JSCO2024 "Frontier" 3
Genitourinary Cancer

Fri., October 25, 2024 10:00-11:30 Room 3 | 201+202, 2F, Fukuoka International Congress Center

Chair : Masaki Shiota (Department of Urology, Graduate School of Medical Sciences, Kyushu University)
Chair : Nobuaki Matsubara (Department of Medical Oncology, National Cancer Center Hospital East)
Discussant : Kazuhiro Matsumoto (Department of Urology, Keio University School of Medicine)
Discussant : Takashi Kobayashi (Department of Urology, Kyoto University Graduate School of Medicine)

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Updated Efficacy and Safety Results for Adjuvant Pembrolizumab (pembro) Versus Placebo (pbo) for Clear Cell Renal Cell Carcinoma (ccRCC) in the Phase 3 KEYNOTE-564 East Asian Subgroup
Hiroshi Kitamura (Faculty of Medicine, Department of Urology, University of Toyama)

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Eiji Kikuchi (Department of Urology, St. Marianna University School of Medicine)

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Nobuaki Matsubara (Department of Medical Oncology, National Cancer Center Hospital East)

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FR3-1

Updated Efficacy and Safety Results for Adjuvant Pembrolizumab (pembro) Versus Placebo (pbo) for Clear Cell Renal Cell Carcinoma (ccRCC) in the Phase 3 KEYNOTE-564 East Asian Subgroup

Hiroshi Kitamura [1], Yen-Hwa Chang [2], Jae Lyun Lee [3], Toni K. Choueiri [4], Jinsoo Chung [5], Go Kimura [6], Naoya Masumori [7], Kazuo Nishimura [8], Minoru Kato [9], Haruaki Kato [10], Kun-Yuan Chiu [11], Jianxin Lin [12], Aymen Elfiky [12], Joseph Burgents [12], Se Hoon Park [13]

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Background: In the randomized phase 3 KEYNOTE-564 study (NCT03142334) , adjuvant pembro improved disease-free survival (DFS) at the first interim analysis (HR, 0.68, 95 % CI, 0.53-0.87; 1-sided P=0.001) and improved overall survival (OS) at the third interim analysis (IA3; HR, 0.62, 95 % CI, 0.44-0.87, 1-sided P=0.002) compared to pbo in a global population of patients (pts) with ccRCC at increased risk of recurrence after nephrectomy. We report results from the KEYNOTE-564 East Asian subgroup at IA3.

Methods: Adults with ccRCC at increased risk of recurrence after nephrectomy with or without metastasectomy who were enrolled in KEYNOTE-564 at sites in Japan, Republic of Korea, and Taiwan were included in this subgroup analysis. Pts were randomly assigned 1:1 to receive adjuvant pembro 200 mg IV or pbo IV every 3 weeks for ≦ 17 cycles (~ 1 year) . The primary end point was DFS by investigator assessment. Secondary end points included OS (key secondary) and safety. No formal statistical analysis was performed for this subgroup analysis.

Results: 126 pts were enrolled in East Asia (pembro, n=58; pbo, n=68) . As of September 15, 2023, median follow-up was 62.1 mo (range, 49.6-73.0) . Median DFS was not reached (NR) with pembro versus 58.8 mo with pbo (HR, 0.70; 95 % CI, 0.41-1.20) ; estimated 48-mo DFS rates were 61.3 % versus 51.2 %. Median OS was NR in both groups (HR, 0.47; 95 % CI, 0.15-1.49) ; estimated 48-mo OS rates were 94.8 % versus 91.2 %. Treatment-related adverse events occurred in 41 pts (70.7 %; grade 3 or 4, n=17 [29.3 %]) with pembro and 25 pts (36.8 %; grade 3 or 4, n=0) with pbo. No deaths were attributed to pembro.

Conclusions: With updated follow-up in the East Asian subgroup, adjuvant pembro continued to show DFS and OS benefits versus pbo and a safety profile that is consistent with the global results of KEYNOTE-564. These results further support the use of pembro as adjuvant treatment for pts in East Asia with ccRCC at increased risk of recurrence after nephrectomy.

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FR3-2

Belzutifan versus everolimus for previously treated advanced clear cell renal cell carcinoma (ccRCC) in the East Asian subgroup from the randomized, open-label phase 3 LITESPARK-005 trial

Yuji Miura [1], Se Hoon Park [2], Jae Lyun Lee [3], Nobuaki Matsubara [4], Takashi Saika [5], Taigo Kato [6], Naoya Masumori [7], Koshiro Nishimoto [8], Hiroyuki Fujimoto [9], Yu-Li Su [10], Rodolfo F. Perini [11], Aiwen Xing [11], Donna Vickery [11], Toni K. Choueiri [12], Mototsugu Oya [13]

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Background: Belzutifan (BEL) demonstrated longer PFS and higher ORR vs everolimus (EVE) in a global population of patients (pts) with advanced ccRCC following anti-PD- (L) 1 and VEGF-targeted therapies in the phase 3 LITESPARK-005 study (NCT04195750). We report an exploratory analysis of the East Asian subgroup from LITESPARK-005.

Methods: Adults with advanced ccRCC who received 1-3 prior systemic regimens including anti-PD-(L) 1 and VEGF-targeted therapies enrolled in Hong Kong, Japan, South Korea, or Taiwan were randomly assigned to BEL 120 mg QD or EVE 10 mg QD until progression or unacceptable toxicity. Primary end points were PFS per RECIST v1.1 by blinded independent central review (BICR) and OS. Secondary endpoints included ORR per RECIST v1.1 by BICR (key), DOR, and safety.

Results: Overall, 78 pts were enrolled in East Asia (n = 39 in each arm). As of the data cutoff date, median follow-up was 23.3 mo (range, 16.8-34.1). Median PFS was 7.5 mo with BEL vs 5.7 mo with EVE (HR 0.63 [95 % CI, 0.36-1.10]). Median OS was 29.7 mo with BEL vs not reached (NR) with EVE (HR 1.01 [95 % CI, 0.49-2.10]). ORR (95 % CI) was 33 % (19-50) with BEL and 0 % (0-9) with EVE. DOR was NR (range, 12.9-28.6+ mo) with BEL. Treatment-related AEs (TRAEs) occurred in 95 % of patients with BEL and 100 % of patients with EVE (Grade 3-5, 47 % vs 33 %). The most common TRAE was anemia (82 %) in the BEL group and stomatitis (46 %) in the EVE group. 1 pt (3 %) discontinued BEL and 5 (13 %) discontinued EVE due to TRAEs.

Conclusions: PFS and ORR favored BEL over EVE in the East Asian subgroup of LITESPARK-005. In the East Asian subgroup, Grade 3-5 TRAEs were more frequent in the BEL arm, while discontinuation due to TRAEs were more frequent in the EVE arm. Efficacy and safety results were generally consistent with the global population, noting limitations of small sample size and exploratory nature of the analysis.

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FR3-3

Efficacy, Tolerability and Safety of [177Lu] Lu-PSMA-617 (177Lu-PSMA-617) in Patients with Progressive PSMA+ mCRPC：A Prospective, Phase 2, Open-label, Single-arm Trial in Japan

Ryuji Matsumoto [1], Kouji Izumi [2], Yusuke Ito [3], Seiji Hoshi [4], Nobuaki Matsubara [5], Toshinari Yamasaki [6], Takashi Mizowaki [7], Atsushi Komaru [8], Satoshi Nomura [9], Toru Hattori [9], Hiroya Kambara [9], Shaheen Alanee [10], Makoto Hosono [11], Seigo Kinuya [12]

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177Lu-PSMA-617 is the first PSMA-targeted radioligand therapy approved in the US and EU based on VISION study, demonstrating clinical benefit in patients with PSMA+ mCRPC previously treated with ≧ 1 ARPI and 1-2 taxanes. This Phase 2 trial evaluated the efficacy, tolerability, and safety of 177Lu-PSMA-617 in patients with ≧ 1 measurable lesion and progressive PSMA+ mCRPC in Japan.

This study comprises 4 parts; data from 3 parts are presented here. Part 1 evaluated safety and tolerability; Parts 2 (post-taxane) and 3 (pre-taxane/taxane-naive) assessed the ORR (primary endpoint) , and rPFS, DCR, PFS, OS, and safety (secondary endpoints) ; and Part 4 is the expansion part. Patients received 7.4 GBq (± 10 %) 177Lu-PSMA-617 Q6W up to 6 cycles.

Of 35 patients who underwent a 68Ga-PSMA-11 PET/CT scan, 30 received 177Lu-PSMA-617 (post-taxane, n=12; pre-taxane, n=18) ; mean (SD) age was 70.4 (7.07) years. No DLT was noted in Part 1 (n=3) . The median number of cycles was 3 (2-6) in post-taxane and 5 (2-6) in pre-taxane patients. Based on local radiology review, ORR met the pre-specified threshold for the primary endpoint, with the lower limit of 90 % CI above the threshold of 5 % for post-taxane and 12 % for pre-taxane. The ORR (90 % CI) in post-taxane patients was 25.0 % (7.2, 52.7) , with no CR reported and 25 % PR. The ORR in pre-taxane patients was 33.3 % (15.6, 55.4) , with 22.2 % CR and 11.1 % PR. In post- and pre-taxane patients, DCR was 91.7 % and 83.3 %, median rPFS was 3.71 mo and 12.25 mo, and median PFS was 3.71 mo and 5.59 mo. After a median f/u of 11.02 mo and 8.33 mo, the median OS was 14.42 mo and 12.94 mo. Most common AEs (≧ 20 %) in all treated patients (n=30) were constipation (53.3 %) , decreased appetite (26.7 %) , decreased platelet count (23.3 %) , and anemia and nausea (20 % each) .

The primary endpoint (ORR) was met. No major differences in overall safety profile were noted compared to the VISION study and no new safety signal was identified in the Japanese patients with mCRPC.

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FR3-4

Real-world outcomes with avelumab + axitinib (A+Ax) by IMDC risk classification in patients (pts) with advanced renal cell carcinoma (aRCC): subgroup analysis from the long-term J-DART2 study in Japan

Mototsugu Oya [1], Junya Furukawa [2], Taigo Kato [3], Toshinari Yamasaki [4], Keisuke Monji [5], Toshiaki Tanaka [6], Norihiko Tsuchiya [7], Tomoaki Miyagawa [8], Hiroshi Yaegashi [9], Tomoyasu Sano [10], Takashi Karashima [11], Kazutoshi Fujita [12], Jun-Ichi Hori [13], Masahiro Kajita [14], Hirotsugu Uemura [12]

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Objectives: A+Ax was approved in Japan in December 2019 for the treatment of aRCC. Here we report ad hoc subgroup analyses of first-line A+Ax in pts with aRCC by International Metastatic RCC Database Consortium (IMDC) risk classification from the long-term, real-world J-DART2 study in clinical practice in Japan.

Methods: J-DART2 (NCT05650164) was a multicenter, retrospective, observational study that examined baseline characteristics, treatment patterns, and long-term outcomes in pts with aRCC who received first-line A+Ax in Japan between December 20, 2019, and October 17, 2022. Data were collected from medical records (cutoff, October 31, 2022). Results were analyzed according to IMDC risk classification.

Results: Data from 150 pts across 19 sites were analyzed. Median follow-up was 18.7 months (95 % CI, 16.3-20.6 months). IMDC risk was favorable in 39 pts (26.0 %), intermediate (1 risk factor) in 46 (30.7 %), intermediate (2 risk factors) in 36 (24.0 %), and poor in 29 (19.3 %). In the favorable-, intermediate (1 risk factor) -, intermediate (2 risk factors) -, and poor-risk subgroups, median real-world progression-free survival was 31.0 months, 15.3 months, 16.4 months, and 8.1 months, respectively. Median overall survival (OS) was not reached in any subgroup, but 12-month OS rates were 100 %, 95.3 %, 85.3 %, and 77.3 %, respectively, and 24-month OS rates were 95.2 %, 91.3 %, 85.3 %, and 57.6 %. Real-world objective response rates were 54.5 %, 56.8 %, 47.1 %, and 54.2 %, respectively. High-dose corticosteroids were administered for the management of immune-related adverse events in 5.1 %, 8.7 %, 8.3 % and 6.9 % of pts, respectively.

Conclusions: Subgroup analyses from the real-world J-DART2 study confirm the long-term effectiveness of first-line A+Ax across IMDC risk groups in pts with aRCC in Japan. Our findings are consistent with previous clinical trial analyses and support the favorable benefit-risk profile of A+Ax across IMDC risk groups in clinical practice in Japan.

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FR3-5

Final analysis of postmarketing surveillance (PMS) for the safety and effectiveness of avelumab maintenance therapy in patients (pts) with curatively unresectable urothelial carcinoma (UC) in Japan

Eiji Kikuchi [1], Masayoshi Nagata [2], Taito Ito [3], Masashi Sato [3], Mie Ogi [3], Makiko Morita [3], Masahiro Kajita [3], Hiroyuki Nishiyama [4]

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Background: Avelumab maintenance therapy was approved in Japan in Feb 2021 based on results from the JAVELIN Bladder 100 (JB100) phase 3 trial, which demonstrated prolonged overall survival (OS) in pts with advanced UC that had not progressed after prior platinum-based chemotherapy. We report final analyses of PMS of avelumab maintenance therapy in clinical practice in Japan evaluating the safety and effectiveness in the overall population and the safety in subgroups defined by age.

Methods: This PMS is a multicenter, observational surveillance of pts with UC who received ≧ 1 dose of avelumab between Feb 24, 2021, and Dec 7, 2021. Safety and/or effectiveness data were collected from the start of avelumab therapy for ≦ 52 weeks and were analyzed in the overall population and age subgroups.

Results: The analysis set included 453 pts. Median age was 73.0 years; 75 pts (16.6 %) were aged ≦ 64 years, 198 (43.7 %) were aged 65-74 years, and 180 (39.7 %) were aged ≧ 75 years. At data cutoff (Mar 6, 2024), median duration of therapy was 22.0 weeks (IQR, 10.0-52.0) and 128 pts (28.3 %) remained on avelumab treatment. Adverse drug reactions of safety specification of any grade occurred in 144 pts (31.8 %) in the overall population and in 17 (22.7 %) aged ≦ 64 years, 69 (34.8 %) aged 65-74 years, and 58 (32.2 %) aged ≧ 75 years, with grade ≧ 3 in 36 (7.9 %), 2 (2.7 %), 15 (7.6 %), and 18 (10.0 %), respectively. In the overall population, median OS was not reached, the 1-year OS rate was 77.9 % (95 % CI, 73.7-81.5), and median time to treatment failure was 4.6 months (95 % CI, 3.8-5.3).

Conclusions: This final analysis of the PMS is the largest real-world dataset of avelumab maintenance therapy in Japan. Our findings of avelumab maintenance in clinical practice in Japan demonstrate the acceptable safety and tolerability in the overall population and age subgroups and the effectiveness in the overall population, which are comparable to findings from JB100 and real-world studies from other countries.

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FR3-6

ANNAR biomarker study：Fibroblast growth factor receptor alterations（FGFRalt）in locally advanced or metastatic urothelial cancer（mUC）and non-muscle invasive bladder cancer（NMIBC）

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Background: *FGFRalt* are known to be oncogenic, and are found in ～20 % of mUC and 60-70 % of NMIBC samples. ANNAR is a global non-interventional study（NCT03955913）that assessed *FGFRalt* in archival tumor tissue of mUC and NMIBC. This analysis is aimed at understanding the proportion of valid FGFR test results（positive or negative）and reasons for test failure.

Methods: mUC and NMIBC patients ≧ 18 years old with available archival tumor tissue were enrolled from Aug 2019 to Sep 2022. All samples were sent to a central laboratory for testing using QIAGEN *therascreen* FGFR RT-PCR kit. Frequency of FGFR mutations and fusions were assessed.

Results: A total of 2706 mUC and 962 NMIBC samples were tested for *FGFRalt*. Proportion of valid test results was higher in mUC（86.3 %）than NMIBC（65.9 %）, and the proportion decreased with longer archival duration regardless of mUC（<1year & ≧ 3years archival duration: 88.6 %, 76.7 %）or NMIBC（72.4 %, 42.6 %）. In mUC, the proportion of valid test results was higher in primary tumors than metastatic samples（91.6 %, 54.7 %）, but was similar between upper and lower tract samples（87.1 %, 86.2 %）. Common reasons for test failure in mUC and NMIBC were insufficient tumor cells（3.1 %, 3.7 %）, insufficient RNA（3.7 %, 8.4 %）and run controls failure（5.7 %, 20.6 %）. *FGFRalt* were found in 431（18.5 %）mUC and 333（52.5 %）NMIBC samples. FGFR mutations were observed in 15.3 % mUC and 48.1 % NMIBC samples, with FGFR3-S249C and FGFR3-Y373C being the most common. FGFR fusions were observed in 2.8 % mUC and 3.3 % NMIBC samples, with FGFR3-TACC3 V1 as majority.

Conclusions: The proportion of valid FGFR test results was similar in mUC compared to the BLC2001 study（89.7 %）but was lower in NMIBC. Tumor tissue samples with short archival duration and from primary tumor were more likely to yield valid FGFR test results, an important aspect to be considered for treatment selection based on FGFR testing.

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