PHASE 1 STUDY OF ODM-203, A SELECTIVE DUAL FGFR/VEGFR INHIBITOR, IN PATIENTS WITH ADVANCED SOLID TUMOURS

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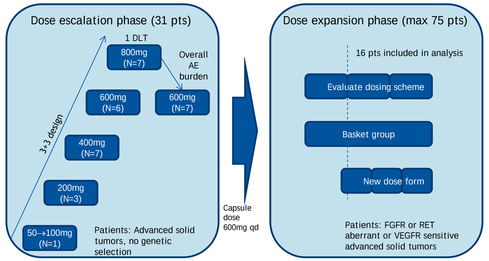
Introduction

Inhibitors of fibroblast growth factor receptors (FGFR) are being developed for treatment of solid tumours, including cholangiocarcinoma (CCA) and urothelial carcinoma, with FGFR genetic alterations. ODM-203 is a small molecule with balanced inhibitory effects on both FGFR 1-4 and VEGFR 1-3 subtypes. We present updated results from the first-in-man study with focus on patients with cholangiocarcinoma.

Study Design

The KIDES study is an open, non-randomized, multicenter first-in-man study of ODM-203 in patients with advanced solid tumors. In a 3+3 dose escalation design, 31 patients received ODM-203 at doses between 50-800mg daily in a 4 week cycle. In the ongoing expansion phase of the study data are available for a further 16 patients who received ODM-203 to further evaluate the recommended phase 2 dose and dosing scheme.

Figure 1. KIDES study outline



Study Objectives

- Safety and tolerability
- Identify maximum tolerated dose (MTD)
- Identify recommended phase 2 dose (RP2D)
- Pharmacokinetics
- Initial indications of target interaction and tumor response

Patient selection

Patients with advanced solid tumors, without alternative treatment options, ECOG 0-1 with organ function within defined limits. During dose escalation there was no requirement for relevant genetic aberration. Patients in dose expansion are required to have tumors that either harbour activating FGFR or RET genetic aberrations (based on local screening) or anticipated VEGFR sensitivity.

Endpoints/measures

Safety: Adverse events (CTCAE), safety labs, ECHO/MUGA, ECG, vitals

Target interaction: Phosphate, blood pressure, soluble markers (FGF23, VEGF etc.) tumor response every 8 weeks (RECIST 1.1)

The study is ongoing at 7 sites in Spain, Finland, France, Denmark, UK and Italy

Data cut-off Dec 2016

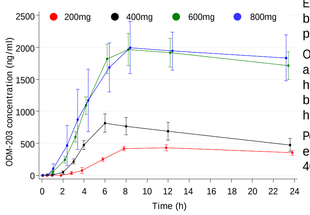
Results

As of 5th October 2016 a total of 47 patients had been treated with ODM-203 to 8 weeks or disease progression. Ongoing cohorts are confirming the dose and dosing schedule and implementing a new formulation.

Table 1. Baseline characteristics

		N (%)	Primary tumour	N (%)
Age, median (range) years		56 (28-80)	Cholangiocarcinoma	12 (25.5)
Gender	Male	19 (40.4)	Colorectal	9 (19.1)
	Female	28 (59.6)	Sarcoma	5 (10.6)
Race	Caucasian	45 (95.7)	Thyroid	4 (8.5)
ECOG			Breast	4 (8.5)
	0	24 (51.1)	Lung	3 (6.4)
	1	23 (48.9)	RCC	3 (6.4)
			Other	7 (14.9)

Figure 2. ODM-203 Day 1 mean concentrations



Exposure increased with dose but was variable between patients.

ODM-203 absorption was slow and prolonged. Elimination half-life is difficult to assess but appears to exceed 40 hours.

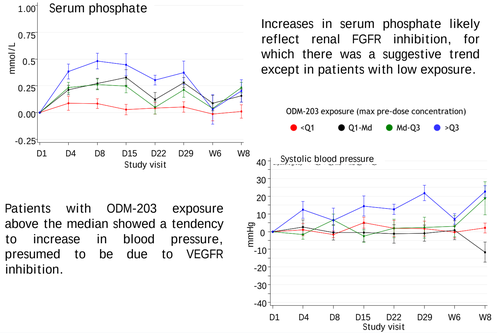
Potentially therapeutic exposures were achieved at 400mg qd upwards .

Target interactions

Dose interruptions for the management of increased bilirubin probably affected the size of pharmacodynamic changes. There was evidence of activity on both FGFR and VEGFR pathways.

Figure 3. Biomarkers of FGFR and VEGFR pathways

Change from baseline. Data presented by quartile of ODM-203 plasma exposure



Increases in serum phosphate likely reflect renal FGFR inhibition, for which there was a suggestive trend except in patients with low exposure.

Patients with ODM-203 exposure above the median showed a tendency to increase in blood pressure, presumed to be due to VEGFR inhibition.

Safety and tolerability

Table 2. Common adverse events in >10% of patients on ODM-203

Preferred Term*	Total (N=47) n (%)	400 MG (N=7) n (%)	600 MG (N=29) n (%)	800 MG (N=7) n (%)	Gr 3-4 AE All doses n (%)
Hyperbilirubinemia	32 (68.1)	5 (71.4)	20 (69.0)	7 (100)	21 (44.7)
Diarrhea	27 (57.4)	3 (42.9)	20 (69.0)	4 (57.1)	2 (4.3)
Arthralgia	18 (38.3)	2 (28.6)	12 (41.4)	4 (57.1)	2 (4.3)
Jaundice	17 (36.2)	3 (42.9)	10 (34.5)	4 (57.1)	2 (4.3)
Fatigue	15 (31.9)	1 (14.3)	11 (37.9)	3 (42.9)	2 (4.3)
Stomatitis	15 (31.9)	1 (14.3)	10 (34.5)	4 (57.1)	
Asthenia	15 (31.9)	2 (28.6)	10 (34.5)	3 (42.9)	1 (2.1)
Dry mouth	15 (31.9)	1 (14.3)	14 (48.3)		
Decreased appetite	15 (31.9)	2 (28.6)	11 (37.9)	2 (28.6)	
Epistaxis	14 (29.8)	1 (14.3)	9 (31.0)	3 (42.9)	
Alopecia	14 (29.8)	1 (14.3)	8 (27.6)	5 (71.4)	1 (2.1)
Weight decreased	13 (27.7)	3 (42.9)	9 (31.0)	1 (14.3)	
Palmar-plantar erythro-dysesthesia syndrome	12 (25.5)	1 (14.3)	10 (34.5)	1 (14.3)	2 (4.3)
Hyperphosphatemia	10 (21.3)	2 (28.6)	5 (17.2)	3 (42.9)	
Dysgeusia	10 (21.3)	1 (14.3)	7 (24.1)	2 (28.6)	
Anemia	8 (17.0)	1 (14.3)	6 (20.7)	1 (14.3)	2 (4.3)
Vomiting	8 (17.0)	1 (14.3)	7 (24.1)		1 (2.1)
Myalgia	8 (17.0)	1 (14.3)	5 (17.2)	2 (28.6)	1 (2.1)
Nausea	8 (17.0)	1 (14.3)	7 (24.1)		
Headache	8 (17.0)	1 (14.3)	5 (17.2)	2 (28.6)	
Cough	6 (12.8)		5 (17.2)	1 (14.3)	
Nasal dryness	6 (12.8)	1 (14.3)	5 (17.2)		
Constipation	6 (12.8)		4 (13.8)	2 (28.6)	
Hypertension	6 (12.8)		6 (20.7)		1 (2.1)
Onycholysis	6 (12.8)		4 (13.8)	2 (28.6)	
Abdominal pain	6 (12.8)		6 (20.7)		
Back pain	6 (12.8)		4 (13.8)	1 (14.3)	
Paronychia	5 (10.6)	1 (14.3)	4 (13.8)		2 (4.3)

200mg dose group is included in the total number of AEs.

All patients reported at least 1 AE. One DLT of corneal punctate keratitis was reported at 800mg but MTD according to protocol was not identified. 6 patients discontinued ODM-203 due to possibly related adverse events (corneal punctate keratitis, fatigue, paronychia and cheilitis, pulmonary embolus, anemia and Takotsubo syndrome).

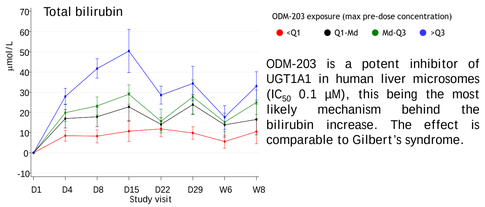
Sevelamer was introduced for increased phosphate to 7 patients, although no patients required dose interruption or reduction for this effect.

Increases in bilirubin were universal at the highest dose but did not lead to permanent ODM-203 discontinuation in any patient.

Patient tolerability on prolonged dosing was largely determined by accumulation of grade I/II events such as stomatitis, diarrhea and arthralgia.

Increases in serum total bilirubin were commonly observed, that were both greater in magnitude and speed of onset at higher doses. The increases were primarily in the unconjugated fraction, not associated with transaminase increases and reversed rapidly on interruption of ODM-203. Temporary discontinuation or dose reduction for increased bilirubin was common above 400mg/day.

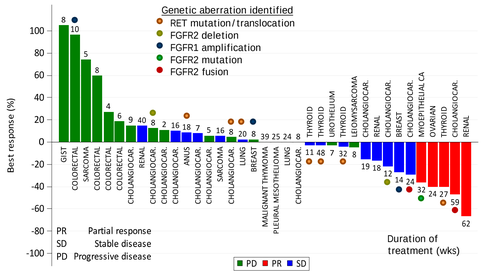
Figure 4. Change from baseline in bilirubin



ODM-203 is a potent inhibitor of UGT1A1 in human liver microsomes (IC_{50} 0.1 µM), this being the most likely mechanism behind the bilirubin increase. The effect is comparable to Gilbert's syndrome.

Anti-tumor activity

Figure 5. ODM-203 best tumor response (RECIST)



Patients were generally not selected by molecular screening and tumor genetic profiling data are incomplete.

5 partial responses were seen with durable stable disease in a number of other patients. 2 patients have received ODM-203 treatment for >1 year. Reductions in target lesions were seen in patients with significant FGFR genetic aberrations as well as in patients with VEGFR-sensitive tumors without FGFR genetic aberration.

Activity in cholangiocarcinoma

Table 3: baseline characteristics of cholangiocarcinoma patients

		N (%)
Age, median (range) years		55 (28-71)
Gender	Male	5 (41.7)
	Female	7 (58.3)
Race	Caucasian	12 (100)
ECOG	0	4 (33.3)
	1	8 (66.7)
Prior Chemotherapy lines		
	≥3	7 (58.3)
	2	2 (16.7)
	1	3 (25.0)

12 patients with cholangiocarcinoma have been treated with ODM-203 to date: 3 patients had potentially activating FGFR2 genetic aberrations (a further single amino acid deletion was considered not of relevance). Most patients had received extensive prior chemotherapy.

One patient with FGFR2 fusion had a prolonged partial response, treated for more than 1 year

Figure 6. Best tumor response (RECIST) in patients with cholangiocarcinoma

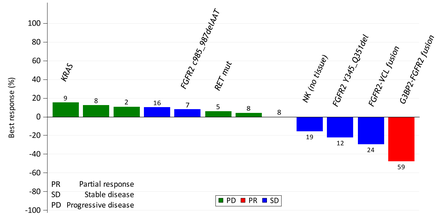
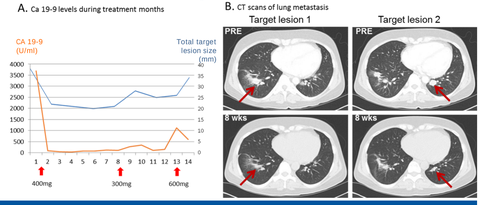


Figure 7. Treatment response in a patient with FGFR2 fusion

A 51 year old female with 9 year history of metastatic cholangiocarcinoma. Previous therapies included multiple chemotherapy agents such as the combination of cisplatin and gemcitabine, gemcitabine and capecitabine, panitumumab, paclitaxel, capecitabine and paclitaxel, and sorafenib. Treatment response lasted >1 year and was associated with changes in CA 19-9 levels.



Conclusions

- Adequate exposure was achieved but was somewhat variable using the capsule formulation. A new formulation is being tested in the study.
- Adverse events reported are mostly typical for FGFR or VEGFR inhibitors. Anticipated phosphate and blood pressure increases were less pronounced than with selective inhibitors although may have been somewhat affected by dose interruptions due to bilirubin increase. Diarrhea and mucocutaneous events occurred commonly after several weeks treatment, and responded to temporary discontinuation or dose reduction of ODM-203.
- Bilirubin increases due to UGT1A1 inhibition by ODM-203 were very common but not associated with other signs of liver injury and responded rapidly to dose interruptions.
- Durable tumor responses have been seen in both FGFR aberrant and VEGFR sensitive (FGFR negative) tumors, confirming clinically important activity on both FGFR and VEGFR pathways.
- There was preliminary evidence of activity in patients with cholangiocarcinoma harboring FGFR2 fusion or an activating FGFR2 mutation.

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