Phase II study of pembrolizumab (pembro) plus enzalutamide for enzalutamide-resistant metastatic castration-resistant prostate cancer (mCRPC): Cohorts C(4) and 5 update from KEYNOTE-199


1Internal Medicine, Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; 2Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; 3Oncology and Hematology, Kantopinspital St. Gallen, St. Gallen, Switzerland; 4Medical Oncology, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; 5Medicine/Hematology and Oncology, Duke Cancer Center, Cleveland, OH, USA; 6Medical Oncology, VIVO, Weill Cornell Medical College, New York, NY, USA; 7Medical Oncology, Henry Ford Health System, Detroit, MI, USA; 8Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; 9Medical Oncology, Erasmus MC, Rotterdam, Netherlands; 10Hematology/Oncology, Tallaght University Hospital, Dublin, Ireland; 11Medical Oncology, Radboud Medical Center, Nijmegen, Netherlands; 12Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA; 13Experimental Cancer Medicine, The Royal Marsden NHS Foundation Trust, London, UK; 14Oncofertility, Johns Hopkins University, Baltimore, MD, USA

Background: Chemotherapy-naive patients (pts) with mCRPC who had disease progression with enzalutamide enrolled in C4 and C5 of the multicohort phase II KEYNOTE-199 study (NCT02787005).

Methods: Pts who did or did not previously take abiraterone acetate were eligible if they developed resistance to enza after prior response. Cohorts were composed of pts who had RECIST-measurable (C4) or bone-predominant nonmeasurable (C5) disease. Pts received pembrolizumab 200 mg Q3W for up to 35 cycles + enza QD until progression, toxicity, or withdrawal. The primary end point was ORR per RECIST v1.1 by blinded independent central review in C4; DOR was also analyzed. Secondary end points (both cohorts) were DCR, rPFS, OS, time to cytotoxic chemotherapy, time to new anticancer therapy, and safety.

Results: A total of 126 pts (C4, 81; C5, 45) were treated. Median (range) time from enrollment to data cutoff was 15 mo (7-21) in C4 and C5, respectively. In C4, ORR (95% CI) was 12% (6-22) (2 CRs, 8 PRs) and median (range) DOR was 6.3 mo (2.5+ to 13.4); 4 responders (73% by Kaplan-Meier estimation) had a response ≥6 mo (Table). Median time to cytotoxic chemotherapy was 11.1 and 11.3 mo in C4 and C5, and time to PSA progression was 4.2 mo in both cohorts (Table). A total of 26% and 24% of pts in C4 and C5, respectively, experienced grade ≥3 treatment-related adverse events (TRAEs). Two pts in C4 died of immune-related AEs (Miller Fisher syndrome and myasthenia gravis). Incidence of any-grade/grade 3 or 4 rash (33%/6%), regardless of treatment relatedness, was higher than previously reported for individual agents but manageable with standard-of-care treatments.

Table: 227P Efficacy outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cohort 4 RECIST Measurable</th>
<th>Cohort 5 Bone Predominant Nonmeasurable</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, by RECIST v1.1 by bCR, n/n (%)</td>
<td>10/81 (12)</td>
<td>NA</td>
</tr>
<tr>
<td>DCR, n/n (%)</td>
<td>41/81 (51)</td>
<td>23/45 (51)</td>
</tr>
<tr>
<td>PSA response rate in patients with baseline PSA, n/n (%)</td>
<td>13/80 (16)</td>
<td>4/45 (9)</td>
</tr>
<tr>
<td>Time to PSA progression Median (95% CI), mo</td>
<td>4.2 (4.1-4.4)</td>
<td>4.2 (4.2-4.4)</td>
</tr>
<tr>
<td>rPFS</td>
<td>4.2 (2.5-6.0)</td>
<td>4.4 (3.4-6.2)</td>
</tr>
<tr>
<td>OS, %</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Median (95% CI), mo</td>
<td>NR (15.9-9)</td>
<td>18.8 (14.0-9)</td>
</tr>
<tr>
<td>Time to cytotoxic chemotherapy</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td>Median (95% CI), mo</td>
<td>11.1 (8.5-11.5)</td>
<td>11.3 (9.0-14.5)</td>
</tr>
<tr>
<td>Event-free survival 12 mo, %</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Time to new anticancer therapy</td>
<td>9.4 (7.2-11.1)</td>
<td>9.5 (5.9-12.1)</td>
</tr>
<tr>
<td>Event-free survival 12 mo, %</td>
<td>38</td>
<td>35</td>
</tr>
</tbody>
</table>

Conclusions: After enza resistance, pembrolizumab plus enzalutamide activity and manageable toxicity in chemotherapy-naive, enzalutamide-resistant mCRPC. Pembrolizumab + enza is being evaluated in the ongoing phase III KEYNOTE-641 trial (NCT03834440).

Clinical trial identification: NCT02787005, June 1, 2016.

Disclosure: U.N. Vaishampayan: Advisory/Consultancy, Research grant/Funding (self); Merck & Co., Inc. T. Elliott: Research grant/Funding (self), Research grant/Funding (institution): Per-patient payments, Pfizer, Bayer, Astellas, AstraZeneca, Janssen, Travel/ Accommodation/Expenses: Janssen. A.G. Omlin: Advisory/Consultancy: Astellas, Bayer, Sanofi, Roche, Janssen, MSD, Molecular Partners; Speaker Bureau/Expert testimony: Astellas, Janssen, Bayer, Travel/ Accommodation/Expenses: Astellas, Bayer, Sanofi, Janssen; Research grant/Funding (institution): Teva, Janssen. J.N. Graff: Advisory/Consultancy: Takeda, Sanofi, April, Genentech, Novartis, Astellas, Travel/ Accommodation/Expenses: Sanofi, Clovis, Janssen, Bayer. J.S. de Bono: Honoraria (self); BMS, Genentech, Seattle Genetics; Advisory/Consultancy: Seattle Genetics, Merck, Biocris; Precise; Speaker Bureau/Expert testimony: BMS, Genentech, Seattle Genetics, Eisai; Research grant/Funding (institution): Merck, Seattle Genetics, Genentech, Novartis, Astellas, Travel/ Accommodation/Expenses: Sanofi, Clovis, Janssen, Bayer.

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA.

Funding: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Results: A total of 232 pts were enrolled in the KEYNOTE-641 study (NCT03834440) with mCRPC and had enzalutamide resistance.

Conclusions: KEYNOTE-641 is an ongoing phase III study assessing pembrolizumab plus enzalutamide as first-line treatment for mCRPC and is intended to enroll 500 pts with mCRPC and enzalutamide resistance at 75 sites in the USA and elsewhere.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.10.447

228P Symptoms and impacts of metastatic castration-resistant prostate cancer (mCRPC) among Japanese patients designated to receive Ra-223

H. Umura1, K. Akakura1, K. Miyazaki2, A. Stroupe3, C. Seo4, A. Uzucom5, K. McCarther6, D. Ledesma7

1Department of Urology and Renal Transplantation, Yokohama City University Medical Center, Yokohama, Japan; 2Department of Urology, ICHO Tokyo Shinjuku Medical Center, Shinjuku, Japan; 3School of Public Health, Washington University Graduate School of Medicine, Kyoto, Japan; 4Patient-Centered Outcomes, Pharmerit International, Newton, MA, USA; 5Patient-Centered Outcomes, Pharmerit International, Bethesda, MD, USA; 6Market Access Oncology, Bayer Yakuhin, Ltd., Tokyo, Japan

Background: Radium-223 (Ra-223) received regulatory approval for castration-resistant prostate cancer (CRPC) with bone metastasis in Japan in 2016. This study aimed to reveal emerging symptoms, impacts, and concerns within the Japanese patient experience of living with mCRPC and the burden of bone metastasis prior to Ra-223 treatment, through patient and physician interviews.

Methods: This non-interventional, qualitative study consisted of interviews with 23 bone metastatic CRPC patients prior to their first Ra-223 treatment cycle, and 3 treating physicians in Japan. Patients were recruited via purposive sampling. Inclusion criteria were: (1) a diagnosis of bone metastatic CRPC, and (2) designated to start receiving Ra-223 in routine clinical practice. Physicians included those who had prescribed at least one Ra-223 treatment cycle in the past 12 months and are currently prescribing Ra-223. All interview data were entered into ATLAS.ti v8.0 for coding, assessment of concept frequency, themes and saturation analysis.

Results: The patients’ mean age was 75.8 y.o., with 45% symptomatic at the time of enrollment. Forty-seven mCRPC symptoms were reported, including pain, fatigue, nocturia, muscle loss, and various side effects related to previous PC treatment and/or disease stage. Around mCRPC diagnosis, patients reported back pain (45%), hip pain (23%) and pain specifically in their bones (27%). Life impacts reported included 45 concepts, with the most frequently mentioned being worry for their disease...
progression and how it would impact their family and lives, the impact that mCRPC has on their daily, physical abilities (e.g. difficulty walking, muscle loss) and the impact a patient's mCRPC has on the family and caregivers. Patients had high expectations from Ra-223 in terms of cessation of disease progression (32%) and pain alleviation (23%), but also worry about adjusting to the treatment. All 3 physicians cited the need for information sharing about Ra-223.

Conclusions: The symptoms and impacts of living with mCRPC and the associated burden of bone metastasis and skeletal-related symptoms are considerable and varied, and information sharing is key to easing concerns in utilizing Ra-223 treatment.

Legal entity responsible for the study: Bayer Yakuhin, Ltd.

Funding: Bayer Yakuhin, Ltd.


https://doi.org/10.1016/j.annonc.2020.10.448

229P

Expanding the role of supervised exercise on fatigue in prostate cancer patient receiving androgen deprivation therapy: A meta-analysis of randomized controlled trial

N. Yogiswara1, Y. Azmi2, Y.A. Azmi2

1Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; 2Urology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Background: Fatigue is a common adverse effect suffered by prostate cancer patients receiving androgen deprivation therapy (ADT). A growing body of evidence has proposed exercise as a treatment to relieve and prevent the adverse effects of ADT. Recently, high-quality randomized clinical trials (RCTs) using supervised exercise have been conducted to get more assessment. However, the pooled estimate for the effect of supervised exercise on fatigue has not been established yet. This study aims to determine the pooled effect of supervised exercise on fatigue in prostate cancer patients receiving ADT.

Methods: A literature search was conducted from PubMed, Clinicaltrial, and Cochrane Library, published up to January 2020 following the PRISMA guideline. We screened RCTs with our inclusion criteria and assessed the quality using the tools provided by Cochrane. The primary outcome analyzed in this study was fatigue measured as Standardized Mean Difference (SMD) with 95% Confidence Intervals (CI). Heterogeneity was assessed using the I² test. Subgroup analysis was conducted to determine the difference in exercise duration (<12 weeks and ≥12 weeks), modality (aerobic, resistance, and combination), and the onset of ADT (initiation and long-term). All analysis was performed using STATA 16.

Results: A total of 7 RCTs comprising 455 patients reported the fatigue using the FACT-Fatigue, EQD2 phantom, EQ-5D-3L, and Schwartz Cancer Fatigue Scale. The included studies presented a low risk of bias. Supervised exercise showed an overall reduction on fatigue (SMD = 0.25, 95%CI 0.07-0.44, p = 0.01, I² = 0%). The subgroup test results showed no significant difference between exercise duration (p = 0.4), modality (p = 0.67), and onset of ADT (p = 0.57). The Egger’s test results showed no indication of publication bias (p = 0.64).

Conclusions: Supervised exercise reduces fatigue in prostate cancer patients receiving ADT. The available data show that there is no difference between exercise duration and modality. Furthermore, our findings highlight the benefits of supervised exercise in the initiation of ADT for preventing toxicities as well as relieving adverse effects in long-term ADT.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.10.449

230P

Molecular profiling and clinical characteristics of Chinese patients with prostate cancer

G. Liu1, T. Yang2, H. Wang2, F. Lou3, S. Cao2

1Urology Surgery, The Second Hospital of Tianjin Medical University, Tianjin, China; 2Department of Medicine, Beijing Aocomed Biotechnology Co., Ltd., Beijing, China

Background: Prostate cancer (PCa) is one of the most common types of cancer in men. Androgen deprivation therapy (ADT) is the main choice of PCa treatment. However, major investigations have focused on Caucasians population. Here, we intended to explore the molecular characteristics and clinical characteristics between localized and metastatic of Chinese PCa patients.

Methods: 29 PCa patients with localized or metastatic tumor were enrolled. Somatic and germline mutations were identified via targeted next generation sequencing with paired end panel including 808 genes associated with tumor development. Sequencing data were analyzed to call tumor specific single nucleotide variants (SNV), small insertions and deletions (InDels), copy number alterations (CNA) and chromosomal rearrangements. Clinical data of the cohort was collected and analyzed.

Results: Median age was 68 yrs (range 53-80), 62% were classified as metastatic (M), and 17% had received one prior ADT drug. The most common somatic mutations were observed in TP53 (24%), FOXA1 (21%), CDK2 (17%), AR (10%), KRAS (7%), PIK3CA (7%), SPOP (7%), PTCH1 (7%), ATM (7%), and TSC2 (3%) genes. Median tumor mutational burden (TMB) was 7 MuSV/MB(1-22). Germline pathogenic or likely pathogenic mutations occurred 17% of PCa patients, 45% mutations were DNA damage response genes, and 4 patients had metastatic PCa. AR was shared by both localized and metastatic PCa (2 in ADT-1 and 1 in ADT+). Mutated CDK12 was only detected in patients without any history of ADT drug(3 in M- and 2 in M+). Interestingly, TP53 mutations were only detected in metastatic PCa(7/18 M+). FOXA1 mutations were preserved more frequently in patients with localized PCa(4/15M- versus 2/18 M+).

Conclusions: These findings show differences in the genomics alterations of metastatic and localized prostate cancer. Germline mutations are more likely to be detected in patients with advanced prostate cancer. Mutations in the TP53 gene are more common in advanced prostate cancer. Additional correlative analyses are ongoing.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: T. Yang, H. Wang, F. Lou, S. Cao: Full/Part-time employment: Beijing Aocomed Biotechnology Co., Ltd., All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.10.450

231P

Phase II study of pembrolizumab in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer (PROCEP): Updated follow-up of cohorts (C) 1-3 from KEYNOTE-199

J.H. Goh1, J.M. Piliats2, M. Gross-Goupil,1 U.N. Vaishampayan,2 R. de Wit,2 T. Abut,3 S. Fukasawa,1 K. Tabata,2, S. Feyerabend9, R. Berger10, H. Wu,11 J. Kim11, C. Schloss11, J.S. de Bono12, E.S. Antonarakis13

1Medical Oncology, Royal Brisbane and Women’s Hospital, Herston, Australia; 2Medical Oncology, Catalan Cancer Institute, Barcelona, Spain; 3Medical Oncology, Bergonie Institute, Cancer Center, Bordeaux, France; 4Internal Medicine, Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; 5Medical Oncology, Erasmus MC, Rotterdam, Netherlands; 6Medical Oncology, Dokrates Cancer Center, Helsinki, Finland; 7Medical Oncology, Chiba Cancer Center, Chiba, Japan; 8Medical Oncology, Kitasato University School of Medicine, Kanagawa, Japan; 9Studienpraxis Urologie, Studienpraxis Urologie, Nürtingen, Germany; 10Medical Oncology, The Chaim Sheba Medical Center at Tel Hashomer, Ramat Gan, Israel; 11Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA; 12Experimental Cancer Medicine, The Royal Marsden NHS Foundation Trust, London, UK; 13Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Background: Pembrolizumab monotherapy has shown antitumor activity and acceptable safety in patients with mCRPC previously treated with a hormonal agent (HAA) and docetaxel.

Methods: The KEYNOTE-199 phase II study (NCT02787005) enrolled patients with RECIST-measurable PD-L1+ disease, RECIST-measurable PD-L1- disease, and bone-predominant disease irrespective of PD-L1 status in C1, C2, and C3, respectively. Patients had prior treatment with ≥1 NHA and 1 or 2 chemotherapies, including docetaxel, and received pembrolizumab 200 mg Q3W for 35 cycles or until progression/toxicity. The primary end point was ORR per RECIST v1.1 by blinded independent central review. Key secondary end points were time to PSA progression, DCR, PSA response rate, rPFS, OS, DOR, and safety.

Results: In total, 258 patients were treated (C1: 133; C2: 67; C3: 58), of whom 6 completed therapy (C1: 4; C3: 2). The median (range) time from enrollment to data cutoff was 31.3 mo (26.7-34.7), 30.6 mo (28.0-34.1), and 32.6 mo (27.4-34.4) in C1, C2, and C3, respectively. Patients had prior treatment with ≥1 NHA and 1 or 2 chemotherapies, including docetaxel, and received pembrolizumab 200 mg Q3W for 35 cycles or until progression/toxicity. The primary end point was ORR per RECIST v1.1 by blinded independent central review. Key secondary end points were time to PSA progression, DCR, PSA response rate, rPFS, OS, DOR, and safety.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.10.449