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& ONCOLOGY
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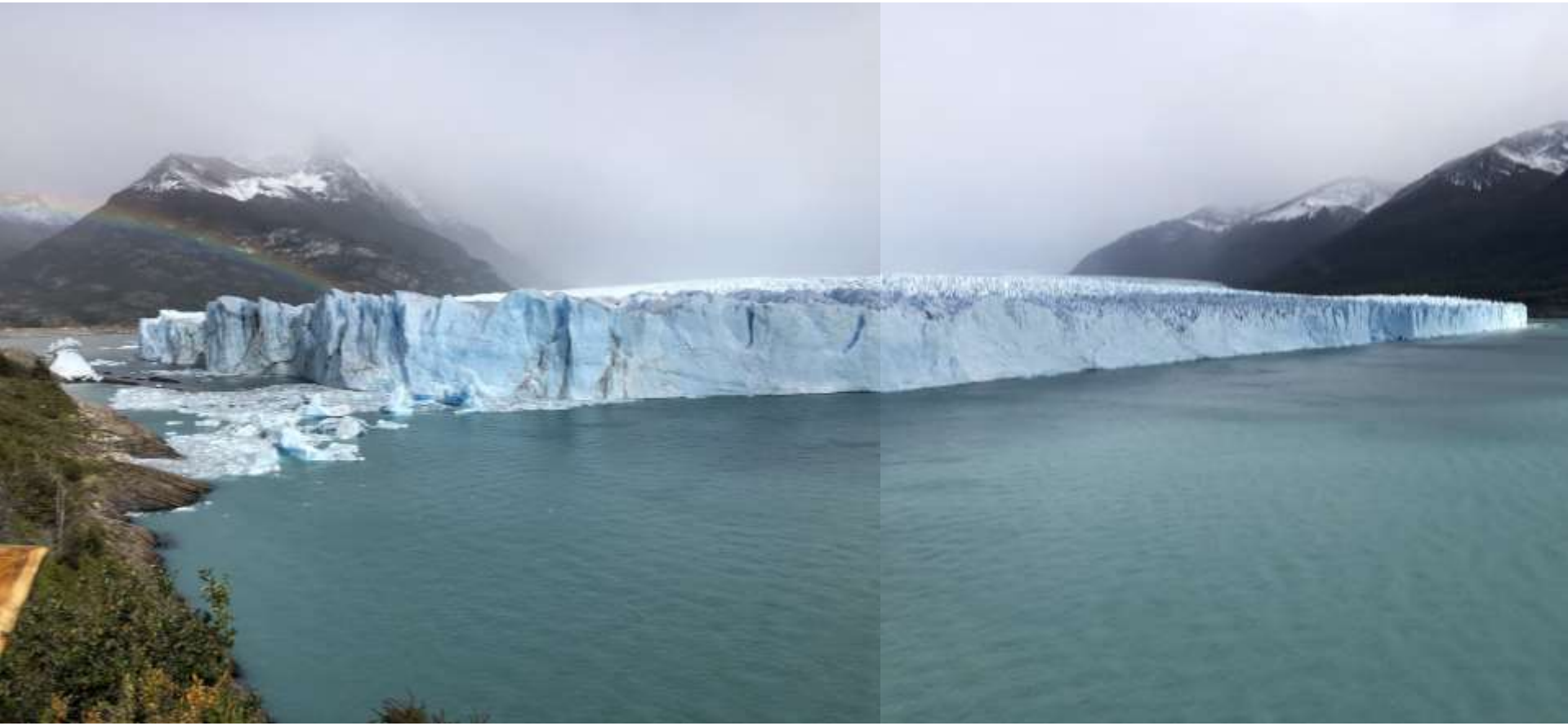
El Perito Moreno



Parque nacional de los glaciares

El 4 de abril 2019

3° Taller Internacional Multidisciplinario de Cáncer de Mama

&

1° Simposio de Cáncer Ginecológico

&

1° Taller de Planificación y Control de Calidad para Radiocirugía

"De la práctica a las bases teóricas"

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Debería el perfil molecular influenciar el tratamiento locoregional?

No tengo ningún conflicto de interés.

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Molecular subtyping & locoregional treatment

1. Introduction

2. Molecular subtyping & & locoregional treatment

3. Discussion

4. Conclusions

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3° Taller Internacional Multidisciplinario de Cáncer de Mama

&

1° Simposio de Cáncer Ginecológico

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1° Taller de Planificación y Control de Calidad para Radiocirugía

"De la práctica a las bases teóricas"

Vienen escucharme mañana!

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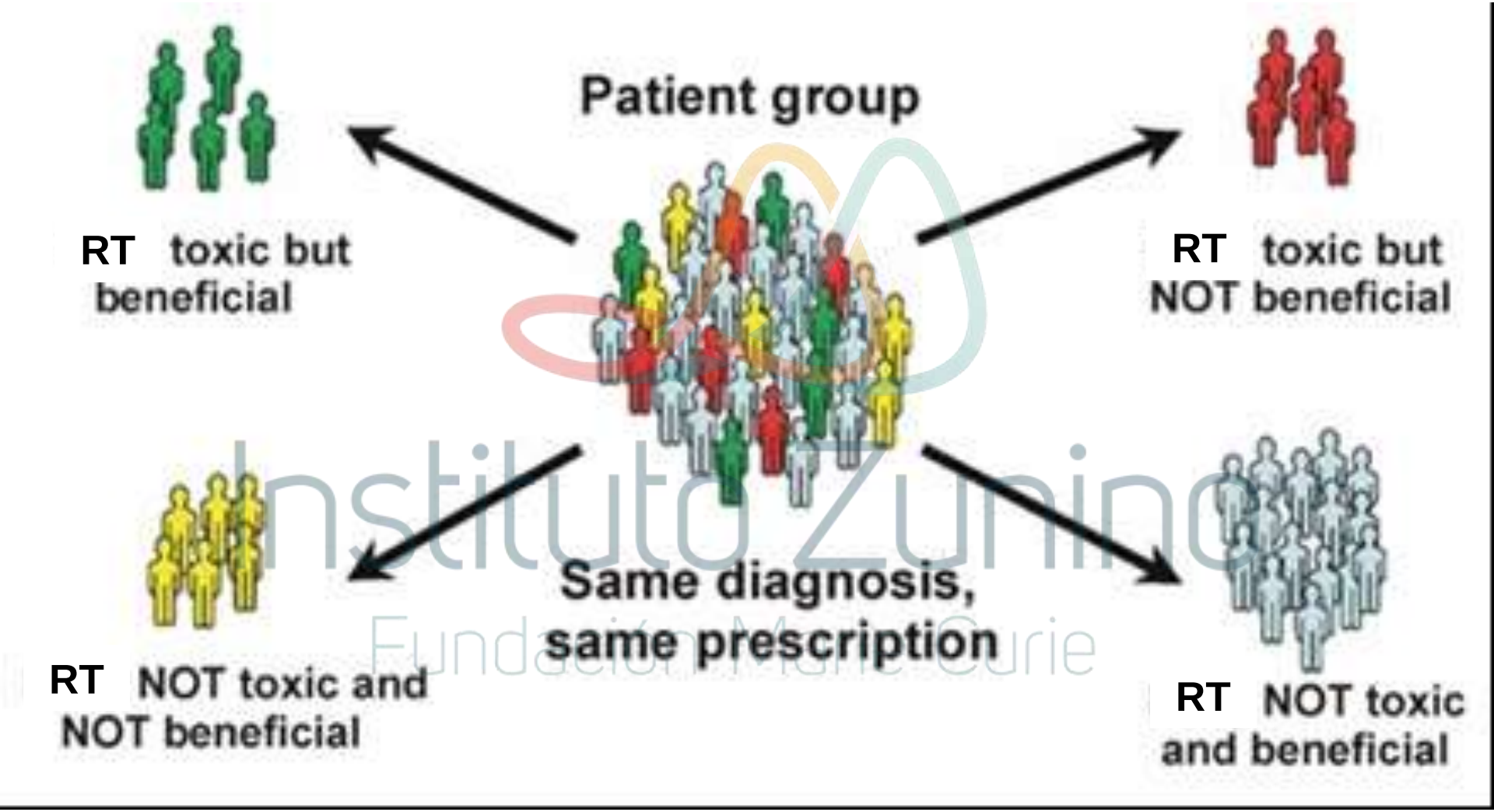
El manejo de los ganglios axilares: Una batalla entre la cirugía y la radioterapia?

Molecular subtypes & locoregional ttm: *Introduction*



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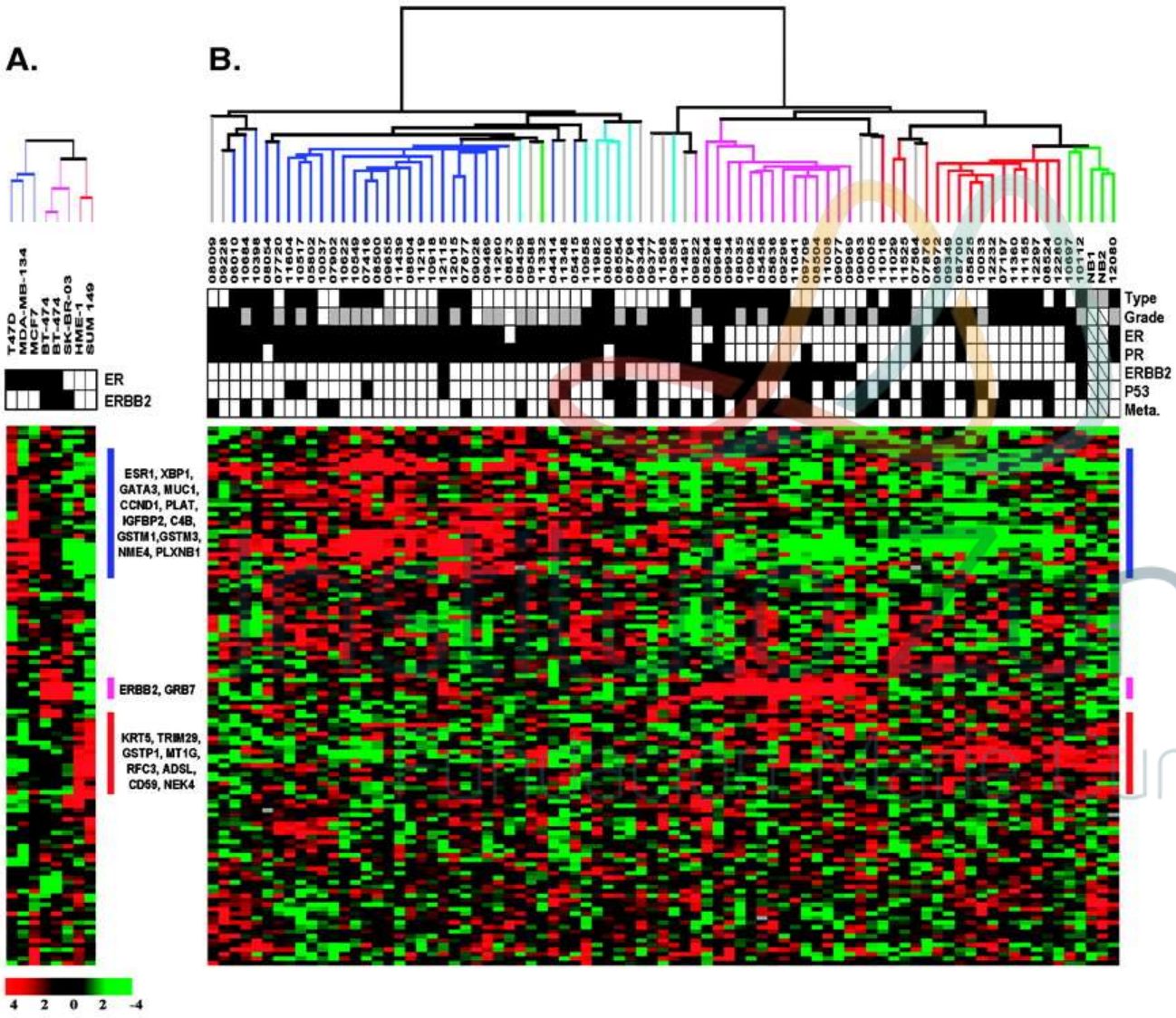
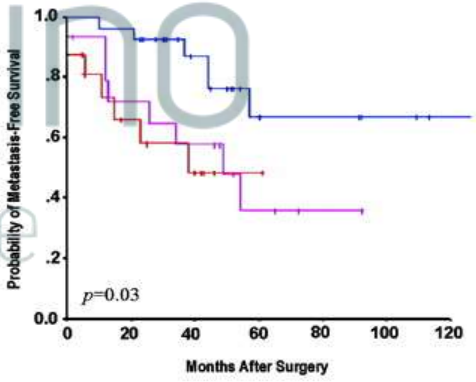
Molecular subtypes & locoregional ttm: *Introduction*



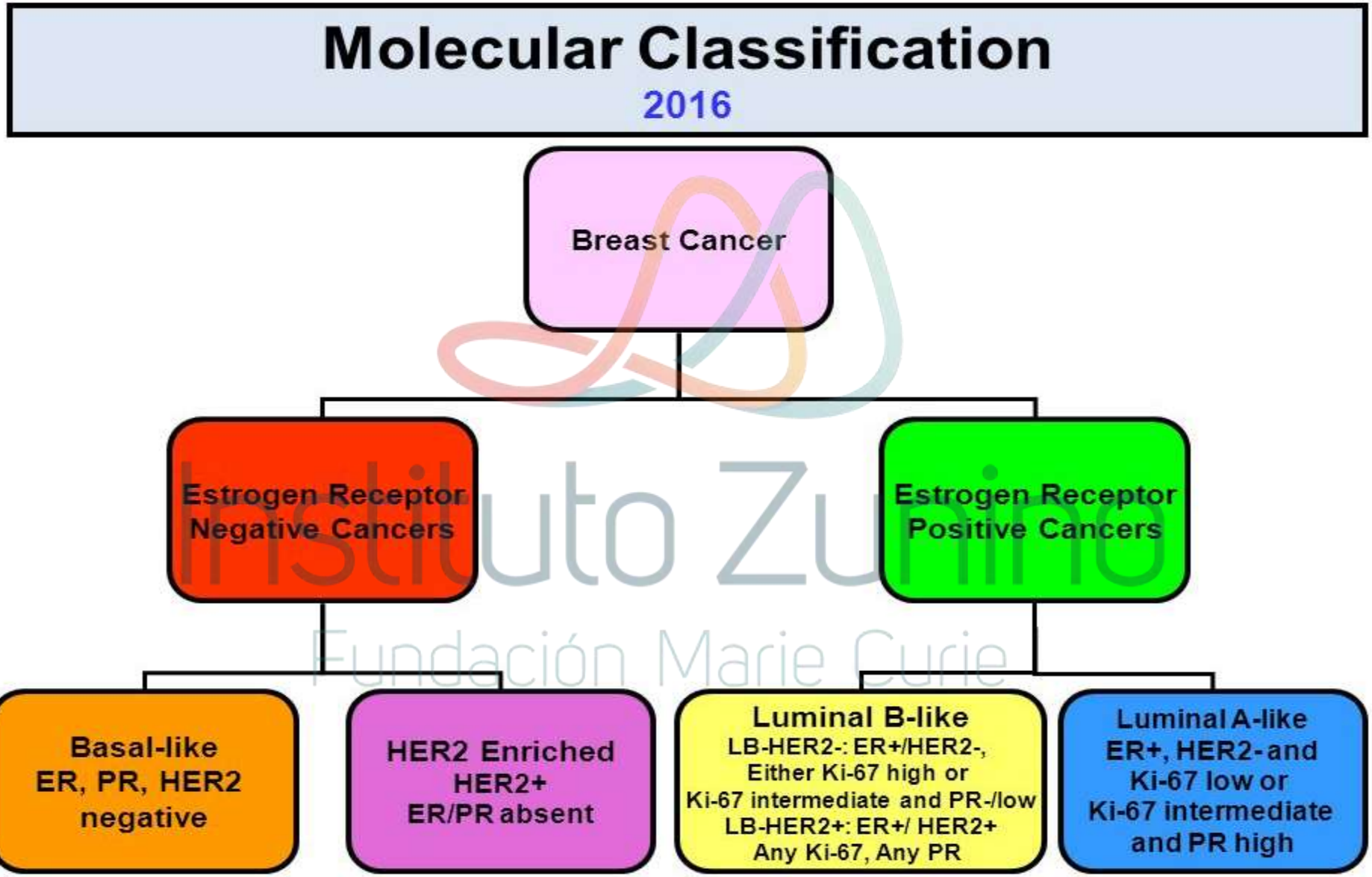
C.

	Luminal A	Luminal B	ERBB2+	Basal	Normal breast-like	NA
NIBC	12	4	6	8	2	12
ER pos (%)	100	100	0	12.5	100	83.3
PR pos (%)	100	100	16.7	12.5	100	100
ERBB2 pos (%)	0	50	100	0	0	8.3
IBC	14	3	9	8	2	1
ER pos (%)	100	100	11.1	0	100	0
PR pos (%)	92.9	66.7	22.2	0	100	0
ERBB2 pos (%)	7.1	0	100	0	50	0

D.



Molecular subtypes & locoregional ttm: *Introduction*



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Molecular subtyping & locoregional treatment

1. Introduction
2. Molecular subtyping & & locoregional treatment
3. Discussion
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Molecular subtypes & locoregional ttm: *Early experience*

Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials☆

Marie Overgaard[a,*], Hanne M. Nielsen[a,b], Jens Overgaard[b]

Parameter	1–3 pos. nodes	4+ pos. nodes
Endpoint: loco-regional recurrence		
Relative risk reduction	87%	82%
Absolute risk reduction	20%	24%
Number of patients needed to treat to avoid an LRR	5	4
Endpoint: death		
Relative risk reduction	17%	11%
Absolute risk reduction	9%	10%
Number of patients needed to treat to avoid a death	11	10

ABSOLUTELY IDENTICAL!

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A bright future for radiotherapy in breast cancer

Editorial

Philip Poortmans*

Molecular subtypes & locoregional ttm: *Early experience*

High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: A subgroup analysis of DBCG 82 b&c ☆

Marianne Kyndi [a,b,*], Marie Overgaard [c], Hanne M. Nielsen [a], Flemming B. Sørensen [b], Helle Knudsen [d], Jens Overgaard [a]

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Molecular subtypes & locoregional ttm: *Early experience*

DBCG 82 b&c

1982 – 1990 n = 3083

Either: pN+

T3-T4

Invasion of the pectoral fascia

Al,l patients received CMF or Tamoxifen

MRM ® ± RT

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Molecular subtypes & locoregional ttm: *Early experience*

DBCG 82 b&c

5 favourable criteria:

≤ 3 N+ ≤ 2 cm T G1
ER + Her-2-neu –

➔ *Low risk = ≥ 4/5 favourable criteria*

3 unfavourable criteria:

> 3 N+ > 5 cm T G3

➔ *High risk = ≥ 2/3 unfavourable criteria*

➔ *Intermediate risk = all others*

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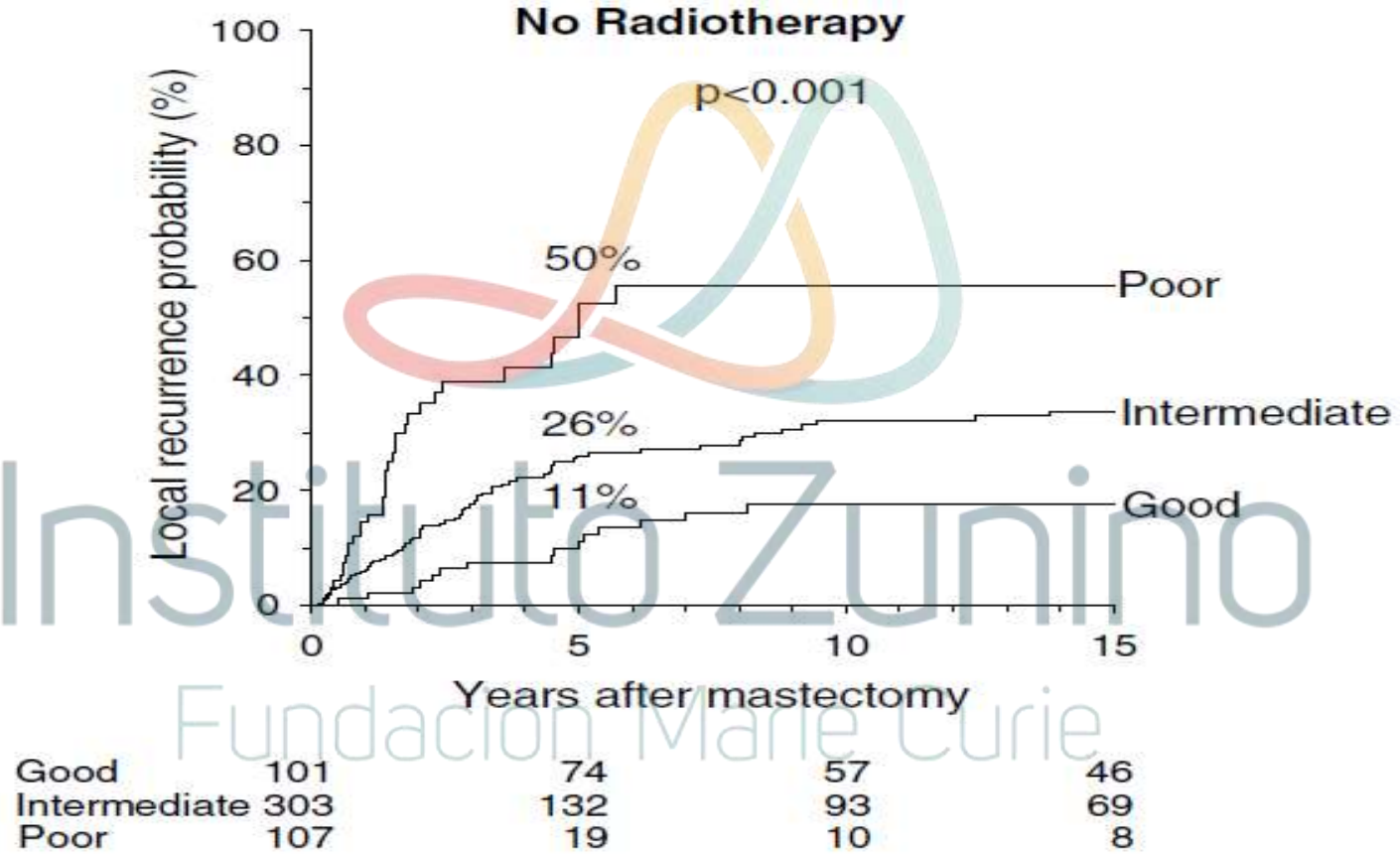
Molecular subtypes & locoregional ttm: *Early experience*



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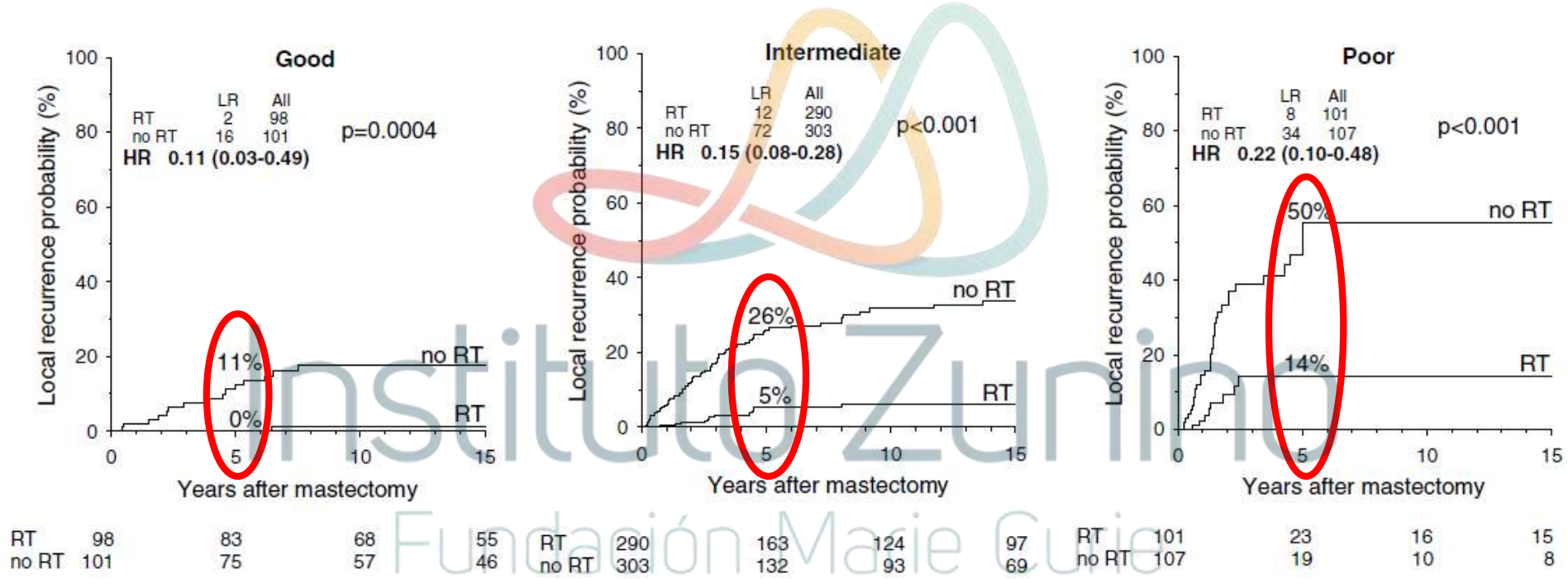
Molecular subtypes & locoregional ttm: *Early experience*

LRR



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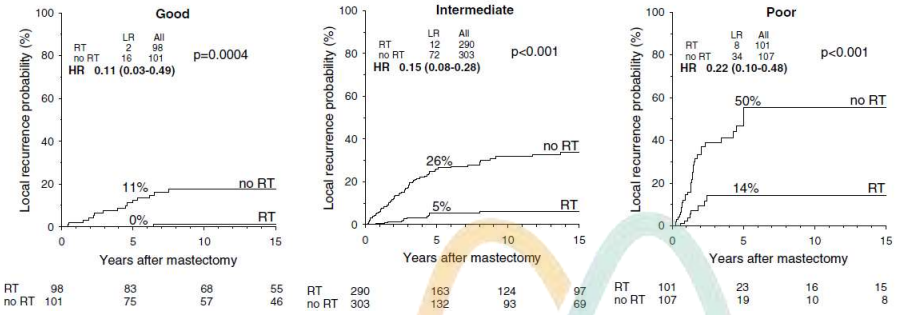
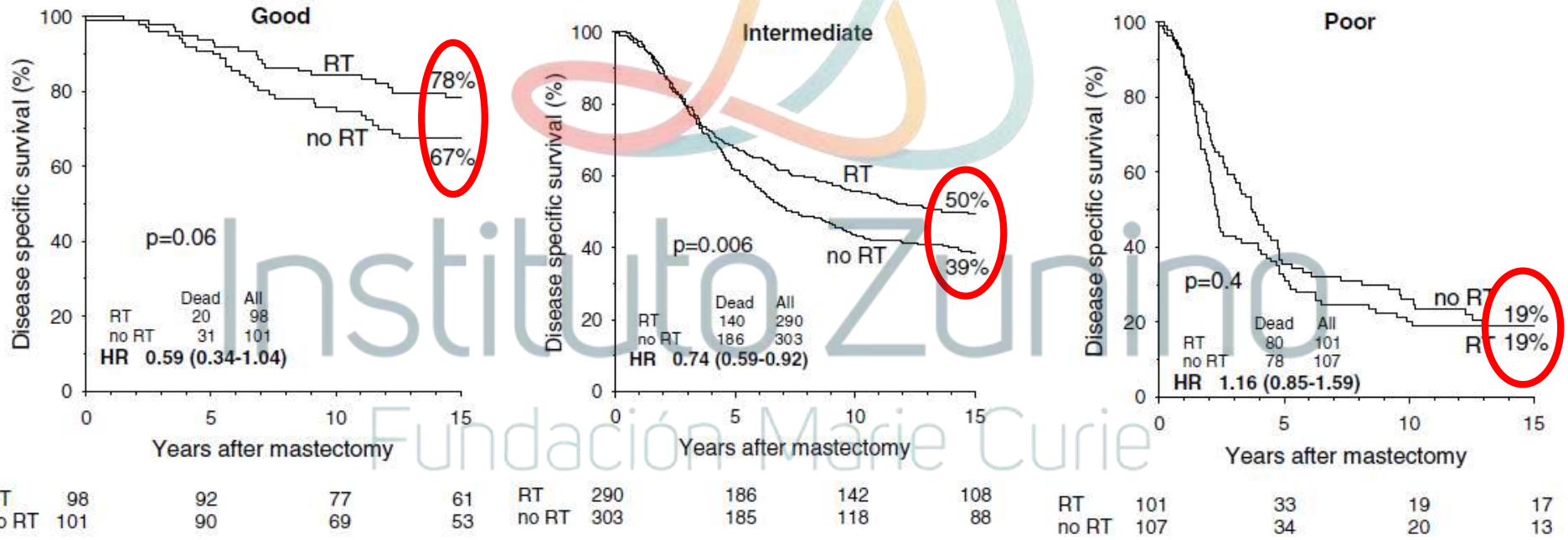
Molecular subtypes & locoregional ttm: *Early experience*

DSS





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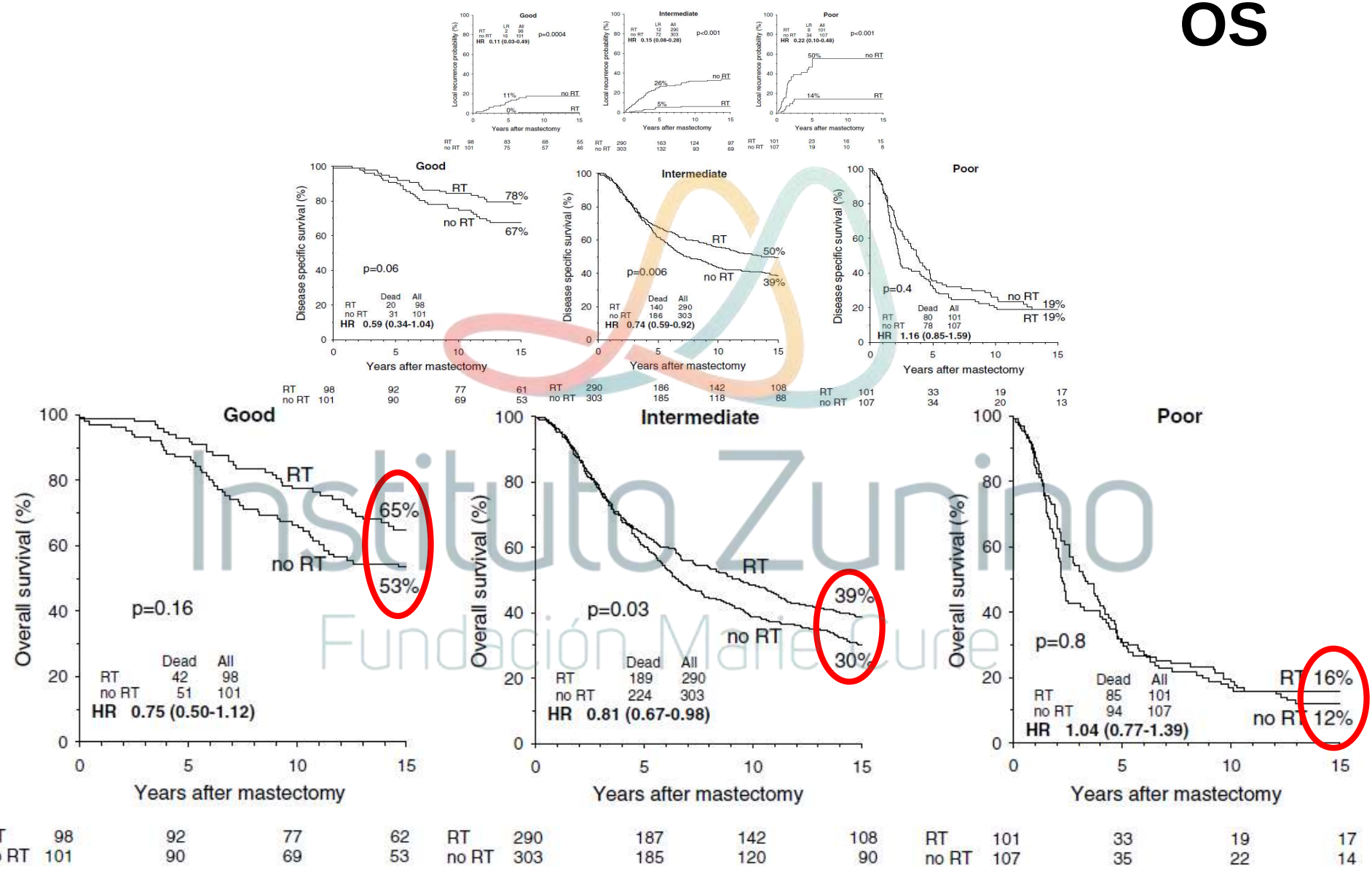
Molecular subtypes & locoregional ttm: *Early experience*

OS



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Molecular subtypes & locoregional ttm: *Early experience*

Risk:	Low			Intermediate			High		
Treatment:	(-)		RT	(-)		RT	(-)		RT
LR at 5y:	11	-11 →	0	26	-21 →	5	50	-36 →	14
DSS at 15y:	67	+11 →	78	39	+11 →	50	19	+0 →	19
OS at 15y:	53	+12 →	65	30	+9 →	39	12	+4 →	16

➔ **~ 1/1** **~ 1/2** **~ 1/9**

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Molecular subtypes & locoregional ttm: *Molecular based experience*

Estrogen Receptor, Progesterone Receptor, HER-2, and Response to Postmastectomy Radiotherapy in High-Risk Breast Cancer: The Danish Breast Cancer Cooperative Group

Marianne Kyndi, Flemming B. Sørensen, Helle Knudsen, Marie Overgaard, Hanne Melgaard Nielsen, and Jens Overgaard

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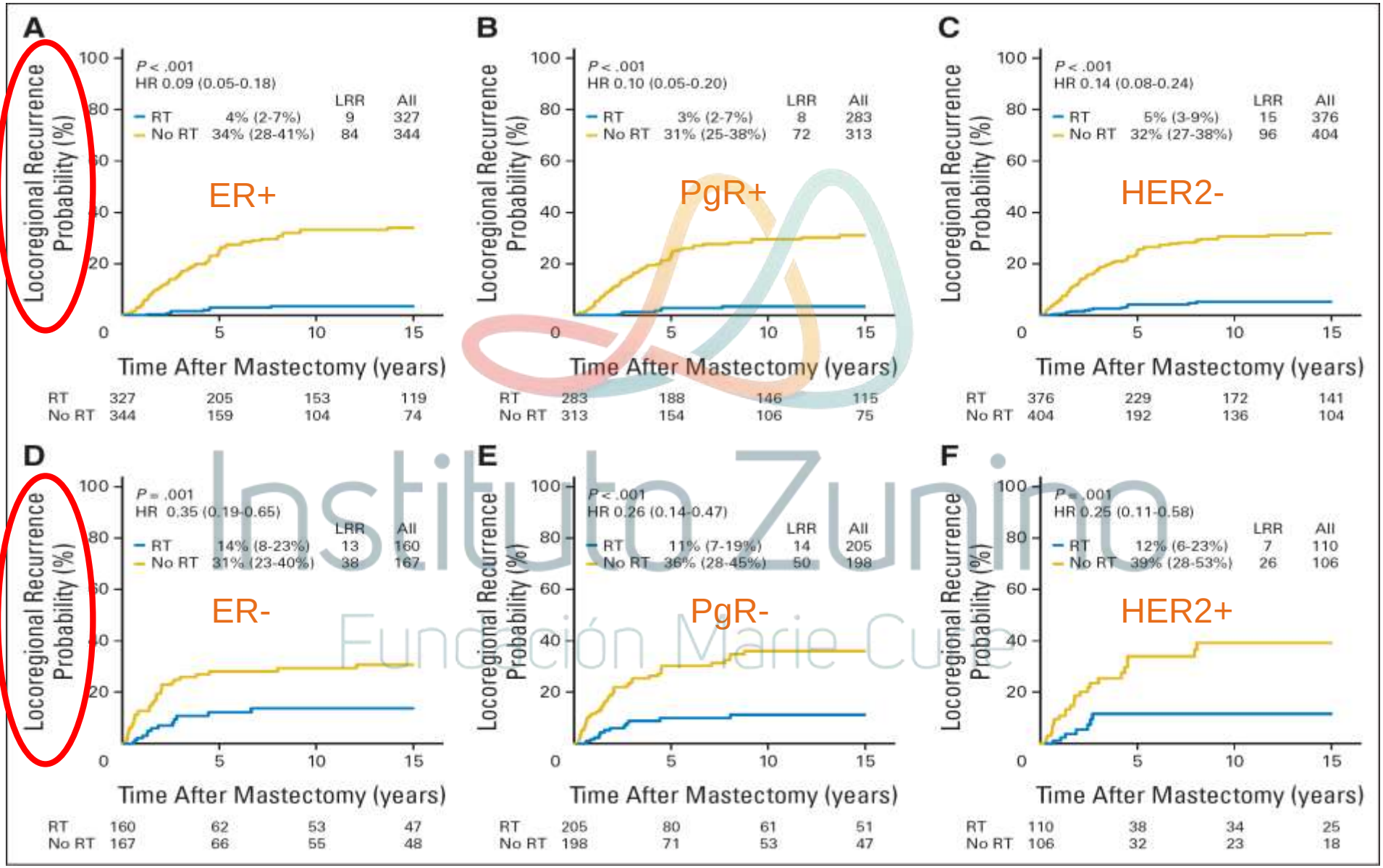
The same DBCG 82 b&c cohort, N=1000

Molecular subtypes & locoregional ttm: *Molecular based experience*



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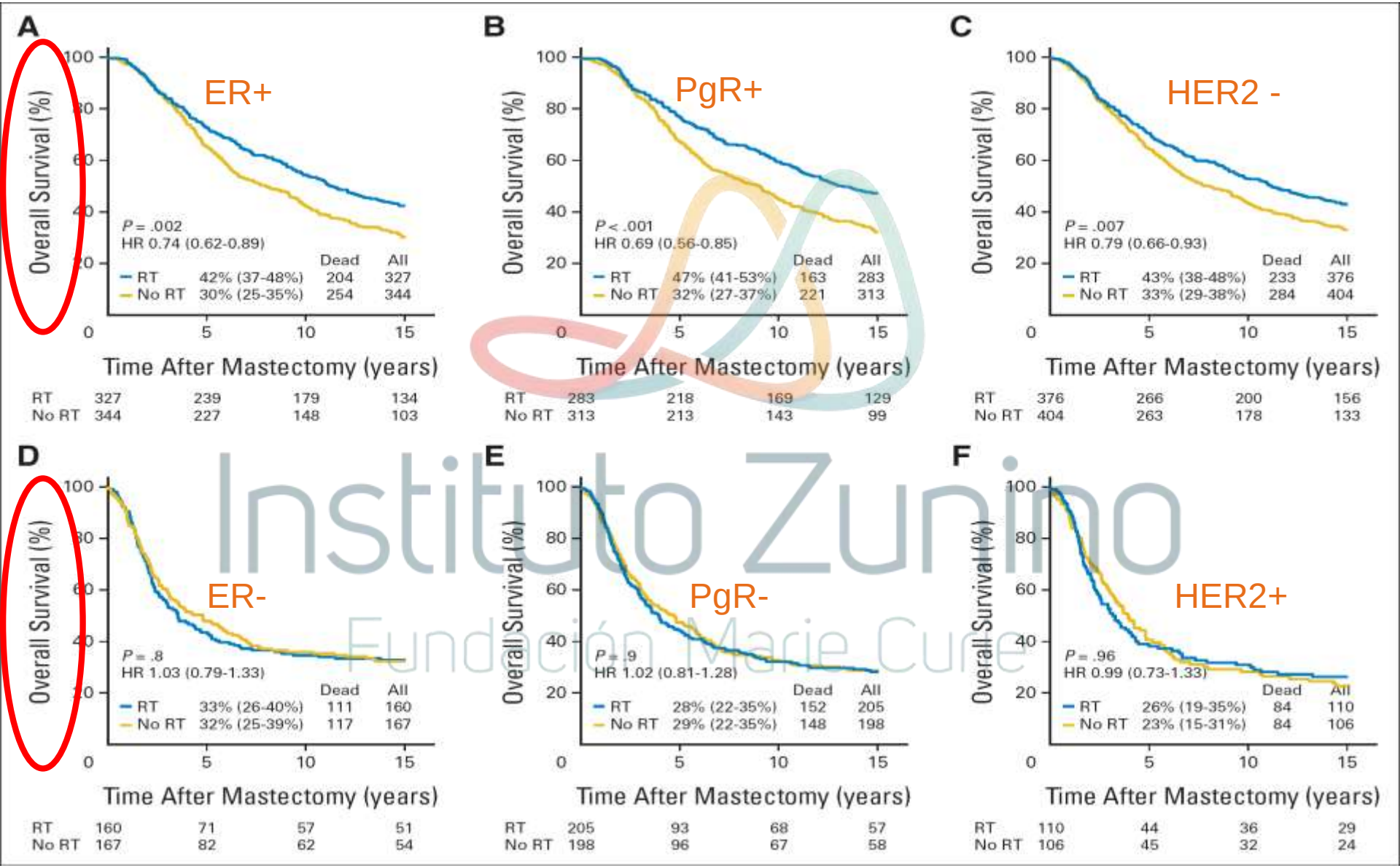
Kyndi M, et al. JCO 2008;26:1419-14.

Molecular subtypes & locoregional ttm: *Molecular based experience*



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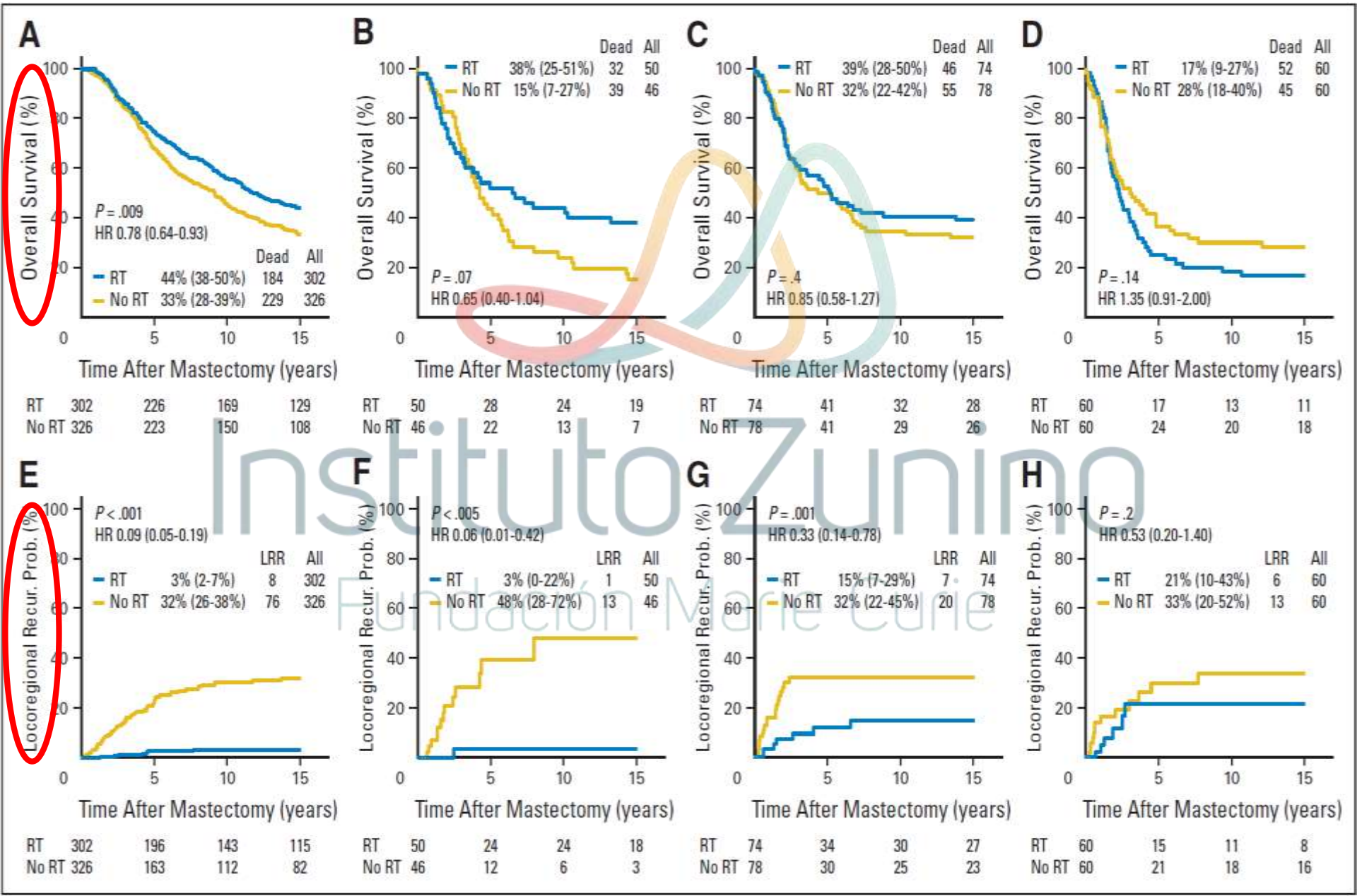
Kyndi M, et al. JCO 2008;26:1419-14.

Rec+, HER2-
"Luminal A"
63%

Rec+, HER2+
"Luminal B"
10%

Triple neg
"Basal like"
15%

Rec-, HER2+
"HER2 like"
12%



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Rec+, HER2- "Luminal A" 63%	Rec+, HER2+ "Luminal B" 10%	Triple neg "Basal like" 15%	Rec-, HER2+ "HER2 like" 12%

This study supports the spectrum hypothesis:

- Local disease in Luminal-A

- Micrometastases in triple negative and HER-2

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Rec+, HER2- "Luminal A" 63%	Rec+, HER2+ "Luminal B" 10%	Triple neg "Basal like" 15%	Rec-, HER2+ "HER2 like" 12%

This study supports the spectrum hypothesis:

- Local disease in Luminal-A
- Mixed in Luminal-B
  - *With adjuvant endocrine treatment & CMF*
- Micrometastases in triple negative and HER-2
  - *Insufficient systemic treatment in the 80^{ties}*

To be explored further:

- Influence of adjuvant systemic treatments

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Rec+, HER2- "Luminal A" 63%	Rec+, HER2+ "Luminal B" 10%	Triple neg "Basal like" 15%	Rec-, HER2+ "HER2 like" 12%

This study supports the spectrum hypothesis:

- Local disease in Luminal-A
- Mixed in Luminal-B
  - *With adjuvant endocrine treatment & CMF*
- Micrometastases in triple negative and HER-2

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To be explored further:

- Role of radioresistance of Rec- and HER-2

Molecular subtypes & locoregional ttm: *Molecular based experience*

VOLUME 26 · NUMBER 14 · MAY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Breast Cancer Subtype Approximated by Estrogen Receptor, Progesterone Receptor, and HER-2 Is Associated With Local and Distant Recurrence After Breast-Conserving Therapy

Paul L. Nguyen, Alphonse G. Taghian, Matthew S. Katz, Andrzej Niemierko, Rita F. Abi Raad, Whitney L. Boon, Jennifer R. Bellon, Julia S. Wong, Barbara L. Smith, and Jay R. Harris

BCS 1998-2001; N=793

FU = 70 months

Systemic therapy:

Chemotherapy 88% of N+ and 29% of N0

Hormonal therapy to 88% of patients with ER+ / PgR+ disease

No trastuzumab

Radiation therapy:

WBI + boost

Supraclavicular / axillary field if N2-disease

- *Luminal A: ER+ or PgR+ and HER2-*
- *Luminal B: ER+ or PgR+ and HER2+*
- *HER2: ER- or PgR- and HER2+*
- *Basal: triple neg*

N = 18 isolated located recurrences

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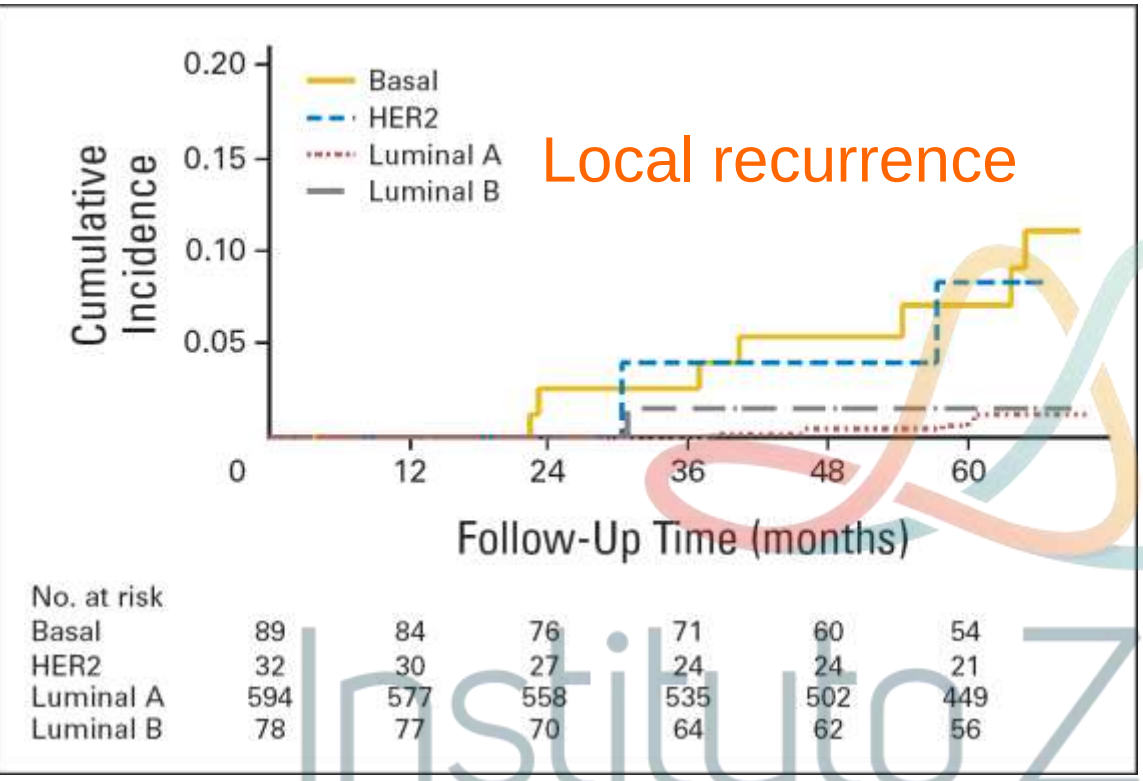
Molecular subtypes & locoregional ttm: *Molecular based experience*



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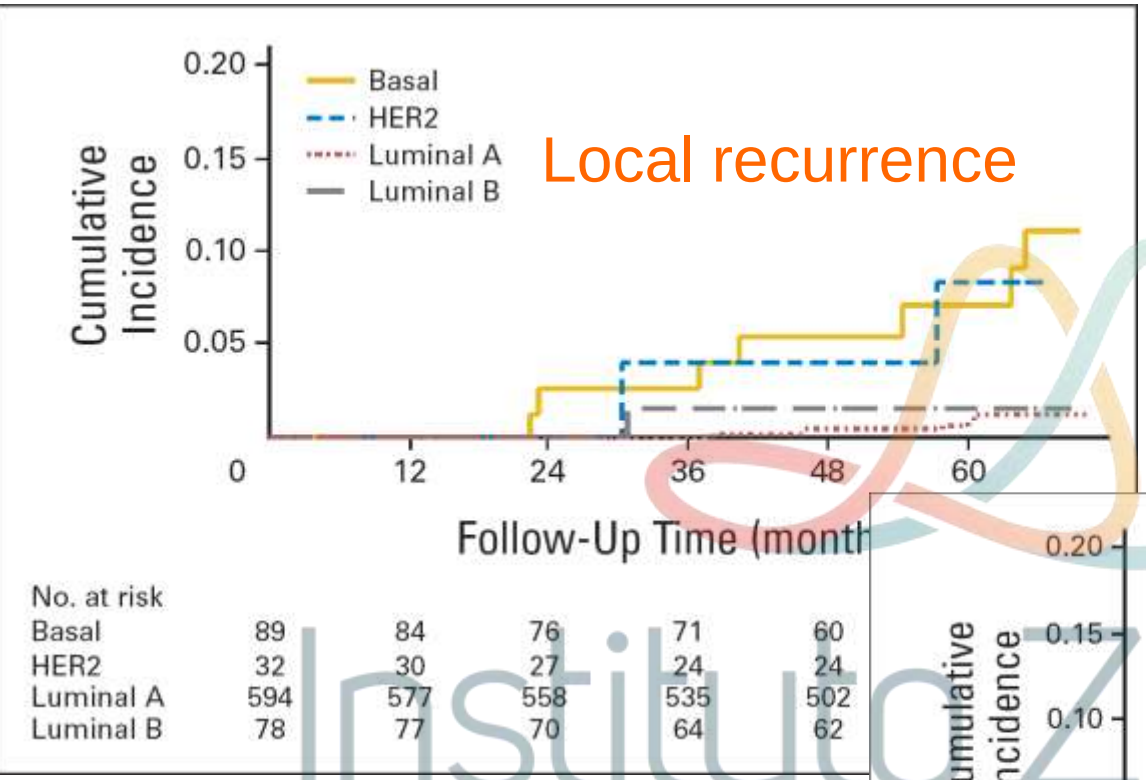
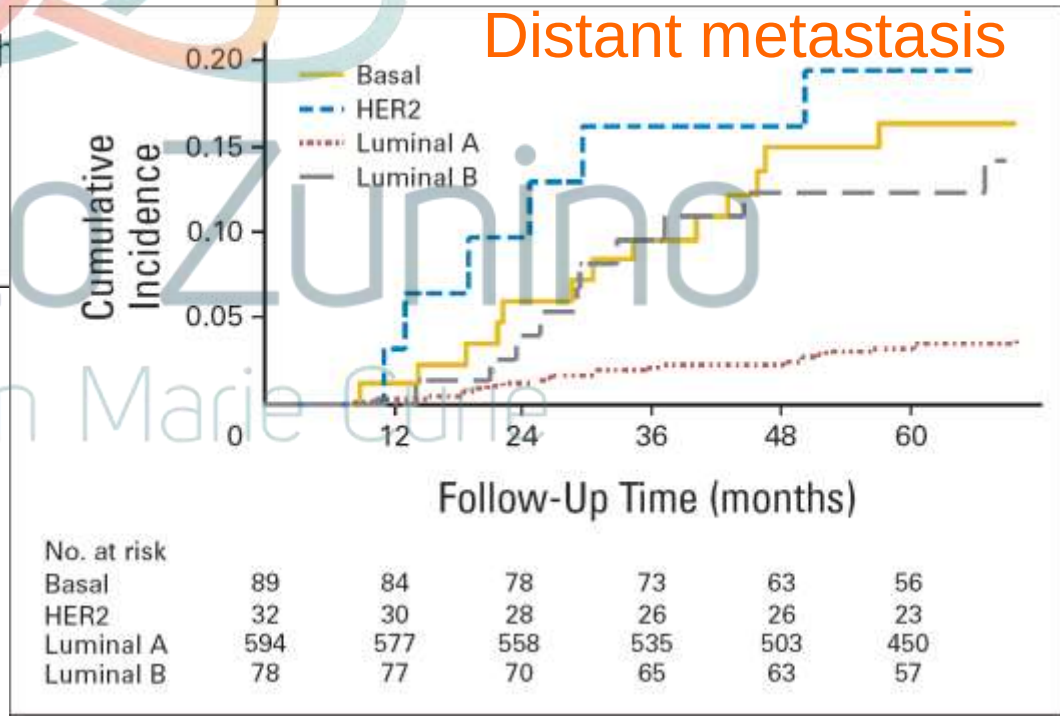
Molecular subtypes & locoregional ttm: *Molecular based experience*

Local recurrence



No. at risk					
Basal	89	84	76	71	60
HER2	32	30	27	24	24
Luminal A	594	577	558	535	502
Luminal B	78	77	70	64	62

Distant metastasis



No. at risk						
Basal	89	84	78	73	63	56
HER2	32	30	28	26	26	23
Luminal A	594	577	558	535	503	450
Luminal B	78	77	70	65	63	57

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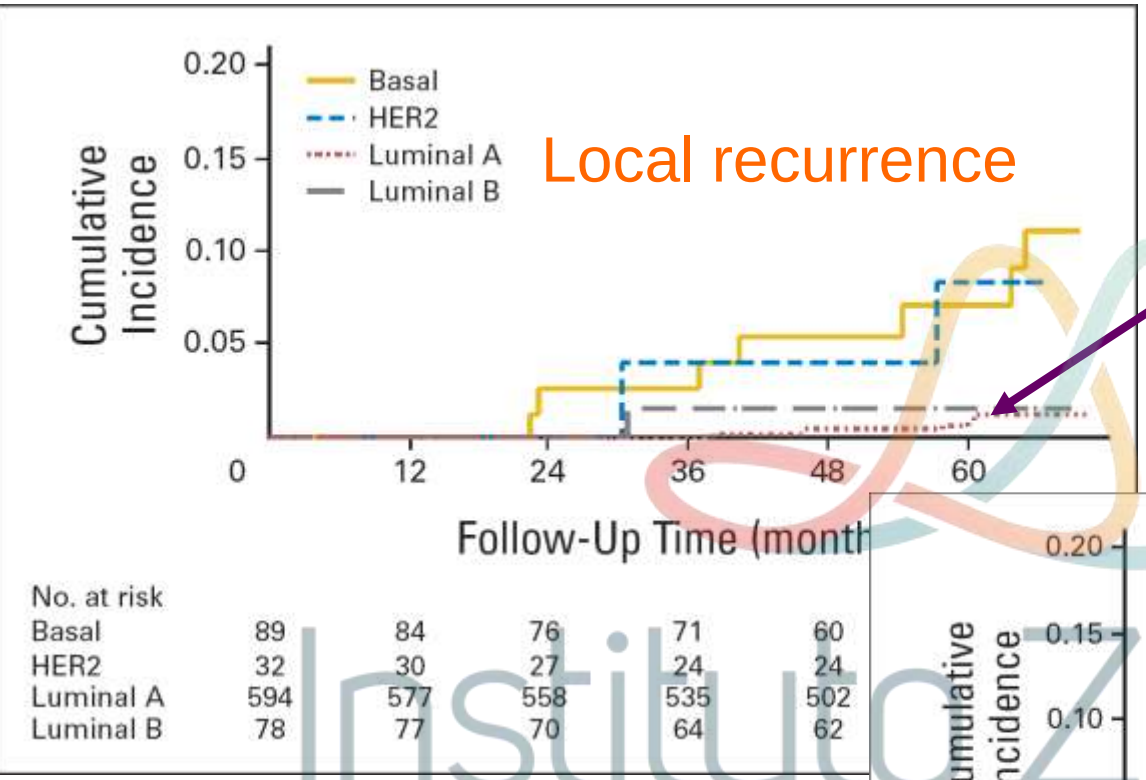
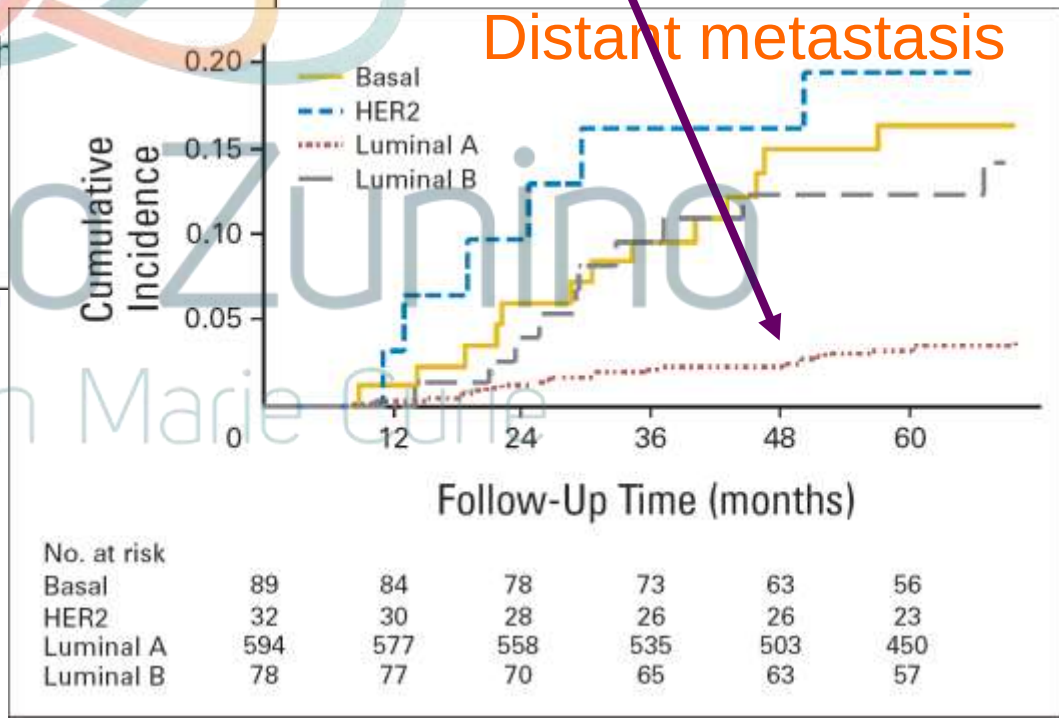
Molecular subtypes & locoregional ttm: *Molecular based experience*



Luminal A has a particularly low recurrence rate



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Molecular subtypes & locoregional ttm: *Molecular based experience*

VOLUME 28 · NUMBER 10 · APRIL 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Association Between the 21-Gene Recurrence Score Assay and Risk of Locoregional Recurrence in Node-Negative, Estrogen Receptor–Positive Breast Cancer: Results From NSABP B-14 and NSABP B-20

Eleftherios P. Mamounas, Gong Tang, Bernard Fisher, Soonmyung Paik, Steven Shak, Joseph P. Costantino, Drew Watson, Charles E. Geyer Jr, D. Lawrence Wickerham, and Norman Wolmark

BCS+RT or MRM 1982-1993; 2 randomised trials:

- B-14 : 5 year Tamoxifem vs placebo, later on Tam 5 vs 10 y
- B-20 : Tamoxifen +/- chemo

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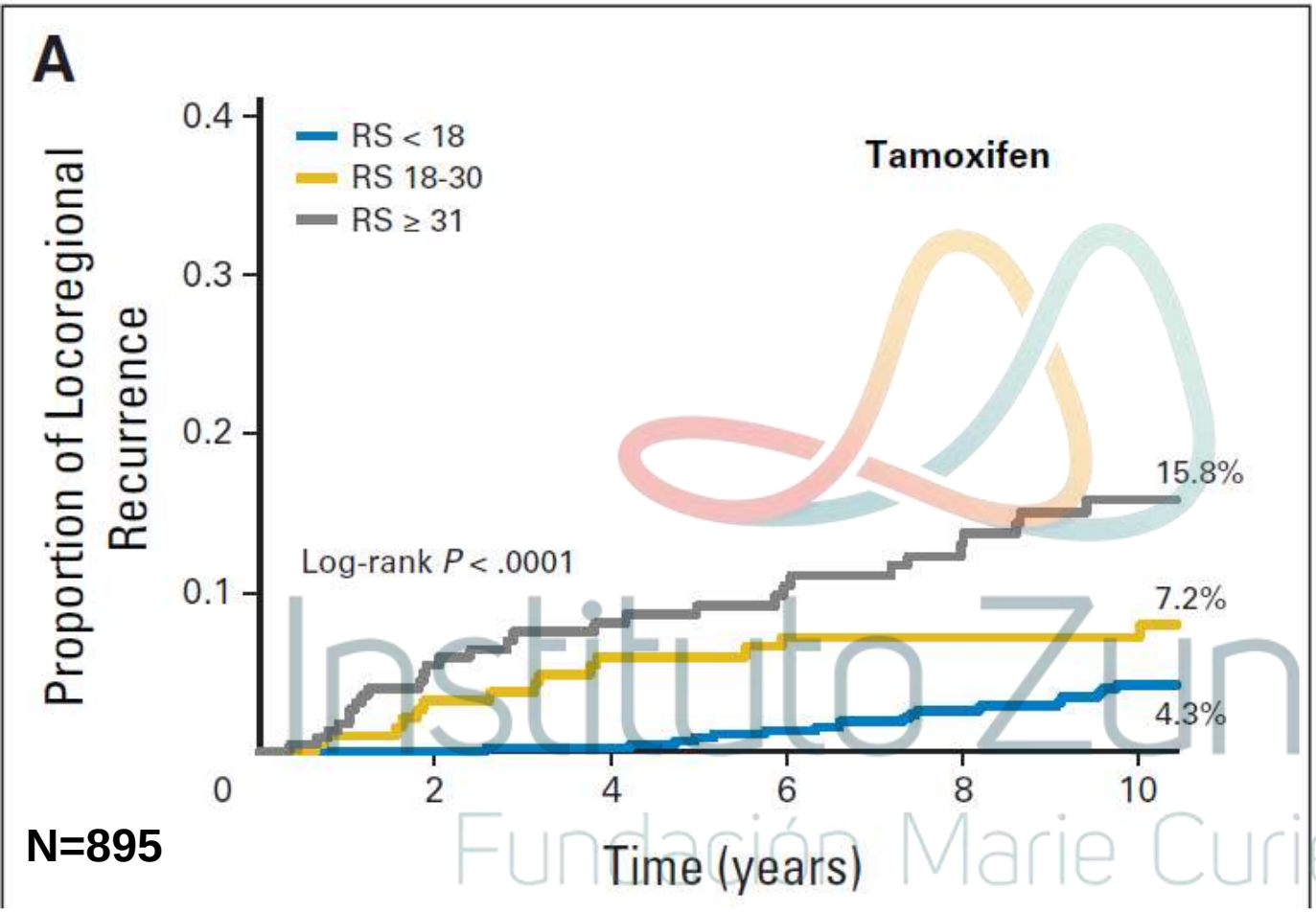
✓ The 21-gene OncotypeDX recurrence score (RS) assay can predict distant recurrence risk in patients with tumors ER+ and N0

? Can the 21-gene assay predict locoregional recurrence risk?

Molecular subtypes & locoregional ttm: *Molecular based experience*



N=895

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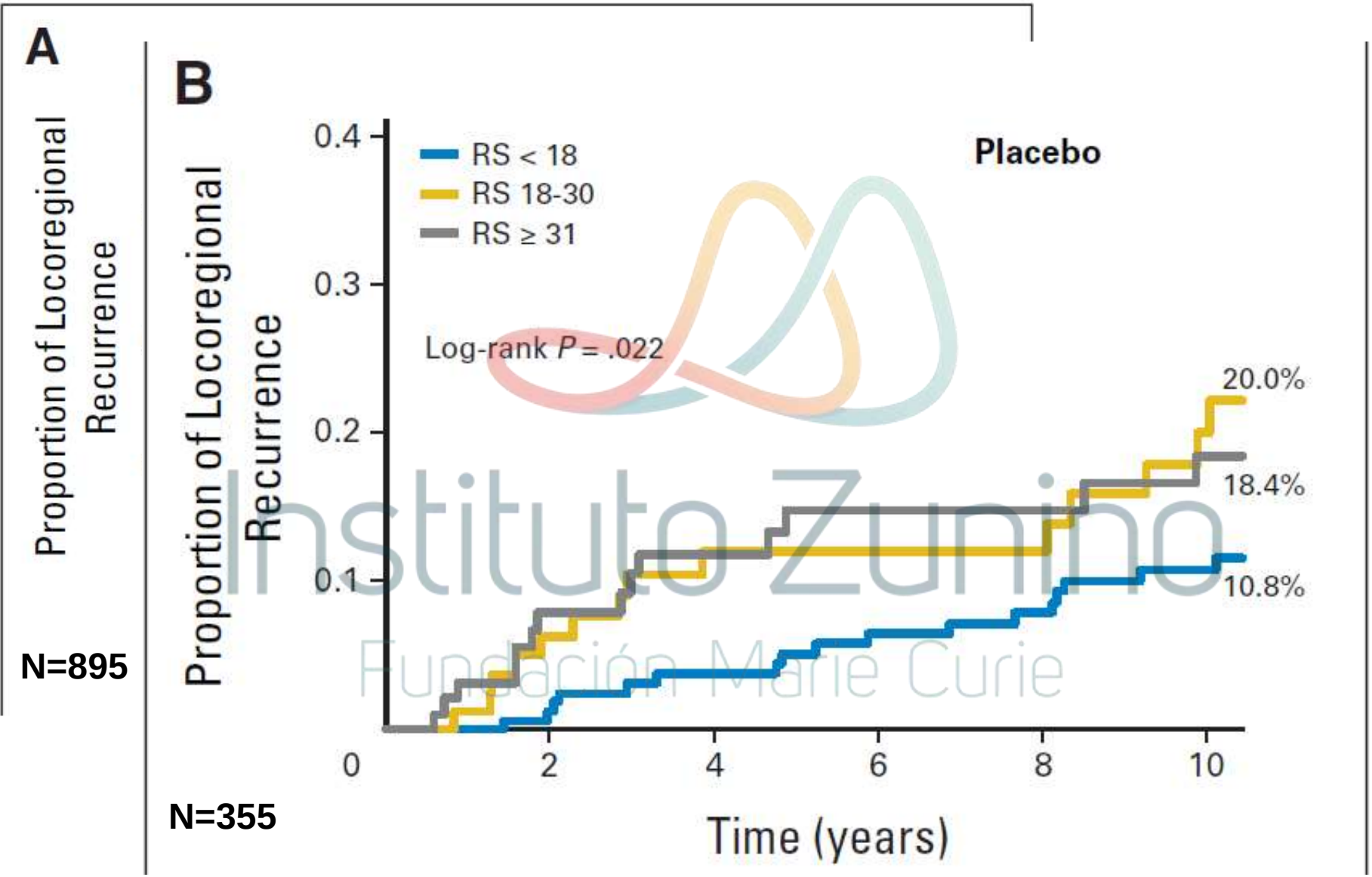
Molecular subtypes & locoregional ttm: *Molecular based experience*



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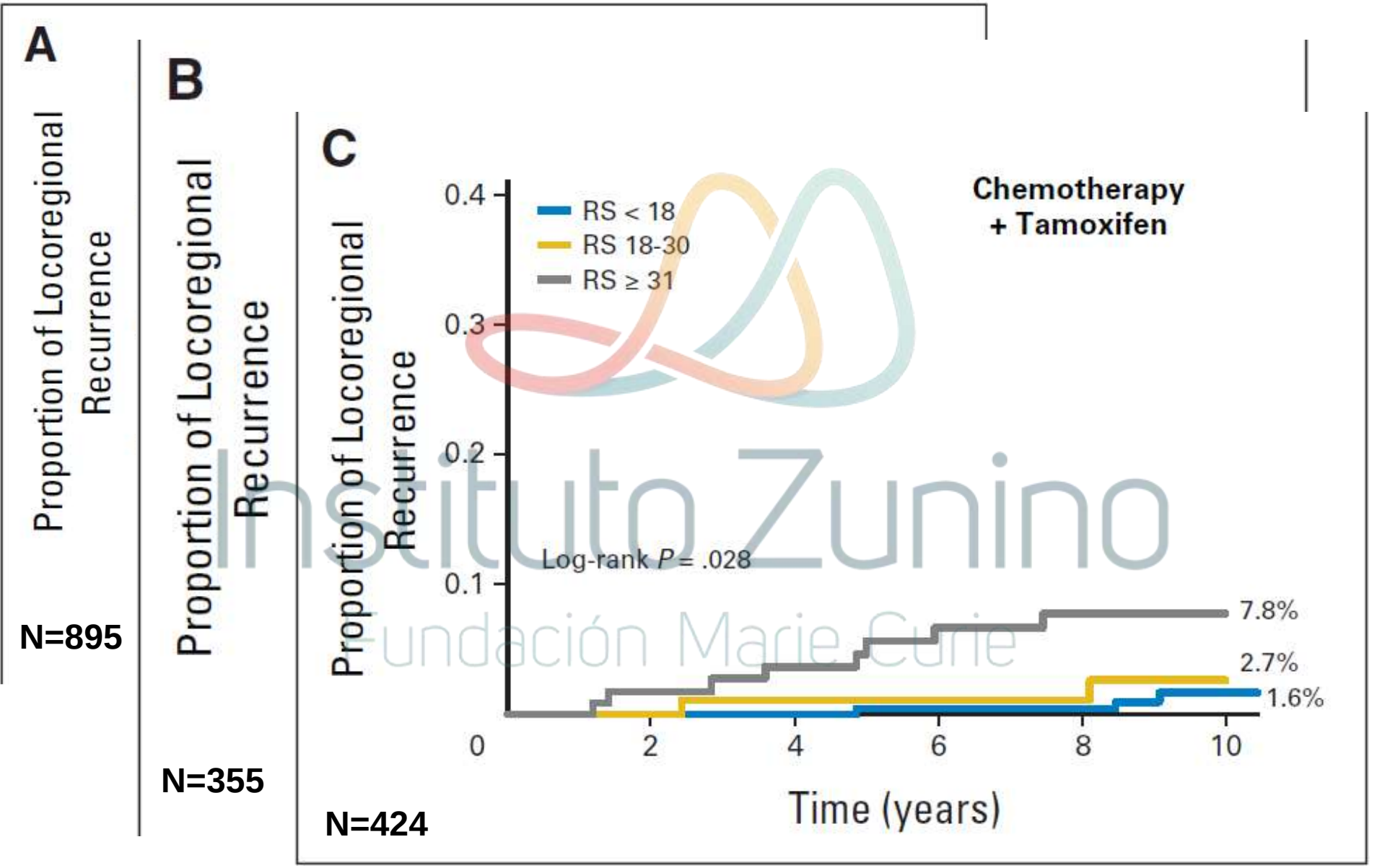
Molecular subtypes & locoregional ttm: *Molecular based experience*



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Conclusion:

The 21-gene assay locoregional recurrence risk

- In this group of ER+ and N0 patients
- With this adjuvant systemic treatment

Further studies required:

- To confirm the low LRR risk group ➔ without RT
- To define the high LRR risk group ➔ new RT indications

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Molecular subtypes & locoregional ttm: *Molecular based experience*

Chen *et al. World Journal of Surgical Oncology* 2014, **12**:212
http://www.wjso.com/content/12/1/212

WORLD JOURNAL OF SURGICAL ONCOLOGY

RESEARCH Open Access

The efficacy of molecular subtyping in predicting postoperative recurrence in breast-conserving therapy: a 15-study meta-analysis

Jing Chen[1†], Peng Jiang[1†], Han-jin Wang[1], Jia-yi Zhang[2], Yang Xu[2], Mu-hong Guo[1], Bin Zhang[1], Chong-yin Tang[1], Hong-yong Cao[3] and Shui Wang[4*]

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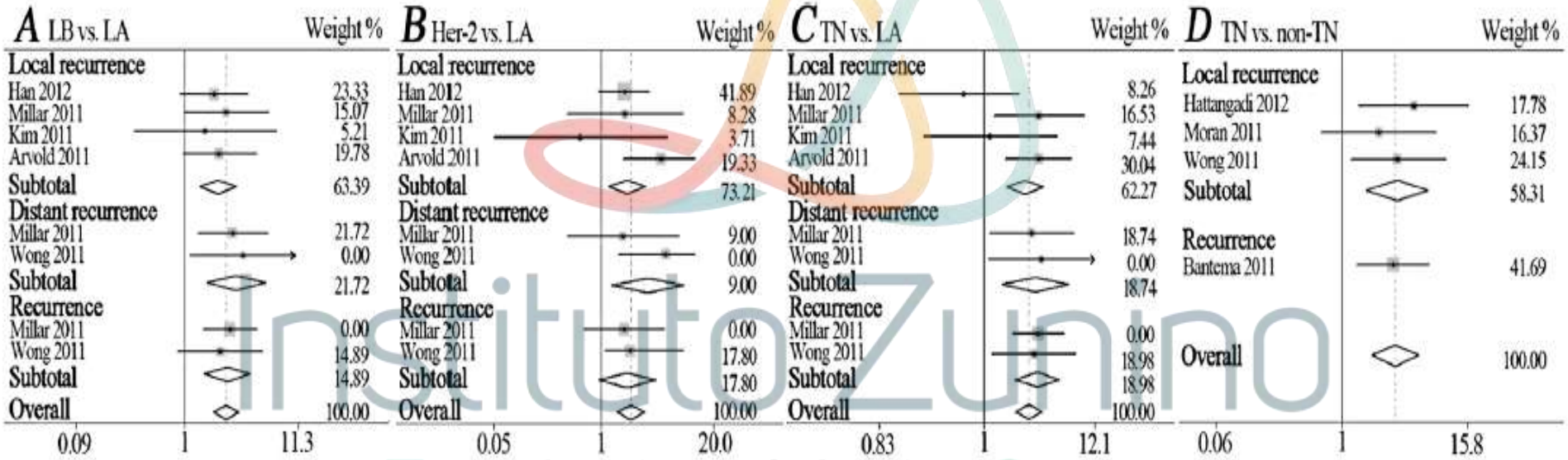
N = 21.654

Molecular subtypes & locoregional ttm: *Molecular based experience*



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Molecular subtypes & locoregional ttm: *Molecular based experience*

Table 4 Pooled HRs, 95% CIs, and *P* values of different dichotomous status of ER, PR, and Her-2 protein stratified by recurrence types

Types of recurrence	LB *vs.* LA			Her-2 *vs.* LA			TN *vs.* LA			TN *vs.* non-TN		
	N	HR (95% CI)	*P*	N	HR (95% CI)	*P*	N	HR (95% CI)	*P*	N	HR (95% CI)	*P*
Overall	6	2.23 (1.55, 3.19)[a]	<0.01	6	2.26 (1.42, 3.60)[a]	0.001	6	2.90 (1.84, 4.58)[a]	<0.01	4	3.19 (1.91, 5.31)[a]	<0.01
Local recurrence	4	2.05 (1.31, 3.23)[a]	0.002	4	2.33 (1.35, 4.02)[a]	0.002	4	2.64 (1.48, 4.71)[a]	0.001	3	3.31 (1.69, 6.45)[a]	<0.01
Distant recurrence	2	3.08 (1.62, 5.86)[a]	0.001	2	3.64 (1.33, 9.97)[a]	0.012	2	3.60 (1.57, 8.25)[a]	0.002	0	-	-
Recurrence	2	2.54 (1.54, 4.19)[a]	<0.01	2	2.04 (0.93, 4.49)[a]	0.075	2	3.77 (2.17, 6.55)[a]	<0.01	1	3.03 (1.37, 6.67)	-

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Molecular subtypes & locoregional ttm: *Molecular based experience*

VOLUME 29 · NUMBER 21 · JULY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Increased Risk of Locoregional Recurrence for Women With T1-2N0 Triple-Negative Breast Cancer Treated With Modified Radical Mastectomy Without Adjuvant Radiation Therapy Compared With Breast-Conserving Therapy

Bassam S. Abdulkarim, Julie Cuartero, John Hanson, Jean Deschênes, David Lesniak, and Siham Sabri

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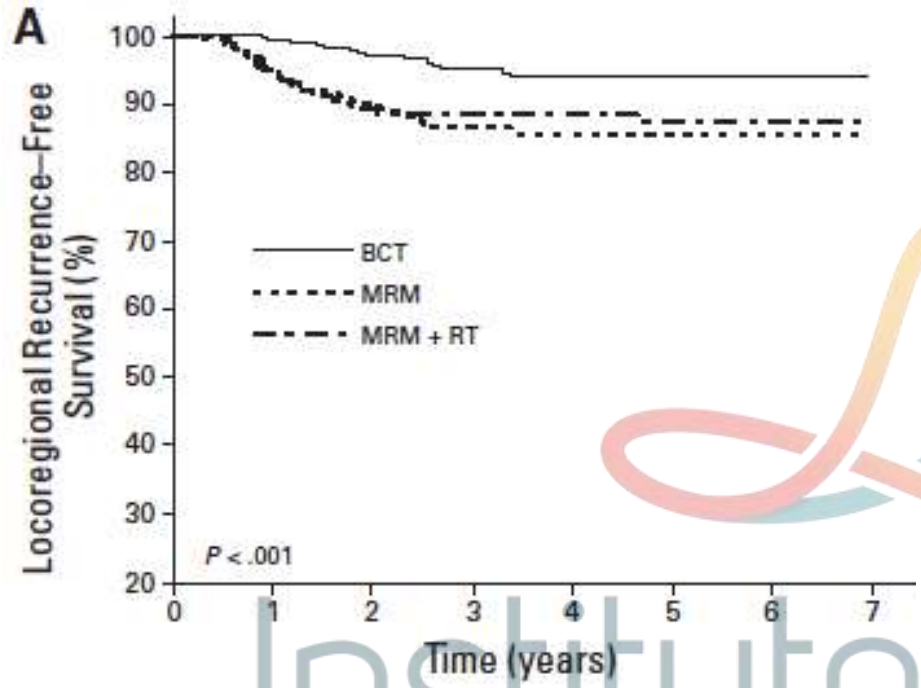
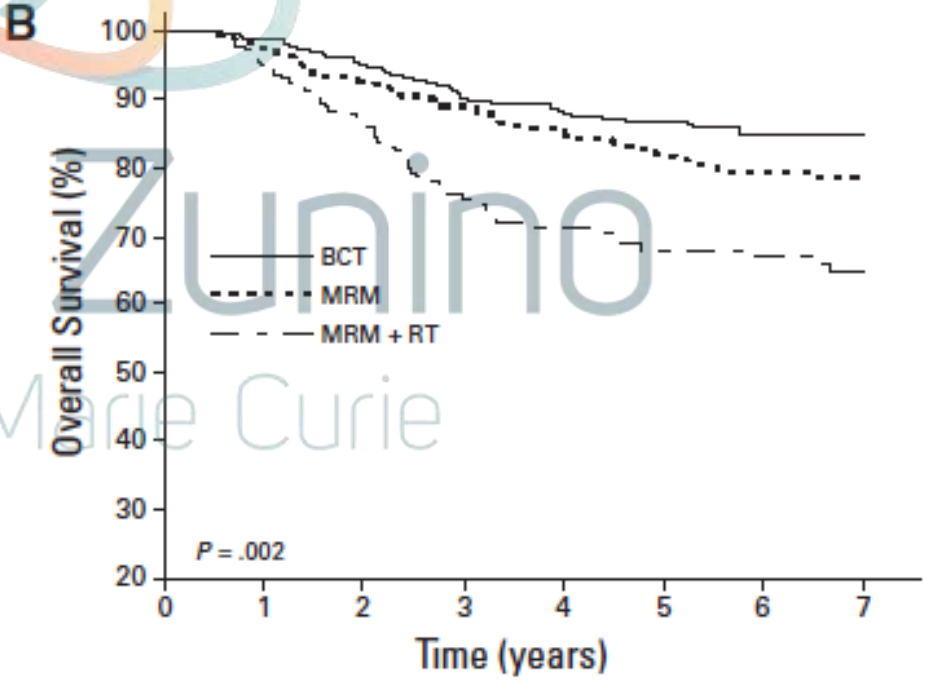
Single institution; N = 768

Molecular subtypes & locoregional ttm: *Molecular based experience*





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Molecular subtypes & locoregional ttm: *Molecular based experience*

Table 3. Multivariate Analysis of Predictors for LRR and OS of Patients With TNBC

Variable	LRR			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Tumor size						
T1	1			1		
T2	1.14	0.70 to 1.85	.6078	1.8	1.25 to 2.60	< .001
T3	1.42	0.63 to 3.21	.4018	2.16	1.19 to 3.90	.0109
Tumor grade						
1-2	1			1		
3	1.07	0.57 to 2.00	.83	1.06	0.67 to 1.67	.811
LN status						
N0	1			1		
N1 (one to three positive)	3.54	1.95 to 6.40	< .001	2.64	1.69 to 4.14	< .001
N2-N3 (> three positive)	8.67	4.33 to 17.38	< .001	6.48	3.83 to 10.94	< .001
LVI						
Negative	1			1		
Positive	2.08	1.23 to 3.51	.0062	1.86	1.27 to 2.71	< .001
Treatment						
Locoregional therapy						
BCT	1			1		
MRM	3.44	2.04 to 5.80	< .001	1.31	0.81 to 1.92	.3267
MRM + RT	0.72	0.36 to 1.43	.34	0.87	0.55 to 1.40	.5744
Adjuvant chemotherapy						
No	1			1		
Yes	0.39	0.24 to 0.66	< .001	0.29	0.20 to 0.42	< .001

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Molecular subtypes & locoregional ttm: *Molecular based experience*

The Breast 24 (2015) 384–390

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Translating the concept of intrinsic subtypes into an oncoplastic cohort of more than 1000 patients – predictors of recurrence and survival

M. Rezai [a, 1], S. Kellersmann [a, b, 1, 2], S. Knispel [a, b, 1, 2], H. Lax [c, 3], R. Kimmig [b, 2], P. Kern [a, b, *, 2]

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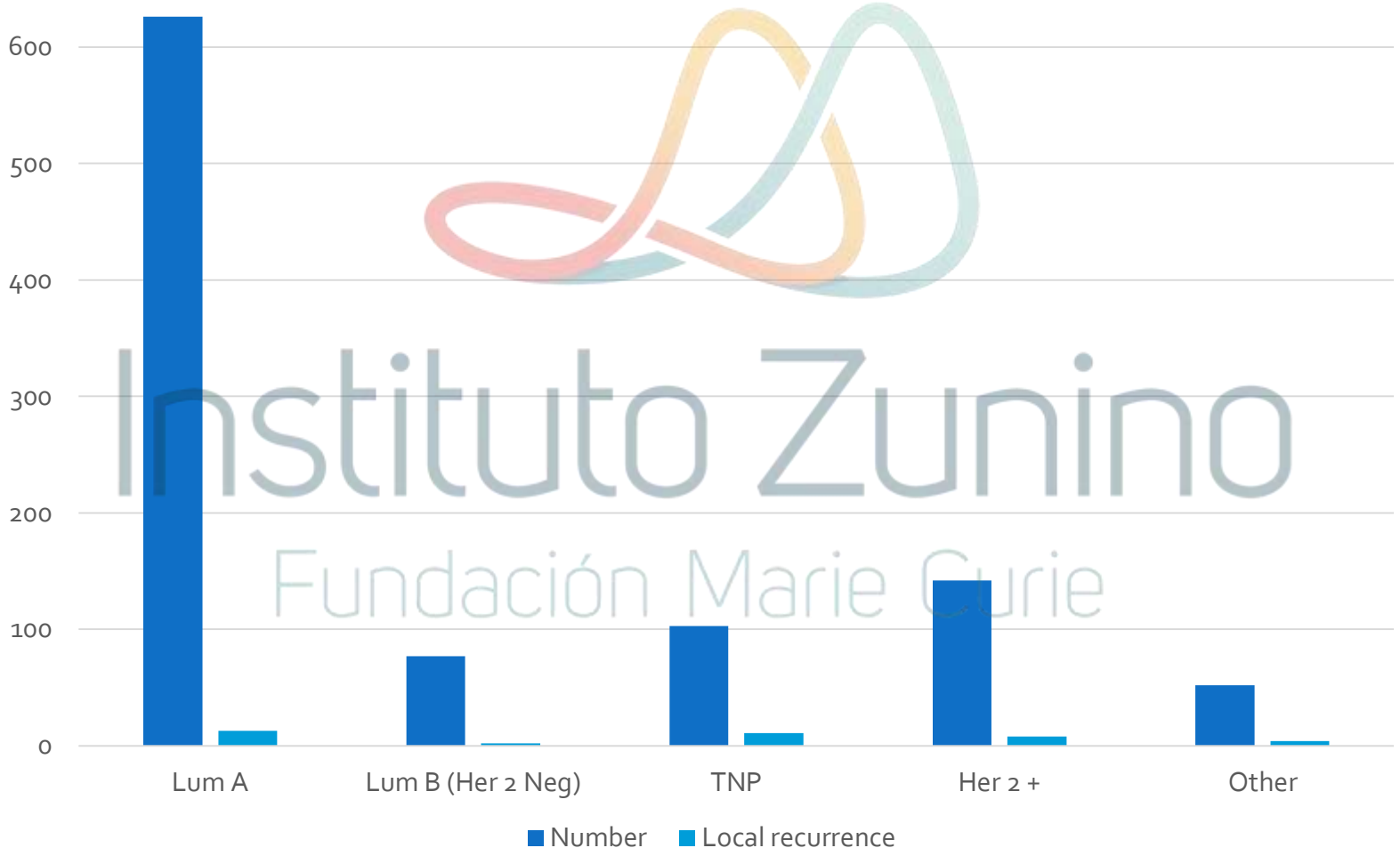
Molecular subtypes & locoregional ttm: *Molecular based experience*

LRR: 2.2% 2.7% 11.3% 9.3%

Lum B HER-2 +: 3.8%



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Molecular subtyping & locoregional treatment

1. Introduction
2. Molecular subtyping & locoregional treatment
3. Discussion
4. Conclusions

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Molecular subtypes & locoregional ttm: *Discussion*

Risk factors for local recurrence:

- After mastectomy
- After lumpectomy +/- WBRT
- After lumpectomy +/- WBRT +/- boost
- After APBI

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Molecular subtypes & locoregional ttm: *Discussion*

Interaction systemic and locoregional treatments

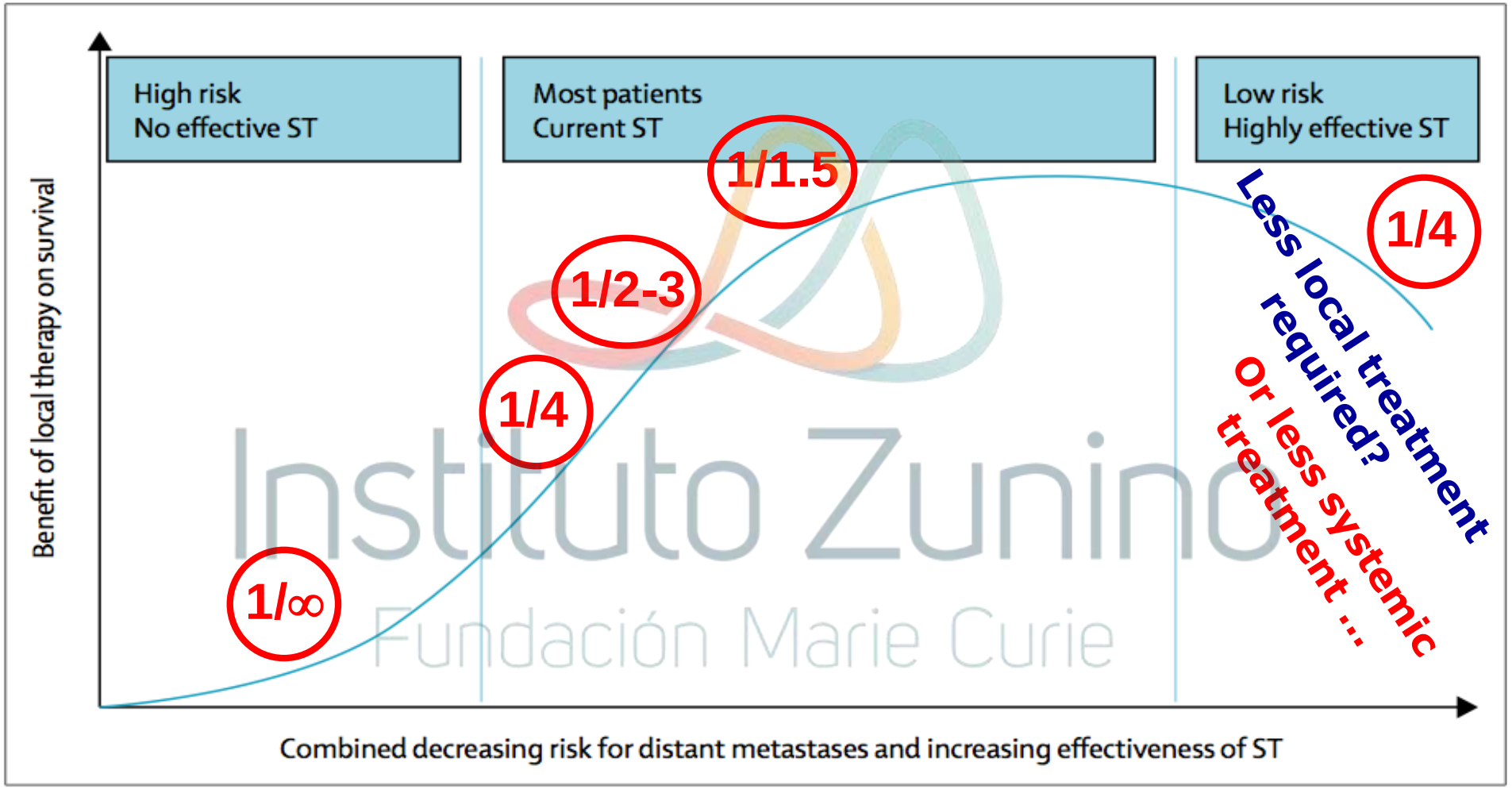

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***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

Molecular subtypes & locoregional ttm: *Discussion*

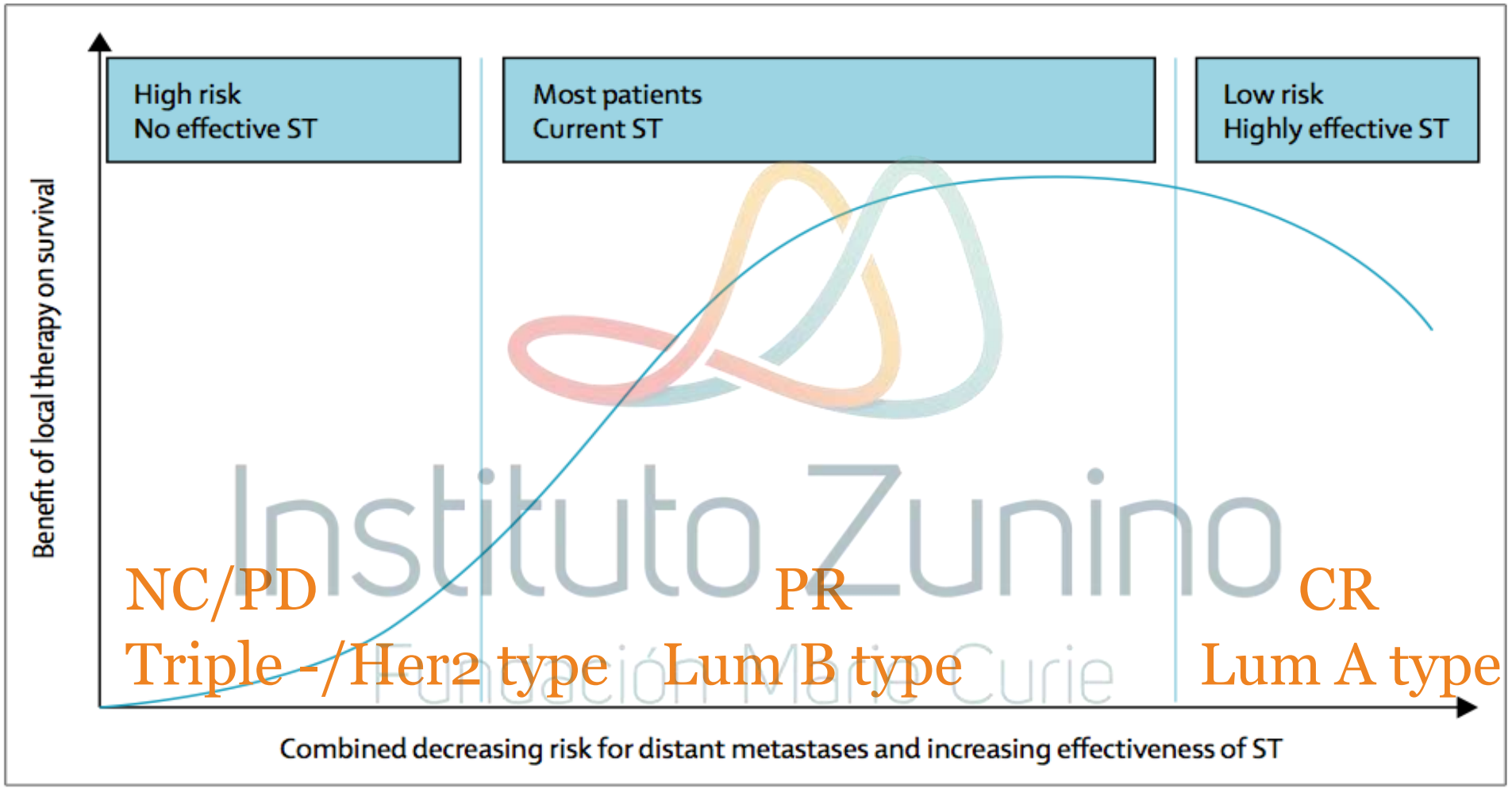

***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

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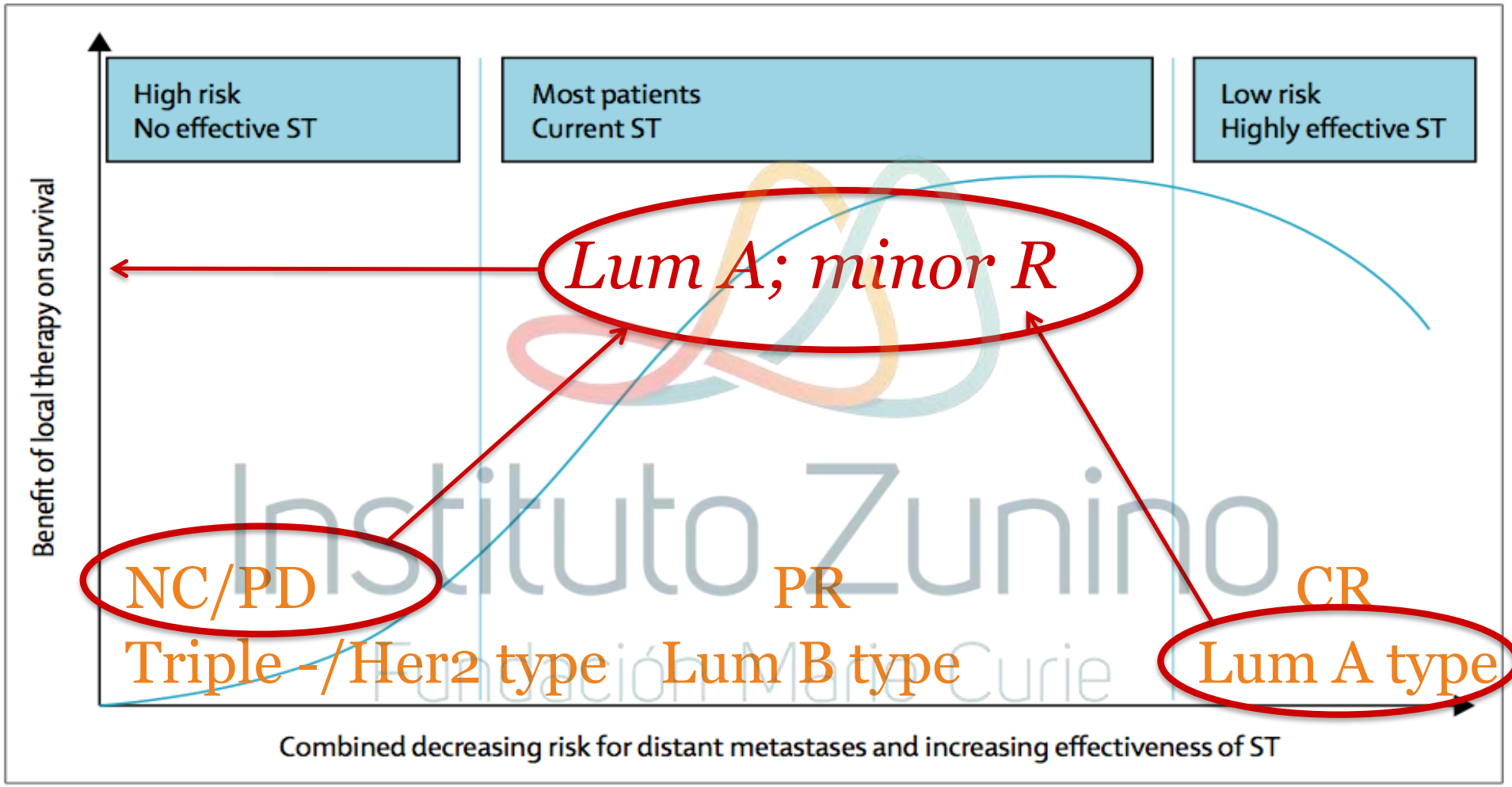
Molecular subtypes & locoregional ttm: *Discussion*



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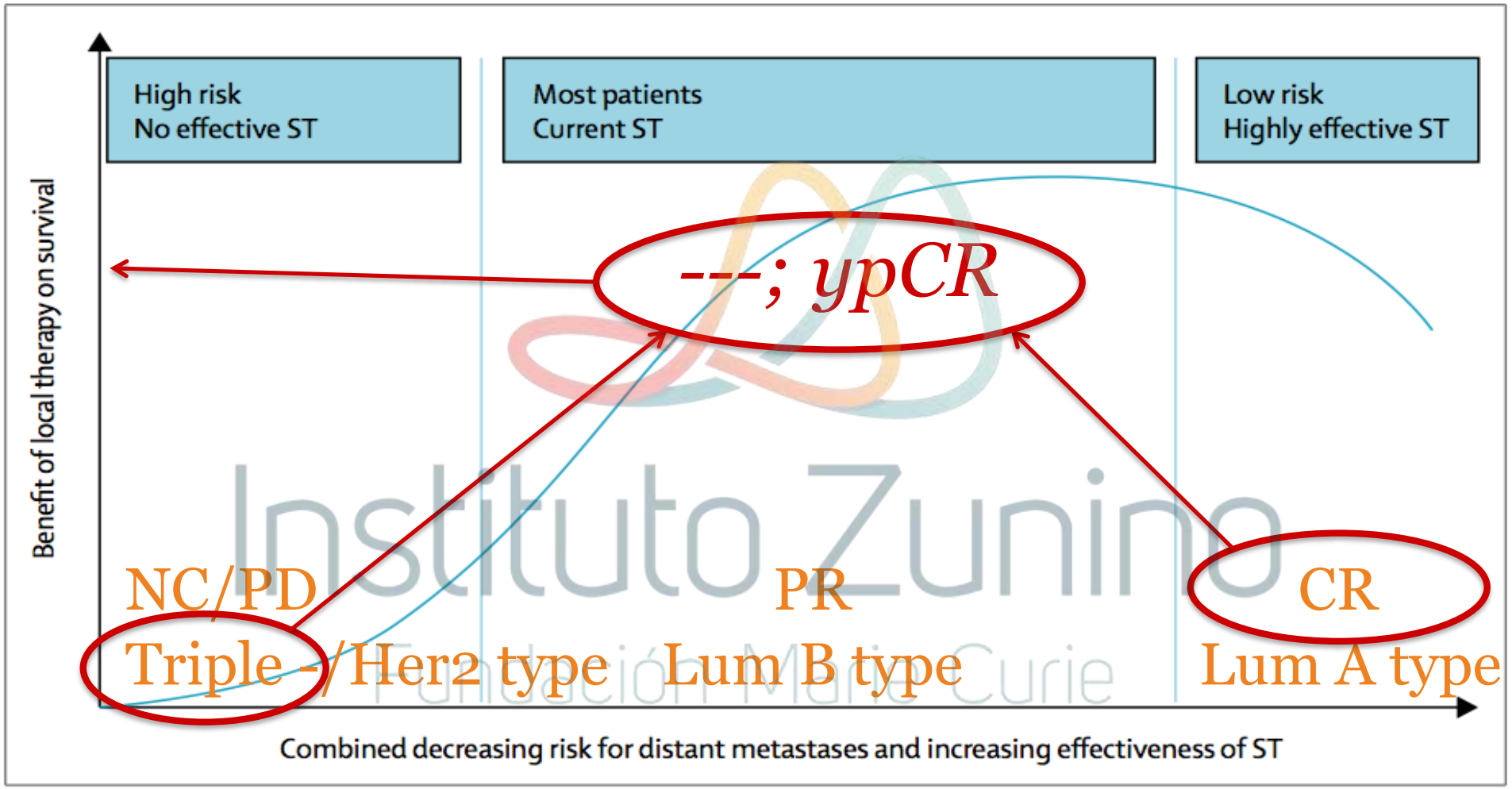
Molecular subtypes & locoregional ttm: *Discussion*



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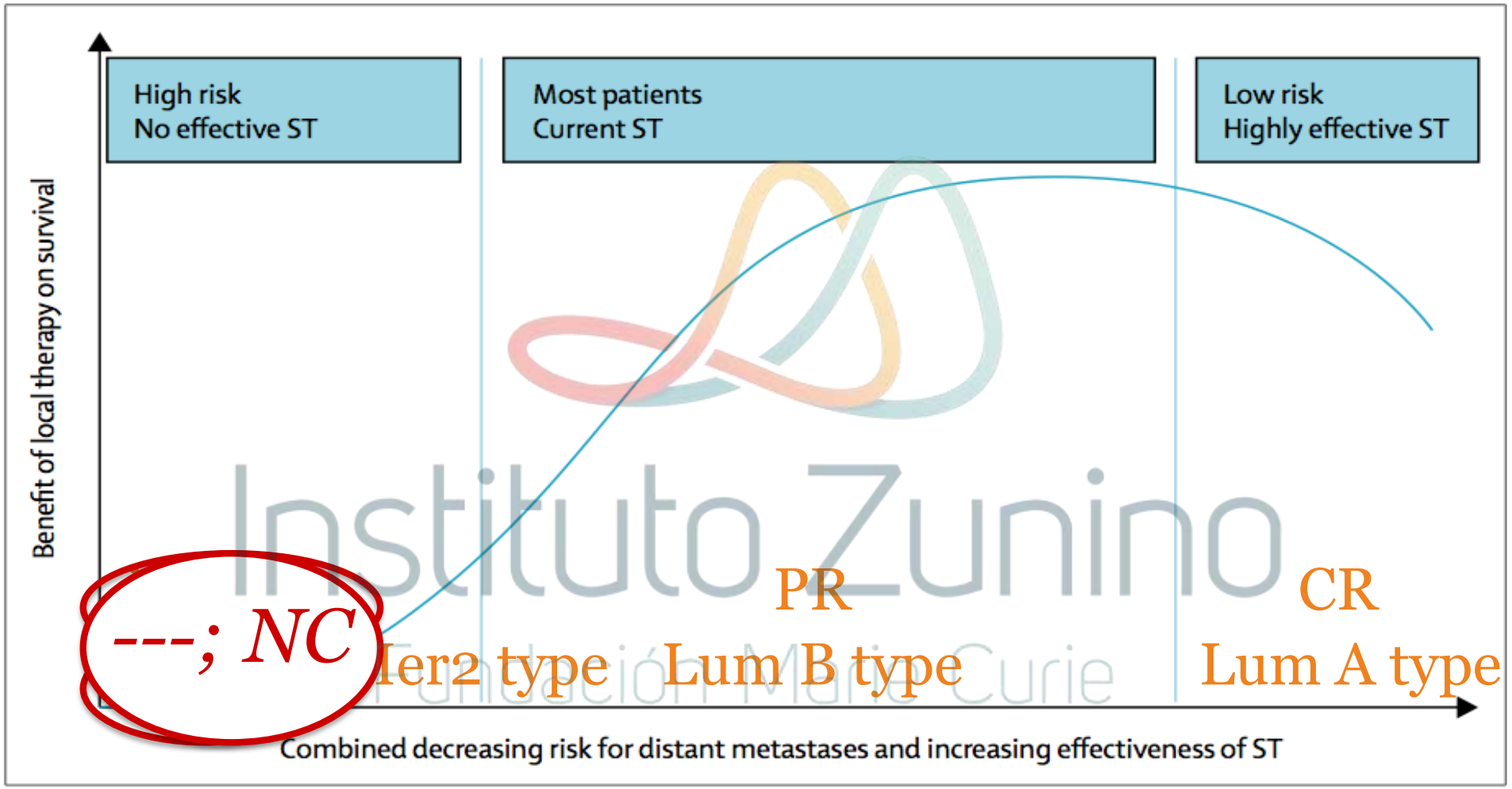
Molecular subtypes & locoregional ttm: *Discussion*



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L. van 't Ve ature 415, p530-536, 2002 M. vd Vijver et al, NEJM 347; 1999-2009, 2002

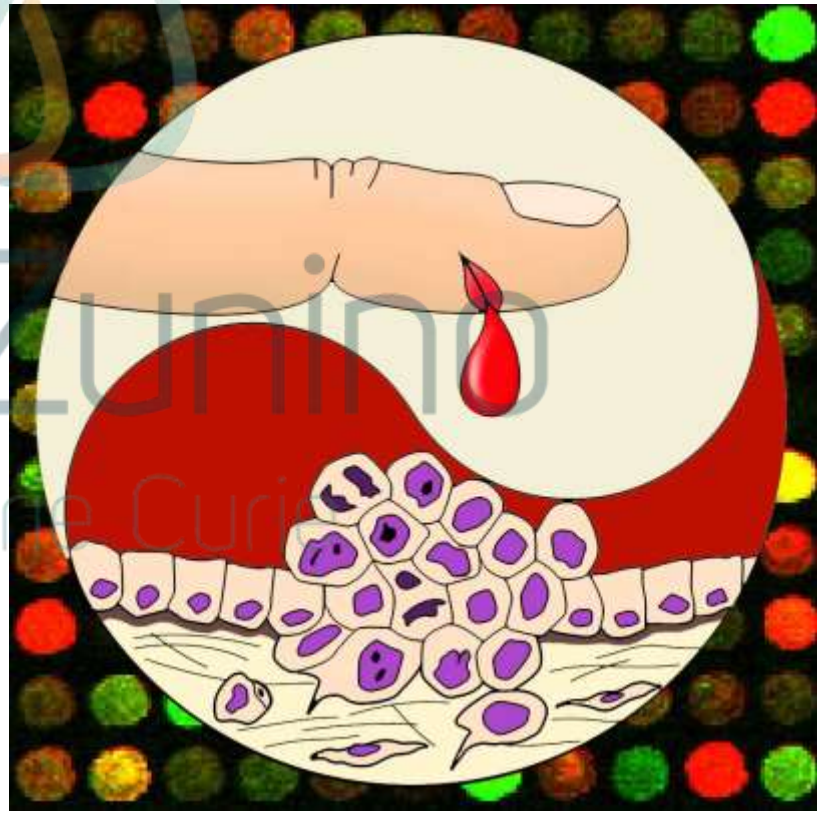
Molecular subtypes & locoregional ttm: *Discussion*

Wound Response Signature

In vitro Wound Model – 516 genes

Prognostic Significance in

- Breast
- Lung
- Gastric cancer



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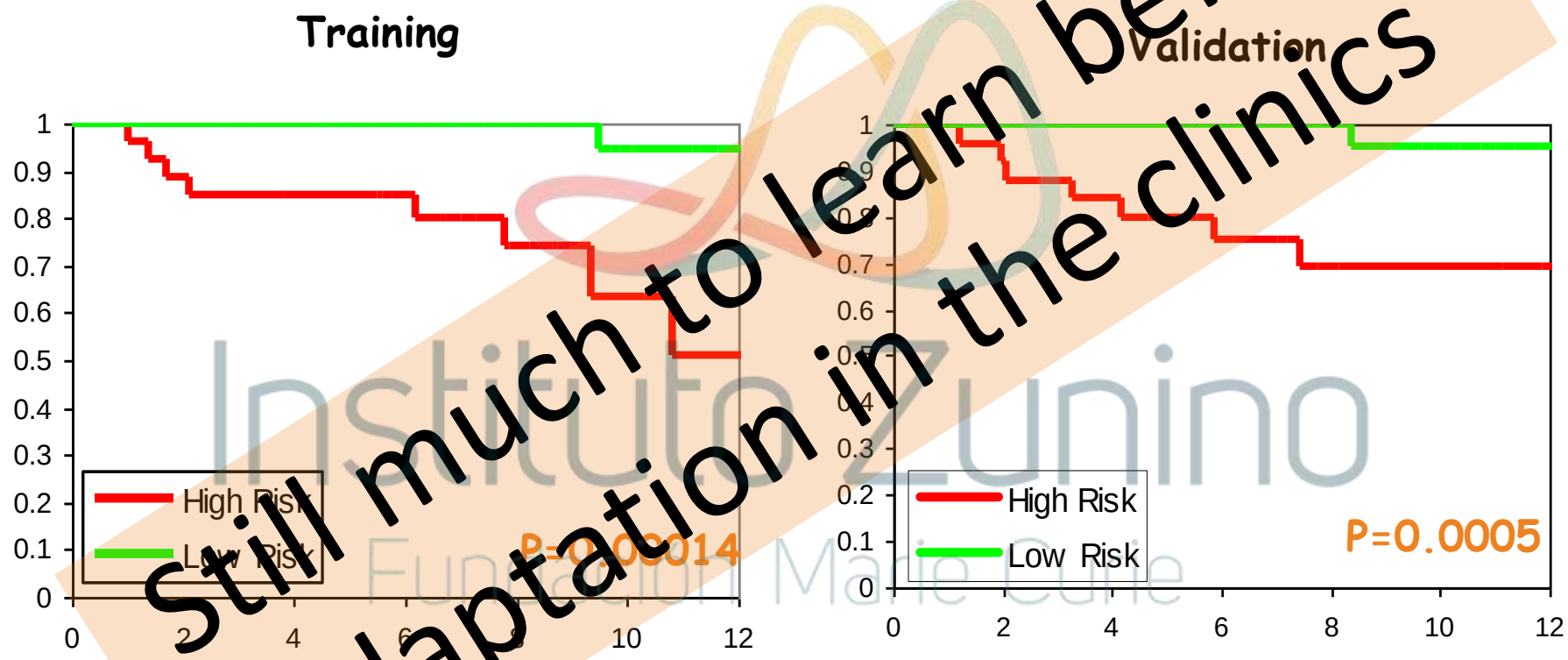
Molecular subtypes & locoregional ttm: *Discussion*

Predict of Local Recurrence in Early Breast Cancer



Still much to learn before adaptation in the clinics

Institute Gustave Roussy
Fondation Marie Curie

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Molecular subtypes & locoregional ttm: *Conclusions*

- ✓ Validated risk factors are known
  - After mastectomy
  - After BCS +/- WBRT +/- boost
  - After APBI
- ✓ Risk factors change over time ➔ role of systemic treatment

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Molecular subtypes & locoregional ttm: *Conclusions*

Evolution of sites of recurrence after EBC over the last 20 years

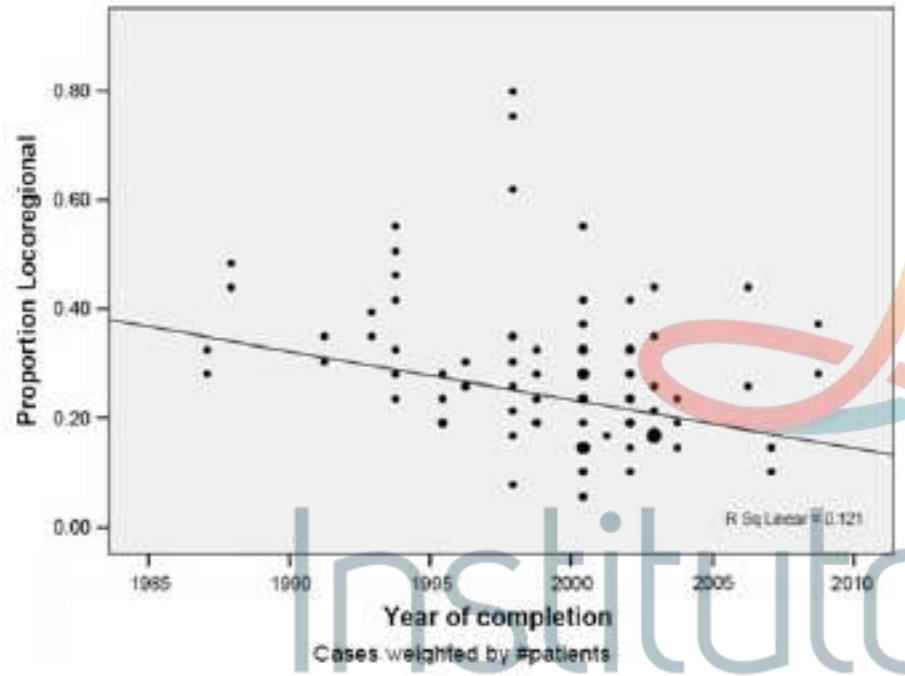

Fig. 1 Proportion of locoregional recurrences over time

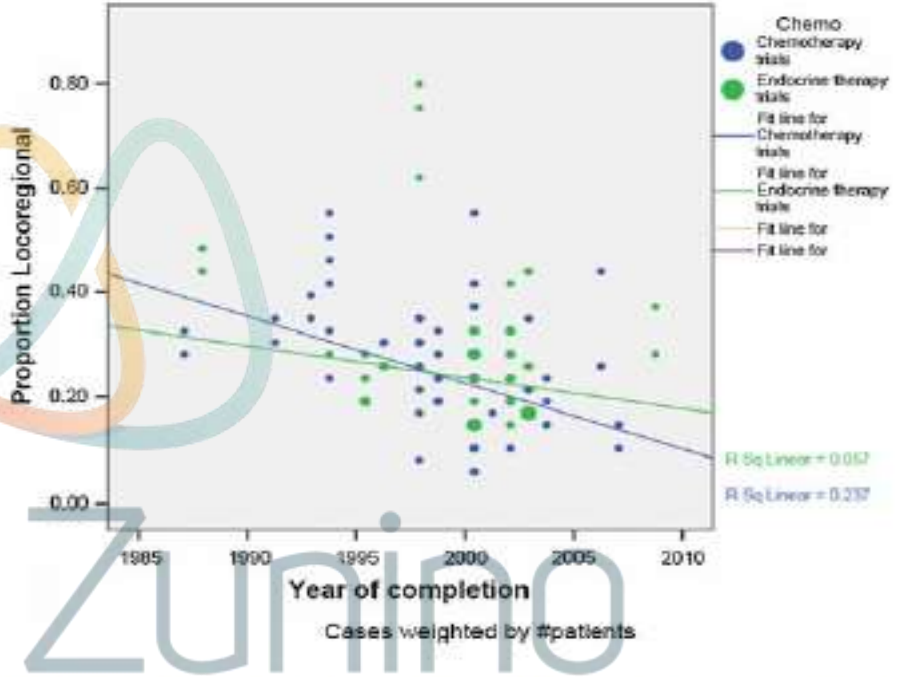

Fig. 2 Proportion of locoregional recurrences for endocrine and chemotherapy over time

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Advances in treatment have differentially reduced the proportion of LRR compared with DR ➔ down to 10-15% of all recurrences ➔ influence design new clinical trials.

Molecular subtypes & locoregional ttm: *Conclusions*

Still a lot of work to be done!

- Predictive molecular and genetic testing of normal tissue and tumour responsiveness.
- The role of the immune system and host response.
- Test general hypotheses relating to radiation genomics and normal tissue responses.
- Large databases incl radionomics
- Nanoparticles as radiosensitisers.
- Sequential/serial biopsies.
- Overall treatment time.

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Molecular subtypes & locoregional ttm: *Conclusions*

Lancet Oncol 2016
Published Online
December 16, 2016
http://dx.doi.org/10.1016/
S1470-2045(16)30660-X

Comment

*Philip Poortmans, Orit Kaidar-Person, Paul Span

Radiation oncology enters the era of individualised medicine

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CORRESPONDENCE

Lorenzo Livi and Icro Meattini
Orit Kaidar-Person
Philip M. Poortmans

Elective Nodal Irradiation in Breast Cancer: Time for Trials on the Basis of Tumor Biology

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Molecular subtypes & locoregional ttm: *THM*

Take home messages

- The molecular subtype influences the recurrence risk ...
- ... as well as the relative distribution of recurrences!
- Systemic treatments modify the recurrence risks and distribution ...
- ... and thereby modify the contribution of optimising locoregional control!
- Probably most benefit of locoregional ttm on OS for patients with low-risk tumours (Lum-A) and those treated with effective systemic treatment (Her2; TN)

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Molecular subtypes & locoregional ttm: *THM*

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Molecular subtypes & locoregional ttm:

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- Liesbeth Boersma
- Sandra Hol
- Icro Meattini
- And many others!

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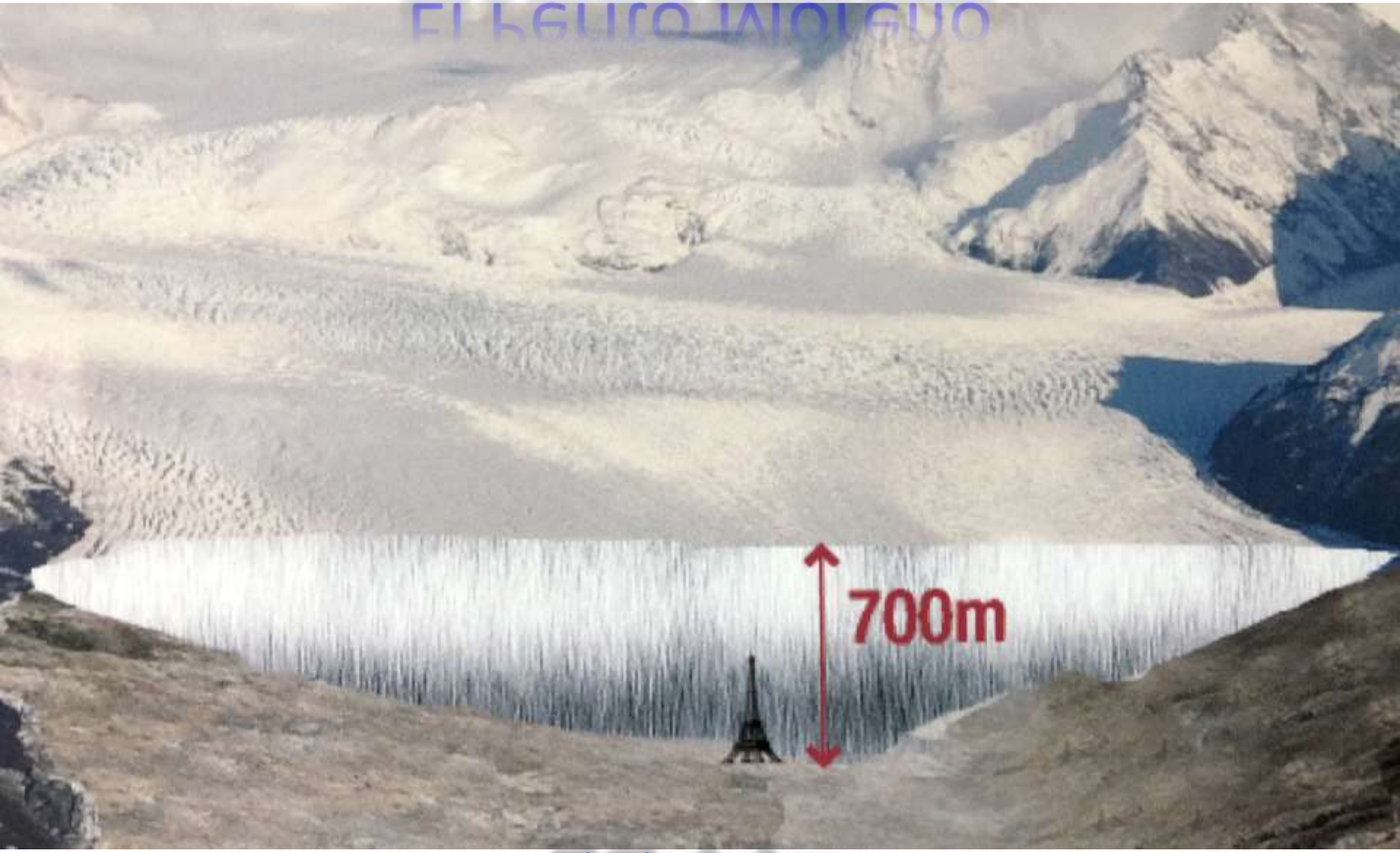
El Perito Moreno



El Glaciarium

El 5 de abril 2019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