Author's response to reviews

Title: BRCA1-mutated and basal-like breast cancers have similar aCGH profiles and a high incidence of protein truncating TP53 mutations

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Version: 2 Date: 22 April 2010

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To the attention of

Dr. Melissa Norton
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Amsterdam, April 22, 2010

Dear Dr. Norton,

Please find attached our manuscript entitled ‘BRCA1-mutated and basal-like breast cancers have similar aCGH profiles and a high incidence of protein truncating TP53 mutations’, by Holstege et al., which we would like to submit for publication in BMC Cancer. We expect this manuscript to be interesting for BMC Cancer for the following reasons:

1. In this work we show that molecular characteristics previously thought to be specific for BRCA1-mutated tumors are shared with basal-like breast tumors. We found that BRCA1-mutated and basal-like tumors have similar aCGH profiles, similar amounts of copy number aberrations and similar TP53 mutation frequency and types. All these features are different from luminal breast tumors.

2. We identified overlapping genomic regions of gain and loss that differentiate BRCA1-mutated and basal-like from luminal tumor groups. Clustering on the basis of these regions separated luminal tumors from the BRCA1-mutated and basal-like breast tumors.

3. By complete p53 sequencing of BRCA1-mutated, basal-like and luminal breast cancer subtypes, we found that p53 is mutated in almost all tumors of the BRCA1-mutated and basal-like breast cancer groups compared with 25%-40% of the luminal tumors. This marked increase in p53 mutations in BRCA1-mutated and basal-like tumors is caused by a selective increase in complex TP53 mutations such as insertions and deletions, resulting in a truncated gene product.

4. Complex TP53 gene mutations in the BRCA1-mutated breast tumors may be due to its genomically instable phenotype, suggesting that the increase of complex TP53 mutations in basal-like breast tumors may be due to a similar defect in DNA repair.

These molecular tumor characteristics support the notion that a fraction of basal-like breast tumors, like BRCA1-mutated tumors, might be effectively targeted with combinations of DNA-damaging drugs or PARP inhibitors (which target the double-strand break repair defect of BRCA1-deficient cells) and therapeutics that are synthetic lethal with p53-deficiency.

As possible reviewers we would like to suggest the following experts:
I am looking forward to hearing from you.

Yours sincerely,

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