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Name of Journal: *World Journal of Gastrointestinal Oncology*

ESPS Manuscript NO: 22024

Manuscript Type: REVIEW

Oct 9, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: **22024**-review.doc).

Title: **Molecularly targeted therapy for advanced hepatocellular carcinoma - a drug development crisis?**

Author: Kiruthikah Thillai, Paul Ross, Debashis Sarker

Name of Journal: *World Journal of Gastrointestinal Oncology*

ESPS Manuscript NO: 22024

The manuscript has been improved according to the suggestions of reviewers:

11 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

Reviewer 1

Comment on the manuscript 22024 by Thillai, et al. Thillai et al comprehensively summarized the current up-date of the genetic abnormality of HCC. The content is timely and useful for clinical and basic researchers of HCC. A total of 5 minor revisions are required for corrections:

1) Next generation sequencing analyses revealed that TERT is the most frequently up-regulated gene due to promoter mutation in HCC. Then authors should refer that TERT is the promising target in "Perspective".

A section on TERT mutations has been added to the section entitled 'The genetic background of HCC'

2) Is the reference '13' in Introduction (page 3, line 31) correct?

This reference has been amended

3) Cited articles for next generation sequencing are old and the sample number is small. The authors should cite the article by Totoki Y, et al (Nature Genetics, 2014) and Schulze K, et al (Nature Genetics, 2015).

The suggested papers are now discussed in the section entitled 'The genetic background of HCC'

4) In "Underlying liver cirrhosis", direct acting antivirals drug for HC infection should be referred (as combination therapy in "Perspective").

A section of direct acting anti-viral therapy has been added to this section

5) Clinical trial by anti-PDL1 agent nivolumab might be presented by Anthony B. El-Khoueiry in ASCO 2015. It should be clearly stated.

This has now been referenced

Reviewer 2

I suggest that the authors could provide the discrimination between western and eastern therapeutic effects on HCC patients in the table 3

An extra column citing geographical locations for each trial has now been included

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Oncology*.

Sincerely yours,

A handwritten signature in cursive script that reads "K Thillai".

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