2023 European Society for Medical Oncology (ESMO) Congress

Meeting highlights

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Cite as: Chi KN, Canil C, Alimohamed N, et al. 2023 European Society for Medical Oncology (ESMO) Congress: Meeting highlights. *Can Urol Assoc J* 2024;18(1):E46-52. http://dx.doi.org/10.5489/cuaj.8688

INTRODUCTION

The European Society for Medical Oncology (ESMO) Congress, held in Madrid, Spain and online on October 20–24, 2023, provided a comprehensive update on the latest breakthroughs in cancer research. The program focused on recent advances in basic science, translational research, and clinical study results, as well as prevention, screening, and early diagnosis, and aimed to help participants understand and optimize the clinical implementation of these advancements. This year's congress included over 2500 abstracts, with more than 33 000 participants from 155 countries.

Following the congress on November 1, the Canadian Urological Association (CUA) held an online webinar, where Canadian experts reviewed the latest evidence in urologic cancers. This report highlights the most relevant and cutting-edge advances in prostate, kidney, and bladder cancers. The entire webinar can be viewed on UROpedia Canada, and meeting abstracts can be found on ESMO oncologyPRO.

PROSTATE CANCER

Dr. Kim Chi presented novel and potentially impactful findings in prostate cancer. The final analysis of the MAGNITUDE trial, a phase 3, randomized, double-blind, placebo-controlled study, evaluated the combination of niraparib (NIRA), a poly(ADP-ribose) polymerase inhibitor (PARPi), with abiraterone acetate plus prednisone (AAP) as first-line therapy in patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations.[1] mCRPC patients with HRR gene alterations, *BRCA1* and *BRCA2* in particular, have poor outcomes compared to patients without these gene alterations.

At primary analysis, MAGNITUDE demonstrated significant improvement in radiographic progression-free survival (rPFS) with NIRA + AAP compared with placebo + AAP in patients with *BRCA*-mutated mCRPC (hazard ratio [HR] 0.53, p=0.001). The final, pre-planned, event-driven overall survival (OS) analysis was conducted after a median followup of 35.9 months, with a focus on patients with *BRCA*-mutated mCRPC. The median treatment duration was 20.5 months for the NIRA + AAP arm and 14.4 months for the placebo + AAP arm. Final OS analysis demonstrated no significant difference, with a median survival of 30 months for those on NIRA compared to 28.6 months for those on placebo (HR 0.788). A pre-planned multivariate analysis adjusting for baseline imbalances demonstrated an OS benefit favoring NIRA + AAP (HR 0.663, p=0.0237), this despite 70% of NIRA vs. 86% of placebo patients receiving subsequent life-prolonging therapy, including over 40% of placebo patients receiving a subsequent PARPi or cisplatin-based chemotherapy. Other endpoints, such as time to symptomatic progression and time to cytotoxic chemotherapy, were also in favor of NIRA. Adverse events (AEs) were as expected, with greater AEs associated with NIRA.

This analysis supports the positive benefit-risk profile of first-line NIRA with AAP as a new standard of care for patients with *BRCA*-mutated mCRPC. This further demonstrates the benefit of earlier use of PARPi with androgen receptor pathway inhibition (ARPI) as first-line therapy for mCRPC in patients with *BRCA1/2* mutations in line with the PROpel[2] and TALAPRO-2[3] studies. These studies emphasize the need for tumor and germline testing to identify HHR alterations for patients with metastatic prostate cancer.

A health-related quality-of-life (QoL) analysis was performed in patients participating in the EMBARK study.[4] In this study, patients with non-metastatic hormone-sensitive prostate cancer (nmHSPC) with

high-risk biochemical recurrence who were treated with enzalutamide plus leuprolide acetate or enzalutamide monotherapy experienced increased metastasis-free survival (MFS) compared to those treated with placebo plus leuprolide acetate.[5] No significant differences in time to first and confirmed clinically meaningful deterioration were seen among treatment groups in Functional Assessment of Cancer Therapy-Prostate total score, Brief Pain Inventory Short Form worst pain, or European QoL 5-Dimensions 5-Levels visual analogue scale; however, the median time to clinical decision in the physical well-being subdomain score was significantly shorter for enzalutamide plus leuprolide acetate and for enzalutamide monotherapy compared to placebo plus leuprolide acetate. Moreover, the median time to clinical decision in the prostate cancer subscale score and advanced prostate symptom index was significantly shorter for enzalutamide monotherapy compared to placebo plus leuprolide acetate. In terms of sexual activity, time to clinical decision was significantly longer with enzalutamide monotherapy compared to placebo plus leuprolide acetate. Thus, enzalutamide plus leuprolide acetate or enzalutamide monotherapy improved MFS compared to placebo plus leuprolide acetate without negatively affecting overall health-related QoL in patients with nmHSPC. Understanding the proportion of patients with maintained, worsened, or improved QoL over time is important for providers and patients deciding on treatment.

Prostate cancer remains a leading cause of cancer deaths worldwide, and patients with mCRPC have a poor prognosis.[6] STEAP1 is a cell surface antigen highly expressed in prostate cancer and associated with poor survival.[7] Xaluritamig is a STEAP1-targeted T cell engager being evaluated for the treatment of prostate cancer. In preclinical studies, xaluritamig, which binds to T cells through the CD3 receptor and then to cancer cells through STEAP1, thus facilitating immune system-mediate cancer cell lysis, showed broad anti-cancer effects in prostate cancer xenograft models.[8]

Interim results from a phase 1 study of xaluritamig (AMG-509) in patients with mCRPC were presented.[9] The safety profile during dose exploration was generally manageable. Treatment-emergent adverse events (TEAEs) were reported in all patients (grade ≥3, 74.2%); 95.9% reported treatment-related AEs (TRAEs) (grade ≥3, 52.6%). The most common AEs were cytokine release syndrome (CRS, 72.2%), which was consistent with the mode of action and occurred primarily in cycle 1, was low grade (1 or 2), and manageable. Confirmed prostate-specific antigen (PSA) responses were observed across cohorts. PSA50 response (≥ 50% PSA decline) occurred in 49% of all patients, while cohorts receiving higher doses saw a 59% response. Overall, 24% of patients demonstrated a partial response (PR), while those in high-dose cohorts saw a PR rate of 41%. Preliminary durability is encouraging but immature.

ENZA-P, a randomized, phase 2 trial, evaluated enzalutamide and Lutetium-177-PSMA-617 (^{177}Lu-PSMA-617) vs. enzalutamide alone in poor-risk mCRPC patients in the first-line.[10] Previous studies demonstrated that enzalutamide and lutetium-177-prostate-specific membrane antigen-617 (LuPSMA) improve OS in mCRPC, suggesting synergy between LuPSMA and ARPI. Here, patients with mCRPC not previously treated with chemotherapy or ARPI, and at least two risk factors associated with early progression on enzalutamide, were randomized to either enzalutamide alone or enzalutamide plus adaptive dosing of LuPSMA. At a median followup of 20 months, PSA-PFS was longer with enzalutamide plus LuPSMA vs. enzalutamide alone (median 13 vs. 7.8 months, HR 0.43, p<0.001). PSA50RR and PSA90RR were higher with enzalutamide plus LuPSMA vs. enzalutamide-alone, 93% vs. 68% (p<0.001), and 78% vs. 37% (p<0.001), respectively. These findings demonstrate a greater anti-cancer efficacy for the combination of enzalutamide and LuPSMA in the first-line treatment of mCPRC. The incorporation of adaptive dosing introduces a compelling dimension to precision medicine that needs to be further evaluated.

The VISION study previously demonstrated that targeted radioligand therapy for PSMA-positive mCRPC with ^{177}Lu-PSMA-617 post-chemotherapy improves OS.[11] The PSMAfore, a phase 3 trial, aimed to determine if the same is true in chemotherapy-naive mCRPC patients.[12] Patients who had progressive mCRPC with PSMA-positive metastatic lesions, who progressed once on prior second-generation ARPI, were candidates for change in ARPI, and taxane-naive patients not candi-

> “ MAGNITUDE demonstrated the benefit of early treatment with PARPi/ARPI combo for mCRPC in patients with BRCA mutations. ”

dates for PARPi, were selected. The primary endpoint of rPFS was met (HR 0.41, p<0.0001); median rPFS was 12 months for ^{177}Lu-PSMA-617-treated patients compared to 5.59 months in the ARPI change group. In all the prespecified subgroups, ^{177}Lu-PSMA-617 demonstrated a benefit. Radiographic response rate was high with ^{177}Lu-PSMA-617, including 21% complete response (CR) rate compared to 2.7% in the ARPI change group. PSA response was also greater, with confirmed PSA50 of 57.6% compared to 20.4%. Prespecified crossover-adjusted OS trended favorably (HR 0.8), although the 84.2% crossover rate may have confounded intention-to-treat analysis. OS data collection continues. ^{177}Lu-PSMA-617 had a manageable safety profile and was well-tolerated. Therefore, ^{177}Lu-PSMA-617 is highly active pre-chemotherapy and indication will likely expand into the chemo-naive state.

Advancements in prostate cancer treatment were showcased by MAGNITUDE trial results, with niraparib and abiraterone acetate plus prednisone demonstrating the benefit of early treatment with PARPi in combination with ARPI for mCRPC in patients with *BRCA1/2* mutations. These results further highlight the importance of tumor and germline sequencing to identify HHR alterations. The EMBARK study revealed improved MFS without compromising overall QoL with enzalutamide-based therapies. The ENZA-P and PSMAfore trials collectively support the evolving role of ^{177}Lu-PSMA-617, showcasing its promising effectiveness in both first- and second-line treatment for mCRPC patients.

KIDNEY CANCER

Dr. Christina Canil presented studies focusing on advanced metastatic renal cell carcinoma (RCC) with clear-cell (cc) histology, looking to further build upon the current Canadian treatment landscape.

In the first-line setting, the phase 3 RENOTORCH trial evaluated toripalimab, an anti-PD-1 antibody, combined with axitinib, an antiangiogenic, vs. sunitinib for the treatment of advanced RCC.[13] This trial was conducted exclusively in China and included 421 patients with untreated unresectable or metastatic ccRCC who were intermediate or poor risk per International mRCC Database Consortium (IMDC) criteria. The immune-oncology (IO) plus vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI) combination (toripalimab plus axitinib) arm exhibited a significant improvement in median PFS compared to the sunitinib arm (18.0 vs. 9.8 months, HR 0.65). Additionally, the objective response rate (ORR) was notably higher in the toripalimab plus axitinib group (56.7%) compared to the sunitinib group (30.8%). Median OS was immature but tended to favor the combination group (NE vs. 26.8 months, HR 0.61). These findings support toripalimab plus axitinib as a favorable first-line treatment option for advanced RCC, with a well-tolerated safety profile.

The Tide-A, a phase 2 study, evaluated avelumab, an anti-PD-L1 antibody, plus intermittent axitinib in previously untreated patients with metastatic RCC.[14] This is a de-escalation study looking to determine if axitinib can be discontinued in patients who have tumor response. The trial included 75 patients with measurable ccRCC; all patients were post-nephrectomy and without symptomatic/bulky disease or liver metastases. Patients received avelumab 800 mg and axitinib 5 mg for 36 weeks. Those who achieved PR or CR discontinued axitinib and continued on avelumab alone. Of the 75 patients, 57 (76%) had a tumor response; however, due to various exclusion criteria, only 38.2% (29 patients) discontinued axitinib at 36 weeks and continued on the study. There was a 72.4% PFS rate eight weeks following axitinib interruption. The median duration of first axitinib discontinuation was 16.0 weeks. All grades and grade 3–4 axitinib-related AEs were reported in 34.2% and 11.4% of overall patients, respectively, and dropped to 3.4% and 0% for those who discontinued axitinib. Axitinib discontinuation proved safe, reducing toxicity while maintenance with immunotherapy-delayed tumor progression. Although the TIDE-A study showed that reducing toxicity through the discontinuation of VEGF-TKI treatment is achievable, the impact on tumor toxicity remains uncertain, and alternative de-escalation strategies, such as intermittent breaks or patient selection based on specific biomarkers, should be explored.

In the second-line setting and beyond, there is a lack of robust studies guiding the treatment of patients who have previously received immune checkpoint inhibitors (ICI), as well as those who have received a combination of prior VEGF-TKI and ICI. The LITESPARK studies investigated the efficacy of belzutifan in these challenging patient populations. The HIF pathway is central to the pathophysiology of ccRCC and von Hippel-Lindau (VHL) disease. Belzutifan is a first-in-class oral HIF-2α

> “ Studies show belzutifan is safe and effective in patients with advanced ccRCC after prior IO and anti-angiogenic treatments. ”

inhibitor that has demonstrated clinical activity in pre-treated advanced ccRCC.[15]

LITESPARK-005, a randomized open-label phase 3 study, evaluated belzutifan vs. everolimus in patients with previously treated advanced ccRCC.[16] In ccRCC patients with unresectable locally advanced or metastatic disease that progressed after 1–3 prior systemic therapies (including IO and VEGF-TKI), belzutifan demonstrated a statistically significant improvement in PFS and ORR compared to everolimus. ORR and CR rates were 22.7% and 3.5%, respectively, with belzutifan, compared to 3.5% and 0%, respectively, with everolimus. PFS and ORR benefits were maintained at both the first and second interim analyses, with more patients remaining progression-free at 12 and 18 months with belzutifan. OS difference has not reached statistical significance and final analysis is pending.

The safety profile of belzutifan was consistent with prior reports, with no new safety signals identified. Drug discontinuation was significantly lower, with 5.9% discontinuing belzutifan compared to 14.7% discontinuing everolimus. Patient-reported QoL measures also favored belzutifan. Overall, these findings support the efficacy and safety of belzutifan as a promising therapeutic option for patients with advanced ccRCC following prior immunotherapies and anti-angiogenic treatments.

Updated results from the phase 2 LITESPARK-003 study demonstrated the enduring anti-tumor activity and safety of the combination therapy involving belzutifan and cabozantinib in patients with advanced ccRCC.[17] Cohort 1, consisting of previously untreated patients, exhibited a median duration of response (DOR) of 28.6 months, while cohort 2, comprising of patients with prior immunotherapy exposure, showed a DOR of 31.5 months. ORR in both cohorts was promising, with 70% in cohort 1 and 31% in cohort 2. The safety profile remained consistent with earlier observations, with manageable rates of grade 3–5 TRAE. These findings underscore the potential of combining an HIF-2α inhibitor and VEGFR-TKI as a viable treatment option for advanced ccRCC in both first- and subsequent-line settings.

A target trial emulation using real-world data from the International Metastatic RCC Consortium compared the efficacy of cabozantinib vs. sunitinib as second-line treatments following first-line nivolumab plus ipilimumab.[18] A total of 121 patients received cabozantinib, while 123 received sunitinib after first-line nivolumab plus ipilimumab. Patients on cabozantinib demonstrated a significantly higher ORR (27%) compared to sunitinib (20%), with a median time to treatment failure of 8.5 months for cabozantinib and 4.5 months for sunitinib. The median OS was notably extended with cabozantinib (21.4 months) compared to sunitinib (10.1 months), supporting cabozantinib as a favorable second-line treatment option for mRCC following nivolumab plus ipilimumab in real-world settings.

In the surgical space, one poster assessed the efficacy of cytoreductive nephrectomy (CN) in metastatic ccRCC patients in the era of IO. This analysis involved the national cancer database (U.S.) and identified metastatic ccRCC patients with stage 4 disease who received IO with or without CN. Over 7000 patients were included in the analysis and were divided into three groups: IO alone, IO followed by CN, and CN followed by IO. Patients in the CN groups exhibited significant risk reductions in mortality compared to those receiving IO alone. The study underscores the potential benefits of CN in select metastatic ccRCC patients, providing valuable insights while awaiting further prospective trial outcomes.

Final takeaways from ESMO on kidney cancer: the spotlight was on toripalimab plus axitinib, emerging as a promising first-line IO/VEGF option for mRCC, particularly impactful in the Chinese population, pending confirmation of OS. De-escalating VEGF-TKI in mRCC was acknowledged as a critical concept, yet the optimal patient population and de-escalation strategy require further elucidation. Belzutifan demonstrated activity in heavily pre-treated metastatic RCC patients and holds potential for combination therapy, with ongoing phase 3 studies aimed at defining its optimal indications and partners. Real-world evidence from IMDC, highlighted cabozantinib's improved OS compared to sunitinib post-nivolumab plus ipilimumab. The role of CN in the era of ICIs remains uncertain, awaiting clarification from phase 3 studies.

BLADDER CANCER

Dr. Nimira Alimohamed presented recent advances in bladder cancer.

Metastatic urothelial carcinoma (UC) remains an aggressive disease, with low five-year survival rates. Platinum-based chemotherapy has remained the standard of care in the first-line setting for decades. While the addition of avelumab to chemotherapy in patients with SD/PR/CR has improved survival, first-line combinations of chemotherapy and ICI have yielded negative results to date.

The EV-302 study, a phase 3 randomized trial, assessed the efficacy of enfortumab vedotin (an

> “ EV-302 revealed a promising OS of 31.5 months with the EV/pembrolizumab combo in the first-line for patients with mUC. ”

antibody-drug conjugate against nectin-4) plus pembrolizumab (EV+P) compared to standard platinum-based chemotherapy in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC).[19] Enfortumab vedotin and pembrolizumab have individually demonstrated improvements in survival in pretreated patients with mUC. In this study, in the first-line setting, the combination of EV+P significantly extended median PFS to 12.5 months compared to 6.3 months with chemotherapy (HR 0.45), representing a 55% reduction in the risk of progression or death. At 18 months, 44% of patients in the combination group were progression-free compared to 12% in the chemotherapy arm.

Median OS was also significantly prolonged with EV+P, nearly doubling to 31.5 months compared to 16.1 months with chemotherapy (HR 0.47), reducing the risk of death by 53%. The observed benefits were consistent in the overall population and in all prespecified subgroups and stratification factors. Confirmed ORR was notably higher with the combination at 68% vs. 44% with chemotherapy, with a CR rate of 29% with the combination compared to 12.5% with chemotherapy.

Grade ≥3 TRAEs occurred less frequently with EV+P (56% compared to 70% with chemotherapy), and common AEs were manageable, with no new safety concerns identified. Neuropathy, rash, diarrhea, and decreased appetite were more common with EV+P compared to chemotherapy, while cytopenias were less common. These results support EV+P as a promising new first-line standard of care for la/mUC.

CheckMate 901, a phase 3 study, evaluated the combination of nivolumab, an ICI, plus gemcitabine-cisplatin (GC) vs. GC alone in the first-line for previously untreated unresectable or mUC.[20,21] Previous studies evaluating ICI plus chemotherapy combinations in this setting were negative.

Here, cisplatin-eligible patients were randomized to receive nivolumab in combination with GC chemotherapy vs. GC alone. With a median followup of 33.6 months, the combination of nivolumab plus GC demonstrated improvements in both OS and PFS compared to GC alone. Median OS was 21.7 months with the combination compared to 18.9 months with GC alone (HR 0.78, p=0.017). PFS was 7.9 with the combination vs. 7.6 months with GC alone (HR 0.72, p=0.0012). The ORR was higher in the nivolumab plus GC arm (57.6%) than in the GC arm (43.1%), with a notable CR rate of 21.7% compared to 11.8%. The safety profile was manageable, with no new toxicity signals identified. Importantly, nivolumab plus GC represents the first frontline concurrent ICI plus chemotherapy combination to enhance OS in this context.

These studies unveil promising outcomes, with potential practice-changing implications. The combination of EV+P is likely to become a new standard of care for patients with mUC in the first-line setting. Nevertheless, several questions remain unanswered. There is a need for additional data to define the treatment trajectory following antibody-drug conjugate therapy. Similarly, the optimal treatment plan for patients who progress on adjuvant immunotherapy with nivolumab remains to be elucidated. Questions regarding cost and availability in Canada must also be evaluated.

The phase 3 THOR study evaluated erdafitinib, an oral pan-fibroblast growth factor receptors (FGFR) TKI vs. pembrolizumab in pretreated patients with advanced or mUC with select fibroblast growth factor receptor alterations.[22] Previously reported cohort 1 results demonstrated improved OS with erdafitinib compared to chemotherapy in patients who had received ICI therapy. In cohort 2, erdafitinib, did not demonstrate superiority to pembrolizumab and showed comparable efficacy in anti-PD-(L)1-naive patients. The primary endpoint of OS was not met, with median OS at 10.9 months for erdafitinib and 11.1 months for pembrolizumab. Pembrolizumab exhibited similar outcomes in FGFR-altered mUC patients to those reported for FGFR-unselected populations, and both agents displayed manageable safety profiles consistent with prior knowledge. These findings support the use of ICI therapy in patients with FGFR alterations.

The EV-103 trial investigated perioperative treatment with EV monotherapy in cisplatin (cis)-ineligible patients with muscle-invasive bladder cancer (MIBC); findings from the neoadjuvant treatment portion of cohort L were presented.[23] Patients received three cycles of neoadjuvant monotherapy with EV, underwent surgery, and then received adjuvant EV. Among the 51 treated patients, 34.0% achieved a pathologic CR and 42.0% experienced pathologic downstaging following radical cystectomy and pelvic lymph node dissection. These findings support the ongoing phase 3 trials evaluating EV plus pembrolizumab in MIBC.

Limited treatment options exist for patients with recurrent non-muscle-invasive bladder cancer (NMIBC) following intravesical chemotherapy or bacillus Calmette-Guérin (BCG). TAR-210, a novel intravesical drug delivery system, aims to provide continuous local release of erdafitinib within the bladder while minimizing systemic toxicities.[24] This phase 1 study evaluated the safety, pharmacokinetics, and efficacy of TAR-210 in NMIBC patients with select FGFR alterations. Cohort 1 included BCG-experienced, high-risk NMIBC patients, while cohort 3 involved intermediate-risk NMIBC patients. Results presented included 16 patients in cohort 1 and 27 in cohort 3. In cohort 1, 82% achieved recurrence-free status, and in cohort 3, 87% achieved CR. Common TRAEs were grade 1/2 lower urinary tract issues, with no dose-limiting toxicities or deaths. Pharmacokinetics demonstrated sustained erdafitinib concentrations in urine and minimal plasma exposures.

In the context of BCG-unresponsive high-risk NMIBC patients, the SunRISe-1 study evaluated TAR-200, another intravesical drug delivery system that provides sustained release of gemcitabine.[25] CR rate was 77%, with the median DOR not reached, emphasizing the promising efficacy and favorable tolerability profile of TAR-200 in patients ineligible for or refusing radical cystectomy.

Among the notable findings in bladder cancer at ESMO 2023, the EV-302 study showcased groundbreaking results, revealing an exceptionally promising OS of 31.5 months when employing EV in combination with pembrolizumab for patients with mUC in the first-line setting. This compelling combination is poised to redefine the standard of care, prompting a critical consideration of optimal use and management of associated toxicities.

CONCLUSIONS

ESMO 2023 unveiled groundbreaking findings poised to reshape the landscape of genitourinary cancer treatment. Notably, the MAGNITUDE trial advocates for first-line niraparib as a new standard of care for *BRCA*-mutated mCRPC. The ENZA-P and PSMAfore trials suggest an expanded role for ^{177}Lu-PSMA-617, demonstrating its efficacy in both first- and second-line treatments for mCRPC patients. Additionally, in kidney cancer, toripalimab plus axitinib showcased promising outcomes, while belzutifan emerged as a potential therapeutic option for previously treated ccRCC. In bladder cancer, the groundbreaking combination of enfortumab vedotin plus pembrolizumab revealed in the EV-302 study establishes a new standard of care, with significant improvements in OS, prompting considerations for optimal use and toxicity management. These findings contribute invaluable insights into the evolving treatment paradigms across urologic cancers.

COMPETING INTERESTS: Dr. Chi has received grants/honoraria from Astellas, AstraZeneca, Daiichi Sankyo, Janssen, Merck, Novartis, Pfizer, Point Biopharma, Roche, and Sanofi. Dr. Canil has been on advisory boards for Advanced Accel, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, Kidney Cancer Canada, Merck, Novartis, Pfizer, and Seagen; has received travel educational grants from EMD Serono; and has participated in clinical trials supported by EMD Serono and Pfizer. Dr. Alimohamed has had advisory/consultancy roles with AstraZeneca, Bayer, BMS, EMD Serono, Gilead, Janssen, Merck, Pfizer, and Seagen; and has received research funding (to institution) from EMD Serono. Dr. Soulières has been on advisory boards for Bayer, BMS, Merck, and Novartis; has received grants/honoraria from BMS, Merck, and Pfizer; and has received research funding fro BMS, Merck, Novartis, and Pfizer. Dr. Breau has been on advisory boards for Astellas, Ferring, Knight Therapeutics, Merck, Novartis, TerSera, and Tolmar; and has received research funding from Tolmar.

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