EFFICACY STUDY OF CELON PHARMA FGFR KINASE INHIBITOR IN TWO PATIENT-DERIVED TUMOUR XENOGRAFT (PDTX) MODELS

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INTRODUCTION

A number of malignancies are associated with altered fibroblast growth factor receptor (FGFR) signaling resulting from mutation, amplification or overexpression of the FGFR genes. Solid tumors with amplification of *FGFR2* was shown in less than 10% of gastric cancers and 20% of non-small cell lung (NSCLC) cancers [1-5]. The Celon Pharma lead compound, named CPL-304-110, is a potent and selective inhibitor of FGFR1-3 kinases. Here, we tested this inhibitor in two of Patient-Derived Tumor Xenograft (PDTX) models with amplification of *FGFR2*. Use of PDTX models yields more reliable results than cell xenografts models during *in vivo* preclinical evaluation, because this kind of tumors better reflect neoplasms developed in patients, both in histological and molecular characteristic.

The aim of this study was to determine the antitumor effect of CPL-304-110 in two PDTX models with *FGFR2* amplification.

MATERIALS AND METHODS

PDTX Models
Two PDTX models derived and proprietary to Crown Biosciences, Inc., were chosen: LU6429, a non-small cell lung cancer (NSCLC) and GA1224, a gastric cancer.

Table 1. Characteristic of PDTX models

Model ID	Tumor type	Ethnicity	FGFR status	AZD4547	Pathology diagnosis
LU6429	Lung cancer, NSCLC	Caucasian	*FGFR2* slightly amplification	sensitive	75 yr old male ex smoker (20yrs), squamous cell carcinoma
GA1224	Gastric cancer, adenocarcinoma	Asian	*FGFR2* amplification	sensitive	76 yr old male, poorly differentiated adenocarcinoma of gastric cardia with hepatic metastases

Tumor Inoculation
Fragments of fresh surgical primary human tumor samples were implanted subcutaneously in both flanks of 1-2 immunocompromised female MF-1 nude (LU6429 model) or BALB/c nude (GA1224) mice. When tumors reached the exponential growth phase tumors were removed from donor mice, reduced into small fragments, and serially transplanted subcutaneouslly in new recipient mice for tumor development.

Study Design
When average tumor size reached approximately 100-150mm^3, mice were randomised into 4 groups for LU6429 model and 4 groups for GA1224. Each group contained 10 mice. The day of grouping was denoted as day 0. Dosing was started on day 1. Mice were dosed orally, twice daily, at an interval of 12 hours, for three weeks with vehicle placebo (2%NMP/33%PEG300/65%H2O) or CPL-304-110 at three dose levels: 30, 40 and 50mg/kg.

Tabele 2. Group Assigment and Treatment Plan of each PDTX model

Group	N	Compound	Dose Level (mg/kg)	Dosing Route	Dosing Volume (ml/kg)	Dosing Schedule
1	10	Vehicle - placebo	-	p.o.	10	BID*21
2	10	304-110	30	p.o.	10	BID*21
3	10	304-110	40	p.o.	10	BID*21
4	10	304-110	50	p.o.	10	BID*21

Observation
The body weights of the mice were monitored daily. Tumor size was measured three times weekly after randomization. The tumor volumes were expressed in mm^3 using the formula: TV = 0,5 a x b, where a and b are the long and short diameters of the tumor, respectively. Tumor volumes (V) and percentage tumor growth inhibition (%TGI) were used for the evaluation of antitumor efficacy. After finished dosing, mice were observed for one additional week.

RESULTS

GA1224 and LU6429 *in vivo* response to CPL-304-110

GA1224 model - significant reduction in tumor growth resulting in stabilization of tumor growth was seen following treatment with all three doses of CPL-304-110. During the treatment phase, tumor regression was observed in all treatment groups. There was statistically significant inhibitory effect of treatment on tumor growth for CPL-304-110 at all three doses when compared with the vehicle group (two-way ANOVA, p value < 0,001). During the 7-day treatment free observation period, no tumor regrowth was observed in all treatment groups.

LU6429 model - during the treatment phase, there was statistically significant inhibitory effect of treatment on tumor growth for CPL-304-110 when compared with the vehicle group (two-way ANOVA, p value <0,001) in LU6429 model. During the 7-day treatment free observation period, tumor regrowth was observed in all treatment groups in a dose-dependent manner. Two animals in Group 1 on day 13 with oversized tumor were humanely euthanized prior to termination day of vehicle group.

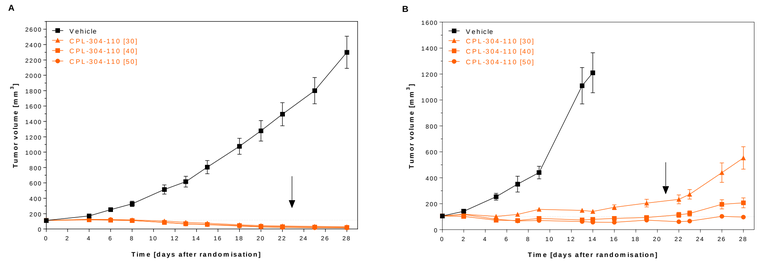

Figure 1. Tumor volume (A) GA1224 model, (B) LU6429 model. Details the mean tumor volume of each study groups; data presents as mean ±SEM; the start of treatment free observation period is marked with black arrow.

Antitumor activity of CPL-304-110 in PDTX models with *FGFR2* amplification

To evaluate antitumor activity, tumor growth inhibition (TGI) was calculated according with formula: TGI = (1-(Ti-T0)/(Ci-C0)) x 100%, where Ti and Ci is the mean tumor volumes of the treatment and control groups as the measurement day; T0 and C0 is the mean tumor volumes of the treatment and control groups on day 0. Celon's CPL-304-110 exibited stronger tumor suppressive activity in gastric cancer PDTX model, compared to lung cancer PDTX with *FGFR2* amplification.

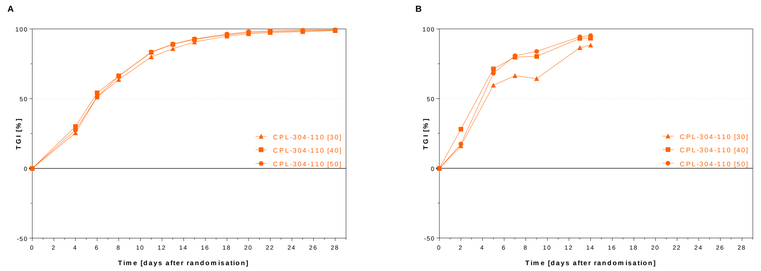

Figure 2. *In vivo* Tumor Growth Inhibition (TGI, %); (A) GA1224 model, (B) LU6429 model.

RESULTS

Body weight

Celon's compound (CPL-304-110) was generally well tolerated in both PDTX models at all three dose levels. No significant body weight loss or adverse clinical signs were observed in the majority of the mice of LU6429 model during the dosing phase, apart of one mice from Group 2 which was found dead on the day of termination (day 28), but no abnormalities were observed at necropsy. Since GA1224 model is a cachexic model, moderate body weight loss was observed in the vehicle group as well as treatment groups. During the dosing phase, two mice in Group 4 had dosing breaks for 2-4 days due to body weight loss.

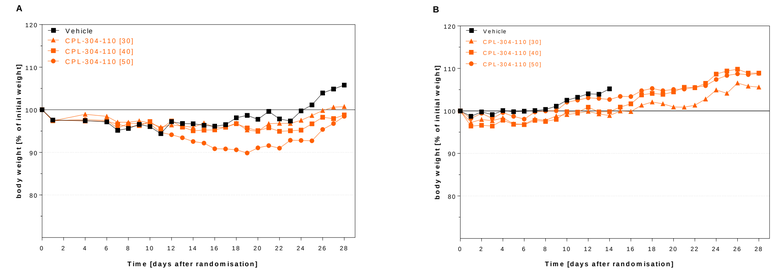

Figure 3. Relative body weight (**A**) GA1224 model, (B) LU6429 model

SUMMARY

A statistically significant effect in tumor growth over the course of the study was observed with CPL-304-110 treatment at all doses when compared with vehicle control in both models. During the treatment free period, tumor regrowth was observed in LU6429 in a dose dependent manner whereas no regrowth was observed for any of the treatment groups in GA1224 model.

CONCLUSIONS

Oral administration of FGFR kinase inhibitor CPL-304-110 resulted in strong antitumor efficacy in both FGFR2-dependent xenograft models. The activity of CPL-304-110 in PDTX models qualifies it for the consideration as a drug in clinical use for cancer patients with lung and gastric *FGFR2* amplification.

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