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Moderator : Masatoshi Eto (Department of Urology, Kyushu University)
Moderator : Shusuke Akamatsu (Department of Urology, Nagoya University Graduate School of Medicine)
Discussant : Kouji Izumi (Department of Integrative Cancer Therapy and Urology, Kanazawa University)
Discussant : Ryuichi Mizuno (Department of Urology, School of Medicine, Keio University)

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Matthew R. Smith (Genitourinary Oncology Program, Massachusetts General Hospital Cancer Center, USA)

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FR2-1

Time to pain progression (TTP) by disease volume with darolutamide (DARO) in combination with androgen-deprivation therapy (ADT) and docetaxel (DOC) in the phase 3 ARASENS study

Matthew R. Smith [1], Bertrand Tombal [2], Fred Saad [3], Karim Fizazi [4], Cora N. Sternberg [5], E. David Crawford [6], Jeanny B. Aragon-Ching [7], Martin Schostak [8], Ronald Tutrone [9], Ateesha F. Mohamed [10], Natasha Littleton [11], Rui Li [10], Shankar Srinivasan [10], Maha Hussain [12]

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Background: In ARASENS, DARO + ADT + DOC significantly reduced the risk of death from metastatic hormone-sensitive prostate cancer (mHSPC) by 32.5 % (HR 0.68, 95 % CI 0.57-0.80; $P<0.0001$) and significantly delayed TTP (HR 0.79, 95 % CI 0.66-0.95; one-sided $P=0.006$) vs placebo (PBO) + ADT + DOC. We report TTP in patients with high/low disease volume (HV/LV).

Methods: Patients with mHSPC were randomized 1:1 to oral DARO 600 mg twice daily or PBO, both with ADT + DOC. Pain progression was defined on the Brief Pain Inventory short form "pain at its worst" score (WPS) as an increase ≧ 2 points from nadir (and absolute WPS ≧ 4 if >0 at baseline) or initiation of opioid therapy for ≧ 7 consecutive days. A post-hoc sensitivity analysis assessed pain progression after completion of DOC. HV/LV subgroups were defined per CHAARTED.

Results: 1305 patients (DARO 651, PBO 654) were analyzed; 1005 (77 %) /300 (23 %) patients had HV/LV disease. At baseline, the mean (standard deviation) WPS was 1.5 (1.9) vs 1.4 (1.8) in the DARO vs PBO groups; 258 (40 %) vs 274 (42 %) patients had no pain (WPS 0). DARO + ADT + DOC had a robust impact on delaying TTP vs PBO + ADT + DOC in the overall population and HV subgroup (prespecified sensitivity analysis, overall population: stratified HR 0.75, 95 % CI 0.62-0.90; post-hoc sensitivity analyses, HV: stratified HR 0.69, 95 % CI 0.56-0.86, LV: stratified HR 0.87, 95 % CI 0.60-1.27). WPS change from nadir was the main driver of pain progression events. Rates of serious adverse events (44.8 % vs 42.3 %) and adverse events leading to discontinuation (13.5 % vs 10.6 %) were similar in the DARO vs PBO groups.

Conclusions: In patients with mHSPC, the addition of DARO to ADT and DOC provided clinically meaningful benefit through delayed TTP, notably in patients with HV disease. Increased overall survival, a delay in TTP, and a favorable safety profile set DARO + ADT + DOC as one of the new standards of care for patients with mHSPC.

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FR2-2

Clinical Outcomes by Prostate-Specific Antigen Decline With Enzalutamide + Androgen Deprivation Therapy in Metastatic Hormone-Sensitive Prostate Cancer：ARCHES Post Hoc Analysis

Taro Iguchi [1], Andrew J Armstrong [2], Arnulf Stenzl [3], Neal D Shore [4], Arnauld Villers [5], Francisco Gomez-Veiga [6], Antonio Alcaraz [7], Boris Alekseev [8], Russell Z Szmulewitz [9], Daniel P Petrylak [10], Jeffrey Holzbeierlein [11], Brad Rosbrook [12], Jennifer Sugg [13], Jie Ma [13], Fabian Zohren [12], Gabriel P. Haas [13], Arun A. Azad [14]

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Background: In the Phase 3 ARCHES trial (NCT02677896), enzalutamide (ENZA) + androgen deprivation therapy (ADT) improved overall survival (OS) and radiographic progression-free survival (rPFS) vs placebo (PBO) + ADT in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC). We report efficacy over time based on the prostate-specific antigen (PSA) reduction achieved with treatment.

Methods: In ARCHES, men with mHSPC were randomized 1:1 to ENZA (160 mg/day) + ADT or PBO + ADT, stratified by disease volume and prior docetaxel treatment. This *post hoc* analysis of men with detectable baseline PSA (≥0.2 ng/mL) evaluated OS and rPFS by PSA decline (none, <50 %, ≥50-<90 %, ≥90-<100 %, or undetectable) from baseline to treatment month (mo) 3 or 6. Analyses used the Kaplan-Meier method and log-rank test.

Results: Among pts with detectable baseline PSA (N=1018), a ≥90 % decline or undetectable PSA at 3 and 6 months (mos) was achieved by 69.7 % and 73.8 %, respectively, on ENZA + ADT vs 24.5 % and 25.6 %, respectively, on PBO + ADT. From 3 to 6 mos, PSA declined by ≥1 category for 18.4 % on ENZA + ADT vs 14.4 % on PBO + ADT, while 7.8 % vs 15.4 %, respectively, had worsened PSA. In pts with available 6-mo PSA values, 59.8 %, 30.1 %, and 10.1 % on ENZA + ADT (n=465) vs 15.4 %, 43.5 %, and 41.0 % on PBO + ADT (n=441) had a PSA level of <0.2, 0.2-4, and >4 ng/mL, respectively. Median OS was not evaluable (NE), NE, and 32.3 mos and median rPFS was NE, NE, and 12.4 mos for ENZA + ADT pts with 6-mo PSA levels of <0.2, 0.2-4, and >4 ng/mL, respectively. Greater PSA declines at 3 and 6 mos and lower PSA values at 6 mos were prognostic for both OS and rPFS and were more commonly observed with ENZA + ADT.

Conclusions: Greater PSA declines and lower PSA values in men with mHSPC are strongly associated with improved long-term clinical outcomes after 3 and 6 mos of treatment and are more commonly observed with ENZA + ADT vs PBO + ADT.

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FR2-3

Phase 3 study of talazoparib + enzalutamide versus placebo + enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer：TALAPRO-2 Japanese subgroup analysis

Nobuaki Matsubara [1], Hideaki Miyake [2], Hiroji Uemura [3], Atsushi Mizokami [4], Hiroaki Kikukawa [5], Takeo Kosaka [6], Kazuo Nishimura [7], Motonobu Nakamura [8], Kazuki Kobayashi [9], Atsushi Komaru [10], Yuko Mori [12], Shigeyuki Toyoizumi [12], Natsuki Hori [12], Yoshiko Umeyama [12], Hirotsugu Uemura [11]

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Background: TALAPRO-2 (NCT03395197) is the first phase 3 study to combine the poly (ADP-ribose) polymerase inhibitor talazoparib (TALA) with the androgen receptor inhibitor enzalutamide (ENZA). Patients (pts) unselected for alterations in DNA damage repair genes, directly or indirectly involved in homologous recombination repair (HRR), received TALA+ENZA or placebo (PBO) +ENZA as 1L treatment for mCRPC. TALA+ENZA (402 pts) significantly prolonged the primary endpoint, radiographic progression-free survival (rPFS), vs PBO+ENZA (403 pts): median rPFS was not reached (NR) vs 21.9 months, respectively (hazard ratio [HR], 0.63; 95 % CI, 0.51-0.78; $P<0.0001$). Here, we investigated the efficacy, safety, and pharmacokinetics (PK) in Japanese (Jpn) pts. **Methods:** Pts randomized 1:1 to TALA 0.5 mg or PBO (all received ENZA 160 mg/day) were stratified by prior abiraterone and/or docetaxel for castration-sensitive PC and HRR deficiency status. Primary endpoint was rPFS by BICR per RECIST 1.1 and PCWG3. Secondary endpoints included ORR, safety, and PK (evaluated for trough concentrations [C_{trough}] at pre-dose through Week 17). **Results:** 116 Jpn pts were randomized to TALA+ENZA (n=60) or PBO+ENZA (n=56); 13 pts (21.7 %) and 11 pts (19.6 %) had HRR deficiency with prospective HRR tests, respectively. Median rPFS (95 % CI) was NR (27.9-NR) in TALA+ENZA vs NR (24.9-NR) in PBO+ENZA (HR, 0.89; 95 % CI, 0.45-1.75). ORR (95 % CI; pts) was 54.5 % (23.4-83.3; 6/11) vs 36.4 % (10.9-69.2; 4/11) with CR rate 54.5 % vs 27.3 %. Common all-causality adverse events (AEs) (all grade [grade 3/4]) were anemia (75 [55] % vs 11 [7] %), neutrophil count decreased (58 [38] % vs 5 [2] %), platelet count decreased (37 [10] % vs 5 [0] %), malaise (35 [0] % vs 13 [0] %). AEs led to discontinuation of TALA in 26.7 % vs PBO 7.1 %. The range of TALA C_{trough} in Jpn pts was generally comparable to the overall population. **Conclusion:** TALA+ENZA was also efficacious and toxicity generally manageable in Jpn pts with mCRPC.

Funding: Pfizer

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FR2-4

Characteristics of genome alterations in circulating tumor DNA in patients with advanced renal cell carcinoma：Nationwide SCRUM-Japan MONSTAR SCREEN study

Taigo Kato [1], Nobuaki Matsubara [2], Masaki Shiota [3], Masatoshi Eto [3], Yota Yasumizu [4], Nobuyuki Tanaka [4], Mototsugu Oya [4], Takahiro Osawa [5], Takashige Abe [5], Nobuo Shinohara [5], Koshiro Nishimoto [6], Takao Fujisawa [7], Yoshiaki Nakamura [8,9], Takayuki Yoshino [8], Norio Nonomura [1]

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Background:

Circulating tumor DNA（ctDNA）is an emerging resource for the diagnosis and prognosis in various types of cancer as an alternative to tissue-based genomic profiling. However, clinical utility of ctDNA in metastatic renal cell carcinoma（mRCC）is still largely unknown, especially in untreated mRCC with immune checkpoint inhibitor（ICI）-based combination therapy.

Methods:

We enrolled 124 mRCC patients in SCRUM-Japan MONSTAR-SCREEN between Apr 2019 and Sep 2021, an observational ctDNA-based screening study, and performed ctDNA sequencing（FoundationOne Liquid CDx）before and at the time of resistant to systemic therapy. Additionally, we also performed tissue-based genomic profiling（FoundationOne CDx）for 34 patients.

Results:

ctDNA was assessed in 181 samples comprising of 432 mutations. The most frequently altered genes were *TP53*（14.7 %）, *DNMT3A*（12.1 %）, *TET2*（7.0 %）, and *VHL*（7.0 %）. When we focus on major oncogenic pathway, the mutation rate in genes related to PI3K and DNA damage response（DDR）pathway was 16.1 % and 15.3 %, respectively. Twenty-one and 15 mutations in ctDNA were newly appeared in post- VEGF therapy and post- ICI therapy samples, respectively, 27 mutations（75.0 %）exclusively appeared in different types of treatment. With respect to concordance between ctDNA and tissue DNA, 31.8 %（29/91 genes）of mutations identified in ctDNA were also identified in tissue, whereas 68.2 %（62/91 genes）of the mutations were found only in ctDNA. Interestingly, in 70 patients with ICI-based combination therapy, responders had significantly lower tumor fraction（TF）at baseline when compared non-responders（p=0.04）, leading to significantly better overall survival in responders（p=0.0008）.

Conclusions:

Our findings revealed that many mutations in ctDNA were associated with acquired resistance to VEGF or ICI therapy, leading to be possible targets in clinical trials . TF status can also serve as a predictive marker for response to ICI-based therapy.

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FR2-5

Genomic profiling and clinical utility of circulating tumor DNA in metastatic prostate cancer：SCRUM-Japan MONSTAR SCREEN project

Masaki Shiota [1], Nobuaki Matsubara [2], Taigo Kato [3], Masatoshi Eto [1], Takahiro Osawa [4], Takashige Abe [4], Nobuo Shinohara [4], Koshiro Nishimoto [5], Yota Yasumizu [6], Nobuyuki Tanaka [6], Mototsugu Oya [6], Takao Fujisawa [8], Yoshiaki Nakamura [7], Takayuki Yoshino [7], Norio Nonomura [3]

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Background: Circulating tumor DNA (ctDNA) testing has emerged as a novel tool for cancer precision medicine. This nation-wide, prospective, observational study investigated the genomic profiling and clinical utility of ctDNA in metastatic prostate cancer.

Patients and methods: The patients treated systemically for metastatic castration-sensitive prostate cancer (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC) were included. ctDNA was analyzed with FoundationOne®Liquid CDx at enrollment. In subset of patients, ctDNA after disease progression and tissue were tested by FoundationOne®Liquid CDx and FoundationOne®CDx, respectively.

Results: The frequency of *AR* alterations and homologous recombination deficiency (HRD) was higher in mCRPC compared with mCSPC. Tumor mutational burden was correlated between tissue and pre-treatment ctDNA, as well as between pre-treatment and post-treatment ctDNA. HRD was associated with shorter time to castration resistance in androgen deprivation therapy/combined androgen blockade, but not in androgen receptor pathway inhibitor, compared with non-HRD in mCSPC. Time to treatment failure in patients with *AR* amplification or *AR* W742C/L was shorter compared with patients without *AR* alterations in mCRPC, and differed between abiraterone treatment and enzalutamide treatment.

Conclusions: This study reveals valuable insights in the clinical practice of metastatic prostate cancer. In particular, predictive factors such as HRD in mCSPC and *AR* alterations in mCRPC need to be validated in the future.

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FR2-6

Genomic profiling and clinical utility of circulating tumor DNA in advanced urothelial cancer : SCRUM-Japan MONSTAR SCREEN project

Takahiro Osawa [1], Nobuaki Matsubara [2], Taigo Kato [4], Takashige Abe [1], Nobuo Shinohara [1], Masaki Shiota [3], Masatoshi Eto [3], Koshiro Nishimoto [5], Yota Yasumizu [6], Nobuyuki Tanaka [6], Mototsugu Oya [6], Takao Fujisawa [7], Yoshiaki Nakamura [8], Takayuki Yoshino [8], Norio Nonomura [4]

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Background: In this nation-wide prospective observational study, we performed the exploratory analyses of cross-sectional and serial circulating tumor DNA (ctDNA) measurements to predict clinical outcome and map the evolutionary trajectories of advanced/metastatic urothelial carcinoma (UC) .Patients and methods: We performed targeted sequencing of cross-sectional ctDNA samples from 133 patients with advanced UC (bladder cancer, BC: 74 patients, upper urinary tract cancer, UTC: 68 patients, 9 patients overlapped) . Serial ctDNA samples were collected from 23 patients before and after cisplatin or carboplatin-containing regimens and from 22 patients before and after pembrolizumab. ctDNA was analyzed by FoundationOne®Liquid CDx at enrollment. A subset of patients underwent tissue testing with FoundationOne®CDx and ctDNA analysis with FoundationOne®Liquid CDx at disease progression.Results: In the cross-sectional analysis, patients with high pretreatment ctDNA level were significantly associated with poor overall survival ($p<0.0001$) compared to low ctDNA level. There were 4 gene alterations significantly associated with overall survival: FGF3 and FGF4 amplification and TERT and TP53 mutation has poor prognosis. In addition, the prevalence of KRAS gene alterations was significantly higher in UTC compared with BC ($p<0.05$) . In the sequential cohort, the gene discordance rate before and after cisplatin or carboplatin-containing regimens was 38 % (disappeared: 26 %, appeared: 12 %, respectively) and before and after pembrolizumab was 34 % (disappeared: 16 %, appeared: 18 %, respectively) .Conclusion: This study provided valuable insights into the clinical management of advanced UC. Specifically, pretreatment high ctDNA level was associated with survival outcomes. Although small in number, our exploratory findings warrant validation in future studies of advanced UC ctDNA genomics.

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FR2-7

Final analysis of a postmarketing surveillance for avelumab and axitinib combination therapy for patients with curatively unresectable or metastatic renal cell carcinoma in Japan

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Background: Based on results of the phase 3 JAVELIN Renal 101 trial, avelumab + axitinib (ave+axi) was approved in Japan in Dec 2019 for the treatment of patients (pts) with curatively unresectable or metastatic renal cell carcinoma (CU/mRCC). Due to a limited number of Japanese pts (33) in the ave+axi group, postmarketing surveillance (PMS) was required to evaluate safety and effectiveness in real-world clinical practice in Japan.

Methods: This multicenter, noncomparative, noninterventional, observational PMS was conducted in pts with CU/mRCC and included all pts who received ≧ 1 dose of avelumab from Dec 20, 2019, to Feb 28, 2021. Maximum observation period for each pt was 52 weeks.

Results: Data cutoff for final analysis was Mar 22, 2023; the analysis set included 328 pts. Median age was 70 years (range, 12-89); 228 pts (69.5 %) were ≧ 65 years; 98 pts (29.9 %) were ≧ 75 years. IMDC risk classification populations included were: favorable, 90 pts (27.4 %); intermediate, 149 pts (45.4 %); and poor, 60 pts (18.3 %). Adverse drug reactions of safety specifications were seen in 173 pts (any grade; 52.7 %) and 56 pts (grade ≧ 3; 17.1 %). At 52 weeks, the overall survival rate was 83.7 % (95 % CI, 78.9-87.4), objective response rate was 36.0 % (95 % CI, 30.8-41.4), and disease control rate was 75.6 % (95 % CI, 70.6-80.2).

Conclusions: The PMS final analysis provides insight into baseline characteristics of pts with CU/mRCC who received ave+axi in general clinical practice settings in Japan. Ave+axi safety, tolerability, and effectiveness were comparable to outcomes reported in previous clinical trials.

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