CADTH

CADTH PCODR INITIAL CLINICAL GUIDANCE REPORT

Clinical Report

SONIDEGIB (ODOMZO)

(Sun Pharma Canada Inc.)

Indication: For the treatment of adult patients with histologically confirmed locally advanced basal cell carcinoma (laBCC) that is not amenable to radiation therapy or curative surgery.

Service Line:	CADTH pCODR Clinical Guidance Report
Version:	Initial
Publication Date:	March 4, 2021
Report Length:	128 Pages

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Abbreviations 7

1 Guidance In Brief 9

1.1 Introduction 9

1.2 Key Results and Interpretation 9

1.2.2 Additional Evidence 17

1.2.3 Factors Related to Generalizability of the Evidence 20

1.2.4 Interpretation 21

1.3 Conclusions 24

2 Background Clinical Information 28

2.1 Description of the Condition 28

2.2 Accepted Clinical Practice 28

3 Summary of Patient Advocacy Group Input 31

3.1 Condition and Current Therapy Information 32

3.2 Information about the Drug Being Reviewed 34

3.3 Companion Diagnostic Testing 35

3.4 Additional Information 35

4 Summary of Provincial Advisory Group (PAG) Input 36

4.1 Currently Funded Treatments 36

4.2 Eligible Patient Population 36

4.3 Implementation Factors 37

4.4 Sequencing and Priority of Treatments 37

4.5 Companion Diagnostic Testing 38

4.6 Additional Information 38

5 Summary of Registered Clinician Input 39

5.1 Current Treatments 39

5.2 Eligible Patient Population 39

5.3 Relevance to Clinical Practice 39

5.4 Sequencing and Priority of Treatments with New Drug Under Review 40

5.5 Companion Diagnostic Testing 41

5.6 Implementation Questions 41

5.7 Additional Information 41

6 Systematic Review 42
6.1 Objectives 42
6.2 Methods 42
6.3 Results 43
6.4 Ongoing Trials 99
7 Supplemental Questions 100
7.1 Summary and Critical Appraisal of a Published Unanchored MAIC 100
7.2 Summary and Critical Appraisal of a Published Meta- analysis Comparing Sonidegib with other sonic Hh inhibitors for the Treatment of Patients with BCC 107
8 Comparison with Other Literature 115
Disease Characteristics in the mBCC Subgroup 115
9 About this Document 120
References 124

Tables

Table 1: Highlights of Key Efficacy and Safety Outcomes in Patients with laBCC (for efficacy results) and Overall (both laBCC and mBCC for safety results) from the BOLT Trial 16
Table 2: Assessment of generalizability of evidence for sonidegib for the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery 20
Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions 25
Table 4: Challenges of Living with BCC 32
Table 5: Selection Criteria 43
Table 6: Summary of Trial Characteristics of the Included Studies 45
Table 7: Tumour Response Evaluations Used for laBCC Patients in the BOLT Trial 50
Table 8: Composite Assessment via mRECIST Criteria for laBCC Patients 51
Table 9: Options for Event Dates Used in PFS, TTP, and DOR Sensitivity Analyses 53
Table 10: Decision Operating Characteristics for the Primary Endpoint and a Secondary Endpoint of the BOLT Trial Design 56
Table 11: Summary of Protocol Amendments in the BOLT trial 57
Table 12: Demographics and Disease History at Baseline in laBCC Patients of the BOLT Trial (FAS) 58
Table 13: Disease Characteristics of laBCC Patients in the BOLT trial (FAS) 60
Table 14: Measurable Disease at Baseline in laBCC Patients in the BOLT trial (FAS) 62

Table 15: Dose Reduction Steps for Sonidegib in the BOLT Trial 63
Table 16: Summary of Treatment Exposure in the BOLT Trial (Safety Analysis Set) 64
Table 17: Dose Reductions and Dose interruptions of Study Drug in the BOLT Trial (Safety Analysis Set) 65
Table 18: Participant Disposition of the Overall Population Patients in the BOLT Trial at the Primary and 42-Month Data Cut-Off (FAS and pEAS) 66
Table 19: Participant Disposition of laBCC Patients in the BOLT Trial at the 42-Month Data Cut-Off (FAS and pEAS) 67
Table 20: Protocol Deviations in the laBCC Patients of the BOLT Trial at the 42-Month Data Cut-Off (FAS) 68
Table 21: Reasons for Exclusion from the laBCC FAS in the BOLT Trial 69
Table 22: Summary of IRC-assessed ORR in the Overall Population (both laBCC and mBCC) Patients of the BOLT Trial (pEAS) 74
Table 23: Summary of IRC-assessed ORR in the laBCC Patients of the BOLT Trial (pEAS) 76
Table 24: Summary of IRC-assessed ORR in the laBCC Patients of the BOLT Trial (FAS) 77
Table 25: Summary of DOR and CRR Analyses in the laBCC Subgroup of the BOLT Trial 82
Table 26: Summary of Other Secondary Outcomes in the laBCC Patients of the BOLT Trial 83
Table 27: Summary of the Sensitivity Analysis for IRC-Assessed ORR in laBCC Patients Using Updated mRECIST Criteria for laBCC Patients in the pEAS 85
Table 28: Summary of the Sensitivity Analysis for IRC-Assessed ORR in laBCC Patients Using Updated mRECIST Criteria for laBCC Patients in the FAS 86
Table 29: Time to Definitive Deterioration in the SF-36 for All Patients of the BOLT trial (FAS) 91
Table 30: Overview of the Adverse Events at Each Data Cut-Off for All Patients of the BOLT trial (Safety Analysis Set) 92
Table 31: 'All Grade' Adverse Events, Irrespective of Causality Occurring in at Least 5% of Either Treatment Group for All Patients in the BOLT Trial (Safety Analysis Set) 93
Table 32: Grade 3 or 4 Adverse Events, Irrespective of Causality Occurring in at Least 2% of Either Treatment Group for All Patients in the BOLT Trial (Safety Analysis Set) 94
Table 33: Serious Adverse Events Occurring in at Least 1% of Either Treatment Group for All Patients in the BOLT Trial (Safety Analysis Set) 95
Table 34: On-Treatment Deaths for All Patients in the BOLT Trial (Safety Analysis Set) 96
Table 35: Adverse Events Occurring in at Least 1% of Either Treatment group Requiring Discontinuation of Study Drug for All Patients in the BOLT Trial (Safety Population) 97
Table 36: Adverse Events Occurring in at Least 2% of Either Treatment Group Leading to Dose Reduction or Dose Interruptions for All Patients in the BOLT Trial (Safety Population) 98
Table 37: Subsequent Treatments for Patients in the BOLT trial (FAS) 99

Table 38: Overview of trial designs, including outcome definitions 102
Table 39: Overview of trial patient baseline characteristics 103
Table 40: Baseline Characteristics of the Included Trials Before and After Matching 104
Table 41: Efficacy Outcome Parameters Before and After Matching 105
Table 42: Efficacy Results from the Included Studies 110
Table 43: Safety Results from the Included Studies 111
Table 44: Efficacy of sonic Hh inhibitors molecules for all patients, laBCC patients, and mBCC patients 112
Table 45: Characteristics at Baseline in mBCC Patients in the BOLT trial (FAS) 115
Table 46: Summary of Best Overall Response in mBCC patients per Central Review of the BOLT Trial (pEAS) 117
Table 47: Summary of the Secondary Efficacy Outcomes for the Primary Data Cut-off and the 42-month data cut-off of the BOLT Trial 118

Figures

Figure 1: Flow Diagram for Study Selection 44
Figure 2: BOLT Study Design Flow Chart 48
Figure 3: Exploratory Subgroup Analyses of ORR per Central Review Using mRECIST in laBCC and RECIST v1.1 in mBCC (pEAS) 79
Figure 4: EORTC QLQ-C30 profiles: QoL or Global Health Status of All Patients of the BOLT Trial (FAS) 87
Figure 5: EORTC QLQ-C30 profiles: Individual Scales for All Patients of the BOLT (FAS) 88
Figure 6: EORTC QLQ-H&N35 Profiles: Individual Scales for All Patients of the BOLT Trial (FAS) 89
Figure 7: Kaplan-Meier Plots of Time to Deterioration of EORTC QLQ-C30 Scales for All Patients in the BOLT Trial (FAS) 90

Abbreviations

AE	adverse event
BCC	basal cell carcinoma
BOR	best overall response
CBR	clinical benefit rate
CDA	Canadian Dermatology Association
CGP	Clinical Guidance Panel
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase myocardial band
CR	complete response
CRR	complete response rate
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC	European Organisation for Research and Treatment of Cancer FAS full analysis set
H&N35	Head and Neck Cancer Module 35
Hh	hedgehog
HrQoL	health related quality of life
iDMC	independent data monitoring committee
INV	investigator
IRC	independent review committee
IRT	interactive response technology
ITC	indirect treatment comparisons
KM	Kaplan-Meier
laBCC	locally advanced basal cell carcinoma
MA	meta-analysis
MAIC	matching-adjusted indirect comparison
mBCC	metastatic basal cell carcinoma
MIC	minimal important change
mRECIST	modified Response Criteria in Solid Tumors
NE	not estimable
NR	not reached

ORR	overall response rate
OS	overall survival
PAG	Provincial Advisory Group
PD	disease progression
pEAS	primary efficacy analysis set
pERC	pCODR Expert Review Committee
PFS	progression-free survival
PPD	product of the perpendicular diameter
PRO	patient reported outcome
PRO	partial response
PTCH1	protein patched homolog 1
QLQ-C30	Quality of Life Questionnaire-Core 30
QTc	corrected QT
QTcF	Fridericia's formula corrected QT
RCT	randomized controlled trial
RECIST	Response Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SF-36	The Medical Outcomes Study Short Form 36 (SF-36, version 2, Acute)
TP53	tumour protein p53
TTR	time to tumour response
ULN	upper limit of normal
WHO	World Health Organization

1 Guidance In Brief

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 sonidegib (Odomzo) for locally advanced basal cell carcinoma (laBCC). 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 CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; 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, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of sonidegib for the treatment of adult patients with histologically confirmed locally advanced basal cell carcinoma (laBCC) that is not amenable to radiation therapy or curative surgery.

On June 12th, 2020, Health Canada issued a Notice of Compliance (NOC), without conditions, for sonidegib for the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery.[1] The CADTH reimbursement request is aligned with the Health Canada NOC.

Sonidegib is an inhibitor of the Hedgehog (Hh) pathway, and it binds to and inhibits Smoothened (SMO). SMO is a transmembrane protein involved in the Hh signal transduction pathway, which leads to the activation and nuclear localization of glioma-associated oncogene transcription factors and induction of Hh target genes that are involved in proliferation, survival, and differentiation. SMO inhibition by sonidegib inactivates mutations in Patched 1 (PTCH1) gene or activates mutations in SMO, which prevents Hh signal transduction.[1]

Sonidegib is administered orally, in capsule form. The Health Canada recommended dose is 200 mg taken once daily on an empty stomach, at least one hour before or two hours after a meal. Patients should continue treatment until disease progression or unacceptable toxicity.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

BOLT

BOLT was an international, double-blind, phase II randomized trial that evaluated the efficacy and safety of two doses of sonidegib in adult patients with histologically confirmed laBCC not amenable to radiotherapy or curative surgery, or metastatic basal cell carcinoma

(mBCC) for which all existing available treatment options had been exhausted. As the objective of this systematic review was to evaluate the efficacy and safety of sonidegib in laBCC patients, the study results (i.e., patient demographics, disease demographics, patient disposition, efficacy, and HRQoL results) will focus on the laBCC subgroup and brief results of the overall trial population will be summarized, when relevant. Safety results (including drug exposure) will be described for the overall trial population (i.e. both laBCC and mBCC patients together).

Eligible patients were randomized in a 1:2 ratio to receive either 200 mg once daily or 800 mg once daily dose of sonidegib.[2] The 200 mg dose was investigated in the trial as it represented the lowest dose level tested that had demonstrated evidence of anti-tumour activity, and the 800 mg dose was investigated as it represented the highest, well-tolerated biologically-active dose of sonidegib.[3] It was hypothesized that an 800 mg dose would be more efficacious than 200 mg, and therefore the 1:2 ratio was planned to ensure that more patients would be randomized to the 800 mg dose.[4] Of note, the 200 mg dose was shown in the trial to be more tolerable with similar efficacy to the 800 mg dose, and thus, it is the recommended dose and focus of this report.[3] Patients received sonidegib once daily on a continuous dosing schedule until documented disease progression (PD), intolerable toxic effects, withdrawal of consent, death, discontinuation at an investigator's discretion, dose interruption lasting longer than 21 days (unless the patient was responding to study treatment and had not progressed, in which case resumption of treatment was permitted at the investigator's discretion), use of a prohibited medication, start of another antineoplastic therapy, or study termination.[2]

The primary efficacy endpoint was overall response rate (ORR) in the overall population (both laBCC and mBCC patients) as assessed by an independent review committee (IRC), and ORR was defined as the proportion of patients with a confirmed best overall response (BOR) of complete response (CR) or partial response (PR).[2,5] Treatment was considered to be efficacious if the observed ORR on any treatment arm was greater than or equal to 30% and clinically meaningful if the lower bound of the 95% confidence intervals (CI) exceeded 20%.[5,6] This threshold was determined by a literature review and consultation with experts and regulatory agencies.[7] Disease control rate was also calculated, defined as the proportion of patients with a CR, PR, or stable disease (SD). IRC-assessed ORR was analyzed using the primary efficacy analysis set (pEAS), which was defined as all patients with fully assessable tumours by modified Response Evaluation Criteria in Solid Tumors (mRECIST) in patients with laBCC (i.e. patients with tumours that have been adequately assessed by photographs or radiologic scans [MRI or CT] or both) and all patients with mBCC (all patients with mBCC were assessed by Response Evaluation Criteria in Solid Tumors version 1.1. [RECIST v1.1]).[2,4] The full analysis set (FAS) was defined as all patients randomized, irrespective of whether they had received study medication, which was in accordance with the intention-to-treat principle.[2] The key secondary efficacy outcomes were IRC-assessed duration of response (DOR) and IRC-assessed complete response rate (CRR).[4] Other secondary efficacy outcomes included IRC-assessed progression-free survival (PFS) and overall survival (OS).

Patient-reported outcomes (PROs) were assessed as an exploratory end point using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), its associated head and neck cancer-specific module (QLQ-H&N35) , and the Medical Outcomes Study Short Form 36 (SF-36) version 2, Acute.[4] Patients completed the EORTC QLQ-C30 and QLQ-H&N35 at baseline, at week 9, week 17, every eight weeks thereafter for year one, and every 12 weeks (± 3 days) thereafter until the

end of treatment. Summary scores for the outcomes were calculated for the FAS by summing the item responses on the questions for each domain according the scoring manual and the developers for the questionnaires.[4] Descriptive statistics and change from baseline of the summary scores for each post baseline assessment were provided by treatment group. Proportions of patients with improvement, no change, or decline from baseline were also calculated from the best reported scores post-baseline.[2] Median time to deterioration was also calculated for each subscale, and was defined as a worsening of at least 10 points in a score from baseline without a subsequent improvement. Patients completed the SF-36 at baseline, and then 16 weeks for year one, and every 24 weeks (± 3 days) thereafter until the end of treatment.

Safety outcomes (i.e. adverse events [AEs], serious adverse events [SAEs], and deaths) were assessed in the safety analysis set, defined as all patients who received at least one dose of study medication and had at least one post-baseline safety assessment.[4] Patients were analyzed according to the dose received, which was defined as the treatment assigned if it was received for at least one dose or, otherwise, the initial treatment received. Safety was assessed by IRC and investigators.[2]

An interim analysis was performed after the first 48 randomized patients had been treated for 16 weeks or had discontinued treatment.[4] Efficacy analyses were based on the FAS and safety analyses were based on the safety set. The results of this interim analysis indicated that the study should continue.[2] The primary analysis was performed on all efficacy and safety data reported up to six-months (corresponding to when the final randomized patient would have either completed 24 weeks of treatment or discontinued prior to this time point) with a data cut-off date of June 28, 2013.[8] Four additional analyses have been conducted: 12-month analysis (50 weeks following enrollment of the last patient) with a data cut-off date of December 31, 2013; 18-month analysis (78 weeks following enrollment of the last patient) with a data cut-off date of July 11, 2014; 30-month analysis (130 weeks following enrollment of the last patient) with a data cut-off date of July 10, 2015 ; and 42-month analysis (182 weeks following enrollment of the last patient) with a data cut-off date of July 8, 2016. The IRC remained blinded for the primary, 12-month, 18-month, 30-month, and 42-month analyses.

Study Population

A total of 230 patients were enrolled in the BOLT trial, of which 194 patients had laBCC and 36 had mBCC. Overall, the baseline patient demographics were balanced between the two groups. The median age was similar between the two groups (200 mg sonidegib: 67.0 years [range: 25.0 to 92.0 years]; 800 mg sonidegib: 66.0 years [range: 24.0 to 93.0 years]), however a slightly higher proportion of patients in the 200 mg sonidegib group were 65 years of age or older compared to the 800 mg sonidegib group (57.6% versus 53.9%). Most patients were White (89.4% in the 200 mg sonidegib group versus 96.1% in the 800 mg sonidegib group) and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (66.7% versus 68.0%, respectively).

Efficacy

The results of the primary and secondary outcomes of the BOLT trial are summarized in Table 1. At the time of the primary data cut-off, the median follow-up time was 13.9 months (interquartile range [IQR]: 10.1 to 17.3 months).[2] The median follow-up times for each further data cut-off were as the following: 20.0 months for the 12-month analysis (31-Dec-2013 data cut-off), 26.3 months for the 18-month analysis (11-Jul-2014 data cut-off), 38.2

months for the 30-month analysis (10-Jul-2015 data cut-off), and 50.2 months for the 42-month analysis (08-Jul-2016 data cut-off).

In the overall population (both laBCC and mBCC patients), the IRC-assessed ORR was greater than 30% with the lower bound of the 95% CI exceeding 20% (which was considered to be clinically meaningful) for both treatment groups at each of the analyses, and therefore the primary endpoint of the trial was met.[5] At the time of the primary data cut-off, 36.4% (95% CI: 23.8 to 50.4) of patients in the 200 mg sonidegib group and 33.6% (95% CI: 25.1 to 43.0) of patients in the 800 mg sonidegib group had achieved an objective response.

In the laBCC patients, the IRC-assessed ORR in the pEAS was greater than 30% with the lower bound of the 95% CI exceeding 20% for both treatment doses at each of the analyses.[8] At the time of the primary data cut-off, 42.9% (95% CI: 27.7 to 59.0) of laBCC patients in the 200 mg sonidegib group and 37.6% (95% CI: 27.8 to 48.3) of laBCC patients in the 800 mg sonidegib group had achieved an objective response.[2,5] In the laBCC 200 mg sonidegib subgroup, a total of 18 patients achieved a CR or PR, which included 2 (4.8%) patients that achieved a CR and 16 (38.1%) patients that achieved a PR. In the laBCC 800 mg sonidegib subgroup, all patients who achieved an objective response had a PR (n = 35; 37.6%). Disease control (i.e. CR, PR, or SD) was achieved in 93% of patients in the laBCC 200 mg sonidegib subgroup and in 88% of patients in the laBCC 800 mg sonidegib subgroup. Overall, results at the following data cut-offs were consistent with the primary data analysis. To note in the laBCC 200 mg sonidegib subgroup, ORR increased to 57.1% at the 12-month analysis, which was revised to 54.8% as of the 18-month analysis due to a re-review of missing MRI images at further evaluations.[8] The ORR of 54.8% was maintained through to the 42-month data cut-off, suggesting that most laBCC patients who responded, responded by 12 months. These results should be interpreted with caution as the sample size was not calculated to provide power for the laBCC subgroup.

As of the primary data cut-off, median DOR was not estimable for either treatment dose for the laBCC patients.[8] The number of progression events increased throughout the data cut-offs, with a median DOR of 12.9 (95% CI not estimable) months in the laBCC 200 mg sonidegib subgroup and 23.7 (95% CI: 10.8 to 29.6) months in the laBCC 800 mg sonidegib subgroup as of the 42-month data cut-off. For the outcome of CRR as of the primary data cut-off, two patients (4.8%) had achieved a CR in the laBCC 200 mg sonidegib subgroup compared to zero patients in the laBCC 800 mg subgroup.[8] The number of patients with a CR remained constant in the laBCC 200 mg subgroup at later data cut-offs. In the laBCC 800 mg sonidegib subgroup, one (1.1%) of patients had achieved a CR as of the 12-month data cut-off, which increased to two (2.2%) as of the 30-month data cut-off.

Other secondary outcomes included IRC-assessed PFS, IRC-assessed TTR, IRC-assessed ORR per RECIST v1.1, and OS. At the primary data cut off, TTR was 3.9 months (95% CI: 2.1 to 4.0) in the laBCC 200 mg sonidegib subgroup and 3.7 months (95% CI: 2.0 to 3.8) in the laBCC 800 mg sonidegib subgroup, which remained relatively consistent through to later data cut-offs.[8] At the primary data cut off, PFS was not estimable in either group for the laBCC patients. In the laBCC 200 mg sonidegib subgroup, median PFS was 22.1 months as of the 18-month cut-off, which decreased to 19.0 months as of the 30-month data cut-off.[8] In the laBCC 800 mg sonidegib subgroup, median PFS was 21.5 months as of the 12-month data cut-off, which decreased to 19.4 months as of the 18-month data cut-off. At the time of the primary data cut-off, one (1.5%) patient had died in the laBCC 200 mg sonidegib subgroup and seven (5.5%) had died in the laBCC 800 mg subgroup.[8] As of the 42-month

data cut-off, six (9.1%) patients had died in the laBCC 200 mg sonidegib subgroup and 12 (9.4%) patients had died in the laBCC 800 mg sonidegib subgroup. Median OS was not estimable for either treatment dose in the laBCC patients at any of the data cut-offs.[8] It should also be noted that survival information was missing for 43.9% of patients in the laBCC 200 mg sonidegib subgroup and 29.7% of patients in the laBCC 800 mg sonidegib subgroup by the time of the 42-month follow-up, which may infer that deaths could be underreported in the BOLT trial.[7]

Patient Reported Outcomes

The EORTC QLQ-C30 and the QLQ-H&N35 were evaluated at the primary data cut-off and was assessed in the overall population (both laBCC patients and mBCC patients).[2] Compliance rates of both treatment arms of patients completing the EORTC QLQ-30 and EORTC QLQ-H&N35 questionnaires were 93.0% and 93.9% at baseline, respectively, and at 44.3% and 45.2% at Week 33 (~7.6 months), respectively.[9] The proportion of patients who completed the questionnaires at baseline and at least one post-baseline assessment was 88.7% and 90.0% for the QLQ-C30 and QLQ-H&N35, respectively.[9] Over the course of treatment, the majority of patients (both laBCC and mBCC) either maintained and/or had improvement in the health status, functioning, and disease-related symptoms.[9] The mean scores for the pre-specified subscales of the EORTC QLQ-30 (physical functioning, social functioning, pain, and fatigue) and for the EORTC QLQ-H&N35 (trouble with social contact, head and neck pain, and weight loss) demonstrated maintenance of each of the prespecified scale scores in both treatment groups and for both patient subgroups, with the exception of a trend toward worsening weight loss among patients on study at Week 41. In the 200 mg sonidegib group, deterioration was seen for fatigue and weight loss, with median times to deterioration being 13.7 months (95% CI: 9·3 to NE) and 16.6 months (95% CI: 13·9 to NE), respectively.[2] In the 800 mg sonidegib group, deterioration was seen in physical functioning, social functioning, fatigue, and weight loss with median time to deterioration being 11.1 months (95% CI: 9.0 to NE), 11.3 months (95% CI: 7.6 to NE), 5.6 months (95% CI: 5.5 to 9.4), and 16.5 months (95% CI: 10.7 to 16.6), respectively.

The SF-36 was evaluated at the primary data cut-off and was assessed in the overall population (both laBCC patients and mBCC patients). Compliance rates of both treatment arms of patients completing the SF-36 questionnaires were 94.3% at baseline, and 43.0% at Week 33.[10] The proportion of patients who completed the questionnaires at baseline and at least one post-baseline assessment was 80.9% and 90.0%. Median time-to-deteriorations in the 200 mg sonidegib group were the following: bodily pain - 7.6 months, physical component - 8.5 months, role physical - 11.3 months, and not estimable for all other components.

Harms

Harms outcomes were assessed in the overall population (both laBCC patients and mBCC patients). As of the primary analysis, median treatment exposure time was 8.9 (range: 1.3 to 21.4) months in the 200 mg sonidegib group and 7.4 (range: 0.3 to 19.1) months in the 800 mg sonidegib group.[6] As of the 42-month analysis, median treatment exposure time was 11.0 (range: 1.3 to 53.2) months in the 200 mg sonidegib group and 6.6 (range: 0.3 to 53.9) months in the 800 mg sonidegib group.

At the primary analysis, 94.9% of patients in the 200 mg group had experienced at least one AE, with 30.4% of patients experiencing Grade 3 or 4 AEs. Additionally, 13.9% of patients experienced an SAE. There was a slight increase in the incidence of events of the safety

outcomes at subsequent data analysis time points, with a notable increase of Grade 3 to 4 AEs at the 12-month data cut-off to 38.0% of patients. For all the AE categories, a higher rate proportion of patients experienced an event in the 800 mg sonidegib group compared to the 200 mg sonidegib group.[11] At the primary analysis, 100% of patients in the 800 mg group had experienced at least one AE, with 56.0% of patients experiencing Grade 3 or 4 AEs. Additionally, 30.0% of patients experienced an SAE. similar to the 200 mg sonidegib group, there was a slight increase in the incidence of events of the safety outcomes at subsequent data analysis time points.[11]

The most common AEs of any grade, irrespective of causality, that occurred in the 200 mg group as of the primary data cut-off and the 42-month data cut-off, respectively, were muscle spasms (49.4% and 54.4%), alopecia (43.0% and 49.4%), dysgeusia (38.0% and 44.3%), and nausea (32.9% and 39.2%). The most common grade 3 or 4 AEs that occurred in the 200 mg group at the primary data cut-off and the 42-month data cut-off, respectively, were blood creatine phosphokinase increase (6.3% and 6.3%), lipase increase (5.1% and 6.3%), asthenia (2.5% and 3.8%), muscle spasms (2.5% and 2.5%), hypertension (2.5% and 2.5%, and weight decrease (1.3% and 5.1%). At all the data cuts, asthenia was the only grade 3 to 4 AE that occurred in more patients in the sonidegib 200 mg group compared to the 800 mg sonidegib group (with a ≥ 2.5% difference). At all the data cuts, the Grade 3 to 4 AE occurring more frequently in the sonidegib 800 mg group compared to the 200 mg sonidegib group (with a ≥ 2.5% difference) were increased blood creatinine phosphokinase (CK), anemia, muscle spasms, decreased appetite, and decreased weight.

At the primary data cut-off, SAEs included pneumonia, angina pectoris, bipolar disorder, blood CK increased, and rhabdomyolysis. By the 42-month analysis, a total of 16 (20.3%) SAEs occurred in the 200 mg group, and pneumonia was the only SAE that occurred in more than one patient (n=2; 2.9%), and a few fractures (total of 4) were reported affecting the cervical vertebral (n=1), femoral neck (n=1), lumbar vertebral (n=1), and upper limb (n=1). In the 800 mg sonidegib group, a higher proportion of SAEs occurred at the time of the primary analysis compared to the 200 mg group, which increased to 38.7% (n = 58) by the time of the 42-month analysis. At the time of the primary analysis the most frequently occurring SAEs in the 800 mg group compared to the 200 mg were rhabdomyolysis (3.3% versus 1.3%), vomiting (2.7% versus 0%), nausea (2.0 % versus 0%), and blood CK increase (2.0% versus 1.3%).[11]

Of the four on-treatment deaths reported at the primary data cut-off which all occurred in the 800 mg sonidegib group, two were due to progressive disease (PD) (both patients had mBCC).[2] The other two deaths were due to congestive cardiac failure and cardiac death (one each) in laBCC patients with pre-existing confounding conditions at baseline. None of the deaths were reported as being due to treatment with sonidegib. By the 12-month analysis, three additional deaths occurred that were not reported as being due to treatment with sonidegib.[11] One death was due to cardiac arrest, another death was due to sepsis, and one death was due to respiratory arrest. No additional deaths occurred at subsequent analysis time points, however, as per the protocol deviations, survival information was missing for a significant proportion of patients (29 [43.9%] in the 200 mg sonidegib group and 38 [29.7%] patients in the 800 mg sonidegib group) and thus, data on deaths is likely incomplete and underestimated.[7]

As of the primary data analysis, 17 patients (21.5%) in the 200 mg group and 54 patients (36.0%) in the 800 mg group had discontinued treatment due to an AE. As of the 42-month data cut-off, 24 patients (30.4%) in the 200 mg group and 60 patients (40.0%) in the 800 mg

group had discontinued due to AEs. In the 200 mg group, AEs that led to discontinuation at the time of the primary analysis included muscle spasms (3.8%), dysgeusia (2.5%), weight decreased (2.5%), and nausea (2.5%), and at the time of the 12-month analysis, additional AEs that led to discontinuation included asthenia (3.8%), fatigue (2.5%). AEs that led to discontinuation at subsequent time points remained consistent in the 200 mg group.[11]

Limitations and Potential Sources of Bias

The BOLT was a phase II trial that evaluated the efficacy and safety of two doses of sonidegib in adult patients with laBCC not amenable to radiotherapy or curative surgery, or mBCC for which all existing available treatment options had been exhausted. The primary objective of the trial was to evaluate the proportion of patients with an ORR, which was considered an appropriate end point for this patient population when considered with key secondary end points such as DOR and PFS. ORR was assessed by IRC, which was a strength of the study. The randomization of patients to the two different doses of sonidegib and blinding procedures were appropriately performed. Protocol defined criteria for study treatment administration, such as appropriate dosing, were generally followed. The procedures employed in the BOLT trial included generally appropriate methods for statistical analyses, and overall study methodology.

The major limitations and potential sources of bias associated with the BOLT trial, based on the CADTH Methods Team's critical appraisal of the evidence, are summarized below. The complete list is available in Section 6.

- As of amendment 2 (November 17th, 2011), at which point 26 patients had already been enrolled, tumour response evaluation by RECIST v1.1 was changed to mRECIST for the laBCC subgroup. Per amendment 2, laBCC patients were required to have annotated or non-annotated photographs and mandatory baseline MRI scans (unless contraindicated). Thus, patients who did not have this baseline assessment were excluded from the pEAS, which may have introduced selection bias, however it was not suspected to have affected efficacy or safety outcomes, or the generalizability of the results. It should be noted these patients that were excluded in the pEAS were included in the FAS analyses, however IRC assessment was also introduced in amendment 2 and thus, the 26 patients that were enrolled prior to amendment 2 were retrospectively assessed for IRC-assessed ORR. Analyses conducted using the FAS would have included patients that were both retrospectively and prospectively assessed for response, and thus, efficacy results may be affected. For example, patients retrospectively assessed by IRC as PD, but were not assessed by INV as PD, may have been continuing study treatment when it should have been discontinued; and thus, safety outcomes may be overreported and median duration of treatment may be longer than it should have been if assessment was prospective. This may introduce some degree of uncertainty in the reported results.
- The targeted study sample size was calculated by using decision operating characteristics for the primary endpoint. The sample size calculation was for both the laBCC and the mBCC patients combined (i.e. it wasn't calculated for laBCC and mBCC individually). While the results of the laBCC subgroup are consistent with the overall trial population, the efficacy results meeting the 30% threshold may be a spurious result as the sample size was not calculated specifically for the laBCC subgroup. Additionally, the recommended dose of sonidegib is 200 mg, however 800 mg was hypothesized to be the more efficacious dose without compromising safety during the design of the study; thus, randomization was 1:2 to the 200 mg and 800 mg groups. The randomization ratio led to a smaller number of patients being assigned to the 200 mg subgroup, which was even smaller when limited to the laBCC subgroup. The laBCC subgroup was not the main consideration in the overall trial sample size calculation; and thus, while the results

of the 200 mg laBCC subgroup are consistent with the overall trial results and met the clinically significant threshold, this could have been a spurious finding.

- There were several subgroup analyses and multiple secondary efficacy outcomes assessed in the trial that were not adjusted to account for multiple comparison testing to control the risk of type 1 error. As the trial was not powered to test specific hypotheses in these additional subgroups and outcomes, the results of these analyses should be interpreted with some degree of caution.
- The BOLT trial did not include a placebo or active comparator. All participants and investigators were aware that the patient was receiving sonidegib, potentially biasing the results of the outcome assessments. At the time of implementation of the study, no established systemic treatments were available for patients with laBCC or mBCC; however, preliminary results from a phase I study demonstrated encouraging efficacy data.[3] The trial therefore included two study groups evaluating two doses of sonidegib. The currently funded treatment for patients with BCC is vismodegib. The comparative effectiveness of sonidegib to vismodegib was not assessed in these studies. The sponsor provided the results of one published unanchored matching-adjusted indirect comparison (MAIC) and one published meta-analysis (MA) that estimated the comparative efficacy and safety of sonidegib to vismodegib, as well as to other comparators. Refer to Section 7 for a summary and critical appraisal of the MAIC and MA.

Table 1: Highlights of Key Efficacy and Safety Outcomes in Patients with laBCC (for efficacy results) and Overall (both laBCC and mBCC for safety results) from the BOLT Trial

Efficacy Outcome	Primary analysis: 28-Jun-2013 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)
Median follow-up, months	13.9		50.2	
Primary Outcome (pEAS)				
ORR: IRC-assessed				
n (%)	18 (42.9)	35 (37.6)	23 (54.8)	44 (47.3)
95% CI	27.7 to 59.0	27.8 to 48.3	38.7 to 70.2	36.9 to 57.9
CR, n (%)	2 (4.8)	0 (0.0)	2 (4.8)	2 (2.2)
PR, n (%)	16 (38.1)	35 (37.6)	21 (50.0)	42 (45.2)
SD, n (%)	21 (50.0)	39 (41.9)	16 (38.1)	33 (35.5)
PD, n (%)	0	0	0	1 (1.1)
Unknown, n (%)	3 (7.1)	19 (20.4)	3 (7.1)	15 (16.1)
Secondary Outcomes (pEAS)				
CRR: IRC-assessed				
% (95% C)	4.8 (0.6 to 16.2)	0.0 (0.0 to 3.9)	4.8 (0.6 to 16.2)	2.2 (0.3 to 7.6)
DOR: IRC-assessed				
Median (95% CI, months)	NE	NE	12.9 (NE)	23.7 (10.8 to 29.6)
PFS: IRC-Assessed				
Median (95% CI, months)	NE	NE	19.0 (NE)	19.4 (13.8 to 30.5)
TTR: IRC-Assessed				
Median (95% CI, months)	3.9 (2.1 to 4.2)	3.7 (2.6 to 3.8)	4.0 (3.8 to 5.6)	3.7 (2.0 to 5.5)

Secondary Outcomes (FAS)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)
OS				
Median (95% CI) months	NE	NE	NE	NE
Harms Outcome (SAS), n (%)	**200 mg sonidegib (n=79)**	**800 mg sonidegib (n=150)**	**200 mg sonidegib (n=79)**	**800 mg sonidegib (n=150)**
Harms Outcome, n (%)				
AE (any grade)	75 (94.9)	150 (100)	77 (97.5)	150 (100)
Grade 3/4 SAE	24 (30.4)	84 (56.0)	34 (43.0)	96 (64.0)
SAE	11 (13.9)	45 (30.0)	16 (20.3)	58 (38.7)
AE leading to dose discontinuation	17 (21.5)	54 (36.0)	24 (30.4)	60 (40.0)
AE leading to dose interruption and/or reduction	25 (31.6)	90 (60.0)	34 (43.0)	100 (66.7)
Deaths**	0	4 (2.7)	1 (1.3)	7 (4.7)

AE = adverse event, CI = confidence interval, CRR = complete response rate, DOR = duration of response, FAS = full analysis set, HRQoL = health-related quality of life, IRC = Independent Review Committee, NE = not estimable, OS = overall survival. PFS = progression-free survival, SAE = serious adverse event, SAS = safety analysis set, TTR = time to response

Analysis sets:

FAS = all patients randomized, irrespective of whether they had received study medication, which was in accordance with the intention-to-treat principle.[2]

pEAS = all patients with fully assessable tumours by mRECIST in patients with laBCC (i.e. patients with tumours that have been adequately assessed by photographs [those with annotated photographs or those without annotated photographs and documentation of the absence of palpable sub-dermal components outside the margins of the photographed lesions] or radiologic scans [MRI or CT] or both) and all patients with mBCC (all patients with mBCC were assessed by RECIST v1.1).[2,4]

SAS = all patients who received at least one dose of study medication and had at least one post-baseline safety assessment.[4]

*43.9% of patients were missing survival information at the time of the 42-month analysis as reported in protocol deviations

Data sources: Health Canada Module 2.7.3;[8] Health Canada Module 2.7.4[11]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One joint patient advocacy group input from Melanoma Network of Canada (MNC) and Save your Skin Foundation (SYSF) was submitted for the review of sonidegib for the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery. MNC gathered responses by conducting an online survey between May 21st, 2020 to June 22nd, 2020, which was open to all patients/caregivers regardless of the stage of disease. The survey generated a total of 49 respondents, 36 of whom were patients and 13 of whom were caregivers. SYSF conducted a separate survey, which yielded a total of three patient respondents from the United Sates, all of whom had experience with sonidegib. From the patient perspective, the most challenging symptoms of the disease reported by patients were scarring and disfigurement and fear and anxiety. As the cancer occurs in the head and neck regions, many patients also reported a negative impact to self-image, family or social life since the scarring and disfigurement is visible. Current treatments for BCC include surgery, topical creams, cryotherapy and radiation, which can cause significantly impairing side-effects and can affect patients' ability to eat, swallow, breathe,

speak and sleep. Due to the burdensome nature of the disease, caregivers also reported a lot of physical and emotional stress from their caregiving duties. Patients and caregivers also complained that successive surgeries and radiation are associated with long wait times and excess travel, which can be time intensive and financially draining. In terms of patients' values and expectations for a new treatment, patients value treatments that are less invasive and can effectively stop the progression of the disease, and treatments that cause less pain, scarring, and disfigurement to ultimately improve quality of life (QoL). All three patients who had experience with sonidegib reported a positive experience with the drug; agreed that the benefits of the treatment outweighed the side effects, and that they preferred the option of sonidegib over debilitating surgery.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) and one federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation of sonidegib:

Clinical factors:

- Switching and/or sequencing with vismodegib, if appropriate

Economic factors:

- Distribution program

Registered Clinician Input

A total of two registered clinician inputs were provided for the review of sonidegib for the treatment of adult patients with laBCC: one from an individual oncologist from the Canadian Dermatology Association (CDA) and one group input on behalf of five oncologists from Cancer Care Ontario (CCO). Both groups of clinicians practice in Ontario. Although both groups of clinicians agreed with inclusion and exclusion criteria of the BOLT trial, the clinician from CDA noted that the trial did not include patients who had been previously treated, were intolerant to, or progressed with vismodegib. The clinician stated that sonidegib should be made available to all patients (i.e., laBCC and mBCC patients). Although there are no head-to-head trials comparing sonidegib with vismodegib, the clinician from CDA noted that sonidegib has greater efficacy than vismodegib. Both groups of clinicians noted that compared to vismodegib, sonidegib has a better toxicity profile (although muscle spasms continue to be a concern), has less adverse events, and can be dose-reduced which makes it a better option for patients who are intolerant to vismodegib. The clinician from CDA noted that sonidegib is also a desirable option for elderly patients, patients who are physically active, and patients that develop alopecia. Both groups of clinicians noted that currently there is no evidence to inform sequencing; however, the clinicians from CCO stated that there may be evidence to inform the use of sunitinib after failure on sonidegib. The clinician from CDA noted that there have been cases where sonidegib has worked after previous treatment with vismodegib, and that sonidegib may be considered for patients progressing on vismodegib and vice versa. Both groups expressed interest to use sonidegib in patients who are intolerant to vismodegib. Both groups of clinicians stated that currently there is no evidence supporting the use of sonidegib for prevention of recurrence after surgery or radiation therapy. All clinicians responded that it is reasonable for patients to take a drug holiday with sonidegib and resume treatment upon progression.

Summary of Supplemental Questions

The following supplemental question were identified during the development of the review protocol as relevant to the CADTH review of sonidegib:

The CADTH review team identified no trials directly comparing sonidegib with vismodegib, which was identified as the relevant comparator in Canadian clinical practice for laBCC patients. In the absence of a direct head-to-head comparison of sonidegib with vismodegib, the sponsor submitted one published and publicly available unanchored MAIC, and one published and publicly available MA, that included vismodegib and other comparators.

Supplemental Issue 1: Summary and critical appraisal of a published unanchored MAIC comparing sonidegib with vismodegib for the treatment of patients with laBCC who are ineligible for curative surgery or radiotherapy[12]

Two trials were included: the BOLT trial which provided individual patient data (IPD) for sonidegib and the ERIVANCE trial which provided aggregate data for treatment with vismodegib. No statistical comparisons between the treatments were provided and minimal adjustment for potential effect modifiers and prognostic factors was provided. Further, no assessment of residual confounding was performed. As such, no conclusions can be made regarding the comparative efficacy of sonidegib and vismodegib based on the submitted unanchored MAIC.

See section 7.1 for more information.

Supplemental Issue 2: Summary and critical appraisal of a published MA comparing sonidegib with other sonic Hh inhibitors, including vismodegib, for the treatment of patients with BCC.[13]

A published MA was identified which aimed to determine and compare the efficacy and safety of sonic Hh inhibitors as a class for treating BCC. The publication included four treatments: sonidegib, vismodegib, itraconazole, and TAK-441. Only sonidegib and vismodegib are approved in Canada for the treatment of patients with laBCC. Numerous critical limitations to the analyses were identified, limiting the generalizability of the results to the Canadian context. Therefore, the results of the MA should be interpreted with caution.

See section 7.2 for more information.

Comparison with Other Literature

The CGP identified that patients with mBCC are generally treated similarly to patients with laBCC who are not amendable to radiation therapy or surgery. In addition, both the CGP and PAG are seeking evidence on the efficacy of sonidegib for the treatment of patients with mBCC. The efficacy results of the mBCC subgroup analysis from the BOLT trial were summarized and examined. The results suggested that IRC-assessed ORR was not clinically meaningful because it was lower than the ORR for overall trial population and the laBCC subgroup. The lower bound of the 95% CI was below the clinically meaningful threshold. However, this was a subgroup analysis that was limited by a very small size, and thus the reported results are uncertain. The CGP do not expect sonidegib to perform differently in mBCC patients when compared to vismodegib since the mechanism of action for both drugs is similar.

A summary of the mBCC subgroup efficacy analyses from the BOLT trial are provided in section 8.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for sonidegib for the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG PS 2	A total of 4 (6.1%) patients were ECOG PS 2 who were treated with 200 mg in the laBCC subgroup.[7]	Can the results be applied to patients with ECOG PS 2?	The results can be applied to patients who have an ECOG PS 2.
	Age and comorbidities	The median age of laBCC patients in the BOLT trial was 67.0 years (range = 24.0 to 93.0).[7] A total of 107 patients (55.2%) were 65 years of age or older. There was no reported information from the BOLT trial on patient comorbidities.	Is the age of included patients in the BOLT trial representative of what would be seen in clinical practice? Can the results be applied to patients with comorbidities?	The laBCC patients included in the BOLT trial appeared to be younger than what would be seen in clinical practice. Younger patients may have less comorbidities, and thus the included patient population in the BOLT trial may be more fit than patients that would be seen in clinical practice. This may have enhanced the efficacy outcomes and/or influenced the side effect and tolerability profile reported in the trial; however, it is expected that older patients who may have more comorbidities would derive similar clinical benefit from sonidegib.
Intervention	Administration of intervention	Patients received sonidegib once daily on a continuous dosing schedule until documented disease progression, intolerable toxic effects, withdrawal of consent, death, discontinuation at an investigator's discretion, dose interruption lasting longer than 21 days (unless the patient was responding to study treatment and had not progressed, in which case resumption of treatment was permitted at the investigator's discretion), use of a prohibited medication, start of another antineoplastic therapy, or study termination.[2]	Would the intervention be administered differently (e.g., dose or schedule) in clinical practice than in the trial? In the absence of PD, would there be any criteria or length of time before a patient may take a treatment holiday before resuming sonidegib?	Sonidegib would not be administered differently in terms of dose or schedule in clinical practice. However, in the event of toxicities alternative dosing strategies may be implemented, similar to other drugs, to avoid stopping treatment such as dosing the drug every other day. This should be done on a case-by-case basis and would be dependent on the type and severity of toxicity the patient is experiencing. Similar to vismodegib, patients may be able to take a treatment holiday, which is done on a case-by-case basis and is dependent on a patient's needs (considered a social lifestyle strategy). The length and time would depend on the patient's

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				needs and preferences, as well as assessment of the disease status.
Comparator	Standard of care	The BOLT trial did not include a comparison to other relevant treatments for this patient population (i.e. vismodegib).	Are the findings of the BOLT trial generalizable to patients who would have been eligible to receive vismodegib?	Yes, criteria would be the same.
Outcomes	Appropriateness of primary and secondary outcomes	The primary outcome was ORR by IRC assessment.[4] Secondary outcomes included DOR, CRR, PFS, OS, TTR, safety outcomes, and PROs.	Were the selection of endpoints appropriate and of clinical relevance to this indication and therapeutic setting?	Yes, in the context of an incurable disease, ORR was an appropriate outcome that is supported by the secondary outcomes studied such as DOR and PFS.
Settings	Countries participating in the trial	The BOLT trial was conducted in 12 countries (Australia, Canada, Belgium, France, Germany, Greece, Hungary, Italy, Spain, Switzerland, United Kingdom, and the United States).[2]	Are there any known differences in the practice patterns between Canada and other countries that the trial was conducted in? Can the results be applied to Canadian patients?	The CGP does not anticipate significant differences in practice patterns between other participating countries and Canada due to the limited treatment options in this patient population. The results can be applied to Canadian patients.

CGP = Clinical Guidance Panel, CRR = complete response rate, DOR = duration of response, ECOG PS = Eastern Cooperative Oncology Group Performance Status, FDA = Food and Drug Administration, Hh = Hedgehog, IRC = Independent Review Committee, laBCC = locally advanced basal cell carcinoma, mBCC = metastatic basal cell carcinoma, ORR = objective response rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PRO = patient reported outcome, TTR = time to response

1.2.4 Interpretation

Burden of Illness and Need

Non-melanoma skin cancer (NMSC) represents 30% of all new cancer cases in Canada, and BCC is the most prevalent form of NMSC accounting for 74% of all cases in Canada.[14,15] Since the 1970s, incidence of BCC has risen annually by 2 to 4%.[15] While BCCs are usually amenable to local therapy with recurrence rates varying from 5% to 14% after initial resection, a small proportion of BCCs may progress to an advanced state that is no longer amenable to available treatments, which can result in considerable morbidity and cause severe disfigurement.[16,17] BCC is relatively common, however laBCC and mBCC are relatively uncommon, and it is estimated that laBCCs and mBCCs account for up to 10% and up to 0.5% of all BCCs, respectively.[18]

The primary goal of treatment of BCC is to provide the best chance for a cure by complete removal of the tumour and maximal preservation of function and cosmesis.[19,20] Various therapeutic options are used to treat BCC, which include surgery, photodynamic therapy, radiotherapy, and approved topical treatments. Typically, localized disease is associated with an excellent prognosis.[21] In contrast, the outcomes of patients with advanced BCC (i.e., laBCC and/or mBCC) are much less favourable. A combination of different treatment modalities is often required, and the clinical decision-making can be complex and

challenging. Locally advanced BCC and mBCC may not be amenable to surgery.[22] While surgery is preferred and may provide improved disease control rates, in some cases of laBCC, surgery may not be an acceptable treatment option as the required procedure may lead to significant deformity or disfigurement, or to detrimental impact on QoL. Indeed, the required procedure may not be technically feasible due to the extent of the disease.[23] Radiotherapy remains an option for advanced BCC patients not amenable to surgery, but can also be limited in achieving disease control.[22] Radiotherapy may cause irreversible damage to involved or surrounding organs such as the eyes and nerves. Furthermore, radiotherapy cannot be provided to anatomical sites which had previously received maximal radiation doses. When surgery and/or radiation are contraindicated, chemotherapy may be used; however, no standard regimen exists and evidence supporting the use of chemotherapy is lacking.[22] Cisplatin alone or in combination with other agents such as paclitaxel, 5-fluorouracil, and doxorubicin have been used, though tumour responses are variable, and no long-term survival and QoL benefit have yet been demonstrated.[24-26] Furthermore, laBCC most commonly develops in an older population, which often has significant comorbid illnesses, which increases the potential for severe treatment toxicity and further limits the potential palliative benefit of systemic chemotherapy.

Molecular studies have shown that almost all BCCs contain genetic alterations in the Hh signaling pathway, which results in aberrant pathway activation and uncontrolled proliferation of basal cells.[27,28] Mutations in PTCH1 and SMO most commonly cause the loss of function in Hh signaling pathway.[28] In Canada, vismodegib, a Hh inhibitor, is the only currently approved systemic treatment option for patients with laBCC who are not amendable to curative surgery or radiation therapy, and for patients with mBCC. Vismodegib is funded across most jurisdictions.[29,30]

Sonidegib is a selective and orally available small molecule inhibitor of the Hh signaling pathway, which received a NOC from Health Canada on June 12th, 2020 for the treatment of patients with laBCC, not amenable to curative surgery or radiation therapy.[31] Although laBCC is a relatively uncommon disease, it can lead to significant morbidity in patients. Thus, there remains an unmet need to have therapeutic choices that have comparable efficacy to existing options, to offer improved tolerability and reduced toxicities, and to be accessible at a lower cost. Sonidegib represents a potential alternative treatment choice when vismodegib is contraindicated or cannot be tolerated by patients.

Effectiveness

BOLT was an international, double-blind, phase II randomized trial that evaluated the efficacy and safety of two doses (200 mg once daily or 800 mg once daily) of sonidegib in adult patients with histologically confirmed laBCC not amenable to radiotherapy or curative surgery, or in patients with mBCC.[2] A total of 230 patients were enrolled in the BOLT trial, of which 194 (84.3%) patients had laBCC and 36 (15.7%) had mBCC. While two doses were tested initially, the 200 mg appeared to be as efficacious as 800 mg and was associated with significantly less toxicity. Consequently, the 200 mg dose was approved for clinical use. As laBCC is the indication under review, in this section, the primary focus will be upon analyses of the laBCC subgroup treated with the 200 mg dose.

The primary efficacy endpoint was IRC-assessed ORR, which is considered a clinically relevant endpoint in the context of an incurable disease.[2,5] The other secondary endpoints such as DOR, PFS, and OS, are also considered relevant in evaluating efficacy in this patient population.[8] At the time of the primary analysis, the IRC-assessed ORR was greater than 30% and the lower bound of the 95% CI exceeded the clinically meaningful threshold of

20%. For the overall trial population (both laBCC and mBCC patients) the ORR was 36.4% (95% CI: 23.8 to 50.4) in the 200 mg group. For the laBCC subgroup analysis, the ORR was 42.9% (95% CI: 27.7 to 59.0).[2,5] The CRR of the laBCC subgroup was only 4.8%.[8] However, in this patient population, the disease control rate (i.e. the proportion of patients who achieve CR, PR, or SD) was high at 93%. The findings at the long-term follow-up data cut-offs were consistent with the primary analysis. Specifically, in the laBCC subgroup, ORR was maintained from 54.8% at 12 months through to the 42-month data cut-off. This consistency in the response rate at these time points, is suggestive that most laBCC patients with a favourable response, will have done so by 12 months.

ORR was supported by the key secondary outcome of IRC-assessed DOR. At the 42-month analysis, the DOR in the laBCC subgroup was 12.9 months, which may be slightly inflated due to censoring rules.[8] An additional secondary endpoint, IRC-assessed PFS, was 19.0 months at the 42-month analysis. PFS may also be inflated because the censoring rules did not account for the start of a new treatment as an event. Upon sensitivity analysis, the PFS was adjusted to 14.9 months, which is still considered clinically meaningful.[9] As of the 42-month data cut-off, one (1.3%) patients had died in the laBCC group and median OS was not estimable at any of the data cut-offs.[8] The results of OS are limited in interpretability as 43.3% of patients in the 200 mg sonidegib group and 39.7% of patients in the 800 mg sonidegib group were censored due to loss to follow-up.[32] It remains unclear why survival data could not be obtained by the sponsor. Although survival is not the primary efficacy outcome of interest, this population tends to be older and have many comorbidities at diagnosis which would impact survival analyses.

Though the results support the efficacy of sonidegib in the laBCC subgroup, several limitations must be acknowledged, such as the potential for selection bias (patients in the trial were younger than would be in clinical practice), the lack of information on patient comorbidities, the lack of a direct comparator, biased censoring rules, and reliance upon subgroup analyses (the overall trial was not designed specifically for the laBCC subgroup and 200 mg dose level being considered). Measures of HRQoL were assessed in the trial for the overall population (laBCC and mBCC) using the EORTC QLQ-C30 and the EORTC QLQ-H&N35.[4] There was no apparent detriment to HRQoL over the course of the study, although the magnitude cannot be interpreted due to the lack of a comparator.

At the time the BOLT trial was conducted, vismodegib was not yet a funded therapy, and thus, the CGP considered the lack of a direct comparator acceptable. In the absence of a direct comparator, the sponsor submitted a published unanchored MAIC comparing sonidegib with vismodegib for the treatment of patients with laBCC who are ineligible for curative surgery or radiotherapy.[12] Two trials were included: the BOLT trial which provided IPD for sonidegib, and the ERIVANCE trial which provided aggregate data for treatment with vismodegib. No statistical comparisons between the treatments were provided and minimal adjustment for potential effect modifiers and prognostic factors was performed. Furthermore, no assessment of residual confounding was performed. Consequently, no conclusions could be made regarding the comparative efficacy of sonidegib and vismodegib based on the submitted unanchored MAIC. The STEVIE trial, which provides longer term efficacy and safety data on vismodegib was also not considered in the MAIC, even though the STEVIE trial would have provided better quality data on vismodegib. The sponsor also submitted a published MA comparing sonidegib with other sonic Hedgehog pathway inhibitors for the treatment of patients with BCC.[13] The publication included four treatments: sonidegib, vismodegib, itraconazole, and TAK-441. Only sonidegib and vismodegib are approved in Canada for the treatment of patients with laBCC, and numerous critical limitations to the

analyses were identified. The generalizability of the results to the Canadian context were extremely limited, and the results of the analyses could not be considered for this review. Thus, the comparative efficacy and safety of vismodegib and sonidegib remains largely unknown due to the poor quality of the indirect treatment comparisons provided with this submission.

Safety

Sonidegib is administered once daily as an oral therapy, and in the BOLT trial, the median duration of treatment in the 200 mg at the time of the primary analysis was 8.9 months (range = 1.3 to 21.4), and at the 42-month analysis, was 11.0 months (range = 1.3 to 53.2).[8] Safety was assessed for overall trial population (both laBCC and mBCC patients), however the focus of this section will remain with the 200 mg group. As of the primary data cut-off, at least one AE had been experienced by 94.9% of patients in the 200 mg group, and 30.4% of patients had experienced Grade 3 or 4 AEs.[11] There was a minor increase in grade 3 or 4 AE rates from 38% at 12 months to 43% at 42 months. The proportion of patients that experienced a SAE also increased from 13.9% to 20.3% by the 42-month analysis; however less than 5% SAEs were suspected to be related to study treatment at the primary and 42-month analyses.

At the time of the primary data cut-off, the most common AEs of any grade that occurred in the 200 mg group were muscle spasms (49.4%), alopecia (43.0%), dysgeusia (38.0%), nausea (32.9%), fatigue (29.1%), diarrhea (24.1%), myalgia (19.0%), and decreased appetite (19.0%).[11] A significant proportion of patients experienced an any-grade AE based on investigations, which included blood CK increased (29.1%), and weight loss (26.6%). The most frequently occurring grade 3 to 4 AEs at the time of the primary analysis were due to laboratory abnormalities, such as increased CK (6.3%), and elevated lipase (5.1%). Generally, there was no detriment to HRQoL reported and it is unlikely that these changes resulted in clinical manifestations. Other grade 3 to 4 AEs included asthenia (2.5%), muscle spasms (2.5%), and hypertension (2.5%), which are expected with this class of Hh inhibitors and considered manageable. At the time primary data cut-off, no SAE occurred in more than one patient. By the 42-month analysis, 20.3% of patients experienced a SAE in the 200 mg group, and pneumonia was the only SAE that occurred in more than one patient (n = 2; 2.5%). One death occurred at the time of the 18-month analysis in a laBCC patient who received the 200 mg dose and was due to acute respiratory distress syndrome associated with septic shock. The very low mortality rate on treatment is suggestive that a highly selected patient population was included in the BOLT trial which may not be reflective of clinical practice. It should also be noted that survival information was missing for 43.9% of patients by the time of the 42-month follow-up, which may infer that deaths could be underreported in the BOLT trial.[7] Nevertheless, the toxicity profile of sonidegib is considered safe and manageable, with no unexpected adverse events.

1.3 Conclusions

The CGP concluded that there may be a clinical benefit with the use of sonidegib in patients with laBCC not amenable to curative surgery or radiation therapy. This conclusion is based on evidence from the BOLT trial, which was a phase II trial randomizing patients to a 200 mg or 800 mg dose of sonidegib and which included both laBCC and mBCC patients. For those in the laBCC subgroup who received the 200 mg dose, a clinically meaningful ORR, DOR, and prolongation of PFS were achieved. Furthermore, the CGP concluded that vismodegib, the only relevant comparator in Canadian clinical practice, would continue to be the

preferred treatment regimen due to longer-term data and clinical experience with vismodegib. Sonidegib provides a reasonable alternative for patients who cannot tolerate vismodegib. In reaching these conclusions, the CGP considered the following factors:

- As the disease is incurable, ORR was considered an appropriate primary endpoint when interpreted with secondary efficacy endpoints such as DOR and PFS.
- While OS is not the primary endpoint of interest in this patient population, the impact of sonidegib on OS remains uncertain. In the BOLT study analysis, a high proportion of patients were censored due to loss to follow-up and therefore the impact of sonidegib on OS may have been overestimated.
- The submitted indirect treatment comparison and meta-analysis comparing sonidegib and vismodegib were poorly conducted with several limitations. The comparative efficacy and safety of sonidegib and vismodegib remains unknown.
- There was no apparent detriment to HRQoL; however, in the absence of a direct comparator, the magnitude of the benefit remains unknown.
- Sonidegib has a reasonably safe toxicity profile. There were no unexpected toxicities, and most toxicities are considered manageable.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

PAG Implementation Questions	CGP Response
Currently Funded Treatments	
PAG noted that treatment of laBCC generally involves surgery and/or radiation therapy. In patients who experience disease recurrence or are ineligible to receive such treatments, therapeutic options are limited to vismodegib (another Hh pathway inhibitor). The latter is indicated and reimbursed in all provinces for the treatment of laBCC and mBCC patients with measurable disease who are not candidates for surgery or radiation therapy. The BOLT trial did not compare sonidegib to another treatment. PAG is seeking comparison to vismodegib in patients with laBCC.	The indirect treatment comparisons submitted were poorly conducted and did not use up-to-date data on vismodegib (i.e. the STEVIE trial), and thus, limited conclusions can be drawn on the comparison between sonidegib and vismodegib for the treatment of patients with laBCC. Based on clinical experience and response data from the ERIVANCE and BOLT trials, sonidegib is expected to be at least as efficacious as vismodegib. Sonidegib may also provide an alternative toxicity profile that may be suitable for some patients when vismodegib is not well tolerated. Overall, due to longer-term data and clinical experience with vismodegib, vismodegib would still be the preferred treatment in this patient population and sonidegib would be used as an alternative option.
Eligible Patient Population	
The funding request of sonidegib is for the treatment of adult patients with locally advanced basal cell carcinoma that is not amenable to surgery or radiation therapy. In view of the inclusion and exclusion criteria and subgroups of the phase II BOLT trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with sonidegib: • Patients with mBCC • Patients intolerant of vismodegib • High-risk post-surgical and RT patients (as adjuvant therapy)	• **Patients with mBCC:** In the BOLT trial, the results of the mBCC subgroup analysis revealed an IRC-assessed ORR that was lower than the overall trial population and the laBCC subgroup, and the lower bound of the 95% CI was below the clinically meaningful threshold. However, this was a subgroup analysis that was limited by a very small size (n=36), and thus the reported results are uncertain. The CGP do not expect sonidegib to perform differently in mBCC patients when compared to vismodegib since the mechanism of action for both drugs is similar. Metastatic BCC patients represent an unmet need because life expectancy is typically much shorter than laBCC patients and few patients would be expected to be eligible for sonidegib due to poor performance status and comorbidities. Nonetheless, the few patients that may be eligible for sonidegib could potentially have dramatic responses similar to vismodegib and if sonidegib is available at a lower cost, it may be a preferred treatment option for mBCC patients.

PAG Implementation Questions	CGP Response
	• **Patients intolerant of vismodegib:** Sonidegib would be used in patients intolerant of vismodegib. • **High-risk post-surgical patients:** It would not be used as adjuvant therapy in high-risk patients post-surgery or radiation therapy when there is no obvious residual disease.
If recommended for reimbursement, patients experiencing tolerability issues with vismodegib may prefer to switch to sonidegib (if still otherwise eligible) and would need to be addressed on a time-limited basis.	Patients experiencing tolerability issues with vismodegib, if still otherwise eligible, could switch to sonidegib.
PAG also identified potential indication creep of sonidegib in patients who failed vismodegib therapy.	There is no evidence to suggest that patients who failed vismodegib would derive clinical benefit to another Hh inhibitor, and some patients develop acquired resistance to Hh inhibitors. Thus, sonidegib would not use in patients who failed vismodegib.
Implementation Factors	
The recommended dose of sonidegib is 200 mg taken orally once daily on an empty stomach, at least 1 hour before or 2 hours after a meal, administered until disease progression or unacceptable toxicity. Sonidegib is available in oral capsules of 200 mg, which hampers dose adjustments and may lead to drug wastage. PAG is seeking advice on modified dosing schedules (e.g. every other day) as alternatives to interrupting or stopping treatment due to toxicity. PAG also seeks clarification on the definition of “disease progression” to help identify criteria for treatment discontinuation.	Per the BOLT trial, doses were only interrupted due to toxicity and not adjusted. Thus, drug wastage is considered minimal. In clinical practice, modified dosing schedules such as dosing every other day, could be used as an alternative to interrupting or stopping treatment due to toxicity, however if toxicities persist despite a modified dosing schedule, then treatment should be interrupted. The BOLT trial used a strict definition for PD based on mRECIST using MRI, digital photography, and histopathology (via biopsies). In clinical practice, PD may be assessed by a number of evaluations that are not limited to radiographical or photographical assessment. Clinical evaluation of PD in practice can include MRI, clinical photography and the amount of wound care requirements. The assessment of PD is best left to the discretion of the treating clinician.
PAG remarked that vismodegib is controlled by a distribution program. Because sonidegib is in the same class, PAG would like to know if there will be a similar program in which pharmacies will need to complete checklists with patients prior to each dispensation. PAG noted that such a program requires yearly training and certification and is labour-intensive; adding a second independent program for a similar drug would be a barrier to implementation.	The distribution program for vismodegib was mandated by Health Canada. Per the Health Canada product monograph, sonidegib is only available through a controlled distribution program called the ODOMZO Pregnancy Prevention Program.[1]
Sequencing and Priority of Treatment	
PAG is seeking guidance on the appropriate place in therapy of sonidegib and overall sequencing of all treatments available for laBCC. In particular, PAG would need information on the following aspects: • Potential adjuvant use of sonidegib for prevention of recurrence after surgery or RT. • Circumstances and rationale for preferring sonidegib or vismodegib. • Evidence informing sequencing of sonidegib and vismodegib, understanding that they have similar mechanisms of action.	• **Potential adjuvant use of sonidegib for prevention of recurrence after surgery or RT:** As per the earlier comment, sonidegib would not be used as adjuvant therapy post-surgery or radiation therapy. • **Circumstances and rationale for preferring sonidegib or vismodegib:** Vismodegib would be the preferred treatment in this patient population, and sonidegib would be used if vismodegib cannot be tolerated or is contraindicated for a patient. Sonidegib would not be used upon progression to vismodegib. • **Evidence informing sequencing of sonidegib and vismodegib, understanding that they have similar**

PAG Implementation Questions	CGP Response
• Switching between sonidegib and vismodegib due to intolerance. • Options upon progression with sonidegib or vismodegib.	**mechanisms of action**: There is no evidence to support sequencing of sonidegib and vismodegib as neither treatment has been studied in second line, which remains an unmet need in this patient population. Some patients may acquire resistance to Hh inhibitors, which may affect response to a second Hh inhibitor. • **Switching between sonidegib and vismodegib due to intolerance:** Patients can be switched from sonidegib to vismodegib, or vice versa, due to intolerance. Patients should not be switched due to failure on either treatment. • **Options upon progression with sonidegib or vismodegib:** There are no approved or well-studied treatment options upon progression with sonidegib or vismodegib. Patients are typically treated with unapproved chemotherapy.

CGP = Clinical Guidance Panel, Hh = Hedgehog, IRC = Independent Review Committee, laBCC = locally advanced basal cell carcinoma, mBCC = metastatic basal cell carcinoma, mRECIST = modified Response Evaluation Criteria in Solid Tumors, ORR = objective response rate, PAG = Provincial Advisory Group, PD = progressive disease, RT = radiation therapy

2 Background Clinical Information

2.1 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.[33] 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 detected amongst younger patients.[34] 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.[35]

Most BCCs are generally diagnosed and treated early, however some BCCs become extensive and infiltrative, posing a greater risk to patients.[18] Generally, it is a slow growing tumour with a doubling rate between six months to one year, but 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.[36] In BCCs occurring in the periocular region, perineural progression can lead to invasion of the orbital structures and result in pain, paresthesias, eye muscle weakness and blindness.[37] Metastasis of BCC is rare with rates of 0.0028 to 0.55%. Most common sites of metastatic spread are lymph nodes and lungs.[38] Squamous differentiation may be present in the primary or metastatic sites and may contribute to the aggressive phenotype in these rare cases.

2.2 Accepted Clinical Practice

The principal modality of therapy for BCC is surgery. Curettage and electric dissection are commonly employed with cure rates up to 98%.[39] 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.[40]

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.[41]

Chemotherapy has been used to manage both metastatic and uncontrolled locally advanced BCCs.[42] However, the results have been very disappointing. Patients with metastatic BCC have a life expectancy of 10 to 20 months, which is dependent upon the sites and extent of disease and the overall patient performance status.[43] 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.

Basal Cell Nevus Syndrome (BCNS) or Gorlin Syndrome is, an inherited autosomal dominant condition. The gene on chromosome 9 which encodes PTCH1 is mutated which leads to loss of autoregulation of SMO.[44] 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.[45] 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.

Treatment in patients with locally advanced BCC or metastatic BCC

Although laBCC and mBCC 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. With respect to 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, 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 BCC or mBCC most commonly occurs in older population which often has significant comorbid illnesses which further limit the palliative benefit of systemic chemotherapy

The Hh signal pathway appears to be critical in the pathogenesis of BCCs.[46] 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.[47] The locus encodes for PTCH1, a transmembrane receptor which inhibits SMO signaling and the downstream activation of cellular proliferation.[48] Because abnormalities in the Hh signaling pathway are common in sporadic cases of BCC, routine testing to determine the precise nature of the signaling aberration is not recommended for clinical practice.

Currently, the only approved Hh inhibitor in Canada is vismodegib, which is approved for both laBCC and mBCC. The efficacy of vismodegib was evaluated in the multicenter phase II trial, ERIVANCE trial which included 33 patients with mBCC and 63 patients with locally advanced disease.[49] 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. In STEVIE, an international open label trial of vismodegib (n=1232) response rates were 68.5% in laBCC, 36.9% in mBCC.[50]

Sonidegib is a selective and orally available small molecule inhibitor of the Hh signaling pathway, which received a notice of compliance (NOC) from Health Canada on June 12th, 2020 for the treatment of patients with laBCC not amenable to curative surgery or radiation therapy.[31] This report focuses on the evidence from the BOLT, phase II trial, which evaluated the use of sonidegib at dose levels, 200 mg and 800 mg, in both laBCC and mBCC patients.

3 Summary of Patient Advocacy Group Input

One joint patient group input from MNC and SYSF was provided for the review of sonidegib for the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery. MNC gathered responses by conducting an online survey between May 21st, 2020 to June 22nd, 2020, which was open to all patients/caregivers regardless of the stage of disease. A letter detailing the purpose of the survey and the survey link was emailed to specific dermatologists in Canada and a few, select locations in the United States. The survey was also circulated online through the MNC website as well as Facebook and Twitter. The survey generated a total of 49 respondents, 36 of whom were patients and 13 of whom were caregivers. Out of the 36 patient respondents, 28 were female and eight were male. One of the respondents was from the United Sates and the rest were from Canada. Out of the patient respondents, two (5.6%) were between the ages of 41 to 50 years, five (14.29%) were between the ages of 51 to 60 years, 18 (50%) were between the ages of 61 to 70 years and 11 (30.56%) were above the age of 70. Two of the patient respondents had mBCC, 24 had early stage BCC and nine respondents reported that they did not know what stage of the disease they were in. None of the patient respondents from the MNC survey had experience with sonidegib. SYSF provided the results of an additional survey of three patient respondents from the United Sates, all of whom were male participants over the age of 65 who had experience with sonidegib. All three patients were male and over the age of 65 years.

From the patient perspective, living with BCC was significantly challenging, causing debilitating physical and emotional symptoms. The most challenging symptoms of the disease reported by patients were scarring and disfigurement and fear and anxiety. As the cancer occurs in the head and neck regions, many patients also reported a negative impact to self-image, family or social life due to the disturbing nature of the scarring and disfigurement caused by this disease. The patient groups providing input stated that current treatments for BCC including surgery, topical creams, cryotherapy and radiation, can result in significantly impairing side effects and can affect patients' ability to eat, swallow, breathe, speak and sleep. Due to the burdensome nature of the disease, caregivers also reported a lot of physical and emotional stress from their caregiving duties. Patients and caregivers were also concerned that successive surgeries and radiation are associated with long wait times and excess travel, which can be time intensive and financially draining. All three patients who had experience with sonidegib reported a positive experience with the drug. One patient did not experience any side effects, while one patient experienced alopecia and another experienced mild dysgeusia. The patients reported that the benefits of the treatment outweighed the side effects and that they were very pleased with having the option of an oral treatment. Patients and caregivers of BCC value treatments that are less invasive and can effectively stop the progression of the disease, and treatments that cause less pain, scarring, and disfigurement to ultimately improve quality of life.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

Patients were asked to describe the physical and emotional impact of the disease (Table 4). Approximately half of the 21 respondents reported scarring or disfigurement (n=12, 57.14%). MNC and SYSF commented that since the cancer occurs mostly in the head and neck region, it can be very visible and disfiguring. The cancer also was reported by the patient groups to have a debilitating effect on patients' mental health. Fear and anxiety were reported by nine (42.86%) patients, and eight (38.10%) patients reported a negative impact to self-image, family and social life. MNC and SYSF commented that the advanced age of many of the patients has made travel, home support and dealing with other health issues even more challenging. Scarring, disfigurement, pain, social isolation and depression can be even more prominent with advanced or metastatic disease. MNC and SYSF highlighted that advanced surgery practices that can reduce scaring and disfigurement are considered the standard of care in some provinces but are not yet available in all provinces across Canada.

Table 4: Challenges of Living with BCC

Answer Choices	Responses	
	n	%
Pain	3	14.29
Scarring or disfigurement	12	57.14
Edema or fluid retention	1	4.76
Peripheral neuropathy (nerve pain or damage)	5	23.81
Disrupted sleep	3	14.29
Fear or anxiety	9	42.86
Fatigue	3	14.29
Depression	4	19.05
Negative impact to self image, family or social life	8	38.10
Financial loss or job loss	1	4.76
Impact on sexuality	2	9.52
None - there has been no impact	4	19.05
Answered:	**21**	

Below are some patient comments regarding their disease experience:

- *"I never thought it was serious. Most people said it was nothing. Then it keeps coming up all over. I am tired of having to go all the time and have things cut out. My face and shoulders look horrible. I often feel depression and don't want to see anyone. It is painful and I am scared and scarred to go outside."*
- *"Anxiety is the factor that affects my quality of life as the scarring is on my nose. I have experienced feelings of lower self-esteem."*
- *"Quality of life has been experienced re less social time with friends and family. I am quite fit and exercise everyday. I have not been able to exercise and miss the social interaction."*
- *"It has affected my ability to eat, smile, close my mouth. I am very upset all the time with the way I look. I no longer want to go out much. I am scared of new procedures but worry that it may not stop."*

3.1.2 Patients' Experiences with Current Therapy

MNC and SYSF stated that most cases of locally advanced or metastatic BCC are treated with surgery, topical creams, cryotherapy and/or radiation. The disease can be quite challenging to treat because it mostly occurs on the head and neck regions. Current surgical procedures and side-effects of radiation can significantly impair patients' quality of life as patients often experience significant physical scarring, along with severe pain and emotional issues. The patient groups noted that currently there is no standard protocol for chemotherapy for the treatment of laBCC or mBCC.

Below are some patient comments regarding their experiences with current therapy:

- *"I had a lot of radiation after many surgeries. I think the radiation was the worst. Lots of trips in where I had to travel 2 hours each way. I finally had to move in with my daughter as I had to go 30 times."*
- *"Waiting for Mohs surgery, weeks and weeks to wait. People wait 12-14 months here, by then BCC has spread! Not sure what the outcome with the end of my nose but expect it to be extensive as see signs of it growing. Very stressful waiting and there are not very many doctors in B.C. to do it, so wait lists are extensive! One dermatologist in Kelowna 12-14 mths wait, one dermatologist in Kamloops that is off the medical system as they don't pay dermatologists enough in B.C. to stay he says."*
- *"I feel that not knowing if all of the cancer was removed by the 2nd surgery to my nose is very stressful. Have to wait a long time to see Surgeon for results."*
- *"The problem was the surgery was around my eye. Can't close it very well now, but I guess it is as good as it can be. But my eye is weeping all the time and I think I don't see very well. I am old so maybe I shouldn't complain."*
- *"Surgery and radiation are both very painful. The treatment lotion burned my skin severely. It looked horrific."*

3.1.3 Impact on Caregivers

Caregivers participating in the MNC survey reported that their caregiving duties can be significantly burdensome, as caregiving requires an excess amount of physical and financial resources. It was also reported that as patients are often above the age of 60, spouse caregivers may also concurrently deal with their own health issues and are often not able to effectively care for the patients. Caregivers expressed a need for psychosocial support to treat depression and anxiety. Physical care needs such as frequent wound changing were reported to be quite challenging to manage. Caregivers also mentioned that frequent treatment sessions lead to increased travel expenses and time commitments (one caregiver reported four to five hours of travel one way), often several times a week, and that the COVID-19 pandemic has led to added travel delays and cancellations causing increased stress and difficulties.

The following are some comments by caregivers regarding their caregiving challenges:

- *"Long wait times in British Columbia made us seek out treatment for him in Alberta. Care was excellent in Calgary. BC Medical paid for the surgery but not for the air fare."*
- *"Long wait time to see doctors for diagnoses and receive biopsy. Then scheduling of surgery. Total time was over a year."*
- *"Not really. I have to travel a lot to go see the dermatologist and the oncologist for treatment. It is time and costs a lot to travel and park. We don't live in the city so not so easy."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Both patients and caregivers had similar responses when asked of expectations of new therapies for BCC. Effectively halting progression of the disease was the most important outcome desired by respondents. The second most important outcome was less invasive treatments. The patient group input noted that surgery, radiation and topical agents are often associated with debilitating side effects that are especially more pronounced for elderly patients. This combined with the fear of recurrence, long wait times, increased travel and other associated costs could all lead to a physically and emotionally draining treatment experience. A tolerable side effect profile was the third most important outcome desired by respondents. MNC and SYSF commented that therapies such as sonidegib can provide the option for an effective and convenient oral treatment with minimal side effects. An effective treatment option can also potentially reduce the amount of successive surgeries and radiation, which can not only be beneficial to patients, but also reduce the burden of care to caregivers. MNC and SYSF further highlighted the lack of effective treatment options currently available and commented that based on the results of the research, sonidegib is a promising treatment option as it may be associated with an improved PFS rate and OS rate.

The following are some patient comments regarding improved oral therapies:

- *"I had infiltrating basal cell carcinoma on my nose. I have been told I have a 2% chance of a local recurrence and a 50% chance elsewhere on my body in the next 5 years. Immediately after my Mohs surgery I was diagnosed with breast cancer. I have now had 5 different kinds of cancer in my lifetime. I will always consider new treatments to make my life better."*
- *"It would help to alleviate the stress and anxiety felt everyday. Improvement in time management of access to doctors is greatly needed. Dermatologist need to be more sensitive to the needs of their patient. I was handed a pamphlet about BCC and to book an appointment for a biopsy. Could not get an appointment until 6 months later. Two weeks before biopsy Appt I was told I would have to wait another 2 weeks as Dr was going on vacation. I was devastated. Thankfully my general Dr got me in to see a wonderful plastic surgeon. We need better treatment to deal with this stuff and actual access to doctors in a timely fashion."*
- *"That would be beyond wonderful! I already had one BCC on my lower eyelid 2 yrs. ago, so this is my second one on the end of my nose and I see more areas that probably more are starting. I didn't even know I had BCC and probably had it for a few years as I had a lump below the skin that my gp didn't seem worried about, now I am worried sick!"*
- *"I think I am at high risk as they can't control it so far. If there was a good treatment, I wish I would have been offered that before surgery so I wouldn't look the way I do. I worry that I may die from this and it won't be a good way to go!"*

3.2.2 Patient Experiences to Date

All three respondents from the survey circulated by SYSF had experience with sonidegib, all of whom accessed the drug through private insurance. All patients had previous surgery around the head and neck areas which they reported to be quite painful. All patients had completed the treatment protocol. One patient suffered from alopecia, one patient reported mild dysgeusia and one patient did not report any side effects. The two patients who reported side-effects explained that those were manageable and that they were aware of potential side effects before the treatment started. All three patients reported that the

benefits of the treatment outweighed the side effects and concluded that having the option of an oral treatment over surgery was quite life changing.

3.3 Companion Diagnostic Testing

None identified.

3.4 Additional Information

MNC and SYSF emphasized some points based on the patient and caregiver responses. The patient groups emphasized that existing therapies are associated with significant side effects which may negatively impair the quality of life of patients and their caregivers. The patient groups asserted the importance of providing effective therapies much earlier in the course of the disease, as opposed to much later when patients have gone through intensive surgeries and radiation. They believed delays in treatment and lack of availability of effective treatments across the country could especially be troublesome. The patient groups also noted that, considering the aging population, the incidence of the disease is expected to increase.

4 Summary of Provincial Advisory Group (PAG) Input

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 CADTH website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) and one federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation of sonidegib for laBCC:

Clinical factors:

- Switching and/or sequencing with vismodegib, if appropriate.

Economic factors:

- Distribution program.

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that treatment of laBCC generally involves surgery and/or radiation therapy. In patients who experience disease recurrence or are ineligible to receive such treatments, therapeutic options are limited to vismodegib (another Hh pathway inhibitor). The latter is indicated and reimbursed in all provinces for the treatment of laBCC and mBCC in patients with measurable disease who are not candidates for surgery or radiation therapy.

The BOLT trial did not compare sonidegib to another treatment. PAG is seeking comparison to vismodegib in patients with laBCC.

4.2 Eligible Patient Population

The funding request of sonidegib is for the treatment of adult patients with laBCC that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy. In view of the inclusion and exclusion criteria and subgroups of the phase II BOLT trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with sonidegib:

- Patients with mBCC
- Patients intolerant of vismodegib
- High-risk post-surgical patients

PAG noted that the draft product monograph mentions adverse changes in growing bone and teeth in animal studies. Consequently, there are concerns regarding the safety of sonidegib in the pediatric population.

If recommended for reimbursement, patients experiencing tolerability issues with vismodegib may prefer to switch to sonidegib (if still otherwise eligible) and would need to be addressed on a time-limited basis.

PAG is concerned with potential indication creep of sonidegib to patients with mBCC, as adjuvant therapy in high-risk patients in remission after surgery and RT, and in patients who failed vismodegib therapy.

4.3 Implementation Factors

The recommended dose of sonidegib is 200 mg taken orally once daily on an empty stomach, at least one hour before or two hours after a meal, administered until disease progression or unacceptable toxicity. Sonidegib is available in oral capsules of 200 mg, which hampers dose adjustments and may lead to drug wastage. PAG is seeking advice on modified dosing schedules (e.g. every other day) as alternatives to interrupting or stopping treatment due to toxicity. PAG also seeks clarification on the definition of "disease progression" to help identify criteria for treatment discontinuation.

PAG noted that sonidegib would be a replacement of vismodegib in laBCC. There may similarities in the management of patients using members of the Hedgehog inhibitor class. This includes management of musculoskeletal adverse reactions and monitoring of CPK levels. PAG also noted known developmental toxicity from sonidegib and highlights the need for male and female contraception in patients using this drug.

PAG remarked that vismodegib is controlled by a distribution program. Because sonidegib is in the same class, PAG would like to know if there will be a similar program in which pharmacies will need to complete checklists with patients prior to each dispensation. PAG noted that such a program requires yearly training and certification and is labour-intensive; adding a second independent program for a similar drug would be a barrier to implementation.

PAG noted that sonidegib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair time would be required. PAG identified the oral route of administration is an enabler to implementation and that once daily dosing (with or without food) would be convenient for patients.

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.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate place in therapy of sonidegib and overall sequencing of all treatments available for BCC. In particular, PAG would need information on the following aspects:

- Potential adjuvant use of sonidegib for prevention of recurrence after surgery or RT.
- Circumstances and rationale for preferring sonidegib or vismodegib.
- Evidence informing sequencing of sonidegib and vismodegib, understanding that they have similar mechanisms of action.

- Switching between sonidegib and vismodegib due to intolerance.
- Options upon progression with sonidegib or vismodegib.

4.5 Companion Diagnostic Testing

None needed.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of two registered clinician inputs were provided for the review of sonidegib for treatment of adult patients with laBCC that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy: one from an individual oncologist from the CDA and one group input on behalf of five oncologists from CCO. Both groups of clinicians practice in Ontario. Although both groups of clinicians agreed with inclusion and exclusion criteria of the BOLT trial, the clinician from CDA noted that the trial did not include patients who had been previously treated with, were intolerant to, or progressed with vismodegib. The clinician stated that sonidegib should be made available to patients with laBCC and mBCC patients. Although there are no head-to-head trials comparing sonidegib with vismodegib, the clinician from CDA noted that sonidegib has greater efficacy than vismodegib. Both groups of clinicians noted that compared to vismodegib, sonidegib has a better toxicity profile, less adverse events and can be dose reduced which makes it a better option for patients who are intolerant to vismodegib. The clinician from CDA noted that sonidegib is also a desirable option for elderly patients and patients who are physically active. Both groups of clinicians noted that currently there is no evidence to inform sequencing; however, the clinicians from CCO stated that there may be evidence to inform the use of sunitinib after failure on sonidegib. The clinician from CDA noted that there have been cases where sonidegib has worked after previous treatment with vismodegib. Both groups of clinicians stated that currently there is no evidence supporting the use of sonidegib for prevention of recurrence after surgery or radiation therapy. All clinicians responded that it is reasonable for patients to take a drug holiday with sonidegib and resume treatment upon progression.

Please see below for details from the clinician inputs.

5.1 Current Treatments

The joint group of clinicians from CCO agreed with the treatments listed under the provincial algorithm. The clinician from CDA emphasized that vismodegib is the most appropriate comparator for sonidegib and is currently funded.

5.2 Eligible Patient Population

Both groups of clinicians agreed that the inclusion and exclusion criteria of the trial are applicable to clinical practice and that the patient population in the funding request aligns with the need in clinical practice. However, the clinician from CDA noted that the study did not assess patients who have been previously treated with vismodegib, patients who were intolerant to vismodegib or patients whose tumour had progressed even with treatment. Patients who had been treated with a previous Hh inhibitor were excluded from the trial. The clinician asserted that since not all patients tolerate vismodegib or respond to it, there is a need for another Hh inhibitor. The clinician believes that sonidegib should be made available to patients with both laBCC and mBCC patients, and not just a subgroup of patients.

5.3 Relevance to Clinical Practice

The clinicians from CCO stated that unlike vismodegib, treatment with sonidegib can be dose reduced. Patients often don't tolerate treatments with vismodegib and are unable to reduce the dose. The clinicians further commented that the toxicity profile of sonidegib

seems milder, but muscle spasms can still be a concern. The clinicians would like to have the option to use sonidegib upfront and not just restricted to patients who have recurred.

The individual clinician from CDA compared the pharmacokinetic profiles of vismodegib and sonidegib. The clinician noted that the maximum serum concentration of vismodegib occurs with 150 mg, and that higher doses do not increase the unbound drug in the plasma. Increasing the dose of sonidegib increases the unbound drug in the plasma until dose-limited absorption occurs. The clinician providing input also stated that sonidegib is more lipophilic than vismodegib. The concentration of sonidegib is six times higher in the skin than in the plasma, whereas vismodegib is mostly present in the plasma. Additionally, the half-lives of the two drugs are quite different. Sonidegib has a longer half-life of 28 to 30 days, whereas vismodegib has a half-life of 4 to 12 days. The clinician noted that median time to response for sonidegib was 3.9 months in the BOLT trial and the median time to response for vismodegib was 5.6 months in the ERIVANCE trial. It was acknowledged in the clinician input that there are currently no head-to-head trials comparing sonidegib to vismodegib; however, an analysis of sonidegib vs. vismodegib indicates that sonidegib has greater efficacy.

The clinician from CDA further explained that a review of pivotal trials shows that sonidegib is associated with less frequent AEs which are less severe with the exception of fatigue that occurs usually later on in the course of the treatment. Additionally, muscle spasms (42.4% vs. 71.2%) and alopecia (49.4% vs. 66.3%) occurred less frequently in the BOLT trial at 30 months vs. the ERIVANCE trial at 39 months. The clinician noted patients often don't wish to take vismodegib due to alopecia, which is often permanent, and therefore a drug which has a lower likelihood of causing alopecia would be preferred by many patients. Since patients with laBCC and mBCC are often frail and elderly, they have difficulty tolerating medication and therefore a medication with an improved safety profile is very desirable. Additionally, the clinician noted that there was a lack of improvement in QoL in the ERIVANCE trial, whereas the BOLT trial showed an improved or sustained QoL, despite the AEs. It was noted, however, that the STEVIE trial with vismodegib did show improvement in the emotional domain in the SKindex-16. The clinician concluded that the result of the trial suggests that sonidegib may be better tolerated even if it is discontinued due to AEs. Since it has a longer elimination half-life, the drug may still be treating the cancer.

The clinician from CDA stated that the contraindications are similar for sonidegib and vismodegib. Sonidegib may be considered for patients whose tumour is progressing on vismodegib, and vice versa. In adults who are physically active, muscle aches and elevated CK levels are common. Sonidegib may also be considered for patients who have an active lifestyle or an active work environment and patients who develop alopecia. Patients who develop these side effects on vismodegib and have progressive BCC might also be considered for sonidegib; however, the clinician cautioned that there are no clinical trials to inform this decision.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

Both clinician groups acknowledged that currently there is no data to inform sequencing. The clinician from CDA noted that the binding to SMO, the pharmacodynamic profiles and adverse events profile are different for sonidegib and vismodegib. Resistance mutations can develop with Hh inhibitors and therefore one may be substituted for another. The binding mutations to SMO can similarly affect both vismodegib and sonidegib; however, many

mutations only affect binding of vismodegib, making sonidegib more efficacious. The clinician stated that there have been cases where sonidegib has worked after previous treatment with vismodegib. Similarly, the clinicians from CCO stated that there is interest to use sonidegib for patients who are intolerant to vismodegib. The clinicians also stated that there may be evidence in the future to inform the use of sunitinib after failure on sonidegib.

5.4.1 Is there evidence on the use of sonidegib for prevention of recurrence after surgery or radiation therapy (i.e., adjuvant use)?

Both groups of clinicians noted that currently there is no evidence to inform this.

5.4.2 What would be the circumstances and rationale for preferring sonidegib or vismodegib for the treatment of locally advanced or metastatic BCC?

The clinician from CDA noted that although there are currently no head-to-head trials that suggest the use of one drug over the other, the data suggest that sonidegib has a longer duration of response than vismodegib. It is better tolerated with fewer side effects, particularly alopecia. Better tolerance of the drug also makes it a preferable option for elderly patients. Additionally, physically active patients, specifically those who work in professions that require manual labour would better tolerate sonidegib due to reduced likelihood of muscle spasms. If a patient in intolerant to vismodegib, sonidegib should be considered.

Similarly, the clinicians from CCO reiterated that sonidegib would be preferred over vismodegib due to lower toxicity, and the ability to dose reduce. Additionally, the CCO clinicians stated that sonidegib has similar, if not, better efficacy compared to vismodegib.

5.5 Companion Diagnostic Testing

The clinicians from CCO noted that companion diagnostic testing is not required for sonidegib. However, there is some emerging evidence that suggests that some patient mutations may affect treatment activity, but this finding is still in its initial stages.

5.6 Implementation Questions

5.6.1 Some patients take a drug holiday with vismodegib and then resume upon progression. Would this be reasonable with sonidegib as well?

Both clinician input documents indicated that this is reasonable. The clinician from CDA noted that in the BOLT trial, dose interruption up to 21 days occurred to manage AEs. Additionally, patients in the 800 mg arm were able to de-escalate the doses to 400 mg and 200 mg afterwards to manage AEs. Most AEs were resolved in 12 to 14 days, after which treatment was continued.

5.7 Additional Information

None identified.

6 Systematic Review

6.1 Objectives

The primary objective of this systematic review is to evaluate the efficacy and safety of sonidegib for the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery.

Supplemental issues and Comparison with Other Literature relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined below. More details are provided in in section 7 and section 8.

- **Supplemental Issues:** The CADTH review team identified no trials directly comparing sonidegib with vismodegib, which was identified as the relevant comparator in Canadian clinical practice for laBCC patients. In the absence of a direct head-to-head comparison of sonidegib with vismodegib, the sponsor submitted one published and publicly available unanchored MAIC, and one published and publicly available MA, that included vismodegib and other comparators.
  - Summary and critical appraisal of a published unanchored MAIC comparing sonidegib with vismodegib for the treatment of patients with laBCC who are ineligible for curative surgery or radiotherapy.[12]
  - Summary and critical appraisal of a published MA comparing sonidegib with other sonic Hh inhibitors, including vismodegib, for the treatment of patients with BCC.[13]
- **Comparison with Other Literature:** The CGP identified that patients with mBCC are generally treated similarly to patients with laBCC that are not amendable to radiation therapy or surgery, and both the CGP and PAG are seeking evidence on the efficacy of sonidegib for the treatment of patients with mBCC.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH 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. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 5: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes

Published or unpublished RCTs
 	
In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of sonidegib should be included
	Adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery
	
	Subgroups
	• Genetic mutations (e.g. TP53, PTCH1, etc.)
	• WHO Status Grade
	• ECOG PS
	• Number of prior lines of therapy (if applicable)
	• High-risk features including:
	  ○ Depth/invasion
	  ○ Tumor size
	  ○ Tumor location
	  ○ Histological subtype (aggressive versus not aggressive)
	  ○ Recurrent/refractory lesions
	  ○ Previous radiotherapy
		Sonidegib	Vismodegib	• ORR
				• CRR
				• TTR
				• DOR
				• **PFS**
				• OS
				• **AEs**
				• **HRQoL**

AE = adverse event; CRR = complete response rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; HRQoL = health related quality of life; laBCC = locally advanced basal cell carcinoma; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PTCH1 = protein patched homolog 1; RCT = randomized controlled trial; TP53 = tumour protein p53; TTR = time to tumour response; WHO = World Health Organization.

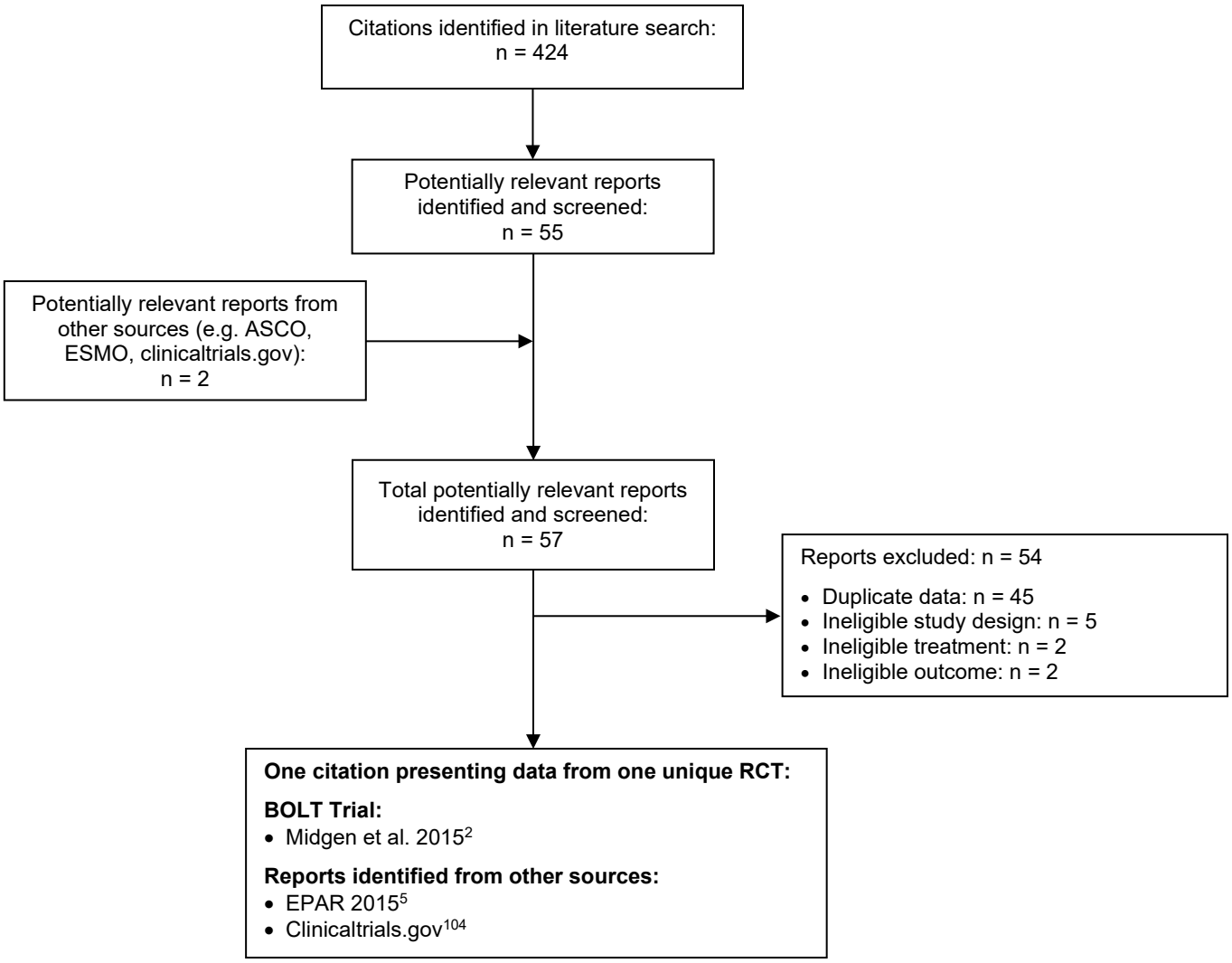
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 12 potentially relevant reports identified, four studies were included in this CADTH systematic review and eight studies were excluded (Figure 1). Studies were excluded because they reported duplicate data,[51-96] data from an ineligible study design,[12,13,97-99] data from an ineligible treatment,[100,101] or data for an ineligible outcome.[102,103] No ongoing trials were identified that would have met the review protocol of the systematic review.

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to the BOLT trial were also obtained through requests to the Sponsor by CADTH [Clinical Study Protocol, 2016;[4] 6-month Clinical Study Report, 2014;[9] 42-month Clinical Study Report 2017;[32] Final Clinical Study Report 2018;[105] Clinical Summary, 2020;[106] Additional Information August 20, 2020;[7] Additional Information September 25, 2020;[107] Additional Information October 22, 2020;[10] Health Canada Module 2.7.3;[8] Health Canada Module 2.7.4[108]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

One RCT, BOLT, met the selection criteria of the systematic review.[2] Key characteristics of the BOLT trial, including study design, eligibility criteria, interventions, and trial outcomes, are summarized in Table 6.

Table 6: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: BOLT9 NCT01327053 **Characteristics:** Phase II, double-blind, randomized (1:2), two dose levels • N randomized = 230 200 mg dose: n=79 800 mg dose: n=151 • N treated = 268 200 mg dose: n=79 800 mg dose: n=150 **Settings:** 58 sites in 12 countries (Australia, Canada, Belgium, France, Germany, Greece, Hungary, Italy, Spain, Switzerland, United Kingdom, United States) **Patient Enrolment Dates:** July 20, 2011 to Jan 10, 2013 **Data cut-off:** June 28, 2013 **Study completion date (last patient, last visit):** June 29, 2018 **Funding:** Novartis Pharmaceuticals Corporation (sonidegib sold to Sun Pharma in 2016)	**Key Inclusion Criteria:** • Patients ≥ 18 years of age • Histologically confirmed laBCC not amenable to radiotherapy or curative surgery, or mBCC for which all existing available treatment options had been exhausted • For patients with laBCC: at least one measurable lesion ≥ 10 mm in at least one direction via MRI of colour photography • For patients with mBCC: at least one measurable non-nodal lesion of at least double the slice thickness or 10 mm that can be accurately measured in at least one dimension by spiral CT or MRI, or nodal lesion ≥ 15 mm in the short axis by spiral CT or MRI • WHO status grade of ≤ 2 • Adequate bone marrow function (absolute neutrophil count ≥ 1.5 x 10^9 cells/L, haemoglobin ≥ 90 g/L, and platelet count ≥ 100 x 10^9 cells/L), liver function (total bilirubin concentration in serum ≤ 1.5 x ULN, aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN or ≤ 5 x ULN in patients with liver metastases), and renal function (creatine kinase concentration in serum ≤ 1.5 x ULN, creatinine concentration in serum ≤ 1.5 x ULN or 24 hour creatinine clearance ≥ 0.84 mL/s per m^2) **Key Exclusion Criteria:** • Previously treated with systemic sonidegib or with other Hh pathway inhibitors • Patients who are receiving treatment with medications known to be moderate and strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and	**Intervention:** Sonidegib orally once daily on a continuous dosing schedule Two doses: • 200 mg once daily • 800 mg once daily **Comparator:** None	**Primary:** • ORR **Secondary:** • DOR • CRR • PFS • TTR • OS **Exploratory:** • PRO (EORTC QLQ-C30 and the QLQ-H&N35, SF-36)

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	that cannot be discontinued before starting treatment with sonidegib • Had major surgery within four weeks of initiation of study medication • Concurrent, uncontrolled medical comedications that may interfere with participation or potentially affect the interpretation of the study • Unable to take oral drugs or lack of physical integrity of the upper gastrointestinal tract or known malabsorption syndromes • Patients with neuromuscular disorders, are on concurrent treatment with drugs that may cause muscle damage, or on concurrent therapy with other anti-neoplastic agents • Patients planning on starting a new strenuous exercise regimen after initiation of study treatment (as muscular activities that can result in significant increases in plasma CK levels should be avoided while on sonidegib treatment) • Patients who had taken part in an experimental drug within four weeks of initiation of study medication • Pregnant or nursing women		

CK = creatine kinase; CRR = complete response rate; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; H&N35 = Head and Neck Cancer Module 35; Hh = hedgehog; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; QLQ-C30 = Quality of Life Questionnaire-Core 30; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcomes; SF-36 = The Medical Outcomes Study Short Form 36 (SF-36, version 2, Acute); TTR = time to tumour response; ULN = upper limit of normal; WHO = World Health Organization.
Data Sources: Midgen et al. 2015,[2] EPAR 2015,[5] Final Clinical Study Report 2018,[105] Clinicaltrials.gov[104]

a) Trials

BOLT was an international, double-blind, phase II randomized trial that evaluated the efficacy and safety of two doses of sonidegib in adult patients with histologically confirmed laBCC not amenable to radiotherapy or curative surgery, or mBCC for which all existing available treatment options had been exhausted.[2] This study was conducted at 58 sites across 12 countries, which are listed in Table 6, and included three Canadian patients.

As the objective of this systematic review is to evaluate the efficacy and safety of sonidegib in laBCC patients, the study results (i.e., patient demographics, disease demographics, patient disposition, efficacy, and HRQoL results) will focus on the laBCC subgroup and brief results of the overall trial population will be summarized, when relevant. Safety results (including drug exposure) will be described for the overall trial population (i.e. both laBCC and mBCC patients together).

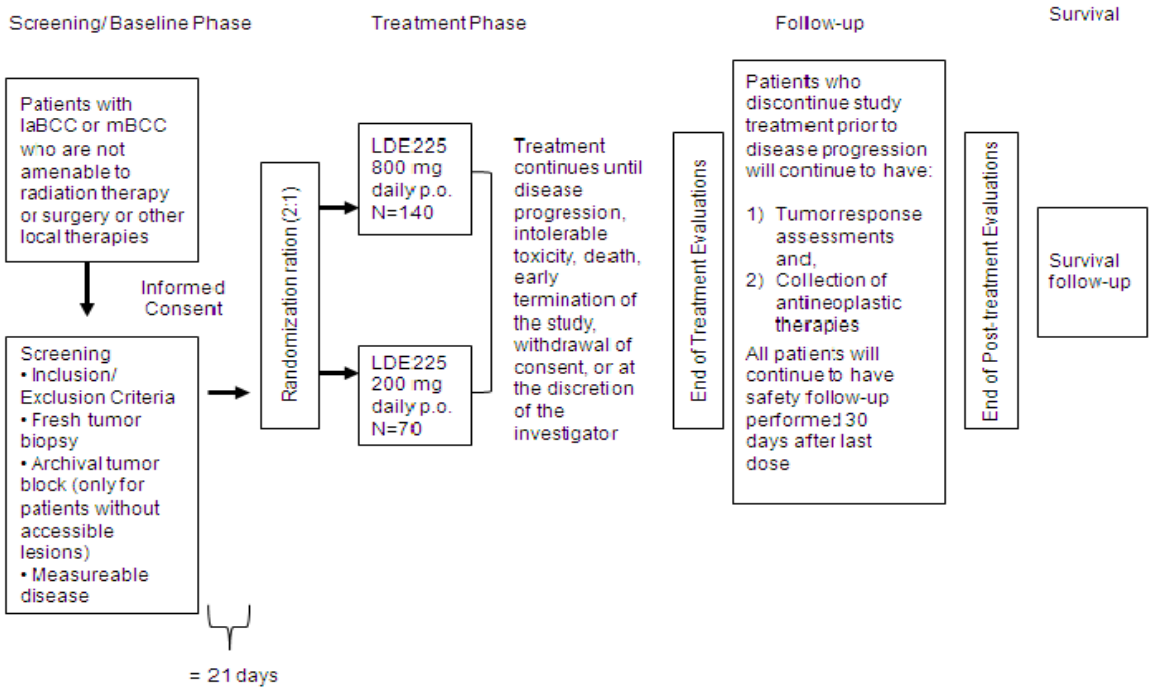
Trial Design

Screening, Eligibility Criteria, and Randomization

The BOLT study design is depicted in Figure 2.[2] Key eligibility criteria are outlined in Table 6. In brief, eligible patients had to have histologically confirmed laBCC not amenable to radiotherapy or curative surgery, or mBCC for which all existing available treatment options had been exhausted; a WHO status grade of less than or equal to 2; and adequate bone marrow, liver, and renal function. Patients were excluded if they had previously been treated with systemic sonidegib or with other Hh pathway inhibitors; were receiving treatment with medications known to be moderate and strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have a narrow therapeutic index and could not be discontinued before starting treatment with sonidegib; had neuromuscular disorders or were on concurrent treatment with drugs that could cause muscle damage; or were planning on starting a new strenuous exercise regimen after initiation of study treatment. Following a protocol amendment on November 17, 2011 (at which point 26 patients had been previously enrolled), confirmation of BCC by central histopathological review was considered necessary to ensure patients had the disease.[2]

Eligible patients were randomized in a 1:2 ratio by interactive response technology to receive either 200 mg once daily or 800 mg once daily dose of sonidegib.[2] The 200 mg dose was investigated in the trial as it represented the lowest dose level tested that had demonstrated evidence of anti-tumour activity, and the 800 mg dose was investigated as it represented the highest, well-tolerated biologically-active dose of sonidegib.[3] It was hypothesized that an 800 mg dose would be more efficacious than 200 mg, and therefore the 1:2 ratio was planned to ensure that more patients would be randomized to the 800 mg dose.[4] Of note, the 200 mg dose was shown in the trial to be more tolerable with similar efficacy to the 800 mg dose, and thus, it is the recommended dose and the focus of this report.[3] Randomization was stratified on disease state (locally advanced versus metastatic), histological subtype for locally advanced disease (nonaggressive [*including micronodular, infiltrative, basosquamous (metatypic or squamous differentiation ≥ 50%) or sclerosing (morpheaform) BCCs*] versus aggressive [*including nodular BCC, nodular BCC with focal squamous differentiation < 50%, or extensive superficial BCCs*]), and geographical region.[105] A randomization list from which patients were automatically assigned numbers linked to treatment groups and medication was produced by an independent provider, and sites could access the list online or via a voice-activated telephone system. The trial funder used a separate randomization list to assign numbers to treatment packs. The patients, investigators or site staff, and the funder were blinded to the dose allocations from randomization until primary analysis. The packaging and labelling, appearance, odour, and dosing schedules were identical for both treatment groups. Unmasking was permitted when a second dose modification was necessary or in an emergency where knowledge of treatment might have been required for ensure a patient's wellbeing. The IRC formed to review safety data remained blinded for the primary, 12-month, 18-month, 30-month and 42-month analysis.[3]

Figure 2: BOLT Study Design Flow Chart



Data Source: 6-month Clinical Study Report, 2014[9]

Study Assessments

Tumour assessments were performed by an IRC and by investigator (INV) assessment at baseline (≤ 21 days prior to starting treatment), at week 5, week 9 and week 17 (± 3 days) after initiation of treatment, followed by every eight weeks (± 3 days) for year one, and subsequently every 12 weeks (± 3 days) until PD confirmation, start of a new antineoplastic therapy, loss to follow-up, or 78 weeks from the date of enrollment of the last patient, whichever came first.[5] Punch biopsies from representative lesions were collected at screening, week 9, week 17, end of treatment, at any time a response assessment was confounded by ulceration, cysts, and/or scarring/fibrosis, and to confirm all assessments of CR.[2]

Treatment response assessments were performed using the mRECIST for patients with laBCC (after a protocol amendment on November 17, 2011, further described below under *Protocol Amendments*).[2] The mRECIST was used for patients with laBCC due to the potential for ulceration, cyst formation, scarring, fibrosis, or ill-defined lesion borders after treatment which RECIST v1.1 would be inadequate to assess. The response assessments involved MRI, colour photography, and histological analysis. In patients with mBCC, treatment response was assessed using the RECIST v1.1 using CT or MRI scans.[2] Colour photography of skin lesions (if present) were also analyzed. Whole body-imaging was conducted at baseline, and if skeletal lesions were identified that were not visible on the chest, abdomen, or pelvic CT/MRI scan, subsequent assessments were imaged by local CT/MRI scans.[2]

Patients who discontinued treatment due to PD were followed to determine survival status every 12 weeks until death, withdrawal of consent, or time of final analysis.[2] Patients who discontinued treatment prior to PD for any reason other than death or withdrawal of consent underwent tumour assessments every eight weeks for the first year, and then every 12 weeks thereafter until PD, start of new antineoplastic therapy, loss to follow up, or time of final analysis.

Biomarker assessments were performed on all available samples from patients in the full analysis set (all randomized patients) and on all available samples from patients in the safety analysis set (all patients who received at least one dose of sonidegib) to explore the association between biomarkers and safety outcomes.[2]

Cardiac enzymes (including cardiac troponin, CK, and creatine kinase myocardial band [CK-MB]), were measured at baseline (≤ 21 days prior to starting treatment at screening). CK was also measured during treatment weekly for the first two months and every four weeks thereafter, and one week following the final dose of sonidegib.[2] For patients taking pravastatin, CK was measured weekly during the first eight weeks, every other week during the following eight weeks, and then every four weeks thereafter. If CK elevations were found, monitoring frequency was increased until resolution to grade 1 or less and measurement of cardiac troponin and CK-MB were performed. Treatment was interrupted, resumed at a lower dose, or discontinued depending on the level of CK elevation and associated muscle-related symptoms. The monitoring schedule was not altered for patients with asymptomatic grade 1 CK elevation (except for patients in France). Other cardiac tests were possible depending on clinical need.

Study Endpoints and Statistical Analyses

Efficacy Outcomes: The primary efficacy endpoint was ORR in the overall population (both laBCC and mBCC patients) as assessed by an IRC, and ORR was defined as the proportion of patients with a confirmed BOR of CR or PR.[2,5] Based on the BOR, the disease control rate was also calculated, which was defined as the proportion of patients with CR, PR or SD. Responses of CR or PR required repeat assessments for confirmation, which occurred within four weeks of the first determination of response.[2] IRC-assessed ORR was analyzed using the pEAS, which was defined as all patients with fully assessable tumours by mRECIST in patients with laBCC (i.e. patients with tumours that have been adequately assessed by photographs [those with annotated photographs or those without annotated photographs and documentation of the absence of palpable sub-dermal components outside the margins of the photographed lesions] or radiologic scans [MRI or CT] or both) and all patients with mBCC (all patients with mBCC were assessed by RECIST v1.1).[2,4] The FAS was defined as all patients randomized, irrespective of whether they had received study medication, which was in accordance with the intention-to-treat (ITT) principle.[2] Supportive analyses of tumor response per mRECIST for laBCC and RECIST v1.1 for mBCC were also conducted using the FAS.

For patients with laBCC, mRECIST was used to assess an integrated composite ORR (see Table 7) based on MRI, digital clinical photography, and histopathology (via biopsies).[3] Measurable lesions were those that could be accurately measured in at least one lesion that was 10 mm or larger in at least one dimension via MRI or colour photography.[5] Lesions previously treated with radiotherapy were considered as non-target lesions unless it was measurable and showed clear progression. MRI tumor response was evaluated by RECIST v1.1; CR corresponded to disappearance of all target lesions and PR corresponded to greater than or equal to 30% unidirectional reduction in the sum of diameters of all target

lesions.[3] Clinical photographs were evaluated in accordance with WHO criteria; CR corresponded to disappearance of all target lesions, PR corresponded to a greater than or equal to 50% reduction in the sum of the product of the perpendicular diameters of a lesion (PPD), and PD corresponded to a greater than or equal to 25% increase in the PPD of a lesion from nadir. Histopathology was evaluated by biopsies of the target lesions to confirm the presence or absence of tumors.[5] Biopsies were taken each time that a response assessment was confounded by the presence of ulceration, cyst(s), and/or scarring/fibrosis for histopathologic evaluation to confirm responses. CRs required multiple punch biopsies per lesion and CR criteria corresponded to greater than or equal to two negative biopsies. Histopathologic evaluation was not a criterion for PR.[3]

The composite assessment criteria by mRECIST in patients with laBCC is summarized in Table 8.[2] Of note, if biopsy data was missing, histopathology was considered as 'positive' for the composite overall response determination, except when a response of CR had been determined at previous assessments, at which point further biopsy samples were not required until photographic or radiographic evidence of PD.[5] In these instances, missing biopsy data was considered 'negative' for histopathology. If the disease was not assessible by MRI at baseline, the composite overall response was based on photography and histology. If the disease was not assessible by photography at baseline, the composite overall response was based on MRI and histology. If the disease was assessible by either MRI or by photography at baseline, but then was missing at any post-baseline assessment, the criteria (MRI or photography dependent on which was missing) was considered 'unknown'.

For patients with mBCC, tumors were assessed by CT or MRI scan and evaluated per RECIST v1.1.[2] Measurable lesions were defined as at least one non-nodal lesion that could be accurately measured in at least one dimension as no less than double the slice thickness or 10 mm, whichever is greater, by spiral CT or MRI, or nodal lesions 15 mm or larger in the short axis by spiral CT or MRI (irrespective of slice thickness).[5] Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that were evaluable by CT or MRI could also be considered as measurable lesions. Similar to laBCC patients, lesions previously treated with radiotherapy were considered as non-target lesions unless it was measurable and showed clear progression. Colour clinical photography could be used for skin lesions.

Table 7: Tumour Response Evaluations Used for laBCC Patients in the BOLT Trial

Tumour Response Evaluation Parameter	mRECIST
CR (histologically confirmed)	• Disappearance of all lesions • ≥ 2 biopsies (surveying biopsies based on lesion surface area, ≥ 30 days apart) • Single, independent review panel
PR	• Photograph (bidimensional): ≥ 50% reduction in the sum of products of perpendicular diameters per WHO • MRI (unidimensional): ≥ 30% reduction in the sum of diameters of all target lesions per RECIST 1.1

CR = complete response; mRECIST = modified Response Evaluation Criteria in Solid Tumours; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; WHO = World Health Organization
Data Source: Clinical Summary, 2020[106]

Table 8: Composite Assessment via mRECIST Criteria for laBCC Patients

Composite overall response	MRI	Clinical photography	Histopathology
CR	CR	CR, PR(s/f), SD(s/f), or NA[a]	Negative
CR	NA[b]	CR, PR(s/f), or SD(s/f)	Negative
PR	PR	CR, PR(s/f), or SD(s/f)	Negative
PR	SD	CR, PR(s/f), or SD(s/f)	Negative
PR	CR	CR, PR(s/f), NA[a]	Positive or unknown
PR	CR	PR	Any
PR	PR	CR, PR(s/f)	Positive or unknown
PR	PR	PR, NA[a]	Any
PR	SD	CR, PR(s/f)	Positive or unknown
PR	SD	PR	Any
PR	NA[b]	CR, PR(s/f)	Positive or unknown
PR	NA[b]	PR	Any
SD	CR	SD	Any
SD	CR	SD(s/f)	Positive or unknown
SD	PR	SD	Any
SD	PR	SD(s/f)	Positive or unknown
SD	SD	SD, NA[a]	Any
SD	SD	SD(s/f)	Positive or unknown
SD	NA[b]	SD	Any
SD	NA[b]	SD(s/f)	Positive or unknown
Unknown	Any (except PD)	Unknown[c]	Any
Unknown	Unknown[d]	Any (except PD)	Any
PD	PD	Any	Any
PD	Any	PD	Any

CR = complete response; NA = not available; PD = disease progression; PR = partial response; SD = disease stabilization; s/f = scar/fibrosis only

[a] Disease unevaluable by photography at baseline; also includes scenarios where photographic data are unavailable

[b] Disease unevaluable by MRI scan at baseline; also includes scenarios where MRI data are unavailable

[c] As a result of missing assessment or other reasons post-baseline while disease is evaluable by photography at baseline

[d] As a result of missing assessment or other reasons post-baseline while MRI scan at baseline was available.

Data Source: 6-month Clinical Study Report, 2014[9]

The key secondary efficacy outcomes that were assessed in the trial are outlined below:[4]

- IRC-assessed DOR: The analysis population for DOR was the pEAS and only included patients who achieved a response of CR or PR per mRECIST for patients with laBCC and per RECIST v1.1 in patients with mBCC. DOR was defined as the time from first occurrence of CR or PR until the date of first documented PD or death due to underlying cancer; if a patient had not progressed and had received other anti-cancer therapy, DOR was censored at the date of the last adequate tumour assessment. If a patient had not progressed but had received other anti-cancer treatment, DOR was censored at the date of the last adequate tumour assessment prior to initiating the anti-cancer therapy. The distribution of DOR on each treatment arm was estimated separately using Kaplan-Meier (KM) curves. Supportive analyses of tumor response per mRECIST for laBCC and RECIST v1.1 for mBCC were also conducted using the FAS.
- IRC-assessed CRR: The analysis population for CRR was the pEAS and was defined as the proportion of patients who achieved CR according to mRECIST for patients with laBCC and per RECIST v1.1 in patients with mBCC. Supportive analyses of tumor response per mRECIST for laBCC and RECIST v1.1 for mBCC were also conducted using the FAS.

Other secondary efficacy outcomes assessed in the trial included:

- IRC-assessed PFS: PFS was assessed according to mRECIST in patients with laBCC and per RECIST v1.1 in patients with mBCC, and was defined as the time from date of enrollment to the date of the first documented PD or death from any cause. PFS was right censored at the date of the last adequate tumour assessment for patients who had not experienced PD or were alive at the time of the data cut-off, or when they received any other anti-cancer therapy. PFS was analyzed in the pEAS.
- IRC-assessed TTR: TTR was according to mRECIST for patients with laBCC and per RECIST v1.1 in patients with mBCC. The analysis population for TTR included patients who achieved a response of CR or PR and was defined as the time from date of enrollment to the date of first documented CR or PR. TTR was analyzed in the pEAS.
- ORR, DOR, PFS, and TTR: INV-assessed using the pEAS and according to mRECIST in patients with laBCC and per RECIST v1.1 in patients with mBCC.
- ORR, DOR, PFS, and TTR: INV-assessed using the FAS and per RECIST v1.1 applied to both laBCC and mBCC patients.
- ORR, DOR, PFS, and TTR: IRC-assessed using the FAS and per RECIST v1.1 applied to both laBCC and mBCC patients.
- OS: OS was defined as the time from date of enrollment to the date of death from any cause or censored at the last date the patient was known to be alive at the time of the data cut-off. OS was assessed in the FAS.

For analyses using RECIST v1.1 for both laBCC and mBCC, the overall lesion response for each evaluation was determined according the following criteria:[4]

- For laBCC patients for whom only one imaging modality (photography or MRI scans) was used, the overall lesion response was determined as per RECIST v1.1 based on those assessments.
- For laBCC patients for whom both photos and MRI scans were used, the overall lesion response was first determined per RECIST v1.1 for each modality. The overall lesion response based on photography prevailed unless MRI overall lesion response indicated PD. This modality was selected as the priority as photographs, particularly annotated photographs, were deemed to provide the most precise quantitative assessment of lesion response.[10]
- For mBCC patients, the overall lesion response was determined as per RECIST v1.1 based on assessments from CT/MRI scans.

Analyses for the response rate outcomes (i.e. ORR and CRR) were performed using 95% exact binomial CIs by treatment group.[2] Treatment was considered to be efficacious if the observed ORR on any treatment arm was greater than or equal to 30% and clinically meaningful if the lower bound of the 95% CI exceeded 20%.[5,6] This threshold was determined by a literature review and consultation with experts and regulatory agencies.[7] No between group statistical comparisons were planned; however, the difference in ORR between the two treatment arms was summarized descriptively along with the 95% CIs. [5] The proportion of patients in the pEAS population who underwent surgical resection after PR was also summarized along with the 95% CIs. Analyses for the time-to-event outcomes (i.e. TTR, DOR, PFS) were performed using the KM non-parametric maximum likelihood estimates to calculate median (or other percentiles) times and 95% CIs by treatment group.[2]

Subgroup analyses

The following pre-specified subgroups analyses were considered for efficacy analyses in pEAS and FAS:[3]

- mBCC patients and laBCC patients (further subdivided in aggressive and nonaggressive histological subtype based on interactive response technology data)
- mBCC patients and laBCC patients (further subdivided in aggressive and nonaggressive histological subtype based on IRC assessed histology data)
- baseline performance ECOG PS (0, ≥1)
- sex
- age (< 65 years and ≥ 65 years)
- race (Caucasian and non-Caucasian)

Sensitivity analyses

The potential pre-specified potential sensitivity analyses are displayed in Table 9.[4] Key analyses included in this report were: 1) new anti-cancer therapy given being treated as an event rather than censored for the outcomes of PFS and DOR; and 2) progression or death after two or more missing assessments treated as an event rather than censored. A sensitivity analysis was also conducted for IRC-assessed ORR using updated mRECIST criteria which applied similar methodology to that used for the vismodegib ERIVANCE trial.[8] The difference comes from 1) the difference in the way that lesion photography and MRI data were prioritized between mBCC and laBCC and 2) the fact that central assessments of MRI and photographs were independent committees. Thus, index lesions could not be matched between the two for centrally read efficacy analyses.[109]

Table 9: Options for Event Dates Used in PFS, TTP, and DOR Sensitivity Analyses

	Situation	Options for end-date (progression or censoring?) (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	Date of randomization/start of treatment[a]	Censored
B	Progression at or before next scheduled assessment	Date of progression Date of next scheduled assessment[b]	Progressed Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death) Date of next scheduled assessment[b]	Progressed Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate assessment[b] Date of next scheduled assessment[b] Date of progression (or death)	Censored Progressed Progressed
D	No progression	Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	Date of last adequate assessment Date of secondary anti0cacner therapy N/A	Censored Censored Event ignored

	Situation	Options for end-date (progression or censoring?) (1) = default unless specified differently in the protocol or analysis plan	Outcome
G	Deaths due to reason other than deterioration of 'Study indication'	Date of last adequate assessment	Censored (only TTP and DOR)

DOR = duration of response; N/A = not applicable; PFS = progression-free survival; TTP = time to progression.
Notes:
[a] After the last adequate tumor assessment.
[b] Rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.
Data Source: Clinical Study Protocol, 2016[4]

Safety Outcomes: Safety outcomes (i.e. AEs, SAEs, and deaths) were assessed in the safety analysis set, defined as all patients who received at least one dose of study medication and had at least one post-baseline safety assessment.[4] Patients were analyzed according to the dose received, which was defined as the treatment assigned if it was received for at least once or, otherwise, the initial treatment received. Safety was assessed by central review and investigators.[2] Monitoring of AEs was performed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Muscle-related events were also assessed by an IRC and adjudication committee comprised of three external experts. In the original protocol, these monitoring and assessment of AEs were to be performed from the first dose until 30 days after the final dose in patients who received at least one dose of sonidegib;[2] however, in Protocol Amendment 7, the study was extended by an additional 104 weeks, and long term safety data was collected, and patients were followed until 130 weeks following enrollment of the last patient.[4]

Patient-Reported Outcomes: Patient-reported outcomes (PROs) were assessed as an exploratory end point using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), its associated head and neck cancer-specific module (QLQ-H&N35) , and the Medical Outcomes Study Short Form 36 (SF-36) version 2, Acute.[4]

The EORTC QLQ-C30 contains 30 questions composed of nine multi-item scales (five functional scales: physical, role, cognitive, emotional, and social; three symptom scales: fatigue, pain, and nausea and vomiting; and a global health and quality-of-life scale) as well as single-item symptom measures (dyspnea, insomnia, appetite, constipation, diarrhea, and financial impact).[4] The associated QLQ-H&N35 module is designed to be used with the EORTC QLQ-C30 and contains 35 questions composed of seven multi-item scales (pain, swallowing, senses [taste and smell], speech, social eating, social contact and sexuality) as well as 11 single-item symptom and side effect measures. A high score for a functional scale represents a high level of functioning, a high score for the global health status (GHS)/QoL scale represents a high QoL, and a high score for a symptom scale/single item represents a high level of symptomatology or problems. Patients completed the questionnaires at baseline, at week 9, week 17, every eight weeks thereafter for year one, and every 12 weeks (± 3 days) thereafter until the end of treatment. Summary scores for the outcomes were calculated for the FAS by summing the item responses on the questions for each domain according the scoring manual and the developers for the questionnaires.[4] Descriptive statistics and change from baseline of the summary scores for each post baseline assessment were provided by treatment arm. Proportions of patients with improvement, no change, or decline from baseline were also calculated from the best reported scores post-baseline.[2] Median time to deterioration was also calculated for each subscale, and was defined as a worsening of at least ten points in a score from baseline

without a subsequent improvement. The MCID definition and whether it was consistent with guidelines from the literature was unclear.[110]

The SF-36, version 2, Acute is a self-administered questionnaire for adults and contains 36 items composed of eight multi-item dimensions (physical functioning, role limitation due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health) as well as a single-item measure on health change over the past year.[4] Item scores for each dimension are coded, summed and transformed to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state), and a higher value indicates a better health. Summary scores of physical and mental health can be calculated, with scoring is norm-based using normative values at 50 and no floors or ceilings. Definitive deterioration was defined as the minimal important change (MIC) or more decrease from the baseline score, with no later improvement above this threshold observed during the course of the study. The MIC for individual components were the following: 3.4 for physical component summary or role physical, 4.3 for physical functioning, 4.5 for role emotional, 4.6 for mental component summary, 6.2 for bodily pain, vitality, or mental health, 6.9 for social functioning, and 7.2 for general health.[10] The questionnaire has a one week recall period. In addition, the SF-6D, a utility measure of health states, can be derived from the SF-36. Patients completed the questionnaires at baseline, and then 16 weeks for year one, and every 24 weeks (± 3 days) thereafter until the end of treatment.

Sample Size: The original sample size for the BOLT trial was 120 patients, which was increased to 150 patients following Amendment 2 (further described below) to obtain additional safety and efficacy data, and then again increased to 210 patients following Amendment 4 to ensure a sufficient number of patients were included in the pEAS.[5] The targeted enrollment of 210 patients in the BOLT trial, allowed for 150 patients to be included in the pEAS if the study were to continue past the interim analysis.[5] The decision operating characteristics for the primary endpoint (ORR by mRECIST in the laBCC patients and by RECIST v1.1 in mBCC patients per IRC in the pEAS) and a secondary endpoint (ORR per RECIST v1.1 per local investigator; note: while the decision operating characteristics for this particular secondary endpoint was checked and found to be adequate, it was not the determinant of sample size) for the probability of observing an ORR of greater than or equal to 30% based on the true ORR is displayed in Table 10.[5,10] According to the table, inclusion of 150 patients in the pEAS provided control of type I (false-positive) error rate of 0.3% for 800 mg -group and 2.4% for 200 mg group if the true ORR in the respective treatment groups is 20% or less, and inclusion of 210 patients in the FAS provided control of type I error rate 0.3% for 800 mg group and 2.5% for 200 mg group if the true ORR on the respective arms is 20% or less. The pEAS and the set of patients used for the interim analysis were assumed to be mutually exclusive, and it was assumed there was a high degree of concordance between the primary endpoint for the interim analysis and the primary endpoint of the study.

Table 10: Decision Operating Characteristics for the Primary Endpoint and a Secondary Endpoint of the BOLT Trial Design

True ORR	Probability of observing ORR of ≥30%					
	Primary endpoint [a]			Secondary Endpoint [b]		
	800 mg arm with 100 patients in pEAS at the primary analysis	200 mg arm with 50 patients in pEAS at the primary analysis	200 mg arm with 100 patients in pEAS at the primary analysis	800 mg arm with 140 patients in FAS at the primary analysis	200 mg arm with 70 patients in FAS at the primary analysis	200 mg arm with 120 patients in FAS at the primary analysis
0.20	0.003	0.024	0.005	0.003	0.025	0.005
0.25	0.083	0.150	0.089	0.090	0.169	0.101
0.30	0.424	0.417	0.405	0.475	0.473	0.449
0.35	0.805	0.703	0.769	0.852	0.761	0.793
0.40	0.961	0.884	0.921	0.971	0.913	0.928
0.45	0.993	0.962	0.971	0.994	0.969	0.972

FAS = full analysis set; ORR = overall response rate; pEAS = primary efficacy analysis set.

Notes:

[a] Primary endpoint: ORR by mRECIST in the laBCC patients and ORR by RECIST v1.1 in mBCC patients per central review in the pEAS

[b] Secondary endpoint: ORR per RECIST v1.1 per local investigator

Data Source: EPAR, 2015[5]

Interim Analyses: An interim analysis was performed after the first 48 randomized patients had been treated for 16 weeks or had discontinued treatment.[4] Efficacy analyses were based on the FAS and safety analyses were based on the safety set. The outcomes were assessed by an independent data monitoring committee (iDMC).[106] The decision as to whether to terminate or continue the study was made by the sponsor in consultation with the Study Steering Committee, with consideration from the recommendations from the DMC.[4] The results of this interim analysis indicated that the study should continue.[2]

The primary analysis was performed on all efficacy and safety data reported up to six-months (corresponding to when the final randomized patient would have either completed 24 weeks of treatment or discontinued prior to this time point) with a data cut-off date of June 28, 2013.[8] Four additional analyses have been conducted:

- 12-month analysis (50 weeks following enrollment of the last patient) with a data cut-off date of December 31, 2013
- 18-month analysis (78 weeks following enrollment of the last patient) with a data cut-off date of July 11, 2014
- 30-month analysis (130 weeks following enrollment of the last patient) with a data cut-off date of July 10, 2015
- 42-month analysis (182 weeks following enrollment of the last patient) with a data cut-off date of July 8, 2016

The IRC remained blinded for the primary, 12-month, 18-month, 30-month, and 42-month analyses. The study was closed on June 29, 2017, at which point a final report was conducted for the cumulative safety data of all patients, including the 11 patients who were ongoing post 42-month analysis. No further efficacy analysis was performed after the 42-month analysis.

Protocol Amendments

A total of nine protocol amendments occurred, which have been summarized in Table 11.[4,5,105]

Table 11: Summary of Protocol Amendments in the BOLT trial

Amendment Number (Date) No. Patients recruited prior to the amendment	Amendment summary
Amendment 1 (April 19, 2011) 0	Clarification of wording on contraceptive precautions to align with the UK Guideline of Prevention of Pregnancies in Participants in Clinical Trials
Amendment 2 (November 17, 2011) 26	Clarification on the eligibility to ensure only patients who are not eligible for curative surgery, radiotherapy, or other local therapies are enrolled Incorporation of confirmation of diagnosis via central histopathology review to ensure patients have BCC (patients enrolled prior to this amendment and who have not provided fresh or archival tissue may be replaced and patients whose diagnosis cannot be confirmed by central histopathology review are replaced) Revision of tumour response assessment for patients with laBCC from RECIST v1.1 criteria to mRECIST criteria (RECIST v1.1 inadequate to assesses tumours associated with ulceration, cysts, and scarring/fibrosis). This included the need for MRI at baseline for laBCC patients. Revision of primary endpoint analysis to be based on IRC assessment Increase in sample size from 80 to 100 in 800 mg arm and from 40 to 50 in 200 mg arm to obtain additional safety and efficacy data
Amendment 3 (November 23, 2011) 29	Revision of monitoring for patients in France who experience asymptomatic treatment-emergent grade 1 CK elevation – weekly monitoring implemented until CK resolves to normal or baseline value
Amendment 4 (June 28, 2012) 150	Introduction of the pEAS (subset of the FAS in which laBCC patients excluded as they were not eligible for tumour assessment per mRECIST from the Amendment 2 changes) were removed. Increase in sample size to approximately 210 patients to ensure a sufficient number of patients were included in the pEAS
Amendment 5 (June 3, 2013) 230	Revision of ORR assessment according to RECIST v1.1 to be derived from IRC assessment by MRI and photography independently without lesions matching between MRI/photography and lesions
Amendment 6 (November 14, 2013) 230	Clarification on how the colour photography, MRI, and histology for the mRECIST criteria will be integrated by an IRC to determine the composite overall response for patients with laBCC
Amendment 7 (April 21, 2013) 230	Extension of the duration of the study by an additional 104 weeks to collect long term efficacy and safety data – patients will continue to be assessed every 12 weeks and receive study drug (after unblinding at 78 weeks after the last patient is enrolled, open label drug will be dispensed every 12 weeks). Patients in post-treatment follow up to continue with tumor assessment every 12 weeks until PD determined, start of a new anti-neoplastic therapy, lost to follow-up, or 182 weeks from the date of enrollment of the last patient. Patients on survival follow-up (i.e. those patients who have PD) to continue with survival follow up visits every 12 weeks until death, withdrawal of consent, or 182 weeks from the date of enrollment of the last patient. Addition of further analyses for long term follow-up of safety and efficacy data at 50 weeks, 78 weeks, and 130 weeks following enrollment of the last patient. Final analyses to be conducted at 182 weeks from the date of enrollment of the last patient

Amendment Number (Date) No. Patients recruited prior to the amendment	Amendment summary
Amendment 8 (February 24, 2015) 230	Clarification on the composition of the Data Monitoring Committee members
Amendment 9 (March 16, 2016) 230	Allowance of on treatment patients (post week 182) who are deriving clinical benefit, to continue to receive study drug until PD, intolerable toxicity, death, withdrawal of consent to continue study treatment. Modification of the visit evaluation schedule and study assessments to be performed according to standard clinical practices. All central assessments and procedures changed to local assessments and procedures.

BCC = basal cell carcinoma; CK = creatinine phosphokinase; FAS = full analysis set; IRC = Independent Review Committee; laBCC = locally advanced basal cell carcinoma; mRECIST = modified Response Criteria in Solid Tumors; ORR = objective response rate; PD = progressive disease; pEAS = primary efficacy analysis set; RECIST = Response Criteria in Solid Tumors; UK = United Kingdom
Data Sources: EPAR, 2015;[5] Final Clinical Study Report, 2018;[105] Clinical Study Protocol, 2016[4]

Funding

The trial was funded by Novartis Pharmaceuticals Corporation.[2] The funder and the senior author of the Migden et al. 2015[2] publication jointly designed the study. The funder had no role in data collection, but did have a role in data analysis, data interpretation, and writing of the report.

b) Populations

Demographic Characteristics in the laBCC Subgroup

The baseline demographic characteristics of the laBCC patients in the FAS are summarized in Table 12.[7] A total of 230 patients were enrolled in the BOLT trial, of which 194 patients had laBCC and 36 had mBCC. Overall, the baseline patient demographics were balanced between the two groups. The median age was similar between the two groups (200 mg sonidegib: 67.0 years [range: 25.0 to 92.0 years]; 800 mg sonidegib: 66.0 years [range: 24.0 to 93.0 years]), however a slightly higher proportion of patients in the 200 mg sonidegib group were 65 years of age or older compared to the 800 mg sonidegib group (57.6% versus 53.9%). Most patients (200 mg sonidegib group versus 800 mg sonidegib group) were White (89.4% versus 96.1%) and had an ECOG PS of 0 (66.7% versus 68.0%).

Table 12: Demographics and Disease History at Baseline in laBCC Patients of the BOLT Trial (FAS)

Demographic	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	All patients (n=194)
Age, years			
Mean (SD)	64.5 (15.94)	63.8 (15.11)	64.1 (15.36)
Median (min, max)	67.0 (25.0, 92.0)	66.0 (24.0, 93.0)	67.0 (24.0, 93.0)
Age category, years n (%)			
<65 years	28 (42.4)	59 (46.1)	87 (44.8)
≥65 years	38 (57.6)	69 (53.9)	107 (55.2)
Sex, n (%)			
Male	38 (57.6)	78 (60.9)	116 (59.8)

Demographic	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	All patients (n=194)
Female	28 (42.4)	50 (39.1)	78 (40.2)
ECOG PS, n (%)			
0	44 (66.7)	87 (68.0)	131 (67.5)
1	16 (24.2)	33 (25.8)	49 (25.3)
2	4 (6.1)	6 (4.7)	10 (5.2)
Unknown	2 (3.0)	2 (1.6)	4 (2.1)
Race, n (%)			
Black or African American	0	0	0
White	59 (89.4)	123 (96.1)	182 (93.8)
Other	7 (10.6)	5 (3.9)	12 (6.2)
Ethnicity, n (%)			
Hispanic or Latino	1 (1.5)	1 (0.8)	2 (1.0)
Not Hispanic or Latino	58 (87.9)	112 (87.5)	170 (87.6)
Unknown	7 (10.6)	15 (11.7)	22 (11.3)
Weight (kg)			
Mean (SD)	79.3 (21.76)	81.3 (20.27)	80.6 (20.75)
Median (min, max)	75.8 (44.5, 180.6)	77.8 (47.7, 160.0)	76.9 (44.5, 180.6)
Height (cm)			
Mean (SD)	171.9 (11.40)	171.5 (10.18)	171.6 (10.59)
SD	11.40	10.18	10.59
Median (min, max)	172.5 (147.0, 200.0)	171.5 (148.0, 193.0)	172.0 (147.0, 200.0)
Unknown, n (%)	0	2 (1.6)	2 (1.0)
BSA (m^2)			
n	66	126	192
Mean (SD)	1.9 (0.30)	2.0 (0.27)	1.9 (0.28)
Median (min, max)	1.9 (1.4, 3.0)	1.9 (1.5, 2.9)	1.9 (1.4, 3.0)
Unknown, n (%)	0	2 (1.6)	2 (1.0)

BSA = body surface area; ECOG PS = Eastern Cooperative Oncology Group performance status; FAS = full analysis set; SD = standard deviation.
Data Source: Additional Information Requested August 20, 2020[7]

Disease Characteristics in the laBCC Subgroup

Disease characteristics of laBCC patients in the BOLT trial are summarized in Table 13.[7,8,105] In the 200 mg sonidegib group, 74.2% of patients had received any type of prior antineoplastic therapy indicated for BCC, with 72.7% having received prior surgery. In the 800 mg group, 81.3% of patients received any prior therapy, with 80.5% having received prior surgery.[8] In the 200 mg sonidegib group, 50.0% of patients had non-aggressive laBCC, compared to 49.2% of patients in the 800 mg sonidegib group.[7] Skin was the most frequently reported primary site of the cancer in both groups (200 mg: 36.4%; 800 mg: 45.3%). The most frequently reported type of BCC in both groups was infiltrative (200 mg: 39.4%; 800 mg: 37.5%), followed by nodular (200 mg: 36.4%; 800 mg: 28.9%).

Table 13: Disease Characteristics of laBCC Patients in the BOLT trial (FAS)

Disease characteristic, n (%)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	All patients (n=194)
Prior antineoplastic therapy indicated for BCC			
Any therapy	49 (74.2)	104 (81.3)	153 (78.9)
Surgery	48 (72.7)	103 (80.5)	151 (77.8)
Radiotherapy	5 (7.6)	10 (7.8)	15 (7.7)
Prior number antineoplastic	5 (7.6)	7 (5.5)	12 (6.2)
1 prior regimen	1 (1.5)	5 (3.9)	9 (4.6)
2 prior regimes	0	1 (0.8)	2 (1.0)
Unknown number	0	1 (0.8)	1 (0.5)
Primary Site of Cancer			
Chin	0	1 (0.8)	1 (0.5)
Ears	1 (1.5)	7 (5.5)	8 (4.1)
Eyelids	1 (1.5)	4 (3.1)	5 (2.6)
Forehead	6 (9.1)	8 (6.3)	14 (7.2)
Head	6 (9.1)	10 (7.8)	16 (8.2)
Inner canthus	1 (1.5)	1 (0.8)	2 (1.0)
Lips	2 (3.0)	0	2 (1.0)
Lower extremities	3 (4.5)	3 (2.3)	6 (3.1)
Neck	1 (1.5)	2 (1.6)	3 (1.5)
Other	10 (15.2)	22 (17.2)	32 (16.5)
Preauricular	1 (1.5)	2 (1.6)	3 (1.5)
Scalp	6 (9.1)	6 (4.7)	12 (6.2)
Skin	24 (36.4)	58 (45.3)	82 (42.3)
Trunk	2 (3.0)	4 (3.1)	6 (3.1)
Upper extremities	2 (3.0)	0	2 (1.0)
Predominant histology/cytology (site)			
Non-aggressive (low-risk)	33 (50.0)	63 (49.2)	96 (49.5)
Aggressive (high-risk)	33 (50.0)	62 (48.4)	95 (49.0)
Undetermined	0	3 (2.3)	3 (1.5)
BCC Type			
BCC - basosquamous (metatypic or keratonizing)	1 (1.5)	4 (3.1)	5 (2.6)
BCC - infiltrative	26 (39.4)	48 (37.5)	74 (38.1)
BCC - micronodular	0	2 (1.6)	2 (1.0)
BCC - multifocal	1 (1.5)	4 (3.1)	5 (2.6)
BCC - nodular	24 (36.4)	37 (28.9)	61 (31.4)
BCC - sclerosing (morpheaform)	5 (7.6)	6 (4.7)	11 (5.7)
BCC - superficial	9 (13.6)	24 (18.8)	33 (17.0)
Other	0	3 (2.3)	3 (1.5)
Metastatic sites			
Yes	1 (1.5)	1 (0.8)	2 (1.0)
No	65 (98.5)	127 (99.2)	192 (99.0)

Disease characteristic, n (%)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	All patients (n=194)
Current extent of disease (metastatic sites)			
Lung	1 (1.5)	0	1 (0.5)
Other Lymph Nodes	0	1 (0.8)	1 (0.5)
Parotid lymph nodes	0	1 (0.8)	1 (0.5)
Submandibular lymph nodes	0	1 (0.8)	1 (0.5)
Types of lesions at baseline			
Target only	37 (56.1)	69 (53.9)	106 (54.6)
Non-target only	0	2 (1.6)	2 (1.0)
Both target and non-target	29 (43.9)	56 (43.8)	85 (43.8)
Missing	0	1 (0.8)	1 (0.5)
Total of lesions at baseline			
One lesion	30 (45.5)	53 (41.4)	83 (42.8)
More than one lesion	36 (54.5)	74 (57.8)	110 (56.7)
No lesions	0	1 (0.8)	1 (0.5)
Time from initial diagnosis of primary site to first dose[a]			
< 6 months	16 (24.2)	23 (18.0)	39 (20.1)
6 to < 12 months	1 (1.5)	5 (3.9)	6 (3.1)
12 to < 24 months	3 (4.5)	6 (4.7)	9 (4.6)
≥ 24 months	44 (66.7)	86 (67.2)	130 (67.0)
Unknown	2 (3.0)	8 (6.3)	10 (5.2)
Time from initial diagnosis to first recurrence/relapse			
< 1 month	5 (7.6)	4 (3.1)	9 (4.6)
1 to < 2 months	2 (3.0)	4 (3.1)	6 (3.1)
2 to < 3 months	1 (1.5)	1 (0.8)	2 (1.0)
≥ 3 months	35 (53.0)	72 (56.3)	107 (55.2)
Unknown	23 (34.8)	47 (36.7)	70 (36.1)
Time from most recent relapse to first dose[a]			
< 1 month	7 (10.6)	10 (7.8)	17 (8.8)
1 to < 2 months	6 (9.1)	13 (10.2)	19 (9.8)
2 to < 3 months	8 (12.1)	11 (8.6)	19 (9.8)
≥ 3 months	25 (37.9)	54 (42.2)	79 (40.7)
Unknown	20 (30.3)	40 (31.3)	60 (30.9)

BCC = basal cell carcinoma; FAS = full analysis set; laBCC = locally advanced basal cell carcinoma; pEAS = primary efficacy analysis set.
Notes:
[a] Randomization date is used if patient did not receive any dose.
Data Sources: Final Clinical Study Report, 2018;[105] Health Canada Module 2.7.3;[8] Additional Information Requested August 20, 2020;[7] Additional Information September 25, 2020[107]

The measurable disease characteristics at baseline of patients with laBCC in the BOLT trial are summarized in Table 14.[7] Per IRC assessment, the median sum of the longest diameters per MRI was 36.0 mm (min: 10.0 mm; max: 86.0 mm) in the 200 mg sonidegib group and 27.0 mm (min: 10.0 mm; max: 145.0 mm) in the 800 mg group, and was 48.7 mm (min: 10.8 mm; max: 262.0 mm) and 48.0 mm (min: 10.9 mm; max: 414.5 mm) respectively when measured by photo. The sum of the perpendicular diameters per WHO by photo was

1542.6 mm^2 (min: 82.1 mm^2; max: 54996.4 mm^2) and 1037.2 mm^2 (min: 97.8 mm^2; max: 57035.0 mm^2) in the 200 mg and 800 mg sonidegib groups respectively.

Table 14: Measurable Disease at Baseline in laBCC Patients in the BOLT trial (FAS)

n (%)	200 mg sonidegib (n = 66)	800 mg sonidegib (n = 128)	All (n = 194)
Total of laBCC patients assessed by MRI or photograph at baseline			
MRI only	2 (3.0)	12 (9.4)	14 (7.2)
Photo only	13 (19.7)	15 (11.7)	28 (14.4)
MRI and photo	49 (74.2)	99 (77.3)	148 (76.3)
Missing	2 (3.0)	2 (1.6)	4 (2.1)
per IRC assessment			
Sum of the longest diameters (mm) for laBCC patients per RECIST v1.1 by MRI			
n	35	79	114
Mean (SD)	36.0 (16.49)	33.8 (24.93)	34.5 (22.62)
Median (min, max)	36.0 (10.0, 86.0)	27.0 (10.0, 145.0)	30.0 (10.0, 145.0)
Sum of the longest diameters (mm) for laBCC patients per RECIST v1.1 by photo			
n	53	105	158
Mean (SD)	64.4 (51.57)	62.8 (53.59)	63.3 (52.76)
Median (min, max)	48.7 (10.8, 262.0)	48.0 (10.9, 414.5)	48.1 (10.8, 414.5)
Sum of the products of the perpendicular diameters (mm^2) for laBCC patients per WHO by photo			
n	53	105	158
Mean (SD)	4292.5 (8307.42)	3495.1 (7289.38)	3762.6 (7628.78)
Median (min, max)	1542.6 (82.1, 54996.4)	1037.2 (97.8, 57035.0)	1211.7 (82.1, 57035.0)
per INV assessment			
Sum of the longest diameters (mm) for laBCC patients per RECIST v1.1 by MRI			
n	29	65	9
Mean (SD)	39.8 (23.90)	44.1 (40.05)	42.8 (35.78)
Median (min, max)	36.0 (14.0, 130.0)	34.0 (10.0, 230.0)	35.9 (10.0, 230.0)
Sum of the longest diameters (mm) for laBCC patients per RECIST v1.1 by photo			
n	62	107	169
Mean (SD)	62.8 (41.36)	69.3 (118.82)	66.9 (97.67)
Median (min, max)	50.0 (10.0, 220.0)	42.0 (10.0, 1155.0)	45.0 (10.0, 1155.0)
Sum of the products of the perpendicular diameters (mm^2) for laBCC patients per WHO by photo			
n	60	106	166
Mean (SD)	2910.7 (3382.93)	3526.5 (7945.73)	3303.9 (6660.09)
Median (min, max)	1461.0 (100.0, 14000.0)	1012.5 (30.0, 520000.0)	1096.0 (30.0, 520000.0)

FAS = full analysis set; INV = investigator; IRC = Independent Review Committee; laBCC = locally advanced basal cell carcinoma; RECIST = response evaluation criteria in solid tumors; SD = standard deviation; WHO = World Health Organization

Data Source: Final Clinical Study Report, 2018;[105] Additional Information Requested August 20, 2020[7]

c) Interventions

Treatment

Patients received sonidegib orally once daily on a continuous dosing schedule until documented PD, intolerable toxic effects, withdrawal of consent, death, discontinuation at an investigator's discretion, dose interruption lasting longer than 21 days (unless the patient was responding to study treatment and had not progressed, in which case resumption of treatment was permitted at the investigator's discretion), use of a prohibited medication, start of another antineoplastic therapy, or study termination.[2] Sonidegib was supplied as 200 mg hard-gelatin capsules.[5] Patients in the 200 mg arm received one 200 mg capsule and three matching placebo capsules, and patients in the 800 mg arm received four 200 mg capsules.

Surgery, radiation therapy, other investigational therapies, growth factors, erythropoietin, blood transfusions and/or granulocyte colony-stimulating factor were not permitted during study treatment.[2,5] Medications to treat AEs, manage cancer symptoms or concurrent table disease and supportive care agents were permitted.

Treatment Modification

Dose reduction steps are summarized in Table 15.[5] Dose adjustments were permitted for patients who were unable to tolerate the dosing schedule or for toxicities that were suspected to be related to the study drug. Patients in the 200 mg group were allowed one reduction to placebo only (i.e. no longer receiving active treatment), and discontinued treatment if a further reduction was necessary. Patients in the 800 mg group were allowed up to two dose reductions. For patients who underwent dose interruptions, if the same toxicity occurred after re-initiation of sonidegib, irrespective of duration, the second re-initiation was resumed at a lower dose. If the patient required a dose interruption greater than 21 days from the previous dose, then the patient was discontinued from study treatment. Dose reductions were managed by Interactive Response Technology to ensure that blinding was maintained for the first dose reduction.[4] Patients who had dose reductions were not permitted to have dose re-escalation.[109] Patients who were placebo dose reduced continued on the study and were not considered to have been discontinued.

Table 15: Dose Reduction Steps for Sonidegib in the BOLT Trial

		Dose reduction[a]	
	Starting dose level 0	Dose level -1	Dose level -2
Sonidegib dose (mg)	800	400	200
Sonidegib dose (mg)	200	placebo	n/a

[a] Dose reduction was based on the worst toxicity demonstrated.

n/a = not applicable.
Data Source: 6-month Clinical Study Report, 2014[9]

Drug Exposure

The drug exposure in the safety analysis set of the entire trial population (both laBCC and mBCC patients who received at least one dose of study drug) is displayed in Table 16.[6] As of the primary analysis, median exposure was 8.9 (range: 1.3 to 21.4) months in the 200 mg sonidegib group and 6.5 (range: 0.3 to 19.1) months in the 800 mg sonidegib group. The

median relative dose intensity was 97.2% (range: 13.8% to 123.3%) in the 200 mg sonidegib group and 91.8% (range: 29.6% to 437.5%) in the 800 mg sonidegib group. As of the 42-month analysis, median exposure was 11.0 (range: 1.3 to 53.2) months in the 200 mg sonidegib group and 6.6 (range: 0.3 to 53.9) months in the 800 mg sonidegib group. The median relative dose intensity was 96.6% (range: 7.7% to 123.3%) in the 200 mg sonidegib group and 89.9% (range: 27.1% to 437.5%) in the 800 mg sonidegib group.

Table 16: Summary of Treatment Exposure in the BOLT Trial (Safety Analysis Set)

	Primary analysis: 28-Jun-2013 data cut-off		12-month analysis: 31-Dec-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off		30-month analysis: 10-Jul-2015 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
Duration of exposure (months)	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150
Treatment ongoing[1]	39 (49.4)	46 (30.7)	21 (26.6)	29 (19.3)	11 (13.9)	18 (12.0)	6 (7.6)	9 (6.0)	6 (7.6)	5 (3.3)
Exposure categories, n (%)										
< 1	0	7 (4.7)	0	7 (4.7)	0	7 (4.7)	0	7 (4.7)	0	7 (4.7)
1 - <4	7 (8.9)	38 (25.3)	7 (8.9)	38 (25.3)	7 (8.9)	38 (25.3)	7 (8.9)	38 (25.3)	7 (8.9)	38 (25.3)
4 - < 8	29 (36.7)	50 (33.3)	18 (22.8)	40 (26.7)	18 (22.8)	40 (26.7)	18 (22.8)	40 (26.7)	18 (22.8)	40 (26.7)
8 - <12	22 (27.8)	27 (18.0)	20 (25.3)	20 (13.3)	20 (25.3)	20 (13.3)	20 (25.3)	19 (12.7)	20 (25.3)	19 (12.7)
12 - <16	14 (17.7)	13 (8.7)	12 (15.2)	19 (12.7)	8 (10.1)	10 (6.7)	8 (10.1)	11 (7.3)	8 (10.1)	11 (7.3)
16 - <20	6 (7.6)	15 (10.0)	14 (17.7)	12 (8.0)	9 (11.4)	14 (9.3)	7 (8.9)	12 (8.0)	7 (8.9)	12 (8.0)
≥ 20	1 (1.3)	0	8 (10.1)	14 (9.3)	17 (21.5)	21 (14.0)	19 (24.1)	23 (15.3)	19 (24.1)	23 (15.3)
Cumulative exposure, n (%)										
≥ 1	79 (100.0)	143 (95.3)	79 (100.0)	143 (95.3)	79 (100.0)	143 (95.3)	79 (100.0)	143 (95.3)	79 (100.0)	143 (95.3)
≥ 4	72 (91.1)	105 (70.0)	72 (91.1)	105 (70.0)	72 (91.1)	105 (70.0)	72 (91.1)	105 (70.0)	72 (91.1)	105 (70.0)
≥ 8	43 (54.4)	55 (36.7)	54 (68.4)	65 (43.3)	54 (68.4)	65 (43.3)	54 (68.4)	65 (43.3)	54 (68.4)	65 (43.3)
≥ 12	21 (26.6)	28 (18.7)	34 (43.0)	45 (30.0)	34 (43.0)	45 (30.0)	34 (43.0)	46 (30.7)	34 (43.0)	46 (30.7)
≥ 16	7 (8.9)	15 (10.0)	22 (27.8)	26 (17.3)	26 (32.9)	35 (23.3)	26 (32.9)	35 (23.3)	26 (32.9)	35 (23.3)
≥ 20	1 (1.3)	0	8 (10.1)	14 (9.3)	17 (21.5)	21 (14.0)	19 (24.1)	23 (15.3)	19 (24.1)	23 (15.3)
Duration of exposure										
N	79	150	79	150	79	150	79	150	79	150
Mean (SD)	9.5 (4.33)	7.4 (5.02)	11.7 (6.00)	8.9 (6.76)	12.9 (7.57)	9.8 (8.30)	14.0 (9.63)	10.8 (10.66)	14.9 (11.89)	11.4 (12.47)
Median	8.9	6.5	11.0	6.6	11.0	6.6	11.0	6.6	11.0	6.6
Min-max	1.3-21.4	0.3-19.1	1.3-27.8	0.3-27.8	1.3 - 33.5	0.3 - 31.5	1.3-41.3	0.3-43.5	1.3-53.2	0.3-53.9
Relative dose intensity (%)										
Mean (SD)	90.3 (17.15)	84.8 (35.49)	90.3 (18.21)	83.5 (35.74)	90.1 (18.94)	83.0 (35.88)	90.1 (18.87)	82.6 (35.96)	90.1 (18.86)	82.6 (35.98)
Median	97.2	91.8	97.0	90.8	96.8	90.7	96.6	89.9	96.6	89.9
Min-max	13.8-123.3	29.6-437.5[a]	10.1-123.3	27.4-437.5[a]	7.9 - 123.3	27.4 - 437.5[a]	7.7 - 123.3	26.9-437.5[a]	7.7-123.3	27.1- 437.5[a]

FAS = full analysis set; SD = standard deviation.
Notes:
[1] Ongoing at the time of the data cut-off
[a] Value attributed to a single patient with discrepant drug accountability and dose administration records.
Data Source: Health Canada Module 2.7.3[6]

As of the primary data cut off, dose reductions had occurred in 11 (13.9%) patients had in the 200 mg sonidegib group (i.e. the patients were reduced to placebo) and in 45 patients (30.0%) of patients in the 800 mg sonidegib group (39 [26.0%] with one reduction, and 6 [4.0%] patients with two dose reductions) (Table 17).[108] As of the 42-month data cut off, dose reductions had occurred in 13 (16.5%) patients had in the 200 mg sonidegib group (i.e. the patients were reduced to placebo) and in 55 patients (36.7%) of patients in the 800 mg sonidegib group (44 [29.3%] with one reduction, and 11 [7.3%] patients with two dose reductions).

Table 17: Dose Reductions and Dose interruptions of Study Drug in the BOLT Trial (Safety Analysis Set)

	Primary analysis: data cut-off: 28-Jun-2013		12-month analysis: data cut-off: 31-Dec-2013		18-month analysis: data cut-off: 11-Jul-2014		30-month analysis: data cut-off: 10-Jul-2015		42-month analysis: data cut-off: 08-Jul-2016	
	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150
Reductions										
Patients with dose reductions, n (%)	**11 (13.9)**	**45 (30.0)**	**13 (16.5)**	**51 (34.0)**	**13 (16.5)**	**53 (35.3)**	**13 (16.5)**	**54 (36.0)**	**13 (16.5)**	**55 (36.7)**
1 dose reduction[1]	11 (13.9)	39 (26.0)	13 (16.5)	42 (28.0)	13 (16.5)	42 (28.0)	13 (16.5)	43 (28.7)	13 (16.5)	44 (29.3)
2 dose reductions[1]	0	6 (4.0)	0	9 (6.0)	0	11 (7.3)	0	11 (7.3)	0	11 (7.3)
Percent actual days dosed[2]										
Mean (standard deviation)	97.6 (3.97)	94.1 (8.54)	97.3 (4.32)	93.6 (8.97)	97.1 (4.41)	93.6 (8.99)	97.2 (4.39)	93.6 (9.01)	97.0 (4.47)	93.6 (9.00)
Median	99.4	98.1	99.1	97.8	99.1	97.8	99.1	97.6	99.1	97.8
Minimum, maximum	80.1, 100	57.1, 100	79.3, 100	57.7, 100	76.7, 100	49.4, 100	76.7, 100	46.6, 100	76.7, 100.0	46.6, 100.0
Percent of days received full dose[2]										
Mean (standard deviation)	93.4 (15.42)	80.1 (28.10)	92.4 (17.63)	78.1 (28.99)	91.8 (18.49)	77.6 (29.35)	91.8 (18.50)	77.4 (29.28)	91.7 (18.49)	77.1 (29.47)
Median	99.4	96.0	99.1	94.3	99.1	94.4	99.1	94.2	99.1	94.2
Minimum, maximum	14.3, 100	8.2, 100	10.5, 100	6.0, 100	8.3, 100	4.7, 100	8.1, 100	3.3, 100	8.1, 100.0	2.6, 100.0
Interruptions (delays)										
Patients with any dose interruption, n (%)	**49 (62.0)**	**91 (60.7)**	**52 (65.8)**	**97 (64.7)**	**54 (68.4)**	**98 (65.3)**	**54 (68.4)**	**98 (65.3)**	**54 (68.4)**	**98 (65.3)**
1 dose interruption	20 (25.3)	36 (24.0)	19 (24.1)	39 (26.0)	20 (25.3)	37 (24.7)	19 (24.1)	35 (3.3)	19 (24.1)	34 (22.7)
≥2 dose interruptions	29 (36.7)	55 (36.7)	33 (41.8)	58 (38.7)	34 (43.0)	61 (40.7)	35 (44.3)	63 (42.0)	35 (44.3)	64 (42.7)
Reason for dose interruption										
Adverse events	22 (27.8)	66 (44.0)	27 (34.2)	74 (49.3)	28 (35.4)	76 (50.7)	30 (38.0)	77 (51.3)	31 (39.2)	77 (51.3)
Dosing error	22 (27.8)	42 (28.0)	26 (32.9)	44 (29.3)	28 (35.4)	45 (30.0)	28 (35.4)	45 (30.0)	28 (35.4)	47 (31.3)
Technical problems	15 (19.0)	19 (12.7)	17 (21.5)	21 (14.0)	18 (22.8)	23 (15.3)	18 (22.8)	23 (15.3)	18 (22.8)	24 (16.0)
Dispensing error	4 (5.1)	2 (1.3)	0	0	--	--			0	1 (0.7)
Lack Of Efficacy	--	--	--	--	1 (1.3)	0			--	--

Notes:
[1] Per protocol, patients in the sonidegib 200-mg group were only allowed one dose reduction whereas patients in the sonidegib 800-mg group were allowed a maximum of two dose reductions
[2] Denominator is based on potential days dosed.
Data Source: Health Canada Module 2.7.4[108]

d) Patient Disposition

Overall Population

Of the 269 BCC patients (both laBCC and mBCC) who were screened for trial eligibility, 230 underwent randomization.[2] A total of 39 (14.5%) patients were excluded prior to randomization for the following reasons: 30 (11.2%) did not meet eligibility criteria, six (2.2%) were not enrolled per patient's decisions, and three (1.1%) for physician's decision. The FAS included 66 laBCC patients who were randomized to 200 mg sonidegib and 194 who were randomized patients to 800 mg sonidegib. The pEAS included 42 patients randomized to 200 mg sonidegib and 93 patients randomized to 800 mg sonidegib.

The disposition of the overall population (both laBCC and mBCC) patients included in both the FAS and the pEAS at the primary data cut-off and the 42-month data cut-off is summarized in Table 18.[8] In the 200 mg group FAS, 20.3%, 19.0%, 6.3%, and 3.8% of patients had discontinued treatments for AEs, PD, withdrawal by subject, and physicians'

decision, respectively, which had increased to 29.1%, 36.7%, 10.1%, and 12.7% as of the 42-month data cut-off. In the 800 mg group FAS, 31.8%, 4.0%, 18.5%, and 6.6% of patients had discontinued treatments for AEs, PD, withdrawal by subject, and physicians' decision, respectively, which had increased to 37.7%, 15.9%, 23.2%, and 9.3% as of the 42-month data cut-off.

Table 18: Participant Disposition of the Overall Population Patients in the BOLT Trial at the Primary and 42-Month Data Cut-Off (FAS and pEAS)

Patient Disposition, n (%)	Primary analysis: 28-Jun-2013 data cut-off				42-month analysis: 08-Jul-2016 data cut-off			
	FAS		pEAS		FAS		pEAS	
	200 mg sonidegib (n = 79)	800 mg sonidegib (n = 151)	200 mg sonidegib (n = 55)	800 mg sonidegib (n = 116)	200 mg sonidegib (n = 79)	800 mg sonidegib (n = 151)	200 mg sonidegib (n = 55)	800 mg sonidegib (n = 116)
Patients randomized								
Treated	79 (100.0)	150 (99.3)	55 (100.0)	115 (99.1)	79 (100.0)	150 (99.3)	55 (100.0)	115 (99.1)
Not treated	0	1 (0.7)	0	1 (0.9)	0	1 (0.7)	0	1 (0.9)
Treatment ongoing [a]	39 (49.4)	46 (30.5)	31 (56.4)	34 (29.3)	6 (7.6)	5 (3.3)	5 (9.1)	2 (1.7)
Discontinued treatment	40 (50.6)	104 (68.9)	24 (43.6)	81 (69.8)	73 (92.4)	145 (96.0)	50 (90.9)	113 (97.4)
Adverse events	16 (20.3)	48 (31.8)	9 (16.4)	38 (32.8)	23 (29.1)	57 (37.7)	16 (29.1)	47 (40.5)
Death	0	4 (2.6)	0	4 (3.4)	1 (1.3)	5 (3.3)	1 (1.8)	5 (4.3)
Loss to follow-up	1 (1.3)	4 (2.6)	0	2 (1.7)	2 (2.5)	4 (2.6)	0	2 (1.7)
Non-compliance	0	3 (2.0)	0	3 (2.6)	0	5 (3.3)	0	5 (4.3)
Physician decision	3 (3.8)	10 (6.6)	3 (5.5)	9 (7.8)	10 (12.7)	14 (9.3)	6 (10.9)	12 (10.3)
Progressive disease	15 (19.0)	6 (4.0)	10 (18.2)	5 (4.3)	29 (36.7)	24 (15.9)	22 (40.0)	18 (15.5)
Protocol violation	0	1 (0.7)	0	1 (0.9)	0	1 (0.7)	0	1 (0.9)
Withdrawal by subject	5 (6.3)	28 (18.5)	2 (3.6)	19 (16.4)	8 (10.1)	35 (23.2)	5 (9.1)	23 (19.8)
Continued to the next trial phase	27 (34.2)	57 (37.7)	18 (32.7)	47 (40.5)	51 (64.6)	89 (58.9)	36 (65.5)	71 (61.2)
Post-treatment follow-up	11 (13.9)	30 (19.9)	7 (12.7)	22 (19.0)	19 (24.1)	40 (26.5)	12 (21.8)	31 (26.7)
Survival follow-up	16 (20.3)	27 (17.9)	11 (20.0)	25 (21.6)	32 (40.5)	49 (32.5)	24 (43.6)	40 (34.5)

FAS = full analysis set; pEAS = primary efficacy analysis set

Notes:

[a] Ongoing at the time of the data cut-off

[b] Primary reason for treatment discontinuation

Data Source: Health Canada Module 2.7.3[8]

laBCC Subgroup

The disposition of the laBCC patients included in both the FAS and the pEAS at the 42-month data cut is summarized in Table 19.[7] In the FAS, most patients in both groups had discontinued treatment (92.4% of patients in the 200 mg sonidegib group and 95.3% of patients in the 800 mg sonidegib group). Fewer patients in the 200 mg sonidegib group compared to the 800 mg group, respectively, had discontinued due to AEs (28.8% versus 41.4%) or due to withdrawal by subject (12.1% versus 23.4%), however more had

discontinued due to PD (31.8% versus 11.7%). In the 200 mg sonidegib group, 24.2% of patients were in post treatment follow-up and 39.4% were in survival follow up, compared to 29.7% and 28.1% respectively in the 800 mg sonidegib group.

Table 19: Participant Disposition of laBCC Patients in the BOLT Trial at the 42-Month Data Cut-Off (FAS and pEAS)

Patient Disposition, n (%)	FAS			pEAS		
	200 mg sonidegib (n = 66)	800 mg sonidegib (n = 128)	All patients (n = 194)	200 mg sonidegib (n = 42)	800 mg sonidegib (n = 93)	All patients (n = 135)
Patients randomized						
Treated	66 (100.0)	127 (99.32	193 (99.5)	42 (100.0)	92 (98.9)	134 (99.3)
Not treated	0	1 (0.8)	1 (0.5)	0	1 (1.1)	1 (0.7)
Treatment ongoing [a]	5 (7.6)	5 (3.9)	10 (5.2)	4 (9.5)	2 (2.2)	6 (4.4)
Discontinued treatment	61 (92.4)	122 (95.3)	183 (94.3)	38 (90.5)	90 (96.8)	128 (94.8)
Adverse events	19 (28.8)	53 (41.4)	72 (37.1)	12 (28.6)	43 (46.2)	55 (40.7)
Death	1 (1.5)	4 (3.1)	5 (2.6)	1 (2.4)	4 (4.3)	5 (3.7)
Loss to follow-up	2 (3.0)	4 (3.1)	6 (3.1)	0	2 (2.2)	2 (1.5)
Non-compliance	0	3 (2.3)	3 (1.5)	0	3 (3.2)	3 (2.2)
Physician decision	10 (15.2)	12 (9.4)	22 (11.3)	6 (14.3)	10 (10.8)	16 (11.9)
Progressive disease	21 (31.8)	15 (11.7)	36 (18.6)	14 (33.3)	9 (9.7)	23 (17.0)
Protocol violation	0	1 (0.8)	1 (0.5)	0	1 (1.1)	1 (0.7)
Withdrawal by subject	8 (12.1)	30 (23.4)	38 (19.6)	5 (11.9)	18 (19.4)	23 (17.0)
Continued to the next trial phase	42 (63.6)	74 (57.8)	116 (59.8)	27 (64.3)	56 (60.2)	83 (61.5)
Post-treatment follow-up	16 (24.2)	38 (29.7)	54 (27.8)	9 (21.4)	29 (31.2)	38 (28.1)
Survival follow-up	26 (39.4)	36 (28.1)	62 (32.0)	18 (42.9)	27 (29.0)	45 (33.3)
Treatment unblinded by the site						
No	61 (92.4)	116 (90.6)	177 (91.2)	40 (95.2)	86 (92.5)	126 (93.3)
Yes	5 (7.6)	11 (8.6)	16 (8.2)	2 (4.8)	6 (6.5)	8 (5.9)

FAS = full analysis set; pEAS = primary efficacy analysis set

Notes:

[a] Ongoing at the time of the data cut-off

[b] Primary reason for treatment discontinuation

Data Source: Additional Information Requested August 20, 2020[7]

Protocol Deviations: Details of the protocol deviations as of the 42-month data cut-off are listed in Table 20.[7] In the 200 mg sonidegib group, 64 (97.0%) patients had at least one protocol deviation. In the 800 mg sonidegib group, 122 (95.3%) of patients had at least one protocol deviation. Most protocol deviations were related to key procedures not performed as per protocol (200 mg: 95.5%; 800 mg: 93.8%). Key procedures not performed as per protocol included tumour evaluation criteria were not met in 52 (78.8%) patients in the 200 mg sonidegib group and 72 (56.3%) patients in the 800 mg sonidegib group. Additionally, biomarker requirements were not met in 35 (53.0%) patients in the 200 mg sonidegib group and in 72 (56.3%) patients in the 800 mg sonidegib group, pharmacokinetic assessment were not performed in 19 (28.8%) and 29 (22.7%) patients, respectively, survival information

was not provided in 29 (43.9%) and 38 (29.7%) patients, respectively, and tumour evaluation criteria not met in 52 (78.8%) and 72 (56.3%) patients, respectively. Selection criteria was not met in 17 (25.8%) patients in the 200 mg sonidegib group and in 25 (19.5%) of patients in the 800 mg sonidegib group.

Table 20: Protocol Deviations in the laBCC Patients of the BOLT Trial at the 42-Month Data Cut-Off (FAS)

Deviation	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)
Patients with at least one protocol deviation	64 (97.0)	122 (95.3)
GCP related deviation	13 (19.7)	26 (20.3)
GCP not followed	13 (19.7)	26 (20.3)
Key procedures not performed as per protocol	63 (95.5)	120 (93.8)
Baseline performance status criteria not met	2 (3.0)	1 (0.8)
Biomarker and histopathology assessment requirements not met	11 (16.7)	19 (14.8)
Biomarker requirements not met	35 (53.0)	72 (56.3)
Cardiac safety assessment not performed	28 (42.4)	37 (28.9)
Lab assessments not completed	2 (3.0)	11 (8.6)
Pharmacokinetic assessment not performed	19 (28.8)	29 (22.7)
Safety assessments not completed	0	1 (0.8)
Survival information not provided	29 (43.9)	38 (29.7)
Tumour evaluation criteria not met	52 (78.8)	72 (56.3)
Not discontinued after meeting withdrawal criteria	1 (1.5)	0
Dosing criteria not followed	1 (1.5)	0
Selection criteria not met	17 (25.8)	25 (19.5)
Entry criteria not met	15 (22.7)	17 (13.3)
Lab criteria entry not met	1 (1.5)	2 (1.6)
Measurable disease criteria entry not met	0	2 (1.6)
Study entry treatment criteria entry not met	0	3 (2.3)
Written informed consent not obtained	2 (3.0)	1 (0.8)
Study treatment deviation	4 (6.1)	7 (5.5)
Dosing criteria not followed	4 (6.1)	7 (5.5)
Use of prohibited concomitant medication	2 (3.0)	8 (6.3)
Concomitant medication requirements not followed	2 (3.0)	8 (6.3)

FAS = full analysis set; GCP = good clinical practice; laBCC = locally advanced basal cell carcinoma.
Notes:
A patient with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category.
Patients may have protocol deviations in more than one protocol deviation category.
A patient with multiple occurrences of a protocol deviation is counted only once in the protocol deviation row.
Data Source: Additional Information Requested August 20, 2020[7]

laBCC Patients Excluded from the pEAS: A total of 59 (30.4%) patients (200 mg: n = 24 (36.4%); 800 mg: n =35 (27.3%) were excluded from the pEAS but were included in the FAS. [32] Details of the exclusions are provided in Table 21.

Table 21: Reasons for Exclusion from the laBCC FAS in the BOLT Trial

Reason, n (%)	200 mg sonidegib	800 mg sonidegib	All patients
Patients included in the FAS, n	66	128	194
laBCC Patients excluded from pEAS	24 (36.4)	35 (27.3)	59 (30.4)
MRI + no photo (without valid reason)	1 (1.5)	1 (0.8)	2 (1.0)
MRI + non-annotated photo (with palpable sub-dermal components or not done)	10 (15.2)	20 (15.6)	30 (15.5)
No MRI (with valid reason) + non-annotated photo (with palpable sub-dermal components or not done)	1 (1.5)	2 (1.6)	3 (1.5)
No MRI (without valid reason) + annotated photo	6 (9.1)	5 (3.9)	11 (5.7)
No MRI (without valid reason) + no photo (without valid reason)	2 (3.0)	2 (1.6)	4 (2.1)
No MRI (without valid reason) + non-annotated photo (with palpable sub-dermal components or not done)	3 (4.5)	3 (2.3)	6 (3.1)
No MRI (without valid reason) + non-annotated photo (without palpable sub-dermal components)	1 (1.5)	2 (1.6)	3 (1.5)

FAS = full analysis set; laBCC = locally advanced basal cell carcinoma; pEAS = primary efficacy analysis set.

Data Source: 42-month Clinical Study Report 2017[32]

e) Limitations/Sources of Bias

The BOLT was a phase II trial that evaluated the efficacy and safety of two doses of sonidegib in adult patients with laBCC not amenable to radiotherapy or curative surgery, or mBCC for which all existing available treatment options had been exhausted. The primary objective of the trial was to evaluate the proportion of patients with an ORR, which was considered an appropriate end point for this patient population when considered with key secondary end points such as DOR and PFS. ORR was assessed by IRC, which was a strength of the study. The randomization of patients to the two different doses of sonidegib and blinding procedures were appropriately performed. Protocol defined criteria for study treatment administration, such as appropriate dosing, were generally followed. The procedures employed in the BOLT trial included generally appropriate methods for statistical analyses, and overall study methodology. Overall, patients at baseline in both study groups generally had demographics and disease characteristics that would be seen in Canadian clinical practice, although the patient population was younger than would be seen in Canadian clinical practice and the number and type of comorbidities affecting patients is unknown, resulting in a potentially highly selected population. As per the CGP, the median duration of follow-up time was considered an appropriate length of time to assess trial outcomes. Additionally, the CGP noted that response to treatment for lesions in clinical practice is not typically performed with biopsies. If it apparent that the lesion has disappeared, a biopsy will not be performed. In the BOLT trial, tumour response included biopsies for histological confirmation in the laBCC patients, when response assessment was confounded by ulceration, cyst(s), and/or scarring/fibrosis. Therefore, the response assessments may have been more strict than real-world practice.

The CADTH Methods Team identified the following limitations and potential sources of bias that should be considered when interpreting the trial results:

- As of amendment 2 (November 17th, 2011), at which point 26 patients had already been enrolled, tumour response evaluation by RECIST v1.1 was changed to mRECIST for the laBCC population. Per amendment 2, laBCC patients were required to have annotated or non-annotated photographs and mandatory baseline MRI scans (unless

contraindicated). Thus, patients who did not have this baseline assessment were excluded from the pEAS, which may have introduced selection bias, however it was not suspected to have affected efficacy or safety outcomes, or the generalizability of the results. It should be noted these patients that were excluded in the pEAS were included in the FAS analyses, however IRC assessment was also introduced in amendment 2 and thus, the 26 patients that were enrolled prior to amendment 2 were retrospectively assessed for IRC-assessed ORR. Analyses conducted using the FAS would have included patients that were both retrospectively and prospectively assessed for response, and thus, efficacy results may be affected. For example, patients retrospectively assessed by IRC as PD, but were not assessed by INV as PD, may have been continuing study treatment when it should have been discontinued; and thus, safety outcomes may be overreported and median duration of treatment may be longer than it should have been if assessment was prospective. This may introduce some degree of uncertainty in the reported results.

- The targeted sample size was calculated by using decision operating characteristics for the primary endpoint. The sample size calculation was for both the laBCC and the mBCC patients combined (i.e. it wasn't calculated for laBCC and mBCC individually). While the results of the laBCC subgroup are consistent with the overall trial population, the efficacy results meeting the 30% threshold may be a spurious result as the sample size was not calculated specifically for the laBCC subgroup. Additionally, the recommended dose of sonidegib is 200 mg, however 800 mg was hypothesized to be the more efficacious dose without compromising safety during the design of the study; thus results for the laBCC 200 mg dose group are based on subgroup of full trial by dose and disease type. The laBCC 200 mg dose subgroup was not the main consideration in the overall trial sample size calculation; and thus while the results of the 200 mg laBCC subgroup are consistent with the overall trial results and met the clinically significant threshold, this could have been a spurious finding.
- The median DOR in the FAS at the 42-month data cut-off was considerably longer for the laBCC 200 mg sonidegib subgroup compared to the median DOR in the pEAS (26.1 months compared to 12.9 months) indicating that there may have been a potential for the patients with better prognosis to be excluded from the pEAS. Patients who were eligible under the original protocol may have had less severe disease as it did not have to be measured by the criteria introduced in the amendment and thus, the efficacy results reported in the FAS are uncertain and may be overestimated. However, analyses of IRC-assessed ORR in the FAS were similar to analyses conducted in the pEAS, whereby the ORR was greater than 30% with the lower bound of the 95% CI exceeding 20% (which was considered to be clinically meaningful)[5] for both treatment arms at each of the analyses. Overall, the results were consistent with the analysis in the pEAS population, indicating that the primary analyses results are robust and are similar to the ITT population
- There were several subgroup analyses and multiple secondary efficacy outcomes assessed in the trial that were not adjusted to account for multiple comparison testing to control the risk of type 1 error. As the trial was not powered to test specific hypotheses in these additional subgroups and outcomes, the results of these analyses should be interpreted as exploratory in nature.
- The BOLT trial did not include a comparator. All participants and investigators were aware that the patient was receiving an active treatment, potentially biasing the results of the outcome assessments. At the time of implementation of the study, no established systemic treatments were available for patients with laBCC or mBCC, however preliminary results from a phase I study demonstrated encouraging efficacy data.[3] The trial therefore included two study groups evaluating two doses of sonidegib. No comparisons were made to placebo or to an active control arm. The currently funded treatment for patients with BCC is vismodegib. The comparative effectiveness of sonidegib to vismodegib was not assessed in these studies. The sponsor provided the results of one published unanchored MAIC and one published MA that estimated the

comparative efficacy and safety of sonidegib to vismodegib, as well as to other comparators. Refer to Section 7 for a summary and critical appraisal of the MAIC and MA.

- For the analysis of PFS and DOR, patients receiving a new anti-cancer therapy prior to an event were censored, and this outcome was not treated as an event. As per the FDA, this is considered a biased censoring rule, and generally starting another treatment before an event should be considered as an event.[111]
  - At the 42-month data cut-off, 20.7% and 9.0% of patients in the 200 mg and 800 mg laBCC sonidegib subgroups, respectively, had been censored for the PFS analysis.[8] Sensitivity analyses were performed in which new antineoplastic therapy and missing two or more assessments were treated as events. These sensitivity analyses demonstrated shorter estimated medians for PFS in the laBCC 200 mg sonidegib subgroup (median PFS at 42-months: 19.0 in primary analysis versus 14.9 months in sensitivity analysis for new antineoplastic therapy treated as an event versus 14.8 months in sensitivity analysis for missing two or more assessments treated as an event). This indicates that the results of the primary analyses for PFS may have been inflated.[32]
  - At the 42-month data cut-off, 31.0% and 29.0% of patients in the 200 mg and 800 mg laBCC sonidegib subgroups, respectively, had been censored for the DOR analysis.[8] Sensitivity analyses were performed in which new antineoplastic therapy and missing two or more assessments were treated as events. These sensitivity analyses demonstrated similar estimated medians for DOR in the laBCC 200 mg sonidegib group (median PFS at 42-months: 12.9 months in primary analysis versus 12.9 months in either sensitivity analysis). This indicates that the results of the primary analyses for DOR may be robust.
- For the analysis of DOR at the time of the 42-month analysis, over half of patients (53.8% of laBCC patients treated with 200 mg and 55.6% treated with 800 mg) were censored due to adequate assessment no longer being available. Similarly, at the time of the 42-month analysis of PFS, over half of laBCC patients (58.6% treated with 200 mg and 53.7% treated with 800 mg) were censored due to adequate assessment no longer being available.[32] Depending on the type of patients that continued to have adequate assessments, this may have over or underestimated DOR and/or PFS, but in the absence of a sensitivity analysis this remains unknown. This may introduce some level of uncertainty to DOR and PFS results due to the high proportion of censoring due to lack of adequate assessments to reasonable determine PFS and/or DOR.
- At the time all the data cut-offs, the median OS was not estimable for either laBCC treatment dose group, and therefore the magnitude of long-term survival benefit is currently unknown. Survival data may be confounded by the use of subsequent anticancer treatments following discontinuation (subsequent treatments received by patients from the BOLT trial are summarized in Table 37). For example, 14 (21.2%) patients in the laBCC 200 mg sonidegib group had subsequent anticancer surgery (of which seven patients underwent surgical resection after PR) which could have contributed to better survival in the 200 mg laBCC subgroup.[107] At the time of the 42-month data cut-off, protocol deviations for 'survival information not provided' was reported for 29 (43.9%) patients in the laBCC 200 mg sonidegib group and 38 (29.7%) patients in the laBCC 800 mg sonidegib group. As indicated in the protocol, patients who were alive at the end of the study or were lost to follow-up were right censored at the date of last contact for OS (42-month data cut-off: laBCC patients of the 200 mg sonidegib group, 90.9% censored with 43.3% censored due to loss to follow-up).[32] Therefore, survival estimates may be over estimated due to the high proportion of censoring for missing survival information, introducing considerable uncertainty in the reported OS results. Health Canada also included a statement in the NOC that the indication was granted market authorization based on ORR, however OS benefit in the trial cannot be confirmed.[1] Additionally, as per the CGP, patients in this setting typically have competing morbidities that affect survival, however data on patient comorbidities

was not reported. Thus, the impact of comorbid conditions, which are often seen in this patient population, on OS remains unknown.

- Protocol deviations occurred in almost all patients in the trial (97.0% in the laBCC 200 mg sonidegib subgroup and 95.3% in the laBCC 800 mg sonidegib subgroup had at least one protocol violation), which could affect the validity of the reported results. Important deviations are outlined below:
  - The selection criteria were not met in 25.8% of patients in the laBCC 200 mg sonidegib subgroup and in 19.5% of patients in the laBCC 800 mg sonidegib subgroup, with eligibility criteria not being met as the main reason. Patients with missing assessments were either included or excluded from the pEAS based on whether the patient's tumours had been adequately assessed by photograph, radiological scans or both. If a patient's tumour was not adequately assessible, they were excluded from the pEAS. There may have been a potential for selection bias of patients in the pEAS if certain tumour characteristics systematically led to a higher or lower chance for a tumour to be adequately assessible.
  - At the 42-month data cut-off, 95.5% in the laBCC 200 mg sonidegib subgroup had protocol deviations for key procedures not performed as per protocol. At the time of the 42-month analysis, these protocol deviations included cardiac safety assessment not performed (42.4%), pharmacokinetic assessment not performed (28.8%), biomarker requirements not met (53.0%), survival information not provided (43.9%), and tumor evaluation criteria not met (78.8%). Details of the missed cardiac and pharmacokinetic assessments were not captured, and thus related safety events could have been missed, and therefore potentially under reported. It was not clear what biomarker requirements were not met, and how this impacts efficacy and/or safety. As discussed in an earlier point, the significant proportion of patients with missing survival information were censored in OS analyses, and thus, there is considerable uncertainty in the reported OS results for the BOLT trial.
- Interpretation of the HRQOL results were limited as there was no comparator treatment. Additionally, compliance in responding to the questionnaires dropped below to below 50% by week 33.[9] To note, baseline score and change in scores from baseline at various timepoints were not provided, and thus, it is unclear whether the reported improvements met MCID thresholds for EORTC-QLQ-C30 domains as defined in the literature.[110]
- Overall, the results per INV-assessment were substantially higher than IRC-assessed ORR at each of the time points. At the 42-month data analysis, concordance rates between investigator and IRC-assessed ORR was 0.64 in the laBCC 200 mg sonidegib subgroup, and 0.53 in the labCC 800 mg sonidegib subgroup.[8] These rates were similar to previous data cut-offs. This lack of concordance between the two assessment methods may indicate a potential bias for higher rates of 'positive response to treatment' when the outcome is assessed by the investigator.
- Dose adjustments were permitted for patients who were unable to tolerate the dosing schedule or for toxicities that were suspected to be related to the study drug. Patients in the 200 mg group were allowed one reduction to placebo only (i.e. no longer receiving active treatment), and discontinued treatment if a further reduction was necessary, while patients in the 800 mg group were allowed up to two dose reductions. If patients in the 200 mg group were to require the second dose reduction to be discontinued from treatment, there may have been concerns with maintaining blinding.
- The sponsors Novartis Pharmaceuticals Corporation funded the trial and were involved in several aspects of the study conduct, including the study design, data analysis, data interpretation, and writing of the reports. The extent to which the sponsors' involvement may have influenced the results and reporting of the trial is unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy results for the primary outcome of ORR are presented for the overall trial population (i.e. both laBCC and mBCC patients combined) as this was the only end point considered in sample size calculations for the overall trial population and all other secondary end points are exploratory as none were controlled for multiplicity. Results for the primary outcome will also be presented for the laBCC subgroup, and all other secondary outcomes as outlined in the systematic review protocol (DOR, TTR, PFS, OS, and HRQoL), will be reported for the laBCC subgroup only as this is the indication under review. Safety results are presented for the full trial population (both laBCC and mBCC patients).

Efficacy Outcomes

The reported results in this section will generally focus on the primary analysis and 42-month analysis, unless otherwise noted. The primary analysis data cut-off date was June 28, 2013 and the median duration of follow-up was 13.9 months (interquartile range (IQR): 10.1 to 17.3 months).[2] Median duration of follow-up for further data analysis timepoints were the following: 20.0 months for the 12-month analysis (31-Dec-2013 data cut-off), 26.3 months for the 18-month analysis (11-Jul-2014 data cut-off), 38.2 months for the 30-month analysis (10-Jul-2015 data cut-off), and 50.2 months for the 42-month analysis (08-Jul-2016 data cut-off).[8]

Primary Efficacy Outcome: IRC-assessed ORR using the pEAS

Overall Population: Details of the primary efficacy outcome for the overall population (n=171) (both laBCC and mBCC) at each of the data cut-offs are presented in Table 22.[8] The IRC-assessed ORR was greater than 30% with the lower bound of the 95% CI exceeding 20% (which was considered to be clinically meaningful) for both treatment groups at each of the analyses.[5] At the time of the primary data cut-off, 36.4% (95% CI: 23.8 to 50.4) of patients in the 200 mg sonidegib group and 33.6% (95% CI: 25.1 to 43.0) of patients in the 800 mg sonidegib group had achieved an objective response. In the 200 mg sonidegib group, a total of 20 patients achieved a CR or PR, which included 2 (3.6%) patients that achieved a CR and 18 (32.7%) patients that achieved a PR. In the 800 mg sonidegib group, all patients who achieved an objective response had a PR (n = 39; 33.6%). Overall, results at the following data cut-offs were consistent with the primary data analysis. To note in the 200 mg sonidegib group, ORR increased to 45.5% at the 12-month analysis, which was revised to 43.6% as of the 18-month analysis due to a re-review at further evaluations. The ORR of 43.6% was maintained through to the 42-month data cut-off, suggesting that patients who responded, responded by 12 months.

Table 22: Summary of IRC-assessed ORR in the Overall Population (both laBCC and mBCC) Patients of the BOLT Trial (pEAS)

	Primary analysis: 28-Jun-2013 data cut-off		12-month analysis: 31-Dec-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off		30-month analysis: 10-Jul-2015 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
	All patients		All patients		All patients		All patients		All patients	
	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116
Objective Response Rate (ORR: CR+PR)										
n (%) 95% CI (%)	20 (36.4) (23.8, 50.4)	39 (33.6) (25.1, 43.0)	25[a] (45.5) (32.0, 59.4)	47 (40.5) (31.5, 50.0)	24[b] (43.6) (30.3, 57.7)	48 (41.4) (32.3, 50.9)	24 (43.6) (30.3, 57.7)	48 (41.4) (32.3, 50.9)	24 (43.6) (30.3, 57.7)	48 (41.4) (32.3, 50.9)
Diff. between tmt groups % 95% CI (%)	-2.7 (-18.73, 12.45)		-4.9 (-21.07, 11.00)		-2.3 (-18.45, 13.56)		-2.3 (-18.45, 13.56)		-2.3 (-18.45, 13.56)	
Best Overall Response, n (%)										
CR, n (%)	2 (3.6)	0	2 (3.6)	1 (0.9)	2 (3.6)	1 (0.9)	2 (3.6)	2 (1.7)	2 (3.6)	2 (1.7)
95% CI	(0.4, 12.5)	(0.0, 3.1)	(0.4, 12.5)	(0.0, 4.7)	(0.4, 12.5)	(0.0, 4.7)	(0.4, 12.5)	(0.2, 6.1)	(0.4, 12.5)	(0.2, 6.1)
PR	18 (32.7)	39 (33.6)	23[a] (41.8)	46 (39.7)	22[b] (40.0)	47 (40.5)	22 (40.0)	46 (39.7)	22 (40.0)	46 (39.7)
SD	31 (56.4)	54 (46.6)	26 (47.3)	51 (44.0)	27 (49.1)	50 (43.1)	27 (49.1)	50 (43.1)	27 (49.1)	50 (43.1)
PD	0	1 (0.9)	0	2 (1.7)	0	2 (1.7)	0	2 (1.7)	0	2 (1.7)
UNK	4 (7.3)	22 (19.0)	4 (7.3)	16 (13.8)	4 (7.3)	16 (13.8)	4 (7.3)	16 (13.8)	4 (7.3)	16 (13.8)

BOR = best overall response; CI = confidence interval; CR = complete response; NR = not reached; ORR = overall response rate; OS = overall survival; pEAS = primary efficacy analysis set; PD = progressive disease; PR = partial response; SD = stable disease.

Notes:

[a] Best overall response for a patient was changed from PR to SD for the 12-month analysis during central re-review due to new evidence received (new lesion identified in the photo image.

[b] Best overall response for a patient was changed from PR to SD for the 18-month analysis during central re-review due to confirmation of missing MRI images at evaluations 7 and 8 for that patient. Following mRECIST criteria, the corresponding overall responses at evaluations 7 and 8 were updated to UNK, and hence contributed to the change in BOR from PR to SD.

Data Source: Health Canada Module 2.7.3[8]

laBCC Subgroup: Details of the primary efficacy outcome as assessed in the pEAS for the laBCC subgroup (n=135) at each of the data cut-offs are presented in Table 23.[8] The IRC-assessed ORR was greater than 30% with the lower bound of the 95% CI exceeding 20% (which was considered to be clinically meaningful) for both treatment arms at each of the analyses. At the time of the primary data cut-off, 42.9% (95% CI: 27.7 to 59.0) of patients in the 200 mg sonidegib group and 37.6% (95% CI: 27.8 to 48.3) of patients in the 800 mg sonidegib group had achieved an objective response.[2,5] In the 200 mg sonidegib group, a total of 18 patients achieved a CR or PR, which included 2 (4.8%) patients that achieved a CR and 16 (38.1%) patients that achieved a PR. In the 800 mg sonidegib group, all patients who achieved an objective response had a PR (n = 35; 37.6%). Disease control (i.e. CR, PR, or SD) was achieved in 92.9% of patients in the 200 mg sonidegib group and in 79.5% of patients in the 800 mg sonidegib group. Overall, results at the following data cut-offs were consistent with the primary data analysis. To note in the 200 mg sonidegib group, ORR increased to 57.1% at the 12-month analysis, which was revised to 54.8% as of the 18-month analysis due to a re-review of missing MRI images at further evaluations.[8] The ORR

of 54.8% was maintained through to the 42-month data cut-off, suggesting that most laBCC patients who responded, responded by 12 months. These results should be interpreted with caution as the sample size was not calculated to provide power for the laBCC subgroup.

In the pEAS, one patient (2.4%) in the sonidegib 200 mg sonidegib group had underwent surgical resection following confirmed PR per IRC-assessment.[8] In the FAS, two (3%) patients in the 200 mg group and three (2.3%) patients in the 800 mg sonidegib group underwent surgical resection following confirmed PR per central review arm.[8]

Supportive Analyses – IRC-assessed ORR in the laBCC Subgroup using the FAS: Details of the supportive efficacy outcome for the laBCC subgroup in the FAS (i.e. the ITT population) at each of the data cut-offs are presented in Table 24.[8] Similar to the primary analysis in the pEAS, the IRC-assessed ORR was greater than 30% with the lower bound of the 95% CI exceeding 20% (which was considered to be clinically meaningful) for both treatment arms at each of the analyses.[5] Overall, the results were consistent with the analysis in the pEAS population, indicating that the primary analyses results are robust and are similar to the ITT population.

Table 23: Summary of IRC-assessed ORR in the laBCC Patients of the BOLT Trial (pEAS)

	Primary analysis: 28-Jun-2013 data cut-off		12-month analysis: 31-Dec-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off		30-month analysis: 10-Jul-2015 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)
ORR										
n (%)	18 (42.9)	35 (37.6)	24 (57.1)	43 (46.2)	23[a] (54.8)	44 (47.3)	23 (54.8)	44 (47.3)	23 (54.8)	44 (47.3)
95% CI	27.7 to 59.0	27.8 to 48.3	41.0 to 72.3	35.8 to 56.9	38.7 to 70.2	36.9 to 57.9	38.7 to 70.2	36.9 to 57.9	38.7 to 70.2	36.9 to 57.9
Difference, % (95% CI)	-5.2 (-23.68 to 12.69)		-10.9 (-28.75 to 7.72)		-7.5 (-25.50 to 11.22)		-7.5 (-25.50 to 11.22)		-7.5 (-25.50 to 11.22)	
BOR										
CR, n (%, 95% CI)	2 (4.8, 0.6 to 16.2)	0 (0.0, 0.0 to 3.9)	2 (4.8, 0.6 to 16.2)	1 (1.1, 0.0 to 5.8)	2 (4.8, 0.6 to 16.2)	1 (1.1, 0.0 to 5.8)	2 (4.8, 0.6 to 16.2)	2 (2.2, 0.3 to 7.6)	2 (4.8, 0.6 to 16.2)	2 (2.2, 0.3 to 7.6)
PR, n (%)	16 (38.1)	35 (37.6)	22 (52.4)	42 (45.2)	21[a] (50.0)	43 (46.2)	21[a] (50.0)	42 (45.2)	21[a] (50.0)	42 (45.2)
SD, n (%)	21 (50.0)	39 (41.9)	15 (35.7)	34 (36.6)	16 (38.1)	33 (35.5)	16 (38.1)	33 (35.5)	16 (38.1)	33 (35.5)
PD, n (%)	0	0	0	1 (1.1)	0	1 (1.1)	0	1 (1.1)	0	1 (1.1)
Unknown, n (%)	3 (7.1)	19 (20.4)	3 (7.1)	15 (16.1)	3 (7.1)	15 (16.1)	3 (7.1)	15 (16.1)	3 (7.1)	15 (16.1)

BOR = best overall response; CI = confidence interval; CR = complete response; NR = not reached; ORR = overall response rate; OS = overall survival; pEAS = primary efficacy analysis set; PD = progressive disease; PR = partial response; SD = stable disease.

Notes:

[a] Best overall response for one patient was changed from PR to SD for the 18-month analysis during central re-review due to confirmation of missing MRI images at evaluations 7 and 8 for that patient. Following mRECIST criteria, the corresponding overall responses at evaluations 7 and 8 were updated to UNK, and hence contributed to the change in BOR from PR to SD.

Data Source: Health Canada Module 2.7.3[8]

Table 24: Summary of IRC-assessed ORR in the laBCC Patients of the BOLT Trial (FAS)

	Primary analysis: 28-Jun-2013 data cut-off		12-month analysis: 31-Dec-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off		30-month analysis: 10-Jul-2015 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)
ORR										
n (%)	31 (47.0)	45 (35.2)	38 (57.6)	56 (43.8)	37[a] (56.1)	58 (45.3)	37 (56.1)	58 (45.3)	37 (56.1)	59 (46.1)
95% CI	34.6 to 59.7	26.9 to 44.1	44.8 to 69.7	35.0 to 52.8	43.3 to 68.3	36.5 to 54.3	43.3 to 68.3	36.5 to 54.3	43.3 to 68.3	37.2 to 55.1
Difference, % (95% CI)	-11.8 (-26.51 to 3.10)		- 13.8 (-28.27 to 1.52)		-10.7 (-25.35 to 4.58)		-10.7 (-25.35 to 4.58)		-10.0 (-24.55 to 5.35)	
BOR										
CR, n (%, 95% CI)	2 (3.0, 0.4 to 10.5)	0 (0.0 to 2.8)	3 (4.5, 0.9 to 12.7)	2 (1.6, 0.2 to 5.5)	3 (4.5, 0.9 to 12.7)	1[a] (0.8, 0.0 to 4.3)	3 (4.5, 0.9 to 12.7)	2 (1.6, 0.2 to 5.5)	3 (4.5, 0.9 to 12.7)	2 (1.6, 0.2 to 5.5)
PR, n (%)	29 (43.9)	45 (35.2)	35 (53.0)	54 (42.2)	34 (51.5)	55 (44.5)	34 (51.5)	56 (43.8)	34 (51.5)	57 (44.5)
SD, n (%)	29 (43.9)	55 (43.0)	22 (33.3)	48 (37.5)	23 (34.8)	47 (36.7)	23 (34.8)	47 (36.7)	23 (34.8)	46 (35.9)
PD, n (%)	1 (1.5)	0	1 (1.5)	1 (0.8)	1 (1.5)	1 (0.8)	1 (1.5)	1 (0.8)	1 (1.5)	1 (0.8)
Unknown, n (%)	5 (7.6)	28 (21.9)	5 (7.6)	23 (18.0)	5 (7.6)	22 (17.2)	5 (7.6)	22 (17.2)	5 (7.6)	22 (17.2)

BOR = best overall response; CI = confidence interval; CR = complete response; NR = not reached; ORR = overall response rate; OS = overall survival; pEAS = primary efficacy analysis set; PD = progressive disease; PR = partial response; SD = stable disease.

Notes:

[a] BOR for one patient was changed from PR to SD for the 18-month analysis during central re-review due to confirmation of missing MRI images at evaluations 7 and 8 for that patient. Following mRECIST criteria, the corresponding overall responses at evaluations 7 and 8 were updated to UNK, and hence contributed to the change in BOR from PR to SD.

[b] BOR for a patient was changed from CR to unknown for 18-month analysis during central re-review due to confirmation of missing MRI images. BOR for another patient was changed from CR to PR during central re-review due to new evidence (MRI imaging data) that was received after the 31-Dec-2013 cut-off for the 12-month analysis. Lastly, BOR for another patient was changed from PR to CR during central re-review. The net result was one less CR for sonidegib 800 mg for the 18-month analysis.

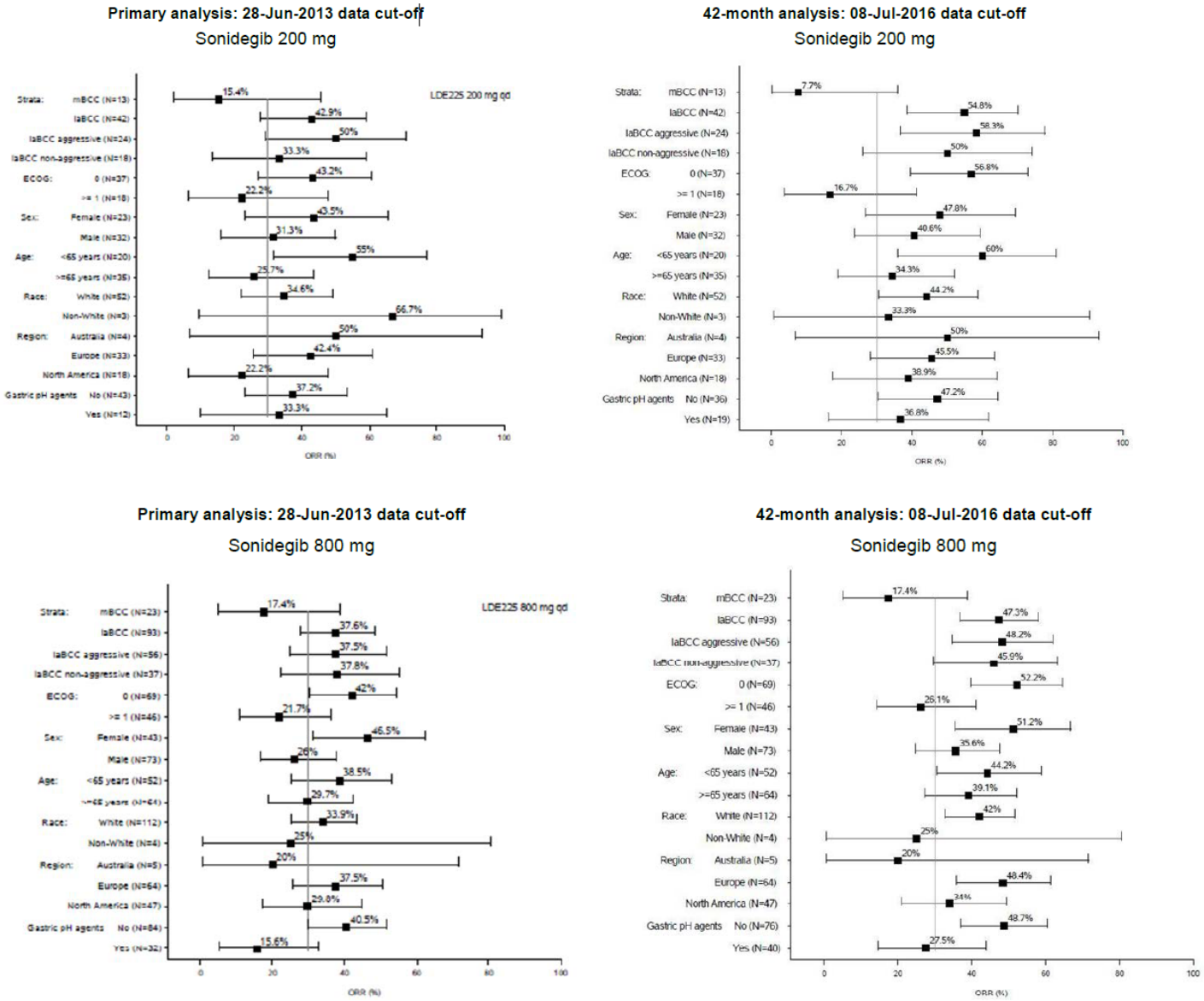
Data Source: Health Canada Module 2.7.3[8]

Subgroup Analyses of IRC-assessed ORR, Overall Trial Population (both laBCC and mBCC): The results of subgroup analyses for the entire trial population (both patients with laBCC and patients with mBCC) for IRC-assessed ORR in the pEAS at both the primary and 42-month analyses are shown in Figure 3.[8] For most subgroups, the median ORR was greater than or equal to 30%, showing a response rate with 95% CIs in which the lower bound exceeded 20%.[8] The subgroup of patients with aggressive laBCC and non-aggressive laBCC in the 200 mg sonidegib group had a median ORR of 50% and 58.3% at the primary data cut-off and the 42-month data cut-off respectively, with the lower bounds of the confidence interval exceeding 20%, consistent with the primary analysis results. Conversely, the subgroup of patients with non-aggressive laBCC had a median ORR of 33.3% and 50% at the primary data cut-off and the 42-month data cut-off respectively, however the lower bound of the confidence interval did not exceed 20% at the primary data-cut off, but it did exceed 20% at the time of the 42-month data cut-off. In the FAS (figures not displayed), IRC-assessed ORR at the primary data cut-off for patients with aggressive laBCC was 54.1% (95% CI: 36.9 to 70.5) for the 200 mg sonidegib group and 34.7% (95% CI: 24.0 to 46.5) in the 800 mg sonidegib group.[2] For patients with non-aggressive laBCC, ORR was 37.9% (95% CI: 20.7 to 57.7) in the 200 mg sonidegib group and was 35.8 % (95% CI: 23.1 to 50.2%) in the 800 mg sonidegib group.

As shown in Figure 3, subgroups in the pEAS with IRC-assessed median ORR less than 30% for the 200 mg sonidegib group included: mBCC (both data cut-offs); ECOG PS of greater or equal to 1 (both data cut-offs), patients from North America (at the primary data cut-off), patients aged 65 or older (at the primary data cut-off). The confidence interval was also lower than the clinically meaningful threshold of 20% for the aforementioned subgroups, as well as the following subgroups: males (primary data cut-off), non-White patients (both data cut-offs), patients from Australia (both data cut-offs), and patients on gastric pH agents (both data cut-offs). When interpreting the results of the subgroup analyses, it should be considered that these analyses were conducted in the overall trial population (where appropriate), and the study was not powered for the subgroups. For subgroup analysis results of the 800 mg dose, please see Figure 3.

The following subgroups of interest identified in the systematic review protocol that were not analysed in the BOLT trial: WHO status grade, number of prior lines of therapy, high-risk features (including depth/invasion, tumour size, tumour location, recurrent/refractory lesions), and previous radiotherapy.

Figure 3: Exploratory Subgroup Analyses of ORR per Central Review Using mRECIST in laBCC and RECIST v1.1 in mBCC (pEAS)



Data Source: Health Canada Module 2.7.3[8]

Key Secondary Outcomes – IRC-assessed CRR and DOR

laBCC Subgroup: The results for the IRC-assessed CRR in the pEAS in the laBCC subgroup were consistent with those of the overall population (Table 25). As of the primary data cut-off, two patients (4.8%) had achieved a CR in the 200 mg sonidegib group compared to zero patients in the 800 mg group.[8] The number of patients with a CR remained constant in the 200 mg group at later data cut-offs. In the 800 mg sonidegib group, one (1.1%) patient had achieved a CR as of the 12-month data cut-off, which increased to

two (2.2%) as of the 30-month data cut-off. CRR in the pEAS and the FAS for patients with laBCC per INV-assessment were higher than the IRC-assessments (results not displayed).

As of the primary data cut-off, in the 200 mg and 800 mg sonidegib group respectively, three and one progression events had occurred, and median IRC-assessed DOR in the pEAS was not estimable in either group (Table 25).[8] The number of events increased throughout the data cut-offs, with a median DOR of 12.9 (95% CI not estimable) months in the 200 mg group and 23.7 (95% CI: 10.8 to 29.6) months in the 800 mg sonidegib group as of the 42-month data cut-off. At the 42-month data cut-off, 13 (31.0%) patients were censored in the 200 mg sonidegib group and 27 (29.0%) were censored in the 800 mg sonidegib group. In 200 mg and 800 mg sonidegib group, respectively, 7 (53.8%) and 1 (55.6%) patients were censored due to adequate assessment no longer available, and 3 (23.1%) and 3 (11.1%) patients were censored due to new cancer therapy being added.[32] One patient was censored in the 200 mg group due to an event after two or more missing assessments, no patients in the 800 mg group were censored due to this. In the sensitivity analysis of DOR in which the start of new antineoplastic therapy was considered disease progression, median DOR was not estimable in either group at the primary data cut-off, and was 12.9 (95% CI not estimable) months in the 200 mg group and 15.7 (95% CI: 10.8 to 29.6) months in the 800 mg sonidegib group as of the 42-month data cut-off. In the sensitivity analysis of DOR in which two or more missing assessments were treated as event, the results at the 42-month data cut-off were consistent with the primary DOR analysis. At the primary data cut-off, IRC-assessed DOR per mRECIST in the FAS (a supportive analysis to the primary DOR analysis) was not estimable in either group.[8] By the 30-month data cut-off, the median DOR was 26.1 months (95%CI: NE) in the 200 mg sonidegib group, which remained consistent at the 42-month data cut-off. The median DOR in the FAS was considerably longer for the 200 mg sonidegib group compared to the median DOR in the pEAS (26.1 months compared to 12.9 months). Median DOR in the pEAS and the FAS for patients with laBCC per INV-assessment were lower than the IRC-assessments (results not displayed).

Other Secondary Outcomes

laBCC Subgroup: Detailed results for the secondary efficacy outcomes are summarized in Table 26.[8]

At the primary data cut off, PFS was not estimable in either group. In the 200 mg sonidegib group, median PFS was 22.1 months as of the 18-month cut-off, which decreased to 19.0 months as of the 42-month data cut-off.[8] In the 800 mg sonidegib group, median PFS was 21.5 months as of the 12-month data cut-off, which decreased to 19.4 months by the 42-month data cut-off. As of the 42-month data cut-off, 29 (69.0%) patients were censored in the 200 mg sonidegib group and 67 (72.0%) patients were censored in the 800 mg sonidegib group. In the 200 mg and 800 mg sonidegib group, respectively, 17 (58.6%) and 36 (53.7%) patients were censored due to adequate assessments no longer being available, and 6 (20.7%) and 6 (9.0%) patients were censored due to initiation of new anticancer therapy.[32] A total of 3 (10.3%) patients in the 200 mg group and 6 (9.0%) patients in the 800 mg group were censored due to two or more missing assessments. Results of the sensitivity analyses for PFS are also summarized in Table 26. For the analyses of PFS in which the start of new antineoplastic therapy was considered disease progression, at the 42-month data cut-off, the median PFS was 14.9 months (95% CI: 13.7 to 22.1) in the 200 mg group, and was 19.4 month (95% CI: 13.2 to 29.3) in the 800 mg group.[32] For analyses in which missing assessments were considered as an event, the median PFS was 14.8 months (95% CI: 13.7 to 39.6) in the 200 mg group and was 19.3 month (95% CI: 12.1 to 29.3) in the 800

mg group. The results of these analyses demonstrated a shorter PFS for the 200 mg sonidegib group than what was reported in the primary analysis, indicating the censoring rules likely inflated the reported results of the primary analyses. Median PFS in the pEAS and the FAS for patients with laBCC per INV-assessment were higher than the IRC-assessments (results not displayed).

At the primary data cut off, IRC-Assessed TTR per mRECIST in the pEAS was 3.9 months (95% CI: 2.1 to 4.0) in the 200 mg sonidegib group and 3.7 months (95% CI: 2.0 to 3.8) in the 800 mg sonidegib group, which remained relatively consistent through to later data cut-offs (Table 26).[8] Median TTR in the pEAS and the FAS for patients with laBCC per INV-assessment were lower than the IRC-assessments (results not displayed).

At the primary data cut off, IRC-assessed ORR per RECIST v1.1 applied to all laBCC patients in the FAS was 56.1% (95% CI: 43.3 to 68.3) in the 200 mg sonidegib group and 49.2% (95% CI: 40.3 to 58.2) in the 800 mg sonidegib group, which increased to 71.2% (95% CI: 58.7 to 81.7) and 58.6% (95% CI: 49.6 to 67.2), respectively, as of the 42-month data cut-off.[10] The data for the 12-month, 18-month, and 30-month data cut-offs for this outcome were not provided for this report.

At the time of the primary data cut-off, one (1.5%) patient had died in the 200 mg sonidegib group and seven (5.5%) patients had died in the 800 mg group.[8] As of the 42-month data cut-off, 6 (9.1%) patients had died in the 200 mg sonidegib group and 12 (9.4%) patients had died in the 800 mg sonidegib group. Median OS was not estimable for either group at any of the data cut-offs.[8] As of the 42-month data cut-off, 60 (90.9%) patients were censored in the 200 mg sonidegib group and 116 (90.6%) were censored in the 800 mg sonidegib group. In the 200 mg and 800 mg sonidegib groups, respectively, 26 (43.3%) and 46 (39.7%) patients were censored due to loss to follow-up.[32]

Table 25: Summary of DOR and CRR Analyses in the laBCC Subgroup of the BOLT Trial

	Primary analysis: 28-Jun-2013 data cut-off		12-month analysis: 31-Dec-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off		30-month analysis: 10-Jul-2015 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)
CRR (IRC-assessed in the pEAS)										
n of CR	2	0	2	1	2	1	2	2	2	2
% (95% CI)	4.8 (0.6 to 16.2)	0.0 (0.0 to 3.9)	4.8 (0.6 to 16.2)	1.1 (0.0 to 5.8)	4.8 (0.6 to 16.2)	1.1 (0.0 to 5.8)	4.8 (0.6 to 16.2)	2.2 (0.3 to 7.6)	4.8 (0.6 to 16.2)	2.2 (0.3 to 7.6)
DOR (IRC-assessed in the pEAS)										
n of progressions	3	1	6	8	9	14	9	16	10	17
n censored	15	34	18	35	14	30	14	28	13	27
Median (95% CI) months	NE	NE	NE	NE	NE	24.8 (10.8 to 26.4)	12.9 (NE)	23.7 (10.8 to 29.6)	12.9 (NE)	23.7 (10.8 to 29.6)
Sensitivity Analysis for DOR: new antineoplastic therapy treated as event										
Median (95% CI) months	NE	NE	NR	NR	NR	NR	NR	NR	12.9 (NE)	15.7 (10.8 to 29.6)
Sensitivity Analysis for DOR: two or more missing assessments treated as event										
Median (95% CI) months	NE	NE	NR	NR	NR	NR	NR	NR	12.9 (NE)	23.7 (10.8 to 29.6)
	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)
Supportive Analysis: IRC-Assessed DOR (applying RECIST v1.1 to all laBCC patients in the FAS)										
n of progressions	4	3	7	11	10	17	11	20	12	23
n censored	27	42	31	45	27	41	26	38	25	36
Median (95% CI) months	NE	NE	NE	15.7 (NE)	NE	24.8 (12.2 to 26.4)	26.1 (NE)	23.7 (12.2 to 29.6)	26.1 (NE)	23.3 (12.2 to 29.6)

CI = confidence interval; CR = complete response; CRR = complete response rate; DOR = duration of response; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; NE = not estimable; NR = not reported; pEAS = primary efficacy analysis set.

Data Sources: 6-month Clinical Study Report, 2014;[9] 42-month Clinical Study Report, 2017;[32] Health Canada Module 2.7.3[8]

Table 26: Summary of Other Secondary Outcomes in the laBCC Patients of the BOLT Trial

	Primary analysis: 28-Jun-2013 data cut-off		12-month analysis: 31-Dec-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off		30-month analysis: 10-Jul-2015 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)	200 mg sonidegib (n=42)	800 mg sonidegib (n=93)
IRC-Assessed PFS (per mRECIST in the pEAS)										
n of events	5	8	8	17	12	23	12	25	13	26
n censored	37	85	34	76	30	70	30	68	29	67
Median (95% CI) months	NE	NE	NE	21.5 (NE)	22.1 (NE)	19.4 (13.8 to 30.5)	19.0 (NE)	19.4 (13.8 to 30.5)	19.0 (NE)	19.4 (13.8 to 30.5)
Sensitivity Analysis for PFS: new antineoplastic therapy treated as event										
Median (95% CI) months	7 (16.7)	12 (12.9)	NR	NR	NR	NR	NR	NR	18 (42.9)	31(33.3)
PDs, n	7 (16.7)	8 (8.6)	NR	NR	NR	NR	NR	NR	18 (42.9)	26 (28.0)
Median (95% CI)	NE	NE	NR	NR	NR	NR	NR	NR	14.9 (13.7 to 22.1)	19.4 (13.2 to 29.3)
Sensitivity Analysis for PFS: two or more missing assessments treated as event										
N (%)	6 (14.3)	14 (15.1)	NR	NR	NR	NR	NR	NR	16 (38.1)	32 (34.4)
PDs n	6 (14.3)	10 (10.8)	NR	NR	NR	NR	NR	NR	16 (38.1)	23 (24.7)
Median (95% CI)	NE	NE	NR	NR	NR	NR	NR	NR	14.8 (13.7 to 39.6)	19.3 (12.1 to 29.3)
IRC-Assessed TTR (per mRECIST in the pEAS)										
Median (95% CI) months	3.9 (2.1 to 4.2)	3.7 (2.6 to 3.8)	4.0 (3.8 to 5.6)	3.8 (3.7 to 5.5)	4.0 (3.8 to 5.6)	3.8 (3.7 to 5.5)	4.0 (3.8 to 5.6)	3.7 (2.0 to 5.5)	4.0 (3.8 to 5.6)	3.7 (2.0 to 5.5)

	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)
IRC-Assessed ORR (applying RECIST v1.1 to all laBCC patients in the FAS)										
n (%)	37 (56.1)	63 (49.2)	NR	NR	NR	NR	NR	NR	47 (71.2)	75 (58.6)
95% CI	43.3 to 68.3	40.3 to 58.2	NR	NR	NR	NR	NR	NR	58.7 to 81.7	49.6 to 67.2
IRC-Assessed DOR (applying RECIST v1.1 to all laBCC patients in the FAS)										
n of progressions	4	3	7	11	10	17	11	20	12	23
n censored	27	42	31	45	27	41	26	38	25	36
Median (95% CI) months	NE	NE	NE	15.7 (NE)	NE	24.8 (12.2 to 26.4)	26.1 (NE)	23.7 (12.2 to 29.6)	26.1 (NE)	23.3 (12.2 to 29.6)
OS (FAS)										
n of deaths (%)	1 (1.5)	7 (5.5)	1 (1.5)	8 (6.3)	3 (4.5)	9 (7.0)	5 (7.6)	11 (8.6)	6 (9.1)	12 (9.4)
N censored (%)	65 (98.5)	121 (94.5)	65 (98.5)	120 (93.8)	63 (95.5)	119 (93.0)	61 (92.4)	117 (91.4)	60 (90.9)	116 (90.6)
Median (95% CI) months	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

CI = confidence interval; CR = complete response; CRR = complete response rate; DOR = duration of response; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; mRECIST = modified Response Criteria in Solid Tumors; NE = not evaluable; NR = not reported; ORR = overall response rate; OS = overall survival; pEAS = primary efficacy analysis set; PFS = progression-free survival.
Data Sources: 6-month Clinical Study Report, 2014;[9] 42-month Clinical Study Report, 2017;[32] Health Canada Module 2.7.3;[8] Additional Information Requested October 22, 2020[10]

At the time of the primary data cut-off, INV-assessed ORR in the pEAS was 66.7% and 58.1% in the 200 mg and 800 mg sonidegib group, respectively, which increased to 71.4% and 61.3% by the 18-month data cut-off before remaining consistent to the 42-month data cut-off (table not provided).[8] Overall, the results per INV-assessment were substantially higher than IRC-assessed ORR at each of the time points. At the 42-month data analysis, concordance rates between investigator and IRC-assessed ORR was 0.64 in the 200 mg sonidegib group, and 0.53 in the 800 mg sonidegib group. These rates were similar to previous data cut-offs.

Results for the sensitivity outcome analyses for IRC-assessed ORR using updated mRECIST criteria are displayed in Table 27 for the pEAS and in Table 28 for the FAS.[8] Overall results for ORR using the updated mRECIST criteria were higher for all the data cut-offs in both the pEAS and FAS.[8] Likewise, the results using updated mRECIST criteria for INV-assessed ORR (not displayed) demonstrated higher response rates compared to the primary analyses.

Table 27: Summary of the Sensitivity Analysis for IRC-Assessed ORR in laBCC Patients Using Updated mRECIST Criteria for laBCC Patients in the pEAS

	Primary analysis: 28-Jun-2013 data cut-off		12-month analysis: 31-Dec-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off		30-month analysis: 10-Jul-2015 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
	laBCC		laBCC		laBCC		laBCC		laBCC	
	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93
Objective Response Rate (ORR: CR+PR)										
n (%) 95% CI (%)	22 (52.4) (36.4, 68.0)	45 (48.4) (37.9, 59.0)	26 (61.9) (45.6, 76.4)	51 (54.8) (44.2, 65.2)	25 (59.5) (43.3, 74.4)	52 (55.9) (45.2, 66.2)	25 (59.5) (43.3, 74.4)	52 (55.9) (45.2, 66.2)	25 (59.5) (43.3, 74.4)	52 (55.9) (45.2, 66.2)
Best Overall Response, n (%)										
CR, n (%) 95% CI	7 (16.7) (7.0, 31.4)	28 (30.1) (21.0, 40.5)	8 (19.0) (8.6, 34.1)	30 (32.3) (22.9, 42.7)	9 (21.4) (10.3, 36.8)	31 (33.3) (23.9, 43.9)	8 (19.0) (8.6, 34.1)	31 (33.3) (23.9, 43.9)	8 (19.0) (8.6, 34.1)	31 (33.3) (23.9, 43.9)
PR	15 (35.7)	17 (18.3)	18 (42.9)	21 (22.6)	16 (38.1)	21 (22.6)	17 (40.5)	21 (22.6)	17 (40.5)	21 (22.6)
SD	17 (40.5)	30 (32.3)	13 (31.0)	27 (29.0)	14 (33.3)	26 (28.0)	14 (33.3)	26 (28.0)	14 (33.3)	26 (28.0)
PD	0	0	0	1 (1.1)	0	1 (1.1)	0	1 (1.1)	0	1 (1.1)
UNK	3 (7.1)	18 (19.4)	3 (7.1)	14 (15.1)	3 (7.1)	14 (15.1)	3 (7.1)	14 (15.1)	3 (7.1)	14 (15.1)

CI = confidence interval; CR = complete response; laBCC = locally advanced basal cell carcinoma; mRECIST = modified Response Criteria in Solid Tumors; ORR = overall response rate; pEAS = primary efficacy analysis set; PD = progressive disease; PR = partial response; SD = stable disease; UNK = unknown.
Data Source: Health Canada Module 2.7.3[8]

Table 28: Summary of the Sensitivity Analysis for IRC-Assessed ORR in laBCC Patients Using Updated mRECIST Criteria for laBCC Patients in the FAS

	Primary analysis: 28-Jun-2013 data cut-off		12-month analysis: 31-Dec-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off		30-month analysis: 10-Jul-2015 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
	laBCC		laBCC		laBCC		laBCC		laBCC	
	Sonidegib 200 mg N=66	Sonidegib 800 mg N=128	Sonidegib 200 mg N=66	Sonidegib 800 mg N=128	Sonidegib 200 mg N=66	Sonidegib 800 mg N=128	Sonidegib 200 mg N=66	Sonidegib 800 mg N=128	Sonidegib 200 mg N=66	Sonidegib 800 mg N=128
Objective Response Rate (ORR: CR+PR)										
n (%) 95% CI (%)	36 (54.5) (41.8, 66.9)	58 (45.3) (36.5, 54.3)	41 (62.1) (49.3, 73.8)	66 (51.6) (42.6, 60.5)	40 (60.6) (47.8, 72.4)	69 (53.9) (44.9, 62.8)	40 (60.6) (47.8, 72.4)	69 (53.9) (44.9, 62.8)	40 (60.6) (47.8, 72.4)	70 (54.7) (45.7, 63.5)
Best Overall Response, n (%)										
CR, n (%) 95% CI	10 (15.2) (7.5, 26.1)	35 (27.3) (19.8, 35.9)	13 (19.7) (10.9, 31.3)	38 (29.7) (21.9, 38.4)	15 (22.7) (13.3, 34.7)	38 (29.7) (21.9, 38.4)	14 (21.2) (12.1, 33.0)	38 (29.7) (21.9, 38.4)	14 (21.2) (12.1, 33.0)	39 (30.5) (22.6, 39.2)
PR	26 (39.4)	23 (18.0)	28 (42.4)	28 (21.9)	25 (37.9)	31 (24.2)	26 (39.4)	31 (24.2)	26 (39.4)	31 (24.2)
SD	24 (36.4)	43 (33.6)	19 (28.8)	39 (30.5)	20 (30.3)	37 (28.9)	20 (30.3)	37 (28.9)	20 (30.3)	36 (28.1)
PD	1 (1.5)	0	1 (1.5)	1 (0.8)	1 (1.5)	1 (0.8)	1 (1.5)	1 (0.8)	1 (1.5)	1 (0.8)
UNK	5 (7.6)	27 (21.1)	5 (7.6)	22 (17.2)	5 (7.6)	21 (16.4)	5 (7.6)	21 (16.4)	5 (7.6)	21 (16.4)

CI = confidence interval; CR = complete response; FAS = full analysis set; laBCC = locally advanced basal cell carcinoma; mRECIST = modified Response Criteria in Solid Tumors; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease; UNK = unknown.
Data Source: Health Canada Module 2.7.3[8]

Patient-Reported Outcomes

EORTC QLQ-C30 and the QLQ-H&N35, Overall Trial Population (laBCC and mBCC patients)

The EORTC QLQ-C30 and the QLQ-H&N35 were evaluated at the primary data cut-off and are reported here for the overall trial population.[2] Compliance rates of both treatment arms of patients completing the EORTC QLQ-30 and EORTC QLQ-H&N35 questionnaires were 93.0% and 93.9% at baseline, respectively, and at 44.3% and 45.2% at Week 33, respectively.[9] The proportion of patients who completed the questionnaires at baseline and at least one post-baseline assessment was 88.7% and 90.0% for the QLQ-C30 and QLQ-H&N35, respectively.[9]

Over the course of treatment, the majority of patients (both laBCC and mBCC) either maintained and/or had improvement in the health status, functioning, and disease-related symptoms.[9] The pre-specified subscale scores for the EORTC QLQ-30 (physical functioning, social functioning, pain, and fatigue) and for the EORTC QLQ-H&N35 (trouble with social contact, head and neck pain, and weight loss) are displayed in Figure 4, Figure 5, and Figure 6. The mean scale scores demonstrated maintenance of each of the prespecified scale scores in both treatment arms for both patient subgroups, with the exception of a trend toward worsening weight loss among patients on study at Week 41.

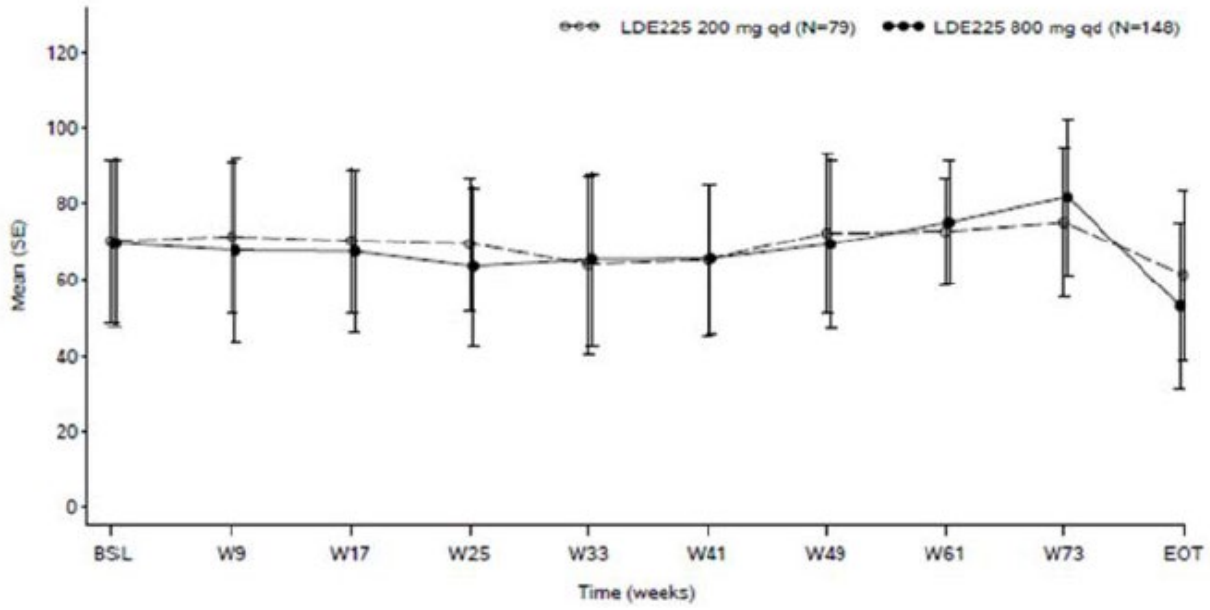
In laBCC patients treated with 200 mg of sonidegib, improvements in EORTC QLQ-C30 scales of physical functioning, social functioning, pain, and fatigue were recorded in 36.1% (n=22), 26.2% (n=16), 31.1% (n=19), and 37.7% (n=23), respectively.[9] For the pre-specified EORTC QLQ-H&N35 scales, in the 200 mg laBCC subgroup, improvements in trouble with social contact, head and neck pain, and weight loss were recorded in 43.1% (n=25), 18.3% (n=11), and 15.5% (n=9), respectively.[9]

In laBCC patients treated with 800 mg of sonidegib, improvements in EORTC QLQ-C30 scales of physical functioning, social functioning, pain, and fatigue were recorded in 31.8% (n=35), 20.2% (n=22), 32.7% (n=36), and 19.3% (n=21), respectively.[9] For the pre-specified

EORTC QLQ-H&N35 scales, in the 800 mg laBCC subgroup, improvements in trouble with social contact, head and neck pain, and weight loss were recorded in 30.0% (n=33), 17.9% (n=20), and 7.3% (n=8), respectively.[9]

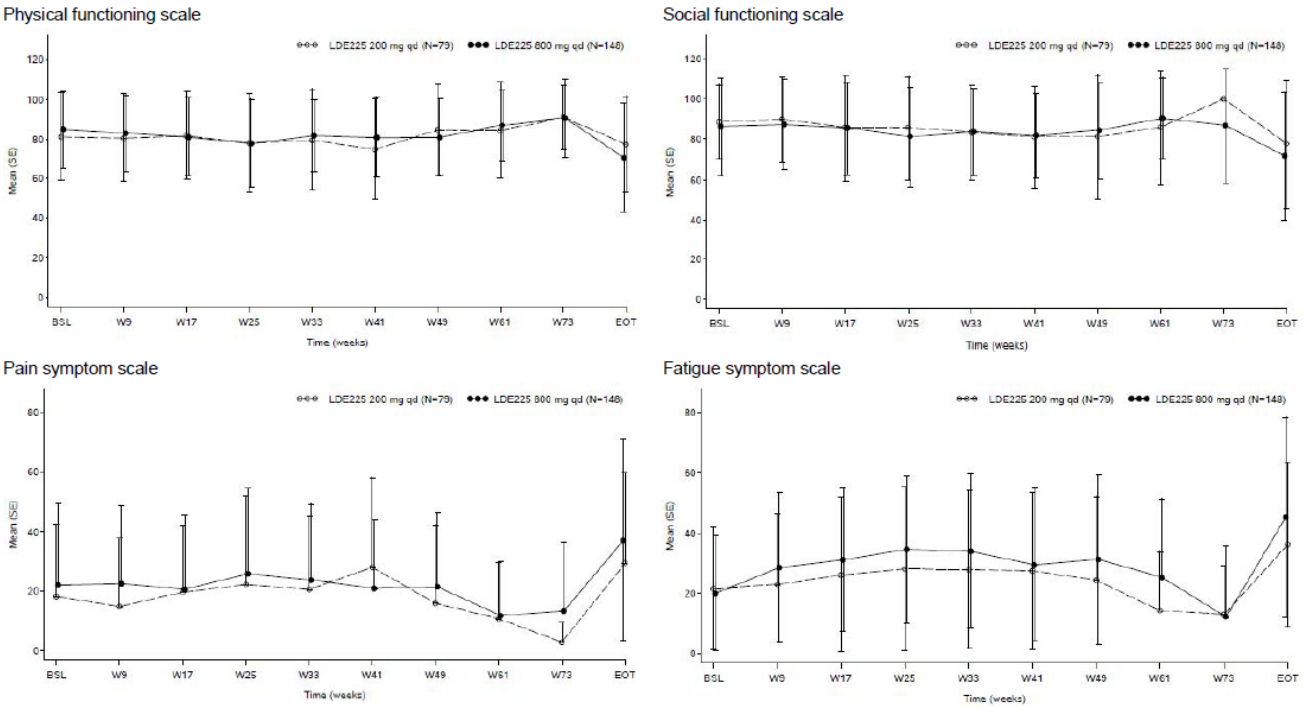
To note, the baseline scores and changes from baseline at post-baseline assessments for the individual domains of the EORTC QLQ-C30 and QLQ-H&N were not reported.It is unclear for the reported maintenance or improvement on individual domains is based on a pre-defined MCID threshold for the BOLT trial. Further, it could not be verified if any deterioration occurred on individual domains, due to lack of access to this data. It is also unclear if the MCID definition that was used for reported improvements and maintenance is consistent with the standard MCID in the literature.[110]

Figure 4: EORTC QLQ-C30 profiles: QoL or Global Health Status of All Patients of the BOLT Trial (FAS)



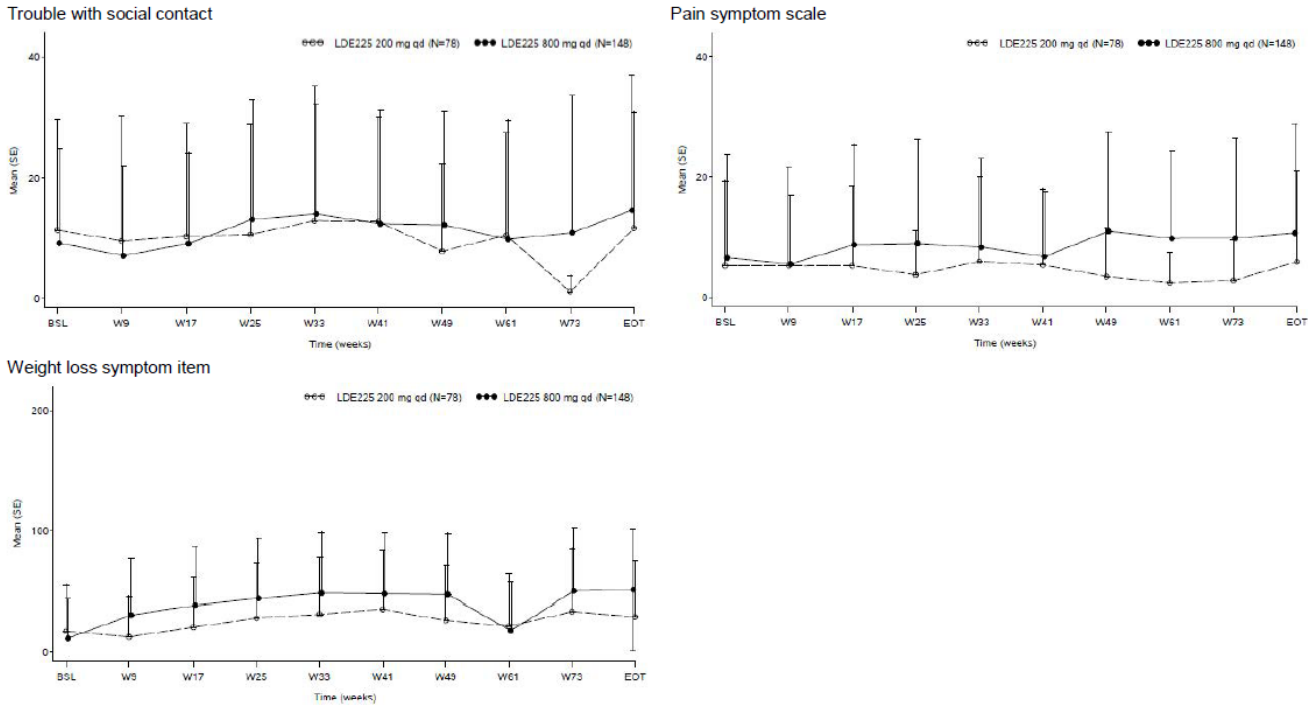
BSL = baseline; EORTC = European Organisation for Research and Treatment of Cancer; EOT = end of treatment; FAS = full analysis set; QLQ-C30 = Quality of Life Questionnaire-Core 30; QoL = quality of life; SE = standard error.
Data Source: Health Canada Module 2.7.3[8]

Figure 5: EORTC QLQ-C30 profiles: Individual Scales for All Patients of the BOLT (FAS)



BSL = baseline; EORTC = European Organisation for Research and Treatment of Cancer; EOT = end of treatment; FAS = full analysis set; QLQ-C30 = Quality of Life Questionnaire-Core 30; SE = standard error.
Data Source: 6-month Clinical Study Report 2014[9]

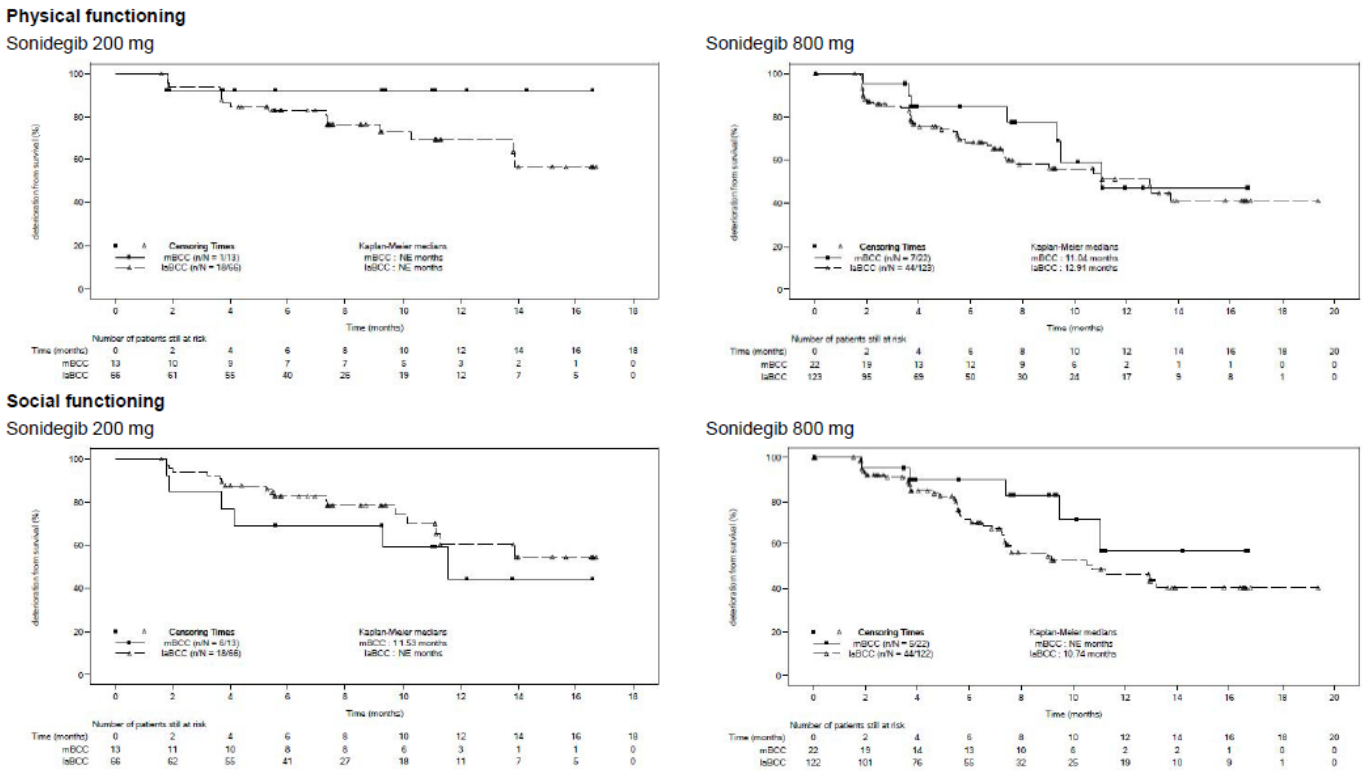
Figure 6: EORTC QLQ-H&N35 Profiles: Individual Scales for All Patients of the BOLT Trial (FAS)



BSL = baseline; EORTC = European Organisation for Research and Treatment of Cancer; EOT = end of treatment; FAS = full analysis set; H&N35 = Head and Neck Cancer Module 35); SE = standard error.
Data Source: 6-month Clinical Study Report 2014[9]

The KM curves for time-to-deterioration (greater than 10-point worsening without subsequent improvement) at the primary data cut-off of the EORTC QLQ-C30 scales assessed in the overall trial population (i.e. both patients with laBCC and mBCC) are displayed in Figure 7.[8,9] In the 200 mg sonidegib group, deterioration was seen for fatigue and weight loss, with median times to deterioration being 13.7 months (95% CI: 9.3 to NE) and 16.6 months (95% CI: 13.9 to NE), respectively.[2] In the 800 mg sonidegib group, deterioration was seen in physical functioning, social functioning, fatigue, and weight loss with median time to deterioration being 11.1 months (95% CI: 9.0 to NE), 11.3 months (95% CI: 7.6 to NE), 5.6 months (95% CI: 5.5 to 9.4), and 16.5 months (95% CI: 10.7 to 16.6), respectively.

Figure 7: Kaplan-Meier Plots of Time to Deterioration of EORTC QLQ-C30 Scales for All Patients in the BOLT Trial (FAS)



EORTC = European Organisation for Research and Treatment of Cancer; EOT = end of treatment; FAS = full analysis set; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; QLQ-C30 = Quality of Life Questionnaire-Core 30.

Data Source: 6-month Clinical Study Report, 2014[9]

SF-36: The SF-36 was evaluated at the primary data cut-off. Compliance rates of both treatment arms of patients completing the SF-36 questionnaires were 94.3% at baseline, and 43.0% at Week 33.[10] The proportion of patients who completed the questionnaires at baseline and at least one post-baseline assessment was 80.9%. The time-to-deterioration for each of the components is displayed in Table 29. Median time-to-deteriorations in the 200 mg sonidegib group were reported to be 7.6 months for bodily pain, 8.5 months for physical component, 11.3 months for role physical, and not estimable for all other components.

Table 29: Time to Definitive Deterioration in the SF-36 for All Patients of the BOLT trial (FAS)

Component, median (95% CI), months	Primary analysis: 28-Jun-2013 data cut-off	
	200 mg sonidegib (n=79)	800 mg sonidegib (n=151)
Bodily Pain	7.6 (7.4 to NE)	7.4 (6.5 to 11.1)
General Health	NE (11.2 to NE)	11.0 (7.4 to 12.6)
Mental Component	NE (7.6 to NE)	7.4 (5.6 to 7.8)
Mental Health	NE	7.8 (7.4 to 11.1)
Physical Component	8.5 (7.4 to NE)	6.7 (4.1 to 7.4)
Physical Functioning	NE (11.6 to NE)	7.4 (5.5 to 11.1)
Role Emotional	NE (16.5 to NE)	7.3 (4.4 to 7.8)
Role Physical	11.3 (7.4 to NE)	7.0 (4.1 to 7.4)
Social Functioning	NE (11.3 to NE)	11.1 (7.4 to NE)
Vitality	NE (11.1 to NE)	7.0 (4.1 to 7.6)

CI = confidence interval; FAS = full analysis set; NE = not estimable; SF-36 = The Medical Outcomes Study Short Form 36 (SF-36, version 2, Acute)

Data Source: Additional Information Received October 22, 2020[10]

Harms Outcomes

Harms outcomes are presented for the overall trial population (both patients with laBCC and patients with mBCC) and include all patients that received at least one dose of study drug.

Adverse Events

Table 30 provides an overview of the AEs categories occurring in the BOLT trial at each of the data cut-offs.[11] At the primary analysis, 94.9% of patients in the 200 mg group had experienced at least one AE, with 30.4% of patients experiencing Grade 3 or 4 AEs. Additionally, 13.9% of patients experienced a SAE. There was a slight increase in AEs at subsequent data analysis time points, with a notable increase of Grade 3 to 4 AEs at the 12-month data cut-off to 38.0% of patients.[11]

For all the AE categories, a higher rate proportion of patients experienced an event in the 800 mg sonidegib group compared to the 200 mg sonidegib group.[11] At the primary analysis, 100% of patients in the 800 mg group had experienced at least one AE, with 56.0% of patients experiencing Grade 3 or 4 AEs. Additionally, 30.0% of patients experienced a SAE. Like the 200 mg sonidegib group, was a slight increase in the events of the safety outcomes at subsequent data analysis time points.[11]

Table 30: Overview of the Adverse Events at Each Data Cut-Off for All Patients of the BOLT trial (Safety Analysis Set)

	Primary analysis: data cut-off: 28-Jun-2013 Sonidegib		12-month analysis: data cut-off: 31-Dec-2013 Sonidegib		18-month analysis: data cut-off: 11-Jul-2014 Sonidegib		30-month analysis: data cut-off: 10-Jul-2015 Sonidegib		42-month analysis: data cut-off: 08-Jul-2016 Sonidegib	
	200 mg N=79	800 mg N=150	200 mg N=79	800 mg N=150	200 mg N=79	800 mg N=150	200 mg N=79	800 mg N=150	200 mg N=79	800 mg N=150
Adverse events (AEs)	**75 (94.9)**	**150 (100)**	**77 (97.5)**	**150 (100)**	**77 (97.5)**	**150 (100)**	**77 (97.5)**	**150 (100)**	**77 (97.5)**	**150 (100.0)**
Grade 3-4 AEs	24 (30.4)	84 (56.0)	30 (38.0)	89 (59.3)	31 (39.2)	95 (63.3)	34 (43.0)	96 (64.0)	34 (43.0)	96 (64.0)
AE with suspected causality	**68 (86.1)**	**142 (94.7)**	**70 (88.6)**	**143 (95.3)**	**70 (88.6)**	**143 (95.3)**	**70 (88.6)**	**143 (95.3)**	**70 (88.6)**	**143 (95.3)**
Grade 3-4 AEs with suspected causality	18 (22.8)	63 (42.0)	22 (27.8)	64 (42.7)	23 (29.1)	65 (43.3)	24 (30.4)	65 (43.3)	25 (31.6)	65 (43.3)
Deaths on-treatment[1]	**0**	**4 (2.7)**	**0**	**7 (4.7)**	**1 (1.3)**	**7 (4.7)**	**1 (1.3)**	**7 (4.7)**	**1 (1.3)**	**7 (4.7)**
Serious AEs (SAEs)	**11 (13.9)**	**45 (30.0)**	**13 (16.5)**	**49 (32.7)**	**14 (17.7)**	**56 (37.3)**	**16 (20.3)**	**58 (38.7)**	**16 (20.3)**	**58 (38.7)**
SAEs with suspected causality	3 (3.8)	18 (12.0)	2 (2.5)	21 (14.0)	2 (2.5)	23 (15.3)	3 (3.8)	24 (16.0)	4 (5.1)	26 (17.3)
AEs leading to discontinuation	**17 (21.5)**	**54 (36.0)**	**22 (27.8)**	**56 (37.3)**	**24 (30.4)**	**59 (39.3)**	**24 (30.4)**	**60 (40.0)**	**24 (30.4)**	**60 (40.0)**
Grade 3-4 AEs leading to discontinuation	7 (8.9)	19 (12.7)	10 (12.7)	22 (14.7)	11 (13.9)	22 (14.7)	11 (13.9)	22 (14.7)	11 (13.9)	22 (14.7)
AEs requiring dose interruption and/or reduction	**25 (31.6)**	**90 (60.0)**	**30 (38.0)**	**96 (64.0)**	**31 (39.2)**	**99 (66.0)**	**34 (43.0)**	**100 (66.7)**	**34 (43.0)**	**100 (66.7)**

[1] Deaths on treatment are deaths which occurred up to 30 days after last date of study treatment.
Categories are not mutually exclusive.
Adverse events occurring more than 30 days after last date of study treatment are not summarized.

AE = adverse event; SAE = serious adverse event
Data Source: Health Canada Module 2.7.4[11]

Table 31 provides a summary of the AEs of any grade, irrespective of causality, occurring in at least 5% of patients in either treatment group.[11] The most common AEs of any grade that occurred in the 200 mg group as of the primary and 42-month data cut-offs, respectively, were muscle spasms (49.4% and 54.4%), alopecia (43.0% and 49.4%), dysgeusia (38.0% and 44.3%), and nausea (32.9% and 39.2%).

Table 31: 'All Grade' Adverse Events, Irrespective of Causality Occurring in at Least 5% of Either Treatment Group for All Patients in the BOLT Trial (Safety Analysis Set)

	Primary analysis: data cut-off: 28-Jun-2013		12-month analysis: data cut-off: 31-Dec-2013		18-month analysis: data cut-off: 11-Jul-2014		30-month analysis: data cut-off: 10-Jul-2015		42-month analysis: data cut-off: 08-Jul-2016	
	Sonidegib		Sonidegib		Sonidegib		Sonidegib		Sonidegib	
	200 mg N=79	800 mg N=150	200 mg N=79	800 mg N=150	200 mg N=79	800 mg N=150	200 mg N=79	800 mg N=150	200 mg N=79	800 mg N=150
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Muscle spasms	39 (49.4)	100 (66.7)	41 (51.9)	104 (69.3)	43 (54.4)	104 (69.3)	43 (54.4)	104 (69.3)	43 (54.4)	104 (69.3)
Alopecia	34 (43.0)	83 (55.3)	39 (49.4)	86 (57.3)	39 (49.4)	87 (58.0)	39 (49.4)	87 (58.0)	39 (49.4)	87 (58.0)
Dysgeusia	30 (38.0)	89 (59.3)	32 (40.5)	90 (60.0)	35 (44.3)	90 (60.0)	35 (44.3)	90 (60.0)	35 (44.3)	90 (60.0)
Nausea	26 (32.9)	68 (45.3)	28 (35.4)	71 (47.3)	31 (39.2)	71 (47.3)	31 (39.2)	71 (47.3)	31 (39.2)	71 (47.3)
Fatigue	23 (29.1)	54 (36.0)	23 (29.1)	54 (36.0)	23 (29.1)	55 (36.7)	24 (30.4)	55 (36.7)	26 (32.9)	55 (36.7)
Diarrhea	19 (24.1)	33 (22.0)	24 (30.4)	34 (22.7)	25 (31.6)	36 (24.0)	25 (31.6)	36 (24.0)	25 (31.6)	36 (24.0)
Blood CK increased	23 (29.1)	56 (37.3)	24 (30.4)	56 (37.3)	24 (30.4)	56 (37.3)	24 (30.4)	56 (37.3)	24 (30.4)	56 (37.3)
Weight decreased	21 (26.6)	57 (38.0)	23 (29.1)	63 (42.0)	24 (30.4)	64 (42.7)	24 (30.4)	65 (43.3)	24 (30.4)	65 (43.3)
Decreased appetite	15 (19.0)	46 (30.7)	18 (22.8)	48 (32.0)	18 (22.8)	52 (34.7)	18 (22.8)	53 (35.3)	18 (22.8)	53 (35.3)
Myalgia	15 (19.0)	39 (26.0)	15 (19.0)	39 (26.0)	15 (19.0)	42 (28.0)	15 (19.0)	42 (28.0)	15 (19.0)	42 (28.0)
Arthralgia	10 (12.7)	12 (8.0)	12 (15.2)	15 (10.0)	13 (16.5)	17 (11.3)	13 (16.5)	18 (12.0)	13 (16.5)	18 (12.0)
Headache	12 (15.2)	20 (13.3)	12 (15.2)	20 (13.3)	12 (15.2)	20 (13.3)	12 (15.2)	20 (13.3)	12 (15.2)	20 (13.3)
Asthenia	6 (7.6)	8 (5.3)	8 (10.1)	9 (6.0)	10 (12.7)	9 (6.0)	10 (12.7)	9 (6.0)	10 (12.7)	9 (6.0)
Vomiting	5 (6.3)	39 (26.0)	6 (7.6)	41 (27.3)	9 (11.4)	42 (28.0)	9 (11.4)	43 (28.7)	9 (11.4)	43 (28.7)
Abdominal pain	7 (8.9)	7 (4.7)	8 (10.1)	8 (5.3)	8 (10.1)	8 (5.3)	8 (10.1)	8 (5.3)	8 (10.1)	9 (6.0)
Hypertension	5 (6.3)	11 (7.3)	7 (8.9)	11 (7.3)	7 (8.9)	13 (8.7)	8 (10.1)	15 (10.0)	8 (10.1)	16 (10.7)
Dizziness	7 (8.9)	14 (9.3)	7 (8.9)	14 (9.3)	7 (8.9)	15 (10.0)	7 (8.9)	16 (10.7)	7 (8.9)	16 (10.7)
Nasopharyngitis	6 (7.6)	9 (6.0)	7 (8.9)	12 (8.0)	7 (8.9)	12 (8.0)	7 (8.9)	12 (8.0)	7 (8.9)	13 (8.7)
Abdominal pain upper	6 (7.6)	10 (6.7)	7 (8.9)	10 (6.7)	7 (8.9)	12 (8.0)	7 (8.9)	12 (8.0)	7 (8.9)	12 (8.0)
Cough	7 (8.9)	11 (7.3)	7 (8.9)	10 (6.7)	7 (8.9)	11 (7.3)	7 (8.9)	11 (7.3)	7 (8.9)	11 (7.3)
Dyspepsia	4 (5.1)	8 (5.3)	7 (8.9)	10 (6.7)	7 (8.9)	10 (6.7)	7 (8.9)	10 (6.7)	7 (8.9)	10 (6.7)
Urinary tract infection	6 (7.6)	5 (3.3)	7 (8.9)	7 (4.7)	7 (8.9)	8 (5.3)	7 (8.9)	8 (5.3)	7 (8.9)	8 (5.3)
Constipation	6 (7.6)	20 (13.3)	5 (6.3)	22 (14.7)	6 (7.6)	23 (15.3)	6 (7.6)	24 (16.0)	6 (7.6)	24 (16.0)
Back pain	5 (6.3)	15 (10.0)	5 (6.3)	15 (10.0)	5 (6.3)	15 (10.0)	6 (7.6)	16 (10.7)	6 (7.6)	16 (10.7)
Lipase increased	6 (7.6)	12 (8.0)	6 (7.6)	12 (8.0)	6 (7.6)	12 (8.0)	6 (7.6)	13 (8.7)	6 (7.6)	13 (8.7)
Pruritus	5 (6.3)	7 (4.7)	5 (6.3)	9 (6.0)	6 (7.6)	10 (6.7)	6 (7.6)	11 (7.3)	6 (7.6)	12 (8.0)
Upper respiratory tract infection	5 (6.3)	5 (3.3)	5 (6.3)	6 (4.0)	5 (6.3)	9 (6.0)	6 (7.6)	11 (7.3)	6 (7.6)	11 (7.3)
Pneumonia	5 (6.3)	5 (3.3)	5 (6.3)	5 (3.3)	5 (6.3)	6 (4.0)	6 (7.6)	6 (4.0)	6 (7.6)	6 (4.0)
Depression	2 (2.5)	8 (5.3)	3 (3.8)	9 (6.0)	3 (3.8)	9 (6.0)	4 (5.1)	9 (6.0)	5 (6.3)	9 (6.0)
Fall	3 (3.8)	2 (1.3)	4 (5.1)	3 (2.0)	5 (6.3)	4 (2.7)	5 (6.3)	4 (2.7)	5 (6.3)	5 (3.3)
Pain in extremity	4 (5.1)	8 (5.3)	4 (5.1)	8 (5.3)	4 (5.1)	8 (5.3)	5 (6.3)	8 (5.3)	5 (6.3)	8 (5.3)
Anemia	2 (2.5)	10 (6.7)	4 (5.1)	10 (6.7)	4 (5.1)	13 (8.7)	4 (5.1)	13 (8.7)	4 (5.1)	13 (8.7)
Bronchitis	4 (5.1)	5 (3.3)	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)
Dry mouth	4 (5.1)	7 (4.7)	4 (5.1)	7 (4.7)	4 (5.1)	8 (5.3)	4 (5.1)	8 (5.3)	4 (5.1)	8 (5.3)
Hypotension	2 (2.5)	3 (2.0)	2 (2.5)	4 (2.7)	4 (5.1)	5 (3.3)	4 (5.1)	5 (3.3)	4 (5.1)	5 (3.3)
Influenza	4 (5.1)	7 (4.7)	4 (5.1)	7 (4.7)	4 (5.1)	7 (4.7)	4 (5.1)	7 (4.7)	4 (5.1)	7 (4.7)
Muscular weakness	3 (3.8)	8 (5.3)	3 (3.8)	8 (5.3)	3 (3.8)	8 (5.3)	4 (5.1)	8 (5.3)	4 (5.1)	8 (5.3)
Musculoskeletal pain	4 (5.1)	4 (2.7)	4 (5.1)	5 (3.3)	4 (5.1)	5 (3.3)	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)
Oropharyngeal pain	3 (3.8)	6 (4.0)	3 (3.8)	6 (4.0)	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)
Paraesthesia	3 (3.8)	7 (4.7)	4 (5.1)	7 (4.7)	4 (5.1)	7 (4.7)	4 (5.1)	7 (4.7)	4 (5.1)	7 (4.7)
Pyrexia	3 (3.8)	4 (2.7)	3 (3.8)	4 (2.7)	4 (5.1)	4 (2.7)	4 (5.1)	5 (3.3)	4 (5.1)	5 (3.3)
Squamous cell carcinoma	3 (3.8)	1 (0.7)	3 (3.8)	3 (2.0)	3 (3.8)	6 (4.0)	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)
Ageusia	0	13 (8.7)	0	13 (8.7)	1 (1.3)	14 (9.3)	1 (1.3)	15 (10.0)	1 (1.3)	15 (10.0)
Dehydration	0	8 (5.3)	1 (1.3)	8 (5.3)	1 (1.3)	8 (5.3)	1 (1.3)	8 (5.3)	1 (1.3)	8 (5.3)
Hypogeusia	0	8 (5.3)	0	8 (5.3)	0	8 (5.3)	0	8 (5.3)	0	9 (6.0)
Vertigo	0	9 (6.0)	0	10 (6.7)	0	11 (7.3)	0	11 (7.3)	0	11 (7.3)

CK = creatine phosphokinase

Notes:

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Adverse events occurring more than 30 days after the last date of study treatment are not summarized.

Data Source: Health Canada Module 2.7.4[11]

Table 32: Grade 3 or 4 Adverse Events, Irrespective of Causality Occurring in at Least 2% of Either Treatment Group for All Patients in the BOLT Trial (Safety Analysis Set)

	Primary analysis: data cut-off: 28-Jun-2013		12-month analysis: data cut-off: 31-Dec-2013		18-month analysis: data cut-off: 11-Jul-2014		30-month analysis: data cut-off: 10-Jul-2015		42-month analysis: data cut-off: 08-Jul-2016	
	Sonidegib		Sonidegib		Sonidegib		Sonidegib		Sonidegib	
	200 mg N=79 Grade 3-4	800 mg N=150 Grade 3-4	200 mg N=79 Grade 3-4	800 mg N=150 Grade 3-4	200 mg N=79 Grade 3-4	800 mg N=150 Grade 3-4	200 mg N=79 Grade 3-4	800 mg N=150 Grade 3-4	200 mg N=79 Grade 3-4	800 mg N=150 Grade 3-4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any grade 3-4 AE	**24 (30.4)**	**84 (56.0)**	**30 (38.0)**	**89 (59.3)**	**31 (39.2)**	**95 (63.3)**	**34 (43.0)**	**96 (64.0)**	**34 (43.0)**	**96 (64.0)**
Blood CK increased	5 (6.3)	19 (12.7)	5 (6.3)	20 (13.3)	5 (6.3)	20 (13.3)	5 (6.3)	20 (13.3)	5 (6.3)	20 (13.3)
Lipase increased	4 (5.1)	8 (5.3)	5 (6.3)	8 (5.3)	5 (6.3)	8 (5.3)	5 (6.3)	8 (5.3)	5 (6.3)	8 (5.3)
Weight decreased	1 (1.3)	8 (5.3)	2 (2.5)	9 (6.0)	2 (2.5)	9 (6.0)	4 (5.1)	9 (6.0)	4 (5.1)	10 (6.7)
Asthenia	2 (2.5)	0	3 (3.8)	0	3 (3.8)	0	3 (3.8)	0	3 (3.8)	0
Muscle spasms	2 (2.5)	8 (5.3)	2 (2.5)	8 (5.3)	2 (2.5)	8 (5.3)	2 (2.5)	8 (5.3)	2 (2.5)	8 (5.3)
Hypertension	2 (2.5)	4 (2.7)	2 (2.5)	4 (2.7)	2 (2.5)	5 (3.3)	2 (2.5)	5 (3.3)	2 (2.5)	5 (3.3)
Hypotension	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	2 (2.5)	1 (0.7)	2 (2.5)	1 (0.7)	2 (2.5)	1 (0.7)
Decreased appetite	0	6 (4.0)	0	6 (4.0)	1 (1.3)	6 (4.0)	1 (1.3)	6 (4.0)	1 (1.3)	6 (4.0)
Rhabdomyolysis	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)
ALT increased	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)
AST increased	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)
Nausea	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)
Syncope	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)	1 (1.3)	4 (2.7)
Dehydration	0	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)
Fatigue	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)
Hyperkalemia	0	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)
Pneumonia	0	2 (1.3)	0	2 (1.3)	0	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)
Anemia	0	3 (2.0)	0	3 (2.0)	0	6 (4.0)	0	6 (4.0)	0	6 (4.0)
Myalgia	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)

ALT= alanine aminotransferase; AST= aspartate aminotransferase; CK=creatine phosphokinase.
Notes:
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Adverse events occurring more than 30 days after the last date of study treatment are not summarized.
The event with maximum severity is counted for patients who experienced multiple episodes of an event.
Data Source: Health Canada Module 2.7. [11]

Table 33 provides a summary of the SAEs occurring in at least 1% of patients in either treatment group at each of the data cut-offs.[11] At the primary data cut-off SAEs were reported in 11 (13.9%) patients in the 200 mg sonidegib group, and no SAE occurred in more than one patient. Serious AEs included pneumonia, angina pectoris, bipolar disorder, blood CK increased, and rhabdomyolysis. By the 42-month analysis, a total of 16 (20.3%) SAEs occurred in the 200 mg group. Pneumonia was the only SAE that occurred in more than one patient (n = 2; 2.9%), and a few fractures (a total of 4) affecting the cervical vertebra (n = 1)l, femoral neck (n = 1), lumbar vertebral (n = 1), and upper limb (n = 1) were reported. In the 800 mg sonidegib group, a higher proportion of SAEs occurred at the time of the primary analysis (n = 45; 30.0%) compared to the 200 mg group, which increased to 38.7% (n = 58) by the time of the 42-month analysis. At the time of the primary analysis the most frequently occurring SAEs in the 800 mg group compared to the 200 mg were rhabdomyolysis (3.3% versus 1.3%), vomiting (2.7% versus 0%), nausea (2.0 % versus 0%), and blood CK increase (2.0% versus 1.3%).[11]

Table 33: Serious Adverse Events Occurring in at Least 1% of Either Treatment Group for All Patients in the BOLT Trial (Safety Analysis Set)

	Primary analysis: data cut-off: 28-Jun-2013		12-month analysis: data cut-off: 31-Dec-2013		18-month analysis: data cut-off: 11-Jul-2014		30-month analysis: data cut-off: 10-Jul-2015		42-month analysis: data cut-off: 08-Jul-2016	
	Sonidegib		Sonidegib		Sonidegib		Sonidegib		Sonidegib	
	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)
Any SAE	**11 (13.9)**	**45 (30.0)**	**13 (16.5)**	**49 (32.7)**	**14 (17.7)**	**56 (37.3)**	**16 (20.3)**	**58 (38.7)**	**16 (20.3)**	**58 (38.7)**
Pneumonia	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)	1 (1.3)	3 (2.0)	2 (2.5)	3 (2.0)	2 (2.5)	3 (2.0)
Acute respiratory distress syndrome	0	0	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Acute kidney injury	0	0	0	0	0	0	1 (1.3)	0	1 (1.3)	0
Angina pectoris	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Bipolar disorder	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Blood CK increased	1 (1.3)	3 (2.0)	1 (1.3)	4 (2.7)	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)	1 (1.3)	6 (4.0)
Blood CK mb increased	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Bronchitis	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Cellulitis	0	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Cerebrovascular accident	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Cervical vertebral fracture	0	0	0	1 (0.7)	0	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Dehydration	0	2 (1.3)	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)
Dyspnea	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	1 (1.3)	2 (1.3)
Endocarditis	0	0	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Escherichia urinary tract infection	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Facial pain	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Fall	0	0	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Femoral neck fracture	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Gastric ulcer	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
General physical health deterioration	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Hemorrhage intracranial	0	0	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Hypoglycemia	0	0	0	0	0	0	1 (1.3)	0	1 (1.3)	0
Hypotension	0	1 (0.7)	0	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Joint dislocation	0	0	0	0	0	0	1 (1.3)	0	1 (1.3)	0
Invasive papillary breast carcinoma	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Lower respiratory tract infection	0	0	0	0	0	0	1 (1.3)	0	1 (1.3)	0
Lumbar vertebral fracture	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Orthostatic hypotension	0	0	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Pleural effusion	0	0	0	0	0	0	1 (1.3)	0	1 (1.3)	0
Rhabdomyolysis	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)
Sepsis	0	0	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Syncope	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)
Upper limb fracture	0	0	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Urinary tract infection	0	0	1 (1.3)	1 (0.7)	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)
Septic shock	0	0	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Abscess limb	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Anemia	0	3 (2.0)	0	3 (2.0)	0	5 (3.3)	0	5 (3.3)	0	5 (3.3)
Basal cell carcinoma	0	0	0	1 (0.7)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Decreased appetite	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Diarrhea	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Deep vein thrombosis	0	1 (0.7)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Nausea	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)
Renal failure acute	0	1 (0.7)	0	1 (0.7)	1 (1.3)	1 (0.7)	0	0	0	0
Small intestinal obstruction	0	1 (0.7)	0	1 (0.7)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Vomiting	0	4 (2.7)	0	4 (2.7)	0	4 (2.7)	0	4 (2.7)	0	4 (2.7)

Preferred terms are presented in descending order of frequency in the sonidegib 200-mg column-42-month analysis.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Adverse events occurring more than 30 days after the last date of study treatment are not summarized.
CK=creatine phosphokinase

Data Source: Health Canada Module 2.7.4[11]

Table 34 provides a summary of on-treatment deaths at the each of the data cut-offs.[11] Of the four on-treatment deaths reported as of the primary data cut-off, which all occurred in the 800 mg sonidegib group, two were due to PD (both patients had mBCC).[2] The other two deaths were due to congestive cardiac failure and to cardiac death (one each) in laBCC patients with pre-existing confounding conditions at baseline. None of the deaths were reported as being due to treatment with sonidegib.

By the 12-month analysis, three additional deaths occurred that were not reported as being due to treatment with sonidegib.[11] One death was due to cardiac arrest, another death was due to sepsis, and one death due to respiratory arrest. No additional deaths occurred at subsequent analysis time points, however as outlined in the earlier section under protocol deviations, survival information was missing for a significant proportion of patients and thus, data on deaths is likely incomplete and underestimated.

Table 34: On-Treatment Deaths for All Patients in the BOLT Trial (Safety Analysis Set)

	Primary analysis: data cut-off: 28-Jun-2013		12-month analysis: data cut-off: 31-Dec-2013		18-month analysis: data cut-off: 11-Jul-2014		30-month analysis: data cut-off: 10-Jul-2015		42-month analysis: data cut-off: 08-Jul-2016	
	Sonidegib		Sonidegib		Sonidegib		Sonidegib		Sonidegib	
	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)
Primary reason for death										
Study indication	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)
Other	0	3 (2.0)	0	6 (4.0)	1 (1.3)	6 (4.0)	1 (1.3)	6 (4.0)	1 (1.3)	6 (4.0)
Death by system organ class and preferred term										
General disorders and administration site conditions	**0**	**2 (1.3)**	**0**	**2 (1.3)**	**0**	**2 (1.3)**	**0**	**2 (1.3)**	**0**	**2 (1.3)**
Cardiac death	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)
Disease progression	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)		
Euthanasia[1]									0	1 (0.7)
Cardiac disorders	**0**	**1 (0.7)**	**0**	**2 (1.3)**	**0**	**2 (1.3)**	**0**	**2 (1.3)**	**0**	**2 (1.3)**
Cardiac failure congestive	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)
Cardiac arrest	0	0	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)
Infections and infestations	**0**	**0**	**0**	**1 (0.7)**	**0**	**1 (0.7)**	**0**	**1 (0.7)**	**0**	**1 (0.7)**
Sepsis	0	0	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**0**	**1 (0.7)**	**0**	**1 (0.7)**	**0**	**1 (0.7)**	**0**	**1 (0.7)**	**0**	**1 (0.7)**
Basal cell carcinoma	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)
Respiratory, thoracic, and mediastinal disorders	**0**	**0**	**0**	**1 (0.7)**	**1 (1.3)**	**1 (0.7)**	**1 (1.3)**	**1 (0.7)**	**1 (1.3)**	**1 (0.7)**
Acute respiratory distress syndrome	**0**	**0**	**0**	**0**	1 (1.3)	0	1 (1.3)	0	1 (1.3)	**0**
Respiratory arrest	0	0	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)

Only deaths occurring during treatment or within 30 days after the last study treatment are included.

Data Source: Health Canada Module 2.7.4[11]

Dose discontinuations, interruptions, or reductions due to AEs: AEs leading to a dose discontinuation at each of the data cut-offs are listed in Table 35.[11] As of the primary data analysis, 17 patients (21.5%) in the 200 mg group and 54 patients (36.0%) in the 800 mg group had discontinued treatment due to an AE. As of the 42-month data cut-off, 24 patients (30.4%) in the 200 mg group and 60 patients (40.0%) in the 800 mg group had discontinued due to AEs. In the 200 mg group, AEs that led to discontinuation at the time of the primary analysis included muscle spasms (3.8%), dysgeusia (2.5%), weight decreased (2.5%), and nausea (2.5%), and at the time of the 12-month analysis, additional AEs that led to discontinuation included asthenia (3.8%) and fatigue (2.5%). AEs that led to discontinuation at subsequent time points remained consistent in the 200 mg group. In the 800 mg group, AEs that led to discontinuation at the time of the primary analysis included muscle spasms (8.7%), alopecia (6.0%), decreased appetite (5.3%), dysgeusia (4.7%), weight decreased (4.7%), and nausea (4.0%), and AEs leading to discontinuation at subsequent time points were highly consistent with the primary analysis.

Table 35: Adverse Events Occurring in at Least 1% of Either Treatment group Requiring Discontinuation of Study Drug for All Patients in the BOLT Trial (Safety Population)

	Primary analysis: data cut-off: 28-Jun-2013		12-month analysis: data cut-off: 31-Dec-2013		18-month analysis: data cut-off: 11-Jul-2014		30-month analysis: data cut-off: 10-Jul-2015		42-month analysis: data cut-off: 08-Jul-2016	
	Sonidegib		Sonidegib		Sonidegib		Sonidegib		Sonidegib	
	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)
AE leading to discontinuation	**17 (21.5)**	**54 (36.0)**	**22 (27.8)**	**56 (37.3)**	**24 (30.4)**	**59 (39.3)**	**24 (30.4)**	**60 (40.0)**	**24 (30.4)**	**60 (40.0)**
General disorders and administration site conditions	**3 (3.8)**	**7 (4.7)**	**6 (7.6)**	**7 (4.7)**	**6 (7.6)**	**7 (4.7)**	**6 (7.6)**	**8 (5.3)**	**6 (7.6)**	**8 (5.3)**
Asthenia	1 (1.3)	1 (0.7)	3 (3.8)	1 (0.7)	3 (3.8)	1 (0.7)	3 (3.8)	1 (0.7)	3 (3.8)	1 (0.7)
Fatigue	1 (1.3)	3 (2.0)	2 (2.5)	3 (2.0)	2 (2.5)	3 (2.0)	2 (2.5)	4 (2.7)	2 (2.5)	4 (2.7)
General physical health deterioration	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Chest discomfort	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Musculoskeletal and connective tissue disorders	**4 (5.1)**	**17 (11.3)**	**5 (6.3)**	**17 (11.3)**	**5 (6.3)**	**17 (11.3)**	**5 (6.3)**	**17 (11.3)**	**5 (6.3)**	**17 (11.3)**
Muscle spasms	3 (3.8)	13 (8.7)	4 (5.1)	13 (8.7)	4 (5.1)	12 (8.0)	4 (5.1)	12 (8.0)	4 (5.1)	12 (8.0)
Arthralgia	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Nervous system disorders	**2 (2.5)**	**16 (10.7)**	**4 (5.1)**	**15 (10.0)**	**5 (6.3)**	**15 (10.0)**	**5 (6.3)**	**15 (10.0)**	**5 (6.3)**	**15 (10.0)**
Dysgeusia	2 (2.5)	7 (4.7)	3 (3.8)	7 (4.7)	3 (3.8)	7 (4.7)	3 (3.8)	7 (4.7)	3 (3.8)	7 (4.7)
Headache	0	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Cerebrovascular accident	0	0	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Ageusia	0	3 (2.0)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Hypogeusia	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Investigations	**5 (6.3)**	**11 (7.3)**	**5 (6.3)**	**12 (8.0)**	**5 (6.3)**	**14 (9.3)**	**5 (6.3)**	**14 (9.3)**	**5 (6.3)**	**14 (9.3)**
Weight decreased	2 (2.5)	7 (4.7)	2 (2.5)	7 (4.7)	2 (2.5)	9 (6.0)	2 (2.5)	9 (6.0)	2 (2.5)	9 (6.0)
Blood creatine phosphokinase increased	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)
Amylase increased	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Blood creatine phosphokinase mb increased	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Lipase increased	1 (1.3)	0	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Gastrointestinal disorders	**2 (2.5)**	**12 (8.0)**	**3 (3.8)**	**13 (8.7)**	**3 (3.8)**	**12 (8.0)**	**3 (3.8)**	**12 (8.0)**	**3 (3.8)**	**12 (8.0)**
Nausea	2 (2.5)	6 (4.0)	3 (3.8)	7 (4.7)	3 (3.8)	6 (4.0)	3 (3.8)	6 (4.0)	3 (3.8)	6 (4.0)
Dysphagia	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Abdominal pain upper	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Dry mouth	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Constipation	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Metabolism and nutrition disorders	**1 (1.3)**	**11 (7.3)**	**1 (1.3)**	**10 (6.7)**	**2 (2.5)**	**10 (6.7)**	**2 (2.5)**	**10 (6.7)**	**2 (2.5)**	**10 (6.7)**
Decreased appetite	1 (1.3)	8 (5.3)	1 (1.3)	7 (4.7)	2 (2.5)	7 (4.7)	2 (2.5)	7 (4.7)	2 (2.5)	7 (4.7)
Dehydration	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.3)**	**1 (0.7)**	**2 (2.5)**	**1 (0.7)**	**2 (2.5)**	**1 (0.7)**	**2 (2.5)**	**1 (0.7)**	**2 (2.5)**	**1 (0.7)**
Invasive papillary breast carcinoma	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Prostate cancer	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Psychiatric disorders	**2 (2.5)**	**0**	**2 (2.5)**	**0**	**2 (2.5)**	**0**	**2 (2.5)**	**0**	**2 (2.5)**	**0**
Agitation	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Depression	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Skin and subcutaneous tissue disorders	**1 (1.3)**	**9 (6.0)**	**2 (2.5)**	**9 (6.0)**	**2 (2.5)**	**10 (6.7)**	**2 (2.5)**	**10 (6.7)**	**2 (2.5)**	**10 (6.7)**
Alopecia	1 (1.3)	9 (6.0)	1 (1.3)	9 (6.0)	1 (1.3)	9 (6.0)	1 (1.3)	9 (6.0)	1 (1.3)	9 (6.0)
Pruritus	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Injury, poisoning and procedural complications	**1 (1.3)**	**0**	**1 (1.3)**	**1 (0.7)**	**1 (1.3)**	**1 (0.7)**	**1 (1.3)**	**1 (0.7)**	**1 (1.3)**	**1 (0.7)**
Lumbar vertebral fracture	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	1 (0.7)	1 (1.3)	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (1.3)**	**0**	**1 (1.3)**	**0**	**1 (1.3)**	**0**	**1 (1.3)**	**0**
Dyspnea exertional	0	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Vascular disorders	**0**	**3 (2.0)**	**0**	**4 (2.7)**	**0**	**4 (2.7)**	**0**	**4 (2.7)**	**0**	**4 (2.7)**
Hypertension	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Cardiac disorders	**0**	**3 (2.0)**	**0**	**3 (2.0)**	**0**	**3 (2.0)**	**0**	**3 (2.0)**	**0**	**3 (2.0)**
Blood and lymphatic system disorders	**0**	**2 (1.3)**	**0**	**2 (1.3)**	**0**	**2 (1.3)**	**0**	**2 (1.3)**	**0**	**2 (1.3)**
Anemia	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)

Preferred terms are presented in descending order of frequency by System Organ Class in the sonidegib 200-mg column-42-month analysis.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Adverse events occurring more than 30 days after the last date of study treatment are not summarized.

AE = adverse event.
Data Source: Health Canada Module 2.7.4[11]

As of the primary analysis, 31.6% of patients in the 200 mg group and 60.0% of patients in the 800 mg group had experienced an AE requiring dose interruption and/or reduction, which increased to 43.0% in the 200 mg group and 66.7% in the 800 mg as of the 42-month data cut off (Table 36). The most commonly occurring AEs leading to a dose interruption or reduction at the time of the primary analysis in the 200 mg group was blood creatinine increased (6.3%), lipase increased (5.1%), and nausea (3.8%), and at the time of the 12-month analysis, diarrhea (5.1%) also became a frequently occurring AE leading to discontinuation or reduction. AEs were generally consistent across time points for the 200 mg group. In the 800 mg group, the most frequently occurring AEs leading to a dose interruption or reduction at the time of the primary analysis were muscle spasms (16.0%), blood creatinine phosphokinase increased (11.3%), nausea (10.7%), dysgeusia (7.3%), and vomiting (6.7%), which remained the most frequently occurring AEs leading to dose interruption or reduction across subsequent analysis time points.

Table 36: Adverse Events Occurring in at Least 2% of Either Treatment Group Leading to Dose Reduction or Dose Interruptions for All Patients in the BOLT Trial (Safety Population)

	Primary analysis: data cut-off: 28-Jun-2013		12-month analysis: data cut-off: 31-Dec-2013		18-month analysis: data cut-off: 11-Jul-2014		30-month analysis: data cut-off: 10-Jul-2015		42-month analysis: data cut-off: 08-Jul-2016	
	Sonidegib		Sonidegib		Sonidegib		Sonidegib		Sonidegib	
	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)
Any AE requiring dose interruption or reduction	**25 (31.6)**	**90 (60.0)**	**30 (38.0)**	**96 (64.0)**	**31 (39.2)**	**99 (66.0)**	**33 (41.8)**	**100 (66.7)**	**34 (43.0)**	**100 (66.7)**
Gastrointestinal disorders	**5 (6.3)**	**29 (19.3)**	**10 (12.7)**	**33 (22.0)**	**11 (13.9)**	**34 (22.7)**	**11 (13.9)**	**36 (24.0)**	**11 (13.9)**	**36 (24.0)**
Nausea	3 (3.8)	16 (10.7)	4 (5.1)	17 (11.3)	5 (6.3)	17 (11.3)	5 (6.3)	18 (12.0)	5 (6.3)	19 (12.7)
Vomiting	1 (1.3)	10 (6.7)	2 (2.5)	12 (8.0)	5 (6.3)	12 (8.0)	5 (6.3)	12 (8.0)	5 (6.3)	12 (8.0)
Diarrhea	2 (2.5)	7 (4.7)	4 (5.1)	8 (5.3)	4 (5.1)	8 (5.3)	4 (5.1)	8 (5.3)	4 (5.1)	8 (5.3)
Investigations	**10 (12.7)**	**35 (23.3)**	**10 (12.7)**	**38 (25.3)**	**10 (12.7)**	**38 (25.3)**	**10 (12.7)**	**38 (25.3)**	**10 (12.7)**	**38 (25.3)**
Blood creatine phosphokinase increased	5 (6.3)	17 (11.3)	5 (6.3)	18 (12.0)	5 (6.3)	18 (12.0)	5 (6.3)	18 (12.0)	5 (6.3)	18 (12.0)
Weight decreased	0	8 (5.3)	0	10 (6.7)	0	9 (6.0)	0	9 (6.0)	0	9 (6.0)
Lipase increased	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)	4 (5.1)	6 (4.0)
Alanine aminotransferase increased	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)
Aspartate aminotransferase increased	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)
Myoglobin blood increased	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)
Infections and infestations	**6 (7.6)**	**9 (6.0)**	**7 (8.9)**	**12 (8.0)**	**7 (8.9)**	**12 (8.0)**	**8 (10.1)**	**13 (8.7)**	**8 (10.1)**	**14 (9.3)**
Urinary tract infection	0	0	2 (2.5)	1 (0.7)	3 (3.8)	1 (0.7)	3 (3.8)	1 (0.7)	3 (3.8)	2 (1.3)
Gastroenteritis viral	2 (2.5)	2 (1.3)	2 (2.5)	2 (1.3)	2 (2.5)	2 (1.3)	2 (2.5)	2 (1.3)	2 (2.5)	2 (1.3)
Pneumonia	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	2 (2.5)	3 (2.0)	2 (2.5)	3 (2.0)
General disorders and administration site conditions	**4 (5.1)**	**9 (6.0)**	**4 (5.1)**	**10 (6.7)**	**5 (6.3)**	**11 (7.3)**	**7 (8.9)**	**11 (7.3)**	**7 (8.9)**	**11 (7.3)**
Fatigue	2 (2.5)	5 (3.3)	2 (2.5)	6 (4.0)	2 (2.5)	7 (4.7)	3 (3.8)	6 (4.0)	3 (3.8)	6 (4.0)
Malaise	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)	0	3 (2.0)	0	3 (2.0)
Musculoskeletal and connective tissue disorders	**4 (5.1)**	**31 (20.7)**	**6 (7.6)**	**32 (21.3)**	**5 (6.3)**	**32 (21.3)**	**5 (6.3)**	**33 (22.0)**	**5 (6.3)**	**35 (23.3)**
Muscle spasms	0	24 (16.0)	1 (1.3)	25 (16.7)	1 (1.3)	25 (16.7)	1 (1.3)	25 (16.7)	1 (1.3)	28 (18.7)
Myalgia	1 (1.3)	5 (3.3)	2 (2.5)	5 (3.3)	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)
Rhabdomyolysis	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)
Nervous system disorders	**2 (2.5)**	**19 (12.7)**	**3 (3.8)**	**20 (13.3)**	**4 (5.1)**	**20 (13.3)**	**4 (5.1)**	**22 (14.7)**	**4 (5.1)**	**22 (14.7)**
Dysgeusia	1 (1.3)	11 (7.3)	2 (2.5)	12 (8.0)	3 (3.8)	12 (8.0)	3 (3.8)	12 (8.0)	3 (3.8)	12 (8.0)
Dizziness	1 (1.3)	2 (1.3)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)	1 (1.3)	3 (2.0)
Metabolism and nutrition disorders	**1 (1.3)**	**9 (6.0)**	**2 (2.5)**	**10 (6.7)**	**2 (2.5)**	**10 (6.7)**	**3 (3.8)**	**12 (8.0)**	**3 (3.8)**	**12 (8.0)**
Decreased appetite	1 (1.3)	6 (4.0)	1 (1.3)	7 (4.7)	1 (1.3)	7 (4.7)	2 (2.5)	7 (4.7)	2 (2.5)	7 (4.7)
Cardiac disorders	**2 (2.5)**	**1 (0.7)**	**2 (2.5)**	**1 (0.7)**	**2 (2.5)**	**1 (0.7)**	**2 (2.5)**	**2 (1.3)**	**2 (2.5)**	**2 (1.3)**
Injury, poisoning and procedural complications	**2 (2.5)**	**0**	**2 (2.5)**	**0**	**2 (2.5)**	**0**	**2 (2.5)**	**0**	**2 (2.5)**	**0**
Psychiatric disorders	**1 (1.3)**	**1 (0.7)**	**1 (1.3)**	**2 (1.3)**	**1 (1.3)**	**2 (1.3)**	**1 (1.3)**	**2 (1.3)**	**2 (2.5)**	**2 (1.3)**
Respiratory, thoracic and mediastinal disorders	**1 (1.3)**	**2 (1.3)**	**1 (1.3)**	**3 (2.0)**	**1 (1.3)**	**3 (2.0)**	**2 (2.5)**	**3 (2.0)**	**2 (2.5)**	**3 (2.0)**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**0**	**2 (1.3)**	**1 (1.3)**	**3 (2.0)**	**1 (1.3)**	**3 (2.0)**	**1 (1.3)**	**3 (2.0)**	**1 (1.3)**	**3 (2.0)**
Skin and subcutaneous tissue disorders	**1 (1.3)**	**7 (4.7)**	**1 (1.3)**	**8 (5.3)**	**1 (1.3)**	**9 (6.0)**	**1 (1.3)**	**10 (6.7)**	**1 (1.3)**	**10 (6.7)**
Alopecia	1 (1.3)	6 (4.0)	1 (1.3)	7 (4.7)	1 (1.3)	7 (4.7)	1 (1.3)	7 (4.7)	1 (1.3)	7 (4.7)
Renal and urinary disorders	**0**	**5 (3.3)**	**0**	**5 (3.3)**	**0**	**5 (3.3)**	**0**	**4 (2.7)**	**0**	**4 (2.7)**

Adverse events are presented in descending frequency in the sonidegib 200-mg column by system organ class (SOC) and then by preferred term in each SOC.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Adverse events occurring more than 30 days after the last date of study treatment are not summarized.

AE = adverse event.
Data Source: Health Canada Module 2.7.4[11]

Subsequent antineoplastic therapies: A summary of the subsequent anti-cancer treatments that patients received is provided in Table 37.[107] Overall, the number of patients who received any type of subsequent treatments was similar between the 200 mg sonidegib group and the 800 mg sonidegib group, although there was a slightly higher proportion for any location of radiotherapy in the 200 mg group (11.4% versus 4.6%). Notably, in laBCC patients in the 200 mg sonidegib group, 6 (9.0%) patients received subsequent target therapy, 4 (6.1%) underwent a subsequent biopsy (of which two patients underwent surgical resection after PR), 14 (21.2%) underwent 'other' antineoplastic surgery (of which Seven patients underwent surgical resection after PR), and 6 (9.1%) underwent radiotherapy of 'any location'.

Table 37: Subsequent Treatments for Patients in the BOLT trial (FAS)

	All Patients		laBCC patients		mBCC Patients	
	200 mg sonidegib (n=79)	800 mg sonidegib (n=151)	200 mg sonidegib (n=66)	800 mg sonidegib (n=128)	200 mg sonidegib (n=13)	800 mg sonidegib (n=23)
Antineoplastic medication						
Targeted therapy	11 (13.9)	13 (8.6)	6 (9.0)	10 (7.8)	5 (38.5)	3 (13.0)
Biological response modifiers	2 (2.5)	1 (1.0)	2 (3.0)	1 (1.0)	0	0
Chemotherapy	1 (1.3)	2 (1.3)	1 (1.5)	0	0	2 (8.7)
Cryotherapy	0	1 (1.0)	0	1 (1.0)	0	0
Phototherapy	0	1 (1.0)	0	1 (1.0)	0	0
Unknown	1 (1.3)	4 (2.6)	1 (1.5)	1 (1.0)	0	3 (13.0)
Antineoplastic surgery						
Biopsy	5 (6.3)	5 (3.3)	4 (6.1)[a]	2 (1.6)[c]	1 (7.7)	3 (13.0)
Other	15 (19.0)	27 (17.9)	14 (21.2)[b]	21 (16.4)[d]	1 (7.7)	6 (26.1)[a]
Radiotherapy location						
Any location	9 (11.4)	7 (4.6)	6 (9.1)	6 (4.7)	3 (23.1)	1 (4.3)
Eyelids	1 (1.3)	0	0	0	1 (7.7)	0
Skin	1 (1.3)	0	0	0	1 (7.7)	0
Head	2 (2.5)	1 (1.0)	2 (3.0)	1 (1.0)	0	0
Trunk	1 (1.3)	1 (1.0)	1 (1.5)	1 (1.0)	0	0
Spinal cord	1 (1.3)	0	1 (1.5)	0	0	0
Scalp	1 (1.3)	0	1 (1.5)	0	0	0
Bone	0	2 (1.3)	0	1 (1.0)	0	1 (4.3)
Other[e]	2 (2.5)	3 (2.0)	1 (1.5)	3 (2.3)	1 (7.7)	0

BCC = basal cell carcinoma; laBCC = locally advanced BCC; mBCC = metastatic BCC.

Notes

[a] Two patients underwent surgical resection after PR

[b] Seven patients underwent surgical resection after PR

[c] One patient underwent surgical resection after PR.

[d] Eight patients underwent surgical resection after PR.

[e] Includes right temple, prostate, right face, orbital left, left groin.

Data Source: Additional Information September 25, 2020[107]

6.4 Ongoing Trials

No ongoing trials were identified as being relevant to this review.

7 Supplemental Questions

The following supplemental question was identified during the development of the review protocol as relevant to the CADTH review sonidegib for the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery:

- **Supplemental Issue:** The CADTH review team identified no trials directly comparing sonidegib with vismodegib, which was identified as the relevant comparator in Canadian clinical practice for laBCC patients. In the absence of a direct head-to-head comparison of sonidegib with vismodegib, the sponsor submitted one published and publicly available unanchored MAIC, and one published and publicly available MA, that included vismodegib and other comparators. The following is presented in section 7.1 and 7.2:
  - Summary and critical appraisal of a published unanchored MAIC comparing sonidegib with vismodegib for the treatment of patients with laBCC who are ineligible for curative surgery or radiotherapy.[12]
  - Summary and critical appraisal of a published MA comparing sonidegib with other sonic Hedgehog pathway inhibitors, including vismodegib, for the treatment of patients with BCC.[13]

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary and Critical Appraisal of a Published Unanchored MAIC

7.1.1 Objective

To summarize and critically appraise the methods and findings of the published unanchored MAIC comparing sonidegib with vismodegib for the treatment of patients with laBCC who are ineligible for curative surgery or radiotherapy.

7.1.2 Findings

Methods

The objective of the published unanchored MAIC was to estimate the comparative efficacy of sonidegib to vismodegib in patients with laBCC who are ineligible for curative surgery or radiotherapy. The report further aimed to compare the results of the analyses obtained while adjusting for differences in selected patient baseline characteristics using a MAIC versus making unadjusted indirect treatment comparisons (ITCs). The MAIC was based on the results from two single arms of non-comparative trials (BOLT and ERIVANCE).

A feasibility assessment was conducted to determine the suitability of conducting an unanchored MAIC with the two trials by comparing the trial designs, outcome definition, and baseline patient characteristics. A targeted literature review was performed, and clinical advisors were consulted to identify baseline patient characteristics that may be considered prognostic for the outcomes of interest for the analyses. From BOLT (n=269), only the laBCC subgroup from the pEAS treated with the 200 mg dose of sonidegib (n=66) was included in the analyses because the mBCC subgroup and the 800 mg sonidegib dose were not included in the product label.[12] From ERIVANCE (n= 104),[49] the laBCC cohort was included in the analyses (n=63).[12]

Details of the two trials are summarized in Table 38. Some similarities and differences were noted between the trial designs and the eligibility criteria. Both trials were multicentre, international phase II trials. BOLT was a randomized double-blind trial investigating two doses of sonidegib (200 mg and 800 mg),[12] and ERIVANCE was a single arm, non-randomized trial investigating one dose of vismodegib (150 mg).[49] Both trials required patients to have a histologically confirmed diagnosis, with one or more lesions with measurable disease of greater than or equal to 10 mm in at least one dimension, and disease not amenable to surgery (BOLT also specified patients not being eligible for radiotherapy or other local therapies). In the BOLT trial, patients were not required to have received any prior therapy, however in the ERIVANCE trial, patients were required to have been given radiotherapy unless it was contraindicated or inappropriate. In the ERIVANCE trial, patients were excluded if their life expectancy was greater than 12 weeks or if they had superficial multifocal BCC that may be considered unresectable due to breadth of involvement.[49] The primary outcome was ORR by central review for both trials. In the BOLT trial, tumour response was assessed using mRECIST, comprised of a composite assessment of MRI (per RECIST v1.1), photograph, and histology.[12] In the ERIVANCE trial, tumour response was assessed using a composite assessment of MRI or photograph (per RECIST v1.0), ulceration, and histology. Refer to Section 6 for efficacy endpoint definitions in the BOLT trial. In ERIVANCE, response in the laBCC patients was defined as a decrease of 30% or more in the externally visible or radiographic dimension (if applicable) or complete resolution of ulceration (if present at baseline).[49] To note, ulceration/new lesion was not considered PD in BOLT but was considered PD in ERIVANCE.

Table 38: Overview of trial designs, including outcome definitions

Trial characteristics	BOLT	ERIVANCE
Study description	(i) Multicenter, international, randomized, double-blind, phase 2 study to investigate the safety and efficacy of sonidegib (ii) Patients were randomized to receive either 200 mg or 800 mg[a] of sonidegib [5]	(i) Single-arm, multicenter, international, nonrandomized, phase 2 study to investigate the safety and efficacy of vismodegib [8]
Key inclusion criteria	(i) Histologically confirmed diagnosis, with measurable disease of ≥1 lesion, ≥10 mm in at least 1 dimension by MRI or color photograph (ii) Patients were not amenable to radiation therapy, curative surgery, or other local therapies (iii) Patients were not required to have received any prior therapy [5]	(i) Histologically confirmed diagnosis, with measurable disease of ≥1 lesion, ≥10 mm in the longest dimension (ii) Patients were considered to be inoperable or medically contraindicated to surgery (iii) Patients were required to have been given radiotherapy unless radiotherapy was contraindicated or inappropriate [8]
Key exclusion criteria	(i) Life expectancy was not mentioned (ii) Presence of superficial multifocal BCC that may be considered unresectable was not mentioned [5]	(i) Patients with life expectancy <12 weeks [8] (ii) Patients with superficial multifocal BCC that may be considered unresectable due to breadth of involvement [9]
Periods for reported results (minimum duration of follow-up)	(i) Primary analysis (6 months of follow-up) [14] (ii) 12-Month update (12 months of follow-up) [5] (iii) 18-Month update (18 months of follow-up) [7]	(i) Primary analysis (9 months of follow-up) [8] (ii) 6-Month update (15 months of follow-up) [15] (iii) 12-Month update (21 months of follow-up) [16] (iv) 18-Month update (27 months of follow-up) [17] (v) 24-Month update (33 months of follow-up) [18] (vi) 30-Month update (39 months of follow-up) [19]
Primary efficacy endpoint	(i) ORR by central review	(i) ORR by central review
Other efficacy and safety outcomes available	(i) DOR (ii) Complete response rate (iii) PFS (iv) Overall survival (v) Time to response (vi) Specific adverse events	(i) DOR (ii) Complete response rate (iii) PFS (iv) Overall survival (v) Specific adverse events
Assessment of tumor response	(i) mRECIST: composite assessment of MRI (per RECIST v1.1) [20], photograph (per WHO [21]), and histology (ii) Prespecified sensitivity analysis using ERIVANCE-like criteria	(i) Composite assessment of MRI or photograph (per RECIST v1.0) [22], ulceration, and histology

BCC: basal cell carcinoma; DOR: duration of response; mRECIST: modified RECIST; MRI: magnetic resonance imaging; ORR: objective response rate; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; WHO: World Health Organization. [a]Only patients with locally advanced BCC in the 200 mg arm are included in this analysis.

Source: Odom et al., 2017. Copyright 2017 Hindawi. Reprinted in accordance with Creative Commons Attribution License CC BY 4.0[12]

Data from the BOLT 18-month analysis (18 months following enrollment of the last patient) and from the ERIVANCE 12-month analysis (12 months of follow-up, after a nine-month study; 21 months following enrollment of the last patient) were used for the MAIC as they provided the longest common duration of follow-up. The primary efficacy outcome of both trials, ORR, was selected as an outcome to be analyzed. The authors stated that PFS was also analyzed as an outcome that could be used to evaluate cost effectiveness, and DOR as it may be clinically relevant to the patient population. As the two trials used different response criteria for ORR and DOR, a sensitivity analysis was conducted using response criteria which attempted to more closely align the response criteria of the BOLT trial (the trial

with IPD) with the response criteria used in the ERIVANCE trial. The details of this methodology were not described in the publication; however ,some differences were noted from the trial publications as described previously (for example, ulceration/new lesion was not considered PD in BOLT but was considered PD in ERIVANCE).

An overview of the available patient characteristics in both trials are listed in Table 39. The matching variables were selected based on the availability and consistency of reporting, distributional differences between the trials (based on visual inspection), and whether they were potentially prognostic for the efficacy outcomes based on clinical advisor input and literature. The number of matching variables was restricted to two, with the rationale provided being the sample size of the BOLT study (n=66). The authors reported that there was distribution differences between the trials for prior radiotherapy for BCC and prior surgery for BCC, and therefore selected these variables for matching in the MAIC.

Table 39: Overview of trial patient baseline characteristics

Potential matching variable	Available and presented consistently in BOLT and ERIVANCE?	Distribution differs between BOLT and ERIVANCE?	Is the variable prognostic?
Age	Yes	No (i) BOLT = 64.6 (mean) (ii) ERIVANCE = 61.4 (mean)	BOLT exploratory analysis suggests prognostic [7], but Chang et al. [25] suggest nonsignificant relationship with ORR
Sex	Yes	No (i) BOLT = 57.6% (male) (ii) ERIVANCE = 55.6% (male)	Unknown
Race	Yes	No (i) BOLT = 89.4% white, 10.6% other (ii) ERIVANCE = 100% white	Unknown
ECOG status	Yes	No (i) BOLT: (a) ECOG status 0 = 66.7% (b) ECOG status 1 = 24.2% (c) ECOG status 2 = 6.1% (ii) ERIVANCE (a) ECOG status 0 = 76.2% (b) ECOG status 1 = 20.6% (c) ECOG status 2 = 3.2%	BOLT exploratory analysis suggests prognostic [7]
Prior radiotherapy for BCC	Yes	Yes (i) BOLT = 7.6% (ii) ERIVANCE = 20.6% for target and 27.0% for current or prior	Chang et al. [25] suggest nonsignificant relationship with ORR
Prior systemic therapy for BCC	Yes	No (i) BOLT = 6.1% (ii) ERIVANCE = 11.1% (systematic or topical)	Chang et al. [25] suggest significant relationship with ORR
Prior surgery for BCC	Yes	Yes (i) BOLT = 72.7% (ii) ERIVANCE = 88.9%	Clinical advisors suggest highly prognostic in refractory population

BCC: basal cell carcinoma; ECOG: Eastern Cooperative Oncology Group; ORR: objective response rate. *Note.* BOLT summaries are based on the 200 mg full analysis set population [7]; ERIVANCE summaries are based on Sekulic et al. [8] and the European Medicines Agency assessment report [9].

Source: Odom et al., 2017. Copyright 2017 Hindawi. Reprinted in accordance with Creative Commons Attribution License CC BY 4.0[12]

The unanchored MAIC was conducted using SAS statistical software v9.3 or higher. A base case analysis was conducted by performing naïve indirect comparisons using unadjusted results from the two studies. To conduct the unanchored MAIC analyses, the methodologies by Signorovitch et al. were applied [112,113]. The IPD available for patients from the BOLT trial was weighted so that the proportions for the two selected baseline variables (i.e. prior

radiotherapy for BCC and prior surgery for BCC) matched the aggregate data for the proportions from the ERIVANCE trial. The Newton-Raphson algorithm was used to obtain the solution for the weights, and weights were examined for extreme values. After matching, weighted statistical analysis of the BOLT IPD was applied using SAS via a weighted chi-square test (PROC FREQ) or weighted Kaplan-Meier analysis (PROC LIFETEST) to produce the efficacy endpoints. Finally, the reweighted BOLT efficacy results were compared to the ERIVANCE efficacy results similarly to the naive indirect comparisons.

Results

Baseline characteristics before and after matching are displayed in Table 40. The sample sizes were 66 patients from the BOLT trial and 63 patients from the ERIVANCE trial. Prior to weighting, a lower percentage of patients in the BOLT trial compared to the ERIVANCE trial had received prior BCC radiotherapy (7.6% versus 20.6%) and prior BCC surgery (72.7% versus 88.9%). These characteristics were similar after matching, with some differences. Post matching, there were more patients aged 65 or greater or male in the BOLT trial, and there were more patients with an ECOG PS of 0 in the ERIVANCE trial. The calculated weights had a mean equal to 1 (SD: 0.573; range: 0.40–2.72).[12] No other characteristics were adjusted for in the comparisons.

Table 40: Baseline Characteristics of the Included Trials Before and After Matching

	BOLT[a], sonidegib 200 mg		ERIVANCE[a], vismodegib 150 mg (n = 63)
	Prematched (n = 66)	Postmatched (n = 66)	
Matched baseline characteristics			
Prior BCC radiotherapy, n[b] (%)	5 (7.6%)	(20.6%)	13 (20.6%)
Prior BCC surgery, n[b] (%)	48 (72.7%)	(89.0%)	56 (88.9%)
Unmatched baseline characteristics			
Age in years			
Mean	64.6	64.6	61.4
Median	67.0	67.0	62.0
Standard deviation	15.9	15.5	16.9
Age range in years, n[b] (%)			
18–40	6 (9.1%)	(8.6%)	7 (11.1%)
41–64	22 (33.3%)	(31.6%)	26 (41.3%)
≥65	38 (57.6%)	(59.8%)	30 (47.6%)
Race, n[b] (%)			
White	59 (89.4%)	(90.8%)	(100.0%)
Other	7 (10.6%)	(9.2%)	(0.0%)
ECOG status, n[b,c] (%)			
0	44 (66.7%)	(69.3%)	48 (76.2%)
1	16 (24.2%)	(21.5%)	13 (20.6%)
2	4 (6.1%)	(6.0%)	2 (3.2%)
Sex, n[b] (%)			
Male	38 (57.6%)	(60.8%)	35 (55.6%)
Female	28 (42.4%)	(39.2%)	28 (44.4%)
Prior systemic therapy for BCC, n[b] (%)	4 (6.1%)	(5.4%)	7 (11.1%)[d]

BCC: basal cell carcinoma; ECOG: Eastern Cooperative Oncology Group. [a]BOLT data analysis was based on the 18-month update (i.e., 18 months of patient follow-up) [7]; ERIVANCE summary information was based on the 12-month update (i.e., 21 months of patient follow-up) [16]; [b]postmatched BOLT results were weighted at the person level; therefore, the number of patients was not available; [c]two patients had missing ECOG status at baseline; [d]Systemic or topical.

Source: Odom et al., 2017. Copyright 2017 Hindawi. Reprinted in accordance with Creative Commons Attribution License CC BY 4.0[12]

The results of the efficacy outcomes from the trials before (unadjusted) and after matching are displayed in Table 41. For patients treated with sonidegib (i.e. in the BOLT trial) ORR was 56.1% (95% CI: 44.1 to 68.0) in the pre-matched population and 56.7% (95% CI: 44.7 to 68.6) in the post-matched population, while in patients treated with vismodegib (i.e. in the ERIVANCE trial), ORR was 47.6% (95% CI: 35.5 to 60.6).

Median PFS was 22.1 months (95% CI: 14.8 to NE) for both the pre- and post-matched sonidegib analyses and was 9.5 months (95% CI: 7.4 to 14.8) for vismodegib. Median DOR based on investigator review was 14.3 months (95% CI: 12.0 to 20.2) in the pre-matched sonidegib population, 15.7 months (95% CI: 12.9 to 23.1) in the post-matched sonidegib population, and NE (95% CI: 9.0 to NE) in the vismodegib population. DOR based on IRC for the vismodegib population was 9.5 months (95% CI: 7.4 to 21.4).

In the sensitivity analyses of the BOLT trial population (using response criteria which attempted to more closely align the response criteria of the BOLT trial with the response criteria used in the ERIVANCE trial although the exact methodology is unknown), ORR was 60.6% (95% CI: 48.4 to 72.4) in the pre-matched sonidegib population, and 59.5% (95% CI: 47.6 to 71.3) in the post-matched population. Median DOR was 14.9 months (95% CI: 12.0 to 20.2) in the pre-matched BOLT population, and 15.7 months (95% CI: 12.9 to 24.0) in the post-matched BOLT population.[12]

Table 41: Efficacy Outcome Parameters Before and After Matching

Efficacy outcome	BOLT[a], sonidegib 200 mg		ERIVANCE[a], vismodegib 150 mg (n = 63)
	Prematched (n = 66)	Postmatched (n = 66)	
ORR, n[b] (%) (95% CI[c])	37 (56.1%) (44.1–68.0)	(56.7%) (44.7–68.6)	30 (47.6%) (35.5–60.6)
Median PFS in months (95% CI)	22.1 (14.8 to NE)	22.1 (14.8 to NE)	9.5 (7.4–14.8)
Median DOR[d] in months (95% CI)	14.3 (12.0–20.2)	15.7 (12.9–23.1)	NE[e] (9.0 to NE)
Sensitivity analysis (ERIVANCE-like criteria)			
ORR, % (95% CI)	60.6% (48.4–72.4)	59.5%[c] (47.6–71.3)	
Median DOR[d] in months (95% CI)	14.9 (12.0–20.2)	15.7 (12.9–24.0)	

CI: confidence interval; DOR: duration of response; NE: not estimable; ORR: objective response rate; PFS: progression-free survival. [a]BOLT data analysis was based on the 18-month update (i.e., 18 months of patient follow-up) [7]; ERIVANCE summary information was based on the 12-month update (i.e., 21 months of patient follow-up) [16]; [b]postmatched BOLT results were weighted at the person level; therefore, the number of patients was not available; [c]BOLT CIs for ORR were based on Wald asymptotic confidence limits (owing to the incorporation of weights); [d]DOR was based on investigator review; [e]median DOR based on independent review facility was reported to be 9.5 months (95% CI: 7.4–21.4).

Source: Odom et al., 2017. Copyright 2017 Hindawi. Reprinted in accordance with Creative Commons Attribution License CC BY 4.0[12]

Critical Appraisal of Indirect Treatment Comparisons

While the stated objective of the analyses was to estimate the comparative efficacy of sonidegib and vismodegib in patients with laBCC who are ineligible for curative surgery or radiotherapy, no statistical comparisons between the treatments were provided, limiting the ability to make conclusions and the value of the unanchored MAIC from a decision-making perspective .

The analyses in the publication were based on the results from two trials: the BOLT trial for the sonidegib data, and the ERIVANCE trial for the vismodegib data. The authors did not describe whether any literature search had been performed to identify additional data or studies, and therefore the completeness of the available evidence can not be evaluated. Additionally, a vismodegib trial which evaluated safety and efficacy in this patient population,

STEVIE,[50] was not included, and the rationale for not including this trial was not provided. The authors also did not describe the methods for data extraction from the included trials, whether other potentially relevant comparators were considered, or if the quality of the trials and risk of bias were examined.

Several substantial limitations of the methodology of the analyses should be considered. The comparisons were unanchored because no common comparator was identified between the two treatments for this patient population. Limited details were provided as to the methodology that was used for the authors' assessment. The trial designs and eligibility criteria between the two trials were similar, and it was not mentioned whether clinical experts were consulted to determine the similarity. The authors did not describe assessing for an effective sample size, nor did they report assessing for residual confounding. The magnitude of the residual bias in the analyses is therefore uncertain, and, in the absence of such analyses, the NICE DSU considers the amount of bias in an unanchored MAIC "likely to be substantial".[114]

Differences were apparent between the trials in terms of study design (BOLT: randomization to two doses, double-blind trial; ERIVANCE: single arm, non-randomized trial), eligibility criteria (e.g. BOLT: patients were not required to have received any prior therapy; ERIVANCE: patients were required to have been given radiotherapy unless it was contraindicated or inappropriate and patients were excluded if their life expectancy was less than 12 weeks or if they had superficial multifocal BCC that may be considered unresectable due to breadth of involvement), and response assessment method (i.e. BOLT: mRECIST; ERIVANCE: RECIST v1.0). Based on the literature, responses assessments evaluated by RECIST v1.0 and RECIST v1.1 in a number of other solid tumours are highly concordant, potentially mitigating this limitation,[115] however ulceration/new lesion was considered PD in ERIVANCE[49] and not in BOLT.

The definitions of the efficacy endpoints (i.e. ORR, PFS, and DOR) were not provided, and therefore it is not possible to determine whether the outcomes were evaluated similarly between the trials. To note, DOR was INV-assessed for BOLT and IRC-assessed for ERIVANCE, and therefore the DOR in BOLT was likely inflated. It was also not possible to determine how similar the outcome assessment criteria was between the trials in the sensitivity analysis using response criteria which attempted to more closely align the response criteria of the BOLT trial (the trial with IPD) with the response criteria used in the ERIVANCE trial. Additionally, the censoring rules for time-to-event outcomes were not clear. In the BOLT trial, censoring rules were not aligned with FDA guidance[111] and likely inflated, and it was not clear if the same censoring criteria were applied to both trials.

The authors stated that they restricted the matching to two variables to avoid the potential for extreme weights and unstable results due to the study sample sizes. The matching variables were selected based on the availability and consistency of reporting, distributional differences between the trials (which is not a recommended approach from the NICE DSU),[114] and whether they were potentially prognostic for the efficacy outcomes based on clinical advisor input and literature. No details were provided for the methodology used by the clinical advisors or the literature search in identifying the variables, and no list of potential variables (i.e. those that were available from both trials and any other potential variables that hadn't been available from both trials) was provided. Additionally, the authors stated they attempted to identify prognostic factors, however unanchored MAIC requires effect modifiers and prognostic factors,[114] which the authors did not describe. Therefore, limited conclusions can be made about the assessments used by the authors surrounding

their inclusion of only the two variables as prognostic factors, and whether attempts were made to identify additional variables and/or effect modifiers.

The matching was performed on two variables with different distributions between the two trials (prior radiotherapy for BCC and prior surgery for BCC). The authors however stated that their literature search revealed that there was a non-significant relationship of prior radiotherapy for BCC and did not comment on the input from the clinical advisor on this variable. Some other baseline factors appeared to differ between the two trials before matching, potentially introducing clinical heterogeneity that was not accounted for (e.g. race: BOLT – 89.4% white and 10.6 % other, ERIVANCE – 100% white; ECOG PS: BOLT – Status 0 – 66.7%, ERIVANCE – Status 0 – 76.2%; prior systemic therapy for BCC: BOLT – 6.1%, ERIVANCE – 11.1% including both systemic and topical).[12] These characteristics remained unbalanced between the trials post-matching. Furthermore, the patients from the BOLT trial were a subgroup of the full trial population (which included both laBCC and mBCC) and therefore, randomization between the two dose arms may not have been upheld.

Overall, the results cannot be considered generalizable to the Canadian context for the population of patients with laBCC who are ineligible for curative surgery or radiotherapy, due to the substantial limitations to the analyses and highly selected trial populations. The treatment analyzed as the comparator (vismodegib) is the standard of care in Canada for these patients, and therefore the comparison was relevant. Outcomes related to safety and HRQoL were not analyzed, and therefore no conclusions can be drawn comparing the treatments for these outcomes.

7.1.3 Summary

In the absence of direct evidence comparing sonidegib and vismodegib for the treatment of patients with laBCC who are ineligible for curative surgery or radiotherapy, the sponsor submitted a published unanchored MAIC comparing the two treatments in this patient population. Two trials were included: the BOLT trial which provided IPD for sonidegib, and the ERIVANCE trial which provided aggregate data for treatment with vismodegib. No statistical comparisons between the treatments were provided and minimal adjustment for potential effect modifiers and prognostic factors was provided. Further, no assessment of residual confounding was performed. As such, no conclusions can be made regarding the comparative efficacy of sonidegib and vismodegib based on the submitted unanchored MAIC.

7.2 Summary and Critical Appraisal of a Published Meta-analysis Comparing Sonidegib with other sonic Hh inhibitors for the Treatment of Patients with BCC

7.2.1 Objective

To summarize and critically appraise the methods and findings of the published MA[13] comparing sonidegib with other sonic Hh inhibitors for the treatment of patients with BCC.

7.2.2 Findings

Methods

Systematic Review

The objective of the published MA was to determine and compare the efficacy and safety of sonic Hh inhibitors as a class for treating BCC. The MA was based on a systematic literature review (SLR) performed to retrieve all studies involving the treatment of BCC with sonic Hh inhibitors. The authors searched clinicaltrials.gov to identify sonic Hh inhibitors used to treat BCC, then performed a broad search of the following databases using the key words ''vismodegib'', ''Erivedge'', ''sonidegib'', ''odomzo'', ''itraconazole'', and ''TAK-441'' for articles published until the end of 2016: PubMed, clinicaltrial.gov, Embase, and Cochrane Central Register of Clinical Trials. Of note, sonidegib for the treatment of laBCC is the indication under review in this report, and vismodegib is the standard of care in Canadian clinical practice. All other sonic Hh inhibitors are investigational and/or are not approved or used in this patient population, and thus this section will focus on the results relevant to the indication under review (i.e. results of sonidegib and vismodegib).

Two independent authors screened the list of potential articles obtained from the database search, the list was then narrowed to include clinical trials, prospective case series, and retrospective medical record reviews on human subjects written in English. Case reports, studies providing only outcomes after surgery or radiotherapy, studies of sonic Hh inhibitors used concurrently with additional treatments, and studies without quantitative measurements were excluded. Eligible full-length studies were then screened for final inclusion by the authors. No information was provided as to how potential conflicts were resolved, and details on the reasons full-text articles (and how many per criteria) did not meet specific inclusion or exclusion criteria were not provided. Two authors independently extracted data into standardized Excel sheets and assessed the quality of evidence using the Oxford Center for Evidence-Based Medicine levels. Variables included in extraction were study size, medication, median follow-up and drug exposure in months, response rates, type of response (central and independent review favoured), and AE rates. Study quality was individually assessed by the two authors, followed by a joint evaluation. Details were not provided as to how quality/bias assessment conflicts (if any) were resolved, except for one disagreement on the cut-off between large and small studies (settled on 50 or more patients for large studies).

Meta-analysis

The primary outcomes for the analyses were ORR (defined by the publication authors as the proportion of patients with CR or PR after treatment) and CRR (defined by the publication authors as the percentage of patients with a CR). Clinical benefit rate (CBR) (defined by the publication authors as the proportion of patients with CR, PR, or SD) was analyzed as a secondary outcome. The outcome definitions from the individual studies were not provided in the publication. The methods of outcome assessment varied (e.g. evaluation by central RECIST, investigator RECIST, etc.). Safety outcomes analyzed included the prevalence of the following AEs: dysgeusia, muscle spasms, alopecia, fatigue, nausea, weight loss, diarrhea, decreased appetite, skin squamous cell carcinoma (SCC), myalgias, vomiting, amenorrhea, and increased creatine kinase.[13] As with the efficacy outcomes, the definitions of the AEs and how these safety outcomes were reported in the individual studies were not provided in the publication. The publication stated that an absolute difference of greater than

10% between the sonic Hh inhibitors was considered clinically important, however no rationale or literature was provided to justify this conclusion.

The authors pooled the data from multiple dosing regimens from the included studies. The identified studies were heterogenous in their design and population size, and the authors were unable to access the variance or data to calculate the variance from most studies. As such, the variance was imputed with relative per-study sampling variances equal to 1/√population size, thus giving more weight to larger studies. Linear models with fixed-effect meta-analysis were used to pool data for the meta-analyses, along with the 95% CIs and P values. Bayesian random-effect models were performed as sensitivity analyses. Funnel plots and the trim-and-fill method were used to assess publication bias. Forest plots and the I^2 statistic were used to assess heterogeneity. Subgroup analyses were performed for patients with laBCC and patients with mBCC, however this was not clearly described in the methods, and did not appear to be a priori analyses. These analyses were performed only for sonidegib and vismodegib as there were studies for these SSHis that reported results for the patient subgroups. All analyses were performed in R.

Results

Systematic Review

The titles/abstracts from 306 articles/studies were screened, of which 130 were screened at the full-text review, and 21 articles representing 18 individual studies were selected for data extraction (14 studies of vismodegib, 2 studies of sonidegib, and one study each of itraconazole and TAK-441). Of these, 14 studies contributed data for both the efficacy analyses and the safety analyses, two studies provided data for the efficacy analyses only, and two studies provided data for the safety analyses only (total 16 studies each for efficacy and safety analyses).

Of the 18 included studies, 13 were industry sponsored (providing 95.8% of the patients in the meta-analysis). Median follow-up time was 11 months (range: 1.3 to 36 months) and median drug exposure was 5.25 months (range: 1.3 to 21 months). The sample size included from the studies ranged from 4 to 499 patients. The design of the studies was heterogenous, with RCTs, non-randomized clinical trials, single arm trials, cohort studies, case series, and case reports included. Of the 16 studies included in the efficacy analyses, response criteria assessments included two studies which used centrally-assessed RECIST, six studies which used investigator-assessed RECIST, five studies which used clinical outcomes, and one study each which used a mixed design (RECIST plus clinical outcomes), histopathologic clearance, or did not provide information. Further details of the included studies are provided in Table 42 (studies included in the efficacy analyses) and Table 43 (studies included in the safety analyses).[13]

Efficacy outcomes from the individual included studies are presented in Table 42. ORR ranged from 20.0% to 100.0%, CRR ranged from 0% to 54.2%, and CBR ranged from 66.7% to 100.0%.

Table 42: Efficacy Results from the Included Studies

Study name	Study type	Quality of evidence*	Molecule	Response criteria	Patients, N	ORR, %	CRR, %	CBR, %
BOLT[14,34]	Double-blinded RCT, no placebo	2	Sonidegib	Central RECIST	200	49.5	2.5	98.5
Viscusi, 2015[19]	Prospective case series	4	Vismodegib	Unknown	24	95.8	54.2	100.0
Tauber, 2015[20]	Prospective case series	4	Vismodegib	Investigator RECIST	7	57.1	0	100.0
STEVIE[21]	Open-label, multicenter, single-arm clinical trial	2	Vismodegib	Investigator RECIST	456	68.6	34.0	96.7
ERIVANCE[4,22]	Prospective cohort study (2 cohorts)	2	Vismodegib	Central RECIST	92	44.6	15.2	90.2
Ozgur, 2015[23]	Retrospective case reviews	4	Vismodegib	Investigator RECIST	12	66.7	16.7	83.3
Sofen_2015[24]	Open-label, nonrandomized 3-arm clinical trial	2	Vismodegib	Histology	65	38.5	38.5	95.4
Demirci, 2015[25]	Retrospective case reports	4	Vismodegib	Investigator RECIST	6	100.0	33.3	100.0
Kim, 2014[16]	Open-label, nonrandomized 3-arm clinical trial with placebo	2	Itraconazole	Clinical	8	50.0	0	NA
EAS[26]	Open-label, nonrandomized 2-cohort, single-arm clinical trial	2	Vismodegib	Investigator RECIST	88	43.2	9.1	96.6
Gill, 2013[27]	Prospective case series	4	Vismodegib	Clinical	5	100.0	40.0	100.0
Von Hoff LoRusso[12,28]	Phase 1 trial	2	Vismodegib	Mixed	33	54.5	6.1	87.9
Simone, 2016[29]	Prospective case series	4	Vismodegib	Clinical	6	66.7	16.7	66.7
NCT01350115[33]	Phase 2 double-blinded RCT, with placebo	1	Sonidegib	Clinical	7	85.7	42.9	100.0
RegiSONIC[30]	Prospective cohort	2	Vismodegib	Clinical	88	69.3	47.7	NA
Goldman, 2015[15]	Phase 1 trial	2	TAK-441	Investigator RECIST	5	20.0	0	100.0

CBR, Clinical benefit rate; *CRR*, complete response rate; *EAS*, expanded access study; *NA*, not available or ascertained; *ORR*, overall response rate; *RCT*, randomized clinical trial; *RECIST*, response evaluation criteria in solid tumors; *SHHi*, sonic hedgehog inhibitor.
*Quality of evidence assessed per Oxford Centre for Evidence-based Medicine.

Reprinted from J Am Acad Dermatol, 79(6), Xie P & Lefrançois P, efficacy, safety, and comparison of sonic hedgehog inhibitors in basal cell carcinomas: a systematic review and meta-analysis, 1089-1100, Copyright 2018, with permission from Elsevier[13]

AEs from the included studies are presented in Table 43. The following AEs were reported from the studies: muscle spasm (12.1 to 100.0%), dysgeusia (6.1 to 92.5%), alopecia (16.7 to 100.0%), weight loss (12.1 to 83.3%), fatigue (12.1 to 47.5%), nausea (0 to 65.0%), myalgia (3.0 to 23.6%), vomiting (0 to 20.5%), skin SCC (0 to 28.6%), increased CK (10.9 to 28.6%), diarrhea (3.0 to 26.9%), decreased appetite (6.1 to 41.7%), and amenorrhea (in the premenopausal women subgroup) (27.6 to 50.0%). AEs from the trial investigating TAK-441 were presented for both BCC and non-BCC malignancies, and therefore data from this trial was not included in the pooled prevalence. For itraconazole, only two AEs were reported: fatigue and heart failure.[13]

Table 43: Safety Results from the Included Studies

Study name	Study type	Quality of evidence*	Molecule	Response criteria	Patients, N	Muscle spasm, %	Dysgeusia, %	Alopecia, %	Weight loss, %	Fatigue, %	Nausea, %	Myalgia, %	Vomiting, %	Skin SCC, %	Increased CK, %	Diarrhea, %	Decreased appetite, %	Amenorrhea, %†
BOLT[14,34]	Double-blinded RCT, no placebo	2	Sonidegib	Central RECIST	229	63.3	53.3	54.6	37.6	33.6	41.0	23.6	20.5	NA	10.9	25.3	28.8	NA
Viscusi, 2015[19]	Prospective case series	4	Vismodegib	Unknown	22	54.5	59.1	54.5	36.4	31.8	NA	NA	NA	4.5	NA	NA	NA	NA
Tauber, 2015[20]	Prospective case series	4	Vismodegib	Investigator RECIST	7	100.0	71.4	42.9	NA	NA	NA	NA	NA	28.6	NA	NA	NA	NA
STEVIE[21]	Open-label, multicenter, single-arm clinical trial	2	Vismodegib	Investigator RECIST	499	63.5	53.9	61.5	32.5	16.0	16.0	7.8	NA	1.0	NA	16.6	25.3	27.6 (29)
ERIVANCE[4,22]	Prospective cohort study (2 cohorts)	2	Vismodegib	Central RECIST	104	74.0	55.8	68.3	51.9	42.3	33.7	NA	NA	NA	NA	26.9	27.9	33.3 (6)
Ozgur, 2015[23]	Retrospective case reviews	4	Vismodegib	Investigator RECIST	12	100.0	75.0	75.0	83.3	33.3	25.0	16.7	0.0	NA	NA	16.7	41.7	NA
Sofen, 2015[24]	Open-label, nonrandomized, 3-arm clinical trial	2	Vismodegib	Histology	74	75.7	50.0	58.1	NA	20.3	17.6	NA	NA	NA	NA	8.1	10.8	NA
Demirci, 2015[25]	Retrospective case reports	4	Vismodegib	Investigator RECIST	8	75.0	25.0	50.0	NA	NA	NA	NA	NA	NA	NA	12.5	NA	NA
EAS[26]	Open-label, nonrandomized, 2-cohort, single-arm clinical trial	2	Vismodegib	Investigator RECIST	119	70.6	70.6	58.0	16.0	19.3	19.3	NA	NA	0.8	NA	25.2	NA	50.0 (8)
Gill, 2013[27]	Prospective case series	4	Vismodegib	Clinical	5	20.0	20.0	20.0	NA	NA	NA	NA	NA	20.0	NA	NA	20.0	NA
Tang, 2016[32]	Double-blinded RCT, with placebo	1	Vismodegib	None	40	100.0	92.5	100.0	62.5	47.5	65.0	NA	NA	0	NA	NA	NA	NA
Von Hoff LoRusso[12,28]	Phase 1 trial	2	Vismodegib	Mixed	33	12.1	6.1	NA	12.1	12.1	3.0	3.0	3.0	NA	NA	3.0	6.1	NA
Simone, 2016[29]	Prospective case series	4	Vismodegib	Clinical	12	100.0	16.7	16.7	16.7	25.0	0	NA	NA	8.3	NA	NA	NA	NA
NCT01350115[33]	Phase 2 double-blinded RCT, with placebo	1	Sonidegib	Clinical	7	42.9	14.3	28.6	NA	28.6	28.6	14.3	NA	NA	28.6	14.3	NA	NA
MIKIE[31]	Phase 2 double-blinded RCT, not placebo	2	Vismodegib	NA	227	77.5	66.1	63.9	19.8	22.0	16.3	13.2	4.8	2.6	11.5	16.7	16.7	NA
RegiSONIC[30]	Prospective cohort	2	Vismodegib	Clinical	88	45.5	50.0	36.4	17.0	NA	NA	NA	NA	NA	NA	NA	NA	NA

CK, Creatine kinase; *EAS*, expanded access study; *NA*, not available or ascertainable; *RCT*, randomized clinical trial; *RECIST*, response evaluation criteria in solid tumors; *SCC*, squamous cell carcinoma; *SHHi*, sonic hedgehog inhibitor.
*Quality of evidence assessed per Oxford Centre for Evidence-based Medicine.
†Parentheses refer to the number of the premenopausal women subgroup for whom data are available.

Reprinted from J Am Acad Dermatol, 79(6), Xie P & Lefrançois P, efficacy, safety, and comparison of sonic hedgehog inhibitors in basal cell carcinomas: a systematic review and meta-analysis, 1089-1100, Copyright 2018, with permission from Elsevier[13]

Analyses

Since the vismodegib is the only relevant comparator to Canadian clinical practice, the results reported in this section will focus on sonidegib and vismodegib.

a) Efficacy results

The pooled ORR for all patients (i.e. all sonic Hh inhibitors) obtained using fixed-effect linear models was 59.6% (95% CI: 40.3% to 78.9%) (Table 44). The sensitivity analysis using Bayesian models with random effect produced an ORR of 58.5% (95% CI: 36.5% to 79.4%). The pooled ORR by treatment was estimated to be 61.9% (95% CI: 40.2% to 83.6%) for vismodegib and 55.2% (95% CI: 7.4% to 103.0%) for sonidegib. ORR for the subgroup analysis of patients with laBCC was 68.7% (95% CI: 44.7% to 92.8%) for vismodegib and was 56.6% (95% CI not available) for sonidegib (treatment difference P value not reported). For patients with mBCC, ORR was 39.7% (95% CI: -1.9% to 80.6%) for vismodegib and 14.7% (95% CI not available) for sonidegib (treatment difference P = 0.007, Fischer's exact

test). The I^2 test for heterogeneity was negative. Publication bias assessed using trim-and-fill demonstrated that one left-sided study was lacking.

The pooled CRR for all patients (i.e. all sonic Hh inhibitors) obtained using fixed-effect linear models was 23.5% (95% CI: 4.3% to 42.8%). The sensitivity analysis using Bayesian models with random effect produced an ORR of 23.2% (95% CI: 3.3% to 42.5%). The pooled CRR by treatment was estimated to be 28.0% (95% CI: 6.3% to 49.7%) for vismodegib and 8.9% (95% CI: -39.0% to 56.7%) for sonidegib. CRR for the subgroup analysis of patients with laBCC was 30.9% (95% CI: 6.9% to 55.0%) for vismodegib and was 3.0% (95% CI not available) for sonidegib (treatment difference P < 0.0001, Fischer's exact test). For patients with mBCC, CRR was 3.3% (95% CI: -38.0% to 44.6%) for vismodegib and 0% (95% CI not available) for sonidegib (treatment difference P value not reported). Publication bias assessed using trim-and-fill indicated that no study was missing.

The pooled CBR for all patients (i.e. all sonic Hh inhibitors) was 94.9% (95% CI: 74.4% to 115.4%). The pooled CBR by treatment was estimated to ve 93.9% (95% CI: 70.8% to 116.9%) for vismodegib and 98.7% (95% CI: 50.9% to 146.6%) for sonidegib. CBR for the subgroup analysis of patients with laBCC was 94.9% (95% CI: 69.0% to 120.9%) for vismodegib and was 98.8% (95% CI not available) for sonidegib (treatment difference P value not reported). For patients with mBCC, CBR was 88.8% (95% CI: 53.7% to 130.0%) for vismodegib and was 97.1% (95% CI not available) for sonidegib (treatment difference P value not reported). No results were presented for the sensitivity analysis using Bayesian models or for results from a publication bias assessment.[13]

Table 44: Efficacy of sonic Hh inhibitors molecules for all patients, laBCC patients, and mBCC patients

	All Patients			laBCC Patients			mBCC Patients		
Sonic Hh inhibitors	**ORR, % (95 % CI)**	**CRR, % (95 % CI)**	**CBR, % (95 % CI)**	**ORR, % (95 % CI)**	**CRR, % (95 % CI)**	**CBR, % (95 % CI)**	**ORR, % (95 % CI)**	**CRR, % (95 % CI)**	**CBR, % (95 % CI)**
Pooled sonic Hh inhibitors	59.6 (40.3 to 78.9)	23.5 (4.3 to 42.8)	94.9 (74.4 to 115.4)	-	-	-	-	-	-
Vismodegib	61.9 (40.2 to 83.6)	28.0 (6.3 to 49.7)	93.9 (70.8 to 116.9)	68.7 (44.7 to 92.8)	30.9 (6.9 to 55.0)	94.9 (69.0 to 120.9)	39.4 (-1.9 to 80.6)	3.3 (-38.0 to 44.6)	88.8 (53.7 to 130.0)
Sonidegib	55.2 (7.4 to 103.0)	8.9 (-39.0 to 56.7)	98.7 (50.9 to 146.6)	56.6 (NA)	3.0 (NA)	98.8 (NA)	14.7 (NA)	0 (NA)	97.1 (NA)

CBR = clinical benefit rate; CI = confidence interval; CRR = complete response rate; Hh = hedgehog inhibitors; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; NA = not applicable; ORR = overall response rate

Notes:

Per base analysis with frequentist fixed-effect models.

Reprinted from J Am Acad Dermatol, 79(6), Xie P & Lefrançois P, efficacy, safety, and comparison of sonic hedgehog inhibitors in basal cell carcinomas: a systematic review and meta-analysis, 1089-1100, Copyright 2018, with permission from Elsevier[13]

b) Safety results

The most commonly reported AEs and the corresponding pooled prevalence (i.e. all sonic Hh inhibitors) were muscle spasms (67.1%, 95% CI: 49.6% to 84.6%), dysgeusia (54.1%, 95% CI: 36.6% to 71.6%), alopecia (57.7%, 95% CI: 39.8% to 75.5%), weight loss (32.2%, 95% CI: 13.2% to 51.2%), fatigue (25.9%, 95% CI: 7.1% to 44.7%), and nausea (24.2%, 95% CI: 5.0% to 43.5%).

An absolute difference in AE prevalence ± 10% of sonidegib compared with vismodegib was demonstrated (reported as vismodegib versus sonidegib) for the following: nausea (21.2% versus 39.2%) and myalgias (9.6% versus 22.2%).[13] Of note, amenorrhea and SCC diagnosis were only evaluated for vismodegib.

Critical Appraisal

The published MA was critically appraised according to guidance from the A MeaSurement Tool to Assess systematic Reviews (AMSTAR)-2 tool.[116]

The MA was based on a SLR performed to retrieve all studies involving the treatment of BCC with sonic Hh inhibitors. It was unclear whether the search strategy was comprehensive for multiple reasons; only the names of the four treatments that had been identified from a search of clinicaltrials.gov were included, and the search identified literature only until the end of 2016. Therefore, other potential treatments, and more recent literature may have been missed. No PICOS table was provided to detail the inclusion and exclusion criteria, and details were not provided as to how screening and study quality assessment conflicts (if any) were resolved. Additionally, there was no list of studies excluded at the full-text stage provided, and therefore it was not possible to assess whether potentially eligible studies may have been excluded.

Differences were apparent between the studies in terms of trial design (RCTs, cohort studies, retrospective case series, open-label, non-randomized, phase I or II, etc.), sample size (range of 5 to 499 patients), response criteria assessment (central RECIST, investigator RECIST, histology, clinical, mixed, unknown), and quality of evidence (Oxford Centre for Evidence-based Medicine Grades 2 to 4). The inclusion/exclusion criteria for patients in the studies was not provided, nor were any baseline patient characteristics, limiting the ability to appraise the comparability of the patient populations. Additionally, the definitions of both the efficacy and safety endpoints from the studies were not provided, and therefore it is not possible to determine whether the outcomes were evaluated similarly between the studies.

Several substantial limitations of the methodology of the analyses should be considered. Limited details were provided for how the between-treatment comparisons were performed. No rationale was provided for the selection of fixed-effect or random-effect models, or for the selection of frequentist versus Bayesian models. Random-effect models were used in a sensitivity analysis using Bayesian methodology, however the assumptions about heterogeneity were not discussed. Additionally, the CIs ranged from below 0% to over 100%, which is beyond the range of the outcome variable. The authors did not provide an explanation for this, but the observed uncertainty in the CIs could be related to the methods used to impute the variances for the individual studies.

The authors merged the data from multiple dosing regimens (e.g. 200 mg sonidegib and 800 mg sonidegib, although only 200 mg is currently the approved dose by Health Canada) from the included studies. Combining data from different doses does not allow for the assessment of treatment response for specific doses, of which are approved and/or used in Canada. The methods for pooling single arm studies with studies that had multiple arms were not described. It was not clear which studies contributed data for the subgroup analyses of patients with laBCC or mBCC, however patients in BOLT, ERIVANCE, and STEVIE were not randomized separately based on their BCC-type; therefore the within-study randomization may not have been preserved in the subgroup analyses. Additionally, these analyses appeared to be post-hoc analyses, and may not have been prespecified.

Overall, the numerous limitations identified in this publication lead to a lack of generalizability to the Canadian context for the population of patients with laBCC who are ineligible for curative surgery or radiotherapy. Analyses also included investigational treatments that would not be relevant to this patient population. The efficacy outcomes reported for the laBCC subgroup appeared to be post-hoc analyses, which limit the interpretability of the conclusions. Other relevant efficacy outcomes such as PFS and OS, and outcomes related to HRQoL were not analyzed, and therefore no conclusions can be drawn comparing the treatment for these outcomes.

7.2.3 Summary

In the absence of direct evidence comparing sonidegib with other sonic Hh inhibitors for the treatment of patients with laBCC who are ineligible for curative surgery or radiotherapy, a published MA was identified which aimed to determine and compare the efficacy and safety of sonic Hh inhibitors as a class for treating BCC. The publication included four treatments: sonidegib, vismodegib, itraconazole, and TAK-441. Only sonidegib and vismodegib are approved in Canada for the treatment of patients with laBCC. Numerous critical limitations to the analyses were identified, limiting the generalizability of the results to the Canadian context. The results of the analyses should be interpreted with extreme caution in light of the limitations.

8 Comparison with Other Literature

The CGP identified that patients with mBCC are generally treated similarly to patients with laBCC that are not amendable to radiation therapy or curative surgery, and both the CGP and PAG are seeking evidence on the efficacy of sonidegib for the treatment of patients with mBCC. This section presents the results of the efficacy analyses from the BOLT trial in the mBCC patient subgroup. Safety results for the pooled trial population are presented in Section 6.3.2.2 (Harms Outcomes).

Disease Characteristics in the mBCC Subgroup

The disease characteristics at baseline of patients with mBCC (200 mg sonidegib group: n = 13; 800 mg sonidegib group: n = 23) in the BOLT trial are summarized in Table 45.[8,105] In the 200 mg sonidegib group, 92.3% of patients had received any type of prior antineoplastic therapy indicated for BCC, with 84.6% having received surgery, compared to 100% with any prior therapy in the 800 mg sonidegib group, with 100% having received surgery.[8] Per INV-assessment, the median sum of the longest diameters per MRI or CT was 50.0 mm (min: 23.0 mm; max: 164.0 mm) in the 200 mg sonidegib group and 51.0 mm (min:12.0 mm; max: 502.0 mm) in the 800 mg group, and was 38.5 mm (min: 24.0 mm; max: 121.0 mm) and 50.5 mm (min:16.0 mm; max: 146.0 mm) respectively by IRC-assessment.[105]

Table 45: Characteristics at Baseline in mBCC Patients in the BOLT trial (FAS)

n (%)	200 mg sonidegib (n = 13)	800 mg sonidegib (n = 23)	All (n = 36)
Prior antineoplastic therapy indicated for BCC			
Any therapy	12 (92.3)	23 (100)	35 (97.2)
Surgery	11 (84.6)	23 (100)	34 (94.4)
Radiotherapy	3 (23.1)	4 (17.4)	7 (19.4)
Prior antineoplastic regimens	3 (23.1)	7 (30.4)	10 (27.8)
1 prior regimen	3 (23.1)	6 (26.1)	9 (25.0)
2 prior regimes	0	1 (4.3)	1 (2.8)
Sum of the longest diameters (mm) for mBCC patients per RECIST 1.1 by MRI or CT (per investigator review)			
n	13	23	36
Mean (SD)	76.0 (54.27)	87.0 (100.79)	83.0 (86.16)
Median (min, max)	50.0 (23.0, 164.0)	51.0 (12.0, 502.0)	50.5 (12.0, 502.0)
Sum of the longest diameters (mm) for mBCC patients per RECIST 1.1 by MRI or CT (per central review)			
n	12	20	32
Mean (SD)	53.3 (34.28)	58.2 (33.50)	56.3 (33.32)
Median (min, max)	38.5 (24.0, 121.0)	50.5 (16.0, 146.0)	46.0 (16.0, 146.0)

BCC = basal cell carcinoma; FAS = full analysis set; mBCC = metastatic basal cell carcinoma; SD = standard deviation.

Data Source: Final Clinical Study Report 2018,[105] Health Canada Module 2.7.3[8]

Efficacy Outcomes

Primary Efficacy Outcome: IRC-assessed ORR

Details of the primary efficacy outcome at each of the data cut-offs are presented in Table 46.[8] The IRC-assessed ORR was less than 30% (≥ 30% was considered to be clinically meaningful)[5] for both treatment doses in the mBCC subgroup at each of the analyses. At the time of the primary data cut-off, 15.4% (95% CI: 1.9% to 45.4%) of patients in the 200 mg sonidegib group and 17.4% (95% CI: 5.0% to 38.8%) of patients in the 800 mg sonidegib group had achieved an objective response.[8] No patient in either treatment arms had achieved a CR. Overall, results at the following data cut-offs were consistent with the primary data analysis, with one patient being removed from having achieved an ORR in the 200 mg sonidegib group after the primary data analysis (due to new evidence indicating SD rather than PR). The results of the ORR by INV-assessment demonstrated slightly higher response rates at all the data cut-offs (not displayed).

Secondary Efficacy Outcomes

Detailed results for the secondary efficacy outcomes (ORR, DOR, CRR, TTR, and PFS) evaluated by IRC and by INV at the primary data cut-off and the 42-month data cut-off are summarized in Table 49.[8]

At the primary data cut off and per IRC-assessment, TTR was 4.6 months (95% CI: 1.8 to 7.4) in the 200 mg sonidegib group and 1.0 months (95% CI: 1.0 to 2.1) in the 800 mg sonidegib group.[8] DOR per IRC-assessment was not estimable in the 200 mg sonidegib group and was 8.3 months (95% CI: not estimable) in the 800 mg sonidegib group. PFS per IRC-assessment was 13.1 months (95% CI: 5.6 to 13.1) in the 200 mg sonidegib group and was 7.6 months (95% CI: 6.2 to 11.1) in the 800 mg sonidegib group. As of the 42-month data cut-off and per IRC-assessment, TTR was 9.2 months (95% CI: NE) in the 200 mg sonidegib group and remained at 1.0 months (95% CI: 1.0 to 2.1) in the 800 mg sonidegib group.[8] DOR per IRC-assessment was 24 months (95% CI: NE) estimable in the 200 mg sonidegib group and was not estimable in the 800 mg sonidegib group. PFS per IRC-assessment was 13.1 months (95% CI: 5.6 to 33.1) in the 200 mg sonidegib group and was 11.1 months (95% CI: 7.3 to 16.6) in the 800 mg sonidegib group.

At the time of the primary data cut-off, one (7.7%) patient had died in the 200 mg sonidegib group and two (8.7%) patients had died in the 800 mg group.[8] Median OS was note estimable for either treatment group. As of the 42-month data cut-off, five (38.5%) patients had died in the 200 mg sonidegib group and 11 (47.8%) patients had died in the 800 mg sonidegib group. Median OS was 47.6 months (95% CI: NE) in the 200 mg sonidegib group and was 33.8 months (95% CI: NE) in the 800 mg sonidegib group.

Table 46: Summary of Best Overall Response in mBCC patients per Central Review of the BOLT Trial (pEAS)

	Primary analysis: 28-Jun-2013 data cut-off		12-month analysis: 31-Dec-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off		30-month analysis: 10-Jul-2015 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
	200 mg sonidegib (n=13)	800 mg sonidegib (n=23)	200 mg sonidegib (n=13)	800 mg sonidegib (n=23)	200 mg sonidegib (n=13)	800 mg sonidegib (n=23)	200 mg sonidegib (n=13)	800 mg sonidegib (n=23)	200 mg sonidegib (n=13)	800 mg sonidegib (n=23)
ORR										
n (%)	2 (15.4)	4 (17.4)	1[a] (7.7)	4 (17.4)	1 (7.7)	4 (17.4)	1 (7.7)	4 (17.4)	1 (7.7)	4 (17.4)
95% CI	1.9 to 45.4	5.0 to 38.8	0.2 to 36.0	5.0 to 38.8	0.2 to 36.0	5.0 to 38.8	0.2 to 36.0	5.0 to 38.8	0.2 to 36.0	5.0 to 38.8
Difference, % (95% CI)	2.0 (-28.76 to 27.53)		9.7 (-19.96 to 33.15)		9.7 (-19.96 to 33.15)		9.7 (-19.96 to 33.15)		9.7 (-19.96 to 33.15)	
BOR										
CR, n (%, 95% CI)	0 (0.0 to 24.7)	0 (0.0 to 14.8)	0 (0.0 to 24.7)	0 (0.0 to 14.8)	0 (0.0 to 24.7)	0 (0.0 to 14.8)	0 (0.0 to 24.7)	0 (0.0 to 14.8)	0 (0.0 to 24.7)	0 (0.0 to 14.8)
PR, n (%)	2 (15.4)	4 (17.4)	1[a] (7.7)	4 (17.4)	1 (7.7)	4 (17.4)	1 (7.7)	4 (17.4)	1 (7.7)	4 (17.4)
SD, n (%)	10 (76.9)	15 (65.2)	11 (84.6)	17 (73.9)	11 (84.6)	17 (73.9)	11 (84.6)	17 (73.9)	11 (84.6)	17 (73.9)
PD, n (%)	0 (0.0)	1 (4.3)	0 (0.0)	1 (4.3)	0 (0.0)	1 (4.3)	0 (0.0)	1 (4.3)	0 (0.0)	1 (4.3)
Unknown, n (%)	1 (7.7)	3 (13.0)	1 (7.7)	1 (4.3)	1 (7.7)	1 (4.3)	1 (7.7)	1 (4.3)	1 (7.7)	1 (4.3)

BOR = best overall response; CI = confidence interval; CR = complete response; mBCC = metastatic basal cell carcinoma; NR = not reached; ORR = overall response rate; OS = overall survival; pEAS = primary efficacy analysis set; PD = progressive disease; PR = partial response; SD = stable disease.

Notes:

[a] Best overall response for one patient was changed from PR to SD for the 12-month analysis during central re-review due to new evidence (new lesion identified in the photo image) that was received after the 28-Jun-2013 cut-off for the primary analysis.

Data Source: Health Canada Module 2.7.3[8]

Table 47: Summary of the Secondary Efficacy Outcomes for the Primary Data Cut-off and the 42-month data cut-off of the BOLT Trial

Efficacy Outcome	Primary analysis: 28-Jun-2013 data cut-off		42-month analysis: 08-Jul-2016 data cut-off	
	200 mg sonidegib (n=13)	800 mg sonidegib (n=23)	200 mg sonidegib (n=13)	800 mg sonidegib (n=23)
TTR [a]				
Central review: months (95% CI) Investigator review: months (95% CI)	4.6 (1.8 to 7.4)	1.0 (1.0 to 2.1)	9.2 (NE)	1.0 (1.0 to 2.1)
DOR [a]				
Central review: Number of events, n Duration, months (95% CI) EFS probability at 9 months, % (95% CI) Investigator review: Number of events, n Duration, months (95% CI) EFS probability at 9 months, % (95% CI)	 0 NE 100.0 (NE) 0 NE 100.0 (NE)	 1 8.3 (NE) 0 (NE) 1 10.2 (NE) 100.0 (NE)	 1 24.0 (NE) 100.0 (NE) 2 18.1 (17.7 to 18.4) 100.0 (NE)	 1 NE 50.0 (0.6 to 91.0) 4 10.2 (NE) 66.7 (19.5 to 90.4)
PFS [a]				
Central review: Number of events, n Duration, months (95% CI) EFS probability at 12 months, % (95% CI) Investigator review: Number of events, n Duration, months (95% CI) EFS probability at 12 months, % (95% CI)	 4 13.1 (5.6 to 13.1) 64.9 (24.9 to 87.4)	 10 7.6 (6.2 to 11.1) 15.7 (1.0 to 47.7)	 8 13.1 (5.6 to 33.1) 58.9 (23.4 to 82.5)	 13 11.1 (7.3 to 16.6) 42.3 (17.7 to 65.1)
OS [b]				
Number of patients who died, n (%) Number of patients censored, n (%) Median OS, months (95% CI) Rate at 12 months, % (95% CI)	1 (7.7) 12 (92.3) NE 87.5 (38.7 to 98.1)	2 (8.7) 21 (91.3) NE 91.3 (69.5 to 97.8)	5 (38.5) 8 (61.5) 47.6 (NE) 90.9 (50.8 to 98.7)	11 (47.8) 12 (52.2) 33.8 (NE) 91.3 (69.5 to 97.8)

CI = confidence interval; CR = complete response; EFS = event-free survival NE = not estimable; OS = overall survival; pEAS = primary efficacy analysis set; PFS = progression-free survival; PR = partial response; TTR = time-to-tumour response.

Notes:

[a] Evaluated in the pEAS

[b] Evaluated in the FAS

Data Source: Health Canada Module 2.7.3[8]

Critical Appraisal Summary

As noted in section 6.3.2.1 Detailed Trial Characteristics, under e) Critical Appraisal: Limitations and Potential Sources of Bias, the BOLT trial was subject to a number of limitations. The CADTH Methods Team identified the following limitations and potential sources of bias that should be considered when interpreting the trial results:

- The targeted sample size for the trial was calculated by using decision operating characteristics for the primary endpoint. The sample size calculation was for both the laBCC and the mBCC patients combined (i.e. it wasn't calculated for laBCC and mBCC individually). The mBCC subgroup included a small sample size (200 mg sonidegib group, n = 13; 800 mg sonidegib group, n = 23). The efficacy results for the mBCC patients may be a spurious result as the sample size was not calculated specifically for

this subgroup. Additionally, the recommended dose of sonidegib is 200 mg, however 800 mg was hypothesized to be the more efficacious dose without compromising safety during the design of the study; thus, results for are based on a subgroup of full trial by dose and disease type (200 mg mBCC subgroup). The mBCC 200 mg dose subgroup was not the main consideration in the overall trial sample size calculation; and thus, the results could have been a spurious finding.

- The BOLT trial did not include a comparator. All participants and investigators were aware that the patient was receiving an active treatment, potentially biasing the results of the outcome assessments. At the time of implementation of the study, no established systemic treatments were available for patients with laBCC or mBCC, however preliminary results from a phase I study demonstrated encouraging efficacy data.[3] The trial therefore included two study groups evaluating two doses of sonidegib. No comparisons were made to placebo or to an active control arm. The currently funded treatment for patients with mBCC is vismodegib. The comparative effectiveness of sonidegib to vismodegib was not assessed in these studies. No ITCs were examined for the mBCC subgroup comparing these treatments.
- For the analysis of PFS, patients receiving any other anti-cancer therapy were censored, and this outcome was not treated as an event. As per the FDA, this is considered a biased censoring rule, and generally starting another treatment before PD should be considered as an event. Therefore, the PFS results may have been inflated.
- As of the 42-month data cut-off, Median OS was 47.6 months (95% CI: NE) in the 200 mg sonidegib group and was 33.8 months (95% CI: NE) in the 800 mg sonidegib group.[8] Survival data could be confounded by the use of post-trial treatments. In the overall population (both laBCC and mBCC) Protocol deviations for survival information not provided for 33 (41.8%) patients in the 200 mg sonidegib group and 46 (30.5%) patients in the 800 mg sonidegib group.[105] Therefore, survival estimates may be over estimated due to the high proportion of censoring for missing survival information, introducing considerable uncertainty in the reported OS results. Additionally, as per the CGP, patients in this setting typically have competing morbidities that affect survival, however data on patient comorbidities was not reported. Thus, the impact of comorbid conditions, which are often seen in this patient population, on OS remains unknown.

Conclusions

The subgroup analysis of the mBCC population suggested that IRC-assessed ORR was not clinically meaningful because it was lower than the ORR for overall trial population and that for the laBCC subgroup. The lower bound of the 95% CI was below the clinically meaningful threshold. However, this was a subgroup analysis that was limited by a very small size, and thus the reported results are uncertain. The CGP do not expect sonidegib to perform differently in mBCC patients when compared to vismodegib since the mechanism of action for both drugs is similar.

9 About this Document

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

CADTH 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 Procedures for the CADTH pan-Canadian Oncology Drug Review. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Initial Clinical Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Clinical Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Clinical Guidance Report will supersede this Initial Clinical Guidance Report.

Appendix 1: Literature Search Strategy and Detailed Methodology

Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** May 2020**, Embase** 1974 to 2020 June 24**, Ovid MEDLINE(R) ALL** 1946 to June 24, 2020

Search strategy:

#	Searches	Results
1	(sonidegib* or Odomzo* or Odomozo* or Odomo* or erismodegib* or LDE-225 or LDE225 or NVPLDE225 or 0RLU3VTK5M).ti,ab,ot,kf,kw,hw,nm,rn.	1165
2	1 use cctr	81
3	1 use medall	209
4	*sonidegib/ or (sonidegib* or Odomzo* or Odomozo* or Odomo* or erismodegib* or LDE-225 or LDE225 or NVPLDE225).ti,ab,kw,dq.	736
5	4 use oemezd	464
6	(conference review or conference abstract).pt.	3843476
7	5 not 6	254
8	3 or 7	463
9	limit 8 to english language	449
10	2 or 9	530
11	remove duplicates from 10	331
12	5 and 6	210
13	limit 12 to english language	210
14	limit 13 to yr="2015 -Current"	127
15	11 or 14	458

Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#3	Search (publisher[sb]) AND (sonidegib [Supplementary Concept] OR 0RLU3VTK5M[rn] OR sonidegib*[tiab] OR Odomzo*[tiab] OR Odomozo*[tiab] OR Odomo*[tiab] OR erismodegib*[tiab] OR LDE-225[tiab] OR LDE225[tiab] OR NVPLDE225[tiab]) Filters: English	8
#2	Search publisher[sb]	406,452
#1	Search sonidegib [Supplementary Concept] OR 0RLU3VTK5M[rn] OR sonidegib*[tiab] OR Odomzo*[tiab] OR Odomozo*[tiab] OR Odomo*[tiab] OR erismodegib*[tiab] OR LDE-225[tiab] OR LDE225[tiab] OR NVPLDE225[tiab]	207

Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

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

The European Clinical Trial Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Search: Odomzo/sonidegib, basal-cell carcinoma

Select international agencies including:

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

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

Search: Odomzo/sonidegib, basal-cell carcinoma

Conference abstracts:

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

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

Search: Odomzo/sonidegib, basal-cell carcinoma — last five years

Literature Search Methods

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[117]

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) 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 concept was Odomzo (sonidegib).

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of January 20, 2021.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[118] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry,

Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials, and the European Clinical Trials Registry), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. As well, the sponsor of the drug was contacted for additional information, as required by the CADTH Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the CADTH Methods Team made the final selection of studies to be included in the review.

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

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the CGP and other members of the CADTH Review Team. Additional limitations and sources of bias were identified by the CADTH Review Team.

Data Analysis

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

Writing of the Review Report

This report was written by the Methods Team, the CGP and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH CGP provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

References

1. Odomzo (sonidegib): 200 mg oral capsules [product monograph]. Brampton (ON): Sun Pharma Canada Inc; 2020 Jun 11.
2. Migden MR, Guminski A, Gutzmer R, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. *Lancet Oncol.* 2015;16(6):716-728.
3. Common technical document. Section 2.5: clinical overview [internal sponsor's report]. In: pCODR sponsor submission: Odomzo (sonidegib), 200 mg oral capsules. Brampton (ON): Sun Pharma Canada Inc; 2020 Jun 15.
4. McDowell A, Yi T, Opio S, Castro H, Zhou J, Sellami D. Protocol CLDE225A2201: A phase II, randomized double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma [internal sponsor's report]. In: pCODR sponsor submission: Odomzo (sonidegib), 200 mg oral capsules. Brampton (ON): Sun Pharma Canada Inc; 2020 Jun 15. 2016.
5. Odomzo: EPAR - Public assessment report. Amsterdam (NL): European Medicines Agency; 2015 Jun 25: https://www.ema.europa.eu/en/documents/assessment-report/odomzo-epar-public-assessment-report_en.pdf. Accessed 2020 Jul 17.
6. Hou X, Rokohl AC, Ortmann M, Heindl LM. Effective treatment of locally advanced periocular basal cell carcinoma with oral Hedgehog pathway inhibitor? *Graefes Arch Clin Exp Ophthalmol.* 2020;258(10):2335-2337.
7. Additional information provided by Sun Pharma Canada. 2020 Aug 20.
8. Common technical document. Section 2.7.3: summary of clinical efficacy [internal sponsor's report]. In: pCODR sponsor submission: Odomzo (sonidegib), 200 mg oral capsules. Brampton (ON): Sun Pharma Canada Inc; 2020 Jun 15.
9. Clinical study report CLDE225A2201: A phase II, randomized, double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma (BOLT): primary 6-month analysis [internal sponsor's report]. In: pCODR sponsor submission additional information: Odomzo (sonidegib), 200 mg oral capsules. Brampton (ON): Sun Pharma Canada Inc; 2020 Jun 15.
10. Additional information provided by Sun Pharma Canada. 2020 Oct 22.
11. Common technical document. Section 2.7.4: summary of clinical safety [internal sponsor's report]. In: pCODR sponsor submission: Odomzo (sonidegib), 200 mg oral capsules. Brampton (ON): Sun Pharma Canada Inc; 2020 Jun 15.
12. Odom D, Mladsi D, Purser M, et al. A matching-adjusted indirect comparison of sonidegib and vismodegib in advanced basal cell carcinoma. *J Skin Cancer.* 2017:6121760.
13. Xie P, Lefrancois P. Efficacy, safety, and comparison of sonic Hedgehog inhibitors in basal cell carcinomas: a systematic review and meta-analysis. *J Am Acad Dermatol.* 2018;79(6):1089-1100.e1017.
14. Melanoma: deadliest type of skin cancer is on the rise. Toronto (ON): Canadian Cancer Society; 2014 May 28: https://www.cancer.ca/en/about-us/for-media/media-releases/national/2014/2014-canadian-cancer-statistics/?region=on. Accessed 2020 Nov 19.
15. Guenther LC, Barber K, Searles GE, Lynde CW, Janiszewski P, Ashkenas J. Non-melanoma skin cancer in Canada Chapter 1: Introduction to the guidelines. *J Cutan Med Surg.* 2015;19(3):205-215.
16. Wong CS, Strange RC, Lear JT. Basal cell carcinoma. *BMJ.* 2003;327(7418):794-798.
17. Sartore L, Lancerotto L, Salmaso M, et al. Facial basal cell carcinoma: analysis of recurrence and follow-up strategies. *Oncol Rep.* 2011;26(6):1423-1429.
18. Mohan SV, Chang ALS. Advanced basal cell carcinoma: epidemiology and therapeutic innovations. *Curr Dermatol Rep.* 2014;3(1):40-45.
19. Zloty D, Guenther LC, Sapijaszko M, et al. Non-melanoma skin cancer in Canada Chapter 4: Management of basal cell carcinoma. *J Cutan Med Surg.* 2015;19(3):239-248.
20. Puig S, Berrocal A. Management of high-risk and advanced basal cell carcinoma. *Clin Transl Oncol.* 2015;17(7):497-503.
21. Hamid O, Goldenberg G. Identifying patients at risk for recurrent or advanced BCC. *J Drugs Dermatol.* 2013;12(11):1246-1252; quiz 1253-1244.
22. Bichakjian CK, Olencki T, Aasi SZ, et al. Basal cell skin cancer, version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2016;14(5):574-597.
23. Lear JT, Corner C, Dziewulski P, et al. Challenges and new horizons in the management of advanced basal cell carcinoma: a UK perspective. *Br J Cancer.* 2014;111(8):1476-1481.
24. Moeholt K, Aagaard H, Pfeiffer P, Hansen O. Platinum-based cytotoxic therapy in basal cell carcinoma--a review of the literature. *Acta Oncol.* 1996;35(6):677-682.
25. Ganti AK, Kessinger A. Systemic therapy for disseminated basal cell carcinoma: an uncommon manifestation of a common cancer. *Cancer Treat Rev.* 2011;37(6):440-443.
26. Fecher LA, Sharfman WH. Advanced basal cell carcinoma, the Hedgehog pathway, and treatment options - role of smoothened inhibitors. *Biologics.* 2015;9:129-140.
27. Scales SJ, de Sauvage FJ. Mechanisms of Hedgehog pathway activation in cancer and implications for therapy. *Trends Pharmacol Sci.* 2009;30(6):303-312.

28. Epstein EH. Basal cell carcinomas: attack of the Hedgehog. *Nat Rev Cancer.* 2008;8(10):743-754.
29. PrErivedge® (vismodegib): 150 mg capsules [product monograph]. Mississauga (ON): Hoffmann-La Roche; 2020 May 11: https://www.rochecanada.com/PMs/Erivedge/Erivedge_PM_E.pdf. Accessed 2020 Nov 19.
30. pCODR Expert Review Committee (pERC) final recommendation for: vismodegib (Erivedge) for basal cell carcinoma. *Sponsor: Hoffmann La Roche*. Ottawa (ON): CADTH; 2014 Jan 10: https://www.cadth.ca/sites/default/files/pcodr/pcodr-erivedge-bcc-fn-rec.pdf. Accessed 2020 Nov 19.
31. PrOdomzo® (sonidegib): 200 mg sonidegib (as phosphate) oral capsules [product monograph]. Sharjah (AE): Sun Pharma Global FZE; 2020 Jun 11: https://www.sunpharma.com/sites/default/files/files/OdomzoPM-en-clean_11jun2020.pdf. Accessed 2020 Nov 19.
32. Clinical study report: CLDE225A2201. A phase II, randomized, double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma (BOLT): 42-month analysis [internal sponsor's report]. In: pCODR sponsor submission additional information: Odomzo (sonidegib), 200 mg oral capsules. Brampton (ON): Sun Pharma Canada Inc; 2020 Jun 15.
33. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol.* 2010;146(3):283-287.
34. Christenson LJ, Borrowman TA, Vachon CM, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. *JAMA.* 2005;294(6):681-690.
35. Erba P, Farhadi J, Wettstein R, Arnold A, Harr T, Pierer G. Morphoeic basal cell carcinoma of the face. *Scand J Plast Reconstr Surg Hand Surg.* 2007;41(4):184-188.
36. Niazi ZB, Lamberty BG. Perineural infiltration in basal cell carcinomas. *Br J Plast Surg.* 1993;46(2):156-157.
37. Leibovitch I, McNab A, Sullivan T, Davis G, Selva D. Orbital invasion by periocular basal cell carcinoma. *Ophthalmology.* 2005;112(4):717-723.
38. Ting PT, Kasper R, Arlette JP. Metastatic basal cell carcinoma: report of two cases and literature review. *J Cutan Med Surg.* 2005;9(1):10-15.
39. Spiller WF, Spiller RF. Treatment of basal cell epithelioma by curettage and electrodesiccation. *J Am Acad Dermatol.* 1984;11(5 Pt 1):808-814.
40. Bart RS, Schrager D, Kopf AW, Bromberg J, Dubin N. Scalpel excision of basal cell carcinomas. *Arch Dermatol.* 1978;114(5):739-742.
41. Thissen MR, Neumann MH, Schouten LJ. A systematic review of treatment modalities for primary basal cell carcinomas. *Arch Dermatol.* 1999;135(10):1177-1183.
42. Robinson JK. Use of a combination of chemotherapy and radiation therapy in the management of advanced basal cell carcinoma of the head and neck. *J Am Acad Dermatol.* 1987;17(5):770-774.
43. Farmer ER, Helwig EB. Metastatic basal cell carcinoma: a clinicopathologic study of seventeen cases. *Cancer.* 1980;46(4):748-757.
44. Gailani MR, Bale SJ, Leffell DJ, et al. Developmental defects in Gorlin syndrome related to a putative tumor suppressor gene on chromosome 9. *Cell.* 1992;69(1):111-117.
45. Gorlin RJ, Goltz RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome. *N Engl J Med.* 1960;262:908-912.
46. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the Hedgehog pathway in advanced basal-cell carcinoma. *N Engl J Med.* 2009;361(12):1164-1172.
47. Hahn H, Wicking C, Zaphiropoulous PG, et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. *Cell.* 1996;85(6):841-851.
48. Adolphe C, Hetherington R, Ellis T, Wainwright B. Patched1 functions as a gatekeeper by promoting cell cycle progression. *Cancer Res.* 2006;66(4):2081-2088.
49. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med.* 2012;366(23):2171-2179.
50. Basset-Séguin N, Hauschild A, Kunstfeld R, et al. Vismodegib in patients with advanced basal cell carcinoma: primary analysis of STEVIE, an international, open-label trial. *Eur J Cancer.* 2017;86:334-348.
51. Burness CB, Scott LJ. Sonidegib: a review in locally advanced basal cell carcinoma. *Target Oncol.* 2016;11(2):239-246.
52. Casey D, Demko S, Shord S, et al. FDA approval summary: sonidegib for locally advanced basal cell carcinoma. *Clin Cancer Res.* 2017;23(10):2377-2381.
53. Chen L, Aria AB, Silapunt S, Lee HH, Migden MR. Treatment of advanced basal cell carcinoma with sonidegib: perspective from the 30-month update of the BOLT trial. *Fut Oncol.* 2018;14(6):515-525.
54. Chen L, Silapunt S, Migden MR. Sonidegib for the treatment of advanced basal cell carcinoma: a comprehensive review of sonidegib and the BOLT trial with 12-month update. *Fut Oncol.* 2016;12(18):2095-2105.
55. Dummer R, Guminksi A, Gutzmer R, et al. Long-term efficacy and safety of sonidegib in patients with advanced basal cell carcinoma: 42-month analysis of the phase II randomized, double-blind BOLT study. *Br J Dermatol.* 2020;182(6):1369-1378.
56. Dummer R, Guminski A, Gutzmer R, et al. The 12-month analysis from Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT): A phase II, randomized, double-blind study of sonidegib in patients with advanced basal cell carcinoma. *J Am Acad Dermatol.* 2016;75(1):113-125.e115.

57. Lear JT, Migden MR, Lewis KD, et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. *J Eur Acad Dermatol Venereol.* 2018;32(3):372-381.

58. Migden MR, Chang ALS, Dirix L, Stratigos AJ, Lear JT. Emerging trends in the treatment of advanced basal cell carcinoma. *Cancer Treat Rev.* 2018;64:1-10.

59. Ramelyte E, Amann VC, Dummer R. Sonidegib for the treatment of advanced basal cell carcinoma. *Expert Opin Pharmacother.* 2016;17(14):1963-1968.

60. Silapunt S, Chen L, Migden MR. Hedgehog pathway inhibition in advanced basal cell carcinoma: latest evidence and clinical usefulness. *Ther Adv Med Oncol.* 2016;8(5):375-382.

61. Villani A, Fabbrocini G, Costa C, Scalvenzi M. Sonidegib: safety and efficacy in treatment of advanced basal cell carcinoma. *Dermatol Ther.* 2020;10(3):401-412.

62. Wahid M, Jawed A, Dar SA, Mandal RK, Haque S. Differential pharmacology and clinical utility of sonidegib in advanced basal cell carcinoma. *Onco Targets Ther.* 2017;10:515-520.

63. Chang ALS, Dummer R, Guminski A, et al. Randomized, double-blind study of sonidegib (LDE225) in patients with advanced basal cell carcinoma [abstract]. *J Clin Aesthet Dermatol.* 2015;8(5 Suppl 1):S9-S10.

64. Kudchadkar R, Dummer R, Gutzmer R, et al. Patient-reported quality of life (QoL) with sonidegib (LDE225) in advanced basal cell carcinoma [abstract]. *J Clin Aesthet Dermatol.* 2015;8(5 Suppl 1):S10.

65. Chen L, Aria A, Silapunt S, Migden M. The use of Hedgehog pathway inhibitors for locally advanced and metastatic basal cell carcinoma [abstract]. *J Am Acad Dermatol.* 2018;79(3 Suppl 1):AB294.

66. Combemale P, Dummer R, Migden M, et al. Efficacy of sonidegib in patients with locally advanced basal cell carcinoma (laBCC) by tumor burden [abstract]. *J Am Acad Dermatol.* 2016;1):AB197.

67. Dummer R. Sonidegib preplanned subgroups analyses of objective response rates: Final 42-month results from the BOLT study [abstract]. *Ann Oncol.* 2018;29(Suppl 8):viii462.

68. Dummer R, Lear JT. Clinical impact of muscle-related adverse events in patients receiving sonidegib: 42-Month BOLT results [abstract]. *J Am Acad Dermatol.* 2019;81(4 Suppl 1):AB32.

69. Dummer R, Migden M. Long-term effects of sonidegib on tumor burden: 30-month results from the phase 2 randomized bolt trial [abstract]. *Ann Oncol.* 2017;28(Suppl 5):v436.

70. Dummer R, Migden M, Combemale P, et al. BOLT 18-month analysis: efficacy and safety with sonidegib in locally advanced BCC (laBCC) [abstract]. *J Am Acad Dermatol.* 2016;74(5 Suppl 1):AB194.

71. Dummer R, Migden M, Guminski A, et al. Investigator-assessed efficacy and safety of sonidegib in patients with locally advanced basal cell carcinoma and metastatic basal cell carcinoma: results of the BOLT 30-month analysis [abstract]. *Melanoma Res.* 2016;26(Suppl 1):e3.

72. Dummer R, Migden MR, Guminski A, et al. Efficacy and safety of sonidegib in patients (pts) with locally advanced (la) or metastatic (m) basal cell carcinoma (BCC): BOLT 30-month analysis [abstract]. *J Clin Oncol.* 2016;34(Suppl 15).

73. Dummer R, Sondak V, Grichnik J, et al. BOLT 18-month analysis: Efficacy and safety of sonidegib in patients with locally advanced basal cell carcinoma (laBCC) and evaluation of tumor response using 2 sets of composite assessment criteria [abstract]. *Eur J Cancer.* 2015;51(Suppl 3):S683-S684.

74. Dummer R, Sondak VK, Grichnik JM, et al. Composite assessment of treatment response in patients (pts) with locally advanced basal cell carcinoma (laBCC): sonidegib efficacy using two sets of response criteria [abstract]. *J Clin Oncol.* 2015;33(15 Suppl 1).

75. Guminski A. Sonidegib safety at 30 months: results from the phase 2 BOLT trial [abstract]. *Australas J Dermatol.* 2018;59(Suppl 1):68.

76. Guminski A. Quality of life in patients with basal cell carcinoma treated with sonidegib [abstract]. *Australas J Dermatol.* 2018;59(Suppl 1):68.

77. Guminski A. Sonidegib's duration of response: pivotal phase 2 BOLT study over 30 months in patients with locally advanced basal cell carcinoma [abstract]. *Australas J Dermatol.* 2018;59(Suppl 1):31.

78. Guminski A, Stull D, Houghton K, et al. Change in fatigue and correlations with clinical outcome in patients with advanced basal cell carcinoma treated with sonidegib in the BOLT study [abstract]. *Value Health.* 2016;19(3):A159.

79. Lear J, Guminski A, Gutzmer R, et al. Sonidegib safety in patients with locally advanced Basal Cell Carcinoma and efficacy based on tumor aggressiveness [abstract]. *Melanoma Res.* 2016;26(Suppl 1):e72-e73.

80. Lear J, Migden M, Guminski A, et al. Efficacy of sonidegib in patients with aggressive and nonaggressive subtypes of locally advanced basal cell carcinoma [abstract]. *J Am Acad Dermatol.* 2016;74(5 Suppl 1):AB197.

81. Lear JT, Migden M. Sonidegib preplanned subgroup analyses of objective response rates: 30-month results from the BOLT study [abstract]. *J Am Acad Dermatol.* 2018;79(3 Suppl 1):AB267.

82. Lewis KD, Migden MR. Effects of sonidegib dose reduction or delay in locally advanced basal cell carcinoma: 42-month data from BOLT [abstract]. *J Clin Oncol.* 2018;36(15 Suppl 1).

83. Migden M. Sonidegib's duration of response: results from the pivotal phase 2 BOLT study over 30 months in patients with locally advanced basal cell carcinoma [abstract]. *J Eur Acad Dermatol Venereol.* 2017;31(Suppl 3):39.

84. Migden M, Gutzmer R, Guminski A, et al. A 12-month update of BOLT, a phase 2, randomized, double-blind study of sonidegib (LDE225) in patients with locally advanced or metastatic basal cell carcinoma [abstract]. *J Am Acad Dermatol.* 2015;72(5 Suppl 1):AB178.

85. Migden M, Lear J, Guminski A, et al. Quality of life in patients with advanced basal cell carcinoma treated with sonidegib (LDE225) [abstract]. *J Am Acad Dermatol.* 2015;72(5 Suppl 1):AB191.

86. Migden M, Lewis K. 42-month follow-up of sonidegib efficacy and safety in advanced basal cell carcinoma: final analysis from BOLT [abstract]. *Australas J Dermatol.* 2019;60(Suppl 1):64.

87. Migden M, Lewis KD. Long-term results of investigator-assessed efficacy and safety of 200mg dose of sonidegib for locally advanced basal cell carcinoma: 30-month BOLT analysis [abstract]. *J Clin Aesthet Dermatol.* 2018;11(5 Suppl 1):S15.

88. Lewis K, Squittieri N, Migden MR. Efficacy and safety of sonidegib in patients with aggressive and nonaggressive subtypes of locally advanced basal cell carcinoma: long-term 42-month results from the BOLT study [abstract]. *J Am Acad Dermatol.* 2019;81(4 Suppl 1):AB199.

89. Migden MR. Treatment of advanced basal cell carcinoma with sonidegib: duration of response and quality of life evaluation from BOLT [abstract]. *Ann Oncol.* 2018;29(Suppl 8):viii462.

90. Migden MR, Dummer R. Time to tumor response and planned subgroup analyses from the BOLT trial for sonidegib in advanced basal cell carcinoma [abstract]. *J Am Acad Dermatol.* 2018;79(3 Suppl 1):AB297.

91. Migden MR, Dummer R, Guminski A, et al. Sonidegib for patients with advanced basal cell carcinoma: long-term efficacy and safety results in the BOLT 30-month analysis [abstract]. *Pigment Cell Melanoma Res.* 2017;30(1):121.

92. Migden MR, Lewis KD. 42-month follow-up of sonidegib efficacy and safety in advanced basal cell carcinoma: final analysis from BOLT [abstract]. *J Clin Oncol.* 2018;36(15 Suppl 1).

93. Plummer R, Lear J, Gutzmer R, et al. Efficacy following discontinuation of sonidegib treatment in patients with locally advanced basal cell carcinoma (laBCC) [abstract]. *J Am Acad Dermatol.* 2016;74(5 Suppl 1):AB197.

94. Stockfleth E. Sonidegib tolerability across 30-months: results from the phase 2 randomized BOLT trial [abstract]. *J Invest Dermatol.* 2017;137(10 Suppl 2):S285.

95. Stockfleth E. Sonidegib duration of response across 30 months: results from the randomized phase 2 BOLT trial [abstract]. *J Invest Dermatol.* 2017;137(10 Suppl 2):S284.

96. Morton C, Midgen M, Yi T, Mone M, Sellami D, Dummer R. Efficacy of sonidegib in patients with metastatic BCC (mBCC) [abstract]. *J Am Acad Dermatol.* 2016;74(5 Suppl 1):AB198.

97. Khoo AB, Ali FR, Lear JT. Defining locally advanced basal cell carcinoma and integrating smoothened inhibitors into clinical practice. *Curr Opin Oncol.* 2016;28(2):180-184.

98. Dummer R, Ascierto PA, Basset-Seguin N, et al. Sonidegib and vismodegib in the treatment of patients with locally advanced basal cell carcinoma: a joint expert opinion. *J Eur Acad Dermatol Venereol.* 2020;28:28.

99. Odom D, Mladsi DM, Purser M, et al. A matching adjusted indirect comparison of sonidegib and vismodegib in advanced basal cell carcinoma [abstract]. *Value Health.* 2016;19(3):A122.

100. Ali FR, Lear JT. Systemic treatments for basal cell carcinoma (BCC): the advent of dermato-oncology in BCC. *Br J Dermatol.* 2013;169(1):53-57.

101. Jacobsen AA, Aldahan AS, Hughes OB, Shah VV, Strasswimmer J. Hedgehog pathway inhibitor therapy for locally advanced and metastatic basal cell carcinoma: a systematic review and pooled analysis of interventional studies. *JAMA Dermatol.* 2016;152(7):816-824.

102. Dummer R, Lear JT. Practical management of adverse events using dosing strategies for patients receiving sonidegib for advanced basal cell carcinoma [abstract]. *J Am Geriatr Soc.* 2019;67(Suppl 1):S83.

103. Migden M, Lear J, Gutzmer R, et al. Inhibition of the Hedgehog pathway with sonidegib (LDE225) in advanced basal cell carcinoma [abstract]. *J Am Acad Dermatol.* 2015;72(5 Suppl 1):AB186.

104. Novartis Pharmaceuticals. NCT01327053: A phase II study of efficacy and safety in patients with locally advanced or metastatic basal cell carcinoma (BOLT). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2011; Update 2019 Aug 28: https://clinicaltrials.gov/show/NCT01327053. Accessed 2020 Nov 19.

105. Clinical study report LDE225A2201: A phase II, randomized double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma: final [internal sponsor's report]. In: pCODR sponsor submission: Odomzo (sonidegib), 200 mg oral capsules. Brampton (ON): Sun Pharma Canada Inc; 2020 Jun 15.

106. Odomzo® (sonidegib): clinical summary [internal sponsor's report]. Chesterbrook (PA): AmerisourceBergen. 2020. In: pCODR sponsor submission: Odomzo (sonidegib), 200 mg oral capsules. Brampton (ON): Sun Pharma Canada Inc; 2020 Jun 15; 2020.

107. pCODR checkpoint meeting Record of Decision (ROD) responses. 2020 Sep 25.

108. Sonidegib. In: Drugs and Lactation Database (LactMed). Bethesda (MD): U.S. National Library of Medicine; 2006-2018 Dec 3.

109. Additional information provided by Sun Pharma Canada. 2020 Nov 4.

110. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer.* 2012;48(11):1713-1721.

111. Clinical trial endpoints for the approval of cancer drugs and biologics: guidance for industry. Silver Spring (MD): U.S. Food and Drug Administration; 2018 Dec: https://www.fda.gov/media/71195/download. Accessed 2020 Nov 11.

112. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics.* 2010;28(10):935-945.

113. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health.* 2012;15(6):940-947.

114. Phillippo D, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. Sheffield (UK): University of Sheffield; 2016: http://nicedsu.org.uk/wp-content/uploads/2017/05/Population-adjustment-TSD-FINAL.pdf. Accessed 2020 Aug 25.

115. Kim JH. Comparison of the RECIST 1.0 and RECIST 1.1 in patients treated with targeted agents: a pooled analysis and review. *Oncotarget.* 2016;7(12):13680-13687.

116. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.

117. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.

118. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2020 Jun 24.