Supplementary material

Phase I/IIa, Open-Label, Multicenter Study to Evaluate the Optimal Dosing and Safety of ODM-203 in Patients with Advanced or Metastatic Solid Tumors

Petri Bono[1#], Christophe Massard[2], Katriina J. Peltola[3], Analía Azaro[4], Antoine Italiano[5], Rebecca S. Kristeleit[6], Guiseppe Curigliano[7], Ulrik N. Lassen[8], Hendrik-Tobias Arkenau[9], Pasi Hakulinen[10], Chris Garratt[10], Tarja Ikonen[10], Mika V.J. Mustonen[10*], Jordi Rodon Ahnert[4], KIDES study investigators

In the KIDES-203 study the classification of fibroblast growth factor receptor mutations as activating was performed retrospectively based on the following publications:

1. Greulich H and Pollock PM. Trends Mol Med 2011 (1)
2. Liao RG, et al. Cancer res 2013 (2)
3. Gallo LH, et al. Cytokine Growth Factor Rev, 2015 (3)
4. Helsten T, et al. Clin Cancer Res, 2016 (4)
5. Babina IS and Turner NC. Nat Rev Cancer, 2017 (5)

Supplementary Table S1. Definition of a DLT

Any of the following toxicities (grading according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] ver. 4.03 (6)) determined as related to ODM-203 and occurring during the first 28 days of the study treatment: • Prolonged grade 4 neutropenia (ANC $<0.5\times10^9$/L) for >7 days • Febrile neutropenia (ANC of $<1.0\times10^9$/L [grade 3 or 4] and fever of >38.3°C [single occurrence] or ≥38.0°C sustained for more than 1 hour) • Grade 4 thrombocytopenia ($<25.0\times10^9$ /L) or, grade 3 or 4 thrombocytopenia with clinically significant bleeding • Persistent nausea, vomiting, diarrhea grade ≥3 despite optimal medical intervention (not used as a prophylactic regimen • Grade 3 increase in AST and ALT lasting for more than 7 days • Persistent grade 3 hypertension despite appropriate therapy; as hypertension is a common side effect of VEGFR inhibitors, the onset of clinically manageable hypertension was not itself regarded as a DLT • Serum phosphate >10.0 mg/dL or >7.0 mg/dL and not responding to phosphate lowering therapy 14 days after discontinuation of the study treatment • Any other toxicity which, in the judgement of the investigator and/or sponsor, was viewed as a DLT • Any AE which, in the opinion of the investigator and sponsor, was attributed to a patient's underlying disease was not to be considered a DLT

ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose limiting toxicity; VEGFR, vascular endothelial growth factor receptor.

Supplementary Table S2: Inclusion and exclusion criteria

Inclusion criteria
1. Male and female patients over the age of 18.
2. Patients with histologically or cytologically confirmed locally advanced or metastatic solid tumors with at least one measureable lesion for whom no effective standard therapy existed or whose disease was refractory or resistant to conventional therapy. Patients in Part 2 had to have a tumor or genetic aberration. Molecular aberrations were to be based on analysis of a tumor sample taken after the most recent course of chemotherapy, if applicable.
3. Availability of FFPE tumor sample for central genetic analysis either from recent sampling, archival or other source.
4. Adequate hemopoetic, hepatic and renal function, evidenced by:
a) Absolute neutrophil count > 1.5 x 10^9 L.
b) Platelet count >100 x 10^9 L.
c) Hemoglobin >9 g/dL in the absence of transfusions within 2 weeks prior to the start of study treatment.
d) Bilirubin <1.5 x ULN; alternatively ≤3x ULN could be accepted if liver metastases were present after agreement with the sponsor and the medical monitor.
e) AST and/or ALT <3x ULN; alternatively ≤5x ULN could be accepted if liver metastases were present after agreement with the sponsor and the medical monitor.
f) Albumin ≥3.0 g/dL.
g) Serum creatinine <1.5x ULN or calculated creatinine clearance ≥60 ml/min/1.73 m^2 for patients with creatinine levels above normal limit.
5. ECOG performance status of 0–1.
6. Adequate serum mineral levels, evidenced by:

a) Phosphate: 2.5 mg/dL (0.8 mM) < value ≤4.5 mg/dL (1.44 mM).
b) Calcium: 8.8 mg/dL (2.2 mM) < value ≤10.4 mg/dL (2.6 mM).
c) Magnesium: 1.2 mg/dL (0.5 mM) < value ≤3.0 mg/dL (1.23 mM).
d) Potassium: 11.7 mg/dL (3.0 mM) < value ≤ 21.5 mg/dL (5.5 mM).
e) Sodium: 299 mg/dL (130 mM) < value ≤ 345 mg/dL (150 mM).

7. Recovery from reversible adverse events of previous systemic anticancer therapies to baseline or grade 1 except for alopecia; stable neuropathy of grade 2 which was induced by prior cancer treatment.
8. Life expectancy of 12 weeks or more.

In order not to unnecessarily deny access to the study to otherwise eligible patients, in Part 2 the medical monitor could apply some discretion to patients with laboratory results that deviated from the limits in inclusion criteria 5 and 7. The medical monitor could permit enrollment of individual patients with laboratory deviations judged to be of no clinical significance provided this was deemed to be in the best interests of the patient.

Exclusion criteria

1. Any prior anti-VEGFR or -FGFR treatment-related AE that, in the judgement of the investigator, was considered severe/life threatening.
2. Patients receiving warfarin. Patients receiving LMWH were allowed in the study.
3. Active CNS metastases not controlled by prior surgery or radiotherapy and/or low dose steroids for a period of 4 weeks or more.
4. Patients with current evidence of endocrine alteration of calcium-phosphate homeostasis including but not limited to parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis.
5. Concomitant therapies that were known to increase serum phosphorus and/or calcium levels and could not be discontinued or switched to a different medication were not permitted within 14 days before the first dose of ODM-203, e.g. calcium, phosphate, potassium phosphate supplements (oral or intravenous), some antacids, bisphosphonate therapy, phosphate-containing enemas and laxatives (rectal/oral), vitamin D, and parathyroid hormone.

6. Significant cardiovascular conditions or circumstances as follows:
    a) Active or unstable cardio/cerebrovascular disease. Examples included, but were not limited to, uncontrolled ventricular arrhythmia, recent (within 6 months) myocardial infarction, congestive heart failure (NYHA class III-IV), coronary artery bypass graft or symptomatic cerebrovascular accident.
    b) Uncontrolled hypertension (systolic BP ≥150 mmHg and/or diastolic BP ≥90 mmHg with optimized antihypertensive therapy).
    c) History of severe arrhythmia, familial arrhythmia, clinically significant conduction abnormality or congenital long QT syndrome.
    d) Concomitant therapies known to prolong QT interval and associated with a risk of TdP were not permitted within 7 days before the first dose. Amiodarone was not permitted for 90 days before the first dose. **Note:** Patients could be eligible if concomitant therapy could be discontinued or switched to a different medication and patient's status was stable for sufficient duration prior to starting study treatment.
    e) Repeatable prolongation of QTcF interval ≥450 msec or any clinically significant abnormality in the ECG at screening period in 2/3 recordings.
    f) LVEF <50% evaluated by ECHO or MUGA scan at screening period or within 28 days of first dosing.
7. Patients who received systemic anticancer treatment prior to the first dose of ODM-203 within the following timeframes:
    a) Less than 28 days since the last dose of antineoplastic therapy, or longer for drugs depending on the product's use with the exception of LHRH analogues.
    b) 28 days of wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) or 14 days of limited field radiation for palliation.
8. Major surgery or serious infection within 21 days of the first dose of study treatment.
9. Known gastrointestinal disease or a procedure that could affect absorption of study treatment.
10. Serious concurrent medical condition or psychiatric illness.
11. History and/or current evidence of ectopic mineralization/calcification including but not limited to the soft tissue, kidneys, intestine,

myocardium and lung with the exception of calcified lymph nodes and breast tissue, tumor calcification and asymptomatic coronary calcification.

12. Known active or past history (within the last 2 years prior to screening) of other primary malignancy (unless treated with a curative intent or with the exception of non-melanoma skin cancers, superficial bladder cancer or in situ breast or cervical cancer).
13. Female patients of childbearing potential (i.e. menstruating or less than 2 years postmenopausal) being pregnant (had to have a negative pregnancy test before the first dose of study medication) or breast-feeding.
14. Female patients of childbearing potential or male patients with female partner of childbearing potential who did not agree to use effective contraception (e.g. implants, injectables, combined oral contraceptives, intrauterine device, barrier method, sexual abstinence, surgical sterilization) for the duration of the study and 3 months after last dose of study medication.
15. Known hypersensitivity to the study treatment excipients.
16. Any condition that, in the opinion of the investigator could have impaired the patient's ability to comply with study procedures e.g. uncontrolled diabetes mellitus, infection/inflammation, intestinal obstruction, unable to swallow study treatment capsules.
17. Participation in another interventional clinical trial and any concurrent treatment with any investigational drug within 4 weeks prior to start of the study treatment.

Waivers from exclusion criteria were not permitted.

AE, adverse event; BP, blood pressure; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin embedded; FGFR, fibroblast growth factor receptor; LHRH, luteinizing hormone-releasing hormone; LMWH, low molecular weight heparin; LVEF, Left ventricular ejection fraction; MUGA, multigated acquisition; NYHA, New York Heart Association; TdP, Torsades de Pointes; ULN, upper limit of normal; VEGFR, vascular endothelial growth factor receptor.

Supplementary Table S3. ODM-203 best tumor response (RECIST) and associated FGFR aberrations

Observation	Best RECIST status	Type of FGFR aberration	Amplified FGFR pathway gene	Activating FGFR mutation	Non-activating FGFR mutation	FGFR rearrangement
1	PD	Amplification	FGFR1			
2	PD	Amplification	FGFR4; FRS2			
3	PD	Amplification	FGFR1			
4	PD	Mutation			FGFR2 M391R	
5	PD	Mutation		FGFR2 S252W		
6	SD	Mutation			FGFR2 N329del	
7	SD	Mutation + Translocation		FGFR3 R248C		FGFR2-BICC1
8	PD	Amplification	FGFR1			
9	SD	Amplification	FGFR2			
10	PD	Mutation		FGFR3 S249C		
11	PD	Mutation		FGFR3 G380R		
12	SD	Amplification	FGFR1			
13	PD	Translocation				FGFR3-TACC3
14	SD	Amplification	FRS2			
15	SD	Amplification	FGFR1			
16	SD	Mutation		FGFR4 N535K		
17	SD	Amplification	FGFR3			
18	SD	Mutation		FGFR2 C382R		
19	PD	Amplification	FGFR1			
20	SD	Amplification	FRS2			
21	SD	Amplification + Mutation	FGFR1	FGFR3 S249C		
22	SD	Amplification	FGFR1			
23	SD	Amplification	FGFR1			
24	PD	Amplification	FGFR1			
25	SD	Amplification + Mutation	FGFR1		FGFR2 Y345_Q351del	
26	SD	Amplification + Translocation	FGFR1			FGFR1 intergenic
27	SD	Translocation				FGFR2-VCL
28	SD	Translocation				FGFR2

				rearrangement
29	PR	Mutation	FGFR2 C382R	
30	PR	Translocation		G3BP2-FGFR2
31	PR	Mutation	FGFR2 C382R	
32	PR	Mutation	FGFR3 S249C	

BICC, BicC family RNA binding protein, FGFR, fibroblast growth factor receptor; PD, progressive disease; RNA, ribonucleic acid; PR, partial response; SD, stable disease; TACC, transforming acidic coiled-coil containing; VCL, Vinculin

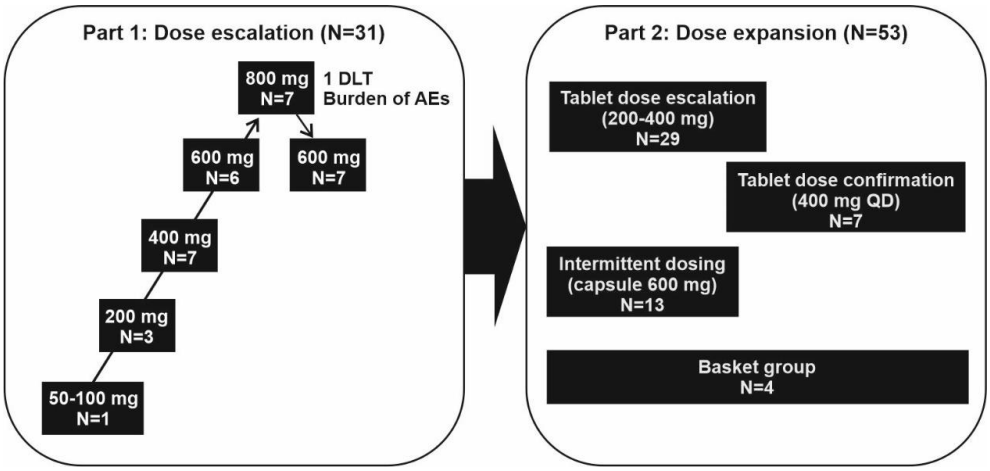
Supplementary Table S4. Best tumor response (RECIST)

	Capsule			**Tablet**			**Total**
	400 mg (n=7)	**600 mg (n=26)**	**800 mg (n=6)**	**200 mg (n=3)**	**300 mg (n=3)**	**400 mg (n=26)**	**(N=71[a])**
PR	1 (14.3)	3 (11.5)	1 (16.7)	0 (0.0)	0 (0.0)	2 (7.7)	7 (9.9)
SD	2 (28.6)	12 (46.2)	3 (50.0)	1 (33.3)	2 (66.7)	16 (61.5)	36 (50.7)
PD	4 (57.1)	11 (42.3)	2 (33.3)	2 (66.7)	1 (33.3)	8 (30.8)	28 (39.4)

[a]ITT 76 patients, 4 patients with low exposure (100–200 mg) and 1 patient with non-evaluable non-target lesions (600 mg) are not included. Unscheduled visits are included in the data.

ITT, intention to treat; PR, partial response; PD, progressive disease; SD, stable disease.

Supplementary Figure S1 KIDES study design

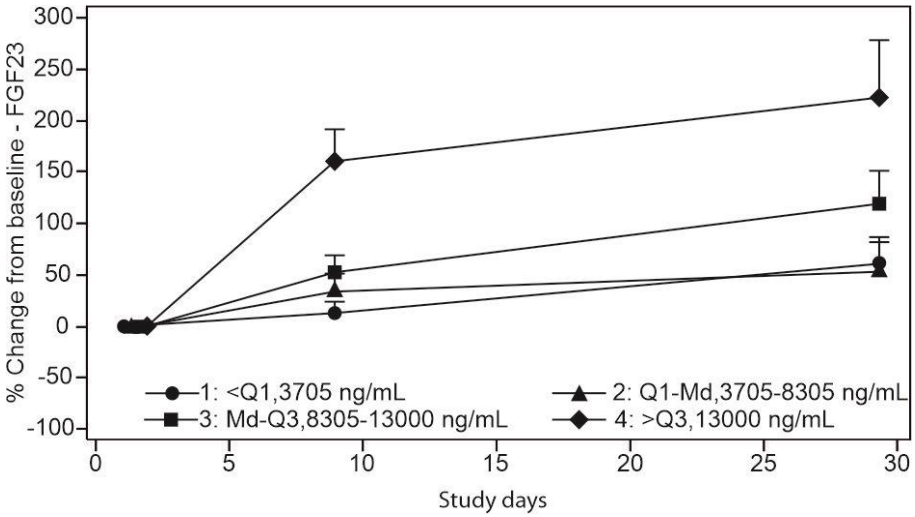


AE, adverse event; DLT, dose-limiting toxicity; QD, once a day.

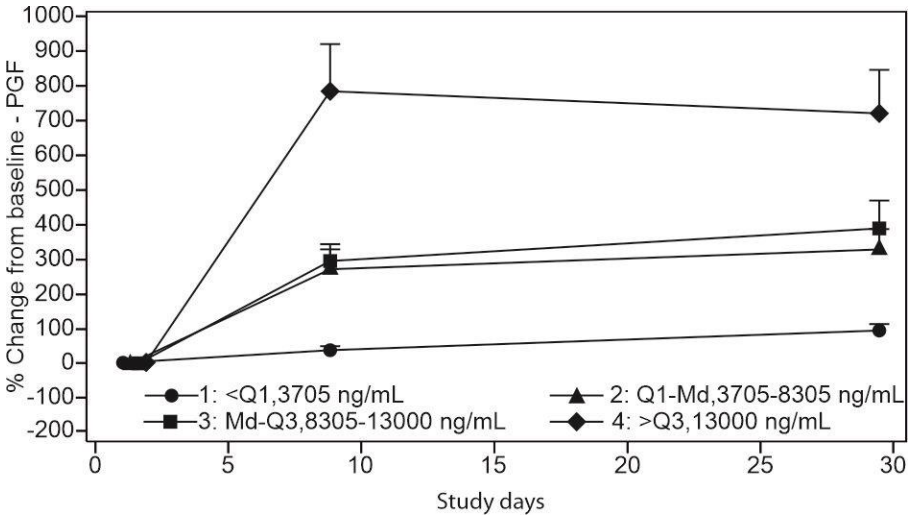
Supplementary Figure S2. Biomakers of FGFR and VEGR pathways

Percentage mean change from baseline in FGF23 (**A**), PGF (**B**), VEGF (**C**) and VEGFR2 (**D**). Grouped by plasma exposure quatiles <Q1, 3705ng/mL; Q1-Md, 3705-8305 ng/mL; Md-Q3, 8305-13000 ng/mL and >Q3, 13000 ng/mL. Subjects are classified by plasma exposure categories according the highest pre-dosing concentration up to day 29. All patients and dose levels included.

(**A**)



(**B**)



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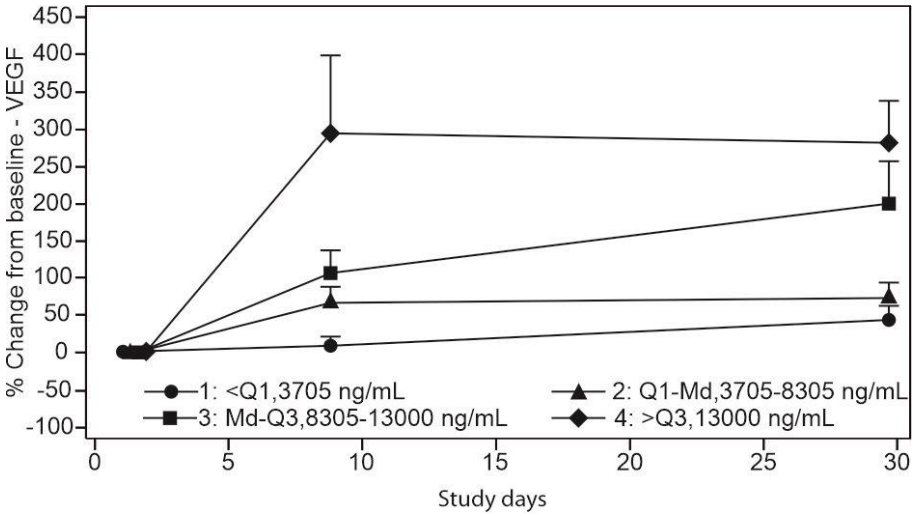

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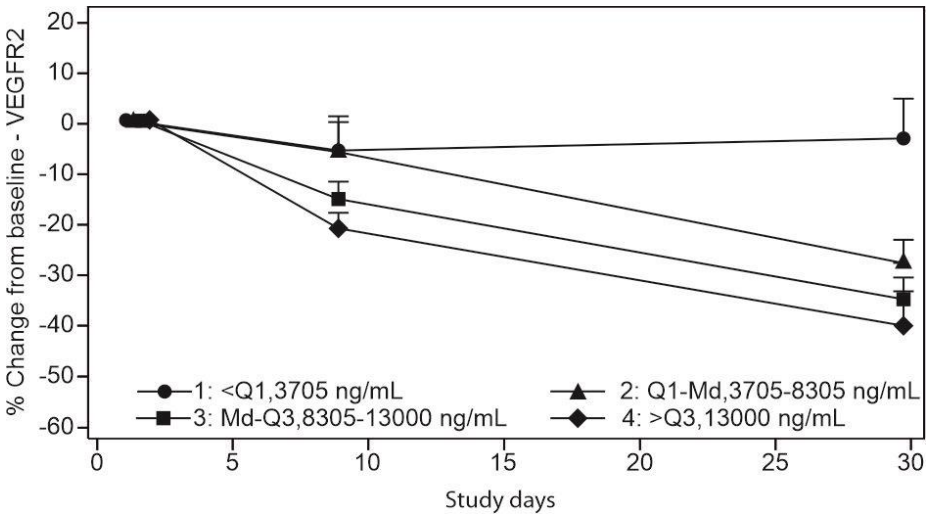

FGF, fibroblast growth factor; PGF, platelet growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

References

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