A Phase 1 study of enadenotucirev, an oncolytic Ad11/Ad3 chimeric group B adenovirus, administered intravenously – Analysis of disease control and repeat cycle cohorts in patients with metastatic colorectal cancer (mCRC)

Marta Gil-Martín1, Antonio Cubillos2, Jean-Pascal Machiels2, Sylvie Rottey1, Feby Mardjauli, Karen Geboes3, Ramon Salazar2, Christopher Elliss2, John Beadle2, Kerry Fisher2, Christine Blanee4, Emiliano Calve5
1 Early Clinical Research Unit, Institut Català d’Oncologia, Hospital Clinic, Hospital Clínic de Barcelona, Spain. 2 St.Mart, Centro Integral Oncológico Clara Campell, Hospital Madrid Noja Sancheiezmo, Madrid, Spain. 3 Christopher Elliss Laboratory, University of Cambridge, Cambridge, UK. 4 Department of Medical Oncology, Hospital General Universitari Joan XXIII, Tarragona, Spain. 5 PSI-OXUS Therapeutics Limited, Milton Park, Abingdon, United Kingdom.

1. BACKGROUND
Enadenotucirev (EnAd or ColoAd1) is a tumour selective chimeric Ad11/Ad3 adenovirus that was developed using a process of DNA-directed Replication-Enhanced Adenovirus (DREA) that has demonstrated oncolytic activity in a range of tumor models and Phase 1 studies show high levels of replication in normal and non-carcinoma cells, and cell killing for a broad range of epithelially derived tumor cell lines with little replication in normal and non-carcinoma cells. Studies suggest that the presence of neutralizing antibodies against group B adenoviruses is low2, and pre-clinical work has further shown that EnAd retains oncolytic activity in the presence of fresh whole human blood1, suggesting that EnAd may be particularly suited to intravenous (i.v.) delivery compared to other oncolytic viruses.

2. STUDY DESIGN
EnAd has demonstrated preclinical activity in a range of tumor models and Phase 1 studies show high levels of replication in normal and non-carcinoma cells. Fever is a common side effect of EnAd treatment, and preclinical work has further shown that EnAd retains oncolytic activity in the presence of fresh whole human blood1, suggesting that EnAd may be particularly suited to intravenous (i.v.) delivery compared to other oncolytic viruses.

3. ANALYSES IN DOSE EXPANSION AND REPEAT CYCLE COHORTS
Once enrolled, the dose recommended for Phase II studies was 6.125 x 10^14 vp. The majority of patients (8/14) enrolled in the Expansion cohort did not progress to the next dose level and median time to progression was 3 cycles (range 0-6). The antibody titre was determined at a cut point on an MSD ELISA.

4. METHODOLOGY
Antibody assays were performed on serum samples collected at day 1 before i.v. treatment, and at days 22, 61 and 120 post first dose of EnAd.

5. PATIENT CHARACTERISTICS AND EXPOSURE
Data was collected for all patients, but few samples were collected beyond day 61. Proportional decrease in CEA levels was observed in all patients over time (p<0.0001).

6. METABOLIC RESPONSE – PET IMAGING
PET scans were performed before treatment and at days 8 and 61 post first dose of EnAd.

7. REPLICATION IN TUMOUR TISSUE
Biopsies were taken from inflammatory wall metastasis 16 days after last of 3 doses of 6x10^12 vp (days 1,3,5). Following a first cycle of EnAd, there is an increase in anti-EnAd antibody titre, which remains raised and relatively constant following successive cycles of EnAd, over the measured time period.

8. EXPLORATORY LABORATORY RESULTS
Compliance with a pan hexon monoclonal antibody (ab8251) in a GCP compliant laboratory using an automated protocol was carried out with a pan hexon monoclonal antibody (ab8251) in a GCP compliant laboratory using an automated protocol.

9. SAFETY SUMMARY
Tumour response assessed according to RECIST.

10. CONCLUSIONS
The administration of repeat cycles of EnAd is feasible every 21 days at the dose of 6x10^12 vp administered IV.

REFERENCES

Figure 1. Anti-EnAd antibody titres

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Results were measured by an MSD ELISA.

Carcinoembryonic antigen (CEA) and circulating tumour cells (CTC) were measured in blood samples at pre-treatment and at days 22, 61 and 120 after first dose of EnAd.

Analysis of metabolic response by FDG-PET

Follow-up safety & progression

Followed by dose expansion with 10-fold increase until MTD or MFD

PET: Phase I dose expansion stage

PET: Phase II dose expansion stage

Events were mostly NCI-CTCAE Grade 1 or 2

Conclusive results on the safety and tolerability of EnAd administered by i.v.

A new i.v. product, EnAd, was developed using a process of DNA-directed Replication-Enhanced Adenovirus (DREA) that has demonstrated oncolytic activity in a range of tumor models and Phase 1 studies show high levels of replication in normal and non-carcinoma cells, and cell killing for a broad range of epithelially derived tumor cell lines. Fever is a common side effect of EnAd treatment, and preclinical work has further shown that EnAd retains oncolytic activity in the presence of fresh whole human blood, suggesting that EnAd may be particularly suited to intravenous (i.v.) delivery compared to other oncolytic viruses.

With the exception of the repeat cycle cohort, the patients were not clothed to progression and received only one or two cycles of EnAd.

Assessment of disease control and repeat cycle cohorts in patients with metastatic colorectal cancer (mCRC).