Dosing, safety, and pharmacokinetics of combination therapy with darolutamide, androgen-deprivation therapy, and docetaxel for metastatic hormone-sensitive prostate cancer in the ARASENS study

Ji Sun,[1] Matthew R. Smith,[2] Bertrand Tombal,[3] Maha Hussain,[4] Fred Saad,[5] Karim Fizazi,[6] Cora N. Sternberg,[7] E. David Crawford,[8] Natasha Littleton,[9] Yuan Wang,[10] Weijiang Zhang,[10] Rui Li,[10] Arash Rezazadeh Kalebasty[11]

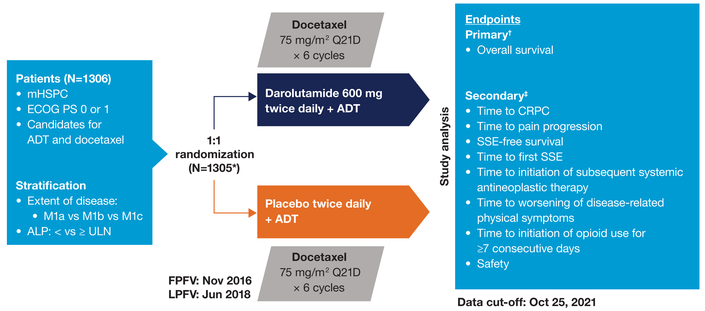
[1]UC San Diego Moores Cancer Center, La Jolla, CA, USA; [2]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [3]Division of Urology, IREC, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [5]University of Montreal Hospital Centre, Montreal, QC, Canada; [6]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France; [7]Englander Institute for Precision Medicine, Weill Cornell Department of Medicine, Meyer Cancer Center, New York-Presbyterian Hospital, New York, NY, USA; [8]UC San Diego School of Medicine, San Diego, CA, USA; [9]Bayer Ltd., Dublin, Ireland; [10]Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA; [11]University of California, Irvine, Orange, CA, USA

INTRODUCTION

- In ARASENS, darolutamide in combination with androgen-deprivation therapy (ADT) and docetaxel significantly reduced the risk of death by 32.5% (hazard ratio 0.68, 95% confidence interval 0.57–0.80; *P*<0.0001) versus placebo plus ADT and docetaxel in patients with metastatic hormone-sensitive prostate cancer (mHSPC)[1]
  - Incidences of treatment-emergent adverse events (TEAEs) were similar between groups
- Darolutamide has a weak induction effect on cytochrome P450 (CYP) 3A4 and an inhibitory effect on organic anion-transporting polypeptide (OATP)1B1 and OATP1B3, whereas docetaxel is a substrate for CYP3A4, OATP1B1, and OATP1B3[2,3]
- Here we present dosing, safety, and pharmacokinetics (PK) analyses evaluating the potential for drug–drug interactions with coadministration of darolutamide and docetaxel with ADT from ARASENS

ARASENS STUDY DESIGN

Global, randomized, double-blind, placebo-controlled, phase 3 study (NCT02799602)[1]



*1 enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations.
†The primary analysis was planned to occur after ~509 deaths.
‡Secondary efficacy endpoints were tested hierarchically.
ADT, androgen-deprivation therapy; ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; mHSPC, metastatic hormone-sensitive prostate cancer; Q21D, every 21 days; SSE, symptomatic skeletal event; ULN, upper limit of normal.

PHARMACOKINETIC EVALUATIONS

First 25 patients: dense PK sampling*	All other randomized patients: sparse PK sampling*
• First day of docetaxel administration (≥14 days after start of darolutamide/placebo): – Pre-dose, after start of docetaxel infusion: 20±10 minutes, 1 hour, 90 minutes, 2, 3, 4, 6, and 8 hours • Two additional samples at two subsequent docetaxel cycles	• Two samples on first day of study drug intake, ≥30 minutes after first dose, approximately 1 hour apart • Two samples during two docetaxel cycles as one sample per cycle at any time relative to study drug administration and after docetaxel administration on same day to determine potential effect of darolutamide on docetaxel PK

Effect of darolutamide on docetaxel PK: Noncompartmental analysis (NCA) from the first 25 patients with dense PK data and population PK (popPK) analysis combining dense and sparse PK data from all patients in ARASENS

Effect of docetaxel on darolutamide PK: Darolutamide exposure in ARASENS (with docetaxel) was compared with that in ARAMIS (NCT02200614; without docetaxel) by popPK meta-analysis of the two studies, with consideration of baseline patient characteristics (age, body weight, region, race)

*Concentrations of diastereomers of darolutamide, metabolite keto-darolutamide, and docetaxel were determined by validated liquid chromatography–tandem mass spectrometry method. Darolutamide concentration was calculated as sum of the diastereomers' concentrations. PK samples were collected from all patients to maintain blinding, but PK samples from the placebo group were not analyzed.

Darolutamide can be effectively and safely administered with docetaxel in patients with mHSPC without clinically relevant changes in the PK of either agent

DOSING AND SAFETY RESULTS

- The median treatment duration was longer with darolutamide versus placebo (**Figure 1**)
- More than twice as many patients receiving darolutamide versus those receiving placebo were still receiving treatment at the data cut-off date of October 25, 2021 (**Figure 2**)
- Most patients (>85%) completed the full 6 cycles of docetaxel in both groups (**Figure 3**)

Figure 1. Median treatment duration

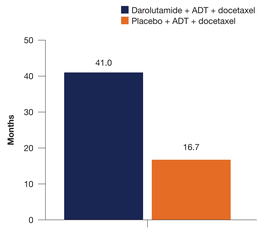


Figure 2. Patients still receiving treatment

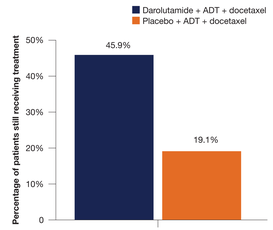
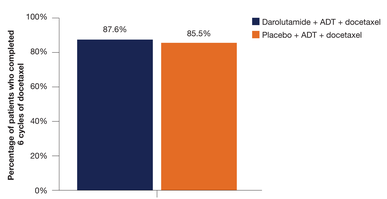


Figure 3. Patients who completed 6 cycles of docetaxel

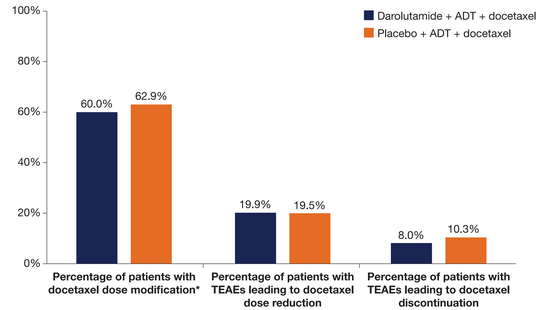


ADT, androgen-deprivation therapy.

Proportions of patients requiring docetaxel dose modifications were similar between treatment groups (**Figure 4**)

- Of docetaxel dose modifications, 46.5% in the darolutamide group and 43.2% in the placebo group were due to TEAEs
- Rates of TEAEs leading to docetaxel dose reduction or discontinuation were similar between treatment groups
  - Decreased neutrophil count was the most common TEAE leading to docetaxel dose reduction (5.4%, 6.0%) and discontinuation of docetaxel (0.8%, 0.5%)

Figure 4. Proportion of patients with TEAEs leading to dose modification, reduction or discontinuation of treatment



*Interruptions/delays or reductions in docetaxel dose. Other reasons for docetaxel dose modifications included investigator discretion, scheduling/holidays, medical procedures, and other medical conditions.
ADT, androgen-deprivation therapy; TEAE, treatment-emergent adverse event.

PHARMACOKINETIC RESULTS
EFFECT OF DOCETAXEL ON DAROLUTAMIDE PK

- PK meta-analysis of ARASENS and ARAMIS, which considered patients' baseline intrinsic characteristics as covariates (e.g., age, body weight, region, race; **Table 1**), indicated a 10% lower $AUC_{0\text{-}12ss}$ of darolutamide in patients receiving docetaxel versus those not receiving docetaxel, which is not considered clinically relevant

Table 1. Comparison of select baseline covariate distributions between ARASENS and ARAMIS

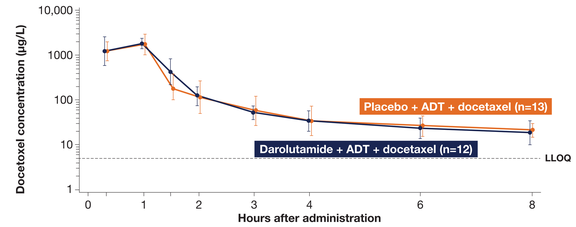
Covariate	ARASENS (n=652)	ARAMIS (n=388)
Age, median (SD), years	67 (7.9)	75.5 (8.1)
Body weight, median (SD), kg	75.4 (16.2)	83.0 (16.8)
Age <65 years, n (%)	243 (37.5)	41 (10.3)
Region = Japan, n (%)	63 (9.7)	61 (15.3)
Region = mainland China, n (%)	105 (16.2)	0
Race = White, n (%)	343 (52.9)	296 (74.4)
Race = Asian, n (%)	230 (35.5)	83 (20.9)

$AUC_{0\text{-}12ss}$, area under the curve from time 0 to 12 hours after nominal twice daily dosing to steady state; PK, pharmacokinetics; SD, standard deviation.

PHARMACOKINETIC RESULTS
EFFECT OF DAROLUTAMIDE ON DOCETAXEL PK

- Docetaxel plasma concentrations with and without darolutamide were overlapping at most time points, indicating no effect of darolutamide on docetaxel PK (**Figure 5**)
- Results of the NCA and popPK analysis were consistent, indicating no clinically relevant effect of darolutamide on docetaxel PK (**Table 2**)

Figure 5. Plasma concentrations (semi-log, geometric means ± SD) of docetaxel on the first day of docetaxel administration after multiple doses of darolutamide or placebo*



*Docetaxel 75 mg/m² was initiated ≥14 days after randomization/start of darolutamide or placebo and administered every 21 days × 6 cycles.
ADT, androgen-deprivation therapy; LLOQ, lower limit of quantitation; NCA, noncompartmental analysis; PK, pharmacokinetics; popPK, population pharmacokinetics; SD, standard deviation

NCA of dense PK data

- No clinically relevant effect of darolutamide was observed on docetaxel PK (**Table 2**)
- A slight numeric increase in docetaxel exposure was observed with darolutamide versus placebo:
  - 15% higher C_{max} and 6% higher $AUC_{0\text{-}tlast}$
  - This small numeric increase is unlikely to be clinically relevant given the variability in docetaxel exposure (coefficient of variation, 23–54%)

Table 2. NCA of docetaxel PK data

Docetaxel PK parameter, geometric mean (CV)	Darolutamide + ADT + docetaxel (n=11*)	Placebo + ADT + docetaxel (n=12*)
$AUC_{0\text{-}tlast}$, µg·h/mL	2.10 (30%)	1.99 (33%)
C_{max}, µg/mL	1.93 (23%)	1.68 (54%)

*Two patients (one in each treatment arm) were excluded from calculation of PK parameters due to errors in drug concentration values.
ADT, androgen-deprivation therapy; $AUC_{0\text{-}tlast}$, area under concentration–time curve from time 0 to time of last concentration above lower limit of quantification; C_{max}, maximum observed drug concentration; CV, coefficient of variation; NCA, noncompartmental analysis; PK, pharmacokinetics.

PopPK analysis of dense and sparse PK data

- PopPK analysis of docetaxel data from 1152 patients indicated docetaxel PK in patients with mHSPC was generally consistent with docetaxel PK reported in the literature[4]
- Docetaxel clearance in the darolutamide plus docetaxel arm was approximately 5% higher than in the placebo plus docetaxel arm, indicating no clinically relevant drug–drug interaction of darolutamide with docetaxel

CONCLUSIONS

- **In patients with mHSPC, darolutamide in combination with ADT and docetaxel increased overall survival with a similar overall incidence of TEAEs compared with ADT and docetaxel, and no drug–drug interactions between darolutamide and docetaxel were observed**
- **The most common reasons for docetaxel dose reduction were known TEAEs of docetaxel**
- **Darolutamide can be effectively and safely administered with docetaxel in patients with mHSPC without clinically relevant changes in the PK of either agent**
- **Darolutamide in combination with ADT and docetaxel should be considered as one of the new standards of care for patients with mHSPC**

References: **1.** Smith MR, et al. *N Engl J Med* 2022;386:1132–1142. **2.** Lee HH, et al. *Mol Cancer Ther* 2015;14:994–1003. **3.** Shore N, et al. *Target Oncol* 2019;14:527–539. **4.** Bruno R, et al. *J Pharmacokinet Biopharm* 1996;24:153–172.

Acknowledgments: We thank the patients and their families, and all investigators involved in these studies. The ARASENS study was supported by Orion Pharma and Bayer. Bart Ploeger and Carsten Zieschang Medical writing support was provided by Michelle McDermott, PharmD, and Alex Morrison, MSc, of OPEN Health Communications (London, UK), with financial support from Bayer HealthCare Pharmaceuticals (Whippany, NJ, USA). Statistical analyses were provided by Jon Moss and Blesson Chacko of BAST Inc Limited, UK, and Bart Ploeger and Carsten Zieschang of Bayer HealthCare Pharmaceuticals.

Disclosures:
JS: Has nothing to disclose. **MRS**: Consulting or Advisory Role - Amgen, Astellas Pharma, Bayer, Janssen Oncology, Lilly, Novartis, Pfizer; Research Funding - Bayer (Inst), ESSA (Inst), Janssen Oncology (Inst), Lilly (Inst), ORIC Pharmaceuticals (Inst). **BT**: Honoraria - Amgen, Astellas Pharma, Bayer, Ferring, Janssen, Myovant Sciences, Pfizer, Sanofi; Consulting or Advisory Role - Astellas Pharma, Bayer, Ferring, Janssen, Myovant Sciences, Pfizer/Astellas, Sanofi, Steba Biotech, Takeda; Speakers' Bureau - Amgen, Astellas Pharma, Janssen; Research Funding - Ferring; Expert Testimony - Steba Biotech; Travel, Accommodations, Expenses - Amgen, Astellas Pharma, Bayer, Ferring, Janssen, Sanofi. **MH:** Advisory Boards - Bayer, GSK, Novartis; Honoraria - Academic CME, AstraZeneca, International Genitourinary Cancer Conference, Merck, MJH Life Sciences, Mubarak Mahdi Almansour; Funding - Arvinas, AstraZeneca, Bayer, Genentech. **FS**: Honoraria - AbbVie, Advanced Accelerator Applications, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen Oncology, Knight Therapeutics, Merck, Myovant Sciences, Novartis, Pfizer, Sanofi; Consulting or Advisory Role - AbbVie, Advanced Accelerator Applications, Astellas Pharma, AstraZeneca/MedImmune, Bayer, Janssen Oncology, Knight Therapeutics, Myovant Sciences, Novartis, Pfizer, Sanofi; Research Funding - Advanced Accelerator Applications (Inst), Astellas Pharma (Inst), AstraZeneca (Inst), Bayer (Inst), Bristol Myers Squibb (Inst), Janssen Oncology (Inst), Merck (Inst), Novartis (Inst), Pfizer (Inst), Sanofi (Inst). **KF**: Honoraria - Astellas Pharma (Inst), Bayer (Inst), Janssen (Inst), Sanofi (Inst); Consulting or Advisory Role - Amgen (Inst), Astellas Pharma (Inst), AstraZeneca (Inst), Bayer, Bristol Myers Squibb (Inst), Clovis Oncology (Inst), ESSA (Inst), Janssen Oncology (Inst), Novartis (Inst), Orion, Pfizer (Inst), Sanofi (Inst); Travel, Accommodations, Expenses - AstraZeneca, Janssen, Merck - for US audiences. **CNS**: Consulting or Advisory Role - Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb/Medarex, Foundation Medicine, Genzyme, Gilead, IMPACT Medical Systems, Incyte, Janssen, Medscape, Merck, Pfizer, Roche, UroToday; **EDC**: Employment - Blue Earth Diagnostics; Leadership - Blue Earth Diagnostics; Consulting or Advisory Role - Bayer, Janssen Oncology, MDxHealth, Pfizer/Astellas, Tolmar; Speakers' Bureau - Bayer. **NL**, **YW**, **WZ**, and **RL** are employees of Bayer HealthCare Pharmaceuticals. **ARK:** Stock and Other Ownership Interests - ECOM Medical; Consulting or Advisory Role - AstraZeneca, Bayer, Bristol Myers Squibb, EMD Serono, Exelixis, Genentech, Gilead Sciences, Immunomedics, Novartis, Pfizer; Speakers' Bureau - Amgen, Astellas Medivation, AVEO, Bristol Myers Squibb, Eisai, AstraZeneca, EMD Serono, Exelixis, Genentech/Roche, Gilead Sciences, Janssen, Merck, Myovant Sciences, Novartis, Pfizer, Sanofi, Seattle Genetics/Astellas; Research Funding - Astellas Pharma, AstraZeneca, Bavarian Nordic, Bayer, BeyondSpring Pharmaceuticals, BioClin Therapeutics, Bristol Myers Squibb, Clovis Oncology, Eisai, Epizyme, Exelixis, Genentech, Immunomedics, Janssen, Macrogenics, Seattle Genetics; Travel, Accommodations, Expenses - Astellas Medivation, AstraZeneca, Bayer, Eisai, Exelixis, Genentech, Janssen, Novartis, Pfizer, Prometheus.

Previously presented at the 2023 American Society of Clinical Oncology Genitourinary Cancers meeting

Corresponding author contact: j2sun@health.ucsd.edu