenges, including the negative impact on their caregivers and children. Respondents who have experience with vismodegib reported that side effects were mild or moderate and included muscle cramps, some hair loss, weight loss, irregular liver test results and change in taste. Respondents were willing to accept side effects and the serious risks associated with a future new drug, such as vismodegib, if they know those side-effects can be effectively managed. According to the survey conducted by the MNC, 80% of the respondents also noted they would be willing to take all the necessary steps to manage those side-effects. Positive effects were ease of administration as it was taken at home and allowed the patients to avoid repeated surgeries and visits to the hospital. More importantly, respondents who have taken vismodegib reported that their condition had stabilized without progression, many for the first time in their lives. The patient advocacy groups believe that vismodegib is a very important option for BCCNS patients.

Please see below for a summary of specific input received from the patient advocacy group.

4.2 Condition and Current Therapy Information

4.2.1 Experiences patients have with Advanced BCC

Melanoma Network of Canada ("MNC") indicates that basal Cell Nevus Syndrome or Nevoid Basal Cell Carcinoma Syndrome ("BCCNS") is a genetic disorder affecting one in 40,000 that may affect all systems of the body, and affected individuals have a 90% risk of developing multiple basal cell skin cancers. MNC submits that to date there have been very few effective treatments for this disorder and no approved therapies in Canada that appear to stop its progression.

The Save Your Skin Foundation ("SYSF") reports the aspects of disease that were important to respondents to control include the side effects of radiation and the scars from surgery to remove BCC, as these greatly impacted the physical appearance of the patient. It was reported that, as these respondents were greatly impacted by the physical appearance of the scars. Some of the ongoing symptoms that affect the day-to-day life of the respondents include various psychological effects (e.g., fear, anxiety and depression). The respondents noted experience having moderate to severe emotional distress as a result of BCC. In addition, respondents reported certain limitations that included being unable to continue employment.

Respondents report that they face the certainty of disease progression including ongoing advancement of basal cell carcinomas despite repeated surgeries, radiation and courses of medication. Some of the comments from patients include:

- *I never get done paying for treatments, bandages, topicals. I seldom get invited to attend friends social functions due to my grotesque facial features including scaring, open wounds, frequent recovery periods, facial distortion. I tire easily and feel that people shun me. As a child growing up, I was teased & taunted, which is now referred to as "bullying".*

- *My BCCs have spread from my neck and back to my chest, lung and muscle. I have lost my left ear and hearing on my left side and cannot keep a job. I am very weak, tired and in pain.*

- *The number of appointments with dermatologist and all that it entails, i.e. freezing, scraping, burning = scars that it will leave behind, time off work. The "look" people will give you. Effect that it has on my boys…but what hurts most is seeing my son who inherited this disease having to go through the same thing.*

From a patient perspective, new targeted therapies, such as vismodegib, provide a measure for patients to stop disease progression, and to experience a good quality of life.

4.2.2 Patients' Experiences with Current Therapy for Advanced BCC

According to the MNC survey, it was reported that all 13 respondents had experience with surgeries including curettage, excisions, freezing with liquid nitrogen, MOHS surgery, skin grafts and cryosurgery. Most had also tried photo dynamic therapy (PDT) and a few had tried radiation to control their BCCs. At least 5/13 of the patients surveyed had had experience with topical creams such as Aldara, Effudex or Tazorac. A few patients (3/13) had experience with an oral medication such as 5 FU (Flourouracil) or Celebrex. One patient had tried interferon and one reported having been on a clinical trial.

Overall one of the biggest side-effects from these treatments was depression and the psychological impact from constant surgeries, hospital stays, time off work or inability to work and disfigurement. The treatment most extensively reported on by the 13 respondents as having severe and debilitating side-effects were the often multiple and repeated surgeries. The side-effects from surgery reported on by the 13 respondents include scars, loss of use of limbs, chronic pain, distorted features, disfigurement, infection, long healing times, muscle spasms and inability to be active in the short-term and often times in the long-term. It was reported that PDT caused blistering and oozing for weeks. The side-effects from Aldara and other prescription topical creams included nausea and vomiting, depression and fatigue.

Most respondents noted direct experience with the serious and severe side effects of therapies currently available; however, the survey results indicate that 100% of the respondents were still willing to accept side effects and the serious risks associated with a future new drug (such as vismodegib) if they know those side-effects can be effectively managed. 80% of the respondents also said they would be willing to take all the necessary steps to manage those side-effects.

Of the 13 respondents surveyed, 6 reported difficulties with accessing current treatments. More specifically, patients reported that they had long wait times or had to go to the US for treatment because it was not available in Canada (e.g. Photo Dynamic Therapy or clinical trials). Below were comments from a few of the patients that were surveyed:

- *We really had to fight with and be insistent to get support from Ontario health programs. Not all doctors have PDT; I've even gone to the USA for treatment I could not get here including MOHS. They can't keep up with the BCC and it only gets worse. I had to wait for some to get through clinical trials. Not everyone has the right equipment to perform PDT.*

- *I had a lot of difficulty accessing treatment for the wide-area ALA-PDT that I needed to control hundreds of bcc skin lesions. Originally I tried to go to Buffalo where there was a wide-area ALA-PDT treatment clinic that would treat children, but the Ontario Health government said that they would not pay for me to go there and get treated. There is only one centre in Canada that provides wide-area ALA-PDT and I have to travel to London, Ontario when I need to get that treatment. I have been doing that, with my Mom, for the past 10 years now, once and sometimes twice a year.*

In addition to the above, 90% of respondents interviewed by the SYSF were not able to get on a clinical trial for vismodegib and were disappointed that there were not more trials in Canada opened. Respondents noted that they would be willing to travel in order to obtain the treatment.

The SYSF also reported that the therapies that exist are not current. Moreover, there is a concern that the psychological aspect is not taken into consideration. One respondent stated, "*I feel that current therapy ignores the effects of BCC surgeries and the psychological toll that this diagnosis takes on a person*."

4.2.3 Impact of Advanced BCC and Current Therapy on Caregivers

MNC reports that the impact of BCCNS on caregivers is significant. MNC notes that caregivers provide supportive care to the patient in managing adverse side-effects, providing emotional support, having to make-up for loss of income of the ill spouse, and

assuming additional unpaid work duties in the home. A caregiver's paid work and community and social involvement are adversely affected by the physical requirements, time commitments, and emotional stress of caring for a patient with BCCNS. The following are comments from caregivers who participated in Part III of the survey:

- *I care for my son and daughter who both have BCCNS. We spend all of our vacations getting treatments, surgeries, while trying to take care of the oral cysts surgeries. My wife is exhausted and she works a night job so she can get the kids to their doctor's appts. I have been passed over for promotions at work which would require more face to face contact with business customers and clients which reduces my ability to provide income for my family.*

- *I not only have BCC's but care for my mother with it. She has dozens and no longer wants people to see her. She is reclusive due to the stares, remarks and giving up to this disease. Surgery is no longer tolerable. She deserves a more comprehensive treatment. My life is devoted to taking us to office visits, bandages, cleaning, packing and trying to stay afloat. She is totally dependent on me and severely debilitated. The surgeries have affected her vision, given her severe neuropathy, and diminished her life.*

- *The syndrome requires multiple surgeries on an annual basis. Challenges include taking the patient to & from surgical visits which means time away from work. Post-op tending of wounds (cleaning, dressing, bandaging etc.). Dealing with the anxiety, apprehension, depression, moodiness etc. of the patient when faced with seemingly unending surgeries, scars and the fear of even worse outcomes.*

- *In our household our 18 year old son is the BCCNS patient, and has been since the age of 4. For the last 12 years he has undergone various treatments and surgeries, and multiple doctor visits – too numerous to list. For our household, treatments and surgeries do impact our daily routine and lifestyle. When our son has a treatment or a surgery it means that he misses time from school, and I miss time from work. It also means that my focus is mainly on him during his recovery, nursing him, changing wound coverings, cleaning excision sites and stitches, which takes my time away from the rest of our family.*

In addition to the above, the SYSF noted the challenge for the caregiver is in respect of the confusion over the disease, the lack of knowledge and information about the disease and treatment options.

4.3 Information about the Drug Being Reviewed

4.3.1 Patient Expectations for and Experiences To Date with Vismodegib

MNC noted that there has yet to be an effective treatment approved for metastatic basal cell carcinoma in Canada. MNC stated that current therapies have proven to be ineffective at stopping disease progression and have severe side-effects leading to decreased quality of life, loss of income and mental health challenges, including the negative impact on their caregivers and children. Respondents were asked the following in the survey: "If you were to consider taking a new drug to treat BCCNS, how would you rate the importance of quality of life ("QoL") while on the drug in your decision to take it or not take it? All respondents with the exception of one (who said it is somewhat important) stated QoL is an important aspect of taking a new treatment.

MNC noted that many of the affected patients are very young and have potential to lead a normal life with new and effective treatment options. The expectations of new therapies, including vismodegib, would be for a measureable and improved impact on QoL for patients and their families (e.g., experience a normal life without constant surgeries, medical appointments, time lost at work and first and foremost permanent disfigurement and psychological challenges). The Save Your Skin Foundation also reported that any improvement in the condition is adequate as long as patients are aware of possible side effects.

It is believed that risks associated with vismodegib are manageable and respondents have indicated that they are more than willing to accept that risk.

With respect to the five respondents who have experience with vismodegib, it was reported that side effects were mild or moderate and included muscle cramps, some hair loss, weight loss, irregular liver test results and change in taste. Positive effects were ease of administration as it was taken at home and allowed the patients to avoid repeated surgeries and visits to the hospital. Some comments from patients with vismodegib experiences include:

- *I can never get rid of this disease. I was born this way but now I don't have open wounds intimacy with spouse has improved. It has reduced the advancement of new BCCs, completely resolved and healed existing BCCs. It has healed a significant BCC in the nasal fold. I would have required extensive surgery and repair. No new BCCs have appeared. It has softened keloids in previous scar tissue and saved my nose from further morbid surgery.*

- *Increased self-esteem and a feeling of "the burden has been lifted"; co-workers treat me better; interpersonal relations have improved.*

- *It has allowed me to manage the progression of BCCs and provide a manageable care plan for the future. I will not lose my facial features.*

One respondent interviewed by the SYSF stated that the regimen of the trial was found to be time consuming and came off the trial; but this resulted in having the disease extend. The respondent was unable to return to the trial. As a result, the respondent felt that this treatment would be beneficial to patients with advanced BCC.

All respondents who have taken vismodegib reported that their condition has stabilized without progression, many for the first time in their lives. Some of the overall comments from respondents include:

- *I am tired of the cutting, burning and no control of the advancing BCCs. Nothing else treats the cause, just the symptoms. It is a powerful treatment and gives one the opportunity to stop BCC's in their tracks.*

- *It is the only treatment to tackle the reason for the formation of BCC's rather than treating after the damage has already occurred.*

- *It is important for BCCNS patients to have access to Erivedge. It would improve our Quality of Life by helping to control the growth of the cancerous lesions and would reduce the amount of surgeries and/or treatments, or eliminate them, to treat skin tumours. It would give BCCNS patients that are affected by multiple basal cell carcinomas another effective, but less-invasive and non-disfiguring tool to choose from for treatment options.*

4.4 Additional Information

Melanoma Network of Canada reported that it was a challenge to reach out to a group of patients who have a disease that affects only 1/40,000. MNC was pleased with obtaining 13 responses to the questionnaire, considering there is no formalized BCCNS group in Canada. MNC found the responses were very helpful and gave a good representation of what life is like for people battling this rare disease is like at present. After reviewing the responses with the 13 responses, MNC truly believe that this new treatment option will change the lives of Canadian patients with BCCNS should they obtain access.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for vismodegib (Erivedge)for advanced basal cell carcinoma (aBCC). The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the vismodegib (Erivedge) review was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, it was noted that vismodegib fills a therapeutic gap as there is no current standard of care therapy for BCC. PAG noted that the ease of administration of vismodegib will make accessibility to patients in both rural and urban settings possible. Accessibility may however be impacted in some jurisdictions depending on how patients with aBCC currently access health care (eg. via dermatology or oncology). PAG noted that "indication creep" may be a barrier to implementation. PAG expects additional implementation cost in terms of workload to make a new systemic therapy available in a previously untreated patient population and the requirement for controlled distribution since vismodegib is a teratogen.

5.1 Factors Related to Comparators

PAG noted that currently, there is no standard of care therapy for basal cell carcinoma. As such, this drug may fill a therapeutic gap.

PAG noted that other potential comparators for cases of BCC not amenable to surgery may be radiation or topical treatments (fluorouracil, imiquimod) depending on the extent and location of disease.

5.2 Factors Related to Patient Population

PAG noted that the pCODR funding request closely aligns with the inclusion criteria of the key clinical study that is for patients with advanced basal cell carcinoma in whom surgery is deemed inappropriate. PAG also noted that metastatic BCC is an uncommon disease where only a small number of patients will advance to a locally advanced or metastatic stage. The small patient population would be an enabler to implementation of funding recommendation.

PAG indicated a possibility for "indication creep" that could affect implementation. This may occur if clinicians desire to use vismodegib in patients as a second line treatment following surgery or in patients not suitable for radiation therapy.

PAG would like the long-term patient tolerability or acceptability of vismodegib related adverse events be addressed, especially whether patients may discontinue vismodegib due to adverse events with chronic therapy instead switching to surgery.

5.3 Factors Related to Accessibility

PAG noted that vismodegib is an oral drug for BCC that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the oral route of administration, in which patients could easily use in the community, as an enabler.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

5.4 Factors Related to Implementation Costs

The main barrier to dosing identified by PAG was the inability to modify the treatment dose as there is only one dosage strength available. PAG considered that dose reduction was not possible and noted that in the event of adverse or serious adverse events the alternative option was to stop treatment. PAG questioned if alternative dosing schedules, eg every other day to limit toxicity, would be appropriate as an alternative rather than stopping treatment.

5.5 Other Factors

PAG questioned if there would be a need to test for Hedgehog (Hh) signalling pathway alteration, as more than 90% of patients with basal cell carcinoma have the alteration. PAG also noted that the relatively short treatment duration (10 months) to be an enabler.

The main barrier identified by PAG involved the additional workload and resources that would be required to serve this previously untreated patient population. Normally patients with BCC who are inappropriate for surgery are treated with supportive care consisting of wound care and treatment for complications such as infection. PAG indicated that the addition of a new systemic therapy in this patient population is likely to impact workload. PAG noted this would be true at both the community clinic and pharmacy level. PAG also identified potential additional costs for dispensing requirements as vismodegib is a teratogen and fetal exposure needs to be avoided.

Packaging of the drug may present as either a barrier or enabler. PAG indicated that supplies in unit-of-use would be preferred while capsules supplied in a bulk bottle would require additional costs through the need of a biological safety cabinet.

5.6 Other Factors

The pivotal trial in the study was a phase II single arm trial. PAG noted that efficacy data derived from this would have inherent limitations and could further translate into uncertainty when examining cost-effectiveness.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the beneficial and harmful effects of vismodegib on patient outcomes compared to standard therapies or best supportive care in patients with histologically confirmed metastatic or locally advanced basal cell carcinoma (BCC) inappropriate for surgery or radiotherapy.

See Table # in Section 6.2.1 for outcomes of interest and appropriate comparators.

- Note: No Supplemental Questions relevant to the pCODR review or to the Provincial Advisory Group were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

[Table #]. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs In the absence of RCT data, fully published prospective controlled or uncontrolled trials. Case reports and case series will be excluded	Adult patients with histologically confirmed metastatic BCC or locally advanced BCC inappropriate for surgery or radiotherapy Subgroups: Locally advanced BCC metastatic BCC Gorlin syndrome	Vismodegib 150mg PO daily	Chemotherapy Best supportive care Placebo	Overall survival **Progression-free survival** **Quality of life** Objective response **Time to progression** Proportion of patients with dose adjustments **Adverse events** **Serious adverse events** Withdrawals due to adverse events
BCC=basal cell carcinoma; PO=by mouth				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 9 of 12) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's

MeSH (Medical Subject Headings), and keywords. The main search concepts were Erivedge and vismodegib.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of October 3, 2013.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

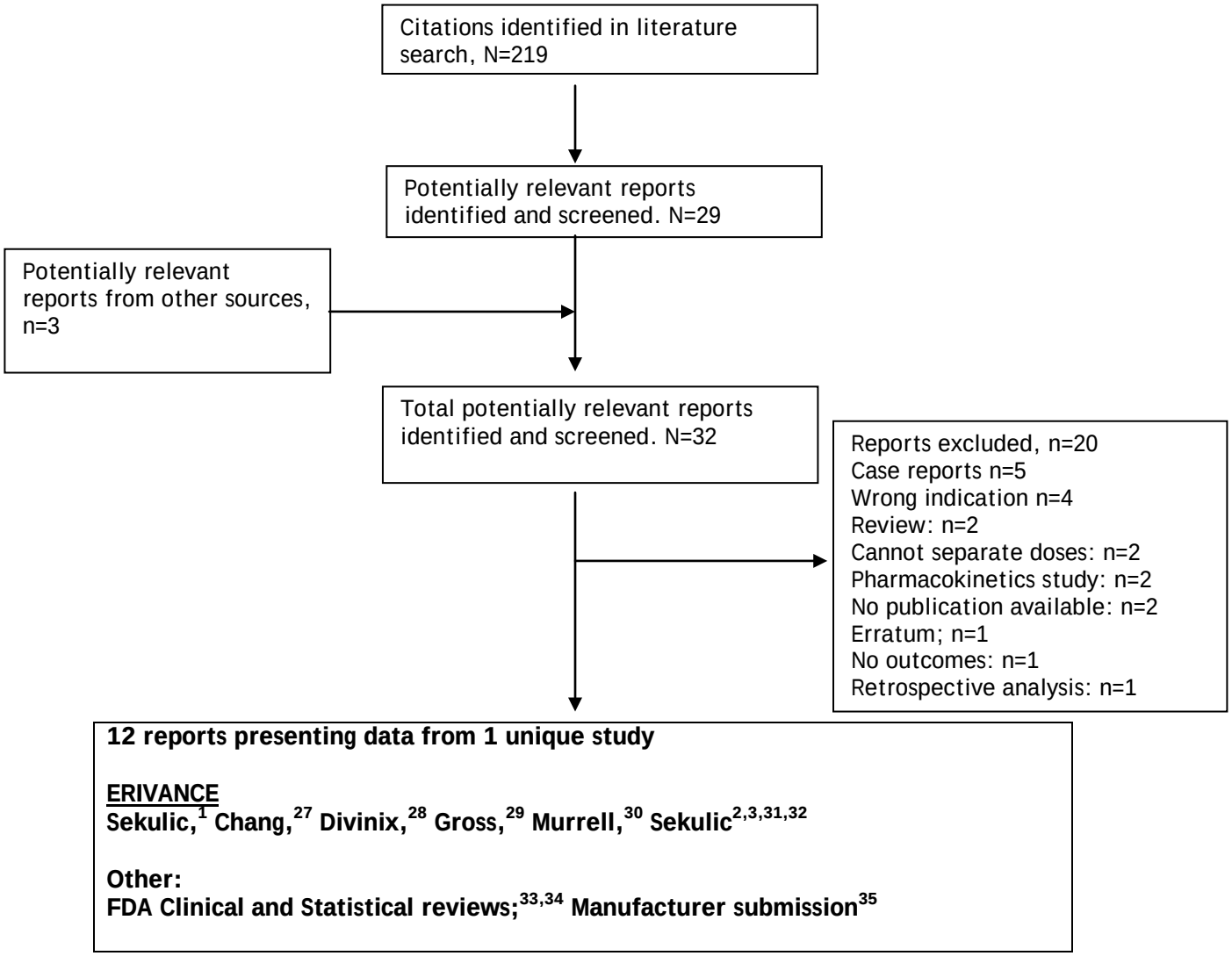
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 32 potentially relevant reports identified, 12 studies were included in the pCODR systematic review[1-3,27-35] and 18 studies were excluded. Studies were excluded because they were case reports[36-40] wrong indication,[41-44] review,[45,46] cannot separate doses,[21,26] pharmacokinetics study,[47,48] no publication available,[7,8] erratum,[49] no outcomes of interest,[50] or retrospective analysis.[51]

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

One study met the inclusion criteria for this review. ERIVANCE lacked a control group, and included two cohorts of patients, one with laBCC and one with mBCC.

6.3.2.1 Detailed Trial Characteristics

6.3.2.2 Table 2. Summary of Trial Characteristics of Included Studies

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
ERIVANCE Non-RCT Two cohort	18 years old Adequate organ function ECOG ≤2 Patients with mBCC had measurable disease (including nodal metastases) according to RECIST Patients with laBCC had ≥1 lesion of ≥10mm considered inoperable or surgery inappropriate (one or both of: recurrence after ≥2 surgeries and expect curative resection unlikely or substantial morbidity/deformity expected) <u>Exclusion criteria:</u> Life expectancy <12 weeks	**Vismodegib 150mg PO daily**	<u>Primary</u>: Objective response(independent review) <u>Major Secondary</u>: Duration of response

ECOG=Eastern cooperative oncology group; **laBCC**=locally advanced basal cell carcinoma; **mBCC**=metatstatic basal cell carcinoma; **PO**=by mouth; **RECIST**=response evaluation criteria in solid tumours

a) Trials

One multicentre manufacturer-sponsored study was included in this review. ERIVANCE was described as a cohort study, and lacked a control group. Data for the primary analysis of ERIVANCE is available in a full published report, while all updates for ERIVANCE are only available as abstracts.

ERIVANCE was conducted at 31 sites (USA, Europe, Australia). There were two cohorts enrolled, one with laBCC and one with mBCC. Patients with mBCC had to have measurable disease with nodal involvement, while patients with laBCC had to have a lesion of at least 10mm that was considered inoperable or surgery was deemed inappropriate. Patients were treated until disease progression or unacceptable toxicity.

All patients underwent physical exam and lab testing at baseline and every 4 weeks thereafter. Radiographic assessment was performed at baseline and every 8 weeks for all patients with measurable disease (all mBCC patients and certain patients with laBCC). Tumours were assessed using physical examination documented by photography at baseline and every 8 weeks. Data on adverse events were collected for up to 45 days after the last administration of vismodegib or after withdrawal from the study, whichever was later.

The primary outcome of ERIVANCE was objective response. The primary objective was to test whether the response rate was greater than 10% among patients with metastatic basal-cell carcinoma and greater than 20% among patients with locally advanced basal-cell carcinoma, as determined with the use of exact binomial one-sided tests. Duration of response was a key secondary outcome of ERIVANCE.

b) Populations

There were 104 patients enrolled in ERIVANCE, although eight laBCC patients from ERIVANCE were excluded from the efficacy analysis because the independent pathologist did not identify BCC in specimens obtained at baseline.

Baseline characteristics

	ERIVANCE[1]	
	mBCC n=33	**laBCC n=63**
Mean age (SD), y	61.6 (11.4)	61.4 (16.9)
Median age [range], y	62.0 [38-92]	62.0 [21-101]
Male, n (%)	24 (73)	15 (56)
Caucasian	33 (100)	63 (100)
mBCC	33	
laBCC		63
Contraindications to surgery or radiotherapy		
-inoperable tumour	NA	24 (38)
-surgery inappropriate	NA	39 (62)
---multiple recurrences	NA	16 (25)
---substantial morbidity or deformity expected	NA	32 (51)
-previous radiotherapy	NA	13 (21)
-radiotherapy inappropriate or contraindicated	NA	50 (79)
laBCC=locally advanced basal cell carcinoma; **mBCC**=metastatic basal cell carcinoma; **NA**=not applicable; **SD**=standard deviation		

The majority of patients were male and almost all were Caucasian. Patients were 61 years of age on average (Mean ±SD for laBCC: 61.4 ±16.9; mBCC: 61.6 ±11.4). Two-thirds of patients had locally advanced BCC, and the remainder had metastatic BCC, the two populations that are included in the indication. Most of the patients had undergone prior surgical intervention (laBCC: 89% of patients; mBCC: 97%). The majority of the laBCC patients were considered inappropriate for surgery (62%) or inoperable (38%).

c) Interventions

There were no comparators in ERIVANCE. According to the manufacturer, in advanced BCC there are no widely accepted alternatives for chemotherapy, and vismodegib is indicated in cases where surgery is not appropriate, thus surgery would not be an appropriate comparator.

In ERIVANCE, vismodegib was administered at its approved dosing regimen, 150mg daily, orally. Patients were treated until disease progression, unacceptable toxicity or discontinuation of the study. ERIVANCE continued beyond its primary analysis, and the latest update provided by the manufacturer is 18 months beyond the primary analysis and 27 months following first treatment of the last enrolled patient. As of this point (May 29, 2012), 21 patients remained on therapy.

d) Patient Disposition

In ERIVANCE the data cutoff for the primary analysis was 9 months from the date the last patient was enrolled (November 26, 2010), however as noted in the previous section, this is an ongoing study with data updates out to 18 months past this date. In ERIVANCE, 39 patients (55%) withdrew from treatment in the laBCC cohort and 14 patients (42%) in the mBCC cohort at the time of the primary analysis, and the most common reason for withdrawal was 'patient decision to stop therapy' (laBCC: 18 patients, 25%; mBCC: 2 patients, 6%).[35]

e) Limitations/Sources of Bias

The key limitation and source of bias for ERIVANCE was the lack of a control group. This makes it difficult to place the results into context, assumptions must be made about the relative benefits and harms of vismodegib that might not be valid. One is left to rely on natural history data to place results into context. One possible method for addressing this issue would be to present data from a matched historical control, although the manufacturer did not provide such an analysis. A key issue with performing such a comparison is that the populations being compared may differ on important characteristics.

A key benefit of a randomized controlled trial is that the randomization process ensures that as much as possible the groups being compared are similar to each other in terms of both known and unknown confounding factors, such that any differences between the groups seen in results during the trial can be attributed solely to the intervention. The importance of this limitation can be seen when looking at the results of the studies included in this review. These differences in results may arise for a number of reasons: differences in populations, design, methods of assessment, concomitant interventions, known and unknown confounding factors, etc. Patients enrolled in a clinical trial are also under much closer scrutiny and are likely to receive better care than they would in the community, and this also makes it difficult to compare results of a clinical trial to natural history data.

The lack of a control group also severely limits any conclusions that can be drawn from patient-reported outcomes such as quality of life. It also introduces significant bias into the analysis. In a blinded placebo-controlled study, for example, patients are unaware of their treatment status and as such, there is less risk of bias. A placebo group also helps to control for the placebo effect, as any improvement in quality of life or other subjective

outcomes may simply be due to a perceived benefit of receiving treatment, rather than a true improvement.

6.3.2.3 Detailed Outcome Data and Summary of Outcomes

Summary of efficacy outcomes

	ERIVANCE[1]	
	mBCC N=33	**laBCC n=63**
Survival at one year, patients	75.5%	91.6%
Median overall survival, months [95% CI]	NE	NE
Progression-free survival, median	9.5 months	9.5 months
Median duration of response-independent review	7.6 months	7.6 months
-investigator assessment	12.9 months	7.6 months
Objective response, patients n (%) independent review [95% CI]	10 (30) [16, 48]	27 (43) [30, 56]
-complete	0	13 (21)
-partial	10 (30)	14 (22)
Stable disease	21 (64)	24 (38)
Progressive disease	1 (3)	8 (13)
Missing/not evaluable	1 (3)	4 (6)
CI=confidence interval; **laBCC**=locally advanced basal cell carcinoma; **mBCC**=metastatic basal cell carcinoma; **NE**=not evaluable; **NR**=not reported		

Efficacy Outcomes

Survival

In ERIVANCE, data for overall survival at one year was described as not mature in the published report, but was reported as 92% with laBCC and 76% with mBCC in the Clinical Summary.[35] In the abstracts that reported efficacy updates, one year survival was higher in patients with laBCC, and was approximately 93% with laBCC and 78% with mBCC through all the updates up to 18 months.[2,3]

Progression-free survival

In ERIVANCE, median progression-free survival was 9.5 months in both cohorts, assessed by independent review. Dispersion around the median was not reported in the publication.[1] This data were unchanged at the 12 month update, published in abstract form.[3] Progression-free survival was longer in the laBCC cohort when assessed by investigators (12.9 months) but was similar to independent reviewers in the mBCC cohort (9.3 months).[35]

Quality of life

Quality of life was not reported on in the published reports of ERIVANCE, however, information on SF-36 was collected. There are more specific quality of life instruments available both for cancer and dermatology, and these likely would have been a more

appropriate choice for this study. There was also a large amount of missing data in both cohorts, and the lack of a control group, which makes it impossible to interpret these data in the context of BCC.

Objective response

In ERIVANCE, objective responses were assessed both by independent review (primary analysis) and by the investigator. Tumours were assessed using physical examination documented by photography at baseline and every 8 weeks. Response was defined as a ≥30% reduction in the externally visible or radiographic dimension. Responses had to be confirmed within 4 weeks of initial documentation.[1]

Objective response rates by independent review were higher in the laBCC (27 patients, 43%) than the mBCC cohort (10 patients, 30%), and in each case exceeded the pre-defined criteria for a minimally acceptable response (20% and 10%, respectively). No patients with mBCC had a complete response, while 21% of patients with laBCC had a complete response. Investigator-assessed objective response rates were higher in both the laBCC (38 patients, 60%) and mBCC (15 patients, 45%) cohorts when compared to independent review.[1]

There were 21 patients (22%) in ERIVANCE with Gorlin syndrome or suspected Gorlin syndrome, identified from case report forms. All had locally advanced disease. In the Summary of Clinical Efficacy, the manufacturer presented a subgroup analysis of the primary outcome, and the objective response rate was 67% [95% CI: 45%, 85%] for these patients, compared to 30% [95% CI: 19%, 46%] in the other 42 patients with laBCC. This was a post hoc analysis.

Time to progression

The median duration of response was 7.6 months in both the laBCC and mBCC cohorts in ERIVANCE, assessed by independent review. Dispersion around the median was not reported in the publication.[1]

Patients with dose adjustments

This outcome was not specifically reported.

Harms Outcomes

Serious adverse events

In ERIVANCE, 26 (25%) of patients overall experienced a serious adverse event, and fatal adverse events were reported in 7 (7%) patients (unknown cause in 3 patients, while the other deaths were due to hypovolemic shock, myocardial infarction, meningeal disease and ischemic stroke). The authors reported that the connection between the drug and these deaths is unknown.[35] The most common serious adverse events were 'death of unknown cause' in 3 (3%) of patients, and cardiac failure, pneumonia, and pulmonary embolism in 2 (2%) patients each.[1]

Adverse events

In ERIVANCE, the primary analysis of safety was performed at a median duration of therapy of 9.7 months for laBCC and 10.0 months for mBCC. The most common adverse events were muscle

spasms (68% of patients), alopecia (63%), dysgeusia (51%) and weight loss (46%). The most common grade 3-4 events were weight loss (5%), muscle spasms (4%) and fatigue (4%).[1]

Withdrawals due to adverse event

In ERIVANCE, 13 (12%) patients overall had an AE leading to discontinuation of study drug. The most common reason was muscle spasm, although this only occurred in two patients.[1]

6.4 Ongoing Trials

STEVIE is an ongoing safety study that is of similar design to ERIVANCE, in that it lacks a control group, and includes both patients with laBCC and patients with mBCC. This study did not meet the inclusion criteria for this review, as it has not been published. The only reports of STEVIE come from abstracts, and these data are summarized in 2.1.4 of this report. Due to the limited reporting from these abstracts, it is not clear to what extent the data from STEVIE will be able to fill gaps remaining from ERIVANCE. However, given their similar design, STEVIE would be expected to have the same significant limitation as ERIVANCE, that is the lack of a control group. If, for instance, STEVIE were to use HRQoL instruments that were appropriate for this population, interpretation of these results would still be limited by the lack of control group and the bias associated with patients being aware of their treatment allocation. The manufacturer has noted that results from STEVIE are expected to be available sometime in 2014.

7 SUPPLEMENTAL QUESTIONS

No Supplemental questions were identified for this review.

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR Melanoma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on vismodegib (Erivedge) for advanced basal carcinoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Melanoma Clinical Guidance Panel is comprised of vismodegib (Erivedge) for advanced basal carcinoma.The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **Embase** 1974 to Present (oemezd)**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present (pmez)

Initial search date: July 2, 2013

#	Searches	Results
1	(erivedge* or vismodegib* or GDC0449 or GDC-0449 or HhAntag691 or NSC747691 or NSC 747691 or R 3616 or R3616 cpd or RG 3616 or RG3616).ti,ot,ab,sh,rn,hw,nm.	666
2	879085-55-9.rn,nm.	314
3	or/1-2	666
4	3 use pmez	145
5	(erivedge* or vismodegib* or GDC0449 or GDC-0449 or HhAntag691 or NSC747691 or NSC 747691 or R 3616 or R3616 cpd or RG 3616 or RG3616).ti,ab.	308
6	*vismodegib/	84
7	or/5-6	317
8	7 use oemezd	205
9	4 or 8	350
10	exp animals/	35927682
11	exp animal experimentation/ or exp animal experiment/	1707016
12	exp models animal/	1112174
13	nonhuman/	4082074
14	exp vertebrate/ or exp vertebrates/	34995255
15	animal.po.	0
16	or/10-15	37115447
17	exp humans/	27742798
18	exp human experimentation/ or exp human experiment/	325577

19	human.po.	0
20	or/17-19	27744878
21	16 not 20	9372158
22	9 not 21	312
23	limit 22 to english language	303
24	remove duplicates from 23	209

2. Literature search via PubMed

Initial search date: July 2, 2013

Search	Add to builder	Query	Items found	Time
#3	Add	Search **#1 AND #2**	7	16:25:41
#2	Add	Search **publisher [sb]**	431947	16:25:41
#1	Add	Search **erivedge OR vismodegib OR GDC0449 OR GDC-0449 OR HhAntag691 OR NSC747691 OR NSC 747691 OR R 3616 OR R3616 cpd OR RG 3616 OR RG3616**	137	16:25:40

3. Cochrane Central Register of Controlled Trials (Central)

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There are 5 results from 712779 records for your search on 'erivedge* or vismodegib* or GDC0449 or GDC-0449 or HhAntag691 or NSC747691 or NSC 747691 or R 3616 or R3616 cpd or RG 3616 or RG3616 in title abstract keywords in Trials

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: Erivedge OR vismodegib OR GDC0449 OR GDC-0449 OR HhAntag691 OR NSC747691 OR "NSC 747691" OR "R 3616" OR "R3616 cpd" OR "RG 3616" OR RG3616

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: Erivedge or vismodegib

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search terms: Erivedge or vismodegib or GDC-0449 or GDC0449 or HhAntag691 or NSC747691 or NSC 747691 or R 3616 or R3616 cpd or RG 3616 or RG3616 / last 5 years

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