Lerociclib (GT318), a continuously dosed oral CDK4/6 inhibitor, with fulvestrant in HR+/HER2- advanced breast cancer patients: Updated phase II results and dose selection

I. Bulat1, M. Magakelidze2, B. Kra este3, H.T. Arkenau4, C. Murias4, R.D. Baird5, R. Roylan ce2, A.M. Wardley7, A. Crijanovschi1, M. Gogiladze2, Y. Lu8, A. McCullough9, S. Jain1, C.D. W olfgang1, R. Malik1, A.P. Beelen1

1Institute of Oncology, Aresia Exploratory Medicine Research Unit, Chisinau, Moldova; 2Institute of Oncology, Aresia Exploratory Medicine LLC, Tbilisi, Georgia; 3Department of Medical Oncology, MHIAT for Women's Health – Nadoeho, Softis, Bulgaria; 4Biostatistics, Sarah Cannon Research Institute, London, UK; 5Department of Oncology, Cambridge Cancer Centre, Cambridge, UK; 6Department of Oncology, NIH University College London Hospitals Biomedical Research Centre, London, UK; 7NIHR Manchester Clinical Research Facility at The Christie, The Christie Clinical Research Centre, Manchester Academic Health Science Centre, Manchester, UK; 8Biostatistics, G1 Therapeutics, Inc., Research Triangle Park, NC, USA; 9Research and Development, G1 Therapeutics, Inc., Research Triangle Park, NC, USA

Background: CDK4/6 inhibitors (CDK4/6i) combined with fulvestrant (F) are the established standard of care for HR+/HER2- advanced breast cancer (ABC). Two of the three approved CDK4/6i cause dose-limiting neutropenia requiring a drug holiday, and the third is limited by gastrointestinal (GI) toxicity. Lerociclib is a potent, selective CDK4/6i that is dosed continuously. Initial data presented at SABCS 2019 indicated that lerociclib + F had low rates of GI toxicity and Grade 4 neutropenia, and antitumor activity was comparable with other CDK4/6i + F combinations.

Methods: This phase I/II study assessed lerociclib with 500 mg F in patients (pts) with HR+/HER2- ABC that had followed progressing endocrine therapy. Up to 2 prior chemotherapies in the advanced setting in patients with hormone-sensitive disease (eligibility calculation), and 1 prior in phase I of the study. Participants were allocated to receive lerociclib + F or CDK4/6i exposure within each phase II. The objectives were to evaluate DLTs, safety, tolerability, PK, preliminary efficacy, and determine the recommended dose of lerociclib when combined with F for future randomized trials.

Results: As of Jan 31, 2020, 110 pts had been enrolled across doses of 200–650 mg once daily and 100–400 mg twice daily (BID). Two of 150 pts received 150 mg for a median 6.9 (range 1.7–27.8) months, with median age of 55 years (range 33–84). ECOG of 0 (85%), and median 1 line (range 0–5) of prior anticancer therapy in the advanced setting. The most common lerociclib-related AEs at 150 mg BID were neutropenia (50%), diarrhea (26%), and anemia (20%). Rates of Grade 3 and 4 neutropenia were 30% and 5%, respectively. There were no reports of Grade ≥ 3 nausea, vomiting, or diarrhea. Nineteen pts at 150 mg BID were evaluable for tumor response based on RECIST version 1.1. Six pts (32%) had a confirmed PR; 9 (47%) had SD; 4 (21%) had PD. The CBR (CR+PR+SD ≥ 4 weeks) was 74% (14/19).

Subgroup analyses revealed that pts who received no prior chemotherapy in the advanced setting (8/19 pts) had the highest CBR of 89%.

Conclusions: Lerociclib 150 mg BID dosed continuously demonstrated a differentiated profile with low rates of GI toxicity and Grade 3/4 neutropenia. Efficacy compares favorably to approved CDK4/6 + F combinations.

Clinical trial identification: NCT02983071.

Legal entity responsible for the study: G1 Therapeutics, Inc.

Funding: G1 Therapeutics, Inc.

Disclosure: B. Kraeste: Research grant (funding) (institution): G1 Therapeutics; Research grant/ funding (institution): Lilly; Research grant (funding) (institution): Roche; Honoraria (self): Celgene; Honoraria (self): Novartis; Honoraria (self): AstraZeneca; Advisory/Consultancy, Research grant/funding (institution): AstraZeneca.


A.M. Wardley: Advisory/Consultancy: Pfizer; Advisory/Consultancy, Travel/Accommodation/Expenses: Daiichi Sankyo; Advisory/Consultancy, Research grant/funding (institution): AstraZeneca; Research grant/funding (institution): Novartis; Research grant (funding) (institution): Roche; Honoraria (institution): Pfizer; Honoraria (institution): MSD; Honoraria (institution): Novartis; Advisory/Consultancy, Travel/Accommodation/Expenses: G1Therapeutics; Travel/Accommodation/Expenses: Roche; Travel/Accommodation/Expenses: AstraZeneca; Research grant/funding (institution): Novartis; Research grant (funding) (institution): Boehringer Ingelheim; Research grant/funding (institution): Boehringer Ingelheim; Research grant (funding) (institution): G1 Therapeutics; Research grant (funding) (institution): Carrick Therapeutics; Research grant/funding (institution): Roche; Research grant (funding) (institution): Roche.

R. Roylance6: Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution): Novartis; Advisory/Consultancy, Speaker Bureau/Expert testimony: Novartis; Advisory/Consultancy, Speaker Bureau/Expert testimony: Roche; Research grant/funding (institution): G1 Therapeutics; Research grant (funding) (institution): Lilly.

F. Cardoso: Advisory/Consultancy: Amgen; Advisory/Consultancy, Speaker Bureau/Expert testimony: Novartis; Advisory/Consultancy, Speaker Bureau/Expert testimony: Roche; Advisory/Consultancy, Speaker Bureau/Expert testimony: Pfizer; Advisory/Consultancy: Guardant Health; Advisory/Consultancy, Speaker Bureau/Expert testimony: Roche.

P. Marchetti: Advisory/Consultancy, Speaker Bureau/Expert testimony: Novartis.


M. Campone: Shareholder/Stockholder/Stock options, Full/Part-time employment: Roche.

S. Jain: C.D. Wolfgang: Full/Part-time employment: G1 Therapeutics. R. Malik: Full/Part-time employment: G1 Therapeutics. A.P. Beelen: Full/Part-time employment: G1 Therapeutics. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.435

Resistance to CDK4/6 inhibitors: Clinical practice of liquid biopsy to identify KRAS-mutations in ctDNA and overexpression of CDK9 in plasma derived exosomes

L. Raimondi, M. Pietranera, G.P. Spinelli

1Department of Medical-Surgical Sciences and Biotechnologies, UOC Territorial Oncology - Aprilia (IT) – ASL Latina, University of Rome “Sapienza”, Latina, Italy; 2Centro Medico Diagnostico, Salus, Civitavecchia, Italy

Background: Despite therapeutic improvements, all patients (pts) sooner or later acquire resistance to CDK4/6 inhibitors. Mutations in KRAS have been thought to be the main cause of resistance in several cancers, but have not been analysed extensively yet in breast cancer in the era of Palbociclib+Fulvestrant (P+F). In our study, using liquid biopsy, we correlated the presence of KRAS-mutated exosomes and plasma-derived exosomes with resistance to P+F as first line metastatic treatment in HR+/HER2-Metastatic Breast Cancer (MBC).

Methods: A total of 948 blood samples were collected from 106 pts with HR+/HER2- MBC treated with P+F as first-line metastatic therapy (Dec17-Mar20). KRAS ctDNA levels in plasma were determined in Bio-Rad QX200 ddPCR system; we used exoNexy kit to analyze CDK4/6 expression.

Results: KRAS mutations were detected in ctDNA of 54% (57pts) of pts before starting P+F treatment: detection of KRAS ctDNA was significantly associated with resistance, recurrence and prognosis (p<0.001). At 18-month follow up [1-NA], pts with KRAS-mutated ctDNA and overexpression of CDK9 had a median PFS of 3 months [1-6months,95%CI 0.8-3.6] contrary to ones with no detection of KRAS ctDNA whose PFS had not yet been reached (p<0.001). We demonstrated the association between the sum of copies/ml of KRAS-mutated ctDNA and tumor burden: higher number of metastatic sites correlated with higher mutant ctDNA copy number (p<0.0001). Moreover, lower LMR (<5.0) was associated with progression disease within 12months (p<0.001).

Conclusions: Despite the study’s limitations, our findings suggest detection of KRAS ctDNA levels, which correlates with overexpression of CDK9, enables to predict the onset of resistance to P+F treatment. Monitoring KRAS status with liquid biopsy, we could predict who will take advantage from P+F, offering highly individualized treatment plans. With a careful treatment selection, we could decrease wastes of resources ensuring the best pts’ quality of life.

Legal entity responsible for the study: ASL Latina - Università di Rome “Sapienza”.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.437