Poster #2576

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

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Introduction

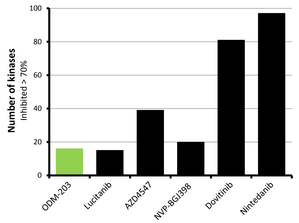
ODM-203 is a small molecule with balanced inhibitory effects on both FGFR 1-4 and VEGFR 1-3 subtypes and also RET. FGFR alterations have an impact on patient survival in different tumor types such as bladder, breast, lung and gastric. Meanwhile both VEGFR and FGFR are drivers for angiogenesis and consequently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

ODM-203 and study design

In vitro kinase activity*

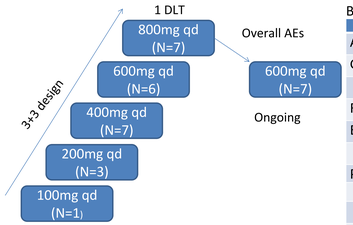
IC50 (nM)	ODM-203	Lucitanib	AZD4547
FGFR1	11	58	0.3
FGFR2	16	186	0.2
FGFR3	6	253	1
FGFR4	35	> 1000	7
VEGFR1	26	162	87
VEGFR2	9	9	55
VEGFR3	5	34	35
RET	8	ND	22
Ratio FGFR1/VEGFR2	1:1	1:5	200:1

In vitro kinase selectivity*



- In addition to its primary targets ODM-203 only suppresses 9 kinases out of 317 by more than 70% at 1 uM

Figure 1. ODM-203 is a balanced selective dual FGFR/VEGFR inhibitor (1.)



Total 31 patients treated with ODM-203 so far

Baseline characteristics

		N (%)
Age, median range years		54 (28-80)
Gender	Male	11 (35.5)
	Female	20 (64.5)
Race	Caucasian	29 (94.5)
ECOG	0	15 (48.4)
	1	16 (51.6)
Primary tumour		
Colorectal		8 (25.8)
Cholangiocarcinoma		6 (19.4)
Breast		4 (12.9)
Lung		3 (9.7)
RCC		2 (6.5)
Other		8 (25.8)

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

Figure 2. Dose escalation design of KIDES

Results

A total of 31 patients have been treated with ODM-203 so far. The dose escalation phase was initiated in a standard 3+3 design aiming at dose increase until MTD was reached. Optimal dosing scheme is currently being investigated.

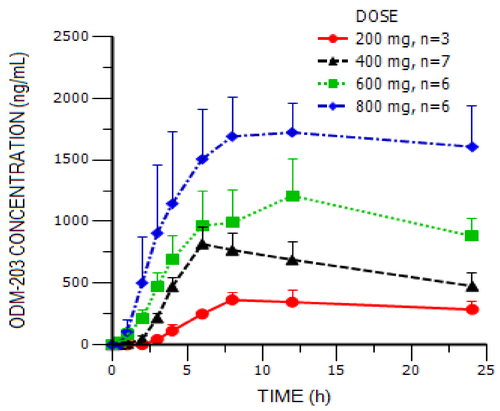
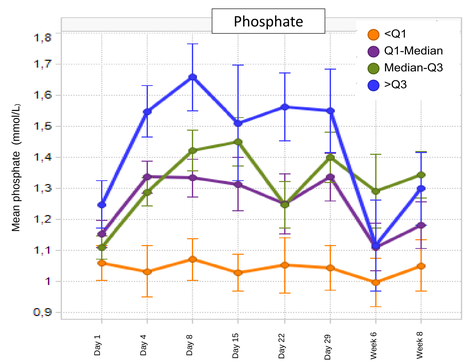


Figure 3. ODM-203 Day 1 mean concentrations

Exposure increased with dose but was highly variable. ODM-203 absorption was slow and prolonged. Potentially therapeutic exposures achieved at 400mg qd and upwards .



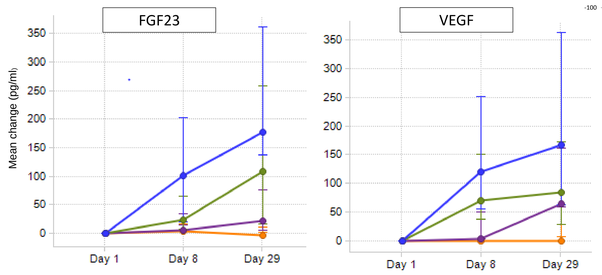


Figure 3. Biomarkers of FGFR and VEGFR pathways

Increased phosphate reflects renal FGFR inhibition. No discontinuations due to phosphate increase, 3 received sevelamer at 800 mg qd.

Changes in soluble markers of FGFR/VEGFR activity have been very variable. Hypertension rare, although increases in mean BP were seen.

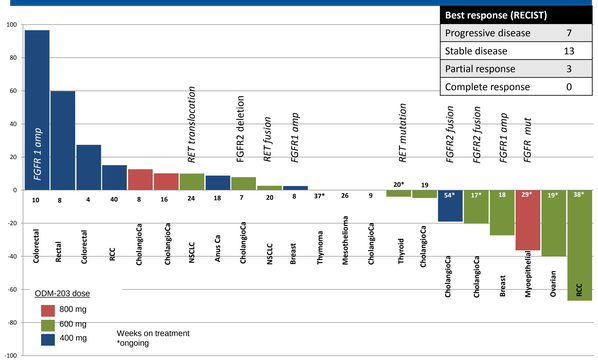
Safety and tolerability

Common adverse events in >10% of patients on ODM203

Preferred Term*	Total (N=31) n (%)	400 MG (N=7) n (%)	600 MG (N=13) n (%)	800 MG (N=7) n (%)	Gr 3-4 AE All doses n (%)
Bilirubin increased	22 (71.0)	5 (71.4)	10 (76.9)	7 (100)	15 (48.4)
Diarrhoea	14 (45.2)	3 (42.9)	7 (53.8)	4 (57.1)	3 (9.7)
Alopecia	12 (38.7)	1 (14.3)	5 (38.5)	5 (71.4)	
Increased phosphate	7 (22.6)	2 (28.6)	3 (23.1)	2 (28.6)	
Jaundice	10 (32.3)	3 (42.9)	3 (23.1)	4 (57.1)	1 (3.2)
Epistaxis	11 (35.5)	1 (14.3)	6 (46.2)	3 (42.9)	
Stomatitis	10 (32.3)	1 (14.3)	5 (38.5)	4 (57.1)	
Fatigue	8 (25.8)	1 (14.3)	4 (30.8)	3 (42.9)	1 (3.2)
Decreased appetite	8 (25.8))	2 (28.6)	4 (30.8)	2 (28.6)	
Arthralgia	12 (38.7)	2 (28.6)	6 (46.2)	4 (57.1)	1 (3.2)
Asthenia	10 (32.3)	2 (28.6)	4 (30.8)	3 (42.9)	1 (3.2)
Dysgeusia	7 (22.6)	2 (28.6)	3 (23.1)	2 (28.6)	
Palmar-plantar erythrodysaesthesia	11 (35.5)	2 (28.6)	8 (61.5)	1 (14.3)	2 (6.5)
Headache	6 (19.4)	1 (14.3)	3 (23.1)	2 (28.6)	

200 mg dose level is included in the total number of AEs

Antitumor activity



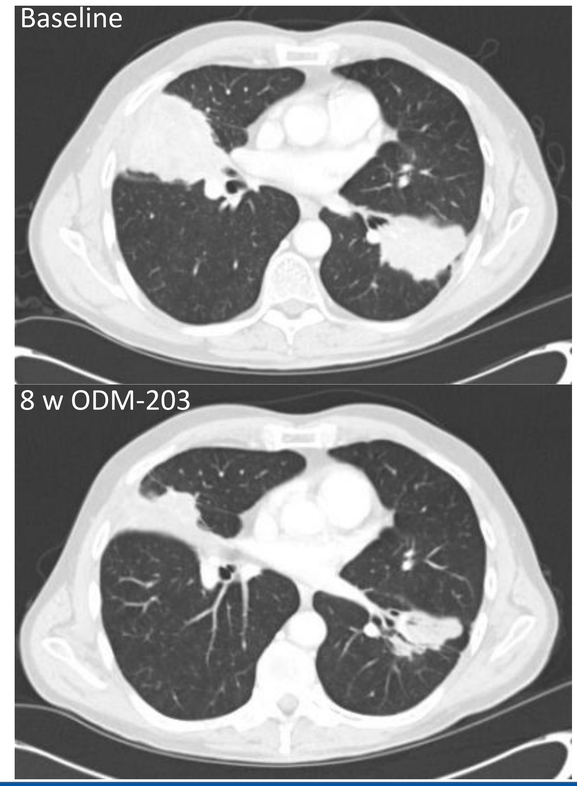
Best response (RECIST)	
Progressive disease	7
Stable disease	13
Partial response	3
Complete response	0

Figure 4. ODM-203 best tumor response

Unselected patient population, molecular screening has not been carried out for all. Patients at 100/200 mg are excluded due to low exposure.

CT scan in a patient with myoepithelial carcinoma with FGFR2 mutation (p.C382R) after 8 weeks of treatment showing a 36;5 % reduction in tumour burden. Previous treatments include cisplatin and vinorelbine.

At 800 mg one related SAE of colitis was reported and one DLT of corneal punctate keratitis. MTD according to protocol was not identified. A reversible dose dependent increase in unconjugated bilirubin, without concomitant transaminase increase, commonly resulted in temporary discontinuation or dose reduction above 400mg/day. Target-related AEs developed during prolonged treatment and were reversible. ODM-203 showed potent inhibition of UGT1A1 in human liver microsomes (IC50 0.1 µM) being the most likely mechanism behind bilirubin increase.



Conclusions

- ODM-203 is a balanced FGFR1-4 and VEGFR1-3 inhibitor.
- Exposure increased with dose up to 800 mg qd, achieving anticipated therapeutic dose, although somewhat variable.
- UGT1A1 inhibition of ODM-203 caused dose dependent bilirubin increases, resulting in early dose reduction, especially at 800mg qd.
- Diarrhoea and mucocutaneous events occurred commonly after several weeks treatment, and responded to temporary discontinuation or dose reduction of ODM-203.
- On target effects on phosphate, blood pressure and soluble markers may have been affected by temporary discontinuations but suggest activity on both FGFR and VEGFR pathways
- Significant clinical responses were observed in patients with RCC, ovarian, myoepithelial and FGFR aberrant cholangio carcinoma.

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