Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled 'Clinical and prognostic significance of CCR8 protein expression in gastrointestinal stromal tumors'. (ID: 55152).

We have studied reviewer's comments carefully and tried our best to revise our manuscript according to the comments. We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours respectfully

Wan-jiang Xue, PhD

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E-mail: xuewanjiang@ntu.edu.cn

List of Response

Responds to the reviewer's comments: (point by point)

Reviewer #1:

1. Reviewer: 1.Conclusion says that CCR8 is predictive biomarker. CCR8 coud be only prognostic marker.We do not know this patient patient or metastatic or receving any teratment.We can not say predictive biomarker.

Response: Thank you very much for this comment. It is very helpful for revising and improving our paper. According to your suggestion, we have modified the conclusion to"CCR8 is a prognostic biomarker for malignant potential of GISTs, with high expression correlated with malignancy and poor prognosis.", making the statement more accurate.

2.Reviewer：2.If You have follow-up data in adjuvant setting what is the disease free survival Please show us Which patients dou you have.We can not put in same basket adjuvant and metastatic disease

Response: Thank you for your comments. Since the cases included in this study ranged from 2002 to 2012, it was the time period from the initial application to mature application of imatinib for the treatment of GIST. Our hospital did not introduce imatinib at that time. Thus, patients we enrolled had not been treated with postoperative tyrosine kinase inhibitors during the research(we have stated in the materials and methods), besides, All patients included in this study were treated with surgical resection, without preoperative radiotherapy or chemotherapy. Cases with distant metastasis were not enrolled in the research. In the following study, we have enrolled patients with preoperative or postoperative adjuvant therapy and increased the data of disease-free survival.

Imatinib has been approved for the usage of the following diseases in recent years:

Imatinib, a tyrosine kinase inhibitor, is a small molecule protein kinase inhibitor that blocks the action of one or more protein kinases. Clinically used for the treatment of chronic myelogenous leukemia and malignant gastrointestinal stromal tumors.

Approved for the treatment of chronic myeloid leukemia in 2001, accelerated in 2002 for the treatment of advanced or metastatic GIST. In 2008, it was routinely approved for metastatic GIST treatment.

In 2008, it was accelerated for adjuvant therapy in patients who had resected GIST tumors but still had high risk of recurrence. At present, the indication has been modified, and the post-operative medication time has been extended from the previous standard of 1 year to 3 years.

In August 2011, the National Comprehensive Cancer Network updated its clinical practice guidelines to recommend adjuvant treatment with imatinib for high-risk GIST patients for 3 years.

Reviewer #2:

1. Reviewer: In this study, Li and colleagues assessed clinical and prognositic significance of CR8 protein expression in GIST. They analysed a large number of tissues with immunohistochmistry and found that there is a close relationship between the prognosis of GIST and expression of CCR8. Moreover, they showed immune regulation networks using KEGG/GO enrichment analysis. This is a carefully done study and the findings are of considerable interest. A few minor revisons are listed below. 1. Table 1, Numbers are inconsistent in Tumor location 2. Table 2, The title should be univariate and 'multivariate' analyses.

Response: Thank you very much for this comment. It is very helpful for revising and improving our paper. According to your suggestion, we have modified the data and the table.

Characteristic	n	CCR8-	CCR8+	Pearson χ^2	P
Total	12	51(40.80)	74(59.20)		
Gender				1.439	0.230
Male	62	22(35.48)	40(64.52)		
Female	63	29(46.03)	34(53.97)		
Age				2.268	0.132
≤60 years	81	37(45.68)	44(54.32)		
>60 years	44	14(31.82)	30(68.18)		
Tumor size, cm				8.999	0.018*
<5	25	16(64.00)	9(36.00)		
5-10	80	30(37.50)	50(62.50)		
>10	20	5(25.00)	15(75.00)		

Mitotic index (per 50 HPFs)				8.196	0.017*
0-5	70	34(48.57)	36(51.43)		
6-10	30	13(43.33)	17(56.67)		
>10	25	4(16.00)	21(84.00)		
Gross classification				1.035	0.309
Single nodule	92	40(43.48)	52(56.52)		
Multiple nodules	33	11(33.33)	22(66.67)		
Tumour location				11.673	0.003*
Stomach	69	34(49.28)	35(50.72)		
Intestine	42	9(21.42)	33(78.57)		
Others	14	9(64.29)	5(35.71)		
AFIP-Miettinen risk				4.308	0.038*
Very low–Moderate risk	85	40(47.06)	45(52.94)		
High risk	40	11(27.50)	29(72.50)		

Table 2 Univariate and multivariate analyses of factors affecting prognosis in

Variable	Year	Univariate analysis				Multivariate analysis			
		P>|z|		95% CI		P>|z|		95% CI	
Gender									
Male vs Female	10	0.448	0.754	0.364	1.563				
	5	0.140	0.547	0.246	1.219				
Age (years)									
≤60 vs >60	10	0.964	0.983	0.469	2.060				
	5	0.524	0.767	0.339	1.735				
Tumour size (cm)									
<5 vs 5-10 vs >10	10	0.004*	2.417	1.336	4.371	0.047*	1.876	1.010	3.487
	5	0.019*	2.160	1.137	4.102				
Mitoticindex/5HPFs									
0-5 vs 6-10 vs >10	10	<0.001*	2.696	1.687	4.310	0.002*	2.177	1.345	3.523
	5	<0.001*	2.727	1.645	4.522	<0.001*	2.335	1.401	3.889
Gross classification									
Single vs Multiple	10	0.300	1.569	0.670	3.677				
	5	0.315	1.601	0.639	4.009				
Tumour location									
Stomach vs Intestine	10	0.185	1.396	0.853	2.284				
	5	0.281	1.339	0.787	2.279				
CCR8 expression									
High vs Low	10	0.011*	2.738	1.261	5.949	0.037*	2.663	1.062	6.677
	5	0.005*	4.651	1.593	13.580	0.027*	3.432	1.151	10.232

GISTs