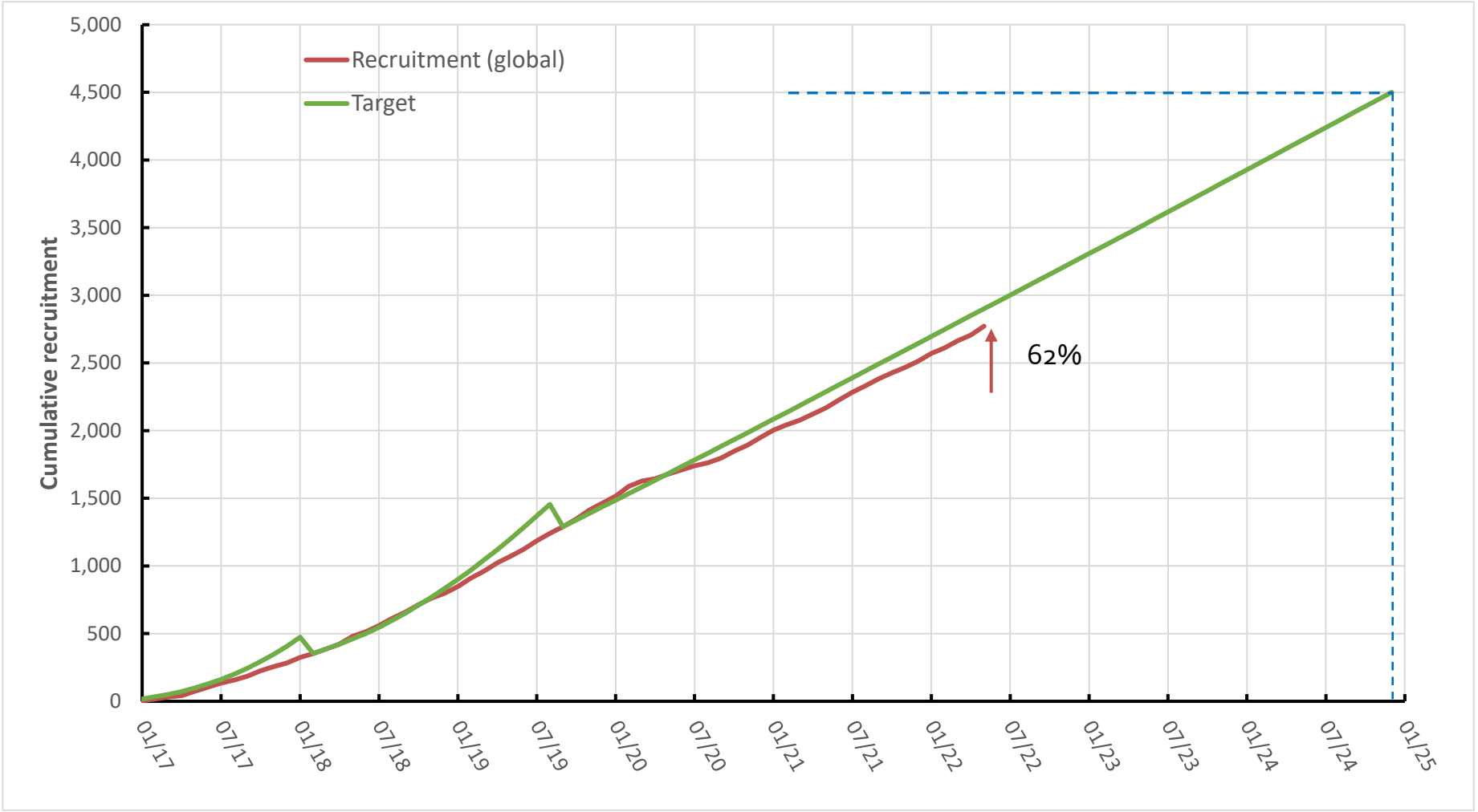
OPTIMA FUTURE - INTERNATIONAL EXPANSION AND MORE

The not-so short history of OPTIMA

optima
personalised treatment of breast cancer

"Chemo vs not" (EBCC6, Berlin)	2008	Chemospare outline funding application to NIHR HTA
Chemospare (LHD)	2009	Chemospare full application rejected
	2010	
OPTIMA Trial Office opened	2011	OPTIMA outline grant application to NIHR HTA
1st prelim pt recruited (12/10/12)	2012	OPTIMA prelim grant full application (HTA)
	2013	OPTIMA prelim intent to fund letter
prelim closes [N=412] (26/08/14)	2014	OPTIMA main grant application to HTA
	2015	OPTIMA main trial grant approved
Main OPTIMA trial launch	2016	
Main trial opens! (16/01/17)	2017	Excess Treatment Costs & contractual issues resolved
	2018	HTA allows international expansion
OPTIMA Norway opens (10/2018)	2019	HTA agrees end 2024 as realistic completion date
	2020	OPTIMA allowed to remain open during COVID pandemic
main trial recruitment reaches 50% 111 UK & 9 Norway sites	2021	Veracyte acquires Prosigna test; commence discussions about company support for international expansion
	2022	
	2023	
	2024	

Recruitment



OPTIMA is making good progress and is following its agreed recruitment trajectory

OPTIMA patient characteristics

Median age = 56 (range 40-83)

Menopausal status

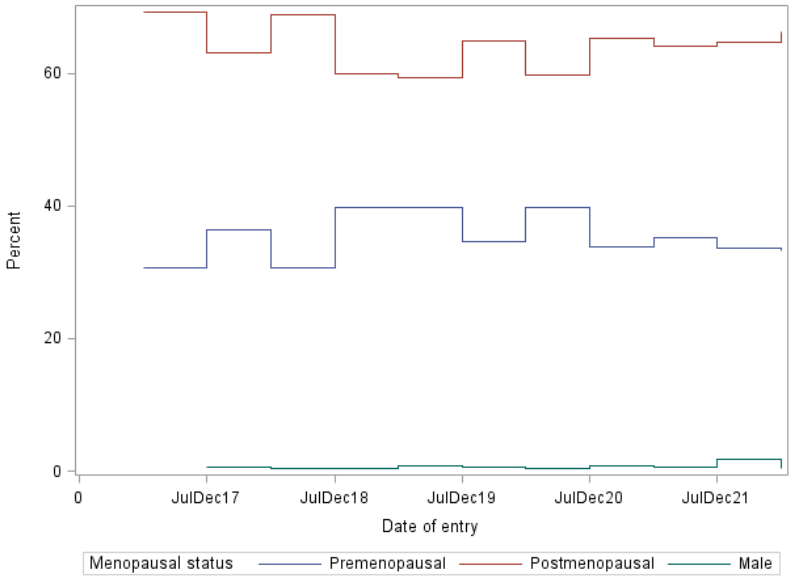
- premenopausal 36%
- postmenopausal 63%
- male 1%

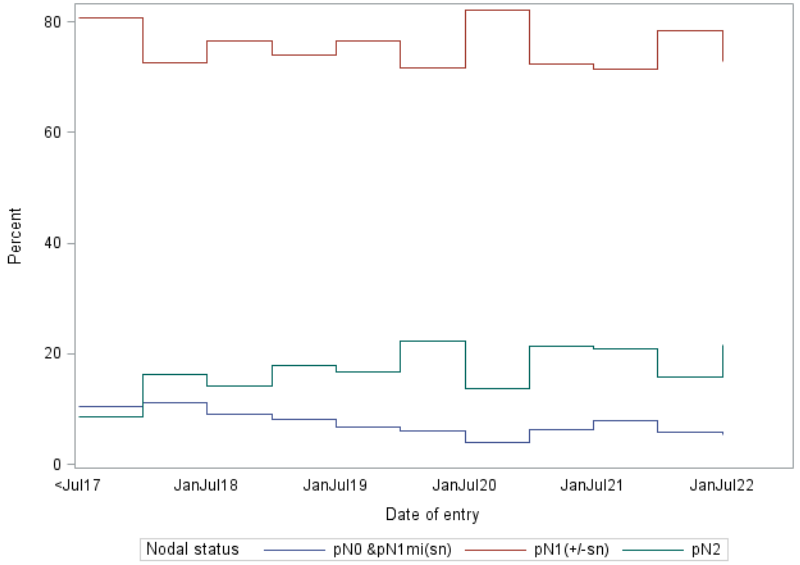
Lymph node status

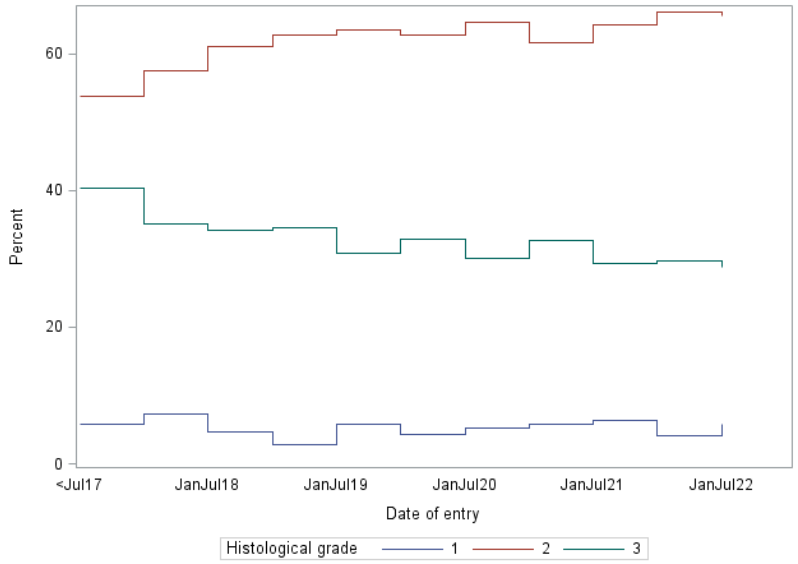
- No/ N1mi 7%
- N1 (±SN) 75%
- N2 18%

Tumour grade

- Grade 1 5%
- Grade 2 63%
- Grade 3 32%

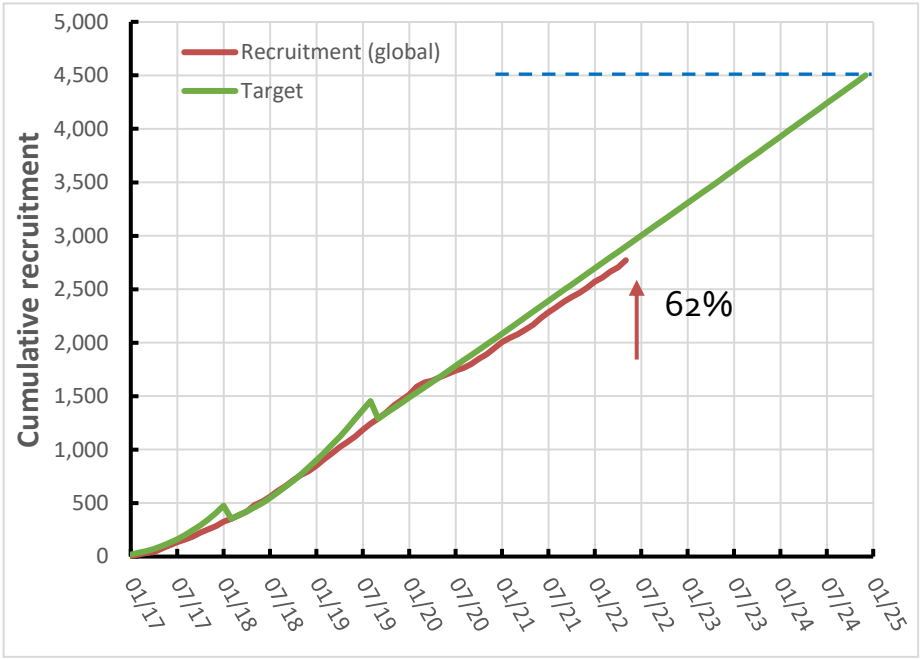






The Recruitment Challenge

- OPTIMA needs to recruit c. 1700 participants between now the end of 2024 to reach its 4500-patient target
  - This equates to 57 patients monthly
- Failure to achieve the target will reduce the ability of the trial to deliver a credible result
- Recruitment is currently ~11 weeks behind target – the effects of the pandemic
  - UK recruitment has yet to recover to pre-pandemic levels -average 41 pcm over last 6 months
  - Norwegian recruitment has averaged 10 pcm over the same period
- The challenge is to close the gap whilst coping with an uncertain future …



RxPONDER continues to cause problems …

The RxPONDER postmenopausal data look convincing but a high level of statistical uncertainty remains

Were the results to be widely adopted and later prove incorrect, a credible estimate is that breast cancer mortality would increase by 3% in the affected population.

- The time horizon for the chemotherapy effect on breast cancer mortality for ER+ve disease is up to 10 years.
- It would likely take at least as long for this to be discovered.

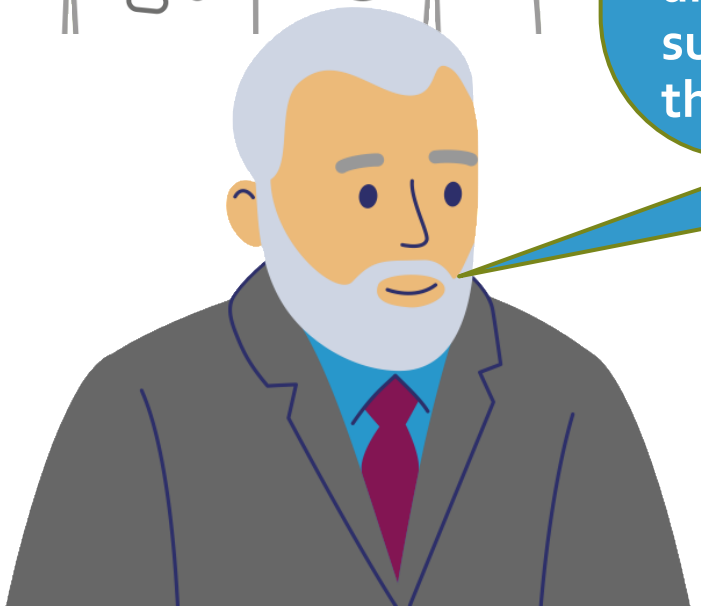
It's not yet a done deal …

The Oxford Overview has consistently failed to demonstrate any tumour characteristic that influences outcome in response to chemotherapy including grade and more recently Ki67

It is understandable that everybody wants to believe the RxPONDER postmenopausal result. It is however very important we get this right.

If we aspire to the practice of evidence-based medicine, we should generate that evidence and not take the risk of harming our patients by premature adoption of results supported by inadequate evidence.

The promotion of the result by the trialists and by an industry which is currently subject to very limited regulation* is not in the long-term interests of our patients.



optima
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images courtesy of HealthCreatives

*Commercialisation (2022) in UK is on the basis of CE mark only; there is no formal approval process unlike for higher risk medical devices and pharmaceuticals. The UK government has a stated an intention to strengthen regulations under powers provided by the Medicines and Medical Devices Act 2021. MHRA will continue as regulator; new authorisation rules will apply from 1 Jul 2023 but details are not yet available.

EU regulation 2017/746 on in vitro diagnostics, which applies in NI but not elsewhere in the UK, sets out a comprehensive approvals framework and tightens standards including a prohibition on false or misleading claims made by manufacturers.

U.S. regulation by the FDA is limited in practice; it remains to be seen whether the Theranos fraud will lead to change.

The case for international expansion

International expansion will both add value to OPTIMA and help solve the recruitment challenge

- The results of a multinational trial will always carry more weight with the wider breast cancer community than a single nation study of equal quality.
- Recruitment from an ethnically diverse population increases the likelihood of acceptance of the findings by the wider breast cancer community
  - current ethnicity is 95% Caucasian, which is typical for UK cancer clinical trials.
- International acceptance of the results helps ensure that the findings of OPTIMA will benefit breast cancer patients globally.
- International expansion increases the likelihood of successful completion of recruitment and may help deliver an earlier trial result.
  - international expansion mitigates against future UK risks to successful trial completion

The obstacles (and their solutions)…

1. **Funding**

   Most countries are unable to join non-commercially sponsored clinical trials

   Veracyte acquired the Prosigna test in 2020 and has now agreed to support international expansion, particularly through provision of test kits

2. **Trial documents**

   OPTIMA was designed as a UK-trial. Extensive local adaptions are needed for some trial documents, particularly the PIS/ CF

3. **Governance and contracts**

   Countries with multiple sites need a coordinating centre as WCTU lacks QA capacity

   Contracting can be very slow!

It all needs a lot of patience and perseverance!

New OPTIMA international partners

Country	Scope	Recruitment ambition	Lab site	Status
Malaysia	1 site	50 p.a.	UK	All approvals in place. Awaiting contracts
Australia/ NZ	50 sites	200 p.a./ 600 total	Local	Local setup in progress
Hong Kong	up to 8 sites	50 p.a.	Local	Operational issues now mostly agreed
Taiwan	2 sites	60 p.a.	UK	Discussion of operational issues ongoing
Brazil	1 site	TBA	UK	At relatively early stage
EU (various)				Very limited progress
USA/ Canada				No realistic prospects

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
- This has been agreed as realistic by NIHR but requires their formal agreement to extend the trial
  - NIHR has now invited an application for a 27-month extension
  - The timescale for a decision is not known at present
  - The current official end to recruitment is 31 Dec 2022; this will be adjusted before it is reached!

Protocol version 9

- The current protocol needs updating – v9 will be submitted for approval in August-September
- Addition of adjuvant abemaciclib to the protocol
  - the current protocol allows its use by default but contains no reference to it
  - it needs to added as a stratification factor to avoid confounding risk & for analysis
- Incorporation of change to statistical analysis plan
  - this can only be done once NIHR has approved the extension
  - if NIHR approval is delayed then this will require a separate amendment
- Minor changes - adjustments to inclusion & exclusion criteria for clarity

CRF changes

- OPTIMA was designed as a pragmatic trial with an intent to minimise data collection
  - The CRFs have gradually become more complex as the trial has evolved
- Some of the questions are difficult to answer and are frequently left blank
  - example – start dates for con meds, details of bisphosphonate prescriptions
- We are currently reviewing all CRFs to remove data items that we don't really need
- It will not be possible to remove all complexity, but we will do our best
- We hope to have the new CRFs ready for early Autumn
  - The changes are not tied to protocol v9 (eligibility form excepted)

A reminder why OPTIMA matters

- **It is the only trial that can answer the "premenopausal question"**
  - Premenopausal patients make up 36% of the OPTIMA population
  - It is essential to recruit these patients rather than make assumptions based on RxPONDER
- **It 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
- **It is the only trial that will include patients treated with CDK4/6 inhibitors**
  - Abemaciclib availability for early breast cancer in the NHS is expected during 2022
  - Approximately 20% of the Prosigna low-score patients will be eligible under the UK licence
- **It will provide independent data on test use for 1-3N+ patients**
  - Conclusive proof that tumour gene expression tests predict chemotherapy sensitivity will require meta-analysis

In conclusion …

- We have made extraordinary progress despite living and working in very difficult circumstances since early 2020
- We should all be very proud of that
- There are still a few corners before we reach the home straight but its not so far now

Please continue to support OPTIMA. The sooner we complete recruitment the sooner everybody can benefit.

Thank you for joining us today