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Efficacy and Safety of Sonic Hedgehog Inhibitors and PD-1 Inhibitors in Locally Advanced Basal Cell Carcinoma Management: A Systematic Review and Meta-analysis (2013-2023)

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Abstract

The management of advanced basal cell carcinoma (aBCC), in contrast to non-advanced BCC, is often a significant challenge for patients and treating physicians. Nevertheless, sonic Hedgehog inhibitors and, more recently, immune checkpoint inhibitors have offered new hope for improved clinical outcomes. A thorough evaluation of the potential adverse effects of these systemic therapies is also crucial. This review provides detailed information on the clinical efficacy and safety of various regimens of sonic Hedgehog pathway inhibitors and immune checkpoint inhibitors in locally advanced basal cell carcinoma (laBCC) management over the last decade. Our systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We analyzed the data specific to patients with laBCC who received Hedgehog pathway and immune checkpoint inhibitors between 2013 and 2023 and presented the outcomes accordingly. Eleven articles were included in our systematic review, and ten articles were eligible for overall response rate (ORR) and complete response rate (CRR) meta-analysis. ORRs for vismodegib, sonidegib, cemiplimab, and nivolumab were 74%, 50%, 31%, and 17%, respectively. The complete response rate (CRR) was significantly higher for vismodegib at 40%, compared to sonidegib (2%) and cemiplimab (6%). The most common adverse effects of hedgehog pathway inhibitors include muscle spasms, dysgeusia, and alopecia, while cemiplimab is frequently associated with fatigue, diarrhea, and pruritus. The systemic therapies present a promising approach for the management of laBCC; however, their use is often limited by adverse effects. Among available options, vismodegib demonstrates superior ORR and CRR compared to sonidegib and immunotherapy, highlighting its potential as a preferred option.

Keywords**:** *basal cell carcinoma; systematic review; meta-analysis; sonic Hedgehog inhibitors; PD-1 inhibitors*

1. Introduction

Basal cell carcinoma (BCC) is the most common cutaneous cancer in humans, and most are successfully treated with surgery (Bichakjian et al., 2018). It is estimated that 3.6 million cases of BCCs are diagnosed in the United States every year (Skin Cancer Facts & Statistics, n.d.). A descriptive study by Oh et al., (2021) in Singapore concluded that from 1986 to 2016, age-standardized incidence rates for BCC among males and females were 6.1 and 5.5 per 100,000 person-years in the country's Chinese population while 2.1 and 2.2 per 100,000 person-years in Malays, respectively (Oh et al., 2021). The age-specific incidence of skin cancer in male and female patients from 2016 to 2018 was reported at 4.0 and 4.6 per 100,000 person-years in Thailand (Rojanamatin et al., 2021). Most BCCs are curative, especially when diagnosed early. However, due to the lack of early

diagnosis or delay in management, it is noted that approximately 1% to 10% end up with advanced (i.e., locally advanced or metastatic) disease (Sekulic et al., 2022). The term "locally advanced basal cell carcinoma" (laBCC) is used in clinical trials to describe a group of difficult-to-treat BCCs that often need a multidisciplinary team for effective management. The involvement of essential or functionally significant structures (such as the periocular region) and difficulties achieving complete resection are hallmark traits of laBCC. The anatomically based Tumor, Node, Metastasis (TNM) classification system, commonly used for staging cancer, has notable limitations. One key drawback is its inability to incorporate important clinical factors beyond anatomical spread, such as tumor biology or patient characteristics. In the case of basal cell carcinomas (BCCs), this system is particularly inadequate, as regional and distant metastases are rare, making TNM staging less effective for accurately classifying and guiding the management of BCCs (Niebel et al., 2020).

Multiple expert groups have collaborated to define laBCC. One group from the United Kingdom defined laBCCs as tumors with a 2 cm or larger diameter (American Joint Committee on Cancer Staging 8th Edition, stage II or higher) where tumor or patient factors contraindicate surgery. Size, location, quantity, subtype, and the likelihood of a curative course of action are all considered tumor variables. At the same time, age, performance status, treatment preferences, comorbidities, hereditary illnesses, and treatment morbidity affect the patient (Lear et al., 2014). Advanced BCCs have a highly unpredictable disease course and there are few effective treatments available. In patients with lymph node involvement, Mohs micrographic surgery may be used with lymph node dissection to treat laBCC (Weinstock, & Still, 2011). Radiation therapy may be helpful with post-surgery recurrences or with tumors that cannot be operated on (Saelee et al., 2022). Still, its usefulness is constrained by the location of the lesion, prior radiation exposure, and the presence of genetic syndromes like nevoid basal cell carcinoma syndrome (NBCCS) (Fecher, 2013; Weinstock & Still, 2011). Surgery, radiation, hedgehog pathway inhibitors, and immunotherapy are different treatment options for managing laBCC (Niebel et al., 2020; Yenchitsomanus, 2024). Hedgehog pathway inhibitors (HHIs) have a significant role in the management of laBCCs following approval in Europe, Switzerland, Australia, and the US (De Giorgi et al., 2021).

Despite being uncommon, the impact of laBCC can be severe, and management options can often be limited. Numerous clinical trials promising results prompt medical institutes and practitioners to use systemic medications, where indicated, to manage locally advanced basal cell carcinoma (Ketkomol et al., 2024). This study aims to assess the efficacy and safety of Hedgehog inhibitors and programmed cell death-1 (PD-1) inhibitors in treating locally advanced basal cell carcinoma (laBCC). This systematic review and meta-analysis may provide valuable insights into these medications and help inform future treatment policies for laBCC.

2. Objectives

1) To provide detailed information on the clinical efficacy and safety of various doses of Hedgehog pathway inhibitors and immunotherapy in managing locally advanced basal cell carcinoma.

2) To determine the prevalence of each adverse effects associated with each treatment regimen.

3. Materials and Methods

Search Strategy

In February 2024, three databases (Cochrane Library, PubMed, and Google Scholar) were searched to identify all data from 2013 to 2023. The search included all the listed databases, and their advanced search or search engines were used to detail our searches further. Medical subject heading (MeSH) terms searched included "carcinoma, basal cell", "hedgehog proteins", and "cell cycle checkpoints". For each database, the relevant MeSH terms were first searched, identified, and incorporated into the advanced search or search engine. Boolean operators (AND, OR), and field tags [tw] and [tiab] were applied to each keyword to target terms in titles, abstracts, and text words. Search terms included basal cell carcinoma, Hedgehog proteins, Hedgehog inhibitors, immunotherapy, immune checkpoint inhibitors, and specific agents such as vismodegib, sonidegib, cemiplimab, and nivolumab.

The inclusion criteria for studies were as follows: (1) study design: randomized controlled trials, randomized trials, and prospective or retrospective studies evaluating clinical effectiveness, particularly regarding complete and/or overall response rates, were included. Studies investigating locally advanced basal cell carcinoma (laBCC) treated with varying dosages of Hedgehog pathway inhibitors (HHIs) and reporting adverse effects were considered, provided they were published in English, (2)

participants: patients aged 18 years or older with locally advanced cutaneous basal cell carcinoma, regardless of comorbidities, (3) intervention: Hedgehog pathway inhibitors, immune checkpoint inhibitors targeting PD-1, and (4) outcomes: complete and overall response rates, and adverse effects. A revised collaboration tool, Risk of Bias Version 2 (RoB2), was used to assess the risk of bias in randomized controlled clinical trials, and the Newcastle-Ottawa Scale was used for non-randomized controlled trials. The heterogeneity in the data from the included studies was discussed. Meta-analysis and subgroup analyses were presented using figures and tables. The reviewers extracted the data and checked separately before agreeing on the final data for the review and analysis. The data were analyzed using Microsoft Excel 2016 Windows version 16 and Stata Statistical Software version 17.

The analysed data were presented in the two forest plots, representing the overall and complete response rates. Given the advanced nature of the tumors in patients, different disease severity assessments, and lack of randomization or absence of a control group in some studies, these factors were expected to impact the pooling and analysis of the data. The risks of bias, such as selection, performance, attribution, detection, and reporting biases in all included studies, are minimized using quality-assessment tools. Heterogeneity data were assessed to determine the suitability of conducting a meta-analysis. Consistent with the nature of systematic reviews and meta-analyses, the reviewers focused on data from locally advanced BCC specifically to our primary outcomes, i.e., Overall Response Rate (ORR) and Complete Response Rate (CRR). The characteristics of the examined studies are shown in Table 1, and the quality assessments of the included studies are summarized in Table 2(a) and (b).

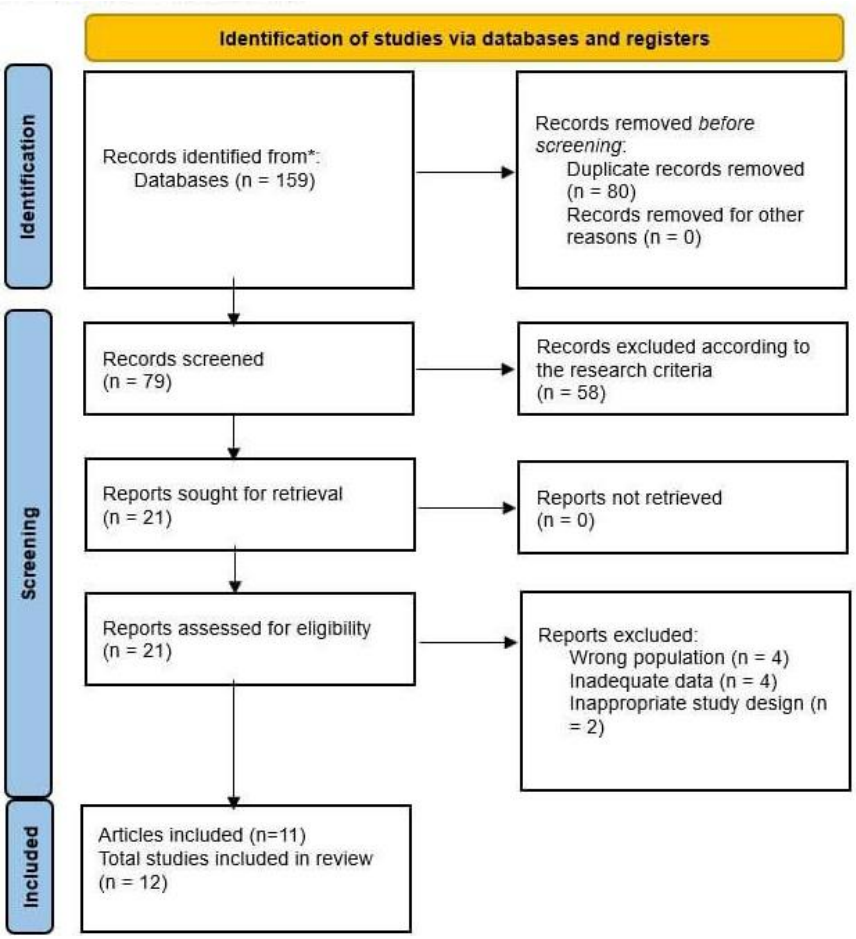


Figure 1 PRISMA flow diagram according to our study criteria

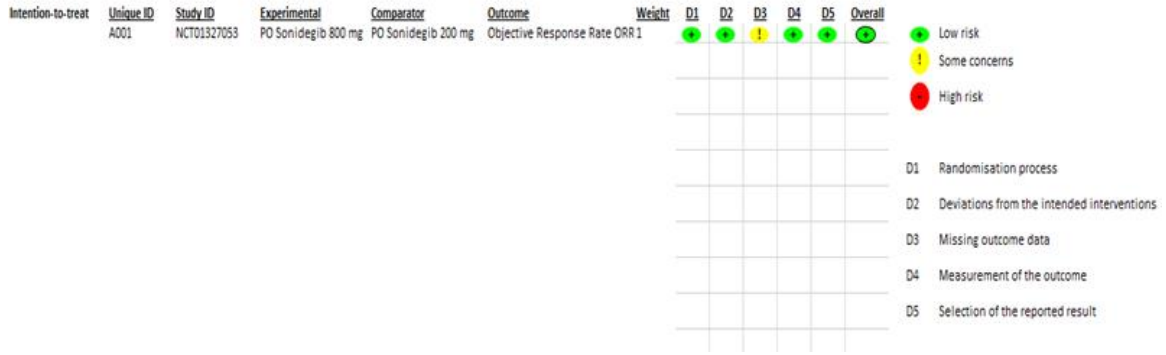
Table 1 Characteristics of the Included Studies

Author	Study Name/Year	Study Design	Patients with laBCC	Median age (mean)	Age group (years)	Intervention	Median duration of intervention (months)	Criteria for treatment response	Median Time to Response (months)	Median duration of response (months)
Sekulic et al., 2022	RegiSONIC 2022	Prospective multi-centre cohort study	115	66	34-99	Vismodegib 150 mg	6.31	Clinical outcome	#N/A	17.5
Bertrand et al., 2021	VISMONEO 2021	Open-label trial	55	73.1	35.5-95.2	Vismodegib 150 mg	6	Investigator RECIST 1.1	#N/A	#N/A
Kahana et al., 2021	VISORB 2021	Prospective phase IV, open-label	34	68.5	48-95	Vismodegib 150 mg	8.6	Investigator RECIST 1.1	#N/A	#N/A
Verkouteren et al., 2017	2021	Retrospective study	44	75.5	36-98	Vismodegib 150 mg	6.4	Clinical & radiographic	#N/A	10.3
Xavier et al., 2021	2021	Retrospective longitudinal	13	71	54-96	Vismodegib 150 mg	10.5	Tumor size	#N/A	13
Dummer et al., 2020	BOLT 2020	Double-blind phase II randomized trial	66 128	67 65	25-92	Sonidegib 200 OD Sonidegib 800 OD	11 6.6	Central modified RECIST	4 3.8	26.1 23.3
Sekulic et al., 2017	ERIVANCE 2017	Prospective multi-centre phase II	63	62	61.4±16.9	Vismodegib 150 mg	12.7	Clinical or radiographic outcome	4.6	26.2
Basset-Séguin et al., 2017	STEVIE 2017	Open-label multi-centre single-arm clinical trial	1077	72	18-101	Vismodegib 150 mg	8.6	RECIST v1.1	3.7	
Danial et al., 2016	NCT01529450/2015	Open-label, intervention trial	5	56	45-91	Sonidegib 800 mg after Vismodegib resistance	1.5	mRECIST v1.1	#N/A	
Stratigos et al., (2021)	NCT03132636/ 2021	an open-label, multi-centre, single-arm, phase 2 trial	84	70	61-79	IV infusion of Cemiplimab 350 mg every 3 week	10.8	RECIST v1.1	4.3	
Véron et al., 2022	NCT03012581/2022	Phase 2, prospective and multicentre basket trial	29	70.5	65-83	IV perfusion of Nivolumab 240 mg Day 1 of every 14-day cycle	8.1	RECIST v1.1	5.3	

IV= intravenous; RECIST = response evaluation criteria in solid tumors; OD= Once daily; N/A, not available

Table 2 Quality Assessment of Included Studies
(a) Quality Assessment Overall Response Rate

	Study Name	Year	Intervention	ORR	Number of laBCC patients	Tools		
						Risk of Bias 2	Newcastle-Ottawa Scales	
1	REGISONIC	2022	Vismodegib	85.10%	115		6*	Fair Quality
2	VISMONEO	2021	Vismodegib	70.90%	55		7*	Good Quality
3	VISORB	2021	Vismodegib	85%	34		7*	Good Quality
4	Xavier et al., 2021	2021	Vismodegib	76.90%	13		6*	Fair Quality
5	ERIVANCE	2017	Vismodegib	60.30%	63		7*	Good Quality
6	STEVIE	2017	Vismodegib	68.50%	1077		6*	Fair Quality
7	BOLT	2020	Sonidegib 200	56%	66			
8	BOLT	2020	Sonidegib 800	46.10%	128			
9	NCT03012581	2022	Nivolumab	17%	29		8*	Good Quality
10	NCT03132636	2021	Cemiplimab	31%	84		6*	Fair Quality



(b) Quality Assessment Complate Response Rate

	Study Name	Year	Intervention	CRR	Number of laBCC patients	Tools		
						Risk of Bias 2	Newcastle-Ottawa Scales	
1	REGISONIC	2022	Vismodegib	63.40%	115		6*	Fair Quality
2	VISMONEO	2021	Vismodegib	25.50%	55		7*	Good Quality
3	VISORB	2021	Vismodegib	56%	34		7*	Good Quality
4	Verkouteren et al., 2017	2021	Vismodegib	33.90%	44		5*	Fair Quality
5	Xavier et al., 2021	2021	Vismodegib	30.80%	13		6*	Fair Quality
6	ERIVANCE	2017	Vismodegib	31.75%	63		7*	Good Quality
7	STEVIE	2017	Vismodegib	33.40%	1077		6*	Fair Quality
8	BOLT	2020	Sonidegib 800	5.00%	66			
9	BOLT	2020	Sonidegib 200	1.60%	128			
10	NCT03132636	2021	Cemiplimab	6%	84		6*	Fair Quality

4. Results and Discussion

4.1 Primary Outcomes: ORR and CRR

For the primary outcome analysis, ten studies (6 on vismodegib, 2 on sonidegib, and 1 each on cemiplimab and nivolumab) were included for the overall response rate (ORR). In comparison, ten studies (7 on vismodegib, 2 on sonidegib, and 1 on cemiplimab) contributed to the complete response rate (CRR).

4.2 Overall Response Rate

The RegiSONIC study (Sekulic et al., 2022) reported that the overall response rate of 85.1% to vismodegib, which was nearly identical to 85% reported in the VISORB Trial by Kahana et al., (2021). Similarly, a retrospective study in a tertiary cancer center in Portugal by Xavier et al., (2021) found that vismodegib brought an overall response rate of 76.90%, and a multi-center phase 2 trial (VISMONEO) from France reported 70.90%

(Bertrand et al., 2021). Moreover, in an international clinical trial, STEVIE (Basset-Séguin et al., 2017), reported an ORR of 68.50%, while the ERIVANCE BCC study (Sekulic et al., 2017) showed it at 60.30%. The BOLT study (Dummer et al., 2020), a phase 2 randomized, double-blind study, reported an ORR of 56% for sonidegib 200 mg and 46.10% for sonidegib 800 mg once daily doses, respectively. In contrast, the ORR was lower in a different category of drugs, specifically PD-1 inhibitors, with 17% for nivolumab (Véron et al., 2022) and 31% for cemiplimab (Stratigos et al., 2021) (Table 3).

Table 3 Overall Response Rates of the Included Studies

	Study Name	Year	Intervention	ORR
1	RegiSONIC	2022	Vismodegib	85.10%
2	VISMONEO	2021	Vismodegib	70.90%
3	VISORB	2021	Vismodegib	85.00%
4	Xavier et al., 2021	2021	Vismodegib	76.90%
5	ERIVENCE	2017	Vismodegib	60.30%
6	STEVIE	2017	Vismodegib	68.50%
7	BOLT	2020	Sonidegib 200	56.00%
8	BOLT	2020	Sonidegib 800	46.10%
9	NCT03012581	2022	Nivolumab	17.00%
10	NCT03132636	2021	Cemiplimab	31.00%

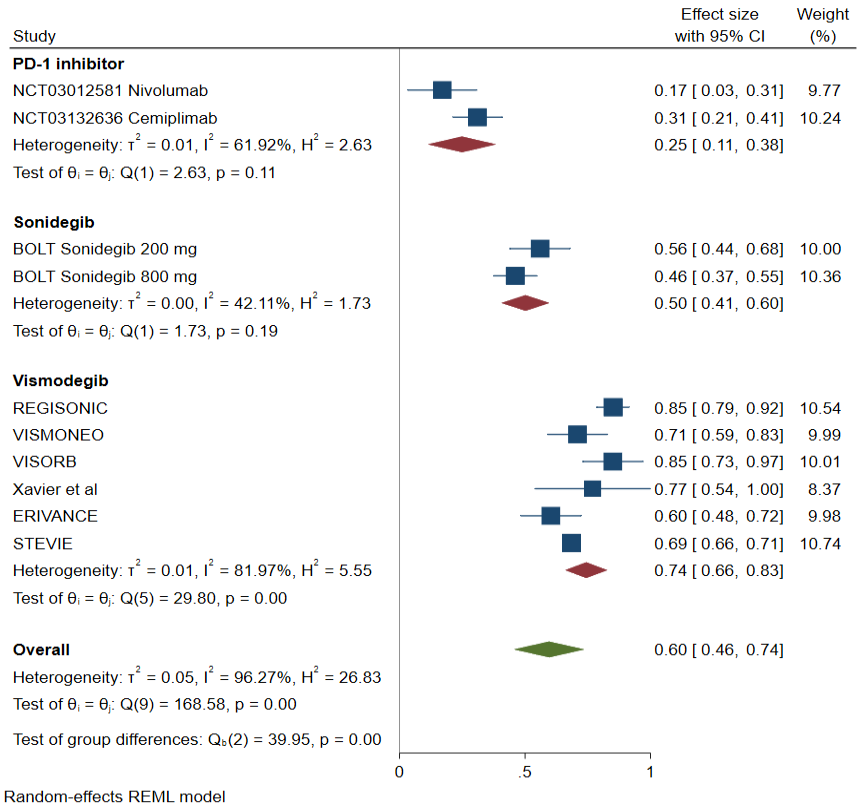


Figure 2 Forest plot representing Meta-analysis of ORR

Note: Forest plots of combined ORR using Random-effects REML model. The estimates for individual studies are represented with blue squares with their 95% CIs; the numerical values are appended to the right side. The estimates and 95% CI for each subgroup are represented with the red diamond and pooled estimate and its 95% CI for the overall effect is presented with the green diamond at the bottom center of the graph; CI, confidence interval; PD-1 inhibitor, programmed cell death 1 inhibition Immunotherapy; REML, restricted-maximum likelihood; RE, random effects, ORR, overall response rate

The meta-analysis result of the overall response rate (ORR) yielded a pooled estimate 0.60 (95% CI, 0.46 – 0.74, forest plot, Figure 2) ($p = 0.161$). Heterogeneity was high, and I^2 was at 96.27%. It implied that the percentage of the variability in effect estimates is due to heterogeneity rather than sampling error (chance). Moreover, the number of studies included was not very small. We selected a random-effects model to account for variability across studies and enhance the validity of the results. The results of subgroup meta-analyses of the PD-1 inhibitors, sonidegib, and vismodegib were found at 0.25 (95% CI, 0.12 – 0.38), at 0.50 (95% CI, 0.41 – 0.60) and 0.74 (95% CI, 0.66 – 0.83) respectively. In the heterogeneity summary, the overall I^2 value across all studies was 96.27%, indicating significant heterogeneity. Substantial heterogeneity was found in the immunotherapy subgroup ($I^2 = 61.92\%$), and the vismodegib subgroup ($I^2 = 81.97\%$). The sonidegib subgroup demonstrated a moderate heterogeneity with an I^2 of 42.11%.

4.3 Complete Response Rate

The RegiSONIC (Sekulic et al., 2022) and VISORB (Kahana et al., 2021) studies reported complete response rates of 63.40% and 56%, respectively. In contrast, five other studies (Bertrand et al., 2021; Verkouteren et al., 2017; Xavier et al., 2021; Sekulic et al., 2017; Basset-Séguin et al., 2017) reported relatively lower complete response rates, ranging from 25.50% to 33.90%. The CRR of sonidegib at both 200 mg and 800 mg doses was lower than that of vismodegib, with rates of 5% and 1.6%, respectively (Dummer et al., 2020). Additionally, a study on cemiplimab, a PD-1 inhibitor, reported a CRR of 6% (Stratigos et al., 2021) (Table 4).

Meta-analysis showed a complete response rate of 0.28 (95% CI, 0.15 – 0.41, forest plot, Figure 3 ($p = 0.0009, < 0.05$), and I^2 was 98.21% for the overall analysis. The significant Q value indicated that the effect sizes among the subgroups likely differed, suggesting that the observed differences between the groups were not due to random chance. The subgroup meta-analysis for immunotherapy could not be conducted, as only one study was available for this group. The meta-analysis of the sonidegib subgroup was not statistically significant, reporting a value of 0.02 (95% CI, 0.00 – 0.05). On the other hand, the meta-analysis for the vismodegib subgroup yielded a significant result with a value of 0.4 (95% CI, 0.28 – 0.5). There was a low heterogeneity in the sonidegib subgroup ($I^2 = 21.12\%$). In contrast, substantial heterogeneity was found in the vismodegib subgroup ($I^2 = 88.33\%$). Therefore, it can be said that the variation among the studies was beyond chance. As part of our systematic review, a small study on sonidegib management in advanced BCC patients with vismodegib resistance (Danial et al., 2016), which was not included in the meta-analysis, was also discussed. Out of 9 patients, 5 were with laBCC. It was noted that 2 of those five laBCC patients saw stable disease although the other three faced progressive disease while on sonidegib treatment. This study (Danial et al., 2016) concluded that, despite some limitations, laBCC patients who are resistant to vismodegib may benefit from treatment with another Smoothened inhibitor.

Table 4 Complete Response Rates of the Included Studies

	Study Name	Year	Intervention	CRR
1	RegiSONIC	2022	Vismodegib	63.40%
2	VISMONEO	2021	Vismodegib	25.50%
3	VISORB	2021	Vismodegib	56.00%
4	Verkouteren et al., 2017	2021	Vismodegib	33.90%
5	Xavier et al., 2021	2021	Vismodegib	30.80%
6	ERIVANCE	2017	Vismodegib	31.75%
7	STEVIE	2017	Vismodegib	33.40%
8	BOLT	2020	Sonidegib 200	5.00%
9	BOLT	2020	Sonidegib 800	1.60%
10	NCT03132636	2021	Cemiplimab	6.00%

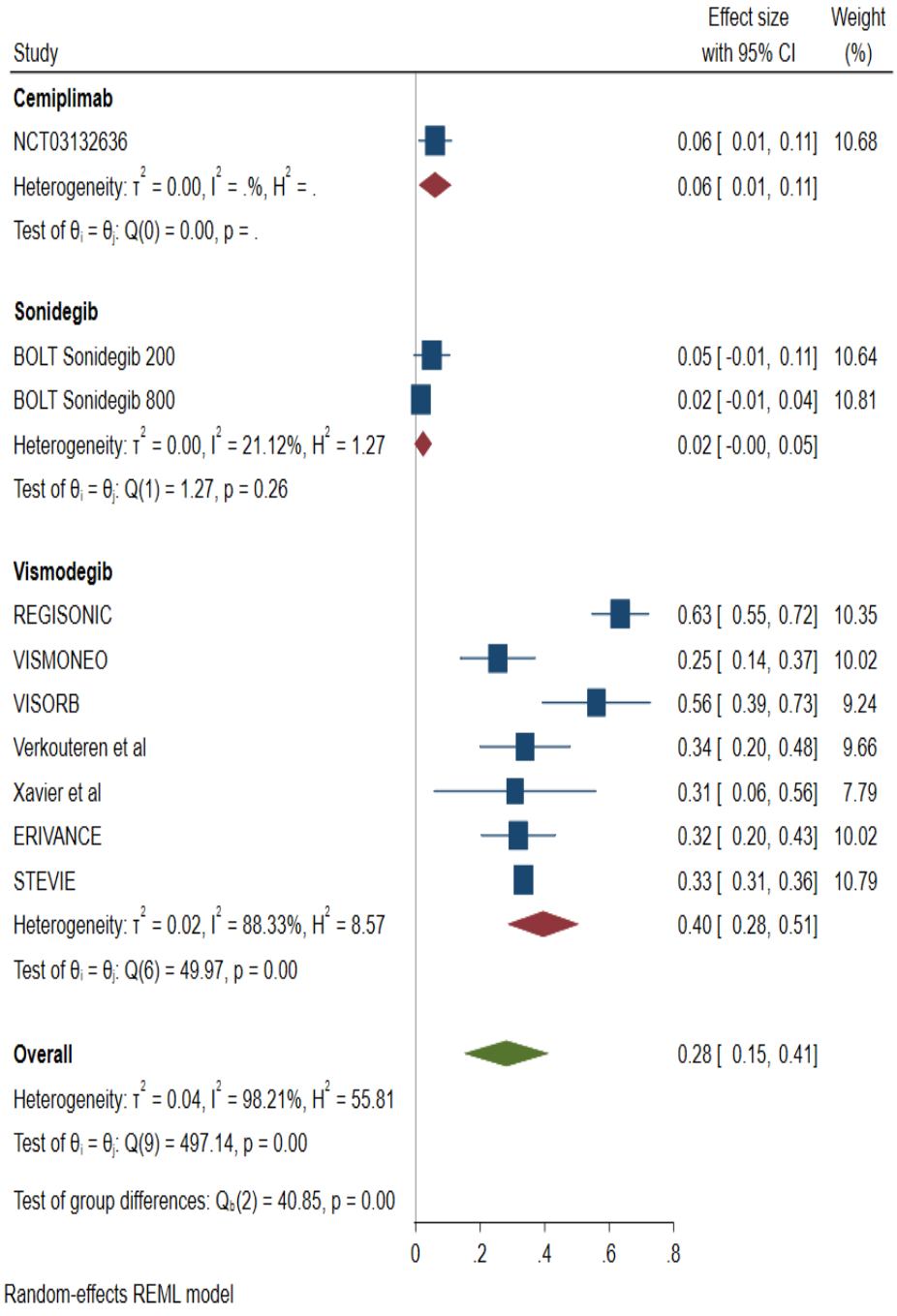


Figure 3 Forest plot representing the meta-analysis of complete response rates (CRR)

Note: The combined CRR was analyzed using a random-effects model with restricted maximum likelihood (REML) estimation. Estimates for individual studies are shown as blue squares with their corresponding 95% confidence intervals (CIs). Numerical values are listed on the right. Subgroup estimates and their 95% CIs are represented by red diamonds, while the pooled overall estimate and its 95% CI are displayed as a green diamond at the bottom center of the plot.

Abbreviations: CI, confidence interval; REML, restricted maximum likelihood; RE, random effects; CRR, complete response rate.

4.4 Secondary Outcome: Prevalence of Adverse Effects

Seven studies were included to analyze the prevalence of adverse effects found in patients with laBCC: four studies on vismodegib, two on sonidegib, and one on cemiplimab, respectively. In addition, combined data from two vismodegib studies and one nivolumab study, which included both locally advanced and metastatic BCC cases, were also analyzed. The common reported adverse effects are summarized in Table 5.

Table 6 summarizes the analyzed prevalence of adverse effects of associated with different medications used in the management of laBCC. The most common adverse effects associated with vismodegib include dysgeusia (66.80%), muscle spasms (63.59%), alopecia (53%), weight loss (22.12%), and fatigue (13.36%). These findings are consistent with those observed in studies of sonidegib at both 200 mg and 800 mg doses. In contrast, the immunotherapy study with cemiplimab reported different common side effects, including fatigue (30%), diarrhea (24%), pruritus (21%), appetite loss (15%), and urinary tract infections (15%). Additionally, adverse effects such as urinary tract infections, diabetes, hypertension, and ischemic heart disease were reported (Table 6). The BOLT Trial (on sonidegib) and NCT03132636 (on cemiplimab) presented laboratory findings related to their treatments. In the BOLT Trial (Dummer et al., 2020), the sonidegib 200 mg group showed increased creatine kinase and serum lipase levels, each with 6%. The 800 mg group exhibited a greater increase in creatine kinase, with an increase of 13.3%. In the other study, NCT03132636 (Stratigos et al., 2021), the cemiplimab treatment was associated with an increase in blood creatinine levels (10%), leukocytosis (8%), hypoalbuminaemia (6%), hypokalaemia (5%), hyponatraemia (4%), and hyperkalaemia (3%).

The two trials on vismodegib, ERIVANCE by Sekulic et al., (2017) and STEVIE by Basset-Séguin et al., (2017) were also analyzed. Since they were reported as combined adverse effects from both laBCC and mBCC groups (Basset-Séguin et al., 2017; Sekulic et al., 2017), the analyses of their data were described here, separately from the above data specific to laBCC. The most common adverse effects include muscle spasms (66.80%), alopecia (61.87%), and dysgeusia (54.66%). Other significant adverse events include weight loss (41.47%), fatigue (25.47%), and anorexia (25.17%). Notably, 30.48% of patients discontinued treatment due to treatment-emergent adverse events (TEAEs). Squamous cell carcinoma (SCC) was reported in 4.78% of cases. Overall, 98.26% of patients with advanced BCC (aBCC) experienced adverse effects during treatment. A study on nivolumab, a PD-1 inhibitor, by Véron et al., (2022) reported adverse effects that are not commonly seen with other medications. It is, thus, worth mentioning here, despite its data being obtained from patients with both laBCC and mBCC. The reported side effects included diabetes mellitus (21.88%), bullous pemphigoid (6.25%), colitis (6.25%), myocardial infarction (3.13%), and lymphopenia (3.13%) (Véron et al., 2022).

4.5 Discussion

Our review found that while systematic medications show promising clinical results, their adverse effects have considerably limited their use. In general, vismodegib exhibited a greater ORR and CRR for laBCC when compared to sonidegib, or immunotherapy, suggesting its potential advantage over other systemic medications in clinical practice. A small study found that patients with BCC resistant to vismodegib do not respond well to sequential therapy with sonidegib (Danial et al., 2016). This lack of response may be attributed to a combination of patient and tumor-related factors. Further research is needed to determine whether advanced basal cell carcinoma that has shown resistance to one hedgehog pathway inhibitor remains susceptible to another hedgehog pathway inhibitor.

Table 5 Prevalence of adverse effects associated with Hedgehog pathway inhibitors (HHIs) in the management of locally advanced BCC

Study Nmae/ Year	Intervention	No. of laBCC patient	Median follow-up (month)	% of AE occurrence	Dysgeusia	Muscle spasm	Alopcia	Weight loss	Fatigue	Nausea	Diarrhoea	Anorexia	Arthralgia	Teeament discontinued due to TEAE	Disease recurrence	Cutaneous SCC reported
RegiSONIC 2022	Vismodegib	115	25.4	90.43%	61.73%	57.39%	50.34%	25.22%	#N/A	#N/A	#N/A	#N/A	#N/A	20.90%	23.80%	12.17%
VISMONEO 2021	Vismodegib	55	#N/A	98.20%	78.00%	73.00%	64.00%	27.00%	38.00%	#N/A	13.00%	13.00%	11.00%	12.72%	36.36%	#N/A
VISORB 2021	Vismodegib	34	6.6	97.00%	74.00%	67.00%	47.00%	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	5.90%	#N/A	#N/A
Xavier et al., 2021	Vismodegib	13	15.9	84.00%	46.20%	69.00%	46.20%	30.76%	61.50%	30.76%	7.70%	30.76%	7.70%	7.68%	#N/A	0.00%
BOLT 2020	Sonidegib 200	66	13.9	43.00%	44.30%	54.40%	49.00%	30.40%	32.90%	39.30%	31.70%	22.80%	#N/A	30.00%	#N/A	#N/A
BOLT 2020	Sonidegib 200	128	13.9	43.00%	60.00%	69.30%	58.00%	58.00%	36.70%	47.40%	24.00%	35.30%	#N/A	40.00%	#N/A	#N/A

Table 6 Prevalence of Adverse Effects in laBCC Management: (a) vismodegib, (b) sonidegib, and (c) cemiplimab

(a) Vismodegib		(b) Sonidegib			(c) Cemiplimab	
Adverse Effects	Prevalence	Adverse Effects	Prevalence		Adverse Effects	Prevalence
			200 mg	800 mg		
Dysgeusia	66.80%	Muscle spasm	54.40%	69.30%	Fatigue	30%
Muscle spasm	63.59%	Dysgeusia	44.30%	60%	Diarrhea	24%
Alopecia	53%	Alopecia	49%	58%	Pruritus	21%
Weight loss	22.12%	Weight loss	30.40%	43.20%	Anorexia	15%
Fatigue	13.36%	Nausea	39.30%	47.40%	UTI	15%
Anorexia	5.07%	Fatigue	32.90%	36.70%	Nausea	14%
Diarrhea	3.69%	Appetite loss	22.80%	35.30%	Arthralgia	13%
Arthralgia	3.23%	Diarrhea	31.70%	24%	Hypothyroidism	10%
Nausea	1.84%				Hypertension	9%
Cutaneous SCC reported	6.45%				Weight loss	8%
					Tumor hemorrhage	8%
Treatment discontinued due to TEAE	15.67%	Discontinued due to AE	30%	40%	BCC reported	7%
Disease recurrence	21.66%	Disease recurrence	Nil	Nil	Colitis	5%
		Treatment-related death	Nil	Nil	Myocardial infarction	1%
					Discontinued treatment due to AE	11%
Overall	93.09%	Overall	43%	64%	Overall	97%

TEAE = treatment-emergent adverse effect; UTI = urinary tract infection; BCC = basal cell carcinoma; Nil = no reported events

Regarding safety, common adverse effects of both vismodegib and sonidegib include dysgeusia, muscle spasms, alopecia, fatigue, weight loss, nausea, appetite loss, and diarrhea. However, a higher number of patients treated with sonidegib reported discontinuing the treatment due to these adverse effects. It is important to note that the treatment groups for advanced BCC receiving PD-1 inhibitors had previously undergone different treatments. Therefore, comparing their clinical effectiveness and safety to HHIs could be controversial. In addition, the patient demographics, stage of tumor, underlying diseases, or comorbidities, adverse effects from past treatments, tolerance to the medication, and so forth should also be considered. Overall, 93.09% of patients with locally advanced basal cell carcinoma (laBCC) treated with vismodegib experienced treatment-emergent adverse effects (TEAEs). Among them, 15.67% discontinued the therapy and 6.45% developed cutaneous squamous cell carcinoma as a secondary malignancy. In comparison, the discontinuation rates for patients on sonidegib were higher, with 30% and 40% stopping treatment at doses of 200 mg and 800 mg, respectively. However, sonidegib was associated with a lower overall incidence of adverse effects in patients with laBCC. We emphasize the point estimate and the 95% confidence interval (CI) displayed in the forest plot when interpreting the overall response rate to systemic medications, notwithstanding the p-value of 0.161 in ORR. The point estimate represents the best available estimate of the treatment effect, while the 95% CI offers a range of plausible values for this effect, providing a more comprehensive understanding of the potential variability in the treatment response. Due to the limited number of clinical trials and available data, there is insufficient evidence to draw definitive conclusions about cemiplimab and nivolumab. However, in general, it can be said that over 90% of patients with cemiplimab reported adverse effects, despite its therapeutic efficacy.

4.6 Limitation

The inclusion of 10 studies in each meta-analysis allows for a consolidated examination of evidence, contributing to a more comprehensive understanding of the topic despite the small sample sizes. However, the advanced stage of cancer in the study population, coupled with the small sample sizes in the primary studies, may limit the generalizability of the findings and introduce potential bias due to the restricted scope of participant characteristics.

5. Conclusion

This systematic review and meta-analysis indicate that Hedgehog pathway and PD-1 inhibitors, particularly vismodegib, are beneficial in treating locally advanced basal cell carcinoma. However, the associated adverse events limit the use of these medications. When administering these drugs, closely monitoring the treatment response and potential side effects is essential. Both categories of drugs are considered alternative treatments for locally advanced basal cell carcinoma patients who have contraindications to the first-line standard treatment, such as Mohs micrographic surgery. Nonetheless, further studies on the use of these medications for locally advanced basal cell carcinoma will help improve future outcomes for patients.

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7. References

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