Survey of the impact of BOLT-trial data on oncologists' and dermatologists' decision-making in treating patients with locally advanced basal cell carcinoma

Luigi Scarpato,[1] Marco Palla,[1] Sabino Strippoli,[2] Luca Tagliaferri,[3] Luca Fania,[4] Maristella Saponara,[5] Anna Carbone,[6] Francesco Spagnolo,[7] Flavia Silvestri,[8] Paolo Antonio Ascierto[1]

[1]Unit of Melanoma, Cancer Immunotherapy and Innovative Therapies Unit, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples; [2]Rare Tumors and Melanoma Unit, Istituto Tumori IRCCS "Giovanni Paolo II", Bari; [3]Department of Diagnostic for Imaging, Radiation Oncology and Hematology, "A. Gemelli" University Polyclinic Foundation IRCCS, Rome; [4]Istituto Dermopatico dell'Immacolata IRCCS, Rome; [5]Melanoma and Sarcoma Medical Treatment Unit, European Institute of Oncology, Milan; [6]U.O. Clinical Dermatology, IFO San Gallicano, Rome; [7]Department of Plastic and Reconstructive Surgery, Azienda Ospedaliera Universitaria San Martino HSM, Genoa; [8]Section of Dermatology, Department of Health Sciences, University of Florence, Italy

Correspondence: Paolo Antonio Ascierto, Unit of Melanoma, Cancer Immunotherapy and Innovative Therapies Unit, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", via Mariano Semmola, 52, 80131 Naples, Italy.
E-mail: p.ascierto@istitutotumori.na.it

Key words: sonidegib; BOLT trial; basal cell carcinoma; locally advanced BCC.

Contributions: PAA, LS, MP, study conception and design; PAA, LS, MP, SS, LT, LF, MS, AC, FrS, FlS, collection and interpretation of data, manuscript editing; LS, MP, statistical analysis, manuscript drafting. All the authors approved the final version to be published.

Conflict of interest: the authors declare no potential conflict of interest, except for PAA. He has/had a consultant/advisory role for Bristol Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Merck Serono, Pierre-Fabre, AstraZeneca, Sun Pharma, Sanofi, Idera, Sandoz, Immunocore, 4SC, Italfarmaco, Nektar, Boehringer-Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, Oncosec, Nouscom, Lunaphore, Seagen, iTeos, Medicenna, Bio-Al Health, ValoTX, Replimmune. He also received research funding from Bristol Myers Squibb, Roche-Genentech, Pfizer, and Sanofi and travel support from Pfizer. The funders of this study had no role in the design of the study, in the collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

Funding: this study was partially supported by the Italian Minister of Health through "Ricerca Corrente" grant L2/1 to PAA.

Ethics approval and consent to participate: not applicable.

Availability of data and materials: data presented in this study are available from the corresponding author upon reasonable request.

Acknowledgments: we thank all clinicians who consented to this study.

Received: 19 December 2023.
Accepted: 10 March 2024.

Dermatology Reports 2025; 17:9882
doi:10.4081/dr.2024.9882

Abstract

Basal cell carcinoma (BCC) is the most common malignant tumor in white populations. Multiple studies demonstrated that the aberrant activation of Hedgehog signaling is a driver of BCC development, and its blockade represents a potential therapeutic target. In Italy, clinicians can prescribe Hedgehog inhibitors (HhIs) vismodegib and sonidegib. To highlight the treatment choice of clinicians, we conducted an online survey between November 1 and November 18, 2020, with 33 Italian clinicians from 27 reference hospitals, in which each participant received an anonymous survey consisting of two multiple-choice questions on the clinical efficacy and safety profile of sonidegib and vismodegib. Respondents reported their opinions on which efficacy and tolerability data of the pivotal phase-II BOLT trial were more relevant in patients' treatment choices with locally advanced BCC (laBCC). This survey shows that the overall response rate (ORR) and the duration of response (DoR) are the most expected across dermatologists and oncologists. The different pharmacokinetic profiles of the two HhIs are behind their diverse toxicity spectrum; dose and schedule modification seem to address the choice between vismodegib and sonidegib among dermato-oncology prescribers.

Introduction

Several effective therapeutic approaches are available to treat basal cell carcinomas (BCCs), but the treatment of choice remains surgical excision.[1,2] The healthcare workload burden of most BCCs, including small, well-defined tumors in low-risk areas, is substantial within dermatology departments. In a small proportion of patients, BCCs become more difficult to treat and can progress to advanced stages: metastatic BCC (mBCC) and locally advanced BCC (laBCC).[1,2] Locally advanced disease is more difficult to characterize due to heterogeneity and the fact that no formal, widely accepted definition exists. In this context, multidisciplinary care (MC) is essential to ensure patients' best treatment. MC includes professional figures such as dermatologists, oncologists, surgeons, radiation oncologists, radiologists, and pathologists, allowing the optimization of the care process for the management of patients suffering from severe forms of BBC.

Once evolved to laBCC or mBCC, curative surgery and radiotherapy are not feasible, or they could be highly destructive and disfiguring. In these cases, the most appropriate therapeutic option is targeted therapy through Hedgehog inhibitors (HhIs).[3,4] In Italy, both oncologists and dermatologists can prescribe the two

approved HhIs by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA): vismodegib and sonidegib.[5,6] Vismodegib was approved for the treatment of laBCC and mBCC based on outcomes from the ERIVANCE study;[5,7] sonidegib gained approval for laBCC treatment based on the results of the BOLT study.[6,8] The pharmacokinetic profile of sonidegib is different from that of vismodegib, and this might translate into potential differences in efficacy and toxicity.[3,4] Overall response rate (ORR) was the primary endpoint of both pivotal studies; at the 21-month follow-up of ERIVANCE, the primary endpoint (ORR by central review using RECIST) for vismodegib 150 mg was 47.6% (95% CI: 35.5-60.6).[9] Whereas at the 18-month follow-up of BOLT, the primary endpoint (ORR by central review using RECIST-like criteria) for sonidegib 200 mg was 60.6% (95% CI: 47.8-72.4).[10] Interestingly, published data from both pivotal studies showed that sonidegib had an approximately 10% lower incidence of most adverse events (AEs) compared with vismodegib at final analyses.[3,11,12] Because a head-to-head trial is unavailable, HhIs prescribers must carefully weigh the clinical endpoints from pivotal studies and real-world evidence. In this national survey, oncologists and dermatologists from reference hub structures for laBCC were asked questions about the efficacy and tolerability data of the pivotal phase-II BOLT trial they consider relevant to choosing sonidegib in their clinical practice. This survey can inform debates and reflections that are applicable not only in Italy but also in various other countries with similar realities.

Materials and Methods

We conducted a survey among Italian oncologists and dermatologists to collect opinions on which efficacy and tolerability data of the pivotal phase-II BOLT trial they consider relevant to decision-making in the treatment of patients with laBCC. Respondents were contacted by direct e-mail, and a total of 15 oncologists and 18 dermatologists from 27 hub hospitals for patients affected by laBCC accepted to participate in the survey, which was conducted between November 1 and November 18, 2020. The median age of the participants was 37.5 years (range 32-43 years) with >5 years of experience, and 55% were female. Participants were administered a questionnaire consisting of two multiple-choice questions on the clinical efficacy and safety data of sonidegib. For each question, participants were asked to choose one or two items from a limited list of choices; they were also allowed to answer "other". All data were collected anonymously, with no personal information.

Results

When asked about efficacy outcomes from BOLT trials affecting treatment decisions, oncologists stated duration of response, objective response rate, and progression-free survival are influential factors (28%, 24%, and 20%, respectively) (Figure 1). The percentage of dermatologists is similar, but they tend to prioritize objective response rate (35%) over duration of response (DoR) (24%). Disease control rate and time to response are perceived by the responders as less important outcomes for the efficacy. Disease control rate was rated higher by oncologists than dermatologists (16% *vs.* 6%), but time to response scored higher for dermatologists (12% *vs.* 4%). There were minor differences in how participants reported perceptions about the safety outcomes of BOLT trial, and both oncologists and dermatologists identified incidence and severity of AEs of high relevance and importance to sonidegib treatment. A small descriptive trend emerged: a slightly higher percentage of oncologists focused on the incidence of AEs rather than their severity, showing some concern that AEs, although just mild or moderate, can still impact the quality of life of patients as they could be daily and chronic. Overall, a total of 23% to 31% of the respondents identified alternative dosing of high relevance and importance for choosing sonidegib to treat

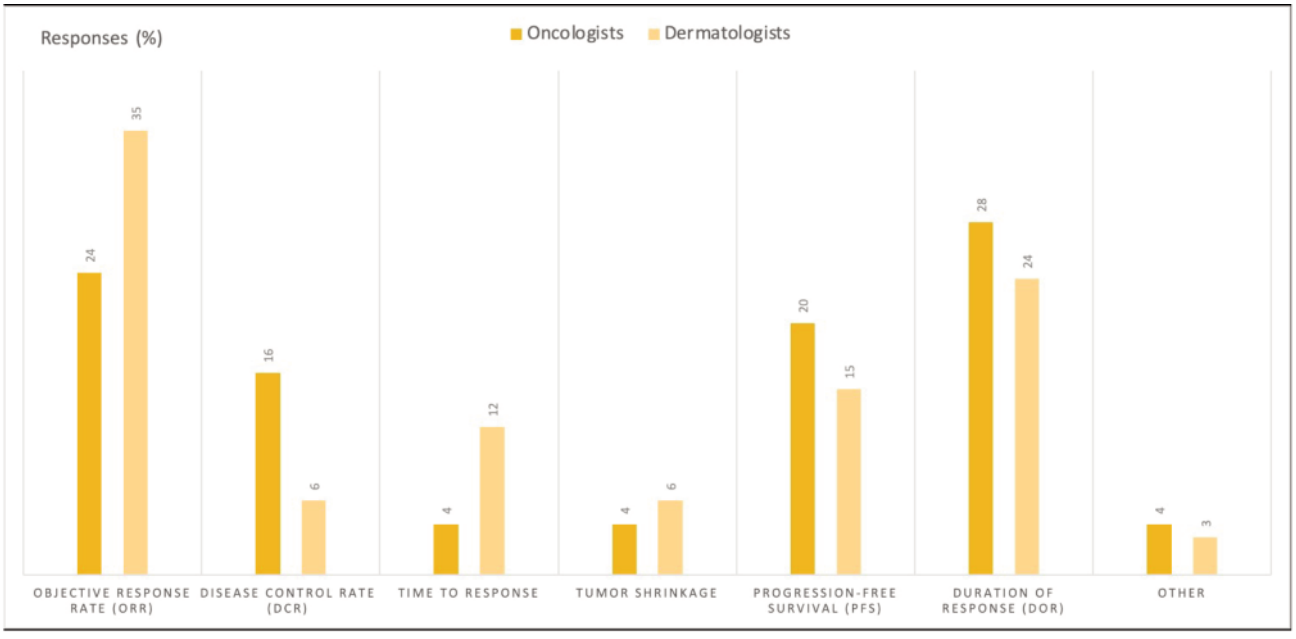

Figure 1. Respondents' answers to the question, "What efficacy outcomes of BOLT trial are most relevant for your clinical decision-making?".

laBCC patients (Figure 2). Respondents did not use the option "other" for the second part of the questionnaire.

Discussion

All the dermatologists and oncologists enrolled in this survey have experience using HhIs in clinical practices. This survey emerged with several key messages and, at the same time, enables a discussion of the multiple ways that oncologists and dermatologists perceive BOLT-trial data affecting the treatment of laBCC patients with sonidegib.

First, according to the majority of participants in the survey, the DoR of sonidegib is the most important measure among secondary endpoints, and unexpectedly, a slightly higher percentage of oncologists admit that the duration of response DoR is affecting their clinical choice more than the primary endpoint of BOLT study. Obtaining a good response and maintaining it over time is fundamental for a disease such as laBCC, which impairs not only functional but also emotional and social domains. The magnitude of the expected clinical benefit of this measure should be evaluated considering that the centrally reviewed median DoR (mDoR) with sonidegib in BOLT was higher than those observed with vismodegib in ERIVANCE (26.1 months *vs.* 9.5 months).[3,9,10] This may reflect the pharmacokinetic profile differences between sonidegib and vismodegib; the former accumulates extensively within tissues, while the distribution of the latter is mainly limited to the plasma.[7,8]

A second finding of our survey is that alternate-day dosing has become a priority to refine patients' quality of life (QoL). The availability of an alternative administration schedule included in the label of sonidegib (200 mg every other day) is very helpful in managing specific AEs, such as high creatine kinase levels. Thus, the rate of treatment discontinuation may be lowered.[8]

BCCs are of increasing concern in the elderly, and clinicians are aware that drug therapy in the old age population is much more challenging and complex than in younger adults, especially due to comorbidities and the higher number of drugs for the treatment of different diseases. For instance, laBCC patients that require concomitant use of potent inhibitors of CYP3A4, such as ritonavir, telithromycin, and ketoconazole, have the possibility, by product label, to reduce sonidegib dose to 200 mg every other day, avoiding overexposure.[8] The product label of vismodegib does not provide any advice on dose adjustment if co-administration is necessary.[7] Third, answers revealed that overall, participants ignore the time-to-onset of AEs registered in the BOLT study. Neglecting these relevant measures could explain the low use of neoadjuvant therapy with HhIs before surgery,[13] or radiotherapy, despite the high potential to improve patients' (QoL) and clinical benefit.[14] In this setting, the use of sonidegib may be of interest since AEs seem to appear slightly later than with vismodegib.[3] This would provide a suitable time to treat the patients for a few months with sonidegib before surgery or radiation therapy without significant tolerability issues, considering that its concentration is sixfold higher in the skin compared with plasma. Additionally, the median time to respond, according to an investigator review, was 2.5 months at the 42-month follow-up for sonidegib[12] and 4.7 months at the 39-month analysis for vismodegib.[11] Again, this places sonidegib in a good potential position in a neoadjuvant setting that typically involves a multidisciplinary approach and represents the most effective therapeutic strategy in locally advanced disease.

This survey is meant to be descriptive, and the small sample size limits our ability to make comparisons; however, laBCC is not particularly common and is managed in a limited number of reference centers. Thus, our survey provides an important context for assessing the priorities and attitudes of sonidegib prescribers. Oncologists and dermatologists play an important role in enhancing awareness of HhIs therapy in tumor board settings, along with other specialists who steer laBCC patients' journeys. It is essential to evaluate each patient individually due to the complexity of their disease, and a multidisciplinary team must assess the risk/benefit ratio of systemic treatments.

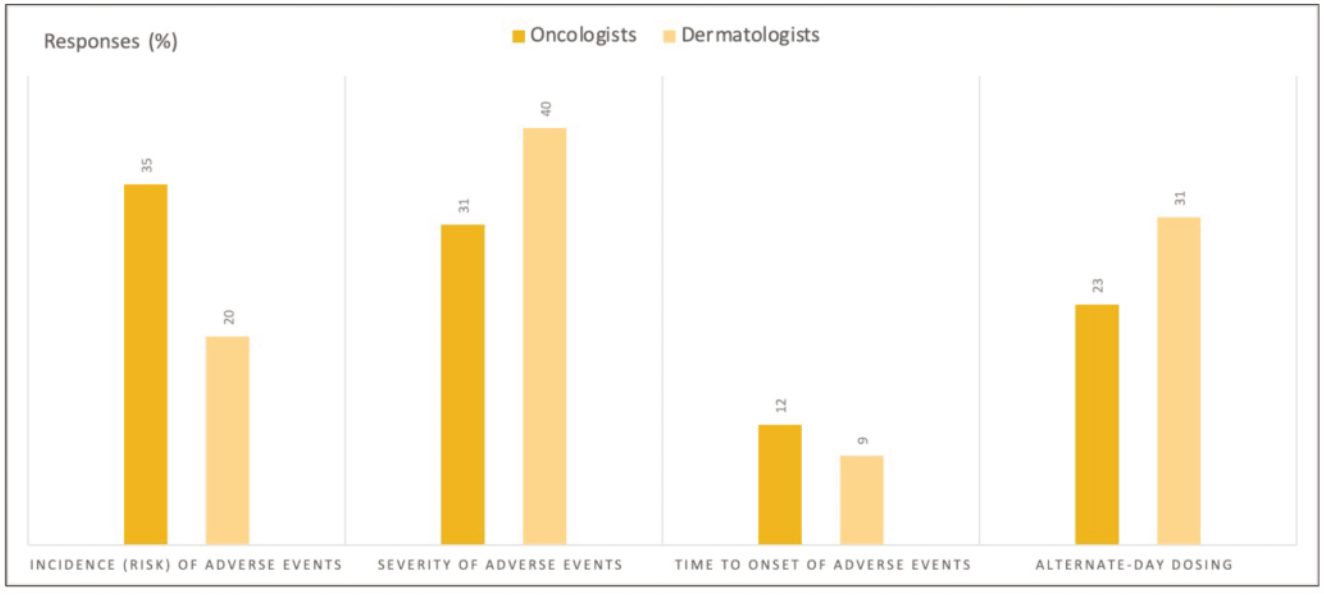

Figure 2. Respondents' answers to the question, "What efficacy outcomes of BOLT trial are most relevant for your clinical decision-making?".

Conclusions

LaBCC is a disfiguring, painful, and functionally limiting cancer. HhIs are the established primary systemic treatment option that has demonstrated clinically meaningful outcomes in patients with laBCC, including the ones with nevoid basal cell carcinoma syndrome (NBCS). Various strategies have been tested for the treatment of HhI-resistant BCC, such as HhIs plus cemiplimab or vismodegib in combination with pembrolizumab.[15] However, such strategies did not prove to increase efficacy whilst worsening the overall toxicity profile. Only recently, cemiplimab was approved by the US Food and Drug Administration fully for locally advanced BCC and accelerated for metastatic BCC for patients who were not candidates for further HHI therapy due to progression or intolerance.[16]

Increased knowledge about this neoplasm, leading to a broader spectrum of therapeutic options, does not overcome the data and observations reported in this study since physicians still need to base their decisions on the specific characteristics and clinical history of every patient, with the aim of maximizing the duration of each therapeutic modality and, ultimately, the overall sequential treatment strategy.

This survey shows that overall response and the DoR are the most expected results from sonidegib and vismodegib among dermatologists and oncologists. The two HhIs' different pharmacokinetic profiles are behind their diverse toxicity spectrum. Dose and schedule modification seem to address the choice between vismodegib and sonidegib among dermato-oncology prescribers.

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