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Interim analysis of the multinational, post-authorization safety study (NISSO) to assess the long-term safety of sonidegib in patients with locally advanced basal cell carcinoma

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Abstract

Background: Following the pivotal phase II trial BOLT, the Hedgehog (Hh) inhibitor sonidegib was approved in the EU to treat locally advanced basal cell carcinoma (laBCC) in patients not amenable to surgery or radiotherapy. We report safety data from the interim analysis of the real-world NISSO study.

Methods: NISSO is an ongoing non-interventional, multinational, post-authorization safety study (NCT04066504). Patients with laBCC are treated with sonidegib 200 mg orally once daily and followed for 3 years. Dose modifications were allowed according to the local prescribing information.

Results: Between May 6, 2019, and March 15, 2022, 321 patients with laBCC were enrolled at 46 European sites (data cut-off: June 22, 2023). Treatment was discontinued in 241 (75.1%) patients, with the main reasons being the patient/guardian decision (n = 69, 28.6%), treatment success (n = 40, 16.6%) and the physician decision (n = 35, 14.5%). The median duration of sonidegib exposure was 8.8 months (4.4-13.7 months). Overall, 284 (88.5%) patients had ≥ one treatment-emergent adverse event (TEAE). Most TEAEs were ≤ grade 2 and the most common were muscle spasms (n = 141; 43.9%), dysgeusia (n = 119; 37.1%), and alopecia (n = 97; 30.2%). After 3 months of treatment, the cumulative rates of muscle spasms, dysgeusia, and alopecia were 21.8%, 16.2%, and 3.7%, respectively. TEAEs led to treatment discontinuation in 59 (18.4%) patients, while 149 (46.4%) patients had at least one TEAE leading to dose reduction or interruption. Serious drug-related TEAEs were reported in 13 (4.1%) patients.

Conclusions: These results confirm the safety profile previously observed. Most patients experienced the onset of common TEAEs after 3 months of treatment, and the cumulative incidence of most common TEAEs was 10-20% lower compared to the BOLT study, except for dysgeusia and fatigue that had a similar incidence. The percentage of patients experiencing TEAEs requiring interruption or dose reduction was similar to the BOLT study, while the proportion of patients with TEAE leading to discontinuation of sonidegib was lower. This study demonstrates that the tolerability of sonidegib is manageable in routine clinical practice.

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Background and Aim

- The approval of sonidegib was based on the phase II, multicentre, double-blind trial BOLT conducted in patients with laBCC or mBCC[1,2]
  - Using ERIVANCE-like criteria, the ORR in patients with laBCC receiving sonidegib 200 mg once daily was 60.6% (95% confidence interval [CI]: 47.8–72.4) by central review and 74.2% (95% CI: 62.0–84.2) by investigator review
  - A total of 79 adult patients were exposed to sonidegib for a median of 11 months
  - Sonidegib was associated with an acceptable and manageable safety profile characterized by predictable events, primarily of low to moderate grade, which were generally reversible
- Safety data from patients with long-term exposure to sonidegib in the real world are limited. Here, we report the interim analysis of the NISSO long-term post-authorization safety study (PASS) in order to **further characterize the long-term safety and tolerability profile of sonidegib under routine clinical practice conditions**[3]

laBCC: locally advanced basal cell carcinoma; mBCC: metastatic basal cell carcinoma;
PASS: post-authorization safety study; CI: confidence interval

[1]Gutzmer et al. BMC Cancer. 2021;21(1):1244. [2]Migden MR et al. Lancet Oncol. 2015;16(6):716–28.
[3]Gutzmer R et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z.

Methods

- NISSO is an ongoing **non-interventional, multinational, post-authorization safety study** (NCT04066504)
- **Inclusion criteria**
  - Aged 18 years or older
  - Diagnosis of laBCC and who were not amenable to curative surgery or radiation therapy
  - Patients with Gorlin syndrome could be enrolled if all other criteria were met
- **Exclusion criteria**
  - Patients treated with any HHI besides sonidegib within 3 months prior to study entry
- **Treatment**
  - Patients were treated with sonidegib 200 mg orally taken once daily
  - Dose modifications according to the approved local country prescribing information were permitted
  - Sonidegib treatment was started either at the first visit for this study or prior to study entry
  - Patients were followed up for the duration of 3 years after enrolment
- **Primary objective** is to assess the long-term safety and tolerability profile of sonidegib in the treatment of laBCC as determined by the occurrence of AEs, serious AEs, deaths and discontinuation

laBCC: locally advanced basal cell carcinoma; AEs: Adverse Events

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Between May 6, 2019, and March 15, 2022, **321 patients with laBCC** were enrolled and treated with sonidegib at **46 study sites** in **Germany, Italy, Spain, and Switzerland** (data cut-off: June 22, 2023)

Table 1 Baseline demographics and characteristics

	***N* = 321**
Age, years, median (range)	77 (33–101)
Gender, n (%)	
Male	198 (61.7)
Female	123 (38.3)
Gorlin syndrome, n (%)	39 (12.2)
Primary tumour localization, n (%)	
Head and neck	233 (72.5)
Trunk and abdomen	30 (9.3)
Multiple locations	22 (6.8)
Extremities	19 (5.9)
Genital region	4 (1.2)
Unknown	13 (4.1)
BCC histotype (multiple answers possible), n (%)	
Nodular	79 (24.6)
Infiltrative	78 (24.3)
Superficial	26 (8.1)
Basosquamous	16 (5.0)
Morphoeic	15 (4.7)
Micronodular	9 (2.8)
Multifocal	8 (2.5)
Multiple histotypes	3 (0.9)
Unknown	92 (28.7)
Other	36 (11.2)

laBCC: locally advanced basal cell carcinoma; BCC: basal cell carcinoma

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Re-challenge with a different HHI, such as switching from vismodegib to sonidegib to improve tolerability, is documented in the literature[3-8]

Table 1 Baseline demographics and characteristics [1]

	***N* = 321**
Largest diameter of primary tumour, mm, median (range)	22.0 (0.25–400.0)
Prior surgery, n (%)	130 (40.5)
Prior systemic therapies, n (%)	53 (16.5)
Sonidegib	6 (1.9)
Vismodegib	41 (12.8)
Immunotherapy	6 (1.9)
Cemiplimab	4 (1.2)
Pembrolizumab	2 (0.6)
Prior radiotherapy, n (%)	32 (10.0)
Prior other local therapy, n (%)	30 (9.3)
Other prior therapies*, n (%)	4 (1.2)

* Acitretin, imiquimod, photodynamic therapy, topical sonidegib

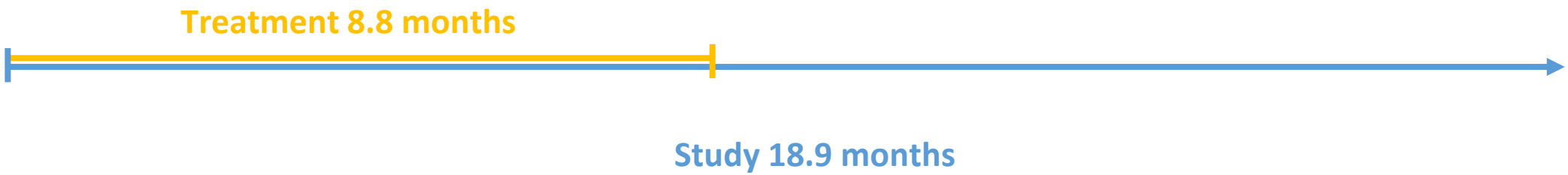
NISSO has a **similar target population to BOLT**, **except for the proportion of those previously treated with surgery and/or radiotherapy** (76% and 32% of the BOLT patients had previously undergone surgery or radiotherapy respectively)[2]

HHI: Hedgehog's Inhibitors

[1]Gutzmer R et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z. [2]Migden MR et al. Lancet Oncol. 2015;16(6):716–28. [3]Grossmann LE et al. Cancers (Basel). 2022;14(10). 27. [4]Di Raimondo C et al. Arch Clin Med Case Rep. 2022;6:636–8. 28. [5]Comito F et al. Ital J Dermatol Venerol. 2023;158(2):150–2. [6]Piccerillo A et al. Dermatol Ther. 2021;34(5): e15095. 30. [7]Puig S et al. Drugs Context. 2022;11. [8]Venturi F et al. Skin Health Dis. 2023;3(5): e260

Time on treatment and on study

- The **median duration of sonidegib treatment** was **8.8 months** (interquartile range [IQR]: 4.4–13.7 months) **including days off treatment** and **7.2 months** (IQR: 4.2–12.8 months) **excluding days off treatment**
- **Median time on study** (time from start of sonidegib treatment until either date of last contact for patients who ended the study or date of last visit for patients remaining in study) was **18.9 months** (IQR: 12.3–27.9 months).



IQR: Interquartile Range

Gutzmer R et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z.

Reasons for end of treatment

- At the time of data cut-off, treatment was ended in 241 (75.1%) patients, among which the reasons were[1]:
  - patient/guardian decision (n=69; 28.6%),
  - **treatment success** (n=40; 16.6%),
  - physician decision (n=35 14.5%),
  - disease progression (n=30; 12.5%),
  - **toxicity** (n=22; 9.1%),
  - lost to follow-up (n=19; 7.9%),
  - death (n=13; 5.4%; deemed not drug-related by investigators),
  - regular end of study (3 years of follow-up after enrolment) (n=8; 3.3%),
  - organizational reason (n=3; 1.2%), and
  - missing reason (n=2; 0.8%).

- **More patients discontinued due to treatment success than to toxicity**
- This is in line with the results of the French national registry CARADERM that reported sonidegib discontinuation as being more related to clinical benefit rather than AEs and with the high efficacy results from the pivotal trials of HHIs[2]
- **A high discontinuation rate should not be perceived as negative per se as reasons such as satisfactory efficacy or treatment holidays may be signifcant and cannot be overlooked**

AEs: Adverse Events

[1]Gutzmer et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z.
[2]Basset-Seguin N et al. J Eur Acad Dermatol Venereol. 2024 Dec 16. doi: 10.1111/jdv.20496. Online ahead of print.

Post-sonidegib therapy

- Of the 209 patients who ended the sonidegib treatment for a reason other than death or were lost to follow-up, **160 (76.6%) received no further laBCC treatment**[1]
- Among the 49 (23.4%) patients who went on to a further laBCC therapy[1]:
  - surgery (n=7; 3.3%),
  - radiotherapy (n=3; 1.4%),
  - other local therapy (n=4; 1.9%)
  - systemic therapy (n=35; 16.7%; of which 26 patients with immunotherapy and 4 with vismodegib)

Growing evidence points to the potential use of HHIs as a **neoadjuvant approach** prior to surgery for laBCC, **due to significant tumour shrinkage** seen during the pivotal trial[2-6]

Cemiplimab is the only **second-line** treatment approved in laBCC and is recommended **for patients developing progression while on HHI therapy (resistance) or in case of persisting toxicities despite failure of long-term management of AEs**[7,8]

HHI: Hedgehog's Inhibitors; laBCC: locally advanced basal cell carcinoma; AEs: Adverse Events

[1]Gutzmer et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z. [2]Migden MR et al. Lancet Oncol. 2015;16(6):716–28. [3]Bertrand N et al. EClinicalMedicine. 2021;35: 100844. [4]Dika E et al. Exp Dermatol. 2023;32(11):2038–9. [5]Paradisi A et al. J Dermatol. 2024;51(1):106–9. [6]Villani A et al. Oncologist. 2022;27(6): e533. [7]Bossi P et al. Crit Rev Oncol Hematol. 2023;189: 104066. [8]Heppt MV et al. Cancers (Basel). 2022;14(19).

Table 2 Overview of TEAE[1]

	N = 321 *n (%)*
Patients with TEAE	284 (88.5)
Patients with drug-related TEAE	252 (78.5)
Patients with TEAE leading to death*	17 (5.3)
Patients with TEAE leading to discontinuation of sonidegib‡	59 (18.4)
Patients with TEAE leading to dose reduction	73 (22.7)
Patients with TEAE leading to interruption	98 (30.5)
Patients with serious TEAE	87 (27.1)
Patients with serious drug-related TEAE#	13 (4.1)

* Considered not drug-related by investigator

‡ The only TEAE leading to discontinuation that occurred in more than 2% of patients was basal cell carcinoma (*n* = 17, 5.3%)

Myocardial infarction, vertigo, nausea, vomiting, fatigue, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatine phosphokinase increased, hepatic enzyme increased, muscle spasms, basosquamous carcinoma, squamous cell carcinoma of skin, chronic obstructive pulmonary disease, and dyspnoea

The percentage of NISSO patients with TEAEs requiring **interruption or dose reduction** was **consistent with the BOLT[2] study**, while the proportion of patients with **TEAEs leading to discontinuation** of sonidegib was **lower**

TEAEs: Treatment Emergent Adverse Events

[1]Gutzmer R et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z.
[2]Dummer R et al. Br J Dermatol. 2020;182(6):1369–78.

Two **expert consensus** papers by Bossi et al. and by Heppt et al. discussed how **dose reductions and interruptions followed by re-exposure, together with active AE pharmacological treatment, can be successfully used to manage AEs** related to HHI therapy[2,3]

As **HHIs represent, so far, the most effective treatment to achieve an early, high and long-lasting response, the goal is to extend HHI therapy as much as possible**[2,3]

Table 3 Interruptions and dose reductions[1]

	***N*=321**
Median duration of treatment interruption, month days	31 (13–91)
Number of patients with at least one therapy interruption, n (%)	156 (48.6)
Number of therapy interruptions, median (range)	1 (1–13)
Reasons for treatment interruptions, n (%)	
AE*	107 (33.3)
Serious AE	3 (0.9)
Patient's wish	30 (9.3)
Tumour progression	7 (2.2)
Unknown	8 (2.5)
Complete response / achieved therapy goal	14 (4.4)
(Un)Availability of care / drug	7 (2.2)
Physician's decision	12 (3.7)
Scheduled interruptions	8 (2.5)
Other	6 (1.9)

According to the German NIELS study, **this approach of AE management, with interruptions and re-challenge, still led to a satisfactory objective response with vismodegib**[4]

HHI: Hedgehog's Inhibitors; AEs: Adverse Events

[1]Gutzmer R et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z.
[2]Bossi P et al. Crit Rev Oncol Hematol. 2023;189: 104066. [3]Heppt MV et al. Cancers (Basel). 2022;14(19).
4Gutzmer R et al. J Eur Acad Dermatol Venereol. 2021;35(8):1678–85.

Dose reduction (one capsule every other day), in case this is required to reduce AEs, is **only within the label of sonidegib**[2]

Table 3 Interruptions and dose reductions[1]

	***N*=321**
Number of patients with at least one dose reduction, n (%)	132 (41.12)
Number of dose reductions, median (range)	1 (1–3)
Reasons for dose reduction, n (%)	
AE[#]	86 (26.8)
Serious AE	1 (0.3)
Patient's wish	12 (3.7)
Tumour progression	2 (0.6)
Unknown	12 (3.7)
Complete response / achieved therapy goal	8 (2.5)
(Un)Availability of care / drug	1 (0.3)
Continuation after interruption	1 (0.3)
Physician's decision	17 (5.3)
Missing	1 (0.3)

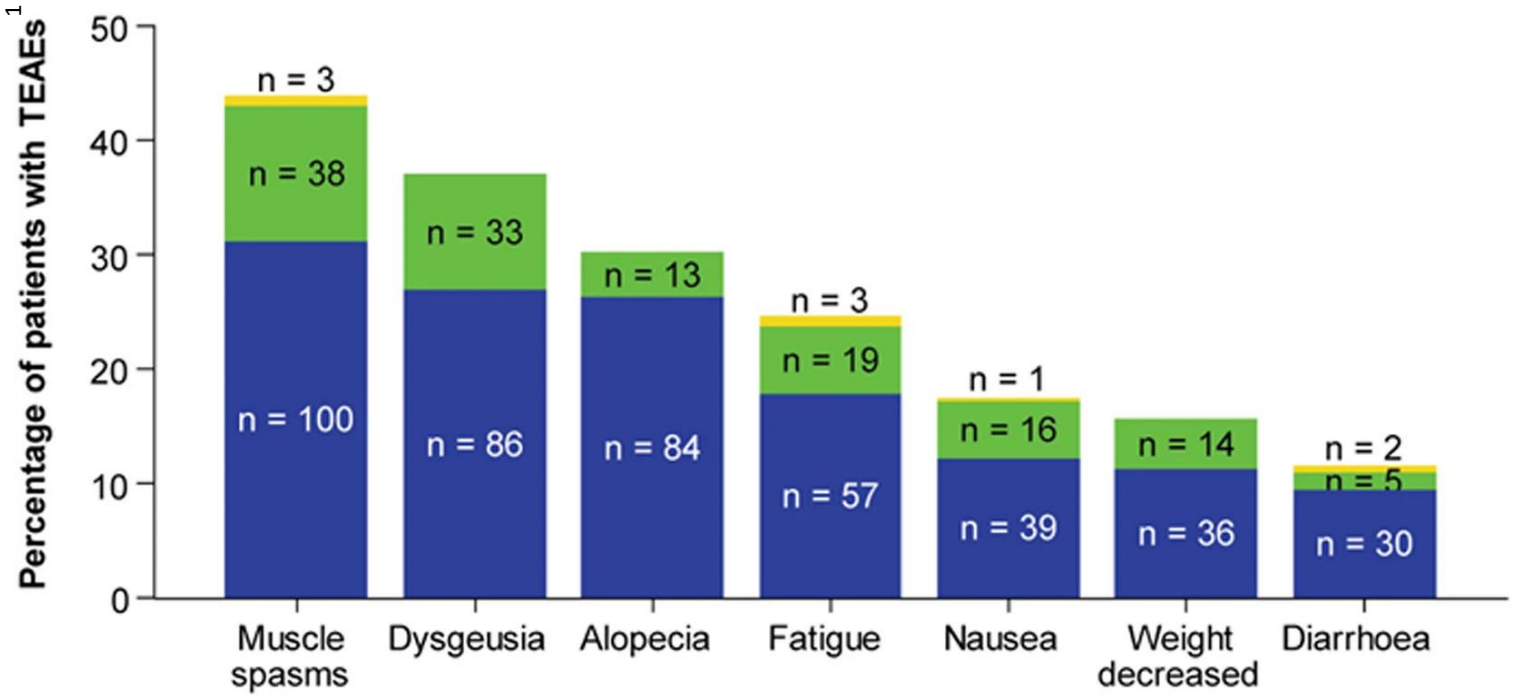
[*] TEAEs leading to treatment interruptions that occurred in more than 2% of patients were muscle spasms (*n*=25, 7.8%), dysgeusia (*n*=18, 5.6%), nausea (*n*=13, 4.1%), blood creatine phosphokinase increased (*n*=10, 3.1%), fatigue (*n*=8; 2.5%), alopecia (*n*=8, 2.5%), weight decreased (*n*=7, 2.2%), decreased appetite (*n*=7, 2.2%)

[#] TEAEs leading to dose reduction that occurred in more than 2% of patients were muscle spasms (*n*=29, 9.0%), dysgeusia (*n*=14, 4.4%), nausea (*n*=12, 3.7%), alopecia (*n*=10, 3.1%), fatigue (*n*=7; 2.2%)

A retrospective observational study of 82 sonidegib patients in Spain showed **significantly less AEs and comparable clinical effectiveness between daily dose and every other day dose,** which is consistent with data from the BOLT study and from real life[3]

AEs: Adverse Events; TEAEs: Treatment Emergent Adverse Events

[1]Gutzmer R et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z. [2]EMA. Summary of Product Characteristics Odomzo. [3]Moreno-Arrones OM et al. Actas Dermosifiliogr. 2023;114(7):T565–71.



No Grade 4 or 5 TEAEs were reported.
TEAE, treatment-emergent adverse event.

These are **expected class effects associated with on-target inhibition of the Hh signalling pathway** and are common with other HHIs such as vismodegib[2]

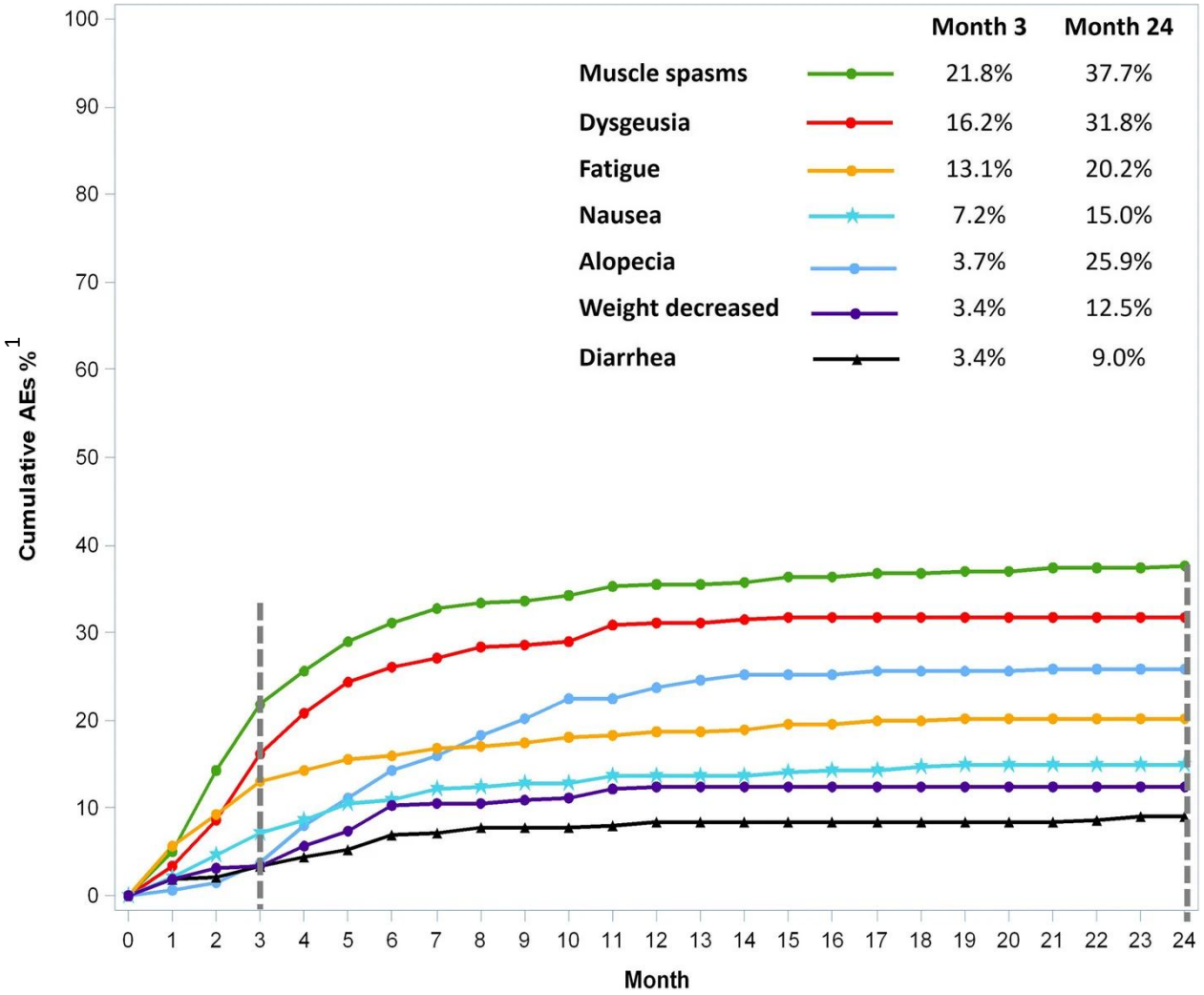
- **Incidences** of the common TEAEs dysgeusia and fatigue were similar to those in the **BOLT** study, while any other common TEAE occurred in fewer patients[2]
- The percentage of patients with **serious TEAEs** was in line with that reported in the **BOLT** study[3]
- Compared to the vismodegib safety study **STEVIE**, a lower **incidence** of muscle spasm, dysgeusia, alopecia, decreased weight and reduced appetite was observed in NISSO, while the rates for fatigue, nausea and diarrhoea were similar[4]
- Assessment of published data from pivotal studies of sonidegib and vismodegib showed that sonidegib had slightly less frequent and less severe common AEs compared with vismodegib at final analyses[5]

TEAEs: Treatment Emergent Adverse Events; HHI: Hedgehog's Inhibitors

[1]Gutzmer et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z. [2]Gutzmer R, et al. Dermatol Ther (Heidelb). 2021;11(5):1839–49. [3]Dummer R et al. Br J Dermatol. 2020;182(6):1369–78. [4]Basset-Séguin N et al. Eur J Cancer. 2017;86:334–48. [5]Dummer et al. J Eur Acad Dermatol Venereol. 2020;34(9):1944–56.

Median time to onset[1]

- 2.2 months for fatigue
- 2.7 months for muscle spasm
- 3.0 months for dysgeusia
- 3.2 months for nausea
- 4.3 months for diarrhoea
- 4.4 months for weight decrease
- 5.5 months for alopecia



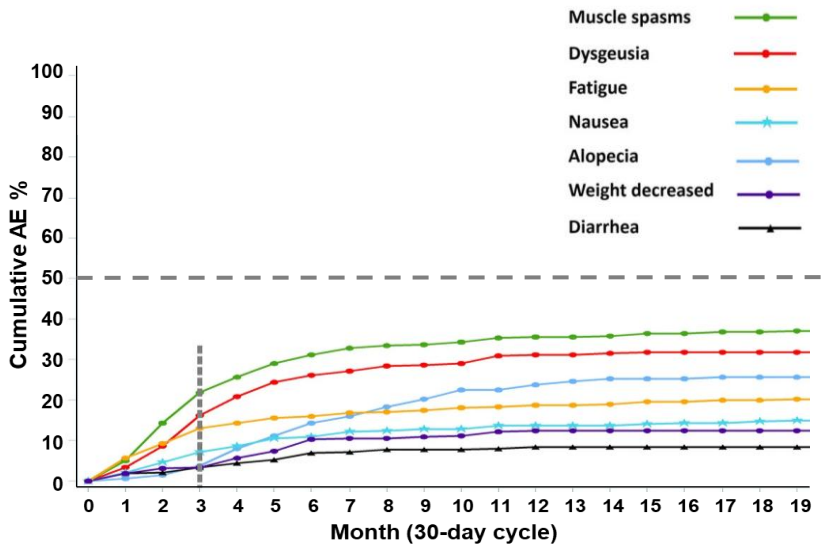
A post-hoc analysis of the sonidegib BOLT study and the expanded-access, open-label vismodegib study revealed that **patients treated with sonidegib had a later median time to onset for all common AEs than patients treated with vismodegib, except fatigue and weight decrease**[2]

- **Most NISSO patients experienced the onset of common TEAEs after 3 months of treatment and the cumulative rate remained approx stable from month 10 to month 24**[1]
- At month 3 of sonidegib use, less patients experienced muscle spasms and nausea compared to BOLT. The proportion of patients with other common TEAEs was similar[2]
- These NISSO data confirm the existence of a **window of opportunity in roughly the first 3 months of treatment** in which most patients have not yet experienced the most common AEs but may already have achieved a response, meaning that that they could have obtained a tumour shrinkage sufficient to make their lesion amenable to local therapies such as surgery or radiotherapy[1]

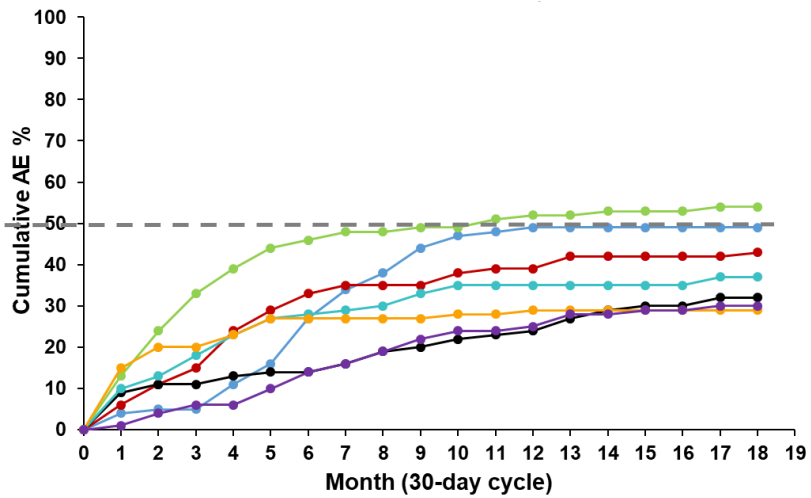
TEAEs: Treatment Emergent Adverse Events; AEs: Adverse Events

[1]Gutzmer et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z. [2]Gutzmer R et al. Dermatol Ther (Heidelb). 2021;11(5):1839–49.

Sonidegib (NISSO study)[1]



Sonidegib (BOLT study)[2]



AEs: Adverse Events

[1]Gutzmer et al. BMC Cancer. 2024 Nov 14;24(1):1401.
[2]Gutzmer et al. Dermatol Ther (Heidelb). 2021 Oct;11(5):1839-1849.

Conclusions

- These results **confirm the safety profile previously observed**[1]
- **Most patients experienced the onset of common TEAEs after 3 months of treatment**[1]
- The cumulative **incidence of most common TEAEs was 10–20% lower compared to the BOLT study, except for dysgeusia and fatigue** that had a similar incidence[1,2]
- The **percentage of patients experiencing TEAEs requiring interruption or dose reduction was similar to the BOLT study** while the **proportion of patients with TEAE leading to discontinuation of sonidegib was lower**[1,3]
- **This study demonstrates that the tolerability of sonidegib is manageable in routine clinical practice**[1]

TEAEs: Treatment Emergent Adverse Events

[1]Gutzmer R et al. BMC Cancer. 2024 Nov 14;24(1):1401. doi: 10.1186/s12885-024-13101-z. [2]Gutzmer R, et al. Dermatol Ther (Heidelb). 2021;11(5):1839–49. [3]Dummer R et al. Br J Dermatol. 2020;182(6):1369–78