Letter to Editor and Reviewers

We are very grateful to the editor and reviewers for their helpful and constructive suggestions. We have made the following changes in line with these suggestions:

Editorial suggestions:

1. Author contributions. We have added the text: *"Author contributions: All authors contributed their views in this Editorial. All authors read and agreed to the final manuscript."*

2. We have added a section on Supportive Foundations: "*Supportive Foundations: DM would like to acknowledge support by the Saudi Arabian government ; AT and AHS acknowledge Breast Cancer Now ; CW acknowledges the UK Engineering and Physical Sciences Research Council and SPL acknowledges the Scottish Funding Council."*

3. Telephone and Fax numbers have been added.

4. The Audio Core Tip has now been prepared and submitted.

5. For the references, the PMID and DOI has been added. Reference 17 (now reference 21) has been identified in the text.

6. With the addition of extra references, the reference numbers have changed throughout

7. A reference to Table 1 has now been made in the text.

Changes requested by the Reviewers:

Reviewer 1:

1. As for Core type. Sentence "Ki67 expression at baseline and after 2 weeks (after that?) can provide useful prognostic and predictive information...' It will be more understandable if adjuvant therapy is mentioned before it.
   - *We have added the phrases "In neo-adjuvant studies" and "treatment" to make this clearer.*

2. The article is excellent, but do you need so many co-authors, if this is not original research work?
   - *The co-authors contributed their views which were combined in the final manuscript*

Reviewer 2:

1. This is a useful general outline of the endocrine therapy predictive biomarkers landscape in breast cancer. It may serve as a general reference on the subject and a look-out for upcoming developments. Some specific points: - In the first paragraph of page 4 it should be clarified that the discussion refers to metastatic disease.
   - *The word "metastatic" has now been inserted before disease.*

2. - In the second paragraph of page 5 it should be clarified that the described acquired resistance related to ER loss happens following neo-adjuvant treatment.
    - *The word "neo-adjuvant" has been added to clarify.*

3. - In the last paragraph of page 5 continuing in the next page a reference to CDK inhibitors as a means of overcoming resistance and putative predictive markers should be mentioned in addition to the other inhibitors of PI3K and mTOR considering that CDK-CyclinD-Rb may be positioned downstream.
    - *The word "CDK" has been included along with the other inhibitors.*

4. - In the multigene signature section it should be stressed that the use of these signatures are in adjuvant setting.
    - *The phrase "in the adjuvant setting" has been added.*

5. - The last sentence of the 1st paragraph of page 7 is not very clear. All predictive biomarkers are derived from studying groups of patients and define a statistical probability for the individual patient. In addition, the oncotype dx signature mentioned just below provides a specific distant recurrence probability at 10 years in the individual patient.
    - *This last sentence has been deleted*

6. - Later in the same paragraph it should be mentioned that the recently published intermediate group TAILORx study does not exclude a benefit of chemotherapy for pre-menopausal patients with a high-intermediate score.
    - *We have added the sentence "The trial results though did not exclude a benefit of chemotherapy for patients aged < 50 years with a high-intermediate score. [28]."*

7. -In page 8, third paragraph. The sentence implies that prognostic markers (in this case of distant recurrence) are also predictive of response to therapy (in this case chemotherapy) which is not correct. Authors should modify.
    - *We have modified "In this trial, it was demonstrated that the group of patients identified as high risk for recurrence according to clinical and pathological factors but who were classified as Low Risk by MammaPrint did not benefit from chemotherapy and in these patients endocrine therapy alone was adequate [36]. This supports the potential value of a molecular approach over more traditional criteria."*

      to

      "In this trial, it was demonstrated that the group of patients identified as high risk for recurrence according to clinical and pathological factors but who were classified as Low Risk by MammaPrint were unlikely to benefit from chemotherapy [36]."

8. - In page 10 NET should be explained.
    - *We have converted this to "neoadjuvant endocrine therapy"*

9. - In the table it should be MKI67 and ERBB2 (instead of HER2).
    - *We have modified these to MKI67 and ERBB2.*

10. Also in the table it could be useful to add columns with the indications of the tests and populations that have validation data.
    - *We have added key references for each test in Table 1*

11. - A brief discussion of alternative ERs (ERbeta, truncated ERs and GPER1) as predictive biomarkers could be of interest.
    - *We have added a new paragraph: "Other forms of ER include ER-beta, G-protein coupled ER (GPER1) (previously GPR30) and mutated versions of ER-alpha and these have all been investigated as predictive markers of response to endocrine therapy. The role of ER-beta appears complex and dependent on whether ER-alpha is present leading to a bi-faceted role [8], however several clinical studies have suggested predictive effects for specific ER-beta isoforms [8, 9]. Low expression of the membrane-bound GPER1 is associated with favourable outcome to tamoxifen [10] while high expression has been associated with tamoxifen resistance [11]. The role of ER mutants is discussed below."*

Reviewer 3 did not suggest any changes

We hope these changes are sufficient and appropriate to allow the manuscript to be accepted.

We look forward to your response

Simon Langdon