LOR-253 is an anticancer small molecule that is currently in a Phase I clinical study in patients with advanced or metastatic solid tumours. LOR-253 has a novel anticancer mechanism based on chelation of intracellular labile zinc, induction of the tumour suppressor Kruppel-like factor 4 (KLF4). In preclinical studies, LOR-253 has shown potent anticancer activity against several cancers, including non-small cell lung cancer (NSCLC) and colon cancer, without significant toxicity. To support the clinical development of LOR-253 in combination with chemotherapy, we investigated the effect of dose scheduling of LOR-253. LOR-253 chemotherapy agents are anticipated to be administered in combination with 5-fluorouracil (5-FU), oxaliplatin, docetaxel, docetaxel, and cisplatin and cisplatin. In vitro with docetaxel, paclitaxel, or cisplatin for two days followed by increasing concentrations of LOR-253 (0.0026uM–50uM) for concurrent studies, or treated 48h later with increasing LOR-253 concentrations for sequential studies. After 5 days, cell proliferation analysis of LOR-253 plus docetaxel against H226 tumours in mice treated with repeat concentrations of LOR-253 plus chemotherapy drugs demonstrate strong anti-cancer activities in NSCLC and colon cancer, providing support for the design of LOR-253 combination strategies for treatment of these cancers.

In vivo H226 xenograft combination studies

**Introduction**

- LOR-253 is a second generation novel chemical entity currently in Phase I Clinical trial study in patients with advanced or metastatic solid tumours.
- Treatment with LOR-253 mono-therapy in colon and NSCLC xenograft mouse models and cell lines demonstrates efficacy.
- To support the clinical development of LOR-253 in combination with chemotherapeutics, we investigated the effect of dose scheduling of LOR-253 plus chemotherapy agents in NSCLC (H226) and colon cancer (SW620) cell lines.
- In initial in vitro studies were conducted examining LOR-253 in combination with multiple chemotherapeutic agents clinically relevant to either NSCLC or colon cancer.
- In vivo ED₅₀ studies (defined as the effective dose at which 50% tumour inhibition was achieved) were carried out for the chemotherapeutic agents utilized in combination with LOR-253.
- LOR-253 and docetaxel were used in vivo in combination studies in an H226 xenograft mouse model and LOR-253 and oxaliplatin were used in vivo in combination studies in an SW620 xenograft mouse model.

The present studies investigate the scheduling options for combination therapy involving LOR-253 plus chemotherapy on anti-cancer activity in NSCLC (H226) and colon cancer (SW620) cells, which will be used in the planning of future clinical studies.

**Methods**

- LOR-253 IC₅₀ was determined previously. *P<0.05.*
- Parameter optimization and establishment of in vitro cell viability was conducted using the MTT (3- [4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay. All animal studies were approved by the Institutional Animal Care and Use Committee at Lorus Therapeutics.

**Summary of Results**

- Synergy was observed when LOR-253 is used in sequential treatment with docetaxel, paclitaxel or cisplatin in combination with oxaliplatin or docetaxel, in H226 cells in vitro.
- Synergy was also observed when LOR-253 is used in sequential or concurrent treatment with oxaliplatin and in concurrent treatment with 5-FU or CPT-11, in SW620 cells in vitro.
- Sequential treatment with a sub-ED₅₀ dose of oxaliplatin followed by the optimal dose of LOR-253 in a SW620 xenograft model resulted in significant anti-cancer activity. Significant results were also observed when the reverse sequence of treatment was administered.
- Significant anti-cancer activity was observed in an H226 xenograft model where treated sequentially with the ED₅₀ dose of docetaxel, followed by the sub or optimal sub-dose of LOR-253. LOR-253 treatment resulted in tumour regression and in colon cancer. LOR-253 and oxaliplatin combination therapy demonstrated strong anti-cancer activities in NSCLC and colon cancer, providing support for the design of LOR-253 combination strategies for treatment of these cancers in future clinical studies.