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Research Report

Qualitative Analysis of Pain in Patients With Locally Advanced or Metastatic Urothelial Carcinoma

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Abstract.
BACKGROUND: Pain is not well described in patients with locally advanced or metastatic urothelial cancer (la/mUC).
OBJECTIVE: To characterize pain and assess the content validity of the Brief Pain Inventory Short Form (BPI-SF) worst pain item in patients with la/mUC receiving first-line treatment in the US.
METHODS: Qualitative interviews were conducted in patients aged ≥ 45 years with confirmed la/mUC, self-reported la/mUC-attributed pain before enrollment, and no major surgery ≤ 3 months prior to being interviewed. Interview participants were asked open-ended questions about their la/mUC symptoms and pain. "Think aloud" cognitive debriefing was conducted for the BPI-SF worst pain item.
RESULTS: Ten participants with laUC and six (38%) with mUC were interviewed. First-line treatments included cisplatin ($n = 14$; 88%) or carboplatin ($n = 2$; 13%). The average past-week worst pain score (0–10 scale) was 6.2 (range, 3–10); seven (44%) participants reported severe pain (score ≥ 7). Pain was most frequently reported in the back ($n = 14$; 88%) and/or pelvic/lower abdominal area ($n = 10$; 63%). Pain impacted all participants' physical and daily activities; 81% reported it impacted their overall quality of life. All participants interpreted and completed the BPI-SF worst pain item without difficulty; 15 (94%) reported it was relevant to their la/mUC experience. Participants understood the 24-hour recall period; most supported daily ($n = 13$; 81%) or weekly ($n = 14$; 88%) assessment, preferring electronic administration using their phone ($n = 14$; 88%).
CONCLUSIONS: Pain attributed to la/mUC impacted physical and daily activities in all participants undergoing first-line treatment for la/mUC. Content validity was demonstrated for the BPI-SF worst pain item in this population.

Keywords: Brief pain inventory short form, pain, patient-reported outcomes, qualitative, urothelial cancer

INTRODUCTION

Urothelial carcinoma (UC) was estimated to be the sixth most common cancer in the United States (US) in 2020; it was estimated that 81,400 new cases would be diagnosed and 17,980 people would die of the

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disease in 2020 [1, 2]. At diagnosis, approximately 7% of patients have regional disease (ie, spread to regional lymph nodes) and 5% have metastatic UC (mUC); 5-year relative survival is 36.5% for patients with regional disease and 5.5% for patients with distant metastases [1]. Individuals living with locally advanced/mUC (la/mUC) report symptoms of dysuria, urinary tract obstruction, and pain [3, 4].

Although cancer pain management has improved in recent years, two-thirds of patients with advanced, metastatic, or terminal cancer experience pain [5]; pain is undertreated in approximately one-third of cancer patients [6]. Patients with cancer may underreport pain for several reasons including its subjective nature, their stoicism or belief that pain is an inevitable and unrelievable part of the cancer experience, their uncertainty on the validity or usefulness of the symptom, or worries about being a nuisance or overstretching the healthcare system [7–9]. Patients or their caregivers may also have concerns or misconceptions about addiction, side effects, or tolerance regarding the use of analgesics for cancer pain [9, 10].

Limited data have been published about pain management or the severity and impact of pain in the la/mUC population. Optimal approaches to cancer pain assessment are evolving and must be tailored to the specific cancer type and patient. Controversy remains regarding the precise interval of assessment in addition to defining the optimal method of assessment [11]. This is of particular importance in the setting of la/mUC, as fluctuations in pain are relatively common as patients experience changes in cancer control status and the side effects of treatment.

The Brief Pain Inventory Short Form (BPI-SF) is a patient-reported outcome (PRO) instrument that is widely used to assess cancer pain [12]. The US Food and Drug Administration (FDA) Guidance on PRO measurement states that a PRO instrument must demonstrate content validity (ie, that the instrument measures the concept[s] it is intended to measure) based on evidence from qualitative studies in the target patient population [13]. The validity of the BPI-SF questionnaire in representing pain outcomes has been demonstrated in other cancer populations, such as in patients with castration-resistant prostate cancer [14], but not yet in patients with la/mUC. Previous studies that have evaluated pain in the la/mUC population used non–pain-specific instruments, such as the 36-item Short Form survey (SF-36) or the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire (EORTC QLQ-C30), rather than a questionnaire focused on pain such as the BPI-SF [15, 16]. Thus, the objective of this study was to characterize pain and its impact in patients with la/mUC treated in the first-line setting, and to assess the content validity of the BPI-SF worst pain item in this population.

METHODS

Participant recruitment/selection

Patients in the US with la/mUC were identified and included as study participants if they met the following criteria: English-speaking patients aged ≥ 45 years with a physician-confirmed histologically documented diagnosis of la/mUC who were currently receiving first-line treatment (platinum-based and/or immunotherapy); had a self-reported activity level consistent with an Eastern Cooperative Oncology Group status of 0, 1, or 2; reported experiencing pain attributed to la/mUC; had no major surgeries ≤ 3 months prior to study participation; and were willing to participate in a 1-hour telephone interview. A written consent document was provided to participants for review prior to the telephone interview and all participants provided consent verbally during the telephone call. The need for ethical approval was waived by the RTI International Office of Research Protection.

In addition to the eligibility criteria, patients with specific characteristics were sought to ensure a diverse and representative study sample, as recommended in the FDA PRO Guidance and reports from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) PRO Good Research Practices Task Force [13, 17, 18]. The goal was to include at least four participants who reported experiencing severe pain due to la/mUC in the prior week, which was defined as a report of 7 or higher on a scale of 0 (no pain) to 10 (pain as bad as you can imagine), with at least one of these participants reporting a score of 9 or higher. Goals of at least eight male participants, at least four participants who were not white, and at least four participants with no more than a high school or high school–equivalent education were also targeted to give a diverse range of participants that could represent the la/mUC population.

Interview procedures

Qualitative interviews were conducted by telephone using a semi-structured interview guide. Each

interview lasted approximately 60 minutes and was audio recorded and transcribed. The interviews began with a short introduction, followed by approximately 10 minutes of questioning on overall and current issues due to cancer, 25 minutes on participants' pain due to la/mUC, and 20 minutes on the BPI-SF worst pain item. Each interview was conducted by two researchers: one asked questions and served as the primary interviewer while the other served as scribe, ensured all questions were answered, and identified the need for additional questions or probes. Verbal informed consent was obtained and recorded before interviews began.

Participants were first asked open-ended questions about their general experiences with la/mUC, including current symptoms perceived to be due to cancer and symptoms experienced at time of diagnosis. Participants were asked about their symptoms as they may affect an individual's perception and report of pain. After the initial symptom discussion, participants were asked to focus on their experience of pain due to la/mUC; during this section of the interview, areas of interest that were not spontaneously mentioned were then probed. First, participants were asked to describe their pain, including the frequency, consistency, and location(s), as well as their strategies to manage pain (eg, medications) and their ability to attribute the pain to la/mUC. Next, participants were asked to describe the impacts of pain associated with la/mUC on their lives. An open-ended elicitation was conducted to allow for spontaneous reports, followed by probed impacts of interest, including daily and physical activities, overall health, and quality of life. In addition, participants were asked probing questions about specific activities similar to items from the EORTC QLQ-C30 assessing strenuous activities like carrying a heavy shopping bag or a suitcase; taking long or short walks; and eating, dressing, bathing, or using the toilet. Finally, participants were asked which of all the impact areas they mentioned during their interview was the most bothersome for their la/mUC pain.

In the last section of the interview, "think aloud" cognitive debriefing was conducted for the worst pain item of the BPI-SF questionnaire, which asks participants to rate their pain at its worst in the last 24 hours on a scale from 0 (no pain) to 10 (pain as bad as you can imagine) [12]. Participants were asked to read the item aloud, select a response, and respond to follow-up questions asked by the interviewers; this method was used to elicit the participant's comprehension of the question and response options, ease of response, and reasons for selecting a specific response option. Participants were also asked to provide feedback regarding how burdensome daily assessment would be over the timespan of a clinical trial (ie, 3 to 4 months in duration), as well as thoughts regarding less frequent assessment (ie, weekly or every 3 weeks). The final question asked whether participants would prefer to complete the BPI-SF worst pain item on paper or using a small electronic device or smartphone, and also gathered their feedback on answering the questionnaire on their own phone using an application.

Analysis

A sample size of 16 interview participants was predetermined and targeted to reach concept saturation among patients with pain [13, 17]. Participant characteristics were summarized using descriptive statistics: continuous variables were reported as mean and range, and categorical variables were reported as number and percentage. Analysis of the qualitative data was conducted to ensure the capture of an accurate reflection of the results across all interviews. Transcripts were verified by multiple researchers through an iterative process of technical and editorial review. Researchers reviewed the results of the interviews to summarize and identify patterns [19] in how participants described their experiences with pain and how they interpreted and responded to the worst pain item.

RESULTS

Participant characteristics

Sixteen participants (laUC, $n = 10$ [63%]; mUC, $n = 6$ [38%]) were interviewed. The mean participant age was 53.8 years, 50% of the participants were male ($n = 8$), and 56% of participants ($n = 9$) were Hispanic (Table 1). The mean time from la/mUC diagnosis to interview participation was 2.7 months. All participants were currently receiving first-line treatment with a regimen containing cisplatin ($n = 14$; 88%) or carboplatin ($n = 2$; 13%). The most commonly administered treatment regimen was MVAC ($n = 9$; 56%). The average worst pain score over the past week was 6.2 (range, 3–10); seven participants (44%) reported severe pain (score ≥ 7), including two participants (13%) with scores of ≥ 9 (Supplemental Table 1).

Table 1
Participant Characteristics

Characteristic	Total ($N = 16$)
Age, mean (range), years	53.8 (46–64)
Male, n (%)	8 (50)
Race/ethnicity, n (%)	
White	6 (38)
Hispanic	9 (56)
Black	1 (6)
Time since la/mUC diagnosis, mean (range), months	2.73 (1–5)
Type of urothelial carcinoma, n (%)	
Metastatic	6 (38)
Locally advanced	10 (63)
Treatments, n (%)	
Cisplatin and gemcitabine	3 (19)
MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin)	9 (56)
Paclitaxel, cisplatin, and gemcitabine	2 (13)
Carboplatin and gemcitabine	2 (13)
Worst pain in past week, mean (range)	6.2 (3–10)

la/mUC locally advanced or metastatic urothelial carcinoma.

Symptoms due to locally advanced/metastatic UC

Aside from pain, which was required for study enrollment, tiredness (tired/low energy/fatigue) was the most frequently reported la/mUC symptom and was spontaneously reported by 10 participants (63%). Participants reported pain and tiredness as symptoms associated with the time of diagnosis as well as symptoms that continued during treatment. Less frequent symptom reports included feeling generally unwell ($n = 3$; 19%), lack of appetite ($n = 1$; 6%), and dizziness ($n = 1$; 6%).

Pain due to locally advanced/metastatic UC

Participants' descriptions of pain varied from overall achiness to deep, shooting, and intense pain (Supplemental Table 2). Most participants stated that they experienced pain daily and that pain consistency and intensity varied throughout the day. Only one participant (6%) included a description of "bone" pain.

Most participants ($n = 14$; 88%) stated they attributed their pain to la/mUC based on the proximity of the onset of pain with the cancer diagnosis ($n = 10$; 63%) or pain location ($n = 4$; 25%). Pain was frequently reported in the back ($n = 14$; 88%) and/or pelvic/lower abdominal area ($n = 10$; 63%; Table 2). When describing back pain, most participant descriptions ($n = 9$; 64%) included lower back pain. Reports of back pain also included the tailbone ($n = 2$; 14%) and midback ($n = 2$; 14%) and were described separately or in addition to the lower back pain. Four participants (29%) reported "back" without further specification of location.

Table 2
Participant-Reported Location of Pain[a]

Location	Total, n (%) ($N = 16$)
Back	14 (88)[b]
Pelvic area/lower abdomen[c]	10 (63)
Urethra	1 (6)
Testicle area	1 (13)[d]
Joints (ankles/wrist)	1 (6)
Overall body	1 (6)

[a]Locations were not mutually exclusive. [b]Participant descriptions of back pain ($N = 14$) included lower back pain ($n = 9$; 64%), "back" without further specification ($n = 4$; 29%), and the tailbone ($n = 2$; 14%) and midback ($n = 2$; 14%) (each described separately or in addition to lower back pain). [c]Includes participants who reported a location of stomach or bladder. [d]Eight participants (50%) were female (ie, $N = 8$ for testicle pain).

Nearly all participants (94%) reported frequent use of medications to manage pain, with half of participants ($n = 8$) noting some use of narcotics (Table 3). The dosage, frequency, and duration of pain medication use varied by pain severity over time. Participants noted that they reserved narcotic medications for when pain was severe or intense, whereas non-narcotic medication use was more common on days with less intense pain.

Impact of pain due to locally advanced/metastatic UC

All participants reported that pain due to la/mUC negatively impacted their physical and daily activities

Table 3
Participant-Reported Pain Medication Use

Medication Use	Total, n (%) ($N = 16$)
Pain Medication[a]	
Ibuprofen+narcotic[b]	6 (38)
Ibuprofen only	6 (38)
Vicodin only	2 (13)
Pain medication, unspecified[c]	1 (6)
Not reported	1 (6)
Administration	
As needed	8 (50)
Daily	2 (13)
Daily+as needed	2 (13)
Not reported	4 (25)

[a]Categories were mutually exclusive. [b]Vicodin, hydrocodone, or oxycodone. [c]Participant stated "pain killer" only.

(Table 4). Upon probing, most participants reported that pain negatively impacted their overall quality of life ($n = 13$; 81%) and nearly all participants reported that pain impacted their family life ($n = 15$; 94%). Of participants reporting impacts on family life, most ($n = 12$; 75%) reported pain negatively impacted their family life, but three participants (19%) reported it had a positive impact, such as receiving increased support and care from their family. Combining spontaneous and probed reports, negative impacts on social life ($n = 14$; 88%), hobbies and leisure ($n = 13$; 81%), and emotions ($n = 13$; 81%) were frequently reported or endorsed. When asked about the most bothersome impact of their la/mUC pain, participants most frequently reported decline in physical or daily activities ($n = 6$; 38%), followed by emotional impacts ($n = 3$; 19%) and sleep impacts (concept evaluated in 14 interviews; $n = 3$ participants; 21%).

In response to probing questions regarding specific EORTC QLQ-C30–like activities, participants reported strenuous activities ($n = 13$; 81%), long walks outside the home ($n = 12$; 75%), and getting up and down stairs ($n = 10$; 63%) as the daily and physical activities most affected by la/mUC pain (Table 5).

Cognitive debriefing

All participants interpreted and completed the BPI-SF worst pain item without difficulty; 15 participants (94%) reported it was relevant to their la/mUC experience, demonstrating content validity. The one participant who reported that the item was not relevant stated that his response was because pain was only a part of his overall cancer experience. Participants understood the 24-hour recall period and most supported daily ($n = 13$; 81%) or weekly ($n = 14$; 88%) assessment. When asked about assessment every 3 weeks, most participants ($n = 13$; 81%) reported that this interval, while the least burdensome, might not provide a full picture of the experience of pain, due to potential variability in pain over the longer time span. Most participants ($n = 14$; 88%) preferred electronic administration of the worst pain item using an application on their own phone; two participants (13%) preferred to use a paper and pen.

DISCUSSION

This study was focused on understanding the impact of pain on patients with la/mUC. Patients who reported pain associated with la/mUC were recruited to participate in qualitative interviews.

Table 4
Impacts of Pain Reported by Study Participants[a]

Activity	Participants, n (%)[a] ($N = 16$)		
	Spontaneous	Probing	Total
Daily activities	14 (88)	2 (13)	16 (100)
Physical activities	13 (81)	3 (19)	16 (100)
Social life	5 (31)	9 (56)	14 (88)
Family life	0 (0)	15 (94)[b]	15 (94)
Intimate life	3 (19)	NA[c]	3 (19)
Hobbies/leisure activities	2 (13)	11 (69)	13 (81)
Emotions	3 (19)	10 (63)	13 (81)
Overall health	0 (0)	12 (75)	12 (75)
Overall quality of life	0 (0)	13 (81)	13 (81)
Ability to concentrate	2 (13)	7 (44)	9 (56)
Sleep	2 (14)[d]	7 (50)[d]	9 (64)[d]

NA not applicable. [a]Categories were not mutually exclusive. [b]Three participants (19%) reported positive impact (ie, increased family support). [c]The intimate life concept was not probed upon (spontaneous reports only). [d]The sleep concept was added as a probe beginning with the third interview, so percentages are based on a total of 14 participants.

Table 5
Daily and Physical Activity Impacts of Pain Reported by Study Participants[a]

Activity	Total, n (%) ($N = 16$)
Strenuous activities (such as lifting groceries or a heavy suitcase)[b]	13 (81)
Long walks outside the home[c]	12 (75)
Getting up and down stairs	10 (63)
Ability to take care of self (such as dressing and bathing)[d]	5 (31)
Short walks outside the home[e]	4 (25)

EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire. [a]Reported in response to probing questions regarding specific activities; categories were not mutually exclusive. [b]EORTC QLQ-C30 item: Do you have any trouble doing strenuous activities like carrying a heavy shopping bag or a suitcase? [c]EORTC QLQ-C30 item: Do you have any trouble taking a long walk? [d]EORTC QLQ-C30 item: Do you need help with eating, dressing, washing yourself or using the toilet? [e]EORTC QLQ-C30 item: Do you have any trouble taking a short walk outside of the house?

Among these participants, pain was a key symptom of la/mUC and most participants reported that pain negatively impacted their physical and daily activities and overall quality of life. Most participants in our demographically diverse study population experienced pain daily, attributed their pain to la/mUC, and reported pain most frequently in the back (most often the lower back) and/or pelvic/lower abdominal area.

Participants reported pain had a significant impact on their physical activities and quality of life. This is consistent with previous database analyses in older, predominantly male patients with muscle-invasive UC, which found clinically and/or statistically significant decreases in physical health-related quality of life [15, 16]. Our study sample was younger (age range, 46–64 years) and more diverse (50% female, 38% white) compared with the study populations in the muscle-invasive UC studies (mean age, 70.4–76.9 years; 21.9%–29.9% female; 84.4% white). However, even in a younger population with fewer comorbidities, participants with la/mUC in our study reported significant quality-of-life effects, suggesting that quality of life is an important need/consideration for many patients with la/mUC. Our results are also similar to a previous qualitative interview study among patients with non-resected la/mUC treated with chemotherapy followed by a PD-1/L1 inhibitor in which 75% of participants reported pain; participants also identified pain as one of the most salient la/mUC symptoms and stated la/mUC symptoms affected their health-related quality of life [20].

Our finding that 50% of participants with la/mUC pain used narcotics is consistent with the results of previous studies. A 2018 survey reported that 43% of cancer patients use opioids to manage their pain [21]. In recent US claims database analyses, pre- and post-diagnosis opioid use rates were 49.9% and 53.3%, respectively, in patients with metastatic prostate cancer with skeletal-related events, and pre- and post-diagnosis opioid prescription rates were 46.8% and 81.4%, respectively, in patients with metastatic breast cancer [22, 23].

The results of our qualitative interviews indicated the BPI-SF worst pain item is an appropriate pain measure in patients with la/mUC on first-line treatment who experience pain (ie, the study population). All participants interpreted and completed the BPI-SF worst pain item without difficulty and content validity was shown by 15 of the 16 participants reporting that the item was relevant to their experience with la/mUC. This is consistent with previous qualitative interview studies that support the content validity of the BPI-SF worst pain item in oncology patients such as those with castration-resistant prostate cancer with bone metastases [14] and patients with pleural and peritoneal mesothelioma [24]. In both studies, the worst pain item was easily understood and interpreted correctly by interview participants with cancer-related pain [14, 24], and participants with castration-resistant prostate cancer in the study by Gater and colleagues believed that the worst pain item accurately reflected their cancer pain [14].

Participants preferred daily or weekly pain assessment and a number of patients stated that administration every 3 weeks would not accurately capture their cancer pain. This is an important finding and could help inform pain assessment in future clinical trials in oncology. Furthermore, our study participants preferred electronic administration of the BPI-SF worst pain item using an application on their own phone. Although this may be related to the relatively young population in our study (mean age, 54 years), older populations have reported similar

preferences for digital reporting in recent studies. A qualitative study of cancer patients (mean age, 66 years) experiencing pain conducted by Adam and colleagues demonstrated interest in and/or support for digital pain monitoring tools and identified digital technologies as an opportunity to tailor care for cancer patients [25]. In the qualitative study of participants with mesothelioma conducted by Gelhorn and colleagues, nearly all participants in the usability testing subgroup (mean age, 67 years) had positive impressions of using a handheld device to complete an electronic version of the BPI-SF, and researchers found few differences in responses between the paper and electronic versions [24].

Our findings, although important, should be considered in the context of some limitations. This qualitative study was designed to produce insights into participants' individual experiences of la/mUC pain, so the results are not necessarily generalizable to a broader la/mUC population. Although our study population was demographically diverse, included a range of pain severity levels, and was appropriate for the study objective, the sample size was small and may not reflect individuals with la/mUC who choose to participate in a clinical trial, a setting in which the BPI-SF worst pain item may be used. For example, the mean age of our study participants (∼54 years) was younger compared to the populations of large clinical trials in first-line UC (eg, median ages of 68–69 years in KEYNOTE-361 [26], 67–69 years in IMvigor130 [27]). In addition, our younger study cohort was evenly divided between female and male participants, so the symptoms and impacts reported herein may differ among the general la/mUC population, which is older and predominately male. Further, the study population did not include patients who did not have pain, so our results cannot contribute to understanding the overall prevalence of pain in patients with la/mUC. To minimize pain from non-UC sources and focus predominantly on cancer pain, we enrolled participants who had not had surgery within 3 months so that participants would have recovered from surgery by the time they participated in the interviews. This study only included one interview, so we cannot provide results for changes in participants' responses over time. Finally, it is possible that interview participants may have underreported their cancer pain, since pain can be subjective and cancer patients' tolerance of and attitudes toward pain can vary [28].

Our objective was to characterize pain and its impact in patients with la/mUC treated in the first-line setting and to assess the content validity of the BPI-SF worst pain item in this population. These exploratory results can be used to guide future studies implementing electronic pain management questionnaires in patients with bladder cancer as there is an unmet need for a pain management questionnaire that can not only characterize a patient's pain but also determine the effects of pain on their daily lives. Cognitive debriefing to align the pain concepts and impacts noted in this research may be useful in future evaluations of other existing pain questionnaires or to form the basis of future studies that correlate questionnaire results to more advanced pain metrics. Additional opportunities for future research include the use of surveys to further add to our understanding of the patient experience, as well as studies examining the timing and duration of pain over time. The use of additional metrics such as whether pain is breakthrough or adequately controlled by treatment, as well as long-term follow-up of patient pain, would also be beneficial to collect in addition to the BPI-SF worst pain item. Further work incorporating detailed assessments of change in patient-reported pain in response to medication adjustments is needed.

CONCLUSIONS

These qualitative results indicate that pain associated with la/mUC impacts physical and daily activities in participants with la/mUC who are receiving first-line treatment and who experience pain. Our results also demonstrate that the BPI-SF worst pain item has content validity in this population, but further psychometric analysis may be needed to confirm whether the BPI-SF worst pain item is fit for purpose in measuring pain among patients with la/mUC. The inclusion of instruments within a clinical trial that accurately capture the experiences of patients with la/mUC will enhance understanding of the patient experience during treatment, as well as the potential benefits of treatment in terms of pain control in addition to treatment efficacy. The finding that participants with la/mUC who experience pain preferred daily or weekly pain assessment using a digital device may help inform the design of future clinical trials in this population.

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AUTHOR CONTRIBUTIONS

SM: conception, performance of work, interpretation or analysis of data; NH: performance of work, interpretation or analysis of data; AM: conception, performance of work, interpretation or analysis of data, writing the article; ZH: conception, interpretation or analysis of data, writing the article; SS: conception, interpretation or analysis of data. All authors had access to the data.

CONFLICT OF INTEREST

SM reports consultancy fees from RTI Health Solutions (RTI-HS). SS reports stock ownership from Pfizer Inc. and consultancy fees from Astellas Pharma, Inc. and Adelphi Values, PROVE. ZH reports stock ownership and employment from Seagen Inc. NH has nothing to disclose. AM reports personal fees from Astellas Pharma, Inc., AstraZeneca, Bayer, Sanofi, Advanced Accelerator Applications, Myovant, Clovis, Exelixis, Blue Earth, and Janssen; grants from Bayer; and research collaboration from Bayer, Sanofi, Genentech, and Seagen.

SUPPLEMENTARY MATERIAL

Please see appendix for Supplemental Tables 1 and 2.

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