Poster #370P

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

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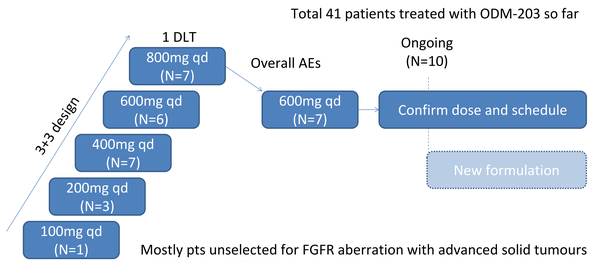
Introduction

ODM-203 is a small molecule with balanced inhibitory effects on both FGFR 1-4 and VEGFR 1-3 subtypes and also RET[1]. FGFR alterations have an impact on patient survival in different tumour types such as bladder, breast, lung and gastric. Meanwhile both VEGFR and FGFR are drivers for angiogenesis and consequently hallmarks of tumorigenesis. We present here the updated results of the ongoing phase I KIDES trial.

Study design

Figure 1. Dose escalation design of KIDES



Mostly pts unselected for FGFR aberration with advanced solid tumours
Safety: AE's (CTCAE), labs, ECHO
Target effects: phosphate, BP, FGFR/VEGFR
Tumour response: RECIST 1.1 every 8 weeks

Results

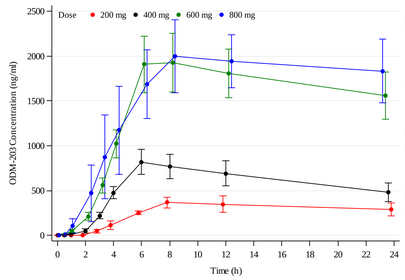
As of 1st Sept 2016 a total of 41 patients had been treated with ODM-203 to 8 weeks or disease progression. Ongoing cohorts are confirming the dose and dosing schedule and implementing a new formulation.

Table 1. Baseline characteristics

		N (%)
Age, median (range) years		56 (28-80)
Gender	Male	15 (36.6)
	Female	26 (63.4)
Race	Caucasian	39 (95.1)
ECOG	0	21 (51.2)
	1	20 (48.8)
Primary tumour		
Cholangiocarcinoma		12 (29.3)
Colorectal		8 (19.5)
Thyroid		4 (9.8)
Breast		4 (9.8)
Lung		3 (7.3)
RCC		3 (7.3)
Other		7 (17.1)

Acknowledgement: data presentations with assistance by Pasi Hakulinen, Orion Pharma

Figure 2. ODM-203 Day 1 mean concentrations



Exposure increased with dose but was variable between patients.

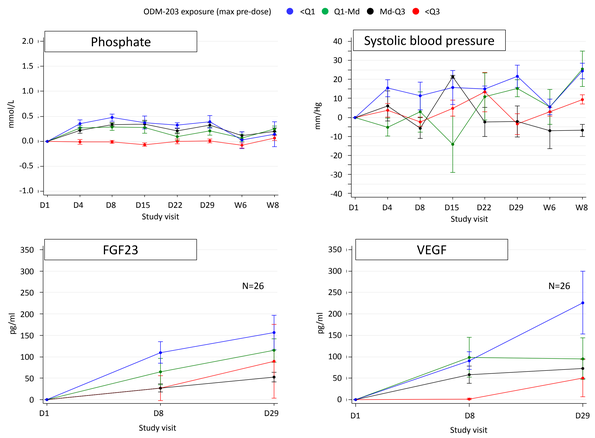
ODM-203 absorption was slow and prolonged.

Elimination half-life is difficult to assess but appears to exceed 40 hours.

Potentially therapeutic exposures were achieved at 400mg qd upwards .

Figure 3. Biomarkers of FGFR and VEGFR pathways

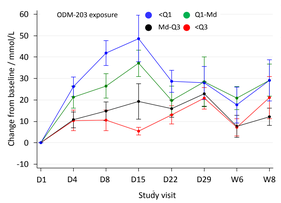
Change from baseline. Data presented by quartile of ODM-203 plasma exposure



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. 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.

Increases in the soluble markers FGF23 and VEGF appeared dose-dependant but with high variability.

Figure 4. Changes in bilirubin



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.

ODM-203 is a potent inhibitor of UGT1A1 in human liver microsomes (IC50 0.1 µM), this being the most likely mechanism behind the bilirubin increase. The effect is comparable to Gilbert's syndrome

Safety and tolerability

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

Preferred Term*	Total (N=41) n (%)	400 MG (N=7) n (%)	600 MG (N=23) n (%)	800 MG (N=7) n (%)	Gr 3-4 AE All doses n (%)
Hyperbilirubinaemia	31 (75.6)	5 (71.4)	19 (82.6)	7 (100)	21 (51.2)
Diarrhoea	22 (53.7)	3 (42.9)	15 (65.2)	4 (57.1)	2 (4.9)
Arthralgia	17 (41.5)	2 (28.6)	11 (47.8)	4 (57.1)	2 (4.9)
Jaundice	16 (39.0)	3 (42.9)	9 (39.1)	4 (57.1)	1 (2.4)
Fatigue	14 (34.1)	1 (14.3)	10 (43.5)	3 (42.9)	2 (4.9)
Stomatitis	14 (34.1)	1 (14.3)	9 (39.1)	4 (57.1)	
Palmar-plantar erythrodysaesthesia syndrome	13 (31.7)	2 (28.6)	10 (43.5)	1 (14.3)	2 (4.9)
Alopecia	12 (29.3)	1 (14.3)	6 (26.1)	5 (71.4)	1 (2.4)
Epistaxis	12 (29.3)	1 (14.3)	7 (30.4)	3 (42.9)	
Asthenia	10 (24.4)	2 (28.6)	4 (17.4)	3 (42.9)	1 (2.4)
Dry mouth	10 (24.4)	1 (14.3)	9 (39.1)		
Decreased appetite	9 (22.0)	2 (28.6)	5 (21.7)	2 (28.6)	
Hyperphosphataemia	9 (22.0)	2 (28.6)	4 (17.4)	3 (42.9)	
Myalgia	7 (17.1)	1 (14.3)	4 (17.4)	2 (28.6)	1 (2.4)
Dysgeusia	7 (17.1)	2 (28.6)	3 (13.0)	2 (28.6)	
Headache	7 (17.1)	1 (14.3)	4 (17.4)	2 (28.6)	
Nasal dryness	6 (14.6)	1 (14.3)	5 (21.7)		
Nausea	6 (14.6)	1 (14.3)	5 (21.7)		
Vomiting	6 (14.6)	1 (14.3)	5 (21.7)		
Hypertension	5 (12.2)		5 (21.7)		
Onycholysis	5 (12.2)		3 (13.0)	2 (28.6)	
Paronychia	5 (12.2)	1 (14.3)	4 (17.4)		1 (2.4)

200 mg dose level is included in the total number of AEs. Data updated 1st Sept 2016

Almost 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. 3 patients discontinued ODM-203 due to possibly related adverse events (corneal punctate keratitis, pulmonary embolus and Takotsubo syndrome).

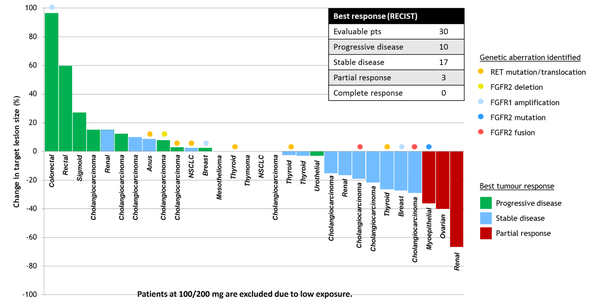
Sevelamer was administered for increased phosphate to 6 patients, although no patients required dose interruption or reduction for this effect.

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, diarrhoea and arthralgia.

Antitumour activity

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

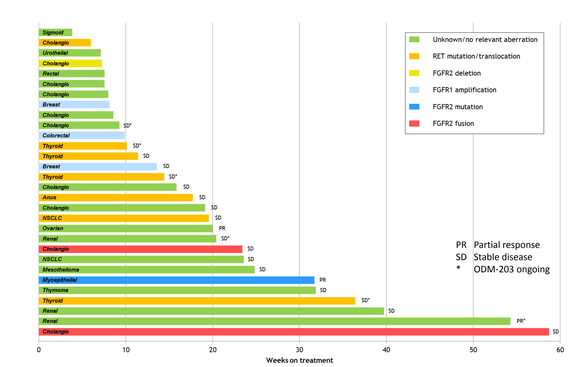


Patients were generally not selected by molecular screening and tumour genetic profiling data are incomplete.

3 confirmed partial responses (per investigator) 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 tumours without FGFR genetic aberration. 2 cholangiocarcinoma patients with tumour response have unknown FGFR status.

Figure 6. Duration of treatment with ODM-203



Conclusions

- ODM-203 is a balanced FGFR1-4 and VEGFR1-3 inhibitor.
- 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. Diarrhoea 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 tumour responses have been seen in both FGFR aberrant and VEGFR sensitive (FGFR negative) tumours, confirming clinically important activity on both FGFR and VEGFR pathways.

Poster presented at ESMO 2016
October 7-11, 2016, Copenhagen, Denmark

KIDES trial is sponsored by Orion Corporation Orion Pharma (NTC02264418)

1. Holmström T., et al. Cancer Res 2015;75(15 Suppl)

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