optima
personalised treatment of breast cancer

OPTIMAL PERSONALISED TREATMENT OF EARLY BREAST CANCER USING MULTI-PARAMETER ANALYSIS

A trial of a diagnostic test in ER+ve HER2-ve breast cancer

OUTLINE

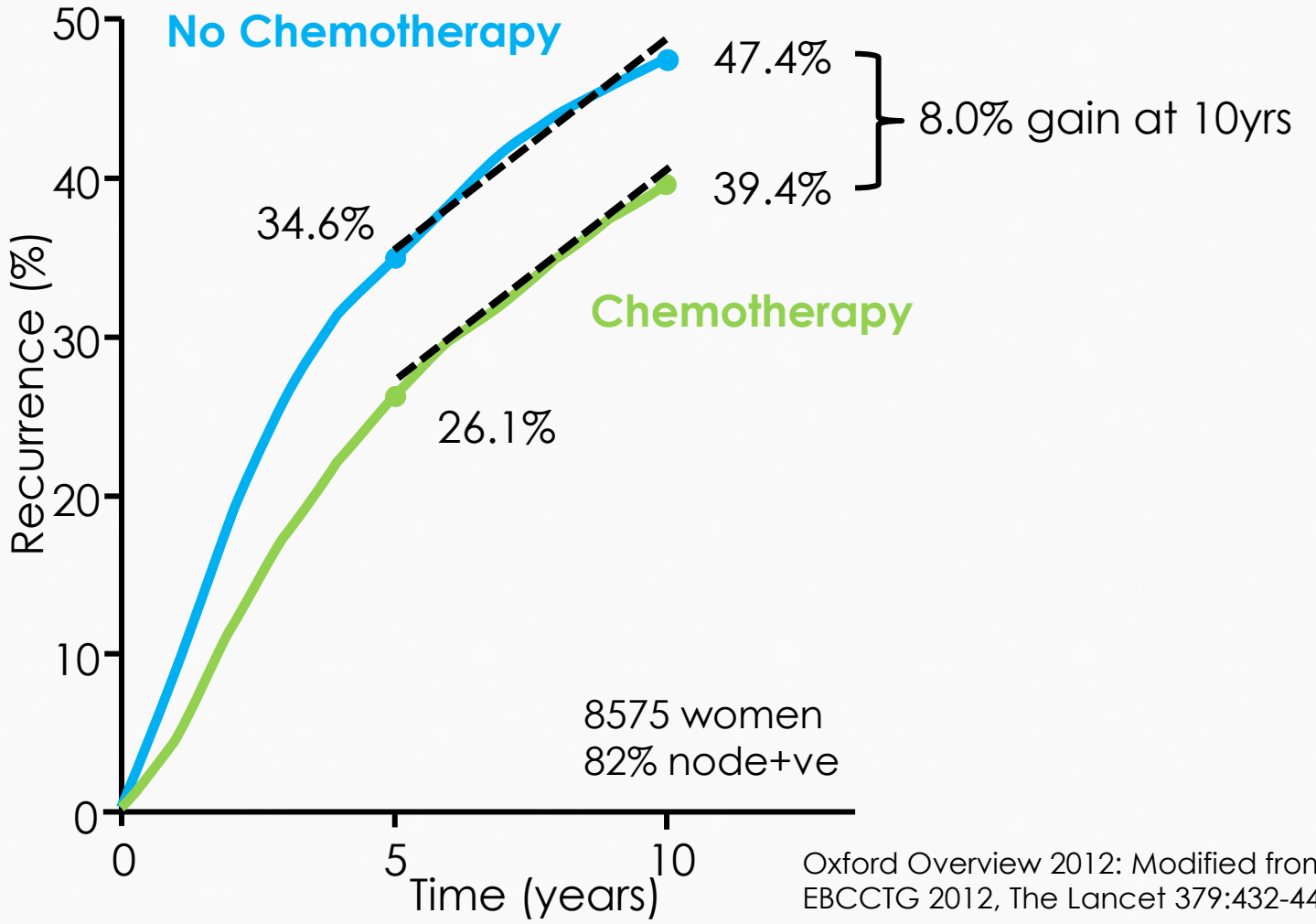
- Background to OPTIMA
- Multi-parameter assays
- Ongoing trials
- The OPTIMA trial

THE BACKGROUND QUESTION

WHO SHOULD WE TREAT WITH CHEMOTHERAPY?

BENEFIT OF ANTHRACYCLINE CHEMOTHERAPY IN EARLY BREAST CANCER

- Chemotherapy has very little if any effect on recurrence after 5years
- Chemotherapy affects BC mortality for up to 10 years
- Gains from modern chemo are expected to be greater than historic regimens but only a minority of patients will benefit

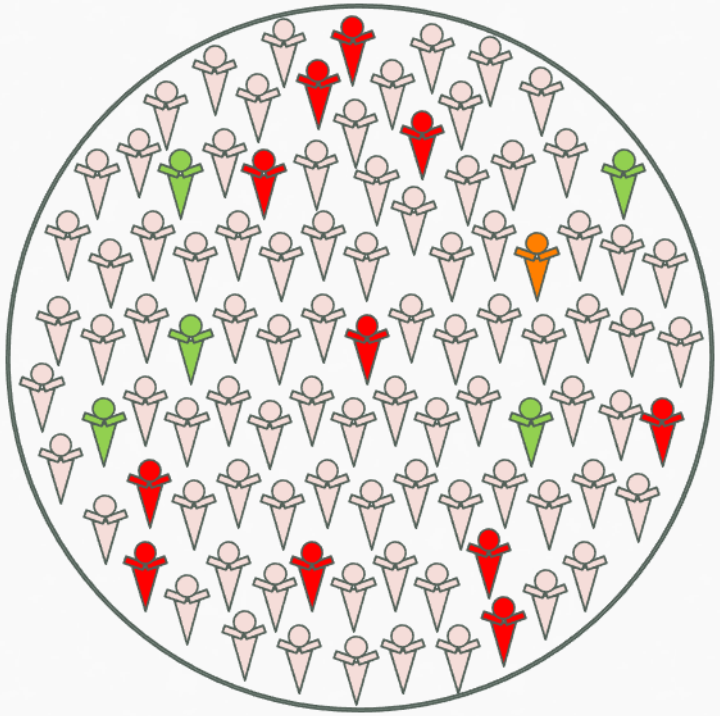


Oxford Overview 2012: Modified from EBCCTG 2012, The Lancet 379:432-444

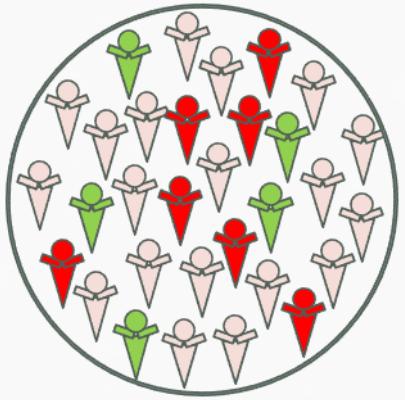
BREAST CANCER CHEMO-SENSITIVITY: THE OXFORD META-ANALYSIS

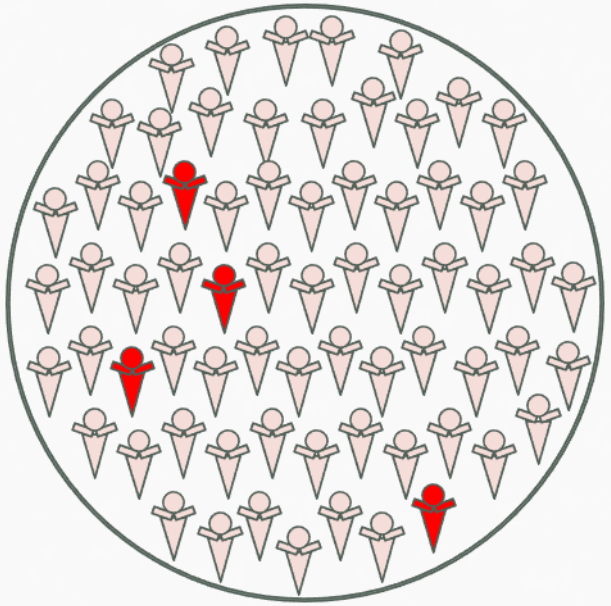
- Oxford Overview demonstrates that patients with ER-positive breast cancer benefit from adjuvant chemotherapy.
- The relative benefits for chemotherapy are the same for all patients.
  - No identified factors including ER status predict chemo-sensitivity.
  - Little information on tumour grade in the analysis.
- The overall benefit from chemotherapy is modest
  - Patients not destined to relapse cannot benefit from treatment!

CHEMOTHERAPY SENSITIVITY



Chemo-sensitive group





Chemo-insensitive group

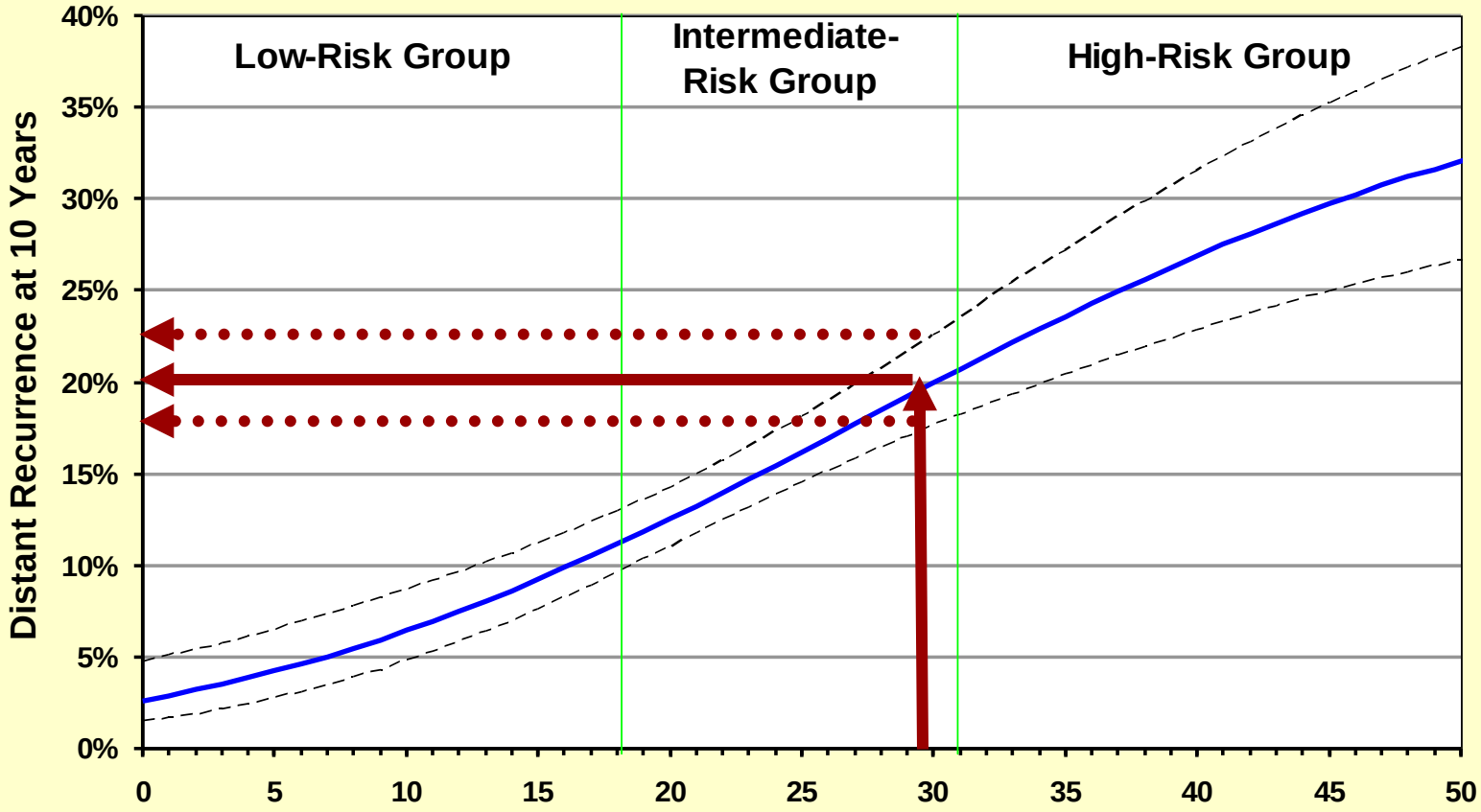
Hypothetical breast cancer population with one third improvement 10yr BCSS from chemotherapy

PROGNOSIS AND PREDICTION

- Prognostic factors give information about likely disease outcome
  - lymph node status
- Predictive factors give information about treatment response
  - BRCA mutation & PARP inhibitor therapy
- Some factors are both prognostic and predictive
  - ER & HER2 status

MULTI-PARAMETER ASSAYS

ONCO*TYPE* DX: RS AS CONTINUOUS PREDICTOR IN TAM TREATED PATIENTS



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

MULTI-PARAMETER ASSAYS IN UK & EUROPE

Test*	Parameters	1° Validation Population	Location
Oncotype DX	16 +5 genes RT-PCR	ER+ (pN0) +ET	Central/ USA
MammaPrint	70 genes array	ER+/- (pN0-1)	Central/ NL
Prosigna (PAM50)	50 +5 genes NanoString	ER+ HER2- (pN0-2) +ET	Local
EndoPredict	8 +4 genes RT-PCR	ER+ HER2- (pN1-3) +ET +CT	Local
IHC4	4 proteins IHC4	ER+ HER2- (pN0-2) +ET	Local/ Central

MPA TESTS ARE ANALYTICALLY "UNIQUE"

prosigna™ Breast cancer gene signature assay		oncotype DX	agendia decoding cancer. nmaPrint			IHC4	myriad GENETIC LABORATORIES EndoPredict
ACTR3B	KRT5	**BAG1**	AA555029_RC	GRHL2 (LOC100131053)	RASSF7	**ERBB2**	AZGP1
ANLN	MAPT	**BCL2**	ALDH4A1	GSTM3	RECQL5	**ESR1**	**BIRC5**
BAG1	MDM2	**BIRC5**	AP2B1	HRASLS	RFC4	**MKi67**	DHCR7
BCL2	**MELK**	**CCNB1**	AYTL2	IGFBP5	RTN4RL1	**PGR**	IL6ST
BIRC5	MIA	CD68	BBC3	JHDM1D	RUNDC1		MGP
BLVRA	**MKI67**	CTSL2	C16orf61 (CMC2)	**KNTC2 (NDC80)**	**SCUBE2**		RBBP8
CCNB1	MLPH	**ERBB2**	C20orf46 (TMEM74B)	LETMD1	SERF1A		STC2
CCNE1	**MMP11**	**ESR1**	C9orf30 (TMEFF1)	LGP2	SLC2A3		**UBE2C**
CDC20	**MYBL2**	GRB7	CCNE2	LIN9	SPEF1		
CDC6	MYC	GSTM1	CDC42BPA	LOC100288906	STK32B		CALM2
CDCA1 (NUF2)	NAT1	**MKI67**	CDCA7	LOC730018	STMN1		OAZ1
CDH3	**ORC6L**	**MMP11**	CENPA	MCM6	TGFB3		RPL37A
CENPF	**PGR**	**MYBL2**	COL4A2	**MELK**	TSPYL5		
CEP55	PHGDH	**PGR**	DCK	MMP9	UCHL5		
CXXC5	PTTG1	**SCUBE2**	DIAPH3	MS4A7	WISP1		
EGFR	RRM2	STK15	DTL	MTDH	ZNF533		
ERBB2	SFRP1		EBF4	MYRIP			
ESR1	SLC39A6	TFRC	ECT2	NMU			
EXO1	TMEM45B	RPLPO	EGLN1	NUSAP1			
FGFR4	TYMS	GUS	ESM1	**ORC6L (ORC6)**			
FOXA1	**UBE2C**	GAPDH	EXT1	OXCT1			
FOXC1	UBE2T	ACTB	FGF18	PALM2			
GPR160			FLT1	PECI			
GRB7	MRPL19		GMPS	PITRM1			
KIF2C	PSMC4		GNAZ	PRC1			
KNTC2 (NDC80)	SF3A1		GPR126	QSCN6L1			
KRT14	ACTB		GPR180	RAB6B			
KRT17	RPLP0						

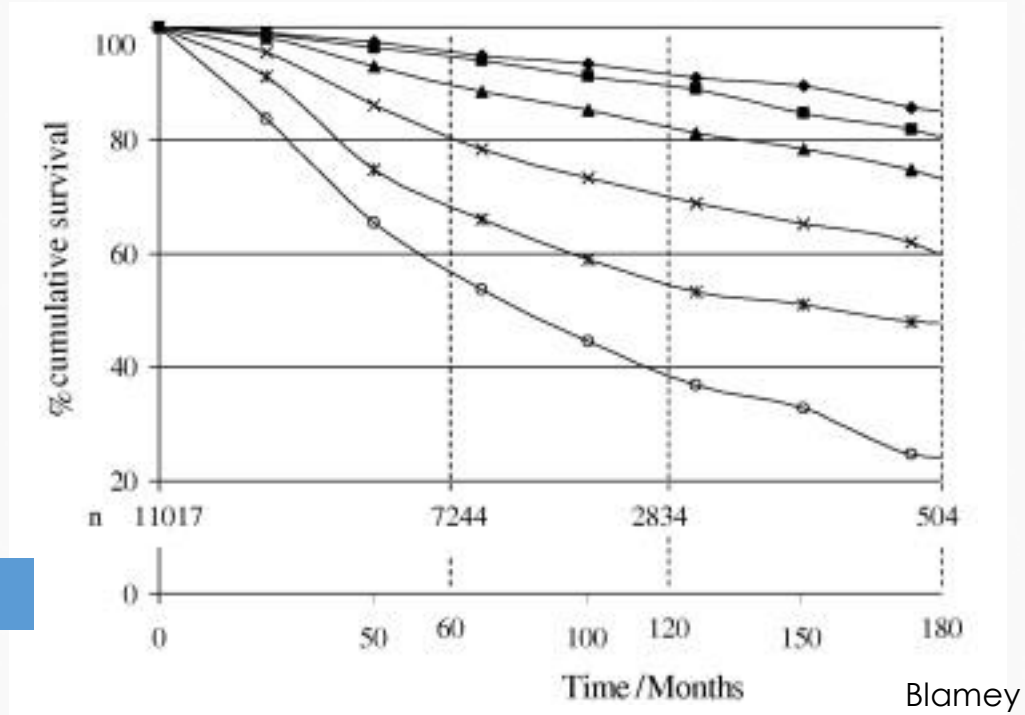
RISK OF RECURRENCE IS INFLUENCED BY BOTH TUMOUR BIOLOGY AND STAGE

Nottingham Prognostic Index = sum of:

- grade (grade 1 =1, grade 2 =2, grade 3 =3)
- node status (0 nodes =1, 1-3 nodes =2, ≥4 nodes = 3)
- tumour diameter (cm) x 0.2

To a 1st approximation tumour grade and stage are independent and equal risk factors

Overall Survival (Kaplan–Meier) by NPI in the ONCOPOOL data set



NPI score

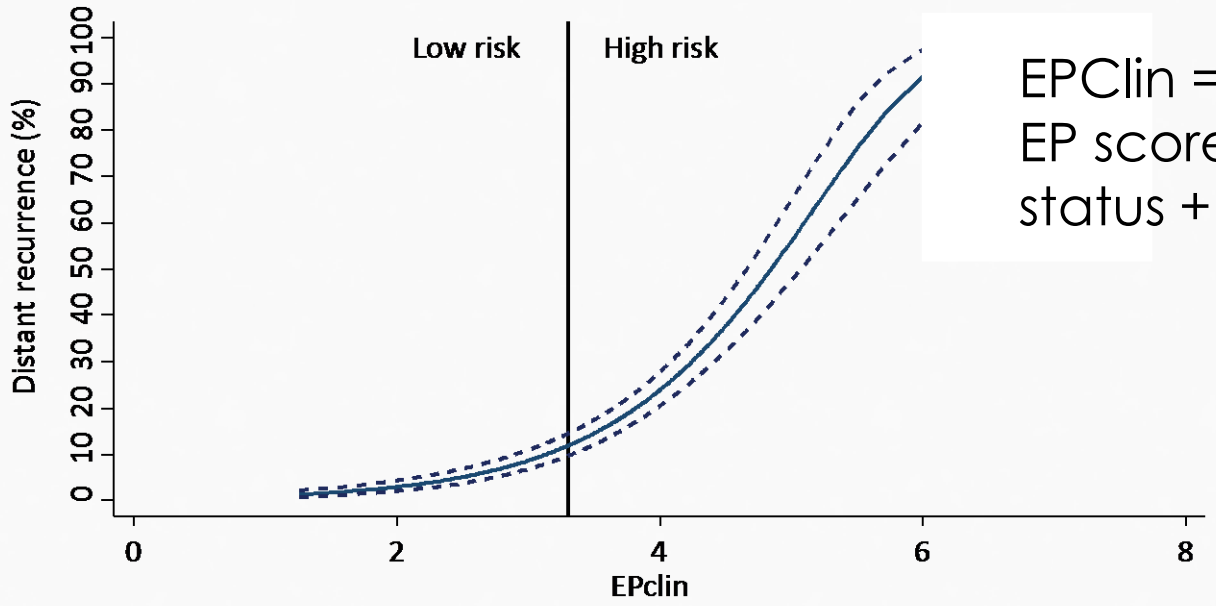
- ♦ ≤2.4
- ■ 2.41–3.4
- ▲ 3.41-4.4
- X 4.41-5.4
- ∗ 5.41-6.4
- ○ ≥6.41

the first multi-parameter test

Blamey 2010: European Journal of Cancer, 46:56–71

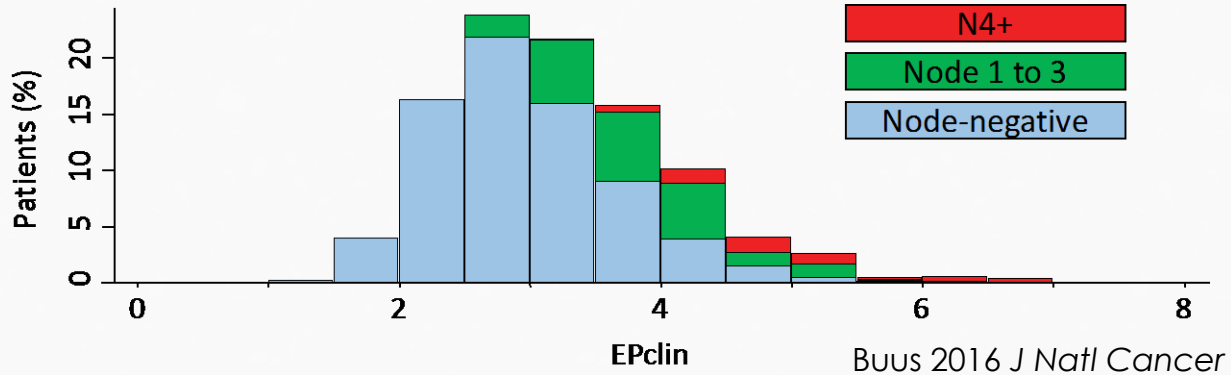
INFLUENCE OF NODAL STATUS ON ENDOPREDICT RISK SCORE

928 patients from transATAC



EPClin = combined EP score + node status + tumour size

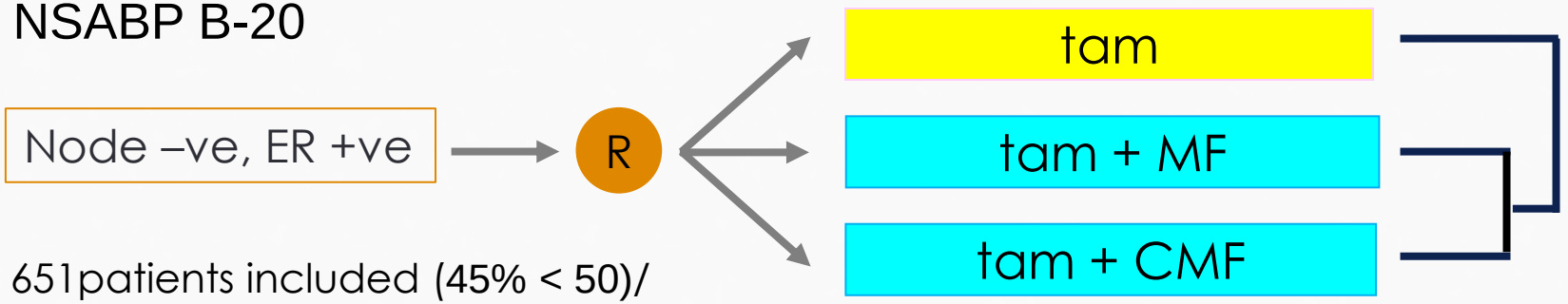
the majority of patients with N+ disease fall into high-risk groups because of nodal status



Buus 2016 *J Natl Cancer Inst*; 108(11):djw149

THE NSABP B-20 & SWOG 88-14 ONCOTYPE DX STUDIES

NSABP B-20

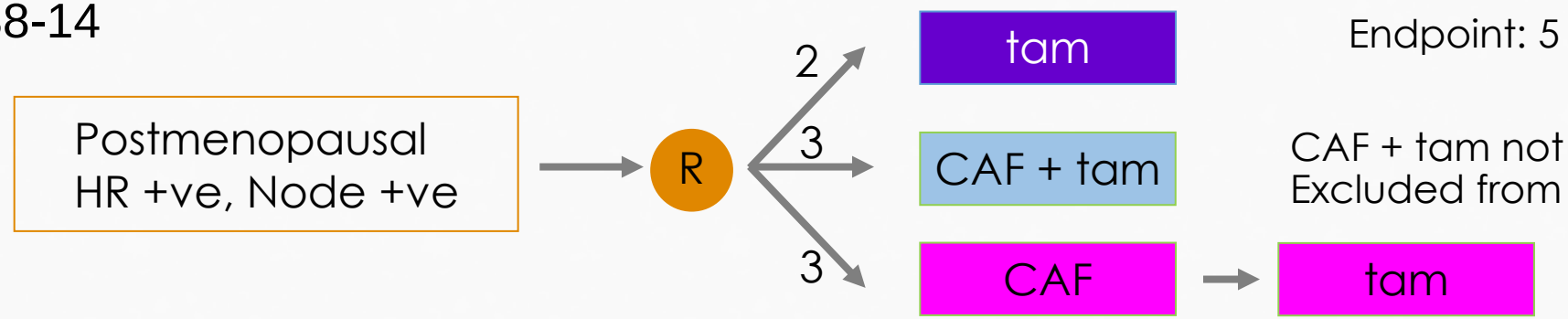


Endpoint 10yr DDFS; chemo arms combined

Patients & outcome consistent with parent B-20 study; CMF & MF the same

651patients included (45% < 50)/ 2299 patients in parent study.

SWOG 88-14



Endpoint: 5 & 10yr DFS

CAF + tam not superior to tam
Excluded from Oncotype study

367 blocks from tam & CAF-T arms (=40% recovery); demographics representative of parent; 227 pN1, 140 pN2. 2299 patients in parent study.

Endocrine therapy continued to 5 years

RESULTS & LIMITATIONS

Both studies show chemotherapy benefit is confined to patients with high RS tumours

- Both studies small, especially SWOG 88-14
- Both studies contained HER2-positive patients (12% in SWOG 88-14)
  - B-20 re-analysis to adjust for HER2 2018: result still significant but weaker
  - 88-14 very limited analysis for HER2 – non evaluable
- B-20 tam patients formed the main population used for Oncotype DX derivation
  - Artificial increase in goodness of fit
- Neither study preserved original stratifications

I can see your error bars using Google Earth.

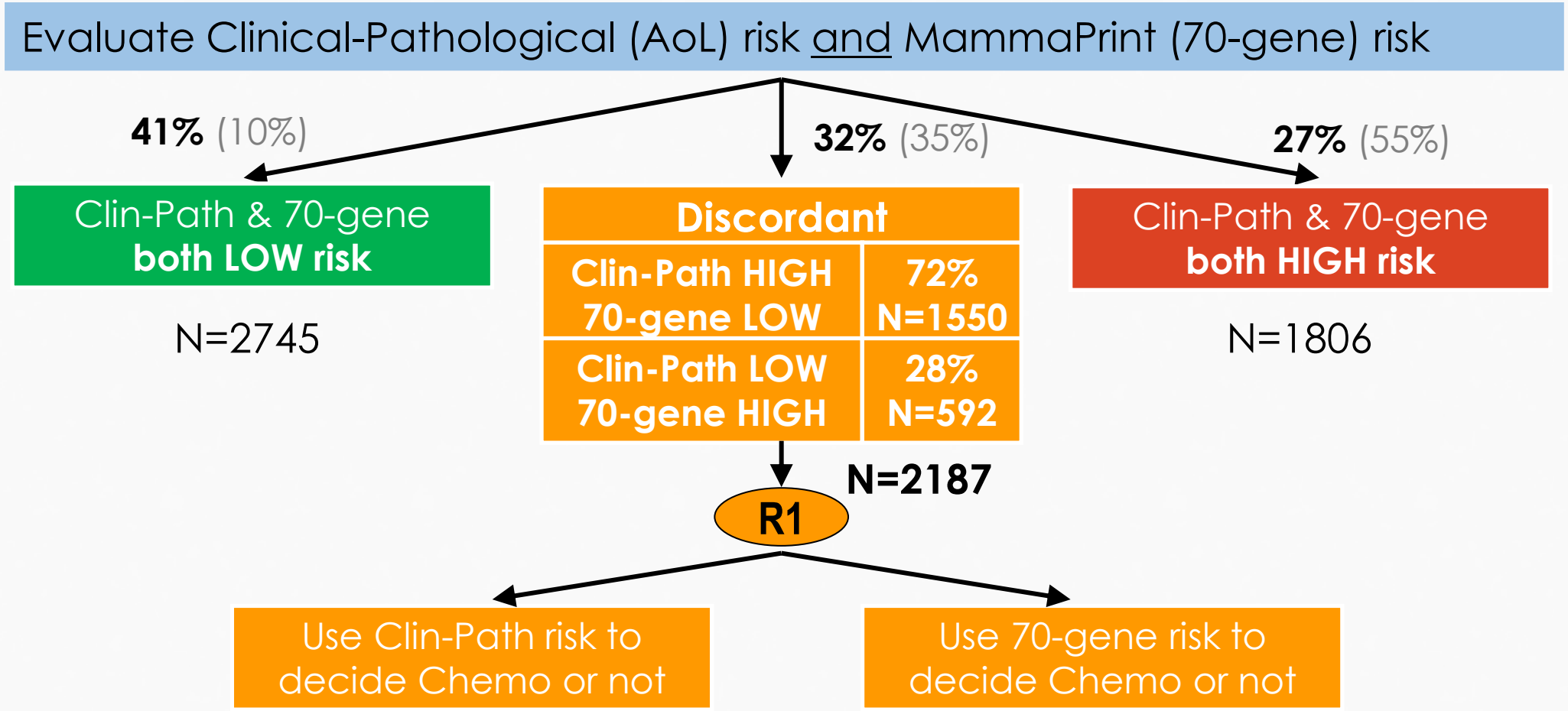
Q: Are the results correct? A: probably but they hardly constitute level 1 evidence

PROSPECTIVE CLINICAL TRIALS

WHY DO WE NEED OPTIMA?

EORTC-BIG MINDACT TRIAL DESIGN

6,693 women enrolled: 79% pN0, 81% ER-pos HER2-neg

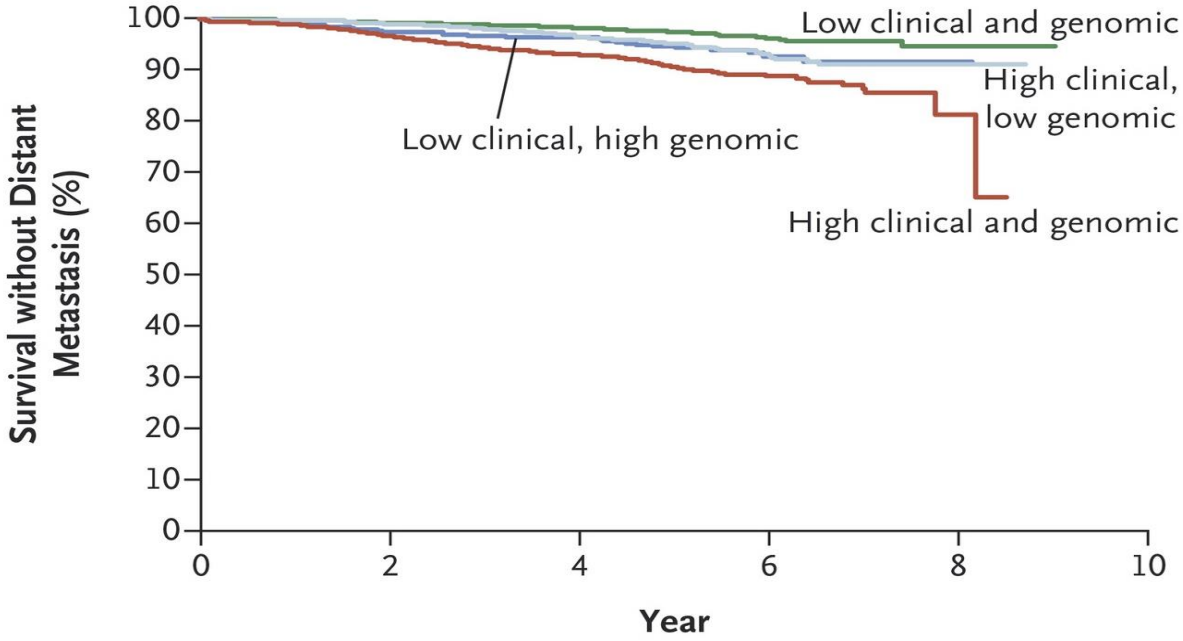


MINDACT RESULTS

- Complex trial, heterogeneous pop^{n} (10% TNBC, 9.5% HER2 pos; 21% pN1)
- Insufficient power to compare randomised groups
- Primary EP = 95% chance of 5-yr DDFS >92% for genomic low/ clin high no chemo group: **achieved**

- Genomic low/ clin high risk 5yr DMFS Δ chemo vs not =1.5%
- Genomic high/ clin low risk 5yr DMFS Δ chemo vs not = 0.8%
- All chemo vs not pNS

- Error in risk assessment affected 16% genomic high/ clin low



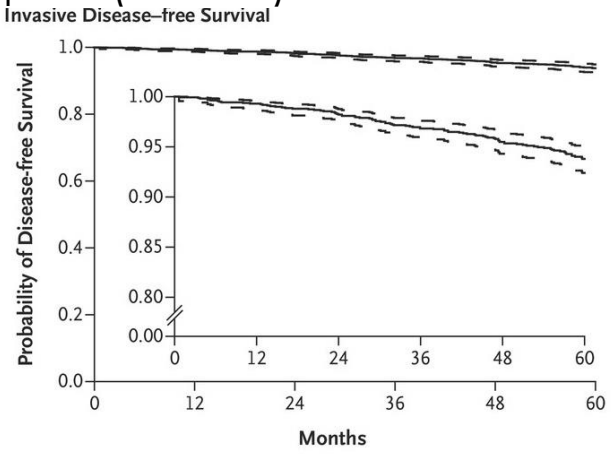
Cardoso 2016 NEJM **375:717**

TAILORX & PLANB COHORT STUDIES – ENDOCRINE THERAPY ONLY

- TAILORx pN0 cohort study (RS <11) Sparano 2015 NEJM 373:2005
- PlanB pN0-1 (RS ≤11) Nitz 2017 BCRT 165:573

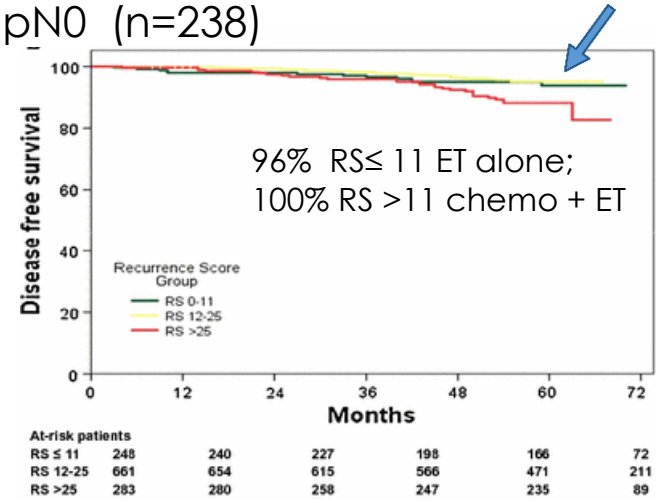
Excellent outcome: confirms prognostic utility of ODX (small pN1 cohort)

pN0 (n=1626)

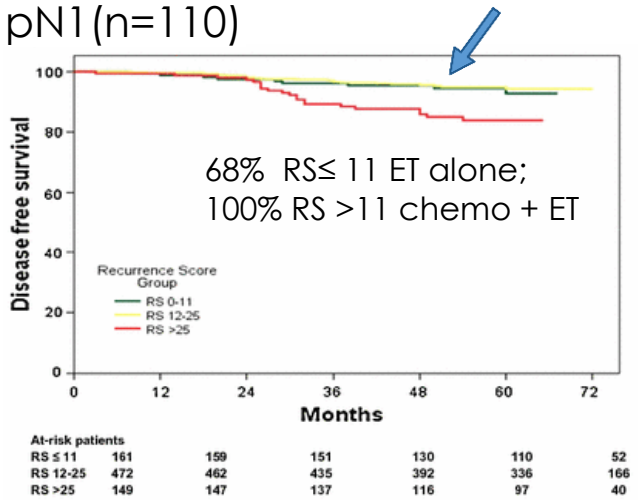


TAILORx Five-year IDFS
pN0 93.8% [92.4-94.9%]

pN0 (n=238)

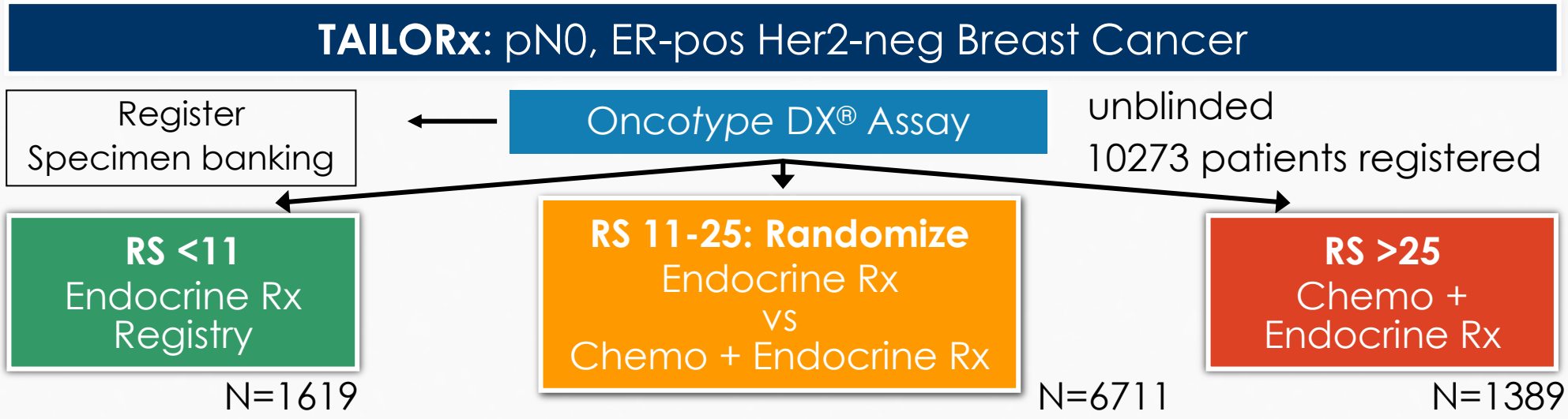


pN1(n=110)



PlanB Five-year DFS ET alone: pN0 94.2% [90.4–98.0%]
pN1 94.4% [89.5–99.3%]

TAILORx



- 1° outcome IDFS (local recurrence exc DCIS, metastatic disease, any death, 2nd cancer)
- 2° outcomes: RFI, DRFI (i.e. BC-specific DFS & DDFS includes BC death), OS
- Statistical hypothesis = non-inferiority of IDFS (failure to demonstrate superiority) - 5yr control-arm IDFS 90%, Δ3% ⇒HR 1.322 – 10% 1-sided significance, 95% power
- Sample size adjusted for 12% non-adherence
- Event-driven analysis – threshold 835

Sparano 2018 NEJM doi: 10.1056/NEJMoa1804710

TAILORx RCT CONDUCT

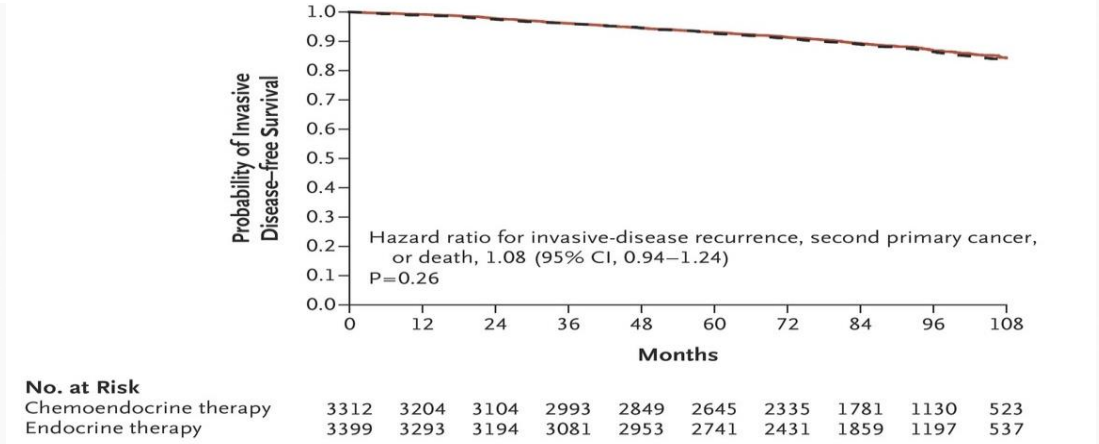
- Trial population & treatment:
  - 33% <50yrs/ 36% pre-menopausal
  - Median tumour size 1.5cm: IQR 1.2-2.0 cm (i.e. 75% ≤2.0 cm)
  - 29% grade 1/ 57% grade 2/ 14% grade 3
  - 72% "clinical low risk"

- Chemotherapy (arm c): 56% TC, 29% anthracycline-non taxane
- 5.4% non-compliance with assignment in endocrine therapy arm/ 18.4% in chemo-endocrine arm

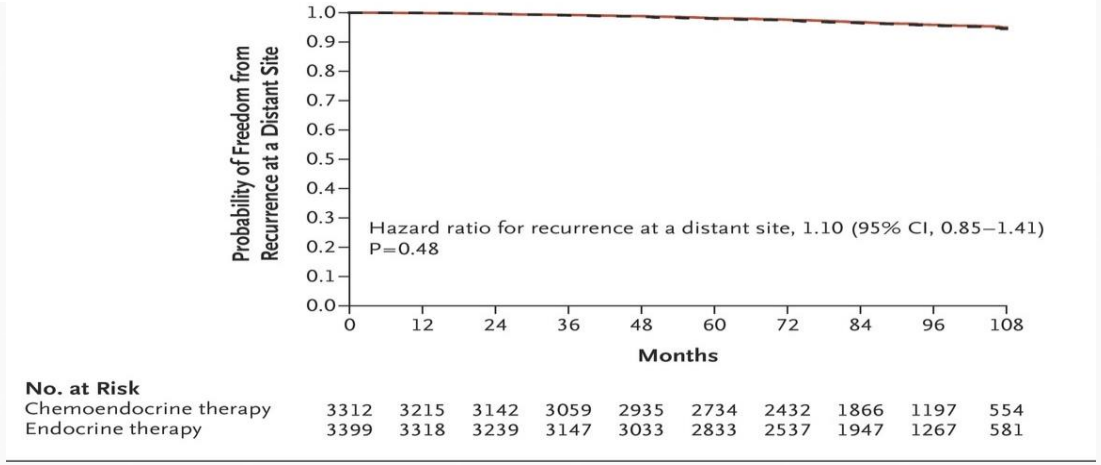
- Analysis at median fu 7.5yrs

TAILORx MAIN RESULT

Invasive Disease-Free Survival



Distant Recurrence-Free Interval



9-year outcome	Hazard ratio (CE/E) [95%CI]	Pre-specified boundary
IDFS	1.08 [0.94-1.24]	1.322
DRFI	1.10 [0.85-1.41]	1.61

Events (ITT)		Endo	Chemo-Endo
IDFS	5-years	7.2%	6.9%
	9-years	16.7%	15.7%
DFRI	5-years	2.0%	1.8%
	9-years	5.5%	5.0%

Primary outcome met

TAILORx ANALYSIS: COMMENTARY

- Number of events, particularly DRFI very small.
- Prolonged f.u. required for analysis (late recurrence not influenced by chemo)
- Likely reflects the very low risk nature of population
- No data on events vs clinical risk available
- More 2nd cancers than distant recurrence: with hindsight IDFS not the ideal primary outcome

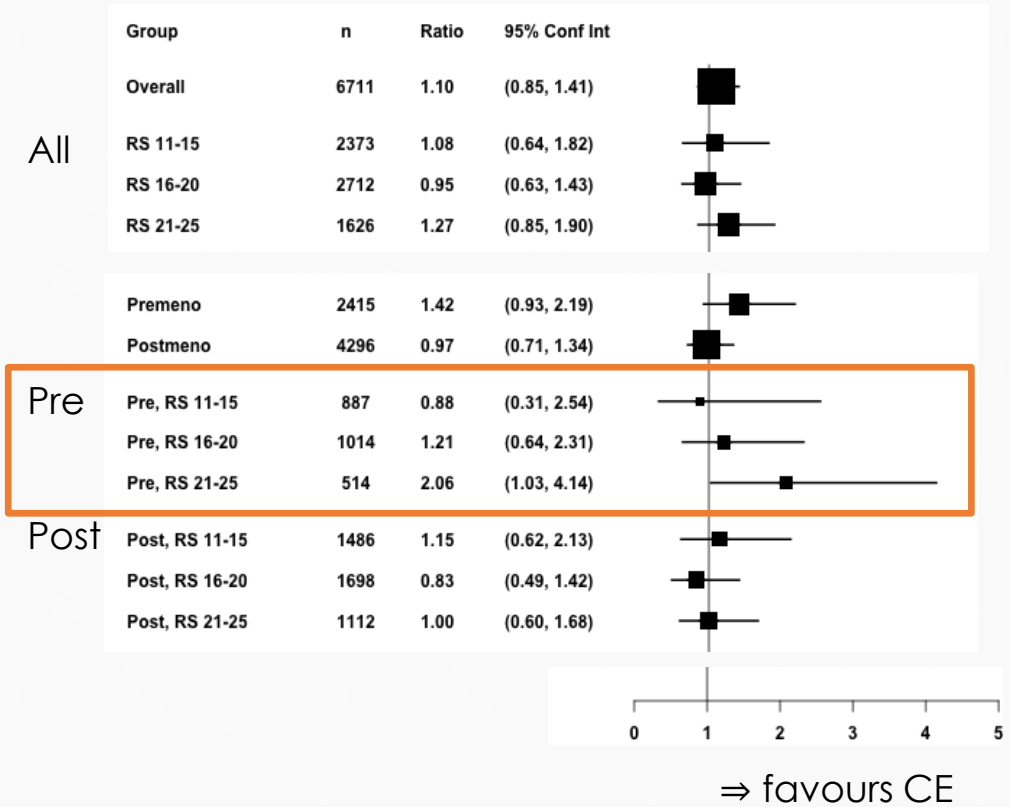
Crude number of events in TAILORx (ITT)

	E: n (%)	CE: n (%)	Difference (E-CE) n
loco-regional (LR)	67 (15.3%)	62 (15.5%)	5
opposite BC	44 (10.1%)	48 (12.0%)	4
DR ± LR	107 (24.5%)	92 (23.0%)	15
2nd cancer	145 (33.3%)	146(36.5%)	1
Death (NOS)	63 (14.4%)	52 (13.0%)	11
Total	436/3399	400/3312	36

None of this detracts from the achievement of the TAILORx investigators

EVIDENCE FOR ONCOTYPE DX AS A PREDICTOR OF CHEMOTHERAPY BENEFIT IN TAILORx

Exploratory subgroup analysis:
DFRI vs RS + menopausal status



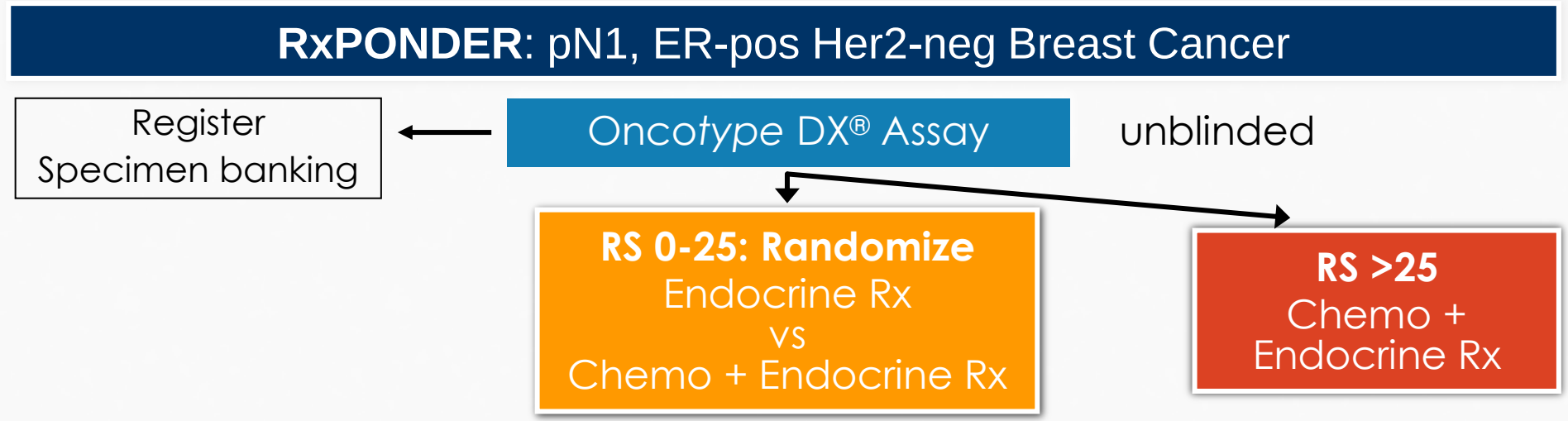
Sparano 2018 NEJM doi: 10.1056/NEJMoa1804710 fig S11

Similar results for analysis by RS + age and for alternative outcomes (IDFS, RFI).

Significant interactions between treatment and combinations of outcome, RS & age ≤50/ pre-menopausal status in some of these analyses.

- **Data could be interpreted as showing that RS is predictive of chemotherapy sensitivity in ≤50/ pre-menopausal population.**
- **Chemotherapy-induced menopause a potential confounder: no data collected.**

RxPONDER



- Accrual complete
- No information about randomised population
- Same design & issues as TAILORx randomised study
- ? Will report 2020

OPTIMA

WHAT WE EXPECT TO LEARN

ASSUMPTIONS UNDERPINNING OPTIMA

- Multi-parameter assays predict chemotherapy sensitivity
- Tumour stage is prognostic for all patients irrespective of multi-parameter assay score
- Advanced stage patients with poor prognosis will not benefit from chemotherapy if the tumour has a low multi-parameter assay score
  - Example – few patients multi-node positive low molecular grade tumours will benefit from chemotherapy

OPTIMA MAIN STUDY DESIGN

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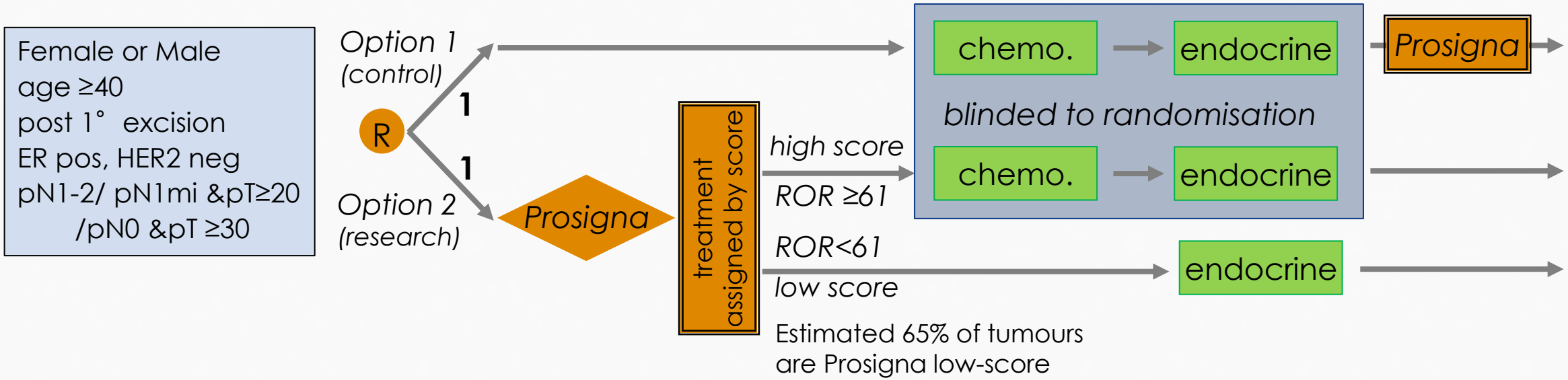

1° Outcome = Non-inferiority of IDFS (Δ=-3%, 5yr, control-arm IDFS =85%; HR ≤1.22)
Cost effectiveness evaluation of test-directed treatment

key 2° Outcome = Non-inferiority of IDFS in low-score patients (Δ=-3.5%)

Sample size = 4500 patients (+ OPTIMA prelim)

Recruitment period = 60 months
commenced Jan 2017

THE PROSIGNA TEST

- Measures PAM50 gene expression set
- Outputs = Risk of Recurrence Score (ROR-PT) & Intrinsic Subtype
- ROR inputs = Intrinsic subtype, proliferation, tumour size
- Runs on multi-purpose proprietary hardware (NanoString) as "black box" test
  - Versatile, scalable, highly robust & reproducible
- Can be performed in any suitably qualified lab (NHS)
- Validated in several trial data sets – transATAC, ABSCG12
- Predictive of response to neoadjuvant chemotherapy

TREATMENT IN OPTIMA

- Chemotherapy pre-specified from a menu of regimens stratified by efficacy.
- Chemotherapy allocation blinded to avoid potential bias in chemo administration.
- Endocrine therapy: standard
  - AI for post-menopausal,
  - tam for men
  - OS + tam/AI for pre-menopausal at trial entry
- Adjuvant bisphosphonates recommended for all.
- Patients may join other studies – e.g. AddAsprin

OPTIMA POPULATION

Main Inclusion Criteria

- "Adequate surgery"
- Women or Men
- Age ≥40
- ER-pos HER2-neg (local lab)
- pN1-2 / pN1mi & T≥20mm / pN0 & T≥30mm
- Fit for chemotherapy

Main Exclusion Criteria

- Advanced stage – pN3/ IM node involvement
- Neoadjuvant therapy
- Previous IBC – surgically treated DCIS permitted

PROTOCOL V6 (JULY 2018)

- Clarification of inclusion/ exclusion criteria
  - Bilateral cancers
- Permit short-term neoadjuvant endocrine therapy
  - Neoadjuvant chemotherapy not permitted
- Update permitted chemotherapy
  - Include regimens commonly used in Norway
- Update analysis plan
- Admin changes
  - Make international involvement explicit
  - GDPR compliance with improvement of PIS & consent form and separate data transparency statement

RECRUITMENT: THE QRS

Recruitment into trials of less treatment is difficult!

- Explanation to potential participants is different from superiority trials

Systematic study of Qualitative Recruitment Study in OPTIMA prelim & main study: (MRC CONDUCT-II hub, University of Bristol)

QRS IN ACTION

Two **iterative** and **flexible** stages:

Phase 1: Understand recruitment (and identify challenges)

- *Analysis of screening log data*
- *In-depth interviews*
- *Observations of site visits and meetings*
- *Review study documentation*
- *Audio recordings of recruitment consultations*

Phase 2: Develop and deliver strategies to improve recruitment

- *Group training sessions*
- *Individual feedback*
- *Tips documents*
- *Amend patient documentation*

TEAMWORK

Think of Optima as a **team trial** involving all the professionals that a patient may encounter:

Patients will have established trust in their surgeon and breast care nurse and what they say.

Engage **all** your colleagues, make them feel part of the recruitment process.

Provide assurances that :

- Prosigna gives a better measure of grade than histopathology
- Small delays in chemotherapy start are not harmful.

Secure the commitment of your colleagues to convey a consistent message to patients :

“the value of chemotherapy is uncertain”

THE OPTIMA TEAM IS VERY EXCITED ABOUT NORWEGIAN PARTICIPATION

THANK YOU FOR INVITING ME TO YOUR COUNTRY TO PRESENT THE STUDY

UK TRIAL MANAGEMENT

Sponsor

Co-ordinating Centre

Principal Funder

Affiliates :

THE OPTIMA TRIAL TEAM

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Patient Representative
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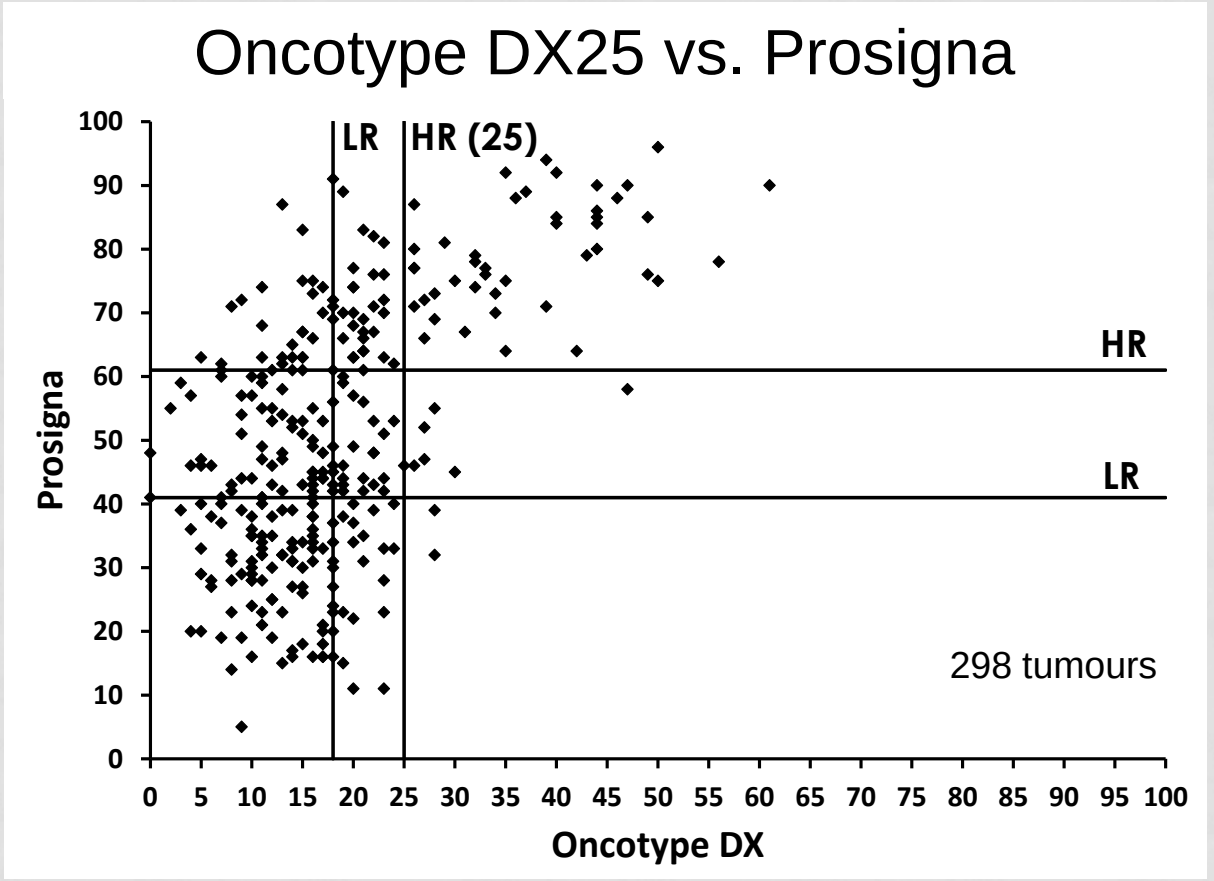
AGREEMENT BETWEEN MULTI-PARAMETER TESTS (DATA FROM OPTIMA PRELIM)

Do the tests tell us the same thing?

AGREEMENT BETWEEN TESTS FOR INDIVIDUAL TUMOURS IN OPTIMA PRELIM



HR = pre-defined "high risk" boundary
LR = pre-defined "low risk" boundary

Stein 2016 Health Technol Assess 20(10)
Bartlett 2016 J Natl Cancer Inst 108(9)

KAPPA STATS FOR TESTS PROVIDING RISK PREDICTIONS (NOT HIGH VS HIGH)

Kappa statistic (95% confidence interval)	Prosigna (Low/Int)	MammaPrint (Low)	IHC4 (Low/Int)	IHC4-AQUA (Low/Low-Mid)
Oncotype DX ≤25 (OPTIMA low risk)	0.45 (0.34-0.55)	0.40 (0.30-0.50)	0.52 (0.40-0.64)	0.41 (0.31-0.52)
Prosigna (Low/Int)		0.53 (0.43-0.63)	0.39 (0.27-0.50)	0.43 (0.31-0.54)
MammaPrint (Low)			0.33 (0.21-0.44)	0.42 (0.30-0.53)
IHC4 (Low/Int)				0.60 (0.50-0.70)

Interpretation: >0.8 indicates "excellent agreement"; 0.4-0.6 indicates "modest agreement"