Dermatology Reports
https://www.pagepress.org/journals/index.php/dr/index

eISSN 2036-7406

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Please cite this article as: Scarpato L, Palla M, Strippoli S, et al. Survey of the impact of BOLT-trial data on oncologists' and dermatologists' decision-making in treating patients with locally advanced basal cell carcinoma. Dermatol Rep 2024 [Epub Ahead of Print] doi: 10.4081/dr.2024.9882

Submitted: 19/12/2023 – Accepted 10/03/2024

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

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

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, FSp, FSi, 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 with the exception of 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, Sanofi. Travel support by 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 P.A. Ascierto.

Ethical approval and consent to participate: not required.

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

Abstract

Basal cell carcinoma (BCC) is the most common malignant tumour 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 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 the treatment choice of patients with locally advanced BCC (laBCC). This survey shows that overall response rate (ORR) and the duration of response (DoR) are the most expected across dermatologists and oncologists. The different pharmacokinetic profile 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 the best possible treatment. MC includes professional figures such as dermatologists, oncologists, surgeons, radiation oncologists, radiologists, pathologists, allowing the optimization of the care process for the management of the patient 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 the target therapy through Hedgehog inhibitors (HhIs) [3,4]. In Italy, both oncologists and dermatologists can prescribe the two approved HhIs by the FDA and EMA: vismodegib and sonidegib [5, 6].

Vismodegib was approved for treatment of laBCC and mBCC based on outcomes from the ERIVANCE study [5, 7]; Sonidegib gained the approval for laBCC treatment based on the results of the

BOLT study [6, 8]. The pharmacokinetic profile of Sonidegib is different from 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 vismodegib150 mg was 47.6% (95% CI: 35.5–60.6)[9] whereas at 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 incidences of most adverse events (AEs) compared with vismodegib at final analyses [3, 11, 12]. Because a head-to-head trial is not available, HhIs prescribers must carefully weigh the clinical endpoints coming from pivotal studies and real-world evidence.

In this national survey oncologists and dermatologists from reference hub structures for laBCC were asked questions on which efficacy and tolerability data of the pivotal phase-II BOLT trial they consider relevant to choose Sonidegib in their clinical practice. This survey can inform debates and reflection 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 Nov. 1 and Nov. 18, 2020. The median age of the participants was 37.5 yr (range, 32-43 yr) with > 5 years of experience and 55% were female. Participants were administered a questionnaire consisting of two multiple-choice questions on clinical efficacy and safety data of Sonidegib. For each question, participants are 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 trial affecting treatment decision, oncologists stated duration of response, objective response rate and progression-free survival are influential factors (28%, 24% and 20% respectively; Fig 1). The percentage of dermatologists is similar (Fig. 1), but they tend to prioritize objective response rate (35%) than 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 (Fig.2). A small descriptive trend emerged: a slightly higher percentage of oncologists focused on incidence of AEs , rather than their severity, showing some concern that AE, although just mild or moderate, can still impact 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 laBCC patients (Fig.2). Respondents did not avail the option "other" for the second part of the questionnaire.

Discussion

All the dermatologists and oncologists enrolled in this survey have experience in using HhIs into clinical practices. From this survey emerged several key messages, and at the same time, it 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 oncologist 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 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 the quality of life (QoL) of patients. The availability of an alternative administration schedule included in the label of Sonidegib (200 mg every other day) is very helpful in managing the entity of specific AEs, such as high creatine kinase levels, and 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 co-morbidities and to the higher number of drugs for the treatment of different diseases. For instance,

laBCC patients that requires 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 time-to-onset of AEs registered in BOLT study. Neglecting of these relevant measures could be a possible explanation of the low use of neoadjuvant therapy with HhIs before surgery [13], or radiotherapy, in spite of 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 suitable time to treat the patients for 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 response 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 limited number of reference centers. Thus, our survey provides an important context to assess priorities and attitudes of sonidegib prescribes. Oncologists and dermatologists play an important role to enhance awareness on HhIs therapy in tumor board settings with other specialists that steer laBCC patient's journey. As in all complex diseases, it is critical that each patient be evaluated on an individual basis, and the risk/benefit ratio of systemic treatment must be evaluated by multidisciplinary teams.

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 naevoid 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].

The increased knowledge about this neoplasm leading to a broader spectrum of therapeutic options [16] does not overcome data and observations here reported, 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 across dermatologists and oncologists. The different pharmacokinetic profile 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.

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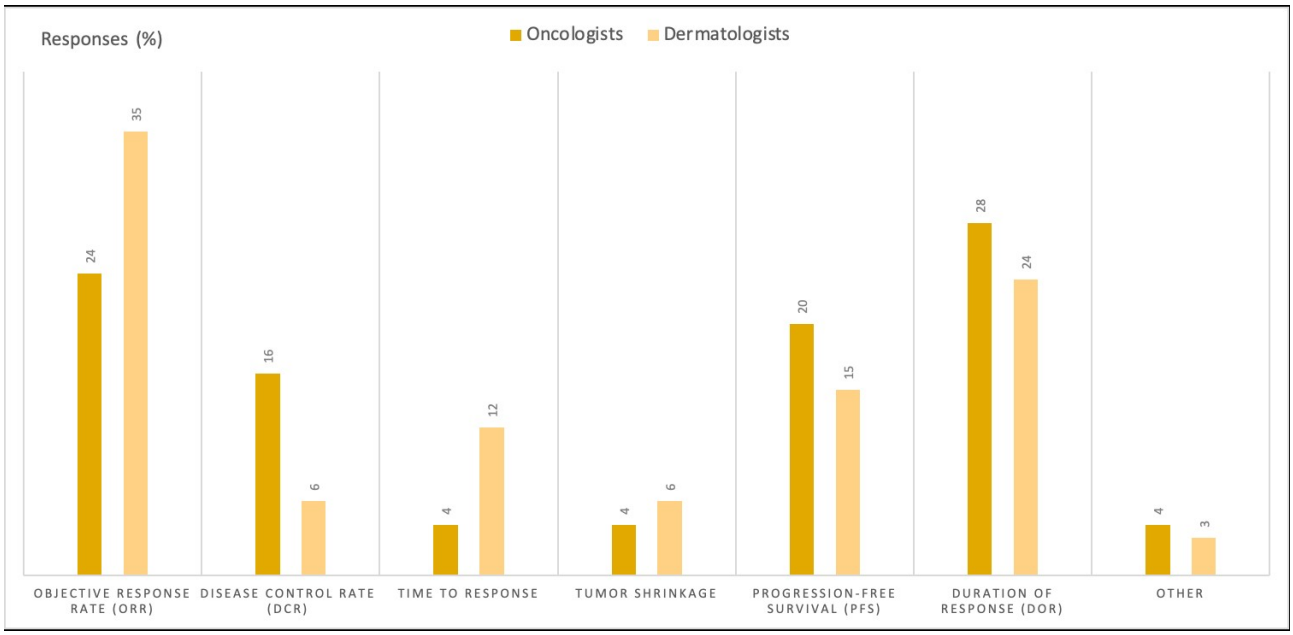

Figure 1. Respondent answers to "What efficacy outcomes of BOLT trial are most relevant for your clinical decision-making?".

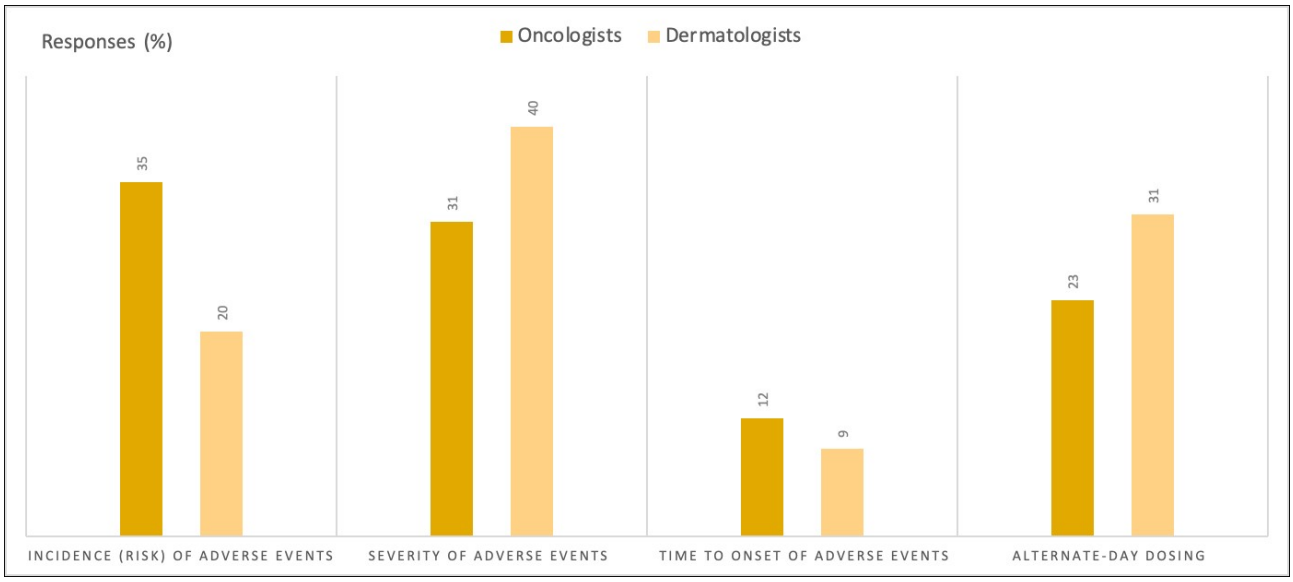

Figure 2. Respondent answers to "What safety characteristics of Sonidegib are most relevant for your clinical decision-making?".