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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6820
Title: Targeting receptor tyrosine kinases in gastric cancer
Reviewer code: 02769326
Science editor: Qi, Yuan
Date sent for review: 2013-10-29 19:26
Date reviewed: 2013-11-07 03:05

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

The manuscript entitled "Targeting receptor tyrosine kinases in gastric cancer" by Asahiro Morishita is a mostly well written overview of the completed and ongoing phase III trials involving the addition of RTK inhibitors to standard treatments of care. The manuscript sets out to delineate the underlying molecular basis of the RTK pathways in gastric carcinoma, a potentially important and timely topic, however the execution is incomplete and the manuscript requires major revision and additional review to be publishable. There are two significant major concerns. The first is that Figure 2 appears to be a duplicate of that already found in the literature previously published by this group. Without clarification of this issue this manuscript is not publishable. The second significant concern that needs to be addressed is a more complete and up to date review of other RTKs involved in gastric carcinoma (for instance the role of the TAM RTK family (Tyro3, Axl, MerTK) in gastric carcinoma has been multiply described), details of which are included in the suggestions below. Suggestions to authors: -Please define all of the abbreviations in the 'Core Tips' section and throughout the paper. -Core tips section needs some grammatical corrections. -What makes Receptor TKs different specifically is that they contain an extracellular portion, this should be clarified as only the transmembrane and kinase motif are mentioned. -Intro section should use generic instead of brand names for the therapeutics since the brand names vary by country of marketing. -'RTKs in cellular signaling' section is incomplete. There is no discussion of down-stream activation of pathways many of which are described, and the resulting cellular changes. MUCH too brief. Also some discussion of the normal functions of RTKs, ie they are necessary for a variety of normal cellular physiologic processes. And in many cases are NORMALLY present. The implication from this section is that they are only present in malignant cells. -The authors refer to the use of RTK

inhibition in multiple clinical trials and then cite clinical trials that do not target RTKs, ie imatinib in the case of CML, while imatinib does target the KIT RTK in GIST. Again confusing the concept of targeting RECEPTOR TKs versus just TKs. - In the 'RTKs in gastric cancer' section, the authors discuss the 21 families of RTKs, and discuss the 'potential for intrafamilial dimerization in gastric cancer', however this potential is there in normal settings and perhaps physiologically relevant for normal function, this should be clarified. - There needs to be some commentary on how each of the RTKs introduced in the manuscript differs and how each RTK inhibitor works, and in general that there is more than one way to target an RTK. Ie inhibiting/decreasing receptor expression, sequestering ligand, and or directly inhibiting the ATP binding activation site. -the 'RTKs in gastric cancer' section needs to be more complete. The explanation of the molecular biology and intracellular signaling of RTKs relies on studies conducted 15 to 20 years ago (References 16-18, 20). Surely there have been some more recent advances on the understanding of RKT signaling. I am aware of several reports on the significance of the TAM (aka Axl family) RTK family in gastric carcinoma prognosis and several studies that inhibit it with some efficacy. These should be discussed for completeness. There may be others to be discussed. Anticancer Res. 2002 Mar-Apr;22(2B):1071-8.Clinical significance of AXL kinase family in gastric cancer. Wu CW, Li AF, Chi CW, Lai CH, Huang CL, Lo SS, Lui WY, Lin WC. Mol Carcinog. 2007 Feb;46(2):155-64.Growth arrest-specific gene 6 and Axl signaling enhances gastric cancer cell survival via Akt pathway. Sawabu T, Seno H, Kawashima T, Fukuda A, Uenoyama Y, Kawada M, Kanda N, Sekikawa A, Fukui H, Yanagita M, Yoshibayashi H, Satoh S, Sakai Y, Nakano T, Chiba T. -The 'targeting other RT

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COMMENTS TO AUTHORS

The review by Morishita et al provides a well documented revisión of the literatura on the role of receptor tyrosine kinase inhibitors to treat advanced gastric cancer. There are some modifications that shuld be considered. First, Figure 2 does not seem to add to the already published article (ref. 22) and could be removed. the authors could choose to provide a schematic representation of RTKs with increased expression in AGC, but its message would be similar to that of figure 1. Abbreviations are missing for most genes on first appearance in the text. They should be indicated there and used consistently afterwards. For instance, in page 8 appears "human epidermal growth factor receptor" and "platelet-derived growth factor receptor", which have been designated by their abbreviations previously. In page 14 appears gastroesophageal cancer (GEJ), which have been used without abbreviation earlier. The meaning of 5-FU is not indicated. Does the sentence "The survival rate of gastric cancer has remained at 20-30% over the past 35 years. (page 4, line 9)" refers to a 5-year interval? Please clarify. The sentences "Receptor tyrosine kinases (RTKs) consist of/are characterized by a transmembrane and tyrosine kinase domain…" (pages 4 and 6) have to refer to the existence of an extracellular domains, that are the regions that identify the subfamilies of RTKs. In page 9 there are several instances of words/sentences written in a different letter size. Despite the extense list of references, the rapidly growing literature adds new studies everyweek. Although it is imposible to include them all, the authors should consider to include the recent developments on the use of Trastuzumab: Singh R, Kim WJ, Kim PH, Hong HJ.ExpMol Med. 2013 Nov 1;45:e52. doi: 10.1038/emm.2013.111. and Qiu MZ, Li Q, Wang ZQ, Liu TS, Liu Q, Wei XL, Jin Y, Wang DS, Ren C, Bai L, Zhang DS, Wang FH, Li YH, Xu RH.Int J Cancer. 2013 Oct 23. Page 6. “metabolism pathways” should be “metabolic pathways” Page 7. “which are characterized by similar structures

and the potential for intrafamilial dimerization in gastric cáncer" Please, clarify. "It has been reported that common alterations and mutations that may serve as targets for molecularly targeted treatments have been identified in gastric cancer." Not clear In page 14 "Regarding adverse events, grade 4 cardiac toxicity and vomiting were observed in 47 patients with metastatic gastric cáncer" has to provide %.