

MEDCAC 2015

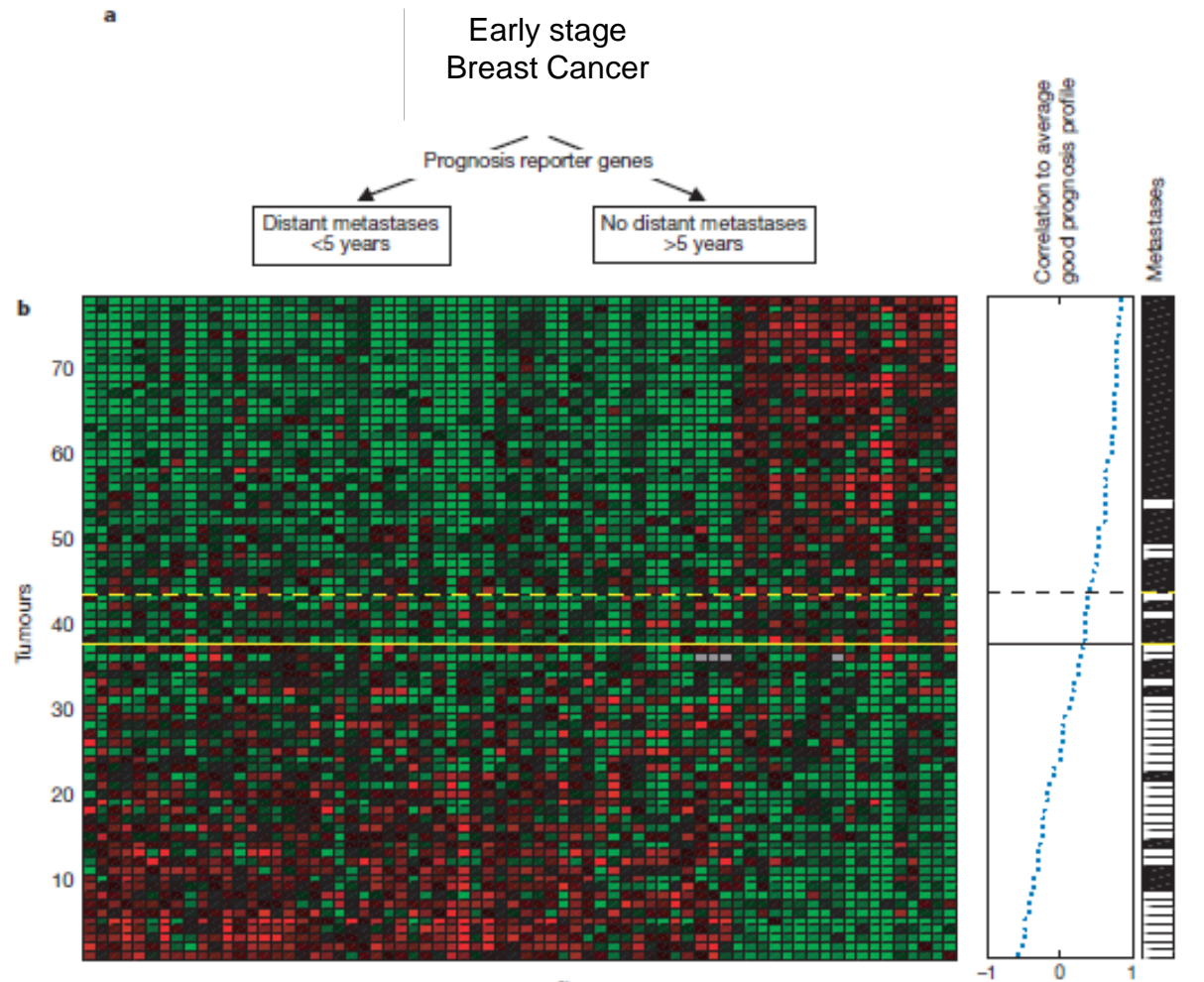
Analytical Validity, Clinical Validity and Clinical Utility MammaPrint

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Disclosures

- Employee of Agendia

MammaPrint developed to protect over treatment of patients



Analytical and Clinical Performance

Performance Characteristic	Definition	MammaPrint Performance
Accuracy	Closeness of agreement between a test result and an accepted reference value. if compared to gold standard (e.g. MammaPrint FDA cleared version) then NPA/PPA if compared to clinical parameter then use NPV/PPV	See NPA/PPA or NPV/PPV
Sensitivity	The fraction of patients that are High Risk by MammaPrint among those that did develop a metastases within 5 or death within 10 years	5 yrs: 0.90 (0.78 – 0.95) 10 yrs: 0.84 (0.73 – 0.92)
Specificity	The fraction of patients that are Low Risk by MammaPrint among those that did not develop metastases within 5 or 10 years	5 yrs: 0.42 (0.36 – 0.48) 10 yrs: 0.42 (0.36 – 0.49)
Positive Predictive Value (PPV)	The proportion of High Risk patients that did develop a metastases	5 yrs: 0.22 (0.16-0.28) 10 yrs: 0.29 (0.22-0.35)
Negative Predictive Values (NPV)	The proportion of patients that are classified as Low Risk and did not develop a metastases	5 yrs: 0.95 (0.91-0.99) 10 yrs: 0.90 (0.85-0.96)
DMFS 5 years	Distant Metastases free survival at 5 years	Low Risk: 0.95 (0.91 - 0.99) High Risk: 0.78 (0.72 - 0.84)
DMFS 10 years	Distant Metastases free survival at 10 years	Low Risk: 0.90 (0.85-0.96) High Risk: 0.71 (0.65-0.78)
Repeatability	Closeness of agreement between results of successive measurements of the same sample (same operators/batches) according to EP5-A2	Median stdev =0.02 Relative precision: 99.0%
Precision	Closeness of agreement between results of successive measurements of the same sample (different operators/batches) according to EP5-A2	Median stdev =0.021 Relative precision: 99.0%
Reproducibility	Closeness of agreement between results of measurements of the same sample (control sample) carried out under changed conditions	Median stdev= 0.023 Reproducibility: 98.9%
Reproducibility (index based)	Site to site reproducibility	99.5%
Reproducibility (outcome based)	NPA reflects the proportion of non-reference standard to whom the new version of MammaPrint indicates Low Risk PPA reflects the proportion of non-reference standard to whom the new version of MammaPrint indicates High Risk	NPA=98.3% PPA=100%
LOD	Limit of detection, lowest amount of analyte in a sample that can be distinguished from the background of negative control	2log(intensity)= 5.8

MammaPrint's Prognostic Accuracy

Performance of MammaPrint in Fresh and FFPE tissue in the Raster Trial

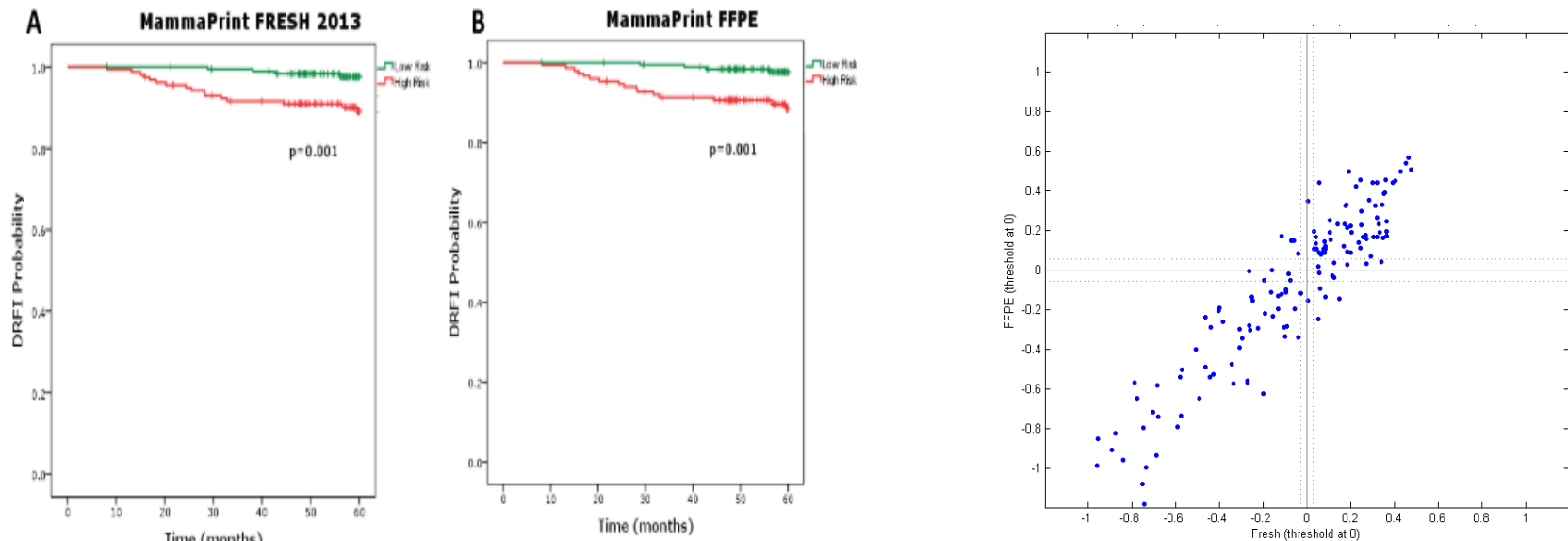


Figure 5.1: Kaplan-Meier analysis of the 5 year DRFI probability among 345 patients with LN0 breast cancer that were part of the Raster study for **A)** MammaPrint Fresh and **B)** MammaPrint FFPE

MammaPrint Analytical and Clinical Validity

Externally confirmed in 6 FDA clearances

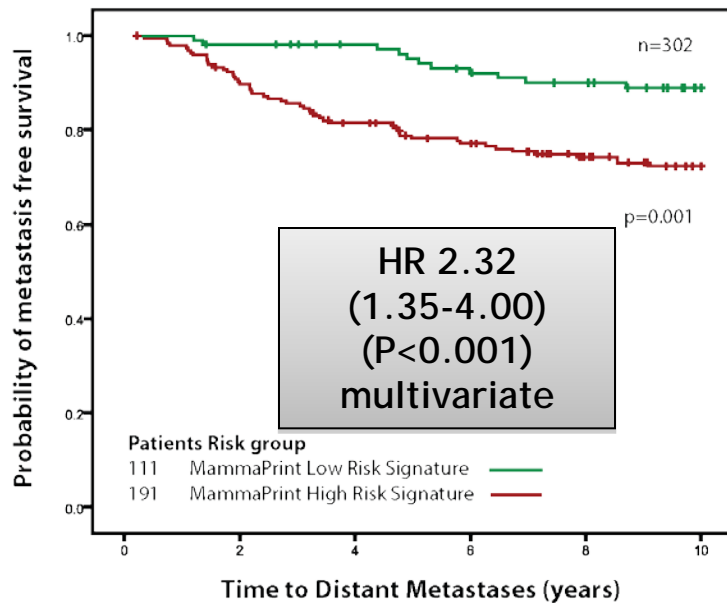
Clearance	Year	Clearance
MammaPrint Fresh Frozen	2007	K062694
MammaPrint Ambient Temperature	2007	K70675
Use of High Density Microarray Chip	2008	K08252
MammaPrint in post menopausal women	2009	K81092
MammaPrint in all Agendia controlled Laboratories	2011	K101454
MammaPrint in Formalin Fixed Paraffin Embedded Tissue	2015	K141142

2007 DE Novo 510K

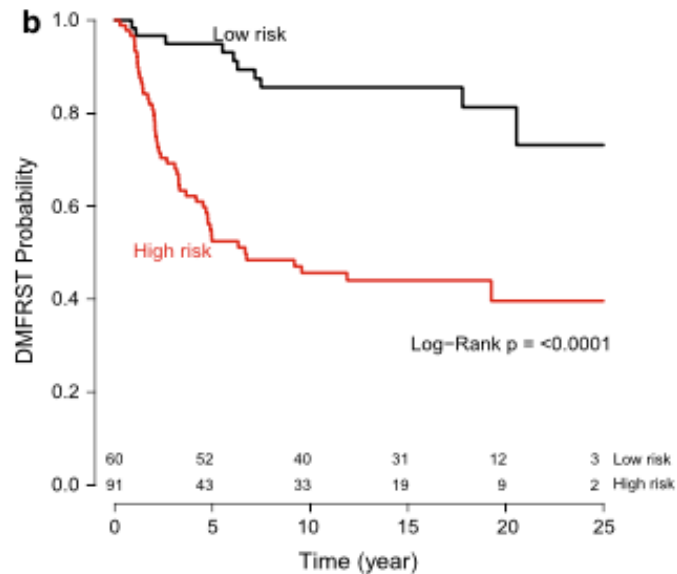
MammaPrint is the predicate devices for future multi gene assays for breast cancer prognosis FDA clearances



DMFS rates for Low and High Risk patients at 10 and 25 years



Buyse et al (2006) JNCI



Drukker et al (2014) BrCResTR



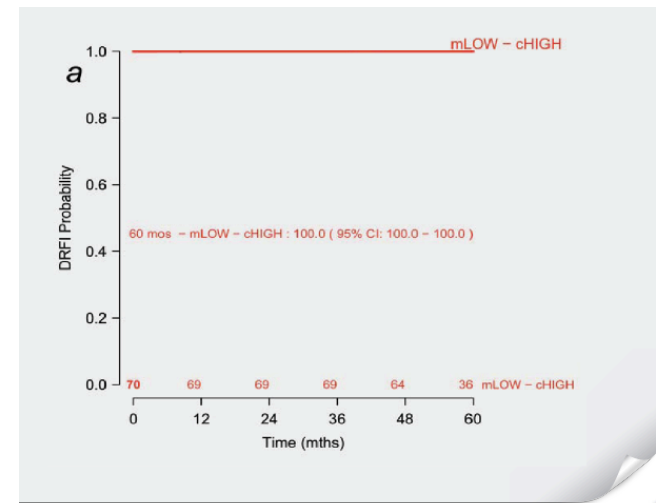
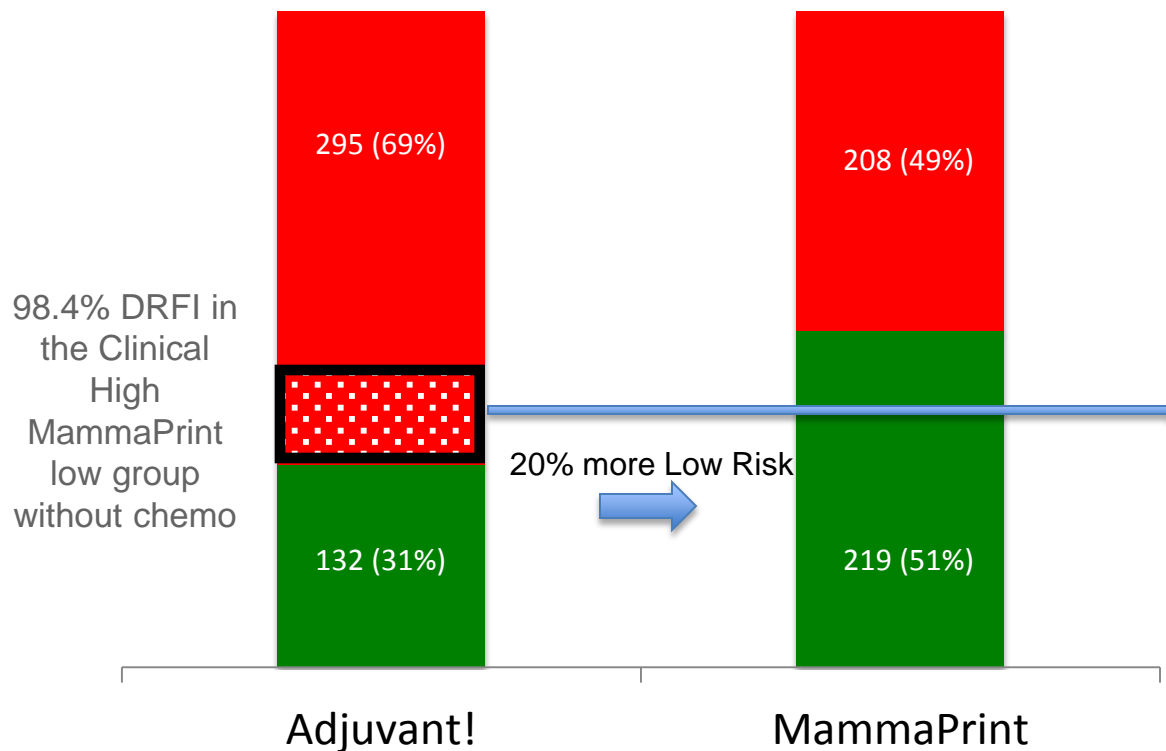
agendia®

decoding cancer.

RASTER TRIAL 5 year Outcome

Influence health outcome; No Harm

No harm, same effect at lower cost

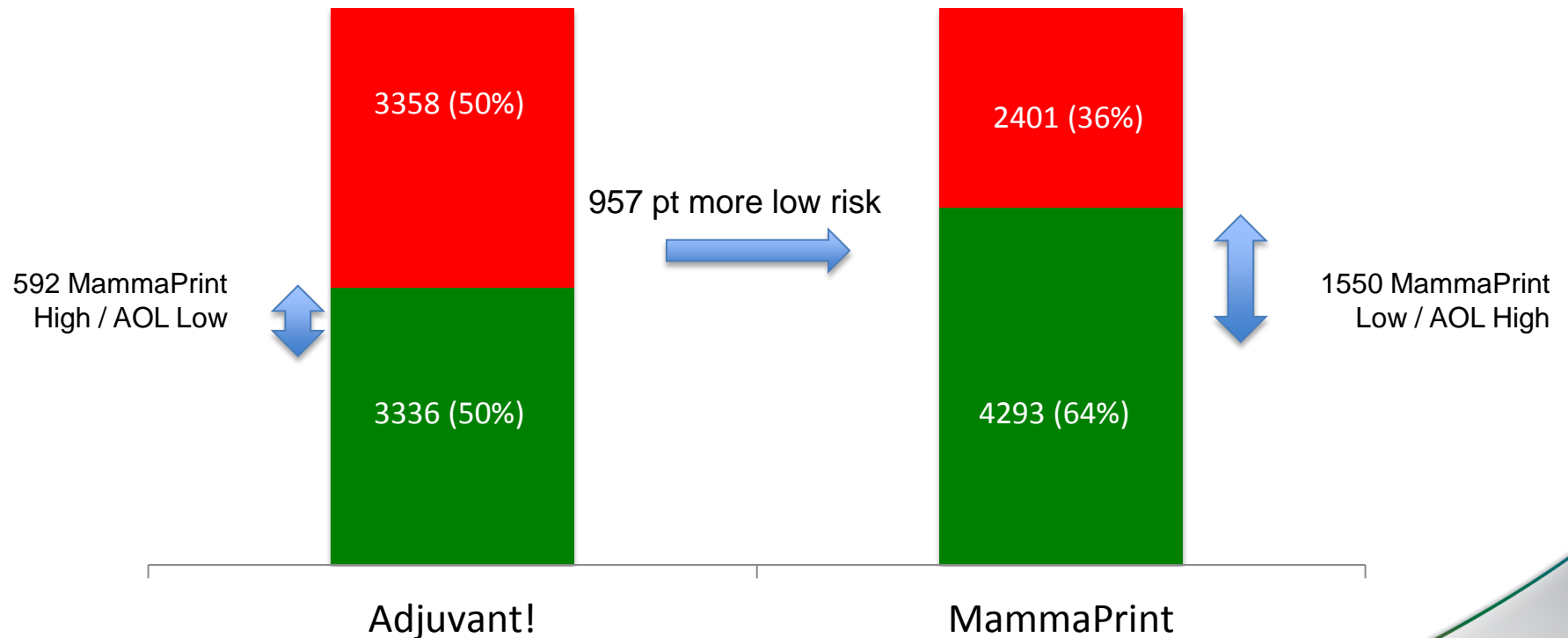


No AST, 100% survival

38% Discordance between MammaPrint and Clinical risk assessment

Influence health outcome

Discordance between Clinical Risk assessment and MammaPrint in MINDACT N = 6694



32% Discordance between MammaPrint and Clinical risk assessment

Discussion: Genomic Variations

- Agreement between two different samples of the same tissue 95%¹
- Agreement between two assays using the same mRNA is 99%¹
- MammaPrint validated in different ethnicities
 - MammaPrint validated in Japanese cohort²
 - MammaPrint investigated in African American Cohort³
 - MammaPrint investigated in Metabolic Syndrome⁴

1. Delahaye et al 2013
2. Ishitobi et al 2010
3. Nunes ASCO 2013
4. Robinson SABCS 2014

Discussion: FDA vs. CLIA

Unlike FDA oversight of diagnostics, CLIA:

- Does not regulate the safety and effectiveness of diagnostic tests
- Does not require pre-market review of tests;
- Does not require demonstration of clinical validity;
- Does not require systematic adverse event reporting; and
- Does not have a process for corrections or recalls.

Appendix 1

MammaPrint key validation studies

MammaPrint Studies	Validation	Details	Results/Comments
Van de Vijver et al, (2002) NEJM;347,1999-2009	First validation in consecutive series*	295 patients 151 patients LN-, 5% adj treatment, 7.3 yrs follow-up	10 year DMFS: Low Risk: 87% High Risk: 44%
Buyse et al, (2006) JNCI;17,1183-1192	Independent validation	302 patients no adj treatment 13.6 yrs follow-up	10 year DMFS: Low Risk: 88% High Risk: 71%
Wittner et al. (2008) CCR;14, 2988-2993	Validation in US patients*	100 patients 45% adj treatment 11.3 yrs follow-up	10 year DMFS: Low Risk: 100% High Risk: 90%
Mook et al, (2009) BrCResTr;116(2):295-302	LN+ patients (1-3)	241 patients 91% adj treatment 7.8 yrs follow-up	10 year DMFS: Low Risk: 91% High Risk: 76%
Mook et al. (2010) Ann Onc;21(4):717-722	Postmenopausal (>55-70 yrs)	148 patients 18% adj treatment 11.6 yrs follow-up	10 year DMFS: Low Risk: 81% High Risk: 68%
Ishitobi et al (2010) Jpn JCO;40(6):508-512	Japanese patients*	102 patients 92% adj treatment 7.1 yrs follow-up	5 year DMFS: Low Risk: 100% High Risk: 94%
Mook et al. (2010) Ann Surg Onc; 17(5):1406-13	T1 tumors	964 patients Pooled analysis 7.1 yrs follow-up	10 year DMFS: Low Risk: 87% High Risk: 72%
Knauer et al. (2010) Br J Cancer;103(12):1788-1793	HER2+ tumors	168 patients Pooled analysis 5.4 yrs follow-up	10 year DMFS: Low Risk: 89% High Risk: 64%
Knauer et al (2010) BrCResTr;120(2):655-661	Benefit of Chemotherapy	541 patients 42% adjuvant chemotherapy 51% LN+	MammaPrint BCSS at 5 years Low ET only 97% Low ET+CT 99% High ET only 81% High ET + CT 94%
Drukker et al (2013) A Int J Cancer 133(4):929-36.	LN- patients < 61 5 year prospective outcome	427 patients 5 years follow up High risk 81% chemotherapy Low risk 15% chemotherapy	DRFI by MammaPrint at 5 year Low Risk: 97% High Risk: 91.2%
Drukker et al (2014) BrCResTr:143(3):587-92	25 years follow up	295 patients 151 patients LN-, 5% adj treatment, 25 yrs follow-up	Hazard Ratio at 25 years 4.75