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Circadian - circadian rhythm impact on triple negative breast cancer (tnbc) response to neoadjuvant immunotherapy– a feasibility randomized trial

Guedes A*[1], M.J. Oliveira[2], S. C. Silva[1], J. Cabral[1], I. I.L. Leao[1], C. P. Marques[1], A. F. Baptista Capela[1]

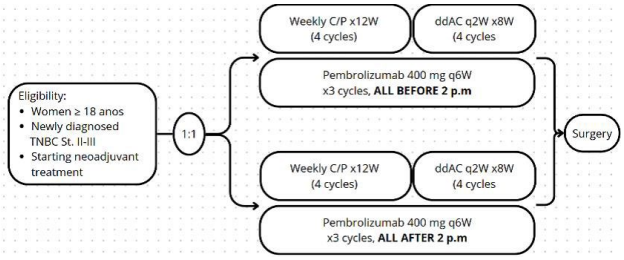
[1]Medical Oncology Department, Portugal

[2]i3S - Institute for Research and Innovation in Health of the University of Porto, Portugal

There is an unmet need regarding biomarkers of response to immune checkpoint inhibitors (ICI). Recently, a retrospective-studies based meta-analysis revealed improved survival and response rates in patients receiving morning versus afternoon ICI infusions. This may be related to circadian regulation of immune-cell functions and trafficking and unveiling these potential regulation mechanisms may lead to new biomarkers of response and therapeutic modulation. We aim to prospectively confirm the influence of ICI infusions' time-of-day on TNBC response to neoadjuvant treatment and explore the biological determinants behind it.

CIRCADIAN is a prospective randomized clinical trial designed to evaluate the impact of pembrolizumab infusions' time-of-day on pathological complete response (pCR) rate among TNBC patients undergoing neoadjuvant treatment. Patients will be randomized 1:1 to receive all neoadjuvant pembrolizumab cycles (400 mg every 6 weeks) before versus after 2 p.m. Subjects will be stratified based on clinical stage at diagnosis (St. II vs III). Primary outcome will be pCR rate. As a secondary outcome, we will assess for treatment related toxicity. For planned exploratory circadian rhythm evaluation, daily body temperature and salivary cortisol variation will be measured before each ICI infusion and the Munich Chronotype Questionnaire (MCTQ) will be applied. To assess for emotional stress, physical exercise habits, stimulating substances use and light exposure, patients will also be subjected to the Distress Thermometer and a lifestyle questionnaire. For planned exploratory biomarker research, tumor infiltrating lymphocytes (TILs) analysis will be performed on the initial diagnostic biopsy and after surgery, on residual tumor (in patients not achieving pCR). Cytokine quantification and bulk RNA sequencing plus flow cytometry studies for immune populations profiling will be performed on peripheral blood, at baseline and before surgery, to check for potential biomarkers of circadian modulation.

Recruitment started on September 2024, and is expecting to continue until September 2025. This study has been approved by the ethics committee.



C/P: carboplatin AUC 1.5 and paclitaxel 80 mg/m2 on D1, D8, D15 q21 days.

ddAC: doxorrubicin 60 mg/m2 eand cyclophosphamide 600 mg/ m2, q2 weeks (dose dense).