La gestione della paziente con carcinoma mammario: situazioni particolari

Metastasi cerebrali nelle pazienti con carcinoma mammario HR+/HER2-: quale terapia sistemica antitumorale nel 2019?

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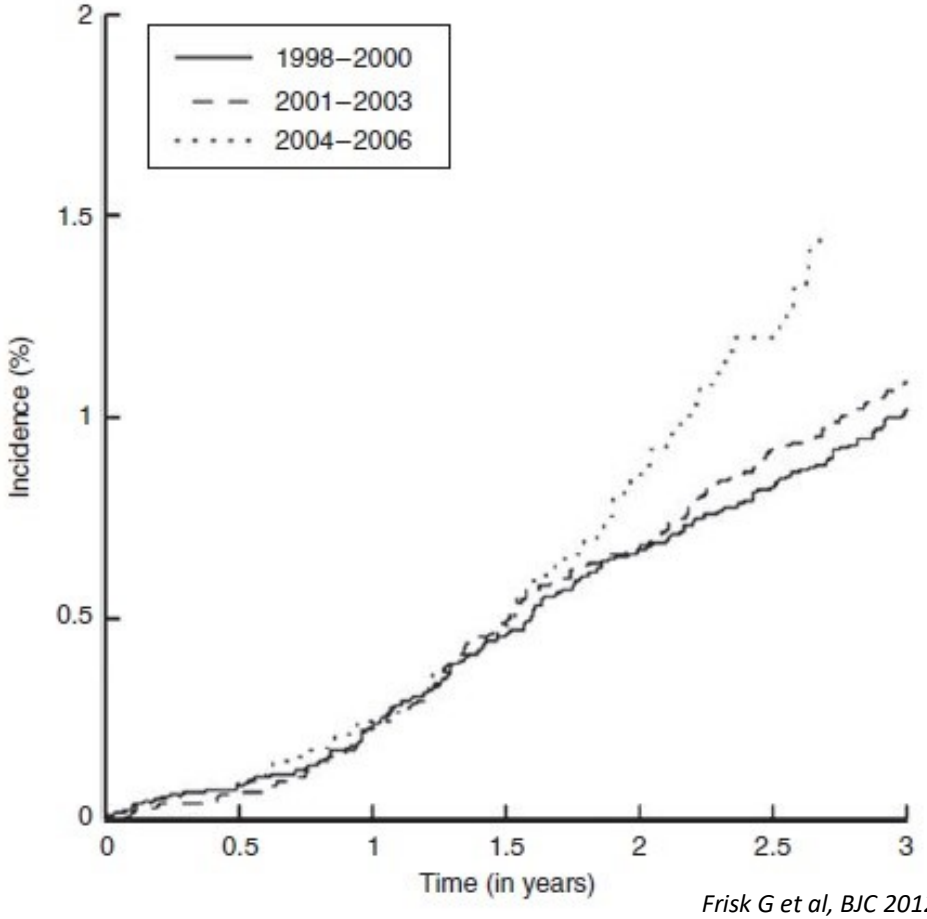
IOV - IRCCS

Brain metastasis in breast cancer (BC) patients

The incidence of brain metastasis from BC has increased in recent years and varies according to tumor biology



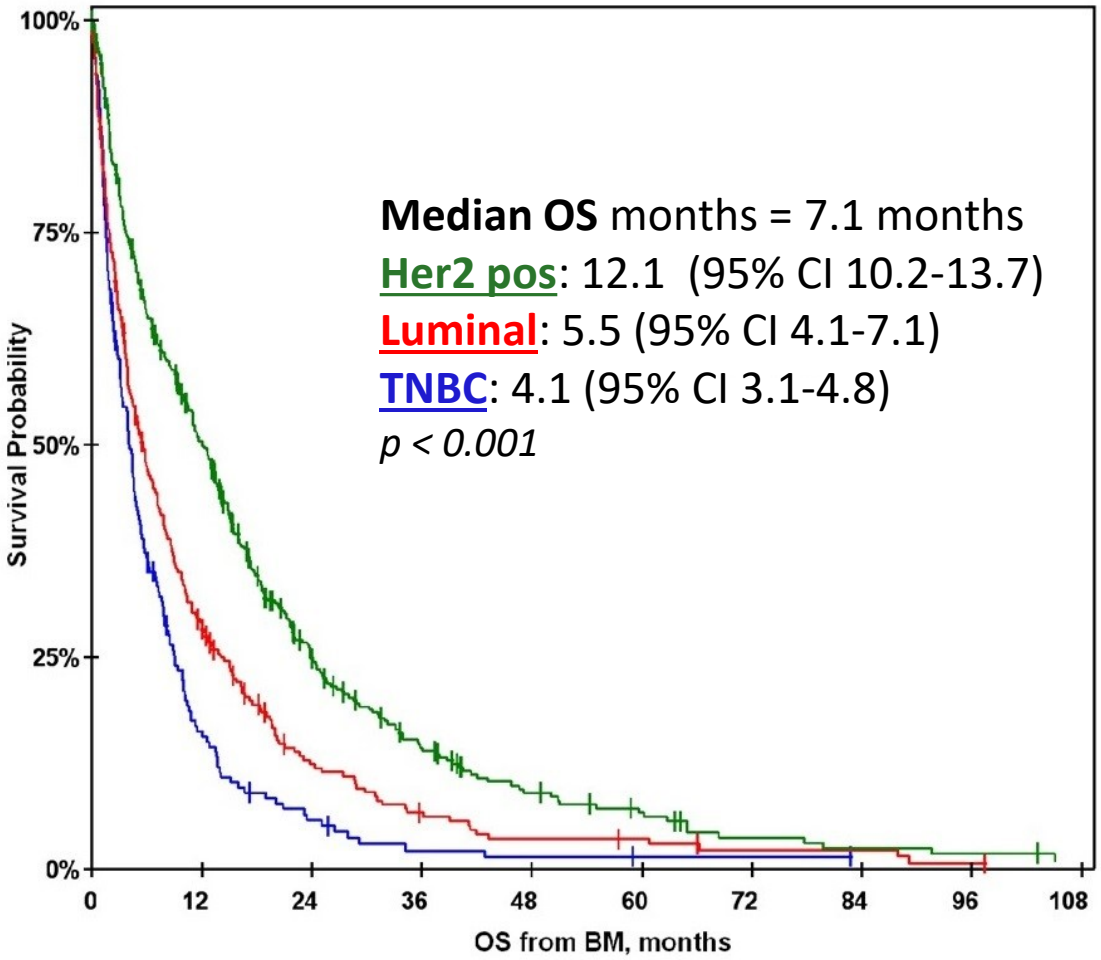
Frisk G et al, BJC 2012

FREQUENCY OF BRAIN METASTASIS AMONG PATIENTS WHO DEVELOPED DISTANT DISEASE

Subtype	No. of Patients	Brain	
		No.	%
Luminal A	458	35	7.6
Luminal B	378	41	10.8
HER2 positive, ER/PR positive	117	18	15.4
HER2 positive, ER/PR negative	136	39	28.7
Basal-like	159	40	25.2
TN nonbasal	109	24	22.0
P		< .001	

Kennecke H et al, JCO 2010

Brain metastasis and clinical outcome



Median OS months = 7.1 months
Her2 pos: 12.1 (95% CI 10.2-13.7)
Luminal: 5.5 (95% CI 4.1-7.1)
TNBC: 4.1 (95% CI 3.1-4.8)
p < 0.001

Mueller V et al, ASCO 2016

SUBTYPES AND SURVIVAL IN TWO DIFFERENT TIME PERIOD

Parameter	Year of diagnosis		p-value
	2000–2009	2010–2015	
	N (%)	N (%)	
	N = 507	N = 893	
Subtype			
TNBC	105 (20.7)	198 (22.2)	
Luminal like	144 (28.4)	303 (33.9)	
HER2 positive	258 (50.9)	392 (43.9)	0.0331
	N = 623	N = 967	
Median overall survival	Months (95% CI) 7.6 (6.5–9.2)	Months (95% CI) 5.8 (5.0–6.5)	<0.0001

Witzel I. et al, Eur J Cancer 2018

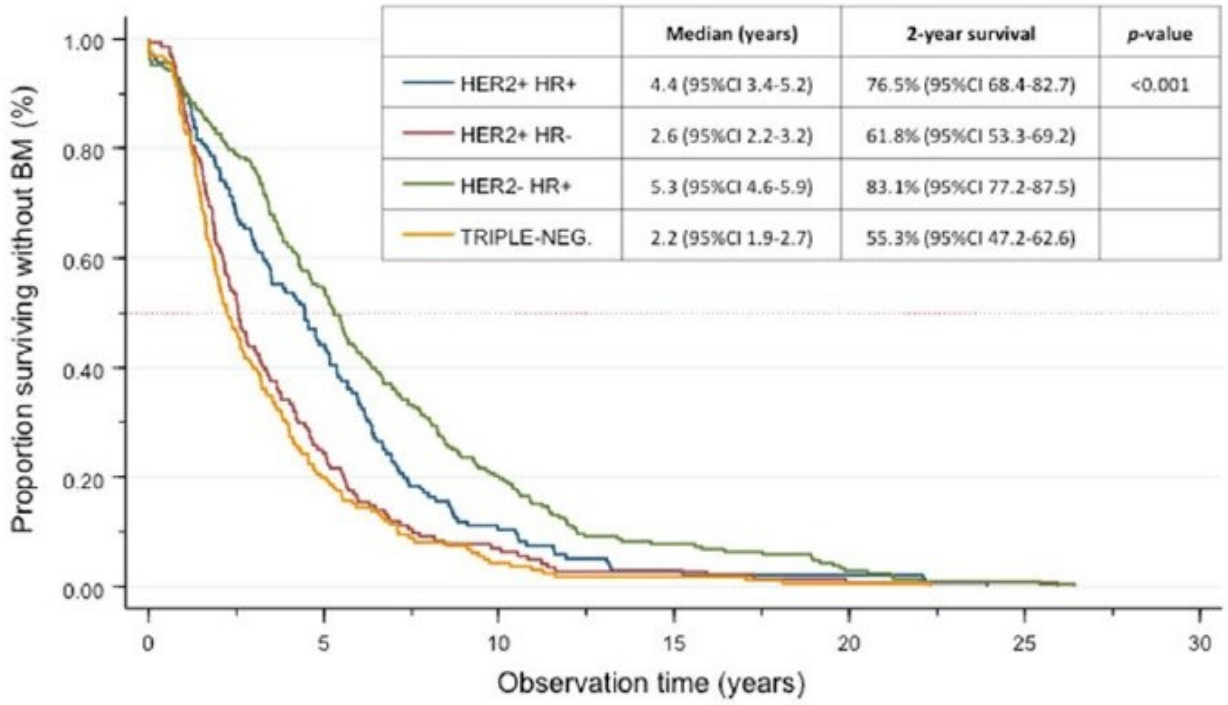
Journal of Neuro-Oncology (2018) 138:369–382
https://doi.org/10.1007/s11060-018-2805-9

CLINICAL STUDY

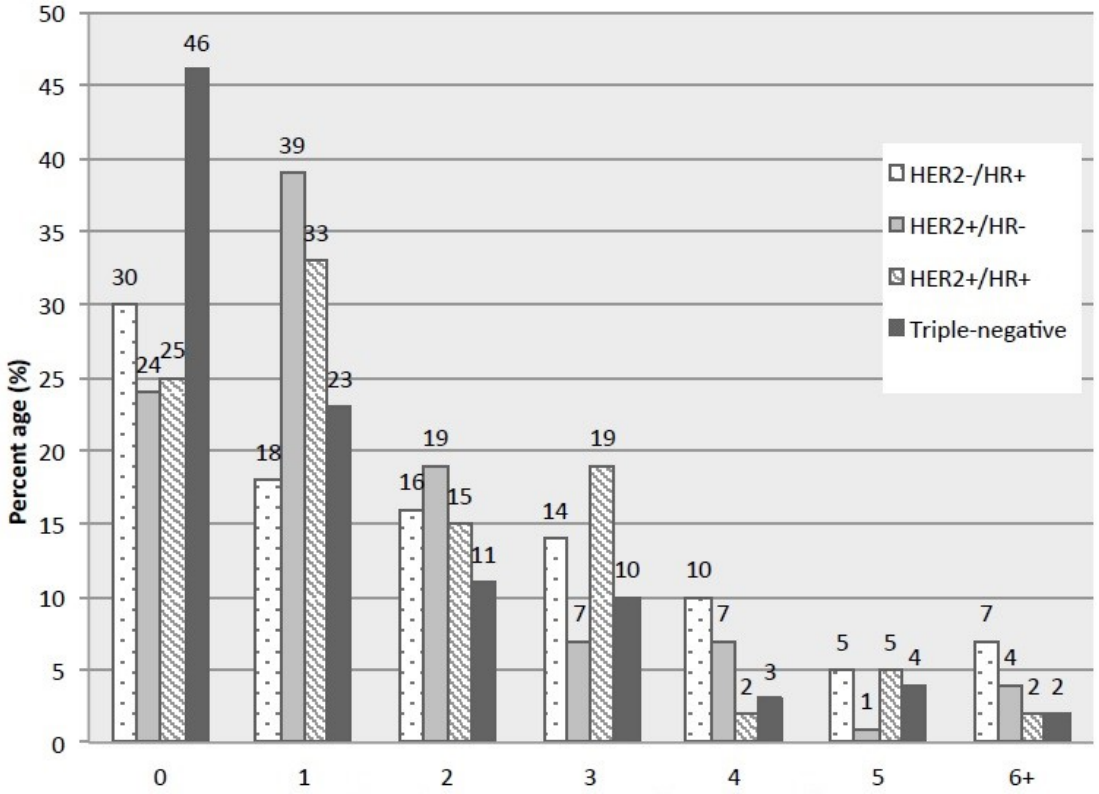
Hormone receptors status: a strong determinant of the kinetics of brain metastases occurrence compared with HER2 status in breast cancer

Amélie Darlix[1] · Gaia Griguolo[2,3] · Simon Thezenas[4] · Eva Kantelhardt[5,6] · Christoph Thomssen[5] · Maria Vittoria Dieci[2,3] · Federica Miglietta[2,3] · PierFranco Conte[2,3] · Antoine Laurent Braccini[7] · Jean Marc Ferrero[8] · Caroline Bailleux[8] · William Jacot[1] · Valentina Guarneri[2,3]

BRAIN METASTASIS-FREE SURVIVAL



N° OF PREVIOUS METASTATIC CT LINES

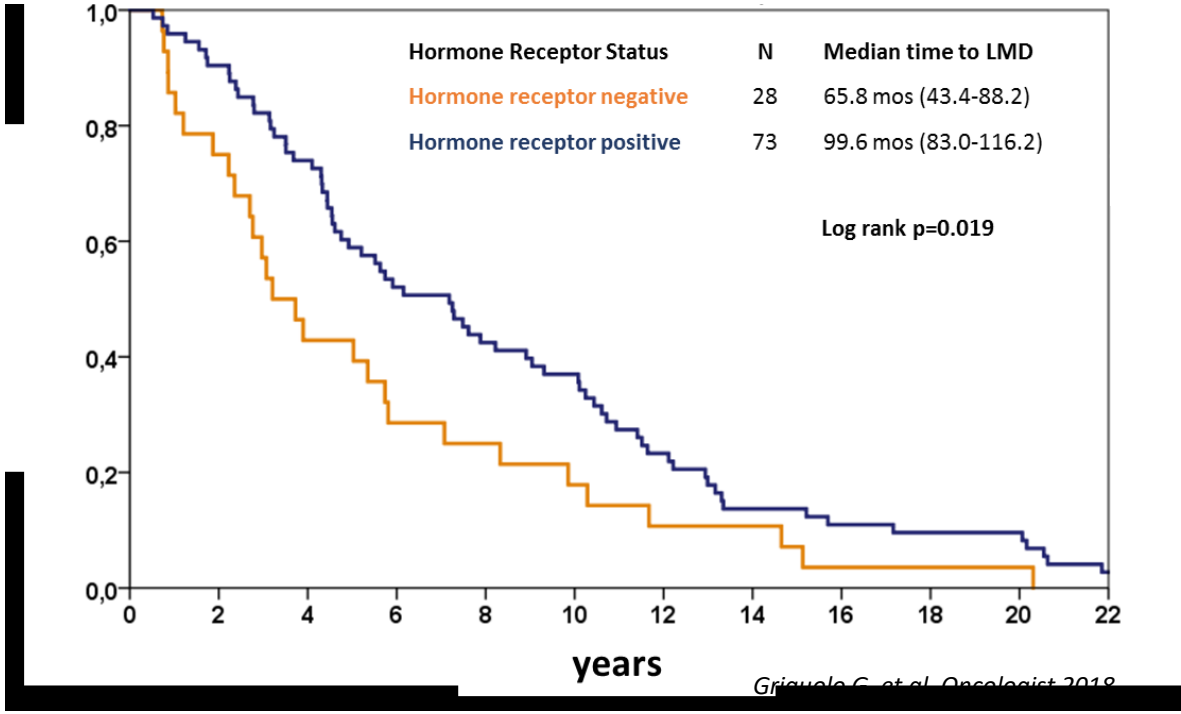


Darlix A. et al, J Neurooncol 2018

Leptomeningeal disease in HR+ breast cancer

- Breast cancer is one of the solid tumors most commonly associated with leptomeningeal disease (LMD)
- Survival is extremely short (3.9 months).
- Incidence and time to LMD is different among tumor subtypes.

Characteristics at time LMD diagnosis	Pts (%)
Tumor subtype	153 (100)
HR+/HER2- HR+/HER2+ HR-/HER2+ TN	78 (51) 20 (13.1) 11 (7.2) 23 (15.1)



Griguolo G, et al. Oncologist 2018

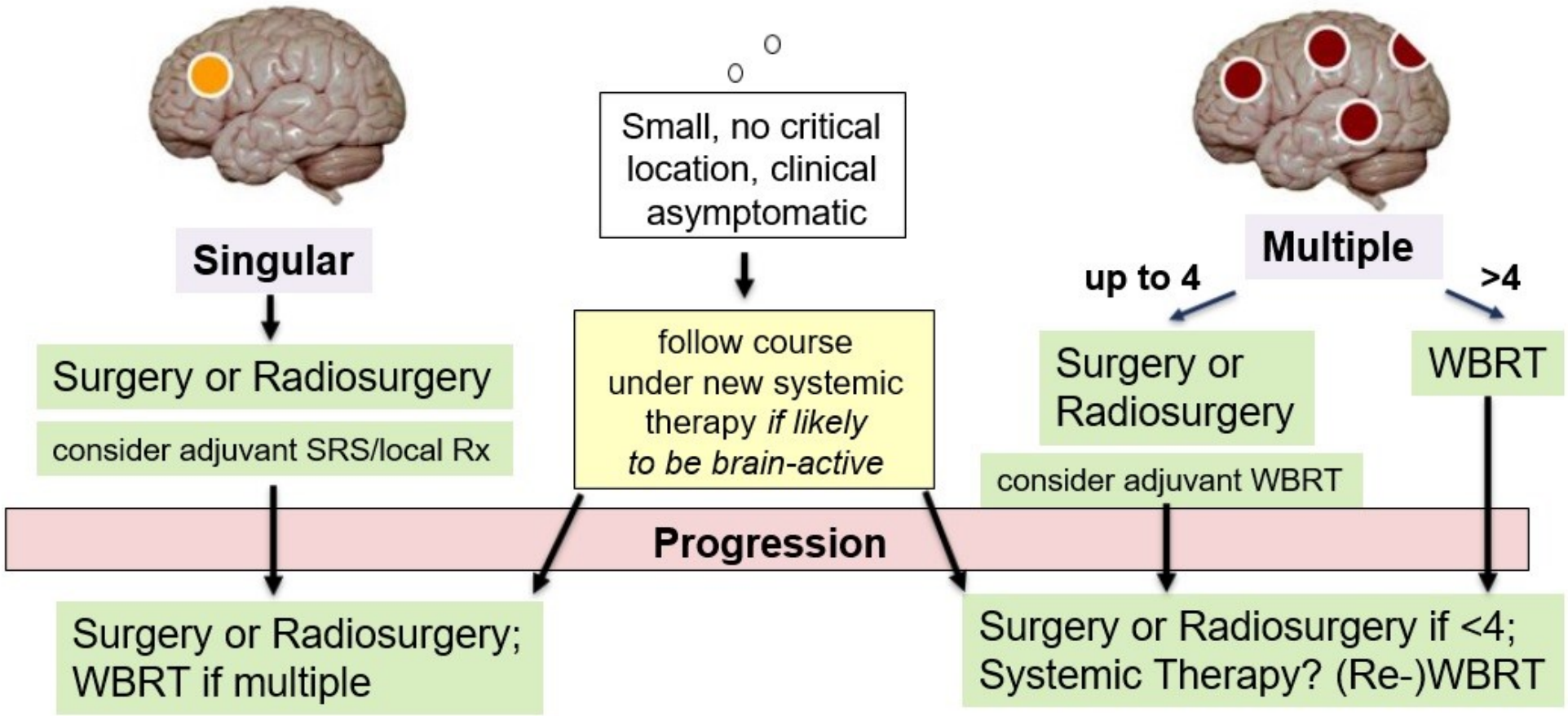
Differences in clinical behavior by tumor subtypes

Clinical features	HER2-positive	TNBC	Luminal
Timing of CNS relapse	Continuous over time	Tends to be early	Tends to be late
Control of extracranial disease at time of CNS relapse	Frequent	Uncommon	Varies
Median OS from time of CNS relapse	≈12 months	≈4-5 months	≈5-6 months
Leptomeningeal involvement	Less frequent	More frequent and tends to be early	More frequent and tends to be late

Mueller V. ASCO 2016, Witzel I. Eur J Cancer 2018, Darlix A. J Neurooncol 2018, Lin NU Clin Cancer Res 2013

Brain metastasis in breast cancer: therapy

No specific treatment guidelines are available for the management of brain metastasis in breast cancer, with the exception of HER2+ BC (ASCO Guidelines JCO 2018)

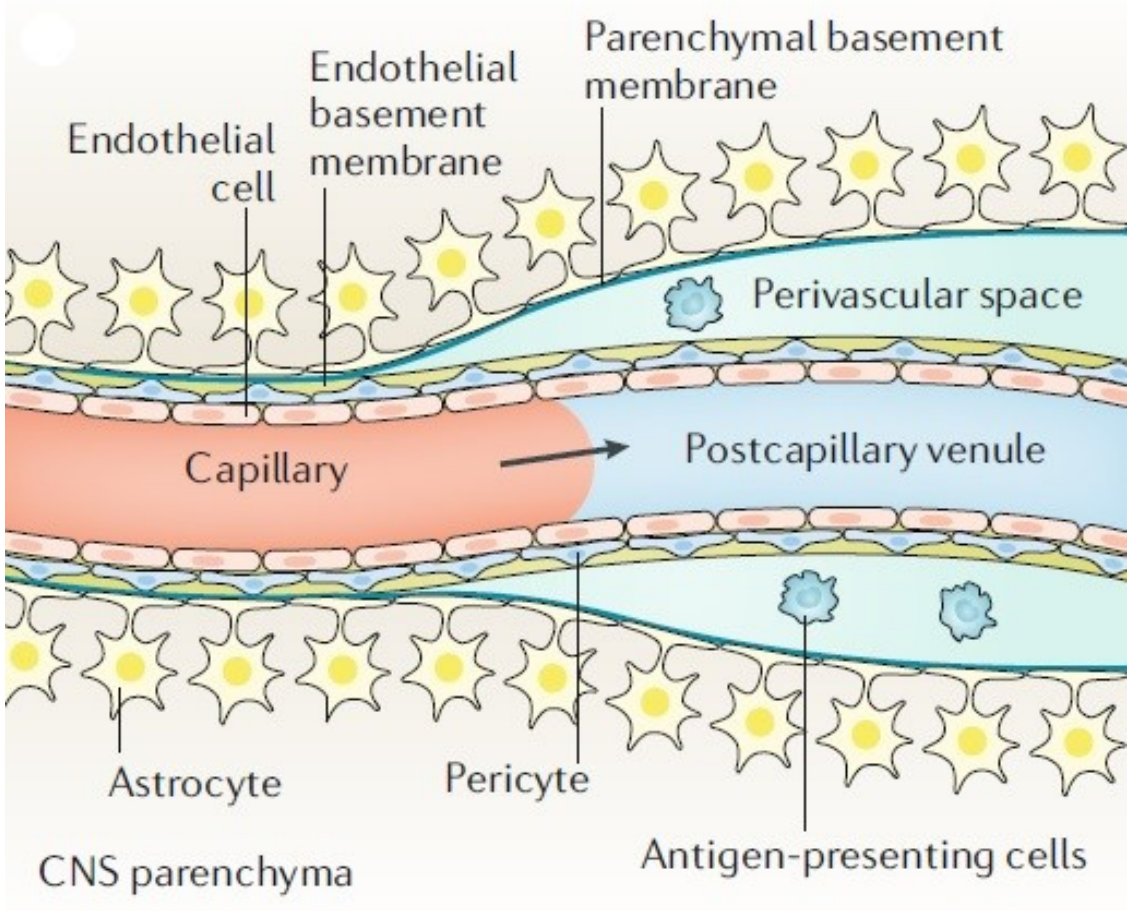


Winkler, ESMO 2018

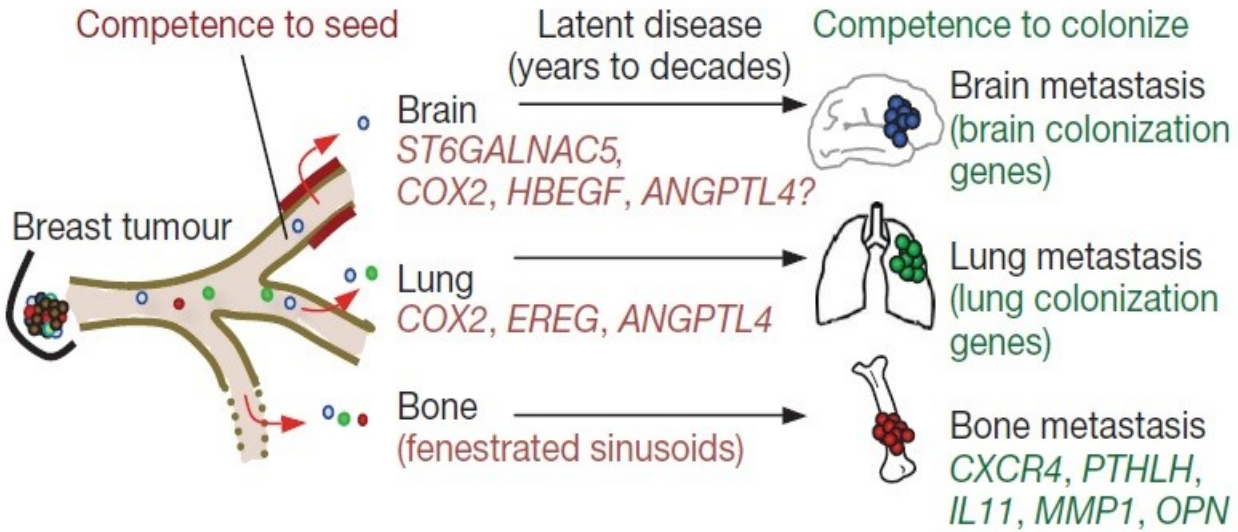
No systemic agents with a specific indications for treatment of BC brain metastases

Challenges in treatment of BC brain metastasis

The blood-brain barrier: a complex barrier that regulates what enters the brain (drugs, tumor cells…)



Achrol AS et al, Nat Rev 2019



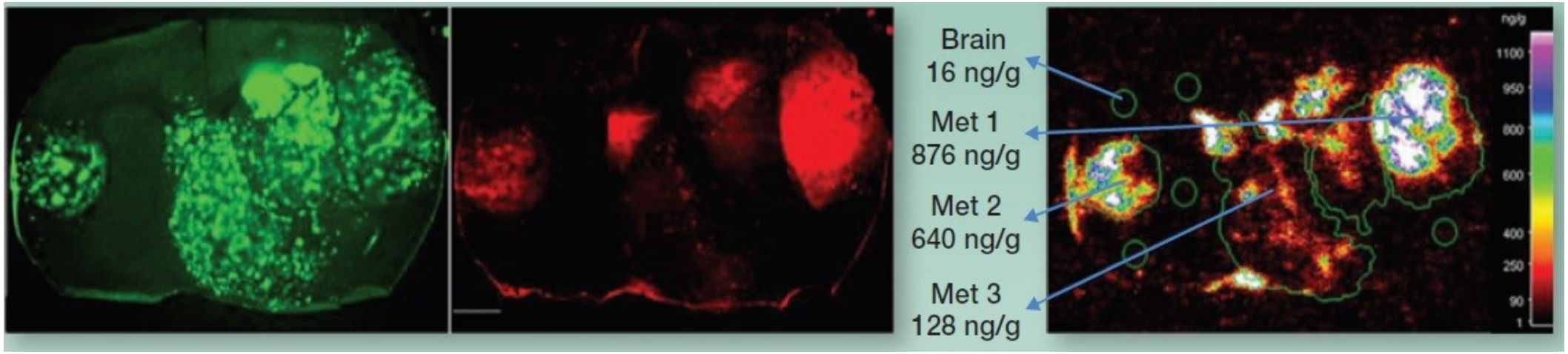
Specific interactions between BBB and tumor cells can increase extravasation into the brain

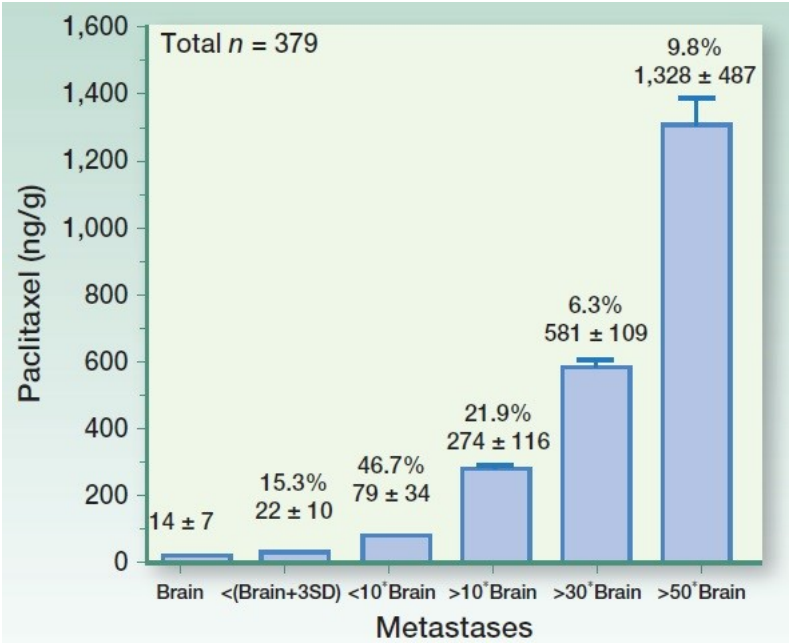
Bos PD et al, Nature 2009

Challenges in treatment of BC brain metastasis

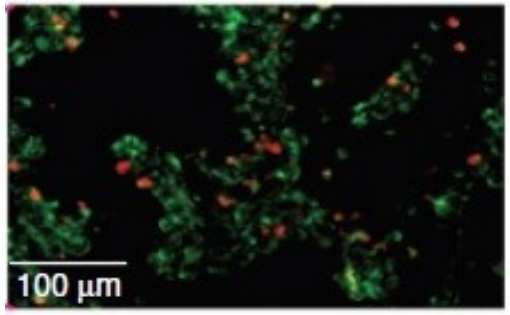
The blood-tumor barrier and its permeability

HETEROGENEOUS UPTAKE OF ^{14}C-PACLITAXEL

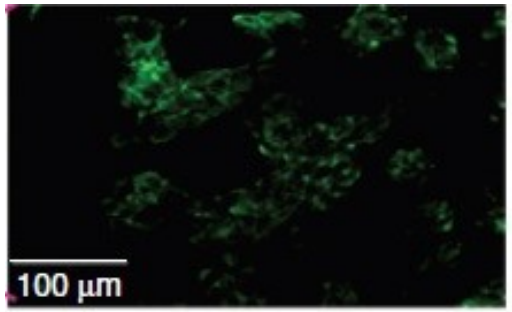




High ^{14}C-paclitaxel uptake



Low ^{14}C-paclitaxel uptake



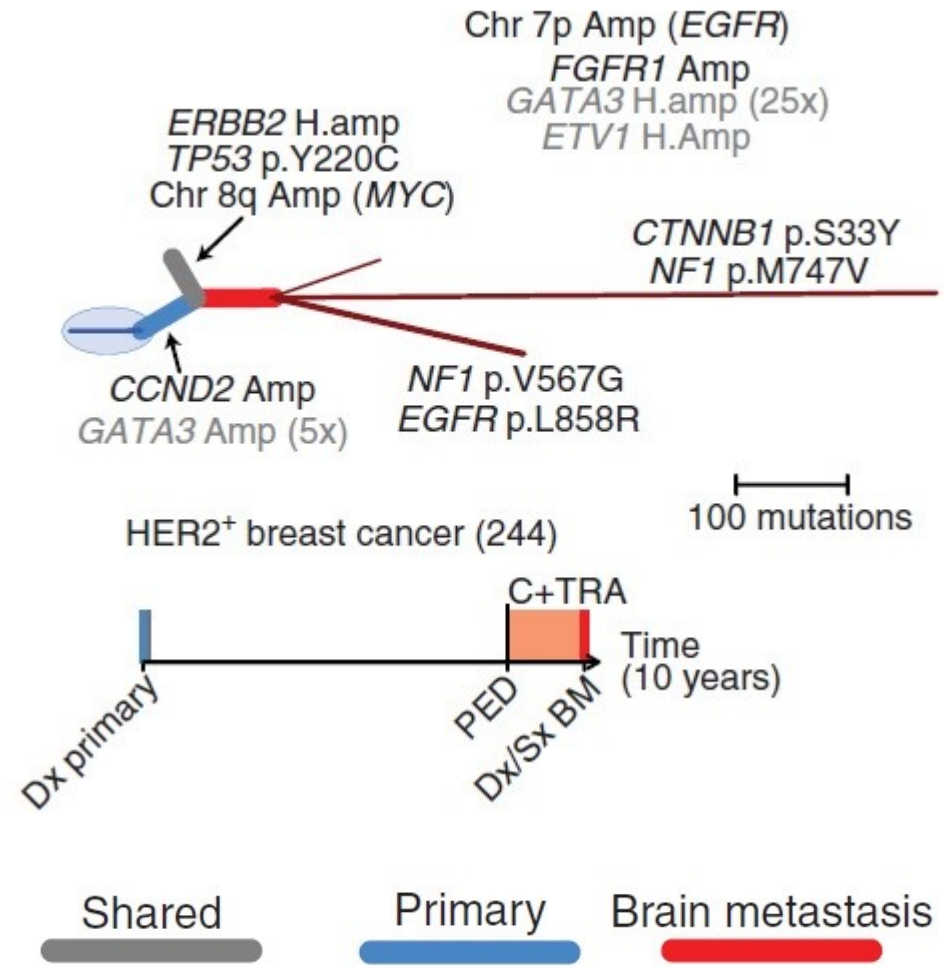
Cleaved Caspase-3

Is drug penetration the primary reason for resistance to systemic therapy in brain metastasis?

Lockman PR et al, Clin Cancer Res 2010

Challenges in treatment of BC brain metastasis

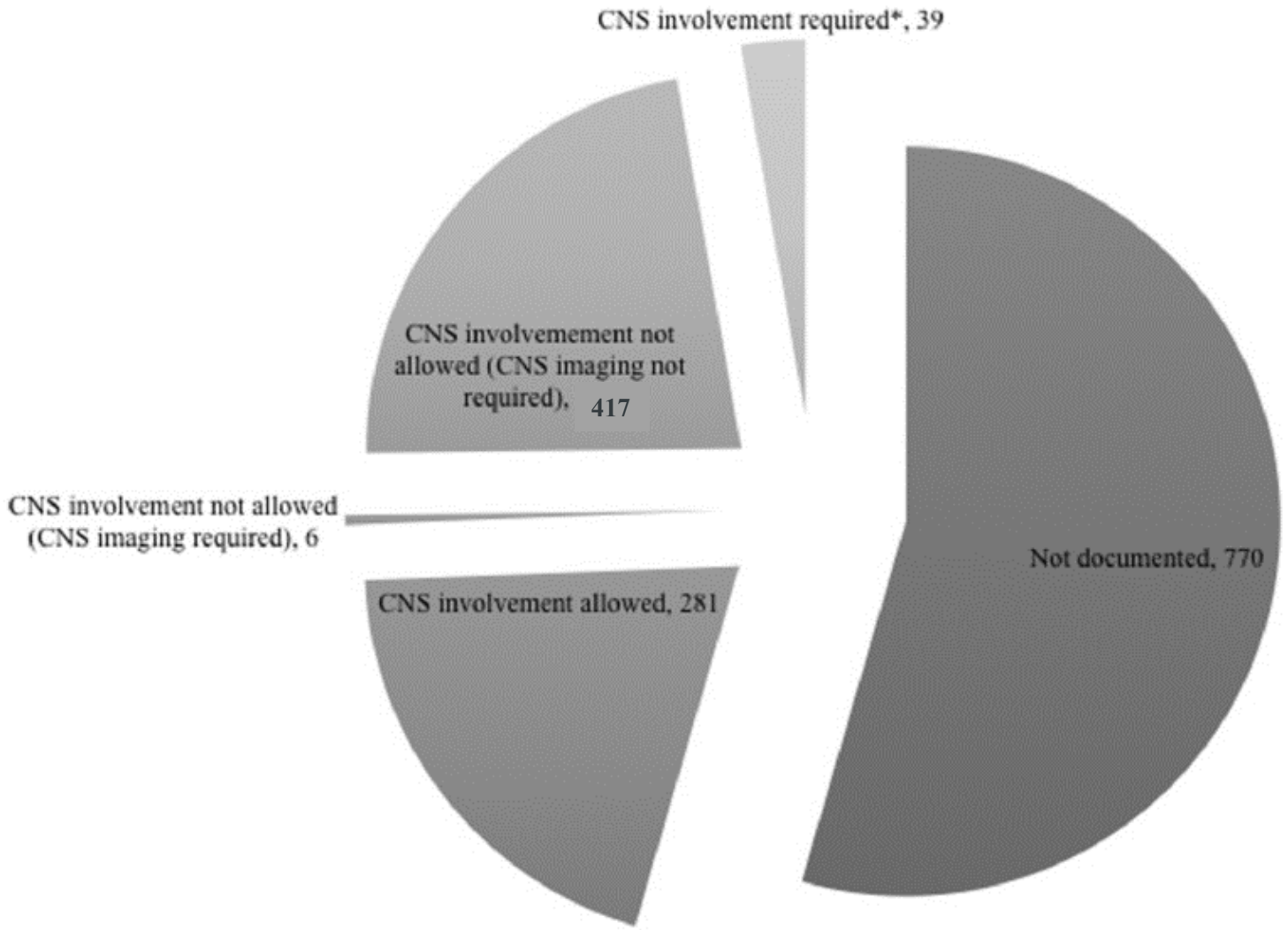
Differences between brain metastases and matched primary-tumor samples



- Potentially oncogenic alterations that contribute to the limited role of systemic treatment
- Clinically actionable target in brain metastases: need for clinical trials

Brastianos P et al, Cancer Disc 2015

Brain metastasis in breast cancer: clinical trials



Total: 1474 trial

Among **109** early phase studies limited to **HR+/HER2- MBC**

- **17** (15.6%) allowed history of CNS involvement

Need to include brain metastasis patients in clinical trial

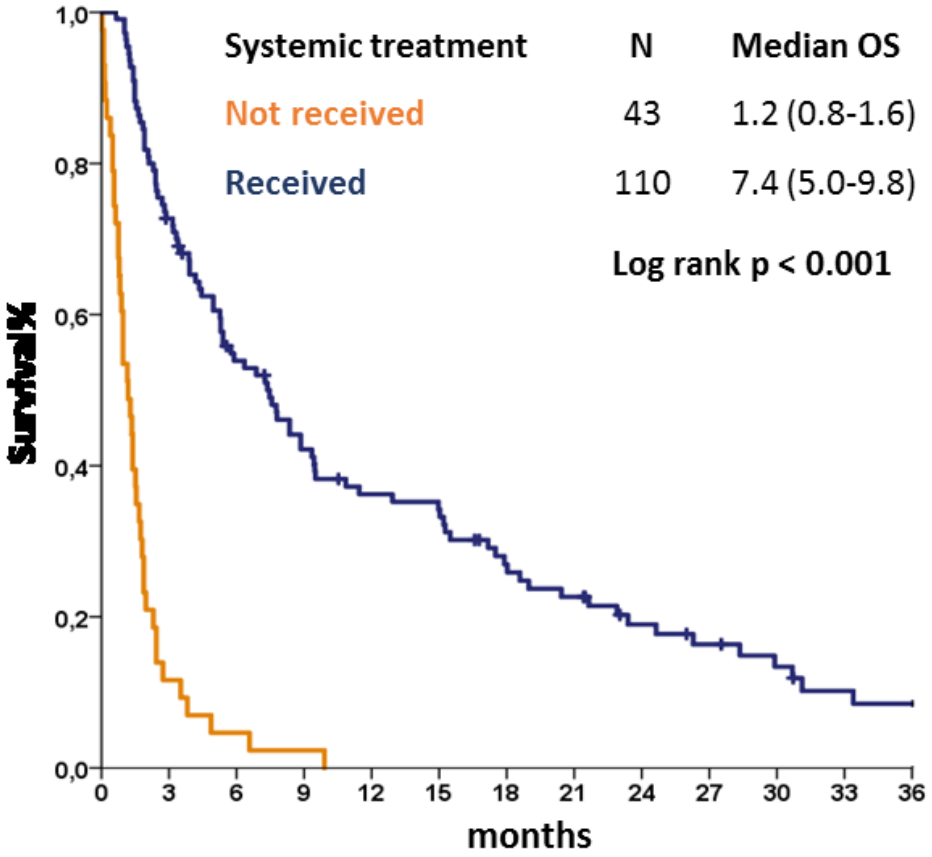
Costa R. et al, Cancer Treat Rev 2017

CNS involvement in BC: systemic therapy

BRAIN METASTASIS

Factors	Median OS (95% CI)	Univariate HR	p	Corrected for BS-GPA category
BS-GPA index				
3.5-4	18.8 (15.2–22.5)	ref.	**0.014**	
2.5-3	8.8 (3.8–13.8)	1.58 (0.91–2.74)		
1.5-2	6.2 (2.2–10.2)	1.86 (1.04–3.34)		
0-1	3.6 (0.75–6.4)	2.97 (1.49–5.93)		
Number of local treatments				
0	3.0 (1.6–4.3)	ref.	**<0.001**	ref.
1	8.8 (6.1–11.6)	0.50 (0.35–0.72)		0.52 (0.35–0.77)
2	21.0 (15.0–27.0)	0.34 (0.19–0.63)		0.48 (0.25–0.92)
3	35.1 (33.0–37.1)	0.19 (0.07–0.48)		0.14 (0.05–0.42)
Systemic treatment received				
No	3.1 (1.1–5.0)	ref.		ref.
Yes	13.8 (9.9–17.6)	0.41 (0.29–0.57)	**<0.001**	0.47 (0.31–0.70)

LEPTOMENINGEAL CARCINOMATOSIS



Griguolo G. et al, J Neuroncol 2017, Oncologist 2018

Systemic therapy for HR+ BC brain metastasis

AVAILABLE STRATEGIES
Endocrine therapy
Chemotherapy

NEW PERSPECTIVES
CDK 4/6 inhibitors
PI3K/AKT/mTor inhibitors
Nanoparticle delivery systems
Immunotherapy

Endocrine therapy

No randomized trials, activity reported in case reports

Author	Endocrine therapy	Age	Time to brain metastasis	Other location	CNS response	Other sites response	Duration of CNS response
Carey, 1981	**Tamoxifen**	43 yr	5 yr	Soft tissue, breast	CR	PR	14 mo
Colomer, 1988	**Tamoxifen**	56 yr	0	Bone, breast	CR	PR	34 mo
Pors, 1991	**Tamoxifen**	68 yr	27 yr	Breast	PR	CR	58 mo
Stewart, 1995	**Megestrol acetate**	56 yr	--	--	PR	--	24 mo
Madhup, 2006	**Letrozole**	48 yr	3 yr	Bone	PR	CR	19 mo

CNS involvement is a late event when most patients have already developed hormone resistant tumors.

Chemotherapy

Case reports/case series and prospective, non-randomized study

- Capecitabine

Rivera, Cancer 2006
Ekenel, J Neuroncol 2007

- Anthracyclines

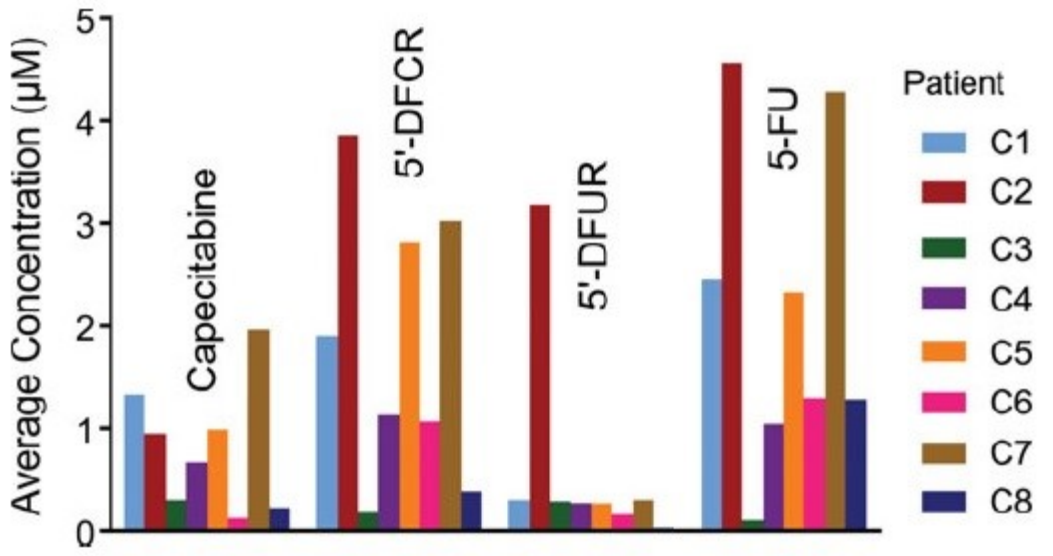
Rosner, Cancer 1986
Caraglia, cancer 2007
Linot , J Neurooncol 2014

- Platinum salts

Cocconi, Cancer Invest 1990
Franciosi, Cancer 1999
Christodoulou, J Neuroncol 2005

- Temozolomide

Cross BBB and achieve brain tumor levels higher than serum levels



Morikawa A. et al, Neuro Oncol 2015

Chemotherapy: temozolomide

Reference	Regimen	# breast ca pts treated	CNS ORR in breast ca pts
Trudeau Ann Oncol 2006	TMZ	19	0%
Abrey J Neurooncol 2001	TMZ	10	0%
Siena Ann Oncol 2010	TMZ	51	4%
Iwamoto J Neurooncol 2008	TMZ + vinorelbine	11	0%

WBRT WITH CONCURRENT TMZ

ORR	Arm WBRT No. of patients (%) *N* = 50	Arm WBRT + TMZ No. of patients (%) *N* = 50
CR	0	0
PR	18 (36)	15 (30)
SD	26 (52)	18 (36)
PD	3 (6)	4 (8)
Not evaluated	3 (6)	13 (26)

Median OS months

WBRT arm 11.1 (95% CI 8.3-15.3)

WBRT + TMZ 9.4 (95% CI 7.3-13.4)

p=0.592

Median PFS

WBRT arm 7.4 (95% CI5.3-13.1)

WBRT + TMZ 6.8 (95% CI4.6-8.6)

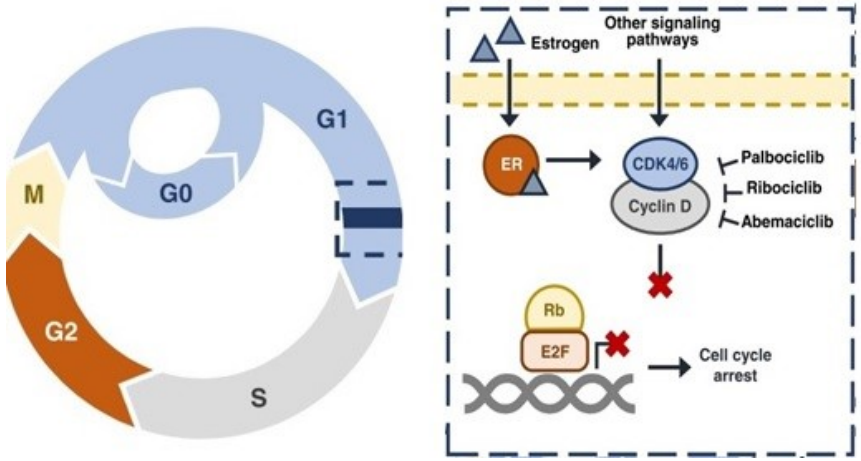
p=0.754

Lin NU ASCO 2017, Cao K.I. Ann. Oncol 2015

CDK 4/6 inhibitors

First-line setting, AI sensitive

Study	n	PFS CDK4/6	PFS Placebo	HR (95%CI)
PALOMA-2 Let +/- Palbolbociclib	666	24.8	14.5	0.58 (0.46-0.72)
MONALEESA-2 Let +/- Ribociclib	668	25.3	16.0	0.57 (0.46-0.70)
MONARCH-3 AI +/- Abemaciclib	493	28.8	14.8	0.54 (0.42-0.70)



Sammons SL et al, Curr Cancer Drug Target 2017

Second-line setting, endocrine pretreated

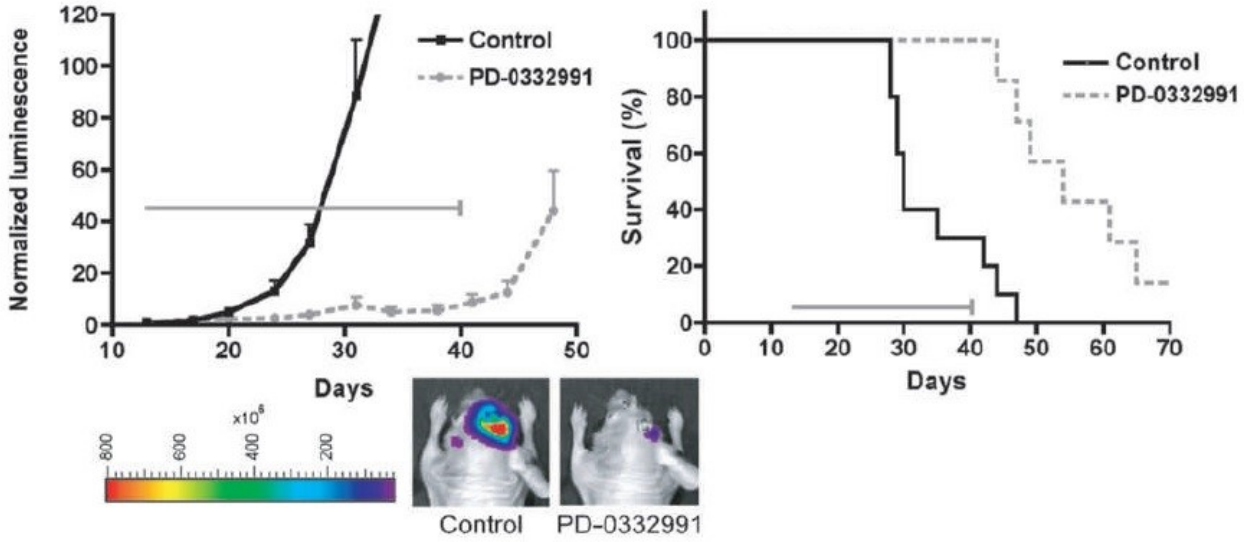
Study	n	PFS CDK 4/6	PFS Placebo	HR (95%CI)
PALOMA-3 Fulv +/-Palbociclib	521	9.5	4.6	0.46 (0.36–0.59)
MONARCH-2 Fulv +/- Abemaciclib	669	16.4	9.3	0.55 (0.45-0.68)

…and patients with brain metastasis?

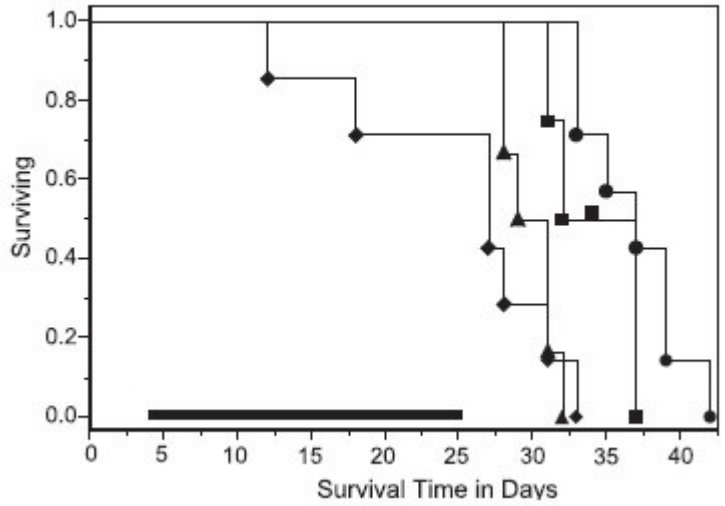
CDK 4/6 inhibitors: brain exposure

Activity in intracranial glioblastoma xenograft model

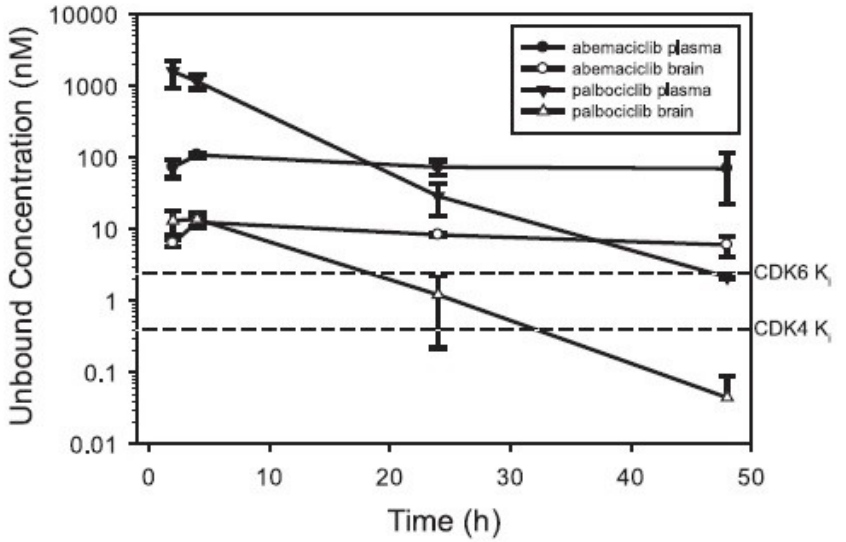
PALBOCICLIB



ABEMACICLIB



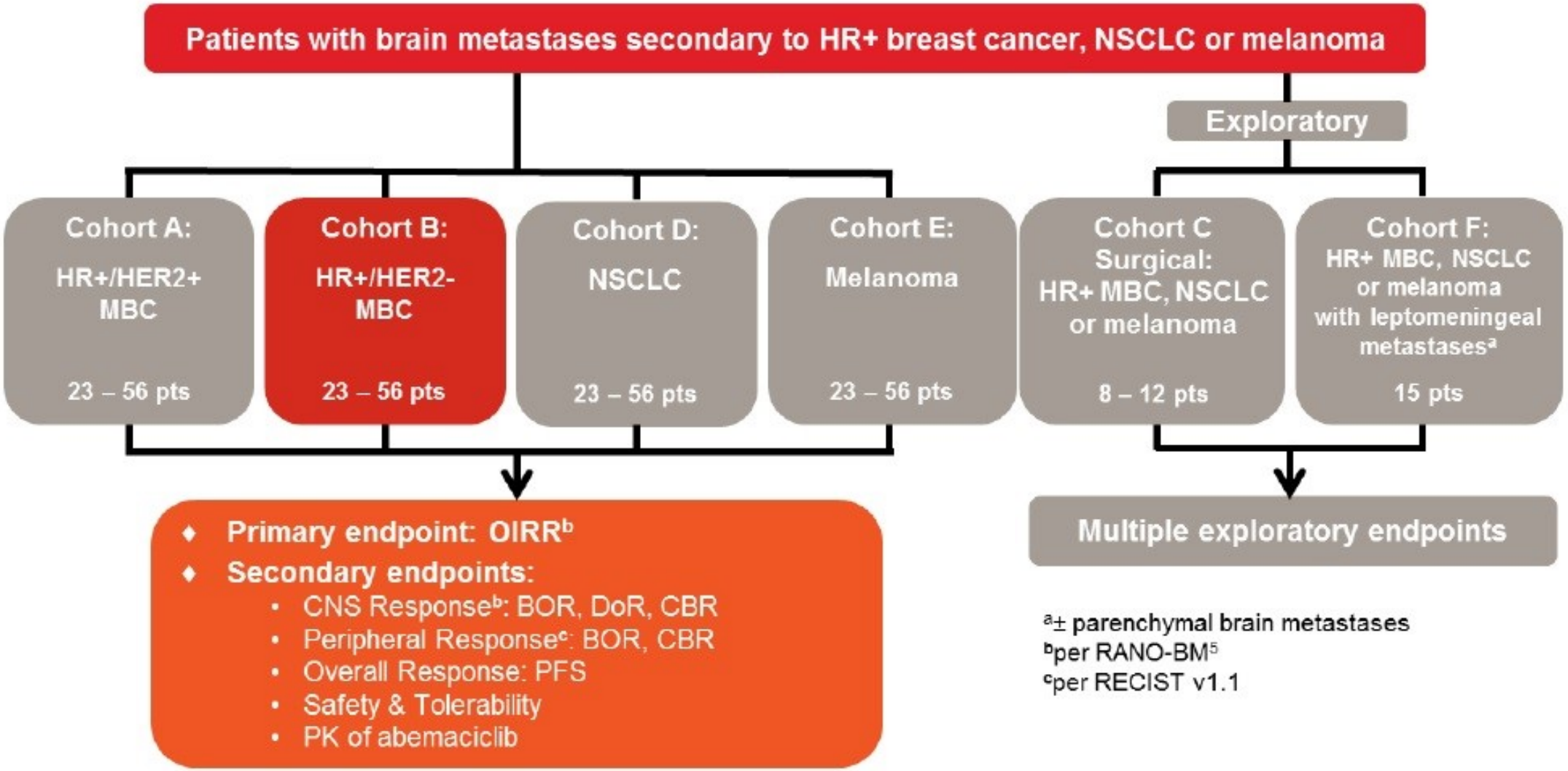
Symbol	Group (mg/kg)
◆	Vehicle (0)
▲	Abemaciclib (20)
■	Abemaciclib (40)
●	Abemaciclib (80)



Abemaciclib brain levels are reached at lower doses and target longer than Palbociclib.

Raub TJ et al, Drug Metab Dispos 2015
Michaud K et al, Cancer Res 2010

Abemaciclib in brain metastasis: JPBO study



[a]± parenchymal brain metastases
[b]per RANO-BM[5]
[c]per RECIST v1.1

Tolaney S. Et al, ASCO 2017

JPBO study: HR+/HER2- metastatic BC

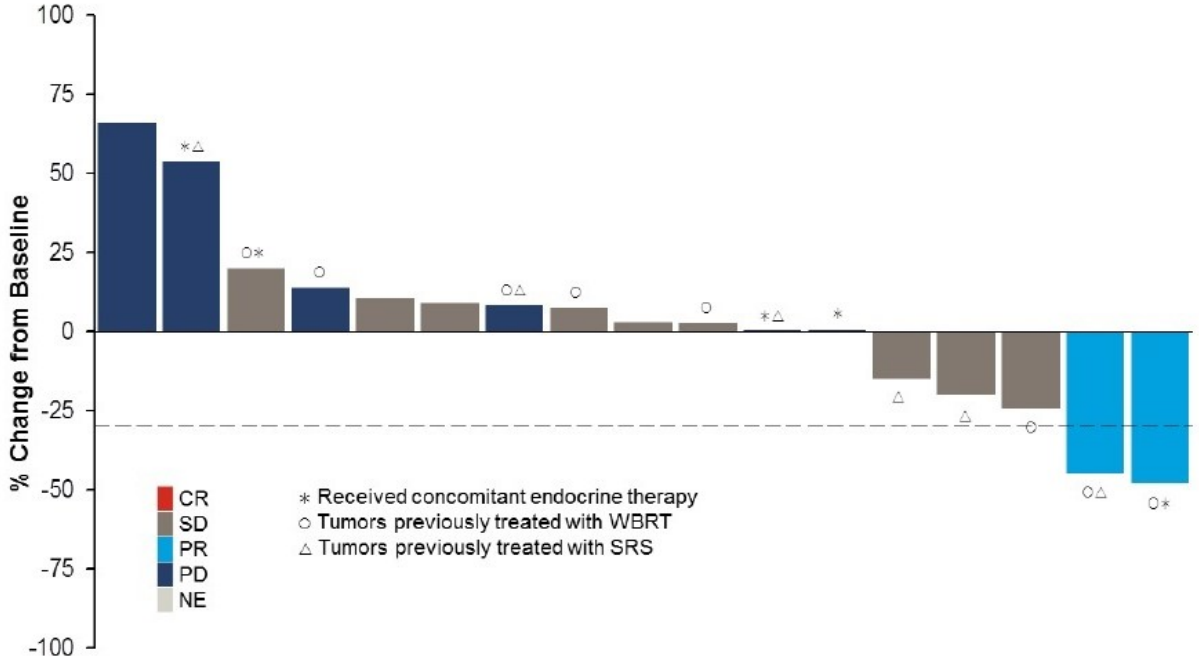
Baseline pts characteristics (N=23)	n (%)
Median age (range)	52 (35-69)
Age≥65 years	5 (21.7)
KPS	
≥ 90	14 (60.9)
80	8 (34.8)
70	1 (4.3)
Prior systemic therapy for metastatic disease	
1 regimen	5 (21.7)
2 regimens	5 (21.7)
≥ 3 regimens	10 (43.4)
Endocrine therapy	17 (73.9)
Chemotherapy	15 (65.2)
1 regimen	4 (17.4)
2 regimens	6 (26.1)
≥ 3 regimens	5 (21.7)
Immunotherapy	3 (21.7)
Other	10 (43.5)

Baseline CNS disease (N= 22)	N (%)
TARGET CNS LESIONS	
1 lesion	12 (54.4)
2 lesions	5 (22.7)
≥ 3 lesions	5 (22.7)
PRIOR THERAPY FOR TARGET CNS LESIONS	
Prior surgery	1 (4.5)
Prior WBRT	10 (45.5)
Prior SRS	6 (27.7)
Baseline peripheral disease (N = 21)	**N (%)**
Visceral	14 (66.7)
Bone only	4 (17.4)
Visceral + Bone	8 (38.1)
Other	9 (42.9)

JPBO study: HR+/HER2- metastatic BC

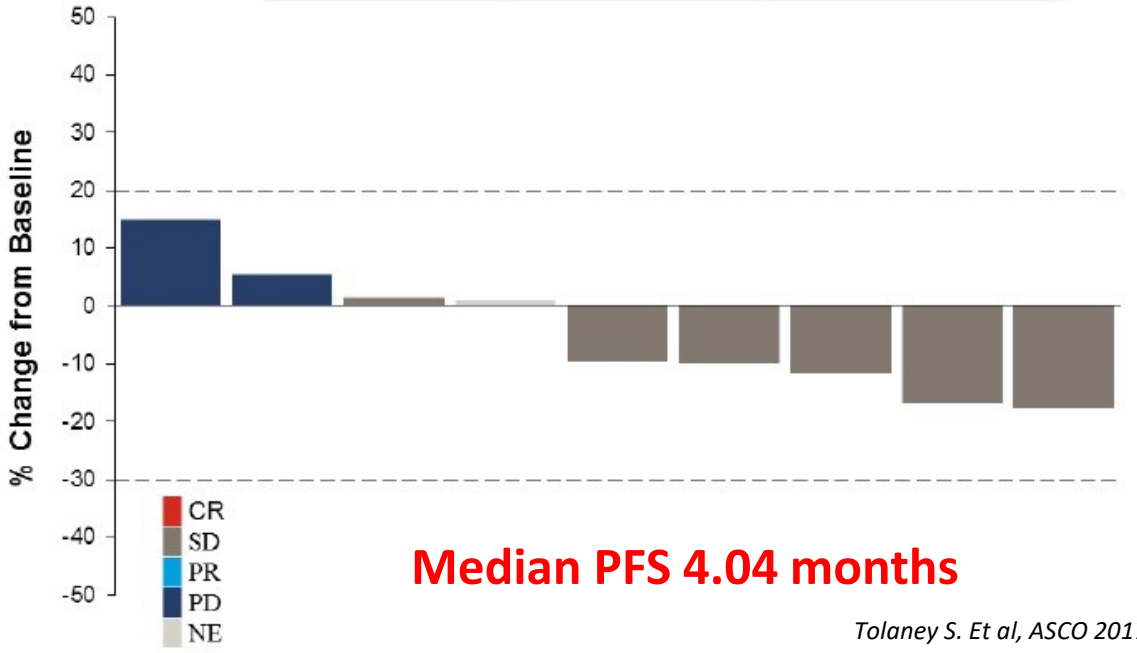
CNS Response

Patients with Response		N=23
OIRR	n (%), (95% CI)	2 (8.7), (0.0, 20.2)
CR	n (%)	0
PR	n (%)	2 (8.7)
SD	n (%)	10 (43.5)
SD[c] ≥ 6 months	n (%)	2 (8.7)
PD or early death	n (%)	8 (34.8)
CBR	n (%), (95% CI)	4 (17.4), (1.9, 32.9)



Peripheral Response

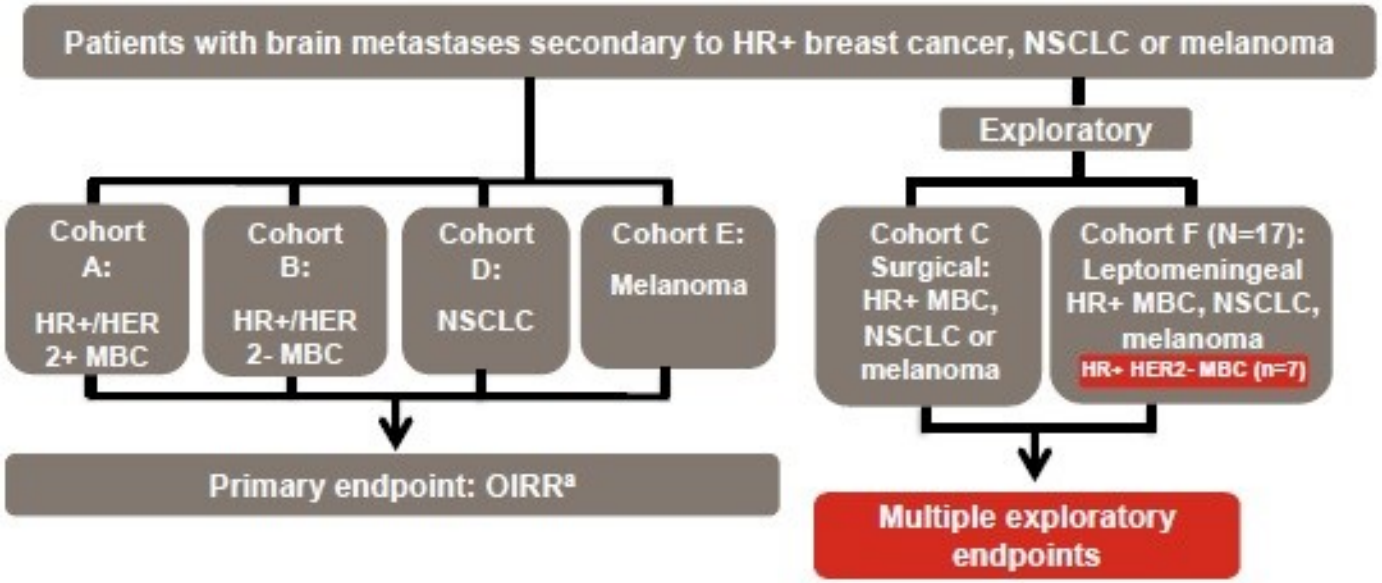
Patients with Response[e]		N=13
ORR	n (%)	0
CR	n (%)	0
PR	n (%)	0
SD	n (%)	6 (46.2)
SD[c] ≥ 6 months	n (%)	1 (7.7)
PD	n (%)	2 (15.4)
CBR	n (%), (95% CI)	1 (7.7), (0.0, 22.2)



Median PFS 4.04 months

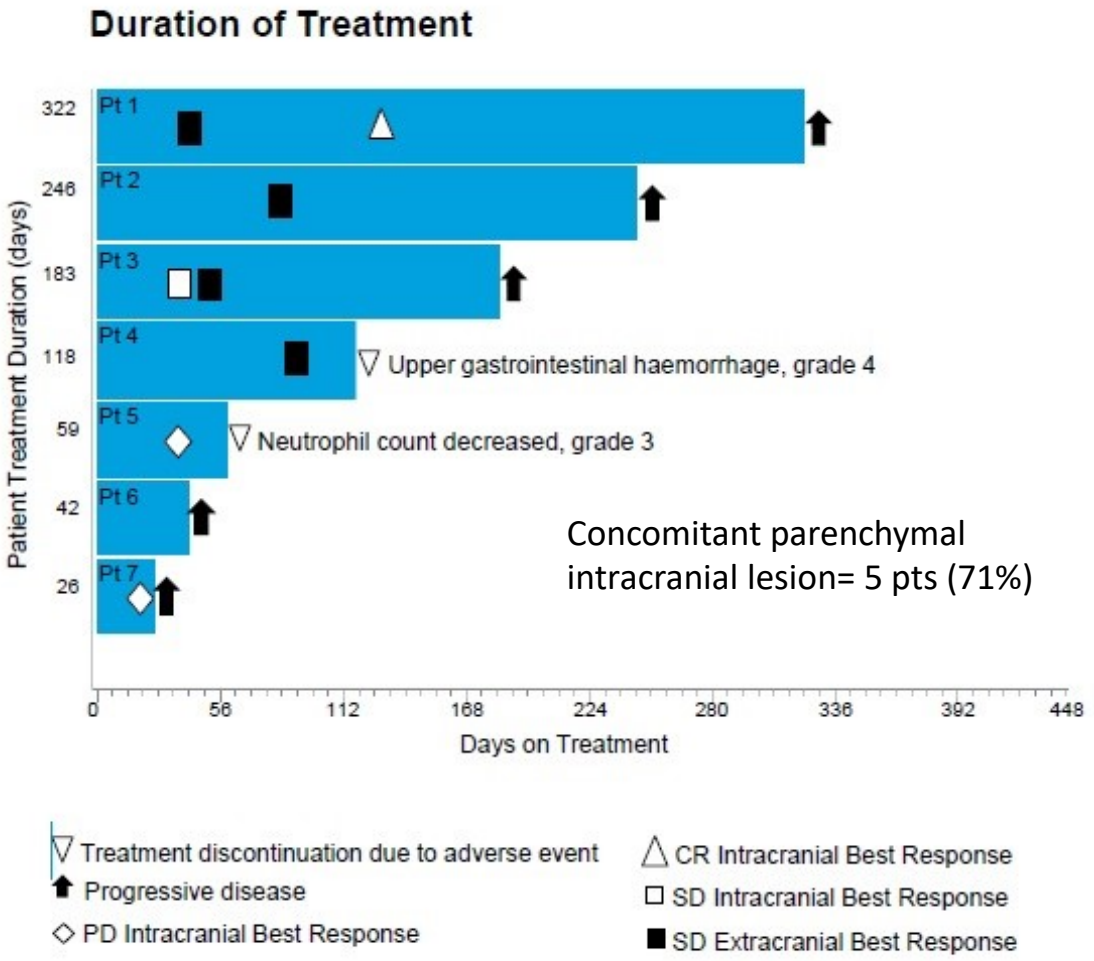
Tolaney S. Et al, ASCO 2017

JPBO study: leptomeningeal disease



Baseline Characteristics

HR+ Breast Cancer with LM (N=7)	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Age (in years)	53	41	39	54	60	57	47
Race	White	White	White	White	White	White	NA
Radiotherapy prior to IC target lesion							
SRS-treated	Yes	NA	Yes	NA	NA	NA	Yes
WBRT	Yes	NA	No	NA	NA	NA	Yes
Prior chemotherapy for metastatic disease							
Number of regimens	NA	≥3	≥3	2	0	≥3	≥3
Steroid use at time of enrollment	NA	Yes	Yes	NA	Yes	Yes	Yes



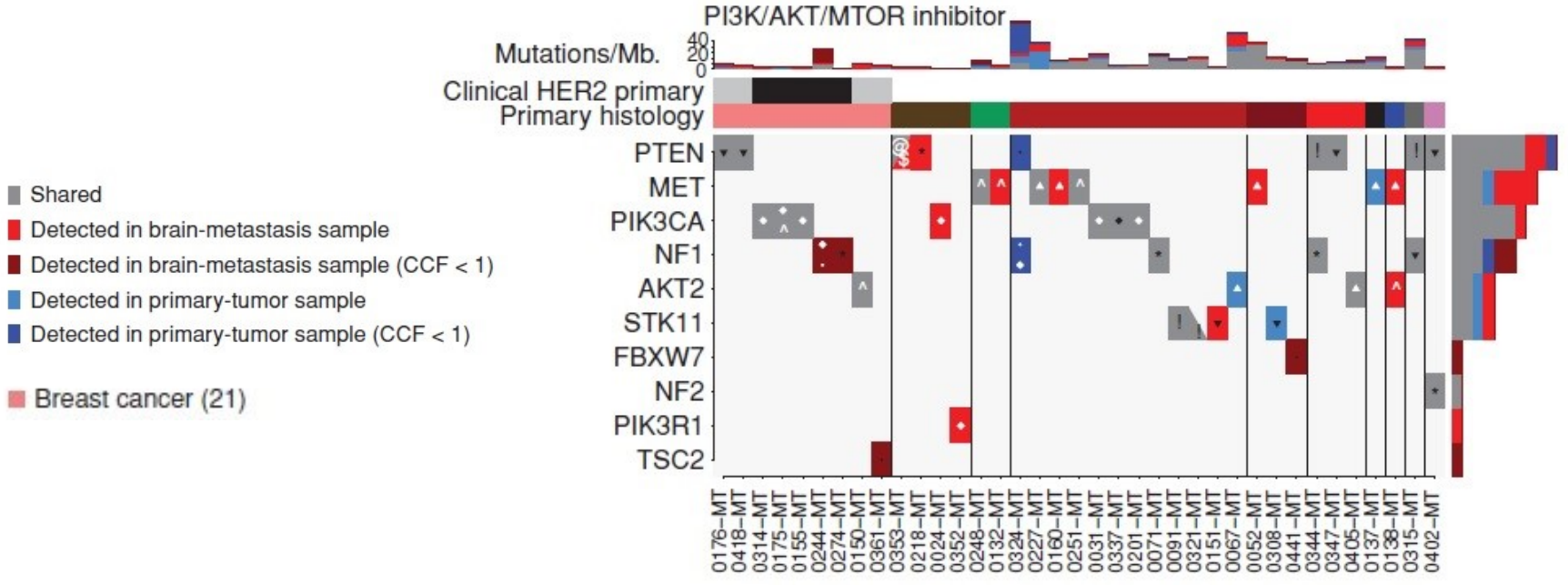
Concomitant parenchymal intracranial lesion= 5 pts (71%)

Median OS = 8.4 months (95% CI 3.3, NE)

Tolaney S. Et al, SABC 2018

PI3K/AKT/mTOR inhibitors

Mutations of PI3K/AKT/mTOR pathway occurred frequently in brain metastases from breast cancer



Brastianos P et al, Cancer Disc 2015

<u>No published data for EVEROLIMUS in HR+ breast cancer brain metastases</u>

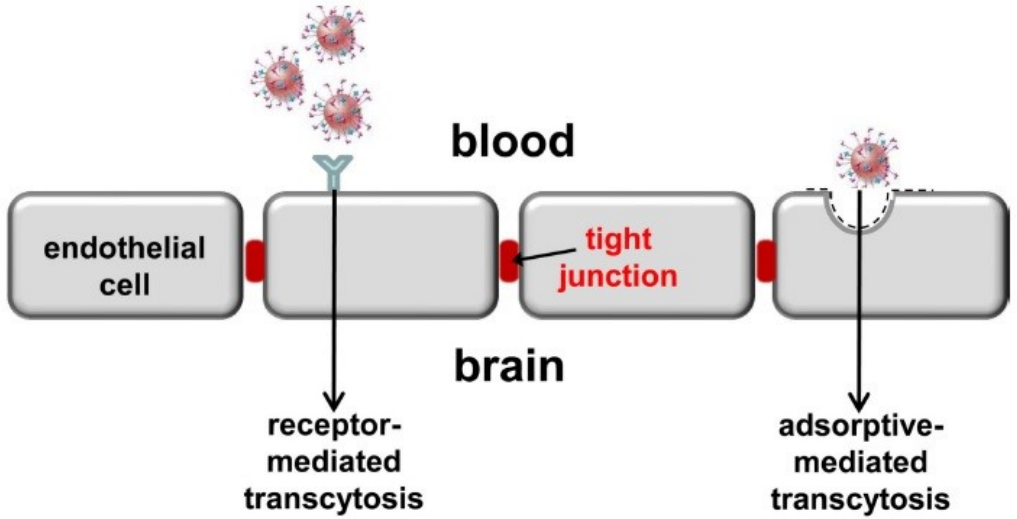
<u>Everolimus penetrates the BBB</u>

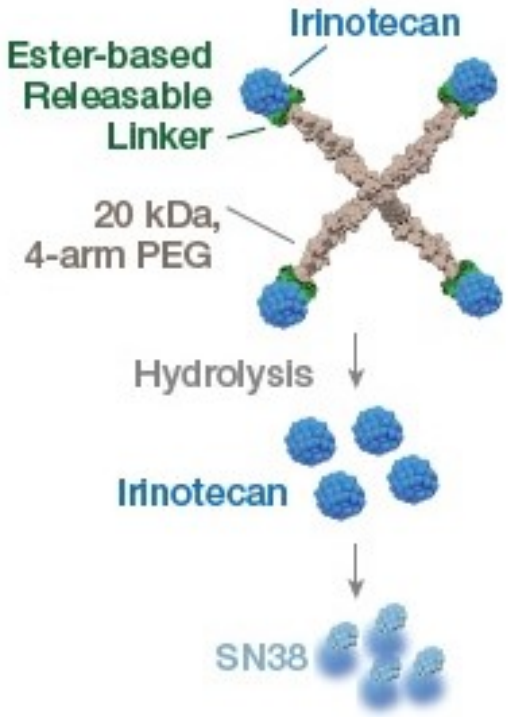
- FDA-approved to treat intracranial subependymal giant cells astrocytomas associated with tuberous sclerosis.

<u>Ongoing trial exploring efficacy of mTOR/PI3K inhibitors</u>

Nanoparticle delivery systems

1. Prolong systemic circulation
2. Cross the BBB
3. Enhance permeation and retention





ETIRINOTECAN PEGOL

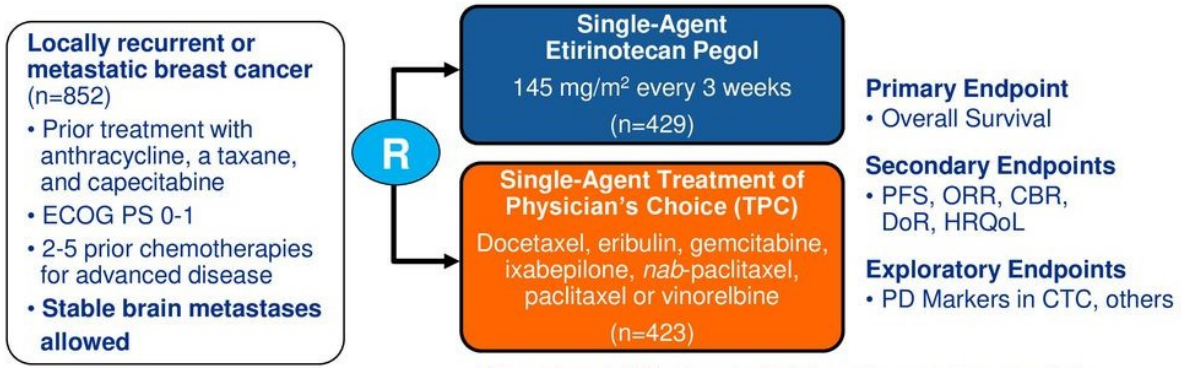
EP is a next-generation long-acting topoisomerase-1 inhibitor designed to improve the PK and distribution of SN-38.

Improved survival in preclinical intracranial tumor model compared with conventional irinotecan

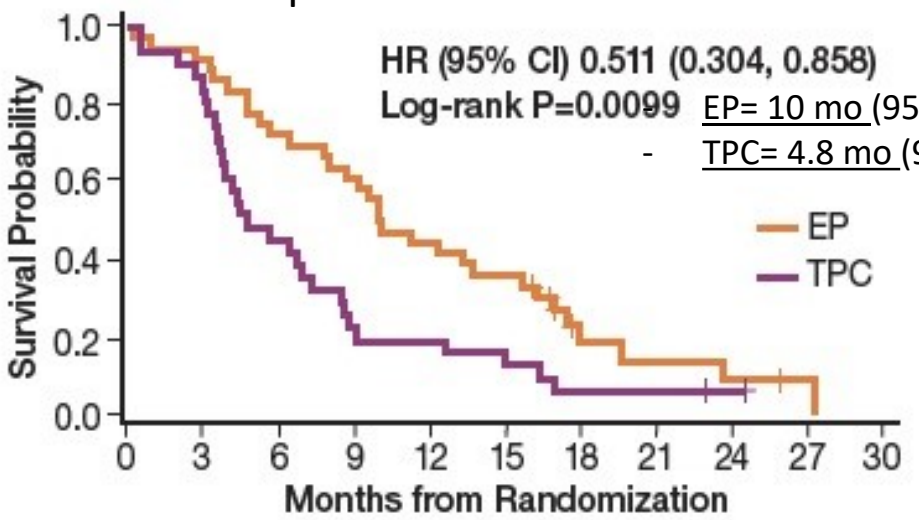
Perez EA et al, Lancet 2015
Patel T et al, Adv Drug Deliv Rev 2012

Etirinotecan pegol

BEACON phase 3 study



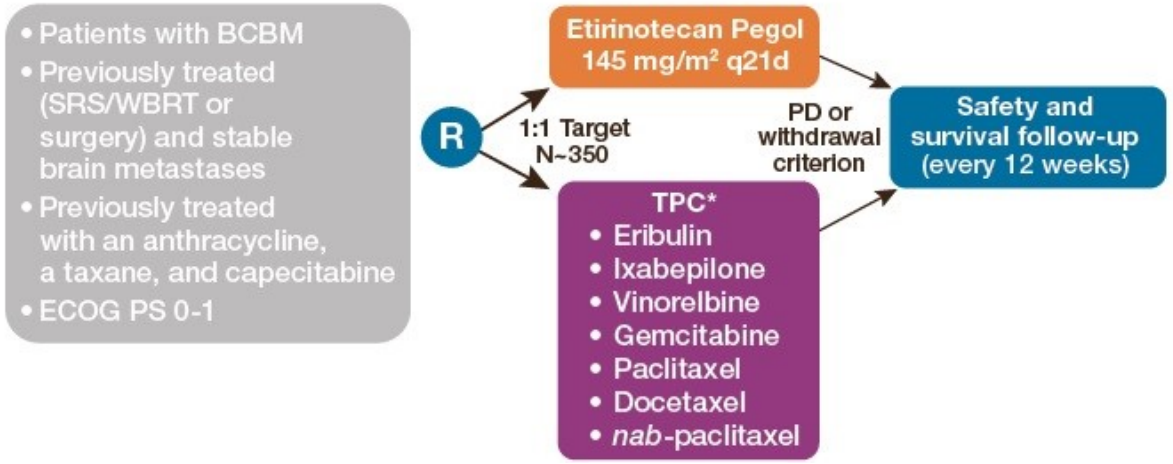
67 pts with brain metastases



- EP= 10 mo (95% CI 7.8-15.7)
- TPC= 4.8 mo (95% CI 3.7-7.3)

Triphaty D, ASCO 2017

ATTAIN phase 3 study



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

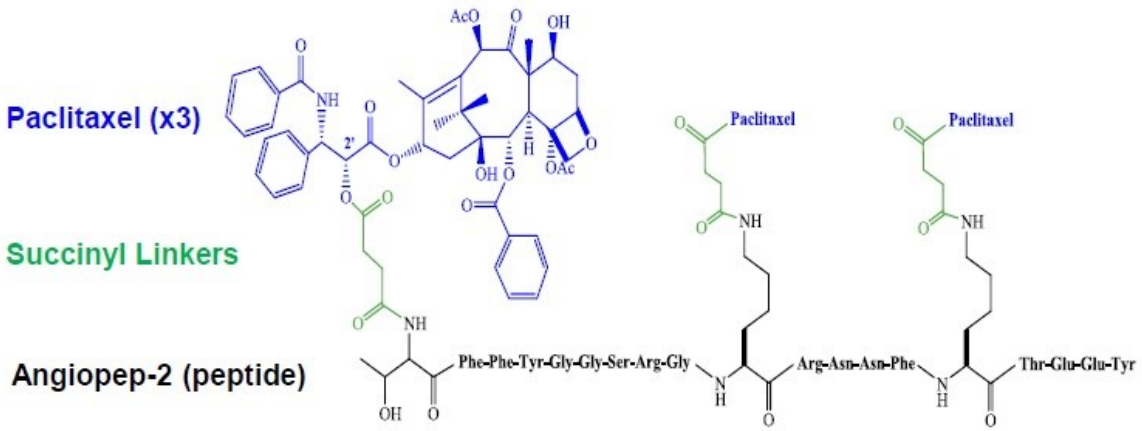
Refusal of the marketing authorisation for Onzeald (etirinotecan pegol)

Outcome of re-examination

On 20 July 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Onzeald, intended for the treatment of advanced breast cancer that has spread to the brain. The company that applied for authorisation is Nektar Therapeutics UK Limited.

The company requested a re-examination of the initial opinion. After considering the grounds for this request, the CHMP re-examined the opinion, and confirmed the refusal of the marketing authorisation on 9 November 2017.

ANG1005

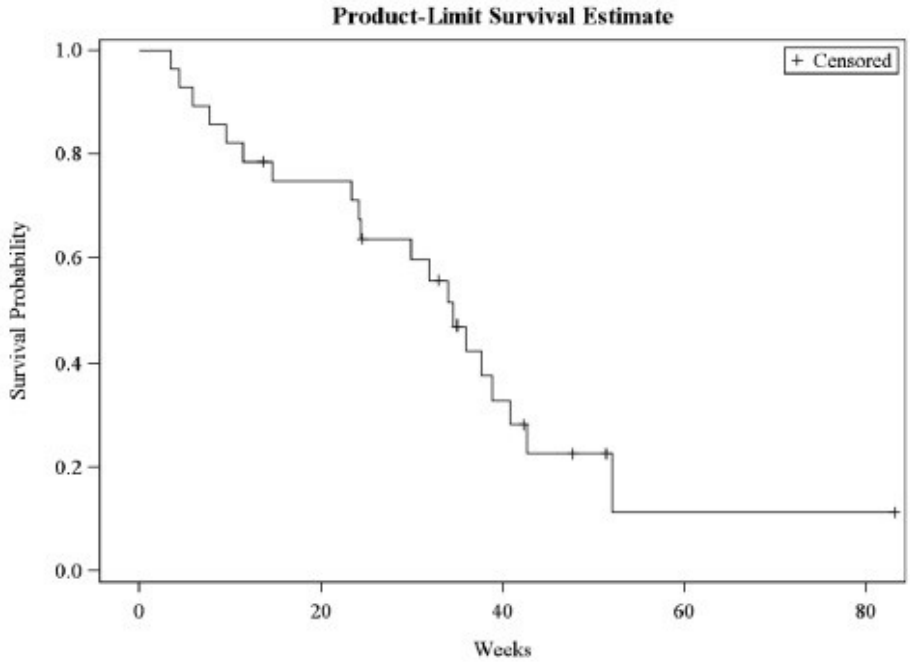


Paclitaxel linked to Angiopep-2 that cross the BBB and the BCB via the LRP-1 transport system.

ANG1005-CNL-04: phase II study in breast cancer brain metastasis +/- leptomeningeal disease

Outcome by CNS RECIST	All (n=58)	HER2+ (n=28)	HER2- (n=30)	TNBC* (n=12)
PR (confirmed)	9 (16%) 3 (5%)	5 (18%) 2 (7%)	4 (13%) 1 (3%)	2 (17%) -
SD	32 (55%)	18 (64%)	14 (47%)	5 (41%)
PD	17 (29%)	5 (18%)	12 (40%)	5 (42%)
Pt. Benefit	41 (71%)	23 (82%)	18 (60%)	7 (58%)

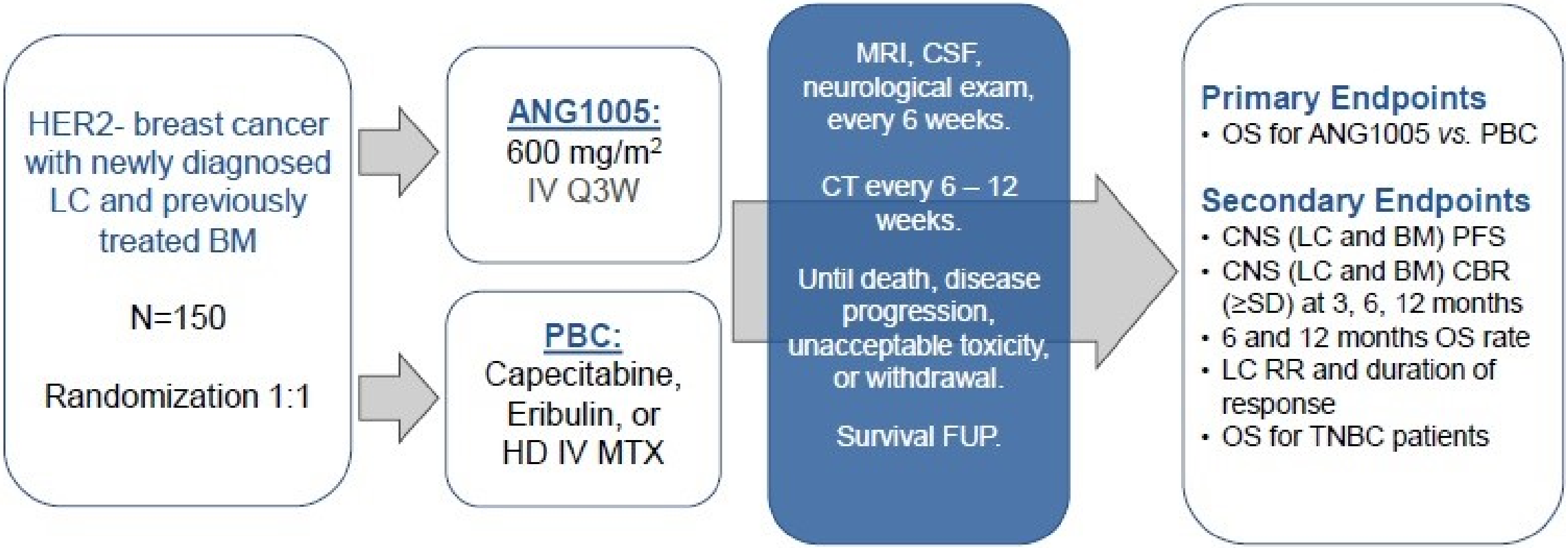
LC pts (N =23)



Tang SC et al, ESMO 2016

Median OS = 34.0 wks/7.9 months (95% CI 23.4-40.9 wks)

ANGLeD: phase III study

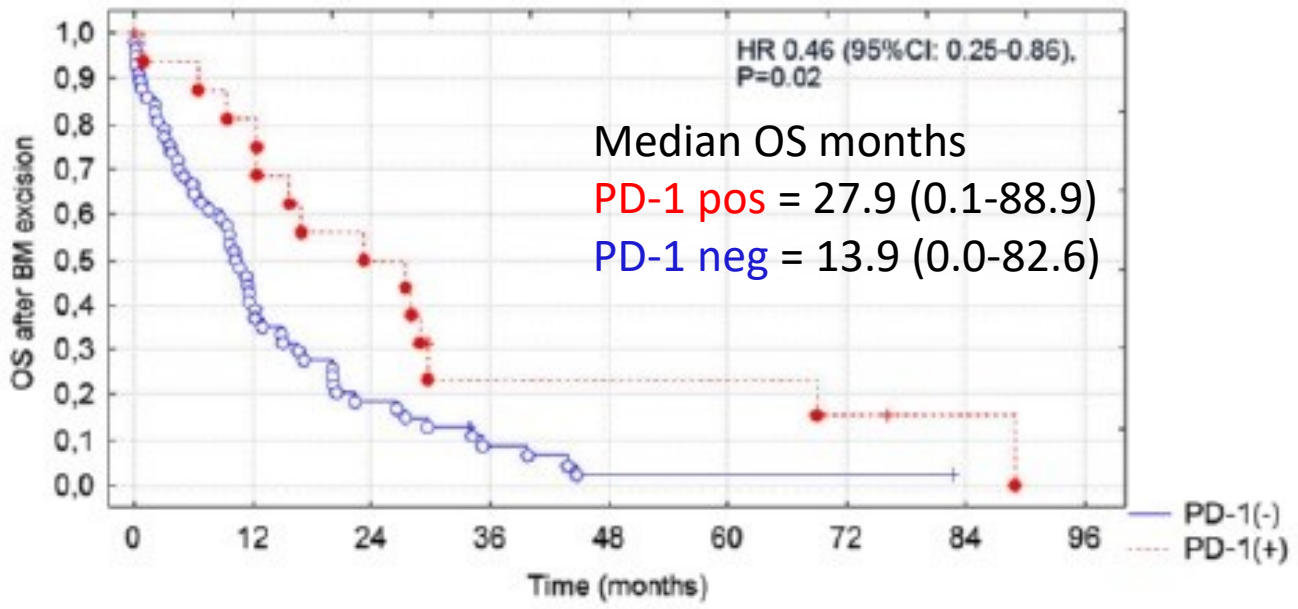


Kumthekar T. et al, SABS 2018

Immunotherapy

BCBM phenotypes	N (tot=84)	% (100)
HR-/HER2-	24	29
HR+/HER2-	16	19
HR+/HER2+	19	23
HR-/HER2-	24	29
Unknown	1	1

PDL-1 expression 53%
PDL-2 expression 36%
Not related to BCBM phenotype



Role of checkpoint inhibitors in HR+ breast cancer brain metastasis?

Duchnowska R. Et al, Breast Can Res 2016

Checkpoints inhibitors in brain metastases

Activity in brain metastases from NSCLC and melanoma

Trial	Drug(s)	Phase	*N* (ITT)	Disease	PD-L1 status	CNS ORR	Median CNS PFS (months)	Median PFS (months)	Median OS (months)
NCT00623766	Ipilimumab 10 mg/kg q3W × 4 doses, then 10 mg/kg q12W	2	51	Melanoma (asymptomatic BMs)	NA	16% (8/51)	1.5	1.4	7
			21	Melanoma (symptomatic BMs or on steroids)	NA	5% (1/21)	1.2	1.2	3.7
NIBIT-M1	Ipilimumab 10 mg/kg q3W × 4 doses, then 10 mg/kg q12W + fotemustine 100 mg/m2 q3W	2	20	Melanoma (asymptomatic BMs)	NA	40% (8/20)	3	4.5	13.4
NCT02085070	Pembrolizumab 10 mg/kg q2W	2	18	Melanoma	Any	22% (4/18)	not reported	not reported	NR
			18	NSCLC	≥ 1%	33% (6/18)	not reported	not reported	7.7
CheckMate 204	Nivolumab 1 mg/kg q3W + Ipilimumab 3 mg/kg q3W	2	75	Melanoma	Any	56% (42/75)	not reported	not reported	not reported
NCT02374242	Nivolumab 1 mg/kg q3W + Ipilimumab 3 mg/kg q3W	2	35	Melanoma (asymptomatic BMs)	Any	46% (16/35)	NR	13.8	NR
	Nivolumab 3 mg/kg q2W		25	Melanoma (asymptomatic BMs)	Any	20% (5/25)	2.5	2.6	18.5
	Nivolumab 3 mg/kg q2W		16	Melanoma (symptomatic BMs, failed local therapy)	Any	6% (1/16)	2.3	2.6	5.1

Activity of nivolumab in mRCC untreated or previous treated brain metastases: NIVOREN trial

868PD Brain objective response (modified RECIST)

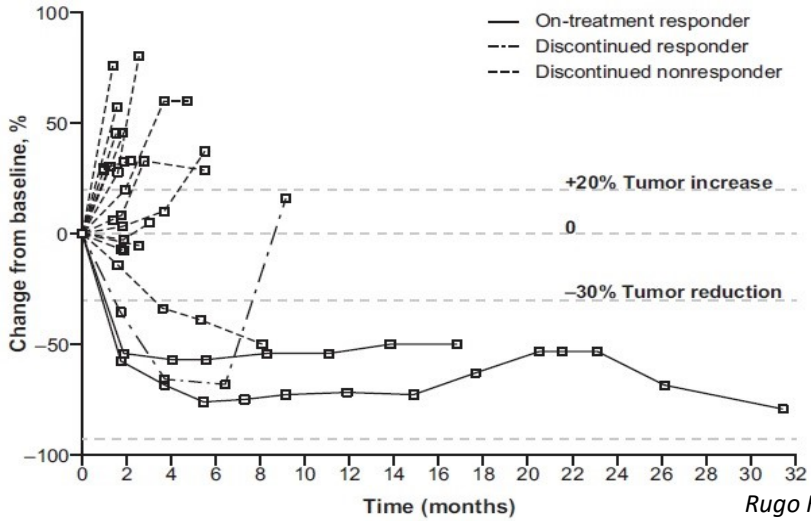
	Untreated (N = 33)	Prior focal treatment (N = 39)	Overall (N = 72)
Missing	3**	5**	8**
CR	4* (13.3%)	3 (8.8%)	7 (10.9%)
PR	0 (0.0%)	4 (11.8%)	4 (6.3%)
SD	12 (40.0%)	16 (47.1%)	28 (43.8%)
PD	14 (46.7%)	11 (32.4%)	25 (39.1%)

Kamath SD, Front Oncol 2018
Flippot R, ESMO 2018

Immunotherapy: challenges in brain metastasis BC

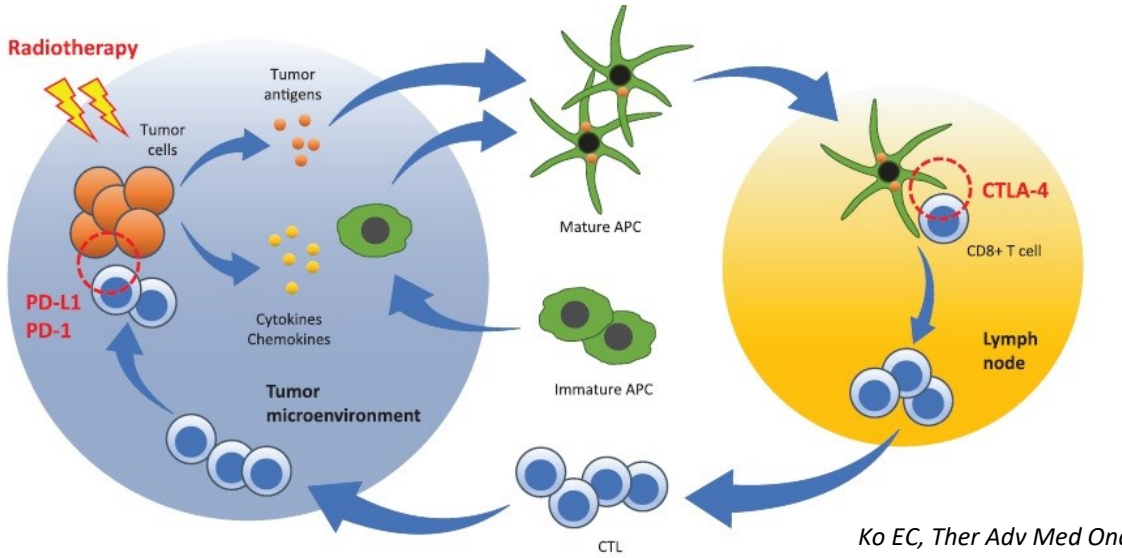
To date, no published data of checkpoint inhibitors in brain metastases from breast cancer

Checkpoint inhibitors in HR+/HER2- BC: Pembrolizumab has a modest but durable overall response in heavily treated HR+/HER2– BC pts PD-L1–positive.



Rugo HS, Clin Cancer Res 2018

Integration of radiotherapy with immunotherapy: possible activity in BC brain metastases?



Ko EC, Ther Adv Med Oncol 2018

Take-home messages

Because of the improvements in the treatment of HR+ breast cancer, brain and leptomeningeal metastasis have become one of the major limitation of life expectancy and quality of life.

Systemic treatment has an impact on post-BM survival: multidisciplinary approach is essential.

The landscape of systemic treatment for advanced HR+/HER2- BC patients is rapidly evolving (i.e. CDK4/6i, PI3K/AKT/mTORi): the effect on BM of these new therapies is largely unknown.

Promising studies also including new drugs are ongoing specifically for patients with BM and may hold promises for HR+/HER2-: abemaciclib, nanodrug-delivery systems (ANG1005), checkpoint inhibitors.

There is an urgent need to include patients with CNS metastasis into large clinical trials in order to investigate signals of activity.