Short Communication

Journal of **Comparative Effectiveness Research**

A qualitative evaluation of patient and healthcare provider knowledge, attitudes, and behavior for safety and use of pexidartinib

Maribel Salas*[,1,2], Michele Julian[3], Leonidas Drogaris[1], Zahidul Islam[1], Mackenzie Henderson[1], Annette Stemhagen[3], Natalie O'Donnell[3] & Nora Tu[1]

[1]Daiichi Sankyo, Inc., 211 Mount Airy Dr., Basking Ridge, NJ 07920, USA

[2]CCEB/CPeRT, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

[2]UBC, 920 Harvest Dr, Blue Bell, PA 19422, USA

*Author for correspondence: Tel.: +1 908 992 6819; msalas@dsi.com

Aim: Pexidartinib is approved in the USA for the treatment of symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery. Due to risk of serious liver injury, a survey of patient and healthcare provider (HCP) knowledge, attitudes, and behavior (KAB) of the risks was required. **Materials & methods:** Prior to KAB survey execution, structured telephone interviews with 12 patients and 12 HCPs were conducted. **Results:** The interviews revealed that patients had difficulty with the complexity and wordiness of some of the questions, while HCPs noted that some questions were repetitive with terminology that was not self-explanatory. Of the 15 questions initially in the patient survey, nine were modified for survey inclusion. For the HCP survey, 10 of 18 questions were modified. **Conclusion:** Qualitative research prior to KAB surveys is recommended to improve comprehension and data quality.

First draft submitted: 15 July 2020; Accepted for publication: 30 November 2020; Published online: 21 January 2021

Keywords: KAB • pexidartinib • QR • qualitative research • REMS • survey

TURALIO® (pexidartinib) is a small molecule tyrosine kinase inhibitor for oral use that targets CSF1R, KIT proto-oncogene receptor tyrosine kinase and FMS-like FLT3 harboring an internal tandem duplication mutation. It was approved on 2 August 2019 in the USA for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery. Pexidartinib is the first systemic therapy approved for this rare condition.

In the pivotal Phase III ENLIVEN trial, the safety and efficacy of pexidartinib was compared with placebo in 120 patients with unresectable advanced TGCT [1]. Patients in the pexidartinib group received a loading dose of 1000 mg pexidartinib per day orally (400 mg morning; 600 mg evening) for the first 2 weeks, followed by 800 mg per day (400 mg twice a day) for 22 weeks. The overall response rate was significantly higher for pexidartinib than placebo at week 25 (39% vs zero) and the responses were durable (all 13 responding patients who were followed for ≥12 months maintained the response). The most common pexidartinib-associated adverse events were hair color changes, fatigue, AST increase, nausea, ALT increase and dysgeusia. Three patients given pexidartinib developed aminotransferase elevations three or more times the upper limit of normal with total bilirubin and ALP 2 or more times the upper limit of normal [1]. The USA prescribing information includes a boxed warning advising healthcare providers (HCPs) and patients about the risk of serious and potentially fatal liver injury.

In accordance with section 505(1)(f)(3)(A) of the US Federal Food, Drug, and Cosmetic Act, the US FDA determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary for pexidartinib to ensure that its benefits outweighed the risk of serious adverse events [2]. A component of the pexidartinib REMS assessment plan was the conduct of a quantitative knowledge, attitudes, and behavior (KAB) evaluation survey with HCPs

Future Medicine

and patients to assess their knowledge of the risks associated with pexidartinib and of the requirements of the pexidartinib REMS. The KAB survey underwent comprehension pretesting of select survey questions, referred to as qualitative research (QR), with a representative sample of the target populations.

The objectives of the QR were to: review key risk message survey questions and response options with respect to comprehension, ease of recall, relevance and clarity; identify terms, questions or topics that require clarification or revision based on areas of confusion or misinterpretation by participants; evaluate alternate language and phrasing based on participants' feedback within the constraints of any existing REMS materials; and make recommendations for potential changes to the surveys based on QR findings [3].

Materials & methods

Anonymized, one-on-one, 45–60-min telephone interviews with HCPs and patients were conducted. This research was conducted by UBC on behalf of Daiichi Sankyo, Inc.

Participant recruitment

The primary recruitment strategy for patients was to target a population having a general diagnosis of metastases/sarcomas of the connective tissue (soft tissue such as fat, muscle, blood vessels, deep skin tissue, nerves, cartilage) or bone tumors. Because pexidartinib was newly approved at the time of this QR, patients with TGCT enrolled in the pexidartinib REMS were not yet available for recruitment. Additional eligibility criteria for patients were as follows: were ≥18-year old; able to read and speak English fluently; had access to a computer and were able to access the internet during the interview; were willing to sign an interview release form (IRF) to participate in the research; had not participated in a healthcare-related market research interview within the past 3 months; and had not worked in or consulted for the pharmaceutical industry, UBC or the FDA. For patients only, the moderator also administered the Rapid Estimate of Adult Literacy in Medicine (REALM®) to assess literacy for basic medical terms [4].

The eligibility criteria for HCPs were as follows: treated patients with metastases/sarcomas of the connective tissue (soft tissue such as fat, muscle, blood vessels, deep skin tissue, nerves, cartilage) or bone tumors, prioritizing those with symptomatic TGCT; specialized in oncology, orthopedics or internal medicine/family medicine; treated patients at least 75% of their professional time; were able to read and speak English fluently; had access to a computer and were able to access the internet during the interview; willing to sign an IRF to participate in the research; had not participated in a healthcare-related market research interview within the past 3 months; and had not worked in or consulted for the pharmaceutical industry, UBC or the FDA. There were no requirements for practice setting, gender, years in practice or clinical degree. The survey protocol was also sent to each HCP's Institutional Review Board.

A recruitment facility identified patients and HCPs who met the inclusion criteria and none of the exclusion criteria for the QR. Various outreach methods, including email and/or cold calls (up to 3 attempts), were utilized to reach nonresponders. When a respondent met all eligibility criteria, the facility staff collected the participant's information and scheduled him/her for an interview; sent and collected the IRF; sent a confirmation letter; and notified participants that upon completion of the interview, payment would be mailed as compensation for his/her time. UBC did not share personal identification or participant contact information with Daiichi Sankyo to maintain confidentiality.

Interview design

All interviews followed a standard process and were led by a prescripted discussion guide. The moderator informed participants that the transcribed interviews may be shared with the sponsor and regulatory agencies; however, neither participant's name nor other identifying information would be associated with the audio recording or the responses provided. The moderator also explained that any adverse event, product complaint or medical information request reported would be forwarded to the research sponsor. The moderator then remotely assisted the participant in logging in to the secure website to take the survey. For patients only, the moderator also administered the REALM to assess literacy for basic medical terms [4].

Qualitative analysis

Data from all 24 research interviews, including transcripts, audio-recorded discussions and interviewer notes, were thoroughly reviewed. A systematic content analysis approach was used to assess the participant's understanding

Table 1. Demographics of survey participants – patients.

Parameter	Patients (n = 12)
Mean age (range), years	52 (25–81)
Sex, n (%)	
– Male	5 (43%)
– Female	7 (57%)
Education	
– High School/GED	3 (25%)
– Some College/Associate's degree	5 (42%)
– Bachelor's 4-year degree	4 (33%)
Employment	
– Full-time	6 (50%)
– Not currently working	4 (33%)
– Retired or semiretired	2 (17%)
Diagnosis, n (%)	
– Metastasis/sarcomas of connective tissue/bone	12 (100%)

Table 2. Demographics of survey participants – healthcare providers.

Parameter	HCPs (n = 12)
Practice setting	
– Solo or independent practice	5 (42%)
– Group practice	4 (33%)
– Hospital based	2 (17%)
– Outpatient clinic	1 (8%)
Primary medical specialty	
– Orthopedics	9 (75%)
– Oncology	3 (25%)
Degree	
– MD	12 (100%)
Years as practicing physician (range)	22 (8–36)
Time spent seeing patients	
– 75%	1 (8.3%)
– 90%	2 (16.7%)
– 95%	1 (8.3%)
– 99%	2 (16.7%)
– 100%	6 (50.0%)

HCP: Healthcare provider; MD: Medical degree.

of concepts associated with the survey questions, response options and patient REMS materials. Emphasis was placed on identifying areas of ambiguity or disagreement with and/or gaps in understanding the survey questions, response options and REMS materials and suggested changes for clarification and revision.

As this research was qualitative and exploratory in nature with a limited sample size, the number of respondents who made a particular comment about specific language in the survey questions/response options was not quantified. Instead, the qualitative findings highlighted overall common themes to help inform any revisions to the survey questions discussed.

Results

Twelve patients (Table 1) and 12 HCPs (Table 2) were interviewed from 1 to 8 October 2019.

All patients had bone cancer and/or metastases/sarcomas of the connective tissue; none were known to have TGCT. Their mean age was 52 years (range: 25–81 years); 43% were male and 57% were female.

Among the 12 HCPs interviewed, 67% treated patients with TGCT, their primary specialty was orthopedics (75%), and all were male with a mean of 22 years of practice. Most HCPs worked in a solo (5 of 12) or group (4 of 12) practice.

Patient interview findings

The primary finding based on the patient interviews were that patients were confused with the term of 'HCP', believing that it could mean doctor, nurse, pharmacist or even an insurance company. Note that this product has a

call center that offers reimbursement and other patient services, but some patients seemed to lack the ability to differentiate between the activities of the REMS and the call center.

Additional sources of confusion for patients were as follows: unfamiliarity with the acronym 'REMS'; difficulty in reading and comprehending lengthy answer statements, which were considered too complex, especially for the less literate patients, and not understanding that when presented with multiple choices, they could choose only one answer. Some terminology was also unclear to patients: for example, Question 3 stated: "*Please answer yes, no or I do not know to the following statement: You should tell your healthcare provider right away if you have any symptoms of liver problems, at any time, while taking pexidartinib*." Some patients understood this question while others were unsure what a 'liver problem' was. Overall, of the 15 questions initially in the patient survey, nine were modified for survey inclusion.

HCP interview findings

The HCP interviews revealed that some of the questions were repetitive and difficult to read. Some of the specialist terminology was not familiar to the HCPs. For example, orthopedic surgeons were often unfamiliar with the terms 'ductopenia' and 'cholestatic' (a term directly from the prescribing information). For example, Question 2 stated: "*Please answer true, false or I do not know about the following statement: Hepatotoxicity with ductopenia and cholestasis has occurred in patients treated with pexidartinib."* Orthopedic surgeons were often unfamiliar with the term 'ductopenia.' The statement was revised to "*Hepatoxicity with ductopenia and cholestasis has occurred in patients treated with pexidartinib. Ductopenia refers to reduction in the number of intrahepatic bile ducts (pathology finding), a process that ultimately leads to cholestasis*." Given the varied medical specialties treating this condition, potentially unfamiliar medical terms will be explained.

Similarly, Question 3 stated: "*Please answer true, false or I do not know about the following statement: The mechanism of cholestatic hepatotoxicity is known and can be controlled if identified in the first 3 months of treatment with pexidartinib*." This question was interpreted slightly differently by the various medical specialties. For clarity, the question was revised to make it a true statement: "*The mechanism of cholestatic hepatotoxicity is unknown and its occurrence cannot be predicted*."

In addition, the interviews revealed that questions related to specific pexidartinib dosing required more clarity; for example, related to specific pexidartinib dosing changes when there is an increase in hepatic enzymes. For example, Question 10 stated: "*Please select all that apply to the below statement. HCPs should do which of the following if a patient presents with an increased ALT and/or AST greater than three to five-times upper limit of normal (ULN): withhold pexidartinib and monitor liver tests weekly; If AST and ALT are less than or equal to three-times ULN within 4 weeks, resume at reduced dose; If AST or ALT is not less than or equal to three-times ULN in 4 weeks, permanently discontinue pexidartinib; all of the above; none of the above; I do not know*." The majority of HCP respondents struggled to read and answer this question. After seeing 'greater than three to five-times ULN' in the question, some became confused to see 'three-times ULN' in subsequent answer statements. In addition, they did not see this as a stepwise process, they were confused to have to answer statements that referred alternately to withholding, resuming and discontinuing the medication and orthopedic surgeons did not know what 'ULN' referred to. The recommendation was to spell out 'ULN' in the question statement: "*HCPs should do which of the following if a patient presents with an increased ALT and/or AST greater than three to five-times upper limit of normal*." Answer options B and C were revised to clarify that this is a stepwise process and these two steps occurred after pexidartinib has been withheld (e.g., "*After pexidartinib has been withheld, if AST and ALT are reduced to less than or equal to three-times ULN within 4 weeks, resume pexidartinib at reduced dose"*). Further, more clarity was requested about the exact definition of 'reduced dose.'

Overall for the HCP survey, 10 of 18 questions were modified before survey execution.

Discussion

Pexidartinib was approved in 2019 in the US with a REMS to ensure that its benefits outweigh the risk of serious and potentially fatal liver injury. A component of the pexidartinib REMS assessment plan was the conduct of a quantitative KAB evaluation survey with HCPs and patients to assess their knowledge of the risks associated with pexidartinib and of the requirements of the REMS [2]. In other contexts, KAB surveys have been shown to be useful in determining if REMS effectively communicate risk and safe-use messages to patients and HCPs [5–7]. In preparation for fielding the KAB survey, QR was conducted on a subset of questions from the draft KAB survey in order to evaluate the comprehension, ease of recall, relevance and clarity of the questions among the patient and

HCP participants. The goal was to make informed recommendations for potential changes to the surveys based on the QR findings.

Twelve HCPs and 12 patients were interviewed and provided a number of important findings regarding the pexidartinib KAB survey. The questions/statements tested were generally clear and easily understood as worded; however, a few areas of confusion were raised. Patients generally raised concerns about the complexity and wordiness of the questions, while HCPs pointed out some repetition, unclear phrasing and the lack of explanation of specialist terminology. Overall, of the 15 questions initially in the patient survey, nine were modified for survey inclusion. For the HCP survey, ten of 18 questions were modified before survey execution.

Since pexidartinib is the first systemic compound approved for the treatment of TGCT, it is critical that the educational goals of the REMS are being achieved. Effective KAB surveys informed by prior QR are useful to ensure that understanding of the REMS key risk messages is being evaluated accurately and that patients and HCPs are informed about the risks of serious livery injury associated with the use of pexidartinib.

Conclusion

Feedback from HCPs and patients received during the QR process will enhance overall participant comprehension of the pexidartinib KAB survey, which will assist in the evaluation of the TURALIO® KAB survey. Overall, the QR will improve the quality of data collected and thus the effectiveness of the REMS, which will ultimately mitigate the risks associated with the use of pexidartinib in patients with TGCT.

Summary points

- Pexidartinib is currently the only approved treatment for symptomatic tenosynovial giant cell tumors.
- Prior to the stakeholder knowledge, attitudes, and behavior (KAB) surveys required by the pexidartinib Risk Evaluation and Mitigation Strategy, a qualitative evaluation of the key risk message questions was undertaken.
- Structured telephone interviews with 12 patients and 12 healthcare providers (HCPs) were conducted to determine their understanding of the questions and to provide recommendations on alternative language, phrasing and structure.
- All patients reported a diagnosis of metastasis or sarcomas of the connective tissue or bone; the mean age was 52 years; 58% were female; and 42% reported some college.
- HCPs were all medical doctors and the majority (67%) treated patients with tenosynovial giant cell tumors; 100% were male; the mean years in practice was 22; all spent 75% or more time seeing patients; and the primary specialty was orthopedics.
- The interviews revealed that patients commented on the complexity and wordiness of some of the questions, while HCPs noted that some questions were repetitive and some terminology was not self-explanatory.
- Of the 15 questions initially in the patient survey, nine were modified for survey inclusion.
- For the HCP survey, ten of 18 questions were modified before survey launch.
- Qualitative research prior to knowledge, attitudes, and behavior (KAB) survey execution is recommended to improve respondent comprehension and data quality.

Acknowledgments

We thank the patients and HCPs for their participation in the survey.

Financial & competing interests disclosure

This study was sponsored by Daiichi Sankyo, Inc. M Salas, L Drogaris, Z Islam, M Henderson and N Tu are employees of Daiichi Sankyo. M Julian, A Stemhagen, and N O'Donnell are employees of United BioSource (UBC). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing assistance was provided by UBC.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

References

1. Tap WD, Gelderblom H, Palmerini E *et al.* Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised Phase III trial. *Lancet* 394(10197), 478–487 (2019).
2. US Food and Drug Administration. REMS assessment: planning and reporting. Guidance for industry (2019). www.fda.gov/media/119790/download
3. Salas M, Julian M, Drogaris L *et al.* Evaluation of patient and healthcare provider (HCP) knowledge, attitudes, and behavior for safety and use of pexidartinib. Presented at: *American Society of Clinical Oncology 2020 Annual Meeting*, (Abstract e23580) (2020).
4. Davis TC, Long SW, Jackson RH *et al.* Rapid estimate of adult literacy in medicine: a shortened screening instrument. *Fam. Med.* 25(6), 391–395 (1993).
5. Giannetta N, Dionisi S, Cassar M *et al.* Measuring knowledge, attitudes and behavior of nurses in medication management: cross-cultural comparisons in Italy and Malta. *Eur. Rev. Med. Pharmacol. Sci.* 24(9), 5167–5175 (2020).
6. Brandenburg NA, Bwire R, Freeman J *et al.* Effectiveness of Risk Evaluation and Mitigation Strategies (REMS) for lenalidomide and thalidomide: patient comprehension and knowledge retention. *Drug Saf.* 40(4), 333–341 (2017).
7. Frame JN, Jacobson JO, Vogel WH *et al.* Assessment of risk evaluation and mitigation strategies in oncology: summary of the oncology risk evaluation and mitigation strategies workshop. *J. Oncol. Pract.* 9(2), e24–e39 (2013).