

Scientific Abstract

Phase II, Single Arm, Single Institution Clinical Trial of Docetaxel and Doxorubicin in combination with local administration of Ad5CMV-p53 (RPR/INGN201) in Locally Advanced Breast Cancer

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Locally Advanced Breast Cancer (LABC) accounts for 5% to 15% of newly diagnosed breast cancer cases in the United States and 40% to 60% of new cases in non-industrialized countries. Patients with LABC have a poor prognosis when treated by surgery, radiotherapy or both. The five-year overall survival (OS) rate of patients treated with surgery or radiotherapy is less than 20%.

In the last 15 years the management of locally advanced breast cancer (LABC) has changed and primary or induction chemotherapy (IC) is presently part of the multimodality approach to this entity. Clinical and pathological response to IC represent the most important prognostic factor in LABC. Many attempts have been made to improve pathological complete remission rate; mainly they have focused on the use of non-cross resistant chemotherapy combinations and more intense induction regimens. The majority of these approaches have failed to demonstrate any significant advantage over conventional doxorubicin-based IC. These results have prompted the search for possible molecular determinants of chemoresistance to be utilized as targets for new therapeutic strategies. Among them, p53 alterations have been documented with higher frequency in LABC (50% to 55%) compared to early breast cancer (25% to 30%) suggesting that this may be a late phenomenon in breast cancer tumorigenesis. The majority of preclinical data also suggest that loss of p53 function confers chemoresistance and radioresistance. From preclinical and *in vivo* models, reintroduction of wtp53 has been demonstrated associated with increased drug sensitivity (in particular to doxorubicin and docetaxel).

The rationale of this study is to increase sensitivity to IC by injecting adenoviral-p53 (Ad5CMV-p53) directly into the primary breast lesion. This strategy should allow enhanced complete remission rates compared to standard chemotherapy translating in improved survival for this poor prognosis group of patients. The primary objective is to determine the therapeutic efficacy and safety of docetaxel plus doxorubicin given as an every 3-week regimen together with Ad5CMV-p53. Biological phenomena associated with this strategy (i.e. apoptosis, inhibition of angiogenesis) will be evaluated as possible surrogate endpoints of response.

Patient eligibility for the trial includes documented stage III A-B (excluding inflammatory breast carcinoma) or localized stage IV (ipsilateral supraclavicular lymph nodes) breast cancer that are candidate for IC. The strategy is to administer IC, a combination of doxorubicin and docetaxel along with two injections of intralesional Ad5CMV-p53. This approach is repeated every three weeks for 4 cycles before definitive surgery.

A maximum of 60 patients will be enrolled in the trial, with an assumption of 30% pCR rate with the new combination treatment, the sample size will provide 82% power to rule out an alternative rate of 15% (0.05 Type I error).