KURZPROTOKOLL
VIOLETTE

Öffentlicher Titel	Phase II Studie zu Olaparib, AZD6738 und Adavosertib bei dreifach negativem Brustkrebs
Wissenschaftl. Titel	A Phase II, Open Label, Randomised, Multi-centre Study to Assess the Safety and Efficacy of Agents Targeting DNA Damage Repair in Combination with Olaparib versus Olaparib Monotherapy in the Treatment of Metastatic Triple Negative Breast Cancer Patients Stratified by Alterations in Homologous Recombinant Repair (HRR)-related Genes (including BRCA 1/2)
Kurztitel	VIOLETTE
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, Pharma-Studie, zweiarmig
Studienphase	Phase II
Erkrankung	Geschlechtsorgane: Brustkrebs: Zweitlinie oder höher
Einschlusskriterien	- Informed consent prior to any study specific procedures - Male or female >=18 years of age - Progressive cancer at the time of study entry - stologically or cytologically confirmed TNBC at initial diagnosis with evidence of metastatic disease and HER2 negative as per ASCO-CAP HER2 guideline recommendations 2013 - Patients must have received at least 1 and no more than 2 prior lines of treatment for metastatic disease with an anthracycline (eg, doxorubicin, epirubicin) and/or a taxane (eg, paclitaxel, docetaxel) unless contraindicated, in either the neo-adjuvant, adjuvant or metastatic setting - Confirmed presence of qualifying HRR mutation or absence of any HRR mutation in tumour tissue by the Lynparza HRR assay - At least one measurable lesion that can be accurately assessed at baseline by computed tomography (CT) (magnetic resonance imaging [MRI] where CT is contraindicated) and is suitable for repeated assessment as per RECIST 1.1 - Patients must have normal organ and bone marrow function measured within 28 days prior to randomization (defined in the protocol) - ECOG PS 0-1 within 28 days of randomisation - Postmenopausal or evidence of non-childbearing status for women of childbearing potential (contraception restrictions apply to participants and their partners) - Patient is willing to comply with the protocol requirements - Life expectancy of >=16 weeks
Ausschlusskriterien	- ytotoxic chemotherapy, hormonal or non hormonal targeted therapy within 21 days of Cycle 1 Day 1 is not permitted. Palliative radiotherapy must have been completed 21 or more days before Cycle 1 Day 1. The patient can receive a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study as long as these were started at least 5 days prior to study treatment - More than 2 prior lines of cytotoxic chemotherapy for metastatic disease (prior treatments with hormonal, non-hormonal, biologics or the combination of an aromatase inhibitor and everolimus are not counted as a prior line of therapy) - Previous randomisation in the present study - Previous treatment with a PARP inhibitor (including olaparib) or other DDR inhibitor (unless less than 3 weeks duration and at least 12 months has elapsed between the last dose and randomization) - Exposure to a small molecule IP within 30 days or 5 half-lives (whichever is longer) prior to randomisation. The minimum washout period for immunotherapy shall be 42 days - Patients with second primary cancer (exceptions defined in the protocol)

- Mean resting corrected QTc interval using the Fridericia formula (QTcF) >470 msec/female patients and >450 msec for male patients (as calculated per institutional standards) or congenital long QT syndrome
- Any of the following cardiac diseases currently or within the last 6 months: unstable angina pectoris, congestive heart failure >= Class 2 as defined by the New York Heart Association, acute myocardial infarction, conduction abnormality not controlled with pacemaker or medication (patients with a conduction abnormality controlled with pacemaker or medication at the time of screening are eligible), significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)
- Concomitant use of known strong or moderate cytochrome P (CYP) 3A inhibitors, strong or moderate CYP3A inducers, or sensitive CYP3A4 substrates or CYp3A4 substrates with a narrow therapeutic index
- Persistent toxicities (>= CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 2 peripheral neuropathy
- Major surgery within 2 weeks of starting study treatment: patients must have recovered from any effects of any major surgery
- Immunocompromised patients, eg, human immunodeficiency virus (HIV)
- Patients with known active hepatitis (ie, hepatitis B or C)
- Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non malignant systemic disease or active, uncontrolled infection
- Patients with symptomatic uncontrolled brain metastases
- Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication
- Patients with a known hypersensitivity to olaparib, adavosertib, AZD6738, or any of the excipients of the products
- Pregnant or breast feeding women

Alter	18 Jahre und älter
Molekularer Marker	HER2/neu neg. Triple neg (HER2/ER/PR neg) ER/PR neg.
Prüfzentren	**Agaplesion Markus Krankenhaus** (Geschlossen) Wilhelm-Epstein-Straße 4 60431 Frankfurt am Main PD Dr. med. Marc Thill Tel: 069 95332228 Fax: 069 95332733 marc.thill@fdk.info
Sponsor	Astra Zeneca (Hauptsponsor)
Registrierung in anderen Studienregistern	EudraCT 2017-002361-22 ClinicalTrials.gov NCT03330847 (primäres Register)