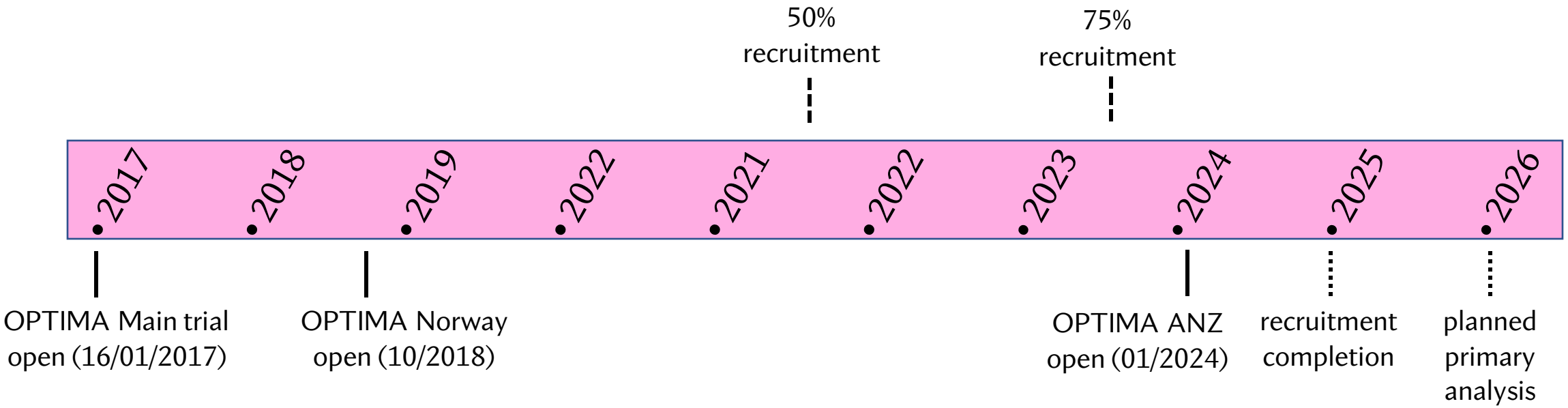
optima
personalised treatment of breast cancer

COMPLETING OPTIMA

OPTIMA timetable & completion dates

- The current OPTIMA timetable assumes:
  - Completion of recruitment on 31 Dec 2024
  - Primary analysis with a minimum follow-up of 12 months, i.e. early 2026
  - Further analyses to be performed after additional follow-up, details TBA



Trial analysis plan

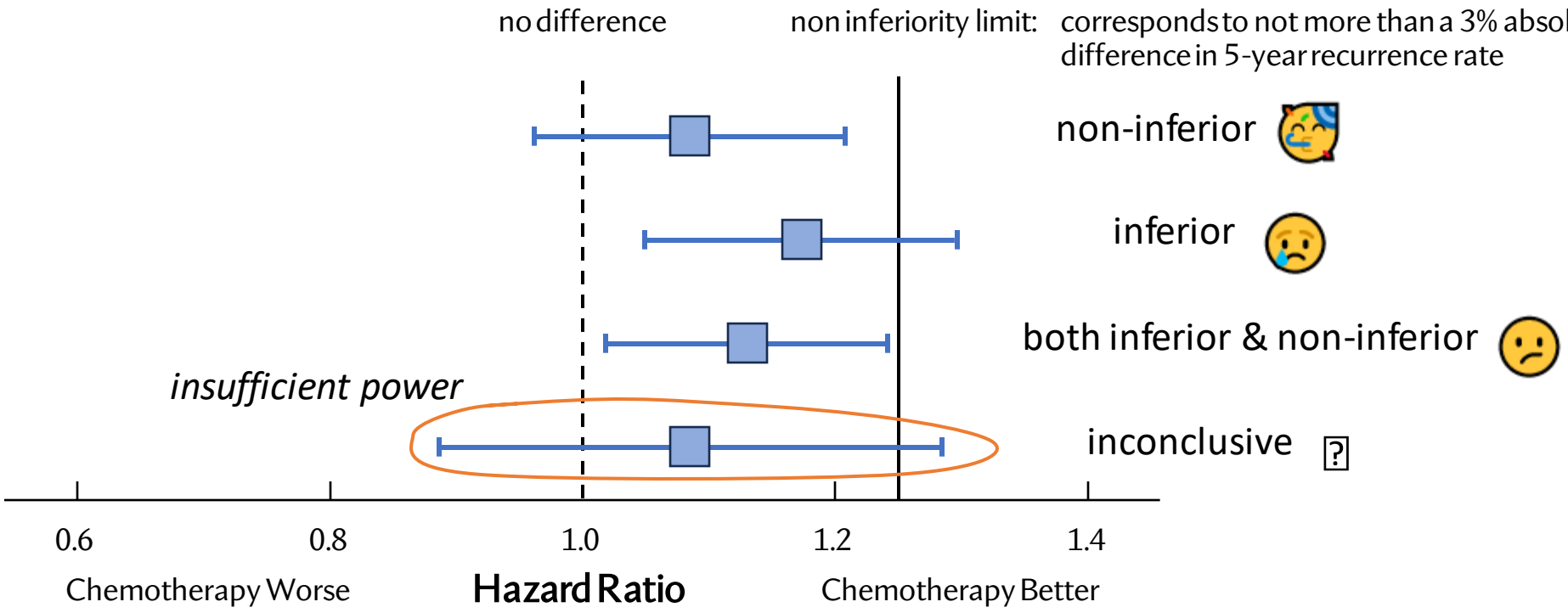
- The OPTIMA analysis plan follows updated guidelines for non-inferiority trials to ensure the results are robust
- Second cancers are no longer considered to be recurrence events
  - Second cancers are common but very few are related to chemotherapy use
  - This has the effect of masking any true difference between trial arms
  - Technically, the recurrence measure has been changed to “Invasive Breast Cancer Free Survival (IBCFS)”
- The trial will now be analysed per protocol rather than intention to treat
  - Patients who reject their treatment allocation so cross-over will not be included
  - We will still perform an ITT analysis on all patients but this will now be a secondary analysis
- *Both second cancers and cross-over affected TAILORx and RxPONDER; neither are currently a problem for OPTIMA but may become so with time*

Low Prosigna Score analysis group

- The primary OPTIMA analysis plan includes all eligible patients irrespective of Prosigna Score
  - Approximately 32% of trial participants have Prosigna Scores >60
  - These patients are all treated with chemotherapy
  - This analysis is important for Health Economics
- The key secondary endpoint is non-inferiority in the low Prosigna Score group
  - To do this analysis we need to test UK patients/ tumours in the control-arm
  - We are currently exploring funding for this and hope to complete testing in time for the primary analysis

The objective of the OPTIMA analysis

is to deliver a robust, clear and unambiguous result.

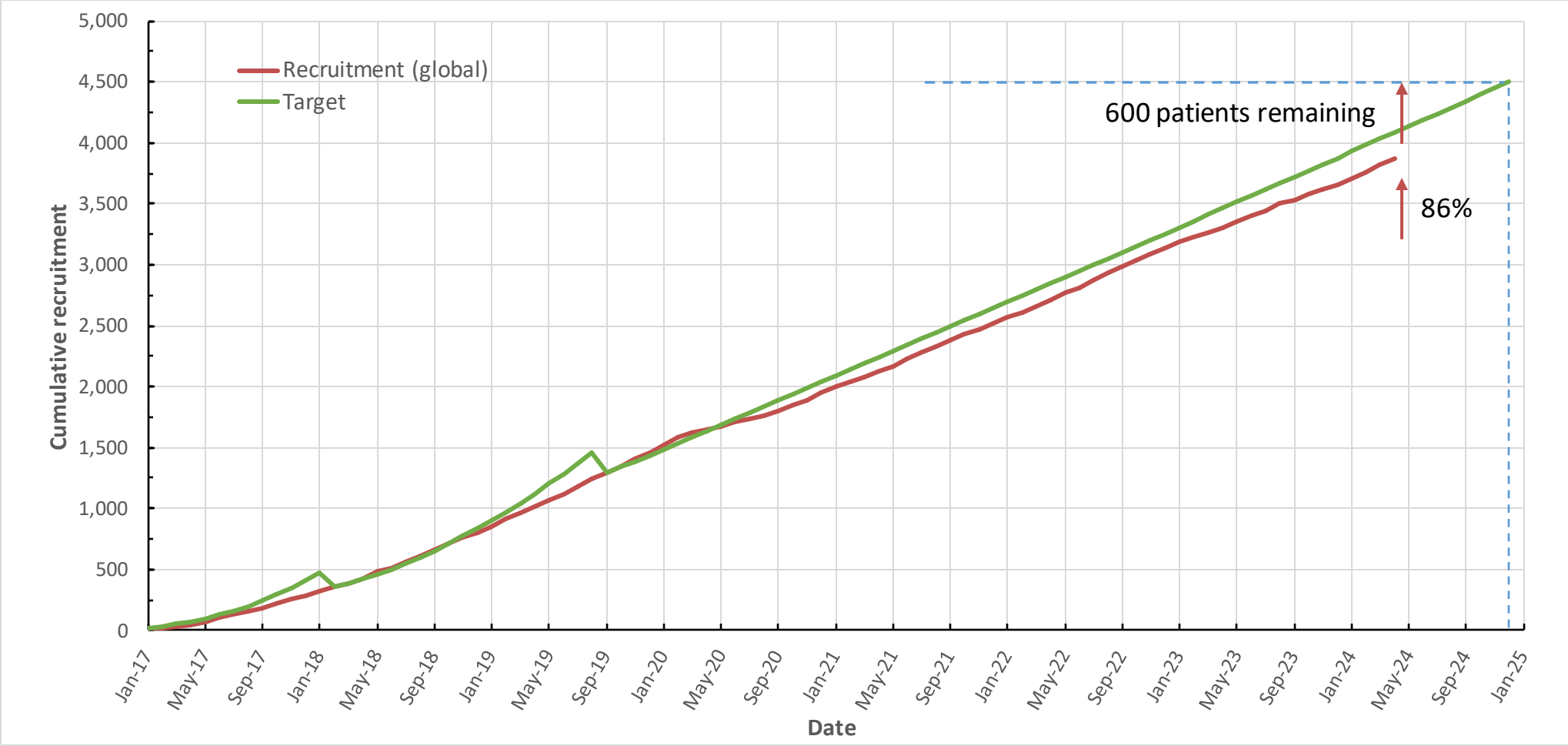


Avoiding an inconclusive outcome

Three steps to minimise the risk of an inconclusive outcome

1. Recruit sufficient patients
2. Minimise complete withdrawals
3. Minimise missing data

Recruitment



OPTIMA patient characteristics

Median age = 56 (range 40-83)

data at 1 Nov 2023

Menopausal status

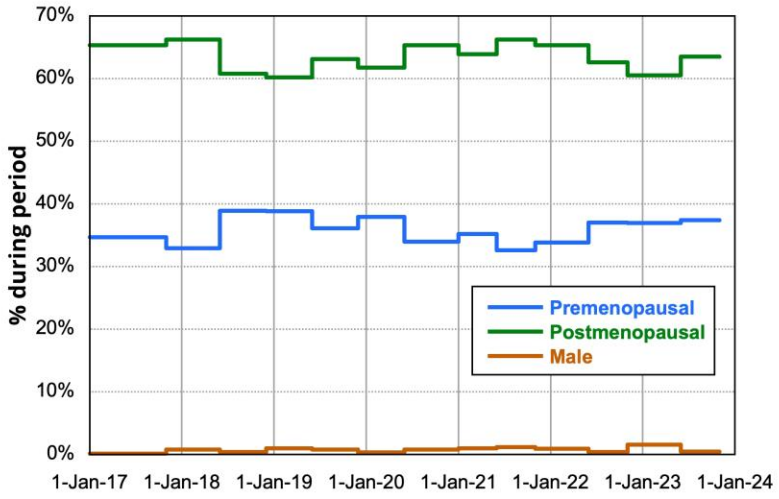
- premenopausal 36%
- postmenopausal 63%
- male 0.7%

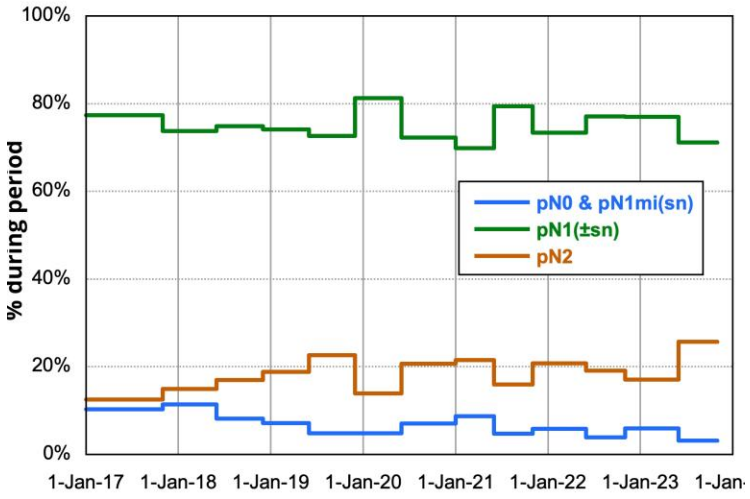
Lymph node status

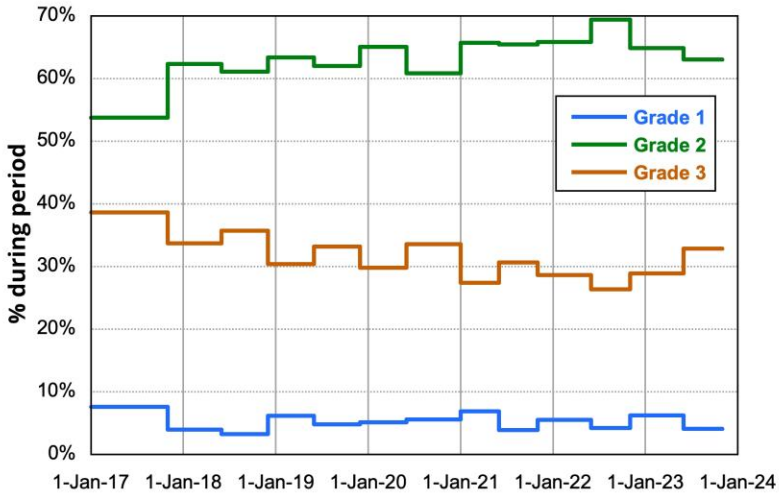
- N0/ N1mi 7%
- N1 (±SN) 75%
- N2 18%

Tumour grade

- Grade 1 5%
- Grade 2 64%
- Grade 3 31%







time trends plots - % recruitment during ~6m time intervals

OPTIMA patient treatment (intent)

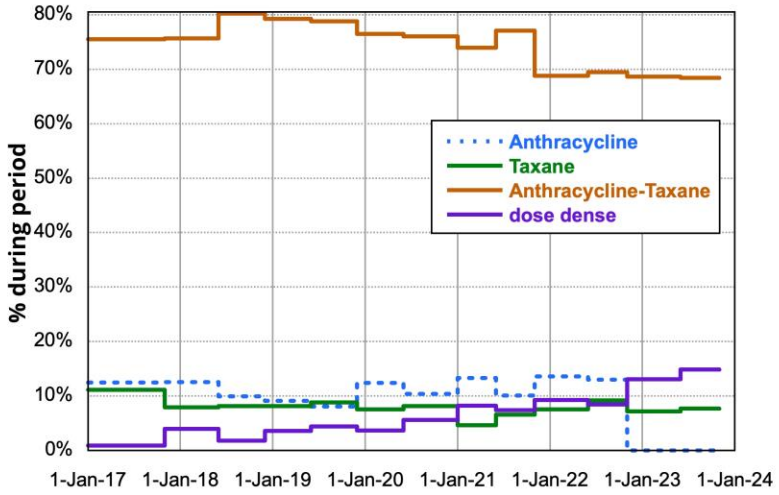
data at 1 Nov 2023

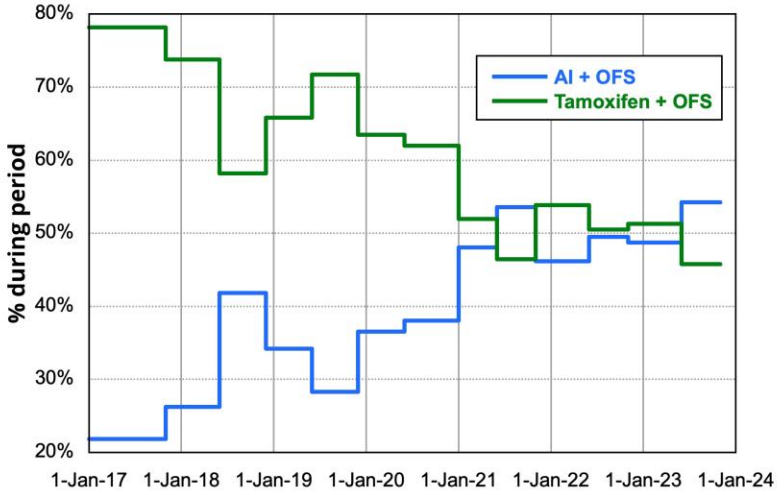
Chemotherapy

- anthracycline only 11%
- taxane only 8%
- anthracycline-taxane 76%
- dose-dense 5%

Premenopausal ET

- OFS + tamoxifen 59%
- OFS + AI 41%

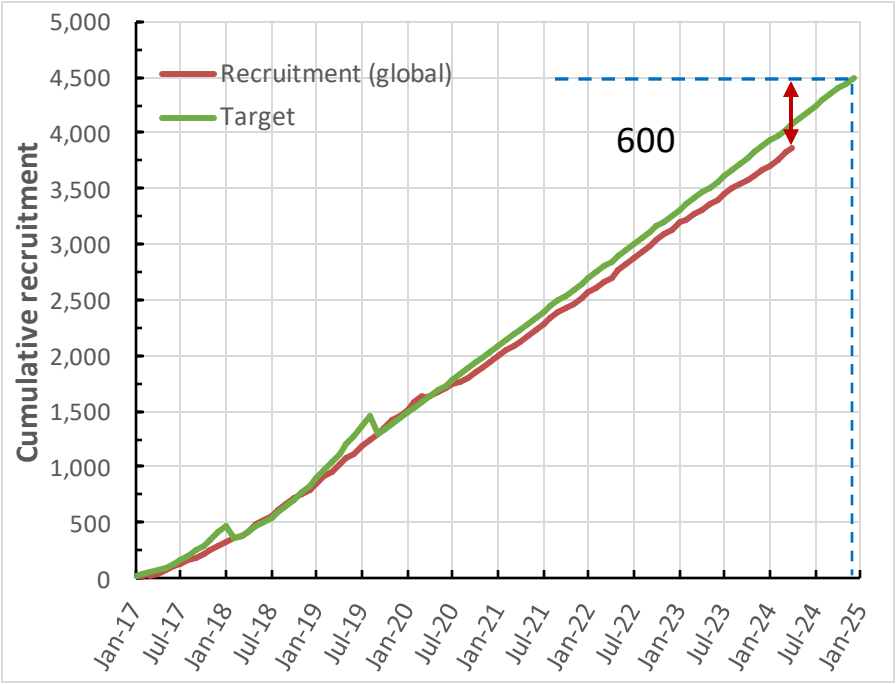




time trends plots - % recruitment during ~6m time intervals

The Recruitment Challenge

- OPTIMA needs to recruit c. 600 participants in the next 7.5 months to reach its 4500-patient target
  - This requires a sustained increase in monthly recruitment
- Failure to achieve the target creates a risk of an inconclusive final result
- Recruitment is currently ~4 months behind target
  - UK recruitment has declined during the last 18 months
  - Norwegian recruitment remains steady (18% of the 2023 total)
  - The ANZ recruitment ambition is 300 patients – they are just starting (currently 17% of the 2024 total)



- The challenge is to catch up – there will be no further extension to recruitment

New OPTIMA international partners

Country	Scope	Recruitment ambition	Lab site	Status
Thailand	single site	50 p.a.	Local	Recruitment commencement imminent.
Pakistan	single site (2 hospitals)	150 p.a.	UK	Awaiting sponsor contracts
Malaysia	single site	50 p.a.	UK	Awaiting sponsor contracts

NICE DG58

- NICE supports the use of Oncotype DX, Prosigna and EndoPredict for postmenopausal women (and men) with 1-3 involved lymph nodes.
- NICE has concluded that Oncotype DX can predict chemotherapy benefit.
  - i.e. Oncotype can identify tumours that are insensitive to chemotherapy
- Their decision is based on a review of the evidence from the RxPONDER trial and the SWOG 8814 Oncotype re-analysis study

- NICE has also concluded that Prosigna and EndoPredict can identify people with a sufficiently low risk to enable them to avoid chemotherapy
  - Fewer people will avoid chemotherapy using Prosigna and EndoPredict than Oncotype

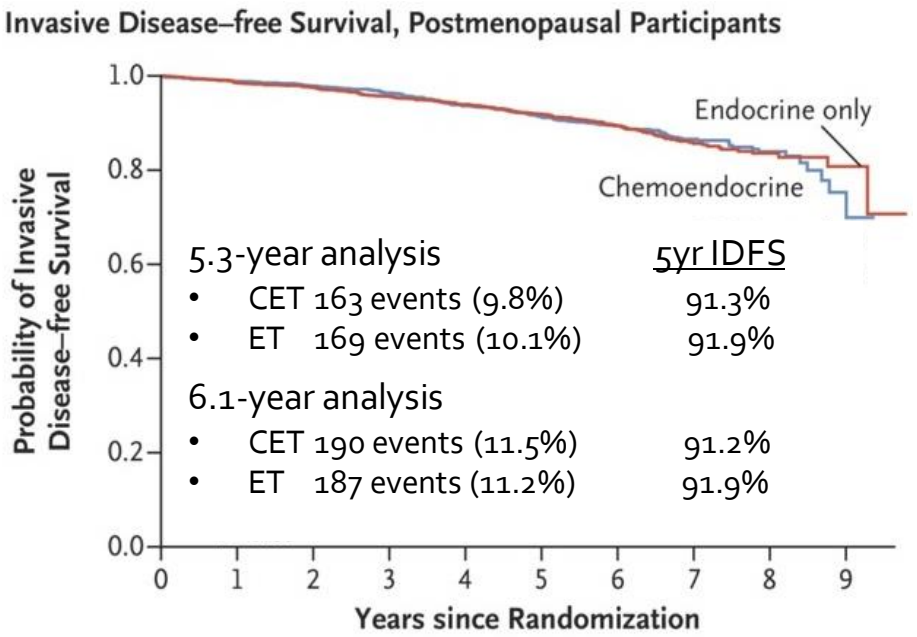
nice.org.uk/guidance/dg58

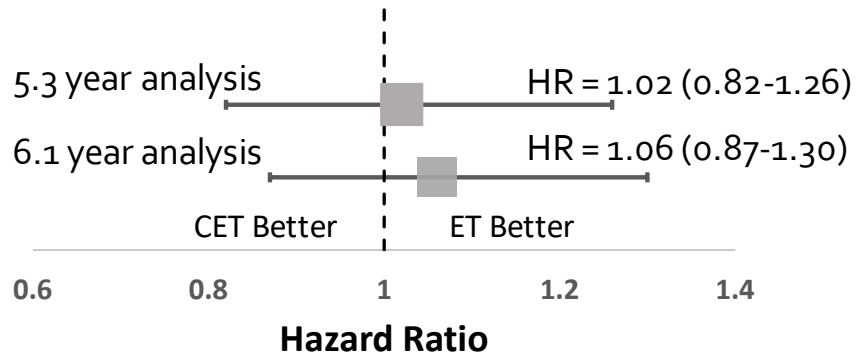
The RxPONDER postmenopausal result is uncertain

No difference reported between endocrine therapy only (ET) and chemo-endocrine therapy (CET).

It looks very convincing, but the devil is in the detail ...

1. RxPONDER was analysed for superiority not non-inferiority.
   - Lack of superiority does not prove non-inferiority
2. The 1° analysis was performed using IDFS which created a spurious impression of statistical certainty.
   - IDFS is an extremely broad measure of recurrence
   - RxPONDER recruited low risk patients - 66% 1N+/ 9% with 3N+/ unknown number of pN1mi; 26% G1 tumours
   - The consequence: 53% of IDFS events were unrelated to breast cancer (2nd cancer & death without cancer recurrence)
   - frequency not influenced by chemotherapy (a prior from EBCTCG)
3. 11.4% of patients crossed between trial arms (4.7% in ET arm & 18.1% in CET arm) – this dilutes any difference between trial arms
   - per-protocol analysis similar to ITT analysis – only performed for IDFS

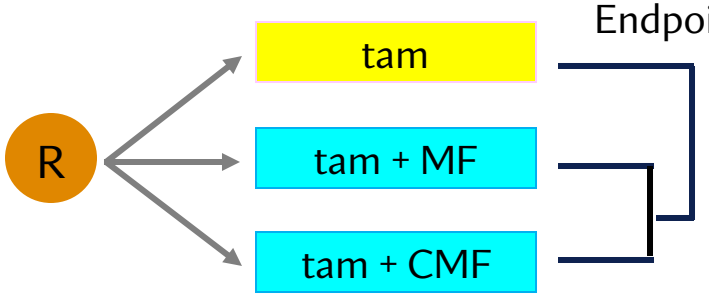




The NSABP B-20 & SWOG 8814 Oncotype DX re-analyses

NSABP B-20

Node neg, ER pos

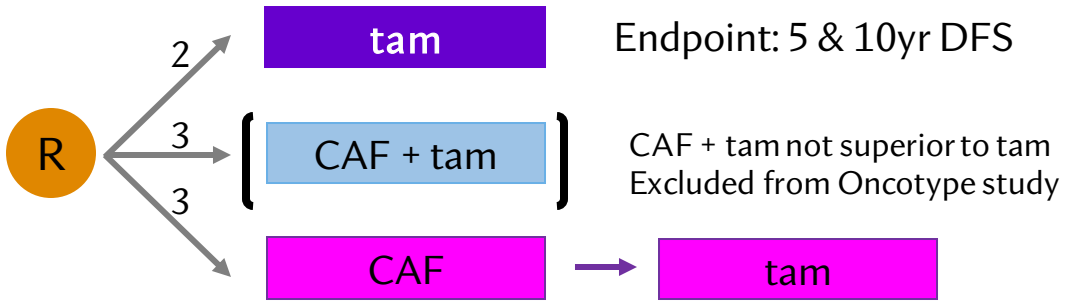


CMF & MF not different. Combined in Oncotype study

28% of all 2299 patients included; 45% aged < 50

SWOG 8814

Postmenopausal, Node pos, HR pos



40% of 927 eligible patients included; 227 pN1, 140 pN2

Disproportionate chemo benefit for patients with high RS in both studies; supports predictive hypothesis

- B-20 limitations
  - re-analysed (2018) to remove HER2 +ve patients (13%); result still significant but weaker
  - B20 tam patients formed the main population used for Oncotype DX derivation – overfitting likely
- 8814 limitations
  - 11% tumours HER2+ve; likely most had high RS. No analysis adjusting for HER2 status available.
  - small study, not always possible to separate pN1 & pN2 analyses
  - not all analyses support predictive hypotheses

Paik, J Clin Oncol 2006 24:3726
Geyer, npj Breast Cancer 2018; 4:37
Albain, Lancet Oncol 2010; 11:55

The Oxford Overview shows modest absolute & the same relative chemotherapy benefit for all patients

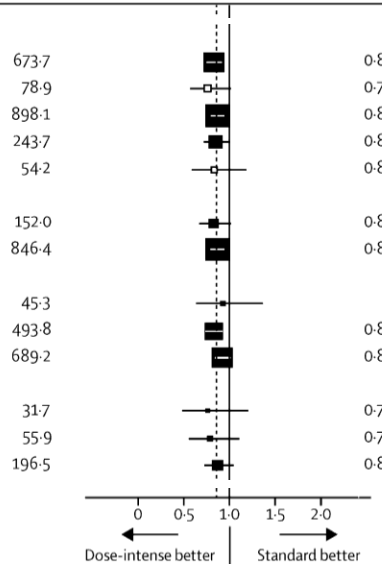
Key findings:

1. Chemotherapy reduces recurrence & mortality risk for patients with ER-positive EBC
2. The chemotherapy effect on recurrence is time-limited
   - 80% in the first 5 years
   - no effect after 7-8 years
3. Outcome is independent of all identified tumour pathology features

EBCTCG findings **do not** rule out the possibility that MPAs predict chemotherapy benefit but **do** demand a high standard of supporting evidence.

Chemotherapy effect on recurrence for ER, HER2, grade & Ki67 subgroups - 9418 events in trials of dose-intense vs standard chemo

	Events/Women		Dose-intense events		Ratio of annual event rates	Rate ratio and CI
	Allocated Dose-intense	Allocated Standard	Logrank O–E	Variance of O–E	Dose-intense : standard	
(F) ER and PR status (χ^2_1=0·1; 2p>0·1; NS)						
ER negative, PR any	1394/4630 (30·1%)	1618/4695 (34·5%)	−125·7	673·7		0·83 (0·75–0·92)
ER?, PR any	163/659 (24·7%)	201/669 (30·0%)	−21·6	78·9		0·76 (0·57–1·02)
ER positive, PR positive	1786/9297 (19·2%)	1985/9267 (21·4%)	−127·3	898·1		0·87 (0·80–0·95)
ER positive, PR negative	490/1916 (25·6%)	563/1944 (29·0%)	−40·5	243·7		0·85 (0·72–1·00)
ER positive, PR?	107/557 (19·2%)	126/563 (22·4%)	−9·9	54·2		0·83 (0·59–1·18)
(G) HER2 status (χ^2_1=0·3; 2p>0·1; NS)						
HER2 positive	358/1503 (23·8%)	395/1491 (26·5%)	−29·1	152·0		0·83 (0·67–1·02)
HER2 negative	1728/7811 (22·1%)	1971/7868 (25·1%)	−124·6	846·4		0·86 (0·79–0·94)
(H) Tumour grade (trend χ^2_1=0·2; 2p>0·1: NS)						
Well differentiated	95/896 (10·6%)	97/848 (11·4%)	−3·3	45·3		
Moderately differentiated	970/5190 (18·7%)	1114/5188 (21·5%)	−93·2	493·8		0·83 (0·74–0·93)
Poorly differentiated	1395/5317 (26·2%)	1586/5401 (29·4%)	−96·6	689·2		0·87 (0·79–0·96)
(I) Ki67 (trend χ^2_1=0·7; 2p> 0.1: NS)						
Ki67 <10%	74/564 (13·1%)	86/518 (16·6%)	−8·6	31·7		0·76 (0·48–1·20)
Ki67 ≥10% to <20%	121/803 (15·1%)	150/826 (18·2%)	−13·5	55·9		0·79 (0·56–1·11)
Ki67 ≥20%	413/2084 (19·8%)	491/2168 (22·6%)	−27·4	196·5		0·87 (0·72–1·05)



similar findings from analysis of older trials comparing chemotherapy with no chemotherapy

from EBCCTG 2012, The Lancet 379:432
EBCTCG 2019, The Lancet 393:1140
EBCTCG 2023, The Lancet 401:1277

There is no consensus between guidelines

- NICE considers that both RxPONDER and the SWOG 8814 Oncotype re-analysis studies to be uncertain.
- They reached their conclusion on prediction because both studies say the same thing!
- NICE accepts the importance of OPTIMA and encourages encourages clinicians to "continue to promote enrolment"

- The Scottish Health Technology Group (SHTG) reviewed the same evidence as NICE
- Their October 2023 recommendation is that tests should not be used for patients with involved lymph nodes

- MSAC (Australia) considers most evidence for MPA use to be inadequate/biased including all 3 published RCTs and has rejected Oncotype, MammaPrint & Prosigna use.

nice.org.uk/guidance/dg58
shtg.scot/our-advice/
msac.gov.au/internet/msac/publishing.nsf

It's not just about postmenopausal women with 1-3 involved nodes ...

- **OPTIMA will be the first trial to provide unbiased premenopausal data**
  - Premenopausal patients make up 36% of the OPTIMA population
- **OPTIMA is the only trial that recruits patients with >3 involved nodes**
  - If patients with 1-3 N+ and low test-score tumours can safely avoid chemotherapy, then this should also apply to those with higher nodal involvement
- **OPTIMA is the only trial that includes patients treated with CDK4/6 inhibitors**
  - Abemaciclib availability for OPTIMA participants began rolling out in July 2022
  - Approximately 35% of Prosigna low-score patients should be eligible under the UK licence
- The OPTIMA IDMC encourages increased recruitment of these patient subgroups*
- It is essential sites that adopt N+ testing continue to recruit these patients
  - Several sites are already doing this

*Meeting on 30 November 2023

Multi-parameter assay use for pre-menopausal women

- All existing MPA trials (MINDACT, TAILORx & RxPONDER) show pre-menopausal women benefit from chemotherapy.
- Age-related differences in breast cancer chemotherapy sensitivity may exist
  - The TAILORx subgroup analysis is suggestive but not definitive
  - Young age is an independent risk factor for recurrence.
- Four historic trials of chemotherapy vs GnRH agonists included in a patient-level meta-analysis show neither treatment to be superior*.
  - Implies that observed chemotherapy effect in MPA trials to date is at least partly the result of POI.
- The demonstrated chemotherapy benefit can only be understood by controlling for chemotherapy-induced POI.

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

Multi-parameter assay use for patients with 4-9 involved nodes

- It is widely considered that tests are not indicated for patients with high-level node involvement.
  - This arises from MPA marketing decisions and is not evidence-based
  - If patients with 1-3 N+ and low test-score tumours can safely avoid chemotherapy, then there is no logical reason why this should also apply to those with higher nodal involvement
- 38% of patients in the SWOG 8814 Oncotype re-analysis study had 4-9 involved nodes
  - The result depends on the inclusion of these patients
- OPTIMA is the only study to include this patient group

Withdrawals

Randomised (100%)

- found to be ineligible post randomisation – 0.6%
- complete withdrawal before treatment allocation/ start – 1.8%
- rejected treatment allocation (cross-over) – 3.0%

ITT analysis group with follow-up data – 97.7%

per-protocol analysis group - 94.7%

Patients who withdraw from the trial prior to starting treatment cannot generate any outcome data. This weakens the trial.

If their reason for withdrawal is because of treatment preference, it is better that they remain in the trial and are treated according to their preference.

Data at 1 November 2023

Missing data

- Patients with missing critical data cannot contribute to the trial analysis
- The effect is to reduce total recruitment into the trial

Form group	Form return
Baseline forms	95.8%
Chemotherapy forms	86.6%
Endocrine therapy forms	88.7%
Annual follow-up forms	89.9%

- Please keep up the good work 😬

OPTIMA-Young

- We expect that OPTIMA will show that outcomes are the same for premenopausal and postmenopausal patients
  - This will provide important supporting evidence for test directed chemotherapy use in this population
  - OPTIMA is not large enough to allow separate non-inferiority analysis in these two groups
- OPTIMA-Young is a proposed separate international trial run by BIG, which will recruit only premenopausal patients
  - Premenopausal women who join OPTIMA will be included in the analysis
  - This will allow a formal non-inferiority analysis for this patient group, intended for 2030
- OPTIMA-Young should commence recruitment in mid 2025 - if funded
  - The trial will be available to current OPTIMA sites from 2025

In conclusion …

- OPTIMA is now on the home straight
- We should all be very proud of that
- But we can't afford to relax

Please continue to support OPTIMA. We need your continuing efforts to get us over the line.

Thank you for joining us today