

PSCA-Targeted CAR T-Cell Therapy Demonstrates Safety, Anticancer Activity in mCRPC

RYAN SCOTT

The use of prostate stem cell antigen (PSCA)-targeted CAR T-cell therapy was well tolerated and produced evidence of anticancer effects in patients with metastatic castration-resistant prostate cancer (mCRPC), according to final data from a phase 1 study (NCT03873805) presented at the 2023 ASCO Annual Meeting.

Among 14 evaluable patients, grade 3 cystitis was a dose-limiting toxicity (DLT) experienced by 2 of 6 patients treated with PSCA CAR T cells plus standard lymphodepletion (dose level 2). This prompted the modification of the lymphodepleting chemotherapy regimen, with cyclophosphamide dosed at 300 mg/m² instead of 500 mg/m² on days -5 to -3 for patients treated at dose level 3. No DLTs were reported in 5 patients treated at dose level 3; however, grade 2 cystitis occurred in 1 patient.

No grade 3 or higher cytokine release syndrome was reported. No instances of immune effector cell-associated neurotoxicity syndrome were observed, and no treatment-related deaths occurred.

Regarding efficacy, rates of stable disease were 0% for patients treated with PSCA CAR T cells alone (dose level 1; n = 3), 66% for patients treated at dose level 2 (n = 6), and 60% for those treated at dose level 3 (n = 5). One patient treated at dose level 3 received a second infusion of 1.0 x 10⁸ CAR T cells

with a clinical response and lower-grade toxicity after the second infusion.

Expansion of CAR T cells was enhanced by lymphodepletion and not significantly impaired with modified lymphodepletion

“Expansion of CAR T cells was enhanced by lymphodepletion and not significantly impaired with modified lymphodepletion; persistence through day 28 was similar,” lead study author Tanya B. Dorff, MD, a professor in the Department of Medical Oncology and Therapeutics Research, and section chief of the Genitourinary Disease Program at City of Hope in Duarte, California. “Cytokine expression was also enhanced with lymphodepletion.”

PSCA is highly expressed on the surface membrane of mCRPC cells and has limited expression on healthy tissue. Preclinical studies demonstrated that 4-1BB co-stimulated CAR T cells targeting PSCA gravitated toward bone metastases and eradicated tumors, leading to the first-in-human trial evaluating PSCA-CAR T-cell therapy.

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Post-Hoc Analysis Confirms Safety of Maintenance Avelumab in Urothelial Carcinoma

ASHLING WAHNER

The addition of first-line maintenance avelumab (Bavencio) to best supportive care (BSC) has sustained tolerability in patients with advanced urothelial carcinoma, according to long-term post hoc safety findings from the phase 3 JAVELIN Bladder 100 trial (NCT02603432) that were presented at the 2023 ASCO Annual Meeting.

At a median follow-up of 38.0 months (95% CI, 36.1-40.5), any-grade treatment-related adverse effects (TRAEs) occurred at any time in 78.2% (n = 269) of patients who received avelumab plus BSC (n = 344) and after at least 12 months of avelumab treatment (n = 118) in 50.0% (n = 59) of patients in this population. Grade 3 or greater TRAEs occurred in 19.5% (n = 67) of patients in the avelumab plus BSC arm at any time and in 11.9% (n = 14) of these patients after at least 12 months of avelumab treatment. The median duration of avelumab treatment

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BRCA Mutations Associated with Worse Survival in HRR-deficient mCRPC

JONAH FELDMAN

Patients with homologous recombination (HRR)-deficient mutations and metastatic castration-resistant prostate cancer (mCRPC) who also harbored *BRCA* mutations experienced poorer survival outcomes vs patients without *BRCA* mutations and those with non-*BRCA* HRR mutations, according to an analysis from the CAPTURE trial presented at the 2023 ASCO Annual Meeting.

Findings showed that patients with *BRCA* mutations had significantly worse radiographic progression-free survival (rPFS), time to second objective disease progression (PFS2), and overall survival (OS) than the full non-*BRCA* mutation population and worse PFS2 and OS than those who had other HRR mutations but were *BRCA* wild-type.

“These results further support the importance of screening for germline and

somatic *BRCA1/2* alterations to deliver more precise care for our patients, especially in light of phase 3 trials that suggest poor outcomes for *BRCA* patients, and maybe other HRR [deficiencies], can be averted by adding a PARP inhibitor,” David Olmos, MD, PhD, of Hospital Universitario 12 de Octubre in Madrid, Spain, stated in his oral presentation.

Cohort 1 of the CAPTURE trial, part of the PROCURE

biomarker study platform, combined the populations with mCRPC enrolled in 4 separate trials: PROREPAIR-B (NCT03075735), PROSENZA (NCT02922218), PROSTAC (NCT02362620), and PROSABI (NCT02787837). They were evaluated in a custom next-generation sequencing panel with paired somatic/germline DNA analysis for HRR mutations in *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *HDAC2*, *PALB2*, *RAD51B*, and *RAD54L*. Patients were considered to have HRR deficient status if they had mutations in at least 1 allele of at least 1 gene.

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Post-Hoc Analysis Confirms Safety of Maintenance Avelumab in Urothelial Carcinoma (from page 1)

was 5.8 months (range, 0.5-49.7), and the median number of infusions was 11.5 (range, 1.0-106.0).¹

“Post hoc analyses of JAVELIN Bladder 100 confirm the tolerable and manageable long-term safety profile of avelumab first-line maintenance,” lead study author, Joaquim Bellmunt, MD, PhD, of Dana-Farber Cancer Institute in Boston, Massachusetts, said in a presentation on the data.

JAVELIN Bladder 100 enrolled patients with unresectable locally advanced or metastatic urothelial carcinoma who had achieved a complete response, partial response, or stable disease with 4 to 6 cycles of standard gemcitabine with either cisplatin or carboplatin.

A total of 700 patients were randomly assigned 1:1 to receive either avelumab plus BSC (n = 350) or BSC alone (n = 350) until disease progression, unacceptable toxicity, or patient withdrawal. Patients were stratified by best response to first-line chemotherapy and site of metastatic disease when initiating first-line chemotherapy.

The primary end point of this trial was overall survival (OS), with key secondary end points of progression-free survival (PFS) per RECIST v1.1 and safety. The primary analysis

populations included all randomly assigned patients and the patients with PD-L1-positive disease.

Previously reported findings from JAVELIN Bladder 100 showed that at a median follow-up of at least 38 months, avelumab maintenance elicited a significantly longer median OS compared with BSC alone, at 23.8 months (95% CI, 19.9-28.8) vs 15.0 months (95% CI, 13.5-18.2) in patients who did not progress after first-line platinum-based chemotherapy (HR, 0.76; 95% CI, 0.631-0.915; *P* = .0036). The 30-month OS rates were 43.7% (95% CI, 38.2%-49.0%) and 33.5% (95% CI, 28.4%-38.7%) in the avelumab and BSC alone arms, respectively. In addition, the median PFS was 5.5 months (95% CI, 4.2-7.2) with avelumab vs 2.1 months (95% CI, 1.9-3.0) in the BSC alone arm (HR, 0.54; 95% CI, 0.457-0.645; *P* < .0001), and the 30-month PFS rates were 19.3% (15.0%-24.0%) and 6.3% (95% CI, 3.8%-9.5%), respectively.²

Furthermore, the safety profile of first-line avelumab maintenance therapy was consistent with that seen in prior studies with avelumab monotherapy, and the investigators identified no new safety signals with the agent. In primary findings from JAVELIN Bladder 100, any-grade adverse effects (AEs)

were observed in 98.0% of patients in the avelumab group and 77.7% of patients in the BSC alone group. Additionally, grade 3 or higher AEs occurred in 47.4% and 25.2% of patients in the avelumab and BSC alone arms, respectively.³

At the 2023 ASCO Annual Meeting, investigators reported findings from long-term safety analyses of JAVELIN Bladder 100 that were conducted in all patients who received avelumab plus BSC, as well as in a subgroup of patients who were treated for at least 12 months.¹

In these analyses, the most common grade 3 or higher TRAEs that occurred at any time were increased lipase (3.5%) and increased amylase (2.3%). The most common grade 3 or higher TRAE that occurred after at least 12 months of avelumab treatment was increased lipase (1.7%).

A total of 11.6% (n = 40) of patients experienced TRAEs leading to avelumab discontinuation, the most common being infusion-related reaction (1.2%) at any time and interstitial lung disease (1.7%) after at least 12 months of avelumab treatment.

Any-grade immune-related AEs occurred in 32.3% (n = 111) of patients at any time, the most common being thyroid disorders

Further Research Needed to Inform the Management of Post-Chemo Residual Nonretroperitoneal Disease in Testicular Cancer

COURTNEY FLAHERTY

Teratoma in the primary tumor site was associated with a higher incidence of teratoma in residual nonretroperitoneal (non-RP) disease post-chemotherapy, according to findings from a retrospective study. However, this feature could not be used to conclusively identify patients with nonseminomatous germ cell tumors who could forgo surgical resection. Accordingly, more research is needed to inform recommendations for surveillance and resection in this patient subset, according to Jennifer M. King, MD.

A retrospective review of 129 patients with non-RP residual disease post-chemotherapy identified 75 patients who had teratoma in the primary tumor site. Of these patients, 41 (55%) had

teratoma, 23 (31%) had non-teratoma active germ cell tumor, and 21 (28%) had necrosis in the resected tumor. Regarding patients without teratoma in the primary tumor, 9 (17%) had at least one non-teratomatous element, 30 (56%) had non-teratoma active germ cell tumor, and 20 (37%) had necrosis in the resected non-RP specimens.

Investigators found that the presence of teratoma in the primary tumor may be predictive of teratomatous elements in postchemotherapy residual non-RP disease for patients who do not undergo retroperitoneal lymph node dissection. However, both groups of patients had comparable rates of teratoma or active germ cell tumor in residual non-RP disease.

“The most important thing is that we didn’t find any clear criteria to recommend surveillance or observation of residual non-RP disease,” said King, who is an assistant professor of clinical medicine in the Department of Medicine, Division of Hematology/Oncology, at Indiana University (IU) School of Medicine in Indianapolis and a physician-scientist at the IU Melvin and Bren Simon Comprehensive Cancer Center. “... [Therefore,] the absence of teratoma in the primary should not preclude surgical resection of this disease.”

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(12.8%), immune-related rash (10.8%), immune-related nephritis/renal dysfunction (2.3%), immune-related pneumonitis (2.0%), immune-related colitis (1.7%), immune-related hepatitis (1.5%), type 1 diabetes (1.2%), and other immune-related AEs (2.9%).

Any-grade immune-related AEs occurred in 22.9% (n = 27) of patients after at least 12 months of avelumab treatment, the most common being immune-related rash (10.2%), immune-related nephritis/renal dysfunction (3.4%), thyroid disorders (1.7%), immune-related pneumonitis (1.7%), immune-related colitis (1.7%), type 1 diabetes (0.8%), and other immune-related AEs (3.4%).

Grade 3 or higher immune-related AEs occurred in 7.6% (n = 26) and 4.2% (n = 5) of patients at any time and after at least 12 months of avelumab treatment, respectively. The most common grade 3 or higher immune-related AEs that occurred at any time were immune-related rash (1.5%), immune-related hepatitis (1.5%), immune-related colitis (0.9%), type 1 diabetes (0.9%), immune-related nephritis/renal dysfunction (0.6%), immune-related pneumonitis (0.3%), thyroid disorders (0.3%), and other immune-related AEs (0.3%). No category of grade 3 or higher immune-related AE

occurred in more than 1 patient after at least 12 months of avelumab treatment. Immune-related rash, immune-related nephritis/renal dysfunction, immune-related colitis, and type 1 diabetes occurred in 1 patient each.

Immune-related AEs that occurred at any time led to avelumab discontinuation in 6.1% (n = 21) of patients, the most common being immune-related hepatitis (1.2%) and immune-related nephritis/renal dysfunction (1.2%). Immune-related AEs that occurred after at least 12 months of avelumab treatment led to avelumab discontinuation in 4.2% (n = 5) of patients, the most common being immune-related pneumonitis (1.7%) and immune-related nephritis/renal dysfunction (1.7%), from which 1 patient died.

In all patients who received avelumab, 1, 2, 3, and at least 4 immune-related AEs occurred in 17.7%, 8.7%, 3.2%, and 2.6%, respectively. In the patients who had received at least 12 months of avelumab treatment, 1, 2, 3, and at least 4 immune-related AEs occurred in 15.3%, 3.4%, 2.5%, and 1.7%, respectively.

“These results further support the use of avelumab first-line maintenance until disease progression as standard of care for patients with advanced urothelial carcinoma that have

not progressed with first-line platinum-based chemotherapy,” Bellmunt concluded. ■

Disclosures: Dr Bellmunt reports stock and other ownership interests with Rainier Therapeutics; honoraria from UpToDate; consulting or advisory roles with Astellas Pharma, AstraZeneca/MedImmune, Bristol-Myers Squibb, Genentech, Merck, Novartis, Pfizer, Pierre Fabre; research funding from Millennium (Inst), Pfizer/EMD Serono (Inst), and Sanofi (Inst); patents, royalties, or other intellectual property from UpToDate Bladder Cancer; and travel, accommodations, or expenses from Ipsen, MSD Oncology, and Pfizer.

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PSCA-Targeted CAR T-Cell Therapy Demonstrates Safety, Anticancer Activity in mCRPC (from page 1)

The study enrolled adult patients with mCRPC experienced disease progression following a minimum of 1 prior androgen receptor-targeted therapy. Notably, prior taxane chemotherapy was allowed but not required, and there was no limit to the number of prior lines of therapy.

Patients in cohort 1 received 1.0×10^8 PSCA-CAR T cells without lymphodepletion; those in cohort 2 were dosed with 1.0×10^8 PSCA-CAR T cells after lymphodepletion consisting of 500 mg/m² of cyclophosphamide plus 30 mg/m² of fludarabine on days -5 to -3; and patients in cohort 3 were administered 1.0×10^8 CAR T cells after modified lymphodepletion with 300 mg/m² of cyclophosphamide plus 30 mg/m² of fludarabine on days -5 to -3.

Moreover, PSCA tissue staining by immunohistochemistry (IHC) was performed prior to lymphodepletion, then again on day 28 post-CAR T-cell therapy.

DLTs and safety served as the trial's primary end points. Secondary end points included the persistence of CAR T cells through day 28 and disease response.

In cohort 1, the median age was 62 years (range, 59-69), and all 3 patients were treated with both prior enzalutamide (Xtandi) and abiraterone acetate (Zytiga). Two patients were treated with both docetaxel and cabazitaxel. The median prostate-specific antigen (PSA) level was 16.5 (range, 10.7-20.4). Two patients had only lymph node metastases, no patients had bone metastases, and 1 patient had visceral metastases.

In cohort 2, the median age was 70 years (range, 42-73). Five patients received previous treatment with enzalutamide, 6 received previous abiraterone, and 5 received both. Moreover, 5, 3, and 3 patients received previous treatment with docetaxel, cabazitaxel, or both, respectively. The median PSA level was 88.0 (range, 11.7-590.2). One patient had only lymph node metastases, 4 had bone metastases with or without lymph node involvement, and 1 had visceral metastases.

In cohort 3, the median age was 69 (range, 62-72). Two patients had prior

treatment with enzalutamide, 2 had prior abiraterone, and 1 patient received prior treatment with both. Additionally, 5, 3, and 3 patients received previous treatment with docetaxel, cabazitaxel, or both, respectively. The median PSA was 235.3 (range, 1.79-3260). No patients had only lymph node metastases, 4 patients had bone metastases with or without lymph node involvement, and 1 had visceral metastases.

Regarding PSCA expression, 36% of patients at screening had an IHC of 3+ and 60% to 100% of cells; 43% of patients had an IHC of 2+ and 80% to 100% of cells; 14% of patients had an IHC of 2+ and 50% to 60% of cells; and 7% of patients had an IHC of 1+ and 20% to 30% of cells.

At baseline, 43% of patients had an IHC of 3+ and 60% to 100% of cells; 7% had an IHC of 2+ and 80% to 100% of cells, 7% of patients had an IHC of 1+ and 20% to 30% of cells, and 43% of patients had no sample. Post-CAR T-cell therapy, all 7 evaluable patients with samples had a PSCA IHC of 3+ and 60% to 100% of cells, and the other 7 patients had no sample.

At day 28, the persistence of CAR T cells was 66%, 66%, and 60% for dose levels 1, 2, and 3, respectively.

Additional safety data showed that at dose level 1, 2 patients experienced grade 3 anemia and 1 patient had grade 3 decreased lymphocytes. At dose level 2, 2 patients experienced grade 3 anemia, 2 had grade 3 fatigue, 1 had grade 3 pain, 1 had grade 3 hematuria, and 1 experienced grade 3 rash. At dose level 3, 1 patient experienced grade 3 decreased lymphocytes.

"Given evidence of anticancer effect, and based on clinical plus preclinical toxicity data, a phase 1b trial [NCT05805371] has opened, testing multiple doses of PSCA-CAR T cells to achieve higher total dose," Dorff and colleagues concluded. ■

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CG0070 Plus Pembrolizumab Produces Durable Responses in BCG-Unresponsive NMIBC

HANNAH CLARKE

The cancer-selective oncolytic adenovirus crenostimogene grenadenorepvec (CG0070) plus pembrolizumab (Keytruda) elicited synergistic activity leading to durable responses and could provide an effective treatment alternative for patients with *Bacillus Calmette-Guérin* (BCG)-unresponsive, carcinoma in situ (CIS)-containing non-muscle invasive bladder cancer (NMIBC) who cannot undergo radical cystectomy, according to Roger Li, MD.

The phase 2, single-arm CORE-001 trial (NCT04387461) evaluated CG0070 and pembrolizumab in this population. Updated results presented at the **2023 American Urological Association (AUA) Annual Meeting** showed that the combination elicited an overall complete response (CR) rate of 85% (n=29/34). By the 12-month time point, the CR rate was maintained in 68% (n = 17/25) of patients with available response data.¹ In comparison, the 12-month CR rate with CG0070 monotherapy was 28% (n = 13/46) in the phase 2 BOND-002 trial (NCT02365818).²

The regimen's adverse effect (AE) profile was generally consistent with prior studies of each agent alone. Moreover, there was no clear evidence of synergistic toxicity.¹

These results support ongoing and future studies of CG0070 in non-muscle and muscle-invasive bladder cancer, including the single-arm phase 3 BOND-003 trial (NCT04452591) of CG0070 monotherapy, the phase 1/2 CORE-002 trial (NCT04610671) of CG0070 plus nivolumab (Opdivo), and the planned phase 3 PIVOT-001 trial of CG0070 plus immune checkpoint inhibitors.

"We're excited to launch that trial soon, show the synergistic efficacy from the combination, and hopefully be able to

bring this combination to patients soon,” Li said, regarding the planned phase 3 trial for CG0070 plus pembrolizumab.

In an interview with *OncLive*[®], Li, who is a genitourinary oncologist at Moffitt Cancer Center in Tampa, Florida, discussed how the synergistic mechanism of pembrolizumab plus CG0070 could address unmet needs in BCG-unresponsive NMIBC, safety and efficacy data for the combination from CORE-001, and how those data support planned research efforts for CG0070 in NMIBC.

OncLive: Could you discuss the rationale for investigating CG0070 plus pembrolizumab in patients with BCG-unresponsive NMIBC?

Li: In the BCG-unresponsive setting, there are very limited therapeutic options. The standard of care remains radical cystectomy. Unfortunately, a lot of patients that are elderly and frail are unable to undergo that procedure. Hence the [need] for more efficacious treatment options that will enable patients to preserve their bladder. In the past, CG0070 has demonstrated efficacy in this setting as did pembrolizumab. We hypothesized that there could be a synergistic mechanism between the 2 agents and launched this study to see whether that holds true.

Please describe the mechanism of action of CG0070. What made this agent a good candidate to evaluate in combination with pembrolizumab?

CG0070 is a cancer-selective oncolytic adenovirus that attaches to cancer cells specifically through its mechanism of action of having a human E2F promoter. [CG0070] only acts on the cancer cells that are defective in the retinoblastoma protein [Rb] pathway, which will increase the expression level of the E2F protein. In these cancer cells, the virus replicates and [causes] cell lysis. In doing that, [CG0070] also releases the cancer-specific neoantigens in the tumor microenvironment to attract the immune cells for an immunogenic attack. The reason to combine [CG0070] with pembrolizumab is that pembrolizumab has demonstrated efficacy in the BCG-unresponsive setting. It also reinvigorates lymphocytes that may become exhausted over time. The oncolytic virus and pembrolizumab creates a one-two punch to eliminate the cancer.

What updated findings from this study were presented at the 2023 AUA Meeting?

We reported the most up-to-date efficacy and safety data from the trial. All the patients have been accrued to the trial. [We enrolled a] total of 35 patients with BCG-unresponsive, CIS-containing NMIBC. We followed 25 patients out to the 12-month mark, which is the primary end point of the study, to assess for the CR rate as assessed by random bladder biopsies, cystoscopy, and urine cytology. Of these 25 patients, 68% achieved a durable CR at the 1-year time-frame. In addition, the toxicity of the combination does not seem to be synergistic at all. [There is] some added toxicity from both the intravesical treatment as well as pembrolizumab, but [there were] no surprises in that regard. Although there were a few cases of immune-related AEs those tended to be very transient and [were] eliminated after the patients came off therapy.

Why is the durability of the CR rate seen with this regimen notable?

In the past, pembrolizumab as well as nadofaragene firadenovec-vncg [Adstiladrin] have been approved for the BCG-unresponsive CIS-containing cohort. However, the CR rates for those therapies at 1 year range between 20% and 25%. Most patients [who receive these therapies] have recurrence and will require additional therapy for that. The durable response that we’re seeing in this combination trial is very encouraging and points to the fact that we can help patients keep their bladder for 1 year longer.

Are any next steps planned for this research?

We’re continuing to follow these patients beyond the primary end point of this study, [up] to 2, 3 and even 4 years after the first 2 years on trial at 6-month intervals to see what the long-term response rate is in this patient population.

In addition to the follow-up that we are planning for patients enrolled onto this trial, we’re also actively launching a randomized control trial comparing the combination of CG0070 and pembrolizumab vs pembrolizumab alone in this patient population.

What other studies were you looking forward to seeing presented at this year’s meeting?

There were a couple of different trials in the BCG-unresponsive setting that reported out [at the 2023 AUA Annual Meeting]. We know that cohort A of the [phase 2] KEYNOTE-057 trial [NCT02625961] has

The durable response that we’re seeing in this combination trial is very encouraging and points to the fact that we can help patients keep their bladder for 1 year longer.

been reported out in the past. [In terms of] efficacy, the 1-year response rate was around 20%. I [was] interested in learning about cohort B, which included patients with papillary-only BCG-unresponsive [disease] and seeing the efficacy of pembrolizumab in that setting. The [investigators] also reported some of the data from cystectomy specimens obtained from those patients after coming off trial because of disease recurrence.

An additional study that I looked forward to hearing the results from [was] the [phase 2b] SunRISe-1 trial [NCT04640623], which tested the combination of TAR-200 and cetrelimab [JNJ-63723283] in the BCG-unresponsive setting, along with a few other arms testing the efficacy of TAR-200 monotherapy as well as cetrelimab by itself. ■

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Lutetium Lu 177 Vipivotide Tetraxetan Provides HRQOL Benefit, Reduces Skeletal Events in mCRPC

KYLE DOHERTY

The addition of lutetium Lu 177 vipivotide tetraxetan (Pluvicto; formerly 177Lu-PSMA-617) to standard-of-care treatment delayed time to worsening of health-related quality of life (HRQOL) and skeletal events compared with standard of care alone for patients with metastatic castration-resistant prostate cancer (mCRPC), according to findings from the phase 3 VISION trial (NCT03511664) published in *Lancet Oncology*.¹

At the October 23, 2019, data cutoff patients who received lutetium Lu 177 vipivotide tetraxetan plus standard of care (n = 385) experienced a median time to first skeletal event or death was 11.5 months (95% CI, 10.3-13.2) compared with 6.8 months (95% CI, 5.2-8.5) in the standard-of-care group (n = 196; HR, 0.50; 95% CI, 0.40-0.62). Moreover, time to worsening by FACT-P (HR, 0.54; 95% CI, 0.45-0.66; $P < .001$), BPI-SF pain intensity score (HR, 0.52; 95% CI, 0.42-0.63; $P < .001$), and EQ-5D-5L utility score (HR, 0.65; 95% CI, 0.54-0.78; $P < .001$) all favored the combination arm vs standard of care.¹

Lutetium Lu 177 vipivotide tetraxetan is a prostate specific membrane antigen (PSMA)-directed radioligand therapy that possess high tumor-to-tissue uptake. Previously published data from VISION showed that the agent plus standard of care offered a benefit vs standard of care alone in terms of median overall survival (OS; HR, 0.62; 95% CI, 0.52-0.74; 1-sided $P < .001$) and radiographic progression-free survival (rPFS; HR, 0.40; 99.2% CI, 0.29-0.57; 1-sided $P < .001$) among patients with advanced PSMA-positive mCRPC.² Additional post-hoc survival and prostate-specific antigen level outcomes were reported at the 2022 ESMO Congress.³

The open-label, multicenter VISION trial is the first phase 3 study of lutetium Lu 177

vipivotide tetraxetan, enrolling adult patients with progressive mCRPC with an ECOG performance status of 2 or less. Eligible patients also needed to have a life expectancy of at least 6 months, had undergone treatment with 1 androgen receptor inhibitor and 1 or 2 taxane-containing regimens, and had adequate, hepatic, renal, and bone marrow function. Patients who were candidates for additional chemotherapy at the time of screening and those who required treatments not permitted under the study protocol were excluded.¹

Patients were randomly assigned 2:1 to receive lutetium Lu 177 vipivotide tetraxetan plus standard of care or standard of care alone. Lutetium Lu 177 vipivotide tetraxetan was administered every 6 weeks for 4 cycles plus 2 optional additional cycles for patients who tolerated the agent and displayed evidence of response. A dose of lutetium Lu 177 vipivotide tetraxetan could be reduced or delayed for a maximum of 4 weeks. Standard of care therapies were selected by the investigator and included approved hormonal agents, bisphosphonates, and radiotherapy.

Patients were stratified by baseline lactate dehydrogenase concentration (≤ 260 IU/L vs > 260 IU/L), presence of liver metastases (yes vs no), ECOG performance status (0 to 1 vs 2), and if an androgen receptor inhibitor was included in standard of care (yes vs no). The coprimary end points were OS and rPFS. Key secondary end points included time to first symptomatic skeletal event, overall response rate, and disease control rate. Additional secondary end points included safety, HRQOL and pain outcomes, and PFS.

The median age was 71 years (range, 65-75) in the investigational arm vs 72 years (range, 66-76) in the control arm. Most patients in both arms were White (87% vs

BRCA Mutations Associated with Worse Survival in HRR-deficient mCRPC (continue from page 2)

The patients either received novel hormonal therapy (60.4%) or a taxane (39.6%) as first-line mCRPC treatment, including docetaxel (Taxotere), cabazitaxel (Jevtana), abiraterone acetate (Zytiga), and enzalutamide (Xtandi). Over 80% went on to receive second-line treatment after progression.

A total of 729 patients on the trials volunteered to undergo genomic analysis, and were hierarchically classified as *BRCA1/2*, HRR non-*BRCA*, and non-HRR. They were also classified by germline, somatic, or none, and biallelic, monoallelic, or none. Of the patients, 223 (30.6%) had HRR mutations, 96 (13.2%) of whom had *BRCA* mutations, and 127 (17.4%) of whom had HRR non-*BRCA* mutations. Twenty-five (3.4%) had germline *BRCA* mutations and 71 (9.8%) had somatic *BRCA* mutations. Of the HRR non-*BRCA* mutations, the most common were *ATM* in 64 patients (8.8%) and *FANCA* in 38 patients (5.2%).

Investigators did not see an association between the choice of first-line treatment and the *BRCA*/HRR status, but Olmos said they noted a difference in second-line treatment, with more than 90% receiving additional therapy compared with less than 80% for other subgroups.

Outcome analyses comparing *BRCA1/2* patients with other groups used a propensity score weighted Kaplan-Meier curves and adjusted hazard ratios (HR) and p-values by inverse probability weighted Cox models. The *BRCA1/2* subgroup had a median rPFS of 7.1 months (95% CI, 6.4-8.6) vs 10.3 months (95% CI, 9.6-11.5) for all non-*BRCA*-mutated patients (HR, 1.70; 95% CI, 1.32-2.19; $P < .0001$), suggesting outcomes were worse for *BRCA* patients. Data for rPFS were missing for 2 patients in this analysis. The median PFS2 for *BRCA1/2* group was 12.6 months (95% CI, 11.3-13.9) vs 15.9 months (95% CI, 15.1-16.8) for the non-*BRCA* group (HR, 1.81; 95% CI, 1.44-2.27; $P < .0001$). The median OS for the *BRCA1/2* group was 19.4 months (95% CI, 16.8-21.1) vs 27.9 months (95% CI, 25.8-29.6) for the non-*BRCA* group (HR, 1.95; 95% CI, 1.55-2.45; $P < .0001$).

When compared with the HRR non-*BRCA* group, median rPFS for *BRCA1/2* was 7.1

months (95% CI, 6.2-8.5) vs 9.0 months (95% CI, 7.1-10.8) for HRR non-*BRCA* patients (HR, 1.34; 95% CI, 0.98-1.81; $P = 0.0641$), not reaching statistical significance. The median PFS2 for the *BRCA1/2* group was 12.3 months (95% CI, 11.1-13.5) vs 13.6 (95% CI, 11.9-15.9) for the HRR non-*BRCA* group (HR, 1.42; 95% CI, 1.07-1.88; $P = .0143$). The median OS for the *BRCA1/2* group was 18.4 months (95% CI, 16.7-20.3) vs 21.9 months (95% CI, 18.3-24.4) for the HRR non-*BRCA* group (HR, 1.40; 95% CI, 1.06-1.84; $P = .0166$).

“We may conclude that *BRCA* patients have significant worse outcomes than patients with mutations in HRR non-*BRCA*, and those with alterations in HRR non-*BRCA* genes have worse outcomes than non-mutated patients,” said Olmos.

An exploratory analysis within the *BRCA1/2* cohort was performed to evaluate differences in response to novel hormonal therapy versus taxane, germline versus somatic mutation, biallelic versus monoallelic, and *BRCA1* versus *BRCA2*. These analyses were largely not statistically significant due to the small sample sizes, but no difference was seen based on choice of first-line treatment or number of mutated alleles. Patients with germline mutations appeared to have shorter median rPFS but longer median OS. There was also a consistent trend showing longer rPFS, PFS2, and OS for *BRCA1* versus *BRCA2*.

“Our study demonstrated that both germline and somatic *BRCA1/2* alterations are associated with shorter rPFS, PFS2, and OS independent of the initial treatment of choice. [Patients with] *BRCA1/2* [mutations] had worse outcomes than patients [in the] HRR non-*BRCA* subgroup, although we need to better understand the particular contribution of certain HRR genes that might also help prognosis,” concluded Olmos. ■

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Olmos D, Lorente D, Alameda D, et al. Presence of somatic/germline homologous recombination repair (HRR) mutations and outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) receiving first-line (1L) treatment stratified by *BRCA* status. *J Clin Oncol*. 2023;41(suppl):5003. doi: 10.1200/JCO.2023.41.16_suppl.5003.

85%) and the study dropout rates were 64% vs 78%, respectively.

Patients in the lutetium Lu 177 vipivotide tetraxetan and the standard-of-care arms completed the end-of-treatment FACT-P (49% vs 45%), BPI-SF (50% vs 46%), and EQ-5D-5L (50% vs 45%) questionnaires at similar rates.

Additional findings from the trial showed that most patients in both the investigational and control arms experienced a symptomatic skeletal event or death, at rates of 66% vs 70%, respectively. Symptomatic skeletal events (16% vs 17%) included radiation to relieve bone pain (11% vs 11%), symptomatic pathological bone fracture (3% vs 1%), spinal cord compression (1% vs 6%), and tumor-related orthopedic surgical intervention (< 1% vs 1%). The median follow-up times were 17.0 months (range 15.9-17.3) and 16.9 months (range, 11.5-not estimable [NE]), respectively, and the median time to events were 11.5 (range, 10.3-13.2) and 6.8 (range, 5.2-8.5). Patients experienced a benefit in terms of skeletal events with the addition of lutetium Lu 177 vipivotide tetraxetan to standard of care whether they received a bone-targeted agents (HR, 0.49; 95% CI, 0.36-0.68) or not (HR, 0.50; 95% CI, 0.37-0.68).

In the post-hoc analyses, FACT-P total score (HR, 0.46; 95% CI, 0.35-0.61), BPI-SF pain intensity (HR, 0.45; 95% CI, 0.33-0.60), and EQ-5D-5L utility score (HR, 0.49; 95% CI, 0.40-0.62) all favored the investigational arm. In the investigational and control arms, respectively, the median follow-up time for FACT-P score was 4.4 months (range, 1.02-8.80) vs 0.76 months (range, 0.15-2.71). The median time to follow-up for BPI-SF pain intensity scale was 4.14 months (range, 1.64-8.77) vs 0.66 months (range, 0.20-2.56), respectively.

In terms of safety, the median follow-up was 14.78 months (range, 9.10-19.35) and 10.64 months (range, 5.09-17.22) in the investigational ($n = 529$) and control ($n = 205$) arms, respectively. The most common any-grade adverse effects (AEs) included fatigue (43% vs 23%), dry mouth (39% vs < 1%), nausea (35% vs 17%), anemia (32% vs 13%), back pain (23% vs 15%), arthralgia

(22% vs 13%), and decreased appetite (21% vs 15%). Grade 3 or 4 hematologic AEs consisted of decreased hemoglobin (15% vs 6%), decreased lymphocyte counts (51% vs 19%) and decreased platelet counts (9% vs 2%). Treatment-related AEs leading to death were reported in no patients in the control arm and 5% of patients in the investigational arm. Events leading to death included pancytopenia ($n = 2$), bone marrow failure ($n = 1$), subdural hematoma ($n = 1$), and intracranial hemorrhage ($n = 1$).

Study authors concluded: “Treatment with lutetium Lu 177 vipivotide tetraxetan plus standard of care delayed rPFS and extended OS in patients with mCRPC and was associated with a longer period without deterioration in patient-reported HRQOL and pain than seen with standard of care alone. Low rates of hematological and renal toxicity were observed with lutetium Lu 177 vipivotide tetraxetan. These findings strengthen the rationale for use of lutetium Lu 177 vipivotide tetraxetan as a treatment option in patients with mCRPC who received previous androgen receptor pathway inhibitor and taxane treatment.” ■

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Further Research Needed to Inform the Management of Post-Chemo Residual Nonretroperitoneal Disease in Testicular Cancer (continue from page 2)

In an interview with *OncoLive*[®], King expanded on the design and methodology of this retrospective review, shared key findings regarding the correlation between teratoma in the primary tumor and rates of post-chemotherapy teratoma in residual non-RP disease, and emphasized the need for more data to inform management decisions in residual non-RP testicular cancer.

OncoLive: What was the rationale for investigating factors that may guide the management of residual non-RP disease in post-chemotherapy nonseminomatous germ-cell tumors?

King: Testicular cancer is a great success story. Most patients are cured with first-line chemotherapy, but there [are some] patients who have residual disease after chemotherapy. Most of the time those patients have RP residual disease in addition to non-RP disease, but there is a subset of patients who have only residual non-RP disease without any residual RP disease. There's limited data on how to guide the management of those patients and identify who truly needs resection so that we can try to minimize the treatment burden for these patients as much as possible.

Please describe the design and key objectives of this study.

This was a retrospective review using our Indiana University testicular cancer database. Previous work has demonstrated an association between having teratoma in the primary [tumor site] and having teratoma in the residual RP disease. Our main objective with this study was to determine if the presence of teratoma in the primary orchiectomy was associated with a higher rate of teratoma in post-chemotherapy residual non-RP disease.

Could you expand on the patient population that was included in the study? Were there any notable baseline characteristics?

Patients with metastatic non-seminoma, who had residual non-RP disease in the absence of any residual RP disease were

included. [These patients had residual non-RP disease] either post first-line chemotherapy or post salvage chemotherapy. Some patients were included who did have RP metastasis at the time of diagnosis, but their RP disease normalized after chemotherapy. Over half of patients who were included were International Germ Cell Cancer Collaborative Group [IGCCCG] intermediate or high risk, and the majority of the non-RP resection sites were lung resections. About 65% of patients had a lung resection. Other [resection sites] included [the] liver and bone, as well as cervical and mediastinal lymph nodes.

What did this study reveal about the prevalence of teratoma and active germ cell tumor in patients with residual non-RP disease alone following chemotherapy?

Of the patients who had teratoma in their primary orchiectomy site, 55% had at least 1 post-chemotherapy non-RP resection with teratoma. In those who did not have teratoma in the primary, that percentage was only 17%. That was statistically significant. In those who did not have teratoma in the primary [tumor site], 56% had active germ cell tumor in the residual non-RP disease. That was compared [with] 31% of patients who had teratoma in the primary [orchiectomy site] and was also statistically significant.

We [also] found that teratoma in the primary site was associated with a higher rate of teratoma in non-RP residual disease.

What did findings indicate about the need for surgical resection in patients without teratoma in the primary tumor?

What's important [to note] with these data is [that] we couldn't find clear criteria to recommend observation for these patients [over resection]. Patients who had teratoma in the primary [did] have a higher rate of teratoma in the residual non-RP disease. [However], there were pretty high rates of active germ cell tumor in patients who did not have teratoma in the primary.

We tried to identify other factors like tumor markers or either first-line chemotherapy vs salvage chemotherapy, [but] we

still could not find a correlation between these other factors and the presence of either active germ cell tumor or teratoma.

Were any results from this study particularly surprising?

Interestingly, we found higher rates of active germ cell tumor in the residual non-RP disease for all sites when we compare that to the 10% to 15% chance of having active germ cell tumor in RP residual disease. We're not entirely clear why that is, but we postulate that it has something to do with differences in the biology for hematogenous metastasis compared with lymphatic metastasis, like you would see with RP disease.

What limitations from this study are important to note?

This was a retrospective study, so selection bias was a limitation. [However,] one benefit of our testicular cancer database is that it is prospectively maintained, so we included consecutive patients who are seen at our institution.

What next steps are planned for this research?

Our next step would be looking at outcomes for this patient population. Previous work has found no impact on survival for patients who have teratoma either in the primary site or in residual RP disease. We are looking to evaluate [this impact on] outcomes for this subset of patients who have residual non-RP disease.

What ongoing or future research in the field of genitourinary cancer are you most excited about?

Moving forward, there's a lot of exciting research into microRNA and circulating tumor DNA. This is an area that may help to further delineate patients who truly need to undergo surgical resection vs those who could be safely followed with surveillance. ■

REFERENCE

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