

# Enhancing Treatment Response in Relapsed/Recurrent Osteosarcoma with Hydroxychloroquine



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## PROPOSED TREATMENT

Incorporate hydroxychloroquine (HCQ), approved for the treatment of malaria, into the recommended treatment combination of gemcitabine and docetaxel for patients with relapsed/recurrent disease to improve therapy efficacy in OS patients.

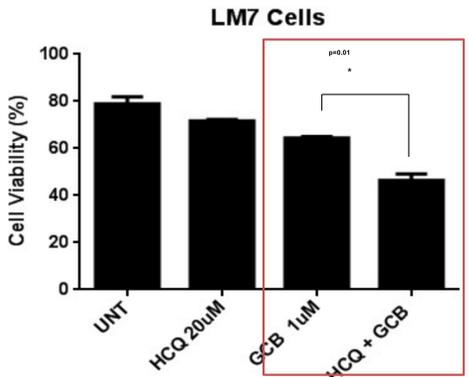


Fig.2 Decreased viability of LM7 OS cells and enhanced efficacy of GCB treated cells upon addition of HCQ

Autophagy is a survival mechanism that protects OS cells from dying upon stressful conditions such as chemotherapy, often leading to relapsed/recurrent disease. We have previously shown that gemcitabine (GCB) induces autophagy in various OS cells (LM7, one of them) and that blocking autophagy using HCQ enhanced the efficacy of gemcitabine (GCB) (Fig. 2), one of the known drugs recommended as second-line therapy in OS.

Thus, we believe that the addition of HCQ as part of the treatment plan in OS may prove fruitful.

Based on these data, we developed a first-in-kids Phase I/II clinical trial exploring the feasibility, safety and potential efficacy of HCQ in combination with GCB and docetaxel in relapsed/recurrent OS patients. The proposed treatment has the potential to immediately impact the care of children and adolescents with OS by rapidly augmenting efficacy of the current chemotherapeutic treatment. As all three drugs are FDA approved, this novel therapy can be readily available to all patients.

## SUMMARY STATEMENT

### Evaluating the efficacy of hydroxychloroquine as an additional drug to enhance treatment response of gemcitabine and docetaxel in 30 pediatric and adolescent patients with relapsed/recurrent osteosarcoma

## DISEASE/CONDITION

Osteosarcoma (OS) is an orphan disease affecting approximately 400 children and adolescents in the US each year. It almost always metastasizes to the lungs which often results in a fatal outcome for both children and adults

First signs of OS include:

- Intermittent pain around affected area, exacerbated with weight bearing
- Limp
- Pathologic fracture after trauma or fall

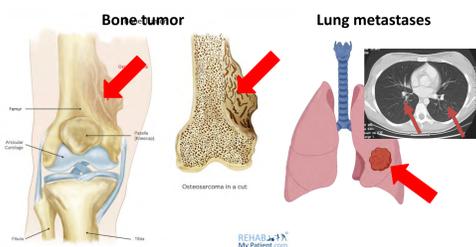


Fig. 1 Osteosarcoma primary bone tumor (left) and pulmonary metastases (right).

Patients with relapsed/recurrent disease have limited therapeutic options and long-term survival rates are less than 20%.

## CURRENT TREATMENT

Current standard treatment of OS includes combinations containing anywhere from two to seven drugs, often resulting in severe long term side effects.

Overall treatment includes:

- Neoadjuvant chemotherapy
- Surgery
- Adjuvant chemotherapy

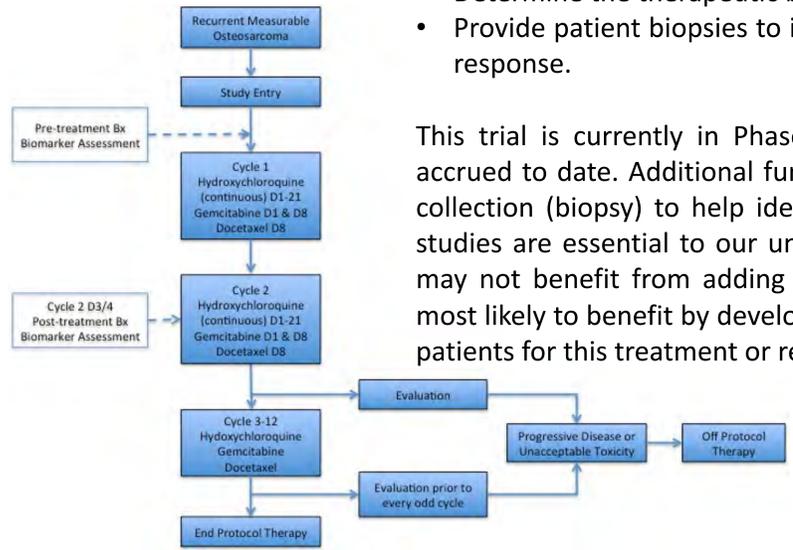
Despite aggressive chemotherapy and successful control of the primary tumor, treatment options for patients who relapse are limited.

## PROJECT

A Phase I/II clinical study to investigate the safety and efficacy of combining therapy HCQ plus gemcitabine and docetaxel and to identify potential biomarkers of response/resistance in pediatric and adolescent patients ( $\geq 12$  yrs) with relapsed/recurrent OS.

This ongoing trial will enroll up to 30 patients (25 on Phase 2 dose expansion) with relapsed/recurrent OS in order to:

- Determine the therapeutic benefit of blocking autophagy in OS patients.
- Provide patient biopsies to identify potential biomarkers associated with response.



This trial is currently in Phase 2, and a total of 17 patients have been accrued to date. Additional funding will support the continuation of tissue collection (biopsy) to help identify potential predictive biomarkers. These studies are essential to our understanding of why certain patients may or may not benefit from adding HCQ. If we can identify which patients are most likely to benefit by developing biomarkers, this could be used to select patients for this treatment or related clinical trials in the future.

If successful, this research has the potential to improve survival for pediatric and adolescent patients with OS.



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