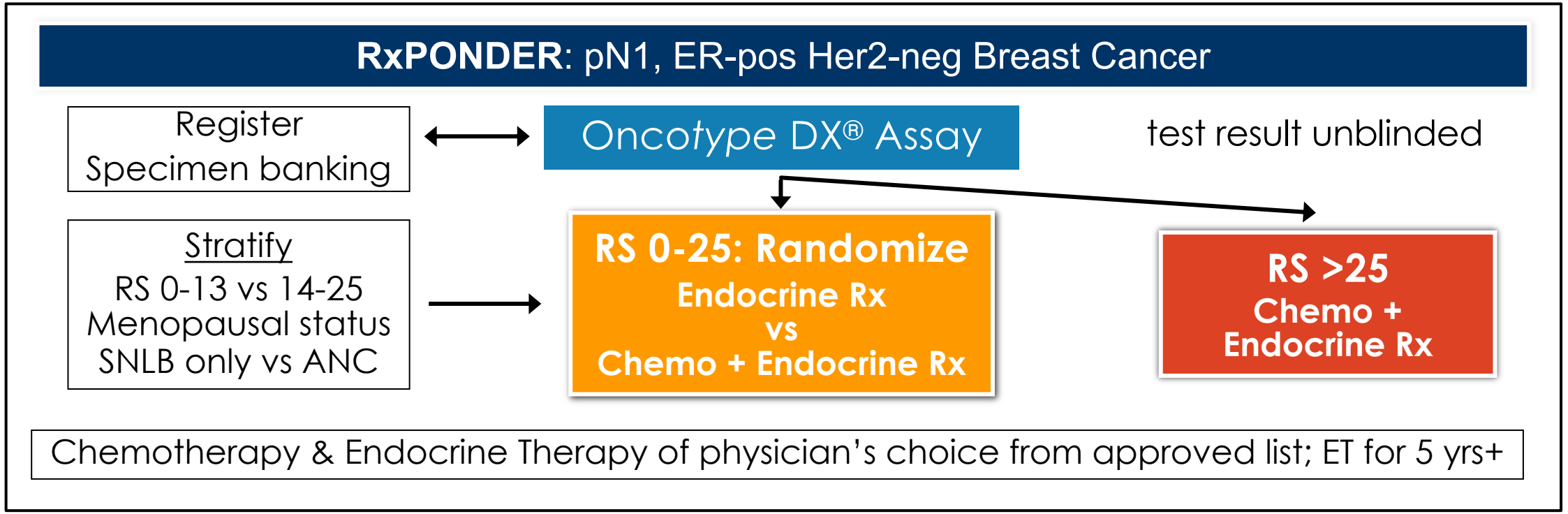
optima
personalised treatment of breast cancer

THE 2020 RxPONDER INTERIM ANALYSIS

a summary and commentary on the results

February 2021

RxPONDER design



- Primary outcome measure = IDFS; 2° outcome measures = OS, DDFS; event-driven analysis
  - Invasive Disease Free Survival includes all breast cancer events, 2nd cancers & death from any cause
- Objective to demonstrate chemotherapy benefit (if any) greater at higher vs lower RS
  - No planned non-inferiority analysis

RxPONDER trial population

- 5083 patients randomised; 5013 patients analysed
- Population/ tumour characteristics well-balanced between arms
- Tumour characteristics of premenopausal and postmenopausal patients very similar
  - Patients evenly distributed between Recurrence Score subgroups (0-13, 14-25)
- Some relevant subgroups are small – limits the generalisability of the result?

Characteristic	Distribution in analysed population
Grade	Grade 1: 25%; Grade 2: 65%; Grade 3 10%
Tumour size	T1: 58%; T2-3: 42%
Number of nodes	1N+: 66%; 2N+: 25%; 3N+: 9%

- More patients with grade 1 tumours / fewer patients with grade 3 tumours than expected in BC population
- Majority of patients were 1N+ (66%); fewer with 2N+ and especially 3N+ (9%)
- OPTIMA has fewer patients with grade 1 tumours and is less dominated by 1N+ patients than RxPONDER

RxPONDER results summary

- Interim analysis at median 5.1 years follow-up presented at SABCS 2020
- Analysis showed menopausal status influenced chemotherapy benefit
  - Premenopausal: statistically significant IDFS and OS benefit for chemotherapy
    - the reason why the DMC released the data
  - Postmenopausal: no evidence of chemotherapy benefit
- No evidence for increasing chemotherapy benefit according to RS; i.e. the primary objective was not met
  - Only 50% of IDFS events required for primary analysis available for interim analysis
  - Current analysis performed on the basis of demonstrating superiority of chemotherapy + ET vs ET alone

The premenopausal result

The analysis showed a convincing demonstration of chemotherapy superiority for both Invasive Disease Free Survival and Overall Survival.

This is likely due to an imbalance in treatment caused by chemotherapy-induced menopause?

- GnRHa use was reported for 16% of patients in the ET arm and 3% in the chemotherapy + ET arm
- 31% of patients were age >50, 61% were age 40-50; chemotherapy-induced menopause is common with older pre-menopausal patients

- **Historic trials comparing (CMF) chemotherapy & GnRH agonists show no difference in either recurrence rate or breast cancer specific survival***
- Data on menopausal status during the trial may be available but is unreported
- The chemotherapy - menopause issue also affects both TAILORx & MINDACT

*LHRH-agonists in Early Breast Cancer Overview group. Lancet 2007;369:1711

The premenopausal result

The analysis showed a convincing demonstration of chemotherapy e… both Invasive Disease Free Survival and Overall Survival

This is likely due to an imbalance in tre… menopause?

- GnRHa use was re… …otherapy + ET arm
- 31%… …apy-induced menopause is common

…chemotherapy & GnRH agonists show no difference in … of breast cancer specific survival*

- …menopausal status during the trial may be available but is unreported
- The chemotherapy - menopause issue also affects both TAILORx & MINDACT

By mandating ovarian suppression, only OPTIMA can establish whether test-directed chemotherapy is safe for premenopausal women.

*LHRH-agonists in Early Breast Cancer Overview group. Lancet 2007;369:1711

The postmenopausal result

optima
personalised treatment of breast cancer

No benefit from chemotherapy was demonstrated for patients with RS ≤25

- Numerically fewer distant recurrence events for chemotherapy + ET group but far from achieving statistical significance in a superiority analysis
- There was no evidence for any subgroup effect
  - In particular, results for the 1N+ and combined 2-3N+ group were the same
    - the confidence interval for the 2-3N+ group is very broad as they make up only 34% of the postmenopausal population

We consider the postmenopausal result is provisional and does not establish the safety of test-guided chemotherapy for these patients

"An immediate practise-changing study!"

"... the certainty is its a game-changer for that group of [postmenopausal] women!"

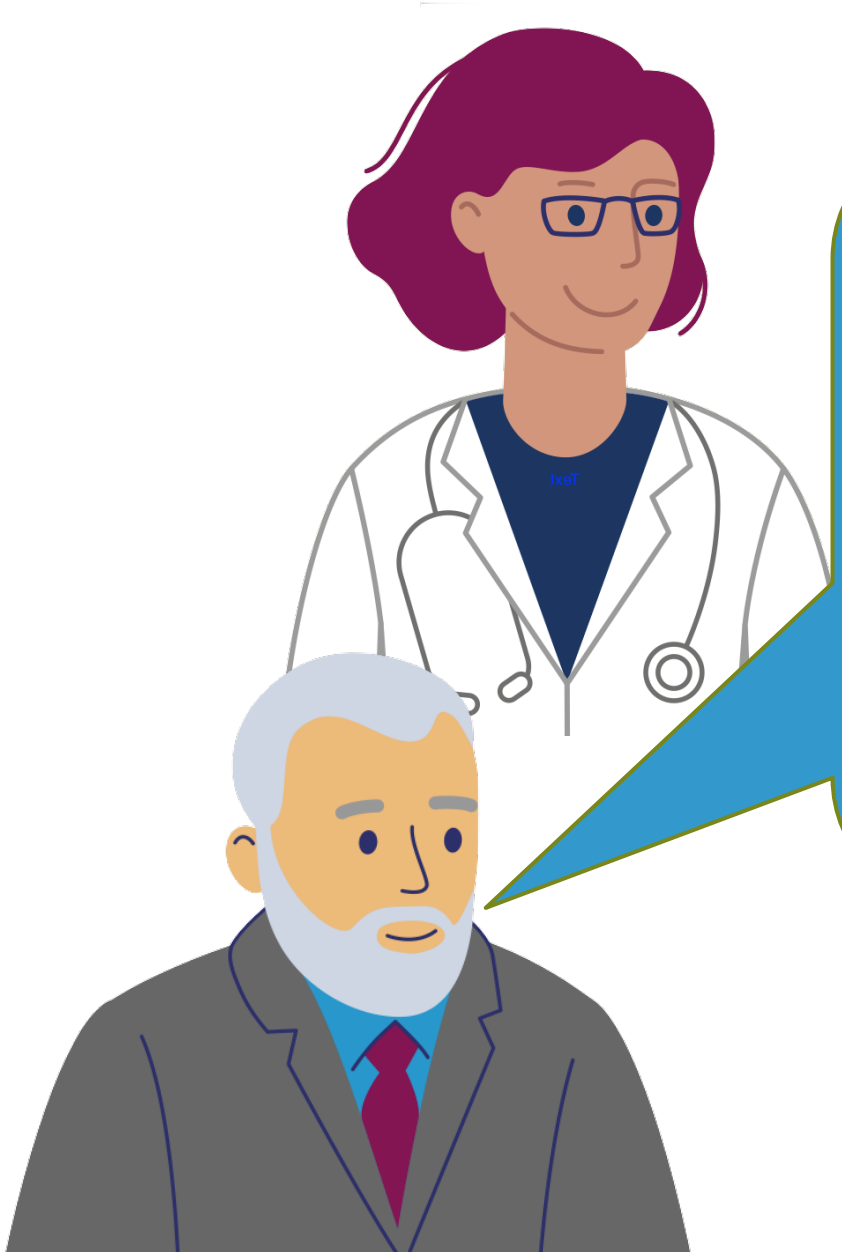
Extravagant claims about the postmenopausal result have been made on behalf of commercial interests who are subject to limited regulation[1,2]

[1]Commercialisation (2021) in EU & UK is on the basis of CE mark; there is no formal approval process unlike for higher risk medical devices and pharmaceuticals

[2]EU Regulation 2017/746 on in vitro diagnostics comes into force in May 2022 but will not apply in the UK. The UK government has a stated intention to strengthen regulations under powers provided by the Medicines and Medical Devices Bill (to become law in 2021). MHRA will retain regulatory responsibility; there is currently no detail of any proposed regulatory change. Registration of in vitro diagnostics is required by 1 Jan 2022 & new authorisation rules will apply from 1 Jul 2023. Different rules will apply in NI!

images courtesy of HealthCreatives

optima
personalised treatment of breast cancer



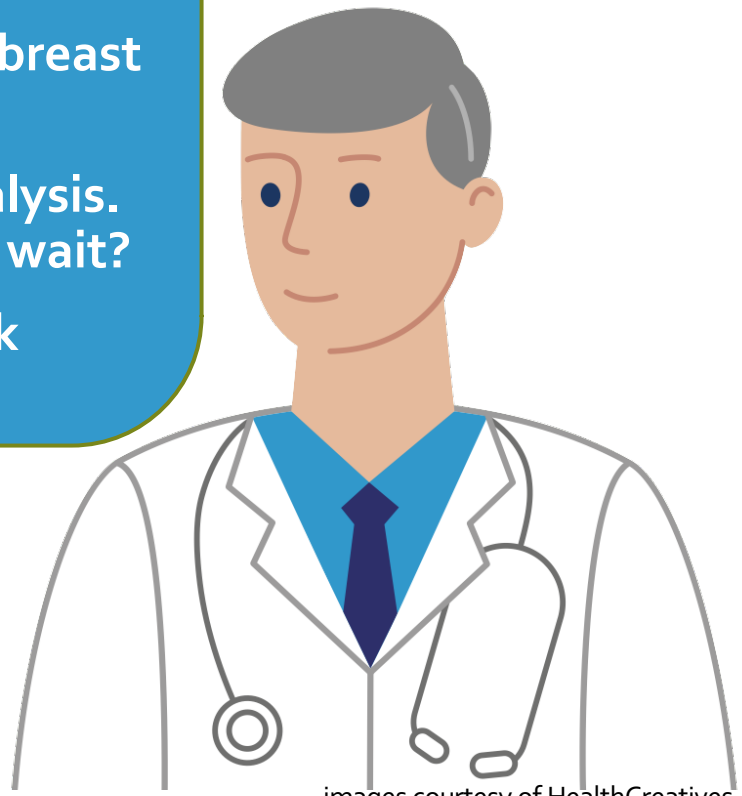
Not so fast! We need answers to some questions before we can accept the postmenopausal result ...

Firstly, does the postmenopausal result demonstrate non-inferiority?

Secondly, what influence do non-breast cancer events have on the result?

Thirdly, this is only an interim analysis. Is that good enough or should we wait?

Finally, what about the higher-risk subgroups?



images courtesy of HealthCreatives

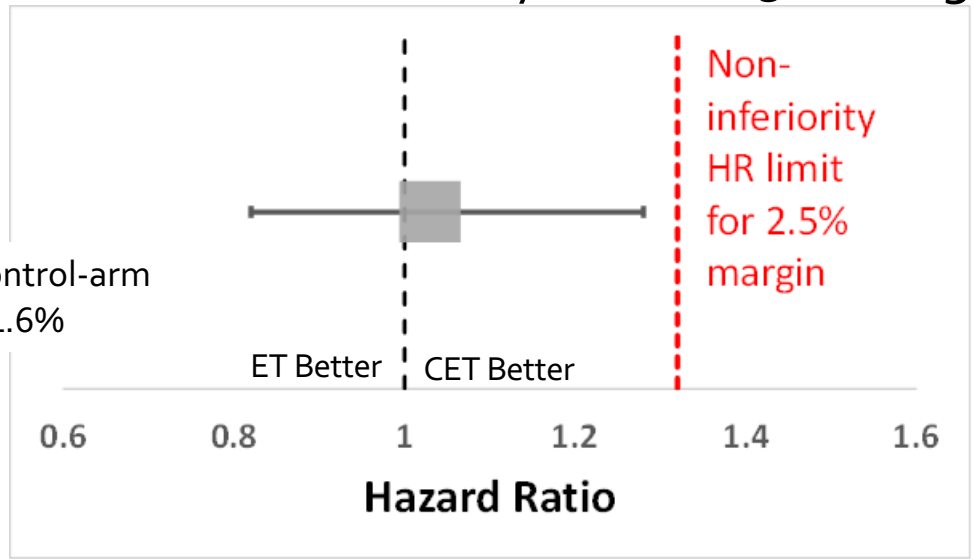
1. Does the RxPONDER postmenopausal result demonstrate non-inferiority?

- **Not as presented …**

- Data were analysed to test whether chemotherapy + ET is superior to ET and not for non-inferiority of ET
- Results show that there is no evidence of a significant difference between arms
  - Unclear how much difference the trial could detect as not the primary outcome measure
- Demonstrating no difference <u>is not the same as</u> demonstrating non-inferiority
  - "Noninferiority cannot be established on the basis of the absence of a significant difference between treatments in a superiority study."
    (Mauri L and D'Agostino RB, Sr. Challenges in the Design and Interpretation of Noninferiority Trials. N Engl J Med. 2017;377:1357)

1. A post-hoc exploratory non-inferiority analysis of the RxPONDER data

- The OPTIMA team applied standard non-inferiority statistical methods to the RxPONDER post-menopausal results using the postmenopausal sample size & observed 5 year control-arm IDFS
- According to this analysis, RxPONDER may demonstrate non-inferiority with a 2.5% margin



To perform this analysis, the hazard ratio has been inverted from data as presented. The HR shown here is the risk of an event for ET compared to CET rather than CET compared to ET as presented.

- This analysis looks encouraging but does not allow for the effect of events unrelated to breast cancer (2nd cancers, e.g. colorectal & death from unrelated cause, e.g. RTA) on non-inferiority that are included in IDFS

2. What is the effect of non-breast cancer-related events on the result?

optima
personalised treatment of breast cancer

- All RxPONDER outcome measures (IDFS, DDFS & OS) include 2nd cancers and death from any cause
  - These capture serious chemotherapy harms but also many completely unrelated events
- If the trial is analysed for chemotherapy + ET superiority then unrelated events make this harder to prove and hence more likely to give a non-significant result
- If the trial is analysed for non-inferiority of ET compared to chemotherapy + ET then then unrelated events may lead to false non-inferiority conclusions
- **54% of the reported postmenopausal events were unrelated to breast cancer**
  - 0.3% absolute difference between arms
- **A convincing non-inferiority analysis for a de-escalation trial should include a breast cancer-specific outcome measure such as RFI or DRFI***

*Distant Recurrence Free Interval: includes only invasive breast cancer recurrence and death from breast cancer

3. Will additional follow-up add certainty to the RxPONDER postmenopausal result?

- RxPONDER may be able to meet its primary objective with additional follow-up.

but ..

- It will not be easy to include the premenopausal group in this analysis and there may not be sufficient events to perform the analysis for postmenopausal patients only
- Non breast cancer events will continue to occur with the difficulties that causes
- Most recurrences that can be prevented by chemotherapy occur within 5 years*
  - Chemotherapy is unlikely to have any effect on late (post 7-8 years) recurrence

*EBCTCG (polychemotherapy meta-analysis) - Lancet 2012; 379: 432-44
EBCTCG (dose intense chemotherapy meta-analysis) - Lancet 2019; 393:1440-1452

4. Does the RxPONDER postmenopausal result apply to higher risk subgroups?

- As the RxPONDER analysis included a subgroup analysis for 1N+ and 2-3N+ groups - the OPTIMA team also performed a post-hoc exploratory non-inferiority analysis for these subgroups
- The result is consistent with the entire postmenopausal population BUT numbers in the subgroups are small, particularly for 2-3N+, which causes substantial uncertainty
- The unrelated events issue also applies to this analysis

- Is it legitimate to argue that the overall result from a de-escalation trial applies to small high-risk subgroups?
  - There is no consensus here as all patients will contribute to the final result even if the subgroup is very small

The postmenopausal result

No benefit from chemotherapy was demonstrated for patients with R

- Numerically fewer distant recurrence events for chem
  from achieving statistical significance in a su
- There was no evidence for any
  - In particular, results f
    - the confi
      ake up only 34% of the

t is provisional and does not establish the safety of these patients

OPTIMA is needed to help establish whether test-directed chemotherapy is safe for postmenopausal women with node-positive disease. RxPONDER has not achieved this

Is this not all a case of the pot calling the kettle black?

- **Perhaps, but only up to a point!**

- Non-inferiority trial methods are not yet standardised & continue to evolve
- OPTIMA was correct to mandate ovarian suppression
- OPTIMA uses IDFS as its primary outcome measure so may be subject to the same unrelated events issue as both RxPONDER & TAILORx
  - IDFS is a legitimate outcome measure because it captures treatment harms
- OPTIMA will not claim non-inferiority on the basis of IDFS alone …
  - The analysis plan includes DRFI as a 2° outcome measure
  - DRFI includes only distant recurrence and breast cancer death so highly relevant to chemotherapy decisions
- **An individual patient-level meta-analysis can answer the subgroup question**

Conclusions

✗ **"Premenopausal women with positive nodes and RS 0-25 likely benefit significantly from chemotherapy"** **… in the absence of ovarian suppression**

Only OPTIMA can establish whether test-directed chemotherapy is safe for premenopausal women.

✗ **"Postmenopausal women with 1-3 positive nodes and RS 0-25 can likely safely forego adjuvant chemotherapy without compromising IDFS"** **… a premature conclusion**

The current RxPONDER result does not allow a definite conclusion to be drawn about the postmenopausal group.
We await formal publication of the current analysis but it may not be possible to answer the postmenopausal question from either this or the full primary analysis

Use of genomic testing during the pandemic

We are aware that some sites are making greater use of genomic testing at this time – we should not allow a change of practice made in exceptional circumstances to become established practice by default

No individual site will be able to detect harms if the test-directed hypothesis for node-positive breast cancer proves to be incorrect

We need to generate evidence to practise evidence-based medicine!

The OPTIMA Independent Data Monitoring Committee reviewed the study in December 2020 with knowledge of the RxPONDER result:

- The IDMC stated that the trial question remains relevant and important
- The IDMC had no safety concerns after reviewing the trial data

Stay part of this potentially practice changing study

Please continue to recruit into OPTIMA

Thank you