ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

ORIGINAL RESEARCH

Efficacy of sonic hedgehog inhibitors rechallenge, after initial complete response in recurrent advanced basal cell carcinoma: a retrospective study from the CARADERM database

A. Bassompierre[1*], S. Dalac[2], B. Dreno[3], E. M. Neidhardt[4], E. Maubec[5], C. Capelle[1], F. Andre[1], H. Behal[6], V. Dziwniel[1,7], G. Bens[8], M. T. Leccia[9], N. Meyer[10], F. Granel-Brocard[11], M. Beylot-Barry[12], O. Dereure[13], N. Basset-Seguin[14] & L. Mortier[1,15]

[1]Department of Dermatology, Lille University, CHU Lille, Lille; [2]Department of Dermatology, Dijon University Hospital, Dijon; [3]Department of Dermatology, Dieu Hospital, Nantes; [4]Department of Dermatology, Léon Bérard Center, Lyon; [5]Department of Dermatology, AP-HP, Avicenne University Hospital, Bobigny; [6]Health Technology and Medical Practice Assessment, ULR 2694-METRICS, Lille University Hospital, University of Lille, Lille; [7]Languages Department, Centrale Lille Institut, Villeneuve d'Ascq; [8]Department of Dermatology, Orleans Regional Hospital, Orleans; [9]Department of Dermatology, Grenoble University Hospital, Grenoble; [10]Department of Dermatology, IUC and CHU de Toulouse, Toulouse; [11]Department of Dermatology, Nancy University Hospital, Nancy; [12]Department of Dermatology, Bordeaux University Hospital, Bordeaux; [13]Department of Dermatology, University of Montpellier, Montpellier; [14]Department of Dermatology, Saint-Louis Hospital, AP-HP, Paris University Hospital, Paris; [15]INSERM U1189, CARADERM, CHU Lille, Lille, France

Available online xxx

Background: Smoothened (SMO) inhibitors, blocking the sonic hedgehog pathway, have been approved for advanced basal cell carcinoma (aBCC). Safety analyses reveal a high rate of adverse events (AEs) and, most of the time, vismodegib is most commonly stopped when the best overall response is reached. The long-term evolution of aBCC after vismodegib discontinuation is poorly described. The aim of this study is to evaluate the efficacy and safety of the SMO inhibitors (SMOis) available (vismodegib and sonidegib) following rechallenge after complete response (CR) following an initial treatment by vismodegib.

Materials and methods: This real-life, retrospective, multicenter and descriptive study is based on an extraction from the CARADERM accredited database, including 40 French regional hospitals, of patients requiring BCC systemic treatment.

Results: Of 303 patients treated with vismodegib, 110 achieved an initial CR. The vast majority of these patients (98.2%) stopped vismodegib, notably due to poorly tolerated AEs. The CARADERM database provided a median follow-up of 21 months (13.5-36.0 months) after CR. Of the 110 patients, 48.1% relapsed after a median relapse-free survival of 24 months (13.0-38.0 months). Among them, 35 patients were retreated by an SMOi and the overall response rate was 65.7% (34.3% of CR and 31.4% of partial response). The median duration of retreatment was 6.0 months (4.0-9.5 months).

Conclusion: Our real-life study, carried out on patients with complex clinical pictures, shows that after treatment discontinuation, 48.1% of patients achieved CR relapse within an average of 24 months (13.0-38.0 months). It emphasized that even though rechallenge can be considered as a therapeutic option, efficacy seems to decrease, suggesting the development of resistance mechanisms.

Key words: advanced BCC, SMO inhibitor, vismodegib, recurrence, relapse, retreatment, rechallenge, resistance, CARADERM

INTRODUCTION

A small share of basal cell carcinomas (BCCs) is diagnosed belatedly and considered as advanced BCCs (aBCCs) or, rarely, as metastatic BCCs (mBCCs) with high morbidity and heavy psychologic burden.[1-4] aBCCs form a heterogeneous group, with a blurred definition that can be explained by the many factors involved (tumor site and size, tumor invasion of adjacent anatomical structures, number, histologic subtype). For an elderly population with comorbidities and significant impairment of general conditions, carcinologic surgery is often inadequate.

The sonic hedgehog pathway (SHh) has a key role in BCC oncogenesis.[5,6] In sporadic BCC, mutations inducing cell proliferation are observed in >90% of cases: mainly in the protein patched homolog 1 gene (*PTCH1*), but also in the Smoothened gene (*SMO*) and the suppressor of fused homolog gene (*SUFU*).[7,8]

*Correspondence to: Dr Adrien Bassompierre, Department of Dermatology, CHU Lille, Claude Huriez Hospital, 33 rue Michel Polonowski, Lille, France. Tel: +33-698458121; Fax: +33-320446838

E-mail: a.bassompierre@gmail.com (A. Bassompierre).

Vismodegib blocks the SHh by binding the SMO protein receptor and its activation. It was approved in 2012-2013 for aBCC and mBCC unsuitable for treatments.[9] Subsequently, sonidegib, a new SMO inhibitor (SMOi), was approved for aBCC in 2016.

In both ERIVANCE and STEVIE vismodegib studies, efficacy analyses showed a response rate varying from 68.5% at 17.9 months to 60.3% at 39 months with rather comparable rates of partial responses (PR) and complete responses (CR).[10-13] Nevertheless, safety analyses revealed a high rate of adverse events (AEs) (98%). Thus, most of the time, to limit toxicity, SMOi was prescribed intermittently or stopped as soon as the best overall response (BOR) was achieved.[13]

In view of the increase in the number of current patients on vismodegib, maintaining CR after treatment discontinuation is of interest. So far, the long-term evolution has rarely been reported.[14] Herms et al. studied, as a secondary objective, the relapse management [including rates, relapse-free survival (RFS), treatment modalities and efficacy]. The authors showed that in 27 patients with rechallenge, the BOR rate was 85%, but tolerance was not described.[15]

The aim of this study, based on a national, real-life database, is to evaluate the efficacy and toxicity of the SMOi available (vismodegib and sonidegib) rechallenge, and the median duration, in relapsing aBCC, after discontinuation of vismodegib and initial CR.

MATERIALS AND METHODS

Study design and patients

This real-life, retrospective, multicentric, observational and descriptive study is based on an extraction from the CARADERM (RAre DERMatological CAncers) accredited database.[16]

CARADERM is a French national hospital network database on rare skin cancers, gathering 40 referent centers.

BCC patients included into the CARADERM database have an inoperable or metastatic histologically confirmed BCC or Gorlin syndrome with systemic treatment by SMOi.

The non-inclusion criteria were: under 18 years of age and lack of consent.

Among the patients with aBCCs and mBCCs from November 2013 (initiation of the database) to 27 May 2020, we selected those with rechallenge due to a relapse during follow-up after an initial CR. CR was defined clinically or, more rarely, histologically by the local investigators. Relapse was clinically assessed by a new typical BCC lesion on the targeted area, of any size, and confirmed.

Patients received vismodegib 150 mg daily until disease progression, disabling AEs, or other reasons. Concerning the rechallenge, treatment could be vismodegib or sonidegib, left to the physician's appreciation. The frequency of visits varied from 1 to 6 months but was mostly every 3 months. Tumor response was evaluated, by analogy with RECIST version 1.1, according to the following clinical achievements: CR as complete eradication, PR with tumor shrinkage $\geq$30% in size, stable disease (SD) with tumor shrinkage $<$30% in size or with increase in size $<$20%, progression (P) with increase in size $>$20% compared to the baseline. Tolerance was evaluated with the Treatment-Emergent Adverse Events system defined as AEs appearing between the 1st day and the 30th day after discontinuation of vismodegib treatment and grading was according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Radiological exams were not systematically carried out.

All the patients included in this base—or their legal representatives—have signed a consent form and each center has been declared to the National Commission for Information Technology and Liberties.

Procedures

The collected data were as follows: age, sex, metastatic stage, patients with Gorlin syndrome, location of the target lesion, histological subtype, former treatments, BOR; AEs and grade; reasons for stopping and rechallenge treatment.

The main dates (initiation and discontinuation of vismodegib and obtaining CR) were also specified.

Treatments initiated after relapse were noted, as well as their efficacy and safety.

Outcomes

The primary objective was to evaluate the response rate of the rechallenge with SMOi (vismodegib or sonidegib) after discontinuation and initial CR.

Secondary objectives were as follows: RFS—the time to relapse or death—for patients with initial CR; AEs with occurrence and grading, after rechallenge of SMOi in comparison with the first course (appearance or disappearance of AEs and grade improvement or worsening) and details of a further rechallenge after potential subsequent discontinuation.

Concerning tolerance, the data were related to the mode of treatment: intermittent—'holiday regimen'—or not, varying from once every 2 days to 1 month every 3 months.

Patients lost to follow-up were censored.

Statistical analysis

Continuous variables were described using the mean and standard deviation or the median and interquartile range (IQR). Categorical variables were expressed by frequency and percentage.

The RFS was estimated using the Kaplan—Meier method. Relapse or death was considered as events. The database lock was 27 May 2020, and some patients were censored.

The statistical analyses were carried out with SAS software version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of patients with initial CR under vismodegib

As shown in Figure 1, 303 patients received vismodegib, with an overall response rate (ORR) of 86.5% (36.3% of CR

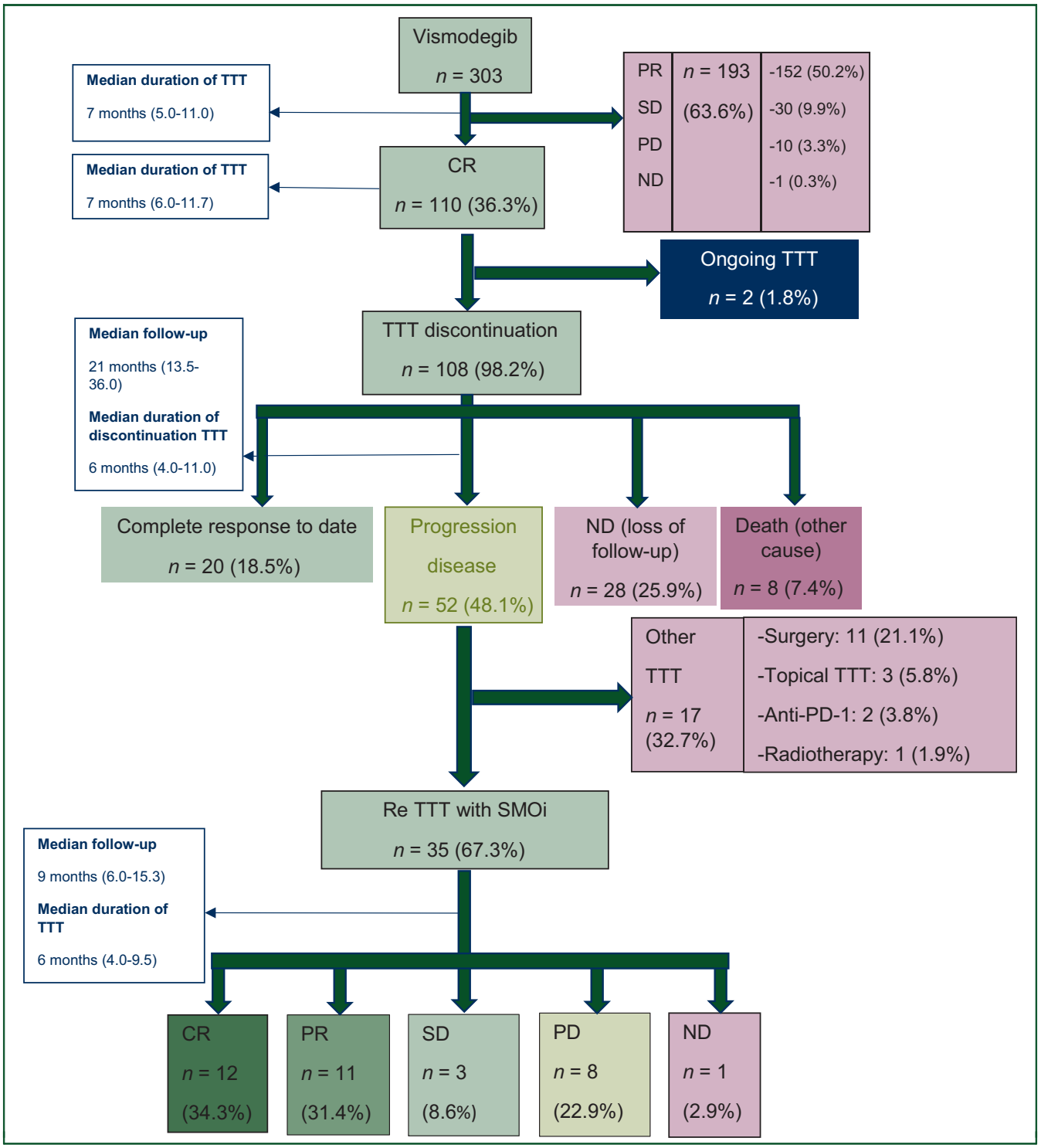

Figure 1. Flow chart of the survey.
CR, complete response; PD, progression disease; PR, partial response; ND, unknown; Re TTT, vismodegib retreatment; SD, stable disease; SMOi, Smoothened inhibitors (vismodegib: 33 and sonidegib: 2); STOP, vismodegib discontinuation; TTT, vismodegib treatment.

and 50.2% of PR). The median duration for this first course of vismodegib was 7 months (IQR: 5.0-11.0 months).

Of the 303 patients with vismodegib treatment, 110 (36.3%) achieved an initial CR after a median time of 6 months (IQR: 4.0-8.0 months) and a median duration of treatment of 7 months (IQR: 6.0-11.7 months). For these patients, the mean age was 72.2 years. Gorlin syndrome was diagnosed in 13 patients (11.8%). The most frequent site was the head in 84.5% of cases (ocular region for 22.7%, nasal region for 19.1% and auricular region for 14.5%). The histologic subtype of tumors was infiltrative for 35.5%, nodular for 20.0% and morpheaform for 11.8%. Thirty-seven of the tumors were recurrences, after surgery or radiotherapy (33.6%). The most frequent AEs related to

Table 1. Baseline characteristics and demographics of all patients treated with vismodegib

	Patients with CR (n = 110)	Patients with CR and rechallenge (n = 35)
Men	70 (63.6)	19 (54.3)
Age, mean (SD), years	72.2 (15.9)	69.6 (18.6)
Age group >65 years	76 (69.1)	21 (60.0)
Gorlin syndrome		
Yes	13 (11.8)	6 (17.1)
No	85 (77.3)	27 (77.1)
Unknown	12 (10.9)	2 (5.7)
Site		
Head	93 (84.5)	31 (88.6)
Auricular region	16 (14.5)	3 (8.6)
Ocular region	25 (22.7)	4 (11.4)
Front	5 (4.5)	2 (5.7)
Nose	21 (19.1)	10 (28.6)
Cheek	8 (7.3)	4 (11.4)
Scalp	7 (6.4)	4 (11.4)
Temple	3 (2.7)	0 (0)
Mandible/chin	1 (0.9)	1 (2.9)
Lip	2 (1.8)	1 (2.9)
Multiple	3 (2.7)	2 (5.7)
Neck	0 (0.0)	0 (0)
Trunk	7 (6.4)	2 (5.7)
Upper limp	7 (6.4)	0 (0)
Lower limb	0 (0.0)	0 (0)
Multiple	3 (2.7)	2 (5.7)
Metastatic stage	6 (5.5)	2 (5.7)
Histology		
Morpheaform	13 (11.8)	8 (22.9)
Nodular	22 (20.0)	5 (14.3)
Infiltrative	39 (35.5)	8 (22.9)
Other	7 (6.4)	2 (5.7)
Unknown	27 (24.5)	12 (34.3)

Values are expressed by frequency (percentage) unless otherwise indicated. CR, complete response; SD, standard deviation.

vismodegib, which concerned 93 patients (84.5%), were as follows: cramps (63.6%), dysgeusia (57.3%), alopecia (51.8%), asthenia (21.8%), weight loss (19.1%) and anorexia (8.2%). Most of them were mild, with grade 1 or 2 (93.6%) and a minority were grade 3 or 4 (5.4%) (Tables 1 and 2).

To date, only two patients were still under treatment with persistent CR after a median follow-up of 13 months (IQR: 11.0-15.0 months). The vast majority discontinued vismodegib (108 patients; 98.2%), mainly due to poorly tolerated AEs.

After obtaining CR, the median follow-up was 21 months (IQR: 13.5-36.0 months) and 52 patients (48.1%) had relapsed on the same site. The median RFS (relapse or death) was 24 months (IQR: 13.0-38.0 months) (Figure 2). The CR was persistent in 20 patients (18.5%) after a median follow-up of 24 months (IQR: 16.5-39.5 months) (Figure 1).

Characteristics of patients with rechallenge of SMOi

After relapse, a rechallenge with an SMOi was prescribed to 35 patients (33 patients with vismodegib and 2 with sonidegib). Their baseline characteristics were comparable to those of the whole cohort, except for the most frequent histologic subtype which was morpheaform (eight patients, 22.9%) (Table 1).

The median duration of retreatment was 6 months (IQR: 4.0-9.3 months) and the ORR after retreatment was 65.7% (with 34.3% of CR and 31.4% of PR) with a median RFS of 18.0 months. There were also three patients with SD and eight patients with progression disease (PD). Of the two patients with sonidegib as second course, one reached CR and the other progressed (Figure 1).

Among these 35 patients, after a follow-up of 9 months (IQR: 6.0-15.3 months), 6 patients received a second rechallenge (third course) of treatment by SMOi. This second rechallenge had a median time of duration of 7 months (IQR: 5.5-13.5 months). A response was observed in two patients (one with CR and one with PR or 16.7%, respectively), two patients were stable and two others in progression.

On balance, we observed, on a population with CR only, a CR rate gradually decreasing to 34.3% (12/35 patients) during the first relapse, and then to 16.7% during the second relapse (1/6 patients).

Concerning tolerance, among the 33 patients with vismodegib, 23 (69.7%) had at least one AE, compared to 87.8% of first-course patients. The most common AEs were cramps (45.5%), alopecia (39.4%), dysgeusia (39.4%) and weight loss (9.1%). Most of them were grade 1 or 2, but toxicity was severe (grade 3 or 4) for six patients (18.2%) with dysgeusia, cramps and weight loss (Table 2).

Compared to the first course, keeping in mind the lower median duration, tolerance in terms of appearance (worsening) or disappearance (improvement) of at least one AE was improved for 13 patients (33.4%), 5 of them with 'holiday regimen', and worsened for 10 patients (30.3%) with 1 patient on 'holiday regimen'. It was stable for nine patients (27.3%). Of the 34 persistent AEs during the rechallenge, 2 were improved (with grade 2 to 1), 25 stable (with 19 at grade 1 and 6 at grade 2) and 7 worsened (with grade 1 to 2) (Annexe 1, available at https://doi.org/10.1016/j.esmoop.2021.100285).

For the two patients under sonidegib, the AEs were asthenia (grade 2) for one and dysgeusia (grade 3), weight loss (grade 1) and cramps (grade 1) for the other.

Concerning the 32 patients included with Gorlin syndrome, 13 (40.6%) of them achieved CR for the target BCC compared to 33.4% for sporadic BCCs. This first course had a median duration of 7.5 months (5.0-13.8 months). The median time to CR was 9 months (5.0-13.0 months) and median RFS was 19 months (15.0-24.0 months). Tolerance was comparable with 90.6% of them who experienced AEs. A rechallenge was applied to six patients, with five responses (three patients with CR and two with PR) and one progression. The retreatment median time was 10 months, compared to 6 months for the global population with SMOi rechallenge.

DISCUSSION

The recurrence after vismodegib discontinuation is an emerging challenge and we report the most important

Table 2. Treatment-Emergent Adverse Events (TEAEs) related with vismodegib

	Patients treated with vismodegib (n = 303)			Patients treated with vismodegib with complete response (n = 110)			Patients with vismodegib rechallenge after discontinuation and complete response (n = 33)		
Patients with adverse events	242 (79.9)			93 (84.5)			23 (69.7)		
Patients without adverse events	35 (11.6)			13 (11.8)			9 (27.3)		
Number of events	640			244			48		
Dysgeusia	169 (55.8)	Grade 1/2	164 (54.1)	63 (57.3)	Grade 1/2	61 (55.4)	13 (39.4)	Grade 1/2	9 (27.3)
		Grade 3/4	5 (1.7)		Grade 3/4	2 (1.8)		Grade 3/4	4 (12.1)
Cramps	181 (59.7)	Grade 1/2	175 (57.7)	70 (63.6)	Grade 1/2	68 (61.8)	15 (45.5)	Grade 1/2	14 (42.4)
		Grade 3/4	6 (2.0)		Grade 3/4	2 (1.8)		Grade 3/4	1 (3.0)
Alopecia	127 (41.9)	Grade 1/2	122 (40.3)	57 (51.8)	Grade 1/2	56 (50.9)	13 (39.4)	Grade 1/2	13 (39.4)
		Grade 3/4	5 (1.6)		Grade 3/4	1 (0.9)		Grade 3/4	0 (0.0)
Asthenia	77 (25.4)	Grade 1/2	76 (25.1)	24 (21.8)	Grade 1/2	24 (21.8)	2 (6.1)	Grade 1/2	2 (6.1)
		Grade 3/4	1 (0.3)		Grade 3/4	0 (0.0)		Grade 3/4	0 (0.0)
Weight loss	59 (19.5)	Grade 1/2	56 (18.5)	21 (19.1)	Grade 1/2	20 (18.2)	3 (9.1)	Grade 1/2	2 (6.1)
		Grade 3/4	3 (1.0)		Grade 3/4	1 (0.9)		Grade 3/4	1 (3.0)
Anorexia	27 (8.9)	Grade 1/2	27 (8.9)	9 (8.2)	Grade 1/2	9 (8.2)	2 (6.1)	Grade 1/2	2 (6.1)
		Grade 3/4	0 (0.0)		Grade 3/4	0 (0.0)		Grade 3/4	0 (0.0)
Unknown	26 (8.6)			4 (3.6)			0 (0.0)		

Values are expressed by frequency (percentage).

multicenter study on aBCC with CR and its management. More specifically, we evaluated the efficacy and the toxicity of the rechallenge with SMOis due to relapse after initial CR under first vismodegib course. We chose to study vismodegib rather than sonidegib as a first course since it has been in use for a longer period, in larger cohorts.

Herms et al. first reported 27 patients with rechallenge following relapse after CR.[15] The relapse rate after the initial treatment by SMOi was similar in Herms et al.'s and our study, respectively, 46.6% after a follow-up of 36 months for Herms et al. and 48.1% after a median follow-up of 21 months (13.5-36.0 months) in our study of 35 patients. The ORR was 85% (37% with CR) compared to 65.7% in our study (34.3% with CR).

The main difference is that Herms et al. described 82.4% of patients who were part of clinical studies (76.5% in the STEVIE study and 5.9% in the MIKIE trial), which represents a large proportion compared to our real-life population. One of the assets of our study is that the cohort selected is more representative of the clinical practice, with less strict inclusion or non-inclusion criteria and more patients.

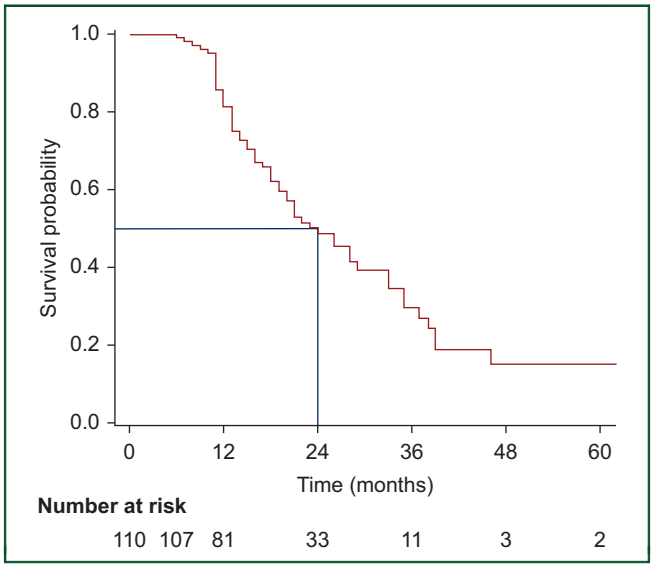

Figure 2. Relapse-free survival (RFS) of patients in complete response with first course of vismodegib.
IQR, interquartile range.

Likewise, the AEs mentioned are also consistent with the ones observed in previous studies (dysgeusia, muscle spasm, alopecia, weight loss, loss of appetite and asthenia). At least one AE was observed for 98% of cases in the STEVIE study, and for 84.5% in ours. These AEs were commonly not severe with only 5.4% with grade 3 or 4 but tend to alter life quality of patients and frequently lead to treatment discontinuation. Toxicity is for a large part reversible. The STEVIE study demonstrates that 12 months after treatment discontinuation, 54.5% of the patients were free of any AE.[13] Guidelines have been published to enable optimal therapeutic benefits with AEs related to a class effect.[17]

In our study based on a comprehensive approach, tolerance after rechallenge was improved compared to the initial course, with 69.7% of patients with at least one AE, compared to the 84.5% during the first treatment. This could be explained in part, by the 'holiday regimen' treatment administered. This practice is currently often adopted for the rechallenge, as suggested by recent studies and other case reports, such as the MIKIE trial by Dréno et al., with better tolerance and undiminished efficiency.[18] In our study, eight patients (24.2%) were offered 'holiday regimen' for the rechallenge. However, this must be weighed against a treatment duration that remains shorter during rechallenge (5.5 months versus 7 months) as AEs appear within few months of treatment.

Thus, in our patients initially in CR (35; 100%), a new CR could be observed in 12 patients only (34.3%) and the PD rate was 22.9% after rechallenge. The CR rate decreased to 16.7% (one out of six patients) after the second one. For these rechallenges, the median retreatment times were similar to those for the initial CR. Beyond this tendency, our study raises questions about the relapse mechanism and a

potential secondary resistance and offers therapeutic interest when other options remain extremely limited.

As expected, the proportion of CR was much higher in patients with Gorlin syndrome than in patients with sporadic BCC (40.6% versus 33.4%). This difference may be explained by the fact the tumors are not necessarily aBCC, but numerous usual BCCs, the number of which being considered as equivalent to an aBCC—in the setting of a genetic syndrome. The other explanation for the better response rate for Gorlin syndrome patients may be the unique oncodriving upstream mutation in the SHh pathway, compared to the selection of cells with somatic SMO mutations in sporadic BCC under therapeutic pressure, resulting in secondary lack of efficiency of SMOi.[19] Concerning the rechallenge, we observed in our small sample of six patients a better ORR (five responses among them) than in sporadic aBCC, which reveals re-inducible responses in Gorlin syndrome patients with rare secondary resistance.[20]

Results show an ORR in 65.7% of patients with rechallenge after relapse. This residual disease after vismodegib discontinuation and re-inducible response with this treatment have recently been explored in mice and humans (with tissue samples). SMOi leads to BCC regression by cellular differentiation and apoptosis but a small part persists in a quiescent state, characterized by the expression of Lgr5 (expressed in epithelial stem cells). This expression depends on the SHh pathway as well as on the Wnt pathway. This is why it drastically drops with SMOi but persists at a low level. This has nothing to do with genetic resistance, as the tumor is not growing during treatment. However, the relapse after discontinuation is common, secondary to its re-entrance in the cell cycle proliferation of the quiescent cells. In studies, new treatment cycles enable new responses. Lastly, *in vivo* models have showed a synergy in the inhibition of both the SHh and Wnt pathway with an eradication of quiescent cells and the prevention of tumor relapse.[21-23]

Due to a high best ORR, an innovative alternative could be surgery—the gold standard method—after initial response (PR or CR). The objective here would be to operate on patients as soon as eligibility is reached, from a neoadjuvant perspective, especially for tumors in sensitive locations. Some case reports and a preliminary study (11 patients) confirm this idea.[24,25] Mortier et al. have led a large study, VISMONEO, on 55 patients treated with vismodegib for 4-10 months, until best response before surgery was carried out.[26]

Programmed cell death protein 1 (PD-1) immunotherapy also seemed to show good outcomes in metastatic BCC treated in first line with systemic therapy including SMOi. Major expression of PD-1 is secondary to other treatments, as shown in several case reports.[27,28] Stratigos et al. reported in a phase II single arm-trial an ORR of 31% on 84 patients with a novel PD-1 inhibitor REGN2810 used in aBCCs, metastatic or not after SMOi (due to progression or intolerance).[29] A second phase II trial is in progress, using pembrolizumab with or without vismodegib (ClinicalTrials.gov identifier: NCT02690948).

This study obviously presents some limitations as all retrospective studies, with data missing and lost to follow-up. The different assessments were not centrally reviewed, and CARADERM being recent, the number of patients is limited, particularly those with rechallenge. However, these data remain relevant, reflecting the current population in 40 comprehensive cancer centers in France, from the largest to the smallest ones.

Conclusion

Our study suggests that rechallenge with SMOi following relapse after previous SMOi-induced CR is a therapeutic option, despite slightly degraded efficacy. The biocellular mechanisms of response and resistance to this approach have increasingly been identified, such as the relapse and secondary resistance mechanisms. Combined therapies or neoadjuvant strategies might therefore be considered in patients with recurrent aBCC, although further investigations need to be carried out to confirm these findings.

FUNDING

This work was supported by public funds by CARADERM (Institut National du Cancer).

DISCLOSURE

EMN: Consulting or advisory role: Novartis, Pierre Fabre, Bristol-Myers Squibb, MSD. EM: Consulting or advisory role: MSD, Pierre Fabre, Novartis, Sanofi; research funding: MSD (Inst); travel, accommodations, expenses: MSD Oncology, Pierre Fabre, Novartis. NM: Consulting or advisory role or research funding: Bristol-Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Merck, Sanofi, Sun Pharmaceutical Industries. MB-B: Research funding: Roche; consulting or advisory role: Sun Pharmaceutical Industries. NB-S: Consulting or advisory role: Sanofi, Sun Pharmaceutical Industries. LM: Consulting or advisory role: Sanofi, Sun Pharmaceutical Industries, MSD Oncology, Bristol-Myers Squibb, Novartis. The remaining authors have declared no conflicts of interest.

REFERENCES

1. Alam M, Goldberg LH, Margolis DJ, et al. Delayed treatment and continued growth of nonmelanoma skin cancer. *J Am Acad Dermatol*. 2011;64(5):839-848.
2. Amici JM, Battistella M, Basset-Seguin M, et al. Defining and recognising locally advanced basal cell carcinoma. *Eur J Dermatol*. 2015;25(6):586-594.
3. McCusker M, Basset-Seguin N, Hauschild A, et al. Metastatic basal cell carcinoma: prognosis dependent on anatomic site and spread of disease. *Eur J Cancer*. 2014;50(4):774-783.
4. Haves AW, Schaffer PR, Carucci JA. The impact of inoperable advanced basal cell carcinoma: the economic, physical, and psychological burden of the disease. *J Drugs Dermatol*. 2013;12(suppl 10):s151-s153.
5. Daya-Grosjean L, Couvé-Privat S. Sonic hedgehog signaling in basal cell carcinomas. *Cancer Lett*. 2005;225(2):181-192.
6. Lo Muzio L. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). *Orphanet J Rare Dis*. 2008;3:32.

7. Iwasaki JK, Srivastava D, Kouba DJ, Moy RL, Lin HJ. The molecular genetics underlying basal cell carcinoma pathogenesis and links to targeted therapeutics. *J Am Acad Dermatol*. 2012;66(5):e167-e178.
8. Scales SJ, de Sauvage FJ. Mechanisms of Hedgehog pathway activation in cancer and implications for therapy. *Trends Pharmacol Sci*. 2009;30(6):303-312.
9. Vismodegib. US Food and Drug Administration. 2012. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203388s012lbl.pdf. Accessed January 2, 2021.
10. Sekulic A, Migden MR, Hauschild A, et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. *J Am Acad Dermatol*. 2015;72(6):1021-1026.e8.
11. Sekulic A, Migden MR, Hauschild A, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. *BMC Cancer*. 2017;17(1):332.
12. Basset-Seguin N, Hauschild A, Hansson J, et al. Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. *Lancet Oncol*. 2015;16(6):729-736.
13. Basset-Seguin N, Hauschild A, Hansson J, 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.
14. Alfieri S, Bergamini C, Bossi P, Granata R, Locati L, Licitra L. Retreatment with vismodegib after progression in advanced basal cell carcinoma: first-time report of a single-institution experience. *Target Oncol*. 2018;13(2):253-256.
15. Herms F, Lambert J, Basset-Seguin N, et al. Follow-up of patients with complete remission of locally advanced basal cell carcinoma after vismodegib discontinuation: a multicenter French Study of 116 patients. *J Clin Oncol*. 2019;37(34):3275-3282.
16. Caraderm. Available at http://www.caraderm.org/. Accessed January 1, 2014.
17. Lacouture ME, Dréno B, Kunstfeld R, et al. Characterization and management of hedgehog pathway inhibitor-related adverse events in patients with advanced basal cell carcinoma. *Oncologist*. 2016;21(10):1218-1229.
18. Dréno B, Kunstfeld R, Schadendorf D, et al. Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomised, regimen-controlled, double-blind, phase 2 trial. *Lancet Oncol*. 2017;18(3):404-412.
19. Tang JY, Ally MS, Epstein EH Jr, et al. Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2016;17(12):1720-1731.
20. Sinx KAE, Roemen GMJM, Mosterd K, et al. Vismodegib-resistant basal cell carcinomas in basal cell nevus syndrome: clinical approach and genetic analysis. *JAAD Case Rep*. 2018;4(5):408-411.
21. Biehs B, GJP Dijkgraaf, de Sauvage FJ, et al. A cell identity switch allows residual BCC to survive Hedgehog pathway inhibition. *Nature*. 2018;562(7727):429-433.
22. Sánchez-Danés A, Larsimont J-C, Blanpain C, et al. A slow-cycling LGR5 tumour population mediates basal cell carcinoma relapse after therapy. *Nature*. 2018;562(7727):434-438.
23. Dessinioti C, Plaka M, Stratigos AJ, Dimitrakopoulou A. Complete response is reversible upon vismodegib withdrawal and re-inducible upon vismodegib rechallenge in a patient with locally advanced basal cell carcinoma. *J Eur Acad Dermatol Venereol*. 2019;33(5):e187-e188.
24. Ally MS, Aasi S, Tang JY, et al. An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma. *J Am Acad Dermatol*. 2014;71(5):904-911.e1.
25. Kwon GP, Ally MS, Tang JY, et al. Update to an open-label clinical trial of vismodegib as neoadjuvant before surgery for high-risk basal cell carcinoma (BCC). *J Am Acad Dermatol*. 2016;75(1):213-215.
26. Bertrand N, Guerreschi P, Mortier L, et al. Vismodegib in neoadjuvant treatment of locally advanced basal cell carcinoma: first results of a multicenter, open-label, phase 2 trial (VISMONEO study): neoadjuvant vismodegib in locally advanced basal cell carcinoma. *EClinicalMedicine*. 2021;35:100844.
27. Ikeda S, Goodman AM, Kurzrock R, et al. Metastatic basal cell carcinoma with amplification of PD-L1: exceptional response to anti-PD1 therapy. *NPJ Genomic Med*. 2016;1:16037.
28. Lipson EJ, Lilo MT, Taube JM, et al. Basal cell carcinoma: PD-L1/PD-1 checkpoint expression and tumor regression after PD-1 blockade. *J Immunother Cancer*. 2017;5:23.
29. Stratigos A-J, Sekulic A, Fury M-G, et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single arm, phase 2 trial. *Lancet Oncol*. 2021;22:848-857.