

Patterns of hedgehog inhibitor (HHI) treatment interruptions and reinitiations among patients with basal cell carcinoma (BCC) in real-world clinical practice

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Synopsis

- In the US, it is estimated that >2 million patients are diagnosed with basal cell carcinoma (BCC) annually.¹
- Most cases of BCC are treatable by surgery; however, in approximately 1% of patients who develop advanced BCC (including metastatic and locally advanced BCC) additional therapies are required.¹⁻⁸
- Oral targeted therapies such as the hedgehog inhibitors (HHIs) vismodegib and sonidegib have shown clinical benefit in advanced BCC.^{8,9} However, patients treated with HHIs commonly experience side effects, which may require permanent or temporary treatment discontinuation.^{9,10}
- We hypothesized that HHI treatment patterns may vary according to the selected grace period.

Objective

- To assess the impact of grace period selection on patterns of HHI treatment discontinuation, treatment duration, and reinitiations among patients with BCC.

Methods

- This retrospective, observational cohort study used data from the IBM MarketScan[®] Commercial and Medicare claims database.
- We identified new users of HHIs (vismodegib or sonidegib) by selecting the first HHI dispensation (date of first dispensation = index date) during the study period (January 1, 2013 and March 30, 2019) and requiring ≥6 months of continuous health plan enrollment with medical and pharmacy benefits (i.e. baseline period). To be included in the study, patients were also required to be ≥18 years on the index date and to have ≥1 diagnosis of BCC during the baseline period (including the index date).
- HHI use was identified using National Drug Codes, and BCC diagnoses were identified using International Classification of Diseases (ICD)-9 and ICD-10 codes.
- HHI use was categorized according to whether it was HHI only, potentially adjuvant, neoadjuvant, or both neoadjuvant and adjuvant use:
 - HHI only: no surgery or radiotherapy within 60 days before or after initiation of HHIs
 - Potential adjuvant: surgery or radiotherapy followed by initiation of HHIs within 60 days
 - Potential neoadjuvant: initiation of HHIs followed by surgery and radiotherapy within 60 days
 - Both: surgery or radiotherapy both within 60 days before and after HHI initiation.
- Surgery and radiotherapy were identified using ICD-9 and ICD-10 procedure codes, Current Procedural Terminology, 4th Edition codes, or Healthcare Common Procedure Coding System codes.
- HHI treatment discontinuations were defined as the lack of an HHI dispensation before the exhaustion of the days' supply and allotted grace period. A grace period is the gap between the exhaustion of the days' supply and a subsequent refill that is permitted for treatment to be considered continuous.
 - HHIs are generally dispensed in 30-days' supply, benefit of treatment is continuously assessed, and treatment interruptions are commonly employed during HHI therapy.¹⁰ We, therefore, used grace periods of 14, 30, 60, 90, and 120 days.
- HHI treatment duration was estimated as days between the index date to the end of treatment (last dispensation + days' supply).
- Reinitiation was defined as ≥1 HHI dispensation after treatment interruption.
- The risk of HHI treatment discontinuation at 12 months, and median time (95% confidence intervals [CIs]) to treatment discontinuation was estimated via Kaplan-Meier survival analysis using different grace periods and stratified by type of HHI use (i.e. potential adjuvant, neoadjuvant, or both neoadjuvant and adjuvant use) using a 60-day grace period.

- Among patients with HHI treatment discontinuation, the risk of 12-month HHI reinitiation, median time (95% CIs) to reinitiation, and the risk of treatment discontinuation following second HHI use at 12 months was estimated via Kaplan-Meier analysis and stratified by type of HHI use (i.e. potential adjuvant, neoadjuvant, or both neoadjuvant and adjuvant use) using a 60-day grace period.

Results

Patient demographics

- A total of 526 patients who initiated HHIs were included in this study (Table 1).
- The mean (standard deviation [SD]) age was 67.0 (15.8) years; 65.4% were men.
- The proportion of patients covered by commercial insurance was 53.4%.
- The majority (75.9%) of patients had BCC of the head and neck.

Table 1. Baseline characteristics of patients with BCC initiating HHI treatment

	N=526
Age, years	
Mean (SD)	67.0 (15.8)
Median (Q1-Q3)	64.0 (56.0-81.0)
Male, n (%)	344 (65.4)
Payer, n (%)	
Commercial	281 (53.4)
Medicare	245 (46.6)
Geographic US region, n (%) ^a	
Midwest	107 (21.7)
Northeast	72 (14.6)
South	233 (47.3)
West	81 (16.4)
HHI index year, n (%)	
2013-2014	166 (31.6)
2015-2016	176 (33.5)
2017-2018	145 (27.6)
2019	39 (7.4)
Vismodegib, n (%)	522 (99.2)
Potential adjuvant or neoadjuvant HHI use, n (%)	
HHI only	366 (69.6)
Potential neoadjuvant	20 (3.8)
Potential adjuvant	117 (22.2)
Both ^b	23 (4.4)
BCC location, n (%) ^a	
Head and neck	399 (75.9)
Limb	140 (26.6)
Trunk	166 (31.6)
CCI score, n (%)	
0	518 (98.5)
≥1	8 (1.5)

^aGeographic data is missing for 33 (6.3%) patients. Percentages are calculated per number of patients with available data.
^bSurgery or radiotherapy both within 60 days before and after HHI initiation.
^cTumor locations are not mutually exclusive. Patients can have tumors at multiple sites.
 CCI, Charlson comorbidity index (excluding cancer); Q, quintile.

Type of HHI treatment

- The majority of patients (99.2%) initiated HHI therapy with vismodegib.
- Most patients (69.6%) were treated solely with HHIs. HHIs were used as adjuvant therapy in 22.2% of patients and neoadjuvant therapy in 3.8% of patients.

Patterns of HHI discontinuations using different grace periods

- Risk of treatment discontinuation at 6 months ranged from 78.8% when requiring a 14-day grace period to 52.5% when requiring a 120-day grace period (Figure 1).
- Median treatment durations were 94 days (95% CI: 90-109) using a grace period of 14 days, 144 days (95% CI: 131-162) using a grace period of 60 days, and 172 days (95% CI: 155-190) using a grace period of 120 days (Figure 1).

Patterns of HHI reinitiation using different grace periods

- The risk of HHI reinitiation at 12 months was 40.9% (95% CI: 35.6-45.7) using a grace period of 14 days, 19.7% (95% CI: 15.0-24.2) using a grace period of 60 days, and 13.6% (95% CI: 9.3-17.6) using a grace period of 120 days (Table 2).
- Among patients reinitiating HHIs, median time to subsequent discontinuation was 64 days (95% CI: 59-81) using a grace period of 14 days, 118 days (95% CI: 89-172) using a grace period of 60 days, and 171 days (95% CI: 114-318) using a grace period of 120 days (Table 2).

Patterns of HHI discontinuations using a 60-day grace period, stratified by type of HHI use

- Risk of treatment discontinuation at 6 months was 52.0% (95% CI: 23.4-69.9) with potential neoadjuvant use and 63.3% (95% CI: 52.1-71.9) with potential adjuvant use (Table 3).
- Median treatment duration from HHI initiation to first treatment discontinuation was 107 days (95% CI: 86-not applicable [NA]) with potential neoadjuvant use, and 128 days (95% CI: 118-171) with potential adjuvant use (Table 3).

Patterns of HHI reinitiation using a 60-day grace period, stratified by type of HHI use

- The risk of subsequent HHI reinitiation was 16.9% (95% CI: 0-35.9) with potential neoadjuvant HHI use, and 22.0% (95% CI: 11.7-31.1) with potential adjuvant HHI use (Table 3).
- Median treatment duration following HHI reinitiation was 183 days (95% CI: 114-NA) with potential neoadjuvant HHI use and 118 days (95% CI: 63-NA) with potential adjuvant HHI use (Table 3).

Table 3. Patterns of HHI discontinuation and reinitiation using a 60-day grace period, stratified by type of HHI use

	First episode of HHI use				HHI reinitiation following first discontinuation		Second episode of HHI use	
	Starting sample size, n	Patients discontinuing HHIs, n	Median treatment duration, days, (95% CI)	Risk of discontinuation at 6 months, % (95% CI)	Patients reinitiating HHIs, n	Probability of reinitiation at 12 months, % (95% CI)	Patients discontinuing HHIs, n	Median treatment duration days, (95% CI)
Overall	526	360	144 (131-162)	60.1 (55.0-64.6)	75	19.7 (15.0-24.2)	53	118 (89-172)
Potential neoadjuvant use	20	16	107 (86-NA)	52.0 (23.4-69.9)	2	16.9 (0-35.9)	2	183 (114-NA)
Potential adjuvant use	117	82	128 (118-171)	63.3 (52.1-71.9)	21	22.0 (11.7-31.1)	16	118 (63-NA)
Both	23	15	90 (40-NA)	71.7 (39.3-86.9)	3	13.3 (0-28.9)	2	89 (51-NA)
HHIs only	366	247	148 (134-172)	59.0 (52.7-64.4)	49	19.4 (13.7-24.9)	33	122 (87-174)

^aSurgery or radiation both within 60 days before and after HHI initiation. NA, not applicable due to small patient numbers.

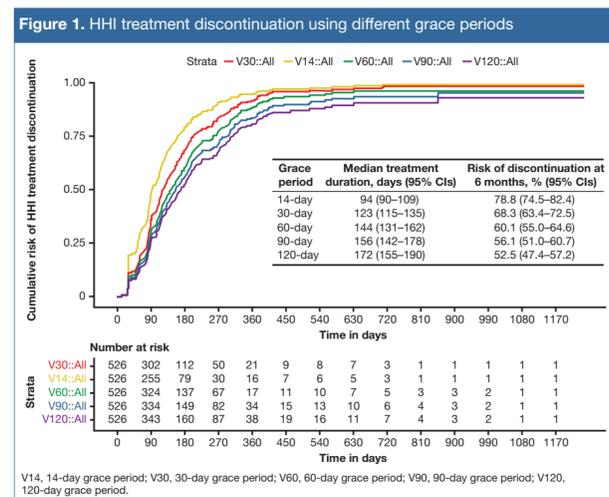


Table 2. Patterns of HHI reinitiation among patients discontinuing HHIs

Grace period	Probability of reinitiation following first HHI discontinuation		Time to second HHI discontinuation among those who reinitiated HHIs		
	Patients discontinuing HHIs, n	Patients reinitiating HHIs, n	Probability of reinitiation at 12 months, % (95% CI)	Patients discontinuing HHIs, n	Median treatment duration, days, (95% CI)
14-day	425	170	40.9 (35.6-45.7)	145	64 (59-81)
30-day	387	105	27.0 (21.9-31.7)	80	97 (81-136)
60-day	360	75	19.7 (15.0-24.2)	53	118 (89-172)
90-day	341	61	15.8 (11.4-20.1)	43	137 (112-189)
120-day	322	53	13.6 (9.3-17.6)	34	171 (114-318)

Limitations

- Unable to distinguish between permanent versus temporary discontinuation of HHI treatment.
- Information pertaining to reasons for discontinuing HHI treatment as well as disease severity were not available.
- There was no information regarding indication of HHI treatment, i.e. whether it was used as neoadjuvant or adjuvant therapy.

Summary and Conclusion

- The majority (>99%) of patients initiated vismodegib.
- Most patients (~70%) used HHIs alone versus using HHIs as potential neoadjuvant or adjuvant treatment.
- Although variability was observed based on the selected grace period, median treatment duration was <180 days even when using a 120-day grace period.
 - Median duration of HHI treatment was considerably shorter than the median treatment duration (8.6-13.3 months) reported in the pivotal clinical trials of vismodegib.^{8,9}
 - Median duration of use was shorter (by >20 days) for patients using HHIs as potential neoadjuvant or adjuvant treatment compared to patients using HHI monotherapy.
- Few patients reinitiated HHIs after discontinuation.
 - The probability of HHI reinitiation within 12 months of discontinuation was 20% using a grace period of 60 days.
 - The probability of reinitiation at 12 months was similar among patients using HHIs only and those taking HHIs potentially neoadjuvantly.
- Characterizing real-world persistence on HHIs is challenging due to the likely use of drug holidays, as treatment discontinuations, treatment duration, and reinitiations were sensitive to the duration of the grace period selected. Moreover, results were sensitive to the type of HHI use (i.e. potential adjuvant or neoadjuvant treatment).
- Real-world studies of medications with tolerability issues should consider use of drug holidays, and in oncology, the intent of treatment (i.e. adjuvant/ neoadjuvant) use should be considered when characterizing drug exposure.

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Disclosures

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