Primary Results of a Phase III RCT: Transdermal Oestradiol (tE2) versus LHRHa for Androgen Suppression in Locally Advanced Prostate Cancer

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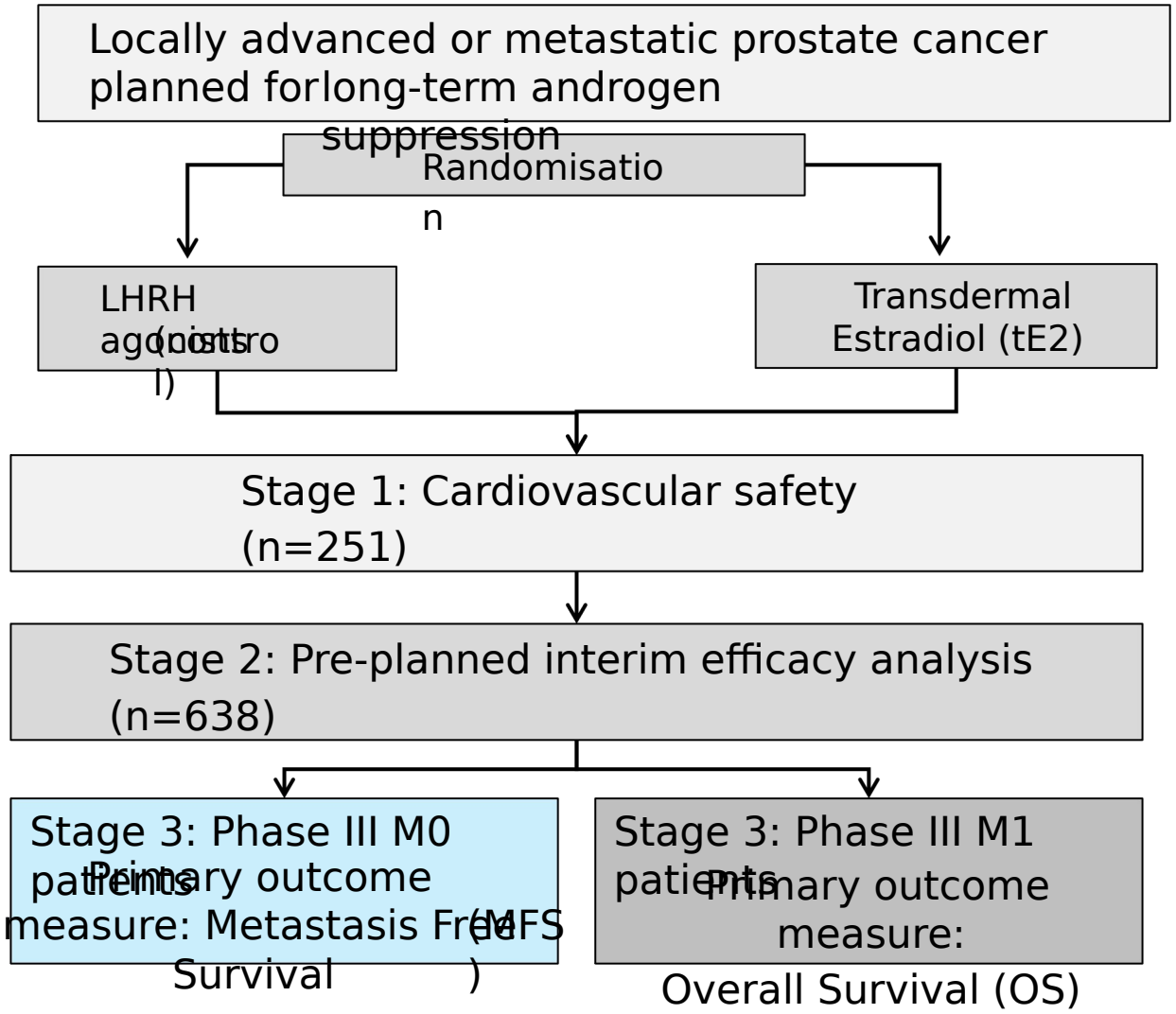
Randomised Phase 2/3 Adaptive Trials Programme

- Transdermal oestradiol (tE2) is an alternative to LHRHa
- Lowers testosterone without oestrogen depletion effects (osteoporosis, adverse effects and hot flushes)
- Transdermal approach (patch) avoids first-pass metabolic hepatic metabolism and thromboembolic toxicities



Open Label, Non inferiority, Phase III Randomised Trial

LHRHa versus transdermal oestradiol (tE2) patches

High risk locally advanced prostate cancer (M0) about to start androgen deprivation therapy (ADT)- included histologically confirmed newly diagnosed high-risk M0 (locally advanced or node-positive) prostate cancer or those relapsing with PSA ≥ 4 ng/ml and doubling in <6 months, PSA ≥ 20 ng/ml,or N positive.

Treatment included standard LHRH agonist versus
Patches release 100 mcg oestradiol/24 hours

- 4 patches changed twice weekly for ≥ 2 years
- when testosterone < 1.7nmol/L ;3 patches changed twice weekly

Prostate radiotherapy and docetaxel were permitted.

Primary Outcome

Metastasis-free survival (MFS) - randomization to confirmed metastases or death

- non-inferiority study - to rule out an absolute 4% detriment in 3-year MFS

- 85% power and 1-sided significance of 5% alpha

Secondary Outcome included

—

overall survival,
castration rates, and
toxicity.

Results – Baseline Characteristics

Between 2007-2022

1360 randomised from 75 UK sit

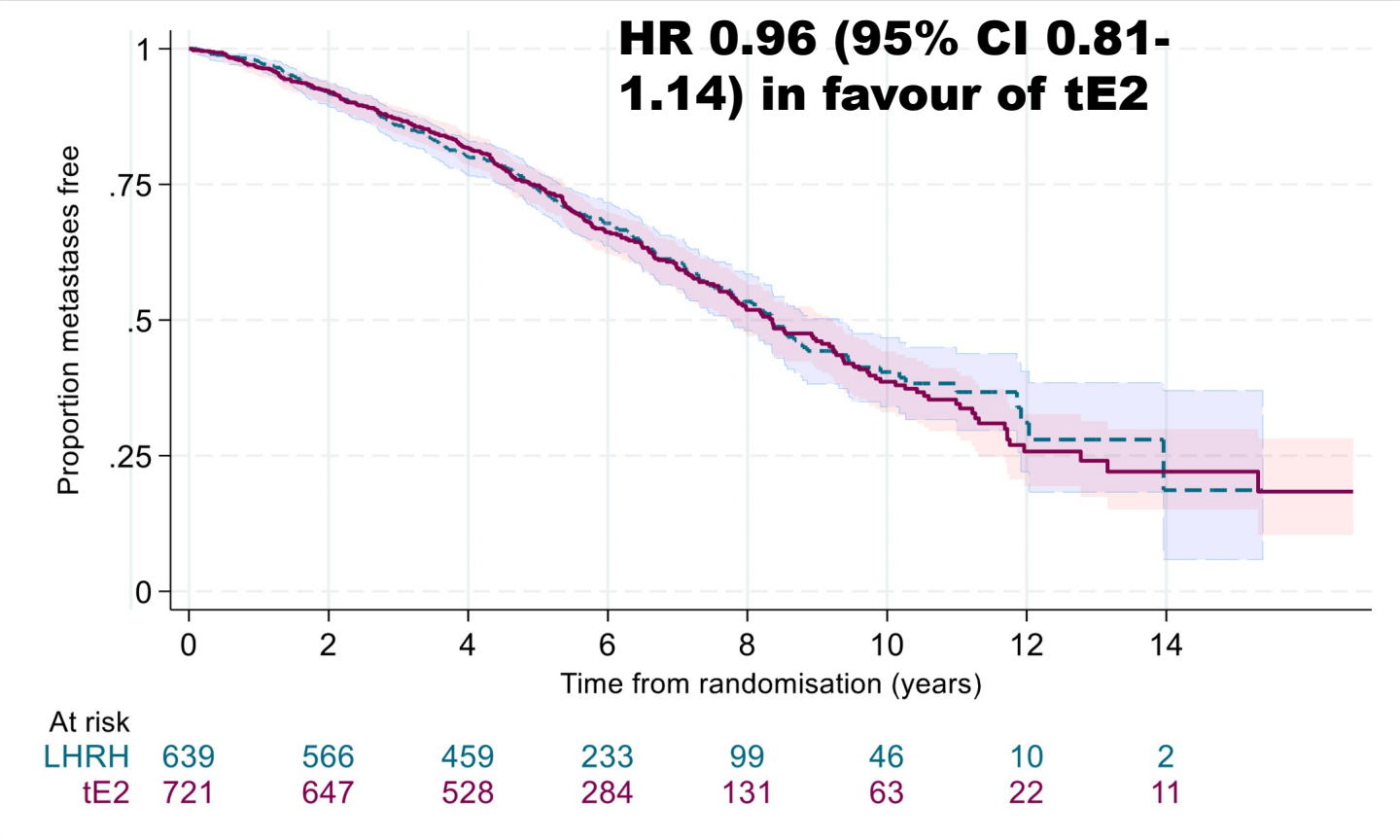
Baseline characteristics were well-balanced between randomized groups

		Treatment Arm					
		LHRHa N=639		tE2 N=721		Total N=1360	
		No.	%	No.	%	No.	%
Age	Median (IQR)	72 (67 – 77)		72 (68 – 77)		72 (68 – 77)	
	Range	50 - 89		46 - 90		46 - 90	
WHO PS	0	488	76%	544	75%	1,032	76%
	1	139	22%	154	21%	293	22%
	2	12	2%	23	3%	35	3%
PSA	Median (IQR)	23.8 (11.3 – 53.1)		25.2 (12.0 – 54.9)		24.4 (11.8 – 54.1)	
Gleason Sum Score	≤6	39	6%	39	5%	78	6%
	7	213	33%	253	35%	466	34%
	8-10	387	61%	423	59%	810	60%

Median age 72 years
Median PSA 24 ng/ml

85% T3 and 65% N0

Primary Outcome - Metastasis Free Survival (MFS)

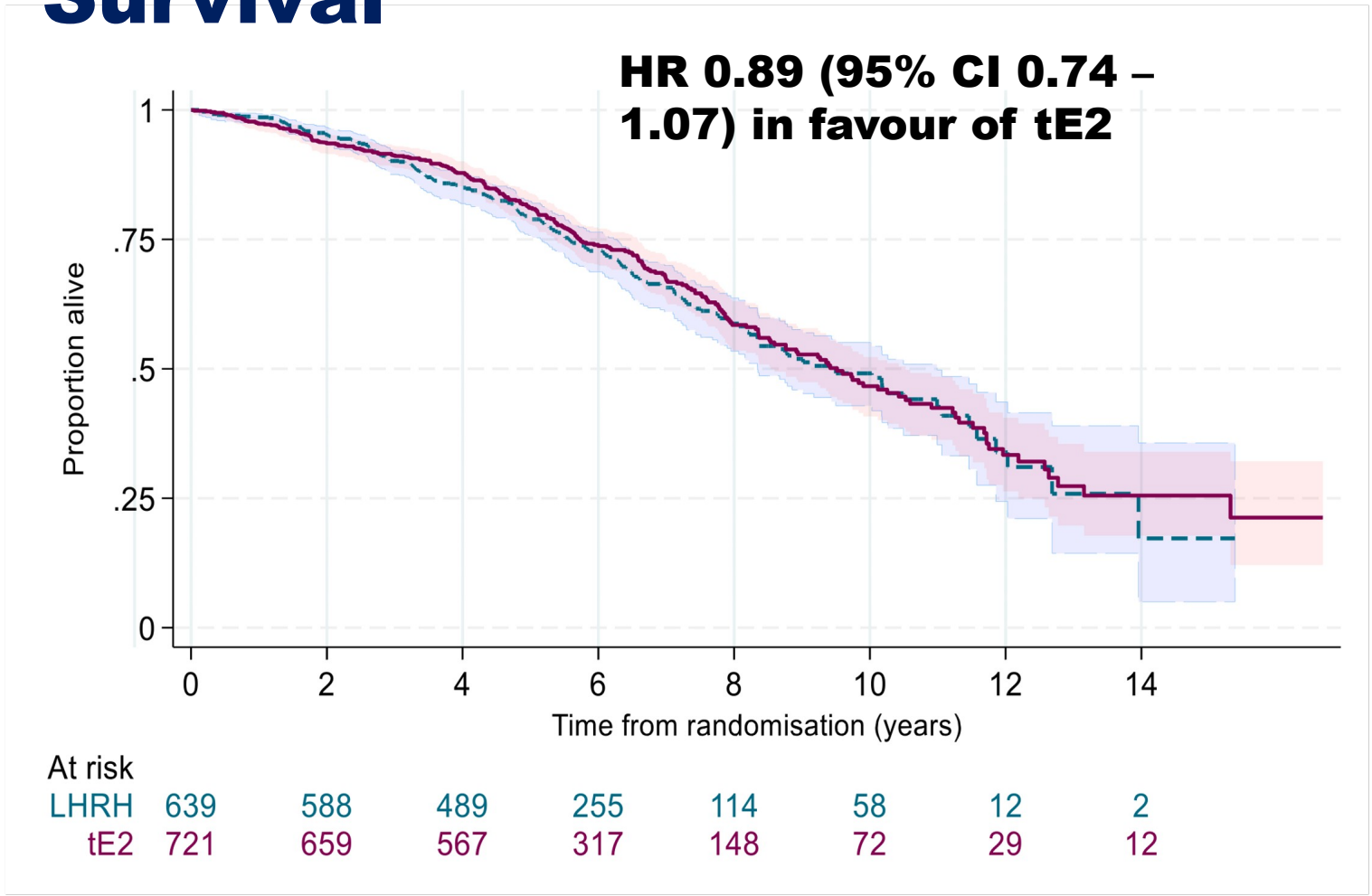


- **LHRHa 3-year MFS 87%** giving a target non-inferiority margin of 1.31
- **tE2 3-year MFS**
- **86%**

Non-inferiority demonstrated

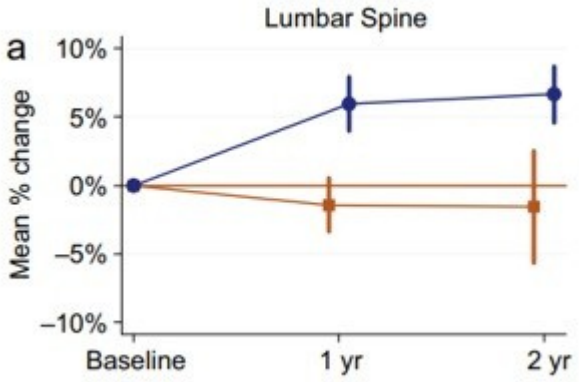
excluding a 2% difference in MFS

Secondary Outcome - Overall Survival



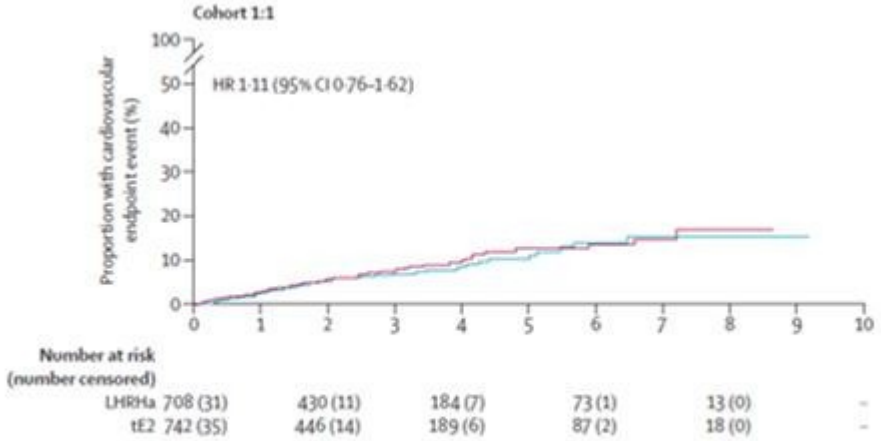
- Similar castration rates
  Hot flushes any grade LHRHa 89% v tE2 44%
- Gynaecomastia any grade LHRHa 42% v tE2 85%

Transdermal Oestradiol (tE2) v LHRHa Programme Results M0 and M1



Improved Bone Mineral Density[1]

●tE2 ▪ LHRHa



No excess cardiovascular toxicity[2]

Improve overall Quality of Life scores

Mean difference in 6-month overall score in favour of tE2 (p=0.006)[3]

+4·2 (1·2, 7·1)

1,
2

Conclusions

- Compared to LHRH agonists, transdermal estradiol lowers testosterone more rapidly, maintains bone mineral density, and improves metabolic outcomes and quality of life.
- Importantly, transdermal administration avoids the cardiovascular toxicity of oral estrogen.
- tE2 is **as effective** as LHRHa and there is no detriment in terms of prostate cancer outcomes or overall survival in starting androgen suppression with tE2
- tE2 provides **choice** about expected side-effects and route of administration allowing for personalised treatment plans
- tE2 should be a standard of care **ADT option** in M0

Thanks