CO175

Systematic Literature Review of Outcomes in Patients with Advanced Basal Cell Carcinoma (BCC) Who Progressed on or Are Intolerant to Hedgehog Inhibitors (HHI)

Eleanor Paul,[1] Patrick R. LaFontaine,[2] Yingxin Xu,[3] Timothy J. Inocencio,[3] Kokuvi Atsou,[4] Joseph Ader,[1] Chieh-I Chen,[3] Patricia Guyot,[4] Ping Wu,[1] Kevin Bouliane,[1] Peter Quon,[3] Shannon Cope[1]

[1]PRECISIONheor, Vancouver, BC, Canada, [2]Sanofi, Cambridge, MA, USA, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, [4]Sanofi, Chilly-Mazarin, France

Introduction

- Basal cell carcinoma (BCC) is the most common skin cancer globally, accounting for approximately 80% of non-melanoma skin cancer[1]
- Metastatic BCC (mBCC) and locally advanced BCC that is not suitable for surgery or radiotherapy (laBCC), hereafter advanced BCC, are rare, each occurring in <1% of BCC cases[1,2]
- Although mortality attributed to laBCC is not well described in the literature, patients with mBCC generally have a poor prognosis[3,4]
- Hedgehog inhibitors (HHIs) are the only first-line systemic treatments for advanced BCC licensed by the European Medicines Agency (EMA)[5,6]
- In June 2021, the EMA approved cemiplimab for the treatment of adult patients with laBCC or mBCC who have progressed on or are intolerant to an HHI, making it the first treatment and immunotherapy available for this population[7,8]

Objective

- To identify and characterise clinical trials and observational studies evaluating overall survival (OS), progression-free survival (PFS), and/or response rates of patients with advanced BCC receiving systemic therapy or best supportive care (BSC) post-HHI therapy (i.e., the second-line advanced BCC setting)

Methods

- A systematic literature review was performed to identify clinical trials and observational studies in the post-HHI advanced BCC population
- Predefined searches of the EMBASE, MEDLINE, and CENTRAL databases (no date restriction) were conducted in March 2020 and updated in October 2021
- Relevant conferences from January 2018 to October 2021 were also searched and included the American Society of Clinical Oncology, European Society for Medical Oncology, Society for Immunotherapy of Cancer, and American Academy of Dermatology
- Given the anticipated limited evidence base in advanced BCC, the search was designed to be as inclusive as possible (**Table 1**), including case studies and case reports in the study design

Table 1. PICOS criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adult patients with "advanced", "aggressive", "inoperable" or "invasive" BCC who experienced disease progression on HHI therapy, or were intolerant of prior HHI therapy[a]	• Patients with other skin cancers (e.g., squamous cell carcinoma, melanoma) • Patients with local or locally advanced BCC who are candidates for surgery or radiation
Interventions	• Any intervention	• Radiotherapy • Surgery (including adjuvant or neoadjuvant therapy)
Comparator	• Any comparator	None
Outcomes	• Overall survival • Progression-free survival (or time to progression) • Tumour response (objective response, complete response, partial response, stable disease, progressive disease) • Duration of response	None
Study design	• Randomized controlled trials • Non-randomized controlled trials • Single-arm trials • Observational studies - Case studies or case series - Chart reviews	• Literature reviews - Systematic literature reviews[b] - Narrative review • Epidemiological studies (i.e., studies without reference to treatment or aim to quantifying prevalence of BCC)
Other	• English language papers only	• Non-English papers (even if abstract is available in English)

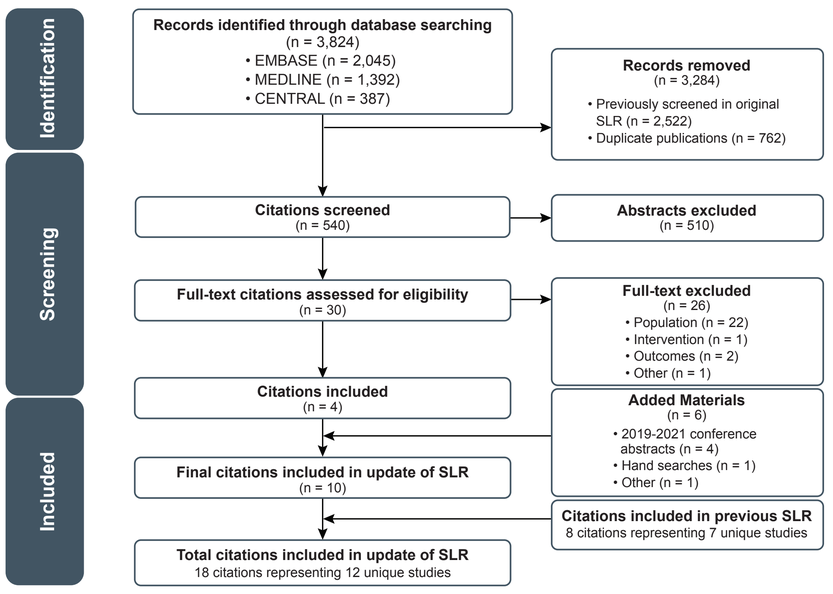
Abbreviations: BCC, basal cell carcinoma; HHI, hedgehog inhibitor.
[a]While there was no restriction of BCC histology type, patients with advanced BCC were defined as those with either metastatic BCC or locally advanced BCC who were not candidates for surgery or radiation (including any studies where patients were "refractory to standard therapy"). During abstract screening, studies with "advanced solid tumours" were included; at full-text screening, these studies were included if they had outcomes reported for the advanced BCC subgroup. [b]Bibliographies of systematic literature reviews were reviewed to check for supplementary data.

- Title, abstract, and full text screening was conducted by two independent reviewers with discrepancies resolved by a third reviewer
- Data were extracted regarding study and patient characteristics and outcomes of interest (OS, PFS, tumour response)
- The Newcastle-Ottawa Scale was used to assess the quality of single-arm trials and observational studies[9]

Results

- In the October 2021 SLR update, 540 records were screened. In total, 12 studies (18 citations) reporting post-HHI outcomes in patients with advanced BCC were included (**Figure 1**)
  - Eight studies were clinical trials: one pilot study,[10] three phase 1 trials,[11-13] one phase 1/2 trial,[14] three phase 2 trials[15-17]
    - All trials were open-label except Jimeno 2013,[12] which was a dose escalation trial, and all were single-arm except Chang 2019[14]
  - The remaining four studies were observational, including two cohort studies (one prospective,[18] one retrospective[19]) and two case series[20,21]
- Nine (75%) of the identified studies included fewer than 10 patients with post-HHI advanced BCC (**Table 2**). The largest trial identified was Study 1620 (NCT03132636)[16] (n=138)
  - Only five studies included post-HHI advanced BCC patients alone[10,15,16,19,20]; the other seven studies also included broader patient populations
- Study 1620 was the only study that evaluated a therapy that is approved for use in the post-HHI advanced BCC population
  - Only one study, Cowey et al. 2021,[19,22] presented evidence on the outcomes of patients receiving BSC
  - Eleven studies evaluated therapies that are not licensed in patients with post-HHI advanced BCC: arsenic trioxide plus itraconazole,[15] taladegib,[11] vismodegib,[18,20,21] sonidegib,[10] sonidegib plus buparlisib,[17] pembrolizumab,[14] electrochemotherapy plus bleomycin,[13] IPI-926,[12] and mixed chemotherapy/immunotherapies[19]
- Substantial heterogeneity in patient characteristics was observed across studies, four of which reported baseline characteristics for the total BCC population only (i.e., not exclusively the target post-HHI population)[11,12,14,18] (**Table 2**)
  - Median patient age ranged from 68-80 years across four studies[16,17,19,20]; mean age, reported in two studies, was lower (52 years,[15] 57.4 years[10])
  - Reasons for discontinuation of prior HHI therapy were reported in seven studies,[10,15-17,19-21] but no clear trends were observed

Figure 1. PRISMA study selection flow diagram



Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; EMBASE, Excerpta Medica database; MEDLINE, Medical Literature Analysis and Retrieval System Online; SLR, systematic literature review.

- Five studies reported OS outcomes[14-16,20,22] and four reported PFS outcomes[10,14,16,17] in the target population. Of these, only Study 1620,[16] a clinical trial, and Cowey et al. 2021,[19,22] an observational study, reported OS Kaplan–Meier data
- All but one study (Cowey et al. 2021[19,22]) reported objective response rates, which varied substantially across studies (**Table 3**)
- Quality assessment suggested eight studies were of adequate quality (5 or 6 stars)[10-12,15-17,20,23] and four studies were of poor quality (3 or 4 stars)[13,18,21,22], but there is no direct connection between study quality and the quality of clinical evidence for the target aBCC population

Limitations

- Although Cowey et al. 2021[19,22] presented outcomes of patients receiving BSC, the sample size was limited, and key differences were identified in patient characteristics, study design, and outcome definitions compared with Study 1620
- For all other active treatments, there was limited evidence on their effectiveness in the target population
- Objective response rates should be interpreted with caution for studies with small sample sizes (n<10); potential selection bias for observational studies should also be considered

Table 2. Treatment and patient characteristics of included studies

Study (Location)	Intervention	Target population n (Total study N) [Disease status]	Age, years	ECOG, n (%)		Discontinuation of prior HHI therapy, n (%)		Prior therapy, n (%)	
				0	1	Intolerant	Progressed	Surgery	Radiation
Interventional studies									
Ally 2016[15] (NCT01791894) (US)	Arsenic trioxide + Itraconazole	5 (5) [mBCC]	Mean (range): 52 (43-62)	--	--	0	5 (100)	--	2 (40)
Bendell 2018[11] (US)	Taladegib	31 (84)[a] [laBCC, mBCC]	Patient characteristics reported in broader population than post-HHI advanced BCC						
Chang 2019[14] (NCT02690948) (US)	Pembrolizumab	9 (16)[b] [laBCC: 3, mCC: 6]	Patient characteristics reported in broader population than post-HHI advanced BCC						
Danial 2016[10] (NCT01529450) (US)	Sonidegib	9 (9) [laBCC: 4, mBCC: 5]	Mean (range): 57.4 (42-91)	--	--	0	9 (100)	--	--
Jimeno 2013[12] (NR)	IPI-926	9 (94)[c] [laBCC, mBCC]	Patient characteristics reported in broader population than post-HHI advanced BCC						
Kis 2019[13] (Hungary)	Electro-chemotherapy (bleomycin)	1 (12)[d] [--]	64	--	--	--	--	1 (100)	--
Study 1620[16,24-26] (NCT03132636) (International)	Cemiplimab	138 (138) [laBCC: 84, mBCC: 54]	Median (range): 68 (57-77)	87 (63)	51 (37)	50 (36)	101 (73)	116 (84)	74 (54)
Tran 2018[17] (NCT02303041) (US)	Sonidegib and buparlisib	5 (10)[e] [laBCC, mBCC]	--	--	--	0	5 (100)[e]	4 (80)	2 (40)
Observational studies									
Alfieri 2018[20] (US)	Vismodegib	6 (6) [laBCC: 5, mBCC: 1]	Median (range): 77 (72-82)	--	--	0	6 (100)	2 (33)	2 (33)
Apalla 2021[18] (Greece)	Vismodegib	8 (67)[f] [--]	Patient characteristics reported in broader population than post-HHI advanced BCC						
Banvolgyi 2020[21] (Hungary)	Vismodegib	1 (11)[g] [laBCC]	55	--	--	1 (100)	0	1 (100)	1 (100)
Cowey 2021[19,22] (US)	Systemic treatment	4 (4) [laBCC, mBCC][h]	Median (range): 68.7 (48.4-71.1)	3 (100)[i]		0	4 (100)	--	--
	No treatment (BSC)	15 (15) [laBCC, mBCC][h]	Median (range): 80.2 (49.6-90)	10 (83.3)[i]		14 (93)	1 (7)	--	--

Abbreviations: BSC, best supportive care; HHI, hedgehog inhibitors; ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; NR, not reported; US, United States; WHO, World Health Organization. -- indicates data were not reported.
[a]Of the 84 patients enrolled, 47 patients had BCC and 31 BCC patients had received prior HHI therapy. [b]Of the 16 patients enrolled, 9 had progressed or intolerant to prior vismodegib (the other 7 patients achieved stable or partial response to prior vismodegib). [c]Of the 94 patients enrolled, 39 patients had BCC and 9 BCC patients had prior HHI therapy. [d]Of the 12 BCC patients enrolled, 1 had prior HHI therapy. [e]Only 5 out of 10 BCC patients received prior HHI. [f]Of the 67 BCC patients enrolled, 8 had prior HHI therapy. [g]Of the 11 patients enrolled, 7 patients had laBCC and 1 had received prior HHI. [h]Of the 19 patients included, 3 had mBCC and 16 had laBCC. [i]Percentage calculated from 12 non-initiators and 3 initiators.

Table 3. Tumour response and survival outcomes reported in the included studies

Study ID	Intervention	Target population N	Group	Tumour response outcomes, n (%)							Survival	
				RECIST Criteria	ORR	CR	PR	SD	PD	NE	OS	PFS
Interventional studies												
Ally 2016[15] (NCT01791894)	Arsenic trioxide + Itraconazole	5	--	v1.1	0	0	0	3 (60)	1 (20)	1 (20)	80% survival after 12.6 mo	--
Bendell 2018[11]	Taladegib	31	--	v1.1	11 (36)	--	--	--	--	--	--	--
Chang 2019[23] (NCT02690948)	Pembrolizumab	9	laBCC + mBCC	v1.1	4 (44)	--	--	--	--	--	89% at Year 1	62% at Year 1
Danial 2016[10] (NCT01529450)	Sonidegib	5	laBCC	v1.0	0	0	--	2 (40)	3 (60)	0	--	1-13 mo
		4	mBCC	v1.0	0	0	--	1 (25)	2 (50)	1 (25)	--	
Jimeno 2013[12]	IPI-926	9[a]	--	v1.0	0[a]	--	--	--	--	--	--	--
Kis 2019[13]	Electrochemotherapy (bleomycin)	1	--	v1.1	1 (100)	1 (100)	0	0	0	0	--	--
Study 1620[16] (NCT03132636)	Cemiplimab	138	laBCC + mBCC	v1.1	40 (29)	7 (5)	33 (24)	56 (41)	25 (18)	12 (9)	Not reached	Median (95% CI): 12.9 months (8.4-18.7)[b]
Tran 2018[17] (NCT02303041)	Sonidegib and buparlisib	1	laBCC	v1.1	1 (100)	0	1 (100)	0	0	0	--	17.4 mo
		4	mBCC	v1.1	0	0	--	2 (50)	2 (50)	0	--	2-18.6 mo
Observational studies												
Alfieri 2018[20]	Vismodegib	6	laBCC + mBCC	v1.1	3 (50)	0	3 (50)	2 (33)	1 (17)	--	13.5 mo (3-19+)	--
Apalla 2021[18]	Vismodegib	8	--	--	8 (100)	5 (63)	3 (38)	0	0	0	--	--
Banvolgyi 2020[21]	Vismodegib	1	--	--	1 (100)	0	1 (100)	0	0	0	--	--
Cowey 2021[19]	Systemic treatment	4	2L initiators	--	--	--	--	--	--	--	1 death observed	--
	No treatment (BSC)	15	2L non-initiators	--	--	--	--	--	--	--	5 deaths observed	--

Abbreviations: BCC, basal cell carcinoma; BSC, best supportive care; CR, complete response; IA, investigator assessed; ICR, independent central review; mo, months; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; v, version. -- indicates data were not reported.
[a]There were no objective responses among the nine patients previously treated with vismodegib. [b]PFS as assessed by independent central review.

Summary and Conclusion

- Study 1620 represents the largest trial to date and thus the best available evidence of a systemic treatment post-HHI for patients with advanced BCC
- Prior to the availability of cemiplimab, clinical experts considered BSC the standard of care in this population, however only one study was identified reporting outcomes for patients receiving BSC (Cowey et al. 2021)
- In view of the small sample sizes and heterogenous nature of studies evaluating other possible treatment options, including BSC, Study 1620 represents a clinically meaningful development and supports cemiplimab as a standard of care in this patient population

References

1. Berking C, et al. *Dtsch Arztebl Int.* 2014;111:389-395. **2.** Goldenberg G, et al. *J Am Acad Dermatol.* 2016;75:957-966.e2. **3.** Vu A, et al. *Eplasty.* 2011;11:ic8. **4.** McCusker M, et al. *Eur J Cancer.* 2014;50:774-783. **5.** European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/erivedge-epar-product-information_en.pdf. Accessed July 11, 2019. **6.** European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/odomzo-epar-product-information_en.pdf. Accessed July 11, 2019. **7.** European Medicines Agency. https://www.ema.europa.eu/en/documents/variation-report/libtayo-h-c-004844-ii-0012-epar-assessment-report-variation_en.pdf. Accessed January 18, 2022. **8.** Sanofi: Libtayo® (cemiplimab) approved by the European Commission as the first immunotherapy indicated for patients with advanced basal cell carcinoma. June 25, 2021. Accessed October 4, 2022. https://www.sanofi.com/en/media-room/press-releases/2021/2021-06-25-05-15-26-2252997 **9.** Wells GS, et al. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed October 1, 2016. **10.** Danial C, et al. *Clin Cancer Res.* 2016;22:1325-1329. **11.** Bendell J, et al. *Clin Cancer Res.* 2018;24:2082-2091. **12.** Jimeno A, et al. *Clin Cancer Res.* 2013;19:2766-2774. **13.** Kis EG, et al. *Sci Rep.* 2019;9:4285. **14.** Chang A. *J Am Acad Dermatol.* 2019;81:AB8. **15.** Ally MS, et al. *JAMA Dermatol.* 2016;152:452-456. **16.** Stratigos AJ, et al. *Lancet Oncol.* 2021;22(6):848-857. **17.** Tran DC, et al. *J Am Acad Dermatol.* 2018;78:1011-1013.e3. **18.** Apalla Z, et al. *J Am Acad Dermatol.* 2021;85:1589-1592. **19.** Cowey L, et al. *Dermatol Ther (Heidelb).* 2022;12:1211–1224. **20.** Alfieri S, et al. *Target Oncol.* 2018;13:253-256. **21.** Banvolgyi A, et al. *J Dermatolog Treat.* 2020;31:387-398. **22.** Golozar A, et al. *Pharmacoepidemiol Drug Saf.* 2021;30:287. **23.** Chang ALS, et al. *J Am Acad Dermatol.* 2019;80:564-566. **24.** Lewis K, et al. *J Immunother Cancer.* 2020;8:A260-A261. **25.** Stratigos AJ, et al. *J Clin Oncol.* 2021;39:9566. **26.** Stratigos AJ, et al. *Ann Oncol.* 2020;31:S1175-S1176.

Acknowledgments

Medical writing/editorial support was provided by Catherine Mirvis and Beth Lesher of OPEN Health, Bethesda, MD, and funded by the study sponsor.

Disclosures

This study was funded by Regeneron Pharmaceuticals, Inc.