Reviewer’s report

Title: Frequent expression loss of Inter-alpha-trypsin inhibitor heavy chain (ITIH) genes in multiple human solid tumors: A systematic expression analysis

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Reviewer: Piotr Potemski

Reviewer’s report:

General
In the present study the authors examined the expression of ITIH genes in human tumors. The question raised by the authors is quite novel and important. They used two methods of assessing gene expression on mRNA level and one method on protein level and evaluated a broad spectrum of malignant and normal tissues with a special interest to breast cancer.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Why was HER2 expression not evaluated? It is a strong prognostic factor involved in biology of breast cancer.

2. Table 5 is unclear. P values of log-rank test are shown but patient groups that are compared are not easily defined. One may assume that groups are defined on the basis of clinicopathological factors. If so, how do the authors explain such strong prognostic value of every clinicopathological factor except for histological type and estrogen receptor status? It is especially striking with respect to, for example, progesterone receptor status where highly significant differences in both tumor-related deaths and recurrences are observed.

Moreover, I have found an error in line ‘Histological type other’ where in a group of 17 pts evaluated for recurrence a total number of events equals 50.

3. The authors have found highly significant association between ITIH2 and estrogen receptor. In order to assess the prognostic value of ITIH2 not only all patients but also uniform groups with respect to estrogen receptor status should be evaluated. It seems to be possible especially in ER-positive subgroup (31 vs 66 pts).

4. I would strongly suggest to avoid of using a statement that ITIH2 expression is associated with reduced survival in breast cancer even with the reservation that this relationship is not significant. Every other clinicopathological factor except for histological grade is much more related with survival than ITIH2 (Table 5).

5. In my opinion, survival analysis in its present form adds very little if any to the scientific quality of the paper.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Details on adjuvant treatment should be added to Table 2.
2. What was the reason for choosing ITIH2 for detailed analysis in breast cancer? It should be explained somewhere in Discussion.
3. Page 11/35 line 3 from the bottom: instead of ‘remission’ should be ‘recurrence’.
4. Immunohistochemical scoring system for ITIH2 is not described. The authors have only mentioned that it was based on a scale consisted of 12 (0-12) points. Details should be provided.
5. In this study, the maximum number of axillary lymph nodes involved equals 3. Why were patients with higher number of lymph nodes excluded?

Discretionary Revisions (which the author can choose to ignore)

I have found the paper definitely too long. It needs to be shortened remarkably.

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'