Welcome to...

optima
personalised treatment of breast cancer

'Lunch with OPTIMA'

- Please mute your microphone
- Please turn off your camera
- "Raise your hand" for attention **or** type any questions in the conversation window

The meeting will start at 12:30

This meeting is being recorded.

UCL University of BRISTOL NIHR National Institute for Health Research WARWICK CLINICAL TRIALS UNIT

Learning Outcomes:

By the end of this session, the participants will be better informed about recent advances in breast cancer clinical research and how they affect clinical decision making

This course provides 1 CPD credit in accordance with the CPD Scheme of The Royal College of Radiologists.

UCL University of BRISTOL NIHR National Institute for Health Research WARWICK CLINICAL TRIALS UNIT

San Antonio Breast Cancer Symposium 2021

Dr Andreas Makris

Mount Vernon Cancer Centre

Early Breast Cancer

1. Metformin Trial (MA32)

2. Ovarian suppression + Tamoxifen or AI
   SOFT + TEXT Trial joint analysis

3. Final results of PALLAS Trial

4. Antibiotic use in patients with triple negative EBC

5. RxPONDER Trial

CCTGMA.32: Phase 3 randomised double-blind placebo controlled adjuvant trial of metformin (MET) vs placebo (PBO) in eBC

General Session [GS1-08]: Dr Pamela Goodwin (Mount Sinai Hospital/Lunenfeld-Tanenbaum Research Institute, University of Toronto, Canada)

Background: MET has been associated with beneficial anti-cancer effects in epidemiologic and pre-clinical research. **CCTGMA.32** investigated the effect of MET vs PBO (in addition to standard therapy) on adjuvant BC outcomes. Here, the primary efficacy analysis is reported.

Trial: CCTGMA.32 (NCT01101438).

Population: Patients 18–74 years old with an invasive BC diagnosis within 1 year excised with negative margins, without diabetes, with high-risk T1c–3, N0–3 M0 BC, and with adequate cardiac, renal and hepatic function. Patients were stratified by HR+ vs HR-, BMI < vs > 30 kg/m^2, HER2+ vs HER2-, any CT vs no CT.

Study Design: 2,533 patients were randomised 1:1 to receive 5 years of MET 850 mg BID or PBO BID (one caplet). The following analyses were presented: (1) primary analysis (HR+, any HER2 status); (2) follow-up of futility result (HR-, any HER2 status); (3) exploratory analysis (HER2+; any HR status).

Primary Outcome: IDFS.

Secondary Outcomes: OS, DRFS, BC specific survival (BCSS), BC free interval (BCFI), contralateral BC, cardiovascular (CV) events, new diabetes.

Results:

- The primary analysis efficacy results at a median follow-up of 96.2 months are shown in Table 1. The addition of MET to standard therapy in moderate/high-risk HR+ BC did not improve IDFS, OS or other BC outcomes and MET should not be used as BC treatment in this population. MET should also not be used in the HR- BC population.
- Patients with HER2+ BC (notably those with at least 1 “C” allele of the rs 11212617 snp) experienced improved IDFS and OS with MET, consistent with MET effect on pCR in the neoadjuvant setting. However, replication in a prospective trial focusing on a HER2+ population is required.
- Any Grade >3 toxicity was similar in MET and PBO arms (21.7% and 18.7%; p=0.06).

Table 1: Primary analysis efficacy results (MET vs PBO)

Population [n]	IDFS	OS
HR+ (any HER2 status) [n=2,533]*	HR 1.01; 95% CI 0.84, 1.21; p=0.92	HR 0.89; 95% CI 0.64, 1.23; p=0.46
HR- (any HER2 status) [n=1,116]	HR 1.01; 95% CI 0.79, 1.30; p=0.92	HR 0.89; 95% CI 0.64, 1.23; p=0.46

*in HR+ BC HRs were similar for BCFI, DRFS, BCSS (ranging from 0.98–1.09).

Authors’ Conclusion: MET did not improve IDFS or other BC outcomes in HR+ BC and should not be used as adjuvant treatment. Exploratory findings suggested benefit in HER2+ BC should be further investigated.

Abbreviations: BC, breast cancer; BCSS, breast cancer specific survival; BCFI, breast cancer free interval; BID, twice daily; BMI, body mass index; CI, confidence interval; CT, chemotherapy; CV, cardiovascular; DRFS, distant relapse-free survival; ER, oestrogen receptor; HER2+, human epidermal growth factor receptor 2-positive; HR(+/-), hormone receptor (positive/negative); HR, hazard ratio; IDFS, invasive disease-free survival; MET: metformin; OS, overall survival; PBO: placebo; pCR, pathological complete response; PR, progesterone receptor.

Adjuvant exemestane (EXE) + OFS vs tamoxifen (TAM) + OFS in premenopausal women with HR+ eBC: Update from the combined SOFT and TEXT trials

General Session 2 [GS2-05]: Dr Meredith Regan (International Breast Cancer Study Group, Breast International Group, and North American Breast Cancer Groups, Switzerland)

Dr Meredith Regan presented a planned update analysis of the combined SOFT and TEXT trials, with a focus on distant recurrence and OS, and later treatment benefits. The trials enrolled premenopausal women with HR+ eBC:

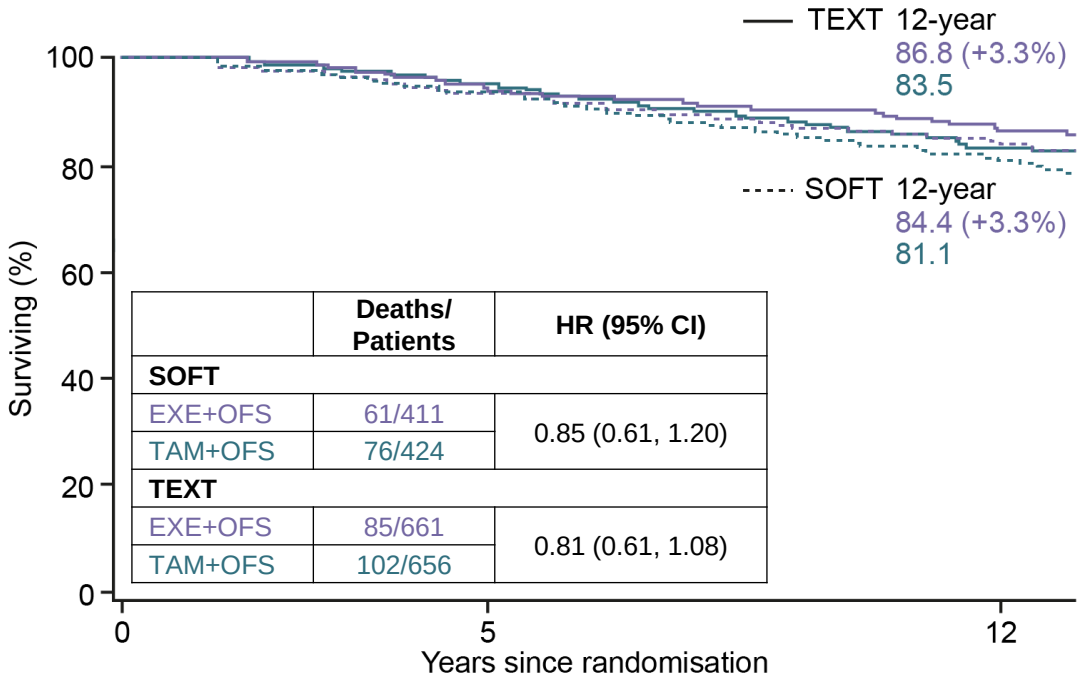
- In SOFT, women (ITT n=3,066) were randomised to 5 years of EXE+OFS, TAM+OFS or TAM alone ≤12 weeks after surgery if no CT was planned, or ≤8 months after completing (neo)adjuvant CT. Median follow-up was 12 years.
- In TEXT, women (ITT n=2,672) were randomised ≤12 weeks after surgery to 5 years EXE+OFS or TAM+OFS; CT was optional and concurrent with OFS. Median follow-up was 13 years.

This analysis focused on a comparison of adjuvant AI vs TAM, in combination with OFS, and included 4,690 patients from the relevant SOFT/TEXT treatment arms.

Results:

- 12-year DRFI was 88.4% in patients assigned to EXE+OFS vs 86.6% in patients assigned to TAM+OFS (Δ1.8%; HR 0.83; p=0.03).
- 12-year OS was high in both groups: 90.1% in patients assigned to EXE+OFS vs 89.1% in patients assigned to TAM+OFS (Δ1.0%; HR 0.93; p=0.43).
- HER2- tumours predominated in both trials. There was an emerging OS benefit for EXE+OFS vs TAM+OFS (Δ3.3% at 12 years) in patients with HER2- tumours who received CT in both trials (Figure 1).

Figure 1: SOFT and TEXT OS in HER2- disease (CT cohort)



	Deaths/ Patients	HR (95% CI)
SOFT		
EXE+OFS	61/411	0.85 (0.61, 1.20)
TAM+OFS	76/424	
TEXT		
EXE+OFS	85/661	0.81 (0.61, 1.08)
TAM+OFS	102/656	

Authors' Conclusion: Adjuvant EXE+OFS compared to TAM+OFS showed a sustained reduction in the risk of recurrence, which was more consistent in patients with HER2- disease and in those with high-risk disease features, e.g. indication for adjuvant CT and G3 tumours. Oncologists may use this information to discuss potential benefits of EXE+OFS with individual patients.

Abbreviations: AI, aromatase inhibitor; CI, confidence interval; CT, chemotherapy; DRFI, distant recurrence-free interval; eBC, early breast cancer; EXE, exemestane; HER2-, human epidermal growth factor receptor-2 negative; HR/HR(+), hazard ratio/hormone receptor (positive); ITT, intention-to-treat; OFS, ovarian function suppression; OS, overall survival; TAM, tamoxifen.

PALLAS: Adjuvant PAL in patients with HR+/HER2- eBC

General Session 1 [GS1-07]: Prof Michael Gnant (Medical University of Vienna, Austria)

Prof Michael Gnant presented the final protocol-planned analyses of the global Phase 3 PALLAS trial (NCT02513394), investigating whether the addition of the CDK4/6i PAL to adjuvant ET improved outcomes over ET alone for patients with HR+/HER2- eBC.

Population: Patients with Stage II–III HR+/HER2- BC who had undergone surgery ± CT and radiotherapy. Patients had to be within 12 months of their diagnosis, and within 6 months of starting adjuvant ET.

Study Design: Patients were randomised (1:1) to receive either 2 years of PAL (3 weeks on/1 week off) with adjuvant ET or ET alone (aromatase inhibitor or tamoxifen, +/- LHRH agonist).

Primary Outcome: IDFS.

Secondary Outcomes: DRFS, LRFS, OS and safety.

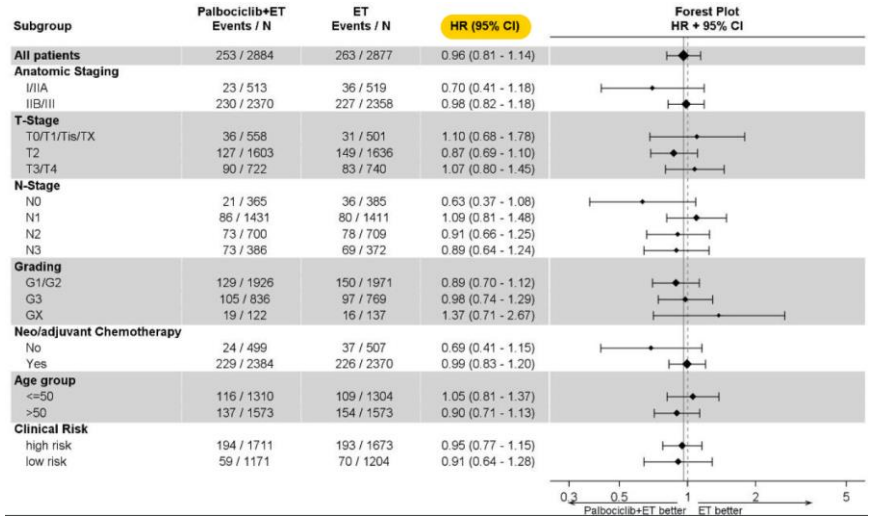
Results: 5,761 patients were randomised. At the time of final analysis cut-off, median follow-up was 31 months and 516 IDFS events had been recorded.

Authors' Conclusion: At this final protocol-planned analysis, the **PALLAS** trial showed that the addition of 2 years of PAL to ongoing adjuvant ET did not improve survival endpoints in patients with Stage II–III HR+/HER2- eBC. Analysis of clinicopathologic subgroups did not identify a population of patients who benefitted from adjuvant PAL, although this analysis was limited by the small number of events.

Results (cont'd):

- At the time of this analysis, IDFS was similar between the two arms, with a 4-year IDFS of 84.2% with PAL+ET vs 84.5% with ET alone (HR 0.96; 95% CI 0.81, 1.14; p=0.65). There was no statistically significant difference in secondary outcomes.
- Subgroup analyses found no significant interactions between treatment effect and other factors (including risk category) (Figure 1).
- Overall, 44.9% of patients discontinued PAL by the 2-year analysis. The safety profile of PAL was as expected, with Grade 3/4 neutropenia the most common side effect (safety population: 62.0% vs 0.4%).

Figure 1: IDFS in subgroups



Subgroup	Palbociclib+ET Events / N	ET Events / N	HR (95% CI)
All patients	253 / 2884	263 / 2877	0.96 (0.81 - 1.14)
Anatomic Staging			
I/IIA	23 / 513	36 / 519	0.70 (0.41 - 1.18)
IIB/III	230 / 2370	227 / 2358	0.98 (0.82 - 1.18)
T-Stage			
T0/T1/Tis/TX	36 / 558	31 / 501	1.10 (0.68 - 1.78)
T2	127 / 1603	149 / 1636	0.87 (0.69 - 1.10)
T3/T4	90 / 722	83 / 740	1.07 (0.80 - 1.45)
N-Stage			
N0	21 / 365	36 / 385	0.63 (0.37 - 1.08)
N1	86 / 1431	80 / 1411	1.09 (0.81 - 1.48)
N2	73 / 700	78 / 709	0.91 (0.66 - 1.25)
N3	73 / 386	69 / 372	0.89 (0.64 - 1.24)
Grading			
G1/G2	129 / 1926	150 / 1971	0.89 (0.70 - 1.12)
G3	105 / 836	97 / 769	0.98 (0.74 - 1.29)
GX	19 / 122	16 / 137	1.37 (0.71 - 2.67)
Neo/adjuvant Chemotherapy			
No	24 / 499	37 / 507	0.69 (0.41 - 1.15)
Yes	229 / 2384	226 / 2370	0.99 (0.83 - 1.20)
Age group			
<=50	116 / 1310	109 / 1304	1.05 (0.81 - 1.37)
>50	137 / 1573	154 / 1573	0.90 (0.71 - 1.13)
Clinical Risk			
high risk	194 / 1711	193 / 1673	0.95 (0.77 - 1.15)
low risk	59 / 1171	70 / 1204	0.91 (0.64 - 1.28)

Abbreviations: BC, breast cancer; CDK4/6i, cyclin dependent-kinase 4/6 inhibitor; CI, confidence interval; CT, chemotherapy; DRFS, distant recurrence-free survival; eBC, early breast cancer; ET, endocrine therapy; HER2-, human epidermal growth factor receptor-2 negative; HR, hormone receptor; IDFS, invasive disease-free survival; LHRH, luteinising hormone-releasing hormone; LRFS, locoregional recurrence-free survival; OS, overall survival; PAL, palbociclib.

Poster highlights: Antibiotic use and mortality from TNBC

Poster Session 3 [P3-12-34]: Dr Julia Ransohoff (Stanford University, Palo Alto, CA, USA)

Background: Gut-associated lymphoid tissue is the largest component of the body's immune system, and influences both local and systemic immune responses. Gut microbiome dysbiosis related to antimicrobial exposure may be associated with decreased circulating and tumour-infiltrating lymphocytes and decreased immune repertoire, which may adversely impact survival in patients with TNBC.

The authors hypothesised that increasing antimicrobial exposure may lead to higher overall mortality (OM) and BC-specific mortality (BCM) in the presence of time-varying absolute lymphocyte count (ALC).

Methods:

- Women with TNBC were identified in the Oncoshare database, a BC registry integrating data from the SEER Registry and electronic medical records from two California healthcare systems.
- Antibiotic use was defined in 3 ways at each time point: (1) current use ("Antibiotic Use"), (2) total number of prescriptions ("Total Antibiotics"), and (3) total number of unique antibiotics prescribed ("Unique Antibiotics") to study overall OM and BCM.
- Marginal structural Cox proportional hazards (PH) multivariate models were used in the analysis, with time-varying covariates (antibiotic use and ALC) to avoid immortal time bias.

Results:

- 772 women were diagnosed with TNBC and treated, median follow-up time (including time to death) was 104 (IQR [61.66, 147.03]) months.
- 654 (85%) patients ever used antibiotics after TNBC diagnosis:
  - There were 24/118 (20%) deaths among patients who never took antibiotics and 153/654 (23%) deaths in patients who ever took antibiotics during the study period.
  - Antibiotic use was associated with higher OM and BCM using definitions (2) and (3), but not definition (1) (Table 1).

Table 1: OM and BCM in women with TNBC (cox PH models)

	OM	BCM
Antibiotic use	1.54 (0.99, 2.39)	1.50 (0.90, 2.47)
Total no. antibiotics	1.07* (1.04, 1.09)	1.07* (1.04, 1.10)
No. unique antibiotics	1.17* (1.12, 1.23)	1.18* (1.12, 1.25)

*p<0.05

Authors' Conclusion: Higher number of antibiotic prescriptions and of unique antibiotics prescribed was associated with overall and breast cancer-specific mortality among women with TNBC. Future research on the role of the microbiome in mediating ALC and immune response may inform interventions to reduce TNBC mortality.

Abbreviations: ALC, absolute lymphocyte count; BC, breast cancer; BCM, breast cancer mortality; IQR, interquartile range; OM, overall mortality; PH, proportional hazards; SEER, Surveillance, Epidemiology, and End Results Program; TNBC, triple-negative breast cancer.

Updated results from Phase 3 RxPONDER: participants with 1–3 positive lymph nodes, HR+/HER2- BC with RS ≤25 randomised to ET +/- CT

General Session 2 [GS2-07]: Dr Kevin Kalinsky (Emory University Winship Cancer Institute [SWOG], Atlanta, GA, USA)

Background: Previous analyses from RxPONDER have shown that postmenopausal women with HR+/HER2- BC and RS ≤25 did not experience a CT benefit for IDFS or DRFS when treated with ET+CT. However, a CT benefit was observed in premenopausal women. Updates from RxPONDER on IDFS and DDFS with additional follow-up, as well as DRFI and post-hoc analyses in premenopausal women are presented here.

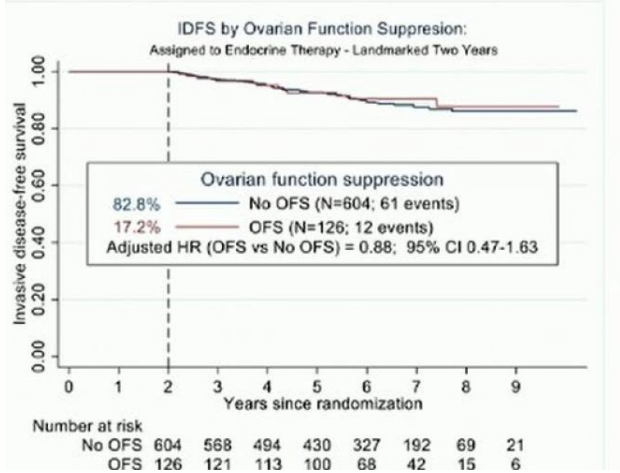
Results:

- There was no IDFS, DRFS or DRFI benefit of CT in addition to ET in postmenopausal women with HR+/HER2- BC.
- However, an IDFS (HR 0.64; 95% CI 0.47, 0.87; p=0.004), DRFS (HR 0.66; 95% CI 0.45, 0.97; p=0.03) and DRFI (HR 0.64; 95% CI 0.43, 0.95; p=0.26) benefit was observed in premenopausal patients.
- Post-hoc analyses evaluated the effect of ovarian function suppression (OFS) in premenopausal women. Although higher in the ET arm, the rate of OFS remained low and consistent in both arms. In the first 24 months following randomisation to the ET arm, there was no IDFS difference in those who underwent OFS or not (Figure 1).
- Post hoc analyses also evaluated the effect of regular menstrual periods in premenopausal women. 58.9% and 80.8% of premenopausal women stopped having periods within the first 24 months in the ET (n=676) and ET+CT (n=677) arms, respectively.

Results (cont'd):

- A numerical IDFS benefit was observed in premenopausal patients no longer having regular menstrual periods in both the ET and ET+CT treatment arms.

Figure 1: 2-year IDFS by OFS in premenopausal patients in ET arm



Authors' Conclusion: RxPONDER was not powered for subgroup differences, and data interpretation in premenopausal patients can be challenging, given that confounding factors can change over time. It remains unclear if OFS can replace CT in premenopausal women with HR+/HER2- BC. Future randomised trials should be considered to address this important clinical question.

Abbreviations: BC, breast cancer; CT, chemotherapy; DDFS, distant disease-free survival; DFRI, distant recurrence-free survival; ET, endocrine therapy; HR, hazard ratio; HR+, hormone receptor positive; HER2-, human epidermal growth factor receptor-2 negative; IDFS, invasive disease-free survival; OFS, ovarian function suppression; RS, recurrence score.

Monitoring disease with circulating DNA

1. Metastatic Breast Cancer
   PADA-1 Trial

2. Early Breast Cancer
   cTRAK Trial

Phase 3 PADA-1 trial: FUL-PAL vs continuing AI-PAL upon detection of circulating *ESR1* mutation in HR+ HER2- mBC patients

General Session 3 [GS3-05]: Dr François-Clément Bidard (Institut Curie, Paris, France)

Background: *ESR1* mutations are known drivers of resistance to 1L AI-based therapy in HR+ HER2- mBC patients, but their clinical actionability remains unknown. **PADA-1** evaluated the clinical benefit associated with a switch to FUL-PAL upon the detection of a rising *ESR1* mutation in blood (b$ESR1_{mut}$) in HR+ HER2- mBC patients treated with 1L AI-PAL.

Trial: PADA-1 (NCT03079011); a multicentre randomised, open-label Phase 3 trial.

Population: HR+ HER2- mBC patients with no prior systemic therapy for mBC in the absence of AI-resistance.

Study Design: Following treatment with 1L AI-PAL and centralised b$ESR1_{mut}$ screening every two months, the 172 patients with rising b$ESR1_{mut}$ with no clinical/imaging concomitant disease progression were randomised to continuing the same therapy (AI-PAL; standard arm; n=84) or switching to FUL-PAL (experimental arm; n=88). Optional crossover was available to FUL-PAL following tumour progression for patients randomised in the standard arm.

Co-primary Outcomes: PFS per RECIST v1.1, Grade ≥3 haematological AEs.

Secondary Outcomes: Second PFS after crossover, non-haematological Grade ≥3 AEs and SAEs.

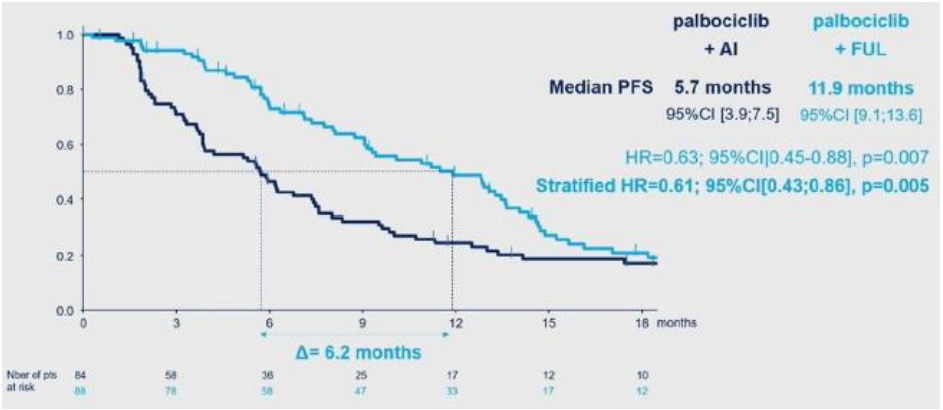
Results:

- Figure 1 presents PFS results (standard vs experimental arm) at a median follow-up of 26 months (136 PFS events).

Results:

- Among the 69 patients who subsequently developed a disease progression in the AI-PAL arm, 47 were included in the optional crossover cohort. With a median follow-up of 14.7 months and 37 PFS events, the median second-PFS observed in the crossover cohort was 3.5 months (95% CI 2.7, 5.1).
- The most common Grade 3 AEs were (AI+PAL vs FUL+PAL): neutropenia (34.5% vs 36.4%), leukopenia (6.0% vs 6.8%) and pain (1.2% vs 4.5%).

Figure 1: PFS in standard vs experimental arm after randomisation



Authors' Conclusion: PADA-1 is the first clinical trial to demonstrate the clinical utility of b$ESR1_{mut}$ monitoring in optimising the ET partner of PAL, and reported a doubling in the subsequent median PFS. No new safety signals were observed.

Abbreviations: 1L, first-line; AE, adverse event; AI, aromatase inhibitor; b$ESR1_{mut}$, *ESR1* mutation in blood; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; CI, confidence interval; FUL, fulvestrant; HR+, hormone receptor positive; HER2-, human epidermal growth factor receptor-2 negative; mBC, metastatic breast cancer; PAL, palbociclib; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse events.

Utilising ctDNA in patients with BC: Results from the cTRAK

General Session 3 [GS3-06]: Prof Nicholas Turner (The Institute of Cancer Research, London, UK

Primary results of the cTRAK TN trial: Utilising ctDNA mutation tracking to detect minimal residual disease and trigger intervention in patients with moderate and high-risk early TNBC.

- cTRAK was a multicentre Phase 2 study that assessed prospective use of ctDNA assays in patients treated for early TNBC, who were at higher risk of relapse.
- 208 patients registered for the study and 161 patients continued to the ctDNA surveillance phase. At 12 months, the rate of ctDNA+ was 27.3% (44/161; 95% CI 20.6, 24.9).
- Following surveillance, 45 ctDNA+ patients entered the therapeutic trial (pembro n=32; observation n=14). Of patients allocated to pembro, 71.9% (23/32) had overt metastatic disease on staging at time of ctDNA detection.
- Relatively few patients commenced treatment with pembro (n=5): 3 experienced disease recurrence and 1 discontinued treatment due to AEs. No patients had sustained ctDNA clearance 6 months after commencing pembro.

Authors' Conclusion: Issues with this trial include the relatively high rate of undiagnosed metastatic disease when imaged and the small number of patients who commenced pembro treatment, precluding assessment of activity. However, these findings do have implications for future trial design, e.g. the importance of starting ctDNA testing early.

Abbreviations: AE: adverse event; C2D1, day 1 of cycle 2; ctDNA(+), circulating tumour DNA (positive); CI, confidence interval; D15, day 15 of cycle 1; HER2, human epidermal growth factor receptor-2; HR, hazard ratio.

Metastatic Breast Cancer

1. Antibody drug conjugates
    a. Trastuzumab deruxtecan in HER2+ve MBC (DESTINY 03 Trial)
    b. Datopotamab deruxtecan in mTNBC
2. KEYNOTE 355 Trial Analysis of CPS score cut-offs
3. Emerald Trial: Elacestrant (oral SERD)

Subgroup analysis of DESTINY-Breast03: Enhertu® (trastuzumab deruxtecan; T-DXd) vs Kadcyla® (trastuzumab emtansine; TE) in patients with HER2+ mBC

General Session 3 [GS3-01]: Prof Sara Hurvitz (University of California and Jonsson Comprehensive Cancer Center, LA, USA); Poster Discussion 8 [PD8-02]: Dr Véronique Diéras (Centre Eugène Marquis, Rennes, France)

Trial: DESTINY-Breast03 (NCT03529110).

Population: Patients with HER2+ mBC that had been previously treated with trastuzumab+taxane. Patients with clinically-stable BMs were eligible.

Study Design: Randomised, multicentre, open-label, Phase 3 study in which patients were randomised 1:1 to receive T-DXd or TE Q3W.

Primary Outcome: PFS by BICR.

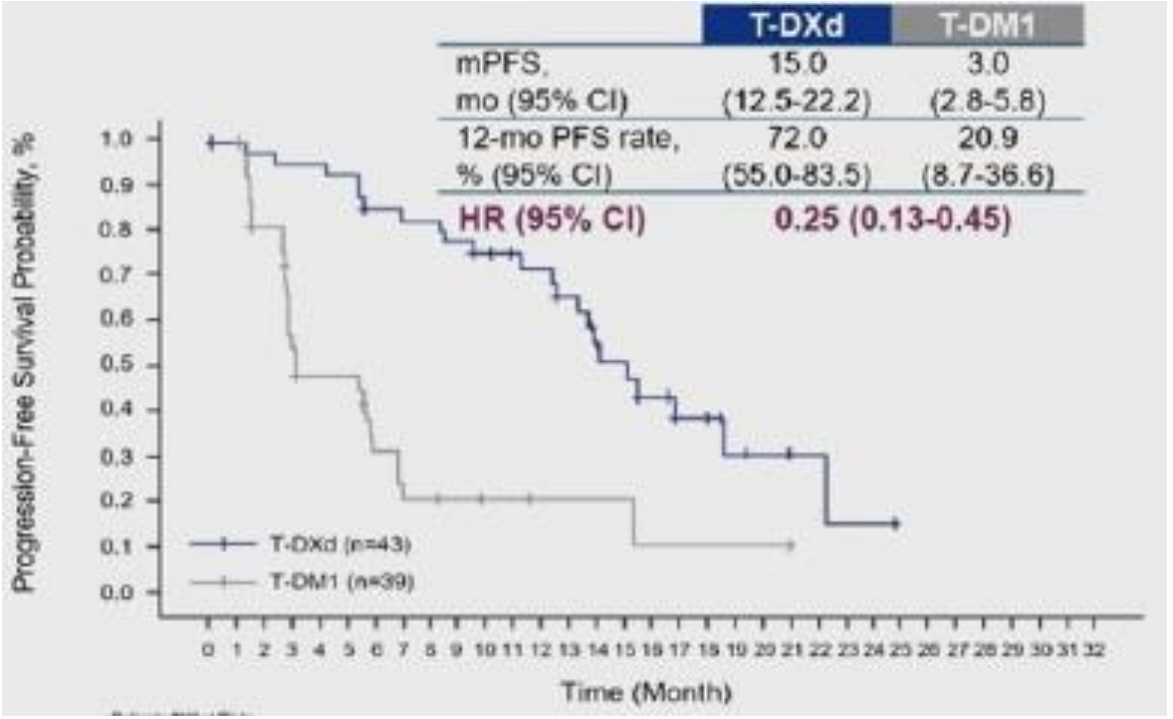
Key Secondary Outcome: OS.

Other Outcomes: Safety; PFS and ORR were analysed for subgroups.

Results:

- At data cut-off (21st May 2021), 524 patients were randomised to T-DXd (n=261) or TE (n=263) and median follow-up was 15.9 mo.
- T-DXd demonstrated superior PFS vs TE (HR 0.28; 95% CI 0.22, 0.37; p=7.8 x 10^{-22}); median PFS by BICR was not reached (95% CI 18.5-NE) for T-DXd vs 6.8 mo (95% CI 5.6, 8.2) for TE. PFS for patients with stable BMs at baseline (n=82) is presented in Figure 1.
- Overall, confirmed ORR for T-DXd was 79.7% vs 34.2% for TE. For patients with stable BMs at baseline, confirmed ORR was 67.4% for T-DXd vs 20.5% for TE.
- T-DXd had a manageable and tolerable safety profile. Grade ≥3 TEAE incidence was 52.1% vs 48.3% and serious TEAE incidence 19.1% vs 18.0% in patients treated with T-DXd and TE, respectively.

Figure 1: PFS KM curve in patients with BM at baseline



Dr Véronique Diéras presented the Phase 2 **DAISY** study of T-DXd in patients with mBC regardless of HER2 status: T-DXd showed clinically meaningful activity in patients with HER2 overexpressing mBC and, interestingly, also in those with HER2-low and HER2-nul mBC.

Abbreviations: BICR, blinded independent central review, BM: brain metastases; CI, confidence interval, HER2+: human epidermal growth factor receoptor-2 positive, HR, hazard ratio; KM, Kaplan-Meier; mBC, metastatic breast cancer; mo, months; mPFS, median progression-free survival; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab emtansine; TE, trastuzumab emtansine; TEAE, treatment-emergent adverse event.

Datopotamab deruxtecan in mTNBC: Results from the TROPION-PanTumor01 study

General Session 1 [GS1-05]: Dr Ian Krop (Dana-Farber Cancer Institute, Boston, MA, USA).

Trial: TROPION-PanTumor01 (NCT03401385).

Background: Datopotamab deruxtecan (Dato-DXd) is an ADC consisting of a humanised anti-TROP2 IgG1 monoclonal antibody conjugated to a potent topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker.

Study Design: Phase 1, multi-centre, open-label study evaluating Dato-DXd in previously treated patients with solid tumours (including mBC, NSCLC and other tumour types). Updated results from patients with mTNBC who have relapsed/progressed on standard therapies (n=44) are presented here.

Outcomes: Safety and efficacy, including ORR* and disease control rate.

Authors' Conclusion: Preliminary results showed that Dato-DXd demonstrates promising anti-tumour activity with a manageable safety profile in patients with previously treated mTNBC; confirmatory studies in patients with BC are warranted.

Efficacy: ORR* was 34% in all patients with mTNBC (n=44), and 52% in patients with mTNBC who had not been treated with a prior topoisomerase I inhibitor-based ADC (n=27). Disease control rate was 77% and 81% for all patients with mTNBC and patients with mTNBC who had not been treated with a prior topoisomerase I inhibitor-based ADC.

Safety: All-cause TEAEs (Grade ≥3) were observed in 23% of patients. A summary of safety data are shown in Table 1. Most common AEs were nausea and stomatitis (Grade 1 and 2).

Table 1: Summary of TEAEs in TROPION-PanTumour01 (TNBC cohort)

Patients, n (%)	TNBC (n=44)
All-grade TEAEs	43 (98)
Grade ≥3	20 (45)
All-grade treatment-related TEAEs	43 (98)
Grade ≥3	10 (23)
Dose adjustments	
Dose reduction due to AEs	8 (18)
Treatment interruption due to AEs	6 (14)
Treatment discontinuation due to AEs	1 (2)
Serious TEAEs	8 (18)
Treatment related	2 (5)
Fatal TEAEs	0
Treatment related	0

*RECIST version 1.1 by blinded independent central review.

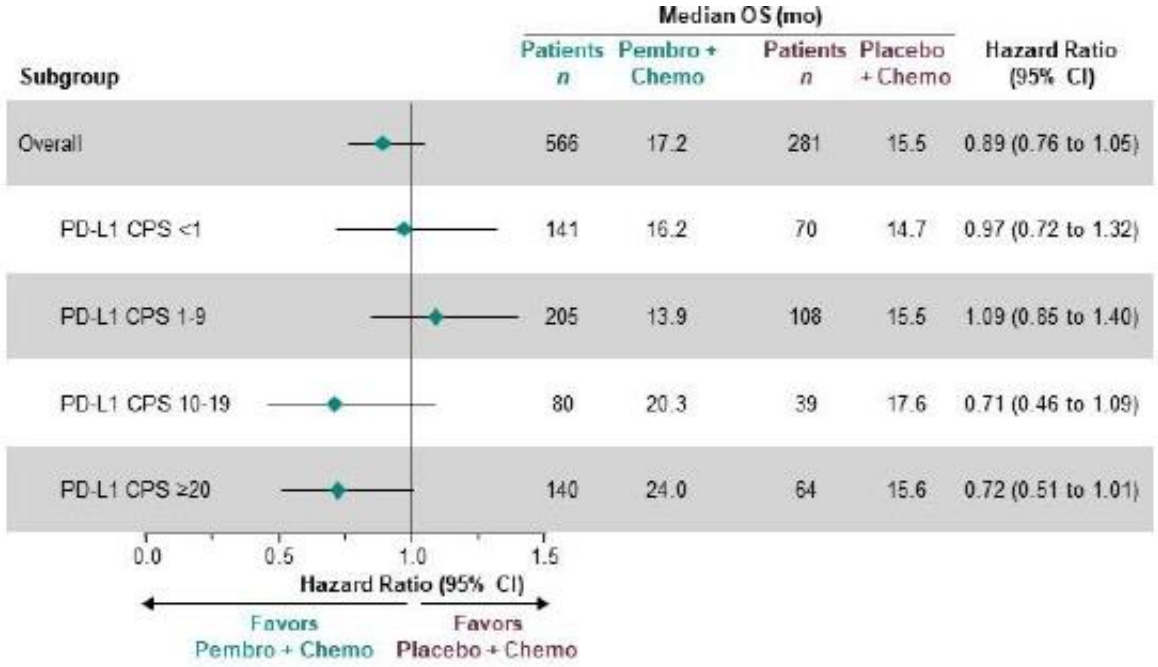
Abbreviations: ADC, antibody drug conjugate; AE, adverse event; BC, breast cancer; BICR, blinded independent central review; Dato-DXd, datopotamab deruxtecan; HER2, human epidermal growth factor receptor-2; IgG1, immunoglobin G1; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; TNBC, triple negative breast cancer; ORR, objective response rate; TEAE, treatment-emergent adverse event; TNBC, triple negative breast cancer; TROP2, trophoblast cell surface antigen 2.

KEYNOTE-355 update: KEYTRUDA® (pembrolizumab; pembro) + CT for patients with previously-untreated locally recurrent inoperable or metastatic TNBC

General Session 1 [GS1-02]: Prof Javier Cortes (Spain and Vall d-Hebron Institute of Oncology, Barcelona, Spain)

- Prof Javier Cortes presented the final results of the KEYNOTE-355 study (NCT02819518), in which 847 patients with previously untreated, locally recurrent inoperable or mTNBC were randomised (2:1) to treatment with pembro+CT or PBO+CT. This analysis compared outcomes in patient subgroups by various CPS cut-offs.
- Baseline characteristics of patients in the PD-L1 CPS 1–9, 10–19, and ≥20 subgroups were generally similar to those of the ITT population.
- In the final analyses, the HRs (95% CI) for OS were 0.73 (0.55, 0.95) in the CPS ≥10 subgroup, 0.86 (0.72, 1.04) in the CPS ≥1 subgroup, and 0.89 (0.76, 1.05) in the ITT population; HRs (95% CI) for PFS were 0.66 (0.50, 0.88), 0.75 (0.62, 0.91), and 0.82 (0.70, 0.98), respectively.
- Efficacy data for the additional CPS subgroups are shown in Figure 1:
  - For median OS, results in the CPS 1–9 subgroup showed comparable efficacy for pembro+CT and PBO+CT; however, results in the CPS 10–19 and CPS ≥20 subgroups showed a similar treatment benefit with the addition of pembro.
  - Results for PFS were generally consistent with those for OS.
- Safety was consistent with the known profiles of each regimen, with no new safety concerns. Any grade/Grade 3–5 immune-related AEs occurred in 26.5%/5.3% of pembro+CT-treated patients and 6.4%/0.0% PBO+CT-treated patients.

Figure 1: OS results in additional patient subgroups by CPS



Analysis (HR and 95% CI) in the overall population based on the stratified Cox regression model; analysis in the subgroups is based on the unstratified Cox model. OS in the CPS1–9 and 1–19 populations were post-hoc exploratory analyses; OS in the CPS <1 and CPS ≥20 populations were prespecified exploratory analyses. Data cutoff 15 Jun 2021.

Authors' Conclusion: These results provide support that CPS ≥10 is a reasonable cutoff to define the mTNBC population expected to benefit from pembro+CT.

Abbreviations: AE, adverse event; CI, confidence interval; CPS, combined positive score; CT, chemotherapy; HR, hazard ratio; ITT, intention to treat; (m)TNBC, (metastatic) triple-negative breast cancer; OS, overall survival; PBO, placebo; pembro; pembrolizumab; PFS, progression-free survival.

Elacestrant, an oral SERD, vs investigator's choice of endocrine monotherapy for ER+/HER2- mBC following progression on prior ET and CDK4/6i therapy: EMERALD

General Session 2 [GS2-02]: Dr Aditya Bardia (Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA)

Background: Elacestrant (RAD1901) is an oral SERD that blocks ER and inhibits oestradiol-dependent gene transcription induction and cell proliferation in ER+ BC cell lines, with higher efficacy than fulvestrant.

Trial: The Phase 3 EMERALD study (NCT03778931).

Population: Men and postmenopausal women with ER+/HER2– mBC. Patients had progressed or relapsed on or after 1 or 2 lines of ET for mBC, one of which was given in combination with a CDK4/6i. Patients could have received ≤1 line of CT for their mBC.

Study Design: Patients (N=477) were randomised 1:1 to receive elacestrant 400 mg daily or investigator's choice of SOC (FUL, ANA, LET, EXE).

Co-Primary Outcomes: PFS in all patients and PFS in tumours harbouring *mESR1* mutations.

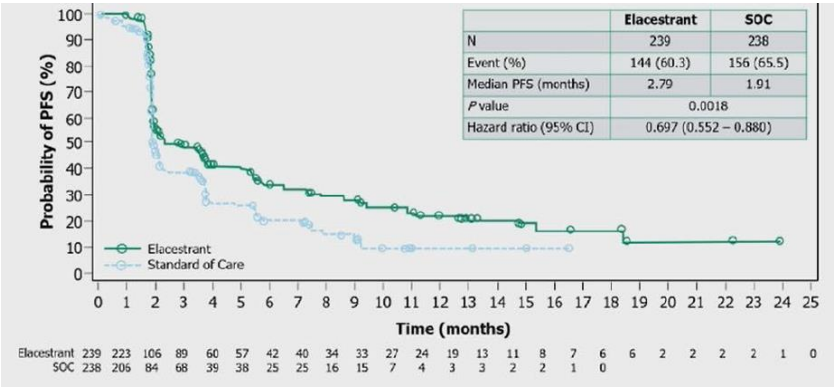
Secondary Outcomes: OS.

Authors' Conclusion: Elacestrant is the first oral SERD to demonstrate a statistically significant and clinically meaningful improvement of PFS vs SOC ET in a randomised Phase 3 study in patients with ER+/HER2– BC in the 2nd/3rd-line post-CDK4/6i setting, including those whose tumours harbour *mESR1* mutations. Elacestrant was well-tolerated, and has the potential to become the new standard of care for this population.

Results:

- Elacestrant was associated with a 30% reduction in the risk of progression or death, and demonstrated a significant improvement in PFS vs SOC in all patients with ER+/HER2– mBC following a CDK4/6i (Figure 1).
- In patients habouring the *mESR1* mutation (n=228), those who received elacestrant had a 45% reduced risk of progression or death compared with SOC (HR 0.546; 95% CI 0.387, 0.768; p=0.0005).
- Early OS data showed a trend favouring elacestrant vs SOC, however, this was not significant.
- TEAEs leading to discontinuation of elacestrant or SOC were infrequent in both arms (6.3% vs 4.4%, respectively) and there were no treatment-related deaths in either group.

Figure 1: PFS in all patients (ITT; N=477)



Abbreviations: ANA, anastrozole; BC, breast cancer; CDK4/6i, cyclin dependent 4/6 inhibitor; CI, confidence interval; CT, chemotherapy; ER, oestrogen receptor; ET, endocrine therapy; EXE, exemestane; FUL, fulvestrant; HER2-, human epidermal growth factor receptor-2 negative; HR, hazard ratio; ITT: intention-to-treat; LET, letrozole; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; SERD, selective oestrogen receptor degrader; SOC, standard of care; TEAE, treatment emergent adverse event.

Thank you

A full set of slides with discussion of more SABCS 2021 abstracts can be found at

www.rocheresources.co.uk

RxPONDER trial

Luke Hughes-Davies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer

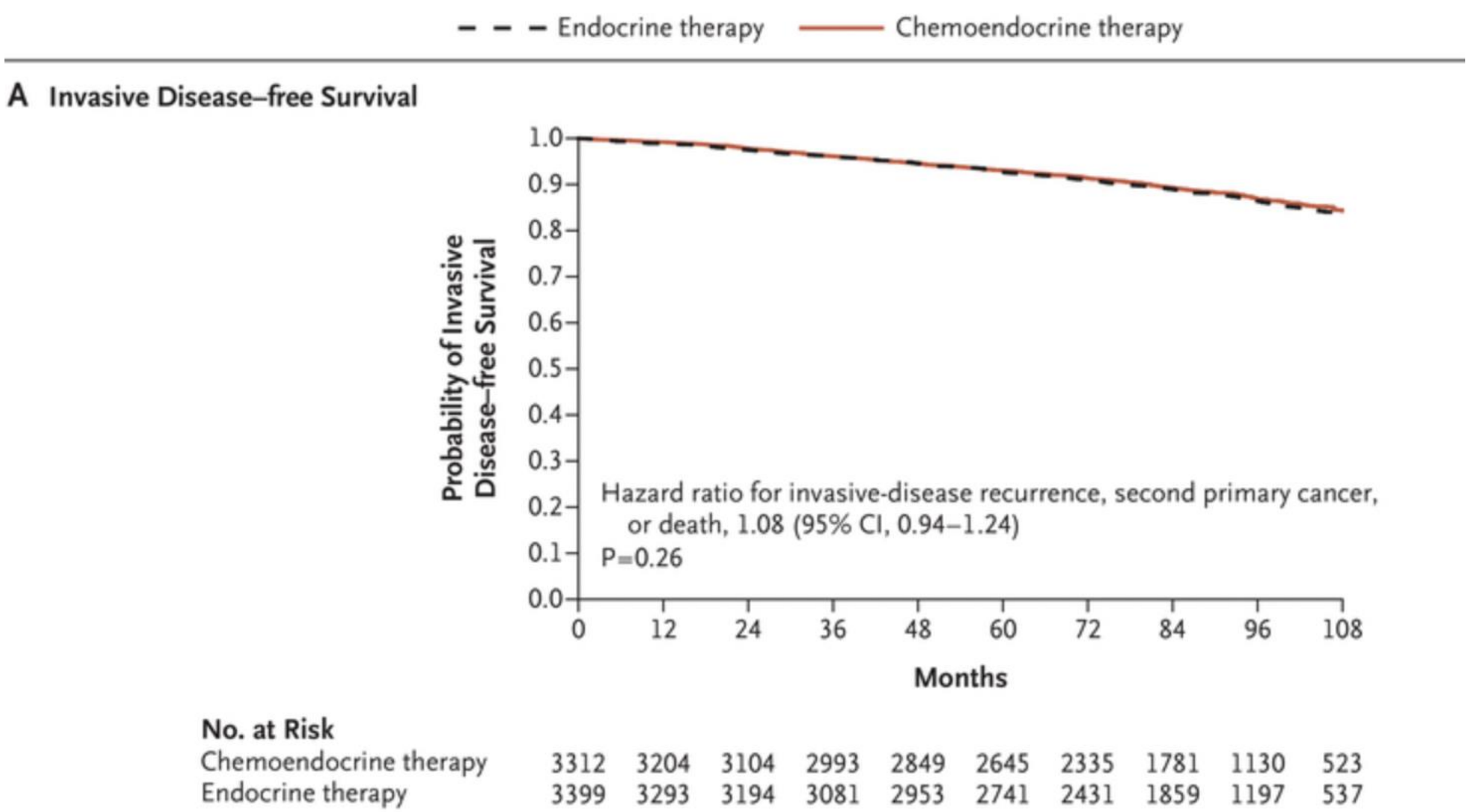
K. Kalinsky, W.E. Barlow, J.R. Gralow, F. Meric-Bernstam, K.S. Albain, D.F. Hayes, N.U. Lin, E.A. Perez, L.J. Goldstein, S.K.L. Chia, S. Dhesy-Thind, P. Rastogi, E. Alba, S. Delaloge, M. Martin, C.M. Kelly, M. Ruiz-Borrego, M. Gil-Gil, C.H. Arce-Salinas, E.G.C. Brain, E.-S. Lee, J.-Y. Pierga, B. Bermejo, M. Ramos-Vazquez, K.-H. Jung, J.-M. Ferrero, A.F. Schott, S. Shak, P. Sharma, D.L. Lew, J. Miao, D. Tripathy, L. Pusztai, and G.N. Hortobagyi

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 12, 2018 VOL. 379 NO. 2

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.


Endocrine therapy
Chemoendocrine therapy
A Invasive Disease–free Survival
Probability of Invasive Disease–free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Hazard ratio for invasive-disease recurrence, second primary cancer, or death, 1.08 (95% CI, 0.94–1.24)
P=0.26
0
12
24
36
48
60
72
84
96
108
Months
No. at Risk
Chemoendocrine therapy 3312 3204 3104 2993 2849 2645 2335 1781 1130 523
Endocrine therapy 3399 3293 3194 3081 2953 2741 2431 1859 1197 537

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer

K. Kalinsky, W.E. Barlow, J.R. Gralow, F. Meric-Bernstam, K.S. Albain, D.F. Hayes, N.U. Lin, E.A. Perez, L.J. Goldstein, S.K.L. Chia, S. Dhesy-Thind, P. Rastogi, E. Alba, S. Delaloge, M. Martin, C.M. Kelly, M. Ruiz-Borrego, M. Gil-Gil, C.H. Arce-Salinas, E.G.C. Brain, E.-S. Lee, J.-Y. Pierga, B. Bermejo, M. Ramos-Vazquez, K.-H. Jung, J.-M. Ferrero, A.F. Schott, S. Shak, P. Sharma, D.L. Lew, J. Miao, D. Tripathy, L. Pusztai, and G.N. Hortobagyi


Kevin Kalinsky, MD, MS
Emory Winship Cancer Institute
Atlanta, Georgia

Gabriel Hortobagyi

Jul 20, 2021 17:39:18 EDT
New England Journal of Medicine

Disclosure Purpose: 21-08873

Summary of Interests

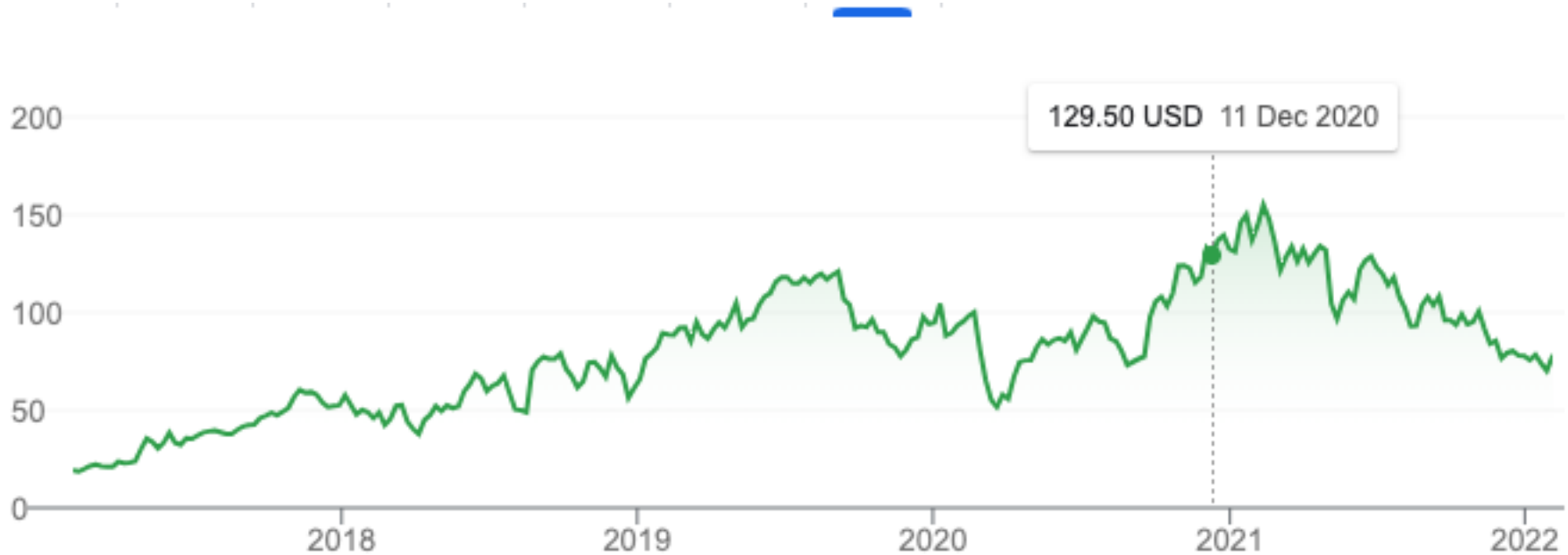
I do not have any interests to disclose at this time.

Disclosure Purpose: 21-08873

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
4D Pharma	Consultant	Self
Category: Consultant *Additional Information:*	*Description:*	
Acetylon	Grant / Contract	Other - Institution
Recipient Name: Institution *Grant / Contract Description:* *Additional Information:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research	
Ambryx	Other	Self
Category: Other *Additional Information:*	*Description:* steering committee	
Amgen	Grant / Contract	Other - Institution
Recipient Name: Institution *Grant / Contract Description:* *Additional Information:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research	
Array BioPharma	Employment	Spouse/Partner
Title: *Additional Information:*	*Position Description:*	
AstraZeneca	Other	Self
Category: Other *Additional Information:*	*Description:* steering committee	
AstraZeneca	Consultant	Self
Category: Consultant *Additional Information:*	*Description:*	
AstraZeneca	Travel	Self
Location(s): *Additional Information:*	*Purpose:*	
Calithera	Grant / Contract	Other - Institution
Recipient Name: Institution *Grant / Contract Description:* *Additional Information:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research	
cyclocel	Consultant	Self
Category: Consultant *Additional Information:*	*Description:*	
Cytomx	Grant / Contract	Other - Institution
Recipient Name: Institution *Grant / Contract Description:* *Additional Information:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research	
Daiichi Sankyo Company	Consultant	Self
Category: Consultant *Additional Information:*	*Description:*	
Eisai	Consultant	Self
Category: Consultant *Additional Information:*	*Description:*	
Eli Lilly and Company	Grant / Contract	Other - Institution
Recipient Name: Institution *Grant / Contract Description:* *Additional Information:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research	
Eli Lilly and Company	Other	Self
Category: Other *Additional Information:*	*Description:* Speakers' Bureau	
Eli Lilly and Company	Consultant	Self
Category: Consultant *Additional Information:*	*Description:*	
Eli Lilly and Company	Travel	Self
Location(s): *Additional Information:*	*Purpose:*	
Genentech	Grant / Contract	Other - Institution
Recipient Name: Institution *Grant / Contract Description:* *Additional Information:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research	
Genentech	Other	Self
Category: Other *Additional Information:*	*Description:* steering committee	
Grail	Employment	Spouse/Partner
Title: *Additional Information:*	*Position Description:*	
Immunomedics	Grant / Contract	Other - Institution
Recipient Name: Immunomedics *Grant / Contract Description:* *Additional Information:*	*Recipient Type:* Institution *Grant / Contract Purpose:*	
Immunomedics	Other	Self
Category: Other *Additional Information:*	*Description:* steering committee	
Merck	Consultant	Self
Category: Consultant *Additional Information:*	*Description:*	
Novartis	Grant / Contract	Other - Institution
Recipient Name: Institution *Grant / Contract Description:* *Additional Information:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research	
Novartis	Consultant	Self
Category: Consultant *Additional Information:*	*Description:*	
oncosec	Consultant	Self
Category: Consultant *Additional Information:*	*Description:*	
Pfizer	Grant / Contract	Other - Institution
Recipient Name: Institution *Grant / Contract Description:* *Additional Information:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research	
Pfizer	Consultant	Self
Category: Consultant *Additional Information:*	*Description:*	
Pfizer	Travel	Self
Location(s): *Additional Information:*	*Purpose:*	
Seattle Genetics	Grant / Contract	Other - Institution



Open	77.19	Mkt cap	13.44B	52-wk high	158.00
High	78.44	P/E ratio	-	52-wk low	66.80
Low	73.21	Div yield	-		

The Oncotype DX test reveals individual tumour biology based on measuring the expression of 21 genes

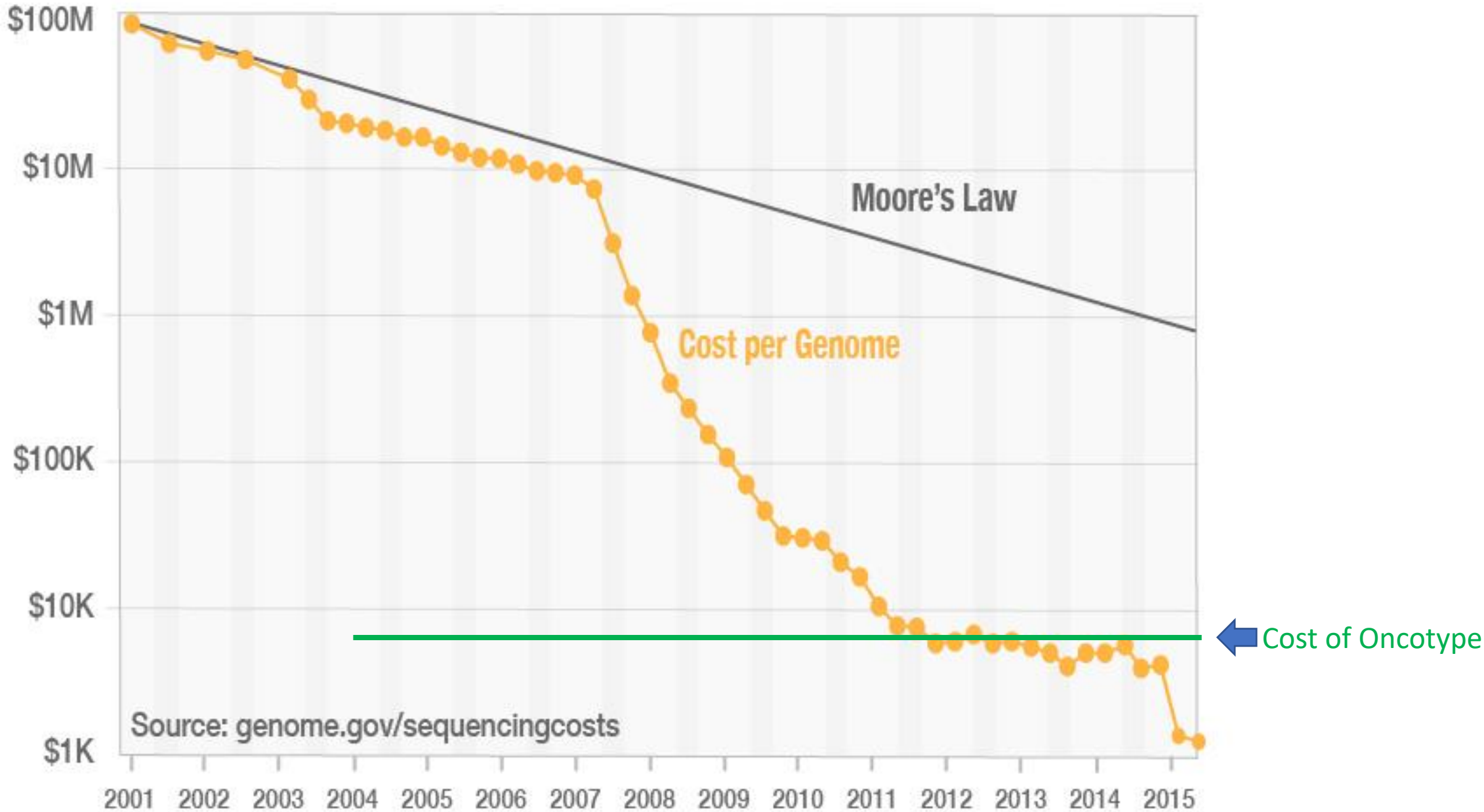
16 Cancer Genes and **5 Reference Genes**

JAMA Oncology | Original Investigation

Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor–Positive Breast Cancer

A Secondary Analysis of a Randomized Clinical Trial

Ivana Sestak, PhD; Richard Buus, PhD; Jack Cuzick, PhD; Peter Dubsky, MD; Ralf Kronenwett, MD; Carsten Denkert, MD; Sean Ferree, PhD; Dennis Sgroi, MD; Catherine Schnabel, PhD; Frederick L. Baehner, MD; Elizabeth Mallon, PhD; Mitch Dowsett, PhD


$100M
$10M
$1M
$100K
$10K
$1K
Moore's Law
Cost per Genome
Source: genome.gov/sequencingcosts
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Cost of Oncotype

KEVIN T. CONROY

CHIEF EXECUTIVE OFFICER, PRESIDENT, AND CHAIRMAN OF THE BOARD

Joined Exact Sciences: 2009

Kevin Conroy is the Chief Executive Officer, President, and Chairman of the Board of Exact Sciences. He became CEO 11 years ago and he has been part of a team that transformed Exact Sciences into one of the world's premier cancer diagnostics companies with more than 4,500 employees.

Mr. Conroy has led Exact Sciences through the development, clinical trial, regulatory approval, and commercialization of its noninvasive colorectal cancer screening test, Cologuard®. This culminated with Cologuard becoming the first medical device or diagnostic to receive simultaneous FDA approval and national Medicare coverage. Since 2014, millions of Americans have used Cologuard to screen for colorectal cancer, the

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer

K. Kalinsky, W.E. Barlow, J.R. Gralow, F. Meric-Bernstam, K.S. Albain, D.F. Hayes, N.U. Lin, E.A. Perez, L.J. Goldstein, S.K.L. Chia, S. Dhesy-Thind, P. Rastogi, E. Alba, S. Delaloge, M. Martin, C.M. Kelly, M. Ruiz-Borrego, M. Gil-Gil, C.H. Arce-Salinas, E.G.C. Brain, E.-S. Lee, J.-Y. Pierga, B. Bermejo, M. Ramos-Vazquez, K.-H. Jung, J.-M. Ferrero, A.F. Schott, S. Shak, P. Sharma, D.L. Lew, J. Miao, D. Tripathy, L. Pusztai, and G.N. Hortobagyi

Screened 9383 women with ER+ HER2 negative disease and 1-3 LN positive.

Then randomised 5083 women 1-3 LN positive and with RS 25 or lower to chemo or no chemo

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Endocrine-Only Group (N=2507)	Chemoendocrine Group (N=2511)	All Participants (N=5018)
Median age (range) — yr	57.2 (18.3–86.0)	57.9 (28.0–87.6)	57.5 (18.3–87.6)
Age category — no. (%)			
<40 yr	80 (3.2)	67 (2.7)	147 (2.9)
40–49 yr	547 (21.8)	530 (21.1)	1077 (21.5)
50–59 yr	838 (33.4)	837 (33.3)	1675 (33.4)
60–69 yr	761 (30.4)	777 (30.9)	1538 (30.6)
≥70 yr	281 (11.2)	300 (12.0)	581 (11.6)
Menopausal status — no. (%)			
Premenopausal	831 (33.1)	834 (33.2)	1665 (33.2)
Postmenopausal	1676 (66.9)	1677 (66.8)	3353 (66.8)
Recurrence score — no. (%)†			
0–13	1071 (42.7)	1076 (42.9)	2147 (42.8)
14–25	1436 (57.3)	1435 (57.1)	2871 (57.2)
Axillary surgery — no. (%)			
Axillary lymph-node dissection, with or without sentinel-node mapping	1571 (62.7)	1569 (62.5)	3140 (62.6)
Sentinel-node biopsy without axillary lymph-node dissection	936 (37.3)	942 (37.5)	1878 (37.4)
Positive nodes — no. (%)			
1 node	1647 (65.7)	1628 (64.8)	3275 (65.3)
2 nodes	623 (24.8)	643 (25.6)	1266 (25.2)
3 nodes	229 (9.1)	231 (9.2)	460 (9.2)
Not reported	8 (0.3)	9 (0.4)	17 (0.3)

	Premenopausal		Postmenopausal	
	Chemoendocrine Therapy	Endocrine Therapy	Chemoendocrine Therapy	Endocrine Therapy
Total Number	829	826	1658	1671
Adjuvant Chemotherapy	(n=721)	(n=53)	(n=1332)	(n=53)
Anthracycline w/o Taxane	35 (5%)	1 (2%)	35 (3%)	3 (6%)
Anthracycline and Taxane	387 (54%)	25 (47%)	522 (39%)	19 (36%)
Taxane & Cyclophosphamide	298 (41%)	25 (47%)	758 (57%)	30 (57%)
Other	1 (<1%)	2 (4%)	17 (1%)	1 (2%)
None/Not Reported	108	773	326	1618

Hormonal therapy was not stringent or balanced.

Premenopausal patients 6.3% vs 19.0% had ovarian suppression

Compliance with hormonal treatment was affected by chemotherapy.

18.1% non compliance in chemoendocrine arm
4.7% non compliance in endocrine arm

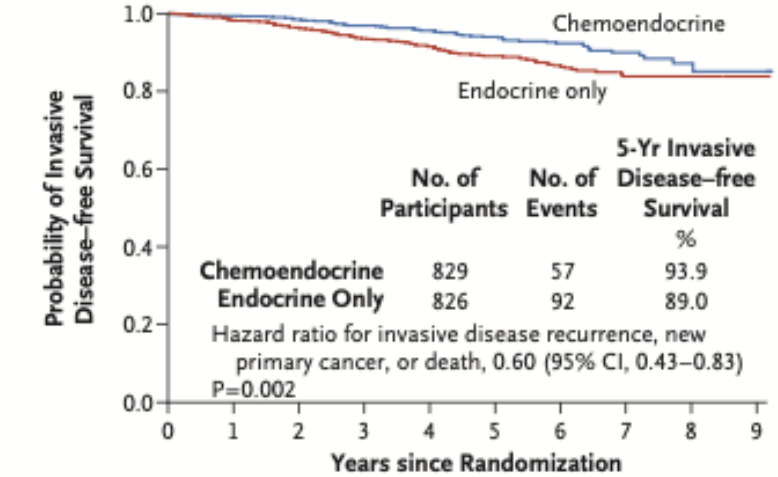
The Result…….

Postmenopausal DFS 91.9% vs 91.3% (HR 1.02)

Premenopausal 89% vs 93.9% (HR 0.60)

The relative chemotherapy benefit did not increase as the RS increased

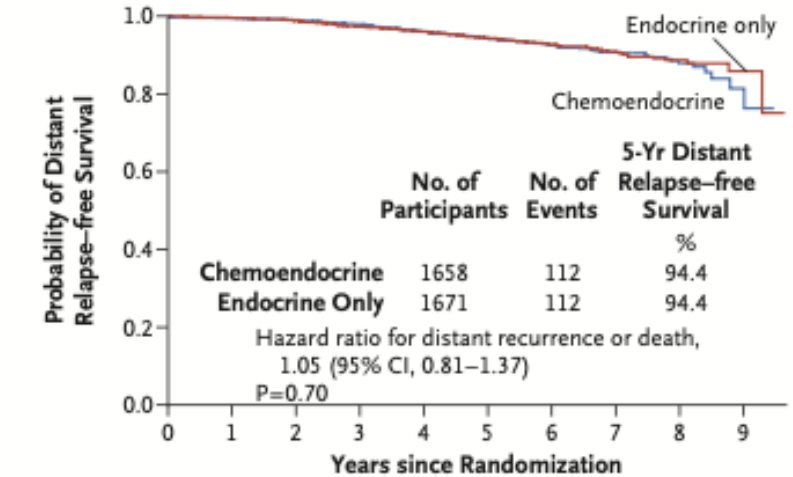
C **Invasive Disease–free Survival, Premenopausal Participants**



No. at Risk

Chemoendocrine group	829	764	710	642	546	484	312	153	46	5
Endocrine-only group	826	760	703	622	542	463	290	138	44	2

E **Distant Relapse–free Survival, Postmenopausal Participants**

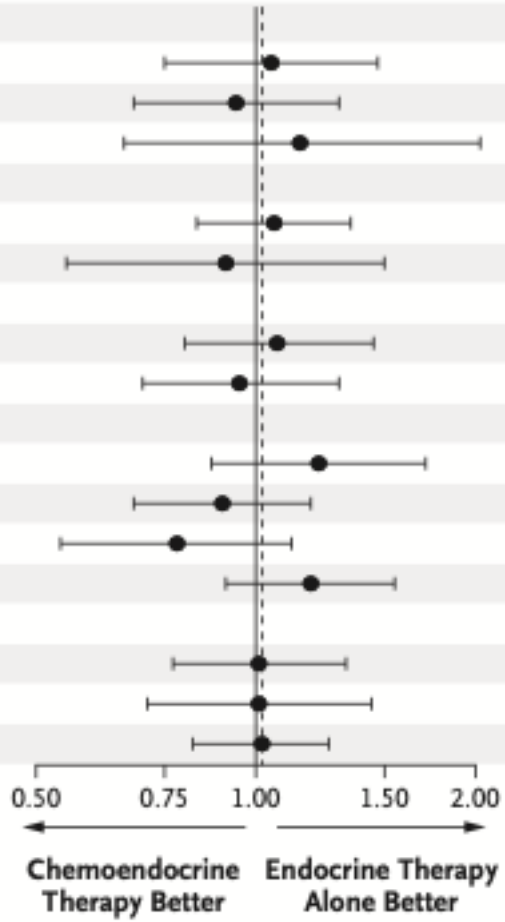


No. at Risk

Chemoendocrine group	1658	1525	1429	1320	1175	1026	686	382	139	16
Endocrine-only group	1671	1583	1492	1368	1226	1059	706	386	144	22

A **Postmenopausal Women**

Subgroup	No. of Participants	No. of Events	Hazard Ratio for Invasive Disease Recurrence, New Primary Cancer, or Death (95% CI)
Age			
>65 yr	1180	138	1.05 (0.75–1.47)
55–65 yr	1637	145	0.94 (0.68–1.30)
<55 yr	511	49	1.15 (0.66–2.03)
Grade			
Intermediate or high	2433	265	1.06 (0.83–1.35)
Low	850	62	0.91 (0.55–1.50)
Tumor size			
T2 or T3	1360	173	1.07 (0.80–1.45)
T1	1966	159	0.95 (0.70–1.30)
Nodes			
2 or 3 positive	1146	133	1.22 (0.87–1.71)
1 positive	2181	199	0.90 (0.68–1.19)
Sentinel node	1306	118	0.78 (0.54–1.12)
Full axillary lymph-node dissection	2022	214	1.19 (0.91–1.55)
Recurrence score			
14–25	1837	206	1.01 (0.77–1.33)
0–13	1492	126	1.01 (0.71–1.44)
Overall	3328	332	1.02 (0.82–1.26)



B Premenopausal Women

Subgroup	No. of Participants	No. of Events	Hazard Ratio for Invasive Disease Recurrence, New Primary Cancer, or Death (95% CI)
Age			
≥50 yr	509	44	0.98 (0.54–1.78)
45–49 yr	615	46	0.46 (0.25–0.86)
<45 yr	531	59	0.49 (0.28–0.84)
Grade			
Intermediate or high	1280	125	0.58 (0.41–0.84)
Low	357	23	0.67 (0.29–1.55)
Tumor size			
T2 or T3	728	80	0.64 (0.41–0.99)
T1	925	69	0.53 (0.32–0.88)
Nodes			
2 or 3 positive	574	55	0.62 (0.36–1.06)
1 positive	1081	94	0.57 (0.37–0.87)
Sentinel node	556	60	0.61 (0.36–1.02)
Full axillary lymph-node dissection	1099	89	0.60 (0.39–0.91)
Recurrence score			
14–25	1015	113	0.63 (0.43–0.91)
0–13	640	36	0.49 (0.24–0.99)
Overall	1655	149	0.60 (0.43–0.83)

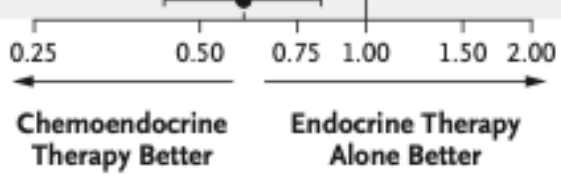


Figure 3. Invasive Disease–free Survival among Women with a Recurrence Score of 25 or Lower Who Received Chemoendocrine Therapy or Endocrine Therapy Only.

Tumor sizes range from T1 (≤2 cm) to T3 (≥5 cm). All hazard ratios shown in the figure were adjusted for the continuous recurrence score except for the hazard ratios for recurrence-score categories.

Recurrence score was not predictive of chemotherapy benefit

Women ≤50 yr			
≤10, endocrine only	145	91.0±2.6	0.31 (0.10–0.94)
≤10, chemoendocrine	135	97.9±1.5	
11–15, endocrine only	247	93.1±1.8	0.71 (0.33–1.51)
11–15, chemoendocrine	235	95.4±1.6	
16–20, endocrine only	227	85.1±2.6	0.58 (0.33–1.00)
16–20, chemoendocrine	224	92.2±2.0	
21–25, endocrine only	107	80.0±4.3	0.56 (0.27–1.17)
21–25, chemoendocrine	98	90.0±3.6	
Postmenopausal women			

the proliferation markers capture a biologic process implicated in chemotherapy sensitivity. However, the proliferation markers have a threshold of a single default value when the score is below a certain value, and this may have contributed to the overall lack of a prediction of chemo- therapy benefit in participants with a recurrence score of 0 to 25 in our trial.

Discussion points: what people say about RxPONDER

“The design of RxPONDER meant that it was not a non-inferiority trial. So the lack of superiority of the chemotherapy arm cannot be inferred as non-inferior”

Discussion points: what people say about RxPONDER

"This was an interim analysis"

“Although the RxPONDER trial was not designed as a noninferiority trial, the curves in the postmenopausal group (3353 women) may be superimposed at 5-year follow-up and with close to 60% of the expected events already observed. In a previous meta-analysis, chemotherapy reduced recurrences within the first 5 years, with a limited effect on late recurrences. Thus, it is highly unlikely that a clinically meaningful benefit will emerge with longer follow-up. Overall survival data are not mature. “

Discussion points: what people say about RxPONDER

"Over 50% of the reported events were unrelated to breast cancer and occurred in equal frequency between the two arms, hence favouring non-inferiority"

	ARM NAME					
	CET N = 1658		ET N = 1671		Total	
	N	Percentage	N	Percentage	N	Percentage
IDFS EVENT TYPE						
Any Distant Recurrence	44	27.0%	46	27.2%	90	27.1%
Local/Regional Recurrence	12	7.4%	16	9.5%	28	8.4%
Opposite Breast (recurrence or new primary)	12	7.4%	9	5.3%	21	6.3%
Non-Breast New Primary	44	27.0%	51	30.2%	95	28.6%
Recurrence not Classified	10	6.1%	6	3.5%	16	4.8%
Death not due to Recurrence or Second Primary	41	25.1%	41	24.3%	82	24.7%
Total	163		169		332	

Discussion points: what people say about RxPONDER

"Even if you just look at distant recurrence-free survival (DRFS) 82 out of 224 events were due to unrelated deaths"

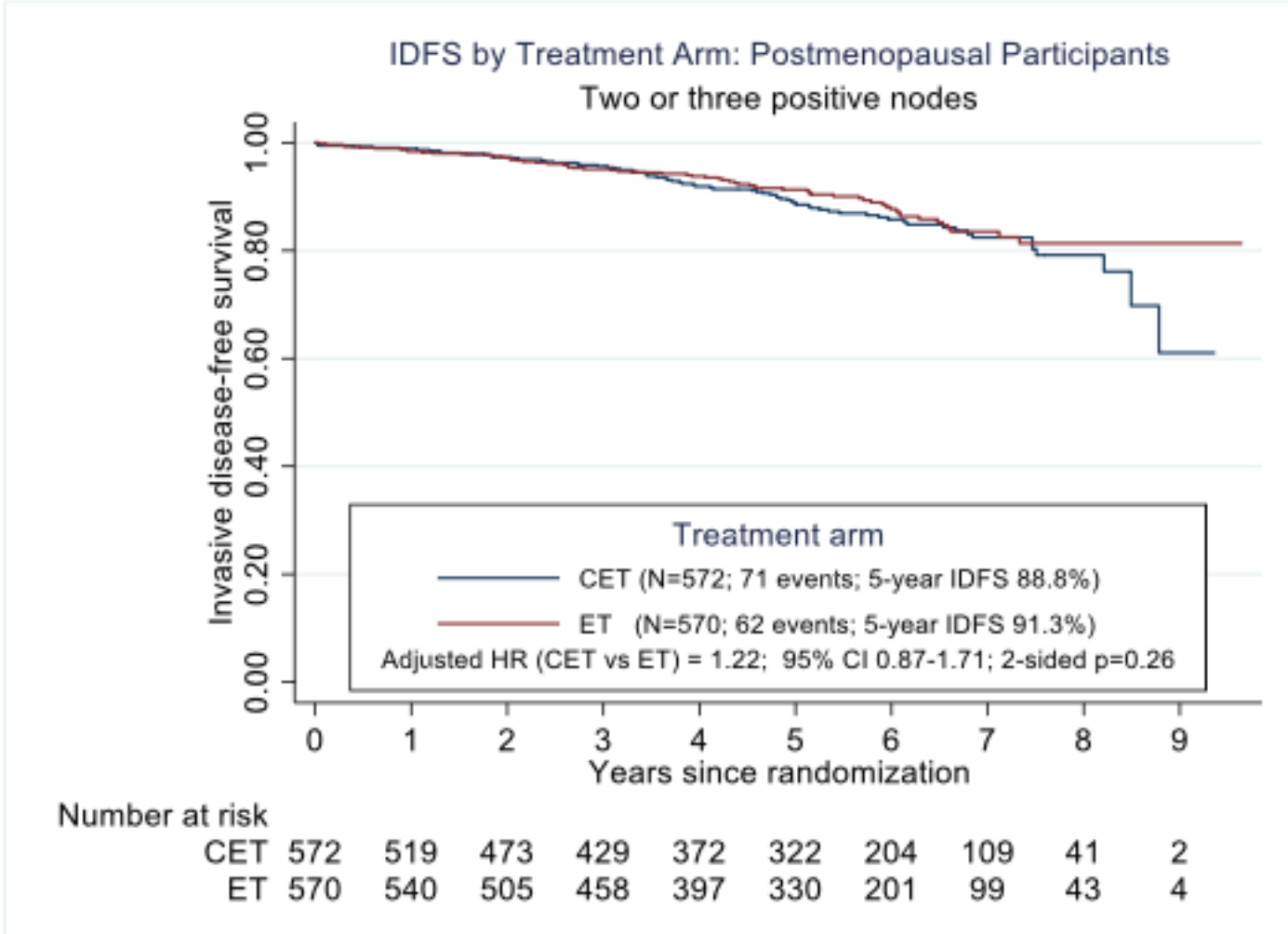
Discussion points: what people say about RxPONDER

"11.4% of patients in the intention to treat analysis declined their allocated treatment arm and crossed over, further favouring non-inferiority women"

Discussion points: what people say about RxPONDER

"Although all patients had node positive disease and were considered by US doctors to be high clinical risk, the majority (65.5%) had a single involved node and only 9% had three involved nodes. 58% had T1 tumours and only 5% T3 tumours, while only 10% were grade 3"

6B. Invasive Disease-Free Survival in Postmenopausal Patients with 2-3 Lymph No



Discussion points: what people say about RxPONDER

"For premenopausal patients, ovarian suppression was not prespecified. This is a major flaw for the interpretation of the results in this important group of patients as the benefit of chemotherapy maybe due to the endocrine effect of chemotherapy in premenopausal women"

optima
personalised treatment of breast cancer

matters because….

- Properly powered for non-inferiority
- Enrolling genuinely higher risk patients
- Properly controls hormonal therapy
- Looking for cheaper and better tests