LBA23 **MonarcHER: A randomized phase II study of abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with HR+, HER2+ advanced breast cancer (ABC)**

S.M. Tolaney[1], A.M. Wardley[2], S. Zambelli[3], J. Hilton[4], T. Troso-Sandoval[5], F. Ricci[6], S-A. Im[7], S-B. Kim[8], S.R.D. Johnston[9], A. Chan[10], S. Goel[11], K. Catron[12], Z. Yang[13], C. Gainford[12], F. André[14]

[1]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [2]The Christie NHS Foundation Trust & Division of Cancer Sciences University of Manchester, The NIHR Manchester Clinical Research Facility, Manchester, UK, [3]Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy, [4]Medical Oncology, Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada, [5]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [6]Medical Oncology, Institut Curie, Paris, France, [7]Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [8]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [9]Department of Medicine, Royal Marsden Hospital, London, UK, [10]Medical Oncology, Breast Cancer Research Centre BCRC - WA, Nedlands, Australia, [11]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [12]Oncology, Eli Lilly and Company, Indianapolis, IN, USA, [13]Statistics-Oncology, Eli Lilly and Company, Indianapolis, IN, USA, [14]Breast Cancer Unit, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France

Background: Abemaciclib, an oral selective inhibitor of CDK4 & 6, showed efficacy & tolerability in patients (pts) with HR+, HER2- ABC. In preclinical models, inhibition of CDK4 & 6 by abemaciclib enhanced the activity of HER2-directed agents and re-sensitized resistant tumors to HER2 blockade, suggesting a crosstalk between HER2 signaling and the cyclin D1/CDK4 signaling pathways in HR+ tumors only.

Methods: monarcHER (NCT02675231), a phase II study, compared 3 treatment arms in pts with HR+, HER2+ ABC; arm A (abemaciclib 150mg PO Q12H Days 1-21 of a 21-day cycle + trastuzumab [T] IV infusion Day 1 of 21-day cycle + fulvestrant 500 mg IM Cycle 1 D1 and D15 and Cycle 2 D8, then Q4W), arm B (abemaciclib + T), vs arm C (T + investigator's choice chemotherapy, 21-day cycle). Eligible pts were postmenopausal women, $\geq$2 HER2-directed therapies for ABC, prior T-DM1 and taxane, ECOG PS $\leq$ 1. 237 pts were randomized 1:1:1 and stratified by number of prior systemic

regimens for ABC (2 to 3 vs > 3) and measurable vs nonmeasurable disease. The gated primary objective was to compare investigator assessed PFS of Arm A to C and, if positive, then B to C. Secondary objectives include: OS, objective response rate (ORR), safety, patient reported outcomes, and pharmacokinetics. Primary analysis was planned after approximately 165 PFS events, providing 80% power to detect superiority of Arm A over C, assuming a HR of .667 at 1-sided $\alpha = .1$.

Results: Analysis was performed at 169 events. Median PFS was longer in Arm A vs C (HR [95% CI], 0.673 [0.451 – 1.003]; p = 0.0253; 8.3 vs 5.7 mo). No difference in Arm B vs C (HR [95% CI], 0.943 [0.643 – 1.383]; p = 0.385; 5.7 vs 5.7 mo). ORR was 35.4%, 16.5% and 22.8% in arms A, B, and C respectively. Most common grade 3/4 adverse events (AEs) in Arms A, B, and C were neutropenia (26.9%, 22.1%, and 26.4%), leukopenia (10.3%, 2.6%, and 9.7%), thrombocytopenia (10.3%, 6.5%, and 2.8%), and diarrhea (9.0%, 6.5%, and 2.8%). AE-on treatment related deaths: 2 in arm A, 1 in B, and 1 in C.

Conclusions: The study met its primary endpoint of improved PFS in the ITT population in Arm A over Arm C. Safety data was similar to the known safety profile of abemaciclib.

Clinical trial identification: NCT02675231.

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A.M. 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J. Hilton: Advisory / Consultancy: Eli Lilly and Company; Advisory / Consultancy: AstraZeneca; Advisory / Consultancy: Pfizer; Advisory / Consultancy: Merck; Advisory / Consultancy: Novartis; Advisory / Consultancy, Officer / Board of Directors: BMS. T. Troso-Sandoval: Research grant / Funding (institution): Eli Lilly and Company. S. Im: Advisory / Consultancy, Research grant / Funding (institution): AstraZeneca; Research grant / Funding (institution): Pfizer; Honoraria (self), Advisory / Consultancy, Travel / Accommodation / Expenses: Novartis; Advisory / Consultancy: Eisai; Advisory / Consultancy: Amgen; Advisory / Consultancy: Roche; Advisory / Consultancy: Hanmi. S. Kim: Research grant / Funding (institution): Norvartis; Research grant / Funding (institution): Sanofi-Genzyme; Research grant / Funding (institution): Dingkook Inc. S.R.D. 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Gainford: Shareholder / Stockholder / Stock options, Full / Part-time employment: Eli Lilly and Company. F. André: Research grant / Funding (institution): Eli Lilly and Company; Research grant / Funding (institution), Travel / Accommodation / Expenses: AstraZeneca; Research grant / Funding (institution), Travel / Accommodation / Expenses: GlaxoSmithKline; Research grant / Funding (institution), Travel / Accommodation / Expenses: Novartis; Research grant / Funding (institution), Travel / Accommodation / Expenses: Roche; Research grant / Funding (institution): Pfizer. All other authors have declared no conflicts of interest.