New Therapeutic Strategy for CNS Metastases in Breast Cancer

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- Clinical characteristics of breast cancer brain metastases (BCBM)
- Prognostic assessement for BCBM
- Current status of new targeted therapeutics for BM
  - Targeting blood brain barrier
  - Anti-HER2 treatment
  - Immunotherapeutic approaches
  - Others

Brain Metastases and Breast Cancer

- Brain metastases(BM)
  - Most common intracranial malignancy in adults
  - Originating from lung cancer(40-50%), breast cancer(15-25%), melanoma(5-20%), and renal cell carcinoma

- Unmet need of BM
  - median survival of less than 6 months for decades
  - neurologic impairment - major limitation of QOL
  - underrepresented population of clinical trials due to poor prognosis and presumed lack of intracranial efficacy of drug

- Increasing prevalence of BCBM as a result of
  - True increase in incidence due to effective treatment of systemic disease and improved survival from diagnosis of primary cancer
  - Improved imaging modalities and detection of subclinical disease earlier

In the beginning of BC-BM, 'HER2+ BC'

- After introduction of trastuzumab in late 1990s, clinicians began to observe an apparent increase in the incidence of BM

- Small retrospective studies of HER2(+) metastatic BC patients
  - Who were treated in late 1990s ~ early 2000s
  - Incidence of BM 25-48%
  - Median survival from BM 4-13 months
  - 50 % of patients died of progressive CNS disease
  - Greater risk of isolated CNS progression

<u>Increased incidence of BM in HER2+ BC</u>
Poor CNS penetration of trastuzumab?
Unmasking of otherwise asymptomatic BM by prolonged survival?
Biology-linked brain tropism?

Bendell 2003; Altaha 2004; Clayton 2004; Yau 2006; Burstein 2005

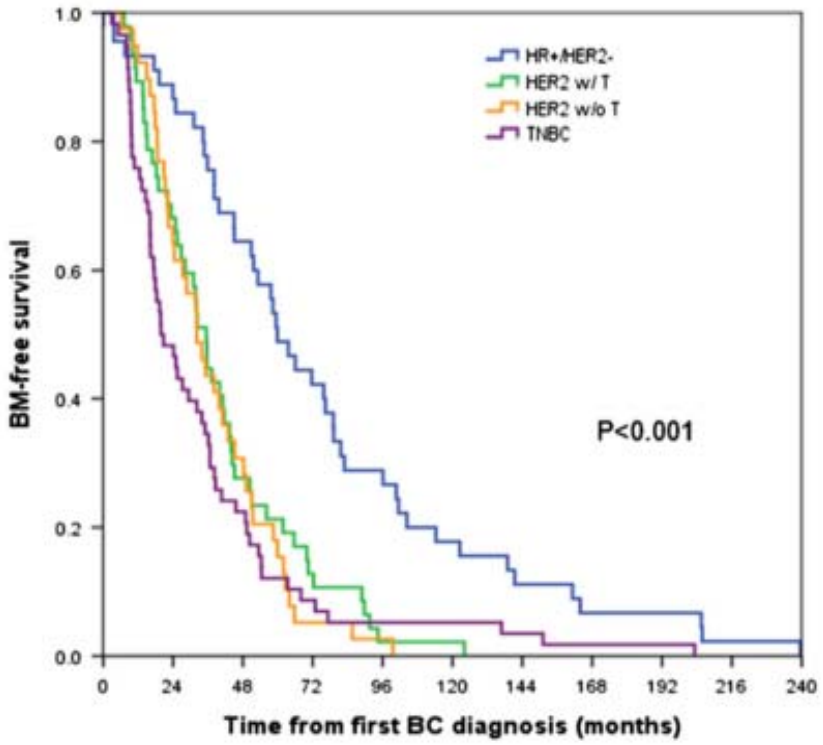
Differences in clinical features of BM & BC subtypes

Reference	# Patients	Period	ER(+) Incidence Median survival	HER2(+) Incidence Median survial	TNBC Incidence Median survival
Retrospective studies on metastatic disease					
Bendell 2003	Stage IV N=122 (42 BM) Median f/u 23 mo	1998-2000	- 	34% 13mo	-
Nam 2008	Stage IV N=682 (126 BM) Median f/u 31 mo	2001-2006	8% 7.3mo	25% 13mo	25% 3.4mo
Lin 2008	Stage IV N=116 (53 BM)	2000-2006	-	-	46% 4.9 mo
Eichler 2008	N=83 BM	2001-2005	11.0mo	17.1mo	4.0 mo
Metro 2011	N=81 (30 BM)	2006-2009	-	27.9mo	-
Park 2009	N=251 (77 BM)	1999-2006	-	14.9 mo	-
Yap 2012	N=280 BM	2006-2008	-	18.5 mo	-

- Incidence of BM : HER2(+) & TNBC > ER(+)
- Survival of BM : HER2(+) > ER(+) > TNBC

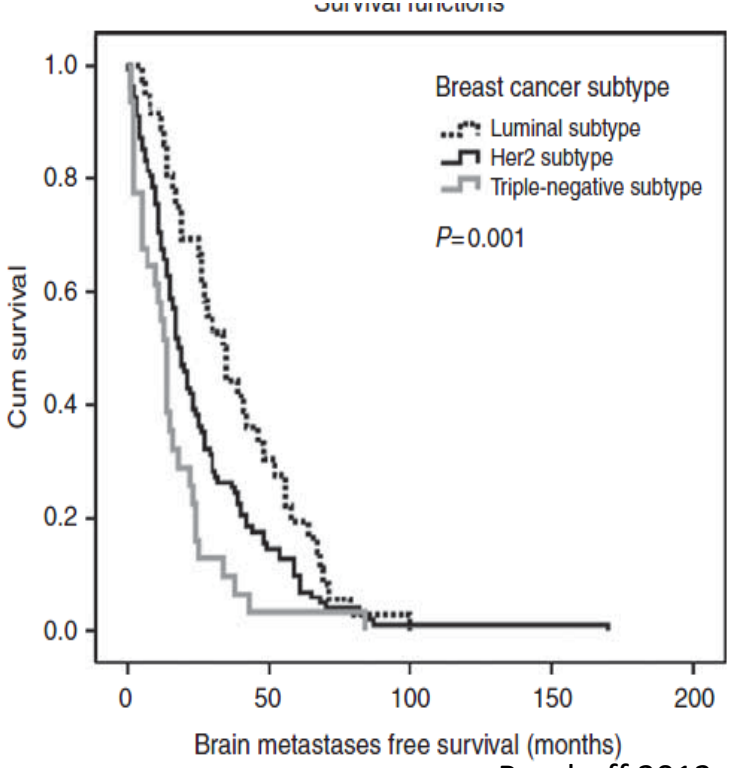
Timing of BM occurrence according subtype of BC

BM free survival
from initial BC diagnosis



Ahn et al. 2013

BM free survival
from initial metastasis



Berghoff 2012

Duration of BM free survival : ER(+) > HER2(+) > TNBC
→ Need for identification of high-risk population and early preventive intervention?

Initial management of BM

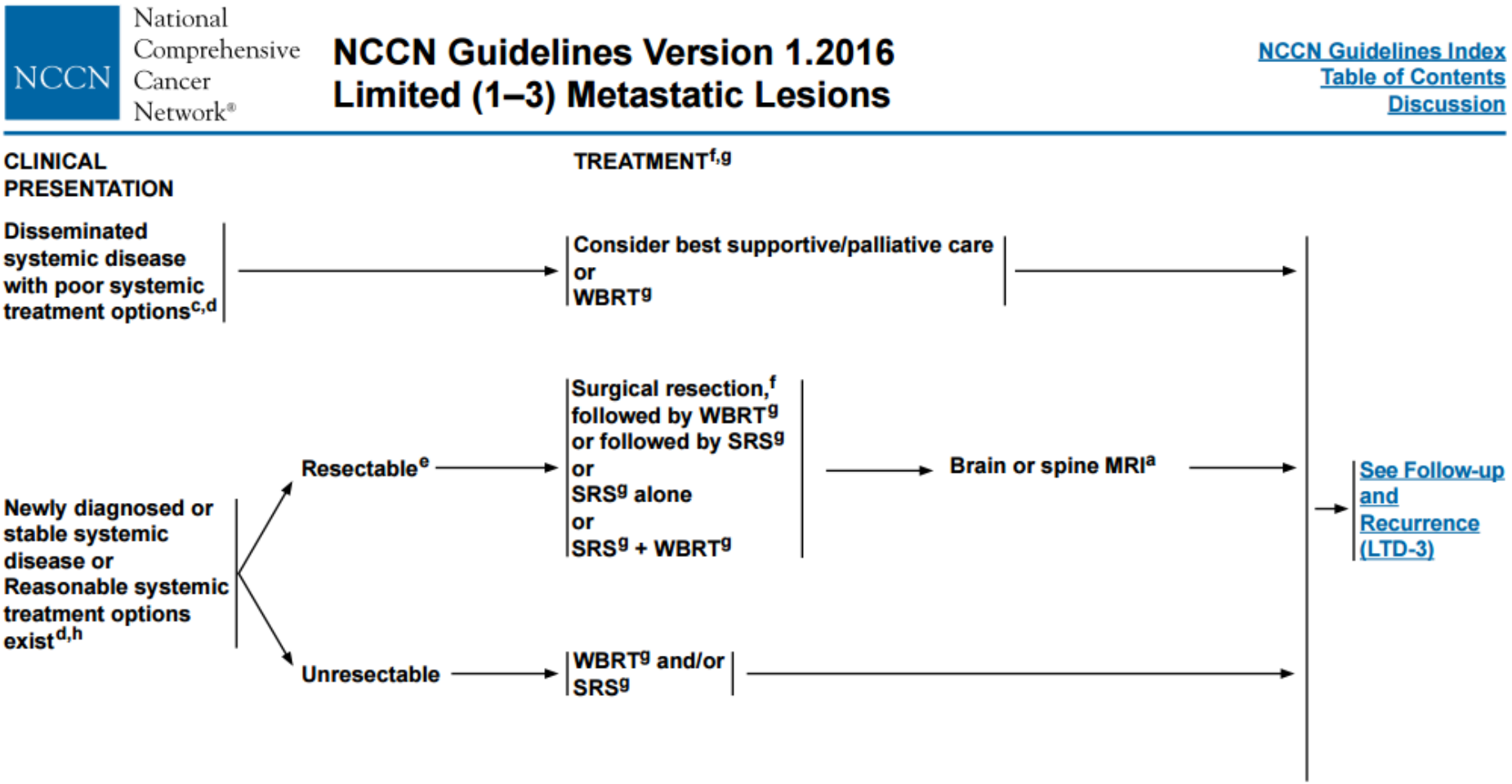
- Despite increasing knowledge of different behavior of BM according to tumor subtype,
- Primary tumor-adapted guidelines for BM treatment is lacking

- Current **standard treatment option** for BM is local treatment including
  - Surgery
  - Stereotactic radiosurgery (SRS)
  - Whole brain radiotherapy (WBRT)

- Initial **assessment of prognosis** is important

  To predicting the results of therapeutic interventions

  To comparing treatment results in clinical trials



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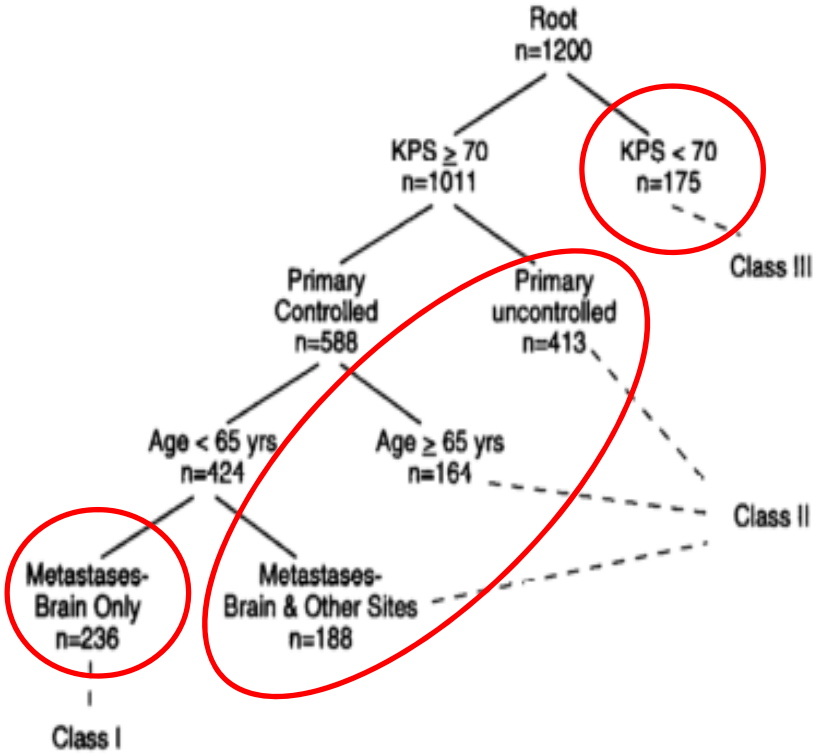
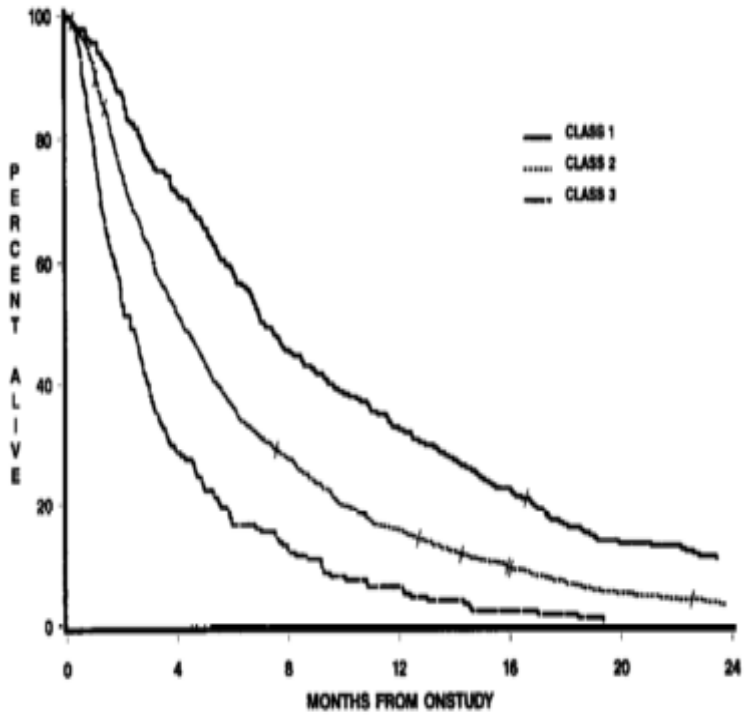
  - Whole brain radiotherapy (WBRT)

- Initial **assessment of prognosis** is important
  - To predicting the results of therapeutic interventions
  - To comparing treatment results in clinical trials

Recursive Partitioning Analysis (RPA)

- 1200 pts from three RTOG trials (1979-1993)
- Primary cancer : Lung 61%, Breast 12%, Others 21%
- Median survival
  : 2.3 months (Class 3) vs. 4.2 months (Class 2) vs. 7.1 months (Class 1)





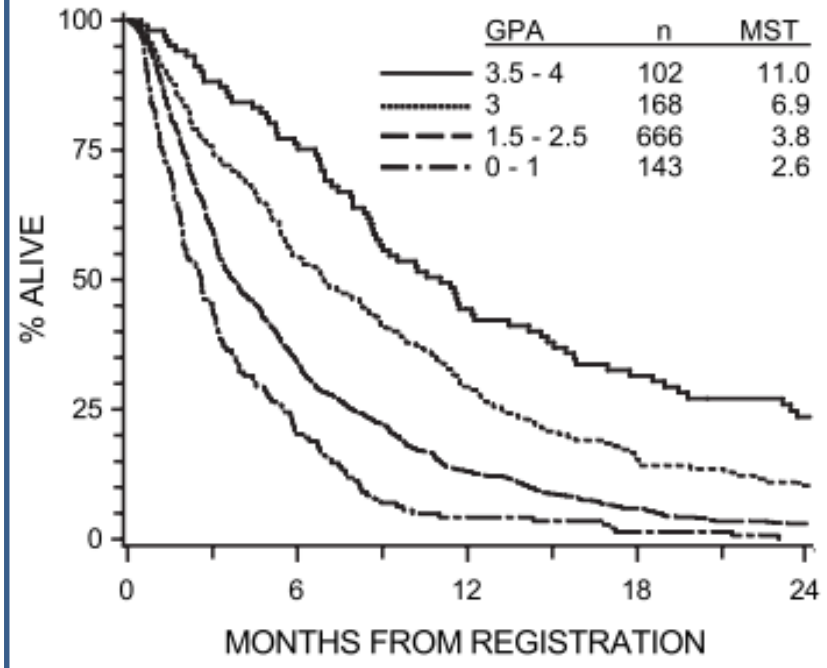
Gaspar et al. IJROBP 1997

Graded Prognostic Assessment (GPA)

1,960 patients from five RTOG trials

GPA index

	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



Basic Score for Brain Metastases (Lorenzoni 2004)

	Score	
	0	1
KPS	50–70	80–100
Control of primary tumor	No	Yes
Extracranial metastases	Yes	No

Score Index for Radiosurgery (Weltman 2000)

	Score		
	0	1	2
Age (y)	≥60	51–59	≤50
KPS	≤50	60–70	80–100
Systemic disease	Progressive	Stable	CR or NED
No. of lesions	≥3	2	1
Volume of largest lesion (ml)	>13	5–13	<5

Sperduto et al. IJROBP 2008

Diagnosis-specific GPA

- 4,529 patients from 1985-2007

GPA of newly diagnosed BMs	Significant prognostic factors	GPA scoring criteria				
NSCLC/SCLC		0	0.5	1	—	—
	Age	>60	50–60	<50	—	—
	KPS	<70	70–80	90–100	—	—
	ECM	Present	—	Absent	—	—
	No. of BMs	>3	2–3	1	—	—
Melanoma/ renal cell cancer		0	1	2	—	—
	KPS	<70	70–80	90–100	—	—
	No. of BMs	>3	2–3	1	—	—
Breast/GI cancer		0	1	2	3	4
	KPS	<70	70	80	90	100

Diagnosis	Overall	DS-GPA 0–1.0	DS-GPA 1.5–2.5	DS-GPA 3.0	DS-GPA 3.5–4.0	p* (log–rank)
NSCLC	7.00 (6.53–7.50)	3.02 (2.63–3.84)	6.53 (5.90–7.10)	11.33 (9.43–13.10)	14.78 (11.79–18.80)	<.0001
SCLC	4.90 (4.30–6.20)	2.79 (2.04–3.12)	5.30 (4.63–6.83)	9.63 (7.50–14.95)	17.05 (6.10–27.43)	<.0001
Melanoma	6.74 (5.90–7.57)	3.38 (2.73–4.27)	4.70 (4.17–5.42)	8.77 (6.83–10.77)	13.23 (9.40–15.64)	<.0001
RCC	9.63 (7.66–10.91)	3.27 (2.17–5.10)	7.29 (3.73–10.91)	11.27 (8.83–14.80)	14.77 (9.72–19.79)	<.0001
Breast cancer	11.93 (9.69–12.85)	6.11 (3.88–8.28)	9.37 (7.92–11.24)	16.89 (13.96–19.90)	18.74 (11.31–29.37)	<.0001
GI cancer	5.36 (4.30–6.30)	3.13 (2.40–4.57)	4.40 (3.37–6.53)	6.87 (5.03–11.63)	13.54 (9.92–27.12)	<.0001
Other	6.37 (5.22–7.49)	—	—	—	—	—
Total	7.23 (6.90–7.60)	3.43† (3.02–3.84)	6.40† (5.78–6.90)	11.56† (10.47–12.78)	14.77† (12.85–17.05)	<.0001†

Sperduto et al. IJROBP 2010

Refined Diagnosis-specific GPA

Incorporation of **tumor subtype** of breast cancer

Non–small-cell and small-cell lung cancer

Prognostic Factor	0	0.5	1.0	GPA Scoring Criteria	Patient Score
Age, years	> 60	50-60	< 50		____
KPS	< 70	70-80	90-100		____
ECM	Present	—	Absent		____
No. of BM	> 3	2-3	1		____
Sum total					____

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

Prognostic Factor	0	1.0	2.0	GPA Scoring Criteria	Patient Score
KPS	< 70	70-80	90-100		____
No. of BM	> 3	2-3	1		____
Sum total					____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

Prognostic Factor	0	0.5	1.0	1.5	2.0	GPA Scoring Criteria	Patient Score
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		____
Sum total							____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma

Prognostic Factor	0	1.0	2.0	GPA Scoring Criteria	Patient Score
KPS	< 70	70-80	90-100		____
No. of BM	> 3	2-3	1		____
Sum total					____

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

GI cancers

Prognostic Factor	0	1	2	3	4	GPA Scoring Criteria	Patient Score
KPS	< 70	70	80	90	100		____

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

KPS
Subtype
Age

Sperduto et al. JCO 2012

Anti-HER2 Tx and Survival after BM

	Anti-HER2 Tx (+)	Anti-HER2 Tx (-)	
Bendell 2003	N=42 13 months		Trastuzumab before onset of BM (n=31) After onset of BM (n=9)
Nam 2008	N=21 12.8 months	N=35 4.0 months	Trastuzumab after onset of BM
Park 2009	N=42 14.9 months	N=35 4.0 months	Trastuzumab
Yap 2012	N=114 18.5 months	N=168 5.7 months	Trastuzumab or Lapatinib

Anti-HER2 treatment improves survival from BM diagnosis

Extracranial disease status and Prognosis of BM from BC

- Retrospective study on 51 patients with BM who received SRS

	Sperduto *et al.* (2) Reference for MST	Data from current study MST (and no.) by group	Subgroup by ECD Status	MST (and no.) by subgroup*
Group (score)				
1 (0.0–1.0)	3.4 mo	NA (n = 2)	Absent/stable	NA (n = 1)
			Progressive	NA (n = 1)
2 (1.5–2.0)	7.7 months	8.2 months (n = 12)	Absent/stable	74.7 mo (N = 3)
			Progressive	8.2 mo (n = 9)
3 (2.5–3.0)	15.1 mo	18.7 months (n = 21)	Absent/stable	31.2 mo (n = 8)
			Progressive	8.5 mo (n = 13)
4 (3.5–4.0)	25.3 mo	22.8 months (n = 14)	Absent/stable	NR (n = 6)
			Progressive	19.7 mo (n = 8)

- Multivariate analysis on survival from BM in a retrospective study (n=171)

	Hazard Ratio (HR)	*P* value	95% CI
KPS ≥70	0.51	.0002	0.36–0.74
Age <70	0.23	.002	0.09–0.60
HER2 positivity	2.06	.005	1.24–3.45
Trastuzumab use	0.54	.017	0.33–0.90
Triple negativity	2.03	.002	1.29–3.18
Extracranial disease control	0.57	.002	0.41–0.81

Dyer et al. 2012; Ahn et al. 2012

Initial Consideration in BM Treatment

- Number , size, location of BM & Resectability
- Mass effect/neurological symptoms
- Prognosis (Expected survival)
  - Performance status
  - Age
  - Status of extracranial disease
  - Subtype of breast cancer

→ *Aggressive local treatment in patients with good prognosis*

Challenges in targeting therapeutics of BM

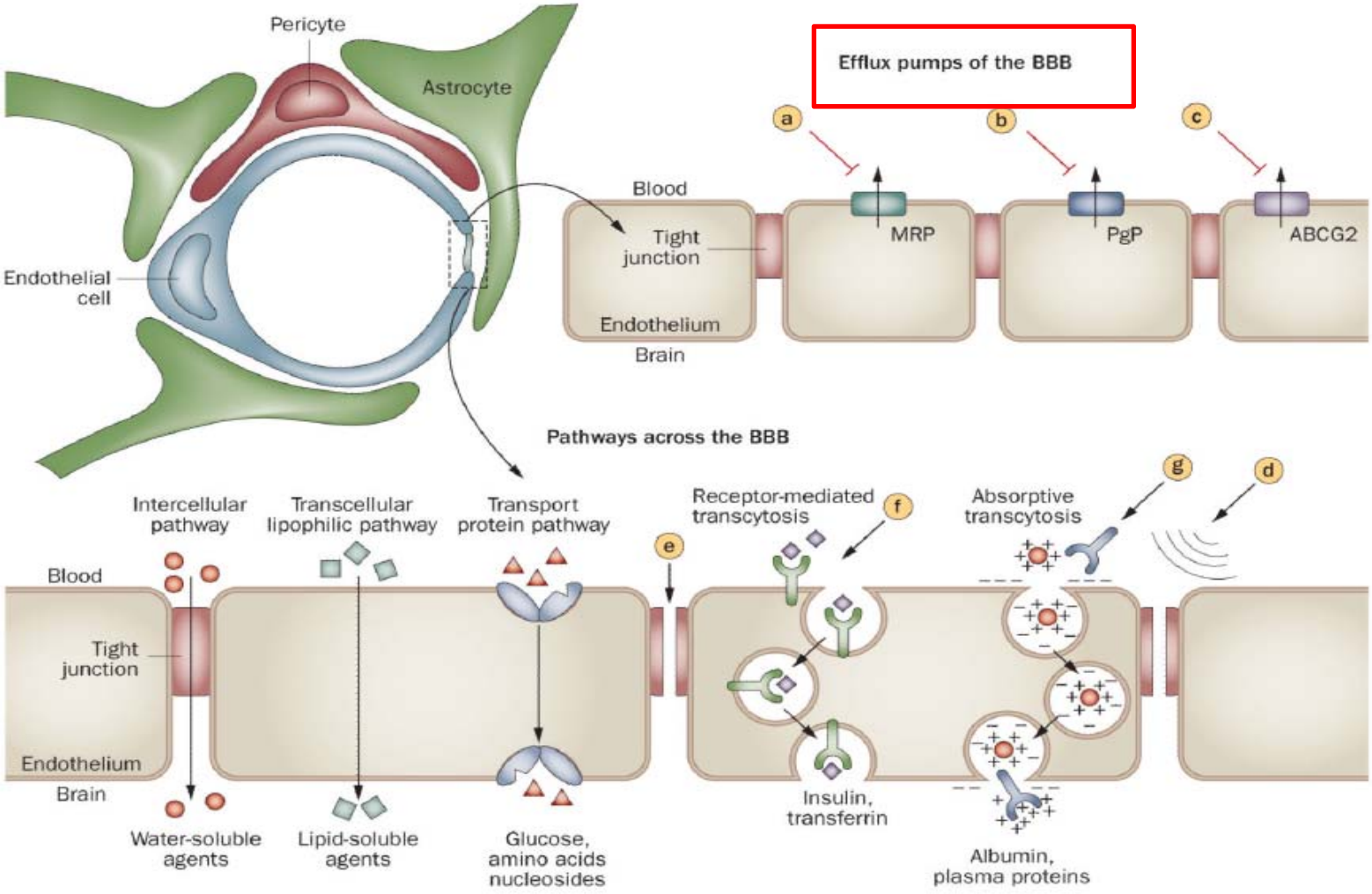
Impressions from HER2+ BCBM

- ✓ Poor intracranial penetration of systemic drug
  → better penetration of BBB?

- ✓ Biology – linked brain tropism of cancer
  → targeting processes BM

- ✓ Extracranial disease control

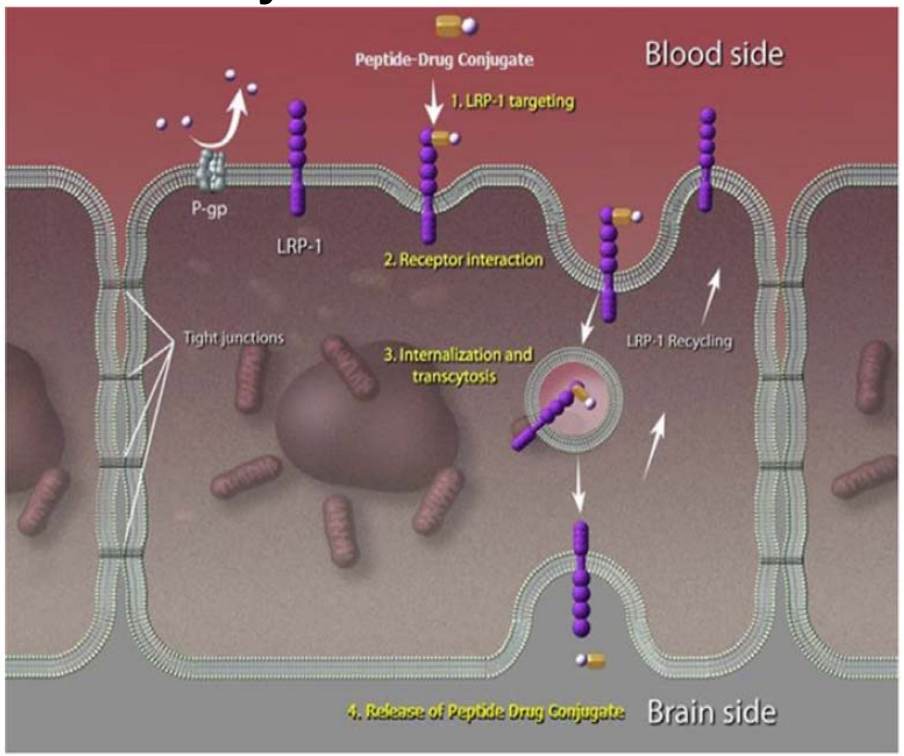
Targeting Blood-Brain Barrier for better drug penetration



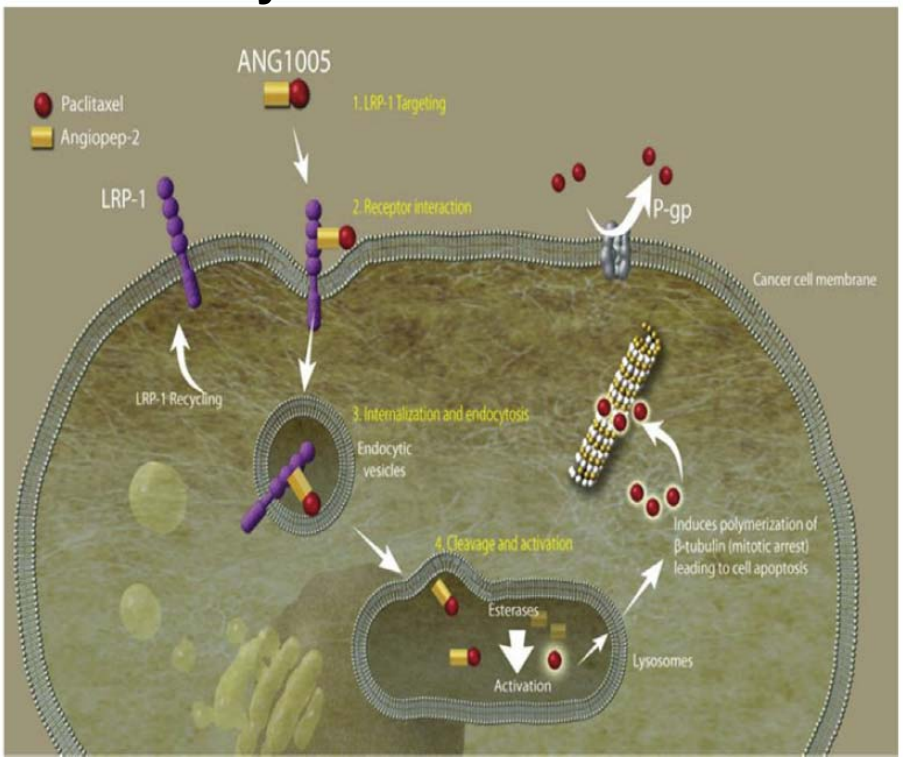
Passage of large hydrophilic molecules is difficult without receptor mediated transcytosis

ANG1005 : A peptide drug conjugate (Angiopep-2+Paclitaxel)

LRP-1 Receptor-mediated transcytosis across the BBB

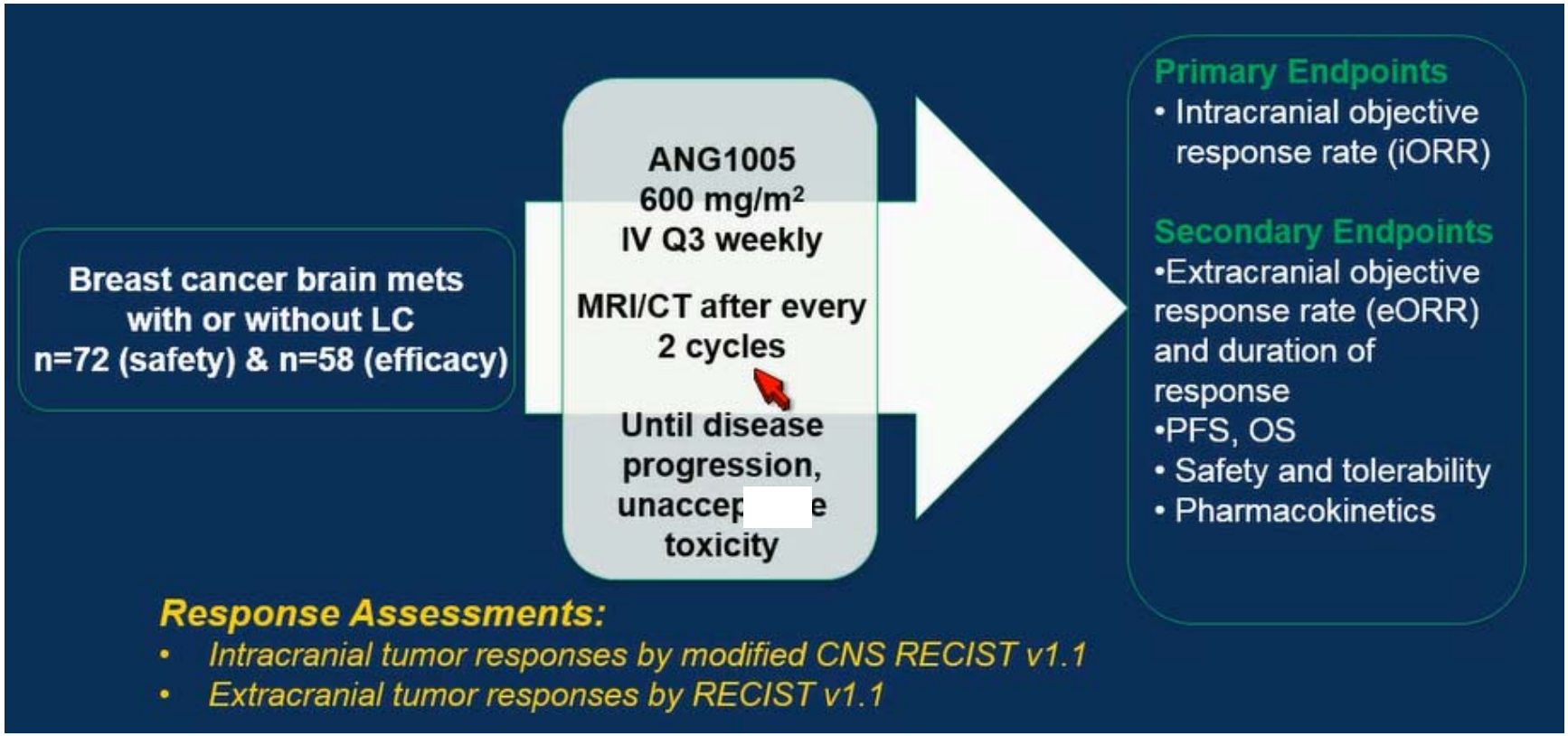


LRP-1 Receptor-mediated endocytosis into tumor cells



Tang. Genes & Diseases 2017

A Phase II trial of ANG1005 for BC-BMs (ANG1005-CLN-04)



- Enrolled patients were heavily pretreted for BM from BC
  - ✓ Median time from initial BM 1.0 year
  - ✓ HER2+ 42%, TNBC 26%
  - ✓ Leptomeningeal carcinomatosis 39%
  - ✓ Prior intracranial RT 84%
  - ✓ Prior taxane 84%

Kumthekar et al. 2016 ASCO meeting .abstr#2004

Efficacy of ANG1005 for BM from BC

Intracranial Objective Response Rate (Per-Protocol Patients)

	All Patients	HER2+	HER2-
Sample size, n[a]	58	28	30
PR, n (%)	8 (14%)	4 (14%)	4 (13%)
Confirmed PR, n (%)[b]	3 (5%)	2 (7%)	1 (3%)
SD, n (%)	33 (57%)[c]	19 (68%)[c]	14 (47%)
PD, n (%)	17 (29%)	5 (18%)	12 (40%)
Clinical benefit (SD+PR), (%)	71%	82%	60%

Extracranial Objective Response Rate (Per-Protocol Patients)

	All Patients	HER2+	HER2-
Sample size, n[a]	30	13	17
CR, n (%)	1 (3%)	0	1 (6%)
PR, n (%)	2 (7%)	0	2 (12%)
SD, n (%)	24 (80%)	12 (92%)	12 (70%)
PD, n (%)	3 (10%)	1 (8%)	2 (12%)
Clinical benefit (SD+PR), (%)	80%	92%	82%

Kumthekar et al. 2016 ASCO meeting .abstr#2004

Efficacy of ANG1005 for Leptomeningeal Carcinomatosis

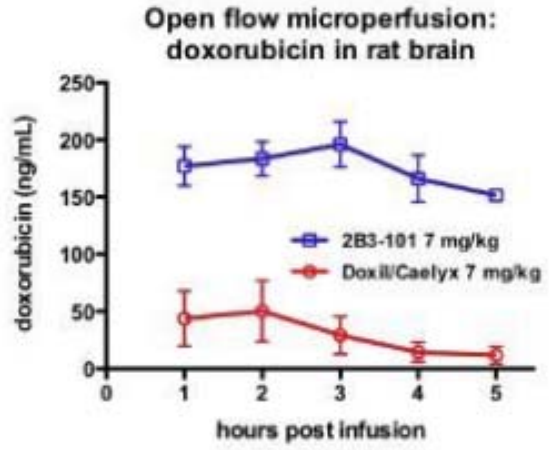
	All LC Patients	HER2+	HER2-
Sample size, n[a]	23	15	8
PR, n (%)	5 (22%)	4 (27%)	1 (13%)
Confirmed PR, n (%)[b]	2 (9%)	2 (13%)	0
SD, n (%)	12 (52%)[c]	8 (53%)[c]	4 (50%)
PD, n (%)	6 (26%)	3 (20%)	3 (37%)
Clinical benefit (SD+PR), (%)	74%	80%	63%

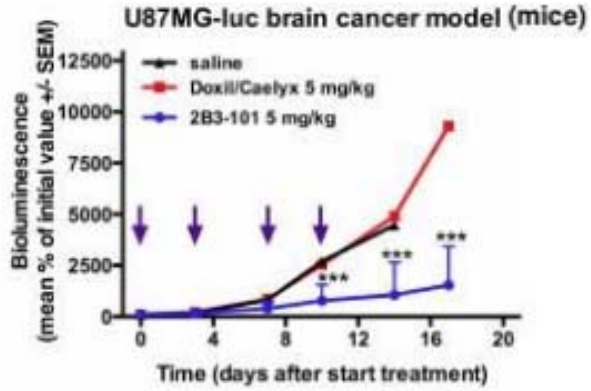
- median survival of patients with LC 8.0 months, OS at 6 moths 63.6%
  compared with 3-4 months of OS in patients with leptomeningeal carcinomatosis from historical controls

Kumthekar et al. 2016 ASCO meeting .abstr#2004

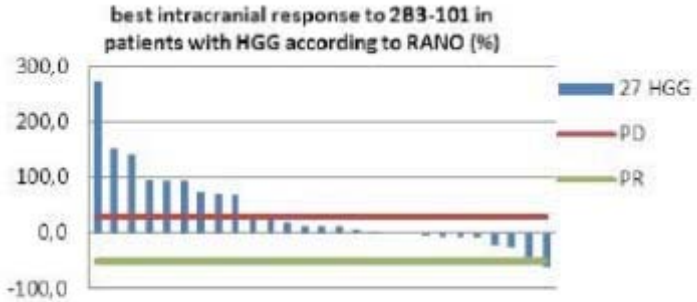
2B3-101 : Glutathione PEGylated liposomal doxorubicin

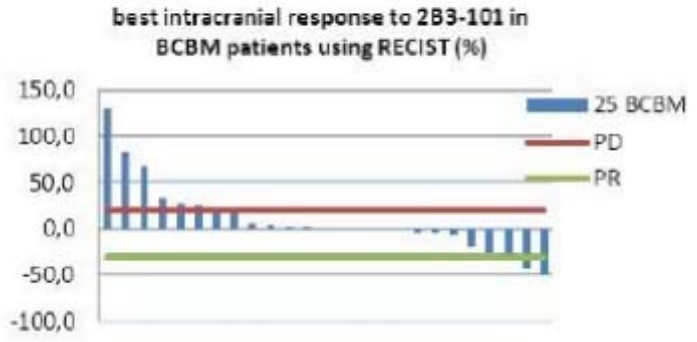
- Glutathione is actively transported across the BBB
- Additional glutatione coating of pegylated liposomal doxorubicin





- In a Phase 1/2a study as a single agent or combined with trastuzumab in patients with HER2+ metastatic BC,
  - ✓ 21 BCBM (16 HER2+) were enrolled
  - ✓ intracranial response 19%
  - ✓ 'PR+SD' 62%
  - ✓ 12-weeks PFS rate 52%

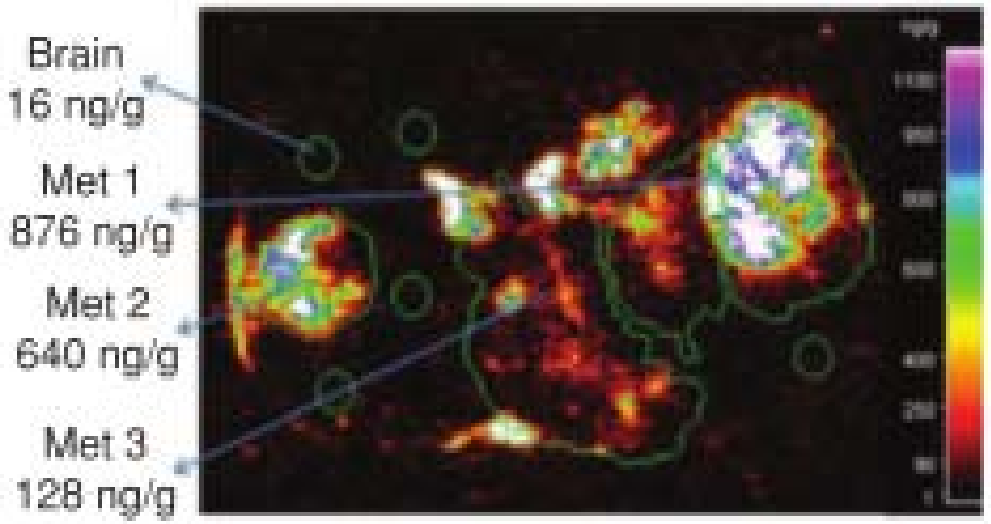




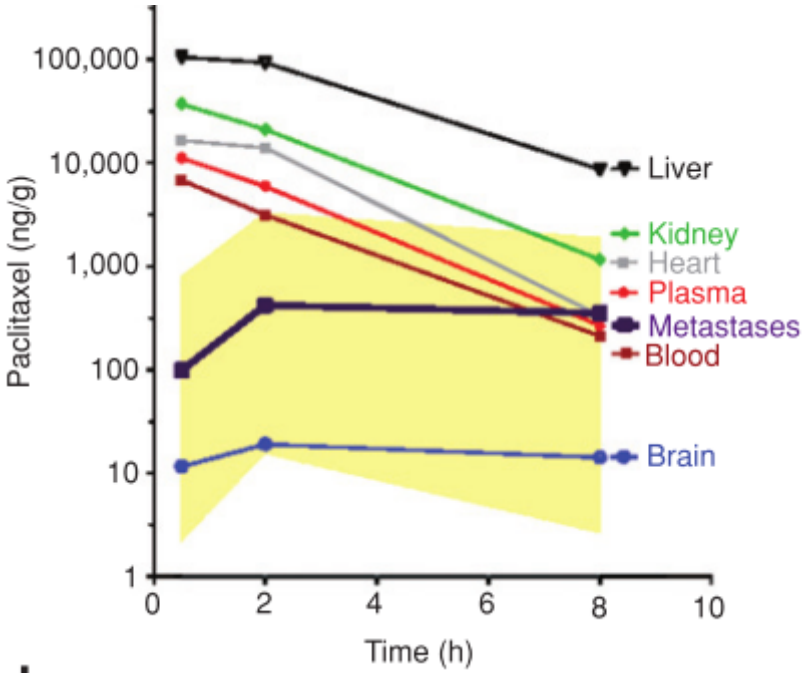
Gaillard et al. Plos One 2014; Aftimos et al. SABCS 2014

Heterogenous blood-tumor barrier permeability in experimental BM of BC

Heterogenous distribution of paclitaxel in BM



Mean concentration of paclitaxel

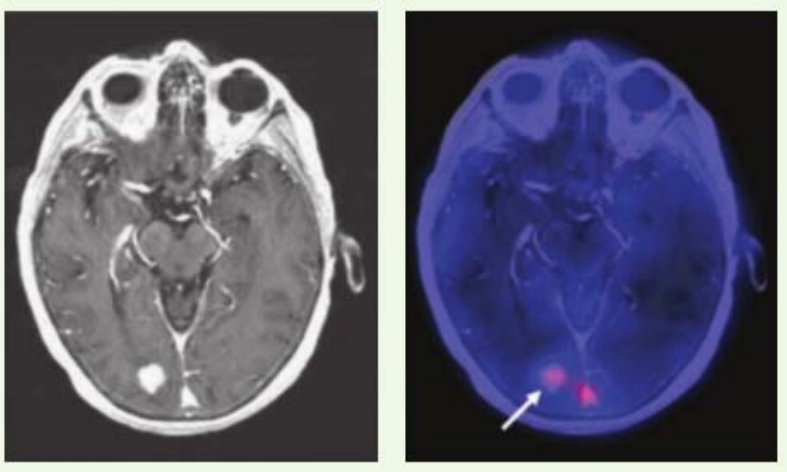


Partial BTB permeability was compromised in many BMs.
Magnitude of permeability is different within and between BM lesions.

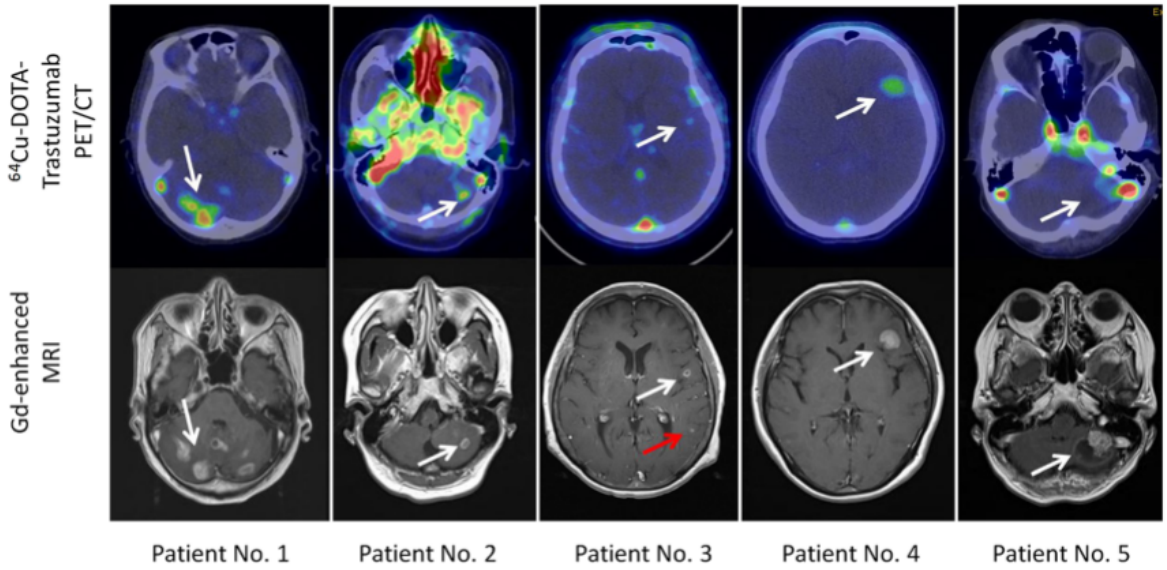
Lockman et al. Clin Cancer Res 2010

Trastuzumab penetrates blood tumor barrier of BM

❖ ^{89}Zr-trastuzumab uptake in HER2(+) BM



❖ ^{64}Cu-DOTA-trastuzumab PET



Dijkers et al. Clin Pharmacol Ther 2010; Kurihara et al. 2015

Better Anti-HER2 Tx and Better survival after BM

	Anti-HER2 Tx (+)	Anti-HER2 Tx (-)	
Bendell 2003	N=42 13 months		Trastuzumab before onset of BM (n=31) After onset of BM (n=9)
Nam 2008	N=21 12.8 months	N=35 4.0 months	Trastuzumab after onset of BM
Park 2009	N=42 14.9 months	N=35 4.0 months	Trastuzumab
Yap 2012	N=114 18.5 months	N=168 5.7 months	Trastuzumab or Lapatinib

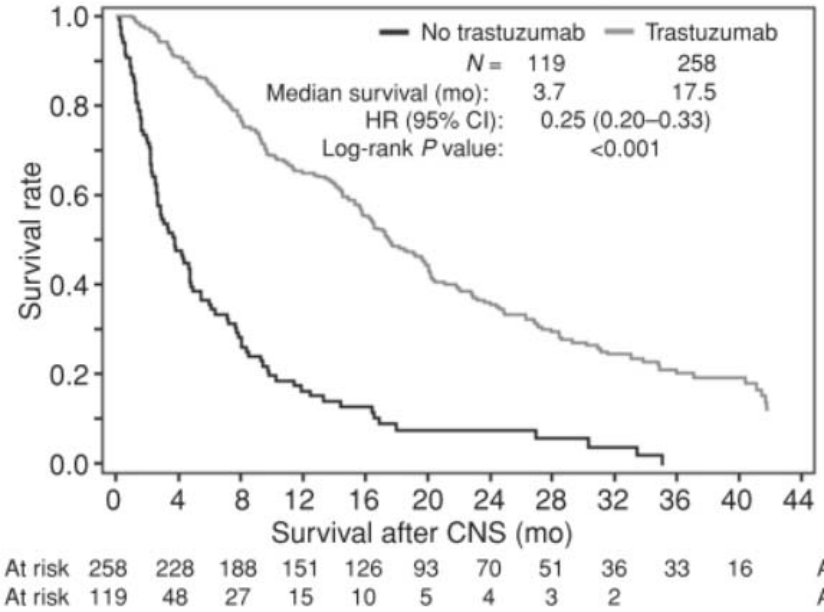
Anti-HER2 treatment improves survival from BM diagnosis

- ✓ *Role of extracranial disesase control of anti-HER2 treatment?*
- ✓ *Role of direct intracranial efficacy?*

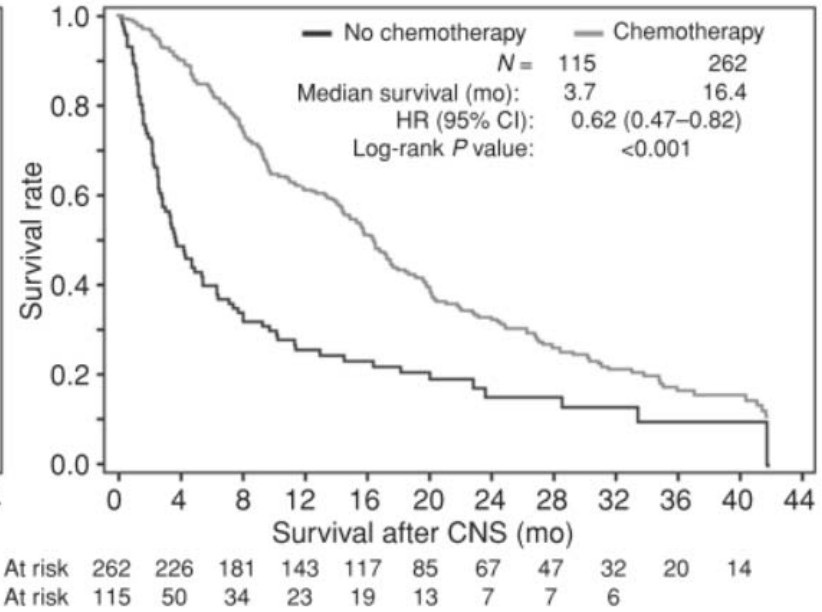
Role of Trastuzumab continuation for HER2(+) BCBM

- A prospective observational registHER trial

Survival after CNS mets by Trastuzumab continuation



Survival after CNS mets by chemotherapy



In HER2+ BCBM patients with trastuzumab resistance, continuation of Trastuzumab was associated with longer overall survival.

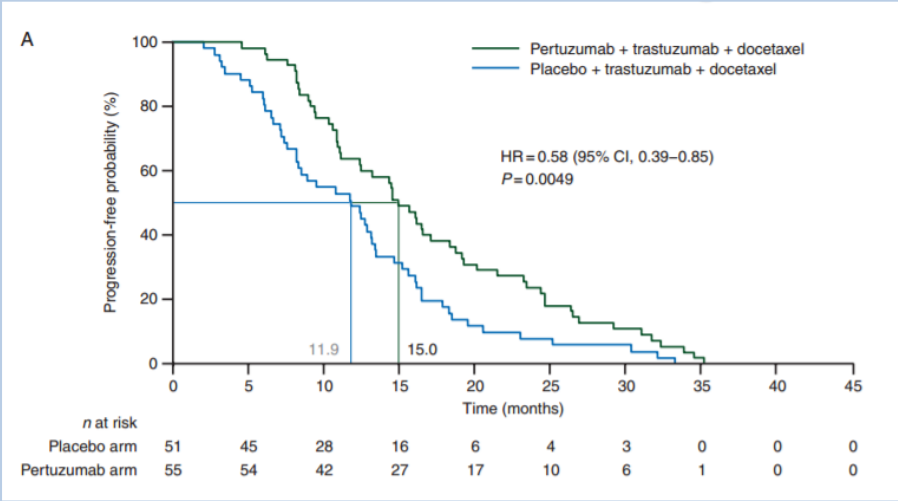
Brufsky et al. Clin Cancer Research. 2011

Pertuzumab and CNS metastases

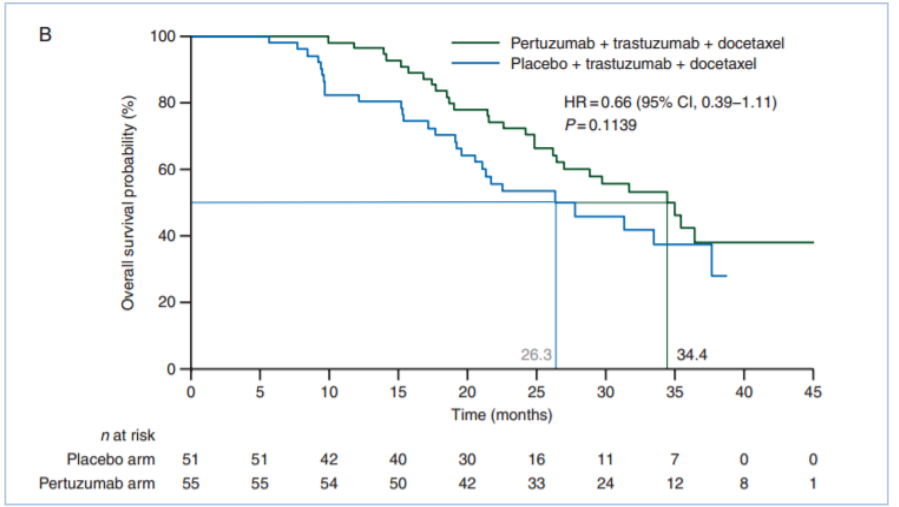
- Exploratory analyses of the incidence and time to CNS mets in patients from CLEOPATRA trial.

- Incidence of CNS mets as first site of disease progression (ITT population)
  : 51 of 406 (12.6%) in control arm vs. 55 of 402 (13.7%) in pertuzumab arm

- <u>Adding Pertuzumab to docetaxel and trastuzumab delays the onset of CNS metastases</u>.



Time to CNS mets as first site of PD

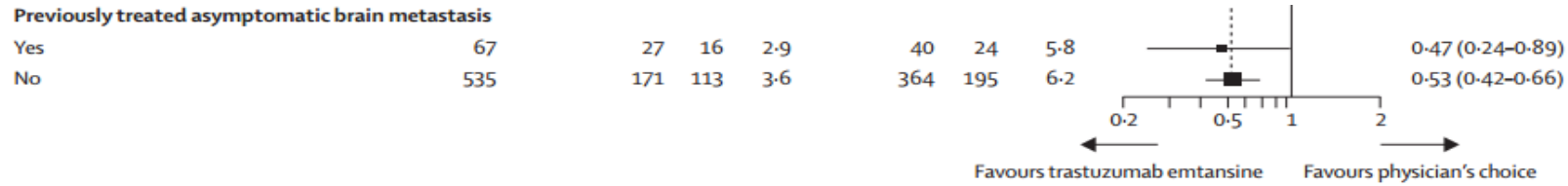


OS in patients who developed CNS mets

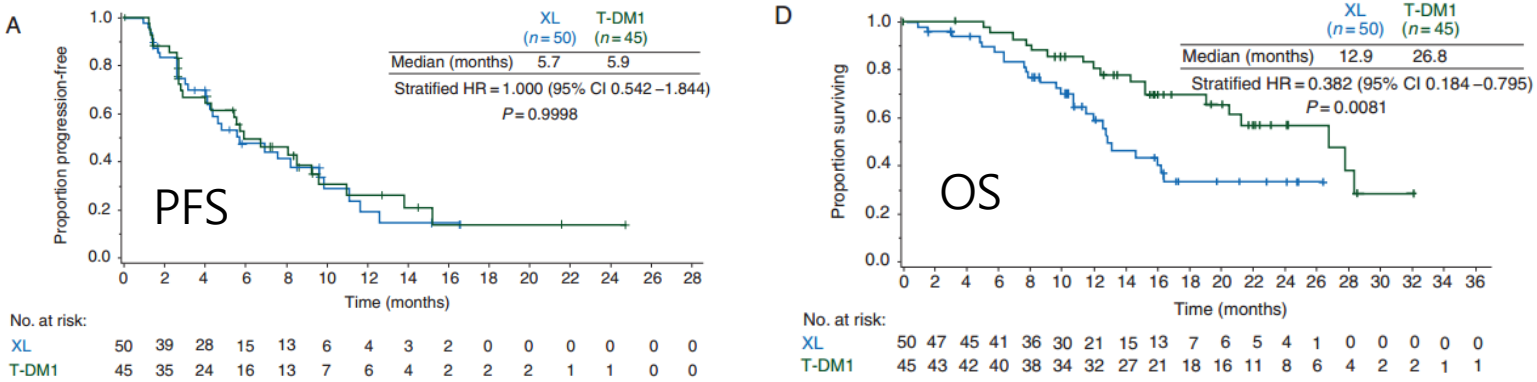
Swain et al. Ann Oncol. 2014

Efficacy of T-DM1 for patients of BC with BM

- Subset analysis of TH3RESA trial
  : PFS benefit of T-DM1 compared with physician's choice in patients with asymptomatic or treated BM



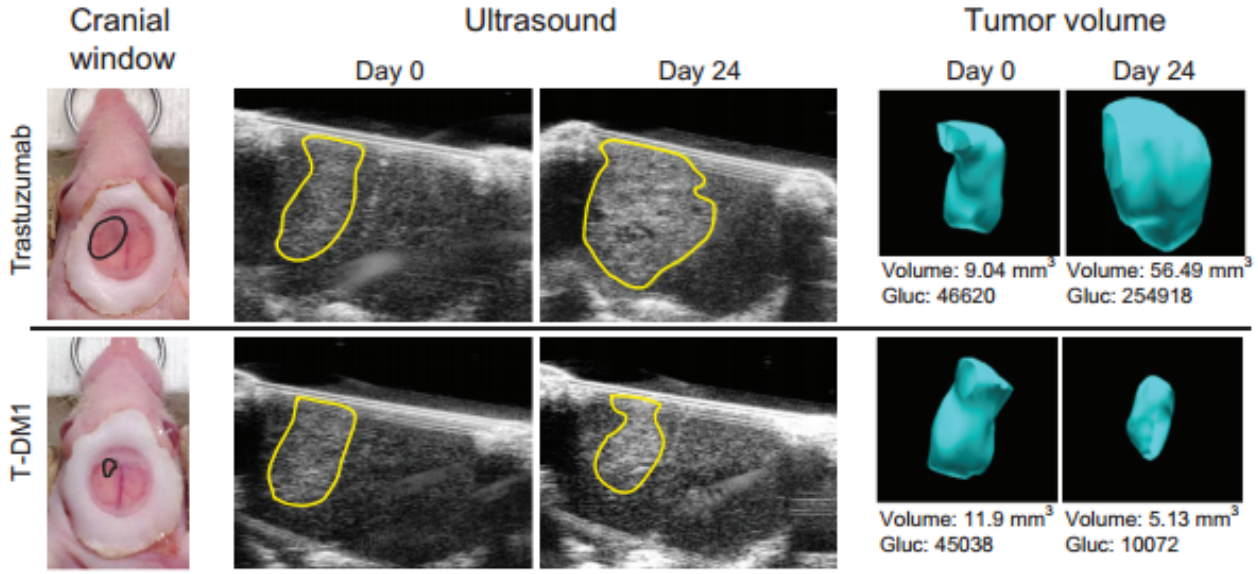
- Exploratory analysis in EMILIA
  95 of 991 had CNS metastases at baseline (45 T-DM1 arm, 50 L+C arm)
  T-DM1 vs. L+C : PFS benefit? No / OS benefit? Yes

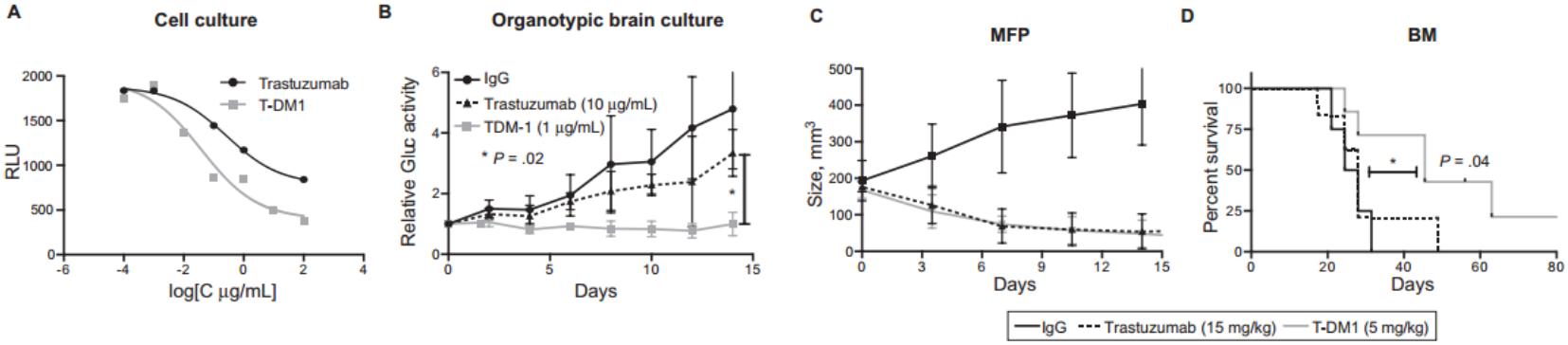


Similar rate of CNS as a first site of progression in both arms
No baseline - BM 9/450 (2%) of T-DM1 and 3/446 (0.7%) of L+C arm
Baseline BM- 10/45 (22.2%) of T-DM1 and 8/50 (16.0%) of L+C arm

Krop et al. Lancet. 2014; Olson et al. Ann Oncol 2012; Krop et al. Ann Oncol 2014.

Preclinical intracranial efficacy of T-DM1





Askoxylakis et al. JNCI 2016.

T-DM1 has direct intracranial efficacy for HER2+ BM from BC

- A retrospective study of 10 patients
  - Ten patients with newly diagnosed, asymptomatic, or progressive BM from HER2+ BC
  - Prior Trastuzumab (n=10), Lapatinib (n=6), Pertuzumab (n=3), radiotherapy (n=8)
  - median time from BM to T-DM1 initiation 12 months

  - Evaluation : Brain MRI every 12 weeks
  - Best intracranial response by RANO criteria: PR (n=3), SD(n=4), PD (n=3)

  - CNS Clinical benefit rate (CR+PR+SD $\geq$ 6 months) 50%
  - median OS from BM 42 months
  - median PFS from T-DM1 5 months, OS from T-DM1 8.5 months

- A largest retrospective study in five French centers (39 BC patients with BM , 30 uncontrolled)
  - 30 uncontrolled/progressive BM, 36 (95%) patients with prior loco-regional treatment for BM.

  - CR 0, PR 17 (44%)
  - median PFS 6.1 months
  - first progression site : brain (n=14), leptomeninges (n=2), extracranial lesion (n=5), both intra- and extra-cranial lesion (n=3)

- In a retrospective of 20 patients with BC treated with T-DM1, CNS was subsequent metastasis site in 65%.

Bartsch et al. Clin Exp Metastasis 2015; Jacot et al. Breast Cancer Res Treat 2016.

Lapatinib(L) and Capecitabine(C) for HER2(+) BM

Reference	Tx	Study design	# Pts	CNS ORR	TTP/PFS months
Lin 2008 JCO	L	Phase 2 Prior WBRT/SRS 95%	39	2.6%	3.0
Lin 2009 CCR	L	Phase 2 Prior WBRT 95% Prior Trastuzumab 100%	237	6%	2.4
Lin 2009 CCR	L+C	Phase 2	50	20%	3.6
Sutherland 2010 BJC	L+C	Expanded access Study Prior WBRT 94% Prior Trastuzumab 100%	34	21%	5.1
Metro 2011 Ann Oncol	L+C	Retrospective Prior WBRT/SRS 87% Prior Trastuzumab 100%	22	32%	5.1
Lin 2011 J Neurooncol	L+C	Phase 2 Prior WBRT/SRS and Trastuzumab	13	38%	NR

Low CNS ORR, but most of the subjects were heavily pretreated or had disease progression in CNS after local treatment.

Adapted from Lin et al. 2013

Upfront Lapatinib + Capecitabine for HER2+ BCBM (LANDSCAPE)

- Eligibility (n=45)
  - HER2(+) BC patients with multiple BMs
  - 93% with prior trastuzumab
  - median # of BM 3, Breast cancer GPA index 3-4
  - No previous WBRT or SRS

- Primary endpoint: objective CNS response rate (Brain MRI q 6 weeks)
  - >50% volumetric reduction of CNS lesion
  - Absence of increased steroid use
  - Absence of progressive neurological symptoms
  - Absence of extra-CNS disease

- Results
  - » CNS ORR 65.9% (95% CI 50.1-79.5)
  - Median TTP 5.5 months
  - Median time to CNS progression 5.5 months
  - Median time to radiotherapy 8.3months
  - Median OS 17.0 months

✓ ASCO guideline for HER2(+) BC and BM suggests that a particularly important consideration is the **role of WBRT in management of limited brain metastatic disease.**

✓ No data regarding neurocognitive function and QOL

Bachelot et al. Lancet Oncology 2013

Neratinib for progressive BM from HER2+ BM (TBCRC 022)

- Neratinib: irreversible panHER inhibitor
- In NEfERT-T Phase 3 trial, neratinib+paclitaxel showed delayed time to CNS (HR 0.45, 95% CI 0.26-0.78) compared with trastuzumab+paclitaxel.

- Patient population
  - HER2(+) BC patients with progressive BMs after local Tx
  - Previous WBRT and/or SRS 100%, Trastuzumab 90%, Lapatinib 85%

- Neratinib 240mg orally once per day

- **Primary endpoint: composite CNS objective response rate**
  - ≥ 50% reduction in volumetric sum of target CNS lesion
  - Absence of CNS or extracranial disease progression
  - Absence of progressive neurological symptoms
  - Absence of increased steroid use

Best Response	Cohort 1 (N = 40)
CR	0 (0)
PR	3* (8; 95% CI, 2% to 22%)
SD six or more cycles	4 (10)
SD less than six cycles	12 (30)
PD	
PD in CNS only	10 (25)
Symptomatic deterioration/clinical progression (CNS or non-CNS)	7 (18)
PD in CNS and non-CNS	2 (5)
Off treatment before restaging for toxicity	2 (5)

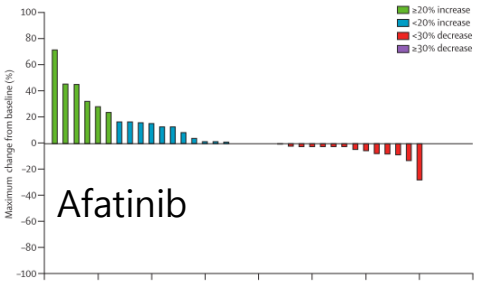
Freedman et al. JCO 2016; Awada et al. JAMA Oncol 2016.

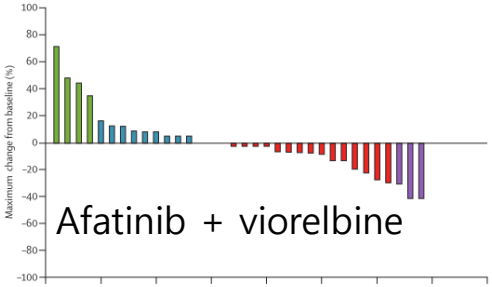
Afatinib for progressive BM from HER2+ BC (LUX-breast3)

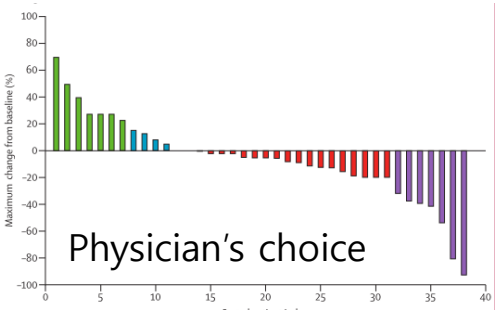
- Population
  - HER2(+) BC patients with progressive BMs
  - Prior trastuzumab 100%, prior lapatinib 80%, prior brain RT 83%
  - # of BM ≤3 in 40%

- Afatinib(n=40) vs. Afatinib + vinorelbine (n=38) vs. Physician's choice (n=43)
- Most of the physician's choices were 'Trastuzumab+vinorelbine' or 'Lapatinib+Capecitabine'

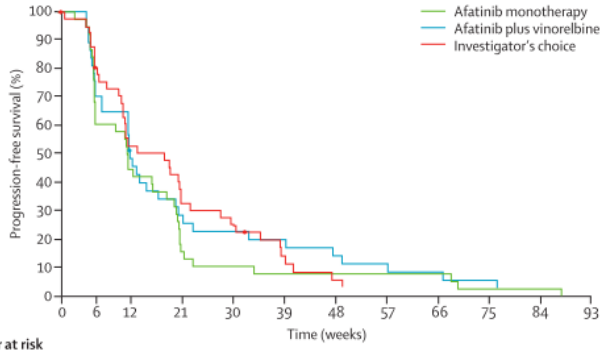
- **Primary endpoint: patient benefit at 12 weeks**
  - Absence of CNS or extracranial disease progression
  - Absence of new neurological symptoms
  - Absence of new steroid use
  - » **30% vs. 34.2% vs. 41.9%**







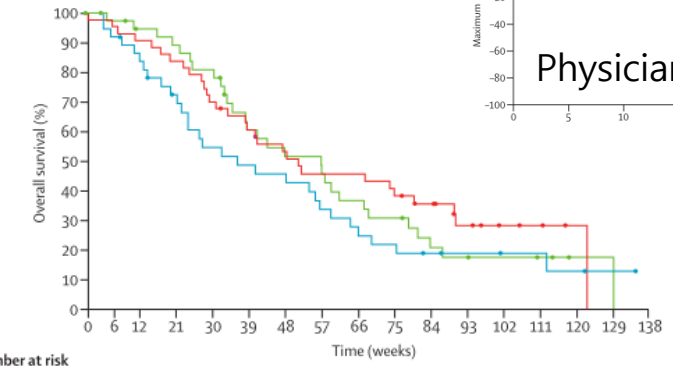
PFS



Number at risk

Afatinib monotherapy	40	32	19	9	4	3	3	3	3	1	1	0
Afatinib plus vinorelbine	38	30	24	10	8	7	5	4	3	2	1	1
Investigator's choice	43	36	22	16	10	5	2	1	1	1	1	1

OS



Number at risk

Afatinib monotherapy	40	37	36	33	29	22	18	17	12	10	7	5	4	3	1	0
Afatinib plus vinorelbine	38	35	32	26	18	16	15	12	9	7	5	4	3	3	2	1

Cortes et al. Lancet Oncol 2015.

Lapatinib as a radiosensitizer for BM

- **Lapatinib /WBRT Ph I trial (n=35)**

[Design]

D1 Lapatinib 750mg twice/d followed by 1000mg(DL1),1250mg(DL2),1500mg(DL3) once daily, 4hrs before RT

WBRT 2500Gy/15fx was begun between D1-8 of lapatinib

After WBRT, trastuzumab 2mg/kg weekly + lapatinib 1000mg once daily

[DLTs]

None in 1000mg

In 7/27 patients in **1250mg** (rash, diarrhea, hypoxia, pulmonary embolus) **MTD**

In 2/5 patients in 1500mg (mucositis, rash)

→ predefined feasibility criteria(DLT <3/27 at MTD) was not met

[Efficacy]

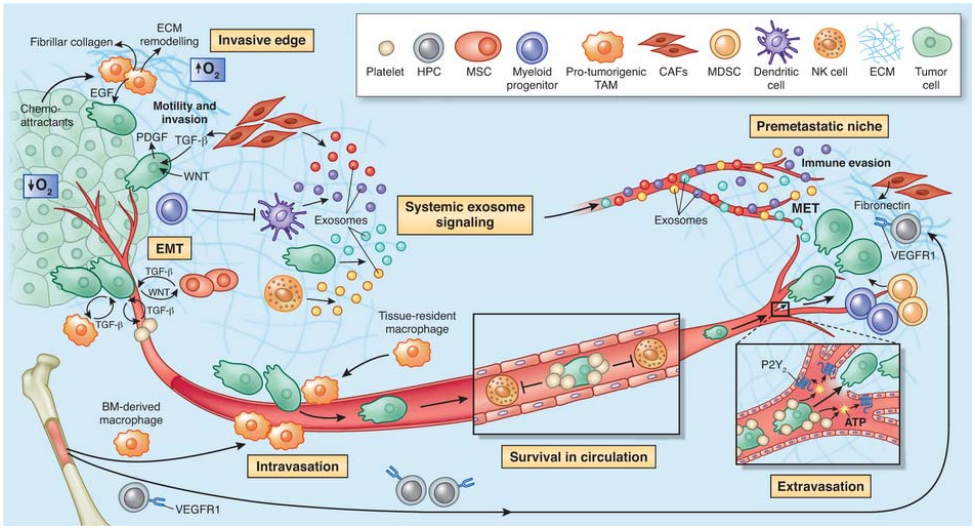
CNS ORR 79% by volumetric criteria among 28 evluable patients

6 month PFS rate 46%

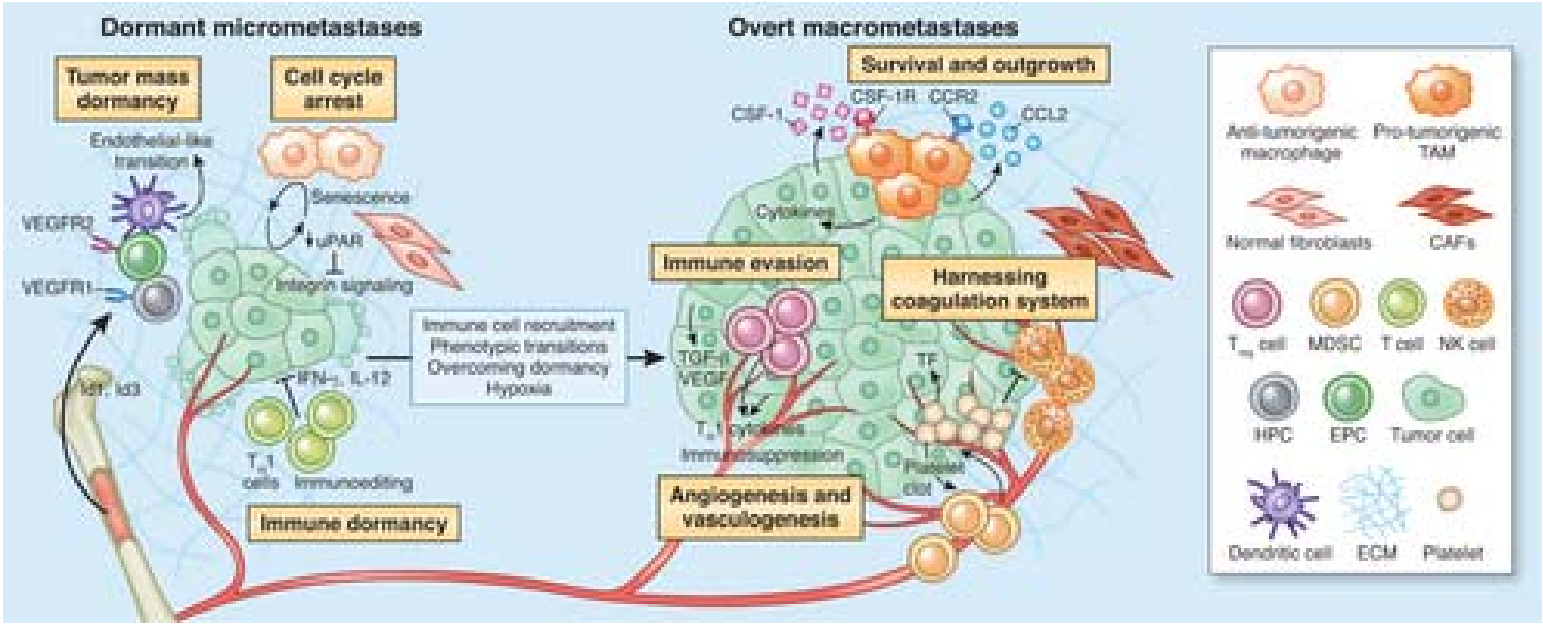
- Randomized Phase 2 trial of WBRT +/- Lapatinib is ongoing (NCT01622868)

Lin et al. Breast Cancer Res Treat 2013

Immune microenvironment as a therapeutic target



The process of metastasic spread including BM are supported by immune cells such as tumor associated macrophages, chemokine pair CXCR4/CXCL12, tumor infiltrating lymphocytes.

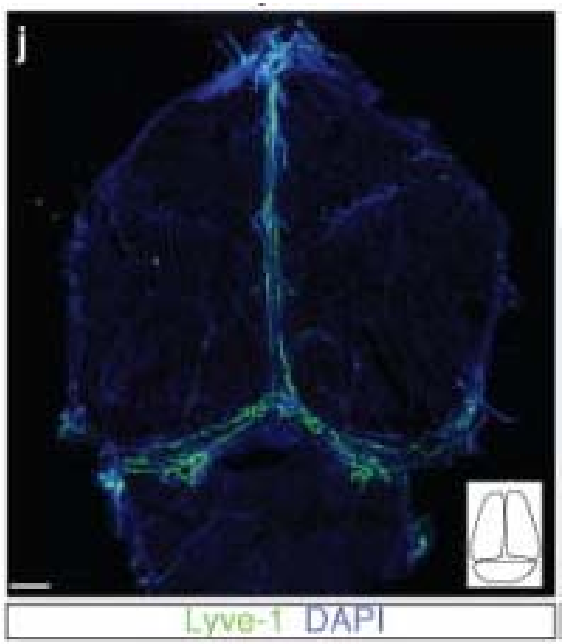


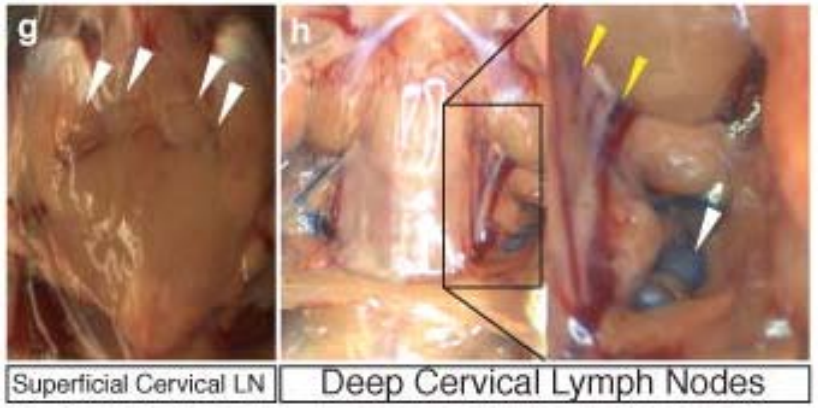
Targeting immune microenvironment of BM

- Brain as a ‘immune previlege’ site?

- It does not mean that brain parenchyma suppresses of any immune responses. Brain parenchyma initiates and tightly regulates immune responses

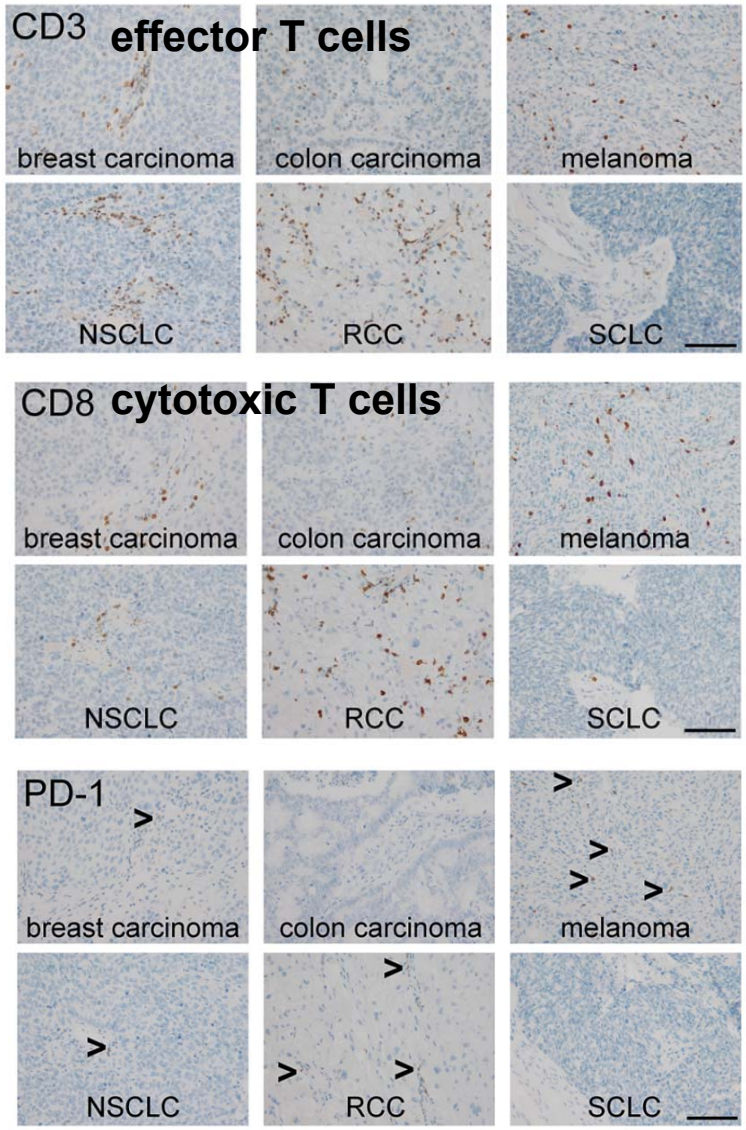
Discovery of functional lymphatic system in CNS and its drainage to cervical LNs in an animal brain

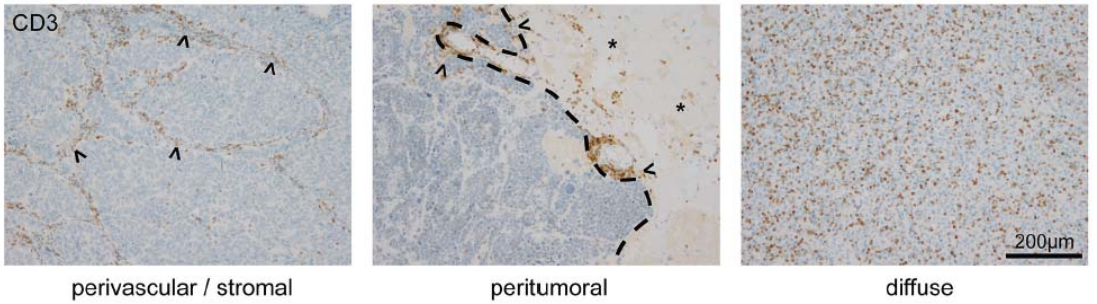


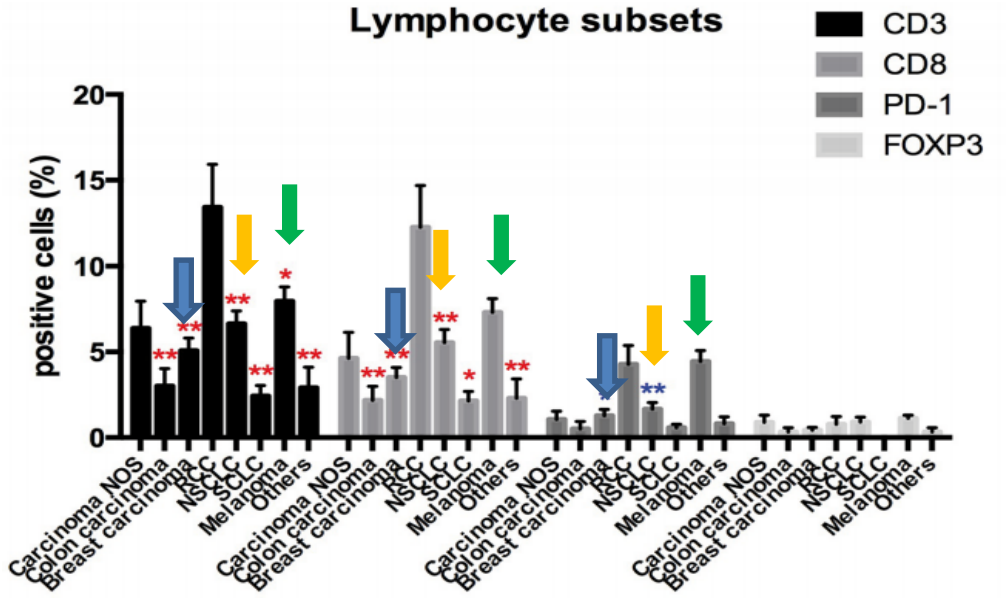


Galea et al. Trends in Immunology. 2007; Louveau et al. 2015

TILs in BM Tumor Tissue



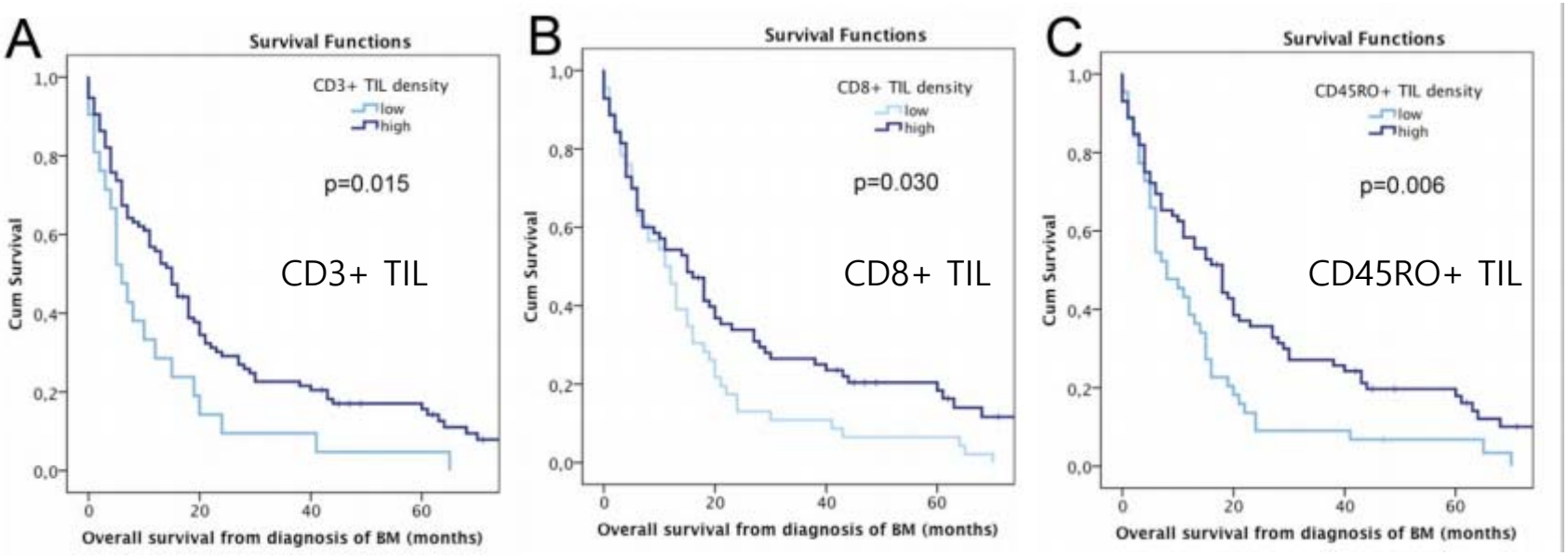




Harter et al. Oncotarget 2015;

High density of TILs is associated with improved survival of BM

116 BM specimens from various solid cancers including 17 breast cancer



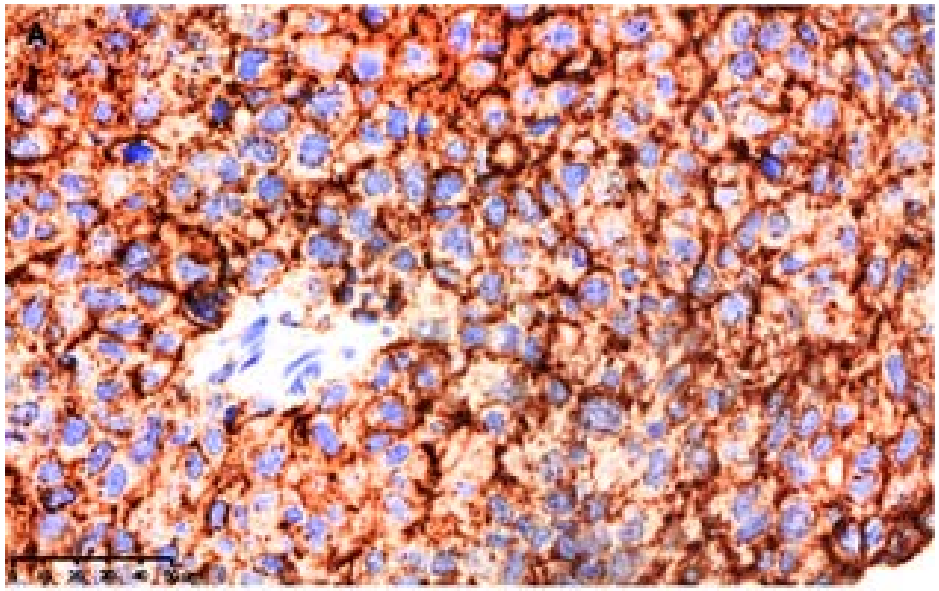
Immune system as a potential biomarker and therapeutic target in patients with BM

Berghoff et al. OncoImmunology 2016

PD-L1 expression in BM Tumor Tissue

- **PD-L1 expression in TNBC (Xiu et al. SABCS 2015)**
  40% of BM (n=54)
  8% of liver mets (n=,172)
  17% of bone mets(n=47)
  15% of breast tumor (n=1570)

- **PD-L1 expression in other brain tumors**
  46% in Melanoma BM
  52% in Lung Cancer BM
  88% in Glioblastoma



PD-L1 expression in Melanoma BM

Harter et al. Oncotarget 2015; Berghoff et al. Histopathol 2015

Immunotherapy for BM from BC? No direct evidences yet.

➢ **Immune checkpoint inhibitors for BM from Melanoma or NSCLC**

Reference	Tx	Study design	# Pts	CNS ORR	OS months
Margolin 2012	Ipilimumab 10mg/kg iv q3wks	Phase 2 Prior WBRT or SRS 41 & 48%	51 (asymptomatic) 21 (stable steroids) Melanoma	16% 5%	7.0 3.7
Di Giacomo 2012	Ipilimumab/fotemustine	Phase 2 Prior WBRT or SRS 35%	20 (asymptomatic) melanoma	25%	13.4
Goldberg 2016	Pembrolizumab 10mg/kg iv q2wks	Phase 2 Untreated (n=14) or progressive , asymptomatic BM	18 melanoma 18 NSCLC	22% 33%	Not reached 7.7

➢ Immune checkpoint inhibitors for BC

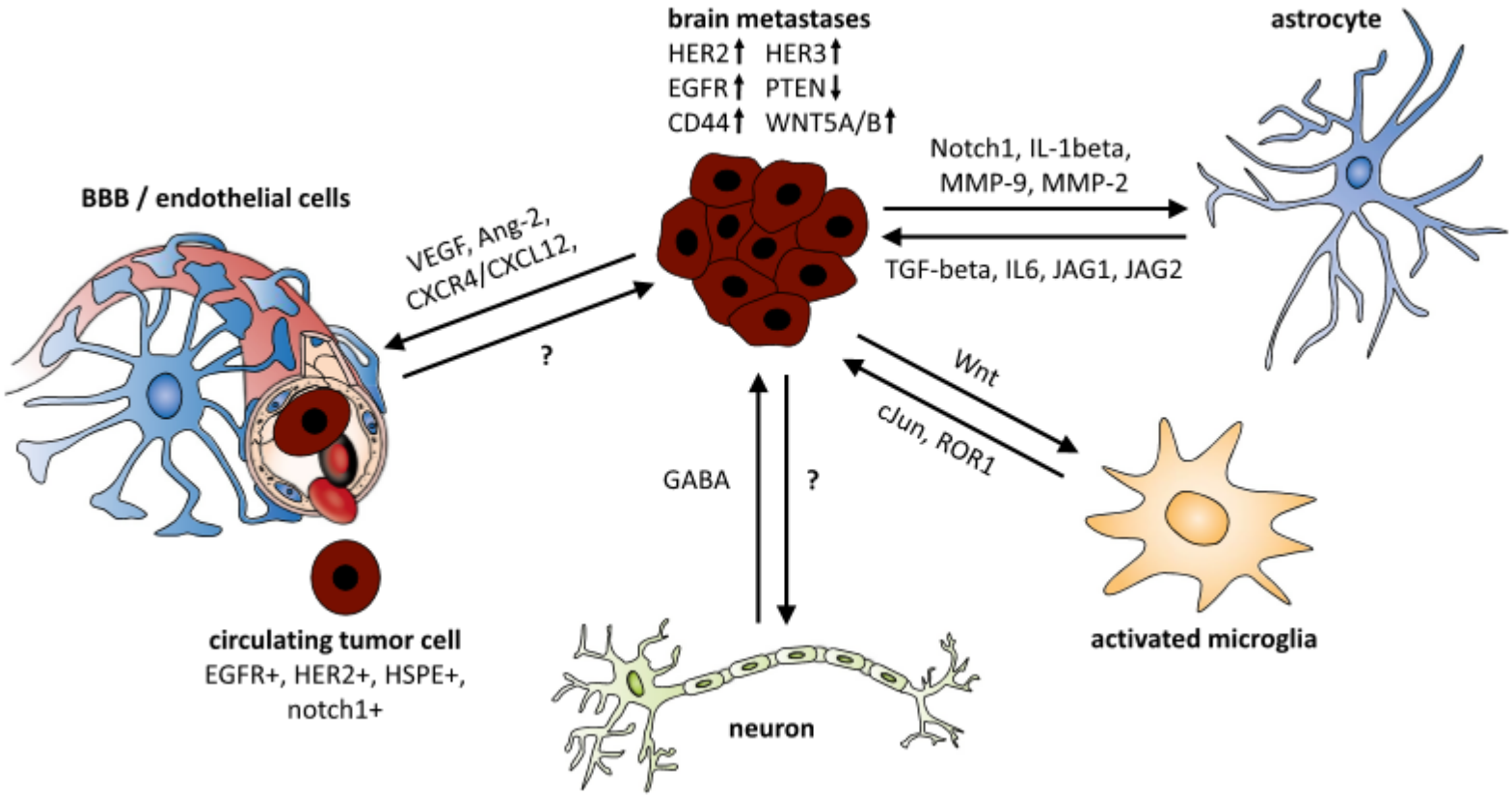
- KEYNOTE-012 Phase IB (32 TNBCs) : Pembrolizumab 10mg/kg every 2wks
  - ORR 18.5%, median PFS 1.9 months, median OS 11.2 months, DCR at 24weeks 25.9%
  - Three patients with BM enrolled, Efficacy regarding BM is not known.

- JAVELIN Phase IB (58 TNBCs): Avelumab 10mg/kg every 2wks
  - ORR 8.6%, DCR 31.0%
  - Patients with CNS metastases was excluded

➢ Oncoing Ph II trials
  - Durvalumab(anti-PD-L1) monotherapy, Tremelimumab (CTLA-4 mAb) with WBRT or SRS

Nanda et al. JCO 2016; Dirix et al. SABCS 2015

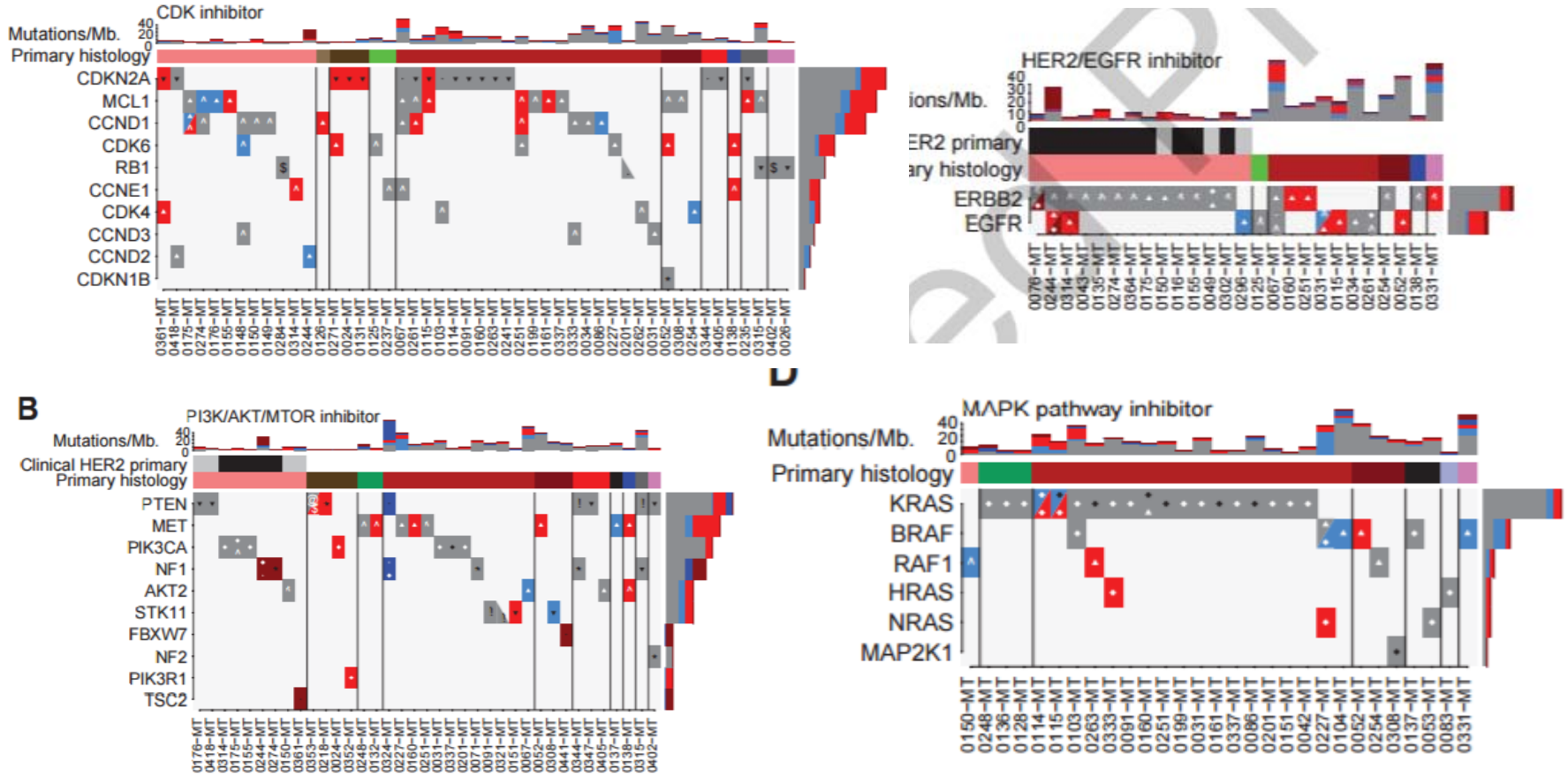
Cross-talk between the BM and resident cells



Witzel et al. Breast Cancer Research 2016

Signaling pathways involved in BM

The Landscape of potentially actionable genomic alterations in BM from various solid cancers



Whole exome sequening of 86 matched BM and primary tumors revealed alterations associated with sensitivity to PI3K/AKT/mTOR, CDK, and HER2/EGFR inhibitors in BM.

Brastinos et al. Cancer Discovery. 2015

Signaling pathways as mediators of BM

- *Potential mediators of BM from 368 breast tumors (Bos et al. Nature 2009)*

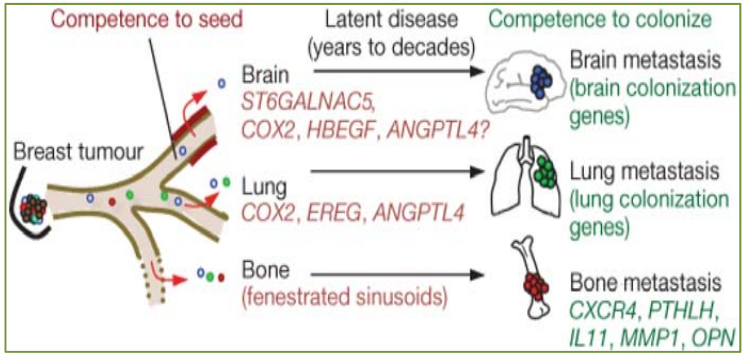
  COX2: promotes extravasation

  EGFR ligands: heparin-binding EGF(HBEGF), epiregulin

  – induces cancer cell motiligy and invasiveness

  ST6GALNAC5: brain-specific sialyltransferase

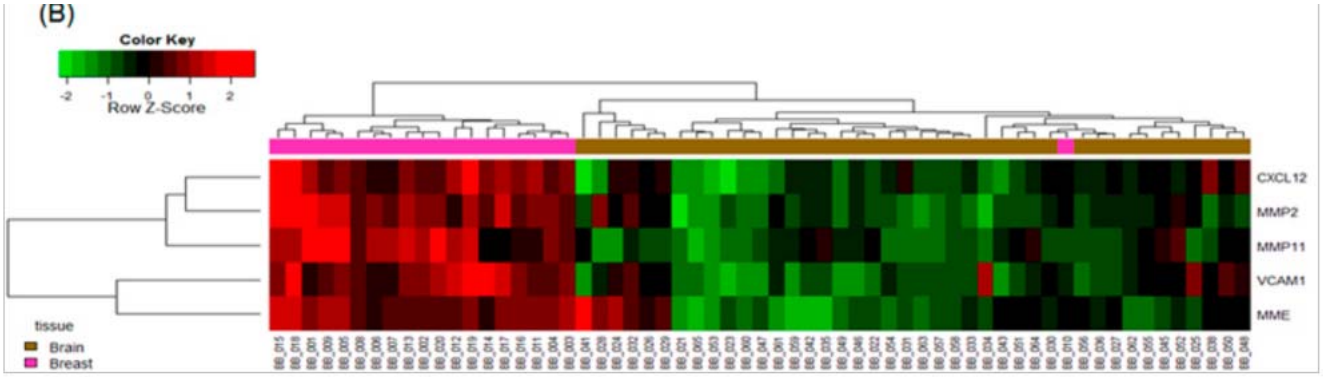
Model of organ-specific metastatic extravasation of BC cells



- Matched gene expression analysis between 20 primary BC and 41 BCBM (Lee et al. 2016)

  upregulated genes in primary BC

  - CXCL12, MMP2, MMP11, VCAM1, MME
  - assoaicted with tumor progression, angiogenesis, and metastasis



BM from Luminal type of Breast Cancer

- Lower frequency of BM in Luminal BC
  - 5-year cumulative incidence of BM
    : 0.1% (Luminal A) vs. 3.3% (Luminal B) vs. 3.7% (HER2) vs. 7.4% (TNBC)
- Multiple case reports descrbing response of BM to endocrine Tx
- Development of BM at later course of metastatic BC
- Most ER(+) breast cancers become endocrine-refractory by the time of BM development
- Altered hormone receptor expression during the process of BM
  : ER Loss in 57%, PR Loss in 44%

Pair No.	PAM50	
	Breast	Brain
1	LumA	LumB
2	LumA	LumA
3	Basal	Basal
4	Her2	LumA
5	LumA	Her2
6	Her2	Her2
7	LumA	Her2
8	Basal	Basal
9	Her2	Her2
10	Basal	Basal
11	LumA	LumB
12	Her2	Normal
13	Basal	Basal
14	Basal	Basal
15	LumA	Her2
16	Basal	Basal
18	Normal	Basal

Arvold et al. Breast Cancer Res Treat 2012; Duchnowska et al. Breast Cancer Research 2012. Lee et al. Oncotarget 2016.

Challenges in designing and interpreting clinical trials of BM

- Subjects
  - ✓ In the refractory setting? Systemic therapy as an upfront therapy for BM?
  - ✓ Symptoms of BM? Requirement on steroids?
  - ✓ leptomeningeal carcinomatosis – unmet need of unmet need

- Appropriate primary endpoint?
  - ✓ Intracranial efficacy vs. Extracranial efficacy vs. Both
  - ✓ Response evaluation
    - RECIST
    - RANO criteria for BM was suggested in 2015

- Identifying higher risk group for BM/Trials on secondary prevention

Summary

- Targeting BBB : ANG1005 with promising efficacy in leptomeningeal carcinomatosis

- Anti-HER2 Treatment for BC-BM
  - Adding Pertuzumab delays time to CNS progression.
  - Survival benefit after CNS mets : Pertuzumab, T-DM1, continuation of trastuzumab
  - Intracranial efficacy of T-DM1 in retrospective studies
  - Lapatinib+Capecitabine have a role as an upfront Tx for BM
  - For heavily pretreated patients with prior brain RT and trastuzumab, currently available anti-HER2 agents had limited intracranial efficacy.

- Immune checkpoint inhibitors for BM
  - Inflammatory microenvironment can be a target of BM treatment
  - Efficacy shown in phase 2 trials only in BM from melanoma or non-small cell lung cancer

Summary

Oldies, but goodies

姜是老的辣

本木に勝るうら木無し。

구관이 명관

Old friend in treating BM = local modalities

More understanding of BM biology would lead us to find better targeted treatment of BM.