Management of Patients With Advanced Urothelial Carcinoma in an Evolving Treatment Landscape: A Qualitative Study of Provider Perspectives of First-Line Therapies

Petros Grivas,1 Caroline Huber,2,# Vivek Pawar,3 Meaghan Roach,2 Suepattra G. May,2 Isha Desai,2,# Jane Chang,4 Murtuza Bharmal3

Abstract

Treatment decision-making processes for advanced urothelial carcinoma (aUC) are not well defined; therefore, we conducted a qualitative interview study with US oncologists and oncology nurses. Providers preferred platinum-based first-line (1L) chemotherapy regimens followed by switch-maintenance immune checkpoint inhibitor (ICI) among those without disease progression (reserving 1L ICI monotherapy for frail patients). Overall, providers adhered to guidelines for decision-making in the 1L aUC setting.

Introduction: The treatment landscape in locally advanced/unresectable or metastatic urothelial carcinoma (aUC) has evolved with the use of immune checkpoint inhibitors (ICIs) in the first line (1L) and platinum-refractory settings and with the recent approval of avelumab as 1L maintenance therapy for patients achieving disease control with platinum-containing regimens. Oncology provider perspectives and decision-making processes regarding aUC management, especially with the integration of recently approved strategies, such as maintenance therapy, have not been well-described. Patients and Methods: Qualitative interview study with US oncologists and oncology nurses in academic and community settings in August 2020. Interviews explored decision-making around aUC 1L treatment eligibility determinants and selection, programmed cell death 1 ligand 1 (PD-L1) testing practices, and use of maintenance therapy. Thematic analysis was used to identify drivers of 1L treatment decisions. Results: Eighteen oncologists (women, 11%; >15 years in practice, 55%; academic, 39%) and 18 oncology nurses (women, 94%; >15 years in practice, 34%; academic, 50%) participated. Providers preferred platinum-based regimens in 1L setting and reserved 1L ICI monotherapy for frail patients. Providers preferred chemotherapy followed by switch maintenance ICI, as opposed to concurrent combination chemotherapy and ICI, followed by ICI as continuation maintenance. Decision-making was driven by need to adhere to treatment decision-making guidelines, characteristics of the patient, treatment efficacy and patient preference. Conclusion: Providers adhered to guidelines and level I evidence in decision-making in the aUC 1L setting. Future studies should further evaluate barriers to the adoption of standard-of-care strategies and factors impacting decision-making in the real-world setting.

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Abbreviations: 1L, first-line; aUC, advanced/unresectable urothelial carcinoma; ECOG, Eastern Cooperative Oncology Group; ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1; UC, urothelial carcinoma; US, United States.

1University of Washington, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, WA
2PRECISIONHeor, New York, NY
3EMD Serono, Billerica, MA
4Pfizer Inc, New York, NY

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Address for correspondence: Petros Grivas, MD, PhD, University of Washington; Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, 1144 Eastlake Ave E, LG-405, 98109, Seattle, WA,
E-mail contact: pgrivas@uw.edu
* Affiliation at the time the study was conducted.
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Management of Patients With Advanced Urothelial Carcinoma

Introduction
For years, standard first-line (1L) treatment for patients with locally advanced unresectable or metastatic urothelial carcinoma (aUC hereafter), primarily comprised cisplatin- and carboplatin-based chemotherapy regimens.\(^1\) Among patients with aUC who receive platinum-based regimens, the median overall survival has been 12 to 15 months, with progression-free survival about 6 to 9 months from the beginning of chemotherapy.\(^2\,3\) More recently, immune checkpoint inhibitors (ICIs) using programmed cell death 1 protein (PD-1)/programmed cell death 1 ligand 1 (PD-L1) inhibition have been approved in the platinum-refractory setting.\(^4\) A number of patients with aUC are ineligible for platinum-based chemotherapy because of age, medical comorbidities, and poor performance status.\(^1\,5\) Atezolizumab and pembrolizumab have been approved in the 1L setting for patients with aUC who are ineligible for any platinum-based chemotherapy (regardless of PD-L1 in US) or are ineligible for cisplatin and have tumors with high PD-L1 expression.\(^6\) ICIs have demonstrated durable responses and tolerable safety profiles, but few patients respond to ICI monotherapy relative to chemotherapy.\(^3\,6\,8\)

In June 2020, the US Food and Drug Administration approved the anti–PD-L1 agent avelumab as a 1L switch maintenance therapy for patients with aUC who achieve disease control with platinum-containing chemotherapy based on the results from the phase 3, randomized, multicenter, and JAVELIN Bladder 100 trial.\(^9\,10\) Although maintenance therapy has been widely integrated into clinical practice for other metastatic tumor types including nonsmall cell lung cancer (NSCLC) and ovarian, colon, and breast cancer,\(^11\,12\) it had not been approved for aUC until recently. In the JAVELIN Bladder 100 trial, median overall survival in patients who received avelumab 1L maintenance plus best supportive care was 21.4 months compared with 14.3 months in patients who received best supportive care alone (hazard ratio, 0.69, in all randomized patients).\(^10\) First-line maintenance therapy with avelumab has since been integrated into clinical practice guidelines and value frameworks, including those by the National Comprehensive Cancer Network and the European Society for Medical Oncology.\(^5\,13\)

The evolving standard of care for aUC treatment provides a unique opportunity to more comprehensively understand provider perspectives, beliefs, and experiences as new therapies are integrated into real-world practice. The goal of this qualitative interview study with medical oncologists and oncology nurses was to explore treatment decision-making processes in patient management and to assess the role of new treatment strategies and therapeutic options, particularly as they relate to 1L regimens in aUC. Understanding providers’ perspectives regarding maintenance therapy in aUC is critical to better understanding the barriers to and facilitators of its adoption, its potential impact on clinical workflows, and its role in improving clinical outcomes. This study sought to elicit clinicians’ perspectives on and experiences with current and emerging treatments for aUC, including the clinical, patient-level, and treatment-specific factors that influence their treatment recommendations.

Material and Methods

Study Design, Setting, and Participants
This qualitative study incorporated semistructured in-depth interviews with medical oncologists and oncology nurses treating patients with aUC. The research was determined to be exempt by the Advarra institutional review board.

Participants (n = 36) in the study were identified through a medical market research firm and were purposively selected to represent both academic and community practitioners across geographic census regions in the United States (US) to ensure a range of perspectives. Although not exhaustive, the sample size was expected to provide sufficient diversity of opinion and confirmation and validation of shared views across participants in accordance with established qualitative research guidelines for sampling.\(^14\,15\)

Study invitations were emailed to potential participants, directing them to an online screener to determine potential eligibility and willingness to participate. Interested and eligible participants were invited to participate in a web-based interview with a member of the research team (CH, MR, SM). All potential participants were required to be adults (≥18 years), able to speak and read English, provide verbal consent, and be willing to participate in an in-depth interview. Medical oncologist participants were required to be board certified, actively licensed, and practicing in the US, and treat an average of at least 5 patients with aUC per month. Oncology nurse participants were required to be registered nurses certified in oncology and treat an average of at least 5 patients with aUC per month. Participants were compensated for study completion.

Interviews
Structured interviews, lasting 45 to 60 minutes, were conducted between August 13 and 28, 2020. Three members of the research team with graduate-level training in qualitative interviewing techniques (CH, MR, SM) conducted the in-depth interviews, and one member of the study team (ID) observed the interviews and took field notes. Complementary, semistructured, in-depth interview guides were used to elicit oncologists’ and oncology nurses’ perspectives and experiences. The interview guides were developed by research team members with qualitative, cancer-focused research experience after reviewing the existing peer-reviewed literature, along with input from clinical oncologists. Interview domains queried participants about treatment decision-making processes, emerging treatment strategies in aUC, and challenges and recommendations for improving outcomes of patients with aUC. Sample interview discussion guide questions are detailed in Table 1. Interviews were audio recorded and professionally transcribed verbatim into a document ready for export to the Dedoose qualitative software program.\(^16\)

Analysis
We employed the constant comparative method, facilitated by the use of the Dedoose program (version 8.3.35), to analyze the data.\(^15\,17\) This approach involves looking for similarities and differences in the way participants discussed their perspectives and experi-
en, performed through the following key stages: (1) reading all data for conceptual elements and themes and to develop a general impression of the data; (2) developing a coding framework and subsequent classification (coding) of conceptual elements and themes generated inductively and derived from the original interview questions; and (3) coding each transcript for the frequency, order, and context of the codes; yielding a “map” of the conceptual elements that comprise the topics of interest. Using the constant comparative method, concepts and patterns emerged from the data that were then refined into meaningful categories and themes by the analytic team.17,18

Results

Provider Demographics

A total of 18 medical oncologists and 18 oncology nurses participated in the study (see Table 2). The medical oncologist sample was predominantly male (89%) with a mean age of 51.3 years (SD, 9). Most oncologists (55%) had been in practice for at least 16 years. University or academic medical centers (39%) and partnership practices (28%) represented the most common principal practice types. The sample included geographic representation across the 4 US census regions with the Midwest (33%) being the most represented location. Most oncologists (66%) saw an average of 11 to 50 patients with a new or existing urothelial carcinoma (UC) diagnosis each month, and 61% of oncologists saw an average of 11 to 25 patients with aUC each month.

The oncology nurse sample was predominantly female (94%), with a mean age of 43.8 years (SD, 11.1). Most (62%) of the sample had been practicing oncology nursing for 11 years or more. University and academic medical centers (33%) and hospital-based practices (22%) represented the most common principal practice types. Similar to the oncologist sample, the nurse sample had geographic representation across the 4 census regions, with 39% from the Northeast. Most oncology nurses (78%) saw an average of 1 to 25 patients with UC each month, and 1 to 10 patients with aUC each month.

Providers whose primary practice locations were university/academic medical centers or National Cancer Institute-designated cancer centers were considered to be in an “academic setting,” while those whose primary location were solo or partnership practices, multispecialty group practices, or hospital-based practices were considered to be in a “community setting.”

Patient Diagnosis and Referral Practices

To establish a baseline understanding of practice norms, participants were first asked to describe the typical patterns of patient diagnosis and/or referral at their respective institutions. Most oncologists and oncology nurses reported that they treated aUC cases upon UC progression, referred to them predominantly by urology groups, with a subset of patients referred by primary care doctors or from inpatient settings. Patients who were diagnosed with de novo aUC were more likely to have their cases presented at a tumor board.
### Table 2  Oncologist and Oncology Nurse Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oncologists (n = 18)</th>
<th>Oncology Nurses (n = 18)</th>
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<tbody>
<tr>
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<td>Years practicing oncology/oncology nursing</td>
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</table>

Abbreviation: UC = urothelial cancer.

* Providers could select more than one specialty or certification.
Conversely, patients whose UC progressed to metastatic typically did not require a multidisciplinary review unless palliative radiation was being considered.

Providers described the role and use of PD-L1 testing, specifically its timing in the diagnosis process. Oncologists across both academic and community settings reported a shift to more widespread and earlier use of PD-L1 testing, especially as part of a standard next-generation sequencing panel once patients present with metastatic disease. This panel was ordered to inform initial treatment recommendations and potential future treatment options:

“Now we’re testing almost everybody. anybody who has invasive bladder cancer, or metastatic disease. It’s part of the protocol that the pathologists use. We get PD-L1 testing on everybody.” – Oncologist, Community

Approximately 89% of oncologists reported that PD-L1 testing was done on histological samples of their patients at the time of aUC diagnosis, while only 11% reported testing after initial eligibility for aUC treatment was determined. No differences in PD-L1 testing practices among oncologists practicing in academic settings compared with those practicing in community settings emerged from the data.

First-Line Treatment Decision-Making and Practices for aUC

Our analysis revealed 4 primary drivers (ie, motivating factors) undergirding treatment decision-making and recommendations in the 1L setting: (1) adherence to treatment guidelines, (2) presenting patient characteristics and comorbidities, (3) effectiveness of treatment on response and overall survival, and (4) patient goals and preferences for treatment.

First, adherence to treatment guidelines was a key factor in decision making not only because guidelines represented the most up-to-date treatment data and knowledge clinically, but also because established guidelines needed to be followed explicitly for reimbursement. Participants cited National Comprehensive Cancer Network (NCCN) as the most frequently referenced, largely because it was considered most up to date on therapeutic options.

Second, study participants cited a number of criteria used to inform cisplatin-based chemotherapy eligibility based on presenting patient characteristics and comorbidities. Kidney function (as measured by glomerular filtration rate [GFR]), Eastern Cooperative Oncology Group (ECOG) performance status, neuropathy, cardiac dysfunction, and ototoxicity were the most reported criteria by providers. Oncologists did not provide standardized GFR cutoffs, but ranges cited included GFR of >50 to >90 mL/min. More generally, oncologists also discussed the frailty and comorbidity profiles of patients with aUC and how these were used as general criteria to assess cisplatin-based eligibility:

“So pretty much, patients who we consider a candidate for cisplatin-based therapy, they need to have good kidney function, meaning their glomerular filtration rate or creatinine clearance [waal] more than 60 [cc/min]. You need to have hearing capability before you consider them for cisplatin-based therapy, and they should not have poor performance status, meaning their ECOG should be 0 or 1, and also these patients should not have any significant history of neuropathy.” – Oncologist, Academic

Oncologists preferred platinum-based regimens in the 1L, specifically cisplatin-gemcitabine, or for patients who may otherwise be cisplatin ineligible, carboplatin-gemcitabine. Patients considered ineligible for platinum-based regimens, including those whom oncologists believed were too frail or elderly to tolerate platinum-based chemotherapy, received monotherapy immunotherapy in the 1L setting. Pembrolizumab was the most frequently cited ICI, with atezolizumab also recommended by oncologists. Regimen recommendations and preferences did not vary by practice setting.

Third, duration and response to therapy was a key driver of decision-making in the 1L setting. Among patients with aUC who received platinum-based chemotherapy regimens, 4 to 6 cycles were typically recommended by oncologists (see Figure 1). No oncologists reported recommending >6 cycles, while toxicity and tolerability were cited as reasons for administering fewer (eg, 4) cycles. Oncology nurses reported a broader range, with most reporting 4 to 6 cycles.

“I’d say I try to get them to 6 cycles, particularly in the light of the recent approval of avelumab as maintenance. But in general, even before that approval, I’d still go with trying to get them 6 cycles of treatment.” – Oncologist, Community

Oncologists and nurses also were asked how many chemotherapy cycles were typically administered to patients before assessing treatment response. The most common response among both oncologists and nurses was 2 to 4 cycles. At this point in treatment, oncologists noted they would assess response to the regimen using radiological confirmation and continue if the patient had not demonstrated progression and had tolerated therapy.

Providers were also asked about the role of patient preferences in 1L treatment determination. While patient preference alone did not drive decision-making, providers were aware of and accounted for patient goals and preferences. Providers noted that overall survival and maintaining quality of life were the most important goals of treatment for patients, and that patients preferred therapies that minimized adverse effects, required fewer infusions, and provided durable response.

“I think that there are only two treatment goals. One is that efficacy, which is overall survival, and that is the most sort of highest priority. The second one is quality of life, right? If a patient says, ‘I don’t really, don’t worry about, you know, helping me live longer, but I really don’t want to suffer too much.’ So those are two maybe sometimes contradictory goals that I work with the patient.” – Oncologist, Academic

Further, providers noted that they sometimes had to educate patients on dated misconceptions of chemotherapy. Although infrequent, providers described scenarios whereby some patients expressed a strong preference for immunotherapy as their 1L treatment, largely driven by observing a family member or friend who experienced toxicity from chemotherapy, and wanting to avoid this for themselves. While oncologists noted that they account for
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**Emerging Treatment Strategies in aUC**

In light of avelumab’s recent approval (interviews conducted in August 2020; FDA approval on June 30, 2020), participants were asked questions related to the role and use of maintenance therapy in aUC. This discussion was guided by a schematic (Figure 2) adapted from the literature and designed to elicit perspectives on potential different maintenance therapy strategies within aUC. Treatment Strategy A in the schematic represented chemotherapy followed by ICI switch maintenance, which is the currently approved strategy in aUC based on level I evidence. Treatment Strategy B represented concurrent chemotherapy and ICI, followed by ICI continuation maintenance therapy.

Oncologists reported recent implementation of Strategy A in their practice, primarily due to the recent avelumab approval at the time of this study. While few oncologists had current experience with the regimen, oncologists noted that avelumab trial data were already shifting their clinical practice. Providers were asked which strategy they would recommend in a hypothetical scenario where both strategies had similar degree of overall survival benefit. Overall, 66.6% of oncologists and 71.4% of nurses indicated they would recommend Strategy A, while 33.3% of oncologists and 28.6% of nurses would recommend Strategy B. Those who expressed a preference for Strategy A cited the potential for reduced toxicity/adverse effects, lower costs, and the availability of clinical data to support the strategy’s use.

“So [Strategy A] is not only more effective at least right now from the data, but it’s actually more tolerable and the toxicity is less than when you combine the two together. So, in fact, with [Strategy A] you are gaining both on efficacy as well as on toxicity and that’s what makes it very effective as well.” – Oncologist, Community

“Typically, for the UC patients, I see more of the treatment [Strategy A] where they’ll begin with the chemo potentially and then switch to immunotherapy maintenance, or they’ll just go straight to the immunotherapy if they’re not a good candidate for the traditional chemo, in the UC setting in particular.” – Nurse, Community

Familiarity with Strategy B guided preferences for the regimen, specifically data from and used in other tumor types, such as NSCLC, for which it is currently used. The perceived potential for a durable and deeper response with combination chemotherapy and ICI was also cited as a potential benefit of Strategy B. Adverse effects and toxicity, and the lack of additional treatment options in the event of disease progression, were noted as concerns around use of Strategy B.

“I prefer [Strategy B], and the reason why, because I think adding immunotherapy as early as when we start chemotherapy is proba-


ibly better. We’ve had now a lot of data in other cancers when we integrate immunotherapy with chemo in an upfront setting showed improvement in outcomes, and the biggest example is lung cancer now.” – Oncologist, Academic

I worry about us using all our chips on first-line, and not having anything when patients progress, because once patients fail chemotherapy and immunotherapy, I mean, what do you have left?” – Oncologist, Community

Providers were also asked about the role of maintenance therapy dosing logistics on their decision-making process. Although frequency of dosing was not cited as a major factor in an oncologist’s recommendation for a maintenance regimen, both oncologists and nurses preferred regimens with less-frequent dosing.

“…it is not a big factor. If the patient is doing well, they are willing to do whatever it takes to continue to do well. If it takes them to come every 3 weeks, they will. If we make it every 6 weeks, even better for them, but it’s not a big factor for decision-making.” – Oncologist, Community

Discussion

Although patients diagnosed with aUC typically face a poor prognosis, the treatment landscape has significantly evolved in the last few years, most recently with the approval of avelumab as 1L maintenance therapy following disease control with platinum chemotherapy. In light of new therapeutic options, this qualitative study sought to more comprehensively understand treatment-related decision-making for patients with aUC. Providers reported practices aligning with current clinical guidelines and standard of care, especially as relates to 1L treatment regimens, assessment of chemotherapy eligibility, and implementation of maintenance avelumab in clinical practice.8,13

Providers in the study described a more widespread integration of PD-L1 testing early in the aUC diagnosis and treatment course to inform current and future therapy options. Oncologists did not systematically report barriers to testing, such as insurance coverage, logistics, and cost, but they may be less aware of such issues if they are not directly responsible for them. Most providers recommended platinum-based chemotherapy regimens (cisplatin-gemcitabine or carboplatin-gemcitabine) as 1L treatment and assessed eligibility based on GFR, ECOG performance status, medical comorbidities, and general frailty.

The use of immunotherapies was viewed by providers as a treatment paradigm shift, in both the upfront20,21 and, most recently, maintenance settings. Although the use of maintenance therapy in aUC is nascent, providers expressed both satisfaction with the data currently available for Strategy A. There was also strong interest in additional evidence generation, especially as it relates to patient types who may best respond to a maintenance therapy strategy, longer-term data to better understand patient outcomes, and treatment duration of maintenance therapy.

In general, providers did note several challenges that remain in the treatment of patients with aUC. These included a lack of reliable predictors of treatment response, adverse-effect management, durability response, and financial costs of treatment. They also cited the need for greater patient education around UC more generally, as many patients are not aware of UC symptoms and may receive a delayed diagnosis.
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**Limitations**

A strength of the study design is the use of qualitative interview techniques, which enables the capturing of perspectives and opinions across a spectrum of oncology care providers. The methodology allows for an in-depth exploration of perspectives not possible in quantitative surveys. While this work better elucidates the treatment decision-making processes and decisions that providers representing diverse health systems and practice settings make when treating patients with aUC, it is not without inherent limitations that merit consideration. First, the findings represent the views of a small convenience sample of providers that volunteered for this study and who may be more enthusiastic about the subject matter in comparison to other providers who treat patients with aUC. Last, the interviews were conducted soon after avelumab approval in the 1L maintenance setting, and prior to pembrolizumab receiving regular FDA approval in the 1L setting only for patients who are ineligible for platinum-based chemotherapy. In addition to the potential selection bias, relative lack of more quantitative data and possible confounding factors may possibly impact the results. Despite these limitations, which are inherent to a qualitative study design, our findings raise interesting hypotheses and set the stage for larger-scale studies to validate and assess the generalizability in the real-world setting.

**Clinical Practice Points**

*What is already known about this subject?*

- Standard of care first-line (1L) treatment for patients with advanced urothelial carcinoma (aUC) is cisplatin- or carboplatin-based chemotherapy
- In June 2020, the US Food and Drug Administration approved avelumab (anti-PD-L1) as 1L maintenance therapy for patients with aUC with disease control following platinum-containing chemotherapy
- Approval was based on the results of the phase 3, randomized, multicenter, JAVELIN Bladder 100 trial; median OS in patients who received avelumab 1L maintenance plus best supportive care was 21.4 months versus 14.3 months in patients who received best supportive care alone (hazard ratio of 0.69) in all randomized patients

Avelumab 1L maintenance is now a recommended standard of care in international treatment guidelines, including NCCN and ESMO

- Although maintenance therapy has been widely integrated into clinical practice for other metastatic tumor types, including nonsmall cell lung, ovarian, colon, and breast cancer, it had not been approved for aUC until recently

*What are the new findings?*

- In our qualitative study, we interviewed medical oncologists and oncology nurses to understand their treatment decision-making processes regarding patient management for aUC
- Providers preferred 1L platinum-based chemotherapy regimens or chemotherapy followed by ICI maintenance among those without disease progression; 1L ICI monotherapy was reserved for frail patients
- Providers noted several challenges, such as a lack of reliable predictors of treatment response, management of adverse events, durability of response, and the cost of treatment

**How might it impact clinical practice in the foreseeable future?**

- With this evolving treatment landscape, our findings elucidate the decision-making processes that providers face when treating patients with aUC
- Further, our findings raise interesting hypotheses setting the stage for larger-scale studies to assess generalizability in real-world settings

**Author Contributions**

Conceptualization: PG, VP, JC, MB
Data curation and formal analysis: CH, MR, SM, ID, MB
Funding acquisition: VP, JC, MB
Project administration: CH, MR, SM, ID, MB
Writing/reviewing: PG, CH, VP, MR, SM, ID, JC, MB

**Disclosure**

PG has, in the last 3 years, unrelated to this manuscript, provided consulting to AstraZeneca, Astellas Pharma, Bayer, Bristol Myers Squibb, Clovis Oncology, Dyania Health, Driver, the healthcare business of Merck KGaA, Darmstadt, Germany, Exelixis, Foundation Medicine, Genentech/Roche, Genzyme, GlaxoSmithKline, Guardant Health, Heron Therapeutics, Immunomedics/Gilead, Infinity Pharmaceuticals, Jansen, Merck & Co., Kenilworth, NJ, Mirati Therapeutics, Pfizer, Regeneron Pharmaceuticals, QED Therapeutics, Seattle Genetics, UroGen, 4D Pharma PLC; his institution has received research funding from Bavarian Nordic, Bristol Myers Squibb, Clovis Oncology, Debiopharm, the healthcare business of Merck KGaA, Darmstadt, Germany, GlaxoSmithKline, Immunomedics/Gilead, Kure It Cancer Research, Merck & Co. Kenilworth, NJ, Mirati Therapeutics, Pfizer, QED Therapeutics, JC is an employee of Pfizer. VP and MB are employees of EMD Serono, Billerica, MA, USA. MR, SM, and ID are employees of PRECISIONthero that was hired by the healthcare business of Merck KGaA, Darmstadt, Germany, to conduct this research. SM owns equity interest in Precision Medicine Group, the parent company of PRECISIONthero.

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