The ROYAL MARSDEN
NHS Foundation Trust

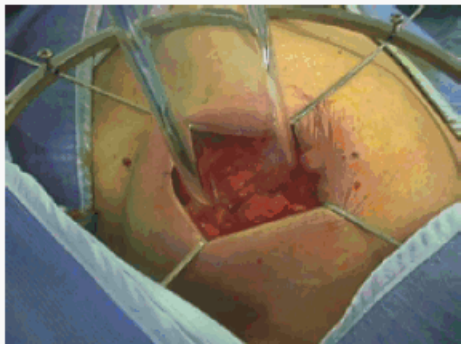
Risk-Benefit of Intra-Operative RT

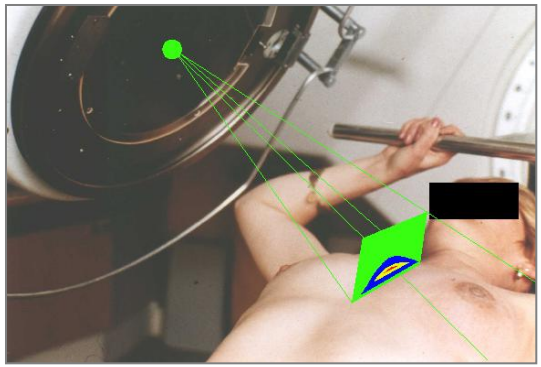
John Yarnold
Institute of Cancer Research &
Royal Marsden NHS Foundation Trust
Sutton, UK

ELIOT Trial (n=1305)

Eligibility: Age>48yr; T<25mm

Surgery: Local excision





Randomisation

*IORT	WBRT
21Gy/1F	50Gy/25F WB 10Gy/5F boost

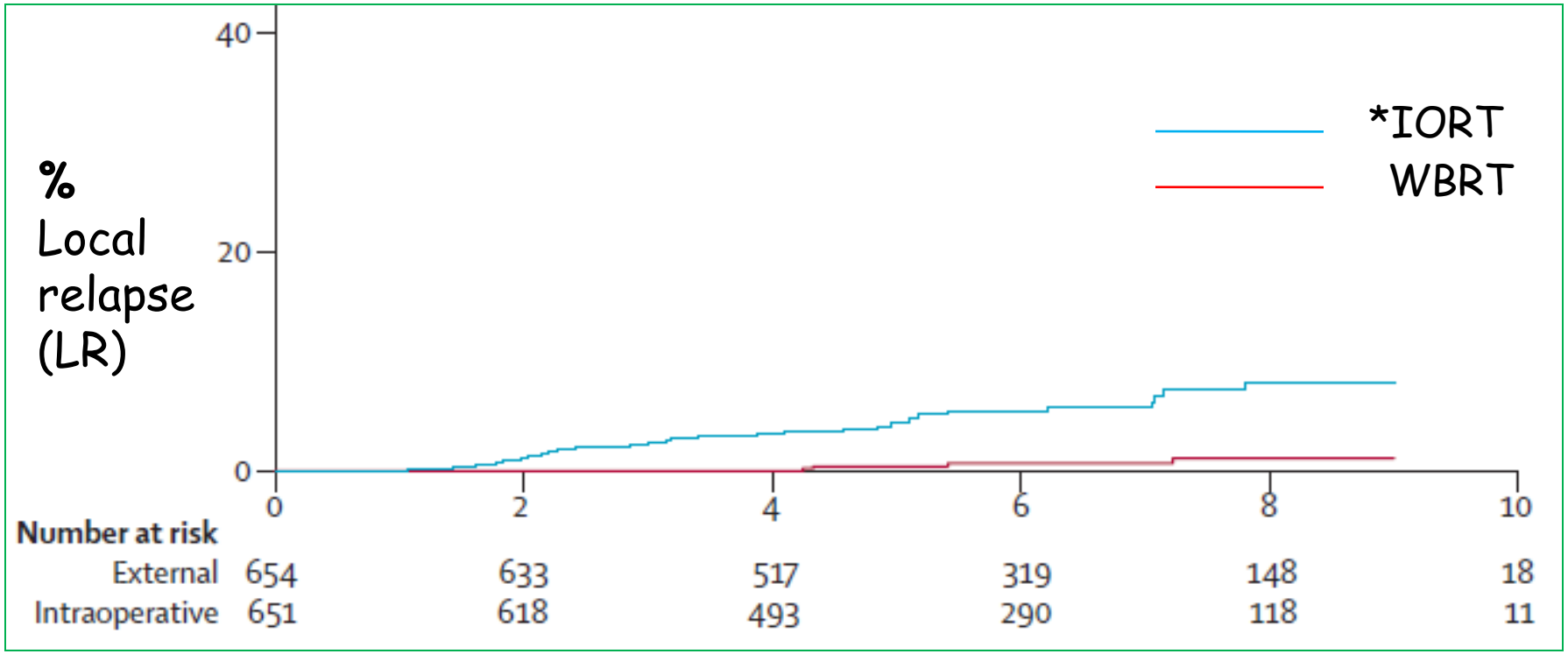
*IORT= intra-operative RT

ELIOT: Patients & Tumours

Age ≥60	52%
pT1	85%
Ductal	80%
G1 or 2	75%
pN1	25%
Adj Sys Tr	96%

Orecchia, Lanc Onc, 2013, 14:1269-77

ELIOT: Breast Cancer Local Relapse Median FU=6yr



Cumulative LR (%)						
Ext RT	0	0	0	0.8	1.3	1.3
ELIOT	0	1.0	3.7	5.9	9.1	11.8

*IORT= intra-operative RT

Orecchia, Lanc Onc, 2013, 14:1269-77

ELIOT: Factors Associated with Local Relapse

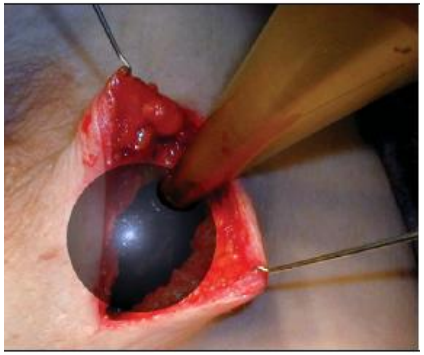
Factor	5yr LR n/N	(%)
≥pT2	10/83	(11)
G3	15/129	(12)
ER-	8/63	(15)
Ki67>20%	22/244	(9)
Triple -ve	7/43	(19)

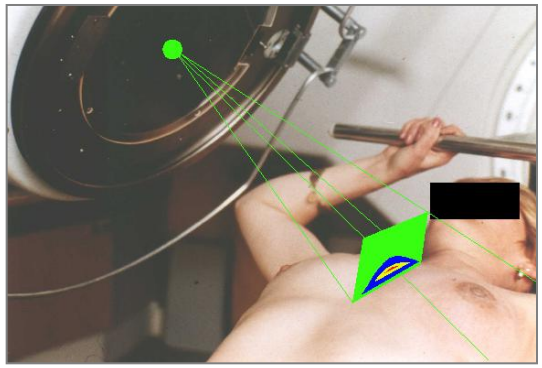
Orecchia, Lanc Onc, 2013, 14:1269-77

TARGIT Trial (n=3451)

Eligibility: Age>45yr; T<35mm; unifocal IDC

Surgery: Local excision





Randomisation

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21Gy/1F	50Gy/25F WB 10Gy/5F boost

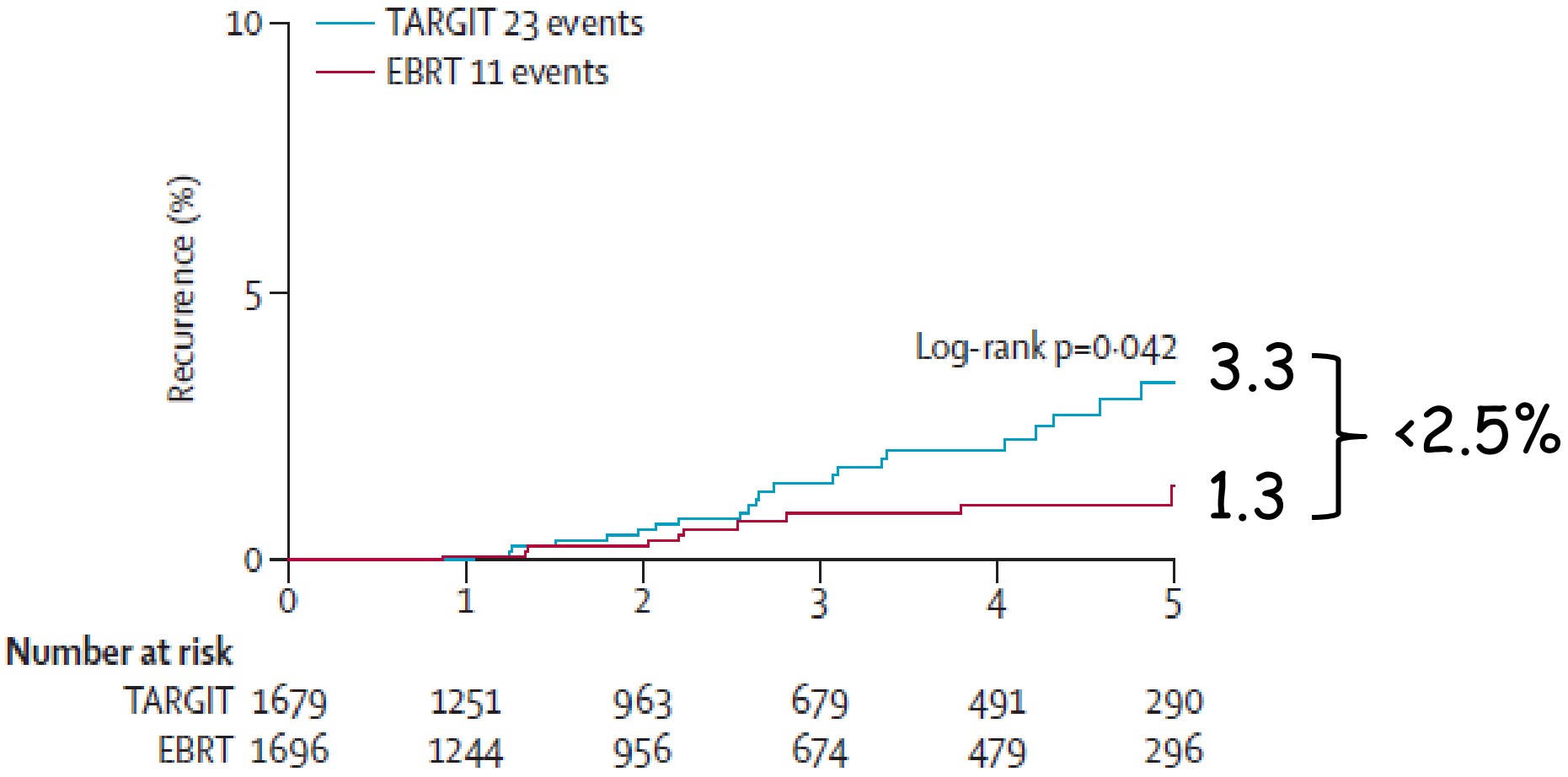
*IORT= intra-operative RT

TARGIT: Analysis Plan

- Non-inferiority design aiming to detect a 2.5% inferiority in local relapse (LR) at 5 years after IORT with 80% power at the 5% significance level
- Sample size based on analysis of whole population

Vaidya, Lancet, 2014, 383:603-13

TARGIT: Local Relapse (LR)



Vaidya, Lancet, 2014, 383:603-13

TARGIT: Absolute Differences in Outcome (Table 1)

	Events; 5-year cumulative risk (95%CI)		Absolute difference*
	TARGIT	EBRT	
All patients			
Local recurrence (n=3375)	23; 3·3% (2·1–5·1)	11; 1·3% (0·7–2·5)	12 (2·0%)
Any other recurrence (n=3375)	46; 4·9% (3·5–6·9)	37; 4·4% (3·0–6·4)	9 (0·5%)
Death (n=3451)	37; 3·9% (2·7–5·8)	51; 5·3%(3·9–7·3)	−14 (−1·4%)
Prepathology†			
Local recurrence (n=2234)	10; 2·1% (1·1–4·2)	6; 1·1% (0·5–2·5)	4 (1·0%)
Any other recurrence (n=2234)	29; 4·8% (3·1–7·3)	25; 4·7% (3·0–7·4)	4 (0·1%)
Death (n=2298)	29; 4·6% (1·8–6·0)	42; 6·9% (4·3–9·6)	−13 (−2·3%)
Postpathology‡			
Local recurrence (n=1141)	13; 5·4% (3·0–9·7)	5; 1·7%(0·6–4·9)	8 (3·7%)
Any other recurrence (n=1141)	17; 5·2% (3·0–8·8)	12; 3·7% (1·9–7·0)	5 (1·5%)
Death (n=1153)	8; 2·8% (1·3–5·9)	9; 2·3% (1·0–5·2)	−1 (0·5%)

TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. *In Kaplan-Meier point estimate at 5 years (TARGIT minus EBRT). †TARGIT given at same time as lumpectomy. ‡TARGIT given after lumpectomy, as separate procedure.

Table 1: **Results of primary (local recurrence in the conserved breast), secondary (death), and exploratory (any other recurrence) outcomes for all patients and the two strata as per timing of randomisation and delivery of TARGIT**

Vaidya, Lancet, 2014, 383:603-13

Criticisms by Cuzick & Haviland of How Non-Inferiority Statistics Applied (Table 1)

	Events; 5-year cumulative risk (95%CI)		Absolute difference*
	TARGIT	EBRT	
All patients			
Local recurrence (n=3375)	23; 3·3% (2·1–5·1)	11; 1·3% (0·7–2·5)	12 (2·0%) -
Any other recurrence (n=3375)	46; 4·9% (3·5–6·9)	37; 4·4% (3·0–6·4)	9 (0·5%)
Death (n=3451)	37; 3·9% (2·7–5·8)	51; 5·3%(3·9–7·3)	-14 (-1·4%)

Cuzick, Lancet, 2014, 383:1716
Haviland, Lancet, 2014, 383; 1716-17

Vaidya, Lancet, 2014, 383:603-13

TARGIT: Comparison of Effects using Binomial Proportions (Table 3)

	Median follow-up	Number of events	Absolute difference (90% CI) in the binomial proportions of local recurrence* in the conserved breast (TARGIT minus EBRT)	Z score	$p_{non\text{-}inferiority}$
Whole trial					
All patients (n=3451)	2 years 5 months	34	0·72% (0·2 to 1·3)	−5·168	<0·0001
Mature cohort (n=2232)	3 years 7 months	32	1·13% (0·3 to 2·0)	−2·652	0·0040
Earliest cohort (n=1222)	5 years	23	1·14% (−0·1 to 2·4)	−1·750	0·0400
Prepathology†					
All patients (n=2298)	2 years 4 months	16	0·37% (−0·2 to 1·0)	−5·954	<0·0001
Mature cohort (n=1450)	3 years 8 months	14	0·6% (−0·3 to 1·5)	−3·552	0·0002
Earliest cohort (n=817)	5 years	9	0·76% (−0·4 to 2·0)	−2·360	0·0091
Postpathology‡					
All patients (n=1153)	2 years 4 months	18	1·39% (0·2 to 2·6)	−1·503	0·0664
Mature cohort (n=782)	3 years 7 months	18	2·04% (0·3 to 3·8)	−0·429	0·3339
Earliest cohort (n=405)	5 years	14	1·8% (−1·2 to 4·8)	−0·382	0·3511

The prespecified non-inferiority margin was 2·5%. Mature cohort consisted of 2232 patients for whom data was previously reported in 2010. Earliest cohort excluded patients enrolled in the last 4 years of the study. TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. *Binomial proportion=number of recurrences/number of patients. †TARGIT given at same time as lumpectomy. ‡TARGIT given after lumpectomy, as separate procedure.

Table 3: Calculation of $p_{non\text{-}inferiority}$ for the whole cohort, the mature cohort, and the earliest cohort

Vaidya, Lancet, 2014, 383:603-13

Criticism by Cuzick of How Binomial Proportions Applied (Table 3)

	Median follow-up	Number of events	Absolute difference (90% CI) in the binomial proportions of local recurrence* in the conserved breast (TARGIT minus EBRT)
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Earliest cohort (n=1222)	5 years	23	1·14% (–0·1 to 2·4)

611 (18%) patients have 5yr FU

For comparison of 5yr rates, <u>all</u> patients must have 5yr FU

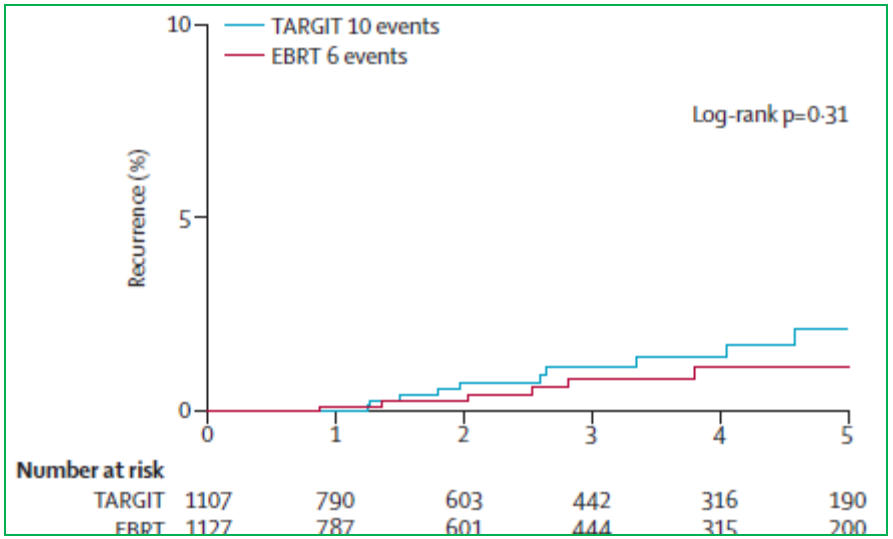
Cuzick, Lancet, 2014, 383:1716

TARGIT: Scheduling of IORT

- 2/3rd randomisation occurred at lumpectomy (pre-path)
- 1/3rd definitive pathology already available (post-path)

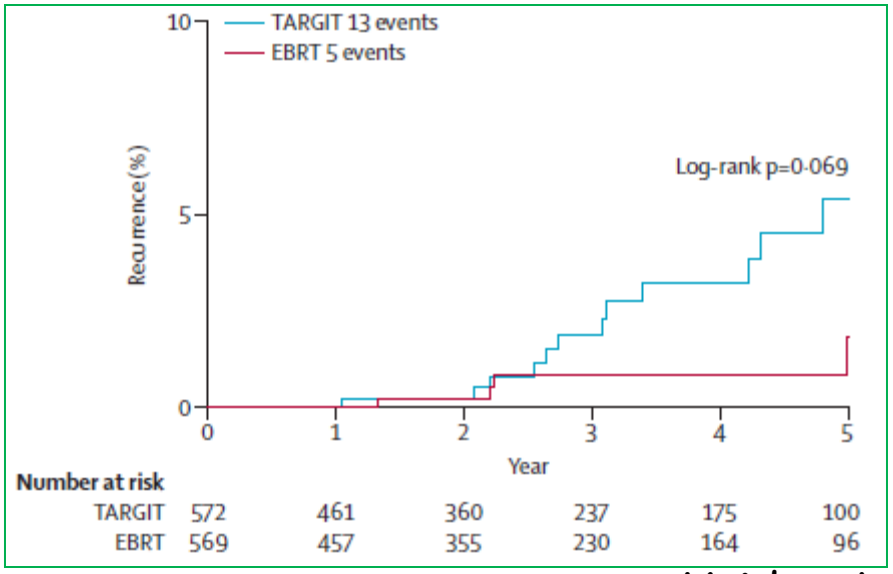
TARGIT: LR in Pre- & Post-pathology Strata

Pre-pathology



Total 390 with 5yr FU

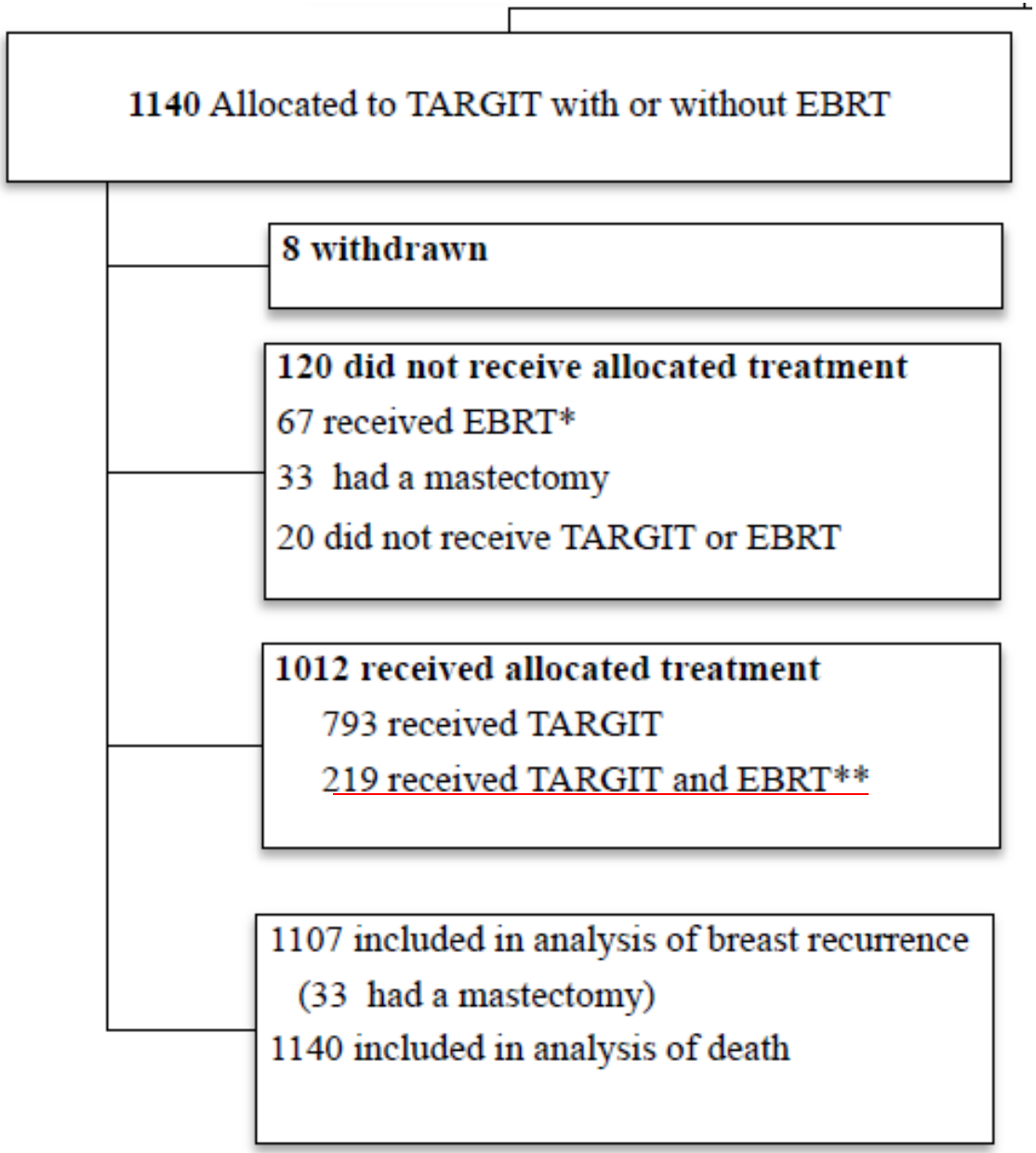
Post-pathology



Total 196 with 5yr FU

Vaidya, Lancet, 2014, 383:603-13

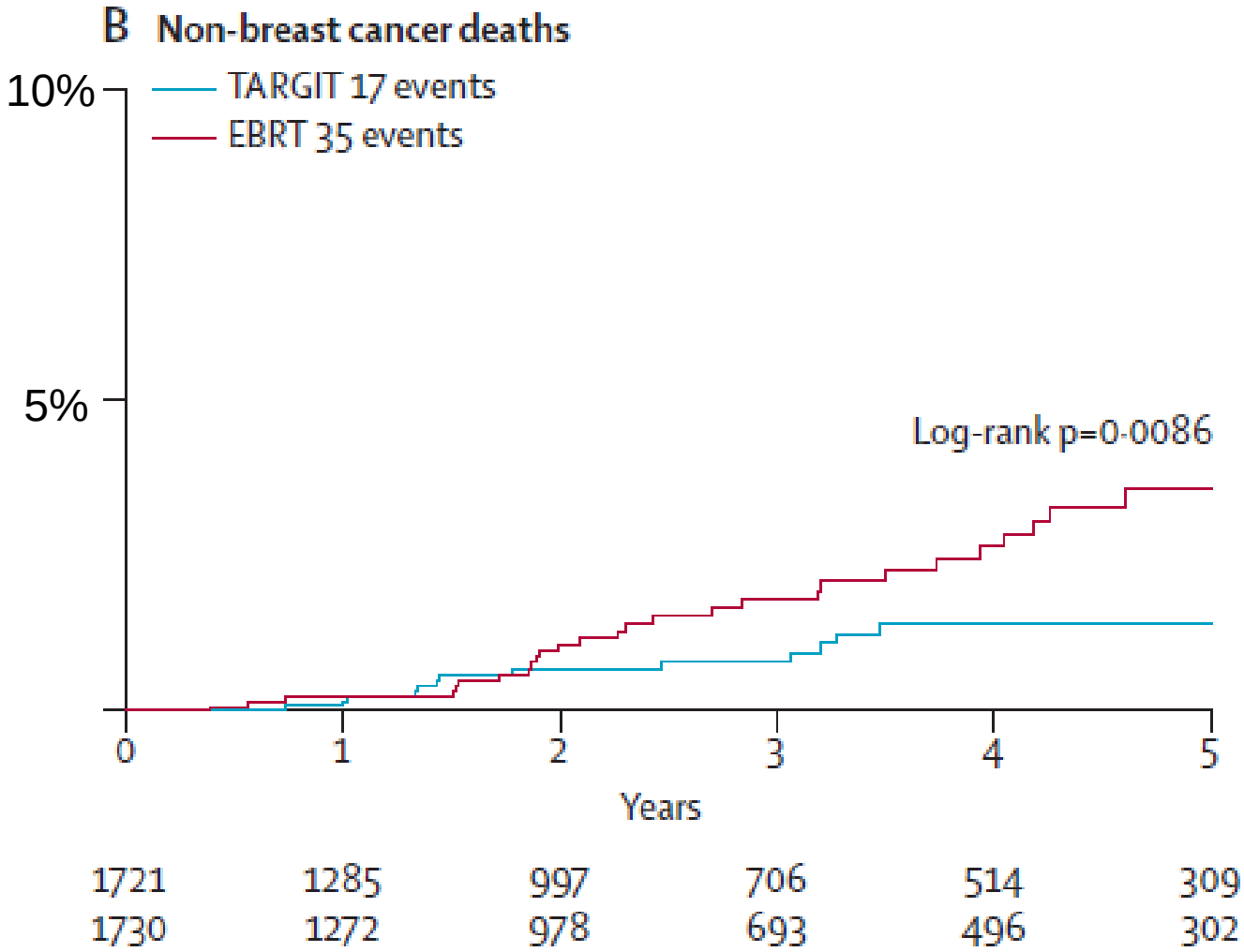
Pre-Pathology Stratum



319/1140=28%
have some form of
whole breast therapy
ie. 'risk adapted'

Vaidya, Lancet, 2014,
383:603-13

TARGIT: Non-Breast Cancer Deaths (Figure 1)



Vaidya, Lancet, 2014, 383:603-13

TARGIT: Non-Breast Cancer Deaths, Table 2

	TARGIT	EBRT
Other cancers	8	16
Cardiovascular causes		
Cardiac*	2	8
Stroke	0	2
Ischaemic bowel	0	1
Other†	7	8
Total	17	35

5-year risk 1·4% for TARGIT versus 3·5% for EBRT; log-rank p=0·0086.

Vaidya, Lancet, 2014, 383:603-13

UK National Institute of Clinical Excellence (NICE) Consultation Document, July 2014

"Uncertainties generated by the evidence"

"The Committee considered that the criterion for non-inferiority was not appropriately defined and the trial was therefore underpowered and the results could not be considered robust enough to determine whether Intrabeam was non-inferior to EBRT in terms of local recurrence."

http://www.nice.org.uk/guidance/gid-tag353/documents/breast-cancer-early-intrabeam-radiotherapy-system-appraisal-consultation-document

NICE, September 2014
Further Analyses Requested

Including,

K-M survival analyses of LR with 95% CI around each estimate

Full patient-level dataset of patients with 5yr follow up for independent appraisal

http://www.nice.org.uk/guidance/indevelopment/gid-tag353

Finally, Research Governance

- International Steering Committee has no independent members
- Independent Data Monitoring Committee; Prof J Cuzick, Mrs H Thornton; Prof A Rodger

Cuzick, Lancet, 2014, 383:1716

Conclusions

- Randomised trials of partial breast RT need time to mature!
- IORT should not yet be offered as a standard of care