Poster #420P

PHASE 1/2 STUDY OF ODM-203, A SELECTIVE DUAL FGFR/VEGFR INHIBITOR, IN PATIENTS WITH ADVANCED SOLID TUMOURS

P Bono[1], C Massard[2], K Peltola[1], A Azaro[3], A Italiano[4], R Kristeleit[5], G Curigliano[6], U Lassen[7], H-T Arkenau[8], P Hakulinen P[9], C Garratt[9], T Ikonen[9], M Mustonen[9], J Rodon[3]

[1]Comprehensive Cancer Center, Helsinki University Hospital and University of Helsinki, Finland; [2]Institut Gustave Roussy, Gustave Roussy Cancer Centre, Villejuif, France; [3]Molecular Therapeutics Research Unit. Department of Medical Oncology. Vall d´Hebron University Hospital, Barcelona, Spain; [4]Bergonie Institute, Bordeaux, France; [5]UCL Cancer Institute, University College London, London, UK; [6]European Institute of Oncology (IEO), University of Milano, Division of Early Drug Development for Innovative Therapies, Milan, Italy; [7]Rigshospitalet - University Hospital Copenhagen, Department of Oncology, Phase 1 Unit, Copenhagen, Denmark; [8]Sarah Cannon Research Institute (SCRI), London, UK; [9]Orion Corporation Orion Pharma, Finland

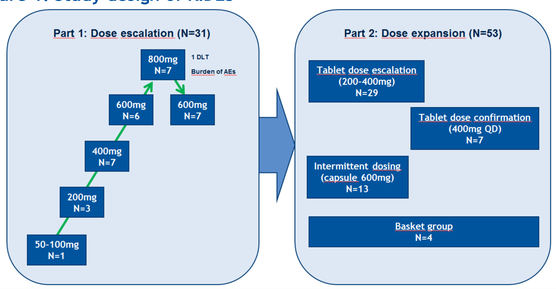
Introduction

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 results of the phase 1/2 KIDES trial.

Study design

The KIDES study is an open-label, non-randomized, multicentre phase 1/2 first-in-man study of ODM-203 in patients with advanced solid tumors (**Table 1**). In the Part 1 dose escalation (3+3), ODM-203 was evaluated in 31 patients between 50-800mg daily with food to identify the maximum tolerated dose (MTD). Part 2 expansion included 53 patients to evaluate new tablet formulation, recommended phase 2 dose and the dosing schedule. Patients continued ODM-203 treatment until progression of disease or dose limiting toxicity (**Figure 1**).

Figure 1. Study design of KIDES



Results

In total 84 patients (median 59 years, range 28-80), with the most common tumor types being cholangio, breast, colorectal, endometrium, ovarian and thyroid carcinoma, were included, with most patients in Part 2 having FGFR alterations (**Table 1**). Six patients remain still on treatment (data cut-off 8th of April 2018).

Table 1. Baseline characteristics

		N (%)
Age, median (range) years		59 (28-80)
Gender	Male	30 (35.7)
	Female	54 (64.3)
Race	Caucasian	79 (94.0)
ECOG	0	36 (42.9)
	1	48 (57.1)
Primary tumour		
Cholangiocarcinoma		12 (14.3)
Colorectal		10 (11.9)
Breast		10 (11.9)
Thyroid		5 (6.0)
Ovarian		5 (6.0)
Endometrial		5 (6.0)
Lung		4 (4.8)
Renal		4 (4.8)
Other		29 (34.5)
FGFR aberration		38 (45.2)

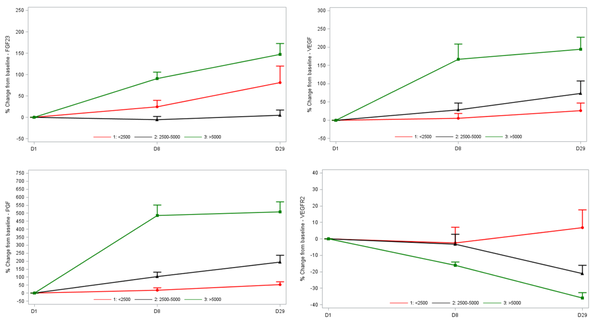
In the dose-escalation Part 1, 800mg/day was considered the highest dose that could not be tolerated although MTD was not formally identified. This was because of general adverse event (AE) burden and increased bilirubin in most patients. Isolated bilirubin increase was due to UGT1A1 inhibition by ODM-203, not associated with transaminase increases, and resolved in all cases upon dose reduction/interruption. In Part 2, the optimal tablet dose was determined to be 400mg/day with food, and therapeutic exposures were achieved in all patients although with variation in PK (**Table 2**).

Table 2. Pharmacokinetics of ODM-203: 400mg/day, tablet with food

	Visit day					
		Day 1			Day 15	
	Tmax	Cmax	AUClast	Tmax	Cmax	AUClast
N	19	19	19	18	18	18
Mean	8,4	2200	37000	6,1	11000	220000
SD	4,8	940	16000	5,3	6100	120000
Min	3	550	10000	0	1500	17000
Median	6	2100	35000	5	10000	210000
Max	24	4000	63000	24	22000	410000
CV%	58	43	43	87	53	52

Dose interruptions for the management of increased bilirubin probably affected pharmacokinetics results for some patients and thus likely also the magnitude of pharmacodynamic changes. Still, there was evidence of activity on both FGFR and VEGFR pathways. Percentage mean changes in the soluble markers FGF23, VEGFR2, VEGF and PGF appeared dose dependent by concentration quartiles (**Figure 2**).

Figure 2. Biomarkers of FGFR and VEGFR pathways



Percentage mean change from baseline. Grouped by plasma exposure categories <2500ng/ml, 2500-5000ng/ml and >5000ng/ml. Subjects are classified by plasma exposure categories according the highest pre-dosing concentration up to day 29. All patients and dose levels included.

Most AE's the patients experienced were grade 1-2 (**Table 3**), with the most common AEs being increased bilirubin (76%), fatigue and asthenia (68%), diarrhoea (60%), stomatitis (41%), arthralgia (41%) and decreased appetite (41%). The most common grade >3 AE's (Table 3) were bilirubin increase (45%), fatigue (6%) and diarrhoea (6%), and 11 patients (14.1%) discontinued ODM-203 due to possibly related adverse events (anemia, stress cardiomyopathy, keratitis, gastrointestinal disorders, fatigue, infections, transient ischaemic attack and pulmonary embolism).

Table 3. Most common adverse events in >15% of patients on ODM-203

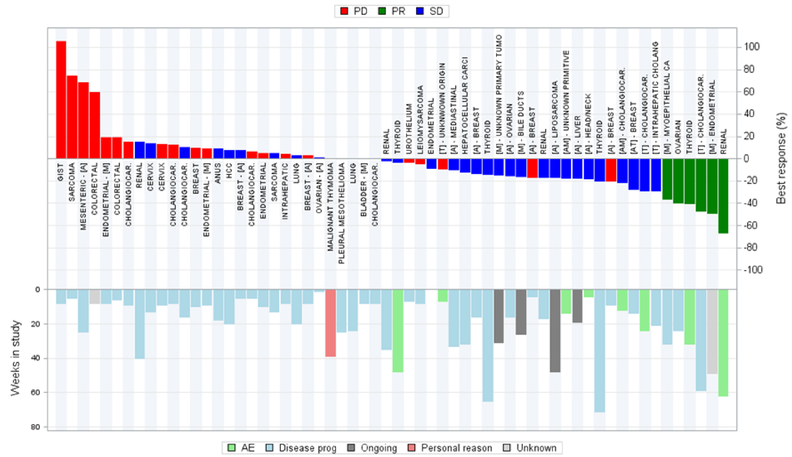
Preferred Term*	Total (N=84) n (%)	400 MG Tablet* (N=30) n (%)	Gr 3-5 AE All doses n (%)
Hyperbilirubinaemia	64 (76.1)	25 (83.3)	38 (45.2)
Diarrhoea	50 (59.2)	21 (70.0)	5 (5.9)
Stomatitis	34 (40.5)	17 (56.7)	3 (3.6)
Arthralgia	34 (40.5)	12 (40.0)	2 (2.4)
Decreased appetite	34 (40.5)	15 (50.0)	
Palmar-plantar erythrodysaesthesia syndrome	30 (35.7)	15 (50.0)	4 (4.8)
Dry mouth	30(35.7)	13 (43.3)	
Epistaxis	30(35.7)	15 (50.0)	
Jaundice	29 (34.5)	11 (36.7)	2 (2.4)
Asthenia	29 (34.5)	10 (33.3)	2 (2.4)
Fatigue	28 (33.3)	11 (36.7)	5 (5.9)
Alopecia	27 (32.1)	10 (33.3)	1 (1.2)
Dysgeusia	25 (29.8)	12 (40.0)	
Weight decreased	25 (29.8)	8 (26.7)	1 (1.2)
Nausea	20 (23.8)	11 (36.7)	
Vomiting	20 (23.8)	10 (33.3)	
Hypertension	18 (21.4)	10 (33.3)	3 (3.6)
Hyperphosphataemia	16 (19.0)	8 (26.7)	
Headache	14 (16.7)	6 (20.0)	
Myalgia	14 (16.7)	5 (16.7)	2 (2.4)
Nasal dryness	13 (15.5)	6 (20.0)	
Constipation	13 (15.5)	6 (20.0)	

*) 400mg tablet group includes various dosing schema.

As assessed by Investigators, there were 6 (9%) partial responses (PR), and additionally 24 (35%) patients achieved target lesion reduction. Also, 31 (45%) patients had disease stabilisation (SD) with median of 20 weeks on the study. Thus, the clinical benefit rate, as calculated by CR+PR+SD, was 37/69 (54%).

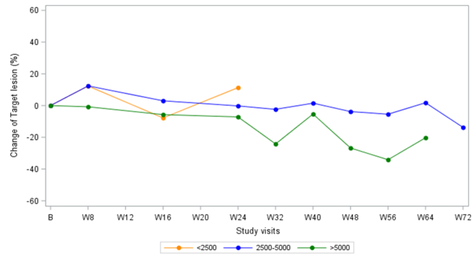
ODM-203 tumour responses and treatment durations are presented in **Figure 3**. Four patients have received ODM-203 treatment for more than 1 year, the longest being 498 days.

Figure 3. ODM-203 best tumour response (RECIST) and duration of treatments



FGFR alteration type (if identified): A = Amplification, M = Mutation, T = Translocation.
Patients with the highest pre-dose (up to day 29) plasma concentration >2500ng/ml presented. One ongoing patient has plasma concentration below 2500ng/ml, and one has been less than 8wks on treatment (no imaging done).

Figure 4. Target lesion change by ODM-203 concentration



Percentage mean change from baseline . Grouped by plasma exposure categories <2500ng/ml, 2500-5000ng/ml and >5000ng/ml. Subjects are classified by plasma exposure categories according to the highest pre-dosing concentration up to day 29. All patients and dose levels included.

Conclusions

- ODM-203 is a balanced FGFR1-4 and VEGFR1-3 inhibitor showing evidence of clear pharmacodynamic activity on both FGFR and VEGFR pathways
- ODM-203 AE profile is typical for FGFR or VEGFR inhibitors
- Bilirubin increases due to UGT1A1 inhibition by ODM-203 were common but not associated with signs of liver injury, and responded rapidly to dose reduction or interruptions
- Durable tumour responses have been seen in both FGFR aberrant and non-aberrant tumours, indicating clinically important inhibition of both FGFR and VEGFR pathways at the same clinical dose

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1. Holmström T et al. Mol Cancer Ther 2018 *in press*

Corresponding author: petri.bono@helsinki.fi