



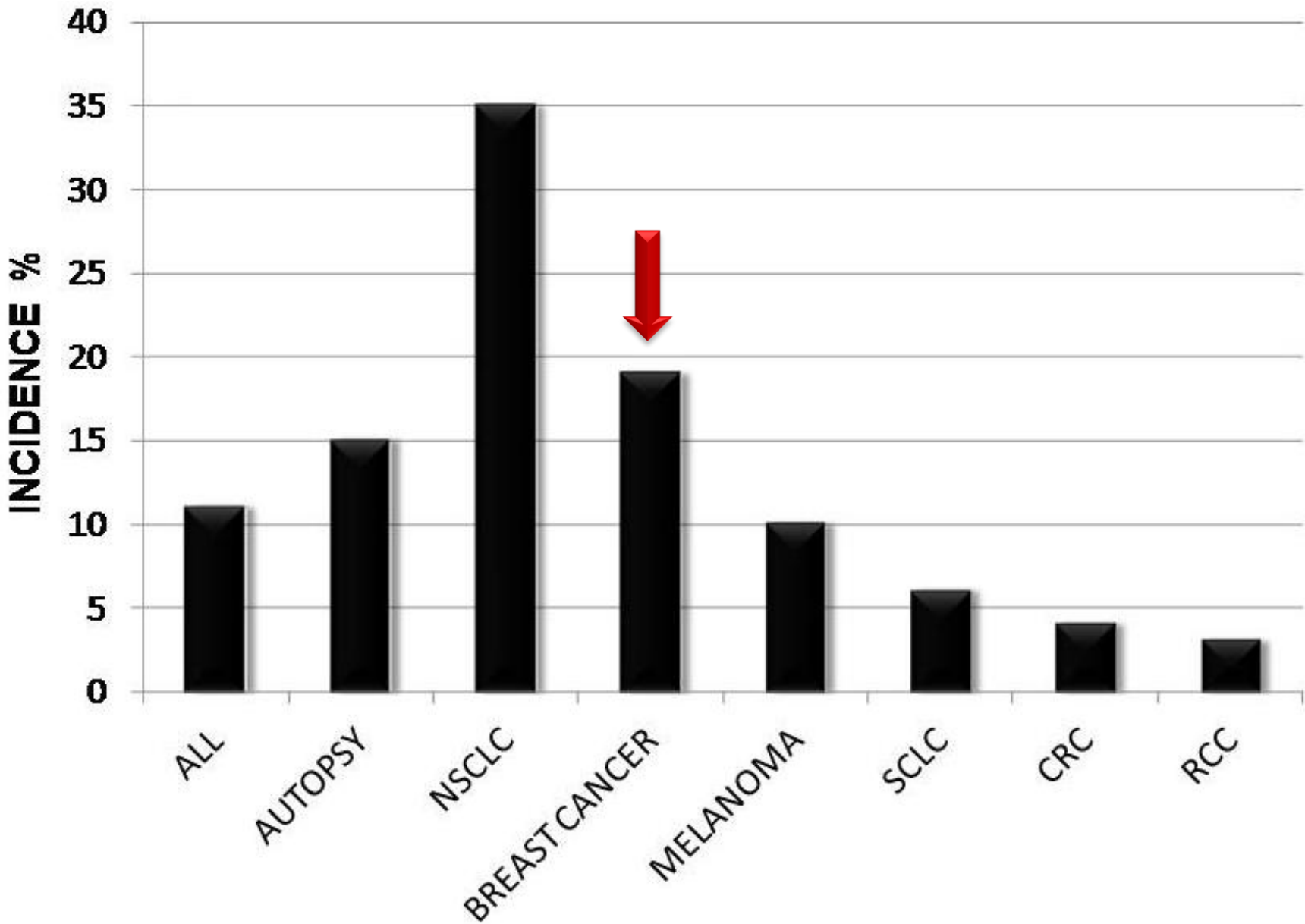
***METASTASI
CEREBRALI da
CARCINOMA
MAMMARIO
HER2-POSITIVO:***

***incidenza e
prognosi
nei sottotipi***

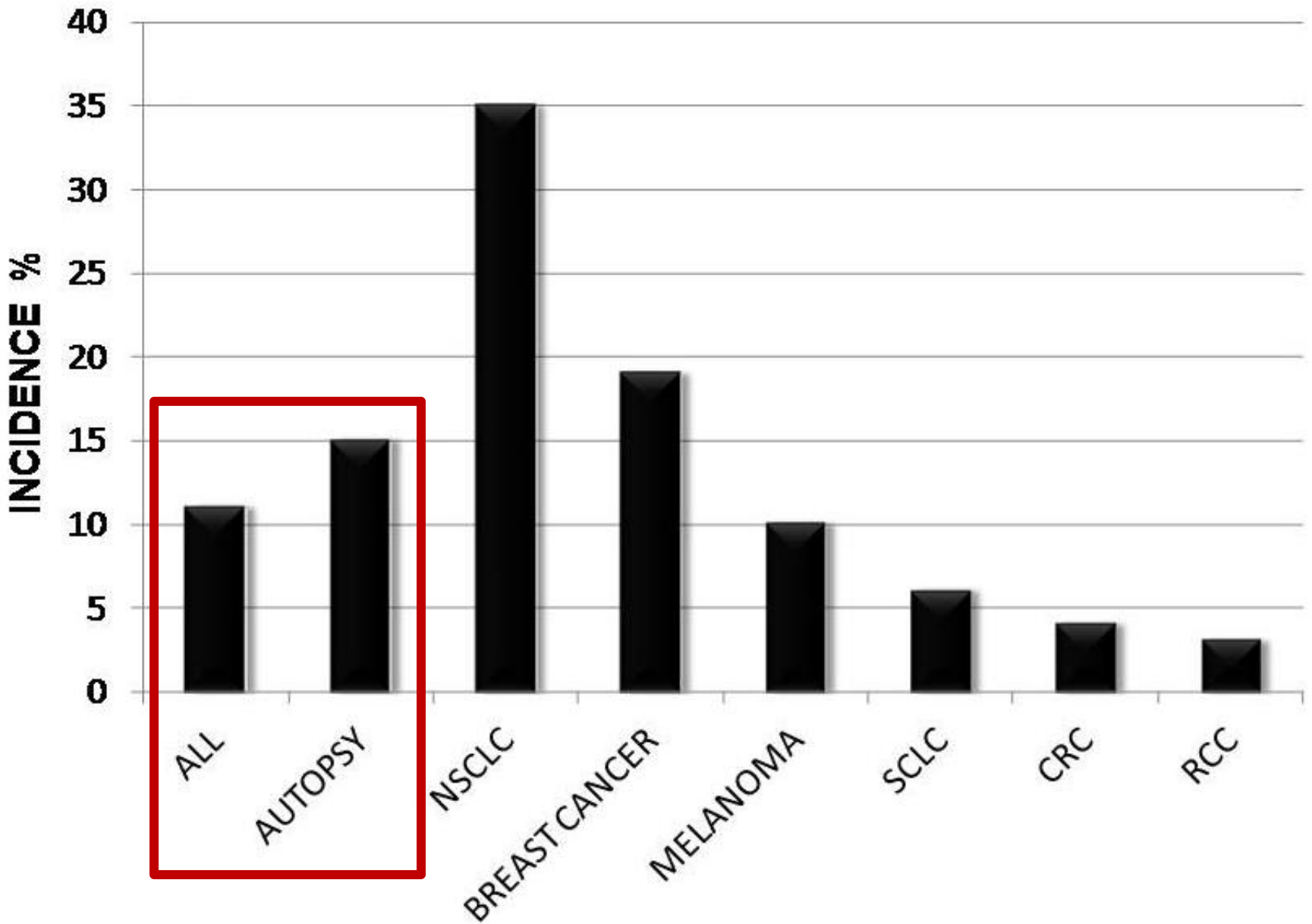
Dr. Caterina Fontanella

Dipartimento di Oncologia, Ospedale Universitario di Udine

INCIDENCE OF BRAIN METASTASES



INCIDENCE OF BRAIN METASTASES



BRAIN METASTASES from BREAST CANCER: An underestimated problem?

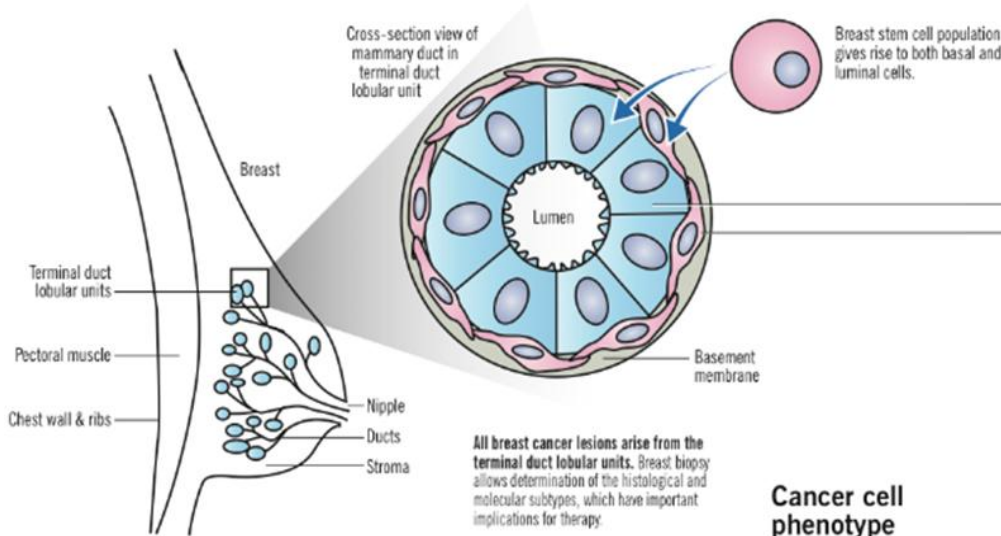
Overall incidence of CNS involvement in mBC patients reported in literature range from 10 to 16%

Prevalence determined on the basis of autopsy data could be as high as 30%

In the CEREBEL trial almost 20% of screened asymptomatic mBC patients were diagnosed with brain metastases



HOW MANY DIFFERENT DISEASES?



All breast cancer lesions arise from the terminal duct lobular units. Breast biopsy allows determination of the histological and molecular subtypes, which have important implications for therapy.

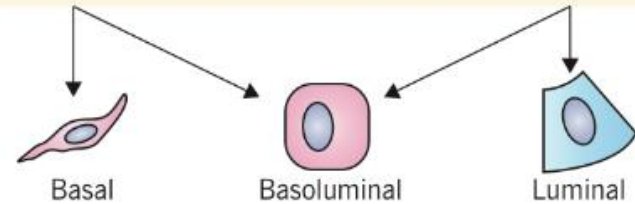
Normal breast stem cells or progenitor cells transform into breast cancer cells. The cancer cells are similar in phenotype to the normal basal and luminal cells of the ductal structure.

Basal or myoepithelial cells

- Contractile cells for milk ejection
- Estrogen receptor –
- Progesterone receptor –

Luminal or epithelial cells

- Respond to hormonal stimulation for milk production
- Estrogen receptor +
- Progesterone receptor +/-



Cancer cell phenotype

Histological subtypes	Ductal	Lobular	Molecular subtypes	Triple negative	HER2+	Luminal B	Luminal A
				ER-, PR-, HER2-			
Preinvasive cancer 25% Cells limited to basement membrane	Ductal carcinoma in situ (DCIS) 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral	Lobular carcinoma in situ (LCIS) 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cadherin loss 1% progress per year Can be bilateral	% of breast cancers	15-20%	10-15%	20%	40%
Invasive cancer 75% Extension beyond the basement membrane	Invasive ductal carcinoma (IDC) 79% Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood	Invasive lobular carcinoma (ILC) 10% Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+	Receptor expression		HER2		ER+/PR+
			Histologic grade Level of cell differentiation	High (grade III)			Low (grade I)
			Prognosis Correlates to histologic grade	Poor			Good
			Response to medical therapy	(Chemotherapy)	Trastuzumab		Endocrine

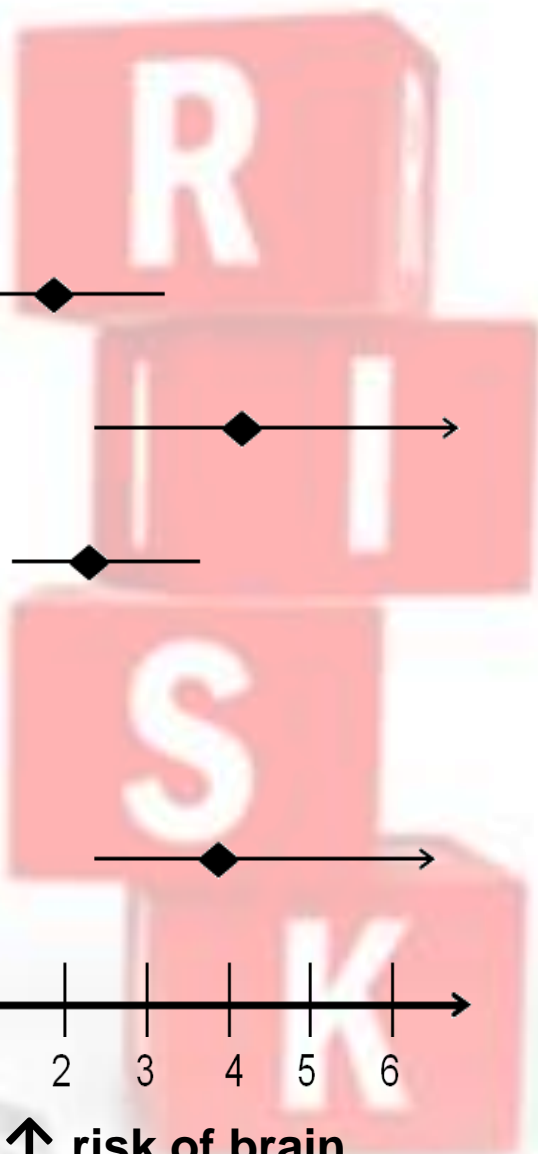
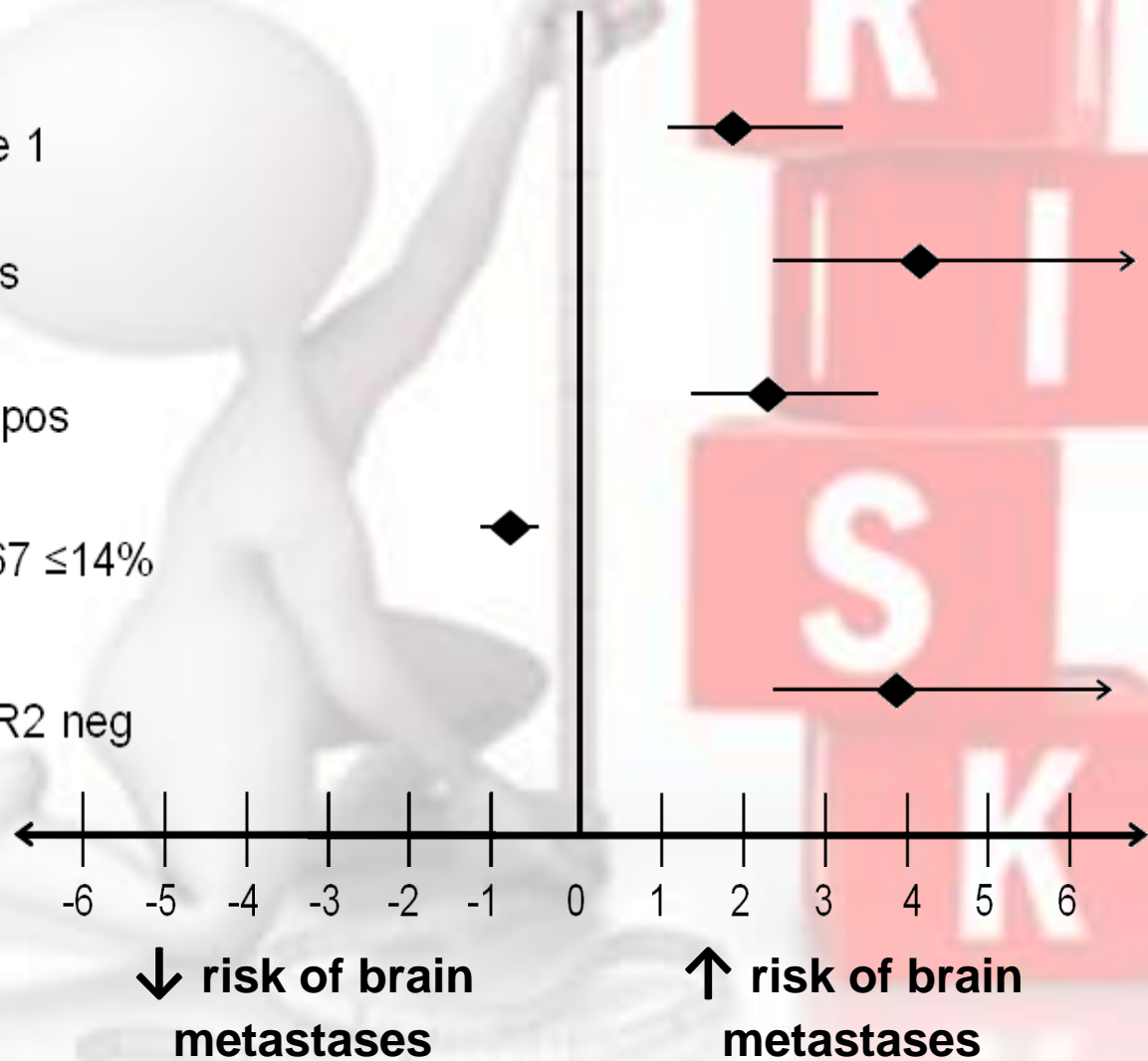
Grade 3 vs. Grade 1

ER neg vs. ER pos

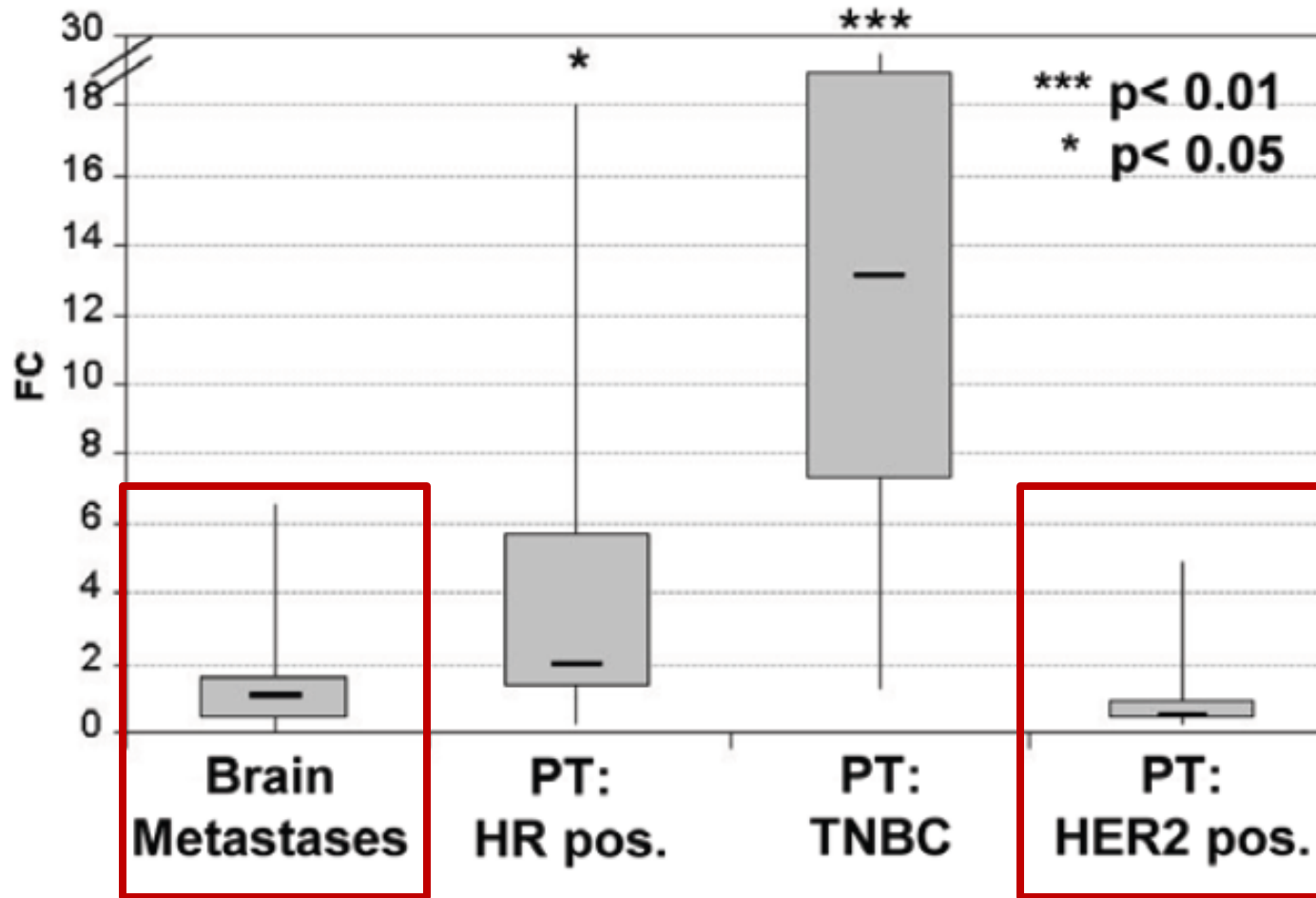
PgR neg vs. PgR pos

Ki67 >14% vs. Ki67 ≤14%

HER2 pos vs. HER2 neg

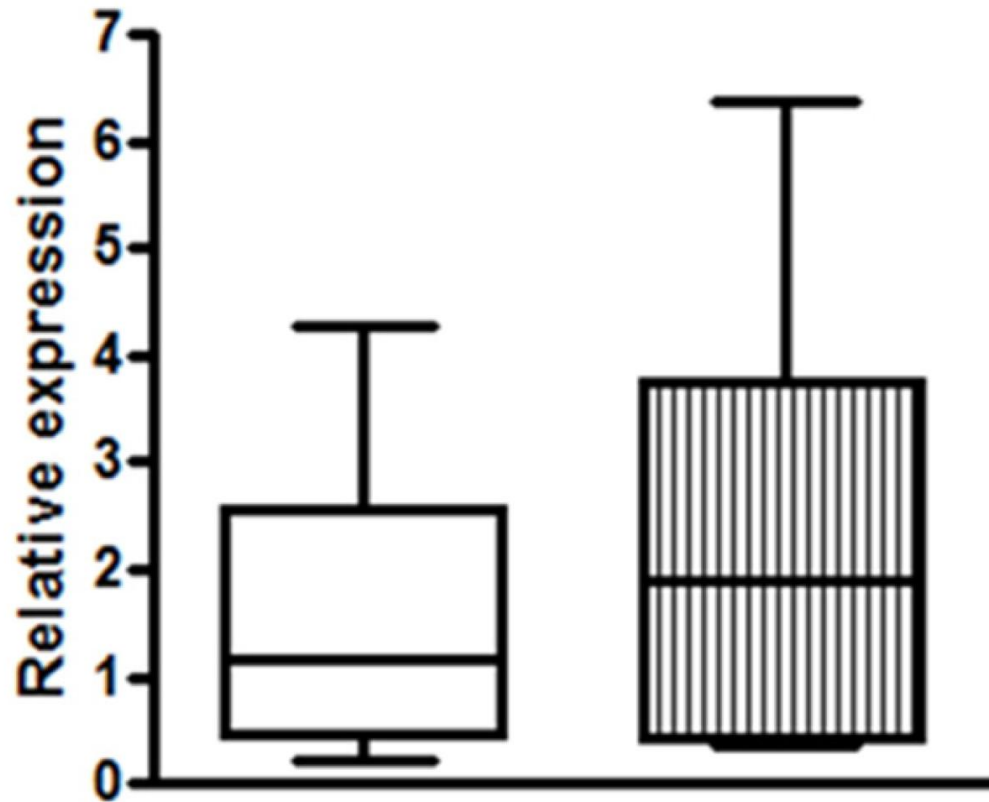


CADM1



microRNA-10b

- Breast cancers without mets
- ▨ Breast cancers with brain mets





Why HER2-POSITIVE BC patients have the highest risk of SNC involvement?

Drug with low penetrance through the BBB may:

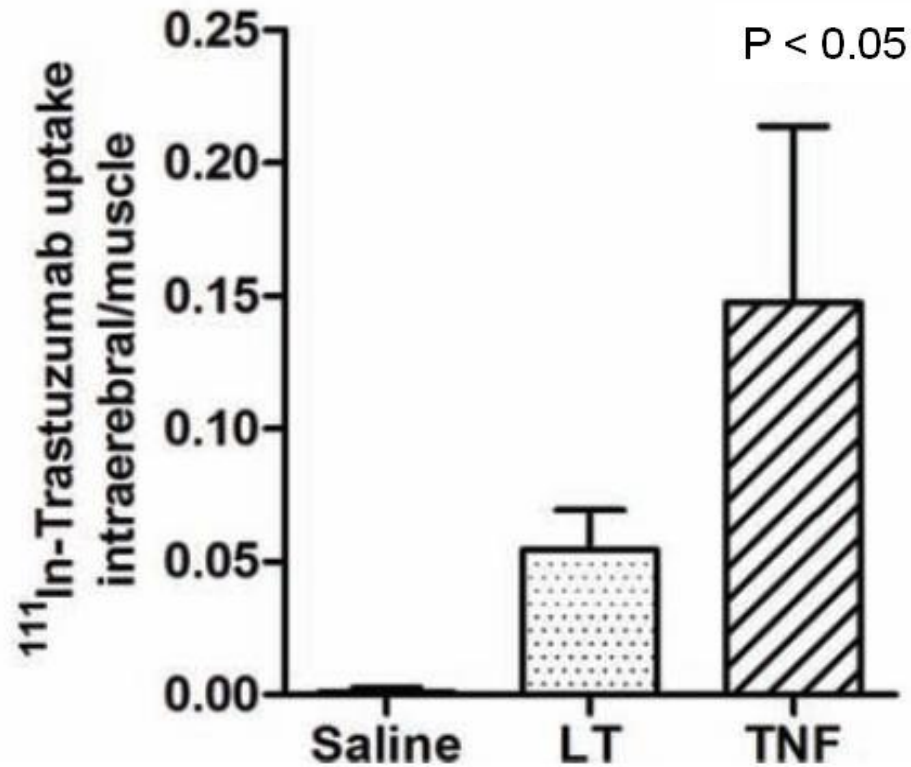


↓ risk of distant metastases

↑ overall survival

↑ risk of brain metastases

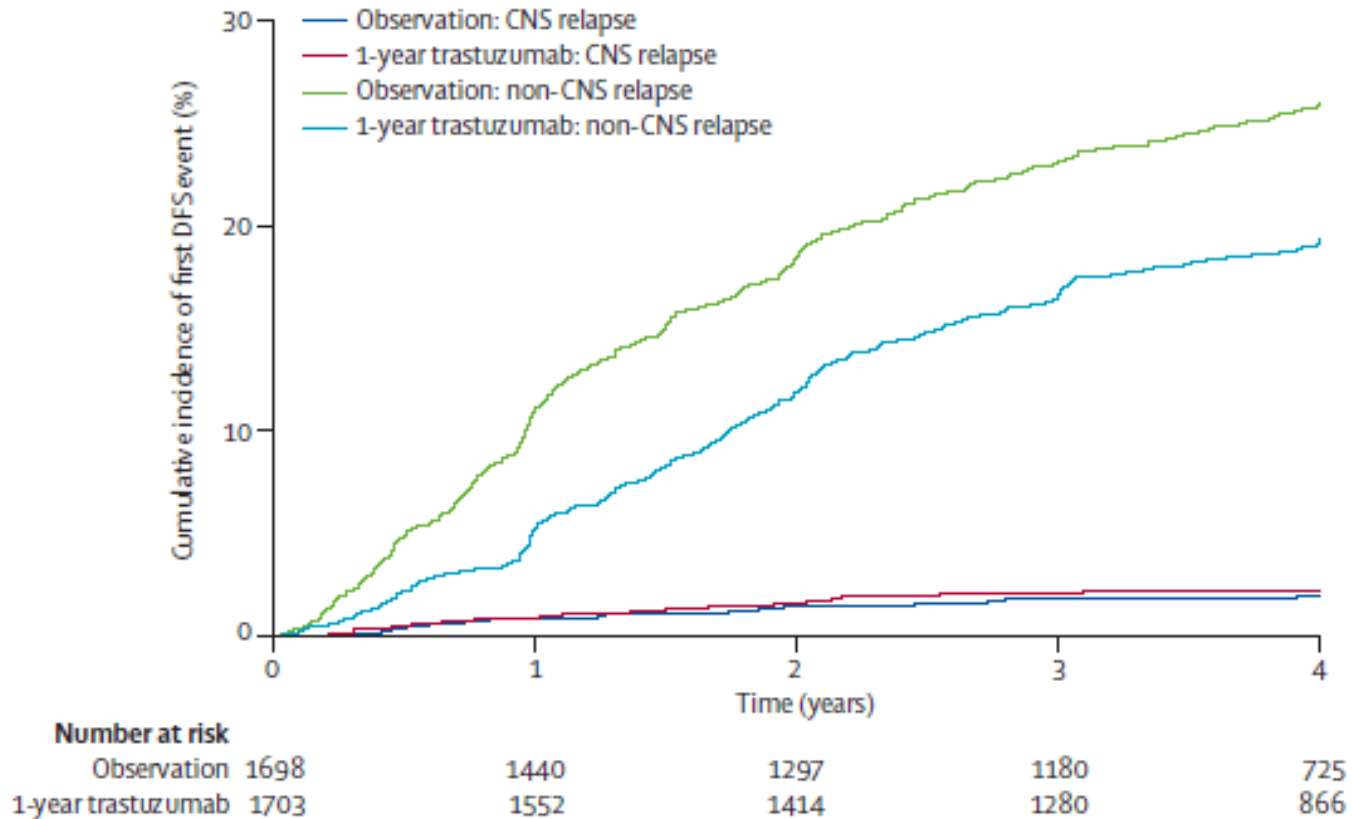
IN PRECLINICAL MODELS



Trastuzumab in common saline solution did not cross the BBB.

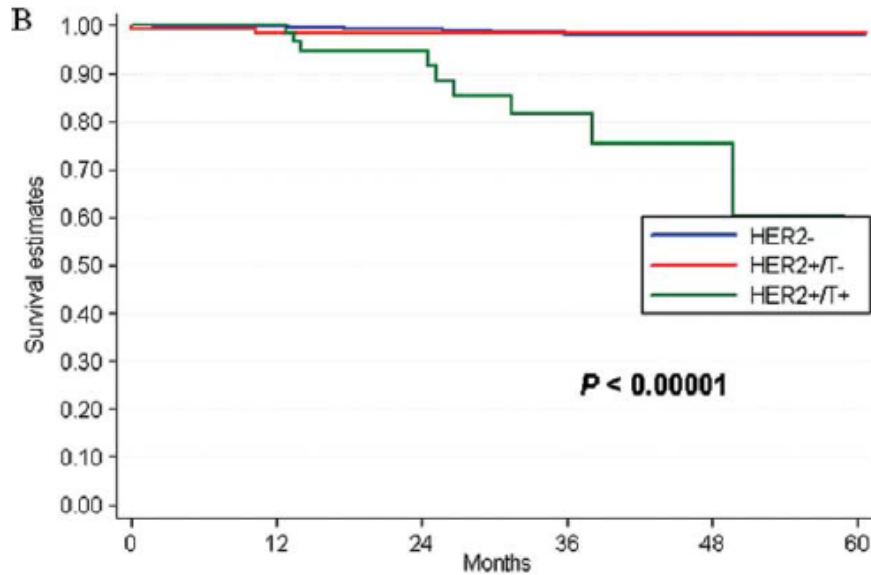
TNF injected intravenously increased the BBB permeability to trastuzumab.

ADJUVANT SETTING



In the HERA trial adjuvant trastuzumab did not increase the risk of CNS relapse.

ADJUVANT SETTING



	Total	Events	Censored	%	M.T.	S.E.	CI95%
HER2-	1210	15	1195	98.7	20.75	0.30	20.15-20.91
HER2+T-	128	2	126	98.4	5.8	0.20	5.45-5.90
HER2+T+	86	9	77	89.5	26.7	0.20	25.96-26.83

1.3% HER2-negative,
1.6% HER2-positive
without trastuzumab,
10.5% HER2-positive with
trastuzumab ($p < 0.00001$)

Meta-analysis of the NSABP B-31, NCCTG N9831, and HERA trials ↑ incidence
of BM in the trastuzumab arms (RR 1.57, 95% CI 1.03–2.37; $p = 0.033$)

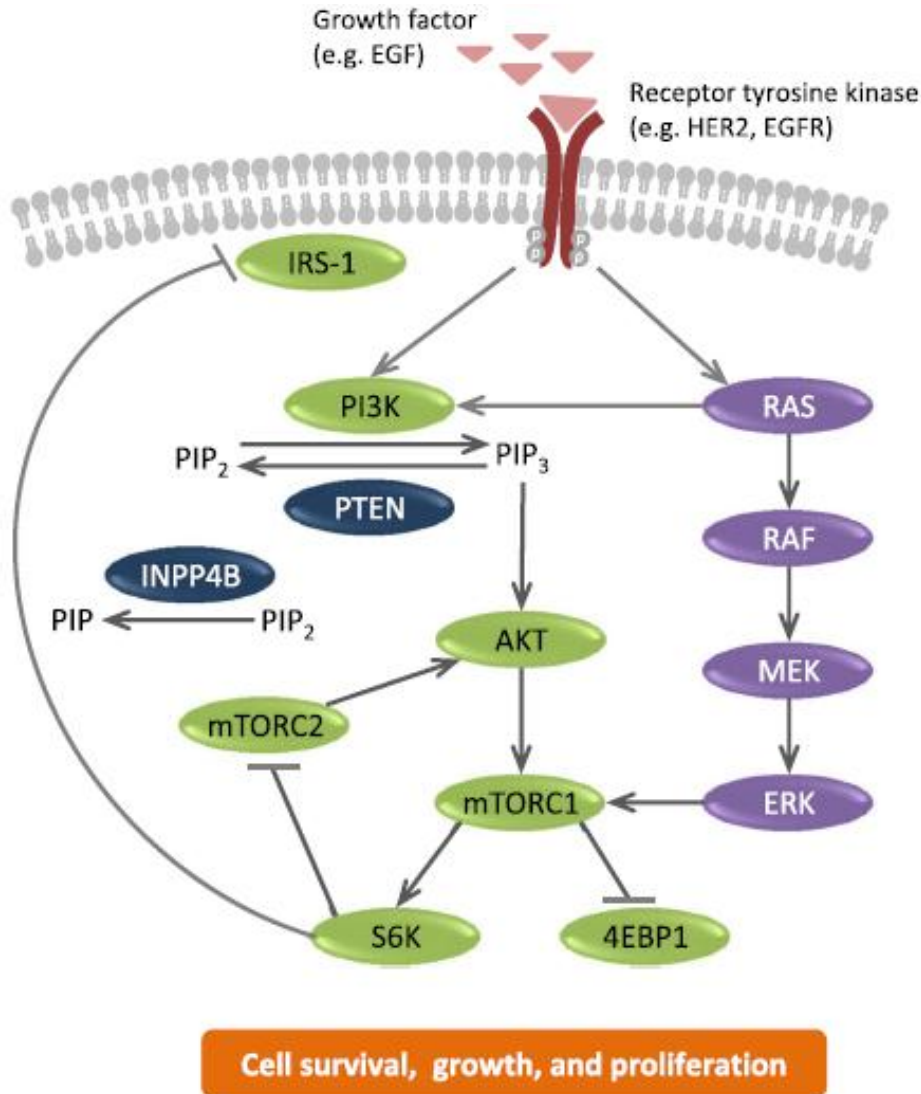
METASTATIC SETTING

Risk for CNS metastases ↑ in patients treated with trastuzumab in ≥ 2 lines (58.5 vs. 24.1%, $p < 0.001$).

Median TTBM 17.5 months in Luminal, 13.7 months in HER2-positive with trastuzumab, 5.8 months in HER2-positive not trastuzumab, and 2.9 months in TNBC ($p < 0.001$).

Intrinsic biological features of the HER2-positive BC may be related with the ↑ risk of CNS metastases.

IN PRECLINICAL MODELS



Alterations in EGFR, HER2, and PTEN higher in BC brain metastases tumor tissue vs. primary BC ($p < 0.05$)

HER2 overexpressed in 16% primary BC vs. 41% of brain metastatic BC ($p < 0.05$)

17% of *de novo* HER2-positive status.

Genetic alterations in EGFR and PTEN common in TNBC

IN PRE and CLINICAL MODELS relationship with lung metastases

COX2, EGFR ligand, and α 2,6-sialyltransferase ST6GALNAC5 are mediators of cancer cell passage through the BBB.

EGFR ligands and COX2 linked to BC lung diffusion. Lung involvement as site of first distant recurrence is not a significant risk factor of CNS involvement ($p = 0.23$). However, an association between lung and CNS involvement was observed ($p = 0.0017$).



**NO
TREATMENT**

**OS
<1 month**

**1950s
WBRT**

**OS
4-6 months**

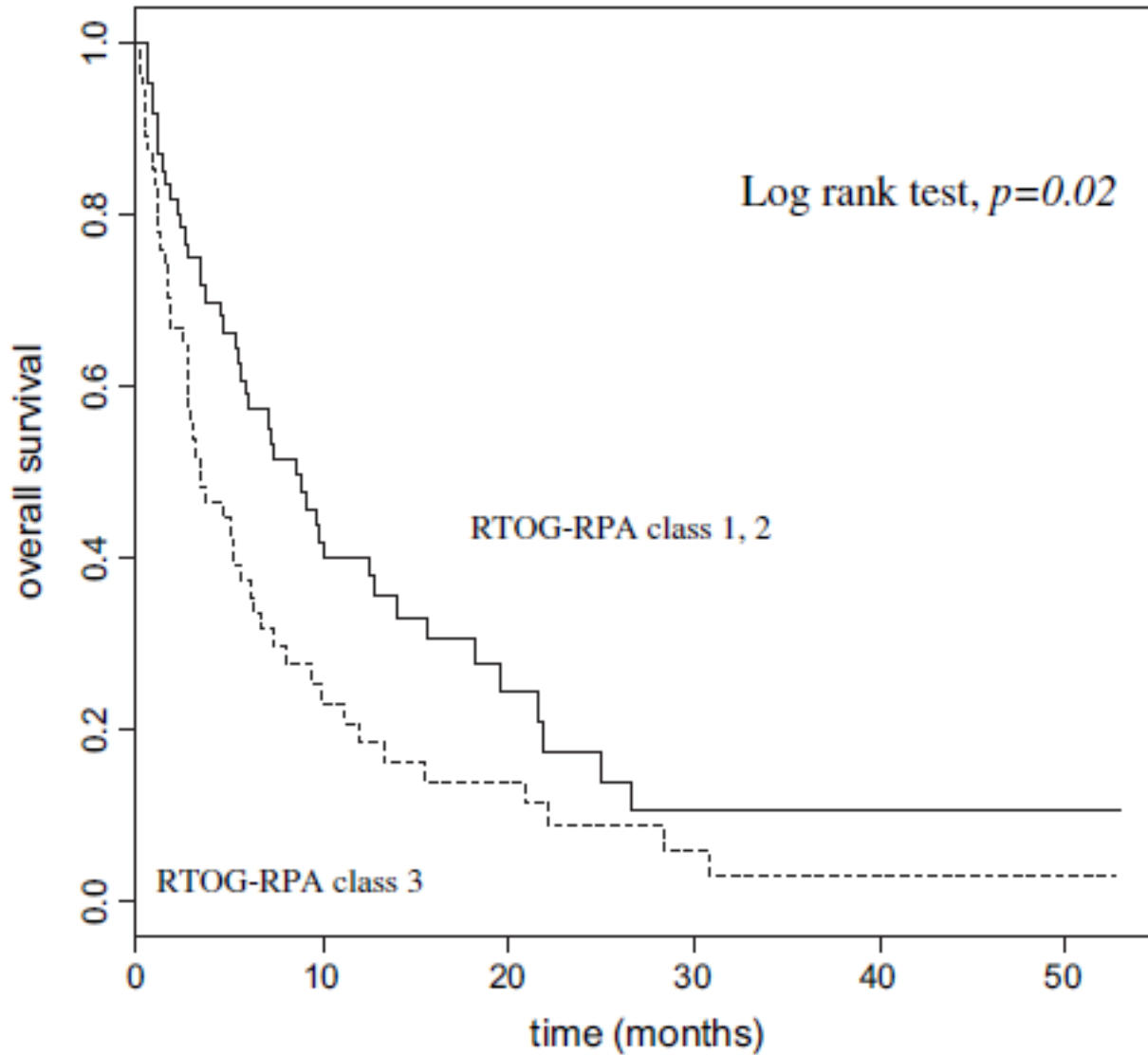
**1990s
SURGICAL
RESECTION**

**OS
≈10 months**

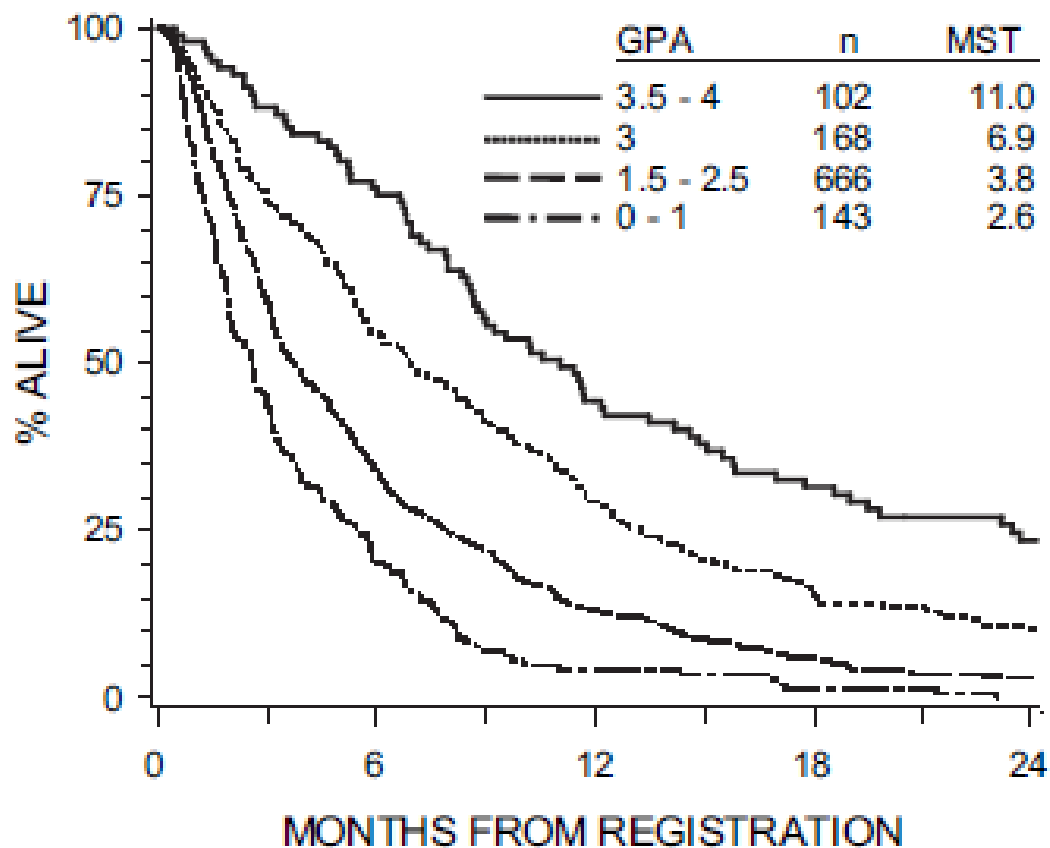
**2000s
SRS**

**OS
≈10 months**

RPA: Recursive Partitioning Analysis



GPA: Graded Prognostic Assessment

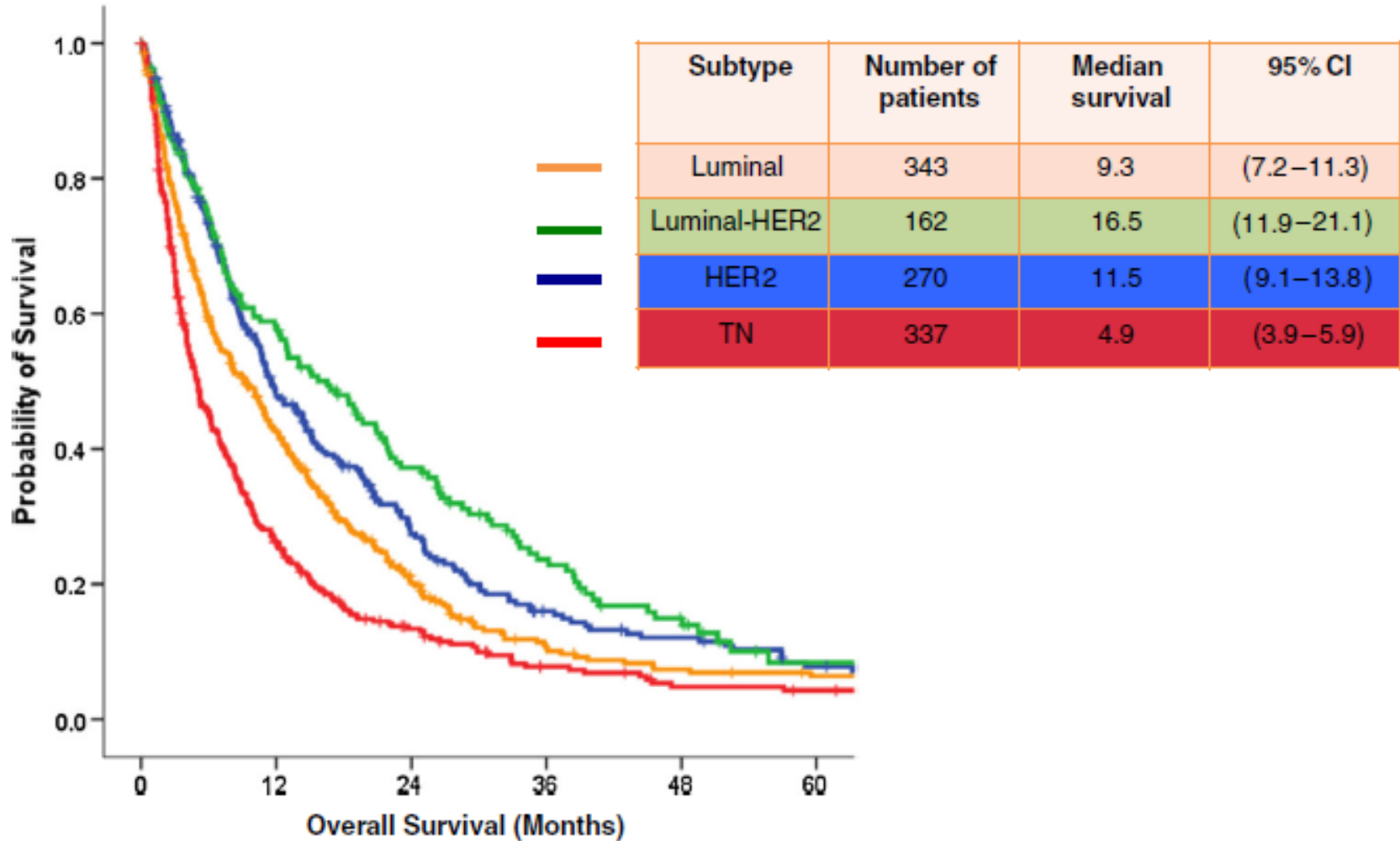


	Score		
	0	0.5	1.0
Age	>60	50-59	<50
KPS	<70	70-80	90-100
No. of CNS metastases	>3	2-3	1
Extracranial metastases	Present	—	None

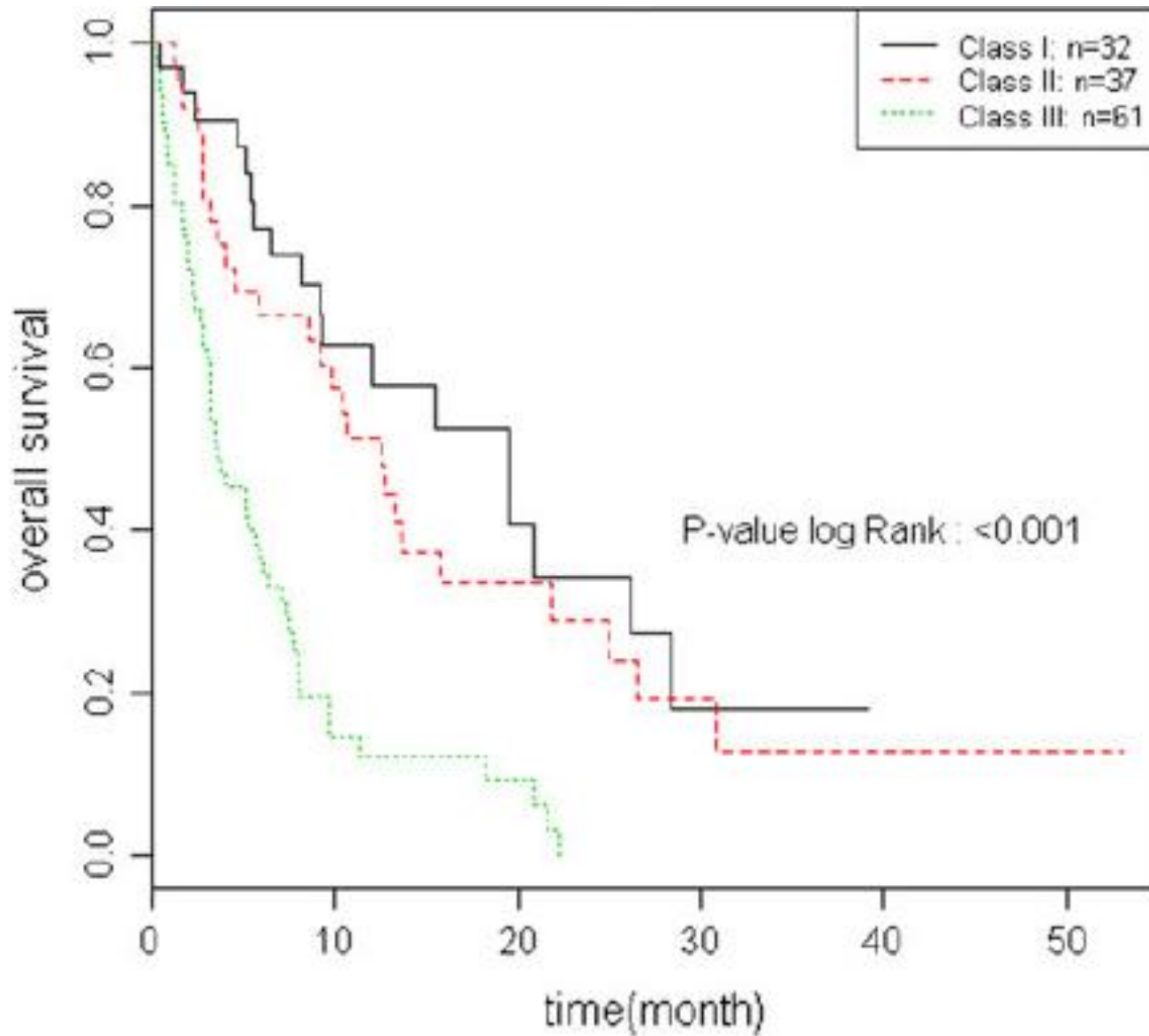
***MEDIAN SURVIVAL AFTER BRAIN
METASTASES DIAGNOSIS IS
DIFFERENT IN BREACT CANCER
SUBTYPES***



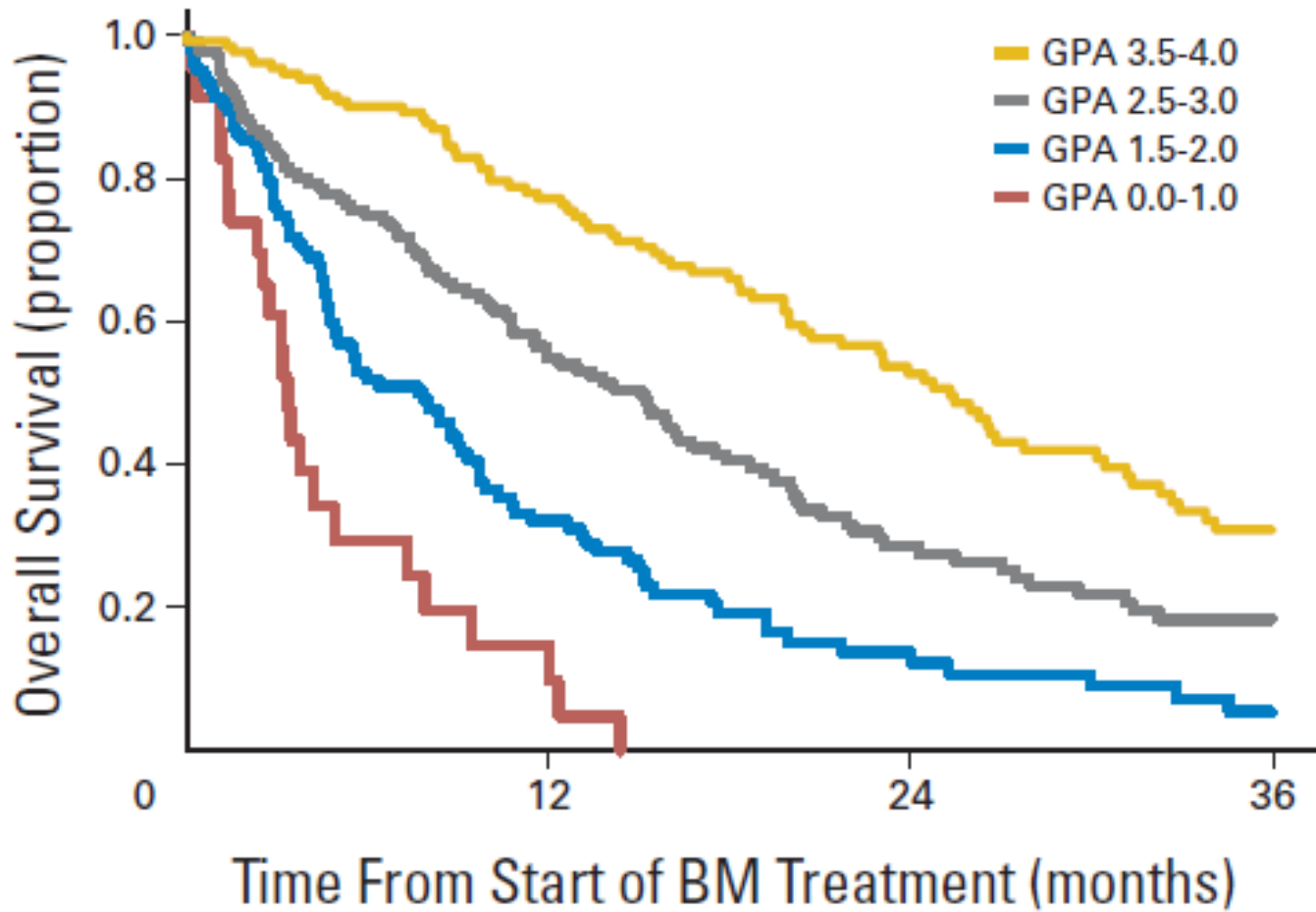
OS after developing of brain metastases



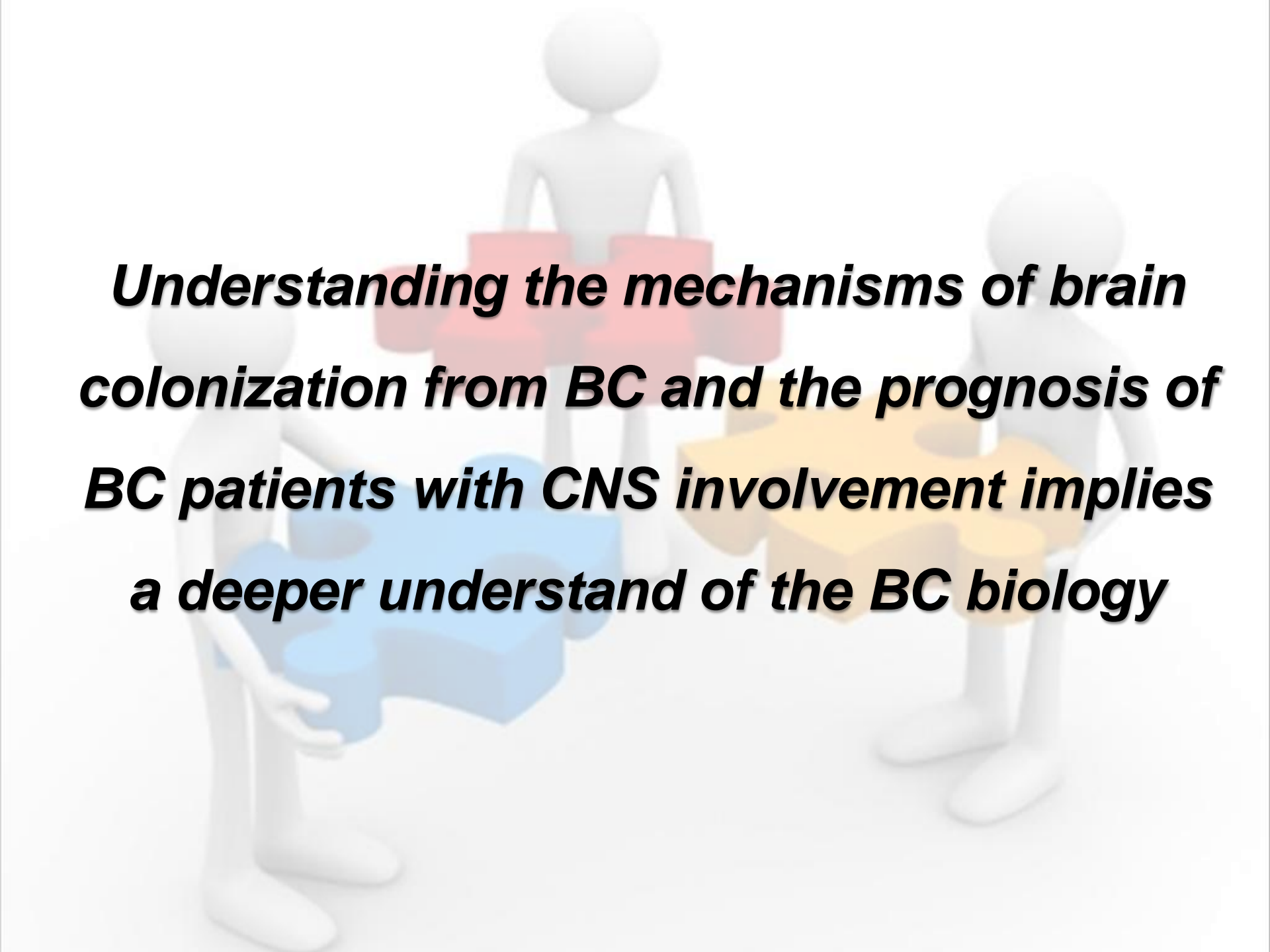
BMBC RPA



BMBC GPA



Prognostic Factor	GPA Scoring Criteria					Patient Score
	0	0.5	1.0	1.5	2.0	
KPS	≤ 50	60	70-80	90-100	n/a	—
Subtype	Basal	n/a	LumA	HER2	LumB	—
Age, years	≥ 60	< 60	n/a	n/a	n/a	—

The background features three semi-transparent 3D rendered human figures. The figure in the center holds a large red puzzle piece. The figure on the left holds a large blue puzzle piece. The figure on the right holds a large yellow puzzle piece. The puzzle pieces are interlocking and appear to be part of a larger assembly.

***Understanding the mechanisms of brain
colonization from BC and the prognosis of
BC patients with CNS involvement implies
a deeper understand of the BC biology***