Highlights report of ASCO 2022

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DESTINY-Breast04: ENHERTU® (trastuzumab deruxtecan; T-DXd) vs TPC in patients with HER2-low unresectable and/or metastatic BC

Plenary #LBA3: Dr Shanu Modi (Memorial Sloan Kettering Cancer Center, New York, NY, USA)

Approximately 55% of metastatic BCs typically categorised as HER2-negative express low levels of HER2 (IHC 1+ or IHC 2+/ISH− by ASCO/CAP 2018 guidelines). T-DXd has shown promising efficacy in HER2-low mBC in a Phase 1 study (NCT02564900). This is the primary report from DESTINY-Breast04 (NCT03734029).

Population: Patients with centrally confirmed HER2-low unresectable and/or mBC treated with 1–2 prior lines of CT in the metastatic setting.

Study Design: 557 patients were randomised (2:1) to T-DXd 5.4 mg/kg Q3W or TPC (capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel).

Primary Outcome: PFS by BICR in patients with HR+ mBC.

Key Secondary Outcomes: PFS by BICR in the FAS (HR+ and HR- patients), and OS in patients with HR+ mBC and in the FAS.

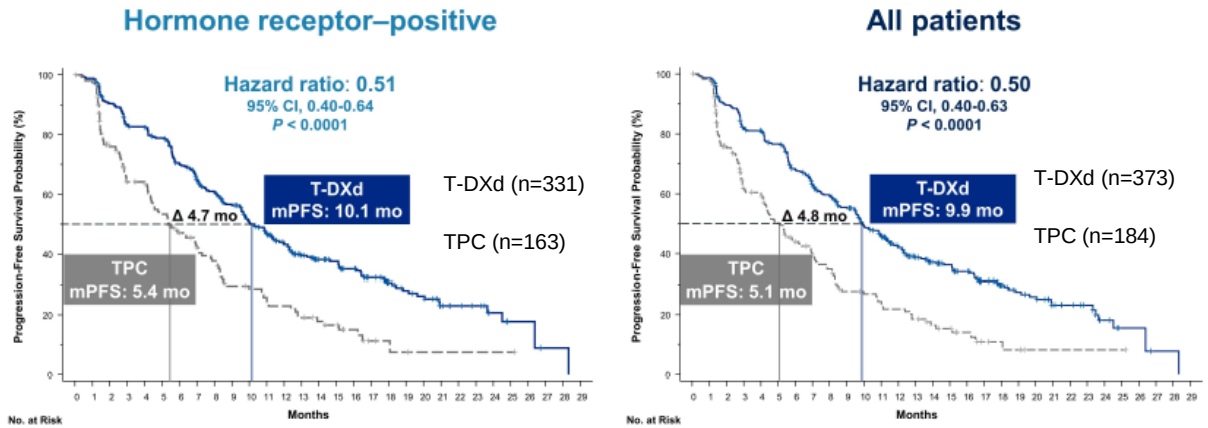
Results:

- 373 and 184 patients (88.7% and 88.6% HR+ mBC) were assigned to T-DXd and TPC, respectively. Median follow-up was 18.4 months; median treatment duration was 8.2 months with T-DXd and 3.5 months with TPC.
- PFS in the HR+ population and the FAS are presented in Figure 1. There was a similar magnitude of benefit across all patient subgroups.
- Improvements in OS were seen at this analysis: in the HR+ group, OS was 23.9 months in the T-DXd arm vs 17.5 months in the TPC arm (HR 0.64; p=0.0028) and OS was improved to a similar extent in the FAS.

Results (cont.)

- 53% of patients treated with T-DXd vs 67% of patients with TPC experienced Grade ≥3 TEAEs. With T-DXd, 45 patients (12.1% [10.0% Grade 1/2, 1.3% Grade 3/4, 0.8% Grade 5]) had independently adjudicated drug-related ILD/pneumonitis vs 1 patient (0.6% Grade 1) with TPC.

Figure 1: PFS in HR+ and all patients



Authors' Conclusion: This is the first HER2-directed therapy to show a statistically significant and clinically meaningful benefit in PFS and OS compared to SOC treatment in patients with HER2-low mBC, regardless of HR status.

MAINTAIN: CDK4/6i treatment after progression on a CDK4/6i + anti-oestrogen therapy in patients HR+/HER2- unresectable or metastatic BC

[Metastatic] Oral Presentation #LBA1004: Dr Kevin Kalinsky (Winship Cancer Institute, Emory University, Atlanta, GA, USA)

Trial: Phase 2 MAINTAIN trial (NCT02632045).

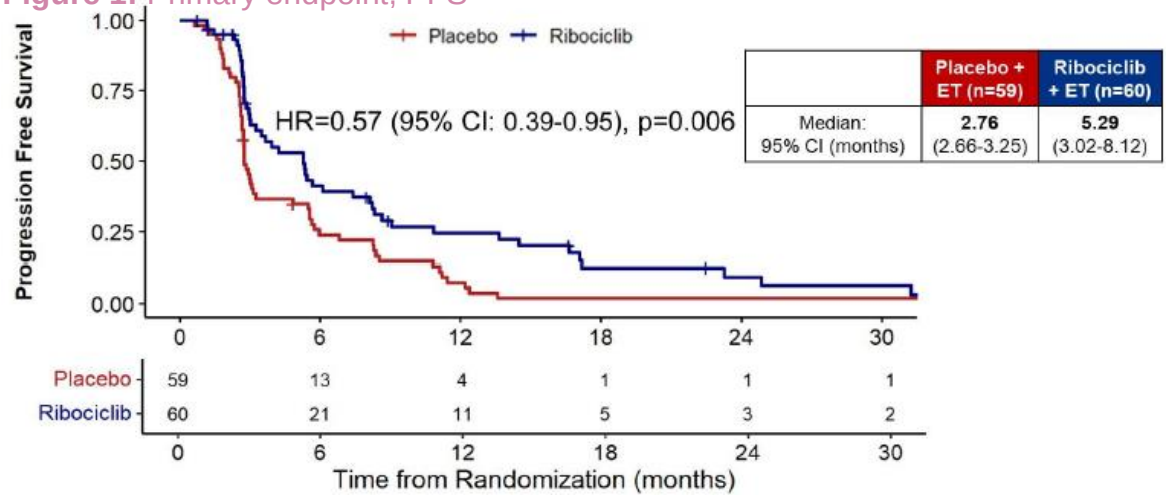
Population: Patients with unresectable or metastatic HR+/HER2- BC* who had progressed on ET and any CDK4/6i.

Study Design: 120 participants† were randomised (1:1) to RIB + a switch of ET, or PBO + a switch of ET. FUL was used as the ET in patients with progression on a prior AI for mBC and no prior FUL; the protocol was amended to allow EXE as ET if patients had progressed on prior FUL.

Primary Outcome: PFS (RECIST V1.1).

Secondary Outcomes: ORR, CBR, safety, tumour and blood markers (including ctDNA).

Figure 1: Primary endpoint, PFS



Results:

- 45% of participants had de novo metastatic disease at diagnosis, 60% of participants had visceral metastases.
- 9% of participants had received CT for their mBC. The prior CDK4/6i was PAL in 87% of patients, RIB in 12% of patients and ABE in 2% of patients. Median duration of prior CDK4/6i was 15.5 months in the PBO+ET arm and 17 months in the RIB+ET arm.
- RIB+ET was associated with a statistically significant improvement in PFS compared to PBO+ET in patients with tumour progression following a prior CDK4/6i (Figure 1).
- There was a 40% reduction in the risk of progression or death with RIB+ET vs PBO+ET within the FUL subgroup (83% of patients [n=99]). In an exploratory analysis in this subgroup, the benefit seemed limited to *ESR1* WT, although the *ESR1* mutant subgroup was small, with a higher rate of CCND1 and/or FGFR1 amplifications.
- In the PBO+ET arm, 20% of patients experienced dose reductions due to AEs, vs 53% in the RIB+ET arm, whilst dose reductions due to AEs occurred in 8.5% vs 23% of participants. The most frequently reported AEs were neutropenia in the RIB+ET arm (72%) and fatigue in the PBO+ET arm (32%).

Authors' Conclusion: This is the first randomised trial to show the benefit of RIB and switching ET after CDK4/6i progression.

Final OS analysis from the PALOMA-2 trial

[Metastatic] Oral Presentation #LBA1003: Dr Richard Finn (David Geffen School of Medicine at UCLA, Los Angeles, CA, USA)

Trial: PALOMA-2 (NCT01740427).

Population: Postmenopausal women with ER+/HER2- mBC, who had received no prior treatment for advanced disease and had ECOG PS 0–2.

Study Design: 666 participants were randomised (2:1) to PAL 125 mg/day (3 weeks on. 1 week off) + LET 2.5 mg daily, or matching PBO+LET.

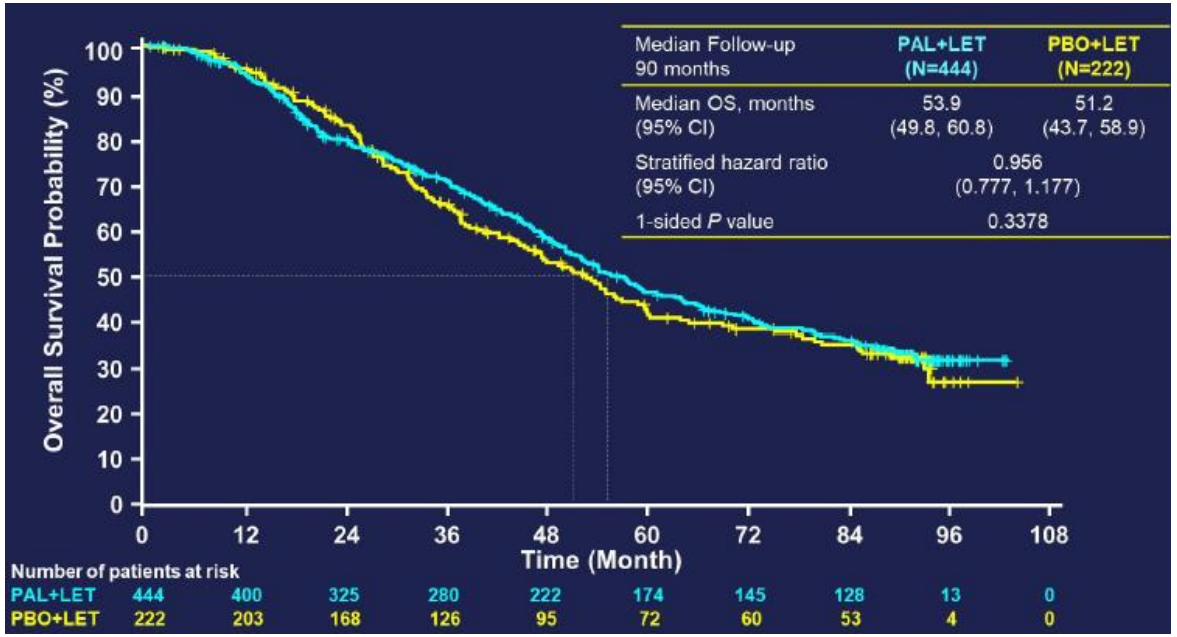
Primary Outcome: Investigator-assessed PFS.

Secondary Outcomes: OS, response, safety, biomarkers, PROs.

Results:

- At this data cut-off, median follow-up was 90 months.
- Median OS was 53.9 months in the PAL+LET arm vs 51.2 months in the PBO+LET arm (HR 0.956; 95% CI 0.777, 1.777; Figure 1).
- A proportion of patients were not available for follow-up (withdrew consent or lost to follow-up) and were censored: 21% in the PBO+LET arm vs 13% in the PAL+LET arm.
- A post-hoc sensitivity analysis excluding these patients resulted in a median OS of 51.6 months (95% CI 46.9, 57.1) with PAL+LET vs 44.6 months (37.0, 52.3) with PBO+LET (HR 0.869; 95% CI 0.706, 1.069).
- No new safety findings were observed and there was no evidence of cumulative toxicity. The two most common any-Grade AEs (PAL+LET vs PBO+LET) were neutropenia (82% vs 6%) and infections (64% vs 46%).

Figure 1: OS in the ITT population



Authors' Conclusion: PALOMA-2 met its primary outcome of improving PFS. OS was numerically longer in the PAL+LET arm vs the PBO+LET arm, but the results were not statistically significant. Interpretation of OS in PALOMA-2 is limited by the large and disproportionate censoring of patients with missing survival data.

Disparities in BC

[Local/Regional/Adjuvant] Poster Discussion Session #515: Dr Olga Kantor (Dana-Farber Brigham and Women's Cancer Center, Boston, MA, USA); #516: Dr Julia Foldi (Yale School of Medicine, New Haven, CT, USA); [Metastatic] Poster Discussion Session #1013: Dr Susrutha Puthanmadhom Narayanan (University of Pittsburgh Medical Center Cancer Center, Pittsburgh, PA, USA)

Dr Olga Kantor presented a poster on racial/ethnic disparities in LRR in patients with HR+/N- BC who were enrolled in the TAILORx trial (Figure 1). Racial/ethnic differences in LRR were seen in patients with T1-2N0 HR+/HER2- BC, despite high rates of treatment adherence in this clinical trial population. The highest LRR rates were observed in non-Hispanic Black and Asian patients.

The effect of socioeconomic status (measured by Neighborhood Deprivation Index) on survival in mBC was investigated by Dr Susrutha Puthanmadhom Narayanan *et al*. Survival probability was lower in African American than Caucasian women (Figure 2), but race was no longer a significant predictor of survival when socioeconomic status was accounted for. The authors therefore concluded that there is an urgent need for healthcare investments in low socioeconomic status neighborhoods.

Dr Julia Foldi's poster on clinical outcomes and immune markers by race in a Phase 1/2 trial of neoadjuvant IMFINZI® (durvalumab) + CT in patients with eTNBC found that pCR rates were similar in African American and non-African American patients. Stromal TILs, PD-L1 status, 3-year OS and EFS (Figure 3), and the frequency of irAEs were also similar. The authors concluded that these results suggest that when patients receive identical treatment and are monitored closely, disparities in outcomes can be mitigated or abolished.

Figure 1: Kaplan-Meier LRR incidence curves by race/ethnicity in TAILORx

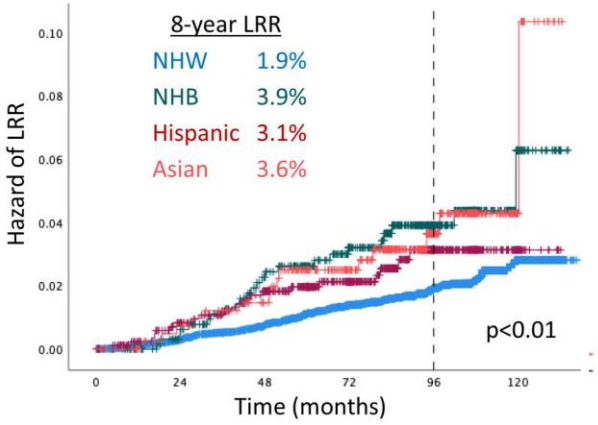


Figure 2: Kaplan-Meier survival plot for African Americans vs Caucasians

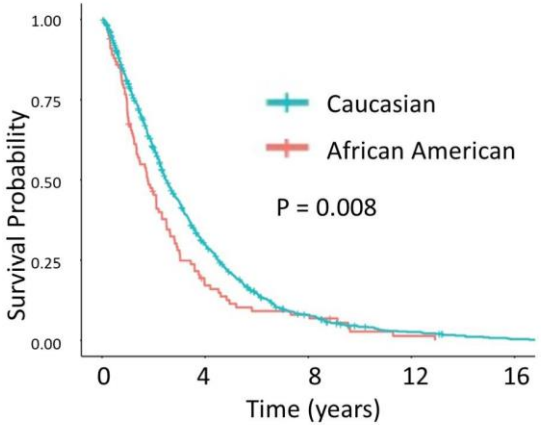
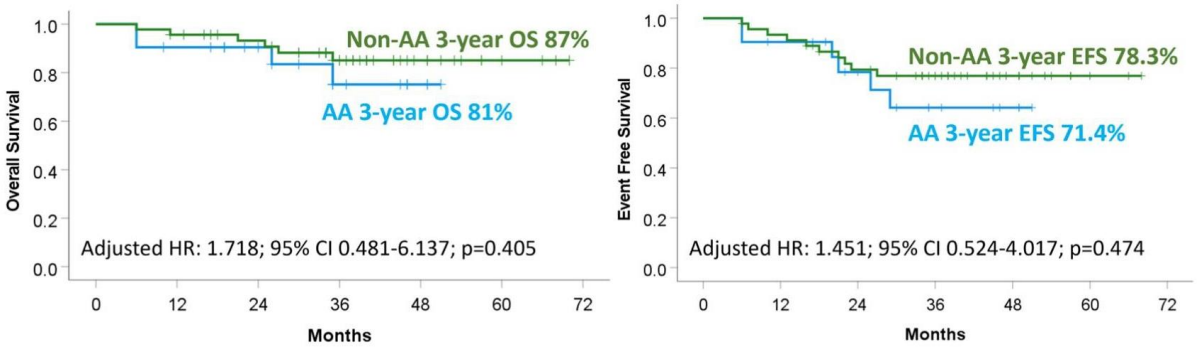


Figure 3: OS and EFS by race with durvalumab treatment



NRG-BR002: A Phase 2R/3 trial of SOC systemic therapy +/- stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic BC

[Metastatic] Oral Presentation #1007: Prof Steven Chmura (The University of Chicago Medicine, Chicago, IL, USA)

Metastases-directed treatment with SBRT or SR in addition to SOC systemic therapy has improved PFS and OS compared with SOC systemic therapy alone in prospective and retrospective studies of patients with oligometastatic breast cancer (OMBC). However, randomised evidence of this treatment benefit are lacking. The randomised Phase 2R/3 NRG-BR002 trial sought to determine the efficacy of SOC systemic therapy + metastasis-directed treatment (SBRT or SR) as 1L treatment of OMBC.

Population: Patients with OMBC with controlled locoregional disease and ≤4 metastases on standard imaging, who had been on SOC systemic therapy for ≤12 months without progression. Patients with brain metastases or prior radiation treatment were excluded.

Study Design: Participants were randomised (1:1), stratified by number of metastases (1 vs ≥2), HR and HER2 status, and use of prior CT for mBC, to:

- Arm 1 – Symptom-directed palliative therapy as needed + SOC systemic therapy, or
- Arm 2 – Total ablation of all metastases, + SOC systemic therapy.

Authors' Conclusion: Improved PFS or OS with the addition of metastasis-directed treatment to SOC systemic therapy was not observed in patients with OMBC. The trial will not proceed to Phase 3.

Results:

- 125 eligible patients were enrolled in the trial (Arm 1=65, Arm 2=60). Median follow-up was 35 months.
- Key baseline characteristics: median age 54 years, 89% HR+, 12% HER2+, 8% TNBC. 60% had 1 metastasis and 22% of patients with metastases presented synchronously with primary disease.
- Systemic therapy was delivered to 95% of participants in both arms after randomisation, and 93% of patients within Arm 2 received ablation via SBRT.
- Due to the lack of improved PFS, OS was also reported (Table 1). Median PFS was 23 months in Arm 1 vs 19.5 months in Arm 2; median OS was not reached in either arm.

Table 1: PFS and OS results

	Arm 1 (n=65)	Arm 2 (n=60)
36-month PFS, % (70% CI)	32.8 (26.0, 39.5)	38.1 (29.7, 46.6)
HR (70% CI)	0.92 (0.71, 1.17)	
36-month OS, % (95% CI)	71.8 (58.9, 84.7)	68.9 (55.1, 82.6)
HR (95% CI)	1.23 (0.63, 2.39)	

- There were fewer new metastases inside the treated/index area for Arm 2 compared to Arm 1 (7% vs 29%).
- There were no Grade 5 TRAEs, 1 Grade 4 AE in Arm 1, and 6 and 3 Grade 3 AEs in Arms 1 and 2, respectively.

TROPiCS-02: A randomised Phase 3 study of TRODELVY® (sacituzumab govitecan; SG) vs treatment of physician's choice (TPC) in patients with HR+/HER2- mBC

[Metastatic] Oral Presentation #LBA1001: Prof Hope Rugo (University of California and Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA)

Background: HR+/HER2- disease is the most common type of mBC. International treatment guidelines recommend 1L ET+CDK4/6is; however, optimal sequencing post progression on ET+CDK4/6is remains unclear. The SOC for ET-resistant disease is sequential single-agent CT; however, additional lines are associated with decreasing response rates and QoL.

Trial: TROPiCS-02 (NCT03901339).

Population: Patients (N=543) with metastatic or locally recurrent inoperable HR+/HER2- BC, who progressed following ≥1 prior taxane, CDK4/6i, and ET in any setting. Patients who received 2–4 prior CT regimens for mBC were eligible; 1 prior therapy for mBC was allowed if disease progressed ≤12 months after (neo)adjuvant therapy.

Study Design: Patients were randomised 1:1 to receive SG (10 mg/kg IV on Days 1 and 8, every 21 days; n=272) or TPC (capecitabine, eribulin, vinorelbine, or gemcitabine; n=271) until disease progression or unacceptable toxicity.

Primary Outcome: PFS (RECIST v1.1 by BICR [final analysis]).

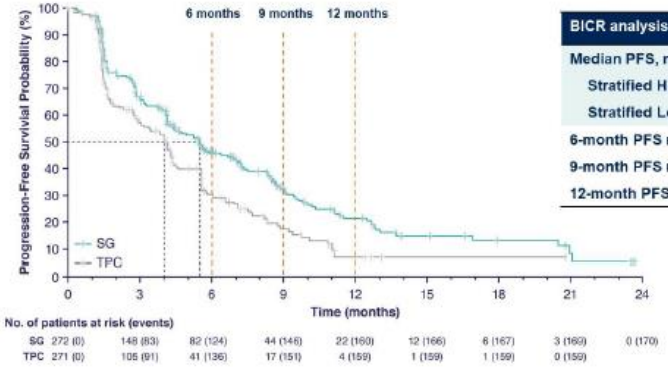
Key Secondary Outcomes: OS (first planned interim analysis).

Authors' Conclusion: SG produced a statistically significant, clinically meaningful PFS benefit over single-agent CT and had a manageable safety profile in patients with heavily pre-treated HR+/HER2-, endocrine-resistant, unresectable locally advanced or mBC, who have limited treatment options.

Results:

- SG improved median PFS vs TPC (5.5 vs 4.0 months; HR 0.66; 95% CI 0.53, 0.83; p=0.0003; Figure 1). PFS benefit was consistent across predefined subgroups, including patients with ≥3 prior CT regimes for mBC, visceral metastases, and aged ≥65 years.
- Although OS data are not yet mature, SG showed a numeric but non-significant improvement in OS vs TPC (13.9 vs 12.3 months; HR 0.84; 95% CI 0.67, 1.06; p=0.14). A further 2 OS analyses are planned.
- ORR (21% vs 14%; OR 1.63; p=0.03) and CBR (34% vs 22%; OR 1.84; p=0.002) were higher with SG vs TPC; median DOR was 7.4 vs 5.6 months, respectively.
- Overall, 74% vs 60% of patients (SG vs TPC) had Grade ≥3 TEAEs; neutropenia (51% vs 38%) and diarrhoea (9% vs 1%) were most common. TEAEs leading to discontinuation were low (6% with SG vs 4% with TPC). There was 1 treatment-related death with SG and none with TPC.

Figure 1: PFS results



BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	0.66 (0.53–0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)

Alpelisib (ALP)-associated hyperglycaemia in mBC

Metastatic] Poster Discussion Session #1016: Dr Sherry Shen (Memorial Sloan Kettering Cancer Center, New York, NY, USA)

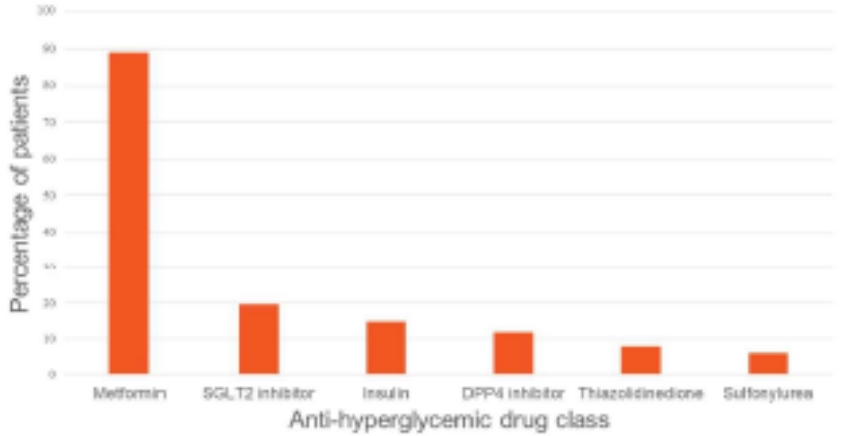
ALP+FUL improves PFS in women with HR+/HER2- mBC with *PIK3CA* mutations. Hyperglycaemia is a well-known AE associated with PIK3 inhibitors such as ALP.

Study Design: Retrospective study of 247 patients with mBC treated with ALP (84.2% of patients had HER2- disease).

Results:

- 152 patients (61.5%) developed hyperglycaemia; 72 patients (29.2%) developed Grade 3/4 hyperglycaemia.
- Among patients developing hyperglycaemia, 101 (40.9%) received treatment (Figure 1) and 49 (19.8%) were referred for endocrinology consultations.

Figure 1: Percentage of participants treated with each class of anti-hyperglycemic agent



Results (cont.):

- 42 patients (17%) required ALP dose reductions and 11 (4.5%) discontinued ALP due to hyperglycaemia.
- BMI ≥25 kg/m^2 and haemoglobin A1c ≥5.7% (prediabetic or diabetic range) were strongly predictive of:
  - Developing any-Grade hyperglycaemia ($p=0.036$ and $p<0.01$, respectively) and Grade 3/4 hyperglycaemia ($p<0.001$ for both), and
  - ALP dose reduction or discontinuation ($p<0.001$ and $p=0.015$ respectively).
- There was no significant difference in PFS by hyperglycaemia status or grade.

Authors' Conclusion: Pre-diabetic or diabetic haemoglobin A1c values and overweight BMI were strongly predictive of developing ALP-associated hyperglycaemia and ALP dose reductions or discontinuations due to hyperglycaemia**.** Management of these co-morbidities prior to ALP treatment should be strongly considered.

Abbreviations: AE, adverse event; ALP, alpelisib; BMI, body mass index; FUL, fulvestrant; HER2-, human epidermal growth factor receptor-2 negative; mBC, metastatic breast cancer; PFS, progression-free survival.

ABCSG-18 trial: Long-term outcomes of adjuvant PROLIA® (denosumab; Dmab) – fracture reduction and survival results

[Local/Regional/Adjuvant] Oral Presentation #507: Prof Michael Gnant (Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria)

Trial: ABCSG-18 (NCT00556374)

Population: 3,425 postmenopausal patients with HR+ eBC on adjuvant AI therapy.

Study Design: Prospective, randomised, PBO-controlled, double-blind, Phase 3 trial. Participants were randomised to receive either Dmab 60 mg Q6M or PBO SC Q6M.

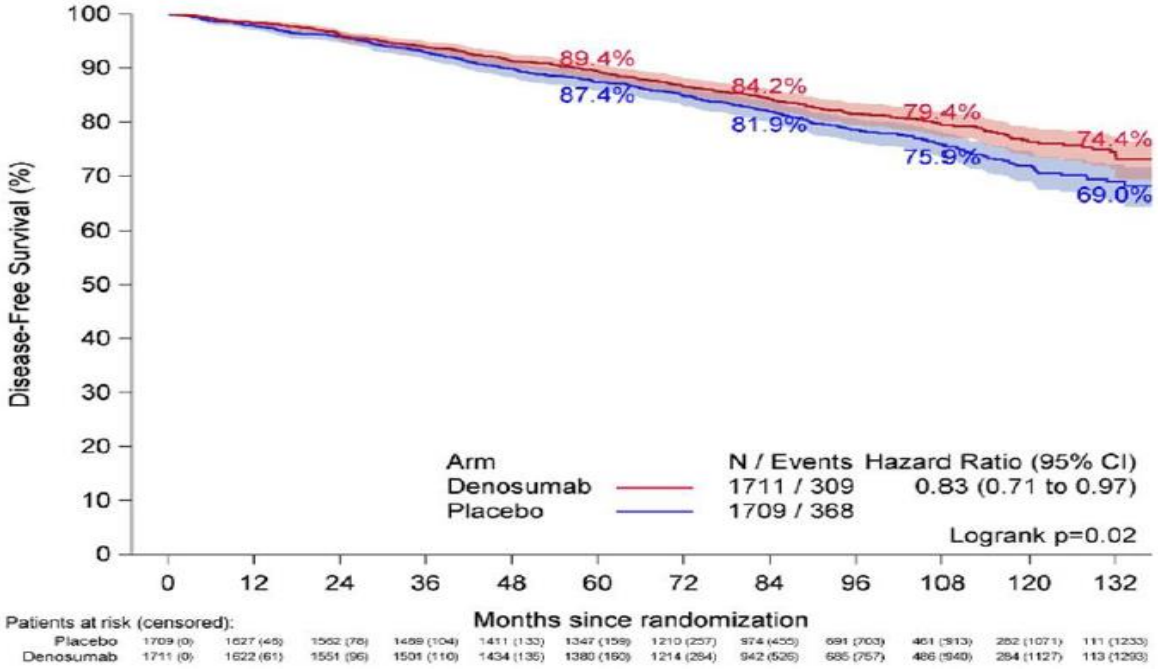
Primary Outcome: Time to first clinical fracture.

Secondary Outcomes: % change from baseline in BMD, vertebral fractures, DFS, BMFS and OS.

Results:

- For this final protocol-defined analysis, median follow-up was 8 years (Q1,3: 6.0, 9.6).
- There were no new toxicities with this longer follow-up. There were 3 treatment-emergent (but not treatment-related) deaths in the Dmab arm, and no positive osteonecrosis of the jaw adjudication reported over the study period.
- DFS was improved in the Dmab group versus the PBO group (Figure 1).
- BMFS was improved in the Dmab vs PBO group (HR 0.81; 95% CI 0.65, 1.00; p=0.05), and OS was numerically improved in the Dmab vs PBO group (HR 0.80; 95% CI 0.63, 1.01; p=0.06).

Figure 1: ABCSG-18 DFS result



Authors' Conclusion: Adjuvant Dmab 60 mg Q6M during AI therapy had an acceptable safety profile and markedly reduced treatment-induced clinical fractures, even in the long-term. DFS, BMFS, and OS were improved in this descriptive final long-term analysis. Adjuvant Dmab should be considered for routine clinical use in postmenopausal patients with HR+ breast cancer on AI treatment.

Abbreviations: AI, aromatase inhibitor; BMD, bone mineral density; BMFS, bone metastasis-free survival; CI, confidence interval; DFS, disease-free survival; Dmab, denosumab; eBC, early breast cancer; HR+, hormone receptor-positive; HR, hormone receptor; OS, overall survival; PBO, placebo; Q, quartile; Q6M, every 6 months; SC, subcutaneous.

A randomised pre-surgical trial of alternative dosing of exemestane (EXE) in postmenopausal women with ER+ eBC

[Local/Regional/Adjuvant] Poster Discussion Session #519: Dr Andrea De Censi (EO Ospedali Galliera, Genoa, Italy)

Background: Successful therapeutic cancer prevention requires definition of the minimal effective dose of the agent. Prior Phase 2 studies suggest EXE activity at a dose <25 mg QD. Here, 2 alternative dosing schedules of EXE are presented.

Trial: Multi-centre, pre-surgical, double-blind, non-inferiority Phase 2b study (NCT02598557).

Population: Postmenopausal women with histologically confirmed ER+ eBC.

Study Design: 180 patients were randomised to either EXE 25 mg/day (QD; n=59), 25 mg/3x/week (TIW; n=58), or 25 mg QW (n=63) for 4–6 weeks before surgery.

Primary Outcome: The primary aim was a non-inferiority percent change of circulating oestradiol relative to the standard dose.

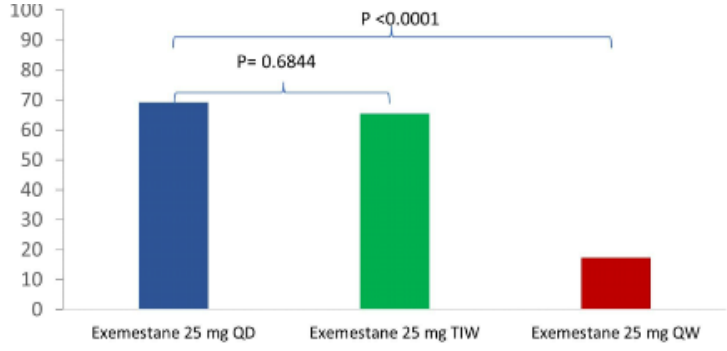
Secondary Outcomes: Change in Ki-67 and PgR expression in cancer tissue, blood sex hormones, lipid profile, toxicity and menopausal symptoms.

Authors' Conclusion: EXE 25 mg TIW has comparable activity to 25 mg QD in decreasing oestradiol and oestrone levels. This new schedule should be further assessed in prevention studies and in women on adjuvant treatment who cannot tolerate the EXE QD dose.

Results:

- Percentage of participants with oestradiol suppression is shown in Figure 1.
- The median percentage change of oestradiol (E2 SPE; pmol/L) was -98%, -98%, and -70% for EXE QD (n=55), TIW (n=56) and QW (n=60), respectively, with no significant difference between the QD and TIW arms (p=0.5428).
- Ki-67 and PgR expression at 4–6 weeks were reduced in all arms. For the TIW vs QD arms, median change at 4–6 weeks was -5.0% vs -7.5% for Ki-67 (p=0.120), and -9.0 vs -17.0 for PgR (p=0.246).
- AEs (measured by CTCAE v4.0) and menopausal symptoms (measured using MENQOL) were relatively similar in all arms, for example hot flushes were reported in 19.3% vs 21.1% of women in the TIW vs QD arms, respectively. However, the short treatment time may mean that this toxicity profile is not representative of longer-term follow-up.

Figure 1: Percentage of participants with oestradiol suppression



Disparity between Ki67 measurements and tumor gene expression tests in hormone-sensitive early breast cancer patients from the OPTIMA prelim trial

Robert C. Stein[1], Andrea Marshall[2], Jane Bayani[3], Andreas Makris[4], Iain R. MacPherson[5], Luke Hughes-Davies[6], Monika Sobol[7], Tammy Piper[7], Georgina Dotchin[2], Helen Higgins[2], Sarah E. Pinder[8], Abeer Shaaban[9], Janet Dunn[2], John M.S. Bartlett[7], OPTIMA Trial Management Group

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Background

- Ki67 is an established prognostic biomarker in hormone-sensitive EBC.
- Low on-treatment Ki67 expression identifies endocrine therapy-sensitive tumors.
- Ki67 is included in the FDA adjuvant abemaciclib.
- Ki67 has been proposed as an alternative to tumor gene-expression tests for assisting adjuvant chemotherapy recommendations.
- Information on the relationship between Ki67 and gene-expression tests is unclear.
- We have performed a comparative study using data collected in the OPTIMA prelim trial.

Methods

OPTIMA prelim

- OPTIMA is an ongoing international RCT of tumor gene-expression test-directed chemotherapy with a non-inferiority design that recruits patients at high clinical risk of recurrence.
- OPTIMA prelim was the OPTIMA feasibility study, which recruited patients from 32 UK hospitals from 2012-14.
- OPTIMA prelim included a comparison between tumor gene-expression tests; this showed significant disagreement between tests at an individual tumor level[1].
- Outcome data from OPTIMA prelim is not yet available.

Measurements

- Ki67 was measured in a single laboratory on triplicate tissue micro-arrays using quantitative image analysis (as an average) with a 10% manual quality control check.
- Oncotype DX®, Prosigna® and MammaPrint® were measured using standard methods by their manufacturer.
- Kappa statistics were used to measure agreement between tests, divided into groups using the pre-defined test score boundaries for high vs. not high risk.

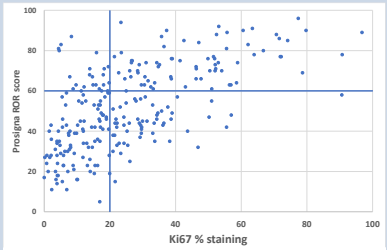
Trial registration and funding

OPTIMA prelim is registered as ISRCTN42400492 and approved by the NHS HRA London Surrey Research Ethics Committee.

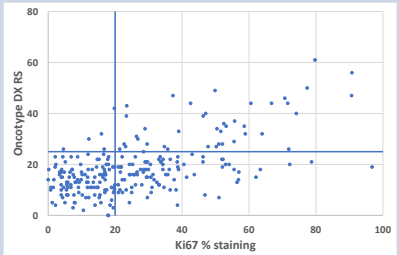
The study is funded by the UK National Institute for Health and Care Research Health Technology Assessment (NIHR HTA) Programme (project number 10/34/01. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

The bottom line

- Agreement between Ki67 and tumor gene expression tests is limited.
- Ki67 values cannot accurately be used to reflect any of the molecular scores assessed here, all of which are well validated prognostic biomarkers.
- Agreement is best when Ki67 high staining is defined as ≥30%.
- Validation of Ki67 use in chemotherapy decisions is required before it can replace existing tests.
- Tumor gene expression tests may prove useful for recommendations on adjuvant abemaciclib.



Scatterplot of Prosigna ROR scores by Ki67 (Spearmans' correlation coefficient = 0.63)



Scatterplot of Oncotype DX RS by Ki67 (Spearmans' correlation coefficient = 0.48)

Results

Patient characteristics

Number & age		Invasive tumor size	
Number of participants with complete data	250	0-19 mm	26%
		20-49 mm	64%
Age: median (range)	58 (40-78)	≥50mm	10%
Grade		**Nodal status**	
Grade 1	7%	pN0 & pN1 mi	18%
Grade 2	65%	pN1/ pN1(SN)	67%
Grade 3	28%	pN2	16%

	Ki67 <20%	Ki67 ≥20%	Total
Total	N =121 (48.4%)	N = 129 (51.6%)	N = 250
Prosigna ROR score	**agreement =69%**	**Kappa =0.38 (95% CI 0.28-0.50)**	
Prosigna ROR ≤60	101 (83.5%)	57 (44.2%)	158 (63.2%)
Prosigna ROR >60	20 (16.5%)	72 (55.8%)	92 (36.8%)
Oncotype RS	**agreement =62%**	**Kappa =0.26 (95% CI 0.17-0.35)**	
Oncotype RS ≤25	116 (95.9%)	89 (69.0%)	205 (82.0%)
Oncotype RS >25	5 (4.1%)	40 (31.0%)	45 (18.0%)
MammaPrint	**agreement =68%**	**Kappa =0.37 (95% CI 0.26-0.48)**	
MammaPrint low	96 (79.3%)	54 (41.9%)	150 (60.0%)
MammaPrint high	25 (20.7%)	75 (58.1%)	100 (40.0%)

- Kappa values in the range 0.21-0.40 indicate only "fair" agreement between Ki67 with a high vs low score cut-off of 20% and Prosigna, MammaPrint & Oncotype DX.
- Kappa values using a Ki67 cut-off of 30% staining are 0.49 (95% CI 0.38-0.60), 0.42 (0.30-0.53) and 0.33 (0.21-0.46) for Prosigna, MammaPrint & Oncotype DX.
- Values in the range 0.41-0.60 indicate "moderate" agreement. We previously reported similar agreement levels between individual tumor gene expression tests.[1]

[1]Bartlett et al 2016 J Natl Cancer Inst. 2016;108:djw050 doi: 10.1093/jnci/djw050

Presented at ASCO Annual Meeting 2022 - abstract 567

OPTIMA Main Trial design

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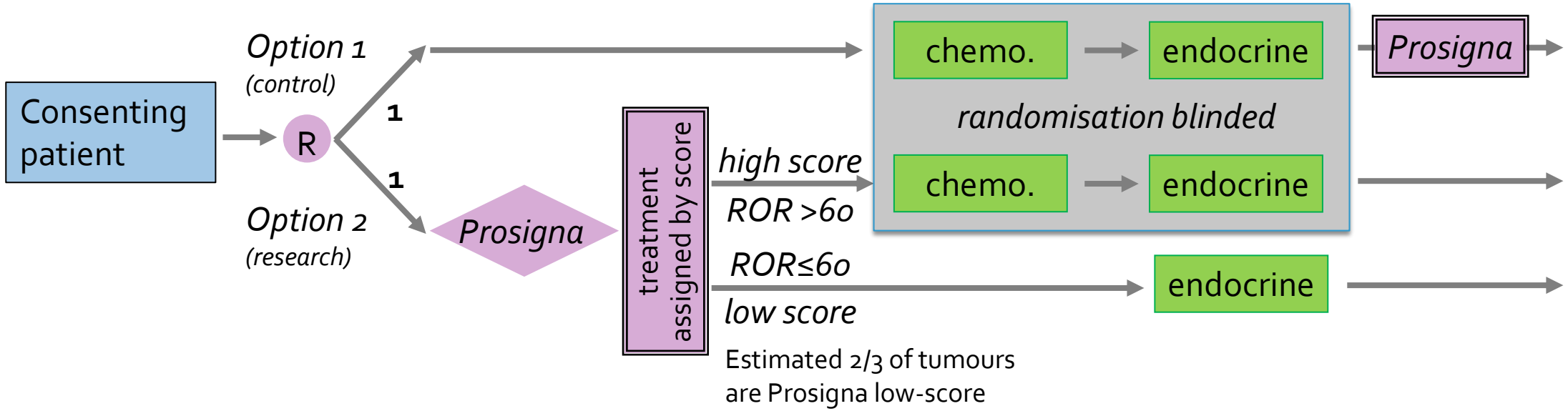


1° end points	= Non-inferiority of IDFS (Δ= -3%, control arm 5yr IDFS 85%: HR 1.22) Cost effectiveness evaluation of test-directed treatment
key 2° end point	= Non-inferiority of IDFS for low-score patients (Δ=-3.5%)
other 2° outcomes	= DRFI; BCSS; OS; Health Resource Use & QoL

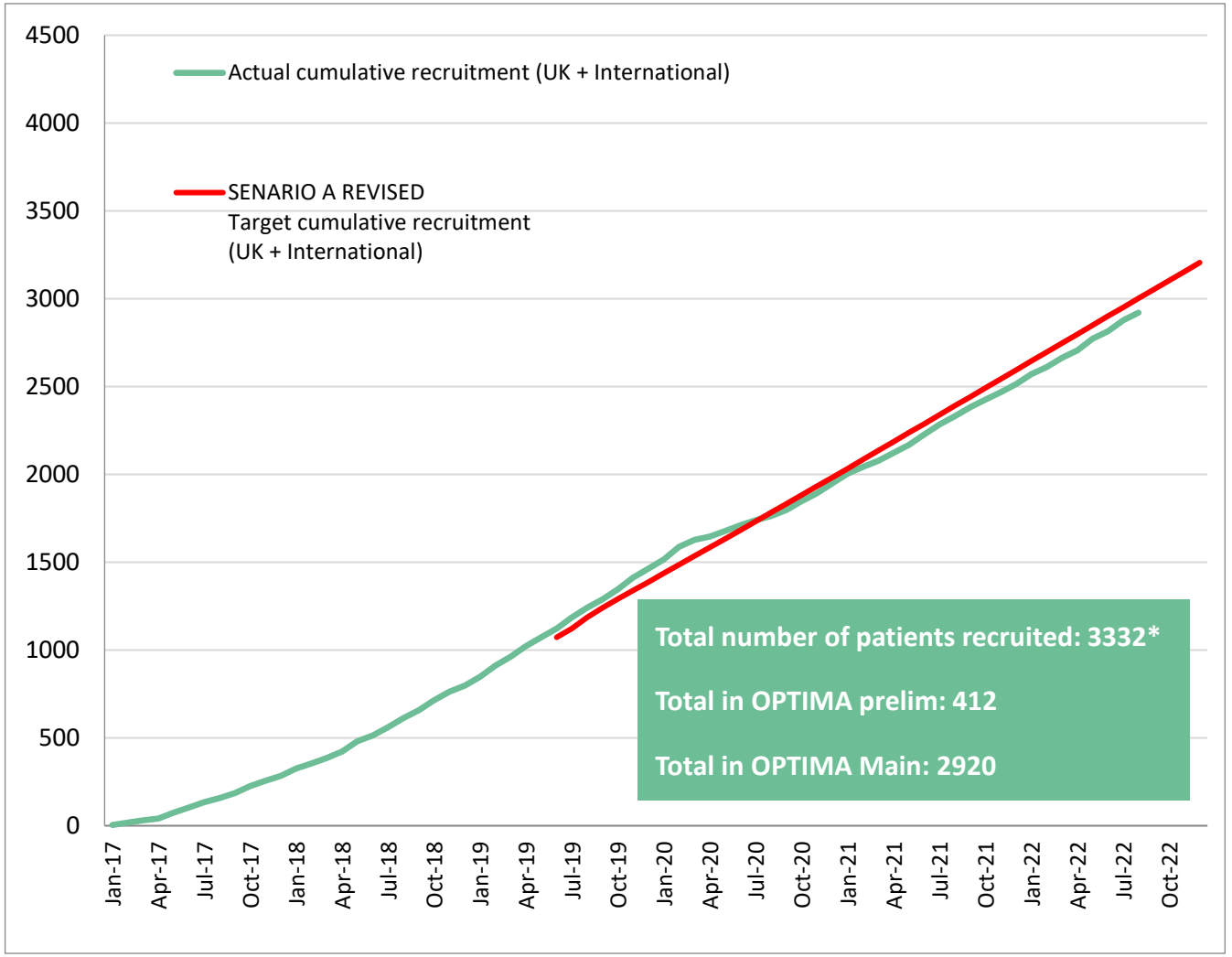
Use of Abemaciclib in the OPTIMA Trial

- **Patients in the OPTIMA Trial can receive adjuvant abemaciclib**
- **Adjuvant abemaciclib has received market authorization by the EMA and MHRA within it's licensed indication but not restricted by Ki67 (as per FDA approval)**
- **NICE have approved adjuvant abemaciclib for patients within it's licensed indication (not restricted by Ki67) on the 17th June 2022**
  - Abemaciclib with endocrine therapy is recommended, within its marketing authorization, as an option for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer in adults whose disease is at high risk of recurrence, defined as pathological tumour involvement in
    - at least 4 positive axillary lymph nodes, or
    - 1 to 3 positive axillary lymph nodes, and at least one of the following criteria:

      grade 3 disease (defined as at least 8 points on the modified Bloom-Richardson grading system or equivalent), or

      primary tumour size of at least 5 cm

OPTIMA trial Update



Date	No. of UK sites	No. of Intl. sites	Total recruitment (UK + Intl)
Jan-20	103	4	51
Feb-20	103	5	73
Mar-20	104	5	40
Apr-20	104	5	17
May-20	104	5	33
Jun-20	104	5	32
Jul-20	105	5	29
Aug-20	105	5	23
Sep-20	105	5	35
Oct-20	106	5	51
Nov-20	108	6	44
Dec-20	108	7	57
Jan-21	108	7	55
Feb-21	108	7	39
Mar-21	108	8	34
Apr-21	109	8	46
May-21	110	8	45
Jun-21	111	9	60
Jul-21	111	9	56
Aug-21	111	9	47
Sep-21	111	9	51
Oct-21	111	10	44
Nov-21	111	10	41
Dec-21	111	10	47
Jan-22	111	11	57
Feb-22	112	11	39
Mar-22	112	11	54
Apr-22	112	11	41
May-22	113	11	67
Jun-22	113	11	42
Jul-22	113	11	64
Aug-22*	114	11	42