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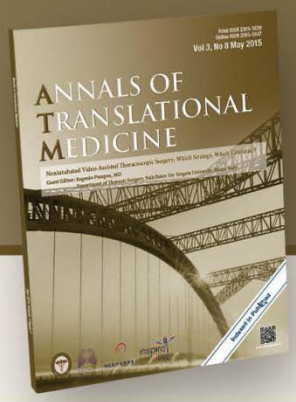

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Reviewer:

1. This study belongs to case series in clinical research design. So I suggest the authors to indicate this clearly in their title.

: I agree with your comment. I rewrite title of our manuscript as your comment as below.

[Treatment Strategy for Papillary Renal Cell Carcinoma Type 2: a case series of seven patients treated based on next generation sequencing data]

Page 1 line 1,2 : ***Treatment Strategy for Papillary Renal Cell Carcinoma Type 2: a case series of seven patients treated based on next generation sequencing data***

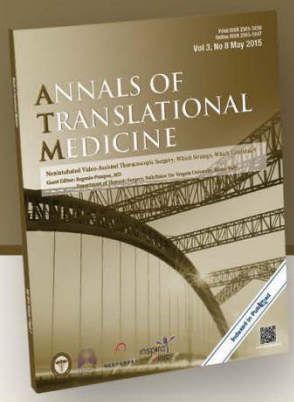
2. The section, patients and methods, should follow introduction section. Please re-organize accordingly.

: Thanks for your comment. I re-organized our manuscript according your comment.

Page 5 line 17- Page 7 line 19 : Patients and Methods section

3. Introduction seems inadequate. What has been known and has been unknown on precision oncology treatment of PRCC2, and the authors' comments on current progress should be presented in detail.

: Your comment is helpful to improve our manuscript. However, there have been no clinical trials or explorative treatments for PRCC2 based on genetic information due to rarity of PRCC2. In addition, current treatment guideline could not reflect the advance of comprehensive genomic analysis in PRCC2. Treatment guideline recommended only bevacizumab plus erlotinib treatment for HLRCC among PRCC2.



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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

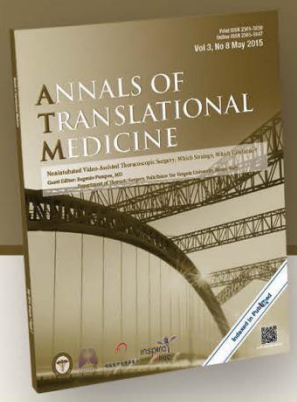
SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[f]		
Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Clinical trial • Sunitinib	• Cabozantinib • Everolimus	• Axitinib • Bevacizumab or biosimilar[e] • Erlotinib • Lenvatinib + everolimus • Nivolumab • Pazopanib • Bevacizumab or biosimilar[e] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) • Bevacizumab or biosimilar[e] + everolimus • Temsirolimus[d] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

Therefore, there are no reports of precision treatment of PRCC2 to introduce in our manuscript.

Page 5 line 2-7: ***However, current treatment guideline could not reflect the advance of comprehensive genomic analysis in PRCC2. Current treatment guideline suggested sunitinib or clinical trial as the first line treatment for metastatic non-clear renal cell carcinoma, including PRCC2. Treatment guideline recommended only bevacizumab plus erlotinib treatment for HLRCC among PRCC2. Moreover, there have been no clinical trials of treatment based on genomic information of PRCC2 because of disease rarity.***

4. I agree with the importance of precision treatment, but relying on genetic heterogeneity to provide treatment might be insufficient because clinical heterogeneity must also be considered.

: We definitely agree with your opinion. Clinical heterogeneities of tumor characteristics including metastatic site and number of metastatic site and risk models which consisted of interval from diagnosis to treatment, performance status and laboratory tests should be



considered for treatment of patient with metastatic renal cell carcinoma.

In metastatic renal cell carcinoma, two risk models have been frequently used to direct treatment: (1) Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model and (2) International Metastatic Renal Cell Carcinoma Database Consortisum (IMDC) Criteria.

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RISK MODELS TO DIRECT TREATMENT

Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model[a]

Prognostic factors	Prognostic risk groups
• Interval from diagnosis to treatment of less than 1 year	• Low-risk group: no prognostic factors
• Karnofsky performance status less than 80%	• Intermediate-risk group: one or two prognostic factors
• Serum lactate dehydrogenase (LDH) greater than 1.5 times the upper limit of normal (ULN)	• Poor-risk group: three or more prognostic factors
• Corrected serum calcium greater than the ULN	
• Serum hemoglobin less than the lower limit of normal (LLN)	

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria[b]

Prognostic factors	Prognostic risk groups
1. Less than one year from time of diagnosis to systemic therapy	• Favorable-risk group: no prognostic factors
2. Performance status <80% (Karnofsky)	• Intermediate-risk group: one or two prognostic factors
3. Hemoglobin < lower limit of normal (Normal: 120 g/L or 12 g/dL)	• Poor-risk group: three to six prognostic factors
4. Calcium > upper limit of normal (Normal: 8.5–10.2 mg/dL)	
5. Neutrophil > upper limit of normal (Normal: 2.0–7.0×10^9/L)	
6. Platelets > upper limit of normal (Normal: 150,000–400,000)	

Therefore, we added the information of prognostic risk group of patients with metastatic PRCC2. In addition, we revised our manuscript as your comment in discussion section.

Page 8 lines 5-6: ***Two patients had poor prognostic risk groups and one of intermediate risk group according to Memorial Sloan Kettering Cancer Center Prognostic Model [28].***

Page 14 line 18- page 15 line 2: ***Moreover, in terms of prognostic risk group according to clinical characteristics, this patient was categorized into intermediate risk group, not poor risk group in which other two patients with metastatic PRCC2 harboring FH mutation [27]. Therefore, we treated PRCC2 as clear cell RCC with axitinib and he might be have favorable***

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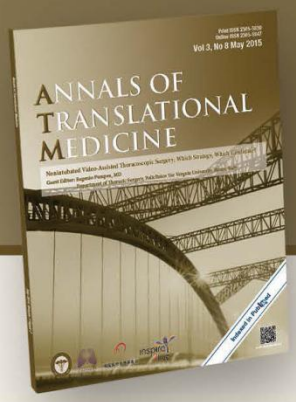


treatment outcome in this case.

The relationship between genetic alteration and clinical characteristics including risk groups have not been revealed neither previous studies nor our study. Further large scaled genetic studies of metastatic PRCC2 would give the information of the relationship between genetic and clinical characteristics to guide treatment of metastatic PRCC2.

Page 22 lines 1-4 Table1. Clinical information of papillary renal cell carcinoma type 2

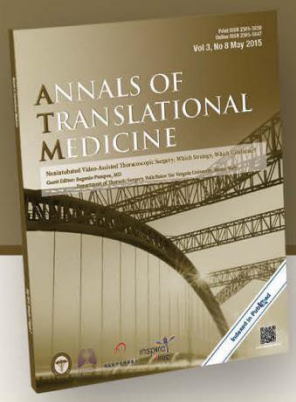
A. Clinical and pathological baseline characteristics

	Age (YO)[1]	Sex	Prognostic risk group	Stage	Grade	FU (Mo)[2]	Status	Tumor	Normal	Sampletype
1	30	M	NA	3	4	95.20	NED[3]	Kidney[6]	Kidney	Freshfrozen
2	74	M	NA	1	3	46.83	NED	Kidney[6]	Kidney	Freshfrozen
3	82	M	Intermediate	4	3	69.40	Dead	Kidney[6]	Kidney	Freshfrozen
4	63	M	NA	1	3	81.17	NED	Kidney[6]	Kidney	Freshfrozen
5	51	M	NA	1	3	108.60	NED	Kidney[6]	PB[4]	Freshfrozen
6	27	M	High	4	NA	14.50	Dead.	Bone[7]	PB	FFPE[5]
7	26	F	High	4	3	35.83	Dead	Kidney[7]	PB	FFPE

[1]Year-old; [2]Months; [3]No evidence of disease; [4]Peripheral blood; [5]Formalin fixed paraffin embedded; [6]Surgical specimen; [7]Percutaneous needle biopsy specimen

5. Treatment outcomes such as survival and time to progression should be provided in detail.

: We described treatment outcome and time to progression in table 1B. As your comment, we added more information of treatment outcome and overall survival in result section



and table 1B.

Page 9 line 23- page 10 line 5: *After we found the FH germline mutation, the patient was treated with a combination of bevacizumab (an anti-VEGF antibody) and erlotinib (an epithelial growth factor receptor [EGFR] TKI) and showed a durable response of 40 weeks (Figure 4A). Disease progression after bevacizumab and erlotinib treatment, there was no effective treatment strategy. In this patient, overall survival (OS) duration between diagnosis to death was 14.5months.*

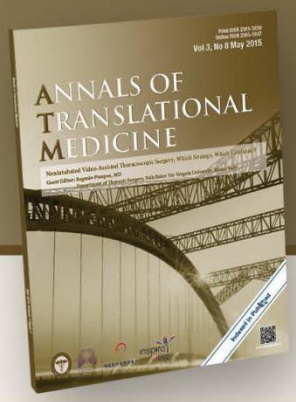
Page 10 lines 9-12: *Time to progression of pazopanib treatment was 52weeks. Her disease also harbored PMS2 alteration (Figure 4B). However, her performance status did not permit further treatment, such as immune check point inhibitor. She had 35.8 months of overall survival.*

Page 10 lines 16-17: *He responded axitinib treatment for a long duration (87weeks) until adverse events forbade him from receiving treatment (Table 1B) (Figure 4C).*

Page 22 lines 5-7 Table1. Clinical information of papillary renal cell carcinoma type 2

B. Medical treatment of stage IV PRCC2 patients.

.	Metastasis Sites	Treatment	No.of cycle	Time to progression (weeks)	Best Response	Treatment off	Overall survival duration
3	Lung	Temsirolimus	Week 12	23	SD[1]	Adverse event	69.4months
	Adrenal	Axitinib	22	87	PR[2]	Patient	



	gland					wish	
6	Bone, liver, Lymph node	Temsirolimus	Week 4	4	PD[3]	PD[3]	14.5months
		Axitinib	1	4	PD[3]	PD[3]	
		Gemcitabine plus cisplatin	1	4	PD[3]	PD[3]	
		Pembrolizumab	2	2	PD[3]	PD[3]	
		Bevacizumab + erlotinib‡	13	40	SD[1]	PD[3]	
		Nivolumab+ipilimumab	1	2	PD[3]	PD[3]	
7	Bone	RTx1*				PD[3]	35.8months
	Liver	Temsirolimus	Week 26	26	SD[1]	PD[3]	
	Adrenal gland	High dose interleukin-2	6	19	SD[1]	PD[3]	
	Peritoneum	RTx2[†]				PD[3]	
		Pazopanib‡	14	52	PR[2]	PD[3]	

*Tomotherapy at bone metastasis; [†]Tomotherapy at bone, adrenal gland, abdomen wall, pelvis metastasis; ‡Precision treatment using NGS data; [1]Stable disease; [2]Partial response; [3]Progressive disease

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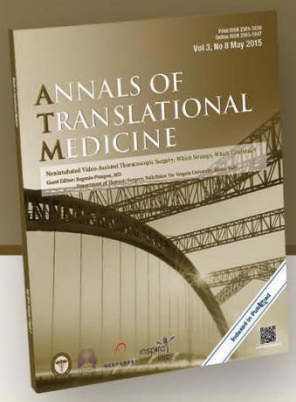

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