Ixazomib (MLN9708) in Combination with Carboplatin in Pretreated Women with Advanced Triple Negative Breast Cancer

Protocol Number: AGMT_MBC-10 (CARIXA)

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Protocol Synopsis:

Indication:	Advanced (locally advanced inoperable or metastatic) triple negative breast cancer (mTNBC) progressing after first-line therapy
Study design:	open-label phase I/II study
Planned sample size:	Phase I: 9 to 24 patients Phase II: 41 patients
Duration:	Q3 2016 - Q2 2019 (expected)
Study medication:	Ixazomib (MLN9708), Carboplatin
Treatment-line:	beyond first-line
Recruitment:	2 patients (as of March 2017)
Estimated number of sites:	
Phase I:	6 selected AGMT-centers in Austria
Phase II:	approximately 11 AGMT-centers in Austria

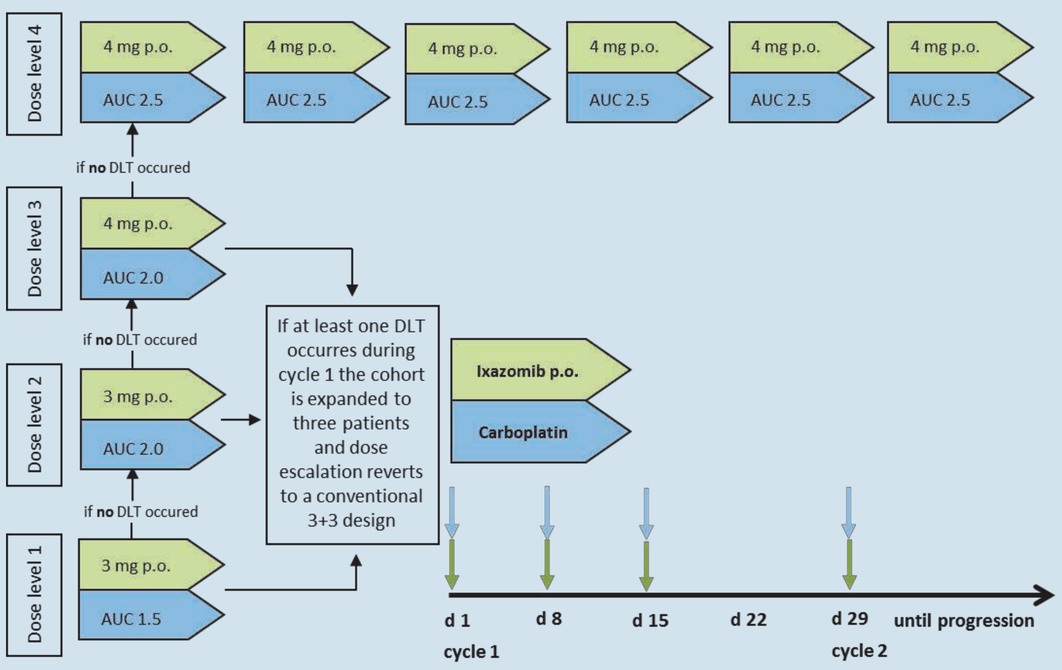
Phase I

Primary objective:	Determination of MTD (maximum tolerated dose) and DLTs (dose limiting toxities)
Secondary objectives:	Safety and tolerability

Phase II

Primary objective:	Overall response rate
Secondary objectives:	Clinical benefit rate (CR, PR or SD for 24 weeks) Progression free survival (PFS) Safety profile Quality of Life

Study Design—Enrollment Phase I:



DLT - Dose Limiting Toxicity:

- Any grade 3/4 non-hematologic toxicity (excluding alopecia)
- Grade 3 or greater nausea and/or emesis
- Grade 3 or greater diarrhea
- Grade 2 peripheral neuropathy with pain or polyneuropathy ≥ grade 3
- Neutropenia grade 4 for more than 7 days
- Febrile neutropenia grade 3
- Thrombocytopenia grade 4
- Thrombocytopenia grade 3 with bleeding

Moderate Toxicity:

- Any grade 2 non-hematologic toxicity (excluding alopecia)
- Any grade 3 hematologic toxicity

Dosing Regimen:

Phase I: In the **accelerated dose-escalation** phase, a single-patient cohort per dose level will be enrolled, until one dose limiting toxicity (DLT) or 3 moderate toxicities are observed during cycle 1, or until dose level 4 is reached. At this dose level, the cohort is expanded to three patients and dose escalation reverts to a conventional 3+3 escalation design.

Beginning with the 2nd cycle an intrapatient dose escalation is allowed to reduce the number of patients treated at sub-effective doses within the phase I part of the trial. This is separate from the alternate dose escalation design of the phase I part.

Phase II: After establishing a MTD in phase I, accrual continues to evaluate the efficacy and safety of the combination. A total of 41 patients will be included.

Inclusion Criteria (selected):

- Female patients, age ≥ 18 years
- Triple negative subtype defined as the absence of staining for estrogen receptor (IHC <1%), progesterone receptor (IHC <1%) and HER2/neu (IHC 0 - 1+, or 2+ if FISH-test is negative, or ISH ratio of < 2.0 between Her2 gene copy number and centromere of chromosome 17 or a copy number of 4 or less)
- At least one measurable lesion according to RECIST 1.1 criteria
- At least one prior line of chemotherapy for metastatic or locally advanced disease or disease progression within 12 months of completion of adjuvant chemotherapy

Exclusion Criteria (selected):

- Radiation of the target lesion or metastatic bone lesions within the last 4 weeks prior to randomization
- Prior radiation to ≥ 30% of bone marrow
- Concurrent cancer therapy (chemotherapy, immunotherapy or biologic therapy) or concurrent treatment with an investigational drug or participating in another clinical trial
- Pretreatment with a platine derivate or with a proteasome inhibitor
- Active bacterial, viral or fungal infection
- Clinically apparent brain metastases or evidence of spinal cord compression

An academic clinical trial
Sponsor: Arbeitsgemeinschaft medikamentöse Tumortherapie gemeinnützige GmbH, Clinical-Scientific Director: R. Greil