Using adaptive designs for decision making within the OPTIMA trial: Optimal personalised treatment of early breast cancer using multi-parameter tests

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On behalf of all OPTIMA Investigators.

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Health Technology Assessment

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- Commissioned call '**clinical and cost effectiveness**' of personalised care in the treatment of women with breast cancer

- **Question:** Does personalised care improve ***outcomes*** and reduce harmful treatment effects in women with breast cancer?

- **Technology:** Diagnostic tests to direct choice of therapy including IHC, tumour markers & multi-gene breast cancer assays

Advances in breast cancer

	Luminal A	Luminal B	HER2	Basal
Prognosis	Good	Moderate	Poor	Poor
Proliferation	Low	Moderate or High	High	High
Chemosensitivity	?Low /nil	?Moderate	?High	?High
Estrogen receptor	Strong	Variable	Nil	Nil
Her2 amplification	Uncommon	In subset	Frequent	Nil

Assay	Details of Multi-parametric assay	Material	Test Output
Oncotype DX (Genomic Health Inc)	A 21 gene qRT-PCR expression assay (using 16 cancer related and 5 normalisation genes)	FFPE	risk score
MammaPrint (Agendia)	A 70 gene microarray based expression signature.	Fresh/ frozen	risk score
Rotterdam signature (academic)	A 76 gene microarray based expression signature; not commercially available.	Fresh/ frozen	risk score
PAM50	A 50 gene expression assay using RT-PCR or the nanoString system.	FFPE	subtyping & risk score
Breast Cancer Index (bioTheranostics)	A 7 gene qRT-PCR expression assay	FFPE	risk score
Blueprint (Agendia)	A microarray based assay used in conjunction with MammaPrint	Fresh/ frozen	subtyping
Genomic Grade (Ipsogen)	A 97 gene microarray based expression signature.	Fresh/ frozen	risk score
Randox Breast Cancer Array	A 23 gene assay using bio-chip technology	Fresh/ frozen	subtyping
IHC4 (HistoRx & non-proprietary)	Quantitative immunohistochemical assay for ER, PgR, Her2, Ki67	FFPE	risk score
Mammostrat(GE Healthcare)	A 5 gene immunohistochemical assay.	FFPE	risk score
NPI plus	A 10 gene immunohistochemical assay.	FFPE	risk score

Oncotype DX® 21-Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION
Stromelysin 3
Cathepsin L2

CD68

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

Category	RS (0 -100)
Low risk	RS <18
Int risk	RS 18 - 30
High risk	RS ≥ 31

Paik et al. *N Engl J Med.* 2004;351:2817

Oncotype DX: RS as Continuous Predictor in tamoxifen treated patients

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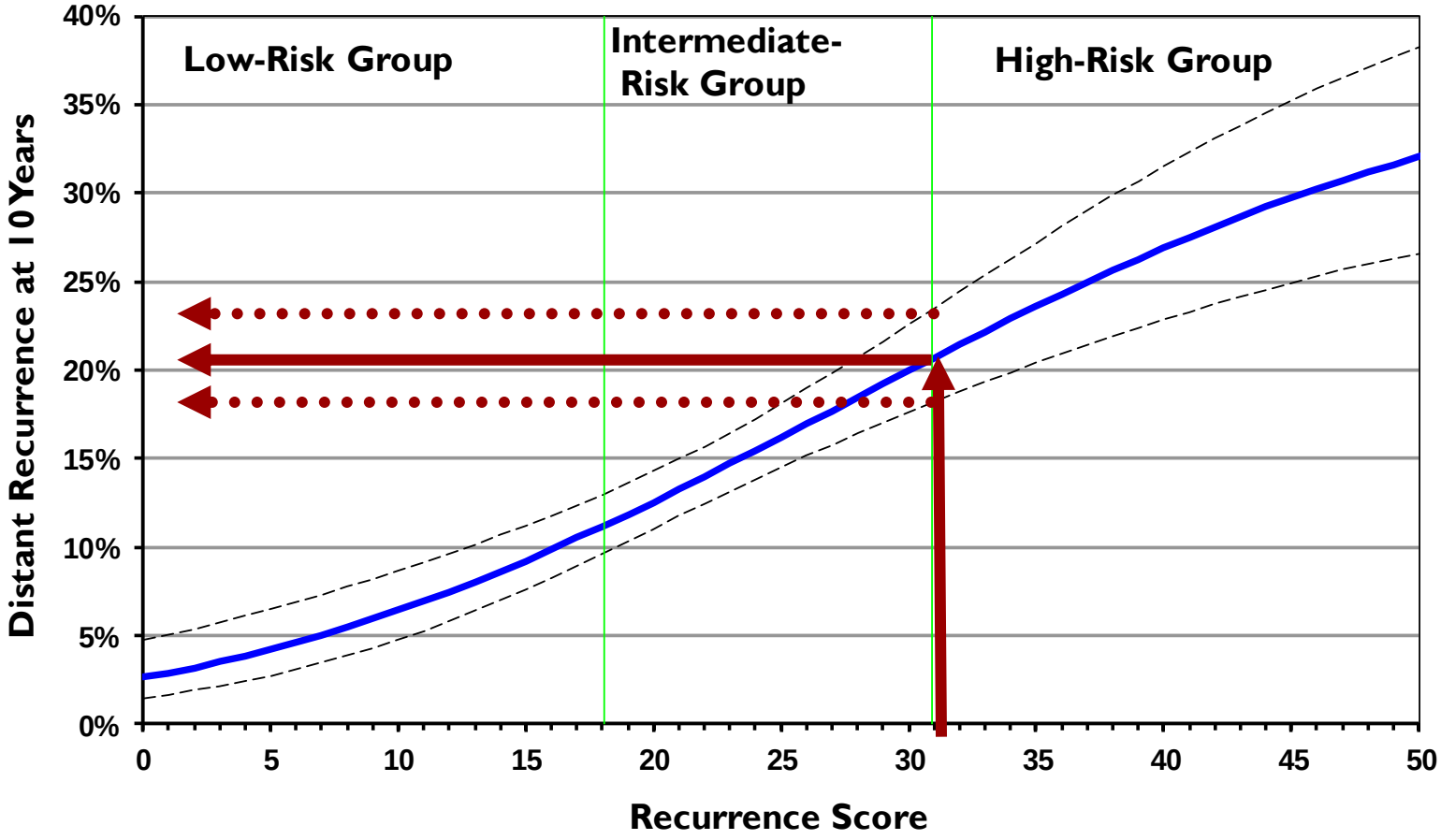

Data from NSABP B14: Paik NEJM 2004, 351:2817

Ongoing RCT's

Study-	Technology	Country	Population	Target size	Start date	Likely analysis date
TAILORx	Oncotype DX	USA Canada	ER+ HER2- N0	11,248 (cohort)	2006	2015
MINDACT	MammaPrint	EU	ER+ N0-1	6,600 (cohort)	2006	2015?
RxPONDER	Oncotype DX	USA Canada	ER+ HER2- N1	4,000 (rand)	2011	2017

On 25th September 2013 NICE recommended the use of Oncotype DX for ER+ve, HER2-ve, N0 early breast cancer patients as a 'prognostic tool'

Further evidence needed for use in N+ patients – i.e. randomise into OPTIMA

OPTIMA objectives

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1. To establish a method of selecting patients with hormone *sensitive primary bre*ast cancer who are likely to benefit or not benefit from post-operative chemotherapy.
2. To establish the cost-effectiveness of alternative test-guided treatment strategies compared to standard practise.

Things we still need to know

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- **How reliable is Oncotype DX?**
  – especially in node +ve population

- **How does Oncotype DX perform compared to other tests?**

- **Which technology is most cost-effective in UK healthcare?**

Feasibility Study (OPTIMA *prelim*)

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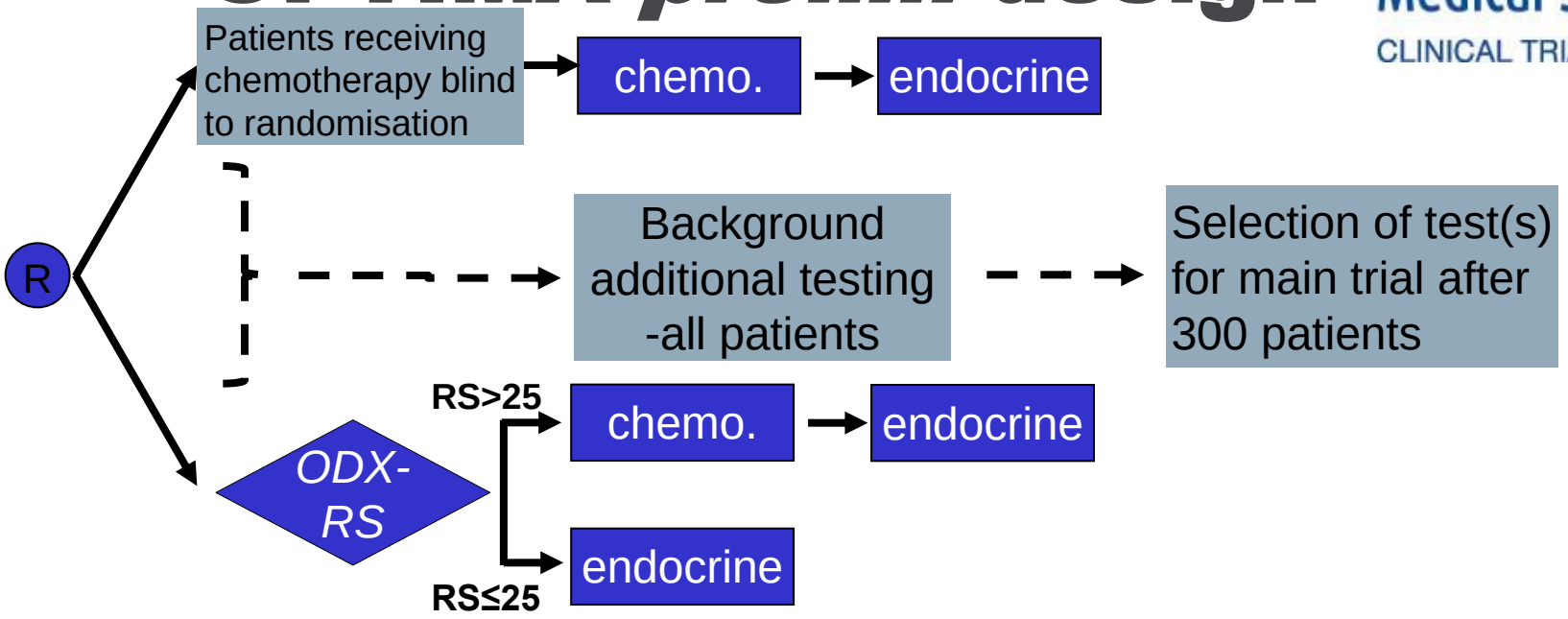
1. Evaluate the performance and health-economics of alternative multi-parameter tests to determine which technology(s) are to be evaluated in the main trial.

2. Establish the acceptability to patients and clinicians of randomisation to test-directed treatment assignment.

3. Establish efficient and timely sample collection and analysis essential to the delivery of multi-parameter tests driven treatment.

OPTIMA *prelim* design



Sample size to demonstrate feasibility and select test for main study = 300 patients to test concordance at 0.8 with lower 95% CI of 0.7

Recruitment over 24 months in 25 “representative” UK centres

Added in a 200 patients extension to allow ‘roll over’ to main study

Feasibility Success Criteria

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- Recruitment of 300 patients in not more than 2 years from the first centre opening to recruitment
- For the final 150 patients:
  1. patient acceptance rate will be at least 40%
  2. recruitment will take no longer than 6 months
  3. chemotherapy will start within 6 weeks of signing the OPTIMA consent form for no less than 85% of chemotherapy assigned patients.

Selection of technology

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- Test(s) must have analytical validity and reproducibility
- Ability to commercialise the test for use within the NHS
- Test(s) selection needs to be cost-effective informed by Health-economic modelling
- Concordance (?Biological concordance)
- Do not have 5-year outcome data within OPTIMA prelim – need to model external data

- Must be acceptable to clinicians and patients

OPTIMA design

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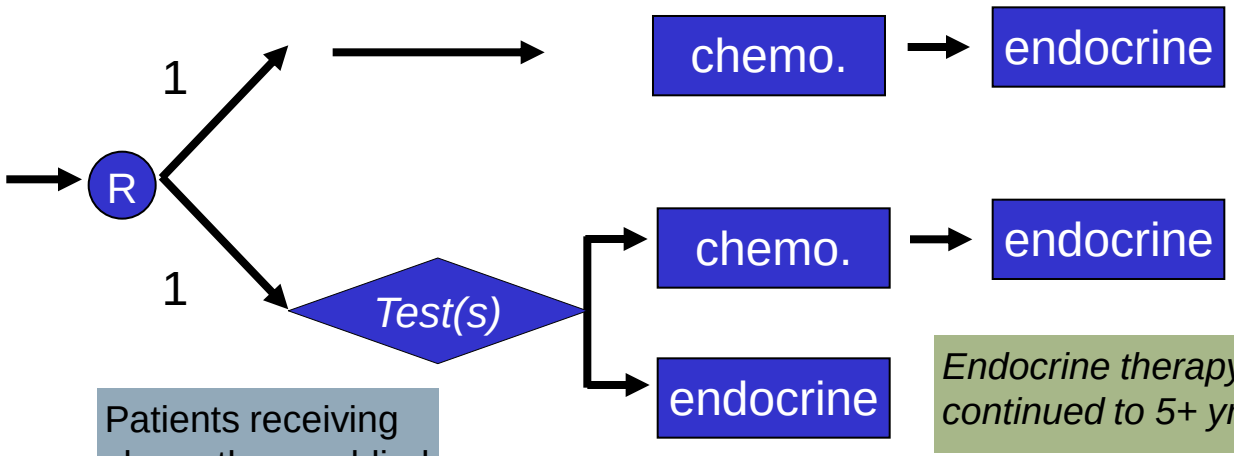
Adequate surgery
Age ≥ 40
ER +ve, HER2 –ve
N+/ N0 & T>30mm
Central confirmation of ER & HER2



Exclusion: advanced stage = ≥ 10 N+/ IM+

Patients receiving chemotherapy blind to randomisation

Endocrine therapy continued to 5+ yrs

Radiotherapy given according to local practise

Sample size to demonstrate non-inferiority (-3%) = 1860 per arm

Permitted chemotherapy: pre-specified by patient before randomization
- FEC75-100 x 6 cycles
- TC x 4 cycles
- FEC100-T
- E-CMF

Permitted endocrine therapy: postmenopausal - any AI
premenopausal - GnRH agonist (3 yrs) + tamoxifen

Summary

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- OPTIMA prelim uses an adaptive trial design
  - Most efficient use of patients and costs
- Endpoints are ‘short term’ not ‘longer-term’
- Need to evaluate:
  - Cost-effectiveness models
  - Patient acceptability/screening/pathways/decisions
  - Populations
  - Evaluate alternative tests (biological concordance)

- Statistical considerations have been challenging but methodology very interesting!

The OPTIMA trial team

Oncologists
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Helena Earl (Cambridge)
Luke Hughes-Davies (Cambridge) co-CI
Iain MacPherson (Beatson)
Andreas Makris (Mt Vernon) co-CI
Chris Poole (U Warwick)
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Health Economics
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Peter Hall (U Leeds)
Clare Hulme (U Leeds)

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