Long term strategy options in the treatment of laBCC and the role of HHIs

Sun Pharma

LONG TERM STRATEGY OPTIONS IN THE TREATMENT OF LABCC AND THE ROLE OF HHIS AND IMMUNOTHERAPY

AGENDA

Part 1: First line therapy of HHI: efficacy and tolerability

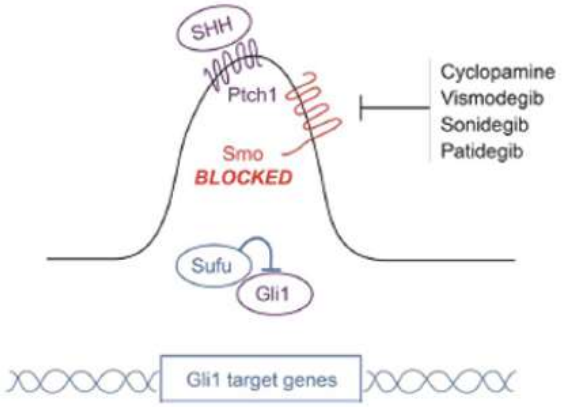
Part 2: Methods to prevent discontinuation HHI therapy

HHIs ARE VERY EFFECTIVE BECAUSE THEY TARGET THERE WERE THE MUTATIONS ARE: IN THE HEDGEHOG-SIGNALING PATHWAY

1. Mutations that lead to an overactivation of the HH pathway:[1]

The majority of BCC are caused by **inactivating mutations** that result in a loss of function of PTCH. Less frequently, mutations involving SMO

2. Mechanistic action of HHI: Binding to Smoothened and disrupt the signaling cascade[2]

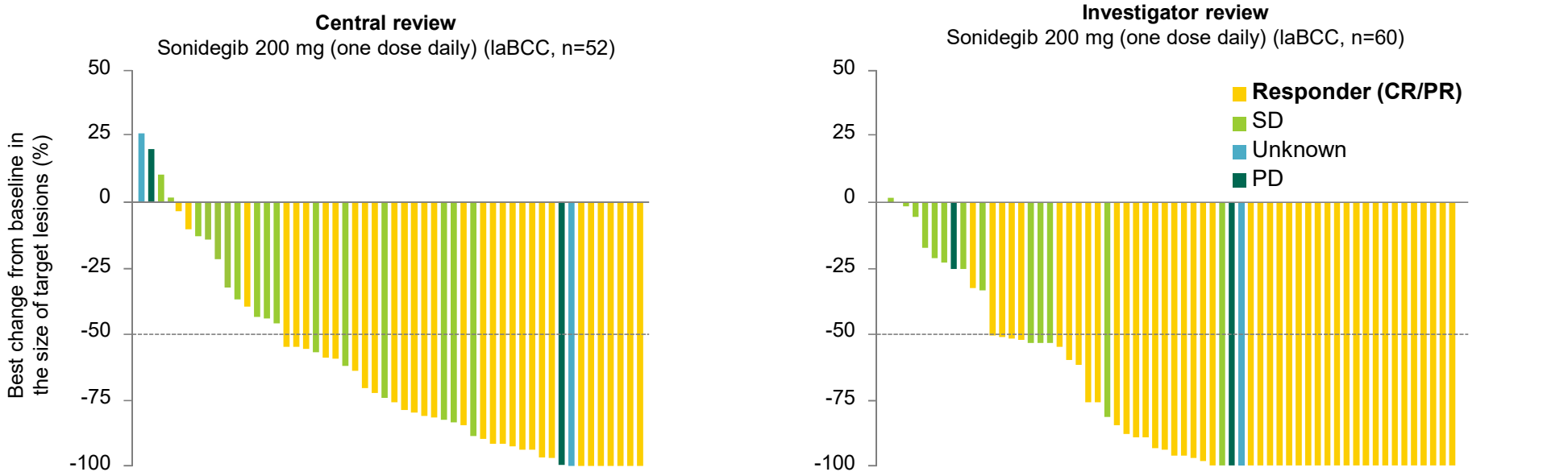


Hedgehog inhibitors like **Sonidegib** and **Vismodegib** bind to Smoothened.

1. Danhof et al. Am J Clin Dermatol 2017; DOI 10.1007/s40257-017-0319-4. **2**. R. Gutzmer, A. Solomon Targeted Oncology (2019) 14:253–267.

HHIs ARE VERY EFFECTIVE BECAUSE THEY TARGET THERE WERE THE MUTATIONS ARE IN THE HEDGEHOG-SIGNALING PATHWAY

Individual Shrinkage of tumor size in pivotal study



92% tumor shrinkage, 71% of patients more than 50% shrinkage [3]

92% tumor shrinkage, 80% of patients more than 50% shrinkage [3]

Best percentage change from baseline in the sum of the products of perpendicular diameters in target lesion(s) assessed by photography per World Health Organization (WHO) criteria in patients with laBCC treated with sonidegib 200 mg per central and investigator review. Patients were excluded from the analysis if percentage change in the size of target lesions was not available or was contradicted by an overall lesion response of unknown or progressive disease.[2]

1. Lear JT et al J Eur Acad Dermatol Venereol. 2017;32(3):372-381; **2.** Lear JT et al J Eur Acad Dermatol Venereol. 2017;32(3):372-381 Supplement; **3.** Dummer R et al. J Am Acad Dermatol. 2016;75(1):113-125.

EFFICACY OF SONIDEGIB: 42 MONTHS ANALYSIS OF THE BOLT STUDY

patients with LaBCC	RECIST Central review (n=66)	RECIST Investigator Review (n=66)
ORR n (%; 95% CI)	40 (60.6%; 47.8-72.4)	49 (74.2%; 62-84)
CR, n (%)	14 (21.2%)	19 (28.8%)
PR, n (%)	26 (39.4%)	30 (45.5%)
SD, n (%)	20 (30.3%)	11 (16.7%)
PD, n (%)	90.9	91
Unknown, n (%)	1 (1.5%)	1 (1.5%)

DURATION OF RESPONSE (DOR) OF SONIDEGIB

Sonidegib 200 mg QD	Central review RECIST n=66
Median duration of treatment exposure, months	11.0[1]
DOR KM median (95% CI), months	26.1 (NE)[1]

1. Gutzmer et al. BMC Cancer. 2021 Nov 19;21(1):1244.

BOLT EFFICACY ANALYSIS AT 42 MONTHS
EFFICACY OF SONIDEGIB IN HISTOLOGIC SUBTYPES

JAAD Journal of the American Academy of Dermatology

Log in

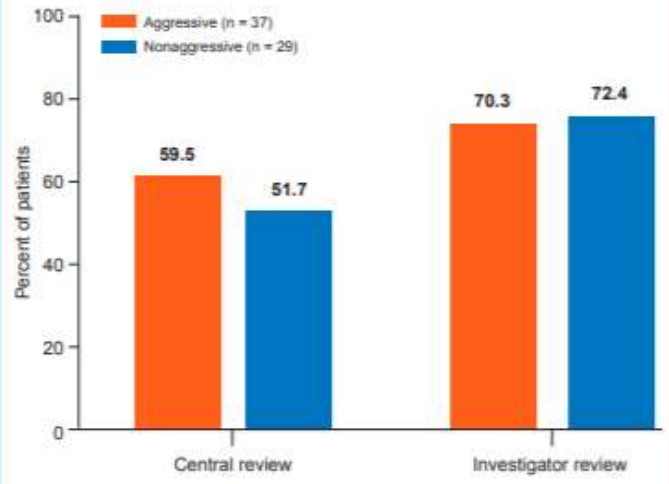
RESEARCH LETTER | VOLUME 84, ISSUE 4, P1162-1164, APRIL 01, 2021

Efficacy of sonidegib in histologic subtypes of advanced basal cell carcinoma: Results from the final analysis of the randomized phase 2 Basal Cell Carcinoma Outcomes With LDE225 Treatment (BOLT) trial at 42 months

Reinhard Dummer, MD • John T. Lear, MD • Alex Guminski, MD, PhD • Liang Joo Leow, MBBS, MPH&TM • Nicholas Squittieri, MD • Michael Migden, MD

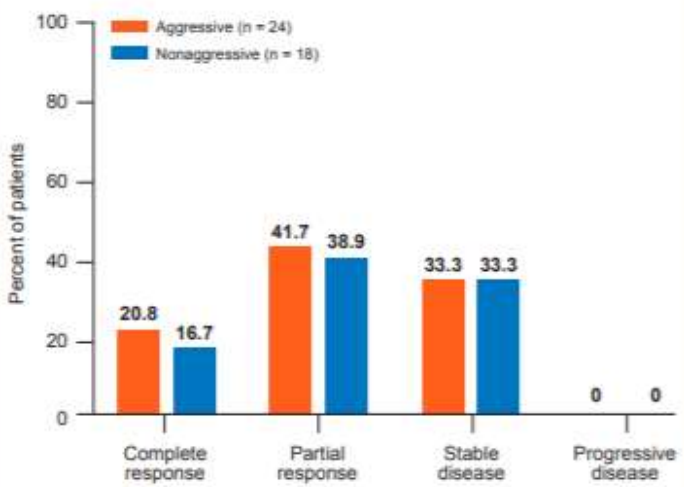
Open Access • Published: December 23, 2020 • DOI: https://doi.org/10.1016/j.jaad.2020.08.0

Figure 3. Objective response rate by central and investigator review using RECIST



Objective response rate is the proportion of patients with a confirmed complete or partial response by mRECIST as their best overall response. Aggressive includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes; nonaggressive includes nodular and superficial histological subtypes.
mRECIST, modified Response Evaluation Criteria in Solid Tumours.(sonidegib) Treatment.

Figure 4. Best overall response by central review using RECIST



Aggressive includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes; nonaggressive includes nodular and superficial histological subtypes.
RECIST, Response Evaluation Criteria in Solid Tumors.

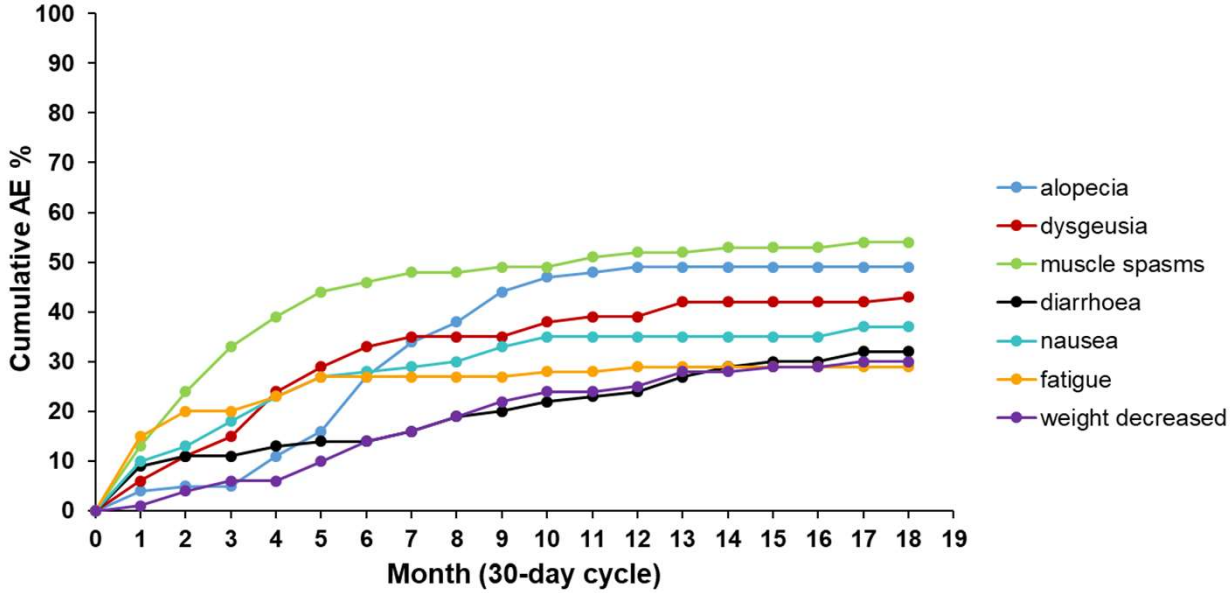
1. Dummer et al. Journal of the American Academy of Dermatology 84.4 (2021): 1162-1164.

SAFETY OF SONIDEGIB: ADVERSE EVENTS

Dermatol Ther (Heidelb)
https://doi.org/10.1007/s13555-021-00588-8

BRIEF REPORT

Key Clinical Adverse Events in Patients with Advanced Basal Cell Carcinoma Treated with Sonidegib or Vismodegib: A Post Hoc Analysis



TOLERABILITY PROFILE IN PATIENTS TREATED CONSECUTIVELY WITH BOTH HHIs[1]


cancers

MDPI

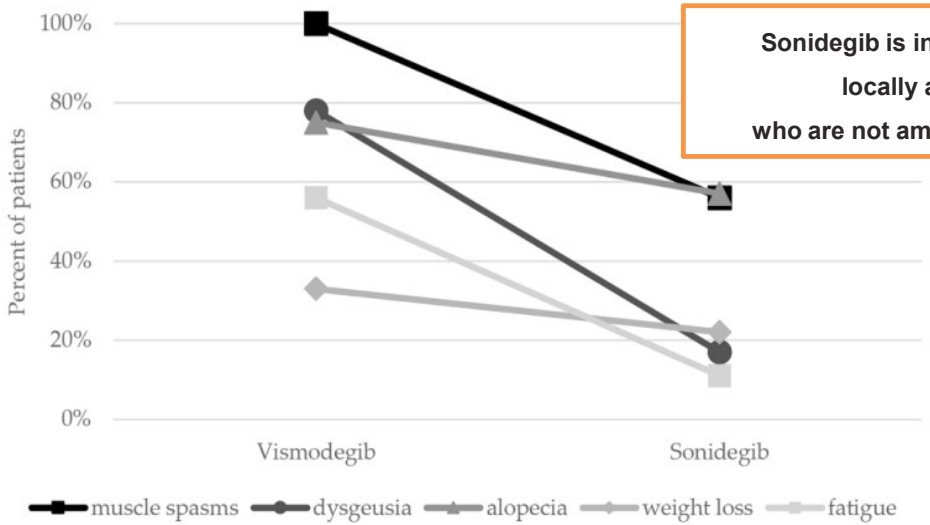
Article

Eight Years of Real-Life Experience with Smoothened Inhibitors in a Swiss Tertiary Skin Referral Center

Lara E. Grossmann *, Egle Ramelyte, Mirjam C. Nägeli † and Reinhard Dummer †

Adverse events for patients with first vismodegib and sonidegib subsequently

Retrospective, single-center analysis* (N=33 of which 12 were treated with sonidegib; 9/12 among sonidegib patients were previously treated with vismodegib)[1]



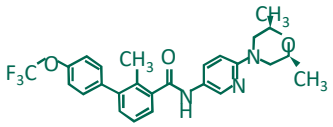
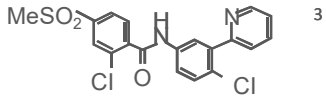
Sonidegib is indicated for the treatment of adult patients with locally advanced Basal Cell Carcinoma (laBCC) who are not amenable to curative surgery or radiation therapy[2]

HHi, hedgehog inhibitors

*In this retrospective single-center analysis, data from 33 adult patients who were treated with vismodegib or sonidegib were analyzed. Indication criteria for vismodegib and sonidegib included laBCC and mBCC** ineligible for surgery and radiotherapy due to repeated recurrence after surgical procedures with curative intent or due to an expected considerable morbidity and deformity after surgery, or severe comorbidities. Data on age, gender, comorbidities, tumor location, previous therapies, indication for treatment with HhIs (laBCC, mBCC or multiple BCCs), type of HHI therapy, treatment dosage, dosing regimen (intermittent vs continuous), duration of intake, combination with other drugs, adverse events, management of adverse events, reason for therapy discontinuation and subsequent treatments we collected. All patients were analyzed for safety.

**Odomzo® is approved for mBCC in Switzerland and Australia only

HEDGEHOG PATHWAY INHIBITORS IN ADVANCED BCC: TWO DIFFERENT MOLECULES

		Odomzo® (sonidegib)	vismodegib
	Molecular structure	 [1]	 [3]
	Dosing	200 mg orally once daily (empty stomach)*[2]	150 mg orally once daily [4]
	Approved dose modifications	Alternate day dosing [2]	None
At steady state	**Half-life (T ½)**	~28 days [2]	~4 days [4]
At steady state	**Plasma peak concentration (Cmax)**	1030 ng/ml [1]	11449 ng/ml [5]
At steady state	**Lowest plasma concentration (Cmin)**	890 ng/ml [1]	10493 ng/ml [5]
At steady state	**Skin concentration**	6-fold higher in skin than in plasma [2]	Not measured
At steady state	**Apparent volume of distribution (Vss/F)**	9170 litres [2]	16.4-26.6 litres [4]

* at least two hours after a meal and at least one hour before the following meal

1. Odomzo® US prescribing information 2019. **2.** Odomzo® summary of product characteristics 2019. **3.** Erivedge® US prescribing information 2019. **4.** Erivedge® summary of product characteristics 2019. **5.** Sharma MR, Clin Cancer Res. 2013 Jun 1;19(11):3059-67.

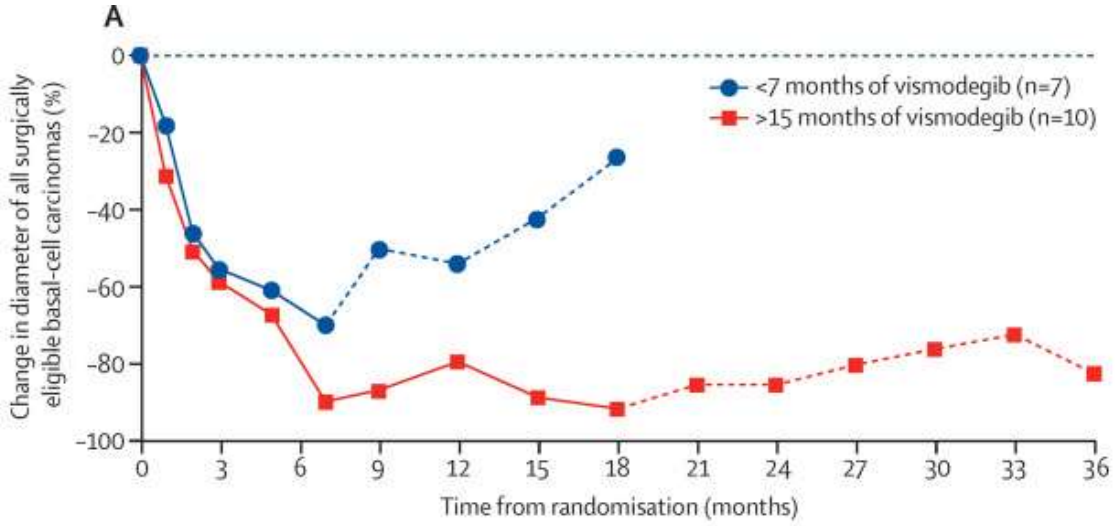
PATIENTS TREATED FOR LONGER PERIODS OF TIME HAVE A LONGER DURATION OF BENEFIT AFTER STOPPING THE DRUG

THE LANCET
Oncology
Volume 17, Issue 12, December 2016, Pages 1720-1731

Articles

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

Jean Y Tang MD [a, b, †], Mina S Ally MD [a, b, †], Anita M Chanana BS [a], Julian M Mackay-Wiggan MD [c], Michelle Aszterbaum MD [d], Joselyn A Lindgren MS [a], Grace Ulerio BA [c], Melika R Rezaee BA [a], Ginny Gildengorin PhD [a], Jackleen Marji MD [c], Charlotte Clark MD [c], Prof David R Bickers MD [c], Dr Ervin H Epstein Jr MD [a]



In patients who took vismodegib continuously for at least 15 months (n=10), the anti-basal-cell carcinoma effect was maintained (*i.e.*, there was no return to baseline tumour burden) for 18 months after discontinuing the drug

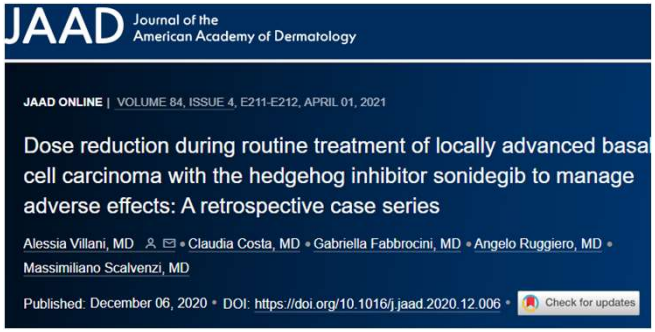
1. Tang et al. New England Journal of Medicine 366.23 (2012): 2180-2188.

METHODS TO PREVENT DISCONTINUATION AND PROLONGING HHI THERAPY

1. Every-other-day-dosing*
2. Treatment interruption (on-off-treatment)
3. Rechallenge with HHI after treatment discontinuation
4. Active treatments of side effects

* Alternate day dose in label treatment for sonidegib

1. DOSE-REDUCTION (EVERY-OTHER-DAY-DOSING)*


JAAD Journal of the American Academy of Dermatology

JAAD ONLINE | VOLUME 84, ISSUE 4, E211-E212, APRIL 01, 2021

Dose reduction during routine treatment of locally advanced basal cell carcinoma with the hedgehog inhibitor sonidegib to manage adverse effects: A retrospective case series

Alessia Villani, MD • Claudia Costa, MD • Gabriella Fabbrocini, MD • Angelo Ruggiero, MD • Massimiliano Scalvenzi, MD

Published: December 06, 2020 • DOI: https://doi.org/10.1016/j.jaad.2020.12.006 • Check for updates

Retrospective case series of 20 laBCC patients

- 12 (60%) patients were considered with CR, 6 (30%) with PR, 2 (10%) with SD. None presented PD.
- Patients receiving alternate day dose (9/20) showed comparable clinical responses, with milder AEs compared with patients receiving daily dosing regimen
  - In the dose adjustment group, 66.7% (6/9) patients and 33.3% (3/9) presented CR and PR, respectively.
  - All of the 9 patients experienced mild (grade 1-2) AEs

Table 1. Characteristics of the 9 patients treated with dose adjustment

Patient/ (sex; age)	Localization	Dose reduction scheme	Response at treatment end	Adverse effects	Degree of adverse effects	Observation period (months)
1/ M; 80y	left leg	16 wk 1/1; 16 wk 1/2	CR	dysgeusia, muscle spasms	1-2	8 months
2/ M; 67y	periauricular region	12 wk 1/1; 16 wk 1/2	CR	muscle spasms	1-2	7 months
3/ M; 68y	central face	16 wk 1/1; 12 wk 1/2	PR	fatigue, muscle spasms, dysgeusia	1-2	7 months
4/ M; 96y	central face	20 wk 1/1; 8 wk 1/2	CR	muscle spasms, fatigue, alopecia	1-2	7 months
5/ M; 84y	ocular region	24 wk 1/1; 8 wk 1/2	PR	diarrhea, dysgeusia, muscle spasms	1-2	8 months
6/ M; 96y	multiple BCCs central face	12 wk 1/1; 12 wk 1/2	CR	dysgeusia	1	6 months
7/ F; 82y	Nose	16 wk 1/1; 16 wk 1/2	CR	muscle spasms,dysgeusia	1-2	8 months
8/ M; 82y	multiple BCCs central face	12 wk 1/1; 16 wk 1/2	PR	muscle spasms, fatigue, alopecia	1-2	7 months
9/ M; 85y	Forehead	16 wk 1/1; 12 wk 1/2	CR	muscle spasms, dysgeusia	1-2	7 months

wk: week of treatment; 1/1 once daily; ½ once every second day

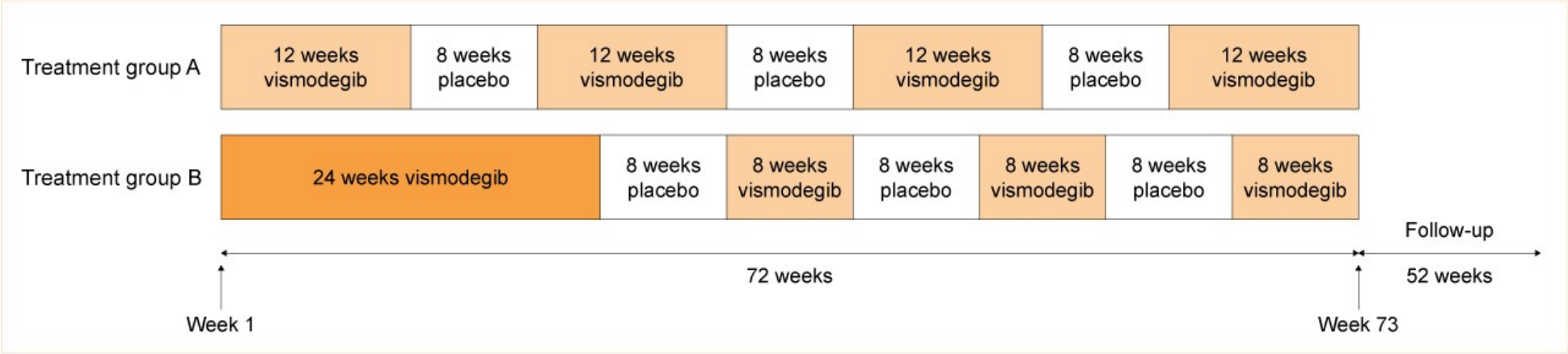
** Alternate day dose in label treatment for sonidegib*

1. Villani A et al. J Am Acad Dermatol. 2020 Dec 7;S0190-9622(20)33150-9. doi: 10.1016/j.jaad.2020.12.006. Online ahead of print.

2. TREATMENT INTERRUPTION (ON-OFF-TREATMENT)

Two intermittent vismodegib dosing regimens in patients with multiple BCC (MIKIE)[1]

- Randomized, regimen-controlled, double-blind.



	MIKIE[1] N=229	STEVIE[2] N=1215	ERIVANCE[3] N=104
AEs leading to discontinuation	23% Group A: 20%, Group B: 34%	31%	57%*
AE ≥ Grade 3	31%	44%	56%
mDoT (weeks)	71	38	56

Conclusion: intermittent dosing schedules could be a useful strategy for patients with multiple BCCs who need long-term treatment.

*Combined number of patients who discontinued because of patient decision (26%), physician decision (10%) and AEs (21%).
AE = adverse event, mDoT = median duration of treatment

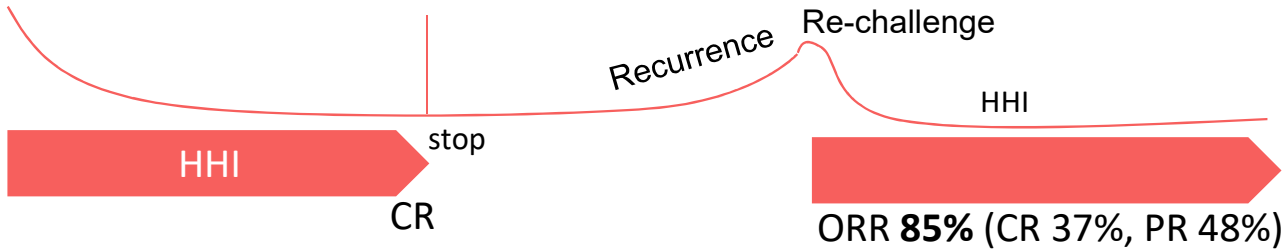
1. Dréno B *et al. Lancet Oncol* 2017;18:404–412. **2.** Basset-Seguin N et al. European Journal of Cancer 2017; 86: 334-348. **3.** Sekulic A et al. BMC Cancer 2017; 17: 332

3. RECHALLENGE WITH HHI AFTER TREATMENT DISCONTINUATION = INTERRUPTION OF TREATMENT

Follow-Up of Patients With Complete Remission of Locally Advanced Basal Cell Carcinoma After Vismodegib Discontinuation: A Multicenter French Study of 116 Patients

Florian Herms, MD[1,2]; Jerome Lambert, MD[1,2]; Jean-Jacques Grob, MD, PhD[3]; Luc Haudebourg, MD[1,2]; Martine Bagot, MD, PhD[1,2]; Sophie Dalac, MD[4]; Caroline Dutriaux, MD[5,6]; Bernard Guillot, MD, PhD[7]; Geraldine Jeudy, MD[4]; Christine Mateus, MD[8]; Sandrine Monestier, MD[3]; Laurent Mortier, MD, PhD[9]; Nicolas Poulalhon, MD[10]; Sorilla Prey, MD, PhD[5,6]; Caroline Robert, MD, PhD[8]; Pierre Vabres, MD, PhD[4]; Celeste Lebbe, MD, PhD[1,2]; Nicolas Meyer, MD, PhD[11]; and Nicole Basset-Seguin, MD, PhD[1,2]

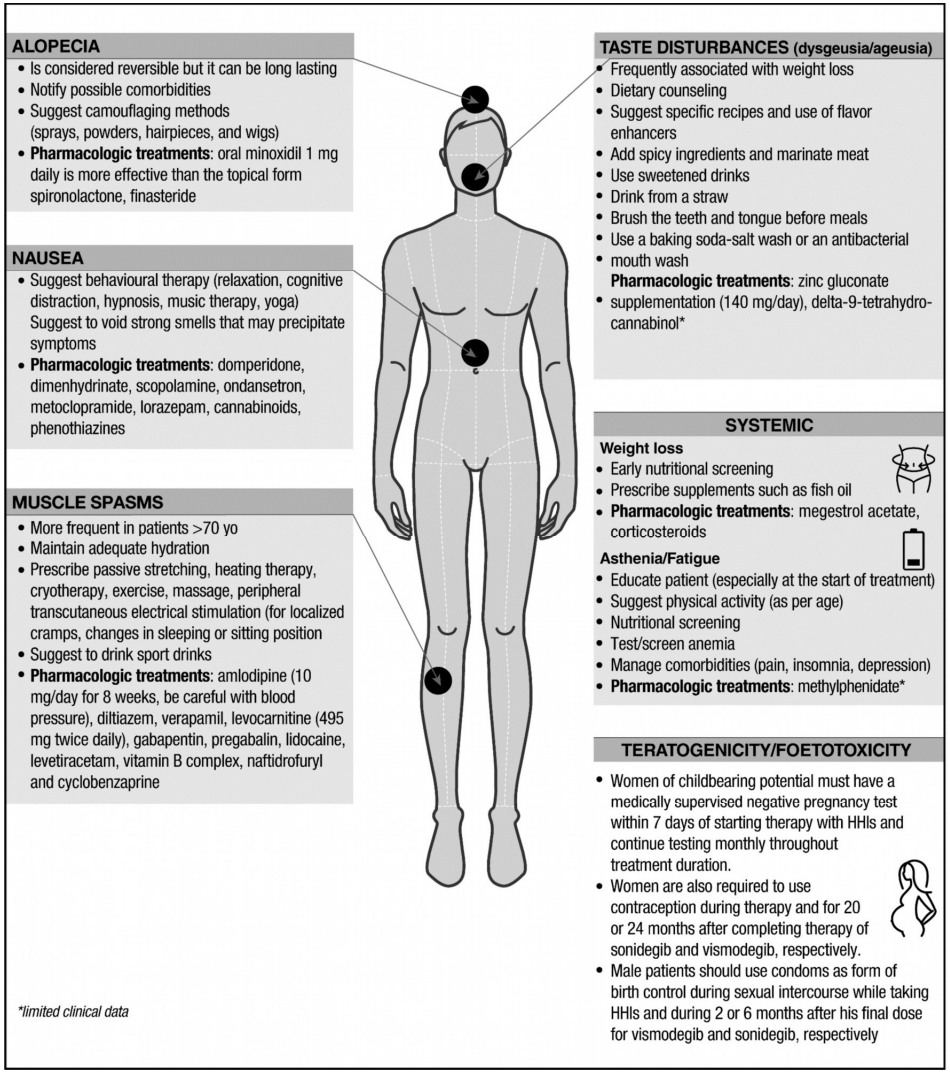
- 54 patients who experienced relapse during follow-up, 27 (50%) were retreated with vismodegib.
- Among them, 23 (85%) had an objective response again.
- 24 patients (42%) were eligible for surgery



Discontinuation = temporary interruption of treatment
Median treatment duration with vismodegib after CR: 1.0 M (0.3-3.8)
mRFS 18.4 months after discontinuation for the whole group

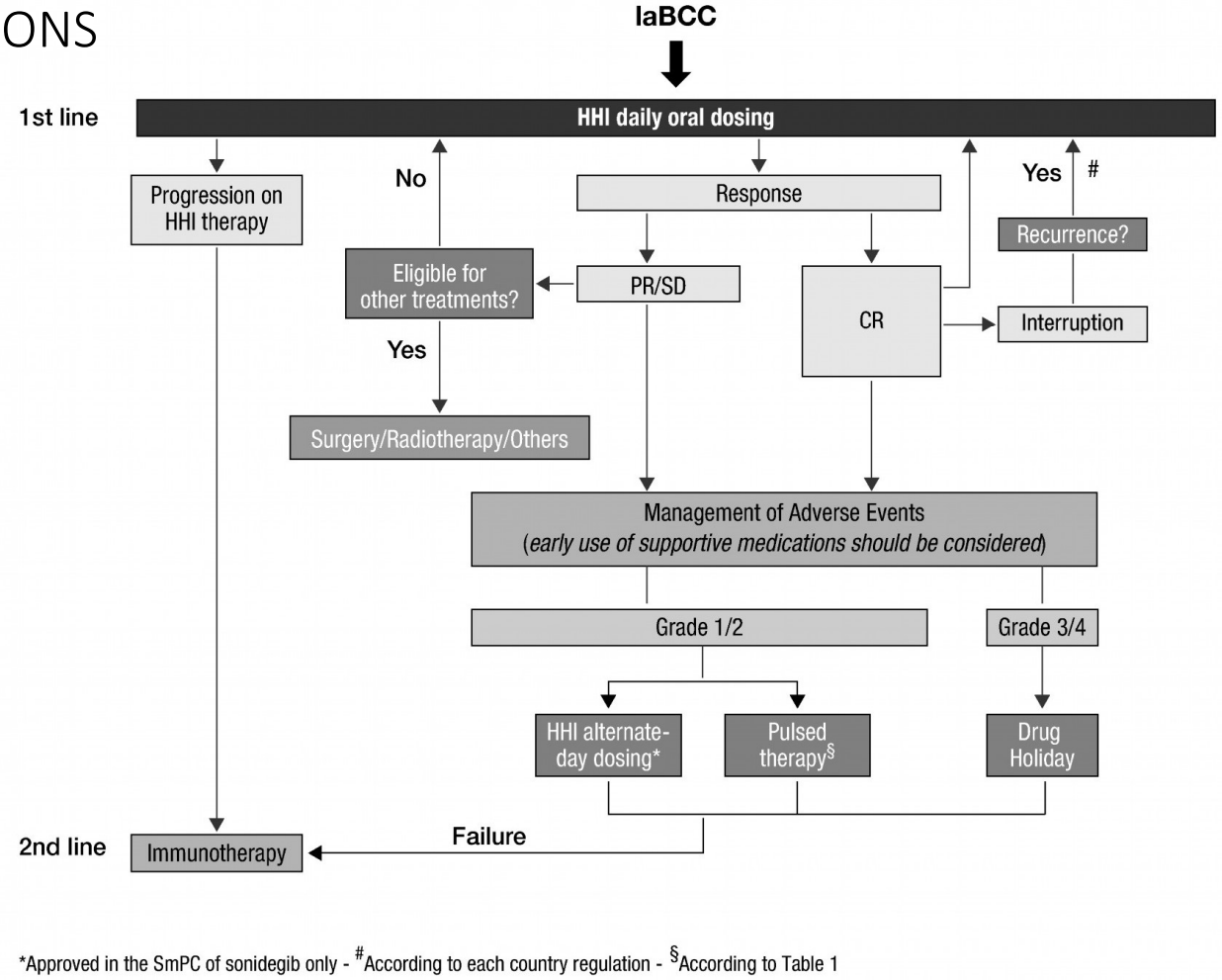
1. Herms F et al. J Clin Oncol. 2019 Dec; 37(34):3275-3282

MANAGEMENT OF ADVERSE EVENTS



1. Bossi et al. Long-term strategies for management of advanced basal cell carcinoma with hedgehog inhibitors. Crit Rev Oncol Hematol. 2023 Jul 11;189:104066

THERAPEUTIC ALGORITHM FOR ADVANCED BCC: 1ST AND 2ND TREATMENT OPTIONS



*Approved in the SmPC of sonidegib only - #According to each country regulation - §According to Table 1

1. Bossi et al. Long-term strategies for management of advanced basal cell carcinoma with hedgehog inhibitors. Crit Rev Oncol Hematol. 2023 Jul 11;189:104066