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Multi-center phase II clinical trial of everolimus in Japanese patients with unresectable or metastatic renal cell carcinoma (mRCC) after failure of treatment with 1st-line tyrosine kinase inhibitor (TKI) therapy.

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Comprehensive Support Project (CSP)

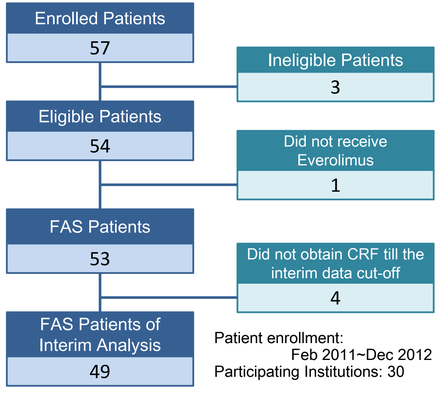
Background

Everolimus has shown the efficacy and the safety in the phase III trial (RECORD-1) in patients with mRCC after failure of Vascular Endothelial Growth Factor Receptor-TKI. However, 26% of patients received two TKIs (sunitinib and sorafenib) as previous therapy in RECORD-1. In addition, as pre-treatment before TKI, 65% of patients received cytokine therapy and 13% of patients received chemotherapy. Therefore, there is still no clear evidence of everolimus as second line setting after failure of 1st-line TKI therapy.

Methods

This study is an open-label, multi-center, single-arm, phase II trial. Primary endpoint is progression-free survival (PFS), and secondary endpoints are overall survival, objective response rate, time-to-treatment-failure, safety and quality of life (EORTC QLQ-C30, FKSI-DRS, EQ-5D). Key eligibility criteria are RCC with clear cell component, patients who received one TKI as first line therapy, patients who did not receive cytokine and chemotherapy and ECOG performance status 0-1.

Number of Subjects, FAS



Patient enrollment:
Feb 2011~Dec 2012
Participating Institutions: 30

Baseline Characteristics of the patients (n=49)

Gender, n (%)	Male	30 (61)
	Female	19 (39)
Median age, years (range)		63 (40-86)
ECOG Performance Status, n (%)	0	36 (73)
	1	13 (27)
Median duration from the diagnosis, days (range)		857 (3-7110)
Tumor histopathology, n (%)	Clear	48 (98)
	Unknown	1 (2)
Stage at the diagnosis, n (%)	I	9 (19)
	II	8 (16)
	III	8 (16)
	IV	24 (49)
Major sites of metastasis, n (%)	Lung	16 (33)
	Bone	6 (12)
	Liver	2 (4)
	Brain	2 (4)
	Others	15 (31)
Previous nephrectomy, n (%)	Yes	39 (80)

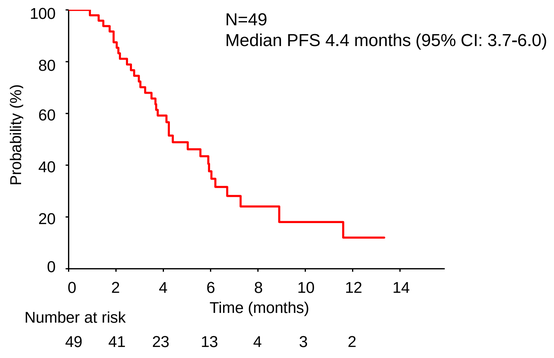
Response of the 1st-line TKI therapy, n(%)

Overall response	Sunitinib 34 (69)	Sorafenib 11 (22)	Axitinib 4 (8)	Total 49 (100)
CR	0 (0)	0 (0)	0 (0)	0 (0)
PR	8 (24)	4 (36)	2 (50)	14 (29)
SD	15 (44)	4 (36)	2 (50)	21 (43)
PD	10 (29)	3 (27)	0 (0)	13 (27)
NE	1 (3)	0 (0)	0 (0)	1 (2)
CR+PR	8 (24)	4 (36)	2 (50)	14 (29)

Objective response rate (ORR), n(%)

CR	PR	SD	PD	NE	CR+PR
0 (0)	4 (8)	28 (57)	15 (31)	2 (4)	4 (8)

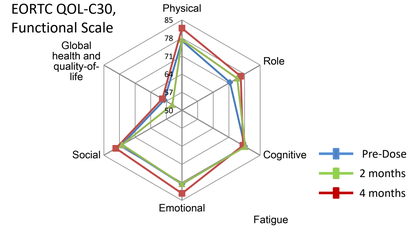
Progression-Free Survival (PFS)

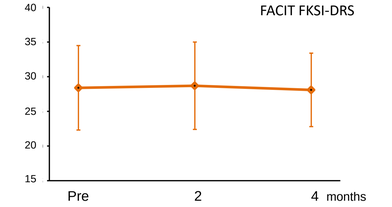


Adverse Events, (≥10% Incidence)

AEs, %	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Stomatitis	24	18	10	0	49
Hypertriglyceridemia	14	10	2	0	27
Hypercholesterolemia	16	8	0	0	24
Anemia	10	8	4	0	22
Thrombocytopenia	10	8	4	0	22
Interstitial lung disease	8	6	6	0	20
LDH increased	14	2	0	0	16
Rash	6	4	4	2	16
Hyperglycemia	8	4	4	0	16
Leukopenia	10	2	2	0	14
Fatigue	8	4	0	0	12
Hypoalbuminemia	8	2	0	0	10
CRP increased	10	0	0	0	10

QOL





Treatment with the administration of Everolimus

Median treatment duration, months (range)	4.4 (0.5-13.3)
Median relative dose intensity, %	81
Dose interruptions, n (%)	20 (41)
Dose reductions, n (%)	20 (41)
Reason for discontinuation, n (%)	
Progressive disease	28 (57)
Adverse event	9 (18)
Patient transfer	1 (2)
Other	1 (2)

Conflict of Interest

This study was funded by Comprehensive Support Project (CSP) of Public Health Research Foundation. The corporate and individual sponsors of this study are listed on the CSPOR website (http://www.csp.or.jp/cspor/kyousan_e.html).
The pharmaceutical manufacturer/distributor who had provided financial contribution as a corporate sponsor took no part in this study other than providing information relevant to proper use of the study drug(s).

Results

Fifty seven patients were enrolled from 02/11 to 12/12. Median age was 63 years, major sites of metastasis were lung (33%) and bone (12%), 80% had previous nephrectomy, previous TKI therapy were Sunitinib (69%), Sorafenib (22%) and Axitinib (8%). Median PFS was 4.4 months (95% confidence interval: 3.7-6.0). 8% had partial response and 57% had stable disease according to RECIST v.1.0. The incidence of adverse events (AEs) of all grades was 96%. Major AEs were stomatitis (49%), hypertriglyceridemia (27%) and hypercholesterolemia (24%). Serious AEs were stomatitis (10%), interstitial lung disease (6%) and rash (6%). There were no treatment related deaths. All QOL scores were not changed at 2 months, while dyspnea and global health scores of EORTC QLQ-C30 and FKSI-DRS score were worsened at 4 months.

Conclusion

This study is a first report of Everolimus as second line setting after failure of 1st-line TKI. Further study and long-term follow-up would be warranted.