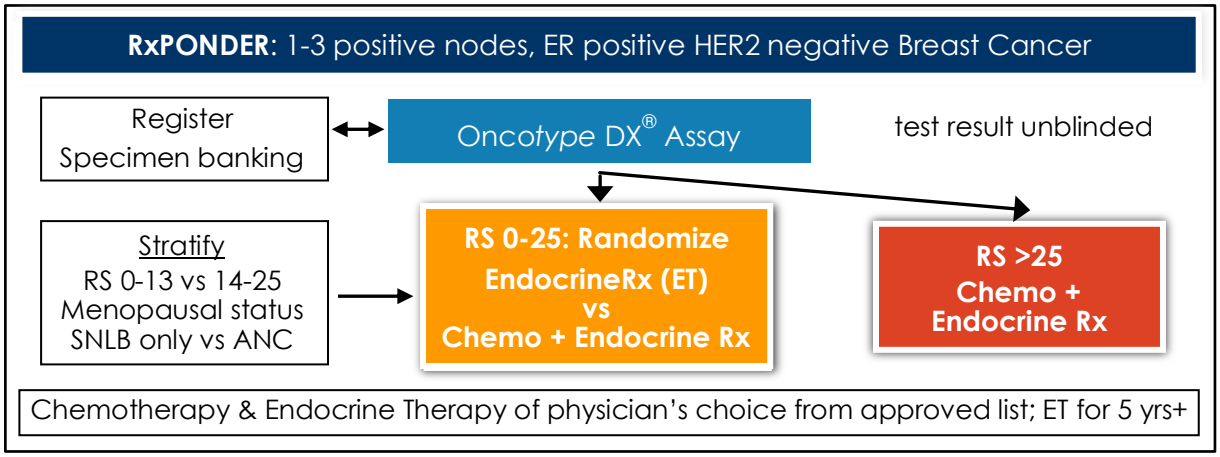
Summary and Evaluation of the RxPONDER Interim Results

Summary

Trial Design and Objectives

The RxPONDER trial aims to demonstrate that the Multi-parameter gene expression assay (MPA), Oncotype DX, can predict chemotherapy benefit for patients with 1-3 involved axillary nodes (1-3N+).



Key: RS = Oncotype DX recurrence score; SNLB = sentinel lymph node biopsy; ANC = axillary node clearance; ET = endocrine therapy; vs = versus.

RxPONDER resembles TAILORx in overall design, the key difference being that the RxPONDER primary analysis is designed to detect whether any chemotherapy benefit increases according to Oncotype DX recurrence score (RS), rather than to demonstrate noninferiority like TAILORx. The primary outcome measure is invasive disease free survival (IDFS; includes local invasive, regional and distant breast cancer recurrence, death from any cause and second cancers); secondary outcomes include overall survival and distant disease free survival (DDFS; i.e. distant recurrence, death from any cause and second cancers).

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Results from the third interim analysis were released by the Data Monitoring Committee (DMC) because of a convincing benefit for chemotherapy in the premenopausal group. There is a well-documented increasing use of Oncotype DX for all node-positive patients in the USA and elsewhere. This interim analysis was performed with a median follow-up of 5.1 years and included only 50% of the pre-specified number of events required for the primary analysis. All publicly information about the analysis that is currently available is from the SABCS presentation.

Patient population summary

A total of 5083 patients with luminal-type (i.e. ER positive, HER2 negative) breast cancer were randomised with 5015 included in the analysis. There were no major imbalances between either the trial arms or the premenopausal and postmenopausal groups.

Characteristic	**Distribution in analysed population**		
Menopausal status	*Premenopausal*: 33%	*Postmenopausal*: 67%	
RS (premenopausal)	*0-13*: 39%	*14-25*: 61%	
RS (postmenopausal)	*0-13*: 45%	*14-25*: 55%	
Tumour grade	*Grade 1*: 25%	*Grade 2*: 65%	*Grade 3*: 10%
Tumour size	*T1 (<= 2cm)*: 25%	*T2-3 (>2cm)*: 42%	
Number of involved nodes	*1N+*: 66%	*2N+*: 25%	*3N+*: 9%

Results

The trial hypothesis, that there would be a proportionally greater chemotherapy benefit as RS increases, was not met (interaction of chemotherapy and RS p-value = 0.30) so the analysis was performed on the basis of simple superiority for chemotherapy.

The rate of treatment non-acceptance was about 5.5% across trial arms. Only 3% of premenopausal patients in the chemotherapy plus endocrine therapy (ET) arm and 16% in the ET alone arm received ovarian suppression. (The proportion of premenopausal patients aged ≥50 at trial entry was 31%.) Overall, 54% of events in the postmenopausal group and 19% of events in the premenopausal group were unrelated to breast cancer. These were equally frequent in both trial arms (absolute difference =0.3%).

a. Premenopausal result:

- There is unequivocal benefit for chemotherapy use (absolute IDFS benefit at 5 years =5.2%; adjusted hazard ratio (HR) =0.54: 95% confidence interval (CI) 0.38-0.76, p=0.0004)
- The IDFS benefit applies across the RS subgroups and to the 1N+ subgroup. (For the RS sub-groups, absolute IDFS benefit at 5 years for RS 0-13 =3.9%, p=0.04; RS 14-25 =6.2%, p=0.005.)
- Overall survival for the chemotherapy plus ET group was significantly superior (HR=0.47: 95% CI 0.24-0.94, p=0.03).

b. Postmenopausal result:

- There was a minimal (non-significant) absolute IDFS difference of 0.3% between the chemotherapy plus ET arm and the ET alone group (HR =0.97: 95% CI 0.78-1.22, p=0.82).
- There were more IDFS events in the higher RS subgroup compared to the lower RS subgroup (191 vs 114 respectively) but no difference between trial arms in either subgroup.
- IDFS was not significantly different between trial arms in either the 1N+ or the 2-3N+ subgroups. (Note: there were nearly twice as many patients in the 1N+ subgroup than in the 2-3N+ subgroup.)

Evaluation

The RxPONDER population is appropriate to answer the trial question although tends towards lower clinico-pathological risk. In particular, the proportion of patients with 2 and especially 3 involved nodes is lower than might be expected. Patients with grade 1 tumours are over-represented whilst those with grade 3 are under-represented.

The influence of tumour grade on the result is uncertain. Some, but not all, previous analyses have shown that grade remains prognostic in the presence of Oncotype DX RS. Similar data are lacking for other MPA's although fewer such analyses have been performed.

The premenopausal result is likely to be the consequence of imbalance between the arms resulting from chemotherapy-induced menopause. This also affected TAILORx and MINDACT. A patient-level meta-analysis of 4 historic trials comparing (CMF) chemotherapy and GnRH agonists shows no difference in recurrence rates or breast cancer mortality between these treatments[1]. Whilst it is possible that there is a genuine biological difference in chemotherapy sensitivity of luminal-type breast cancer between premenopausal and postmenopausal breast cancer, this cannot be established without controlling for chemotherapy-induced menopause. OPTIMA, through mandating ovarian suppression, is widely recognised as the only trial that can establish the utility of MPA use for premenopausal patients.

The postmenopausal result, in showing that there is no chemotherapy benefit for patients with 1-3 involved lymph nodes, appears to support the predictive hypothesis. There is however uncertainty about the result for several reasons.

1. The data were analysed for chemotherapy superiority rather than for non-inferiority despite de-escalating treatment. Non-inferiority however cannot be established on the basis of the absence of a significant difference between treatments in a superiority study[2].

An exploratory analysis using a non-inferiority hypothesis would suggest for this postmenopausal group, that the upper limit of the 95% CI for the HR allows the 5-year IDFS rate for the ET only group to be up to 2.2% lower than the chemotherapy plus ET group. This analysis is however limited by the inclusion of non-breast cancer events.

2. IDFS captures all events related to breast cancer and its treatment but additionally includes events entirely unrelated to breast cancer. Unrelated events make superiority harder to prove but can lead to false conclusions of non-inferiority. In the case of RxPONDER, 54% of events in postmenopausal patients were unrelated to breast cancer and occurred with equal frequency in both trial arms. Had the exploratory non-inferiority analysis been able to adjust for unrelated events then it is doubtful whether an acceptable non-inferiority level could have been established.

Whilst IDFS is a legitimate endpoint for de-escalation studies as it captures treatment harms, it is difficult to claim non-inferiority based on IDFS alone. Demonstrating non-inferiority using a more breast-cancer specific outcome measure such as recurrence-free interval (RFI) or distant recurrence-free interval (DRFI) as in the case of TAILORx strongly supports non-inferiority conclusions drawn from IDFS. There is no currently available information about future plans for a non-inferiority analysis of the RxPONDER postmenopausal data or the inclusion of RFI or DRFI as an outcome measure.

3. The data as presented are from an interim analysis that includes only 50% of the pre-specified number of events required for the primary analysis. This does not affect the premenopausal result but means that it is not yet possible to draw firm conclusions about the outcome for the postmenopausal population according to the available details of the analysis plan.

4. The IDFS outcome for the two nodal subgroups (1N+, 2-3N+) are individually similar to the entire postmenopausal population but the confidence intervals are broader, which is the consequence of their limited size and number of events reported to date. There is no consensus as to whether the results from a de-escalation study apply to small high-risk subgroups. Few trials are adequately powered to answer subgroup questions, which are most convincingly addressed by a meta-analysis.

Overall, we consider the RxPONDER results to be preliminary:

- Only 50% of events required for the planned primary analysis have occurred.
- The postmenopausal result, whilst superficially supporting abandoning chemotherapy for patients with 1-3 positive nodes and RS ≤25, is associated with substantial uncertainty arising from the limited number of events reported and the influence of the 54% of events in the analysis being unrelated to breast cancer. Further follow-up and an additional analysis based on DRFS or preferably DRFI (which only includes distant recurrences and deaths from breast cancer), is required to make a convincing case.
- The premenopausal result emphasises the risk from changing clinical practice without robust evidence. Only OPTIMA is able to explore the effect of chemotherapy-induced menopause.

These comments are made in advance of a formal peer-reviewed publication; this is likely during 2021.

[1] LHRH-agonists in Early Breast Cancer Overview group. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet 2007;369:1711

[2]Mauri & D'Agostino. Challenges in the Design and Interpretation of Noninferiority Trials. N Engl J Med. 2017;377:1357.