833P AZD8186, a potent and selective inhibitor of PI3K*β*/*δ*, as monotherapy and in combination with abiraterone acetate plus prednisone (AAP), in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: The PI3K pathway plays an important role in cell growth and survival of *PTEN*-null tumours. An ongoing phase 1/2 study (NCT01884285) previously reported that AZD8186, a potent and selective inhibitor of PI3Kβ (minimal PI3Kδ activity), can be well tolerated in pts with solid tumours; here we present preliminary data in heavily pretreated mCRPC.

Methods: Pts with mCRPC received escalating doses of AZD8186 (5 days on, 2 days off; 2 days on, 5 days off; or continuous schedules) as monotherapy (study Part A) or in combination with AAP (1000 mg qd + prednisone 10 mg qd, study Part C1) until progressive disease (PD) or dose-limiting toxicities. Analyses included tolerability, RECIST tumour response, prostate-specific antigen response, circulating tumour cell counts and cell-free DNA.

Results: Fifty-two pts with mCRPC were treated with AZD8186 as monotherapy (n = 39) or in combination with AAP (n = 13). Prior treatment status: AAP (n = 14), enzalutamide (enza, n = 10), both (n = 21) or AAP/enza-naive (n = 7). Diarrhoea (39%) and nausea (27%) were the most frequently reported adverse events (AEs, all grades) related to AZD8186. Grade 3 AEs of interest included diarrhoea/colitis (10%), which was fully reversible with dose interruption/SoC treatment, and rash (7%). Two (4%) pts had grade 4 AEs (thrombocytopenia, hypokalaemia); no grade 5 AEs. AZD8186 did not appear to alter tolerability of AAP. Among pts with RECIST measurable disease, one had a confirmed partial response (Part C1), 10 had stable disease, nine had PD. Nine (17%) pts had reduction in PSA >30%. Twelve pts completed >16 weeks of treatment, five pts >24 weeks (PTEN-proficient [n = 0], PTEN-deficient [n = 3], PTEN-unknown [n = 2]). Recruitment of pts with PTEN-deficient mCRPC into an expansion phase in combination with AAP is ongoing.

Conclusions: Data from this phase 1/2 study indicates that the tolerability of AZD8186 supports combination treatment with AAP in pts with metastatic prostate cancer. Preliminary evidence of antitumour activity has been observed. Updated results will be presented.

Clinical trial identification: NCT01884285.

Editorial acknowledgement: Medical writing and editorial assistance was provided by Tyrone Daniel from Bioscript Medical (Macclesfield, UK) and funded by AstraZeneca.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: J.S. de Bono: Advisory board member: AZ, GSK, Merck Serono, MSD, Sanofi Aventis, Taiho, Genentech-Roche, Seattle Genetics, Bayer, Endocyte, Shattuck, Harpoon, Pfizer Oncology, Janssen, Menarini, Daiichi; Research support: GSK, Sanofi, Genentech, Daiichi, Taiho, Merck Serono, MSD, Bayer, AZ. A. Hansen: Research support: Genentech/Roche, Merck, GlaxoSmithKline, Bristol Myers Squibb, Novartis, Boston Biomedical, Boehringer-Ingelheim, Karyopharm. A.D. Choudhury: Honoraria: Bayer, Astellas, Janssen. C. Higano: Advisory boards and/or steering committees: Astellas, Bayer, Blue Earth Diagnostics, Clovis Oncology, Ferring, Janssen, Myriad, and Tolmar; Institutional research funding: Aptevo, Aragon, Astellas, AstraZeneca, Bayer, Hoffman LaRoche, Janssen, Medivation, Pfizer; Spouse is a co-founder of, and has a leadership role at, CTI Biopharma. D.E. Rathkopf: Advisory/consulting fees: Janssen; Research funding for institution: AstraZeneca, Astellas Pharma, Celgene, Genentech, Janssen, Medivation, Millenium, Novartis, Pfizer, Roche, Taiho, Tracon. K.B. Wisinski: Advisory board: AstraZeneca. S. Barry, E. de Bruin, W. Brugger, S. Colebrook, T. Klinowska, P.G.S. Mortimer: Employment and stock ownership: AstraZeneca. M. Moschetta: Employee: AstraZeneca. L.L. Siu: Honoraria: AstraZeneca/MedImmune. G. Shapiro: Consulting/advisory relationship: Eli Lilly, Pfizer, G1 Therapeutics, Merck/EMD Serono, Roche, Almac; Research funding: Lilly, Pfizer, Merck/EMD Serono. All other authors have declared no conflicts of interest.