SUPPLEMENTARY ONLINE MATERIALS

SOLTI NeoPARP: A phase II randomized study of two schedules of iniparib plus paclitaxel versus paclitaxel alone as neoadjuvant therapy in patients with triple-negative breast cancer

Corresponding author: Dr. Antonio Llombart-Cussac, Medical Oncology, Arnau de Vilanova Hospital, Valencia, Spain; e-mail: allombart1@yahoo.com; telephone number: +34699433392; fax number: +34963513435

PATIENTS AND METHODS

Patients

Centralized confirmation of the triple-negative status was required and performed at the pathology laboratory of the Center Jean Perrin (Dr. Penault-Llorca; Clermont-Ferrand, France). The primary tumor was required to be ≥2 cm in diameter, measured by physical examination and mammography (mandatory), plus either breast and axilla ultrasonography or MRI. Additional inclusion criteria included: ECOG performance status of 0 or 1, absolute neutrophil count ≥1.5 x 10^9/L, platelets count ≥100 x 10^9/L, hemoglobin ≥ 9 g/dL, serum bilirubin ≤1.0 time the upper limit of normal (ULN) or <1.5 ULN due to Gilbert's syndrome, ALT and AST ≤1.5 x ULN, and creatinine clearance ≥60 mL/min.

Patients with metastatic, locally advanced (any T4 including inflammatory or any N3) or multicentric breast cancer, as well as concomitant bilateral breast cancer, or history of contralateral breast cancer were not candidates for the study. Other exclusion criteria included: any prior treatment for primary breast cancer; other malignancy 5 years

before randomization, except adequately treated in situ uterine carcinoma or non melanomatous skin cancer; and any severe or uncontrolled medical condition.

Statistical Analysis

The sample size calculation was based on the Simon's two-stage minimax design [1], assuming a 28% pCR rate in the control (PTX) arm based on a previous study by Green et al [2]. The null hypothesis (H0) that the true response (pCR) rate was ≤20% versus the alternative hypothesis (Ha) that the true response (pCR) rate was ≥40% was to be tested. The significance level (i.e., the probability of rejecting H0 when H0 is true) was 5% with 90% power. Based on this, a total of 135 patients (45:45:45) were to be randomized and treated.

An intermediate analysis was planned for the first 24 patients treated and evaluable for pCR in each iniparib arm (ie, surgery performed and anatomo-pathological results available or patients with PD during the study treatment period). If ≤ 5 pCRs of 24 were observed in either experimental arm during this period, accrual to that arm would be stopped. Investigational arms achieving ≥ 6 pCRs of 24 were to continue recruitment up to a total of 45 treated patients. At the end of the study, ≥ 14 pCRs among the 45 patients were required for each investigational arm to recommend further investigation of the combination. Finally, a safety assessment in the first 6 patients receiving treatment in each experimental arm was predefined. Dose-limiting toxicity definitions by NCI CTC 4.02 were used.

The analysis was based in the ITT population: all randomized patients who had given their informed consent and for whom there was a confirmation of successful allocation of a randomization number through the IVRS. This population was used for the efficacy analysis. All efficacy analyses were based on the treatment arm assigned by IVRS.
Evaluable Patients (EP) population for pathologic response: This population included all treated patients with assessment at surgery. Patients who prematurely discontinued

treatment due to lack of efficacy or no response to treatment were included in the evaluable population and were considered as non-responders. This population was used for the supportive efficacy analysis on pCR. Safety population: A subset of randomized patients who received at least one (even incomplete) dose of the study treatments. This population was used for the safety analysis. All analyses using this population were based on the treatment actually received.

REFERENCES SUPPLEMENTARY ONLINE MATERIALS

1. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials, Volume 10, Issue 1, March 1989, Pages 1-10.
2. Green MC, Buzdar AU, Smith T et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J Clin Oncol. 2005;23:5983-92.