Patients' and Physicians' Preferences for Approaches to Bone Metastases Treatment in Turkey

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ABSTRACT

Bone metastases and associated skeletal-related events (SREs) are common in patients with advanced breast, lung, and prostate cancer. Bone-targeted agents (BTAs) are available for the treatment of bone metastases, but little is known about patients' and physicians' preferences for the various attributes of these agents. We evaluated preferences for BTAs used to prevent SREs among patients with bone metastases and physicians involved in treating such patients in Turkey. Participants completed an online discrete-choice experiment survey of 10 questions, choosing between pairs of hypothetical treatment profiles, defined by five BTA attributes: time to first SRE, time to worsening of pain, annual risk of osteonecrosis of the jaw (ONJ), annual risk of renal impairment, and administration regimen. The analysis included 91 patients and 99 physicians. Both groups rated annual risk of renal impairment, time to worsening of pain, and time to first SRE as the most important BTA attributes. For patients, the preference weights for all levels of these attributes were significantly different, whereas for physicians, preference weights were significantly different for all levels except time to a 2-point increase in "Brief Pain Inventory" score by 6 months or 10 months. Annual risk of ONJ was judged by patients and physicians to be the least important of the BTA attributes. This study adds to the information available on the preferences of patients and physicians for BTAs and provides useful data to aid clinicians in decision-making by understanding the treatment goals that are important to patients in Turkey.

Keywords: Bone-targeted agents, Bone metastases, Discrete-choice experiment, Patient preference, Physician preference, Skeletal-related event

ÖZET

Türkiye'de Kemik Metastazı Tedavisine Yaklaşımda Hasta ve Hekim Tercihleri

Kemik metastazları ve bunlardan kaynaklanan iskeletle ilişkili olaylar (İİO) ilerlemiş meme, akciğer ve prostat kanseri olan hastalarda yaygındır. Kemik metastazlarının tedavisi için kemiği hedef alan ilaçlar (BTA'lar) bulunmakla birlikte, hastaların ve hekimlerin bu ilaçların çeşitli özellikleriyle ilgili tercihlerine ilişkin bilgiler sınırlıdır. Türkiye'de yapılan bu çalışmada, kemik metastazları olan hastalar ile bu tip hastaların tedavisini yürüten hekimlerin SRE'lerin önlenmesine yönelik BTA'larla ilgili tercihleri değerlendirilmiştir. Katılımcılar çevrimiçi yapılan ve 10 soru içeren çoktan seçmeli deney anketini tamamlayarak beş BTA özelliği ile tanımlanan hipotetik tedavi profili çiftleri arasında seçim yapmıştır: ilk SRE'ye kadar geçen süre, ağrının kötüleşmesine kadar geçen süre, yıllık çene osteonekrozu (ONJ) riski, yıllık böbrek yetmezliği riski ve uygulama rejimi. Analize 91 hasta ve 99 hekim dahil edilmiştir. Her iki grup da yıllık böbrek yetmezliği riski, ağrının kötüleşmesine kadar geçen süre ve ilk İİO'ya kadar geçen süreyi en önemli BTA özellikleri olarak değerlendirmiştir.

Hastalar açısından bu özelliklerin tüm düzeylerine ilişkin tercih ağırlıkları anlamlı fark sergilerken, hekimler açısından tercih ağırlıkları 6 ay veya 10 aylık "Kısa Ağrı Envanteri" skorunda 2 puanlık artışa kadar geçen süre hariç tüm düzeylerde anlamlı fark sergilemiştir. Hastalar ve hekimler yıllık ONJ riskini BTA'larla ilgili en az önemli özellik olarak değerlendirmiştir. Bu çalışma hastaların ve hekimlerin BTA'larla ilgili tercihleri konusundaki bilgileri artırmakta ve klinisyenlerin Türkiye'deki hastalar açısından önemli olan tedavi hedeflerini anlayarak karar vermelerine yardımcı olabilecek yararlı veriler sunmaktadır.

Anahtar Kelimeler: Kemiği hedef alan ilaçlar, Kemik metastazları, Çoktan seçmeli deney, Hasta tercihi, Hekim tercihi, İskeletle ilişkili olay

INTRODUCTION

Lung, breast and prostate cancers are the most common malignancies among adults in Turkey. According to the World Health Organization, an estimated 24500 new cases of lung cancer, 15200 new cases of breast cancer, and 12700 new cases of prostate cancer were diagnosed in Turkey in 2012.¹ Bone metastases are common when any of these cancers reach an advanced stage, affecting up to 40% of patients with advanced lung cancer, up to 75% of those with advanced breast cancer, and up to 90% of patients with advanced prostate cancer.²⁻⁴

Patients with bone metastases from solid tumors often experience bone complications, also known as skeletal-related events (SREs). These are commonly defined as pathologic fracture, radiation to bone, surgery to bone, and spinal cord compression.² Because bone complications are associated with loss of mobility and social functioning, a decrease in quality of life, and a substantial increase in medical costs,⁵⁻⁹ the management of these patients is complex and requires a multidisciplinary approach.¹⁰ In recent years, bone-targeted agents (BTAs) have become a valuable addition to available options for managing bone metastases,¹¹ which previously included radiotherapy, use of opioids and other systemic therapies. In Turkey, bisphosphonates such as zoledronic acid and the targeted agent denosumab (a RANK ligand inhibitor) are approved for the prevention of SREs among patients with metastatic bone disease from solid tumors.

Well-designed clinical trials have provided evidence of the relative efficacy and safety of BTAs. In particular, denosumab demonstrated superior efficacy in preventing SREs relative to zoledronic acid in patients with bone metastases secondary to solid tumors; however, there are very few studies examining physicians' preferences for BTA attributes (relating to efficacy, safety, mode of administration, etc.). In addition, at a time when the way that physicians treat patients is moving from a disease-centered approach to patient-centered care, more attention is being given not only to patients' awareness of their disease but also to their preferences regarding treatment options and delivery of care.^{12,13}

A discrete-choice experiment (DCE), which is a specific conjoint analysis elicitation format to evaluate the importance of different aspects in decision-making, was used to evaluate preferences for attributes corresponding to currently available BTAs. Preferences were elicited among patients with bone metastases from solid tumors and among physicians involved in the care of those patients in Turkey.

MATERIALS AND METHODS Study Population

Patients and physicians were recruited from 111 hospitals (79 research and training hospitals, 23 university hospitals and 9 private hospitals) in the following cities in Turkey: Ankara, Antalya, Istanbul, Izmir, and Samsun. Physicians currently treating patients with bone metastases from solid tumors were eligible to participate and were recruited by an independent agency via a telephone call or faceto-face invitation. Patients aged 18 years or older and residing in Turkey were eligible if they had a self-reported physician diagnosis of bone metastases from any type of solid tumor. Only patients that were able to read and write and complete the questionnaire themselves were recruited. Owing to the low awareness among patients of their disease status (i.e. whether or not they had bone metastases), we asked physicians to identify which of their patients were aware of their bone metastasis status and then recruited those individuals via personal invitation. All participants provided informed consent.

Development of the Survey Instrument

The methodology used for developing the DCE instrument was similar to one previously described.^{14,15} DCEs are a valid and reliable approach for assessing trade-off preferences between different health interventions.¹⁶⁻¹⁸ In such analyses, the key attributes of a treatment are identified in order to derive preference information between hypothetical treatment options.

A web-enabled DCE was developed and used with physicians during a face-to-face interview. For the patients, however, a pencil-and-paper DCE instrument was used and administered in hospital,¹⁹ because adults in Turkey, especially elderly individuals, do not routinely use the Internet.²⁰ The content of both survey instruments was tested during open-ended interviews with 8 physicians and 15 patients in the United States of America. Before administering the surveys, Turkish translations of the instruments were locally validated in terms of the quality of the translation and for context and relevance.

Both the patient and physician versions of the final DCE instrument contained three sections: 1) screening questions and informed consent; 2) questions on either patients' demographic and clinical characteristics or physicians' demographic characteristics and current level of experience in treating patients with bone metastases; and 3) discrete-choice questions.

To ensure the discrete-choice questions were understandable by patients, the second section of the DCE instrument also provided patients with a written description of each attribute that was illustrated by clinical examples.¹⁴ The discrete-choice questions in the survey asked patients and physicians to choose between hypothetical treatments based on the treatments' key attributes and the level to which each option fulfilled these attributes. Choices were used to infer preferences for the attributes and attribute levels. Preferences for attributes levels were then used to predict participant's preferences for currently available treatment options. **Table 1.** Description and levels of attributes of BTAs used in

 the discrete-choice questions

Attribute	Levels ^a	
Months until you have a compli- cation of bone metastases (Months until first SRE)	28 months 18 months 10 months	
Months until your pain gets worse (Months until worsening of pain)	10 months 6 months 3 months	
Chance of a problem with your teeth and/or jaw bone each year because of the medicine (Annual risk of ONJ)	None 1 out of 100 (1%) 5 out of 100 (5%)	
Chance of kidney damage be- cause of the medicine each year (Annual risk of renal impairment)	None 4 out of 100 (4%) 10 out of 100 (10%)	
How you take the medicine (Administration regimen)	Daily oral tablet Injection every 4 weeks 15-minute infusion every 4 weeks 120-minute infusion every 4 weeks	
^a Data used to define the attribute levels were taken from European Summaries of Product Characteristics and published literature. BTA= bone-targeted agent; ONJ= osteonecrosis of the jaw;		

According to guidelines on good research practices for DCEs in healthcare, the attributes and attribute levels developed for a survey instrument must be supported by evidence.¹⁹ After reviewing the prescribing information for currently approved products, searching for published results from clinical trials, and consulting with clinical experts, five attributes were selected to describe the available BTAs (Table 1). For the majority of attributes, three clinically-relevant and well-defined levels were identified, with the exception of mode of administration regimen, for which there were four levels based on current treatment options.

Forty discrete-choice questions were developed, each consisting of a choice between two hypothetical treatment profiles derived from combinations of BTA attribute levels (Table 2), and displayed as "medication A" or "medication B", without referring to the names of any drug (Figure 1 and 2).

Table 2. Treatment profiles for the BTAs investigated				
	Treatment profile			
BTA attribute	Denosumab	Zoledronic acid	Clodronate	Pamidronate
Time to first SRE	27.7 months	19.5 months	15–20 months (assumed 17.5 months)	10.9 months
Time to a 2-point increase in pain on the BPI	5.9 months	5.6 months	3 months	Between 0.03 months and several months (assumed 3 months)
Risk of ONJ each year	1.8%	1.3%	Yes, but value not stated (assumed 1 %)	Yes, but value not stated (assumed 1%)
Risk of 0.5 mg/dL increase in baseline creatinine	0%	9.3%	Yes, but value not stated	8.1%
Administration regimen	Injection every 4 weeks	15-minute infusion every 4 weeks	Daily oral tablet	120-minute infusion every 4 weeks

Data for time to worsening of pain for denosumab and zoledronic acid were based on von Moos et al. [24]; all other data were derived from prescribing information.

BPI= brief pain Inventory; BTA= bone-targeted agent; ONJ= osteonecrosis of the jaw; SRE= skeletal-related event

Medication feature	Medication A	Medication B
Months until you have a complication of bone metastases	28 months	18 months
Months until your pain gets worse	3 months	6 months
Chance of a problem with your teeth and/or jaw bone each year because of the medicine	5 out of 100 (5%)	
Chance of kidney damage because of the medicine each year	4 out of 100 (4%)	10 out of 100 (10%)
How you take the medicine	120-minute infusion every 4 weeks	Injection every 4 weeks
Which would you choose?		

Figure	1. Example	discrete-choice	question	(Patients'	Questionnaire))
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BPI= brief pain inventory; ER= estrogen receptor; HER= human epidermal growth factor receptor; ONU= osteonecrosis of the jaw; PR= progesterone receptor; SRE= skeletal-related event; TC= docetaxel with cyclophosphamide

Figure 2. Example discrete-choice question (Physicians' Questionnaire)

Patient 1: A 57-year old woman who was diagnosed with breast cancer and developed bone metastases along with 2cm mediastinal and supraclavicular adenopathy 3 years after her initial diagnosis. She initially received treatment with docetaxel and cyclophosphamide adjuvant chemotherapy. The tumour is oestrogen receptor/progesterone receptor positive and HER-2 negative. She was on an adjuvant aromatase inhibitor at the time of her relapse. Her recurrence was noted by examination identifying the supraclavicular adenopathy. On further questioning, she admits to increasing mid-back (thoracic area) pain, which she rates as a 4 on a scale of 0 to 10*. The patient's health is otherwise good (high Karnofsky performance status) with no history of kidney disease and no significant comorbidities.

Or

Patient 2: A 71-year-old man who was initially diagnosed with Gleason 8-10 prostate cancer 3 years ago. He is now castration-resistant and has developed bone metastases. His PSA level is \geq 10. He is complaining of left hip pain when he walks and low back pain if he sits too long, which he rates as a 4 on a scale from 0 - 10*. The patient's health is otherwise good (high Karnofsky performance status) with no history of kidney disease and no significant comorbidities.

*: Where 0 is no pain and 10 is worst pain imaginable

Peoplegrams (visual representations using images of people to depict the proportion of patients affected by a particular attribute) were used to present the levels of risk of developing osteonecrosis of the jaw (ONJ) and risk of increasing renal impairment. Four versions of the DCE were created, with 10 choice questions each. Physicians were randomly assigned to one of these web-enabled versions, while patients were sequentially assigned to pencil-and-paper versions to control for order effects.

All participants were asked to complete a sample discrete-choice question (Figure 1) before completing the discrete-choice section of the survey instrument. Because physicians see patients at all stages of disease, two patient profiles for what may be considered a typical patient with bone metastases secondary to breast cancer and a typical patient

 Table 3. Patient baseline characteristics

Characteristic	Patient population (n= 91
Gender	
Female	41 (45.1)
Male	50 (54.9)
Age (years)	
18–45	14 (15.4)
46–65	50 (55.0)
≥ 66	27 (29.7)
Which of the following complications of bone metastases worries you the most?	
A bone fracture	47 (51.6)
Radiation therapy to prevent a fracture and/or to treat bone pain	4 (4.4)
Surgery to the bone to prevent a fracture	6 (6.6)
Increased pressure on the spinal cord	34 (37.4)
Type of cancer that led to bone metastases	
Breast	42 (46.2)
Prostate	19 (20.9)
Lung	20 (22.0)
Kidney	10 (11.0)
ess than 2 years since diagnosed with cancer	57 (62.6)
_ess than 1 year since diagnosed with bone metastases	68 (74.7)
Currently taking treatment for bone metastases	60 (65.9)
Losing ability to move around affected the patient the most in the past 2 weeks	36 (39.6)
Had a complication because of bone metastases	13 (14.3)
Severity of worst pain in the past week for any reason	
No pain	12 (13.2)
Mild	13 (14.3)
Moderate	33 (36.3)
Severe	33 (36.3)

with bone metastases secondary to prostate cancer were provided (Figure 2).¹⁴ Physicians were then asked to make hypothetical treatment decisions based on these profiles.

Analyses

The patterns of physicians' and patients' preferences were analyzed using random-parameters logit (RPL) models, which estimate a preference weight for each attribute level in the study. RPL models avoid potential estimation bias from unobserved preference heterogeneity among participants by estimating a distribution of preferences across participants for each preference parameter.²¹ The distance between the preference weight for the best and worst levels of an attribute can be interpreted as the relative importance of the attribute to the patients' and physicians' treatment choice.

Predicted choice probabilities (PCPs) were calculated using RPL model results to evaluate relative preferences for full treatment profiles. PCPs predict the percentage of participants who would select a treatment profile with particular characteristics. PCPs do not account for market conditions (e.g., real-world available treatment substitutes, limitations in information available to patients). PCPs were estimated for BTA profiles with characteristics similar to denosumab, zoledronic acid, clodronate, and pamidronate. Estimated preferences were based on participants' responses to the 10 choice questions. Drug names and drug information were not provided at any time to the participants.

Characteristic	Physician population (n= 99)
Age (years)	
26–35	30 (30.3)
36–45	36 (36.4)
≥ 46	33 (33.3)
How many years have you been in practice since completing your r	nedical training?
4–9	19 (19.2)
≥ 10	80 (80.8)
Which of the following describes your practice? (Check all that appl	(y)
Private hospital	8 (8.1)
State hospital	5 (5.1)
University hospital	26 (26.3)
Training and research hospital	62 (62.6)
Private office	1 (1.0)
Which of the following best describes your area of specialization?	
Radiation oncology	56 (56.6)
Medical oncology	43 (43.4)
On average, how many patients with bone metastases from solid to	umors do you treat each week?
≤ 10	51 (52.0)
> 10	47 (48 0)

RESULTS

Participant Characteristics

A total of 94 patients and 101 physicians completed the DCE survey. Three patients and two physicians always chose the same answer, medication A or medication B, in the choice questions, indicating a lack of attention to the questions, 17 these participants were excluded from the analysis. The final sample included 91 patients and 99 physicians.

More than half of patients (55 %) reported that they were 46–65 years old (Table 3). Breast cancer was the most common malignancy among the patients. Most patients (75%) had only recently (within the past year) been diagnosed with bone metastases and 66 % were receiving treatment for bone metastases. Approximately 70% of patients had experienced moderate or severe pain in the week preceding the DCE (Table 3). Over 85% of patients had never experienced dental problems or kidney damage.

Physicians in the sample were specialists in either radiation or medical oncology (57% and 43%, respectively) (Table 4). Most physicians (81%) had

10 or more years of experience in clinical practice and the majority (63%) worked in a training and research hospital.

Preference Weights for Patients and Physicians

Patients and physicians were aligned with regard to their preferences for the most important BTA attributes. Annual risk of renal impairment was considered the most important attribute for both groups of participants. While patients believed that the second and third most important attributes were time to worsening of pain and time to first SRE, respectively, these factors were ranked in the reverse order by physicians (Figure 3). For patients, the preference weights for all levels of these attributes were significantly different (p< 0.05), whereas for physicians, the preference weights for all levels of these three attributes were significantly different except for time to a 2-point increase in Brief Pain Inventory score by 6 months or 10 months.

In terms of administration regimen, patients preferred daily oral tablets over injections and infusions, while physicians preferred a 15-minute





Figure 3. Preference weights for each level of five attributes of the bone-targeting agents investigated. (a) Patients, (b) Physicians

Table 5. Predicted choice probabilities for treatment profiles with characteristics similar to the bone-targeted agents investigated			
Treatment profile	Patients (n= 91)	Physicians (n= 99)	
Denosumab	100.0% (99.6–100.0%)	85.8% (72.6–93.0%)	
Zoledronic acid	0.0% (0.0–0.1%)	6.8% (2.8–14.6%)	
Clodronate	0.0% (0.0–0.2%)	6.6% (3.1–13.2%)	
Pamidronate	0.0% (0.0–0.0%)	0.8% (0.2–2.6%)	
Data are mean (95% confidence interval).			

infusion every 4 weeks. For both patients and physicians, there was no significant difference between injection and 15-minute infusion (p > 0.05).

Annual risk of ONJ was judged by patients and physicians to be the least important of the BTA attributes. For both groups, the preference weights for a 1 % risk of ONJ and a 5 % risk of ONJ were not significantly different (p> 0.05), and for patients, these levels were not ordered as expected on the basis of risk rates.

Predicted Choice Probabilities

The PCPs, which show the percentage of participants who would choose one treatment over another on the basis of their attributes, are presented in Table 5. Using the preference weights from the DCE results, it was predicted that the entire patient sample (100%; 95% confidence interval [CI], 99.6-100%) and the majority of physicians (86%; 95%) CI, 73-93%) would prefer a BTA profile with characteristics similar to denosumab (Table 5).

DISCUSSION

To our knowledge, this is the first study to evaluate the preferences of patients and physicians in Turkey for the various attributes of bone metastases treatments. The three BTA attributes rated as most important by patients and physicians were annual risk of renal impairment, time to worsening of pain, and time to first SRE.

Given the considerable morbidity and mortality associated with SREs, it is unsurprising that time to first SRE was ranked highly by both patients and physicians. However, this attribute was outranked by annual risk of renal impairment by both groups. Renal impairment is common in patients with cancer,²² given the nephrotoxicity of some chemotherapy regimens, the preference for a BTA with a low risk of renal impairment could reflect a desire of patients and physicians to ensure that any treatment for bone metastases does not compromise the use of chemotherapy.

In contrast to patients, the preference weights for physicians for time to an increase in pain by 6 and 10 months did not reach statistical significance. This is interesting in the context of the widespread under-treatment of cancer pain in clinical practice.^{23,24} Notably, in the current study, the majority of patients had experienced moderate or severe pain in the past week. Patients may not communicate their pain to their physician owing to misconceptions about opioid addiction and adverse effects, and their physician's ability to address the problem.²⁵ Some patients also under-report pain owing to an acceptance that a certain amount of pain will be experienced during the course of their disease.²⁶ Bone pain has a negative effect on quality of life and has been shown to correlate with reduced survival.^{27,28} Therefore, treatment options that prevent or delay the worsening of pain are highly desirable. Annual risk of ONJ was considered the least important BTA attribute by both patients and physicians. Although this is a serious adverse effect of anti-resorptive therapies, preventive dental measures and dental monitoring throughout treatment with a BTA can reduce the risk of ONJ and may have influenced the preferences seen in this study.29 Furthermore, only a small proportion (15%) of patients reported ever experiencing dental problems in the past, which may mean that most patients did not appreciate the morbidity that could be associated with ONJ.

Patients preferred a once-daily tablet administration regimen. This may reflect a desire of patients to avoid travel to hospitals in order to receive medication or could be due to needle phobia. In contrast, there were no significant differences between the physicians' preferences for administration regimen, although a 15-minute infusion every 4 weeks was the highest ranked option. Physicians may prefer administration options that involve contact with patients. Treatment adherence may also be easier to monitor with injections or infusions than with oral tablets, which are taken outside the hospital.

Two DCEs with similar designs have recently been conducted in other countries. A study of patients and physicians in France, Germany, and the UK also found that time to SRE, risk of renal impairment, and time to worsening of pain were the most important BTA attributes for both patients and physicians.^{14,15} In a study of physicians, patients, caregivers, and nurses in the USA, out-of-pocket cost to patients, time to first SRE, and risk of renal impairment were rated as the most important BTA attributes by each group.³⁰⁻³² These studies confirm that treatments that delay SREs and worsening of pain with a low risk of renal impairment are desirable in the opinions of both patients and physicians across Europe and the USA.

Our data reflect the preferences of patients and physicians in real-world clinical practice. However, DCEs have some limitations; participants are asked to evaluate hypothetical treatment profiles, so responses to questions can differ from treatment decisions in the real-world setting. In addition, the financial implications of the decisions made by patients and physicians were not considered in this study but are likely to influence treatment choices in clinical practice.

Recruiting patients for this study was more challenging than for previous similar DCEs.^{14,15} This was thought to be because of a lack of awareness among patients about their disease status. Although studies show that, in some countries, full disclosure of diagnosis and prognosis by physicians to patients with cancer is increasing,^{33,34} in Turkey there may still be reluctance among physicians, relatives, and caregivers regarding revealing the severity of a condition to the patient. A diagnosis of cancer may be considered as a "death sentence", and therefore patients' relatives and physicians may insist on avoiding discussing the stage of the cancer in detail.¹³ Sharing decision-making between patients and physicians has been shown to have a positive effect on treatment adherence and health outcomes.^{35,36} Therefore, increasing the involvement of patients in treatment decisions in clinical practice is advocated.

In conclusion, when considering treatment choices for preventing bone complications associated with bone metastases from solid tumors, patients and physicians in Turkey focused mainly on the risk of renal impairment, delaying SREs and worsening of pain. The range of ONJ risk levels included in this study did not deter patients and physicians from selecting treatments that could help to delay SREs or pain. This study adds to the information available on the preferences of patients and physicians regarding BTA attributes and provides useful data on the treatment goals that are important to patients in Turkey, which will aid clinicians in decisionmaking. The shared preferences of patients and physicians suggest that a collaborative approach to decision-making is feasible and may be beneficial given the value placed upon treatment options with superior efficacy and safety in terms of risk of renal impairment. This study may also aid payers in deciding which treatment options to reimburse.

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Conflict of Interest

RTI Health Solutions, an independent research institution, received funding from Amgen to complete this study. Juan Marcos Gonzalez, Brett Hauber, and Joshua Posner are employees of RTI Health Solutions. Francesca Gatta is an employee

of Amgen (Europe) GmbH. Gulnihal Ertugrual is an employee of Amgen Turkey and owns stock. Yi Qian and Jorge Arellano are employees of Amgen Inc. and own stock.

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