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Reply to E. Younger et al

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In a letter to the editor entitled "Health-Related Quality of Life in Patients With Sarcoma: Enhancing Personalized Medicine," Younger et al[1] provide critical insight into the opportunities and barriers related to using patient-reported outcomes (PROs) in the management of soft tissue and bone sarcoma (STSB). Our previously published work has highlighted the importance and challenges related to capturing PRO information to enhance clinician decision making when assessing adverse events[2] and physical function.[3] Despite recent advances in the development of PROs in solid tumors and hematologic disorders,[4] there are a number of important factors to consider when developing, validating, and using PROs in STSB.

As has been acknowledged,[1] there are more than 50 different types of STSB, each with unique natural history, biology, presentation, treatment, and prognosis. Thus, the development of a one-size-fits-all PRO instrument in STSB is not meaningful. Increasingly, clinical trials in STSB are conducted for each subtype, where the annual incidence may be as low as a few hundred patients. In such trials, a validated PRO tool (eg, the US National Cancer Institute PRO version of the Common Terminology Criteria for Adverse Events[5]) may be used as a primary or key end point. To facilitate the process of developing novel PRO measures or using established PRO instruments when seeking to establish a patient-reported end point for labeling purposes in drug development, the US Food and Drug Administration (FDA) released a guidance for industry report entitled "PRO Measures: Use in Medical Product Development To Support Labeling Claims."[6] This regulatory document contains specific expectations for the conceptual framework, content validity, construct validity, reliability, and ability to detect clinically meaningful score changes of a given PRO measure.

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To our knowledge, only two STSB subtype–specific PRO tools have been developed following these FDA guidelines. The first was developed in tenosynovial giant-cell tumor/pigmented villonodular synovitis (TGCT/PVNS) and incorporated as a key end point in an ongoing phase III study of pexidartinib in TGCT/PVNS.[7] A second PRO (Memorial Sloan Kettering/Desmoid Tumor Research Foundation [MSK/DTRF] instrument) was developed in desmoid tumors or aggressive fibromatosis.[8] These are prime examples of the rigor that is necessary to adhere to the FDA recommendations in PRO development. Although content validity of these tools was established through the patient-driven qualitative processes of concept elicitation and cognitive interviews, before the instruments can be used to independently characterize disease-related symptoms or impacts, the psychometric properties of the TGCT/PVNS and MSK/DTRF instruments must be evaluated prospectively in the clinical trial setting through the side-by-side administration of validated legacy PRO measures that capture similar concepts. The development of such instruments in rare and ultra cancers is time and resource intensive and a daunting challenge. However, this can be overcome, as exemplified by the development of the MSK/DTRF instrument, which was accomplished through a partnership with a patient advocacy group (ie, DTRF). This patient advocacy group helped in not only funding the work but also rapidly identifying and recruiting patients with desmoid tumors to participate in PRO development. Our experience demonstrates the power of patient advocacy groups as critical partners in this work. Successful development of PRO in rare cancers will require not only funding from government or private agencies but also close partnerships with academia, industry, and patient advocacy groups.

Although ideal, we recognize the practical challenges of capturing the symptoms and impacts related to each STSB subtype to develop unique PRO instruments. To help ameliorate the resource burden, one solution would be to consolidate sarcomas exhibiting similar natural histories, presentations, and treatments under aggressive, intermediate, and indolent categories. From a clinical standpoint, patients with intermediate or indolent STSB may experience a unique set of disease-related complications that affects them for the remainder of their lives, without a direct impact on survival. Patients with aggressive, metastatic STSB have the shortest survival expectation (ie, 11 to 20 months) but may potentially have a more uniform symptomatic experience relative to those with intermediate or indolent STSB.

To accelerate the development of PRO instruments, we advocate for the formation and use of STSB patient registries. Guidelines for collecting PRO information in patient registries have recently been established,[9] and several such sarcoma-specific registries exist.[10] Deploying the recommendations from the FDA PRO guidance to develop PRO instruments in STSB patient registries would help to ensure that we are using valid, reliable, disease-relevant items that are well understood by patients and are clinically responsive to prospective changes in health state. Ultimately, developing PRO instruments in STSB patient registries would potentially accelerate the process of providing patients with tools that are tailored to their specific conditions.

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REFERENCES

1. Younger E, Wilson R, van der Graff WTA, et al.: Health-related quality of life in patients with sarcoma: Enhancing personalized medicine. J Clin Oncol 36: 1642–1643, 2018 [PubMed: 29668370]
2. Atkinson TM, Ryan SJ, Bennett AV, et al.: The association between clinician-based common terminology criteria for adverse events (CTCAE) and patient-reported outcomes (PRO): A systematic review. Support Care Cancer 24:3669–3676, 2016 [PubMed: 27260018]
3. Atkinson TM, Stover AM, Storfer DF, et al.: Patient-reported physical function measures in cancer clinical trials. Epidemiol Rev 39:59–70, 2017 [PubMed: 28453627]
4. Gnanasakthy A, DeMuro C, Clark M, et al.: Patient-reported outcomes labeling for products approved by the Office of Hematology and Oncology Products of the US Food and Drug Administration (2010–2014). J Clin Oncol 34:1928–1934, 2016 [PubMed: 27069082]
5. Basch E, Reeve BB, Mitchell SA, et al.: Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 106:dju244, 2014 [PubMed: 25265940]
6. US Food and Drug Administration: Guidance for industry: Patient-reported outcome measures—Use in medical product development to support labeling claims. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
7. Gelhorn HL, Tong S, McQuarrie K, et al.: Patient-reported symptoms of tenosynovial giant cell tumors. Clin Ther 38:778–793, 2016 [PubMed: 27041409]
8. Paty J, Maddux L, Gounder MM: Prospective development of a patient reported outcomes (PRO) tool in desmoid tumors: A novel clinical trial endpoint. J Clin Oncol 35, 2017 (suppl; abstr 11022)
9 . Gliklich RE, Dreyer NA, Leavy MB (eds): Registries for Evaluating Patient Outcomes: A User's Guide (ed 3). Rockville, MD, Agency for Healthcare Research and Quality, 2014
10. Maretty-Nielsen K, Aggerholm-Pedersen N, Keller J, et al.: Population-based Aarhus Sarcoma Registry: Validity, completeness of registration, and incidence of bone and soft tissue sarcomas in western Denmark. Clin Epidemiol 5:45–56, 2013 [PubMed: 23687450]