

183MO Capivasertib and fulvestrant (F) for patients (pts) with aromatase inhibitor (AI)-resistant HR+/HER2- advanced breast cancer (ABC): Second progression-free survival (PFS2) and time to first subsequent chemotherapy (TFSC) in the CAPITello-291 trial

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Background: In the phase III CAPITello-291 trial, the addition of capivasertib (a potent, selective pan-AKT inhibitor) to F in pts with AI-resistant, HR+/HER2- ABC, significantly improved PFS compared with placebo + F (hazard ratio [HR] 0.60; 95% confidence interval [CI] 0.51–0.71; $p < 0.001$), including in patients with *PIK3CA/ACT1/PTEN*-altered tumours (HR 0.50; 95% CI 0.38–0.65; $p < 0.001$). We report outcomes after study therapy (data cut-off 15 Aug 2022).

Methods: Details of subsequent anti-cancer treatments were recorded after the progression of disease on study therapy (PFS). PFS2 was a secondary endpoint, defined as the time from randomisation to second progression (i.e. the earliest of either death or a progression event following treatment start after first progression). Time from randomisation to the start of subsequent chemotherapy (TFSC; defined as the first of death or chemotherapy treatment start) was an exploratory endpoint.

Results: 708 pts were randomised to capivasertib + F ($n = 355$) or placebo + F ($n = 353$): 289 pts (40.8%) had *PIK3CA/ACT1/PTEN*-altered tumours (289/602, 48.0% of pts with known tumour sequencing results). At the time of this analysis, 238 (67.0%) pts in the capivasertib + F arm and 264 (74.8%) pts in the placebo + F arm had received subsequent anti-cancer therapy; most commonly cytotoxic chemotherapy (56.1% vs 61.2%), hormonal therapy (27.6% vs 30.3%) and targeted therapy (18.9% vs 25.8%). PFS2 and TFSC favoured capivasertib + F over placebo + F in the overall and *PIK3CA/ACT1/PTEN*-altered populations (Table).

Conclusions: Subsequent treatments were similar between arms, and the benefit of capivasertib + F was retained through PFS2. In addition, capivasertib + F also resulted in a clinically meaningful delay in the initiation of chemotherapy compared to F alone.

Clinical trial identification: NCT04305496.

Editorial acknowledgement: AstraZeneca-funded medical writing support was provided by Suzanne Patel, PhD, from Boldscience Inc. Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: H.S. Rugo: Financial Interests, Personal, Other, Consultancy/advisory support: NAPO, Mylan/Viatris, Daiichi Sankyo, Eisai; Financial Interests, Institutional, Invited Speaker: Novartis, Lilly, Pfizer, OBI Pharma, F. Hoffmann-La Roche AG/Genentech, Inc., Daiichi, AstraZeneca, Gilead Sciences, Inc., Merck; Financial Interests, Institutional, Research Grant: Stemline Therapeutics, Ambray; Non-Financial Interests, Advisory Role, I advise a number of companies without compensation: various. M. Oliveira: Financial Interests, Personal, Advisory Board: AstraZeneca, Daiichi Sankyo / AstraZeneca, Gilead, Lilly, MSD, Relay Therapeutics, Roche, Seagen, Cure Science, iOne, Pfizer; Financial Interests, Personal, Invited Speaker: Eisai, Gilead, Pfizer, Roche, Seagen, AstraZeneca, Lilly, Medscape,

AstraZeneca, AstraZeneca; Financial Interests, Personal, Other, Educational activity: Libbs; Financial Interests, Institutional, Invited Speaker: AstraZeneca, Boehringer-Ingelheim, GSK, Roche, Seattle Genetics, Zenith Epigenetics, Gilead, Ayala Pharmaceuticals, Pfizer; Financial Interests, Invited Speaker: Roche; Non-Financial Interests, Member of Board of Directors, Howell: SOLTI Breast Cancer Research; Other, Travel Grant: Pierre Fabre, Eisai, Gilead, AstraZeneca. S.J. Howell: Financial Interests, Institutional, Sponsor/Funding, Study sponsor. Per patient payments to institution: AstraZeneca; Financial Interests, Institutional, Research Grant: Eli Lilly UK; Financial Interests, Personal, Other, Consulting fees: Pfizer; Financial Interests, Personal, Other, Payment or honoraria for lectures, presentations, speakers bureaus, abstract writing or educational events: Eli Lilly UK, Pfizer Ltd., Novartis, AstraZeneca; Financial Interests, Personal, Other, Travel and accommodation: Novartis; Financial Interests, Personal, Advisory Board, Participation on a Data Safety Monitoring Board or Advisory Board: Eli Lilly UK; Non-Financial Interests, Institutional, Other, Medical writing support (no payments): BOLDSCIENCE. F. Dalenc: Financial Interests, Institutional, Other, Honoraria: Lilly, Gilead, AstraZeneca; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: Daiichi Sankyo, Novartis, Gilead, Pfizer. J. 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Y.H. Park: Financial Interests, Personal, Advisory Board: AstraZeneca, Pfizer, Roche, Novartis, MSD, Daiichi Sankyo; Financial Interests, Personal, Invited Speaker: AstraZeneca, Pfizer, Roche, Novartis, MSD, Daiichi Sankyo; Financial Interests, Institutional, Other, Research Grant: AstraZeneca, Pfizer, Roche, MSD; Financial Interests, Institutional, Invited Speaker: Pfizer; Non-Financial Interests, Principal Investigator: AstraZeneca, Pfizer, Novartis, MSD, Lilly, Roche, Daiichi Sankyo. M. 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Table: 183MO

		Overall population		<i>PIK3CA/ACT1/PTEN</i> -altered population	
		Capivasertib + F (n = 355)	Placebo + F (n = 353)	Capivasertib + F (n = 155)	Placebo + F (n = 134)
PFS2	Events; n (%)	176 (49.6)	207 (58.6)	79 (51.0)	87 (64.9)
	Median; months	14.7	12.5	15.5	10.8
	HR (95% CI)	0.70 (0.57–0.86)		0.52 (0.38–0.71)	
TFSC	Events; n (%)	217 (61.1)	248 (70.3)	103 (66.5)	100 (74.6)
	Median; months	11.0	6.8	11.0	6.0
	HR (95% CI)	0.63 (0.52–0.75)		0.56 (0.42–0.74)	

member: British Journal of Cancer, Asian Journal of Surgery, Asian Journal of Breast Surgery, Translation Breast Cancer Research; Other, Associate editor: Scientific Reports, Breast Cancer Research and Treatment, Cancer Science, Frontiers in Women's Cancer. M. Fulford: Financial Interests, Personal, Full or part-time Employment: AstraZeneca. C. D'Cruz: Financial Interests, Personal, Full or part-time Employment: AstraZeneca; Financial Interests, Personal, Stocks/Shares: AstraZeneca. I. Wadsworth: Other, Personal, Full or part-time Employment: AstraZeneca. N. Turner: Financial Interests, Personal, Advisory Board: AstraZeneca, Lilly, Novartis, Pfizer, Roche/Genentech, GSK, Zentaris pharmaceuticals, Repare therapeutics, GSK, Relay therapeutics, Gilead, Inivata, Guardant, Exact Sciences; Financial Interests, Institutional, Funding: AstraZeneca, Pfizer, Roche/Genentech, Merck Sharpe and Dohme, Invitae, Inivata, Personalis, Natera; Financial Interests, Institutional, Other, provision of materials: BioRad; Financial Interests, Institutional, Other, Provision of assays: Guardant Health. All other authors have declared no conflicts of interest.

<https://doi.org/10.1016/j.esmooop.2024.103205>

184MO First-in-human phase I/IIa study of the first-in-class, next-generation CDK4-selective inhibitor PF-07220060 in combination with endocrine therapy (ET) in patients (pts) with HR+/HER2- metastatic breast cancer (mBC) who progressed on prior CDK4/6 inhibitors (CDK4/6i): Safety and efficacy update

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Background: PF-07220060 is a novel potent oral CDK4i with significant sparing of CDK6. Preliminary safety and dose escalation data from this phI/IIa study were previously presented. Here we report updated safety and efficacy data in pts with HR+/HER2- mBC, who progressed on prior CDK4/6i and ET, treated with PF-07220060 + ET.

Methods: This study in pts with advanced solid tumors was enriched for pts with HR+/HER2- mBC who received ≥2 lines of treatment including ET and CDK4/6i. Prior fulvestrant and chemotherapy were allowed. Study objectives were to assess safety, tolerability, and antitumor activity of PF-07220060 alone and in combination with ET.

Results: At data cutoff (Nov 1, 2023), 33 pts received PF-07220060 (300mg/400mg BID) in combination with letrozole or fulvestrant (Parts 1B + 1C). Median age was 62.0y (range 41–82); ECOG PS was 0 (36.4%) or 1. Median prior lines of systemic therapy (advanced setting) was 4.0 (range 1–11). All pts had prior CDK4/6i treatment, 24 (72.7%) had prior fulvestrant, and 22 (66.7%) had prior chemotherapy in the advanced/metastatic setting. Most frequent treatment-emergent adverse events (TEAEs) were neutropenia (54.5%; 18.2% Grade 3 [G3]), diarrhea (42.4%; 0% G3), and nausea (42.4%; 3.0% G3), with no >G3 TEAEs. Dose modifications due to TEAEs included: 1 (3.0%) pt discontinued PF-07220060, 5 (15.2%) pts had dose reduction, and 10 (30.3%) pts had dose interruptions. In 25 pts with measurable disease who progressed on prior CDK4/6i + ET, 8 (32.0%) had confirmed RECIST v1.1 objective responses (1 CR, 7 PR). Clinical benefit response (CR, PR, or ≥24 wks stable disease) was seen in 20/33 (60.6%) pts. Median progression-free survival was 8.1 months (95% CI: 5.3, 10.9). Confirmed objective responses (PRs) were observed irrespective of ESR1 or PI3K pathway mutations.

Conclusions: PF-07220060 + ET showed a favorable safety profile with few hematologic adverse events and infrequent dose modifications, and promising efficacy despite prior CDK4/6i treatment, irrespective of key mutations.

Clinical trial identification: NCT04557449.

Editorial acknowledgement: Medical writing support, conducted in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines, was provided by Kathleen Richter, PhD and Rachel C. Brown, PhD of Oxford Pharmacogenetics, Inc., Newtown, PA.

Legal entity responsible for the study: Pfizer, Inc.

Funding: Pfizer Inc.

Disclosure: T.A. Yap: Financial Interests, Personal, Other, Consultant: Almac, Aduro, AstraZeneca, Atrina, Axiom, Bayer, Bristol Myers Squibb, Clovis, Cybrexa, EMD Serono, Guidepoint, Ignyta, I-Mab, Janssen, Merck, Pfizer, Repare, Roche, Schrodinger, Varian, Zai Labs, AbbVie, Acvion, Adagene, Amphista, Artios, Athena, Avoro, Baptist Health Systems, BeiGene, Boxer, C4 Therapeutics, Calithera, Cancer Research UK, Diffusion, F-Star, Genmab, Glenmark, GLG, Globe Life Sciences, GSK, Idience, ImmuneSensor, Institut Gustave Roussy, Intellisphere, Kyn, MEI Pharma, Mere, Natera, Nexys, Novocure, OHSU, OncoSec, Ono Pharma, Pegascy, PER, Piper-Sandler, Prolynx, resTORbio, Theragnostics, Versant, Vibliome, Xinthera, ZiehlBio, Radiopharm Theranostics, Sanofi, CUHK Committee, EllipsesLife, LRG1, Panangium, Pliant Therapeutics, Seagen, Synthis, Tessellate Bio, TD2 Theragnostics, Tome Biosciences, Zentaris; Financial Interests, Personal, Other, University of Texas MD Anderson Cancer Center, where I am Medical Director of the Institute for Applied Cancer Science, which has a commercial interest in DDR and other inhibitors (IACS30380/ART0380 was licensed to Artios); MD Anderson Cancer Center, Institute for Applied Cancer Sciences; Financial Interests, Personal, Stocks/Shares: Seagen; Financial Interests, Institutional, Other, Grant/Research support: Bayer, Cytel, EMD Serono, GSK, Karyopharm, Pfizer, Repare, Sanofi, Artios, AstraZeneca, BeiGene, BioNTech, Blueprint, BMS, Clovis, Constellation, Eli Lilly, Forbuis, F-Star, Genentech, Haihe,

ImmuneSensor, Ionis, Ipsen, Jounce, KSQ, Kyowa, Merck, Mirati, Novartis, Ribon Therapeutics, Regeneron, Rubius, Scholar Rock, Seattle Genetics, Tesaro, Vivace, Acvion, Zenith; Financial Interests, Institutional, Other, Grant/Research Support: Acvion; Financial Interests, Institutional, Research Grant: Boundless Bio, Ideaya. M.R. Sharma: Financial Interests, Personal, Other, Research funding/grant support: AbbVie, Adcentrx Therapeutics, Agenesis, Alkermes, Alissa Immune Sciences, ALX Oncology, Artios, Astellas Pharma, AstraZeneca, Black Diamond Therapeutics, Boehringer Ingelheim, Bolt Biotherapeutics, Boundless Bio Therapeutics, Bristol Myers Squibb, Celgene. E.P. Hamilton: Financial Interests, Personal, Other, Research funding/grant support: AbbVie, Accutar Biotech, Acerta Pharma, ADC Therapeutics, Akeso Biopharma, Amgen, Aravive, ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond Therapeutics, Bliss Biopharmaceutical, Boehringer Ingelheim, Bristol Myers Squibb, Cascadia, P. Lorusso: Financial Interests, Personal, Other, Research funding/grant support: Genentech; served as consultant for AbbVie, ABL Bio, Actuate Therapeutics, Agenesis, Amgen, AstraZeneca, Atreca, BAKX Therapeutics, Boehringer Ingelheim, Compass Therapeutics, Cullinan Oncology, DAAN Biotherapeutics, EMD Serono, GSK, I-Mab, ImCh. C. Basu, M. Delioukina, F. Liu, H. Neumann, J. Park: Financial Interests, Personal, Stocks/Shares: Pfizer Inc; Financial Interests, Personal, Full or part-time Employment: Pfizer Inc. A. Giordano: Financial Interests, Personal, Other, Consultant: Pfizer Inc.

<https://doi.org/10.1016/j.esmooop.2024.103206>

185P Safety, tolerability, and antitumor activity of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2+ metastatic breast cancer (mBC) and active brain metastases (BM) in DESTINY-Breast07 (DB-07)

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Background: DEBBRAH, ROSET-BM, TUXEDO-1, and a pooled DB-01, -02, -03 analysis indicate robust efficacy of T-DXd in pts with stable/active BM; however, efficacy in pts with BM is not yet fully established. DB-07 is a phase Ib/II, multicenter, open-label study exploring the safety, tolerability, and antitumor activity of T-DXd alone or in combination with other anticancer agents (NCT04538742). Results are from an interim analysis of the dose-expansion phase of T-DXd monotherapy in pts with active BM.

Methods: Pts had locally assessed HER2+ mBC with measurable disease. No or one prior line of therapy for mBC was allowed; a disease-free interval of ≥12 months from (neo)adjuvant HER2-directed therapy or chemotherapy was required. Pts had untreated BM not requiring local therapy or progressing BM after treatment with local therapy. Ongoing use of systemic corticosteroids (>2 mg dexamethasone daily or equivalent) for control of BM symptoms was exclusionary. Pts received T-DXd 5.4 mg/kg intravenously every 3 weeks. Primary endpoints were safety and tolerability; secondary endpoints included objective response rate (ORR) and progression-free survival (PFS) per RECIST 1.1 and Response Assessment in Neuro-Oncology (RANO)-BM.

Results: Thirty-five pts with active BM were treated (median age 49 years); median follow up was 11.5 months (range 5.3–24.6). As of August 1, 2023, the most common any-grade adverse events (AEs) were nausea (74.3%; Grade 3, 5.7%) and vomiting (45.7%; Grade 3, 2.9%); no Grade ≥4 nausea or vomiting was reported. By RANO-BM, confirmed ORR was 57.1% and PFS rate at 12 months was 74.6% (Table).

Conclusions: The safety profile is consistent with the known profile for T-DXd and data confirm promising efficacy in pts with active BM; a median PFS has not been reached after 11.5 months. Ongoing analyses will provide more mature data.

Clinical trial identification: NCT04538742.

Editorial acknowledgement: Medical writing support, under the direction of the authors, was provided by Katie Ryding, PhD, of Helios Medical Communications.

Legal entity responsible for the study: AstraZeneca.

Funding: This study is sponsored by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

Disclosure: C. Anders: Financial Interests, Personal, Advisory Role: Genentech/Roche, Eisai, Ipsen, Seagen, AstraZeneca, Elucida Oncology, Immunomedics, Athenex, Roche; Financial Interests, Personal, Other, Expenses: Eisai; Financial Interests, Personal, Royalties: Up to Date.com, Jones and Bartlett; Financial Interests, Personal, Other, Honoraria: Eisai, Genentech/Roche, IPSEN, Seagen,