Evolutionary Patterns of microRNA expression through the Course of Disease and Treatment in Recurrent Breast Cancer

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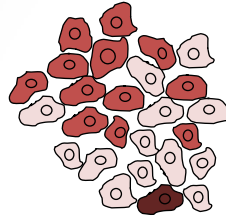**Tel-Hashomer, Ramat Gan, ISRAEL**

Disclosure
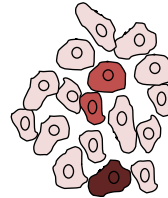
Nothing to declare

Longitudinal approach to identify significant molecular signatures for breast cancer progression

Primary tumor — Treatment → Residual tumor — Recurrence
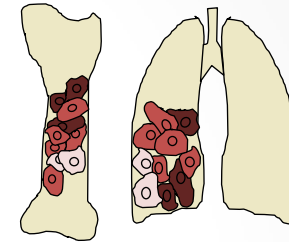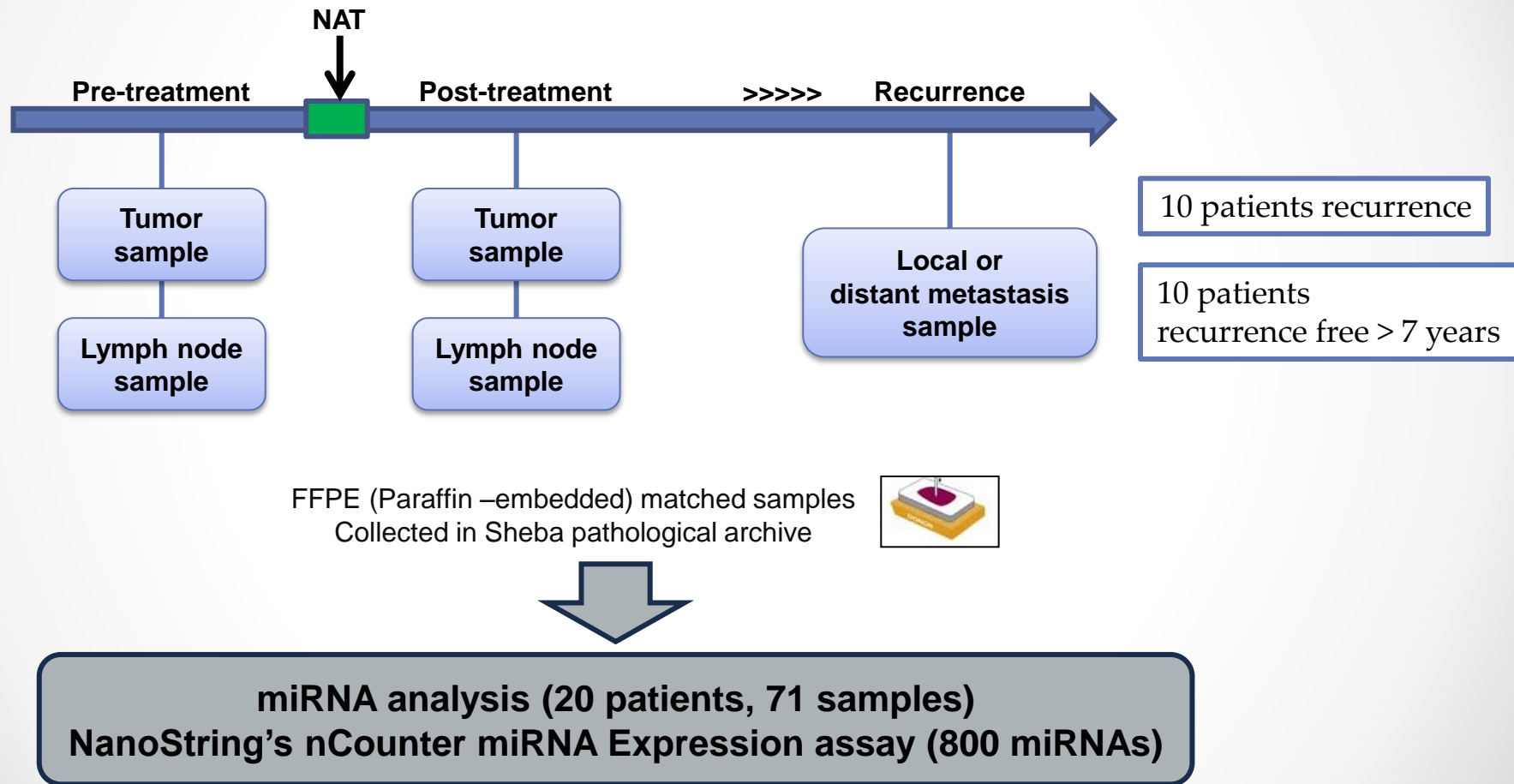
Hypothesis: Expression modulations in **individual** patients through their course of disease can identify informative prognostic signature

Can we identify miRNAs expression **patterns** that correlate with disease progression ?

Study Design

Tumor sampling through the course of disease in individual patients who underwent pre-operative neo-adjuvant therapy (NAT)

NAT

Pre-treatment   **Post-treatment**   **>>>>>**   **Recurrence**

Tumor sample   **Tumor sample**   **Local or distant metastasis sample**

Lymph node sample   **Lymph node sample**

10 patients recurrence

10 patients recurrence free > 7 years

FFPE (Paraffin –embedded) matched samples
Collected in Sheba pathological archive

miRNA analysis (20 patients, 71 samples)
NanoString's nCounter miRNA Expression assay (800 miRNAs)

Patients' clinical and pathologic characteristics

	Cohort 1 (Recurrent disease) N=10	Cohort 2 (Disease Free) N=10
Mean Age (Range) years	53 (40-69)	51 (40-67)
Subtype (N,%)		
Hormone Positive	5 (50)	6 (60)
Triple negative	2 (20)	
HER2+\hormone negative	1 (10)	
HER2+\hormone positive	2 (20)	4 (40)
Treatment regimen (N,%)		
AC-T	9 (90)	10 (100)
AC-TH	1 (10)	
Pathological Response (N, %)		
CR	2 (20)	1 (10)
PR	7 (70)	8 (80)
SD	1 (10)	1 (10)
Median RFS (range) years	2.5 (1-6)	NA *

* Median follow up time, 9 (8-10) years

Identify expression patterns through the course of disease

Pre-treatment   Post-treatment   Recurrence

miRs above threshold (~200)

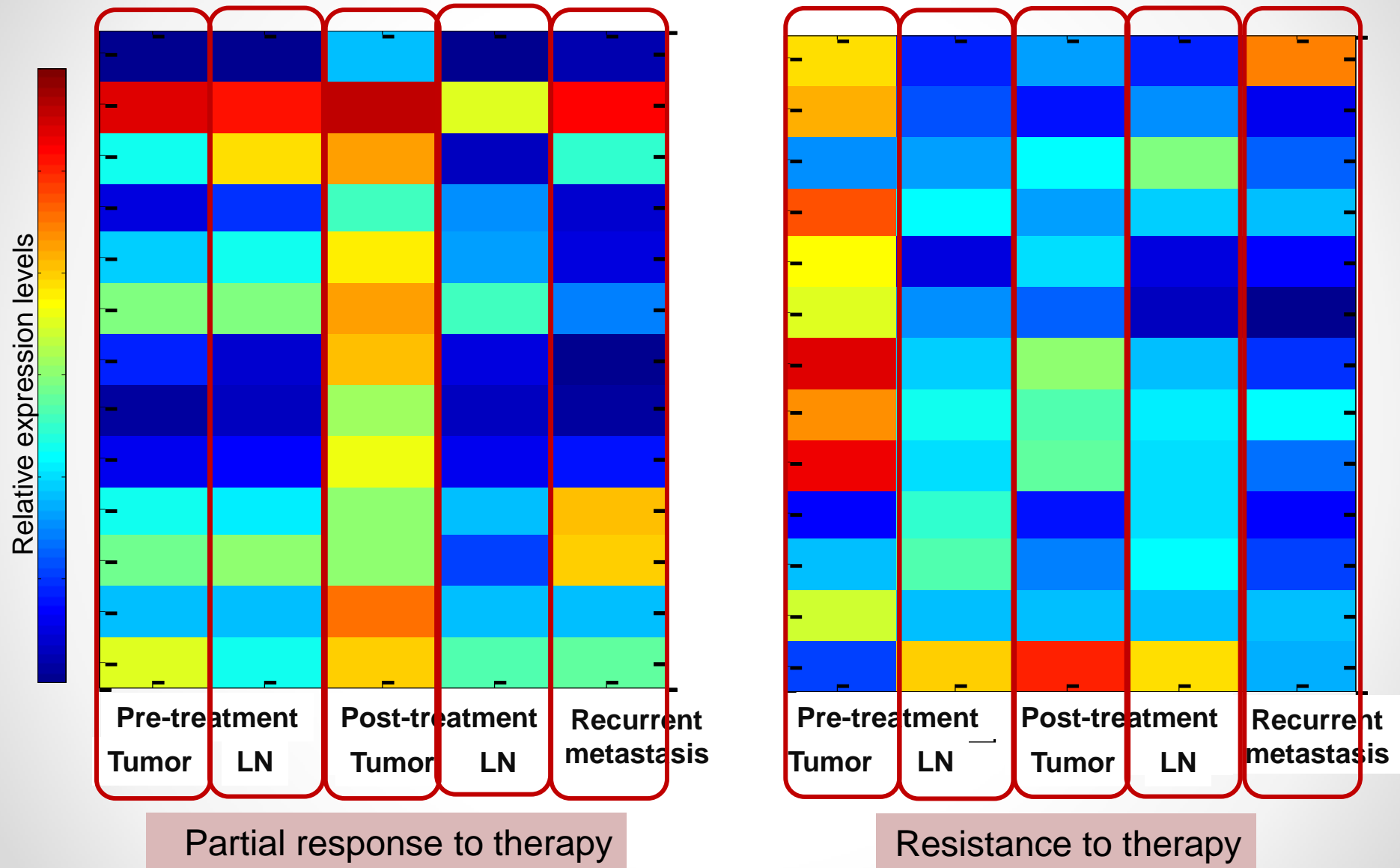Expression pattern

miRNAs clustered according to their temporal patterns

Pre-treatment   Post-treatment   Recurrence

Possible patterns of expression modulations

Identify significant miRNAs in a given pattern

miRNAs that show similar pattern in several patients

Modulation of at least 1.5 fold	Shared by at least 3 patients

hsa-miR-125b

21 miRs

Enrichment in breast cancer expression databases

miRNA expression dataset (Caldas, Dvinge et al)Nature 2013	Target enrichment

13 miRs

Identify a significant set of miRNAs

significantly down-regulated in breast cancer	Significantly enriched for cell cycle pathway

Individual patient's profile in the identified miRNA set correlates with disease progression

Relative expression levels

Pre-treatment Tumor | LN | Post-treatment Tumor | LN | Recurrent metastasis

Partial response to therapy

Pre-treatment Tumor | LN | Post-treatment Tumor | LN | Recurrent metastasis

Resistance to therapy

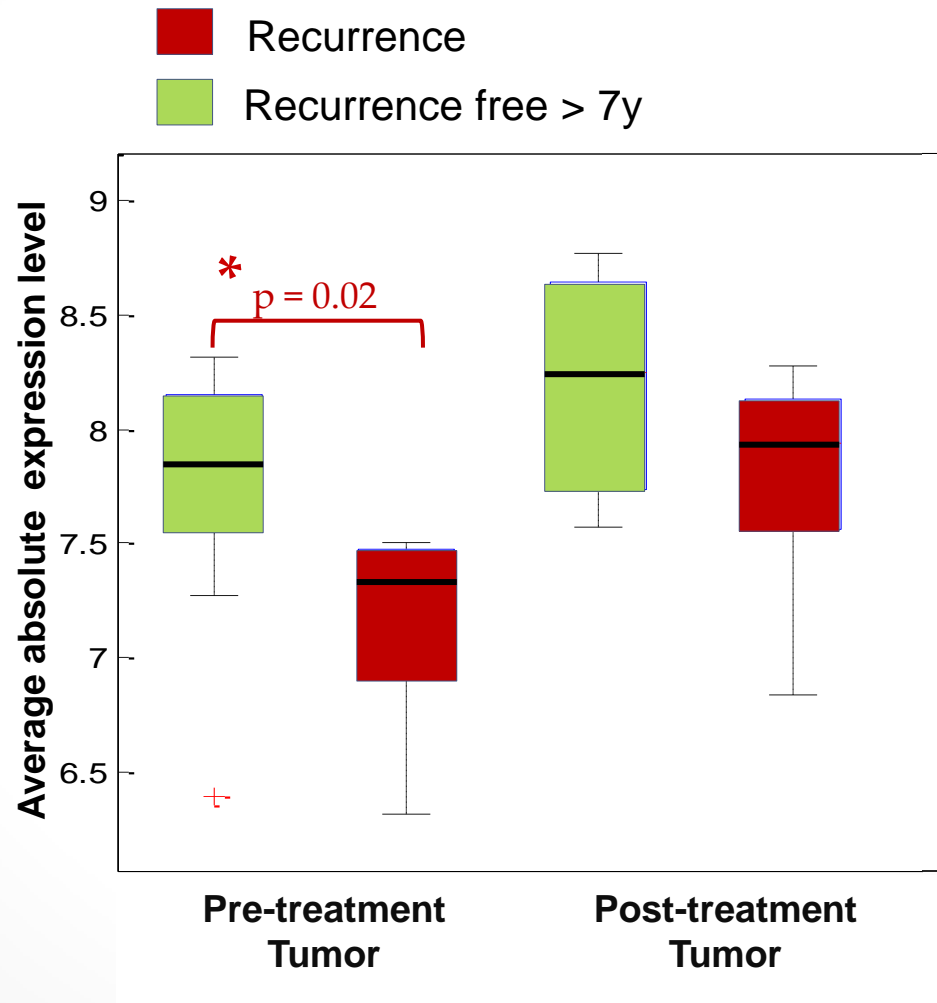# Expression levels for the miRNAs set in all patients

Expression profile of tumors post-treatment was significantly higher than pre-treatment

Expression profile of recurrent sample was significantly lower than all samples

Expression profile of lymph nodes was not significantly different before and after treatment

The identified miRNAs set profile differs between patients having recurrence and recurrence free patients

Conclusions

- **Longitudinal analysis of expression patterns in individual patients can identify informative set of miRNAs that modulate throughout the course of disease**

- **The expression pattern of the identified miRNAs set correlates with disease progression and with response to therapy in each individual patient**

- **The average expression of the identified miRNAs set correlates with disease free survival and may have prognostic value.**

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